STUDY PROTOCOL

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A Randomized Phase II Study of Bortezomib Plus ICE (BICE) Versus Standard ICE for Patients with Relapsed/Refractory Classical Hodgkin Lymphoma

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PROTOCOL SUMMARY

Title: A Randomized Phase II Study of Bortezomib Plus ICE (BICE) Versus Standard ICE for Patients with Relapsed/Refractory Classical Hodgkin Lymphoma

Objectives

The primary objectives of this study are to:

- To determine the objective response rate (ORR), partial remissions (PR), and complete remissions (CR) after 3 cycles of bortezomib plus ICE (BICE) versus ICE in patients with relapsed/refractory classical Hodgkin lymphoma (cHL).
- To evaluate 2-year progression-free survival (PFS) in patients treated with 3 cycles of BICE versus ICE.

The secondary objectives of this study are to:

- To compare PET scan response after 3 cycles of BICE versus ICE chemotherapy.
- To compare serum levels of tumor necrosis factor (TNF) proteins (APRIL, BLyS, sCD30, and CD40L) and CC thymus and activation-related cytokine (TARC) at baseline and after 3 cycles of BICE versus ICE chemotherapy.
- To correlate baseline cytokine/chemokine levels with response to therapy.

Patient population

Patients with relapsed/refractory cHL who have received prior front-line anthracyline-containing chemotherapy. Specific inclusion and exclusion criteria are detailed in section 3.2.

Number of patients

Maximum number of patients planned to enroll is 50.

Study design and methodology

Randomized study to 2 arms of therapy. Arm A is VELCADE or Bortezomib plus ICE (BICE) chemotherapy and Arm B is ICE (Ifosfamide, Carboplatin, and Etoposide) chemotherapy. Patients will have imaging done at baseline with CTs and PET/CT and then repeated after 3 cycles to assess response. Patients can also provide consent to participate in the optional correlative studies. For these studies blood will collected at baseline and after 3 cycles of therapy in order to perform serum protein analyses of TNF and TARC protein levels.

Treatments administered

Arm A: BICE: VELCADE on Day 1 and 4, ICE from Day 1 to 3, Neulasta on Day 5.

Arm B: ICE from Day 1 to 3, Neulasta on Day 4.

Efficacy data collected

The following evaluations will be conducted to assess the efficacy of VELCADE:

- CTs and PET/CT scans will be performed at baseline and after 3 cycles to assess response to treatment.

Correlative studies collected (optional)

- For patients who provide consent optional correlative studies will be performed. For these studies

blood will collected at baseline and after 3 cycles of therapy in order to perform serum protein analyses of TNF and TARC protein levels.

Safety data collected

The following evaluations will be conducted to assess the safety of VELCADE:

- Patients will undergo careful monitoring while on study. This includes weekly blood work and detailed parameters for retreatment as specified in the protocol including for absolute neutrophil count (ANC), platelet, bilirubin, alkaline phosphatase, AST, ALT, and creatinine. Additional safety monitoring is also incorporated for peripheral neuropathy for retreatment, as well as other non-hematologic, non-nephrologic, and non-hepatic toxicities.

Statistical procedures

The phase II part of this study is to compare ICE only and BICE in treating patients with classical Hodgkin lymphoma. The primary outcome is complete remission. The estimated accrual rate is 2 or 4 patients per month. A maximum of 50 patients will be accrued. Patients will be evaluated for response after 0.75 months after receiving treatment for 3 cycles (14 days per cycle). The patients will be randomized between ICE and BICE arms using a Bayesian adaptive algorithm. In general, the trial will proceed as follows: The initial 20 patients will be randomized fairly with probability of 0.50 each between the two arms, so that the number of patients in each arm is equal at the start of the trial. Thereafter, as the trial proceeds patients will be randomized to the two groups with unequal probabilities in favor of the treatment that, on average, yields better response rate. Consequently, each successive patient is more likely to receive the treatment with a better response rate, on average. The details of the adaptive randomization scheme are as follows:

Denote the response rate at each of the two treatment arms by $\{\pi_1, \pi_2\}$ (1 for ICE, 2 for BICE). Based on the currently available data, we assume the prior distribution for the response rate is $\pi_1 \sim$ Beta (0.5, 0.5) and $\pi_2 \sim$ Beta (0.6, 0.4), respectively. The resulting prior mean (95% credible interval) for ICE and BICE are 0.5(0.002, 0.99) and 0.6(0.007, 0.99), respectively. After the initial first 20 patients being randomized to two treatment groups with an equal probability, each new patient will be randomized to receive treatment i with probability $\rho_i = \text{prob}(\pi_i > \pi_j, j \neq i | \text{ Data})$, i, j=1,2. If one of these two randomization probabilities falls below 0.025 then that arm will be dropped. In addition, if $\text{prob}(\pi_i > 0.25 | \text{data}) < 0.05$, i.e. the data indicates that the response rate in that arm is highly unlikely to be larger than 0.25, then that arm will be dropped. On the other hand, if one of the two randomization probabilities exceeds 0.975 then the trial will be terminated and that treatment arm will be selected. If the trial does not stop early and the maximum 50 patients are accrued, a treatment is selected as being "better" if the probability that one treatment's response rate is larger than the other's response rate exceeds 0.95.

Furthermore, serum levels of TNF proteins (APRIL, BLyS, sCD30, and CD40L) and TARC as determined at baseline compared to post-treatment with will be analyzed for both the BICE and ICE treatment groups by Mann-Whitney U test. Second, serum levels for each protein as determined at baseline compared to post-treatment will be analyzed for both the BICE and ICE treatment groups according to response rates as determined by IWG 1999 response criteria (CR, PR, SD, versus PD) by the Kruskal-Wallis test. Third, serum levels for each protein as determined at baseline compared to post-treatment will be analyzed for both the BICE and ICE treatment groups according to PET scan results (PET negative versus PET positive) at completion of therapy by the Kruskal-Wallis test. Significance will be set for $p \leq 0.05$.

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ABBREVIATIONS LIST

Abbreviation	Definition
°C	degrees Celsius
μM	micromolar
20S	20S proteasome subunit
AE	adverse event
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplant
ASH	American Society of Hematology
Bc1-2	B-cell lymphoma-2; a gene that inhibits apoptosis
BICE	Bortezomib (VELCADE), Ifosfamide, Carboplatin, and Etoposide
BSA	body surface area
CAM	cell adhesion molecules
cHL	classical Hodgkin lymphoma
CLL	chronic lymphocytic leukemia
cm	centimeter
CR	complete response or remission
CT	computed tomography
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
dL	deciliter
DLT	Dose Limiting Toxicity
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HDAC	histone deacetylase
ht	height
ICE	Ifosfamide, Carboplatin, and Etoposide
IκB	I kappa B kinase; cytokine response kinase that activates

Abbreviation	Definition
	transcription factor NF-kappa b at serine 32 and 36
ICAM-1	intercellular adhesion molecule 1
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IPS	International Prognostic Score
IRB	Institutional Review Board
IV	intravenous
IκBα	I kappa B alpha-associated protein kinase
IWG	International Working Group
kg	kilogram
Ki	inhibitory constant
lbs	pounds
m^2	square meters
mg	milligram
min	minute
mL	milliliter
mm^3	cubic millimeters
mmol	millimole
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NF-κB	nuclear factor-κB
ng	nanogram
NHL	non-Hodgkin lymphoma
nM	nanomole
OS	overall survival
p21	p21(ras) farnesyl-protein transferase
p27	cyclin-dependent kinase inhibitor
p53	tumor suppressor protein with molecular weight of 53 kDa
PD	progression of disease
PET	positron emission tomography
PFS	progression-free survival

Abbreviation	Definition
PR	partial response or remission
RS cells	Reed-Sternberg cells
SAE	serious adverse event
SD	stable disease
TNF	tumor necrosis factor
TARC	CC thymus and activation-related cytokine
US	United States
USP	United States Pharmacopeia
VCAM-1	vascular cell adhesion molecule 1
w/w	weight-to-weight ratio
wt	weight

1 INTRODUCTION AND STUDY RATIONALE

1.1 Overview of the Disease

1.1.1 Relapsed/Refractory Classical Hodgkin Lymphoma

Although Hodgkin lymphoma (HL) is considered highly curable, up to 15% of stage I/II and 40% of stage III/IV patients will experience relapse, and 10-15% of patients will have primary refractory disease. This paired with the incidence in patients who are in their 20s to 30s makes successful treatment of relapsed/refractory disease of critical importance. Only patients who obtain a positive response to 2nd-line chemotherapy followed by an autologous stem cell transplant (ASCT) have the potential of long-term disease-free survival. In addition, patients who achieve complete remission with 2nd-line chemotherapy prior to ASCT have higher disease-free survivals than those who do not (Moskowitz et al., 2001).

1.2 VELCADE (bortezomib) for Injection

1.2.1 Scientific Background

VELCADE™ (bortezomib) for Injection is a small molecule proteasome inhibitor developed by Millennium Pharmaceuticals, Inc., (Millennium) as a novel agent to treat human malignancies. VELCADE is currently approved by the United States Food and Drug Administration (US FDA) and it is registered in Europe for the treatment of multiple myeloma patients front-line and relapsed and mantle cell lymphoma patients who have received at least 1 prior therapy.

By inhibiting a single molecular target, the proteasome, bortezomib affects multiple signaling pathways. The anti-neoplastic effect of bortezomib likely involves several distinct mechanisms, including inhibition of cell growth and survival pathways, induction of apoptosis, and inhibition of expression of genes that control cellular adhesion, migration and angiogenesis. Thus, the mechanisms by which bortezomib elicits its antitumor activity may vary among tumor types, and the extent to which each affected pathway is critical to the inhibition of tumor growth could also differ. Bortezomib has a novel pattern of cytotoxicity in National Cancer Institute (NCI) in vitro and in vivo assays (Adams et al., 1999). In addition, bortezomib has cytotoxic activity in a variety of xenograft tumor models, both as a single agent and in combination with chemotherapy and radiation (Steiner et al., 2001; Teicher et al., 1999; Cusack et al., 2001; LeBlanc et al., 2002; Pink et al., 2002). Notably, bortezomib induces apoptosis in cells that over express bcl-2, a genetic trait that confers unregulated growth and resistance to conventional chemotherapeutics (McConkey et al., 1999).

Bortezomib is thought to be efficacious in multiple myeloma via its inhibition of nuclear factor κB (NF-κB) activation, its attenuation of interleukin-6 (IL-6)-mediated cell growth, a direct apoptotic effect, and possibly anti-angiogenic and other effects (Hideshima et al., 2001).

1.2.2 Nonclinical Pharmacology

Pharmacokinetic (PK) and pharmacodynamic studies were conducted in the rat and cynomolgus monkey. Upon intravenous (IV) bolus administration, bortezomib displays a rapid distribution phase ($t_{1/2}\alpha$ <10 minutes) followed by a longer elimination phase ($t_{1/2}\beta$ 5–15 hours). Bortezomib has a large volume of distribution (range 5–50 L/kg). The plasma PK profile is well described by a 2-compartment model.

The pharmacodynamic action of bortezomib is well established and can be measured through an ex vivo assay (20S proteasome activity) (Lightcap et al., 2000). This assay was used to determine the duration of drug effect in lieu of the PK data in the early preclinical toxicology studies as well as to set a guide for dose escalation in humans. Following dosing with bortezomib in the rat and cynomolgus monkey, proteasome inhibition in peripheral blood had a half-life less than 24 hours, with proteasome activity returning to pretreatment baseline within 24 hours in monkey and within 48 to 72 hours in rat after a single dose of bortezomib. Further, intermittent but high inhibition (>70%) of proteasome activity was better tolerated than sustained inhibition. Thus, a twice-weekly clinical dosing regimen was chosen in order to allow return of proteasome activity towards baseline between dose administrations.

1.2.3 Nonclinical Toxicity

Single-dose IV toxicity studies were conducted with bortezomib in the mouse, rat, dog, and monkey to establish the single-dose maximum tolerated dose (MTD). The MTDs were 0.25 mg/kg (1.5 mg/m^2) and 0.067 mg/kg (0.8 mg/m^2) in the 2 most sensitive species, rat and monkey, respectively.

Repeat-dose multi-cycle toxicity studies of 3 and 6 months in the rat and 9 months in the monkey, each with 8-week recovery periods, were conducted to characterize the chronic toxicity of bortezomib when administered by the clinical route and regimen of administration. The MTD in the 6-month rat study was 0.10 mg/kg (0.6 mg/m^2) and the key target organs were the gastrointestinal (GI) tract, hematopoietic and lymphoid systems. The MTD in the 9-month monkey study was 0.05 mg/kg (0.6 mg/m^2) and the key target organs were the GI tract, hematopoietic and lymphoid systems, peripheral nervous system, and kidney. Full or partial reversibility was observed for each of the toxicities described to date.

In general, the nature of the toxicity of bortezomib is similar across species, and target organs of toxicity in animals have been largely predictive of human toxicity. The toxicity of bortezomib in animals is characterized by a steep dose-response with mortality seen at dosages above the MTD. The cause of death at acutely lethal dosages is considered to be related to indirect cardiovascular (CV) effects of hypotension and vascular changes with secondary bradycardia and the cause of death in long-term studies has been attributed to GI or hematologic toxicity. The pharmacologic effects of bortezomib on the CV system have been extensively characterized and have demonstrated that indirect effects on CV function occur only at acutely lethal dosages and are abrogated by routine supportive care.

Additional detailed information regarding the nonclinical pharmacology and toxicology of bortezomib may be found in the 2006 Investigator's Brochure.

1.2.4 Clinical Pharmacokinetics and Pharmacodynamics

The clinical pharmacology characterization of bortezomib has been determined from phase 1 studies in subjects with solid tumors and hematological malignancies, and confirmed in phase 2 studies in subjects with multiple myeloma.

Bortezomib demonstrates multi-compartmental pharmacokinetics. Following intravenous administration of 1.0 mg/m^2 and 1.3 mg/m^2 dose, the mean first-dose maximum observed plasma concentrations of bortezomib were 57 and 112 ng/mL, respectively in 11 patients with multiple myeloma and creatinine clearance values >50 mL/min participating in a pharmacokinetics study. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1.0 mg/m^2 dose and 89 to 120 ng/mL for the 1.3 mg/m^2 dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours. Bortezomib is eliminated more rapidly following the first dose. Mean Total Body Clearances were 102 and 112 L/h following the first dose for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1.0 and 1.3 mg/m^2, respectively. Clinical experience has shown that the change in clearance does not result in overt toxicity from accumulation in this multidose regimen in humans.
In subjects with advanced malignancies, the maximum pharmacodynamic effect (inhibition of 20S activity) occurred within 1-hour post dose. At the therapeutic dose of 1.3 mg/m^2 in subjects with multiple myeloma, the mean proteasome inhibition at 1-hour post dose was approximately 61%.

The time course of proteasome inhibition in subjects is characterized by maximum inhibition observed within the first hour after administration, followed by partial recovery of proteasome activity over the next 6 to 24 hours to within 50% of the pretreatment activity. On the Day 1, 4, 8, and 11 schedule, variable (10%–30%) levels of proteasome inhibition have been observed at next scheduled dosing. In theory, this advantage allows cells to recover proteasome activity for normal cellular housekeeping functions between doses.

The relationship between bortezomib plasma concentrations and proteasome inhibition can be described by a maximum effect (E_{max}) model. The E_{max} curve is initially very steep, with small changes in plasma bortezomib concentration over the range of 0.5 to 2.0 ng/mL relating to large increases in the percent inhibition (0–60%). After that, a plateau occurs where marginal increases of proteasome inhibition are observed in spite of large changes in plasma bortezomib concentrations.

1.2.5 Clinical Experience in Myeloma

It is estimated that more than 55,000 patients have been treated with VELCADE, including patients treated through Millennium-sponsored clinical trials, Investigator-Initiated Studies, the

US NCI Cancer Therapy Evaluation Program (CTEP), and with commercially available drug. VELCADE has been commercially available since 13 May 2003.

The overall goal of the Millennium phase I program was to determine the MTD and dose-limiting toxicity (DLT) of VELCADE in a number of therapeutic settings involving subjects with various advanced malignancies. In a Phase I trial in patients with refractory hematologic malignancies, the MTD for a twice weekly for 4 weeks of a 42 day cycle was 1.04 mg/m^2/dose, with DLTs of thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise (Orlowski et al., 2002). The toxicity was greatest during the third and fourth weeks of therapy. In the 3-week schedule of VELCADE monotherapy (4 doses, given on Days 1, 4, 8, and 11 of a 21-day treatment cycle), the DLT occurred at 1.56 mg/m^2/dose (3 subjects with Grade 3 diarrhea and 1 with peripheral sensory neuropathy). Therefore, the MTD at this schedule was 1.3 mg/m^2/dose. In a 35-day treatment cycle with 4 weekly doses of VELCADE monotherapy, the MTD was 1.6 mg/m^2/dose and DLT included hypotension, tachycardia, diarrhea, and syncope.

In phase 1 clinical studies, anti-tumor activity was reported in subjects with NHL, multiple myeloma, Waldenström's Macroglobulinemia, squamous cell carcinoma of the nasopharynx, bronchoalveolar carcinoma of the lung, renal cell carcinoma, and prostate cancer.
The safety and efficacy of VELCADE in subjects with multiple myeloma were investigated in two phase 2 clinical studies, studies M34100-024 (subjects with first relapse) (Jagannath et al, 2004) and M34100-025 (subjects with second or greater relapse and refractory to their last prior therapy) (Richardson et al, 2003). In M34100-025, 202 heavily pre-treated subjects with refractory multiple myeloma after at least 2 previous treatments received VELCADE, 1.3 mg/m^2 on Days 1, 4, 8, and 11 of a 21-day treatment cycle. The European Group for Blood and Marrow Transplant (EBMT) response criteria, as described by Blade (Blade et al., 1998) were utilized to determine disease response. CRs were observed in 4% of subjects, with an additional 6% of patients meeting all criteria for CR but having a positive immunofixation test. PR or better was observed in 27% of subjects, and the overall response rate (CR, PR and minor response [MR] combined) was 35%. Seventy percent of subjects experienced stable disease or better.

The phase 3 study (M34101-039) (Richardson et al, 2005), also referred to as the APEX study, was designed to determine whether VELCADE provided benefit (time to progression [TTP], response rate, and survival) to patients with relapsed or refractory MM relative to treatment with high-dose dexamethasone. The study was also designed to determine the safety and tolerability of VELCADE relative to high-dose dexamethasone, and whether treatment with VELCADE was associated with superior clinical benefit and quality of life relative to high-dose dexamethasone. A total of 669 patients were enrolled and 663 patients received study drug (VELCADE: 331; dexamethasone: 332). Patients randomized to VELCADE received 1.3 mg/m^2 I.V. push twice weekly on days 1, 4, 8, and 11 of a 3-week cycle for up to eight treatment cycles as induction therapy, followed by 1.3 mg/m^2 VELCADE weekly on days 1, 8, 15, and 22 of a 5-week cycle for three cycles as maintenance therapy. Patients randomized to dexamethasone received oral dexamethasone 40 mg once daily on days 1 to 4, 9 to 12, and 17 to 20 of a 5-week cycle for up to four treatment cycles as induction therapy, followed by dexamethasone 40 mg once daily on days 1 to 4 followed of a 4-week cycle for five cycles as maintenance therapy. The European

Group for Blood and Marrow Transplant (EBMT) response criteria, as described by Blade (Blade et al., 1998) were utilized to determine disease response. There was a 78% increase in TTP for the VELCADE arm. Median TTP was 6.2 months for the VELCADE arm and 3.5 months for the dexamethasone arm (*P*<.0001). CR (complete response) + PR (partial response) was 38% with VELCADE vs. 18% with dexamethasone (*P*<.0001). CR was 6% with VELCADE vs. <1% with dexamethasone (*P*<.0001). The CR + nCR rate was13% with VELCADE vs. 2% with dexamethasone. In patients who had received only one prior line of treatment (VELCADE: 132; dexamethasone: 119), CR + PR was 45% with VELCADE vs. 26% with dexamethasone (*P*=.0035). With a median 8.3 months of follow-up, overall survival was significantly longer (*P*=.0013) for patients on the VELCADE arm vs. patients on the dexamethasone arm. The probability of survival at one year was 80% for the VELCADE arm vs. 66% for the dexamethasone arm, which represented a 41% decreased relative risk of death in the first year with VELCADE (*P*=.0005). In patients who had received only one prior line of treatment, the probability of survival at one year was 89% for the VELCADE arm vs. 72% for the dexamethasone arm, which represented a 61% decreased relative risk of death in the first year with VELCADE (*P*=.0098). Updated response rates and survival data were reported for M34101-039 (Richardson ASH, 2005). The updated CR (complete response) + PR (partial response) rate was 43% with VELCADE. The CR + nCR rate was 16% with VELCADE. With a median 22 months of follow-up, overall survival was significantly longer for patients on the VELCADE arm vs. patients on the dexamethasone arm. The median overall survival was 29.8 months (95% CI: 23.2, not estimable) for the VELCADE arm vs 23.7 months (95% CI: 18.7, 29.1) for the dexamethasone arm (hazard ratio = 0.77, *P*= 0.0272). The probability of survival at one year was 80% for the VELCADE arm vs. vs 67% for the dexamethasone arm (*P*=0.0002).

Studies using VELCADE as monotherapy and in combination with other chemotherapy agents are continuing.

1.2.6 Potential Risks of VELCADE

More than 55,000 people have been exposed to VELCADE.

Table 1 Known Anticipated Risks of VELCADE by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Blood and Lymphatic System Disorders	
Most common	Thrombocytopenia that may increase the risk of bleeding*, anemia*
Very common	Neutropenia*
Common	Lymphopenia, pancytopenia*, leukopenia*
Uncommon	Febrile neutropenia
Cardiac Disorders	
Common	Arrhythmias including tachycardia, atrial fibrillation, and palpitations; acute development or exacerbation of cardiac failure, including congestive heart failure*; pulmonary edema*
Uncommon	Cardiogenic shock*, new onset of decreased left

	ventricular fraction*, atrial flutter, cardiac tamponade*, bradycardia, atrioventricular block (complete), cardiac arrest, cardiopulmonary failure
Ear and Labyrinth Disorders	
Uncommon	Deafness, hearing impairment
Eye Disorders	
Common	Blurred vision, conjunctival infection and irritation
Uncommon	Conjunctival hemorrhage
Gastrointestinal Disorders	
Most common	Constipation, diarrhea*, nausea, vomiting*
Very common	Gastrointestinal and abdominal pain, excluding oral and throat
Common	Dyspepsia, pharyngolaryngeal pain, gastroesophageal reflux, abdominal distension, stomatitis and mouth ulceration, dysphagia, gastrointestinal hemorrhage (upper and lower gastrointestinal tract)*, rectal hemorrhage (includes hemorrhagic diarrhea)
Uncommon	Eructation, tongue ulceration, retching, upper gastrointestinal hemorrhage*, hematemesis*, oral mucosal petechiae, ileus paralytic*, odynophagia, enteritis, colitis, oesphagitis, fungal oesphagitis, enterocolitis, acute pancreatitis*, gastritis
General Disorders and Administration Site Conditions	
Most common	Asthenic conditions, including weakness, fatigue, lethargy, and malaise; pyrexia
Very common	Rigors, edema of the lower limbs
Common	Neuralgia, chest pain, mucosal inflammation*
Uncommon	Injection site pain and irritation, injection site phlebitis, general physical health deterioration*, injection site cellulitis, catheter site cellulitis, injection site infection
Hepatobiliary Disorders	
Common	Abnormal liver function tests
Uncommon	Hyperbilirubinemia, hepatitis*
Immune System Disorders	
Uncommon	Drug hypersensitivity, angioedema

Infections and Infestations	
Very common	Upper respiratory tract infection, nasopharyngitis, lower respiratory tract and lung infections*, pneumonia*, Herpes zoster*
Common	Herpes zoster disseminated,*, postherpetic neuralgia, sinusitis, pharyngitis, oral candidiasis, urinary tract infection*, catheter-related infection*, sepsis and bacteremia*, cellulitis and other skin infections*, Herpes simplex
Uncommon	Bronchitis, gastroenteritis*, septic shock*, urosepsis*, aspergillosis*, tinea infections, Herpes zoster ophthalmic, Herpes simplex ophthalmic, meningoencephalitis herpetic, varicella, empyema
Injury, Poisoning, and Procedural Complications	
Common	Catheter-related complication
Uncommon	Subdural haematoma
Investigations	
Common	Increased ALT, increased AST, increased alkaline phosphatase
Uncommon	Increased GGT, oxygen saturation decreased*, blood albumin decreased
Metabolism and Nutritional Disorders	
Most common	Decreased appetite and anorexia, which may result in dehydration and/or weight loss
Very common	Dehydration*
Common	Hyperglycemia, hypoglycemia, hyponatremia, hypokalemia, hypercalcemia*
Musculoskeletal and Connective Tissue Disorders	
Very common	Bone pain, pain in limb, myalgia, arthralgia
Nervous System Disorders	
Most common	Peripheral neuropathy (including all preferred terms under the MedDRA high-level term peripheral neuropathy NEC)
Very common	Paresthesia and dysesthesia; dizziness, excluding vertigo; headache
Common	Polyneuropathy, syncope, dysgeusia
Uncommon	Convulsions, loss of consciousness, ageusia, encephalopathy, paralysis*, reversible posterior leukoencephalopathy syndrome, autonomic neuropathy
Neoplasms, Benign, Malignant, and Unspecified (including cysts and polyps)	
Uncommon	Tumor lysis syndrome*
Psychiatric Disorders	
Very common	Anxiety
Common	Confusion, insomnia
Uncommon	Delirium
Renal and Urinary Disorders	
Common	Renal impairment, including renal failure and increased serum creatinine*; hematuria
Uncommon	Difficulty in micturition
Respiratory, Thoracic, and Mediastinal Disorders	
Very common	Cough, dyspnea
Common	Epistaxis, exertional dyspnea, pleural effusion*, rhinorrhea, hypoxia*
Uncommon	Hemoptysis*, acute respiratory distress*, respiratory

	failure*, pneumonitis*, lung infiltrates, pulmonary alveolar hemorrhage*, interstitial lung disease*, pulmonary hypertension*, pleurisy, pleuritic pain
Skin and Subcutaneous Tissue Disorders	
Very common	Skin rash, which can be pruritic, erythematous, and can include evidence of leukocytoclastic vasculitis
Common	Urticaria
Uncommon	Leukocytoclastic vasculitis
Vascular Disorders	
Very common	Hypotension*
Common	Orthostatic/postural hypotension, petechiae
Uncommon	Cerebral hemorrhage*

Most common = ≥ 30%, Very common = 10% to 29%, Common=1% to 9%, Uncommon= < 1%,

* Fatal outcomes have been reported

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; GGT = gamma glutamyl transferase

Table 2 Reports of Adverse Reactions from Postmarketing Experience

System Organ Class Preferred Term	Observed Incidence[a]
Blood and lymphatic system disorders	
Disseminated intravascular coagulation	Rare
Cardiac Disorders	
Atrioventricular block complete	Rare
Cardiac tamponade	Rare
Ear and labyrinth disorders	
Deafness bilateral	Rare
Eye Disorders	
Ophthalmic herpes	Rare
Gastrointestinal Disorders	
Acute pancreatitis	Rare
Ischemic colitis	Rare
Hepatobiliary disorders	
Hepatitis	Uncommon
Liver failure	Unknown
Infections and infestations	
Herpes meningoencephalitis	Rare
Immune System Disorders	
Angioedema	Rare
Nervous System Disorders	
Autonomic neuropathy	Rare
Dysautonomia	Unknown
Encephalopathy	Rare
Respiratory, thoracic and mediastinal disorders:	
Acute diffuse infiltrative pulmonary disease	Rare
Acute respiratory distress syndrome (ARDS)	Unknown
Interstitial pneumonia	Unknown
Pneumonitis	Unknown
Skin and subcutaneous system disorders	
Toxic epidermal necrolysis	Unknown

a Incidence is assigned using the following convention: very common (>1/10); common (>1/100 and <1/10); uncommon (>1/1000 and <1/100); rare (>1/10,000 and <1/1000); very rare (<1/10,000, including isolated reports).

Other medical events of interest that are considered not causally related to VELCADE include hepatic failure and QT prolongation. Fatal outcomes have been reported.

Women of childbearing potential should avoid becoming pregnant while being treated with VELCADE. Genotoxicity testing has shown that bortezomib is negative in the in vitro Ames assay and in the in vivo micronucleus assay, but it is a clastogen in the in vitro chromosomal aberration assay.

Additional details on the potential risks of VELCADE may be found in the Investigator's Brochure.

1.3 VELCADE (bortezomib) plus ICE for Classical HL

1.3.1 Rationale for BICE Treatment and Study Endpoints

1.3.1a Outcomes for ICE followed by ASCT for relapsed/refractory classical HL

Salvage treatment of relapsed/refractory Hodgkin lymphoma patients with 2nd-line chemotherapy with ICE followed by an autologous stem cell transplant results in a 40 to 60% long-term event-free survival rate. In addition, patients who have evidence of CR after ICE have a 20% improvement in event-free survival compared to patients in PR and approximately 20-25% of patients achieve CR as evaluated by International Working Group (IWG) 1999 CT criteria after 2-3 cycles of ICE (Moskowitz et al., 2001; Abali et al., 2008).

1.3.1b Significance of PET scans in early response assessment and prediction of outcomes

PET scans have emerged as a powerful method of response rate assessment in lymphoma. The key advantage of PET scans over CT scans is the ability to distinguish between viable tumor and necrosis or fibrosis present after completion of treatment. This is particularly important in HL patients who often can present with bulky and/or mediastinal masses which commonly result in residual masses on CT scan after treatment completion. Given this positive benefit the 1999 IWG criteria (Cheson et al., 1999) for response assessment of malignant lymphoma were updated in 2007 with CR now being assessed if PET scan positive areas prior to treatment have become PET scan negative regardless of size (Cheson et al., 2007). This is in striking difference to the original IWG criteria published in 1999 which for CR requires the complete disappearance of all detectable radiographic evidence of disease on CT scans (Cheson et al., 1999).

PET-based criteria are now routinely used in HL to assess response to front-line therapy. PET scan response has been shown to predict progression-free survival (PFS) and overall survival (OS) after 2 cycles of chemotherapy with a 2-year PFS in PET negative patients of 96% compared to 0% for PET positive patients (Hutchings et al., 2006). In addition, recent analysis

has shown that PET scan assessment after course 2 of ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) chemotherapy is better than the commonly referenced International Prognostic Score (IPS) in prognostic value with 2-year PFS of 95% for those with negative PET scans after cycle 2 of treatment compared to 13% for those with positive PET scans (Gallamini et al., 2007).

1.3.1c Relevance of PET scans for response assessment in relapsed/refractory cHL patients

While substantial data exists for the use of PET scans and the revised 2007 IWG criteria in the front-line setting, the use of PET scans in the relapsed/refractory 2nd-line and higher treatment setting is still being defined. Emerging data however shows that there is prognostic significance of PET scan response pre-ASCT in predicting outcomes post-ASCT (Seam et al., 2007). In a retrospective clinical study in lymphoma patients undergoing ASCT the event-free survival (EFS) rate was 80% in patients who had negative pre-ASCT PET images as compared to 43% in patients who had positive pre-ASCT PET images (Filmont et al., 2007). Another study showed retrospectively that the median PFS was 19 months for patients with negative pre-ASCT PET scans as compared to 5 months for patients with positive pre-ASCT PET scans (Svoboda et al., 2006). It has also been demonstrated that early PET assessment after 2 cycles of 2nd-line chemotherapy in combination with their recurring Hodgkin score (Josting et al., 2002) was useful in identifying four categories of risk for relapse after ASCT (Schot et al., 2007). Further evaluation of PET scan response in a prospective clinical trial holds the ability to further define the relevance of PET scan response pre-ASCT after 2nd-line chemotherapy through correlation with PFS.

1.3.1d Significance of the diversity of the nuclear factor (NF)-κB signaling pathway and activation through TNF receptor binding

The importance of NF-κB signaling was first identified in multiple myeloma and led to the development and approval of bortezomib. Data has now emerged which supports the role of both classical (canonical) and alternative (noncanonical) NF-κB pathways. The diversity of these pathways allow for NF-κB activity even in the setting of genetic abnormalities. The classical pathway when activated results in nuclear translocation of the heterodimer of p50/p65 while the alternative pathway results in nuclear translocation of the heterodimer of p52/relB. Bortezomib blocks proteasome degradation of phosphorylated IκBα and p100 in respectively the classical and alternative pathways, and thus prevents nuclear translocation of the p50/65 and p52/relB heterodimers and inhibits NF-κB activity. Furthermore, the TNF receptor family which includes BCMA, TACI, BR3, CD30, and CD40 have been shown to be able to activate the NF-κB pathway (Annunziata et al., 2007).

1.3.1e Significance of the interdependence of Reed-Sternberg cells on the microenvironment.

The unique biology of Hodgkin lymphoma is related to the interdependence of the rare RS cells with the surrounding microenvironment (Figure 1). This microenvironment is composed of B and T cells and macrophages which provide survival signals to the RS cells and thus support Hodgkin lymphoma tumor growth. The TNF superfamily of proteins has a key role in the microenvironment cross-signaling with the RS cells and is composed of APRIL, BLyS, CD30L/CD30, and CD40L/CD40.

APRIL and BLyS are TNF ligands which have important roles in the both malignant and benign B cell function and are expressed by macrophages which surround RS cells. APRIL and BLyS bind to BCMA and TACI and BLyS can bind a third receptor BR3 (Bossen et al., 2006). These receptors are found on both normal and malignant B cells, including chronic lymphocytic leukemia (CLL) cells and Hodgkin RS cells. In CLL BLyS was found to bind to BR3 and activate the alternative NF-κB pathway, while BLyS and APRIL were found to bind to BCMA and TACI and activate the classical NF-κB pathway (Endo et al., 2007). Similar to RS cells CLL cells are also dependent on cytokine support from nurselike cells in the microenvironment which also express high levels of ARRIL and BLyS. In a retrospective non-Hodgkin lymphoma (NHL) study, serum BLyS levels at time of diagnosis were found to correlate with disease outcome with patients who had BLyS levels > 40 ng/mL having a poorer median overall survival. In addition, BLyS levels increased in patients after transformation of follicular lymphoma to large B cell lymphoma suggesting the BLyS expression may also correlate with disease severity (Novak et al., 2004).

CD30 has dense expression on RS cells, but rare expression on normal cells (Yazbeck et al., 2006). Benefit has been seen in HL clinical trials which have targeted CD30 through antibodies or antibody-drug conjugates (Ansell et al., 2007; Bartlett et al., 2008; Hamblett et al., 2005). CD30L (CD153) is a transmembrane protein which is expressed by the surrounding B and T cells, but is not expressed by RS cells and has paradoxical effects on cell survival when compared to CD30 by inducing cell death of CD30 RS cells. In addition, the soluble form of CD30 (sCD30) has been found to be an independent negative prognostic factor for event-free survival (EFS) and is thought to potentially protect CD30 tumor cells from CD30L induced apoptosis (Younes et al., 1997). In a retrospective analysis of HL patients treated with front-line chemotherapy a baseline sCD30 level of ≥ 100 U/mL as compared to ≤ 100 U/mL predicted for a 5-year EFS of 60% versus 88% (Nadali et al., 1998).

CD40 expression is less restricted that CD30 and is expressed by B and T cells and the Hodgkin RS cells. RS cells do not express CD40L (CD154), but receive CD40L signals from the surrounding microenvironment. CD40 can be targeted for the treatment of HL and NHL, and currently two antibodies are being evaluated for treatment (Forero-Torres et al., 2006; Hsu et al., 2006). While the role of soluble CD40L in predicting prognosis has not yet been fully evaluated in lymphoma, prognostic significance has been demonstrated in patients with acute coronary syndromes. Soluble CD40L is shed from stimulated lymphocytes and released after platelet stimulation, and soluble CD40L > 5 μg/L in patients with unstable coronary artery disease identified patients at increased risk of further coronary events and those who would benefit from antiplatelet therapy (Heeschen et al., 2003).

Although not a TNF family protein, CC thymus and activation-related cytokine (TARC) is a protein highly produced by RS cells and antigen-presenting cells and attracts T cells by stimulating the CC chemokine receptor 4 (CCR4). Thus, TARC is thought to have a role in allowing RS cells to provide positive feedback to the microenvironment T cells. A retrospective study of HL patients treated with front-line chemotherapy demonstrated the prognostic significance of baseline TARC levels with levels of > 2,000 pg/mL being correlated with a higher rate of relapse and inferior survival (Weihrauch et al., 2005).

1.3.1f Relevance of APRIL, BLyS, sCD30, CD40L, and TARC to predict response in relapsed/refractory HL treatment

The clinical significance of baseline serum levels of BLyS, sCD30, and TARC have been retrospectively evaluated in patients receiving front-line treatment for lymphoma (Novak et al., 2004; Nadali et al., 1998; Weihrauch et al., 2005; Oki et al., 2007). However, the significance of baseline and post-2nd-line treatment values in the relapsed/refractory setting has not yet been determined. Further evaluation holds potential value of developing surrogate markers to predict radiographic response to chemotherapy.

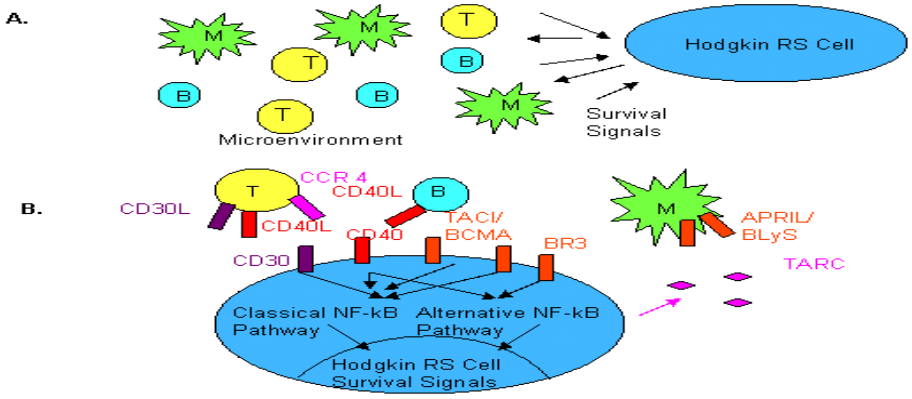

Figure 1A&B: Signaling Between Microenvironment and the Reed-Sternberg Cells The microenvironment consisting of B and T cells with macrophages provide cytokine signaling to the Hodgkin RS cells and allow for activation of the classical and alternative pathways of NF-κB.

1.3.2 Preliminary Studies

We have previously evaluated bortezomib both preclinically and clinically, shown that PET scan negativity in HL correlates with EFS, and have demonstrated the potential role of serum levels of BLyS and TARC as prognostic and predictive markers.

1.3.2a Preclinical evaluation of bortezomib in HL cells

Bortezomib demonstrated high antiproliferative activity by cell cycle arrest at the G2-M phase and induced apoptosis. These effects were independent of mutations in IκBα. Treatment with bortezomib activated the caspase cascade, increased p21 and Bax levels, decreased Bcl-2 levels, and enhanced the effect of gemcitabine (Zheng et al., 2004).

1.3.2b Pilot Clinical Evaluation of Bortezomib in Heavily Pretreated HL Patients

14 patients with HL who were refractory to their last treatment were treated with 1.3 mg/m2 of bortezomib on days 1, 4, 8, and 11 of a 21-day cycle. Patients had received a median of 4 prior treatment regimens and 93% of patients were previously treated with ASCT. One patient who had received 9 prior treatments and had extensive pulmonary, splenic, and nodal involvement achieved a PR and 2 patients had stable disease (SD). These results suggested low single-agent activity in heavily pretreated patients with similar results seen in three other HL trials, but a combination treatment with chemotherapy was planned to evaluate activity in less heavily pretreated patients (Younes et al., 2006; Trelle et al., 2006; Blum et al., 2006; Stauss et al., 2006).

1.3.2c Phase I study of bortezomib Plus ICE (BICE) for patients with relapsed/refractory classical HL (MDACC 2006-0527)

Combined therapies with bortezomib in myeloma and solid tumors have shown positive results, including with platinum-based chemotherapy (San Miguel et al., 2008; Palumbo et al., 2007; Davies et al., 2004; Fanucchi et al., 2006). Thus we designed this clinical study to evaluate BICE as 2nd-line treatment for patients with relapsed/refractory HL. Bortezomib was given on Days 1 and 4 and ICE was given on Days 1 to 3 with Neulasta given on Day 5. Dose levels of bortezomib were 0 = 1.0 mg/m2, 1 = 1.3 mg/m2, and 2 = 1.5 mg/m2. Cycles were repeated on Day 14 if ANC $\geq$ 1000 cells/m3 and platelets $\geq$ 100,000 cells/m3. After 3 cycles patients were evaluated for response by CTs and PET. Hematologic DLT was defined as grade 4 thrombocytopenia or neutropenia lasting greater than 14 days.

Median age of patients was 32 and 42% of patients had primary refractory disease. To date 12 patients are evaluable for toxicity and 12 patients for response. By 1999 IWG response criteria there are 4/12 CR/CRu, 5/12 PR, and 3/12 progressive disease (PD). All patients with PD had primary refractory disease. PET scans post-treatment were negative for 9/12 patients (CR + PR 1999 IWG response criteria patients). To date 8/9 patients have completed ASCT (1 patient declined ASCT). No 2nd phereses have been needed for stem cell collection. Reversible grade 4 neutropenia and thrombocytopenia occurred in respectively 40% and 50% of the patients. Median day for retreatment was Day 20 for cycle 2 and Day 21 for cycle 3. There were no toxicities of peripheral neuropathy, febrile neutropenia, or infection (Fanale et al., 2008).

1.3.2d Depletion of B cells from the microenvironment improves efficacy of ABVD and EFS

Rituximab (R) depletes B cells from the microenvironment and R plus ABVD is believed to increases responses by decreasing survival factors that stimulate RS cell growth. Of the 70 patients enrolled in this front-line study 50% had stage II disease and 50% had stage III/IV disease. By the IPS model 55% had a score of 2 or higher. Rituximab was given weekly for the first 6 weeks to the standard dose and schedule of ABVD. R-ABVD improved EFS in all patients but had the highest benefit in those with IPS > 2 with an EFS of 77%. PET also became negative in 78% of patients after 2 to 3 cycles of R-ABVD which corresponded to a 5-year EFS of 93% for those who were PET negative and 75% for those who were PET positive (Wedgwood et al., 2007).

1.3.2e Serum BLyS level as a prognostic factor in front-line HL treatment

Serum samples were obtained in 93 healthy volunteers and 50 patients with HL. ELISA was used to assess BLyS levels. Levels of BLyS in healthy volunteers had a median value of < 0.3 ng/mL and in newly diagnosed patients had a median value of 2.0 ng/mL. Newly diagnosed patients who had a serum BLyS level of ≥ 2.0 ng/mL had shorter 2-year PFS than those who had BLyS levels of < 2.0 ng/mL at respectively 64% versus 100% (Oki et al., 2007).

1.3.2f Serum TARC levels decrease with clinical responses to HDAC inhibition in relapsed/refractory HL treatment

MGCD0103 is an oral histone deacetylase (HDAC) inhibitor. In a phase II clinical study patients were treated with doses 3 times a week in 4 week cycles and serum TARC levels were determined by ELISA prior to starting treatment and on Day 8. Serum TARC levels decreased by at least 40% in 5 patients and all achieved responses of CR + PR. Thus, early decreases of TARC levels were shown to potentially predict response to treatment (Younes et al., 2007).

1.3.3 Potential Risks of BICE (Bortezomib, Ifosfamide, Carboplatin, Etoposide)

1.3.3a Bortezomib (VELCADE)

See section 1.2.6 for details.

1.3.3b Ifosfamide

- Common Trade Names
  - Ifex
- Class
  - Alkylating Agent
  - Antineoplastic Agent
  - Nitrogen Mustard
- FDA-Labeled Indications
  - Testicular cancer, germ cell, third-line in combination with other agents
  - (Hodgkin lymphoma is a non-FDA labeled indication)
- Dose Adjustments
  - None formally listed
- Administration
  - administer as a slow IV infusion over at least 30 min
  - reconstituted solution may be diluted with D5W, NS, LR, or Sterile Water for Injection to a final concentration of 0.6 to 20 mg/mL
  - reconstitute powder with Sterile Water for Injection or Sterile Bacteriostatic Water for Injection to a final concentration of 50 mg/mL

- Monitoring
  - CBC; prior to each dose and during therapy
  - urinalysis; prior to each dose and during therapy
  - serum chemistries including phosphorous, alkaline phosphatase, and other appropriate laboratory studies
- How Supplied
  - Intravenous Powder for Solution: 1 GM, 3 GM
- Contraindications
  - hypersensitivity to ifosfamide or mesna products
  - severe bone marrow depression
- Precautions
  - extravasation
  - hemorrhagic cystitis
  - may inhibit wound healing
  - neurologic manifestations requiring discontinuation of therapy (coma, confusion, hallucinations, somnolence)
  - patients with impaired renal function and/or prior exposure to cisplatin
  - potentially carcinogenic and mutagenic
  - pregnancy
  - severe myelosuppression (given with other chemotherapy agents)
  - total ifosfamide doses above 49.6 to 100 grams/m(2), especially in pediatric patients
  - use proper procedures for handling and disposal of chemotherapy
- Adverse Events
  - COMMON
    - **Dermatologic:** Alopecia
    - **Gastrointestinal:** Nausea and vomiting (58%)
  - SERIOUS
    - **Endocrine metabolic:** Metabolic acidosis (31%)
    - **Hematologic:** Myelosuppression
    - **Neurologic:** Neurotoxicity (12%)
    - **Renal:** Disorder of urinary tract, Nephrotoxicity (6%)

1.3.3c MESNA

- Common Trade Names

- Mesnex
- Class
  - Hemorrhagic Cystitis Inhibitor
- FDA-Labeled Indications
  - Prophylaxis for Ifosfamide-induced hemorrhagic cystitis
- Dose Adjustments
  - None formally listed
- Administration
  - administer as an IV bolus injection
  - can dilute with D5W, NS, or LR to a final concentration of 20 mg/mL
- Monitoring
  - urine, for presence of hematuria; every morning prior to ifosfamide therapy
  - nausea, vomiting, and diarrhea
- How Supplied
  - Intravenous Solution: 100 MG/ML
- Contraindications
  - hypersensitivity to mesna/other thiol compounds
- Precautions
  - None formally listed
- Adverse Events
  - COMMON
    - **Gastrointestinal:** Nausea and vomiting
    - **Neurologic:** Headache, Pain in limb
    - **Other:** Fatigue
  - SERIOUS
    - **Cardiovascular:** Hypotension

1.3.3d Carboplatin

- Common Trade Names
  - Paraplatin
- Class
  - Antineoplastic Agent
  - Platinum Coordination Complex
- FDA-Labeled Indications
  - Ovarian cancer, Advanced (as initial treatment in combination with other approved chemotherapy agents)
  - Ovarian cancer, Advanced (palliative treatment of recurrent disease)

  - (Hodgkin lymphoma is a non-FDA labeled indication)
- Dose Adjustments
  - hematologic: dosage adjustments in single-agent or combination therapy are based on the lowest post-treatment platelet and neutrophil counts- for platelets greater than 100,000/neutrophils greater than 2,000, adjusted dose is 125% from prior course; for platelets less than 50,000/neutrophils less than 500, adjusted dose is 75% from prior course
  - renal impairment: for the initial course of therapy- CrCl 41-59 mL/min give 250 mg/m(2); CrCl 16-40 mL/min give 200 mg/m(2)
- Administration
  - (infusion) administer over 15 minutes or longer; pre- or post-treatment hydration or forced diuresis is not required
  - may be further diluted to concentrations as low as 0.5 mg/mL with D5W or NS; use within 8 hours after dilution
- Monitoring
  - evidence of tumor response
  - peripheral blood counts
  - renal and hepatic function
  - signs and symptoms of myelosuppression
- How Supplied
  - Intravenous Powder for Solution: 50 MG, 150 MG, 450 MG
  - Intravenous Solution: 10 MG/ML
- Contraindications
  - hypersensitivity to cisplatin/platinum products or mannitol
  - severe myelosuppression/significant bleeding
- Precautions
  - aluminum reacts with carboplatin to form an inactive precipitate; therefore, intravenous sets and needles containing aluminum which may come in contact with carboplatin should not be used
  - extravasation
  - patients over 65 years of age or those previously treated with cisplatin are at increased risk of developing carboplatin-induced peripheral neuropathy
  - prior aminoglycoside therapy may potentiate carboplatin-induced renal toxicity
  - renal impairment
  - use proper procedures for handling and disposal of chemotherapy
- Adverse Events

- COMMON
  - **Gastrointestinal:** Nausea and vomiting
- SERIOUS
  - **Endocrine metabolic:** Electrolyte imbalance
  - **Hematologic:** Myelosuppression
  - **Immunologic:** Immune hypersensitivity reaction (2% to 9.2%)
  - **Neurologic:** Peripheral neuropathy
  - **Ophthalmic:** Visual disturbance (rare)

1.3.3e Etoposide

- Common Trade Names
  - Vepesid
- Class
  - Antineoplastic Agent
  - Mitotic Inhibitor
- FDA-Labeled Indications
  - Small cell carcinoma of lung, in combination therapy with other approved chemotherapeutic agents as first-line therapy
  - Testicular cancer, refractory (as combination therapy with other approved chemotherapeutic agents in patients who have already received appropriate surgical, chemotherapeutic, and radiotherapeutic therapy)
  - (Hodgkin lymphoma is a non-FDA labeled indication)
- Dose Adjustments
  - compromised bone marrow reserve: adjust dose to account for myelosuppression caused by concurrent drugs, radiation therapy, or prior chemotherapy
  - hematologic: platelet count <50,000 cells/mm(3) or absolute neutrophil count (ANC) <500 cells/mm(3); withhold further therapy until blood counts have sufficiently recovered
  - renal impairment: an initial dose of 75% the recommended dose of etoposide for patients with a CrCl 15-50 mL/min
- Administration
  - avoid rapid IV injection; administer over 30 to 60 minutes to avoid hypotension
  - dilute with D5W or NS to concentration of 0.2 to 0.4 mg/mL; MAXIMUM concentration 0.4 mg/mL (precipitation may occur)

- do not use undiluted in acrylic or ABS plastic because cracking and leaking may occur

- Monitoring
  - evidence of tumor response
  - CBC; prior to and periodically during therapy
- How Supplied
  - Intravenous Solution: 20 MG/ML
- Contraindications
  - hypersensitivity to podophyllum
- Precautions
  - administer etoposide over 30 to 60 minutes to reduce risk of hypotension
  - concomitant administration of drugs that inhibit phosphatase activities, high dose cyclosporin A
  - elderly patients (increased sensitivity to alopecia, gastrointestinal effects, infectious effects, nephrotoxicity, and myelosuppression); careful monitoring is warranted
  - extravasation (irritant)
  - impaired renal or hepatic function
  - low serum albumin may increase risk of etoposide toxicity
  - potential carcinogen
  - use proper procedures for handling and disposal of chemotherapy
- Adverse Events
  - COMMON
    - **Dermatologic:** Alopecia
    - **Endocrine metabolic:** Shivering
    - **Gastrointestinal:** Diarrhea, Inflammatory disease of mucous membrane, Loss of appetite, Nausea, Vomiting
    - **Neurologic:** Asthenia
    - **Other:** Fever, Malaise
  - SERIOUS
    - **Cardiovascular:** Congestive heart failure, Myocardial infarction
    - **Dermatologic:** Stevens-Johnson syndrome, Toxic epidermal necrolysis
    - **Hematologic:** Acute leukemia (rare), Myelosuppression, Dose-limiting (frequent)

- **Hepatic:** Hepatotoxicity
- **Immunologic:** Immune hypersensitivity reaction (0.7-2%)

1.4 Study Rationale and Selection of Drug Doses

Please refer to section 1.3.1 for details. Selection of drug doses is based from our phase I trial of BICE as described in section 1.3.2c.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objectives of this study are to:

- To determine the objective response rate (ORR), partial remissions (PR), and complete remissions (CR) after 3 cycles of bortezomib plus ICE (BICE) versus ICE in patients with relapsed/refractory classical Hodgkin lymphoma (cHL).
- To evaluate 2-year progression-free survival (PFS) in patients treated with 3 cycles of BICE versus ICE.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- To compare PET scan response after 3 cycles of BICE versus ICE chemotherapy.
- To compare serum levels of tumor necrosis factor (TNF) proteins (APRIL, BLyS, sCD30, and CD40L) and CC thymus and activation-related cytokine (TARC) at baseline and after 3 cycles of BICE versus ICE chemotherapy.
- To correlate baseline cytokine/chemokine levels with response to therapy.

3 INVESTIGATIONAL PLAN

3.1 Overall Design and Plan of the Study

3.1.1 Pretreatment Evaluations

3.1.1.a Within 28 to day 1

1) Physical examination.
2) Assess ECOG performance status and record the CTAE grade of any peripheral neuropathy symptoms.
3) Review medical history and concomitant medications.
4) Record the type and number of prior treatment regimens.
5) Laboratory tests: CBC with differential, lytes, BUN, creatinine, bilirubin, AST, ALT, alkaline phosphatase, Hepatitis B and C serologies, and HIV serology.
6) Imaging: (Within 61 days) Chest x-ray, CT scans of neck, chest, abdomen and pelvis; and PET/CT scan (within 61 days to day 1).
7) Beta-hCG serum test for women of childbearing potential.
8) If your doctor thinks it is needed, you will have a bone marrow biopsy to check the status of the disease.
9) Echo/MUGA.

3.1.1b Within 3 Days to day 1 of cycle 1 of BICE or ICE treatment

1) Physical examination.
2) Review concomitant medications.
3) Laboratory tests: CBC with differential, lytes, BUN, creatinine, bilirubin, AST, ALT, and alkaline phosphatase.
4) For patients who consent for optional procedure collect blood for serum evaluations of TNF and TARC proteins.

3.1.2 Evaluations During Treatment

1) <u>On each day of BICE or ICE administration:</u> CBC with differential, lytes, BUN, creatinine, AST, ALT, alkaline phosphatase, and bilirubin.
2) <u>While receiving BICE or ICE treatment until repeat staging has been completed:</u> Weekly CBC with differential and electrolytes.
3) <u>Within 3 days of retreatment:</u> CBC with differential, lytes, BUN, creatinine, AST, ALT, alkaline phosphatase, and bilirubin.

End of Treatment Visit (After completing 3 cycles of Bice or ICE)

<u>Within 21 days (+ / - 7 days) from start of Cycle 3 or Early Termination:</u> Physical examination, review of concomitant medications, and documentation of adverse events. Laboratory analysis with CBC with differential, lytes, BUN, creatinine, AST, ALT, alkaline phosphatase, and bilirubin. Repeat Chest x-ray, CT scans of neck, chest, abdomen, and pelvis, and PET/CT. Patients will have a bone marrow biopsy to check the status of the disease. For patients who consent for optional procedure blood for serum evaluations of TNF and TARC proteins will be collected.

**** For Outside Physician Participation During Treatment, please refer to section 8.8***

3.1.3 Duration of Treatment

1) Autologous stem cell transplant candidates: Patients will receive a minimum of 3 cycles of BICE or ICE and a maximum of 6 cycles. Stem cell collection may be performed after cycle 3 or 4 of BICE or ICE.
2) Non-transplant candidates: Patients can receive up to a maximum of 6 cycles of BICE or ICE if tolerated

3.1.4 Follow-up Evaluations

1) Patients who are eligible for autologous stem cell transplant will proceed on to this therapeutic intervention.
2) All patients will undergo follow-up evaluations every 4 months for 2 years with: Physical exam, review of adverse events, laboratory analysis with CBC with differential, lytes, BUN, creatinine, AST, ALT, alkaline phosphatase, and bilirubin, and repeat imaging with chest x-ray and CT scans of neck, chest, abdomen and pelvis.

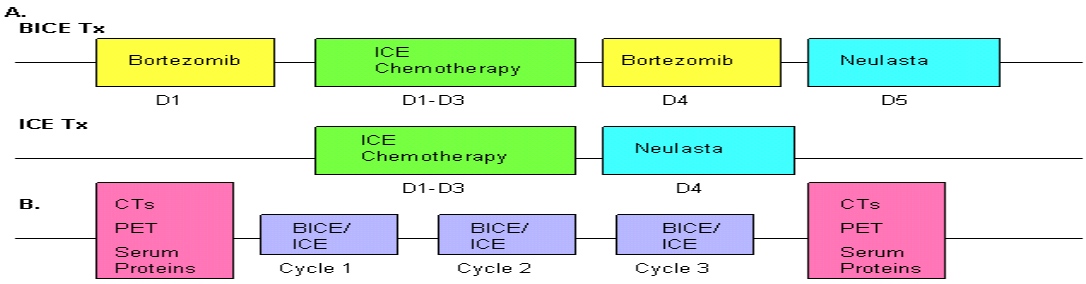

Figure 2A: BICE and ICE Treatment Schema BICE: Bortezomib will be given on Day 1 and 4 at a dose of 1.5 mg/m2 and ICE on Days 1 to 3 with Neulasta given on Day 5 (While Neulasta is preferred, appropriate equivalent doses of filgrastim can be used). ICE: ICE on Days 1 to 3 with Neulasta given on Day 4. Treatment will be repeated every 14 days if ANC > 1000 cells/mm3 and platelets ≥ 90,000 cells/mm3. Treatment may be delayed by 14 days to allow for adequate count recovery. Patients will undergo weekly blood work with CBC with diff, lytes, BUN/Cr, and LFTs. Figure 2B: Determination of Response Evaluation of ORR and CR will be performed according to IWG 1999 response criteria (Cheson et al., 1999) with PET scans assessed as a secondary endpoint. CT and PET scans will be performed prior at enrollment and 21 days after completion of cycle 3 of treatment. Serum protein levels will be assessed at enrollment and on day of repeat imaging after cycle 3.

A study flow chart is provided in section 0.

3.2 Selection of Patients

The maximum number of patients to be enrolled on this study is 50 (see section 5.1). Enrollment is defined as the first day of BICE versus ICE treatment (i.e., Day 1 of Cycle 1).

3.2.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1) Relapsed or refractory classical Hodgkin lymphoma
2) Patients must have received a front-line standard anthracycline-containing regimen, such as ABVD, Stanford V, or BEACOPP.
3) Bi-dimensionally measurable disease with at least 1 lesion ≥ 2.0 cm in a single dimension.
4) Patients must meet the following required baseline laboratory data: a) absolute neutrophil count (ANC) ≥ 1,500/μL, b) platelet count ≥ 100,000/ μL, c) hemoglobin ≥ 8 g/dL, d) serum bilirubin < 2.0 mg/dL, e) alkaline phosphatase < 2 x upper limits of normal (ULN), f) AST and ALT < 2 x ULN, g) serum creatinine ≤ 1.5 mg/dL.
5) Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 2 (see section 8.2).
6) Age ≥ 16 years.
7) Females of childbearing potential must have a negative serum beta-hCG pregnancy test and must agree to use 2 highly effective contraceptive methods (hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) during the study and for 3 months after completion of protocol treatment. Females of non-childbearing potential are those who are postmenopausal for greater than 1 year or whom have had a bilateral tubal ligation or hysterectomy.
8) Males who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 3 months after completion of protocol treatment.
9) Voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.

3.2.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1) Lymphocyte predominant Hodgkin lymphoma histology.
2) More than one prior chemotherapy regimen.
3) Prior autologous or allogeneic stem cell transplant.
4) Presence of CNS involvement with Hodgkin lymphoma.
5) Known HIV infection or AIDS.
6) Active Hepatitis B or C infection or history of cirrhosis.
7) Grade 2 or greater peripheral neuropathy within 14 days of enrollment.
8) Hypersensitivity to boron or mannitol.
9) Prior bortezomib therapy.

10) Another primary malignancy (other than squamous cell and basal cell carcinoma of the skin, in situ carcinoma of the cervix, or squamous intraepithelial lesion on PAP smear, or treated prostate cancer with a stable PSA) for which the patient has not been disease-free for at least 3 years.
11) Patients with congestive heart failure, Class III or IV (see section 8.4), by New York Heart Association (NYHA) criteria.
12) Patients with a myocardial infarction 6 months prior to enrollment, uncontrolled angina, severe uncontrolled ventricular arrthymias, or ECG evidence of acute ischemia or active conduction system abnormalities.
13) Patient with other medical or psychiatric illness that is likely to interfere with participation in this clinical study.
14) Female subject that is pregnant or breast-feeding.
15) Patient that has received other investigational drugs within 14 days of enrollment.
16) Patients using concurrent therapy with corticosteroids at greater than or equal to 20 mg/day of prednisone equivalent.
17) Patients with active systemic bacterial, viral, or fungal infections that have required IV antimicrobials within 4 weeks prior to protocol treatment.

3.3 Study Treatments

3.3.1 Clinical Trial Materials

VELCADE (bortezomib) for Injection is a sterile lyophilized powder for reconstitution and is supplied in vials containing VELCADE and mannitol at a 1:10 ratio. For example, vials containing 3.5 mg of VELCADE contain 35 mg of mannitol.

Ifosfamide, MESNA, Carboplatin, and Etoposide are packaged and prepared per UT MD Anderson Cancer Center pharmacy's standard operating procedures.

3.3.2 Preparation, Handling, and Storage of Drugs

Vials containing lyophilized VELCADE for Injection should be stored according to the label requirements. For the United States, store at USP Controlled Room Temperature which is 25ºC (77ºF); excursions permitted from 15 to 30ºC (59 to 86ºF). For Europe, do not store above 30ºC (86ºF). To date, stability data indicate that the lyophilized drug product is stable for at least 18 months when stored under the recommended conditions. Stability studies are ongoing, and Millennium Pharmaceuticals, Inc. will notify the investigator should this information be revised during the conduct of the study.

VELCADE is cytotoxic. As with all cytotoxic drugs, caution is required when preparing and handling VELCADE solutions. Cytotoxic drugs should only be handled by staff specially trained in the safe handling of such preparations. The use of gloves and other appropriate protective clothing is recommended. In case of skin contact, wash the affected area immediately

and thoroughly with soap and water for at least 15 minutes. If product contacts eye, immediately flush eye thoroughly with water for at least 15 minutes. Always contact a physician after any form of body contact. All materials that have been used for preparation should be disposed of according to standard practices. A log must be kept of all disposed materials.

Drug is available in sterile, single use vials containing 3.5 mg of VELCADE. Each vial of VELCADE for Injection should be reconstituted under a laminar flow biological cabinet (hood) within eight hours before dosing with 3.5 mL of normal (0.9%) saline, Sodium Chloride Injection USP, so that the reconstituted solution contains VELCADE at a concentration of 1 mg/mL. Prior to reconstitution the vials should remain in the cartons to protect them from light. Dissolution is completed in approximately 10 seconds. The reconstituted solution is clear and colorless, with a final pH of 5 to 6. Reconstituted VELCADE should be administered promptly and in no case more than 8 hours after reconstitution. All materials that have been used for preparation should be disposed of according to standard practices. A log must be kept of all disposed materials.

Ifosfamide, MESNA, Carboplatin, and Etoposide are prepared, handled, and stored per UT MD Anderson Cancer Center pharmacy's standard operating procedures.

3.3.3 Drug Administration and Dosage Schedule

Drug will be administered only to eligible patients under the supervision of the principal investigator or identified sub-investigator(s). Treatment will be delivered in the hospital under the supervision of the principal investigator or a sub-investigator. The pharmacist will prepare the drug under aseptic conditions. The amount (in mg) of drug to be administered will be determined based on body surface area. Body surface area is to be calculated based on body weight using a standard nomogram (see section 0). For patients with a calculated BSA of ≥ 2.1 m^2 use of adjusted body weight for drug dosing (see section 8.3) can be considered to calculate an adjusted BSA. The dose should be calculated on Day 1 of each cycle; the dose administered should remain the same throughout each cycle but should be recalculated at the start of the next cycle.

The appropriate amount of VELCADE will be drawn from the injection vial and administered as an intravenous (IV) push over 5 seconds followed by a standard saline flush or through a running IV line. Vials are for single use administration.

3.3.3a Arm A: BICE Treatment

Treatment will consist of bortezomib plus ICE (ifosfamide, carboplatin, etoposide) chemotherapy (BICE) (Table 3).

Table 3: Arm A Treatment with BICE

Day	Drug	Dose Level	Infusion Time
1 and 4 (+/- 2 days)	Bortezomib	1.5 mg/m^2	IV push (5 seconds)
1	Ifosfamide + MESNA	5 gm/m^2 + 5 gm/m^2	IV continuous infusion over 24 hrs
2	MESNA	2 gm/m^2	Start after completion of 24 hrs Ifosfamide and MESNA continuous 24 hour, IV continuous infusion over 12 hrs
1	Carboplatin	Target AUC = 5 mg/mL/min (Maximum dose of 800 mg)	IV over 1 hr
1 through 3	Etoposide	100 mg/m^2/day	IV over 2 hrs daily x 3 doses

3.3.3b Arm B: ICE Treatment

Treatment will consist of ICE (ifosfamide, carboplatin, etoposide) chemotherapy (Table 4).

Table 4: Arm B Treatment with ICE

Day	Drug	Dose Level	Infusion Time
1	Ifosfamide + MESNA	5 gm/m2 + 5 gm/m2	IV continuous infusion over 24 hrs
2	MESNA	2 gm/m2	IV continuous infusion over 12 hours to start after the completion of the 24 hour continuous infusion of Ifosfamide and Mesna
1	Carboplatin	Target AUC = 5 mg/mL/min (Maximum dose of 800 mg)	IV over 1 hr
1 through 3	Etoposide	100 mg/m2/day	IV over 2 hrs daily x 3 doses

3.3.4 Dose Modification and Delay

Before each drug dose, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 (see section 0).

Table 5 Management of Patients with VELCADE Related Peripheral Sensory or Motor Neuropathy at Retreatment

Recommended Dose Modification at Retreatment for VELCADE Related Peripheral Sensory or Motor Neuropathy	
Severity of Peripheral Neuropathy Signs and Symptoms	**Modification of Dose and Regimen**
Grade 1 (paresthesias, weakness and/or loss of reflexes) without loss of function)	*No action, continue VELCADE at 1.5 mg/m^2/dose
Grade 2 (interfering with function but not with activities of daily living)	*Reduce VELCADE dose to 1.3 mg/m^2/dose
Grade 3 (interfering with activities of daily living) or Grade 4 (Sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue treatment on clinical protocol
Grading based on NCI Common Terminology Criteria CTCAE v3.0 NCI Common Terminology Criteria website - http://ctep.info.nih.gov/reporting/ctc.html	

ADL = activities of daily living

Note: If the VELCADE dose has been reduced to 1.3 mg/m^2/dose during prior cycle secondary to these dose reduction guidelines then if patient has grade 2 or less peripheral neuropathy at retreatment the dose level should remain at 1.3 mg/m^2/dose

The neurotoxicity-directed questionnaire (see section 8.7) is an optional but useful tool for determining the presence and intensity of peripheral neuropathy from the patient's perspective. Neuropathic symptoms are more prominent than abnormalities on the clinical examination.

3.3.4a Cycles of treatment and retreatment criteria

Patients will be eligible for retreatment every 14 days if below criteria are met:

1) Laboratory criteria: a) absolute neutrophil count (ANC) ≥ 1,000/μL, b) platelet count ≥ 90,000/ μL, c) serum bilirubin < 2.0 mg/dL, e) alkaline phosphatase < 2 x upper limits of normal (ULN), f) AST and ALT < 2 x ULN, and g) serum creatinine ≤ 1.5 mg/dL.

2) Clinical criteria: a) peripheral neuropathy of grade 2 or less, b) lack of a grade 3 or 4 non-hematologic, non-nephrologic, or non-hepatic toxicity that cannot be controlled by supportive care.

Retreatment may be delayed a maximum of 14 days to allow for above criteria to be met.

3.3.4b Dose modification/toxicity management

A number of measures will be taken to ensure the safety of patients participating in this clinical treatment protocol. In the phase I (MDACC 2006-0527) no hematologic or non-hematologic dose limiting toxicities (DLT) were noted for bortezomib given at the maximum dose of 1.5 mg/m2 on Days 1 and 4 in combination with standard ICE chemotherapy (see section 1.3.2c and Fanale et al., 2008).These include the patient eligibility criteria (see section 3.2) and scheduled monitoring. Patients enrolled in this study will be evaluated clinically with standard laboratory tests before and during their participation in this study (see section 3.1). Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

1) Bortezomib: In the phase I (MDACC 2006-0527) no hematologic or non-hematologic dose limiting toxicities (DLT) were noted for bortezomib given at the maximum dose of 1.5 mg/m^2 on Days 1 and 4 chemotherapy (see section 1.3.2c and Fanale et al., 2008). Any patient who experiences a Common Terminology Criteria for Adverse Events v3.0 (CTAE) of a grade 3 peripheral neuropathy that does not resolve to grade 2 peripheral neuropathy by time of retreatment, grade 4 peripheral neuropathy, or a grade 3 to 4 non-hematologic toxicity that is attributed to bortezomib will be removed from the study. For patients who have grade 2 peripheral neuropathy at retreatment dose should be reduced to bortezomib 1.3 mg/m^2 (see Table 5). Patients will need to meet laboratory criteria for retreatment (see section 3.3.4a). Patients who experience a grade 4 thrombocytopenia or neutropenia for greater than 2 weeks will be removed from the study.

2) Ifosfamide, MESNA, Carboplatin, and Etoposide: Patients will need to meet laboratory and clinical criteria for initial treatment and retreatment (see section 3.3.4a). Dose adjustments can be considered based on judgment of clinician but laboratory criteria for initial treatment and retreatment should be met.

3.3.5 Treatment Assignment

Patients will be assigned to treatment arms A (BICE) and B (ICE) following the adaptive Bayesian statistical design (see section 3.6.1).

3.3.6 Packaging and Labeling

VELCADE will be supplied in vials as open-label stock. Both the box label and vial label will fulfill all requirements specified by governing regulations.

Ifosfamide, MESNA, Carboplatin, and Etoposide will be supplied via the UT MD Anderson Cancer Center pharmacy through standard operating procedures which fulfill all requirements as specified by governing regulations.

3.3.7 Concomitant Treatment

Required Concurrent Therapy

The following medications/supportive therapies are required during study participation, as applicable:

1) Patients will receive Neulasta 6 mg subcutaneously 24 hours after completion of chemotherapy. While Neulasta is preferred, appropriate equivalent doses of filgrastim can be used.
2) In addition, standard prophylactic antimicrobials or appropriate equivalent will be given with: a) ciprofloxacin 500 mg po bid, b) fluconazole 100 mg po daily, c) valcyclovir 500 mg po daily; all starting on day 5 for 10 days.
3) The use of erythropoietin is allowed per standard ASCO/ASH guidelines.

Prohibited Concurrent Therapy

1) Any investigational agent other than VELCADE.

3.3.8 Treatment Compliance

All drug will be administered to eligible patients under the supervision of the investigator or identified sub-investigator(s). The pharmacist will maintain records of drug receipt (if applicable), drug preparation, and dispensing, including the applicable lot numbers, patients' height, body weight, and body surface area (see section 0), and total drug administered in milliliters and milligrams. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.

3.4 Duration of Treatment and Patient Participation

3.4.1 Duration of Treatment

1) Autologous stem cell transplant candidates: Patients will receive a minimum of 3 cycles of BICE or ICE and a maximum of 6 cycles. Stem cell collection may be performed after cycle 3 or 4 of BICE or ICE.

2) Non-transplant candidates: Patients can receive up to a maximum of 6 cycles of BICE or ICE if tolerated.

3.4.2 Follow-up Evaluations

1) Patients who are eligible for autologous stem cell transplant will proceed on to this therapeutic intervention.

2) All patients will undergo follow-up evaluations every 4 months for 2 years with: Physical exam, laboratory analysis with CBC with differential, lytes, BUN, creatinine, AST, ALT, alkaline phosphatase, and bilirubin, and repeat imaging with chest x-ray and

CT scans of neck, chest, abdomen and pelvis.

3.5 Termination of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Intercurrent illness
- Occurrence of an unacceptable adverse event
- A treatment cycle delay or VELCADE interruption of >2 weeks or missing three of four VELCADE doses within a treatment cycle because of toxicity
- Patient request
- Protocol violations
- Non-compliance
- Administrative reasons
- Failure to return for follow-up
- General or specific changes in the patient's condition unacceptable for further treatment in the judgment of the investigator
- Progressive disease at any time

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for a patient's withdrawal from the study is to be recorded in the source documents.

3.6 Efficacy, Correlative studies, and Safety Measurements

3.6.1 Efficacy Measurements

Response rates for BICE and ICE treatment groups will be assessed by 1999 IWG (CT alone) (Cheson et al., 1999) (Table 6) and compared to 2007 IWG (CT plus PET) (Cheson et al., 2007) (Table 7) criteria.

Table 6: 1999 IWG Response Criteria

Response Category	Physical Examination	Lymph Nodes/ Masses	Bone Marrow
Complete Remission (CR)	Normal	Normal	Normal
Partial Remission (PR)	Normal	Normal	Positive
	Normal	≥ 50% Decrease	Irrelevant

	Decreasing Liver/ Spleen	≥ 50% Decrease	Irrelevant
Stable Disease (SD)	Less than a PR but not Relapse/ Progressive Disease		
Relapse/ Progressive Disease (PD)	Enlarging Liver/ Spleen; New Sites	New or Increased	Reappearance

Table 7: 2007 IWG Response Criteria

Response Category	Definition	Nodal Masses	Spleen; Liver	Bone Marrow
CR	Disappearance of all evidence of disease	a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology IHC should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in sum of the product of diameters (SPD) of up to the 6 largest dominant masses; no increase in size of other nodes a) FDG-avid or PET positive prior to therapy; one of more PET positive at previously involved site b) Variably FDG-avid or PET negative, regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of		

		disease and no new sites on CT or PET b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	a) Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis b) Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

3.6.2 Correlative Studies (optional)

For patients who consent for optional procedure blood for serum evaluations of TNF (APRIL, BLyS, sCD30, CD40L) and TARC proteins will be collected within 3 days of cycle 1 of BICE or ICE treatment and after 3 cycles of BICE or ICE treatment at 21 days (+/- 7 days).

3.6.3 Safety Measurements

Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

4 ADVERSE EVENTS

4.1 Definitions

4.1.1 Adverse Event Definition

An **adverse event** (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (eg, including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug, whether or not it is considered to be drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

4.1.2 Serious Adverse Event Definition

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 inpatient **hospitalization or prolongation of existing hospitalization**. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (eg, surgery performed earlier than planned).
- Results in **persistent or significant disability/incapacity**. Disability is defined as a substantial disruption of a persons' ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an **important medical event**. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. 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.

Clarification should be made between the terms "serious" and "severe" since they ARE NOT synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as "serious," which is based on patient/event outcome or action criteria described above and are usually associated with events that pose a threat to a patient's life or functioning. A severe adverse event does not necessarily need to be considered serious. For example, persistent nausea

of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

4.2 Procedures for AE and SAE Reporting

Investigator-sponsor must report all (SAE) regardless of relationship with any study drug or expectedness to Millennium Pharmacovigilance (or designee) as soon as possible, but no later than 5 calendar days of the investigator-sponsor's observation or awareness of the event. All sub-investigators must report all SAEs to the investigator-sponsor so that the investigator-sponsor can meet his/her foregoing reporting obligations to Millennium Pharmacovigilance.

Investigator-sponsor must also provide Millennium Pharmacovigilance with a copy of all communications related to the Study or Drug with the applicable regulatory authority, including, but not limited to, telephone conversation logs, as soon as possible but no later than 5 calendar days of that communication.

Millennium Pharmacovigilance will send to the investigator-sponsor a monthly listing of the SAE reports received for SAE verification. Investigator-sponsor will be responsible for forwarding such reports to any sub-investigator(s) and providing any follow-up safety information requested by Millennium Pharmacovigilance.

SAE Reporting Contact Information
PPD, Inc.
Safety and Medical Management
Fax: +1 (888) 488-9697
Hotline number (24/7): +1 (800) 201-8725

For both serious and non-serious adverse events, the investigator or sub-investigator must determine both the intensity of the event and the relationship of the event to drug administration.

Relationship to drug administration will be determined by the investigator or sub-investigator responding yes or no to the question: Is there a reasonable possibility that the adverse event is associated with the drug?

Intensity for each adverse event, including any lab abnormality, will be determined by using the NCI CTCAE, version 3.0, as a guideline, wherever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

4.3 Monitoring of Adverse Events and Period of Observation

Adverse events, both serious and non-serious, and deaths that occur during the patient's study participation will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

4.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects she is pregnant while participating in this study, she must inform her treating physician immediately and permanently discontinue drug therapy. All pregnancies and suspected pregnancies must also be reported to Millennium Pharmacovigilance (or designee, see section 4.2) immediately. The pregnancy must be followed through outcome (i.e. delivery, still birth, miscarriage).

If a female partner of a male subject becomes pregnant during the male subject's participation in this study, Millennium Pharmacovigilance must be contacted immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

5 STATISTICAL PROCEDURES

5.1 Bayesian Adaptive Algorithm

The phase II part of this study is to compare ICE only and BICE in treating patients with classical Hodgkin lymphoma. The primary outcome is complete remission. The estimated accrual rate is 2 or 4 patients per month. A maximum of 50 patients will be accrued. Patients will be evaluated for response after 0.75 months after receiving treatment for 3 cycles (21 days per cycle). The patients will be randomized between ICE and BICE arms using a Bayesian adaptive algorithm (Berry and Eick,, 1995). In general, the trial will proceed as follows: The initial 20 patients will be randomized fairly with probability of 0.50 each between the two arms, so that the number of patients in each arm is equal at the start of the trial. Thereafter, as the trial proceeds patients will be randomized to the two groups with unequal probabilities in favor of the treatment that, on average, yields better response rate. Consequently, each successive patient is more likely to receive the treatment with a better response rate, on average. The details of the adaptive randomization scheme are as follows:

Denote the response rate at each of the two treatment arms by $\{\pi_1, \pi_2\}$ (1 for ICE, 2 for BICE). Based on the currently available data, we assume the prior distribution for the response rate is $\pi_1 \sim$ Beta (0.5, 0.5) and $\pi_2 \sim$ Beta (0.6, 0.4), respectively. The resulting prior mean (95% credible interval) for ICE and BICE are 0.5(0.002, 0.99) and 0.6(0.007, 0.99), respective
ely. After the initial first 20 patients being randomized to two treatment groups with an equal probability, each new patient will be randomized to receive treatment i with probability $\rho_i = \text{prob}(\pi_i > \pi_j, j \neq i | \text{ Data})$, i, j=1,2. If one of these two randomization probabilities falls below 0.025 then that arm will be dropped. In addition, if $\text{prob}(\pi_i > 0.25|\text{data}) < 0.05$, i.e. the data indicates that the response rate in that arm is highly unlikely to be larger than 0.25, then that arm will be dropped. On the other hand, if one of the two randomization probabilities exceeds 0.975 then the trial will be terminated and that treatment arm will be selected. If the trial does not stop early and the maximum 50 patients are accrued, a treatment is selected as being "better" if the probability that one treatment's response rate is larger than the other's response rate exceeds 0.95.
Table 8 below summarizes operating characteristics of the design based on an accrual of 50 patients, and shows the results when the number of patients accrued per month are 2. The number of patients treated (and evaluated) row is the average number of patients treated on a given arm under the given scenario. The calculations were done from 1,000 simulations.

Table 8: Operating Characteristics for the Adaptive Randomization When 2 Patients Are Accrued Per Month

	Treatment Arms	
	ICE	**BICE**
True Prob(Complete Remission)	0.2	0.3
Average # Patients Treated	13.4 (2, 33)	16.5 (1, 37)
Pr(Selected)	0.058	0.375
Pr(Selected Early)	0.009	0.08
Pr(Dropped Early)	0.491	0.098
Average Trial Length (months)	14.9	

The trial will be conducted using a website developed in the Division of Quantitative Sciences at UT MD Anderson Cancer Center. Through the web interface, which is ideal for a multicenter trial, the users can randomize patients and update last evaluation date and current patient status. When a patient is randomized, the calculations are based on all available data entered into the website. The results of the randomization are displayed to the screen for the user to view. All data will be stored in a secure SQL server database. In addition, safety monitoring will also be performed in conjunction with the MDACC Data Safety Monitoring Board (DSMB).

5.2 Efficacy Analysis

In addition, response rates based on 1999 IWG (Cheson et al., 1999) versus 2007 IWG (Cheson et al., 2007) criteria will also be summarized for each treatment group (see section 3.6.1). Response rate improvement by PET scan assessment will also be described for patients with PR based on IWG 1999 criteria but who by IWG 2007 criteria are found to be in CR because of PET scan negativity in residual masses.

5.3 Correlative TNF and TARC Serum Protein Level Analysis

Furthermore, serum levels of TNF proteins (APRIL, BLyS, sCD30, and CD40L) and TARC as determined at baseline compared to post-treatment with will be analyzed for both the BICE and ICE treatment groups by Mann-Whitney U test. Second, serum levels for each protein as determined at baseline compared to post-treatment will be analyzed for both the BICE and ICE treatment groups according to response rates as determined by IWG 1999 response criteria (CR, PR, SD, versus PD) by the Kruskal-Wallis test. Third, serum levels for each protein as determined at baseline compared to post-treatment will be analyzed for both the BICE and ICE treatment groups according to PET scan results (PET negative versus PET positive) at completion of therapy by the Kruskal-Wallis test. Significance will be set for $p \leq 0.05$.

6 ADMINISTRATIVE REQUIREMENTS

6.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

6.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (see section 8.5). The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator. Millennium requests that informed consent documents be reviewed by Millennium or designee prior to IRB/IEC submission.

6.3 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

6.4 Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from Millennium or its designees and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

6.5 Protocol Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Millennium and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited

review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to Millennium and the regulatory authority(ies) in accordance with the governing regulations.
Any departures from the protocol must be fully documented in the source documents.

6.6 On-site Audits

Regulatory authorities, the IEC/IRB and/or Millennium's clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

6.7 Drug Accountability

Accountability for the drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at the site (if applicable), use by each patient, and return to Millennium or disposal of the drug (if applicable and if approved by Millennium) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

All material containing VELCADE will be treated and disposed of as hazardous waste in accordance with governing regulations.

6.8 Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the investigator or Millennium, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Millennium by the terminating party. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug

Should the study be closed prematurely, all study materials must be returned to Millennium.

6.9 Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

7 REFERENCES

Abali H, Urun Y, Oksuzoglu B, et al. Comparison of ICE (ifosfamide-carboplatin-etoposide) versus DHAP (cytosine arabinoside-cisplatin-dexamethasone) as salvage chemotherapy in patients with relapsed or refractory lymphoma. Cancer Invest. 2008;26:401-406.

Adams J, Palombella VJ, Sausville EA, Johnson J, Destree A, Lazarus DD et al. Proteasome inhibitors: a novel class of potent and effective antitumor agents. Cancer Res 1999; 59 (11):2615-22.

Annunziata C, Davis R, Demchenko Y, et al. Frequent engagement of the classical and alternative NF-kappaB pathways by diverse genetic abnormalities in multiple myeloma. Cancer Cell. 2007;12:115-130.

Ansell SM, Horwitz SM, Engert A, et al. Phase I/II Study of an Anti-CD30 Monoclonal Antibody (MDX-060) in Hodgkin's Lymphoma and Anaplastic Large-Cell Lymphoma 10.1200/JCO.2006.07.8972. J Clin Oncol. 2007;25:2764-2769.

Bartlett NL, Younes A, Carabasi MH, et al. A phase 1 multidose study of SGN-30 immunotherapy in patients with refractory or recurrent CD30+ hematologic malignancies. Blood. 2008;111:1848-1854.

Berry, DA and Eick, SG. Adaptive assignment versus balanced randomization in clinical trials: A decision analysis. Statistics in Medicine. 1995.14:231-246.

Blade J, Samson D, Reece D, Apperley J, Bjorkstrand B, Gahrton G et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol 1998; 102 (5):1115-23.

Blum KA, Johnson JL, Niedzwiecki D, Cannellos GP, Cheson BD, Bartlett NL. A phase II study of bortezomib in relapsed Hodgkin lymphoma: Preliminary results of CALGB 50206. J Clin Oncol (Meeting Abstracts). 2006;24:7576-.

Bossen C, Schneider P. BAFF, APRIL and their receptors: structure, function and signaling. Semin Immunol. 2006;18:263-275.

Cheson BD, Horning SJ, Coiffier B, et al. Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas. J Clin Oncol. 1999;17:1244-

Cheson BD, Pfistner B, Juweid ME, et al. Revised Response Criteria for Malignant Lymphoma. J Clin Oncol. 2007;25:579-586.

Cusack JC, Jr., Liu R, Houston M, Abendroth K, Elliott PJ, Adams J et al. Enhanced chemosensitivity to CPT-11 with proteasome inhibitor PS-341: implications for systemic nuclear factor-kappaB inhibition. Cancer Res 2001; 61 (9):3535-40.

Davies AM, Lara PN, Lau DH, et al. The proteasome inhibitor, bortezomib, in combination with gemcitabine (Gem) and carboplatin (Carbo) in advanced non-small cell lung cancer (NSCLC): Final results of a phase I California Cancer Consortium study. ASCO Meeting Abstracts. 2004;22:7106-.

Endo T, Nishio M, Enzler T, et al. BAFF and APRIL support chronic lymphocytic leukemia B-cell survival through activation of the canonical NF-{kappa}B pathway. Blood. 2007;109:703-710.

Fanale MA, Fayad LE, Pro B, et al. A Phase I Study of Bortezomib in Combination with ICE (BICE) in Patients with Relapsed/Refractory Classical Hodgkin Lymphoma. ASH Annual Meeting Abstracts. 2008;112:3048-.

Fanucchi MP, Fossella FV, Belt R, et al. Randomized phase II study of bortezomib alone and bortezomib in combination with docetaxel in previously treated advanced non-small-cell lung cancer. J Clin Oncol. 2006;24:5025-5033.

Filmont JE, Gisselbrecht C, Cuenca X, et al. The impact of pre- and post-transplantation positron emission tomography using 18-fluorodeoxyglucose on poor-prognosis lymphoma patients undergoing autologous stem cell transplantation. Cancer. 2007;110:1361-1369.

Forero-Torres A, Furman RR, Rosenblatt JD, et al. A humanized antibody against CD40 (SGN-40) is well tolerated and active in non-Hodgkin's lymphoma (NHL): Results of a phase I study. J Clin Oncol (Meeting Abstracts). 2006;24:7534-.

Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000; 18 (12):2354-62.

Fossella F. Docetaxel + Cisplatin (DC) and Docetaxel + Carboplatin (DCb) vs Vinorelbine + Cisplatin (VC) in chemotherapy-naïve patients with advanced and metastatic non-small cell lung cancer (NSCLC): Results of a multicenter, randomized phase III study. European Journal of Cancer, European Cancer Conference, ECCO 11, 2001; Lisbon, Portugal. 37(suppl 6):S154. Abstract 562

Gallamini A, Hutchings M, Rigacci L, et al. Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. J Clin Oncol. 2007;25:3746-3752.

Hamblett KJ, Barton J, Cerveny CG, et al. SGN-35, an Anti-CD30 Antibody-Drug Conjugate, Exhibits Potent Antitumor Activity for the Treatment of CD30+ Malignancies. ASH Annual Meeting Abstracts. 2005;106:610-.

Heeschen C, Dimmeler S, Hamm CW, et al. Soluble CD40 Ligand in Acute Coronary Syndromes. N Engl J Med. 2003;348:1104-1111.

Hideshima T, Richardson P, Chauhan D, Palombella VJ, Elliott PJ, Adams J et al. The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. Cancer Res 2001; 61 (7):3071-6.

Hsu SJ, Esposito LA, Aukerman SL, Kantak S, Mirza AM. HCD122, an Antagonist Human Anti-CD40 Monoclonal Antibody, Inhibits Tumor Growth in Xenograft Models of Human Diffuse Large B-Cell Lymphoma, a Subset of Non-Hodgkins Lymphoma. ASH Annual Meeting Abstracts. 2006;108:2519-.

Hutchings M, Loft A, Hansen M, et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. Blood. 2006;107:52-59.

Jagannath S, Barlogie B, Berenson J et al. A Phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. Br J Haematol 2004: 127:165-172

Josting A, Franklin J, May M, et al. New Prognostic Score Based on Treatment Outcome of Patients With Relapsed Hodgkin's Lymphoma Registered in the Database of the German Hodgkin's Lymphoma Study Group. J Clin Oncol. 2002;20:221-230.

LeBlanc R, Catley LP, Hideshima T, Lentzsch S, Mitsiades CS, Mitsiades N et al. Proteasome inhibitor PS-341 inhibits human myeloma cell growth in vivo and prolongs survival in a murine model. Cancer Res 2002; 62 (17):4996-5000.

Lightcap ES, McCormack TA, Pien CS, Chau V, Adams J, Elliott PJ. Proteasome inhibition measurements: clinical application. Clin Chem 2000; 46 (5):673-83.

McConkey DJ, Pettaway C, Elliott P, Adam J, Papandreou C, Herrmann JL et al. The proteasome as a new drug target in metastatic prostate cancer. 7th Annual Genitourinary Oncology Conference, 1999; Houston, TX. Abstract

Moskowitz CH, Nimer SD, Zelenetz AD, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. Blood. 2001;97:616-623.

Nadali G, Tavecchia L, Zanolin E, et al. Serum Level of the Soluble Form of the CD30 Molecule Identifies Patients With Hodgkin's Disease at High Risk of Unfavorable Outcome. Blood. 1998;91:3011-3016.

Novak AJ, Grote DM, Stenson M, et al. Expression of BLyS and its receptors in B-cell non-Hodgkin lymphoma: correlation with disease activity and patient outcome 10.1182/blood-2004-02-0762. Blood. 2004;104:2247-2253.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

Oki Y, Georgakis GV, Migone T-S, Kwak LW, Younes A. Prognostic significance of serum B-lymphocyte stimulator level in Hodgkin's lymphoma. Haematologica. 2007;92:269-270.

Orlowski RZ, Stinchcombe TE, Mitchell BS, Shea TC, Baldwin AS, Stahl S et al. Phase I Trial of the Proteasome Inhibitor PS-341 in Patients with Refractory Hematologic Malignancies. J Clin Oncol 2002; 20 (22):4420-7.

Palumbo A, Ambrosini MT, Benevolo G, et al. Bortezomib, melphalan, prednisone, and thalidomide for relapsed multiple myeloma. Blood. 2007;109:2767-2772.

Papandreou C, Daliani D, Millikan RE, Tu S, Pagliaro L, Adam J. Phase I Study of Intravenous (I.V.) Proteasome Inhibitor PS-341 in Patients (Pts) with Advanced Malignancies. Proc Am Soc Clin Oncol, 2001. Abstract 340

Pink MM, Pien CS, Ona VO, Worland P, Adams J, Kauffman MG. PS-341 enhances chemotherapeutic effect in human xenograft models. Proc Am Assoc Cancer Res, 2002; San Francisco, CA. Abstract 787

Richardson PG, Barlogie B, Berenson J et al. A Phase II study of Bortezomib in Relapsed, Refractory Myeloma. N Engl J Med 2003; 348:2609-2617

Richardson PG, et al., Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma. N Engl J Med 2005; 352:2487-98.

Richardson et al, Bortezomib Continues to Demonstrate Superior Efficacy Compared With High-Dose Dexamethasone in Relapsed Multiple Myeloma: Updated Results of the APEX Trial. Blood, 2005; 106: Abstract 2547.

San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus Melphalan and Prednisone for Initial Treatment of Multiple Myeloma. N Engl J Med. 2008;359:906-917.

Schot BW, Zijlstra JM, Sluiter WJ, et al. Early FDG-PET assessment in combination with clinical risk scores determines prognosis in recurring lymphoma. Blood. 2007;109:486-491.

Seam P, Juweid ME, Cheson BD. The role of FDG-PET scans in patients with lymphoma. Blood. 2007;110:3507-3516.

Steiner P, Neumeier H, Lightcap E, Sadis S, Pien C, Pink M et al. Adaptation of Human Tumor Cell Lines to PS-341. AACR-NCI-EORTC International Conference, 2001; Miami Beach, FL. Millennium Pharmaceuticals, Inc., 75 Sidney Street, Cambridge, MA 02139. Abstract

Strauss SJ, Maharaj L, Hoare S, et al. Bortezomib Therapy in Patients With Relapsed or Refractory Lymphoma: Potential Correlation of In Vitro Sensitivity and Tumor Necrosis Factor Alpha Response With Clinical Activity. J Clin Oncol. 2006;24:2105-2112.

Svoboda J, Andreadis C, Elstrom R, et al. Prognostic value of FDG-PET scan imaging in lymphoma patients undergoing autologous stem cell transplantation. Bone Marrow Transplant. 2006;38:211-216.

Teicher BA, Ara G, Herbst R, Palombella VJ, Adams J. The proteasome inhibitor PS-341 in cancer therapy. Clin Cancer Res 1999; 5 (9):2638-45.

Trelle S, Sezer O, Naumann R, et al. Bortezomib Is Not Active in Patients with Relapsed Hodgkin's Lymphoma: Results of a Prematurely Closed Phase II Study. ASH Annual Meeting Abstracts. 2006;108:2477-.

VELCADE (bortezomib) [package insert]. Cambridge, MA: Millennium Pharmaceuticals, Inc.; 2003.

Wedgwood AR, Fanale MA, Fayad LE, et al. Rituximab + ABVD Improves Event-Free Survival (EFS) in Patients with Classical Hodgkin Lymphoma in All International Prognostic Score (IPS) Groups and in Patients Who Have PET Positive Disease after 2 3 Cycles of Therapy. ASH Annual Meeting Abstracts. 2007;110:215-.

Weihrauch MR, Manzke O, Beyer M, et al. Elevated Serum Levels of CC Thymus and Activation-Related Chemokine (TARC) in Primary Hodgkin's Disease: Potential for a Prognostic Factor. Cancer Res. 2005;65:5516-5519.

Yazbeck V, Georgakis GV, Wedgwood A, Younes A. Hodgkin's lymphoma: molecular targets and novel treatment strategies. Future Oncol. 2006;2:533-551.

Younes A, Consoli U, Snell V, et al. CD30 ligand in lymphoma patients with CD30+ tumors. J Clin Oncol. 1997;15:3355-3362.

Younes A, Pro B, Fayad L. Experience with bortezomib for the treatment of patients with relapsed classical Hodgkin lymphoma. Blood. 2006;107:1731-1732.

Younes A, Pro B, Fanale M, et al. Isotype-Selective HDAC Inhibitor MGCD0103 Decreases Serum TARC Concentrations and Produces Clinical Responses in Heavily Pretreated Patients with Relapsed Classical Hodgkin Lymphoma (HL). ASH Annual Meeting Abstracts. 2007;110:2566-.

Zheng B, Georgakis GV, Li Y, et al. Induction of Cell Cycle Arrest and Apoptosis by the Proteasome Inhibitor PS-341 in Hodgkin Disease Cell Lines Is Independent of Inhibitor of Nuclear Factor-{kappa}B Mutations or Activation of the CD30, CD40, and RANK Receptors. Clin Cancer Res. 2004;10:3207-3215.

8 APPENDICES

8.1 Study Flow Chart

Assessment	Screening	Screening	Pre-treatment	Cycle 1	Inter-cycle	Pre-treatment	Cycle 2	Inter-cycle	Pre-treatment	Cycle 3	Inter-cycle	End of Treatment (EOT)	Follow-up
	Within 61 days to Day 1	Within 28 days to Day 1	Within 3 Days to Day 1 of Cycle 1	Day 1 to Day 5	Weekly	Within 3 Days to Day 1 of Cycle 2	Day 1 to Day 5	Weekly	Within 3 Days to Day 1 of Cycle 3	Day 1 to Day 5	Weekly	Within 21 days (+/- 7 days) from start of Cycle 3 or Early Termination	Every 4 months for 2 years
Physical Exam		X	X			X			X			X	X
ECOG PS		X											
Baseline Grade of Peripheral Neuropathy		X											
Review Medical History		X	X										
Record Meds		X	X			X			X			X	
CBC + diff		X	X	X[c]	X	X	X[c]	X	X	X[c]	X	X	X
Lytes		X	X	X[c]	X	X	X[c]	X	X	X[c]	X	X	X

BUN/Cr, LFTs		X	X	X[c]		X	X[c]		X	X[c]		X	X
Hep B/C & HIV serologies		X											
CXR & CT scans		X	X									X	X
PET/CT	X											X	
BmBx		X										X[e]	
Echo		X											
B-HCG		X[a]											
Informed Consent	X		X										
Optional serum collection			X[b]									X[b]	
ICE or BICE chemo					X[d]			X[d]			X[d]		
Neulasta				X[d]			X[d]			X[d]			
Review Adverse Events				X		X	X		X	X		X	X

[a] Beta-hCG serum test will be done for women of childbearing potential (see section 3.2).

[b] For patients who sign an optional consent blood will be collected for serum evaluations of TNF proteins (APRIL, BLyS, sCD30, and CD40L) and CC thymus and activation-related cytokine (TARC).

[c] CBC with differential, Lytes, BUN, creatinine, AST, ALT, alkaline phosphatase, and bilirubin will be assessed on each day of BICE (Days 1 through 4) or ICE (Days 1 through 3) administration.

[d] ICE chemotherapy will be given on Days 1 through 3 with Neulasta given on Day 4 and BICE will be given on Days 1 through 4 with Neulasta on Day 5 (see section 3.3.3).

e If the doctor thinks it is needed, the patient will have a bone marrow biopsy to check the status of the disease at screening. On Day 21 (+/- 7 days) of Cycle 3, the patient will have a bone marrow biopsy to check the status of the disease.

8.2 ECOG Performance Status Scale

The following table presents the ECOG performance status scale (Oken et al., 1982):

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

8.3 Body Surface Area and Creatinine Clearance Calculations

Body surface area (BSA) should be calculated using a standard nomogram that yields the following results in meters squared (m^2):

Body Surface Area:

$$BSA(m^2): \ ((ht(cm) * wt(kg)) / 3600)^{1/2}$$

Ideal Body Weight For Drug Dosing:

Males(kg): 50 + 2.3*(ht(in)-(60 in))

Females(kg): 45.5 + 2.3*(ht(in)-(60 in))

Adjusted Body Weight For Drug Dosing:

ABW(kg): IBW(kg) + 0.4*(wt(kg)-IBW(kg))

Creatinine clearance (CrCl) can be calculated using the Cockroft-Gault equation as follows:

$$CrCl \ (ml/min) = \frac{(140\text{-age}) \ (\text{actual wt in kg})}{72 \times \text{serum creatinine (mg/dl)}}$$

For females use 85% of calculated CrCl value.

Note: In markedly obese patients, the Cockroft-Gault formula will tend to overestimate the creatinine clearance. (Adipose tissue tends to contribute little creatinine requiring renal clearance.)

8.4 New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

8.5 Declaration of Helsinki

World Medical Association Declaration of Helsinki:

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for

those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

8. Physicians should abstain from engaging in research projects involving human subjects

unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

11. The subjects must be volunteers and informed participants in the research project.

12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The

specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

8.6 Common Terminology Criteria for Adverse Events Version 3.0

http://ctep.cancer.gov/reporting/ctc.html

8.7 FACT/GOG-Neurotoxicity Questionnaire, Version 4.0

FACT/GOG-Neurotoxicity Questionnaire, Version 4.0

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

Sources: Cella DF, Tulsky DS, Gray G, Sarafian B, Lloyd S, Linn E, et al. The functional assessment of cancer therapy (FACT) scale: development and validation of the general measure. *J Clin Oncol* 1993;11(3):570-79.

8.8 Outside Physician Participation During Treatment

1	MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record
2	A letter to the local physician will outline the patient's participation in the clinical trial and will request local physician agreement to supervise the patient's care
3	Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.
4	Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.
5	A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.
6	Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.
7	The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.
8	Patients will return to MDACC after 3 cycles for evaluation.
9	Patients randomized to the ICE alone treatment group will be allowed to receive ICE with their local MD or at MDACC. For those randomized to the BICE group, they will be receive BICE at MDACC.