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A Phase II Study of Allogeneic Hematopoietic Stem Cell Transplantation for Multiple Myeloma Using a Conditioning Regimen of Fludarabine, Melphalan, and Bortezomib

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BLOOD AND MARROW TRANSPLANTATION PROGRAM
HACKENSACK UNIVERSITY MEDICAL CENTER

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ABBREVIATIONS LIST

Abbreviation	Definition
°C	degrees Celsius
μM	Micromolar
20S	20S proteasome subunit
AE	adverse event
ANC	absolute neutrophil count
Bc1-2	B-cell lymphoma-2; a gene that inhibits apoptosis
BSA	body surface area
CAM	cell adhesion molecules
cm	Centimeter
CR	Complete Response
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
dL	Deciliter
DLT	Dose Limiting Toxicity
DNA	deoxyribonucleic acid
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ht	Height
IκB	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
IκBα	I kappa B alpha-associated protein kinase
kg	Kilogram
Ki	inhibitory constant
lbs	Pounds
m^2	square meters
mg	Milligram
min	Minute

Abbreviation	Definition
mL	Milliliter
mm^3	cubic millimeters
mmol	Millimole
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NF-κB	nuclear factor-κB
ng	Nanogram
nM	Nanomole
p21	p21(ras) farnesyl-protein transferase
p27	cyclin-dependent kinase inhibitor
p53	tumor suppressor protein with molecular weight of 53 kDa
SAE	serious adverse event
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

Multiple myeloma is the second most prevalent blood cancer (10%) after non-hodgkin's lymphoma. It represents approximately 1% of all cancers and 2% of all cancer deaths. Although the peak age of onset of multiple myeloma is 70 years of age, recent statistics indicate both increasing incidence and earlier age of onset.

Multiple myeloma affects slightly more men than women. African Americans and Native Pacific Islanders have the highest reported incidence of this disease in the United States and Asians the lowest. Results of a recent study found the incidence of myeloma to be 9.5 cases per 100,000 African Americans and 4.1 cases per 100,000 Caucasian Americans. Among African Americans, myeloma is one of the top 10 leading causes of cancer death.

1.2 Clinical Studies of High-Dose Therapy of Multiple Myeloma

Standard dose therapy for most plasma cell disorders includes regimens such as low-dose melphalan (32 mg/m^2/month) with prednisone. For patients with multiple myeloma, this regimen results in a 40% overall response rate, but few patients achieve a complete remission and the median duration of response is only 2 years. The median survival is in the range of 3 years and few (<15%) survive 5 years. More aggressive chemotherapy regimens, including VAD, VBMCP and M2, induce remissions more quickly but overall survival rates are not substantially improved (Alexanian and Dimopoulos, 1994).

These poor outcomes led many investigators explored high-dose chemotherapy regimens. In 1983, McElwain used melphalan 140 mg/m^2 without stem cell support as a salvage therapy in nine patients with refractory myeloma and noted all patients responded to treatment with five patients achieving complete biochemical and bone marrow responses (McElwain and Powles, 1983). This observation of dose-response led to a series of phase I/II trials with and without stem cell support in both newly diagnosed and refractory disease (Attal et al., 1992; Harousseau et al, 1995).

A matched-pair analysis by the Arkansas group and SWOG comparing dose-intense with standard-dose therapy demonstrated the benefit of autologous HSC transplantation for the treatment of multiple myeloma (Barlogie et al., 1997). Event-free (49 vs 27 months) and overall survivals (62+ vs 48 months) were improved for patients treated with dose-intense therapy as part of the initial treatment.

1.3 Autologous hematopoietic stem cell transplantation for multiple myeloma

High-dose therapy and autologous stem cell transplantation (ASCT) is an integral component of the myeloma treatment for patients considered eligible for the procedure. The majority of the randomized clinical trials demonstrated a superior progression-free and overall survival among patients undergoing ASCT compared with those treated with only conventional therapies. Currently, the "novel" agents of thalidomide, lenalidomide and bortezomib appear best suited to be used as first-line therapy, enhancing the quality of responses prior to proceeding to ASCT and diminishing early mortality from the disease. Tandem transplantation has been shown to improve the event-free survival and overall survival of patients with myeloma (4,5). A study of 399 previously untreated patients with

myeloma randomized these patients to receive either single or double transplantation. The probability of surviving event-free for seven years after the diagnosis was 10 percent in the single-transplant group and 20 percent in the double-transplant group (P=0.03). The estimated overall seven-year survival rate was 21 percent in the single-transplant group and 42 percent in the double-transplant group. Therefore, as compared with single autologous stem-cell transplantation after high-dose chemotherapy, double transplantation improves overall survival among patients with myeloma, especially those who do not have a very good partial response after undergoing one transplantation. Yet most patients will relapse at a median of three years after transplantation.

1.4 Allogeneic stem cell transplantation for multiple myeloma

Allogeneic transplantations have been performed for multiple myelomas since the 1980's (6). The initial rationale in performing these transplants was to administer high-dose chemotherapy to eradicate myeloma cells and provide the patient with a disease-free marrow. It soon became apparent that a graft-versus-myeloma effect exists(7). Although the relapse/progression rates appeared lower, the initial enthusiasm for performing allogeneic transplantation in MM was tempered by the elevated treatment-related toxicity, approaching 40% in trials involving total body irradiation or busulfan based myeloablative regimens. In an EBMT retrospective case-matched analysis of 378 patients, the overall survival was inferior compared to autologous transplantation as a result of this high risk transplant-related mortality(8). Ablative regimens were used in these original transplants and the main causes of death were severe infections often combined with severe GVHD. The EBMT database and the US Intergroup trial showed a plateau at approximately 25% indicating a probable cure for an otherwise incurable disease.

1.5 Transplant regimen intensity

Based on the idea that the graft-versus-myeloma (GVM) effect is more important than the intensity of the conditioning regimens, the Seattle group developed an allogeneic transplant modality using considerably lower intensity in the conditioning regimen(9). Transplant-related mortality was reduced significantly but relapses after transplantation remains a major concern with this approach. In a recent retrospective study by the EBMT, reduced intensity conditioning was compared to myeloablative conditioning(10). A dose of melphalan less than 140 mg/m2, a busulfan dose of 8 mg/kg or less and a cyclophosphamide dose less than 120 mg/kg was considered to be reduced intensity. If total body irradiation was used, a dose of radiation less than 6 Gy or up to 6 Gy fractionated was accepted as reduced intensity. With this definition, reduced intensity conditioning was associated with lower non-relapse mortality but a higher relapse rate compared to myeloablative conditioning. The progression-free survival was superior with myeloablative conditioning but there was no significant difference in overall survival. It is therefore concluded that the intensity/activity of the conditioning regimen does have an impact on relapse-free survival. New supportive treatment modalities in recent years and better GVHD prophylaxis, has lead to a reduction in mortality for patients receiving

ablative regimens. The EBMT data has shown a significant reduction in mortality for patients transplanted after 1994(11).

Most recently, a strategy using high dose melphalan with autologous ASCT for maximal cytoreduction followed by an non-myeloablative regimen to allow for eradication of residual disease by GVM has shown considerable promise. Response rates usually exceed 50% with transplant-related mortality in the 10-15% range. When this approach was compared directly to tandem ASCT, the auto-allo patients had superior PFS and OS compared to tandem ASCT. A similar prospective randomized US trial which enrolled 710 patients will provide mature data in the first quarter 2010.

Unfortunately, even with this strategy of ASCT for maximal cytoreduction and a tandem reduced intensity allogeneic transplant for eradication of minimal residual disease, patients continue to relapse, even in the setting of GVHD. Thus, we believe the major limitation to improving outcomes is disease relapse after the allogeneic transplant.

1.6 Fludarabine- melphalan conditioning regimen for multiple myeloma

The combination of fludarabine and melphalan has been studied as a preparative regimen for allogeneic transplantation for patients with multiple myeloma (12). Twenty-two patients with multiple myeloma between 1996 and 2000 received the combination of fludarabine and melphalan. Eighteen patients received fludarabine 30 mg/m2 for 5 days with melphalan 140 mg/m2 as a single dose and 4 patients received fludarabine 25 mg/m2 for 5 days with melphalan 90 mg/m2 daily for 2 days. The actuarial overall survival and progression-free survival at 2 years was 30% and 19% respectively. Non-relapse mortality was 19% at day 100. Similarly, Kroger et al. reported on the fludarabine-melphalan combination (13). The treatment-related mortality at day 100 was 11%. Fifty-five percent of the patients obtained a complete remission and 27% a partial remission, giving an overall response rate of 82%. The updated overall survival and disease-free survival was 68% and 42%, respectively. Kroger et al have recently published their collective results of salvage therapy after allogeneic transplant. Patients were treated with donor lymphocyte infusions (DLI) with one or more novel agents (bortezomib; thalidomide). High response rates were observed with prolonged progression-free survival indicating that post-transplant novel therapies can still achieve significant anti-myeloma effects which may enhance the efficacy of DLI (to induce GVM). Furthermore, this study showed the feasibility and toxicities of post-allogeneic novel therapy administration.

1.7 Bortezomib

Bortezomib is a small molecule proteasome inhibitor developed by Millennium Pharmaceuticals, Inc., (Millennium) as a novel agent to treat human malignancies. Bortezomib 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 induces apoptosis in cells that over express bcl-2, a genetic trait that confers unregulated growth and resistance to conventional chemotherapeutics. 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. Bortezomib has shown synergy when combined with various chemotherapeutics in pre-clinical and clinical models (14,15).

We are conducting a phase I/II clinical study of bortezomib with dose-intense melphalan with autologous peripheral blood stem cell transplantation in patients with disease progression or less than partial response after a prior PBSCT (tandem transplant). Primary exclusion criteria are active infection at time of PBSCT, cardiac amyloid deposition, and creatinine clearance of <20 ml/min. Peripheral neuropathy of less than grade 4 is not an exclusion. Bortezomib is given on days -4 and -1 with melphalan 200 mg/m^2 (actual weight) given on day -2 before PBSCT. For the phase I study, bortezomib was given at rising doses of 1.0, 1.3, and 1.6 mg/m^2. Three patients were to be enrolled at each dose level, with an additional 3 patients enrolled in case of a serious toxicity event at any level. An additional 20 patients are being enrolled in the phase II portion of the study with 15 patients enrolled as of 12/1/09 (patient accrual will be completed before enrollment into this study).

Twelve patients (median age, 58 yrs) were treated in the phase I study with 6 patients treated at the 1.0 mg/m^2 level after 1 patient experienced a serious adverse event (SAE) of prolonged diarrhea, and 3 patients treated at each of the subsequent levels. Eleven patients had 1 prior and 1 patient tandem prior cycles of dose-intense melphalan. All patients experienced the expected pancytopenia requiring red cell and/or platelet support. Ten patients had febrile neutropenia with bacteremia identified in 3 patients. One patient had mild tumor lysis not requiring medical intervention. Mucositis was minimal and comparable to PBSCT with melphalan alone. All patients engrafted at a median time to ANC>500/uL of 11 days (range, 9-19) and platelet>20,000/uL of 14 days (range, 11-27). No other SAEs occurred in the phase I study beyond the usual events of high-dose therapy. No neurological SAEs, including severe peripheral neuropathies, were observed. A bortezomib dose of 1.6 mg/m^2 was chosen for the phase II study.

Fifteen patients (median age, 56 yrs) are now treated in the phase II study. Six patients had disease progression and 9 patients had less than a partial response (PR) after a prior PBSCT. All patients experienced pancytopenia and evaluable patients engrafted with median time to ANC>500/uL of 10 days (range, 8-13) and platelet>20,000 of 11 days (range, 9-65). Eleven patients had febrile neutropenia with 3 patients with positive blood cultures and 1 patient with RSV bronchitis. Three SAEs are reported in the phase II portion: 1 patient expired of complications of Candida krusei infection and 1 of MRSA sepsis (before ANC recovery). A third patient developed tumor lysis requiring dialysis. One patient had a dysphoric reaction to anti-emetics and did not receive the 2nd

bortezomib dose. No neurological SAEs attributable to this regimen were observed in this population.

Patients underwent restaging studies at monthly intervals after transplantation with marrow examination at 3 and 12 months. Response classification is in accordance to standard definitions. Three patients underwent subsequent allogeneic PBSC and 2 patientss died of transplant-related complications and are not evaluable for response. Two patients succumbed to progressive disease. The remaining 20 patients are in ongoing follow-up. Eight patients including 6 of 11 patents with stable disease or minimal response after prior dose-intense melphalan achieved a CR. Six patients remain in continuous CR at 11+ to 23+ months (median, 15+ months) after PBSCT with 2 patients having disease progression at 12 and 26 months after PBSCT.

These data indicate that bortezomib can be added to dose-intense melphalan in this schedule with acceptable toxicities. Strikingly, 8 of 22 pts achieved CR after minimal response to dose-intense melphalan alone or disease progression after a prior PBSCT, and 2 patients showed tumor lysis, indicating a synergistic effect of adding bortezomib to dose-intense melphalan..

1.8 Bortezomib in allogeneic transplantation

Bortezomib exerts numerous biologic effects that include blocking the activation of the transcription factor, nuclear factor-κB. NF-κB is implicated in the regulation of many genes that code for mediators of the immune and inflammatory responses. Bortezomib has been used as an immunomodulatory agent in the context of allogeneic transplantation. The Dana-Farber group used a GVHD prophylaxis regiment of bortezomib, methotrexate and tacrolimus in a study of patients undergoing related,unrelated donor transplantation for malignancies.(16). The incidence of grade II-IV acute GVHD was 13% and the incidence of chronic GVHD was 41%. These results appear to compare favorably to standard prophylactic regimens. In addition, numerous reports of bortezomib for the treatment of graft versus host disease have been published.

2 Study Rationale

In this study we are proposing to treat patients with advanced multiple myeloma using the combination of fludarabine, melphalan and bortezomib followed by allogeneic hematopoietic stem cell transplantation. The hypothesis is that we can maximize the efficacy of the preparative regimen without increasing the regimen-related mortality.

2.1 Primary Objective:

The primary objective of this study is determine if the addition of two doses of bortezomib to a standard regimen of fludarabine and melphalan followed by allogeneic HSC transplantation will improve progression-free survival at two years after transplantation for patients with multiple myeloma.

2.2 Secondary Objectives:

To investigate:

- 2.2.1 Overall survival (OS): Defined as time from the first dose of administration to death from any cause
- 2.2.2 Overall response rates: Defined as the composite endpoint of response to treatment which includes Complete Response (CR), Partial Response (PR), stable disease (SD) as defined in International Response Criteria. We will also analyze Complete Response rate
- 2.2.3 Univariate analysis of the risk of progression/relapse and mortality: In addition, multivariate analysis of the risk of progression/relapse and overall mortality will be conducted to assess influence of variables measured after the start of treatment
- 2.2.4 Regimen-related toxicity of this regimen

3 Investigational Plan

3.1 Overall Design and Plan of Study

This is a single institution non-randomized phase II study to determine if allogeneic hematopoietic stem cell transplantation using the fludarabine, melphalan and bortezomib regimen is superior to historical controls.

3.2 Patient Inclusion and Exclusion Criteria

3.2.1 Patient Inclusion Criteria:

- 3.2.1.1 Diagnosis of multiple myeloma
- 3.2.1.2 Have a suitable related or unrelated donor (Section 3.3)
- 3.2.1.3 Age ≥18 but <70 yrs
- 3.2.1.4 KPS of ≥70%
- 3.2.1.5 Recovery from complications of previous therapies

3.2.2 Patient Exclusion Criteria

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

- 3.2.2.1 Diagnosis other than multiple myeloma
- 3.2.2.2 Chemotherapy or radiotherapy within 21 days of initiating treatment in this study
- 3.2.2.3 Prior dose-intense therapy requiring HSC support within 56 days of initiating treatment in this study
- 3.2.2.4 Uncontrolled bacterial, viral, fungal or parasitic infections
- 3.2.2.5 Uncontrolled CNS metastases
- 3.2.2.6 Known amyloid deposition in heart
- 3.2.2.7 Organ dysfunction
  - 3.2.2.7.1 LVEF <40% or cardiac failure not responsive to therapy
  - 3.2.2.7.2 FVC, FEV_1, or DLCO <50% of predicted and/or receiving supplementary continuous oxygen
  - 3.2.2.7.3 Evidence of hepatic synthetic dysfunction, or total bilirubin >2x or AST >3x ULN
  - 3.2.2.7.4 Calculated creatinine clearance <20 ml/min
  - 3.2.2.7.5 Sensory peripheral neuropathy grade 4 within 14 days of enrollment
- 3.2.2.8 Karnofsky score <70% unless a result of bone disease directly caused by myeloma
- 3.2.2.9 Life expectancy limited by another co-morbid illness
- 3.2.2.10 Diagnosed or treated for another malignancy within 3 years of enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in

situ malignancy, or low-risk prostate cancer after curative therapy

3.2.2.11 Female subject is pregnant or breast-feeding (women) or unwilling to use acceptable birth control methods (men or women) for twelve months after treatment. Confirmation that the subject is not pregnant must be established by a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women.

3.2.2.12 Documented hypersensitivity to fludarabine or melphalan or to bortezomib, boron or mannitol or any components of the formulation

3.2.2.13 Patients unable or unwilling to provide consent

3.2.2.14 Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure (see section 8.4), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening has to be documented by the investigator as not medically relevant

3.2.2.15 Patient has received other investigational drugs with 14 days before enrollment

3.2.2.16 Serious medical or psychiatric illness likely to interfere with participation in this clinical study

3.3 Donor Inclusion and Exclusion Criteria

3.3.1 Donor Inclusion Criteria:

3.3.1.1 HLA 6/6 (HLA-A, B, DrB1) related donor or 7/8 (HLA-A, B, C, DrB1) unrelated donor

3.3.1.1.1 Related donors will be evaluated in accordance with HUMC standard practice guidelines for the evaluation and management of allogeneic donors

3.3.1.1.2 Unrelated donors will be identified, evaluated, and managed in accordance with National Marrow Donor Program standards

3.3.1.2 Age ≥18 and <70 yrs

3.3.1.3 KPS of ≥70%

3.3.1.4 Willing to donate peripheral blood HSC by leukapheresis

3.3.1.5 Have adequate veins for apheresis or agree to placement of a central venous catheter (femoral, subclavian)

3.3.2 Donor Exclusion Criteria

3.3.2.1 Identical twin

3.3.2.2 Female donors who are pregnant or breastfeeding

3.3.2.3 Infection with HIV or viral hepatitis (B or C)

3.3.2.4 Known allergy to filgrastim

3.3.2.5 Current serious systemic illness

3.3.2.6 Uncontrolled bacterial, viral, or fungal infection

3.3.2.7 Receiving experimental therapy or investigational agents

3.3.2.8 History of cancer other than treated basal cell cancer of the skin or carcinoma in situ of the cervix. Cancer treated with curative intent >5 yrs before donation will be reviewed on a case-by-case basis by the principal investigator

3.4 Patient Evaluation

Pre-transplant evaluation must be performed within 30 days of transplant conditioning

3.4.1 History with full details of the patient's prior treatments and responses

3.4.2 Physical exam with determination of Karnofsky score and findings related to underlying malignancy

3.4.3 Chemistry profile to include serum creatinine, AST, alkaline phosphatase, and bilirubin

3.4.4 CBC with differential

3.4.5 ABO and Rh

3.4.6 Serum pregnancy test, if female gender with child-bearing potential

3.4.7 HIV, Hepatitis B, Hepatitis C, CMV serology

3.4.8 Disease Staging:

3.4.8.1 Quantitative immunoglobulin measurement

3.4.8.2 Serum protein electrophoresis and immunofixation with measurement of monoclonal protein

3.4.8.3 Quantitative serum free light chain measurement

3.4.8.4 Serum beta 2 microglobulin (β2m)

3.4.8.5 24 hr urine collection for quantitation of total protein, protein electrophoresis and immunofixation

3.4.8.6 Radiological studies of any sites of bone pain or bone scan abnormalities

3.4.8.7 Skeletal survey if not performed within 6 months of start of study treatment

3.4.9 Pulmonary function tests with DLCO

3.4.10 MUGA scan or cardiac echo

3.4.11 EKG

3.5 Donor Evaluation

Pre-donation evaluation must be performed in accordance with HUMC Standard Operating Procedures for the evaluation and management of related HSC donors, or with NMDP Standard Operating Procedures for the evaluation and management of unrelated HSC donors.

3.6 HSC Product Evaluation

3.6.1 TNC, CD34+, and CD3+ cell counts

3.7 Post-Transplant evaluation

3.7.1 Physical exam daily until hematological recovery and resolution of serious regimen-related complications,

3.7.2 History and physical exam weekly through day 100 after transplantation, then at 6 months, 9 months, 12 months after transplantation, and then yearly until 3 yrs after transplantation

3.7.2.1 Assessment and staging of acute and chronic GvHD will be performed and recorded at these visits

3.7.3 Once weekly assessment of toxicity in accordance with NCI toxicity guidelines from day-1 until resolution of all Grade 3/4 treatment-related toxicities

3.7.4 CBC daily from day 0 until ANC ≥500/ul on two sequential days after nadir reached (engraftment).

3.7.5 Chemistry profile 2 times per week until documentation of engraftment

3.7.6 Chimerism evaluation at 4 weeks (+/- 1 week) then monthly for 3 months (+/- 10 days).

3.7.7 Record of all medications administered during inpatient course.

3.8 Post transplant re-staging of disease

3.8.1 Restaging by serum and urine should be done at 4 weeks intervals (±7 days) starting at day +28 after transplantation for 3 months and then at 3 months

intervals until 3 years after transplantation or demonstration of disease progression requiring therapy, if earlier.

3.8.1.1 Quantitative immunoglobulin measurements

3.8.1.2 Serum protein electrophoresis and immunofixation with measurement of monoclonal protein

3.8.1.3 Quantitative serum free light chain measurements

3.8.1.4 Serum beta 2 microglobulin (β2m)

3.8.1.5 24 hr urine collection for quantitation of total protein, protein electrophoresis and immunofixation

3.9 Study Medications

3.9.1 Bortezomib (VELCADE) 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. 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. The 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.

3.9.2 Melphalan for Injection is a sterile lyophilized powder for reconstitution and will be obtained from the manufacturer in accordance with standard pharmacy purchasing criteria. Melphalan will be reconstituted by pharmacy staff, in accordance with usual pharmacy practices, immediately before patient infusion. Melphalan is a bifunctional alkylating agent that acts principally through covalent reactions with DNA, resulting in the formation of drug-DNA adducts with cross-linking of DNA strands. Melphalan's cytotoxic effects are related to its concentration and the duration of exposure to melphalan of the cell. Enhanced repair of DNA interstrand crosslinks may be a mechanism of resistance that develops after prior exposure to this drug. Melphalan is actively transported into cells by the high-affinity L-amino acid transport system; glutamine and leucine compete for carrier uptake and high levels of these amino acids can reduce drug uptake. Other drugs such as tamoxifen, chlorpromazine, and indomethacin can also impair melphalan uptake and accumulation. Studies of the pharmacokinetics of oral melphalan were complicated by the highly variable absorption of the drug. Moreover, studies of intravenous melphalan have also showed considerable inter-patient variability in plasma clearance. Pinguet et al studied the pharmacokinetics of melphalan administered at a dose of 140 mg/m^2 in combination with other chemotherapeutic agents to 20 patients undergoing autologous PBSC transplantation. The medians time to neutrophil and platelet recoveries were 16 and 14.6 days, and the majority of patients (80%) developed WHO grade 3/4 stomatitis. Plasma concentration profiles were biphasic and fitted with a two-compartment model. The maximal concentration at the end of infusion averaged 7.94±3.73 mg/l (range, 1.65-14.5). The mean elimination half-life and the mean residence time were 83.1±27.1 minutes (range, 51.6-166.81) and 98.7±26.9 minutes (range 59.5-166.9), respectively. The volume of distribution averaged 1.00±0.62 l/kg (range 0.46-3.12) and total plasma clearance 548.3±300.0 ml/min/m^2 (range, 218.6-1378.8). Plasma levels were below the limits of detection for all patients by 24 hours after melphalan administration. These authors noted large inter-individual variability of these pharmacokinetic parameters. Total clearance of melphalan was significantly correlated with creatinine clearance ($r=0.49$, $p<0.05$). A relationship between melphalan clearance and renal function was also described by Kergueris et al., but this relationship did not explain the large variation in inter-individual overall clearance of the drug (Kergueris et al., 1994). Similar pharmacokinetic results were reported for 20 pediatric and 10 adult patients treated with melphalan 140 mg/m^2 as a single agent. For the adult patients, the elimination half-life ($t_{½\beta}$) was 50±7 minutes for patients treated with 140 mg/m^2 dose and 41±12 minutes for the higher dose of 180 mg/m^2. Plasma clearance averaged 525 ml/min/m^2 at 140 mg/m^2 and 532 ml/min/m^2 at 180 mg/m^2.

3.9.3 Fludarabine: Fludarabine is a fluorinated nucleotide analogue of the antiviral vidarabine. It acts as a purine antagonist antimetabolite. Synonyms: 2-F-ara-AMP. Bone-marrow suppression from fludarabine is dose-limiting, manifesting

as neutropenia, thrombocytopenia, and anemia. Other adverse effects include fever, chills, cough, Dyspnea, pneumonia, gastrointestinal disturbances, stomatitis, edema, the tumor lysis syndrome, skin rashes, auto-immune hemolytic anemia and thrombocytopenia, and hemorrhagic cystitis. Neurological disturbances include peripheral neuropathy, agitation, confusion, visual disturbances, seizures, and coma; high doses have been associated with progressive encephalopathy, blindness, and death.Dosage should be reduced in renal impairment and fludarabine should not be given if creatinine clearance is less than 30 mL/minute. Intravenous fludarabine phosphate is rapidly dephosphorylated to fludarabin, which is taken up by lymphocytes and rephosphorylated to the active triphosphate nucleotide. Peak intracellular concentrations of fludarabine triphosphate are seen about 4 hours after a dose. Fludarabine has a bioavailability of about 50 to 65% after doses of the phosphate by mouth.Clearance of fludarabine from the plasma is triphasic with a terminal half-life of about 20 hours. Elimination is mostly via renal excretion: 60% of a dose is excreted in the urine. The pharmacokinetics of fludarabine exhibit considerable interindividual variation.

3.9.4 Anti-thymocyte globulin (ATG)

Antithymocyte globulins are antibodies, which act against lymphocytes, and in particular against T-cells, to produce suppression of cell-mediated immunity

Common adverse reactions include fever, chills, and skin reactions including rash, pruritus, and urticaria, which may be manifestations of hypersensitivity. Dyspnea, hypotension, chest, back or flank pain may indicate anaphylaxis, which can occur in up to 1% of patients. Rashes and arthralgia may represent serum sickness, especially in patients with aplastic anemia. Use with other immunosuppressants may reduce the incidence or severity of hypersensitivity but increase the risk of acquired systemic infections, such as CMV or herpes simplex. Enhanced immunosuppression may also increase the incidence of post-transplant lymphoproliferative disease or other malignancies. Leucopenia and thrombocytopenia are also common. Although usually transient, dosage adjustment may be necessary if they become severe or prolonged, and if unremitting, they may warrant stopping therapy. Other adverse effects include headache, abdominal pain, gastrointestinal disturbances, hypertension, peripheral edema, asthenia, hyperkalaemia, and tachycardia. Nephrotoxicity has been reported.

3.10 Outline of Treatment Plan

Table 1: Treatment Schema for Conditioning Regimen

	Day of Transplant											
		-5	-4	-3	-2	-1	0	+1	+3	+6	+9	+11
Fludarabine 30mg/m2		X	X	X	X							
Bortezomib 1.6mg/m2			X			X						
Melphalan 140 mg.m2					X							
rATG (unrelated donor)				X	X	X						
Tacrolimus					X→							
Stem cell infusion							X					
Methotrexate 5 mg/m2								X	X	X		X
Filgrastim 5 ug/kg											X→	

3.11 Conditioning Regimen:

3.11.1 Fludarabine will be administered at a dose of 30 mg/m2 IV daily for 4 days starting on transplant day -5.

3.11.2 Melphalan will be administered at a dose of 140 mg/m2 on transplant day-2

3.11.3 Bortezomib will be administered by rapid IV push at a dose of 1.6mg/m2 on days-4 and -1. The bortezomib should be given at least 20 hours after the melphalan.

3.11.4 Patients receiving cells from an unrelated donor will also receive rabbit antithymocyte globulin (Thymoglobulin) at a dose of 0.5 mg/kg IV on day -3, 1.5 mg/kg on day -2 and 2 mg/kg on day -1

3.11.5 Dose adjustment for the fludarabine, methotrexate and antithymocyte globulin will be as follows:

3.11.5.1 If patient weighs less than 100% of ideal body weight (IBW), dosing is based on actual body weight.

3.11.5.2 If patient weighs 120-150% of IBW, dosing is based on adjusted body weight (ABW).

3.11.5.3 If patient weighs greater than 150% of IBW, actual weight will be capped at 150% of ideal body weight, and this will be used in the adjusted body weight formula.

3.11.5.4 Corrected body weight formula: ABW= IBW + [(0.25) x (actual BW-IBW)].

3.11.6 Melphalan and bortezomib will be dosed based on patient actual weight.

3.12 Stem cell infusion:

3.12.1 Stem cell infusion will occur at least 18 hrs or later after the second bortezomib infusion. Day 0 for purposes of methotrexate administration is defined as the

day the HSC infusion is completed. The infusion of peripheral blood stem cells will be done in accordance with the Blood and Marrow Transplant program standard operating procedures

3.13 Graft versus host disease (GVHD) prophylaxis:

3.13.1 GvHD prophylaxis consists of tacrolimus 0.03 mg/kg (or 0.015 mg/kg for age ≥65) using ideal body weight, IV total daily dose starting on transplant day -2 and adjusted based on blood levels. Methotrexate at a dose of 5 mg/m2 IV will be administered on transplant days +1, +3, +6 and +11

3.14 Supportive care after transplantation

3.14.1 Supportive care including transfusions, hydration and prophylactic antibiotics will be provided as per current transplant program standard operating procedures.

3.15 Post-transplant cytokine administration

3.15.1 Filgrastim will be administered at a dose of 5 mcg/kg (rounded to vial size) every day starting on day+9 until neutrophil engraftment

3.16 GvHD management

3.16.1 Management of GvHD is not defined in this protocol. Patients may be treated in accordance with usual practices and are encouraged to enroll into clinical studies of the management of these complications of transplantation

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:

4.1.2.1 Results in death.

4.1.2.2 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.

4.1.2.3 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).

4.1.2.4 Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a persons' ability to conduct normal life functions.

4.1.2.5 Is a congenital anomaly/birth defect.

4.1.2.6 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

The Principle Investigator-sponsor must report all serious adverse events (SAE) regardless of relationship with any study drug or expectedness to the IRB as required by the institution.

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

4.3 Assessment of Toxicity

4.3.1 Common Terminology Criteria for Adverse Events (CTCAE) will be used for the assessment and grading of all toxicities experienced by patients enrolled into this study (http://ctep.cancer.gov/forms/CTCAE_Index.pdf)

4.3.1.1 If the nature of the adverse experience is listed in the CTCAE, the maximum grade and time of maximum grade will be reported.

4.3.1.2 If the adverse experience is not listed on the NCI CTG Expanded Toxicity Criteria Appendix D, report the toxicity grade using the following criteria.

4.3.1.2.1 Grade 1 = Mild: an adverse experience which is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.

4.3.1.2.2 Grade 2 = Moderate: an adverse experience which is sufficiently discomforting to interfere with normal everyday activities.

4.3.1.2.3 Grade 3 = Severe: an adverse experience which is incapacitating and prevents normal everyday activities.

4.3.1.2.4 Grade 4 = Life Threatening: an adverse experience which places the patient at immediate risk of death.

4.4 Assessment of Causality

4.4.1 Every effort should be made by the investigator to explain each adverse experience and assess its relationship, if any, to study drug treatment. Causality should be assessed using the following categories: Not Related, Unlikely, Suspected (Reasonable Possibility), Probable.

4.4.1.1 Not related: The adverse experience is definitely not related to the test drug.

4.4.1.2 Unlikely: There are other, more likely causes and the drug is not suspected as a cause.

4.4.1.3 Suspected (reasonable possibility): A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug.

4.4.1.4 Probable: There probably is a direct cause and effect relationship between the adverse experience and the study drug.

4.4.2 The degree of certainty with which an adverse experience is attributed to drug treatment (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of one or more of the following:

4.4.2.1 Known pharmacology of the drug

4.4.2.2 Reaction of similar nature being previously observed with this drug or class of drug. The experience having often been reported in literature for similar drugs as drug related e.g. skin rashes, blood dyscrasia. The experience being related by time to drug ingestion terminating with drug withdrawal (dechallenge) or reproduced on rechallenge

4.5 Follow-up of Adverse Experiences

4.5.1 Patients with grade ¾ adverse experiences will be actively followed until the event has subsided (disappeared) or until the condition has stabilized.

4.5.2 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).

5 Statistical Evaluation

This is a phase II study to determine if allogeneic hematopoietic stem cell transplantation using the fludarabine, melphalan and bortezomib regimen is superior to historical controls that received fludarabine and melphalan as the conditioning regimen.

5.1 Endpoints

5.1.1 Primary Endpoint

5.1.1.1 The main primary endpoint of this study is two-year progression free survival. Patients are considered a failure with respect to PFS if they die or experience disease progression or relapse. The time to this event is the time from transplantation to relapse/progression, initiation of non-protocol anti-myeloma therapy, or death from any cause. Subjects alive without confirmed disease progression will be censored at the time of last disease evaluation. Deaths without progression are treated as failures no matter when they occur.

5.1.2 Secondary Endpoints

Secondary endpoints will include:

5.1.2.1 Overall survival (OS): Defined as time from the first dose of administration to death from any cause

5.1.2.2 Overall response rates: Defined as the composite endpoint of response to treatment which includes Complete Response (CR), Partial Response (PR), stable disease (SD) as defined in International Response Criteria. We will also analyze Complete Response rate

5.1.2.3 Univariate analysis of the risk of progression/relapse and mortality: In addition, multivariate analysis of the risk of progression/relapse and overall mortality will be conducted to assess influence of variables measured after the start of treatment

5.1.2.4 Regimen-related toxicity: Graded and presented in a descriptive nature.

5.2

Descriptive analysis of baseline characteristics and demographics in this study will be performed in the following manner. Continuous measurements will be summarized as mean (SD) or median (inter-quartile range) based on whether or not the data come from a normal distribution as validated by Shapiro-Wilks test of normality. Categorical measurements will be summarized as frequency (percentage). Proportion of overall survival will be estimated by the Kaplan-Meier

product limit method. The univariate probability of the relapse and treatment–related mortality (TRM) will be calculated using cumulative incidence function.

5.3 Accrual, Registration and Follow-up

The targeted sample size for the single arm is 55 subjects. It is estimated that four years of accrual will be necessary to enroll this number of subjects. The Blood and Marrow Transplantation Program at HUMC treats about 12 patients with this diagnosis every year. In the last two years 28 multiple myeloma patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) used the fludarabine, melphalan and bortezomib (FluMelVel) conditioning regimen. After eligibility is established, subjects will be enrolled into the single arm using FluMelVel as a conditioning regimen. It is assumed that patients will enroll into the study uniformly over the accrual period. All subjects will be "on-study" for three years post-transplant, during which they will be monitored for the effects of treatment through regular clinic. With four years of planned accrual, and a minimum of three years of additional follow-up post-transplant, subjects will be followed for progression-free survival for at least 36 months.

5.4 Sample Size and Power Calculations

In this section, the power of the analysis of time to progression or death is considered and performed based on the proportion surviving without progression at two years. The power of a one-sided log-rank test of surviving probability was calculated using PASS 2008.

The study design considers PFS at two-years post-transplant ranging from 35% to 55%. The standard FluMel conditioning regimen is assumed to have PFS of 35%. It is posited that the FluMelVel conditioning regimen will increase the two year PFS to 55%. Thus, to detect the 20 % difference in PFS between the two groups using a desired power of 80%, for this one-side log rank test at 5% level of significance, four year accrual, 2 year follow-up and dropout rate of 10%, 55 patients on FluMelVel are required. This calculation achieved power of 80.06%. This calculation from PASS 2008 was obtained by treating subjects in arm control arm as though they were randomized. Since the subjects in this arm were historical controls on FluMel conditioning regimen, the method of Simon and Dixon (17) was also used to derive the sample size. Further, it was assumed that there are 50 patients on FluMel available for comparison with outcomes of the new conditioning regimen. Assuming an accrual rate of 1 patient per month, 80% power target, 5% level of significance and ratio of FluMel hazard rate to FluMelVel hazard rate of 1.7557, 50 patients on the FluMelVel regimen are required. Furthermore, adjusting the sample size of the singe arm for a dropout rate of 10 % yielded a size of 55, which is the same as the sample obtained in PASS 2008.

5.5 Efficacy analysis

In this Phase II study, we wish to ascertain if allogeneic hematopoietic stem cell transplantation using the fludarabine, melphalan and bortezomib regimen is superior to historical controls that received fludarabine and melphalan as the conditioning regimen.

5.6 Statistical Hypothesis

The null hypothesis is that the two-year progression free survival rate in treatment arm A is 35%. The alternative hypothesis for this study posits that the treatment plan consisting allogeneic transplantation with fludarabine, melphalan-bortezomib (experimental arm) will increase the two-year progression free survival to 55% which is 20 % more than PFS in the historical arm.

Thus, we will evaluate the hypotheses

H_O: $S_C(2) \geq S_E(2)$

H_A: $S_C(2) < S_E(2)$

where $S_C(2)$ = the two-year progression free surviving proportion of historical control (FluMel), which is assumed to be 0.35, $S_E(2)$ = the two-year progression free surviving proportion of the experimental arm (FluMelVel). The patients in the FluMelVel conditioning regimen will be matched with patients in the FluMel by Cytomegalovirus (CMV) PCR status. To account for heterogeneity of outcome due to risk status of patients in the treatment arms, the comparative analysis will be stratified on risk status. Thus, a one-sided log-rank test stratified on risk status will be conducted to determine if allogeneic transplantation with fludarabine and melphalan-bortezomib improves the progression free survival over that observed in the historical controls using fludarabine and mephalan alone at the 5% level of significance.

5.7 Primary endpoint

To compare the two-year PFS between the historical control (FluMel) with the single arm (FluMelVel) consisting of 55 subjects. This sample size calculation is based on the assumption that the expected PFS of the standard transplant arm using FluMel is 35% at 2 years (CIBMTR data).
The primary analysis will include all eligible allogeneic transplantation subjects that receive the FluMelVel conditioning regimen and historical control using FluMel conditioning regimen. The single arm trial subjects will be matched to historical controls by CMV PCR status. The treatment arms will be compared using a one-sided log-rank test. All tests will be performed using the significance level of 5%.

5.8 Secondary endpoints

5.8.1 Response to Treatment

The rates of complete remission (CR) and very good partial remission (VGPR) according to the International Uniform Response Criteria (Section 3.2) will be calculated at two years after transplantation. The analyses of the two-year response rates are planned as soon as those data become available in all subjects, at one and two years after the close of accrual. The comparison of the response rate to the transplant with respect to the overall and CR component will be performed using Fisher's exact test at the 5% level of significance.

5.8.2 Overall Survival

The event is death from any cause. The time to this event is the time from transplantation to the documented time of death, loss to follow-up or the end of the study, whichever comes first. Patients alive at the time of last observation are considered censored. The Kaplan-Meier estimate of survival will be estimated separately for each treatment-group. For the comparison of the OS between the two conditioning regimens, a one-side log-rank test will be conducted at the 5% level of significance, analogous to the analysis of PFS described above.

5.8.3 Association of Prognostic Factors and Risk of Progression/Relapse and Mortality

A comparative analysis of risk outcomes relapse/progression, TRM, and overall Mortality will be conducted while adjusting for imbalance in other risk factors using a Cox proportional hazards model (18). To fit the multivariate model, a stepwise backward selection procedure will be used while considering the type of conditioning regimen (FluMelVel versus FluMel), relapse risk status (low risk, high risk), age at transplant and Karnosfky performance score (<90 versus ≥90) , donor-gender, CMV, HLA match grade, and stem cell source as covariates. Graft-versus host disease (GVHD) will be entered as a time- dependent covariate. Both acute GVHD and chronic GVHD will be considered as subtypes of GVHD. An examination of the goodness-of-fit will be performed using Grambsch-Therneau and Martingale residual plots (19) and lowess smooth of Cleveland (20). Covariates yielding a p-value of 0.05 or less will be an indication of statistical significance. The proportionality assumption for Cox regression will be validated by introducing a time-dependent covariate for each risk factor and outcome. Since BM blast cell count, presence of peripheral blood blast, and whether or not the patient is in CR at transplant are collinear only one variable will be used in single model fitting attempt. Thus, three different models will be considered when examining the association risk factors and PFS and OS. This analysis will be presented in terms of relative risks (RR) along with the corresponding p values for each covariate.

5.9 Safety Analysis

Safety Analysis will be performed on all patients who have at least one dose of medication on either treatment arms over the course of this study. The severity of the toxicities will be graded according to the NCI CTCAE v3.0 whenever possible. Events during the first 100 days after transplantation will be considered possibly related to the transplant for this analysis. Regimen-related toxicity will be graded and presented in a descriptive nature as incidence rates and corresponding 95% confidence intervals.

5.9.1 Safety Monitoring Endpoints

The incidence of toxicities of grade 3 or higher toxicities (CTCAE version 3.0), the incidence of probable viral fungal and bacterial infections, and the incidence of treatment-related morality, i.e., from causes other than relapse or progression, will be recorded for each patient at set intervals over the course of the study. Safety data will be described in a variety of ways, both graphical and tabular, and incidence

will be compared across time points and treatment arms. The Data and Safety Monitoring Board will be presented with a comprehensive semi-annual report that will contain both solicited and unsolicited adverse event reports.

5.9.2 Stopping rules

If the non-relapse mortality rate in the experimental group receiving Fludarabine, melphalan and Bortezomib within the first 3 month post transplantation exceeds 20% then the study will be stopped. It is assumed that non-relapse mortality in the standard regimen is 10%. Resumption of patient accrual will only be permitted after review of interim results by the Institutional Review Board and the Data Safety Monitoring Board. Operationally, using 10% as the acceptable rate of NRM and 20% as the unacceptable, Wald's Sequential Probability Ratio Test (SPRT), the accrual will be halted for death occurring in:

Table 1: Stopping Rule for Toxicity

Stage {k}	Maximum number of patients accrued by stage {n_k}	Stop trial if
1	4	r≥4
2	10	r≥5
3	17	r≥6
4	24	r≥7
5	31	r≥8
6	38	r≥9
7	45	r≥10
8	52	r≥11

Note r is the number of non-relapse mortality events.

This schedule of stopping rule was calculated using Wald's SPRT algorithm in SISA (21) and has at least 80 power of halting the trial when the toxicity is above 20%.

5.10 Monitoring Compliance

Patients enrolled into the study will monitored for treatment actually received. Failure to comply with study conditioning regimen would first trigger an intervention to improve compliance.

5.11 Data Management and Analysis

Case report forms will be created for management of data collected during this study. A database in Access will be created based on the case report forms. All study data will be imported into SAS and data management will be utilized to flag, and generate queries on

out of range data issues until they are resolved. All analysis will be performed using SAS software version 9.2 (SAS Institute Inc. Cary, NC).

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. 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, 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. .

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).

A conference will be held with the patient and family to discuss this study and alternative treatments available for treatment of the underlying disease. All potential risks associated with the use of fludarabine , bortezomib, melphalan and HSCT will be discussed as objectively as possible. It will be explained that patients offered this treatment have advanced malignancy with life expectancy of months to no more than 1-2 years with conventional treatments. Informed consent from the patient will be obtained using the IRB-approved consent form describing this protocol. The patient has the right to review and correct the results of the pre-transplant evaluation

6.4 Donor information and informed consent

Related donor informed consent will be obtained in accordance with Standard Operating Practice

Unrelated donor informed consent will be obtained in accordance with the Standard Operating Procedures of the NMDP and the donor center

6.5 Protocol Registration

6.5.1 All patients will be assigned a unique patient number (UPN) in accordance with HUMC Standard Practice.

6.6 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 patient's

confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

6.7 Record Retention

6.7.1 The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). The licensed medical records department, affiliated with the institution where the patient receives medical care, maintains all original inpatient and outpatient chart documents.

6.8 Investigational New Drug Exemption

All of the drugs employed in this protocol are commercially available and an IND exemption is not required for the conduct of this study. The study will be conducted in accordance with current Good Clinical Practice guidelines.

7 Karnofsky Performance Status Scale

The following table presents the Karnofsky performance status scale[1]:

Points	Description
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most of his/her needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization indicated. Death not imminent
20	Very sick; hospitalization necessary; active support treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

8 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):

$$\text{BSA} = \sqrt{\frac{Ht(inches) \times Wt(lbs)}{3131}}$$

or

$$\text{BSA} = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$$

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

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

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.)

9 New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease:

[1] Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale: an examination of its reliability and validity in a research setting. *Cancer* 1984;53:2002-2007.

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.

10 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.

11 Common Terminology Criteria for Adverse Events Version 3.0

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

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