ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

CALGB 50801

PHASE II TRIAL OF RESPONSE-ADAPTED THERAPY BASED ON POSITRON EMISSION TOMOGRAPHY (PET) FOR BULKY STAGE I AND STAGE II CLASSICAL HODGKIN LYMPHOMA (HL)

Access to FDG-PET/CT imaging and FTP transfer capability is a requirement for institutions enrolling patients on this protocol. Institutions must be credentialed by the Alliance Imaging Core Lab prior to enrolling patients.

ClinicalTrials.gov Identifier: NCT01118026

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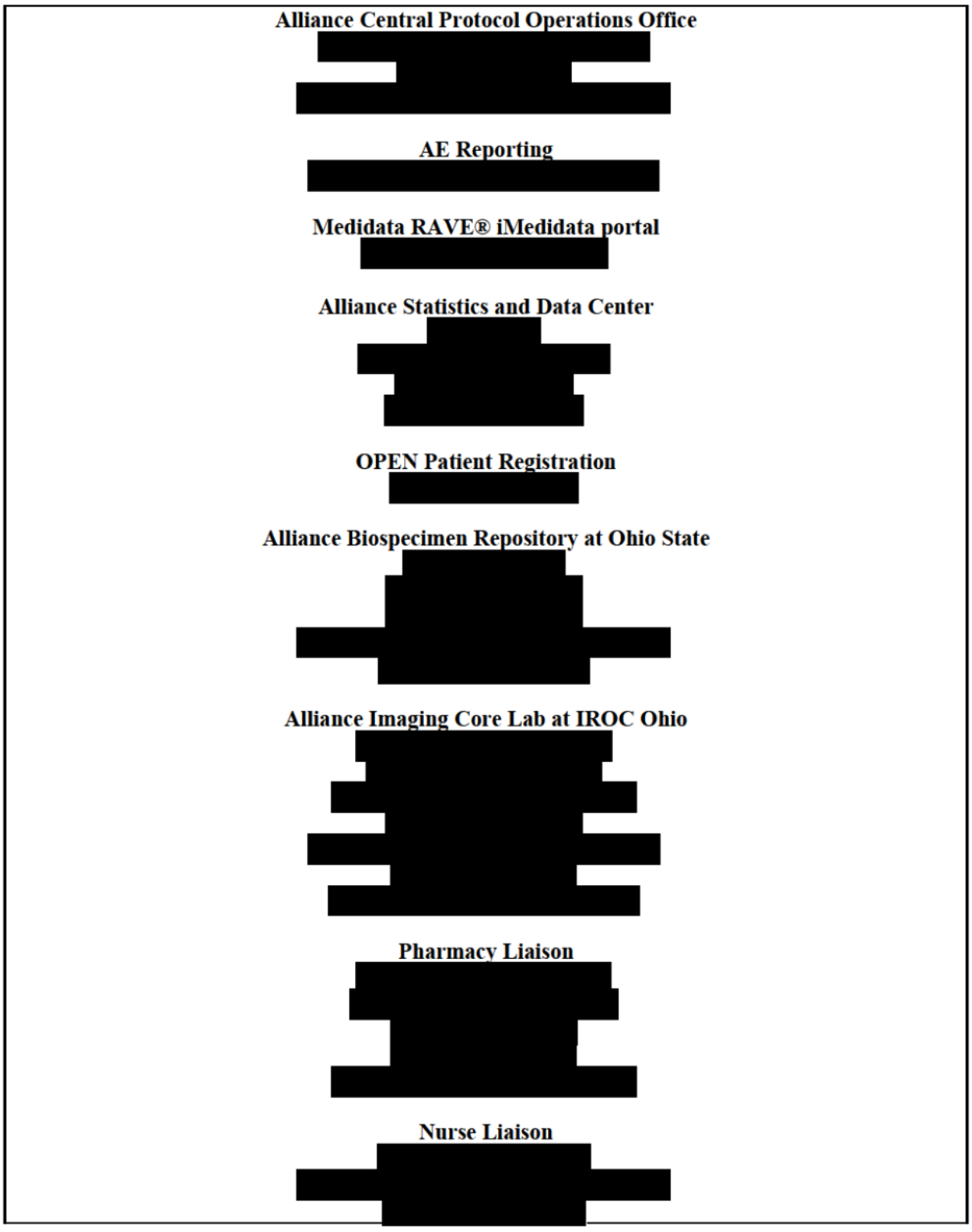
Participating Organizations: **ALLIANCE**/Alliance for Clinical Trials in Oncology, **ECOG-ACRIN**/ECOG-ACRIN Cancer Research Group, **SWOG**/SWOG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Alliance Biospecimen Repository at Ohio State
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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	For patient enrollments:	For study data submission:
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] to receive further instructions and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at [redacted] Contact the CTSU Help Desk with any OPEN-related questions at [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at [redacted] Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions (i.e. patient eligibility or treatment-related) see the Protocol Contacts, Page 2.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – [redacted] All calls and correspondence will be triaged to the appropriate CTSU representative.		

PHASE II TRIAL OF RESPONSE-ADAPTED THERAPY BASED ON POSITRON EMISSION TOMOGRAPHY (PET) FOR BULKY STAGE I AND STAGE II CLASSICAL HODGKIN LYMPHOMA

Schema

Eligibility Criteria

Histologically documented stage IA, IB, IIA, IIB classical Hodgkin lymphoma.

Nodular lymphocyte predominant Hodgkin lymphoma is excluded.

Mass >10 cm or > 0.33 maximum intrathoracic diameter (see Section 4.1.2).

No currently active second malignancy other than non-melanoma skin cancers.

No prior treatment for Hodgkin lymphoma, apart from one cycle of ABVD (see Section 4.3).

ECOG Performance Status 0-2.

LVEF by ECHO or MUGA within institutional normal limits.[2]

DLCO ≥ 60% with no symptomatic pulmonary disease.[2]

Patients with known HIV must have a CD4 count > 350 and be on concurrent antiretrovirals.

Non-pregnant and non-nursing.

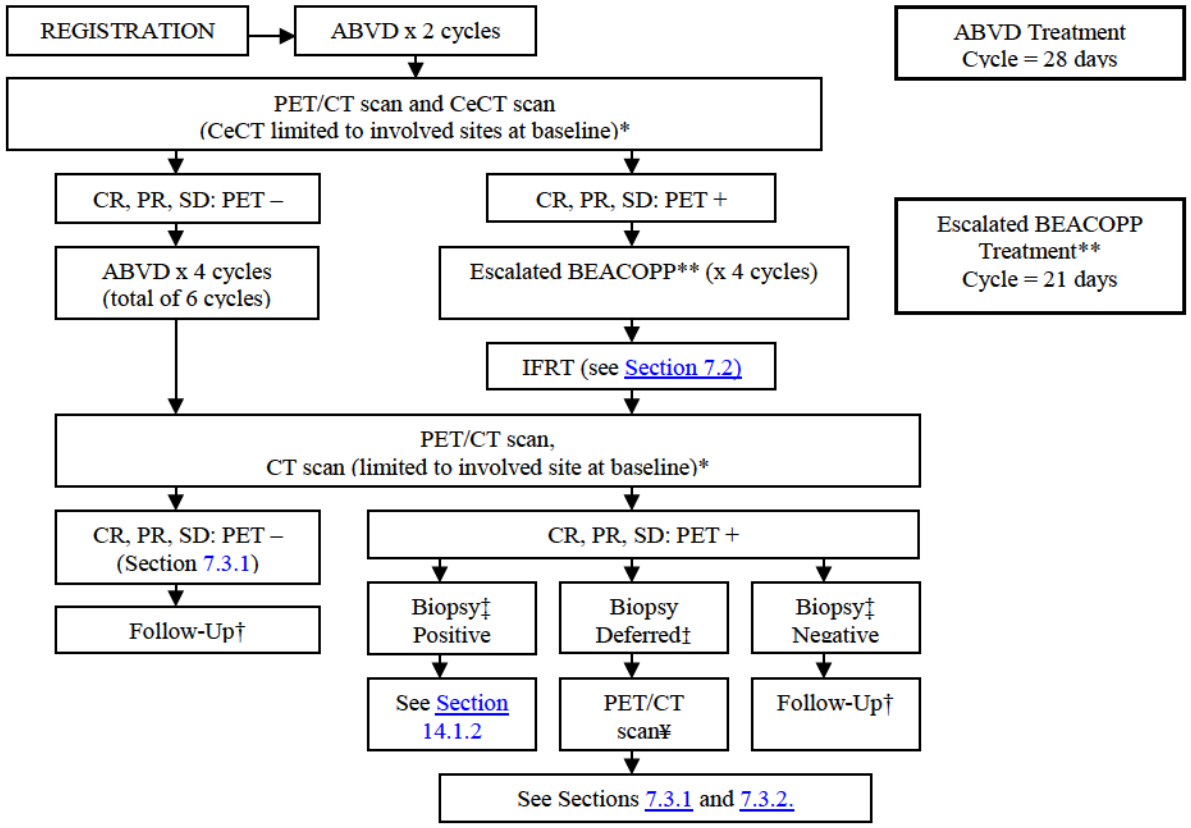
Age 18-60 years.

Initial Required Laboratory Values

ANC	≥ 1000/μL
Platelet Count	≥ 100,000/μL
Serum Creatinine	≤ 2 mg/dL
Bilirubin[1]	≤ 2 x ULN
AST	≤ 2 x ULN

[1]In the absence of Gilbert's disease
[2]Unless thought to be disease related

Access to FDG-PET/CT is a requirement for institutions enrolling patients on this protocol. Institutions must be credentialed by the Alliance Imaging Core Lab at IROC Ohio prior to enrolling patients (see Section 8.1.1).



* If the PET/CT scan was performed prior to contrast-enhanced CT (CeCT) and shows disease confined to a specific anatomic location/s (e.g. neck, chest, abdomen, pelvis), CeCT after two cycles of ABVD and at end of treatment can be limited to the involved anatomic location.

** For HIV positive patients, standard BEACOPP will be used instead of escalated BEACOPP (see Section 7.1.3).

† Follow-up according to the post-treatment schedule in Section 6.0.

‡ Biopsy may be performed if medically necessary at the discretion of the treating physician. If biopsy is neither clinically indicated nor medically appropriate, then patient should undergo a repeat PET/CT three months later as noted in the footnote (¥) below.

¥ If biopsy is neither clinically feasible nor appropriate, then repeat PET/CT should be obtained 3 months later (see Section 7.3.2).

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1.0 INTRODUCTION

1.1 Treatment of Bulky Early Stage Hodgkin Lymphoma

The majority of patients with early stage Hodgkin lymphoma (HL) and bulky mediastinal disease, typically defined as a mass measuring > 10 cm or one-third the maximal diameter of the thoracic cavity, receive combined modality therapy with 4-6 cycles of chemotherapy followed by involved field radiation [1, 2]. Multiple retrospective studies have demonstrated significant long-term toxicities associated with mediastinal radiotherapy. A recent analysis indicates that there is a cumulative incidence of secondary malignancies of 14% at 5 years and 23% at 10 years [3, 4]. Solid tumors predominate, with breast cancer and lung cancer being the most common secondary malignancies. In women, the relative risk of developing breast cancer is related to age at treatment, with patients younger than 15 having the highest relative risk (111.8-times) and patients up to age 40 having a persistently higher relative risk (3.4-times) [3]. Other toxicities of mediastinal radiation include valvular damage, accelerated coronary artery disease and pericardial fibrosis [5, 6].

Two randomized studies and one phase 2 study in patients without bulky disease suggest that ABVD chemotherapy alone results in similar overall survival compared with combined modality therapy or radiation alone [7-9]. A recent study from Italy randomized 160 patients with bulky disease, defined as a mass greater than 5 cm in greatest dimension who achieved a negative PET following 6 cycles of VE-BEP (vinblastine, etoposide, bleomycin, epirubicin, and prednisone) to radiotherapy versus observation [10]. At a median follow-up of 40 months, 14% of patients in the chemotherapy only arm relapsed compared to 4% of patients who received chemotherapy plus radiotherapy (2 cases of HL and one carcinoma in the radiation field). All of the relapses in the chemotherapy only arm occurred in the bulky site and contiguous nodal regions. PET scans were not obtained at mid-cycle restaging.

1.2 Role of PET Scanning in Hodgkin Lymphoma

Recent evidence suggests that early restaging PET scans are highly predictive of outcome in HL [11-13]. Hutchings and colleagues evaluated the predictive value of PET in 77 patients with stages I-IV HL [13]. Following 2 cycles of chemotherapy, 61 patients were PET negative and 16 were PET positive. At a median follow-up of 23 months, three of the PET negative patients, all of whom had advanced stage disease, relapsed. Eleven of 16 PET positive patients recurred. Of 16 PET positive patients, five had early stage disease and only one relapsed. All early stage patients received involved field radiotherapy (IFRT) following chemotherapy. The impact of bulky disease in early stage patients was not specifically addressed. The manuscript, therefore, concluded that positive early restaging PET scans were highly predictive of recurrent HL in patients with advanced stage disease.

A recent study by Gallamini evaluated 260 patients with stage IIB-IV HL who underwent PET scans after 2 cycles of chemotherapy [11]. The majority of patients received ABVD with or without radiotherapy. Treatment was not altered based on result of the PET. Fifty of 260 patients had a positive restaging PET and 210 were PET negative. The definition of PET positive was described as "clearly increased activity relative to the background." Two central radiologists reviewed PET scans that showed "minimal residual uptake," and scans with standardized uptake values (SUV) of 2-3.5 were considered negative for the analysis. At a median follow-up of 2 years, the progression-free survival (PFS) in PET negative patients was 95%, whereas only 12.8% of patients with a positive PET scan were free from disease. Approximately one-third of patients had bulky disease, which was not an independent predictor of outcome.

CALGB 50203 evaluated early restaging PET scans in patients with non-bulky stage I and II HL treated with 6 cycles of AVG (Adriamycin, vinblastine and gemcitabine) without IFRT. The complete response rate (CR/CRu) was 67% and estimated 1 and 2 year PFS rates were 81% and 71%, respectively. The study did not meet its primary endpoint. Although the negative predictive value of a positive PET scan after two cycles was comparable to other studies at 91%, the positive predictive value was 48%. It is unclear whether this difference is related to the inclusion of exclusively early stage patients, the novel chemotherapy regimen or possibly differences in the definition of a positive PET scan. Earlier studies used less stringent definitions, and relied on SUV's. CALGB 50203 was consistent with recently published guidelines where a negative PET is defined as uptake lower than that of mediastinal blood pool structures for residual nodes $\geq$ 2 cm. For nodes less than 2 cm, positivity is defined as uptake greater than surrounding background nodal structures [14].

1.3 BEACOPP in Hodgkin Lymphoma

BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone) is an intensive chemotherapy regimen developed by the German Hodgkin Lymphoma Study Group (GHSG). The regimen, which is given every three weeks, substitutes etoposide for dacarbazine and vincristine for vinblastine and incorporates increased dose cyclophosphamide. A large randomized study compared standard dose BEACOPP, dose escalated BEACOPP and COPP-ABVD [15]. 1,201 patients with stage IIB-IV were randomized. The study was closed early after interim analysis revealed the COPP-ABVD arm was inferior with respect to PFS and OS, compared to the other two arms. With long term follow-up of 10 years, freedom from treatment failure rates were 64%, 70%, and 82% and overall survival rates were 75%, 80%, and 86% for COPP-ABVD , standard BEACOPP, and escalated BEACOPP, respectively ($p < 0.001$) [16]. Hematologic toxicity of escalated BEACOPP was significant with 90% and 47% of patients developing grade 4 leukopenia and thrombocytopenia respectively. Myelodysplasia or secondary acute myeloid leukemia was seen in one of 260 evaluable patients treated with COPP-ABVD compared with 4 of 469 treated with standard BEACOPP and 9 of 466 with escalated BEACOPP. Infertility was nearly universal in patients receiving escalated BEACOPP.

An Israeli study treated 69 patients with early unfavorable stage HL (defined as B symptoms, bulky disease, >4 involved nodal regions, ESR >50, lymphocyte depleted histology or extranodal disease) or advanced stage disease with an International Prognostic Index of less than or equal to 2 with two cycles of standard dose BEACOPP. 27 patients had bulky mediastinal disease. Those who were PET or 67Ga negative after two cycles were continued on standard BEACOPP, while those who were PET or 67Ga positive were switched to escalated BEACOPP. The 5-year PFS and OS were similar for both groups at 84%, and 90% respectively. [17]. In addition, the GHSG recently presented an interim analysis of their study in early unfavorable HL. Patients were randomized to 2 cycles of escalated BEACOPP followed by 2 cycles of ABVD plus IFRT compared to 4 cycles of ABVD plus IFRT. 1127 of a total 1600 planned patients were evaluable. With a median follow-up of 32 months, the CR rates were 93.7% and 95% and OS 91% and 95% for the ABVD and escalated BEACOPP arms, respectively.

1.4 Rationale for IFRT Dose

Multiple randomized studies have shown that combined modality therapy provides superior disease control compared to radiation therapy alone [2, 18, 19] or chemotherapy alone [7, 20, 21] in early stage Hodgkin lymphoma (HL). However, the optimal dose of involved-

field radiation therapy (IFRT) in combined modality treatment programs is unknown. Potential cardiac and pulmonary complications related to mediastinal irradiation, as well as induction of secondary malignancies, have led to trials examining lower IFRT doses.

One of the first such trials was from the German Hodgkin Lymphoma Study Group (HD1) [22]. This trial enrolled 146 patients with stage I-IIIa HL with adverse prognostic factors including large mediastinal adenopathy (LMA), massive splenic involvement, more than five lesions, and/or extranodal involvement. All patients responding to 4 cycles of combination chemotherapy (COPP/ABVD) were randomized to 20 Gy versus 40 Gy IFRT. However, all patients with LMA received 40 Gy. The 4-year freedom from treatment failure did not differ between the treatment arms (79% and 80%, respectively).

The Children's Cancer Group 5942 study randomized children and adolescents younger than 21 years of age to IFRT or observation after achieving a complete response to chemotherapy (COPP-ABV) [21]. LMA was present in a minority of patients (25%). All patients randomized to IFRT, regardless of disease bulk, received 21 Gy. The 3-year event-free survival was 85% for patients randomized to observation and 93% for patients receiving IFRT (p=0.057). Outcomes for patients with LMA were not specifically reported.

For patients with favorable disease presentations, preliminary results from more recent studies also support a lower RT dose. The EORTC H9-F compared 36 Gy, 20 Gy, and 0 Gy IFRT after 6 cycles of EBVP [23]. The 4-year event-free survival was 87%, 84%, and 70%, respectively. The observation arm was dropped after an interim report showed inferior outcomes. The German Hodgkin Lymphoma Study Group trial HD10 randomized patients with early stage, favorable HL to 2 versus 4 cycles of ABVD with a secondary randomization to 20 Gy versus 30 Gy of IFRT [24]. Preliminary results showed no difference in freedom from treatment failure between 30 Gy and 20 Gy. Longer follow-up will be necessary to confirm the findings from these two trials.

There are no published randomized trials evaluating the optimal IFRT dose for patients with LMA. A retrospective analysis from Duke and Yale examining 83 patients with HL with LMA treated with combined modality therapy suggested that low dose IFRT may be adequate [25]. Relapse-free survival was 100% in patients receiving < 20 Gy (n=12), 71% after 20-25 Gy (n=24), 83% after 25-30 Gy (n=30) and 75% after > 30 Gy (n=12). A smaller study from the University of Michigan also found equivalent failure rates after low doses (19.8-25.2 Gy) compared with higher doses (30-44 Gy) [26]. However, firm conclusions cannot be drawn given the retrospective nature of the analyses and small patient numbers.

Consideration of treatment-related toxicities must be taken into account when formulating treatment programs for patients with HL. There is increasing data suggesting that RT-induced toxicities, in particular cardiac complications and secondary malignancies, are dose related. In a retrospective study from Duke, there was a significant difference in the incidence of secondary malignancies between patients treated with RT alone (mean dose 37.9 Gy), compared with patients treated with combined modality therapy with low dose IFRT (mean dose 25.5 Gy) [27]. The 20-year actuarial risk of secondary malignancies was 16% with RT alone compared with 0% with combined modality utilizing low dose IFRT. The RT fields were also smaller in the combined modality therapy group, which also likely contributed to the decrease in secondary malignancies. In a retrospective study from Stanford, the risk of death from heart disease appeared to be dose related. Doses above 30 Gy were associated with a relative risk of 3.5, while doses less than 30 Gy conferred no excess risk [28].

In the present study of patients with bulky supradiaphragmatic HL, the use of IFRT will be based on response to chemotherapy. Patients who achieve a PET CR after 2 cycles of chemotherapy will not receive IFRT. Patients who respond slowly to chemotherapy, or

have a positive PET scan but negative biopsy after chemotherapy will receive IFRT. Given the prognostic uncertainty of chemotherapy response kinetics, combined with the uncertainty of the optimal dose in unfavorable early-stage HL with LMA, we will use 30 Gy IFRT, which is a reasonable compromise between disease control and toxicity.

1.5 Rationale for Current Study

The majority of patients with HL with bulky mediastinal disease who are PET negative following 6 cycles of chemotherapy alone remain disease free at more than 3 years of follow-up and are spared the potential long-term toxicity of radiotherapy. As the negative predictive value of early PET is high, we propose that all patients will undergo PET scanning after 2 cycles of chemotherapy. Given the results of CALGB 50203 (AVG), we will administer ABVD chemotherapy in this study. Patients who are PET negative will receive 6 cycles of chemotherapy only. In the Italian study of patients with bulky disease who were PET negative after 6 cycles of therapy, 86% of patients remained in remission after chemotherapy only. The Gallamini study demonstrates that patients who are PET positive after 2 cycles of ABVD are unlikely to remain in remission with continuation of standard therapy (4 additional cycles of ABVD followed by IFRT). Therefore, these patients will then receive 4 cycles of escalated BEACOPP, followed by IFRT.

1.6 Inclusion of Women & Minorities

Although there is no evidence to suggest that the outcome will differ by gender or ethnicity and there is insufficient power to detect small or moderate effects, we will, in a secondary analysis, report the results by gender and ethnicity. Both men and women of all races and ethnic groups are eligible for this study.

PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	1	1	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	3	0	0	6
White	45	43	1	1	90
More Than One Race	1	1	0	0	2
Total	50	48	1	1	100

2.0 OBJECTIVES

2.1 Primary Objective

2.1.1 To determine the progression-free survival (PFS) at 36 months from enrollment for patients with bulky stage I and II Hodgkin lymphoma. All patients will begin treatment with ABVD. Patients who are PET negative after 2 cycles of chemotherapy will receive 6 cycles of ABVD without radiotherapy. Patients who are PET positive after 2 cycles of ABVD will then receive 4 cycles of escalated BEACOPP followed by IFRT. A comparison will be made of the 36-month PFS between patients who are PET positive and those who are PET negative following 2 cycles of ABVD.

2.2 Secondary Objectives

2.2.1 To evaluate the complete response (CR) rate of patients diagnosed with bulky stage I and II Hodgkin lymphoma following PET response-adapted chemotherapy with or without radiation therapy.

2.2.2 To determine the predictive value of FDG uptake using various semiquantitative approaches, at baseline, after 2 cycles of ABVD and at completion of therapy.

2.2.3 To determine the predictive value of volumetric vs. 2 dimensional (2-D) measurement changes on CT between baseline and after 2 cycles, at the end of chemotherapy (PET negative patients only) and after RT (PET positive patients only) and compare with PET parameters.

2.2.4 To determine if changes in both qualitative and semiquantitative FDG-PET findings between baseline and after cycle 2, at end of chemotherapy (PET negative patients only) and after RT (PET positive patients only) with combination analyses with incorporating changes obtained from dedicated CT scans, correlate with response and PFS.

2.2.5 To compare the predictive value of both qualitative and semiquantitative FDG-PET changes, 2-D and volumetric CT changes, and combinatorial analyses (PET+dedicated CT data) with molecular parameters, and conventional parameters, including IPS.

2.2.6 To assess whether elevated baseline serum soluble CD30 (sCD30), IL10, CCL17, and CCL22 correlate with clinical response and PFS.

2.2.7 To assess whether persistent or recurrent elevation of serial serum sCD30, IL10, CCL17, or CCL22 correlate with relapse/progression or PET scan results.

2.2.8 To confirm independently useful tissue biomarkers (bcl-2, MAL, FOXP3, CD68, GzB) for risk stratification in patients with bulky stage I and II Hodgkin lymphoma treated with this regimen.

2.2.9 To compare mediastinal bulk on standing PA and lateral chest x-ray (> 0.33 maximum chest diameter) with chest CT (mass > 10 cm).

3.0 ON-STUDY GUIDELINES

This clinical trial can fulfill its objectives only if patients appropriate for the trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. To maximize patient safety, patients should be treated on this protocol only at centers having ready access to blood product support and adequate staff to care for the severely neutropenic patient. Physicians should consider the risks and benefits of any therapy and therefore only enroll patients for whom the agents administered are appropriate. **Although they will not be considered as formal eligibility (exclusion) criteria, as part of the decision-making process physicians should recognize that the following may increase the risk to the patient entering this protocol:**

- Serious medical illness or psychiatric condition that could prevent compliance with treatment or informed consent.
- Uncontrolled or severe cardiovascular disease including recent (< 6 months) myocardial infarction. Patients with cardiac arrhythmias requiring treatment may be entered at their physician's discretion.

4.0 ELIGIBILITY CRITERIA

All questions regarding eligibility criteria should be directed to the Study Chair. Please note that the Study Chair cannot grant waivers to eligibility requirements.

Institutions must be credentialed by the Alliance Imaging Core Lab at IROC Ohio prior to enrolling patients (see **Section 8.1.1**).

4.1 Documentation of Disease

4.1.1 Histologically documented Hodgkin lymphoma subclassified according to the WHO modification of the Rye Classification and staged according to the modified Ann Arbor Staging Classification system. Patients must have clinical stage IA, IB, IIA or IIB. Patients with "E" extensions will be eligible if all other criteria have been met. Nodular lymphocyte predominant Hodgkin lymphoma is excluded.

Core needle biopsies are acceptable if they contain adequate tissue for primary diagnosis and immunophenotyping. Fine needle aspirates are not acceptable. If multiple specimens are available, please submit the most recent. **Failure to submit pathology materials within 60 days of patient registration will be considered a major protocol violation (see Section 5.3).**

4.1.2 Patients must have a mediastinal mass > 0.33 maximum intrathoracic diameter on standing postero-anterior chest x-ray or mass measuring > 10 cm in its largest diameter.

4.2 Second Malignancy

No "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are considered by their physician to be at less than 30% risk of relapse.

4.3 Prior Therapy

Patients may have had one cycle only of ABVD prior to enrolling on study. No other prior treatment (chemotherapy or radiation therapy) for Hodgkin lymphoma is allowed.

If patient has had one cycle of ABVD, in order to be eligible to enroll on CALGB 50801, the patient must have had all of the following tests prior to starting the first cycle of ABVD:

- LVEF by ECHO or MUGA
- PFTs (including DLCO/FVC)
- CT scan (neck*, chest, abdomen, pelvis)
- FDG-PET/CT scan
- Chest X-ray, PA & Lateral
- CBC, differential, platelets
- ESR
- Serum creatinine
- Glucose
- AST
- Alkaline phosphatase
- Bilirubin
- LDH

*Patients with a negative FDG-PET/CT scan do not need to have had a dedicated neck CT scan prior to starting the previous cycle of ABVD.

4.4 ECOG Performance

ECOG performance status 0-2.

4.5 LVEF and DLCO

LVEF by ECHO or MUGA within institutional normal limits unless thought to be disease related. DLCO ≥ 60% with no symptomatic pulmonary disease unless thought to be disease related.

4.6 HIV Infection

Patients with known HIV must have a CD4 count > 350 and be on concurrent antiretrovirals (See Section 12.1). Patients with a history of intravenous drug abuse or any behavior associated with an increased risk of HIV infection should be tested for exposure to the HIV virus. An HIV test is not required for entry on this protocol, but is required if the patient is perceived to be at risk.

4.7 Pregnancy Restrictions

Non-pregnant and non-nursing. Due to the teratogenic potential of the agents used in this study, pregnant or nursing women may not be enrolled. Women and men of reproductive potential should agree to use an effective means of birth control.

4.8 Age Restricitions

Age 18 – 60 years.

4.9 Initial Required Laboratory Data:

ANC	≥ 1000/μL
Platelet count	≥ 100,000/μL
Serum Creatinine	≤ 2 mg/dL
Bilirubin*	≤ 2 x upper limit of normal
AST	≤ 2 x upper limit of normal

* In the absence of Gilbert's disease

5.0 REGISTRATION, DATA SUBMISSION, HISTOLOGIC REVIEW, AND CORRELATIVE SCIENCE SAMPLE PROCUREMENT AND SUBMISSION

5.1 Registration

5.1.1 Informed Consent

The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts. Human subjects protection committee approval of this protocol and of its consent form are required.

5.1.2 Baseline FDG-PET/CT Scan

A baseline FDG-PET/CT scan will be obtained ≤ 28 days prior to registration. In the case of a patient who already had a baseline FDG-PET/CT scan at another facility, the scan must be submitted to the Alliance Imaging Core Lab at IROC Ohio within 30 days of patient registration (see Section 8.2).

5.1.3 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account [redacted] In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) [redacted] Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at < [redacted] For questions, please contact the RCR ***Help Desk*** by email at [redacted]

5.1.4 CTSU Site Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participation roster at the registering site

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Downloading site registration documents:

Site registration forms may be downloaded from the CALGB 50801 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to [redacted] and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the Alliance link to expand, then select trial protocol #CALGB 50801
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements for CALGB-50801 site registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- Imaging Core Lab (ICL) confirmation. Institutions must be credentialed by the Alliance Imaging Core Lab at IROC Ohio (see **Section 8.1.1**).

Submitting Regulatory Requirements

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal:
www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:

[redacted]

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] in order to receive further instructions and support.

Checking Your Site's Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to [redacted] and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

5.1.5 Patient Enrollment through OPEN

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account

(check at [redacted] and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data. OPEN can be accessed at [redacted] or from the OPEN tab on the CTSU members' side of the website at [redacted] To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at [redacted] or at [redacted] For any additional questions contact the CTSU Help Desk at [redacted].

5.1.6 Registration to Companion Studies

There is one substudy within CALGB 50801 (**CALGB 150903**). This correlative study must be offered to all patients enrolled on CALGB 50801, though patients may opt not to participate. The two components of this substudy are:

Serum and plasma markers (Section 10.1 and 10.2)

Immunohistochemical markers (Section 10.3)

If a patient answers "yes" to "My specimen(s) may be used for the research described above" (model consent question #1), then the patient should be registered to CALGB 150903 at the same time that s/he is registered to the treatment trial (50801) and samples submitted per Section 5.4.

5.2 Data Submission

As of Update #12 to the protocol, this study will use Medidata Rave® for remote data capture (RDC) of all future data collection. All data originally received by the Alliance and Statistics and Data Center (SDC) (either electronically using the "Print and/or Submit to CALGB" button [i.e. Teleform form] or by mail) has been transferred to Medidata Rave ® and can be accessed via the Medidata Rave ® system. If necessary, data originally submitted to the SDC electronically (or by mail) can be amended via the Medidata Rave ® system.

Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < [redacted] >) and the appropriate Rave role (Rave CRA, Read-Only, CRA, Lab Admin, SLA, or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin

role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. The Rave system can be accessed through the iMedidata portal at [redacted]. For additional information regarding account setup or training, please visit the training section of the Alliance website. Forms should be submitted in compliance with the table below, and a copy of the All Forms Packet can be downloaded from the Alliance website.

Upon initial site registration approval for the study in RSS, site personnel with Rave roles assigned on the appropriate roster may receive a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login [redacted] using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. Personnel who did not receive an invitation should contact the Alliance Service Center.

Users who have not previously activated their iMedidata/Rave account at the time of an initial site registration approval for a study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website's Rave tab under the Rave Resource Materials heading (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at [redacted] or by e-mail at [redacted].

Form*		Submission Schedule
Baseline		
	50801 Registration Worksheet	Within one month of registration
	50801 Eligibility Checklist	
C-1877	50801 On-Study Form	
LY-4	Lymphoma Pre-Study Flow Sheet	
C-1878	50801 PET and CT Measurement Form	
C-1883	50801 FDG-PET Adjunctive Data Sheet	
Report	Baseline PET, CT, and Pathology reports	
Treatment* **		
C-1880	50801 Treatment Summary Form	Submit after each cycle of ABVD, BEACOPP, or IFRT
S-068	50801 Medication Calendar††	
C-1881	50801 Adverse Event Form**	
LY-5	Lymphoma Flow Sheet	
C-1882	50801 Follow-up Form	PET negative: Submit after cycle 2 and cycle 6 of ABVD PET positive: Submit after cycle 2 of ABVD, cycle 6 of BEACOPP (C-1882 only), and following IFRT
C-1878	50801 PET and CT Measurement Form	
C-1883	50801 FDG-PET Adjunctive Data Sheet	
Report	Copies of PET/CT scans and pathology reports	
Follow-up (Post-treatment)		
C-1882	50801 Follow-up Form	Submit every 3 months for the first year post treatment, every 6 months for years 2 and 3, and annually at years 4 and 5
C-1878	50801 PET and CT Measurement Form	
C-1883	50801 FDG-PET Adjunctive Data Sheet†	
Report	Copies of PET/CT scans and pathology reports	
C-400	Long Term Follow-up Form	Submit annually years 6-10
Other		
RT-1	Radiation Dosimetry Summary Form	Submit per Section 7.2.13
RT-2	Radiation Total Dose Record	
C-300	Off Treatment Form	At end of all protocol treatment
C-113	Notification of Death	At time of death
C-1001	New Malignancy Form	At time of diagnosis of new malignancy
C-1820	Adverse Events Addendum Form	Complete if additional space is needed to report other adverse events. See form for instructions.
C-1742	CALGB Confirmation of Lost to Follow Up	See form for submission instructions

* Use CALGB Remarks Addenda (C-260) if additional comments are necessary or additional writing space is needed.

** Submit AE form until all protocol treatment related events have resolved or until non-protocol treatment begins. If patient death is reported via CTEP-AERS, report Grade 5 event of AE form even if patient is off protocol treatment.

*** If patient never starts treatment, submit all baseline data and the C-300 Off-Treatment Form. No other follow-up forms are required for submission.

† Only submit through year 3.

†† Submission only for those patients receiving escalated BEACOPP.

Common Terminology Criteria for Adverse Events (CTCAE): This study will utilize the Common Terminology Criteria for Adverse Events version 4.0 for toxicity and adverse event reporting. However, CTCAE version 5.0 must be used for serious AE reporting through CTEP-AERS as of April 1, 2018.

5.3 Histologic Review

Submission of a tissue block is critical for lymphoma diagnosis confirmation. High quality hematoxylin and eosin-stained sections and any required confirmatory studies (such as immunohistochemistry and in situ hybridization) is done most efficiently from the tissue block in laboratories of the Alliance Biorepository at Ohio State.

Within 60 days of registration, send a formalin-fixed, paraffin-embedded block of well-fixed lymphoma tissue containing adequate material for histologic confirmation of diagnosis. A block at least 1 cm x 1 cm x 2 mm is preferable, although smaller is acceptable if no other block is suitable. If only one block exists, and the tissue is sufficiently large, it is acceptable to split the block into two and submit one. Contact Dr. Eric Hsi (216-444-5230) with questions.

Specimens for patients registered on this study must be logged and shipped using the online Alliance Biospecimen Management System (BioMS).

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance/CALGB trials. Authorized individuals may access BioMS at the following URL: [redacted], using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [redacted] For assistance in using the application or questions or problems related to specific specimen logging, please contact: [redacted].

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

The requested tissue block should be labeled with the protocol number (50801), institutional surgical pathology number, CALGB patient ID, institution, date of acquisition, and tissue source. A copy of the shipping manifest produced by BioMS must be printed and placed in the shipment with the specimens. In addition to the pathology specimen and the shipping manifest, send a copy of the pathology report (include consultative pathology reports, if available) and CT/MRI scan report(s) to the Alliance Biorepository at Ohio State:

[redacted]

Failure to submit pathology specimens **within 60 days** of patient registration will be considered a major protocol violation.

If patient has consented to allow their tissue to be used for current research described in Section 10.3 (model consent question #1) or kept for future research (model consent questions #2 and #3, only one tissue block need be submitted to accommodate both histologic confirmation of diagnosis and correlative science studies (see Section 5.4.2).

The Alliance/CALGB has instituted special considerations for the small percentage of institutions whose policies prohibit release of any blocks. If, due to institutional policy, a block cannot be sent, please call [redacted] to obtain a protocol for submission of representative tissue from your institution.

5.4 Correlative Science Sample Submission

All participating institutions must ask patients for their consent to participate in the components of the correlative substudy (**CALGB 150903)**, although patient participation is optional. Rationale and methods for these studies are described in Section 10.0.

Specimens for patients registered on this study must be logged and shipped using the online Alliance Biospecimen Management System (BioMS).

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance/CALGB trials. Authorized individuals may access BioMS at the following URL: [redacted], using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [redacted] For assistance in using the application or questions or problems related to specific specimen logging, please contact: [redacted]

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

	Sample Type		
Sample Collection Time Points[1]	Whole Blood (Serum)*	Whole Blood (Plasma)**	FFPE Tissue
Prior to initiation of therapy (Baseline)	X	X	X***
Time of 2nd PET/CT scan (post-cycle 2)	X	X	
Time of 3rd PET/CT scan At chemo completion for PET negative patients Post IFRT completion for PET positive patients	X	X	
During year 1 follow-up (at 3, 6, 9, and 12 months post-tx)	X	X	
During year 2 follow-up (at 18 and 24 months post-tx)	X	X	
During year 3 follow-up (at 30 and 36 months post-tx)	X	X	
Progression or Relapse			X[2]

			(Section 5.4.3)

* Whole blood for serum (10mL) is collected at the time of each PET/CT scan and at the time of each CT scan during the first 3 years of follow-up.

** Whole blood for plasma (10mL) is collected at the time of each PET/CT scan and at the time of each CT scan during the first 3 years of follow-up.

*** An FFPE tissue block is mandatory for histologic confirmation of diagnosis and if patient has consented to allow tissue to be kept for current and/or future research, only one block needs to be submitted.

1 Patients who answered, "yes" to model consent question #1.

2 Patients who answered, "yes" to model consent question #2 and #3.

5.4.1 Serum and Plasma Submission for the Correlative Substudy (150903)

For patients who consent to participate (model consent question #1), both serum and plasma will be used for the biomarker analyses described in Sections 10.1 and 10.2. Submission of both specimen types is required.

Whole blood (20 mL) will be collected at baseline (prior to initiation of therapy), at each of the first two PET/CT scans, and at the time of each PET/CT scan during the first 3 years of post-treatment follow-up. That is, blood will be collected at the following 11 or 12 time points:

1. Prior to initiation of therapy
2. At the time of the second PET/CT scan (post cycle 2)
3. At the time of the third PET/CT scan (at chemo completion for PET negative patients; at post IFRT completion for PET positive patients)
4. 3 months post-treatment
5. 6 months post-treatment
6. 9 months post-treatment
7. 12 months post-treatment
8. 18 months post-treatment
9. 24 months post-treatment
10. 30 months post-treatment
11. 36 months post-treatment

5.4.1.1 Serum Collection Procedures

For patients who consent to participate (model consent question #1), serum samples will be used for the studies described in Section 10.1.

1. Collect blood in 10 mL Red Top Tube. After collection, tubes ("vacutainers") should sit upright after the blood is drawn at room temperature for a minimum of 30 to a maximum of 60 minutes to allow the clot to form. Note: Use red top (serum) tubes (silicon-coated)—no additives and not SST (serum separator tubes).
2. Centrifuge the blood sample at the end of the clotting time (30-60 minutes) in a horizontal rotor (swing-out head) for 20 minutes at 1100-1300 g at room temperature.
3. Use a pipette to transfer the serum (Recommendation: do not pour). Pipette serum into the labeled cryovials (recommended cryovials are

described in Section 5.4.1.3). Aliquot volume is to be 500 µL. Close the caps on the vials tightly. This process should be completed within 1 hour of centrifugation. Note: Be very careful not to pick up red blood cells when aliquoting. This can be done by keeping the pipet above the red blood cell layer and leaving a small amount of serum in the tube.

4. Check that all aliquot vial caps are secure and that all vials are labeled.
5. Place all aliquots upright in a specimen box or rack in an -80°C or colder freezer. All specimens should remain at -80°C or colder prior to shipping. The CALGB 50801 samples should not be thawed prior to shipping. Serum should be shipped on dry ice according to the shipping procedures in Section 5.4.1.3.

5.4.1.2 Plasma Collection Procedures

For patients who consent to participate (model consent question #1), plasma samples will be used for the studies described in Section 10.2.

1. Collect blood in 10 mL Purple Top Tube. After collection, gently mix the blood by inverting the tube 8 to 10 times. Store vacutainer tubes upright at 4°C until centrifugation. Blood samples should be centrifuged within four hours of blood collection.
2. Centrifuge blood samples in a horizontal rotor (swing-out head) for 10 to 20 minutes at 1100-1300 g at room temperature. Warning: Excessive centrifuge speed (over 2000 g) may cause tube breakage and exposure to blood and possible injury. If needed, RCF for a centrifuge can be calculated. For an on-line calculator tool, please refer to: [redacted]
3. After centrifugation, plasma layer will be at the top of the tube. Mononuclear cells and platelets will be in a whitish layer, called the "buffy coat", just under the plasma and above the red blood cells.
4. Carefully collect the plasma layer with an appropriate transfer pipette without disturbing the buffy coat layer. Pipette the plasma into the labeled cryovials (recommended cryovials are described in Section 5.4.1.3). Aliquot volume is to be 500 µL. Close the caps tightly and place on ice. This process should be completed within 1 hour of centrifugation.
5. Check that all aliquot vial caps are secure and that all vials are labeled.
6. Place all aliquots upright in a specimen box or rack in an -80°C or colder freezer. All specimens should remain at -80°C or colder prior to shipping. The samples should not be thawed prior to shipping. Plasma should be shipped on dry ice according to the shipping procedures in Section 5.4.1.3.

5.4.1.3 Plasma and Serum Shipping Procedures

The Alliance strongly recommends the usage of 2 ml cryovials for storage of plasma and serum specimens. Acceptable cryovials include:

Company Name	Catalog Number
Nalgene	03-337-7Y (through Fisher) NNI No.: 5012-0020
Fisher brand	05-669-57 (through Fisher)
Corning	03-374-21 (through Fisher), CLS430659 (through Sigma), Corning: 430488
VWR	16001-102

Samples should be logged and shipped via BioMS, see Section 5.4 for instructions. A copy of the shipping manifest produced by BioMS must be printed and placed in the shipment with the specimens.

All submitted specimens must be labeled with the protocol number (50801), CALGB patient ID, patient's initials, date and time of specimen collection and type of specimen collected (e.g., whole blood).

Please be sure to use a method of shipping that is secure and traceable. Ship specimens Monday through Thursday by overnight service to assure receipt. Do not ship specimens on Fridays or Saturdays. **All plasma and serum specimens must be shipped on dry ice to the following address:**

5.4.2 Formalin-Fixed Paraffin-Embedded (FFPE) Tissue Block Submission for the Correlative Substudy (150903)

The Alliance/CALGB Lymphoma Committee is committed to conducting correlative science studies utilizing tissue from consenting patients enrolled on treatment trials, and has chosen tissue microarrays (TMAs) as the method of archiving tissue. TMAs are constructed by removing two 1 mm diameter tissue cores from the lymphoma tissue block using a specially designed instrument (Beecher Instruments, Sun Prairie, WI). The resulting tissue array can contain 100 cases in a single tissue block, and allows rapid, high throughput analysis of markers by immunohistochemistry or in situ hybridization. The original tissue block remains intact with only a small amount of tissue removed with no significant distortion. The original block may then be returned to the submitting institution.

Samples should be logged and shipped via BioMS, see Section 5.4 for instructions. A copy of shipping manifest produced by BioMS must be printed and placed in the shipment with the specimens.

All submitted specimens must be labeled with the protocol number (50801), CALGB patient ID, patient's initials, date and time of specimen collection and type of specimen collected (e.g., whole blood).

Please be sure to use a method of shipping that is secure and traceable. Ship specimens Monday through Thursday by overnight service to assure receipt. Do not ship specimens on Fridays or Saturdays.

If a patient has consented and agreed to allow their tissue to be used in current correlative studies described in Section 10.3 (model consent question #1) **OR** has agreed to allow their tissue to be kept for future research (model consent questions #2 and #3), send a formalin-fixed, paraffin-embedded block of well-fixed lymphoma tissue to:

If patient has consented to allow their tissue to be kept for current and/or future research, only one tissue block need be submitted to accommodate both histologic confirmation of diagnosis and correlative science studies (see Section 5.3).

5.4.3 Progression or Relapse FFPE Tissue Sample Submission for the Correlative Substudy (150903)

Samples should be logged and shipped via BioMS, see Section 5.4 for instructions. A copy of the shipping manifest produced by BioMS must be printed and placed in the shipment with the specimens.

All submitted specimens must be labeled with the protocol number (50801), CALGB patient ID, patient's initials, date and time of specimen collection and type of specimen collected (e.g., whole blood).

Please be sure to use a method of shipping that is secure and traceable. Ship specimens Monday through Thursday by overnight service to assure receipt. Do not ship specimens on Fridays or Saturdays.

At the time of progression or relapse (see Section 13.1.4), if a patient has consented to allow their tissue to be kept for future research (model consent questions #2 and #3), and if a biopsy has been performed, please submit a formalin-fixed, paraffin-embedded block of well-fixed lymphoma tissue for future correlative science to:

The Alliance has instituted special considerations for the small percentage of institutions whose policies prohibit release of any blocks. If, due to institutional policy, a block cannot be sent, please call [redacted] to obtain a protocol for submission of representative tissue from your institution.

6.0 REQUIRED DATA

Guidelines For Pre-Study Testing

To be completed within 16 DAYS before registration:

- All blood work
- History and physical examination

To be completed within 28 DAYS before registration:

- Any scan of any type (e.g., PET, CT, or MRI) that is utilized for tumor measurement

To be completed within 42 DAYS before registration:

- Any baseline exams used for screening (i.e., MUGA, PFTs)
- Any scan of any type, or ultrasound of uninvolved organs that is not utilized for tumor measurement

Tests & Observations	Prior to Study	Day 1 of Each Cycle*	Day 15 of Each Cycle**	Time of Restaging	Post Treatment Follow-up (after cycle 2 of ABVD and following either cycle 6 of ABVD or IFRT)***
History and Progress Notes	X	X			X
Physical Examination	X	X			X
Height/Weight/BSA	X				
Performance Status	X	X			
Tumor Measurements	X	A		X	X
Drug Toxicity Assessment		X	X	X	X
Laboratory Studies					
CBC, Differential, Platelets	G	X	X**	X	
ESR	G			X	
Serum Creatinine	G	X		X	
Glucose	G			X	
AST, Alkaline Phosphatase, Bilirubin	G	X		X	
Serum or urine βHCG	X				
LDH	G				
LVEF by ECHO or MUGA	F				PRN
PFTs (including DLCO/FVC)	F				PRN
HIV (if required, see section 4.5)	B				
Staging					
CT scan (neck, chest, abdomen/pelvis)	F, H			X	D
FDG-PET/CT scan†	E, F			C [1-3]	
Chest X-ray, PA & Lateral	F				
Histologic Review (see Section 5.3)	X				
CALGB 150903 (consenting patients)					
FFPE tissue	At baseline and at the time of progression / relapse.				
Whole blood for marker analysis	Prior to registration; at the time of the post-cycle 2 PET/CT scan, chemo completion PET/CT scan; post IFRT PET/CT scan (if post-cycle 2 PET/CT scan is positive); at 3, 6, 9, 12, 18, 24, 30 and 36 months post-treatment follow-up.				

† Institutions must be credentialed by the Alliance Imaging Core Lab at IROC Ohio prior to enrolling patients (see Section 8.1.1). It is critical that all FDG-PET/CT scans be performed in an identical way

to the baseline scan, with the same scanner, same scan direction, and consistent arm positioning. The interval between FDG injection and initiation of emission scanning should be the same or similar to the baseline scan.

* Within 48 hours prior to day 1 of ABVD or BEACOPP.

** Within 48 hours prior to day 15 of each treatment cycle of ABVD.

*** Every 3 months for one year from the response assessment at the completion of therapy, then every 6 months for years 2 and 3, and then annually for a maximum of ten years from study entry.

A If accessible to physical examination, record measurements on day 1 of each cycle.

B An HIV test is not required for entry on this protocol, but is required if the patient is perceived to be at risk.

C[1] Post-cycle 2 FDG-PET/CT scans must be performed 8-10 days after the Day-15 dose of ABVD during cycle 2. (i.e. on day 23, 24 or 25 of cycle 2, see Section 8.2 for acceptable FDG-PET/CT scan completion days).

C[2] For patients who are PET negative after 2 cycles of ABVD, post-treatment completion FDG-PET/CT will be performed ≥ 3 and ≤ 8 weeks after completion of chemotherapy.

C[3] For patients who are PET positive after 2 cycles of ABVD, post-IFRT FDG-PET/CT scans must be performed ≥12 weeks and ≤16 weeks after completion of IFRT.

D Contrast-enhanced helical/spiral CT scans of the chest, abdomen, and pelvis will be obtained every 3 months for year one and every 6 months for years 2-3 and annually for years 4-5. Follow-up routine CTs of the neck will not usually be necessary, since most recurrences in the neck will be found by physical examination.

E Baseline FDG-PET/CT will be obtained ≤ 28 days prior to registration. See Section 5.1.2 in the case of a patient who has already had a baseline scan at another facility.

F If a patient has had one previous cycle of ABVD prior to enrolling on study, the patient must have had the following tests prior to starting the previous cycle of ABVD: LVEF, PFTs, CT scan, FDG-PET/CT scan, and chest x-ray. These tests do not need to be repeated prior to study in those patients with a previous cycle of ABVD.

G If a patient has had one previous cycle of ABVD prior to enrolling on study, the patient must have had the following tests prior to starting the previous cycle of ABVD: CBC, differential, platelets; ESR; serum creatinine; glucose; AST, alkaline phosphatase, bilirubin; and LDH. These tests do not need to be repeated prior to study in those patients with a previous cycle of ABVD.

H Patients with a negative FDG-PET/CT scan do not need to have a dedicated neck CT scan prior to study.

PRN As clinically indicated.

7.0 TREATMENT PLAN

Institutions must be credentialed by the Alliance Imaging Core Lab at IROC Ohio prior to enrolling patients (see **Section 8.1.1**).

Patients must begin treatment within 7 days of registration. Questions regarding treatment may be directed to the Study Chair.

A missed or vomited dose of oral agent should not be made up.

7.1 Chemotherapy Regimens

Mondays and Tuesdays are recommended as therapy initiation days to assure a timely central PET reading.

7.1.1 ABVD

Therapy will consist of doxorubicin, bleomycin, vinblastine, and dacarbazine on Days 1 and 15 of each cycle. A cycle will be considered 28 days.

Doxorubicin 25 mg/m^2 IV on Days 1 and 15 of each cycle

Bleomycin 10 units/m^2 IV on Days 1 and 15 of each cycle

Vinblastine 6 mg/m^2 IV on Days 1 and 15 of each cycle

Dacarbazine 375 mg/m^2 IV infusion on Days 1 and 15 of each cycle

All patients will receive 2 cycles of ABVD. For patients who have had one previous cycle of ABVD prior to registration, the previous cycle will be considered cycle 1. Patients who achieve a CR, PR, or SD and whose PET scans are **negative** after two cycles of ABVD (see Section 8.2 for timing of imaging studies) will receive four more cycles of ABVD (a total of six cycles).

See Section 9.0 for dose modifications and management of toxicity. See Section 12.0 for ancillary therapy.

7.1.2 Escalated BEACOPP

Patients who achieve a CR, PR, or SD and whose PET scans are **positive** after two cycles of ABVD will receive four cycles of escalated BEACOPP followed by involved-field radiotherapy (see section 7.2):

Bleomycin 10 units/m^2 IV on Day 8 of each cycle

Etoposide 200 mg/m^2 IV over 60 minutes on Days 1, 2 and 3 of each cycle

Doxorubicin 35 mg/m^2 IV on Day 1 of each cycle

Cyclophosphamide 1250 mg/m^2 IV over 60 minutes on Day 1 of each cycle

Vincristine 1.4 mg/m^2 (maximum 2 mg) IV on Day 8 of each cycle

Procarbazine* 100 mg/m^2 (rounded to nearest 50 mg) orally on Days 1-7 of each cycle

Prednisone* 40 mg/m^2 (rounded to nearest 5 mg) orally on Days 1-14 of each cycle

Repeat escalated BEACOPP treatment every 21 days for four cycles.

Filgrastim (G-CSF)* 5 mcg/kg subcutaneously on Days 8 -14 of each cycle. G-CSF may be discontinued when, after reaching the nadir, the neutrophil count has remained over 1,000/mm^3 on 3 successive days. Do not give escalated BEACOPP within 48 hours of filgrastim.

Antibiotic prophylaxis* with cotrimoxazole, one double strength tablet twice daily is required on days 8-15 of each cycle. Dapsone (50 mg orally twice daily) or pentamidine may be substituted for Pneumocystis prophylaxis in subjects allergic to cotrimoxazole.

See Section 9.0 for dose modifications and management of toxicity. See Section 12.0 for ancillary therapy.

* Patients should record the doses of procarbazine, prednisone and antibiotic taken, as well as the day in which G-CSF injection is given on the CALGB form S-068 (50801 Medication Calendar). (See Section 5.2)

7.1.3 Standard BEACOPP

Patients who are HIV-positive and whose PET scans are **positive** after two cycles of ABVD will receive four cycles of standard BEACOPP followed by involved-field radiotherapy (see section 7.2).

Bleomycin 10 units/m2 IV on Day 8 of each cycle

Etoposide 100 mg/m2 IV over 60 minutes on Days 1, 2 and 3 of each cycle

Doxorubicin 25 mg/m2 by IV on Day 1 of each cycle

Cyclophosphamide 650 mg/m2 IV over 60 minutes on Day 1 of each cycle

Vincristine 1.4 mg/m2 (maximum 2 mg) IV on Day 8 of each cycle

Procarbazine* 100 mg/m2 (rounded to nearest 50 mg) orally on Days 1-7 of each cycle

Prednisone* 40 mg/m2 (rounded to nearest 5 mg) orally on Days 1-14 of each cycle

Repeat standard BEACOPP treatment every 21 days for four cycles.

Filgrastim (G-CSF)* 5 mcg/kg subcutaneously on Days 8 -14 of each cycle. G-CSF may be discontinued when, after reaching the nadir, the neutrophil count has remained over 1,000/mm3 on 3 successive days. Do not give standard BEACOPP within 48 hours of filgrastim.

Antibiotic prophylaxis* with cotrimoxazole, one double strength tablet twice daily is required on days 8-15 of each cycle. Dapsone (50 mg orally twice daily) or pentamidine may be substituted for Pneumocystis prophylaxis in subjects allergic to cotrimoxazole.

See Section 9.0 for dose modifications and management of toxicity. See Section 12.0 for ancillary therapy.

* Patients should record the doses of procarbazine, prednisone and antibiotic taken, as well as the day in which G-CSF injection is given on the CALGB form S-068 (50801 Medication Calendar). (See Section 5.2)

7.2 Involved-Field Radiation Therapy (IFRT)

7.2.1 Administration of IFRT

Administration of involved-field radiation therapy (IFRT) will depend on PET response (see Section 8.0) after 2 cycles of ABVD as follows:

1. Patients who are PET negative after 2 cycles of ABVD **will not** receive IFRT.

2. Patients who are PET positive after 2 cycles of ABVD, **will** receive IFRT following 4 cycles of escalated BEACOPP. These patients will receive 30.6 Gy IFRT.

A period of 3-6 weeks will elapse between the beginning of the last dose of chemotherapy and the beginning of radiation therapy, IFRT may not begin until the WBC is > 2,000/microliter and the platelet count is > 100,000/microliter.

7.2.2 Equipment

Energy: 4-10 MV photons are required for all disease sites. Cobalt-60 is not allowed. IMRT is not allowed. Proton therapy is not allowed.

Geometry: In general, parallel opposed equally weighted fields (AP/PA) are most appropriate. Isocentric technique with SAD ≥ 80 cm is preferable, with the patient supine in the same position for both the AP and PA treatments. For large field sizes (e.g., neck plus mediastinum), extended distance and SSD technique are allowed, with the SSD in the 110-120 cm range. In this setting, SSD technique where the patient turns from supine to prone is acceptable.

Simulation: CT based treatment planning is required for all patients.

Calibration: All therapy units used for this protocol shall have calibrations verified by the Radiological Physics Center.

7.2.3 Required Benchmarks

Centers participating in this protocol using 3D-CRT are required to complete the 3D Benchmark. Benchmark materials may be obtained from the Quality Assurance Review Center (www.qarc.org) and must be submitted before patients on this protocol can be evaluated.

7.2.4 Planning Target Volume

Guidelines for delineating the involved field have been previously published [29]. Briefly, a region, not individual lymph nodes, is treated. In general, pre-chemotherapy volumes are utilized, with the exception of the transverse diameter of mediastinal disease. To spare normal tissue, post-chemotherapy volumes are treated in this circumstance. All sites involved at presentation need to be included in the treatment fields. Treatment will include the volumes as described below. Original extent of disease plus 2.0 cm margin must be included; this supersedes all other requirements. The only exception is for fields near critical organs (lungs) when a 1-1.5 cm margin may be acceptable (see below).

The **Gross Tumor Volume** (GTV) is defined as the volume occupied by visible or palpable disease, and will be limited to areas of disease as defined at presentation and includes residual disease present after the completion of chemotherapy. The **Clinical Target Volume** (CTV) is the anatomical compartment(s) in which the GTV is located. The **Planning Target Volume** (PTV) is defined as the margin around the CTV to account for patient motion and set-up variability. The PTV fields are outlined below.

- **Unilateral Cervical/Supraclavicular Region:** Involvement at any unilateral cervical level with or without involvement of the ipsilateral supraclavicular (SCL) nodes. Arms akimbo or at sides.

Upper Border: 1-2 cm above the lower tip of the mastoid process and midpoint through the chin. If only the SCL nodes are involved (no cervical nodal involvement), the upper border should be placed at the top of the larynx.

Lower Border: 2 cm below the bottom of the clavicle.

Lateral Border: To include the medial 2/3 of the clavicle.

Medial Border:

(a) If the supraclavicular nodes are not involved, place the border at the ipsilateral transverse processes except when medial nodes close to the vertebral bodies are present on initial staging, in which case the border should allow 2 cm margin or include the entire vertebral body.

(b) When the ipsilateral supraclavicular nodes are involved, the border should be placed at the contralateral transverse processes.

Blocks:

(a) Mid-neck calculations should be performed to determine the maximum spinal cord dose.

(b) A small anterior larynx block may be used throughout treatment unless this block would shield disease.

- **Bilateral Cervical/Supraclavicular Region:** Treat both cervical and supraclavicular regions as described above. Use a posterior mouth block on the posterior-anterior field to block the upper field diverging through the mouth. Blocks may be used as described above.

- **Mediastinum:** Involvement of the mediastinum and/or the hilar nodes. The field includes also the bilateral medial SCL nodes even if not clinically involved. Arms akimbo, at sides, or up.

  Upper Border: C5-C6 interspace if the SCL nodes were not originally involved. If SCL nodes were involved, the upper border should be placed at the top of the larynx and the lateral border should be adjusted as described in the section on treating neck nodes.

  Lower Border: 5 cm below the carina or 2 cm below the pre-chemotherapy inferior border, whichever is lower.

  Lateral Border: Post-chemotherapy GTV with 1.5 cm margin.

  Hilar Area: To be included with 1 cm margin (except where GTV requires 1.5 cm margin).

  Heart: Treatment of the entire pericardium should be limited to patients with extensive pericardial involvement; in this case, the whole heart can be treated to 14.4 Gy. Selected pericardial treatment is reasonable in other clinical situations, such as extension of an internal mammary node to the pericardium, or right-sided pericardial fat pad involvement abutting the pericardium without effusion.

- **Mediastinum with involvement of the cervical nodes:** When both cervical regions are involved, the field is a mantle without axillae using the guidelines described above. If only one cervical chain is involved, the vertebral bodies, contralateral upper neck, and larynx can be blocked as previously described.

- **Axillary Region:** The ipsilateral axillary, infraclavicular, and supraclavicular areas are treated when the axilla is involved. Whenever possible use CT-based planning for this region.

  Upper Border: C5-C6 interspace or inferior border of the larynx (if no SCL involvement; otherwise modify field as noted above).

  Lower Border: The tip of the scapula or 2 cm below the lowest axillary node, whichever is lower.

  Medial Border: Ipsilateral cervical transverse process. Include the vertebral bodies only if the SCL is involved.

  Lateral Border: Flash axilla.

- **Unusual Sites (Waldeyer's Ring):** To be discussed with the CALGB 50801 Radiation Oncology Co-Chair.

7.2.5 Target Dose

All fields will be treated to a total dose of 3,060 cGy, calculated at the isocenter or at the central axis at midplane. Each daily fraction will be 180 cGy.

7.2.6 Time-Dose Considerations

Prescribe 180 cGy per fraction to the prescription point. Treat with 1 fraction/day, 5 fractions/week. Treat all fields each day. No dose adjustments will be made for treatment interruptions.

7.2.7 Dose Uniformity and Reference Points

Every effort shall be made to make the dose uniform throughout the treatment volume. The dose should be 3,060 cGy ± 7.5% throughout the treatment volume. Doses should be carried at the central axis, 2 cm above the inferior field edge and 2 cm below the superior field edge. Off-axis reference points should also be carried, as appropriate for the field (e.g., mid-neck, mid-axilla, SCL). Compensators/boosting/blocking is allowed when necessary to achieve the ± 7.5% homogeneity.

7.2.8 Heterogeneity Corrections

Calculations that take into account tissue heterogeneities shall be used.

7.2.9 Treatment Techniques

Patient Position: Supine throughout is preferable. Generally treat with arms akimbo (hands on hips). If axillary lymph nodes are involved, positioning with the arms up is also acceptable. Other specific positioning recommendations are noted above. Appropriate immobilization devices are highly recommended.

Field Shaping: Use custom shielding with divergent and individually cut blocks or multileaf collimators. Treatment will be verified with weekly portal films.

7.2.10 Normal Tissue Sparing

The maximum dose to any point in the spinal cord will be ≤ 4,000 cGy.

The volume of lung receiving over 20 Gy (V20) will be ≤ 35%.

7.2.11 Calculations and Treatment Planning

Prescription Point: This should be the isocenter. However, in a field where the isocenter falls beneath a block, an appropriate off-axis point may be used.

Critical Organs/Reference Points: The maximum dose to the spinal cord shall be calculated and reported on the RT-2 form. A dose volume histogram for the spinal cord and lung shall be submitted.

7.2.12 Quality Assurance Documentation

Quality Assurance Review Center (QARC) will be performing two separate reviews of the radiation therapy in this protocol: (1) a Rapid Review at the initiation of radiotherapy, and (2) a Final Review at the completion of radiotherapy. The data shall be sent to:

(1) Rapid Review: Within 3 days of the onset of radiotherapy, submit the following data for on-treatment review:

- Copies and reports of CT scans, PET scans, and other diagnostic determinations used for the planning target volumes. This includes the studies done prior to treatment (pre-chemotherapy) and those done prior to radiotherapy (post-chemotherapy).
- Copies of DRR's for each field.
- Copies of portal films for each field. Double exposure technique showing anatomical landmarks is preferred.
- Photographs of the patient in the treatment position.
- RT-1 (Dosimetry Summary Form).
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.
- Isodose distributions for the total treatment plan in the axial, sagittal and coronal planes through the center of the treatment or planning target volume. The planning target volume, isocenter and the normalization method must be clearly indicated.
- A dose volume histogram for the lung and spinal cord.

(2) Final Review: Upon completion of radiotherapy, submit the following data for final review:

- Copies of localization films and portal films depicting any field modifications made after submission of the initial reporting of data for on-treatment review.
- Copies of calculations, isodoses, and DVH's for any changes made after submission of the data for on-treatment review.
- RT-2 (Radiotherapy Total Dose Record Form).
- A copy of the patient's daily treatment chart.

Digital Data: The treatment plan may be submitted in digital format. Please refer to www.QARC.org [redacted] under "Digital Data" for guidelines regarding digital submissions. All submissions, including those that are digital, require hard copy submission of the other items included in this list.

Questions regarding the radiotherapy section of this protocol should be directed to the CALGB 50801 Radiation Oncology Co-Chair:

[redacted]

Questions regarding the dose calculations and documentation should be directed to:

[redacted]

7.2.13 Definitions of Deviation in Protocol Performance

Prescription Dose

Minor Deviation: The dose to the prescription point differs from that in the protocol by between 6% and 10%.

Major Deviation: The dose to the prescription point differs from that in the protocol by more than 10%.

Dose Uniformity

Minor Deviation: The variation of dose in one of the target volumes exceeds ± 7.5% but is within ± 15%.

Major Deviation: The variation of dose in one of the target volumes exceeds± 15%. The dose to the prescription point differs from that in the protocol by more than 15%.

Critical Organ

Minor Deviation: The maximum dose to the spinal cord is > 4,000 cGy. The lung V20 is > 35%.

Major Deviation: The maximum dose to the spinal cord is > 5,000 cGy. The lung V20 > 40%.

Volume

Tight Volumes

Minor Deviation: Field margins are less than the protocol-specified margin.

Major Deviation: Field margins shield, miss, or transect target volumes.

Excessive Volumes

Minor Deviation: Field margins are 1-3 cm beyond protocol-specified margins.

Major Deviation: Field margins are > 3 cm beyond protocol-specified margins.

7.3 Treatment Duration and Staging

Patients who achieve a CR, PR, or SD and whose PET scans are **negative** after two cycles of ABVD will receive four additional cycles of ABVD (a total of six cycles). Patients who achieve a CR, PR, or SD and whose PET scans are **positive** after two cycles of ABVD will receive 4 cycles of escalated BEACOPP and involved-field radiation therapy. Patients with

PD at any time will be removed from protocol therapy. Patients will be evaluated for response after cycle 2 and after completion of treatment chemotherapy. Post completion of treatment PET/CT scans must be obtained ≥ 3 weeks but ≤ 8 weeks from completion of last cycle of chemotherapy for PET negative patients only. Patients receiving escalated BEACOPP + IFRT will also undergo a PET/CT scan ≥ 12 weeks and ≤ 16 weeks after completion IFRT.

7.3.1 CR, PR, or SD and PET Negative after Completion of Treatment

Patients who achieve a CR, PR, or SD and who are PET negative after completion of treatment will be followed according to the post-treatment follow-up schedule in Section 6.0.

7.3.2 CR, PR, or SD and PET Positive after Completion of Treatment

For patients who achieve a CR, PR, SD and who are PET positive after completion of treatment, a biopsy may be performed at the discretion of the treating physician. If biopsy negative, then the patient should be followed according to the post-treatment follow-up schedule in Section 6.0. If biopsy positive, then the patient should be followed per Section 14.1.2. If a biopsy is neither clinically indicated nor medically feasible, then the patient should undergo repeat PET/CT and CT scans three months later.

If PET negative after three months, then the patient will be followed according to the post-treatment follow-up schedule in Section 6.0.

If PET positive after three months, then at the discretion of the treating physician the patient may undergo a biopsy if clinically feasible and appropriate.

If, at three months, biopsy is neither clinically appropriate nor medically feasible, then the patient should be followed according to the post-treatment follow-up schedule in Section 6.0.

8.0 IMAGING

FDG-PET Imaging, Interpretation, PET and CT Data Submission, and Semiquantitative Analysis.

8.1 Institution Credentialing Procedures for FDG-PET/CT Imaging

Prior to enrollment of patients, institutions must be credentialed to participate in the trial by the Alliance Imaging Core Laboratory (ICL) at IROC Ohio if they have not previously been credentialed for any other CALGB trials (see Section 8.1.1). The Imaging Core Lab has developed and will provide a site manual that outlines all of the details as they relate to the image acquisition and reconstruction.

8.1.1 FDG-PET/CT Requirements for Participation

The participating center must have, or have access to, a facility with an integrated positron-emission tomography and computed tomography (PET/CT) scanner.

The participating center must have the ability to submit PET and CT studies electronically to the ICL in digital DICOM format (other formats: BITMAP, JPG, hardcopy or scanned files are not acceptable). See Section 8.9 for submission procedures.

Participating sites must be credentialed by the ICL so that the performance characteristics and infrastructure requirements are met:

If a site has been credentialed by the ICL for participating in CALGB 50303 PET/CT imaging study, a protocol refreshment only will be needed for participating in CALGB 50801.

If a site has never been credentialed by the ICL, however the site participated or is participating in any other Alliance/CALGB PET or CT imaging trials, a protocol refreshment (and a Virtual Site Visit, if necessary) is required for participating CALGB 50801.

If a site has neither been credentialed by the ICL nor participated in any Alliance/CALGB PET or CT imaging trials, the Alliance/CALGB ICL will adhere to the ACRIN criteria for PET imaging approval procedures. Consistency in the acquisition protocol both from a time and an acquisition mode is required. In addition, data management must be done in a standardized process. In order for an institution to be approved to participate in this study, they are required to submit the following for technical and quality review by the Alliance Imaging Core Lab at IROC Ohio:

1) Two test patient studies (FOR ALL PET/CT instruments utilized)

Images of two unidentified patients shall consist of three volume or multislice files as follows: a) Whole body CT from PET/CT scanner; b) Whole body (torso) emission with attenuation correction (A/C); and c) Whole body (torso) emission without A/C.4

2) Uniform phantom data with the SUV measurement of the phantom (FOR ALL PET/CT instruments utilized)

Water-fillable uniform phantom: The phantom must be filled with water, and a known amount of F-18 (either as fluoride or as FDG) should be injected into the phantom. The activity injected should be determined by measurement of the syringe before and after the injection in a properly calibrated dose calibrator. The injected activity should be chosen to result in an activity concentration similar to that encountered in clinical FDG imaging (i.e., 1-1.5 mCi of F-18 should be added to the 6,283 mL phantom: 2 mCi for the 9.293 mL phantom). After thoroughly mixing the phantom, the phantom must be scanned with the same protocol used for the patient imaging. The images also must be reconstructed with the same algorithm and filters used for patient imaging. A circular or elliptical region of interest (ROI) covering most of the interior of the phantom must be drawn over all slices, and the average SUV and standard deviation must be measured and reported in the PET/CT Instrument Technical Specifications Form (Appendix IV). The expected SUV for the uniform phantom is 1.0 and the acceptable range is 0.9 to 1.1.

(Alternatively) Ge-68/Ga-68 calibration phantom: This phantom can readily be scanned with the same protocol used for patient imaging. The assay date and activity from the calibration certificate of this phantom must be reported on the PET/CT Instrument Technical Specifications Form (Appendix IV). The images must be reconstructed with the same algorithm and filters used for patient imaging. A circular or elliptical ROI covering most of the interior of the phantom must be drawn over all slices, and the average SUV and standard deviation must be measured and reported in the PET Instrument Technical Specification form. The expected SUV for the uniform phantom is 1.0 and the acceptable range is 0.9 to 1.1.

3) Appendix IV: PET/CT Instrument Technical Specifications Form (FOR ALL PET/CT instruments utilized)

4) Appendix V: Imaging Site Personnel Form

The Imaging Core Lab regularly performs team telephone calls as well as virtual site visits, and serves as consultant to help the local sites resolve questions with regard to adherence to the acquisition and reconstruction protocol.

8.2 PET/CT Imaging Timelines

The following PET/CT and IV contrast CT scans will be collected digitally for archival:

- **Baseline PET/CT scan** must be obtained ≤ 28 days prior to registration. In the case of a patient who already had a baseline FDG-PET/CT scan at an outside facility, the scan must be submitted to the Alliance Imaging Core Lab at IROC Ohio within 30 days of patient registration. Furthermore, these patients will not be included in the quantitative evaluations.
- **Post cycle 2 FDG-PET/CT scan** will be 8-10 days after the Day-15 dose of ABVD during Cycle 2 (i.e. on day 23 or 24 or 25 of cycle 2). The day in which cycle 2 of ABVD is started will determine what day of the cycle 2 (day 23, 24, or 25) the post cycle 2 FDG-PET/CT scan can be completed. Please refer to the below table to determine what day to complete the post cycle 2 FDG-PET/CT scan:

Cycle 2 start day	SU	M	T	W	T	F	S	S	M	T	W	T	F	S	SU	M	T	W	T	F	S	SU	M	T	W	T	F	S	SU	M	T	W	T	F	S
Sunday	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	*1*	*2*	*3*	*4*	*5*	*6*	*7*
Monday	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	*1*	*2*	*3*	*4*	*5*	*6*	
Tuesday	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	*1*	*2*	*3*	*4*	*5*		
Wednesday	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	*1*	*2*	*3*	*4*			
Thursday	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	*1*	*2*	*3*				
Friday	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	*1*	*2*					
Saturday	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	*1*						

The days in which post cycle 2 FDG-PET/CT scans can be completed appear shaded. This table is based on a 72-hour turn around (business days only) from the time of image receipt at the Alliance Imaging Core Lab at IROC Ohio. The second PET scan should be scheduled at the start of Cycle 2 of treatment to ensure appropriate timing of response scans. Mondays or Tuesdays are recommended as therapy initiation days. If FDG-PET/CT is performed on Day 23, images should be submitted to the core lab within 48 hrs. If FDG-PET/CT is performed on Day 24, images should be submitted to the core lab within 24 hrs. If FDG-PET/CT is performed on Day 25, images should be submitted to the core lab within less than 24 hrs.

If FDG-PET/CT is performed on Day 23, images should be electronically submitted to the core lab within 48 hrs.

If FDG-PET/CT is performed on Day 24, images should be electronically submitted to the core lab within 24 hrs.

If FDG-PET/CT is performed on Day 25, images should be electronically submitted to the core lab within less than 24 hrs.

- Post-cycle 6 for patients who are PET negative after 2 cycles of ABVD and are receiving chemotherapy (between 3-8 weeks after last chemotherapy administration);
- After completion of radiotherapy for patients receiving 2 cycles of ABVD and 4 cycles of BEACOPP plus IFRT treatment (between 12-16 weeks after completion of IFRT)

All post-therapy PET/CT and IV contrast CT scans should be performed on the same scanner with the same specifications as those performed at baseline. Ideally, the IV contrast CT scan should be done on the same day following the PET/CT scan. However, if the IV contrast CT is obtained on a separate day, the time difference between PET/CT and IV contrast CT should not exceed 15 days at baseline and should not exceed 5 days after any cycle of therapy. In the case of a patient who has already had a baseline FDG-PET/CT scan at an outside facility, the scan must be submitted to the Alliance Imaging Core Lab at IROC Ohio within 30 days of patient registration. Furthermore, these patients will not be included in the quantitative evaluations.

For reproducible and accurate results, post-therapy PET/CT scans should be acquired using the same FDG uptake time (post-injection interval) as the pre-therapy scan. The difference in waiting period after injection of FDG between the baseline and post-therapy (after cycle 2 of ABVD and following either cycle 6 of ABVD for PET negative patients, or IFRT for PET positive patients) PET/CT scans should not exceed 10 minutes for maintaining consistency and ensuring accuracy for quantitative studies.

8.3 CT Data Acquisition

Contrast enhanced helical/spiral CT scans of the chest, abdomen, and pelvis (neck will be included if baseline CT documents presence of disease in the neck) should be obtained on all patients according to protocol requirements at baseline. The same CT scans should also be performed after 2 cycles and 4 cycles, either coinciding with the date of the PET/CT or within 5 days of the PET/CT.

During further follow-up, contrast enhanced helical/spiral CT scans of the chest, abdomen, pelvis, and neck (if involved at baseline) every 3 months for the first year from the response assessment at completion of therapy, every 6 months for years 2 and 3, and then annually for years 4 and 5 according to the post-treatment follow-up schedule in Section 6.0.

Patient CT scans should follow institutional standards with following minimum criteria:

- **Scan mode:** Multi-detector and/or helical
- **Enhancement:** IV and oral contrast unless contraindicated
- **Section thickness:** maximum 5mm, preferable 2.5mm or less
- **Increment:** continuous or overlapping sections; no gaps
- **Matrix size:** 512 × 512 or better
- **Reconstruction:** Institutional standard

CT scans should be performed in a consistent manner for follow-up from the baseline, with the same section or slice thickness, increment, reconstruction protocol and image matrix size as well as patient positioning.

8.4 PET/CT Data Acquisition

All data acquisitions and reconstructions will be performed on a PET/CT system. A phantom study will be performed to standardize all PET/CT systems prior to the initiation of the protocol.

8.4.1 Prior to FDG Injection and During Uptake Period

Patients must fast for at least four hours before the PET/CT scan. Oral hydration is strongly encouraged prior to and during injection of ^{18}F-FDG (250-500 mL water can be given PO during the uptake period) and during the uptake period after administration of ^{18}F-FDG. IV furosemide (10 mg) may be administered (but is

not mandatory) to increase urinary elimination of the tracer and minimize image artifacts caused by urinary stasis in the abdomen and pelvis. Intravenous fluids containing dextrose or parenteral feeding should be withheld for at least 6 hours prior to the injection of ^{18}F-FDG. **No steroid administration is allowed for at least 7 days prior to FDG-PET imaging.** Active exercise should be discouraged for at least 24 hours prior to the study. Muscle stress, tension, chewing, and movement during the uptake period should be minimized to decrease muscle uptake. Patients should not speak during the injection and uptake period. Interviews with the patient should be withheld until after completion of the imaging study.

The blood glucose level should be checked before ^{18}F-FDG injection. Blood sugar (measured by glucometer) must be less than 200 mg/dL at the time of the FDG-PET/CT study. If the blood glucose level is greater than 200 mg/dL, the FDG-PET/CT imaging should be rescheduled. If the blood glucose level still exceeds 200 mg/dL on the following scheduled day for PET scanning, the patient will not be included in the trial. Insulin administration immediately before the PET/CT study to reduce the glucose levels is not allowed. Patients with diabetes should continue to adhere to their oral agents or insulin routines. These medications should not be administered near the ^{18}F-FDG injection time. In insulin-dependent patients, insulin should be administered at least 5 hours prior to the ^{18}F-FDG injection. Patients with diabetes who are on diabetic medication should take their medication 4-5 hours prior to the test. If blood sugar exceeds 150 mg/dL (but less than 200 mg/dL), a note should be made in on the case report form.

Metallic objects should be removed from the patients whenever possible. Patients should be kept in a warm waiting room prior to ^{18}F-FDG injection to avoid brown adipose tissue uptake. In anxious and claustrophobic patients, administration of oral diazepam (0.06-0.10 mg/kg) is recommended 30-40 minutes prior to the initiation of the imaging study.

Weight (kg), height (cm), blood glucose (mg/dL), and the date and time of chemotherapy and colony stimulating administration (e.g., GCSF, GMCSF) will be recorded prior to the injection of ^{18}F-FDG.

10-20 mCi of ^{18}F-FDG will be administered IV, depending on the manufacturer's recommendation. A 10-20 mL saline flush is recommended in reducing the venous retention of ^{18}F-FDG. The patient must wait for at least 60 minutes prior to the initiation of the PET/CT acquisition for all PET/CT scans (both pre-and post-therapy scans). The wait period should be kept within a maximum of **10 minutes** among patients. The wait period must not exceed 80 minutes at baseline. **It is NOT acceptable to start imaging with wait periods of less than 60 minutes and longer than 80 minutes for both pre- and post-therapy PET/CT scans.** The time difference between baseline and other PET studies (after cycle 2 of ABVD, and following either cycle 6 of ABVD for PET negative patients, or IFRT for PET positive patients) should **not** be > 10 minutes. A time difference of > 15 minutes between PET/CT studies is **NOT** acceptable.

The imaging will start after voiding the bladder. 150-200 mL of water must be given to the patient immediately prior to the study acquisition before they are positioned on the table to distend stomach and avoid physiologic stomach uptake.

8.4.2 PET/CT Image Acquisition

Patients will be positioned on the table in a headfirst, supine position with arms elevated above the head to reduce beam-hardening artifacts at the level of the liver. A separate head and neck imaging will be pursued for those whose primary disease site is in the neck with the arms positioned along the side. The use of oral contrast is at the discretion of each facility. However, IV-contrast dedicated CT acquisition should follow PET imaging with non-contrast low dose CT to avoid variations in FDG uptake in the blood pool and the tumor that is caused by the IV contrast agent. The low dose CT associated with PET should be acquired using a current of not less than 80 mA/second.

It is critical that all post-therapy PET/CT scans be performed in an identical way to the baseline scan with the same scanner, same scanning direction (skull to thighs or thighs to skull) and consistent arm positioning.

For PET imaging, six to seven contiguous volumes will be chosen, depending on the patient's height, to ensure data acquisition of the entire region of interest (ROI), the level of the skull base to the 1/3 proximal femurs. The time/bed position should be in accordance with the manufacturer's recommendations for optimal imaging. Adjacent fields of view should share overlapping slices.

8.4.3 PET/CT Image Processing

Follow the manufacturer's recommendation for image reconstruction. The emission data will be corrected for scatter, random coincidence events, and system dead-time using provided software. An iterative reconstruction (ordered subsets expectation maximization) and CT-based attenuation correction will be used for the PET images. Reconstructions should be archived both with and without attenuation correction to resolve issues arising from potential artifacts generated by the CT-based attenuation correction procedure.

8.5 Evaluation of PET/CT Data

All images will be read centrally by the Alliance Imaging Core Laboratory at IROC Ohio.

To ensure the highest standards and consistency between different centers, all FDG-PET scans (baseline, interim, and end of treatment PET scans) must be submitted to the Alliance Imaging Core Lab at IROC Ohio for centralized review (See Section 8.9). Response determinations and treatment decisions (e.g. continuation of ABVD or switch to BEACOPP) must be 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 will be 8-10 days after the Day-15 dose of ABVD during Cycle 2 (i.e. on day 23 or 24 or 25 of cycle 2, see Section 8.2 for acceptable FDG-PET/CT scan completion days). The second PET scan should be scheduled at the start of Cycle 2 of treatment to ensure appropriate timing of response scans.

Centralized review will be performed by a member of a team of PET/CT readers. There will be an adjudicator from the same pool of reviewers in the case of disagreement. There will be one reviewer, Dr. Nathan Hall, who will provide back-up PET/CT reviewer services within the Alliance Imaging Core Lab at IROC Ohio. The Alliance Imaging Core Lab at IROC Ohio will transmit the scans to the expert reviewers for response determination and then will transmit the results to the Alliance Statistics and Data Center and to the sites primary contact with 72 hours of image receipt (not including weekends).

The central PET/CT expert review will only focus on the assessment of Hodgkin lymphoma disease sites. This central expert review will NOT provide a comprehensive assessment of the entire PET/CT study and will thus NOT record incidental findings and abnormalities unrelated to Hodgkin lymphoma. Centralized PET/CT is done for the purpose of this trial; it does NOT relieve local PET/CT readers of their responsibility to issue a comprehensive PET/CT report.

Cycle 3 of chemotherapy must not be administered until the results of the second PET scan are available. Determination of FDG-PET positivity or negativity will be performed using a 5 point scoring system on guidelines established by an international PET harmonization conference convened in London in May 2007 (See Appendix I). According to these guidelines, scans will be judged to be positive if lesions are more hypermetabolic than the liver by visual, qualitative inspection. Borderline metabolism in a lesion will be considered negative in concordance with the policies of Gallamini and Hutchings whose studies established the value of early interim FDG-PET imaging.[11-13, 30]

8.6 Primary Objective/Endpoint: Definition of Response by Metabolic Criteria

The primary endpoint is progression free survival (PFS) at 36 months from enrollment for patients with bulky stage I and II Hodgkin lymphoma. The total number of cycles of chemotherapy (± IFRT) will be determined by metabolic response as visually assessed by PET/CT imaging after 2 cycles using criteria provided in Appendix I.

8.6.1 Negative PET Scan (Metabolic Responders)

All PET/CT interpretations will be performed on both axial and coronal slices. Mainly, findings on axial slices should be confirmed by findings on coronal slices, as comparison with the liver is usually easier and more accurate on coronal slices.

Upon qualitative evaluation, tumor FDG uptake that is less than or equal to the liver in target or non-target tumors, regardless of their location, and absence of new lesions that are deemed to be tumor and absence of non-target tumors will be considered negative for the presence of residual lymphoma (Appendix I).

8.6.2 Positive PET Scan

Upon qualitative evaluation, diffuse or focal uptake exceeding that seen in the liver in target or non-target tumors, regardless of their location, will be considered positive for residual tumor.

8.7 Secondary Objectives/Endpoints

8.7.1 Semiquantitative Analysis: In patients with multiple tumor sites, the six sites with the highest uptake will be designated as the target sites. For these lesions, SUV measurements will be determined at baseline, after cycle 2, at completion of chemotherapy, and after IFRT in respective patient groups, as outlined below.

At baseline, a 3D volume of interest (VOI) will be taken over the tumor on axial, sagittal, and coronal multi-planar reformatting (MPR) views that visually show the most prominent uptake. Maximum SUV body weight (SUVbw), SUVpeak and SUV lean body mass (SUVlbm) will be obtained over the lesion.

A similar VOI will be obtained in the:

1) adjacent background that does not correspond to physiologically or pathologically active sites away from the FDG avid sites;

2) Mediastinal blood pool (MBP) taken in the mid-aortic level or within 2 slices of the aortic arch;

3) approximately mid-liver region or in sections that are within 3 slices of the porta hepatis regions.

In order to take metabolic variability into consideration, two SUV measurements on two different axial slices will be obtained for items 1-3 above and the average SUVs will be used (mean SUVbw and mean SUVlbm of two axial slices).

After cycle 2 of ABVD and following either cycle 6 of ABVD (for PET negative patients) or IFRT (for PET positive patients), in patients with metabolically active residual tumors, as well as in those with metabolically nonactive CT masses, the same steps as described above will be repeated.

8.7.2 Using receiver operator curves (ROC), most optimal cutoff for absolute decrease in maximum SUVbw, SUVpeak and SUVlbm, absolute uptake in the tumor/s and relative uptake in tumor/s versus various reference anatomic sites (liver, mediastinal blood pool, and background), as well as various cutoffs for post-therapy maximum SUVbw, SUVpeak and SUVlbm, will be determined and compared after cycle 2 of ABVD and following either cycle 6 of ABVD (for PET negative patients) or IFRT (for PET positive patients).

8.7.3 In patients with multiple tumor sites, the six sites correlating with the PET target lesions will be designated as the target sites. In each lymph node region the lesions with the highest uptake will be chosen. If there is any lesion that demonstrates uptake after therapy other than the designated target lesions, they will be non-target lesions and will be evaluated in the same fashion as target lesions. For these lesions, volumetric vs. 2 dimensional (2-D) measurement changes between baseline and after cycle 2 of ABVD and following either cycle 6 of ABVD or IFRT, will be determined from dedicated CT scans. Using receiver operator curves (ROC), the most optimal cutoff for absolute decrease and percent decrease will be determined. A combinatorial analysis will be performed incorporating the changes from PET data and dedicated CT data to determine if this approach increases the predictive value of both tests combined compared to each test alone.

8.7.4. Qualitative and semi quantitative FDG-PET findings/changes, 2-D and volumetric CT changes, and combinatorial analyses (PET+dedicated CT data) will be compared with molecular parameters, and conventional parameters, including IPS in the prediction of response and PFS.

8.8 Post-Therapy Follow-Up of Tumors

At any point after therapy, the decision for biopsy of any lesion is at the discretion of the treating physician. After completion of treatment, for those patients who achieve a CR or PR who are PET negative, CT scans will be obtained every 3 months for the first year, then every 6 months for years 2 and 3, and annually years 4 and 5 according to the post-treatment follow-up schedule in Section 6.0.

8.9 PET and CT Data Submission

The complete PET and CT studies must be electronically submitted to the Alliance Imaging Core Lab at IROC Ohio in digital DICOM format, any other formats such as Bitmap, JPG, hardcopy files or scanned films are unacceptable. De-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the CALGB patient ID number and CALGB protocol number separately.

Imaging data shall be submitted to the Imaging Core Lab within no more than 3 business days once the image acquisition is completed at site. For Post cycle 2 FDG-PET/CT scans, images must be submitted to the Core lab within or less than 24-48 hrs (see Section 8.2 for details).

Images may be electronically transferred by either Web-based (a PC with internet access be needed) or FTP-based (a PC with both internet access and any FTP software installed be needed) transfer approaches. The standard and secure online access information will be provided separately through the specific trial e-mail [redacted] per the request by participating sites before their first data submission.

Once the electronic imaging data submission is done, send an e-mail to the Imaging Core Lab at [redacted] to inform them that the study has been completely uploaded from the institution. Please include the basic information of submitted data sets as follows:

1) CALGB 50801 patient identifier
2) Scan time point
3) Date of scans
4) Date of first day of protocol treatment
5) Institution name

Institutions must send CALGB form C-1960 (50801 PET and CT Measurement Form) and CALGB form C-1821 (50801 FDG-PET Adjunctive Data Sheet) to the Alliance Statistics and Data Center with a copy to the Imaging Core Lab at IROC Ohio.

[redacted]

Questions concerning the FDG imaging procedure, interpretation of FDG-PET/CT scans and the definition of PET positivity should be directed to:

[redacted]

9.0 Dose Modifications And Management of Toxicity

9.1 Dose Modifications for ABVD

9.1.1 Neutropenia

There are no dose delays or reductions for ABVD for neutropenia.

For febrile neutropenia on the day of treatment, delay ABVD until resolution then resume ABVD at the previous doses. Prophylaxis with antibacterial therapy is recommended for the subsequent cycle (e.g. levofloxacin [or equivalent] 500 mg po daily, days 4-13 and days 18-27). Continued anti-bacterial antibiotic use thereafter is at the discretion of the treating physician. In addition, abbreviated G-CSF may be considered (e.g. days 5-10 and/or days 19-23 of each cycle).

For grade 3 or 4 infection resulting from neutropenia, delay ABVD until infection improves to $\leq$ grade 2, then resume ABVD with a decrease in the doses of

vinblastine and doxorubicin to 75% of the last dose received for the next cycle (in addition to above antibiotic and G-CSF supportive care measures). Re-escalation is at the discretion of the treating physician.

9.1.2 Thrombocytopenia

For platelets ≥ 75,000 – 100,000 on the day of treatment (or within 48 hours), continue ABVD with a decrease in the doses of vinblastine and doxorubicin to 75% of the last dose received for the next cycle. Re-escalation is at the discretion of the treating physician. For platelets < 75,000 on the day of treatment (or within 48 hours), delay treatment until platelets ≥ 75,000, then resume ABVD with a decrease in the doses of vinblastine and doxorubicin to 75% of the last dose received for the next cycle.

9.1.3 Hepatic Dysfunction

All patients with bilirubin ≤ 2 x the upper limit of normal (ULN) will receive a full initial dose of doxorubicin and vinblastine. If the bilirubin increases to > 2 x ULN and is ≤ 5 x ULN, the doxorubicin and vinblastine doses should be reduced by 50% of the last dose. Full doses should be administered if the bilirubin recovers to ≤ 2 x ULN. If the bilirubin exceeds 5 x ULN, doxorubicin and vinblastine should be omitted for that cycle. If the bilirubin has not recovered to ≤ 2 x ULN by the time the next cycle is due, then remove the patient from protocol treatment. In cases of biliary obstruction by a tumor mass, a biliary drainage stent should be placed 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%

9.1.4 Cardiotoxicity

For persistent arrhythmia (including sinus tachycardia with severe symptoms and with no demonstrable cause); congestive heart failure; or a decrease in ejection fraction by ≥ 15% (absolute percentage points) from baseline or to less than 45%, discontinue protocol therapy.

9.1.5 Skin Toxicity

Vinblastine and doxorubicin are vesicants; stop infusion immediately if extravasation is suspected and administer the drug at another site. Institutional standard measures for treatment of extravasation should be employed.

9.1.6 Neurotoxicity

For grade 3 sensory neuropathy, or for severe constipation with ileus, reduce dose of vinblastine by 50% for all subsequent doses.

For grade 4 sensory neuropathy, vinblastine will be omitted from all future doses.

9.1.7 Pulmonary Toxicity

Bleomycin induced pneumonitis may be difficult to diagnose clinically. A high resolution CT scan of the chest and pulmonary function tests should be performed at the slightest suspicion. As there are no reproducible clinical or histologic

findings for bleomycin-induced pneumonitis, the diagnosis must be made on clinical, radiologic, and/or histologic findings after excluding other etiologies. If these studies suggest bleomycin toxicity, bleomycin should be discontinued. Later resumption should only be considered if the suspicion for bleomycin-induced toxicity has proved unfounded.

9.2 Dose Modifications for escalated BEACOPP

9.2.1 A cycle of BEACOPP should not begin until leukocytes > 2,500 and platelets > 80,000. If leukocytes < 2,500 or platelets < 80,000 on day 1 of a cycle of BEACOPP, delay treatment until leukocytes ≥ 2,500 and platelets ≥ 80,000. CBC should be rechecked after 3, 7, 10 and 14 days. The first cycle of BEACOPP may begin two weeks after cycle 2 of ABVD in patients with a positive interim PET scan, regardless of leukocyte count.

9.2.2 Dose reductions for escalated BEACOPP follow a defined de-escalation scheme based on the occurrence of toxic events in the previous cycle. There are no dose re-escalations.

9.2.3 The following are considered dose reduction events on BEACOPP:

Decreased while blood cells/Leukopenia: grade 4 (leukocytes < 1000) for > 4 days.

Platelet count decrease/Thrombocytopenia: grade 4 (platelets < 25,000) on one or more days.

Infection: grade 4.

Other toxicity: grade 4 (e.g. mucositis);(see below for dose reductions for bilirubin and pulmondary).

Postponement of treatment for more than 2 weeks due to inadequate recovery of blood values.

9.2.4 Should one or more dose-reduction events occur in a given cycle, the dose in all following cycles will be reduced by one dose level. If any toxic event occurs in 2 successive cycles, the following cycle is administered at standard BEACOPP doses. No reduction is made for treatment postponement of up to 2 weeks.

9.2.5 All patients with bilirubin ≤ 2 x the upper limit of normal (ULN) will receive a full initial dose of doxorubicin and vincristine. If the bilirubin increases to > 2 x ULN and is ≤ 5 x ULN, the doxorubicin and vincristine doses should be reduced by 50% of the last dose. If the bilirubin exceeds 5 x ULN, doxorubicin and vincristine should be omitted for that cycle. If the bilirubin has not recovered to ≤ 2 x ULN by the time the next cycle is due, then remove the patient from protocol treatment. In cases of biliary obstruction by a tumor mass, a biliary drainage stent should be placed prior to chemotherapy.

Bilirubin	Doxorubicin dose	Vincristine 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%

9.2.6 Pulmonary Toxicity

Bleomycin induced pneumonitis may be difficult to diagnose clinically. A high resolution CT scan of the chest and pulmonary function tests should be performed at the slightest suspicion. As there are no reproducible clinical or histologic findings for bleomycin-induced pneumonitis, the diagnosis must be made on clinical, radiologic, and/or histologic findings after excluding other etiologies. If these studies suggest bleomycin toxicity, bleomycin should be discontinued. Later resumption should only be considered if the suspicion for bleomycin-induced toxicity has proved unfounded

9.2.7 Intolerance not qualifying as a dose reduction event

In case of drug specific intolerance (e.g. vincristine neuropathy, procarbazine allergy), single drugs may be dropped from the regimen without substitution. The reason for a deviation should always be recorded on the corresponding treatment forms.

9.2.8 Dose Levels of Escalated BEACOPP

Treatment always begins with Dose Level 0. Doses of bleomycin, vincristine, procarbazine and prednisone are not reduced.

Dose Level 0	**Dose**	**Route**	**Schedule**
Cyclophosphamide	1250 mg/m^2	IV	Day 1
Doxorubicin	35 mg/m^2	IV	Day 1
Etoposide	200 mg/m^2	IV	Days 1-3

Dose Level -1	**Dose**	**Route**	**Schedule**
Cyclophosphamide	1150 mg/m^2	IV	Day 1
Doxorubicin	35 mg/m^2	IV	Day 1
Etoposide	175mg/m^2	IV	Days 1-3

Dose Level -2	**Dose**	**Route**	**Schedule**
Cyclophosphamide	950 mg/m^2	IV	Day 1
Doxorubicin	35 mg/m^2	IV	Day 1
Etoposide	150mg/m^2	IV	Days 1-3

Dose Level -3	**Dose**	**Route**	**Schedule**
Cyclophosphamide	800 mg/m^2	IV	Day 1
Doxorubicin	35 mg/m^2	IV	Day 1
Etoposide	125 mg/m^2	IV	Days 1-3

Standard BEACOPP	**Dose**	**Route**	**Schedule**
Cyclophosphamide	650 mg/m^2	IV	Day 1
Doxorubicin	25 mg/m^2	IV	Day 1
Etoposide	100 mg/m^2	IV	Days 1-3

9.2.9 Treatment Postponement and Dose Modifications for standard BEACOPP

A cycle of BEACOPP should not begin until leukocytes > 2,500 and platelets > 80,000. If leukocytes < 2,500 or platelets < 80,000 on day 1 of a cycle of BEACOPP, delay treatment until leukocytes ≥ 2,500 and platelets ≥ 80,000. CBC should be rechecked after 3, 7, 10 and 14 days. The first cycle of BEACOPP may begin two weeks after cycle 2 of ABVD in patients with a positive interim PET scan, regardless of leukocyte count.

Treatment Delay	Dose Modification
< 1 week*	No dose reduction
1-2 weeks	25% dose reduction for cyclophosphamide, doxorubicin , procarbazine and etoposide
> 2 weeks	50% dose reduction for cyclophosphamide, doxorubicin , procarbazine and etoposide

* No dose reductions will be performed if delays of leukocyte or platelet recovery are less than one week. Otherwise dose reductions will follow the schema described by the German Hodgkin Disease Study Group.[31]

9.3 Dose Modification for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. **Therefore, all dosing is to be determined solely by (1) the patient's BSA as calculated from actual weight or (2) actual weight without any modification (with the exception of the cap on vincristine doses in BEACOPP as noted in Section 7.1).** This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. **Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation.** Physicians who are uncomfortable with administering chemotherapy dose based on actual body weight should not enroll obese patients on CALGB protocols.

10.0 Correlative Science Companion Studies

There is one correlative science companion comprised of two study components that must be presented to all patients, though patients may opt not to participate. The first component will be to evaluate serum and plasma markers and to correlate with clinical outcomes. The second component will be to evaluate immunohistochemical markers for prognosis. Both components will comprise the companion study **CALGB 150903**.

10.1 Serum Markers

10.1.1 Background

Several serum markers have been suggested to be of predictive value with regard to progression-free and overall survival. Among the most promising are IL10, soluble CD30 (sCD30), CCL17, and CCL22 [32]. Elevated sCD30 has been associated with poor event-free survival [33-35] and elevated IL10 has been associated with poor failure-free survival in multivariable analyses [36, 37]. In addition, chemokines CCL17 (TARC) and CCL22 (MDC) are elevated in approximately 75% of patients with Hodgkin lymphoma and have been shown to fall with successful treatment [38-40]. Furthermore, elevated TARC at diagnosis has been shown to correlate with poor overall survival [40]. These have not been well studied prospectively and their correlation with PET scan results and ability to predict relapse after remission induction are unknown. Therefore, we propose

to assess these promising biologic serum markers by ELISA to predict outcome at diagnosis and to follow serial levels at the time of imaging studies in order to assess whether these markers can predict relapse.

10.1.2 Objectives

10.1.2.1 To assess whether elevated baseline serum soluble CD30 (sCD30), IL10, CCL17, and CCL22 correlate with clinical response and PFS.

10.1.2.2 To assess whether lack of normalization or recurrent elevation of serial serum sCD30, IL10, CCL17, or CCL22 correlate with relapse/progression or PET scan results.

10.1.3 Methods

Sample Collection and Laboratory Methods: In patients who consent, 10 mL peripheral venous blood for plasma and serum will be collected at baseline (prior to initiation of therapy), after cycle 2 of ABVD and following either cycle 6 of ABVD (for PET negative patients) or IFRT (for PET positive patients), and at 3, 6, 9, 12, 18, 24, 30 and 36 months during post-treatment follow-up. ELISA assays will be performed according to manufacture protocol at Cleveland Clinic Reference Laboratory using commercially available ELISA kits (R & D systems). Results will be reported to the Alliance Statistics and Data Center in picograms/mL via a coded excel spreadsheet format. Normal ranges have been established by the manufacturer.

10.2 Plasma Markers

10.2.1 Background

One of the striking histologic features of cHL is the dominant inflammatory background present in most cases. We are now beginning to recognize that these cells provide a complex network of cytokines and chemokines that provide a permissive microenvironment. The T-cell heavy infiltrate of cHL is heavily skewed towards a Th2 and regulatory T-cell (Treg) composition [41, 42]. HRS cells secrete numerous cytokines and chemokines such as IL-5, IL-6, IL-8, IL-9, IL-10, IL-13, TGFß, APRIL, BAFF, CCL28, IP10/CXCL10, RANTES/CCL5), MCP4 (CCL13), TARC/CCL17, and MDC/CCL22 [41-45]. While some may act as autocrine growth factors for HRS cells themselves (IL-13, APRIL, BAFF) [43, 46], others appear to attract and shape the immune microenvironment. For example, IL-5 and CCL28 serve to attract eosinophils, while IL-6 and CCL28 attract plasma cells [41, 42, 44, 45]. IL-10 promotes a Th2 response and an immunosuppressed microenvironment [45]. TARC and MDC production by HRS cells also promote a Th2 environment [42]. Likewise, galectin 1 secretion promotes an immune privileged microenvironment by promoting a Th2 response and expansion of Tregs [47]. These soluble factors have been examined as prognostic factors in HL. Several of these factors have been shown to be of potential prognostic significance in HL. In particular soluble CD30 (sCD30) and IL10 have been shown in several studies to be of prognostic significance at baseline (Appendix III). TARC and MDC, highly expressed in HRS cells, are also elevated in serum of HL patients [39, 48, 49]. Thus, these markers may be indicative of tumor burden and, in the case of TARC, may also be of prognostic significance. Importantly, these markers, characteristically produced by HRS cells, may also be indicative of relapse. We propose studying plasma levels of these

IL10, sCD30, TARC, and MDC in patients at baseline, at time of PET scans and selected time points during follow-up in order to determine whether these markers have prognostic value in the cooperative groups setting.

10.2.2 Objectives

10.2.2.1 To assess whether elevated baseline plasma soluble CD30 (sCD30), IL10, CCL17, and CCL22 correlate with clinical response and EFS.

10.2.2.2 To assess whether lack of normalization or recurrent elevated serial plasma sCD30, IL10, CCL17, or CCL22 correlate with relapse/progression.

10.2.2.3 To assess whether elevated plasma biomarker levels correlate with abnormal PET scan results.

10.2.3 Methods

Sample Collection and Laboratory Methods: In patients who consent, 10 mL peripheral venous blood for plasma will be collected at baseline (prior to initiation of therapy), after cycle 2 of ABVD, and following either cycle 6 (for PET negative patients) or IFRT (for PET positive patients), and at 3, 6, 9, 12, 18, 24, 30 and 36 months during post-treatment follow-up. ELISA assays will be performed according to manufacture protocol at Cleveland Clinic Reference Laboratory using commercially available ELISA kits (TARC, MDC, IL10 from R&D systems, Minneapolis, MN and sCD30 Alexis Biochemicals, Plymouth Meeting, PA). Samples will be run in duplicate and correlated with clinical outcomes.

10.3 Immunohistochemical Markers

10.3.1 Background

Recent data suggest that there are biologic predictors of outcome in Hodgkin lymphoma. Predictors of poor outcome in single institution series in heterogeneously treated patients include Bcl-2 and MAL expression in the Hodgkin lymphoma cells [50-53]. In addition, FOXP3+ cells (as a marker of regulatory T-cells within the non-neoplastic lymphocytes) have been reported to be a marker of favorable outcome [54]. MAL and FOXP3 have not been validated in other series and none of these markers have been tested specifically in patients with early stage HL or in patients treated with this regimen. In addition to FOXP3, markers of effector T-cells, such as granzyme B (GzB; activated cytotoxic T-cells) [55, 56] and mast cells (tryptase/CD117) [57] will be assessed as a complement to the suppressive regulatory T-cells. Both GzB+ T-cells and mast cells have been associated with poor outcome in HL [55-58]. CD68+ macrophages have also emerged as an important microenvironmental factor with cases showing less than 5% CD68+ cells having a favorable prognosis compared to those with $\geq$ 5%.

10.3.2 Objective

To determine whether these tissue biomarkers correlate with clinical outcome in patients with bulky stage I and II Hodgkin lymphoma treated with this regimen.

10.3.3 Methods

Sample Collection and Laboratory Methods: In patients who consent, TMAs will be constructed from formalin-fixed, paraffin-embedded tissue collected prior to initiation of therapy. Monoclonal antibodies to GzB (Ventana), FOXP3 (Abcam,

Cambridge, UK), CD117 (Ventana), CD68 (KP1, DAKO), and MAL (Dr. M. Alonso, CNIO) will be used to perform automated immunohistochemistry at the Alliance Biorepository at Ohio State according to standard protocols. Numbers of GzB, FOXP3, and CD117 will be scored as number of positive cells/5 hpf. MAL will be considered positive if > 20% of HRS cells express this marker [51]. Bcl-2 will be considered positive if > 10% of HRS cells show strong Bcl-2 expression compared to an internal T-cell control (Appendix II). CD68 will be assessed by manual counting as < 5%, 5-25%, 26-50%, and > 50% [59].

11.0 DRUG FORMULATION, AVAILABILITY, AND PREPARATION

11.1 Qualified Personnel

Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.

11.2 Discarding Unused Agents

Discard unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents (i.e., Sterile Water for Injection USP or 0.9% Sodium Chloride for Injection USP) within eight hours of vial entry to minimize the risk of bacterial contamination.

11.3 Calculated Dose Range

The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

11.4 Doxorubicin HCL

Please refer to the FDA-approved package insert for doxorubicin for product information, extensive preparation instructions, and a comprehensive list of adverse events.

AVAILABILITY

Doxorubicin is commercially available as a lyophilized powder for reconstitution in 10, 20, 50, and 150 mg vials. Also available are 2 mg/mL solution for injection in 10, 20, 50, 75, and 200 mg vials of doxorubicin in solution.

STORAGE & STABILITY

Intact vials of doxorubicin solution should be stored in the refrigerator. Intact vials of powder for reconstitution should be stored at room temperature. Reconstituted solutions are stable for 7 days at room temperature and 15 days under refrigeration when protected from light. Commercially available solutions labeled as such are intended to be multidose vials.

PREPARATION

Reconstitute the vials with 5, 10, 25, or 50 mL, respectively, of sodium chloride for injection, USP, resulting in a concentration of 2 mg/mL.

ADMINISTRATION

Doxorubicin is administered intravenously over 3-5 minutes. Avoid extravasation, as severe local tissue necrosis may result.

TOXICITIES

Hematologic: leukopenia (dose-limiting), thrombocytopenia, anemia. Nadir in 10-14 days with recovery usually in 21 days.

Dermatologic: alopecia (usually complete; reversible) radiation recall reactions; increased sensitivity to sunlight.

Gastrointestinal: nausea and vomiting (doxorubicin is generally considered moderately to highly emetogenic), anorexia, diarrhea, mucositis (stomatitis, esophagitis).

Cardiovascular: cardiomyopathy may occur and is related to total cumulative lifetime dose. The risk for cardiomyopathy increases with total doses > 450 mg/m^2. ECG changes and less often, arrhythmias, are seen. Rarely, sudden death has occurred.

Other: red discoloration of urine for 24-48 hours after drug administration. Doxorubicin is a vesicant and can cause tissue necrosis if extravasated.

11.5 Bleomycin

Please refer to the FDA-approved package insert for bleomycin for product information, extensive preparation instructions, and a comprehensive list of adverse events.

AVAILABILITY

Bleomycin is commercially available in vials containing 15 or 30 units of lyophilized powder for reconstitution. (1 unit = 1 mg)

STORAGE & STABILITY

Intact vials should be stored in the refrigerator. Reconstituted solutions prepared with bacteriostatic diluents are stable for 28 days at room temperature or under refrigeration.

PREPARATION

Reconstitute the vial with 1-5 mL of water for injection or 0.9% sodium chloride with bacteriostat resulting in a concentration of 3-15 units/ml (15 unit vial) or 6-30 units/ml (30 unit vial).

ADMINISTRATION

Bleomycin is administered IV.

TOXICITIES

Dermatologic: skin reactions are common (50%) and may include, hyperpigmentation, edema, erythema, thickening of nail beds, and alopecia. Bleomycin is not a vesicant and has been administered by SQ or IM injection.

Pulmonary: interstitial pneumonitis, pulmonary fibrosis. Pneumonitis is related to total cumulative dose (e.g., it is more likely to occur with cumulative doses > 400 units). However, the occurrence in individual patients is somewhat unpredictable. Signs and symptoms include dyspnea, cough, fine rales, radiographic findings resembling pneumonia, and altered pulmonary function status.

Hypersensitivity: anaphylactoid reactions are reported to occur in about 1% of lymphoma patients. The reaction is characterized by severe hyperpyrexia, with subsequent cardiovascular collapse.

Other: Fever with or without chills is often seen (up to 50% of patients) soon after administration and may last for 4-12 hours. Pre treatment with acetaminophen may decrease the likelihood or severity of fever

11.6 Vinblastine Sulfate

Please refer to the FDA-approved package insert for vinblastine for product information, preparation instructions, and a comprehensive list of adverse events.

AVAILABILITY

Vinblastine is commercially available in vials of 10 mg as a powder for reconstitution.

STORAGE & STABILITY

Store intact vials under refrigeration. Once reconstituted with bacteriostatic diluent, solutions are stable for 21 days at room temperature or under refrigeration.

PREPARATION

Reconstitute with 10 mL bacteriostatic H_2O or 0.9% NaCl, or 0.9% NaCl or sterile H_20 for injection, to yield a concentration of 1 mg/mL. Bacteriostatic diluent should be used when vials will be stored as described in "Storage & Stability."

ADMINISTRATION

IV over 3-5 minutes.

TOXICITIES

Hematologic: myelosuppression is among the most common side effects, and may be dose limiting.

Gastrointestinal: nausea and vomiting may occur, but vinblastine is generally considered mildly emetogenic when used as a single agent.

Neurotoxicity: vinblastine is associated with qualitatively the same neurotoxicity as is seen with vincristine (e.g., peripheral neuropathy, autonomic dysfunction, even ileus), but quantitatively, vinblastine is much less neurotoxic than vincristine. Higher doses are more likely to cause neurotoxicity.

Vesicant: vinblastine is a vesicant and may cause tissue damage upon extravasation.

Other: alopecia; vinblastine has been associated with Raynaud's phenomenon.

11.7 Dacarbazine (DTIC)

Please refer to the FDA-approved package insert for dacarbazine for product information, extensive preparation instructions, and a comprehensive list of adverse events.

AVAILABILITY

Dacarbazine is commercially available in vials containing 100 mg, 200 mg, or 500 mg of lyophilized powder for reconstitution.

STORAGE & STABILITY

Intact vials should be under refrigeration and protected from light. They are reported to be stable for 4 weeks at room temperature. Once reconstituted, vials are stable for 4 hours at room temperature or 96 hours under refrigeration. Further diluted solutions for infusions are stable for 24 hours at room temperature and protected from light.

Note: A change in color of solution from pale yellow to pink is indicative of decomposition of the drug.

PREPARATION

The 100 mg, 200 mg, and 500 mg vials should be reconstituted with 9.9 mL, 19.7 mL, and 49.5 mL of sterile water, respectively, resulting in a concentration of 10 mg/mL. More concentrated solutions (e.g. 20 mg/mL) may also be used. The desired volume should then be withdrawn and injected into 150-1000 mL D5W or 0.9% NaCL, for IV infusion.

ADMINISTRATION

Dacarbazine should be administered by IV infusion over 30 minutes or longer. Dacarbazine administration may be associated with pain/irritation. Painful administration is minimized with the use of slow and dilute infusions.

TOXICITIES

Hematologic: myelosuppression; nadir of WBC and platelet depression occurs approximately 7-10 days after treatment.

Dermatologic: alopecia, photosensitivity. Dacarbazine is considered an irritant. Extravasation may result in pain, but is not associated with tissue damage.

Gastrointestinal: nausea and vomiting. Dacarbazine is considered highly emetogenic.

Other: flu-like syndrome (with fever, malaise, myalgia) may occur within 7 days of treatment.

11.8 Etoposide

Please refer to the FDA-approved package insert for etoposide for product information, extensive preparation instructions, and a comprehensive list of adverse events.

AVAILABILITY

Etoposide is commercially available in 5 mL, 25 mL, and 50 mL vials containing 20 mg/mL. Solutions contain polysorbate 80.

STORAGE & STABILITY

Unopened vials should be stored at room temperature and protected from light. Solutions diluted to a concentration of 0.2 and 0.4 mg/mL (in D5W or NS) are stable for 96 and 48 hours, respectively, at room temperature under normal light.

PREPARATION

The dose of etoposide should be further diluted with D5W or normal saline for injection to a final concentration of less than or equal to 0.4 mg/mL.

ADMINISTRATION

Etoposide is delivered by IV infusion over at least 45-60 minutes; administration that is too rapid may be associated with hypotension.

TOXICITIES

Hematologic: myelosuppression.

Gastrointestinal: anorexia, nausea and vomiting (etoposide is considered mildly emetogenic).

Dermatologic: alopecia.

Other: hypersensitivity reactions including chills, fever, tachycardia, bronchospasm, dyspnea and hypotension are reported rarely.

11.9 Cyclophosphamide

Please refer to the FDA-approved package insert for cyclophosphamide for product information, extensive preparation instructions, and a comprehensive list of adverse events.

AVAILABILITY

Commercially available as a powder for reconstitution in vials containing 100, 200, 500, 1000, and 2000 mg.

Storage & Stability

Intact vials should be stored at room temperature. Reconstituted solutions are stable for 24 hours at room temperature and 6 days in a refrigerator. Further diluted solutions are also stable for 24 hours at room temperature and 6 days under refrigeration.

PREPARATION

Reconstitute 100 mg, 200 mg, 500 mg, 1 g and 2 g vials with 5, 10, 25, 50, or 100 mL of SWI or NS to give a final concentration of 20 mg/mL. Vigorous shaking may be necessary for non-lyophylized preparations. Bacteriostatic water for injection (paraben preparations only) may be used; benzyl alcohol derivatives may NOT be used. Solutions may be further diluted in D5W or NS for IV infusion.

ADMINISTRATION

Cyclophosphamide may be administered as an IV bolus or IV infusion.

TOXICITY

Hematologic: myelosuppression; expected nadir for neutropenia is approximately 10 days.

Gastrointestinal: nausea and vomiting; the dose of cyclophosphamide in escalated dose BEACOPP is considered highly emetogenic. The cyclophosphamide dose in standard dose BEACOPP is considered moderately emetogenic (when administered as a single agent).

Dermatologic: alopecia.

Genitourinary: hemorrhagic cystitis is thought to be due to the presence of the cyclophosphamide metabolite, acrolein, in the bladder. Hydration and frequent voiding help to minimize the occurrence of hemorrhagic cystitis. In addition, in this study, mesna may be administered with cyclophosphamide. SIADH is seen less frequently than hemorrhagic cystitis. SIADH generally resolves within 24 hours with fluid restriction.

Other: heart failure and cardiac necrosis occur rarely after high dose cyclophosphamide. (doses higher than those used in this study)

11.10 Vincristine

Please refer to the FDA-approved package insert for vincristine for product information, extensive preparation instructions, and a comprehensive list of adverse events.

AVAILABILITY

Vincristine is commercially available as a solution 1 and 2 mg vials at a concentration of 1 mg/mL.

STORAGE & STABILITY

Intact vials should be stored under refrigeration. They are reported to be stable for up to 30 days at room temperature. Most vials are intended to be multi-dose vials. Solutions further diluted for IV infusion in D5W or NS are stable for 7 days or under refrigeration or 2 days at room temperature.

ADMINISTRATION

Vincristine is administered intravenously. Numerous reports of fatalities following inadvertent intrathecal administration of vincristine underlie the recommendation for administration as a short IV infusion rather than a bolus IV injection.

TOXICITY

The dose limiting toxicity of vincristine is neurotoxicity. Both sensory and motor neuropathies are common. Other manifestations of neurotoxicity include cranial nerve palsies, constipation and ileus, and orthostatic hypotension. Alopecia is also common. Fatalities have been reported following inadvertent intrathecal administration of vincristine

and care should be taken to avoid this error. Vincristine is considered a vesicant and ulceration can occur upon extravasation.

11.11 Procarbazine

Please refer to the FDA-approved package insert for procarbazine for product information, extensive preparation instructions, and a comprehensive list of adverse events.

AVAILABILITY

Procarbazine is commercially available as 50 mg capsules for oral administration.

STORAGE & STABILITY

Procarbazine capsules should be stored at room temperature and stability is as noted by the manufacturer(s).

ADMINISTRATION

Procarbazine should be administered orally, once daily. Administration at bedtime may help to minimize nausea.

TOXICITY

Central nervous system: neurotoxicity including mood disorders and CNS depression is commonly suggested to occur with procarbazine, although the incidence is not well documented. In the German Hodgkin's Lymphoma Study Group study (NEJM 2003; 348:2386) the frequency of grade 3 or 4 neurologic adverse events was 5% with standard dose BEACOPP, 4% with escalated dose BEACOPP and 4% with COPP-ABVD. All regimens also included vincristine and the details of neurotoxicity are not described.

Hematologic: myelosuppression, hemolysis in patients with G-6-PD deficiency.

Gastrointestinal: nausea and vomiting (procarbazine is considered moderately emetogenic); increasing the dose in a stepwise fashion over several days may minimize this, as may administration of entire dose at bedtime.

Genitourinary: reproductive dysfunction >10%.

Other: second malignancies (cumulative incidence 2% to 15% reported with MOPP combination therapy).

INTERACTIONS

Procarbazine is a weak monoamine oxidase (MAO) inhibitor. Usual cautions regarding avoidance of tyramine-containing foods are commonly exercised to avoid the possibility of hypertensive crisis. Foods with the highest amounts of tyramine include boursault, camembert, cheddar, emmenthaler, and stilton cheese; caviar; pickled herring; fermented sausages (bologna, pepperoni, salami, summer sausage); Chianti wine; fava beans (contain dopamine); yeast extract (baked goods, however, do not contain high amounts of tyramine). There are no reports in humans of hypertensive crisis following ingestion of tyramine-containing foods in which procarbazine was the MAO inhibitor. The same caution is applied for tricyclic antidepressants and sympathomimetic agents.

Procarbazine is commonly said to result in a disulfiram reaction when taken with alcohol. The reported reaction consisted of facial flushing (red, hot).

CNS depression: See discussion of nervous system toxicity above. Procarbazine is suggested to add to the effects of other CNS depressants.

11.12 Prednisone

Please refer to the FDA-approved package insert for prednisone for product information, extensive preparation instructions, and a comprehensive list of adverse events.

AVAILABILITY

Prednisone is commercially available in 1, 2.5, 5, 10, 20, and 50 mg tablets and in an oral solution (containing alcohol) in concentrations of 1 mg or 5 mg of prednisone/mL.

STORAGE & STABILITY

Prednisone should be stored at room temperature.

ADMINISTRATION

Prednisone is administered orally.

TOXICITY

Short-term use of prednisone (e.g., ≤ 4 weeks) may be associated with gastrointestinal side effects (dyspepsia, ulceration); insomnia, nervousness, and occasionally, psychosis; and hyperglycemia. Immunosuppression with an increasing risk of infection is also seen.

12.0 ANCILLARY THERAPY

12.1 Supportive Care

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on the flow sheets. HIV positive patient should be managed according to institutional guidelines. Zidovudine and stavudine may not be administered as part of the antiretroviral therapy for HIV positive patients. See Sections 7.1.2, 7.1.3 and 9.1.1.

12.2 Conditions for Other Therapy

Treatment with hormones or other chemotherapeutic agents may not be administered except in the following circumstances: Steroids may be administered for adrenal failure. Hormones may be administered for non-disease-related conditions (e.g., insulin for diabetes). Dexamethasone may be administered on the day of chemotherapy for (acute) chemotherapy-induced nausea or vomiting.

12.3 Prophylaxis for Prevention of Hemorrhagic Cystitis

Mesna may be administered for patients getting cyclophosphamide to prevent/minimize the occurrence of hemorrhagic cystitis. If used, mesna should be given according to institutional guidelines.

12.4 Antiemetic Therapy

Antiemetic therapy should include 5-HT3 receptor antagonists (e.g. ondansetron, granisetron).

12.5 Transfusions

Erythrocyte and platelet transfusions may be administered as necessary at the discretion of the treating physician.

13.0 CRITERIA FOR RESPONSE, PROGRESSION, AND RELAPSE

For the purposes of this study, patients will be re-evaluated after two (2) cycles of ABVD therapy. Patients with a negative PET scan will be re-evaluated after 6 cycles of ABVD. Patients with a positive PET scan will be re-evaluated following IFRT. Response assessments must be performed using the same imaging modality (PET) as used at the time of pre-study evaluation.

13.1 Definitions of Response [60]

13.1.1 Complete Response (CR)

Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

13.1.2 Partial Response (PR)

At least a 50% decrease in the sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: a) they should be clearly measurable in at least two perpendicular dimensions; b) if possible, they should be from disparate regions of the body; and c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

No increase should be observed in the size of other nodes, liver, or spleen.

Splenic nodules must regress by ≥ 50% in their SPD, or, for single nodules, in the greatest transverse diameter.

With the exception of splenic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

No new sites of disease should be observed.

If the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.

13.1.3 Stable Disease (SD): Patient fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see below). The PET should be positive at prior sites of disease, with no new areas of involvement on the post-treatment CT or PET.

13.1.4 Progression (PD) or Relapse

Lymph nodes should be considered abnormal if the long axis is > 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is > 1.0. Lymph nodes ≤ 1.0 cm by ≤ 1.0 cm will not be considered as abnormal for relapse or progressive disease.

Appearance of any new lesion > 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously

unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of < 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm, or > 1.5 cm in the long axis.

At least a 50% increase in the longest diameter of any single previously identified node > 1.0 cm in its short axis.

Lesions should be PET-positive if a typical FDG-avid lymphoma or the lesion was PET-positive prior to therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

13.2 Guidelines for Evaluation of Measurable Disease

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

13.2.1 Clinical Lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes).

13.2.2 Chest X-ray: Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

13.2.3 Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen, and pelvis. Head & neck and extremities usually require specific protocols.

13.2.4 Ultrasound (US) should not be used to measure tumor lesions that are clinically not easily accessible when the primary endpoint of the study is objective response evaluation. It is a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

13.3 Response Assessment Table

Response Category	Definition	Nodal Masses	Spleen
CR	Disappearance of all evidence of disease	a) PET positive at baseline; mass of any size permitted if PET negative b) Variably PET negative at baseline; regression to normal size CT	Not palpable, nodules disappeared
PR	Regression of measurable disease, no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes a) PET positive at baseline; one or more PET positive at previously involved site b) Variably PET negative at baseline; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of spleen
SD	Failure to attain CR, PR, or PD	a) PET positive at baseline; PET positive at prior sites of disease and no new sites on CT or PET b) Variably PET negative at baseline; no change in size of previous lesions on CT	
PD	Any new lesion increase by ≥ 50% of previously involved disease sites	Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET positive prior therapy.	≥ 50% increase from nadir in the SPD of any previous lesions

13.4 Definition of Progression-Free Survival

Progression-free survival (PFS) is measured as the time from study entry to disease progression or death.

14.0 Removal Of Patients From Protocol Therapy

14.1 Duration of Treatment

14.1.1 Continue treatment at the highest tolerable dose for a total of 6 cycles +/- IFRT or until the appearance of disease progression or unacceptable toxicity. Remove from protocol therapy any patient with rapid or documented disease progression.

14.1.2 **Post-Treatment Patient Follow-Up:** After cycle 6 with or without IFRT, patients will be monitored depending on response achieved, PET scans, and, if performed, biopsy results as follows:

CR, PR and PET negative: Patients will be followed according to the post-treatment follow-up schedule in Section 6.0.

CR, PR, PET positive, and biopsy positive: Patients may be treated at investigator discretion and will be followed for survival and secondary malignancies or new primaries.

CR, PR, or SD, PET positive, and biopsy not performed: Patients will have repeat PET/CT and CT scans performed three months later. If PET scan becomes negative, patients will be followed according to the post-treatment follow-up schedule in Section 6.0. If PET remains positive, then a biopsy may be performed if medically appropriate or clinically feasible at the discretion of the treating physician. If biopsy is positive, patients will be followed for survival and

secondary malignancies or new primaries. If biopsy is negative, patients will be followed according to the post-treatment follow-up schedule in Section 6.0.

14.2 Extraordinary Medical Circumstances:

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Notify the Study Chair.
- Document the reason(s) for discontinuation of therapy on flow sheets.
- Follow the patient for relapse, progression, and secondary malignancy or new primaries.

15.0 STATISTICAL CONSIDERATIONS

15.1 Study Design

This is single-arm phase II clinical trial of response-adapted therapy based on PET for bulky stage I and stage II Hodgkin lymphoma. A maximum of 123 patients will be entered to the study.

15.2 Primary Endpoint

The primary outcome of this study is progression-free survival (PFS), defined as the time from study entry to disease progression or death.

15.2.1 Analysis Plan

The patients who have CR, PR or SD after 2 cycles of ABVD will undergo the first PET/CT scan. We want to show that by receiving 4 cycles of escalated BEACOPP and IFRT, the PFS of PET+ patients will have a PFS that is close to that of PET- patients receiving 4 additional ABVD. Let λ_+ and λ_- denote the annual hazard rates of PFS for PET+ and PET- patient groups, respectively, and $\Delta = \lambda_+/\lambda_-$ their hazard ratio. Based on the projected hazard rates for PET+ and PET- patient groups as discussed in Section 15.2.2, we want to test H_0: $\Delta=4.1$ vs. H_1: $\Delta<4.1$ using univariate Cox regression method with one-sided $\alpha=0.15$ [61]. The final analysis will be conducted when 44 events (progressions or deaths) are observed, which is expected to occur about 3 years after the completion of patient accrual. Kaplan-Meier curves of PFS will be estimated for the two patient groups.

The univariate Cox regression tests on the hazard ratio between two patient groups, so that it does not require specification of the PFS for each group. Let $S_+(3)$ and $S_-(3)$ denote the 3 year PFS for PET+ and PET- patient groups, respectively. For various PFS levels and by assuming exponential PFS models, the 3 year PFS for two patient groups under H_0: $\Delta=4.1$ and H_1: $\Delta=2.29$ are represented as follows:

S-(3)	75%	80%	85%	90%
S+ (3) under H_0	31%	40%	51%	65%
S+ (3) under H_1	52%	60%	69%	79%

As a secondary analysis, we will test H_0: $S_+(3)=40\%$ vs. H_1: $S_+(3)>40\%$ using the asymptotic result of the Kaplan-Meier estimator of $S_+(3)$ with one-sided $\alpha=0.15$

15.2.2 Sample Size Calculation

Picardi et al. [10], using a smaller size limit to define bulky disease (> 5 cm compared to > 10 cm in this study), observed a 3 year PFS of about 86% in patients receiving chemotherapy only. Based on literature including this data, we expect that, following 6 cycles of ABVD without radiotherapy, the 3-year PFS for PET- and PET+ patients (after 2 cycles of ABVD) will be about 80% and 40%, respectively. We expect that for PET+ patients, the aggressive treatment by 4 cycles of escalated BEACOPP followed by radiotherapy for PET+ patients will increase the 3-year PFS probability from 40% to 60%.

Assuming exponential distributions for PFS, these hypotheses imply H_0: $\Delta=4.1$ and H_1: $\Delta<4.1$. Assuming an annual accrual of 25 patients, 3 years of additional follow-up and 30% of PET positivity after two cycles of ABVD, a sample size of N=110 eligible patients (about 34 PET+ and 76 PET- patients) guarantees 80% of power by the log-rank test statistic for non-unity hazard ratio under H_0 [61] with one-sided $\alpha=0.15$ and H_0: $\Delta=4.1$ (based on $S_-(3)=0.8$, $S_+(3)=0.4$) against H_1: $\Delta=2.29$ (based on $S_-(3)=0.8$, $S_+(3)=0.6$).

Under these assumptions, with the expected 34 PET+ patients, the secondary analysis for testing H_0: $S_+(3)=40\%$ vs. H_1: $S_+(3)>40\%$ using the Kaplan-Meier estimator of $S_+(3)$ with one-sided $\alpha=0.15$ will have about 90% power to detect H_1: $S_+(3)=60\%$.

15.3 Accrual and Follow-Up

Assuming up to 10% of dropout, ineligibility, or progressive disease after 2 cycles of ABVD (the latter expected to be less than 5%), we will accrue a maximum of 123 patients. The expected accrual is approximately 25 patients per year, so that it will take about 60 months for patient accrual. Patients will be followed for up to 10 years for survival data.

15.4 Sample Size Modification

Due to the lower accrual rate than expected, the accrual goal is lowered from 123 to 100 in April 2017, when about 95 patients have registered and the real accrual rate has been only about 14 patients per year, compared to 25 patients per year expected at the development of this study. In this sample size recalculation, we assume (i) an annual accrual rate of 14 patients and (ii) 7% of attrition due to dropout, ineligibility, or progressive disease after 2 cycles of ABVD, while assuming other design parameters the same as before (as in section 15.2.2). With n=93 (=100x0.93) eligible and evaluable patients, (about 28 PET+ and 65 PET- patients), we have 80% of power by the log-rank test statistic for non-unity hazard ratio under H_0 [61] with one-sided $\alpha=0.15$ and H_0: $\Delta=4.1$ (based on $S_-(3)=0.8$, $S_+(3)=0.4$) against H_1: $\Delta=2.29$ (based on $S_-(3)=0.8$, $S_+(3)=0.6$).

Under these assumptions, with the expected 28 PET+ patients, the secondary analysis for testing H_0: $S_+(3)=40\%$ vs. H_1: $S_+(3)>40\%$ using the Kaplan-Meier estimator of $S_+(3)$ with one-sided $\alpha=0.15$ will have about 90% power to detect H_1: $S_+(3)=60\%$.

The final analysis will be conducted when D=42 events (progressions or deaths) are observed, which is expected to occur after approximately 3 years of additional follow-up. The study will take about 122 months (86 months for patient accrual and 36 months for additional follow-up).

The power analysis for the secondary objectives and correlative endpoints is unchanged (i.e. based on n=110 eligible and evaluable patients).

As of protocol Update #13, the following change has been made:

Revised final analysis timing due to low event rate:
This study closed to accrual in September 2017, having registered 101 patients. A total of 94 patients were eligible, had a PET/CT scan after cycle 2, and will be included in the primary endpoint analysis (25 PET+ and 69 PET-). As of September 2019, the pooled event rate was much lower than that specified by the study design. With a median follow-up of 3.6 years (IQR 2.5 to 5.5), the observed number of events at this time was 9 (based on protocol assumptions, we would have expected approximately 33 events). In order to provide a timely final analysis, the final analysis will be performed when all patients have been followed for at least 3 years, which is expected in September 2020.

15.5 Inclusion of Women & Minorities

Although there is no evidence to suggest that the outcome will differ by gender or ethnicity and there is insufficient power to detect small or moderate effects, we will, in a secondary analysis, report the results by gender and ethnicity.

15.6 Predictive Value of FDG-PET

In analysis, the ratio between the SUVmax after two cycles and the SUVmax at baseline will be used as the observation for each patient. (A ratio smaller than 1 means decrease in post-therapy SUVmax from the baseline.) We expect that about 30% of patients will be PET positive after cycle 2.

15.7 Secondary Objectives

PFS and CR rate will be estimated for PET positive and negative patient groups after 2 cycles of ABVD. PFS for each group will be estimated by Kaplan-Meier method. The confidence interval (CI) for CR rate will be based on exact binomial distribution. The point-wise CI's for PFS will be estimated based on the normal distribution approximations.

Predictive values, sensitivity and specificity of semiquantitative evaluation of FDG uptake will be estimated with respect to PFS and CR using various approaches, including receiver operating characteristic (ROC) curves for different cutoff values, percent decrease in SUV, and absolute SUVs after 2 and 6 cycles in PET- patient group and after 2 cycles of chemotherapy and IFRT in PET+ patient group. For PFS, time-dependent ROC method (Heagerty et al. 2004) will be used in the presence of censoring within 3 years. The expected sample size is 110 for both cycle 2 data analysis and cycle 6 (for PET- group) or post IFRT (for PET+ group) data analysis. Assuming 80% OR rate (or 80% event free at year 3), the estimated sensitivity (N=110x0.2=22) will have a standard error (SE) of maximum 0.107 and the estimated specificity (N=110x0.8=88) will have a variance of maximum 0.053. Further, assuming 30% of PET positivity after cycle 2, the estimated positive predictive value (N=110x0.3=33) will have a standard error (SE) of maximum 0.087 and the estimated negative predictive value (N=110x0.7=77) will have a variance of maximum about 0.057. Similar analysis will be conducted for PET data after RT from the patients with positive PET outcome after 2 cycles of chemotherapy.

Predictive values, sensitivity and specificity of volumetric changes on CT will be estimated with respect to PFS and CR after 2 and 6 cycles (for PET- group) or post IFRT (for PET+ group) in respective patient groups. For PFS, time-dependent ROC method will be used in the presence of censoring within 3 years [62]. Similar analysis will be conducted for PET data after RT from the patients with positive PET outcome after 2 cycles of chemotherapy.

Predictive values, sensitivity and specificity of FDG-PET imaging will be estimated using a more liberal qualitative reading scale by using the liver as a reference background. The

same analyses as in Section 15.6 will be conducted using liver-based PET data. For semiquantitative PET data, the change between baseline and after cycle 2, and after chemotherapy (for PET- group) or after IFRT (for PET+ group) will be correlated with OR and PFS. Similar analysis will be conducted for the change between baseline and after RT for the patients with positive PET outcome after 2 cycles of chemotherapy.

Predictive value will be compared among metabolic parameters (both visual and quantitative changes), volumetric CT changes, and molecular parameters. ROC curves from correlated markers will be compared using the method by Delong et al [63].

15.8 Correlative Endpoints

All eligible patients who consent to the correlative science sample collection will be included in the correlative studies. Based on our experience from previous studies, we assume 70% of patients will consent (70% of 110 eligible patients, n=77) to the correlative science sample collection.

15.8.1 Serum and Plasma Markers

Serum markers will be analyzed as a continuous variable as well as a binary (elevated versus not elevated) variable.

Baseline serum marker values will be correlated with response (overall response vs. no response) at the end of treatment. Assuming 80% of overall response (OR=CR+PR), a two-sample t-test with two-sided α=0.05 has 80% power to detect a standardized effect size of 0.8 using continuous serum marker values. For a dichotomous serum marker, we assume that the baseline serum marker value will be elevated for about 60% of patients. Then, a chi-squared test with two-sided α=0.05 has 89% power when the probabilities of elevation in serum marker are 50% for OR and 90% for non-OR.

Baseline serum marker values will be correlated with PFS using Cox regression method. Suppose that the 3-year PFS is 85% for the whole population, and we assume 4 years of accrual and 3 years of additional follow-up after completion of accrual. Using a continuous serum marker, a Cox regression with two-sided α=0.05 has 84% power to detect a log hazard ratio (log-HR) of 0.7 between two patient groups with marker values one standard deviation away. We assume that the marker value (or its transformation) follows a normal distribution. For a dichotomous serum marker, the log-rank test with two-sided α=0.05 has 87% power when the probability of elevated serum marker is about 60% and the 3-year PFS is 75% for the patient group with an elevated serum marker and 93% for the other group.

We will conduct multivariate regression analyses (logistic regression for response and Cox regression for PFS), including treatment indicator, different markers, and known predictors. These multivariate analyses are to test if a baseline serum marker is an independent predictor after adjusting for other predictors, or a surrogate marker with respect to response or PFS.

The serum marker values at each PET scan will be correlated with the PET outcome using an ROC method. We will compare the areas under the ROC curves among different serum markers by combining the data from two PET scans using Emir et al. [64]. Probability of positive PET outcome will be compared among the groups defined by the trend of marker values around each PET scan.

Similar analyses will be conducted for plasma marker data.

15.8.2 Immunohistochemical Markers

IHC markers will be correlated with response at the end of treatment. IHC marker values will be correlated with PFS using Cox regression method. We will conduct multivariate regression analyses (logistic regression for response and Cox regression for PFS) including treatment indicator, different markers and known predictors. These multivariate analyses are to test if an IHC marker is an independent predictor after adjusting for other predictors, or a surrogate marker with respect to response or PFS.

15.8.3 CT versus PA/Lateral Chest X-Ray

We want to compare mediastinal bulk as defined by CT scan (> 10 cm) and PA/lateral chest x-ray (> 0.33 maximal chest diameter) at baseline. We expect that the imaging data will be available for about 90% of 110 eligible patients, i.e. n=99 for this study objective. If the correlation between the two imaging data is 0.3, the two-sample t-test will have 92% to detect a standardized effect size (difference in mean divided by standard deviation) of 0.4 with two-sided alpha=5%. We will consider taking a log-transformation of the measurements to improve the normality and variance stabilization of the distribution.

16.0 ADVERSE EVENT REPORTING (AER)

Investigators are required by Federal Regulations to report serious adverse events as defined below. Investigators are required to notify the Alliance Central Office, the Study Chair, and their Institutional Review Board (IRB) if a patient has a reportable serious adverse event. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning April 1, 2018.

All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site [redacted] All reactions determined to be "reportable" in an expedited manner must be reported using the NCI CTEP Adverse Event Reporting System (CTEP-AERS).

Reporting of cases of secondary AML/MDS should be done using CTEP-AERS. New primary malignancies should be reported using Study Form C-1001.

In the rare occurrence when Internet connectivity is lost, an AE report may be submitted using CTEP's Adverse Event Expedited Report – Single Agent or Multiple Agent paper template (available at [redacted]) and faxed to [redacted]. A 24-hour notification is to be made to CTEP by telephone at [redacted], **only** when Internet connectivity is disrupted. Once Internet connectivity is restored, an AE report submitted on a paper template or a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

16.1 CALGB 50801 Adverse Event Reporting Requirements

Phase 2 and 3 Trials: CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of Treatment

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5	Grades 4 & 5
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	Unexpected without Hospitalization	Expected with Hospitalization	Expected without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	10 Calendar Days	10 Calendar Days

[1]Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment require reporting as follows:

CTEP-AERS 10 calendar day report:

- Grade 4 unexpected events
- Grade 5 expected or unexpected events

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines defined:
- "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

16.2 Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements for CALGB 50801:

- All grade 5 events must be reported via CTEP-AERS within 10 calendar days.
- All grade 4 events that are unexpected and that are at least possibly related to treatment must be reported via CTEP-AERS within 10 calendar days.
- All grade 4 events that are unexpected that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS within 10 calendar days.
- Grade 4 events that are expected do not require CTEP-AERS, regardless of attribution or hospitalization. These events should be submitted as part of study results.
- A list of specific expected adverse events can be found in Section 11.0 (Drug Formulation, Availability, and Preparation).
- CTEP-AERS reports are to be submitted electronically [redacted].
- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.

- The reporting of adverse events described in the table above is in addition to and does not supplant the reporting of adverse events as part of the report of the results of the clinical trial, e.g., study summary forms or cooperative group data reporting forms (see Section 5.2 for required CALGB forms).
- **Secondary malignancy:** A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

  CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. In CTCAE version 5.0, three options are available to describe the event:

  -Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])

  -Myelodysplastic syndrome (MDS)

  -Treatment-related secondary malignancy

  Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

  Second malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.
- Pregnancy loss is defined as "Death in utero," and any pregnancy loss should be reported expeditiously as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC as currently CTEP-AERS recognizes this event as a patient death.

  A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.
- Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.,* radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

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APPENDIX I LONDON/DEAUVILLE CRITERIA

Negative Scan

- Score 1 no uptake
- Score 2 uptake ≤ mediastinum
- Score 3 update > mediastinum and ≤ liver

Positive Scan

- Score 4 moderately ↑ > liver
- Score 5 markedly ↑ uptake > > liver

Score X:
New areas of update unlikely to be related to lymphoma.

APPENDIX II IMMUNOHISTOCHEMICAL ANALYSIS AND IMAGING PROCEDURES

Immunohistochemical stains will be performed using automated immunostains for BCL2, FOXP3, GzB, tyrptase, and MAL on a Ventana Benchmark stainer (Ventana, Tucson AZ) with IVIEW™ diaminobenzadine detection in the CLIA-certified laboratory of the Cleveland Clinic Pathology and Laboratory Medicine Institute. Staining conditions are summarized in **Table A1**.

Stains will be quantitated by manual counting per 5/high power oil objective fields. The within run reproducibility of manual TMA immunostaining counting by Dr Hsi (random recounting) for multiple markers is excellent with Pearson correlation coefficients of 0.82 or greater (P<.001). Specific assay precision across immunostaining runs has been characterized by repetitive consecutive runs of control tissue with quantitation of serial sections. The coefficient of variation taking into account both technical and counting variability for BCL2, FOXP3, GzB and trypase is 5%, 7%, 8%, and 5% respectively. Precision for MAL has not yet been characterized but will be performed prior to study and is anticipated to be less than 10%.

Table A1: Immunohistochemistry

Antibody	Clone	Vendor	Antigen retrieval
BCL2 clone	124	Ventana	HIER*
MAL	6D9	M. Alonso	HIER
FOXP3	22510	Abcam	Protease 2
GzB	GrB-7	Accurate	HIER
Tryptase	AA1	DAKO	Protease 2

*head induced epitope retrieval, CC1 standard

Imaging:

Image analysis of the immunostains will also be performed for comparison to the manual methods. Slides will analyzed using the Ariol SL-50 automated slide scanner (Applied Imaging, San Jose, CA) to quantitate the amount of positive staining for each area of interest. Thresholds for each image are applied based on multiple parameters: RGB algorithm, shape, and size. Positive staining is calculated by applying two color thresholds, with one recognizing blue background counterstain (hematoxylin) and another recognizing brown immunostain positive cells. Individual cells were discriminated by incorporating the shape and size thresholds, providing, with the color thresholds, and actual cell counts. For nuclear antigens the percentage of positivity is the cell number detected by the brown threshold divided by the total cell number, detected by the brown and blue thresholds. Total tissue area analyzed may also be included in the final analysis.

APPENDIX III SUMMARY OF BIOLOGIC PROGNOSTIC MARKERS IN CLASSICAL HL (≥50 PTS)

Serum Markers	N	Impact	Endpoint	Significant on Multivariable Analysis
sCD30				
Cassanovas 2007 [33]	519	adverse	EFS	YES
Gause 1991 [65]	90	adverse	TTF	NO
Nadali 1994 [34]	117	adverse	EFS	YES
Visco 2006 [35]	321	adverse	FFS	YES
Zanotti 2002 [66]	101	adverse	FFS	YES
Axdorph 2000 [67]	93	adverse	CSS	YES
IL-10				
Cassanovas 2007 [33]	519	adverse	EFS	NO
Axdorph 2000 [67]	123	adverse	CSS	YES
Bohlen 2000 [68]	64	adverse	FFTF	YES
Sarris 1999 [36]	101	adverse	FFS	YES
Vassilakopoulos 2001 [37]	122	adverse	FFS	YES
Visco 2004 [69]	69	adverse	PFS	YES
Viviani 2000 [70]	73	adverse	FFP	YES
TARC				
Weihrauch 2005 [40]	63	adverse	OS	NO

APPENDIX IV CALGB 50801 PET/CT INSTRUMENT TECHNICAL SPECIFICATIONS FORM

CALGB 50801 PET/CT INSTRUMENT TECHNICAL SPECIFICATIONS FORM
(From ACRIN Credentialing Application, 2005)

Page 1 of 5

Institution:	**Date:**
Institution Address:	
Institution Contact Name and Telephone Number:	
E-mail:	**Fax:**
PET Center Name:	**Date:**
PET Center Address:	
PET Center Contact Name and Telephone Number:	
E-mail:	**Fax:**

Type of Scanner:
(e.g., GE Discovery ST, Siemens Biograph, Philips Gemini, GE Advance, Siemens/CTI ECAT, etc.)

Transmission Source:
(e.g., ^{68}GE-rods, ^{137}Cs-point, CT)

Method of Attenuation Correction:
(e.g., segmentation, subtraction of emission contribution to transmission scan, CTAC)

Routine QC Testing Performed

Daily:

Monthly:

Quarterly:

Yearly:

Other:

CALGB 50801 PET/CT INSTRUMENT TECHNICAL SPECIFICATIONS FORM
(From ACRIN Credentialing Application, 2005)

UNIFORM PHANTOM SCAN INFORMATION

Phantom Length: **Phantom Diameter:**

Phantom Volume:

Radionuclide:

For Water-Fillable Phantoms, Provide the Following Data**:**

Assayed Activity in Syringe before injection: **mCi** **Time:**

Assayed Activity in Syringe after injection: **mCi** **Time:**

For Ge-68/Ga-68 Calibration Phantoms, Provide the Following Data**:**

Calibration Date: **Time:**

Calibration Activity: **mCi** **Time:**

Number of Pixels in ROI:	**Slice #**	**Average SUV in ROI[1]**	**Std Dev of SUV (if available)**
Report info for EVERY slice of the phantom	1	_____	_____
	2	_____	_____
	3	_____	_____
	4	_____	_____
	5	_____	_____
	6	_____	_____
	7	_____	_____
	8	_____	_____
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	15	_____	_____
	16	_____	_____
	17	_____	_____
	18	_____	_____
	19	_____	_____
	20	_____	_____

[1] A circular or elliptical region of interest (ROI) covering most of the interior of the phantom.

CALGB 50801 PET/CT INSTRUMENT TECHNICAL SPECIFICATIONS FORM
(From ACRIN Credentialing Application, 2005)

FOR IMAGING CORE LABORTORY USE ONLY:

Phantom Images Review:

Date:
Comments:

☐ **Approved**

☐ **Disapproved**

_____ _____
Signature Date

CALGB 50801 PET/CT INSTRUMENT TECHNICAL SPECIFICATIONS FORM
(From ACRIN Credentialing Application, 2005)

WHOLE BODY FDG-PET <u>TEST PATIENT #1</u>:

File Name: **Patient Height:** **Patient Weight:**

FDG Dose (mCi): **Dose Assay Time:**

Blood glucose prior to FDG administration (mg/dL):

Injection Time: **Start Time of Emission Scan:**

ACQUISITION No. of Bed Positions:

EMISSION TIME (MIN/BED): **TRANSMISSION TIME (MIN/BED):**

RECONSTRUCTION ALGORITHM: (e.g., 2D FBP, 2D OSEM, 3D FORE/OSEM, 3D RAMLA)	**PIXEL SIZE (mm)** X-Y: Z:

Scatter Correction Applied: ☐ **Yes** ☐ **No**

(Include algorithm type, e.g., model-based, tail-fit, Bergstrom):

Randoms Correction Applied: ☐ **Online** ☐ **Smoothed Randoms (offline)** ☐ **None**

FOR IMAGING CORE LABORTORY USE ONLY:

<u>Test Patient #1</u> Review:

Date:
Comments:

☐ **Approved**

☐ **Disapproved**

_____ _____
Signature Date

CALGB 50801 PET/CT INSTRUMENT TECHNICAL SPECIFICATIONS FORM
(From ACRIN Credentialing Application, 2005)

WHOLE BODY FDG-PET TEST PATIENT #2:

File Name: **Patient Height:** **Patient Weight:**

FDG Dose (mCi): **Dose Assay Time:**

Blood glucose prior to FDG administration (mg/dL):

Injection Time: **Start Time of Emission Scan:**

ACQUISITION No. of Bed Positions:

EMISSION TIME (MIN/BED): **TRANSMISSION TIME (MIN/BED):**

RECONSTRUCTION ALGORITHM: (e.g., 2D FBP, 2D OSEM, 3D FORE/OSEM, 3D RAMLA)	**PIXEL SIZE (mm)** X-Y: Z:

Scatter Correction Applied: ☐ **Yes** ☐ **No**

(Include algorithm type, e.g., model-based, tail-fit, Bergstrom):

Randoms Correction Applied: ☐ **Online** ☐ **Smoothed Randoms (offline)** ☐ **None**

FOR IMAGING CORE LABORTORY USE ONLY:

Test Patient #2 Review:

Date:
Comments:

☐ **Approved**

☐ **Disapproved**

_____ _____
Signature Date

APPENDIX V CALGB 50801 IMAGING SITE PERSONNEL FORM

CALGB 50801 IMAGING SITE PERSONNEL FORM

Responsible CRA Contact Complete Address E-mail Phone Number Fax Number	**Radiology Department Contact** Complete Address E-mail Phone Number Fax Number

Please provide the information requested above. Provide the middle initial for individuals who commonly use them. Also, please add or correct the degree/title as necessary. This information will be retained by the Alliance Imaging Core Lab at IROC Ohio.

Once completed, you may **send this form to:**

[redacted]

Call the Imaging Core Laboratory at [redacted] or [redacted] with any questions. Thank you for your assistance.