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Protocol Page

Bortezomib (Velcade®) and Reduced-Intensity Allogeneic Stem Cell Transplantation for Patients with Lymphoid Malignancies
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Core Protocol Information

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- (●) The Clinical Research Committee - (CRC)

Protocol Body

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Abbreviation	Definition
C	degrees Celsius
M	micromolar
20S	20S proteasome subunit
AE	adverse event
ANC	absolute neutrophil count
ANLL	Acute non-lymphocytic leukemia
AUC	Area under the curve
Bc1-2	B-cell lymphoma-2; a gene that inhibits apoptosis
BCNU	Carmustine
BEAM	BCNU, Etoposide, Cytarabine, Melphalan
BSA	body surface area
BUN	Blood, urea, nitrogen
CAM	cell adhesion molecules
CBC	Complete blood count
cc	Cubic centimeter
cGVHD	Chronic graft-versus-host disease
cm	centimeter
CNS	Central nervous system

CR	Complete Response
CRC	Clinical review committee
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CV	cardiovascular
CXR	Chest x-ray
DFS	Disease free survival
DLCL	Diffuse Large Cell Lymphoma
DLCO	Diffuse Lung Capacity for Carbon Monoxide
dL	deciliter
DLI	Donor lymphocyte infusion
DLT	Dose Limiting Toxicity
DNA	deoxyribonucleic acid
EBMT	European Group for Blood and Marrow Transplant
EF	Ejection fraction
E-max	Maximum effect
FCR	Fludarabine, Cyclophosphamide, rituximab
FDA	Food and Drug Administration
FL	Follicular Lymphoma
FEV1	Forced Expiratory Volume in the first second
FISH	Fluorescence in situ hybridization
FVC	Forced Expiratory Vital Capacity
GCP	Good Clinical Practice
GF	Graft Failure
GI	gastrointestinal
GLP	Good Laboratory Practice
GVHD	Graft versus host disease

GVL	graft-versus-lymphoma
Hg	mercury
HIV	Human immunodeficiency virus
hr	hour
HTLV-I	Human T-cell lymphotrophic virus - I
ht	height
IB	I kappa B kinase; cytokine response kinase that activates 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
IRB	Institutional Review Board
IV	intravenous
IVPB	Intravenous piggyback
I·B·	I kappa B alpha-associated protein kinase
kg	kilogram
Ki	inhibitory constant
lbs	pounds
m2	square meters
mg	milligram
MCL	Mantle Cell Lymphoma
min	minute
mL	milliliter
mm	millimeter
mm3	cubic millimeters
mmol	millimole

MR	Minor response
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NF-B	nuclear factor-B
NHL	Non-Hodgkin's Lymphoma
ng	nanogram
nM	nanomole
NS	Normal saline
NST	Non-myeloablative allogeneic stem cell transplantation
OS	Overall survival
p21	p21(ras) farnesyl-protein transferase
p27	cyclin-dependent kinase inhibitor
p53	tumor suppressor protein with molecular weight of 53 kDa
PCR	Polymerase chain reaction
PET	Positron emissions test
PK	Pharmacokinetic
PR	Partial remission
prn	As needed
PS	Performance status
q	every
SAE	serious adverse event
SPD	Stable or progressive disease
TBI	total body irradiation
Temp	temperature
TTP	Time to progression
US	United States
USP	United States Pharmacopeia

VCAM-1	vascular cell adhesion molecule 1
VS	Vital signs
w/w	weight-to-weight ratio
wt	weight

2.0 Objectives

2.1 Primary Objective:

2.1.1. To determine the maximum tolerated dose (MTD) and dose limiting toxicity (DLT) of VELCADE® (bortezomib) in patients with lymphoid malignancies undergoing allogeneic peripheral blood stem cell or bone marrow transplantation.

2.1.2 To determine the 1-year disease-free-survival (DFS) and the toxicity profile of VELCADE® (bortezomib) in patients with lymphoid malignancies undergoing allogeneic peripheral blood stem cell or bone marrow transplantation.

2.2 Secondary Objective:

2.2.1. To compare the incidence of GVHD with historical controls.

3.0 Background

3.1 Non-myeloablative Allogeneic Stem Cell Transplantation for Lymphoid Malignancies

In conventional transplants, high-dose chemotherapy plus radiation, is used to destroy as many lymphoma cells as possible. However, these high dose therapies are responsible for most of the treatment-related morbidity and mortality that are associated with conventional stem cell transplantation. This has restricted the use of conventional transplantation to younger patients who may be more able to undergo this treatment.

In a European Bone Marrow Transplantation Group study in which the majority of patients received total body irradiation (TBI)-based preparative (pretransplant) regimens, the treatment-related mortality for the allogeneic group was 25% compared with 11% for the autologous group.[1] Another multicenter analysis of allogeneic transplantation in 113 patients with advanced low-grade lymphoma reported a treatment-related mortality of 40%.[2] A similar high mortality has been seen using the chemotherapy conditioning regimen of cyclophosphamide, carmustine and etoposide.[3]

Non-myeloablative allogeneic stem cell transplantation (NST) was developed following the observation that leukemia/lymphoma patients, who had received allogeneic transplantation and then subsequently relapsed, went back into remission following infusions of donor lymphocytes.[4] This and other findings confirmed that a graft-versus-tumor effect, where donor lymphocytes recognize cancer cells as foreign and then destroy them, is responsible for at least part of the efficacy of allogeneic bone marrow transplantation. If donor lymphocytes can control, or even eradicate, malignant cells that have proved resistant to high-dose chemotherapy and irradiation, then these highly toxic therapies may not be necessary for the success of allogeneic stem cell transplantation strategies.

Evidence for a graft-versus-lymphoma (GVL) effect includes the observation that patients who develop chronic graft-versus-host-disease (cGVHD) following allogeneic transplantation, where the donor's immune cells attack the patient's normal tissue, have a lower probability of relapsing than patients who do not develop cGVHD. Chopra, et. al. demonstrated a lower incidence of relapse in patients who acquired cGVHD (0% relapse with cGVHD versus 35% relapse with no cGVHD).[1] Perhaps the most direct data supporting the evidence and clinical significance of GVL comes from small studies and case reports whereby patients with progressive disease after allogeneic transplantation undergo withdrawal of drugs to suppress their immune system and induce cGVHD, which is often accompanied by a simultaneous decrease in the size of their lymphomas Van-Besien demonstrated that of 9 patients who relapsed after allogeneic transplantation, 4 (44%) responded to withdrawal of immunosuppression drugs (2 complete remissions, 2 partial remissions), with responses that lasted nearly 2 years.[5]

The aim of NST is to establish immunological tolerance between the patient's immune system and the new stem cells from the donor, and to use this as a platform for immunotherapy involving the activation of immune cells, with donor lymphocytes as the active agent.[6] In NST, the patient receives low doses of chemotherapy and radiation, as well as drugs to suppress the immune system in order to prevent rejection of the donor stem cells. The donor stem cells are then infused into the patient. The patient's suppressed immune system allows the donor cells to travel to the bone marrow where they produce replacement blood cells. This process is known as engrafment. Once engrafment occurs, the patient's new blood and immune systems, resulting from the donor cells, have the ability to recognize and eradicate both the patient's remaining stem cells and the lymphoma cells.

Therefore, although non-myeloablative transplantation was initially designed to decrease transplant related morbidity so that elderly patients, patients with other serious conditions, and patients relapsing from prior autologous transplants could be more safely treated, it is now seen as an effective form of

immunotherapy for possibly all lymphomas.

3.2 Preparative Regimens for Non-myeloablative Transplantation With Sibling Donors and Outcome

The low-dose transplant regimen must (a) produce suppression of the patient's immune system to prevent rejection of the donor cells and (b) suppress the lymphoma sufficiently to prevent marked progression of the tumor and allow time for the GVL effect to occur. Our studies at M. D. Anderson involved a combination of fludarabine,cyclophosphamide and rituximab (FCR) as a conditioning regimen for patients who had chemosensitive disease (Protocol ID99-035) and who were to receive a transplant from a compatible sibling donor.[7] Patients who had refractory disease received instead the more intense BEAM/Rituximab regimen (Protocol, ID99-411).

3.2.1 Outcome With FCR Followed By Sibling Donor Transplant

We have recently reported an update of our experience with the FCR regimen in patients (pts) with relapsed NHL.[8] Seventy-eight consecutive pts were treated. Median age was 53 years (range, 21-68). Forty-three (55%) were males. Median # of prior chemoregimens was 3. Twenty-one (27%) had failed a prior autologous, and one a prior allogeneic transplantation. Histologies included follicular (FL) =47 pts (60%), diffuse large cell (DLCL)=16 pts (21%) and mantle cell (MCL) =15 pts (19%) Thirty-nine (50%) were in partial remission (PR), five (6%) had stable or progressive disease (SPD) and 34 (44%) were in complete remission (CR) at study entry.

Peripheral blood was the source of graft in 71 pts (91%). Tacrolimus and methotrexate were used for graft-versus-host disease (GVHD) prophylaxis. Median time for an absolute neutrophil count recovery of > 500 was 10 days. Sixty pts did not require any platelet transfusion. All but 2 pts who had SPD, converted to CR post transplant. All pts engrafted donor cells.

Six had a secondary graft failure (GF), two of which occurred in the setting of disease progression. With a median follow-up time of 34 months (mos) (range, 3 to 70 mos), only 6 pts (8%) relapsed. Five patients received donor lymphocyte infusion (DLI) for disease progression one achieved CR; the 4 other pts (two were in GF) did not respond. DLI was also given successfully to two other pts because of cytopenia related to a viral infection (1), and because of decreasing chimerism (1). Overall survival (OS) for all pts was 88%, 82% and 74% at 1,2 and 3-yr, respectively. By univariate analysis, OS was 95% at 3-yr for those who had failed a prior autologous transplant (P = 0.04). Patients with FL histology had also a better 3-yr survival than DLCL [88% vs 51% (*P=0.008)*]; the difference

with MCL (65% at 3-yr) was not statistically significant (P =0.2). Non-relapse related mortality was 11%, 13%, and 19% at 1, 2 and 3-yr, respectively. The incidence of acute II-IV GVHD was 17%. Two pts developed chronic GVHD post DLI. The incidence of chronic extensive and limited GVHD was 51% and was not statistically different between various histologies. We concluded that NST with FCR for NHL is an effective treatment even in pts who failed a prior autologous transplantation and is associated with a low incidence of acute GVHD. The lower than expected relapse rate observed may be indicative that NST could be curative for these diseases.

3.2.2 Outcome With BEAM/rituximab Followed By Sibling Donor Transplant

We have used the BEAM/rituximab (BCNU = 300 mg/m^2, etoposide and cytarabine = 200 mg/m^2 x8, Melphalan 140 mg/m^2) regimen for patients with NHL who were not eligible for NST because of kinetic failure or refractory disease.[9] We have treated 11 patients. OS and DFS were 63% and 57% respectively, at 3-year. All patients had grade 2 gastrointestinal toxicity, and two had multi-organ failures. The rates of GVHD were also substantially higher than the ones seen after FCR despite using the same GVHD prophylaxis. The incidence of acute II-IV GVHD was 60%, and all patients suffered from chronic GVHD. This difference is most likely related to the different intensity of the preparative regimens used. Although responses were promising, strategies to decrease toxicity and GVHD are needed.

3.3 VELCADE® (bortezomib)

3.3.1 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 who have received at least one 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. [10] 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.[11-15] Notably, bortezomib induces apoptosis in cells that over express bcl-2, a genetic trait that confers unregulated growth and resistance to conventional chemotherapeutics.[16] Bortezomib is thought to be efficacious in multiple myeloma via its inhibition of nuclear factor B (NF-B) activation, its attenuation of interleukin-6 (IL-6)-mediated cell growth, a direct apoptotic effect, and possibly anti-angiogenic and other effects.[17]

3.3.2 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 (t½ <10 minutes) followed by a longer elimination phase (t½ 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).[19] 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 donkey, 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.

3.3.3 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/m2) and 0.067 mg/kg (0.8 mg/m2) 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/m2) 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/m2) 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 step 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.

3.3.4 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/m2 and 1.3 mg/m2 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/m2 dose and 89 to 120 ng/mL for the 1.3 mg/m2 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/m2 and 1.3 mg/m2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1.0 and

1.3 mg/m2, 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/m2 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 (Emax) model. The Emax 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.

3.3.5 Clinical Experience

It is estimated that as of August 2006, more than 44,000 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 1 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/m2/dose, with DLTs of thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise.[18] 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/m2/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/m2/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) and M34100-025 (subjects with second or greater relapse and refractory to their last prior therapy). In M34100-025, 202 heavily pre-treated subjects with refractory multiple myeloma after at least 2 previous treatments received VELCADE, 1.3 mg/m2 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[20] 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), 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/m2 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/m2 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[20] 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 0*.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).[19]

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

VELCADE® has been used in combination with high dose Melphalan and Fludarabine under protocol 2004-0439 at MDACC, as conditioning regimen for patients with multiple myeloma or acute myelogenous leukemia who are undergoing allogeneic stem cell transplantation. Thus far, the combination has been well tolerated and no additive toxicity was observed with the addition of VELCADE® to the conditioning regimen.

3.3.6 Potential Risks of VELCADE®

Over 44,000 subjects have been exposed to VELCADE®. Most common side effects of VELCADE® (i.e., incidence ≥ 30%) observed in subjects are weakness, fatigue, and general discomfort; gastrointestinal effects such as constipation, diarrhea, nausea, vomiting and anorexia, which may result in dehydration and/or weight loss; fever; peripheral neuropathy (including painful sensations or numbness or tingling in hands and feet that may not get better after discontinuation of VELCADE®); anemia; and thrombocytopenia that may increase the risk of bleeding and may require platelet transfusions.

Very common side effects of VELCADE (i.e., incidence 10–29%) observed in subjects are neutropenia that may increase the risk of infection; abdominal pain; symptoms of flu and other upper respiratory tract infections; arthralgias; myalgias; bone pain; skin rash that can be erythematous, pruritic and display evidence of leukocytoclastic vasculitis at biopsy; hypotension; dizziness; fluid retention; cough; dyspnea; lower respiratory/lung infections including pneumonia; headache; blurred vision; changed sense of taste; insomnia; anxiety; and herpes zoster, which occasionally results in persistent pain and can sometimes spread over large areas of the body.

Common side effects of VELCADE (i.e., incidence 1–9%) observed in subjects are palpitations; tachycardia; bradycardia; atrial fibrillation; angina pectoris; worsening of or acute onset of congestive heart failure including pulmonary edema (subjects with risk factors for, or existing, heart disease should be closely monitored); pleural effusion; hypoxia; tinnitus; conjunctivitis; oral and esophageal mucositis; dyspepsia; upper and lower gastrointestinal bleeding; epistaxis; renal failure and impairment; urinary tract infection; sinusitis; pharyngitis; gastroenteritis; skin infections; sepsis; hyperglycemia; hypoglycemia (subjects on oral antidiabetic agents may require close monitoring of their blood sugar levels.); hematuria; confusion and depressive disorders; orthostatic hypotension; abnormal liver function tests (including increases in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase); leucopenia; hypokalemia; and hypercalcemia.

Uncommon side effects of VELCADE (i.e., incidence <1%) observed in subjects are injection site reaction and infection; pain in the mouth and throat when swallowing; fungal esophagitis; aspergillosis; superficial fungal infections of the skin and nails; loss of hearing; ileus paralytic/small bowel obstruction; cardiogenic shock; hemoptysis; cerebral hemorrhage; tumor lysis syndrome; drug hypersensitivity reactions including angioedema; severe muscle weakness and paralysis; convulsions; toxic epidermal necrolysis; septic shock; hepatitis; liver failure (reported in subjects receiving multiple concomitant medications and with serious underlying medical conditions); pulmonary alveolar hemorrhage; and severe, life threatening, or fatal acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, and Acute Respiratory Distress Syndrome (ARDS). These pulmonary events were seen more often in patients treated in Japan. Fatal ARDS has been reported in a study of VELCADE in combination with high-dose cytarabine delivered by continuous infusion and daunorubicin, in patients with relapsed acute myeloid leukemia. Isolated cases of QT-interval prolongation have been reported, but are not thought to be related to VELCADE treatment.

Complications arising from these VELCADE® toxicitites may result in death.

The effect of VELCADE® on reproduction and its safety in pregnancy are unknown. Laboratory tests show that VELCADE® may damage DNA therefore it is possible that VELCADE® may cause infertility in men and women. Women of childbearing potential should avoid becoming pregnant while being treated with VELCADE.

Further details on the potential risks of VELCADE® may be found in the Investigator Brochure.

3.4 VELCADE® activity and synergy with Rituximab in lymphoid malignancies

NF-kB has been shown to be important for B-cell maturation and function and is found in a constitutively activated state in many lymphoid malignancies. In B-cells, active, nuclear, NF-kB positively regulates the transcription of genes encoding anti-apoptotic members of the BCL-2 family of proteins. BCL-2 proteins modulate the activity of caspases, the effector proteases which comprise the final common pathway of programmed cell death.[22,23] Other targets for NF-kB include factors which are important for cell cycle progression.

Several preclinical studies suggested additive efficacy when VELCADE® was combined with Rituximab.[24-26] In one study, it was demonstrated that while VELCADE® induced apoptosis in 18.3% of mantle cell lymphoma cell lines, and rituximab induced apoptosis in 24.5%, the combination treatment resulted in 57.4%apoptosis at 48 hours.[26] The underlying mechanism for such a synergy is not well understood. One study suggested modulation of expression of the C-terminal region of CD20.[25]

3.5 VELCADE® and GVHD

GVHD represents a major hurdle impeding the efficacy of allogeneic stem cell transplantation. It has been recently found that VELCADE® can potently inhibit *in vitro* mixed lymphocyte responses and promote the apoptosis of alloreactive T-cells. [27] VELCADE® given at the time of allogeneic transplantation in mice resulted in significant protection from acute GVHD. Reductions in GVHD-associated parameters and biological evidence of proteasome inhibition were observed with this strategy but with no adverse effects on long-term donor reconstitution. Assessment of graft-versus-tumor responses in advance leukemia-bearing mice demonstrated that the combination of allogeneic transplant and T-cells with VELCADE® promoted significant increases in

survival. Increased cytotoxic T-cell killing of the tumor was also observed. Thus, the combination of proteasome inhibition with selective immune attack can markedly increase the efficacy of allogeneic transplant in cancer.[27]

The impact of VELCADE® on GVHD is however dependent on the timing of infusion of VELCADE® in relation to the transplant. In marked contrast to its effects on GVHD prevention when administered immediately after transplant, delayed administration of VELCADE® resulted in significant acceleration of GVHD-dependent morbidity.

Pathologic assessment revealed that significant increases in gastrointestinal lesions occurred following delayed administration of VELCADE® during GVHD. This pathology correlated with significant increases of type I tumor necrosis factor a (TNF-¹) receptor transcription in gastrointestinal cells and with significant increases of TNF- ¹ interleukin 1â (IL-1â), and IL-6 levels in the serum. These results indicate that the differential effects of proteasome inhibition with VELCADE® on GVHD are critically dependent on the timing of VELCADE® administration.

3.6 Rationale for Current Study Proposal

It is clear that results of allografting for patients with lymphoid malignancies who are not in remission need to be improved upon. Intensification of the preparative regimen has been associated with increased toxicities with no improvement in outcomes. Immune manipulation with donor lymphocytes or rapid immune suppression withdrawal has been associated with increased risk of GVHD without documented improvements in survival. The BEAM-rituximab regimen caused significant gastrointestinal toxicity and subsequent GVHD. Decreasing the dose of etoposide and cytarabine by 50%, as suggested by other studies using the same regimen in the autologous setting may decrease these toxicities and allow older patients to benefit. In addition, current studies at MDA are suggesting that the use of melphalan at 100 mg/m^2 does allow engraftment of donor cells and is well tolerated in elderly patients with hematologic malignancies. Because of its synergistic activity with rituximab and its activity against many lymphoid cell lines, the addition of VELCADE® to the conditioning regimen, may improve responses. The use of VELCADE® pre-transplant may also reduce the risk of GVHD. Therefore we have proposed a phase I/II trial of VELCADE® of 1.3-1.6 mg/m^2 starting day -13, -6, -1 and +2 of the transplant, to be added to rituximab (day -13,-6,+1,+8) and reduced-BEAM (days -6 to -1) followed by an allogeneic stem cell transplant on day 0.

4.0 Patient Eligibility

4.1 Inclusion:

1. Up to 70 years of age .
2. Any histological subtype of CD20+ lymphoid malignancies or T-cell lymphoid malignancies.
3. Patients with CD20+ lymphoid malignancies in relapse after failing $\geq$ 1 prior regimen of conventional treatment and not eligible for non-myeloablative transplant. Patients with T-Cell lymphoid malignancies can either be in relapse or newly diagnosed with high risk features (such as high IPI of $\geq$ 2).
4. Patients with prior non-myeloablative transplant are eligible if not from the same donor.
5. A fully-matched or one-antigen mismatched sibling or unrelated donor.
6. Left ventricular EF $\geq$ 40% with no uncontrolled arrythmias or symptomatic heart disease.
7. FEV1, FVC and DLCO $\geq$ 40%.
8. Serum creatinine < 1.8 mg/dL. Serum bilirubin < 3X upper limit of normal,
9. SGPT < 3X upper limit of normal.
10. Voluntary signed, written IRB-approved 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.
11. Men and women of reproductive potential must agree to follow accepted birth control methods for the duration of the study. Female subject is either post-menopausal or surgically sterilized or willing to use an acceptable method of birth control (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) for the duration of the study. Male subject agrees to use an acceptable method for contraception for the duration of the study.

4.2 Exclusion

1. Past history of anaphylaxis following exposure to rituximab or VELCADE®, boron or mannitol
2. History of grade 3 or 4 NCI toxicity with prior VELCADE® therapy.
3. Patient with active CNS disease.
4. Pregnant (Positive Beta HCG test in a woman with child bearing potential defined as not post-menopausal for 12 months or no previous surgical sterilization) or currently breast-feeding. Pregnancy testing is not required for post-menopausal or surgically sterilized women.
5. Known infection with HIV, HTLV-I, Hepatitis B, or Hepatitis C.
6. Patients with other malignancies diagnosed within 2 years prior to Study Day-13 (except skin squamous or basal cell carcinoma).
7. Active uncontrolled bacterial, viral or fungal infections.
8. Major surgical procedure or significant traumatic injury within 4 weeks prior to Day -13.

9. Serious, non-healing wound, ulcer, or bone fracture.
10. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 3 months prior to Day -13.
11. History of Stroke within 6 months.
12. Myocardial infarction within the past 6 months prior to Study Day 1, or has New York Heart Association (NYHA) Class III or IV heart failure or arrythmias, unstable angina, uncontrolled congestive heart failure or arrythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening must be documented by investigator as not medically relevant.
13. Uncontrolled hypertension (>/=140/90)
14. Uncontrolled chronic diarrhea.
15. A prior allogeneic transplant from the same donor.
16. Serious medical or psychiatric illness likely to interfere with participation in this clinical study.
17. Patient has received other investigational drugs within 3 weeks before enrollment.
18. Active peripheral neuropathy $\geq$ grade 2.

5.0 Treatment Plan

Patients must be off any prior biological therapy, chemotherapy, radiotherapy, or other investigational therapy within 3 weeks prior to start treatment (day -13).

Patients will be treated with peripheral blood stem cell or bone marrow transplantation using BEAM/Rituximab as the preparative regimen. Patients with T-cell lymphoid malignances will receive BEAM without Rituxan. BCNU will be administered intravenously at a dose of 300mg/m^2 IV on day –6, cytarabine 100 mg/m^2 IV twice a day on day –5 through –2 (total 8 doses), etoposide 100 mg/m^2 IV twice on day -5 to -2 (total 8 doses), and melphalan 100 mg/m^2 IV on day -1. Rituximab will be given on day –13 at a dose of 375 mg/m^2 , then the dose would be repeated at 1000 mg/m^2 on days –6, +1, and +8 of transplant. Patients receiving a matched unrelated or mismatched donor will also be given thymoglobulin on day -2 through day -1. The preparative regimen has been used widely at MDACC.

As part of this preparative regimen patients will also receive VELCADE®
VELCADE® starting dose level 2: 1.3 mg/m^2 IV will be given on days -13, -6, -1 and +2. If the starting dose is tolerated (only one of 6 patients experience DLT), then dose will be escalated to 1.6 mg/m^2 on days -13, -6, -1 and +2 in the next cohort.

The first dose of rituximab and VELCADE® will be given outpatient. The remaining doses will be given inpatient.

If unacceptable toxicity occurs at the starting dose of 1.3 mg/m^2, then dose will be

de-escalated to 1.0 mg/m^2 on days -13, -6, -1 and +2 in the next cohort.

Our toxicity outcome will be defined as a grade 3 or 4 neurological toxicity, or graft failure, or death from graft versus host disease (GVHD). Toxicity will be evaluated within the first 90 days. If there is a high probability that the toxicity rate is greater than 20% we will decrease the dose as described above. If unacceptable toxicity occurs at the lower dose, we shall terminate the trial early.

5.1 Supportive Treatment

Supportive treatment as defined by antibiotic prophylaxis, treatment, and prevention of GVHD and blood product support will follow current departmental guidelines. Patients will receive tacrolimus and methotrexate (5 mg/m^2 on days 1, 3, and 6 after transplant for matched related donors and on days 1,3,6, and 11 after transplant for matched unrelated or mismatched donors) for prevention of GVHD. Valtrex 500 mg once a day or acyclovir 200 mg twice a day will be provided to prevent Herpes Zoster infection. Flagyl 500 mg three times a day, starting on day -6, will be given until absolute neutrophil count (ANC) recovery $\geq$ 1,000.

Data from this clinical trial will be shared with PA17-0544 which is a retrospective data analysis study. No new testing will be undertaken on any specimen. (See Waiver of Informed Consent.)

6.0 Clinical Trial Materials

Vials containing lyophilized VELCADE® for Injection should be stored according to package directions. To date, stability data indicate that the lyophilized drug product is stable for at least 12 months when stored under the recommended conditions. Stability studies are ongoing and Millennium will notify the investigator should this information be revised during the conduct of this 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. Study drug will be supplied 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. 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. Refer to the VELCADE® Material Safety Data Sheet for First Aid Precautions. 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.

6.1 VELCADE® Administration

VELCADE® will be administered at 1.3 mg/m2 on days -13, -6, -1, and +2 of transplant (See Section 4.0 for the treatment plan).

Study drug will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Patients may be treated on an outpatient basis, if possible. The pharmacist will prepare the study drug under aseptic conditions. The amount (in mg) of study drug to be administered will be determined based on the body surface area. 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. If a patient experiences a notable change in weight (e.g., loss or gain of $\geq$8 lbs or 3.6 kg) within a cycle, as determined by an unscheduled weight assessment, then the patient's dose should be recalculated at that time. The appropriate amount of VELCADE® will be drawn from the injection vial and administered as an intravenous push over 3 to 5 seconds followed by a standard saline flush or through a running IV line. Vials are for single use administration.

6.2 Treatment Compliance

All drug will be administered to eligible patients under the supervision of the

investigator or identified sub-investigator (s). The pharmacist will remain records of patient's height, body weight, and body surface area, and total drug administered. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.

7.0 Pretreatment evaluation

7.1 Patient

This will be performed within 30 days prior start of therapy. This includes:

- A complete history and physical including the following information: diagnosis, histologic subtype, PS, stage, prior therapy and response, pulmonary function tests, MUGA or Echo.

- All patients should have a lymph node biopsy whenever possible.

- Staging of diseases: i.e. CT neck, chest, abdomen, pelvis, bone marrow biopsies and aspiration, CxR, PET or Gallium scan, cytogenetics, PCR/ fluorescence in situ hybridization (FISH) studies that are disease-specific, and immunophenotyping.

- Laboratory studies shall include:

- CBC with differential, platelet count, PT, PTT, creatinine, SMA-12, Beta 2 microglobulin level, Hepatitis serology, HIV, HTLV-1, quantitative serum immunoglobulins, baseline peripheral CD4/CD8 counts and immunodeficiency panel.

Bortezomib (Velcade®) and reduced intensity allo SCT for lymphoid malignancies 2006-0066												
Issa F. Khouri, MD	Evaluation											
BMT	Pretreatment		During Study (post transplant)									
	within 30 days		25-35 days		3 Months		6 Months		9 Months		12 Months	
Assessment	R	Date	R	Date	R	Date	R	Date	R	Date	R	Date
History & Physical												
Physical Examination	X		X		X		X		X		X	
Diagnosis	X											
Histology	X											
PS	X											
Stage	X											
MUGA/Echo	X											
Lymph node Biopsy	X											
GVHD & toxicity evaluation			X		X		X		X		X	
Staging of disease												
CT Neck	X		X		X		X		X		X	
CT Chest	X		X		X		X		X		X	
CT Abdomen & Pelvis	X		X		X		X		X		X	
B M biopsies & aspiration	X		X		X		X		X		X	
CxR	X											
PET/Gallium scan	X		X		X		X		X		X	
Cytogenetics	X		X		X		X		X		X	
PCR/FISH (Disease specific)	X		X		X		X		X		X	
Laboratory studies												
CBC	X		X		X		X		X		X	
Platelet Counts	X		X		X		X		X		X	
PT	X											
PTT	X											
Creatinine	X											
SMA-12	X											
2 microglobulin level	X											
Hepatitis serology	X											
HIV	X											
HTLV-1	X											
CD4/CD8 (PB)	X											
Immunodeficiency panel	X											
Liver function test			X		X		X		X		X	
BUN			X		X		X		X		X	
Creatinine			X		X		X		X		X	
CD4/CD8			X		X		X		X		X	
Immunodeficiency panel (PB)	X		X		X		X		X		X	
Chimeric Studies (PB, T-cells, Myeloid)			X		X		X		X		X	
Quantitive immunoglobulins	X		X		X		X		X		X	

Note: Patients will be evaluated every 6 months after the first year while on study.

8.0 Evaluation During Study

Evaluation during this study will be performed between days 25-35 post transplant.

This includes:

- A brief physical examination, GVHD and toxicity evaluation.
- Complete blood count with differential, platelet count, liver function tests, BUN, creatinine, quantitative serum immunoglobulins, CD4/CD8, immunodeficiency panel from peripheral blood.
- CT scans of neck. chest, abdomen and pelvis.
- PET or Gallium if either was positive any time in the past.
- Bone marrow aspiration and biopsy.
- PCR /FISH studies.
- Chimeric studies of T-cells and myeloid in peripheral blood.
- Beyond this point, patients in CR and have 100% donor cells, will be evaluated every 3 months during the first year and then every 6 months while the patient is on study.
- Patients who do not achieve CR or who progress within one year will receive immunomodulation with rituximab and donor lymphocyte infusion (DLI) as per BMT standard of care. Those who progress after DLI will be taken off study.

9.0 Background Drug Information

9.1 VELCADE®

See appendix E (VELCADE® package insert)

9.2 Rituximab

Rituximab is associated with hypersensitivity reactions that may respond to adjustments in the infusion rate. Hypotension, bronchospasm, and angioedema have occurred in association with rituximab infusion as part of an infusion-related symptom complex. In most cases, patients who have experienced non-life-threatening reactions have been able to complete the full course of therapy. Medications for the treatment of hypersensitivity reactions, such as epinephrine, antihistamines, and corticosteroids, should be available for immediate use in the event of a reaction during administration.

Patients who develop clinically significant arrhythmias as a result of rituximab therapy should undergo cardiac monitoring during and after subsequent infusions of rituximab. Patients with pre-existing cardiac conditions, including arrhythmias and angina, have experienced recurrences during Rituximab therapy and should be monitored during and immediately after the infusion.

Rituximab rapidly decreases levels of benign and malignant CD20+ cells. Tumor lysis syndrome has been reported to occur within 12 to 24 hr after the first rituximab infusion in patients with high numbers of circulating malignant lymphocytes. Patients with high tumor burden (ie, bulky lesions) may also be at risk. Patients at risk of developing tumor lysis syndrome should be followed up closely and appropriate laboratory monitoring performed.

After treatment for and resolution of tumor lysis syndrome, subsequent rituximab therapy has been administered in conjunction with prophylactic therapy for this syndrome in a limited number of cases.

For more information, consult the M.D. Anderson pharmacy at 713-792-6125.

9.3 Etoposide

9.3.1 Description

Etoposide (VP-16) is a semisynthetic podophyllotoxin derivative with antineoplastic activity.

9.3.2 Pharmaceutical data

VP-16 is supplied as 100 mg/5cc ampules.

9.3.3 Solution preparation

The contents of the vial are diluted with 0.9% sodium chloride for injection, USP. The final concentration of the admixture must be 0.2 mg/mL - 0.4 mg/mL. Solutions prepared above 0.4 mg/mL may contain precipitate.

9.3.4 Route of administration

Oral or slow IV infusion.

9.3.5 Known side-effects

Myelosuppression, primarily granulocytopenia is the dose-limiting toxicity. Other side effects include gastrointestinal toxicity comprising of nausea, emesis and mucositis. At high doses reversible hepatotoxicy is seen. Acute side effects inlcude occasional bronchospasm and hypotension. These can be avoided by slow intravenous administration.

9.3.6 Pharmacokinetics

The main site of metabolism is in the liver. Major metabolites of etoposide are hydroxy acids and cistactone which appear in the plasma and urine. The half-life of the drug is 4 to 11 hours.

9.3.7 Mechanism of action

Two different dose dependent responses are seen. At high concentrations (10 ug/ml) lysis of cells entering mitosis is seen. At low concentrations (0.3 to 10 ug/ml) cells are inhibited from entering

prophase. The predominant macromolecular affect of etoposide appears to be the induction of DNA strand breaks by an interaction with DNA topoisomerase II or by the formation of free radicals.

9.4 Melphalan

9.4.1 Description

Melphalan is an alkylating agent with cell cycle nonspecific cytotoxic effects on tumor cells.

9.4.2 Dosing information

The usual dose for conditioning in stem cell transplantation is 100-200 mg/m^2 intravenously.

9.4.3 Pharmacokinetics

Orally administered melphalan demonstrates considerable variation in bioavailability, does not undergo active metabolism, and is primarily eliminated in the feces. However, compromised renal function may significantly impact melphalan excretion.

9.4.4 Known side effects

Leukopenia and thrombocytopenia are the major dose limiting side effects; pulmonary fibrosis and infiltrates, amenorrhea, alopecia, sterility, and inappropriate ADH secretion have also occurred. Although less frequent,nausea and vomiting and oral ulcerations have occurred.

9.4.5 Clinical applications

Melphalan has a broad spectrum of antitumor activity, but its main use in the palliative treatment of multiple myeloma and non-resectable.

9.5 Cytarabine

9.5.1 Description

Cytarabine is a synthetic antimetabolite antineoplastic agent.

9.5.2 Dosing information

Usual induction dose for ANLL (acute non-lymphocytic leukemia) has been 100 to 200 mg/m(2) daily for 5 to 7 days (in combination with other cytoxic agents). Usual intrathecal dose has been 30 mg/m(2) every 4

days. Investigational high-dose therapy has consisted of 3 grams/m(2) every 12 hours.

9.5.3 Pharmacokinetics

Following IV administration, cytarabine is widely distributed to areas including the CNS and tears; the drug is orally active. Cytarabine is metabolized in the liver to an inadctive metaolite; both cytarabine and its metabolite are excreted in the urine. The eliminiation half-life is between 1 and 3hours.

9.5.4 Known side effects

The major toxic effect of cytarabine is myelosuppression resulting in megaloblastic changes in erythropoiesis and reticulocytopenia. Other adverse effects include neuropathies, GI distress, hepatic toxicity, and hypersensitivity.

9.5.5 Clinical applications

Cytarabine is useful in various neoplastic disorders including myelocyticleukemia, lymphoblastic leukemia, and non lymphocytic.

9.6 Carmustine

9.6.1 Description

Carmustine is a nitrosourea derivative alkylating agent.

9.6.2 Dosing information

As a single agent 150 to 200 mg/m(2) IV every 6 weeks given as a single dose or divided into 2 daily doses. Dosage adjustments for repeated doses need to be based on hematological response. Children have received 100 mg/m^2 every 6 to 8 weeks for meningeal leukemia and osteogenic sarcomas.

9.6.3 Pharmacokinetics

Carmustine is highly lipid soluble and readily crosses into the CSF. The drug is rapidly metabolized with no intact drug detectable in the plasma after 15 minutes; some metabolites are known to be active. About 60 to 70% of a dose is eliminated in the urine.

9.6.4 Known side effects

Delayed and cumulative myelosuppression is the most frequent and profound toxicity of Carmustine. Thrombocytopenia is usually more serious than leukopenia; however, both may be dose-limiting. Other adverse effects include pulmonary fibrosis, nausea and vomiting, hepatotoxicity, and nephrotoxicity.

9.6.5 Clinical applications

Carmustine is used alone or in combination with other appropriate therapeutic measures in the treatment of various neoplastic conditions such as Hodgkin's disease, brain tumors, multiple myeloma, and non-Hodgkin's lymphoma.

9.7 Thymoglobulin

Thymoglobulin® (Rabbit anti-thymocyte globulin Sangstat Medical Corporation) will be used as an in vivo fortification of both the pretransplant immunosuppression and the post-transplant immunoprophylaxis against graft-vs-host disease (GVHD). The Thymoglobulin will be given during the 2 days preceding the graft infusion, thus it will both deplete circulating T-cells from the donor and, due to its long half-life it will deplete infused T-cells from the graft, contributing to both engraftment and decreasing the risk for developing clinically serious GVHD.

10.0 Adverse Events

Expected events related to this study are described in section 9.0 and in appendix A and E. These events will be scored using NCI version 3.0 scoring scale.

Also, in this study, patients are expected to experience changes in laboratory parameters such as electrolyte imbalances, uric acid changes, liver function abnormalities, including elevations of GPT, GOT, LDH, and alkaline phosphatase. These changes are due to the underlying disease and the nature of the treatment including stem cell transplantation and chemotherapy. These expected changes will not be considered Adverse Events and will not be recorded in the CRF unless in the view of the investigator they are judged clinically significant.

10.1 Reporting Requirements

Serious and unexpected adverse events will be reported according to MDACC guidelines and the BMT reporting requirements. The end of active treatment is the day of the last dose of Rituximab (D+8). These events will be reported to the study chairman, who in turn will notify the MDACC surveillance committee.

Also Investigator-sponsor must report all serious adverse events regardless of

relationship with study drug or expectedness to Millennium 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.

Investigator-sponsor must also provide Millennium 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's Product Safety Department 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.

SAE Reporting Contact Information (North America Reporting)
Millennium Product Safety
Fax: (617)551-3746
Telephone: (617)551-2972
E-mail: productsafety@mpi.com

SAE Reporting Contact Information (Rest of World Reporting)
PRA Safety Management Services
Fax: 49-621-878-2181
Telephone: 49-621-878-2154

10.2 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).

10.3 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. Millennium must also be contacted immediately by faxing a completed Pregnancy Form to either Millennium Product Safety for North America or PRA Safety Management Services for rest of world. The pregnancy must be followed

through outcome (i.e. delivery, still birth, miscarriage).

11.0 Criteria for Study Evaluation

11.1 Toxicity

Toxicity will be graded according to CTC AE Version 3.0 (Appendix B).

11.2 Response and relapse

Response will be evaluated using the standard criteria response for lymphoma (Appendix G).

11.3 Acute and Chronic GVHD

Patients who develop acute GVHD may be treated according to standard care or any existing protocol as long as not other investigational agents are given.

11.4 Engraftment

Engraftment will be recorded as the day the absolute neutrophil count exceeded $0.5X10^9$/mL and chimerism studies demonstrated donor hematopoiesis. Graft failure will be defined as failure to achieve donor cell engraftment by day 30 post transplant or an ANC of <500 more than 3 days in a row not responding to at least
7 days of growth factor support.

11.5 Survival

Survival will be recorded by the day of death and the cause of death.

12.0 Off Study Evaluation

1. Patient withdrawal of the informed consent
2. Patient not being compliant or fails to return for follow-up
3. An increasing or unexpected pattern of toxicity observed deemed unacceptable by the study chairman
4. Disease progression after donor lymphocyte infusion
5. Investigator judgment when the well being and best interest of the patient is compromised
6. Intercurrent illness
7. Two missed doses of investigational agent bortezomib
8. Protocol violation
9. Administration reasons

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.

13.0 Statistical Considerations

This is a phase I/II study with an objective of determining both the efficacy and toxicity when using Velcade in patients with lymphoid malignancies who will undergo allogeneic peripheral blood stem cell or bone marrow transplantation. There will be two steps to this trial. The first step is a phase I component where the maximum tolerated dose (MTD) will be selected from 3 possible dose levels of Velcade. Once the MTD is determined we will proceed with a phase II portion of the trial. The patients enrolled at the MTD in the phase I portion will be included in the phase II portion. The maximum total sample size will be 52 patients, with an accrual rate of 0-1 patients per month. A maximum of 18 patients will be enrolled in the phase I portion. A maximum of 40 patients will be evaluated in the phase II portion, 6 of which were also enrolled in the phase I portion. Therefore the resulting maximum sample size is 52.

Phase I

The phase I part of this trial is aimed at finding the MTD of Velcade. Three possible dose levels will be evaluated: 1.0 mg/m2, 1.3 mg/m2 and 1.6 mg/m2. We will start at dose level 2, 1.3 mg/m2. A dose limiting toxicity (DLT) will be defined as a grade 3-4 neurological toxicity, graft failure, or death due to GVHD. We will evaluate the patients for DLTs for 90 days after the start of treatment. A standard 3+3 design will be employed to evaluate safety.

The 3+3 algorithm that we will follow is described below.

- Enroll 3 patients at dose level 2, 1.3 mg/m2.
- If 0 patients experience a DLT then escalate to dose level 3 (1.6 mg/m2) and enroll a cohort of 3 patients.
- If 2 or 3 patients experience a DLT then de-escalate to dose level 1 (1.0 mg/m2)
- If only 1 of the 3 patients experiences the DLT at a given dose level, enroll 3 additional patients at the current dose level.
- If only 1 of 6 patients experiences the DLT at a given dose level, escalate to the next higher dose level and enroll a cohort of 3 patients.
- If at least 2 of 3 or 2 of 6 patients experience the DLT at a given dose level, then the MTD has been exceeded.
- Once the MTD has been exceeded, treat another 3 patients at the previous dose level if there were only 3 patients treated at that dose level.

- The MTD is the highest dose level at which 0/6 or 1/6 patients experience DLTs.

However, if the lowest level, 1.0 mg/m2, has more than 1/6 subjects with DLTs the trial will be suspended. Since there are only 3 doses to be considered, and since we will have only a maximum of 6 patients at the MTD, the maximum number of patients enrolled in this phase I portion will be 18.

Phase II

Once we have established an MTD from the phase I portion of the trial, we will enroll additional patients until we have treated at most 40 patients at the MTD. The patients treated at the MTD in the phase I portion will be included in this phase II trial. This study will be monitored for both efficacy and toxicity. The efficacy measure will be the 1-year disease free survival (DFS) rate. We desire this DFS rate be no lower than 40%. If there is a low probability that the 1-year DFS rate is greater than 40% we will stop the trial early. Our toxicity outcome will be defined as a grade 3 or 4 neurological toxicity, or graft failure, or death from graft versus host disease (GVHD). Toxicity will be evaluated within the first 90 days. If there is a high probability that the toxicity rate is greater than 20% we will also terminate the trial early. Additionally, we will institute a separate monitoring rule for patients who receive a transplant from an unrelated donor. For these patients, if there is a high probability that the death rate is greater than 20%, we will stop enrolling this cohort of patients into the trial. The method of Thall, Simon, and Estey Thall PF, Simon R, and Estey EH. "New statistical strategy for monitoring safety and efficacy in single-arm clinical trials", Journal of Clinical Oncology, 14(1):296-303 (1996). will be employed to perform the interim monitoring.

When monitoring both the efficacy and toxicity rate, each a binary outcome, there are four possible elementary outcomes. These are 1 = [efficacy, toxicity], 2 = [no efficacy, toxicity],
3 = [efficacy, no toxicity], 4 = [no efficacy, no toxicity]. We denote the corresponding standard outcome probability vector by qS, and the probability vector with the experimental treatment
by qE. We assume a Dirichlet (16, 24, 64, 96) prior on qS, which in particular has mean 1-year DFS rate of 40% and a mean toxicity rate of 20%. We assume Dirichlet (0.80, 1.20, 3.20, 4.80) prior on qE, which has the same prior rates but carries little prior information.

The maximum sample size for trial will be 40, which will ensure that if, for example 16/40 (40%) patients are observed to be disease free at 1-year, then the posterior 95% credible interval for the probability of the 1-year DFS rate, based on the marginal beta (4.0, 6.0) prior assumed, will run from 27% to 54%.

Safety Monitoring

For all patients combined, the following decision criteria will be applied after each cohort

of 5 patients has been evaluated, up to the 40th patient accrued. Targeting a 40% 1-year DFS rate and allowing a 20% toxicity rate (grade 3-4 neurological toxicity, graft failure or death due to GVHD) by day 90, the trial will be stopped early according to the following two monitoring rules:

1) 1-year DFS rate

$$Pr[qS(\text{DFS rate}) < qE(\text{DFS rate}) \mid \text{data}] < 0.075$$

That is, if at any time during the trial we determine that we have less than a 7.5% chance of showing that the average 1-year DFS rate in the experimental treatment group is higher than what would be expected on the standard of care (i.e. 40%) we will stop the study. Stopping boundaries corresponding to this probability criterion are to terminate the trial if

(# of patients disease free at 1-year) / (# patients evaluated) $\leq$
0/10, 2/15, 4/20, 5/25, 7/30, or 9/35.

Or 2) Toxicity rate

$$Pr[qS(\text{Tox}) < qE(\text{Tox}) \mid \text{data}] > 0.925$$

That is, if at any time during the study we determine that there is more than a 92.5% chance that the average toxicity rate at day 90 in the experimental treatment group is more than would be expected on the standard of care (i.e. 20%) we will stop the study. Stopping boundaries corresponding to this probability criterion are to terminate the trial if

(# of patients with toxicity by day 90) / (# patients evaluated) $\geq$
4/5, 6/10, 7/15, 8/20, 10/25, 11/30, or 12/35.

If we see 3 toxicities in the first 4 patients, we will suspend accrual and wait for patient number 5 to be evaluated for toxicity in the 90-day window.

The operating characteristics of this study design are illustrated in Table 1.

Table 1. Operating Characteristics for Monitoring Rules

	Early Stopping Probability	Achieved Sample Size 25th, 50th, 75th Percentiles		
0.4, 0.2 (acceptable target rates)	0.16	40	40	40
0.3, 0.2 (poor 1-year DFS rate)	0.46	20	40	40
0.2, 0.2 (very poor 1-year DFS rate)	0.89	15	20	30

0.4, 0.3 (acceptable DFS rate but poor toxicity rate)	0.47	20	40	40
0.4, 0.4 (acceptable DFS rate by very poor toxicity rate)	0.85	15	20	30
0.3, 0.3 (poor DFS rate and poor toxicity rate)	0.67	15	30	40
0.2, 0.4 (very poor DFS rate and very poor toxicity rate)	0.98	10	15	20
0.5, 0.2 (good DFS rate and acceptable toxicity)	0.07	40	40	40
0.5, 0.1 (good DFS rate and good response rate)	0.01	40	40	40

Additionally, a separate monitoring rule will be instituted to insure the safety of patients who receive a transplant from an unrelated donor. We expect to enroll no more than 20 such patients. For these patients, we will denote the probability of death by day 100 in these patients by $\varnothing_D$. We will assume that $\varnothing_D$ follows a Beta(0.1,1.9) prior distribution. We will stop enrolling patients with a transplant from an unrelated donor if there is reasonable evidence that the death rate at 100 days is greater than 20%. Formally, we will use the following rule: we will stop enrollment for these patients if at any time during the trial:

(3) $\Pr[\varnothing_D > 20\% \mid \text{data}] \geq 0.95$

This rule leads to the following stopping boundaries: stop enrollment if:

(# of patients dead at 100 days) / (# of patients with unrelated donor evaluated at 100 days)
$\geq$ 3/3, 4/5, 5/8, 6/11, 7/15, or 8/18

If the true death rate for these patients is 10%, this cohort will be terminated on average 0.8% of the time. If the true death rate is 20%, this cohort will be terminated 8.7% of the time, and if the true death rate is 40%, this cohort will be terminated 66.0% of the time.

Secondary Objectives

Descriptive statistics such as frequencies and percentages will be used to summarize the toxicities that were seen. In addition, we also will examine the cumulative incidence of acute GVHD and chronic GVHD using the method of Gooley Gooley, T.A., Leisenring, W., Crowley, J., Storer, B.E., "Estimation of failure probabilities in the presence of competing risks: new representations of old estimators", Statistics in

Medicine, 18: 695-706 (1999). et al as disease recurrence or death without GVHD are competing risks. The GVHD rates will also be compared to historical controls.

Gooley, T.A., Leisenring, W., Crowley, J., Storer, B.E., "Estimation of failure probabilities in the presence of competing risks: new representations of old estimators", Statistics in Medicine, 18: 695-706 (1999).

14.0 Administrative Requirements

14.1 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.

14.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. 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.

14.3 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).

14.4 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.

14.5 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.

14.6 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.

14.7 Drug Accountability (I am checking into this Dr. Khouri)

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.

14.8 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.

14.9 Record Retention

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

15.0 References

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