Response Adapted Therapy with Bortezomib/Dexamethasone Followed by Addition of Lenalidomide in non Responders as Initial Treatment for Patients with Multiple Myeloma

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Primary Objective:

The primary objective of the study is to determine the overall response rate (defined as Partial Response (PR) after 4 cycles of response-adapted sequential therapy using bortezomib and dexamethasone, followed by the addition of lenalidomide in suboptimal responders.

Patient Population

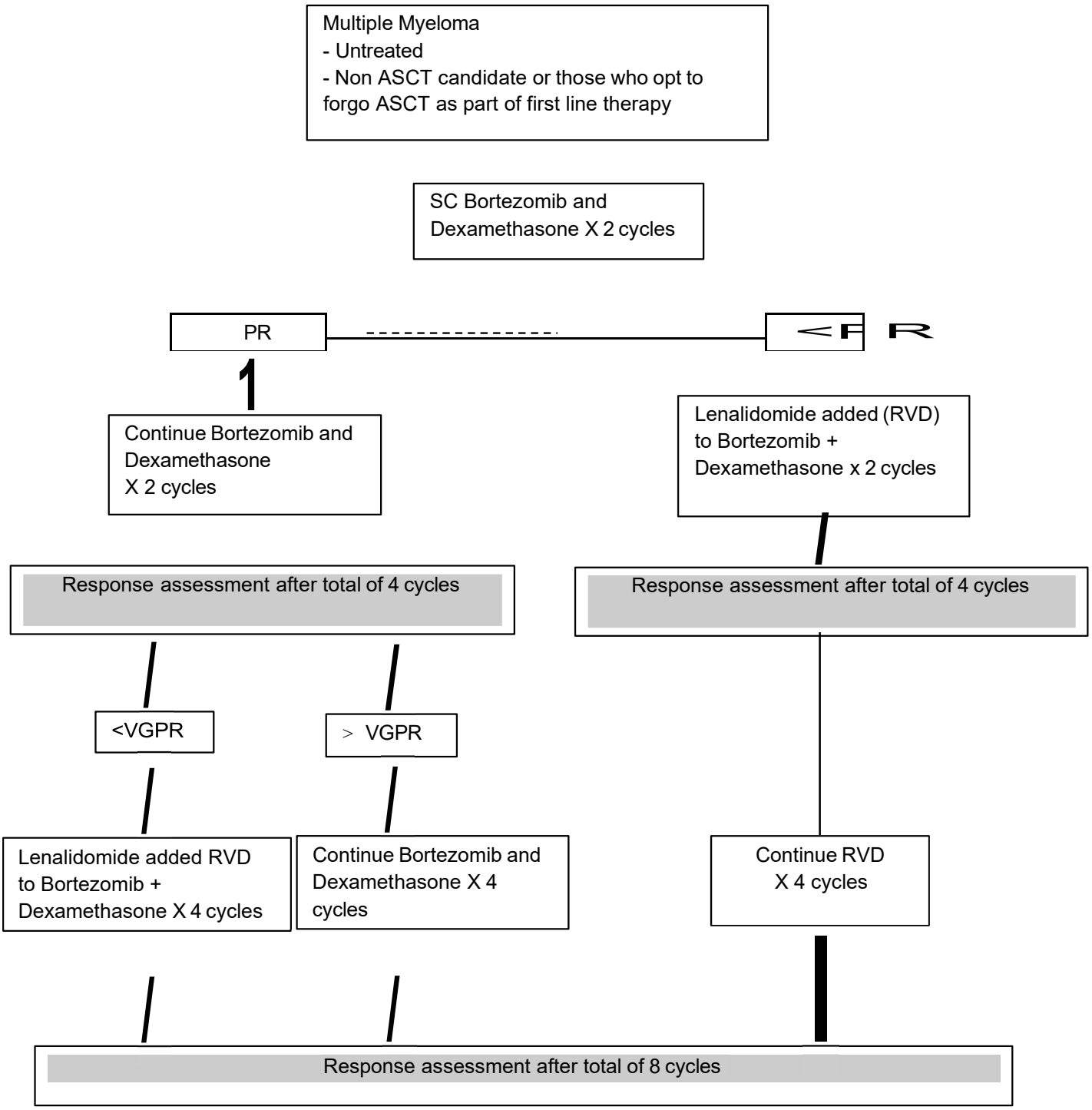
Patients diagnosed with *symptomatic* multiple myeloma based on the revised International Myeloma Working Group (IMWG) diagnostic criteria. The following criteria must be met at screening time prior to initiation of protocol therapy: 1) Monoclonal plasma cells in the bone marrow 10% and/or presence of a biopsy-proven bony or extramedullary plasmacytoma; 2) Any one or more of the following myeloma defining events: Clonal bone marrow plasma cell percentage 60%, Involved:Uninvolved serum free light chain ratio 100, >1 focal lesions on MRI studies (each focal lesion must be 5 mm or more in size), presence of organ damage related to the myeloma as defined by the CRAB criteria (hyperCalcemia, Renal failure, Anemia, Bone lesions); 3) Measurable monoclonal protein (M-protein) present in the serum and/or urine as per IMWG criteria. Non transplant candidates are eligible.

Study Design

This is a phase II, single center clinical trial designed to evaluate the response rate and toxicity of a response-adapted, sequential therapy, using bortezomib and dexamethasone, followed by the addition of lenalidomide in non-responders, in patients with untreated MM. According to the statistical plan detailed in section 14, a Simon's optimal two-stage design will be implemented where an overall response rate of 70% after four cycles of therapy is considered unpromising and a rate of 90% is considered promising. The maximum sample size for the trial is 28 patients.

Treatment Plan (See schema below)

SCHEMA



Note

- Lenalidomide may be added to the patient's regimen at any time if there is evidence of hematologic disease progression.
- Patients could proceed with stem cell collection after at least 4 cycles if adequate response (PR) has been achieved, at the discretion of the treating physician. These patients may resume treatment on study after stem cell collection for addition cycles (not to exceed a total of 8 cycles on study). All other patients will continue therapy on study up to 8 cycles.

- All patients including those who proceed to stem cell collection or are removed from treatment for reasons other than POD, will return for follow-up once every 2 months until progression of disease (POD).

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary objective:

- To determine the overall response rate (defined as.:::_ PR) after 4 cycles of response-adapted sequential therapy using bortezomib and dexamethasone (BD) followed by the addition of lenalidomide in suboptimal responders.

Secondary objectives:

- To determine the overall response rate for the entire population after up to 8 cycles of response-adapted sequential therapy
- To determine the CR, VGPR, PR after 4 cycles and after 8 cycles (for those completing 8 cycles) of response adapted sequential therapy
- To determine the toxicity of response-adapted sequential therapy
- To measure quality of life (QOL) using this response adapted sequential therapy
- To determine the PFS of patients after response adapted sequential therapy

Correlatives:

- Aim 1: Characterization of genomic mutations of targetable genes
- Aim 2: Characterization of immunomodulatory checkpoint pathways in multiple myeloma

3.0 BACKGROUND AND RATIONALE

3.1 Overview on First Line Treatment of Multiple Myeloma

Multiple myeloma (MM) is a malignant plasma cell disorder that accounted for an estimated 20,180 (1.32%) new cancer cases in the United States (US) in 2010, as well as approximately 10,650 deaths[1]. Although multiple myeloma is uniformly fatal, treatment has dramatically improved over the last several decades with the introduction of cytotoxic drugs, high-dose therapy and autologous transplant, and the development of novel agents.

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 MM presenting with myeloma-related organ damage (a condition referred to as *symptomatic* myeloma as opposed to *asymptomatic* myeloma). Organ damage includes hypercalcemia, renal failure, anemia, and bone disease (CRAB).

Standard first line treatment for patients with symptomatic MM deemed eligible for transplantation consists of 2 phases of treatment: The first is referred to as the *induction* therapy and consists of various combinations of therapeutic agents. The second consists of high dose melphalan followed by autologous stem cell transplantation (HDM/ASCT)[4-6]. For patients who are considered ineligible for HDM/ASCT because of

advanced age or co-morbidities, the treatment has included an induction treatment followed by a maintenance regimen, often consisting of the same drugs used during induction but administered at lower doses and slightly modified schedule, for a variable period of time[7-17].

3.1.1 Induction therapy

MM is sensitive to a number of cytotoxic drugs such as alkylating agents, anthracyclines, and corticosteroids for initial treatment. Melphalan plus prednisone (MP) has been the standard chemotherapy regimen. Other older chemotherapy regimens still recommended in the NCCN guidelines include single-agent dexamethasone[3]; VAD (vincristine-adriamycin-dexamethasone); and DVd (liposomal doxorubicin, vincristine, and dexamethasone). The last several years, however, have witnessed the introduction of several newer agents such as bortezomib, thalidomide, and lenalidomide that have been effective in the treatment of multiple myeloma, as demonstrated by improved response rates and, in the case of bortezomib, improved 5-year survival[17]. Combination chemotherapy regimens with these newer agents currently recommended in the NCCN guidelines include: VMP (bortezomib, melphalan, prednisone)[7,17]; MPT (melphalan, prednisone, thalidomide)[8,18]; Thal-Dex (thalidomide-dexamethasone)[19-22]; RevDex (lenalidomide/low-dose dexamethasone[23]; V-Dex (bortezomib-dexamethasone)[24,25]; and bortezomib, dexamethasone, and either lenalidomide[26] or thalidomide[27]. Despite the marked increase in the number of therapeutic options, the disease remains incurable and there remains a need for new and better agents as well as a better understanding of when and how to combine effective or novel agents.

3.1.2 Autologous Stem Cell Transplantation

There have been several large prospective trials in France (IFM 90)[4,28-30] and in UK (MRC 9)[5], and one large retrospective study of myeloma patients in Nordic countries[31], showing a survival benefit for HDM/ASCT compared to conventional chemotherapy. In the larger study, IFM 90, newly diagnosed untreated patients less than 65 years of age with OS stage II or III MM were randomized to either SCT after up to 6 cycles of VMCP alternating with BVAP or conventional chemotherapy with 18 cycles of VMCP alternating with BVAP. Recombinant interferon alpha (IFNa) 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 studies have confirmed these results. 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 patients eligible for the procedure. Smaller studies have reached similar conclusions.

Although HDM/ASCT has improved response rate and in some trials overall survival rate in patients with MM, all patients eventually relapse and the disease remains incurable and relapse occurs in almost all patients, with a median survival period of 5 to 7 years. Although ASCT remains a cornerstone of therapy following induction chemotherapy in transplant eligible patients, the high response rates reported with novel agents in transplant eligible and ineligible patients has raised the question of the utility of early ASCT in newly diagnosed multiple myeloma (NDMM) and there currently is an interest in clinical trials that delay ASCT until disease progression.

3.2 Rationale for the Concept of the Current Clinical Trial

The aggressive approach to first line treatment of MM, which has lead to the incorporation of ASCT, has also been adopted during the induction phase of the treatment. Investigators have strived to develop

successive combination regimens aiming at achieving ever higher response rates. While the combination of dexamethasone, doxorubicin, and vincristine (VAD) was standard induction for a long time, achieving 75% ORR and 10% >VGPR, several new induction regimens have included novel drugs (proteasome inhibitors and immunomodulators). These combinations have proven more effective, achieving higher ORR than their predecessors. They consisted initially of doublets like thalidomide/dexamethasone[22,32], lenalidomide/dexamethasone[23,33], and bortezomib/dexamethasone[34,35], but were expanded to include triplet and quadruplet drug regimens. Several phase III trials[8,9,36-40] of thalidomide plus melphalan and prednisone (MPT) versus melphalan and prednisone (MP) showed increased ORR with MPT in patients ineligible for ASCT, with OS benefit shown in some trials. Likewise, the phase III VISTA trial demonstrated superior efficacy with bortezomib plus melphalan and prednisone (VMP) versus MP in previously untreated patients ineligible for ASCT[15-17]. Cavo et al, in a randomized study for ASCT eligible patients showed the combination of dexamethasone, bortezomib and thalidomide (VTD) to achieve still greater results with 93% ORR and 60% >VGPR[41]A[2]. Recently, Richardson et al demonstrated that the combination of lenalidomide, bortezomib and dexamethasone (RVD) administered to 66 transplant and non-transplant patients resulted in 49 patients achieving at least a PR after 4 cycles of treatment (6% CR/nCR; 5% VGPR, and 64% PR). Improvement in response by at least one response category was noted in 75% of the 56 patients that continued on therapy from cycle 4 through cycle 8, with further improvement in response noted in 20 of 37 patients who continued beyond cycle 8 with maintenance therapy resulting in 100% ORR and 74% >VGPR[26]A[3]. Hence, it has become fairly common practice for patients to receive more aggressive induction regimens whether eligible for ASCT or not.

However, this aggressive approach to therapy, whether pertaining to ASCT or to induction, is not without controversy. Regarding ASCT, Fermand et. al demonstrated that the OS of patients receiving ASCT as first-line therapy is identical to OS of those who receive it at relapse, suggesting that the perceived benefit to the ASCT arm over the conventional therapy arm in the randomized phase III trial mentioned above, may well be ascribed to the availability of an additional treatment modality rather than to the aggressive upfront approach combining induction to ASCT[44]. Further supporting this concept, a meta-analysis by Koreth comparing ASCT to conventional chemotherapy showed advantage in PFS but not OS[45]. This data indicates that although more aggressive therapy in the form of ASCT may lead to improved ORR and PFS, it may not necessarily translate into improved OS. In this context, an international trial is currently evaluating the need for ASCT upfront in the era of novel agents, comparing RVD with and without upfront ASCT.

Likewise, regarding the induction phase, and although the improved ORR of multiple drug regimens has been ascertained, it is not universally accepted that this improved ORR translates into improved long term outcome, i.e. OS. This uncertainty becomes even more important when one considers the toxicity profile associated with multi-drug regimens that expose patients simultaneously to several drugs with distinct and sometimes additive side effects.

Whether patients should be exposed to doublet, triplet, or quadruplet combinations during induction remains one of the major unanswered questions haunting physicians treating MM patients, whether transplant candidates or not. While improved ORR associated with simultaneous exposure to multiple drugs has been established, it is conceivable that such a benefit could be retained while toxicity profile improved by a response adapted sequential introduction of drugs.

In the proposed trial we would like to test the efficacy and the toxicity of such a sequential response adapted approach, starting therapy with subcutaneous Bortezomib and dexamethasone, adding Revlimid based on the response to Bortezomib/Dexamethasone.

3.3 Rationale for the Drugs and doses chosen in the Current Clinical Trial

Several clinical studies have established the effectiveness of bortezomib, the first proteasome inhibitor, and lenalidomide in the treatment of new diagnosed multiple myeloma. Since these agents have differing mechanisms of action, clinical trials of 2- and 3-drug regimens incorporating proteasome inhibition (bortezomib), IMiD (lenalidomide), and dexamethasone have been conducted in NDMM. These combinations have been shown to be effective with phase 3 combination trials ongoing.

3.3.1 Clinical Experience with Lenalidomide and Dexamethasone in NDMM

Lenalidomide is a thalidomide analogue that has significant clinical activity in multiple myeloma. Lenalidomide in combination with dexamethasone is approved by the FDA for the treatment of multiple myeloma patients who have received at least 1 prior therapy. Based on the activity of this combination in the relapse/refractory setting, clinical trials have been completed in patients with NDMM. The Eastern Cooperative Oncology Group (ECOG) conducted a randomized phase 3, multicenter, open-label study (E4A03) in 445 patients with NDMM[23]. The primary outcome of the trial was to determine whether low-dose dexamethasone (40 mg on Days 1, 8, 15, and 22 of a 28-day cycle) plus lenalidomide (Ld) was noninferior to high-dose dexamethasone (40 mg on Days 1 through 4, 9 through 12, and 17 through 20 of a 28-day cycle) plus lenalidomide (LO). After 4 cycles of therapy, patients could either discontinue the planned protocol therapy to undergo a stem-cell transplant or continue on protocol therapy until disease progression. Results showed that Ld is associated with better overall survival and a lower toxicity profile compared to LO. At the 1-year, second interim analysis, overall survival was 96% (95% CI 94-99) in the Ld group compared with 87% (82-92) in the LD group (p = 0.0002) and toxicity was higher in the high dose group. Consequently, the trial was stopped and patients on high-dose therapy were crossed over to low-dose therapy.

The Southwest Oncology Group (SWOG) conducted a randomized, phase 3, double-blind, crossover, placebo-controlled, multicenter study in patients with NDMM[33]. The primary endpoint was to compare the progression-free survival (PFS) of patients treated with dexamethasone plus lenalidomide or placebo. The target accrual was 500 patients; however the study closed early with an accrual of 198 after results of the ECOG trial E4A03 reported improved survival using Ld versus LO. The estimated 1-year PFS was 77% in the 100 patients treated with lenalidomide-dexamethasone and 55% in the 98 with dexamethasone plus placebo; however, 1-year overall survival was similar in both groups (93% vs 91%). The response rate was 85.3% (22.1% CR) versus 51.3% (3.8% CR) in the groups respectively.

3.3.2 Clinical experience with bortezomib

It is estimated that as of June 2011, more than 300,000 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[46]. The toxicity was greatest during the 3rd and 4th 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 Lymphoma (NHL), MM, Waldenstrom's Macroglobulinemia, squamous cell carcinoma of the nasopharynx, bronchoalveolar carcinoma of the lung, renal cell carcinoma, and prostate cancer4[6,49].

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)[50] and M34100-025 (subjects with second or greater relapse and refractory to their last prior therapy)[51]. 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 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)[25], 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 in abstract form in 2005 for

M34101-039. 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[52]. 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 was reported in abstract form in 2007 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[53]. 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/m2 and prednisone 60 mg/m2 on Days 1 to 4, alone or in combination with bortezomib1.3 mg/m2 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[17], 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)[17]. In an abstract updated analysis of overall survival based on 387 deaths (median follow-up 60.1 months) performed in 2011, the median overall survival for VMP was 56.4 months and the MP was 43.1 months, with a hazard ration of 0.695 (95% CI: 0.57, 0.85).

SUBCUTANEOUS ADMINISTRATION

A randomized Phase 1 pilot study in 24 subjects with multiple myeloma demonstrated that both the IV and SC routes of bortezomib administration have similar systemic drug exposure and proteasome inhibition. Importantly, SC and IV administration of bortezomib appeared to result in similar efficacy profiles (ie, response rate) and similar safety profiles. The pilot study also provided preliminary evidence of good local tolerance for SC injection of bortezomib, when administered at 1 mg/ml concentration[54].

The data from the Phase 1 pilot study formed the basis of the design of a randomized, Phase 3 study that compared the efficacy and safety of subcutaneous versus intravenous bortezomib at the approved 1.3 mg/m^2 dose and twice per week schedule in patients with relapsed multiple myeloma[55]. 222 patients were randomly assigned in a 2:1 ratio to receive either subcutaneous (n=148) or intravenous (n=74) bortezomib. The response-evaluable population consisted of 145 patients in the subcutaneous group and 73 in the intravenous group. Patients received a median of eight cycles (range one to ten) in both groups.

The ORR (CR+PR) after 4 cycles of treatment, assessed by computer algorithm implementation of EBMT response criteria, was 42 % in both the SC and IV treatment groups for the response-evaluable population. The ORR after 4 cycles in the IV arm was consistent with what was observed in historical single-agent bortezomib trials with relapsed multiple myeloma subjects. The stratified Mantel Haenszel estimate of the relative risk of achieving response for SC treatment group versus IV treatment group was 0.99 with 95% CI (0.71, 1.37). The 95% CI for ORR_SC - 0.6 ORR_IV was (6.1, 27.1), which excludes 0. Thus the study met the noninferiority objective (p-value for the noninferiority hypothesis was 0.00201). Results in the ITT population were similar; noninferiority of SC versus IV was also demonstrated.

The CR rate after 4 cycles of treatment was 6% in the SC treatment group and 8% in the IV treatment group; the nCR rate after 4 cycles of treatment was 6% in the SC treatment group and 5% in the IV treatment group; the VGPR rate after 4 cycles of treatment was 4% in the SC treatment group and 3% in the IV treatment group. Therefore, 17% subjects in the SC treatment group and 16% subjects in the IV treatment group had obtained at least VGPR after the first 4 cycles.

The ORR (CR+PR) after 8 cycles of treatment was 52% in both the SC and IV treatment groups for the response-evaluable population. The stratified Mantel-Haenszel estimate of the common relative risk of achieving response for SC versus IV was 1.00 with 95% CI (0.77, 1.31). Twenty-five percent of subjects in the SC treatment group and 25% of subjects in the IV treatment group had obtained at least VGPR during the first 8 cycles.

The median TTP (Kaplan-Meier estimate) was 10.4 months in the SC treatment group and 9.4 months in the IV treatment group. The hazard ratio was 0.839 with 95% CI (0.564, 1.249), and the p=0.3866 (stratified log-rank test), indicating similar results between the SC and IV arm.

The median PFS (Kaplan-Meier estimate) was 10.2 months in the SC treatment group and 8.0 months in the IV treatment group. The hazard ratio was 0.824 with 95% CI (0.574, 1.183), and the p=0.2945 (stratified log-rank test), indicating comparable results between the SC and IV arm.

After a median follow-up of 11.8 months, the 1-year survival rate was 72.6% in the SC arm and 76.7% in the IV arm. The p-value for the difference in 1-year survival rate was 0.5037, indicating similar results between the SC and IV arm.

The median time to first response (Kaplan-Meier estimate) was 3.5 months for both the SC and IV treatment groups. The hazard ratio was 1.059 with 95% CI (0.716, 1.567), and the p=0.7725 (stratified log-rank test), indicating similar results between the SC and IV arm. Among the responders, the median time to first response was 1.4 months (44 days) in the SC arm and 1.4 months (43 days) in the IV arm. Among the responders, the median duration of response (Kaplan-Meier estimate) was 9.7 months in the SC treatment group, compared with 8.7 months in the IV treatment group.

Overall, similar efficacy results were observed in the SC and IV treatment groups, and the study demonstrated that bortezomib SC administration is not inferior to bortezomib IV administration[55].

The value of the addition of dexamethasone to the bortezomib therapeutic regimen was assessed in patients who participated in phase 2 studies M34100-025 (SUMMIT)[56] and M34100-024 (CREST)[57]. Patients with PD after the first 2 cycles or stable disease (SD) after 4 cycles of bortezomib monotherapy were permitted to add dexamethasone 20 mg PO on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day treatment cycle. Additional responses were observed in 28 of 100 patients. The toxicities reported during combination therapy were manageable, and their incidence was not increased compared with single-agent bortezomib therapy. Similarly, patients administered bortezomib SC or IV in Study 26866138-MMY-3021 were permitted to receive dexamethasone after completion of 4 cycles of treatment if they had no response and had not progressed. Eighty-two (68%) SC-treated patients and 39 (32%) IV-treated patients received dexamethasone starting in Cycle 5. The addition of dexamethasone improved response in both groups: of patients with no response at the end of Cycle 4, 30% in both SC- and IV-treated groups obtained a partial response later; patients with a PR at the end of Cycle 4 improved to CR later in 13% of patients in both the SC- and IV-treated groups.

3.3.3 Clinical Experience with Bortezomib Plus Lenalidomide and Dexamethasone

Evidence to support combining bortezomib with immunomodulatory analogues, includes preclinical data demonstrating synergistic effects on apoptosis, clinical efficacy seen with the combination of bortezomib, lenalidomide, and dexamethasone in relapsed/ refractory disease, and the clinical activity of these agents in NDMM patients. Richardson and colleagues conducted a phase 1/2 study combining lenalidomide, bortezomib, and dexamethasone in NDMM patients[26]. The primary end points were to determine the MTD of this combination (phase 1) and to evaluate response rate (> PR) to the combination (phase 2). Response assessments were done after 4 and 8 cycles of therapy. Patients received lenalidomide on Days 1 through 14, bortezomib on Days 1, 4, 8, and 11, and dexamethasone on Days 1, 2, 4, 5, 8, 9, 11, and 12, for eight 21-day cycles. Patients with a CR or nCR/PR after Cycle 4 could proceed at any point to stem cell mobilization and transplantation. Patients with stable or responding disease without unacceptable toxicity at the completion of Cycle 8, were allowed to continue onto the maintenance phase of the study which comprised of 3-week cycles of bortezomib on Days 1 and 8, lenalidomide on Days 1 through 14 at the doses tolerated at the completion of cycle 8, and dexamethasone 10 mg the day before and after bortezomib (Days 1, 2, 8, and 9). In the phase 1 portion of the study, the combination of lenalidomide 25mg, bortezomib1.3 mg/m2, with reduced dexamethasone (20/10 mg), was determined to be the MTD of the combination and the RP2D. Overall 66 patients were enrolled to this study (Phase 1 n=31; Phase 2 n=35). Results indicated that the combination of

lenalidomide, bortezomib, and dexamethasone was highly active in patients with NDMM, with all patients (100%) achieving at least a pre-ASCT response of PR and high rates of VGPR or better (CR + nCR + VGPR). In both the phase 2 population and overall, 74% and 67% respectively achieved a VGPR or better. Overall, 49 patients achieved at least a PR after 4 cycles of treatment (6% CR/nCR; 5% VGPR, and 64% PR). Improvement in response by at least one response category was noted in 75% of the 56 patients that continued on therapy from cycle 4 through cycle 8, with further improvement in response noted in 20 of 37 patients who continued beyond cycle 8 with maintenance therapy. With a median follow-up of 21 months, neither the median DOR nor median OS has been reached. The authors concluded the bortezomib, lenalidomide and dexamethasone (VRD) combination was a highly effective regimen for patients with NDMM.

In the proposed trial, we will be using this latter phase II trial as benchmark for comparison and hypothesize that the sequential, response adapted approach proposed in this trial will lead to comparable response rates after 4 and also after 8 cycles with lesser exposure to drugs and associated side effects.

3.4 Rationale for the Concept of the Correlatives for this Clinical Trial

As the development of molecularly targeted and immune based therapies continues, incorporating knowledge of mutational and immune checkpoint "status" into clinical practice will enable rapid identification of patients eligible for clinical trials with genetically- and immunophenotypically-defined entry criteria.

Aim 1: Characterization of genomic mutations of targetable genes: In recent years candidate gene and genome-wide studies have identified somatic genetic alterations that may contribute to hematopoietic transformation in a wide spectrum of hematopoietic malignancies. Moreover, in many cases these newly discovered lesions have therapeutic and/or prognostic significance, such as the identification of BRAF V600E mutations in a subset of myeloma, which may be potentially amenable to therapy with available drugs. Although a small set of genetic alterations, most commonly gene mutations or chromosomal translocations, have found tangible applications in the clinical arena, the clinical significance of many recently identified genetic alterations are not well understood. Indeed, for the majority of genetic alterations in MM, there are few retrospective or prospective studies available to allow clinicians and researchers to determine if these mutations have clinical value. Thus, additional studies, which cast a broad net across pharmacologically targetable genes, may be a more pragmatic and fruitful means to realize the potential of personalized molecularly targeted therapies for individual patients with MM. The first goal of the correlative studies being proposed is to pursue such an approach using next generation sequencing of known targetable genes. Using serially obtained samples in the context of a response adjusted Vd followed by VRd treatment program we will Characterize and correlate mutational frequency with treatment outcome using Nimblgen capture followed by next-generation sequencing of all exons of a set of 600 genes known to be important to the pathogenesis of hematopoietic malignancies.

Aim 2: Characterization of immunomodulatory checkpoint pathways in multiple myeloma: In the past decade, immune checkpoint blockade has emerged as a promising means to achieve durable disease control through enhanced anti-tumor immunity. Ipilimumab, which blocks the function of CTLA-4, was the first drug in this class to gain FDA approval for the treatment of melanoma based on a doubling of overall survival reported in a phase III study in 2010. In the past several years, promising results with PD-1 pathway blockade and combined CTLA-4/PD-1 blockade have further demonstrated the therapeutic potential of targeting immune regulatory receptors. To date, therapeutics targeting 8 distinct pathways are in various stages of clinical development and offer the possibility to fine tune adaptive immunity to effectively eradicate malignancies.

In MM, the PD-1 checkpoint pathway is felt to play a role in pathogenesis based on an observed greater expression of the PD-1 ligand (PD-L1) on malignant plasma cells than normal plasma cell counterparts. However, data on the role of other checkpoint blockade molecules in the natural history of multiple myeloma is lacking. Furthermore, little is known about the sensitivity of MM to therapeutic manipulation of checkpoint pathways. Thus, the goal of this specific aim is to develop an understanding of the natural history of MM relative to immunomodulatory checkpoint receptor expression status.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a phase II, single center clinical trial designed to evaluate the response rate and toxicity of a response-adapted, sequential therapy, using bortezomib, dexamethasone, and lenalidomide, in patients with untreated MM. The patients will be started on bortezomib and dexamethasone (BO) for 2 cycles. The response will be evaluated at the end of every cycle. Lenalidomide will be added (RVD) to the subsequent cycles if PR has not been achieved after 2 cycles of BO or if VGPR has not been achieved after 4 cycles of BO. Lenalidomide may be added to the patient's regimen at any time if there is evidence of hematologic disease progression. Patients could proceed with stem cell collection after at least 4 cycles if adequate response (PR) has been achieved, at the discretion of the treating physician. These patients may resume treatment on study after stem cell collection at the discretion of the treating physician (not to exceed a total of 8 cycles on study). All patients will continue therapy on study up to 8 cycles. All patients, whether completing the 8-cycles, or are removed from treatment for reasons other than POD, will return for follow-up once every 2 months until progression of disease (POD).

According to the statistical plan detailed in section 14, a Simon's optimal two-stage design will be implemented where an overall response rate of 70% after four cycles is considered unpromising and a rate of 90% is considered promising. The maximum sample size for the trial is 28 patients.

4.2 Intervention

<u>Initial 2 cycles with bortezomib and dexamethasone (BO)</u>

- Length of cycle: 35 days
- These cycles will consist of:
  - Bortezomib SC (or IV if SC not tolerated) 1.5 mg/m2 on days 1, 8, 15, and 22
  - Dexamethasone PO or IV 40mg on days 1, 8, 15, and 22 or on a split-dose regimen (20mg BIW).
- The following prophylactic medications are recommended: acyclovir 400mg BID; sulfamethoxazole and trimethoprim OS, TIW; fluconazole 100 mg daily; and omeprazole 20 mg daily. Alternative prophylactic medications are allowed if sensitivity to the drugs occurs.
- Bisphosphonates are recommended as clinically indicated.
- Erythropoietin is allowed

<u>Treatment cycles beyond cycle 2 may include the addition of lenalidomide (RVD)</u>

Lenalidomide may be added based on the response to prior cycles (if less than PR after 2 cycles of BO or if less than VGPR after 4 cycles or as described in the design above and below.) If lenalidomide is not added,

the treatment schedule used during the initial 2 cycles will be unchanged. If lenalidomide is added, the following schedule will apply:

- Length of cycle: 28 days
- The cycles including Revlimid will consist of:
- Bortezomib SC (or IV if SC not tolerated) 1.3 mg/m2 on days 1, 8, and 15
- Dexamethasone 40 mg PO or IV on days 1, 8, and 15 or on a split-dose regimen (20mg BIW).
- Lenalidomide 15 mg PO (or dose adjusted to renal function as per guidelines) daily on days 1-21. If well tolerated, the dose of lenalidomide could be escalated with subsequent cycles incrementally by 5 mg, not to exceed 25 mg, days 1-21,
- The following prophylactic medications are recommended: acyclovir 400mg BID; sulfamethoxazole and trimethoprim OS, TIW; fluconazole 100 mg daily; omeprazole 20 mg daily; and aspirin 325 mg or aspirin 81mg or prophylactic doses of Low Molecular Weight Heparin (LMWH). Alternative prophylactic medications are allowed if sensitivity to the drugs occurs.
- Bisphosphonates are recommended as clinically indicated.
  Erythropoietin is not recommended because of the risk of thrombosis.
  Lenalidomide may be added to the patient's regimen at any time if there is evidence of hematologic disease progression. Patients could proceed with stem cell collection after at least 4 cycles if adequate response(PR) has been achieved, at the discretion of the treating physician. These patients may resume treatment on study after stem cell collection for additional cycles (not to exceed a total of 8 cycles on study). All patients will continue therapy on study up to 8 cycles. All patients, whether completing the 8-cycles, or are removed from treatment for reasons other than POD, will return for follow-up once every 2 months until progression of disease (POD).

- Beyond 8 cycles, the treatment will be left to the discretion of the treating physician. The following maintenance treatment is recommended: Lenalidomide maintenance (21 days out of 28 day-cycle) at the last tolerated dose for patients who received lenalidomide during the first 8 cycles, and bortezomib on a maintenance schedule (every other week or 4 weeks ON followed by 4 weeks OFF) if lenalidomide was not added during the first 8 cycles.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Bortezomib

5.1.1 Scientific Background

Bortezomib for Injection is a small-molecule proteasome inhibitor developed by Millennium Pharmaceuticals, Inc., (Millennium) as a novel agent to treat human malignancies. Bortezomib is currently approved by the United States Food and Drug Administration (US FDA) 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), bortezomib 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[1-9]. 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.[20-32] Notably, bortezomib induces apoptosis in cells that over express bcl-2, a genetic trait that confers unregulated growth and resistance to conventional chemotherapeutics.[33]

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-a, tumor suppressor protein p53, angiogenesis factors, and many others. Bortezomib is thought to be efficacious in multiple myeloma via its inhibition of nuclear factor KB (NF-KB) activation, its attenuation of interleukin-6 (IL-6)-mediated cell growth, a direct apoptotic effect, and possibly anti-angiogenic and other effects.[34-41]

5.1.2 Preparation, Handling, Storage, and Destruction of Drugs

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

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

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.

For commercially-labeled bortezomib for IND-exempt studies, please contact your Millennium Clinical Operations representative to arrange for return of study drug. Any unused or expired BORTEZOMIB must be returned to Millennium. Be sure to document drug return on your drug accountability logs.

5.1.3 Bortezomib 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.

There must be at least 3 days between each dose of bortezomib.

5.1.4 Subcutaneous Administration

INTRAVENOUS AND SUBCUTANEOUS ROUTE OF ADMINISTRATION HAVE DIFFERENT RECONSTITUTED CONCENTRATIONS. CAUTION SHOULD BE USED WHEN CALCULATING THE VOLUME TO BE ADMINISTERED.

Drug is available in sterile, single use vials containing 3.5 mg of bortezomib. Each vial of bortezomib for Injection should be reconstituted under a laminar flow biological cabinet (hood) within eight hours before dosing with 1.4 ml of normal (0.9%) saline, Sodium Chloride Injection USP, so that the reconstituted solution contains bortezomib at a concentration of 2.5 mg/ml for subcutaneous administration.

Subcutaneous Administration Precautions:

- The drug quantity contained in one vial (3.5 mg) may exceed the usual dose required. Caution should be used in calculating the dose to prevent overdose.
- When administered subcutaneously, sites for each injection (thigh or abdomen) should be rotated.
- New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, erythematous, or indurated.
- If local injection site reactions occur following bortezomib administration subcutaneously, the IV route of administration should be considered.
- In clinical trials of bortezomib IV, local skin irritation was reported in 5% of patients, but extravasation of bortezomib was not associated with tissue damage. In a clinical trial of subcutaneous bortezomib, a local reaction was reported in 6% of patients as an adverse event, mostly redness.

5.1.5 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.

5.1.6 Treatment Compliance

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

Drug accountability for lenalidomide and dexamethasone (if taken PO) will be assessed with the use of a pill diary for each cycle of treatment.

5.1.7 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 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.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error situation should immediately contact MedComm Solutions (see below) and report the event.

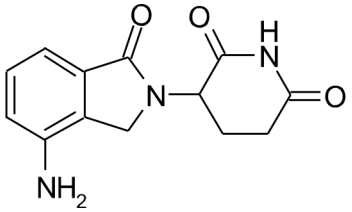
For Product Complaints or Medication Errors, call MedComm Solutions at 1-510-740-1273 (international number) 1-866-835-2233 (for US sites)

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, an SAE form should be completed and sent to PPD (refer to Section 17.2.1).

5.2 Lenalidomide

5.2.1 Preparation, Handling, Storage, and Destruction of Drugs

Lenalidomide (L) (REVLIMID®, CC-5013), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2H-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:



3-(4-amino-1-oxo 1,3-dihydro-2H-isoindol-2-yl) piperidine-2,6-dione

The empirical formula for lenalidomide is C13H13N3O3, and the gram molecular weight is 259.3. Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

Lenalidomide is available in 5 mg, 10 mg, 15 mg and 25 mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

5.2.2 Lenalidomide Administration

Lenalidomide is an analogue of thalidomide, a known human teratogen that causes severe life-threatening human birth defects. Because of this toxicity, and to limit potential fetal exposure to lenalidomide, patients must follow the birth control guidelines outlined in Appendix E. All women of childbearing potential must follow the protocol-dictated timelines for pregnancy testing.

Lenalidomide is administered orally. It may be taken with or without food at approximately the same time each day.

5.2.3 Prescribing Information

Prescriptions must be filled within 14 days, unless the patient is a female of childbearing potential, in which case the prescription must be filled within 7 days. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

Accurate records will be kept of all study drug administration, including dispensing and dosing, in the source documents.

5.2.4 Packaging

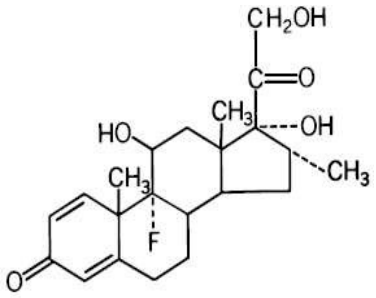
Lenalidomide will be shipped directly to patients. Bottles will contain a sufficient number of capsules for one cycle of dosing.

5.3 Dexamethasone

5.3.1 Preparation, Handling, Storage

Dexamethasone is a synthetic adrenocortical steroid. Corticosteroids are naturally-occurring chemicals produced by the adrenal glands located above the kidneys. Corticosteroids affect the function of many cells within the body and suppress the immune system. Corticosteroids also block inflammation and are used in a wide variety of inflammatory diseases affecting many organs.

The molecular weight for dexamethasone is 392.47. It is designated chemically as 9-fluoro-11p,17,21-trihydroxy-16a-methylpregna-1,4-diene-3,20-dione. The empirical formula is C22H29FOs and the structural formula is:



Dexamethasone is stable in air and almost insoluble in water.

Dexamethasone is a white to practically white, odorless, crystalline powder. It is available in 2 or 4 mg tablets (commercially) for oral administration. Each tablet contains dexamethasone as the active ingredient, and the following inactive ingredients: calcium phosphate, lactose, magnesium stearate, and starch. The tablet shell may contain the following: D&C Yellow 10, FD&C Yellow 6, and/or FD&C Blue 1.

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access. Dexamethasone should be stored at controlled room temperature, 68-77°F (20-25°C) and not frozen, and according to label requirements.

Dexamethasone should be handled by trained pharmacy staff. The use of gloves and other appropriate protective clothing is recommended as necessary.

Dexamethasone supply will be obtained through commercial supply.

If Dexamethasone is given PO, it should be taken with food at approximately the same time each day.

At the end of the study, unused supplies of dexamethasone should be destroyed and documented according to institutional policies.

5.3.2 Administration

During initial therapy, each participant will receive dexamethasone as a single oral or IV dose. The investigator or designee will order drug supply from commercial supply.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Age 18 or greater at the time of signing the informed consent document.
- Patients diagnosed with *symptomatic* multiple myeloma based on IMWG Diagnostic Criteria. According to these criteria, patient must have Monoclonal plasma cells in the bone marrow 10% and/or presence of a biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following myeloma defining events:
    - Clonal bone marrow plasma cell percentage 60% (Note: clonality should be established by showing kappa/lambda-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate, the highest value should be used)
    - Involved:Uninvolved serum free light chain ratio 100 (values are based on the serum Freelite assay) The involved free light chain must be 10 mg/dl
    - >1 focal lesions on MRI studies (each focal lesion must be 5 mm or more in size)
    - [C] Calcium elevation in the blood, defined as serum calcium> 11 mg/dl or> 1 mg/dl higher than the upper limit of normal
    - [R] Renal insufficiency, defined as serum creatinine > 2 mg/di or creatinine clearance < 40 ml/min
    - [A] Anemia, defined as hemoglobin <10 g/dl or > 2 g/dl below the lower limit of normal
    - [B] Lytic bone lesions, one or more osteolytic lesions on skeletal radiography, CT, or PET-CT (if bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement)

- Patients must have symptomatic multiple myeloma *without* advanced organ damage (such as multiple fractures or advanced bone disease causing immobilization, renal failure, spinal cord compression, or organ compromise due to soft tissue plasmacytoma). If immediate therapy with radiation and high-dose steroids (eg, for spinal cord compression) or if triple therapy is clearly advisable from the start, the patient is not eligible for this trial.

- Patients with measurable disease defined as one or more of the following: serum M-protein 1.0 g/dl, urine M-protein 200 mg/24h, and/or serum FLC assay: involved FLC level 10 mg/di with abnormal serum FLC ratio.

- Only non transplant candidates or those who opt to forgo ASCT during first line therapy are eligible

- ECOG performance status .:::_2

- Female patients must:
  - be postmenopausal for at least 1 year before the Screening visit, OR
  - be surgically sterile, OR
  - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 30 days after the last dose of study treatment, OR agree to completely abstain from heterosexual intercourse

- Male patients, even if surgically sterilized (ie, status post-vasectomy), must:
  - Agree to practice effective barrier contraception during the entire study treatment period and through 30 days after the last dose of study treatment, OR
  - Agree to completely abstain from heterosexual intercourse

- Patients must be able to provide voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.

6.2 Subject Exclusion Criteria

- Participant treated with any prior systemic therapy with the exception of the following:
  - Treatment by localized radiotherapy for a specific indication within 2 weeks of initiation of treatment.
  - Treatment with corticosteroids, not to exceed the equivalent of 160 mg of dexamethasone over a four-week period before initiation of protocol therapy.

- Presence of Primary or associated amyloidosis (AL)

- Participants who plan to proceed with ASCT as part of first line therapy

- Poor tolerability or known allergy to lenalidomide, bortezomib and/or dexamethasone or compounds that have similar chemical or biologic composition to these study drugs.

- Platelet count< 50,000/mm^3 within 21 days of initiation of protocol therapy for patients in whom <50% of bone marrow nucleated cells are plasma cells; or platelet count <30,000/mm^3 for patients in whom 50% of bone marrow nucleated cells are plasma cells. Transfusion is not allowed to meet platelet eligibility criteria.

- ANC < 1,000 cells/mm^3 within 21 days of initiation of protocol therapy. Growth factor administration is not allowed to meet ANC eligibility criteria.

- Hemoglobin< 8 g/dl within 21 days of initiation of protocol therapy. Transfusion may be used to meet hemoglobin eligibility criteria.
- Hepatic impairment, defined as bilirubin > 1.5 x institutional upper limit of normal (ULN) [Patients with benign hyperbilirubinemia (e.g., Gilbert's syndrome) are eligible] or AST (SGOT), or ALT (SGPT), or alkaline phosphatase 2 x ULN, within 21 days of initiation of protocol therapy.
- Renal insufficiency, defined as creatinine clearance < 30 ml/min within 21 days of initiation of protocol therapy. Creatinine clearance will be the primary eligibility criteria in determining renal insufficiency. The Cockcroft-Gault formula (See Appendix) should be used for calculating creatinine clearance values.

- Active hepatitis B or C infection

- HIV 1 or 2 positivity

- Female participant who is pregnant or breast-feeding.

- Inability to comply with an anti-thrombotic treatment regimen (e.g., administration of aspirin, enoxaparin, or low molecular weight heparin administration).

- Peripheral neuropathy;:: Grade 2 on clinical examination, within 21 days of initiation of protocol therapy.

- Participant who had myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.
- Participant who has hypersensitivity to bortezomib, boron, or mannitol.

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

- Participant diagnosed or treated for another malignancy within 2 years of enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy. Patients who have had prior malignancies within the past 2 years but are considered to be "cured" with a low likelihood of recurrence may be eligible at the discretion of the Principal Investigator.

- Any other medical condition or laboratory evaluation that, in the treating physician's or principle investigator's opinion, makes the patient unsuitable to participate in this clinical trial.

7.0 RECRUITMENT PLAN

This study will be conducted at MSKCC. All patients will be recruited from the large pool of newly diagnosed patients referred to the myeloma service whether transplant or non-transplant candidates. About 8-10 newly diagnosed patients are seen per month at MSKCC main campus and we therefore anticipate no difficulty enrolling to this protocol. About 30% of them are non-transplant candidates. Since this protocol is the only trial available for non-transplant patients, we anticipate that these patients will constitute the bulk of patients enrolled. Efforts will be made to ensure that women and minority groups are adequately represented in this trial. All patients will be seen by MSKCC myeloma physicians and associated MSKCC co-investigators, enrolled and registered at 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, and 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

<u>The following tests will be performed within 21 days prior to treatment:</u>

- History & Physical exam including height and weight for BSA and neurologic examination
- Full Symptom assessment
- ECOG Performance status (See Appendix)
- QOL assessment (See Appendix)
- Serum myeloma studies: Serum protein electrophoresis (SPEP), serum immunofixation (IF), quantitative immunoglobulins, and serum free light chain assay
- Urine myeloma studies: Twenty-four hour urine for total volume and total protein (TV, TP), immunofixation (IF), protein electrophoresis (UPEP), N-telopeptides, and creatinine clearance
- CBC with differential, comprehensive metabolic panel, LOH, Mg, Phos, Uric acid, C-reactive protein, beta2-microglobulin, PT&APTT, BNP, and troponin.
- Serum -HCG Pregnancy test (for women of childbearing potential)
- Urinalysis
- Optional blood research sample

<u>The following tests will be performed within 12 weeks prior to patient enrollment:</u>

- 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 and FISH analysis for myeloma markers, and optional BMA research sample
- Electrocardiogram (EKG)
- A skeletal survey that should be reviewed at MSKCC if not performed at MSKCC (Not required if MRI of total spine, MRI of the totaty body or PET/CT is performed
- PET/CT (MRI of the total spine or MRI of the total body could be done alternatively)

The following tests will be performed within 6 months prior to patient enrollment:

- Hepatitis A, B, C serologies
- HIV 1/2 test

9.0 TREATMENT/INTERVENTION PLAN

9.1 Treatment Plan

9.1.1 Initial first 2 cycles of treatment:

Patients who have signed the consent form and are deemed eligible for this clinical trial will start therapy with bortezomib and dexamethasone (BO) with the following schedule:

- Length of cycle: 35 days
- These cycles will consist of:
  - Bortezomib SC (or IV if SC not tolerated) 1.5 mg/m2, days 1, 8, 15, and 22
  - Dexamethasone 40 mg PO or IV days 1, 8, 15 and 22 or on a split-dose regimen (20mg BIW).
- The following prophylactic medications are recommended: acyclovir 400mg BID; sulfamethoxazole and trimethoprim OS, TIW; fluconazole 100 mg daily; and omeprazole 20 mg daily. Alternative prophylactic medications are allowed if sensitivity to the drugs occurs.
- Bisphosphonates are recommended as clinically indicated.
- Erythropoietin is allowed

Patients will be assessed at the end of every cycle as shown in table.

9.1.2 Treatment beyond the first 2 cycles:

- Lenalidomide may be added based on the response to prior cycles (if less than PR after 2 cycles of BO or if less than VGPR after 4 cycles or POD at any time of induction). If lenalidomide is not added, the treatment schedule used during the initial 2 cycles will be unchanged. If lenalidomide is added, the following schedule will apply:

- Length of cycle: 28 days
- The cycles including Revlimid will consist of:
  - Bortezomib SC (or IV if SC not tolerated) 1.3 mg/m2, days 1, 8, and 15
  - Dexamethasone 40 mg PO or IV days 1, 8, and 15 or on a split-dose regimen (20mg BIW).

- Lenalidomide 15 mg PO (or dose adjusted to renal function as per guidelines) daily, days 1-21. If well tolerated, the dose of lenalidomide can be escalated with subsequent cycles incrementally by 5 mg, not to exceed 25 mg, days 1-21.

- The following prophylactic medications are recommended: acyclovir 400mg BID; sulfamethoxazole and trimethoprim OS, TIW; fluconazole 100 mg daily; omeprazole 20 mg daily; and aspirin 325 mg or aspirin 81mg or prophylactic doses of LMWH. Alternative prophylactic medications are allowed if sensitivity to the drugs occurs.
- Bisphosphonates are recommended as clinically indicated.

▶ All other patients will continue treatment with BO with the schedule detailed above.

▶ All patients will receive at least a total of 4 cycles of treatment.

Patients could proceed with SC collection after at least a total of 4 cycles if adequate response (PR) has been achieved, or will continue therapy until 8 cycles on study. If stem cells are collected, patients will resume treatment on study after stem cell collection for additional cycles (not to exceed a total of 8 cycles on study). All patients, whether completing the 8-cycles, or are removed from treatment for reasons other than POD, will return for follow-up once every 2 months until progression of disease (POD).

▶ Patients who have progression of disease (POD) after 2 cycles of RVD will be taken off study

▶ Patients who have stable disease (SD) after 2 cycles of RVD may be taken off study at the discretion of the treating physician

▶ Beyond 8 cycles, the treatment will be left to the discretion of the treating physician. The following maintenance treatment is recommended: Lenalidomide maintenance at the last tolerated dose for patients who received lenalidomide during the first 8 cycles (21 days out of 28 day-cycle), and bortezomib on a maintenance schedule (every other week or 4 weeks ON followed by 4 weeks OFF) if lenalidomide was not added during the first 8 cycles.

9.1.3 Stem cell collection

After at least 4 cycles of treatment, patients who have achieved at least a PR may proceed with stem cell mobilization and collection as per institutional guidelines. A leukapheresis catheter may be placed if deemed necessary for stem cell collection. Leukapheresis will begin as per SOP of the Blood Donor Room. 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 at least 2 stem cell transplantations in a patient's lifetime. We will seek a minimal acceptable collection of 2 x 10^6 CD34+ cells per kg, allowing at least one ASCT procedure. Patients failing to collect the minimum dose may be mobilized a second time as per MSKCC guidelines, at the discretion of the treating physician. Patients who are mobilized twice and have less than 2 x 10^6 CD34+ cells per kg will continue on study without plan for transplantation. Peripheral blood stem cells will be cryopreserved according to standard operating procedures of the Cytotherapy Laboratory.

9.2 Pre-Treatment Criteria

9.2.1 Criteria for initiation of New Cycle of BD or RVD Therapy (Day 1):

A new cycle of treatment may begin on the scheduled Day 1 of a new cycle of BO or RVD if the following criteria are met:

- ANC.:::. 1,000/ mm^3 (growth factor support is permitted during cycles of BO or RVD, with the exception of Cycle 1 Day 1; it is allowed on the same day as treatment administration)
- Platelet count.:::_ 50,000/ mm^3 (platelet support is permitted during cycles of BO or RVD; it is allowed on the same day as treatment administration)
- Any lenalidomide-related allergic reaction/hypersensitivity or sinus bradycardia/other cardiac arrhythmia adverse event that may have occurred has resolved to grade 1 severity.
- Any other lenalidomide or bortezomib-related adverse event that may have occurred has resolved to grade 2 severity.
- Grade 1 peripheral neuropathy with pain or grade 2 peripheral neuropathy without pain requires dose modification, and grade 2 peripheral neuropathy with pain requires that bortezomib be held.
- Herpes Zoster lesions are dry

If these conditions are not met on Day 1 of a new cycle, the participant will be evaluated weekly and a new cycle of therapy will not be initiated until the toxicity has resolved as described above. The maximum amount of time for which a drug may be held due to toxicity is 6 weeks. If drug is held for more than 6 weeks due to toxicity, the participant will be removed from study treatment.

9.2.2 Criteria for intra-cycle Therapy (Days 8, 15 and 22):

Treatment on Days 8, 15 and 22 during a cycle may be administered if the following criteria are met:

- ANC .:::_ 750/mm^3 (growth factor support is permitted)
- Platelet count.:::. 30,000/mm^3 (Transfusion to support platelet count is permitted at investigator discretion)

9.3 Dose Modifications/Delays

Before each drug dose, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), Version 4.0 http://ctep.cancer.gov/reporting/ctc.html). Dose modifications or delays will be done based on the toxicity experienced during a cycle of therapy or newly encountered on day 1 of each cycle. The participant may continue on therapy if the toxicity can be managed according to the dose modification guidelines as outlined below.

Dose delays beyond what is specified in section 10.0 or for reason(s) other than toxicity may be allowed with Principal Investigator approval.

9.3.1 General Guidelines

If there were dose modifications or delays in the previous cycle, use the following guidelines:

- Once one of the treatment doses (lenalidomide, bortezomib, or dexamethasone) is reduced for toxicity, no re-escalation will be allowed with the exception of lenalidomide in case of renal insufficiency during RVD therapy.
- Reduction and/or temporary suspension of one agent and not the others is appropriate if toxicity is related primarily to one of the agents.

- Drug may be held for no more than 6 weeks due to toxicity. During RVD cycles, if all three concerned treatments are held for more than 6 weeks, the patient will be withdrawn from the study treatment and will be followed until disease progression.

9.3.2 Dose Reduction Steps and Guidelines

Dose Reduction Steps for Lenalidomide during RVD therapy

Starting dose of lenalidomide	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction	4th Dose Reduction	5th Dose Reduction
15mgPOqd	10 mg PO qd	5 mg PO qd x	2.5 mg PO qd	2.5 mg PO qod	Discontinue lenalidomide

If the dose of lenalidomide was escalated to 20mg or 25mg as per guidelines in paragraph 9.1.2, and dose reduction is subsequently mandated, the dose would be de-escalated incrementally by 5mg per cycle to 15mg and 20mg respectfully.

If there were dose modifications or delays in the previous cycle, use the following guidelines:

- If the cycle was completed without requiring further dose modification, then the next cycle will start at the same reduced dose of lenalidomide.
- If Lenalidomide was held during the previous cycle and restarted at a reduced dose level, without interruption for the remainder of the cycle, then the reduced dose level will be initiated on Day 1 of the new cycle.
- If Lenalidomide dosing was omitted for the remainder of the previous cycle or if a new cycle is delayed due to lenalidomide-related toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction.

Dose Reduction Steps for Bortezomib

Starting dose of bortezomib	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction	4th Dose Reduction
1.5 mg/m^2	1.3 mg/m^2	1.0 mg/m^2	0.7 mg/m^2	Discontinue Bortezomib

See Table in section 9.3.3 for separate dose modification guidelines for peripheral neuropathy.

If there were dose modifications or delays in the previous cycle, use the following guidelines:

- In case of dose reduction during initial BO or RVD therapy, the participant will receive the reduced dose levels (the last level applied during initial therapy)
- If any two or more doses of bortezomib were held during the cycle (either consecutively or two or more in one cycle), then the new cycle will be started with one level dose reduction.
- If the new cycle is delayed due to bortezomib-related toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction.

- If after bortezomib has been held, the toxicity does not resolve, then bortezomib must be discontinued.

Dose Reductions Steps for Dexamethasone

Starting dose of dexamethasone	1st Dose Reduction	2nd Dose Reduction	Yd Dose Modification
40 mg/d	20 mg/d	10 mg/d	Discontinue dexamethasone

Dexamethasone doses can be split over 2 days.

9.3.3 Dose Modification Guidelines for Specific Drug-Associated Adverse Events

Each Adverse Event should be attributed to a specific study drug if possible so that dose modifications can be made accordingly. **Reduction and/or temporary suspension of one agent and not the others is appropriate if toxicity is related primarily to one of the agents.** Further clarification can be obtained in consultation with the PI. If multiple toxicities are noted, the dose adjustment should be made according to the most severe toxicity guidelines. Drug may be held for no more than 6 weeks to allow resolution of toxicity.

Drug Related Adverse Event Dose Modification Guidelines during RVD therapy

CTCAE Category	AGENTS	Toxicity During a Cycle
Grade 3 neutropenia associated with fever (temperature 38.SC) or Grade 4 neutropenia **and/or** **Platelet count < 10,000/mm^3 or G3 thrombocytopenia with bleeding**	**Lenalidomide**	Hold therapy (interrupt). Follow CBC on days 8 and 15. Use of G-CSF is allowed and recommended. If neutropenia resolved to ***S*** grade 2, resume lenalidomide with one level dose reduction and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by one dose level at the start of the next cycle. Omitted doses are not made up. If thrombocytopenia resolved to *S* grade 2, resume lenalidomide with one dose level reduction and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by one dose level at the start of the next cycle. Omitted doses are not made up.
	Bortezomib	Hold therapy Use of platelet transfusion is allowed. If thrombocytopenia resolved to ***S*** grade 2 and neutropenia resolves to *S* grade 2 and if the Day 8, 15 or 22 dose is held, that dose should be omitted and treatment should continue with next planned dose (i.e., if Day 8 or 15 is skipped, the next dosing day is Day 15 or 22, respectively)

		of bortezomib at same dose. If thrombocytopenia resolved to .:=:. grade 2 and neutropenia resolves to.:=:. grade 2 and if any 2 or more doses were held due to toxicity (either consecutive or two or more in one cycle), then reduce the bortezomib dose by one level.
Non-blistering rash **Grade 3**	**Lenalidomide**	Hold (interrupt dose). Follow weekly. If the toxicity resolves to .:=:. grade 1, restart lenalidomide with one level dose reduction and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by one dose level at the start of the next cycle. Omitted doses are not made up.
Non-blistering rash **Grade 4**		Discontinue lenalidomide study drug for grade 4 toxicity.
Desquamating (blistering) rash- any Grade or Erythema multiforme Grade 3	**Lenalidomide**	Discontinue lenalidomide study drug.
Sinus bradycardia/ other cardiac arrythmia Grade 2	**Lenalidomide**	Hold (interrupt) dose. Follow at least weekly. If the toxicity resolves to .:=:. grade 1 restart at next lower dose level.
Sinus bradycardia/ other cardiac arrythmia Grade 3		Discontinue lenalidomide study drug for grade 3
Allergic reaction or hypersensitivity Grade 2-3	**Lenalidomide**	Hold (interrupt) dose. Follow at least weekly. If toxicity resolves to .:=:. grade 1 restart at next lower dose level
Allergic reaction or hypersensitivity Grade 4		Discontinue lenalidomide study drug.
Hyperthyroidism or Hypothyroidism	**Lenalidomide**	Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide at investigator's discretion. For toxicity attributable to lenalidomide, reduce the dose by one dose level.
Peripheral Neuropathy	**Bortezomib**	See table
Neuropathy **Grade 3**	**Lenalidomide**	Hold (interrupt) dose. Follow at least weekly. If the toxicity resolves to.:=:. grade 1, restart lenalidomide at next lower dose level and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by one dose level at the start of the next cycle. Omitted doses are not made up.

Grade 4		Discontinue lenalidomide.
Herpes Zoster reactivation any grade	**Bortezomib**	Hold therapy until lesions are dry. Increase antiviral from prophylactic to therapeutic dose for 10 days or until lesions are healing and dry.
Venous Thrombosis/embolism Grade 3	**Lenalidomide/ Bortezomib**	Hold dose and start anticoagulation; restart at investigator's discretion (maintain dose level).
Moderate renal impairment 30s Creat Clear<50 ml/min	**Lenalidomide**	10mg once daily. The dose may be escalated to 15mg/d after 2 cycles if the patient is tolerating the treatment
Severe renal impairment Creat Clear<30 ml/min (not requiring dialysis)	**Lenalidomide**	15mg every other day. The dose may be escalated to 10mg/d if the patient is tolerating the treatment.
Severe renal impairment Creat Clear<30 ml/min (requiring dialysis)	**Lenalidomide**	5mg once daily. On dialysis days, the dose should be administered following dialysis. Alternate etiology for severe renal impairment should be evaluated.
Other lenalidomide or bortezomib related non-hematologic toxicity Grade 3	**Lenalidomide Bortezomib**	Determine attribution of toxicity and hold appropriate therapy. If toxicity resolves to.': grade 2, resume therapy with one level dose reduction.

Patients with mild hepatic impairment (bilirubin s 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 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.

Dose modifications for Bortezomib-Related Neuropathic Pain and/or Peripheral Sensory Neuropathy

Patients who experience bortezomib-related neuropathic pain or peripheral sensory neuropathy are to be managed as presented in the following table. Once the dose is reduced for peripheral neuropathy, the dose may not be re-escalated.

Management of Patients With bortezomib-Related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Severity of Peripheral Neuropathy Signs and Symptomsa	Modification of Dose and Regimen
Grade 1 (asymptomatic; loss of deep tendon reflexes or parasthesias) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities or Daily Living [ADL]b)	Reduce BORTEZOMIB to 1.0 mg/m^2
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADLc)	Withhold BORTEZOMIB therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of BORTEZOMIB at 0.7 mg/m^2 once per week.
Grade 4 (life-threatening consequence; urgent intervention indicated)	Discontinue BORTEZOMIB

Source: VELCADE® USPI issued January 2012.
Abbreviations: AOL = activities of daily living
a Grading based on NCI Common Terminology Criteria for Adverse Events (CTCAE) v3.0.
b Instrumental AOL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc

c Self care AOL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Dose modifications for specific dexamethasone associated adverse events

Dexamethasone dose modifications

Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level
	Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart and decrease one dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
	Acute pancreatitis	Discontinue dexamethasone and do not resume.
Cardiovascular	Edema Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and decrease dexamethasone dose by 1 dose level; if edema persists despite above measures, decrease dose another dose level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Neurology	Confusion or Mood alteration	Hold dexamethasone until symptoms resolve. Restart

	Grade 2 (interfering with function +/- interfering with activities of daily living)	with one dose level reduction. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Musculoskeletal	Muscle weakness Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living	Decrease dexamethasone by one dose level. If weakness persists despite above measures decrease dose by one level. Discontinue dexamethasone and do not resume if symptoms persist.
Metabolic	Hyperglycemia Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by one dose level until levels are satisfactory.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Evaluation During the Treatment Phase

Study Procedures	**Screening Period**	**Treatment Periodk**					**End of 8 cycles of treatment and At disease progressiont**	**2-Month Follow-upm**
	Within 21 days before treatment	Day1[p]	Day 8	Day 15	Day 22	Day [L] 29		
Informed Consent	X							
History, System Review, Complete Physical	X	Xg						
Interval history, System review, Complete physical		Xg					X	
ECOG Performance Status	X	Xg					X	
Concomitant meds, supportive Rx assessment	X	Xg					X	
Adverse event assessment		Xg					X	
Quality of life assessment	X	xg					X	
Neurologic Examination	X	xg					X	
CBC	X	X	X	X	X		X	X
Comprehensive Metabolic Panel	X	Xg					X	X
LOH	X	xg					X	X
Mg	X	Xg					X	X
Phos	X	Xg					X	X
Uric acid	X	Xg					X	X
C-reactive protein	X						X	
2.microglobulin	X	Xg					X	
PT&APTT	X	Xg					X	
Urinalysis	X	xg					X	
Serum -HCG Pregnancy Test	xa,b	xa,b, C					xa,b,c	X
BNP	X						X	
Troponin	X						X	
HIV 1/2 test	Xd							
Hepatitis A, B, and C Tests	Xd							

Serum Multiple Myeloma Disease Assessment • Serum protein electrophoresis (SPEP) • Quantitative immunoglobulins (IgG/IgA/IgM) • Serum Immunofixation • Serum Free Light Chains	X	Xg				xh,L	X	X
24 hour Urine Multiple Myeloma Disease assessment • Urine protein electrophoresis (UPEP) • Immunofixation • Total protein • Creatinine clearance • N-telopeptides	**X**	Xg				xh,L	**X**	**X**
Bone Marrow Aspirate and Biopsy for: • Morphology • Cytogenetics/FISH	x•	**X;**					**X**	As indicated
Electrocardiogram	x•						As indicated	As indicated
Skeletal Survey	xer						**X**	As indicated
PET/CT (or MRI of the total spine or MRI of the total body could be done alternatively)	x•						As indicated	As indicated
Optional Blood and Bone Marrow Research Samples	)(i	xg,j					**Xi**	
Bortezomib Dosing[o]		**X**	**X**	**X**	xq			**X"**
Dexamethasone		**X**	**X**	**X**	xq			**X"**
Lenalidomide		Daily Days 1-21					LJ	**X"**

a Pregnancy tests for women of childbearing potential, defined as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e. has not had menses at any time in the preceding 24 consecutive months);

b If lenalidomide is added to the regimen of a female that is of childbearing potential, pregnancy tests must occur within 28 days and again within 24 hours prior to initiation of lenalidomide. A pregnancy test must be done on Day 1 of each consecutive cycle while on therapy, at discontinuation of lenalidomide, and at Day 28 post the last dose of lenalidomide.

c All participants on RVD must be counseled about pregnancy precautions, risks of fetal exposure and other risks. The counseling must be done on Day 1 of RVD (or at a minimum of every 28 days) and at drug discontinuation.

d Must be done within 6 months prior to registration

• Must be done within 12 weeks prior to registration

l Within 4 weeks after completion of treatment

9 May be done +/- 3 days of Day 1. Multiple myeloma assessment tests do not need to be repeated on C3D1 and C5D1 since they would have been done as per footnote h, on C2D29 and C4D29

h Mandatory only for Cycles 2 and 4 to assess response and anticipate decision making for Cycles 3 and 5. These labs should be done on Day 29 of Cycles 2 and 4 (for cycle 4, only if lenalidomide had not been added to cycle 3) and would not need to be repeated on day 1 of Cycles 3 and 5. A +5 day window from Day 29 is allowed and Cycles 3 and 5 can be delayed up to one week to allow for these assessments to result

' To confirm CR (complete response) or progression of disease

l Patients that consent to the correlative research portion of the study will have 20-30 cc of peripheral blood and 10-20 cc of bone marrow aspirate collected during screening, on Cycle 5 Day 1 if bone marrow is clinically indicated, and at the End of treatment, when possible. If patient has had a bone marrow aspiration within a month prior, the procedure would not be need to be performed again.

kif treatment is delayed, labs and assessments do not need to be redone if performed within 1 week, including correlative study samples.

LDay 29 is not applicable for Cycles 1, 3, 5, 6, 7, and 8. It is also not applicable to cycle 4 if lenalidomide has been added in cycle 3.

mpatients that complete the 8-cycles, and/or are removed from treatment will be followed up once every 2months (+/- 2 weeks) until POD.

"Beyond 8 cycles, the treatment will be left to the discretion of the treating physician. The following maintenance treatment is recommended: Lenalidomide maintenance at the last tolerated dose for patients who received lenalidomide during the first 8 cycles, and bortezomib on a maintenance schedule (every other week or 4 weeks ON followed by 4 weeks OFF) if lenalidomide was not added during the first 8 cycles.

0 A dosing delay with bortezomib on days 8, 15, and 22 is allowed for up to 3 days, provided that safety labs are done within 24 hours of administration of bortezomib. Subsequent treatment days with Bortezomib must be adjusted accordingly.

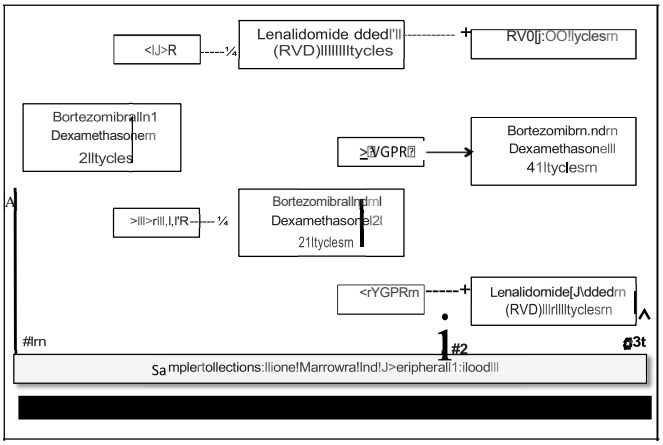
P Day 1 of any cycle may be delayed for up to 7 days.

qBortezomib and Dexamethsone will not be administered on day 22 if Lenalidomide has been added.

'Skeletal Survey is not required for screening if either a PET/CT or MRI have been performed

10.1.2 Correlative Studies

In patients that agree to participate in this portion of the study, we propose collection of peripheral blood (20-30 cc using CPT or sodium heparin tubes) and bone marrow aspirate (5-10 cc in EDTA and 5-10 cc in sodium heparin tubes) at the timepoints indicated in the Table above and in **Figure 1** (right). The bone marrow sample collected in EDTA will be sent to the Hematologic Oncology Tissue Bank (HOTS) for subsequent studies and eventually sequenced in the genomics core facility The peripheral blood and bone marrow samples collected in sodium heparin will be analyzed under the supervision of Alexander M. Lesokhin.



11.0 TOXICITIES/SIDE EFFECTS

11.1 Potential Risks of Bortezomib

To date, more than 300,000 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 0-1 and Table 0-2. 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 0-1 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, pericardia! effusion, pericarditis, pericardia! disease±, cardiopulmonary failure±
Ear and Labyrinth Disorders	
Uncommon	Deafness, hearing impaired
Eye Disorders	
Common	Blurred vision, conjunctivitis, conjunctiva! haemorrhage
Gastrointestinal Disorders	
Most common	Constipation, diarrhoea*, 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 mucosa! petechiae, ileus paralytic*, ileus, odynophagia, enteritis, colitis, oesophagitis, enterocolitis, diarrhoea 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, mucosa! 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

Table 0-1 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Infections and Infestations	
Very common	Upper respiratory tract infection, nasopharyngitis, pneumonia*, Herpes zoster*
Common	Lower respiratory tract infection*, sinusitis, 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,

Table 0-1 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
	reversible posterior leukoencephalopathy syndrome±, posterior reversible encephalopathy syndrome <1>
Psychiatric Disorders	
Very common	Anxiety, insomnia
Common	Confusional state
Uncommon	Delirium
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	Hemoptysis*, 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: VELCADE® (bortezomib) for Injection Investigator's Brochure Edition 15.

Most common= :2: 30%, Very c01mnon = 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.

<1> Effective MedDRA update to version 14.0, the term 'reversible posterior leukoencephalopathy syndrome' updated to 'posterior reversible encephalopathy syndrome (PRES)'.

Table 0-2 Reports of Adverse Reactions From Postmarketing Experience

System Organ Class Preferred Term	Observed Incidence•
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
lschemic colitis	Rare
Hepatobiliary disorders	
Hepatitis	Uncommon
Liver failure	Unknown
Infections and infestations	
Herpes meningoencephalitis	Rare
Septic shock	Rare
Progressive multifocal leukoencephalopathy	Very 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 diseaseb	Rare
Acute respiratory distress syndrome (ARDS)	Rare
Interstitial pneumonia	Rare
Lung infiltration	Rare
Pneumonitis	Rare
Pulmonary hypertension	Rare

Table 0-2 Reports of Adverse Reactions From Postmarketing Experience

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

Source: VELCADE®(bortezomib) for Injection Investigator's Brochure Edition 15, Addendum 1.

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 oflnterstitial 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.

SAFETY SUMMARY FOR SUBCUTANEOUS ADMINISTRATION

While the safety profile between the SC and IV treatment groups in general was comparable in most SOCs, a difference in incidence in certain safety parameters in favor of the SC treatment group was noted. One hundred and forty (95%) subjects in the SC treatment group and 73 (99%) subjects in the IV treatment group reported at least 1 treatment-emergent adverse event. In the SC treatment group, there was a lower incidence of Grade :2:3 adverse events as compared with the IV treatment group (57% vs. 70%, respectively); a lower incidence of adverse events leading to treatment discontinuations (22% in the SC treatment group and 27% in the IV treatment group); and a lower incidence of adverse events leading to dose modifications in the SC group: dose reduction (33% in the SC treatment group compared with 45% in the IV treatment group); dose withholding (30% in the SC treatment group compared with 39% in the IV treatment group); or cycle delay (20% in the SC treatment group compared with 34% in the IV treatment group). Serious adverse events were similar between the 2 treatment groups (36% in the SC treatment group and 35% in the IV treatment group). Deaths during treatment (within 30 days of last dose) were 5% in the SC treatment group and 7% in the IV treatment group.

The SC treatment group reported a lower incidence in several adverse events associated with BORTEZOMIB toxicity. The incidence of peripheral neuropathy events (all Grades) was 38% in the SC treatment group and 53% in the IV treatment group; the incidence of Grade :2:2 peripheral neuropathy events was 24% in the SC treatment group and 41% in the IV treatment group; and the incidence of Grade :2:3 peripheral neuropathy event was 6% in the SC treatment group and 16% in the IV treatment group. There also appeared to be a trend towards lower incidence in gastrointestinal adverse events (37% for SC and 58% for IV, predominantly

due to differences in Grade 1-2 abdominal pain, diarrhea, and dyspepsia); as well as a 25% difference in incidence of Grade 3 and 4 hematology laboratory results in the SC treatment group compared with the IV treatment group for WBC (8% in the SC treatment group compared with 18% in the IV treatment group), neutrophil count (22% in the SC treatment group compared with 28% in the IV treatment group) and platelets (18% in the SC treatment group compared with 23% in the IV treatment group).

Local tolerability of SC administration was acceptable. Nine (6%) subjects reported a local reaction to SC administration as an adverse event. Eighty-five (58%) subjects in the SC treatment group reported at least 1 local injection site reaction. The most common local injection site reaction was redness which was reported in 84 (57%) subjects. The majority of subjects with worst injection site reactions were assessed as mild (38%) or moderate (18%). Only 2 (1%) subjects were reported as having severe injection site reactions. All local site reactions resolved completely and rarely led to treatment modifications.

In conclusion, the SC administration of BORTEZOMIB has good local tolerance. The systemic safety profile for the SC administration of BORTEZOMIB was associated with a lower incidence of Grade 23 adverse events, and treatment modifications (discontinuations and dose reductions). In particular, there was a lower incidence of peripheral neuropathy NEC reported.

RISKS DURING PREGNANCY

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. Non-sterilized 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,_Q[completely abstain from heterosexual intercourse.

11.2 Potential Risks of Lenalidomide

The following is a list of adverse events that are associated with the use of lenalidomide:

Likely

Events that have occurred in >20% of individuals treated with lenalidomide include constipation, neutropenia, anemia, thrombocytopenia, fatigue, diarrhea, and constipation.

Less likely

Events that have occurred in ::; 20% of individuals treated with lenalidomide include hypothyroidism, nausea, vomiting, chills, edema of the limbs, fever, infection, decreased lymphocyte count, weight loss, leukocytopenia, anorexia, arthralgia, back pain, muscle cramps, myalgia, dizziness, headache, insomnia, cough, dyspnea, hyperhidrosis, pruritis, rash, pyroderma gangrenosum, and stroke.

Rare but serious

Events that have occurred in 1 % of individuals treated with lenalidomide include risk of DVT, PE, and blood clots that could lead to stroke, heart attack, or organ failure, febrile neutropenia, atrial fibrillation, pneumonia or lung infections, sepsis, dehydration and renal failure.

Events that have occurred in <3% of individuals treated with lenalidomide include rare treatment-emergent adverse events of angioedema, serious skin reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme, or an allergic skin reaction similar to that seen with thalidomide, tumor lysis syndrome (TLS), tumor flare reaction (TFR), rhabdomyolysis, leukemia secondary to oncology chemotherapy, myelodysplastic syndrome, leukoencephalopathy, pancreatitis, anaphylaxis, increased lipase and acute kidney injury. In addition, lenalidomide has been shown to increase the level of digoxin in the blood in some patients. Patients will be instructed to inform their doctor if taking digoxin.

There may be an increased risk of second cancers in patients who are on lenalidomide maintenance therapy after a bone marrow transplant.

11.3 Potential Risks of Dexamethasone

Events that have occurred in 10-15% of individuals treated with dexamethasone include increased appetite, weight gain, sleep disturbance, hypertension, fluid retention, ankle swelling, bruising, infection, mood changes, slow wound healing, depression, and hyperglycemia, which may lead to fatigue, weight loss, excessive thirst and frequent urination.

Events that have occurred in 1-9% of individuals treated with dexamethasone include loss of appetite, muscle twitching, increased thirst, frequent urination, increased perspiration, diarrhea, nausea, headache, bone thinning, spinal fracture or fracture of bones, tachycardia, fungal infections.

Events that have occurred in <1% of individuals treated with dexamethasone include blurred vision, personality changes, stomach ulcers with bleeding that may cause hematemesis, blood in the stool and abdominal pain.

Other, less frequent, events may include bowel perforation, irritation and bleeding of the esophagus, heart failure, allergic reaction that may lead to facial redness, shortness of breath, abdominal cramps and hypotension, convulsions, brain swelling, dizziness, cataracts, glaucoma and increased pressure in the eye, development of diabetes, pancreatic inflammation, abdominal swelling, hypokalemia, DVT or PE, malaise, swelling and/or redness of skin, allergic skin reactions, itching, hirsutism, muscle weakness or loss of muscle mass, rupture of tendons, menstrual cycle disturbances, facial puffiness leading to the appearance of a "moon face", hormonal disturbances, and hiccups.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Definition of Measurable Disease

Measurable disease is disease that can be measured either by serum or urinary evaluation of the monoclonal component or by serum assay of FLC and is defined by at least one of the following three measurements.

- Serum M-protein 1 g/dl
- Urine M-protein 200 mg/24 h
- Serum FLC assay: Involved FLC level 10 mg/di provided serum FLC ratio is abnormal.

12.2 Methods for Evaluation of Measurable Disease

Response will be assessed by M-protein quantification using protein electrophoresis and immunofixation from serum or 24-hour urine collection, or serum Freelite™ testing. In addition, bone marrow aspiration and biopsy, as well as skeletal survey will be performed to determine overall response or confirm response, if deemed necessary.

The same method of assessment and technique should be used for disease measurement at baseline and during follow-up.

12.3 International Myeloma Working Group Response Criteria

Response criteria for all categories and subcategories of response except CR are applicable only to patients who have 'measurable' disease, as defined in Section 12.1.

Stringent CR: CR as defined below plus normal free light chain ratio and absence of clonal cells in bone marrow· by immunohistochemistry or immunofluorescence•.

*Presence/absence of clonal cells is based upon the k/A. ratio. An abnormal k/1 ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/A. of> 4:1 or < 1:2.

CR: Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and 5% plasma cells in bone marrow.

VGPR: Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100mg per 24 hours.

PR: .:::, 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by > 90% or to < 200mg per 24 hours. If the serum and urine M-protein are unmeasurable, a .:::, 50% decrease in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria (definition of measurable disease in Section 10.2.3). If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, .:::, 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was.:::, 30%. In addition to the above listed criteria, if present at baseline, a > 50% reduction in the size of soft tissue plasmacytomas is also required.

SD: Not meeting criteria for CR, VGPR, PR or progressive disease. This is not recommended as an indicator of response; stability of disease is best described by providing the time to progression estimates.

PD: > 25% increase of serum M-protein (which must also be an absolute increase of 0.5 g/dl) and/or urine M-protein (which must also be an absolute increase of 200 mg/24hr). If serum and urine M-protein are unmeasurable, there must be an absolute increase of 10 mg/dl between involved and uninvolved FLC levels. PD is also measured by an absolute increase in bone marrow plasma cells.:::, 10%. In addition to the above listed criteria, progression may also be measured by a definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas or development of hypercalcemia (corrected serum calcium.:::, 11.5 mg/dl or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder.

<u>Freelite™ Disease Response Criteria</u>

Complete Response: For those patients being followed by serum free light chain (and NO measurable serum or urine M-spike), which were immunofixation negative at enrollment, normalization of serum free light chain ratio.

- Normalization is defined as the serum free light chain ratio being within the normal range. If the serum free light chain ratio is not within the normal range, but the individual kappa and lambda light chain values are within normal range, this may be considered CR.

Partial Response: If only measurable parameter is serum immunoglobulins free light chain (FLC), EITHER of the following changes qualifies as partial response:

- A 50% decrease in the difference between involved and uninvolved FLC levels; OR

- A 50% decrease in the level of involved FLC AND a 50% decrease (or normalization) in the ratio of involved/uninvolved FLC

Progressive Disease: If only measurable parameter is serum immunoglobulins free light (FLC), either of the following qualify as progression:

- 50% increase in the difference between involved and uninvolved FLC levels from the lowest response level, which must also be an absolute increase of at least 10 mg/dl; OR

- 50% increase in the level of involved FLC AND a 50% increase in the ratio of involved/uninvolved FLC from the lowest response level.

12.4 QOL Questionnaire

Qol will be assessed in this study using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30) and its corresponding multiple myeloma module (EORTC QLQ-MY20).

The EORTC QLQ-C30 is a valid, reliable and widely used cancer-specific, multi-dimensional core Qol instrument that incorporates nine multi-item scales including five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting, and pain) and a global health and quality of life scale. Six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) are included. Response options are a 4-point Likert-type scale from "not at all" to "very much" or a ?-point Likert-type scale from "very poor" to "excellent."

Designed to be used in conjunction with the EORTC QLQ-C30, the EORTC QLQ-MY20 scale has been well-validated and was designed to evaluate the effect of the disease and drug therapy in patients with multiple myeloma. This measure is comprised of four scales (disease symptoms, side effects, body image, and future perspective).

The EORTC QLQ-C30 and MY20 collectively take approximately 12 minutes to complete (Aaronson et al., 1993; Cocks et al., 2007; Hjermstad et al., 1995) and are designed to be self-administered. However, a designated person at the study site will be responsible for administering the surveys to participants and providing materials to assist in survey completion (i.e., a clipboard, pen, and envelope to enclose the survey in when completed). This person will also be responsible for collecting the completed survey, verifying that no items have missing responses, and answering any questions that arise from the participant regarding the survey.

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 is *required* to withdraw patients from the study for any of the following reasons:

- If after at least one cycle of RVD treatment a patient shows evidence of hematologic disease progression
- If at any time a patient develops unacceptable toxicity
- General or specific changes in the patient's condition unacceptable for further treatment in the judgment of the investigator

The investigator may *consider* withdrawing patients from the study for any of the following reasons:

- If after at least 2 cycles of RVD the patient is shown to have only stable disease the investigator needs to consider withdrawal of the patient
- If there is protocol violation
- Non-compliance
- Administrative reasons
- Failure to return for follow-up

14.0 BIOSTATISTICS

14.1 Primary Endpoint

The goal of this phase II trial is to investigate the efficacy of a sequential drug regimen in symptomatic multiple myeloma patients. The primary endpoint is the overall response rate (PR or better) after four cycles of therapy. Patients who withdraw prior to the primary endpoint evaluation for reasons related to progression of disease or drug-related toxicity will be considered treatment failures.

The study will employ a Simon optimal two-stage design. The sequential drug regimen is considered promising if the overall response rate after 4 cycles is 90% or higher and unpromising if the overall response rate is 70% or lower. These numbers are based on the results achieved in a phase II clinical trial describing the effectiveness of the combination of drugs lenalidomide, bortezomib, and dexamethasone (RVD) given concomitantly in untreated multiple myeloma patients. The probabilities of a type I error and type II error are each set at 0.10. We will enroll 9 patients in the first stage. If 6 or fewer patients respond after 4 cycles, the trial will be terminated. If not, then an additional 19 patients will be enrolled to a total of 28. Upon completion of the trial, if there are 23 or more patients who have achieved a PR or better, the drug combination will be considered promising for further investigation.

With an anticipated accrual of 1-2 patients per month, the duration of this trial is approximately 2 years.

14.2 Secondary Endpoints

There are a number of secondary endpoints in this trial. The proportion of patients in each response category (CR, VGPR, PR, SD, and PD) will be tabulated after the completion of cycle four and cycle eight (for those who would have completed 8 cycles), and the overall response rate for the entire population after up to eight cycles will be estimated and compared to the responses reported in the phase II study by Richardson et al. using the 3-drug-combination[26]. For patients going to transplantation prior to completion of 8 cycles, the response prior to transplantation will be considered the best response.

The toxicities of the sequential drug regimen will be investigated. The toxicities outlined in section 11 will be tabulated overall for the study population and by whether the two or three drug combination was given at the time of the noted toxicity. The toxicities for the entire population will be compared to previously reported and tabulated toxicities in the phase II study by Richardson et al. using the 3-drug-combination, focusing on grade 3 and 4 toxicities[26]. For toxicity analysis, only toxicity prior to transplantation will be considered.

QOL will be collected at Screening, on day 1 of each treatment cycle, and at the end of study. The two QOL questionnaires for this trial are described in subsection 12.4. Graphical and descriptive measures will used to summarize the changes in the nine scales of C30 and four scales of MY20 from baseline to the completion of cycles four and eight. Comparison between patients having received 2 versus 3 drugs will be described. QOL data will only be collected up to the time of transplantation

Lastly, progression-free survival will be estimated for all patients using Kaplan-Meier methodology. This analysis will include all patients regardless of their transplantation status.

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 consenURA or verbal scripURA, 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 28 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

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to MSKCC and collaborating centers IRB guidelines.

Patients will be eligible for this trial regardless of gender or racial/ethnic background. All patients must follow the guidelines for pregnancy testing birth control and counseling related to the risk of fetal exposure to lenalidomide and bortezomib as outlined in Appendix F and Table in section 10.1.

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

Potential risks and benefits

The potential risks of this therapy may outweigh the potential benefit in an individual patient. The potential risks to patients are related to drug induced adverse effects and are outlined in Section 11.0. Appropriate exclusion criteria for patients are listed in Section 6.0: Patient Eligibility. Appropriate exclusion of patients with significant organ dysfunction or infection will help avoid treatment-related toxicity. Careful monitoring of laboratory parameters and patient symptoms, along with serial assessment for disease recurrence, will be carried out routinely in order to minimize the risk of adverse effects during this study.

Alternatives/Options for treatment

Patients with newly diagnosed standard-risk multiple myeloma have many treatment options. Alternative therapy for patients who choose not to enroll on this study include standard chemotherapy, including thalidomide, steroids, bortezomib, lenalidomide, some combination of the above, autologous or allogeneic stem cell transplant, other clinical trials, observation, or supportive care.

Costs

Patients will be responsible for all costs related to treatment and complications of treatment, including all hospitalizations.

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

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.

17.2.1 Serious Event Reporting to Millennium

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).

The sponsor-investigator is responsible to meet all regulations and requirements applicable to the sponsor-investigator.

(Millennium will not report SAEs on behalf of the sponsor-investigator to any regulatory agency [eg, US FDA] or to the sponsor-investigator's IRB.)

Definitions

Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with

this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

For this protocol an abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

Serious Adverse Event Definition

Serious adverse event (SAE) means any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification below on planned hospitalizations in Section 0).
- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent.

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

With respect to the suspected transmission via a medicinal product of an infectious agent; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), whether pathogenic or non-pathogenic, is considered an infectious agent.

Clarification should be made between the terms *serious* and *severe* because they ARE NOT the same. The term *severe* is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as *serious,* which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but may not be considered an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Procedures for Reporting Serious Adverse Events (SAEs)

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 Hani Hassoun 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 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, version used at your institution, 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 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.

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

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). Millennium must be contacted immediately by faxing the CRDB report or other approved equivalent form to the Millennium Pharmacovigilance or designee (see Section 17.2.1). 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, Millennium must also be contacted immediately by the CRDB report. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

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.

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20.0 APPENDICES

Appendix A Cockcroft-Gault estimation of CrCl

Appendix B ECOG Performance Status

Appendix C Performance Status Criteria

Appendix D Quality of Life Questionnaire

Appendix E Recommendations for Pregnancy

Appendix F Hartford Alliance Protocol Addendum