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CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Activated: 1-14-2013
Closed:

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Amendment #: 5

CHILDREN'S ONCOLOGY GROUP

AHOD1221

A PHASE 1/2 STUDY OF BRENTUXIMAB VEDOTIN (SGN35, IND# 117117) IN COMBINATION WITH GEMCITABINE FOR PEDIATRIC AND YOUNG ADULT PATIENTS WITH RELAPSED OR REFRACTORY HODGKIN LYMPHOMA

Phase 1*: Participation Limited to the COG Phase 1 Consortium and the following institutions:

***As of amendment 4, Phase I was completed.**

Children's Hospital of Los Angeles, Los Angeles, CA	Dr. Leo Mascarenhas
Children's Hospital and Research Center at Oakland, Oakland, CA	Dr. Carla B. Golden
Dana-Farber Cancer Institute, Boston, MA	Dr. Carlos Rodriguez-Galindo
Johns Hopkins University, Baltimore, MD	Dr. Kenneth J. Cohen
Loma Linda University Medical Center, Loma Linda, CA	Dr. Albert Kheradpour
Lucile Packard Children's Hospital Stanford University, Palo Alto, CA	Dr. Neyssa M. Marina
Montefiore Medical Center- Moses Campus, Bronx, NY	Dr. Peter Cole
Nationwide Children's Hospital, Columbus, OH	Dr. Mark Ranalli
University of Kentucky, Lexington, KY	Dr. Lars Wagner
Vanderbilt University, Nashville, TN	Dr. Howard Katzenstein

Phase 2: Open to COG Institutions Groupwide

NCI Supplied Agent:
Brentuximab Vedotin (SGN-35, IND #117117, NSC# 749710)
IND sponsor for Brentuximab Vedotin: DCTD, NCI

STUDY CHAIR

[redacted]
The Children's Hospital at Montefiore
111 E 210 St
Bronx, NY 10467
[redacted]

For Group Operations and Statistics & Data Center Contacts
See: http://members.childrensoncologygroup.org

TABLE OF CONTENTS

SECTION			PAGE
STUDY COMMITTEE			5
ABSTRACT			7
EXPERIMENTAL DESIGN SCHEMA			8
1.0	GOALS AND OBJECTIVES (SCIENTIFIC AIMS)		9
	1.1	Primary Aims	9
	1.2	Secondary/Exploratory Aims	9
2.0	BACKGROUND		9
	2.1	Introduction: Relapsed/Refractory HL.	9
	2.2	Gemcitabine/Vinorelbine	10
	2.3	Rationale for the substitution of brentuximab vedotin for vinorelbine	10
	2.4	Preclinical Studies with brentuximab vedotin	10
	2.5	Adult Studies of brentuximab vedotin	10
	2.6	Pediatric Studies of brentuximab vedotin	11
	2.7	Pulmonary Toxicity	12
	2.8	Progressive multifocal leukoencephalopathy (PML)	12
	2.9	Rationale for Complete Response (CR) as Primary Response Endpoint	12
	2.10	Background for Exploratory Correlative Studies	13
	2.11	Overview of Proposed Pediatric Study	14
	2.12	Amendment Expanding Enrollment at Dose Level 2 (August 2013)	14
	2.13	Amendment Opening Phase 2 (Part B)	14
3.0	STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY		15
	3.1	Patient Registration	15
	3.2	IRB Approval	15
	3.3	Reservation Requirements	16
	3.4	Study Enrollment	16
	3.5	Timing	17
	3.6	Institutional Pathology Report	17
4.0	PATIENT ELIGIBILITY CRITERIA		18
	4.1	Inclusion Criteria	18
	4.2	Exclusion Criteria	21
5.0	TREATMENT PLAN		23
	5.1	Overview of Treatment Plan	23
	5.2	Therapy Delivery Map	25
	5.3	Dose Escalation Schema	27
	5.4	Grading of Adverse Events	27
6.0	DOSE MODIFICATIONS FOR ADVERSE EVENTS		28
	6.1	Dose Modifications for Hematological Toxicity	29
	6.2	Dose Modifications for Non-Hematological Toxicity	29
7.0	SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY		34
	7.1	Concurrent Anticancer Therapy	34
	7.2	Investigational Agents	34
	7.3	Supportive Care	34
	7.4	Growth Factors	34
	7.5	Concomitant Medications	35

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED 35
8.1 Required Clinical, Laboratory and Disease Evaluation 35
8.2 Required Observations Following Completion of Protocol Therapy 37
8.3 Radiology Studies 37
8.4 Mobilization and Collection of Peripheral Blood Stem Cells 39
8.5 Correlative Biology Studies (As of amendment 4, Part A was completed. This section is for Part B.) 41

9.0 DRUG INFORMATION 42
9.1 Brentuximab vedotin 42
9.2 Agent Ordering and Agent Accountability 47
9.3 Clinical Drug Request 47
9.4 Agent Inventory Records 48
9.5 Gemcitabine 48

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA 51
10.1 Criteria for Removal from Protocol Therapy 51
10.2 Off Study Criteria 51

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS 52
11.1 Sample Size and Study Duration 52
11.2 Definitions for Part A 52
11.3 Dose Escalation and Determination of MTD (Part A) 53
11.4 Evaluation of Expansion Cohort at Dose Level 2 Using Revised DLT Definitions (Amendment #2) 54
11.5 Response Analysis for Part A 54
11.6 Study Design for Part B 54
11.7 Methods of Analysis for Part B 55
11.8 Evaluability for Response for Part B 55
11.9 Evaluability for Toxicity 56
11.10 Inclusion of Children, Women and Minorities 57
11.11 Gender and Minority Accrual Estimates 57

12.0 EVALUATION CRITERIA 58
12.1 Common Terminology Criteria for Adverse Events (CTCAE) 58
12.2 Imaging Lesion Evaluation 58
12.3 Response Criteria 61

13.0 ADVERSE EVENT REPORTING REQUIREMENTS 63
13.1 Purpose 63
13.2 Determination of reporting requirements 63
13.3 Steps to Determine If an Adverse Event Is To Be Reported In an Expedited Manner 64
13.4 When to Report an Event in an Expedited Manner 67
13.5 General Instructions for Expedited Reporting via CTEP-AERS 67
13.6 Definition of Onset and Resolution of Adverse Events 68
13.7 Other Recipients of Adverse Event Reports 69
13.8 Reporting Secondary AML/MDS 69
13.9 Reporting Pregnancy, Fetal Death, and Death Neonatal 70
13.10 Routine Adverse Event Reporting 71

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN 71
14.1 Categories of Research Records 71
14.2 CDUS 72

14.3 CRADA/CTA 72
14.4 Data and Safety Monitoring Plan 73

15.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING 74
15.1 Pregnancy 75
15.2 Recommended Technique 75
15.3 FDG Dosing and Injection 76
15.4 PET Scanning Protocol 76
15.5 After Completion of the PET Scan 77
15.6 FDG Handling and Dose Documentation 77
15.7 PET Imaging Quality Control Standards 77

REFERENCES 79

APPENDIX I: PERFORMANCE STATUS SCALES/SCORES 82

APPENDIX II: CTEP AND CTSU REGISTRATION PROCEDURES 83

APPENDIX III: CORRELATIVE STUDIES GUIDE (AS OF AMENDMENT 4, PART A IS CLOSED. THIS IS ONLY FOR PART B.) 85

APPENDIX IV: GUIDELINES FOR PERIPHERAL BLOOD STEM CELL (PBSC) COLLECTION PROCEDURE (AS OF AMENDMENT 4, PART A IS CLOSED. THIS IS ONLY FOR PART B.) 86

APPENDIX V: PERIPHERAL BLOOD STUDIES FORM (AS OF AMENDMENT 4, PART A IS CLOSED. THIS IS ONLY FOR PART B.) 88

APPENDIX VI: BPC SPECIMEN TRANSMITTAL FORM FOR PERIPHERAL BLOOD STUDIES (AS OF AMENDMENT 4, PART A IS CLOSED. THIS IS ONLY FOR PART B.) 89

APPENDIX VII: PREGNANCY INFORMATION FORM 90

APPENDIX VIII: CYP3A4 INDUCERS AND INHIBITORS 91

APPENDIX IX: POSSIBLE DRUG INTERACTIONS 92

APPENDIX X: YOUTH INFORMATION SHEETS 93

STUDY COMMITTEE

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NCI-Supplied Agent:
Brentuximab Vedotin (SGN-35, NSC #749710, IND# 117117)
IND Holder: DCTD, NCI

Commercial Agent :
Gemcitabine (Gemzar, NSC # 613327)

SEE APPENDIX V FOR SPECIMEN SHIPPING ADDRESSES

ABSTRACT

Brentuximab vedotin (previously known as SGN35; currently marketed under the brand name Adcetris) is an antibody-drug conjugate containing an anti-CD30 murine/human chimeric monoclonal antibody (cAC10; brentuximab) linked to monomethylauristatin E (MMAE; vedotin). After binding CD30, a transmembrane receptor highly expressed in both Hodgkin Lymphoma (HL) and anaplastic large cell lymphoma (ALCL), brentuximab vedotin is internalized and MMAE is released into the cytoplasm where it causes M-phase cell cycle arrest and apoptosis. Brentuximab vedotin has been evaluated in adults, at the MTD of 1.8 mg/kg every three weeks. The observed complete response (CR) rate was 34% among patients with HL (95% CI, 25-45%) and 53% (95% CI: 40-67%) among patients with ALCL. The most common treatment related toxicity was peripheral sensory neuropathy (44%). Based partly on these results, the FDA has approved brentuximab vedotin for the treatment of patients with refractory HL or ALCL.

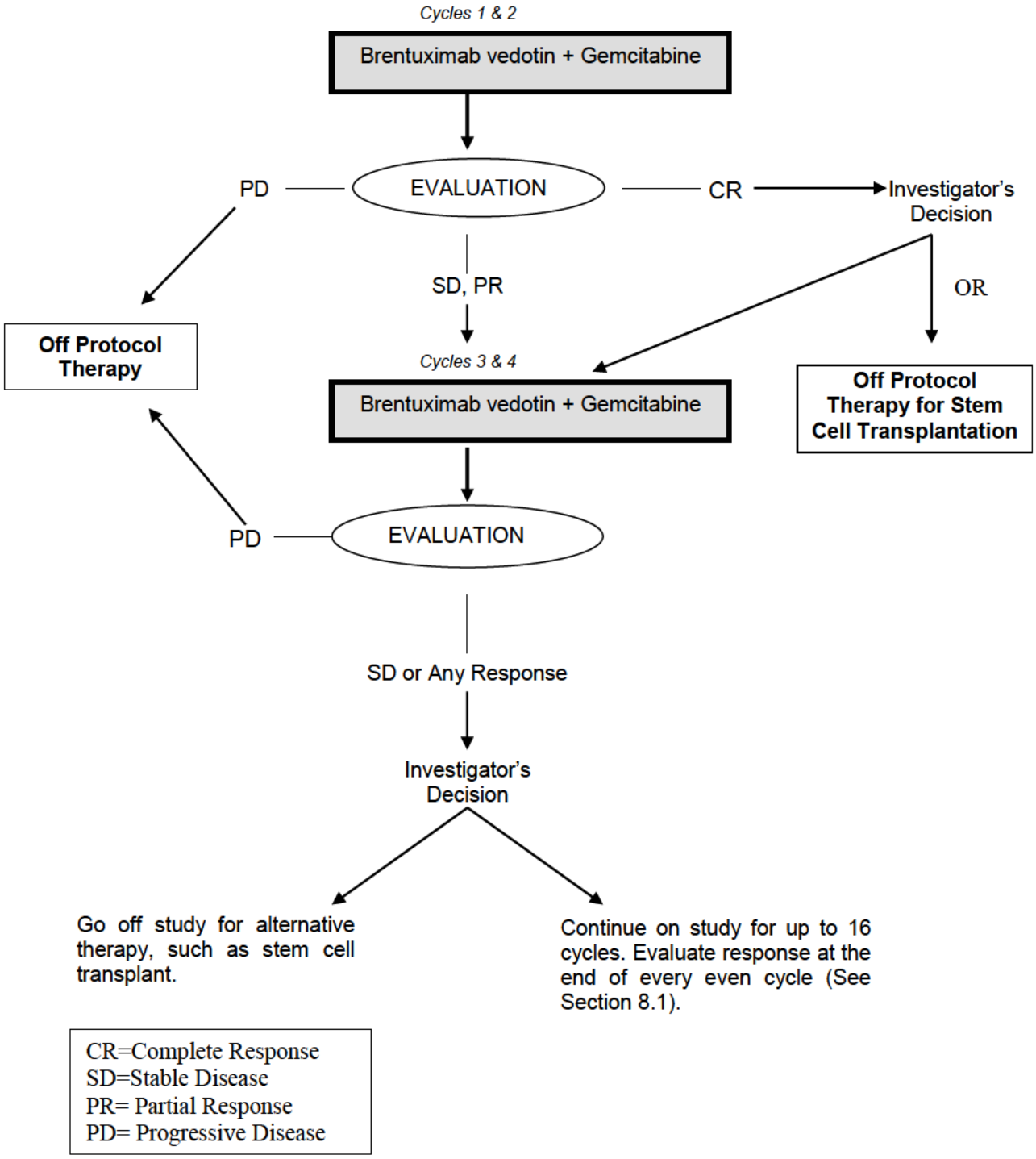
This COG trial will study brentuximab vedotin in the context of a novel combination regimen, with gemcitabine, for pediatric patients with high-risk relapsed or refractory Hodgkin lymphoma. The primary objectives of this study are to define the appropriate dose of brentuximab vedotin when given in combination with gemcitabine, to describe the toxicity associated with this regimen, and to determine the CR rate among patients with relapsed or refractory HL treated with this combination. Exploratory objectives include describing the proportion of patients able to mobilize stem cells after treatment with this regimen and describing the relationship between disease response and changes in serum TARC and miRNA profiles.

Part A will enroll patients with relapsed/refractory HL in a phase 1 dose finding study of brentuximab vedotin in combination with gemcitabine. Gemcitabine will be administered on days 1 and 8 of a 21 day cycle at a fixed dose. Brentuximab vedotin will be investigated at a starting dose of 1.4 mg/kg administered on day 1 and escalated if tolerated. **As of amendment 4, Part A was completed.**

Part B will evaluate the response rate in patients with HL to the combination of gemcitabine and brentuximab vedotin at the dose defined in Part A.

EXPERIMENTAL DESIGN SCHEMA

Treatment Schedule Table (21-day Cycle)		
Day	**Brentuximab vedotin** (i.v. over 30 min)	**Gemcitabine** (i.v. over 100 min)
1	X	X
8		X



1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To estimate the maximum tolerated dose (MTD) and/or recommended Phase 2 dose of brentuximab vedotin in combination with gemcitabine administered every three weeks to children with relapsed or primary refractory Hodgkin lymphoma (HL).

1.1.2 To define and describe the toxicities of brentuximab vedotin in combination with gemcitabine administered on this schedule.

1.1.3 To determine the CR rate after treatment with four cycles of gemcitabine with brentuximab vedotin among patients with relapsed or refractory HL.

1.2 Secondary/Exploratory Aims

1.2.1 To preliminarily define the antitumor activity of brentuximab vedotin in combination with gemcitabine within the confines of a Phase 1 study.

1.2.2 To describe the overall response rate (ORR) after 4 cycles of therapy among patients with relapsed or refractory HL.

1.2.3 To describe the proportion of patients with HL able to mobilize an adequate yield of CD34+ stem cells after gemcitabine with brentuximab vedotin.

1.2.4 To describe the relationship between disease response among patients with HL and changes in TARC during treatment, and to determine if specific miRNA profiles correlate with response to treatment.

1.2.5 To describe the frequency of the FcγRIIIa-158 V/F polymorphism among patients who experience pulmonary toxicity on this protocol.

2.0 BACKGROUND

2.1 Introduction: Relapsed/Refractory HL.

A minority of patients with advanced stage HL will fail to achieve a CR with first-line therapy, and as many as 30% of those who initially respond will subsequently relapse. Multiple second-line chemotherapy regimens have been associated with high overall response rates for patients with refractory or relapsed HL, and have been the subject of recent reviews.[1,2] Some patients with low-risk relapses (limited-stage initial disease and late relapse more than one year after completion of therapy) may be cured with conventional chemotherapy alone. For those patients with primary refractory disease or

higher risk relapse (early relapse; advanced stage disease), long-term disease-free survival remains relatively low.

High-dose therapy with autologous stem cell rescue (ASCR) appears to significantly improve outcome relative to treatment with standard-dose chemotherapy alone for patients with refractory disease or high-risk relapses. However, lack of a CR after reinduction therapy, indicated by residual FDG avidity on PET scanning, portends an increased risk of relapse after ASCR.[3-6] Therefore, it is critically important to identify a retrieval regimen that will maximize the CR rate for patients with relapsed or refractory HL prior to ASCR.

Patients with second or subsequent relapse, or recurrence after ASCR, will be excluded from this Phase I/II trial due to the concern that this more heavily treated patient population will be at an increased risk of hematologic toxicity from this experimental regimen.

2.2 Gemcitabine/Vinorelbine

The Children's Oncology Group (COG) has demonstrated the safety and efficacy of combination chemotherapy with Gemcitabine/Vinorelbine (GV) for pediatric patients with relapsed/refractory HL (76% overall response rate by CT criteria; 45% CR by PET criteria).[7,8] Successful mobilization of stem cells for subsequent autologous transplantation has also been demonstrated following this regimen.[9] The COG HL Committee is interested in further developing GV (1) as a backbone for testing novel retrieval strategies and (2) for incorporation within therapeutic protocols for patients with newly diagnosed HL. Compared to alternative intensification and retrieval regimens, this combination offers the advantage of avoiding the addition of agents that are associated with late treatment sequelae, such as anthracyclines or alkylators.

2.3 Rationale for the substitution of brentuximab vedotin for vinorelbine

As described below, the antibody-drug conjugate brentuximab vedotin exerts its cytotoxic effect through a mechanism similar to vinorelbine. However, a greater overall response rate has been described after treatment with brentuximab vedotin (76%, with 34% CRs) than has been reported for vinorelbine (50%, with few CRs).[10-12] The clinical study of the combination of gemcitabine with brentuximab vedotin is further supported by preclinical data demonstrating that CD30 targeting will sensitize lymphoma cells to gemcitabine.[13,14]

2.4 Preclinical Studies with brentuximab vedotin

Brentuximab vedotin (previously known as SGN35) is an antibody-drug conjugate containing an anti-CD30 murine/human chimeric monoclonal antibody (cAC10; brentuximab) covalently linked to monomethylauristatin E (MMAE; vedotin) by an enzyme-cleavable peptide linker. CD30 is a transmembrane receptor highly expressed in both HL and ALCL. After binding to CD30, brentuximab vedotin is internalized and is transported to lysosomes, where the peptide linker is selectively cleaved, releasing MMAE into the cytoplasm. Like vinorelbine, MMAE exerts its antineoplastic effect through inhibition of tubulin polymerization, leading to M-phase arrest and apoptosis.

2.5 Adult Studies of brentuximab vedotin

The safety and efficacy of brentuximab vedotin has been evaluated in adults with HL or ALCL, using the MTD of 1.8 mg/kg every three weeks. Treatment related toxicity included peripheral sensory neuropathies (44%), fatigue (42%), nausea (41%), diarrhea (34%), pyrexia (31%), neutropenia (21%) and vomiting (20%). Among 102 patients with HL, the observed ORR was 76% (95% CI 65-83%), with a CR rate of 34% (95% CI 25-45%).[15] The median time to objective response was 5.7 weeks (range, 5.1 to 56 weeks), and the

median time to CR was 12 weeks (range, 5.1 to 56 weeks). Among the 102 patients enrolled, the median number of cycles on this study was 9 (range, 1 to 16 cycles), the mean number of cycles was 10.

Following the recommended intravenous (IV) dose of 1.8 mg/kg every 3 weeks, maximum concentrations were typically observed at the end of infusion. A multi-exponential decline in brentuximab vedotin serum concentrations was observed with a terminal half-life of approximately 4 to 6 days. Exposures were approximately dose proportional. After multiple-dose administration of brentuximab vedotin, steady-state was achieved by 21 days, consistent with the terminal half-life estimate. Minimal to no accumulation was observed with multiple doses at the q3wk (every 3 weeks) schedule.

[redacted]

Brentuximab vedotin is being investigated for use in earlier lines of therapy for adults with HL. Ongoing studies include a phase 3 randomized, placebo-controlled trial evaluating brentuximab vedotin for the treatment of HL patients at high risk for relapse after autologous stem cell transplant (SCT), a phase 2 study evaluating the efficacy and safety of retreatment with brentuximab vedotin, a phase 2 study evaluating the efficacy and safety of brentuximab vedotin in patients with CD30-positive NHL, a phase 2 study evaluating the efficacy and safety of brentuximab vedotin in patients with CD30-positive non-lymphomatous malignancies, a phase 1 study evaluating the safety of brentuximab vedotin in combination with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) or AVD (doxorubicin, vinblastine, dacarbazine) for patients with newly-diagnosed HL, and a phase 1 study evaluating the safety of brentuximab vedotin in sequence and in combination with multi-agent chemotherapy for patients with newly diagnosed CD30-positive mature T-Cell and NK-Cell neoplasms, including systemic ALCL.

2.6 Pediatric Studies of brentuximab vedotin

There have been no pediatric-specific trials of brentuximab vedotin. Nine patients on the early phase trials of brentuximab vedotin were less than 18 years old (5 HL, 4 ALCL; age range 12-17 years).[16] Four of the nine had undergone prior ASCT. All nine patients were treated with brentuximab vedotin as a single agent on either phase I or phase 2 trials, given either weekly (0.8-1.2 mg/kg/dose from between 6-9 doses) or every three weeks (1.2 – 1.8 mg/kg/dose for 6-26 cycles). Six of these were treated with 1.8 mg/kg every 3 weeks, for a median of 15 cycles.[16] [redacted]

2.7 Pulmonary Toxicity

2.7.1 Pulmonary toxicity due to gemcitabine is rare

When gemcitabine is administered alone, severe pulmonary toxicity is rare (~1%).[17] Gemcitabine induces pulmonary toxicity at greater frequency only when combined with other therapies known to cause lung injury, such as bleomycin.[18] No cases of noncardiogenic pulmonary edema were observed among pediatric patients treated with gemcitabine and vinorelbine on AHOD0321.[8]

2.7.2 Pulmonary toxicity after gemcitabine with SGN30

It is possible that the combination of gemcitabine with brentuximab vedotin will be associated with unacceptable pulmonary toxicity. Grade 3-5 pneumonitis was observed among five adults (aged 36-62) out of 23 treated with the unconjugated anti-CD30 antibody (SGN30), in combination with gemcitabine, vinorelbine, and pegylated liposomal doxorubicin.[19] Of note, all five patients with pulmonary toxicity had a V/F polymorphism in the FcγRIIIa gene ($p = 0.008$).

Nevertheless, clinical data suggest that pulmonary toxicity may be less frequent among pediatric lymphoma patients treated with the combination of gemcitabine and brentuximab vedotin. The dose of the unconjugated anti-CD30 antibody (SGN30) that was associated with pulmonary toxicity (12 mg/kg on days 1 and 8 of each 21-day cycle, a total of 24 mg/kg/cycle) was significantly higher than the phase 2 dose of brentuximab vedotin (1.8 mg/kg/cycle, given every 3 weeks). No clinically meaningful pulmonary toxicity signal has been associated with brentuximab vedotin monotherapy at this dose.[15,20]

2.7.3 Pulmonary toxicity from brentuximab vedotin in combination with bleomycin.

Severe pulmonary toxicity has been described in 10 of 25 patients treated with brentuximab vedotin in combination with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD).[21] Patients presented with cough and dyspnea. Interstitial infiltration and/or inflammation were observed on plain films and/or computed tomography of the chest. Five patients had a maximum severity ≥ Grade 3 (3 with Grade 3 and 2 with Grade 4). Most patients responded favorably to corticosteroid therapy. In contrast, no further pulmonary toxicity was observed among patients treated with brentuximab vedotin plus doxorubicin, vinblastine and dacarbazine (AVD),[22] suggesting that brentuximab vedotin can be successfully combined with chemotherapy agents not frequently associated with pulmonary toxicity.

2.8 Progressive multifocal leukoencephalopathy (PML)

In January 2012, the US Food and Drug Administration (FDA) issued a warning to health care professionals noting that three cases of progressive multifocal leukoencephalopathy (PML) have been described among patients treated with brentuximab vedotin, including two diagnosed with PML after the FDA approval of brentuximab vedotin for patients with relapsed/refractory lymphoma. A mechanism by which brentuximab vedotin causes PML is not known. Due to the serious nature of PML, a new Boxed Warning highlighting this risk has been added to the drug label. The FDA recommends that healthcare professionals suspend brentuximab vedotin dosing if PML is suspected, and discontinue the drug therapy if a diagnosis of PML is confirmed.

2.9 Rationale for Complete Response (CR) as Primary Response Endpoint

Among patients with primary refractory disease or early relapse of lymphoma, high-dose therapy with autologous stem cell rescue improves outcome relative to patients treated with standard-dose chemotherapy alone. However, lack of a CR after reinduction therapy, indicated by residual FDG avidity on PET scanning, portends an increased risk of relapse after autologous SCT.[3-6] Therefore, identifying a retrieval regimen that will allow the greatest number of patients to achieve a CR prior to autologous SCT is an objective with greater clinical relevance than maximizing ORR.

2.10 Background for Exploratory Correlative Studies

2.10.1 TARC as a biomarker for response among patients with HL

Hodgkin's Reed–Sternberg (HRS) cells typically reside among a background of reactive inflammatory cells, consisting of a dense infiltrate of T cells, histiocytes, eosinophils, and plasma cells. These inflammatory cells support the HRS cells by secreting both immunosuppressive factors and pro-survival factors. HRS cells appear to attract these cells to the microenvironment by secreting type 2 helper T chemokines and cytokines, such as thymus and activation-regulated chemokine (TARC, or CCL17).[23] Serum levels of TARC correlate with disease activity in patients with HL.[24-26] Recent data from University Medical Center Groningen, (n=60) showed that using plasma TARC, response to chemotherapy can be assessed after one cycle of chemotherapy in both early and advanced stage HL patients.[27] In this study, plasma will be collected from patients prior to the start of therapy and at the end of each cycle to determine if TARC can provide an early measure of disease response in pediatric HL.

2.10.2 Prognostic value of circulating miRNA

MicroRNAs (miRNAs) are small, non-coding RNA molecules that regulate gene expression via post-transcriptional suppression of mRNA translation. Recently, it has been shown that tumor cells release miRNAs into the circulation where they can be detected in serum or plasma.[28] Moreover, these studies showed that miRNAs in serum or plasma remain stable after shipment. Circulating miRNAs have been described as disease specific biomarkers in patients with pancreatic, gastric, breast, ovarian and colorectal cancer and even in other diseases states such as acute myocardial infarction.[29] Previous work has identified differential expression of 38 circulating miRNAs (including miR-9, miR-19a and miR-20a) in adult HL patients compared to tissue derived from reactive lymph nodes,[30] and 30 miRNAs in microdissected HRS cells compared to CD77+ progenitor cells.[31] miRNAs appear to regulate several growth pathways involved with H/RS cell proliferation, including p21 and NF-κB.[32,33] We propose to explore the significance of circulating miRNA in pediatric HL patients by collecting serum prior to start of treatment and at the end of each cycle.

2.10.3 FcγRIIIa-158 receptor single nucleotide polymorphisms (SNPs)

The FcγRIIIa receptor 158 valine (V) allotype displays a higher affinity for human immunoglobulin G1 and increased antibody-dependent cellular cytotoxicity (ADCC).[34] As described above (section 2.7.2) this polymorphism was present in five of five patients who experienced Grade 3 or 4 pulmonary toxicity after treatment with SGN30 in combination with gemcitabine, vinorelbine, and pegylated liposomal doxorubicin.[19] To determine if there is a similar association

between FcγRIIIa (V/F) heterozygosity and pulmonary toxicity after treatment with gemcitabine plus brentuximab vedotin, peripheral blood mononuclear cells will be banked for retrospective analysis. If pulmonary toxicity is observed during this trial, analysis of this SNP will be performed on all patients with available sample.

2.11 Overview of Proposed Pediatric Study

This is a single-arm, nonrandomized trial studying the combination of brentuximab vedotin with gemcitabine. The optimal dose of brentuximab vedotin for use in combination with gemcitabine will be determined in the Phase 1 portion of the study, Part A. Two dose levels will be tested. The Phase 2 portion, Part B, will test the efficacy of gemcitabine in combination with brentuximab vedotin at the dose level identified as optimal in the Phase 1 portion.

In both phases, brentuximab vedotin and gemcitabine will be administered in three-week cycles. Therapy will be interrupted if there is evidence of progressive disease or drug related dose-limiting toxicity that requires removal from therapy. Response will be evaluated after every two cycles.

After the first two cycles, patients with CR are allowed the option of going off protocol therapy for stem cell transplantation (See Section 8.4). Patients with PD will be removed from protocol therapy. All other patients will continue on therapy to cycles three and four.

After every subsequent response evaluation (i.e. after cycle 4, and every subsequent even-numbered cycle), patients without PD have the option of either continuing treatment or going off protocol therapy for alternative treatment, such as stem cell transplantation. Therapy may otherwise continue for up to a total of 16 cycles (approximately 12 months from study enrollment).

2.12 Amendment Expanding Enrollment at Dose Level 2 (August 2013)

As of August 2013, 9 patients have been treated on AHOD1221: three at dose level 1 and six at dose level 2. None of the patients treated at dose level 1 experienced dose limiting toxicity. Two patients treated at dose level 2 experienced non-hematologic dose limiting toxicity. One patient presented to the emergency room with suspected sepsis and was found to be hypotensive, requiring medical management (Grade 3 hypotension). This patient was subsequently demonstrated to have pre-existing, steroid-induced adrenal insufficiency, which likely contributed to the hypotension. The other patient developed asymptomatic Grade 3 elevation of liver enzymes on Day 8 of the first treatment cycle, which decreased to eligibility criteria by Day 21 of the cycle. Both patients had resolution of all toxicity, and continued on study treatment with dose reduction as prescribed by protocol. We therefore plan to accrue an additional six patients at dose level 2 to further evaluate toxicity.

2.13 Amendment Opening Phase 2 (Part B)

Six patients enrolled in the dose level 2 expansion cohort. None of these six patients experienced a non-hematologic dose limiting toxicity (DLT). One of these was found to be ineligible for evaluation of hematologic DLT, because filgrastim was administered during the first cycle of therapy in preparation for stem cell harvesting. None of the five remaining patients experienced a hematologic DLT.

After Amendment 3, criteria were defined for the evaluation of the dose level 2 expansion cohort (See Section 11.4). Per this section, dose level 2 is determined to be the

recommended phase 2 dose (RP2D), because the number of DLTs in this expansion cohort did not exceed one. Phase 1 (Part A) can close and the protocol can proceed to Phase 2 (Part B). Patients treated on the Phase 1 component at dose level 2 will be included in analysis of response for Part B provided that they are eligible and evaluable for response.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

Note: This study is not on the CTSU Menu (i.e. it is not posted to the CTSU web site) but is supported by the CTSU Regulatory Office, OPEN and Rave.

3.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the COG Registry system 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.

In order for an institution to maintain COG membership requirements, every newly diagnosed patient needs to be offered participation in ACCRN07, *Protocol for the Enrollment on the Official COG Registry, The Childhood Cancer Research Network (CCRN)*.

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 II 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.

3.2 IRB Approval

Sites must obtain IRB/REB approval for this protocol and submit IRB/REB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSU IRB Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (https://www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

IRB/REB approval documents may be faxed (1-215-569-0206),
E-mailed (CTSURegulatory@ctsu.coccg.org) or mailed to the CTSU Regulatory office.
When a site has a pending patient enrollment within the next 24 hours, this is considered a "Time of Need" registration. For Time of Need registrations, in addition to marking your submissions as 'URGENT' and faxing the regulatory documents, call the CTSU Regulatory Helpdesk at: 1-866-651-CTSU. 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. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on 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.

3.3 Reservation Requirements

Prior to obtaining informed consent and enrolling a patient, a reservation must be made following the steps below. Reservations may be obtained 24 hours a day through the Oncology Patient Enrollment Network (OPEN) system.

Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the Registration system in OPEN. Prior to discussing protocol entry with the patient, site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available for the patient. Once a slot-reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

If the study is active, a reservation can be made by following the steps below:

1) Log in to https://open.ctsu.org/open/ using your CTEP IAM user name and password.
2) In order to make a reservation, the patient must have an OPEN patient number. Click on the 'Slot Reservation' tab to create an OPEN patient number, under 'Patients'.
3) Using the OPEN patient number '**RESERVE'** a slot for that patient.
4) On the 'Create Slot Reservation' page, select the Protocol Number, enter the COG Patient ID, and choose the required stratum (if applicable) in order to obtain a reservation.

Refer to the 'SITE – Slot Reservation Quick Reference' guide posted under the 'Help' tab in OPEN for detailed instructions:
https://www.ctsu.org/readfile.aspx?fname=OPEN/OPEN_SlotReservation_QuickReference_SiteUserGuide_102612.pdf&ftype=PDF

3.4 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://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the lead protocol organization (LPO) or participating organization roster.

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.

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.

3.5 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. **Patients who are started on protocol therapy on a Phase II study prior to study enrollment will be considered ineligible**.

3.6 Institutional Pathology Report

Immediately following enrollment, the most recent institutional pathology report for the diagnosis under which the patient is being enrolled must be uploaded into RAVE. The report must include the associated study number and COG patient registration and accession numbers. Personal identifiers, including the patient's name and initials must be removed from the institutional pathology report prior to submission. Note that, as detailed in Section 4.1.2, all patients must have histologic verification of Hodgkin disease at the time of relapse, and the institutional pathology report from this biopsy should be submitted. No additional biopsy is required for patients with primary refractory disease (i.e. no prior CR); for these patients, the initial diagnostic pathology report should be sent.

4.0 PATIENT ELIGIBILITY CRITERIA

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical or research record which 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 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) 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 must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

Clarification in timing when counting days: As an example, please note that if the patient's last day of prior therapy is September 1st, and the protocol requires waiting at least 7 days for that type of prior therapy, then that patient cannot be enrolled until September 8th.

See Section 8.1 for required studies to be obtained prior to starting protocol therapy.

4.1 Inclusion Criteria

4.1.1 Age: Patients must be > than 12 months and ≤ 30 years of age at the time of study enrollment.

4.1.2 Diagnosis: Patients must have had histologic verification of the malignancy at original diagnosis. Patients must have histologic verification of recurrent Hodgkin disease at the time of relapse. No additional biopsy is required for patients with primary refractory disease (i.e. no prior CR).

4.1.2.1 Parts A and B- Patients with Hodgkin lymphoma (HL) are eligible for both the phase 1 and 2 portions, if they are in one of the following categories:

- Primary refractory disease (i.e. no prior CR)
- Very early relapse (< 6 months from the end of initial therapy, including chemotherapy ± radiation)
- Advanced stage (III or IV) at diagnosis who relapse less than one year from the end of initial therapy.

Note that patients with low-stage disease (IA or IIA) at initial diagnosis, who were treated with radiation alone or fewer than four cycles of chemotherapy will NOT be eligible (See Section 4.2.6)

4.1.3 Disease Status:

Patients must have measurable disease, documented by clinical and radiographic

criteria. See Section 12 for criteria for measurable disease.

4.1.4 Life Expectancy: Patients must have a life expectancy of ≥ 8 weeks (≥ 56 days).

4.1.5 Performance Level: Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50 for patients ≤ 16 years of age (See Appendix I). Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

4.1.6 Prior Therapy

4.1.6.1 Patients must have fully recovered from the acute toxic effects of all prior anti-cancer chemotherapy.

a. Myelosuppressive chemotherapy:
At least 14 days after the last dose of myelosuppressive chemotherapy (28 days if prior nitrosourea). Note: Cytoreduction with hydroxyurea can be initiated and continued for up to 24 hours prior to the start of therapy.
b. Hematopoietic growth factors: At least 14 days after the last dose of a long-acting growth factor (e.g. Neulasta) or 7 days for short-acting growth factor. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair.
c. Biologic (anti-neoplastic agent): At least 7 days after the last dose of a biologic agent. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair.
d. Immunotherapy: At least 42 days after the completion of any type of immunotherapy, e.g. tumor vaccines.
e. Monoclonal antibodies: At least 3 half-lives of the antibody after the last dose of a monoclonal antibody. (See table on DVL homepage listing monoclonal antibody half-lives: https://members.childrensoncologygroup.org/_files/disc/dvl/Half-lifetableforeligibility.pdf.)
f. XRT:
At least 14 days after local palliative XRT (small port); At least 150 days must have elapsed if prior TBI, craniospinal XRT or if ≥ 50% radiation of pelvis; At least 42 days must have elapsed if other substantial BM radiation.
g. Stem Cell Infusion without TBI: Patients with prior autologous or allogeneic Stem Cell Transplant (SCT) are excluded from this study.
h. Bleomycin: At least 28 days must have elapsed since the most recent dose of bleomycin, to allow adequate time to detect evidence of bleomycin-related pulmonary toxicity.

4.1.7 Organ Function Requirements

4.1.7.1 Adequate Bone Marrow Function Defined as:
As of amendment 4, Part A was completed.

a. Part A: For patients without known bone marrow involvement:
- Peripheral absolute neutrophil count (ANC) ≥ 1000/μL
- Platelet count ≥ 100,000/μL (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)

b. Part B: For patients without known bone marrow involvement:
- Peripheral absolute neutrophil count (ANC) ≥ 750/μL
- Platelet count ≥ 75,000/μL (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)

c. Patients with lymphoma metastatic to bone marrow who have granulocytopenia, anemia, and/or thrombocytopenia will be eligible for study but not evaluable for hematologic toxicity (In Part A, there will be a maximum of one per cohort). Such patients must meet the blood counts in 4.1.7.1.a (may receive transfusions provided they are not known to be refractory to red cell or platelet transfusions). If dose-limiting hematologic toxicity is observed, all subsequent patients enrolled in Part A must be evaluable for hematologic toxicity.

4.1.7.2 Adequate Renal Function Defined as:
- Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m^2 or
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
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 GFR[35] (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

4.1.7.3 Adequate Liver Function Defined as:
- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
- SGPT (ALT) < 2.5 x upper limit of normal (ULN) for age. For the purpose of this study, the ULN for SGPT is 45 U/L.
- Serum albumin ≥ 2 g/dL.

4.1.7.4 Adequate Pulmonary Function Defined as:
- No evidence of dyspnea at rest, no exercise intolerance due to pulmonary insufficiency, and a pulse oximetry > 92% while breathing room air.
- FEV1/FVC > 60% by pulmonary function test (PFT), unless due to large mediastinal mass from HL. Carbon monoxide diffusion capacity (DLCO), FEV1, and Forced Vital Capacity all > 50% predicted value. **Note:** Pulmonary function testing is not required for children < 8 years old, or for any child who is developmentally unable to comply with pulmonary function testing.

4.1.7.5 Adequate Neurologic Function Defined as:
- Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled.
- Nervous system disorders (CTCAE v4) resulting from prior therapy must be < Grade 2.

4.2 Exclusion Criteria

4.2.1 Pregnancy or Breast-Feeding

Pregnant or breast-feeding women will not be entered on this study due to risks of fetal or teratogenic toxicities as seen in animal/human studies. Pregnancy tests must be obtained in girls who are post-menarchal. 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 brentuximab vedotin. Abstinence is an acceptable method of birth control.

4.2.2 Concomitant Medications

4.2.2.1 Corticosteroids: Patients receiving stable or decreasing corticosteroids for other concurrent conditions (e.g. asthma, autoimmune diseases, rash, documented adrenal insufficiency) are eligible for this study.

4.2.2.2 Investigational Drugs: Patients who are currently receiving another investigational drug are not eligible.

4.2.2.3 Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible.

4.2.3 Infection: Patients who have an uncontrolled infection are not eligible.

4.2.4 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.

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

4.2.6 Prior Therapy

4.2.6.1 Patients with prior exposure to brentuximab vedotin are not eligible. NOTE: Prior exposure to gemcitabine is NOT an exclusion criterion.

4.2.6.2 Patients who have undergone prior autologous or allogeneic SCT are not eligible.

4.2.6.3 Patients with HL who were stage IA or IIA at initial diagnosis and treated with either radiation alone or < 4 cycles of chemotherapy are not eligible.

4.2.7 Patients who have received a prior solid organ transplantation are not eligible.

4.2.8 Patients with known hypersensitivity to E.coli-derived proteins, Filgrastim, or any component of Filgrastim are not eligible.

4.2.9 Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.

4.2.10 Regulatory Requirements

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

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

5.0 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).

5.1 Overview of Treatment Plan

Treatment Schedule Table		
Day	**Brentuximab vedotin*** (IV over 30 min)	**Gemcitabine^** (IV over 100 min)
1	X	X
8		X

a. **Brentuximab vedotin** will be administered intravenously over 30 minutes **on Day 1.** *Brentuximab vedotin should be administered BEFORE gemcitabine on Day 1. Please note that **only the NCI-supplied investigational agent** (and not the commercial drug of brentuximab vedotin) should be used for this study.

b. **Gemcitabine (1,000 mg/m^2/day)** will be administered intravenously over 100 minutes on **Day 1 and Day 8**.

Previous investigations have shown that cellular accumulation of the active metabolite of gemcitabine is saturated at plasma concentrations above 10 to 20 µM[36,37], a concentration that is exceeded when gemcitabine is infused faster than 6 to 10 mg/m^2/min.[37,38] Accumulation of higher intracellular dFdCTP concentrations, which may result in an enhanced antineoplastic activity, cannot be achieved by higher dosage, but only by prolonged infusion time. Prolonged infusions are well-tolerated[39-44] and may provide increased clinical benefit over bolus administration. Gemcitabine should therefore be infused over 100 minutes for this study.[45]

A cycle of therapy is considered to be 21 days. A cycle may be repeated 15 times (16 cycles total), up to a total duration of therapy of approximately 12 months.

*Drug doses of **brentuximab vedotin** should be adjusted based on weight measured within 7 days prior to the beginning of each cycle.

^Drug doses of **gemcitabine** should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle.

*A maximum weight of 100 kg will be used for the prescribed dose of brentuximab vedotin, based on pharmacokinetic analyses in early-phase adult studies. The MAXIMUM DOSE of brentuximab vedotin will therefore be 140 mg for patients treated at Dose Level 1 and 180 mg for patients treated at Dose Level 2. There is no maximum dose for gemcitabine, which should be dosed based on the calculated BSA.

5.1.1 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 21 days if the patient has at least stable disease and has again met laboratory parameters as defined in the eligibility section, Section 4.0 except for the following repeat cycle modified starting criteria: ANC ≥ 750/μL, platelets ≥ 50,000/μL. Patients with lymphoma metastatic to bone marrow at study enrollment, who have granulocytopenia and/or thrombocytopenia due to disease on scheduled start of Cycle 2 may begin, regardless of blood counts. All subsequent cycles, if given, should not begin until the ANC is ≥ 750/μL and the platelet count is ≥ 50,000/μL (transfusion independent, defined as at least 2 days after last platelet transfusion).

Response will be evaluated after every even-numbered cycle. Patients with CR after any cycle may go off protocol therapy for stem cell transplantation (See Section 8.4) or continue with two more cycles per investigator decision. After every subsequent response evaluation (i.e. after cycle 4, and every subsequent even-numbered cycle), patients have the option of going off protocol therapy for alternative treatment, such as stem cell transplantation. Therapy may otherwise continue for up to a total of 16 cycles (approximately 12 months from study enrollment). Therapy will be interrupted if there is evidence of progressive disease or drug related toxicity that requires removal from therapy.

5.2 Therapy Delivery Map

5.2.1 Therapy Delivery Map	_____ Patient COG ID number	_____ DOB

*A cycle of therapy is considered to be 21 days. A cycle may be repeated up to a total of 16 cycles if the patient has met the criteria for starting subsequent cycles (see Section 5.1). Each cycle should not begin until the ANC is ≥ 750/μL and the platelet count is ≥ 50,000/μL. This Therapy Delivery Map is on one **(1)** page.*

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Brentuximab vedotin (Bv)	IV over 30 minutes	1.8 mg/kg/dose (Max dose 180 mg)	Day 1	Administer **before** gemcitabine on Day 1 Drug doses of brentuximab vedotin should be adjusted based on weight measured within 7 days prior to the beginning of each cycle. Do NOT give as IV push Do not use an in-line filter. See Section 5.1 for treatment details.
Gemcitabine (GEM)	IV over 100 minutes	1,000 mg/m2	Day 1 and 8	Drug doses of gemcitabine should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle. See Section 5.1 for treatment details.

Enter Cycle #: _____ Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Bv ____mg	GEM ____mg	Studies for cycle 1@	Studies for subsequent cycles^	Comments
			Enter calculated dose above and actual dose administered below				
		1	____mg	____mg	1, 2, 3+, 5	1, 2, 3&, 4, 5, 6, 7	
		8		____mg	1, 2, 3+	1, 3&	
		15			1, 2, 3+		
		21	**End of cycle** See Section 5.1.1 for criteria to start the next cycle.			8*, 9#, 10$, 11 If last cycle, see end of therapy studies in Section 8.1	

@ See Section 8.1for all baseline studies

\+ If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity.

^ Studies may be obtained within 72 hours prior to the start of the subsequent cycle, unless otherwise specified.

& If patients develop Grade 4 neutropenia then CBCs should be checked every 3 to 4 days until recovery to Grade 3.

* Between Days 15 and 21 of every even-numbered cycle

\# Only required if preceding bone marrow biopsy demonstrated involvement by lymphoma. Biopsy is every even-numbered cycle only.

$ Between Days 15 and 21 of cycles 2 and 4 and then every 4 cycles

See Section 5.0 for Dose Modifications for Toxicities and the COG website posted materials for Supportive Care Guidelines.

5.2.2 Required Observations

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

1	History; Physical Exam with vital signs
2	Performance Status; Electrolytes including Ca^{++}, PO_4, Mg^{++}
3	CBC, differential, platelets
4	Correlative biology studies. See Section 8.5and Appendix III for specifics on the correlative biology studies.
5	Height, weight, BSA
6	Creatinine, ALT, bilirubin
7	Sedimentation Rate (ESR)
8	Tumor Disease Evaluation; Imaging Studies (CT scan, FDG-PET). See Sections 12.2, 12.3 and 15. Response will be evaluated between Days 15 and 21 of every even-numbered cycle and as clinically indicated
9	Bone marrow biopsies (at least 2 sites) every even-numbered cycle.
10	Pulmonary Function Tests (PFTs) and Pulse Oximetry should be obtained between Days 15 and 21 of cycles 2 and 4 and then every 4 cycles. (Pulmonary function testing is not required for children < 8, or for any child who is developmentally unable to comply with pulmonary function testing.) **If pulmonary toxicity occurs, study therapy should be held, and the Study Chair and Research Coordinator should be notified within 48 hours.**
11	PBSC Collection in patients. See Section 8.4 and Appendix IV for details. Peripheral blood stem cells can be collected after any cycle except for patients with bone marrow involvement. Patients who had bone marrow involvement at the time of study entry must undergo repeat bone marrow biopsies (at least two sites) until negative prior to stem cell collection. If the bone marrow biopsies are positive after 2 cycles of therapy, the patient can be harvested the end of the next two cycles of therapy.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE. See Section 8.1

5.3 **Dose Escalation Schema**

PART A: Per amendment 4, Part A was completed.
Phase 1 dose-finding study (Phase 1 Consortium plus limited institutions)

5.3.1 Inter-Patient Escalation for Brentuximab vedotin

Per amendment 4, Part A was completed.
The starting dose will be 1.4 mg/kg with dose levels for subsequent groups of patients as follows.

Dose Level	Brentuximab vedotin Dose (mg/kg)	Maximum Dose of Brentuximab vedotin
1*	1.4	140 mg
2	1.8	180 mg

*starting dose level

There will be no escalations beyond dose level 2 (1.8 mg/kg).

5.3.2 Intra-Patient Escalation **Per amendment 4, Part A was completed.**

Part A: Patients treated at dose level 1 (1.4 mg/kg) who have not experienced DLT in any cycle of therapy, and who do not have a CR after two cycles of therapy are allowed to escalate to dose level 2 (1.8 mg/kg) for all subsequent cycles. At the discretion of the treating physician, they may also continue treatment at dose level 1.

Part B: No intra-patient escalation of phase in the phase 2 portion of the study as patients will be treated at the MTD or recommended phase 2 dose as established in Part A.

PART B: Phase 2 component of the study (COG Groupwide)

5.3.3 Patients on Part B of the study will be receive brentuximab vedotin at 1.8 mg/kg/day (the recommended phase 2 dose as determined in Part A).

5.4 **Grading of Adverse Events**
Adverse events (toxicities) will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov). Any suspected or confirmed dose-limiting toxicity should be reported immediately (within 24 hours) to the Study Chair.

Definition of Dose-Limiting Toxicity (DLT)
DLT will be defined as any of the following events that are possibly, probably or definitely attributable to protocol therapy. The DLT observation period for the purposes of dose-escalation will be the first cycle of therapy.

Dose limiting hematological and non-hematological toxicities are defined differently.

5.4.1 Non-Hematological Dose-Limiting Toxicity

- Any Grade 3 or greater non-hematological toxicity, except for the following:
  - Grade 3 nausea and/or vomiting of < 3 days duration
  - Grade 3 or 4 fever < 5 days duration
  - Grade 3 infection < 5 days duration
  - Grade 3 rash < 5 days duration
  - Grade 3 pruritis < 5 days duration
  - Grade 3 fatigue < 5 days duration
  - Grade 3 non-hematologic laboratory abnormalities that resolve within 14 days to grade 1, or to initial eligibility criteria, or to baseline (if the patient entered the study with existing toxicity). Note: for the purposes of this study the ULN for ALT is defined as 45 U/L.
  - Grade 3 infusion reactions < 24 hours duration (See Section 6.2.4)
  - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia, or hypomagnesemia responsive to oral supplementation.
- Grade ≥ 2 pancreatitis (See Section 6.2.8 for dose modifications and instructions on subsequent treatment).
- Any other Grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption will also be considered a DLT.
- Note: Allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

5.4.2 Hematological Dose Limiting Toxicity

5.4.2.1 Hematological dose limiting toxicity is defined as:

In patients evaluable for hematologic toxicity (See Section 4.1.7.1):

- Grade 4 neutropenia or thrombocytopenia that does not resolve to an ANC of ≥ 500/μL and platelets ≥ 20,000/μL within 7 days after the next scheduled dose of brentuximab vedotin.

5.4.2.2 Note: Grade 4 febrile neutropenia will not be considered a dose-limiting toxicity.

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

Note that these dose modifications apply to brentuximab vedotin only. The dose of gemcitabine will not be modified for toxicity.

The Study Chair must be notified of any use of myeloid growth factor for hematologic toxicity and of any other dosage modification described below.

The Study Chair and Research Coordinator must be notified within 48 hours of detection of pulmonary toxicity, as described in Section 6.2.6.

6.1 Dose Modifications for Hematological Toxicity

6.1.1 Patients who have thrombocytopenia meeting the definition for DLT in Section 5.4.2.1: Grade 4 thrombocytopenia that does not resolve to platelets ≥ 20,000/µL mm3 within 7 days of the next scheduled dose of brentuximab vedotin) should receive subsequent cycles at a reduced dose of brentuximab vedotin, 1.2 mg/kg, maximum dose 120 mg.

Patients who have neutropenia meeting the definition for DLT in Section 5.4.2.1 (Grade 4 neutropenia that does not resolve to an ANC of ≥ 500/mL within 7 days of the next scheduled dose of brentuximab vedotin) should receive the same dose of brentuximab vedotin in the next cycle with myeloid growth factor support. Each subsequent course of brentuximab vedotin with gemcitabine, after the first, should begin no sooner than Day 21 of the preceding course, and should not begin unless the ANC is ≥ 750/mL. GCSF may be administered at a dose of 5 mg/kg daily beginning on day 9, and continuing for a minimum of 7 days and until the post-nadir neutrophil count increases to ≥ 1,500/mL. Note that higher doses of GCSF (10-16 micrograms/kg/day) are recommended for use during cycles (post cycle 2 or higher) when stem cell collection is being attempted (See Section 8.4.3). The use of Neulasta is not allowed.

If neutropenia meeting the definition for DLT in Section 5.4.2.1 recurs after myeloid growth factor is added, then the patient should be given a reduced dose of brentuximab vedotin for subsequent cycles, 1.2 mg/kg, maximum dose 120 mg. If neutropenia recurs in a patient that has received a dose level reduction but has not received myeloid growth factor, then myeloid growth factor should be administered or the patient should be removed from protocol therapy.

6.1.2 Patients who experience thrombocytopenia meeting the definition for DLT in Section 5.4.2.1 after dose reduction or neutropenia meeting the definition for DLT in Section 5.4.2.1 after addition of myeloid growth factor and one dose reduction, must be removed from protocol therapy.

6.1.3 Patients who have a hematological toxicity meeting the definition for DLT in Section 5.4.2.1 that does not resolve to baseline within 21 days after the planned start of the next treatment cycle must be removed from protocol therapy.

6.2 Dose Modifications for Non-Hematological Toxicity

6.2.1 Patients who have any non-hematological toxicity meeting the definition for DLT in Section 5.4.1 may continue on protocol therapy upon meeting eligibility lab requirements or baseline but should receive subsequent cycles at a reduced dose of brentuximab vedotin, 1.2 mg/kg, maximum dose 120 mg.

6.2.2 If the same non-hematological toxicity meeting the definition for DLT in Section 5.4.1 recurs after one dose reduction, the patient must be removed from protocol therapy.

6.2.3 Patients who have a non-hematological toxicity meeting the definition for DLT in Section 5.4.1 that does not resolve to baseline within 21 days after the planned start of the next treatment cycle must be removed from protocol therapy.

6.2.4 Dose modifications for infusion reactions

Infusion-related reactions (IRR), including anaphylaxis, were uncommon (approximately 12%) in adult studies with brentuximab vedotin. Infusion interruption for IRR treatment generally led to the successful completion of the dose and continued treatment with brentuximab vedotin with or without IRR prophylaxis, according to the clinical judgment of the investigator. Although the experience with IRRs related to brentuximab vedotin is limited, in part due to the low incidence observed to date, data support brentuximab vedotin administration by appropriately trained personnel without the need for routine prophylaxis.

If IRR symptoms develop, the infusion should be interrupted and appropriate medical management instituted. The infusion may be restarted at a slower rate after symptom resolution. Premedication with diphenhydramine should be administered for subsequent infusions in patients who have experienced a prior IRR. Dosing of diphenhydramine can be according to institutional standards, or 1 mg/kg PO or IV (maximum of 50 mg). If anaphylaxis occurs, brentuximab vedotin should be immediately and permanently discontinued and appropriate medical management instituted.

Suggested dose modification for infusional reactions to brentuximab vedotin

Therapy modifications for patients who develop infusional reactions to brentuximab vedotin should be:

Grade	Action
Grade 1 Transient flushing or rash, drug fever < 38◦ C (<100.4 ◦ F) And Grade 2 Rash, flushing, urticaria, dyspnea, drug fever ≥ 38◦ C (≥100.4 ◦ F)	For first reaction: • Hold the infusion and wait 30 to 60 minutes (depending upon the reaction severity) • Treat reactions with diphenhydramine 1 mg/kg (max 50 mg), or follow local institution guidelines. If diphenhydramine is not available, a similar antihistamine may be used, following local institution guidelines. Depending on the reaction severity, dexamethasone 0.2 mg/kg (max 10 mg) IV 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 approximately 30 minutes before restarting the infusion. Acetaminophen can also be considered. • **Dosing of SGN-35 should be administered at half of the previously administered rate.** For subsequent doses: • Utilize diphenhydramine with or without acetaminophen as pre-treatment for all subsequent infusions. If diphenhydramine is not available, a similar antihistamine may be used, following local institution guidelines. • Dosing should be administered over the shortest period that was well tolerated. If Grade 1-2 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 Symptomatic bronchospasm with or without urticaria, allergy-related edema/ angioedema, hypotension	• Stop infusion immediately • Administer diphenhydramine hydrochloride 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. If diphenhydramine is not available, a similar antihistamine may be used, following local institution guidelines. Hospital admission should be considered. •Brentuximab vedotin should not be resumed for that course •Subsequent courses of brentuximab vedotin may be considered at physicians' discretion, **after a discussion with the Study Chair, DVL leadership and CTEP.** • All subsequent infusions should be given with the following dose modifications: 1. Premedication with diphenhydramine hydrochloride 1 mg/kg IV (max 50 mg), and dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent). If diphenhydramine is not available, a similar antihistamine may be used, following local institution guidelines.

Grade	Action
	2. The infusion should be administered at 50% of the previous infusion rate
Grade 4 Anaphylaxis	• Stop infusion immediately • Administer diphenhydramine hydrochloride 1 mg/kg (max 50 mg) IV, dexamethasone 0.2 mg/kg (max 10mg) IV (or equivalent), and other anaphylaxis medications as indicated. If diphenhydramine is not available, a similar antihistamine may be used, following local institution guidelines. Epinephrine or bronchodilators should be administered as indicated. Hospital admission for observation may be indicated • Study therapy should be discontinued.

6.2.5 Dose modifications for Peripheral Neuropathy

Peripheral neuropathy is an effect of cumulative exposure to brentuximab vedotin. In adult studies, the first onset of any grade peripheral neuropathy increased with increasing numbers of cycles. Dose delay and reduction appeared to mitigate worsening of neuropathy.

All dose modifications should be based on the highest grade toxicity in the preceding cycle.

- Grade 2-3 neuropathy: Treatment should be delayed until neuropathy improves to Grade 1 or baseline. Treatment with brentuximab vedotin in subsequent cycles should be reduced, 1.2 mg/kg, maximum dose 120 mg.

  If Grade 2 or 3 neuropathy recurs after dose reduction as described above, patients will be taken off protocol therapy, and brentuximab vedotin will be discontinued. Patients who experience a delay in therapy > 14 days due to peripheral neuropathy will be taken off protocol therapy, and brentuximab vedotin will be discontinued.

- Grade 4 neuropathy: Brentuximab vedotin should be discontinued.

6.2.6 Dose modifications for pulmonary toxicity

Pulmonary toxicity requiring modification of therapy will occur for dyspnea ≥ Grade 3, hypoxia ≥ Grade 3 and ≥ Grade 3 pneumonitis that is attributable to the treatment regimen. Dose modifications will also be considered for Grade 2 pneumonitis (See below). Factors to consider in assessing the attribution include the presence of left atrial hypertension, congestive heart failure, infection, metabolic abnormalities, or cancer related causes (e.g. malignant pericarditis). **Upon occurrence of pulmonary toxicity, as defined above, study therapy should be held, and the Study Chair and Research Coordinator should be notified within 48 hours**.

Patients who develop pulmonary toxicity due to gemcitabine and brentuximab vedotin may benefit from treatment with corticosteroids. However, there are no published guidelines to suggest the most appropriate dosing or duration of treatment. Administration of 100 mg of oral or intravenous prednisolone in single

daily or two divided doses has been reported to improve symptoms in adults with pulmonary toxicity secondary to gemcitabine.[46] The suggested dose for patients on AHOD1221 who develop pulmonary toxicity is methylprednisolone 1 mg/kg IV every 12 hours for a minimum of seven days.

Patients who develop pulmonary toxicity, Grade ≥ 3, attributed to the treatment regimen will be taken off protocol therapy. Patients who develop Grade 2 pneumonitis that resolves to Grade ≤ 1 may be retreated with the study regimen, after discussion with the Study Chair. CTEP will be notified within 7 days of study chair notification of each instance of pulmonary toxicity. The Study Chair will consult with CTEP, the study statistician, and DVL leadership (Part A: **As of amendment 4, Part A was completed**) or Hodgkin committee leadership (Part B) to review the history of the affected patient and the pulmonary toxicity for the trial as a whole before proceeding with the recommendation to resume protocol therapy at a lower dose. Failure to discuss a case of pulmonary toxicity will lead to suspension of accrual.

6.2.7 Dose modifications for Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the brain that is caused by the John Cunningham virus (JCV). It typically occurs in immunocompromised individuals and can be fatal. Presenting features may include altered mental status, motor deficits such as hemiparesis or ataxia, visual disturbances, or higher cortical dysfunction such as dysphasia or agnosia. Seizures have also been reported in PML patients (approximately 20%). Cognitive decline without accompanying deficits in motor or sensory function is uncommon. Optic nerve involvement, fever, and spinal cord disease are not typically associated with PML. In addition, peripheral neuropathy, which has been reported with brentuximab vedotin treatment, is not commonly reported with PML.

If PML is suspected, a diagnostic work-up should be performed. The work-up may include, but is 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, which 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 PML is suspected. If PML is confirmed, brentuximab vedotin should be permanently discontinued.

6.2.8 Dose modifications for Pancreatitis

Therapy modifications for patients who develop pancreatitis should be:

Grade	Action
Grade 2 Pancreatitis	• Withhold dose until toxicity has returned to baseline, then continue on protocol therapy but should resume at one dose reduction as per Section 6.2.1. • If Grade 2 pancreatitis recurs after one dose reduction, the patient must be removed from protocol therapy.
Grade 3-4 Pancreatitis	• Permanently discontinue brentuximab vedotin.

7.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

7.1 Concurrent Anticancer Therapy

Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, immunomodulating agents (with the exception of corticosteroids) or biologic therapy may NOT be administered to patients receiving study drug. If these treatments are administered the patient will be removed from protocol therapy.

7.2 Investigational Agents

No other investigational agents may be given while the patient is on study.

7.3 Supportive Care

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary, **with the exception that corticosteroids should not be used as antiemetics**. For general Supportive Care Guidelines see https://members.childrensoncologygroup.org/_files/protocol/Standard/SupportiveCareGuidelines.pdf.

7.4 Growth Factors

Growth factors that support platelet or white cell number or function can only be administered in accordance with Section 6.1.1 or for culture proven bacteremia or invasive fungal infection. In addition, GCSF is recommended for stem cell mobilization (See Section 8.4.3). **The use of Neulasta is not allowed.**

7.5 Concomitant Medications

No other cancer chemotherapy or immunomodulating agents can be used.

Corticosteroid therapy is permissible as supportive care, with the exception that corticosteroids should not be used as antiemetics. Examples of indications for corticosteroid use include, but are not limited to, the following:

- Treatment or prophylaxis for anaphylactic reactions or for treatment of pulmonary toxicity (See Section 6.2).
- Clinical sepsis and signs of severe septic shock, if relative adrenal insufficiency is suspected.
- Diffuse rash or pruritis (may be treated with topical or systemic corticosteroids)
- Asthma exacerbation.

NSAIDs should be used with caution, due to one reported occurrence of Stevens-Johnson Syndrome (SJS) noted in a patient utilizing brentuximab vedotin and a short course of an NSAID. The cause of SJS is unknown.

Patients should be monitored for potential drug-interaction when administered drugs known to be a strong CYP3A4 inhibitor/inducer with SGN-35. See Appendix VIII for a list of CYP3A4 inducers and inhibitors.

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

8.1 Required Clinical, Laboratory and Disease Evaluation

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility (see Section 4.0) must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) 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 must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary). Patients with bone marrow involvement must also have a bone marrow biopsy within 14 days prior to the start of protocol therapy.

STUDIES TO BE OBTAINED	Pre-Study	During Cycle 1	Subsequent Cycles^	End of Protocol Therapy
History	X	Weekly	Days 1, 8	X
Physical Exam with vital signs	X	Weekly	Days 1, 8	X
Neurologic Exam[1]	X			X
Height, weight, BSA	X	X	X	
Pregnancy Test[2]	X			
Performance Status	X	Weekly	Day 1	
CBC, differential, platelets	X	Weekly[3]	Days 1, 8[4]	X
Urinalysis	X			
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly	Day 1	
Creatinine, ALT, bilirubin	X	-	Day 1	
Total protein/albumin	X			
Sedimentation Rate (ESR)	X		Day 1	X
Tumor Disease Evaluation[5]	X	-	Every even cycle[5]	X
Bone marrow biopsies (at least 2 sites)	X[6]		Every even cycle[7]	
Imaging Studies (CT scan, FDG-PET) See Sections 12.2, 12.3 and 15.0	X	-	Every even cycle[5]	X
Pulmonary Function Tests (PFTs)	X	-	Every other cycle x 2, then q 4 cycles[8]	
Pulse oximetry[8]	X	-	Every other cycle x 2, then q 4 cycles[8]	
PBSC Collection[9]		-	X[9]	
Correlative Biology Studies [10]	X[10]		X[10]	

^ Studies may be obtained within 72 hours prior to the start of the subsequent cycle, unless otherwise specified.

1 Nervous system disorders (CTCAE v4) resulting from prior therapy must be < Grade 2.

2 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 brentuximab vedotin. Abstinence is an acceptable method of birth control.

3 If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity.

4 If patients develop Grade 4 neutropenia then CBCs should be checked every 3 to 4 days until recovery to Grade 3.

5 See Sections 12 and 15. Response will be evaluated between Days 15 and 21 of every even-numbered cycle and as clinically indicated.

6 If bone marrow involvement is suspected clinically.

7 Only required if preceding bone marrow biopsy demonstrated involvement by lymphoma.

8 Pulmonary Function Tests and pulse oximetry should be obtained between Days 15 and 21 of cycles 2 and 4 and then every 4 cycles. Pulmonary function testing is not required for children < 8, or for any child who is developmentally unable to comply with pulmonary function testing.

9 See Section 8.4 and Appendix IV for details of PBSC collection. Peripheral blood stem cells can be collected after any cycle except for patients with bone marrow involvement. Patients who had bone marrow involvement at the time of study entry must undergo repeat bone marrow biopsies (at least two sites) until negative prior to stem cell collection. If the bone marrow biopsies are positive after 2 cycles of therapy, the patient can be harvested the end of the next two cycles of therapy.

10 See Section 8.5 and Appendix III for specifics on the correlative biology studies.

8.2 Required Observations Following Completion of Protocol Therapy

The following studies are required until the patient is off study as defined in Section 10.2. These observations are not applicable to patients enrolled on Part A who are not treated at the MTD.

STUDIES TO BE OBTAINED	30 Days After Last dose	Every 3 Months up to 12 Months (Months 3, 6, 9, 12)	Every 6 Months up to 24 Months (Months 6, 12, 18, 24)	Annually up to 60 Months (Months 36, 48, 60)
History	X	X	X	X
Physical Exam with vital signs	X	X	X	X
CBC, differential, platelets, and ESR[1]	X	X	X	X
Creatinine, SGPT, bilirubin[1]	X	X	X	X
Electrolytes including Ca^{++}, PO_4, Mg^{++2}	X	X	X	X
Disease evaluation[2]	X		X	X

[1] Repeated as clinically indicated

[2] Imaging studies should be obtained only if disease progression is suggested by symptoms, physical findings, or abnormal laboratory values (e.g., increased ESR)

8.3 Radiology Studies

8.3.1 Central Radiology Review for Response (Part A)

This is for Part A only. As of amendment 4, Part A was completed. Patients who respond (CR, PR) to therapy or have long term stable disease (SD) on protocol therapy (≥ 6 cycles) will be centrally reviewed. COG Operations Center will notify the Imaging Center of any patient requiring central review. The Imaging Center will then request that the treating institution forward the requested images for central review. The central image evaluation results will be entered into RAVE for review by the COG Operations Center.

The images are to be forwarded electronically to the Imaging Research Center at Children's Hospital Los Angeles via the grid.

COG institutions that are not connected to the grid can send the images on hard copy film, CD ROM, or by FTP. Submitted imaging studies should be clearly marked with the COG patient ID, study number (AHOD1221) and date and shipped to [redacted] at the address below:

[redacted]
Imaging Research Center
Data Administrator
Children's Hospital Los Angeles
4650 Sunset Boulevard, MS # 81
Los Angeles, CA 90027
[redacted]

In addition, all imaging studies for patients with HL treated in Part A must be

submitted for central review by IROC Rhode Island (QARC) (See Section 8.3.2).

8.3.2 Central Review of Imaging Studies (Parts A and B): **As of amendment 4, Part A was completed. The below information is for Part B.**
Central review of images will be performed to validate data reporting for quality assurance. Real time FDG-PET central review can be requested on a case-by-case basis for clarification or adjudication of conflicting institutional imaging studies which may be helpful for clinical assessment (See Section 12.2).

The following imaging studies and corresponding radiology reports should be submitted to IROC Rhode Island (QARC) at the following time points:

- Pre-study Neck/Chest/Abdomen/pelvis CT; FDG-PET scan
- Post cycle 2 Neck/Chest/Abdomen/pelvis CT FDG-PET scan
- Post cycle 4 Neck/Chest/Abdomen/pelvis CT; FDG-PET scan
- Neck/Chest/Abdomen/pelvis CT; FDG-PET scan at progression (if different from the time points above).

Submission of Diagnostic Imaging data in digital format is required. Digital files must be in DICOM format. These files can be submitted via sFTP. Information for obtaining an sFTP account and submission instructions can be found at www.QARC.org. Follow the link labeled digital data. Alternatively, if sFTP is not feasible, the imaging may be burned to a CD and mailed to IROC RI (QARC) 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 (QARC) 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 (QARC)
640 George Washington Highway, Suite 201
Building B
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601
Web: http://www.qarc.org

8.4 Mobilization and Collection of Peripheral Blood Stem Cells

8.4.1 Description of Studies

One of the secondary aims of this study (See Section 1.2.3) is to document the proportion of patients able to mobilize sufficient stem cells after treatment with gemcitabine and brentuximab. This is a clinically relevant question because most patients eligible for this study will eventually go on to high-dose chemo with stem cell rescue. However, it is not yet proven that stem cells can be collected from patients treated with this regimen.

Autologous peripheral blood stem cells will be collected from consenting patients (both Parts A and B) after any cycle of therapy. Patients who had bone marrow involvement at the time of study enrollment must undergo repeat bone marrow biopsies (at least two sites) prior to stem cell collection. Stem cells will not be collected until the bone marrow biopsies are negative for disease involvement. Stem cells may be collected following ANY cycle of therapy, subsequent to the demonstration of negative bone marrow biopsies and at least 2 cycles of chemotherapy.

Institutional standard operating procedures should be used for the collection procedure. The following sections present suggested guidelines. See also Appendix IV.

8.4.2 Catheter Use

PBSC may be collected using a large bore double lumen central venous catheter that will allow the flow rates required for apheresis. Depending on institutional practices, an appropriate double-lumen leukapheresis-grade catheter may be placed prior to cycle 1 and used for medication administration, intravenous fluids, and transfusions, in addition to the apheresis procedure. Alternatively, a temporary peripherally inserted central leukapheresis-grade catheter can be placed prior to peripheral blood stem cell collection and removed following completion of the leukapheresis.

8.4.3 Stem cell mobilization with chemotherapy and G-CSF

During the mobilization cycle, treatment with granulocyte colony stimulating factor (G-CSF) should be started one day after the second dose of gemcitabine (i.e. on day 9). G-CSF should be administered daily, subcutaneously (preferred) or intravenously, at a dose of 10-16 micrograms/kg/day, and continuing until completion of PBSC collection. It is critical that G-CSF be given daily until PBSC collection is complete. If the WBC is > 60,000, decrease G-CSF dose to 5 micrograms/kg/day. The PBSC collection should be timed with the neutrophil rise. Institutions which time collections using circulating CD34 cell counts will generally begin when the CD34+ count is > 10 cells/μL. These guidelines are summarized in the table below. **The use of Neulasta is not allowed.**

Test	Result	Action
WBC	< 60,000/μL	• Continue G-CSF at 10μg/kg/d • Check ANC
	> 60,000/μL	• Decrease G-CSF to 5 mcg/kg
ANC	> 1000/μL	• Check CD34 count
	> 5000/μL	• Proceed with leukapheresis
CD34 count	> 10/μl	• Proceed with leukapheresis
	<10/μl	• Continue G-CSF • Repeat CD34 count in one day

Table 8.4.3. Suggested guidelines for G-CSF administration and stem cell harvesting based on peripheral white blood cell (WBC) count, absolute neutrophil count (ANC), and CD34+ counts.

Previous studies of mobilization with gemcitabine/vinorelbine showed a range of 4-14 days from first day of G-CSF to collection. Therefore, close monitoring in a patient with a significant left shift and/or a rapidly rising WBC count may provide an opportunity for earlier collection. It is suggested to monitor blood counts every other day in order to plan for the optimal timing of collection.

When stem cell collection is attempted, the subsequent cycle of therapy may be delayed a maximum of an additional seven days if necessary for adequate collection of stem cells.

8.4.4 Cell dose to be harvested

It is recommended that large volume apheresis be performed on all patients for each collection. During each leukopheresis procedure, the typical target volume of whole blood processed will be approximately 3-5 blood volumes.

A successful PBSC harvest is defined by the collection of at least 2 x10^6 CD34+ cells/kg within 5 collection days. If the designated cell dose/kg is not achieved, bone marrow harvest or repeat stem cell mobilization/collection is suggested for further patient management at the investigator's discretion.

The use of plerixifor for stem cell mobilization following failed conventional PBSC harvest is neither encouraged nor forbidden for patients treated on AHOD1221; however, its use should be documented.

8.5 Correlative Biology Studies (As of amendment 4, Part A was completed. This section is for Part B.)

8.5.1 Description of Studies and Assay

Biology studies from peripheral blood in all patients for Part B will be used to assess TARC expression and miRNA profiles, as well as to bank host DNA to examine FcRIIIγ polymorphisms in the event of brentuximab pulmonary toxicity. We hypothesize that TARC expression will correlate with reduction in tumor volume and may be a surrogate marker for early PET response. We also hypothesize that specific miRNA profiles will correlate with response to therapy.

8.5.1.1 *Thymus and Activation-Related Chemokine (TARC)*

TARC will be assessed as an early marker of treatment response and compared with functional imaging (PET) as an early marker of disease response.

8.5.1.2 *Circulating miRNA studies*

miRNAs are found in high abundance in the serum of patients and previous studies have shown that specific miRNAs correlate with treatment response.

All samples will be sent to the BPC, where they will be processed and batched and sent to the laboratory of Anke van den Berg, PhD (University Medical Center Groningen, The Netherlands) at the end of the study.

University Medical Center Groningen
Pathology & Medical Biology
HPC: EA10
Hanzeplein 1
9713 GZ Groningen
Netherlands
Phone 00-31-50-3611476
FAX 00-31-50-3619107

Shipment notification should be sent by the BPC to [redacted].

8.5.2 Sampling Schedule (See Appendix V)

Blood samples will be collected at baseline and prior to therapy on Day 1 of each subsequent cycle.

8.5.3 Sample Collection and Handling Instructions

Blood samples will be collected in all patients for Part B before treatment and prior to brentuximab vedotin infusion on Day 1 of each subsequent cycle. 5 mL will be collected in a gold-top serum separator tube (If serum separator tubes are unavailable, tubes with no preservative may be used instead) and 5 mL will be collected in into a heparinized tube (either Na-heparin or Lithium heparin are acceptable).

8.5.4 Sample Processing

No processing of the samples is required for analysis of TARC or miRNA profiling. Samples should be shipped the same day as collected, when possible. Samples that cannot be shipped the same day should be stored at 4°C and shipped as soon as possible. See Appendices V and VI.

8.5.5 Sample Labeling

Each tube must be labeled with the, patient's COG patient ID number, specimen type (blood) and the date the sample was drawn. Data should be recorded on the Peripheral Blood Studies Form in Appendix V and the Specimen Transmittal Form in Appendix VI, both of which must accompany the sample(s).

8.5.6 Sample Shipping Instructions

Samples should be shipped the same day they are collected when possible. See Appendices V and VI for sample shipping instructions.

9.0 DRUG INFORMATION

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

9.1 Brentuximab vedotin

(SGN35, Adcetris™, NSC#749710, IND# 117117) (11/9/2015)

9.1.1 Structure and molecular weight

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.

9.1.2 Supplied by:

Seattle Genetics, Inc. and the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

9.1.3 Formulation

The agent 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.

9.1.4 Storage

Store vial dry under refrigeration at 2-8°C (36-46°F) in the original carton to protect from light until reconstitution and use.

9.1.5 Solution Preparation

Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.

Please note that the dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.

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 SGN-35 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. SGN-35 solution is compatible in polyvinylchloride (PVC), ethylene vinyl acetate (EVA), polyolefin, or polyethylene.
4. Do not shake. Gently invert the syringe or bag to mix.
5. The prepared syringe or IV bag 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 syringe or IV bag for discoloration or floating particulates. Do not use the IV solution if the solution is discolored or/and have particulates.

9.1.6 Stability:

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.

9.1.7 Administration

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 syringe or IV bag does NOT need light protection during the IV administration.

Potential drug interaction: In vitro data indicates that the active metabolite of SGN-35, 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 SGN-35. In vitro, MMAE is a substrate of P-gp transporter and is not an inhibitor of P-gp. See Appendix VII for a list of CYP3A4 inducers and inhibitors.

Patient Care Implications:

- New signs and symptoms of CNS system abnormalities may indicate progressive multifocal leukoencephalopathy (PML).
- Tumor lysis syndrome, particularly in patients with highly proliferative tumors or high tumor burden prior to treatment.
- Infusion-related reactions, including anaphylaxis, may occur. Refer to protocol for the management of infusion-related reactions.
- Signs and symptoms of peripheral neuropathy such as tingling or numbness of the hands, feet, or any muscles weakness.
- Steven-Johnson syndrome
- High fever (≥ 100.5° F) or other signs of potential infection.

9.1.8 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 555 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 2.3, October 2, 2015[1]

Adverse Events with Possible Relationship to SGN-35 (brentuximab vedotin) (CTCAE 4.0 Term) [n= 555]			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)***
	Blood and lymphatic system disorders - Other (lymphadenopathy)		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dyspepsia		
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)[2]	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infections and infestations - Other (herpes zoster)		
	Lung infection		
Upper respiratory infection			***Upper respiratory infection (Gr 2)***
INVESTIGATIONS			
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		
	Weight loss		
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***

Adverse Events with Possible Relationship to SGN-35 (brentuximab vedotin) (CTCAE 4.0 Term) [n= 555]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Back pain		
	Bone pain		
	Musculoskeletal and connective tissue disorder - Other (muscle spasms)		
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		
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		
	Depression		
	Insomnia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
		Respiratory, thoracic and mediastinal disorders - Other (pulmonary toxicity)[3]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		
	Hyperhidrosis		
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		
		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]Hepatotoxicity may manifest as increased ALT/AST, bilirubin, alkaline phosphatase, and/or GGT.

[3]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 also 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 - Febrile neutropenia
CARDIAC DISORDERS - Myocardial infarction; Pericardial effusion; Sinus tachycardia
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Infusion related reaction; Non-cardiac chest pain
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (oral candidiasis); Meningitis; Pharyngitis; Sepsis; Sinusitis; Skin infection; Urinary tract infection
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Investigations - Other (blood LDH increased); Lymphocyte count decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness; Myositis; Neck pain
NEOPLASMS BENIGN, MALIGNANT, AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Myelodysplastic syndrome
NERVOUS SYSTEM DISORDERS - Dysesthesia; Encephalopathy; Seizure; Syncope
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (pyelonephritis)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (groin pain)
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome[3]; Pleural effusion[3]; Pneumothorax[3]; Productive cough; Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain)
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.

9.2 Agent Ordering and Agent Accountability

NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) 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), Curriculum Vitae, Supplemental Investigator Data Form (IDF), 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 investigator at that institution.

9.3 Clinical Drug Request

Active CTEP-registered investigators and investigator-designated shipping designees and

ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application at https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

9.4 Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record (DAR) Form. (See the CTEP home page at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage and to obtain a copy of the DARF and Clinical Drug Request form.)

9.5 Gemcitabine

2'-deoxy-2',2' difluorocytidine monohydrochloride, LY18801,Gemzar®) NSC #613327

9.5.1 Source and Pharmacology

Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the cytotoxic diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. Gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA. After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands. In CEM T lymphoblastoid cells, gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death. Gemcitabine pharmacokinetics are linear and are described by a 2-compartment model. Gemcitabine half-life for short infusions (< 70 minutes) ranged from 42 to 94 minutes, and the value for long infusions varied from 245 to 638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions. The lower clearance in women and the elderly results in higher concentrations of gemcitabine for any given dose. The volume of distribution was increased with infusion length. Volume of distribution of gemcitabine was 50 L/m^2 following infusions lasting < 70 minutes, indicating that gemcitabine, after short infusions, is not extensively distributed into tissues. For long infusions, the volume of distribution rose to 370 L/m^2, reflecting slow equilibration of gemcitabine within the tissue compartment. The maximum plasma concentrations of 2'-deoxy-2',2'-difluorodeoxyuridine (dFdU) (inactive metabolite) were achieved up to 30 minutes after discontinuation of the infusions and the metabolite is excreted in urine without undergoing further biotransformation. Over one week, 92% to 98% of a gemcitabine dose is excreted in urine. Unchanged drug constitutes only a small

portion of urinary excretion (about 5%), the remainder being dFdU. The metabolite did not accumulate with weekly dosing, but its elimination is dependent on renal excretion, and could accumulate with decreased renal function.

9.5.2 Formulation and Stability

Gemcitabine is available as a 200 mg white, lyophilized powder in a 10 mL size sterile single use vial and a 1000 mg white, lyophilized powder in a 50 mL size sterile single use vial. Store at controlled room temperature (20°-25°C, 68°-77°F). Excursions permitted between 15° and 30°C (59° and 86°F).

9.5.3 Guidelines for Administration

See Treatment and Dose Modification sections of the protocol.

To reconstitute, add 5 mL of NS to the 200 mg vial or 25 mL of NS to the 1000 mg vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL which includes the accounting for the displacement volume of the lyophilized powder. The total volume upon reconstitution will be 5.26 mL or 26.3 mL, respectively. Complete withdrawal of the vial contents will provide 200 mg or 1000 mg of gemcitabine**,** respectively. The appropriate amount of drug may be administered as prepared or further diluted with NS to concentrations as low as 0.1 mg/mL. Gemcitabine solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F). Solutions of reconstituted gemcitabine should not be refrigerated, as crystallization may occur. After reconstitution with NS, the pH of the resulting solution lies in the range of 2.7-3.3 and can cause irritation if administered through a peripheral line.

Previous investigations have shown that cellular accumulation of the active metabolite of gemcitabine is saturated at plasma concentrations above 10 to 20 μM[36,37], a concentration that is exceeded when gemcitabine is infused faster than 6 to 10 mg/m^2/min.[37,38] Accumulation of higher intracellular dFdCTP concentrations, which may result in an enhanced antineoplastic activity, cannot be achieved by higher dosage, but only by prolonged infusion time. Prolonged infusions are well-tolerated[39-44] and may provide increased clinical benefit over bolus administration. **Gemcitabine should therefore be infused over 100 minutes for this study.**[45]

9.5.4 Supplier

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

9.5.5 Toxicities (10/30/12)

The table below lists the toxicity profile of GEMCITABINE (IV)

Common (>20% of patients)	Alopecia, rash maculopapular, constipation, diarrhea, nausea, vomiting, anemia, white blood cell decreased, neutrophil count decreased, platelet count decreased, alkaline phosphatase increased, alanine aminotransferase increased, aspartate aminotransferase increased, bilirubin increased, infection[1], peripheral motor neuropathy, peripheral sensory neuropathy, paresthesia, hematuria, proteinuria, dyspnea, fatigue, fever, pain
Occasional (5-20% of patients)	Edema limbs, localized edema, hypotension, hyperglycemia, hypocalcemia, hypomagnesemia, anorexia, mucositis oral, pharyngeal mucositis, hemorrhage, bone pain, headache, somnolence, psychiatric disorders – other: mood disorders, serum creatinine increased, investigations – other: increased blood urea nitrogen, flu-like syndrome
Rare (<5% of patients)	Cardiac disorders, other: arrhythmias, heart failure, myocardial infarction, vasculitis, bullous dermatitis, skin infection, infusion site reaction, radiation recall reaction, febrile neutropenia, hepatic failure, hepatobiliary disorders – Other: sinusoidal obstruction syndrome, anaphylaxis, hearing impaired, arthrlagia, myalgia, hemolytic uremic syndrome, acute kidney injury, blood and lymphatic system disorders – Other: thrombotic microangiopathy, adult respiratory distress syndrome, bronchospasm, respiratory, thoracic and mediastinal disorders – Other: interstitial lung disease, pulmonary edema, pulmonary fibrosis, respiratory failure
Pregnancy/Lactation:	**Pregnancy Category D** Gemcitabine is embryotoxic causing fetal malformations (cleft palate, incomplete ossification) at doses of 1.5 mg/kg/day in mice (about 1/200 the recommended human dose on a mg/m^2 basis). Gemcitabine is fetotoxic causing fetal malformations (fused pulmonary artery, absence of gall bladder) at doses of 0.1 mg/kg/day in rabbits (about 1/600 the recommended human dose on a mg/m^2 basis). In mice, embryolethality was observed following doses of 0.25 mg/kg/day (approximately $1/1300^{th}$ the recommended human dose on a mg/m^2 basis). Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. It is not known whether gemcitabine or its metabolites are excreted in human milk.

[1]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Criteria for Removal from Protocol Therapy

a) Clinical (including physical examination or serum tumor markers) or radiographic evidence of progressive disease (See Section 12).
b) Adverse Events requiring removal from protocol therapy (See Section 6).
c) Refusal of further protocol therapy by patient/parent/guardian
d) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
e) Completion of 16 cycles of therapy.
f) Patients with CR after two cycles may go off protocol therapy for stem cell transplantation.
g) Patients with SD or any response may go off protocol therapy after the fourth cycle or after the response evaluation following any subsequent cycle of therapy.
h) Physician determines that continuing study therapy is not in the patient's best interest.
i) Repeated eligibility laboratory studies (CBC with differential, bilirubin, ALT (SGPT) or serum creatinine) are outside the parameters required for eligibility prior to the start of brentuximab vedotin and gemcitabine (See Section 8.1).
j) Development of second malignancy.
k) Study is terminated by Sponsor.
l) Pregnancy

Patients who are removed from protocol therapy during cycle 1 should continue to have the required observations in Section 8.1 until the originally planned end of the cycle or until all adverse events have resolved per Section 13.6.4, whichever happens LATER. The only exception is with documentation of the patient's withdrawal of consent. Patients who are removed from protocol therapy in subsequent cycles should have the necessary observations to ensure adequate clinical care.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Ongoing adverse events, or adverse events attributable to protocol therapy that emerge after the patient is removed from protocol therapy, but within 30 days of the last dose of investigational agent, must be followed and reported via RAVE and CTEP-AERS (if applicable). Serious adverse events that occur during the follow-up period (more than 30 days after the last administration of investigational agent) and have an attribution of possible, probable, or definite require reporting per Footnote 1 of Table A. Follow-up data will be required unless they meet the off study criteria below.

10.2 Off Study Criteria

a) Thirty days after the last dose of the investigational agent (patients on Part A not enrolled at the MTD).
b) The fifth anniversary of the date the patient was enrolled on this study (patients on Part A enrolled at the MTD and all patients enrolled on Part B)
c) Death
d) Lost to follow-up
e) Withdrawal of consent for any further required observations or data submission.
f) Enrollment onto another COG therapeutic (anti-cancer) study

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

Part A: Phase 1 dose-finding component
As of amendment 4, Part A was completed.

Part B: Phase 2 component
This study includes Part A (Phase 1) and Part B (Phase 2). During Part A, two dose levels of brentuximab vedotin were tested: 1.4 mg/kg (dose level 1) and 1.8 mg/kg (dose level 2). Initially, three evaluable patients were enrolled on dose level 1 and six on dose level 2. Since amendment #2, an expansion cohort of 6 patients have been enrolled onto dose level 2 using the revised definitions for dose-limiting toxicity. This cohort was evaluated separately from the six patients initially enrolled at dose level 2 for the purpose of determination of the MTD. None of these six patients experienced a non-hematologic dose limiting toxicity (DLT). One of these was found to be ineligible for evaluation of hematologic DLT, because filgrastim was administered during the first cycle of therapy in preparation for stem cell harvesting. None of the five remaining patients experienced a hematologic DLT. Per Section 11.4, dose level 2 is determined to be the recommended phase 2 dose, because the number of DLTs in this expansion cohort did not exceed one.

Patients treated on the Phase 1 component at dose level 2 will be included in analysis of response for Part B provided that they are eligible and evaluable for response. Part B will accrue up to 41 patients evaluable for the primary response endpoint. Considering a 15% rate for ineligible/invaluable patients, Part B may enroll a maximum of 48 patients.

The average accrual rate from the 2 prior COG studies on HL patients with first-relapse (AHOD00P1 and AHOD0521) was 27-30 patients per year excluding the initial 6 months delay for IRB approvals. Part B will be conducted COG group-wide. Given that certain relapsed patients with favorable prognosis will be excluded from participation on the study, we estimate it would take about 2.5-3 years to complete accrual for Part B (up to 41 response evaluable patients).

11.2 Definitions for Part A
As of amendment 4, Part A was completed.

11.2.1 Evaluable For Adverse Effects

Any patient who experiences DLT at any time during protocol therapy is considered evaluable for Adverse Effects. Patients without DLT who receive at least 85% of the prescribed dose per protocol guidelines and had the appropriate toxicity monitoring studies performed are also considered evaluable for Adverse Effects. Patients who are not evaluable for Adverse Effects at a given dose level during Cycle 1 will be replaced.

11.2.2 Maximum Tolerated Dose

The MTD will be the maximum dose at which fewer than one-third of patients experience DLT (See Section 5.5) during Cycle 1 of therapy. In the event that two DLTs observed out of 6 evaluable patients are different classes of Adverse Effects (e.g. hepatotoxicity and myelosuppression), expansion of the cohort to 12

patients will be considered if all of the following conditions are met:

- One of the DLTs does not appear to be dose-related
- The Adverse Effects are readily reversible
- The study chair, DVL statistician, DVL committee chair or vice chair, and IND sponsor all agree that expansion of the cohort is acceptable

Expansion will proceed according to the rules of the 3+3 design (Section 11.3): Three additional patients will be studied. If none of the initial three additional patients experiences DLT, the dose will be escalated.* If one of the initial three additional patients experiences DLT, expansion to a total of 12 patients will continue. If fewer than 1/3 of patients in the expanded cohort experience dose-limiting toxicities, the dose escalation can proceed.*

*If the expansion occurs in the last dose level, the recommended phase 2 dose has been defined and Part A will be closed.

11.3 Dose Escalation and Determination of MTD (Part A)

As of amendment 4, Part A was completed.

11.3.1 Three patients are studied at the first dose level.

11.3.2 If none of these three patients experience DLT, then the dose is escalated to the next higher level in the three subsequent patients.

11.3.3 If one of three patients experiences DLT at the current dose, then up to three more patients are accrued at the same level.

a) If none of these three additional patients experience DLT, then the dose is escalated in subsequent patients. If there are no further dose escalations, then the RP2D has been confirmed.

b) If one or more of these three additional patients experiences DLT, then patient entry at that dose level is stopped. (See Section 11.2.2 for exception to rule). Up to three more patients are treated at the next lower dose (unless six patients have already been treated at that prior dose).

11.3.4 If two or more of a cohort of up to six patients experience DLT at a given dose level, then the MTD has been exceeded and dose escalation will be stopped (see Section 11.2.2 for exception to rule). Up to three more patients are treated at the next lower dose (unless six patients have already been treated at that prior dose). The highest dose with less than two DLTs out of six evaluable patients will be the estimated MTD.

11.3.5 Using this dose escalation scheme, the probability of escalating to the next dose level, based on the true rate of DLT at the current dose, is given by the following table:

	True Adverse Effects at a Given Dose					
	10%	20%	30%	40%	50%	60%
Probability of Escalating	.91	.71	.49	.31	.17	.08

Thus, if the true underlying proportion of toxic events is 30% at the current dose, there is a 49% chance of escalating to the next dose.
In addition to determination of the MTD, a descriptive summary of all toxicities will be reported.

11.4 Evaluation of Expansion Cohort at Dose Level 2 Using Revised DLT Definitions (Amendment #2)

11.4.1 Three additional patients are studied at Dose Level 2.

11.4.2 If none or one of these three patients experience DLT, then up to three more patients are accrued at the same level.

11.4.3 If two or more of a cohort of up to six patients experience DLT at Dose Level 2, then the MTD has been exceeded, and the study will be closed to accrual (See Section 11.2.2 for exception to rule).

11.4.5 If ≤ one patient out of six experiences DLT, the MTD/RP2D has been defined. Part A will be closed and the study will continue to Part B.

11.5 Response Analysis for Part A

As of amendment 4, Part A was completed.

While the primary aim of Part A is to evaluate the toxicity of brentuximab vedotin in combination with gemcitabine, patients will have disease evaluations performed as indicated in Section 8.1. Disease response will be assessed according to the evaluation criteria in Section 12.0, and will be reported descriptively.

All these analyses will be descriptive and exploratory and hypotheses generating in nature.

11.6 Study Design for Part B

The primary aim for the Phase 2 component is to evaluate the CR rate among HL patients treated with 4 cycles of gemcitabine with brentuximab vedotin. In the adult Phase I and II trials, Brentuximab vedotin alone had an estimated CR by PET rate of 34% in HL patients. Six of 9 pediatric patients included in these trials achieved CR (2/5 HL and 4/4 ALCL).[16] In the prior COG study on the combination of Gemcitabine/Vinorelbine (AHOD0321), CR by CT was achieved in 6/25 (24%) evaluable patients at the end of treatment, and CR by PET criteria in 6/13 patients (46%) after 2 cycles. Based on these data, in Part B we expect to achieve a CR rate of about 60% after 4 cycles of brentuximab vedotin among HL patients, and will consider the study unsuccessful if the data suggests a CR rate that is significantly lower than 60% (such as 40%). The study adopts a Simon 2-stage MinMax rule: reject this combination and terminate the study if 11 or fewer CR are observed in the first 28 evaluable patients, and reject this combination if 20 or fewer CR are observed in a total of 41 evaluable patients. Type I error and type II error are both 0.1; in other words, this rule will reject gemcitabine with brentuximab vedotin 10% of the time when the true CR rate is 60%, and 90% of the time when the true CR rate is 40%. The expected sample size is 33.8 if the true CR rate is 40% and is 40.7 if the true CR rate is 60%.

Patients treated on the Phase 1 component, at dose level 2 (1.8 mg/kg) for brentuximab vedotin used in the Phase 2 component, will be included in Part B provided that they are eligible and evaluable for response (See Section 11.8). Enrollment will be stopped after Stage 1 to evaluate response for Stage 1 enrollments, and will only reopen to Stage 2 when

sufficient responses for Stage 1 are observed. However, if sufficient responses for Stage 1 are observed prior to reaching Stage 1 accrual target, enrollment will not be stopped after Stage 1 and will proceed directly to Stage 2.

The two stage design for Part B is illustrated below:

	Cumulative Number of Responses	Decision
Stage 1: Enter 28 evaluable patients	Up to 11	Terminate the trial because the agent is ineffective.
	12 or more	Proceed to Stage 2.
Stage 2: Enter 13 additional evaluable patients	Up to 20	Terminate the trial because the agent is ineffective.
	21 or more	Terminate the trial because the agent is effective.

11.7 **Methods of Analysis for Part B**

All patients treated on the phase 1 component, at dose level 2 (1.8 mg/kg) of brentuximab vedotin used in the Phase 2 component, will be included in the analyses provided they are eligible and evaluable for the particular endpoint (response, toxicity, etc.). CR and ORR after 4 cycles and at the end of treatment will be estimated. Toxicities among patients who received at least 1 dose of gemcitabine or brentuximab vedotin will be summarized by individual toxicity counts and incidence rate. The proportion of patients who were able to mobilize sufficient stem cells after treatment with gemcitabine/brentuximab vedotin will be estimated. Plasma level of TARC will be considered a continuous variable, and be summarized by standard descriptive statistics such as mean, standard deviation, median, and range. Plasma level of TARC after each cycle or the change in level of TARC from baseline will be compared between patients with CR vs. < CR by two-sample t-test or two-sample Wilcoxon rank sum test. Specific miRNA levels in serum will also be considered continuous variables and summarized by appropriate descriptive statistics. The association between response and miRNA profile will be explored by comparing the specific miRNA level or change over time between patients with CR vs. < CR by 2-sample tests such as 2-sample t-test or Wilcoxon rank sum test. Among patients who experience any pulmonary toxicity, the frequency of the FcγRIIIa-158 V/F polymorphism will be described.

11.8 **Evaluability for Response for Part B**

In Part B, each patient will receive a minimum of 4 cycles, except that per protocol patients might go off study therapy prior to cycle 4 if they have achieved CR or have PD. Primary endpoint for Part B is CR by the international harmonization criteria after 4 cycles. Complete responders are those who achieve CR any time during/after 4 cycles, except that a patient will be considered PD if becoming PD after CR during the first 4 cycles. A response of CR or PD prior to 4 cycles will be considered to be carried on as the 4-cycle response. Evaluable patients are those with disease evaluation after 4 cycles (including those do not actually complete 4 cycles but have a carried-over response of CR/PD), and those who complete at least 2 cycles and have disease evaluation after 2 cycles. In other words, a patient who had a response of non-CR/PD after cycle 2 but somehow did not complete 4 cycles per protocol and went off protocol prior to cycle 4 without a CR/PD will be considered evaluable and included in the analysis as non-CR.

In addition, all patients treated on Part A, at the dose selected for use in Part B (1.8 mg/kg), will be included in the final evaluation of response, provided they meet all eligibility criteria for Part B and are evaluable for response, as defined above.

Primary endpoint/analyses will be based on central review of response which will not be performed real time; treatment/clinical decisions will be based on institution assessment of response.

11.9 Evaluability for Toxicity

For Part B, all patients who received at least 1 dose of brentuximab vedotin or gemcitabine will be evaluable for toxicity and included in the toxicity tables and summaries. In addition, all patients treated on Part A, at the dose selected for use in Part B (1.8 mg/kg), will be included in the final toxicity summaries, provided they meet all eligibility criteria for Part B and are evaluable for toxicity, as defined above.

Monitoring for Excessive Pulmonary Toxicity during Part B. The incidence of brentuximab vedotin-related pulmonary toxicity will be monitored in all patients treated with at least one dose of gemcitabine with brentuximab vedotin at the Phase 2 dose level (1.8 mg/kg) of brentuximab vedotin on either Phase 1 or Phase 2. Therefore, the 41 response-evaluable patients for Part B will be included in this analysis plus some additional patients who were not evaluable for response but received at least one dose of the combination; the maximum number of patients for the analysis, which is the maximum number of patients on the study that can be treated at the final dose of brentuximab vedotin combining Phase 1 and 2, is likely 60 patients (up to 48 patients from Phase 2 plus 12 patients from Phase 1 per Amendment #2, unless the Phase 1 component at the final dose expands to 12 additional (total 18) patients according to Section 11.2.2 per Amendment #2 or there are Phase 1 patients at the final dose level who received one dose of combination but were not evaluable for DLT). Pulmonary toxicity will be defined by dyspnea ≥ Grade 3, hypoxia ≥ Grade 3 or pneumonitis ≥ Grade 2. There must be no evidence of other etiologies, including left atrial hypertension, congestive heart failure, infection, metabolic abnormalities, or cancer related causes (e.g. malignant pericarditis). A Bayesian rule is adopted for this monitoring. The prior distribution for the rate of pulmonary toxicity p is a Beta distribution with parameters $\alpha=1$ and $\beta=19$. This Beta distribution for the rate of pulmonary 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 $p \geq 5\%$ is 0.8 or higher, it will be considered compelling evidence that the pulmonary toxicity rate is unacceptable and the study will be referred to DSMC for review and consideration for early closure. This monitoring will be performed for every DSMC report during Part B, which occurs every 6 months during the first 2 years and once every year thereafter. Operationally, it will require, for example, ≥ 2/6, ≥ 3/20, ≥ 5/41, ≥ 5/54, or ≥ 6/60 patients with pulmonary toxicities 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. The study will tolerate at most 4 patients with pulmonary toxicities at the end with 41-54 patients or 5 patients with pulmonary toxicities with 55-60 patients. With a sample size of n=45, if the true rate of toxicity is 5%, 10%, or 15% respectively, the chance of observing 5 or more patients with pulmonary toxicities are 7%, 47%, and 83% respectively.

In addition, Grade 4 or higher toxicities will be reviewed on a case by case basis to see if changes in the protocol are warranted.

11.10 **Inclusion of Children, Women and Minorities**

The study is open to all participants regardless of gender or ethnicity. Review of accrual to past COG studies of new agents demonstrates the accrual of both genders and all NIH-identified ethnicities to such studies. Efforts will be made to extend the accrual to a representative population, but in a trial which will accrue a limited number of patients, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

11.11 **Gender and Minority Accrual Estimates**

Per Amendment #2, the Phase 1 part of the study may accrue a maximum of 24 patients. The Phase 2 part of the study may accrue a maximum of 48 patients. The maximum enrollment for the study is therefore 72 patients.

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	5	5	10
Not Hispanic or Latino	34	28	63
Ethnic Category: Total of all subjects	39	33	*72
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	1	4	5
Black or African American	6	5	11
Native Hawaiian or other Pacific Islander	1	0	1
White	31	24	55
Racial Category: Total of all subjects	39	33	*72

* These totals must agree

This distribution was derived from AHOD00P1 and AHOD0521.

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

12.2 Imaging Lesion Evaluation

Imaging guidelines and response criteria have been revised from previous COG protocols, including AHOD0831, AHOD0031, AHOD0431, CCG 5942, CCG 59704, POG 9425, and POG 9426 and reflect the recent work of the International Lymphoma Working Group's revised recommendations for malignant lymphoma.[47,48].

Establishing strict CT size criteria for presumptive lymphomatous nodal enlargement is complicated by a number of factors, including substantial size overlap between benign reactive lymphoid hyperplasia and malignant lymphadenopathy, interobserver measurement variability, obliquity of node orientation to the scan plane, multiplicity of criteria for size measurement (volumetric vs. bidimensional vs. unidimensional; short axis vs. long axis), variability of normal nodal size with body region and age. For children and younger adolescents, there are no established size limits for normal lymph nodes. Furthermore, in children reactive hyperplasia is common in the cervical, axillary, mesenteric, and inguinal regions, and may be associated with nodes up to 1.5-2 cm in diameter. In other anatomic regions, including the supraclavicular, retroperitoneal, iliac, mediastinal, and hilar regions, normal nodes are typically less than 1-1.5 cm. Despite these limitations, certain features suggest lymphomatous involvement, such as contiguous nodal clustering or matting, and nodal FDG avidity.

With these caveats in mind, the nodal size criterion used by previous HL protocols for newly diagnosed HL will be used for simplicity and consistency. Bulk disease will continue to be defined as a contiguous extramediastinal nodal aggregate that measures > 6 cm in the longest transverse diameter (transaxial measurement), a mediastinal mass where the tumor diameter is > 1/3 the maximal thoracic diameter, and/or macroscopic splenic nodules. For visceral organs (such as 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.). Lesions too small to characterize are considered indeterminate unless follow-up studies allow characterization or tissue sampling is performed.

Measurable disease indicates the presence of at least one measurable lesion. Superficial lesions (e.g., palpable lymphadenopathy) may be measurable by clinical exam. 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 ≥ 1.5 cm, regardless of the short axis. Lymph nodes with a long axis measuring between 1.1-1.5 cm are only considered abnormal if their short axis is ≥ 1.0 cm.

All measurable lesions should be measured in the axial plane on CT. All measurable lesions, up to a maximum of 6 lesions in total, representative of all involved organs, will be measured as target lesions at baseline and followed for response. Target lesions will be

selected on the basis of size (i.e., largest lesions) and suitability for accurate repeated measurements by imaging or clinical exam. Lesions will be recorded with size expressed as the PPD (product of perpendicular diameters). The PPD is obtained by multiplying the longest diameter of the lesion by the maximal diameter perpendicular to the longest diameter, and serves as a surrogate measurement of tumor volume, assuming the mass has a spherical or ellipsoid shape. The SPPD, or sum of the products of the perpendicular diameters, is obtained by adding the products of the perpendicular diameters of measured lesions.

Non-measurable assessable 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.

FDG-PET imaging will be performed as per clinical routine, adhering to the imaging guidelines discussed in Section 15. Although these FDG-PET guidelines are recommendations, a list of FDG PET imaging issues listed in Section 15 should be adhered to as much as possible in this clinical trial to allow for the uniformity of inter- and intra-patient FDG PET imaging and analysis needed for this study.

On FDG-PET imaging, the level of tumor uptake is assessed subjectively by visual inspection, in concordance with the International Working Group criteria.[47,48]. **Semi-quantitative assessment of response by determination of standardized uptake values (SUV) is not utilized in this study.** However, SUV measurements will be available for all PET scans and can be incorporated into reports as per routine clinical practice.

Part B: Central review of all imaging studies will take place at regular intervals, but not on a real-time schedule. Real time FDG-PET central review can be requested on a case-by-case basis for clarification or adjudication of conflicting institutional imaging studies which may be helpful for clinical assessment. Central review will include a visual qualitative assessment of tumor FDG PET positive or negative uptake based on the five-point Deauville scale [49] relative uptake to normal organ FDG activity (1 - no activity above surrounding background, 2 ≤ mediastinal blood pool, 3 ≤ liver and > mediastinal blood pool, 4 - moderately increased above liver, 5 – markedly increased compared to liver). Investigational imaging studies also incorporating semi-quantitative PET tumor SUV-based assessments will also be performed.

12.2.1 Lymph Nodes or Nodal Masses:

12.2.1.1 FDG-PET negative is defined as:

a. For moderately sized or large residual masses (≥ 2 cm in greatest transverse diameter by CT) regardless of their location, mild and diffusely increased FDG uptake with intensity lower than or equal to that of mediastinal blood pool structures (i.e. Deauville scale 1 or 2) should be considered negative. When possible use the ascending aorta or aortic arch for reference mediastinal blood pool.
b. For smaller residual masses or normal sized lymph nodes (< 2 cm in greatest transverse diameter by CT), any FDG uptake less than that of surrounding background activity.

12.2.1.2FDG-PET positive is defined as:

a. For moderately sized or large residual masses (≥ 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 (i.e. Deauville scale 3, 4, or 5) should be considered positive. When possible use the ascending aorta or aortic arch for reference mediastinal blood pool.
b. For smaller residual masses or normal sized lymph nodes (< 2 cm in greatest transverse diameter by CT), any FDG uptake more than that of surrounding background activity.

12.2.2 Lung Nodules:

12.2.2.1FDG-PET positive is defined as:

a. For new lung nodules that are ≥ 1.5 cm in greatest transverse diameter by CT, FDG uptake exceeding that of mediastinal blood pool structures (i.e. Deauville scale 3, 4, or 5) should be considered positive. When possible use the ascending aorta or aortic arch for reference mediastinal blood pool.
b. For new lung nodules < 1.5 cm in greatest transverse diameter by CT, due to partial volume averaging effects, any uptake is considered positive.

12.2.3 Hepatic and Splenic Lesions:

12.2.3.1FDG-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(i.e. Deauville scale 4, or 5), respectively, should be considered positive.
b. For hepatic of splenic lesions < 1.5 cm on CT, FDG uptake greater than that of normal liver or spleen parenchyma (i.e. Deauville scale 4, or 5), 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 focal lesions seen on CT will not be considered for FDG-PET response assessment. This is a modification of the IWG criteria as data regarding the threshold and significance of this finding is still limited in the published literature and potentially complicated by G-CSF effects. To balance the competing needs of maintaining time intensity of chemotherapy cycles and minimizing the G-CSF effects on FDG-PET interpretation, the FDG-PET scan should be obtained at the specified time points (See Section 8.1).

12.2.4 Bone Marrow FDG Uptake:

12.2.4.1FDG-PET positive is defined as:

a. Focal or multifocal FDG uptake in bone marrow. Diffusely increased bone marrow FDG uptake, regardless of level of uptake – including more intense than liver, is not considered positive. A negative bone marrow FDG-PET does not exclude bone marrow involvement or preclude a bone marrow biopsy assessment.

12.3 Response Criteria

Note: In the instance where there is widespread intense diffuse bone marrow uptake secondary to recent G-CSF administration (or other circumstance where the FDG bio-distribution is abnormal such as brown adipose tissue uptake) the FDG PET studies may not be of sufficient quality to adequately assess for response to therapy. In those circumstances CT criteria only should be used to assess for response to therapy. See Table 12.3 below for additional clarification of response criteria definitions.

12.3.1 Complete Response (CR):

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.
2. For patients with bone marrow involvement pre-treatment, negative bone marrow biopsies from at least two sites.
3. HL is typically FDG-avid. 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.
4. The spleen should be normal in size and shape; and pre-therapy nodules should have resolved. If the spleen was originally a site of involvement, there should be no persistent/residual focal FDG uptake in the spleen. (For assessment of diffuse spleen FDG uptake refer to comments on Hepatic and Splenic Lesions in Section 12.2.3.)
5. 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.

12.3.2 Partial Response (PR)

1. At least a 50% decrease in sum of the product of the perpendicular diameters (SPPD) of up to 6 of the largest dominant nodes or nodal masses. These nodes or masses should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. There should be no increase in the size of other lymph nodes.
3. Splenic and hepatic nodules must regress by 50% in their SPPD or, for single nodules, in the greatest transverse diameter.
4. There should be no measurable disease involving other organs.
5. No new sites of disease.
6. 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.

12.3.3 Stable Disease (SD)

1. A patient is considered to have stable disease if he/she fails to attain the response criteria necessary to achieve either a CR or PR, but does not fulfill the criteria for progressive disease (PD).
2. At sites where the FDG-PET scan was positive before therapy, the PET scan is still positive at prior sites of disease, but should not have any new sites of involvement.
3. No new areas of involvement on the post-therapy CT.

12.3.4 Relapsed Disease (after CR) or Progressive Disease (PD)

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.
2. At least 50% increase in the PPD of any of the focal organ lesions.
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.
4. Progression or relapse of non-measurable assessable disease at an extranodal site (e.g., pleural and/or pericardial effusions, bone lesions). Disease that is only assessable will still be considered positive for malignancy unless it is histologically negative.
5. Development of new measurable lesion(s) or new sites of assessable disease.

Table 12.3 Radiographic Response Criteria

PET result	CT result	Nodular Splenic Involvement	RESPONSE
Negative	Complete disappearance of all target nodal masses OR Mass of any size	Negative	Complete Response
Negative	Complete disappearance of all target nodal masses OR Mass of any size	Positive	Partial Response
Positive	Less than complete disappearance but greater than 50% decrease in sum of PPD of up to 6 of the largest nodal masses	Not applicable	Partial Response
Positive	Less than 50% decrease & less than 50% increase in sum of PPD of any of the nodal masses, with NO new lesions	Not applicable	Stable Disease
Positive	Greater than 50% increase in PPD of any of the nodal masses or development of new measurable lesions	Not applicable	Progressive Disease

12.3.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

13.1 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. Adverse events are reported in a routine manner at scheduled times during a trial. (Please follow directions for routine reporting provided in the data collection packet for this protocol). Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care. The following sections provide information about expedited reporting.

13.2 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; and 3) 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 (IND #117117) 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.

13.3 Steps to Determine If an Adverse Event Is To Be Reported In an Expedited Manner

Step 1: Identify the type of adverse event using the NCI CTCAE version 4.0. The descriptions and grading scales found in the revised CTCAE version 4.0 will be used for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

Step 2: Grade the adverse event using the NCI CTCAE.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:
Unrelated, Unlikely, Possible, Probable, and Definite.
Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported according to the instructions above.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in the current Specific Protocol Exceptions to Expedited Reporting (SPEER), as listed in the drug information section of the protocol, or as posted as an update on the protocol page of the COG Member's website.

Step 5: Review Table A in this section to determine if:

- there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring; and/or
- there are any protocol-specific exceptions to the reporting requirements.

Table A: Phase 1 and Early Phase 2 Studies: 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, 2]

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) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
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.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

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.
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 report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events 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 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

- Any medical event equivalent to CTCAE Grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration

on all reports.

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 1 Trials Utilizing an Agent under a CTEP-IND or Non-CTEP IND:

- Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence/progression must be reported via CTEP-AERS for an agent under a CTEP or non-CTEP IND agent per the timelines outlined in the table above.

- Myelosuppression, including Grade 4 lymphopenia, does not require expedited reporting whether it is expected or unexpected, unless it is associated with hospitalization.

- Grade 1 and 2 adverse events listed in the table below do **not** require expedited reporting via CTEP-AERS:

Category	Adverse Events
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Anemia
GASTROINTESTINAL DISORDERS	Constipation
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Chills
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Edema Limbs
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Infusion related reaction
METABOLISM AND NUTRITION DISORDERS	Anorexia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Back pain
NERVOUS SYSTEM DISORDERS	Dizziness
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Alopecia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Rash maculo-papular

- See also the Specific Protocol Exceptions to Expedited Reporting (SPEER) in Section 9.1.8 of the protocol.

As referenced in the CTEP Adverse Events Reporting Requirements, an AE that resolves and then recurs during a subsequent cycle does not require CTEP-AERS reporting unless (1) the Grade increases; or (2) hospitalization is associated with the recurring AE.

13.4 **When to Report an Event in an Expedited Manner**

- Some adverse events require notification **within 24 hours** (refer to Table A) to NCI via the web at:
  http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf
  (Telephone the Investigational Drug Branch (IDB) at: **240-276-6565** within 24 hours of becoming aware of the event if the CTEP-AERS 24-Hour Notification web-based application is unavailable) and by telephone call to the Study Chair. Once internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

- **Upon occurrence of pulmonary toxicity, as defined in Section 6.2.6, study therapy should be held, and the Study Chair and Research Coordinator should be notified within 48 hours.**

- When the adverse event requires expedited reporting, submit the report **within 5 or 7 calendar days** of learning of the event (refer to Table A).

- Expedited AE reporting for this study must only use CTEP-AERS. An expedited AE report must be submitted electronically via CTEP-AERS at: https://eapps-ctep.nci.nih.gov/ctepaers

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

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting and are located on the CTEP website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
All appropriate treatment areas should have access to a copy of the CTCAE.

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 (eg, 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 # 626-303-1768; 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.**

13.6 Definition of Onset and Resolution of Adverse Events

Note: These guidelines below are for reporting adverse events on the COG data submission forms and do not alter the guidelines for CTEP-AERS reporting.

13.6.1 If an adverse event occurs more than once in a course (cycle) of therapy only the most severe grade of the event should be reported.

13.6.2 If an adverse event progresses through several grades during one course of therapy, only the most severe grade should be reported.

13.6.3 The duration of the AE is defined as the duration of the highest (most severe) grade of the Adverse Effects.

13.6.4 The resolution date of the AE is defined as the date at which the AE returns to baseline or less than Grade 1, whichever level is higher (note that the resolution date may therefore be different from the date at which the grade of the AE decreased from its highest grade). If the AE does not return to baseline the resolution date should be recorded as "ongoing."

13.6.5 An adverse event that persists from one course to another should only be reported once unless the grade becomes more severe in a subsequent course. An adverse event which resolves and then recurs during a different course, must be reported each course it recurs.

13.7 Other Recipients of Adverse Event Reports

13.7.1 Events that do not meet the criteria for CTEP-AERS reporting (See Section 13.2) should be reported at the end of each cycle using the forms provided in the data form packet (See Section 14.1).

13.7.2 COG will forward reports and supporting documentation to the Study Chair, to the FDA (when COG holds the IND) and to the pharmaceutical company (for industry sponsored trials).

13.7.3 Adverse events determined to be reportable must also be reported according to the local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

13.8 Reporting Secondary AML/MDS

All cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) that occur in patients on NCI-sponsored trials following their chemotherapy for cancer must be reported to the Investigational Drug Branch (IDB) of the NCI Cancer Therapy Evaluation Program (CTEP) via CTEP-AERS and included as part of the second malignant neoplasm reporting requirements for this protocol (see data submission packet). Submit the completed CTEP-AERS report within 14 days of an AML/MDS diagnosis occurring after treatment for cancer on NCI-sponsored trials.

Note: The AML/MDS Secondary Reporting form is no longer available on the CTEP website. In lieu of this form, AML/MDS events are now to be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either:

1) Leukemia secondary to oncology chemotherapy,
2) Myelodysplastic syndrome, or
3) Treatment-related secondary malignancy.

Non-treatment related cases of AML/MDS for CTCAE v4.0 should be reported using "Neoplasms benign, malignant and unspecified (including cysts and polyps) - Other,

specify."
To grade a non-life-threatening event for "Myelodysplastic syndrome", use "Neoplasms benign, malignant and unspecified (including cysts and polyps) - Other, specify" where the specified term is MDS.

Note: If a patient has been enrolled in more than one NCI-sponsored study, the CTEP-AERS report must be submitted for the most recent trial.

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

13.9 Reporting Pregnancy, Fetal Death, and Death Neonatal

When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or Neonatal loss", the Pregnancy Information Form should be completed and faxed along with any additional medical information to (301) 230-0159. (Appendix VII). The potential risk of exposure of the fetus to the investigational agent should be documented in the "Description of Event" section of the CTEP-AERS report.

13.9.1 Pregnancy

- Patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic. For this reason, pregnancy occurring on study or within 6 months following the last dose of study therapy should be reported in an expedited manner via CTEP-AERS as "Pregnancy, puerperium and perinatal conditions - Other (Pregnancy) under the Pregnancy, puerperium and perinatal conditions SOC and reported as Grade 3.

- There is a possibility that the sperm of male patients treated on studies involving possible teratogenic agents may have been damaged. For this reason, pregnancy in partners of men on study should also be reported and followed as described in this section.

- Pregnancy should be followed up until the outcome of the pregnancy is known at intervals deemed appropriate by her physicians. The "Pregnancy Information Form" should be used for all follow-ups. If the baby is born with a birth defect or other anomaly, then a second CTEP-AERS report is required

13.9.2 Fetal Death

- Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

- Any fetal death should be reported expeditiously, as Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions SOC.

- A fetal death should NOT be reported as "Fetal death," a Grade 5 event

under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

13.9.3 Death Neonatal

- Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

- A neonatal death should be reported expeditiously as Grade 4 "General disorders and administration- Other (neonatal loss)" under the General disorders and administration SOC.

- Neonatal death should NOT be reported as "Death neonatal" under the General disorders and administration SOC, a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.

13.10 **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, routine reporting will include all toxicities reported via CTEP-AERS and all Grade 4 and higher hematologic Adverse Events, all Grade 3-4 and higher non-hematologic Adverse Events, and all respiratory, peripheral neuropathy, and skin of any grade.

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

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

14.1 Categories of Research Records

Research records for this study can be divided into three categories

1. Non-computerized Information: Roadmaps **(Roadmaps were for Part A only),** Pathology Reports, Surgical Reports. These forms are uploaded into RAVE.

2. Reference Labs, Biopathology Reviews, and Imaging Center data: These data accompany submissions to these centers, which forward their data electronically to the COG Statistics & Data Center.

3. Computerized Information Electronically Submitted: All other data will be entered in RAVE with the aid of schedules and worksheets (essentially paper copies of the OPEN AND RAVE screens) provided in the data form packet.

See separate Data Form Packet, which includes submission schedule.

14.2 **CDUS**

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. 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

14.3 **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) 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/industry) 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 investigational 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 investigational 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 NIH, 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 investigational 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 investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively 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.

14.4 Data and Safety Monitoring Plan

Data and safety is ensured by several integrated components including the COG Data and Safety Monitoring Committee.

14.4.1 Data and Safety Monitoring Committee

This study will be monitored in accordance with the Children's Oncology Group policy for data and safety monitoring of Phase 1 and 2 studies. In brief, the role of the COG Data and Safety Monitoring Committee is to protect the interests of patients and the scientific integrity for all Phase 1 and 2 studies. The DSMC consists of a chair; a statistician external to COG; one external member; one consumer representative; the lead statistician of the developmental therapy scientific committee; and a member from the NCI. The DSMC meets at least every 6 months to review current study results, as well as data available to the DSMC from other related studies. Approximately 6 weeks before each meeting of the

Phase 1 and 2 DSMC, study chairs will be responsible for working with the study statistician to prepare study reports for review by the DSMC. The DSMC will provide recommendations to the COG Developmental Therapeutics Chair and the Group Chair for each study reviewed to change the study or to continue the study unchanged. Data and Safety Committee reports for institutional review boards can be prepared using the public data monitoring report as posted on the COG Web site.

14.4.2 Monitoring by the Study Chair and Developmental Therapeutics Leadership for Part A. **This is for Part A only. As of amendment 4, Part A was completed.**

The study chair will monitor the study regularly and enter evaluations of patients' eligibility, evaluability, and dose limiting toxicities into the study database. In addition, study data and the study chair's evaluations will be reviewed by the Developmental Therapeutics Chair, Vice Chair and Statistician on a weekly conference call.

15.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

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 per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

As of Dec 2009, only CT and MRI guidelines are posted on the COG website so the imaging representative on the study committee should be contacted for input. The following COG website posted materials may be useful:

CT and MRI guidelines are available on the COG Member site at:
https://members.childrensoncologygroup.org/_files/reference/RefMaterial/DiagnosticImagingGuidelines_MRI&CT.pdf

For PET scan guidelines please refer to the NCI guidelines for the recommended set of procedures for the acquisition and analysis of 18F-FDG PET scans of patients participating in NCI-sponsored diagnostic and therapeutic clinical trials, which can be found at the following link: http://imaging.cancer.gov/reportsandpublications/publications/Clinical-Trials-Guidelines

The following guidelines are recommendations but follow generally accepted standards for FDG PET or PET/CT imaging protocols, allowing for individual institutional variations. However, 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:

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.
2) Patients should be fasted for at least 4 hours before [^{18}F]FDG administration.

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.
4) PET imaging should begin at 60 ± 10 min after injection of [^{18}F]FDG.
5) For follow-up PET imaging of the same patient, all attempts should be made to image the patient on the same PET/CT scanner.
6) Patient's measured height and weight on the day of the PET scan be recorded for each imaging session.
7) 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)
8) DICOM PET/CT or PET images be available for transfer to COG for Phase II central review.[50]

Please refer to the American College of Radiology (ACRIN) PET Core Laboratory Standard Operating Procedures, which is also adapted from the NCI consensus recommendation,[50] at the following web link for more detailed information, unless otherwise specified below. (http://www.acrin.org/CORELABS/PETCORELABORATORY/PETSOPS/tabid/484/Default.aspx)

15.1 **Pregnancy**

All female patients ≥ 10 years of age should be asked about their pregnancy potential prior to FDG injection. Females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method. 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.

15.2 **Recommended Technique**

Patients should be fasted for at least 4 hours before [^{18}F]FDG administration. 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 the 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 (with ultrashort acting glucose 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.

15.3 FDG Dosing and Injection

[^{18}F]FDG is administered intravenously at a dose of 0.140 to 0.200 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.

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.

15.4 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. If positron-emitting transmission sources are used, we recommend 2-3 minutes per bed position for segmented attenuation correction. With a dedicated NaI PET system, attenuation correction should be done with a Cs-137 source per manufacturer recommendations. With a combined PET/CT scanner, attenuation correction should be done with CT data per manufacturer recommendations. If the COG institution routinely adjusts the CT dose used for attenuation correction it can be adjusted to mA based on weight of patient using the following guidelines if at all possible to limit the CT radiation dose to the patient:

0 to 100 lbs.	use 40 mA	201 to 300 lbs.	use 120 mA
101 to 150 lbs.	use 60 mA	301 to 400 lbs.	use 160 mA
151 to 200 lbs.	use 80 mA		

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 (which use lower energy photons) or FDG imaging may be performed on the

day preceding any of these other nuclear medicine studies.

Emission data must be collected for at least 5 minutes per bed position for BGO, LSO, and GSO systems operated in the 2-D mode; at least 3 minutes per bed position for BGO, LSO, and GSO systems operated in the 3-D mode; and at least 6 minutes per bed position for NaI systems. Images will be corrected for scatter, random events, and dead-time losses using manufacturer's software. Bed positions should be overlapped to avoid large changes in sensitivity at the joints between the bed positions.

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.

15.5 **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.

15.6 **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%. [^{18}F]FDG should be produced in a GMP facility according to FDA required standard-operating-procedures for clinical use.

15.7 **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), which 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. Daily quality assurance includes a simplified chi-square test to assure consistent performance of the PET scanner. The calculation provides a quantitative means of monitoring drift of the scanner electronics with time. A blank scan is also performed daily for later attenuation correction. Either of these measurements may be viewed routinely as an additional measure of performance. A liquid-filled or standardized sealed-source cylinder phantom is used monthly to validate the quantitative accuracy of the images against a dose calibrator. The dose calibrator is itself calibrated daily against standards for constancy and annually for accuracy using NIST-traceable standards. Each month, fine gain calibration of all detectors in the PET system will be performed, followed by recalculation of the sensitivity normalization factors for the scanner.

Transmission scans, each 2-3 minutes in duration for segmented attenuation correction, will be obtained with a rotating Ge-68/Ga-68 rod source emission scan (alternatively, attenuation measurement may be performed with a Cs-137 source or with CT data from a combined PET/CT scanner, in accordance with manufacturer's recommendations). An algorithm to correct for activity in the field of view should be used for processing of these post-injection transmission images, if provided by the vendor. Then the corresponding emission images can be obtained as appropriate (time per bed position for specific detector crystal type and acquisition mode detailed above in the PET Scanning Protocol section). Alternatively, the individual emission and transmission scans may be acquired in alternating fashion. The PET images will be reconstructed by standard vendor-provided reconstruction algorithms, using either filtered back projection with a Hanning filter (frequency cutoff 0.6 x Nyquist [Nq] = 0.3 cycle/pixel) or the manufacturer's recommended iterative reconstruction algorithm with an appropriate filter.

Segmentation of transmission images should be used for attenuation correction. Emission data will be corrected for randoms, dead-time and scatter using vendor-provided algorithms. Multiple-bed position studies must be corrected for radioactive decay. The emission images will be reconstructed both with and without attenuation correction.

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APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

Karnofsky		Lansky	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

APPENDIX II: CTEP AND CTSU REGISTRATION PROCEDURES

CTEP REGISTRATION PROCEDURES

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

CTSU REGISTRATION PROCEDURES

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

Requirements for AHOD1221 Site Registration:

- CTSU IRB Certification (for sites not participating via the CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)
- CTSU RT Facilities Inventory Form
  NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy

component must participate in the IROQ Houston monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

Submitting Regulatory Documents:
Submit completed forms along with a copy of your IRB Approval to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Checking Your Site's Registration Status:
Check the status of your site's registration packets by querying the RSS site registration status page of 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

APPENDIX III: CORRELATIVE STUDIES GUIDE (AS OF AMENDMENT 4, PART A IS CLOSED. THIS IS ONLY FOR PART B.)

Correlative Study	Appx.	Tube Type	Blood Volume per Sample	Volume Cycle 1
Peripheral Blood Studies[a] (TARC, miRNA)	IV & V	Serum separator[b]	5 mL	**5 mL**
	IV & V	Heparinized[c]	5 mL	**5 mL**
Total Volume Cycle 1				**10 mL**

a. In all patients for Part B.
b. If serum separator tubes are unavailable, tubes with no preservative may be used instead.
c. Either Na-heparin or Lithium heparin tubes may be used.

APPENDIX IV: GUIDELINES FOR PERIPHERAL BLOOD STEM CELL (PBSC) COLLECTION PROCEDURE (AS OF AMENDMENT 4, PART A IS CLOSED. THIS IS ONLY FOR PART B.)

Personnel

PBSC should be collected by an experienced team that regularly collects apheresis components. The collection team should consist of at least one physician and two or more individuals experienced in the collection of apheresis components and in the management of apheresis donors. At least one person should be experienced in the management of children. The PBSC collections should be performed in a facility with a pediatric intensive care unit and adequate provision for the emergency care of children.

Apheresis machine

The Cobe Spectra or the Fenwal CS 3000+ is recommended because the continuous flow centrifugation devices are better tolerated in pediatric patients than discontinuous flow machines. Institutional SOPs for the apheresis procedure should be followed.

Priming

Priming of the machine prior to collection should be with ACD and saline according to manufacturer's directions. For patients less than 20-25 kg, a secondary prime with IRRADIATED, leukocyte-reduced red blood cells should be done. The use of an in-line blood warmer on the return line is recommended.

Anticoagulant

Anticoagulant to be used is ACD in a ratio sufficient to prevent extracorporeal clotting. Heparin is not recommended for the collection of PBSC unless symptoms of hypocalcemia preclude the use of sufficient ACD.

Whole Blood Flow Rate

In general, it is desirable to process the required volume of blood in the shortest possible time. Catheter size and/or tolerance of the citrate anticoagulant may be the rate-limiting factors in children. The following guidelines are the whole blood flow rates that can be expected to be achieved in children:
< 2 years (< 15 kg) 20-30 ml/min
2-5 yrs (15-20 kg) 30-40 ml/min
>5 years (> 20 kg) 40-60 ml/min

PBSC Collection Methodology

Typically apheresis for stem cell collection is established at 2-3x total blood volume (TBV) of donor/recipient. This volume will vary, however, and with extended large volume apheresis the cell collection can plateau and begin to decline. For optimum collection, twice TBV should be the minimum volume processed. Repeated leukaphereses should be performed daily for a maximum of 5 days until collection goals are met. Peripheral blood circulating CD34 levels can be monitored to determine optimal apheresis time points. When standard volume leukapheresis procedures are used to collect components to be infused following myeloablative therapy, 1-5 collections are generally required. Large volume eukapheresis procedures are those in which the volume of whole blood processed per procedures is >4-5x TBV (>15L TBV). Protocol-specific collection goals may be met with a single collection procedure.

Collection Goals

The collection goal for autologous PBSC intended to rescue a patient following myeloablative therapy (total, all collections) is a minimum of 2 X 10^6 CD34+ cells/kg. It is suggested that the optimum collection goal should be 5 x10^6 CD34+ cells/kg, stored in at least 2 alliquots of cells, with 2-3 x10^6 CD34+ cells/kg stored as backup for delayed engraftment.

Patient Monitoring
Patients should be observed continuously during the collection procedure by personnel experienced in the nursing care of children and familiar with the standard operation of the apheresis device. Care is required to ensure that the connections between the patient and the machine are not covered with blankets. Vital signs should be taken and recorded, and observations recorded periodically in compliance with institutional policy.

Recommended laboratory tests should include of the following:
Pre-apheresis: WBC, differential; hematocrit, platelet count, serum calcium.
Post-apheresis: Hematocrit, platelet count, serum calcium.

Vascular Access
Continuous flow centrifugation machines require two sites of vascular access. Recommended methods of achieving this access include: two peripheral venous lines, two central venous lines, one peripheral and one central venous line, or one double lumen central venous catheter. One arterial line (for withdrawal) with one venous line (for blood return) is acceptable.

PBSC MOBILIZATION WITH CHEMOTHERAPY PLUS GROWTH FACTOR
Filgrastim administration should begin 24 hours after the second gemcitabine dose in a cycle of chemotherapy, at an increased dose of 10-16 mcg/kg/dose until completion of peripheral stem cell collection (See Section 8.4). Filgrastim should be discontinued after collections are complete.

PBSC COMPONENTS
Each PBSC collection should be monitored with the following:
Culture for bacterial and fungal contamination
Nucleated cell count and differential
CD34+ cell enumeration

Each PBSC collection should be processed and cryopreserved on the day of collection. Processing and cryopreservation methods to be employed should be those demonstrated to reproducibly result in successful hematopoietic reconstitution following marrow ablative therapy.

Positive selection for CD34+ cells, if employed, must be done using a device and reagents approved by the FDA for this indication or under an appropriate IND or IDE.

APPENDIX V: PERIPHERAL BLOOD STUDIES FORM (AS OF AMENDMENT 4, PART A IS CLOSED. THIS IS ONLY FOR PART B.)

COG Pt ID # _____ ACC # _____ BPC # _____
Please do not write patient names on this form or on samples.

Cycle 1, Day 1 Date: |__/__|__/__|__/__| Dose Level: _____mg/kg Dose administered: _____mg

Blood samples (10 ml) will be collected in all patients for part B before treatment and prior to brentuximab vedotin infusion on Day 1 of each subsequent cycle. 5 mL will be collected in a gold-top serum separator tube[1], and 5 mL will be collected in into a heparinized (either Na-heparin or Lithium heparin) tube. Samples may be collected in the same line as drugs are infused.

[1] If serum separator tubes are unavailable, red top tubes with no preservative may be used instead.

Date of the last brentuximab administration |__/__|__/__|__/__| **Dose Administered: _____mg**

Cycle	Scheduled Sample Collection Time	Actual Date Sample Collected	Actual Time Sample Collected
Cycle#_____	Prior to Day 1 infusion	____/____/____	|__|__| : |__|__|

Sample Shipment Procedures

One copy of this Biology Study Form should be uploaded into RAVE. A second copy should be sent with the samples to the BPC along with the specimen transmittal form (Appendix VI) at:

Biopathology Center
Nationwide Children's Hospital
Protocol AHOD1221
700 Children's Drive, WA1340
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897

Samples should be shipped the same day they are collected when possible. Record the date that the sample is collected and the date of the last brentuximab administration. If blood cannot be shipped the day of collection, please store at 4ºC until shipped the next business day.

Ship samples by Federal Express Priority Overnight using a Federal Express shipping label obtained through the BPC Kit Management application. Ship blood on Monday-Friday for a Tuesday-Saturday delivery. It is recommended to ship sample with 1-2 ice packs in non-winter months (April – October) to avoid heat-damage during transport.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date: _____

APPENDIX VI: BPC SPECIMEN TRANSMITTAL FORM FOR PERIPHERAL BLOOD STUDIES (AS OF AMENDMENT 4, PART A IS CLOSED. THIS IS ONLY FOR PART B.)

1) A Specimen Transmittal Form should accompany every shipment of specimen(s) to the Biopathology Center.
   a.) Include one form per patient per shipment
   b.) Document the number and type(s) of specimen(s) sent in shipment (see below)
2) COG patient ID and BPC number must be recorded on each Specimen Transmittal Form for identification purposes.
3) The blood must be labeled with a COG patient ID number, specimen type and the date sample was drawn.

PATIENT/SPECIMEN INFORMATION

Patient Initials (L,F):_____ Date of Birth:_____ (mm/dd/yyyy) Study #:_____

Diagnosis Date:_____ (mm/dd/yyyy) COG PT_ID #:_____ Diagnosis:_____

Institution of Treatment:_____ Primary Site:_____

Inst. # _____ Contact Person: _____

Stage (if applicable):_____

Telephone #:_____

Fed Ex (or other) Tracking Number:_____

Permission Questions:

Patient agreed to participate in the AHOD1221 biology studies. ____Yes ____No ___ N/A

Biopathology Number							P					**(Specimens will NOT be banked without a BPC #)**

Specimen Obtained at

Cycle	Scheduled Sample Collection Time	Actual Date Sample Collected	Actual Time Sample Collected
Cycle#_____	Prior to Day 1 infusion	___/___/___	__|__| : |__|__|

Record Specific Tube Type (e.g, Gold-top serum separator, red-top, sodium heparin, lithium heparin) and Number of each tube present in shipment.

Tube Type: _____ # of tubes _____

Tube Type: _____ # of tubes _____

SPECIMEN SHIPPED TO:	FORM:
	1) Send original form with specimen **2) Retain a copy in patient file at institution**

All samples sent to the BPC will be batched and sent to the laboratory of [redacted] ([redacted] University Medical Center Groningen, The Netherlands) at the address listed in Section 8.5.1 at the end of the study.

APPENDIX VII: PREGNANCY INFORMATION FORM

Attach to CTEP-AERS 5-Day Report

PREGNANCY INFORMATION FAX
FACSIMILE TRANSMISSION
Ticket Number:_____

Study #:
SAF FAX NO: (301) 230-0159
ALTERNATE FAX NO: (301) 897-7404

Initial Report Date: DD - MMM - YY	Follow-up Report Date: DD - MMM - YY
Principal Investigator:	Reporter:
Reporter Telephone #:	Reporter FAX #:

Investigator Number | Subject Number

Complete all of the investigator and subject number boxes provided. Use leading zeros, when necessary, to complete all expected boxes.

Example: Investigator #407 would be filled in as: 0 0 4 0 7

Subject Initials

Record the first letter of the subject's first, middle and last name, in that sequence. If the subject has no middle name, enter a dash.

Example: A - C

Subject's Sex: ☐ Female ☐ Male	Subject's Weight: _____ kg	Subject's Date of Birth: DD - MMM - YYYY

Subject's Ethnicity (check one only): ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Not Available

Subject's Race (check all that apply): ☐ American Indian or Alaska Native ☐ Asian ☐ Black or African American ☐ Native Hawaiian or Other Pacific Islander ☐ White ☐ Not Available

Study Drug:	Study Drug Start Date: DD - MMM - YY Study Drug Stop Date: DD - MMM - YY OR ☐ Study Drug Continuing		
Dose:	Route:	Frequency:	Kit #:

First Day of Last Menstrual Period: DD - MMM - YY Estimated Date of Delivery: DD - MMM - YY

Method of Contraception (check all that apply):
☐ Oral Contraceptive Pills ☐ Condoms ☐ Periodic Abstinence ☐ Progestin Injection or Implants ☐ Spermacide
☐ Diaphragm ☐ Intrauterine Device (IUD) ☐ Tubal Ligation ☐ Other, specify:_____

Reproductive History: ☐ Gravida _____ ☐ Para _____

Tests performed during pregnancy: ☐ None ☐ Unknown
☐ CVS Results: ☐ Normal ☐ Abnormal
☐ Amniocentesis Results: ☐ Normal ☐ Abnormal
☐ Ultrasound Results: ☐ Normal ☐ Abnormal

Pregnancy Outcome
Was pregnancy interrupted? ☐ Yes ☐ No
If yes, specify: ☐ Elective Termination ☐ Spontaneous Abortion ☐ Ectopic
Date of Termination: DD - MMM - YY
If pregnancy was **not** terminated, specify pregnancy outcome (and provide infant outcome information)
☐ Vaginal Birth: ☐ Premature ☐ Term OR ☐ C-Section: ☐ Scheduled ☐ Emergency Date of Delivery: DD - MMM - YY
Infant outcome information: ☐ Normal ☐ Abnormal

Additional Case Details (if needed):

NOTE: For an initial reporting fax both the Pregnancy CTEP-AERS Report and this additional Pregnancy Information Form. For follow-up reporting, fax only this Pregnancy Information Form. See Section 13.7.

APPENDIX VIII: CYP3A4 INDUCERS AND INHIBITORS

Patients should be monitored for potential drug-interaction when administered drugs known to be a strong CYP3A4 inhibitor/inducer with SGN-35. The use of the following medications should be avoided during protocol therapy if reasonable alternatives exist. This is not an inclusive list; please refer to other resources such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx for additional information.

Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors	Other Inhibitors	Inducers
Clarithromycin	Aprepitant	Cimetidine	Amiodarone	Barbiturates
Indinavir	Diltiazem		Bocepravir	Carbamazepine
Itraconazole	Erythromycin		Chloramphenicol	Efavirenz
Ketoconazole	Fluconazole		Ciprofloxacin	Glucocorticoids*
Nefazodone	Grapefruit		Delaviridine	Modanfinil
Nelfinavir	Grapefruit juice		Fluvoxamine	Nevirapine
Posaconazole	Verapamil		Imatinib	Oxcarbazepine
Ritonavir			Mifepristone	Phenobarbital
Saquinavir			Norfloxacin	Phenytoin
Telithromycin			Norfluoxetine (fluoxetine)	Pioglitazone
			Star fruit	Rifabutin
			Telaprevir	Rifampin
			Voriconazole	St. John's wort

*Refer to Section 7.5 regarding use of corticosteroids.

APPENDIX IX: 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 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.*

Gemcitabine

Drugs that may interact with gemcitabine*
o Clozapine, natalizumab, leflunomide, tofacitinib, warfarin

Food and supplements that may interact with gemcitabine**
• Echinacea • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

**Sometimes these drugs are used with gemcitabine on purpose. Discuss all drugs with your doctor.*

Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.* ***The list above does not include everything that may interact with your chemotherapy. Talk to your doctor before starting any new medications, over-the-counter medicines, or herbal supplements and before making a significant change in your diet.

APPENDIX X: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY (Part B only)
(for children from 7 through 12 years of age)

A Study of Brentuximab Vedotin and Gemcitabine for Children with Hodgkin Disease

1. We are asking you to take part in a research study because you have Hodgkin disease that didn't get better with treatment or that has come back after treatment. 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. A research study is when doctors work together to try out new ways to help people who are sick.

2. Children who are part of this study will be will be treated with chemotherapy. Everyone in this study will be treated with two chemotherapy drugs used to treat Hodgkin disease. These drugs are: brentuximab vedotin and gemcitabine. After every 2 cycles of treatment, we will look at changes on scans (called CT and PET scans) to measure how the cancer is responding to therapy.

3. 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 but we don't know for sure if there is any benefit of being part of this study.

4. 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. Other things may happen to you that we don't yet know about.

5. 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.

6. As part of this study, we will collect additional blood. These studies will help us better understand Hodgkin disease and why some people respond to treatment better than other people. The blood draws would be taken when other standard blood tests are being performed.

INFORMATION SHEET REGARDING RESEARCH STUDY (Part B only)
(for teens from 13 through 17 years of age)

A Study of Brentuximab Vedotin and Gemcitabine for Children with Hodgkin Disease

1. We are asking you to take part in a research study because you have Hodgkin disease that either didn't get better with your treatment or came back after the end of treatment. 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. A research study is when doctors work together to try out new ways to help people who are sick.

2. Children and teens who are part of this study will be will be treated with chemotherapy. Everyone in this study will be treated with two chemotherapy drugs used to treat Hodgkin disease. These drugs are: brentuximab vedotin and gemcitabine. After every 2 cycles of treatment, we will look at changes on scans (called CT and PET scans) to measure how the cancer is responding to therapy.

3. 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.

4. 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. Also, the use of brentuximab vedotin and gemcitabine may cause complications. Other things may happen to you that we don't yet know about.

5. 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.

6. As part of this study, we will collect additional blood. These studies will help us better understand Hodgkin disease and why some people respond to treatment better than other people. The blood draws would be taken when other standard blood tests are being performed.