Pilot Study of Bortezomib/Dexamethasone (BD), Followed By Autologous Stem Cell Transplantation and Maintenance Bortezomib/Dexamethasone For the Initial Treatment of Monoclonal Immunoglobulin Deposition Disease (MIDD) Associated With Multiple Myeloma and AL Amyloidosis

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

Principal Investigator/Department:	Hani Hassoun, MD	Medicine /Myeloma Manhattan, West Harrison
Co-Principal Investigator(s)/Department:	Heather Landau, MD	Medicine /BMT
Investigator(s)/Department:	David Chung, MD	Medicine/BMT
	Sergio Giralt, MD	Medicine/BMT Medicine/BMT
	Guenther Koehne, MD	Medicine/Myeloma
	Alex Lesokhin, MD	Medicine/Myeloma
	Nikoletta Lendvai, MD	Medicine/Myeloma
	Neha Korde, MD	Epidemiology and Biostatistics
	Elyn Riedel, MS	Medicine/Renal
	Carlos Flombaum	Medicine/BMT
	Roni Tamari, MD	Medicine/BMT
	Parastoo Dahi, MD	Medicine/BMT
	Esperanza Papadapolous	Medicine/BMT
	Juliet Barker, MBBS	Medicine/BMT
	Hugo Castro-Malaspina, MD	Medicine/BMT
	Alan Hanash, MD	Medicine/BMT
	Katharine Hsu, MD, PhD	Medicine/BMT
	Ann Jakubowski, MD, PhD	Medicine/BMT
	Robert Jenq, MD	Medicine/BMT Manhattan,
	Matthew Matasar, MD	Rockville Centre Medicine/BMT
	Miguel-Angel Perales, MD	Medicine/BMT
	Doris Ponce, MD	Medicine/BMT
	Craig Sauter, MD	Medicine/BMT
	James Young, MD	Medicine/BMT
	Marcel van den Brink, MD, PhD	Medicine/BMT
	Boglarka Gyurkocza, MD	Medicine/BMT Medicine/Neurology
	Brian Shaffer, MDXi Chen, MD	Medicine: Basking Ridge
	Audrey Hamilton, MD	Medicine: Basking Ridge
	Han Xiao, MD	Medicine: Basking Ridge
	Sree Bhavani Chalasani, MD	Medicine: Commack
	Stuart Lichtman, MD	Medicine: Commack
	Steven Sugarman, MD	Medicine: Commack
	Jon Fiore, MD	Medicine: Commack
	Avni Desai, MD	Medicine: Rockville Centre
	Kenneth Ng, MD	

	Pamela Drullinsky, MD	Medicine: Rockville Centre
	Arlyn Apollo, MD	Medicine: Rockville Centre
	Zoe Goldberg, MD	Medicine: Rockville Centre
	Tiffany Troso-Sandoval, MD	Medicine: Rockville Centre
	Philip Caron, MD	Medicine: Sleepy Hollow
	Carolyn Wasserheit-Lieblich, MD	Medicine: Sleepy Hollow
	Sean M. Devlin, PhD	Epidemiology-Biostatistics
	Chau Dang, MD	Medicine/Manhattan and West Harrison
	Diana Lake, MD	Medicine/Manhattan and West Harrison
	Elizabeth Won, MD	Medicine/Manhattan and West Harrison
	Karen Cadoo, MD	Medicine/Manhattan and West Harrison
	Andrew Zelenetz, MD	Medicine/Manhattan and West Harrison
	Kenneth Ng, MD	Medicine/Manhattan and West Harrison
	Ephraim Casper, MD	Medicine/All sites
	Melody Smith, MD	Medicine
	Shani Irby, NP	Nursing
	Megan Scott, NP	Nursing
	Shannon Andersen, NP	Nursing
	Abigail Cohen, NP	Nursing
	Nicole Lestrange, NP	Medicine
	Abigail Staible, PA	Nursing
	Allison Tucker, NP	Nursing
	Tara Wolff, NP	Nursing
	Kara Mosesso, NP	Nursing
	Sheila Kenny, NP	Medicine: West Harrison
	Daniel McFarland, DO	Medicine: West Harrison
	Parisa Momtaz, MD	Medicine: West Harrison
	Michael Mauro, MD	Medicine: West Harrison
	Chung-Han (Joe) Lee, MD	Medicine: Commack
	Sham Mailankody, MD	Medicine: Commack
	Juliana Eng, MD	Medicine: Commack
	Gunjan Shah, MD	Medicine/BMT
	Eric Smith, MD	Medicine/Myeloma
	Jennifer Liu, MD	Medicine/Cardiology
Consenting Professional(s)/Department:	Hani Hassoun, MD	Medicine/Myeloma Manhattan, West Harrison
	Heather Landau, MD	Medicine/BMT

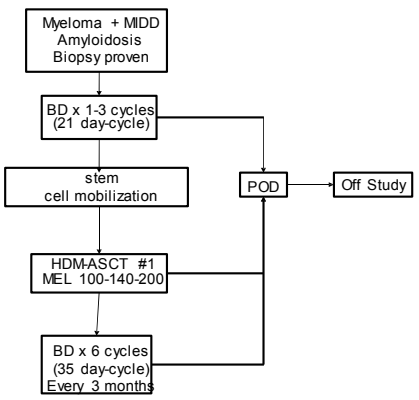
	David Chung, MD	Medicine/BMT
	Sergio Giralt, MD	Medicine/BMT
	Guenther Koehne, MD	Medicine/BMT
	Alex Lesokhin, MD	Medicine/ Myeloma
	Nikoletta Lendvai, MD	Medicine/ Myeloma
	Neha Korde, MD	Medicine/Myeloma
	Roni Tamari, MD	Medicine/BMT
	Parastoo Dahi, MD	Medicine/BMT
	Boglarka Gyurkocza, MD	Medicine/BMT
	Brian Shaffer, MD	Medicine/BMT
	Audrey Hamilton, MD	Medicine: Basking Ridge
	Han Xiao, MD	Medicine: Basking Ridge
	Sree Bhavani Chalasani, MD	Medicine: Basking Ridge
	Stuart Lichtman, MD	Medicine: Commack
	Steven Sugarman, MD	Medicine: Commack
	Jon Fiore, MD	Medicine: Commack
	Avni Desai, MD	Medicine: Commack
	Kenneth Ng, MD	Medicine: Rockville Centre
	Pamela Drullinsky, MD	Medicine: Rockville Centre
	Arlyn Apollo, MD	Medicine: Rockville Centre
	Zoe Goldberg, MD	Medicine: Rockville Centre
	Tiffany Troso-Sandoval, MD	Medicine: Rockville Centre
	Philip Caron, MD	Medicine: Sleepy Hollow
	Carolyn Wasserheit-Lieblich, MD	Medicine: Sleepy Hollow
	Chau Dang, MD	Medicine/Manhattan and West Harrison
	Diana Lake, MD	Medicine/Manhattan and West Harrison
	Elizabeth Won, MD	Medicine/Manhattan and West Harrison
	Karen Cadoo, MD	Medicine/Manhattan and West Harrison
	Andrew Zelenetz, MD	Medicine/Manhattan and West Harrison
	Kenneth Ng, MD	Medicine/Manhattan and West Harrison
	Ephraim Casper, MD	Medicine/All sites
	Melody Smith, MD	Medicine
	Daniel McFarland, DO	Medicine: West Harrison
	Parisa Momtaz, MD	Medicine: West Harrison
	Michael Mauro, MD	Medicine: West Harrison
	Chung-Han (Joe) Lee, MD	Medicine: West Harrison
	Sham Mailankody, MD	Medicine: Commack
	Juliana Eng, MD	Medicine: Commack
	Gunjan Shah, MD	Medicine/BMT
	Eric Smith, MD	Medicine/Myeloma

Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, New York 10065

Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA



AL amyloidosis and Monoclonal Immunoglobulin Deposition Disease (MIDD) are two related entities associated with underlying plasma cell dyscrasia. Although both diseases are caused by mis-folding and deposition in various organs of abnormal immunoglobulin light chains (sometimes intact immunoglobulins) secreted by proliferating plasma cells, the molecular mechanisms differ and lead to dissimilar pathologic and clinical findings. In both diseases however, this immunoglobulin deposition results in organ dysfunction, morbidity and ultimately death.

Treatment of both diseases is aimed at eradicating the plasma cells that produce the pathologic light chain. Because of the similarity to multiple myeloma (MM), a much more common disorder, patients have typically been treated with drugs used to treat multiple myeloma, most commonly melphalan, prednisone, dexamethasone, VAD (Vincristine, Adriamycin, and Prednisone) and more recently in the case of AL amyloidosis, newer agents like thalidomide, bortezomib and revlimid. While the treatment of MM continues to evolve and has resulted in improved outcomes for patients, the treatment of amyloidosis and especially MIDD has lagged behind, mainly because of the small number of patients reported in the literature. Nevertheless, the goal of treatment remains achievement of complete hematologic remission and complete suppression of light chain production, which is key to achieving organ response in both AL and MIDD. However, because of distinct pathologic characteristics and increased susceptibility to toxicity due to organ dysfunction compared to MM patients, the treatment applied to MM cannot be extrapolated to these diseases. Patients with AL amyloidosis and MIDD would benefit from clinical studies addressing specifically these diseases.

This clinical trial is a pilot, single arm study that examines the tolerability/toxicity, and estimates the efficacy of a comprehensive treatment approach in the management of MIDD and AL amyloidosis. The treatment includes 3 phases: Pre-transplant bortezomib based induction (Bortezomib/Dexamethasone or BD); followed by high dose melphalan and autologous stem cell transplantation (HDM/ASCT); and post-transplant consolidation/maintenance therapy with BD. This 3-phase approach is highly effective in multiple myeloma but has never been tested in patients with MIDD or in patients with AL amyloidosis. The goal of the treatment is to achieve a high rate of complete hematologic remission which is necessary for organ improvement. If this pilot study appears promising, we will develop a larger phase II study that we will propose as a cooperative group trial, adopting this comprehensive approach to these 2 rare diseases.

The 3 phases of treatment include:

1. Induction therapy consisting of one to three 21-day-cycles of BD (Patients achieving CR after one or two cycles could forgo remaining cycle(s)):

Bortezomib 1.3 mg/m^2 IV or Subcutaneous Injection (SQ) on days 1, 4, 8, and 11

- Dexamethasone 40 mg IV or po on days 1, 4, 8, and 11

2. HD M/ASCT performed with risk-adapted doses of melphalan IV at 100, 140, or 200 mg/m^2.

3. Post-transplant consolidation/maintenance consisting of six cycles of BD each given every 12 weeks +/- 2 weeks:
- bortezomib 1.3 mg/m^2 IV or SQ on days 1, 8, and 15, and 22
- Dexamethasone 20 mg IV or po administered on days 1, 8, and 15, and 22

Toxicities will be tabulated by type and severity. With 20 patients, the hematologic and renal response rates can be estimated to within +/- 22%.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

The primary objective of this study is:
- To examine the tolerability and toxicity of a 3-phase comprehensive treatment approach including induction with BD, followed by risk adapted HDM/ASCT, followed by consolidation/maintenance therapy with BD in patients with MIDD and AL amyloidosis.

The secondary objectives of this study are:

- To estimate the hematologic response rate [Complete Response (CR), Very Good Partial Response (VGPR) and Partial Response (PR)], achieved at 12 month and at 24 months post-initiation of treatment (following the 3-phase comprehensive treatment approach including induction with BD, followed by risk adapted HDM/ASCT, followed by consolidation/maintenance therapy with BD) in patients with MIDD and AL amyloidosis.

- To estimate the organ response rate at 12 months and at 24 months post-initiation of treatment following the 3 phase comprehensive treatment approach including induction with BD, followed by risk adapted HDM/ASCT, followed by consolidation/maintenance therapy with BD in patients with MIDD and AL amyloidosis.

- To estimate the time to hematologic progression following the 3-phase comprehensive treatment approach including induction with BD, followed by risk adapted HDM/ASCT, followed by consolidation/maintenance therapy with BD in patients with MIDD and AL amyloidosis.

3.0 BACKGROUND AND RATIONALE

3.1 Upfront Treatment of Multiple Myeloma

Multiple myeloma is a malignant plasma cell proliferative disorder that accounts for an estimated 15,000 new cancer cases per year in the United States, as well as approximately 11,000 deaths[1]. Based on the United Kingdom (UK) Myeloma Forum and the Nordic Myeloma Study Group recommendations[2] and National Comprehensive Cancer Network (NCCN) Practice Guidelines[3], chemotherapy is indicated for the management of myeloma presenting with myeloma-related organ damage (referred to as symptomatic myeloma as opposed to asymptomatic myeloma). Despite the potential benefits of newer treatments, multiple myeloma remains an incurable disease and relapse occurs in almost all patients, with a median survival period of 5 to 7 years[4,5].

Standard front-line treatment for patients with symptomatic multiple myeloma who are deemed eligible for transplantation, consists of 2 phases of treatment: The first is referred to as the -initial‖ therapy and consists of various combinations of therapeutic agents. The second consists of high dose melphalan followed by autologous stem cell transplant (HDM/ASCT)[4,5].

3.1.1 Initial therapy

The regimens currently recommended in the NCCN guidelines for initial therapy of MM in patients who are candidates for HDM/ASCT include dexamethasone, thalidomide/dexamethasone, revlimid/dexamethasone, liposomal doxorubicin/vincristine/dexamethasone (DVD), as well as several bortezomib based regimens. Indeed, In previously untreated patients, bortezomib has shown activity as a single agent[6-8] and also in combination with dexamethasone[6,9], thalidomide/dexamethasone[10,11], melphalan/prednisone (MP)[12,13], dexamethasone/adriamycin[14,15] as well as revlimid/dexamethasone. There are currently several large phase III randomized studies ongoing worldwide examining the role of bortezomib in both the transplant and non-transplant settings. It is widely accepted that in patients who will undergo HDM/ASCT, melphalan-containing regimens should be avoided since stem cell collection may be subsequently hampered.

Bortezomib, a potent, reversible, and specific inhibitor of the proteasome, is a first-in-class antineoplastic cytotoxic agent. It was the first proteasome inhibitor to enter the clinic and is the first approved for any clinical indication. Bortezomib specifically and selectively inhibits proteasome function by binding tightly (Ki=0.6 nM) and reversibly to the enzyme‘s chymotrypsin-like site. It is highly selective for the proteasome as exemplified in a screen of related and unrelated proteases where no significant inhibitory activity was seen. The mechanism of action of bortezomib as a cytotoxic agent is described in more details below.

On June 20, 2008, the U.S. Food and Drug Administration approved bortezomib for injection for the treatment of patients with multiple myeloma. This approval results from a clinical trial using Bortezomib as an initial treatment for patients with multiple myeloma.

3.1.2 Autologous Stem Cell Transplantation

There have been two large prospective trials in France (IFM90) and in UK (MRC 9), and one large retrospective study of myeloma patients in Nordic countries, showing a survival benefit for ASCT compared to conventional chemotherapy[16-18]. In the larger study, IFM90, newly diagnosed untreated patients less than 65 years of age with DS stage II or III MM were randomized to either SCT after up to 6 cycles of VMCP alternating with BCNU, vincristine, doxorubicin and prednisone (BVAP) or conventional chemotherapy with 18 cycles of VMCP alternating with BVAP. The SCT regimen was MEL 140 mg/m2 and TBI, and recombinant interferon alpha (IFNα) was administered to patients in both groups until relapse. By intent-to-treat, SCT patients had a significantly higher response rate (CR+VGPR 38% versus 14%) than those receiving conventional chemotherapy. At a median follow-up of 37 months in the chemotherapy group and 41 months in the SCT group, the latter had significantly longer PFS and OS. The other two studies have confirmed these results although the dose of melphalan given was 200 mg/m^2 and radiation therapy was not used. Based on these trials, autologous stem cell transplantation using melphalan 200 mg/m^2 has become part of the standard treatment of symptomatic multiple myeloma.

In patient with renal insufficiency, transplantation with melphalan 200 mg/m^2 has resulted in high rate of side effects, especially severe mucositis. Lower doses have been studied in the literature for these patients. The dose of melphalan 140 mg/m^2 has been chosen in this clinical trial for patients with abnormal creatinine clearance because it has been shown to be safer than melphalan 200 mg/m^2 and has been widely used in patients with renal dysfunction [19-22]. This dose has become the standard of care nowadays for transplantation in patients with renal insufficiency and a creatinine

clearance < 50 ml/min. Our experience at MSKCC also supports this observation and this dose has been adopted as standard of care for patients with creatinine clearance less than 50 ml/min.

3.1.3 Post Transplant Therapy

HDM/ASCT has improved response rate and overall survival rate in patients with MM, but all patients eventually relapse. Clinical trials have investigated the use of consolidation and maintenance therapy post-transplant to extend the duration of response.

In a large study[23], 2 months after ASCT, patients were randomly assigned to receive no maintenance (group A), pamidronate (group B), or pamidronate plus thalidomide (group C; 400 mg/day, dose reduction to a minimum dose of 50 mg was allowed for treatment-related toxicity). At least VGPR was achieved in 55% of patients (group A), 57% of patients (group B), and 67% of patients (group C; P = .03). The 3-year EFS was 36% (group A), 37% (group B), and 52% (group C; P < .009). The 4-year OS was 77% (group A), 74% (group B), and 87% (group C; P < .04). Patients received thalidomide for a median of 15 months and the mean dose of thalidomide was 200 mg/day. In another study[24] thalidomide (200 mg/day for a maximum of 12 months) combined with prednisolone (50 mg on alternate days) was compared with prednisolone alone as maintenance after ASCT. At 12 months after randomization, the thalidomide group had higher PR rate (83% vs 52%; P < .01), better 2-year PFS (63% vs 36%; P < .001), and better 3-year OS (86% vs 75%; P = .02). In a more recent study[25], patients with newly diagnosed MM were randomly assigned to receive either a single ASCT followed by thalidomide maintenance or tandem ASCT. Single ASCT followed by maintenance with thalidomide proved better than tandem ASCT for both 3-year PFS (85% vs 57%; P = .02) and 3-year OS (85% vs 65%; P = .04).

Importantly, preliminary studies from two major large studies recently presented at the last ASCO meeting in 2010, have established maintenance therapy post HDC/ASCT as standard of care for MM. Both studies have shown a statistically significant improvement in the progression free survival when patients were treated with maintenance therapy with Revlimid after HDM/ASCT. The improvement in overall survival is currently not established[26,27].
A recent study using the combination of bortezomib, thalidomide and dexamethasone following a single autologous transplant demonstrated that it is feasible to administer 4 cycles of consolidation chemotherapy post-transplant. With this approach, responses were improved and a proportion of patients (18%) became PCR negative for molecularly detectable residual disease. Although the follow up remains short, no patient who achieved molecular remission relapsed at a median follow up of 42 month[28].

Based on these studies, the use of post transplant maintenance and/or consolidation therapy in multiple myeloma is widely accepted. Several studies are currently investigating the use of bortezomib in the maintenance setting.

3.2 Monoclonal Immunoglobulin Deposition Disease

Monoclonal immunoglobulin deposition disease (MIDD) is a broad entity encompassing several conditions that result from the deposition of a monoclonal paraprotein in various organs (For Review[29-31]). It includes light chain deposition disease (LCDD), the most common pathology; light and heavy chain deposition disease (LHCDD); and heavy chain deposition disease (HCDD). The latter two conditions are rare and have been poorly characterized in the literature. The major organ target in MIDD is the kidney, where the monoclonal paraprotein deposits within the glomerular basement membranes, mesangium, tubular basement membranes and vessel walls. This deposition typically leads to a nodular sclerosing glomerulopathy that eventually manifests with nephrotic syndrome, hypertension and renal insufficiency. Less commonly, other visceral organs can be involved, including heart and liver[29,30,32-36]. Also classified among MIDD is another entity known as

light chain crystal deposition disease (LCCDD) described initially by Terashima[37]. . The pathology in this condition consists of light chain deposition forming intracellular crystals in histiocytes and renal parenchymal cells, particularly the proximal tubular epithelium, with variable involvement of other organs. Proximal tubular involvement typically manifests with light chain Fanconi syndrome (LCFS), which is characterized clinically by type 2 renal tubular acidosis (RTA) that associates a non anion gap metabolic acidosis with hypophosphatemia, glucosuria, and hypouricemia.

MIDD results from the production of a monoclonal paraprotein (light chain, heavy chain, or both) and is therefore associated with an underlying plasma cell dyscrasia that may or may not be evident at the time patients first present. The majority of patients will ultimately be diagnosed with multiple myeloma[29,30,38]. Using the recently developed Free Light Chain Assay that is more sensitive for the detection of serum free light chains, it is likely that virtually all patients with MIDD will have a monoclonal free light chain detected in the serum.

3.2.1 Treatment of MIDD

The treatment of MIDD has not been standardized and remains controversial because of the small number of patients reported in the literature. However, since MIDD is associated with plasma cell dyscrasias, patients have typically been treated with regimens used for multiple myeloma, most commonly melphalan and prednisone and VAD (Vincristine, Adriamycin, and Prednisone)[29, 39,40]. In a few small series, investigators have reported that high-dose chemotherapy followed by autologous stem cell transplantation (HDM/ASCT) can be associated with beneficial results while toxicity remains acceptable in this group of patients[29,41-45]. HDM/ASCT is a therapeutic modality currently accepted as the standard of care for patients with multiple myeloma who are less than 65 years of age. Weichman et al. described 6 patients, 5 with LCDD and 1 with LCCDD, who were treated with HDM/ASCT and who achieved a good outcome with acceptable and expected toxicity[44]. As described in the present report, most patients had complete hematologic remission followed by renal improvement and reversal of dialysis dependence in one case. Royer et al have reported their experience in 11 patients with LHCDD who received a variety of therapeutic regimens. They also observed an overall favorable outcome, including complete hematologic remission in five patients with improvement of kidney function in four[42], and several patients with cardiac and/or hepatic involvement who experienced functional improvement after stem cell transplantation. More recently, Lorenz et al. reported the long-term outcome after autologous stem cell transplantation of six patients. Although one patient did not survive the procedure, 5 had a hematologic response by standard criteria and 4 who were not on dialysis at the time of transplantation had a renal response as assessment by improvement in their glomerular filtration rate[46]. Thus, this experience highlights the potentially important role of stem cell transplantation in MIDD, in striking contrast to the minimal benefit when conventional chemotherapy (including melphalan and prednisone) is used in these patients.

3.2.2 MSKCC Experience with HDM/ASCT in MIDD

We have recently reported our retrospective review of all patients with MIDD who were treated with HDM/ASCT at Memorial Sloan Kettering Cancer Center between 2004 and 2007[47]. We identified 7 patients with monoclonal plasma cell dyscrasia and MIDD who underwent HDM/ASCT.

3.2.2.1 Patient Characteristics

Six patients were male; the median age was 50 (range 33 to 52). All fulfilled criteria for multiple myeloma. The median percentage of plasma cells in the bone marrow was 21 % (10 to 41 %) and immunohistochemical staining for light chain isotype showed kappa clonality in all cases. Serum protein electrophoresis showed a monoclonal spike in one patient, while serum immunofixation showed an IgG kappa monoclonal band in two patients. All seven patients, however, had elevated

serum free kappa light chains and an abnormal kappa-to-lambda ratio with medians of 52.4 mg/dL (5.3 to 385 mg/dL) and 18.34 (3.01 to 203.7), respectively. The monoclonal protein deposited in the kidney consisted of free kappa light chains in all five patients with LCDD, kappa light chain and gamma heavy chain in the patient with LHCDD, and intratubular crystals of kappa light chain in the patient with LCCDD and Fanconi syndrome. The median β2 microglobulin was 9.2 mg/L (2.3 to 18.4 mg/L) and the median serum albumin level 4.4 gm/dL (3.5 to 4.6 mg/L). Using the International Staging System (ISS), five patients had stage III and two stage I disease. All patients were stage IB by Durie-Salmon classification. Cytogenetic analysis in all seven patients and FISH analyses in three demonstrated no chromosomal aberrations.

All seven patients had hypertension that was controlled by antihypertensive medications. The patient with intracytoplasmic light chain crystal deposition (LCCDD) presented with renal insufficiency (serum creatinine of 1.6 mg/dl; creatinine clearance 40 ml/min) and Fanconi syndrome (with type II renal tubular acidosis (RTA II) and non-anion gap metabolic acidosis, glycosuria, and aminoaciduria). The median serum creatinine was 4.6 (1.6 to 6.1), median creatinine clearance 35 ml/min (11 to 79 ml/min), and median 24-hour proteinuria 4373 mg (237 to 8525 mg). Three patients (patients 1, 6 and 7) presented with severe acute renal failure necessitating initiation of dialysis within 2 weeks of initial presentation. These patients continued dialysis throughout the entire treatment including the transplant period.

3.2.2.2 Histopathologic Findings on Renal Biopsy

All patients underwent a diagnostic renal biopsy. The five patients with LCDD and the single patient with LHCDD displayed a nodular sclerosing glomerulopathy with characteristic immunofluorescence profile and corresponding electron dense deposits. The glomerular capillary lumina were diffusely narrowed by mesangial expansion forming large nodules that stained strongly periodic acid-Schiff (PAS)-positive, trichrome-blue and weakly argyrophilic. There was variable thickening of glomerular basement membranes, Bowman's capsule, tubular basement membranes and vessel walls by PAS-positive material. These deposits typically formed ribbon-like, glassy thickenings of the tubular basement membranes, associated with focal tubular atrophy and interstitial fibrosis. One patient with LCDD also exhibited several atypical crystalline, lamellated casts of the myeloma type. In 4 patients, immunofluorescence studies showed intense and diffuse linear staining of all renal basement membranes and the mesangial nodules for kappa light chain, with negative staining for lambda light chain and immunoglobulins, consistent with kappa LCDD. One patient had strong linear staining for IgG and kappa, with negative staining for lambda, consistent with IgG kappa LHCDD. Electron microscopic examination typically showed expansion of mesangial areas with an increase in mesangial matrix forming large nodules containing finely granular mesangial electron dense deposits. Similar finely granular, electron-dense material formed linear band-like deposits involving the inner aspect of the glomerular basement membranes, the outer aspect of the tubular basement membranes and the areas surrounding the medial myocytes of arteries and arterioles.

In contrast to the patients with LCDD/LHCDD, microscopic examination of the patient with light chain crystal deposition disease revealed no evidence of glomerular disease. The proximal tubular epithelial cells displayed irregular cytoplasmic expansion caused by abundant intracellular crystalline inclusions that deformed the cells. The intracytoplasmic crystals stained PAS-negative, trichrome-red and silver-negative. The proximal tubular cells displayed acute injury, including focal shedding of tubular cells into the tubular lumen, loss of brush border, luminal ectasia and regenerative nuclear atypia. In the medulla, a single atypical crystalline lamellated cast of the myeloma type was identified. Tubular atrophy and interstitial fibrosis affected 10% of the cortex. Immunofluorescence performed on pronase-digested paraffin sections showed intense diffuse staining for kappa light chain in the distribution of the proximal tubular intracellular crystals and the single atypical cast, with negative staining for lambda light chain. By electron microscopy, glomeruli were unremarkable, and no electron dense deposits were identified involving renal basement membranes. Intracytoplasmic

crystals were demonstrated in proximal tubular epithelial cells. The findings were interpreted as consistent with the special form of LCCDD known as kappa light chain Fanconi syndrome (KLCFS).

3.2.2.3 Treatment Received and Toxicity

The initial therapy prior to HDM/ASCT included thalidomide (escalated to 200 mg daily) and dexamethasone in pulses (40 mg on days 1-4, 9-12, and 17-20) given for 3 cycles (n = 2), dexamethasone pulses alone for 3 cycles (n = 3), melphalan and dexamethasone for 5 cycles (n = 1), and doxorubicin and dexamethasone for 2 cycles (n = 1). Following initial therapy, five patients were mobilized with high-dose cyclophosphamide (3 gm/m^2) and G-CSF, and two with G-CSF alone (10 mcg/kg daily prior to leukapheresis for 10 days). All seven patients proceeded to HDM/ASCT and received melphalan as conditioning regimen at 140 mg/m^2 divided on days -3 and -2. Stem cells were infused on day 0. Patients received a mean of 5.8 x 10^6 CD34+ cells/kg (3.6 to 8.3 x 10^6 CD34+ cells/kg).

HDM/ASCT was well tolerated. There was no mortality. All patients completed the planned treatment without major or unusual complications. Routine transfusion of blood products, prophylactic broad-spectrum antibiotics, hydration, and analgesic medications for mucositis were administered to all patients. The non-hematologic adverse events included: Neutropenic fever (n=5); mucositis requiring intravenous analgesic medication administered by PCA (n=2); nausea requiring antiemetics (n=6); transient rash (n=2); an episode of syncope attributed to dehydration (n=1); abdominal cramps of uncertain etiology (n=1). Three patients who were on dialysis prior to HDM/ASCT continued dialysis throughout the course of transplant. In these patients, melphalan was given after dialysis.

3.2.2.4 Response to Therapy

At the completion of initial therapy, four patients had achieved a PR, 2 a CR, and one a uCR (no bone marrow biopsy available for confirmation of CR in this patient). Six of the seven patients achieved a hematologic CR after HDM/ASCT. The patient with LCCDD achieved a VGPR as reflected by persistence of low level free kappa chain in the serum (i.e. > 90% reduction in the level of free kappa light chain). This patient showed evidence of hematologic progression 8 months after transplant. He is currently being evaluated for a second autologous stem cell transplantation followed by allogeneic stem cell transplantation from an HLA-matched sibling. With a median follow up time of 23.6 months (range 7.9 to 69.8 months), all other patients remain in hematologic CR.

Among the four patients who were dialysis independent at the time of HDM/ASCT, the serum creatinine has improved in two (patients 3 and 5), remained stable in one (patient 4) who achieved hematologic PR), and worsened in one (patient 2), leading to hemodialysis despite hematologic CR (see figure 4). Proteinuria has improved significantly in the four patients shortly after HDM/ASCT. However, we should caution that although an improvement in the proteinuria may reflect improvement of the renal function, it may also reflect worsening of the disease due to a decrease in the glomerular filtration, as exemplified by patient 2 whose proteinuria continued to improve despite worsening in his creatinine clearance. The three patients who were dialysis-dependent at the time of HDM/ASCT achieved hematologic CR. Two of them have undergone kidney transplantation 14.1 and 45.7 months after HDM/ASCT (patients 1 and 7), and have a normal creatinine clearance 35.9 and 69.8 months after HDM/ASCT. The kidney transplantation was deemed reasonable in these patients since they had achieved a hematologic CR and had no co-morbid condition otherwise. The third patient (patient 6) who also remains in hematologic CR became dialysis independent after HDM/ASCT for a period of 2 months following improvement in his creatinine, but has resumed peritoneal dialysis mainly for symptomatic relief (nausea) and despite a stable creatinine. Discontinuation of his peritoneal dialysis is currently being contemplated.

3.3 Amyloidosis

Systemic AL amyloidosis is a plasma cell dyscrasia that results from mis-folding of abnormal immunoglobulin free light chains (FLC) that form fibrils and deposit as amorphous, congophilic extracellular deposits. These deposits occur in key viscera such as the kidneys, heart, and liver and in the peripheral nervous system[48]. As systemic deposits of amyloid fibrils accumulate, they disrupt organ function leading to organ dysfunction, morbidity and ultimately death. The initial presentation is variable depending on the organ(s) affected. Initial presentations include a nephrotic-range proteinuria with or without renal insufficiency, congestive cardiomyopathy, unexplained hepatomegaly, and sensorimotor and/or autonomic peripheral neuropathy. The disorder has an incidence of 8 to 13 per million persons per year, similar to that of chronic myelogenous leukemia. AL is approximately one-fifth as common as multiple myeloma but is more devastating in that the median survival of patients seen within 1 month of diagnosis is 13.2 months[49]. Moreover, for those who present with congestive heart failure the median survival is 4 months, and historically less than 5% of all AL patients survive 10 years or more from diagnosis[48,50].

Achievement of a hematologic response with normalization of the serum FLCs is associated with organ responses and improved survival.. Therefore, the main goal of treatment in AL amyloidosis is directed at eradication of the FLC producing plasma cell clone, leading to suppression of the abnormal FLC production and deposition in various organs.

3.3.1 Treatment of AL amyloidosis

The median survival of patients with AL was only 18 months in those treated with oral melphalan and prednisone in a large phase III trial conducted for newly diagnosed untreated patients; those receiving colchicine alone had a median survival of eight months[51]. These results highlight that limited progress had been made in reversing AL amyloidosis until the mid 1990's when HDM/ASCT was introduced for the treatment of this disease[52,53]. The effectiveness of HDM/ASCT in reversing the clinical manifestations of AL amyloidosis in nearly two-thirds of surviving patients has been documented at numerous centers. Amyloid P component radionuclide scans have demonstrated resorption of amyloid deposits after reduction or elimination of the plasma cell clone(16-18). As the production of abnormal FLC is halted and amyloid resorbed, both the performance status and the quality of life of AL patients can improve[54].

However, in the early years of SCT for AL, the average 100 day mortality of SCT has ranged from 13% to 43%, which demonstrated that AL patients who undergo HDM/ASCT are prone to major adverse events[54-56]. In these early studies, transplant-related mortality was high because multiple viscera of AL amyloidosis patients were significantly compromised by the disease, rendering patients susceptible to toxicity. Therefore, refinement of patient selection and improvement of peri-transplant clinical management became priorities. In 2007, a French group conducted a randomized trial comparing high-dose intravenous melphalan followed by ASCT with standard-dose melphalan plus dexamethasone in patients with AL amyloidosis. Fifty patients were enrolled in each group. The results were analyzed on an intention-to-treat basis, with overall survival as the primary end point. After a median follow-up of 3 years, the outcome of treatment of AL amyloidosis with ASCT similar to the outcome with standard-dose melphalan plus dexamethasone. It was felt that this lack of benefit for the transplant arm was related to the high transplant related mortality. Of the 37 patients who actually proceeded with transplantation, 9 died within 100 days after ASCT — 5 from multiorgan failure with acute renal failure, 2 from sepsis, and 2 from cardiac arrhythmia. The transplant-related mortality was 24%[57]. However this study was criticized because ASCT was performed in small centers where expertise in transplantation for amyloidosis patients may have been suboptimal.

From these studies we learned that patients with AL undergoing SCT with more than 2 major organs symptomatically involved or with advanced cardiomyopathy were at high risk of death during the peri-transplant period and, therefore, were poor risk candidates for SCT. At the same time, patients with 1 or 2 organs symptomatically involved and those with uncomplicated cardiac disease were appropriate candidates for stem cell transplantation, provided the dose of intravenous melphalan was attenuated based on age and organ compromise. This risk-adapted approach based on extent of organ involvement, dose-related differences in toxicity, (8,22)and on the age-related differences in survival has improved the safety of high dose chemotherapy (Cohen BJH publication) and has been adopted by experienced amyloid transplant centers in the US.

3.3.2 Recent experience with HDM/ASCT followed by consolidation/maintenance therapy at MSKCC

In the first of a series of trials conducted at MSKCC using the risk-adapted approach, IRB #02-031, a phase II trial evaluated risk-adapted HDM/ASCT followed by dexamethasone (D) and thalidomide (T) in an attempt to reduce treatment related mortality (TRM) and overcome any loss of efficacy as a result of attenuated melphalan dosing[58]. Patients (n = 45) with newly diagnosed AL involving < or =2 organ systems were assigned to MEL 100, 140, or 200 mg/m(2) with SCT, based on age, renal function and cardiac involvement. Patients with persistent clonal plasma cell disease 3 months post-SCT received 9 months of consolidation with TD (or D if there was a history of deep vein thrombosis or neuropathy). Organ involved included kidney (67%), heart (24%), liver/GI (22%) and peripheral nervous system (18%), with 31% of patients having two organs involved. TRM was 4.4%. Thirty-one patients began adjuvant therapy, with 16 (52%) completing 9 months of treatment and 13 (42%) achieving an improvement in hematological response. By intention-to-treat, overall hematological response rate was 71% (36% complete response), with 44% having organ responses. With a median follow-up of 31 months, 2-year survival was 84% (95% confidence interval: 73%, 94%). This clinical trial showed that risk-adapted HDCT/SCT with consolidation TD is feasible and results in low TRM and high hematological and organ response rates in patients with AL amyloidosis.

Improved efficacy and toxicity profiles of bortezomib compared to thalidomide in multiple myeloma, prompted us to initiate a new phase II clinical trial in amyloidosis in 2007. We used the same strategy of risk-adapted HDC/ASCT followed by consolidation with bortezomib/dexamethasone (BD) in patients with 1 or 2 organ involvement without advanced heart disease. At the 2009 meeting of the American Society of Hematology, we presented the two-year update for this phase II trial[59]. Patients with newly diagnosed AL involving <=2 organs were assigned to HDM/ASCT with melphalan 100, 140 or 200mg/m2 based on age, renal function and cardiac involvement. Responses were assessed at 2-3 mos, 12 mos and 24 mos post-SCT. Patients with persistent clonal plasma cell disease at 2-3 mos post-SCT received treatment with BD for up to 6 cycles (two 21-day, four 35-day cycles). Thirty-seven patients were enrolled with kidney (68%), heart (43%), liver/GI (14%) and peripheral nervous system (16%) involvement. Forty-one percent had two organ involvement. Four patients with advanced cardiac disease died within 100 days of SCT, resulting in a TRM of 12% (4/33). With a median follow-up of 29 mos, the OS at 12 mos post-SCT was 86%. At 12 and 24 mos, OS in patients with cardiac involvement was 69% and 49% respectively, versus 100% at both time points in those without (P = 0.001). Sixty-eight percent (19/28) received consolidation with BD for persistent clonal plasma cell disease. At 12 mos post-SCT, the hematologic response rate in evaluable patients was 95% (20/21) with 62% achieving sCR and 60% having organ improvement. At 24 mos post-SCT, the overall response rate was 82% (14/17) including 53% who maintained a sCR and 88% (15/17) who had organ improvement. Organs continued to get better over time and 92% (11/12) of patients with kidney involvement had organ responses at 24 mos versus 50% (7/14) at 12 mos. Overall, 87% of patients who received BD improved their hematologic response. There was no correlation between the number of cycles received (median 6; range 1.25-6) and response and interestingly, all responded after only 1 cycle of BD. Of the 19 patients who received post-SCT BD, 79% experienced grade III-IV toxicity, which was most often hematologic toxicity with

thrombocytopenia in 41%. Grade 2 or greater peripheral neuropathy was seen in 32% and became more prevalent as the number of consolidation cycles increased.

This trial showed that in newly diagnosed patients with systemic AL amyloidosis, consolidation with BD following risk-adapted SCT was safe and effective for eradicating persistent clonal plasma cell disease. Hematologic responses were rapid (occurring after 1 cycle) resulting in high overall and unprecedented sCR rates. Improvement in organ function was seen in the majority of patients and continues to occur over time. Relapses are seen following completion of therapy, suggesting that a consolidation plus maintenance regimen following SCT may be worthy of further study.

While consolidation following HDM/ASCT has shown promising results, a Phase II study evaluating the incorporation of bortezomib into the combination of melphalan and dexamethasone as initial therapy (i.e. before HDM/ASCT) for AL amyloidosis has been undertaken and preliminary data has been recently reported[60]. Twenty-four of 29 patients evaluable on this trial (83 %) had a hematologic response with 13 CR (45%) and 16 PR. Organ improvement was seen in 2/10 with cardiac AL, 7/8 with renal and 6/12 patients with nerve involvement. Two of 7 patients without baseline neuropathy developed symptoms by cycle 4. (This trial showed that bortezomib incorporated in the initial therapy also shows promising activity in the treatment of AL. Importantly, this trial includes patients with amyloidosis as well as patients with MIDD.

The data presented above in amyloidosis lays the ground for this more comprehensive approach to the treatment of this disease, which incorporates pre-transplant bortezomib based initial therapy, risk-adapted HDM/ASCT, followed by bortezomib based maintenance therapy.

3.5 Rationale for this Clinical Trial

We believe that the comprehensive treatment approach that we propose in this trial, which borrows the most effective therapeutic concepts used in multiple myeloma, is very promising. This treatment approach includes a highly active initial combination regimen, followed by HDM/ASCT and then post-ASCT consolidation/maintenance therapy, which have been shown to increase the complete hematologic response (CR) and the overall survival (OS) in patients with multiple myeloma. The hematologic effectiveness of this aggressive regimen is crucial because even low levels of circulating free light chains may have deleterious organ consequences in MIDD and AL amyloidosis. Hence, one of the aims of therapy is to suppress the free light chain production to the greatest extent. The success of therapy in curbing organ dysfunction depends on achieving and maintaining a complete hematologic remission. In this context, the comprehensive and effective treatment approach used in this clinical trial is crucial for the achievement of a high CR rate.

We and others have observed a unique sensitivity of these patients to bortezomib-based therapy with the majority of responses seen after only 1 cycle. The incidence of neuropathy in this patient population appears similar to that reported in patients with MM. However the morbidity of neuropathy in MIDD and AL patients who are also at risk for both autonomic and sensory neuropathy may be greater than seen in MM. Our experience with repeated doses of BD as consolidation following HDM/ASCT suggests dose-dependent toxicity. Given the rapidity of response to BD, risk of toxicity, and incidence of relapse, within the context of this comprehensive approach to treatment we propose 1-3 cycles of initial BD therapy (determined by achievement of CR) followed by 6 cycles of consolidation/maintenance BD after HDM/ASCT with cycles administered every 12 weeks.

Although our experience with HDM/ASCT and bortezomib as individual therapies in MIDD and AL amyloidosis is encouraging, there is no precedent for such a comprehensive and aggressive approach that combines the three phases of therapy as proposed in this clinical trial. Whether

patients with MIDD and AL amyloidosis will be able to tolerate such an aggressive and protracted approach, and whether the toxicity of HDM/ASCT combined with pre and post transplant administration of BD will be prohibitive or deleterious to these patients will be evaluated on this pilot study.

Regarding MIDD, although our experience with HDM/ASCT appears encouraging, there has been no prospective study addressing the use of this treatment modality in MIDD. All the data available on the subject, including the MSKCC experience, stems from retrospective analyses that have obviously numerous shortcomings. Despite the fact that all patients in the few series reported received ASCT, treatments administered have been widely variable in terms of initial therapy (treatment received before the ASCT) as well as conditioning regimens prior to transplantation. Regarding the response to treatment in MIDD, the correlation between hematologic response and renal response is poorly characterized, often not even reported in the literature, and much remains to be understood in that regard. This clinical trial represents the first prospective therapeutic clinical trial in MIDD examining the outcome of these patients using a comprehensive treatment that is very effective in multiple myeloma.

In the event this comprehensive treatment strategy is safe and there is a signal of activity, we plan to complete a larger phase II trial which will be most feasible in a cooperative group setting.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a pilot study to gain information and estimate the toxicity/tolerability of 1-3 cycles of BD, followed by HD M/ASCT, and maintenance therapy with BD in patients with MIDD associated with multiple myeloma and AL amyloidosis. A total of 20 patientswill be accrued to the study. We will estimate the hematologic response rates as well as organ response rates at the completion of therapy and at 24 months.

4.2 Intervention

The treatment has three phases:
1) Initial treatment phase: This phase consists of 1-3 21-day-cycles of a combination regimen that includes bortezomib 1.3 mg/m2, IV or SQ, on days 1, 4, 8, and 11; and dexamethasone 40 mg PO or IV, on days 1, 4, 8, and 11.
At the completion of every cycle and prior to initiation of the subsequent cycle, the toxicity of the treatment will be assessed using CTCAE v4.0. Likewise, the hematologic response will also be assessed at the completion of every cycle of treatment based on standard response criteria well established for multiple myeloma. These criteria are based on evaluation of serum and urine M-spike values. Patients who show evidence of progression of disease (POD) with confirmation at any time during this phase of treatment will be taken off study and will be treated at the discretion of their treating physician. All other patients will continue to receive treatment as per protocol and will proceed with the second phase of treatment after 3 cycles. Patients who achieve CR before completion of 3 cycles may forego the remaining cycle(s) and proceed to phase 2 of treatment (HDM/ASCT). A bone marrow biopsy will be performed at the completion of the first phase of treatment to characterize the response to induction BD.

2) Stem cell mobilization and HDM/ASCT: Patients will have peripheral blood stem cells mobilized and collected as per MSKCC's institutional guidelines. All patients will undergo risk-adapted conventional autologous stem cell transplantation with melphalan 100, 140, or 200 mg/m2 (depending on risk. See section 9.0) given in a single dose on day -2 or divided doses given on days

-3 and -2, prior to stem cell reinfusion on day 0. These procedures will be performed as per MSKCC's institutional guidelines..
Toxicity will be assessed during transplant and hematologic and organ responses to HDM/ASCT will be assessed at 12 weeks +/- 2 weeks post-transplantation using standard response criteria. However, organ response being delayed compared to hematologic response, we expect that maximum organ response will be best assessed at 12 months and 24 months from initiation of treatment. Patients who have hematologic POD after transplantation will be taken off study and will be treated at the discretion of their treating physician. All other patients will proceed to the third phase of treatment.

3) Post-ASCT consolidation/maintenance treatment phase: This phase consists of six cycles of bortezomib 1.3 mg/m2, IV or SQ with dexamethasone 20 mg PO or IV administered on days 1, 8, 15, and 22 every 12 weeks +/- 2 weeks. Although bortezomib has not been established as maintenance therapy in multiple myeloma (clinical trials currently in progress), the concept of maintenance therapy after HDM/ASCT has now been shown to increase the CR rate, PFS, and in few studies, OS in patients with multiple myeloma using lenalidomide or thalidomide.
Toxicity and hematologic response will be assessed at the initiation of every cycle based on CTCAE 4.0 criteria and standard response criteria, respectively. Patients who show evidence of POD with confirmation at any time during this phase of treatment will be taken off study and will be treated at the discretion of their treating physician. All other patients will continue to receive treatment as per protocol.
The hematologic and organ responses will be assessed using standard hematologic response criteria in multiple myeloma (including a bone marrow biopsy to confirm CR) at 12 months and at 24 months (+/- 2 weeks) following treatment initiation. We anticipate that in many patients, end of therapy will correspond to the 24 month post-treatment evaluation.

At the completion of treatment, patients will be seen in the clinic every three months until disease progression with no further intervention.

4.3 Outcome measurement

The primary objective of this clinical trial is toxicity/tolerability and we will use CTCAE 4.0 criteria to describe adverse events and measure outcome. Secondary objectives include hematologic and organ response rates at the completion of treatment and 24 months post treatment initiation. The criteria for hematologic response are well established and widely used in the myeloma field and are detailed in section 12.0. The criteria for organ response are also well established for amyloidosis. For MIDD, the response criteria have not been as well defined and are discussed in section 12.0.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Bortezomib

5.1.1 Scientific Background

BORTEZOMIB (Velcade®) 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) for the treatment of patients with multiple myeloma (MM). It is also indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy. In the European Union (EU), BORTEZO MIB in combination with melphalan and

prednisone is indicated for the treatment of patients with previously untreated MM who are not eligible for high-dose chemotherapy with bone marrow transplant. BORTEZOMIB is indicated as monotherapy for the treatment of progressive MM in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation. By inhibiting a single molecular target, the proteasome, BORTEZOMIB affects multiple signaling pathways. The antineoplastic 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.(See ref Appendix 20.5 [i]) 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.(See ref Appendix 20.5 [ii,iii,iv,v,vi,v ii,v iii,ixx,xi,xii,xiii,xiv]) Notably, BORTEZOMIB induces apoptosis in cells that over express bcl-2, a genetic trait that confers unregulated growth and resistance to conventional chemotherapeutics. (See ref Appendix 20.5 [xv])

The mechanisms of action leading up to apoptosis have been more clearly defined and include initiation of the unfolded protein response and direct/indirect effects on various molecular targets including cell cycle control proteins p27 and p21, cyclins, signal transduction molecules, transcription factors c-jun and HIF1-□, tumor suppressor protein p53, angiogenesis factors, and many others. 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. (See ref Appendix 20.5 [xvi,xv ii,xv iii,xix,xx,xxi,xxii,xxiii])

5.1.2 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)[67]. 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.

5.1.3 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 Investigator's Brochure

5.1.4 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.

5.1.5 Clinical Experience

It is estimated that as of January 2009, more than 100,000 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 1 trial in patients with refractory hematologic malignancies, the MTD for a twice weekly dosing for 4 weeks of a 42-day cycle was 1.04 mg/m^2/dose, with DLTs of thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise. (See ref Appendix 20.5 [xxiv]) 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, antitumor activity was reported in subjects with Non-Hodgkin's Lymphoma (NHL), MM, Waldenström's Macroglobulinemia, squamous cell carcinoma of the nasopharynx, bronchoalveolar carcinoma of the lung, renal cell carcinoma, and prostate cancer. (See ref Appendix 20.5 [xxv,xxv i,xxv ii,xxv iii])

The safety and efficacy of BORTEZOMIB in subjects with MM were investigated in two phase 2 clinical studies, studies M34100-024 (subjects with first relapse) (See ref Appendix 20.5 [xxix]) and M34100-025 (subjects with second or greater relapse and refractory to their last prior therapy). (See ref Appendix 20.5[xxx]) In M34100-025, 202 heavily pretreated subjects with refractory MM 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 (See ref Appendix 20.5 [xxxi]) were utilized to determine disease response. Complete responses (CRs) were observed in 4% of subjects, with an additional 6% of patients meeting all criteria for CR but having a positive immunofixation test. Partial response (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) (See ref Appendix 20.5 [xxxii]), 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 IV push twice weekly on Days 1, 4, 8, and 11 of a 3-week cycle for up to 8 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 3 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 4 treatment cycles as induction therapy, followed by dexamethasone 40 mg once daily on Days 1 to 4 of a 4-week cycle for 5 cycles as maintenance therapy. The EBMT response criteria 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 ($p < 0.0001$). CR + PR was 38% with BORTEZOMIB versus 18% with dexamethasone ($p < 0.0001$).

CR was 6% with BORTEZOMIB versus < 1% with dexamethasone (p < 0.0001). The CR + nCR (near CR) rate was 13% with BORTEZOMIB versus 2% with dexamethasone. In patients who had received only 1 prior line of treatment (BORTEZOMIB: 132; dexamethasone: 119), CR + PR was 45% with BORTEZOMIB vs 26% with dexamethasone (p = 0.0035). With a median 8.3 months of follow-up, overall survival was significantly longer (p = 0.0013) for patients on the BORTEZOMIB arm versus patients on the dexamethasone arm. The probability of survival at 1 year was 80% for the BORTEZOMIB arm versus 66% for the dexamethasone arm, which represented a 41% decreased relative risk of death in the first year with BORTEZOMIB (p = 0.0005). In patients who had received only 1 prior line of treatment, the probability of survival at 1 year was 89% for the BORTEZOMIB arm versus 72% for the dexamethasone arm, which represented a 61% decreased relative risk of death in the first year with BORTEZOMIB (p = 0.0098). Updated response rates and survival data were reported for M34101-039. (See ref Appendix 20.5 [xxxiii]) The updated CR + PR 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 versus patients on the dexamethasone arm. The median overall survival was 29.8 months (95% CI: 23.2, not estimable) for the BORTEZOMIB 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 1 year was 80% for the BORTEZOMIB arm versus 67% for the dexamethasone arm (p = 0.0002).

The safety and efficacy of BORTEZOMIB in relapsed or refractory mantle cell lymphoma (MCL) were investigated in an international, phase 2, multicenter study M34103-053, also referred to as the PINNACLE study. (See ref Appendix 20.5 [xxxiv]) The single-arm study was designed to evaluate the response rates, duration of response (DOR), TTP, overall survival (OS), and safety of BORTEZOMIB treatment in patients with relapsed or refractory mantle cell lymphoma. For 141 evaluable patients, the response rate was 31% (8% CR/unconfirmed CR [Cru]). Median time to response was 40 days (range 31-204 days). The median number of cycles administered across all patients was 4; in responding patients, the median number of cycles was 8. The median DOR by algorithm was 9.2 months and 13.5 months in patients with CR/CRu. Median TTP for both groups was 6.2 months. With a median follow-up of 13.4 months, overall survival had not been reached. The most commonly reported adverse events (AEs) were fatigue, peripheral neuropathy, and gastrointestinal events. A time-to-event update to the PINNACLE study (See ref Appendix 20.5 [xxxv]) was reported after a median follow-up of 26.4 months. TTP was 6.7 months for all patients, 12.4 months in all responders. The median DOR was 9.2 months in all responders and had not been reached in patients achieving CR/Cru. Overall survival was 23.5 months in all patients and 36 months in patients with CR/Cru. Survival at 12 months was 69% overall and 91% in responding patients.

The phase 3 study (MMY 3002) known as the VISTA study, evaluated the safety and efficacy of the combination of BORTEZOMIB, melphalan, and prednisone in previously untreated multiple myeloma patients who were not candidates for stem cell transplant. (See ref Appendix 20.5 [xxxv i]) The study was designed to determine the benefit of adding BORTEZOMIB to MP (melphalan and prednisone) as assessed by TTP. Patients (682) were randomized to receive nine 6-week cycles of melphalan 9mg/m^2 and prednisone 60 mg/m^2 on Days 1 to 4, alone or in combination with BORTEZOMIB 1.3 mg/m^2 by IV bolus on Days 1, 4, 8, 11, 22, 25, 29, and 32 during Cycles 1 to 4, and on Days 1, 8, 22, and 29 during Cycles 5 to 9. Response was evaluated every 3 weeks using the EBMT criteria. At a preplanned interim analysis, the independent data monitoring committee recommended that the study be stopped since the prespecified statistical boundary end point of TTP had been crossed. Response rates were 30% with 4% CR. The rates of partial response or better were 71% in the BORTEZOMIB (VMP) group compared to 34% in the MP group (p = 0.001). With follow-up of 16.3 months, the TTP for the VMP group was 24 months compared to 16.6 months in the MP group (p = 0.000001) and was associated with a 52% reduced time to progression. The median DOR was 19.9 months in the VMP group and 13.1 months in the MP group. Overall survival had not been reached in either group. Hematologic toxicity was similar in both groups. The incidence of peripheral

sensory neuropathy and gastrointestinal symptoms was higher in the VMP group. The incidence of herpes zoster was 3% in patients in the VMP group who received antiviral prophylaxis. Fifteen percent of patients in the VMP group discontinued therapy due to AEs compared to 14% in the MP group.
The VISTA study update after extended follow-up of 25.9 months, (See ref Appendix 20.5 [xxxv ii]) confirmed a survival benefit for the VMP group. Overall survival was not reached in either group: VMP group (75) deaths, 3 year OS 72%; MP group (111) deaths, 3 year OS 59% (p = 0.0032). Patients on VMP were less likely to start second-line therapy (VMP 38% vs MP 57% at the time of data cut-off) with a longer time to next therapy (TNT) and treatment free interval (TFI). Of the MP patients who received subsequent therapy, 43% went on to receive BORTEZOMIB.

Based on investigator-reported best responses to subsequent therapies, patients relapsing after therapy with a novel agent were not intrinsically more resistant than after receiving a traditional agent.

In the VISTA study, VMP was associated with prolonged TTP, TNT, TFI, and OS. Patients were successfully treated with subsequent IMiD-based therapy and retreated with BORTEZOMIB. After 36.7 months follow-up, OS continued to be superior for VMP. The OS for VMP had not yet been reached compared to MP (43.1 months). (See ref Appendix 20.5 [xxxv iii])

5.1.6 Potential Risks of Bortezomib

To date, more than 100,000 patients have been treated with BORTEZOMIB in both clinical trials investigating its use in hematological malignancies and solid tumors, and in patients who were treated with commercially available BORTEZOMIB.

Prescribing physicians and health care practitioners are referred to their locally approved product label for BORTEZOMIB regarding Indications and Usage, Contraindications, Warnings, and Precautions.

The known anticipated risks of BORTEZOMIB therapy are presented in Table 1 and Section 11.1. These risks are grouped according to the combined frequency observed in an integrated analysis of AEs in sponsored clinical studies of single-agent BORTEZOMIB dosed at 1.3 mg/m^2 twice weekly on a 21-day schedule, in patients with multiple myeloma and mantle cell lymphoma.

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

System Organ Class Observed Incidence	Preferred Term
Blood and Lymphatic System Disorders	
Most common	Thrombocytopenia*, anaemia*
Very common	Neutropenia*
Common	Lymphopenia, pancytopenia*, leukopenia*, febrile neutropenia
Cardiac Disorders	
Common	Tachycardia, atrial fibrillation, palpitations, cardiac failure congestive*
Uncommon	Cardiogenic shock*, atrial flutter, cardiac tamponade*±, bradycardia, atrioventricular block complete, arrhythmia, cardiac arrest*, cardiac failure, arrhythmia, pericardial effusion, pericarditis, pericardial disease±, cardiopulmonary failure±
Ear and Labyrinth Disorders	
Uncommon	Deafness, hearing impaired
Eye Disorders	
Common	Blurred vision, conjunctivitis, conjunctival haemorrhage
Gastrointestinal Disorders	
Most common	Constipation, diarrhea*, nausea, vomiting*
Very common	abdominal pain (excluding oral and throat)
Common	Dyspepsia, pharyngolaryngeal pain, gastroesophageal reflux, abdominal distension, gastritis, stomatitis, mouth ulceration, dysphagia, gastrointestinal haemorrhage*, lower gastrointestinal haemorrhage*± rectal haemorrhage
Uncommon	Eructation, gastrointestinal pain, tongue ulceration, retching, upper gastrointestinal haemorrhage*, haematemesis*, oral mucosal petechiae, ileus paralytic*, ileus, odynophagia, enteritis, colitis, oesophagitis, enterocolitis, diarrhea haemorrhagic, acute pancreatitis*, intestinal obstruction
General Disorders and Administration Site Conditions	
Most common	Fatigue, pyrexia
Very common	Chills, oedema peripheral, asthenia
Common	Neuralgia, lethargy, malaise, chest pain, mucosal inflammation*
Uncommon	Injection site pain, injection site irritation, injection site phlebitis, general physical health deterioration*, catheter-related complication
Hepatobiliary Disorders	
Uncommon	Hyperbilirubinaemia, hepatitis*±
Immune System Disorders	
Uncommon	Drug hypersensitivity, angioedema
Infections and Infestations	
Very common	Upper respiratory tract infection, nasopharyngitis, pneumonia*, Herpes zoster*
Common	Lower respiratory tract infection*, sinusitis,

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

System Organ Class Observed Incidence	Preferred Term
	pharyngitis, oral candidiasis, urinary tract infection*, sepsis∗, bactaeremia*, cellulitis∗, Herpes simplex, bronchitis, gastroenteritis*, infection
Uncommon	Septic shock*, catheter-related infection*, skin infection*, Herpes zoster disseminated*, lung infection∗, infusion site cellulitis, catheter site cellulitis, infusion site infection, urosepsis*, Aspergillosis*, tinea infection, Herpes zoster ophthalmic, Herpes simplex ophthalmic, meningoencephalitis herpetic±, varicella, empyema±, fungal oesophagitis±
Injury, Poisoning, and Procedural Complications	
Common	Fall
Uncommon	Subdural haematoma
Investigations	
Common	Weight decreased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood alkaline phosphatase increased, liver function test abnormal, blood creatinine increased*
Uncommon	Gamma-glutamyltransferase (GGT) increased, oxygen saturation decreased*, blood albumin decreased, ejection fraction decreased*
Metabolism and Nutritional Disorders	
Very common	Decreased appetite, anorexia, dehydration*
Common	Hyperglycaemia, hypoglycaemia, hyponatraemia, hypokalaemia, hypercalcaemia*
Musculoskeletal and Connective Tissue Disorders	
Very common	Bone pain, myalgia, arthralgia, back pain
Common	Muscular weakness
Uncommon	Limb discomfort
Neoplasms, Benign, Malignant, and Unspecified (including cysts and polyps)	
Uncommon	Tumour lysis syndrome*
Nervous System Disorders	
Most common	Peripheral neuropathy (including all preferred terms under the MedDRA High-level term Peripheral neuropathy NEC)
Very common	Paresthesia, dizziness excluding vertigo, headache
Common	Polyneuropathy, syncope, dysesthesia, dysgeusia, postherpetic neuralgia
Uncommon	Convulsion, loss of consciousness, ageusia, encephalopathy, paralysis*,autonomic neuropathy, reversible posterior leukoencephalopathy syndrome±
Psychiatric Disorders	
Very common	Anxiety, insomnia
Common	Confusional state
Uncommon	Delirium

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

System Organ Class Observed Incidence	Preferred Term
Renal and Urinary Disorders	
Common	Renal impairment*, renal failure*, haematuria
Uncommon	Micturition disorder
Respiratory, Thoracic, and Mediastinal Disorders	
Very common	Cough, dyspnoea
Common	Epistaxis, dyspnoea exertional, pleural effusion*, rhinorrhea, hypoxia*, pulmonary oedema*
Uncommon	Haemoptysis*, acute respiratory distress syndrome*, respiratory failure*, pneumonitis*, lung infiltration, pulmonary alveolar haemorrhage*, interstitial lung disease*, pulmonary hypertension*, pleurisy, pleuritic pain
Skin and Subcutaneous Tissue Disorders	
Very common	Rash
Common	Rash pruritic, rash erythematous, urticaria, petechiae
Uncommon	Cutaneous vasculitis, leukocytoclastic vasculitis ±
Vascular Disorders	
Common	Hypotension*, orthostatic hypotension
Uncommon	Cerebral haemorrhage*

Source: BORTEZOMIB Investigator's Brochure Edition 14.

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

* Fatal outcomes have been reported.

± Indicates a Preferred term not listed in the source table, however the event is deemed medically important and so is included.

Table -2 Reports of Adverse Reactions From Postmarketing Experience

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

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

System Organ Class Observed Incidence	Preferred Term
Skin and subcutaneous system disorders	
Acute febrile neutrophilic dermatosis	Unknown
Toxic epidermal necrolysis	Unknown

Source: BORTEZOMIB Investigator's Brochure Edition 14.

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

b Acute diffuse infiltrative pulmonary disease is a MedDRA Lower Level Term which corresponds to a Preferred Term of Interstitial lung disease.

Other medical events of interest that are considered not causally related to BORTEZOMIB include hepatic failure and QT prolongation. Fatal outcomes have been reported.
Women of childbearing potential should avoid becoming pregnant while being treated with BORTEZOMIB. Genotoxicity testing has shown that BORTEZOMIB is negative in the in vitro Ames assay and in the in vivo micronucleus assay, but it is a clastogen in the in vitro chromosomal aberration assay.

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

5.1.7 Preparation, Handling, Storage, and Return of Bortezomib

Bortezomib will be supplied by Millenium Pharmaceuticals, Inc. for this study.

Vials containing lyophilized BORTEZOMIB (Velcade®) for Injection should be stored according to the label requirements. For the United States, store at USP Controlled Room Temperature which is 25ºC (77ºF); for Europe, do not store above 30ºC (86ºF); excursions permitted from 15 to 30ºC (59-86ºF). 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.

Drug is available in sterile, single-use vials containing 3.5 mg of BORTEZOMIB. Each vial of BORTEZOMIB should be reconstituted under a laminar flow biological cabinet (hood) within 8 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.

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.

Administration

Drug will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Patients may be treated on an outpatient basis, if possible. The drug will be prepared under the supervision of a pharmacist, or appropriately qualified and trained personnel. 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 or calculation. The dose should be calculated on Day 1 of each cycle; the dose administered should remain the same throughout each cycle but should be recalculated at the start of the next cycle. If a patient experiences a notable change in weight within a cycle, as determined by an unscheduled weight assessment, then the patient's dose should be recalculated at that time based on clinical judgment.

The appropriate amount of bortezomib will be drawn from the injection vial and administered as an IV push over 3 to 5 seconds or the drug will be administered as a subcutaneous injection if this method is preferred by the treating physician. Bortezomib administered as an IV push will then be followed by a standard saline flush or through a running IV line. Vials are for single-use administration.

There must be at least 72 hours between each dose of bortezomib.

BORTEZOMIB Return

For commercially-labeled BORTEZOMIB for IND-exempt studies, please contact Millennium to arrange for study drug return procedures. Any unused or expired BORTEZOMIB must be returned to Millennium. Drug return activity must be documented in the drug accountability log.

Millennium Study Drug Product Complaints

A product complaint is a verbal, written, or electronic expression which implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see the following contact information below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium quality representative.

For Product Complaints, call MedComm Solutions at +1-866-835-2233

Blinding, Packaging, and Labeling

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

Prohibited Concurrent Therapy

- Participation in clinical trials with other investigational agents, not included in this trial, within 14 days of the start of this trial and throughout the duration of this trial.

Treatment Compliance

All drug will be administered to eligible patients under the supervision of the investigator or identified subinvestigator(s). The pharmacist will maintain records of drug receipt (if applicable), drug preparation, and dispensing, including the applicable lot numbers, patients' height, body weight, and body surface area (see Appendix 20.3), total drug administered in milliliters and milligrams, and date and time of administration. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.

Precautions and Restrictions

It is not known what effects BORTEZOMIB has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.
Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing the informed consent form through 30 days after the last dose of BORTEZOMIB, or agree to completely abstain from heterosexual intercourse.

It is strongly recommended that at least 1 of these 2 methods be highly effective (see examples below).

Highly effective methods	Other effective methods (barrier methods)
Intra-uterine devices (IUD)	Latex condom
Hormonal contraceptives (birth control pills/oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants)	Diaphragm with spermicide Cervical cap Sponge

If one of the highly effective methods cannot be used, using 2 effective methods at the same time is recommended.

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through a minimum of 30 days after the last dose of study drug, or completely abstain from heterosexual intercourse.

5.2 Melphalan

5.2.1 General information

Generic name: Melphalan, L-phenylalanine mustard
Commercial name: Alkeran
Chemical name: 4-[bis(chloroethyl)-amino]-L-phenylalanine
Melphalan is an alkylating agent coupled to an amino acid.

5.2.2 Formulation

The drug is supplied in a sterile 50 mg vial, prepared as a lyophilized powder with 20 mg of povidone per vial. Ten ml of special diluent is provided for reconstitution. The composition of the diluent is sodium citrate (0.20 g), Propylene glycol (6.00 ml), ethanol (95%) (0.5 ml) and sterile water. The constituted solution is further diluted with 0.9% sodium chloride injection USP to a final concentration of 0.45 mg/ml.

Supplier: Celgene.

ALKERAN for Injection is supplied in a carton containing one single-use
clear glass vial of freeze-dried melphalan hydrochloride equivalent to 50mg melphalan and one 10 ml clear glass vial of sterile diluent.

5.2.3 Administration

The dose is administered intravenously and IV fluids may be given before and after melphalan administration. Furosemide may be given 1 hour after IV melphalan. Intravenous melphalan will be used at doses of 140 and 200 mg/m2. It will be administered in a single dose on 1 day.

5.3 Pegfilgrastim (Neulasta(TM)) (after stem cell transplantation)

Pegfilgrastim is the pegylated form of recombinant methionyl human G-CSF (filgrastim). Pegfilgrastim is produced by covalently binding a 20-kilodalton (kD) monomethoxypolyethylene glycol molecule to the N-terminal methionyl residue of filgrastim.

5.3.1 Formulation

6 MG/0.6 ML SOL. A single fixed dose of 6 milligrams (mg) subcutaneously, given once per chemotherapy cycle, is effective and is recommended.

Supplier: Amgen, Inc

5.3.2 Storage

The manufacturer recommends storage of Neulasta(TM) syringes at 2 to 8 degrees C (36 to 46 degrees F), avoidance of freezing or shaking, and leaving syringes in the carton provided until time of use to protect from light (Prod Info Neulasta(TM), 2002).

5.3.3 Contraindications

Prior hypersensitivity to Escherichia coli-derived proteins, filgrastim, or pegfilgrastim.

5.4 Recombinant human granulocyte-colony stimulating factor (NEUPOGEN®, G-CSF) (for stem cell collection)

Filgrastim is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology. NEUPOGEN® is the Amgen Inc. trademark for Filgrastim, recombinant methionyl human granulocyte colony stimulating factor (r-metHuG-CSF).
NEUPOGEN® is contraindicated in patients with known hypersensitivity to E. coli-derived proteins, Filgrastim, or any component of the product.

The only consistently observed clinical toxicity described with Neupogen® is medullary bone pain. Other clinical toxicities that have been described include skin rash, and cutaneous vasculitis. Since commercial introduction of Neupogen®, there have been rare reports of allergic-type reactions. Biochemical abnormalities that may occur include increases in alkaline phosphatase, uric acid, and lactate dehydrogenase.

If required, NEUPOGEN® may be diluted in 5% dextrose. NEUPOGEN® diluted to concentrations between 5 and 15 mcg/mL should be protected from adsorption to plastic materials by addition of Albumin (Human) to a final concentration of 2 mg/mL.
Do not dilute with saline at any time; product may precipitate.
NEUPOGEN® should be stored in the refrigerator at 2-8 degrees Centigrade (36-46 degrees Fahrenheit). Do not freeze. Avoid shaking. Prior to injection, NEUPOGEN® may be allowed to reach room temperature for a maximum of 24 hours. Any vial left at room temperature for greater than 24 hours should be discarded.
Commercial NEUPOGEN® is available in 1 mL and 1.6 mL vials at a concentration of 300 mcg/mL. Discard unused portions. Use only one dose per vial; do not reenter the vial. Do not save unused drug for later administration

5.5 Dexamethasone (D)

Formulation: Supplied as 4 mg tablets.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Age ≥ 18

- New diagnosis of MIDD or AL amyloidosis based on pathologic findings confirmed at Memorial Sloan Kettering Cancer Center.

- Patients must show the ability to understand the investigational nature of the treatment and to give voluntary informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.

- Female subject is either postmenopausal for at least 1 year before the screening visit, is surgically sterilized or if they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing the informed consent form through 30 days after the last dose of bortezomib, or agree to completely abstain from heterosexual intercourse.

- Male subjects, even if surgically sterilized (i.e., status post-vasectomy) must agree to 1 of the following: practice effective barrier contraception during the entire study treatment period and through a minimum of 30 days after the last dose of study drug, or completely abstain from heterosexual intercourse.

- Adequate organ function defined as follows: Absolute granulocytes ≥ 1,000/mm^3 and platelets ≥ 70,000/mm^3, unless low granulocyte and platelets counts are due to multiple myeloma; total bilirubin ≤ 1.5 ULN; AST, ALT, and alkaline phosphatase < 3 times upper limit of laboratory normal; LVEF ≥ 50% by MUGA or ECHO (the method used at baseline must be used for later monitoring); DLCO > 50 % confirmed at MSKCC; elevated creatinine is not a contraindication to enrollment

- Performance status (ECOG) ≤ 2

6.2 Subject Exclusion Criteria

- Patient has received other investigational drugs with 14 days before enrollment
- Prior initial treatment chemotherapy for MIDD, AL amyloidosis or multiple myeloma with the exception of one cycle of high dose dexamethasone
- Prior bortezomib treatment
- Myocardial infarction within 6 months prior to enrollment or New York Heart Association Class III or IV heart failure (see Appendix 20.2), 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.
- Pregnant or lactating women are ineligible. A pregnancy test will be performed on each fertile premenopausal female 2 weeks prior to entry into the study. Treatment may not begin until the results of the pregnancy test are ascertained. All patients (men and women) must agree to use medically approved contraceptive measures for at least 4 weeks before starting therapy, during therapy, and for at least 3 months after therapy has stopped.
- Pre-existing neuropathy, sensory or neuropathic pain findings, grade 2 or higher on the NCI CTC neurotoxicity scale.
- Concurrent active malignancy other than non-melanoma skin cancers or carcinoma-in-situ of the cervix. Patients with previous malignancies, but which have not required anti-tumor treatment within the preceding 24 months will be allowed to enter the trial. Patients with a history of a T1a or b prostate cancer (detected incidentally at TURP and comprising less than 5% of resected tissue) may participate if the PSA has remained within normal limits since TURP.
- Patients with known HIV positivity or AIDS-related illness. This is based upon the possibility of increasing HIV viral load with therapy
- Any other medical condition or reason that, in the principal investigator's opinion, makes the patient unsuitable to participate in a clinical trial
- Patients with a history of hypersensitivity reactions attributed to bortezomib, boron, or mannitol.
- Radiation therapy within 3 weeks before randomization. Enrollment of subjects who require concurrent radiotherapy (which must be localized in its field size) should be deferred until the radiotherapy is completed and 3 weeks have elapsed since the last date of therapy.

7.0 RECRUITMENT PLAN

This study will be conducted at MSKCC. Patients, community hematologists/oncologists, and nephrologists, will be informed of this trial by the MSKCC website. Efforts will be made to ensure that women and minority groups are adequately represented in this trial. All patients will be seen by MSKCC Hematology physicians and associated MSKCC co-investigators and enrolled at MSKCC and registered through MSKCC. All co-investigators agree to follow the treatment in the

protocol and to conduct the proposed investigation according to recognized principles of good clinical practice. Participation is voluntary. Each patient must be informed about the neoplastic nature of his/her disease and willingly consent to participation in this study. Every patient will be informed of the procedures to be followed, the potential benefits, side effects, risks, discomforts of the trial and of potential therapeutic alternatives. All participants will be required to sign statements of informed consent and research authorization that conform to FDA, IRB and HIPAA guidelines. Informed consent will be documented by the use of a written consent form that has been approved by the MSKCC IRB.

8.0 PRETREATMENT EVALUATION

The following tests will be performed within 2 weeks prior to patient enrollment:

- History & Physical exam, grading for neuropathy, height and weight for BSA, and NCI CTC Scoring
- Serum M-spike studies: Serum protein electrophoresis (SPEP), serum immunofixation (IF) and quantitative immunoglobulins, and serum free light chain assay
- Urine M-spike studies: Twenty-four hour urine for total volume and total protein (TV, TP), immunofixation (IF), protein electrophoresis (UPEP), and creatinine clearance
- Serum for electrolytes, BUN, creatinine, albumin, beta2-microglobulin, C-reactive protein, total bilirubin, ALT, AST, LDH, alkaline phosphatase (AP), calcium, CBC with differential, INR/PTT, and β-HCG for women of childbearing potential, BNP, and troponin.
- Stool for Guaiac Testing – for patients with suspicion of GI involvement

The following tests will be performed within eight weeks prior to patient enrollment:

- Echocardiogram or MUGA scan, and electrocardiogram (EKG)
- Pulmonary function test (PFTs)
- EMG/Nerve conduction studies for patients with suspected nerve involvement
- Cardiac MRI for patients with clinically significant cardiac involvement
- Liver Ultrasound for patients with expected liver involvement
- Hepatitis A, B, C serologies and HIV 1/2 test (unless previously negative at MSKCC within the last six months)
- A skeletal survey that should be reviewed at MSKCC if not performed at MSKCC
- Bone marrow examination, including biopsy sample for H & E stain and immunohistochemical staining for CD 138, CD20, kappa and lambda light chains; bone marrow aspirate samples for Giemsa staining, flow-cytometry, cytogenetic analysis, and FISH analysis for chromosomes 1, 4, 11, 13, 14, 17 abnormalities

The following test will be performed within 12 weeks prior to patient enrollment:

- Organ biopsy (kidney, heart, GI etc…) to confirm the diagnosis of MIDD or AL amyloidosis

9.0 TREATMENT/INTERVENTION PLAN

9.1 Treatment Plan

There are three treatment phases to this protocol.

9.1.1 Initial treatment phase: During this phase, the patients will receive treatment as outpatients and will be followed in the clinic on a regular basis as shown in the schedule below. The patients will receive one to three 21-day-cycles consisting of the following combination:

Bortezomib 1.3 mg/m^{2}IV or SQ on days 1, 4, 8, and 11 as a bolus injection
Dexamethasone 40 mg IV or PO on days 1, 4, 8, and 11

Drugs will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Patients will be treated on an out-patient basis. The pharmacist will prepare the drugs under aseptic conditions. The amount (in mg) of drug to be administered will be determined based on body surface area. Body surface area is to be calculated based on adjusted body weight (ABW) using standard MSKCC nomogram. The dose should be calculated on Day 1 of each cycle; the dose administered should remain the same throughout each cycle but should be recalculated at the start of the next cycle.

The appropriate amount of bortezomib will be drawn from the injection vial and administered as an intravenous (IV) push over 3 to 5 seconds. This injection will be followed by a standard saline flush or through a running IV line. Vials are for single use administration.

Prophylaxis therapy will be initiated at the start of treatment to prevent treatment-related toxicity and will include the following: B-complex vitamin supplement PO containing at least 50 mg of vitamin B6 (pyridoxine) daily; Prilosec 20 mg daily or equivalent; Bactrim DS, 1 tablet PO, daily, three days a week; Diflucan 100 mg PO, daily, and Acyclovir 400 mg PO, twice a day. Doses will be adjusted for renal function.

Toxicity and response will be assessed after every cycle of treatment, before the next cycle and at the completion of the 3 cycles as shown on the schedule below, section 10.1. Patients who achieve CR before completion of 3 cycles may forego the remaining cycle(s) and proceed to phase 2 of treatment. If at any point in time during this phase of treatment a patient shows evidence of progression of multiple myeloma with confirmation, (s)he will be taken off study. All other patients will proceed with the second phase of treatment. Dose adjustments and modifications will be made as shown in the section below entitled –Dose adjustments and modifications‖.

9.1.2 HDM/ASCT phase: After 3 cycles of BD, patients without progression of disease (POD) will proceed with stem cell mobilization and collection as per institutional guidelines. . A leukapheresis catheter will be placed during that admission if deemed necessary for stem cell collection. Leukapheresis will begin as per the SOP of the Blood Donor Room stem cell collection process. Once stem cell collection begins, a target of 10 x 10^6 CD34+ cells per kg will be sought, allowing the collection of adequate stem cells for up to three stem cell transplants in a patient's lifetime. We will seek a minimal acceptable collection of 2-4 x 10^6 CD34+ cells per kg, allowing one to two ASCT procedures with the minimum acceptable dose of 2 x 10^6 CD34+ cells/kg, per SCT. Patients failing to collect the minimum dose may be mobilized a second time as per MSKCC guidelines. Patients who are mobilized twice and have less than 2 million stem cells (CD34+ cells) collected per kg, will be removed from study. The likelihood of this happening is less than 2%. Blood stem cells will be cryopreserved according to standard operating procedures of the Cytotherapy Laboratory.

For HDM/ASCT, patients will be admitted to the hospital. High-dose melphalan will be administered in a single day -2, or split on two consecutive days on days -3 and -2 through a central venous catheter. Melphalan will be administered at a risk adapted dose of 100, 140 or 200 mg/m^2 using adjusted ideal body weight (AIBW) and based on risk group and age as follows:

- For patients with no evidence of cardiac involvement and creatinine clearance ≥ 51ml/min, the dose of IV melphalan will be 200 mg/m^2 if the patient is ≤ 60 years old, 140 mg/m^2 if 61 to 70, and 100 mg/m^2 if ≥ 71.

- For patients with early cardiac amyloid and/or creatinine clearance < 51ml/min, the dose of IV melphalan will be 140 mg/m^2 with stem cell support if the patient is ≤ 60, and 100mg/m^2 if ≥ 61.

Stem cells will be infused on day 0. Patients will receive standard supportive care measures during the HDM/ASCT period as per MSKCC's institutional guidelines [73-75]. After discharge, patients will be followed initially weekly, then biweekly, then monthly, depending on the clinical condition of the patient and as deemed necessary by the treating physician.
The patients' response to the HDM/ASCT will be assessed at 12 weeks +/- 2 weeks after HDM/ASCT as shown on the schedule below. This assessment will include serum, urine and bone marrow testing. Patients without POD will proceed with the third phase of treatment. If at any time post transplant a patient shows evidence of POD with confirmation, (s)he will be taken off study.

9.1.3 Consolidation/maintenance phase: During this phase, the patients will receive treatment as outpatients and will be followed in the clinic on a regular basis as shown in the schedule below. The patients will receive six cycles, each given once every 12 weeks +/- 2 weeks and each consisting of the following combination:

Bortezomib 1.3 mg/m^2, IV or SQ, on days 1, 8, 15, and 22
Dexamethasone 20 mg IV or PO, on days 1, 8, 15, and 22

The patients' response will be assessed with serum and urine testing after every cycle, , and at the completion of the 6 cycles of treatment as shown on the schedule below. If at any point in time during this phase of treatment a patient shows evidence of POD with confirmation or unacceptable toxicity to treatment, (s)he will be taken off study. All other patients will complete the full 6 cycles. The patient's toxicity will be assessed at every encounter and before initiation of every cycle as shown on the schedule below. Dose adjustments and modifications will be made as shown in the section below entitled –Dose adjustments and modifications‖.
Prophylaxis therapy will be initiated at the start of this phase of the treatment and will include the following: B-complex vitamin supplement PO containing at least 50 mg of vitamin B6 (pyridoxine); Prilosec 20 mg PO, daily, or equivalent; Bactrim DS, 1 tablet PO, daily, three days a week; Diflucan 100 mg PO, daily; and Acyclovir 400 mg PO, twice a day. Doses will be adjusted for renal function.
The end of treatment assessment (which will also coincide with the end of study- 24 month post-treatment assessment in the majority of patients) will occur within 4-6 weeks of completion of the last consolidation maintenance dose as shown on the schedule below, section 10.3. This assessment will include blood and urine testing as well as a bone marrow aspirate and biopsy. Organ responses will also be graded at this time point. The patients will be followed in the clinic every 3 months thereafter as per standard practice, with no further intervention, until progression of disease. Long Term Follow Up will cease when all patients on study have fulfilled the requirements for at least five follow up appointments.

9.2 Cycle Delay and Dose Modification Guidelines

On the first day of each new treatment cycle and before each treatment dose, the patient will be evaluated for possible toxicities that may have occurred due to previous doses. Toxicities will be assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0. Cycle delays and dose modifications will be made based on the toxicity experienced during the previous cycle of therapy or the ones encountered on any of the treatment days. Doses of study drug that need to be held WITHIN a cycle are skipped and will not be made up later in the cycle.

9.2.1 Cycle Delay

The following parameters must be met on the first day of each cycle:

- Platelet count ≥50 x 10^9/L
- Hemoglobin ≥8 g/dL ; prior red blood cell (RBC) transfusion or recombinant human erythropoietin use is allowed
- ANC ≥1.0 x 10^9/L
- Non-hematologic toxicity must have recovered to Grade 1 or baseline

If the above parameters are not met, the start of the next cycle will be held for a week for recovery to the specified levels. The start of the new cycle can be delayed on a weekly basis (for a maximum of 3 weeks) until recovery from toxicity to a level allowing continuation of therapy. Delay of a new cycle for more than 3 weeks can only occur if a clear clinical benefit has been observed from the treatment and it is felt by the treating physician that continuation of treatment would be advisable. Otherwise, if there is a delay in the start of a new cycle of more than 3 weeks due to insufficient recovery from toxicity, subjects will discontinue study drug and have procedures performed as outlined for the End of Treatment phase assessment.

9.2.2 Dose Modifications

9.2.2.1 Dose Reduction Steps

Dose escalation will not be allowed in any patient, and there must be at least 72 hours between each dose of bortezomib.

Before each drug dose, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI CTCAE, version 4.0. All previously established or new toxicities observed any time, with the exception of neuropathic pain and peripheral sensory neuropathy, are to be managed as shown below.

Dose reductions steps represented in the following tables for bortezomib and dexamethasone. Patients who have an unacceptable toxicity after 2 dose reductions due to any of the study drugs will discontinue that study drug.

If the patient experiences febrile neutropenia, a grade 4 hematologic toxicity (including a platelet count < 25 x 109/L) or any ≥ grade 3 non-hematologic toxicity considered by the investigator to be related to bortezomib, then drug needs to be held.

If the bortezomib dose is reduced during the initial treatment phase, the starting dose of bortezomib during the Maintenance Treatment Phase should be similarly reduced as well. For example, if the bortezomib dose is reduced from 1.3 mg/m^2 to 1.0 mg/m^2 in the initial phase of treatment, the starting dose in the maintenance phase should also be reduced from 1.3 mg/m^2 to 1.0 mg/m^2.

For nonhematologic toxicities, bortezomib is to be held for up to 2 weeks until the toxicity returns to Grade 1 or better.

If the toxicity resolves, as described above, bortezomib may be restarted at the same schedule the patient was on prior to holding therapy, and the dose must be reduced by approximately 25% as follows:

Dose reduction steps for bortezomib

Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
Bortezomib 1.3 mg/m^2 on Days 1, 4, 8 and 11	Bortezomib 1.0 mg/m2 on Days 1, 4, 8 and 11	Bortezomib 0.7 mg/m2 on Days 1, 4, 8 and 11	Bortezomib 0.7 mg/m^2 on Days 1, 8, 15, and 22 of a 35 day schedule
Bortezomib 1.3 mg/m^2 on Days 1, 8, 15, and 22	Bortezomib 1.0mg/m^2 on Days 1, 8, 15, and 22	Bortezomib 0.7 mg/m^2 on Days 1, 8, 15, and 22	Bortezomib 0.7 mg/m^2 on Days 1 and 15

Dose reduction steps for dexamethasone

Treatment Phase	Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction	Fourth Dose Reduction
Initial Treatment Phase	40 mg QD on Days 1, 4, 8 and 11	20 mg QD on Days 1, 4, 8 and 11	12 mg QD on Days 1, 4, 8 and 11	4 mg QD on Days 1, 4, 8, and 11	Discontinue dexamethasone
Maintenance Treatment Phase	20 mg QD on Days 1, 8, 15, and 22	12 mg QD on Days 1, 8, 15, and 22	4 mg QD on Days 1, 8, 15 and 22	Discontinue dexamethasone	N/A

9.2.2.2 Dose Modifications for Bortezomib-Related Hematologic Toxicity

On any day of bortezomib administration during a cycle, other than Day 1 of each cycle, the hematology results must be:
– Platelet count ≥30 x 10^9/L
– ANC ≥0.75 x 10^9/L
If the above parameters are not met, the bortezomib dose will be skipped; the dose will not be made up later in the cycle.
If in the previous cycle, 2 or more of the 4 doses of bortezomib were skipped due to hematologic toxicity, the dose of bortezomib will be reduced in the following cycles by one step.

Dose (re-)escalations of bortezomib are not allowed.

9.2.2.3 Dose Modifications for Bortezomib-Related Neuropathy

The neurotoxicity-directed questionnaire (see appendix 20.1) is a useful tool for determining the presence and intensity of neuropathic pain and/or peripheral neuropathy from the patient's perspective. Neuropathic symptoms are more prominent than abnormalities on the clinical examination. After the patient completes the neurotoxicity-directed questionnaire, the questionnaire should be reviewed to assist with the evaluation of the onset and intensity of peripheral neuropathy and other neuro-toxicities that may possibly require intervention or dose modification. The table below contains the recommended dose modification for the management of subjects who experience BORTEZOMIB-related neuropathic pain and/or peripheral neuropathy.

Recommended Dose Modification for BORTEZOMIB related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy	
Severity of Peripheral Neuropathy Signs and Symptoms	Modification of Dose and Regimen
Grade 1 (paresthesias, weakness and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce BORTEZOMIB by one level
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold* BORTEZOMIB therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of BORTEZOMIB by one dose level and change treatment schedule to once per week.
Grade 4 (Sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue BORTEZOMIB
Grading based on NCI Common Terminology Criteria CTCAE v4.0 NCI Common Terminology Criteria website - http://ctep.info.nih.gov/reporting/ctc.html	

ADL = activities of daily living
*Key:
Reduce by one dose level: See above tables for reduction levels for bortezomib.
Hold: Interrupt BORTEZOMIB for up to 3 weeks until the toxicity returns to Grade 1 or better.

9.2.2.5 Dose Modifications for Other Non-hematologic Toxicity

If a patient experiences any Grade 3 or 4 non-hematologic toxicity (excluding neuropathy as discussed above) considered by the investigator to be related to study drug(s), then the treatment regimen will be held until the intensity of the side effect decreases to Grade 1 or baseline. After recovery from toxicity to a level allowing continuation of therapy, a dose level

reduction should be instituted for bortezomib. A dose reduction for corticosteroids should occur only for Grade 3 or 4 corticosteroid-related toxicities.

Patients with cardiac toxicity: If during treatment the LVEF falls below normal limits of the institution, or the ejection fraction (LVEF) falls by 20% from the baseline level, bortezomib will be discontinued. The investigator may verify the LVEF from a MUGA by obtaining an ECHO with cardiac consultation. If there is no evidence of cardiac damage determined by ECHO the patient may continue on treatment. Treatment with bortezomib should be discontinued in subjects who experience new onset symptomatic congestive heart failure, or if they experience cardiac dysfunction as indicated by symptomatic arrhythmia, a decrease in LVEF to below the institutional lower limit of normal, or an absolute decrease of 15% or more from the subject's baseline value (e.g. 60% to 45%).

Patients with mild hepatic impairment (bilirubin ≤ 1.5 x ULN) do not require a starting dose adjustment. Please note that patients with bilirubin levels > 1.5 ULN are excluded from enrollment in this protocol. If a patient develops moderate or severe hepatic impairment with bilirubin ≥ Grade 2 (> 1.5 - 3.0 x ULN) while on study, the investigator should hold BORTEZOMIB until the toxicity returns to < Grade 2. Restarting BORTEZOMIB at the next lower dosed level could be considered at the Investigator's discretion and following exclusion of BORTEZOMIB-induced liver impairment and careful consideration of liver disease due to other causes, such as, but not limited to, active infection and multiple myeloma-related liver disease.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Evaluation During the Initial Treatment Phase

Study Procedures	Screening Period	Treatment period				End of Initial Treatment [a]
	D -14 to -1	Day1[g]	Day 4	Day 8	Day 11	
Informed Consent	X					
History, Complete Physical (including orthostatics)	X	X				X
interval history, physical - symptom-directed		X				X
Weight	X	X				X
Vital signs	X	X	X	X	X	X
Concomitant meds, supportive Rx assessment	X	X				X
Adverse event assessment		X	X	X	X	X
Electrocardiogram	X[b]					
Echocardiogram	X[b]					
Cardiac MRI	X[h, b]					
PFTs	X[b]					
Neurologic Examination	X	X				X
Stool for Guaiac Testing	X[i]					
EMG/ Nerve conduction studies	X[e, b]					
Liver Ultrasound	X[f, b]					
Skeletal Survey	X[b]					
Karnofsky Performance Status	X	X				X
Serum Multiple Myeloma Disease Assessment • protein electrophoresis • Quantitative immunoglobulins • Immunofixation • Serum Free Light Chains	X	X				X
24 hour Urine Multiple Myeloma Disease assessment • protein electrophoresis • Immunofixation • Total protein • Creatinine clearance	X	X				X
Bone Marrow Aspirate and Biopsy for: • Morphology • Cytogenetics/FISH	X[b, j]					X
Organ biopsy	X[d]					
CBC	X	X	X	X	X	X
Electrolytes	X	X				X
Glucose	X	X				X
BUN, Creatinine	X	X				X
Total protein	X	X				X
ALT, AST, LDH, Bil, AP	X	X				X
Albumin	X	X				X
Calcium	X	X				X
β_2-microglobulin	X	X				X
C-reactive protein	X	X				X
Urinalysis	X	X				X
Serum β-HCG Pregnancy Test	X[c]	X[c]				
BNP	X	X				X

Troponin	X	X				X
HIV/hepatitis A, B and C tests	X[b]					
Bortezomib Dosing		X	X	X	X	
Dexamethasone		X	X	X	X	

[a]Within 4 weeks of completion of initial treatment; [b]within 8 weeks of registration; [c]for women of childbearing potential; [d]within 12 weeks of registration; [e]for patients with suspected nerve involvement; [f]for patients with expected liver involvement; [g]study procedures excluding Vital signs, AE assessment, CBC, and Pregnancy test can be completed ≤ 10 days prior to Day 1 of treatment; [h]for patients with clinically significant cardiac involvement; [i]for patients with suspicion of GI involvement if clinically indicated

10.2 Evaluation During HDM/ASCT Treatment Phase

The management and evaluation during the transplant admission itself will be performed as per standard operating procedures in use currently at MSKCC.

Study Procedures	Pre-HDM/ASCT[a,b]	Post-HDM/ASCT[a,c]
History, Complete Physical	X	X
interval history, physical - symptom-directed	X	X
Concomitant meds, supportive Rx assessment	X	X
Adverse event assessment	X	X
Chest X-ray	X	
Electrocardiogram	X	
Echocardiogram	X	
Weight	X	X
Vital signs	X	X
Karnofsky Performance Status	X	X
Serum Multiple Myeloma Disease Assessment • protein electrophoresis • Quantitative immunoglobulins • Immunofixation • Serum Free Light Chains	X	X
24 hour Urine Multiple Myeloma Disease assessment • protein electrophoresis • Immunofixation • Total protein • creatinine clearance	X	X
Bone Marrow Aspirate and Biopsy for: • Morphology • Cytogenetics/FISH	X[d]	X
CBC	X	X
Electrolytes	X	X
Glucose	X	X
BUN, Creatinine	X	X
Total protein	X	X
ALT, AST, LDH, Bil, AP	X	X
Albumin	X	X
Calcium	X	X
β_2-microglobulin	X	X
C-reactive protein	X	X
Urinalysis	X	X
Serum β-HCG Pregnancy Test	X	
BNP	X	X
Troponin	X	X
Infectious Disease Testing[a]	X	

[a]all test obtained as per standard MSKCC transplantation SOP; [b]These tests can be part of the end of initial treatment phase evaluation; [c]These tests will be obtained 12 weeks +/- 2 weeks post ASCT; [d]Per MSK SOP

10.3 Evaluation During the Maintenance Treatment Phase and beyond

Study Procedures	Treatment period				12 month Evaluation	End of Treatment Phase (and at 24 months)	Long term Follow up (every 3 months)
	Day1 [d]	Day 8	Day 15	Day 22			
History, Complete Physical (including orthostatics)	X				X	X	X
interval history, physical - symptom-directed	X				X	X	X
Concomitant meds, supportive Rx assessment	X				X	X	X
Adverse event assessment	X	X	X	X	X	X	
Weight	X				X	X	X
Vital signs	X	X	X	X	X	X	X
Neurologic Examination	X				X	X	X
EMG/ Nerve conduction studies	X[bg]				X[b]	X[b]	
Liver Ultrasound	X[cg]				X[c]	X[c]	
Karnofsky Performance Status	X				X	X	X
Electrocardiogram					X	X	
Echocardiogram					X	X	
Cardiac MRI					X[f]	X[f]	X[a, f]
Serum Multiple Myeloma Disease Assessment • protein electrophoresis • Quantitative immunoglobulins • Immunofixation • Serum Free Light Chains	X				X	X	X
24 hour Urine Multiple Myeloma Disease assessment • protein electrophoresis • Immunofixation • Total protein	X				X	X	X
Bone Marrow Aspirate and Biopsy for: • Morphology • Cytogenetics/FISH					X[h]	X[h]	X[a, h]
CBC	X	X	X	X	X	X	X
Electrolytes	X				X	X	X
Glucose	X				X	X	X
BUN, Creatinine	X				X	X	X
Total protein	X				X	X	X
ALT, AST, LDH, Bil, AP	X				X	X	X
Albumin	X				X	X	X
Calcium	X				X	X	X
β_2-microglobulin	X				X	X	X
C-reactive protein	X				X	X	X
Urinalysis	X						X
Serum β-HCG Pregnancy Test	X[e]						
BNP	X				X	X	X
Troponin	X				X	X	X
Bortezomib Dosing	X	X	X	X			
Dexamethasone	X	X	X	X			

[a]This test will be obtained yearly; [b]for patients with suspected nerve involvement; [c]for patients with expected liver involvement; [d]Study procedures excluding Vital signs, AE assessment, CBC, and Pregnancy test can be completed ≤ 10 days prior to Day 1 of treatment; [e]for women of childbearing potential; [f]for patients with clinically significant cardiac involvement; [g]Testing to be done on Day 1 Cycle 1, 12 months and 24 months only if clinically indicated; [h]per MSK SOP.

11.0 TOXICITIES/SIDE EFFECTS

For toxicity scoring we will use NCI CTC Version 4.0 (http://ctep.cancer.gov/reporting/ctc.html).

11.1 Bortezomib

Most Common Bortezomib Risks:

The most common risks are those that have occurred in greater than or equal to 30% of patients who have received bortezomib:

- Feeling weak, tired, and generally uncomfortable
- gastrointestinal effects such as constipation, diarrhea, nausea, vomiting, and loss of appetite. These may result in dehydration and/or weight loss
- fever commonly with shaking chills
- painful feelings or numbness and tingling in hands and feet, which may not get better after stopping bortezomib. Uncommonly, the nerves that control things like your heart rate, gut movement and urinary bladder may be affected
- lowered platelets; that may increase the chance of bleeding
- lowered red cells or anemia which may make you feel tired

Very Common Bortezomib Risks:

The very common risks are those that have occurred in 10-29% of patients who have received bortezomib:

- Neutropenia uncommonly associated with fever; commonly lymphopenia or anemia, leukopenia and thrombocytopenia at the same time
- flu-like symptoms and other upper respiratory tract infections, such as chills, sore throat, and runny nose and sinus and throat infections
- abdominal pain
- aches and pains in muscles and joints, pain in bones and in arms, back and legs
- Peripheral edema.
- cough, feeling short of breath, lung infections including pneumonia and commonly bronchitis
- headache
- skin rash with itching and redness. An uncommon risk is a severe, life-threatening or deadly rash with skin peeling and mouth sores.
- Herpes virus infections such as Herpes Zoster) and herpes simplex virus Herpes Zoster can sometimes spread over large parts of the body. Both may also affect the eyes or brain, but this is uncommon
- Anxiety
- Insomnia
- Myalgia
- Chills
- Dehydration
- Dizziness

Common Bortezomib Risks:

Common risks are those that have occurred in 1-9% of patients who have received bortezomib:

- Hypotension that can commonly cause light headedness and orthostatic symptoms
- Arrhythmias that can cause you to possibly light-headedness, dizziness, fainting, dyspnea, and/or chest pain. This may also cause confusion. An uncommon risk is a possible life threatening arrhythmia
- new or worsening heart failure that can uncommonly be severe.
- infection and/or inflammation of the eye or eyelids
- painful sores of the mouth and/or throat, which may make swallowing difficult
- heartburn, acid reflux and stomach bloating
- severe bleeding, including bleeding in the stomach and intestines (gut) that may be linked with low platelet counts, and blood clotting changes. Uncommonly, this bleeding may cause bloody diarrhea and/or hematemesis.
- epistaxis
- Renal insufficiency; renal failure
- infections of the bladder, sinuses, throat, stomach and intestines, skin and at the area of catheter insertion.
- fungal infections in the mucous membrane such as the mouth and throat and uncommonly in the skin and nails
- life-threatening infections in the blood (sepsis)
- changes in blood sugar have been reported in a few diabetic patients who took oral antidiabetic medicine.
- Hematuria
- Confusion
- Dysgeusia
- abnormal liver function tests and decreased level of serum total protein and albumin
- Hypokalemia, and hyponatremia, and hypercalcemia
- Muscular weakness
- Weight decreased
- Muscle spasms
- Gastrointestinal hemorrhage
- Ileus Neuralgia

Uncommon bortezomib Risks:

Uncommon risks are those that have occurred in less than 1% of patients who have received bortezomib:

- Inflammation, pleural effusions, empyema that may cause breathing problems, and can be life-threatening or lead to death. Pulmonary hypertension has also been reported. This can cause breathing problems and can be life-threatening.
- Pericarditis that may cause chest pain or breathing problems and can be life-threatening or lead to death.
- hepatitis, and liver failure (in patients who also got many drugs and had other serious medical problems).
- pain, redness, swelling and infection in the area of the skin where bortezomib is injected into the vein
- pain in the mouth and throat when swallowing
- loss of hearing
- intestinal obstruction that may reverse spontaneously and inflammation of the intestines, pancreas or stomach
- Hemoptysis

- bleeding in the brain and subdural hematoma
- Tumor lysis syndrome
- allergic reactions that may include skin, swelling of the face or throat and could be severe or life threatening
- severe muscle weakness and paralysis
- changes to the brain that may cause convulsions and confusion
- reversible posterior leukoencephalopathy syndrome that may cause headaches, changes in vision, mental status, or seizures, but is usually reversible
- loss of some to all vision affecting one or both eyes, which may be caused by damage to the nerve in the eye. Loss of vision may or may not be reversible.
- Gastrointestinal perforation
- Adult respiratory distress syndrome
- Cardiac failure

11.2 Dexamethasone

The major potential side effects of dexamethasone are well described and well known. Gastrointestinal prophylaxis will be given to minimize GI upset. Antibiotic and antifungal prophylaxis will be given. Patients who experience toxicity from dexamethasone therapy may have the dose reduced as detailed in section 9.2.

Most Likely Side Effects:

- Hyperglycemia, worsening of diabetes, or cause diabetes
- Insomnia
- Fluid retention and anasarca
- Hypokalemia
- Immunodeficiency. This could lead to more frequent infections, which could be severe. Old infections such as tuberculosis may recur.
- Adrenal insufficiency on withdrawal

Very Likely Side Effects:

- Mood swings, psychosis, personality changes, and/or depression
- Leukocytosis
- Nausea, vomiting,
- Increased appetite and weight gain, or paradoxically loss of appetite and weight loss
- Headache; dizziness; seizures

Likely Side Effects:

- Hiccups
- Hirsutism involving the face or other parts of the body
- Acne, and/or rosacea
- Increased sweating; bruising; trouble healing wounds
- Menstrual cycle disruption
- Infertility in men
- Hypertension
- Opthalmic complications:
    - Cataracts

- Increased pressure inside the eye
- Protrusion of the eyeballs
- Glaucoma.

These may cause decreased vision, blindness, or eye pain.

- Cushing syndrome
- Osteoporosis
- Thrombosis
- Capillary fragility leading to ecchymoses

Uncommon Side Effects:

- Steroid myopathy, which may be severe
- Increased pressure inside your skull
- GI complications including ulcers, esophagitis, gastritis, which may lead to bleeding complications
- Pancreatitis
- Rash, including redness of the skin, hives, itching, and swelling of the skin, face, or throat

11.3 Melphalan

The major systemic toxicity of IV melphalan is bone marrow depression with secondary anemia, leukopenia and thrombocytopenia. This side-effect is exacerbated by prior chemotherapy or radiotherapy.

Side-effects include:

Likely

- Low blood cell counts (bone marrow suppression) that can lead to anemia that requires red blood cell transfusions; a decreased number of white blood cells that increases the risk of infections and is treated with G-CSF injections and with stem cells; and low platelets that increases the risk of bruising and bleeding and is treated with platelet transfusions.
- Fatigue
- Nausea, vomiting
- Hair loss (temporary)
- Mouth sores
- Pain in the mouth requiring pain medicines
- Pain with swallowing requiring pain medicines
- Diarrhea and cramping

Less likely

- Liver damage
- Allergic reactions (which could make you feel short of breath and/or have a skin rash)

Rare but serious

- Secondary leukemia 5 to 10 years after exposure
- Lung damage
- Blood vessel damage
- Red blood cell damage due to an immune reaction
- Death

11.4 Neulasta and Neupogen (G-CSF)

Side-effects of Neupogen include:

Likely

- Body aches
- Pain, swelling and redness at the site of injection
- Bone pain
- Transient and reversible changes in alkaline phosphatase, uric acid and LDH
- Exacerbation of preexisting autoimmune disorders
- Fever
- Muscle cramps and pain in your back or legs (relieved by taking Tylenol)

Less likely

- Inflammation, psoriasis or arthritis may get worse

Rare but serious

- Decreased blood pressure and risk of falling
- Enlargement of the spleen that may lead to rupture
- Hair thinning
- Decreased blood platelets which may increase your risk of bruising or bleeding
- Enlargement of the liver
- Allergic reactions

11.5 Risks and side effects during stem cell mobilization specifically associated with PLERIXAFOR

Likely side effects of plerixafor

- Erythema at the injection site
- Nausea
- Headache

Less Likely side effects of plerixafor

- Dysesthesia in different parts of the body
- Burning and swelling at the injection site
- Diarrhea
- Dizziness
- Chest tightness
- Abdominal distension
- Abdominal pain

All of these symptoms were mild and went away after treatment.

Rare but serious

- Severe decrease in blood platelet count after six days of intravenous infusion of plerixafor was described in one patient with HIV. The patient's platelet count returned to normal within four weeks after the infusion.
- Tachycardia and orthostasis, which can be associated with irregular heartbeats.

11.6 Risks and side effects during stem cell mobilization specifically associated with CYCLOPHOSPHAMIDE

Likely side effects of cyclophosphamide:

- Pancytopenia
- Fatigue
- Hair loss
- Nausea and vomiting
- Hemorrhagic cystitis
- Male infertility

Rare but serious side effects of cyclophosphamide:

- Myocarditis that may result in decrease in ejection fraction
- Pneumonitis
- Hyponatremia
- Bladder cancer
- Allergic skin reactions
- Secondary leukemia

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Measurement of Safety Outcome

The primary endpoint of this study is assessment of toxicity/tolerability at the completion of the treatment. Toxicities will be assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0. All subjects will be evaluated for the presence of treatment related toxicity during active treatment at the end of each cycle as described above in section 9.1. Safety measurements also will be evaluated by physical examination findings, vital signs assessments, clinical laboratory test results, and adverse events. Cycle delays and dose modifications will be made based on the toxicity experienced during the previous cycle of therapy or the ones encountered on any of the treatment days as described above in section 9.2. All adverse events will be reported as described in section 17.2 below. Comprehensive assessments of any apparent toxicity experienced by the subject will be performed throughout the course of the study. Study center personnel will record all adverse events, whether observed by the Investigator or reported by the subject, on the CRF. A physician (either the Principal Investigator or a physician designated by the Principal Investigator) will manage and treat any treatment-emergent toxicity.

12.1 Hematologic Response

The hematologic response to any of the treatment cycle, treatment phase, and comprehensive treatment will be assessed by widely accepted standard response criteria detailed below. These are based on measurement of the monoclonal immunoglobulin in the serum and urine. Bone marrow plasmacytosis and skeletal survey are also used in these response criteria to confirm complete response and progression of disease as detailed in the table below. Serum studies include protein electrophoresis, immunofixation, quantitative immunoglobulin, and free light chain determination. Urine studies include 24 hour urine collection for protein electrophoresis, immunofixation, and total protein. All these tests will be performed as detailed in tables in section 10.0. The response scored within 4 weeks after the conclusion of all therapy is the one of the secondary endpoints of this study.
A Response Review Group that includes a pathologist, a Clinical laboratory scientist, and several Hematologists from the Hematology Service will formally score the response. The

group meets every Tuesday. Research study assistants prepare patient data for review and record response decisions. Usually the response to therapy is straightforward although there are instances in which the multiple tests used give somewhat equivocal results. Hence, the value of group reviews.

RESPONSE	CRITERIA FOR RESPONSE
COMPLETE RESPONSE (CR)	Requires all of the following: • Normalization of the free light chain (FLC) levels and ratio • Negative serum and urine immunofixation • <5% plasma cells in bone marrow
VERY GOOD PARTIAL RESPONSE (VGPR)	• Reduction in the dFLC (difference between involved [iFLC] and uninvolved FLC) to <4mg/dl
PARTIAL RESPONSE (PR)	• ≥ 50% reduction in the dFLC
NO RESPONSE (NR)	• Less than PR
PROGRESSION OF DISEASE (POD)	Requires one or more of the following: • From CR, any detectable monoclonal protein or abnormal free light chain ratio (light chain must double) • From PR, 50% increase in serum M protein to >0.5g/dl or 50% increase in urine M protein to >200mg/day (a visible peak must be present) • Free light chain increase of 50% to >10mg/dl

12.2 Organ Response

12.2.1 Amyloidosis Organ Response

Organ response criteria in AL amyloidosis have been well established by consensus panel and widely used in the literature. The tests and studies listed in section 10.0 will be performed as shown in the schedule to measure organ response using the criteria detailed below. Amyloid-related organ involvement will be scored as improved, stable or worsened at the completion of every phase of treatment.

- Improvement of one or more affected organ(s) is defined by:

Kidneys: a 50% reduction in 24-hour urine protein excretion in the absence of progressive renal insufficiency (defined as 25% worsening of creatinine and creatinine clearance) which has to be at least 0.5 g/24hr.
Heart: a reduction of the BNP or NT-pro-BNP by 30% from baseline.
Liver: a 50% decrease of an initially elevated alkaline phosphatase level or reduction in the size of the liver by at least 2 cm by imaging.
Neuropathy: clinical improvement supported by clinical history, neurologic exam, orthostatic vital signs, resolution of severe constipation or reduction of diarrhea to less than 50% of previous movements/day, and EMG studies if indicated.

- Worsening of one or more affected organ(s) is defined by:

Kidneys: doubling of urinary 24 hour total protein if <3 g/24 hours at baseline, or 50% increase in urinary protein loss if > 3 g/24 hours, or reduction of creatinine clearance by > 50%, or increase in serum creatinine of > 2 mg/dL.
Heart: evidence of decrease in ejection fraction by > 10% or increase of the BNP or NT-pro-BNP by > 30% from baseline or increase of Troponin by 33%.
Liver: >50% increase in the alkaline phosphatase level above lowest value.
Neuropathy: clinical worsening supported by history, worsening orthostatic vital signs and symptoms, and EMG studies if indicated.

- Stable disease is defined when none of the criteria for improvement or for worsening disease are met.

12.2.2 MIDD Organ Response

It is important to highlight that the renal response criteria (since this is the organ that is by far the most affected and most often the only organ affected) for patients with MIDD has not been clearly characterized in the literature and much work needs to be done along this line. Some authors have borrowed the renal response criteria used for amyloidosis to assess the renal response in MIDD. However, we believe that there is a striking difference between these two diseases. In amyloidosis, renal injury mostly leads to the nephrotic syndrome and marked proteinuria, while renal clearance is preserved until very advanced stages of the disease. This is why the renal response is assessed based on the proteinuria in this disease. Conversely, in patients with MIDD, the main clinical feature of the disease is the decrease in the renal clearance. Protein wasting nephropathy is a less prominent component, usually reaching mild to moderate levels, and is highly variable. While 96% of the patients have renal insufficiency, only 40% have nephrotic range proteinuria. Furthermore, with worsening of the renal injury and renal filtration in MIDD, proteinuria usually decreases and no longer reflects the worsening pace of the disease. Overall, in MIDD the degree of proteinuria does not necessarily reflect the severity of the disease at presentation, and subsequent changes in proteinuria may be difficult to interpret. On the other hand, the creatinine clearance is a more reliable parameter that always reflects the renal state in this disease.
In summary, we believe that the amyloid criteria for renal response cannot be used for MIDD We believe that the only valid parameters for response measurement in MIDD are the creatinine and the creatinine clearance or GFR. These parameters will be used to measure the renal outcome in this clinical trial.
Renal response in MIDD will be scored as improved, stable or worsened at the completion of every phase of treatment.

- Progression of renal disease is defined as a decrease in the creatinine clearance by more than 50%.

13.0 CRITERIA FOR REMOVAL FROM STUDY

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

- If at any time during the treatment, a patient shows evidence of hematologic disease progression with confirmation

- If at any time a patient develops unacceptable toxicity
- If there is protocol violation
- Non-compliance
- Administrative reasons
- Failure to return for follow-up
- General or specific changes in the patient's condition unacceptable for further treatment in the judgment of the investigator

14.0 BIOSTATISTICS

This is a pilot study to examine the tolerability, toxicity, and efficacy of 1-3 cycles of BD, followed by HD M/ASCT, and maintenance therapy with BD in patients with MIDD and patients with AL amyloidosis. Twenty patientswill be accrued to the study. Toxicities will be tabulated by type and severity. Stopping rules for treatment-related mortality and grade 3 or 4 neurotoxicity will be employed to monitor the tolerability of the regimen. Patients will be followed for neurotoxicity while on treatment. Stopping rules and the corresponding power calculations are provided in the table below. The calculations for the stopping boundaries are based on the assumption that the endpoints are independent.

Endpoint	# events needed to stop the study	Projected probability of toxicity in the population	Probability of study completion (based on projection)
Treatment Mortality	3 in the first 8 patients 4 in the first 14 patients 5 in the first 20 patients	0.10	0.92
		0.30	0.20
Grade 3/4 Neurotoxicity	2 in the first 10 patients	0.06	0.83
	3 in the first 20 patients	0.20	0.17

The hematologic and organ response rates at the end of treatment and at 24 months post treatment will be estimated along with their corresponding 95% confidence intervals. With 20 patients, the response rates can be estimated to within +/- 22%. Time to hematologic progression from start date of therapy will be calculated using the Kaplan-Meier method. Approximately one patient will be accrued per month so accrual will last approximately 20 months. The study duration will last approximately 4 years.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.
Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.
During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.
All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000.. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or

verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

There is no randomization in this clinical trial

16.0 DATA MANAGEMENT ISSUES

All patients will be enrolled on protocol at Memorial Sloan-Kettering Cancer Center. We expect to be able to enroll the necessary 20 patients into this study in 2 years.
The data manager (Research Study Assistant, RSA) will be responsible for confirming eligibility and assisting the MD with the registration process. All study data will be collected by an assigned RSA who will enter this information into the Clinical Research Database (CRDB). This database will be utilized for data collection and storage and for reporting protocol specific events such as accrual demographics, toxicities and adverse events to the IRB, and the sponsor.
The RSA will collect toxicity and concomitant medication information and patient interviews. Adverse events, including all toxic effects of treatment will be tabulated individually according to severity or toxicity grade. The data manager will also monitor laboratory testing throughout the study. Laboratory data will be tabulated and summarized by descriptive statistics, as well as on the basis of MSKCC specified normal ranges.

16.1 Quality Assurance

Monthly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates, extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.
Random sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled –Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials‖ which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://mskweb2.mskcc.org/irb/index.htm
There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for

Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board. During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

The investigator will grant monitor(s) and auditor(s) from Millennium and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

17.2 Serious Adverse Event (SAE) Reporting

Adverse Events Definition

An adverse event is any unfavorable or unintended sign, symptom or disease temporally associated with the use of medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure. Adverse events will be captured and reported at each protocol visit per the Memorial Sloan Kettering Cancer Center Adult Bone Marrow Transplant (BMT) Adverse Event (AE) and Serious Adverse Event (SAE) Guide.

The following adverse events will be captured and should have corresponding source documentation in the medical record:

- Laboratory data, grades 3-4 (automatically captured through CRDB)
- Unexpected grades 1-5
- Expected grades 2-5 (unless specified in table one of the MSK Adult BMT AE and SAE Guide)

Serious Adverse Event Definition

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event

- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following

  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office

17.2.1 Procedures for AE and SAE Reporting: Millennium requirements

All serious adverse events (SAEs) (regardless of expectedness, causality, and whether commercial or investigational BORTEZOMIB is used) must be reported to Millennium Pharmacovigilance (or designee). See below for the reporting of SAEs.
The sponsor-investigator is responsible to meet all regulations and requirements applicable to the sponsor-investigator.

Adverse events (AEs) may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. AEs which are serious must be reported to Millennium Pharmacovigilance (or designee) from first dose of bortezomib up to and including 30 days after administration of the last dose of bortezomib. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Any SAE that occurs at any time after completion of bortezomib treatment or after the designated follow-up period that the investigator and/or sub-investigator considers to be related to any study drug must be reported to the Millennium Pharmacovigilance (or designee). Planned hospital admissions or surgical procedures for an illness or disease that existed *before the patient was enrolled in the trial* are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). 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).

This is an investigator-initiated study. The principal investigator, Dr. Hani Hassoun (who may also sometimes be referred to as the sponsor-investigator), is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

Sponsor-investigator must report all SAEs, regardless of expectedness or relationship with any study drug, to Millennium Pharmacovigilance (or designee) as soon as possible, but no later than 5 calendar days of the sponsor-investigator's observation or awareness of the event. In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Millennium Pharmacovigilance (or designee) from all sites participating in the study. Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to Millennium Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and sub-investigator(s). Millennium Pharmacovigilance (or designee) may request follow-up information to a reported SAE, which the sponsor-investigator will be responsible for providing to Millennium Pharmacovigilance (or designee).

The SAE report must include event term(s), serious criteria, and the sponsor-investigator's or sub-investigator's determination of both the intensity of the event(s) and the relationship of the event(s) to study drug administration.

Intensity for each SAE, including any lab abnormality, will be determined by using the NCI CTCAE 4.0, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

Relationship to all study drugs for each SAE will be determined by the sponsor-investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

Sponsor-investigator must also provide Millennium Pharmacovigilance with a copy of all communications with applicable regulatory authorities related to the study or study drug(s), including, but not limited to, telephone conversation logs, as soon as possible but no later than 5 calendar days of such communication.

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

Millennium Pharmaceuticals will send to the sponsor-investigator BORTEZOMIB safety letters (real-time safety letters and/or the quarterly safety updates). All safety letters pertaining to the BORTEZOMIB program will be sent to the Investigator-Sponsor via an electronic distribution using Mercury, the Millennium Secure File Transfer (MFT) system. For each safety letter distributed, Sponsor-Investigator will receive an e-mail inviting to download the Adobe/PDF document from Mercury.

To meet GCP requirements, Millennium is required to send Sponsor-Investigators the safety letters within 15 days after the world-wide receipt date of the safety event. Sponsor-Investigators responsibility is to read the safety letter, and provide the safety letter to the Institutional Review Board or Ethics Committee per institution's policy. Sponsor-investigator will be responsible for forwarding such reports to any sub-investigator(s).

Monitoring of Adverse Events and Period of Observation

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

Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and must permanently discontinue study drug(s). All pregnancies and suspected pregnancies must be reported to Millennium Pharmacovigilance (or designee; see Section 17.2.1 for contact information) immediately. The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth,

miscarriage) and Millennium Pharmacovigilance will request this information from the investigator.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to Millennium Pharmacovigilance (or designee) immediately (see Section 17.2.1 for contact information). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

17.3 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The sponsor-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. This is the responsibility of the sponsor-investigator.

17.4 Ethical Considerations

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

17.5 Patient Information and Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risk Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

17.6 Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

17.6 Patient Confidentiality

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

17.7 Protocol Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Millennium and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to Millennium and the regulatory authority(ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

17.8 On-site Audits

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

17.9 Drug Accountability

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

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

17.10 Product Complaints

A product complaint is a verbal, written, or electronic expression which implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see the following) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium quality representative.

For Product Complaints, call MedComm Solutions at +1-866-835-2233

17.11 Premature Closure of the Study

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

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements

- Insufficient complete and/or evaluable data
- Plans to modify, suspend, or discontinue the development of the drug

17.12 Record Retention

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

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form

19.0 REFERENCES

1. Jemal A, Murray T, Ward E, et al: Cancer statistics, 2005. CA Cancer J Clin 55:10-30, 2005

2. Smith A, Wisloff F, Samson D: Guidelines on the diagnosis and management of multiple myeloma 2005. Br J Haematol 132:410-51, 2006

3. NCCN: NCCN, National Comprehensive Cancer Network, Clinical Practice Guidelines in Oncology- Multiple Myeloma. 2006

4. Barlogie B, Shaughnessy J, Tricot G, et al: Treatment of multiple myeloma. Blood 103:20-32, 2004

5. Fermand JP, Katsahian S, Divine M, et al: High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long-term results of a randomized control trial from the Group Myelome-Autogreffe. J Clin Oncol 23:9227-33, 2005

6. Jagannath S, Durie BG, Wolf J, et al: Bortezomib therapy alone and in combination with dexamethasone for previously untreated symptomatic multiple myeloma. Br J Haematol 129:776-83, 2005

7. Richardson P, Chanan-Khan, A, Schlossman, R, Munshi, N, Oaklander,A.L., Heffner, L., Hassoun, H. Avigan, D. Amato,A. Anderson, K: Multicenter Phase 2 Study of Bortezomib in Previously Untreated Multiple Myeloma (MM); Encouraging Single-agent Activity and Tolerability Despite High Rates of Baseline Peripheral Neuropathy. Blood 106, 2005

8. Dispenzieri A, Blood, E., Vesole, D., Fonseca, R., Callender, N., Pr, G., : A phase II study of PS-341 for patients with high risk, newly diagnosed multiple myeloma: A trial of the ECOG group (E2A02). Blood 106, 2005

9. Harousseau JL, Attal M, Leleu X, et al: Bortezomib plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: results of an IFM phase II study. Haematologica 91:1498-505, 2006

10. Wang M, Giralt S, Delasalle K, et al: Bortezomib in combination with thalidomide-dexamethasone for previously untreated multiple myeloma. Hematology 12:235-9, 2007

11. Wang M, Weber DM, Delasalle K, et al: Thalidomide-dexamethasone as primary therapy for advanced multiple myeloma. Am J Hematol 79:194-7, 2005

12. Mateos MV, Hernandez JM, Hernandez MT, et al: Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: results of a multicenter phase 1/2 study. Blood 108:2165-72, 2006

13. Mateos MV, Hernandez JM, Hernandez MT, et al: Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: updated time-to-events results and prognostic factors for time to progression. Haematologica 93:560-5, 2008

14. Oakervee HE, Popat R, Curry N, et al: PAD combination therapy (PS-341/bortezomib, doxorubicin and dexamethasone) for previously untreated patients with multiple myeloma. Br J Haematol 129:755-62, 2005

15. Popat R, Oakervee HE, Hallam S, et al: Bortezomib, doxorubicin and dexamethasone (PAD) front-line treatment of multiple myeloma: updated results after long-term follow-up. Br J Haematol 141:512-6, 2008

16. Attal M, Harousseau JL, Stoppa AM, et al: A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. N Engl J Med 335:91-7., 1996
17. Child JA, Morgan GJ, Davies FE, et al: High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 348:1875-83, 2003
18. Lenhoff S, Hjorth M, Holmberg E, et al: Impact on survival of high-dose therapy with autologous stem cell support in patients younger than 60 years with newly diagnosed multiple myeloma: a population-based study. Nordic Myeloma Study Group. Blood 95:7-11., 2000
19. Badros A, Barlogie B, Siegel E, et al: Results of autologous stem cell transplant in multiple myeloma patients with renal failure. Br J Haematol 114:822-9, 2001
20. Pineda-Roman M, Tricot G: High-dose therapy in patients with plasma cell dyscrasias and renal dysfunction. Contrib Nephrol 153:182-94, 2007
21. Bird JM, Fuge R, Sirohi B, et al: The clinical outcome and toxicity of high-dose chemotherapy and autologous stem cell transplantation in patients with myeloma or amyloid and severe renal impairment: a British Society of Blood and Marrow Transplantation study. Br J Haematol 134:385-90, 2006
22. Carlson K: Melphalan 200 mg/m2 with blood stem cell support as first-line myeloma therapy: impact of glomerular filtration rate on engraftment, transplantation-related toxicity and survival. Bone Marrow Transplant 35:985-90, 2005
23. Attal M, Harousseau JL, Leyvraz S, et al: Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood 108:3289-94, 2006
24. Spencer APH, Roberts A, et al.: Thalidomide improve survivals when use after ASCT Hematologica 92, 2007
25. Abdelkefi A, Ladeb S, Torjman L, et al: Single autologous stem-cell transplantation followed by maintenance therapy with thalidomide is superior to double autologous transplantation in multiple myeloma: results of a multicenter randomized clinical trial. Blood 111:1805-10, 2008
26. McCarthy PL, Owzar K, Stadtmauer EA, et al: Phase III Intergroup Study of Lenalidomide (CC-5013) Versus Placebo Maintenance Therapy Following Single Autologous Stem Cell Transplant for Multiple Myeloma (CALGB 100104): Initial Report of Patient Accrual and Adverse Events. ASH Annual Meeting Abstracts 114:3416-, 2009
27. Attal M, Harousseau JL, Marit G, et al: Lenalidomide After Autologous Transplantation for Myeloma: First Analysis of a Prospective, Randomized Study of the Intergroupe Francophone Du Myelome (IFM2005 02). ASH Annual Meeting Abstracts 114:529-, 2009
28. Ladetto M, Pagliano G, Ferrero S, et al: Major tumor shrinking and persistent molecular remissions after consolidation with bortezomib, thalidomide, and dexamethasone in patients with autografted myeloma. J Clin Oncol 28:2077-84, 2010
29. Pozzi C, D'Amico M, Fogazzi GB, et al: Light chain deposition disease with renal involvement: clinical characteristics and prognostic factors. Am J Kidney Dis 42:1154-63, 2003
30. Buxbaum J, Gallo G: Nonamyloidotic monoclonal immunoglobulin deposition disease. Light-chain, heavy-chain, and light- and heavy-chain deposition diseases. Hematol Oncol Clin North Am 13:1235-48, 1999
31. Buxbaum JN, Genega EM, Lazowski P, et al: Infiltrative nonamyloidotic monoclonal immunoglobulin light chain cardiomyopathy: an underappreciated manifestation of plasma cell dyscrasias. Cardiology 93:220-8, 2000
32. Croitoru AG, Hytiroglou P, Schwartz ME, et al: Liver transplantation for liver rupture due to light chain deposition disease: a case report. Semin Liver Dis 26:298-303, 2006
33. Popovic M, Tavcar R, Glavac D, et al: Light chain deposition disease restricted to the brain: The first case report. Hum Pathol 38:179-84, 2007
34. Toor AA, Ramdane BA, Joseph J, et al: Cardiac nonamyloidotic immunoglobulin deposition disease. Mod Pathol 19:233-7, 2006
35. Pozzi C, Locatelli F: Kidney and liver involvement in monoclonal light chain disorders. Semin Nephrol 22:319-30, 2002

36. Michopoulos S, Petraki K, Petraki C, et al: Light chain deposition disease of the liver without renal involvement in a patient with multiple myeloma related to liver failure and rapid fatal outcome. Dig Dis Sci 47:730-4, 2002

37. Terashima K, Takahashi K, Kojima M, et al: Kappa-type light chain crystal storage histiocytosis. Acta Pathol Jpn 28:111-38, 1978

38. Lin J, Markowitz GS, Valeri AM, et al: Renal monoclonal immunoglobulin deposition disease: the disease spectrum. J Am Soc Nephrol 12:1482-92, 2001

39. Dhodapkar MV, Merlini G, Solomon A: Biology and therapy of immunoglobulin deposition diseases. Hematol Oncol Clin North Am 11:89-110, 1997

40. Heilman RL, Velosa JA, Holley KE, et al: Long-term follow-up and response to chemotherapy in patients with light-chain deposition disease. Am J Kidney Dis 20:34-41, 1992

41. Firkin F, Hill PA, Dwyer K, et al: Reversal of dialysis-dependent renal failure in light-chain deposition disease by autologous peripheral blood stem cell transplantation. Am J Kidney Dis 44:551-5, 2004

42. Royer B, Arnulf B, Martinez F, et al: High dose chemotherapy in light chain or light and heavy chain deposition disease. Kidney Int 65:642-8, 2004

43. Sakakima M, Fujigaki Y, Tsuji T, et al: High dose chemotherapy and stem cell support in a patient of light- and heavy-chain deposition disease with abnormal marrow cell surface antigens and no monoclonal protein. Intern Med 44:970-4, 2005

44. Weichman K, Dember LM, Prokaeva T, et al: Clinical and molecular characteristics of patients with non-amyloid light chain deposition disorders, and outcome following treatment with high-dose melphalan and autologous stem cell transplantation. Bone Marrow Transplant 38:339-43, 2006

45. Salant DJ, Sanchorawala V, D'Agati VD: A case of atypical light chain deposition disease--diagnosis and treatment. Clin J Am Soc Nephrol 2:858-67, 2007

46. Lorenz EC, Gertz MA, Fervenza FC, et al: Long-term outcome of autologous stem cell transplantation in light chain deposition disease. Nephrol Dial Transplant, 2008

47. Hassoun H, Flombaum C, D'Agati VD, et al: High-dose melphalan and auto-SCT in patients with monoclonal Ig deposition disease. Bone Marrow Transplant 42:405-12, 2008

48. Kyle RA, Gertz MA: Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Semin Hematol 32:45-59, 1995

49. Skinner M, Anderson J, Simms R, et al: Treatment of 100 patients with primary amyloidosis: a randomized trial of melphalan, prednisone, and colchicine versus colchicine only. Am J Med 100:290-8, 1996

50. Kyle RA, Gertz MA, Greipp PR, et al: Long-term survival (10 years or more) in 30 patients with primary amyloidosis. Blood 93:1062-6, 1999

51. Kyle RA, Gertz MA, Greipp PR, et al: A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. N Engl J Med 336:1202-7, 1997

52. Gertz MA, Lacy MQ, Dispenzieri A: Myeloablative chemotherapy with stem cell rescue for the treatment of primary systemic amyloidosis: a status report. Bone Marrow Transplant 25:465-70, 2000

53. Kyle RA: High-dose therapy in multiple myeloma and primary amyloidosis: an overview. Semin Oncol 26:74-83, 1999

54. Comenzo RL, Vosburgh E, Falk RH, et al: Dose-intensive melphalan with blood stem-cell support for the treatment of AL (amyloid light-chain) amyloidosis: survival and responses in 25 patients. Blood 91:3662-70, 1998

55. Gertz MA, Lacy MQ, Gastineau DA, et al: Blood stem cell transplantation as therapy for primary systemic amyloidosis (AL). Bone Marrow Transplant 26:963-9, 2000

56. Moreau P, Leblond V, Bourquelot P, et al: Prognostic factors for survival and response after high-dose therapy and autologous stem cell transplantation in systemic AL amyloidosis: a report on 21 patients. Br J Haematol 101:766-9, 1998

57. Jaccard A, Moreau P, Leblond V, et al: High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. N Engl J Med 357:1083-93, 2007
58. Cohen AD, Zhou P, Chou J, et al: Risk-adapted autologous stem cell transplantation with adjuvant dexamethasone +/- thalidomide for systemic light-chain amyloidosis: results of a phase II trial. Br J Haematol 139:224-33, 2007
59. Landau H, Hassoun H, Cohen AD, et al: Adjuvant Bortezomib and Dexamethasone Following Risk-Adapted Melphalan and Stem Cell Transplant in Systemic Light-Chain Amyloidosis (AL): A Phase II Study. ASH Annual Meeting Abstracts 114:533-, 2009
60. Zonder JA, Sanchorawala V, Snyder RM, et al: Melphalan and Dexamethasone Plus Bortezomib Induces Hematologic and Organ Responses in AL-Amyloidosis with Tolerable Neurotoxicity. ASH Annual Meeting Abstracts 114:746-, 2009
61. Adams J, Palombella VJ, Sausville EA, et al: Proteasome inhibitors: a novel class of potent and effective antitumor agents. Cancer Res 59:2615-22, 1999
62. Teicher BA, Ara G, Herbst R, et al: The proteasome inhibitor PS-341 in cancer therapy. Clin Cancer Res 5:2638-45, 1999
63. Cusack JC, Jr., Liu R, Houston M, et al: Enhanced chemosensitivity to CPT-11 with proteasome inhibitor PS-341: implications for systemic nuclear factor-kappaB inhibition. Cancer Res 61:3535-40, 2001
64. LeBlanc R, Catley LP, Hideshima T, et al: Proteasome inhibitor PS-341 inhibits human myeloma cell growth in vivo and prolongs survival in a murine model. Cancer Res 62:4996-5000, 2002
65. McConkey DJ PC, Elliott P, Adam J, Papandreou C, Herrmann JL et al.: The proteasome as a new drug target in metastatic prostate cancer. 1999
66. Hideshima T, Richardson P, Chauhan D, et al: The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. Cancer Res 61:3071-6, 2001
67. Lightcap ES, McCormack TA, Pien CS, et al: Proteasome inhibition measurements: clinical application. Clin Chem 46:673-83, 2000
68. Jagannath S, Barlogie B, Berenson J, et al: A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. Br J Haematol 127:165-72, 2004
69. Richardson PG, Barlogie B, Berenson J, et al: A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 348:2609-17, 2003
70. Blade J, Samson D, Reece D, et al: Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol 102:1115-23, 1998
71. Richardson PG, Sonneveld P, Schuster MW, et al: Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 352:2487-98, 2005
72. Reece DE, Sanchorawala V, Hegenbart U, et al: Weekly and twice-weekly bortezomib in patients with systemic AL amyloidosis: results of a phase 1 dose-escalation study. Blood 114:1489-97, 2009
73. Comenzo RL, Hassoun H, Kewalramani T, et al: Results of a phase I/II trial adding carmustine (300 mg/m2) to melphalan (200 mg/m2) in multiple myeloma patients undergoing autologous stem cell transplantation. Leukemia 20:345-9, 2006
74. Kewalramani T, Zelenetz AD, Hedrick EE, et al: High-dose chemoradiotherapy and autologous stem cell transplantation for patients with primary refractory aggressive non-Hodgkin lymphoma: an intention-to-treat analysis. Blood 96:2399-404, 2000
75. Kewalramani T, Zelenetz AD, Teruya-Feldstein J, et al: Autologous transplantation for relapsed or primary refractory peripheral T-cell lymphoma. Br J Haematol 134:202-7, 2006
76. Comenzo RL, Reece D, Palladini G, Seldin D, Sanchorawala V, et al. Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis. Leukemia 26:2317-25, 2012

77. Gertz MA, Comenzo R, Falk RH, Fermand JP, Hazenberg BP, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL); a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. Am J Hematol 79:319-328, 2005

78. Palladini G, Dispenzieri A, Gertz MA, Kumar S, Wechalekar A, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: Impact on survival outcomes. J Clin Oncol, 2012 [Epub ahead of print]

20.0 APPENDICES

20.1 Neurotoxicity Assessment Tool

NEUROTOXICITY ASSESSMENT TOOL

Patient Name _____ Visit Date _____

Instructions for Patients[1,2]

By circling one (1) number per line, please indicate how true each statement has been for you **during the past 7 days.**

	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have numbness or tingling in my hands	0	1	2	3	4
I have numbness or tingling in my feet	0	1	2	3	4
I feel discomfort in my hands	0	1	2	3	4
I feel discomfort in my feet	0	1	2	3	4
I have joint pain or muscle cramps	0	1	2	3	4
I feel weak all over	0	1	2	3	4
I have trouble hearing	0	1	2	3	4
I get a ringing or buzzing in my ears	0	1	2	3	4
I have trouble buttoning buttons	0	1	2	3	4
I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
I have trouble walking	0	1	2	3	4

Instructions for Health Care Professionals

This assessment tool is provided to help you evaluate peripheral neuropathy in patients receiving chemotherapy. Health care professionals may find discussion of patient responses helpful in determining the grade of neuropathy as defined by the NCI Common Toxicity Criteria listed below; there is no direct correlation between assessment scores and toxicity grades.

NCI Common Toxicity Criteria for Peripheral Neuropathy and Neuropathic Pain[3]

Peripheral Sensory Neuropathy (NCI CTC Grade)

1 Normal
2 Loss of deep tendon reflexes or paresthesia but not interfering with function
3 Objective sensory loss or paresthesia, interfering with function, but not with ADLs (Activities of Daily Living)
4 Sensory loss or paresthesia interfering with ADLs
5 Permanent sensory loss that interferes with function

Neuropathic Pain (NCI CTC Grade)

0 None
1 Mild pain not interfering with function
2 Moderate pain: pain or analgesics interfering with function, but not ADLs
3 Severe pain: pain or analgesics severely interfering with ADLs
4 Disabling

References: 1. Cella DF, Tulsky DS, Gray G, Sarafian B, Lloyd S, Linn E, et al. The functional assessment of cancer therapy (FACT) scale: development and validation of the general measure. *J Clin Oncol* 1993;11(3):570-79. **2.** Calhoun EA, Fishman A, Roland PY, Lurain JR, Change C-H, Cella D. Validity and selective sensitivity of the FACT/GOG-Ntx. Abstract 1751. 36th Annual Meeting of the American Society of Clinical Oncology, May 2000, New Orleans, LA. **3.** National Cancer institute Cancer Therapy Evaluation Program Common Toxicity Criteria, Version 2.0, June 1999.

MILLENNIUM NV0085 8/03

20.2 New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

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

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

20.3 Body Surface Area and Creatinine Clearance Calculations

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

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

or

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

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

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

For females, use 85% of calculated CrCl value.

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

20.4 Common Terminology Criteria for Adverse Events

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

20.5 Bortezomib References

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

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

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

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

[v] Williams S, Pettaway C, Song R, Papandreou C, Logothetis C, McConkey DJ. Differential effects of the proteasome inhibitor bortezomib on apoptosis and angiogenesis in human prostate tumor xenografts. Mol Cancer Ther 2003;2(9):835-43.

[vi] Nawrocki ST, Bruns CJ, Harbison MT, Bold RJ, Gotsch BS, Abbruzzese JL, et al. Effects of the proteasome inhibitor PS-341 on apoptosis and angiogenesis in orthotopic human pancreatic tumor xenografts. Mol Cancer Ther 2002;1(14):1243-53.

[vii] Satou Y, Nosaka K, Koya Y, Yasunaga JI, Toyokuni S, Matsuoka M. Proteasome inhibitor, bortezomib, potently inhibits the growth of adult T-cell leukemia cells both in vivo and in vitro. Leukemia 2004;18:1357-63.

[viii] Boccadoro M, Morgan G, Cavenagh J. Preclinical evaluation of the proteasome inhibitor bortezomib in cancer therapy. Cancer Cell Int 2005;5:18.

[ix] Goel A, Dispenzieri A, Geyer SM, Greiner S, Peng KW, Russell SJ. Synergistic activity of the proteasome inhibitor PS-341 with non-myeloablative 153-Sm-EDTMP skeletally targeted radiotherapy in an orthotopic model of multiple myeloma. Blood 2006;107(10):4063-70.

[x] Mitsiades N, Mitsiades CS, Richardson PG, Poulaki V, Tai YT, Chauhan D, et al. The proteasome inhibitor PS-341 potentiates sensitivity of multiple myeloma cells to conventional chemotherapeutic agents: therapeutic applications. Blood 2003;101(6):2377-80.

[xi] Sayers TJ, Brooks AD, Koh CY, Ma W, Seki N, Raziuddin A, et al. The proteasome inhibitor PS-341 sensitizes neoplastic cells to TRAIL-mediated apoptosis by reducing levels of c-FLIP. Blood 2003;102(1):303-10.

[xii] Yu C, Rahmani M, Conrad D, Subler M, Dent P, Grant S. The proteasome inhibitor bortezomib interacts synergistically with histone deacetylase inhibitors to induce apoptosis in Bcr/Abl+ cells sensitive and resistant to STI571. Blood 2003;102(10):3765-74.

[xiii] O'Connor OA, Smith EA, Toner LE, Teruya-Feldstein J, Frankel S, Rolfe M, et al. The combination of the proteasome inhibitor bortezomib and the bcl-2 antisense molecule oblimersen sensitizes human B-cell lymphomas to cyclophosphamide. Clin Cancer Res. 2006;12(9):2902-11.

[xiv] David E, Sun SY, Waller EK, Chen J, Khuri FR, Lonial S. The combination of the farnesyl transferase inhibitor lonafarnib and the proteasome inhibitor bortezomib induces synergistic apoptosis in human myeloma cells that is associated with down-regulation of p-AKT. Blood 2005;106(13):4322-9.

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

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

[xv ii] Obeng EA, Carlson LM, Gutman DM, Harrington WJ Jr, Lee KP, Boise LH. Proteasome inhibitors induce a terminal unfolded protein response in multiple myeloma cells. Blood 2006;107(12):4907-16.

[xv iii] Ling YH, Liebes L, Ng B, Buckley M, Elliott PJ, Adams J, et al. PS-341, a novel proteasome inhibitor, induces Bcl-2 phosphorylation and cleavage in association with G2-M phase arrest and apoptosis. Mol Cancer Ther 2002;1(10):841-9.

[xix] Yang Y, Ikezoe T, Saito T, Kobayashi M, Koeffler HP, Taguchi H. Proteasome inhibitor PS-341 induces growth arrest and apoptosis of non-small cell lung cancer cells via the JNK/c-Jun/AP-1 signaling. Cancer Sci 2004;95(2):176-80.

[xx] Kaluz S, Kaluzova M, Stanbridge EJ. Proteasomal inhibition attenuates transcriptional activity of hypoxia-inducible factor 1 (HIF-1) via specific effect on the HIF-1alpha C-terminal activation domain. Mol Cell Biol 2006;26(15):5895-907.

[xxi] An WG, Hwang SG, Trepel JB, Blagosklonny MV. Protease inhibitor-induced apoptosis: accumulation of wt p53, p21WAF1/CIP1, and induction of apoptosis are independent markers of proteasome inhibition. Leukemia 2000;14(7):1276-83.

[xxii] Roccaro AM, Hideshima T, Raje N, Kumar S, Ishitsuka K, Yasui H, et al. Bortezomib mediates antiangiogenesis in multiple myeloma via direct and indirect effects on endothelial cells. Cancer Res 2006;66(1):184-91.

[xxiii] Mitsiades N, Mitsiades CS, Poulaki V, Chauhan D, Fanourakis G, Gu X, et al. Molecular sequelae of proteasome inhibition in human multiple myeloma cells. Proc Natl Acad Sci U S A 2002;99(22):14374-9.

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

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

[xxv i] Aghajanian C, Soignet S, Dizon DS, Pien CS, Adams J, Elliott PJ, et al. A Phase I Trial of the Novel Proteasome Inhibitor PS341 in Advanced Solid Tumor Malignancies. Clin Cancer Res 2002;8(8):2505-11.

xxvii Papandreou CN, Daliani DD, Nix D, Yang H, Madden T, Wang X, et al. Phase I trial of the proteasome inhibitor bortezomib in patients with advanced solid tumors with observations in androgen-independent prostate cancer. J Clin Oncol 2004;22(11):2108-21.

xxviii Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC, Castritis E, Bitsaktsis A, Pangalis GA. Treatment of relapsed or refractory Waldenström's macroglobulinemia with bortezomib. Haematologic. 2005;90(12):1655-8.

[xxix] Jagannath S, Barlogie B, Berenson J, Siegel D, Irwin D, Richardson PG, et al. A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. Br J Haematol 2004;127(2):165-72.

[xxx] Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, et al. A Phase 2 Study of Bortezomib in Relapsed, Refractory Myeloma. N Engl J Med 2003;348(26):2609-17.

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

[xxxii] Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma. N Engl J Med 2005;352(24):2487-98.

[xxxiii] Richardson P, Sonneveld P, Schuster M, Irwin D, Stadtmauer E, Facon T, et al. Bortezomib Continues Demonstrates Superior Efficacy Compared with High-Dose Dexamethasone in Relapsed Multiple Myeloma: Updated Results of the APEX Trail. Blood 2005;106(11):Abstract 2547.

[xxxiv] Fisher R, Bernstein S, Kahl B, Djulbegovic B, Robertson M, de Vos S, et al. Multicenter Phase II Study of Bortezomib in Patients With Relapsed or Refractory Mantle Cell Lymphoma. J Clin Oncol 2006;24(30):4867-74.

[xxxv] Goy A, Bernstein S, Kahl B, Djulbegovic B, Robertson M, Vos S, et al. Durable Responses with Bortezomib in Patients with Relapsed or Refractory mantle Cell Lymphoma: Updated Time-to-Event Analyses of the Multicenter PINNACLE Study. Blood 2007;110:Abstract 125.

[xxxv i] San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008;359(9):906-17.

[xxxv ii] San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008;359(9):906-17.

[xxxv iii] Mateos M-V, Richardson PG, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, et al. Bortezomib plus melphalan-prednisone continues to demonstrate a survival benefit vs melphalan-prednisone in the phase III VISTA trial in previously untreated multiple myeloma after 3 years' follow-up and extensive subsequent therapy use. Blood 2009;114:Abstract 3859.