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Protocol Page

Safety and Efficacy of Brentuximab Vedotin Maintenance After Allogeneic and Haploidentical Stem Cell Transplantation in High Risk CD30+ Lymphoma (Hodgkin Lymphoma and ALCL)
2013-0351

Core Protocol Information

Short Title	Brentuximab Vedotin in High-Risk CD30+ Lymphoma Post Allo and Haplo SCT
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Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

1.1 Primary Objective:

1.1.1 To determine the incidence of secondary graft failure with brentuximab maintenance post allogeneic or haploidentical stem cell transplant.

1.2 Secondary Objectives:

1.2.1 To evaluate the hematologic toxicity of brentuximab maintenance after an allogeneic stem cell transplant.

1.2.1 To determine the response rates in patients who start post transplant brentuximab with measurable disease.

1.2.2 To determine the relapse rate in this patient population

1.2.3 To determine the incidence of cytomegalovirus (CMV) reactivation and/or CMV disease.

1.2.4 To determine the incidence of acute graft-versus-host disease (GVHD).

1.2.5 To describe the effect of brentuximab on central and effector memory and naïve CD4 and CD8 cell subpopulations.

1.2.6 To describe the effect of brentuximab on serum CD30 levels both in patient subsets with and without GVHD.

1.2.7 To determine the progression free survival and overall survival of patients on brentuximab maintenance.

2.0 Background

2.1 Allogeneic hematopoietic stem cell transplants for Hodgkin lymphoma:

Hodgkin's lymphoma (HL) is primarily treated with conventional chemotherapy to which it is highly responsive(1). After relapse the standard of care is an autologous stem cell transplant (SCT) (2). The results of auto SCT are variable with recurrence of HL ensuing in 50% of patients after autologous SCT(3). Prognosis of patients who relapse following an auto SCT is generally poor, although allogeneic SCT can induce long-term remissions through a graft-vs.-lymphoma (GVL) effect. The use of myeloablative regimens for allogeneic SCT results in prohibitively high treatment related mortality (TRM), upward of 22% in the first 100 days(4). Reduced intensity conditioning (RIC) treatments have been shown to significantly reduce TRM, although relapse remains a significant problem. Anderlini and colleagues at our institution (5) have demonstrated decreased TRM using fludarabine/melphalan as conditioning with rates of TRM of 7% at day 100 and 15% at 2 years. Their data reveals an overall survival (OS) rate of 64% and progression free survival (PFS) of 32% at 2 years, with a 2-year rate of disease progression or relapse at 55%. In an EBMT analysis of 250 patients who received a reduced intensity allo SCT for found that chemorefractory disease was associated with PFS and OS of 8% and 25% respectively at 2 years. Patients in CR at time of transplant PFS had a 3-year PFS of 42%(6). Sureda et al.(3) reported on RIC allo SCT using fludarabine and melphalan and observed a TRM of 8% at 100 days and 15% at 1 year. The estimated PFS for the entire allografted population was 24% at 4 years and patients allografted in CR had PFS of 50% at 4 years. Alvarez et al.(8) found that patients allografted with chemosensitive disease (including CR patients) at time of transplantation had a PFS at 2 years of

55% ± 16%. These studies illuminate that although patients in CR and with chemosensitive disease have better outcomes, disease progression is still in the range of 50% 2-4 years post transplant. Reduced intensity allogeneic transplant can lead to long term disease free survival, however relapse after allo SCT has very poor outcomes with less than 50% of patients surviving past 3 years(7). Beyond allogeneic transplant there are limited effective therapeutic options.

This is an extremely high risk patient population for progression of disease and brentuximab vedotin has been shown to induce partial and complete responses in patients who relapse post allogeneic transplant with acceptable toxicity.(7) Decreasing the relapse rate will be a substantial factor in improving overall survival for these patients, which is the rationale for using brentuximab vedotin as a maintenance therapy early post-allogeneic transplant.

2.2 Allogeneic hematopoietic stem cell transplantation in anaplastic large cell lymphoma:

Systemic anaplastic large cell lymphoma (ALCL) is a rare, mature T-cell non-Hodgkin lymphoma (NHL) This disease accounts for approximately 3% of adult NHLs, 10-15% of pediatric NHLs and 25% of newly diagnosed peripheral T cell lymphomas in North America(9). ALCLs that do not express anaplastic lymphoma kinase (ALK) have a particularly poor prognosis with fewer than 30% of patients achieving long term disease free survival(10). Patients with relapsed or refractory disease are considered incurable with chemotherapy alone, and often proceed to high dose chemotherapy followed by autologous transplant or allogeneic SCT. Allogeneic transplant may benefit a subset of patients who relapse if they have a good performance status and matched related or unrelated donors. Corradini et al. (10) reported on a phase II study of RIC allogeneic stem cell transplantation in 17 patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) and after a median follow-up time of 28 months, the estimated 3-year OS and PFS rates were 81% and 64%, respectively. The TRM at 2 years was considered acceptable at only 6%10. Two of 13 patients in CR relapsed after transplant while overall 3 of the total 17 patients had progressive disease.

2.3 Haploidentical hematopoietic stem cell transplantation in Hodgkin Lymphoma:
One of the limitations with an allogeneic stem cell transplant is that the majority of patients lack an identical sibling and no more than 50% of patients, searching the Registries for unrelated donors or cord blood units, undergo an allo-SCT (World Marrow Donor Association data, 2012 unpublished). Recently, encouraging results have been obtained with HLA haploidentical-related donor, following an NMA regimen, unfractionated BM and post-transplantation CY (PT-CY) (11).

Twenty-six patients with advanced Hodgkin's disease received a related HLA haploidentical unmanipulated BMT, following a non-myeloablative conditioning with low-dose TBI and GVHD prophylaxis consisted of high-dose post-transplantation CY (PT-CY), mycophenolate and a calcineurin inhibitor. The incidence of grade II–IV acute GVHD and of chronic GVHD was 24% and 8%, respectively. With a median follow-up of 24 months (range 18–44) 21 patients are alive, 20 disease free. The cumulative incidence of TRM and relapse was 4% and 31%, respectively. The actuarial 3-year survival is 77%, the actuarial 3-year PFS is 63%. (12).

Haploidentical transplant has been tested by multiple centers for Hodgkin lymphoma and found to preserve graft versus lymphoma effect without significant additive toxicity.

2.4 CD30 Expression:
Hodgkin Reed-Sternberg cells express the CD30 antigen almost universally (11). Systemic ALCL tumors present with large blastic CD30-expressing cells and the CD30 antigen is also expressed in some cutaneous T-cell lymphomas (CTCLs), other natural killer (NK) and T-cell neoplasms, a subset of B-cell lymphomas and embryonal carcinoma.(13,14) CD30 is a transmembrane glycoprotein receptor member of the tumor necrosis factor (TNF) receptor superfamily 8 (TNFRSF8). The functions of CD30 are not fully understood. Its distribution on normal cells is restricted to activated T and B cells and macrophages(12,15), and it seems to be an activator of the canonical and alternative nuclear factor-kB (NF-kB) pathways, transducing a cell survival signal. (6, 16,18)

Brentuximab vedotin is a CD30-directed antibody-drug conjugate consisting of 3 components: the monoclonal chimeric antibody cAC10 that is specific for human CD30 the potent antimicrotubule agent monomethyl auristatin E (MMAE) a protease-cleavable linker that covalently attaches MMAE to cAC10. The biologic activity of brentuximab vedotin results from a multi-step process. Binding of the antibody-drug conjugate (ADC) to CD30 on the cell surface commences internalization of the ADC-CD30 complex, which then traffics to the lysosomal compartment where MMAE is released via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces the mitotic spindle cell cycle checkpoint and results in growth arrest and apoptotic death of the CD30-expressing tumor cells. (16)

Younes and colleagues reported the initial data in a phase I dose escalation trial that enrolled 45 patients with relapsed or refractory CD30+ hematologic malignancies. They showed 20 objective responses, including 11 complete remissions (CRs), in 17 patients and tumor regression was observed in 86% of evaluable patients. Seventy-three percent of patients in that trial had undergone autoSCT.(19) Subsequently this group presented a phase 2 study using Brentuximab vedotin (1.8 mg/kg intravenously every 3 weeks) after auto SCT for 102 patients with relapsed/refractory CD30+ HL and revealed objective responses in 75% of patients, with CRs observed in 34% of patients.(20) The estimated 12-month survival was 89% and the median PFS was 5.6 months. Adverse events associated with brentuximab vedotin were typically grade 1 or 2 and able to be managed through standard supportive care. Cumulative peripheral neuropathy, the most clinically meaningful adverse event, improved or resolved completely in 80% of patients during the study. Patients who had previously received an alloSCT were excluded from both of these trials.

Pro et al.(18), demonstrated an objective response of 86% and complete remission of 57% in 58 patients with relapsed or refractory systemic anaplastic large cell lymphoma (ALCL) treated at the dose of 1.8 mg/kg every 3 weeks. The median durations of overall response and CR were 12.6 and 13.2 months, respectively. Grade 3 or 4 adverse events in >10% of patients were neutropenia (21%), thrombocytopenia (14%), and peripheral sensory neuropathy (12%).

2.5 Transplantation and use of Brentuximab Vedotin:

More recently Gopal et al.,(7) published their experience with 25 HL patients treated with brentuximab at 1.8 mg/kg every 21 days after relapse post allogeneic SCT. Overall and complete response rates were 50% and 38% respectively, median OS not reached. In their study, the drug was very well tolerated with most common grade >/-3 side effects being: neutropenia (24%), anemia (20%), hyperglycemia (12%) of which all were reversible. CMV was detected in 5 patients and was clinically significant in 1 patient. Sixteen patients (64%) had an objective response after allo SCT, including 14 CRs and 2 PRs. The median interval between allo SCT and first dose of brentuximab vedotin was 42 months (range, 6-116).(7) Adverse events most frequently reported as being related to study drug were peripheral sensory neuropathy (n/12, 48%), nausea (n/ 7, 28%), alopecia and neutropenia (n/6, 24% each), and fatigue and vomiting (n/5, 20% each). Between transplant and brentuximab initiation 17 pts (68%) were reported to have acute/and or chronic GVHD. On brentuximab 9 pts (36%) received transient steroids for non-GVHD indications (B symptoms or infusion reactions). No GVHD was reported after initiation of brentuximab vedotin therapy.

2.6 CD30 expression and Graft versus Host Disease:

CD30 expression on CD8+ T cells may be a potential biomarker for acute GVHD.(20) Chen and colleagues recently published data analyzing CD30 expression on peripheral blood T-cell subsets and soluble CD30 levels in 26 patients at the time of onset of acute GVHD (aGVHD) treatment and then compared them to transplant patients without aGVHD.(22) Analysis by flow cytometry showed that patients with aGVHD had a greater percentage of CD30 expressing CD8+ T cells with the difference especially pronounced in the central memory subset (CD30+CD8+ CD45RO+ CD62L+). Levels of central memory CD30+CD8+ CD45RO+ CD62L+ cells were 6 times higher among patients with acute GVHD than among those without aGVHD. There were similar levels of CD30 expression in naive T cells, CD4+

T cells, and regulatory (CD4+CD127lowCD25+) T cells.1(10)

Plasma levels of soluble CD30 were significantly greater in patients with GVHD and immunohistochemical analysis of affected intestinal tissue showed many CD30+ infiltrating lymphocytes present. These results suggest that CD30 expression on CD8+T-cell subsets or plasma levels of soluble CD30 may be a potential biomarker for aGVHD.

In this study we will evaluate the safety of brentuximab early after allogeneic stem cell transplant and haploidentical allogeneic transplantant and observe if there is a decrease in the risk of relapse.

3.0 Patient Eligibility

3.1 Inclusion Criteria:

3.1.1 Patients with CD30 positive Hodgkin Lymphoma (HL) or anaplastic large cell lymphoma (ALCL) that have undergone allogeneic or haploidentical SCT in the past 60 days (matched related or matched unrelated donors only).
3.1.2 Age 18 to 65 years.
3.1.3 Performance status: Zubrod 0-1 or Karnofsky 80-100.
3.1.4 Serum creatinine < 1.5 mg/dL or creatinine clearance greater than or equal to 40 cc/min as defined by MDRD method from National Kidney Disease Education Program (NKDEP).
3.1.5 Serum direct bilirubin < 1.5 mg/dL (unless Gilbert's syndrome).
3.1.6 SGPT < 200 IU/L unless related to patient's malignancy.
3.1.7 Evidence of neutrophil and platelet engraftment, defined as platelet count equal or greater than 50,000 mm^3 independent of platelet transfusion or thrombopoietin factor and ANC equal or greater to 1000 without growth factor support for at least 5 days.
3.1.8 Patients with previous exposure to brentuximab pre-transplant are eligible for the study.

3.2 Exclusion Criteria:

3.2.1 Pregnancy or breast-feeding (women of childbearing potential, any female who has experienced menarche and who has not undergone surgical sterilization or is post-menopausal with a positive serum pregnancy test.
3.2.2 Presence of steroid-refractory acute graft-versus-host disease (GVHD).
3.2.3 Patients that underwent allogeneic transplantation as a treatment of graft failure.
3.2.4 Dual refractory CMV reactivation to foscarnet and ganciclovir or evidence of CMV disease.

4.0 Treatment Plan

4.1 Treatment Initiation:

Brentuximab will be given as an IV infusion over 30 minutes every 3 weeks for a total of 6 cycles. starting between days 35 and 60 post allogeneic SCT.

Brentuximab dose will be based on actual body weight starting with an initial dose of 1.2 mg/kg for the first 2 cycles and then the dose will be increased to 1.8 mg/kg after the second cycle for all subsequent cycles. Brentuximab dose will be based on actual body weight except for patients weighing more than 100 kg, then dose will be calculated based on 100 kg.

Patients must meet the following criteria to start any cycle of brentuximab:
1. Absolute neutrophil count > 1,000/mm3 not requiring daily growth factor support on the day of the brentuximab infusion.
2. Platelet count greater than 50,000/mm3 independent of platelet transfusions or thrombopoietin factor for at least 5 days.
3. No clinical evidence of life-threatening infection.

4. No active bleeding.
5. No uncontrolled acute GVHD (steroid refractory).
6. No CMV re-activation that is dual-refractory to foscarnet and ganciclovir/ No active CMV disease.
7. Creatinine< 1.5 mg/dL or creatinine clearance greater than or equal to 40 cc/min as defined by MDRD method from National Kidney Disease Education Program (NKDEP)
8. Serum bilirubin <1.5 mg/dL
9. SGPT < 200 IU/L unless related to patient's malignancy

Vital sign monitoring, observation, and treatment of hypersensitivity reactions during and after infusion will be performed per standard of care.

4.2 Dose Modification:

Dose will be reduced from 1.8 mg/kg to 1.2 mg/kg or from 1.2 mg/kg to 1 mg/kg or from 1 mg/kg to stop treatment if:

1. Neutropenia grade 3-4 unresponsive to G-CSF or grade 4 thrombocytopenia are observed.
2. Peripheral neuropathy, new or worsening grade 2 or 3. Withhold treatment until improvement or return to grade 1 or baseline; then resume with a dose reduction.

Dose will be reduced to 1 mg/kg if:

1. Creatinine clearance < 30 cc/min as defined by MDRD method from NKDEP. http://nkdep.nih.gov/lab-evaluation/gfr/estimating.shtml
2. Hepatic impairment defined as bilirubin > 2 mg/dL.

If the patient develops grade 3-4 neutropenia unresponsive to G-CSF: Hold until resolution to grade </= 1 and restart at lower dose.

4.3 Treatment will be discontinued if:

1. If the dose that was administered was 1 mg/kg and the patient develops grade 4 hematological toxicity as described above.
2. If the patient develops both foscarnet and ganciclovir-resistant CMV viremia or histologic CMV end-organ disease.
3. If an anaphylactic reaction is observed.
4. If peripheral neuropathy, grade 4 is observed.
5. If progressive multifocal leukoencephalopathy (PML) is confirmed. Treatment must be withheld until PML is confirmed.
6. If the patient develops Stevens-Johnson syndrome.

4.4 Treatment will not be dose reduced or stopped for:

1. New onset GVHD.
2. An infusion reaction, in which case the infusion will be interrupted and appropriate medical intervention will be administered. Pre-medicate subsequent infusions with acetaminophen, an antihistamine, and/or a corticosteroid.

5.0 Evaluation During Treatment

5.1 Prior to the first cycle (within 5 days prior to receiving first dose of brentuximab):

1. Physical exam including GvHD assessment.
2. CBC with diff and platelets, chemistries.
3. Correlative studies: blood sample for immunophenotyping studies prior to 1st dose, and 1, 3,

and 5 days after first brentuximab dose.
4. Chimerism studies in peripheral blood.

5.2 At each subsequent cycle (within 5 days prior to receiving first dose of brentuximab in each cycle):
1. Physical exam including toxicity and GVHD assessment.
2. CBC with diff and platelets, chemistries.
3. Correlative studies: blood sample prior to the brentuximab dose.

5.3 If patient has a biopsy (skin, GI or liver) at any time for GVHD diagnosis, a blood sample (10 mL) will be taken at that time for correlative studies.

5.4 To be performed at approximately 1, 3, 6 and 12 months post-transplant.
These evaluations follow our standard practice and are done to monitor engraftment and disease status. If clinically indicated these studies may be done at other time points which can replace the nearest planned timepoint.

1. Chimerism studies from peripheral blood performed on separated T-cells and myeloid cells.
2. At each visit, physical examination and adverse event documentation including GvHD assessment.
3. Disease specific assessment with bone marrow aspirate with cytogenetics, serum immunoglobulins in peripheral blood and CT for lymphoma staging as indicated.

5.5 Correlative Studies to be performed by Dr. K Rezvani in her laboratory (no cost to the patients):

5.5.1 T cell immunophenotyping to define:
a. “naïve”(CD45RO-CCR7+) T cells.
b. “effector memory” (CD45RO+CCR7-) T cells.
c. “central memory” (CD45RO+CCR7+) T cells.
d. “terminally differentiated effector memory” (CD45RO-CCR7-) T cells.
e. “regulatory” T cells (CD4+CD25+CD127loFoxp3+).

5.5.2 Functional T cell studies to assess impact of brentuximab on T cell function and recovery including regulatory T cell subsets; will co-stain with CD30. CD30 is also expressed on NK cells and can assess impact of brentuximab on NK cells.

5.5.3 Functional studies of antigen-specific T cell responses to pathogens (CMV and EBV), and if impact on pathogen-specific T cell recovery.

5.5.4 Determine impact of brentuximab on diversity of reconstituting T cell repertoire by flow cytometric analysis.

5.6 To be done with collaboration with pathology department - Assess tissue biopsies from GVHD sites for CD30 expression. Tissue biopsies with matched disease and site specific GvHD will be collected and sued for controls to evaluate CD30 expression in brentuximab treatement patients. (if done for CD30+CD8+ or CD30+CD4+ T cell infiltration)

6.0 Study Criteria

Off Study Criteria:

6.1 Patient withdraws consent.
6.2 Patient can not tolerate treatment.
6.3 Unexpected pattern of toxicity.
6.4 Presence of both steroid and 2nd line treatment refractory GvHD while on treatment with brentuximab.
6.5 Presence of dual-refractory CMV reactivation to foscarnet and ganciclovir or CMV end-organ disease while on treatment with brentuximab.

6.6 Patient's inability of unwillingness to have follow-up visits and/or laboratory tests required by this protocol.
6.7 One year after treatment completion.

Steroid refractory GVHD is defined as: absence of any response 7 days after the initiation of corticosteroids for skin GVHD or 10-14 days after its initiation for GI and liver GVHD. Patients who are steroid refractory are not eligible to be enrolled on protocol, however if a patient develops GVHD while on protocol, brentuximab will not be held.

Secondary graft failure is defined as a sustained declined of ANC $<0.5 \times 10^9$/L for 3 consecutive days after initial documented engraftment with no evidence of disease progression and is not associated with concomitant medication that is known to cause cytopenias.

7.0 Expected Adverse Events and Reporting Requirements

Reporting requirements will adhere with the IRB policy 15.001. The adverse events (AEs) known to be related to brentuximab are listed in section 9.0 of this protocol.

Assessment of the Adverse Events Severity.
The severity of the AEs will be graded according to the Common Terminology Criteria v4.0 (CTCAE). Events not included in the CTCAE chart will be scored as follows:

General grading:
Grade 1: Mild: discomfort present with no disruption of daily activity, no treatment required beyond prophylaxis.
Grade 2: Moderate: discomfort present with some disruption of daily activity, require treatment.
Grade 3: Severe: discomfort that interrupts normal daily activity, not responding to first line treatment.
Grade 4: Life Threatening: discomfort that represents immediate risk of death.

Casualty Assessment.
For the purpose of this study adverse events known to be caused by brentuximab and its direct consequences will be scored as definitive related. When the relationship of the adverse event cannot be ruled out with certainty the AE may be considered probable or possible related. Adverse events known to be related to drugs used for supportive treatment will be scored as unrelated.

The principal investigator will be the final arbiter in determining the casualty assessment.

When possible, signs and symptoms indicating a common adverse event will be noted as 1 comprehensive event.

Events not to be considered AEs in this study are those related to original disease; changes in laboratory parameters such as electrolyte, magnesium and metabolic imbalances, uric acid changes, elevations of GPT, GOT, LDH and alkaline phosphatase. These would not be monitored.

8.0 Statistical Considerations

Study Design

8.1 This is a phase II study in which brentuximab will be initiated after transplant (approximately day 35-60) post engraftment and restaging at day 30 (+10 days) and continued every 21 days for 6 cycles. Dose initiation will be at 1.2 mg/kg for 2 cycles and escalated to 1.8 mg/kg on subsequent 4 cycles. If greater than grade 3 toxicity seen at 1.2 mg/kg dose level then dose will be decreased to 1 mg/kg for all patients at initiation with subsequent cycles at 1.2 mg/kg dose. We will allow intrapatient dose modification based on toxicity.

8.2 Determination of graft failure rate

Based on literature the standard graft failure rate for reduced intensity transplants is higher than that of myeloablative regimens(23), and in the range of 10%(24). With 20 patients, a two-sided 95% confidence interval for a 5% incidence of graft failure would be 0-14.6%. The primary objective of this study will be to assess the safety of brentuximab as a preventative measure after allogeneic MUD or MRD transplant in high risk CD30+ lymphoma patients. Safety is defined by no more than two secondary graft failures within 6 months of transplant (Day 0), based on an observed graft failure rate of <10% using standard of care treatment. If at any time more than two of these events are observed during the specified time frame, the study will be stopped and no further patients will be accrued.

8.3 Determination of hematologic toxicity and CMV disease

The most common grade ≥ 3 side effects on brentuximab after allogeneic transplant(7) are neutropenia (24%), and thrombocytopenia (20%) which were reversible. CMV was detected in 5 patients and was clinically significant in 1 patient.

Brentuximab will be discontinued if patient develops dual foscarnet and ganciclovir-resistant CMV viremia or histologic CMV end-organ disease. In addition, the study drug will be reduced in all future patients if at any time there is >25% grade IV neutropenia rate or >10% CMV disease rate attributable to treatment observed within Day 45- Day 180.

These rates will be monitored in a continuous fashion.

8.4 Determination of incidence of GVHD and assessment of the effects of brentuximab on T cell populations (central and effector memory and naïve CD4 and CD8 cells) and serum CD30 levels both in subsets with and without GVHD

Based on data published by Chen et al., (reviewed above) we hypothesize that down-regulation of CD30 may decrease the incidence of GVHD. We will perform immunological correlative studies on peripheral blood mononuclear cells (PBMC) and serum collected from patients at baseline (prior to initiation of brentuximab therapy) and on days 1, 3, and 5 after initiation of brentuximab and every 21 days thereafter to assess the effect on T cell subsets and their effector function as well as other immune subsets. We will also test both tissue and serum in patients who develop clinically significant GVHD.

8.5 Determination of the response and complete response rates in patients with measurable disease after day +30 restaging and progression free and overall survival of this regimen

Kaplan-Meier (1958) survival curves will be used to estimate overall survival and progression-free survival. Cox proportional hazards regression analysis may be used to model the association between overall survival and progression-free survival and disease and demographic covariates of interest.

9.0 Background Drug Information

9.1 Mechanism of Action

Brentuximab vedotin is an antibody drug conjugate (ADC) directed at CD30 consisting of 3 components: 1) a CD30-specific chimeric IgG1 antibody cAC10; 2) a microtubule-disrupting agent, monomethylauristatin E (MMAE); and 3) a protease cleavable dipeptide linker (which covalently conjugates
MMAE to cAC10). The conjugate binds to cells which express CD30, and forms a complex which is internalized within the cell and releases MMAE. MMAE binds to the tubules and disrupts the cellular microtubule network, inducing cell cycle arrest (G2/M phase) and apoptosis.

9.2 Pharmacodynamics/Kinetics

Distribution: Mean steady state volume of distribution of approximately 6-10 L for ADC.
Metabolism: MMAE: Minimal, primarily via oxidation by CYP3A4/5
Half-life elimination: Terminal: ADC: ~4-6 days
Time to peak: ADC: At end of infusion; MMAE: ~1-3 days

Excretion: MMAE: Feces (~72%, primarily unchanged); urine

9.3 Current Indications:

9.3.1 Hodgkin Lymphoma
Brentuximab vedotin is 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.

9.3.2 Systemic Anaplastic Large Cell Lymphoma
Brentuximab is indicated for treatment of patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen.

9.4 Preparation and Storage:

9.4.1 Reconstitution: Reconstitute each 50mg vial of brentuximab with 10.5ml Sterile Water for Injection, USP, to yield a single-use solution containing 5mg/ml brentuximab vedotin. Direct the stream toward the wall of the vial and not directly at the cake or powder. Gently swirl the vial to aid dissolution. **DO NOT SHAKE.** The reconstituted solution should be clear to slightly opalescent, colorless, and free of visible particulates. Following reconstitution, dilute immediately into an infusion bag, or store the solution at 2-8· C (36-46·F) and use within 24 hours of reconstitution**. DO NOT FREEZE**. Discard any unused portion left in the vial.

9.4.2 Dilution: Calculate the required volume of 5mg/ml reconstituted brentuximab solution needed and withdraw this amount from the vials. Immediately add the reconstituted solution to an infusion bag containing a minimum volume of 100ml to achieve a final concentration of 0.4mg/ml to 1.8mg/ml brentuximab vedotin. The drug can be diluted into 0.9% Sodium Chloride Injection, 5% Dextrose Injection or Lactated Ringer's Injection. Following dilution, infuse the solution immediately.

9.4.3 Storage: The brentuximab vedotin solution may be stored at 2-8·C (36-46·F). **DO NOT FREEZE.** The solution must be used within 24 hours of reconstitution. The single-use vials should be stored in the original carton to protect from light at 2-8·C (36-46·F)

9.5 Administration

9.5.1 Administer only as an intravenous infusion over 30 minutes every 3 weeks

9.5.2 Do not mix brentuximab with, or administer as an infusion with, other medicinal products

9.6 Dosage form and strength

9.6.1 Brentuximab vedotin is available as single-use vials containing 50mg of brentuximab vedotin as a sterile, white to off-white lyophilized, preservative-free cake or powder.

9.7 Adverse Events

9.7.1 The most common adverse reactions (seen in $\geq$ 20% of patients) include neutropenia, anemia, thrombocytopenia, peripheral sensory neuropathy, fatigue, nausea, vomiting, diarrhea, pyrexia, rash, cough and upper respiratory tract infection

9.7.2 Serious but less common adverse reactions include serious infections and opportunistic infections, tumor lysis syndrome, progressive multifocal leukoencephalopathy (PML), Stevens-Johnson syndrome, and embryo-fetal toxicity.

10.0 References

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