CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

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A National Cancer Institute-supported member group of the National Clinical Trials Network

June 22, 2020

Martha Kruhm, MS, RAC
Head, Protocol and Information Office
Operations and Informatics Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Executive Plaza North Room 730
Bethesda, MD 20892

Dear Ms. Kruhm,

Enclosed please find Amendment #6 for protocol **AHOD1331**, *A Randomized Phase 3 Study of Brentuximab Vedotin (SGN-35) for Newly Diagnosed High-Risk Classical Hodgkin Lymphoma (cHL) in Children and Young Adults*, for CTEP review.

This amendment will:

- expand the window to complete the Time 6 timepoint for CIPN and CEA assessments
- and allow institutions flexibility in how CIPN and CEA assessments are administered.

Revisions to the protocol and consent documents are detailed in the pages below. Minor administrative updates (such as the correction of typographical errors or updates to the numbers of referenced sections) are tracked but not specified below.

Please contact me with any questions or concerns.

Sincerely,

Tiffany Liu, MS, MA, Protocol Coordinator (for)

Sharon Castellino, MD, AHOD1331 Study Chair
Kara Kelly, MD, COG Hodgkin Disease Chair
Douglas Hawkins, MD, Children's Oncology Group Chair

SUMMARY OF CHANGES: PROTOCOL DOCUMENT

In accordance with the above discussion, the following specific revisions have been made to the protocol. Additions are in **boldfaced** font and deletions in ~~strikethrough~~ font.

#	Section	Page(s)	Change
1.	Title Page & Throughout	Throughout	Version dates and amendment number have been updated.
2.	Study committee	6-8	The study committee has been updated to reflect the current roster and contact information.
3.	7.3	65	Expanded the window to complete follow-up assessments for the following time points: Time 36 ± ~~3~~ **6** months and Time 48 ± ~~3~~ **6** months.
4.	Appendix VII	156-157	• Corrected an error for internal consistency: "Study measures will be collected by CRAs from each designated rater at each participating institution at ~~five~~ **six** scheduled time points, beginning with the initiation of chemotherapy at 'baseline' through 36 months following the completion of therapy (see Table 1 below)." • Removed the following statements to allow institutions flexibility in how assessments are administered: i. "~~The Time 4, 5, and 6 assessments should be done in person, as well.~~" ii. "~~The timing of the assessments during a planned in clinic visit will also optimize response rates over more remote data collection.~~" • Expanded the window to complete the Time 6 CIPN follow-up assessment from +/- 3 months to +/- 6 months to ensure optimal response rate. • Updated a sentence about what the Time 6 assessments will allow researchers to estimate for protocol consistency.
5.	Appendix VIII	159-160	• Removed the following statement to allow institutions flexibility in how assessments are administered: "~~c. Method of Administration: Self-administered~~" • Expanded the window to complete the Time 6 CEA follow-up assessment from +/- 3 months to +/- 6 months to ensure optimal response rate.

Activated: 03/16/2015
Closed: 08/02/2019

Version Date: 06/22/2020
Amendment #: 6

CHILDREN'S ONCOLOGY GROUP

AHOD1331

A Randomized Phase 3 Study of Brentuximab Vedotin (SGN-35) for Newly Diagnosed High-Risk Classical Hodgkin Lymphoma (cHL) in Children and Young Adults

A Groupwide Phase III Study (Limited to US and Canada sites)

NCI Supplied Agent:
Brentuximab Vedotin (SGN-35 NSC# 749710)
IND sponsor for Brentuximab Vedotin: DCTD, NCI

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CONTACT INFORMATION		
To submit site registration documents:	**For patient enrollments:**	**Submit study data**
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 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 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 https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the Data Submission Schedule in the CRF packet 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 https://www.ctsu.org. 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. 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.		
For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization.		
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 – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

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AGENT	NSC#	IND#
Brentuximab vedotin	749710	
Bleomycin	125066	Exempt
Cyclophosphamide	26271	Exempt
Doxorubicin	712227	Exempt
Etoposide	141540	Exempt
Filgrastim	614629	Exempt
Pegfilgrastim	614371	Exempt
Prednisone	10023	Exempt
Vincristine	67574	Exempt

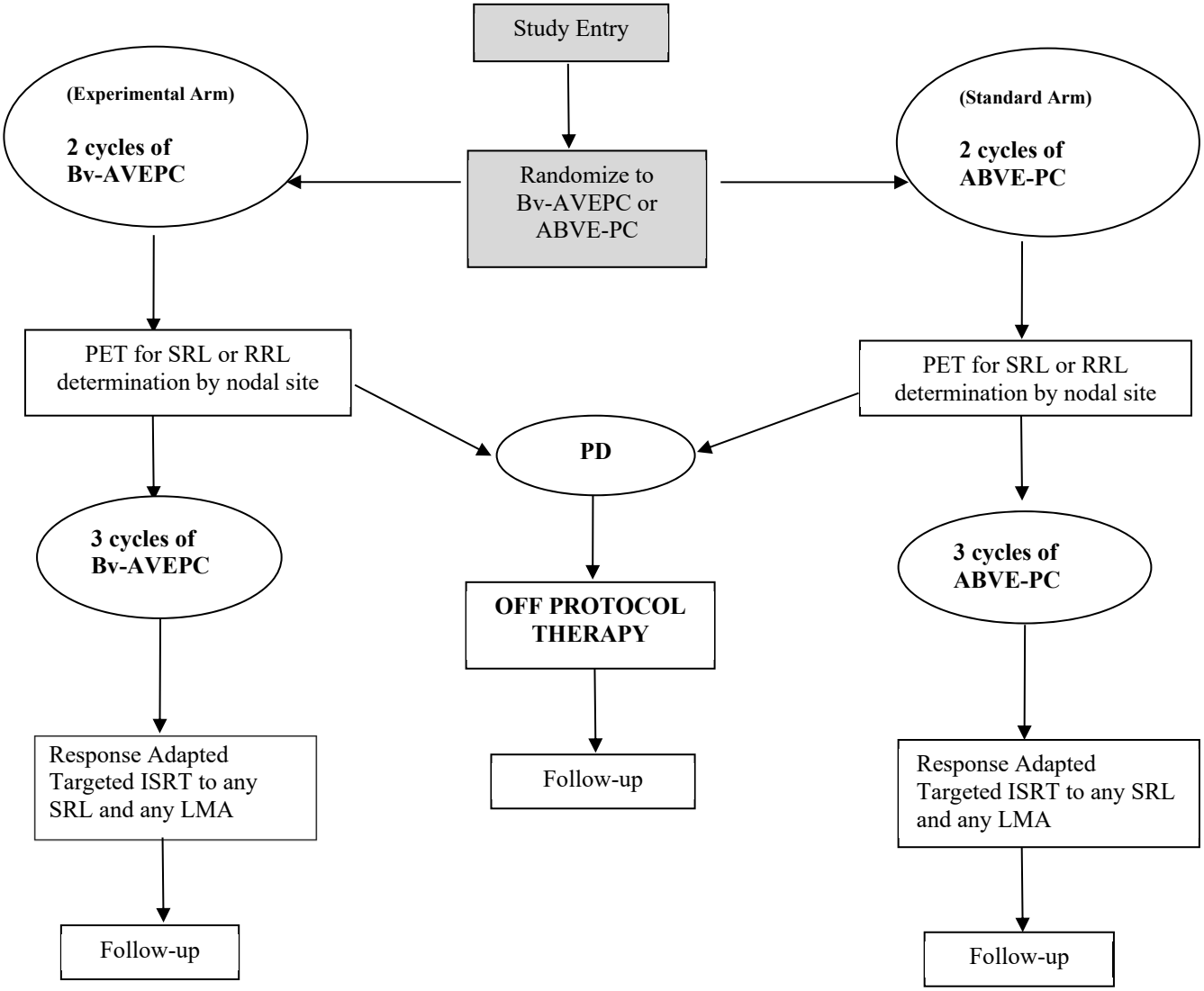
SEE SECTIONS 13 (PATHOLOGY), SECTION 7.2 (BIOLOGY TABLE), SECTION 7.3 (FOLLOW UP TABLE) AND APPENDIX VI (BIOLOGY DETAILS) FOR SPECIMEN SHIPPING ADDRESSES.

ABSTRACT

While contemporary combined-modality therapy in children and adolescents results in 5-10 year survival rates of more than 90% when patients of all stages are evaluated, there remain subgroups of Hodgkin Lymphoma (HL) patients in whom initial cure is suboptimal, and hence these subgroups are deemed as high risk. Evidence supporting the use of response-directed therapy in pediatric HL has been demonstrated in POG 9425, CCG 59704 and AHOD0031. High-risk subgroups of HL patients may have EFS rates of less than 85%, indicating a need for novel therapy approaches beyond escalation of standard chemotherapy with current conventional agents. SEER data have suggested that advances in HL survival among adolescents and young adults (AYAs) may be less robust compared with both older and younger populations.[1]

The hybrid regimen, ABVE-PC, modified from both DBVE-PC regimen of POG 9425 and BEACOPP of CCG 59704, continues to be a tolerable combination of dose-intensive conventional therapy in classical Hodgkin Lymphoma (cHL). Brentuximab vedotin (Bv, Adcetris™), an anti-CD30 murine/human chimeric monoclonal antibody (cAC10; Brentuximab) linked to monomethylauristatin E (MMAE; vedotin), is able to target the Reed-Sternberg Cell (HLRS) in newly diagnosed disease.[2] The primary goal of the current study will be to examine the treatment efficacy (defined by EFS) of a chemotherapy regimen including Bv in high-risk cHL. High-risk cHL patients will be randomized to one of 2 therapy arms: the control arm of ABVE-PC or the experimental arm of Bv-AVEPC. Randomization will occur at the time of enrollment. In keeping with prior studies of response-based treatment, secondary goals will be to determine the response rate after two cycles of therapy on each arm. Those patients who remain FDG-PET positive after 2 cycles, will receive response-based involved site radiation therapy (ISRT). The expected accrual duration is about 4 years. In addition, correlative studies of biology, pharmacokinetics, imaging, radiation, neuropathy and health-related quality of life are incorporated in the evaluation of this new targeted agent for high-risk cHL.

EXPERIMENTAL DESIGN SCHEMA



Bv-AVEPC=Brentuximab vedotin/ Doxorubicin//Vincristine/Etoposide/Prednisone/Cyclophosphamide
ABVE-PC = Doxorubicin/Bleomycin/Vincristine/Etoposide/Prednisone/Cyclophosphamide

PD = Progressive disease
RRL = Rapid responding lesion/nodal site. Favorable response by PET2. See Table 10.3.1
SRL = Slow responding lesion/nodal site. Unfavorable response by PET2. See Table 10.3.1
LMA = Large Mediastinal Adenopathy (see Appendix I).
Response Adapted Targeted: ISRT (2100 cGy) to nodal sites with SRL or to initial LMA (regardless of response to chemotherapy).
ISRT = Involved site radiation therapy (see Section 15)

1.0 GOALS AND AIMS (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To assess the event free survival (EFS) of a novel regimen incorporating brentuximab vedotin (Bv; Adcetris™) in the chemotherapy backbone of doxorubicin (Adriamycin), vincristine, etoposide, prednisone and cyclophosphamide (Bv-AVEPC) in newly diagnosed high-risk cHL compared to those treated with ABVE-PC.

1.2 Secondary Aims

1.2.1 To determine whether children/young adults with high-risk cHL treated with Bv-AVEPC have a higher rate of early response (determined by FDG-PET) and a reduction in response-directed radiation therapy (RT) compared to those treated with ABVE-PC.

1.2.2 To compare the rate of neuropathy ($\geq$ Grade 3) among patients treated on the Bv-AVEPC (experimental arm) to patients treated on the ABVE-PC (standard arm).

1.3 Exploratory Aims

Childhood International Prognostic Score (CHIPS)

1.3.1 To validate and compare the Childhood Hodgkin International Prognostic Score (CHIPS) to conventional Ann Arbor Stage (Stages II B with bulk, III B, IV A or B) in predicting outcome in high-risk childhood cHL.

Biology

1.3.2 To determine the incidence of preferentially expressed antigen in melanoma (PRAME) and testis-specific antigens in EBV- cHL tumors and the incidence of EBV antigens (EBNA1, LMP1, LMP2) in EBV+ cHL tumors, with the goal of developing strategies to integrate cellular therapy into treatment for newly diagnosed high-risk cHL.

Imaging

1.3.3 To incorporate qualitative visual FDG-PET into response-directed treatment algorithms and explore quantitative FDG-PET and CT definitions of tumor burden and response for incorporation into next generation pediatric cHL risk-stratification schemes, exploring the extension of these algorithms to young adults.

Radiation Therapy

1.3.4 To evaluate the reduction in normal tissue irradiation associated with the current treatment approach compared to the volume of historic IFRT fields.

1.3.5 To evaluate EFS and patterns of relapse following protocol-specified RT utilization and treatment volumes.

Patient Reported Outcomes (PRO) of Peripheral Neuropathy and Health-Related Quality of Life

1.3.6 To characterize the extent of chemotherapy induced peripheral neuropathy (CIPN), as reported by patients and parent proxies, through serial administration of the FACT-GOG-NTX.

1.3.7 To describe the Health-Related Quality of Life (HRQL) consequences of peripheral neuropathy over time by correlating total neuropathy scale scores with the individual items with the CHRIs-Global scale (e.g., physical health, pain, emotional functioning).

1.3.8 To perform a cross validation of the FACT-GOG-NTX with the TNS-PV to determine the performance of both measures with the use of brentuximab vedotin in a limited institutional approach in children and young adults with cHL (See Appendix VII).

Economic (For US Institutions Only)

1.3.9 To assess the resource use and cost implications of Bv in combination with chemotherapy and radiotherapy (RT) for newly diagnosed high-risk cHL in children and young adults (See Appendix VIII).

Follow-up of Deauville score 3 lesions on FDG-PET imaging (confirmed by central imaging review)

1.3.10 To estimate the risk of relapse among RRL subjects that have at least one lesion that is Deauville 3 at PET 2.

The pharmacokinetics of brentuximab vedotin

1.3.11 To characterize the pharmacokinetics of brentuximab vedotin in children < 13 years of age.

2.0 BACKGROUND

2.1 Introduction and Rationale for Development

A challenge in treating Hodgkin Lymphoma (HL) is finding the optimal balance between achieving tumor free survival and minimizing treatment-related morbidity and mortality. While contemporary combined modality therapy in children and adolescents and young adults results in 5-10 year survival rates of more than 90% when patients of all stages are evaluated, there remain subgroups of HL patients for whom initial cure rates are suboptimal. It is among these high-risk patients that intensification of treatment with current conventional agents is inadequate. While the peak age for Hodgkin Lymphoma is 20-34 years of age, young adults (18-21 years) may also benefit from the study of novel approaches used in pediatric and adolescent Hodgkin's populations.

Despite risk-adapted, response-based approaches current therapy in adults and pediatric high-risk HL, which rely on initial or salvage regimens containing high doses of alkylating agents, anthracyclines, and RT, are associated with significant risk of premature second

malignancies, cardiovascular disease, and pulmonary toxicity. Hence, despite favorable early outcomes, death rates from treatment-associated morbidity escalate for decades following initial remission.[3-6] Despite decreases in radiation fields and doses with contemporary therapy, the cumulative incidence of Second Malignant Neoplasms (SMN) remains elevated.[7] Our overarching goal is to improve disease control while minimizing treatment burden by incorporating a new agent (brentuximab vedotin, Bv) targeting CD30 on the Reed-Sternberg Cell (HLRS) into the standard chemotherapy backbone treatment regimen (ABVE-PC) for CHL that has been modified to eliminate the bleomycin.

High-risk subgroups of HL patients may have EFS < 85%, indicating a need for novel therapy approaches beyond escalation of standard chemotherapy. In adults, the use of 6 cycles of ABVD therapy for early unfavorable or high-stage Hodgkin lymphoma has reported progression free survival ranges between 68% and 74%.[8-10] The majority of studies of high-risk pediatric HL report EFS of 75-85%, with Stage IVB patients consistently having the poorest outcomes.[11] The dose-intensive pediatric regimens ABVE-PC (adriamycin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide) and OEPA/COPDac for high-stage disease have demonstrated 5-yr EFS of 85-87%, with outcomes in subsets of high-risk patients ranging from 70-94%. The recent pediatric study CCG 59704, reported an EFS of 94% for high-risk patients (Stages IIB and IIIB with bulk, IV) using BEACOPP in an intensive, multidrug regimen with high cumulative alkylator and anthracycline doses; this demonstrates the principle of achieving high disease-free survival with initial therapy, but with significant risk of long- term adverse sequelae of treatment.[11]

The pediatric experience with dose-intensive regimens has suggested that short-term toxicities and the burden of therapy are generally well tolerated. Many centers deliver ABVE-PC as outpatient therapy. With the goal of improved disease control and reduced cumulative alkylator and anthracycline exposure, we propose the evaluation of the targeted agent brentuximab vedotin [(Bv); Adcetris™] into a well-tolerated backbone of dose-dense chemotherapy (Bv-AVEPC) for high-risk cHL patients in a randomized approach. Themes of dose density, response-based therapy and tailored delivery of radiotherapy will be extended from prior COG and legacy group studies. Consistent with recent studies in adult and pediatric HL, we will define the high-risk group to include Ann Arbor Stages: IIB with bulk disease, IIIB, IVA or IVB. We exclude Stage IIB without bulk disease patients based on AHOD0031 data where Stage IIB patients without bulk disease have 3-year EFS at 90%.

In this trial, we will compare 5 cycles of ABVE-PC to 5 cycles of Bv-AVEPC, using 2 cycle response status to delineate those high-risk patients who will subsequently receive involved site radiotherapy (ISRT) following 5 cycles. ISRT will be delivered to sites of slow response to initial chemotherapy, and to sites of initial large mediastinal adenopathy (LMA). The primary outcome will be EFS in the ABVE-PC and Bv-AVEPC groups.

2.2 **Study of Brentuximab Vedotin** (BV; Adcetris™)

Bv, an anti-CD30 murine/human chimeric monoclonal antibody (cAC10; brentuximab) linked to monomethylauristatin E (MMAE; vedotin), is an opportunity to target the specific biology of cHL in newly diagnosed disease.[2] In a single agent phase II trial of Bv in adult patients with relapsed HL following autologous transplant the objective response rate was 75% (34% complete response; 40% partial response) with a median response duration of 6.7 months.[12] Additionally, when Bv was added to a multi-agent chemotherapy regiment with adriamycin, vinblastine and dacarbazine (AVD) in adults with newly diagnosed

Stage IIA bulky or Stage IIB-IV disease in adults an MTD for Bv was not reached and the regiment appeared to be relatively safe.[13]

The approved dose of Bv is 1.8 mg/kg every 3 weeks. Primary Bv-associated toxicities include peripheral sensory neuropathy that is cumulative and reversible and myelosuppression. The corporate trial (ECHELON-1 NCT# 01712490; Millennium, Seattle Genetics) extended the experience in adults to compare the efficacy of 6 cycles of ABVD to 6 cycles Bv-AVD in de novo Stage III or IV Hodgkin disease. Utilizing a Bv dose of 1.2 mg/kg on days 1 and 15, the phase III study endpoint is modified progression free survival, with failure defined as need for any further therapy (radiation or chemotherapy inclusive) beyond 6 cycles. Modified progression free survival benchmarks have been set at 82.5% for the experimental arm versus an expected 75% PFS for the standard ABVD arm (Personal correspondence, Seattle Genetics). The recently published results of this trial limited to adults (ECHELON 1; AVD versus Bv) were released at a median follow-up of 24.6 months. There were 664 patients enrolled on the A+AVD arm and 670 patients on the ABVD arm. The primary endpoints of 2-year modified progression free survival in the A+AVD and ABVD groups were 82.1% and 77.2% respectively (hazard ratio for event of progression, death, or modified progression, 0.77; p=0.03). Myelosuppression and peripheral neuropathy are the primary AEs of concern in the Bv arm.[14]

The use of Bv in pediatric patients with refractory or relapsed HL or ALCL has been reported in several case reports.[15-18] The ongoing dose-escalation Phase 1/2 study (NCT01492088) in pediatric patients is evaluating pharmacokinetics, safety and efficacy of Bv as monotherapy in pediatric patients with relapsed or refractory disease.[19] The maximum tolerated dose and the recommended dose of Bv for phase 2 portion of the study was determined to be 1.8 mg/kg every 3 weeks. While the overall response rates appear favorable (47-64%), there is currently insufficient data to ascertain efficacy in children.[20,21] Treatment emergent adverse events appear similar to that noted in adult trials. There is currently limited information regarding safety and efficacy of Bv in children < 6 years of age. While HL is rare in younger children, in the recent series of COG trials for HL, an estimated 2% of patients were < 6 years at enrollment. Hence study of this agent is warranted in younger children with de novo Hodgkin Lymphoma.

In the published experience of Bv in pediatrics, in 9 children age 12-17 years (5 of whom had HL) there were no common events > Grade 3 and no patients discontinued treatment due to an adverse event.[22] The ongoing phase II study (AHOD1221) of Bv with gemcitabine for relapsed HL will provide further data in the pediatric and adolescent population. We also anticipate additional safety data from the recently opened St. Jude Consortium phase II trial evaluating the safety of Bv in place of vincristine using a chemotherapy backbone of OEPA/COPDac for high-risk HL in children and adolescents (personal correspondence, Metzger).

We propose to incorporate Bv into a modified version of ABVE-PC, termed Bv-AVEPC. Bv will be given at the 1.8 mg/kg dose on Day 1 of cycle. Bleomycin will be eliminated from the backbone in the experimental arm due to the potential risk of pulmonary toxicity when Bv is administered with bleomycin, as was observed in adult phase II trials[13], as well as data from studies suggesting that bleomycin has a less critical role in contemporary multi-agent regimens.[23]

Vincristine is deliberately retained in the experimental arm at Day 8 (but not Day 1) to allow comparison and minimize variability between the arms as much as possible, and to

maintain the dose intensity of the experimental arm (see Tables 2-3). The incidence of Grade 3 or higher motor or sensory neuropathy utilizing 3 to 5 cycles of the backbone regimen ABVE-PC over 3 preceding COG and POG studies (enrolling greater than 2000 subjects) has been consistently less than 3%. However, given theoretical concerns of additive neurotoxicity of dual tubulin inhibitors in the experimental arm, peripheral neuropathy will be closely monitored, with stopping rules for significantly higher than 5% incidence of Grade 3 or 4 peripheral neurotoxicity measured by Balis scale (See Appendix IV) among the first 100 patients treated on Bv-AVEPC. Rates of peripheral neuropathy will be monitored for Bv-AVEPC following Cycle 2 and Cycle 5 of therapy. If stopping rules are met, the experimental arm will be modified to remove Day 8 vincristine. In the event that this is a necessary change, we anticipate minimal reduction in dose intensity of the experimental arm.

All therapy will be given on a 21 day schedule with concomitant growth factor support to mitigate myelosuppressive toxicity.

2.3 Defining High-Risk cHL

There has been no consensus on defining risk groups by Ann Arbor Stage in pediatric or adult North American HL. The recently closed AHOD0831 study categorized Stage IIIB and IVB patients as high risk. Prior to that, CCG 5942 categorized Stage IV to treatment group 3 (most intensive treatment). The P9425 categorized Stages IIB, IIIB and IVA and B as high risk. The St. Jude/Stanford/DFCI consortium assigned IIB, IIIB, IV as high risk and the German Pediatric HOD HD2002 study assigned Stages IIBE, IIIAE, IIIB, IVA, IVB, IVE as advanced stage disease.[24]

Table 1: Definitions of High-Risk HL in Prior Pediatric Studies compared to AHOD1331

GHOD 2002	St. Jude/Stanford/DFCI	P9425	CCG5942	AHOD0831	AHOD1331
IIBE	IIB	IIB			IIB Bulk
IIIAE, IIIB	IIIB	IIIB		III B	IIIB
IV	IV	IV	IV	IV B	IV

Our current proposal has defined stages to high risk based on a combination of other group's categorization and based on outcomes from the recent series of COG and POG legacy studies given the experience with the ABVE-PC based chemotherapy. Despite Stage IIB patients having EFS > 90% on P9425 which included 3 or 5 cycles of chemotherapy and RT to all, on AHOD0031 Stage IIB patients with bulk disease had sub-optimal outcome (3 yr. EFS 75%) , compared to Stage IIB patients without bulk disease (3 yr. EFS 90%). The rationale for omission of Stage IIIA from the proposed high-risk therapy approach is that on AHOD0031 this group (n= 305 Stage IIIA cHL ages < 18; 18% of AHOD0031 population) had excellent outcomes with ABVE-PC based therapy. Specifically the 3-yr EFS was 88.1% (s.e. 1.9%). Similarly, on POG 9425, where patients received either 3 or 5 cycles ABVE-PC and RT, the 5-year EFS for Stage IIIA patients (n=18) was 94% (s.e. 5%). Hence, we do not feel it is justified to increase therapy to 5 cycles of ABVE-PC (over 4 cycles given in AHOD0031) with more intensive cyclophosphamide for this favorable risk group. In addition, this favorable risk group (with an estimated 48 patients per year) will increase the baseline EFS in the standard ABVE-PC arm and thereby potentially decrease our ability to detect a benefit of Bv in the experimental arm.

We will therefore include Ann Arbor Stages IIB with bulk, Stage IIIB and all Stage IV patients in this study. Consistent with AHOD0031, bulk will be defined as any large mediastinal adenopathy (LMA) or nodal aggregate > 6 cm. Refer to Appendix I for additional detail.

2.4 Rationale for AVEPC Chemotherapy Back Bone

Efficacy, tolerability and safety of the ABVE-PC regimen have been well studied in children.[25,26] ABVE-PC was introduced in 1997 in P9425, modifying ABVD by (1) substituting vincristine for the more myelosuppressive vinblastine, (2) replacing dacarbazine with etoposide, (3) adding cyclophosphamide and prednisone to enhance efficacy, and (4) increasing dose density by giving chemotherapy every 3 weeks with use of filgrastim to prevent prolonged marrow nadir.[25] AHOD0031 retained the backbone with some changes in dosing to reduce the 4 cycle cumulative doxorubicin dose to 200 mg /m^2, and AHOD0831 modified the cyclophosphamide dose to augment the cumulative alkylating agent therapy. Importantly, the risk of etoposide- induced secondary malignancy has been < 0.5%, combining data from POG 9425 and COG AHOD0031, that provides a large experience over the time period during which topoisomerase induced secondary leukemias are expected to occur. This observation is also noted in reports regarding the OEPA and BEACOPP regimens. The addition of etoposide in these regimens has allowed for a decrease in alkylator therapy thus limiting infertility risk in young patients, while preserving or improving disease outcomes. Additionally, the anthracycline exposure is lower with 5 cycles of ABVE-PC (250 mg/m^2 in our proposed study) compared to the 6-8 cycles of ABVD (300-400 mg/m^2) more commonly employed in adult regimens. As noted above, the incidence of Grade 3 or higher peripheral motor and sensory neuropathy has been less than 3%. While North American adult HL groups have mainly utilized ABVD based chemotherapy for 6 or more cycles in high-risk settings, European adult HL groups favor the more dose intensive BEACOPP regimen. ABVE-PC entered clinical use in the Pediatric Oncology Group ~15 years ago as a dose-intensive regimen designed to provide more efficacious therapy while decreasing cumulative anthracycline and alkylator exposure compared to ABVD and MOPP/COPP regimens. The dose-dense backbone of ABVE-PC appears to provide better efficacy than standard ABVD, is administered over a shorter time period and delivers lower cumulative doses of anthracycline, thus improving immediate and long-term quality of life. With the substitution of Bv, we anticipate further reduction in treatment burden by avoiding bleomycin and by enhancing rapid response rates, thereby limiting radiation exposure.

In adults, the use of 6-8 cycles of ABVD therapy for early unfavorable or high-stage HL, has reported progression free survival ranges between 68% and 74%.[8-10] There are limited data using ABVD in pediatric patients. In a prior CCG trial where Fryer et. al.[27] administered 12 cycles ABVD to children with advanced-stage HL (n=64), the pulmonary toxicity rate was high at 9%, predominantly occurring before RT was given. The overall survival of this study was 87% at 3 years, sub-optimal by today's standards. P9425 showed an 85% five- year EFS and 95% overall survival for high-risk patients (Stages IIB, IIIB and IV) using ABVE-PC and radiotherapy. On that study, 63% of patients were rapid early responders requiring only 3 cycles (9 weeks) of chemotherapy and IFRT; slow responders received 2 additional cycles of chemotherapy. The higher reported EFS outcomes utilizing the ABVE-PC regimen allow us to set our proposed EFS targets higher in pediatric advanced-stage HL, as the long-term toxicities of salvage regimens remain a significant concern in children, adolescents and young adults. A theme of the dose- intensive regimens is that dose density improves disease control, minimizing the potential need for salvage therapies associated with significant late sequelae of treatment. Tables 2 and 3 (below)

compare the dose density of the chemotherapy agents in each regimen, and the cumulative doses of agents for some relevant regimens used to treat high-stage HL.

Table 2. Comparison of dose density of selected regimens (mg or IU/m^2/week)

	ABVD	Bv-AVD	ABVE-PC*	Bv-AVEPC	OEPA	COPDac	OEPA x2 COPDac x4	Esc-BEACOPP
Doxorubicin	12.5	12.5	16.67	16.67	20		6.67	11.67
Bleomycin	5	-	5					3.3
Vincristine	-	-	0.93	0.47	1.125	0.75	.875	0.46
Etoposide	-	-	125	125	156		52	200
Cyclophosphamide	-	-	400	400		250	167	400
Prednisone	-	-	93	93	210	140	163	187
Procarbazine	-	-	-					233
Vinblastine	3	3	-					-
DTIC	188	188				188	125	
Brentuximab vedotin		0.6		0.6				

* As used in this current proposed trial and AHOD0831. AHOD0031 and P9425 provided 267 mg/m^2/wk of weekly cyclophosphamide. P9425 provided 20 mg/m^2 of weekly doxorubicin.

Table 3. Comparison of cumulative dose exposure of selected regimens (mg or U/m^2)

	ABVD x 6	Bv-AVD x 6	ABVE-PC* x 5	Bv-AVEPC x5	OEPA x2 COPDac x 4	Esc-BEACOPP x 6
Doxorubicin	300	300	250	250	160	210
Bleomycin	120	-	75	-		60
Vincristine	-	-	15	7.5	21	12
Etoposide	-	-	1875	1875	1250	3600
Cyclophosphamide	-	-	6000	6000	4000	7200
Prednisone	-	-	1400	1400	3922	3360
Procarbazine	-	-	-	-		4200
Vinblastine	72	72	-	-		-
DTIC	4500	4500			3000	
Brentuximab vedotin		14.4		9		

* As used on in this current proposed trial and AHOD0831. AHOD0031 provided 3200 mg/m^2 of cyclophosphamide. P9425 provided 180-300 mg/m^2 of doxorubicin depending on the number of cycles administered.

In summary, we propose that ABVE-PC is the North American standard for dose-dense chemotherapy in pediatric HL, and is the most rational backbone upon which to base the addition of a new targeted agent.

2.5 **Correlative studies** (detailed in Appendices V, VI, VII, and VIII)

2.5.1 Imaging Modalities in HL

FDG-PET will be the key clinical determinant of early response in this study. However CT tumor volume at baseline and the change in tumor burden (represented by CT tumor volume between the baseline and post-cycle 2 imaging) will be explored for potential prognostic significance (see Appendix V).

2.5.2 Biology Studies in HL

Despite the enhanced understanding of the biology of HL, few studies have incorporated molecular markers or EBV biology into initial-risk classification or response modification. Studies of immune function in HL patient following chemotherapy and during follow-up will enhance understanding of host response and tumor microenvironment. Further information about the correlative biology studies can be found in Appendix VI.

2.5.3 CIPN, Health Related Quality of Life, and Cost Effectiveness Analysis in HL

Despite the use of vinca alkaloids in many HL regimens, the incidence, prevalence and trajectory of peripheral neuropathy has not been studied in this population. Neuropathy is a recognized side effect of Bv containing regimens in adult lymphoma patients. Chemotherapy induced peripheral neuropathy (CIPN) involves three principal manifestations: sensory; motor; and autonomic. Manifestations vary by drug class, and cumulative exposure. The combination of Bv and vincristine in the experimental arm of the current study warrants evaluation of the incidence and pattern of peripheral neuropathy in children, adolescents and young adults with HL. The possible impact of peripheral neuropathy on quality of life is also an increasing area of attention warranted in HL populations especially given the long life expectancy (see Appendix VII).

Patient report of HRQL will also be useful is establishing quality adjusted life years in comparing and analyzing the cost effectiveness of the Bv containing regimen to the standard regimen in this population with high risk disease (see Appendix VIII).

Note: *the CEA and CIPN sub-studies reached accrual and were closed to further patient entry as of September 8, 2017.* ***Subjects already enrolled on these studies should continue to submit all required measures through Time Point #6 as indicated in Appendix VII and Appendix VIII.***

2.5.4 Radiation Dosimetry

A key step toward reduced toxicity and late effects risk in HL is a reduction of radiation use and normal tissue volume exposure while controlling disease. The use of involved site RT (ISRT) with contemporary radiation approaches holds this promise. In fact the European H10 trial for adults and the Euronet PHL-C2 trial in children employ involved node RT (INRT) following chemotherapy. Involved site RT (ISRT) refers to treatment conceptually similar to INRT, but has modifications allowing for uncertainty of the exact margins of the involved nodes to be targeted in the clinical target volume. With the contemporary capacity for CT planning ISRT is thought to be the best modality in a multi-site trial approach. The goal is to accurately target diseased nodes, while minimizing normal tissue volume exposure.[28,29] We will capture dosimetry to key organs which have proven to be

the source of late morbidity after successful HL therapy. Dose volume histograms shall be collected for the following organs at risk: female breast, heart, lungs, thyroid, liver, and kidney.

2.5.5 CHIPS

Prospective evaluation and validation of a new prognostic score, CHIPS, among children and adolescents with Ann Arbor Stage IIB bulk, IIIB and IV cHL is planned. The CHIPS is a new childhood HL prognostic scoring system which emerged from multivariable predictive modeling of presenting clinical characteristics on the recently completed intermediate risk AHOD0031 trial.[30] The four clinical features most predictive of EFS were:

1. Stage IV disease;
2. Large mediastinal mass (> 1/3 thoracic diameter);
3. Fever (T ≥ 38ºC); and
4. Low albumin (< 3.5 g/dL).

One point is assigned for each adverse presenting feature. The distribution of CHIPS for AHOD0031 patients was: score 0: 36%, score 1: 39.4%, score 2: 19.5%, and score 3: 5.1%. There were no CHIPS 4 patients on AHOD0031 because patients with Stage IV disease and fever would not have been eligible for the study. In data from AHOD0031, CHIPS clearly discriminates groups beyond classical Ann Arbor Staging criteria. Distinct differences in 3-year EFS were noted by CHIPS: 0, 93%; 1, 86%; 2, 77%; 3, 71%[30]. Our proposed study is therefore a prospective collection and validation of CHIPS in this high-risk population; in combination with data from AHOD0031, we will define more precise risk groups for future reduction or escalation of therapy. Given the absence of a standard or consensus for defining risk groups in cHL, we anticipate that validation of CHIPS in participants ≤ 21 years of age could introduce a powerful stratification tool for future trials to incorporate.

2.5.6 Pharmacokinetics (PK) of Brentuximab Vedotin

The safety and efficacy of brentuximab vedotin has been evaluated in adults with relapsed classical HL or systemic ALCL, and the maximum tolerated dose (MTD) determined to be 1.8 mg/kg (max dose of 1800 mg) every 3 weeks.[31] Although less commonly used, weekly dosing was studied in an adult phase I dose escalation trial that determined the maximum tolerated weekly dose to be 1.2 mg/kg.[32] The pharmacokinetic analysis to date is derived from data from five phase 1 and 2 studies that included adult patients. These combined data demonstrate the linear pharmacokinetics of the antibody drug conjugate (ADC) and monomethymuriamine (MMAE). In addition, MMAE exposures appear to be lower than ADC exposure, and body weight seems to be a significant covariate.[33] We currently have very limited PK data for brentuximab vedotin in pediatric patients, and current dosing has been extrapolated from adult studies. Brentuximab vedotin is currently dosed at 1.8 mg/kg on Day 1 of every 21-day cycle of AHOD1331.

Flerlage et al. recently demonstrated a strong relationship between patient weight and clearance of ADC and MMAE, in a sampling (n=16) of their phase II trial (St. Jude's Research Hospital HLHR13) in pediatric patients with advanced HL.[34] The inclusion of weight significantly explained 75, 84, 61, and 94% of the inter-

individual variability in the ADC clearance, ADC volume, MMAE clearance, and MMAE apparent volume, respectively. Overall, the ADC AUC and Cmax in their pediatric study were lower than those reported in adult studies (25 and 11%, respectively, at dose of 1.2 mg/kg and 35 and 16%, respectively, at dose of 1.8 mg/kg). Flerlage et al. also noted ADC clearance and volume differed by sex, with clearance and volume estimated 17% higher ($p = 0.08$ and $p = 0.03$, respectively) in boys compared to girls.[34] However, the range of exposures for these patients have previously been demonstrated to be active (i.e., were associated with partial or complete responses) in adult patients as monotherapy in initial phase 1 studies, thus it is likely that in a multi-agent regimen, these exposures would be expected to be efficacious.

We propose that enrolling subjects under age 13 (i.e., 12 years 11 months and younger) should be sufficient to capture PK data in lower weight pediatric subjects to inform the PK modeling results. In summary, addition of this aim to AHOD1331 with Amendment #2B will provide additional needed pediatric date for the every 21 day dosing and evaluate the PK of brentuximab vedotin in combination with the AVE-PC backbone of chemotherapy.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the Patient Registry module in OPEN once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In order for an institution to maintain COG membership requirements, every patient with a known or suspected neoplasm needs to be offered participation in APEC14B1, *Project:EveryChild A Registry, Eligibility Screening, Biology and Outcome Study*.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

Please see Appendix IX for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures including: how to download site registration documents; requirements for site registration, submission of regulatory documents and how to check your site's registration status.

3.1.2 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 participating roster at the registering site.

For information about the submission of IRB/REB approval documents and other regulatory documents as well as checking the status of study center registration packets, please see Appendix IX.

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' web site by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. 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. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.1.3 Study Enrollment

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 https://ctepcore.nci.nih.gov/iam) and a 'Registrar' role on either the lead

protocol organization (LPO) or participating organization roster. Registrars must hold a minimum of an AP registration type. If a DTL is required for the study, the registrar(s) must also be assigned the OPEN Registrar task on the DTL.

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 and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. 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. If a DTL is required for the study, the IVR or NPIVR must also be assigned the appropriate OPEN-related tasks on the DTL.

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 CTSU members' web site OPEN tab or within the OPEN URL (https://open.ctsu.org). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

3.1.4 Timing

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than five (5) calendar days after the date of study enrollment. All clinical and laboratory studies to determine eligibility must be performed within 14 days prior to enrollment unless otherwise indicated in the eligibility section below.

3.1.5 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this study.

3.1.6 Randomization

Randomization will take place at the time a patient is enrolled via OPEN. The patient will be randomly assigned 1:1 to Bv-AVEPC arm or ABVE-PC arm. Randomization will be stratified by clinical characteristics (Stage IIB with bulk vs. Stage IIIB vs. Stage IVA vs. Stage IVB).

3.2 Patient Eligibility Criteria

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record that will serve as the source document for verification at the time of audit.

All clinical and laboratory studies to determine eligibility must be performed within 14 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than fourteen (14) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within fourteen (14) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 14 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT), albumin and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.

Imaging studies and bone marrow evaluations must be obtained within 21 days prior to start of protocol therapy. Repeat the tumor imaging if necessary (see Section 14.3). Histologic core bone marrow biopsy is required in children < 18 years of age regardless of FDG-PET results. Exceptions to the bone marrow requirement in cases of patients with airway compromise, can be applied if adequate documentation of contraindication to the procedure is noted. However, bone marrow can be obtained after the initiation of emergency steroid therapy in such cases as per Section 4.2 and Section 4.3.

See Section 7.1 for required studies to be obtained prior to starting protocol therapy.

INCLUSION CRITERIA

3.2.1 Age

Ages ≥ 2 - < 22 years at the time of enrollment.

3.2.2 Diagnosis

Patients with newly diagnosed, pathologically confirmed cHL meeting one of the following Ann Arbor stages are eligible:

- Stage IIB with bulk*
- Stage IIIB
- Stage IVA
- Stage IVB

* *Bulk is defined in Appendix I.* **If study eligibility by staging is uncertain, consultation with IROC RI may be obtained prior to study enrollment.**

3.2.3 Organ Function Requirements

3.2.3.1 Adequate Renal Function Defined As:

- Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2 or
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	**Female**
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating[35] utilizing child length and stature data published by the CDC.

3.2.3.2 Adequate Liver Function Defined As:

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
- SGOT (AST) or SGPT (ALT) < 2.5 x upper limit of normal (ULN) for age.

3.2.3.3 Adequate Cardiac Function Defined As:

- Shortening fraction of ≥ 27% by echocardiogram, or
- Ejection fraction of ≥ 50% by radionuclide angiogram.

3.2.3.4 Adequate Pulmonary Function Defined As:

- FEV_1/FVC > 60% by pulmonary function test (PFT), unless due to large mediastinal mass from HL.
- For children who are unable to cooperate for PFTs, the criteria are: no evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry reading of > 92% on room air.

3.2.4 Exclusion Criteria

3.2.4.1 Patients with nodular lymphocyte-predominant HL.

3.2.4.2 Patients with an immunodeficiency that existed prior to diagnosis, such as primary immunodeficiency syndromes, organ transplant recipients and children on current systemic immunosuppressive agents are not eligible.

3.2.4.3 Patients who are pregnant. (Since fetal toxicities and teratogenic effects have been noted for several of the study drugs, a negative pregnancy test is required for female patients of childbearing potential).

3.2.4.4 Lactating females who plan to breastfeed.

3.2.4.5 Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation and for 30 days after the last dose of chemotherapy.

3.2.4.6 Patients known to be positive for HIV are not eligible.

3.2.4.7 Patients who have received any previous chemotherapy or radiation therapy are not eligible.

3.2.4.8 Patients who received systemic corticosteroids within 28 days of enrollment on this protocol, except as specified (See Section 4.2), are not eligible.

Note: Please see Section 4.1.1 for the concomitant therapy restrictions for patients during treatment.

3.2.5 Regulatory Requirements

3.2.5.1 All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.5.2 All institutional, FDA, and NCI requirements for human studies must be met.

4.0 TREATMENT PLAN

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

Therapy will consist of **five** cycles of ABVE-PC or Bv-AVEPC. Each cycle is 21 days. After Cycle 2 (approximately Days 18-22), FDG-PET will be done to determine response. Upon central review, individual lesions will be defined as rapidly responding lesions (RRL) if the Cycle 2 FDG-PET is negative, defined as Deauville score less than or equal to 3 (less than or equal to that of liver). See Table 10.3.1

Individual lesions/nodal sites will be defined as slow responding lesion (SRL) if the FDG-PET after 2 cycles of therapy is positive, defined as Deauville score of 4 or 5 (greater than liver). See Table 10.3.1

Baseline studies should be submitted for central review to IROC Rhode Island (previously QARC) at the time of enrollment. Eligibility criteria (including definitions of bulk and LMA) will be reviewed and confirmed at the time of response assessment after Cycle 2. **Timely submission of studies to IROC Rhode Island is required to avoid unnecessary delays in therapy (see Section 14). Cycle 3 of chemotherapy may commence before results of central review are available, but central review is required prior to initiation of the RT plan following Cycle 5**. Following completion of 5 cycles of chemotherapy, patients will receive response-adapted ISRT (2100 cGy) targeting regions of LMA and SRL. All radiotherapy treatment plans must be submitted to IROC Rhode Island for review and approval prior to the start of radiotherapy (see Section 15).

NOTE: For patients with involvement of the spleen, vaccination against pneumococcus, *Haemophilus influenza* and meningococcus is strongly recommended **prior** to therapy. If not performed at this time, it should be administered prior to beginning radiation therapy.

Patients with progressive or recurrent disease at any time point (see Section 10.3) will go off protocol therapy and treated at the discretion of the treating physician. Patients will remain on study until they meet one of the off study criteria (see Section 8).

4.1.1 Concomitant therapy

4.1.1.1 No other cancer chemotherapy or immunomodulating agents will be used routinely.

a. Corticosteroid therapy is only permissible for anaphylactic reactions, adrenal insufficiency, and severe asthma or as a breakthrough anti-emetic.

4.1.1.2 Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. See COG Supportive Care Guidelines: https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines.

4.1.1.3 Concomitant use of strong cytochrome 3A4 inhibitors or inducers, or P-gp inhibitors (see Appendix III), has the potential to affect the exposure to monomethyl auristan E (MMAE). Moderate or strong CYP3A4 inhibitors or P-gp inhibitors are not permitted in this trial. Specifically, oral **aprepitant** and IV **fosaprepitant** are weak to moderate CYP3A4 inhibitors and substrates. Therefore, we recommend caution for the use of these agents in patients receiving Brentuximab vedotin. Refer to agent-specific drug information for additional details. The use of a single 2 mg/kg (maximum 80 mg) dose of oral aprepitant does not appear to cause clinically significant CYP3A4 inhibition and is permitted on Day 1 of each treatment cycle if a patient fails first line anti-emetic prophylaxis regimens. Use of aprepitant or fosaprepitant on either study arm should be documented on the study Case Report Forms (CRFs) where indicated.

4.1.1.4 Concomitant use of dexrazoxane with the ABVE-PC backbone should be considered with caution, due to concerns of increased risk of myelosuppression and associated adverse events including typhlitis.[25] Use of dexrazoxane should be at investigator discretion and noted on the study CRFs where indicated.

4.2 Standard Therapy ABVE-PC

NOTES:

- All doses will be based on actual body surface area or weight (where applicable). Only brentuximab vedotin, vincristine and colony stimulating factor doses will be capped (refer to details below).
- For patients with involvement of the spleen, vaccination against pneumococcus, *Haemophilus influenza* and meningococcus is strongly recommended prior to therapy. If not performed at this time, it should be administered prior to beginning radiation therapy. Waiting to immunize until after Cycle 5 may be affected by muted immune response at that time.

Standard therapy consists of 5 cycles of ABVE-PC. Each cycle is 21 days in duration. The administration schedule below describes 1 cycle of ABVE-PC and should be repeated for each cycle. Steroids as antiemetics are permitted per institutional guidelines. However, the use of aprepitant, fosaprepitant, or netupitant/palonosetron in the anti-emetic regimen should be approached with caution and needs to be documented on the CRFs on either study arm. (See Section 4.1.1.3 for additional information.)

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://www.cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

DOXOrubicin: Slow IV push or intermittent infusion
Days 1 and 2.
Dose: 25 mg/m^2/dose.
Administer at a concentration not to exceed 2 mg/mL by slow IV push over 1-5 minutes or by intermittent infusion over 1-15 minutes; may prolong to 60 minutes if institutional policies mandate. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl and that it is infused into a large vein.

See the special precautions in Section 6.4.4.

Bleomycin: IV or subcutaneous
Note: the dose is different on each day of administration.
Day 1: **5** Units/m^2/dose.
Day 8: **10** Units/m^2/dose.

IV: Infuse over a minimum of 10 minutes (no greater than 1 unit/minute) and at a concentration not to exceed 3 units/mL.
Subcutaneous: A concentration of 3-15 units/mL can be used for subcutaneous administration. Aspirate prior to injection to avoid injection into a blood vessel.

See the special precautions in Section 6.2.4

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days 1 and 8.
Dose: 1.4 mg/m^2/dose **(maximum dose 2.8 mg)**.

See the special precautions in Section 6.9.4

Etoposide: IV over at least 60-120 minutes
Days 1-3.
Dose: 125 mg/m^2/dose.
Infuse diluted solution (concentration ≤ 0.4 mg/mL); slow rate of administration if hypotension occurs. Rate should not exceed 300 mg/m^2/hour (10 mg/kg/hour) (hypotension risk). The use of an in-line filter during the infusion is suggested.

See the special precautions in Section 6.5.4

Prednisone: PO (may be given IV as methylprednisolone)
Days 1-7.
Dose: 20 mg/m²/dose PO BID. (Total daily dose is 40 mg/m²/day PO, divided BID). May round up to nearest 2.5 mg tablet. If patient is unable to take prednisone by mouth, methylprednisolone may be given IV at 80% of the dose.

CYCLE 1 only: Patients who present with need for emergent treatment for respiratory distress or spinal cord compression may receive prednisone or dexamethasone for up to 4 days immediately prior to completion of diagnostic work-up and before other chemotherapy agents are given. In these cases, a chest X-ray and if possible, a CT scan of the neck, chest, abdomen and pelvis must have been performed and if feasible, a biological specimen obtained for definitive diagnosis prior to the administration of prednisone. The remainder of the diagnostic work-up should proceed as quickly as tolerated. If oral corticosteroids cannot be tolerated, methylprednisolone may be substituted at equipotent prednisone doses. The cumulative equipotent dose of glucocorticoids administered for emergent respiratory distress or spinal cord compression should be considered part of the total 280 mg/m² for this cycle. If methylprednisolone or dexamethasone was used, the dose should be converted to prednisone-equivalent dose and this should be considered part of the total prednisone dose noted above.

Cyclophosphamide: IV over 30-60 minutes
Days 1 and 2.
Dose: 600 mg/m^2/dose.
May be administered as undiluted drug (20 mg/mL, reconstitute with 0.9% NaCl only to avoid hypotonic solution) or further diluted.
Hydrate according to institutional guidelines.
Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion or with hematuria (see Section 5.2.3).

Granulocyte Colony-Stimulating Factor (GCSF)
Patients should receive either Filgrastim or Pegfilgrastim as outlined below:

Filgrastim: subcutaneous preferred (may be given IV)
Dose: 5 micrograms/kg/dose daily, beginning Day 4, 5, 6, 7, 8, or Day 9 inclusive, per institutional policy, and continuing until ANC > 1000 µL post nadir. Every attempt should be made to keep cycles on a 21-day schedule, and therefore stop GCSF by Day 20.

Note: Biosimilar forms of recombinant filgrastim (tbo-filgrastim or filgrastim-sndz) are permitted at institutional discretion.

Pegfilgrastim is permitted: Dose: 100 microgram/kg x 1 dose (max 6 mg) on Day 4, 5, or 6.

See Section 5.0 for Dose Modifications based on toxicities.

The therapy delivery map (TDM) for standard therapy is on the next page.
Following completion of Cycle 1, Cycle 2 starts on Day 22 or when ANC ≥ 750/µL (with patients off filgrastim for at least 2 days or 14 days post pegfilgrastim) and platelets are ≥ 75,000/µL (whichever occurs later).

Following the completion of Cycle 2, patients must be assessed to evaluate for response (see Section 10.3). All initial eligibility criteria, including definitions of bulk and LMA, will be centrally confirmed at this time. THIS RESPONSE EVALUATION REQUIRES CENTRAL REVIEW. Cycle 3 of chemotherapy may commence on time, and should not be delayed for the central review result. If an enrolled patient is found to not meet study eligibility staging criteria at the time of central review for early response assessment (after 2 cycles of chemotherapy) the treating institution will be informed and the patient will be deemed to be ineligible.

Central review of response and LMA is necessary prior to submission and initiation of the radiation therapy plan. Any radiation therapy delivered not consistent with the central review response and LMA categorization will be considered a major protocol violation.

Following the response assessment at the completion of Cycle 2, therapy starts on Day 22 or when ANC ≥ 750/µL (with patients off filgrastim for at least 2 days or 14 days post pegfilgrastim) and platelets are ≥ 75,000/µL (whichever occurs later). All subjects receive 3 additional cycles of ABVE-PC, unless they have progressive disease or other criteria for coming off protocol therapy (see Section 8.1).

Those subjects without initial LMA (see Appendix I) and without any SRL (see Table 10.3.1) of disease complete therapy after 3 additional cycles of chemotherapy. Patients with initial LMA or any SRL will receive RT (see Section 15) after chemotherapy. Patients with progressive disease (see Section 10.3) will go off protocol therapy and will be treated at their physician's discretion. Retrieval chemotherapy and stem cell transplantation using applicable COG clinical trials should be considered.

4.2.1 **Therapy for Patients Randomized to Standard Treatment of ABVE-PC**

There are five cycles of ABVE-PC. Each cycle lasts 21 days. One cycle is described on this therapy delivery map. This TDM is on 1 page. Use a copy of this page for each cycle.

Patient's COG ID# _____ DOB _____

Criteria to start each cycle after the initial cycle of therapy: ANC ≥ 750/µL (with patient off filgrastim for at least 2 days) and platelets are ≥ 75,000/µL (whichever occurs later).

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
DOXOrubicin (DOXO)	Slow IV push over 1-5 min **or** intermittent infusion over 1-15 min	25 mg/m^2/dose	1 and 2	See Section 4.2 for further details.
Bleomycin (BLEO)	IV over at least 10 min **or** SubQ	5 Units/m^2/dose	1	See Section 4.2 for further details.
		10 Units/m^2/dose	8	
VinCRIStine (VCR)	IV Push over 1 min (Or infusion via minibag as per institutional policy).	1.4 mg/m^2/dose **Maximum dose: 2.8 mg.**	1 and 8	See Section 4.2 for further details.
Etoposide (ETOP)	IV over at least 60-120 min	125 mg/m^2/dose	1-3	Slow rate of administration if hypotension occurs. See Section 4.2 for further details.
Prednisone (PRED)	PO	20 mg/m^2/dose BID	1-7	Total Daily Dose: 40 mg/m^2/day, divided BID. IV methylprednisolone may be substituted for oral prednisone at 80% of the dose. **See text specific to Cycle 1 in Section 4.2**
Cyclophosphamide (CPM)	IV over 30-60 min	600 mg/m^2/dose	1 and 2	See Section 4.2 for further details.
Filgrastim or biosimilar (G-CSF)	SubQ preferred (may be given IV)	5 mcg/kg/dose	Daily, begin Day 4,5,6,7,8 or 9, per institutional policy.	Continue until ANC > 1,000/µL post nadir. Pegfilgrastim is permitted (100 mcg/kg SubQ (max 6 mg) x 1 dose on Day 4, 5 or 6).

OBSERVATIONS

a. **Prior to every cycle:** History & physical (document all involved lymph nodes), CBC/Diff, Electrolytes, BUN, Creatinine, AST or ALT, Bili.
b. **Prior to Cycle 3 only**: Bilateral bone marrow biopsy (only if + at diagnosis, *any age*), CT with IV contrast, and FDG-PET[%].
c. **Prior to Cycle 4 only**: ECHO (or MUGA), PFTs, and DLCO if > 5 yrs.
d. **After Cycle 5 or prior to RT:** History & physical (document nodal exam), CBC/Diff, Electrolytes, BUN, Creatinine, AST or ALT, Bili, Biopsy, Bilateral bone marrow biopsy (only if + after Cycle 2, *any age*), CT with IV contrast, and FDG-PET[#].
e. **Day 8, Cycles 2 and 5:** CIPN/CEA assessments *(only if enrolled before CIPN/CEA closed to accrual)*.

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE. (See Section 7.1)

See Section 7.2 Biology Studies Submission Schedule.

If no RT, Cycle 5 reporting period ends 4-6 weeks post last therapy dose, after scans *(and CEA/CIPN if applicable)*. *If RT*, Cycle 5 reporting period ends on Day 1 of RT.

Enter Cycle #: ____ **Ht** _____ **cm** **Wt** _____ **kg** **BSA** _____ **m^2**

Date Due	Date Given	Day	DOXO _____ mg	BLEO _____ Units	VCR _____ mg	ETOP _____ mg	PRED (BID dosing) _____ mg _____ mg	CPM _____ mg	G-CSF _____ mcg	Studies	Comment
			Enter calculated dose above and actual dose administered below							(See Section 7.1)	
		1	_____ mg	_____ Units	_____ mg	_____ mg	_____ mg _____ mg	_____ mg		a, b[%], and c	
		2	_____ mg			_____ mg	_____ mg _____ mg	_____ mg			
		3				_____ mg	_____ mg _____ mg				
		4					_____ mg _____ mg		_____ mcg		
		5					_____ mg _____ mg		_____ mcg		
		6					_____ mg _____ mg		_____ mcg		
		7					_____ mg _____ mg		_____ mcg		
		8		_____ Units	_____ mg				_____ mcg	e (Cycle 2 and 5)	
		9							_____ mcg^		
		15							↓		
		…									
		21	Response is assessed at end of Cycle 2. Cycle 3 should commence on time, and should not be delayed for the central review response. The next cycle starts on Day 22 or when ANC ≥ 750/µL (with patient off filgrastim for at least 2 days) and platelets are ≥ 75,000/µL (whichever occurs later).							d[#]	

^ Continue G-CSF until ANC > 1,000/µL post nadir. First day of G-CSF: ____/____/____ Last day of G-CSF: ____/____/____ Circle Filgrastim or Pegfilgrastim or Tbo-Filgrastim or Filgrastim-sndz

[%] Between Days 18-22 of Cycle 2. [#]Perform PET5 only if PET2 was Deauville ≥4. **SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE COG MEMBER WEB SITE FOR SUPPORTIVE CARE.**

4.3 Experimental Therapy Bv-AVEPC

NOTE: For patients with involvement of the spleen, vaccination against pneumococcus, *Haemophilus influenza* and meningococcus is strongly recommended **prior** to therapy. If not performed at this time, it should be administered prior to beginning radiation therapy. Waiting to immunize until after Cycle 5 may be affected by muted immune response at that time.

Experimental therapy consists of 5 cycles of Bv-AVEPC. Each cycle is 21 days in duration. Each cycle commences on Day 1 if the ANC ≥ 750/μL and platelets are ≥ 75,000/μL. The administration schedule below describes 1 cycle of Bv-AVEPC and should be repeated for each cycle. Steroids as antiemetics are permitted per institutional guidelines. However, the use of aprepitant, fosaprepitant, or netupitant/palonosetron in the anti-emetic regimen, while not prohibited, should be approached with caution and needs to be documented on the CRFs on either study arm. (See Section 4.1.1.3 for additional information).

See the Parenteral Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://www.cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

Brentuximab vedotin*: IV over 30 minutes
Day 1 (prior to other chemotherapy)
Dose: 1.8 mg/kg/dose**.** (Maximum dose is 180 mg based on manufacturer prescribing information and 100 kg maximum weight)

Special precautions: Brentuximab should be administered on Day 1 prior to other chemotherapy. Brentuximab vedotin should be administered over approximately 30 minutes and cannot be mixed with other medications. **In-line filters should not be used during the IV administration.**

***Brentuximab vedotin is supplied by the NCI and should not be dispensed from regular (commercial) pharmacy supply.**

Dosing is based on patient weight according to the institutional standard. Actual weight will be used except for patients weighing greater than 100 kg. The dose for patients with weight greater than 100 kg will be calculated based on 100 kg.

Refer to Section 6.1 for additional details regarding dilution and stability.

DOXOrubicin: Slow IV push or intermittent infusion
Days 1 and 2.
Dose: 25 mg/m^2/dose.
Administer at a concentration not to exceed 2 mg/mL by slow IV push over 1-5 minutes or by intermittent infusion over 1-15 minutes, may prolong to 60 minutes if institutional policies mandate. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl and that it is infused into a large vein.

See special precautions in Section 6.4.4.

Etoposide: IV over at least 60-120 minutes
Days 1-3.
Dose: 125 mg/m^2/dose.
Infuse diluted solution (concentration ≤ 0.4 mg/mL); slow rate of administration if hypotension occurs. Rate should not exceed 300 mg/m^2/hour (10 mg/kg/hour) (hypotension risk). The use of an in-line filter during the infusion is suggested.

See special precautions in Section 6.5.4.

Prednisone: PO (may be given IV as methylprednisolone)
Days 1-7.
Dose: 20 mg/m²/dose PO BID. (Total daily dose is 40 mg/m²/day PO, divided BID). May round up to nearest 2.5 mg tablet.
If patient is unable to take prednisone by mouth, methylprednisolone may be given IV at 80% of the dose.

CYCLE 1 only: Patients who present with need for emergent treatment for respiratory distress or spinal cord compression may receive prednisone or dexamethasone for up to 4 days immediately prior to completion of diagnostic work-up and before other chemotherapy agents are given. In these cases, a chest X-ray and if possible, a CT scan of the neck, chest, abdomen and pelvis must have been performed and if feasible, a biological specimen obtained for definitive diagnosis prior to the administration of prednisone. The remainder of the diagnostic work-up should proceed as quickly as tolerated. If oral corticosteroids cannot be tolerated, methylprednisolone may be substituted at equipotent prednisone doses. The cumulative equipotent dose of glucocorticoids administered for emergent respiratory distress or spinal cord compression should be considered part of the total 280 mg/m² for this cycle. If methylprednisolone or dexamethasone was used, the dose should be converted to prednisone-equivalent dose and this should be considered part of the total prednisone dose noted above.

Cyclophosphamide: IV over 30-60 minutes
Days 1 and 2.
Dose: 600 mg/m^2/dose.
May be administered as undiluted drug (20 mg/mL, reconstitute with 0.9% NaCl only to avoid hypotonic solution) or further diluted.
Hydrate according to institutional guidelines.
Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion or with hematuria (see Section 5.2.3).

VinCRIStine: IV push *over 1 minute or infusion via minibag as per institutional policy*
Day 8 (ONLY)
Dose: 1.4 mg/m^2/dose **(maximum dose 2.8 mg)**.

See special precautions in Section 6.9.4.

Granulocyte Colony-Stimulating Factor (GCSF)
Patients should receive either Filgrastim or Pegfilgrastim as outlined below:

Filgrastim: subcutaneous preferred (may be given IV)
Dose: 5 micrograms/kg/dose daily, beginning Day 4, 5, 6, 7, 8 or Day 9, inclusive, per institutional policy, and continuing until ANC > 1000 µL post nadir. Every attempt should be made to keep cycles on a 2-day schedule, and therefore stop GCSF by day 20.

Note: Biosimilar forms of recombinant filgrastim (tbo-filgrastim or filgrastim-sndz) are permitted per institutional policy.

Pegfilgrastim is permitted: Dose: 100 microgram/kg x 1 dose (max 6 mg) on Day 4, 5 or 6.

See Section 5.0 for Dose Modifications based on toxicities.

The therapy delivery map (TDM) is on the next page. Following completion of Cycle 1, Cycle 2 starts on Day 22 or when ANC ≥ 750/µL (with patients off filgrastim for at least 2 days or 14 days post pegfilgrastim) and platelets are ≥ 75,000/µL (whichever occurs later).

Following completion of Cycle 2, patients must be assessed to evaluate for response (see Section 10.3). All initial eligibility criteria, including definitions of bulk and LMA, will be centrally confirmed at this time. THIS RESPONSE EVALUATION REQUIRES CENTRAL REVIEW. Cycle 3 of chemotherapy may commence on time, and should not be delayed for the central review results of assessment. If an enrolled patient is found to not meet study eligibility staging criteria at the time of central review for early response assessment (after 2 cycles of chemotherapy) the treating institution will be informed and the patient will be deemed to be ineligible.

Central Review of response and LMA is necessary prior to submission and initiation of the radiation therapy plan. Any radiation therapy delivered not consistent with the central review response and LMA categorization will be considered a major protocol violation.

Following the response assessment at completion of Cycle 2, therapy starts on Day 22 or when ANC ≥ 750/µL (with patients off filgrastim for at least 2 days or 14 days post pegfilgrastim) and platelets are ≥ 75,000/µL (whichever occurs later). All subjects receive 3 additional cycles of Bv-AVEPC, unless they have progressive disease or other criteria for coming off protocol therapy (see Section 8.1).

Those subjects without initial LMA (see Appendix I) and without any SRL (see Table 10.3.1) of disease complete therapy after 3 additional cycles of chemotherapy. Patients with initial LMA or any SRL will receive RT (see Section 15) after chemotherapy. Patients with progressive disease (see Section 10.3) will go off protocol therapy and will be treated at their physician's discretion. Retrieval chemotherapy and stem cell transplantation using applicable COG clinical trials should be considered.

4.3.1 **Therapy for Patients Randomized to Experimental Treatment of Bv-AVE-PC**

There are five cycles of Bv-AVEPC. Each cycle lasts 21 days. One cycle is described on this therapy delivery map. This TDM is on 1 page. Use a copy of this page for each cycle.

_____ _____

Patient's COG ID# DOB

Criteria to start each cycle: ANC ≥ 750/μL (with patient off filgrastim for at least 2 days) and platelets are ≥ 75,000/μL (whichever occurs later). No count criteria for cycle 1 only.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Brentuximab vedotin (BREN) Provided by NCI	IV over 30 minutes	1.8 mg/kg/dose (Max dose 180 mg)	1	Give prior to other chemotherapy. Do NOT give as IV push. Do not use an in-line filter. **Do not use commercial supply**
DOXOrubicin (DOXO)	Slow IV push over 1-5 min **or** intermittent infusion over 1-15 min	25 mg/m^2/dose	1 and 2	
Etoposide (ETOP)	IV over at least 60-120 min	125 mg/m^2/dose	1-3	Slow rate of administration if hypotension occurs. See Section 4.3 for further details.
Prednisone (PRED)	PO	20 mg/m^2/dose BID	1-7	Total Daily Dose: 40 mg/m^2/day, divided BID. IV methylprednisolone may be substituted for oral prednisone at 80% of the dose. **See text specific to Cycle 1 in Section 4.3.**
Cyclophosphamide (CPM)	IV over 30-60 min	600 mg/m^2/dose	1 and 2	See Section 4.3for further details.
Filgrastim or biosimilar (G-CSF)	SubQ preferred (may be given IV)	5 mcg/kg/dose	Daily, begin on Day 4,5,6,7,8, or Day 9, per institutional policy.	Continue until ANC > 1,000/μL post nadir. Pegfilgrastim is permitted (100 mcg/kg SubQ (max 6 mg) x 1 dose on Day 4, 5 or 6).
VinCRIStine (VCR)	IV Push over 1 min (or infusion via minibag as per institutional policy).	1.4 mg/m^2/dose **Maximum dose: 2.8 mg.**	8 (only)	See Section 4.3 for further details.

OBSERVATIONS

a. **Prior to every cycle:** History & physical (document all lymph nodes), CBC/Diff, Electrolytes, BUN, Creatinine, AST or ALT, Bili.
b. **Prior to Cycle 3 only**: Bilateral bone marrow biopsy (only if + after diagnosis, *any age*), CT with IV contrast and FDG-PET[%].
c. **Prior to Cycle 4 only**: ECHO or MUGA, PFTs, and DLCO if > 5 yrs
d. **After Cycle 5 or prior to RT:** History & physical (document nodal exam), CBC/Diff, Electrolytes, BUN, Creatinine, AST or ALT, Bili, Biopsy, Bilateral bone marrow biopsy (only if + after Cycle 2, *any age*), CT with IV contrast, and FDG-PET[#].
e. **Day 8, Cycles 2 and 5:** CIPN/CEA assessments *(only if enrolled before CIPN/CEA aim closed to accrual)*.

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE. (See Section 7.1)

Specimen Submission Schedules: See Section 7.2 for Biology Studies; See Section 7.4 for PK Studies as relates to Cycles 4 & 5.

If no RT, Cycle 5 reporting period ends 4-6 weeks post last therapy dose after scans (*and CEA/CIPN if applicable*).
If RT, Cycle 5 reporting period ends on Day 1 of RT.

Enter Cycle #: _____ Ht _____ cm Wt _____ kg BSA _____ m^2

Date Due	Date Given	Day	BREN mg	DOXO mg	ETOP mg	PRED (BID dosing) mg mg	CPM mg	G-CSF^ mcg	VCR mg	Studies (See Section 7.1)	Comment
		Enter calculated dose above and actual dose administered below									
		1	_____ mg	_____ mg	_____ mg	_____ mg _____ mg	_____ mg			a, b[%], and c	
		2		_____ mg	_____ mg	_____ mg _____ mg	_____ mg				
		3			_____ mg	_____ mg _____ mg					
		4				_____ mg _____ mg		_____ mcg			
		5				_____ mg _____ mg		_____ mcg			
		6				_____ mg _____ mg		_____ mcg			
		7				_____ mg _____ mg		_____ mcg			
		8						_____ mcg^	_____ mg	e (Cycle 2 and 5)	
		9						↓			
		15									
		…								d[#]	
		21									
			Response is assessed at end of Cycle 2. Cycle 3 should commence on time, and should not be delayed for the central review response. The next cycle starts on Day 22 or when ANC ≥ 750/μL (with patient off filgrastim for at least 2 days) and platelets are ≥ 75,000/μL (whichever occurs later).								

^ Continue G-CSF until ANC > 1,000/μL post nadir. First day of G-CSF: ____/____/____ Last day of G-CSF: ____/____/____ Circle either Filgrastim or Pegfilgrastim or Tbo-filgrastim or Filgrastim-sndz

[%] Between Days 18-22 of Cycle 2. [#] Perform PET5 only if PET2 was Deauville ≥4. **SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE COG MEMBER WEB SITE FOR SUPPORTIVE CARE**

5.0 DOSE MODIFICATIONS FOR TOXICITIES

5.1 Dose Modifications for Brentuximab Vedotin

Treatment Modification Guidelines for brentuximab vedotin-related Adverse Events are outlined in the tables below.

Dose Level	Dose
Starting Dose	1.8 mg/kg (max dose 180 mg)
Dose Reduction for Toxicity #1	1.2 mg/kg (max dose 120 mg)
Dose Reduction for Toxicity #2	0.8 mg/kg (max dose 80 mg)

Event	CTCAE v5.0 Grade	Action to be Taken
Allergic reactions, or Acute infusional reactions/ cytokine release syndrome	Grade 1	• Continue at same dose level.
	Grade 2	For first reaction: • Hold the infusion and wait 30 to 60 minutes (depending upon the reaction severity). • Treat reactions with oral diphenhydramine 1 mg/kg (max 50 mg), or follow local institution guidelines. Depending on the reaction severity, dexamethasone 0.2 mg/kg (max 10 mg) or equivalent corticosteroid oral should be used. • Upon resolution of the symptoms, at the physician's discretion, it may be possible to resume treatment by administering an H2 blocker such as ranitidine or famotidine approximately 30 minutes before restarting the infusion. Acetaminophen can also be considered. Resume brentuximab vedotin infusion at half the previously administered rate until completion For subsequent doses: • Utilize diphenhydramine with or without acetaminophen as pre-treatment for all subsequent infusions. • Dosing should be administered over the shortest period that was well tolerated. If Grade 2 infusion reactions recur despite the above measures, either during re-challenge or subsequent treatments: • Take the measures outlined above. • With subsequent dosing, add dexamethasone 0.2 mg/kg (max 10 mg) IV or equivalent to medications above prior to infusion.
	Grade 3	• Stop infusion immediately. • Administer diphenhydramine 1 mg/kg IV (max 50 mg), dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent), bronchodilators for bronchospasms, and other medications as medically indicated. • Once symptoms recover, brentuximab vedotin should not be resumed for that cycle. • Subsequent cycles of brentuximab vedotin may be considered at physicians' discretion, after a discussion and approval by CTEP.

<table>
<tr><th>Event</th><th>CTCAE v5.0 Grade</th><th>Action to be Taken</th></tr>
<tr><td></td><td></td><td>• All subsequent infusions should use the following premedications prior to infusion: acetaminophen, diphenhydramine 1 mg/kg IV (max 50 mg), dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent). In addition, the infusion should be administered at 50% of the previous infusion rate.</td></tr>
<tr><td></td><td>Grade 4</td><td>• Stop infusion immediately.
• Administer diphenhydramine 1 mg/kg (max 50 mg) IV, dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent), and other anaphylaxis medications as indicated.
• Epinephrine or bronchodilators should be administered as indicated.
• Hospital admission for observation may be indicated.
• Permanently discontinue brentuximab vedotin.</td></tr>
<tr><td>Anaphylaxis</td><td>Any Grade</td><td>• If anaphylaxis occurs, immediately and permanently discontinue administration of brentuximab vedotin and administer appropriate medical therapy.</td></tr>
<tr><td>Pancreatitis</td><td>Grade 2</td><td>• Withhold dose until toxicity has returned to baseline, then continue on protocol therapy but should resume at one dose reduction.
• If Grade 2 pancreatitis recurs after one dose reduction, the patient must be removed from protocol therapy.</td></tr>
<tr><td></td><td>Grade 3-4</td><td>• Permanently discontinue brentuximab vedotin.</td></tr>
<tr><td colspan="2">Peripheral Neuropathy</td><td><u>Investigational Arm</u>
The investigational arm of this protocol incorporates two agents with potential peripheral neuropathic toxicity. Dose modifications for peripheral neuropathy are determined by the day of treatment cycle, and are designed to maintain brentuximab vedotin dose intensity as much as possible, at the expense of vincristine dose intensity. The modified Balis scale (see Appendix IV) of peripheral neuropathy is to be used to assign a grade of neuropathy.

<table>
<tr><th>Dose Level</th><th>Dose</th></tr>
<tr><td>Starting Dose</td><td>1.8 mg/kg
(max dose 180 mg)</td></tr>
<tr><td>Dose Reduction
for Toxicity #1</td><td>1.2 mg/kg
(max dose 120 mg)</td></tr>
<tr><td>Dose Reduction
for Toxicity #2</td><td>0.8 mg/kg
(max dose 80 mg)</td></tr>
</table>
</td></tr>
</table>

Event	CTCAE v.5.0 Grade		Action to be Taken
Peripheral Neuropathy ***Grades are per the Modified Balis scale in Appendix IV**	Grade 1*		Continue at same dose level.
	Grade 2*	Day 1	• Continue Brentuximab vedotin at same dose level. Day 8 vincristine of this cycle should be dose reduced to 1 mg/m2 (max 2 mg), or held if already dose reduced on a prior cycle. Increase vincristine to full dose with next cycle if neuropathy improves to ≤ Grade 1.
		Day 8	• Decrease vincristine to 1 mg/m2 (max 2 mg). If neuropathy has improved to ≤ Grade 1 by Day 8 of the next cycle, then resume vincristine at full dose.
	Grade 3*	Day 1	• Treatment should be delayed up to 1 week after all other parameters to proceed are met to see if neuropathy improves to ≤ Grade 2. If neuropathy returns to ≤ Grade 2 then proceed with next cycle and reduce brentuximab vedotin by one dose level (see above). If neuropathy remains Grade 3, then brentuximab vedotin should be held for this cycle and then reduced by one dose level for subsequent treatments assuming neuropathy has returned to ≤ Grade 2. • Day 8 vincristine should be held for this and all subsequent cycles. • Patients who develop Grade 3 neuropathy after 2 dose reductions of brentuximab vedotin, will have brentuximab vedotin discontinued. • If treatment has to be delayed for peripheral neuropathy more than once, then brentuximab vedotin should be held for the remainder of treatment.
		Day 8	• Hold vincristine for this and all subsequent cycles.
	Grade 4*		• Discontinue brentuximab vedotin and vincristine.
Pneumonitis	Grade 1		• Continue at same dose level.
	Grade 2		• If suspected, strongly consider administration of oral or intravenous corticosteroid in single daily or two divided doses. The suggested dose for patients who develop pulmonary toxicity is methylprednisolone 1 mg/kg IV every 12 hours for a minimum of seven days.
	Grade 3-4		• If suspected, strongly consider administration of oral or intravenous corticosteroid in single daily or two divided doses. The suggested dose for patients who develop pulmonary toxicity is methylprednisolone 1 mg/kg IV every 12 hours for a minimum of seven days. • Discontinue brentuximab vedotin.

Event	CTCAE v.5.0 Grade	Action to be Taken
Progressive Multifocal Leukoencephalopathy (PML) **(Grade per "Leukoencephalopathy")**	Any Grade	If PML is suspected, a diagnostic work-up should be performed. The work-up may include, but not limited to, the following: • Neurologic examinations and neurology consultation, as warranted. • Brain MRI. Features suggestive of PML include presence of unifocal or multifocal lesions, mainly of the white matter, that are typically non-enhancing and do not have mass effect. • PCR analysis. JCV DNA, detectable in CSF or in a brain biopsy, is suggestive of PML. Brentuximab vedotin dosing should be held if any grade of PML is suspected. If PML is confirmed, brentuximab vedotin should be permanently discontinued. The study chair and CRA should be notified of any case of PML within 48 hours
Lymphopenia	Grade 1-4	• Continue at same dose level.
Neutropenia	Grade 1-2	• Continue at same dose level.
	Grade 3-4	• Patients who are unable to start a cycle > 35 days after the start of the previous cycle (> 14 day delay) with myeloid growth factor support due to neutropenia with no other dose-limiting toxicity should have brentuximab vedotin reduced by 1 dose level.
Thrombocytopenia	Grade 1-2	• Continue at same dose level.
	Grade 3-4	• Thrombocytopenia is expected on this protocol. Continue at current dose level.
Non-hematologic events (not including electrolyte abnormalities)	Grade 1-2	• Continue at same dose level.
	Grade 3-4	• Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then continue on protocol therapy but should resume at one dose reduction. • If same non-hematological Grade 3-4 toxicity recurs after one dose reduction, brentuximab vedotin should be omitted.
Electrolyte Abnormalities	Grade 1-4	• Continue at same dose level, provided electrolyte toxicity is not medically consequential and has been readily corrected. • If electrolyte abnormality is medically consequential, refer to guidelines above for non-hematologic events.

5.2 Dose Modifications for Commercial Agents

5.2.1 Hematologic Toxicity

Full dose chemotherapy should begin on Day 22 if the ANC ≥ 750/μL (with patient off G-CSF for at least 2 days before a cycle of chemotherapy) and platelets are ≥ 75,000/μL. If a patient has not recovered by Day 22, resume chemotherapy as soon as hematological recovery is documented (ANC ≥ 750/μL, platelets ≥ 75,000μL).

5.2.2 Hepatic Toxicity

If patient has direct bilirubin > 1.5x upper limit of normal (ULN) when chemotherapy is due to be given, hold. Resume chemotherapy when direct bilirubin is < 1.5x ULN.

5.2.3 Hematuria

Microscopic hematuria

For transient microscopic hematuria (no more than 2 abnormal urinalyses on 2 separate days during a cycle of therapy), do not modify the cyclophosphamide dose. Administer with increased hydration (3500 - 4000 mL/m^2/day) using a total daily mesna dose equal to 60% of the daily cyclophosphamide dose.

For persistent microscopic hematuria (more than 2 abnormal urinalyses during a cycle of therapy), do not modify the cyclophosphamide dose. Administer with increased hydration (3500 - 4000 mL/m^2/day) using a total daily mesna dose equal to 100% of the daily cyclophosphamide dose.

Note: Document mesna doses in the comments of the Therapy Delivery Map.

5.2.4 Gross hematuria

All episodes of gross hematuria should be evaluated in conjunction with a pediatric surgical consult. Further testing, such as cystoscopy, urine culture, excretory urogram, and voiding cystogram should be considered based on good clinical judgment.

For transient gross hematuria (only 1 episode, which clears to less than gross hematuria) during or following a cycle of therapy, hold cyclophosphamide until hematuria clears. When hematuria clears, restart at 50% of the previous cyclophosphamide dose. Use hydration of 3500 - 4000 mL/m^2/day and mesna at 100% the cyclophosphamide dose as a continuous infusion over 24 hrs. The cyclophosphamide dose may be escalated back to 100%, if tolerated, and mesna given at 100% as continuous infusion.

For persistent gross hematuria after completion of a cycle of therapy, hold subsequent cyclophosphamide doses until the urine clears to less than gross hematuria. Reinstitute cyclophosphamide at 50% of initial dose, with hydration of 3500 - 4000 mL/m^2/day and the mesna at 100% of the cyclophosphamide dose given as a continuous infusion over 24 hours. If this regimen is tolerated, cyclophosphamide dose may be escalated back to the original (100%) dose and mesna given at 100% as continuous infusion during cyclophosphamide doses.

For persistent or recurrent gross hematuria on the mesna continuous infusion regimen, discontinue cyclophosphamide.

5.2.5 Pulmonary

If DLCO (corrected for anemia) in any diffusion capacity test is < 50% of the initial value or predicted value or if both DLCO and FEV/FVC show rapid parallel decrease, obtain blood gases, discontinue further bleomycin.

In patients unable to cooperate with PFTs, bleomycin should be discontinued if patient is symptomatic (respiratory distress with rest or minimal exertion) or O2 sat < 92%.

5.2.6 Cardiac

Patients will get an echocardiogram (or MUGA) following 3 cycles of chemotherapy. If the fractional shortening is < 28% (or the ejection fraction is < 50%), or the lower limit of institutional normal on 2 successive echocardiograms (or MUGAs) at least a week apart, the doxorubicin in subsequent cycles should be held. If, at any time, the patient develops signs and symptoms of congestive heart failure (e.g., pulmonary or peripheral edema, dyspnea on exertion, poor feeding, increased liver size, deterioration in exercise tolerance or Grade IV cardiac toxicity) or prolongation of QTc, that are not attributable to other causes such as sepsis or renal failure, hold doxorubicin and perform repeat ECG and echocardiogram (or MUGA) prior to next planned cycle.

5.2.7 Peripheral Neurotoxicity

Toxicity grading of neurotoxicity is to be based on the modified Balis scale of peripheral neuropathy (See Appendix IV).

Dose modifications of vincristine dosing in the experimental arm (Bv-AVEPC) arm should be as per Section 5.1, and are notably different than the standard arm (ABVE-PC).

Standard arm only: The modified Balis scale (see Appendix IV) of peripheral neuropathy is to be used to assign a grade of neuropathy. Vincristine should be held or reduced only for incapacitating neurotoxicity (e.g., ≥ Grade 3 by Balis Scale). Vincristine can be resumed when the symptoms have improved to Grade 1 toxicity or completely resolved. If held, the subsequent dose will be given at a 25% dose reduction (maximum dose 2.1 mg). **Neuropathy ≥ Grade 2 needs to be reported even if no dose modification is made on the standard arm (See Section 11.5.4 and 11.12).**

5.2.8 Constipation

Constipation or ileus (≥ Grade 3) or typhlitis: Hold vincristine dose(s); institute aggressive regimen to treat constipation if present. When symptoms improve to Grade 1 toxicity or less resume vincristine at 25% dose reduction (maximum dose: 2.1 mg); escalate to full dose with subsequent courses as tolerated.

5.2.9 Hypersensitivity Reaction to Etoposide

If with any dose, patient exhibits signs or symptoms of hypersensitivity reaction (HSR) in relation to administration of etoposide the infusion should be

discontinued and appropriate treatment per institutional guidelines initiated. If additional doses of etoposide are scheduled for the patient to complete therapy, etoposide phosphate (Etopophos) should be substituted at equivalent doses. Pretreatment will consist of patient's first morning scheduled treatment prednisone dose and diphenhydramine 1 mg/kg IV or PO (maximum 50 mg). Appropriate monitoring for HSR signs or symptoms should be instituted during the etoposide phosphate infusion with emergency anaphylactic treatment available. Drug administration should be discontinued and appropriate treatment instituted should a reaction also occur with this product. No further doses of etoposide or etoposide phosphate should be attempted.

5.2.10 Hypersensitivity Reaction (HSR) to Bleomycin

If with any dose, patient exhibits signs/symptoms of HSR in relation to administration of bleomycin, the infusion should be discontinued and appropriate treatment per institutional guidelines initiated. If additional doses of bleomycin are scheduled for the patient to complete therapy, pretreatment will consist of diphenhydramine 1 mg/kg IV or PO (maximum 50 mg), and giving the last (14^{th}) dose of prednisone on the morning of Day 8 concurrent with the Day 8 bleomycin. Appropriate monitoring for HSR signs/symptoms should be instituted during the bleomycin infusion with emergency anaphylactic treatment available. Drug administration should be discontinued and appropriate treatment instituted should a reaction also occur. No further doses of bleomycin should be attempted.

6.0 DRUG INFORMATION

Please see Appendix X for known drug interactions associated with the drugs used in this study.

6.1 BRENTUXIMAB VEDOTIN (04/03/2019)

(SGN-35, AdcetrisTM, NSC#749710)

6.1.1 Source and Pharmacology

Brentuximab vedotin is a CD30-directed antibody-drug conjugate (ADC) consisting of three components: the chimeric IgG1 antibody cAC10, specific for human CD30, the microtubule disrupting agent MMAE, and a protease-cleavable linker that covalently attaches MMAE to cAC10. Approximately 4 molecules of MMAE are attached to each antibody molecule. Brentuximab vedotin is produced by chemical conjugation of the antibody and small molecule components. The antibody is produced by mammalian (Chinese hamster ovary) cells, and the small molecule components are produced by chemical synthesis. Brentuximab vedotin has an approximate molecular weight of 153 kDa.

Brentuximab vedotin consists of a chimeric IgG1 antibody directed against CD30 and a small molecule (MMAE) microtubule disrupting agent, which is covalently attached to the antibody via a linker. Nonclinical data suggest that the anticancer activity of brentuximab vedotin is due to the binding of the ADC to CD30-expressing cells, subsequent internalization of the ADC-CD30 complex, and release of MMAE via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death of the cells.

Binding of MMAE (in vitro) to human plasma proteins ranged from 68-82% and thus MMAE is not likely to displace or to be displaced by highly protein-bound drugs. In vitro, MMAE was a substrate of P-gp but not a potent inhibitor of P-gp. In vivo data suggest that a small fraction of MMAE released from brentuximab vedotin is metabolized. In vitro data indicates that the active metabolite of brentuximab vedotin, monomethyl auristatin E (MMAE) is a substrate and an inhibitor of CYP3A4 but is neither a sensitive substrate nor a strong inhibitor/inducer of CYP3A4. However, patients should be monitored for potential drug-interaction when administered drugs known to be a strong CYP 3A4 inhibitor/inducer with brentuximab vedotin. In vitro, MMAE is a substrate of P-gp transporter and is not an inhibitor of P-gp. See Appendix III for a list of CYP3A4 inducers and inhibitors.

MMAE appeared to follow metabolite kinetics, with the elimination of MMAE appearing to be limited by its rate of release from ADC. Approximately 24% of the total MMAE administered as part of the ADC during a brentuximab vedotin infusion (at 1.8 mg/kg) was recovered in both urine and feces over a 1-week period. Of the recovered MMAE, approximately 72% was recovered in the feces and the majority of the excreted MMAE was unchanged.

6.1.2 Toxicity

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
SGN-35 (brentuximab vedotin, NSC 749710)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 798 patients.* Below is the CAEPR for SGN-35 (brentuximab vedotin).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, February 13, 2019[1]

Adverse Events with Possible Relationship to SGN-35 (brentuximab vedotin) (CTCAE 5.0 Term) [n= 798]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
		Febrile neutropenia	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
		Colitis[2]	

Adverse Events with Possible Relationship to SGN-35 (brentuximab vedotin) (CTCAE 5.0 Term) [n= 798]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
		Enterocolitis	
		Gastrointestinal hemorrhage[3]	
		Gastrointestinal obstruction[4]	
		Gastrointestinal perforation[5]	
		Gastrointestinal ulcer[6]	
		Ileus	
Nausea			***Nausea (Gr 2)***
		Pancreatitis	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
	Edema limbs		
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
	Pain		
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatotoxicity)[7]		
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Lung infection		
	Upper respiratory infection		***Upper respiratory infection (Gr 2)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		
	Weight loss		
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hyperglycemia		
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		
	Muscle cramp		
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		

Adverse Events with Possible Relationship to SGN-35 (brentuximab vedotin) (CTCAE 5.0 Term) [n= 798]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		***Headache (Gr 2)***
		Nervous system disorders - Other (progressive multifocal leukoencephalopathy)	
	Paresthesia		
	Peripheral motor neuropathy		***Peripheral motor neuropathy (Gr 2)***
Peripheral sensory neuropathy			***Peripheral sensory neuropathy (Gr 2)***
PSYCHIATRIC DISORDERS			
	Anxiety		
	Insomnia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
	Oropharyngeal pain		
		Respiratory, thoracic and mediastinal disorders - Other (pulmonary toxicity)[8]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Hyperhidrosis		
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Colitis may also include the term neutropenic colitis.

[3]Fatal and/or serious gastrointestinal hemorrhages have been observed in SGN-35 (brentuximab vedotin) treated patients. Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[4]Fatal and/or serious gastrointestinal obstructions have been observed in SGN-35 (brentuximab vedotin) treated patients. Gastrointestinal obstruction includes Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[5]Fatal and/or serious gastrointestinal perforations have been observed in SGN-35 (brentuximab vedotin) treated patients. Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC. Lymphoma with preexisting GI involvement may increase the risk of perforation.

[6]Fatal and/or serious gastrointestinal ulcers have been observed in SGN-35 (brentuximab vedotin) treated patients. Gastrointestinal ulcer includes Anal ulcer, Colonic ulcer, Duodenal ulcer, Esophageal ulcer, Gastric ulcer, Ileal ulcer, Jejunal ulcer, Rectal ulcer, and Small intestine ulcer under the GASTROINTESTINAL DISORDERS SOC.

[7]Hepatotoxicity may manifest as increased ALT/AST, bilirubin, alkaline phosphatase, and/or GGT.

[8]Pulmonary toxicity, which may manifest as pneumonitis, interstitial lung disease, or adult respiratory distress syndrome (ARDS), has been observed in patients treated in brentuximab vedotin monotherapy trials as well as in combination with bleomycin.

Adverse events reported on SGN-35 (brentuximab vedotin) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that SGN-35 (brentuximab vedotin) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (lymphadenopathy)
CARDIAC DISORDERS - Myocardial infarction; Pericardial effusion; Sinus tachycardia
GASTROINTESTINAL DISORDERS - Dyspepsia; Esophagitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Non-cardiac chest pain
INFECTIONS AND INFESTATIONS - Meningitis; Pharyngitis; Sepsis; Shingles; Sinusitis; Skin infection; Soft tissue infection; Thrush; Urinary tract infection
INVESTIGATIONS - Blood lactate dehydrogenase increased; Carbon monoxide diffusing capacity decreased; Creatinine increased; Lipase increased; Lymphocyte count decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Myositis; Neck pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Myelodysplastic syndrome
NERVOUS SYSTEM DISORDERS - Dysesthesia; Encephalopathy; Nervous system disorders - Other (demyelinating polyneuropathy); Seizure; Syncope
PSYCHIATRIC DISORDERS - Depression
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (pyelonephritis)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Reproductive system and breast disorders - Other (groin pain)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome[8]; Pleural effusion[8]; Pneumothorax[8]; Productive cough; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (bronchitis)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin
VASCULAR DISORDERS - Hot flashes; Hypertension; Hypotension; Thromboembolic event

Note: SGN-35 (brentuximab vedotin) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

6.1.3 Formulation and Stability

Brentuximab vedotin is supplied as a sterile, white to off-white preservative-free lyophilized cake or powder in individually-boxed single-use vials containing 50 mg brentuximab vedotin per vial. Store vial dry under refrigeration at 2-8°C (36-46°F) in the original carton to protect from light until reconstitution and use. The stability testing of the intact vials is ongoing. Reconstituted agent must be diluted and administered within 24 hours.

CAUTION: The single-use lyophilized dosage form contains no antibacterial preservatives. Therefore, the reconstituted product (from Step 1) should be discarded within 8 hours after initial entry/puncture. Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.

Preparation consists of 2 steps: dilution of the stock solution and dilution of the final solution.

Step 1: **Make a 5 mg/mL concentration**. **Use vials from the same Lot number for each dose**.

1. Reconstitute the 50 mg lyophilized powder brentuximab vedotin with 10.5 mL Sterile Water for Injection, USP. Final concentration is 5 mg/mL (Note: total volume is 11 mL).
2. Swirl the vial gently. Do not shake.
3. Let the reconstituted vial settle for one minute to eliminate bubbles. The reconstituted solution should be colorless, clear to slightly opalescent and should NOT have visible particulates.
4. Store the reconstituted vial under refrigeration (2° – 8° C) and protect from light if not used immediately. Discard after 8 hours.

Step 2: **Further dilute the IV solution**.

1. Withdraw the calculated amount of drug from the 5 mg/mL reconstituted vial in step 1.
2. Inject the required amount of drug into 0.9% NS, Lactated Ringer's Solution, USP, or dextrose 5% in Water (D5W), USP to a final concentration between **0.4 – 1.8 mg/mL**.
3. Brentuximab vedotin solution is compatible in polyvinylchloride (PVC), ethylene vinyl acetate (EVA), polyolefin, or polyethylene.
4. Do not shake. Gently invert the bag (or syringe) to mix.
5. The prepared IV bag (or syringe) is to be stored at refrigeration (2° – 8° C) and must be used within 24 hours of initial product reconstitution (or sooner per institutional practice for agents without a preservative). Protect the prepared IV solution from direct sunlight if not used immediately.
6. Prior to administration, inspect the IV bag (or syringe) for discoloration or floating particulates. Do not use the IV solution if the solution is discolored or/and have particulates.

6.1.4 Guidelines for Administration

See Treatment and Dose Modifications sections of the protocol.

Infuse the prepared IV solution over 30 minutes. Do not mix with other medications. Do not administer as an IV push or bolus. Do not use an in-line filter for the IV administration. The IV bag (or syringe) does NOT need light protection during the IV administration.

6.1.5 Supplier

Supplied by Seattle Genetics, Inc. and the Division of Cancer Treatment and Diagnosis (DCTD), NCI. **Do NOT use commercial supply.**

6.1.6 Obtaining the Agent

Agent Ordering

NCI supplied agents may be requested by the eligible participating investigator (or their authorized designee) at each participating institution. The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), NIH Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

6.1.7 Clinical Drug Request

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

6.1.8 Agent Accountability

Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

6.1.9 Investigator Brochure Availability

The current version(s) of the IB(s) for the agent will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator via email.

6.1.10 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/

- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

6.2 BLEOMYCIN (05/06/11)

(Bleomycin Sulfate, Blenoxane® Bleocin®, Bleocris®, Bleolem®, Bleomicina®, Cytorich®) NSC #125066

6.2.1 Source and Pharmacology

Bleomycin is a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of *Streptomyces verticillus*. Of the thirteen identifiable fractions, the main components are bleomycin A2 and B2. A DNA-binding region and an iron-binding region are present at opposite ends of the molecule. The cytotoxic effects of bleomycin result from the formation of oxygen free radicals, which then cause single- and double-strand DNA breaks. Bleomycin-mediated DNA damage requires the presence of a redox-active Fe^{2+} metal ion in the presence of oxygen to generate the activated free radical species. Recently it has also become apparent that bleomycin mediates the oxidative degradation of all major classes of cellular RNAs. The effects of bleomycin are cell cycle specific, as its major effects are mediated in the G_2 and M phases of the cell cycle.

In animal studies, high concentrations of bleomycin are found in the skin, lungs, kidneys, peritoneum, and lymphatics. Tumor cells of the skin and lungs have also been found to have high concentrations of bleomycin in contrast to the low concentrations found in hematopoietic tissue. The low concentrations of bleomycin found in bone marrow may be related to high levels of bleomycin degradative enzymes found in that tissue. After IV administration of 15 units/m^2 bleomycin, there is a rapid biphasic disappearance from the circulation. The initial distribution half-life is on the order of 10 to 20 minutes, whereas the terminal half-life is in the range of 2 to 3 hours. Bleomycin is absorbed rapidly after IM injection, and peak blood levels approximately one-third to one-half those achieved after an IV dose are usually reached in 30 to 60 minutes. In patients with normal renal function, 60% to 70% of an administered dose is recovered in the urine as active bleomycin. In patients with a creatinine clearance of < 35 mL/min, the plasma or serum terminal elimination half-life increases exponentially as the creatinine clearance decreases. It was reported that patients with moderately severe renal failure excreted less than 20% of the dose in the urine.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	High fever (L), chills	Rash (usually in pressure points) (L)	Idiosyncratic reaction similar to anaphylaxis (hypotension, mental confusion, fever, chills, and wheezing), angioedema, nausea, vomiting, phlebitis, pain at tumor site, malaise
Prompt: Within 2-3 weeks, prior to the next course	Raynaud's phenomenon, hyperpigmentation (with pruritus and scratching), mucositis	Taste impairment, anorexia, weight loss	Alopecia, onycholysis (dystrophy, shedding, thickening of the nail bed, and darkening of the nail cuticle), thrombocytopenia
Delayed: Any time later during therapy, excluding the above conditions		Pneumonitis (dose dependent) (L)	Dyspnea, fine rales, pulmonary fibrosis (dose dependent – increased in combination with XRT and/or O_2 resulting rarely in death) (L), scleroderma-like skin changes, in combination with other chemotherapy agents: coronary artery disease, myocardial infarction, arterial thrombosis, cerebrovascular accidents
Unknown Frequency and Timing	Fetal toxicities and teratogenic effects of bleomycin have been noted in animals. Administration of intraperitoneal doses of 1.5 mg/kg/day to rats (about 1.6 times the recommended human dose on a unit/m² basis) on Days 6-15 of gestation caused skeletal malformations, shortened innominate artery and hydroureter. Bleomycin is abortifacient but not teratogenic in rabbits, at IV doses of 1.2 mg/kg/day (about 2.4 times the recommended human dose on a unit/m² basis) given on gestation Days 6-18. It is unknown whether the drug is excreted in breast milk.		

(L) Toxicity may also occur later.

6.2.2 Formulation and Stability

Available in 15 and 30 unit vials as bleomycin sulfate, a white or yellowish lyophilized powder. The sterile powder is stable under refrigeration, 2°-8°C (36°-46°F).

Note: Bleomycin vials in the US are labeled as containing 15 or 30 units (also called USP units). Some countries outside of the US use bleomycin products that are labeled with international units (IU). Each USP unit is equivalent to 1000 international units (i.e., 15 USP units=15,000 international units). Therefore, it is important to check the labeling of the product before compounding the dose.

6.2.3 Guidelines for Administration

See Treatment and Dose Modifications sections of the protocol.

For IV administration: reconstitute to a concentration of ≤ 3 units/mL with NS.
For SubQ administration: reconstitute to a concentration of 3-15 units/mL with NS.

Bleomycin should not be reconstituted or diluted with D5W or other dextrose containing diluents. When reconstituted in D5W and analyzed by HPLC, bleomycin demonstrates a loss of A2 and B2 potency that does not occur when reconstituted in NS. When reconstituted with solutions, bleomycin is stable for 24 hours at room temperature.

6.2.4 Special Precautions

Test dose: it is recommended by the manufacturer because of the possibility of an idiosyncratic reaction similar to anaphylaxis that occurred in approximately 1% of lymphoma patients. Lymphoma patients may receive a test dose of 2 units or less IV or subcutaneously for the first 2 doses. Following administration of the test dose, consider monitoring of vital signs every 15 minutes for at least 1 hour and if no acute reaction occurs, the full dose may be given. Note: test doses may produce a false negative result. Sites are allowed to use their own policies in regards to using the test dose (See Section 5.2.10 for hypersensitivity reaction to Bleomycin).

6.2.5 Supplier

Commercially available from various manufacturers. See package insert for further information.

6.3 CYCLOPHOSPHAMIDE INJECTION (03/13/13)

(Cytoxan) NSC #26271

6.3.1 Source and Pharmacology

Cyclophosphamide is an alkylating agent related to nitrogen mustard. Cyclophosphamide is inactive until it is metabolized by P450 isoenzymes (CYP2B6, CYP2C9, and CYP3A4) in the liver to active compounds. The initial product is 4-hydroxycyclophosphamide (4-HC) that is in equilibrium with aldophosphamide that spontaneously releases acrolein to produce phosphoramide mustard. Phosphoramide mustard, which is an active bifunctional alkylating species, is 10 times more potent *in vitro* than is 4-HC and has been shown to produce interstrand DNA cross-link analogous to those produced by mechlorethamine. Approximately 70% of a dose of cyclophosphamide is excreted in the urine as the inactive carboxyphosphamide and 5-25% as unchanged drug. The plasma half-life ranges from 4.1 to 16 hours after IV administration.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Anorexia, nausea & vomiting (acute and delayed)	Abdominal discomfort, diarrhea	Transient blurred vision, nasal stuffiness with rapid administration, arrhythmias (rapid infusion), skin rash, anaphylaxis, SIADH
Prompt: Within 2-3 weeks, prior to the next course	Leukopenia, alopecia, immune suppression	Thrombocytopenia, anemia, hemorrhagic cystitis (L)	Cardiac toxicity with high dose (acute – CHF hemorrhagic myocarditis, myocardial necrosis) (L), hyperpigmentation, nail changes, impaired wound healing, infection secondary to immune suppression
Delayed: Any time later during therapy	Gonadal dysfunction: azoospermia or oligospermia (prolonged or permanent)[1] (L)	Amenorrhea[1]	Gonadal dysfunction: ovarian failure[1] (L), interstitial pneumonitis, pulmonary fibrosis[2] (L)
Late: Any time after completion of treatment			Secondary malignancy (ALL, ANLL, AML), bladder carcinoma (long term use > 2 years), bladder fibrosis

Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of cyclophosphamide (alone or in combination with other antineoplastic agents) have been noted in humans. Toxicities include: chromosomal abnormalities, multiple anomalies, pancytopenia, and low birth weight. Cyclophosphamide is excreted into breast milk. Cyclophosphamide is contraindicated during breast feeding because of reported cases of neutropenia in breast fed infants and the potential for serious adverse effects.

[1] Dependent on dose, age, gender, and degree of pubertal development at time of treatment.
[2] Risk increased with pulmonary chest irradiation and higher doses.
(L) Toxicity may also occur later.

6.3.2 Formulation and Stability

Cyclophosphamide for injection is available as powder for injection or lyophilized powder for injection in 500 mg, 1 g, and 2 g vials. The powder for injection contains 82 mg sodium bicarbonate/100 mg cyclophosphamide and the lyophilized powder for injection contains 75 mg mannitol/100 mg cyclophosphamide. Storage at or below 25ºC (77ºF) is recommended. The product will withstand brief exposures to temperatures up to 30ºC (86ºF).

6.3.3 Guidelines for Administration

See Treatment and Dose Modifications sections of the protocol.

6.3.4 Cyclophosphamide for Injection

If the drug will be administered as undiluted drug at the 20 mg/mL concentration, then reconstitute to 20 mg/mL with NS ONLY to avoid a hypotonic solution. If the drug will be further diluted prior to administration, then first reconstitute with NS, SWFI, or Bacteriostatic Water for Injection (paraben preserved only) to a concentration of 20 mg/mL. Following reconstitution further dilute in dextrose or saline containing solutions for IV use.

6.3.5 Supplier

Commercially available from various manufacturers. See package insert for further information.

6.4 DOXORUBICIN (05/09/11)

(Adriamycin®) NSC #123127

6.4.1 Source and Pharmacology

An anthracycline antibiotic isolated from cultures of *Streptomyces peucetius*. The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin cytocidal activity. Doxorubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases, and dehydrogenases generate highly reactive species including the hydroxyl free radical (OH•). Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level. Cells treated with doxorubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death. Doxorubicin-induced apoptosis may be an

integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both.

Doxorubicin serum decay pattern is multiphasic. The initial distributive $t_{½}$ is approximately 5 minutes suggesting rapid tissue uptake of doxorubicin. The terminal $t_{½}$ of 20 to 48 hours reflects a slow elimination from tissues. Steady-state distribution volumes exceed 20 to 30 L/kg and are indicative of extensive drug uptake into tissues. Plasma clearance is in the range of 8 to 20 mL/min/kg and is predominately by metabolism and biliary excretion. The P450 cytochromes that appear to be involved with doxorubicin metabolism are CYP2D6 and CYP3A4. Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same time period. Binding of doxorubicin and its major metabolite, doxorubicinol, to plasma proteins is about 74 to 76% and is independent of plasma concentration of doxorubicin.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, pink or red color to urine, sweat, tears, and saliva	Hyperuricemia, facial flushing, sclerosis of the vein	Diarrhea, anorexia, erythematous streaking of the vein (flare reaction), extravasation (rare) but if occurs = local ulceration, anaphylaxis, fever, chills, urticaria, acute arrhythmias
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (leukopenia, thrombocytopenia, anemia), alopecia	Mucositis (stomatitis and esophagitis), hepatotoxicity	Radiation recall reactions, conjunctivitis and lacrimation
Delayed: Any time later during therapy		Cardiomyopathy[1] (CHF occurs in 5-20% at cumulative doses ≥ 450 mg/m²) (L)	Cardiomyopathy[1] (CHF occurs in < 5% at cumulative doses ≤ 400 mg/m²) (L), ulceration and necrosis of colon, hyper-pigmentation of nail bed and dermal crease, onycholysis
Late: Any time after completion of treatment	Subclinical cardiac dysfunction	CHF (on long term follow up in pediatric patients)	Secondary malignancy (in combination regimens)
Unknown Frequency and Timing:	Fetal and teratogenic toxicities. Carcinogenic and mutagenic effects of doxorubicin have been noted in animal models. Doxorubicin is excreted into breast milk in humans		

[1] Risk increases with cardiac irradiation, exposure at a young or advanced age.
(L) Toxicity may also occur later.

6.4.2 Formulation and Stability

Doxorubicin is available as red-orange lyophilized powder for injection in 10 mg[1], 20 mg[1], 50 mg[1]vials and a preservative-free 2 mg/mL solution in 10 mg[1], 20 mg[1], 50 mg[1], 200 mg[2] vials.

[1]Contains lactose monohydrate, 0.9 NS, HCl to adjust pH to 3. The Adriamycin RDF® (rapid dissolution formula) also contains methylparaben, 1 mg per each 10 mg of doxorubicin, to enhance dissolution.

[2] Multiple dose vial contains lactose, 0.9% NS, HCl to adjust pH to 3.

Aqueous Solution Store refrigerated 2°-8°C, (36°-46°F). Protect from light. Retain in carton until contents are used.

Powder for Injection Store unreconstituted vial at room temperature, 15°-30°C (59°-86°F). Retain in carton until contents are used. Reconstitute with preservative-free NS to a final concentration of 2 mg/mL. After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature and 15 days under refrigeration, 2°-8°C (36°-46°F) when protected from light. Doxorubicin further diluted in 50 – 1000 mL of NS or D5W is stable for up to 48 hours at room temperature (25°C) when protected from light.

6.4.3 Guidelines for Administration

See Treatment and Dose Modifications sections of the protocol. Administer IV through the tubing of rapidly infusing solution of D5W or 0.9% NaCl preferably into a large vein. Protect the diluted solution from sunlight. To avoid extravasation, the use of a central line is suggested.

6.4.4 Special Precautions

Medication errors have occurred due to confusion between DAUNOrubicin and DOXOrubicin. DOXOrubicin is available in a liposomal formulation. The conventional and liposomal formulations are NOT interchangeable. Only conventional DOXOrubicin is used in this protocol.

6.4.5 Supplier

Commercially available from various manufacturers. See package insert for further information.

6.5 ETOPOSIDE – INJECTION (11/15/16)

(Toposar ®, Etopophos®,VP-16) NSC #141540

6.5.1 Source and Pharmacology

A semisynthetic derivative of podophyllotoxin that forms a complex with topoisomerase II and DNA that results in single and double strand DNA breaks. Its main effect appears to be in the S and G_2 phase of the cell cycle. The initial $t_{½}$ is 1.5 hours and the mean terminal half-life is 4 to 11 hours. It is primarily excreted in the urine. In children, approximately 55% of the dose is excreted in the urine as etoposide in 24 hours. The mean renal clearance of etoposide is 7 to 10 mL/min/m² or about 35% of the total body clearance over a dose range of 80 to 600 mg/m². Etoposide, therefore, is cleared by both renal and non-renal processes, e.g., metabolism and biliary excretion. The effect of renal disease on plasma etoposide clearance is not known. Biliary excretion appears to be a minor route of etoposide elimination. Only 6% or less of an intravenous dose is recovered in the bile as etoposide. Metabolism accounts for most of the non-renal clearance of etoposide.

The maximum plasma concentration and area under the concentration time curve (AUC) exhibit a high degree of patient variability. Etoposide is highly bound to plasma proteins (~94%), primarily serum albumin. Pharmacodynamics' studies have shown that etoposide systemic exposure is related to toxicity. Preliminary

data suggests that systemic exposure for unbound etoposide correlates better than total (bound and unbound) etoposide. There is poor diffusion into the CSF < 5%.

Etoposide phosphate is a water soluble ester of etoposide that is rapidly and completely converted to etoposide in plasma. Pharmacokinetic and pharmacodynamics data indicate that etoposide phosphate is bioequivalent to etoposide when it is administered in molar equivalent doses.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting	Anorexia	Transient hypotension during infusion; anaphylaxis (chills, fever, tachycardia, dyspnea, bronchospasm, hypotension)
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression (anemia, leukopenia), alopecia	Thrombocytopenia, diarrhea, abdominal pain, asthenia, malaise, rashes and urticaria	Peripheral neuropathy, mucositis, hepatotoxicity, chest pain, thrombophlebitis, congestive heart failure, Stevens-Johnson Syndrome, exfoliative dermatitis
Delayed: Any time later during therapy			Dystonia, ovarian failure, amenorrhea, anovulatory cycles, hypomenorrhea, onycholysis of nails
Late: Any time after completion of treatment			Secondary malignancy (preleukemic or leukemic syndromes)
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of etoposide have been noted in animals at 1/20th of the human dose. It is unknown whether the drug is excreted in breast milk.		

6.5.2 Formulation and Stability

Etoposide for injection is available as a 20 mg/mL solution in sterile multiple dose vials (5 mL, 25 mL, or 50 mL each). The pH of the clear, nearly colorless to yellow liquid is 3 to 4. Each mL contains 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg modified polysorbate 80/tween 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol. Vial headspace contains nitrogen. Unopened vials of etoposide are stable until expiration date on package at controlled room temperature (20˚-25˚C or 68˚-77˚F).

Etoposide phosphate for injection is available for intravenous infusion as a sterile lyophilized powder in single-dose vials containing etoposide phosphate equivalent to 100 mg etoposide, 32.7 mg sodium citrate *USP*, and 300 mg dextran 40. Etoposide phosphate must be stored under refrigeration (2°-8°C or 36°-46°F). Unopened vials of etoposide phosphate are stable until the expiration date on the package.

6.5.3 Guidelines for Administration:

See Treatment and Dose Modifications sections of the protocol.

Etoposide
Dilute etoposide to a final concentration ≤ 0.4 mg/mL in D5W or NS. Etoposide infusions are stable at room temperature for 96 hours when diluted to concentrations of 0.2 mg/mL; stability is 24 hours at room temperature with concentrations of 0.4 mg/mL. The time to precipitation is highly unpredictable at concentrations > 0.4 mg/mL. Use in-line filter during infusion secondary to the risk of precipitate formation. However, the use of an in-line filter is not mandatory since etoposide precipitation is unlikely at concentrations of 0.1-0.4 mg/mL. **Do not administer etoposide by rapid intravenous injection.** Slow rate of administration if hypotension occurs.

Leaching of diethylhexyl phthalate (DEHP) from polyvinyl chloride (PVC) bags occurred with etoposide 0.4 mg/mL in NS. To avoid leaching, prepare the etoposide solution as close as possible, preferably within 4 hours, to the time of administration or alternatively as per institutional policy; glass or polyethylene-lined (non-PVC) containers and polyethylene-lined tubing may be used to minimize exposure to DEHP.

Etoposide Phosphate
Reconstitute the 100 mg vial with 5 or 10 mL of Sterile Water for Injection, D5W, NS, Bacteriostatic Water for Injection with Benzyl Alcohol, or Bacteriostatic Sodium Chloride for Injection with Benzyl Alcohol for a concentration equivalent to 20 mg/mL or 10 mg/mL etoposide equivalent (22.7 mg/mL or 11.4 mg/mL etoposide phosphate), respectively. **Use diluents without benzyl alcohol for patients with hypersensitivity to benzyl alcohol.**

When reconstituted as directed, etoposide phosphate solutions can be stored in glass or plastic containers under refrigeration for 7 days. When reconstituted with a diluent containing a bacteriostat, store at controlled room temperature for up to 48 hours. Following reconstitution with SWFI, D5W, or NS store at controlled room temperature for up to 24 hours.

Following reconstitution, etoposide phosphate may be further diluted to a concentration as low as 0.1 mg/mL of etoposide with D5W or NS. The diluted solution can be stored under refrigeration or at controlled room temperature for 24 hours.

6.5.4 Special Precautions
Etoposide can be mixed in 0.9% NaCl or D_5W. Avoid use of large volumes of D_5W due to potential development of hyponatremia (see Section 5.2.9 for hypersensitivity reaction to Etoposide).

6.5.5 Supplier
Commercially available from various manufacturers. See package insert for more detailed information.

CANADIAN SITES
Etoposide for Injection is available as a 20 mg/mL solution.

Etopophos® (etoposide phosphate) is not commercially available in Canada. Sites may purchase and import the USA commercial supply from Bristol Laboratories

via an International Distributor (Pharma Exports LLC, phone: 1-412-885-3700, fax: 1-412-885-8022, email: pharexp@aol.com) under the authority of the protocol's No Objection Letter (NOL). Drug Accountability Log (DAL) must record Lot #'s and expiry dates of shipments received and doses dispensed. Sites may use their own DAL as long as it complies with all elements of ICH GCP and Division 5 of the Food and Drugs Act. Each site is responsible for the procurement (import +/- purchase) of Etoposide Phosphate (Etopophos). Sites may import and manage a single clinical trial supply for multiple protocols as long as each protocol has an NOL and the protocol the patient is registered on is recorded on the DAL.

6.6 FILGRASTIM, TBO-FILGRASTIM, FILGRASTIM-SNDZ (11/15/16)

(Granulocyte Colony-Stimulating Factor, r-metHuG-CSF, G-CSF, Neupogen®, Granix®, Zarxio®) NSC #614629

6.6.1 Source and Pharmacology

Filgrastim is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology. Filgrastim is a 175 amino acid protein with a molecular weight of 18,800 daltons manufactured by recombinant DNA technology utilizing E coli bacteria into which has been inserted the human granulocyte colony stimulating factor gene. It differs from the natural protein in that the N- amino acid is methionine and the protein is not glycosylated. G-CSF is a lineage specific colony-stimulating factor, which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens). Filgrastim exhibits nonlinear pharmacokinetics with clearance dependent on filgrastim concentration and neutrophil count. Filgrastim is cleared by the kidney. The elimination half-life is similar for subcutaneous and intravenous administration, approximately 3.5 hours. The time to peak concentration when administered subcutaneously is 2-8 hours.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Local irritation at the injection site, headache	Allergic reactions (more common with IV administration than subq): skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea) and cardiovascular (hypotension, tachycardia), low grade fever
Prompt: Within 2-3 weeks, prior to the next course	Mild to moderate medullary bone pain	Increased: alkaline phosphatase, lactate dehydrogenase and uric acid, thrombocytopenia	Splenomegaly, splenic rupture, rash or exacerbation of pre-existing skin rashes, sickle cell crises in patients with SCD, excessive leukocytosis, Sweet's syndrome (acute febrile neutrophilic dermatosis)
Delayed: Anytime later during therapy			Cutaneous vasculitis, ARDS

Late: Anytime after completion of treatment			MDS or AML (confined to patients with severe chronic neutropenia and long term administration)
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of filgrastim in humans are unknown. Conflicting data exist in animal studies and filgrastim is known to pass the placental barrier. It is unknown whether the drug is excreted in breast milk.		

6.6.2 Formulation and Stability

Neupogen® is supplied as a clear solution of 300 mcg/mL in 1 mL or 1.6 mL vials. Neupogen® vials are preservative free single use vials. Discard unused portions of open vials.

Neupogen®, Granix®, and Zarxio® are also available as single use prefilled syringes containing 300 mcg/0.5 mL or 480 mcg/0.8 mL of filgrastim for subcutaneous administration. Store refrigerated at 2º-8ºC (36º-46ºF). Protect from light. Do not shake. Prior to injection, filgrastim and filgrastim-sndz may be allowed to reach room temperature for a maximum of 24 hours (infusion must be completed within 24 hours of preparation). TBO-filgrastim may be removed from 2°C-8°C (36°F-46°F) storage for a single period of up to 5 days between 23°C to 27°C (73°F to 81°F). Avoid freezing and temperatures > 30ºC.

For IV use, dilute filgrastim (Neupogen®) and tbo-filgrastim (Granix®) in D5W only to concentrations >15 mcg/mL. Filgrastim-sndz (Zarxio®) may be diluted in D5W to concentrations between 5 and 15 mcg/mL. At concentrations below 15 mcg/mL, human serum albumin should be added to make a final albumin concentration of 0.2% (2 mg/mL) in order to minimize the adsorption of filgrastim to plastic infusion containers and equipment for all 3 products (communication on file from Teva Pharmaceuticals USA). Filgrastim or Filgrastim-sndz dilutions of 5 mcg/mL or less are not recommended. Tbo-filgrastim dilutions below 2 mcg/mL are not recommended. Diluted filgrastim biosimilar products should be stored at 2º-8ºC (36º- 46ºF) and used within 24 hours. Do not shake.

Do not dilute with saline-containing solutions at any time; precipitation will occur.

6.6.3 Guidelines for Administration

See Treatment and Dose Modifications sections of the protocol.
Filgrastim biosimilar products should not be administered within 24 hours of (before AND after) chemotherapy.

6.6.4 Supplier

Commercially available from various manufacturers. See package insert for further information

6.7 PEGFILGRASTIM (02/10/16)

(pegylated filgrastim, PEG filgrastim, SD/01, Neulasta®) NSC #725961

6.7.1 Source and Pharmacology

Pegfilgrastim is the pegylated form of recombinant methionyl human G-CSF (filgrastim). Pegfilgrastim is produced by covalently binding a 20-kilodalton (kD) monomethoxypolyethylene glycol molecule to the N-terminal methionyl residue of filgrastim. The molecular weight of pegfilgrastim is 39 kD. G-CSF is a lineage

specific colony-stimulating factor which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens).

After subcutaneous injection the elimination half-life of pegfilgrastim ranges from 15 to 80 hours and the time to peak concentration ranges from 24 to 72 hours. Serum levels are sustained in most patients during the neutropenic period post chemotherapy, and begin to decline after the start of neutrophil recovery, consistent with neutrophil-dependent elimination. After subcutaneous administration at 100 mcg/kg in 37 pediatric patients with sarcoma, the terminal elimination half-life was 30.1 (+/- 38.2) hours in patients 0 to 5 years-old, 20.2 (+/- 11.3) hours in patients 6 to 11 years old, and 21.2 (+/- 16) hours in children 12 to 21 years old.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Local irritation at the injection site (pain, induration, and local erythema), headache	Low grade fever, allergic reactions (anaphylaxis, angioedema, or urticaria), generalized erythema and flushing,
Prompt: Within 2-3 weeks, prior to the next course	Mild to moderate medullary bone pain	Increased: alkaline phosphatase, lactate dehydrogenase and uric acid, thrombocytopenia	Splenomegaly, splenic rupture, sickle cell crises in patients with sickle cell disease (SCD), excessive leukocytosis, Sweet's syndrome (acute febrile neutrophilic dermatosis)
Delayed: Anytime later during therapy			ARDS
Unknown frequency and timing:	Fetal toxicities and teratogenic effects of pegfilgrastim in humans are unknown. Conflicting data exist in animal studies. It is unknown whether the drug is excreted in breast milk.		

6.7.2 Formulation and Stability

Supplied as a preservative-free solution containing 6 mg (0.6 mL) of pegfilgrastim (10 mg/mL) in a single-dose syringe with 27 g, ½ inch needle with an UltraSafe® Needle Guard. The needle cover of the prefilled syringe contains drug natural rubber (a derivative of latex). Store refrigerated at 2º-8ºC (36º-46ºF) and in the carton to protect from light. Prior to injection, pegfilgrastim may be allowed to reach room temperature protected from light for a maximum of 48 hours. Avoid freezing.

6.7.3 Guidelines for Administration

See Treatment and Dose Modifications sections of the protocol.

Pegfilgrastim should not be administered in the period between 2 weeks before and 24 hours after chemotherapy. Do not shake. The manufacturer does not recommend use of the 6-milligram (mg) fixed-dose formulation of pegfilgrastim in infants, children, or adolescents under 45 kilograms.

6.7.4 Supplier
Commercially available. See package insert for further information.

6.8 **PREDNISO(LO)NE** (11/16/17)
(Deltasone®, PrediSONE Intensol®, Rayos®, Meticorten®, Liquid Pred®, Pediapred®, Millipred®, OraPred ODT®) NSC #10023 (prednisone), NSC# 9151 (prednisolone)

6.8.1 Source and Pharmacology
Prednisone and prednisolone are synthetic compounds closely related to hydrocortisone. Glucocorticoids produce widespread and diverse physiologic effects on carbohydrate, protein, and lipid metabolism, electrolyte and water balance, functions of the cardiovascular system, kidney, skeletal muscle, and the nervous systems. Glucocorticoids reduce the concentration of thymus-dependent lymphocytes (T-lymphocytes), monocytes, and eosinophils. Glucocorticoids selectively bind to the cortisol receptors on human lymphoid cells that are found in larger numbers on leukemic lymphoblasts. They also decrease binding of immunoglobulin to cell surface receptors and inhibit the synthesis and/or release of interleukins, thereby decreasing T-lymphocyte blastogenesis and reducing expansion of the primary immune response. The specific cellular mechanisms that act to halt DNA synthesis are thought to be related to inhibition of glucose transport or phosphorylation, retardation of mitosis, and inhibition of protein synthesis. Peak blood levels occur within 2 hours of oral intake. Prednisone is approximately 75% protein bound with a plasma $t_{½}$ of 3.2 to 4 hours. (Biologic half-life is 12-36 hours.)

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Insomnia, hyperphagia	Gastritis	Hyperuricemia
Prompt: Within 2-3 weeks, prior to the next course	Immunosuppression, personality changes (mood swings, euphoria, anxiety, depression), pituitary-adrenal axis suppression, acne (L)	Hyperglycemia, facial erythema, poor wound healing, infections (bacterial, fungal, parasitic, viral), edema	Pancreatitis (L), electrolyte imbalance (Na retention, hypokalemia, hypocalcemia) (L), increased intraocular pressure (L), hypertension, psychosis, vertigo, headache
Delayed: Any time later during therapy	Cushing's syndrome (moon facies, truncal obesity)	Striae and thinning of the skin, easy bruising, muscle weakness, osteopenia	Spontaneous fractures (L), growth suppression, peptic ulcer and GI bleeding, pseudotumor cerebri (increased intracranial pressure with papilledema, headache), aseptic necrosis of the femoral and humeral heads (L), urolithiasis[1] (L)
Late: Any time after completion of treatment		Cataracts (that may be reversible on discontinuation of prednisone in children)	
Unknown Frequency and Timing:	Fetal and teratogenic toxicities: Corticosteroids cross the placenta (prednisone has the poorest transport). In animal studies, large doses of cortisol administered early in pregnancy produced cleft palate, stillborn fetuses, and decreased fetal size. Chronic maternal ingestion during the first trimester has shown a 1%		

	incidence of cleft palate in humans. Prednisone is excreted into breast milk in humans; however, several studies suggest that amounts excreted in breast milk are negligible with prednisone doses ≤ 20 mg/day.

[1] Mainly reported in pediatric patients with ALL. Howard SC et al. Urolithiasis in pediatric patients with acute lymphoblastic leukemia. Leukemia 2003; 17: 541-6.
(L) Toxicity may also occur later.

6.8.2 Formulation and Stability

Prednisone is available in 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, and 50 mg tablets. Also available as a solution in 1 mg/1 mL or 5 mg/mL concentrations. Inactive ingredients vary depending on manufacturer but tablet formulations may include calcium or magnesium stearate, corn starch, lactose, erythrosine sodium, mineral oil, sorbic acid, sucrose, talc and various dyes. The solution may include 5-30% alcohol, fructose, sucrose, saccharin, and sorbitol.

Prednisolone is available as 5 mg scored tablets (base) and 10 mg, 15 mg, and 30 mg orally disintegrating tablets (ODT; sodium phosphate [strength expressed as base]). Liquid formulations of prednisolone are available as 15 mg/5 mL oral solution (base); 5 mg/5 mL, 10 mg/5 mL, 15 mg/5 mL, 20 mg/5 mL oral solution (sodium phosphate [strength expressed as base]; and 15 mg/5 mL oral syrup (base). Inactive ingredients vary depending on manufacturer. Tablet formulations may contain dyes and liquid formulations may contain edetate disodium, methylparaben, saccharin sodium.

6.8.3 Guidelines for Administration

See Treatment and Dose Modifications sections of the protocol.

PredniSONE and prednisoLONE are equipotent corticosteroids.

6.8.4 Supplier

Commercially available from various sources. See package insert for further information.

6.9 VINCRISTINE SULFATE (08/16/12)

(Oncovin®, VCR, LCR) NSC #67574

6.9.1 Source and Pharmacology

Vincristine is an alkaloid isolated from Vinca rosea Linn (periwinkle). It binds to tubulin, disrupting microtubules and inducing metaphase arrest. Its serum decay pattern is triphasic. The initial, middle, and terminal half-lives are 5 minutes, 2.3 hours, and 85 hours respectively; however, the range of the terminal half-life in humans is from 19 to 155 hours. The liver is the major excretory organ in humans and animals; about 80% of an injected dose of vincristine sulfate appears in the feces and 10% to 20% can be found in the urine. The p450 cytochrome involved with vincristine metabolism is CYP3A4. Within 15 to 30 minutes after injection, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly bound. It is excreted in the bile and feces. There is poor CSF penetration.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Jaw pain, headache	Extravasation (rare) but if occurs = local ulceration, shortness of breath, and bronchospasm
Prompt: Within 2-3 weeks, prior to the next course	Alopecia, constipation	Weakness, abdominal pain, mild brief myelosuppression (leukopenia, thrombocytopenia, anemia)	Paralytic ileus, ptosis, diplopia, night blindness, hoarseness, vocal cord paralysis, SIADH, seizure, defective sweating
Delayed: Any time later during therapy	Loss of deep tendon reflexes	Peripheral paresthesias including numbness, tingling and pain; clumsiness; wrist drop, foot drop, abnormal gait	Difficulty walking or inability to walk; sinusoidal obstruction syndrome (SOS, formerly VOD) (in combination); blindness, optic atrophy; urinary tract disorders (including bladder atony, dysuria, polyuria, nocturia, and urinary retention); autonomic neuropathy with postural hypotension; 8th cranial nerve damage with dizziness, nystagmus, vertigo and hearing loss
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of vincristine (either alone or in combination with other antineoplastic agents) have been noted in humans. The toxicities include: chromosome abnormalities, malformation, pancytopenia, and low birth weight. It is unknown whether the drug is excreted in breast milk.		

6.9.2 Formulation and Stability

Vincristine is supplied in 1 mL and 2 mL vials that each mL contains vincristine sulfate 1 mg (1.08 µmol), mannitol 100 mg, SWFI; acetic acid and sodium acetate are added for pH control. The pH of vincristine sulfate injection, *USP* ranges from 3.5 to 5.5. This product is a sterile, preservative free solution. Store refrigerated at 2˚-8˚C or 36˚-46˚F. Protect from light and retain in carton until time of use.

Do not mix with any IV solutions other than those containing dextrose or saline.

6.9.3 Guidelines for Administration

See Treatment and Dose Modifications sections of the protocol.

The World Health Organization, the Institute of Safe Medicine Practices (United States) and the Safety and Quality Council (Australia) all support the use of minibag rather than syringe for the infusion of vincristine. The delivery of vincristine via either IV slow push or minibag is acceptable for COG protocols. Vincristine should **NOT** be delivered to the patient at the same time with any medications intended for central nervous system administration. Vincristine is fatal if given intrathecally.

Injection of vincristine sulfate should be accomplished as per institutional policy. Vincristine sulfate must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken to ensure that the needle or catheter is securely within the vein to avoid extravasation during administration. The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion.

6.9.4 Special Precautions

FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

6.9.5 Supplier

Commercially available from various manufacturers. See package insert for more detailed information.

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

For biology specimens, every effort should be made to obtain the time points that occur before chemotherapy starts (i.e. diagnosis or Cycle 1, Day 1). During therapy, missed time points should be omitted. Once therapy is complete and the patient is in follow up, if biology specimens are not obtained at any requested time point, please send specimens at the next requested time point or at the next clinic visit, whichever is sooner.

If CEA/CIPN measures are missed at any requested time point (including the baseline*), please obtain and submit at the next requested time point or at the next clinic visit, whichever is sooner.

*Note: *the CEA and CIPN sub-studies reached accrual and were closed to further patient entry as of September 8, 2017.* ***Subjects already enrolled on these studies should continue to submit all required measures through Time Point #6 as indicated in Appendix VII and Appendix VIII.***

7.1 Required Clinical, Laboratory and Disease Evaluations

Obtain prior to start of cycle unless otherwise indicated. For PK sampling, see Section 7.4.
Baseline: obtain studies prior to therapy. See additional timing requirements in Section 3.2.
Prior to Cycle 3: obtain studies between Days 18-22 of Cycle 2.
End of Cycle 5 *If NO RT*: obtain studies 4-6 weeks from Day 8/last dose of Cycle 5.
End of Cycle 5 *If RT*: obtain studies 3-4 weeks from start of Cycle 5.
End of RT: obtain studies 6-9 weeks from last day of RT.

STUDIES TO BE OBTAINED	Baseline	Prior to each cycle	Day 8 Cycle 2	Prior to Cycle 3	Prior to Cycle 4	Day 8 Cycle 5	End of Cycle 5 (If *NO* RT)	End of Cycle 5 (If RT)	End of RT
History and physical, including nodal exam **Day 1 of cycle unless otherwise indicated**	X	X					X		**X**
CBC/differential, electrolytes, BUN, creatinine, AST or ALT, and bili.	X	X					X	X	X
Albumin	X								
ESR (Erythrocyte Sedimentation Rate)	X								
Tumor biopsy/Pathology Report	X						X^{A}	X^{A}	
Bilateral bone marrow biopsy[B]	X^{B}			X^{B}			X^{B}	X^{B}	
ECG	X								
ECHO or MUGA	X				X				
PFTs[C], DLCO if > 5 years	X^{C}				X^{C}				
CXR (PA lateral)[L]	X								
CT with IV contrast [L]	X			X^{D}			X^{D}	X^{D}	X^{D}
^{18}Flurodeoxyglocose Imaging [L] (FDG-PET)	X (PET0)			X (PET2)			X^{E} (PET5)	X^{E} (PET5)	X^{F} (PET6)
Pregnancy test [G]	X								
Tissue for Correlative Biology[M] (See Table 7.2)	X								
Patient demographics [H] (CIPN study)	X_{Parent} X_{YA}								
FACT-GOG-Ntx [H] (CIPN study)	X_{Parent} X_{Y} X_{YA}		X_{Parent} X_{Y} X_{YA}			X_{Parent} X_{Y} X_{YA}	X_{Parent} X_{Y} X_{YA}		X_{Parent} X_{Y} X_{YA}
CHRIS-Global [H] (CIPN study)	X_{Parent} X_{Y} X_{YA}		X_{Parent} X_{Y} X_{YA}			X_{Parent} X_{Y} X_{YA}	X_{Parent} X_{Y} X_{YA}		X_{Parent} X_{Y} X_{YA}
Health Utility Index 2/3 [K] (CEA)	X_{Parent} X_{Y} X_{YA}		X_{Parent} X_{Y} X_{YA}			X_{Parent} X_{Y} X_{YA}	X_{Parent} X_{Y} X_{YA}		X_{Parent} X_{Y} X_{YA}
Stanford Healthcare Utilization [K] (CEA)	X_{Parent} X_{YA}		X_{Parent} X_{YA}			X_{Parent} X_{YA}	X_{Parent} X_{YA}		X_{Parent} X_{YA}
Caregiver Work Limitation(CEA) [K]	X_{Parent}						X_{Parent}		X_{Parent}

A Recommended (not required): consider biopsy in the absence of alternative explanation for increased metabolic activity. Submission of pathology report is highly recommended.
B Baseline required for children < 18 years old; recommended (not required) in adults ≥ 18. After Cycles 2, 5: in any age patient if positive at previous biopsy.
C Pulmonary Function Tests (PFTs) to include Forced Vital Capacity (FVC); Total Lung Capacity (TLC); Functional Residual Capacity (FRC); Carbon Monoxide Diffusing Capacity (DLCO) corrected for anemia, Residual Volume (RV) and Peak Flows (PIF, PEF).
D CT with IV contrast to include all areas involved at diagnosis. Perform between days 18-22 for Cycle 2.
E PET5: post-chemotherapy FDG-PET/CT performed only if PET2 was Deauville 4 or 5 (See Section 10.3.1). Perform with patient off filgrastim at least 10 days, or 3 weeks after pegfilgrastim.
F PET6: performed after external-beam (or proton) RT only if previous PET5 was positive (Deauville 5 point scale 3, 4 or 5- see Section 10.3.1).
G Women of childbearing potential require a negative pregnancy test prior to starting treatment; males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method during protocol therapy and for at least 30 days after the last dose of chemotherapy. Abstinence is an acceptable method of birth control.
H Required for patients enrolled before CIPN reached accrual on 9/8/2017. See Appendix VII for CIPN and Quality of Life study Parent or patient reported outcomes (CIPN): X_{Parent} refers to parent proxy ratings of CIPNs for all minors 5-17.9 years; X_{Y} refers to youth ages 11 – 17.9 and X_{YA} to young adult self-report of CIPNs.
K Required for patients enrolled before CEA reached accrual on 9/8/2017. See Appendix VIII for Cost Effective Analysis (CEA) study. The Caregiver WLQ is collected from parents of patients ages 5-17.9 and is not collected for patients who are 18 and older. For youth ages 11-17.9 the Stanford HCU measure is collected from parents; for young adults 18 and over, the appropriate version of this form is collected directly from the patient.
L Baseline chest radiograph must be upright CXR with a PA view (portable AP is not acceptable). See Section 14.4 for imaging central review requirements. See Section 15.13 for quality assurance documentation that must be submitted prior to start of RT.
M Tissue for patients who Consent to the Biology Studies should be submitted as per Section 13.0. Also see Section 7.2: if no block is available, 10 unstained slides and 2 H&E slides should be obtained for the Correlative Biology studies.

NOTE: This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as indicated for good clinical care.

7.2 Specimen Submission Schedule for Patients who Consent to the Biology Studies

Time point	Sample type	Specimen Volume *Total for tests listed at time point*	Immune studies	EBV*	TARC*	TMA/GEP*	Cytokine*	Mailing Location
Diagnosis	Tissue biopsy	1 block **or** 10 unstained and 2 H&E stained slides --- 0.5 g frozen tumor	X			X		BPC[1]
	Blood	> 12 kg: 2 mL/kg (max 20 mL) in heparin tubes[2]	X					Bollard lab[1]
Cycle 1 Day 1#	Blood	20 mL in heparin		X	X		X	BPC
Cycle 1 Day 8#	Blood	5 mL in heparin		X				BPC
Cycle 2 Day 1#	Blood	15 mL in heparin		X	X			BPC
Cycle 3 Day 1#	Blood	15 mL in heparin		X	X			BPC
Last day of Cycle 5 ± 30 days	Blood	5 mL in heparin		X				BPC
END OF CHEMOTHERAPY (*Collect* ONLY IF NO RT) -- *Time points are flexible ± 30 days.*								
Last day of Cycle 5	Blood	>12 kg: 2 mL/kg (max 40 mL) in heparin [2,3]	X					Bollard lab
4-6 weeks after last dose of Cycle 5	Blood	5 mL in heparin		X				BPC
END OF RT (SKIP *to Follow-up* IF NO RT*) -- Time points are flexible ± 30 days.*								
Last day of RT	Blood	7-10 mL in heparin		X				BPC
		>12 kg: 2 mL/kg (max 40 mL) in heparin [2]	X					Bollard lab
6-9 weeks after last day of RT	Blood	5 mL in heparin		X				BPC
FOLLOW-UP -- *Time points are flexible ± 30 days unless otherwise indicated.*								
3 months 6 months 9 months 12 months 24 ± 3 months *Time since end of all therapy*	Blood	5 mL in heparin		X				BPC
Relapse (prior to salvage chemotherapy)	Blood	20 mL in heparin						BPC
	Tissue *If Available*	1 block **or** 10 unstained and 2 H&E stained slides --- 0.5 g frozen tumor				X		

1. Refer to Appendix VI for complete sample collection, processing and shipping details, including guidance for packaging samples for temperature stability during non-winter months.
2. For patients weighing < 12 kg collect 1 mL/kg. For all patients: samples for immune studies should be collected in green top heparin tubes (either sodium heparin or lithium heparin are acceptable). **Do NOT use plasma separator tubes (PST)**.
3. For patients weighing < 21 kg who are participating in PK sampling, deduct 2.5 mL from volume to be sent to Bollard lab in order to send 2.5 mL for ATA testing (See Table 7.4).

* Planned studies that will be assessed at the completion of the protocol. Brief descriptions are provided in Appendix VI.

\# Prior to therapy.

Note: Details for collection, processing and shipping of blood samples are provided in Appendix VI, along with details for shipment of tissue samples. Rationale and details of planned correlative studies are also described in Appendix VI.

7.3 Follow-up

Patients should be followed closely off therapy for evidence of recurrent disease. It is recommended that patients also be monitored for the development of long-term toxicity from this therapy. The off-therapy procedures for toxicity monitoring below are based on the therapy in this protocol. However, they should be individualized as clinically indicated. Some patients may require more or less frequent evaluations. See COG Late Effects Guidelines for recommended post treatment follow-up:
http://www.survivorshipguidelines.org/

TIME (*months since end of all therapy*)	Physical Exams[1]	Lab Tests[2]	Labs for subjects that consented to biology study[3]	CIPN and CEA measures[4]	CT[5]
3 ± 1 month	X	X	X		
6 ± 1 month	X	X	X		X
9 ± 1 month	X		X		
12 ± 1 month	X	X	X	X[4]	X
18 ± 3 months	X	X			
24 ± 3 months	X	X	X		
30 ± 3 months	X	X			
36 ± 6 months	X	X		X[4]	
48 ± 6 months	X	X			

1 All PE to include assessment of nodal areas (required). Discuss potential late effects and preventive measures (recommended).

2 CBC every visit recommended until marrow recovery; then per institutional discretion. ALT or AST, BUN, creatinine, bilirubin at baseline into long term follow up - usually at 2 years post completion of therapy (recommended), after that, as clinically indicated.

3 Labs to be collected in participants who consented to biology studies. Follow up specimens are to be submitted to BPC. Refer to Table 7.2 and Appendix VI for sample collection, processing and shipping details,

4 Required for patients enrolled before CIPN/CEA reached accrual on 9/8/2017. CIPN and CEA time points are **12 ± 3** months and **36 ± 6** months off therapy. See Appendix VII and Appendix VIII for details. CEA measures are for US institutions only.

5 CT with IV contrast to include all areas involved at diagnosis. CT of the neck, chest, abdomen and pelvis. MRI neck, chest, abdomen and/or pelvis may be substituted for the CT scan (required) at designated times after completion of therapy. Ultrasound may be substituted, but is limited for visualizing celiac or mesenteric nodes. PET/CT is not recommended for routine surveillance if prior PET is negative.

Note: Follow-up data are expected to be submitted per the Case Report Forms (CRFs) schedule.

7.3.1 At Time of Relapse Sites Must Submit:

1. All imaging and reports documenting first relapse.
2. Blood and tissue (*if available*) samples for biology studies (See Section 7.2 and Appendix VI) if patient consented to the biology study.

7.4 Pharmacokinetics (PK) Studies

Limited to patients who are < 13 years of age who consent to PK sampling and receive treatment on the Experimental Arm (Bv-AVEPC).

Sampling for the PK can be via the same line through which the infusion is administered.

Blood draws will be conducted during Cycles 4-5 for the following assays:

1. Antibody drug conjugate (ADC): serum from 2.5 mL whole blood (per time point) collected in a serum separation tube.
2. Anti-therapeutic antibody (ATA): serum from 2.5 mL whole blood (per time point) collected in a serum separation tube.
3. Monomethymuriamine (MMAE): plasma from 2.7 mL whole blood (per time point) collected in a 3 mL Na Citrate (blue top) tube.

Table 7.4: PK Assessment Time Points and Blood Draw Volumes
Volumes listed are the minimum necessary for a requested sample.

ASSAY *and specimen type*	**Cycle 4**						**Cycle 5**	
	Day 1 *Pre*-dose*	Day 1 *End* of Infusion**	Day 2	Day 3	Day 8	Day 15 *±2 days*	Day 1 *Pre*-dose*	Day 22 *Flexible up to +30 days*
ADC *serum*	2.5 mL	2.5 mL	2.5 mL	2.5 mL	2.5 mL	2.5 mL	2.5 mL	
MMAE *plasma*	2.7 mL	2.7 mL	2.7 mL	2.7 mL	2.7 mL	2.7 mL	2.7 mL	
ATA *serum*	2.5 mL						2.5 mL	2.5 mL
Total volume	*7.7 mL*	*5.2 mL*	*5.2 mL*	*5.2 mL*	*5.2 mL*	*5.2 mL*	*7.7 mL*	*2.5 mL*

* *Pre*-dose: obtain sample ≤ 30 minutes prior to initiating infusion.
** *End* of Infusion: obtain sample ≤ 30 minutes after the end of infusion.

7.4.1 Order PK Sampling Kits before Cycle 2

For each patient consenting to PK sampling, order required PK sampling kits *before the patient begins Cycle 2* to allow adequate time for registration, order processing and shipment of the kits. Detailed instructions for ordering the kits are provided in the PK Guide to Registering and Ordering Kits available on the study web page.

7.4.2 Brief Overview of PK Sample Processing

Consult the current version of the PK Lab Manual available on the study web page for the technical specifics. Blood samples collected in the serum separation tubes will be allowed to clot at room temperature for a specified length of time, centrifuged, and then the serum component aliquoted and frozen without delay. Blood samples collected in the blue top (Na Citrate) tubes will be mixed and immediately cooled, centrifuged, and then the plasma component aliquoted and frozen without delay.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Progressive disease.
b) Refusal of further protocol therapy by patient/parent/guardian.
c) Completion of planned therapy.
d) Physician determines it is in patient's best interest.
e) Development of a second malignancy.
f) Repeat eligibility studies are outside the parameters required for eligibility (if applicable, see Section 3.2).
g) Study is terminated by Sponsor.
h) Pregnancy.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless patient is taken off study.

8.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Patient enrollment onto another COG study with tumor therapeutic intent (e.g., recurrence).
d) Withdrawal of consent for any further data submission.
e) Tenth anniversary of the date the patient was enrolled on this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Design

This is a randomized study that aims to examine the treatment efficacy of Bv in pediatric patients with high-risk classical HL. Primary outcome of interest is event-free-survival where events include disease relapse/progression, second malignancy, or death. Eligible patients are those age 21 or younger with classical HL at Stage IIB with bulk/IIIB/IVA/IVB disease, and will be randomized 1:1 between the standard arm of ABVE-PC and the experimental arm of Bv-AVEPC. After initial 2 cycles of chemotherapy, early response will be assessed by PET to determine slow responding lesions (SRL). At the end of 5 cycles of chemotherapy, patients with SRL at the post 2 cycle assessment will receive involved site radiation (ISRT) to SRL, and all patients with large mediastinal mass (LMA) at initial diagnosis will receive ISRT to LMA.

9.2 Patient Accrual and Expected Duration of Trial

The study will accrue 580 eligible patients with IIB bulk/IIIB/IVA/IVB cHL disease at age 21 or younger, with a maximum accrual of 600 patients. Enrolled patients who are found to not meet study eligibility staging criteria at the time of central review for early response assessment (after 2 cycles of chemotherapy) will be considered ineligible. Patients eligible for this study would have been eligible for and enrolled previously AHOD0031 or AHOD0831. Average annual accrual on AHOD0031 after 6 months from study activation for Stage IIB with bulk/IVA cHL patients age 18 or younger was about 69; average annual accrual on AHOD0831 after 6 months from activation for Stage IIIB/IVB cHL patients age 18 or younger was about 77. Therefore, the estimated accrual rate for patients with cHL at

IIB bulk/IIIB/IVA/IVB and 21 years old or younger is around 146 patients per year. The expected accrual duration for 580-600 patients is about 4 years.

Ineligibility rate on AHOD0031/AHOD00831 was less than 2%, suggesting up to 12 ineligible patients among 600 enrollments. We expect few patients to be ineligible due to incorrect staging criteria found by central review after 2 cycles. On previous COG studies (AHOD0431/AHOD0031/AHOD0831), which enrolled over 2100 patients, approximately 2.5% of patients were found by central reviews to have incorrect bulk disease or stage designation. On this study, even if the presence/absence of bulk disease was incorrectly specified by the institution, the majority of the patients will be eligible regardless. This is because IIIB/IVA/IVB patients are eligible with/without bulk disease and only IIB patients need to have bulk disease to be eligible. IIB bulk patients are projected to account for close to 25% of the total enrollment; given the prior misclassification rate of 2.5%, up to 4 IIB patients may be found ineligible due to incorrect bulk disease designation.

9.3 Statistical Analysis Methods

Statistical analyses methods for aims 1.3.2 - 1.3.3 and 1.3.7 - 1.3.9 are included under the respective sections in the Appendices.

9.3.1 Analysis Methods for Aim 1.1.1

9.3.1.1 Analysis Plan

Primary endpoint is event-free-survival (EFS), where events include disease progression or relapse, second malignancy, or death. Patients without any of these events will be censored at last contact. Primary analysis will be based 1-sided log rank test comparison of EFS curves between the 2 randomized arms per intention-to-treat principle. All eligible randomized patients will be included in the analysis. At final analysis, the significance level required to establish efficacy will take into account interim efficacy monitoring performed per Lan Demets method (see Section 9.3.7).

9.3.1.2. Power estimation

In power estimation, we assume a cure model for EFS curve in which a fraction of the patients will be cured and the failures for the rest of the patients follow an exponential distribution. In such cure model, we expect three quarters of the failures occur within the first 3 years. For standard arm, the projected 3-year EFS rate is 82%; assuming three quarters of failures within the first 3 years, the long-term EFS (cure fraction) for standard arm is 76% and the entire EFS curve is specified by the cure model described above.

The estimate of 82% for 3-year EFS is based on historical data from prior COG studies with similar ABVE-PC chemotherapy backbone, but not with exact same chemotherapy dose/schedule and radiation, because no prior high-risk patients were treated exactly the same as the standard arm of ABVE-PC. On AHOD0031, patients < 18 years of age with Stage IIB bulk/IVA cHL who were treated with 4 cycles of ABVE-PC with/without DECA and with/without involved field radiation (IFRT) had 3-year EFS of 78% and 5-year EFS of 77%. Long-term EFS on

AHOD0831 for IIIB/IVB patients treated with 4-cycles of ABVE-PC with/without IV/RT is not yet available. On POG9425 (3 or 5 cycles of ABVE-PC with radiation), IIB/IIIB/IVA/IVB patients had 3-year EFS of 86% and 5-year EFS of 84%, but this number includes IIB without bulk disease patients who are not included in the current study, due to observations from AHOD0031 that they had 3-year EFS of 90% compared to 3-year EFS of 75% for those with IIB bulk disease. Based on these prior data, we expect the 3-year EFS for control arm to be in low 80% and use 82% as our projected baseline.

Assuming a 3-year EFS of 82% (5-year EFS of 78.4%, long term EFS of 76%) for standard arm, the study will have approximately 86% power for detecting an 8% improvement in 3-year EFS in the Bv-AVEPC arm (3-year EFS of 90%, 5-year EFS of 88.0%, long term EFS of 86.7%) in log rank test when the EFS curves follow cure model as described earlier. Hazard ratio is approximately 0.53. Power estimation is based on 290 eligible patients per arm and 1-sided log rank test with alpha level of 0.05. One-sided test is used since there is no interest in establishing treatment difference in the other direction. The power estimation assumes 4 years of accrual and 1 year of additional follow up after last patient accrual. The number of expected events from 580 eligible patients under the null hypothesis is 99; the number of expected events under the alternative hypothesis is 77.

9.3.2 Analysis Methods for Aim 1.2.1

9.3.2.1 Analysis Plan

Endpoints for this aim include the proportion of patients with early response (i.e. no SRL nor PD at PET2) and the proportion of patients needing response-directed RT.

We are not utilizing the term rapid early response (RER) in the current protocol, as clinical treatment will be based on the response of individual nodal sites/lesions (RRL or SRL). For the purpose of analysis, patients achieving early response are those with no slow responding lesions (SRL) and no PD at all sites (including LMA) after 2 cycles of chemotherapy (Bv-AVEPC or ABVE-PC) determined by PET per Deauville criteria through central review.

Patients on each arm will receive RT to LMA and to any SRL after 2 cycles of chemotherapy. Patients with PD after 2 cycles of chemotherapy on each arm will be taken off protocol therapy but will be considered as needing RT for analysis purpose. RT to LMA is the same on both arms and depends only on baseline characteristics not on chemotherapy. To compare RT between the 2 arms, patients needing response-directed RT (regardless of whether the patient actually receives it) are those with any SRL at sites other than LMA after 2 cycles of chemotherapy and those with PD after 2 cycles of chemotherapy. For patients without LMA, any response-directed RT is the same as any protocol-directed RT (i.e., any SRL) or any PD. For patients with LMA,

response-directed RT is any RT to sites other than mediastinum (i.e., any SRL at sites other than mediastinum) or any PD. As the study does not include Stage I patients, all patients with LMA should have other site(s) of disease. By excluding RT to LMA, response-directed RT removes the "background" RT to LMA which is the same on both arms by design, and directly compares the effect of chemotherapy on RT administration. All randomized patients can either receive or not receive response-directed RT.

The proportion of patients achieving early response (i.e., with no SRL and no PD at all sites including LMA) will be compared between the two randomized arms to see if Bv-AVEPC arm has a higher rate of early response compared to ABVE-PC arm. The proportion of patients needing response-directed RT (including PD) will be compared between the two arms to see if Bv-AVEPC arm has a lower rate for response-directed RT compared to ABVE-PC arm. Two-sample Z test of proportions at 1-sided alpha level of 0.05 will be used for these comparisons.

9.3.2.2 Power estimation for early response rate comparison

For ABVE-PC arm, we project a 70%-80% rate of early response, and we hypothesize that the rate of early response will be at least 9% higher in Bv-AVEPC arm than in ABVE-PC arm. With 290 eligible patients per arm, the power for detecting a 9% increase in early response rate for Bv-AVEPC compared to ABVE-PC is at least 0.80 in two-sample test of proportions with 1-sided alpha of 0.05 when the rate of early response is at least 70% for ABVE-PC. The power is 0.91 when the rate of early response is 80% for ABVE-PC.

The baseline early response rate of 70%-80% in ABVE-PC arm was estimated from prior studies with similar but slightly different chemotherapy and slightly different PET criteria. Patients eligible for this high-risk study (IIB bulk/IIIB/IVA/IVB) were previously treated with ABVE-PC type of regimen on either AHOD0031 or AHOD0831. There were 22 Stage IIB with bulk/IVA patients from AHOD0031 with retrospectively reviewed 2-cycle PET by 5-point criteria; the rate of early response by 5-point criteria was 82% (18/22), and the rate of rapid early response as defined by traditional PET assessment utilized on AHOD0031 was 64% (14/22). Of all Stage IIB bulk and IVB cHL patients on AHOD0031, the rate of rapid early response by PET per traditional PET assessment was 71%, slightly higher than the number of 64% in this small cohort of 22 patients. For Stage IIIB/IVB patients, on AHOD0831 66% of them were rapid responder by PET after 2 cycles per traditional PET assessment utilized on AHOD0831; 5-point criteria PET assessments for these IIIB/IVB patients is not available at this time. Combining those historical high-risk patients, the rate of rapid early response by PET per traditional PET assessment is about 68%. We expect the rate of early response by PET 5-point criteria be slightly higher than that, and therefore project an early response rate of 70%-80% by PET 5-point criteria for ABVE-PC arm.

9.3.2.3 Power estimation for RT rate comparison

With 290 patients per arm, assuming a baseline rate of 25-30% (see below) for response-directed RT in the standard (ABVE-PC) arm, we will have at least 85% power for detecting a reduction of 9-10% (25% vs. 16%, 30% vs. 20%) in the proportion of patients getting response-directed protocol-RT in the experimental (Bv-AVEPC) arm. Power estimation is based on 2-sample test of proportions at 1-sided alpha level of 0.05.

Approximately half of the IIB bulk/IVA patients from AHOD0031 and half of the IIIB/IVB patients from P9425 did not have LMA; thus we project that half of the patients on this study will not have LMA. For IIB bulk/IVA patients on AHOD0031 who did not have LMA, approximately 25% were PET2 positive per the prior traditional PET assessment, slightly lower than 33% PET2 positive for IIB bulk/IV patients with LMA on AHOD0031. For IIIB/IVB patients on AHOD0831 (unfortunately LMA data not available), approximately 34% overall were PET2 positive per the traditional PET assessment. Based on these data, we project 25-30% PET2 positive rate for patients without LMA on the standard arm. This suggests 25-30% of patients without LMA will receive response-directed RT". For patients with LMA, we project a slightly higher rate of positive PET2 than patients without LMA, at 30-40% based on data from AHOD0031 and AHOD0831. For patients with LMA and other sites of disease, a positive PET2 at patient level reported in prior studies can mean a positive PET (i.e., SRL) at either mediastinum and/or other site(s) of disease; therefore the positive-PET2/SRL rate for disease site(s) other than mediastinum will be lower than the overall patient-level PET2 positive rate unless there is perfect correlation of PET2 responses between mediastinum and other sites. Since we expect a high correlation of PET2 outcome for mediastinum and other disease sites, for patients with LMA we project 25-30% for positive PET2/SRL rate at site(s) other than mediastinum. This corresponds to a projection of 25-30% patients with LMA will receive response-directed RT. Combining patients without LMA and patients with LMA, the rate of response-directed RT in the standard arm is estimated to be 25-30%.

9.3.3 Analysis Methods for Aim 1.2.2

9.3.3.1 Analysis Plan

The proportion of patients experiencing Grade 3+ peripheral neuropathy (assessed by modified Balis scale) after the first 2 cycles and after all 5 cycles of chemotherapy will be estimated for Bv-AVEPC arm and for ABVE-PC arm along with the corresponding 95% confidence intervals. For this analysis, all patients that received some protocol chemotherapy will be included. The proportion will be compared between the 2 arms by two-sample Z test of proportions at 1-sided alpha level of 0.05.

9.3.3.2 Power estimation

With 290 eligible patients per arm, we will have > 80% power for detecting a peripheral neuropathy rate increase from 3% to 8%, or from 2% to 7%, or from 1% to 5% for Bv-AVEPC arm compared to ABVE-PC arm at 1-sided alpha of 0.05.

On AHOD0031 and AHOD0831, the rate of Grade 3+ peripheral neuropathy (accessed by CTCAE which is expected to produce data similar to the modified Balis scale) was no more than 3%, and most of such toxicities were reported during the later cycles. On AHOD0031, the rate was < 1% during the first 2 cycles and altogether < 2% of patients reported such toxicities during treatment. On AHOD0831, all 5 patients with such toxicity (3% of total enrollments) reported such events during cycles 3-4.

9.3.4 Analysis Methods for Aim 1.3.1

9.3.4.1 Analysis Plan

For CHIPS, patients are assigned one score for each of the 4 factors: Stage IV disease, fever (≥38°C), LMA (> 1/3 thoracic diameter), and low albumin (< 3.5 g/dL). The total score is the sum over these 4 factors, which can range from 0 to 4.

CHIPS will be computed for all patients and summarized by descriptive statistics. Estimates for the distribution of CHIPS in this study population is lacking, since the only prior COG study that collected all the CHIPS factors is AHOD0031, which did not include Stage IIIB/IVB patients who are expected to make up slightly over half of the patients on this study. Among approximately 260 AHOD0031 Stage IIB bulk/Stage IVA patients with all CHIPS variables available, the distribution was 2% score 0, 40% score 1, 41% score 2, and 17% score 3; score of 4 was not possible on AHOD0031 due to Stage IV patients with any B symptom (including fever) not eligible for AHOD0031. Those high-risk patients with CHIPS 0-1 (42%) had 3-year EFS of 85%, compared to 3-year EFS of 71% for the CHIPS 2-3 (58%) patients. The early response rate by CT as assessed on AHOD0031 for those CHIPS 0-1 high-risk patients was 86%, compared to 74% for those with CHIPS 2-3; PET negativity as assessed on AHOD0031 by the traditional criteria was 76% for CHIPS 0-1 vs. 69% for CHIPS 2-3.

Since this study is limited to high-risk patients defined by the Stage and B symptoms, the population does not include the complete range of cHL patients, even though patients can be any CHIPS score. Patients with the same CHIPS will also be treated differently (Bv-AVEPC vs. ABVE-PC and +/- ISRT) with chemotherapy being randomly assigned while ISRT being non-randomly assigned. We will examine the association between CHIPS and early response by cross-tabulations and Chi-square tests within each arm separately, as well as logistic regression model where early response is the outcome variable and CHIPS the predictor variable combining the 2 arms with adjustment for randomized chemotherapy.

Early response has been shown to correlate with EFS so it can serve as a surrogate for examining the association between CHIPS and EFS.

Response and LMA-adapted RT introduces a complication in estimating and interpreting the association of CHIPS with EFS, as comparisons between CHIPS will be confounded by the non-random administration of RT. It is expected that patients with higher CHIPS (expect higher risk for EFS failures) will more likely be have SRL and thus receive RT which may reduce their risk for failures. Moreover, LMA is both a factor in CHIPS and part of the criteria for RT, which also introduces confounding effect in examining the association between CHIPS and EFS. For patients with otherwise similar CHIPS factors, those with LMA not only have 1 higher CHIPS score but also get RT, compared to those without LMA who may or may not get RT. These confounding effects are expected to attenuate the degree of association between CHIPS and EFS, which means the observed association would potentially conservative and be under-estimated. Despite these complications, we still anticipate observing overall association between CHIPS and EFS, as in the prior COG study AHOD0031 with response-adapted RT where CHIPS identified a cohort of patients with lower EFS who were not identified by early response to therapy. Overall, EFS by CHIPS within each arm and combining both arms will be estimated by Kaplan-Meier curves, and compared by log rank test. Subset analyses and Cox proportional hazards models will also be used to examine the correlation between CHIPS and EFS; interpretation of these subset analyses and adjusted analyses needs to be done carefully. For example, a comparison of CHIPS=1 ABVE-PC no-RT patients to CHIPS=2 ABVE-PC no-RT patients is not a direct comparison for all CHIPS 1 to 2 (treated with ABVE-PC and no-RT), it is comparing the subset of CHIPS 1 or 2 who have no initial LMA and no SRL after 2 cycles. Similarly analyses will be performed to examine the association between the groups defined by the traditional clinical factors (IIB with bulk, IIIB, IVA, and IVB) and clinical outcomes (early response and EFS). Here the groups are categories rather than ordered categories as defined by CHIPS.

9.3.4.2 Power estimation

As described earlier, the projected early response rate for the ABVE-PC arm is 70%-80% and higher on the Bv-AVEPC arm. We also expect the early response rate to be higher in patients with lower CHIPS score, as seen from AHOD0031. The power for detecting a difference in the rate of early response between 2 groups defined by CHIPS (such as 0-1 vs. 2-4) is shown in the table below. These analyses combine patients from both randomized patients. Power estimation is based on a two-sample test of proportions at 1-sided alpha of 0.05.

Table 1. Power for comparing rate of early response (no SRL) between 2 groups defined by CHIPS

% patients with lower CHIPS	% patients with higher CHIPS	% early response in patients with lower CHIPS	% early response in patients with higher CHIPS	Power
40% (n=232)	60% (n=348)	85%	76%	0.85
40% (n=232)	60% (n=348)	80%	70%	0.86
30% (n=174)	70% (n=406)	85%	76%	0.80
30% (n=174)	70% (n=406)	80%	70%	0.81
20% (n=116)	80% (n=464)	85%	74%	0.83
20% (n=116)	80% (n=464)	80%	68%	0.84

We project lower EFS for patients with higher CHIPS, as seen on AHOD0031. Power for comparing EFS between 2 groups defined by CHIPS is shown below. These analyses combine patients from both randomized arms. Power estimation is based on 1-sided log rank test at alpha of 0.05. EFS curves are assumed to follow cure model as specified for the primary aim, with accrual duration and follow-up the same as the primary aim.

Table 2. Power for comparing EFS between 2 groups defined by CHIPS

% patients with lower CHIPS	% patients with higher CHIPS	3-year EFS in patients with lower CHIPS	3-year EFS in patients with higher CHIPS	Power
40% (n=232)	60% (n=348)	90%	82%	0.83
40% (n=232)	60% (n=348)	85%	76%	0.82
30% (n=174)	70% (n=406)	90%	81%	0.83
30% (n=174)	70% (n=406)	85%	75%	0.82
20% (n=116)	80% (n=464)	90%	79%	0.83
20% (n=116)	80% (n=464)	85%	73%	0.82

9.3.5 Analysis Methods for Aim 1.3.4

9.3.5.1 Analysis Plan

For this aim, our hypothesis is that the use of involved site RT (ISRT) will significantly reduce the dose of radiation received by normal tissues compared to prior COG studies that employed involved-field RT (IFRT). We project that 50-60% of patients on ABVE-PC arm will receive ISRT (i.e. 145-174 patients), while a smaller percentage will receive RT on Bv-AVEPC arm. The dose of radiation received by normal tissues for ABVE-PC arm patients on this study will be compared to those for patients from prior studies with similar ABVE-PC chemotherapy backbone such as AHOD0031. Descriptive statistics will be used to summarize RT doses received by normal tissues on this study. Two-sample t-test will be used to compare the doses received on this study to those on prior studies.

9.3.5.2 Power estimation

We have used evaluated radiation dosimetry on 36 patients treated on AHOD0031, which employed IFRT, and found mean organ doses as follows: heart =11.9 Gy, lung = 9.1 Gy, thyroid = 19.2 Gy, bilateral breast = 4.0 Gy. Assuming at least 145 patients on ABVE-PC arm receiving RT on the current protocol, we will have at least 80% power to detect a 20% reduction in thyroid doses and breast doses, and a 25% reduction in heart and lung doses, based on observed standard deviations of 6.2 Gy, 4.3 Gy, 6.3 Gy, and 1.5 Gy for heart, lung, thyroid and breast doses from AHOD0031. Power estimation is based on two-sample t test with 1-sided alpha of 0.05.

9.3.6 Analysis Methods for Aim 1.3.5

9.3.6.1 Analysis Plan

For this aim, we will evaluate the efficacy of ISRT in two ways: 1) by analyzing the event-free survival of patients treated with response-adapted ISRT; 2) by evaluating patterns of relapse following ISRT. The specific hypotheses for these exploratory analyses are: 1) EFS for each chemotherapy arm and for the subset needing ISRT or the subset of SER on each arm will not be significantly worse than 82%; 2) less than 10% of relapses in the proposed study will be isolated nodal relapses that are "marginal misses" resulting from the use of ISRT instead of IFRT.

EFS for patients on each arm as well as those receiving ISRT or those with SER on each arm will be estimated. One-sample log rank test will be used to compare the observed EFS to the assumed baseline of 82% at 3 years to see if the observed EFS is significantly lower than the projection in these subsets. We recognize that the transition to ISRT is not the only change made to the standard therapy compared to prior COG trials, so it will not necessarily be possible to isolate ISRT as the cause if EFS falls significantly below the benchmark. Subset analyses will also be conducted to identify sites of failure and clinical factors associated with relapse. If the observed EFS is not significantly worse than the 82% benchmark, acknowledging that statistical power is limited in some of the subset analyses, this will provide some evidence that, in combination with the chemotherapy regimens used on this trial, ISRT is not associated with an unacceptably high relapse rate.

We will conduct an analysis of the patterns of failure of study patients to evaluate the incidence of isolated failures in nodal regions that would have been treated with IFRT but are not included in ISRT volumes. Patterns of failure analyses of AHOD0031 and AHOD0831 are ongoing and relapse data are currently too sparse to establish a definitive baseline expectation for the occurrence of such marginal failures. Among relapses currently reported in AHOD0831, 4% were isolated Stage I nodal failures. The large majority (81%) of relapses were in multiple nodal ± visceral sites. In the proposed study, we anticipate approximately 80 failures if the experimental arm is better than the standard arm as projected. Three isolated nodal failures in sites marginal to the RT

volume (4% of all relapses, 95% CI = 1%-11%) would be compatible with our current experience with IFRT. A proportion of marginal relapses ≥ 10% (e.g. 8/80 = 10%, 95% CI = 5%-19%) would be considered evidence that ISRT was not appropriate for the high-risk patients treated in this study.

9.3.6.2 Power estimation

For each arm (n=290), the study has at least 80% power to detect a decrease in EFS from the assumed baseline of 82% to 76% in one-sample log rank test with 1-sided alpha of 0.05. Among the subset of patients needing ISRT (patients with LMA or SRL), which is projected to be 50%-60% of the ABVE-PC arm (n=160 for 55%), the study will have at least 80% power for detecting a 3-year EFS of 74% in a similar 1-sample log rank test. Among the subset of SER patients (all needing ISRT), which is projected be about 20-30% on the ABVE-PC arm (n=72 for 25%), the study will have at least 80% power to detect a 3-year EFS of 70%. The proportion of patients getting RT and the proportion with SER are projected to be lower for the experimental arm than the standard arm, which will lead to smaller sample size and reduced power for these same analyses on experimental arm.

9.3.7 Interim Monitoring

9.3.7.1 Interim monitoring on EFS

Final analysis will be performed after the expected number of events under the alternative hypothesis (77 events) are observed. One interim efficacy monitoring will be performed after approximately 50% of the expected events (39 events), to avoid concerns for premature efficacy monitoring from a regulatory standpoint and too much alpha spending on interim analysis. Interim inefficacy/futility analysis will be performed after approximately 25%, 50%, and 75% of the expected events, i.e., after 20, 39, and 58 events. Interim analysis will be based on official data cutoff for COG DSMC review, which occurs every six months. The first inefficacy/futility analysis was performed in October 2017.

Interim efficacy monitoring boundary will be based on Lan-Demets method with spending function αt^2.[38] Information fraction (t) is calculated as the sum of observed events from both arms at the time of analysis divided by the sum of expected events from both arms under the alternative hypothesis (77 events). The interim efficacy monitoring bound will be based on the actual information fraction observed at the time of monitoring. The final analysis will be performed based on Lan-Demets method at the significance level, which maintains the overall alpha of 0.05. For example, if information fraction of exactly 50% was observed at interim monitoring, the boundary nominal p value will be 0.0125 for interim analysis, and the final analysis will be at significance level of 0.0446.

Interim inefficacy/futility analysis will be mostly based on Fleming-Harrington-O'Brien (FHOB) repeated testing of the alternative

hypothesis. Since the commonly used significance level of 0.005 in such repeated testing is considered too conservative under the null hypothesis, the testing boundary will be based on the modified boundary proposed by Anderson and High,[39] which crosses zero at 50% of the information. In this study, it corresponds to testing the alternative hypothesis at significance level of 0.027. Because such repeated testing of the alternative hypothesis can be too aggressive early in the study when the number of events is small, the inefficacy/futility monitoring based on testing of the alternative hypothesis will start at the 2nd monitoring after 39 events, which is also approximately the time inefficacy monitoring in this study should start according to the inefficacy monitoring approach proposed by Freidlin et al.[40] At the first monitoring after 20 events, a "harm" look as proposed by Freidlin et al will be implemented. This "harm" look is based on 1-sided 0.05 test of the null hypothesis in the direction of harm.

The table below shows simulation results (10000 iterations) for probability of rejecting the null hypothesis and early termination under the null hypothesis and the alternative hypothesis for 2 different inefficacy/futility monitoring approaches, both with one interim efficacy monitoring after 39 events based on Lan-Demets method with spending function αt^2. The inefficacy/futility analyses are either based on the FHOB repeated testing at 0.005 significance level at all 3 time points (20, 39, and 58 events), or based on the proposed approach (modified FHOB bound at 2nd/3rd time points with 1st time point being a "harm" look). Accrual of 580 eligible patients is assumed to be uniformly distributed over 4 years. With Amendment #3, the minimum follow-up time for final analysis was changed from 5 years to 3 years. The rationale for this change is that the survival curves for the two predecessor studies (AHOD0031-intermediate risk disease and AHOD0831-high risk disease) plateaued at 3 years after diagnosis, with the majority (91%) of the relapse events occurring within the first 3 years of follow-up. Final analysis is performed after 77 events or 3 years after the last patient enrollment, whichever comes first. The proposed modified-FHOB and "harm-look" approach leads to <1% power loss compared to FHOB boundary at 0.005 level, but has over 20% increase in the chance of early stopping for inefficacy under the null hypothesis.

Table 3. Probability of rejecting the null hypothesis and early termination with 2 different approaches

Truth	Inefficacy monitoring	Chance of Rejecting the Null Hypothesis		Chance of Early Stop with Interim Monitoring	
		No Interim Monitoring	With Interim Monitoring	For Efficacy	For Inefficacy
Null	Proposed	4.82%	4.67%	1.05%	71.8%
	FHOB 0.005		4.72%	1.05%	48.0%
Alternative	Proposed	85.8%	84.6%	36.9%	4.6%
	FHOB 0.005		85.1%	36.9%	1.3%

At the time of interim efficacy monitoring, observed EFS in each arm will be also be compared to the baseline EFS curve under the cure model with 3-year EFS of 82% via one-sample log rank test, as an informal monitoring to ensure that outcome on either arm is not significantly worse than projected. If the true EFS outcome in either arm is 76% at 3 years under the cure model, the power to detect a decrease in EFS from the specified baseline curve in the one-sample log rank is 0.83 at 1-sided alpha level of 0.05. Same monitoring boundary as that for efficacy monitoring will be used for this monitoring.

9.3.7.2 Interim monitoring on peripheral neurotoxicity for Bv-AVEPC arm

Rates of peripheral neuropathy will be monitored for Bv-AVEPC arm following Cycle 2 and Cycle 5 of therapy. Peripheral neurotoxicity (≥ Grade 3 on modified Balis score) rate will be examined for each DSMC report with official monitoring among the first 100 patients treated with Bv-AVEPC. The rate of reported Grade 3+ peripheral neurotoxicity was low (≤ 3%) with 4 or 5 cycles of ABVE-PC in prior POG/COG trials. Monitoring will be done via a Bayesian rule. The prior distribution for the rate of toxicity p is assumed a Beta distribution with parameters $\alpha=1$ and $\beta=19$. This Beta distribution for the rate of toxicity p has a mean of 5%; the support for $p \leq 10\%$ is 86%. If given the observed data at interim monitoring, the posterior probability of $p > 5\%$ is 0.9 or higher, it will be considered compelling evidence that the peripheral neurotoxicity rate is unacceptable and the study will be referred to DSMC for review and for amendment to eliminating Day 8 vincristine. Operationally, it will require, for example, ≥ 4/25, ≥ 6/50, ≥ 8/75, or ≥ 10/100 patients with neurotoxicity for the rule to be met. The exact rule will depend on the number of patients in the denominator at the time of the interim monitoring. If the true rate of toxicity is 5%, 10%, or 15%, the chance of observing ≥ 6/50 patients with toxicity are 4%, 38%, and 78% respectively; similarly, the chance of observing ≥ 10/100 patients with toxicity are 3%, 55%, and 95% respectively.

9.3.8 Analysis Methods for Aim 1.3.10

For the population that is Deauville 3 at PET2 (confirmed by central imaging review), the frequency of patients with persistent Deauville score of 3 at PET5 will be calculated with corresponding standard deviation.

For patients with at least one lesion that is Deauville 3 at PET2 (confirmed by central imaging review), the event time and the cause (death or relapse) will be recorded during follow-up. The cause-specific cumulative hazard of relapse will be calculated to evaluate the risk of relapse among these patients.

EFS and risk of relapse for cases that are RRL, but have Deauville 3 lesions, will be compared to those that are classified as complete metabolic response at PET2 with solely Deauville 1 or 2 lesions. The natural history of Deauville 3 lesions and the appropriateness of this Deauville cutoff at PET2 for determination of need for radiation therapy remains unknown. We will therefore compare the EFS and risk of relapse of patients with or without radiation at same Deauville score level

(2 or 3) and perform Cox multivariate models to include other possible covariates besides of the Deauville score.

9.3.9 Analysis Methods for Aim 1.3.11

Pharmacokinetic analyses will be performed by Seattle Genetics.

Pharmacokinetic concentration time-profile data of BV and MMAE will be evaluated using a population pharmacokinetic (PopPK) approach whereby the PK data from the AHOD1331 trial will be integrated with the brentuximab vedotin population PK models from other datasets. These integrated analyses will extend the understanding of the covariate effect of weight and/or other demographic covariates on the pharmacokinetic properties of brentuximab vedotin and MMAE, and would support an evaluation of what (if any) demographic profiles may require a dose adjustment in order to maximize an individual's benefit/risk.

Initial enrollment data indicates that an age cut-off of < 13 years will be expected to capture approximately 10.3% (22 of 214) of subjects that weigh < 40 kg; and 5.6% (12 of 214) of subjects that weigh below 30 kg. Assuming by the point of amendment there are 300 subjects remaining to enroll (1:1 experimental to standard arm); it is expected that intensive brentuximab vedotin PK data from 15 subjects (10% of 150) will be obtained to further inform our understanding of brentuximab vedotin PK. Of these 15 subjects, half (~8) will be below 30 kg and half (~7) will be between 30-40 kg.

It is also worth pointing out that, with an age cut-off entry criterion into the PK sub-study, there will naturally be subjects who are under the age of 13 and that weigh > 40 kg who will also undergo these additional PK assessments. These predictions are summarized in the following table.

Predicted Enrollment in PK Sub-study with Age < 13 years Entry Criteria.	
Weight	**Number of Subjects Enrolled***
<30 kg	8
30 to 40 kg	7
>40 kg	15
**Assuming 1:1 experimental to standard arm randomization and 300 subjects remaining to enroll in study at the time of Amendment 2B activation.*	

We expect a sample size of 7-8 in each of the under 30 and 30 to 40 kg weight ranges to be sufficient to provide PK data to explore and characterize the demographic effects of weight and/or other covariate factors on the PK of brentuximab vedotin in these pediatric subjects. Additionally, we expect the 15 subjects in the >40 kg group to provide valuable PK information that may assess in exploring the impact of other important factors such as age and sex on brentuximab vedotin PK. Note, in typical first-in-human studies, a sample size of 6 to 8 subjects per cohort is considered sufficient to characterize the PK properties of a drug at a given dose-level.

In summary, the addition of this aim to AHOD1331 will provide additional needed pediatric data for every-21-day dosing and evaluate the PK of brentuximab vedotin in combination with the AVE-PC backbone of chemotherapy.

9.4 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	58	47	105
Not Hispanic or Latino	205	290	495
Ethnic Category: Total of all subjects	263	337	*600
Racial Category			
American Indian or Alaskan Native	1	4	5
Asian	6	17	23
Black or African American	37	45	82
Native Hawaiian or other Pacific Islander	1	1	2
White	218	270	488
Racial Category: Total of all subjects	263	337	*600

* These totals must agree

This distribution was derived from combining patients younger than 18 years of age with Stage IIB bulk and IVA disease on AHOD0031 and those younger than 18 years of age on AHOD0831 according to their projected proportion on this study.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 5.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting, except for the grading of neuropathy, which will use the modified Balis Scale. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: 'CTCAE v5.0' is understood to represent the most current version of CTCAE v5.0 as referenced on the CTEP website (i.e., version 5.02 and all subsequent iterations prior to version 6.0).

10.2 Baseline Imaging Lesion Evaluation at Diagnosis

Imaging guidelines and response criteria have been revised from previous COG protocols, including AHOD0031, AHOD0431, AHOD0831, CCG 5942, CCG 59704, POG 9425, and POG 9426 and incorporate International Lymphoma Working Group's revised recommendations and the Euro net consortium guidelines for malignant lymphoma.[41,42]

Note: The determination of RRL or SRL and CR will be based on interim and end-of-therapy FDG-PET response, and will not be based on size change on CT, with the exception of macronodular splenic involvement. CT-based size criteria will still be used in the determination of PD and in cases of macronodular splenic involvement. As such, diagnostic quality contrast-enhanced CT imaging will still be required for staging and at the time of interim and end of therapy response assessment. This will also facilitate comparison with prior COG studies, and allow the importance of CT imaging to be prospectively assessed within the context of the proposed PET response criteria.

10.2.1 Staging Considerations

Measurable disease indicates the presence of at least one measurable lesion. Superficial lesions (e.g., palpable lymphadenopathy) measurable only by clinical exam or ultrasound are operator dependent and are not admissible as target lesions. A measurable lesion by CT is a lesion that can be accurately measured in 2 orthogonal dimensions. For extranodal sites, this typically involves lesions of at least 1 cm diameter. Lymph nodes are considered abnormal if the long axis is > 2.0 cm, regardless of the short axis. Lymph nodes with a long axis measuring between 1.0-2.0 cm are only considered abnormal if they are part of a conglomerate of nodes and are FDG-PET positive.

10.2.1.1 Evaluable disease

Non-measurable evaluable lesions include permeative bone lesions, malignant ascites, malignant pleural/pericardial effusions, pulmonary or cutaneous lymphangitic spread, and lesions too small to accurately measure in 2 dimensions by CT. All non-target and non-measurable assessable lesions will be recorded at baseline and noted on follow-up.

10.2.1.2 Lymph node involvement

Any lymph node is considered involved if and only if it is FDG-PET positive.

FDG-PET positive is defined as:

a. For moderately sized (≥ 2 cm in greatest transverse diameter by CT) regardless of their location, mild and diffusely increased FDG uptake with intensity higher than that of mediastinal blood pool structures should be considered positive. When possible use the ascending aorta or aortic arch for reference mediastinal blood pool. (See Section 10.3.1)
b. For smaller masses or normal sized lymph nodes (< 2 cm in greatest transverse diameter by CT), any FDG uptake more than that of surrounding background activity should be considered positive.

10.2.1.3 Bulk Disease (See Appendix I)

10.2.1.4 Extra nodal involvement

- Extra-lymphatic structures contiguous with sites of lymph node involvement are considered E-lesions (particularly lung). Exception: liver and/or bone marrow involvement is considered Stage 4.
- Pleural and pericardial effusions alone are not considered E-lesions.
- Pleural, pericardial, or chest wall infiltration by an adjacent nodal lesion that is PET positive is considered an E-lesion.

10.2.1.5 Organ involvement

10.2.1.5.1 *Lung*

Lung involvement is assumed if there is at least one intrapulmonary focus that is >1 cm and is PET positive or 3 or more lesions between 0.5 and 1 cm regardless of FDG-PET activity. Solitary lung nodules that are < 1 cm in transverse diameter, but are FDG avid, are also considered disease.

10.2.1.5.1.1 FDG-PET positive is defined as:

a. For lung nodules that are ≥ 1 cm in greatest transverse diameter by CT, FDG uptake exceeding that of mediastinal blood pool structures should be considered positive. When possible use the ascending aorta or aortic arch for reference mediastinal blood pool.
b. For lung nodules < 1 cm in greatest transverse diameter by CT, due to partial volume averaging effects, any uptake is considered positive.

10.2.1.5.2 *Visceral organs (liver, spleen, kidney)*
Any focal mass lesion large enough to characterize is considered due to lymphomatous involvement unless the imaging characteristics indicate an alternative nature (e.g., cyst, hemangioma, abscess, etc.). Ultrasound or MRI may be utilized if clarification is necessary. Focal splenic lesions seen on an appropriately timed IV contrast enhanced CT scan can be considered positive if they are PET positive; small lesions below limits of detection by PET/CT must be confirmed by ultrasound or MRI. Splenomegaly without focal lesions does not indicate splenic involvement with disease.

10.2.1.5.2.1 Hepatic and Splenic Lesions:
FDG-PET positive is defined as:

a. For hepatic or splenic lesions ≥ 1.5 cm on CT, FDG uptake greater than or equal to that of normal liver or spleen parenchyma, respectively, should be considered positive.
b. For hepatic or splenic lesions < 1.5 cm on CT, FDG uptake greater than that of normal liver or spleen parenchyma, respectively, should be considered positive.
c. In the absence of focal splenic involvement at diagnosis, diffusely increased splenic FDG uptake greater than normal liver parenchymal FDG uptake but in the absence of lesions seen on CT will not be considered evidence of involvement.

10.2.1.5.3 *Bone and bone marrow involvement*
Focal bone lesions that are permeative, sclerotic, or both and are PET positive are considered involved. A bone focus of PET positivity outside the regions included in pre-study diagnostic CT evaluation should be assessed on the attenuation correction CT. Alternatively this can be evaluated individually by dedicated regional CT or preferably MRI. If there are three or more PET positive bony foci with no CT or MRI correlate these likely represent bone marrow involvement and are sufficient to establish Stage IV disease. As part of the Imaging aim, these will be recorded and will be correlated with bone marrow biopsy results at a later time. For this reason bone marrow biopsy results (required in children < 18 years of age; optional in patients who are ≥ 18 years of age) should be recorded on all patients when they are performed.

10.2.1.5.3.1 Bone Marrow FDG Uptake:
FDG-PET positive is defined as:

a. Three or more FDG-PET positive lesions in bone marrow. Suggest MRI correlation for confirmation of these FDG-PET positive marrow foci if possible. Diffusely increased bone marrow FDG uptake, regardless of level of uptake – including more intense than liver, is not considered positive.
b. A negative bone marrow FDG-PET does not exclude bone marrow involvement or preclude a bone marrow biopsy/aspirate assessment.

10.3 Response Criteria

Guidelines for standardization using visual FDG-PET for interim response assessment are still developing with improved outcome on interim PET in Hodgkin Lymphoma when applying a higher visual PET threshold compared to current IWG thresholds.[43,44] The level of tumor uptake on FDG-PET imaging was assessed in the prior COG high-risk protocol, AHOD0831, subjectively by visual inspection, in concordance with the International Working Group criteria adapted to the pediatric oncology population.[25] Incorporation of FDG-PET for lymphoma interim response assessment however is critically dependent on the visual threshold used to determine a positive PET scan (slow responding lesion, SRL) versus a negative PET scan (rapid responding lesion, RRL). A recent study demonstrated that visual 5-point score or Deauville criteria can improve prediction of outcome and are reproducible enough in advanced-stage Hodgkin Lymphoma for recommendation as a standard reporting criterion in clinical practice and for clinical trials.[44,45] Note: Semi-quantitative assessment of response by determination of standardized uptake values (SUV) is not utilized for treatment decisions in this study. However, SUV measurements will be available for all PET scans and can be incorporated into reports as per routine clinical practice.

The COG AHOD1331 high-risk HL initial therapeutics clinical protocol will incorporate interim FDG-PET assessment as an integral part of its risk-adapted treatment stratification scheme. This assessment will consist of central review of the baseline PET (PET0) and post-Cycle 2 PET (PET2) utilizing a 5-point visual scale or Deauville criteria, which has been validated in other HL studies and our own COG retrospective study.

For the purposes of this protocol, FDG-PET response criteria for PET-positive and PET-negative will be used at interim PET2 and at post-chemotherapy PET5. At PET2, individual lesion/nodal response (SRL or RRL) will be determined by FDG-PET. At PET5, for those subjects that have at least one SRL at PET2, overall response (IMR or CMR) will be determined by FDG-PET. CT based size criteria are used in conjunction with FDG-PET to determine progressive disease (PD) at any time point. Note that the definition of PET positive/negative varies depending on the time point of therapy (See Sections 10.3.1 and 10.3.2 and Tables 10.3.1.and 10.3.2).

PET/CT scans using an IV-contrast CT as the attenuation-correction CT component of the PET/CT will be permitted for this study. However, PET/MRI will not be permitted.

10.3.1 Definition of PET Response of Lymph Node or Nodal Masses

Visual PET criteria are scored according to uptake involved by lymphoma from the Deauville 5-point scale from 1 to 5 as follows:

1) No uptake.
2) Uptake ≤ mediastinal blood pool.
3) Uptake > mediastinal blood pool and ≤ normal liver.
4) Moderately increased uptake > normal liver.
5) Markedly increased uptake > normal liver.

10.3.1.1 Baseline PET (PET0) response visual threshold utilizes mediastinal blood pool as the reference activity:

- FDG-PET positive is defined as visual score 3, 4, 5.
- FDG-PET negative is defined as visual score 1, 2.

10.3.1.2 Interim post Cycle 2 PET (PET2) response visual threshold uses normal liver as the reference activity:

- FDG-PET positive is defined as visual score 4, 5.
- FDG-PET negative is defined as visual score 1, 2, 3.

10.3.1.3 End of chemotherapy PET (PET5) response visual threshold also utilizes mediastinal blood pool as the reference activity:

- FDG-PET positive is defined as visual score 3, 4, 5.
- FDG-PET negative is defined as visual score 1, 2.

10.3.2 Splenic Response

In the instance where there is diffuse splenic uptake secondary to recent G-CSF administration the FDG-PET studies may not be of sufficient quality to adequately assess for response to therapy. In those circumstances CT criteria of macroscopic nodular should be used to assess for response to therapy. Decrease of all measurable splenic lesions by 50% in largest transverse diameter is considered a favorable response or ≤ 1 cm is considered a favorable response. Alternative imaging with MRI or ultrasound may be used instead of or in addition to CT scan for assessment.

Table 10.3.1 - Interim FDG-PET/CT (PET2)

Deauville score of PET at Baseline	PET 2 result	CT with contrast result*	Interim Response Stratification
Any PET Positive Lesions**	Deauville 1, 2, 3	Mass of any size	Rapidly Responding Lesion (RRL)&
Deauville 4, 5	Deauville 4, 5	< 50% increase in PPD (product of perpendicular diameter) of any of the nodal masses relative to baseline CT	Slowly Responding Lesion (SRL)#, &
Deauville 4, 5	Deauville 4, 5	≥ 50% increase in PPD of any of the nodal masses relative to prior measurement OR appearance of new lesion(s) > 1.5 cm in any axis.	Progressive Disease (PD)
Deauville 1, 2, 3	Deauville 4, 5	Any	Progressive Disease (PD)@
N/A	Deauville 3, 4, 5	**New Lesion(s)** > 1.5 cm in any axis not seen on baseline CT	Progressive Disease (PD)@

* CT with contrast will be used for radiation therapy planning purposes.
** See Baseline Imaging Lesion Evaluation at Diagnosis criteria, Section 10.2
# Nodal regions with SRL will be detailed for radiation therapy planning purposes
& PET5 is limited to patients with Deauville ≥ 4 PET2 results. PET5 is required for any SRL (Deauville score 4, 5).
@ In the absence of alternative explanation for increased metabolic activity. Consider biopsy if uncertain.
Note: Visual PET criteria are scored according to uptake involved by lymphoma applying the Deauville 5-point scale of 1 to 5 as follows: 1) No uptake, 2) Uptake ≤ mediastinal blood pool, 3) Uptake > mediastinal blood pool and ≤ normal liver, 4) Moderately increased uptake > normal liver, 5) Markedly increased uptake > normal liver.

Table 10.3.2 – End of Chemotherapy FDG-PET/CT (PET5)

PET 2 result	PET 5 result	CT with contrast result	End of therapy Response
RRL and SRL	Deauville 1, 2	Mass of any size	Complete Metabolic Response (CMR)
Deauville 3	Deauville 3	< 50% increase in PPD of any of the nodal masses compared with baseline	Complete Metabolic Response (CMR)
SRL	Deauville 3, 4, 5	< 50% increase in PPD of any of the nodal masses compared to CT 2	Incomplete Metabolic Response (IMR)^
RRL and SRL	Deauville 3, 4, 5	≥ 50% increase in PPD of any of the nodal masses compared to CT 2	Progressive Disease (PD)
RRL	Deauville 4, 5	Any	Progressive Disease (PD)@
N/A	Deauville 3, 4, 5	**New Lesion(s)** > 1.5 cm in any axis compared to any previous CT	Progressive Disease (PD) @

^ SRL with Incomplete metabolic response will require RT boost (see Section 15.3)
@ In the absence of alternative explanation for increased metabolic activity, consider biopsy if uncertain.

10.3.3 Complete Metabolic Response (CMR)

10.3.3.1 HL is typically an FDG-avid lymphoma. Pre-treatment PET scans are required. At sites where the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

10.3.3.2 See Section 10.3.2 for the situation where splenic response cannot be adequately assessed by PET.

10.3.3.3 New FDG-PET positive lung nodules in patients without established pulmonary lymphoma at baseline prior to initiation of therapy and evidence of complete response at all previously known disease site should be considered negative for lymphoma regardless of size or uptake because these typically represent infectious or inflammatory lesions.

Lesions that were Deauville 3 (and hence RRL by definition) at PET2 will be considered as such regardless of PET5 findings; these lesions will not receive RT unless they demonstrate progression at PET5

10.3.4 Incomplete Metabolic Response (IMR)

10.3.4.1 At sites where the FDG-PET scan was positive before therapy, the post-treatment PET is positive at one or more of the previously involved sites. See Section 10.3.1.3 for end of chemotherapy PET (PET5) response visual threshold which utilizes mediastinal blood pool as the reference activity.

10.3.4.2 There should be no progressive disease, including new sites of disease, as defined in Tables 10.3.1.and 10.3.2 and Section 10.3.5.

10.3.4.3 See Section 10.3.2 for the situation where splenic response cannot be adequately assessed by PET.

10.3.5 Relapsed Disease (after CR) or Progressive Disease [PD]

10.3.5.1 At least 50% increase in the product of the perpendicular diameters (PPD) of any of the involved nodes or nodal masses. To be considered progressive or relapsed disease, a lymph node with a short axis diameter of less than 1.0 cm must increase by ≥ 50%, i.e., to a size of 1.5 x 1.5 cm or to more than 1.5 cm in the long axis.

10.3.5.2 At least 50% increase in the PPD of any of the focal organ lesions.

10.3.5.3 Lesions should be FDG positive in order to be considered progressive or relapsed disease, provided they are sufficiently large to be detected by current PET systems (i.e., ≥ 1.5 cm in longest diameter). New FDG-PET positive lung nodules in patients without established pulmonary lymphoma should be considered negative for lymphoma regardless of size or uptake because these typically represent infectious or inflammatory lesions. For enlarging lymph nodes or nodal aggregates that are FDG-negative, biopsy is required to establish progressive or relapsed disease.

10.3.5.4 Increase in Deauville score in previously PET positive lesions. See Table 10.3.1 and Table 10.3.2.

10.3.5.5 Progression or relapse of non-measurable assessable disease at an extranodal site (e.g., pleural and/or pericardial effusions, bone lesions, bone marrow). Disease that is only assessable will still be considered positive for malignancy unless it is histologically negative (this includes bone marrow disease).

10.3.5.6 Development of new measurable lesion(s) or new sites of assessable disease. These new lesions should be PET avid.

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Certain adverse events must be reported in an expedited manner to allow for timely monitoring of patient safety and care. The following sections provide information about expedited reporting.

11.2 Determination of reporting requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label. **Brentuximab vedotin is the investigational agent in this study.**

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- *Concurrent administration*: When an investigational agent is used in combination with a commercial agent, the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- *Sequential administration*: When a study includes an investigational agent and a commercial agent on the same study arm, but the commercial agent is given for a period of time prior to starting the investigational agent, expedited reporting of adverse events that occur prior to starting the investigational agent would follow the guidelines for commercial agents. Once therapy with the investigational agent is initiated, all expedited reporting of adverse events follow the investigational agent reporting guidelines.

11.3 **Expedited Reporting Requirements – Serious Adverse Events** (SAEs)

To ensure compliance with these regulations/this guidance, as IND/IDE sponsor, NCI requires that AEs be submitted according to the timeframes in the AE reporting tables assigned to the protocol, using the CTEP Adverse Event Reporting System (CTEP-AERS).

Any AE that is serious qualifies for expedited reporting. An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A Serious Adverse Event (SAE) is any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse drug experience.
3) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations that are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.4 **Special Situations for Expedited Reporting**

11.4.1 SAEs Occurring More than 30 Days After Last Dose of Study Drug

Any Serious Adverse Event that occurs more than 30 days after the last administration of the investigational agent/intervention **and** has an attribution of a possible, probable, or definite relationship to the study therapy must be reported according to the CTEP-AERS reporting tables in this protocol.

11.4.2 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported via CTEP-AERS if it occurs at any time following treatment with an agent under a NCI IND/IDE since these are considered to be serious AEs.

11.4.3 Death

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- 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.

Any death occurring ***within 30 days*** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring ***greater than 30 days*** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

11.4.4 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 metastasis of the initial neoplasm is not considered a secondary malignancy.

The NCI requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy

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

11.4.5 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 via CDUS unless otherwise specified

11.4.6 Pregnancy, Pregnancy Loss, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, needs to be completed and faxed along with any additional medical information to (301) 230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

11.4.6.1 **Pregnancy**

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy)*"** under the ***"Pregnancy, puerperium and perinatal conditions"*** SOC.

Pregnancy needs to be followed **until the outcome is known**. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

11.4.6.2 **Pregnancy Loss (Fetal Death)**

Pregnancy loss is defined in CTCAE as "*Death in utero*." Any Pregnancy loss should be reported expeditiously, as **Grade 4 "*Pregnancy loss*" under the "*Pregnancy, puerperium and perinatal conditions*" SOC**. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.4.6.3 **Death Neonatal**

Neonatal death, defined in CTCAE as "*Newborn death occurring during the first 28 days after birth*", should be reported expeditiously, as **Grade 4, "*Death Neonatal*" under the "*General disorders and administration*" SOC, when the death is the result of a patient pregnancy or pregnancy in partners of men on study**. Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.5 Reporting Requirements for Specialized Adverse Events

11.5.1 Baseline AEs

Although a pertinent positive finding identified on baseline assessment is not an AE, when possible it is to be documented as "Course Zero" using CTCAE terminology and grade. An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (e.g., elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the study and reported if it fulfills expedited AE reporting guidelines.

a. If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required.

b. If the AE resolves and then recurs, the investigator must re-assess the event to determine if an expedited report is required.
c. No modification in grading is to be made to account for abnormalities existing at baseline.

11.5.2 Persistent AEs

A persistent AE is one that extends continuously, without resolution between treatment cycles.

ROUTINE reporting: The AE must be reported only once unless the grade becomes more severe in a subsequent cycle. If the grade becomes more severe the AE must be reported again with the new grade.
EXPEDITED reporting: The AE must be reported only once unless the grade becomes more severe in the same or a subsequent cycle.

11.5.3 Recurrent AEs

A recurrent AE is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.
ROUTINE reporting: An AE that resolves and then recurs during a subsequent cycle/course must be reported by the routine procedures.
EXPEDITED reporting: An AE that resolves and then recurs during a subsequent cycle/course does not require CTEP-AERS reporting unless:

1) The grade increases OR
2) Hospitalization is associated with the recurring AE.

11.5.4 Neuropathy reporting:

All Grade ≥ 2 neuropathy by the Balis scale is to be noted on the CRF on either study arm.

11.6 Exceptions to Expedited Reporting

11.6.1 Specific Protocol Exceptions to Expedited Reporting (SPEER)

The SPEER for brentuximab vedotin is in Section 6.1.2.

SPEER: Is a subset of AEs within the Comprehensive Adverse Events and Potential Risks (CAEPR) that contains a list of events that are considered expected for CTEP-AERS reporting purposes. (Formerly referred to as the Agent Specific Adverse Event List (ASAEL).)

AEs listed on the SPEER should be reported expeditiously by investigators to the NCI via CTEP-AERS ONLY if they exceed the grade of the event listed in parentheses after the event. If the CAEPR is part of a combination IND using multiple investigational agents and has an SAE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

11.6.2 Special Situations as Exceptions to Expedited Reporting

An expedited report may not be required for a specific protocol where an AE is listed as expected. The exception or acceptable reporting procedures will be specified in the protocol. The protocol specific guidelines supersede the NCI Adverse Event Reporting Guidelines. These special situations are listed under the CTEP-AERS reporting Table A for this protocol.

11.7 **Reporting Requirements - Investigator Responsibility**

Clinical investigators in the treating institutions and ultimately the Study Chair have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention. It is the responsibility of the treating physician to supply the medical documentation needed to support the expedited AE reports in a timely manner.

Note: All expedited AEs (reported via CTEP-AERS) must also be reported via routine reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database.

11.8 **General Instructions for Expedited Reporting via CTEP-AERS**

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. 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 website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

An expedited AE report for all studies utilizing agents under an NCI IND/IDE must be submitted electronically to NCI via CTEP-AERS at: https://eapps-ctep.nci.nih.gov/ctepaers.

In the rare situation where Internet connectivity is disrupted, the 24-hour notification is to be made to the NCI for agents supplied under a CTEP IND by telephone call to (301)-897-7497.

In addition, once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered into the electronic CTEP-AERS system by the original submitter of the report at the site.

- Expedited AE reporting timelines are defined as:
  - **24-Hour; 5 Calendar Days -** The AE must initially be reported via CTEP-AERS within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
  - **7 Calendar Days -** A complete expedited report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any event that results in a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect, or is an IME, which based upon the medical judgment of the investigator may jeopardize the patient and require intervention to prevent a serious AE, must be reported via CTEP-AERS **if the event occurs following investigational agent administration.**

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

- Any death occurring greater than 30 days of the last dose with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

CTEP-AERS Medical Reporting includes the following requirements as part of the report: 1) whether the patient has received at least one dose of an investigational agent on this study; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Any medical documentation supporting an expedited report (e.g., H & P, admission and/or notes, consultations, ECG results, etc.) MUST be faxed within 48-72 hours to the NCI. NOTE: English is required for supporting documentation submitted to the numbers listed below in order for the NCI to meet the regulatory reporting timelines.

Fax supporting documentation **for AEs related to investigational agents supplied under a CTEP IND** to: (**301) 230-0159** (back-up: (301) 897-7404).

Also: Fax or email supporting documentation to COG for **all** IND studies (Fax # (310) 640-9193; email: COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator).

- **ALWAYS include the ticket number on all faxed documents.**
- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

11.9 Reporting Table for Late Phase 2 and Phase 3 Studies – Table A

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:
1) Death.
2) A life-threatening adverse event.
3) Any AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. This does not include hospitalizations that are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6.)

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour Notification
5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not Required</td><td>7 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR. Additional Special Situations as Exceptions to Expedited Reporting are listed below.

Expedited AE reporting timelines are defined as:
"24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour notification.
"7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

11.10 **Protocol Specific Additional Instructions and Expedited Reporting Exceptions**

- **Grades 1-4 myelosuppression (anemia, neutropenia, and thrombocytopenia) do not require expedited reporting.**
- **Grades 1-2 AST/ALT elevations do not require expedited reporting.**
- **Grade 3 AST/ALT elevations do not require expedited reporting if they recover to ≤ Grade 1 (< 2.5 X ULN) or baseline within 7 days of study drug interruption.**
- **Grade 3 febrile neutropenia does not require expedited reporting.**
- **Grade 1-2 pulmonary toxicity does not require expedited reporting.**
- **Grade 3 infection does not require expedited reporting.**
- **Grade 3 nausea and vomiting of < 3 days duration does not require expedited reporting.**
- **Grade 3 hyponatremia, hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation does not require expedited reporting.**
- **Grade 3 GI toxicities – mucositis, stomatitis, diarrhea, gastritis does not require expedited reporting.**
- **Grade 3 Hypersensitivity reactions not related to brentuximab vedotin (e.g. from bleomycin or etoposide) do not require expedited reporting.**
- **Grade 3 anorexia; hyperglycemia; hypoalbuminemia; back pain; bone pain; pruritis do not require expedited reporting.**
- **Constipation (Grade 1, 2, and 3) do not require expedited reporting.**

11.11 **Reporting of Adverse Events for commercial agents – CTEP-AERS abbreviated pathway**

The following are expedited reporting requirements for adverse events experienced by patients on study who have not received any doses of an investigational agent on this study. Commercial reporting requirements are provided in Table B.

COG requires the CTEP-AERS report to be submitted **within 7 calendar days** of learning of the event.

Table B
Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.

CTEP-AERS Reporting Requirements for Adverse Events That Occur During Therapy with a Commercial Agent or within 30 Days[1]

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS

[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent that can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via CTEP-AERS.

11.12 Routine Adverse Event Reporting

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, during protocol treatment, routine reporting will include all toxicities reported via CTEP-AERS, **all Grade ≥ 2 peripheral neuropathy (by the Balis scale) in either study arm,** Grade 3 and higher Adverse Events, and all Grade 2 Adverse Events that result in dose modifications listed in Section 5.0. During off-protocol therapy follow up period, routine reporting will include all toxicities reported via CTEP-AERS, plus all Grade ≥ 2 peripheral neuropathy, all Grade ≥ 3 cardiac Adverse Events, and all Grade ≥ 3 pulmonary Adverse Events – but only for occurrence ***before*** the patient receives any post-protocol (i.e., non-AHOD1331) chemotherapy, radiation, or stem cell transplantation.

12.0 RECORDS AND REPORTING

See the Case Report Forms posted on the COG web site with each protocol under "*Data Collection*". A submission schedule is included.

12.1 CDUS

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

12.2 CRADA/CTA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other

media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential / proprietary information.

13.0 PATHOLOGY GUIDELINES

13.1 Pathology Guidelines and Specimen Procurement Requirements

Please note: Patients may also be enrolled on the current COG Biology Banking study which includes pre-therapy specimens. If patients are enrolled on both AHOD1331 and a biology banking study, the priority is to submit the specimens requested for AHOD1331 through AHOD1331 first.

Please consult with the oncologist and pathologist prior to biopsy to ensure that adequate specimen is procured. Pathology classification is up to the institutional investigators as there is no central pathology review on this study.

Tissue should preferentially be obtained fresh and delivered immediately to the Pathology Laboratory for optimal handling and distribution. Submit representative tissue slices for fixation including, whenever possible, at least one block with 10% buffered formalin using the preferred fixative of the institutional pathologist(s). The fixative utilized and length of time in fixative before processing should be indicated for each respective paraffin block. Fixation times should be appropriate for the fixative to allow optimal antigen preservation and immunophenotypic analysis.

Morphologic evaluation and classification of Hodgkin lymphoma must employ the criteria and nomenclature of the World Health Organization 2008 Classification of Tumours of Haematopoietic and Lymphoid Tissues. Histologic diagnosis is preferred, though cytologic diagnosis may be acceptable if the material is adequate and diagnostic.

A panel of antibodies should be employed for immunophenotypic evaluation and support of the diagnosis per WHO criteria. Methodology may be by any standard technique, usually employing paraffin sections. A recommended minimum panel of antibodies should include CD45, CD3, CD20, CD15 (Leu-M1), CD30 (Ber-H2, Ki-1), and PAX-5. Other markers that may be helpful in some situations include other T-cell markers, B-cell markers, CD68, ALK-1, EMA and EBV-associated markers (LMP1 and EBER in-situ hybridization). If immunophenotyping studies are not available locally, appropriate immunophenotyping studies to establish/confirm the diagnosis may be performed by consulting pathologists and/or reference laboratories.

13.2 Tissue Specimen Submission for Correlative Biology Studies

For those consenting to tissue biology studies, submit snap frozen tumor tissue and at least one paraffin block or 10 unstained slides and 2 H&E stained slides to the COG Biopathology Center.

See Appendix VI for additional information, including packaging instructions and the shipping address for the Biopathology Center.

13.2.1 Blocks or Slides

Fixative should be identified for each block. Fixation of tissue for over 24 hours should be avoided to allow optimal antigen preservation and immunophenotyping analysis. Sections should be placed on silanized slides (i.e. Fisher Superfrost Plus). If paraffin blocks cannot be submitted, then submit ten (10) unstained sections (4 microns thick) of unbaked slides air-dried at room temperature and 2 H&E stained slides from one representative block (see Table 7.2 and Appendix VI).

If the patient was diagnosed by biopsy before referral to the treating institution, a good faith effort should be made to obtain a representative sample of the tissue block with 10 unstained slides and 2 H&E stained slides.

Paraffin blocks will be retained at the COG Biopathology Center unless return is requested by the referring institution. For cases requiring urgent return of paraffin blocks to the primary institution, the referring institution should contact the COG Biopathology Center to request the blocks be returned immediately after removal of sample for biology samples for consenting patients. *Please note that for patients who have consented to the Biology studies, representative cores may be obtained for GEP and tissue array development from the paraffin blocks prior to return.*

13.2.2 Snap Frozen Tumor

Snap frozen tissue in foil is requested from the surgical biopsy. These samples will be used for biology correlative studies-molecular classification (Appendix VI). Snap freeze 0.5 gram of tumor in vapor phase liquid nitrogen (do not submerge the tissue in liquid nitrogen) or cold isopentane. Tip: label foil with the COG Patient ID Number prior to freezing. Place tissue in a bag labeled with the COG Patient ID Number, specimen type (primary or metastatic) and collection date. Anatomic site from which the tissue was collected must be documented on the transmittal form. If not shipped immediately, these samples can be kept adequately in a -70ºC freezer until shipped.

14.0 IMAGING STUDIES REQUIRED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

See Appendix II for detailed guidelines for CT with contrast and PET imaging.

14.1 [^{18}F]Fluorodeoxyglucose (FDG) PET

Note: Since FDG-PET imaging plays a significant role in the management of patients, only dedicated PET scanners will be utilized and gamma camera co-incidence FDG imaging will NOT be included for this protocol.

Exceptional circumstances may require emergent therapy and therapy should not be delayed in these cases. In this setting, baseline FDG-PET scans should be performed within 3 days from initiation of corticosteroid therapy. If FDG-PET is obtained during the 2nd cycle of chemotherapy (PET2 respectively), it should be performed between Day 18-22 of Cycle 2. If FDG-PET is obtained at the end of chemotherapy and prior to RT, it should be performed at least 3-4 weeks from the start of the last cycle of chemotherapy and with patient off G-CSF at least 10 days, in order to minimize potential post-therapy inflammatory changes and bone marrow uptake.

In cases of initial involvement of the spleen with lymphoma: If there was splenic involvement with focal activity initially, FDG-PET imaging too soon after filgrastim or peg-filgrastim shows diffuse splenic uptake that may not be due to disease.

If FDG-PET/CT is obtained at the completion of radiation therapy, for patients not in CR prior to RT, it should be obtained at least 6 to 9 weeks after completion of RT to minimize inflammatory changes. FDG-PET/CT is not required at the end of chemotherapy or at end of radiotherapy for patients with a negative PET2.

14.2 **Computed Tomography** (CT) **with contrast**

Most, if not all, COG institutions will be using multi-detector helical CT scanners. This is preferred in order to decrease scanning time compared to conventional CT, allow image acquisition at the time of peak contrast enhancement, reduce/eliminate the need for sedation, and reduce image degradation from motion artifact.

The volumetric acquisition of helical/spiral CT and the reconstruction of overlapping images increases the conspicuity of small lesions and facilitates multi-planar reconstruction for better depiction of certain lesions. Sagittal and coronal reconstructed images, as well as images reconstructed using a lung algorithm should be submitted where feasible, along with the axial imaging data. CT imaging should be performed with intravenous and oral contrast using age and weight-based adjustments to kVp and mA, in accordance with institutional practice and ALARA/Image Gently guidelines.

MRI may be used as an alternative modality after completion of treatment during the follow up phase only, provided the institution is able to acquire images using phased array surface

coils, cardiac gating and respiratory triggering, in order to minimize artifacts from cardiac motion, diaphragmatic motion and bowel peristalsis. Pulse sequences should include at a minimum axial and coronal T1, axial and coronal fat-saturated FRFSE-T2 and multi-planar post-gadolinium fat-saturated T1 weighted imaging. If MRI is used for imaging of the thorax, abdomen and/or pelvis, an unenhanced CT of the chest should still be obtained to evaluate the lungs.

14.3 CT during PET/CT

Nearly all PET scanners in use today are integrated PET/CT scanners. However, low dose CT scans performed on integrated PET/CT scanners for the purpose of attenuation correction are of non-diagnostic quality, are usually performed without intravenous contrast, and will not be acceptable for staging or response assessment or for RT planning. As noted above, staging CT scans should include intravenous and oral contrast. In some instances – particularly for staging – a diagnostic quality CT will have been performed prior to the PET/CT. In these cases an additional low-dose CT will still be required for attenuation correction of the PET images. While all diagnostic imaging should be obtained within three weeks prior to start of protocol therapy, if the diagnostic quality CT scan has been performed within 28 days of the PET/CT, a repeat diagnostic CT examination is not necessary at the time of PET/CT.

For post-therapy follow-up scans limited to the neck and/or thorax the use of IV contrast alone is sufficient, provided the scanning parameters are optimized to achieve diagnostic quality images. Some institutions perform the low dose attenuation correction CT with intravenous contrast. While this is acceptable for the FDG-PET imaging evaluation, for the purposes of this protocol, these contrast-enhanced attenuation correction CTs cannot be substituted for the required diagnostic quality CT.

14.4 Central Review of Imaging Studies

Central review of images will be performed to confirm institutional reporting.

14.4.1 Real-time central review

Real time central review to assess response for all patients will be done after the second cycle of chemotherapy and at the completion of chemotherapy for patients who had PET positive disease at the end of 2 cycles of chemotherapy. Copies of all imaging studies at baseline and after 2 cycles of chemotherapy should be submitted (baseline PA upright chest radiograph, CT with contrast, FDG-PET imaging) as detailed below. Institutional imaging reports and the AHOD1331 Staging and Response Worksheet should be submitted with these scans. **Sites are encouraged to submit baseline scans directly after enrollment to confirm that all baseline scans required for the central imaging review are available and of adequate quality. Eligibility (including bulk and LMA) will be centrally confirmed using the baseline scans at the time of the Post 2 cycle review.**

In instances in which the central imaging review assessment of disease status differs from that of the institution, a web-based conference will be organized by IROC Rhode Island (previously known as QARC) to expedite resolution of any discrepancies in interpretation of the imaging data. Subjects found to not meet study eligibility specified stages at the time of central review for early response assessment (after 2 cycles of chemotherapy), will be deemed ineligible. Institutions will be notified and the patient will be taken off study. As a reminder, institutions

may seek input from IROC prior to study enrollment if there are questions regarding study eligibility based on imaging measurements regarding LMA or bulk.

14.4.2 Time lines and submissions to IROC RI

For all patients, in the last week of Cycle 2 of ABVE-PC or Bv-AVEPC, and no later than Day 22 of this cycle, the institution must send all scans (PET0 and PET2; CT with contrast; CXR) and institutional reports along with the AHOD1331 Hodgkin Lymphoma Staging and Response Worksheets (done to that point) to IROC RI (see below). If PET/CT is done on day 1 of cycle 3, sites need to ensure that patients proceed to Cycle 3 therapy on schedule. Note that the institution is required to report Deauville score for the hottest lesions present at PET2 (See Appendix II).

- For patients who had PET positive disease after 2 cycles of chemotherapy, the PET and CT with contrast scans done after 5 cycles of chemotherapy should be submitted for central review. The corresponding radiology reports and the AHOD1331 Staging and Response Worksheet should be submitted to IROC RI for central review of response. This response review will determine if an additional RT boost to slow responding areas is required.
- For patients who had PET negative disease (Deauville 1, 2, 3) after 2 cycles of chemotherapy, CT scans with IV contrast should be submitted for a retrospective central imaging review after Cycle 5.
- **At time of relapse for any patient enrolled on the study, all imaging studies done at the time of the first relapse should be sent to IROC RI.**
- **Timely submission of studies to IROC RI is required. ANY RADIATION THERAPY (POST CYCLE 5 OF CHEMOTHERAPY) DELIVERED THAT IS NOT CONSISTENT WITH THE RESPONSE CATEGORIZATION, AS DETERMINED BY CENTRAL REVIEW, WILL BE CONSIDERED A MAJOR PROTOCOL VIOLATION.** The results of the central review will be entered into RAVE.
- All radiotherapy treatment plans must be reviewed by IROC RI and approved prior to the start of radiotherapy.

14.4.3 Studies to be submitted:

- Pre-Study (Baseline): chest radiograph (must be upright CXR with a PA view; portable AP is not acceptable); CT with IV contrast; FDG-PET imaging
- After Cycle 2 of chemotherapy: CT with IV contrast, FDG-PET
- After Cycle 5 of chemotherapy (prior to RT, if RT is indicated): CT with IV contrast and FDG-PET if positive by central review after Cycle 2 (mandatory submission).
- At first relapse: all imaging studies performed.
- Additional studies obtained if used to determine response (MRI, ultrasound).

14.4.4 Technical Details of Submission

To ensure an adequate interpretation of FDG-PET and CT with contrast scans, scans transferred between the treating institutions and the Imaging and Radiation Oncology Core Group IROC RI must be submitted in Digital Imaging and Communications in Medicine (DICOM) format. BMP files, JPG files, or hard copies (films) are unacceptable for adequate interpretation of PET and CT with

contrast scans. Imaging studies must be submitted electronically as outlined in the following paragraph. The images will be made available to study radiologists and nuclear medicine physicians for central review.

Submission of Diagnostic Imaging data in digital format is required. Digital files must be in DICOM format. Due to the critical time constraints for submitting data for the central review of response the following methods should be used to submit imaging data, such as sFTP, Dicommunicator, or on CD (if sent by courier). Digital data submission instructions including instructions for obtaining a sFTP account, can be found at http://irocri.qarc.org. Follow the link labeled digital data. Alternatively, if submission via sFTP or Dicommunicator is not feasible, the imaging may be burned to a CD and mailed to IROC RI at the address below. Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD. Sites using Dicommunicator may submit imaging via that application. Contact IROC RI with questions or for additional information.

For FDG-PET imaging, the transferred imaging data should include uncorrected and attenuation-corrected PET projection data, as well as the reconstructed PET or PET/CT images used by the institution to achieve a response assessment. If low-dose CT was used for attenuation correction, the acquired CT images should also be submitted. The imaging data submitted for central review must allow the study to be reconstructed and displayed in transaxial, sagittal and coronal formats using standard reconstruction techniques. Reconstructed MPEG clips and similar types of reconstructions will not be accepted. CT and MRI images similarly should be submitted in a format that either includes properly reconstructed multi-planar viewing formats in soft tissue and bone windows, or includes the thin-section axial acquisition data from which multi-planar reconstructions can be re-created.

Address for submission:
IROC Rhode Island
Building B, Suite 201
640 George Washington Highway
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601
Web: http://irocri.qarc.org

15.0 RADIOTHERAPY GUIDELINES

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

Radiotherapy (RT) for patients on COG protocols can only be delivered at approved COG RT facilities.

Central Review of response is necessary prior to submission and initiation of the RT plan. Central review will also confirm sites of LMA which will require radiation. Any radiation therapy delivered not consistent with the central review response categorization will be considered a major protocol deviation.

15.1 General Principles – Risk-Adapted RT

In advanced-stage or high-risk patients, involved field radiotherapy (IFRT) has traditionally encompassed a large volume of normal tissue due to anatomically widespread sites of multiple disease and extra-lymphatic spread. One of the aims of this study is to reduce the volume of radiotherapy in order to reduce potential acute and late toxicities, while maintaining disease control. This will be done in two ways: 1) omitting radiotherapy (RT) among patients without large mediastinal adenopathy (LMA) who also have an early response to systemic therapy (RRL as defined in Section 10.3.2) and 2) limiting the volume of RT among patients who receive this treatment by employing involved site RT (ISRT).

15.2 Indications for Radiotherapy

The indications for RT include disease sites with the following characteristics:

1. Initial large mediastinal adenopathy defined in Appendix I. All patients with LMA will receive ISRT regardless of RRL status.
2. SRL as determined by FDG-PET scan residual avidity (Deauville score 4 or 5) after the first 2 cycles of chemotherapy (PET2) (See Section 10.3.2)

With the exception of LMA, disease that reverts to being PET negative after 2 cycles of chemotherapy (RRL) will not be treated with RT.

Based on these guidelines, a volume reduction over standard involved field radiotherapy is envisioned that will help reduce acute and late toxicity. Accordingly, the volume of lung, heart, breasts, salivary glands, and abdominal structures irradiated are likely to be reduced for this patient population. The long-term goal is to maintain high cure rates with lower toxicity.

15.3 Radiotherapy Dose and Schedule for SRL Lesions

Note: Lesions which were Deauville 3 (and hence RRL by definition) at PET2 will be considered as such even if the lesions remain Deauville 3 on PET5; these lesions will **not** receive RT unless they demonstrate progression at PET5.

15.3.1 PET Negative After 5 Cycles of Systemic Therapy (PET score 1-2)

Radiotherapy will consist of 2100 cGy in 14 fractions of 150 cGy per day. The treatment will be given 5 days per week. All fields should be treated once each day. The total elapsed treatment time will be approximately 2.8-3.0 weeks (14 sessions) for each site.

15.3.2 PET Positive After 5 Cycles of Systemic Therapy (PET score 3-5)

For patients receiving RT (who have not been removed from study due to PD) who have PET score 3-5 at the end of chemotherapy, a boost of an additional 900 cGy in 6 fractions is to be prescribed to bring the total dose to 3000 cGy to PET avid sites (i.e. to the post-chemotherapy GTVPET+ volume with an additional PTV margin). The post-chemotherapy CTV and PTV should receive 21 Gy as outlined in Section 15.7. The additional boost dose is only given to that component of the target volume that is PET-avid (defined as PET score 3-5).

15.4 Timing of Radiotherapy and Starting Criteria

Treatment should begin no later than 6 weeks from the start of Cycle 5 of chemotherapy or when blood counts have recovered. Criteria include an ANC $\geq$ 750/µL and platelets $\geq$ 75,000/µL prior to treatment for each site.

15.5 Credentialing Requirements

Patients may receive RT with photons or proton therapy. Intensity Modulated Radiation Therapy (IMRT) or protons are allowed in circumstances where the treating oncologist believes these provide significant clinical benefits compared to conventional anterior-posterior parallel opposed pairs. Investigators may use proton therapy only if their institution has been appropriately credentialed by the IROC Houston QA Center. Credentialing requirements for proton therapy which include, but are not limited to, completion of a proton facility questionnaire, a successful IROC Houston site visit, which identifies the proton technique(s) which can be used, annual monitoring of the proton beam calibration, e.g. IROC Houston's monitoring program, and successful digital phantom data submission to IROC Houston (details for data submission are available at http://rpc.mdanderson.org). Centers not previously credentialed for use of proton therapy treatment of thoracic tumors in COG trials must irradiate the Proton Lung Phantom available from IROC Houston.

The credentialing requirements by treatment modality are summarized in the following table.

RT Credentialing Requirements	Web Link for Credentialing Procedures and Instructions **http://irochouston.mdanderson.org**			
	Treatment Modality			
	3D-CRT	Photon	Proton	Key Information
Facility Questionnaire	**X**	**X**	**X**	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email **irochouston@mdanderson.org** to receive your FQ link.
Credentialing Status Inquiry Form	**X**	**X**	**X**	To determine if your institution has completed the requirements above, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (**http://irochouston.mdanderson.org**).
Phantom Irradiation		**X**	**X**	Sites treating with IMRT and not previously credentialed for its use on COG trials must irradiate IROC Houston's head and neck phantom. Proton centers must complete all required phantom irradiations for IROC Houston credentialing, including the proton lung phantom. Instructions for requesting and irradiating the phantoms are found on the IROC Houston web site. (**http://irochouston.mdanderson.org**).
Motion Management (when used)		**X**	**X**	If treating with IMRT and gating or tracking methods are used to compensate for respiratory motion, IROC Houston's Lung Phantom must be irradiated with its accompanying reciprocating platform to simulate motion. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (**http://irochouston.mdanderson.org**)
Credentialing Notification Issued to:				
Institution				Institution will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution that all desired credentialing requirements have been met.

15.6 Equipment

15.6.1 Modality

Photons with a nominal energy of ≥ 4 MV and ≤ 18 MV are preferred. In the unusual circumstance of an isolated superficial lesion, electron fields may be used. Conventional, conformal, and IMRT techniques are allowed in this study. Patients receiving IMRT should have this delivered with 6 MV photon beams, and 18 MV photon beams should not be used to deliver IMRT.

Proton therapy may be delivered using passively scattered proton or scanning beams provided that the specific beam line in use has been appropriately credentialed. Selected proton energies should be high enough to adequately provide target coverage. Range shifters may be used to make fine adjustment to the maximum proton range.

IMRT or protons may be used in the thoracic region or for treatment of tumors affected by respiratory motion when the degree of motion can be limited to 0.5 cm relative to the mean position (end-to-end tumor motion is less than 10 mm) using motion management techniques if needed. Use of IMRT in conjunction with gating or tracking techniques requires credentialing by the IROC Houston (see Section 15.9 below). The Motion Management Reporting Form shall be submitted with the Quality Assurance Documentation materials whenever motion management techniques are used.

15.6.2 Guidelines and Requirements for the Use of Proton Beam Therapy

Investigators using proton beam therapy will be required to comply with current guidelines for the use of protons in National Cancer Institute sponsored cooperative group trials. These guidelines are available on the IROC Houston website at http://irochouston.mdanderson.org. These guidelines specify the following for the participating institution: dose reporting will be in Cobalt Gy equivalent (1 CGE = 1 proton Gy * 1.1) which is the same as ICRU 78 DRBE; radiation doses shall be prescribed to protocol specified definitions for gross (GTV) and clinical (CTV). For CT number to proton stopping power calibration uncertainties, set-up uncertainties and target motion, additional margin, smearing, range of modulation will be added on a per beam basis for passive scattering and uniform scanning. The proton institution is required to participate in on-site and remote review according to COG requirements.

15.6.3 Treatment Planning

CT (volumetric) based planning is required to optimize dose to the targeted volume while documenting dose to normal tissues. Slices ≤ 5 mm thick should be taken throughout the extent of the irradiated volume. In cases where the mediastinum is being treated, the entire lung volume should be scanned to create accurate estimates of whole lung dose. There are mandatory requirements for submission of the dose to selected normal tissues (see Sections 15.11 and 15.12). A Dose Volume Histogram (DVH) is necessary to determine target coverage and evaluate dose to normal tissues.

15.6.4 In-Room Verification of Spatial Positioning

Image guidance to verify patient position is an important standard feature of contemporary RT delivery. Institutional protocols should be in place common to verify patient position. Orthogonal pair (AP and lateral) portal images (MV or kV) or cone-beam imaging are acceptable. There is no central review of verification imaging.

15.7 Target Volumes

Recommendations of The International Commission on Radiation Units and Measurements (ICRU) for prescription methods and nomenclature will be utilized for this study (Reports 50, 62, and 78).

The indications for RT are outlined in Section 15.3 and should be the principal determinants in defining the gross tumor volume (GTV), the clinical target volume (CTV) and the planning target volume (PTV). It is important to note that the use of bony anatomy to define RT field borders is not employed in this protocol, as the intent is to utilize contemporary image-guided RT and volumetric definitions.

Targets at non-contiguous sites need to be separately identified. Numerical or descriptive suffixes can be used such as GTV2, CTV2, PTV2; or GTV-pelvis, CTV-pelvis, PTV-pelvis, for instance. Generally, in cases for which two PTV targets are >5 cm apart, these should be treated separately unless there is a compelling reason to treat uninvolved tissue in between.

Note: The following definitions apply only to sites of disease that meet the criteria for receiving RT.

15.7.1 Pre-Chemotherapy (or Pre Surgery) GTV

The pre-chemotherapy GTV includes nodal and non-nodal tissues that were involved with lymphoma prior to any treatment, and meet the criteria for requiring RT (LMA or SRL). Imaging criteria for defining whether a nodal or extra-nodal site is involved are described in Section 10.2.

15.7.2 Post-Chemotherapy GTV

The post-chemotherapy GTV includes imaging abnormalities persisting after all planned chemotherapy. For example, residual enlargement of anterior mediastinal tissue that has not returned to normal on anatomic or functional imaging following chemotherapy. Note that for RT planning purposes the residual abnormality seen on CT is considered part of the post-chemotherapy GTV, even when PET-negative. The GTV (and CTV) are not just the PET-avid sites. It is critical to note that the Deauville cutoffs used for PET response differ between PET2 and PET5. Following completion of 5 cycles of chemotherapy, the GTV is subdivided into:

GTVPET+: An area of imaging abnormality demonstrating the lymph node(s) that remain PET avid (Deauville score > 2, uptake greater than mediastinal blood pool. See Table 10.3.2) following completion of all 5 chemotherapy cycles.

GTVPET- : An area of imaging abnormality on CT demonstrating the lymph node(s) as no longer PET avid (Deauville score 1-2) after completion of all 5 chemotherapy cycles.

15.7.3 Post-Chemotherapy Clinical Target Volume (CTV)

The CTV should include the lymph nodes/tissues originally involved with lymphoma (i.e. the pre-chemotherapy GTV), but must take into account the reduction in axial diameter that has occurred with chemotherapy. The concept is that all areas of lymphoma infiltration needs to be targeted, but the aspects of the lymphoma with a pushing border in the mediastinum that displaces normal lung (or para-aortic nodes displacing bowel) need not be targeted when that normal tissue relaxes back into a normal anatomic position as the lymphoma responds to systemic therapy. Anterior mediastinal disease will shrink in axial diameter away from the lung with chemotherapy, and the width of the post-chemotherapy CTV should reflect this change.

Delineation of the CTV requires consideration of the expected routes of disease spread, and the quality of pre-treatment imaging. For example, in some circumstances it can be difficult to clearly rule out disease (e.g. in the aorto-pulmonary window) or not possible to exactly locate the abnormality within an exact location in an axial image of the involved nodal space. Consideration of other clinical and imaging factors (e.g. extent of involvement in nearby nodal regions, bulk of disease) should guide decisions regarding whether to include or exclude such areas from the CTV.

The CTV expansion cannot be rigidly determined a priori as there can be considerable uncertainties inherent with GTV delineation due to inaccuracies in matching patient positioning and the variable internal anatomy shifts that change with disease volume and patient position between diagnostic and treatment positions. Typically, on a given axial cut, the whole nodal fossa/level that contained the initially abnormal node(s) will be contoured as the CTV. As a guideline, a margin of 1.5 cm above and below lymph nodes involving lymphoma is recommended.

Uncommonly, normal nodal tissue may be included in the CTV if located between two anatomically close (i.e. within 5 cm) sites requiring RT that are going to be joined and treated as a single volume.

15.7.4 Internal Target Volume (ITV)

The ITV encompasses the CTV with an added margin to account for variation in shape and motion within the patient. Respiratory motion, for example, will produce movement of the mediastinal structures and spleen, and an additional margin around the CTV is required to account for this.

15.7.5 Planning Target Volume (PTV)

The PTV should encompass the CTV and ITV, and accounts for geometric variation in daily setup. It should take into account the reproducibility of the immobilization, and the accuracy of the daily setup imaging.

Notably, an isometric 5 mm expansion around a CTV that includes inferior mediastinal structures will rarely provide adequate coverage. Typically ITV+PTV margins around CTVs in the neck will be 3-5 mm.

ITV+PTV margins in the mediastinum should range from 8-15 mm and should not be as small as 5 mm. ITV+PTV margins around the spleen should be 10-15 mm, unless 4D simulation demonstrates the need for a larger margin.

When proton therapy is used, the GTV and CTV are the same as for photons.

In patients with moving tumors within the lung, the iGTV is required for calculation of dose for proton therapy. The iGTV includes the GTV with a margin for GTV respiratory motion. The PTV is defined differently for the purpose of dose reporting vs. treatment planning. For dose reporting purposes the PTV will include a margin which is added to the CTV in 3-dimensions. The margin should be

consistent with the motion control and setup accuracy for the particular type of treatment (scattered versus scanning) at the treating proton center.

For treatment planning, the goal will be CTV coverage at 100% directly with specific measures taken for each specific uncertainty. The PTV will vary with each individual field and will require additional adjustment including (1) the lateral margins, (2) smearing of compensator, (3) range of beam (depth of penetration) and, (4) modulation (number of required Bragg peaks). Adjustments to any of the aforementioned parameters (usually 2-7 mm) will be based on the range uncertainty, CT number uncertainty, internal motion, and set up error determined for the particular body site at the individual proton institution. The following parameters must be explicitly reported for each beam when using passive scattering or uniform scanning: range, modulation, smearing radius of the compensator, set-up margin (SM) and PTV margin. The specifics of dose reporting for the proton PTV and recommendations regarding the PTV margin are discussed in Section 15.8.4.

When there is extension within the lung with lymphoma with corresponding respiratory motion of the tumor, certain guidelines are required to ensure appropriate target coverage. For the iGTV approach, adequacy of coverage in both end-inhale and end-exhale phases must be reviewed.

15.7.6 Special Circumstances

15.7.6.1 No residual tissue seen on planning CT

Patients with LMA typically have significant reduction in the mediastinal bulk with chemotherapy. The principle of creating the CTV is to include all nodal tissue originally involved, however this may be challenging to visualize and localize, particularly when a complete response has been achieved at the superior or inferior limits of the initially involved site. When possible, image fusion of the planning CT and the pre-treatment imaging should be employed to identify the superior-inferior extent of disease, and this extent should be included in the CTV. At times, this may require contouring of macroscopically normal anatomy (e.g. the anterior pericardium) in cases where at CR has been achieved.

Similarly, a SRL that requires ISRT may have achieved a CR by the time chemotherapy is completed. In this case, fusion of pre-chemotherapy imaging may aid delineation of the appropriate CTV, recognizing that differences in the patient positioning may create uncertainty about the accuracy of the fusion. The nodal tissue/fossa at the level of the node(s) requiring RT should be contoured as the CTV with a patient-specific margin for uncertainty of target localization given the absence of macroscopic imaging abnormalities.

15.7.6.2 Chest wall invasion

On occasion, HL, at presentation, may involve or invade the chest wall, particularly at the anterior aspect. Despite chemotherapy response that may no longer show gross lymphoma, the involved chest wall should be

included in the CTV definition as an area of lymphoma infiltration that should be targeted. If the chest wall disease is extensive, 3D conformal techniques or IMRT may be used to avoid excess dose to the lungs or heart. Pleural or pericardial effusions are not included in determination of GTV/CTV.

15.7.6.3 Sites of nodal disease adjacent to site of mediastinal bulk

There may be sites of disease adjacent to a LMA mass. With the exceptions noted below, the field edge required to treat the LMA should not cut through initially involved sites of disease, even if the latter do not require RT based on response criteria. For example, involved supraclavicular or neck nodes adjacent to a site of LMA should be included unless they are sufficiently separate to allow the field edge to cover the LMA without cutting through the initially involved sites in the supraclavicular fossa/neck.

This guideline does not apply, however, when the additional toxicity of extending the treatment volume would be potentially significant and avoidable. For example, the irradiation of the axillae in females, the high cervical nodes (and salivary structures, and cardiophrenic/diaphragmatic nodes (heart) should be avoided when these sites do not meet the response criteria for irradiation. In such situations it is permissible to cut through involved sites that do not meet the slow-response indication for RT.

Uninvolved adjacent sites should never be included; with the exception of the linking of two closely approximated sites that each meet criteria for requiring RT (see below). Clinicians may contact IROC RI or one of the study radiation oncologists to discuss specific cases as necessary.

15.7.6.4 Joining separate sites of disease receiving RT

When two or more sites of disease meet criteria for receiving RT, these should typically be treated as separate targets if the PTV volumes are > 5 cm apart. Separate sites may be joined at the discretion of the treating oncologist in cases where the intervening nodal tissue was involved, or when issues of setup variability or concerns about the accuracy of dosimetry within small shielded areas between two treated sites may make linking two volumes preferable. When this is done, care should be taken to consider and treat the appropriate nodal anatomy in the intervening volume.

15.7.7 Specific Anatomic Sites

15.7.7.1 Spleen

Splenic involvement per se is not an indication for splenic RT on this protocol. The spleen will be treated if it is a site of SRL. In such cases, the entire spleen should be targeted as the CTV, not just the slow-responding nodule. The spleen will be treated if it contains a SRL. In such cases, the entire spleen should be targeted as the CTV, not just the slow-responding nodule.

NOTE: For patients with **involvement of the spleen**, vaccination against Pneumococcus, *Haemophilus influenza* and Meningococcus is strongly recommended **prior** to therapy. If not performed at this time, it should be administered prior to beginning radiation therapy. Waiting to immunize until after Cycle 5 may be affected by muted immune response at that time.

15.7.7.2 Lung, heart, liver, bone or other parenchymal nodules

There are explicit definitions of extranodal involvement in Section 10.2.1. These sites are treated only if they are sites of SRL. Whole organ irradiation is to be avoided. If lung parenchymal involvement is adjacent to other sites of GTV, the radiation oncologist may use their discretion about inclusion of such involved sites in the GTV definition with the guiding principal that this protocol aims to reduce the volume of radiotherapy in order to reduce long term toxicities, but irradiate those regions of initial mediastinal bulky involvement or slow response to chemotherapy.

15.7.7.3 Unilateral neck

Only the involved nodal site in the neck should be treated. It is not necessary on this protocol to treat the entire superior-to-inferior extent of the nodal compartment. In most cases fusion of pre-chemotherapy imaging to the planning CT scan can facilitate localization of the appropriate GTV and CTV. In many cases, where there is some uncertainty in exact location of the nodal mass, the entire axial extent of the nodal compartment may be contoured as the CTV, but it is not necessary to treat the entire unilateral neck. In particular, irradiation of the salivary glands should be avoided unless there was immediately adjacent slow responding disease making this necessary.

15.7.7.4 Bilateral neck

If necessary to treat both sides of the neck, the target volumes should be contoured independently. Some patients may have asymmetric irradiation of the neck if the levels of involvement are different.

15.7.7.5 Unilateral axilla

Arms should preferably be positioned akimbo (hands on hips). It is not necessary to treat the entire axillary nodal fossa based on bony landmarks, although in some cases ISRT target volume definitions may be equivalent to doing this. The superior and inferior edge of the ISRT volumes should be defined as per the volumetric definitions described above, not by bony landmarks.

15.7.7.6 Mediastinum (including hila)

In contrast to prior protocols, bony landmarks are not employed to delineate mediastinal volumes. In cases where the mediastinal disease is enmeshed within the major vessels, it is acceptable to contour the entire mediastinum as the CTV at levels above the heart. However, at the level of the heart, effort should be made to localize GTV/CTV volumes as

precisely as possible using the definitions above without including the heart in the CTV (unless there is direct pericardial/cardiac involvement). Hila should be considered independently and included in the GTV/CTV only when staging imaging showed them to be involved at diagnosis. Mediastinal involvement does not automatically require hilar nodes to be encompassed in the target volume. In cases with LMA with internal mammary node involvement, these nodes should be included in the CTV, as should areas of chest wall invasion.

In circumstances when the mediastinum is being treated for protocol-directed indications (mediastinal bulk or slow early response) and when the supraclavicular fossa(e) or neck nodes were involved but responded rapidly (RRL), the field may be extended at the discretion of the treating oncologist to include the involved neck nodes superiorly to avoid placing a field border through involved sites. This is not necessary, and will not be counted as a protocol deviation.

15.7.7.7 Waldeyer's ring

Waldeyer's ring will only be treated if it is a site of SRL. The extent of disease may be difficult to localize based on PET and CT alone. Pre-treatment MRI is preferable, if possible. It is not necessary to treat the entire Waldeyer's ring however, unless there is evidence of bilateral involvement.

15.7.7.8 Spleen only

In those patients scheduled to receive RT to the spleen because of SRL, the entire spleen should be treated with a 1.0 -1.5 cm field margin to account for respiratory movement. The post-chemotherapy spleen volume should be used, as defined by CT scan. If the paraaortic lymph nodes are not part of the GTV, then they do not need to be specifically included.

15.7.7.9 Paraaortic lymph nodes only

Involved para-aortic lymph nodes may be treated in cases where there is a SRL. In cases where the lymph nodes are difficult to visualize following chemotherapy, the CTV should encompass a symmetric expansion around the para-aortic vessels of at least 12 mm. It is not necessary to include the spleen in the CTV unless it would otherwise meet criteria for requiring RT.

15.7.7.10 Pelvic lymph nodes

In cases where the lymph nodes are difficult to visualize following chemotherapy, the CTV should encompass a symmetric expansion around the major pelvic vessels of at least 10 mm. When possible, MRI simulation and/or fusion of pelvic MRI with planning CT should be performed to contour the ovaries and facilitate estimation of ovarian dosimetry. Females should have consideration for an oophoropexy moving the ovaries away from the PTV volume. The male gonads should also be shielded using a clam-shell type block, as appropriate. Positioning the legs apart may facilitate testicular shielding.

15.7.7.11 Pericardium

The intent is to avoid whole heart irradiation. If the pericardium was extensively involved by gross lymphoma and part of the GTV definition, the mean dose to the heart should be limited to < 15 Gy. Where the superior or anterior aspect of the pericardium was involved requiring radiotherapy, that region should be targeted in continuity with the mediastinum where feasible. A shrinking field technique may be required to limit the mean heart dose to < 15 Gy. Pericardial effusions at diagnosis do not require whole heart irradiation. Isolated inferior pericardial or peri-diaphragmatic nodes may be treated separately from the main mediastinal volume when indicated.

15.7.7.12 Sites of metastatic disease or isolated extranodal disease (lung, liver, bone)

Sites of metastatic or isolated extranodal disease are treated only if they meet the definition of SRL. The intent, however, is to avoid whole organ irradiation. For lung nodules, when the SRL criterion applies, the involved portion of lung (or lungs) should be treated with at least a 1.5 cm margin. Larger margins to account for respiratory movement are allowed. In cases of direct extension into the lung from mediastinal disease or limited central pulmonary involvement particularly in a pattern of lymphatic spread, the part of the lung to be irradiated should be in continuity with the mediastinal fields. Patients presenting with a pleural effusion need not receive treatment to the involved hemithorax. Similarly, isolated liver or bone lesions meeting criteria for SRL may be treated with GTV, CTV, and PTV definitions as described above. Whole liver or bone RT is rarely required.

15.7.7.12.1 *Solitary Bone or Bone Marrow Lesion*

If a solitary bone or focal region of marrow is found to be involved at the time of early response assessment, it should be treated to 2100 cGy with at least a 1 cm margin around the radiological abnormality. No more than 3 sites should be considered for radiation if multiple bony sites remain. Some residual metabolic activity in bone may reflect bony healing, and thus interpretation within the context of the response of other involved areas may be appropriate. In these situations WebEx conference between IROC, treating institutions and study committee chairs should be considered. The sites can be determined in evaluation and review with IROC.

15.7.7.12.2 *Multiple Sites of Bone or Bone Marrow Involvement*

These sites need not be irradiated as part of the treatment for Stage IV disease.

15.7.7.13 Supra and subdiaphragmatic disease

Patients requiring RT both above and below the diaphragm can be treated with sequential or concurrent fields at the discretion of the treating oncologist. If the treatment volumes approach what was historically termed subtotal nodal irradiation, sequential RT treatment courses with a three week time interval may help avoid significant myelosuppression.

15.7.7.14 Partial Response at the end of Chemotherapy (PET positive)

Nodal masses that are undergoing RT and have PET score > 2 after 5 cycles of chemotherapy should have received a boost with an additional of 900 cGy in 6 fractions to be delivered to the GTVPET+ plus an appropriate margin (total dose to PET avid sites = 3000 cGy) immediately after completion of 2100 cGy course to the initial PTV.

15.8 Target Dose

The total dose will be 2100 cGy in 14 fractions of 150 cGy. In the case of a partial response with persistent FDG uptake at the end of chemotherapy, a small volume boost of an additional 900 cGy in 6 fractions is to be prescribed to bring the total dose to 3000 cGy to such sites.

15.8.1 Dose Definitions

The absorbed dose is defined in centigray (cGy)-to-muscle. Proton dose will be reported in Gy (relative biological effectiveness, RBE), where 1 Gy (RBE) = proton dose Gy x RBE, and RBE = 1.1.

15.8.2 Plan Normalization

There are several ways in which plans cans be normalized, most commonly normalization to a point or to an isodose surface. In all cases the isodose coverage around GTV, CTV and PTV should be evaluated and the dose uniformity requirements in Section 15.8.4 shall be satisfied. If normalization is to a point, the point should be in solid tissue, not in lung. If the central axis falls beneath a block in any field, an appropriate off-axis point may be used for calculations.

15.8.3 Heterogeneity corrections

Calculations must take into account tissue heterogeneity and should be performed with CT-based treatment planning to generate dose distributions and treatment calculations from CT densities. When treatment beams traverse lung, planning must be performed using an approved dose calculation algorithm. Approved algorithms include: convolution superposition, collapsed cone convolution, and Monte Carlo. When protons are used, correlation between the institutional CT treatment planning system Hounsfield Units and "relative proton stopping power" must be established and documented. Proton therapy should be used with extreme caution when any of the treatment beams traverse normal lung parenchyma.

15.8.4 Dose Uniformity

For all treatments, 95% of the prescription dose must cover > 99% of the CTV and no more than 10% of the CTV or PTV should receive more than 110% of the protocol dose. In addition, 95% of the prescription dose should cover > 95% of the PTV. The maximum dose in the patient should not exceed 120% of the prescription dose.

No more than 0.03 cc of the PTV should receive less than 85% of the prescription dose.

- If > 0.03 cc of the PTV receives 75-85% of the prescription dose, this will be a minor deviation.
- If > 0.03 cc of the PTV receives <75% of the prescription dose, this will be a major deviation.

15.8.4.1 Proton Specific Guidelines:

For protons, treatment planning does not specifically use a traditionally defined PTV for treatment planning. All uncertainties are taken into account explicitly to create a robust plan that provides full dose coverage of the CTV, generally from each beam – proton plans should be evaluated for adequate coverage provided by each individual beam and for PTV coverage from the summation of all beams. For passive scattering and uniform scanning, the aperture margin must include the appropriate beam penumbra for the selected beam energy, and PTV margin. These margins depend on the patient setup techniques used at the treating proton center. The aperture margin may be expanded further if a cold spot occurs near the edge of CTV due to insufficient lateral scatter. The smearing radius for the range compensator must be equal to the PTV margin. The beam range should be equal to the maximum water equivalent depth of the CTV plus a range margin. The main part of the range margin comes from uncertainty in CT accuracy and the conversion of the Hounsfield units to proton stopping power ratios. Additional range margin should be applied if internal motion could increase the water equivalent depth of the CTV. The modulation width should be increased consistently to ensure proximal coverage of the target volume. The beam range may be adjusted at the discretion of the treating radiation oncologist based on normal tissue dose concerns. A PTV should be created by a uniform expansion from CTV for reporting purposes. A potential exception is when the range margin is smaller than the PTV expansion. As a result, the beam may not penetrate deep enough to sufficiently cover the distal portion of the PTV. This may occur for shallow target volumes where the maximum depth of the CTV is small and the range margin is small. This scenario is not expected for this protocol; however, such incomplete coverage of the PTV will not constitute a planning deviation because the plan should be sufficiently robust to cover the CTV with the protocol specified dose accounting for all uncertainties.

15.8.5 Interruptions, Delays and Dose Modifications

There will be no planned rests or breaks from treatment, and once RT has been initiated, treatment will not be interrupted except for any life threatening infection or severe hematologic toxicity defined as ANC < 300/ µL or platelets less than 40,000/µL during the course of treatment. Under these circumstances, RT shall be delayed until the counts have recovered. Blood product support should be instituted according to institutional/protocol guidelines. The reason for any interruptions greater than 3 treatment days should be recorded in the patient's treatment chart and submitted with the QA documentation. There should be no modifications in dose fractionation due to age or field size. If any area has been previously treated (emergently), care should be taken not to exceed normal tissue tolerance levels.

15.9 Treatment Technique

Treatment in most cases should be delivered through AP/PA parallel opposed fields. IMRT or protons may be used provided target coverage and homogeneity requirements are met. In certain circumstances, the use of electron beam RT to treat superficial sites is permitted. Methods of patient immobilization and organ motion can be undertaken as per institutional protocols. Patients receiving RT to the neck should be immobilized in a thermoplastic mask. 4-D simulation and breath-hold techniques are permitted to estimate organ motion and minimize PTV expansions.

15.9.1 Selection of Proton Beam Arrangements

There are uncertainties (1-3 mm) in the distal range of the proton beam in which the RBE may be greater than 1.1; therefore, single proton beam plans which stop in the spinal cord will not be allowed.

15.9.2 Motion Management and Margins to Account for Target Volume and Organ Motion

Considering motion of normal tissues and target volumes is important. The internal target volume (ITV) is defined as the CTV surrounded by the internal motion (IM) component of the PTV and is meant to account for potential motion of the CTV. If adequate clinical data do not exist to define the IM component of the PTV margin, the following suggestions are provided:

- For a CTV susceptible to physiologic motion, a margin of at least 0.5 cm should be added to the CTV prior to PTV margin expansion or a PTV margin of 1 cm should be chosen, unless additional motion management (e.g. active breath hold and/or daily CT imaging) are employed.

- For tumors of the thorax or abdomen, an assessment should be made to determine the extent of motion present. PTV margins should include this motion as a component. In the mediastinum the PTV margin around the CTV should be ≥8 mm.

- IMRT or protons may be used for tumors of the thorax only if the degree of tumor motion is assessed and can be accounted for in an ITV. Motion of the target volume in three dimensions (cranial, caudal, anterior to posterior, and lateral) may be determined by 4-dimensional CT, respiratory gated CT, or other accepted techniques.

- A description of the method used and evidence (i.e., observed motion during fluoroscopy, motion of surrogate markers using camera systems, or analysis of 4-D CT) of the remaining tumor motion should be submitted on the Motion Management Reporting Form with the Quality Assurance Documentation materials as noted in Section 15.13.

  NOTE: For patients treated with IMRT, use of gating or tracking methods to compensate for respiratory motion requires irradiation of IROC Houston's Thorax-Lung Phantom with accompanying reciprocating platform to simulate motion. Contact IROC Houston (http://irochouston.mdanderson.org) for information about their phantoms.

15.10 Treatment Position

The patient should be treated entirely in the supine position. Some institutions may incline female patients to reduce breast dose, and this is acceptable. Reproducible setups are critical, and the use of immobilization devices are strongly encouraged. Consideration should be given to implications for inter- and intra-fraction motion when using non-standard position approaches. Standard immobilization devices for the torso, extremities or head and neck are to be used. For IMRT delivery approaches, the methods used for localization and immobilization of both patient and tumor are critical. The imaging studies should provide a clear assessment of the target volume with the patient in the treatment position. Anesthesia or sedation may be required in certain patients, such as very young patients, to prevent movement during simulation and daily RT treatments.

15.11 Organs at Risk

15.11.1 Lungs

No more than 35% of the entire lung volume (i.e. bilateral lung) shall receive a cumulative dose greater than 2000 cGy (i.e. V20 should be ≤ 35%). The bilateral mean lung dose must be less than 1500 cGy.

15.11.2 Kidneys

If the GTV encroaches on one of the kidneys, the mean dose to the designated ipsilateral kidney should not be greater than 1500 cGy. In that instance, 50% of the contralateral kidney should receive no more than 800 cGy and no more than 25% should receive a cumulative dose greater than 1200 cGy. If both kidneys require treatment (beyond standard APPA fields to the para-aortic region) both kidneys may receive a mean dose of 1200 cGy and no more than 50% of either kidney should receive 1500 cGy.

15.11.3 Liver

No more than 50% of the liver shall receive a cumulative dose greater than 1500 cGy. No more than 25% of the liver may receive a dose greater than 2100 cGy.

15.11.4 Spinal Cord

Whenever the spinal cord is included in adjacent treatment areas, the field borders will be separated by an appropriate gap. The gap dose to the spinal cord at that gap should be calculated and submitted as part of the Quality Assurance Documentation. The maximum dose to the spinal cord for all combined RT treatments must be less than 4500 cGy.

15.11.5 Heart

For a prescribed dose of 2100 cGy, the goal should be to limit the mean heart dose to less than 1500 cGy. If mean heart dose is anticipated to be greater than 1500 cGy, then IMRT deep inspiration breath hold, or proton therapy should be considered. For a prescribed dose of 2100 cGy, a mean heart dose exceeding 1800 cGy will be considered a protocol deviation unless reviewed with IROC and a study radiation oncologist and deemed unavoidable prior to treatment. If a 900 cGy boost is required (i.e. 30 Gy total prescribed dose) the total (composite) mean heart dose should not exceed 2100 cGy.

15.11.6 Other Organs at Risk

It is important that in addition to the OARs noted above, dose volume histograms (DVH) be submitted for the female breast (left, right and combined), and thyroid when any of these tissues are in the entrance or exit path of any beam.

Also a DVH must be submitted for a category of tissue called "unspecified tissue," which is defined as tissue contained within the skin and encompasses all tissues within a volume 2 cm above and below the PTV.

15.12 Dose Calculations and Reporting

15.12.1 Prescribed Dose

The prescribed dose for each target volume and/or phase of treatment shall be submitted using the RT-1 Dosimetry Summary Form or Proton Reporting Form. If IMRT or proton therapy is used, the monitor units generated by the IMRT/ proton therapy planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the patient's plan can be directly applied to a phantom geometry. The total dose delivered shall be calculated and reported on the RT-2 Radiotherapy Total Dose Record.

15.12.2 Scanning Limits

The scanning limits must be adequate to produce whole organ estimates of normal tissue dosimetry as outlined below. Treatment of the mediastinum requires evaluation of the thyroid, female breasts, heart and lungs. Note that treatment of the spleen requires dose estimation to the heart (i.e. requiring scanning and contouring of the heart) in addition to the kidneys and liver.

15.12.3 Normal Tissue Dosimetry

Dose volume histograms (DVH) shall be submitted for the following organs at risk: female breast (left, right and combined), lungs (left, right and combined), thyroid, liver, kidney (right, left), and heart.

These DVHs are required when the organ is in the entrance or exit path of any beam or beam segment. Where these organs are only exposed to "scatter dose" it is not necessary to scan the entire organ only for the purposes of creating a DVH.

A DVH must be submitted for a category of tissue called "unspecified tissue," which is defined as tissue contained within the skin and encompasses all tissues within a volume 2 cm above and below the PTV.

15.13 Quality Assurance Documentation

15.13.1 Digital Submission

Submission of treatment plans as DICOM RT is required. Digital data must include treatment planning CT, structures, plan, and dose files.

Submission may be by sFTP or CD. Due to the critical time constraints for submitting data for pre-treatment review, we encourage sites to submit data via sFTP to ensure that the pre-treatment reviews are completed in a timely manner.

Instructions for data submission by sFTP or CD are on the IROC RI web site at http://irocri.qarc.org/ under "Digital Data." Any items on the list below that are not part of the digital submission may be included with the transmission of the digital RT data or submitted separately. Screen captures are preferred to hard copy for items that are not part of the digital plan.

Please submit the following items at least one week prior to the start of radiotherapy for pre-treatment review:

15.13.1.1 Treatment Planning System Output

- RT treatment plans including CT, structures, dose, and plan files. These items are included in the digital plan.
- Dose volume histograms (DVH) for the composite treatment plan for all target volumes and required organs at risk. When using IMRT, a DVH shall be submitted for a category of tissue called "unspecified tissue." This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVHs are included in the digital plan.
- Digitally reconstructed radiographs (DRR) for each treatment field with outlines of target volumes only. Submission of DRR's is not required for IMRT.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

15.13.1.2 Supportive Data

- All diagnostic imaging used to plan the target volume.
- Copies of reports (radiology, operative, pathology, cytology) and any other information used in defining the target volumes. **Note: Reports and imaging submitted for the central imaging review need not be resubmitted.**
- If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by the IROC and the radiation oncology reviewers.
- Documentation of any emergency RT administered prior to the protocol prescribed course of RT. Documentation should be provided in the form of the RT (treatment chart).

15.13.1.3 Forms

- RT-1 Dosimetry Summary Form
- Proton Reporting Form (if applicable)
- Motion Management Reporting Form (if motion management techniques are used)

Submit the following items within 1 week following the completion of radiotherapy:

- Radiotherapy record (treatment chart) including prescription and daily and cumulative doses to all required areas and organs at risk.
- RT-2 Radiotherapy Total Dose Record Form.

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

Protocol Dosimetrist
IROC Rhode Island
640 George Washington Highway
Building B, Suite 201
Lincoln, RI 02865-4207
Tel: (401) 753-7600
Fax: (401) 753-7601
Email: physics@qarc.org

15.14 Definitions of Deviation in Protocol Performance

	Variation Acceptable	Deviation Unacceptable
Dose	10% PTV receives > 110% of protocol dose but ≤ 115% *or* < 95% but ≥ 90% of the protocol dose covers 95% of PTV or 99% of CTV	10% PTV receives > 115% of protocol dose *or* < 90% of the protocol dose covers 95% of PTV or 99% of CTV
Volume	Margins for CTV/PTV less than specified or excessively large	A portion of the GTV or potentially tumor bearing area (CTV) is not included in the treated volume
Organs at Risk	Dose to any required OAR exceeds the goal stated in Section 15.11	Will be assessed at the time of final review

APPENDIX I: CLINICAL AND STAGING CRITERIA FOR HODGKIN LYMPHOMA

A. Stage

(See the diagram below for definitions of regions).

Stage I: Involvement of single lymph node region (I) or localized involvement of a single extralymphatic organ or site (IE).

Stage II: Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized contiguous involvement of a single extralymphatic organ or site and its regional lymph node(s) with involvement of 1 or more lymph node regions on the same side of the diaphragm (IIE).

Stage III: Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized contiguous involvement of an extralymphatic organ or site (IIIE), by involvement of the spleen (IIIS), or both (IIIE+S).

Stage IV: Disseminated (multifocal) involvement of 1 or more extralymphatic organs or tissues, with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement.

B. Symptoms and Presentations

"A" Symptoms: Lack of "B" symptoms.

"B" Symptoms: At least one of the following:
Unexplained weight loss > 10% in the preceding 6 months;
Unexplained recurrent fever ≥ 38°C in the preceding month; or
Recurrent drenching sweats in the preceding month.

C. Bulk disease

Each of the following presentations are considered "bulk" disease:

- **Large mediastinal Adenopathy (LMA):**
  Mediastinal Bulk (LMA) = transverse tumor diameter > 1/3 the thoracic diameter at the dome of the diaphragm on a 6 foot PA upright CXR. ***A portable exam is not acceptable*** for measuring LMA and if this is the only exam available at the treating institution, a repeat exam must be performed prior to establishing bulk as it is a criterion for targeting subsequent radiotherapy.

  The hilum is technically not part of the anterior mediastinum, but if the hilar adenopathy is confluent with the anterior mediastinal adenopathy, it may be included in the transverse measurement.

- **Large extra-mediastinal nodal aggregate:**
  Extra-mediastinal bulk is defined as a continuous aggregate of nodal tissue outside the mediastinum that measures > 6 cm in transverse dimension on axial CT or longest dimension on coronal or sagittal reformatted CT. This would not include a contiguous chain of small nodes.

D. Splenic lesions:

Splenomegaly without focal lesions does not indicate splenic involvement with disease. Focal splenic lesions seen on an appropriately timed IV contrast enhanced CT scan can be considered positive if they are PET positive; small lesions below limits of detection by PET/CT must be confirmed by ultrasound or MRI, and are also considered positive. Diffusely increased splenic FDG uptake greater than normal liver parenchymal FDG uptake but in the absence of lesions seen on CT will not be considered evidence of involvement at diagnosis.

E. E-Lesions Defined:

Extra-lymphatic structures contiguous with sites of lymph node involvement are considered E-lesions (particularly lung). Pleural, pericardial, or chest wall infiltration by an adjacent nodal lesion that is PET positive would be considered an E-lesion. Liver and/or bone marrow involvement is not considered an E lesion, but rather considered Stage IV. Pleural and pericardial effusions alone are not considered E-lesions.

F. Regions of Nodal Involvement

Peripheral Upper Regions (indicate laterality: right or left)

- Neck: cervical (upper, lower/supraclavicular), occipital, and pre-auricular
- Infraclavicular
- Axilla
- Pectoral
- Epitrochlear
- Brachial

Central Regions

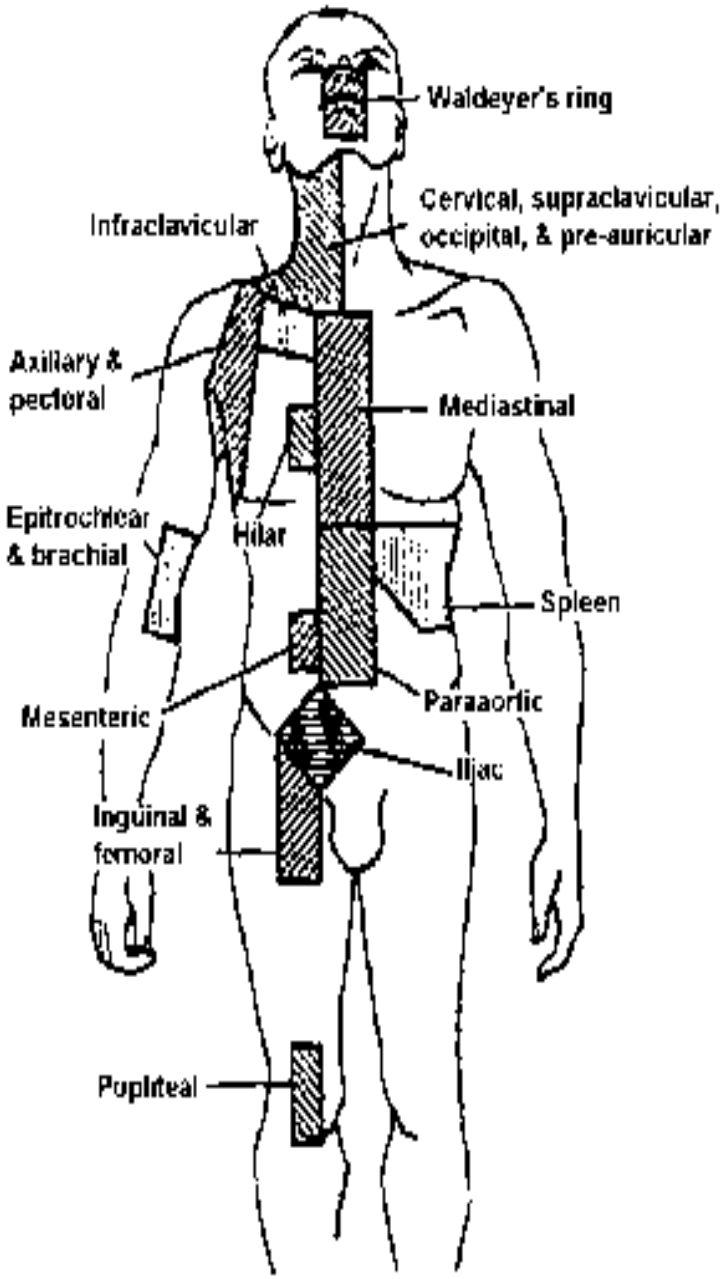
- Waldeyer's ring (including base of tongue)
- Mediastinum (anterior; hilar; cardiophrenic; subcarinal)
- Hilar
- Mesenteric
- Paraaortic (including retrocrural, portal and celiac)
- Splenic/splenic hilar

Peripheral Lower Regions (indicate laterality: right or left)

- Iliac
- Inguinal
- Femoral
- Popliteal

Other Non-Nodal Sites

- Lung (right, left or bilateral)
- Bone
- Bone marrow



Anatomical Regions for the Staging of Hodgkin's Disease

APPENDIX II: RECOMMENDED GUIDELINES FOR IMAGING

CT Scan

CT Image Acquisition

Breath-hold technique should be used in cooperative older children to reduce motion artifact and spatial mis-registration from respiration. In very young children and in uncooperative older children sedation may be used when clinically feasible to minimize image degradation from patient motion.

For staging examinations both intravenous and oral contrast should be used. For follow-up examinations limited to the neck/thorax, only IV contrast is necessary. Because of the difficulty of assessing mediastinal structures on non-contrast examinations, non-contrast scans are inadequate for response assessment. **MRI study is not allowed for baseline or response assessments.** Exceptions to this rule include the following special circumstances: patients with contrast allergies, renal failure, or other contraindications to the use of intravenous CT contrast media. In these cases MRI or non-contrast CT may be used as an alternative imaging modality. The study radiologist must be notified if only the use of non-contrast CT is available as an alternative imaging modality; central review at IROC RI should be notified with an explanation.

For abdomen and pelvic CT scans, oral contrast should be administered at least 45 minutes prior to the exam to allow adequate opacification of the small bowel. The dose of oral contrast will vary with the type of contrast available at an institution and the patient age or size. Imaging during a single phase (i.e., portal venous) after injection usually suffices for intravenous contrast. A dose of 1.5-2.5 mL/kg of low osmolar intravenous contrast is a general guideline. The optimal rate of contrast injection and timing of scanning initiation after contrast injection will vary with patient size, anatomic region of interest, and intravenous line size and location.

Selection of the CT acquisition parameters should be made to achieve the best compromise between lesion conspicuity, acquisition time, and patient dose, and may vary with the imaging equipment available at each institution. The choice of technical CT parameters should be according to standard institutional protocol, optimized for pediatric imaging, with adherence to ALARA principles. Exposure parameters for pediatric CT may be adjusted based on:

1) Child size: guidelines based on individual size/weight parameters.
2) Region scanned: the region of the body scanned should be limited to the smallest necessary area.
3) Organ systems scanned: lower mA and/or kVp settings should be considered for skeletal and lung imaging.
4) Scan resolution: the highest quality images (i.e., those that require the most radiation) may not be necessary to make diagnoses, particularly for routine follow up imaging.

Multiphase CT examinations that use multiple scans obtained during different phases of contrast enhancement are rarely necessary, result in a considerable increase in dose, and in general should be avoided. For staging and duration of protocol therapy, MRI is allowable only in special circumstances as outlined above. For guidance in selecting CT parameters that are optimized for pediatric use, information is readily available at www.imagegently.org.

CT Interpretation

Image display considerations include field-of-view, window width and level, and availability of both thin-section source images and multi-planar reconstructions. Follow-up studies should be performed and interpreted with parameters as close as possible to the baseline study to optimize validity of comparisons. For example, lesions should be measured with the same window settings and reconstruction intervals.

Acquisition slice thickness and collimation are modulated according to age/size. For interpretation, reconstructed slice thicknesses of 3-5 mm are typical for infants and small children, for older children and adolescents a thickness of 5-7 mm is acceptable. Thicker slices decrease spatial resolution, contribute to errors from partial volume effects and are of limited value in assessing small lesions, such as pulmonary nodules.

Helical/spiral CT allows volumetric acquisition and generation of overlapping axial image reconstructions, as well as sagittal and coronal reconstructions, all of which improve the accuracy that lesions are measured and characterized. Because of the wide variability in parameters selected to produce longitudinal (coronal, sagittal) reconstructions which may produce some inaccuracy, as a rule the diameter of lesions should be measured in the axial plane only with the exception of determining whether a nodal lesion represents bulk when it is < 6 cm in the axial plane but > 6 cm. in the craniocaudal plane.

FDG-PET IMAGING

Please refer to the American College of Radiology (ACRIN) PET Core Laboratory Standard Operating Procedures, which is also adapted from the NCI consensus recommendation,[46] at the following weblink for more detailed information, unless otherwise specified below.
(http://www.acrin.org/CORELABS/PETCORELABORATORY/PETSOPS/tabid/484/Default.aspx)

The following generally accepted FDG-PET issues and items should be adhered to as much as possible in this clinical trial to allow for uniformity of inter- and intra-patient FDG-PET imaging and analysis needed for this study:

Summary of Definite Requirements

1) PET/CT, in place of stand-alone PET imaging, should be performed if at all possible for anatomical correlation, especially on the follow-up PET imaging. If a stand-alone PET scan is performed, correlative contemporaneous CT should be provided for anatomical correlation, especially at site of involved disease.
2) Patients should be fasted for at least 4 hours before [^{18}F]FDG administration.
3) PET imaging should begin at 60 ± 10 min after injection of [^{18}F]FDG.
4) For follow-up PET imaging of the same patient, all attempts should be made to image the patient on the same PET/CT scanner.
5) The following PET parameters should be recorded for each imaging session:
    a. Patient's weight and height
    b. [^{18}F]FDG dose and time of administration
    c. Start time of PET imaging
    d. Serum glucose level (or verify that level is less than 200 mg/dL)
    e. Use of low-dose propranolol or fentanyl for pharmacologic suppression of activated brown adipose tissue
6) DICOM PET/CT or PET images should be sent for central review as a full unprocessed data set including PET SUV for possible subsequent quantitative analysis.
7) Institutional radiologist or nuclear medicine physician assessment and report of the PET2 scan for qualitative visual classification (5-point or Deauville criteria) and anatomical location of the single most prominently increased ("hottest") intrapatient lymphoma site.
    a. This visual PET criteria are scored according to uptake in sites initially involved by lymphoma as: (1) no uptake, (2) uptake ≤ mediastinal blood pool, (3) > mediastinal blood pool but ≤ liver, (4) moderately increased uptake > liver, or (5) markedly increased uptake > liver and/or new lesions. Physiologic FDG liver uptake is used as a reference with score of 1 to 3 regarded as PET negative and 4 or 5 as positive.

Summary of Other Optional Recommendations

1) State some type of annual scanner QC/QA.
   Recommend either:
   - American College of Radiology (ACR) - Nuclear Medicine/PET accreditation Program (http://www.acr.org/accreditation/nuclear.aspx) or
   - Intersocietal Commission for the Accreditation of Nuclear Medicine Laboratories (ICANL) PET accreditation (http://www.icanl.org/icanl/index.htm)
     a) If either of these PET QC/QA are not used in your facility, please provide your PET scanner QC/QA accreditation.

2) FDG dosing requirements
   a) Confirm dosing in recommended dosing is in the range of 0.10 – 0.14 mCi/kg
   b) If recommended dose range is not used, state institutional pediatric PET dosing formula or schema.
   c) Dose should not be above 0.15 mCi/kg.

3) After FDG injection, the patient is kept at rest in a warm room through imaging to minimize FDG uptake in activated brown adipose tissue or other physiologic FDG artifacts.

Pregnancy

All female patients ≥ 10 years of age should be asked about their pregnancy potential prior to FDG injection. Patients who are pregnant or breast feeding will only be injected if the PET scan is deemed necessary for clinical management by the patients' primary physician and the patient agrees to the study. Patients who are sexually active and unsure of their pregnancy status should undergo a urine or serum pregnancy test prior to FDG injection. Pregnant guardians should not be allowed in the FDG uptake room.

Recommended Technique

Patients should be fasted for at least 4 hours before imaging. Total parenteral nutrition and intravenous fluids containing glucose should also be discontinued for at least 4 hours before the study. The patient should be well hydrated (oral or intravenous fluid administration) before administration of FDG. Fluids administered for hydration should not contain glucose.

It is suggested that the patient's measured height and weight on the day of the PET scan be recorded for each imaging session.

If intravenous access is not already in place, this should be obtained, typically in the antecubital fossa, for patient hydration (if needed), determination of serum glucose and FDG administration. Good hydration is required as the primary route of FDG excretion is renal. The patient should drink water or receive intravenous fluids after injection to promote urinary FDG excretion.

Venous serum blood glucose will be measured and recorded just prior to injection of the FDG and must be ≤ 200 mg/dL.

Diabetic patients should be scheduled in the morning after an overnight fast before the first meal, and dose of insulin should be titrated appropriately in consultation with the patient's referring physician to keep the serum glucose ≤ 200 mg/dL at the time of scheduled FDG injection. If the serum glucose is significantly elevated (> 200 mg/dL) then the test should be rescheduled if at all possible with better glucose control or, if necessary, insulin can be used to achieve normoglycemia. After regular insulin the patient should wait 2-4 hours (after ultrashort acting insulin, 1-2 hours) prior to administration of FDG in order to minimize physiologic skeletal muscle and myocardial FDG uptake.

In patients with tumors in the pelvis, placement of a Foley catheter is recommended. Patients in whom a Foley catheter is not placed should be asked to void immediately prior to imaging in order to minimize bladder activity and to reduce their radiation exposure.

FDG Dosing and Injection

[^{18}F]FDG is administered intravenously at a dose of 0.10 – 0.14 mCi/kg with a minimum dose of 1.0 mCi and maximum dose of 10 mCi.

After injection, the patient is kept at rest in a warm room until imaging. After voiding the bladder, whole-body imaging should begin at 60 ± 10 min after injection of [^{18}F] FDG. For serial scans of the same patient it is important to start the PET scan with the same delay time after injection of the FDG radiotracer. Therefore, it is recommended that all subsequent PET scans have approximately the same delay time (± 10 min) as the baseline scan. The use of low-dose propranolol or fentanyl for pharmacologic suppression of [^{18}F] FDG uptake in activated brown adipose tissue can be applied as per institutional protocol and recorded.

It is suggested that the net injected FDG dose and time of injection should be recorded. The peripheral IV or central line injection site location should also be recorded.

PET Scanning Protocol

A whole body PET imaging protocol is utilized, covering the area from the base of skull/top of the ears to the proximal/mid-thigh, just below the pubis. If there is suspicion of involvement in the lower extremities, skull, or skull contents, the volume that is imaged may be expanded. The patient will be positioned supine, with arms comfortably positioned above the head if at all possible (to limit attenuation of the thorax), or at the side of the patient if necessary. Scans should proceed upward from the pelvis to diminish the effects of accumulation of FDG activity in the bladder.

Transmission scanning matching the areas covered by the emission scan will need to be performed for attenuation correction of the emission scan. This will be done after injection of FDG. With a combined PET/CT scanner, attenuation correction should be done with non-IV contrast CT data per manufacturer recommendations. It is recommended that the COG institution adjust the CT dose used for attenuation correction to limit the CT radiation dose to the patient without significantly affecting PET quality or anatomic correlation to CT. Please refer to protocol recommendations from the Image Gently website (http://www.imagegently.org/Home.aspx).

The 511 KeV-annihilation photons, produced by interaction of positrons with electrons, are imaged. Because of the short physical half-life of 1.8 hours and the high photon energy of 511 KeV, FDG imaging may follow bone or gallium scintigraphy, or a MUGA study on the same day (that use lower energy photons) or FDG imaging may be performed on the day preceding any of these other nuclear medicine studies.

It is suggested that the following acquisition parameters should be recorded: start time of emission scan and type of transmission scan.

It is recommended that PET images be reconstructed with and without attenuation correction. It is also recommended that for serial scans of the same patient, image reconstruction techniques and parameters be consistent across all scans, including filters and application of the attenuation map.

After Completion of the PET Scan

The patient must empty his or her urinary bladder as soon as possible after imaging. Image reconstruction will depend on the scanner manufacturer. An iterative reconstruction method with parameters chosen to yield 6-8 mm resolution in the reconstructed images is recommended.

FDG Handling and Dose Documentation

FDG is to be synthesized by standard methods and tested for pyrogenicity and radiochemical purity on each production run, or purchased from nuclear pharmacies licensed to sell FDG. The radiochemical purity of the FDG should be > 90%.

PET Imaging Quality Control Standards

FDG-PET imaging will be performed using "state-of-the-art" equipment (either a dedicated NaI, BGO, LSO or GSO full-ring PET system), that will have a field of view appropriate for body imaging (≥ 10 cm), high resolution (FWHM ≤ 6.0 mm), high sensitivity, and post-injection transmission capability.

Daily and monthly steps will be taken to assure quantitative accuracy of PET imaging studies and reliable imaging results at all performance sites, with recommended clinical standards described above under "Summary of Other Optional Requirements" under "State some type of annual scanner QC/QA".

The level of tumor uptake is assessed subjectively by visual inspection as described in the Evaluation Criteria (see Section 10). **Semi-quantitative assessment of response by determination of standardized uptake values (SUV) is not utilized in this protocol response criteria, however SUV parameters can be provided as per routine clinical practice.** Deauville score assessment should be performed utilizing coronal attenuation corrected PET images rather than MIP or fused images.

APPENDIX III: CYP3A4 SUBSTRATES, INDUCERS AND INHIBITORS

This is NOT an all-inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references.

CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Strong Inducers	Moderate Inducers
acalabrutinib[5] alfentanil[4,5] amiodarone[4] aprepitant/fosaprepitant atorvastatin axitinib bortezomib bosutinib[5] budesonide[5] buspirone[5] cabozantinib calcium channel blockers cisapride citalopram/escitalopram cobimetinib[5] conivaptan[5] copanlisib crizotinib cyclosporine[4] dabrafenib dapsone darifenacin[5] darunavir[5] dasatinib[5] dexamethasone[2] diazepam dihydroergotamine docetaxel doxorubicin dronedarone[5] eletriptan[5] eplerenone[5] ergotamine[4] erlotinib estrogens etoposide everolimus[5] fentanyl[4] gefitinib haloperidol ibrutinib[5] idelalisib imatinib indinavir[5] irinotecan isavuconazole[5] itraconazole ivacaftor	atazanavir boceprevir clarithromycin cobicistat darunavir delavirdine grapefruit[3] grapefruit juice[3] idelalisib indinavir itraconazole ketoconazole lopinavir/ritonavir nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole	aprepitant conivaptan crizotinib diltiazem dronedarone erythromycin fluconazole fosamprenavir grapefruit[3] grapefruit juice[3] imatinib isavuconazole mifepristone nilotinib verapamil	barbiturates carbamazepine enzalutamide fosphenytoin phenobarbital phenytoin primidone rifampin St. John's wort	bosentan dabrafenib efavirenz etravirine modafinil nafcillin rifapentin

ketoconazole lansoprazole lapatinib losartan lovastatin[5] lurasidone[5] macrolide antibiotics maraviroc[5] medroxyprogesterone methadone midazolam[5] midostaurin[5] modafinil nefazodone nilotinib olaparib ondansetron osimertinib paclitaxel palbociclib pazopanib quetiapine[5] quinidine[4] regorafenib romidepsin saquinavir[5] sildenafil[5] simvastatin[5] sirolimus[4,5] sonidegib sunitinib tacrolimus[4,5] tamoxifen telaprevir temsirolimus teniposide tetracycline tipranavir[5] tolvaptan[5] triazolam[5] trimethoprim vardenafil[5] vemurafenib venetoclax[5] vinca alkaloids zolpidem				

[1]Certain fruits, fruit juices and herbal supplements (star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP 3A4 isozyme, however, the degree of that inhibition is unknown.
[2]Refer to Section 4.1.1 regarding use of corticosteroids.
[3]The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.
[4]Narrow therapeutic range substrates
[5]Sensitive substrates (drugs that demonstrate an increase in AUC of ≥5-fold with strong inhibitors)

APPENDIX IV: MODIFIED ("BALIS") PEDIATRIC SCALE OF PERIPHERAL NEUROPATHIES

Peripheral Motor Neuropathy:

- Grade 1: Subjective weakness, but no deficits detected on neurological exam, other than abnormal deep tendon reflexes.

- Grade 2: Weakness that alters fine motor skills (buttoning shirt, coloring, writing or drawing, using eating utensils) or gait without abrogating ability to perform these tasks.

- Grade 3: Unable to perform fine motor tasks (buttoning shirt, coloring, writing or drawing, using eating utensils) or unable to ambulate without assistance.

- Grade 4: Paralysis.

Peripheral Sensory Neuropathy:

- Grade 1: Paresthesias, pain, or numbness that do not require treatment or interfere with extremity function.

- Grade 2: Paresthesias, pain, or numbness that are controlled by non-narcotic medications (without causing loss of function), or alteration of fine motor skills (buttoning shirt, writing or drawing, using eating utensils) or gait, without abrogating ability to perform these tasks.

- Grade 3: Paresthesias or pain that are controlled by narcotics, or interfere with extremity function (gait, fine motor skills as outlined above), or quality of life (loss of sleep, ability to perform normal activities severely impaired).

- Grade 4: Complete loss of sensation, or pain that is not controlled by narcotics.

APPENDIX V: CORRELATIVE IMAGING STUDIES

Correlative study design

Aim: To incorporate qualitative visual FDG-PET into response directed treatment algorithms and refine quantitative FDG-PET and CT definitions of tumor burden and response for future incorporation into next generation pediatric HL risk-stratification schemes.

Specific Aim 1: Interim Visual PET - Incorporation of 5-point visual FDG-PET criteria for risk-adapted interim PET response assessment in COG initial therapeutics protocol AHOD1331 for early responders.

Definition of PET response: The COG AHOD1331 high-risk HL initial therapeutics clinical protocol will incorporate interim FDG-PET assessment as an integral part of its risk-adapted treatment stratification scheme. This FDG-PET assessment will consist of central review of the baseline PET (PET0) and post-cycle 2 PET (PET2) utilizing a 5-point visual scale or Deauville criteria that has been used effectively and validated in other HL studies and our own COG retrospective study. This visual PET criteria are scored according to uptake in sites initially involved by lymphoma as: (1) no uptake, (2) uptake ≤ mediastinal blood pool, (3) > mediastinal blood pool but ≤ liver, (4) moderately increased uptake > liver, or (5) markedly increased uptake > liver and/or new lesions. Physiologic FDG liver uptake is used as a reference with score of 1 to 3 regarded as PET negative and 4 or 5 as positive.

Imaging Review Procedure: PET images obtained at COG institutions will be forwarded electronically to the Clinical Trial Quality Assurance Imaging and Radiation Oncology Core Group (IROC Rhode Island) Group (formerly QARC) who will administrate and manage the images. Central review will be performed by consensus of two experienced nuclear medicine physicians and/or radiologists with review of diagnostic quality digital PET and CT images (DICOM files) within 2 weeks of the scan receipt in order for timely risk-adaptive treatment stratification for subsequent radiation need remotely on a high-quality web-based PET and CT software (MIMSoftware™). In the event of disagreement between the two central reviewers, there will be a convened reassessment by the two readers for consensus within three weeks of receipt of the PET and CT images by IROC RI. In the event when two reviewers cannot come to an agreed consensus adjudication by a third nuclear medicine or radiologist central reviewer will occur within four weeks. Discrepancies between the reviewers and/or institutional interpretations will be resolved on regular monthly and/or as needed ad-hoc scheduled teleconference calls. COG HL committee and IROC RI have experience and demonstrated track record with central review performed through a recently completed COG HL high-risk protocol AHOD0831.

In cases where PET2 is positive with intrapatient lymphoma 5-point visual or Deauville score greater than reference liver (Deauville 4 or 5), PET5 central review (end of chemotherapy PET) by consensus of two experienced nuclear medicine physicians and/or radiologists will be performed within two weeks of scan receipt at IROC Rhode Island. In the event of disagreement between the two central reviewers, there will be a rapid convened reassessment with adjudication by a third reviewer within three weeks of receipt of the PET and CT images by IROC-Rhode Island to allow for timely scheduling and start of radiation therapy.

Central review comparison to local institution review: Post-cycle 2 PET (PET2) positive or negative PET interpretation, utilizing a 5-point visual scale with a threshold physiologic FDG liver uptake (score of 1 to 3 regarded as PET negative and 4 or 5 as positive), will be compared between local institutional radiology review and central review.

Specific Aim 2: (**Note: For Central Review Research Purposes Only; Not Required By Institutional Review**)
Interim Quantitative PET and CT Analysis - Quantitative interim FDG-PET-based assessment will assess PET standardized uptake value (SUV) to evaluate (1) absolute tumor interim PET (PET2) SUV based parameters and (2) % change of tumor PET SUV from baseline to mid-therapy and end-of-therapy in order to more accurately differentiate between responders and non-responders. CT tumor volume determined after 2 cycles of chemotherapy (CT2) will be determined and the change in tumor burden as represented by CT tumor volume between the baseline and post-cycle 2 imaging will also be evaluated.

PET Methods: Quantitative baseline PET0 and interim PET2 assessments will be performed on a regular periodic basis for prospective correlation with qualitative 5-point visual scores. Quantitative FDG-PET-based region-of-interest (ROI) analyses will include maximal voxel-based tumor SUV (SUVmax), peak tumor SUV (SUVpeak) with variously defined "peak" parameters, average physiologic liver SUV (Liver SUVavg), and physiologic mediastinal blood pool SUV (Blood pool SUVavg).

Imaging Review Procedure: Individual site qualification for adequate PET/CT imaging will be performed by IROC, (IROC Rhode Island in conjunction with IROC Ohio). Subsequent PET0 and PET2 scan credentialing along with all data management and review facilitation will be performed by IROC Rhode Island (QARC). PET analyses will be performed by consensus of two experienced COG HL nuclear medicine and/or radiology central reviewers retrospectively.

Interim CT tumor burden: CT tumor volume determined after 2 cycles of chemotherapy will be determined and the change in tumor burden as represented by CT tumor volume between the baseline and post-cycle 2 imaging will be determined. Dedicated multi-detector IV contrast CT of the chest, abdomen and pelvis (head/neck as needed) will be required at baseline and at the interim therapy PET2 time points as part of the parent AHOD1331 study concept. An IV contrast CT obtained as the CT portion of the PET/CT used for attenuation correction for PET reconstruction will be accepted. Please see specific aim 3 "baseline tumor burden" section for specifics of the proposed CT volume method.

Specific Aim 3: (**Note: For Central Review Research Purposes Only; Not Required By Institutional Review**)
Baseline PET and CT Tumor Burden - To determine if baseline tumor burden as determined by PET- and CT- derived volumetrics provides prognostic information for risk stratification in pediatric HL.

Baseline PET Tumor Burden*:* To correlate baseline tumor burden at diagnosis as determined by FDG-PET-derived quantitative parameters with clinical outcome (EFS).

PET Methods: Baseline PET images will be analyzed by various PET SUV-based threshold methods to determine a PET-based metabolic volume based on absolute, tumor and physiologic normal organ based values (i.e. tumor SUVmax, tumor SUVpeak, liver SUVavg, and mediastinal blood pool SUVavg). Various tumor SUVmax and SUVpeak threshold percentage will be applied (i.e. 20%, 30%, 40%, 60%). PET parameters will include metabolic tumor volume (MTV), total tumor glycolytic activity (TGA), and average tumor SUV (SUVavg). Of note the FDG-PET metabolic tumor volume using the MIMSoftware™ application does not include central tumor necrosis or non-FDG avid portions of the tumor into the volume contour, therefore providing a "real" metabolic tumor volume.

IV contrast CT method: Dedicated multi-detector IV contrast CT of the chest, abdomen and pelvis (head/neck as needed) will be required at baseline and at the interim therapy PET2 time points as part of the parent AHOD1331 study concept. An IV contrast CT obtained as the CT portion of the PET/CT used for attenuation correction for PET reconstruction will be accepted.

Imaging Review Procedure: Individual site qualification for adequate PET/CT imaging will be performed by IROC (IROC Rhode Island in conjunction with IROC Ohio). Subsequent PET0 and PET2 scan credentialing along with all data management and review facilitation will be performed by IROC Rhode Island (QARC). PET analyses will be performed by consensus of two experienced COG HL nuclear medicine and/or radiology central reviewers retrospectively. These quantitative interim PET analyses will be performed remotely on high-quality web-based PET/CT software (MIMSoftware™).

Baseline CT Tumor Burden: To correlate baseline IV contrast CT-derived bulk tumor volume to clinical outcome (EFS)

Baseline IV CT images will be analyzed remotely using a CT volumetric segmentation algorithm developed in the Laboratory for Computational Image Analysis (CIA Lab) at Columbia University Medical Center (Pending Patent: PCT/US13/36258). An early version of this algorithm can be found in this reference.[47] The algorithm is integrated into a user friendly imaging platform also developed in-house with Interface Description Language (IDL). This platform has major image viewing and manipulation functions and allows tumor contours (i.e., segmentation results) to be superimposed on original image series for radiologist's review and modification if needed. An experienced radiologist in the CIA lab will be responsible for measuring tumor volumes with the help of the segmentation based on the reference noted above. In a recent work published by the CIA lab, it was found that reproducibility of computer-aided volumetric measurements was high. The magnitude of the variability in measuring total tumor burden was [-25%, 35%] at 95% limits of agreement on a radiologist's repeat measurements of tumor volumes).[48]

Comparability of PET and CT Baseline Tumor Burden: To assess the comparability and practical analysis of baseline PET MTV with CT-derived tumor volumes for incorporation into future clinical trials.

Specific Aim 1: Interim Visual PET - Incorporation of 5-point visual FDG-PET criteria for risk-adapted interim response assessment in COG initial therapeutics protocol AHOD1331.

Hypothesis: 5-point visual FDG criteria can be successfully implemented in AHOD1331.

Specific Aim 2: Interim Quantitative PET and CT - Quantitative interim FDG-PET-based assessment will assess PET standardized uptake value (SUV) to evaluate (1) the % change of tumor PET SUV from baseline to mid-therapy and end-of-therapy and (2) assess the absolute tumor interim PET (PET2) SUV based parameters to more accurately differentiate between responders and non-responders. CT tumor volume determined after 2 cycles of chemotherapy (PET2) will be determined and the change in tumor burden as represented by CT tumor volume between the baseline and post-cycle 2 imaging will also be evaluated.

Hypothesis: Quantitative interim post-cycle 2 FDG-PET (PET2) percent change from baseline (PET0) and absolute PET2 PET SUV threshold parameters will correlate with visual PET2 response assessment and EFS.

Specific Aim 3: Baseline PET and CT Tumor Burden-To determine if baseline tumor burden as determined by PET- and CT- derived volumetrics provides prognostic information for risk stratification in pediatric HL.
Hypothesis: Baseline FDG-PET (PET0) and CT based quantification of nodal tumor burden will be correlated with EFS.

Background and Rationale

With the paradigm that early response is more reflective of chemosensitivity than is end of chemotherapy response, our last series of trials required concurrent functional imaging (either gallium or FDG-PET) along with CT so that we could compare the utility of each method in a pediatric population and determine which assessment method was the best predictor of outcome.[26,49] We found that 1) the use of PET added predictive value to CT; 2) omission of RT is optimally based on both PET2 and CT2 response; and 3) the use of either PET2 or CT2 response alone did not adequately define a high-risk population using the ABVE-PC treatment platform. Integration of novel imaging modality questions into the study platform will allow incorporation of such modalities into treatment considerations in subsequent studies. Standardizing measurement of tumor volume by CT and PET is an ongoing challenge as criteria, imaging techniques, and calculation formulas differ between studies.

FDG-PET imaging plays an important role in Hodgkin Lymphoma management. FDG-PET has been incorporated in the 2007 lymphoma international working group (IWG) guidelines to standardize end-of-therapy response criteria for lymphoma, including Hodgkin Lymphoma, using blood pool as a reference visual threshold to determine residual FDG uptake.[41,42] Incorporation and validation of various FDG-PET imaging criteria more specifically for pediatric Hodgkin lymphoma patients in our upcoming trials will provide improved risk stratification and treatment response criteria leading to improved clinical outcome in subsequent studies. We propose to accomplish this in the context of our high-risk pediatric HL study AHOD1331 by validating integral qualitative visual FDG-PET response adapted therapy with quantitative FDG-PET baseline and interim response parameters.

Visual Qualitative Interim PET Incorporation of FDG-PET for lymphoma interim response assessment however is critically dependent on the visual threshold used to determine a positive PET scan (slow-early responder) versus a negative PET scan (rapid early responder). The threshold for response should be adapted to the clinical outcome goals of the study with a threshold for high negative-predictive value chosen if the goal is treatment reduction in order to reduce chemotherapy related toxicity but a threshold for high positive-predictive value applied if the goal is treatment intensification for high-risk disease. Therefore, a graded method of visual criteria that is conducive to different positivity thresholds could be used to adjust for the required test specificity in a given trial design. Guidelines for standardization using visual FDG-PET for interim response assessment are still developing with improved outcome on interim PET in Hodgkin Lymphoma when applying a higher visual PET threshold compared to current IWG thresholds.[43,44] A recent study demonstrated that visual 5-point score or Deauville criteria can improve prediction of outcome and reproducible enough in advanced-stage Hodgkin Lymphoma for recommendation as a standard reporting criterion in clinical practice and for clinical trials.[44,45]

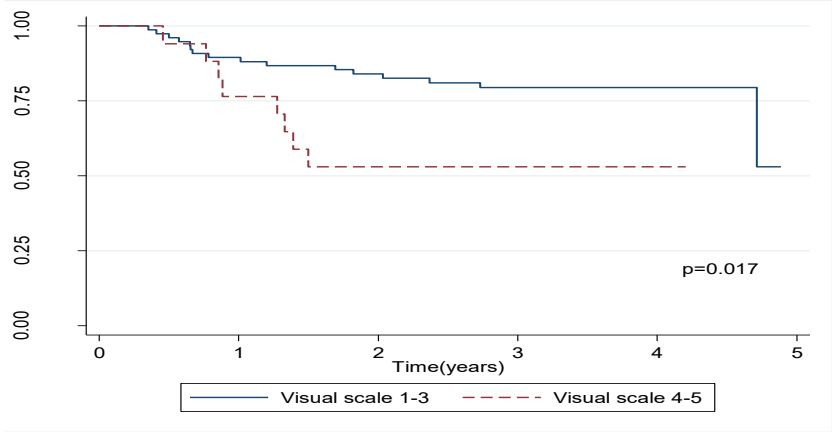


Figure 1. Interim therapy PET (PET2) response assessment using 5-point score visual Deauville criteria, using PET score ≥ 4 (> reference liver) as PET positive.

Our own COG retrospective PET study analyzed multi-site FDG-PET or PET/CT images from AHOD0031,[50] a phase III COG study for newly diagnosed pediatric intermediate-risk HL.[26] FDG-PET was obtained at baseline (PET0), at mid-therapy after 2 cycles of ABVE-PC chemotherapy (PET2) and if the PET2 was positive, after completion of further chemotherapy (PET3). We randomly selected 150 patients with PET2 enrolled since 1/2007, a cohort likely to have high-quality archived PET images, and that represented 5 specific groups (Stage I, IIA, IIB, III, and IV) in proportion to their representation in the AHOD0031 study. From this cohort, a subset of patients (n=94) with qualified PET images were selected for review. Our visual assessment applying a 5-point scale Deauville criteria at PET2 and PET3 demonstrated a pronounced (but not complete) response at mid-therapy, as measured using a five-point visual FDG-PET assessment with liver (not blood pool) as a reference threshold (visual scale ≥ 4 as positive) is highly predictive of EFS, as seen in Figure 1.

Quantitative SUV Interim PET:

Quantitative PET SUV-based response criteria using a percent change in SUV between baseline PET and after two cycles of chemotherapy in non-Hodgkin lymphoma, diffuse large B-cell lymphoma, was found to lead to better performance and interobserver reproducibility compared to the visual criteria, including the Deauville criteria.[51,52] However, for interim PET interpretation in Hodgkin lymphoma, visual assessment is recommended and currently preferred over quantitative SUV-based PET response criteria due to the inherently relatively abrupt and rapidity of the metabolic response seen in Hodgkin lymphoma compared to more gradual FDG-PET response seen in non-Hodgkin lymphoma during therapy.[53] However, a prospective study of FDG-PET response assessment in pediatric Hodgkin lymphoma patients showed the median SUVmax reduction from baseline to interim PET scan was significantly higher in responders (median, 81.3%) compared with non-responders (median, 38.6%), P=0.006. ROC analysis estimated an optimal threshold cutoff value for identification of relapse patients at less than 58% SUVmax reduction at interim PET.[54] A more comprehensive analysis of the prognostic benefit of interim therapy PET SUV measurements in pediatric Hodgkin lymphoma demonstrated by ROC-analysis the most accurate differentiation of responders and non-responders with percent change in SUVmax with an optimal threshold cutoff value of 75%.[55]

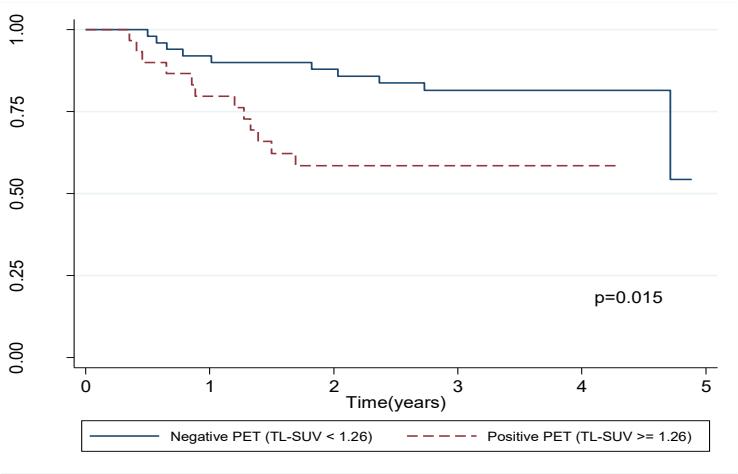


Figure 2. EFS at interim PET (PET2) using an optimized threshold cutoff tumor SUV criteria (tumor SUV normalized to liver uptake).

Our COG retrospective FDG-PET analysis of FDG-PET from AHOD0031,[50] a phase III COG study for newly diagnosed pediatric intermediate-risk HL, also assessed interim PET quantitative tumor SUV parameters. Event free survival (EFS) was chosen as a clinical endpoint of interest and analyzed by Cox proportional hazards model for the SUV parameters. Mid-therapy PET (PET2) Tumor SUVmax normalized to liver SUVavg (TL-SUV) was most highly predictive of EFS (P=0.02). An evaluation of the predictive value of percent change in SUV between PET scans showed that the percent reduction in SUV in the interval from baseline (PET0) to mid-therapy (PET2) was most predictive of EFS using TL-SUV12 (P=0.03). An ROC analysis derived optimized threshold cutoff threshold was determined for TL-SUV (≥ 1.26) to determine PET positive at PET2. Kaplan-Meier curve using this optimized cutoff value for PET2 is shown in Figure 2. Our retrospective analyses and other published studies provide rationale for a systematic comprehensive assessment in our COG study of quantitative PET SUV response assessment in pediatric Hodgkin lymphoma due to the potential for improved interobserver reproducibility and improved accuracy of SUV analysis compared to current 5-point Deauville visual criteria.

Baseline PET and CT Tumor Volumetrics

FDG-PET and CT based tumor volume measurements has been widely applied in solid tumors and is now being reported to be prognostic in non-Hodgkin lymphoma.[56,57] Standardization for the measurement of tumor volume by CT and PET is an ongoing challenge as criteria, imaging techniques, and calculation formulas differ between studies. Reproducible and accurate tumor volume assessment, and definition of bulk tumor at initial diagnosis, can potentially affect risk stratification and consolidation radiation therapy.

Retrospectively COG AHOD0031 FDG-PET based volumetric measurement of our pediatric Hodgkin lymphoma nodal tumor volume was retrospective analyzed at Johns Hopkins University IRAT facility and submitted as an abstract for the 9th International Symposium on Hodgkin Lymphoma. FDG-PET and CT based volumetric measurement of our pediatric Hodgkin lymphoma nodal tumor volume was retrospective analyzed. The purpose of this study was to assess the prognostic value of baseline tumor burden as determined by both FDG-PET and anatomic CT parameters in pediatric HL. Our unpublished data is provided below that demonstrates the prognostic significance of baseline PET and CT volumetric data [pending publication and submitted as an abstract to the 2013 9th international symposium on Hodgkin Lymphoma in Cologne, Germany]. We retrospectively analyzed multi-site FDG-PET/CT images from COG AHOD0031, a phase III study for newly diagnosed pediatric intermediate-risk HL. We randomly selected 150 patients who were randomized or assigned to the same standard therapy and had post-cycle 2 PET with 50 patients each of three response groups in the study based on post-cycle 2 and end-of-therapy CT. From this cohort, a subset of patients (N=90) with qualified PET/CT scans were selected for review. Baseline PET images were analyzed by consensus of 2 readers blinded to clinical outcome data using MIMSoftware™ application. A variety of PET standardized-uptake value (SUV) threshold values based on absolute, liver, blood pool and tumor were assessed to derive PET parameters for total body nodal tumor burden including: average tumor SUV (SUVavg), metabolic tumor volume (MTV) and total tumor glycolytic activity (TGA). Event free survival (EFS) was chosen as a clinical endpoint of interest and

analyzed by log-rank and Cox proportional hazard model. Selected parameters were further assessed using receiver-operating-characteristic (ROC) analysis where the outcome was 2-year EFS. Baseline FDG-PET SUV derived MTV and TGA parameters were found to be highly predictive for EFS for a variety of thresholds (P<0.05). PET SUV threshold values found to be most predictive and reliable included: 1.5Lv + 2xliver standard deviation (1.5Lv+2SD), 2x mediastinal blood pool (2BP) and 20% maximal tumor SUV (TSUVmax). ROC area under the curve (AUC) for MTV using 1.5Lv+2SD, 2BP and TSUVmax threshold was 0.77, 0.84, and 0.79, respectively. Use of an "optimal cut-off" PET MTV value based on the ROC for 1.5Lv+2SD, 2BP and TSUVmax was able to separate EFS groups (P < 0.005). Baseline tumor SUVavg was not found to be predictive for EFS. In conclusion, baseline FDG-PET SUV derived total body tumor burden as represented by tumor volume (MTV) and total tumor glycolytic activity (TGA) was hypothesized to be predictive of EFS in pediatric HL.

Similarly, the optimal imaging study and criteria used to assess tumor burden is not adequately defined, especially as measured by anatomic scans including CT. We retrospectively analyzed multi-site CT images from COG AHOD0031. We randomly selected patients who were randomized or assigned to the same standard therapy and had PET post-cycle 2, with 50 patients from each of the three response groups in the study defined by post-cycle 2 and end-of-therapy CT. From this cohort, a subset of patients (N=84) with qualified CT scans were selected for review. Using software developed by the Computational Image Analysis (CIA) Lab at Columbia University that incorporates an advanced segmentation algorithm for assessment of tumor volume, uni-dimensional, bi-dimensional and 3-dimensional measures of total tumor burden were assessed at baseline and after 2 cycles of chemotherapy. Event free survival (EFS) was chosen as a clinical endpoint of interest. Receiver-operating-characteristics (ROC) analysis was used to select an "optimal" cutoff of tumor burden for predicting 2-year EFS. Association between tumor burden (above/below median or "optimal" cutoff) and EFS was examined by log rank test. Baseline tumor burden as assessed by uni, bi and 3-D measures was highly predictive of EFS (p < 0.05 for analyses with median; < 0.003 with "optimal" cutoffs). Similarly, tumor burden following 2 cycles of chemotherapy was prognostic for EFS (p<=0.05 for analyses with median; < 0.02 with "optimal" cutoffs). Further analyses evaluating percentage change with/without threshold tumor measure were not significantly prognostic of EFS. Baseline and interim total tumor burden but not change in tumor burden as measured by CT is highly predictive of EFS in pediatric HL. Incorporation of tumor burden assessment by CT may be useful for baseline risk stratification and for further refinement of therapy in conjunction with PET as part of a response-based strategy.

Statistical Considerations:
For aim 1, PET2 by 5-point visual scale after 2 cycles will be centrally reviewed to determine early response. We will monitor the rate of initial review completion within 2 weeks of scan receipt and hypothesize that we can have 90% or more reviews successfully completed in time. The study has 90% power to detect an 86% or lower rate of reviews completed in-time in a one-sample test of proportions with one-sided alpha level of 0.05. Descriptive statistics will be used to summarize the review between the 2 blinded reviewers in terms of RRL (i.e., PET2 negative with Deauville score of 1-3) vs. SRL (i.e. PET2 positive with Deauville score of 4-5) for each lesion(s) in a given patient. Inter-reviewer agreement between the 2 blinded reviewers in their initial review will be estimated by Cohen's κ coefficient. Assuming the rate of RER by PET is 70-80% for each reviewer, with 580 eligible patients, the 95% CI for the estimate of Cohen's κ will have half width of 0.08 or less if Cohen's κ is 0.6 or higher. We are also interested in assessing the agreement between institution assessment of positive or negative PET interpretation, utilizing a 5-point visual scale with a threshold physiologic FDG liver uptake (score of 1 to 3 regarded as PET negative and 4 or 5 as positive), and the central review response assessment, and similar approaches will be used to describe and assess the agreement between central review and institution review.

For aim 2, we will assess the quantitative SUV-based PET measures and the quantitative CT tumor burden at 2 cycles and the percent change in these measures from baseline to 2 cycles. Descriptive statistics will be used to summarize these measures and their percentage changes. Association between the PET 5-point scale and these quantitative SUV measures after 2 cycles will be assessed by rank correlation coefficient statistics such as Spearman's ρ and Kendall's τ. We will examine the association between EFS and these interim quantitative SUV-based PET measures/their change from baseline and the interim quantitative CT tumor burden/their change from baseline in log rank test and Cox proportional hazard models. Response (and LMA)-adapted RT introduces confounding effect in examination of the association of these quantitative SUV-based measures with EFS, as the association will be confounded by non-random administration of RT. It is possible that patients with the large values in these measures and especially those with smaller change in these measures from baseline to 2 cycles will be associated with being SER as defined by the PET 5-point visual criteria, and thus more likely to receive RT that may reduce the risk for failures. Such confounding effect is expected to reduce the extent of raw association observed between these measures and EFS, therefore makes the observed association conservative.

For aim 3, we will assess the baseline tumor burden as determined by PET- and CT-derived volumetric measures. Correlation between tumor burden assessed by the PET volumetric measures and CT volumetric measures will be examined by Pearson correlation coefficient. Early response on prior studies has been shown to correlate with EFS, so will be used as one surrogate for examining the association between baseline tumor burden and EFS. We will examine the association between baseline tumor burden measures and early response after chemotherapy by two-sample t-tests and/or Wilcoxon rank sum test within each randomized arm separately. Logistic regression model on early response will also be used to explore the impact of baseline tumor burden combining data from the 2 arms with adjustment for randomized chemotherapy. Due to lack of prior data on the distribution of these tumor burden measures in the high-risk population, power estimation is difficult. Similar to the analyses above on interim quantitative PET- or CT-based measures, response (and LMA)-adapted RT introduces complication in directly examining and interpreting the association of baseline tumor burden with EFS, as the association will be confounded by non-random administration of RT. It is possible that patients with higher baseline tumor burden (expect higher risk for failures) will be more likely to be have LMA and be SER, and thus more likely to receive RT that may reduce their risk for failures. Log rank test and Cox models adjusting for randomization arm will be used to explore the association between the baseline tumor burden acknowledging the potential confounding effect of RT. The expected confounding effect caused by non-random assignment of RT should only reduce the degree of association that makes the estimates conservative.

Power estimation:

For aim 1, we will monitor the rate of initial review completion within 2 weeks of scan receipt and hypothesize that we can have 90% or more reviews successfully completed in time. The study has 90% power to detect an 86% or lower rate of reviews completed in-time in a one-sample test of proportions with one-sided alpha level of 0.05. Inter-reviewer agreement between the 2 blinded reviewers in their initial review will be estimated by Cohen's κ coefficient. Assuming the rate of early response by PET is 70-80% for each reviewer, with 580 eligible patients, the 95% CI for the estimate of Cohen's κ will have half width of 0.08 or less if Cohen's κ is 0.6 or higher.

For aim 2 and 3, power estimation is difficult for these analyses partly due to lack of estimates for the distribution of these interim quantitative SUV-based PET measures and CT measures and baseline tumor burden measures in this high-risk study population. The retrospective analyses on these measures were done in a cohort (from AHOD0031) that included few high-risk patients eligible for this study. Assuming a median cutoff for such interim quantitative measure or baseline tumor burden measure that create 2 groups of patients with equal size (n=290 per group), the individual analysis comparing EFS between the 2 groups defined by above/below the median of a measure will have power similar to that for the primary aim of the study, i.e., > 80% power for 8% EFS difference at 3 years (see Section 9.3.1.2. for details). Similarly, using median as cutoff, the analysis for association between a quantitative measure (defined as either above or below median) with early response will have power similar to that for the secondary aim on early response rate, i.e., > 80% power for 9% difference in early response rate between the 2 groups (see Section 9.3.2.2 for details). Assuming some other cutoff for such quantitative measure that defines 2 groups of patients with the smaller group being 20% to 40% of the total sample size, the power for detecting the association between such measure with early response or EFS are similar to those power discussed for the aim on CHIPS (see Section 9.3.4.2 for details).

APPENDIX VI: CORRELATIVE BIOLOGY STUDIES

Samples will be collected prospectively and will be available for analysis at the end of the clinical trial. Research proposals will be submitted in the future for retrospective studies on these samples. The immune function studies will be performed on prospectively collected peripheral blood, as these studies have to be performed in fresh tissue samples. A brief description is provided of the types of analyses to be done on prospectively collected samples. This section provides a rationale for tissue collection for analysis which can be addressed in future protocols.

Please note: *Patients may also be enrolled on the current COG Biology Banking study which includes pre-therapy specimens.* If patients are enrolled on both AHOD1331 and a biology banking study, the priority is to submit the specimens through AHOD1331 first.

A. SAMPLE COLLECTION SCHEDULE

1. Paraffin Embedded Material: A representative block (preferred) or unstained and stained slides should be processed according to Section 13.2. Send one of the following:
   a. Surgical biopsy specimen: One paraffin block with representative sample (formalin preferred).
   b. If blocks cannot be sent, submit 10 unstained and unbaked sections (4 microns thick) and 2 H&E stained sections from one representative block on silanized slides (i.e. Fisher Superfrost Plus).

   If the patient was diagnosed by biopsy before referral to the treating institution, a good faith effort should be made to obtain either a block or 10 unstained slides and 2 H&E stained slides.

2. Snap frozen tumor tissue: From surgical biopsy. See Section 13.2 for detailed processing instructions. Snap frozen tissue will be collected for future molecular classification studies as described below.

3. Peripheral blood: See Table 7.2 for detailed overview of sample collection time points, volumes and tube types. Shipping and handling instructions for BPC and the Bollard Lab are found on the pages that follow.

   A. Immune function studies (shipped to Bollard lab) should be collected in **heparin tubes** only and held at room temperature until shipment. It is acceptable for blood to be collected from a central line.
      1. Pre-treatment: 2 mL/kg with a maximum volume 20 mL (max 10 mL for patients weighing < 12 kg)
      2. Post-treatment, after completion of all therapy: 2 mL/kg with a max volume 40 mL (max 20 mL for patients weighing < 12 kg).

   B. Other correlative biology studies (shipped to BPC): Planned studies include EBV viral load, TARC, cytokine studies and WBC and plasma banking. The specified volume should be collected in heparin tubes and held at 4°C until shipment (see below). Either sodium heparin or lithium heparin tubes are acceptable. **Please do NOT use plasma separator tubes.**

What if a specified time point is missed?
Every effort should be made to obtain the time points that occur before chemotherapy starts (i.e. diagnosis or Cycle 1 Day 1). During therapy missed time points should be omitted. Once therapy is complete, and the patient is in follow up, if biology specimens are not obtained at any requested time point, please send specimens at the next requested time point or at the next clinic visit, whichever is sooner.

INSTRUCTIONS FOR BIOLOGY SPECIMEN HANDLING AND SHIPPING

Please be aware that biology specimen shipments must comply with IATA standards (www.iata.org).

Specimen Labeling • Label all blood samples with the COG Patient ID number, specimen type (blood), and collection date. *For Bollard Lab specimens also include: protocol number (AHOD1331), accession number, and time point.* • Tissue samples must be labeled with the COG Patient ID number, specimen type (P for primary or M for metastatic) and collection date. Blocks and slides must also include the surgical Pathology ID number and block number from the corresponding pathology report.
Specimen Storage • If not shipped on the day of collection, blood for the BPC should be stored at 4°C until shipment. • Blood for the Bollard Laboratory should be stored at ambient temperature until shipment. • Snap frozen tissue should be stored in a -70ºC freezer until shipment.
Transmittal forms: • An AHOD1331 transmittal form and a pathology report (with tissue submissions) must accompany each shipment of specimens to the BPC. • For shipments to the Bollard lab, please note the patient's WBC (from the day of or immediately prior to the date of collection) on the transmittal form.

SHIPMENT OF SPECIMENS TO THE BPC

Frozen Tissue, blocks or slides and ambient blood at baseline can be shipped to the BPC together in a dual-chambered Specimen Procurement Kit (provided upon request by the BPC via the BPC Kit Management System accessible online at: https://ricapps.nationwidechildrens.org/KitManagement/).

If frozen tissue is not submitted, then blood and block and slides must be shipped in your own container. The shipping container must be insulated to provide temperature stability during shipment.

Specimens may be shipped to the BPC on Monday-Thursday for Tuesday-Friday delivery. Saturday delivery is only available for fresh blood. Do not ship specimens the day before a holiday.

The BPC provides a shipping label for shipment of the dual chambered kit at baseline and shipments of ambient blood. Blocks and/or slides shipped separately are shipped at the institution's expense.

Arrange for FedEx pickup per your usual institutional procedure or by calling 1-800-238-5355. Ship specimens to:

Biopathology Center
Children's Hospital
700 Children's Drive, WA1340*
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

* Be sure to include the room number. Packages received without the room number may be returned to sender.

Instructions for packaging specimens in a dual chambered kit provided by the BPC:

1. Before specimens are placed into the Specimen Procurement Kit they first need to be placed in three separate layers of packaging. Package the frozen specimens and the ambient specimens separately since they will be placed in separate compartments of the kit. Two sets of the biohazard and Tyvek diagnostic envelopes are provided in the kit for this purpose.
   a. Place the specimens in zip lock bags (one bag per specimen type/time point).

   b. Place the zip lock bags in the biohazard envelope with the absorbent material. Expel as much air as possible and seal the envelope securely.
   c. Place the biohazard envelope inside the Tyvek envelope. Expel as much air as possible and seal securely.
2. Frozen specimens should be placed in one of the kit compartments filled with dry ice.
   a. Layer the bottom of the compartment with dry ice until it is approximately one-third full.
   b. Place the frozen specimens on top of the dry ice.
   c. Cover the specimens with the dry ice until the compartment is almost completely full.
   d. Place the cover on top of the kit chamber to insulate the specimens during shipment.
3. Ambient temperature specimens should be shipped in the other kit compartment at room temperature.
   a. Place the transmittal form(s) and any other required paperwork in a plastic bag and place inside the kit chamber with the ambient specimens.
   b. Place the cover on top of the kit chamber to insulate the specimens during shipment.
4. Close the outer lid of the Specimen Procurement Kit and tape with filament or other durable sealing tape.
5. Print a shipping label via the BPC Kit Management application and attach to the top of the kit.
6. Complete the dry ice label (UN 1845). Place the dry ice and Exempt Human Specimen labels on the side of the kit.

SHIPMENT OF SPECIMENS TO THE BOLLARD LABORATORY

Notify Hema Dave or Bollard lab representative prior to shipment of the sample*
Email: cogsamples@childrensnational.org ***OR*** **Phone:** (202) 476 6397 or (202) 476 8005.

* If prior notification is not possible, proceed with shipment without delay and email the FedEx tracking number to: cogsamples@childrensnational.org **.**

DO NOT ship samples for delivery on a weekend or holiday without prior authorization. Contact the Bollard Lab for special instructions if samples are collected on Friday for Saturday delivery. Although not preferred, samples collected on Saturday/Sunday can be shipped Monday for Tuesday arrival. If you have any questions regarding shipping, please contact Dr. Hema Dave at the Bollard Lab.

Blood should be shipped to the Bollard Lab using the COG FedEx account:
See: https://www.cogmembers.org/_files/reference/FEDEXmemo.pdf

Ship specimens by Federal Express Priority Overnight delivery to:

Dr. Catherine Bollard c/o Hema Dave
Children's National Medical Center
111 Michigan Ave NW
5th Floor Main, Rm 5220
Washington DC 20010
Phone: (202) 476 8005

Instructions for Packaging the Bollard Lab Specimens:

1. If a ThermoSafe shipping container is not available, send samples in a comparably thick container such as a Styrofoam box (not a clini-pack).
2. Place blood collection tubes in a primary container, wrapping each collection tube separately to protect from breakage during shipment.
   a. Place at least one ice pack in the secondary/outer container.
   b. If the shipment will be in transit for greater than 24 hours, and during non-winter months (April-October), place additional ice packs in the secondary container (Styrofoam box) to maintain temperature stability during shipment.

3. **Reminders:**
   a. Notify Hema Dave or a Bollard lab representative prior to shipment of the sample.
      Phone: (202) 476-6397 or (202) 476-8005.
      Email: hkdave@childrensnational.org and cogsamples@childrensnational.org
   b. On the AHOD1331 Specimen Transmittal Form, record the exact time and date that the sample is drawn and note the white blood cell count (WBC).

B. SUMMARY OF CORRELATIVE BIOLOGY STUDIES

CORRELATIVE BIOLOGY STUDY 1: To determine the incidence of tumor-specific antigens (PRAME, MAGE-A4, and testis-specific antigens) and the incidence of EBV antigens (EBNA1, LMP1, LMP2) in newly-diagnosed, high-risk cHL, and to determine the difference in immune function (CTL number and function, cytokine secretion) between those treated with standard chemotherapy vs. brentuximab-containing chemotherapy.

Rationale

Many studies have demonstrated the importance of the immune system and the microenvironment in Hodgkin lymphoma.[58,59] However, little is known about the effect of treatment on the immune cells in the microenvironment or the incidence of CTL target antigens in pediatric/AYA HL patients. In high-risk pediatric cHL, absolute numbers of CD3-positive T cells are significantly reduced (CD4 > CD8), and virtually all patients with HD have a degree of lymphopenia. There is an unmet need to assess immune cell recovery between patients treated with standard therapy and those treated with brentuximab-containing chemotherapy. Several previous studies have shown that brentuximab may influence the HL microenvironment, making it more conducive to CTL expansion and function.[58] This information will provide a better understanding of how the recovery of tumor-specific and pathogen specific T cells affects the patient's response to therapy both in terms of disease response and therapy related toxicity (infection). Similarly, if manipulation of tumor-specific antigens is contemplated as a method to prevent relapse, understanding the dynamics of tumor-specific T cells and reconciling their dynamics with clinical changes during therapy are requisite to rationally design a therapeutic intervention using adoptive T cell immunotherapy. The ultimate goal is to determine if CTL therapy can be added to the treatment of high-risk HL patients to prevent relapse.

Hypothesis and specific aims

We hypothesize that patients with TAA (tumor associated antigens) expression will be less likely to relapse. We also hypothesize that patients treated with brentuximab-containing chemotherapy will have a less immunosuppressive environment following treatment, and that patients with a less immunosuppressive micro-environment following chemotherapy will be less likely to relapse. We plan to test these hypotheses with the following specific aims:

1) To determine the incidence of EBV-associated antigens (EBNA1, LMP1 and LMP2) and incidence of tumor-associated antigens (PRAME, MAGE-A4 and testis-associated antigens) in cHL tumors, and to determine if the incidence of tumor-associated antigens correlates with EBV status or EFS; and

2) To characterize pre- and post-treatment systemic immunosuppressive environment:
   a. To determine if specific pre or post-treatment effector immune functions correlate with EFS,
   b. To determine if there are differences between post-treatment or changes over time in specific immune functions between brentuximab-containing chemotherapy vs. standard chemotherapy, and

c. To determine if we can identify pre-treatment immune functions that control brentuximab-mediated treatment effects.

Methods
The incidence of tumor-specific antigens will be determined by immunohistochemistry (IHC) from pre-treatment biopsy tissue. Immune function will be determined by CTL activation (IFN-gamma secretion), cytokine excretion, and gene expression as determined by a GEP array as previously described.[60]

Contribution to current knowledge base
Tumors frequently modulate target antigen expression to prevent T-cell recognition. Based on our preliminary data in the phase I setting,[61] there is an apparent lack of tumor specific t-cell response in non-responding patients. In contrast >50% of relapsed HL patients achieving durable clinical responses post-therapy produce T-cells specific for tumor associated antigens within 2 months. If this therapy is to be expanded to larger patient groups, it is necessary to confirm these observations in a prospective, phase 3 cooperative group setting. The confirmation of the potential importance of eliciting a T-cell response to tumor –associated antigens (TAAs), the adoptive transfer of tumor specific T-cells could be eventually incorporated into upfront therapy in HL.

Preclinical studies
Tumor specific CTLs have been generated in several hematologic malignancies, including ALL,[62] EBV-positive HL[63,64] and EBV negative lymphomas.[65] There have been CTLs generated for multiple tumor-specific antigens, including testis-specific antigens and MAGE-A4.[66] Tissue microarray studies have shown that MAGE-A4 is strongly expressed on most pediatric/AYA tissue biopsy samples collected on the AHOD0031 clinical trial (Bollard, personal communication).[66] CTLs against both EBV and non-EBV antigens have been shown to be specific for the tumor antigen and have generated persistent CTLs production that has generated robust anti-TAA responses in HL mouse xenografts. These CTL are long-lasting and induce sustained complete responses in mouse xenografts.[48]

Clinical studies
The Bollard lab has conducted a phase I study in which relapsed HL adult patients were treated with TAA non-EBV CTL post stem cell transplant.[66] Following treatment they evaluated tumor-specific T-cell specific populations form seven responding patients and five non-responding patient with lymphoma to identify the breadth of the tumor specific T cell response to PRAME, MAGE-A4 and survivin.[49] This study showed that cytotoxic T cells were generated specifically recognizing MAGE-A4 expressed by autologous HL targets. Decitabine, an epigenetic modifier previously shown to increase tumor antigen expression in HL, did not compromise MAGE-A4-specific T-cell phenotype and function. In patients treated with decitabine, expanded MAGE-A4-specific T cells had a broader antitumor T cell repertoire, consistent with increased antigen stimulation in vivo. This suggests that adoptive transfer of MAGE-A4-specific T cells, combined with either epigenetic modifying drugs or other therapies that alter the T-cell peptide antigen repertoire, such as brentuximab, could improve treatment of HL.[66]

Study design
The long-term goal of this study is to further delineate immune responses in the cHL microenvironment. This information is needed to determine if immunotherapy can be incorporated into therapy regimens for newly-diagnosed cHL. Although immunotherapy holds great promise for the future of cHL therapy,[60,64-66] it is necessary to determine if changes in the microenvironment following treatment will allow for the expansion of tumor-specific CTL in vitro.

1) Tissue analysis
The incidence of tumor-specific EBV antigens, MAGE-A4, PRAME and testis-specific antigens will be assessed by one of two methods. If adequate diagnostic tissue blocks are available, tumor specific antigens will be determined using a tissue microarray as described.[67,68] If blocks are not available, the tumor specific antigens will be assessed using pre-treatment biopsy slides obtained from all consenting patients with available unstained slides. Unstained slides will be examined for relevant antigens using IHC and commercially available antibodies as described.[66]

2) Peripheral blood analysis
Peripheral blood will be obtained for immune studies. Immune function assays will include assessment of general immunity and reconstitution (e.g. anti-infectious and anti-tumor specific T-cell immunity). Blood will also be used for analysis of peripheral lymphocyte cell-specific gene expression. Blood will be used to measure general immune reconstitution and in particular the recovery of T cells specific for tumor associated antigens (TAA) such as MAGE A4, PRAME, Survivin, SSX2 and EBV antigens LMP1 and LMP2. Response to these tumor-specific antigens will be determined pre-treatment and at the completion of treatment.

Comparability of methods
We will use the same methods that we have used in previous studies[60-64] and we do not expect technical problems completing either the TAA antigen studies or the immune function assays. These methods have been used to evaluate responders vs. non-responders in a phase I study[61] and these methods will be extended to a larger patient sample set in this phase 3 cooperative group trial.

Reason for selection of assay methodology
No other methodologies have been developed for use with shipped, small volume samples. Our published preliminary date provides evidence that this is the best methodology for evaluating tumor-specific T-cell responses in HL patients.[66]

Technical performance characteristics
ELISPOT analysis will be used to determine the frequency and function of T-cells secreting IFN-γ in response to EBV and tumor-associated antigen peptide mixtures (pepmixes™ (JPT)). Technical performance characteristics have been previously published.[60]

The experience of the investigators with the assay
Dr. Bollard is well published in the role of EBV antigens and the role of CTL immunotherapy.[59-66] Drs. Horton and Bollard have worked together previously on the assessment of tumor-associated antigens in HL samples from the AHOD0031 clinical trial.

Site performing the correlative studies
The Bollard laboratory is in a GMP facility at Nationwide Children's Hospital, a state-of-the-art facility that is actively involved in assessment of immune function and the development of immunotherapy.

Assurance of quality control
The Bollard Laboratory serves as the central pathology review for Phase I/II HL immunotherapy studies. The Bollard Laboratory will use their standard QA/QC procedures during the procedures outlined above.[59-65]

Prevalence of tumor-associated antigens:
Because we are assessing both EBV and non-EBV antigens, the prevalence of different markers will vary. Preliminary data from the Bollard lab and others suggests that EBV antigens are present in approximately 40% of newly-diagnosed HL patients.[66] Based on IHC performed on samples from the AHOD0031 clinical

trial, tumor-associated antigens varied from >80% (MAGE-A4) to approximately 20-40% (Bollard, personal communication).

Proportion of patients on a therapeutic trial will have available sample for correlative study analysis and statistical analysis plan

This study plans to accrue approximately 600 patients. In the last COG phase 3 HL clinical trial (AHOD0031) the BPC acquired 307 blocks from the 1712 eligible patients, or 18% of tissue blocks from eligible patients. However, since tissue samples will be collected prospectively on this study, we expect that our sample acquisition rate will be substantially higher. Assuming a success rate of 30% with prospective collection of tissue, this should result in approximately 180 pre-treatment tissue samples for evaluation (90 samples per treatment arm). In AHOD0031, at least one peripheral blood sample was collected for 40% of patients. Assuming 40% rate of collection of peripheral blood for pre-treatment and post-treatment samples, this should result in blood samples from 240 patients (120 per arm) for each collection. Of the patients with blood samples collected over time, we project approximately 80% will have both pre-treatment and post-treatment samples submitted, which results in 192 patients (96 per arm) with both pre- and post-treatment blood samples.

For estimating the incidence of EBV antigens (EBNA1, LMP1, LMP2) and incidence of tumor-associated antigens (PRAME/MAGE4, testis-associated antigens) in cHL tumors, the binary incidence will be estimated from the tissue samples along with its 95% confidence interval (CI). With 180 samples, at a projected 20-40% incidence for EBV antigens, the standard error for the binary incidence rate estimate will be 3-3.7%; in other words, the width for the 95% CI will be 12-14%. For PRAME/MAGE4, with a projected incidence of 70-80%, the standard error will be 3-3.4% and the width for the 95% CI will be 12-13%. For testis-specific antigens, with a projected incidence of 30-40%, the standard error will be 3.4-3.7% with the width of 95% CI being 13-14%. To examine the correlation between tumor-associated antigen (TAA) and EBV status, the incidence of TAA will be compared between EBV positive and EBV negative tumors. Assuming a 20% EBV positive rate, the comparison has a sample size of 36 vs. 144. It is powered to detect a 26% (or less) difference in the incidence of TAA between the 2 groups; the detectable difference can be less than 26% and varies depending on the incidence rate for the 2 groups. Similarly, if the incidence of positive EBV is 40%, which results in a sample size of 72 vs. 108, the study is powered to detect a 22% (or less) difference in the incidence of TAA between the EBV positive and negative groups. To examine the correlation of TAA with EFS, assuming the tissue samples are obtained from random subsets of the study participants, we will have approximately 23 EFS events for this correlative study (30% of 77 events from the parent study). To detect a difference in EFS between 2 groups with a total of 23 events, it requires a hazard ratio of 4.3/0.23 if the group sizes are 36 vs. 144 (20% vs. 80%), or a hazard ratio of 3.6/0.28 if the group sizes are 54 vs. 126 (30% vs. 70%).

For analyses of immune functions from blood samples (quantitative measures), we project 240 samples will be collected from either pre-treatment or post-treatment collection, and 192 paired samples. To investigate the correlation of pre-treatment immune function with EFS, assuming these samples were from random subset of study participants, we will have approximately 31 events (40% of 77 events from the parent study). For an analysis comparing EFS between 2 groups of patients defined by immune function above/below median (120 vs. 120), we will have power to detect a hazard ratio of 2.7/0.37. To examine the effect of brentuximab-containing treatment on immune functions, we will compare the post-treatment immune functions between the 2 arms. With 120 patients per arm, the power is 80% to detect a 3.7 SD (SD: standard deviation of the post-treatment measure) difference in the mean. We will also compare the change in immune function from pre-treatment to post-treatment between the 2 arms. With 96 patients per arm with paired samples, the detectable difference is 4.1 SD (SD: standard deviation of the change between pre-treatment and post-treatment). In an attempt to identify pre-treatment immune functions that determine brentuximab-mediated treatment effect, we will explore the interaction term between pre-treatment immune

function (2 categories) and treatment arm (total 4 groups) using EFS as outcome. With a total of 31 events, this analysis has limited power due to testing an interaction term. The smallest detectable interaction term (ratio of the hazard ratio) is estimated to be 7.5, but the detectable interaction can be larger than that depending on the number of failures in the 4 groups.

Table 1summarizes the effect sizes for this biology aim:

Table 1: Standard error or effect size (2-sided alpha=5%, power 80%) based on sample size for each experiment (total patients in study: n=600)

1. Antigens measures from pre-treatment biopsy tissue (n=180)	**Samples size**	**Standard Error or Effect-Size**
a. Incidence of EBV* antigens (est. 20-40%)	180	Standard error: 3%-3.7%
b. Incidence of TAA* (est. 70-80% for PRAME /MAGE4, 30-40% for testis-associated antigens)	180	Standard error: 3-3.4%, (PRAME/MAGE4) 3.4-3.7% (testis associated antigens)
c. Correlation of TAA with EBV	36 vs. 144 (if 20% EBV+), 72 vs. 108 (if 40% EBV+)	Detectable difference for incidence of TAA in EBV + vs. EBV - : ≤26% (36 vs. 144), ≤22% (72 vs. 108).
d. Correlation of TAA with EFS	36 vs. 144 (if TAA incidence 80%), 54 vs. 126 (if TAA incidence 30%)	Detectable hazard ratio: 4.3/0.23 (36 vs. 144) 3.6/0.28 (54 vs. 126)
2. Immune function measures from pre-/post treatment blood (n=240)		
a. Correlation of pretreatment immune function (above/below median) with EFS	120 vs. 120	Detectable hazard ratio: 2.7/0.37
b. Compare post-treatment and the change in pre- and post-therapy in immune function by treatment arm.	120 vs. 120 (post-treatment) 96 vs. 96 (change in pre-/post- therapy)	Detectable difference in mean: 3.7 SD (SD: standard deviation of the post-treatment measure) 4.1 SD (SD: standard deviation of the change in pre- &post- measures)
c. Interaction between pre-treatment immune function and treatment arm on EFS	4 groups total 240	Detectable interaction term (ratio of hazard ratio) >7.5

*EBV = Epstein Barr Virus, TAA = Tumor associated antigens

The incidence of EBV-specific antigens, PRAME/MAGE4, and testis-specific antigens will be estimated from pre-treatment biopsy samples along with their 95% confidence intervals. The association between presence of TAA and EBV status will be examined by Chi-square tests. Kaplan-Meir curves will be used to estimate EFS for patients with/without TAA, and log rank test will be used to determine if there is any association between TAA and EFS.

Descriptive statistics will be used to summarize immune function measures from pre-treatment and post-treatment blood samples. Cox proportional hazards models will be used to examine if pre-treatment immune functions (may be analyzed as categorical variable or continuous variable) correlate with EFS. Post-treatment immune functions or change in immune functions from pre-treatment to post-treatment will be compared between the standard arm and the experimental arm via two-sample t-test to determine if brentuximab-containing therapy leads to more suppressed immune function than standard therapy. Cox

proportional hazards models will be used to explore the interaction between pre-treatment immune functions and treatment arm on EFS to see if pre-treatment factors important for brentuximab-mediated treatment effect can be identified. Pre-treatment immune functions may be analyzed as categorical variable or continuous variable for such analysis. Although the power for this interaction analysis will be low due to testing of an interaction effect, we expect the impact of the immune function and treatment with brentuximab-containing chemotherapy will be sufficiently large to be detectable.

Corrections for multiple comparisons
Most of these comparisons are exploratory and we do not plan to correct for multiple comparisons.

Discuss how the results will have an impact on future studies
One of the long-term goals of the COG HL and non-Hodgkin lymphoma (NHL) committees is to incorporate cytotoxic T lymphocyte (CTL) immunotherapy into treatment regimens for HL. CTL therapy is well tolerated and CTLs can be "trained" *in vitro* to recognize tumor specific antigens (EBNA1, LMP1 and LMP2 for EBV-positive HL and PRAME, MAGE4 and SSX in EBV-negative HL). However, one of the challenges in allowing for the expansion of tumor-specific T cells in newly diagnosed HL patients is the immunosuppressive environment surrounding the Hodgkin/Reed Sternberg (H/RS) cells. H/RS cells are surrounded by T-helper cells, regulatory T cells (Tregs), and tumor-activated macrophages, all of which secrete immunosuppressive chemokines/cytokines that suppress CTL expansion *in vivo*.[58] There is an unmet need to determine how to reverse or ameliorate this immunosuppression to allow the expansion of anti-tumor CTLs in HL patients. The ability to comprehensively evaluate tumor-specific T-cell responses will enhance the development of a highly immunogenic and potent cell therapeutics that could prevent relapse in high-risk HL patients.

The objective of this research is to delineate alterations in immune modulation following chemotherapy, both with and without brentuximab. Based on extensive preliminary data from the Bollard lab and our experience collecting patient samples in the cooperative group setting, the proposed translational research will greatly expand the implementation of CTL therapy into the cooperative group setting.

C. ADDITIONAL PLANNED STUDIES
Samples will be stored for these planned studies at the Biopathology Center (BPC in Columbus, OH) and be available for use in future HL research. In the future, specific hypotheses and statistical design will be submitted along with each proposal for tissue samples, and will undergo review as per COG and NCTN policies and procedures.

Planned Biology Study #1: To determine if a molecular classifier can be developed that 1) identifies early response patients at increased risk of relapse, and 2) correlates with 3-year EFS in high-risk pediatric HL.

While early PET response and CHIPs help to stratify patients into treatment arms and determine the need for radiotherapy, many of the patients that subsequently relapse initially respond well to therapy. There is an unmet need to determine which early response patients will require additional, more intensive therapy to prevent relapse occurrence. We propose to identify these patients using a molecular classifier based on transcript, genome and protein analysis.

Prior work in adult HL has used gene, miRNA, and protein expression analyses of HL tumor tissue to identify putative molecular markers prognostic of clinical outcome.[69-82] However, the prognostic significance of these markers in pediatric HL is unknown. We hypothesize that an integrated molecular analysis will assist in risk-stratification for pediatric HL. The goal of these experiments will be to learn more about the biology of HL tumors, and what factors can predict treatment success (early response or 3-year EFS) vs. treatment failure (presence of any SRL, progressive disease or relapse). A comprehensive,

mechanism-based evaluation of cHL will allow for not only the identification of reliable predictors of outcome (3-year EFS), but will also inform us of the mechanisms responsible for adverse outcome, allowing for the identification of molecular pathways that could be targeted with future therapies.

Snap frozen tissue samples will be banked for use at the end of the study. Genome, exome and protein analysis will be submitted at that time to CTEP/NCTN for approval. We expect the methods will include both whole tissue expression arrays using Nanostring (paraffin-embedded tissue) and whole exome sequencing of isolated H/RS cells.

Advances in the field of HL biology have shown suggested that the development of a molecular classifier would be beneficial for several reasons. The first is that a comprehensive analysis of GEP, genetic rearrangements, and protein changes in HL will help us gain a better understanding the biology of AYA-HL. This information will not only aid in finding reliable predictors of outcome, but the predictors should inform us of the mechanisms responsible for adverse events and could aide in determining which patients would potentially benefit from molecularly targeted therapies. Second, similar to adult HL,[83] there is an **unmet need** to identify biomarkers that retain their prognostic significance in the AYA population. Successful completion of these experiments will allow for us to establish a pediatric/AYA biomarker signature that can be tested in future trials to determine the prognostic significance of molecular classification. Third, since most pediatric HL relapses come from patients that initially respond well to therapy, there is a need to be able to accurately identify these patients after their initial treatment in order to aid with risk stratification.

Work from our lab and others have shown that GEP derived from whole tissue biopsy specimens can predict overall survival (OS),[62] indicating the importance of GEP in the microenvironment. Recent studies from have suggested that tumor-associated macrophages predict inferior outcomes in adult cHL,[77] including samples prospectively collected from the E2496 intergroup clinical trial.[84] However, the prognostic value of tumor-associated macrophages could not be reproduced in two small pediatric/AYA cohorts,[85,86] strongly suggesting that biomarkers have to be reassessed in AYA- HL. A current retrospective review of GEP and TMA from the AHOD0031 and AHOD0831 clinical trials is ongoing (AHOD12B2). The data from this retrospective study, in combination with the technology that will have advanced molecular methods, will be combined to propose a series of experiments for the development of a retrospective study to identify prognostic molecular classifiers using prospectively collected samples.

There is an unmet need to determine which patients with a RRL to therapy (as determined by CT/PET) require additional, more intensive therapy to prevent relapse. A molecular will aid in the process of identifying patients with a "high-risk" molecular genetic profile. This classifier will be examined prospectively in the nest clinical trial. The eventual goal, if the classifier is validated, is to combine imaging data and the molecular score with other known risk factors to risk stratify patients following initial chemotherapy. The goal is to improve long-term survival by preventing the under treatment of RER patients and lowering the relapse rate for all patients. The details of the statistical methods will be determined with the submission of the biology trial at the completion of sample collection for this clinical trial. An assessment of clinical utility would be included in any future proposals for molecular analyses.

Planned Biology Study #2: Quantitation of EBV DNA and RNA in serial specimens in cell-free blood to explore their utility as prognostic or tumor markers.

This planned study will characterize EBV DNA and RNA in serial specimens in cell-free blood and explore their utility as prognostic or tumor markers. Samples will be obtained from all consenting patients on study. Plasma will be collected from peripheral blood samples (2 mL/time point) prior to treatment, at 8 days after the start of the first cycle, at the completion of cycles 1 (3 weeks), 2 (6 weeks), 5 (15 weeks), at end of

therapy evaluations 4-6 weeks from the last dose of treatment on Cycle 5 if no RT, or 6-9 weeks from last RT treatment for patients receiving RT, and during follow-up at 3 months, 6 months, 9 months, 12 months, and 24 months after the completion of therapy. Plasma will be used to characterize viral DNA and EBV-associated miRNA. EBV copy number will be determined by Real-Time PCR.

Detection of methylated DNA Enrichment: A new method has been recently developed that efficiently distinguishes tumor DNA from virion DNA by characterizing CpG methylation of viral DNA. This method will be performed as previously described.[87]

Planned Biology Study #3: Expression of TARC as a biomarker for early response to therapy

Research in adult HL has shown that TARC is expressed by H/RS cell in nodular sclerosing HL.[80] Decreases in the chemokine TARC correlate with early response to therapy.[80] In recent work, pre-treatment TARC levels were associated with both increased clinical risk factors and decreased response to treatment in a German Hodgkin Study group trial.[88] Soluble TARC also associated with outcome in an Australian study of 47 patients, particularly when combined with sCD163, which measures tissue-associated microphages.[89] Peripheral blood will be collected from all consenting patients at three time points during therapy: pre-treatment, Day 1 (prior to therapy) of Cycle 2 and Day 1 (prior to therapy) of Cycle 3 (Table 7.2). TARC will be assessed by commercially available ELISA for sCD30. MicroRNA profiling and TARC assays will be done in collaboration with Anke van den Berg, who is experienced in this technique. [89,4,90]

Planned Biology Study #4: Examination of multi-drug resistance proteins, the NF-κB pathway, and soluble CD30/CD168

The goal of this aim is similar to the first in providing and in-depth examination of cell signaling pathways important in cHL resistance to chemotherapy, in particular, the mechanisms of brentuximab resistance. A comprehensive mechanism-based analysis should allow us to identify targeted therapies to overcome brentuximab resistance. Pre-treatment biopsy slides will be collected from consenting patient treated with brentuximab vedotin. The P-glycoprotein (MDR-1) and MRP3 will be detected by immunohistochemistry (IHC) or similar methods using commercially available antibodies as described.[66] DNA from patients with increased MDR-1 or MRP3 will be tested for DNA polymorphisms that result in protein upregulation. NF-κB pathway proteins will be examined in pre-treatment HL tissue using the previously constructed tissue microarray (TMA).[68] Soluble CD30 will be quantitated prior to start of chemotherapy and (if feasible) in post-treatment samples. This is currently not feasible as brentuximab vedotin interferes with CD30 binding of current commercially available antibodies (Seattle Genetics, personal communication).

Planned Biology Study #5: Future research in Host DNA for Hodgkin lymphoma predisposition, treatment, toxicities and long-term complications.

The banking of biologic specimens is a requirement for innovative and potentially therapeutic biologic studies. Thus, this trial will strongly encourage banking of specimens at diagnosis (blood, unstained biopsy slides, and tissue blocks), at the end of each cycle of therapy (peripheral blood), at end of therapy (peripheral blood), and at relapse (biopsy tissue and blood). These samples will be stored at the Biopathology Center for use in future research. Specific hypotheses and statistical design will be submitted along with each proposal for tissue samples, and will undergo review as per COG policies and procedures. Banking of specimens is further outlined in the COG Biospecimen Manual of Procedures.

APPENDIX VII: CORRELATIVE PERIPHERAL NEUROPATHY (CIPN) STUDY

Background: Several widely used chemotherapy agents including the vinca alkaloids, platinum compounds, taxanes, thalidomide, and bortezomib cause peripheral neuropathy (PN),[91-93] although this side effect is often both under-recognized and under-diagnosed.[94] With early recognition and clinical management, often involving dose modification, chemotherapy induced-PN (CIPN) can be effectively managed in the majority of patients. Up to 40% of adult cancer patients, however, experience permanent symptoms and disability.[95]

CIPN typically involves three principal manifestations: sensory; motor; and autonomic. These manifestations vary by drug class and by cumulative exposure. For example, the vinca alkaloids generally cause a sensory neuropathy (e.g., loss of deep tendon reflexes or paresthesias/dysesthesias), but can also produce motor neuropathy and autonomic neuropathy (e.g., constipation/ileus).

Assessment Methods: CIPN is clinically assessed with grading scales, such as the Common Terminology Criteria for Adverse Events (Neuropathy subscales)[96] and in children, the Balis Pediatric Scale of Peripheral Neuropathy. These scales, although widely used, have been found to have variable degrees of inter-rater reliability, a narrow response scale (0-5), and limited responsiveness to change. Substantial floor effects have also been reported.[97]

Hybrid measures, such as the Total Neuropathy Score (TNS), originally developed to assess peripheral neuropathy among adults with diabetes, include subjective symptoms scores and formal neurologic assessment to characterize the deficits. TNS has much better inter-rater reliability and has a much broader response range than the grading scales.[91] The TNS has undergone two modifications, the first for its use with adult patients with breast cancer,[98] and subsequently, for use with children ages 5-18 years.[99] Although the item content was preserved in the modification from adult to pediatric ages, the language was revised to improve understanding, particularly for younger children. After an initial pilot study of 20 children, the ped-m-TNS was tested in 41 children with cancer and 41 controls, demonstrating significant differences between patients and controls across both the subjective symptoms and components of the neurological assessment.[100] The ped-m-TNS identified 40% of subjects with sensory neuropathy and 15% of patients with motor neuropathy who were not identified on clinical grading scales.[101] Separately, Smith et al. further modified the TNS as the TNS-Pediatric Vincristine (TNS-PV) and evaluated it in longitudinal assessment over 15 weeks in 65 children with acute lymphoblastic leukemia; neuropathic pain was assessed with the FACES Pain Scale. Assessments were attainable in nearly all children 6 years and over, but not in younger children. Responsiveness to change was detected, with vibration and reflex items being the most responsive. While this measure has promising application in clinical management, the requisite inclusion of a trained examiner to assess neurologic function in key domains, including vibration, reflex, and strength, precludes its ready inclusion into group-wide clinical trials.

Self-report measures of CIPN have been used successfully in several adult cooperative group studies across a wide range of agents and disease groups. The 11-item Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT-GOG-Ntx),[102,103] the first and most widely used self-report measure in the US, has been found to have strong psychometric properties, including responsiveness to change over time.[104] Similar patterns were also reported by the National Surgical Adjuvant Breast and Bowel Project.[105] Scale scores were related to clinical grading scores non-linearly (i.e., 2.4 for clinical Grade 0 to 24.5 for clinical Grade 3). The scale allowed for discrimination among patients with similar clinical grade and highlighted different symptoms as being bothersome at different points during therapy. As a measure of criterion validity, Huang et al. demonstrated that scale scores were able to discriminate the presence or absence of CIPN, based on clinical grading, with an area under the receiver operating characteristics curve (AUC of ROC) of 81%.[106] *Of note, there are no validated self-report measures of CIPN for children.*

CIPN has been shown to have a negative effect on health-related quality of life (HRQL) in several diverse populations. Large effect sizes, equivalent to two standard deviations, were detected in HRQL comparisons between chemotherapy naïve patients and those with CIPN in a study of women with ovarian cancer.[104] Mols et al. demonstrated in a sample of over 1600 patients that those in the top decile of neuropathy symptoms had statistically significant worse HRQL across all measured domains,[107] a finding echoed in the qualitative research of Textor et al.[108] To date, there have been no reports of the association of CIPN with HRQL in children undergoing cancer treatment. The proposed study will address this important gap.

Objectives: Within the randomized comparison of the role of Brentuximab vedotin in the treatment of children with newly diagnosed classical Hodgkin Lymphoma (cHL), we propose the following specific aims:

I. Primary aim:

1. To characterize the extent of chemotherapy-induced peripheral neuropathy (CIPN), as reported by the patients (ages ≥ 11) and parent proxies of patients 5-17.9, using the serial administration of the FACT-GOG-NTX, from initial HL diagnosis to three years after completion of initial therapy.
    a. In this objective, the extent of CIPN due to vincristine in the standard arm will be compared to CIPN due to the combination of vincristine plus Brentuximab vedotin (Bv) in the experimental arm at the completion of planned chemotherapy.

    Hypothesis: We hypothesize that patients randomly assigned to the experimental arm will have more self-reported or proxy-reported CIPN, at the end of planned chemotherapy. (See Table, Time 4 Assessment).

II. Secondary aims:

1. To describe the trajectory of CIPN over time by study arm and by rater from baseline to 36 months off planned chemotherapy.
2. To compare the FACT-GOG-Ntx scores, as reported by the patients and parent proxies, to clinical grading scale (Balis Pediatric Scale of Peripheral Neuropathy in Appendix IV) at each scheduled assessment points.
3. To describe the HRQL consequences of CIPN by severity and over time by correlating the summary neuropathy scores (as measured by FACT-GOG-Ntx) with summary scores from the CHRIs-Global scale These measures will be collected serially in six planned assessments from initial cHL diagnosis to 36 months after the completion of initial therapy for patients randomly assigned to either study arm.

Rationale for Study Hypothesis: Brentuximab vedotin contains an anti-microtubule agent, monomethyl auristatin E (MMAE), which binds to tubulin and prevents microtubule assembly, leading to cell cycle arrest and cell death (See Figure). In the 2013 report of a Phase 1 dose escalation study of adult patients with newly diagnosed HL, 75% of patients developed peripheral neuropathy (sensory and motor), although most of these events were Grade 1 or 2 and manageable by dose modification.[109] This compares to rates of Vincristine-induced neuropathy of 35-45% across all grades.[91] In the recent AHOD0831 and AHOD0031 protocols, 3% of pediatric/adolescent patients developed Grade 3 or higher Vincristine-induced neuropathy, based on clinical grading scales. Rates of mild to moderate neuropathy were not routinely collected.

Approach: In the absence of validated self-report or proxy-report measures of CIPN in children, we have elected to rely on the well-validated FACT-GOG-Ntx, which has been used in several cooperative group trials across myriad diseases and CIPN-causing agents. In collaboration with the instrument's author, Dr. David Cella, a world-renowned psychometrics expert and leading architect of both the PROMIS and NeuroQOL initiatives, we will modify the FACT-GOG-Ntx in two principal ways. Prior to initiation of the trial, the item content of the FACT-GOG-Ntx will be modified for parent raters (voice change from "I" to

"my child"). Additionally, for youth self-report, item wording will be reviewed, following procedures outlined by Gilchrist et al.[99] and Smith[97] to ensure comprehension by youth 11 years of age and older. Parenthetic descriptors may be added. For example, Gilchrist added a parenthetic tag to the word "numb" as "can hardly feel." The youth report measure will undergo gatekeeper review prior to administration. No planned modifications will be made in the FACT-GOG-Ntx for patients 18 and over, as this measure has been extensively validated for self-report

Patient self-and proxy-rated measures will be collected from all youth 11 years of age and older at time of enrollment and from parents of all child participants ages 5 – 17.99 years at the time of enrollment. Proxy reports will not be collected for participants who are age 18 or older. For each measure for which dual rating is planned, there will be a 'youth' version and a parent proxy version. While the FACT-GOG-Ntx is available in English, Spanish and French in both the parent proxy- and youth self-report versions, the demographics and the CHRIs-Global are available only in English and Spanish. *Therefore, French-speaking participants will complete only the FACT-GOG-Ntx.* The planned demographics assessment, which is a one-time (baseline) assessment, will be collected from the parent of enrolled children 5-17.9 years or directly from the patient, if the patient is 18 years of age or older at the time of enrollment.

Study measures will be collected by CRAs from each designated rater at each participating institution at six scheduled time points, beginning with the initiation of chemotherapy at 'baseline' through 36 months following the completion of therapy (see Table 1 below). Both Times 2 and 3 will be collected Day 8 of the Cycles 2 and 5, respectively, when the Day 8 Vincristine is scheduled. CRAs at each site should endeavor to collect the measures after the administration of the Vincristine, so as to not 'script' the clinical encounter. The rationale of the two on-treatment time points is to capture early onset CIPN and the pattern of change or worsening over time. The Time 4 assessment, corresponding to the end of therapy, is designed to capture the anticipated peak of CIPN temporally associated with the dose density peak exposure of both Bv and Vincristine. The Time 5 time point at 12-month follow up will evaluate persistence of CIPN off planned therapy. Beginning with **Amendment #6**, the assessment window for the Time 6 time point has been expanded from +/- 3 months to +/- 6 months to ensure optimal response rate (see Tables 1a and 1b). Notably, Time 6 at 36-month follow up will allow us to estimate the persistence or reversal of neuropathy at both 1 and 3 years following a period from completion of therapy in children. Similar data on time to resolution of neuropathy in adults, following treatment with brentuximab vedotin, have demonstrated resolution beyond one year. The restricted number of assessments is designed to limit burden to the sites. All measures have a recall period of the past week.

Assessments required for patients enrolled before the CIPN sub-study reached accrual on 9/8/2017:

Table 1a. Assessment Schema by Measure, Rater, and Timepoint for Patients 5-17.9 years

Measure/ Timepoint	**Time 1** (baseline, prior to therapy)	**Time 2** (Day 8 of Cycle 2)	**Time 3** (Day 8 of Cycle 5)	**Time 4** (End of Therapy)	**Time 5** (12 months ± 3 months)	**Time 6** (36 months ± 6 months)
Demographics	X_{Parent}	--	--	--	--	
FACT-GOG-Ntx	X_{Parent}, $X_{Youth \geq 11}$	X_{Parent}, $X_{Youth \geq 11}$	X_{Parent}, $X_{Youth \geq 11}$	X_{Parent}, $X_{Youth \geq 11}$	X_{Parent}, $X_{Youth \geq 11}$	X_{Parent}, $X_{Youth \geq 11}$
CHRIs-Global	X_{Parent}, $X_{Youth \geq 11}$	X_{Parent}, $X_{Youth \geq 11}$	X_{Parent}, $X_{Youth \geq 11}$	X_{Parent}, $X_{Youth \geq 11}$	X_{Parent}, $X_{Youth \geq 11}$	X_{Parent}, $X_{Youth \geq 11}$
X_{Parent} refers to parent proxy ratings of CIPNs for all minors 5-17.9 years; **$X_{Youth \geq 11}$** refers to youth ages 11-17.9 self-report of CIPNs.						

Table 1b. Assessment Schema by Measure and Timepoint for Patients ≥ 18 years

Measure/ Timepoint	**Time 1** (baseline, prior to therapy)	**Time 2** (Day 8 of Cycle 2)	**Time 3** (Day 8 of Cycle 5)	**Time 4** (End of Therapy)	**Time 5** (12 months ± 3 months)	**Time 6** (36 months ± 6 months)
Demographics	X	--	--	--	--	
FACT-GOG-Ntx	X	X	X	X	X	X
CHRIs Global	X	X	X	X	X	X
X refers to self-report measures required at each time point for patients ≥ 18 years of age.						

Collection Timing Specifics: Time 1: baseline, prior to therapy.
Times 2 and 3: Day 8 of Cycle 2 and Cycle 5, respectively.
Time 4: End of Therapy is 4-6 weeks from last dose of Cycle 5 if no RT, or 6-9 weeks from last RT treatment for patients receiving RT.
Time 5: 12 ± 3 months post completion of therapy.
Time 6: 36 ± 6 months post completion of therapy.

Measures: FACT-GOG-Ntx: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group--Neurotoxicity
CHRIs-Global: Child Health Ratings Inventories-Global Quality of Life scale

Analysis Plan:

Preparation for the planned analyses: Mean scale scores and standard deviation will be calculated for each measure by time point and rater, using established scoring algorithms. In the planned CIPN analysis, we will calculate the mean summary scores calculated from the FACT-GOG-Ntx for each rater (youth and parent). In the planned HRQL analysis, mean summary scores will be calculated for the CHRIs-Global scale (for physical and mental health, respectively).

Primary analysis

Non-inferiority assumptions: For the primary analysis, the null hypothesis is that the experimental arm is inferior to the standard arm. $H_0: \mu_e - \mu_s > d$. The alternative hypothesis is that the experimental arm is non-inferior to the standard arm with regard to patient and parent report of CIPN. To compare the mean scores at Time 4 between study arms, we will perform a two-sample t-test, assuming equal variance. This analysis will be performed separately for youth- and parent-reported CIPN scores. A Bonferroni correction has been made to account for multiple comparisons (α=0.05/2=0.025).

Secondary analyses:

1. CIPN:
   a. Longitudinal analysis: Since differences in CIPN are hypothesized between study arms and over time, we propose a longitudinal analysis, a mixed model will be constructed to account for within subject correlations. We expect observations to be correlated within subjects for each of the proposed assessments and between raters (parent and child). Initially, we will model CIPN as a function of rater, time point, and randomization assignment. Where appropriate, both raters will be analyzed in the same model the effect of rater can be measured and the correlation between raters can be modeled. We will test different forms of the time variable (linear and nonlinear) to determine which form provides the best fit. This model will also allow the evaluation of persistence of CIPN over time, especially between Times 4-6.
   b. Distribution of neuropathy by type (sensory vs. motor) to be examined over time by study arm, based on FACT-GOG-Ntx subscores. These will be described as frequencies by time point.
   c. Functional consequences of CIPN will be estimated in two ways: based on specific responses to functional items within the CIPN scale (e.g., I have trouble walking), as well as through correlations between CIPN items and the measures of HRQL. Specifically, motor neuropathy sub scores could be compared to the physical health subscales and pain items of the CHRIs-Global.
   d. Relationship between FACT-GOG-Ntx scores and clinical grading: At each planned assessment CIPN scores will be compared using the Spearman's correlation to clinical grading, based on the Balis Pediatric Scale of Peripheral Neuropathy (see Appendix IV).
   e. To formally assess persistence of CIPN off planned chemotherapy from Time 4 to Time 6, we will calculated the difference in FACT-GOG-Ntx summary scores for those time points and compare that difference between study arms using the two-sample t-test.

2. HRQL: Differences in HRQL, as measured by the CHRIs-Global, are also expected to differ between study arms and over time. To evaluate this we will utilize a mixed model, accounting for within subject correlations. Specifically, we expect observations to be correlated within subjects for each of the proposed assessments and between raters (parent and child). Initially, we will model HRQL as a function of rater, time point, and randomization assignment. Both raters will be analyzed in the same model so the effect of rater can be measured and the correlation between raters can be modeled. We will test different forms of the time variable (linear and nonlinear) to determine which form provides the best fit.

3. Validation: The psychometric performance of the FACT-GOG-Ntx scale will be evaluated among pediatric patients and proxy raters using baseline data from both study arms. Principal components analysis will be performed to confirm the unidimensional scale structure and item-total scale correlations will be calculated using Pearson correlations. Internal consistency reliability will be described for each rater, using Cronbach's α. To establish criterion validity, comparisons with clinical toxicity scales will also be performed using data at Time 2 and Time 3. As a measure of construct validity, we will compare Time 4 assessments by total delivered dose of brentuximab vedotin (experimental arm) and vincristine (experimental and standard arm).

Power Calculation:

Power has been calculated for the primary aim, which is a non-inferiority design with a continuous outcome (CIPN scores). The following assumptions have been made: the significance level is set at 0.05; the power has been set at 80%; and the inferiority limit (**d**) has been set at 0.35 standard deviation units (2.45 points with a scale standard deviation of 7 on the FACT-GOG-Ntx). Based on the experience of recent COG studies with patient-reported outcomes (e.g., AAML1031), we anticipated follow-up rates at our primary endpoint (Time 4) to be no better than 67% (L. Sung, personal communication 4/8/14). Accounting for this attrition over time, we estimated that we would need 101 evaluable subjects per study arm at time point 4 (total sample size of 202). A total of 320 patients were enrolled as of 9/8/17. Accrual is closed to patient entry on this embedded study.

APPENDIX VIII: COST EFFECTIVENESS OF BRENTUXIMAB VEDOTIN FOR US INSTITUTIONS ONLY

Cost Effectiveness Analysis (CEA) of Brentuximab Vedotin in Newly Diagnosed High-Risk Classical Hodgkin lymphoma (cHL) in Children and Young Adults

The study will prospectively compare the cost effectiveness of Bv versus standard chemotherapy among newly diagnosed high-risk cHL patients from diagnosis to 3 years after treatment completion. Addition of Bv is being evaluated in a randomized fashion in the upfront Phase III therapeutic trial (see Study Schema). This ancillary study will be focused on COG institutions in the US and include all enrolled patients between the ages of 5 – 21.9 years. We anticipate enrolling eligible participants over the first two years of the study with two and a half years of planned follow up after the completion of initial therapy. Given the increased incidence of mixed cell histology among Latinos and the higher than anticipated number of Latinos enrolled at the AHOD0831 study, we will offer participation to English- and Spanish-speaking parents. We anticipate approximately 50 within this subgroup.

A. Proposed outcomes with associated measures:

1. Health care cost (direct and indirect) (for Bv arm and standard chemotherapy arm):
   a. Units of health care utilization will be collected prospectively from patients 18 – 21.9 years of age (at the time of enrollment) and from parents of enrolled patients ages 5-17.9 (at the time of enrollment) using the well-validated Stanford Health Care Utilization[110,111] instrument. This 4-item instrument quantifies patient visits to a physician's office, emergency department, hospitalizations, and lengths of hospitalizations. The reference period for data collection has been adjusted to fit the intervals between scheduled assessments. Therefore, study personnel will take note of the different versions of the measure for specific assessment time points.
   b. Utilization units will be monetized using administrative data based on cost component of interest. These include hospitalizations, emergency room visits, major procedures/surgeries, radiation therapy, clinic visits, day-hospitalization/chemotherapy infusions, hematopoietic stem cell transplantation (HSCT) (in those that relapse within the 2.5 years of follow up). To augment planned cost analyses, we will link ICD-9/10 codes to collected adverse events (as routinely collected as part of the upfront trial) and estimate the average costs using administrative data. This information will generate the direct cost components.
   c. Indirect costs will be estimated based on parent (caregiver) productivity loss, measured as parent reported absenteeism and presenteeism. This will be measured by the Caregiver Work Limitations Questionnaire, a 23-item validated questionnaire.[112] For patients 18 years or older at the time of enrollment, the Caregiver WLQ will not be collected.

2. Quality-adjusted life-years (QALYs) determination (for Bv and standard chemotherapy arms):
   a. Serial utility weights will be calculated utilizing the Health Utilities Index (HUI) 2/3,[113-115] a validated preference-based instrument, collected for both the Bv and standard chemotherapy arms. These utility weights will then be multiplied by the duration of observed survival to yield quality-adjusted life years (QALYs).
   b. Respondent Type: Parents of enrolled patients within the 5-17.9 age range at time of enrollment for all study measures; youth 11-17.9 years at time of enrollment will complete the HUI 2/3 only; young adults aged ≥ 18 years at time of enrollment will complete the HUI 2/3 and Stanford Healthcare Utilization only
   c. Language Availability: The Stanford Healthcare Utilization measure and the HUI 2/3 are available in English and in Spanish. The Caregiver Work Limitations Questionnaire is available in English only.
   d. Recall: Past week.

B. Assessment time points:

Required for US patients who enrolled before the CEA sub-study reached accrual on 9/8/2017.

A total of six time points have been selected (see Tables below):

1. Baseline assessment prior to first cycle of chemotherapy. This assessment time point will allow us to compare any differences between study arms prior to the initiation of active treatment. Conventionally, the baseline assessment is the time point against which all change scores are calculated.
2. Day 8 of Cycles 2 and 5 (time points 2 and 3). These will allow us to assess both utilities and healthcare utilization during chemotherapy administration.
3. At the end of planned therapy (time point 4). This will allow us to examine healthcare through the end of therapy.
4. 12 and 36 months off planned therapy. This will allow us to examine healthcare utilization incurred one and three years off planned therapy, inclusive of salvage therapy.

Table 1a. Assessment Schema by Measure, Rater, and Time point for Patients 5-17.9 years

Measure/Timepoint	Time 1	Time 2	Time 3	Time 4	Time 5	Time 6
	Baseline	Cycle 2, Day 8	Cycle 5, Day 8	At the end of therapy	12 months (± 3) off therapy	36 months (± 6) off therapy
Health Utility Index 2/3	X_{Parent} X_{Youth}	X_{Parent} X_{Youth}	X_{Parent} X_{Youth}	X_{Parent} X_{Youth}	$X_{Parent,}$ X_{Youth}	$X_{Parent,}$ X_{Youth}
Stanford Healthcare Utilization	X_{Parent}	X_{Parent}	X_{Parent}	X_{Parent}	X_{Parent}	X_{Parent}
Caregiver Work Limitation Questionnaire	X_{Parent}	----	----	X_{Parent}	X_{Parent}	---

X_{Parent} refers to parent proxy ratings for all minors 5-17.9 years of age;
X_{Youth} refers to youth ages 11-17.9 self-report of CEAs

Table 1b. Assessment Schema by Measure, Rater, and Time point for Patients ≥ 18 years

Measure/Timepoint	Time 1	Time 2	Time 3	Time 4	Time 5	Time 6
	Baseline	Cycle 2, Day 8	Cycle 5, Day 8	At the end of therapy^	12 months (± 3) off therapy	36 months (± 6) off therapy
Health Utility Index 2/3	X	X	X	X	X	X
Stanford Healthcare Utilization	X	X	X	X	X	X

X refers to self-report measures required at each time point for patients ≥ 18 years of age.

Collection Timing Specifics:

Time 1: baseline, prior to therapy.
Times 2 and 3: Day 8 of Cycle 2 and Cycle 5, respectively.
Time 4: End of Therapy is 4-6 weeks from last dose of Cycle 5 if no RT, or 6-9 weeks from last RT treatment for patients receiving RT.
Time 5: 12 ± 3 months post completion of therapy.
Time 6: 36 ± 6 months post completion of therapy.

Measures:

Health Utilities Index 2/3 (HUI 2/3): 15-Item Questionnaire, Self-administered Versions for Self-report or for Parent/Proxy
Stanford Healthcare Utilization: for parent proxy report (for patients 5-17.9 years of age) or for patient self-report (≥ 18 years of age)
Caregiver WLQ: Caregiver Work Limitation Questionnaire (parent only)

Specific hypotheses:

Hypothesis 1: While drug cost will be higher in the Bv arm, overall healthcare utilization will be lower in the Bv arm, based on less radiation and lower relapse rate (resulting in less need for salvage therapy, including hematopoietic cell transplant).

Hypothesis 2: Health-related quality of life (HRQL), as measured by QALYs, will be better for patients treated on the Bv arm as compared to the conventional treatment arm as measured from diagnosis until 3 years after completion of therapy.

Hypothesis 3: Productivity costs will be lower for parent caregivers in the experimental arm compared with the standard arm, as a function of less radiation-associated work loss (absenteeism) and less workplace presentee-ism (poor functioning while at the workplace).

Background:

While 5-year overall survival approaches 98% and event-free survival (EFS) approaches 80% in children and adolescents with low-risk HL,[116] EFS for youth presenting with high-risk HL remains closer to 70%. Despite these high rates of treatment success, these survivors have substantially elevated mortality rates in the decades following treatment.[3,117] The relative risk of all-cause mortality among HL survivors treated in the 1970's and 1980's remains 7-8 fold higher than the general population with an 11.4-year loss of life expectancy.[118-120] Thus, the major challenge in the development of modern therapies is to optimize the balance between maintaining excellent disease control and minimizing treatment-related burden. Improved risk stratification methods, addition of a biologically targeted agent, Bv, and a novel targeted approach to radiation therapy (RT) delivery such that the RT is minimized when necessary, is the approach proposed to attain this balance on the phase III trial for newly diagnosed high-risk cHL in the COG.

We propose to evaluate whether the addition of Bv in high-risk cHL patients alters quality-adjusted health care costs through measurement of health care utilization over the acute treatment phase, and subsequent three-year follow-up period (translating to 3 ½ since diagnosis). We believe this is an important question given the well-documented burden of morbidity and premature mortality in cHL survivors.[3] Understanding acute and subsequent three-year implications of adding Bv to standard of care are important because these periods are when patients are at the highest risk for relapse, and consequently, would require salvage therapy and HSCT. For example, the addition of Bv is hypothesized to increase direct medication costs by $50,000 per patient (5 cycles * $10,000 per cycle) but reduce relapse rates in the first year by 8% over standard therapy. The reduction in the latter costs will in turn reduce the very high costs associated with salvage therapy and HSCT in the second or third year post drug treatment. According to a 2011 Milliman report, the costs of autologous HSCT amounted to $300,000 per patient, including 30-day pre-transplant and medical costs up to 180 days post HSCT alone.[121] As it is estimated 50% of those who undergo autologous HSCT will relapse (within 7 months to 2 years),[122] for the purposes of illustration, we assume that those 50% will also require an allogeneic HSCT. Again according to Milliman, the 30-day pre-transplant and direct medical costs up to 180-days post transplantation for allogeneic transplantation amounted to $800,000 per patient.[121] Our initial estimated calculations suggest accounting for these costs alone will make the inclusion of Bv into standard therapy reduce direct costs to care of the study population by approximately $800,000-1,200,000. We also believe there will also be cost reduction in the care of the treatment arm related to reductions in the use of radiation therapy. Reduction of radiation therapy will reduce the health care costs associated with RT itself, but also reduce the late effects of RT, including second malignant neoplasms (SMN), cardiac and pulmonary disease.[3] The benefits of Bv's inclusion in standard of care include improvements in mortality, morbidity and HRQL for study participants.

By understanding the balance of costs and benefits of this new intervention, stakeholders (e.g., patients, parents, providers, payers, purchasers of health care), and policy makers) can decide whether the

intervention provides "good" value. Bv is patent protected and an extremely expensive new oncologic; cHL is a disease with one of the highest cure rates of any cancer. There is limited (no) information regarding the resource use and/or HRQL implications of incorporating Bv into the treatment of cHL among children, adolescents and young adults. If cost increases are observed alongside improvements in mortality/morbidity or HRQL, the additional immediate burden on the health care system may still be justified. The results of this study will be of high impact to physicians and payers.

In addition, the proposed study will serve as a paradigm proof of principle to the COG and other cooperative groups regarding the feasibility and value of incorporating health utilization outcomes as a component of cancer care delivery research into phase III clinical trials. There have been no resource use or direct medical costs studies incorporated into COG phase III clinical trials to date. We have assembled a team including experts in cHL, survivorship, health economics, cancer control, epidemiology and pediatric HRQL, to help answer this question. This study will build capacity and expertise for future COG studies of the economic burden of innovative treatment on patients, families and the health care system. Lastly, this study answers the call for examination of cancer care delivery research in the Children's Oncology Group cooperative trial setting.

Statistical design:

Endpoints: Endpoints for this study include: estimated cost (for the period from diagnosis until 3 years after therapy completion) and QALYs from the HUI 2/3. These data inputs together will yield an incremental cost effectiveness ratio (ICER), defined as the difference in cost for the two treatment groups divided by the change in QALYs. In healthcare interventions, a "favorable" ICER is estimated to be $50,000, although for cancer treatments this figure is sometimes higher.[123]

Estimated cost:

- The "unit cost" or price associated with each direct cost component (eg, type of clinic visits, radiation therapy, imaging studies, surgeries and other procedures) will be obtained using information from published sources. The unit cost information obtained from published sources will provide information on the ranges of unit cost for a specific item of resource. For example, inpatient costs for a specific admission diagnosis or ICD-9/10 procedure will be retrieved from the HCUPnet (https://hcupnet.ahrq.gov), an on-line query system based on data from the AHRQ's Healthcare Cost and Utilization Project. Outpatient costs will be based on Medicare's resource-based relative value scales (RBRVS) fee schedule. Using DRG codes from the HCUPnet, we can obtain the ranges of hospital costs for interventions across various regions of the country. Similar range for a CPT code can be found in Medicare fee schedule (https://www.cms.gov/Medicare/Medicare.html?redirect=/home/medicare.asp) from adjustments across geographic regions. These form the range of unit cost values for each item of resource. For each patient, we will match patients' geographic region with unit costs reported for that region from the published sources to obtain unit costs most relevant to the patient.

- Costs will be estimated by combining the information of resource use with unit costs. Clinical events gathered from the trial provide information on resource utilization over time. Denote Q_i is the count of resource *i* (e.g., MRI, office visits) and P_i is the unit cost for the health care resource, costs will be calculated as: $P_1 \times Q_1 + P_2 \times Q_2 + \ldots + P_N \times Q_N$. Each item of resource utilization will be identified from DRG, ICD-9/10 diagnosis/procedure code or CPT codes provided by the CRA. Once we obtain information on the "counts" of each resource item from the trial, we will combine the unit cost value with counts to calculate the cost associated with a specific resource item. We then aggregate all resource items to obtain the cost for that patient. That is, all costs of add specifics of cancer care will be tallied for each participant.

- Workplace participation and productivity: Caregiver WLQ scale scores will be computed using established scoring algorithms. Four at-work performance scale scores reflect the percentage of time in the previous 2 weeks emotional and/or physical health problems limited ability to perform specific job tasks. The WLQ scales measure the following 4 dimensions of performance: (1) time management, and performance of (2) physical tasks, (3) mental–interpersonal tasks, and (4) output tasks (e.g., handling the workload and finishing work on time). Scores range from 0% (limited none of the time) to 100% (limited all of the time). A fifth outcome is the WLQ at-work productivity loss score, which may be stated in terms of productivity loss or cost. The productivity loss score, the weighted sum of the 4 scale scores, indicates the percentage reduction in at-work productivity relative to a healthy benchmark group. This is converted to a dollar figure typically by assigning an average annual wage of $50,000 to generate productivity cost. The WLQ Work Absence Module measures self-reported time missed from work in the past 2 weeks because of health or medical care. Absence-related productivity loss is the ratio of time missed in the past 2 weeks to time usually spent working. Using WLQ scale scores, a validated productivity loss score can be computed, which may be stated in terms of productivity loss or costs.

Sample size and monthly accrual rate: The sample size estimates for this aim are designed to detect a clinically meaningful difference (CID) in QALY between the experimental and standard arm of 0.03, based on a standard deviation of 0.13. (Feeny, personal communication, 4/7/14). This CID is empirically derived from several clinical trials, based on differences in the area under the curve (AUC) for QALY for each arm. The calculation assumes six planned assessments and accounts for an estimated 80% participation rate. Further, the calculation accounts for within-person correlation of 0.5, assumes an alpha of 0.05, and 80% power. Two years of recruitment at the targeted enrollment rate of 11-12 patients per month will be sufficient to detect a CID of 0.036. Twenty-seven months of recruitment would be needed to detect a CID of 0.03 (with 130 participants/study arm).

Power calculations were performed separately for the Caregiver WLQ. Assuming a standard deviation of 18 for the WLQ scales, we sought to detect a difference of 6 points between arms, which translates to 1/3 a standard deviation. In this type of measure, differences of 1/3 to 1/2 a standard deviation have been found to be clinically meaningful. Assuming a within-person correlation of 0.5, completed of three assessments (restricted to baseline, Time 4 and 12 months off treatment to minimize burden) and an alpha of 0.05, we would have 80% power to detect this clinically meaningful difference with 127 subjects per arm.

CEA accrual was reached on 9/8/2017 and this embedded study was closed to further patient entry.

Analysis Plan: Differential mean costs will be compared between the two groups (standard arm of ABVE-PC vs. experimental arm Bv-AVEPC). We will assume 1-3% discount rates apply to costs incurred in the second and third years of the study.[124] To examine whether patients randomized to the Bv arm have reduced cost than patients randomized to the standard arm after controlling for confounding factors, we will rely on multivariate statistical models. In addition to the main impact variable — the binary indicators for the "treatment group" — all analyses will control for patient and hospital characteristics that might differ by chance among patients in the two randomization groups. Because cost estimations are generally highly skewed, we will model all of our cost equations using the method of extended estimation equation (EEE).[125] Contrary to the traditional approach of applying least squares to log-transformed data, the EEE method is a recently developed econometric method that specifies a highly flexible mean model to accommodate data of various functional forms, including highly skewed cost data. Total costs will be aggregated for the 2.5 year period by study arm. Similarly, QALYs will be calculated, using global utility scores from the HUI 2/3 for each time period. The AUC of QALYs will then be compared by study arm. The difference in cost will be divided by the difference in QALYs to generate the ICERs.

APPENDIX IX: CTEP AND CTSU REGISTRATION PROCEDURES

CTEP INVESTIGATOR REGISTRATION PROCEDURES

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored clinical trial 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 (https://ctepcore.nci.nih.gov/iam). 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) (https://ctepcore.nci.nih.gov/rcr). 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
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

CTSU REGISTRATION PROCEDURES

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

Requirements for AHOD1331 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)
- IROC Credentialing Status Inquiry (CSI) Form
  NOTE: For studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component.

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office, 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:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- 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.

Data Submission / Data Reporting

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the

appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) 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. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) 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.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (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 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

APPENDIX X: POSSIBLE DRUG INTERACTIONS

The lists below <u>do not</u> include everything that may interact with chemotherapy. Study Subjects and/or their Parents should be encouraged to talk to their doctors before starting any new medications, using over-the-counter medicines, or herbal supplements and before making a significant change in diet.

Brentuximab vedotin

Drugs that may interact with brentuximab vedotin
• Antibiotics o Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin • Antifungals o Itraconazole, ketoconazole, posaconazole, voriconazole • Arthritis medications o Leflunomide, tofacitinib • Anti-rejection medications o Cyclosporine, sirolimus, tacrolimus • Antiretrovirals and antivirals o Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir • Anti-seizure medications o Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone • Heart medications o Nicardipine, verapamil • Some chemotherapy (be sure to talk to your doctor about this) • Many other drugs, including the following: o Aprepitant, bosentan, deferasirox, dexamethasone, lomitapide, natalizumab, nefazodone

Food and supplements that may interact with brentuximab vedotin*
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Bleomycin

Drugs that may interact with bleomycin*
• Arthritis medications like leflunomide or tofacitinib • Some chemotherapy (be sure to talk to your doctor about this) • Other medications like digoxin or natalizumab

Food and supplements that may interact with bleomycin*
• Echinacea

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Cyclophosphamide

Drugs that may interact with cyclophosphamide
• Allopurinol • Chloramphenicol • Cyclosporine • Digoxin • Etanercept • Hydrochlorothiazide • Indomethacin • Nevirapine • Pentostatin • Warfarin

Food and supplements that may interact with cyclophosphamide*
• St. John's Wort • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Doxorubicin

Drugs that may interact with doxorubicin
• Some antiepileptics (carbamazepine, oxcarbazepine, phenobarbital, phenytoin, fosphenytoin) • Some antiretrovirals (stavudine, zidovudine) • Other agents, such as clozapine, cyclosporine, verapamil, and warfarin

Food and supplements that may interact with doxorubicin*
• Echinacea • Glucosamine • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Etoposide

Drugs that may interact with etoposide

• Antibiotics
  ○ Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
• Antidepressants and antipsychotics
  ○ Aripiprazole, clozapine, nefazodone
• Antifungals
  ○ Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  ○ Leflunomide, tofacitinib
• Anti-rejection medications
  ○ Cyclosporine, tacrolimus
• Antiretrovirals and antivirals
  ○ Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir
• Anti-seizure medications
  ○ Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
• Heart medications
  ○ Amiodarone, dronedenarone, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
• Many other drugs, including the following:
  ○ Aprepitant, atovaquone, bosentan, deferasirox, dexamethasone, ivacaftor, lomitapide, mifepristone, natalizumab, pimozide, sitaxentan

Food and supplements that may interact with etoposide*
• Echinacea • Glucosamine • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Prednisone

Drugs that may interact with prednisone
• Arthritis medications o Leflunomide, tofacitinib • Antiretrovirals and antivirals o Boceprevir, ritonavir, telaprevir • Anti-seizure medications o Phenobarbital, phenytoin, primidone • Growth hormones • Heart medications o Diltiazem, verapamil • Some chemotherapy (be sure to talk to your doctor about this) • Some oral contraceptives or birth control medications • Many other drugs, including the following: o Aprepitant, aripiprazole, aspirin, cyclosporine, deferasirox, ibuprofen, itraconazole, mifepristone, natalizumab, rifampin, warfarin

Food and supplements that may interact with prednisone*
• Echinacea

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Vincristine

Drugs that may interact with vincristine
• Antibiotics o Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin • Antidepressants and antipsychotics o Aripiprazole, nefazodone, trazodone • Antifungals o Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole • Arthritis medications o Leflunomide, tocilizumab, tofacitinib • Anti-rejection medications o Cyclosporine, tacrolimus • Antiretrovirals and antivirals o Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tenofovir, tipranavir • Anti-seizure medications o Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone • Heart medications o Amiodarone, digoxin, dronedenarone, propranolol, verapamil • Some chemotherapy (be sure to talk to your doctor about this) • Many other drugs, including the following: o Aprepitant, deferasirox, ivacaftor, lomitapide, mifepristone, natalizumab, pimozide, warfarin

Food and supplements that may interact with vincristine*
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

APPENDIX XI: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY AHOD1331
(for children from 7 through 12 years of age)

A Study of Brentuximab Vedotin for Children with High-risk Hodgkin Disease

1. We have been talking with you about Hodgkin disease. Hodgkin disease is a type of cancer that grows in the tissues in your body that make and store white blood cells. White blood cells help protect your body against infections. Sometimes Hodgkin disease is called "high risk" because it is more likely to come back after treatment. High-risk cancer is treated with stronger medicine to make it less likely to come back. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have high-risk Hodgkin disease. A research study is when doctors work together to try out new ways to help people who are sick. Children with Hodgkin disease are usually treated with chemotherapy and radiation therapy. Chemotherapy is medicine that destroys cancer cells. Radiation therapy is the use of high energy x-rays to kill cancer cells.

   Radiation therapy used to treat Hodgkin disease can cause unwanted side effects. If patients can be treated with less radiation or without radiation completely, then we hope there will be less bad effects later in life. We will use your tumor's response after the first two cycles of chemotherapy to decide if you need radiation therapy. Children whose tumor responds quickly to treatment will not receive radiation. Children whose tumor responds slowly to treatment will receive radiation. Only the areas at high risk for the cancer coming back will receive radiation.

   Chemotherapy used to treat Hodgkin disease can cause unwanted side effects too. We will ask you (only for children 11 or older) and your parent to answer some questions about how you are feeling and doing to better understand how treatment changes your daily life. These questions will be asked at five or six different time points throughout the study.

3. Children who are part of this study will be treated with chemotherapy and some will be treated with radiation therapy. All children will receive 5 cycles of chemotherapy. Some of the children who are part of this study will get the usual treatment doctors use for Hodgkin disease. Some of the children will get the experimental drug brentuximab vedotin in addition to usual chemotherapy. The chemotherapy you get will be decided by chance, like flipping a coin for "heads" or "tails." You will have regular tests during your treatment. These tests help doctors in deciding the best treatment for your Hodgkin disease and to see how you are doing with treatment. Some of the tests may hurt some, but medicines will be given to keep it from hurting too much.

   - If the cancer responds to treatment quickly in all areas, you will not have radiation therapy (except patients with a large tumor in the chest at diagnosis).
   - If the cancer responds to treatment slowly in some areas, you will have radiation therapy.

   It is common for radiation therapy to target all areas of the body that were affected by the cancer. But in this study, we will only target those parts of the body at highest risk of the cancer returning. We hope to lower the risk of side effects.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that your cancer

will go away and that you will have less bad effects later in life. But we don't know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that the study treatment may not get rid of your cancer as well as a non-study treatment.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are asking your permission to collect additional tissue and blood. These studies will help us better understand Hodgkin lymphoma and why some people respond to treatment better than other people. The tissue sample would be taken during the standard biopsy. The blood draws would be taken when other standard blood tests are being performed. We would also like to save any leftover samples for other research tests in the future. You can still take part in this study even if you do not allow us to collect the extra tissue and/or blood samples or save the leftover samples for research.

INFORMATION SHEET REGARDING RESEARCH STUDY AHOD1331
(for teens from 13 through 17 years of age)

A Study of Brentuximab vedotin for Children with High-risk Hodgkin Disease

1. We have been talking with you about Hodgkin disease. (Hodgkin disease is also known as Hodgkin lymphoma.) Hodgkin disease is a type of cancer that grows in the tissues in your body that make and store white blood cells. White blood cells help protect your body against infections. Sometimes Hodgkin disease is called "high risk" because it is more likely to come back after treatment. High-risk cancer is treated with stronger medicine to make it less likely to come back. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have high-risk Hodgkin disease. A research study is when doctors work together to try out new ways to help people who are sick. Children with Hodgkin disease are usually treated with chemotherapy and radiation therapy. Chemotherapy is medicine that destroys cancer cells. Radiation therapy is the use of high energy x-rays to kill cancer cells.

   Radiation therapy used to treat Hodgkin disease can cause unwanted side effects. If patients can be treated with less radiation or without radiation completely, then we hope there will be less bad effects later in life. We will use your tumor's response after the first two cycles of therapy to decide if you need radiation therapy. Children and teens whose tumor responds quickly to treatment will not receive radiation. Children and teens whose tumor responds slowly to treatment will receive radiation. Only areas at high risk for the cancer to come back will receive radiation.

   Chemotherapy used to treat Hodgkin disease can also cause unwanted side effects. We will ask you and your parent to answer some questions about how you're feeling and doing to better understand the side effects of chemotherapy. These questions will be asked at five or six different time points throughout the study.

3. Children and teens that are part of this study will be treated with chemotherapy and some will be treated with radiation therapy. All patients will receive a total of 5 cycles of chemotherapy. Some of the patients in this study will be treated with some of the common chemotherapy drugs used to treat Hodgkin disease. These drugs are: doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide and prednisone. Some of the children and teens who are part of this study will receive an experimental drug called brentuximab vedotin in addition to the usual chemotherapy. The chemotherapy you get will be decided by chance, like flipping a coin for "heads" or "tails." After 2 cycles of chemotherapy, we will look at changes on special scans (called CT and PET scans) to measure how the cancer is responding to therapy. We will use the response after 2 cycles to help decide if you need radiation therapy.

   - If the cancer responds to treatment quickly in all areas, you will not have radiation therapy (except patients with a large tumor in the chest at diagnosis).
   - If the cancer responds to treatment slowly in some areas, you will have radiation therapy.

   It is common for radiation therapy to target all areas of the body that were affected by the cancer. But in this study, we will only target those parts of the body at highest risk of the cancer returning. By targeting the radiation therapy we hope to lower the risk of side effects while keeping up the effectiveness.

4. Sometimes good things can happen to people when they are in a research study. These good things are called “benefits.” We hope that a benefit to you of being part of this study is to get rid of the cancer for as long as possible. We also hope that you will have less bad effects later in life. But we don’t know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” The risks to you from this study are that the study treatment may not get rid of your cancer as well as a non-study treatment. This could increase the chance of the cancer returning. Other things may happen to you that we don’t yet know about.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. We are asking your permission to collect additional tissue and blood. These studies will help us better understand Hodgkin lymphoma and why some people respond to treatment better than other people. The tissue sample would be taken during the standard biopsy. The blood draws would be taken when other standard blood tests are being performed. But, due to the amount of blood draws, it will likely require some extra needles sticks. We would also like to save any leftover samples for other research tests in the future. You can still take part in this study even if you do not allow us to collect the extra tissue and/or blood samples or save the leftover samples for research.

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