A Phase I-II Trial of Brentuximab Vedotin Plus Rituximab as Frontline Therapy for Patients with Lymphomas Associated with Immunosuppression

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Rituximab

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LIST OF ABBREVIATIONS

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CRR	Complete Response Rate
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse Large B-Cell Lymphoma
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EFS	Event-Free Survival
H&P	History & Physical Exam
HRPP	Human Research Protections Program
HIV	Human Immunodeficiency Virus
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
mTOR	Mammalian Target of Rapamycin
NCI	National Cancer Institute
NHL	Non-Hodgkin Lymphoma
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
p.o.	per os/by mouth/orally
PR	Partial Response
PRR	Partial Response Rate
RP2D	Recommended phase II dose
QOD	Every other day
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
WBC	White Blood Cells

STUDY SCHEMA

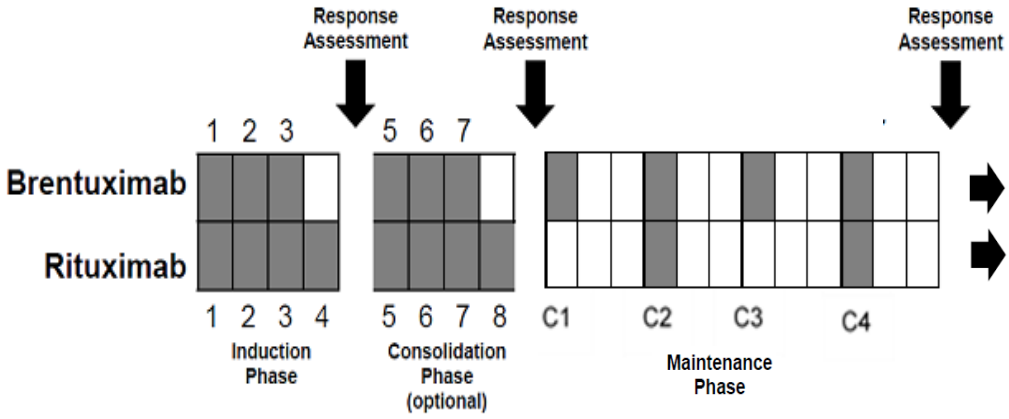
-DLT period (Phase I only): 21 days of induction
-Duration of treatment (Phase I and II): one year, or until POD (whichever occurs first)
-Primary objective assessment: toxicity after week 4 treatment (Phase I only); scans after induction treatment and/or after consolidation treatment (if applicable) (Phase II only)

Phase I
Untreated immunosuppressed lymphoma → **Register** N= 3-9 →
-Brentuximab vedotin
1.2 mg/kg IV weekly x 3*, then 1.8 mg/kg IV q 3 weeks
-Rituximab
375 mg/m2 IV weekly x 4* then q 6 weeks

Phase II
Untreated Immunosuppressed lymphoma → **Register** N= 24 →
-Brentuximab vedotin
(Dose based upon results of Phase I)
-Rituximab
375 mg/m2 IV weekly x 4* then q 6 weeks

*This may be repeated once at discretion of treating investigator; see Section 4.0 (TREATMENT PLAN) for details.

DOSING SCHEMA (in weeks, continued for one year total, or until POD)



STUDY SUMMARY

Title	A Phase I-II Trial of Brentuximab Vedotin Plus Rituximab as Frontline Therapy for Patients with Lymphomas of Immunosuppressed States
Version Date	June 14, 2017 (Amendment 8)
Protocol Number	NU 12H09
Phase	I/II
Methodology	Open-label, single-arm
Study Duration	Approximately 30 months
Study Center(s)	Northwestern University, University of Chicago
Objectives	**Primary objectives:** **Phase I:** Evaluate the safety of brentuximab vedotin and rituximab in patients with immunosuppressed lymphoid malignancies and to determine the recommended phase II dose (RP2D) of the combination. **Phase II:** Evaluate the efficacy of brentuximab vedotin and rituximab in patients with immunosuppressed lymphoid malignancies. **Secondary objectives:** **Phase II:** 1. Further evaluate the frequency and severity of toxicity. 2. Further evaluate the efficacy as measured by one-year PFS and OS. 3. Determine the effects of the combination of brentuximab vedotin and rituximab on markers of EBV activation and proliferation. 4. Further evaluate efficacy as measured by time to initiation of cytotoxic chemotherapy. 5. Further evaluate efficacy as measured by observed rates of graft rejection. **Exploratory objectives (Phase I and II):** Correlate response and outcomes with CD30 expression and EBV markers and levels.
Number of Subjects	Phase I: 3-9 patients; Phase II: 24 patients
Diagnosis and Main Inclusion Criteria	Adult patients with non-Hodgkin's lymphoma (NHL) related to an immunosuppressed state
Study Product(s), Dose, Route, Regimen	Brentuximab vedotin 1.2 mg/kg IV once weekly for 3 weeks, then 1.8 mg/kg IV once every 3 weeks Rituximab 375 mg/m^2 IV once weekly x 4, then once every 6 weeks
Duration of administration	1 year

Statistical Methodology	Our null hypothesis is that the combination of rituximab and brentuximab vedotin will yield no difference in the ORR as compared to that observed with historical treatments. The historical ORR for both PTLD and EBV-related lymphoma of the elderly, when treated with rituximab (with or without chemotherapy) is estimated at approximately 50% [1, 2]. Therefore, the optimal two-stage design to test the null hypothesis that $P = 0.50$ versus the alternative that $P \geq 0.70$ (the hypothesized ORR to rituximab plus brentuximab vedotin) has an expected sample size of 24. Under these conditions, if the combination is actually not significantly more efficacious, there is a < 0.05 probability (also known as the alpha value) of concluding that it is. If the combination is actually significantly more efficacious, there is a < 0.20 probability (also known as the beta value) of concluding that it is not. Early futility may be declared, such that if 8 or fewer responses are observed among the first 15 patients enrolled, the trial will be stopped and considered no more efficacious than therapy with rituximab alone.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

It is estimated that in 2010, there were 65,540 cases of NHL in the United States, and 20,210 deaths from the disease [3]. Diffuse Large B-Cell Lymphoma (DLBCL) is the most common sub-type of NHL, with approximately 20,000 new cases in the United States each year [3]. Chemo-immunotherapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) remains the standard first-line treatment, and autologous stem cell transplant (ASCT) is generally the preferred second-line treatment [4]. However, there remain many patients for whom ASCT is not an option, or who relapse in spite of this therapy, and approximately one-third of all patients with DLBCL will die due to disease relapse [5]. Therefore, additional treatment options are urgently needed.

Chronic immunosuppression significantly increases the risk for a variety of lymphoid malignancies, which together are termed post-transplant lymphoproliferative disorder (PTLD) [6]). These immunosuppressed patients face a roughly six-fold lifetime risk of lymphoma as their immunocompetent counterparts [7]. Although DLBCL is the most common histology, other NHL, as well as Hodgkin's Lymphoma (HL) and Peripheral T-Cell Lymphoma (PTCL) have all been reported as PTLD variants. Up to 86% of PTLD cases are EBV-associated [8]; roughly 70% express CD30 [9]; and over 80% of PTLD express CD20 [10]. Although the PTLD population is a heterogeneous one, outcomes are generally poor, with recent larger studies reporting median overall survival (OS) in the range of 2-4 years [11, 12]. Rates of treatment-related mortality (TRM) of 13-50% are moreover striking when these patients are treated with early cytotoxic chemotherapy [13-15], and significant rates of graft rejection have also been reported in this context

EBV-related lymphoma of the elderly is likewise a variant of aggressive B-cell lymphoma [16], and represents up to 10% of cases of DLBCL in adults [17]. In a vain similar to PTLD, immuno-senescence (of the elderly) is thought to put patients at risk for these tumors, which generally co-express CD20 and CD30. Prognosis is generally poor, including when treated with cytotoxic chemotherapy [18]. Therefore, better and more tolerable treatment strategies are needed for PTLD and EBV-related lymphoma of the elderly.

Finally, autoimmune disorders, such as systemic lupus erythematosis (SLE), rheumatoid arthritis (RA), and Sjogren's syndrome (SS) are associated with increased risk of development of NHL, whether related to underlying disruption of normal lymphocyte function [19], or to pharmacologic immunosupression with cytotoxic agents or TNFα inhibitors [20]. Interestingly, studies suggest that about 60% of such cases are indolent lymphomas [19, 21], suggesting that anthracycline-based therapy may be unnecessarily toxic. No standard of therapy exists for such types of lymphoma, and treatment is generally guided by histologic subtype and the clinical status of the patient.

1.2 Study Agent(s) Background and Associated Known Toxicities

1.2.1 **Brentuximab vedotin**

1.2.1.1 Toxicity Summary

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Brentuximab vedotin was studied as monotherapy in 160 patients in two phase 2 trials. Across both trials, the most common adverse reactions (≥20%), regardless of causality, were neutropenia, peripheral sensory neuropathy, fatigue,

nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough and vomiting.

Brentuximab vedotin was studied in 102 patients with HL in a single arm clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg intravenously every 3 weeks. Median duration of treatment was 27 weeks (range, 3 to 56 weeks). The most common adverse reactions (≥20%), regardless of causality, were neutropenia, peripheral sensory neuropathy, fatigue, upper respiratory tract infection, nausea, diarrhea, anemia, pyrexia, thrombocytopenia, rash, abdominal pain, cough, and vomiting.

Brentuximab vedotin was studied in 58 patients with sALCL in a single arm clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg intravenously every 3 weeks. Median duration of treatment was 24 weeks (range, 3 to 56 weeks). The most common adverse reactions (≥20%), regardless of causality, were neutropenia, anemia, peripheral sensory neuropathy, fatigue, nausea, pyrexia, rash, diarrhea, and pain. Following IV administration of 1.2 mg/kg brentuximab vedotin, both patients with hepatic impairment (Child-Pugh class A-C) and patients with severe renal impairment (CrCl ,30 mL/min) exhibited a trend toward moderate decreases in ADC exposure and increases in MMAE exposure.

In addition, there is an ongoing contemporaneous phase II clinical trial using consecutive doses (q 3 weeks 1.8mg/kg) of 'single-agent' SGN-35 for elderly Hodgkin lymphoma patients. As of May 1st 2013, 11 out of 30 planned patients have been enrolled. Ten of the 11 patients have received at least 2 cycles of SGN-35, while 4 patients have received at least 6 SGN-35 cycles. Among these patients, there have been 2 SAEs identified (grade 3 orthostatic hypotension and weakness in patient with pre-existing resected astrocytoma; and grade 3 alkaline phosphatase elevated in patient with baseline fatty liver disease and baseline abnormal LFTs).

Pancreatitis

Seattle Genetics performed an internal qualitative review of all cases of acute pancreatitis received to date. As of June 30, 2013, Seattle Genetics has received reports of acute pancreatitis associated with brentuximab vedotin resulting in an incidence of 0.27% from clinical trials and compassionate use programs, and 0.07% from other patient exposures. The occurrence of acute pancreatitis contributed to a fatal outcome in 2 patient reports. Most of the cases of acute pancreatitis were reported within the first or second cycle of dosing. Some of the cases were confounded by other possible contributory factors, including concomitant administration of medications known to be associated with pancreatitis and possible alternate etiologies (including cholelithiasis and pancreatic lymphoma progression).

Re-challenge experiences with subsequent dose(s) after resolution of the acute pancreatitis were documented in 3 patients. Two of these patients did not experience recurrent acute pancreatitis on re-challenge. In the third patient, 2 re-challenge doses were administered without an elevation in pancreatic enzyme; however, following the third re-challenge dose, the patient experienced a recurrence of acute pancreatitis.

Based on this information, Seattle Genetics considers acute pancreatitis to be an important potential risk associated with brentuximab vedotin dosing, and will be updating the Investigator's Brochure accordingly.

Infusion reactions
Two cases of anaphylaxis were reported in phase 1 trials. There were no Grade 3 or 4 infusion-related reactions reported in the phase 2 trials, however, Grade 1 or 2 infusion-related reactions were reported for 19 patients (12%). The most common adverse reactions (≥2%) associated with infusion-related reactions were chills (4%), nausea (3%), dyspnea (3%), pruritus (3%), pyrexia (2%), and cough (2%).

Serious adverse reactions
In the phase 2 trials, serious adverse reactions, regardless of causality, were reported in 31% of patients receiving Brentuximab vedotin. The most common serious adverse reactions experienced by patients with HL include peripheral motor neuropathy (4%), abdominal pain (3%), pulmonary embolism (2%), pneumonitis (2%), pneumothorax (2%), pyelonephritis (2%), and pyrexia (2%). The most common serious adverse reactions experienced by patients with sALCL were septic shock (3%), supraventricular arrhythmia (3%), pain in extremity (3%), and urinary tract infection (3%). Other important serious adverse reactions reported included one case each of PML, Stevens-Johnson syndrome and tumor lysis syndrome.

Dose modifications
Adverse reactions that led to dose delays in more than 5% of patients were neutropenia (14%) and peripheral sensory neuropathy (11%).

Discontinuations
Adverse reactions led to treatment discontinuation in 21% of patients. Adverse reactions that led to treatment discontinuation in 2 or more patients with HL or sALCL were peripheral sensory neuropathy (8%) and peripheral motor neuropathy (3%).

1.2.1.2 Mechanism of Action

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

1.2.1.3 Pharmacodynamics

The effect of brentuximab vedotin (1.8 mg/kg) on the QTc interval was evaluated in an open label, single-arm study in 46 evaluable patients with CD30-expressing hematologic malignancies. Administration of brentuximab vedotin did not prolong the mean QTc interval > 10 ms from baseline. Small increases in the mean QTc interval (< 10 ms) cannot be excluded because this study did not include a placebo arm and a positive control arm.

1.2.1.4 Pharmacokinetics

The pharmacokinetics of brentuximab vedotin were evaluated in phase I trials and in a population pharmacokinetic (PK) analysis of data from 314 patients. The pharmacokinetics of 3 analytes were determined: the ADC, MMAE, and total antibody. Total antibody had the greatest exposure and had a similar PK profile as the ADC. Hence, data on the PK of the ADC and MMAE have been summarized.

1.2.1.5 Absorption

Maximum concentrations of ADC were typically observed close to the end of infusion. A multiexponential decline in ADC serum concentrations was observed with a terminal half-life of approximately 4 to 6 days. Exposures were approximately dose proportional from 1.2 to 2.7 mg/kg. Steady-state of the ADC was achieved within 21 days with every 3-week dosing of brentuximab vedotin, consistent with the terminal half-life estimate. Minimal to no accumulation of ADC was observed with multiple doses at the every 3-week schedule. The time to maximum concentration for MMAE ranged from approximately 1 to 3 days. Similar to the ADC, steady-state of MMAE was achieved within 21 days with every 3 week dosing of brentuximab vedotin. MMAE exposures decreased with continued administration of brentuximab vedotin with approximately 50% to 80% of the exposure of the first dose being observed at subsequent doses.

1.2.1.6 Distribution

In vitro, the binding of MMAE to human plasma proteins ranged from 68-82%. MMAE is not likely to displace or to be displaced by highly protein-bound drugs. In vitro, MMAE was a substrate of P-gp and was not a potent inhibitor of P-gp.

In humans, the mean steady state volume of distribution was approximately 6-10 L for ADC.

1.2.1.7 Metabolism

In vivo data in animals and humans suggest that only a small fraction of MMAE released from brentuximab vedotin is metabolized. In vitro data indicate that the MMAE metabolism that occurs is primarily via oxidation by CYP3A4/5. In vitro studies using human liver microsomes indicate that MMAE inhibits CYP3A4/5 but not other CYP isoforms. MMAE did not induce any major CYP450 enzymes in primary cultures of human hepatocytes.

1.2.1.8 Elimination

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

1.2.1.9 Effects of Gender, Age and Race

Based on the population PK analysis, gender, age and race do not have a meaningful effect on the PK of brentuximab vedotin.

1.2.1.10 Clinical studies

1.2.1.10.1 Hodgkin's Lymphoma

The efficacy of brentuximab vedotin in patients with HL who relapsed after ASCT was evaluated in one open-label, single-arm, multicenter trial of 102 patients treated with 1.8 mg/kg of brentuximab vedotin IV over 30 minutes every 3 weeks. An independent review facility performed efficacy evaluations which included overall response rate (ORR = complete remission [CR] + partial remission [PR]) and duration of response as defined by clinical and radiographic measures including computed tomography (CT) and positron-emission tomography (PET) [in accordance with the 2007 Revised Response Criteria for Malignant Lymphoma (modified)]. The 102 patients ranged in age from 15-77 years (median, 31 years) and most were female (53%) and white (87%). Patients had received a median of 5 prior therapies including ASCT.

1.2.1.10.2 Systemic Anaplastic Large Cell Lymphoma (sALCL)

The efficacy of brentuximab vedotin in patients with relapsed sALCL was evaluated in one phase II open-label, single-arm, multicenter trial. This trial included patients who had sALCL that was relapsed after prior therapy. Fifty-eight patients were treated with 1.8 mg/kg of brentuximab vedotin administered IV over 30 minutes every 3 weeks. An independent review facility performed efficacy evaluations which included ORR (CR + PR) and duration of response as defined by clinical and radiographic measures as defined by the 2007 Revised Response Criteria for Malignant Lymphoma (modified). The 58 patients ranged in age from 14-76 years (median, 52 years) and most were male (57%) and white (83%). Patients had received a median of 2 prior therapies; 26% of patients had received prior ASCT. Fifty percent (50%) of patients were relapsed and 50% of patients were refractory to their most recent prior therapy. Seventy-two percent (72%) were anaplastic lymphoma kinase (ALK)-negative.

1.2.1.10.3 Relapsed/refractory CD30+ malignancies

The safety and efficacy of weekly dosing of brentuximab vedotin was also evaluated in patients with relapsed and refractory CD30+ hematologic malignancies [21]. The agent was administered intravenously on Days 1, 8, and 15, of each 28-day cycle at doses ranging from 0.4 to 1.4 mg/kg, with doses escalated in increments of 0.2 mg/kg until dose-limiting toxicity (DLT) was observed. The MTD was 1.2 mg/kg. The most common adverse events were peripheral sensory neuropathy, fatigue, nausea, diarrhea, arthralgia, and pyrexia; and the majority of events were mild to moderate in severity. Tumor regression occurred in 85% of patients and the overall objective response rate was 59% (n = 24), with 34% (n = 14) complete remissions. We are using this data as rationale for weekly induction therapy of brentuximab vedotin.

1.2.2 **Rituximab**

1.2.2.1 Toxicity Summary

The following serious adverse reactions were observed in patients treated with Rituximab, when used either alone or with other agents:

- Infusion reactions
- Tumor lysis syndrome
- Mucocutaneous reactions
- Progressive multifocal leukoencephalopathy
- Hepatitis B reactivation with fulminant hepatitis
- Infections
- Cardiac arrhythmias
- Renal toxicity
- Bowel obstruction and perforation

The most common adverse reactions of rituximab (incidence ≥ 25%) observed in clinical trials of patients with NHL were infusion reactions, fever, lymphopenia, chills, infection, and asthenia. The most common adverse reactions of rituximab (incidence ≥ 25%) observed in clinical trials of patients with CLL were: infusion reactions and neutropenia. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

1.2.2.2 Mechanism of Action

Rituximab binds specifically to the antigen CD20 (human B-lymphocyte-restricted differentiation antigen, Bp35), a hydrophobic transmembrane protein with a molecular weight of approximately 35 kD located on pre-B and mature B lymphocytes. The antigen is expressed on approximately 90% of B-cell NHL, but the antigen is not found on hematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissues. CD20 regulates n early step(s) in the activation process for cell cycle initiation and differentiation, and possibly functions as a calcium ion channel. CD20 is not shed from the cell surface and does not internalize upon antibody binding. Free CD20 antigen is not found in the circulation. Twenty [22] of 38 B cells are believed to play a role in the pathogenesis of rheumatoid arthritis (RA) and associated chronic synovitis. In this setting, B cells may be acting at multiple sites in the autoimmune/inflammatory process, including through production of rheumatoid factor (RF) and other autoantibodies, antigen presentation, T-cell activation, and/or proinflammatory cytokine production. The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effector functions to mediate B-cell lysis *in vitro*. Possible mechanisms of cell lysis include complement-dependent cytotoxicity [23] and antibody-dependent cell mediated cytotoxicity (ADCC). The antibody has been shown to induce apoptosis in the DHL-4 human B-cell lymphoma line. Rituximab binding was observed on lymphoid cells in the thymus, the white pulp of the spleen, and a majority of B lymphocytes in peripheral blood and lymph nodes. Little or no binding was observed in the non-lymphoid tissues examined.

1.2.2.3 Pharmacodynamics

In NHL patients, administration of rituximab resulted in depletion of circulating and tissue-based B cells. Among 166 patients in Study 1, circulating CD19-positive B cells were depleted within the first 3 weeks with sustained depletion for up to 6 to 9 months post treatment in 83% of patients. B-cell recovery began at approximately 6 months and median

B-cell levels returned to normal by 12 months following completion of treatment. There were sustained and statistically significant reductions in both IgM and IgG serum levels observed from 5 through 11 months following rituximab administration; 14% of patients had IgM and/or IgG serum levels below the normal range.

1.2.2.4 Pharmacokinetics

PKs were characterized in 203 NHL patients receiving 375 mg/m^2 rituximab weekly by IV infusion for 4 doses. Rituximab was detectable in the serum of patients 3 to 6 months after completion of treatment. The PK profile of rituximab when administered as 6 infusions of 375 mg/m^2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone. Based on a population PK analysis of data from 298 NHL patients who received rituximab once weekly or once every three weeks, the estimated median terminal elimination half-life was 22 days (range, 6.1 to 52 days). Patients with higher CD19-positive cell counts or larger measurable tumor lesions at pretreatment had a higher clearance. However, dose adjustment for pretreatment CD19 count or size of tumor lesion is not necessary. Age and gender had no effect on the PK of rituximab. PKs were characterized in 21 patients with CLL receiving rituximab according to the recommended dose and schedule. The estimated median terminal half-life of rituximab was 32 days (range, 14 to 62 days).

1.2.2.5 Clinical Studies

Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL

The safety and effectiveness of rituximab in relapsed, refractory CD20+ NHL were demonstrated in 3 single-arm studies enrolling 296 patients.

1.2.2.5.1 Study 1

A multicenter, open-label, single-arm study was conducted in 166 patients with relapsed or refractory, low-grade or follicular, B-cell NHL who received 375 mg/m^2 of rituximab given as an IV infusion weekly for 4 doses. Patients with tumor masses greater than 10 cm or with more than 5000 lymphocytes/uL in the peripheral blood were excluded from the study. The median time to onset of response was 50 days. Disease-related signs and symptoms (including B-symptoms) resolved in 64% (25/39) of those patients with such symptoms at study entry.

1.2.2.5.2 Study 2

In a multicenter, single-arm study, 37 patients with relapsed or refractory, low-grade NHL received 375 mg/m^2 of rituximab weekly for 8 doses.

1.2.2.5.3 Study 3

In a multicenter, single-arm study, 60 patients received 375 mg/m^2 of rituximab weekly for 4 doses. All patients had relapsed or refractory, low-grade or follicular, B-cell NHL and had achieved an objective clinical response to rituximab administered 3.8-35.6 months (median 14.5 months) prior to retreatment with rituximab. Of these 60 patients, 5 received more than one additional course of rituximab.

1.2.2.5.4 Bulky Disease

In pooled data from studies 1 and 3, 39 patients with bulky (single lesion greater than 10 cm in diameter) and relapsed or refractory, low-grade NHL received 375 mg/m^2 of rituximab weekly for 4 doses.

The safety and effectiveness of rituximab in previously untreated, low-grade or follicular, CD20+ NHL were demonstrated in 3 randomized, controlled trials enrolling 1,662 patients.

1.2.2.5.5 Study 4

A total of 322 patients with previously untreated follicular NHL were randomized (1:1) to receive up to eight 3-week cycles of CVP chemotherapy alone (CVP) or in combination with 375 mg/m^2 rituximab (R-CVP) on Day 1 of each cycle in an open-label, multicenter study. The main outcome measure of the study was progression-free survival (PFS) defined as the time from randomization to the first of progression, relapse, or death. Twenty-six percent (26%) of the study population was over 60 years of age, 99% had Stage III or IV disease, and 50% had an International Prognostic Index [24] score greater than 2. The PFS results based on investigator assessment of progression were similar to those obtained by the independent review assessment.

1.2.2.5.6 Study 5

An open-label, multicenter, randomized (1:1) study was conducted in 1,018 patients with previously untreated follicular NHL who achieved a response (CR or PR) to rituximab in combination with chemotherapy. Patients were randomized to rituximab as single-agent maintenance therapy, 375 mg/m^2 every 8 weeks for up to 12 doses or to observation. Rituximab was initiated at 8 weeks following completion of chemotherapy. The main outcome measure of the study was PFS, defined as the time from randomization in the maintenance/observation phase to progression, relapse, or death, as determined by independent review. Of the randomized patients, 40% were over 60 years of age, 70% had Stage IV disease, 96% had ECOG performance status 0-1, and 42% had FLIPI scores of 3–5. Prior to randomization to maintenance therapy, patients had received R-CHOP (75%), R-CVP (22%), or R-FCM (3%); 71% had a complete or unconfirmed complete response and 28% had a partial response. PFS was longer in patients randomized to rituximab as single agent maintenance therapy (HR: 0.54, 95% CI: 0.42, 0.70). The PFS results based on investigator assessment of progression were similar to those obtained by the independent review assessment.

1.2.2.5.7 Study 6

A total of 322 patients with previously untreated low-grade, B-cell NHL who did not progress after 6 or 8 cycles of CVP chemotherapy were enrolled in an open-label, multicenter,

randomized trial. Patients were randomized (1:1) to receive rituximab, 375 mg/m^2 IV infusion, once weekly for 4 doses every 6 months for up to 16 doses or no further therapeutic intervention. The main outcome measure of the study was PFS defined as the time from randomization to progression, relapse, or death. Thirty-seven percent (37%) of the study population was over 60 years of age, 99% had Stage III or IV disease, and 63% had an IPI score of 2 or greater. There was a reduction in the risk of progression, relapse, or death (hazard ratio estimate in the range of 0.36 to 0.49) for patients randomized to rituximab as compared to those who received no additional treatment.

Diffuse Large B-Cell NHL (DLBCL)
The safety and effectiveness of rituximab were evaluated in 3 randomized, active-controlled, open-label, multicenter studies with a collective enrollment of 1854 patients. Patients with previously untreated DLBCL received rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone [25] or other anthracycline-based chemotherapy regimens.

1.2.2.5.8 Study 7

A total of 632 patients age ≥ 60 years with DLBCL (including primary mediastinal B-cell lymphoma) were randomized in a 1:1 ratio to treatment with CHOP or R-CHOP. Patients received 6 or 8 cycles of CHOP, each cycle lasting 21 days. All patients in the R-CHOP arm received 4 doses of rituximab 375 mg/m^2 on Days -7 and -3 (prior to Cycle 1) and 48-72 hours prior to Cycles 3 and 5. Patients who received 8 cycles of CHOP also received rituximab prior to Cycle 7. The main outcome measure of the study was PFS, defined as the time from randomization to the first of progression, relapse, or death. Responding patients underwent a second randomization to receive rituximab or no further therapy. Among all enrolled patients, 62% had centrally confirmed DLBCL histology, 73% had Stage III-IV disease, 56% had IPI scores ≥ 2, 86% had ECOG performance status of ≤ 2, 57% had elevated LDH levels, and 30% had two or more extranodal disease sites involved. Analysis of results after the second randomization in Study 7 demonstrates that for patients randomized to R-CHOP, additional rituximab exposure beyond induction was not associated with further improvements in progression-free survival or overall survival.

1.2.2.5.9 Study 8

A total of 399 patients with DLBCL, age ≥ 60 years, were randomized in a 1:1 ratio to receive CHOP or R-CHOP. All patients received up to eight 3-week cycles of CHOP induction; patients in the R-CHOP arm received rituximab 375 mg/m^2 on Day 1 of each cycle. The main outcome measure of the study was event-free survival, defined as the time from randomization to relapse, progression, change in therapy, or death from any cause. Among all enrolled patients, 80% had Stage III or IV disease, 60% of patients had an age-adjusted IPI ≥ 2, 80% had ECOG performance

status ≤ 2, 66% had elevated LDH levels, and 52% had extranodal involvement in at least 2 sites.

1.2.2.5.10 Study 9
A total of 823 patients with DLBCL, aged 18-60 years, were randomized in a 1:1 ratio to receive an anthracycline-containing chemotherapy regimen alone or in combination with rituximab. The main outcome measure of the study was time to treatment failure, defined as time from randomization to the earliest of progressive disease, failure to achieve a complete response, relapse, or death. Among all enrolled patients, 28% had Stage III-IV disease, 100% had IPI scores of ≥ 1, 99% had ECOG performance status of ≤ 2, 29% had elevated LDH levels, 49% had bulky disease, and 34% had extranodal involvement.

1.3 Rationale

CD20 is expressed in NHL of B-cell origin, as well as in normal B-lymphocytes ([16]. Although its precise function is not fully elucidated, it appears to be important to B-cell development and proliferation [26]. The function of CD30 is likewise incompletely understood, though is known to have a role in stimulation and selection of T-lymphocytes [27]. CD30 expression is nearly universal in cHL and Anaplastic Large Cell Lymphoma (ALCL) [28], occurs commonly in PTLD (as noted above) [9], and is found in other virus-associated lymphoid malignancies, such as Adult T-cell Leukemia/Lymphoma [29] and Primary Effusion Lymphoma [28]. Importantly, CD30 is upregulated in cases of infection with EBV and Human T-lymphotropic Virus (HTLV) [30], and EBV in particular has been shown to induce CD30 expression in B-lymphocytes [31, 32].

Rituximab, a chimeric monoclonal antibody [33] against CD20, has gained regulatory approval for use in NHL, with robust data supporting its use in both the upfront and relapse/refractory disease settings [34]. Brentuximab vedotin, on the other hand, is an anti-CD30 mAb conjugated to the antitubulin agent monomethyl auristatin E (MMAE). It was recently FDA-approved for use in relapsed/refractory HL and ALCL [35]. After demonstrating an 86% ORR in a phase I study [36], similar ORR was achieved in phase II trials of HL (N=102) and ALCL (N=58) [35]. Both mAb's are well-tolerated, with side effect profiles that compare favorably to those of cytotoxic chemotherapy [34, 35].

As noted above, up-front use of aggressive cytotoxic chemotherapy has been plagued by early TRM and graft rejection, and further clinical experience has suggested that a delayed introduction of aggressive chemotherapy may significantly reduce risks of TRM. For instance, a European cooperative group experience demonstrated the apparent advantage of a rituximab-based risk-stratified sequential treatment (RSST) strategy for PTLD patients [1]. In this model, all patients with a new diagnosis of PTLD are treated with 4 doses of weekly rituximab, followed by re-staging. Those with a complete response (CR) then receive an additional four doses of weekly rituximab, followed by observation, while those with any other response receive four cycles of R-CHOP-21. Among the first 40 patients treated, there was a 93% ORR, with 32% of patients able to avoid cytotoxic chemotherapy, and perhaps most notably, with rates of TRM (1/40 patients) that compare very favorably to historical rates. The potential clinical advantages to limiting exposure to cytotoxic chemotherapy have also been recognized in pediatric PTLD [37].Also as noted above, most cases of non-transplant autoimmune-related lymphoma are indolent histology [19]. There is little or no data to establish R-CHOP as frontline therapy for such patients, and anthracycline is potentially "over-treatment" for indolent lymphomas in non-immunocompromised hosts [38].

We therefore hypothesize that brentuximab vedotin and rituximab, used together for the upfront treatment of EBV-related lymphoid malignancies, would optimize efficacy as compared to historical controls by A) improving response rates as compared to single-agent rituximab; B) reducing exposure to cytotoxic therapy, and thereby reduce rates of TRM; and C) ultimately improving PFS and OS. We propose a RSST strategy, similar to that described above, such that those patients failing to achieve a PR or CR to combined brentuximab vedotin and Rituximab therapy can then be treated with cytotoxic chemotherapy, with or without additional mAb therapy. Whereas we predict that EBV positivity may predict for response to anti-CD30 therapy, and that targeting of CD20 will serve to effectively deplete the EBV reservoir, tumor samples need express neither in order to enroll.

Based upon this hypothesis, we propose to conduct a Phase I/II trial combining Brentuximab vedotin with rituximab in patients with newly-diagnosed lymphoid malignancies that are CD30+ and/or EBV+ (as defined by evidence of EBV in either the tumor biopsy specimen, or by positive EBV viral load at time of diagnosis). Phase I will aim to establish the RP2D (which will be defined as the MTD; it is expected that the combination dose of each agent will be identical to that when each is used alone). Phase II will aim to evaluate the efficacy of this regimen as measured by response rates. As we expect the majority of patients to have a history of significant immunosuppression (based upon observed patterns in our patient population), we do not plan to stratify patients based upon transplant history status (ie, those with history of solid organ transplant, versus those without). However, exploratory analyses of this factor may eventually be considered.

In light of the potentially aggressive course of some cases of PTLD and other EBV-related malignancies, we propose a weekly dosing of each agent before transitioning to a treatment schedule of every 3 weeks. Of note, the safety and efficacy of weekly induction has been shown for both brentuximab vedotin and rituximab when used as single agents [21, 39].

It would perhaps be reasonable to have concerns about offering the treatment proposed in this study as frontline therapy to eligible young, otherwise-healthy patients who could also be candidates for other accepted, well-established, frontline therapies with outcomes that are reasonably well-described. However, it is our contention that the TRM associated with early aggressive therapy, makes alternative treatments, such as that offered in this trial, a very attractive means of attempting to reduce risk of early TRM, and that this alone warrants its evaluation as a front-line regimen. Moreover, this trial specifically recommends early cessation of treatment protocol, in favor of more aggressive chemotherapy, for those patients who fail to achieve adequate response, per the discretion of the treating investigator. We believe that this introduces a safety mechanism necessary to the treatment of this patient population that will have a variety of potential clinical acuity.

The acuity of specific patients that are eligible for this trial should be considered at all times by the local treating investigator, and it is the responsibility of the treating investigator to factor in appropriate clinical decisions regarding whether a given patient would be best treated as part of this clinical trial, as opposed to with multi-agent cytotoxic chemotherapy. Because of the very wide variety of patient circumstances, we are unable to precisely define clinical features, other than those specified in sections 3.1 and 3.2, that should result in choosing to enroll, or not enroll, in this trial.

1.4 Correlative Studies

In addition to the overall goals of this study, we plan to assess whether and to what extent immunohistochemical biomarkers might correlate with efficacy and outcome in this

population. We will also plan to collect and store whole blood samples (phase II patients only) for future, unspecified use.

1.4.1 A tissue microarray (TMA) of paraffin-embedded lymphoid tissue biopsies of all patients (enrolled in both Phase I and Phase II) will be created and analyzed by Dr. Amir Behdad, hematopathologist and sub-investigator. This TMA will quantify expression of CD30, markers of EBV proliferation, and other markers known to be of prognostic significance in lymphoma (eg, Ki-67 and C-Myc), in order to determine how such markers correlate with clinical outcome.

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives

2.1.1 Phase I: To evaluate the safety of brentuximab vedotin and rituximab in patients with immunosuppressed lymphoid malignancies, and to determine the RP2D of the combination.

2.1.2 Phase II: To evaluate the efficacy, as measured by response rates, of brentuximab vedotin and rituximab in patients with immunosuppressed lymphoid malignancies.

2.2 Secondary Objectives (Phase II only)

2.2.1 To further evaluate the frequency and severity of toxicity.

2.2.2 To further evaluate the clinical efficacy of the combination of brentuximab vedotin and rituximab, as measured by PFS and OS at one year after the end of treatment.

2.2.3 To evaluate the best response to therapy.

2.2.4 To determine the effects of the combination of brentuximab vedotin and rituximab on markers of EBV activation and proliferation.

2.2.4 Further evaluate efficacy as measured by time to cytotoxic chemotherapy.

2.2.5 Further evaluate efficacy as measured by observed rates of graft rejection.

2.3 Primary Endpoints

2.3.1 The primary endpoint for phase I, dose-limiting toxicity (DLT) will be defined as the occurrence of toxicity as detailed in section 4.2 (using CTCAE v 4.03), experienced during the first 3 weeks of study treatment. The MTD, which constitutes the RP2D, will be defined as described in Section 11 (Study Design).

2.3.2 The primary endpoint for phase II, response after induction or induction/consolidation, will be defined as the detection of SD, PR, or CR by CT or PET/CT, and/or resolution of marrow-only involvement. CR and PR will each be assessed according to the Revised Response Criteria for Malignant Lymphoma. Assessments will be performed after induction and/or consolidation treatment (if applicable).

2.4 Secondary Endpoints:

2.4.1 Adverse events will be defined as those included in CTCAE v 4.03. The occurrence and severity of each will be recorded.

2.4.2 PFS will be defined as the time elapsed between treatment initiation and tumor progression or death from any cause (whichever occurs first), with censoring of patients who are lost to follow-up. OS will be defined as freedom from death by any cause.

2.4.3 Best response will be assessed by CT or PET/CT according to the Revised Response Criteria for Malignant Lymphoma after induction and/or consolidation (if applicable) and every 12 weeks during maintenance treatment.

2.4.4 EBV activation and proliferation will be measured by viral loads as measured at time of enrollment and monthly thereafter in all enrolled patients, until completion of study therapy.

2.4.5 Time to initiation of cytotoxic chemotherapy will be defined as the time elapsed between treatment initiation, and time of first non-targeted cytotoxic chemotherapy.

2.4.6 Graft rejection will be defined as any of the following: documentation of new or progressive rejection by tissue biopsy of the graft; re-transplantation due to graft rejection; clinical diagnosis of new or progressive graft rejection, since start of treatment on protocol, as given by the patient's transplant physician. Escalation of intensity of immunosuppression will not, by itself, be considered evidence of graft rejection. (Note: patients with clinically active graft rejection will not be excluded from trial enrollment, but will not be considered to have treatment-emergent graft rejection unless progression of rejection is documented.)

2.5 Exploratory Objectives

The objectives of the correlative studies are to determine:

2.5.1 whether and to what extent CD30 expression predicts for response and outcome

2.5.2 whether and to what extent expression of EBV markers predicts for response and outcome

2.5.3 whether changes in serum levels of EBV correlate with response and subsequent loss of response to therapy

2.5.4 Collect and store peripheral blood samples for future, unspecified use (phase II patients only).

2.6 Exploratory Endpoints

Levels of CD30 expression, EBV proliferation, and tumor proliferation (ie, Ki-67), all obtained from TMAs performed on pre-treatment tissue samples, will be correlated with ORR, as well as with EFS at one year. Quantitative serum EBV levels will be monitored for the duration of treatment, and change in levels correlated with ORR, duration of response, and progression of disease.

3.0 PATIENT ELIGIBILITY

The target population for this study is patients with CD20+ lymphoid malignancies related to an immunosuppressed state. This will be a multi-center trial conducted at Northwestern University and University of Chicago. Northwestern will serve as the lead site and coordinating center for this study. Participating sites will include Tufts University.

A total of up to 33 subjects will be needed for this trial. Approximately 2 potentially eligible patients are seen per month, and it is anticipated that at least 5 patients will be accrued each month. Potential patients may be referred to the Principal Investigator (PI) at Northwestern University, Dr. Barbara Pro at (312) 695-6180.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Please refer to section 11 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

3.1.1 Patients must have a histologically confirmed CD20+ lymphoproliferative disease that is related to an immunosuppressed state (e.g., PTLD, DLBCL of the elderly, iatrogenic immunodeficiency-associated LPD) and for which rituximab monotherapy would be considered to be appropriate frontline therapy.

3.1.2 In cases of lymphoproliferative disease arising in patients who are pharmacologically immunosuppressed, reduction of immunosuppression (RI) must be attempted prior to or in conjunction with enrollment, with the exception of those for whom RI would pose excessive threat of clinically significant graft rejection (as judged by local investigator).

NOTE: Patients who are otherwise immunosuppressed (for reasons such as immune dysregulation related to autoimmune conditions, in the absence of pharmacological immunosuppression) may be eligible if, in the opinion of the treating investigator, the risk of immediate treatment with R-CHOP outweighs the benefit for these patients.

3.1.3 Patients must have bi-dimensionally measurable disease (at least 1 cm).

NOTE: Patients with fully resected disease are eligible, and will be evaluable for all toxicity and efficacy endpoints except objective response.

3.1.4 Patients must be ≥ 18 years of age.

3.1.5 Patients must have an ECOG performance status ≤ 2.

3.1.6 Patients must have adequate organ and marrow function as defined below (documented within 28 days of registration):

- absolute neutrophil count ≥ 750/mcL
- platelets ≥ 50,000/mcl
- total bilirubin ≤ 2 X institutional upper limit of normal (ULN)
- AST(SGOT)/ALT(SPGT) ≤ 3 X institutional ULN
- creatinine ≤ 2 X institutional ULN

NOTE: Patients who do not meet the above criteria because of disease involvement of the organ in question, or because of acute systemic illness due to lymphoma, may enroll with permission of the study PI and approval from the Data Monitoring Committee. We propose that this flexibility be allowed due to

the heterogeneity of the patient population, the wide range of complications seen in the initial presentation of EBV-related malignancy, and the frequent difficulty encountered in attempting to clearly document that organ dysfunction is the result of an underlying lymphoproliferative disorder.

In addition, patients with abnormal renal function may be included if the abnormal function is due to allograft dysfunction resulting from diagnosis of PTLD, or from reduction/cessation of immunosuppression aimed at treatment of PTLD.

3.1.7 Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 90 days following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.9.1 A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.1.8 Patients must be free of any prior malignancies for ≥1 year.
NOTE: The exception to this would be currently treated squamous cell and basal cell carcinoma of the skin, carcinoma in situ of the cervix, breast, or bladder, or surgically removed melanoma in situ of the skin (stage 0) with histologically confirmed free margins of excision. In addition, it is well-recognized that patients at highest risk for EBV-related lymphoma (ie, those with chronic immunosupression) are also at high risk for various malignancies, both invasive and non-invasive. Therefore, exceptions may also be granted on a case-by-case basis, at the discretion of the PI with approval from the Data Monitoring Committee, for those patients with good clinical control of active malignancy, if the EBV-related lymphoma is considered to be a more immediate threat to the subject's health and/or life.

3.1.9 Patients must have the ability to understand and the willingness to sign a written informed consent. All patients must have signed, witnessed informed consent prior to registration.

3.2 Exclusion Criteria

3.2.1 Patients who have received prior treatment for lymphoma are not eligible.

NOTE: Patients may have received corticosteroids for lymphoma for 10 or fewer days at any dose (no washout period required).
NOTE: Patients may have received up to 1 prior dose of rituximab before registration. In this case, patients will only receive 3 doses of rituximab on study, as specified in section 4 1.1.2.1.

3.2.2 Patients who have received chemotherapy (including monocolonal antibodies) or radiotherapy, administered for any condition, within 4 weeks prior to registration are not eligible.

NOTE: Patients may have received one dose of rituximab prior to enrollment. In such cases, patients will only continue with 3 doses of rituximab during induction (4 total doses).

3.2.3 Patients who have had prior surgical intervention for lymphoma, unless performed for the sake of tissue diagnosis or on an urgent basis for disease-related threat to life, limb, or organ function, are not eligible.

3.2.4 Patients with incomplete recovery from adverse events due to agents administered more than 4 weeks prior to registration are not eligible.

3.2.5 Patients must not have ongoing treatment with any other investigational agents ≤ 14 days prior to registration.

3.2.6 Patients must not have known CNS involvement of lymphoma.

3.2.7 Patients must not have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to brentuximab vedotin and/or rituximab.

3.2.8 Patients must not have an uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.9 Patients must not have known HIV infection.

3.2.10 Patients must not have known JC virus infection and/or progressive multifocal leukoencephalopathy (PML).

3.2.11 Patients are not eligible who have clinically active hepatitis B (tested at screening) or known hepatitis A or C infections.

NOTE: Patients with chronic HCV or HBV infection may enroll if other laboratory criteria are met. Those with HBV surface antigen positivity may enroll only if maintained on appropriate suppressive antiviral therapy, per treating investigator's discretion, for the duration of enrollment in the trial.

3.2.12 Pregnancy or active nursing of an infant is not permitted.

3.2.13 Patients with a prior history of documented pancreatitis are not eligible.

3.2.14 Patients with severe renal impairment (CrCL <30 mL/min) are not eligible. A calculated CrCl is acceptable.

4.0 TREATMENT PLAN

Patients will be treated with combination treatment consisting of brentuximab vedotin and rituximab infusions as detailed below. All patients will receive Induction treatment, and those who achieve response (PR or CR) may have an optional cycle of Consolidation treatment, identical to Induction. Maintenance will then continue for up to one year from the first dose of study treatment.

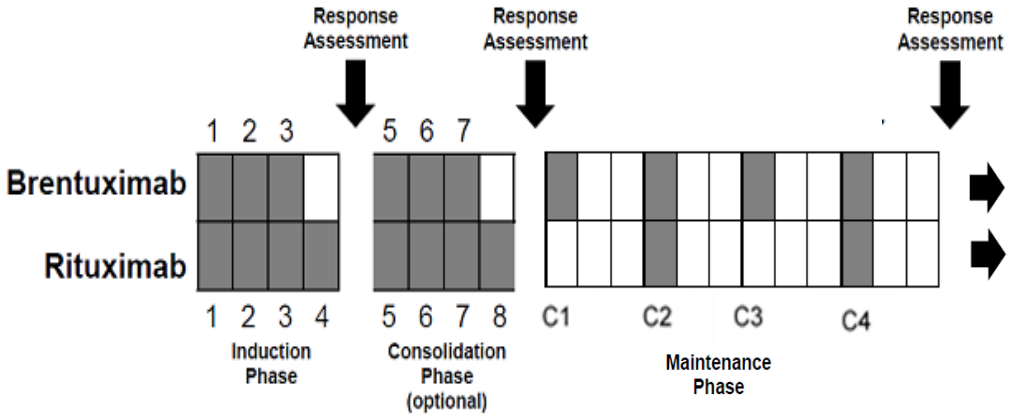


TABLE 1: Dosing Summary			
	Induction (1 cycle = 4 weeks)	**Consolidation* (1 cycle = 4 weeks)**	**Maintenance (1 cycle = 3 weeks)**
Brentuximab Vedotin dosing	1.2 mg/kg IV over 30 mins Weekly x3	1.2 mg/kg IV over 30 mins Weekly x3	1.8 mg/kg IV over 30 mins Once every 3 weeks
Rituximab dosing	375 mg/m2 IV weekly x4	375 mg/m2 IV weekly x4	375 mg/m2 IV once every 6 weeks

*Optional for patients who achieve PR/CR during induction. See section 4.1.3 for stipulations regarding SD.

4.1 Treatment Dosage and Administration

NOTE: A baseline weight and height should be obtained on the first day of treatment for all patients, and weights should be checked at least once per cycle. Treatment dosages will be based upon most recent weight and BSA (preferably from that day of treatment). Dosing is to be subsequently modified if subject weight has changed by more than 10% or the BSA has changed more than 5%.

NOTE: The cycle lengths are as follows:
Induction: 4 weeks (28 days)
Consolidation: 4 weeks (28 days)
Maintenance: 3 weeks (21 days)

4.1.1 Phase I and II dosage:

Because both drugs are well-tolerated and carry low risks of clinically significant toxicity, patients in phase I were treated initially at the most commonly used doses of each drug according to the schedules outlined below. *NOTE: The dose*

for patients with a weight of >100 kg should be calculated for 100 kg (please refer to Section 8.1.6 for details):

The RP2D was established for Phase II on 3/12/2014, and dosing for both Phase I and Phase II is outlined below.

4.1.1.1 Brentuximab vedotin
Induction: 1.2 mg/kg IV infusion over 30 minutes, weekly x 3 (1 cycle = 4 weeks; no brentuximab vedotin is given during the fourth week)
Consolidation (optional): Identical to Induction. Those patients who achieve response (PR or CR) after the Induction course may receive an additional treatment of the same (termed Consolidation). In addition, any patients achieving CR to induction, in whom avoidance of Maintenance therapy is sought, can receive consolidation as their final planned therapy. See section 4.1.3 for stipulations regarding stable disease.
Maintenance: 1.8 mg/kg IV infusion over 30 minutes once every 3 weeks (1 cycle = 3 weeks), for a total of one year from the first induction dose or until progression of disease.

4.1.1.2 Rituximab
Induction: 375 mg/m^2 IV infusion per standard protocol, once weekly for 4 weeks (1 cycle = 4 weeks)
Consolidation (optional): Identical to Induction. Those patients who achieve response (PR or CR) after the Induction course may receive an additional treatment of the same (termed Consolidation). In addition, any patients achieving CR to induction, in whom avoidance of Maintenance therapy is sought, can receive consolidation as their final planned therapy. See section 4.1.3 for stipulations regarding stable disease.
Maintenance: 375 mg/m^2 IV infusion per standard protocol, once every 6 weeks for a total of one year from the first induction dose or until progression of disease.

4.1.1.2.1 Pre-Registration Rituximab
Patients may receive one dos of rituximab prior to registration as specified in 3.1.3. In such cases, the patient will receive a total of four rituximab doses during Induction, with only 3 doses given as part of Induction treatment (weekly, along with brentuximab vedotin).

4.1.1.3 It is intended that all treatments will be administered on an outpatient basis. However, treatment can be initiated during hospitalization (i.e., for newly-diagnosed patients), and can continue during unforeseen hospitalizations, but only at the discretion of the local PI.

4.1.1.4 When both agents are to be administered on the same day, rituximab will be given immediately before brentuximab vedotin. No specific time interval is required between dosing of the agents (for either Phase I or Phase II). In other words, one can be given immediately after the other.

4.1.2 **Phase I treatment plan:**

The DLT detection period will be the first 21 days of treatment, starting on day 1 of induction. The first three patients enrolled on the study will be treated as a single cohort at the doses described above. If none of these first three (0/3) patients experience a DLT (defined below), this will constitute the RP2D.

In the event of 1 DLT among the first 3-patient cohort (1/3), an expansion cohort of an additional three patients will be treated at the same dose. Of the second 3 patients treated, if no additional patients experience DLT (ie, DLT in 1/6 patients), RP2D will not be changed.

In the event of 2 or 3 DLT among the first 3-patient cohort, or in the event that an expansion cohort is required and results in 2 or more DLT among the 6 patients (≥ 2/6) treated in the first and expansion cohorts, dose de-escalation will be explored. De-escalation will consist of brentuximab vedotin at 0.8 mg/kg, with the schedule otherwise unchanged, and with rituximab dose and schedule unchanged.

This dose de-escalation will be studied in a cohort of 3 patients, and if no DLT are observed, the study will commence at this lower dose. In the event that 1 or more DLT are observed at this dose reduction, enrollment will be held and the protocol reviewed.

4.1.3 **Phase II treatment:**

Treatment will be at the RP2D (see section 4.1.1), as determined by the means described above.
Induction: 1.2 mg/kg IV infusion over 30 minutes, weekly x 3 (1 cycle = 4 weeks; no brentuximab vedotin is given during the fourth week)
After First Re-Staging:
Patients achieving **PD** at first re-staging should be taken off treatment and treated with R-CHOP or similar chemotherapy at the discretion of the local treating investigator.

Patients achieving **SD** should likewise be taken off treatment and treated as above. However, at the discretion of the treating investigator, such patients may receive an additional treatment of the same termed "**Consolidation**". Consolidation treatment is identical to Induction. If, after Consolidation treatment, these patients achieve CR or PR, they should proceed to Maintenance (see below for description). If, however, these patients are still SD or have progressed to PD, they should be taken off treatment and treated with R-CHOP or similar chemotherapy at the discretion of the local treating investigator.
Patients achieving **CR** or **PR** after the Induction course may receive an additional treatment of the same termed "**Consolidation**". Consolidation treatment is identical to Induction. For patients achieving CR after Induction, in whom avoidance of maintenance therapy is sought, Consolidation may be given as their final planned therapy. Patients who achieve CR after Induction may proceed directly to Maintenance therapy at the discretion of the treating investigator (for instance, if they are not likely to tolerate Consolidation therapy given the toxicity they experienced during Induction).

Following Consolidation, patients will proceed to **Maintenance**: 1.8 mg/kg IV infusion over 30 minutes once every 3 weeks (1 cycle = 3 weeks), for one year from starting induction or until progression of disease. At the discretion of the treating investigator, patients may discontinue brentuximab vedotin after 10 maintenance doses.

4.1.4 **Dose escalation on a per-patient basis (for both Phase I and Phase II):**

For any patient treated with a brentuximab vedotin dose of 0.8 mg/kg for 2 or more 21-day cycles without DLT, subsequent doses can be increased to 1.2 mg/kg, **but only at the discretion of the treating investigator.** *NOTE: the*

basis for escalation, or lack thereof, should be clearly documented in the Treatment eCRF.

4.1.5 **Recommended treatment off study in the event of progressive disease or loss of response:**

Clinical suspicion of progressive disease (PD) or loss of response should be investigated radiographically, and if confirmed, will result in removal from active therapy (though any such patient will remain in study follow up; see 4.5, Duration of Therapy). In this case, it is strongly recommended that investigators consider early initiation R-CHOP or similar chemoimmunotherapy (off trial).

4.1.6 **Administration details**

Table 2 below summarizes the administration of both agents.

TABLE 2: Regimen Detail

Agent	Premedications*	Dose	Route	Schedule^	Duration
Rituximab	30 min prior: Tylenol 650 mg PO Benadryl 50 mg IVPB PRN for infusion reactions: Solumedrol 125 mg IV over 15 min	375 mg/m^2	IV per standard protocol (see below)	Weekly x 4	4 weeks¥
		375mg/m^2	IV per standard protocol (see below)	Every 6 weeks	1 year or until POD
Brentuximab vedotin		1.2 mg/kg¥	IV over 30 min¥	Weekly x 3 (4th week off)¥	3 weeks¥
		1.8 mg/kg	IV over 30 min	Every 3 weeks	1 year or until POD

*Premedication protocol is the same regardless of which drug is used, and will be used only once when both drugs are administered on the same day, unless ≥ 4 hours passes between start of rituximab infusion and that of brentuximab vedotin, in which case the same premedication protocol can be administered again prior to the start of the second study agent, at the discretion of the treating investigator.

¥The parameters specified in the shaded boxes represent the Induction phase and the optional Consolidation phase, the latter of which is optional (see sections 4.1.1.1 and 4.1.1.2). The non-shaded boxes represent the maintenance phase.

^During Induction and the optional Consolidation phase, 1 cycle = 4 weeks; during maintenance therapy, 1 cycle = 3 weeks

4.1.6.1 Rituximab Administration Guidelines:
DO NOT ADMINISTER AS AN IV PUSH OR BOLUS. Premedicate before each infusion. Administer only as an IV infusion.

4.1.6.1.1 First Infusion:
Initiate infusion at a rate of 50 mg/hr. In the absence of infusion toxicity, increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

4.1.6.1.2 Subsequent Infusions:
Initiate infusion at a rate of 100 mg/hr. In the absence of infusion toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr. Interrupt the infusion or slow the infusion rate for infusion reactions.

Continue the infusion at one-half the previous rate upon improvement of symptoms.

At the discretion of the treating investigator, rapid rituximab infusion is allowable after the first dose, if the initial dose was well-tolerated.

4.2 Dose-Limiting Toxicity (DLT) and Maximally Tolerated Dose (MTD):

For Phase I, DLT evaluation will occur weekly during the first 21 days of induction. (Adverse events, however, will continue to be collected for the duration of treatment). In general, a non-hematologic DLT is defined as any Grade ≥ 3 toxicity, and a hematologic DLT is defined as any Grade ≥ 4 toxicity, both by CTCAE v4.03 criteria. In addition, the following criteria and exceptions apply:

4.2.1 ANC < 500/mm^3 for > 14 days despite GCSF support is a DLT.

4.2.2 Platelet count < 20,000/mm^3 that is considered drug-related is a DLT.

4.2.3 For nausea, vomiting, or diarrhea, patients must have Grade 3 or 4 toxicity that persists at this level despite use of optimal symptomatic treatment, in order for these to be considered a DLT.

4.2.4 Grade 3 thromboembolic events are not considered DLT.

4.2.5 Any Grade 3 rash that resolves to Grade ≤ 2 within a 10 day period (including with symptomatic treatment) will not be considered a DLT.

4.2.6 Cases involving hyperbilirubinemia that is primarily indirect, and considered not reflective of underlying liver disease (ie, resulting from transfusion of red blood cells), will not be considered a DLT.

4.3 Toxicities and Dosing Delays/Dose Modifications

All patients receiving at least one treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events Table (See Section 6.4). Toxicity will be assessed according to the CTCAE v 4.03, and pre-dose lab values must be assessed prior to dosing at each treatment visit. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

Treatment modifications and dosing delays are to follow in Tables 3 and 4 below. For the phase I component, those events constituting a DLT also warrant treatment/modification as outlined below. In the event that both study agents could be responsible for a given toxicity, the treating investigator should first modify only the dose of the most likely offending agent; brentuximab vedotin should be adjusted before that of rituximab, as most toxicities are more common with this agent. Study treatment should not be delayed but rather, skipped & not be made up. Cycles should not be extended, if possible. If the dose of brentuximab vedotin is skipped or decreased due to toxicity, the dose may be restarted or increased for that individual patient in the event that the toxicity resolves completely (at the treating investigator's discretion).

Please also refer to sections of this protocol that contain more detailed information on the potential adverse events and risks associated with each agent (Sections 1.2.1.1 and 1.2.2.1). Any patient missing more than 3 consecutive administrations due to toxicity must be removed from the study. Doses reduced per protocol due to occurrence of adverse events are not counted as missed doses.

TABLE 3a: Drug-Related Hematological Toxicity Dose Reductions for Brentuximab vedotin - ANC

ANC	Action
≥ 1,500/μL	None.
1000-1499/μL	-*1st Occurrence:* Withhold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at previous dose. -*2nd Occurrence*: Withhold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at 50% previous dose. -*3rd Occurrence:* Withhold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at 25% previous dose. -*4th Occurrence*: Discontinue protocol therapy.
500-999/μL	-*1st Occurrence*: Notify treating investigator. Withhold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at 50% previous dose. -*2nd Occurrence*: Withhold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at 25% previous dose. -*3rd Occurrence*: Discontinue protocol therapy.
<500/μL	-*1st Occurrence*: Withhold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Restart next treatment at 25% previous dose. -*2nd Occurrence*: Discontinue protocol therapy.
*G-CSF (Filgrastim), including Neulasta®, may be added for low ANC while a dose reduction is instituted at treating physician's discretions.	

TABLE 3b: Drug-Related Hematological Toxicity Dose Reductions for Brentuximab vedotin - Platelets

Platelets	Action
100,000/μL	None.
75,000-99,000/μL	-*1st Occurrence:* Withhold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at previous dose. -*2nd Occurrence*: Withhold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at 50% previous dose. -*3rd Occurrence:* Withhold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at 25% previous dose. -*4th Occurrence*: Discontinue protocol therapy.
50,000-74,000/μL	-*1st Occurrence*: Notify treating investigator. Withhold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at 50% previous dose. -*2nd Occurrence*: Withhold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at 25% previous dose. -*3rd Occurrence*: Discontinue protocol therapy.
<50,000/μL	-*1st Occurrence*: Withhold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Restart next treatment at 25% previous dose. -*2nd Occurrence*: Discontinue protocol therapy.

TABLE 4 Drug-Related Non-Hematological Toxicity Dose Reductions for Brentuximab vedotin & Rituximab [1]

CTCAE v 4.03 Grade	Brentuximab vedotin	Rituximab
0-2	No change from original starting dose	No change from original starting dose
3-4	Skip treatment until resolved to ≤ Grade 2, then reduce by 33%	*May continue if toxicity is clinically attributed to brentuximab vedotin.* Otherwise, skip treatment until resolved to ≤Grade 2, then resume at same dose
Second episode of grade 3 or 4 toxicity	Skip treatment until resolved to ≤ Grade 2, then reduce by 33%	*May continue if toxicity is clinically attributed to brentuximab vedotin.* Otherwise, skip treatment until resolved to ≤ Grade 2, then resume at same dose
Third episode of grade 3 or 4 toxicity	Remove subject from trial	Remove subject from trial

[1] This table should be followed for all non-hematological toxicities EXCEPT peripheral neuropathy, hyperamylaseemia, and pacreatitis, which should be managed as outlined below. In cases involving hyperbilirubinemia that is primarily indirect, and considered not reflective of underlying liver disease (ie, resulting from transfusion of red blood cells), treating investigators may consider avoiding protocol-specified dose reductions, after consultation with principal investigator.

Management of peripheral neuropathy:

- For new or worsening Grade 2 or 3 peripheral neuropathy, brentuximab vedotin should be withheld until neuropathy improves to Grade 1 or baseline and then restarted at a dose of 1.2 mg/kg. Missed doses will not be made up.
- For grade 4 peripheral neuropathy, discontinue treatment with brentuximab vedotin.

Dose modifications regarding hyperamylaseemia and pancreatitis

- *Asymptomatic elevated amylase and lipase (for patients with amylase elevation >3x upper limit of normal, but no abdominal pain)*:
  - Grade 1 – continue at same dose level
  - Grade 2 – continue at same dose level
  - Grade 3 – withhold treatment until toxicity resolves to ≤ Grade 2 and then resume treatment at the same dose level. Missed doses will not be made up.
  - Grade 4 – withhold treatment until toxicity resolves to ≤ Grade 2 and then resume treatment at reduced dose level or discontinue at the discretion of the treating investigator
- *Mild to moderate pancreatitis (hyperamylasemia syndrome – characterized by abdominal pain of <72 hours duration with amylase and/or lipase elevation)*: Withhold brentuximab vedotin. May consider resuming, with 1 dose level reduction, when signs, symptoms and laboratory values (i.e., amylase and lipase) return to baseline/normalize. If a 2nd episode of mild to moderate pancreatitis occurs, brentuximab vedotin must be permanently discontinued. Missed does will not be made up.
- *Severe pancreatitis (abdominal pain of 72 hours and amylase elevation of 3x normal for > 72 hours duration)*: Permanently discontinue brentuximab vedotin.

4.4 Concomitant Medications/Treatments

4.4.1 Required concomitant medications

4.4.1.1 Tylenol (acetaminophen) 650 mg PI 30 minutes prior to each infusion or equivalent as per standard practice.

4.4.1.2 Benadryl (diphenhydramine) 50 mg IVPB 30 minutes prior to each infusion or equivalent as per standard practice.

4.4.2 Allowed concomitant medications

4.4.2.1 Solumedrol 125 mg IV over 15 minutes as needed for infusion reactions.

4.4.2.2 Symptomatic treatment as needed for nausea, vomiting, and/or diarrhea, including 5-HT3 antagonists, corticosteroids, benzodiazepines, and anti-motility agents.

4.4.2.3 Topical and systemic treatment for rash, including corticosteroids.

4.4.2.4 Hormonal birth control medications.

4.4.2.5 Concurrent antiviral therapy for HBV surface antigen positivity.

4.4.2.6 G-CSF (Filgrastim), including Neulasta®, may be added for low ANC while any requisite dose reduction in study agent is instituted, at treating physician's discretion.

4.4.3 Concomitant medications and treatments NOT allowed

4.4.3.1 Concurrent chemotherapy, radiotherapy within 28 days prior to registration, or other investigational agents within 14 days prior to registration.

4.5 Other Modalities or Procedures

No other treatment modalities or procedures are required as part of the study treatment. Any patient receiving radiation therapy and/or surgery related to progression of malignancy will be removed from protocol therapy. In addition, any patient that subsequently undergoes stem cell transplant will be removed from protocol therapy.

4.6 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for one year or until:

4.6.1 Disease progression

4.6.2 Inter-current illness that prevents further administration of treatment

4.6.3 Unacceptable adverse event(s)

4.6.4 Patient decides to withdraw from the study, OR

4.6.5 General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

Please also refer to Section 4.8 for additional information regarding off-treatment and off-study criteria.

4.7 Duration of Follow Up

Once patients are off treatment (whether treatment is completed or they are withdrawn for any reason) patients will be followed with at least one clinic visit every three months, for up to one year from discontinuation of treatment, then every six months up to 3 years from discontinuation of treatment, or until death, whichever occurs first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

4.8 Removal of Subjects from Treatment and/or Study

Patients can be removed from the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral, or administrative reasons. The reason(s) for discontinuation must be documented and may include:

5.5.1 Patient voluntarily withdraws from treatment (follow-up permitted);

5.5.2 Patient withdraws consent (termination of treatment and follow-up);

5.5.3 Patient is unable to comply with protocol requirements;

5.5.4 Patient demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator);

5.5.5 Patient experiences toxicity that makes continuation in the protocol unsafe;

5.5.6 Treating physician judges continuation on the study would not be in the patient's best interest;

5.5.7 Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

5.5.8 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

5.5.9 Patient is lost to follow-up. If a research subject cannot be located to document survival during the follow-up period (up to 3 year after starting study treatment), the subject may be considered "lost to follow-up." All attempts to contact the subject during the follow-up period must be documented and approved by the Data Monitoring Committee.

4.9 Patient Replacement

During Phase I, all three patients enrolled at the starting dose level must be observed for one cycle (21 days), at which point the study will be temporarily suspended for toxicity evaluation, before which it may either be reopened for an additional cohort (at either the same dose or a lower dose), or proceed to Phase II (as outlined in sections 4.1.2 and 4.1.3). Any DLT noted at any point after treatment begins (up till the end of the DLT evaluation period) shall count toward the total number of DLT, and patients are not replaced. An exception will be made for those patients who are enrolled but, for whatever reason, never receive treatment; such patients should be replaced. If a patient is withdrawn from the study within 21 days of starting therapy, for whatever reason, but without experiencing a DLT prior to withdrawal, an additional patient may be added to that dose level. Patients missing more than three weeks' worth of doses due to toxicity will not be replaced since these patients will be considered to have experienced a dose limiting toxicity.

During Phase II, any patient who is enrolled but not treated on the study, or who completes fewer than two total cycles of therapy and is withdrawn for any reason except POD or toxicity, shall be replaced.

5.0 STUDY PROCEDURES

5.1 Table 5: Time and Events Table

PROCEDURES/ ASSESSMENTS	Baseline/ screening[1]	Induction (1 cycle = 28 days) ± 3 days				Consolidation[7] (1 cycle = 28 days) (Optional[12]) ± 3 days				Maintenance[7] (1 cycle = 21 days) ± 3 days		Off Treatment[10]	Follow-up[11]
										C1D1 +Odd cycles	C2D1 +Even cycles		
Weeks[13]		1	2	3	4	5	6	7	8				
Informed consent	X												
H&P and vital signs	X	X				X				X	X	X	X
Review of eligibility	X												
Performance status	X									X[9]		X	X
Toxicity (include DLT) evaluation	X	X	X	X	X	X	X	X	X	X	X	X	
Scans[2]	X[2]				X[2]				X[2]	X[2]		X	
CBC and serum chemistries[3]	X	X	X	X	X	X	X	X	X	X	X		
Serum amylase[4]	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test	X												
TMA	X[5]												
Serum EBV viral load	X	X				X				X	X		
Hepatitis B[9]	X												
Peripheral Blood Banking[6]	X	X[6]								X[6]	X[6]		
Brentuximab vedotin[7]		X	X	X		X	X	X		X	X		
Rituximab[8]		X	X	X	X	X	X	X	X		X		

[1] All screening procedures should be completed within 28 days of registration

[2]Tumor assessment will be by means of PET/CT at screening, after induction (after fourth dose of induction rituximab and prior to starting consolidation) and after consolidation if applicable (after fourth dose of consolidation rituximab and prior to starting maintenance; patients with a CR after induction do not need to repeat a scan after consolidation). NOTE: Although PET/CT is preferred, patients may be assessed by CT alone at any time point. During maintenance, patients will have CT with contrast every 12 weeks (4 cycles), within 7 days prior to Day 1 of Cycle 1, 5, 9 etc… During the Maintenance phase, the treating physician may assess with CT or PET/CT at his/her discretion. In addition, an End of

Treatment scan will be performed 3-4 weeks after the last dose of study treatment.

[3] CBC and Chemistry panels must be resulted prior to dosing to assess the need for dose delays or modifications.

[4] Serum amylase levels may be drawn up to 72 hours prior to the dosing of brentuximab vedotin. If amylase level is elevated, lipase must also be drawn. See Section 4.3 regarding dose modifications for hyperamylasemia (with or without pancreatitis).

[5] Procurement of tissue and completion of TMA may be done prior to or upon enrollment, but are not required for registration/eligibility purposes.

[6]Phase II patients only: One red top tube and one green top tube will be drawn at baseline OR day 1 of induction, and day 1 of the first 3 maintenance cycles. Blood products will be frozen and stored in the Pathology Core Facility for future, unspecified use.

[7] Brentuximab vedotin will be given intravenously over approximately 30 minutes at the specified time points. The dose will be 1.2mg/kg during induction and optional consolidation (see section 4.1) and 1.8mg/kg during maintenance. Lab values for CBC and Chemistry panels must be resulted prior to dosing to assess for dose delays or modifications. Consolidation treatment should start 7-21 days after the fourth induction dose of rituximab. Maintenance treatment should start 7-21 days after the fourth consolidation dose of rituximab.

[8] Rituximab will be given intravenously at a dose of 375mg/m^2 at the specified time points. Rituximab should be given immediately before brentuximab vedotin on days when both drugs are administered. See section 4.1 for more details. Lab values for CBC and Chemistry panels must be resulted prior to dosing to assess for dose delays or modifications.[9] Hepatitis testing at screening will include HepBsAg and HepBcAb within 4 months prior to registration. [10] The End of Treatment visit should take place 21-28 days after the patient's last dose of study drug.

[11] Patients will be followed every three months for one year following discontinuation of study treatment, then every six months for a total of three years following discontinuation of study treatment, or until death, whichever comes first.

[12] Consolidation treatment is optional for patients who achieve response (PR or CR; see section 4.1.3 regarding SD) after induction. In addition, any patients achieving CR to induction, in whom avoidance of Maintenance therapy is sought, can receive consolidation as their final planned therapy.

[13] Treatment and assessments will take place on Day 1 of each Week

6.0 ASSESSMENT OF ENDPOINTS

6.1 Toxicity Definitions

6.1.1 **Evaluable for toxicity.**
All patients will be evaluable for toxicity from the time of their first treatment with study drug. This includes the primary endpoint of safety and the secondary endpoint of toxicity.

6.1.2 **Safety/tolerability**
Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.03 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html) and modified criteria for hematologic adverse events.

6.2 Efficacy Definitions

6.2.1 Response and progression will be evaluated in Phases I and II using 2007 Revised Response Criteria for Malignant Lymphoma (modified).

6.2.1.1 Evaluable for objective response.
Only those patients who have measurable disease (at least 1cm) present at baseline, have received *at least three doses of brentuximab vedotin*, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

6.2.1.2 Evaluable for Survival
All patients who have had at least one dose of study treatment will be evaluable for PFS and OS.

6.2.1.3 Evaluable for Other Endpoints

- Time to cytotoxic chemotherapy will be evaluated in all patients who receive at least one dose of study treatment.
- Effect on EBV markers will be evaluated in all patients who receive at least one dose of study treatment and have an evaluable TMA collected at baseline.
- Rates of graft rejection will be evaluatd in all patients who receive at least one dose of study treatment

6.2.2 **Antitumor Effect**

6.2.2.1 Response Criteria
Response criteria will be those specified by Cheson, et al [19] as the Revised Response Criteria for Malignant Lymphoma. Please refer to Table 6 for a tabular summary of the below definitions.

6.2.2.1.3 Complete Remission (CR):
The designation of CR requires the following (Table 6):

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

2a. A post-treatment residual mass of any size is permitted as long as it is PET negative.

2b. If a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.

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

6.2.2.1.4 Partial Response (PR):
The designation of PR requires all of the following:

1. At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they 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. No increase should be observed in the size of other nodes, liver, or spleen.

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

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

5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement, will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

6. No new sites of disease should be observed.

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

8. If the pretreatment PET scan was negative, CT criteria should be used.

6.2.2.1.5 Stable Disease (SD):
Stable disease (SD) is defined as the following:

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see "Relapsed Disease [after CR]/Progressive Disease [after PR, SD]," below).

2. The PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

3. If the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

6.2.2.1.6 Relapsed Disease (after CR)/Progressive Disease (after PR, SD)
Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes ≤ 1.0 x ≤ 1.0 cm will not be considered as abnormal for relapse or progressive disease.

1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

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

3. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

4. Lesions should be PET positive if disease lesions were PET positive before therapy, unless the lesion is too small to be detected with current PET systems (<1.5 cm in its long axis by CT). Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

Table 6

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

6.2.2.2 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Response for this Category Also Requires:**
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

6.2.3 Duration of Response

6.2.3.1 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 recurrent disease is objectively documented.

6.2.3.2 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.

6.2.3 **Progression-Free Survival**

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression. PFS will be documented based on clinical follow-up. Results of imaging studies conducted for clinical purposes will be documented, but the nature (eg, PET vs. CT) and frequency is at the discretion of the treating physician (apart from PET/CT obtained after Induction and Consolidation phases, which are mandatory).

6.2.4 **Overall Survival**

Overall survival (OS) is defined as the duration of time from start of treatment to time of death, up to three years from the start of study treatment.

6.2.5 **Time to first cytotoxic chemotherapy**

Time to first cytotoxic chemotherapy (TTFCC) is defined as the time from start of study treatment to time of first dose of antineioplastic cytotoxic chemotherapy that is administered to treat lymphoma. This does not include corticosteroids, antivirals, or chemotherapeutic agents used for either non-neoplastic diseases or other malignant processes (not lymphoma).

7.0 ADVERSE EVENTS

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects 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. All adverse events will be reported on the appropriate eCRF (as outlined in the guidelines in NOTIS). Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

7.1.1 the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;

7.1.2 any abnormal laboratory values have returned to baseline;

7.1.3 there is a satisfactory explanation other than the study drug for the changes observed; or

7.1.4 death.

7.2 Definitions

7.2.1 **Definition of Adverse Event**

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

7.2.2 Severity of Adverse Events

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4.03 is available at http://ctep.cancer.gov/reporting/ctc.html.

If no CTCAE grading is available, the severity of an AE is graded as follows:

7.2.2.1 Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

7.2.2.2 Moderate (grade 2): the event causes discomfort that affects normal daily activities.

7.2.2.3 Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

7.2.2.4 Life-threatening (grade 4): the patient was at risk of death at the time of the event.

7.2.2.5 Fatal (grade 5): the event caused death.

7.2.3 Serious Adverse Events

All SAEs, regardless of attribution, occurring during the study or within 30 days of the last administration of study drug must be reported to the PI upon discovery or occurrence. Additional expedited or routine reporting may be required, depending on the nature of the SAE (as outlined in 7.4.1 below). A "serious" adverse event is defined in regulatory terminology as any untoward medical occurrence that:

7.2.3.1 Results in death.
If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

7.2.3.2 Is life-threatening.
(the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).

7.2.3.3 Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

7.2.3.4 Results in persistent or significant disability or incapacity.

7.2.3.5 Is a congenital anomaly/birth defect

7.2.3.6 Is an important medical event
Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.2.4 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs)

A UPIRSO includes events that are unanticipated in terms of nature, severity, or frequency, place the research subject or others at a different or greater risk of harm, and are deemed to be related or possibly related to participation in the study.

7.3 Steps to Determine If an Adverse Event Requires Expedited Reporting

7.3.1 Step 1: Identify the type of adverse event using the NCI CTCAE v 4.03.

7.3.2 Step 2: Grade the adverse event using the NCI CTCAE v 4.03.

7.3.3 Step 3: Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:

7.3.3.1 Definite – The AE *is clearly related* to the study treatment.
7.3.3.2 Probable – The AE *is likely related* to the study treatment.
7.3.3.3 Possible – The AE *may be related* to the study treatment.
7.3.3.4 Unrelated – The AE *is clearly NOT related* to the study treatment.
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 accordingly.

7.3.4 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:

7.3.4.1 the current known adverse events listed in the Agent Information Section of this protocol;
7.3.4.2 the drug package insert;
7.3.4.3 the current Investigator's Brochure

7.4 Reporting Requirements for Adverse Events

7.4.1 **Expedited Reporting of SAEs**

7.4.1.1 Reporting to the QAM/DMC:

All SAEs must be reported to the assigned QAM within 24 hours of becoming aware of the event. Completion of the NU CRO SAE Form is required. The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number
- Patient's Identification Number
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Hospital Discharge Summary (if available)

All SAEs will be reported to, and reviewed by, the DMC at their next meeting.Reporting to the NU IRB
Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the Northwestern University IRB within 24 hours of notification.

The following SAEs will be reported to the NU IRB within 10 working days of notification:

- Death of a non-NU subject that is unanticipated in nature and at least possibly related to study participation.
- Other UPIRSOs

The following SAEs will be reported to the NU IRB at the time of continuing review:

- All deaths of NU subjects that were not previously reported
- All deaths of non-NU subjects that are deemed to be unanticipated in nature and unrelated to participation
- All other SAEs not previously reported to the NU IRB as UPIRSOs

In addition, participating sites should follow local guidelines for reporting of SAEs to their IRB as required.

7.4.1.2 Reporting to the FDA:
The QAM will notify FDA will be notified within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life-threatening. In these instances, an FDA MedWatch Form will be completed.

7.4.1.3 Reporting to Seattle Genetics:
Any SAE that occurs in a study subject must be reported to Seattle Genetics Drug Safety within 24 hours of first awareness of the event. Notification should be via fax to either 425-527-4308 or 866-333-6627. The NU CRO SAE Form is an acceptable method of reporting. The Principal Investigator will assist Seattle Genetics in investigating any SAE and will provide any follow-up information reasonably requested by Seattle Genetics.

7.4.2 **Routine Reporting**

All other adverse events, such as those that are expected, or are unlikely or definitely not related to the study participation, are to be reported on a regular basis to the assigned QAM for the study in accordance with the Robert H. Lurie Comprehensive Cancer Center's Data Safety Monitoring Plan (DSMP). These will be reviewed by the DMC on an on-going basis. The QAM will notify the FDA within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but not fatal or life-threatening. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DMC). A summary of all these events will be reported annually to the NU IRB as part of the continuing review process.

7.5 Stopping Rules

As noted in Section 5.0, the study will be terminated in the event that ≥ 2/3 patients experience toxicity in cohort -1 (1.2 mg/kg brentuximab vedotin) during Phase I. Likewise, the study will be stopped after the first stage of Phase II if, among the first 15 patients treated, four or fewer patients have a CR or PR, as this will be considered evidence of inadequate efficacy. In addition, the Data Safety Monitoring Committee will monitor the study in accordance with the DSMP and may suspend or close the study to accrual at any point if required, as out lined in the DSMP.

8.0 DRUG INFORMATION

8.1 Brentixumab vedotin

8.1.1 **Other names for the drug(s):** ADCETRIS®

8.1.2 **Classification – type of agent**
Antibody-drug conjugate; the antibody is a chimeric IgG1 directed against CD30 and the small molecule, MMAE, is a microtubule disrupting agent.

8.1.3 **Mode of action**The ADC binds to CD30-expressing cells, followed by internalization of the ADC-CD30 complex, and the release of MMAE via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death of the cells.

8.1.4 **How supplied/Storage and handling**

8.1.4.1 How Supplied
ADCETRIS® (brentuximab vedotin) for Injection is supplied as a sterile, white to off-white preservative-free lyophilized cake or powder in individually-boxed single-use vials:
• NDC (51144-050-01), 50 mg brentuximab vedotin.

8.1.4.2 Storage
Store vial at 2-8˚C (36-46˚F) in the original carton to protect from light.

8.1.4.3 Special Handling
Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published, and are available in the manufacturer's prescribing information insert. Each study site will be responsible for regular inventory checks and disposing of expired drug in a timely manner

8.1.5 **Protocol dose:**
1.2 mg/kg IV weekly x 3, then 1.8 mg/kg IV every 3 weeks.

NOTE: A baseline weight and height should be obtained on the first day of treatment for all patients, and weights should be checked at least every three weeks (once per cycle). Treatment dosages will be based upon most recent weight and BSA (preferably from that day of treatment). Dosing is to be subsequently modified if subject weight has changed by more than 10% or the BSA has changed more than 5%.

8.1.6 **Instructions for Preparation and Administration**
Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published (see manufacturer's prescribing information insert). Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.

8.1.6.1 Reconstitution
Calculate the dose (mg) and number of vials of ADCETRIS® required. The dose for patients with a weight of >100 kg should be calculated for 100 kg. Reconstitute each 50 mg vial of ADCETRIS® with 10.5 mL of Sterile Water for Injection, USP, to yield a single-use solution containing 5 mg/mL brentuximab vedotin. Direct the stream toward wall of vial and not directly at the cake or powder. Gently swirl the vial to aid dissolution. DO NOT SHAKE. Inspect the reconstituted solution for particulates and

discoloration. The reconstituted solution should be clear to slightly opalescent, colorless, and free of visible particulates. Following reconstitution, dilute immediately into an infusion bag, or store the solution at 2-8˚C (36-46˚F) and use within 24 hours of reconstitution. DO NOT FREEZE. Discard any unused portion left in the vial.

8.1.6.2 Dilution

Calculate the required volume of 5 mg/mL reconstituted ADCETRIS® solution needed and withdraw this amount from the vials. The dose for patients with a weight of >100 kg should be calculated for 100 kg. Immediately add the reconstituted solution to an infusion bag containing a minimum volume of 100 mL to achieve a final concentration of 0.4 mg/mL to 1.8 mg/mL brentuximab vedotin. ADCETRIS® can be diluted into 0.9% Sodium Chloride Injection, 5% Dextrose Injection or Lactated Ringer's Injection. Gently invert the bag to mix the solution. ADCETRIS® contains no bacteriostatic preservatives. Following dilution, infuse the ADCETRIS® solution immediately, or store the solution at 2-8˚C (36-46˚F) and use within 24 hours of reconstitution. DO NOT FREEZE.

8.1.7 **Route of administration for this study**

Intravenous infusion.

8.1.8 **Incompatibilities:**

Brentuximab vedotin is not to be mixed with, or administered as an infusion with, other medicinal products. (The only exception is that it may be co-administered, but not mixed with, rituximab, when administered as part of this clinical trial.)

8.1.9 **Availability**

Brentuximab vedotin will be supplied by the study supporter, Seattle Genetics. This drug may be ordered by completing the Investigational Drug Request/Shipment Record Form (see Appendix B), which then may be faxed or emailed as directed on the Form.

8.1.10 **Side effects:**

The most common adverse reactions (≥20%), regardless of causality, were neutropenia, peripheral sensory neuropathy, fatigue, nausea,, upper respiratory tract infection, diarrhea, pyrexia, and vomiting.

Less commonly progressive multifocal leukoencephalopathy (PML), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), tumor lysis syndrome (TLS), acute pancreatitis, pulmonary toxicity, and hepatotoxicity.

NOTE: Current safety data are based on oncology studies (see section 1.2.1). As a result, 1.8mg/kg is the recommended dose for approved indications.

8.1.11 **Return and Retention of Study Drug**

It is NOT expected that excess drug will be returned to the manufacturer, and it is asked that sites destroy drug remaining at the end of the study per their local policy. The manufacturer will provide memos with lot number and expiration dates, and expired drug may also be destroyed per local policy.

8.1.12 **Nursing/patient implications**

•Avoid use in patients with severe renal impairment

•Avoid use in patients with moderate or severe hepatic impairment (Child-Pugh B or C). .

8.2 Rituximab

8.2.1 Other names for the drug(s)

IDEC-C2B8, Rituximab, NSC# 68745

8.2.2 Classification - type of agent

Chimeric murine-derived monoclonal antibody

8.2.3 Mode of action

Rituximab is a chimeric murine/human gamma 1 kappa monoclonal antibody (Chinese hamster ovary [CHO] transfectoma). It recognizes the CD20 antigen expressed on normal B cells and most malignant B-cell lymphomas. It binds with high affinity to CD20-positive cells, performs human effector functions in vitro, and depletes B cells in vivo. The Fab domain of rituximab binds to the CD20 antigen on B-lymphocytes and the Fc domain recruits immune effector functions to mediate B-cell lysis in vitro. The biological effect is manifested by B-cell depletion in peripheral blood, lymph nodes, and bone marrow.

8.2.4 Storage and stability

Rituximab vials are stored at refrigerated temperatures 2° to 8°C (36° to 46°F). Protect vials from direct sunlight. Diluted drug product at a concentration of 0.5 to 4 mg/ml in polyvinylchloride or polyolefin IV bags containing normal saline or dextrose 5% can be stored for up to 24 hours at 2° to 8°C, and at room temperature for an additional 12 hours

8.2.5 Protocol dose

Rituximab will be administered the standard dose of 375 mg/m^2 IV weekly for the first 4 weeks then every 6 weeks thereafter.

8.2.6 Preparation

Withdraw the necessary amount of rituximab and dilute to a final concentration of 1-4 mg/ml into an infusion bag containing either 0.9% Sodium Chloride or 5% Dextrose in Water. Gently invert the bag to mix the solution. Caution should be taken during the preparation of the drug, as shaking can cause aggregation and precipitation of the antibody

8.2.7 Route of administration for this study

Intravenous infusion (see Section 5 for detailed administration instructions).

8.2.8 Incompatibilities

Do not mix or dilute rituximab with other drugs. No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

8.2.9 Availability

Rituximab is commercially available and will not be provided by the study.

8.2.10 Side effects

Adverse events with an incidence > 5% include: fever, chills, rigors, asthenia, headache, angioedema, hypotension, myalgia, dizziness, fatigue, throat irritation, abdominal pain, nausea, abdominal pain, nausea, vomiting, leukopenia, thrombocytopenia, neutropenia, rhinitis, broncospasm, pruritus, rash, utricaria.

8.2.11 Return and Retention of Study Drug

Rituximab will be prescribed to all patients on study. No investigational supply will be purchased or stored for study purposes.

9.0 CORRELATIVES/SPECIAL STUDIES

9.1 The objectives of the correlative studies are to determine:

9.1.1 the frequency of expression of both CD30, and markers of EBV (EBER, LMP-1, and EBNA-2), in NHL and solid tumors

9.1.2 whether and to what extent CD30 expression, and expression of EBV markers, predict for response and outcome on this prospective trial

9.1.3 whether a multivariate model of outcome in PTLD can be prospectively validated, and whether expression of CD30 and EBV markers can be incorporated into a multi-factorial prognostic model for PTLD:

9.1.4 whether changes in serum levels of EBV correlate with response and subsequent loss of response to therapy

9.1.5 Bank whole blood samples for future, unspecified use (phase II patients only).

9.2 Background and Rationale

The Epstein Barr Virus (EBV) is implicated in the pathogenesis not only of multiple lymphoid malignancies, including Hodgkin and Burkitt lymphoma [32], PTLD [9], peripheral T-cell lymphoma (PTCL) [40], but also of various solid tumors, such as nasopharyngeal carcinoma [41] and possibly breast and gastric cancers [42]. Many of these diseases carry poor prognoses, and even among those with generally good prognoses (eg, HL and BL), there are significant subsets of patients who die due to relapsed or refractory disease.

The membrane glycoprotein CD30 is a tumor necrosis factor receptor, was first identified as a marker of Reed–Sternberg (RS) cells in HL [43], and is universally expressed in this disease. It is also frequently expressed in PTCL and PTLD [9], and in virus-infected lymphocytes and activated T-cells [44]. Increased levels of both membrane-bound CD30, and the soluble form (sCD30), which is generated by proteolytic cleavage of the extracellular component of the molecule, are found in patients infected with EBV and HIV [45]. Increased expression of sCD30 is associated with poor outcome in HIV, ALCL and HL [45-47]. In fact, in both ALCL and HL, levels of sCD30 decrease with treatment and subsequently rise with recurrence [46], [47]. Whereas CD30 expression is not routinely evaluated in other types of non-Hodgkin lymphoma (NHL), nor in solid tumors, it is unclear to what extent such tumors might express CD30.

Taken together, these data highlight interesting questions that have yet to be answered. For instance, it remains unclear to whether and to what extent CD30 expression, and its localization, might predict for response to SGN-35. It is also unknown whether markers of EBV expression and/or proliferation, when associated with malignancy, might predict for response to SGN-35, in correlation with, or irrespective to, CD30 expression.

Prognostication for patients with PTLD has not been well studied. In a large cohort of patients with PTLD, Evens, et al, evaluated primarily clinical features of disease, and reported a multivariate model of PFS and OS, which relied upon the presence vs absence of normal albumin levels, CNS involvement, and bone marrow involvement [12]. This model has not been prospectively validated.

9.2.1 **Objective 1.** Determine the frequency of expression of both CD30, and markers of EBV (EBER, LMP-1, and EBNA-2), in NHL and solid tumors:

Pre-treatment biopsy samples, obtained from pathology archives at NMH, will be identified by a search of corresponding pathological diagnoses in approximately the following numbers:

Non-Hodgkin lymphoma (excluding ALCL) N=100
Diffuse large B-cell lymphoma (DLBCL) N=30
Burkitt lymphoma (BL) N=20
Follicular lymphoma (FL) N=30
Other B-cell lymphoma (mantle cell, marginal zone lymphomas) N=20
Nasopharyngeal carcinoma N=20
Gastric adenocarcinoma N=20

Each sample will be evaluated by IHC with respect to expression of CD30 and EBV markers (EBER, LMP-1, and EBNA-2). Percentage of positivity will be estimated by an experienced hematopathologist, with values (0-100%) reported both for the malignant lymphoid cells, and for the stromal cells.

This will be a descriptive analysis of the rates of expression of these markers in various disease states, and no formal statistical analysis is planned.

9.2.2 **Objective 2.** Determine whether and to what extent CD30 expression, and expression of EBV markers, predict for response and outcome on this prospective trial:

As described in Objective 1, each sample will be evaluated by IHC with respect to expression of CD30 and EBV markers (EBER, LMP-1, and EBNA-2). Percentage of positivity will be estimated by an experienced hematopathologist, with values (0-100%) reported both for the malignant lymphoid cells, and for the stromal cells.

In univariate and multivariate analyses, these percentages will be correlated with response (CR/PR vs SD/PD), and PFS.

9.2.3 **Objective 3.** Determine whether a multivariate model of outcome in PTLD can be prospectively validated, and whether expression of CD30 and EBV markers can be incorporated into a multi-factorial prognostic model for PTLD:

We will evaluate the model described above [12] in the patients treated as part of this trial. We will additionally incorporate CD30 expression and markers of EBV into a multivariate analysis to determine whether a more precise clinicopatholo model of prediction is possible.

9.2.4 **Objective 4.** Determine whether changes in serum levels of EBV correlate with response and subsequent loss of response to therapy:

Serum EBV levels will be followed as standard of care, and will be evaluated as a dichotomous variable (undetectable vs detectable). Loss of detectable EBV will be correlated with response (CR/PR vs SD/PD), and emergence of detectable EBV will likewise be correlated with loss of response.

9.2.5 **Objective 5.** Peripheral blood samples will be collected will be collected from patients at baseline, day 1 of induction, and day 1 of the first 3 maintenance cycles. This will be stored for future, unspecified use.

9.3 Sample Collection Guidelines

Original paraffin-embedded pathology samples will be collected for all enrolled subjects and reviewed centrally for correlative studies. Core size to be obtained from these samples will be at the discretion of the Dr. Amir Behdad.. NOTE: This is not needed prior to enrollment or treatment initiation for eligibility purposes. Prior to or upon enrollment, all specimens are to be sent to the Pathology Department at Northwestern Memorial Hospital at the following address:

Amir Behdad,, MD
Professor of Pathology
Northwestern Memorial Hospital
Feinberg 7-210
Chicago, IL 60611

Tissue samples will be received in the Pathology Department and reviewed centrally. The Pathology Core Facility at Northwestern University will then arrange pick-up of the samples for construction of the TMA.

Phase II Patients Only
Peripheral blood samples will be collected at the time points noted below and banked for future, unspecified use. One red top and one green top tube will be drawn at each time point (see section 5.4), and can be drawn before or after any treatment scheduled for that same day. Samples will be picked up by and stored by the Clinical Trials Pathology Office.

- Baseline (within 28 days prior to start of study treatment) OR day 1 of induction therapy.
- Day 1 of the first 3 maintenance therapy cycles
  - If patient misses/skips any of the first 3 maintenance cycles, every attempt will be made to collect the samples at the next cycle initiation (day 1 of X cycle) for a total of **three** maintenance samples.

9.3.1 Blood Processing & Shipping:

Red Top Tube:

a. Red top tube should sit upright after the blood is drawn at room temperature for a minimum of 30 minutes to a maximum of 60 minutes to allow the clot to form.
b. Centrifuge the blood sample at the end of the clotting time for 15 minutes at room temperature at 1500g. If the blood is not centrifuged immediately after the clotting time, the tubes should be refrigerated (4 degrees Celsius) for no longer than 4 hours
c. Pipette serum into the labeled cryovials, Close caps on the vials tightly.

Note: Be careful not to pick up red blood cells when aliquoting. This can be done by keeping the pipet above the red blood cell layer and leaving a small amount of serum in the tube

d. Place all aliquots upright in a specimen box or rack in an -80C or colder freezer. All specimens should remain at -80C prior to shipping. The samples should not be thawed prior to shipping.

Green Top Tube:

a. Transfer/aliquot whole blood from green top tube into 2 cryovials or falcon tubes. Close caps on the vials tightly.
b. Place all aliquots upright in a specimen box or rack in an -80C or colder freezer. All

specimens should remain at -80C prior to shipping. The samples should not be thawed prior to shipping.

Samples are to be labeled with the study participant's study ID number. The following parameters must be recorded for each specimen collection:

- Date and time of blood draw
- Time of specimen processing
- Time specimen was frozen

Frozen samples and associated paperwork should be shipped to the Robert H. Lurie Comprehensive Cancer Center Patchcore Facility Clinical Trials Unit (PCF-CTU). Specimens must be shipped via overnight FedEx on dry ice. Email PCF-CTU staff with details of shipment using the email listed below. It is important that samples do not thaw, therefore all packages should be sent Monday-Thursday only; **batch shipping of specimens is allowable**. All packages should be sent to:

Robert H. Lurie Comprehensive Cancer Center of
Northwestern University
Clinical Trial Pathology Office
Attention: NU 12H09
Olson 8-412
710 North Fairbanks Court
Chicago, IL 60611
312-908-0603
PCF-CTU@northwestern.edu

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints/Data Analysis

10.1.1 **Phase I (also refer to section 4.1.2)**

The first three patients enrolled on the study will be treated as a single cohort. If none of these first three patients experience a dose-limiting toxicity (DLT; defined below), Phase II of the study will subsequently commence at the same dose.

In the event of one DLT among the first three-patient cohort, an expansion cohort of an additional three patients will be treated at the same dose. Of the second three patients treated, if no additional patients experience DLT, Phase II of the study will commence at the same dose.

In the event of two or three DLT among the first three-patient cohort, or in the event of two or more DLT among the six patients treated in the first and expansion cohorts, dose de-escalation will be studied, with Brentuximab vedotin at 1.2 mg/kg, with the schedule otherwise unchanged, and with Rituximab dose and schedule unchanged. This dose de-escalation will be studied in a cohort of three patients, and if no DLT are observed, the study will commence at this dose schedule.

In the event that one or more DLT are observed at this dose reduction, enrollment will be held and the protocol reviewed.

10.1.2 **Phase II**

Our null hypothesis is that the combination of rituximab and brentuximab vedotin will yield no difference in the rate of ORR as compared to that observed with historical treatments. The historical ORR for both PTLD and EBV-related

lymphoma of the elderly, when treated with rituximab (with or without chemotherapy is estimated at approximately 50% [1, 2]. Therefore, the optimal two-stage design to test the null hypothesis that P=0.50 versus the alternative that P>=0.70 (the hypothesized ORR to rituximab plus brentuximab vedotin) has an expected sample size of 24. Under these conditions, if the combination is actually not significantly more efficacious, there is a <0.05 probability (also known as the alpha value) of concluding that it is. If the combination is actually significantly more efficacious, there is a <0.20 probability (also known as the beta value) of concluding that it is not. Early futility may be declared, such that if eight or fewer responses are observed among the first 15 patients enrolled, the trial will be stopped and considered no more efficacious than therapy with rituximab alone.

10.2 Sample Size and Accrual

For Phase I, we anticipate enrolling either three or six patients, depending on whether one or two cohorts are opened. For Phase II, we plan to enroll 24 patients. This results in a total of 27-33 patients. Under current conditions at our centers, we anticipate being able to successfully accrue patients to this protocol at an average rate of 1.5 per month, resulting in a target time frame of approximately 2-2.5 years for completion of Phases I and II.

11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

All investigators will follow the Northwestern University conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.3 Required Documentation (for multi-site studies)

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Research Office.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list

- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation [48]
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

11.4 Registration Procedures

Patients *may not* begin protocol treatment prior to registration. All patient registrations will be registered centrally through the Clinical Research Office (CRO) at Northwestern University before enrollment to study. Please contact the assigned QAM or email the CRO's QA Department at croqualityassurance@northwestern.edu for questions regarding patient registration.

11.4.1 Access to NOTIS

Eligible patients will be registered to the study via the web-based application NOTIS (Northwestern Oncology Trial Information System), which can be found at: https://notis.nubic.northwestern.edu. Please note that a username and password is required to use this program, and will be provided during site activation prior to training on the NOTIS system.

11.4.2 Registering a Patient for the Phase I Portion of the Study

For potential patients for the phase I portion of this study, please email the QA department at NU (croqualityassurance@northwestern.edu) *prior to consenting a patient* to determine whether a slot is available on the current cohort. Slots may be reserved according to the Slot Reservation Procedure (see appendix D). An email confirming the reservation and expiration date will be sent by the QAM. In order for registrations to be processed efficiently, study teams are asked to inform the QAM of the date and time that the patient will need to be registered.

BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive a subject identification number:

- Eligibility eCRF (complete in NOTIS)
- Eligibility checklist (signed and dated by the treating physician – upload in NOTIS)
- Signed and dated informed consent document (upload in NOTIS)
- Pathology Report (upload in NOTIS)

Affiliates sites are required to de-identify, scan, and e-mail the following source documents in order to confirm eligibility prior to registration for phase I patients:

- Complete medical and surgical history, current medications, history of clinically significant infections, and physical exam [including weight, height, ECOG PS, vital signs (pulse, temperature, respiratory rate, blood pressure, oxygen saturation)]
- Lab results (ANC, platelets, bilirubin, AST/ALT, creatinine)
- Negative pregnancy test (if applicable)
- Copy of baseline PET/CT report

For Northwestern University (NU) study teams are NOT required to submit a separate email for NU participants, provided that the required documentation listed above is readily available in the patient's electronic medical record (EMR), a separate e-mail submission is NOT required. However, any information that is

not available in the EMR must be de-identified and emailed to the QAM.

The QAM will review all source documentation required to confirm eligibility. Once the QAM confirms the patient is eligible, he or she will register the patient, assign a subject identification number, provide a cohort assignment, and send a confirmation of registration to involved personnel. Registration will then be complete and the patient may begin study treatment.

11.4.3 Registering a Patient to the Phase II Portion of the Study

BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive a subject identification number:

- Eligibility eCRF (complete in NOTIS)
- Eligibility checklist (signed and dated by the treating physician – upload in NOTIS)
- Signed and dated informed consent document (upload in NOTIS)
- Pathology Report (upload in NOTIS)

The QAM will review the registration, register the patient, assign an identification number, and send a confirmation of registration to involved personnel. Registration will then be complete and the patient may begin study treatment.

11.5 Data Management and Monitoring/Auditing

This study will be monitored as a high risk study, which requires high intensity monitoring, as outlined in the Lurie Cancer Center's DSMP. Please refer to NOTIS for more specific details on the monitoring plan and data submission guidelines. All participating sites are responsible for entering data in the timeframe outlined in the data submission guidelines.

11.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, a IRB modification form must be completed within five [22] business days of making the change.

11.6.2 Other Protocol Deviations

According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

variance protocol deviation is considered an instance of Promptly Reportable Non-Compliance (PRNC) if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

Protocol Deviations: Study personnel will report all deviations to the NU QAM Deviations d be summarized and reported to the IRB at the time of continuing review.

PRNC: Study personnel should report instances of PRNC within one [22] week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

11.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

11.8 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to

his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

REFERENCES

1. Trappe R, e.a., *Sequential Treatment with Rituximab and CHOP Chemotherapy in B-Cell PTLD: Results from a Multicenter Phase II Trial.* Proc Amer Society Hematology 2009. **Abstract 100**.
2. Huang, G., et al., *Human cytomegalovirus in neoplastic cells of Epstein-Barr virus negative Hodgkin's disease.* Int J Oncol, 2002. **21**(1): p. 31-6.
3. Howlader N, N.A., Krapcho M, (eds). , *SEER Cancer Statistics Review, National Cancer Institute. Bethesda, MD* 1975-2008.
4. Zelenetz A, A.J., Advani RH, et al. , *Clinical Practice Guidelines in Oncology for Non-Hodgkin Lymphoma.* J Natl Compr Canc Netw 2011. **9**: p. 484-560.
5. Sehn, L.H., et al., *The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP.* Blood, 2007. **109**(5): p. 1857-61.
6. Penn, I., *The role of immunosuppression in lymphoma formation.* Springer Semin Immunopathol, 1998. **20**(3-4): p. 343-55.
7. Gan, Y.J., et al., *A defective, rearranged Epstein-Barr virus genome in EBER-negative and EBER-positive Hodgkin's disease.* Am J Pathol, 2002. **160**(3): p. 781-6.
8. Meij, P., et al., *Antibody responses to Epstein-Barr virus-encoded latent membrane protein-1 (LMP1) and expression of LMP1 in juvenile Hodgkin's disease.* J Med Virol, 2002. **68**(3): p. 370-7.
9. Haque, T., et al., *Soluble CD30: a serum marker for Epstein-Barr virus-associated lymphoproliferative diseases.* J Med Virol, 2011. **83**(2): p. 311-6.
10. Mitarnun, W., et al., *Epstein-barr virus-associated non-Hodgkin's lymphoma of B-cell origin, Hodgkin's disease, acute leukemia, and systemic lupus erythematosus: a serologic and molecular analysis.* J Med Assoc Thai, 2002. **85**(5): p. 552-9.
11. Caussinus, E., et al., *Simultaneous occurrence of Epstein-Barr virus associated Hodgkin's disease and HHV-8 related multicentric Castleman's disease: a fortuitous event?* J Clin Pathol, 2001. **54**(10): p. 790-1.
12. Evens, A.M., et al., *Multicenter analysis of 80 solid organ transplantation recipients with post-transplantation lymphoproliferative disease: outcomes and prognostic factors in the modern era.* J Clin Oncol, 2010. **28**(6): p. 1038-46.
13. Mamzer-Bruneel, M.F., et al., *Durable remission after aggressive chemotherapy for very late post-kidney transplant lymphoproliferation: A report of 16 cases observed in a single center.* J Clin Oncol, 2000. **18**(21): p. 3622-32.
14. Elstrom, R.L., et al., *Treatment of PTLD with rituximab or chemotherapy.* Am J Transplant, 2006. **6**(3): p. 569-76.
15. Choquet, S., et al., *CHOP-21 for the treatment of post-transplant lymphoproliferative disorders (PTLD) following solid organ transplantation.* Haematologica, 2007. **92**(2): p. 273-4.
16. Swerdlow SH, C.E., Harris NL, et al. (Eds), *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues.* IARC Press, Lyon, 2008: p. 262-8.
17. Krieger, N., et al., *Breast cancer, birth cohorts, and Epstein-Barr virus: methodological issues in exploring the "hygiene hypothesis" in relation to breast cancer, Hodgkin's disease, and stomach cancer.* Cancer Epidemiol Biomarkers Prev, 2003. **12**(5): p. 405-11.
18. Massarweh, S., et al., *HIV-related Hodgkin's disease with central nervous system involvement and association with Epstein-Barr virus.* Am J Hematol, 2003. **72**(3): p. 216-9.
19. Ekstrom Smedby, K., et al., *Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium.* Blood, 2008. **111**(8): p. 4029-38.
20. Mariette, X., et al., *Lymphoma in patients treated with anti-TNF: results of the 3-year prospective French RATIO registry.* Ann Rheum Dis, 2010. **69**(2): p. 400-8.
21. Gandhi M, e.a., *Immunosuppression related lymphoma: solid organ transplant & autoimmune conditions.* Ninth Annual Lewis Landsberg Research Day, 2013(April 2013).
22. http://seer.cancer.gov/csr/1975_2008/results_single/sect_01_table.01.pdf.
23. CDC, *HIV/AIDS Surveillance Report, Rev ed.* Atlanta: U.S. Department of Health and Human Services, 2007. **17**: p. 1-54.
24. Gregory, C.D., et al., *Isolation of a normal B cell subset with a Burkitt-like phenotype and transformation in vitro with Epstein-Barr virus.* Int J Cancer, 1988. **42**(2): p. 213-20.

25. Tschopp, L., et al., *The value of frozen section analysis of the sentinel lymph node in clinically N0 squamous cell carcinoma of the oral cavity and oropharynx.* Otolaryngol Head Neck Surg, 2005. **132**(1): p. 99-102.
26. Sjoberg, J., et al., *Expression of the signal transduction molecule zeta in peripheral and tumour-associated lymphocytes in Hodgkin's disease in relation to the Epstein-Barr virus status of the tumour cells.* Br J Haematol, 2002. **116**(4): p. 765-73.
27. Macak, J., B. Habanec, and P. Fabian, *[Detection of Epstein-Barr virus in Hodgkin's disease].* Cesk Patol, 2001. **37**(3): p. 124-5.
28. Deutsch, Y.E., et al., *CD30: an important new target in hematologic malignancies.* Leuk Lymphoma, 2011. **52**(9): p. 1641-54.
29. Navarro, J.T., et al., *Influence of highly active anti-retroviral therapy on response to treatment and survival in patients with acquired immunodeficiency syndrome-related non-Hodgkin's lymphoma treated with cyclophosphamide, hydroxydoxorubicin, vincristine and prednisone.* Br J Haematol, 2001. **112**(4): p. 909-15.
30. Chiarle, R., et al., *CD30 in normal and neoplastic cells.* Clin Immunol, 1999. **90**(2): p. 157-64.
31. Flavell, K.J., et al., *The effect of Epstein-Barr virus status on outcome in age- and sex-defined subgroups of patients with advanced Hodgkin's disease.* Ann Oncol, 2003. **14**(2): p. 282-90.
32. Siemer, D., et al., *EBV transformation overrides gene expression patterns of B cell differentiation stages.* Mol Immunol, 2008. **45**(11): p. 3133-41.
33. Palandri, F., et al., *Front-line treatment of Philadelphia positive chronic myeloid leukemia with imatinib and interferon-alpha: 5-year outcome.* Haematologica, 2008. **93**(5): p. 770-4.
34. Almasri, N.M. and H.S. Khalidi, *Epstein-Barr virus expression in Hodgkin's disease in Jordan.* Saudi Med J, 2004. **25**(6): p. 770-5.
35. *Adcetris Package Insert.* Seattle Genetics; Seattle, WA, 2011.
36. Younes, A., et al., *Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas.* N Engl J Med, 2010. **363**(19): p. 1812-21.
37. Korbi, S., et al., *[Epstein-Barr virus in Hodgkin's disease: the example of central Tunisia].* Ann Pathol, 2002. **22**(2): p. 96-101.
38. Jacobson, C.A. and A.S. Freedman, *First-line treatment of indolent lymphoma: axing CHOP?* Lancet, 2013. **381**(9873): p. 1163-5.
39. Bollard, C.M., et al., *Cytotoxic T lymphocyte therapy for Epstein-Barr virus+ Hodgkin's disease.* J Exp Med, 2004. **200**(12): p. 1623-33.
40. Piccaluga, P.P., et al., *Pathobiology of Epstein-Barr virus-driven peripheral T-cell lymphomas.* Semin Diagn Pathol, 2011. **28**(3): p. 234-44.
41. Chan, A.T., *Nasopharyngeal carcinoma.* Ann Oncol, 2010. **21 Suppl 7**: p. vii308-12.
42. Hippocrate, A., L. Oussaief, and I. Joab, *Possible role of EBV in breast cancer and other unusually EBV-associated cancers.* Cancer Lett, 2011. **305**(2): p. 144-9.
43. Smith, C.A., et al., *CD30 antigen, a marker for Hodgkin's lymphoma, is a receptor whose ligand defines an emerging family of cytokines with homology to TNF.* Cell, 1993. **73**(7): p. 1349-60.
44. Horie, R. and T. Watanabe, *CD30: expression and function in health and disease.* Semin Immunol, 1998. **10**(6): p. 457-70.
45. Pizzolo, G., et al., *High serum level of the soluble form of CD30 molecule in the early phase of HIV-1 infection as an independent predictor of progression to AIDS.* AIDS, 1994. **8**(6): p. 741-5.
46. Zinzani, P.L., et al., *Clinical implications of serum levels of soluble CD30 in 70 adult anaplastic large-cell lymphoma patients.* J Clin Oncol, 1998. **16**(4): p. 1532-7.
47. Nadali, G., et al., *Serum levels of soluble CD30 are elevated in the majority of untreated patients with Hodgkin's disease and correlate with clinical features and prognosis.* J Clin Oncol, 1994. **12**(4): p. 793-7.
48. this is required if {institution} holds the IND. Otherwise, the affiliate Investigator’s signature on the protocol is sufficient to ensure compliance

APPENDICES

Appendix A: ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Appendix B: **Investigational Drug Request/Shipment Record Form**

SeattleGenetics **INVESTIGATIONAL DRUG REQUEST / SHIPMENT RECORD**

PART I – CLINICAL OPERATIONS SHIPPING REQUEST

Complete this section and email or fax to Seattle Genetics: IST@seagen.com or fax 425-527-2016

PRODUCT NAME:	**BRENTUXIMAB VEDOTIN**
PROTOCOL NO:	**35-IST-**
QUANTITY REQUESTED:	Boxes of 10
DATE NEEDED BY:	
INVESTIGATOR NAME:	
SHIPMENT STATUS (CHECK ONE):	☐ Initial Shipment ☐ Re-Supply

Ship To:

(Contact Name)

_____ (Telephone Number)

_____ (Fax Number)

_____ (Site/Institution Name)

_____ (Site/Institution Address)

_____ (Site/Institution City, State / Province, Zip Code, Country)

_____, _____, _____, _____, _____

SATURDAY DELIVERY REQUESTED: ☐ Yes ☐ No ☐ Not Available

SITE REQUESTOR NAME: _____ **PHONE:** _____

SIGNATURE: _____ **DATE:** _____/_____/_____

SGN LOT#: _____ **ALMAC INVENTORY #:** _____

RA APPROVAL/PART II ☐ Required ☐ Not Required

CLINICAL OPERATIONS APPROVAL: _____ **DATE:** _____/_____/_____

PART II- REGULATORY AFFAIRS SHIPPING APPROVAL

(*Check One*) ☐ **Initial shipment to first site of country:** _____ ☐ **Compassionate Use (Single Patient IND)**

IND accepted? ☐ Yes ☐ No Process released? ☐ Yes ☐ No

Protocol filed to IND? ☐ Yes ☐ No Process ID (Lot prefix): _____

RA APPROVAL: _____ **DATE:** ___/_____/_____

PART III – PACKAGING AND SHIPPING

US: Email to palogistics.clinicalservices@almacgroup.com

Canada/Europe: Email to uklogistics.clinicalservices@almacgroup.com

Shipping details can be located on the Almac Packing List.

Part IV – STUDY SITE RECEIPT ACKNOWLEDGEMENT

Complete this section and fax to +1-425-527-4309
File original in study files

Shipment Receipt Conditions

Package intact?	☐ Yes	☐ No*	Correct quantity per Section I?	☐ Yes	☐ No*
Correct product per Section I?	☐ Yes	☐ No*	Alarm triggered?	☐ Yes	☐ No
Correct lot # per Section I?	☐ Yes	☐ No*			

* Provide explanation in Comments section below

Complete IP Quality Complaints & Temperature Excursions Form (FM.224)

Comments:

RECIPIENT NAME: _____ SIGNATURE: _____ DATE REC'D: _____/_____/_____

Appendix C Protocol History of Changes by Amendment

Original Version Approved by the Northwestern University IRB – October 23, 2012			
Updated Version Approved by the Northwestern University IRB – November 8, 2012			
Amendment 1 – July 25, 2013*** *Approved by Scientific Review Committee – August 7, 2013* *****NOTE: This was originally approved by SRC on June 13, 2013 – the amendment was then updated based on the memo from Seattle Genetics (dated July 9, 2013) and additional changes requested July 25, 2013***** ***Section(s) Affected***	***Prior Version***	***Amendment 1 Changes***	***Rationale***
Cover-page	IND listed as *pending*.	Updates IND# to 117197.	Administrative
Cover-page	Dr. Andrew Evens listed as the local PI for UMass.	Removes UMass as a participating site and adds Dr. Evens as the local PI for Tufts University.	Administrative – Dr. Evens is now at Tufts and UMass will no longer be participating on this trial.
Sections 1.1 (Disease Background) & 1.3 (Rationale)	n/a	Adds background on indolent lymphomas in patients with autoimmune disorders and the lack of data to support R-CHOP as frontline therapy for these individuals.	Provides background and rationale for their inclusion in the study population on a case-by-case basis.
Section 1.2.1.1 (Brentuximab vedotin – Toxicity Summary)	n/a	Adds updated background information regarding pancreatitis and brentuximab vedotin.	Added based on recent observations in other clinical trials and memo from Seattle Genetics summarizing a recent internal review.
Section 3.1 (Inclusion Criteria)	No mention of whether or not non-PTLD cases of immunosuppression are eligible.	Adds the following: ***NOTE: Patients who are immunosuppressed for reasons other than PTLD <u>may</u> be eligible if, in the opinion of the treating investigator, the risk of immediate treatment with R-CHOP outweighs the benefit for these patients.***	Added based on feedback from participating sites/investigators.
Section 3.1 (Inclusion Criteria)	No exceptions mentioned for patients with abnormal renal function.	Adds an exception to allow patients with abnormal renal function in cases where the abnormal function is due to allograft dysfunction resulting from diagnosis of PTLD, or from reduction/cessation of immunosuppression aimed at treatment of PTLD.	Added to avoid excluding patients who might otherwise be eligible and good candidates for the study.

Section 3.2 (Exclusion Criteria)	n/a	Adds that patients diagnosed with DLBCL who do not have a defined history of immunosuppression or EBV-related DLBCL of the elderly should not be enrolled in this study.	Exclusion added based on feedback from participating sites/investigators..
Section 3.2 (Exclusion Criteria)	n/a	Adds exclusion for patients with prior documented pancreatitis.	Added for safety reasons.
Section 4.1.3 (Phase II treatment)	Simply stated that treatment would be at the MTD according to the same schedule used in phase I.	Expands treatment schedule details for induction, consolidation, and maintenance therapy for phase II patients. Gives specific instructions for patients achieving CR, PR, SD, or PD after induction therapy.	Clarifications necessary as trial prepares to enter phase II.
Section 4.1.6 (Administration details)	Does not specify whether rapid infusion of rituximab is allowable.	Clarifies that rapid infusion of rituximab is allowable after the first dose at the discretion of the treating investigator.	Clarification
Section 4.3 [Dose-Limiting Toxicity (DLT) and Maximally Tolerated Dose (MTD)]	n/a	Adds the following as an exclusion to the definition of DLT for future patients: *Cases involving hyperbilirubinemia that is primarily indirect, and considered not reflective of underlying liver disease (ie, resulting from transfusion of red blood cells), will not be considered a DLT.*	Clarification
Section 4.3 – Table 2 (Hematological Toxicity Dose Reductions for Brentuximab vedotin)	For the first occurrence of ANC 500-999/μL, Table 2 stated to hold the current dose.	Changes this to state that the treating investigator should be notified, and it will be at his or her discretion whether to hold the dose.	Changed based on the PI's recommendation to allow for investigator's assessment.
Section 4.3 (Toxicity and Dose Delays/Dose Modifications)	n/a	Adds separate instructions regarding the management of hyperamylaseemia and pancreatitis.	Added for safety reasons and to increase monitoring of these events.
Section 4.3 – Table 3 (Non-Hematological Toxicity Dose Reductions for Brentuximab vedotin & Rituximab)	n/a	Adds the following clarification regarding elevated bilirubin: *In cases involving hyperbilirubinemia that is primarily indirect, and considered not reflective of*	Clarification.

		underlying liver disease (ie, resulting from transfusion of red blood cells), treating investigators may consider avoiding protocol-specified dose reductions, after consultation with principal investigator.	
Section 5.0 Study Procedures)	n/a	Adds serum amylase to be drawn up to 72 hours prior to brentuximab vedotin dosing, with instructions to also test lipase if amylase is elevated and modify dose as needed based on guidelines added to Section 4.3.	Added for safety reasons and to increase monitoring of these events.
Sections 1.4 (Correlative Studies), 2.5 (Exploratory Objectives), 5.1 (Screening and/or Baseline Procedures), 5.2 (Procedures During Treatment), 5.4 (Time and Events Table), 9.1 (Objectives of correlative studies), 9.2.5 (Objective 5), & 9.3 (Specimen Collection Guidelines)	Did not include specific information on peripheral blood to be drawn for correlative testing.	Specifies that one red top and one green top tube will be collected for banking of samples for future, unspecified use. Clarifies that this will be done for phase II patients only. Gives details for procuring and storing the samples. Includes timeframes for these collections (baseline, Day 1 of induction, and Day 1 of the first 3 maintenance therapy cycles).	The protocol allowed for peripheral blood to be drawn for correlatives in section 9.0, but the details were not specified.
Appendices	n/a	Adds Appendix D – Protocol History of Changes by Amendment	Administrative
Amendment 2 – October 15, 2013 *Approved by Scientific Review Committee – October 16, 2013*			
Section(s) Affected	***Prior Version***	***Amendment 2 Changes***	***Rationale***
Schema, 4.0 (Treatment Plan), 5.4 (Table 4 – Time & Events Table),	Cycle length unclear from one phase of treatment to the next.	Clarifies cycle length for induction and consolidation as 4 weeks and for maintenance as 3 weeks. Removes references to specific study weeks as the time between re-staging and the start of the next phase of therapy is meant to be flexible to allow patients to proceed when	Clarification

		they are ready per treating investigators' discretion.	
3.1 (Inclusion Criteria)	n/a	Adds a statement regarding the requirement for measureable disease that *patients are eligible after resection of disease* (and will be evaluable for all endpoints besides response).	Added to enhance eligibility parameters.
3.1 (Inclusion Criteria)	n/a	Adds that patients may have received up to 1 prior dose of rituximab before registration.	Added to enhance eligibility parameters.
4.3 (Toxicities and Dosing Delays/Dose Modifications)	No mention of restarting or increasing doses of brentuximab after interruption/decrease due to toxicity.	Revised to permit restarting and/or increasing the dose of an individual patient's brentuximab vedotin in the event that toxicity completely resolves (for cases where it was stopped or decreased for toxicity in that same patient).	Changed by PI to avoid under-treating patients.
4.3 (Table 3 – Non-hematologic dose reductions)	Rituximab also required to be held in the event of all grade 3-4 non-hematologic toxicities.	Changed to permit continuation of rituximab for grade 3-4 non-hematologic toxicities that are clinically attributed to brentuximab vedotin.	Changed by PI to avoid under-treating patients.
4.3 (Table 2 – Hematologic dose reductions)	Dose modifications listed in one table for both ANC and platelet toxicities.	Splits Table 2 in to Table 2a and 2b to distinguish between ANC and platelet events (they should be handled separately and not as *either*/*or* in terms of when to hold or reduce brentuximab vedotin.	Clarification
7.0 (Adverse Events), 11.0 (Study Management), Appendix C (Data Collection and Submission for Phase I Patients), Appendix E (Data Collection and Submission for Phase II Patients), Appendix F (Slot Reservation Procedure),	Contained outdated and/or generic language pertaining to AE reporting, registration procedures, data submission guidelines and requirements, and study monitoring.	Updates language and introduces new, study-specific procedures, requirements, guidelines, and forms.	Administrative update

Appendix G (Data Safety Monitoring Plan), Appendix H (NU CRO SAE Form)			
Amendment 3 – March 24, 2014 *Approved by Scientific Review Committee: May 2, 2014*			
Section(s) Affected	***Prior Version***	***Amendment 3 Changes***	***Rationale***
4.3 (Toxicities and Dosing Delays/Dose Modifications)	Dose modifications given for asymptomatic hyperamylasemia referenced "normalizing" of lipase and amylase levels prior to restarting brentuximab vedotin.	Revises guidelines for asymptomatic elevated amylase and lipase to reflect instructions by grade (1-2 no change, 3-4 hold dose until ≤ grade 2 and then resume as described).	Changed based on experience with current patients & the advice of Seattle Genetics.
4.1.3 (Phase II Treatment)	Stated that all patients with PR or CR after initial re-staging would proceed to Consolidation.	Changes this to state that patients *may* receive Consolidation but in some cases, those with CR after Induction may proceed directly to Maintenance therapy at the discretion of the treating investigator.	This was changed to avoid excessive toxicity and allow for more flexibility in the treatment plan for each patient.
Amendment 4 – March 18, 2015 *Approved by Scientific Review Committee: March 18, 2015*			
Section(s) Affected	***Prior Version***	***Amendment 4 Changes***	***Rationale***
1.2.1.1 (Brentuximab vedotin Toxicity Summary) & 8.1.10 (Side effects)	***n/a***	Clarified that safety data are based on oncology studies and that 1.8 mg/kg is the recommended dose for the approved indications. Added toxic epidermal necrolysis and pulmonary toxicity with monotherapy as notable adverse events. Added results of studies in patients with hepatic or renal impairment.. Updated side effects.	Updated Version 12 of Brentuximab vedotin IB released.
3.2.12 (Exclusion Criteria)	n/a	Added exclusion "Patients with severe renal impairment (CrCL <30 mL/min). A calculated CrCl is acceptable."	Added due to Updated Version 12 of Brentuximab vedotin IB.

8.1.12 (Nursing /patient implications*)*	n/a	Revised to add: Avoid use in patients with severe renal impairment Avoid use in patients with moderate or severe hepatic impairment (Child-Pugh B or C).	Updated prescribing information released
Amendment 5 – November 16, 2015 *Approved by Scientific Review Committee: December 17, 2015*			
Section(s) Affected	***Prior Version***	***Amendment 5 Changes***	***Rationale***
Cover-Page	Adam Petrich listed as Principal Investigator and IND Holder	Adam Petrich has been removed as PI and Jason Kaplan has been added; contact information and IND Holder Name have been updated appropriately	Administrative: Adam Petrich has left the institution and will no longer serve as the study PI; Jason Kaplan will take over role of PI
Cover-Page, 1.4.1 (Correlative Studies) & 9.3 (Sample Collection Guidelines)	Amy Chadburn listed as Sub-Investigator & hematopathologist	Amy Chadburn has been removed and replaced by Amir Behdad as Sub-Investigator and hematopathologist involved in TMA analysis	Administrative: Amy Chadburn has left the institution and Amir Behdad has taken over her role on this study
Signature Page	Signature Page included	Signature Page removed	Administrative: NU protocol template no longer includes a signature page
4.3 (Toxicities and Dosing Delays/ Dose Modifications)	Language allowed for holding study treatment due to toxicity	Language has been added to clarify that study treatment should be skipped rather than held. Table 2a & 2b reflect changes by replacing the word “Hold” with “Withhold” or “Skip treatment” in each line	Clarification
5.4 (Table 4: Time and Events Table) & 9.3 (Sample Collection Guidelines)	The footnote (#) for peripheral blood banking and instructions in 9.3 called for samples at baseline, day 1 of induction, and day 1 of the first 3 maintenance cycles	The footnote (#) and instructions in 9.3 now state that samples should be collected at baseline OR day 1 of induction. The word “products” has been added to clarify that “blood products” rather than “blood” will be frozen and stored for future, unspecified use	Clarification
5.4 (Table 4: Time	The footnote (@) for serum amylase states	This has been changed to state that the test may be	Clarification

and Events Table	that the test may be drawn 72 hours prior to dosing	drawn *up to* 72 hours prior to dosing	
9.3 (Sample Collection Guidelines)	Pathology Core Facility is listed as the center for picking up correlative samples	Clinical Trials Pathology Office will pick up and store correlative samples	Administrative: Pathology Core Facility has changed their name to Clinical Trials Pathology Office; they will also be responsible for storing samples
9.3.1 (Blood Processing and Shipping)	n/a	Details have been provided for processing and shipping of correlative samples (Red Top Tube and Green Top Tube drawn at Baseline and day 1 of the first 3 maintenance cycles)	Updated with new information for correlative sample analysis
Amendment 6 – March 15, 2016 *Approved by Scientific Review Committee: March 15, 2016*			
Section(s) Affected	***Prior Version***	***Amendment 6 Changes***	***Rationale***
Study Schema, 2.3.3 (Primary Endpoints),	There were many discrepancies in the protocol about when patient scans and the Phase II primary objective assessment would take place	Scans will be performed after induction, after consolidation (if applicable), and every 12 weeks (4 cycles) thereafter during maintenance	Clarification for many discrepancies in the protocol which have caused deviations; new study PI decided on a straightforward scanning schedule of q12weeks
3.0 (Patient Eligibility)	Inclusion and exclusion criteria listed as incomplete phrases	Lists inclusion and exclusion criteria as complete sentences	Grammatical clarification
4.1.1 (Phase I Dosage), 4.1.2 (Phase II Dosage)	Listed maintenance treatment continuing for one year or until PD	Lists maintenance treatment continuing for one year from starting induction or until PD	Clarification – previous language may be interpreted as maintenance continuing for one year, when total treatment (including induction and consolidation) should be one year
4.1.1 (Phase I Dosage)	"Those patients *failing to achieve CR* after the Induction course may receive an additional treatment of the same (termed Consolidation)"	"Those patients *who achieve response (PR or CR)* after the induction course may receive an additional treatment…"	Clarification
Schema; 4.1.2 (Phase I treatment plan); 4.2 (DLT & MTD)	DLT period is first 21 days of treatment / first cycle (cycle = 21 days)	DLT period is the first 21 days of induction	Clarification – prior language was unclear whether DLT period is during induction or maintenance therapy
4.2 (DLT & MTD),	CTCAE v4	CTCAE v4.03	Administrative update

6.1.2 (Safety/ tolerability) 7.2.2. (Severity of AE's)			
5.4 (Table 4: Time and Events Table	Table did not include complete information about study procedures and treatment	Table has been reformatted completely. Changes include: -Separate columns for Induction, Consolidation, and Maintenance, including study visit time points and cycle lengths -Includes a row for Brentuximab vedotin and Rituximab administration -Replaces "Tumor Assessment" and "Response Assessment" with simply "Scans"; timing of scans has also been clarified as being q12weeks in Maintenance -Includes screening window and study visit windows -Replaces footnote symbols with numbers	Major clarifications
9.3.1 (Blood Processing & Shipping)	Listed Clinical Trials Pathology office (CTPO) for sample processing	Changes sample processing center for Pathcore Facility Clinical Trials Unit (PCF-CTU)	Administrative name change
7.1 (Adverse Event Monitoring), 11.5 (Data Management and Monitoring/ Auditing), Appendices	Study monitoring plan and data submission guidelines were included as Appendix C, E, and G	Removes Appendix C, E, and G and any references in the protocol; instead references NOTIS for such guidelines	Administrative – aligns with current departmental policies
Appendices	Included the NU SAE Form as Appendix H	Removes Appendix	Administrative – the most recent version of the SAE form can be found elsewhere
Amendment 7 – November 14, 2016 *Approved by Scientific Review Committee: December 16, 2016*			
Section(s) Affected	***Prior Version***	***Amendment 7 Changes***	***Rationale***
Title Page; Study Summary	Title: "A Phase I-II Trial of Brentuximab Vedotin Plus Rituximab as Front-Line Therapy for Patients with **CD30+ and/or EBV+ Lymphomas**"	Title: "A Phase I-II Trial of Brentuximab Vedotin Plus Rituximab as Front-Line Therapy for Patients with **Lymphomas Associated with Immunosuppression**"	It is no longer a requirement for patients to be CD30+, as long as the lymphoma is associated with a state of immunosuppression as listed in 3.1.1. CD30 and

			EBV status will still be investigated in all patients.
Title Page	n/a	Adds Reem Karmali as sub-Investigator	Administrative – new faculty
Study Schema; Study Summary; 2.1 (Primary Objectives); 3.1.1 (Inclusion Criteria)	Patients were required to have CD30+ and/or EBV+ lymphoma	Patients are not required to specifically have CD30+ or EBV+ lymphoma, but rather a lymphoma that is associated with immunosuppression (e.g. PTLD, DLBCL of the elderly etc. as listed in 3.1.1). This may include patients with CD30+ or EBV+ lymphoma.	The overall purpose of requiring CD30+ or EBV+ status was to ensure patients had lymphoma associated with immunosuppression. Degree of CD30 positivity doesn't correlate to response to BV, and conventional methods of assessing CD30 have limitations. Therefore removing this requirement is appropriate.
Study Summary	Included "Short Title"	Removes "Short Title"	To align with current protocol template and avoid deviating from the title in CT.gov
3.1.5 (Inclusion Criteria)	NOTE: Patients with fully resected disease are eligible, and will be evaluable for all toxicity and efficacy endpoints except response.	NOTE: Patients with fully resected disease are eligible, and will be evaluable for all toxicity and efficacy endpoints except **objective** response.	Clarification to specify that the only efficacy endpoint affected by resected disease is objective response.
4.3 (Toxicities and Dosing Delays/Dose Modifications)	n/a	Adds "pre-dose lab values must be assessed prior to dosing at each treatment visit".	Clarification requested by IRB to avoid inappropriate patient dosing.
4.8 (Removal of Patients from Protocol Therapy); 5.5 (Removal of Subjects from Treatment and/or Study)	Included language in 4.8 on removing patients from treatment, and referenced sections 4.6 and 5.5.	Compiles all language about patient discontinuation into section 4.8 (moved from section 5.5). This incorporates removal from both treatment and study.	Information was previously redundant; language is now simplified and aligns with current protocol template setup.
5.0 (Study Procedures)	• Included paragraph listing of all study procedures prior to the study table • n/a	• Removes paragraph description of study procedures • Adds footnote #3 to state "CBC and Chemistry panels must be resulted prior to dosing to assess the need for dose delays or modifications". Also adds notes to #6 & #7. Re-numbers footnotes.	• Including both descriptions is redundant. The table aligns with the current protocol template. • Clarification requested by IRB to avoid inappropriate patient dosing.
6.1 (Toxicity Definitions);	Listed limited descriptions of	Includes descriptions of evaluability for each study	Clarification requested by internal Quality

6.2 (Efficacy Definitions)	evaluability for endpoints (just overall "toxicity" and objective response)	endpoint (toxicity, safety, survival [PFS, OS], and each exploratory objective)	Assurance team.
6.2.1.1 (Evaluable for objective response)	n/a	Defines measurable disease as "at least 1 cm"	Clarification for consistency
7.2.2 (Severity of AE's)	CTCAE v4.0	CTCAE v4.03	Administrative update
8.1.4.3 (Special Handling)	n/a	"Each study site will be responsible for regular inventory checks and disposing of expired drug in a timely manner"	Clarification requested by the IRB to ensure expired drug is disposed of appropriately and to avoid the risk of dispensing to patients.
11.5 (Data Management and Monitoring/ Auditing	n/a	Adds "All participating sites are responsible for entering data in the timeframe outlined in the data submission guidelines."	Clarification requested by the IRB to encourage timely data submission.
Amendment 8 – June 14th, 2017 *Approved by Scientific Review Committee:*			
Section(s) Affected	***Prior Version***	***Amendment 8 Changes***	***Rationale***
Cover Page	Jason Kaplan was affiliated with Northwestern Medicine Development Therapeutic Institute	Changes affiliation to Developmental Therapeutics Program of Department of Hematology Oncology	Administrative
Study Schema; 2.3.2 (Primary Endpoints)	"Primary objective assessment: after week 4 treatment (Phase I only); after cycle 4 and 8 of maintenance (Phase II only)"	"Primary objective assessment: **toxicity** after week 4 treatment (Phase I only); **scans** after **induction treatment and/or after consolidation treatment (if applicable)** (Phase II only)"	Clarification to align with protocol objectives in each phase and appropriate timing. The intention was to look at response after induction and/or consolidation, when applicable.
Study Summary	Included University of Massachusetts as an affiliate	Removes University of Massachusetts	To fix discrepancy; had been previously removed everywhere else.
Study Summary	IV frequency listed as "weekly" or "every 3 weeks"	Adds **once** weekly and **once** every 3 weeks	Clarification
2.2.3 (Secondary Objectives); 2.4.3 (Secondary Endpoints)	n/a	Adds an objective and endpoint to look at best response to therapy, with scans after induction and/or consolidation, and every 12 weeks during maintenance	Added per PI discretion to analyze more long-term response results
2.3.1 (Primary Endpoints)	Defined DLT as the occurrence of ≥ Grade 3 toxicity	Removes Grade 3 definition and refers to section 4.2, which contains a more detailed definition	DLT definitions are different for non-hematologic (≥G3) vs hematologic (≥G4) toxicities
3.0 (Patient Eligibility)	n/a	Adds introductory language with the overall population,	To align with current NU protocol template

		participating sites, accrual, and registration details.	language
3.1.1 (Inclusion Criteria)	"Patients must have a histologically confirmed CD20+ lymphoid malignancy…"	Replaces "lymphoid malignancy" with lymphoproliferative disease	Clarification – lymphoproliferative disease is inclusive of non-malignant disease, as intended
3.1.2 (Inclusion Criteria)	"In cases of **PTLD** arising in patients who are pharmacologically immunosuppressed…" "NOTE: Patients who are immunosuppressed for reasons other than PTLD may be eligible…"	"In cases of **lymphoproliferative disease** arising…" NOTE: Patients who are **otherwise** immunosuppressed **(for reasons such as immune dysregulation related to autoimmune conditions, in the absence of pharmacological immunosuppression)** may be eligible…"	Clarification; any study patient may have pharmacologic immunosuppression, not just PTLD patient
3.1.3, 3.1.4 (Inclusion Criteria); 3.2.1 (Exclusion criteria)	Requirements to have no prior treatment or surgical intervention included as inclusion criteria	Removed from inclusion and included as exclusion criteria 3.2.1 and 3.2.3.	More appropriate as exclusion criteria
3.2.1 (Exclusion Criteria)	Excluded patients with no history of immunosuppression or EBV-related DLBCL	Removes exclusion criteria	Redundant of inclusion 3.1.1, which states that lymphoproliferative disease must be immunosuppressed
3.2.2, 3.2.1 (Exclusion Criteria); 4.1.1.2.1 (Pre-Registration Rituximab)	n/a	Patients are allowed to receive one dose of rituximab prior to entering the study, and in such cases, patients will only have 3 doses during induction (a total of 4 doses)	Added for clarification and consistency
3.2.4, 3.2.5 (Exclusion Criteria); 4.4.3 (Concomitant medications and treatments not allowed)	n/a	Clarifies timing of washout as 4 weeks or 14 days prior to registration for unrecovered AE's, chemotherapy, radiotherapy or investigational agents, respectively	Clarification
3.2.11 (Exclusion Criteria); 5.0 (Study Procedures)	Patients were not eligible with clinically active Hep A, B, or C	Clarifies that Hep B will be tested at screening, and Hep A and C will be based on known history. Adds Hepatitis B testing within 4 months prior to registration.	Hepatitis B testing is standard prior to rituximab treatment.
4.0 (Treatment Plan)	n/a	Adds paragraph and table as a treatment summary	Added for clarity and simplification

		before subsequent details of dosage and administration (updates all subsequent table numbers and references)	
4.1.1 (Phase I and II dosage); 4.1.3 (Phase II Treatment)	Referred to Phase I dosing only	Refers to both Phase I and II dosing details with a statement that RP2D was found to be the same as Phase I dosing on 3/12/2014. Refers to section 4.1.3 for Phase II instructions for treatment after SD	Updated for accuracy and simplicity
4.1.6 (Administration Details, Table 2)	Rituximab treatment for the full study was listed in a shaded box	Separates rituximab treatment by induction/consolidation vs maintenance, similar to BV	Revised for clarity
4.2 (DLT and MTD)	n/a	Adds “For Phase I…” to preface DLT definitions	Clarification
4.3 (Toxicities and Dosing Delays/Dose Modifications)	Referenced section 1.3.1.1 for risk information	Updates to section 1.2.2.1	Revised for accuracy
	Tables listed dose reduction instructions for hematologic and non-hematologic toxicities	Adds “Drug-related” prior to toxicity descriptions	Added for clarity
4.4 (Concomitant Medications / Treatments)	Required Tylenol and Benadryl with specific doses and timing prior to infusions	Adds “or equivalent as per standard practice”	To allow flexibility and avoid unnecessary deviations
4.7 (Duration of Follow Up); 5.0 (Study Procedures #11)	Follow up was to take place for up to 3 years from start of treatment	Follow up will take place for up to 3 years from **discontinuation** of treatment	Correction of discrepancy and to standardize safety follow-up for all patients
5.0 (Study Procedures)	Listed “Informed consent and demographic information”	Removes “Demographic information”	Demographic information will be collected by default during H&P
	#2: Scans were to take place after week 4 and week 8	• Changes scans to after induction and after consolidation • Adds that patients with a CR after induction do not need to repeat a scan after consolidation • Adds that although PET/CT is preferred, patients may be assessed by CT alone at any time point	• Clarification, allowing flexibility in exact timing of induction and consolidation • To account for standard practice and the possibility of insurance denial • “”
	#7: n/a	#7: Adds that consolidation and maintenance should start 7-21 days after the fourth induction or consolidation dose of	Adds guidance with flexibility

		rituximab	
	#9: Performance status was to be performed every 4 months during maintenance	Removes note about PS	PS is standard to collect at each visit
	n/a	#12: Adds note with criteria for patients to receive optional consolidation	Clarification
	Procedures were listed by weeks with no indication of the actual day of procedures	Adds footnote 13 to clarify that procedures will take place on Day 1 of each week	Clarification
Amendment 9 – December 12, 2017			
Section(s) Affected	***Prior Version***	***Amendment 9 Changes***	***Rationale***
Cover Page; 3.0 (Patient Eligibility)	Study PI was Dr. Jason Kaplan	Updates study PI to Dr. Barbara Pro	Administrative faculty change due to Dr. Kaplan leaving the institution
Cover-page	Dr. Andrew Evens listed as the local PI for Tufts.	Removes Dr. Evens and lists Dr. Andreas Klein as the local PI for Tufts University.	Administrative – Dr. Evens is leaving Tufts and has identified Dr. Klein as the replacement sub-I

Appendix D: Slot Reservation Procedure

1. The Quality Assurance (QA) Department at Northwestern University will coordinate subject and cohort assignments. The QA Department may be contacted by email at croqualityassurance@northwestern.edu.

   All correspondence regarding subject and cohort assignments should only be directed to and received from members of the QA Department.

2. All sites open to accrual will be notified by the QA Department that the study/cohort is open for accrual and the number of slots to be filled in each cohort or part of the study.

3. Upon identification of a potential protocol patient, the site staff should submit the attached Slot Reservation Form. The Slot Reservation Form will capture proposed dates for:

   a) Proposed date of consent

   b) Start of treatment (C1D1).

4. The Slot Reservation Form should then be submitted electronically to the QA Department (croqualityassurance@northwestern.edu. Slot Reservation Forms will ONLY be accepted electronically. Phone calls and faxes will NOT be accepted. Slots will be assigned on a first come, first serve basis.

5. Upon receipt of the Slot Reservation Form, a member of the QA Department will send written documentation to the site within 24 hours that the Slot Reservation Form has been:

   a) Accepted and a slot has been reserved
   b) Added to the waitlist

6. If the Slot Reservation Form is accepted, the site has until the date specified on the approved reservation form to register the patient. After the specified date the slot reservation will expire. 24 hours prior to this expiration, if patient has not yet been registered, site will receive written notification that the slot will expire in 24 hours. At this point, the site can file a Slot Reservation Extension Form; however the Slot Reservation Extension will be granted or denied at the sole discretion of the QA Department. Filing a Slot Reservation Extension Form does NOT guarantee that the extension will be granted. Site will be notified electronically prior to the original Slot Reservation expiration whether or not the Extension has been granted.

7. After receiving official notification that Slot Reservation Form has been approved, patient consent and screening can begin.

8. Please Note: ONLY patients with Slot Reservation Approval electronically signed by a member of the QA Department of Northwestern University will be registered to the study. If patient initials from the approved slot reservation form do not match the initials of the patient site is registering, registration WILL be rejected.

9. If the patient is not eligible or decides not to participate, the QA Department must be notified ASAP. In this case the slot reservation for that patient will be cancelled, and the slot will be returned to the pool for re-allocation.

10. The QA Department will communicate with the sites regularly to update the status of any open slots within a cohort, as well as any suspensions or re-openings.

Slot reservations are per patient, not per institution, and cannot be transferred or held indefinitely.

THE CLINICAL RESEARCH OFFICE OF THE ROBERT H. LURIE COMPREHENSIVE CANCER CENTER OF NORTHWESTERN UNIVERSITY

SLOT RESERVATION FORM

Date of Submission: _____

Site Number/Name: _____

Patient Initials: _____

Planned Date to Obtain Consent: ____/____/____

Planned Date for Cycle 1 Day 1: ____/____/____

Comments:

_____

_____

_____

_____

_____

_____

Form Submitted by: _____

Contact Information: _____

Please email this form to the QA Department at croqualityassurance@northwestern.edu

QA use Only:
Status:_____
Date of Expiration (Slot reservation will expire on this day. The patient will only be registered before this date): _____
QA Signature:_____
Date: _____
(Printed QA name indicates an electronic signature)

THE CLINICAL RESEARCH OFFICE OF THE ROBERT H. LURIE COMPREHENSIVE CANCER CENTER OF NORTHWESTERN UNIVERSITY

SLOT RESERVATION EXTENSION FORM

Date of Submission: _____

Site Number/Name: _____

Patient Initials: _____

Length of Extension Requested: _____

Planned Date for Cycle 1 Day 1: ____/____/____

Reason for Extension Request:

_____

_____

_____

_____

_____

Form Submitted by: _____

Contact Information: _____

Please email this form to the QA Department at croqualityassurance@northwestern.edu

QA use Only:
Status:_____
Length of extension granted: _____
Date of Expiration (Slot reservation will expire on this day. The patient will only be registered before this date): _____
QA Signature:_____ Date:_____
(Printed QA name indicates an electronic signature)