THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Primary Treatment of Waldenstrom's Macroglobulinemia with Bortezomib (Velcade®) and Rituximab followed by autologous stem cell collection 2005-0733

Core Protocol Information

Short Title	Bortezomib/Rituxan for Waldenstrom's Macroglobulinemia
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Which Committee will review this protocol?

(●) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

1.1. Primary Objectives

To assess response rate in newly diagnosed patients with Waldenstrom's Macroglobulinemia treated with bortezomib and rituximab

To assess ability to collect stem cells after treatment with bortezomib and rituximab in newly diagnosed patients with Waldenstrom's Macroglobulinemia.

1.2 Secondary Objectives

To assess overall response rate to treatment with bortezomib and rituximab followed by cladribine, cyclophosphamide and rituximab in newly diagnosed patients with Waldenstrom's Macroglobulinemia

To assess time to progression and time to retreatment, following treatment with bortezomib and rituximab followed by cladribine, cyclophosphamide and rituximab in newly diagnosed patients with Waldenstrom's Macroglobulinemia

To assess toxicity of treatment with bortezomib and rituximab in newly diagnosed patients with Waldenstrom's Macroglobulinemia.

2.0 Background

Macroglobulinemic lymphoma (Waldenstrom's macroglobulinemia) is a low grade lymphoid malignancy characterized by lymphocytic proliferation in the bone marrow, blood or lymph nodes associated with production of monoclonal immunoglobulin M (IgM). This entity includes patients with either small cell lymphocytic lymphoma or chronic lymphocytic leukemia who have monoclonal IgM in the serum. When treated with an alkylating agent (usually chlorambucil) and prednisone, approximately 50-75% of previously untreated patients achieve a remission.[2,3] We have previously treated newly diagnosed patients with 2 courses of 2-chlorodeoxyadenosine (2-CdA) either alone, with prednisone, or with cyclophosphamide(Cy), and achieved 80-90% response rates, with long unmaintained remissions.[4,5] In 10% of these patients, a complete remission, based on disappearance of monoclonal IgM by immunofixation, was achieved.

Rituximab is a monoclonal antibody to CD20 which is highly expressed on the clonal lymphocytes of most patients with Waldenstrom's disease. Remissions have occurred with this agent in many patients with low grade lymphoma and Waldenstrom's disease resistant to prior standard therapies. When we evaluated 2-CdA and Cy alone or in combination with rituximab (Rit), the overall response rates were 89% and 93% respectively. The median time to treatment failure (TTF) was 31.4 months in the 2CdA-Cy arm, and 64.2 months in the 2CdA-Cy-Rit arm. At 4 years, median overall survival has not been reached with either regimen.[6,7,8,9,10,11]

While excellent response rates are seen with 2 CdA-based regimens, the myelosuppressive effects of the drug may hinder subsequent stem cell collection. Accordingly, an alternative chemotherapy regimen that will permit stem collection for autologous transplant at disease relapse would allow for further evaluation of myeloablative therapy with stem cell support.

Bortezomib is a small molecule, which selectively and reversibly inhibits proteasomes, resulting in disruption of pathways and checkpoints that lead to cellular apoptosis. In a recent phase II study of patients with relapsed or refractory Waldenstrom's disease, treated with single-agent bortezomib, 11 of 26 evaluable patients achieved a partial response, and an additional 11 patients achieved a minor response.[12] Results from a second phase II study of 10 patients with relapsed or refractory Waldenstrom's macroglobulinemia treated with single-agent bortezomib showed a partial response in 6 patients, with a minor response in 2 patients and stable disease in 1 patient.[13] Together, these studies suggest a potential role for the drug in the treatment of patients with Waldenstrom's macroglobulinemia.

In this study, we will determine the response rate to treatment with bortezomib and rituximab in previously untreated patients with symptomatic Waldenstrom's macroglobulinemia, and subsequently evaluate the ability to harvest stem cells in these patients after administration of this regimen. All enrolled patients will receive 2 cycles of bortezomib and rituximab. Response to therapy will be assessed, and if neither a response (partial or complete), nor evidence of disease progression is seen, patients will be given an additional cycle of bortezomib and rituximab. Response will be assessed again after this third cycle of therapy. Patients who have not achieved a partial response or better after 3 cycles of bortezomib and rituximab will go on to receive 2 cycles of a regimen containing cyclophosphamide, vincristine, doxorubicin and dexamethasone and rituximab (modified R-Hyper-CVAD) to minimize disease burden.

Patients achieving a partial or complete response with either 2 or 3 cycles of bortezomib-rituximab or with modified R-Hyper-CVAD, will undergo stem cell collection. Following stem cell collection, patients will receive 1 cycle of 2CdA, cyclophosphamide and rituximab for consolidation of response, as this latter regimen has an established high response rate. Patients not responding to either the bortezomib-rituximab or modified R-Hyper-CVAD regimens will be taken off study.

Opportunistic infections represent a potential concern among patients with immune suppression from disease, treatment or both. Among patients with Waldenstrom's disease treated with 2 courses of 2 CdA and cyclophosphamide, serious infections occurred in less than 10 percent of patients, with no associated deaths. Rituximab may reduce the number of normal B cells even further, adding to the risk of combined therapy. Despite these concerns, this agent has been given to large numbers of patients with relapsed lymphoma and extensive prior chemotherapy without a high frequency of serious infection, even when combined with programs such as CHOP. However, a recent study looking at the use of bortezomib in both the induction and consolidation settings found that 39% of patients experienced reactivation of varicella zoster virus while on therapy with bortezomib.[14] Accordingly all patients treated on this protocol will receive prophylaxis with valacyclovir while receiving induction therapy with bortezomib and rituximab.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.1.1 Patients with symptomatic macroglobulinemic lymphoma who have had no prior treatment, or whose prior treatment has been limited to steroids and/or alpha-interferon, are eligible. Macroglobulinemic lymphoma includes patients with either biopsy proven clonal lymphocytic or lymphoplasmacytic proliferation and monoclonal IgM. Also included are symptomatic patients with clonal proliferation producing a pathologic monoclonal IgM that causes cryoglobulinemia, peripheral neuropathy or cold agglutinin hemolytic anemia.

3.1.2 Patients must have acceptable liver function (total bilirubin < 2.5mg/dL) and renal function (creatinine < 2.0mg/dL). Patients with impaired renal function will only be included if the renal failure is secondary to macroglobulinemic lymphoma (i.e. Bence Jones proteinuria, cryoglobulinemia, ureteral obstruction due to mass) that might reverse with improvement of disease.

3.1.3 Female subject is either post-menopausal or surgically sterilized or willing to use an acceptable method of birth control (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) for the duration of the study.

3.1.4 Male subject agrees to use an acceptable method for contraception for the duration of the study.

3.1.5 Patients must voluntarily sign an informed consent form indicating that they are aware of the investigational nature of the study, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future care. The only acceptable consent form is attached at the end of this protocol.

3.1.6 Patient has a heart rate (HR) of greater than or equal to 50 bpm.

3.2 Exclusion Criteria

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

3.2.1 Patient has a platelet count of $<30x10^9$/L within 28 days before enrollment unless due to ≥ 75% marrow infiltration by macroglobulinemic lymphoma or splenomegaly.

3.2.2 Patient has an absolute neutrophil count of $<1.0x10^9$/L within 28 days before enrollment unless due to ≥ 75% marrow infiltration by macroglobulinemic lymphoma.

3.2.3 Patient has a calculated or measured creatinine ≥ to 2.0mg/dL on baseline evaluation. Patients with impaired renal function will only be included if the renal failure is secondary to macroglobulinemic lymphoma (i.e. Bence Jones proteinuria, cryoglobulinemia, uteteral obstruction due to mass).

3.2.4 Patient has ≥ Grade 2 peripheral neuropathy on baseline evaluation.

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

3.2.6 Patient has hypersensitivity to boron, mannitol, or murine proteins.

3.2.7 Female subject is pregnant or breast-feeding. Confirmation that the subject is not pregnant must be established by a negative serum or urine Beta-human chorionic gonadotropin (B-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women.

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

3.2.9 Patient has a serious medical or psychiatric illness that is likely to interfere with participation in this clinical study.

3.2.10 Eastern Cooperative Oncology Group (ECOG) performance status of > 2. (See Appendix H)

3.2.11 Patient with a "currently active" second malignancy, other than non-melanoma skin cancer and carcinoma in situ of the cervix, should not be enrolled. Patients are not considered to have a "currently active" malignancy if they have completed therapy for a prior malignancy, are disease free form prior malignancies for >5 years and are considered by their physician to be at less than 30% risk of relapse.

3.2.12 Patient with a lifetime cumulative dose of > 450 mg/m2 of anthracyclines.

3.2.13 Patients with an active hepatitis B infection.

4.0 Treatment Plan

4.1 Patient Registration

All patients will be registered with the Data Management Office at (713) 792-2626

4.2 Treatment Schedule

There is a +/- 3 Day window for all Day 1 chemo dosing of each cycle.

Patients will receive two 35-day cycles of bortezomib-rituximab:

Bortezomib 1.6mg/m^2 intravenously on Days 1, 8, 15 and 22
Rituximab 375mg/m^2 intravenously on Day 8 and 22

If no partial or complete response to therapy, and no disease progression, patients will receive one additional 35 day cycle of bortezomib-rituximab:

Bortezomib 1.6mg/m^2 intravenously on Days 1, 8, 15 and 22
Rituximab 375mg/m^2 intravenously on Day 8 and 22

In all cycles, Bortezomib will be administered prior to Rituximab on days 8 and 22.

All patients will receive viral prophylaxis with valacyclovir 500 mg orally daily (or acyclovir 200mg orally twice daily) while on therapy with bortezomib-rituximab.

If neither partial nor complete response to therapy is achieved after three cycles of bortezomib-rituximab, or if disease progression is noted after the first or second cycle of bortezomib-rituximab, patients will receive two 28-day cycles of modified R-Hyper-CVAD to reach a minimal disease state:

Cycle 1

Rituximab 375mg/m^2 intravenously on Day 1
Cyclophosphamide 300mg/m2 intravenously every 12 hours on Days 1-4
Doxorubicin 9mg/m^2/day mixed with Vincristine 0.4mg/day (maximum 2 mg) by continuous infusion over 24 hours on Days 1-4
Dexamethasone 40mg/day orally on Days 1-4, 9-12, 17-20

Cycle 2

Rituximab 375mg/m^2 intravenously on Day 1
Cyclophosphamide 300mg/m2 intravenously every 12 hours on Days 1-4
Doxorubicin 9mg/m^2/day mixed with Vincristine 0.4mg/day (maximum 2 mg) by continuous infusion over 24 hours on Days 1-4
Dexamethasone 40mg/day orally (dosing schedule as per Department of Blood and Marrow Transplant)

If partial or complete response is seen with bortezomib-rituximab or with modified R-Hyper-CVAD, patients will undergo stem cell collection (within 10 weeks of documented response), as per protocol of the Department of Blood and Marrow Transplantation (see section 4.3 for details).

Following stem cell collection, patients will receive one cycle of 2CdA-cyclophosphamide-rituximab:

2CdA 3.0mg/m^2 intravenously once daily over 2 hours on Days 1-5
cyclophosphamide 60mg/m^2 orally twice daily on Days 1-5
rituximab 375mg/m^2 intravenously once weekly for 4 consecutive weeks

Patients achieving a PR or CR will be followed (at least every 6 months from the end of treatment for the first 36 months, and then annually thereafter) without further treatment until relapse requiring re-treatment occurs.

Those patients failing to achieve a PR or CR after both bortezomib-rtituxmab and modified R-Hyper-CVAD will be taken off study.

4.3 Stem Cell Collection as per Department of Blood and Marrow Transplant

Patients will be mobilized with either G-CSF or modified R-Hyper-CVAD.

Patients mobilized with G-CSF alone will be given a dose of 6 mcg/kg (rounded off to the nearest vial) SC every 12 hours until completion of apheresis. Peripheral blood CD34+ counts will be monitored at least 3 times a week starting day +3 of G-CSF administration. Apheresis will start when the peripheral blood CD34+ is > 15 cells/µl and will continue till the target CD34+ cell dose of > 6 x 106/kg is reached.

Patients mobilized with R-Hyper-CVAD will undergo chemo mobilization with modified R-HyperCVAD (standard). Twenty-four hours after completion of chemotherapy G-CSF will be administered at a dose of 6 mcg/kg (rounded off to the nearest vial size) SC every 12 hours until completion of apheresis. Upon recovery of counts (WBC > 4.0/mm3) peripheral blood stem cell count will be monitored at least 3 times a week. Apheresis will start when the peripheral blood CD34+ count is > 15 cells/µl and will continue till the target CD34+ cell dose of > 6 x 106/kg is collected. If patients fail to mobilize adequate numbers of peripheral blood stem cells by day 21 of starting chemotherapy, they will receive consolidation with 2CDA/Cytoxan/Rituxan.

Large volume leukapheresis (LVL)
A continuous-flow COBE spectra or Baxter Amicus Blood Cell Separator or equivalent will be used for stem cell collection using the mononuclear cell collection procedure setting. Anticoagulation will be with ACD-A. The total blood volume (TBV) will be calculated by the COBE spectra computer on the basis of the stem cell donor's sex, height and weight. The TBV processed per procedure is 3 times the patients TBV. Continuous IV infusion of CaCl2 solution is administered through the return line during the apheresis procedure. The amount of calcium to be replaced will be calculated as follows:

0.5mg CaCl2 x citrate flow rate x procedure time
The total amount of calcium required will be diluted in 500cc of 0.9% sodium chloride

The apheresis procedure will be repeated on a daily basis till the target stem cell dose is reached.

Quantification of stem cells (CD34+ cells)
CD34+ cells will be determined by the flow cytometry lab, the bone marrow transplant laboratory or the department of transfusion medicine according to standard MDACC procedure.

Cryopreservation of apheresis products
Apheresis products will be processed, and frozen at a controlled freezing rate according to the MDACC laboratory manual.

4.4 Supportive Care
During the course of the study, all enrolled patients should receive full supportive care including transfusions on blood and blood products, antibiotics, antiemetics, erythropoeitin, and filgrastim when appropriate.

4.5 Prohibited Concurrent Therapy
Other anti-cancer therapies including radiation are not permitted while subjects are receiving study drug during the treatment phase of the study.

5.0 Clinical Pharmacology

5.1 Bortezomib (VELCADE) for Injection

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) and it is registered in Europe for the treatment of multiple myeloma patients who have received at least one prior therapy.

By inhibiting a single molecular target, the proteasome, bortezomib affects multiple signaling pathways. The anti-neoplastic effect of bortezomib likely involves several distinct mechanisms, including inhibition of cell growth and survival pathways, induction of apoptosis, and inhibition of expression of genes that control cellular adhesion, migration and angiogenesis. Thus, the mechanisms by which bortezomib elicits its antitumor activity may vary among tumor types, and the extent to which each affected pathway is critical to the inhibition of tumor growth could also differ. Bortezomib has a novel pattern of cytotoxicity in National Cancer Institute (NCI) in vitro and in vivo assays (Adams et al., 1999). In addition, bortezomib has cytotoxic activity in a variety of xenograft tumor models, both as a single agent and in combination with chemotherapy and radiation (Steiner et al., 2001; Teicher et al., 1999; Cusack et al., 2001; LeBlanc et al., 2002; Pink et al., 2002). Notably, bortezomib induces apoptosis in cells that over express bcl-2, a genetic trait that confers unregulated growth and resistance to conventional chemotherapeutics (McConkey et al., 1999).

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

5.1.2 Nonclinical Pharmacology

Pharmacokinetic (PK) and pharmacodynamic studies were conducted in the rat and cynomolgus monkey. Upon intravenous (IV) bolus administration, bortezomib displays a rapid distribution phase (t½ <10 minutes) followed by a longer elimination phase (t½ 5–15 hours). Bortezomib has a large volume of distribution (range 5–50 L/kg). The plasma PK profile is well described by a 2-compartment model.

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

5.1.3 Nonclinical Toxicity

Single-dose IV toxicity studies were conducted with bortezomib in the mouse, rat, dog, and monkey to establish the single-dose maximum tolerated dose (MTD). The MTDs were 0.25 mg/kg (1.5 mg/m2) and 0.067 mg/kg (0.8 mg/m2) in the 2 most sensitive species, rat and monkey, respectively.

Repeat-dose multi-cycle toxicity studies of 3 and 6 months in the rat and 9 months in the monkey, each with 8-week recovery periods, were conducted to characterize the chronic toxicity of bortezomib when administered by the clinical route and regimen of administration. The MTD in the 6-month rat study was 0.10 mg/kg (0.6 mg/m2) and the key target organs were the gastrointestinal (GI) tract, hematopoietic and lymphoid systems. The MTD in the 9-month monkey study was 0.05 mg/kg (0.6 mg/m2) and the key target organs were the GI tract, hematopoietic and lymphoid systems, peripheral nervous system, and kidney. Full or partial reversibility was observed for each of the toxicities described to date.

In general, the nature of the toxicity of bortezomib is similar across species, and target organs of toxicity in animals have been largely predictive of human toxicity. The toxicity of bortezomib in animals is characterized by a steep dose-response with mortality seen at dosages above the MTD. The cause of death at acutely lethal dosages is considered to be related to indirect cardiovascular (CV) effects of hypotension and vascular changes with secondary

bradycardia and the cause of death in long-term studies has been attributed to GI or hematologic toxicity. The pharmacologic effects of bortezomib on the CV system have been extensively characterized and have demonstrated that indirect effects on CV function occur only at acutely lethal dosages and are abrogated by routine supportive care.
Additional detailed information regarding the nonclinical pharmacology and toxicology of bortezomib may be found in the 2005 Investigator's Brochure

5.1.4 Clinical Pharmacokinetics and Pharmacodynamics

The clinical pharmacology characterization of bortezomib has been determined from phase 1 studies in subjects with solid tumors and hematological malignancies, and confirmed in phase 2 studies in subjects with multiple myeloma.
In solid tumor subjects, the mean terminal elimination half life of bortezomib was 9.06 hours. The mean area under the curve (AUC)(0-24) after the first dose (1.3 mg/m^2) of bortezomib was 48.2 hr*ng/mL. The average clearance of bortezomib following a single 1.3 mg/m2 dose was 49.0 L/hr. However, the AUC increased to 81.0 hr*ng/mL after the third dose in the first cycle as a result of a reduction in systemic clearance to 28.2 L/hr with a consequent increase in elimination half-life to 54.0 hours. Clinical experience has shown that the change in clearance does not result in overt toxicity from accumulation in this multidose regimen in humans.
The overall disposition of bortezomib is consistent with a 2-compartment PK model, although the existence of a third compartment cannot be excluded at this time due to the lack of supportive steady-state PK data in humans.
In subjects with advanced malignancies, the maximum pharmacodynamic effect (inhibition of 20S activity) occurred within 1-hour post dose. At the therapeutic dose of 1.3 mg/m^2 in subjects with multiple myeloma, the mean proteasome inhibition at 1-hour post dose was approximately 61%.
The time course of proteasome inhibition in subjects is characterized by maximum inhibition observed within the first hour after administration, followed by partial recovery of proteasome activity over the next 6 to 24 hours to within 50% of the pretreatment activity. On the Day 1, 4, 8, and 11 schedule, variable (10%–30%) levels of proteasome inhibition have been observed at next scheduled dosing. In theory, this advantage allows cells to recover proteasome activity for normal cellular housekeeping functions between doses.
The relationship between bortezomib plasma concentrations and proteasome inhibition can be described by a maximum effect (Emax) model. The Emax curve is initially very steep, with small changes in plasma bortezomib concentration over the range of 0.5 to 2.0 ng/mL relating to large increases in the percent inhibition (0–60%). After that, a plateau occurs where marginal increases of proteasome inhibition are observed in spite of large changes in plasma bortezomib concentrations.

5.1.5 Clinical Experience

It is estimated that as of October 31, 2005, more than 32,000 patients have been treated with bortezomib, including patients treated through Millennium-sponsored clinical trials, Investigator-Initiated Studies, the US NCI Cancer Therapy Evaluation Program (CTEP), and with commercially available drug. bortezomib has been commercially available since 13 May 2003.
The overall goal of the Millennium phase 1 program was to determine the MTD and dose-limiting toxicity (DLT) of bortezomib in a number of therapeutic settings involving subjects with various advanced malignancies. In a Phase I trial in patients with refractory hematologic malignancies, the MTD for a twice weekly for 4 weeks of a 42 day cycle was 1.04 mg/m^2/dose, with DLTs of thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise (Orlowski et al., 2002). The toxicity was greatest during the third and fourth weeks of therapy. In the 3-week schedule of bortezomib monotherapy (4 doses, given on Days 1, 4, 8, and 11 of a 21-day treatment cycle), the DLT occurred at 1.56 mg/m^2/dose (3 subjects with Grade 3 diarrhea and 1 with peripheral sensory neuropathy). Therefore, the MTD at this schedule was 1.3 mg/m^2/dose. In a 35-day treatment cycle with 4 weekly doses of bortezomib monotherapy, the MTD was 1.6 mg/m^2/dose and DLT included hypotension, tachycardia, diarrhea, and syncope.
In phase 1 clinical studies, anti-tumor activity was reported in subjects with NHL, multiple myeloma, Waldenström's Macroglobulinemia, squamous cell carcinoma of the nasopharynx, bronchoalveolar carcinoma of the lung, renal cell carcinoma, and prostate cancer.
The safety and efficacy of bortezomib in subjects with multiple myeloma were investigated in two phase 2 clinical studies, studies M34100-024 (subjects with first relapse) and M34100-025 (subjects with second or greater relapse and refractory to their last prior therapy). In M34100-025, 202 heavily pre-treated subjects with refractory multiple

myeloma after at least 2 previous treatments received bortezomib, 1.3 mg/m2 on Days 1, 4, 8, and 11 of a 21-day treatment cycle. The European Group for Blood and Marrow Transplant (EBMT) response criteria, as described by Blade (Blade et al., 1998) were utilized to determine disease response. CRs were observed in 4% of subjects, with an additional 6% of patients meeting all criteria for CR but having a positive immunofixation test. PR or better was observed in 27% of subjects, and the overall response rate (CR, PR and minor response [MR] combined) was 35%. Seventy percent of subjects experienced stable disease or better.

The phase 3 study (M34101-039), also referred to as the APEX study, was designed to determine whether bortezomib provided benefit (time to progression [TTP], response rate, and survival) to patients with relapsed or refractory MM relative to treatment with high-dose dexamethasone. The study was also designed to determine the safety and tolerability of bortezomib relative to high-dose dexamethasone, and whether treatment with bortezomib was associated with superior clinical benefit and quality of life relative to high-dose dexamethasone. A total of 669 patients were enrolled and 663 patients received study drug (bortezomib: 331; dexamethasone: 332). Patients randomized to bortezomib received 1.3 mg/m^2 I.V. push twice weekly on days 1, 4, 8, and 11 of a 3-week cycle for up to eight treatment cycles as induction therapy, followed by 1.3 mg/m^2 bortezomib weekly on days 1, 8, 15, and 22 of a 5-week cycle for three cycles as maintenance therapy. Patients randomized to dexamethasone received oral dexamethasone 40 mg once daily on days 1 to 4, 9 to 12, and 17 to 20 of a 5-week cycle for up to four treatment cycles as induction therapy, followed by dexamethasone 40 mg once daily on days 1 to 4 followed of a 4-week cycle for five cycles as maintenance therapy. The European Group for Blood and Marrow Transplant (EBMT) response criteria, as described by Blade (Blade et al., 1998) were utilized to determine disease response. There was a 78% increase in TTP for the bortezomib arm. Median TTP was 6.2 months for the bortezomib arm and 3.5 months for the dexamethasone arm (*P*<.0001). CR (complete response) + PR (partial response) was 38% with bortezomib vs. 18% with dexamethasone (*P*.0001). CR was 6% with bortezomib vs. 1% with dexamethasone (*P*<.0001). The CR + nCR rate was 13% with bortezomib vs. 2% with dexamethasone. In patients who had received only one prior line of treatment (bortezomib: 132; dexamethasone: 119), CR + PR was 45% with bortezomib vs. 26% with dexamethasone (*P*=.0035). With a median 8.3 months of follow-up, overall survival was significantly longer (*P* =.0013) for patients on the bortezomib arm vs. patients on the dexamethasone arm. The probability of survival at one year was 80% for the bortezomib arm vs. 66% for the dexamethasone arm, which represented a 41% decreased relative risk of death in the first year with bortezomib (*P*=.0005). In patients who had received only one prior line of treatment, the probability of survival at one year was 89% for the bortezomib arm vs. 72% for the dexamethasone arm, which represented a 61% decreased relative risk of death in the first year with bortezomib (*P*=.0098). (Richardson et al., 2005)

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

5.1.6 Side Effects

The most common side effects of bortezomib (i.e., incidence 30%) observed in patients are weakness, fatigue, and general discomfort; gastrointestinal (GI) effects such as constipation, diarrhea, nausea, vomiting and anorexia, which may result in dehydration and/or weight loss; fever; peripheral neuropathy (including painful sensations or numbness and tingling in hands and feet that may not get better after discontinuation of bortezomib), This damage may affect muscle strength and may interfere with the activities of daily living. It may also cause thrombocytopenia that may increase the risk of bleeding, and anemia.

Very common side effects of bortezomib (i.e., incidence 10–29%) observed in patients are neutropenia that may increase the risk of infection; abdominal pain; dyspepsia; nasopharyngitis; arthralgias; myalgias; skin rash that can be erythematous, pruritic and display leukocytoclastic vasculitis at biopsy; rigors; hypotension; dizziness; fluid retention; pain in limbs and bones; paresthesia; dysesthesia; dyspnea; cough; epistaxis; headache; blurred vision; changed sense of taste; insomnia; anxiety; herpes zoster, and lower respiratory/lung infections including pneumonia.

Common side effects of bortezomib (i.e., incidence 1–9%) observed in patients are lymphopenia; pancytopenia; palpitations; tachycardia; bradycardia; atrial fibrillation; angina pectoris; acute onset of congestive heart failure including pulmonary edema (patients with risk factors for, or existing, heart disease should be closely monitored); pleural effusion; tinnitus; conjunctivitis; abdominal distension; oral and esophageal mucositis; oral candidiasis; upper and lower GI bleeding; bronchitis; sinusitis; urinary tract infection; gastroenteritis; sepsis; hyponatremia; hyperglycemia; hypoglycemia (Patients on oral antidiabetic agents may require close monitoring of their blood

sugar levels.); dehydration; orthostatic hypotension; syncope; convulsions; renal failure; hematuria; depression; confusion; increases in serum AST, ALT, GGT and alkaline phosphatase.

Uncommon side effects of bortezomib (i.e., incidence <1%) observed in patients are febrile neutropenia; atrial flutter; bradycardia; new onset of decreased left ventricular ejection fraction; cardiogenic shock; hearing impairment; ileus paralytic/small bowel obstruction; upper gastrointestinal hemorrhage; oral mucosal petechiae; liver injury including abnormal liver function tests, hyperbilirubinemia, hepatitis, and liver failure (reported in patients receiving multiple concomitant medications and with serious underlying medical conditions); drug hypersensitivity; injection site reaction; aspergillosis; pulmonary embolism; hemoptysis; cerebral hemorrhage; and tumor lysis syndrome. It may also cause quadriplegia (a form of paralysis). Isolated cases of QT-interval prolongation have been reported, but are not thought to be related to bortezomib treatment.

Complications arising from these bortezomib toxicities may result in death.

The effect of bortezomib on reproduction and its safety in pregnancy are unknown. Laboratory tests show that bortezomib may damage DNA therefore it is possible that bortezomib may cause infertility in men and women.

Further details on the potential risks of bortezomib may be found in the 2005 Investigator Brochure.

5.1.7 Preparation, Handling and Storage

Vials containing lyophilized bortezomib for injection should be stored according to the label requirements. The drug should be stored at USP Controlled Room Temperature which is 25°C(77°F); excursions permitted from 15 to 30°C (59 to 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 will all cytotoxic drugs, cautions 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. I case of skin contact, wash the affected area immediately and thoroughly with soap and water for at least 15 minutes. If product come is contact with the eye, immediately flush eye with water for at least 15 minutes. Always contact a physician after any form of body contact. All materials that have been used for preparation should be disposed of according to standard practices. A log must be kept of all disposed materials.

Drug is available in sterile, single use vials containing 3.5mg of bortezomib. Each vial of bortezomib for injection should be reconstituted under a laminar flow biologic cabinet (hood) within eight hours before dosing with 3.5mL of normal (0.9%) saline, sodium chloride injection USP, so that the reconstituted solution contains bortezomib at a concentration of 1mg/mL. Prior to reconstitution the vials should remain in the cartons to protect them from light. Dissolution is completed in approximately 10 seconds. The reconstituted solution is clear and colorless, with a final pH of 5 to 6. Reconstituted bortezomib should be administered promptly and in no case more that 8 hours after reconstitution. All materials that have been used for preparation should be disposed of according to standard practices. A log must be kept of all disposed materials.

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

5.1.8 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. The pharmacist will prepare the drug under aseptic conditions. The amount (in mg) of drug to be administered will be determined based on body surface area. Body surface area is to be calculated based on body weight using a standard nomogram (square root of (weight(kilograms) x height (centimeters)/3600). (see Appendix J) The dose should be calculated on Day 1 of each cycle; the dose administered should remain the same throughout the cycle but should be recalculated at the start of the next cycle. If a patient experiences a notable change in weight (e.g. loss or gain of 8 lbs or 3.6kg) within a cycle, as determined by an unscheduled weight assessment, then the patient's dose should be recalculated at that time. The appropriate amount of bortezomib will be drawn from the injection vial and administered as an intravenous (IV) push over 3 to 5 seconds followed by a standard saline flush or through a running IV line. Vials are for single use administration.

5.1.9 Dose Modification and Delay

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

5.1.9.2 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 (CTC), Version3.0 (Appendix B)

5.1.9.3 All previously established or new toxicities observed any time, with the exception of neuropathic pain and peripheral sensory neuropathy, are to be managed as follows:

For Grade 4 hematologic toxicity and/or grade $\geq$ 3 non-hematologic toxicity, bortezomib will be held for up to 2 weeks, until hematologic toxicity returns to grade 3 or better, and until non-hematologic toxicities return to grade 2 or better. Bortezomib will then be restarted at the next lowest dose level (dose level –1, 1.3 mg/m^2), (dose level –2, 1.0 mg/m^2). Dose interruption or study discontinuation is **not** required for lymphopenia of any grade.

Dose modifications for Bortezomib

1	1.6 mg/m^2
-1	1.3 mg/m^2
-2	1.0 mg/m^2
-3	0.7 mg/m^2

5.1.9.4 Neuropathic Pain and Peripheral Sensory Neuropathy

Peripheral Sensory Neuropathy

Recommended Dose Modification for bortezomib-related Neuropathic Pain and/or Peripheral Sensory Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms	**Modification of Dose and Regimen**
Grade 1 (paresthesias and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce bortezomib by one dose level*
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Hold * bortezomib therapy until toxicity resolves. When toxicity resolves, reinitiate with a reduction by two dose levels and change treatment schedule to once per week*
Grade 4 (Permanent sensory loss that interferes with function)	Discontinue bortezomib.

Grading based on NCI Common Terminology Criteria for Adverse Events CTCAE v3.0
NCI Common Toxicity Criteria website - http://ctep.info.nih.gov/reporting/ctc.html

*Key:

Reduce by one dose level:	Bortezomib dose reduction from 1.6 to 1.3, 1.3 to 1.0, or 1.0 to 0.7 mg/m^2/dose.
Reduce by two dose levels:	Bortezomib dose reduction from 1.6 to 1.0, 1.3 or 1.0 to 0.7 mg/m^2/dose.
Hold:	Interrupt Bortezomib for up to 2 weeks until the toxicity returns to Grade 1 or better.

The neurotoxicity-directed questionnaire (Appendix F) is a useful tool for determining the presence and intensity of neuropathic pain and/or peripheral neuropathy from the patient's perspective. Neuropathic symptoms are more prominent than abnormalities on the clinical examination. After the patient completes the neurotoxicity-directed questionnaire, the questionnaire should be reviewed to assist with the evaluation of the onset and intensity of peripheral neuropathy and other neurotoxicities that may possibly require intervention or dose modification.

5.2 Rituximab

5.2.1 Introduction

Rituximab is supplied as a sterile, colorless, preservative-free liquid concentrate for intravenous (IV) administration. Rituximab is supplied at a concentration of 10 mg/ml in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for IV administration in 9 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dehydrate, 0.7 mg/mL polysorbate 80, and sterile water for injection. The pH is adjusted to 6.5.

Rituximab is administered intravenously. To prevent infusion related or hypersensitivity events, **Rituximab is not to be administered as an intravenous push or bolus.**

Hypersensitivity reactions may occur. Premedication consisting of acetaminophen and diphenhydramine, should be given prior to each infusion. Since transient hypotension may occur during rituximab infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to rituximab infusion.

The infusion rate of the first infusion should be 50mg/hr. If hypersensitivity or infusion-related events do not occur, the infusion rate may be increased in 50mg/hour increments every 30 minutes to a maximum of 400mg/hour. With hypersensitivity events, the infusion should be slowed and continued at one-half the previous rate until symptoms improve. For subsequent infusions, rituximab can be given at 100 mg/hour and increased by 100mg/hour increments every 30 minutes to a maximum of 400mg/hour.

5.2.2 Adverse Reactions

Severe Infusion Reactions:
RITUXAN has caused severe infusion reactions. In some cases, these reactions were fatal. These severe reactions typically occurred during the first infusion with time to onset of 30 to 120 minutes. Signs and symptoms of severe infusion reactions may include hypotension, angioedema, hypoxia or bronchospasm, and may require interruption of RITUXAN administration. The most severe manifestations and sequelae include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. In the reported cases, the following factors were more frequently associated with fatal outcomes: female gender, pulmonary infiltrates, and chronic lymphocytic leukemia or mantle cell lymphoma.

Management of severe infusion reactions: The RITUXAN infusion should be interrupted for severe reactions and supportive care measures instituted as medically indicated (e.g., intravenous fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen). In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Patients requiring close monitoring during first and all subsequent infusions include those with pre-existing cardiac and pulmonary conditions, those with prior clinically significant cardiopulmonary adverse events and those with high numbers of circulating malignant cells ($\geq$ 25,000/mm^3) with or without evidence of high tumor burden.

Tumor Lysis Syndrome [TLS]: Rapid reduction in tumor volume followed by acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatasemia, have been reported within 12 to 24 hours after the first RITUXAN infusion. Rare instances of fatal outcome have been reported in the setting of TLS following treatment with RITUXAN. The risks of TLS appear to be greater in patients with high numbers of circulating malignant cells ($\geq$ 25,000/mm^3) or high tumor burden. Prophylaxis for TLS should be considered for patients at high risk. Correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care, including dialysis, should be initiated as indicated. Following complete resolution of the complications of TLS, RITUXAN has been tolerated when re-administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

Hepatitis B Reactivation with Related Fulminant Hepatitis: Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with RITUXAN. The majority of patients received RITUXAN in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of RITUXAN and approximately one month after the last dose.

Persons at high risk of HBV infection should be screened before initiation of RITUXAN. Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and for up to several months following RITUXAN therapy.

In patients who develop viral hepatitis, RITUXAN and any concomitant chemotherapy should be discontinued and appropriate treatment including antiviral therapy initiated. There are insufficient data regarding the safety of resuming RITUXAN therapy in patients who develop hepatitis subsequent to HBV reactivation.

Hypersensitivity Reactions: RITUXAN has been associated with hypersensitivity reactions (non-IgE-mediated reactions) which may respond to adjustments in the infusion rate and in medical management. Hypotension, bronchospasm, and angioedema have occurred in association with RITUXAN infusion (see Severe Infusion Reactions). RITUXAN infusion should be interrupted for severe hypersensitivity reactions and can be resumed at

a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Treatment of these symptoms with diphenhydramine and acetaminophen is recommended; additional treatment with bronchodilators or IV saline may be indicated. In most cases, patients who have experienced non-life-threatening hypersensitivity reactions have been able to complete the full course of therapy. Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines and corticosteroids, should be available for immediate use in the event of a reaction during administration.

Cardiovascular: Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of RITUXAN. Patients with pre-existing cardiac conditions including arrhythmias and angina have had recurrences of these events during RITUXAN therapy and should be monitored throughout the infusion and immediate post-infusion period.

Renal: RITUXAN administration has been associated with severe renal toxicity including acute renal failure requiring dialysis and in some cases, has led to a fatal outcome. Renal toxicity has occurred in patients with high numbers of circulating malignant cells (>25,000/mm^3) or high tumor burden who experience tumor lysis syndrome (see Tumor Lysis Syndrome) and in patients administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and RITUXAN is not an approved treatment regimen. If this combination is used in clinical trials *extreme caution* should be exercised; patients should be monitored closely for signs of renal failure. Discontinuation of RITUXAN should be considered for those with rising serum creatinine or oliguria.

Severe Mucocutaneous Reactions: Mucocutaneous reactions, some with fatal outcome, have been reported in patients treated with RITUXAN. These reports include paraneoplastic pemphigus (an uncommon disorder which is a manifestation of the patient's underlying malignancy),[16] Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of the reaction in the reported cases has varied from 1 to 13 weeks following RITUXAN exposure. Patients experiencing a severe mucocutaneous reaction should not receive any further infusions and seek prompt medical evaluation. Skin biopsy may help to distinguish among different mucocutaneous reactions and guide subsequent treatment. The safety of readministration of RITUXAN to patients with any of these mucocutaneous reactions has not been determined.

5.2.3 Instructions for Administration

Preparation for Administration: Use appropriate aseptic technique. Withdraw the necessary amount of RITUXAN and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

RITUXAN solutions for infusion may be stored at 2—8°C (36—46°F) for 24 hours. RITUXAN solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since RITUXAN solutions do not contain a preservative, diluted solutions should be stored refrigerated (2—8°C). No incompatibilities between RITUXAN and polyvinylchloride or polyethylene bags have been observed.

Administration: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.
Infusion and hypersensitivity reactions may occur. Premedication consisting of acetaminophen and diphenhydramine should be considered before each infusion of RITUXAN. Premedication may attenuate infusion reactions. Since transient hypotension may occur during RITUXAN infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to RITUXAN infusion.

First Infusion: The RITUXAN solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. RITUXAN should not be mixed or diluted with other drugs. If hypersensitivity or infusion reactions do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If a hypersensitivity (non-IgE-mediated) or an infusion reaction develops, the infusion should be temporarily slowed or interrupted. The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

Subsequent Infusions: If the patient tolerated the first infusion well, subsequent RITUXAN infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr as tolerated. If the patient did not tolerate the first infusion well, follow the guidelines under First Infusion.

Stability and Storage: RITUXAN vials are stable at 2—8°C (36—46°F). Do not use beyond expiration date stamped on carton. RITUXAN vials should be protected from direct sunlight. Do not freeze or shake.

5.3 Cyclophosphamide

Cyclophosphamide is known to cause marked, but reversible myelosuppression at high doses. The syndrome of inappropriate secretion of anti-diuretic hormone (SIADH) has also been described in patients receiving doses in excess of $2gm/m^2$. The most severe extramedullary toxicities seen have been acute onset cardiomyopathy (seen at doses exceeding $6gm/m^2$), and hemorrhagic cystitis. The plasma half-life is 4-6.5 hours, and 60% of an intravenous dose is excreted in the urine within 24 hours. Nausea, vomiting, diarrhea and hair loss may be noted.

5.4 Cladribine (2CdA)

2 CdA is a deoxyadenosine analog resistant to deamination by adenine deaminase. 2CdA is phosphorylated to Chloro ATP which is incorporated into the cell's DNA, producing single strand breaks and triggering the activation of the poly (ADP) ribosylation reaction associated with DNA repair. The metabolism of 2 CdA is not well characterized. There does appear to be some renal clearance via a cationic carrier system, but there are no current recommendations regarding dose adjustments for patients with renal or hepatic dysfunction. Treatment with 2CdA is associated with myelosuppression, occasional nausea, and fever. At significantly higher doses than those proposed in our study, neurotoxicity and nephrotoxicity have been noted. Suppression of CD4 cell counts has also been documented, and this may predispose our patients to opportunistic infections. Skin rash may occasionally be seen.

5.5 Vincristine

Vincristine belongs to the class of vinca alkaloids. It is supplied as a 1 mg/1 ml solution for injection. It can be mixed in 50 mL D5W and infused over 15 minutes. Once vincristine is dispensed in other than the original container, it must be packaged in the provided overwrap bearing the following statement: "DO NOT REMOVE COVERING UNTIL MOMENT OF INJECTION. FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY." It is a vesicant. Accordingly, precautions must be taken to avoid extravasation. Common side effects include alopecia, constipation, diplopia, nausea and vomiting. Myelosuppression, neuropathy and SIADH are also seen. In patients having a direct serum bilirubin value above 3 mg/100 mL, the dose of vincristine must be reduced by 50%. For patients with an SGOT of 60-180, a 50% dose reduction is necessary and for an SGOT > 180, the vincristine dose should be omitted entirely. No specific guidelines are available for dose adjustment in the setting of impaired renal function.

5.6 Doxorubicin

Doxorubicin is an anthracycline. It is a vesicant. Accordingly extravasation must be avoided. Lifetime cumulative doses of doxorubicin should be limited to 450-550 mg/m(2) to decrease cardiac toxicity, and total dose should take into account previous treatment with other anthracyclines/potentially cardiotoxic agents. In the setting of hepatic impairment, a 50% dose reduction should be undertaken for a serum bilirubin of 1.2-3 mg/dL, and a 75% dose reduction should be undertaken for a serum bilirubin of 3.1-5 mg/dL. Its most common side effects are alopecia, nausea and vomiting. However, myelosuppression, arrhythmias and congestive heart failure are also seen.

5.7 Dexamethasone

Dexamethasone is a corticosteroid. Its most serious associated side effects are adrenocortical insufficiency, glaucoma, and hyperglycemia. Other, more common side effects include cataracts, Cushing's syndrome, euphoria/depression, GI distress, growth depression, hypertension, impaired skin healing, increased risk of infection, osteoporosis, skin atrophy, reactivation of tuberculosis, and fluid retention.

6.0 Pretreatment evaluation

6.1 Within 28 days of study entry, the following will be performed (see appendix E for schedule of events):

6.1.1 History and physical examination will be performed emphasizing the documentation of all measurable disease.

6.1.2 Laboratory studies, including a complete blood count with differential and platelet count, BUN, creatinine, calcium, AST, ALT, total bilirubin, alkaline phosphatase, albumin, lactate dehydrogenase, glucose, uric acid, serum protein electrophoresis and immunofixation, Viral Hepatitis panel (Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis B core antibody, Hepatitis C antibody), serum viscosity, immunoglobulin quantitation, β_2-microglobulin, cryocrit, and cold agglutinins will be assessed on blood collected and transported at body temperature. A serum or urine β-HCG will be performed in pre-menopausal women. A 24 hour urine specimen will also be obtained to determine protein excretion and to perform electrophoresis and immunofixation.

6.1.3 12-lead Electrocardiogram

6.1.4 MUGA or ECHO

6.1.5 Radiographic studies: a chest x-ray (If CXR is positive then order CT of the Chest) and CT scan of the abdomen and pelvis will be performed.

6.1.6 Bone marrow aspirates and biopsy will be assessed for lymphocyte count, and monoclonal lymphocyte percentage, as well as for CD20 expression (percentage and intensity) on clonal vs. non-clonal lymphocytes.

6.1.7 Neurotoxicity questionnaire (see Appendix F)

7.0 Evaluation During Study

7.1 Prior to each dose of bortezomib, complete blood counts, toxicity assessment, and vital signs will be performed.

7.2 Within 1 week prior to the start of each cycle of chemotherapy and every 3 months thereafter until partial response is achieved, physical exam, vital signs, height/weight, toxicity assessment, neurotoxicity questionnaire, CBC/diff/plts, chemistry, serum protein electrophoresis, serum immunofixation (if CR is suspected), urine protein electrophoresis and immunofixation (if initially positive), immunoglobulins, and B2-microglobulin will be performed.

7.3 If initial CT scans show lesions consistent with Waldenstrom's macroglobulinemia, they will be repeated after 2 cycles of bortezomib and Rituximab, and every 6 months thereafter until partial response is achieved.

7.4 In patients who have achieved a partial or complete response at the end of all planned therapy, follow up evaluations will be performed at least every 6 months for the first 36 months (from the end of therapy), and then at least annually until re-treatment (in the setting of relapsed disease) is necessary. These evaluations will include a physical exam, vital signs, CBC(diff/plts), BUN, creatinine, AST, ALT, total bilirubin, lactate dehydrogenase, alkaline phosphatase, glucose, and uric acid, serum protein electrophoresis, urine protein electrophoresis (only if initially positive), immunoglobulins, B2-microglobulin, CXR, CT chest/abdomen/pelvis (only if initially positive).

8.0 Criteria for Response

Partial response (PR) is defined as at least $\geq$ 50 % reduction of serum monoclonal IgM concentration determined by protein electrophoresis, $\geq$ 50% decrease in adenopathy / organomegaly on physical examination or on CT scan, and no new symptoms or signs of active disease.

In patients with Waldenstrom's macroglobulinemia, reduction in lymph node size or splenomegaly may lag behind the reduction in serum M-protein, resulting in an underestimation of response. In addition, paradoxic increases in serum IgM levels lasting for many weeks have been reported in patients with WM receiving rituximab therapy. Further, delayed responses may be seen particularly after purine analogue or monoclonal antibody therapy. Accordingly, patients will be followed for $\leq$ 6 months after receiving bortezomib/rituximab or rituximab-modified hyper-CVAD to be considered unresponsive to therapy in accordance with the guidelines of the Consensus Panel of the Third International Workshop on Waldenstrom's Macroglobulinemia. (Kimby et al., 2006).

If a patient has neither $\geq$ 50 % reduction of serum monoclonal IgM concentration determined by protein electrophoresis nor $\geq$ 50% decrease in adenopathy / organomegaly after 3 cycles of bortezomib and rituximab, we will wait up to 6 months before declaring unresponsiveness to therapy.

If evidence of significant amyloid deposition is found on lymph node biopsy, protein criteria alone will be used to determine response to therapy as lymph node size may not decrease significantly if the bulk of the lymphadenopathy is due to amyloid.

Complete response (CR) is defined as a disappearance of serum and urine monoclonal protein determined by immunofixation, absence of malignant cells in bone marrow determined by histologic evaluation, resolution of adenopathy/organomegaly (confirmed by somputed tomography [CT]scan), and no signs or symptoms attributable to WM. Reconfirmation of the CR status is required $\geq$ 6 weeks later with a second immunofixation.

9.0 Criteria for Disease Relapse/Progression

9.1 Reappearance of an IgM peak that had completely disappeared on immunofixation

9.2 25% increase from the lowest level of monoclonal IgM in those patients who did not achieve completely disappearance of IgM peak on immunofixation

9.3 Reappearance of lymphadenopathy, splenomegaly or monoclonal lymphocytosis for patients who achieved a complete remission.

9.4 25% increase in size of lymphadenopathy, splenomegaly or monoclonal lymphocytosis for those patients who did not achieve a complete response.

10.0 Criteria for Removal from the Study

The following events are considered sufficient reasons for discontinuing a subject from the study regimen:

10.1 Failure to achieve a PR or CR following 3 cycles of Bortezomib-Rituximab and 2 cycles of modified R-Hyper-CVAD.

10.2 Disease relapse following all planned therapy that requires re-treatment in the view of the investigator.

10.2 Adverse event(s) occur that in the judgement of the investigator, may cause severe or permanent harm or which rule out continuation of study drug.

10.3 A treatment cycle delay or bortezomib interruption of > 2 weeks, or missing 3 of 4 bortezomib doses within a treatment cycle because of toxicity

10.4 Intercurrent illness or change in patient's condition that in the judgement of the principal investigator deems further treatment to be unacceptable.

10.5 Subject withdraws consent

10.6 Subject is lost to follow-up

10.7 Death

10.8 Non-compliance to study visit schedule.

10.9 Suspected pregnancy.

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for a patient's withdrawal from the study is to be recorded in the source documents.

11.0 End of Study Evaluation

11.1 Physical examination will be performed emphasizing the documentation of all measurable disease, vital signs, height and weight, and toxicity assessment, and neurotoxicity questionnaire.

11.2 Laboratory studies: complete blood count with differential and platelet count, BUN, creatinine, calcium, ALT, AST, total bilirubin, lactate dehydrogenase, alkaline phosphatase, glucose, uric acid, serum protein electrophoresis, immunoglobulin quantitation, β_2-microglobulin, cryocrit, and cold agglutinins (only if initially positive). A 24 hour urine specimen will also be obtained to determine protein excretion and to perform electrophoresis and immunofixation.

11.3 Radiographic studies: If initial CXR, CT scan of the Abdomen or Pelvis showed lesions consistent with Waldenstrom's macroglobulinemia, the imaging study that showed these lesions at the start of therapy will be repeated.

12.0 Statistical Considerations

This is a single-arm, phase II study for previously untreated patients with Waldenstrom's macroglobulinemia. Primary treatment will be induction therapy with Bortezomib-Rituximab. Patients who do not achieve a partial response or better after 3 cycles of Bortezomib-Rituximab, will receive two cycles of R-Hyper-CVAD to achieve a minimal disease state. If partial or complete response is seen with Bortezomib-Rituximab or with R-Hyper-CVAD, patients will undergo stem cell collection, as per protocol of the Department of Blood and Marrow Transplantation. The primary outcomes will be overall response rate to Bortezomib-Rituximab, and autologous stem cell collection rate after induction therapy with Bortezomib-Rituximab, or failing that, with R-Hyper-CVAD. The method of Thall, Simon, Estey (1995, 1996) as extended by Thall and Sung (1998) will be used for trial monitoring.[16,17,18] A maximum of 38 patients will be recruited. This sample size ensures that, if the trial is not terminated early, a posterior 90% credibility interval for overall response rate to Bortezomib-Rituximab will have width at most 0.25, under the assumption of a 40% of overall response rate. Patients are expected to be accrued to the trial at a rate of 1 to 2 patients per month. Coding the four elementary events (OR, SCC) = (No, No), (Yes, No), (No, Yes), (Yes, Yes) as (1, 2, 3, 4), respectively, the historical probability vector of these events is assumed to follow a Dirichlet distribution with parameters (6.3,2.7,0.7,0.3), and the corresponding vector for the experimental treatment is assumed to follow a Dirichlet distribution with parameters (2.52,1.08,0.28,0.12), which has the same mean elementary event probabilities. The assumed mean probabilities for OR and SCC are 0.30 and 0.10, respectively. Denoting the historical probabilities of overall response rate and stem cell collection rate by {p(OR,H) , p(SCC,H)}, the following decision criteria will be applied:

1) Let E correspond to the experimental treatment, stop if
   $\text{Prob}\{p(OR,H) + \delta\ OR < p(OR,E) \mid \text{data}\} < 0.05$, where δ OR =0.10
2) Stop if $\text{Prob}\{p(SCC,H) + \delta\ SCC < p(SCC,E) \mid \text{data}\} < 0.07$, where δ SCC =0.10

Patients will be monitored according to the following stopping boundaries for overall response to Bortezomib-Rituximab.

Number of Patients Evaluated	Recommend Stopping if OR Observed
10	0
20	2
30	4

At the same time, patients will be monitored according to the following stopping boundaries for autologous stem cell collection.

Among These Number of Patients	Recommend Stopping if SCC Observed
10	0
20	1
30	2

The operating characteristics are summarized in the following table.

True SCC rate	True OR rate	Prob(stop the trial early)
0.05	0.20	0.915
	0.30	0.879
	0.40	0.873
	0.50	0.873
	0.60	0.872
0.20	0.20	0.434
	0.30	0.209
	0.40	0.155
	0.50	0.157
	0.60	0.146
0.30	0.20	0.352
	0.30	0.095
	0.40	0.041
	0.50	0.035
	0.60	0.035
0.40	0.20	0.336
	0.30	0.070
	0.40	0.017
	0.50	0.007
	0.60	0.007

Analysis Plan

Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. The chi-square test or Fisher's exact test will be applied to assess the association between two categorical variables. Logistic regression will be utilized to assess the effect of patient prognostic factors, such as age, gender, disease stage, on the response rate and the autologous stem cell collection rate to treatment with bortezomib and rituximab. The overall response (including complete response and partial response) rate to treatment with bortezomib and rituximab followed by cladribine, cyclophosphamide and rituximab will be estimated with the 95% confidence interval. The time-to-event distributions, such as overall survival, progression free survival, and time to re-treatment, will be estimated using the method of Kaplan and Meier. Length of survival is defined as time

from the start date of the study to the date of patient death or last follow-up. Time to progression is defined as the length of time from the start date of the study to patient progression or last follow-up date. Time to re-treatment is defined as the length of time from the start of the study to the date the patient again requires treatment for their Waldenstrom's macroglobulinemia, or else the last follow-up date. Comparison of time-to-event distributions between important subgroups will be made using the log-rank test. Cox proportional hazard regression will be employed for multivariate analysis on time-to-event data including age, gender, disease stage, treatment information, etc. as the covariates. Toxicity data will be summarized using frequency tables. The types and severity of toxicity will be evaluated.

13.0 Adverse Events

13.1 Definitions

13.1.1 Adverse Event Definition

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

13.1.2 Serious Adverse Event Definition

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

· Results in **death**.

· Is **life-threatening**. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.

· Requires inpatient **hospitalization or prolongation of existing hospitalization**. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (eg, surgery performed earlier than planned).

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

· Is a congenital anomaly/birth defect.

· Is an **important medical event**. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

13.2 Procedures for AE and SAE Reporting

Investigator-sponsor must report all serious adverse event (SAE) regardless of relationship with any study drug or expectedness to Millennium as soon as possible, but no later than 5 calendar days of the investigator-sponsor's

observation or awareness of the event. All sub-investigators must report all SAEs to the investigator-sponsor so that the investigator-sponsor can meet his/her foregoing reporting obligations to Millennium. Investigator-sponsor must also provide Millennium with a copy of all communications related to the Study or Drug with the applicable regulatory authority, including, but not limited to, telephone conversation logs, as soon as possible but no later than 5 calendar days of that communication. Millennium's Product Safety Department will send to the investigator-sponsor a monthly listing of the SAE reports received for SAE verification. Investigator-sponsor will be responsible for forwarding such reports to any sub-investigator(s) and providing any follow-up safety information requested by Millennium.

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

For both serious and non-serious adverse events, the investigator or sub-investigator must determine both the intensity of the event and the relationship of the event to drug administration.

Relationship to drug administration will be determined by the investigator or sub-investigator responding yes or no to the question: Is there a reasonable possibility that the adverse event is associated with the drug?

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

13.3 Monitoring of Adverse Events and Period of Observation

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

13.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects she is pregnant while participating in this study, she must inform her treating physician immediately and permanently discontinue drug therapy. Millennium must also be contacted immediately by faxing a completed Pregnancy Form to either Millennium Product Safety for North America or PRA Safety Management Services for rest of world. The pregnancy must be followed through outcome (i.e. delivery, still birth, miscarriage).

14.0 Administrative Requirements

14.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

14.2 Ethical Considerations

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

14.3 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

14.4 Patient Confidentiality

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

14.5 Protocol Compliance

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

14.6 On-site Audits

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

14.7 Drug Accountability

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

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

14.8 Premature Closure of the Study

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

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug

Should the study be closed prematurely, all study materials must be returned to Millennium.

14.9 Record Retention

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

15.0 References

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