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Title: Brentuximab Vedotin Plus AD in Non-bulky Limited Stage Hodgkin Lymphoma

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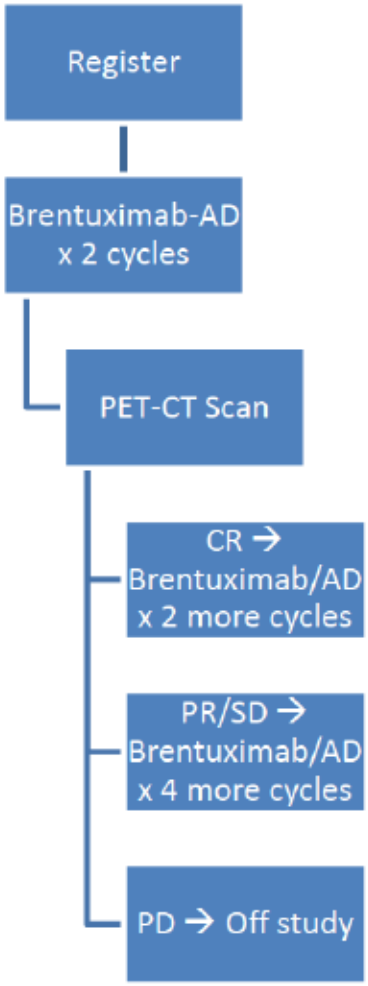
Agent(s):

- Brentuximab Vedotin - Seattle Genetics, Inc.
- Adriamycin
- Dacarbazine

IND #: 113,885

SCHEMA



The primary endpoint is end of treatment complete remission rate

Abbreviations:
AD: Adriamycin, Dacarbazine
CR – Complete Response
PR – Partial Response
SD – Stable Disease
PD – Progressive Disease

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1. OBJECTIVES

1.1 Study Design

This is an open label single arm phase II study to assess the efficacy and safety of Brentuximab Vedotin (hereafter referred to as brentuximab) in combination with Adriamycin and Dacarbazine (AD) in patients with previously untreated stage I and II non-bulky classical Hodgkin lymphoma (cHL). All patients will receive combination therapy with brentuximab and AD with all agents administered on days 1 and 15 of each 28 day cycle. Brentuximab will be administered at 1.2 mg/kg. AD will be administered at standard doses (Adriamycin 25mg/m^2, Dacarbazine 375 mg/m^2). Interim restaging PET-CT will be performed following cycle 2. Patients with progressive disease will be taken off study. Patients in CR will receive a total of 4 cycles of therapy; patients with stable disease or partial response will receive a total of 6 cycles. There is no planned radiotherapy for patients achieving a complete remission at the end of therapy.

1.2 Primary Objective

1.2.1 To investigate the clinical activity of Brentuximab with AD in untreated non-bulky stage I and II Classical Hodgkin Lymphoma (cHL)

1.3 Secondary Objective

1.3.1 To describe the safety and tolerability of Brentuximab combined with AD in previously untreated non-bulky limited stage cHL

1.4 Endpoints

1.4.1 Primary: Complete response rate (CRR) at end of treatment restaging, by the revised International Working Group Criteria (see appendix A)[1]

1.4.2 Secondary:
- Rate of grade III and IV adverse events or discontinuation due to toxicity
- Overall response rate (ORR) at end of treatment restaging

1.4.3 Exploratory:
- Failure-free survival (FFS)
- Overall survival (OS)

2. BACKGROUND

2.1 Study Agent(s)

2.1.1 Brentuximab Vedotin (SGN-35, Adcetris)

Brentuximab vedotin is an anti-CD30 antibody-drug conjugate (ADC) consisting of an IgG1 antibody against CD30 bound to the anti-microtubule agent monomethyl auristatin E (MMAE). There have been two phase II studies of single agent brentuximab in relapsed/refractory cHL and relapsed/refractory systemic anaplastic large cell lymphoma (ALCL).[2,3] In the pivotal phase II study of cHL 102 patients received brentuximab at 1.8 mg/kg every 3 weeks. This patient population was heavily pre-treated with a median of 3.5 prior treatments. Seventy-five percent of patients had an objective response (complete or partial remission) with median duration of approximately 9 months. Thirty-four percent of patients achieved a complete response (CR). In the phase II study of relapsed or refractory ALCL 38 patients received brentuximab also at 1.8 mg/kg every 3 weeks. Seventy-two percent of patients were ALK negative (which typically carries a poor prognosis) and patients had received a median of 2 prior systemic therapies. The objective response rate (ORR) was 86% with CR obtained in 53% of patients (median duration of response not yet reached). Nearly all patients (>90%) in both studies experienced a reduction in tumor volume. A phase I study evaluated the combination of brentuximab vedotin with either ABVD or AVD (without bleomycin).[4] The bleomycin-containing arm was found to induce excess pulmonary toxicity, but brentuximab with AVD was found to be overall well tolerated with excellent efficacy in patients with advanced stage disease. The recommended phase II dose for brentuximab combined with AVD is 1.2 mg/kg every 2 weeks.

Brentuximab has been well tolerated in clinical trials to date (see section 6.1). Treatment-associated adverse events (AEs) occurring in ≥ 20% of patients in the phase II studies combined include peripheral sensory neuropathy (44%), fatigue (42%), nausea (41%), diarrhea (34%), pyrexia (31%), upper respiratory tract infection (28%), neutropenia (21%), and vomiting (20%). These events were primarily Grade 1 or 2, with the exception of neutropenia, for which Grade 3 and grade 4 events were reported for 13% and 7% of patients, respectively. Importantly, most of the peripheral sensory neuropathy events were reversible. Also, of note, similar patterns and incidences of AEs were generally observed for HL and ALCL patients.

Brentuximab pharmacokinetics were as follows. After an intravenous (IV) dose of 1.8 mg/kg every 3 weeks, maximum concentrations were typically observed at the end of infusion. A multi-exponential decline in brentuximab antibody-drug conjugate (ADC) serum concentrations was observed with a terminal half-life of approximately 4 to 6 days. Exposures were approximately dose proportional. Steady-state was achieved by 21 days, consistent with the terminal half-life estimate. Minimal to no accumulation was observed with multiple doses at the q3wk (every 3 weeks) schedule. The primary treatment-related effects of repeat-dose brentuximab administration to rats and monkeys were bone marrow hypocellularity and lymphoid depletion. The no-observed-adverse-effect level (NOAEL) for repeat-dose administration of brentuximab was 0.5 and 1 mg/kg in rat and monkey, respectively. The highest nonseverely toxic dose (HNSTD) for repeat-dose administration of brentuximab was 5 and 3 mg/kg in rat and monkey, respectively. In up to one-month repeat-dose toxicity studies of brentuximab in rats at doses up to 15 mg/kg, the following target organs were identified: bone marrow (hypocellularity), thymus (lymphoid depletion), spleen (lymphoid depletion), liver (focal coagulative necrosis), intestine

(single cell necrosis), testis (seminiferous tubular degeneration), and lung (alveolar histiocytosis) in rat only. Following a 4-week recovery period, all target organ toxicity was reversible except for testicular toxicity. Testicular toxicity in rat was partially resolved following a 16-week off-treatment recovery phase.

Based on the above data, the Oncology Drug Advisory Committee voted unanimously on 7/14/11 to recommend brentuximab vedotin be FDA-approved for relapsed classical Hodgkin Lymphoma and anaplastic large cell lymphoma.

We conducted a phase 2 study of 34 patients with non-bulky limited stage classical Hodgkin lymphoma, which completed accrual in 2014. Though data are immature, the treatment appeared highly effective and overall well tolerated. Preliminarily, all patients achieved complete response after 2 cycles of combinatrion brentuximab-AD and no patients required more than 4 cycles of combination chemotherapy. One patient did relapse after achieving remission and was successfully treated with second-line therapy. One additional patient developed neutropenic sepsis and died in remission during therapy. An initially high rate of neutropenic fever was observed, prompting a protocol amendment requiring the use of GCSF support, after which the incidence of infection and neutropenic fever was much lower.

2.2 Hodgkin Lymphoma

Over the last 40+ years advances in the treatment Hodgkin Lymphoma have led to a remarkable improvement in the long-term outcomes of what was once considered an incurable disease. Classical Hodgkin lymphoma (cHL) now carries one of the most favorable prognoses in oncology with patients with limited stage disease achieving cure rates greater than 85%.[5-8] Combined modality therapy has long been the standard of care for limited stage disease, though treatment paradigms continue to evolve with current efforts focused on preserving high rates of cure while minimizing potentially devastating late effects of radiation and chemotherapy including secondary malignancies and end organ damage such as heart and pulmonary disease.

In the last decade there have been a number of publications describing the long-term outcomes of patients treated with combined modality therapy (i.e. chemotherapy plus radiation) and chemotherapy alone, with similarly excellent results reported in patients with non-bulky limited stage disease. Studies of radiation-containing strategies demonstrate a continued risk of treatment-related morbidity and mortality due to second malignancies and cardiovascular disease well after the risk of HL relapse has peaked. For example, in an analysis of 1,474 patients treated at age less than 41, a significant increase of myocardial infarction (35.7 excess cases per 10,000 pt/y) and congestive heart failure (25.6 excess cases per 10,000 pt/y) were seen in patients treated with mediastinal radiation.[9] These risks were greatly increased if radiation was combined with an anthracycline. In a retrospective review of 1,080 patients with stage IA-IIB disease treated between 1969 and 1997, there was a relative risk of death from secondary cancers of 10-14.5, and from cardiac causes of 2.8 to 4.5.[10]

Given these adverse late outcomes there have been efforts to de-escalate therapy with the hope of reducing toxicity while maintaining high cure rates. A strategy employing 4-6 cycles of ABVD (Adriamycin, Bleomycin, Vinblastine and Dacarbazine) with or without radiation in limited stage disease found no difference in overall survival between these groups at 5 years of follow-up.[7] Analysis of this randomized trial at 12 years, however, demonstrated an improved overall survival in patients treated with 4-6 cycles of ABVD alone over combined modality therapy due to increased late events in patients treated with radiation. Chemotherapy alone yielded a favorable 12 year overall survival of 94%.[11] Multiple other prospective and retrospective analyses have further validated ABVD chemotherapy alone in non-bulky limited stage cHL[12-15]

While a chemotherapy alone approach is appealing, the standard ABVD regimen is not without toxicity. Pulmonary toxicity from Bleomycin is the major non-hematologic toxicity of ABVD with incidence of pneumonitis ranging from 8-14%, and may result in treatment-related mortality. Neutropenia is also common, and may be worse when brentuximab vedotin is added to AVD, based on a high rate of neutropenic fever observed in our phase 2 trial prompting addition of routine growth factor support. We also observed a significant rate of peripheral neuropathy, likely related to the combination of vinblastine and brentuximab vedotin, both of which cause neuropathy due to activity on microtubules.

The German Hodgkin Study group explored whether Bleomycin and Dacarbazine are required to preserve the efficacy of this combination by comparing ABVD, AVB, AVD, and AV.[16] In the final analysis, the omission of Dacarbazine resulted in a significantly inferior outcome, and omission of bleomycin also resulted in a slightly inferior PFS compared to AVD and ABVD. Another attempt to eliminate both bleomycin and dacarbazine in a phase II CALGB trial of AVG (Adriamycin, Vinblastine and Gemcitabine) in non-bulky limited stage patients, however, resulted in disappointing efficacy with a CR rate of 72.7% and 3-year PFS of 77%.[17] These expereicnes suggest that a more potent anti-lymphoma therapy would need to be added in order to omit bleomycin with preserved efficacy.

2.3 Rationale

The clinical efficacy of the ABVD regimen is likely to be preserved or improved by adding brentuximab, the single most active agent ever identified in Hodgkin lymphoma, while eliminating the Bleomycin will remove the potentially devastating risk of bleomycin lung injury. Given the overlapping mechanism of action of vinblastine and brentuximab vedotin targeting microtubules, we hypothesize that substituting brentuximab for vinblastine will preserve efficacy while improving the toxicity profile with a reduction in neutropenia and peripheral neuropathy. We are therefore conducting this phase II trial of brentuximab in combination with AD (Adriamycin and Dacarbazine) as initial therapy for non-bulky limited stage cHL.

3. PARTICIPANT SELECTION

Eligibility tests for subjects must be completed within 42 days prior enrollment, unless otherwise stated.

3.1 Inclusion Criteria

3.1.1 Previously untreated stage IA, IB, IIA, or IIB classical Hodgkin Lymphoma
3.1.2 Non-bulky disease defined as less than 10 cm in maximal diameter
3.1.3 Measurable disease ≥ 1.5 cm as measured on PET-CT
3.1.4 Age ≥ 18
3.1.5 ECOG performance status 0-2 (see Appendix B)
3.1.6 Participants must have initial organ and marrow function as defined below:
- Absolute neutrophil count ≥ 1,000/mcL
- Platelets ≥ 100,000/mcL
- Total bilirubin ≤ 2, unless due to Gilbert's disease
- AST (SGOT)/ALT (SGPT) ≤ 2.5 X institutional upper limit of normal
- Creatinine clearance ≥30 mL/min

3.1.7 LVEF by echocardiogram or MUGA within institutional normal limits
3.1.8 Participant must be willing to use two effective forms of birth control during protocol therapy. Men and women must continue using two effective forms of birth control for 6 months following treatment.
3.1.9 Ability to understand and the willingness to sign a written informed consent document

3.2 Exclusion Criteria

3.2.1 Participants who have had prior cHL-directed chemotherapy or radiotherapy
3.2.2 Participants receiving any other investigational agents
3.2.3 Participants with known CNS involvement of lymphoma
3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to Adriamycin, Dacarbazine, or brentuximab
3.2.5 Pre-existing grade 2 or greater neuropathy
3.2.6 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements
3.2.7 Pregnant women are excluded from this study because brentuximab is an antibody drug conjugate with a linked potent anti-tubule agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with brentuximab, breastfeeding should be discontinued if the mother is treated with brentuximab. These potential risks may also apply to other agents used in this study.
3.2.8 Participants with a history of a different malignancy are ineligible unless they have been disease free for 1 year and considered at low risk for relapse, except for: cervical cancer in situ, ductal carcinoma in situ, localized prostate cancer with

no detectable disease by imaging studies, and non-melanoma cancers of the skin, which are eligible at any time.

3.2.9 Known HIV positivity

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

There is no evidence to suggest that the outcome will differ by gender or ethnicity. Given the small size of our study there is insufficient power to detect small effects in these groups. There is no plan to exclude women, minorities or underrepresented populations and they will be able to participate if eligibility criteria are met.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the Clinical Trials Management System (CTMS) OnCore. Registration must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP#: REGIST-101) must be followed.

4.3 General Guidelines for Other Participating Institutions

Eligible participants will be entered on study centrally at Massachusetts General Hospital by the Coordinating Center. All sites should contact the Coordinating Center to verify treatment availability prior to consenting a patient.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator/Sponsor. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. The Coordinating Center should be notified of participant status changes as soon as possible.

4.4 Registration Process for Other Participating Institutions

To register a subject, the following documents should be completed by the participating institution and forwarded to the Coordinating Center:

- Copy of source documentation for all inclusion/exclusion criteria and screening procedures (See section 3 – Participant Selection and Section 9 – Study Calendar), including but not limited to:
  - Pathology confirming histology and stage
  - Echo or MUGA
  - Laboratories
  - PET CT report
- Demographics information
- Signed study consent form
- Study entry note documenting the informed consent process
- HIPAA authorization form, if applicable
- Eligibility checklist

The Coordinating Center will review the above documentation and contact the participating site to confirm eligibility. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with QACT.
- Fax or e-mail the participant study number, and if applicable the dose treatment level, to the participating site.
- Call the participating site and verbally confirm registration, if necessary.

5. TREATMENT PLAN

This is a phase II trial of brentuximab plus AD (Adriamycin and Dacarbazine) for newly diagnosed, non-bulky, stage I or II classical Hodgkin Lymphoma. Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for brentuximab/AD are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy. All protocol-specified treatments are +/- 3 days of the planned date, unless otherwise specified.

All participants will receive brentuximab/AD for 2 cycles followed by an interim restaging PET-CT scan. Patients in CR will receive 2 additional cycles of brentuximab/AD to complete a total of 4 cycles of therapy; patients with stable disease or partial response will receive 4 additional cycles to complete a total of 6 cycles. Patients with progressive disease will be taken off study. Brentuximab/AD will be administered on days 1 and 15 of each 28 day cycle. On treatment days, participants will receive brentuximab (1.2 mg/kg) followed by Adriamycin (25 mg/m^2 IV) and Dacarbazine (375 mg/m^2 IV).

Brentuximab vedotin will be administered prior to adriamycin and dacarbazine. Adriamycin and dacarbazine will be administered via institutional standards.

5.1 General Concomitant Medication and Supportive Care Guidelines

ABVD is routinely administered at full dose in the setting of neutropenia (see section 6 for dosing guidelines). This is in recognition that though neutropenia is common, the duration of neutropenia is short and fever and infectious complications are uncommon. Further, treatment delay and reduced dose intensity may impair treatment outcome. G-CSF is not routinely included in the care of these patients and thus will be used at the treating investigator's discretion in the setting of neutropenia, and may be used as prophylaxis for subsequent cycles if there is an episode of febrile neutropenia.

5.2 Duration of Therapy

Duration of therapy will depend on individual response and toxicity. In the absence of disease progression or unacceptable toxicity, treatment will continue for 4 to 6 total cycles of brentuximab/AD, depending on treatment response or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s), including Grade 4 neuropathy or other Grade 4 events felt to be related to brentuximab
- Any toxicity requiring dose delays of greater than 2 weeks
- Participant demonstrates an inability or unwillingness to comply with the regimen and/or documentation requirements
- Participant decides to withdraw from the study
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator

5.3 Criteria for Removal from Study Treatment

Participants will be removed from study treatment when intercurrent illness, toxicity, inability to participate or a change in condition occurs. The reason for treatment removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator/Sponsor, Jeremy Abramson, MD at 617-724-4000.

5.4 Duration of Follow Up

All participants will be followed for next line of therapy and overall survival. Additionally, participants who have been removed from study treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.5 Criteria for Removal from Study

Participants will be removed from the study upon death or withdrawal of consent. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF).

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using the CTEP NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1 Anticipated Toxicities for Brentuximab, Adriamycin, Dacarbazine

6.1.1 Anticipated Toxicities for Brentuximab

A list of the adverse events and potential risks associated with the agents administered in this study appear below. Most toxicities related to brentuximab in the phase I and II studies were Grade 2 or less. A table detailing the Grade 3 toxicities in the phase II studies is below.

Peripheral neuropathy has been commonly reported in the phase II with 44% of patients having peripheral sensory neuropathy, and 9% peripheral motor neuropathy. Of these only 11% were Grade 3 and there were no Grade 4 events. The neuropathy was reversible in nearly all patients with median resolution of 6.6 weeks.

Neutropenia occurred in 21% of patients in the phase II studies with 20% of patients ≥ Grade 3 (13% Grade 3 and 7% Grade 4). Neutropenia ≥ Grade 3 tended to develop after a median of 2 doses and lasted a median of approximately 1 week. Of the 7% of patients with Grade 4 neutropenia, only 3 had neutropenia that lasted ≥ 7 days.

Additional toxicity data is as follows:

Treatment-emergent adverse events ≥ Grade 3 occurring in ≥2 HL or systemic ALCL patients in the phase 2 population (Studies SG035-0003 and SG035-0004)

	HL SG035-0003 (N=102) n (%)			ALCL[a] SG035-0004 (N=58) n (%)		
	Grade			Grade		
	≥3	4	5	≥3	4	5
Any event	56 (55)	14 (14)	1 (1)	35 (60)	9 (16)	6 (10)
Neutropenia	20 (20)	6 (6)	0	12 (21)	5 (9)	0
Thrombocytopenia	8 (8)	2 (2)	0	8 (14)	3 (5)	0
Peripheral sensory neuropathy	8 (8)	0	0	6 (10)	0	0
Anaemia	6 (6)	1 (1)	0	4 (7)	0	0
Hyperglycaemia	4 (4)	0	0	1 (2)	0	0
Fatigue	2 (2)	0	0	2 (3)	1 (2)	0
Abdominal pain	2 (2)	1 (1)	0	1 (2)	0	0
ALCL recurrent	0	0	0	3 (5)	0	3 (5)
Diarrhoea	1 (1)	0	0	2 (3)	0	0
Hypokalaemia	1 (1)	0	0	2 (3)	0	0
Peripheral motor neuropathy	1 (1)	0	0	2 (3)	0	0
Pulmonary embolism	2 (2)	2 (2)	0	1 (2)	0	0
Pyrexia	2 (2)	0	0	1 (2)	0	0
Syncope	2 (2)	0	0	1 (2)	1 (2)	0
Urinary tract infection	1 (1)	0	0	2 (3)	0	0
Anxiety	2 (2)	0	0	0	0	0
Deep vein thrombosis	0	0	0	2 (3)	0	0
Demyelinating polyneuropathy	2 (2)	0	0	0	0	0
Hodgkin's disease recurrent	2 (2)	0	1 (1)	0	0	0
Mycosis fungoides	0	0	0	2 (3)	0	0
Pain in extremity	0	0	0	2 (3)	1 (2)	0
Pneumonitis	2 (2)	1 (1)	0	0	0	0
Pyelonephritis	2 (2)	0	0	0	0	0
Vomiting	0	0	0	2 (3)	0	0
Weight decreased	0	0	0	2 (3)	0	0

Preferred terms are sorted by descending frequency by "≥3" in the phase 2 population (Studies SG035-0003 and SG035-0004)

6.1.2 Anticipated Toxicities for Adriamycin

Side Effects for Adriamycin include:

1. Hematologic: Leukopenia (dose-limiting), also thrombocytopenia and anemia. Nadir 10-14 days, recovery customarily within 21 days.
2. Dermatologic: Alopecia; hyperpigmentation of nail beds and dermal creases; radiation recall.
3. Gastrointestinal: Nausea and vomiting, sometimes severe; anorexia, diarrhea; mucositis
4. Cardiovascular: Arrhythmias, ECG changes; rarely sudden death. Congestive heart failure due to cardiomyopathy related to total cumulative dose; risk is greater with total doses > 550 mg/m², mediastinal irradiation pre-existing cardiac disease, advanced age.
5. Other: Red discoloration of urine; fever; anaphylactoid reaction.
6. Local effects: Vesicant if extravasated; flush along vein, facial flush.

Nursing/Patient Implications:

1. Monitor CBC, platelet counts.
2. Vesicant - do not extravasate. Refer to extravasation protocol if inadvertent infiltration occurs.
3. Advise patient of alopecia. Instruct on how to obtain wig, hairpiece, etc. Hair loss generally occurs 2-4 weeks after injection and is usually complete.
4. Advise patient of red discoloration of urine for 24 hours after administration of the drug.
5. Administer antiemetics as indicated.
6. Assess for stomatitis and treat symptomatically. Generally occurs 7-10 days after injection.
7. Be aware of "Adria" flare - most common reaction consists of an erythematous streak up the vein. It is associated with urticaria and pruritus. Occasionally the use of corticosteroids and/or antihistamines has been useful.
8. Monitor for signs and symptoms of cardiomyopathy. Calculate total cumulative dose with each administration.

6.1.3 Anticipated Toxicities for Dacarbazine

Side Effects for Dacarbazine include:

1. Hematologic: Myelosuppression; nadir of WBC and platelet depression occurs approximately 21-25 days after treatment.
2. Dermatologic: Alopecia; facial flushing; extravasation may result in severe pain but has not resulted in tissue damage. Rapid IV push may result in pain along injection site or thrombophlebitis.
3. Gastrointestinal: Severe nausea and vomiting which characteristically lessens with each subsequent daily dose.
4. Hepatic: Increased AST, ALT.
5. Renal: Increased serum creatinine, BUN.
6. Neurologic: Facial paresthesia.
7. Other: Flu-like syndrome (with fever, malaise, myalgia) rarely occurs about 7 days after treatment and lasts 1-3 weeks. Rarely Anaphylaxis.

Nursing/Patient Implications:

1. Administer prophylactic and prn anti-emetics.
2. Monitor CBC, platelet count.
3. May cause pain, burning of the vein with rapid administration. This can be minimized by decreasing the rate of infusion

6.2 Toxicity Management and Dose Modifications/Delays

6.2.1 Supportive care:

Participants should receive full supportive care per institutional routine including blood products, antibiotics, antiemetics, and bowel regimen at the discretion of the provider.

6.2.2 Steroids:

Treatment with steroids for pre-existing conditions, adrenal insufficiency or nausea is allowed provided on a stable dose.

6.2.3 Hematologic Toxicity:

Blood counts should be checked on the day of or day before treatment. Hematologic guidelines are extrapolated from the accepted standard of care with ABVD, which is routinely administered at full dose in the setting of neutropenia, in the absence of fever. This is in recognition that though neutropenia is common, the duration of neutropenia is short and fever and infectious complications are uncommon. G-CSF is not routinely included in the care of these patients outside of the setting of febrile neutropenia or infections.

Blood Counts			Administer % of Full Dose
ANC (neutrophils+bands)		**PLTs**	**Brentuximab, Adriamycin, Dacarbazine Dosing**
≥500	And	≥50,000	100%
<500 and patient afebrile (temp <100.5 F)	And	≥50,000	100%. G-CSF support may be included at discretion of treating investigator.
<500 and patient febrile (temp ≥100.5 F)	Or	<50,000	Hold all chemotherapy and recheck within one week. Treatment of neutropenic fever per institutional guidelines. Restart at full dose on schedule or within one week after counts have rebounded to ANC ≥500 and PLT ≥75,000. G-CSF should be included for future cycles at treating physician's discretion. Treatment may be held for a maximum of 2 weeks, after which patients will be removed from study.

6.2.4 Hepatic Dysfunction

LFT's should be checked on the day of or day prior to treatment. No dose modification required for total bilirubin less than 1.5 mg/dL. Participants with total bilirubin of 1.5 to 2.0 mg/dL at study entry (and not due to Gilbert's disease) will be initiated at a 50% dose reduction of Adriamycin. For total bilirubin greater than 1.5 mg/dL on day 1 or 15, Adriamycin will be administered as below. Brentuximab vedotin will be held for ≥ grade 3 bilirubin (>3 mg/dL) until toxicity is ≤ grade 2. Upon restarting, the brentuximab dose will be reduced to 0.8 mg/kg. If a second dose reduction is required, dose will be reduced to 0.6 mg/kg. There are no dose reductions for dacarbazine based on bilirubin.

Total Bilirubin (mg/dL)	% Brentuximab Dose	% Adriamycin Dose	% Dacarbazine Dose
<1.5	100%	100%	100%
1.5 – 3.0	100%	50%	100%
>3.0-5.0	0%	25%	100%
>5.0	0%	0%	100%

6.2.5 Cardiac toxicity

If any of the following cardiac toxicities occur, participants will be removed from protocol:

- Uncontrolled arrhythmia
- Grade 3 or 4 Congestive heart failure

6.2.6 Gastrointestinal toxicity

- Mucositis, dysphagia and diarrhea:
  For ≥ Grade 3 gastrointestinal toxicities mentioned above, treatment will be held until toxicity decreases to ≤ 1 or baseline, after which treatment will be resumed at full dose. Treatment may be held for a maximum of 2 weeks, after which participants will be removed from study.
- Constipation:
  Start stool softeners and mild bowel stimulants (docusate sodium 100 mg po tid plus senna and/or psyllium and/or milk of magnesia and/or Miralax). Increase regimen and add additional agents as needed.

6.2.7 Peripheral nervous system toxicity

PERIPHERAL NERVOUS SYSTEM TOXICITY		
Grade	**Brentuximab dose**	**Comments**
Grade 1	1.2 mg/kg (100%)	
Grade 2	Reduce dose to 0.8 mg/kg.	
Grade 3	Withhold dose until toxicity is < Grade 2 or has returned to baseline. Resume at a dose of 0.8 mg/kg. If dose has already been reduced to 0.8 mg/kg, reduce dose to 0.6 mg/kg.	While brentuximab is held, the other agents will continue as described, provided treatment criteria are met. The dose of brentuximab will not be re-escalated.
Grade 4	------	Patient to come off of study

6.2.8 Infusion reactions:

Infusion reactions are relatively uncommon (11% of patients in phase II studies). Pre-treatment is not required, however, investigators will add supportive medications during a reaction and with subsequent cycles, as indicated. Patients with prior hypersensitivity reactions must be pre-medicated for hypersensitivity in subsequent cycles as per institutional routine for monoclonal antibody therapy.

6.2.9 Other Brentuximab toxicities:

All other Grade 3-4 toxicity considered possibly, probably, or definitely related to brentuximab (Not including hematologic, cardiac, hepatic, gastrointestinal, peripheral nervous system, or alopecia).

Subjects will be removed from study treatment if a second episode of grade 3-4 toxicity occurs despite dose reduction according to table below.

OTHER TOXICITY			
Grade	**Brentuximab dose**	**AD doses**	**Comments**
Grade 1	1.2 mg/kg (100%)	100%	
Grade 2	1.2 mg/kg (100%)	100%	
Grade 3	Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline. Reduce the dose to 0.8 mg/kg . If a second dose reduction is required, dose will be reduced to 0.6 mg/kg.	Withhold dose until toxicity is ≤ Grade 2 or has returned to baseline, then resume at full dose.	The dose of brentuximab will not be re-escalated.
Grade 4	Withhold dose until toxicity is Grade ≤2 or has returned to baseline, then reduce dose to 0.8 mg/kg and resume treatment, or discontinue at the discretion of the investigator. If a second dose reduction is required, dose will be reduced to 0.6 mg/kg, or discontinue at the discretion of the investigator.	Withhold dose until toxicity is Grade ≤2 or has returned to baseline, then resume at full dose.	The dose of brentuximab will not be re-escalated.

7. DRUG FORMULATION AND ADMINISTRATION

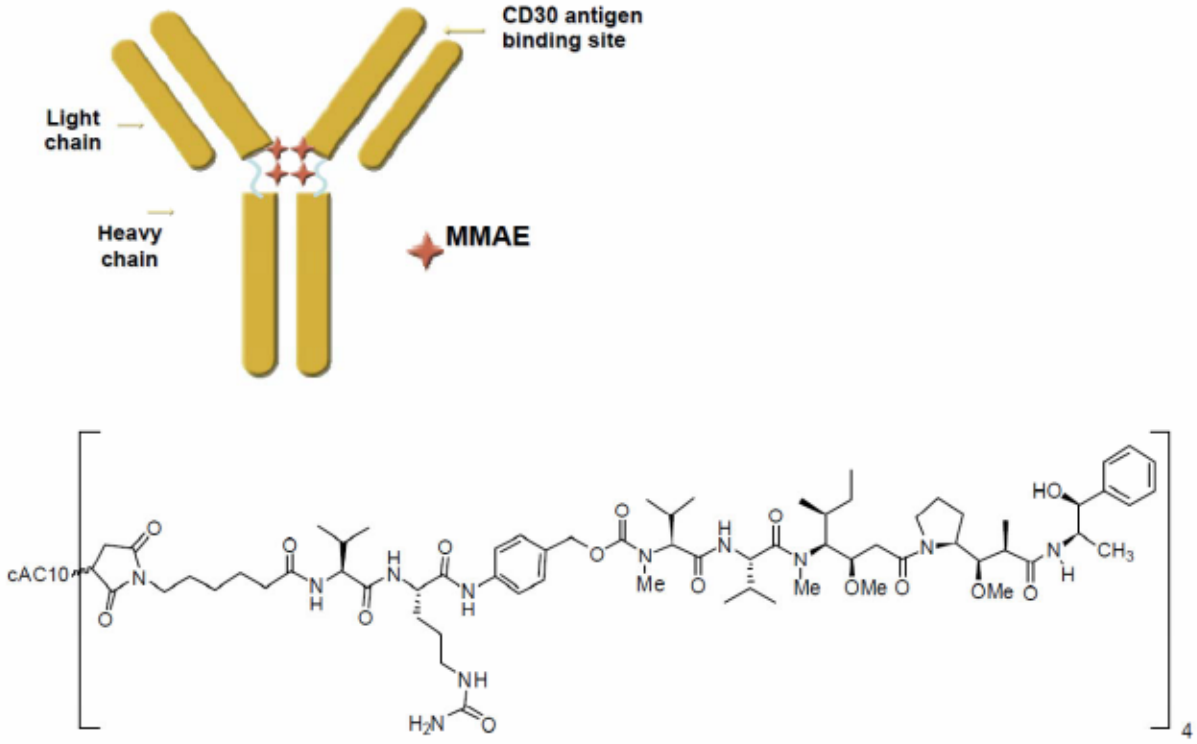
7.1 Brentuximab

7.1.1 Description

Brentuximab is a CD30-directed antibody-drug conjugate (ADC) consisting of three components: 1) the chimeric monoclonal antibody cAC10, specific for human CD30, 2) the highly potent antimicrotubule agent monomethyl auristatin E (MMAE), and 3) a protease cleavable linker that covalently attaches MMAE to cAC10 (Figure 1). Binding of the ADC to CD30 on the cell surface initiates internalization of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell MMAE is released via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest, and results in apoptotic death.

A representative structure of brentuximab vedotin (MR_D=4) is shown in Figure 1.

Figure 1: Structure of brentuximab vedotin



7.1.2 Form

Brentuximab is a sterile, preservative-free, white to off-white lyophilized cake or powder, supplied in single-use vials. Brentuximab drug product is reconstituted with water for injection (WFI), USP. The reconstituted brentuximab drug product is a clear to slightly opalescent, colorless solution with no visible particulate matter. The vial size is 50mg. The reconstituted solution is subsequently diluted in sterile 0.9% Sodium Chloride for Injection, USP, 5% Dextrose Injection USP, or Lactated Ringer's Injection USP, for intravenous (IV) administration

Brentuximab vedotin is the United States adopted name (USAN) and the International Nonproprietary Name (INN) assigned to SGN-35. Adcetris is the United States trade name. Vialed drug product may be labeled as SGN-35, Adcetris or as brentuximab vedotin; the 3 names can be used interchangeably.

7.1.3 Storage and Stability

Each vial contains brentuximab, trehalose, sodium citrate, and polysorbate 80. The drug product vial is reconstituted with the appropriate amount of Sterile Water for Injection. The pH of reconstituted product is approximately 6.6.

Vials containing brentuximab must be stored under refrigeration at 2-8°C. Chemical and physical stability of the reconstituted brentuximab drug product has been demonstrated for 24 hours at 2-8°C. However, brentuximab does not contain preservatives; therefore, from a microbiological standpoint, opened and reconstituted vials should be used immediately. If not used immediately, the in-use storage should not be longer than 24 hours under refrigeration at 2–8°C. It is recommended that brentuximab vials and solutions be protected from direct sunlight until the time of use.

7.1.4 Handling

Recommended safety measures for the handling and preparation of brentuximab for injection include masks, protective clothing, gloves, and vertical laminar airflow safety cabinets.

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

7.1.5 Availability

Brentuximab is an investigational agent and will be supplied by Seattle Genetics, Inc.

7.1.6 Preparation

7.1.6.1 Reconstitution

1. Reconstitute lyophilized brentuximab by adding 10.5 mL Sterile Water for Injection, USP to the 50 mg vial, directing the stream to the side of the vial. The concentration of reconstituted brentuximab is 5 mg/mL with a total volume of 11mL.

2. Gently swirl the vial until contents are completely dissolved. **The vial must not be shaken or vigorously swirled as excess agitation may cause aggregate formation**. Slight "bubbling" of the solution upon reconstitution may be observed.

3. Allow the reconstituted vial to settle for a minute to allow bubbles to dissipate. The reconstituted product should be a colorless, clear to slightly opalescent solution with no visible particulates.

4. The prepared dosing solution must be stored in an infusion bag at the refrigerated condition (2-8°C) and must be used within 24 hours of vial reconstitution. Protect infusion bag from direct sunlight until time of use.

7.1.6.2 Dose Preparation

1. Transfer the required volume of reconstituted product to a 150 mL to 250 mL infusion bag. The following bag types are compatible with brentuximab: polyvinylchloride (PVC), ethylene vinyl acetate (EVA), polyolefin, or polyethylene. A participant in a lower dose cohort (0.8 or 1.2 mg/kg) who has a very low body weight may require less than 150 mL of diluent in order to achieve a concentration of 0.4 to 1.8 mg/mL (see table below).

2. Dilute reconstituted product in either 0.9% Sodium Chloride Injection, USP, Lactated Ringer's solution, USP, or dextrose 5% in water (D5W), USP. The final concentration of brentuximab in infusion bag should be in the range of 0.4-1.8 mg/mL. Final concentration = total dose/total volume of infusion. Example of dose preparation calculations:

PT WEIGHT[C]	DOSE LEVEL	TOTAL DOSE (PT WEIGHT X DOSE LEVEL)	VOLUME OF RECONSTITUTED PRODUCT REQUIRED (TOTAL DOSE (MG) / 5 MG/ML)	VOLUME OF DILUENT [b]	TOTAL VOLUME OF INFUSION	CONCENTRATION (TOTAL DOSE / TOTAL VOLUME OF INFUSION)
45 kg	1.2 mg/kg	54mg	10.8 mL (requires 2 vials[a])	100 mL	110.8 mL	0.49 mg/mL

a Approximately 10mL can be withdrawn from each vial.
b Patients with a low body weight may require less than 150 mL of diluent.
c For patients weighing more than 100 kg, total dose will be calculated using 100 kg.

3. Gently invert the infusion bag. **DO NOT SHAKE** – excess agitation may cause aggregate formation.

4. Prior to administration, inspect the prepared dosing solution (in infusion bag) for any particulate matter or discoloration.

5. Do not prepare a single dose of brentuximab using vials from different lots. Use vials from the same lot number for a given dose.

6. The prepared dosing solution must be stored in an infusion bag at the refrigerated condition (2-8°C) and must be used within 24 hours of vial reconstitution. Protect infusion bag from direct sunlight until time of use.

7.1.7 Administration

Dose and frequency will be administered per study protocol. Dosing should be based on the participant's pre-dose weight determined at day 1 visit of each cycle. Dose may be re-calculated based on weight on day 15 if that is consistent with the institutional standard of care. Brentuximab dose should be rounded to the nearest whole number of milligrams. Infusion time for brentuximab is 30 minutes. The drug may be given at slower infusion at the discretion of the treatment team in the setting of prior hypersensitivity reactions, consistent with institutional standards.

7.1.8 Ordering

Brentuximab vedotin will be supplied by Seattle Genetics and should be obtained by the research pharmacy using the study specific drug order form. Brentuximab vedotin will be supplied free of charge and will be ordered from Seattle Genetics.

7.1.9 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

7.1.10 Destruction and Return

At the end of the study, unused supplies of brentuximab should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

7.2 Adriamycin

Other Names: Doxorubicin

Classification: Anthracycline antibiotic.

Mode of Action: Intercalation between adjoining nucleotide pairs in the DNA helix causes inhibition of DNA and DNA-dependent RNA synthesis. Free radical generation is responsible for cardiac toxicity. Adriamycin also inhibits topoisomerase II.

Storage and Stability: Adriamycin RDF intact vials are stable protected from light at room temperature. Adriamycin PFS vials must be refrigerated. Reconstituted solutions are stable for 24 hours at room temperature and 48 hours under refrigeration. The Adriamycin RDF 150 mg multidose vial is stable after reconstitution for 7 days at room temperature or 15 days if refrigerated and protected from sunlight.

Dose Specifics: Adriamycin will be given intravenously at a dose of 25 mg/m² on days 1 and 15 of each cycle. A cycle will be repeated every 28 days. Use actual weight to calculate body surface area and doses.

Preparation: Add 5, 10, 25, 50, or 75 ml of preservative-free normal saline to the 10, 20, 50, 100, or 150 mg vial to produce a solution containing 2 mg/ml.

Administration: Intravenously as a bolus injection.

Incompatibilities: Physically incompatible with heparin, fluorouracil, aminophylline, cephalothin, dexamethasone, diazepam, hydrocortisone, and furosemide.

Compatibilities: Stable with vincristine in normal saline for 5 days at room temperature protected from light. Also compatible in solution with cyclophosphamide.

Availability: Commercially available as powder for injection in 10, 20, 50, 100, 150 mg vials, and as 2 mg/ml solution for injection in 10, 20, 50, and 200 mg vials.

Adriamycin will be obtained from commercial supply.

See section 6.1.2 for side effects.

See section 6.1.2 for nursing/patient implications.

7.3 Dacarbazine

Other Names: DTIC

Classification: Alkylating agent.
Mode of Action: Activity may be the result of at least 3 mechanisms: 1) alkylation; 2) antimetabolite activity as a purine precursor; and 3) interaction with sulfhydryl (SH) groups in proteins. Dacarbazine appears to be more active in G2 phase but is not particularly cell cycle phase specific.

Storage and Stability: Store vials under refrigeration and protected from light. In solution, Dacarbazine is stable for 96 hours if refrigerated and protected from light, 24 hours if not refrigerated but protected from light. When further diluted in 500 ml D5W or NS, it is stable for 24 hours if refrigerated, and 8 hours at room temperature and protected from light. Photodegradation: The manufacturer of dacarbazine states that the drug does not decompose when left at room temperature under normal lighting conditions for eight hours. NOTE: A change in color of solution from pale yellow to pink is indicative of decomposition of the drug.

Dose Specifics: Patients will receive Dacarbazine intravenously at a dose of 375 mg/m² on days 1 and 15 of each cycle of chemotherapy. Cycles will be repeated every 28 days. Use actual weight to calculate body surface area and doses.

Preparation: Dilute the 100, 200, and 500 mg vials with 9.9, 19.7, and 49.5 ml of sterile water, respectively, resulting in a concentration of 10 mg/ml. Protect the drug from direct light. Do not freeze. Discard if solution turns pink/red. The drug can be further diluted in 50-500 ml of 5% dextrose or normal saline.

Administration: Usually administered by intravenous infusion over 30 minutes or longer; has also been given IV push.

Incompatibilities: Metabolism of dacarbazine may be induced by phenytoin or phenobarbital. Toxicity may be enhanced if given concomitantly with allopurinol,

azathioprine, or mercaptopurine. Dacarbazine is physically incompatible with hydrocortisone sodium succinate and heparin.

Availability: Commercially available in vials containing 100 mg, 200 mg, or 500 mg of lyophilized drug.

Dacarbazine will be obtained from commercial supply.

See section 6.1.4 for side effects.

See section 6.1.4 for nursing/patient implications.

8. STUDY CALENDAR

8.1 Pre-Treatment Evaluations: To be completed within 42 days prior to enrollment unless otherwise specified:

- Signed inform consent
- Vital signs, including temperature, blood pressure, heart rate, and respiratory rate
- Complete physical examination, including height and weight
- Medical history: Detailed documentation of disease and treatment history with outcomes
- ECOG performance status
- Concurrent medical conditions, including peripheral neuropathy
- Concurrent medications
- CBC with differential
- Erythrocyte sedimentation rate (ESR)
- Serum chemistries: Electrolytes (sodium, potassium, chloride, and CO_2), calcium, magnesium, phosphate, blood urea nitrogen (BUN), creatinine, glucose, and liver function tests (aspartate aminotransferase (AST) and alanine aminotransferase (ALT), alkaline phosphatase (ALP), total protein, albumin, and total bilirubin
- Coagulation studies including prothrombin time (PT), partial thromboplastin time (PTT) and international normalized ratio (INR)
- Hepatitis B serology testing (Hepatitis B core antibody, Hepatitis B surface antigen, Hepatitis B surface antibody) (may be performed within 6 months prior to start of study treatment)
- Baseline EKG
- Echocardiogram or MUGA to determine LVEF
- Full-body PET-CT scan (neck, chest, abdomen/pelvis). Tumor measurements will be centrally performed by the DF/HCC tumor imaging metric core (TIMC)

- Assessment of Early Favorable or Early Unfavorable based on GHSG criteria (see footnote 1 in required data table)
- Serum pregnancy test for women of childbearing potential must be performed within 7 days

8.2 Evaluation During Treatment:

The following will be performed on the days of treatment (e.g. days 1 and 15) during each cycle of the protocol (+/- 3 days):

- Vital signs
- Physical examination
- Interval history including recording of adverse events, toxicity assessment, changes in medical conditions or medications
- ECOG performance status
- Neuropathy assessment using FACT/GOG-Neurotoxicity Questionnaire (Appendix D), day 1 only
- CBC with differential
- Serum chemistries: Electrolytes (sodium, potassium, chloride, and CO_2), calcium, blood urea nitrogen (BUN), creatinine, glucose, and liver function tests (aspartate aminotransferase (AST) and alanine aminotransferase (ALT), alkaline phosphatase (ALP), total protein, albumin, and total bilirubin. **LFT's should be checked on the day of or day prior to treatment.**

Objective disease assessment with PET-CT scan is to be performed:

- Cycle 2 days 22-28

8.3 Post-Treatment Evaluation

The following clinical assessments will be performed at the post-treatment evaluation (6 weeks +/- 3 days of the completion of the last dose of therapy):

- Interval history including recording of adverse events, toxicity assessment, changes in medical conditions or medications
- Full physical examination
- Weight and vital signs (blood pressure, pulse rate, respiratory rate, and temperature)
- ECOG Performance Status
- Neuropathy assessment using FACT/GOG-Neurotoxicity Questionnaire (Appendix D)
- Recording of AEs
- Recording of concomitant medications
- Laboratory testing: CBC with differential, serum chemistries (Na, K, Cl, CO_2, glucose, blood urea nitrogen (BUN), creatinine, calcium,

total bilirubin, AST, ALT, alkaline phosphatase, albumin, and total protein)
- PET-CT scan

Participants coming off of treatment: If a participant discontinues treatment for any reason other than completing treatment (e.g., toxicity, disease progression, withdraw of consent, etc.), end of study assessments are to be performed 14 days (+/- 3 days) from the last study dose. If a previous PET/CT was obtained within 28 days of participant stopping study treatment, PET/CT does not need to be repeated at post-treatment evaluation.

If a participant completes all scheduled treatment per protocol (4 cycles of therapy for participants with CR, or 6 cycles for participants with PR or SD), end of study assessments are to be performed 6 weeks (+/- 3 days) from the last study dose. If the participant is not available, the reason for not completing the end of study assessments must be recorded in the participant's source documents.

Long Term Follow-up: Participants will be followed for survival status.

- Years 1-2:
  - History and Physical Exam, CBC with differential and complete metabolic panel every 3 months (+/- 14 days) after the post-treatment evaluation visit.
  - Disease assessments by imaging after the post-treatment evaluation visit:
    - CT scans of the chest, abdomen and pelvis will be performed at 6 months, 1 year, 18 months and 2 years after the completion of therapy PET-CT (+/- 14 days)
  - Neuropathy assessment using FACT/GOG-Neurotoxicity Questionnaire (Appendix D) should be completed every 3 months (+/- 21 days) until resolution of peripheral neuropathy.
  - Toxicities related to study treatment should be followed until resolution
- Years 3-5:
  - History and Physical Exam, CBC with differential and complete metabolic panel every 6 months (+/- 21 days)
  - Toxicities related to study treatment should be followed until resolution
  - Imaging to be performed at the discretion of the treating investigator
- Years 5+:
  - Survival only

Study Procedure	Pre-Study	Brentuximab + AD												End Of Treatment	
		Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5[a]		Cycle 6[a]			
	Screening	D1	D15	D1	D15	D1	D15	D1	D15	D1	D15	D1	D15	Post Txt Evaluation[g]	Long Term Follow Up[h]
Brentuximab/AD[a]		X	X	X	X	X	X	X	X	X	X	X	X		
Informed consent[d]	X														
History/Interval History	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical exam (Ht, Wt, BSA, VS)[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CBC w/differential	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistries[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation[i]	X														
ESR	X														
Hepatitis B serologies[c]	X														
EKG	X														
Echocardiogram or MUGA	X														
β-HCG[e]	X														
Early favorable versus early unfavorable based on GHSG criteria[l]	X														
Adverse event evaluation		X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]
Neuropathy Assessment Questionnaire		X		X		X		X		X		X		X	X
Tumor measurements by radiologic evaluation[f]	X				X									X	X

a. Continued treatment on cycles 5 and 6 will depend on PET-CT response (less than CR but not PD will continue with cycles 5 and 6)
b. Albumin, alkaline phosphatase, total bilirubin, BUN, calcium, chloride, CO_2, creatinine, glucose, potassium, total protein, AST, ALT, sodium. Magnesium and phosphorous are required only with screening labs.
c. Hepatitis B Surface Antigen, Hepatitis B Surface Antibody, Hepatitis B Core Antibody
d. Informed consent must be obtained prior to all study-related procedures.
e. Serum pregnancy test is only required in women of childbearing potential within 7 days of beginning protocol therapy.
f. PET-CT is to be performed within the last 7 days of the treatment cycle (e.g. days 22-28); See footnotes g and h for the end of treatment and follow-up imaging.
g. The post-treatment evaluation will occur 6 weeks (+/- 3 days) from the last dose of therapy for participants that complete all scheduled treatment per protocol. The post-treatment evaluation will occur 14 days (+/-7 days) from the last dose of therapy for participants that discontinue treatment early (e.g., toxicity, disease progression, etc.). If a previous PET/CT obtained within 28 days of participant stopping study treatment early, PET/CT does not need to be repeated at post-treatment evaluation. Imaging at or prior to this visit will be by PET-CT. SAEs require reporting up to 30 days after last dose of therapy.
h. Follow-up: participants will be followed for survival status. During years 1-2 physician visits should be every 3 months and CT scans of the chest/abdomen/pelvis (no PET unless clinically indicated) at 6 months, 1 years, 18 months and 2 years after the end-of treatment restaging scan +/- 21 days). The neuropathy assessment questionnaire should be completed until resolution of neurotoxicity. During years 3-5 provider visits should be every 6 months. Beyond 5 years, participants will be followed for survival only.
i. Coagulation to include PT, PTT and INR.
j. Height required at baseline physical exam only. BSA will be calculated with the Dubois formula, or alternate formula per institutional standard.
k. Toxicities related to study treatment should be assessed at LTFU visits until resolution.
l. GHSG criteria: Presence of any one of these risk factors denotes early unfavorable disease: Mediastinal mass $\geq$10cm, Extranodal disease, $\geq$3 nodal regions, or Elevated ESR. Absence of all risk factors is considered early favorable disease.

9. MEASUREMENT OF EFFECT

9.1 Antitumor Effect

Response and progression will be evaluated in this study using the International Working group criteria (Lugano criteria) for lymphoma response (see appendix A).[1] PET interpretation will be interpreted as positive or negative per the consensus Deauville criteria.[18] The participants will be assessed for response using PET-CT scan between days 22 and 28 of cycle 2 of brentuximab/AD (which will be used to determine disease progression and the number of subsequent cycles of combination brentuximab/AD), and at EOT **6 weeks** after completion of combination therapy (+/- 3 days).

10. ADVERSE EVENT REPORTING REQUIREMENTS

10.1 Definitions

10.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

10.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the participant was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a participant's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or

- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- Elective or pre-planned treatment for a pre-existing condition that did not worsen
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- Respite care
- Non-clinically significant laboratory abnormalities

10.1.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

10.1.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

10.1.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

10.1.4 Attribution

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

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.

- Unrelated - The AE is clearly NOT related to the study treatment.

10.2 Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study. AEs related to study treatment will be followed at Long Term Follow-up visits.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

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

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

10.3 Reporting Requirements

For multi-site trials where a DF/HCC investigator is serving as the principal investigator, each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

10.4 Reporting to the Study Sponsor

10.4.1 DF/HCC Reportable Adverse Event Reporting

In addition to SAEs that meet criteria from section 10.1.2, the Sponsor requires additional events to be reported to the Coordinating Center. All DF/HCC reportable adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the Coordinating Center on the local institutional SAE form. This includes the following:

- Grade 2 (moderate) and Grade 3 (severe) Events events that are unexpected and considered possibly, probably or definitely related/associated with the intervention.

Note: Grade 2 or 3 neutropenia, leukopenia, and lymphopenia are expected with chemotherapy in this patient population and are not required to be reported.

- All Grade 4 (life-threatening or disabling) Events – Unless specifically listed in the protocol as not requiring reporting.

  Note: Grade 4 neutropenia, leukopenia, and lymphopenia are expected with chemotherapy in this patient population and are not required to be reported.

- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

  Note: If the participant is in long term follow up, report the death at the time of continuing review.

Due to the additional expedited reporting criteria, the table below is a tool to summarize the reporting requirements and timelines for SAEs and DF/HCC reportable adverse events to the Coordinating Center.

Attribution	SAEs	DF/HCC Reportable AEs				
	All SAEs (section 11.1.2)	**Gr. 2 & 3 AE Expected#**	**Gr. 2 & 3 AE Unexpected#**	**Gr. 4 AE Expected#**	**Gr. 4 AE Unexpected#**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	1 business day	Not required	Not required	5 calendar days*	5 calendar days*	1 business day
Possible Probable Definite	1 business day	Not required	5 calendar days	5 calendar days*	5 calendar days*	1 business day

If event meets SAE criteria listed in section 10.1.2 in addition to grade, attribution and expectedness, event must be reported within 24 hours.
* If listed in protocol as expected and not requiring reporting, event does not need to be reported.

Participating investigators must report each serious adverse event to the Coordinating Center in accordance with the table above. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere) or within the reporting timeframes listed in the table above, the participating investigator is to report the event within 1 business day after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Coordinating Center
[redacted]

Within the following 1-2 business days, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

10.4.2 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the Coordinating Center on the toxicity Case Report Forms.

10.5 Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

External Participating Sites should report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to:

Coordinating Center
[redacted]

The Coordinating Center will submit SAE reports from outside institutions to the DFCI Office for Human Research Studies (OHRS) according to DFCI IRB policies and procedures in reporting adverse events.

10.6 Reporting to the Food and Drug Administration (FDA)

The DF/HCC Overall Principal Investigator, as holder of the IND, will be responsible for all communication with the FDA. The Coordinating Center will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment.

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

10.7 Reporting to Seattle Genetics

The participating investigator must report each serious adverse event, regardless of attribution, to the Coordinating Center within 1 business day of learning of the occurrence. In the event that the participating investigator does not become aware of

the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 1 business day after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by facsimile to:

Coordinating Center Fax: [redacted]

The Coordinating Center will be responsible for forwarding all serious adverse events to Seattle Genetics Drug Safety Department [redacted] within 30 days of receiving the initial fax notification from participating investigators. Events meeting FDA reporting criteria (see 11.6) will be reported to Seattle Genetics Drug Safety at the same time the FDA is notified by the Coordinating Center.

10.8 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

10.9 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the Principal Investigator/Sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the Coordinating Center and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

11. DATA AND SAFETY MONITORING

11.1 Data Reporting

11.1.1 Method

The QACT and the Coordinating Center will collect, manage, and perform quality checks on the data for this study.

11.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

11.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator/Sponsor and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

11.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Principal Investigator/Sponsor or Coordinating Center. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

12. REGULATORY CONSIDERATIONS

12.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The Principal Investigator/Sponsor or Coordinating Center will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

12.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

12.3 Ethics

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
    - Title 21 Part 50 – Protection of Human Subjects
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
    - Title 21 Part 56 – Institutional Review Boards
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

- Title 21 Part 312 – Investigational New Drug Application
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws

- DF/HCC research policies and procedures
  http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

12.4 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix E.

- *The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.*

- *Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.*

- *Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.*

12.5 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

12.6 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is an open label single arm phase II study to assess the efficacy and safety of brentuximab in combination with Adriamycin and Dacarbazine (AD) in previously untreated stage I and II non-bulky cHL. Brentuximab and AD are administered administered on days 1 and 15 of each 28 day cycle. Interim restaging PET-CT will be performed following cycle 2. Patients with progressive disease will be taken off study. Patients in CR will receive a total of 4 cycles of therapy; patients with stable disease or partial response will receive a total of 6 cycles.

13.1.1 Primary Endpoint and Sample Size

The primary endpoint of this study is complete response rate at EOT restaging. A one-stage design is used. A total of 34 participants will be entered on this study. The expected accrual is 1-2 participants per month. If at least 91% (31) of evaluable participants achieve complete responses, the treatment will be considered promising and worthy of further study. Patients removed from study prior to initial restaging for reasons other than disease progression are not considered evaluable for response. The study has 91% power and 0.09 one-sided type I error to test a CR rate of 95% vs. a CR rate of 81%. With 34 eligible patients the 90% confidence interval for the true response rate will be no wider than 30%. If greater than 2 evaluable participants are seen not to have disease response (CR or PR) following brentuximab-AD therapy, the study will stop. Assuming the null response rate of 81%, the study will stop early with a maximum probability of 0.97. Under the promising rate, the study will stop early with a maximum probability of 0.24.

13.1.2 Secondary and Exploratory Endpoints

Overall Survival (OS) will be measured from date of study entry to date of death and characterized using the Kaplan-Meier method. Failure-free Survival (FFS) will be measured from date of study entry to date of documentation of treatment failure and calculated using the Kaplan-Meier method. Treatment failure is defined as: progressive disease, failure to achieve a complete remission, or relapse after initial response. This study is not powered for FFS, but our hypothesis is that it will achieve a 2 year FFS of $\geq$87%, consistent with all prior studies of

chemotherapy alone in non-bulky limited stage HL.[7,11,12,19,20] Two year FFS less than this will not be considered worthy of further investigation.

All participants who receive treatment, regardless of eligibility, will be assessed for toxicity.

13.1.3 Evaluation of toxicity

All participants will be evaluable for toxicity from the time of their first treatment. Participants will be assessed for toxicity with each treatment and participants with unacceptable toxicity will be removed from the study. All participants who receive treatment, regardless of eligibility, will be evaluated for toxicity.

13.1.4 Evaluation of response

All participants who reach initial restaging scan will be evaluable for response, as will subjects who are removed from study prior to initial restaging due to clinical disease progression. Patients removed from study prior to initial restaging for reasons other than disease progression are not considered evaluable for response. Each participant should be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.

Subjects who are removed from protocol prior to first restaging for reasons other than toxicity or disease progression may be replaced.

All conclusions should be based on all eligible participants. Subanalyses may then be performed on the basis of a subset of participants, excluding those for whom major protocol deviations have been identified (e.g., early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding participants from the analysis should be clearly reported. The 90% confidence intervals should also be provided.

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15. APPENDICES

Appendix A: Objective Response Criteria (see Deauville criteria on next page for interpretation of PET positive/negative)

Revised criteria for response assessment[1]

	PET-CT-based response
	Complete Metabolic Response (CMR)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on 5-point (Daeuville) scale (see below) It is recognized that in Waldeyer's ring or extranodal sites with high physiological uptake or with activation within spleen or marrow, e.g. with chemotherapy or myeloid colony stimulating factors, uptake may be greater than normal mediastinum and/or liver. In this circumstance, CMR may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiological uptake
Non-measured lesion	Not applicable
Organ enlargement	Not applicable
New lesions	None
Bone marrow	No evidence of FDG-avid disease in marrow
	Partial Metabolic Response (PMR)
Lymph nodes and extralymphatic sites	Score 4, 5 with reduced uptake compared with baseline and residual mass(es) of any size. *At interim* these findings suggest responding disease *At end of treatment* these findings indicate residual disease
Non-measured lesions	Not applicable
Organ enlargement	Not applicable

Deauville Criteria for PET scan Interpretation in Lymphoma[18]

Five-point scale:

1. No Uptake
2. Uptake ≤ mediastinum
3. Uptake >mediastinum but ≤ liver
4. Uptake moderately increased compared to liver at any site
5. Uptake markedly increased compared to the liver at any site or/and new sites of disease

X. New uptake felt unrelated to lymphoma

A score of 1-3 is PET NEGATIVE.

A score of 4-5 is PET POSITIVE.

Appendix B: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Description	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix C: Drug interactions

In humans, brentuximab did not affect the PK of midazolam, a sensitive CYP3A4 substrate, suggesting that brentuximab and MMAE are neither inhibitors nor inducers of CYP3A4. In humans, data from coadministration of brentuximab with rifampin, a CYP3A4 and P-gp inducer, or ketoconazole, a strong CYP3A4 and P-gp inhibitor, indicate that MMAE is a substrate of CYP3A4. This is consistent with results from in vitro studies, which show that the metabolites of MMAE are produced primarily through the action of CYP3A4. No dose adjustment should be necessary based on coadministration of a CYP3A4 inducer. Patients receiving strong CYP3A4 or P-gp inhibitors should be closely monitored for AEs when coadministered with brentuximab.

Example strong inhibitors of CYP3A4: some protease inhibitors (atazanavir, ritonavir, indinavir, nelfinavir, saquinavir), clarithromycin, telithromycin, chloramphenicol, ketoconazole, intraconazole, nefazodone, fluvoxamine

Example inhibitors of P-gp: amiodarone, clarithromycin, cyclosporine, diltiazem, erythromycin, indinavir, itraconazole, ketoconazole, nelfinavir, nicardipine, propafenone, quinidine, ritonavir, saquinavir, tacrolimus, tamoxifen, verapamil

Appendix D: Neurotoxicity Questionnaire

FACT/GOG-Neurotoxicity Questionnaire, Version 4.0 [21]

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
I have numbness or tingling in my hands.....	0	1	2	3	4
I have numbness or tingling in my feet.....	0	1	2	3	4
I feel discomfort in my hands.....	0	1	2	3	4
I feel discomfort in my feet.....	0	1	2	3	4
I have joint pain or muscle cramps.....	0	1	2	3	4
I feel weak all over.....	0	1	2	3	4
I have trouble hearing.....	0	1	2	3	4
I get a ringing or buzzing in my ears.....	0	1	2	3	4
I have trouble buttoning buttons.....	0	1	2	3	4
I have trouble feeling the shape of small objects when they are in my hand.....	0	1	2	3	4
I have trouble walking.....	0	1	2	3	4

Patient Name: _____ Date Completed: _____

Patient Signature: _____

DFCI IRB Protocol #: 15-196

APPENDIX E

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

Table of Contents

1.0 INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center (DF/HCC) Multi-center protocol will comply with Federal regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affilitates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, FDA, OBA etc.). The Lead Institution is the home of the DF/HCC Sponsor. The Lead Institution also typicall serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies. The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for

the DF/HCC Multi-Center Protocol.

DF/HCC Quality Assurance Office for Clinical Trials: A group within DF/HCC responsible for registering human subjects for trials, ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. QACT also coordinates quality assurance efforts related to multi-center clinical research.

2.0 GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Jeremy Abramson, MD, will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. CTEP, FDA, OBA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with the FDA (investigator-held IND trials).
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the The Coordinating Center may include but are not limited to:

- Assist in protocol development
- Maintain FDA correspondence .
- Review registration materials for eligibility and register participants from Participating Institutions with DF/HCC QACT.
- Distribute protocol and informed consent document updates to Participating Institutions as needed. Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to DF/HCC Sponsor for timely review.
- Distribute Serious Adverse Events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions. Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with. Carry out plan to monitor Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurance (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites.
- Conduct regular communications with all Participating Institutions (conference calls, emailes, etc) and maintain documentation of all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.

- Submit Serious Adverse Event (SAE) reports to local IRB per local requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3.0 DF/HCC requirements for Multi-Center Protocols

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis

about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent to interventional trials (i.e. drug and/or device trials).

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.
- Participating Institution's IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected

Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB and if applicable NCI/CTEP, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned DF/HCC QACT case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

Please see Section 4.4 of the Protocol

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC QACT before receiving treatment. Treatment may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

The DF/HCC QACT will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC QACT requires each institution to fully comply with this requirement.

3.8 DF/HCC Protocol Case Number

At the time of registration, QACT requires the following identifiers for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case

number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission.

All protocol violations must be sent to the Coordinating Center in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

3.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 10.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.10 Data Management

The DF/HCC QACT develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. The DF/HCC QACT provides a web based training for eCRF users.

3.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following:

Incomplete or Questionable Data

If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC QACT Data Analyst, Coordinating Center or designee. Responses to all queries should be completed and submitted within 14 calendar days. Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

Missing Forms

If study forms are not submitted on schedule, the Participating Institution will receive a Missing Form Report from the Coordinating Center noting the missing forms. These reports are compiled by the DF/HCC QACT and distributed on a monthly basis.

4 REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol section

5 MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the QACT provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. An on-site monitoring visit will be conducted within 3 months of the first subject enrolled at each participating Institution. Subsequent monitoring visits will be conducted every four months via a combination of remote and

on-site monitoring with at least one on-site monitoring visit every 24 months. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion. Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol departures, pharmacy records, response assessments, and data management.

Participating institutions will be required to participate in monthly Coordinating Center initiated teleconferences during the screening/enrollment phase through active treatment.

Remote Monitoring will involve the Participating Institution to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source data verification

and/or

On-Site Monitoring will involve source documentation verification (SDV) will be conducted by having access to participants' complete medical record and source documents.

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports for on-site and remote monitoring of Participating Institutions to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

Accrual for this study are 3 per site annually

6 AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 Audit Plan: DF/HCC Sponsored Trials

One on-site audit will be scheduled by the QACT, assuming at least three participants have been treated on protocol at the site. Approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.2 Audit Notification

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans if applicable. The Coordinating Center, must forward these reports to the DF/HCC QACT per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the DF/HCC Sponsor to implement recommendations or require further follow-up. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Participating Institution Performance

The DF/HCC Sponsor, DFCI IRB and the NCI for CTEP trials, is charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

6.5.1 Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ADCETRIS safely and effectively. See full prescribing information for ADCETRIS.

ADCETRIS® (brentuximab vedotin) for injection, for intravenous use

Initial U.S. approval: 2011

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

See full prescribing information for complete boxed warning.

JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS (5.9, 6.2).

RECENT MAJOR CHANGES

Dosage and Administration (2.1)	11/2014
Warnings and Precautions (5.6, 5.7, 5.8, 5.11)	11/2014
Warnings and Precautions (5.10)	02/2015

INDICATIONS AND USAGE

ADCETRIS is a CD30-directed antibody-drug conjugate indicated for treatment of patients with:

- Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates (1.1).
- Systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen (1.2).

Accelerated approval was granted for the above indications based on overall response rate. An improvement in patient-reported outcomes or survival has not been established. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

DOSAGE AND ADMINISTRATION

- Administer only as an intravenous infusion over 30 minutes every 3 weeks.
- The recommended dose is 1.8 mg/kg (2).
- Reduce dose in patients with mild hepatic impairment (2).
- Continue treatment until disease progression or unacceptable toxicity.

DOSAGE FORMS AND STRENGTHS

For injection: 50 mg lyophilized powder in a single-use vial (3).

CONTRAINDICATIONS

Concomitant use with bleomycin due to pulmonary toxicity (4).

WARNINGS AND PRECAUTIONS

- Peripheral neuropathy: Monitor patients for neuropathy and institute dose modifications accordingly (5.1).
- Anaphylaxis and infusion reactions: If an infusion reaction occurs, interrupt the infusion. If anaphylaxis occurs, immediately discontinue the infusion (5.2).
- Hematologic toxicities: Monitor complete blood counts prior to each dose of ADCETRIS. Closely monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent doses (5.3).
- Serious infections and opportunistic infections: Closely monitor patients for the emergence of bacterial, fungal or viral infections (5.4).
- Tumor lysis syndrome: Closely monitor patients with rapidly proliferating tumor or high tumor burden (5.5).
- Hepatotoxicity: Monitor liver enzymes and bilirubin (5.8).
- Pulmonary Toxicity: Evaluate new or worsening pulmonary symptoms (5.10).
- Serious dermatologic reactions: Discontinue if Stevens-Johnson syndrome or toxic epidermal necrolysis occurs (5.11).
- Embryo-fetal toxicity: Fetal harm can occur. Advise pregnant women of the potential hazard to the fetus (5.12).

ADVERSE REACTIONS

The most common adverse reactions (≥20%) are neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough, and vomiting (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Seattle Genetics, Inc. at 1-855-473-2436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Concomitant use of strong CYP3A4 inhibitors or inducers, or P-gp inh bitors, has the potential to affect the exposure to monomethyl auristatin E (MMAE) (7.1).

USE IN SPECIFIC POPULATIONS

Moderate or severe hepatic impairment or severe renal impairment: MMAE exposure and adverse reactions are increased. Avoid use (5.6, 5.7, 8.6, 8.7).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 02/2015

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ADCETRIS safely and effectively. See full prescribing information for ADCETRIS.

ADCETRIS® (brentuximab vedotin) for injection, for intravenous use

Initial U.S. approval: 2011

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

See full prescribing information for complete boxed warning.

JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS (5.9, 6.2).

RECENT MAJOR CHANGES

Dosage and Administration (2.1)	11/2014
Warnings and Precautions (5.6, 5.7, 5.8, 5.11)	11/2014
Warnings and Precautions (5.10)	02/2015

INDICATIONS AND USAGE

ADCETRIS is a CD30-directed antibody-drug conjugate indicated for treatment of patients with:

- Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates (1.1).
- Systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen (1.2).

Accelerated approval was granted for the above indications based on overall response rate. An improvement in patient-reported outcomes or survival has not been established. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

DOSAGE AND ADMINISTRATION

- Administer only as an intravenous infusion over 30 minutes every 3 weeks.
- The recommended dose is 1.8 mg/kg (2).
- Reduce dose in patients with mild hepatic impairment (2).
- Continue treatment until disease progression or unacceptable toxicity.

DOSAGE FORMS AND STRENGTHS

For injection: 50 mg lyophilized powder in a single-use vial (3).

CONTRAINDICATIONS

Concomitant use with bleomycin due to pulmonary toxicity (4).

WARNINGS AND PRECAUTIONS

- Peripheral neuropathy: Monitor patients for neuropathy and institute dose modifications accordingly (5.1).
- Anaphylaxis and infusion reactions: If an infusion reaction occurs, interrupt the infusion. If anaphylaxis occurs, immediately discontinue the infusion (5.2).
- Hematologic toxicities: Monitor complete blood counts prior to each dose of ADCETRIS. Closely monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent doses (5.3).
- Serious infections and opportunistic infections: Closely monitor patients for the emergence of bacterial, fungal or viral infections (5.4).
- Tumor lysis syndrome: Closely monitor patients with rapidly proliferating tumor or high tumor burden (5.5).
- Hepatotoxicity: Monitor liver enzymes and bilirubin (5.8).
- Pulmonary Toxicity: Evaluate new or worsening pulmonary symptoms (5.10).
- Serious dermatologic reactions: Discontinue if Stevens-Johnson syndrome or toxic epidermal necrolysis occurs (5.11).
- Embryo-fetal toxicity: Fetal harm can occur. Advise pregnant women of the potential hazard to the fetus (5.12).

ADVERSE REACTIONS

The most common adverse reactions (≥20%) are neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough, and vomiting (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Seattle Genetics, Inc. at 1-855-473-2436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Concomitant use of strong CYP3A4 inhibitors or inducers, or P-gp inh bitors, has the potential to affect the exposure to monomethyl auristatin E (MMAE) (7.1).

USE IN SPECIFIC POPULATIONS

Moderate or severe hepatic impairment or severe renal impairment: MMAE exposure and adverse reactions are increased. Avoid use (5.6, 5.7, 8.6, 8.7).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 02/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS *[see Warnings and Precautions (5.9), Adverse Reactions (6.1)]*.

1 INDICATIONS AND USAGE

1.1 Hodgkin Lymphoma

ADCETRIS (brentuximab vedotin) is indicated for treatment of patients with Hodgkin lymphoma (HL) after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.1)]*. An improvement in patient-reported outcomes or survival has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

1.2 Systemic Anaplastic Large Cell Lymphoma

ADCETRIS is indicated for treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.2)]*. An improvement in patient-reported outcomes or survival has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Recommendations

Administer ADCETRIS as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity. See Table 1 for the recommended starting dosage.

Table 1: Recommended ADCETRIS Dosage

	Recommended Starting Dosage
Normal renal and hepatic function	1.8 mg/kg up to 180 mg
Renal impairment	
Mild (creatinine clearance >50–80 mL/min) or moderate (creatinine clearance 30–50 mL/min)	1.8 mg/kg up to 180 mg
Severe (creatinine clearance less than 30 mL/min)	Avoid use *[see Warnings and Precautions (5.6)]*
Hepatic impairment	
Mild (Child-Pugh A)	1.2 mg/kg up to 120 mg
Moderate (Child-Pugh B) or severe (Child-Pugh C)	Avoid use *[see Warnings and Precautions (5.7)]*

2.2 Dose Modification

Peripheral Neuropathy: For new or worsening Grade 2 or 3 neuropathy, dosing should be held until neuropathy improves to Grade 1 or baseline and then restarted at 1.2 mg/kg. For Grade 4 peripheral neuropathy, ADCETRIS should be discontinued.

Neutropenia: The dose of ADCETRIS should be held for Grade 3 or 4 neutropenia until resolution to baseline or Grade 2 or lower. Consider G-CSF prophylaxis for subsequent cycles in patients who experience Grade 3 or 4 neutropenia in the previous cycle. In patients with recurrent Grade 4 neutropenia despite the use of G-CSF prophylaxis, consider discontinuation or dose reduction of ADCETRIS to 1.2 mg/kg.

2.3 Instructions for Preparation and Administration

Administration

- Administer ADCETRIS as an intravenous infusion only.
- **Do not mix ADCETRIS with, or administer as an infusion with, other medicinal products.**

Reconstitution

- Follow procedures for proper handling and disposal of anticancer drugs *[see References (15)]*.
- Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.
- Determine the number of 50 mg vials needed based on the patient's weight and the prescribed dose *[see Dosage and Administration (2.1)]*.
- Reconstitute each 50 mg vial of ADCETRIS with 10.5 mL of Sterile Water for Injection, USP, to yield a single-use solution containing 5 mg/mL brentuximab vedotin.
- Direct the stream toward the wall of vial and not directly at the cake or powder.
- Gently swirl the vial to aid dissolution. **DO NOT SHAKE**.
- Inspect the reconstituted solution for particulates and discoloration. The reconstituted solution should be clear to slightly opalescent, colorless, and free of visible particulates.
- Following reconstitution, dilute immediately into an infusion bag. If not diluted immediately, store the solution at 2–8°C (36–46°F) and use within 24 hours of reconstitution. **DO NOT FREEZE.**
- Discard any unused portion left in the vial.

Dilution

- Calculate the required volume of 5 mg/mL reconstituted ADCETRIS solution needed.

- Withdraw this amount from the vial and immediately add it to an infusion bag containing a minimum volume of 100 mL of 0.9% Sodium Chloride Injection, 5% Dextrose Injection or Lactated Ringer's Injection to achieve a final concentration of 0.4 mg/mL to 1.8 mg/mL brentuximab vedotin.
- Gently invert the bag to mix the solution.
- Following dilution, infuse the ADCETRIS solution immediately. If not used immediately, store the solution at 2–8°C (36–46°F) and use within 24 hours of reconstitution. **DO NOT FREEZE.**

3 DOSAGE FORMS AND STRENGTHS

For injection: 50 mg of brentuximab vedotin as a sterile, white to off-white lyophilized, preservative-free cake or powder in a single-use vial for reconstitution.

4 CONTRAINDICATIONS

ADCETRIS is contraindicated with concomitant bleomycin due to pulmonary toxicity (e.g., interstitial infiltration and/or inflammation) *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Peripheral Neuropathy

ADCETRIS treatment causes a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. ADCETRIS-induced peripheral neuropathy is cumulative. In the HL and sALCL clinical trials, 54% of patients experienced any grade of neuropathy. Of these patients, 49% had complete resolution, 31% had partial improvement, and 20% had no improvement. Of the patients who reported neuropathy, 51% had residual neuropathy at the time of their last evaluation. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Patients experiencing new or worsening peripheral neuropathy may require a delay, change in dose, or discontinuation of ADCETRIS *[see Dose Modification (2.2)]*.

5.2 Anaphylaxis and Infusion Reactions

Infusion-related reactions, including anaphylaxis, have occurred with ADCETRIS. Monitor patients during infusion. If anaphylaxis occurs, immediately and permanently discontinue administration of ADCETRIS and administer appropriate medical therapy. If an infusion-related reaction occurs, the infusion should be interrupted and appropriate medical management instituted. Patients who have experienced a prior infusion-related reaction should be premedicated for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.

5.3 Hematologic Toxicities

Prolonged (≥1 week) severe neutropenia and Grade 3 or Grade 4 thrombocytopenia or anemia can occur with ADCETRIS. Febrile neutropenia has been reported with treatment with ADCETRIS. Complete blood counts should be monitored prior to each dose of ADCETRIS and

more frequent monitoring should be considered for patients with Grade 3 or 4 neutropenia. Monitor patients for fever. If Grade 3 or 4 neutropenia develops, consider dose delays, reductions, discontinuation, or G-CSF prophylaxis with subsequent ADCETRIS doses *[see Dose Modification (2.2)]*.

5.4 Serious Infections and Opportunistic Infections

Serious infections and opportunistic infections such as pneumonia, bacteremia, and sepsis or septic shock (including fatal outcomes) have been reported in patients treated with ADCETRIS. Patients should be closely monitored during treatment for the emergence of possible bacterial, fungal, or viral infections.

5.5 Tumor Lysis Syndrome

Patients with rapidly proliferating tumor and high tumor burden may be at increased risk of tumor lysis syndrome. Monitor closely and take appropriate measures.

5.6 Increased Toxicity in the Presence of Severe Renal Impairment

The frequency of ≥Grade 3 adverse reactions and deaths was greater in patients with severe renal impairment compared to patients with normal renal function. Due to higher MMAE exposure, ≥Grade 3 adverse reactions may be more frequent in patients with severe renal impairment compared to patients with normal renal function. Avoid the use of ADCETRIS in patients with severe renal impairment [creatinine clearance (CLcr) <30 mL/min] *[see Use in Specific Populations (8.6)]*.

5.7 Increased Toxicity in the Presence of Moderate or Severe Hepatic Impairment

The frequency of ≥Grade 3 adverse reactions and deaths was greater in patients with moderate and severe hepatic impairment compared to patients with normal hepatic function. Avoid the use of ADCETRIS in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment *[see Use in Specific Populations (8.7)]*.

5.8 Hepatotoxicity

Serious cases of hepatotoxicity, including fatal outcomes, have occurred in patients receiving ADCETRIS. Cases were consistent with hepatocellular injury, including elevations of transaminases and/or bilirubin. Cases have occurred after the first dose of ADCETRIS or after ADCETRIS rechallenge. Preexisting liver disease, elevated baseline liver enzymes, and concomitant medications may also increase the risk. Monitor liver enzymes and bilirubin. Patients experiencing new, worsening, or recurrent hepatotoxicity may require a delay, change in dose, or discontinuation of ADCETRIS.

5.9 Progressive Multifocal Leukoencephalopathy

JC virus infection resulting in PML and death has been reported in ADCETRIS-treated patients. In addition to ADCETRIS therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider the diagnosis of PML in any patient presenting with new-onset signs and symptoms of central nervous system abnormalities.

Hold ADCETRIS dosing for any suspected case of PML and discontinue ADCETRIS dosing if a diagnosis of PML is confirmed.

5.10 Pulmonary Toxicity

Pulmonary toxicity has been reported in patients receiving ADCETRIS. A causal association with single-agent ADCETRIS has not been established. In the event of new or worsening pulmonary symptoms (e.g., cough, dyspnea), perform a prompt diagnostic evaluation and institute appropriate medical therapy.

5.11 Serious Dermatologic Reactions

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including fatal outcomes, have been reported with ADCETRIS. If SJS or TEN occurs, discontinue ADCETRIS and administer appropriate medical therapy.

5.12 Embryo-Fetal Toxicity

There are no adequate and well-controlled studies of ADCETRIS in pregnant women. However, based on its mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. Brentuximab vedotin caused embryo-fetal toxicities, including significantly decreased embryo viability and fetal malformations, in animals at maternal exposures that were similar to human exposures at the recommended doses for patients with HL and sALCL. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving the drug, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the prescribing information:

- Peripheral Neuropathy *[see Warnings and Precautions (5.1)]*
- Anaphylaxis and Infusion Reactions *[see Warnings and Precautions (5.2)]*
- Hematologic Toxicities *[see Warnings and Precautions (5.3)]*
- Serious Infections and Opportunistic Infections *[see Warnings and Precautions (5.4)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.5)]*
- Increased Toxicity in the Presence of Severe Renal Impairment *[see Warnings and Precautions (5.6)]*
- Increased Toxicity in the Presence of Moderate or Severe Hepatic Impairment *[see Warnings and Precautions (5.7)]*
- Hepatotoxicity *[see Warnings and Precautions (5.8)]*
- Progressive Multifocal Leukoencephalopathy *[see Warnings and Precautions (5.9)]*

- Pulmonary Toxicity *[see Warnings and Precautions (5.10)]*
- Serious Dermatologic Reactions *[see Warnings and Precautions (5.11)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.12)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

ADCETRIS was studied as monotherapy in 160 patients in two phase 2 trials. Across both trials, the most common adverse reactions (≥20%), regardless of causality, were neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough, and vomiting. The most common adverse reactions occurring in at least 10% of patients in either trial, regardless of causality, using the NCI Common Toxicity Criteria Version 3.0, are shown in Table 2.

Experience in Hodgkin Lymphoma

ADCETRIS was studied in 102 patients with HL in a single arm clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg intravenously every 3 weeks. Median duration of treatment was 27 weeks (range, 3 to 56 weeks) *[see Clinical Studies (14.1)]*.

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

Pulmonary Toxicity

In another clinical trial in patients with HL that studied ADCETRIS with bleomycin as part of a combination regimen, the rate of non-infectious pulmonary toxicity was higher than the historical incidence reported with ABVD (adriamycin, bleomycin, vinblastine, dacarbazine). Patients typically reported cough and dyspnea. Interstitial infiltration and/or inflammation were observed on radiographs and computed tomographic imaging of the chest. Most patients responded to corticosteroids. The concomitant use of ADCETRIS with bleomycin is contraindicated *[see Contraindications (4)]*.

Experience in Systemic Anaplastic Large Cell Lymphoma

ADCETRIS was studied in 58 patients with sALCL in a single arm clinical trial in which the recommended starting dose and schedule was 1.8 mg/kg intravenously every 3 weeks. Median duration of treatment was 24 weeks (range, 3 to 56 weeks) *[see Clinical Studies (14.2)]*.

The most common adverse reactions (≥20%), regardless of causality, were neutropenia, anemia, peripheral sensory neuropathy, fatigue, nausea, pyrexia, rash, diarrhea, and pain.

Combined Experience

Table 2: Most Commonly Reported (≥10%) Adverse Reactions

	HL Total N = 102 % of patients			sALCL Total N = 58 % of patients		
Adverse Reaction	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Blood and lymphatic system disorders						
Neutropenia*	54	15	6	55	12	9
Anemia*	33	8	2	52	2	-
Thrombocytopenia*	28	7	2	16	5	5
Lymphadenopathy	11	-	-	10	-	-
Nervous system disorders						
Peripheral sensory neuropathy	52	8	-	53	10	-
Peripheral motor neuropathy	16	4	-	7	3	-
Headache	19	-	-	16	2	-
Dizziness	11	-	-	16	-	-
General disorders and administration site conditions						
Fatigue	49	3	-	41	2	2
Pyrexia	29	2	-	38	2	-
Chills	13	-	-	12	-	-
Pain	7	-	-	28	-	5
Edema peripheral	4	-	-	16	-	-
Infections and infestations						
Upper respiratory tract infection	47	-	-	12	-	-
Gastrointestinal disorders						
Nausea	42	-	-	38	2	-
Diarrhea	36	1	-	29	3	-
Abdominal pain	25	2	1	9	2	-
Vomiting	22	-	-	17	3	-
Constipation	16	-	-	19	2	-
Skin and subcutaneous tissue disorders						
Rash	27	-	-	31	-	-
Pruritus	17	-	-	19	-	-
Alopecia	13	-	-	14	-	-
Night sweats	12	-	-	9	-	-
Dry skin	4	-	-	10	-	-
Respiratory, thoracic and mediastinal disorders						

	HL Total N = 102 % of patients			sALCL Total N = 58 % of patients		
Adverse Reaction	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Cough	25	-	-	17	-	-
Dyspnea	13	1	-	19	2	-
Oropharyngeal pain	11	-	-	9	-	-
Musculoskeletal and connective tissue disorders						
Arthralgia	19	-	-	9	-	-
Myalgia	17	-	-	16	2	-
Back pain	14	-	-	10	2	-
Pain in extremity	10	-	-	10	2	2
Muscle spasms	9	-	-	10	2	-
Psychiatric disorders						
Insomnia	14	-	-	16	-	-
Anxiety	11	2	-	7	-	-
Metabolism and nutrition disorders						
Decreased appetite	11	-	-	16	2	-
Investigations						
Weight decreased	6	-	-	12	3	-

*Derived from laboratory values and adverse reaction data

Infusion reactions

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

Serious adverse reactions

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

Dose modifications

Adverse reactions that led to dose delays in more than 5% of patients were neutropenia (14%) and peripheral sensory neuropathy (11%) *[see Dosage and Administration (2.2)]*.

Discontinuations

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

6.2 Post Marketing Experience

The following adverse reactions have been identified during post-approval use of ADCETRIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: febrile neutropenia *[see Warnings and Precautions (5.3)]*.

Hepatobiliary disorders: hepatotoxicity *[see Warnings and Precautions (5.8)]*.

Infections: PML *[see Boxed Warning, Warnings and Precautions (5.9)]*, serious infections and opportunistic infections *[see Warnings and Precautions (5.4)]*.

Metabolism and nutrition disorders: hyperglycemia.

Gastrointestinal disorders: Pancreatitis (including fatal outcomes). Consider the diagnosis of pancreatitis for patients presenting with severe abdominal pain.

Respiratory, thoracic and mediastinal disorders: pulmonary toxicity *[see Warnings and Precautions (5.10)]*.

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis, including fatal outcomes *[see Warnings and Precautions (5.11)]*.

6.3 Immunogenicity

Patients with HL and sALCL in the phase 2 trials *[see Clinical Studies (14)]* were tested for antibodies to brentuximab vedotin every 3 weeks using a sensitive electrochemiluminescent immunoassay. Approximately 7% of patients in these trials developed persistently positive antibodies (positive test at more than 2 timepoints) and 30% developed transiently positive antibodies (positive in 1 or 2 post-baseline timepoints). The anti-brentuximab antibodies were directed against the antibody component of brentuximab vedotin in all patients with transiently or persistently positive antibodies. Two of the patients (1%) with persistently positive antibodies experienced adverse reactions consistent with infusion reactions that led to discontinuation of treatment. Overall, a higher incidence of infusion related reactions was observed in patients who developed persistently positive antibodies.

A total of 58 patient samples that were either transiently or persistently positive for anti-brentuximab vedotin antibodies were tested for the presence of neutralizing antibodies. Sixty-two percent of these patients had at least one sample that was positive for the presence of neutralizing antibodies. The effect of anti-brentuximab vedotin antibodies on safety and efficacy is not known.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to ADCETRIS with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

In vitro data indicate that monomethyl auristatin E (MMAE) is a substrate and an inhibitor of CYP3A4/5. *In vitro* data indicate that MMAE is also a substrate of the efflux transporter P-glycoprotein (P-gp).

7.1 Effect of Other Drugs on ADCETRIS

CYP3A4 Inhibitors/Inducers: MMAE is primarily metabolized by CYP3A *[see Clinical Pharmacology (12.3)]*. Co-administration of ADCETRIS with ketoconazole, a potent CYP3A4 inhibitor, increased exposure to MMAE by approximately 34%. Patients who are receiving strong CYP3A4 inhibitors concomitantly with ADCETRIS should be closely monitored for adverse reactions. Co-administration of ADCETRIS with rifampin, a potent CYP3A4 inducer, reduced exposure to MMAE by approximately 46%.

P-gp Inhibitors: Co-administration of ADCETRIS with P-gp inhibitors may increase exposure to MMAE. Patients who are receiving P-gp inhibitors concomitantly with ADCETRIS should be closely monitored for adverse reactions.

7.2 Effect of ADCETRIS on Other Drugs

Co-administration of ADCETRIS did not affect exposure to midazolam, a CYP3A4 substrate. MMAE does not inhibit other CYP enzymes at relevant clinical concentrations *[see Clinical Pharmacology (12.3)]*. ADCETRIS is not expected to alter the exposure to drugs that are metabolized by CYP3A4 enzymes.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.12)]*.

Risk Summary

There are no adequate and well-controlled studies with ADCETRIS in pregnant women. However, based on its mechanism of action and findings in animals, ADCETRIS can cause fetal harm when administered to a pregnant woman. Brentuximab vedotin caused embryo-fetal toxicities in animals at maternal exposures that were similar to human exposures at the

recommended doses for patients with HL and sALCL. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

Animal Data

In an embryo-fetal developmental study, pregnant rats received 2 intravenous doses of 0.3, 1, 3, or 10 mg/kg brentuximab vedotin during the period of organogenesis (once each on Pregnancy Days 6 and 13). Drug-induced embryo-fetal toxicities were seen mainly in animals treated with 3 and 10 mg/kg of the drug and included increased early resorption (≥99%), post-implantation loss (≥99%), decreased numbers of live fetuses, and external malformations (i.e., umbilical hernias and malrotated hindlimbs). Systemic exposure in animals at the brentuximab vedotin dose of 3 mg/kg is approximately the same exposure in patients with HL or sALCL who received the recommended dose of 1.8 mg/kg every three weeks.

8.3 Nursing Mothers

It is not known whether brentuximab vedotin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ADCETRIS a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of ADCETRIS have not been established in the pediatric population. Clinical trials of ADCETRIS included only 9 pediatric patients and this number is not sufficient to determine whether they respond differently than adult patients.

8.5 Geriatric Use

Clinical trials of ADCETRIS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Safety and efficacy have not been established.

8.6 Renal Impairment

Avoid the use of ADCETRIS in patients with severe renal impairment (CLcr <30 mL/min) *[See Warnings and Precautions (5.6)]*.

The kidney is a route of excretion for monomethyl auristatin E (MMAE). The pharmacokinetics and safety of brentuximab vedotin and MMAE were evaluated after the administration of 1.2 mg/kg of ADCETRIS to patients with mild (CLcr >50–80 mL/min; n=4), moderate (CLcr 30–50 mL/min; n=3) and severe (CLcr <30 mL/min; n=3) renal impairment. In patients with severe renal impairment, the rate of Grade 3 or worse adverse events was 3/3 (100%) compared to 3/8 (38%) in patients with normal renal function. Additionally, the AUC of MMAE (component of ADCETRIS) was approximately 2-fold higher in patients with severe renal impairment compared to patients with normal renal function. Due to higher MMAE exposure, ≥Grade 3 adverse reactions may be more frequent in patients with severe renal impairment compared to patients with normal renal function.

8.7 Hepatic Impairment

Avoid the use of ADCETRIS in patients with moderate or severe hepatic impairment *[See Warnings and Precautions (5.7)]*.

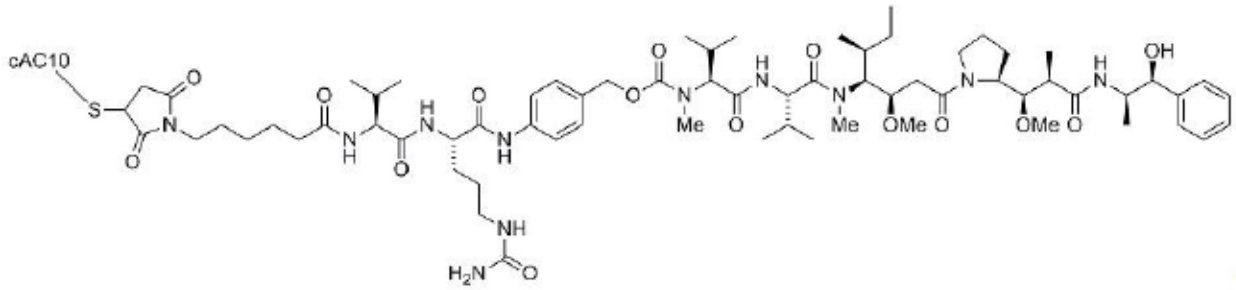
The liver is a route of clearance for MMAE. The pharmacokinetics and safety of brentuximab vedotin and MMAE were evaluated after the administration of 1.2 mg/kg of ADCETRIS to patients with mild (Child-Pugh A; n=1), moderate (Child-Pugh B; n=5) and severe (Child-Pugh C; n=1) hepatic impairment. In patients with moderate and severe hepatic impairment, the rate of ≥Grade 3 adverse reactions was 6/6 (100%) compared to 3/8 (38%) in patients with normal hepatic function. Additionally, the AUC of MMAE was approximately 2.2-fold higher in patients with hepatic impairment compared to patients with normal hepatic function.

10 OVERDOSAGE

There is no known antidote for overdosage of ADCETRIS. In case of overdosage, the patient should be closely monitored for adverse reactions, particularly neutropenia, and supportive treatment should be administered.

11 DESCRIPTION

ADCETRIS (brentuximab vedotin) 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 MMAE, and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10.



Brentuximab vedotin has an approximate molecular weight of 153 kDa. Approximately 4 molecules of MMAE are attached to each antibody molecule. Brentuximab vedotin is produced by chemical conjugation of the antibody and small molecule components. The antibody is produced by mammalian (Chinese hamster ovary) cells, and the small molecule components are produced by chemical synthesis.

ADCETRIS (brentuximab vedotin) for Injection is supplied as a sterile, white to off-white, preservative-free lyophilized cake or powder in single-use vials. Following reconstitution with 10.5 mL Sterile Water for Injection, USP, a solution containing 5 mg/mL brentuximab vedotin is produced. The reconstituted product contains 70 mg/mL trehalose dihydrate, 5.6 mg/mL sodium citrate dihydrate, 0.21 mg/mL citric acid monohydrate, and 0.20 mg/mL polysorbate 80 and water for injection. The pH is approximately 6.6.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

QT/QTc Prolongation Potential

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

12.3 Pharmacokinetics

The pharmacokinetics of brentuximab vedotin were evaluated in phase 1 trials and in a population pharmacokinetic analysis of data from 314 patients. The pharmacokinetics of three analytes were determined: the ADC, MMAE, and total antibody. Total antibody had the greatest exposure and had a similar PK profile as the ADC. Hence, data on the PK of the ADC and MMAE have been summarized.

Absorption

Maximum concentrations of ADC were typically observed close to the end of infusion. A multiexponential decline in ADC serum concentrations was observed with a terminal half-life of approximately 4 to 6 days. Exposures were approximately dose proportional from 1.2 to 2.7 mg/kg. Steady-state of the ADC was achieved within 21 days with every 3-week dosing of ADCETRIS, consistent with the terminal half-life estimate. Minimal to no accumulation of ADC was observed with multiple doses at the every 3-week schedule.

The time to maximum concentration for MMAE ranged from approximately 1 to 3 days. Similar to the ADC, steady-state of MMAE was achieved within 21 days with every 3 week dosing of ADCETRIS. MMAE exposures decreased with continued administration of ADCETRIS with approximately 50% to 80% of the exposure of the first dose being observed at subsequent doses.

Distribution

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

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

Metabolism

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

Elimination

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

Specific Populations

Renal Impairment: *[see Use in Specific Populations (8.6)]*.

Hepatic Impairment: *[see Use in Specific Populations (8.7)]*.

Effects of Gender, Age, and Race: Based on the population pharmacokinetic analysis; gender, age, and race do not have a meaningful effect on the pharmacokinetics of brentuximab vedotin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with brentuximab vedotin or the small molecule (MMAE) have not been conducted.

MMAE was genotoxic in the rat bone marrow micronucleus study through an aneugenic mechanism. This effect is consistent with the pharmacological effect of MMAE as a microtubule disrupting agent. MMAE was not mutagenic in the bacterial reverse mutation assay (Ames test) or the L5178Y mouse lymphoma forward mutation assay.

Fertility studies with brentuximab vedotin or MMAE have not been conducted. However, results of repeat-dose toxicity studies in rats indicate the potential for brentuximab vedotin to impair male reproductive function and fertility. In a 4-week repeat-dose toxicity study in rats with weekly dosing at 0.5, 5, or 10 mg/kg brentuximab vedotin, seminiferous tubule degeneration, Sertoli cell vacuolation, reduced spermatogenesis, and aspermia were observed. Effects in animals were seen mainly at 5 and 10 mg/kg of brentuximab vedotin. These doses are approximately 3 and 6-fold the human recommended dose of 1.8 mg/kg, respectively, based on body weight.

14 CLINICAL STUDIES

14.1 Hodgkin Lymphoma

The efficacy of ADCETRIS in patients with HL who relapsed after autologous stem cell transplant was evaluated in one open-label, single-arm, multicenter trial. One hundred two patients were treated with 1.8 mg/kg of ADCETRIS intravenously over 30 minutes every 3 weeks. An independent review facility performed efficacy evaluations which included overall response rate (ORR = complete remission [CR] + partial remission [PR]) and duration of response as defined by clinical and radiographic measures including computed tomography (CT) and positron-emission tomography (PET) as defined in the 2007 Revised Response Criteria for Malignant Lymphoma (modified).

The 102 patients ranged in age from 15–77 years (median, 31 years) and most were female (53%) and white (87%). Patients had received a median of 5 prior therapies including autologous stem cell transplant.

The efficacy results are summarized in Table 3. Duration of response is calculated from date of first response to date of progression or data cutoff date.

Table 3: Efficacy Results in Patients with Hodgkin Lymphoma

	N=102		
		Duration of Response, in months	
	Percent (95%CI)	Median (95% CI)	Range
CR	32 (23, 42)	20.5 (12.0, NE*)	1.4 to 21.9+
PR	40 (32, 49)	3.5 (2.2, 4.1)	1.3 to 18.7
ORR	73 (65, 83)	6.7 (4.0, 14.8)	1.3 to 21.9+

*Not estimable

+ Follow up was ongoing at the time of data submission.

14.2 Systemic Anaplastic Large Cell Lymphoma

The efficacy of ADCETRIS in patients with relapsed sALCL was evaluated in one phase 2 open-label, single-arm, multicenter trial. This trial included patients who had sALCL that was relapsed after prior therapy. Fifty-eight patients were treated with 1.8 mg/kg of ADCETRIS administered intravenously over 30 minutes every 3 weeks. An independent review facility performed efficacy evaluations which included overall response rate (ORR = complete remission [CR] + partial remission [PR]) and duration of response as defined by clinical and radiographic measures including computed tomography (CT) and positron-emission tomography (PET) as defined in the 2007 Revised Response Criteria for Malignant Lymphoma (modified).

The 58 patients ranged in age from 14–76 years (median, 52 years) and most were male (57%) and white (83%). Patients had received a median of 2 prior therapies; 26% of patients had received prior autologous stem cell transplant. Fifty percent (50%) of patients were relapsed and 50% of patients were refractory to their most recent prior therapy. Seventy-two percent (72%) were anaplastic lymphoma kinase (ALK)-negative.

The efficacy results are summarized in Table 4. Duration of response is calculated from date of first response to date of progression or data cutoff date.

Table 4: Efficacy Results in Patients with Systemic Anaplastic Large Cell Lymphoma

	N=58		
		Duration of Response, in months	
	Percent (95%CI)	Median (95% CI)	Range
CR	57 (44, 70)	13.2 (10.8, NE*)	0.7 to 15.9+
PR	29 (18, 41)	2.1 (1.3, 5.7)	0.1 to 15.8+
ORR	86 (77, 95)	12.6 (5.7, NE*)	0.1 to 15.9+

*Not estimable

+ Follow up was ongoing at the time of data submission.

15 REFERENCES

1. OSHA Hazardous Drugs. *OSHA*. [Accessed on 30 July 2013, from http://www.osha.gov/SLTC/hazardousdrugs/index.html]

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ADCETRIS (brentuximab vedotin) for Injection is supplied as a sterile, white to off-white preservative-free lyophilized cake or powder in individually-boxed single-use vials:

- NDC (51144-050-01), 50 mg brentuximab vedotin.

16.2 Storage

Store vial at 2–8°C (36–46°F) in the original carton to protect from light.

16.3 Special Handling

ADCETRIS is an antineoplastic product. Follow special handling and disposal procedures[1].

17 PATIENT COUNSELING INFORMATION

• Peripheral neuropathy

Advise patients that ADCETRIS can cause a peripheral neuropathy. They should be advised to report to their health care provider any numbness or tingling of the hands or feet or any muscle weakness *[see Warnings and Precautions (5.1)]*.

• Fever/Neutropenia

Advise patients to contact their health care provider if a fever of 100.5°F or greater or other evidence of potential infection such as chills, cough, or pain on urination develops *[see Warnings and Precautions (5.3)]*.

• Infusion reactions

Advise patients to contact their health care provider if they experience signs and symptoms of infusion reactions including fever, chills, rash, or breathing problems within 24 hours of infusion *[see Warnings and Precautions (5.2)]*.

• Hepatotoxicity

Advise patients to report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice *[see Warnings and Precautions (5.8)]*.

• Progressive multifocal leukoencephalopathy

Instruct patients receiving ADCETRIS to immediately report if they have any of the following neurological, cognitive, or behavioral signs and symptoms or if anyone close to them notices these signs and symptoms *[see Boxed Warning, Warnings and Precautions (5.9)]*:

- changes in mood or usual behavior
- confusion, thinking problems, loss of memory
- changes in vision, speech, or walking
- decreased strength or weakness on one side of the body

• Pulmonary Toxicity

Instruct patients to report symptoms that may indicate pulmonary toxicity, including cough or shortness of breath *[see Warnings and Precautions (5.10)]*.

• Pancreatitis

Advise patients to contact their health care provider if they develop severe abdominal pain *[see Adverse Reactions (6.2)]*.

• Pregnancy and Nursing

ADCETRIS can cause fetal harm. Advise women receiving ADCETRIS to avoid pregnancy. Advise patients to report pregnancy immediately *[see Warnings and Precautions (5.12)]*. Advise patients to avoid nursing while receiving ADCETRIS *[see Use in Specific Populations (8.1, 8.3)]*.

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DANA-FARBER CANCER INSTITUTE
Nursing Protocol Education Sheet

Protocol Number:	**15-196**
Protocol Name:	**Phase II Brentuximab Vedotin Plus AD in Non-Bulky Limited Stage Hodgkin Lymphoma**
DFCI Site PI:	Ann LaCase
DFCI Research Nurse:	Rebecca Guy-Hamilton, Karen Francoeur, Victoria Patterson, Kathleen McDermott, Kimberly Coleman

Page the DFCI research nurse or DFCI site PI if there are any questions/concerns about the protocol.
Please also refer to ONC 15: Oncology Nursing Protocol Education Policy
***** Remember to check the ALERT PAGE*****

SPECIAL NURSING CONSIDERATIONS UNIQUE TO THIS PROTOCOL

Study Agent	• Brentuximab vedotin is an anti-CD30 antibody-drug conjugate (ADC) consisting of a chimeric monoclonal antibody, an antimicrotubular agent, and a protease cleavable linker (Section 2.1.1 and 7.1) • Adriamycin is an anthracycline antibiotic (Section 7.2) • Dacarbazine is an alkylating agent (Section 7.3) • A cycle is defined as 28 days (Section 1.1)
Dose Calc.	• Brentuximab is dosed in mg/kg (Section 5) • Adriamycin and Dacarbazine are dosed in mg/m^2 (Section 5) • Brentuximab dosing should be based on the participant's pre-dose weight determined at day 1 visit of each cycle. Dose may be re-calculated based on weight on day 15 if that is consistent with the institutional standard of care (Section 7.1.7) • Adriamycin and Dacarbazine use actual weight to calculate BSA and doses (Sections 7.2 and 7.3). • BSA will be calculated with the Dubois formula, or alternate formula per institutional standard (Footnote J Study Calendar of Events)
Study Drug Administration	Agent *Administration* Guidelines are found in (Sections 5, 6, and 7) • All agents administered intravenously on days 1 and 15 of each 28-day cycle (Section 5) • On treatment days, participants will receive brentuximab **followed by** Adriamycin and Dacarbazine (Section 5) • Brentuximab will be administered over 30 minutes. Note the drug may be given at slower infusion at the discretion of the treatment team in the setting of prior hypersensitivity reactions, consistent with institutional standards (Section 7.1.7) • Adriamycin and dacarbazine will be administered via institutional standards (Section 5) • Management of infusion related reactions and premeds for subsequent cycles are found in (Section 6.2.8)
Dose Mods & Toxicity	*Criteria to Treat, Dose Modifications/Dosing Delay for Toxicity* are outlined in (Section 6) • This protocol uses NCI CTCAE criteria, version 4.0 (Section 6) • Toxicity management and Dose Delay's/Modifications can be found in (Section 6.2)
Con Meds	*Concomitant Therapy* Guidelines are in (Section 5.1) • Please review the cited sections for permitted, prohibited, and "use with caution" medications/therapies/foods
Required Data	*Study Calendar and Assessment Required data* are outlined in (Section 8 and Study Calendar of Events) • **Vital signs:** The time points are found in (Section 8 and Study Calendar of Events) • **EKGs**: EKG baseline during screening (Section 8.1 and Study Calendar of Events) • **Neuropathy Assessments:** Are found in (Section 8 and Study Calendar of Events)
Tips	**All study drugs require documentation of exact administration time.**

FULL PRESCRIBING INFORMATION

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS *[see Warnings and Precautions (5.9), Adverse Reactions (6.1)]*.

1 INDICATIONS AND USAGE

1.1 Hodgkin Lymphoma

ADCETRIS (brentuximab vedotin) is indicated for treatment of patients with Hodgkin lymphoma (HL) after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.1)]*. An improvement in patient-reported outcomes or survival has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

1.2 Systemic Anaplastic Large Cell Lymphoma

ADCETRIS is indicated for treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen.

This indication is approved under accelerated approval based on overall response rate *[see Clinical Studies (14.2)]*. An improvement in patient-reported outcomes or survival has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Recommendations

Administer ADCETRIS as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity. See Table 1 for the recommended starting dosage.

Table 1: Recommended ADCETRIS Dosage

	Recommended Starting Dosage
Normal renal and hepatic function	1.8 mg/kg up to 180 mg
Renal impairment	
Mild (creatinine clearance >50–80 mL/min) or moderate (creatinine clearance 30–50 mL/min)	1.8 mg/kg up to 180 mg
Severe (creatinine clearance less than 30 mL/min)	Avoid use *[see Warnings and Precautions (5.6)]*
Hepatic impairment	
Mild (Child-Pugh A)	1.2 mg/kg up to 120 mg
Moderate (Child-Pugh B) or severe (Child-Pugh C)	Avoid use *[see Warnings and Precautions (5.7)]*