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Study Number: CASE1415

Study Title: A Phase II Study of Single Agent Brentuximab Vedotin in Relapsed/Refractory CD30 Low (<10%) Mature T-Cell Lymphoma (TCL)

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SCHEMA

Title: A Phase II Study of Single Agent Brentuximab Vedotin in Relapsed/Refractory CD30 Low (<10%) Mature T Cell Lymphoma (TCL)

Objectives:

Primary Objective:

- To determine overall response rate (ORR) of Brentuximab Vedotin in CD30 low (<10%) relapsed or refractory mature T cell lymphoma (TCL)

Secondary Objectives:

- Complete remission (CR) rate
- Duration of response (DOR)
- Progression free survival (PFS)
- Overall survival (OS)
- Time to treatment failure (TTF)

Lab Correlatives:

- To assess and compare the sensitivity of immunohistochemistry (IHC) with imaging analysis and RT PCR methods to detect CD30

Patient Population:

- CD30 low (<10%) relapsed or refractory mature T cell lymphoma (TCL) patients who have received at least one prior therapy.

Study Design:

Phase II study of Brentuximab Vedotin in CD30 low (<10%) mature TCL as determined by current standard IHC.

Inclusion Criteria:

- Histologically confirmed relapsed/refractory CD30 low (<10%) TCL - including peripheral TCL not otherwise specified (PTCL NOS), angioimmunoblastic T cell lymphoma (AITL), hepato-splenic T cell lymphoma (HTCL), adult T cell leukemia/lymphoma (ATLL), enteropathy associated T cell lymphoma (EATL), and NK T cell lymphoma (NK/TCL)
- CD30 level to be determined by IHC using the anti-CD30 BerH2 antibody
- At least 1 prior chemotherapy regimen
- Measurable disease ≥1.5 cm seen on CT scan and/or FDG avid disease on PET scan. Splenomegaly measuring >12 cm, if attributed to TCL and/or positive bone marrow involvement with T cell lymphoma are also eligible
- ECOG performance status (PS) of 0-2. ECOG 3 is permitted if the decreased PS is secondary to lymphoma

- Age 18 years and above
- Able to give informed consent
- Adequate organ function
  - Bilirubin ≤1.5X upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3X ULN even in patients with documented hepatic involvement with lymphoma
  - Serum creatinine clearance ≥30 ml/min
  - Absolute neutrophil count (ANC) ≥1000/μL (unless documented bone marrow involvement with lymphoma)
  - Platelet count ≥50,000/μL (unless documented bone marrow involvement with lymphoma)
- At least 6 weeks from autologous stem cell transplantation
- At least 3 months from allogeneic stem cell transplantation and off immunosuppression and no evidence of graft versus host disease (GVHD)
- Previous treatment with Brentuximab Vedotin (BV) will be allowed if it was done 6 months prior to enrollment and pt was not refractory or had progressive disease (PD) while on BV
- Females of childbearing potential must have a negative serum or urine pregnancy test result within 7 days prior to the first dose of study treatment. Women of child-bearing age must agree to use an effective contraception method during the study and for at least 6 months following the last dose of study drug. Females of non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy.
- Males who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 6 months following the last dose of study drug.

Exclusion Criteria:

- Anaplastic large cell lymphoma (ALCL) both alk positive and negative
- Cutaneous T cell lymphomas including transformed MF
- Prior treatment with Brentuximab in the last 6 months or previously refractory to BV or had PD while on BV
- Pregnancy or breast feeding women
- Prior malignancy within the past 3 years except non melanoma skin cancer or other localized cancer treated with curative intent
- Presence of grade >2 peripheral neuropathy or patients with the demyelinating form of Charcot-Marie-Tooth syndrome.
- Presence of central nervous system (CNS) involvement requiring active treatment
- History of progressive multifocal leukoencephalopathy (PML)
- Myocardial infarction within the past 6 months
- Patients with the following medical conditions that could affect their participation in the study:
  - any active acute or chronic or uncontrolled infection
  - liver disease including history of viral hepatitis B or C, evidence of cirrhosis, chronic active or persistent hepatitis
  - a known history of HIV

    - symptomatic cardiac disease, including congestive heart failure, coronary artery disease, and arrhythmias
- Prior hypersensitivity to any component in the ADC formulation
- Treatment with chemotherapy or investigational agents within 2 weeks of start of study treatment

Sample Size
We plan to enroll approximately 31 patients to obtain 28 evaluable for overall response rate.

Safety Assessments

Safety assessments will consist of monitoring of adverse events (AEs), physical examinations and laboratory tests. The severity of the toxicities will be graded according to the NCI CTC version 4.0.

End Points
The primary objective is to evaluate overall response rate. Secondary end points analyzed are CR, PFS, OS, DOR, and TTF. Response will be assessed using CT/PET scans according to the revised Cheson criteria [1]. The distribution of PFS and OS will be estimated using the Kaplan-Meier method.

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Prognostic Index for PTCL (PIT)

APPENDIX 5
Summary of Protocol Changes

LIST OF ABBREVIATIONS

ADC	antibody drug conjugate
AE	adverse event
AITL	angioimmunoblastic T-cell lymphoma
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
ATLL	adult T-cell leukemia/lymphoma
AUC	area under the concentration-time curve
β-hCG	beta human chorionic gonadotrophin
CBC	complete blood count
Ceoi	concentration at the end of infusion
CFR	Code of Federal Regulations
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
Cmax	maximum concentration
CNS	central nervous system
CR	complete remission
CRF	case report form
CT	computed tomography
Ctrough	trough concentration
EATL	enteropathy-associated T-cell lymphoma
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EOT	end of treatment
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
GCP	Good Clinical Practice
HEENT	head, eyes, ears, nose, and throat
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio
HRA	Health Regulatory Authority
HTLV-1	human T-cell leukemia virus-1
ICH	International Conference on Harmonisation
IV	intravenous
IDMC	Independent Data Monitoring Committee
IPI	International Prognostic Index

IEC	Independent Ethics Committee
IND	investigational new drug
INN	International Nonproprietary Name
IRB	Institutional Review Board
JCV	John Cunningham virus
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MF	mycosis fungoides
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
MRU	medical resource utilization
MTD	maximum tolerated dose
MUGA	multi-gated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
NK	natural killer
ORR	objective response rate
OS	overall survival
PCP	Pneumocystis jiroveci pneumonia
PCR	polymerase chain reaction
PD	pharmacodynamics
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PR	partial remission
PRO	patient-reported outcome
PTCL	peripheral T-cell lymphoma
SAE	serious adverse event
sALCL	systemic anaplastic large cell lymphoma
SAP	statistical analysis plan
SCT	stem cell transplant
Tmax	time at which the maximum concentration occurs
ULN	upper limit of normal
USAN	United States adopted name
USP	United States Pharmacopeia
WHO	World Health Organization

1.0 INTRODUCTION

1.1 T Cell Lymphoma (TCL)

T cell lymphomas (TCL) are a heterogeneous group of malignancies that are derived from post-thymic T cells. TCL are less frequent and compromises about 10-15% of all NHL and they are more aggressive with inferior survival compared with B cell non-Hodgkin lymphoma (NHL). Peripheral T cell lymphoma (PTCL) consists of several common subtypes such as PTCL not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma (ALCL), and angioimmunoblastic T cell lymphoma (AITL). Less common subtypes include enteropathy associated T cell lymphoma (EATL), hepato-splenic T cell lymphoma (HTCL), NK T cell lymphoma (NKTCL), and adult T cell leukemia/lymphoma (ATLL) associated with HTLV-1. Due to the low overall incidence of these subtypes, they are all commonly grouped together for the purpose of clinical trials.

Due to paucity of data and rarity of the disease, there is no well-established standard of care for PTCL. The 5-year overall survival (OS) rate with current treatment modalities is 30-35% in most PTCL series except for ALK+ ALCL [2], where OS rates in some series approach 70%. Outcomes in relapsed and/or refractory PTCL are worse with no standard salvage regimen. Failure to demonstrate improved outcome with aggressive chemotherapy regimens necessitates exploration of therapy with biologically targeted novel agents. Even though incremental benefit has been observed in the outcome with the advent of the newer agents, it still remains suboptimal. Currently approved agents like romidepsin and pralatrexate have less than desirable response rate (RR) with overall RR (ORR) ranging from 25-29% with only 11-15% achieving a complete response (CR) [3, 4]. Identifying the key targets and agents directed against these targets is crucial to improve results in PTCL.

1.2 Brentuximab Vedotin in TCL

CD30 is a member of the tumor necrosis factor receptor (TNFR) super family commonly expressed on activated T and B cells. The pleiotropic nature of CD30 signaling can result in either cell proliferation and survival or apoptosis and cell death. Interaction of cytoplasmic domain of CD30 with TNFR associated factor (TRAF) family like TRAF1, TRAF2 and TRAF5 leads to the activation of NF κB, which promotes cell proliferation, survival, and inhibits apoptosis [5-8]. CD30 is highly expressed in ALCL and Hodgkin lymphoma and to varying degree in other subtypes of PTCL, CTCL and B cell lymphoma, making it an attractive target for antibody-based therapy.

Brentuximab Vedotin (SGN-35) is an antibody drug conjugate (ADC) consisting of the chimeric anti-CD30 monoclonal antibody, Brentuximab Vedotin, chemically conjugated to the anti-microtubule agent monomethyl auristatin E (MMAE) [9, 10]. After binding to CD30, the ADC is internalized into lysosomes where cleavage of the ADC linker by the lysosomal proteases releases MMAE. The MMAE causes G2/M phase growth arrest resulting in cell death. Considerable response to this agent has

led to its rapid approval for treatment of the relapsed CD30+ diseases, ALCL and Hodgkin lymphoma.

1.3 Clinical Data

The approval of Brentuximab Vedotin in ALCL was based on the phase II study of Brentuximab Vedotin in 58 relapsed or refractory ALCL patients that demonstrated an ORR of 86%, with 57% CR. Median duration of response (DOR) was 13 months, median progression free survival (PFS) 13 months, and median OS was not reached [11]. Fanale et al presented results for the phase I study combining brentuximab with either CHOP (cyclophosphamide, adriamycin vincristine and prednisone) or CHP (CHOP without vincristine) in ALCL, CD30 positive mature T cell and NK cell lymphomas [12]. Objective RR was 100% with 88% attaining a CR. Interim subset analysis of phase II study of brentuximab in CD30 positive NHL was presented at 2013 International Conference of Malignant Lymphoma (ICML) [13]. This analysis illustrated an ORR of 36% with 27% CR in mature T/NK cell lymphoma. Better outcome was observed in AITL patients with an ORR 50% (5/10) compared to 25% (3/12) in PTCL NOS patients.

1.4 CD30 Detection:

At present, a commonly utilized method to detect CD30 is IHC using the anti-CD30 BerH2 antibody. Other methods include flow cytometry and reverse transcriptase (RT) polymerase chain reaction (PCR). The sensitivity for these methods vary. The basis for the activity of brentuximab in low CD30 positive TCL remains unexplained. It is possible that the current available methods used to detect CD30 are not capturing all the cells that are positive thus providing a less than actual expression rate. Newer methods or antibodies for IHC stain may enhance the detection of CD30 expression.

1.5 Rationale for Brentuximab Vedotin in CD30 low T Cell Lymphoma

Recent data suggest that brentuximab is efficacious in cutaneous TCL (CTCL) and PTCL with varying degree of CD30 expression. Data presented at ICML demonstrated clinical efficacy with brentuximab in patients with either undetectable or up to 15% expression of CD30 [13]. Krathen et al presented data showing significant clinical activity with brentuximab in relapsed/refractory mycosis fungoides regardless of CD30 expression [14]. In this study, CD30 was estimated with immunohistochemistry (IHC) using the BerH2 antibody. The ORR was 68%; moreover, response did not correlate with the CD30 expression. Of the 31 biopsies samples taken from 16/19 patients, 12 were negative for CD30 by IHC staining.

Collectively emerging evidence of clinical activity of brentuximab in CD30 negative TCL is intriguing. If significant activity could be demonstrated in CD30 low (≤10%) PTCL, brentuximab will be a valuable addition to the armamentarium to treat patients with relapsed/refractory disease, which otherwise carries a grim prognosis. Based on these emerging data, we propose a phase II study of Brentuximab Vedotin in CD30 low (≤10%) TCL as determined by current standard IHC.

2.0 OBJECTIVES

2.1 Primary Objective

- To determine overall response rate (CR+PR) of Brentuximab Vedotin in CD30 low (<10%) relapsed or refractory T cell lymphoma (TCL)

2.2 Secondary Objective(s)

- Complete remission (CR) rate
- Duration of response (DOR)
- Progression free survival (PFS)
- Overall survival (OS)
- Time to treatment failure (TTF)

2.3 Lab Correlatives:

- To assess and compare the sensitivity of immunohistochemistry (IHC) with imaging analysis and reverse transcription polymerase chain reaction (RT-PCR) methods to detect CD30

3.0 STUDY DESIGN

This is a non-randomized phase II study of single agent Brentuximab Vedotin in CD30 low, <10%, relapsed/refractory T cell lymphoma subjects. All subjects who meet the eligibility criteria described below will be enrolled to participate in the study. Eligibility criteria may not be waived by the investigator.

3.1 Number of Subjects

We plan to enroll up to 31 patients to obtain 28 evaluable subjects to assess ORR.

3.2 Study Discontinuation

Patients may discontinue the study drug for the following reasons:

- Treatment completion
- Disease progression
- Adverse events (AE)
- Subject consent withdrawal
- Investigator decision

All patient discontinuations should be reported to the primary site, Cleveland Clinic study staff.

4.0 PATIENT SELECTION

Patients who meet all the inclusion criteria and have none of the exclusion criteria can be considered eligible for this study.

4.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment:

4.1.1 Patients must have histologically or cytologically confirmed relapsed/refractory

CD30 low (<10%) TCL:

- peripheral TCL not otherwise specified (PTCL NOS)
- angioimmunoblastic T cell lymphoma (AITL)
- hepato-splenic T cell lymphoma (HTCL)
- adult T cell leukemia/lymphoma (ATLL)
- enteropathy associated T cell lymphoma (EATL)
- NK T cell lymphoma (NK/TCL)

4.1.2 At least 1 prior chemotherapy regimen.

4.1.3 Age ≥18 years.

4.1.4 ECOG Performance status 0-2. ECOG PS 3 will be permitted if the decreased

PS is attributed to the lymphoma [See Appendix A].

4.1.5 Patients must have adequate hematologic, hepatic, and renal function as defined below:

4.1.5.1 Absolute neutrophil count ≥ 1,000/mcL (unless documented bone marrow involvement with lymphoma)

4.1.5.2 Platelet count ≥ 50,000/uL (unless documented bone marrow involvement with lymphoma)

4.1.5.3 Total bilirubin ≤1.5X upper limit of normal (ULN),

4.1.5.4 AST (SGOT≤3X ULN even in patients with documented hepatic involvement with lymphoma

4.1.5.5 ALT (SGPT) ≤3X ULN even in patients with documented hepatic involvement with lymphoma

4.1.5.6 Serum Creatinine clearance ≥30ml/min

4.1.6 At least 6 weeks from autologous stem cell transplantation

4.1.7 At least 3 months from allogeneic stem cell transplantation and off immunosuppression and no evidence of graft versus host disease (GVHD)

4.1.8 Previous treatment with Brentuximab Vedotin will be allowed if it was done 6 months to prior to enrollment and was not refractory to or had PD on BV

4.1.9 Measurable disease ≥1.5 cm seen on CT scan and/or FDG avid disease on PET scan. Splenomegaly measuring >12 cm, if attributed to TCL and/or positive bone marrow involvement with lymphoma are also eligible

4.1.10 Females of childbearing potential must have a negative serum or urine pregnancy test result within 7 days prior to the first dose of study treatment.

The effects of Brentuximab Vedotin on the developing human fetus are unknown. For this reason, women of childbearing potential and men must agree to use adequate contraception (double barrier method of birth control or abstinence) for the duration of study participation and for 6 months after completing treatment.

Should a woman become pregnant or suspect that she is pregnant while she or her partner is participating in this study, she should inform the treating physician immediately.

Males who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 6 months following the last dose of study drug.

4.1.11 Subjects must have the ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

The presence of <u>any</u> of the following will exclude a patient from study enrollment.

4.2.1 Myocardial infarction within the past 6 months

4.2.2 Patients who are receiving any other chemotherapy or investigational agents. Radiation treatment will not be permitted during study treatment. Patients can receive XRT 2 weeks prior to study drug administration or 4 weeks post study completion or discontinuation. Steroids equivalent to prednisone 60 mg daily are permitted prior to study drug administration, but needs to be discontinued 1 day prior to BV administration. Patients receiving steroids for lymphoma symptoms should have measurable disease as mentioned above on baseline scans.

4.2.3 Presence of central nervous system (CNS) involvement requiring active treatment

4.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to Brentuximab Vedotin

4.2.5 Cutaneous T cell lymphomas including transformed MF

4.2.6. Prior treatment with brentuximab in the last 6 months or had refractory or progressive disease to prior BV treatment

4.2.7 Patients with 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.

4.2.8 History of progressive multifocal leukoencephalopathy (PML)

4.2.9. Pregnancy or breast-feeding women are excluded from this study because Brentuximab Vedotin may have the potential for teratogenic or abortifacient effects. Because there is an unknown, but potential risk for adverse events in nursing infants secondary to treatment of the mother with Brentuximab Vedotin, breastfeeding should be discontinued if the mother is treated with Brentuximab Vedotin

4.2.10 A known history of HIV
HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with Brentuximab Vedotin. In addition, these patients are at increased risk of lethal infections when treated with marrow suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

4.2.11 Presence of grade >2 peripheral neuropathy or patients with the demyelinating form of Charcot-Marie-Tooth syndrome

4.2.12 Prior malignancy within the past 3 years except non-melanoma skin cancer or other localized cancer treated with curative intent

4.2.13 Patients with the following medical conditions that could affect their participation in the study:
- any active acute or chronic or uncontrolled infection
- liver disease including history of viral hepatitis B or C, evidence of cirrhosis, chronic active or persistent hepatitis
- symptomatic cardiac disease, including congestive heart failure, coronary artery disease, and arrhythmias

5.0 REGISTRATION

All subjects who have been consented are to be registered in the OnCore™ Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

All subjects will be registered through Cleveland Clinic and will be provided a study number by contacting the study coordinator.

6.0 TREATMENT PLAN

6.1 Brentuximab Vedotin Administration

Subjects will receive Brentuximab Vedotin 1.8 mg/kg intravenously (IV) once every 3 weeks.

The treatment will be continued until disease progression, unacceptable toxicity, stem cell transplantation or at physician discretion. If a patient has completed 17 cycles, the treating physician can determine if to continue or discontinue treatment in event there is no disease progression or unacceptable toxicity.

Appropriate dose modifications for Brentuximab Vedotin are described in Section 7.0.

For reported adverse events see section 8.0 and potential risks of Brentuximab Vedotin are described in Section 9.0.

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Table 1

Treatment Regimen					
Agent	**Pre-medicate / Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Brentuximab Vedotin	None (please see below)	1.8 mg/kg	IV over 30 minutes	Day 1 of each cycle	21 days

All scheduled treatment visits will have a ±3-day window due to unanticipated or unavoidable scheduling conflicts except for cycle 1, day 1.

6.2 Dose and Administration
The investigational agent will be administered IV infusion given over approximately 30 minutes.

In the absence of infusion-related reactions, the infusion rate for all patients should be calculated in order to achieve a 30-minute infusion period. Investigational agent must not be administered as an IV push or bolus. Investigational agent should not be mixed with other medications.

Dosing is based on patient weight according to the institutional standard; however, doses will be adjusted for patients who experience a ≥10% change in weight from baseline. An exception to weight-based dosing is made for patients weighing greater than 100 kg; doses will be based on 100 kg for these individuals. Rounding is permissible within 5% of the nominal dose.

6.3 Required Premedication and Post Medication
Routine premedication should not be administered for the prevention of infusion-related reactions prior to the first dose of study treatment. However, patients who experience an infusion-related reaction may receive subsequent infusions of study treatment with premedication as described in (section 6.5). Patients who experience a Grade 3 or Grade 4 infusion-related reaction may potentially continue to receive treatment at the discretion of the investigator after discussion with the primary investigator.

Patients should be individually evaluated to assess the need for tumor lysis prophylaxis prior to the first dose of investigational agent. Patients should receive prophylaxis as appropriate per the institutional standards

6.4 General Concomitant Medications and Supportive Care Guidelines

There are no required concomitant therapies.

Routine premedication for infusion reactions should not be administered prior to the first dose of Brentuximab Vedotin. However, patients who experience an infusion-related reaction may receive subsequent treatment with premedication as described in Section 6.5.

The use of transfusions, platelet and/or colony-stimulating factors per institutional practice is permitted. Intrathecal prophylactic treatment for cerebral/meningeal disease is permitted at the discretion of the investigator.

All concomitant medications, blood products, and radiotherapy administered will be collected from Day 1 (predose) through the safety-reporting period. Any concomitant medication given for a study protocol-related adverse event should be recorded from the time of informed consent.

Patients may not receive other investigational drugs, immunosuppressive medications, radiotherapy, or systemic anti-neoplastic therapy from Day 1 through end of treatment. In addition, other prohibited concomitant therapies should be excluded in accordance with the approved prescribing information.

6.5 Management of Infusion Reactions

Infusion-related reactions may occur during the infusion of study treatment. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. All supportive measures consistent with optimal patient care should be given throughout the study according to institutional standards. Supportive measures may include extending the infusion time and/or administering medications for infusion-related reactions.

Patients who have experienced an infusion-related reaction should be pre-medicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid administered 30–60 minutes prior to each infusion or according to institutional standards.

If anaphylaxis occurs, study treatment administration should be immediately and permanently discontinued.

6.6 Management of Suspected PML

Signs and symptoms of progressive multifocal leukoencephalopathy (PML) may include altered mental status, motor deficits such as hemiparesis or ataxia, visual disturbances, or higher cortical dysfunction such as dysphasia or agnosia. See the Investigator’s Brochure for further details.
If PML is suspected, hold further dosing and undertake a diagnostic work-up including (but not limited to):

- Neurologic examinations, as warranted
- Brain radiologic features by magnetic resonance imaging (MRI)
- PCR analysis: John Cunningham virus (JCV) DNA detectable in cerebrospinal fluid

If PML is confirmed, Brentuximab Vedotin should be permanently discontinued.

6.7 Expected Duration of Subject Participation

6.7.1 Duration of Therapy

The treatment will be continued until disease progression, unacceptable toxicity, stem cell transplantation, or at physician discretion. If a patient has completed 17 cycles, the treating physician can determine if to continue or discontinue treatment in event there is no disease progression or unacceptable toxicity.

6.7.2 Duration of Follow Up

After completion of the study the subjects will be followed for a total of 3 years. The follow up visits will be done at 6, 12, 24 and 36 months after the last cycle of therapy. If the patient is unable to follow up with the local site in person, virtual visits may be used to capture applicable procedures during long-term follow up only.

The follow up visits should include the following:

- Physical Examination
- Vital signs
- Height and weight
- CBC with differential
- Serum chemistry panel as outlined in section **11.1.2**
- ECOG performance status
- Adverse event evaluation (only the adverse events attributed to the study drug)
- Diagnostic CT neck, chest, abdomen and pelvis scan with IV and PO contrast will be done at 6, 12 and 24 months if no disease progression. Neck CT can be omitted if no involvement at baseline

If a virtual visit is completed in follow up every attempt should be made to complete the required assessments listed above, though if they are not completed it will not be considered a protocol deviation.

Patients who have progressive disease or start a new treatment are not required to come in for clinical follow up. These patients can be contacted over the phone by the study personnel to obtain the following information

- Disease status
- Adverse event evaluation only if patients have residual persistent symptoms related to BV treatment
- Current lymphoma treatment

Patients will be followed for toxicity for 30 days after treatment has been discontinued or until death, whichever occurs first. The clinical course of each event will be followed until resolution, stabilization, or until has been determined that the study treatment or participation is not the cause.

Serious adverse events (SAE) that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

7.0 RECOMMENDED DOSE MODIFICATIONS

Table 2 describes the recommended dose modifications for study treatment-associated neuropathy.

Doses reduced for treatment-related neuropathy should not be re-escalated without discussion with the primary site, CCF study team.

Table 2

Grade of Neuropathy	Recommended Dose Modification	
	Sensory Neuropathy	Motor Neuropathy
1	Continue at same dose	Continue at same dose
2	Continue at same dose	Reduce dose to 1.2 mg/kg
3	Reduce dose to 1.2 mg/kg	Discontinue treatment
4	Discontinue treatment	Discontinue treatment

Brentuximab Vedotin should be held for grade >2 hematological (anemia, neutropenia, and thrombocytopenia only) and non-hematological (except neuropathy) toxicities that are deemed possibly related to BV. Patients with bone marrow involvement at baseline may continue study treatment through cycle 4 despite having grade 3-4 neutropenia or thrombocytopenia. If those counts have not recovered to grade ≤2 prior to beginning cycle 5 and are considered at least possibly related to BV, then you must get approval from the sponsor-investigator (Dr. Jagadeesh) prior to starting cycle 5.

For grade >2 hematological toxicity, the study drug can be restarted at the same dose once the toxicity has resolved to grade ≤2 or has returned to baseline. If study drug was held for neutropenia, growth factor support to be considered for the treatment or prophylaxis with subsequent cycles. Consider discontinuing or dose reducing Brentuximab Vedotin to 1.2 mg/kg in patients with recurring grade 4 neutropenia even with use of growth factors. In patients with grade 3 non-hematological toxicity the study drug can be restarted at the same dose once the toxicity has resolved to grade ≤2 or

has returned to baseline. In patients with grade 4 non-hematological toxicity the study drug can be restarted once the toxicity has resolved to grade ≤2 or has returned to baseline at a reduced dose of 1.2 mg/kg. The study drug can be discontinued at investigator's discretion in patients who developed grade 4 non-hematological toxicity. No further dose reductions of Brentuximab Vedotin other than mentioned above are permitted. If further reduction is required, the study drug should be discontinued. The study drug can be held for 3 weeks for toxicity. Delays >3 weeks are not permitted without approval from the primary study team at CCF.

8.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

The following is a list of AEs (Section 8.2) and the reporting requirements associated with observed AEs and SAEs (Sections 8.3 and 8.4).

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

8.1 Adverse Events and Potential Risks

8.1.1 Brentuximab Vedotin

Brentuximab Vedotin (SGN-35) is an antibody drug conjugate (ADC) consisting of the chimeric anti-CD30 monoclonal antibody, SGN-30, chemically conjugated to the anti-microtubule agent monomethyl auristatin E (MMAE)

Detailed information describing the side effects, preparation, administration, packaging and storage of Brentuximab Vedotin is located in the Pharmaceutical Information (section 9).

8.2 Definitions

8.2.1 Adverse Events

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

- **External adverse events** are adverse events experienced by subjects enrolled in multicenter clinical trials at sites other than the site(s) over which the Institutional Review Board has jurisdiction.

- **Internal adverse events** are adverse events experienced by subjects enrolled at the site(s) under the IRB's jurisdiction for either multicenter or single-center research projects.

8.2.2 Serious Adverse Events

A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Results in **death.**
- Is **life-threatening** adverse experience. The term life threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event, which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:
    - The admission results in a hospital stay of less than 12 hours OR
    - The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study) OR
    - The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

  However, it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.
- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2.3 Adverse Event / Serious Adverse Event Data Collection

All AEs (regardless of relationship to study drug) will be captured from the time the subject signs the ICF through the end of the safety-reporting period.

All active symptoms and current / historical medical conditions present at the time of the baseline assessment will be collected; these will be considered baseline

symptoms / prior medical history.

Any medical condition that was present at the baseline visit (prior to study treatment) and that remains unchanged, or improved, should not be recorded as an AE. If there is a worsening of a medical condition that was present at the baseline visit, then this should be considered a new AE and recorded appropriately.
If a sign or symptom is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page of the CRF.

The following information should be considered when determining whether or not to record a test result, medical condition, or other incident on the Adverse Events and Pre-existing Conditions case report form (CRF):

- Complications that occur in association with any procedure (e.g., biopsy) should be recorded as AEs whether or not the procedure was protocol mandated. Changes in medical conditions and adverse events, including changes in severity, frequency, or character, during the safety-reporting period should be recorded.
- In general, an abnormal laboratory value should not be recorded as an adverse event unless it is associated with clinical signs or symptoms, requires an intervention, results in a serious adverse event, or results in study termination or interruption/discontinuation of study treatment. When recording an adverse event resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record “anemia” rather than “low hemoglobin”).

8.2.4 Adverse Event / Serious Adverse Event Evaluation and Documentation

The investigator or designee is responsible for ensuring that all adverse events (both serious and non-serious) observed by the clinical team or reported by the subject are fully recorded in the subject’s medical records. Source documentation must be available to support all adverse events.

The investigator or sub-investigator will provide the following for all adverse events (both serious and non-serious):

- Event term (as per CTCAE)
- Description of the event
- Date of onset and resolution
- Expectedness of the toxicity
- Grade of toxicity
- Attribution of relatedness to the investigational agent- (this must be assigned by an investigator, sub-investigator, or treating physician)
- Action taken as a result of the event, including but not limited to; no changes, dose interrupted, reduced, discontinued, etc. or action taken with regard to the event, i.e. no action, received conmed or other intervention, etc.
- Outcome of event

All participating investigators will assess the occurrence of AEs from the time the subject signs the ICF through the end of the safety-reporting period. Subjects will be

followed for toxicity for 30 days after treatment has been discontinued or until death, whichever occurs first (safety-reporting period). The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

8.2.5 Significance of an Adverse Event

The significance of an adverse event is used to describe the patient/event outcome or action criteria associated with events that pose a threat to a patient's life or functioning (i.e., moderate, severe or life threatening). Based on the National Cancer Institute Guidelines for the Cancer Therapy Evaluation Program, severity can be defined by the following grades of events:

- Grade 1 is mild adverse event. (e.g., minor event requiring no specific medical intervention; asymptomatic laboratory findings only; marginal clinical relevance)
- Grade 2 is moderate adverse event (e.g., minimal intervention; local intervention; non-invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).
- Grade 3 is severe and undesirable adverse event (e.g., significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).
- Grade 4 is life threatening or disabling adverse events (e.g., complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis; life–threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation).
- Grade 5 is fatal adverse event resulting in death.

In this study, descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 available at http://ctep.cancer.gov will be utilized for AE reporting.

8.2.6 Expectedness

Adverse Events can be Expected or Unexpected.

- **An expected adverse event** is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.
- **An unexpected adverse event** is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

8.2.7 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study drug.
- Probable – The AE is likely related to the study drug.
- Possible – The AE may be related to the study drug.
- Unlikely – The AE is doubtfully related to the study drug.
- Unrelated – The AE is clearly NOT related to the study drug.

8.2.8 Report Form

SAEs and Life Threatening Adverse Events will be recorded on the FDA Form 3500A (MedWatch) but should only be reported as instructed above. The electronic FDA SAE reporting forms should not be used. The form can be downloaded at:

http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

8.3 Serious Adverse Event Reporting Procedures

Serious adverse events that occur beginning with the signing of the informed consent form, during treatment, or within 30 days of the last dose of treatment must be reported to the Sponsor-Investigator (Cleveland Clinic Principal Investigator) within 24 hours of observation or learning of the SAE, regardless of the relationship of the event to the study treatment regimen.

Investigative sites will report serious adverse events to their respective IRB according to the local IRB's policies and procedures.

For initial SAE reports, available case details are to be recorded on an SAE form. At a minimum, the following should be included:

- Patient number
- Date of event onset
- Description of the event
- Study treatment
- Attribution

Participating investigators (all sites) must report all serious adverse events to the Sponsor-Investigator (Cleveland Clinic Principal Investigator) within **24 hours** of discovery or notification of the event. The participating investigator must also provide follow-up information on the SAE until final resolution. The completed SAE form and SAE Cover Sheet are to be scanned within **24 hours** to:

Contact Name: Hillary Sedlacek
Email: [redacted]
Please cc: cancersaeinbox@ccf.org
Telephone: [redacted]

- The Sponsor-Investigator (Cleveland Clinic Principal Investigator) will review the SAE and report the event to the FDA, external collaborator(s), and IRB as applicable.
- It is the Sponsor-Investigator's responsibility (Cleveland Clinic Principal Investigator) to ensure that ALL serious adverse events that occur on the study are reported to all participating sites
- It is the responsibility of each investigator to report the SAEs to their respected institutional review boards

8. 3. 1 Reporting Serious Adverse Events to Seattle Genetics

It is the responsibility of the Sponsor-Investigator (Cleveland Clinic Principal Investigator) to report safety data to the drug supplier (Seattle Genetics) as follows:

Individual expedited SAE reports required by competent health authority (i.e. FDA, Health Canada)	At time of submission to competent authority: Seattle Genetics Drug Safety by: Facsimile (425) 527-4308 or (866) 333-6627 (USA only toll free) Email: drug.safety@seagen.com
Aggregate listing of all SAEs	Monthly: IST@seagen.com or portal

8.3.2 FDA Reporting

- It is the responsibility of the Sponsor- Investigator (Cleveland Clinic Principal Investigator) to communicate with the FDA in accordance with 21 CFR 312.32.
- It is the responsibility of the Sponsor- Investigator (Cleveland Clinic Principal Investigator) to report all events that are suspected to be caused by the investigational product serious and unexpected to the FDA as soon as possible but no later than the time frames in the table below:

Within 15 days	Serious, unexpected, suspected adverse reactions
Within 7 days	Fatal or life-threatening, unexpected* suspected adverse reactions

The Sponsor- Investigator (Cleveland Clinic Principal Investigator) will report any Additional information related to previously submitted IND safety report as soon as the information is available to the FDA as a Follow-up IND Safety Report. Furthermore, the Sponsor-Investigator will maintain records of its efforts to obtain additional information.

8.4 SAEs and OnCore™

- All SAEs will be entered into OnCore™
- A copy of the SAE form(s) submitted to the sponsor-investigator is also uploaded into OnCore™

8.5 Data Safety Toxicity Committee

- It is the responsibility of the PIs (including the CCF PI) to ensure that ALL SAEs occurring at their respective sites (internal or external) are reported to the Case Comprehensive Cancer Center's Data and Safety Toxicity Committee (DSTC). SAEs are automatically reported to the DSTC via OnCore (once an event is entered into OnCore the DSTC is notified of the event).
- The sponsor-investigator is responsible for submitting an annual report to the DSTC as per CCCC Data and Safety Monitoring Plan.

8.6 Pregnancy

Notification to Drug Safety: Based on the estimated date of conception, complete a Pregnancy Report Form for all pregnancies that occur from the time of informed consent to the end of the protocol-defined contraception period, including any pregnancies that occur in the partner of a male study patient. Fax the form to primary study team at CCF and sponsor's Drug Safety Department within 48 hours of becoming aware of the pregnancy. All pregnancies that occur during this time period will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks.

If a woman becomes pregnant or suspects that she is pregnant while participating in the study, she must inform the investigator immediately and must permanently discontinue study drug.

Collection of data: Based on the estimated date of conception, all pregnancies that occur from time of informed consent to within 30 days of last study drug dose, including any pregnancies that occur in the partner of a male study patient, will also be recorded on the Adverse Events and Pre-Existing Conditions CRF. Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the 'serious' criterion above (see definitions 8.0) should be reported as SAEs.

9.0 PHARMACEUTICAL INFORMATION

9.1 Brentuximab Vedotin

9.1.1 Study Drug Description

Brentuximab Vedotin (SGN-35) is a CD30-directed antibody-drug conjugate (ADC) consisting of three components: 1) the chimeric IgG1 antibody cAC10, specific for human CD30; 2) the microtubule-disrupting agent monomethyl auristatin E (MMAE); and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. 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 cell.

9.1.2 Description of Drug Substance

Brentuximab Vedotin is an ADC composed of a CD30 targeted chimeric monoclonal antibody (cAC10) covalently linked, via an enzyme-cleavable linker, to the anti-tubulin agent MMAE (Figure 1). cAC10 has a typical structure of the human IgG1 subclass. Brentuximab Vedotin is produced by the chemical conjugation of MMAE to cAC10. Each antibody molecule has, on average, two of its interchain disulfides reduced and the resulting cysteine residues alkylated with SGD-1006 Intermediate (enzyme-cleavable linker + MMAE), leading to a molar ratio of four drugs per antibody.

Brentuximab Vedotin is a heterogeneous mixture of a range of drug-load variants and isoforms. The overall average drug-to-antibody mole ratio (MRD) is approximately 4. The calculated molecular mass for the nominal form of Brentuximab Vedotin is approximately 153 kDa.

9.1.3 Pharmaceutical Properties

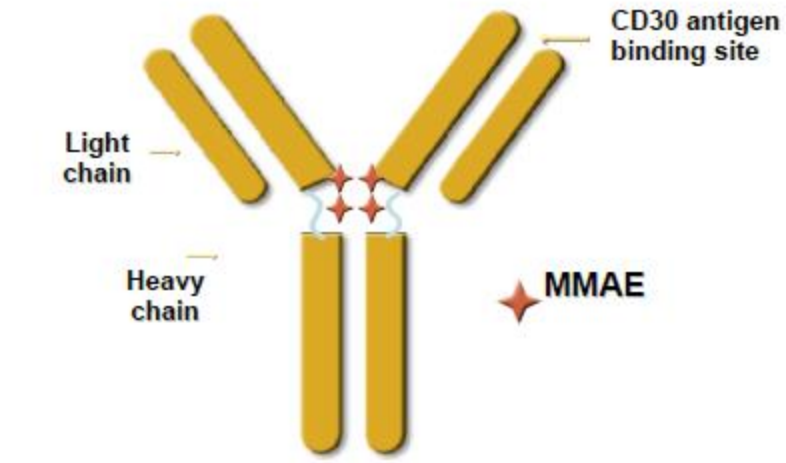
Brentuximab Vedotin is a sterile, preservative-free, white to off-white lyophilized cake or powder, supplied in single-use vials. Brentuximab Vedotin drug product is reconstituted with water for injection (WFI), USP, or equivalent. The reconstituted Brentuximab Vedotin drug product is a clear to slightly opalescent, colorless solution with no visible particulate matter. The reconstituted solution is subsequently diluted in sterile 0.9% Sodium Chloride for Injection, 5% Dextrose Injection, or Lactated Ringer's Injection for intravenous (IV) administration. The diluents should be USP grade or equivalent.

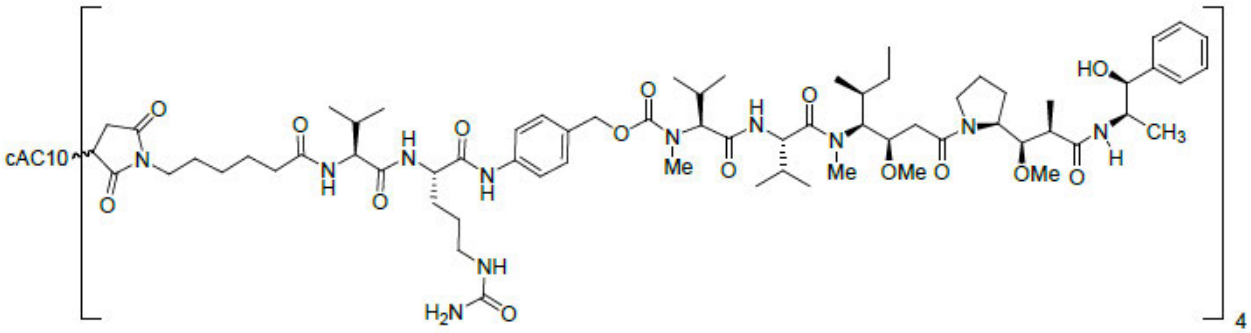
Brentuximab Vedotin is the United States Adopted Name (USAN) and the International Nonproprietary Name (INN) assigned to SGN-35. Drug product vials may be labeled as SGN-35 or as Brentuximab Vedotin; the 2 names can be used interchangeably.

9.1.4 Chemical and Structural Formula

A representative structure of Brentuximab Vedotin (MR_D=4) is shown in Figure 1.

Figure 1: Structure of brentuximab vedotin





9.1.5 Formulation

Each vial contains 55 mg SGN-35 for Injection (Brentuximab Vedotin), trehalose, sodiumcitrate, and polysorbate 80. The 5 mg overfill in each vial is to ensure that the labeled quantity of 50 mg SGN-35 may be withdrawn. The drug product vial is reconstituted with the appropriate amount of Sterile Water for Injection. The pH of reconstituted product is approximately 6.6.

9.2 Method of Procurement

Brentuximab Vedotin will be provided by Seattle Genetics.

9.3 Side Effects

The bulleted list of side effects corresponds to adverse events, which have occurred in patients in pivotal phase 2 studies and are considered to have a possible association with Brentuximab Vedotin by the Sponsor.

Side Effect (Incidence)	MedDRA Term
Abnormal nerve function in arms or legs	Peripheral Neuropathy

(56%)	
Alopecia (hair loss) (13%)	Alopecia
Back pain (12%)	Back pain
Chills (13%)	Chills
Constipation (18%)	Constipation
Cough (19%)	Cough
Diarrhea (34%)	Diarrhoea
Dizziness (13%)	Dizziness
Fever (31%)	Pyrexia
High blood sugar (6%)	Hyperglycaemia
Itching (17%)	Pruritus
Low platelets (10%)	Thrombocytopenia
Low red blood cells (9%)	Anaemia
Low white blood cells (21%)	Neutropenia
Joint pain (15%)	Arthralgia
Muscle pain (16%)	Myalgia
Nausea (41%)	Nausea
Rash (18%)	Rash
Shortness of breath (15%)	Dyspnea
Tiredness (43%)	Fatigue
Upper respiratory tract infection (31%)	Upper and lower respiratory tract infection
Vomiting (20%)	Vomiting

Some additional context for notable expected side effects is presented by topic in the paragraphs that follow the bulleted list.

Side Effect (Incidence)
Infusion-related reactions (11%)
Peripheral neuropathy (see above)
Low blood cell counts (see above for thrombocytopenia, anemia, and neutropenia)
Infection risk (61%)

9.3.1 Other Important Side Effects

This section presents additional serious or potentially life-threatening events that could have possible association to Brentuximab Vedotin. Events in this section have occurred infrequently in patients treated with Brentuximab Vedotin in clinical trials or in the commercial setting.

Side Effect (Incidence[a])
Stevens-Johnson syndrome and toxic epidermal necrolysis (≤0.1%)
Tumor lysis syndrome (≤0.1%)
Progressive multifocal leukoencephalopathy (≤0.1%)
Acute pancreatitis (≤0.5%)
Hepatotoxicity (1%)
Pneumonitis (1%)

a Incidence is derived from the Brentuximab Vedotin global safety database, which includes all spontaneous reports and clinical trial SAEs.

9.4 Pregnancy and Breastfeeding

Brentuximab Vedotin causes miscarriages and birth defects in animals. Brentuximab Vedotin also affects the testes (sperm-producing organs) in animals. Men being treated with Brentuximab Vedotin should not get their partner pregnant.

Recommended contraception duration for men and women receiving Brentuximab Vedotin monotherapy is 6 months from the last dose.

It is not known whether Brentuximab Vedotin or its breakdown products end up in breast milk. If it does end up in breast milk, it could hurt a nursing baby.

9.5 Storage and Handling

The guidelines for the storage should be followed per the Pharmacy Manual.

Refrigeration should be set at 2–8°C for storage of vials and solutions containing Brentuximab Vedotin. The controlled location must be accessible only to the pharmacist or a duly designated person. Brentuximab Vedotin does not contain preservatives; therefore, opened and reconstituted vials should be used immediately. If not used immediately, reconstituted vials and solutions must be stored no longer than 24 hours from vial reconstitution under refrigeration at 2–8°C. It is recommended that vials and solutions be protected from direct sunlight until the time of use. Reconstituted vials and solutions must not be shaken.

Drug accountability instructions are provided in the Pharmacy Manual.

9.6 Packaging and Labeling

Drug product vials may be labeled as Brentuximab Vedotin, the United States adopted name (USAN) and the International Nonproprietary Name (INN), or as SGN-35, the compound code; the 2 names can be used interchangeably.

9.7 Preparation

Brentuximab Vedotin vials are provided via single-use containers. Any partially used vials or diluted dosing solutions should be discarded using appropriate institutional drug

disposal procedures.

Brentuximab Vedotin should be reconstituted with the appropriate amount of Sterile Water for Injection, United States Pharmacopeia (USP), or equivalent standard. The vial should be gently swirled until the contents are completely dissolved. The vial must not be shaken. The reconstituted drug product should be inspected visually for any particulate matter and discoloration.

The required volume of reconstituted drug product should be diluted into an infusion bag. The bag should be gently inverted to mix the solution. The bag must not be shaken. Prior to administration, the reconstituted and diluted drug product should be inspected visually for any particulate matter and discoloration.

9.8 Drug Accountability

The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study drug. All study drugs must be accounted for, including study drug accidentally or deliberately destroyed. Under no circumstances will the investigator allow the investigational drug to be used other than as directed by the protocol. If appropriate, drug storage, drug dispensing, and drug accountability may be delegated to the pharmacy section of the investigative site.

9.9 Drug Destruction

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

10.0 CORRELATIVE STUDIES

The current standard IHC method using the anti-CD30 BerH2 antibody will be utilized to define CD30 positivity. The other lab correlatives used to detect CD30 are imaging analysis and RT-PCR using RNA isolated from formalin fixed paraffin embedded (FFPE) tissue. We propose to correlate the IHC CD30 positivity using the following methods

- Aperio Image Scanner Analysis and ImageScope Software for IHC quantitation
- Quantification of CD30 mRNA expression levels by RT-PCR on FFPE tissue

10.1 Aperio Image Analysis

CD30 stained slides will be scanned using the Aperio Image Scanners in the ePathology Department of Pathology and Laboratory Medicine. Analysis will then be completed by the staff pathologist using ImageScope software for quantification of the CD30 positivity. Results will be correlated with clinical endpoints and with the T-qPCR assay results.

10.2. T-qPCR Assay for CD30

This will be conducted in the Pathology Research Core in the Robert J. Tomsich Pathology and Laboratory Medicine Institute (RT-PLMI) at Cleveland Clinic Foundation.

CD30 (Ki-1, TNFRSF8) is expressed by anaplastic large cell lymphoma, Hodgkin lymphoma, peripheral T-cell lymphoma NOS. CD30 is also found in activated T and B cells. Long isoform of CD30 is located in cell membrane, while short isoform is in cytoplasm.

For extraction of RNA from FFPE tissue, 10 sections of 10 microm paraffin tissues will be deparaffinized and total RNA will be isolated using the FFPE RNA extraction kit (Qiagen, Valencia, CA) according to manufacturer's protocol. The resulting RNA will be converted to cDNA using the Hi Quality RNA to cDNA kit (Applied Biosystems, Foster City, CA). 50ng of cDNA will be used as the starting template for the qPCR with following primers: CD30 Forward (5'- CACATCAGCCACCAACTCC-3'), CD30 Reverse (5'-TGTCCTTCTCAGCCATATCCT -3'), GAPDH Forward (5'-TCTTTTGCGTCGCCAGCCGAG-3') and GAPDH Reverse (5'-GCGCCCAATACGACCAAATCCGTT-3') for resulting amplicons of 95 bp and 87 bp respectively. SYBR Green master mix (BioRad, Hercules, CA) will be used to mix the cDNA and primers. Calculation of the expression level will be determined using the delta-Ct method using GAPDH as the control. CD30 positive cell line Karpas299 and CD30 negative cell line DHL16 will be used as the calibrator cDNA.

10.2.1 Regents

1) Primers
   CD30F: CAC ATC AGC CAC CAA CTC C
   CD30R: TGT CCT TCT CAG CCA TAT CCT (NM-000417)

   CD30 amplicon size: 95bp

   GAPDH-F: TCT TTT GCG TCG CCA GCC GAG
   GAPDH-R: GCG CCC AAT ACG ACC AAA TCC GTT (NM-002046.3)

   GAPDH amplicon size: 87 bp

2) FFPE RNA extraction kit (Qiagen, Valencia CA)
3) High quality RNA to cDNA kit (Applied Biosysyems, Foster City, CA)
4) SYBR Green master mix (BioRad, Hercules, CA)

10.2.2 Equipment

Applied Biosystems 7500 Real-Time PCR system (MMP Lab.)

10.2.3 Cell lines, FFPE Blocks

1) CD30 positive (Karpas 299) and negative cell line (B lymphoma cell line) control

2) FFPE blocks or five 10 micron sections (unbaked on charged slides) of CD30 positive/negative (IHC) tissues.

10.2.4 Experimental Design

1) Set up RT-qPCR with CD30 positive and negative control cell lines at first.
2) Calibration curve of RT-qPCR with series diluted RNA isolated from CD30 positive and negative control cell lines.
3) RT-qPCR for CD30 positive/negative (IHC) tissues
4) Testing with RNA isolated from selected FFPE lymphoma cases and data interpretation.

10.2.5 Possible Issue

Poor RNA quality of some FFPE tissues (Consulting for multiple gene-specific RT protocol using RNA from PPFE sections [16].

10.3 Tissue Procurement

Subjects should have histologically confirmed relapse/refractory disease to participate in the study.

We will collect unstained biopsy slides from the most recent biopsy that confirms the relapse/refractory disease to perform CD30 IHC staining using the Aperio Image Scanner and ImageScope software, and the RT PCR for CD30. The slides should be done after the patient has signed the consent form to participate in the study and within 4 weeks of receiving the study drug.

Please submit the following materials:

1. Fifteen 4 micron unstained sections on charged (plus) slides (for diagnosis confirmation and CD30 IHC) AND
2. Four 10 micron sections (if an incisional or excisional biopsy) or eight 10 micron sections (if needle biopsy) on slides or in a tube (preferred).

Please ship the tissue to the Cleveland Clinic Biorepository at the address provided below:

Robert J. Tomsich Pathology and Laboratory Medicine Institute (RT-PLMI)
ATTN: Dr. Genevieve Crane
2119 East 93 Street, L25
Cleveland, Ohio 44106

Please refer to the Manual of Operating Procedures (MOP) for more specific instructions on shipment of the slides.

10.4 Retaining Samples for Future Research

All unused biospecimen samples will be archived at the Cleveland Clinic Central Biorepository for 10 years for future research with the consent from the participating subjects. The retained samples can be used for any research that pertains to T cell lymphoma including, exploring the molecular biology, development of novel therapies, the biology of sensitivity and resistance mechanisms for drugs, and to identify predictive pharmacodynamic biomarkers for TCL.

11.0 STUDY PARAMETERS AND CALENDAR

11.1 Study Parameters

11.1.1 Screening Evaluation (Day -28 to 1) Screening studies and evaluations will be used to determine the eligibility of each subject for study inclusion. All evaluations must be completed ≤ 28 days prior to administration of protocol therapy.

The labs and clinic visit with the treating physician can be done within 3 days of D1 of cycle 2-17 if needed for scheduling purposes

11.1.2 Screening Visit/Baseline Visit (Day -28 to 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history
- CD30 IHC stain and histological confirmation to be done at site enrolling the patient
- Send tumor biopsy slides to CCF for correlative studies. Biopsy slides should be sent within 4 weeks of start of the study drug. Please see section 10 for detailed information
- Human T-cell leukemia virus-1 (HTLV-1) status
- IPI score
- PIT score (prognostic index for PTCL)
- Diagnostic CT of neck, chest, abdomen, pelvis with IV and oral contrast and PET scan (CT neck can be omitted at the discretion of the study investigator if the suspicion for involvement is low/absent. If unable to obtain both CT and PET scan due to insurance restrictions, either CT or PET are acceptable, but PET scan is preferred
- Bone marrow (BM) aspiration and biopsy if patient had previous history of bone marrow involvement or any suspicion of BM involvement with this relapse - may be obtained within 30 days of the first dose of study treatment. BM biopsy is not needed if there was no evidence of involvement previously and if there is no suspicion of involvement at the time of current relapse
- Concomitant medication documentation including over the counter medication and supplements
- Vital signs, height, and weight
- Electrocardiogram (ECG)
- Echocardiogram (ECHO)
- Pregnancy test for females of childbearing potential
- ECOG performance status
- Serum chemistry panel: sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, glucose, total protein, albumin, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT]
- Lactate dehydrogenase (LDH) level, uric acid, phosphorous.
- CBC with differential
- Physical examination

11.1.4 Treatment Period (21-day cycles)

11.1.5 Every Cycle: Day 1 ±3 days (except Cycle1)

Day 1 pre-dose assessment do not need to be repeated if being done same day as screening. If the same assessments are being used for both screening and day 1, the data should be entered at screening in the database.

- ECOG performance status
- Serum chemistry as detailed above (11.1.2)
- LDH, uric acid and phosphorous only for cycle 1
- CBC with differential
- Physical examination
- Vital signs and weight
- Concomitant medication documentation including over the counter medication and supplements
- Adverse event documentation starting with cycle 2

11.1.6 Cycle #4 and #10 day 15 +5 days

- CT neck, chest, abdomen and pelvis with IV and oral contrast. Neck CT can be omitted at the discretion of the investigator if there was no involvement seen at baseline.

11.1.7 The treatment will be continued until disease progression, unacceptable toxicity, stem cell transplantation or at physician discretion. If a patient has completed 17 cycles, the treating physician can determine if to continue or discontinue treatment in event there is no disease progression or unacceptable toxicity. Patients who have completed 17 cycles of treatment can continue on the protocol at the discretion of the treating physician until disease progression or unacceptable toxicity. For patients continuing beyond 17 cycles, CT neck, chest, abdomen and pelvis with IV and oral contrast will be done every 6 months ±2 weeks as long as they are receiving study treatment**.** Neck CT can be omitted at the discretion of the investigator if there was no involvement seen at baseline. For treatment schedule please refer to section 11.1.5.

11.2 End of Study Treatment Visit

End of study visit will be conducted within 30-45 days of last cycle of therapy

- Physical Examination
- Vital signs
- Height and weight
- Concomitant medication documentation, including over the counter medication and supplements
- CBC with differential
- Serum chemistry panel as mentioned above
- LDH
- Pregnancy test for females of childbearing potential
- ECOG performance status (not required if patient has disease progression)
- Adverse event evaluation

- Diagnostic CT of neck, chest, abdomen, pelvis with IV and oral contrast and PET scan to be done between 30-45 days after the last cycle of therapy. Neck CT can be omitted at the discretion of the investigator if there was no involvement at baseline. If unable to obtain both CT and PET scan due to insurance restrictions, either CT or PET are acceptable, but PET scan is preferred
  - For patients coming off treatment due to disease progression, scans are only required, if the last scan within 60 days did not show disease progression. If the patient had a scan within the last 60 days that document progression, no further scans are needed.
- BM biopsy to be repeated between 30-45 days after the last cycle of therapy if it was positive prior to start of the study drug.
  - BM biopsy may be omitted for patients who are coming off treatment due to disease progression.

11.3 Duration of Follow Up

As stated in section 6.7.2 after completion of the study the subjects will be followed for a total of 3 years. The follow up visits will be done at 6, 12, 24 and 36 months after the last cycle of therapy and will include:

- Physical Examination
- Vital signs, height, and weight
- CBC with differential
- Serum chemistry panel as mentioned above
- LDH
- ECOG performance status
- Adverse events evaluation (only the adverse events attributed to the study drug)
- CT scans - neck, chest, abdomen and pelvis with IV and oral contrast to be done at 6, 12, and 24 months after the last cycle of therapy if no progressive disease. Neck CT can be omitted at the discretion of the investigator if there was no involvement at baseline

If the patient is unable to follow up with the local site in person, virtual visits may be used to capture applicable procedures during long-term follow up only. If a virtual visit is completed in follow up every attempt should be made to complete the required assessments listed above, though if they are not completed it will not be considered a protocol deviation.

Patients who have progressive disease or start a new treatment are not required come in for clinical follow ups. These patients can be contacted over the phone by the study personnel to obtain the following information

- Disease status
- Adverse event evaluation only if patients have residual persistent symptoms related to BV treatment
- Current lymphoma treatment

11.4 Calendar

Screening procedures including scans are to be conducted within 28 days to administration of protocol therapy unless otherwise noted.

Study Calendar

Tasks	Baseline/screening Day -28 to 1	Cycle 1 day 1	Cycle 2 -17 Day 1±3days	Cycle 4 and 10 Day 15+5days	Cycle 18 and beyond; Day 1 ±3days	EOT Day 30-45 post last cycle	Long term follow up[m]			
							6 months	12 months	24 months	36 months
Informed consent	x									
Inclusion/exclusion	x									
Medical history	x									
Physical exam	x	x	x		x	x	x	x	x	x
CD30 status[e]	x									
HTLV-1 status	x									
IPI score	x									
PIT score	x									
ECHO	x									
EKG	x									
Vital signs, Height & weight	x[l]	x	x		x	x	x	x	x	x
CBC with differential	x	x[k]	x		x	x	x	x	x	x
Serum chemistry	x	x[k]	x		x	x	x	x	x	x
LDH	x	x[k]				x	x	x	x	x
Uric, Phosphorous	x	x[k]								
Pregnancy test	x[c]					x				
ECOG performance status	x	x	x		x	x	x	x	x	x
Conmeds	x	x	x		x	x				
AE assessment			x		x	x	X[i]	X[i]	X[i]	X[i]
Tumor tissue[f]	x									
CT neck/chest/abdomen/ Pelvis[a, h]	X[j]			x		x	x[d]	x[d]	x[d]	
BM aspiration and biopsy	X[g]					x[b]				
PET scan	x					x				
Brentuximab Vedotin		x	x		x					

a. Neck CT can be omitted at the discretion of the investigator if there was no involvement at baseline. A +5-day window for scans during Cycle 4 and Cycle 10 is acceptable.
b. Bone marrow biopsy only if positive prior to start of the study drug
c. Pregnancy test to be done within 72 hours of starting the study drug

d. Restaging CT scans not required if disease has progressed
e. CD30 status to be assessed by the site enrolling the patient
f. Tumor biopsy slides should be sent to CCF for correlative studies within 4 weeks of the start of the treatment
g. Bone marrow biopsy only if evidence of involvement previously, and/or suspicion of involvement at the time of current relapse.
h. For Cycles 18 and beyond, scans are to be done every six months +/- two weeks.
i. Only adverse events attributed to the study drug
j. CT neck can be omitted at baseline if the investigator feels there is no or low suspicion for involvement
k. These labs do not need repeated on C1D1 if they were performed at baseline within 72 hours of start of study treatment
l. Height is only required at screening.
m. Long term follow up visits may be completed via virtual visit if necessary. Every attempt should be made to complete the assessments although if they are not completed this is not considered a protocol deviation.

12.0 MEASUREMENT OF EFFECT

12.1 Antitumor Effect

Response will be assessed using CT scans according to the revised Cheson Criteria [1]. Please see section 11.4 for the schedule of the imaging studies. Patients will have pre-treatment and end of treatment FDG-PET and/or CT to monitor their response to treatment. Interim response will be assessed after cycle 4 and 10 using CT scans. During follow up patients will have CT scans done at 6, 12, and 24 months after the last cycle of therapy.

All patients will be evaluable for toxicity from the time of their first treatment with Brentuximab Vedotin

The following guidelines are to be used for establishing tumor measurements at baseline and for subsequent comparison:

- The six largest dominant nodes or extranodal masses must be identified at baseline.
- If there are 6 or fewer nodes and extranodal masses, all must be listed as dominant.
  If there are more than 6 involved nodes or extranodal masses, the 6 largest dominant nodes or extranodal masses should be selected according to the following features:
    - nodes should be clearly measurable in at least two perpendicular measurements
    - nodes should be from as disparate regions of the body as possible
    - nodes should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- Measurements for all dominant nodes and extranodal masses will be reported at baseline. Measurements on non-dominant nodes are not required. The lymph nodes or extranodal masses selected for measurement should be measured in two perpendicular diameters, one of which is the longest perpendicular diameter. The lymph nodes should be measured in centimeters to the nearest one tenth of a centimeter (e.g. 2.0 cm, 2.1cm, 2.2 cm, etc.)
- The two measured diameters of each lymph node site or extranodal mass should be multiplied giving a product for each nodal site or extranodal mass. The

product of each nodal site should be added, yielding the sum of products of the diameters (SPD). The SPD will be used in determining the definition of response for those who have less than a complete response.

12.2 Definitions

12.2.1 Primary Endpoint

12.2.1.1 Overall Response Rate

The primary objective is to evaluate overall response rate (ORR). Overall response rate will be estimated by the total number of patients who achieve a CR and PR divided by the total number of evaluable patients. Response will be assessed using CT scans according to the revised Cheson criteria [1].

- CR is defined as complete resolution of all clinically detectable disease and disease related symptoms that were present prior to therapy
- PR is defined as at least 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses

Patients should have completed at least 1 cycle of treatment to be evaluable for ORR.

12.2.2 Secondary Endpoints

12.2.2.1 Complete Response

CR is defined as complete resolution of all clinically detectable disease and disease related symptoms that were present prior to therapy. A post-treatment residual mass of any size is permitted as long as it is PET negative. CR rate will be calculated by dividing the total number of patients who have achieved a complete response by the total number of evaluable patients.

12.2.2.2 Progression Free Survival

Progression-free survival (PFS) is defined as the time from enrollment into the study to disease progression or death due to any cause. The distribution of PFS will be estimated using the Kaplan-Meier method. Disease progression may be defined as the date of documentation of a new lesion or enlargement of a previous lesion, or the date of the scheduled clinic visit immediately after radiologic assessment has been completed. For a patient who is alive without progression at the end of study follow-up, observation of PFS is censored on the date of last contact.

12.2.2.3 Overall Survival

The OS is defined as the time from enrollment to the time of death due to any cause. For a patient who is alive at the end of study follow-up, observation of OS is censored on the date of last contact. The distribution of OS will be estimated using the Kaplan-Meier method.

12.2.2.4 Duration of Response

Duration of response (DOR) is defined as the time from first documentation of objective tumor response (CR or PR) to the time to tumor progression or death due

to any cause.

12.2.2.5 Time to Treatment Failure

Time to treatment failure (TTF) is defined as the time from enrollment to discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death.

12.3 Response Review

Responses will be reviewed by the investigator (PI or co-investigator) who is treating the patient at each participating site.

13.0 RECORDS TO BE KEPT / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

The Advarra EDC™ and OnCore™ databases will be utilized, as required by the Case Comprehensive Cancer Center and Cleveland Clinic, to provide data collection for both accrual entry and trial data management. Advarra EDC and OnCore™ are Clinical Trials Management Systems housed on secure servers. Access to data through Advarra EDC and OnCore™ is restricted by user accounts and assigned roles. Once logged into the Advarra EDC or OnCore™ system with a user ID and password, Advarra EDC™ and OnCore™ define roles for each user which limits access to appropriate data. Applications for user accounts can be obtained by contacting the OnCore™ Administrator at OnCore-registration@case.edu for OnCore™ access, and taussigoncore@ccf.org for Advarra EDC™ access. Advarra EDC™ is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. When properly utilized, Advarra EDC™ is 21 CFR 11 compliant. This study will utilize electronic Case Report Form completion in the Advarra EDC™ database. A calendar of events and required forms are available in Advarra EDC™.

13.2 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

13.2.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject.

13.2.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

In order to insure patient safety, investigators and study personnel must have up-to-the-minute health information for subjects enrolled to this study. Therefore, electronic medical records must be utilized to obtain medical information in a timely manner.

13.2.3 Accessing Electronic Medical Records for Cleveland Clinic Foundation (CCF)

For Cleveland Clinic, the electronic systems utilized will be EPIC, COPATH to locate archived pathology records; and AGFA and/or EasyViz to access radiology imaging results

Access to these systems is required for the life of this research study. Information obtained from electronic systems will be copied into the Taussig Cancer Institute research chart and/or printed (lab results, physician notes, etc.) and stored in the research chart. Research charts are kept secure and destroyed according to CCF policy.

Study data will be obtained by the PI, co-investigators, study coordinator, and/or data manager for this study via password-protected login. All study personnel involved in this research will adhere to the CCF policies regarding confidentiality and PHI.

13.2.4 Accessing Electronic Medical Records for University Hospitals (UH)

The following electronic systems will be used: SORIAN to access scheduling information; UH Physician Portal or UHCARE to access lab results, physician notes and to locate archived medical and pathology records; PACS to access radiological imaging results.

Access to these systems is required for the life of this research study. Information obtained from electronic systems will be copied into the Seidman Cancer Center Clinical Trials Unit research chart and/or printed (lab results, physician notes, etc.) and stored in the research chart. Research charts are kept secure and destroyed according to UH policy.

Study data will be obtained by the PI, co-investigators, study coordinator, and/or data manager for this study via password-protected login. All study personnel

involved in this research will adhere to the UH policies regarding confidentiality and Protected Health Information.

13.2.5 Retention of records

The Principal Investigator of the Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, case report forms, source documents, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with national and international regulations and the institution in which the study will be conducted, or for the period specified by the sponsor, whichever is longer. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

13.2.6 Audits and Inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the Center to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

13.2.7 Data Safety and Monitoring Plan

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI regulations**.**

14.0 STATISTICAL CONSIDERATIONS

Please refer section 12.2 for endpoint definitions. The primary objective is to evaluate overall response rate. For this patient population, response of 15% or less is unacceptable and 35% or more is promising. Twenty-eight evaluable patients will be accrued; if 8 or more patients respond, then the regimen will be considered promising. The significance level of this one-sided test is 5%, and the power is 82%.

Other end points analyzed are CR, PFS, OS, DOR, and TTF. ORR and CR will be estimated using exact 95% confidence intervals. PFS and OS will be estimated using the Kaplan-Meier method. DOR and TTF will be estimated using standard descriptive statistics such as median and range, or mean and standard deviation.

McNemar’s test will be used to compare incidence of CD30 positivity via IHC with multi- spectral imaging and RT-PCR to see if different methods result in different findings.

15.0 Sample Size

We plan to enroll 31 patients, allowing for 10% ineligibility, to obtain 28 patients evaluable for primary end point, overall response rate.

16.0 Study Sites

Primary site: Cleveland Clinic Foundation (CCF)
Participating sites:

- Site PI: Paolo Caimi, MD, Case Comprehensive Cancer Center
- Site PI:, Dipenkumar Modi, MD Karmanos Cancer Institute
- Site PI: Tatyana Feldman MD, Hackensack Medical Center
- Site PI: Ryan Wilcox MD, University of Michigan

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APPENDIX 1
ECOG PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX 2
IWC RESPONSE CRITERIA (adapted from [1])

IWC+PET-Based Response Designations	Description
CR	CR by IWC with a completely negative PET
	CRu, PR, or SD by IWC with a completely negative PET and a negative BMB if positive prior to therapy
	PD by IWC with a completely negative PET and CT abnormalities (new lesion, increasing size of previous lesion) ≥1.5 cm (≥ 1.0 cm in the lungs) and negative BMB if positive prior to therapy
CRu	CRu by IWC with a completely negative PET but with an indeterminate BMB
PR	CR, CRu, or PR by IWC with a positive PET at the site of a previously involved node/nodal mass
	CR, CRu, PR, or SD by IWC with a positive PET outside the site of a previously involved node/nodal mass
	SD by IWC with a positive PET at the site of a previously involved node/nodal mass that regressed to < 1.5 cm if previously > 1.5 cm, or < 1 cm if previously 1.1-1.5 cm
SD	SD by IWC with a positive PET at the site of a previously involved node/nodal mass (i.e., residual mass)
PD	PD by IWC with a positive PET finding corresponding to the CT abnormality (new lesion, increasing size of previous lesion)
	PD by IWC with a negative PET and a CT abnormality (new lesion, increasing size of previous lesion) of < 1.5 cm (< 1.0 cm in the lungs)

Abbreviations: IWC+PET, International Workshop Criteria plus positron emission tomography; CR, complete response; BMB, bone marrow biopsy; CT, computed tomography; CRu, unconfirmed complete response; PR, partial response; SD, stable disease; PD, progressive disease.

APPENDIX 3
International Prognostic Index (IPI)

Age > 60
Serum LDH above normal
Stage III-IV
ECOG PS ≥2
>1 extranodal site involvement

Each characteristic receive 1 point each and the total score ranges from 0-5

APPENDIX 4
Prognostic Index for PTCL (PIT) Score

Age > 60
Serum LDH above normal
ECOG PS ≥2
Bone marrow involvement

Each characteristic receives 1 point each and the total score ranges from 0-4 [17]

APPENDIX 5
Summary of Protocol Changes

New Protocol Version #/Date: 5/13/2016
Previous Protocol Version #/Date: 3/25/2015

Rational for Changes: Most changes are formatting the protocol/consent. Additionally, we added missed tests that originally should have been included.

Section #/Page #	Change	Rationale
Throughout Protocol	Corrected formatting	Cleaner versions
Study Table/ Page 40 & 43	Added Echo	Missed form original protocol. Heart function should be checked
Study Table / Page 43	Added LDH	Ordered separately from CMP
Treatment / Page 41	Added section 11.1.7	Specifies ability to continue after cycle 17
Treatment / Page 40	Added Vital Signs	Missed from original protocol
Access EMR / Page 47	Removed Coordinator Names	Change to often to be listed in protocol. Specified in Data Management plan.

New Protocol Version #/Date: 8/20/2016
Previous Protocol Version #/Date: 5/13/2016

Section #/Page #	Change	Rationale
Throughout Protocol	Corrected formatting	Cleaner versions
Throughout Protocol	Defined Contraceptive period to 6 months	FDA guidance
Inclusion Criteria / Pg. 4 &15	Added defined ECOG of 3 to 4.1.4	Updated for patients for active disease otherwise ok.
Inclusion Criteria / Pg. 4 &15	Defined 4.1.9	Clarification
Exclusion Criteria / Pg. 4 & 16	Defined 4.2.2 XRT and Steroid Use	Clarification
Treatment Plan /	Treatment	Clarification

Pg. 17	discontinuation defined	
Treatment Plan / Pg. 18	No window added to Cycle 1 day 1	Clarification
Duration of Follow Up / Pg. 20	Defined serum chemistry Panel and added specifics to CT's to adverse event follow up.	Clarification
Tissue Procurement / Pg. 34	Defined Instructions for shipping and retaining samples	Clarification
Screening / Pg. 36	Added PIT score, CT scan instructions, BM Biopsy defined.	PIT scoring I specific to disease. Scans and Biopsy are just Clarifications.
Cycles & Study Table / Pg. Multiple	Outlined expectation for LDH, Uric Acid and Phosphorus	All 3 are ordered separately from CMP and required at specific time points
Cycles & Study Table / Pg. Multiple	Defined Adverse event collection	Clarification
Study Table / Pg. 39	Added PIT, Split AE's/Conmeds, Added Uric Acid and Phosphorus	Clarification
Appendix	Added Appendix 3 & 4	Scoring Systems

New Protocol Version #/Date: 11/19/2016
Previous Protocol Version #/Date: 8/20/2016

Rational for Changes: All Administrative updates

Section #/Page #	Change	Rationale
Title Page / Page 2	Added NCT #	Mandated by Scientific Review Committee
SAE's / Page 26	Removal of Katie Klemencic and addition of Ashley Ochaba	Katie has left the program and Ashley has taken over her duties.

New Protocol Version #/Date: 7/20/2017
Previous Protocol Version #/Date: 11/19/2016

Rational for Changes: Administrative updates to protocol and adding risk of pneumonitis

Section #/Page #	Change	Rationale
Title Page / Page 2	Adding external sites (Hacksack and University of Michigan)	Sites preparing to open study, need added to protocol
11.1.6 / Page 26	Clarifying CT scans to be done at Cycles 4 and 10 (5 day window so scans should be done between days 15 and 20)	Previous verbiage (day 15-20) was unclear and inconsistent
11.4 / Page 38	Clarifying window for CT scans performed at Cycles 4 and 10	The protocol defined 5 day window was not clear in previous version
13.1 & 13.2.4 / Page 41-42	Updating EMR information for University Hospitals and Overture language for data collection	Previous version was outdated
9.3.1 / Page 31	Adding risk of Pneumonitis	This is important information in the current IB

New Protocol Version #/Date: 9/27/2018
Previous Protocol Version #/Date: 7/20/2017

Section #/Page #	Change	Rationale
Schema / Pages 3&4 **4.1 & 4.2./ Page 14&15**	Removing transformed mycosis fungoides as an approved indication for enrollment in this study	Recent FDA approval of the study drug for this indication. Patients with transformed mycosis fungoides may no longer enroll on this study
Schema / Page 3	Adding splenomegaly as indicator of	Updated for patients with splenomegaly

	measurable disease	
Schema / Page 5 **4.2/ Page 15**	Reducing treatment washout time from 4 to 2 weeks before start of study drug	Updated to allow patients with rapid disease progression to enroll without delaying treatment
6.2 / Page 17	The threshold for dose recalculation based on change in body weight is being changed from 5% to 10%	This change was made to be consistent with the pharmacy instructions distributed by Seattle Genetics
7.0 / Pages 20&21	Adding information on when the study drug may be held or modified	Previously the protocol did not provide guidance on when the study drug could/should be held
8.3 / Page 25	Updating CCF SAE reporting contact information	Previous contact information was outdated.
10.3 / Pages 34	Updating information on shipping slides	Previous information was outdates and further detailed instructions are stated to be located in the Manual of Operating Procedures

New Protocol Version #/Date: 2/6/2020
Previous Protocol Version #/Date: 9/27/2018

Section/Page	Change	Rationale
Pages 1 & 2	Updated Karmanos PI and other administrative information	Updated to the most current information
Section 4.1	Corrected numbering for some inclusion criteria	Fixing incorrect numbering of items
Section 7.0	Adding information on when to hold BV	More detailed was added on how to appropriately hold BV for BV-related toxicities
Pages 34-39	Details were added in the schedule of assessments	Height is only required at screening. Clarification that screening and C1D1 is allowed on the same day. Certain EOT procedures are not required for patients with disease progression.

New Protocol Version #/Date: 8/21/2020
Previous Protocol Version #/Date: 2/6/2020

Section/Page	Change	Rationale
Section 6.7.2 & 11.3	Allowing virtual visits for long-term follow up visits	Increasing flexibility to more reliably capture long-term follow up data

New Protocol Version #/Date: 7/6/21
Previous Protocol Version #/Date: 8/21/2020

Section/Page	Change	Rationale
Title Page / Page 1/Section 16	Updating Karmanos PI to Dipenkumar Modi, MD	Change in site PI
Title Page / Page 2	Removing Eric Hsi, MD and Xiaoxian Zhao, PhD., Alex Mejia-Garcia, MD Adding Genevieve Crane, MD	Personnel updates
Section 10.2	Processing for T-qPCR Assay for CD30 updated from Dr. Hsi to the RT-PLMI facility	The RT-PLMI facility will now complete sample processing
Section 10.3	Change Cleveland Clinic Biorepository shipping title and ATTN to Genevieve Crane, MD	Title correction and pathologist replacement
Schema Page 3, Section 2.3, Section 10.0	References to Nuance FX multispectral Imaging camera deleted or changed to Asperio image analysis	To align with current PLMI processes.
Section 8.3	SAE contact info updated	To reflect personnel updates at CCF.
Section 6.7.2, 11.3, study calendar	Clarifying that if a virtual visit is completed in follow up, assessments not completed will not be considered a protocol deviation. Patients that start new treatment enter survival follow up.	For patient convenience.
13.1	Overture changed to Advarra	To be consistent with current EDC used.