HackensackUMC IRB Protocol # Pro00001307

Phase III Randomized Study of Autologous Stem Cell Transplantation with High-Dose Melphalan Versus High-Dose Melphalan and Bortezomib in Patients with Multiple Myeloma 60 Years or Older

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BLOOD AND MARROW TRANSPLANTATION PROGRAM
HACKENSACK UNIVERSITY MEDICAL CENTER

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ABBREVIATION 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
I□B□	I kappa B alpha-associated protein kinase
kg	Kilogram
Ki	inhibitory constant
lbs	Pounds
m^2	square meters
mg	Milligram
min	Minute
mL	Milliliter

ABBREVIATION LIST

Abbreviation	Definition
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 common hematological malignancy, affecting about 55,000 Americans. Limited control of disease can be achieved with conventional dose chemotherapy but randomized studies reported improved response rates for patients who are treated with dose-intense therapy and autologous hematopoietic stem cell (HSC) transplantation. However, most patients who undergo dose-intense therapy will require salvage therapy at a median of two to three years after transplantation. High-dose melphalan (200 mg/m^2) appears to be the most effective conditioning regimen but the potentially greater tumor cell kill of dose-intense melphalan in synergistic combination with other drugs is only now being studied.

1.1.1 Multiple Myeloma

Multiple myeloma is a malignancy of plasma cells and belongs in a family of diseases known as plasma cell dyscrasias. It accounts for about 1% of all cancers and 10% of all hematological malignancies. Thus, it is the second most common "blood cancer," affecting approximately 55,000 Americans. The annual incidence is about 20,000 cases; the annual death rate is about 11,000. The median age at diagnosis is 70 years old. The disease is more common in males (1.3 to 1) and the frequency doubles in African-Americans compared to Caucasians.

1.1.2 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 to explore 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.

A number of randomized studies comparing dose-intense therapy with autologous stem cell support to standard therapy regimens have been conducted. The French Myeloma Intergroup reported a large-scale randomized trial (IFM 90) that randomized two hundred

patients to either conventional dose VMCP/VBAP or autologous bone marrow transplantation with melphalan and total body irradiation after four cycles of induction treatment (Attal et al., 1996). The findings were strikingly in favor of the dose-intense approach with improvements in complete response rates (22% vs 5%) and median probabilities of event-free (27 months vs 18 months) and overall-survivals (60+ months vs 37 months). In contrast, the USIG found no difference in overall survival using the same transplant conditioning regimen but a much more intensive "standard" non-transplant chemotherapy regimen (Barlogie et al., 2006). These authors also acknowledged that the combination of melphalan and TBI is now recognized as an inferior transplant regimen. The French group Myelome Autogreffe (MAG) achieved results comparable to the IFM 90 trial; however, there was no significant difference in overall survivals as a result of unexpected prolonged survivals in the chemotherapy arm (Fermand et al., 2005). The Spanish PETHEMA group did not find a statistically significant difference in EFS and OS between chemotherapy and dose-intensive therapy (Blade et al., 2005). However, only patients who responded (CR: 15%; PR: 68%; MR: 17%) to conventional dose chemotherapy were randomized and patients in the chemotherapy arm were allowed to cross over into the dose-intensive therapy group. The Italian MMSG compared melphalan-prednisone to two courses of melphalan at 100 mg/m^2 with autologous stem cell support (Palumbo et al., 2004). They found significant improvement in CR and EFS in the transplant arm. The Medical Research Council Myeloma VII trial of 407 patients reported similar results for a comparison of six cycles of BCNU, doxorubicin, cyclophosphamide and melphalan to at least three cycles of doxorubicin, vincristine, methylprednisolone, and cyclophosphamide followed by melphalan at 200mg/m^2 and autologous stem cell transplant (Child et al., 2003). This trial deserves special consideration in that it is the most recent of the randomized trials and was carried out in the era of more advanced supportive care and the availability of newer therapeutic agents. It still showed a statistically significant advantage for HDT in terms of CR, EFS and OS. In addition, it did not show any increase in treatment-related mortality relative to conventional therapy. These randomized trials, all of which showed a trend to, or significantly improved results for patients treated with dose-intense therapy, with the support of numerous phase II trials, clearly indicate that dose–intense therapy with autologous HSCT should be offered to appropriate patients as part of their initial treatment. The median EFS is remarkably constant (25-31 months). It is more difficult to analyze OS results since OS partly depends on subsequent salvage therapy. However, median OS was significantly longer in the three studies where differences in EFS were more marked. In all studies, procedure-related death rate was <5% and not greater than that observed with conventional chemotherapy.

Table 1: Randomized Trials Comparing Conventional Chemotherapy vs. High-dose Therapy

				CR rate (%)			Median EFS (m)			Median OS (m)		
	N	Age	MedianF/U	CC	HDT	P	CC	HDT	P	CC	HDT	P
IFM 90	200	<65	7 yr	5	22	<0.001	18	28	0.01	44	57	0.03
MAG91	190	55-65	56 m	NE	NE		19	25	0.05	45	42	NS
PETHEMA	164	≤65	42 m	11	30	0.002	34	42	NS	67	65	NS
Italian MMSG	195	50-70	2 yr	7	26	<0.001	16	28	0.0036	43	58+	0.0008
USIG	50			15	17	NS	21	25	0.05	53	58	NS
MRC7	407	<65	42 m	8	44	<0.001	19.6	31.6	<0.0001	42	54	<0.001

Abbreviations: CC=conventional chemotherapy, CR=complete remission, EFS=event free survival, HDT=high-dose therapy, OS=overall survival, NE=not evaluated, NS=difference not statistically significant.

1.1.3 Age as a Limiting Factor

The plasma cell disorders strike older populations of patients; multiple myeloma is rare for patients under the age of 40 years. The Arkansas group reported a slight increase in 60-day mortality for patients over the age 65 undergoing transplantation for the treatment of myeloma (8% vs 2%). However, median event-free (1.5 vs. 2.8 years) and overall survivals (3.3 vs. 4.8 years) were statistically similar (Siegel et al., 1999).

Age has also not been found to be a significant predictor of transplant related mortality in other series. An analysis of 383 consecutive transplants at Temple University actually noted poorer survival of younger patients compared to older patients, presumably a result of the willingness of physicians to offer aggressive treatment to younger patients with higher risk disease or co-morbid illnesses (Goldberg et al., 1998). Conflicting data on this subject in at least 14 studies (6 no effect, 8 adverse) point to the need for patient selection criteria other than chronological age.

MD Anderson Cancer Center (Qazilbash et al. 2007) treated 26 elderly myeloma patients (>70 years), who received a preparative regimen of melphalan 200 mg/m2 (19 patients), melphalan 180 mg/m2 (six patients) or melphalan 140 mg/m2 (one patient). Twenty-two of the 26 patients were alive after a median follow-up of 25 months (range=8-74). Responses (complete+partial response) were seen in 20 patients (77%), five (19%) of which were complete responses. Median PFS was 24 months, whereas median OS has not been reached. Cumulative incidence of 100-day TRM was 0%. Three-year PFS and OS were 39% (range=16-61) and 65% (range=35-83), respectively. Patients with relapsed disease at transplant and patients with an interval of >12 months between diagnosis and autotransplant, had a shorter OS (P=0.0004 and 0.04).

1.2 Melphalan

1.2.1. Melphalan Non-clinical Pharmacology

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 (Samuels and Bitran, 1995). Melphalan's cytotoxic effects are related to its concentration and the duration of exposure to melphalan of the cell (Hall and Tilby, 1992).

Enhanced repair of DNA interstrand crosslinks may be a mechanism of resistance that develops after prior exposure to this drug (Spanswick et al., 2002). 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.

1.2.2. Clinical Pharmacokinetics and Pharmacodynamics

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 (Pinguet et al., 1997). The median times 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, 51.6-16681) 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 (infused rapidly over 5 minutes; Gouyette et al., 1986). 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.

Melphalan undergoes hydrolysis in the circulation and the amount cleared by the kidneys is not well defined. However, the toxicity of melphalan (hematological or gastrointestinal) is reported higher for patients with diminished renal function. A study of nine patients given a melphalan dose of 5 mg/m^2 (four of whom subsequently treated with 220 mg/m^2) showed highly variable renal clearance of melphalan with the percentage of dose excreted unchanged in the urine ranging from 2.5% to 92.8% (Reece et al., 1988). These authors speculated that the variation in renal clearance observed for these patients could account for the large variation in plasma clearance observed in all studies of melphalan pharmacokinetics.

1.2.3. Clinical Toxicities of Melphalan

Dose-related leukopenia, thrombocytopenia, anemia, usually with nadir 2-3 weeks and with recovery 4-5 weeks after dosing (without HSC support) will occur with moderate melphalan dose schedules. Hematological toxicity is the most prominent serious toxicity associated with

the use of high-dose melphalan regimens, with neutrophil counts falling to <100/uL about 7 days after administration. However, initial hematological recovery occurs about 3 to 5 days later for patients given hematopoietic stem cell and cytokine support. About 50% of patients will require blood component (red blood cells and/or platelet) support or will develop neutropenic fevers during the period of marrow hypoplasia.

Dose-related nausea and vomiting beginning 2-4 hrs after dosing, peaking at 12 hrs, and persisting for several days, and delayed nausea and vomiting starting 24-48 hrs after administration and persist for multiple days to 3 or 4 weeks occurs with high doses of melphalan. Stomatitis will occur in most patients can be almost completely prevented by prophylactic cooling of the mouth with ice during the infusion of melphalan. A small proportion of patients will develop diarrhea.

Melphalan is associated with a number of rare complications including: hemolytic anemia, abnormal liver function tests with jaundice, renal insufficiency, atrial fibrillation, pulmonary fibrosis and interstitial pneumonitis, skin hypersensitivity, seizures (described in patients with renal failure receiving melphalan, hyponatremia and SIADH, secondary leukemia and myelodysplastic syndromes, anaphylaxis (rare), and potentially irreversible sterility.

1.3 VELCADE (bortezomib) for Injection

1.3.1. 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. 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 has a novel pattern of cytotoxicity in National Cancer Institute (NCI) in vitro and in vivo assays (Adams et al., 1999). In addition, bortezomib has cytotoxic activity in a variety of xenograft tumor models, both as a single agent and in combination with chemotherapy and radiation (Steiner et al., 2001; Teicher et al., 1999; Cusack et al., 2001; LeBlanc et al., 2002; Pink et al., 2002). Notably, bortezomib induces apoptosis in cells that over express bcl-2, a genetic trait that confers unregulated growth and resistance to conventional chemotherapeutics (McConkey et al., 1999).

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

1.3.2. Non-clinical Pharmacology

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

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

1.3.3. Non-clinical Toxicity

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

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

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

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

1.3.4. 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/m^2 and 1.3 mg/m^2 dose, the mean first-dose maximum observed plasma concentrations of bortezomib were 57 and 112 ng/mL, respectively in 11 patients with multiple myeloma and creatinine clearance values >50 mL/min participating in a pharmacokinetics study. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1.0 mg/m^2 dose and 89 to 120 ng/mL for the 1.3 mg/m^2 dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours. Bortezomib is eliminated more rapidly following the first dose. Mean Total Body Clearances were 102 and 112 L/h following the first dose for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1.0 and 1.3 mg/m^2, respectively. Clinical experience has shown that the change in clearance does not result in overt toxicity from accumulation in this multidose regimen in humans.

In subjects with advanced malignancies, the maximum pharmacodynamic effect (inhibition of 20S activity) occurred within 1-hour post dose. At the therapeutic dose of 1.3 mg/m^2 in subjects with multiple myeloma, the mean proteasome inhibition at 1-hour post dose was approximately 61%.

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

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

1.3.5. Clinical Experience

It is estimated that more than 55,000 patients have been treated with bortezomib, including patients treated through Millennium-sponsored clinical trials, Investigator-Initiated Studies, the US NCI Cancer Therapy Evaluation Program (CTEP), and with commercially available drug. Bortezomib 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 bortezomib in a number of therapeutic settings involving subjects with various advanced malignancies. In a Phase I trial in patients with refractory hematologic malignancies, the MTD for a twice weekly for 4 weeks of a 42 day cycle was 1.04 mg/m^2/dose,

with DLTs of thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise (Orlowski et al., 2002). The toxicity was greatest during the third and fourth weeks of therapy. In the 3-week schedule of bortezomib monotherapy (4 doses, given on Days 1, 4, 8, and 11 of a 21-day treatment cycle), the DLT occurred at 1.56 mg/m^2/dose (3 subjects with Grade 3 diarrhea and 1 with peripheral sensory neuropathy). Therefore, the MTD at this schedule was 1.3 mg/m^2/dose. In a 35-day treatment cycle with 4 weekly doses of bortezomib monotherapy, the MTD was 1.6 mg/m^2/dose and DLT included hypotension, tachycardia, diarrhea, and syncope.

In phase 1 clinical studies, anti-tumor activity was reported in subjects with NHL, multiple myeloma, Waldenström's Macroglobulinemia, squamous cell carcinoma of the nasopharynx, bronchoalveolar carcinoma of the lung, renal cell carcinoma, and prostate cancer.

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

The phase 3 study (M34101-039) (Richardson et al, 2005), also referred to as the APEX study, was designed to determine whether bortezomib 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 bortezomib relative to high-dose dexamethasone, and whether treatment with bortezomib 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 (bortezomib: 331; dexamethasone: 332). Patients randomized to bortezomib received 1.3 mg/m^2 I.V. push twice weekly on days 1, 4, 8, and 11 of a 3-week cycle for up to eight treatment cycles as induction therapy, followed by 1.3 mg/m^2 bortezomib weekly on days 1, 8, 15, and 22 of a 5-week cycle for three cycles as maintenance therapy. Patients randomized to dexamethasone received oral dexamethasone 40 mg once daily on days 1 to 4, 9 to 12, and 17 to 20 of a 5-week cycle for up to four treatment cycles as induction therapy, followed by dexamethasone 40 mg once daily on days 1 to 4 followed of a 4-week cycle for five cycles as maintenance therapy. The European Group for Blood and Marrow Transplant (EBMT) response criteria, as described by Blade (Blade et al., 1998) were utilized to determine disease response. There was a 78% increase in TTP for the bortezomib arm. Median TTP was 6.2 months for the bortezomib arm and 3.5 months for the dexamethasone arm (P<.0001). CR (complete response) + PR (partial response) was 38% with bortezomib vs. 18% with dexamethasone (P<.0001). CR was 6% with bortezomib vs. <1% with dexamethasone

(P<.0001). The CR + nCR rate was13% with bortezomib vs. 2% with dexamethasone. In patients who had received only one prior line of treatment (bortezomib: 132; dexamethasone: 119), CR + PR was 45% with bortezomib 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 bortezomib arm vs. patients on the dexamethasone arm. The probability of survival at one year was 80% for the bortezomib arm vs. 66% for the dexamethasone arm, which represented a 41% decreased relative risk of death in the first year with bortezomib (P=.0005). In patients who had received only one prior line of treatment, the probability of survival at one year was 89% for the bortezomib arm vs. 72% for the dexamethasone arm, which represented a 61% decreased relative risk of death in the first year with bortezomib (P=.0098). (Richardson et al., 2005). Updated response rates and survival data were reported for M34101-039 (Richardson ASH, 2005). The updated CR (complete response) + PR (partial response) rate was 43% with bortezomib. The CR + nCR rate was 16% with bortezomib. With a median 22 months of follow-up, overall survival was significantly longer for patients on the bortezomib arm vs. patients on the dexamethasone arm. The median overall survival was 29.8 months (95% CI: 23.2, not estimable) for the VELCADE arm vs. 23.7 months (95% CI: 18.7, 29.1) for the dexamethasone arm (hazard ratio = 0.77, P= 0.0272). The probability of survival at one year was 80% for the bortezomib arm vs. 67% for the dexamethasone arm (P=0.0002).

Studies using bortezomib as monotherapy and in combination with other chemotherapy agents are continuing. Potential Risks of bortezomib (this section reflects updates to our standard risks language that have been updated since I gave the modified version of the protocol several months ago.

1.4. Combination of Bortezomib and Other Agents

A pre-clinical study reported by the Dana Farber Jerome Lipper Multiple Myeloma Center demonstrated synergy in cell line kill between bortezomib and other agents such as doxorubicin and melphalan (Mitsiades et al., 2003). Synergy was found with co-incubation of bortezomib with doxorubicin, or with pre-exposure to either of the drugs. Bortezomib exposure after prior doxorubicin exposure achieved the greatest cell kill. Myeloma cell lines known to be resistant to doxorubicin or melphalan confirmed sensitization by bortezomib, as did studies involving freshly isolated myeloma cells from patients known to be resistant to bortezomib or doxorubicin. A proposed mechanism for this enhancement of chemosensitivity is the down-regulation of several effectors involved in the cellular response to genotoxic stress, restoring sensitivity to DNA-damaging chemotherapeutic agents.

Berenson et al recently published a phase I/II trial of bortezomib and low-dose melphalan combination therapy for the treatment of patients with relapsed or refractory multiple myeloma (Berenson et al., 2006). Bortezomib was administered from 0.7 to 1.0 mg/m^2 on days 1, 4, 8, and 11 of a 28-day cycle for up to eight cycles, and oral melphalan was administered in escalating doses form 0.025 to 0.25 mg/kg on days 1 to 4. Thirty-five patients were enrolled and dose-limiting grade 4 neutropenia in two of six patients in the highest dose cohort led to the assignment of bortezomib 1.0 mg/m2 and melphalan 0.10 mg/kg as the maximum-tolerated dose. Responses were observed in 23 of 34 evaluable patients. Myelosuppression was the most prominent toxicity; Grade 1/2 neurotoxicity developed in 8 patients and worsened in 4 of 15 patients with pre-existing neurotoxicity. Diarrhea and

nausea/vomiting were observed at all dose levels and no relationship to drug dosage was evident.

Hollmig et al described treatment of 37 patients with bortezomib and high-dose melphalan (Hollmig et al., 2004). Bortezomib was dosed at 1.0 mg/m^2 or 1.3 mg/m^2 on days -4 and -1 before autologous HSC transplantation, with melphalan (50-200 mg/m^2) given on the same days for 26 patients and on day -1 only for 11 patients. All patients achieved granulocyte (median, 13 days) and platelet (median, 17 days) recoveries. Serious (grade 3/4) mucositis and/or diarrhea occurred in 14% and 29% of patients, respectively. No transplant-related deaths were reported. A partial or better response was observed in 73% of evaluable patients. This same group also reported the use of 3 or 4 fractions of high-dose melphalan given along with bortezomib (1.0 or 1.3 mg/m^2) in a standard day 1, 4, 7, ±10 fashion (Pineda-Roman et al., 2006). Maximum doses of melphalan reached 240-250 mg/m^2. Only 1 of 22 patients treated experienced significant (grade 2) mucositis with grade 3/4 diarrhea (primarily infectious) in 8 patients. These reports suggest a safe starting dose of bortezomib in combination with high-dose melphalan of 1.0 mg/m^2.

A similar phase I trial of bortezomib and pegulated liposomal doxorubicin (PegLD) enrolled 42 patients (24 with multiple myeloma) with advanced hematological malignancies (Orlowski et al., 2005). Bortezomib dosing started at 0.9 mg/m^2 and was advanced in a modified Fibonacci escalation with subsequent steps of 1.05, 1.2, 1.3, 1.4, and 1.5 mg/m^2, and was given on days 1, 4, 8, and 11 of each 21-day cycle. PegLD, 30 mg/m^2, was given on day 4 of each cycle. A bortezomib dose of 1.3 mg/m^2 was recommended for further study because of frequent dose reductions and delays at the MTD of 1.5 mg/m^2. Hematological toxicities were the most common, with fatigue being the most-common non-hematological toxicity. Again, diarrhea was observed at all dose levels. Of the 22 evaluable patients treated for myeloma, 8 achieved a CR or very good PR, and another 8 achieved a PR.

The combination of bortezomib and carboplatin was studied in a phase I trial involving 15 patients with recurrent ovarian or primary peritoneal cancer (Aghajanian et al., 2005). Carboplatin was administered on day 1 at a dose of 5 (AUC), and bortezomib on days 1, 4, 8, and 11 of each three week cycle at dose levels of 0.75, 1, 1.3, and 1.5 mg/m^2. No dose-limiting hematological toxicities were observed; dose-limiting non-hematological toxicities were diarrhea, skin rash, and sensory peripheral neuropathy (all grade 3) and the highest dose level of 1.5 mg/m^2, and the MTD was determined to be 1.3 mg/m^2. An overall response rate of 47% was demonstrated, and one patient with platinum-resistant disease achieved a CR.

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 (Rowley, et al, 2009). 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 patients 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.

2. Study Objectives

2.1 **Primary Objective**:

To compare the progression-free survivals of elderly patients with multiple myeloma treated with either high-dose melphalan or high-dose melphalan in combination with bortezomib

2.2 **Secondary Objective**:

To compare the response rate, overall survival, and regimen-related toxicities of elderly patients with multiple myeloma treated with either high-dose melphalan or high-dose melphalan in combination with bortezomib

3. Investigational Plan

3.1 Overall Design and Plan of Study

This is a single-institution, non-blinded phase III randomized study

3.2 Patient Selection

3.3 Inclusion Criteria

3.3.1 Confirmed diagnosis of multiple myeloma less than 12 months since initiation of systemic therapy

3.3.2 $\geq 2x10^6$ CD34+cells/kg available in cryopreservation

3.3.3 Age $\geq$60 years at time of transplantation

3.3.4 KPS 70-100%

3.3.5 Recovery from complications of prior therapies

3.3.6 Gender: There is no gender restriction

3.4 Exclusion Criteria

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

3.4.1 Diagnosis other than multiple myeloma

3.4.2 Chemotherapy or radiotherapy within 8 days of initiating treatment in this study

3.4.3 Prior dose-intense therapy within 56 days of initiating treatment in this study

3.4.4 Uncontrolled bacterial, viral, fungal or parasitic infections

3.4.5 Uncontrolled CNS metastases

3.4.6 Known amyloid deposition in heart

3.4.7 Organ dysfunction

3.4.8 LVEF <40% or cardiac failure not responsive to therapy

3.4.9 FVC, FEV_1, or DLCO <40% of predicted and/or receiving supplementary continuous oxygen

3.4.10 Evidence of hepatic synthetic dysfunction, or total bilirubin >2x or AST >3x ULN

3.4.11 Calculated creatinine clearance <20 ml/min

3.4.12 Sensory peripheral neuropathy grade 4 within 14 days of enrollment

3.4.13 Karnofsky score <70% unless a result of bone disease directly caused by myeloma

3.4.14 Life expectancy limited by another co-morbid illness

3.4.15 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

3.4.16 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.

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

3.4.18 Patients unable or unwilling to provide consent

3.4.19 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

3.4.20 Patient has received other investigational drugs within 14 days before enrollment

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

3.5 Patient Evaluations

3.5.1 Pre-transplant evaluation must be performed within 60 days of transplant, except for HLA, ABO and Rh typing

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

3.5.3 Careful physical exam with determination of Karnofsky score and findings related to underlying malignancy

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

3.5.5 CBC with differential

3.5.6 ABO, Rh, red cell antibody screen, sickle cell screen (hemoglobin solubility) for African-Americans

3.5.7 PT, PTT

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

3.5.9 HIV, Hepatitis B, Hepatitis C and CMV serology

3.5.10 Infectious disease testing, if previously documented positive, need not be repeated to comply with this requirement

3.5.11 Creatinine clearance (measured)

3.5.12 Disease Staging

3.5.13 Serum and urine protein electrophoreses and immunofixation with measurement of monoclonal protein, serum free light chain

3.5.14 Beta-2 microglobulin

3.5.15 Radiological studies of any sites of bone pain if considered clinically significant

3.5.16 Skeletal survey if not performed within 6 months of start of study treatment but may be deferred if PET CT completed within 6 months

3.5.17 Pulmonary function tests with DLCO

3.5.18 MUGA scan or Cardiac Echocardiogram

3.5.19 Patients with a suspected diagnosis of amyloidosis will undergo echocardiography for the detection of cardiac involvement

3.5.20 EKG

3.6 Analysis of PBSC and Marrow Components

3.6.1 CD34+ cell count

3.7 Post-Transplant Evaluation

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

3.7.2 Daily assessment of toxicity from day-1 until resolution of all Grade 3/4 treatment-related toxicities

3.7.2.1 Presence assessed and scored in accordance with NCI toxicity guidelines

3.7.3 CBC daily from day 0 until ANC ≥500/ul on two sequential days after nadir reached (engraftment). Thereafter, CBC recommended weekly until documentation of transfusion independence (platelet count ≥20,000/ul without transfusion for ≥7 days)

3.7.4 Chemistry profile including magnesium t.i.w. until documentation of engraftment, and then recommended weekly until stabilization of electrolytes is documented

3.7.5 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.

3.8.2 24 hour urine for creatinine clearance, total protein, protein electrophoresis with quantitation of monoclonal protein by immunofixation, serum free light chain measurements at 4 week intervals (±7 days) starting at day +56 after transplantation for 3 months and then at 3 month intervals (or more frequently as clinically necessary) until demonstration of disease progression

3.9 Study Treatments

3.9.1 Study Medications

3.9.1.1 Bortezomib (VELCADE) for Injection is a sterile lyophilized powder for reconstitution and is supplied in vials containing bortezomib and mannitol at a 1:10 ratio. For example, vials containing 3.5 mg of bortezomib contain 35 mg of mannitol. Vials containing lyophilized bortezomib 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. bortezomib is cytotoxic. As with all cytotoxic drugs, caution is required when preparing and handling bortezomib 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 bortezomib. Each vial of bortezomib 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 bortezomib 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 bortezomib 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.

3.9.1.2 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.

3.10 Outline of Treatment Plan

Patients will be randomly assigned to treatment arm A or treatment arm B

Figure 1: Outline of Treatment Schema treatment arm A

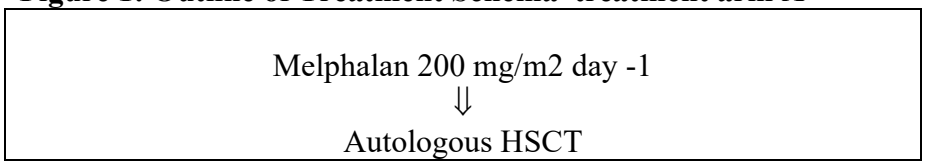
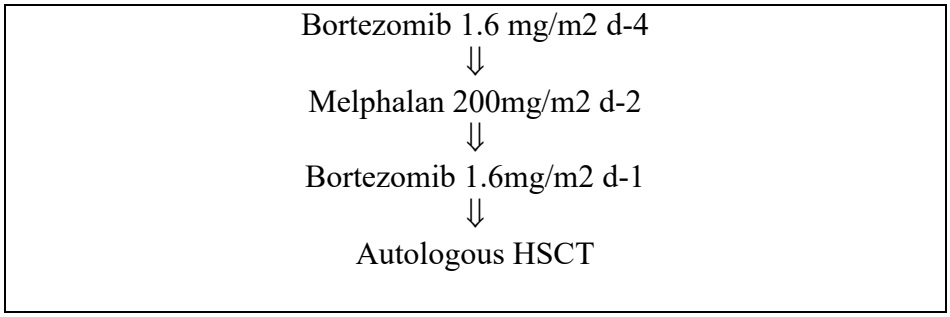


Figure 2: Outline of Treatment Schema treatment arm B



3.11 Conditioning Regimens

3.11.1 Treatment arm A

3.11.2 Melphalan

3.11.2.1 Melphalan is administered by rapid intravenous infusion via a central vein over 60 minutes

3.11.2.2 The final dilution of melphalan is physically and chemically stable for 60 minutes and therefore will be administered within that time period

3.11.2.3 Melphalan will be given as a single dose

3.11.2.4 Patients are encouraged to “chew” ice for 15 minutes before through 1 hour after administration of melphalan

3.11.2.5 Dosing will be based on body surface area calculated using actual body weight

3.11.2.6 Patients will be hospitalized starting at least 1 hr before melphalan administration and continuing until ANC > 500/uL. Hydration will be used for uro-protection for 2 hours pre- and post melphalan infusion

3.11.3 Treatment arm B

3.11.4 Bortezomib

3.11.4.1 Bortezomib is administered subcutaneously in the abdomen or anterior thighs

3.11.4.2 Bortezomib will be administered any time on day -4 and -1, 20 hrs after the start of the melphalan infusion on day -2

3.11.4.3 Dosing will be based on body surface area calculated using actual body weight

3.11.4.4 Dexamethasone is administered at a dose of 20 mg i.v. daily on days -4 and -1 (with bortezomib). Dexamethasone is administered at a dose of 10 mg i.v. as a component of the anti-nausea regimen on day -2 before melphalan administration

3.12 Stem Cell Infusion

3.12.1 Day 0 is defined as the day of first stem cell infusion.

3.12.2 Additional cells may be infused on subsequent days if the volume of the HSC components is deemed too large for a single infusion

3.12.3 HSC will be infused 18 hours or later after bortezomib infusion

3.12.4 Day 0 should be fixed on a Monday – Friday, when possible

3.12.5 All patients will receive unmodified HSCT (other than cryopreservation). These components will not be irradiated

3.12.6 Cells will be infused according to HUMC Standard Practice guidelines

3.13 Post-transplant Cytokine Administration.

3.13.1 Patients will routinely receive filgrastim, 5 ug/kg sc, on days 3, 5, 7, 9 and 10+ after stem cell transplantation. Filgrastim dose may be rounded to vial size (e.g., <60kg: 300 mcg, > 60 kg: 480 mcg, >100 kg: 600 mcg)

3.14 Post-transplant Supportive Care

3.14.1 Hospitalization: Patients will be cared for in the inpatient or outpatient transplant units. Patients will be discharged from the transplant unit when hematological recovery occurs, the patient is clinically stable, and all grade 3/4 toxicities have resolved Mucositis:

3.14.1.1 Patients may receive any anti-emetic regimen determined to be clinically appropriate

3.14.1.2 Patients may receive any anti-diarrhea regimen determined to be clinically appropriate

3.14.2 Central line: Patients will have central venous access or peripheral inserted central catheter (PICC) suitable for blood component support and maintained according to HUMC Standard Practice guidelines

3.14.3 Infection prophylaxis: Patients will receive prophylaxis HSV, bacterial, and fungal infections according to HUMC Standard Practice guidelines

3.14.4 Blood component support: Patients will receive transfusions in accordance with HUMC Standard Practice guidelines

3.14.5 Nutrition: Patients may receive enteral or parenteral alimentation if caloric or protein intake falls below daily basal needs

3.14.6 Post-transplant treatment: There are no restrictions for administration of involved field radiation, chemotherapy, maintenance therapy, or surgical interventions after transplantation

3.14.7 Bisphosphonates: Infusions of bisphosphonate therapy after transplantation should be considered for all patients

3.14.8 Post-transplant vaccinations: Vaccinations will be administered after transplantation in accordance with HUMC Standard Practice guidelines

3.15 Disease Response

3.15.1 Patients should undergo restaging of disease at 2 months and 3 months post-transplant then every 3 months thereafter as defined in section 3.8.

3.16 Dosing of Agents

3.16.1 Melphalan dosing will be based on actual body weight. The amount (in mg) of drug to be administered will be determined based on body surface area. Body surface area is to be calculated based on body weight using a standard nomogram.

3.16.2 Bortezomib dosing will be based on actual body weight. The amount (in mg) of drug to be administered will be determined based on body surface area. Body surface area is to be calculated based on body weight using a standard nomogram

3.16.3 Patient weight will be determined by the nursing or nutrition staff within 7 days of start of conditioning

3.16.4 Administration of Melphalan

3.16.4.1 Melphalan will be dosed based on actual body weight at a dose of 200 mg/m^2 and infused on day -1 (Arm A) or day -2 (Arm B)

3.16.4.2 Administer melphalan IV over 60 minutes through a central catheter. Rapid infusion may result in dizziness, nasal stuffiness, rhinorrhea, or nasal congestion during or immediately after infusion

3.16.4.3 Administer early in the day

3.16.4.4 Have patient empty bladder frequently

3.16.4.5 Patients will receive hydration before and after administration of melphalan

3.16.4.6 "Chewing" on ice may decrease the severity of oral mucositis and is encouraged for all patients starting 15 minutes before, during, and for 60 minutes after the infusion of melphalan

3.16.4.7 Patients will receive an anti-emetic regimen such as lorazepam 1 mg i.v., dexamethasone 10 mg i.v., and Ondansetron 12mg i.v. 30 minutes before melphalan infusion

3.16.5 Administration of Bortezomib

3.16.5.1 Bortezomib will be dosed based on actual body weight administered subcutaneously on day -4, and day -1 before HSC infusion

3.16.5.2 Bortezomib is supplied as a lyophilized white powder in 3.5 mg single-dose vials

3.16.5.3 Bortezomib is reconstituted with 1.2 ml sterile water for injection, without shaking

3.16.5.4 Administration

3.16.5.4.1 Subcutaneously in anterior thighs or abdomen.. Each vial is for a single use administration.

3.16.5.4.2 Second dose of bortezomib will be no less than 20 hrs after melphalan administration

3.16.5.4.3 Dexamethasone, 20 mg i.v., will be given as a pre-medication, before each dose of bortezomib

3.17 Pre-Transplant Therapy

Chemotherapy and/or radiation therapy may be given to reduce tumor bulk as determined on clinical grounds. The referring oncologist may be asked to administer this therapy. The prior therapies are not specified by this protocol

3.17.1 Patients will not proceed to dose-intense therapy any sooner than 8 days after completion of the most recent cycle of chemotherapy or radiotherapy

3.17.1.1 The timing of therapy is in reference to the dose of melphalan

3.17.1.2 Therapy with should be discontinued no less than 7 days before initiation of bortezomib

3.17.2 Collection of Autologous Hematopoietic Stem Cells

The methods of collection of hematopoietic stem cells are not specified by this protocol

3.18 Treatment Assignment

Patients will be assigned to treatment in a randomized fashion with stratification for factors associated with risk of relapse for FISH factors associated with aggressive disease (e.g.: t(4:11), del13q, elevated B_2M at diagnosis).

3.19 Blinding, Packaging, and Labeling

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

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

3.20 Concomitant Treatment

3.20.1 Required Concurrent Therapy

Not applicable. Patients will receive standard care

3.20.2 Prohibited Concurrent Therapy

Any investigational agent

3.21 Treatment Compliance

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

3.22 Duration of Treatment and Patient Participation

Patients will be hospitalized until resolution of serious adverse events. Patients will then be followed, indefinitely, for survival and duration of response to the treatment received.

3.23 Termination of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care.

x The primary reason for a patient's withdrawal from the study is to be recorded in the source documents. The patient will be followed for study endpoints, per study guidelines, unless the patient withdraws consent for study participation.

4. Adverse Events

4.1 Definitions

4.1.1 Adverse Event Definition

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

4.1.2 Serious Adverse Event Definition

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

- Results in death.
- Is life-threatening. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (eg, surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a persons' ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

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

4.2 Procedures for AE and SAE Reporting

Investigator-sponsor must report all serious adverse event (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, 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 (htt;:///ctep.cancer.gov/forms/CTCAE_Index.pdf).

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

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

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

Grade 2 = Moderate: an adverse experience which is sufficienty discomforting to interfere with normal every day activities.

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

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

4.3.2. Assessment of Causality

a. 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.

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

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

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.

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

b. 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.

Known pharmacology of the drug

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.

4.3.3. Follow-up of Adverse Experiences

a. Patients with adverse experiences grade 3/4 will be actively followed until the event has subsided (disappeared) or until the condition has stabilized.

b. 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

5.1.Primary Objective

The primary objective of this randomized Phase III trial is to compare two different treatment regimens for multiple myeloma with respect to three-year progression-free survival (PFS). In particular, the study will provide us with an evaluation of whether the high-dose combination treatment increases the progression-free survival over the standard high-dose treatment. All the patients in the first arm receive a single high-dose of melphalan as the conditioning regimen for the autologous hematopoietic stem cell transplant (treatment arm A), the second arm receives melphalan and bortezomib a conditioning regimen for the autologous hematopoietic stem cell transplant (treatment arm B).

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 (day 0) 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.

5.2.Secondary Objective

Secondary endpoints will include:

a. Overall survival (OS): Defined as time from the first dose of administration to death from any cause.
b. 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.
c. Univariate analyses of the risk of progression/relapse and mortality: In addition, multivariate analyses of the risk of progression/relapse and overall mortality will be conducted to assess influence of variables measured after the start of treatment.
d. Regimen-related toxicity: Graded and presented in a descriptive nature.

Descriptive analysis of baseline characteristics and demographics in the two-treatment arms 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 is 208 (allowing intensive analysis and drop-out) subjects. It is estimated that four years of accrual will be necessary to enroll this number of subjects. HUMC treats about 150-170 of patients with this diagnosis every year, about half of who are believed eligible for this study. It is assumed that patients will enroll into the study uniformly over the accrual period.

The randomization will be stratified by risk status (high, low) where 156 high risk patients and 52 low risk patients are enrolled assuming 3 (high):1 (low) ratio. High risk myeloma patients on this protocol are defined as having a serum Beta 2 microglobulin level > 4 mg/L; and/or abnormalities of chromosome 13 on standard metaphase karyotype analysis; and/or abnormalities of chromosome 17 or translocation 4:14 or 14:16 by FISH analysis at any time prior to transplant. Standard risk myeloma patients on this protocol are defined as having a serum Beta 2 microglobulin level $\leq$ 4 mg/L and absence of cytogenic findings described above. Patients with no karyotype analysis or failed analysis are assumed to not have chromosome 13 abnormalities.

After eligibility is established, subjects will be randomized in equal numbers to the melphalan-HSCT (104), and melphalan and bortezomib-HSCT (104) arms. 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 three years. The power of a two-sample one-sided log-rank test of surviving probability was calculated using PASS 14.

The study design considers PFS at three-years post-transplant ranging from 36% to 56%. The control, arm A, is assumed to have PFS of 36%. The new regimen consisting of melphalan and bortezomib in arm B could increase PFS to 56%. Thus, using a desired power of 90%, for this one-side log-rank test sequentially evaluated at three timepoints (including interim analyses), at 2.5% level of significance, two-year accrual, three-year follow up, we obtained the total sample of 208 with 104 subjects in the arm A and 104 subjects in arm B. This calculation achieved power >= 90.15%. Among 208 patients, 156 high risk patients and 52 low risk patients will be assumed to reflect 3:1 ratio at the beginning of trial. A randomization schedule was created for each risk status cohort and a set of two boxes of sealed envelopes containing the randomized treatment assignment has been maintained by designated members of the study team.

The sequential analysis sample calculation was based on O'Brien-Flemming spending function.

5.5.Efficacy analysis

This is a phase III study comparing transplantation with high-dose melphalan to high-dose melphalan and bortezomib in patient 60 years or older with a diagnosis of multiple myeloma.

5.6.Statistical Hypothesis

The null hypothesis is that the 3 year progression-free survival rate in treatment arm A is 36%. The alternative hypothesis for this study posits that the treatment plan consisting

autologous transplantation with melphalan-bortezomib (treatment arm B) will increase the 3 year progression-free survival to 56% which is 20 % more than PFS in arm A.

Thus, we will evaluate the hypotheses

H_O: $S_A(3) \geq S_B(3)$

H_A: $S_A(3) < S_B(3)$

where $S_A(3)$ = the three year progression free surviving proportion of arm A which is assumed to be 0.36, $S_B(3)$ = the three year progression free surviving proportion of arm B. To account for heterogeneity of outcome due to risk status of patients in the treatment arms, the analysis of the comparison will be stratified on risk status. Thus, a one-sided log-rank test stratified on risk status (high risk 3:low risk1) will be conducted to determine if autologous transplantation with high-dose melphalan-bortezomib improves the progression-free survival that in over high-dose mephalan alone using a 2.5% level of significance.

5.7.Primary endpoints

To compare the PFS at 3 years between the two treatment arms each allocated 104 subjects. This sample size calculation is based on the assumption that the expected PFS of the standard transplant arm (melphalan 200 mg/m2) is 36% at 3 years (CIBMTR data).

The primary analysis will include all randomized subjects, classified according to their randomized treatment assignment; irrespective of treatment actually received [intent-to-treat]. The treatment arms will be compared using a one-sided log-rank test. All tests will be performed using the significance level of 2.5%.

Analysis of PFS using a Cox proportional hazards mode will be conducted while adjusting for imbalance in other risk factors. To fit the multivariate model, a stepwise backward selection procedure will be used while considering the type of conditioning regimen (melphalan versus Melphalan with bortezomib), relapse risk status (low risk, high risk), age at transplant and Karnosfky performance score (<90 versus ≥90). An examination of the goodness-of-fit will be performed using Grambsch-Therneau and Martingale residual plots and lowess smooth of Cleveland. 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 examined by introducing a time-dependent covariate for each risk factor and outcome. The stratified Cox proportional hazards model will be also performed to see the treatment effect in each of high and low risk group. This analysis will be presented in terms of relative risks (RR) along with the corresponding p values for each covariate.

5.7.1.Planned Sequential Analyses for Efficacy and Futility

Planned interim analyses for futility and efficacy will first be conducted one year after the completion of accrual, and will be repeated at 2 years post accrual completion. If accrual is completed in three years, the interim analyses will be performed at 48 and 60 months after study launch.

The rationale for conducting the first sequential analysis for futility and efficacy one year after the completion of accrual is a desire to avoid premature termination of accrual to a study arm based on short term trends that may later reverse. The goal of the trial is to assess long-term PFS and overall survival. The use of a sequential monitoring boundary will permit annual inspections of the data in the latter years of the trial while controlling the type I error of falsely

reporting a treatment difference.

Analyses will be reported to the Data and Safety Monitoring Board (DSMB), whose members meet monthly. The data will be presented by treatment arm, but the identity of the arms will be coded.

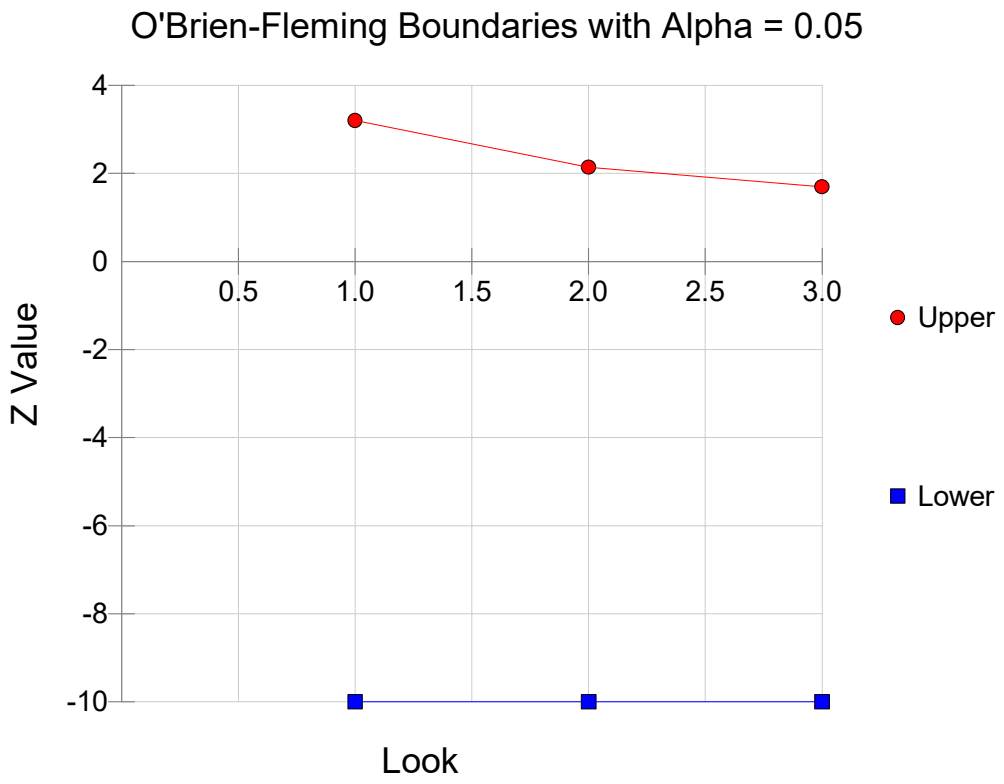
Sequential analyses for efficacy will consist stratified log-rank tests comparing the two conditioning regimen. All testing will be performed at 2.5% level of significance. The p-value is further adjusted for group sequential monitoring using O'Brien Fleming boundaries to conserve type I error.

5.7.2. Operating Characteristics of Sequential Design

Interim analyses planned at 1 and 2 years in addition to the final 3 years after the close of accrual, will operate using the O'Brien-Flemming spending function. The observed value of the one-sided log-rank will be compared to 3.200, 2.141 and 1.69478 boundaries. If the value is less than the boundary at t each interim analysis prior to the final analysis, then trial shall continue to the phase.

Details when Spending = O'Brien-Fleming, S1 = 0.3600, S2 = 0.5600

Look	Time	Lower Bndry	Upper Bndry	Nominal Alpha	Inc Alpha	Total Alpha	Inc Power	Total Power
1	1.0000		3.20010	0.000687	0.000687	0.000687	0.067817	0.067817
2	2.0000		2.14080	0.016145	0.015688	0.016375	0.541227	0.609045
3	3.0000		1.69478	0.045059	0.033625	0.050000	0.291699	0.900744
Drift	2.95809							



Otherwise, the trial will be terminated due to overwhelming significant increase in PFS above that in the standard treatment.

5.8.Secondary endpoints

Secondary endpoints will include:

- Overall survival (OS): Defined as time from the first dose of administration to death from any cause.
- 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.
- Univariate analyses of the risk of progression/relapse and mortality: In addition, multivariate analyses of the risk of progression/relapse and overall mortality will be conducted to assess influence of variables measured after the start of treatment.
- Regimen-related toxicity: Graded and presented in a descriptive nature.

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 will be calculated at three years after randomization. The analyses of the three-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 be performed using Mantel-Haenszel Test stratified on risk status.

5.8.2. Overall Survival

The event is death from any cause. The time to this event is the time from randomization to 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 treatment comparisons, a log-rank test, conducted at a one-sided significance level of .025 analogous to the analysis of PFS described above. In addition, a stratified log-rank test will be performed to examine the treatment effect in high or low risk group.

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 stratified Cox proportional hazards model. To fit the multivariate model, a stepwise backward selection procedure will be used while considering the type of conditioning regimen (melphalan versus Melphalan with bortezomib), relapse risk status (low risk, high risk), age at transplant and Karnosfky performance score (<90 versus ≥ 90). An examination of the goodness-of-fit will be performed using Grambsch-Therneau and Martingale residual plots and lowess smooth of Cleveland. 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. This analysis will be presented in terms of relative risks (RR) along with the corresponding p values for each covariate.

5.8.3. 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.

5.8.3.1. 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. Stopping rules

If the non-relapse mortality rate in the experimental group receiving bortezomib within the first 3 month post exceeds 10% then the study will be stopped. It is assumed that the non-relapse mortality in the standard high dose melphalan regimen is 3%. Resumption of patient accrual will only be permitted after review of interim results by the Institutional Review Board and the Data Safety Monitoring Board.

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 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. Protocol Registration

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

6.5. 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.

6.6. Record Retention

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 card, maintains all original inpatient and outpatient chart documents.

6.7. Investigation 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 Karnofsy 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

[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.

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.) 12.0 New York Heart Association Classification of Cardiac Disease

9. NYHA Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease:

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

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

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

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.

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.

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 judgment 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.

6 Common Terminology Criteria for Adverse Events 3.0

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

7 References

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