



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 05-103 A(14)

**A Phase II Study of the Novel Proteasome Inhibitor Bortezomib in Combination with
Rituximab, Cyclophosphamide and Prednisone in Patients with Relapsed/Refractory
Indolent B-cell Lymphoproliferative Disorders and Mantle Cell Lymphoma (MCL)¹
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL**

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¹Formerly: A Phase I/II Study of the Novel Proteasome Inhibitor Bortezomib in Combination with Rituximab, Cyclophosphamide and Prednisone in Patients with Relapsed/Refractory Indolent B-cell Lymphoproliferative Disorders and Mantle Cell Lymphoma (MCL)



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

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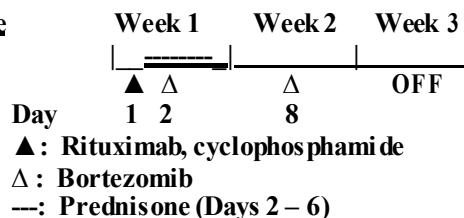
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1.0 SCHEMA

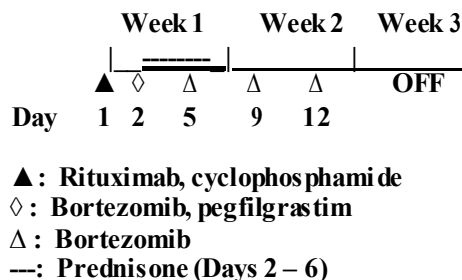
ELIGIBLE PATIENTS (Phase II): Relapsed/Refractory (no more than 3 prior cytotoxic therapies): Indolent B-cell Lymphoproliferative Disorders and Mantle Cell Lymphoma (MCL)

Weekly Dosing Schedule



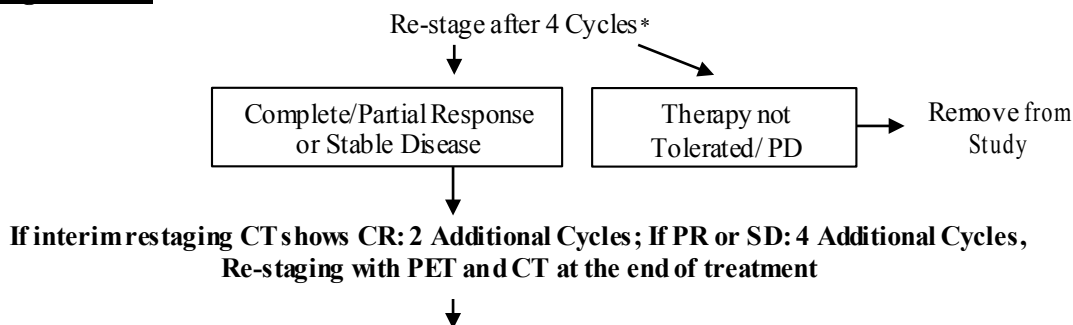
Day 1: Cyclophosphamide 1000 mg/m² IVPB+ Rituximab 375 mg/m² IVPB
 Days 2 and 8: Bortezomib 1.8 mg/m² SC
 Days 2 through 6: Prednisone 100 mg PO

Twice-weekly Dosing Schedule



Day 1: Cyclophosphamide 1000 mg/m² IVPB + Rituximab 375 mg/m² IVPB
 Days 2, 5, 9, 12: Bortezomib 1.3 mg/m² SC
 Days 2 through 6: Prednisone 100 mg PO
 Day 2: Pegfilgrastim, 6 mg SC

Both Dosing Schedules



First two years after completion of treatment: evaluate with CT and visit, no less than every 6 months. Beginning two years post completion of treatment: evaluate with CT and visit, no less than every 12 months.

*One cycle is defined as 21 days. Up to a 2 week delay will be allowed for recovery from any toxicity, and dose reductions will be allowed to the next lower dose level of cyclophosphamide or bortezomib at the discretion of the treating MD.



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2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary Objectives

To determine the frequency and duration of complete and partial responses in patients treated with bortezomib + R-CP (R-CBorP) administered every 21 days for a total of 6-8 cycles. Patients will be treated on two different treatment schedules in a randomized phase II design.

2.2 Secondary Objectives

To evaluate the progression-free survival, event-free survival and overall survival of patients treated with R-CBorP on two different treatment schedules.

To further evaluate the toxicity profile of these two dosing schedules.

3.0 BACKGROUND AND RATIONALE

3.1 Bortezomib for Injection

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, Palombella 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 (Teicher, Ara et al. 1999; Cusack, Liu et al. 2001; Steiner, Neumeier et al. 2001; LeBlanc, Catley et al. 2002; Pink, Pien 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, Pettaway et al. 1999).



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

Clinical Pharmacokinetics and Pharmacodynamics

The clinical pharmacology characterization of bortezomib has been determined from phase 1 studies in subjects with solid tumors and hematological malignancies, and confirmed in phase 2 studies in subjects with multiple myeloma.

Bortezomib demonstrates multi-compartmental pharmacokinetics. Following intravenous administration of 1.0 mg/m² and 1.3 mg/m² dose, the mean first-dose maximum observed plasma concentrations of bortezomib were 57 and 112 ng/mL, respectively in 11 patients with multiple myeloma and creatinine clearance values >50 mL/min participating in a pharmacokinetics study. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1.0 mg/m² dose and 89 to 120 ng/mL for the 1.3 mg/m² dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours. Bortezomib is eliminated more rapidly following the first dose. Mean Total Body Clearances were 102 and 112 L/h following the first dose for doses of 1.0 mg/m² and 1.3 mg/m², respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1.0 and 1.3 mg/m², respectively. Clinical experience has shown that the change in clearance does not result in overt toxicity from accumulation in this multidose regimen in humans.

In subjects with advanced malignancies, the maximum pharmacodynamic effect (inhibition of 20S activity) occurred within 1-hour post dose. At the therapeutic dose of 1.3 mg/m² in subjects with multiple myeloma, the mean proteasome inhibition at 1-hour post dose was approximately 61%.

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

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

Clinical Experience

It is estimated that more than 100,000 patients have been treated with bortezomib, including patients treated through Millennium-sponsored clinical trials, Investigator-Initiated Studies,



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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/m²/dose, with DLTs of thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise (Orlowski, Stinchcombe 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/m²/dose (3 subjects with Grade 3 diarrhea and 1 with peripheral sensory neuropathy). Therefore, the MTD at this schedule was 1.3 mg/m²/dose. In a 35-day treatment cycle with 4 weekly doses of bortezomib monotherapy, the MTD was 1.6 mg/m²/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.

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

3.2 Biology of Proteasome Inhibition

The ubiquitin-proteasome pathway plays an essential role in the degradation of most short- and long-lived intracellular proteins in eukaryotic cells. At the heart of this degradative pathway is the 26S proteasome, an ATP dependent, multicatalytic protease. The 26S proteasome plays a vital role in degrading regulatory proteins that govern cell cycle, transcription factor activation, apoptosis and metastasis. Some of the targets of ubiquitin-proteasome mediated degradation include p53, p21, p27, NF- κ B, and Bcl-2. Preclinical observations suggest that inhibitors of the proteasome can act through multiple mechanisms to arrest tumor growth, induce apoptosis, prevent tumor spread and inhibit angiogenesis. Phase I trials have confirmed tolerability of the proteasome inhibitor bortezomib and have suggested possible clinical activity.

A number of key regulatory proteins are temporally degraded during the cell cycle by the ubiquitin-proteasome pathway, and the ordered degradation of these proteins is required for the cell to progress through the cell cycle and to undergo mitosis (King, Deshaies et al. 1996). One of the targets of ubiquitin-proteasome mediated degradation is the tumor suppressor p53, which acts as a negative regulator of cell growth. P53 is required for the transcription of a number of genes involved in cell cycle control and DNA synthesis and also plays an important function in apoptosis induced by cellular damage including ionizing radiation (Sherr 1996). Cyclins and the cyclin-dependent kinase inhibitors p21 and p27 Kip1 are another set of growth regulatory proteins that are regulated by proteasome-dependent proteolysis (King,



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Deshaies et al. 1996). Both p21 and p27 can induce cell cycle arrest by inhibiting the cyclin D-, E- and A-dependent kinases (Sherr 1996).

In addition, the ubiquitin-proteasome pathway is required for transcriptional regulation. Nuclear factor- κ B (NF- κ B) is a key transcription factor, whose activation is regulated by proteasome-mediated degradation of the inhibitor protein I κ B (Palombella, Rando et al. 1994; Read, Neish et al. 1995). Cell adhesion molecules (CAM) such as E-selectin, ICAM-1, and VCAM-1 are regulated by NF- κ B and are involved in tumor metastasis and angiogenesis *in vivo* (Zetter 1993). During metastasis, these molecules direct the adhesion and extravasation of tumor cells to and from the vasculature to distant tissue sites. As such, tumor cell metastasis will be limited by the down-regulation of NF- κ B dependent cell adhesion molecule expression. NF- κ B is also required in a number of cell types to maintain cell viability as an anti-apoptotic controlling factor (Beg and Baltimore 1996). Inhibiting NF- κ B activation by stabilizing the I κ B protein makes cells more sensitive to environmental stress and cytotoxic agents, ultimately leading to apoptosis.

Altered degradation of cell cycle control proteins can result in accelerated and uncontrolled cell division, and thereby promote cancer growth and spread. Interfering with the temporal degradation of these regulatory molecules by blocking proteasome function can lead to the inhibition of cell growth and the initiation of programmed cell death, thereby arresting malignant cell growth. In addition, inhibition of proteasome-mediated degradation of I κ B will inhibit NF- κ B activation and should make tumor cells more sensitive to chemotherapeutic agents that activate NF- κ B.

Collectively, these observations suggest that inhibitors of the proteasome can act through multiple mechanisms to arrest tumor growth, tumor spread and angiogenesis. The combination of these mechanisms offers a novel approach to treating human malignancies. Consistent with this hypothesis, tumor cells that bear multiple genetic defects, including impaired DNA repair mechanisms and aberrant cell cycle checkpoint controls, are sensitive to the growth inhibitory actions of proteasome inhibitors both *in vitro* and *in vivo*.

Bortezomib is a dipeptidyl boronic acid inhibitor with high specificity for the proteasome, which is being developed by Millennium, Inc. to treat human malignancies. It is the first member of this new class of anti-tumor agents to come to human trials. Phase I clinical studies have demonstrated that bortezomib is a well-tolerated agent with minimal adverse effects. In addition, it has been shown that bortezomib is capable of producing a dose related effect on proteasome inhibition when analyzed one-hour post infusion. There is little inter-patient variability, with responses at the lowest doses studied to date (Papandreou, Daliani et al. 2001; Aghajanian, Soignet et al. 2002).

3.3 Study Disease and Rationale

Non-Hodgkin's lymphomas (NHL) are presently the fifth most common cause of cancer related death in the United States. Collectively, they account for approximately 4 to 5% of all cancer-related deaths in Caucasian and Hispanic populations, and about 2% in African-



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American populations (Cunningham, Zalcberg et al. 1996). However, because NHL tends to afflict a younger population (the average age of all lymphoma patients is about 42 years), the years of life lost is greater than in most other malignancies. This ranks NHL fourth among all cancers with regard to their economic impact in the United States. In 1997, there were approximately 53,600 new cases of NHL, with over 23,800 deaths attributed to the disease (Cunningham, Zalcberg et al. 1996). Thus, the case-fatality rate for non-Hodgkin's lymphoma (ie. the number of deaths attributed to the disease expressed as a percentage of the incidence of the disease) is approximately 44%. As with most hematologic malignancies, there is a slight male predominance, with about 57% of all cases developing in males.

The indolent non-Hodgkin's lymphomas comprise approximately one-third of all NHLs. Indolent lymphoproliferative disorders (including chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), the follicular lymphomas (FL), marginal zone lymphomas (MZL), and lymphoplasmacytoid lymphoma (ie. Waldenstrom Macroglobulinemia (WM)), represent a class of diseases that are characterized by slow, progressive tumor growth that typically responds to alkylating agents. While complete and partial remissions can be obtained in most patients, over time, the disease becomes increasingly more refractory to chemotherapy, prompting the need for additional, non-cross-resistant treatment approaches.

A review of 204 patients treated over a 19 year time span has helped to characterize the natural history of indolent lymphomas (Johnson, Rohatiner et al. 1995). With a median follow-up duration of 12.2

years, the median survival of this mostly conservatively treated group was 9.2 years. The study starkly illustrates the relapsing/recurring nature of the disease, with response rates and duration of response decreasing with subsequent relapses (see table below). Sixty five percent of patients in this study relapsed after initial treatment, with a total of 37 patients ultimately receiving a total of four or more courses of therapy.



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**Comparison of Response Rates, Response Durations and Survival Times After
Treatment of Consecutive Recurrences of Follicular Lymphoma**

Treatment	# Treated	RR (%)	Duration (years)	Survival (years)
First	204	88	2.6	9.2
Second	110	78	1.1	4.6
Third	63	76	1.1	3.5
Fourth	37	68	0.5	1.2

An important finding of this study was that the durations of first and second remission and subsequent survival were heavily influenced by the degree of response to treatment. Of the 77 patients who achieved CR with their first treatment, 5-year disease-free survival (DFS) was 54%, whereas 5-year DFS was about half of that (28%) for patients achieving only a PR. Similarly, median duration of response was 25 months for the 31 patients who achieved a CR after treatment for second relapse, but was only 9 months for those patients achieving PR. It is therefore important to identify new treatment combinations that not only increase response rates, but that have the potential to increase the quality of response.

3.4 Phase II Experience with Bortezomib in NHL

Our group has had a longstanding interest in the development of novel proteasome inhibitors dating back to our conduct of the phase I clinical trial of bortezomib in patients with hematologic and solid tumor malignancies (Aghajanian, Soignet et al. 2002). This and another phase I study (Orlowski, Stinchcombe et al. 2002) demonstrated not only tolerability of the agent, with important pharmacologic endpoints, but also revealed significant activity in patients with multiple myeloma, mantle cell lymphoma, and follicular lymphoma. These observations spawned a single-agent phase II study with bortezomib in patients with indolent lymphoproliferative disorders at MSKCC (protocol 01-049). Based on the promising activity of bortezomib in indolent lymphoma, we expanded this trial to a large, multicenter study. The current protocol seeks to exploit the marked single-agent activity of bortezomib in non-Hodgkin's lymphoma by integrating it into a standard conventional regimen for the treatment of these diseases.

The phase II study of single-agent bortezomib (IRB # 01-049) in patients with predominantly relapsed or refractory indolent non-Hodgkin's lymphoma (NHL) conducted by our group has recently been reported (O'Connor 2004; O'Connor 2005; O'Connor, Moskowitz et al. 2009). Bortezomib was administered at a dose of 1.5 mg/m² on a day 1, 4, 8 and 11 schedule every 21 days. The patients were heavily pre-treated with a median of 3 prior therapies (2 prior therapies in MCL patients). Overall the drug was very well tolerated, with most patients experiencing toxicities well known to be associated with the drug, including thrombocytopenia, sensory



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neuropathy, diarrhea, and asthenia. Among 18 assessable patients with FL, the overall response rate (ORR) was 50%, including 5 partial responses (PR) and 4 patients meeting criteria for complete remission (CR)/complete response unconfirmed (CRu). Of 8 assessable patients with marginal zone lymphoma (MZL), 3 achieved a PR, while only 1 of the 6 patients with SLL showed any response to therapy (PR) (O'Connor et al., Clinical Cancer Research 2009, in press). Among 36 assessable patients with MCL, the ORR was 50%, including 12PR and 6 CR/CRu (O'Connor, Moskowitz et al. 2009). Overall, the median progression free survival (PFS) for responding patients with MCL and all other non-MCL patients has been 7.8 and 12.3 months respectively. The median time to response is also significantly different among the different sub-groups, with MCL and FL lymphoma patients demonstrating a median time to response (TTR) of 5 and 11 weeks, respectively. This particular difference has potentially significant ramifications regarding how much therapy to give before one can adequately assess drug activity in follicular lymphoma.

Goy *et al.* at M.D. Anderson Cancer Center began a broader single-agent, single-institution study of bortezomib in patients with any B-cell neoplasm, regardless of their prior number of treatments (Goy, Younes et al. 2005). Otherwise, this and the MSKCC studies were similar in design. Of 60 registered patients, 33 had mantle cell lymphoma, 12 had diffuse large B-cell lymphoma, and the remainder had a variety of other subtypes, including small lymphocytic lymphoma, follicular lymphoma, Waldenstrom's Macroglobulinemia, and a transformed lymphoma. Overall, this population of patients was more heavily pretreated, with a median number of prior therapies of 3 in the MCL group and 4 in the other NHL patients. The overwhelming majority of patients had markedly elevated LDH and Beta-2-microglobulin prior to study enrollment. Of 29 assessable patients with mantle cell lymphoma, 12 (41%) achieved a major response, with 6 (20.5%) of them attaining a complete remission, and 6 (20.5%) attaining a partial remission. Overall, the duration of response was approximately 6 months. Among the patients with diffuse large B-cell lymphoma, only one of the 12 assessable patients achieved a partial remission, with the other patients demonstrating either stable or progressive disease. No activity was seen in patients with small lymphocytic lymphoma or in the one assessable patient with transformed lymphoma. While the numbers of patients with other sub-types of NHL were small, the collective experience suggests that there may be significant differences among the different sub-types of lymphoma.

In addition to the above studies, two other phase II studies have treated patients with bortezomib at a dose of 1.3 mg/m², using the twice weekly dosing schedule outlined above. The National Cancer Institute of Canada (NCIC) reported on a study in patients with, both treated and untreated, mantle cell lymphoma (Belch, Kouroukis et al. 2004). A total of 30 patients were accrued, of whom 28 were assessable for response at the time of reporting. The number of prior treatments was limited to 2. Interestingly, there was no difference in ORR between chemonaïve and chemotherapy refractory patients. Among the 13 patients who had no prior therapy, 6 achieved a PR (ORR 46.2%), while among the 15 previously treated patients, 6 achieved PR and 1 achieved a CRu (ORR 46.7%). Most adverse events were grade 1 or 2, although there was an unusual vascular leak syndrome that occurred in some patients treated early in the study that may have been attributed to the fact that many of these patients had pre-existing effusions. Interestingly, this toxicity was not seen in other trials. Straus *et*



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al. have enrolled 45 patients with NHL (21 MCL, 12 FL, 5 Waldenstrom's macroglobulinemia (WM), 4 Hodgkin's disease and 3 other) (Strauss, Maharaj et al. 2004). Responses were seen in 7 of 18 MCL patients (1 CR/CRu, 6 PR), 2 of 11 FL patients (both PR with late responses, 3 months after initiation of treatment), and 2 of 5 WM patients (both PR). No responses were seen in patients with aggressive lymphomas. Again, the most common toxicities were grade 3-4 thrombocytopenia, fatigue, and peripheral neuropathy (along with the additional toxicity of grade 3-4 anemia).

The consistent results in MCL prompted the PINNACLE trial - a multicenter phase II registration study of single agent bortezomib in MCL. The centrally reviewed response rate in this trial was 32% (8% CR/CRu), with a median time to progression (TTP) and duration of response (DOR) of 6.7 and 9.2 months, respectively (Goy, Bernstein et al. 2009).

Collectively, these data demonstrate that bortezomib has meaningful activity in select subtypes of lymphoma, and perhaps more importantly, that the duration of response can be clinically significant. The future challenge, of course, is trying to figure out how best to integrate this promising new class of molecules into the present standards of care for lymphoma.

Rationale for R-CBorP

Preclinical data in a SCID-beige lymphoma xenograft model suggest that the efficacy of bortezomib with cytotoxic therapy is schedule dependent. Data from our laboratory (O'Connor 2003) have revealed that bortezomib and cyclophosphamide are at least additive in their ability to delay and reverse xenograft tumor growth. The optimal therapeutic effects are seen when bortezomib is given following cytotoxic therapy. Simultaneous administration is inferior to sequential administration.

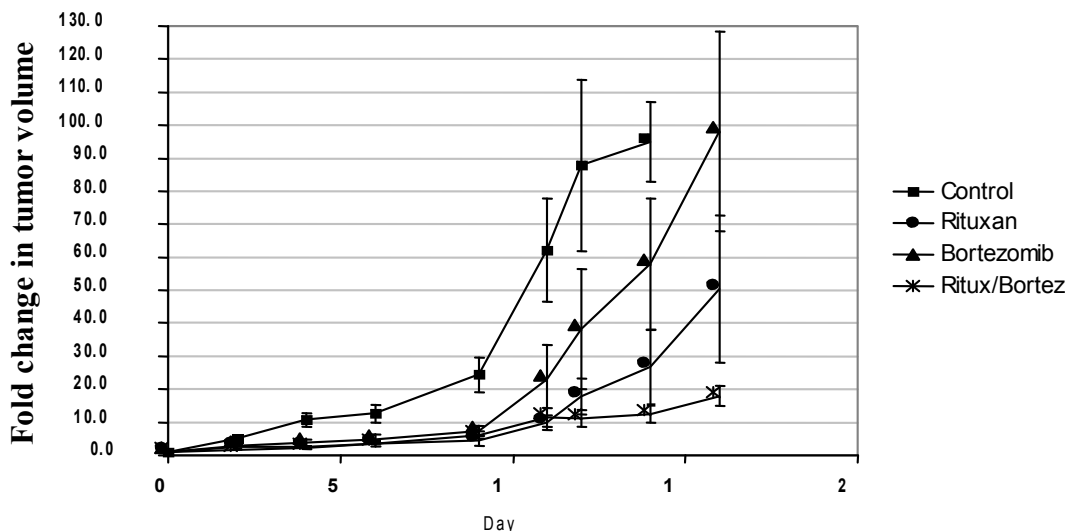
The addition of rituximab to bortezomib in a SCID xenograft model of lymphoma also shows at least an additive benefit (De Vos, McBride et al. 2004) (figure below). In other experiments (data not shown), bortezomib has shown cooperative activity with steroids, as well. These data support the hypothesis that integrating bortezomib in a schedule-dependent manner into certain standard therapies is likely to be at least additive, if not synergistic, in the treatment of non-Hodgkin's lymphoma.



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In-vivo SUDHL-16 tumor growth after treatment with RTX and/or Bortezomib



The importance of vincristine, a cell-cycle dependent antimitotic agent, in the treatment of slowly growing lymphomas is questionable. Single-agent efficacy of vincristine in indolent lymphomas has not been shown in the modern literature. Furthermore, vincristine and bortezomib both incur the potential for neurotoxic adverse effects. Replacing vincristine with bortezomib, a known active agent in indolent lymphomas, in combination with cyclophosphamide, rituximab and prednisone therefore offers the potential for greater activity in patients with relapsed/refractory indolent NHL, and exploits the cooperative interactions of bortezomib with cyclophosphamide, rituximab and steroids.

3.5 Phase I Results

To determine the (MTD) of bortezomib in combination with R-CP, we employed a modified Fibonacci dose escalation schema. We initially sought to explore a weekly dosing schedule of bortezomib, based on promising results from a phase II trial of bortezomib combined with rituximab comparing weekly with twice-weekly administration (Saleh, Dakhil et al. 2005). During this portion of the trial, the starting doses of bortezomib and cyclophosphamide were 1.3 mg/m² and 750mg/m², respectively. On the second cohort (bortezomib 1.6mg/m² and cyclophosphamide 750mg/m²), one patient experienced a grade 3 diarrhea. There were no further DLTs and the maximum pre-planned doses of bortezomib (1.8mg/m²) and cyclophosphamide (1000mg/m²) were therefore considered to be the MTD and Maximum Administered Dose (MAD). However, as we neared the completion of dose escalation using weekly administration, new reports from the bortezomib + rituximab trial cast doubt about whether weekly dosing is the most potent mode of administration. We therefore amended the Phase I trial to allow for dose escalation with a twice-weekly schedule of bortezomib administration in our combination regimen. A minimum of three patients were followed for at least one complete cycle (ie. 3 weeks) of therapy before the trial entered patients at the next



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dose level. Three patients were initially entered in the twice-weekly schedule at a dose of 1.0 mg/m² bortezomib and 750 mg/m² of cyclophosphamide (with a constant dose of rituximab, 375 mg/m² and prednisone, 100 mg/day). Cyclophosphamide dose was increased to 1000 mg/m², and bortezomib was increased to 1.3 mg/m² and 1.5 mg/m². As reported at the 2008 Annual Meeting of the American Society of Clinical Oncology (Gerecitano, Portlock et al. 2008), the second cohort (1.3 mg/m² bortezomib, 750 mg/m² cyclophosphamide) required one expansion due to neutropenic fevers. When a second neutropenic fever was seen, the protocol was amended to include filgrastim support, and six additional patients were added at this dose level to assess safety. One of these patients experienced two DLTs (a grade 4 thrombocytopenia and a grade 4 neuropathy) and the cohort was again expanded, with no further DLTs. Doses were further escalated to the highest pre-planned dose levels (1.5 mg/m² bortezomib, 1000 mg/m² cyclophosphamide) without further DLTs. Although this highest dose level is the MTD as defined by our protocol, we have decided to bring the penultimate dose level (1.3 mg/m² bortezomib, 1000 mg/m² cyclophosphamide) forward into the phase II portion of the study. This decision was made after considerations regarding our phase II experience with single-agent bortezomib and discussions with the attendings on the lymphoma service at MSKCC and Columbia University. In order to allow for maximum dosing flexibility and patient convenience, we investigated the safety and efficacy of using pegylated G-CSF (Neulasta) during bortezomib administration in an expanded cohort at the MTD of the phase I study. A separate cohort of 10 patients was added at the twice-weekly bortezomib (Bor) 1.3 mg/m² + cyclophosphamide (C) 1000 mg/m² level to assess the safety of administering overlapping pegfilgrastim (PegG) instead of filgrastim (G). In this cohort, PegG was given with bortezomib on day 2. To evaluate the safety of pegfilgrastim overlapping with 4 doses of bortezomib, toxicities and CBCs for patients in the PegG group were compared with those of patients treated at identical doses of R-CBorP given non-overlapping G support. All toxicities and CBC trends were similar, with the exception of a significant but mild decline in platelets in the PegG group. Final results of the phase I trial have been recently published (Gerecitano, Portlock et al.).

3.6 Rationale for Subcutaneous Dosing of Bortezomib

In 2008, Moreau et al. first described the subcutaneous administration of bortezomib in a group of patients with multiple myeloma (MM). At the 2010 annual meeting of the American Society of Hematology (ASH), this group presented data from a phase III randomized controlled trial comparing intravenous and subcutaneous routes of administration of bortezomib with or without dexamethasone in patients with MM (Moreau, Pylypenko et al. 2010). As expected, pharmacokinetic parameters were different in the two arms, with peak serum levels greater in the 74 patients in the IV arm (223 ng/ml) compared with the 148 patients in the SC arm (20.4 ng/ml). Interestingly, the area under the curve for both routes of administration was identical. During this trial, it was found that several toxicities, most impressively sensory peripheral neuropathy, was markedly and significantly lower in patients given bortezomib subcutaneously: grade 3-4 toxicity rate was 70% for the IV arm and 57% for the SC arm; any grade peripheral neuropathy was seen in 53% of IV patients and 38% of SC patients, $p = 0.04$). Efficacy of the SC route was indistinguishable from that of the IV



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route of administration, with an overall response rate of 52% in both arms. Based on this randomized trial, the SC mode of administration appears to increase the safety profile of bortezomib while maintaining identical efficacy. We have therefore chosen to incorporate this mode of delivery into the current protocol.

3.7 Design of Phase II

In the phase I portion of this study, both dosing schedules were well tolerated. The phase II portion of this study utilizes a randomized enrollment to further assess these two schedules in a larger number of patients. Both arms will utilize a subcutaneous route of administration for bortezomib.

The weekly dose schedule (Arm A) chosen for phase II was the MTD (see sections 3.5 and 4.1.1). The decision for the phase II dose in the twice-weekly arm (Arm B) was based on several factors: The phase I dose escalation of this schedule proceeded to the highest pre-planned level with filgrastim support without any DLTs. However, our phase II experience with single-agent bortezomib at this dose and schedule showed clinically important adverse effects, especially with respect to neuropathy. Although this highest dose level is the MTD as defined by our protocol, the phase I investigators decided to bring the penultimate dose level (1.3 mg/m² bortezomib, 1000 mg/m² cyclophosphamide) forward into the phase II portion of the study.

Because of the need for a randomized phase II design to assess the optimal dosing schedule, twice the number of patients is required (for two randomized arms).

Interim Safety Analysis

Although the SC route of administration seems to increase the safety of bortezomib administration, it has not been explored in combination with other agents. For this reason, an interim safety analysis is planned after the enrollment of 6 patients in each treatment arm. If any 2 of the first 6 patients enrolled to each arm experiences a dose limiting toxicity (DLT, as defined below), 6 further patients will be enrolled in that arm at a lower dose of bortezomib (see table under section 12.2). One further dose reduction will be allowed in each arm if necessary. The dose level at which < 2/6 patients in each arm experience a DLT will be used for the remainder of the study. If $\geq 2/6$ patients experience a DLT even after 2 dose reductions in either arm, that arm will be terminated, and an amendment to the protocol will be planned to revert to IV treatment in that arm.

Definition of Dose Limiting Toxicity

The definition of DLT used in the phase 1 portion of this trial will be used for the interim safety analysis.

DLT will be defined as any of the following events that are attributed to the study drug combination and occur during the first cycle of drug administration:



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Grade 4 neutropenia (i.e., absolute neutrophil count (ANC) < 500 cells/mm³) for 7 or more consecutive days or febrile neutropenia (i.e., fever $\geq 38.5^{\circ}$ C with an ANC < 1000 cells/mm³);

Grade 4 thrombocytopenia (platelets $< 25,000$ lasting for 7 consecutive days), platelets $< 10,000$ x 1 day, or platelets $< 25,000$ associated with a bleeding episode requiring transfusions.

Neurosensory toxicity of Grade 2 with pain or any neurosensory toxicity higher than grade 2 (by Common Toxicity Criteria 4.0 defined as “a disorder characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and warmth that are experienced in the absence of a stimulus” with “moderate symptoms; limiting instrumental ADL”);

Grade 3 or greater nausea and/or vomiting despite the use of adequate/maximal medical intervention and/or prophylaxis;

Any Grade 3 or greater non-hematological, non-neurosensory toxicity (except Grade 3 injection site reaction, alopecia, fatigue);

Re-treatment delay of more than 3 weeks due to delayed recovery from a toxicity related to treatment with the study drug combination.

In patients with advanced CLL, it may be difficult to evaluate hematologic toxicity. Deterioration in the platelet count, hemoglobin, or granulocyte count may represent either drug toxicity or progression of disease. Therefore, frequent CBCs should be obtained while the patient is on study. If a significant decline in peripheral counts occurs, drug therapy should be stopped and bone marrow examination should be performed to document the mechanism of the deterioration in the blood counts. Hematologic toxicity will be graded according to the following table:



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NCI SPONSORED WORKING GROUP GRADING SCALE FOR
HEMATOLOGIC TOXICITY

Decrease from Pretreatment Value (%)	Toxicity Grade (Platelets/Hemoglobin)
0-10	0
11-24	1
25-49	2
50-74	3
<u>≥</u> 75	4

A decrease in circulating granulocytes is not considered as it is not a reliable index in CLL

A platelet count decreasing to < 10,000 ml will be considered Grade 4 toxicity regardless of the pretreatment level

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Agent Administration

4.1.1 On day 1 of both treatment arms A and B, cyclophosphamide will be dosed at 1000 mg/m² and rituximab will be dosed at 375mg/m². Prednisone will be given orally at a dose of 100 mg per day on days 2 through 6. Each treatment cycle will last 21 days.

4.1.1.1 Arm A (weekly bortezomib): Bortezomib will be administered at a dose of 1.8 mg/m² on days 2 and 8 in the weekly dosing group.

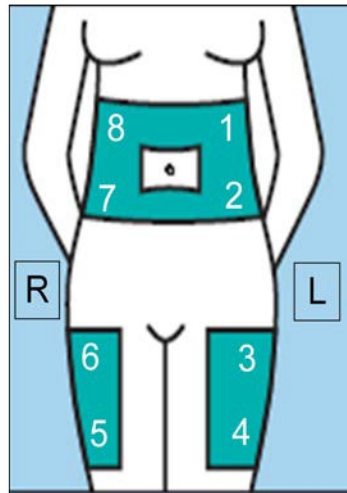
4.1.1.2 Arm B (twice-weekly bortezomib): Bortezomib will be administered at a dose of 1.3 mg/m² on days 2, 5, 9 and 12 in the twice-weekly dosing group. Pegfilgrastim, 6 mg, will be injected subcutaneously on day 2.

4.1.2 Bortezomib will be administered as a subcutaneous (SC) injection administered at a concentration of 2.5 mg/mL normal [0.9%] saline. SC injection sites are the thighs or abdomen. Injection sites will be rotated for subsequent injections within a cycle. See figure below for suggested rotation of injections.



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4.1.3 Pre-treatment parameters: On day 1 of each cycle, platelets must be $\geq 50,000/\mu\text{l}$ and ANC must be $\geq 1,000/\mu\text{l}$. On bortezomib-only treatment days, platelets must be $\geq 25,000/\mu\text{l}$, and ANC must be $\geq 100/\mu\text{l}$.

4.1.4 Treatment will be administered on an outpatient basis. Expected adverse events and appropriate dose modifications for bortezomib are described in Section 12.0. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

4.1.5 Up to a 2 week delay will be allowed for recovery from any toxicity, and dose reductions will be allowed to the next lower dose level of cyclophosphamide or bortezomib at the discretion of the treating MD. Please refer to the protocol section on dosing delays and dose modification for more details (Section 12.0).

4.2 Supportive Care Guidelines

4.2.1 Antiemetic treatment and precautions for cyclophosphamide will be based on current institutional guidelines.

4.2.2 On the weekly dosing schedule, filgrastim or pegfilgrastim may be used in the setting of neutropenic fever (NTPF), or if the patient has experienced NTPF or neutropenia with prior administrations of the study drug combination.

4.2.3 The use of pegylated G-CSF (Neulasta) will be mandated for all patients on the twice-weekly dosing schedule.

4.2.4 Platelet and red blood cell transfusions are allowed, and erythropoiesis-stimulating agents may be given at the treating physician's discretion for anemia with hemoglobin <11 g/dl.



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- 4.2.5** Treatment and precautions for rituximab infusion reactions will be based on the current institutional guidelines. Steroid treatment for infusional reactions is allowed, but should not routinely be used for prophylaxis.
- 4.2.6** Acyclovir and sulfamethoxazole/trimethoprim or equivalent substitutions should be uniformly recommended for all patients, administered prophylactically during treatment. Other prophylactic antibiotics will be allowed at the discretion of the treating physician. Prophylactics will continue for up to 4 months post treatment at the investigator's discretion.
- 4.2.7** Pain management will be addressed promptly by either the Attending Physician managing the patient, or through a consultation with the Pain and Palliative Care Service or similar services at each institution.
- 4.2.8** Additional intravenous normal saline may be given with each injection of bortezomib as deemed necessary by the treating physician.
- 4.2.9** Patients may be allowed treatment with corticosteroids as long as corticosteroids are discontinued at least seven days prior to starting study treatment. Otherwise, the regular use of corticosteroids is prohibited during the treatment phase unless used at physiologic doses (≤ 20 mg prednisone equivalent per day) for conditions not related to lymphoma (e.g. adrenal insufficiency, etc.).
- 4.2.10** Any patient with a baseline neuropathy should be evaluated by a physician in rehabilitation or neurology prior to beginning treatment, and again if symptoms worsen during treatment.
- 4.3 Duration of Therapy**
- 4.3.1** A total of up to 8 cycles will be allowed, depending on response:
- 4.3.1.1** If, after the initial 4 cycles, the patient has achieved a CR based on interim CT and PET scan, then 2 additional cycles will be administered, with re-staging CT at the completion of treatment.
- 4.3.1.2** If, after the initial 4 cycles, the patient has achieved a PR or SD based on interim CT and PET scan, then 4 additional cycles will be administered, with re-staging CT and PET at the completion of treatment.
- 4.3.1.3** If, at any point, the patient is deemed to have progressive disease (PD) based on radiologic study or physical examination, then he or she will be removed from the study.



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5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Bortezomib PS-341 (NSC # 681239)

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.

5.1.1 Availability: Bortezomib is a proteasome inhibitor supplied to investigators by Millennium Pharmaceuticals, Inc.

5.1.2 How Supplied and Preparation: Drug is available in sterile, single-use vials containing 3.5 mg of bortezomib. For SC administration, each vial of bortezomib for Injection should be reconstituted under a laminar flow biological cabinet (hood), within 8 hours before dosing, with 1.4 mL of normal (0.9%) saline, sodium chloride injection, so that the reconstituted solution contains bortezomib at a concentration of 2.5 mg/mL. The reconstituted solution is clear and colorless, with a final pH of approximately 5 to 6. Dissolution is completed in approximately 10 seconds. Reconstituted bortezomib should be administered promptly and in no case more than 8 hours after reconstitution.

Dosage and Administration

Bortezomib may be administered intravenously (IV) at a concentration of 1 mg/mL, or subcutaneously at a concentration of 2.5 mg/mL. When administered intravenously, bortezomib is administered as a 3 to 5 second bolus IV injection.

Because each route of administration has a different reconstituted concentration, caution should be used when calculating the volume to be administered.

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, a less concentrated bortezomib solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously. Alternatively, the IV route of administration should be considered.

Bortezomib is an antineoplastic. Procedures for proper handling and disposal should be considered.



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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.

- 5.1.3 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.
- 5.1.4 Storage and Stability:** 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); 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.
- 5.1.5 Schedule and Route of 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 out-patient basis, if possible. 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 (See Appendix C). The dose should be calculated on Day 1 of each cycle; the dose administered should remain the same throughout each cycle but should be recalculated at the start of the next cycle. If a patient experiences a notable change in weight within a cycle, as determined by an unscheduled weight assessment, then the patient's dose should be recalculated at that time based on clinical judgment. The appropriate amount of bortezomib will be drawn from the injection vial and administered as a subcutaneous injection. Vials are for single use administration.
- Patients randomized to the weekly dosing schedule (Arm A) will receive bortezomib as a subcutaneous injection on days 2 and 8, followed by a one week rest period. Patients randomized to the twice-weekly dosing schedule (Arm B) will receive bortezomib as a subcutaneous injection on days 2, 5, 9, 12, followed by a one week rest period.



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

Bortezomib Return

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

Millennium Study Drug Product Complaints

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

<p>For Product Complaints, call MedComm Solutions at +1-866-835-2233</p>
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5.1.6 Reported Adverse Events and Potential Risks. To date, more than 100,000 patients have been treated with bortezomib in both clinical trials investigating its use in hematological malignancies and solid tumors, and in patients who were treated with commercially available bortezomib.

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

The known anticipated risks of bortezomib therapy are presented in Table 5-1 and Table 5-2. 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/m² twice weekly on a 21-day schedule, in patients with multiple myeloma and mantle cell lymphoma.



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Table 5-1 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class	Preferred Term
Blood and Lymphatic System Disorders	
Most common	Thrombocytopenia*, anaemia*
Very common	Neutropenia*
Common	Lymphopenia, pancytopenia*, leukopenia*, febrile neutropenia
Cardiac Disorders	
Common	Tachycardia, atrial fibrillation, palpitations, cardiac failure congestive*
Uncommon	Cardiogenic shock*, atrial flutter, cardiac tamponade*±, bradycardia, atrioventricular block complete, arrhythmia, cardiac arrest*, cardiac failure, arrhythmia, pericardial effusion, pericarditis, pericardial disease±, cardiopulmonary failure±
Ear and Labyrinth Disorders	
Uncommon	Deafness, hearing impaired
Eye Disorders	
Common	Blurred vision, conjunctivitis, conjunctival haemorrhage
Gastrointestinal Disorders	
Most common	Constipation, 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 mucosal 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, mucosal inflammation*
Uncommon	Injection site pain, injection site irritation, injection site phlebitis, general physical health deterioration*, catheter-related complication
Hepatobiliary Disorders	



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Table 5-1 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Uncommon	Hyperbilirubinaemia, hepatitis*±
Immune System Disorders	
Uncommon	Drug hypersensitivity, angioedema
Infections and Infestations	
Very common	Upper respiratory tract infection, nasopharyngitis, pneumonia*, Herpes zoster*
Common	Lower respiratory tract infection*, sinusitis, pharyngitis, oral candidiasis, urinary tract infection*, sepsis*, bacteraemia*, 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*



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Table 5-1 Known Anticipated Risks of Bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Nervous System Disorders	
Most common	Peripheral neuropathy (including all preferred terms under the MedDRA High-level term Peripheral neuropathy NEC)
Very common	Paresthesia, dizziness excluding vertigo, headache
Common	Polyneuropathy, syncope, dysesthesia, dysgeusia, postherpetic neuralgia
Uncommon	Convulsion, loss of consciousness, ageusia, encephalopathy, paralysis*, autonomic neuropathy, reversible posterior leukoencephalopathy syndrome±
Psychiatric Disorders	
Very common	Anxiety, insomnia
Common	Confusional state
Uncommon	Delirium
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® Investigator's Brochure Edition 14.

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

* Fatal outcomes have been reported.

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



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**Table 5-2 Reports of Adverse Reactions From
Postmarketing Experience**

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



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<i>Lung infiltration</i>	Rare
<i>Pneumonitis</i>	Rare
<i>Pulmonary hypertension</i>	Rare

Skin and subcutaneous system disorders

<i>Acute febrile neutrophilic dermatosis</i>	Unknown
<i>Toxic epidermal necrolysis</i>	Unknown

Source: VELCADE[®] Investigator's Brochure Edition 14.

- a Incidence is assigned using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ and $< 1/10$); uncommon ($\geq 1/1000$ and $< 1/100$); rare ($\geq 1/10,000$ and $< 1/1000$); very rare ($< 1/10,000$, including isolated reports).
- b Acute diffuse infiltrative pulmonary disease is a MedDRA Lower Level Term which corresponds to a Preferred Term of Interstitial lung disease.

Other medical events of interest that are considered not causally related to bortezomib include hepatic failure and QT prolongation. Fatal outcomes have been reported.

Women of childbearing potential should avoid becoming pregnant while being treated with bortezomib. Genotoxicity testing has shown that bortezomib is negative in the in vitro Ames assay and in the in vivo micronucleus assay, but it is a clastogen in the in vitro chromosomal aberration assay.

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

5.1.7 Agent Ordering: Bortezomib will be supplied by Millennium Pharmaceuticals, Inc. free of charge for investigational use only.

5.1.8 Agent 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.



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Precautions and Restrictions

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

Female patients must meet 1 of the following:

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

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

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

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

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

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

5.2 Rituximab (Rituxan®)

5.2.1 Mechanism of action: Rituximab binds to the CD20 antigen expressed on B-cells and causes cell death by complement mediated lysis and Antibody- Dependent Cell-mediated Cytotoxicity (ADCC).



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5.2.2 Formulation: Rituximab is supplied as 100 mg and 500 mg sterile, preservative-free, single use vials.

5.2.3 Preparation: The appropriate dose is withdrawn and diluted to a final concentration of 1-4 mg/ml in either 0.9% sodium chloride or 5% dextrose solution. The solution is then stable at 2° to 8°C for 24 hours and at room temperature for an additional 12 hours.

5.2.4 Storage: Vials can be stored at 2° to 8°C. They should be protected from sunlight.

5.2.5 Administration: The first infusion should be administered at an initial rate of 50 mg/hr. If hypersensitivity or infusion-related events do not occur, the rate may be increased by 50 mg/hr every 30 minutes up to a maximum of 400 mg/hr. Subsequent infusions may be started at 100 mg/hr and the rate increased by 100 mg/hr every 30 minutes to a maximum of 400 mg/hr, as tolerated. Patients will be premedicated with acetaminophen 650-mg orally and diphenhydramine 50 mg IV 30 minutes prior to beginning the rituximab infusion. For severe reactions, the infusion will be stopped and can be resumed at 50% of the prior rate once the reactions are treated and symptoms resolved. If infusion interruption is required, the administration of steroids (the equivalent of 50-100 mg hydrocortisone) prior to restarting the infusion is allowed at the investigator's discretion.

5.2.6 Reported Adverse Events and Potential Risks: Weakness, dizziness, hypo- or hypertension, peripheral edema, anxiety, flushing, headache, nausea or vomiting, diarrhea, rash, pruritus, angioedema, anaphylaxis, chest pain, cardiac arrhythmias, cough, throat irritation, bronchospasm, dyspnea, sinusitis, rhinitis, night sweats, lymphopenia, leukopenia, neutropenia, anemia, thrombocytopenia, infection, nephrotoxicity, hyperglycemia, urticaria, arthralgia, back pain PML

5.2.7 Supplier: Genentech, Inc.

5.3 Cyclophosphamide

5.3.1 Mechanism of action: Activation by hepatic microsomal enzymes forming two major intermediates, aldophosphamide and 4-hydroxycyclophosphamide, which act as powerful alkylating agents and prevent cross linking of DNA strands.

5.3.2 Formulation: Available in both oral and parenteral forms. The parenteral formulation is available as white crystals with sodium chloride as an excipient. The 100 mg dose is provided in a 10 mL vial and a 500 mg dose in a 30 mL vial. For high dose intravenous therapy there are 1 and 2 gram vials which are reconstituted in 50-100 mL of sterile water containing a solution of 20 mg/mL.



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5.3.3 Preparation: The drug may be given by intravenous push or as a slow infusion. Adequate hydration of the patient before and 72 hours after high-dose therapy is recommended to reduce the incidence of hemorrhagic cystitis.

5.3.4 Storage: Solutions reconstituted as described have a 24 hour stability at room temperature.

5.3.5 Toxicity: myelosuppression (predominantly leukopenia), acute sterile hemorrhagic cystitis, SIADH, bladder carcinomas and cellular dysplasia, alopecia, nausea and vomiting, Rare: pneumonitis, infertility, and secondary leukemia.

5.3.6 Supplier: Mead Johnson

5.4 Prednisone

5.4.1 Mechanism of action: Decreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability; suppresses the immune system by reducing activity and volume of the lymphatic system; suppresses adrenal function at high doses. Antitumor effects may be related to inhibition of glucose transport, phosphorylation, or induction of cell death in immature lymphocytes. Antiemetic effects are thought to occur due to blockade of cerebral innervation of the emetic center via inhibition of prostaglandin synthesis.

5.4.2 Preparation: 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 50 mg tablet

5.4.3 Toxicities: euphoria/depression, GI distress, growth depression, hypertension, sodium and fluid retention, impaired skin healing, increased risk of infection, osteoporosis, skin atrophy, adrenocortical insufficiency, cataracts, glaucoma, Cushing's syndrome, hyperglycemia, tuberculosis reactivation

5.4.4 Supplier: The Upjohn Company

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

6.1.1 Patients with B-cell small lymphocytic lymphoma, marginal zone lymphoma (including lymphoplasmacytic lymphoma), follicular lymphoma, grade I, II, IIIa, Waldenstrom's macroglobulinemia or mantle cell lymphoma. Patients with transformed indolent lymphomas will not be eligible for this study. Patients relapsed or refractory after at least one prior chemo or immunotherapeutic modality will be eligible. Pathology should be confirmed at local participating institution.



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- 6.1.2** All patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded as ≥ 2 cm with conventional techniques or as >1 cm with spiral CT scan). Lymph nodes measuring ≤ 1 cm in the short axis are considered normal. Patients with WM and no measurable lymphadenopathy are allowed, and will be assessed using the criteria of the Forth International Workshop on WM.
- 6.1.3** Patients must have received at least one prior chemo or immunotherapeutic regimen of any kind, but no more than three prior regimens of *conventional cytotoxic therapy*, and must be off all cytotoxic chemotherapy for at least four weeks prior to study enrollment (6 weeks for BCNU or mitomycin C, 12 weeks with recovery to baseline counts for radioimmunotherapy). Patients are allowed to have received one course of prior radioimmunotherapy (RIT: either tositumomab or ibritumomab). Prior recipients of stem cell transplantation will be included, with the preparative cytoreductive and high-dose therapies counted collectively as one prior therapy.
- 6.1.4** Patients must not have received any therapeutic monoclonal antibodies (e.g. rituximab, tositumomab, ibritumomab, alemtuzumab, etc.) within 3 months of enrollment. Patients who have been treated with monoclonal antibodies within 3 months may be enrolled if they show progression of disease on this therapy, as long as they have not received the treatment within 7 days of enrollment.
- 6.1.5** Age greater than or equal to 18 years. Because no dosing or adverse event data are currently available on the use of bortezomib in patients ≤ 18 years of age, children are excluded from this study but will be eligible for future pediatric single-agent trials, if applicable.
- 6.1.6** Karnofsky Performance Status $\geq \square 50\%$ (see Appendix B).
- 6.1.7** Patients must have adequate organ and marrow function as defined below (within 14 days of study drug administration):
- Absolute Neutrophil Count (ANC) $\geq 1,000/\text{mcL}$ at enrollment and on day 1 of each cycle (If known lymphomatous involvement of the bone marrow, then $\text{ANC} \geq 500/\text{mcL}$).
 - Platelets $\geq 50,000/\text{mcL}$ at enrollment and on day 1 of each cycle
 - Total bilirubin ≤ 1.5 times institutional upper limit of normal
 - AST (SGOT) and ALT (SGPT) ≤ 2.5 times institutional upper limit of normal (4x ULN if liver involvement)
 - Creatinine < 1.5 times institutional upper limit or creatinine clearance ≥ 50
- 6.1.8** Patients may have febrile episodes up to 38.5°C without evidence of active infection.



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- 6.1.9** The effects of bortezomib on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, and because bortezomib belongs to a new class of antineoplastic agents that may be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.
- 6.1.10** Patients must have no signs of congestive heart failure class III/IV according to the New York Heart Failure Guidelines (see Appendix D) uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening must be documented by the investigator as not medically relevant.
- 6.1.11** Patients must have the ability to understand ramifications of the study, and the willingness to sign a written informed consent document.
- 6.1.12** Voluntary written informed consent must be obtained 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.
- 6.1.13** Female subject is either postmenopausal for at least 1 year before the screening visit, is surgically sterilized or if they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing the informed consent form through 30 days after the last dose of bortezomib, or agree to completely abstain from heterosexual intercourse.
- 6.1.14** Male subjects, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following: practice effective barrier contraception during the entire study treatment period and through a minimum of 30 days after the last dose of study drug, or completely abstain from heterosexual intercourse.

6.2 Subject Exclusion Criteria

- 6.2.1** Patients without prior therapeutic regimen of any kind, or patients who have had more than three prior regimens of *conventional cytotoxic therapy* will be excluded from this clinical trial. Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C, 12 weeks or lack of recovery to baseline counts for RIT) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier, and patients who have received a therapeutic monoclonal antibody within



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3 months (except those with objective evidence of PD) will be excluded from this clinical trial.

- 6.2.2** Patients receiving palliative steroids for the purpose of treating NHL within 7 days of starting the study treatment will be excluded from this clinical trial.
- 6.2.3** Participation in clinical trials with other investigational agents not included in this trial, within 14 days of the start of this trial and throughout the duration of this trial.
- 6.2.4** Patients with known brain metastases or meningeal disease will be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.
- 6.2.5** Patients who have had any major surgery within four weeks of study entry will be excluded from this clinical trial.
- 6.2.6** Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, cerebrovascular accident (CVA) or transient ischemic attack within 6 months of study enrollment, unstable angina pectoris, cardiac arrhythmia, EKG evidence of acute ischemia, or psychiatric illness/social situations that would limit compliance with study requirements will be excluded from this clinical trial.
- 6.2.7** Pregnant and breast-feeding women are excluded from this study because bortezomib is a novel agent that may have the potential for teratogenic or abortifacient effects. Confirmation that the subject is not pregnant must be established by a negative serum β -human chorionic gonadotropin (β -hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women.
- 6.2.8** Patients with uncontrolled hypertension requiring active manipulation of antihypertensive medications will be excluded from this clinical trial.
- 6.2.9** HIV-positive patients on combination antiretroviral therapy are eligible if their HIV is under adequate control with an antiretroviral regimen that has been stable for ≥ 4 weeks, as long as the CD4 count is > 300 . Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.
- 6.2.10** Patients with a history of hypersensitivity to bortezomib, boron or mannitol will be excluded from this clinical trial.



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6.2.11 Patients who had experienced myocardial infarction within 6 months prior to enrollment will be excluded from this clinical trial. Prior to study entry, any ECG abnormality at Screening has to be documented by the investigator as not medically relevant.

6.2.12 Patients diagnosed or treated for another malignancy within 3 years prior to study 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) will be excluded from this clinical trial.

6.2.13 Patients with peripheral neuropathy > grade 1 with pain or grade ≥ 2 will be excluded from this clinical trial. If the patient has baseline neuropathy grade 1 or 2, it is recommended that the patient be referred for evaluation for rehabilitation medicine or neurology prior to beginning treatment, and again if symptoms worsen during treatment.

7.0 RECRUITMENT PLAN

Subjects will be recruited and treated from Memorial Sloan Kettering Cancer Center, The Cancer Institute of New Jersey at Robert Wood Johnson Medical School, Columbia University Medical Center, and the Winship Cancer Institute at Emory University. Adult men and women of all ethnic groups are eligible for this trial. 60 patients total will take part in this Phase II subcutaneous portion of the study. About 42 patients are expected to be treated at MSKCC; the remainder are to be accrued by the subsites. The proposed study population is illustrated in the table below.

Race/Ethnicity						
Gender	White, not of Hispanic Origin	Black, not of Hispanic Origin	Hispanic	Asian or Pacific Islander	Unknown	Total
Male	~46%	1-2%	2-3%	1-2%	-	~53%
Female	~40%	1-2%	2-3%	1-2%	-	~43%
Total	~86%	~3.3%	~5%	~3%	2.7%	100%

8.0 PRETREATMENT EVALUATION

8.1 Pre-Treatment Evaluation must be performed within 14 days of study drug administration unless otherwise noted.



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- 8.1.1** History and physical examination, including height, weight, vital signs, and a comprehensive neurologic examination.
- 8.1.2** Karnofsky Performance status
- 8.1.3** CBC with automated differential and platelet count.
- 8.1.4** Serum chemistries including electrolytes, glucose, BUN, creatinine, magnesium, calcium, phosphorous, albumin, SGOT (AST)/SGPT (ALT), alkaline phosphatase, total bilirubin, LDH, serum cryoglobulins.
- 8.1.5** Beta-2 microglobulins and protein electrophoresis (serum) should be performed pre-study.
- 8.1.6** Documentation of known measurable or assessable disease parameters including radiographic imaging procedures (CT and PET scan) within 6 weeks. If the patient has a history of measurable disease in the neck, a CT of the neck should also be performed at baseline.
- 8.1.7** Urine or serum pregnancy test for woman with childbearing potential.
- 8.1.8** Unilateral bone marrow aspirate and biopsy (within 4 months).
- 8.1.9** EKG
- 8.1.10** Pretreatment paraffin-embedded histologic samples will be obtained from all patients for tissue microarray. Unstained slides (preferably ≥ 20) may be substituted when block is not available.



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9.0 TREATMENT/INTERVENTION PLAN

STUDY CALENDAR

	Screening	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycles 5-8 ^D			Final Visit ^N	Follow Up
	Pre-Study ^K	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3		6, 12, 18, 24, 36, 48, etc., months post final visit ^E
Bortezomib D(2,8) –Arm A D(2,5,9,12)-Arm B		X	X		X	X		X	X		X	X		X	X			
Cyclophosphamide (D1)		X			X			X			X			X				
Rituximab (D1)		X			X			X			X			X				
Prednisone (D2-6)		X			X			X			X			X				
Neulasta® (D2 of Arm B only)		X			X			X			X			X				
Informed consent	X																	
Demographics	X																	
Medical history	X																	
Concurrent meds	X	X			X			X			X			X			X	X
Physical Exam ^A	X	X			X			X			X			X			X	X
Vital signs	X	X			X			X			X			X			X	X
Height	X																	
Urinalysis	X																	
Weight	X	X			X			X			X			X			X	X
Performance status (per RN)	X	X			X			X			X			X			X	X
CBC w/diff. plts ^B	X	X	X		X	X		X	X		X	X		X	X		X	X
Cryoglobulins ^L	X	X			X			X			X			X			X	X
Bone Marrow Aspirate and biopsy	X													X ^I			X ^I	
Serum chemistry and LDH ⁴	X	X			X			X			X			X			X	X
Beta-2-microglobulins	X																X	
Protein Electrophoresis (serum)	X												X ^J				X ^J	
EKG	X																	



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Adverse event evaluation	X	X			X			X			X			X			X	X
Immunofixation (serum) ^M	X												X				X	
Immunoglobulin, quantitative ^M	X												X				X	
Tumor measurements ^H	X ^G													X ^F			X ^G	X
Radiologic evaluation ^G	X ^G												X ^F				X ^G	X
B-HCG (serum) ^C	X																	



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- A: Patients will be seen on or within 7 days prior to day 1 of each cycle, more frequently at treating MD's discretion.
- B: With the exception of screening, CBCs should be performed within a 24 hour window prior to treatment. Day 2 CBCs of each cycle are optional. A CBC should be performed and resulted within 24 hours of all Bortezomib treatments.
- C: Serum pregnancy test (women of childbearing potential only).
- D: Continued treatment follows the same pattern of follow-up examination as cycles 3 and 4. Treatment continues for up to 6 or 8 cycles in total, depending on response. Please see the duration of therapy section in protocol for details (Section 4.3).
- E: Radiologic evaluation and follow up visits will continue after treatment, starting 6 months after the final visit, and continue every 6 months for the first two years, and every 12 months thereafter (or more frequently at discretion of treating MD) until the patient begins another treatment regimen.
- F: Radiologic studies at the end of cycle 4 will include CT: CA, PET scan, and, if the patient had a history of disease in neck, a CT: Neck. CT measurements should be performed during the 3rd week of cycle 4.
- G: Baseline, restaging, and post-treatment radiologic studies will include a CT: CAP, PET scan, and CT: Neck (only if history of disease in neck). All patients on study will have PET and CT scans performed during the Cycle 4 radiologic evaluation. Thereafter, once a patient enters complete remission (CR), then only CT's (chest/abdomen/pelvis and neck, if necessary) should be obtained. End-of treatment restaging radiologic studies should be performed 3-4 weeks after the last dose of bortezomib. Radiologic documentation must also be provided for patients removed from study for progressive disease.
- H: Tumor measurements should be documented after each radiologic assessment that occurs while the patient is on the study (including unscheduled scans ordered at the discretion of the treating physician, scans that require patient to go off study, and any scan ordered per protocol.)
- I: Bone marrow biopsy and aspirate will be included as part of the end of treatment evaluation (final visit) in all patients who achieve a radiologic CR and in whom bone marrow involvement was documented in the pre-study evaluation. If there is radiologic evidence of a CR at interim restaging in patients with documented bone marrow involvement at baseline, a bone marrow biopsy and aspirate should be performed prior to Cycle 6 Day 1 to confirm radiologic CR.
- J: Serum Protein Electrophoresis should be performed at baseline, at restaging, and repeated at end of treatment, if baseline value was abnormal or the patient has Waldenström's Macroglobulinemia.
- K: Baseline laboratory evaluations and physical examination are to be conducted within 14 days prior to administration of study agent. Scans must be done within 6 weeks prior to enrollment. Bone marrow biopsy must be done within 4 months prior to enrollment.
- L: With the exception of screening, serum chemistries should be performed within 7 days prior to treatment. Serum Chemistry includes: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT[AST], SGPT[ALT], sodium, serum cryoglobulins (quantitative), magnesium, phosphorus, uric acid. Serum chemistries do not need to be resulted prior to treatment on Day 1.
- M: Patients with Waldenström's Macroglobulinemia must have these labs performed at screening, restaging and at 6 week follow up from first negative values in CR is achieved. These tests are strongly encouraged for all patients but only required for Waldenström's Macroglobulinemia patients.
- N: Final visit evaluation will take place 30 days +/- one week after the last dose of bortezomib. While every attempt will be made to collect this final visit data, it is understood that medical and/or logistical reasons may arise that could potentially interfere with the ability of the patient to attend the final visit. If any patient is unable to comply with the final visit, the reason(s) for this will be documented in the medical records and this would not be considered a protocol violation.



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10.0 EVALUATION DURING TREATMENT/INTERVENTION

See the Study Calendar (Section 9.0) for scheduled evaluations during treatment. For the purposes of this study, patients will be reevaluated for response with a CT and PET scan after 4 cycles and 3-4 weeks after the last dose of bortezomib. A follow-up visit will be scheduled 1 month after completion of treatment, with repeat CT scans every 6 months in the first two years. Two years post completion of treatment, patients should be re-imaged at least every 12 months, with interim imaging at the discretion of the treating physician.

11.0 TOXICITIES/SIDE EFFECTS

11.1 Expected Adverse Events Associated with Bortezomib

Toxicity will be described according to NCI Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.0. Toxicity will be evaluated on day 1 of each cycle. Expected toxicities are described in the information supplied by Millennium Pharmaceuticals, Inc. For the list of potential risks and adverse events refer to the section detailing Reported Adverse Events and Potential Risks (section 5.1.6). Further details on the potential risks of bortezomib may be found in the Investigator Brochure.

11.2 Expected Adverse Events Associated with Other Study Drugs

11.2.1 Rituximab: Fever, chills, nausea, asthenia, hypotension, angioedema, respiratory distress, tumor lysis syndrome, and neutropenia.

11.2.2 Cyclophosphamide: myelosuppression (predominantly leukopenia) acute sterile hemorrhagic cystitis, SIADH, bladder carcinomas and cellular dysplasia, alopecia, nausea and vomiting. Rare: cardiomyopathy, pneumonitis, infertility, and secondary leukemia.

11.2.3 Prednisone: euphoria/depression, GI distress, growth depression, hypertension, sodium and fluid retention, impaired skin healing, increased risk of infection, osteoporosis, skin atrophy, adrenocortical insufficiency, cataracts, glaucoma, Cushing's syndrome, hyperglycemia, tuberculosis reactivation

12.0 DOSING DELAYS/DOSE MODIFICATIONS

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 Terminology Criteria for Adverse Events (CTCAE), Version 4.0. Neuropathic pain and peripheral sensory neuropathy are to be managed as described in Table 12.2.



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Before day 1 of each cycle, platelets must be $\geq 50,000/\mu\text{l}$ and Absolute Neutrophil Count (ANC) must be $\geq 1,000/\mu\text{l}$. On bortezomib-only treatment days, platelets must be $\geq 25,000/\mu\text{l}$, and ANC must be $\geq 100/\mu\text{l}$.

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

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

- 12.1.1** Patients who develop a febrile neutropenia or Grade 4 hematologic toxicity can be treated with a repeat cycle after holding the dose for up to two weeks and allowing blood count recovery to either the pre-treatment criteria (dose 1 of any cycle – see section 6.1.7), or 25,000/mcl for platelets and 100/mcl for absolute neutrophil count (on days when bortezomib is given alone within each cycle). Cytokine support can be given as outlined in “Supportive Care,” section 4.2. Should the patient develop a second Grade 4 neutropenia or neutropenic fever, then the dose of cyclophosphamide should be reduced to 750 mg/m².
- 12.1.2** If, after treatment has been held, the toxicity does not resolve, as defined above, treatment must be discontinued.
- 12.1.3** Dose interruption or study discontinuation is not required for lymphopenia of any grade.
- 12.1.4** Should the patient develop a second Grade 4 thrombocytopenia, then after resolution as above, the dose of bortezomib should be reduced by one dose level (see table below under section 12.2). A second dose reduction will be allowed if grade 4 thrombocytopenia persists.
- 12.1.5** Drug should be held in patients who develop any treatment-related Grade 3-4 non-hematologic toxicity (except Grade 3 alopecia, injection site reaction, fatigue, or grade 3-4 lab values related to underlying baseline conditions), grade 1 neuropathy with pain or any toxicity that is deemed intolerable by the patient or investigator until symptoms resolve to baseline. Such patients can be re-treated with a reduced dose of bortezomib and/or cyclophosphamide as outlined above. Should the Grade 3-4 toxicity recur after dose reduction, that patient will be removed from study. If a grade 3-4 toxicity is based solely on laboratory abnormalities that are thought to be clinically insignificant by the treating physician, the lab values should be discussed with the principle investigator to decide if dose interruption or reduction is necessary.



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Patients who experience bortezomib-related neuropathic pain or peripheral sensory neuropathy are to be managed as presented in Table 12.2. Once the dose is reduced for peripheral neuropathy, the dose may not be re-escalated.

Table 12.2 Management of Patients with Bortezomib-Related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Recommended Dose Modification for Bortezomib related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy	
Severity of Peripheral Neuropathy Signs and Symptoms	Modification of Dose and Regimen
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental ADL)	Reduce bortezomib to -1 level
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL)	Discontinue bortezomib and remove patient from study
Grade 4 (Life-threatening consequences; urgent intervention indicated)	Discontinue bortezomib and remove patient from study
Grading based on NCI Common Terminology Criteria CTCAE v 4.0 NCI Common Terminology Criteria website - http://ctep.info.nih.gov/reporting/ctc.html	

Table: Bortezomib Dose Reduction Schema

	Weekly dosing group	Twice-Weekly dosing group
Starting dose	1.8 mg/m²	1.3 mg/m²
-1	1.6 mg/m²	1.0 mg/m²
-2	1.3 mg/m²	0.7 mg/m²

Patients with mild hepatic impairment (bilirubin $\leq 1.5 \times$ 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 \geq Grade 2 (> 1.5 -3.0 X ULN) while on study, the investigator should hold bortezomib until the toxicity returns to $<$ Grade 2. Restarting bortezomib at the next lower dosed level could be considered at the Investigator's discretion and following exclusion of



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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.

The neurotoxicity-directed questionnaire (see 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.

13.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

13.1 Definitions

Response and progression of disease will be evaluated in this study using the international criteria proposed by the Cheson et al. (Cheson, Pfistner et al. 2007) for patients with lymphoma, and the Forth International Workshop on Waldenstrom's Macroglobulinemia (Dimopoulos et al, 2009) for patients with Waldenstrom's Macroglobulinemia.. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

13.1.1 Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques (PET, CT) or as ≥ 10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

13.1.2 Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

13.1.3 Target Lesions

All measurable lesions up to a maximum of six lesions representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (determining the product obtained from the longest diameter of two perpendicular measurements) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).



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13.1.4 Non-target lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

13.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations (CT, PET, superficial clinical lesion measurements) should be performed as closely as possible to the beginning of treatment and never more than 6 weeks before the beginning of the treatment. A CT:CAP and PET should be performed at baseline, restaging, and at end of treatment. Post treatment follow-up will be performed with CT scans. A CT:Neck should be performed along with each scheduled CT:CAP if the patient has a history of disease in the neck. Tumor lesions that are situated in a previously irradiated area are considered measurable.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

13.2.1 Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

13.2.2 Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

13.2.3 Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

13.2.4 Ultrasound (US). When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.



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13.2.5 Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

13.2.6 Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. For patients with low-grade lymphomas, quantification and monitoring of any pre-existing monoclonal gammopathy (via serum protein electrophoresis) and Beta-2-microglobulin will be followed if there is an abnormal baseline value.

13.2.7 Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions where known residual benign tumors can remain).

13.2.7.1 The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

13.3 Response Criteria

13.3.1 Response Criteria for patients with NHL

Response criteria are determined through evaluation of target lesions. Response criteria for patients with NHL will follow the guidelines previously reported by Cheson et al., 2007 (Cheson, Pfistner et al. 2007) and are described below. The criteria for NHL are as follows (GTD = Greatest Transverse Diameter; SPD = Sum of the Products of the Greatest Diameter):

13.3.1.1 Complete Remission (CR):

- Disappearance of all evidence of disease.
- No disease related symptoms.
- Lymph nodes, nodal masses regressed to “normal” size:
 - If >1.5 cm before treatment, regressed to ≤ 1.5 cm in GTD.
 - If 1.1 to 1.5 cm before treatment, regressed to ≤ 1 cm in GTD (or >75% in SPD). If PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative. PET is considered negative if target lesions all have uptake values below the level of average uptake in the liver.



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- Spleen and all previously enlarged organs decreased to normal in size.
- If the Bone marrow was involved prior to treatment, it is clear on repeat aspirate and biopsy at the same site.

13.3.1.2 Partial Remission (PR):

- $\geq 50\%$ decrease in SPD of six largest dominant nodes/nodal masses.
- No increase in size of other nodes, liver or spleen.
- Splenic and hepatic nodes regressed at least 50% in SPD
- No new sites of disease.
- If the PET scan was positive before therapy, the post-treatment PET is positive in at least one previously involved site.
- Patients who achieve a CR by the above criteria, but who have persistent bone marrow involvement (or those in whom pre-treatment bone marrow was involved and post-treatment bone marrow involvement was not assessed).

13.3.1.3 Relapsed Disease (RD):

- In patients previously CR :
- New lesion > 1.5 cm in any axis
- Size of previously involved site has increase $\geq 50\%$ in GTD.
- $\geq 50\%$ increase in either:
 - GTD of any previously identified node that was >1 cm in its short axis, or
 - SPD of any node or other lesion.

13.3.1.4 Stable Disease (SD):

- Patients who have achieved less than a partial remission but who have not developed findings consistent with progressive disease.

13.3.1.5 Progressive Disease (PD):

- In patients previously PR or SD.
- $\geq 50\%$ increase from nadir or baseline in SPD or any node or lesion
- $\geq 50\%$ increase from nadir in GTD of any node previously >1 cm in shortest diameter
- Appearance of any new lesion during or at the end of therapy.

13.3.1.6 Evaluation of non-target lesions

- 13.3.1.6.1 Complete Response (CR*):** Disappearance of all non-target lesions and normalization of any tumor markers (i.e. IgM levels in WM). Any post-treatment masses still present that were PET positive prior to treatment must be PET negative at the completion of therapy.



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13.3.1.6.2 Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

13.3.1.6.3 Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of “non-target” lesions only is exceptional, in such circumstances the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair).

***Note:** If tumor markers (i.e. IgM levels in WM) are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

13.3.2 Response Criteria for patients with Waldenström’s Macroglobulinemia

The response criteria used for patients with Waldenström’s Macroglobulinemia (WM) in this study are the criteria from the Forth International Workshop on Waldenström’s Macroglobulinemia (Dimopaulos, *et al* 2009). These specific criteria are defined below:

13.3.2.1 Complete Response (CR):

- Disappearance of monoclonal protein by immunofixation.
- No histologic evidence of bone marrow involvement.
- Resolution of any adenopathy/organomegaly (confirmed by CT scan).
- Resolution of any signs or symptoms attributable to WM.
- Reconfirmation of the CR status is required at least 6 weeks apart with a second immunofixation.

13.3.2.2 Partial Response (PR):

- At least 50% reduction of serum monoclonal IgM concentration on protein electrophoresis.
- At least 50% decrease in adenopathy/organomegaly on physical examination or on CT scan.
- No new symptoms or signs of active disease.

13.3.2.3 Minor Response (MR):

- At least 25% but less than 50% reduction of serum monoclonal IgM by protein electrophoresis.
- No new symptoms or signs of active disease.



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13.3.2.4 Stable Disease (SD):

- A less-than-25% reduction and less-than-25% increase of serum monoclonal IgM by electrophoresis without progression of adenopathy/organomegaly, cytopenias, or clinically significant symptoms due to disease and/or signs of WM.

13.3.2.5 Progressive Disease (SD):

- At least 25% increase in serum monoclonal IgM by protein electrophoresis confirmed by a second measurement or progression of clinically significant findings due to disease (ie, anemia, thrombocytopenia, leukopenia, bulky adenopathy/organomegaly) or symptoms (unexplained recurrent fever of at least 38.4°C, drenching night sweats, at least 10% body weight loss, or hyperviscosity, neuropathy, symptomatic cryoglobulinemia, or amyloidosis) attributable to WM.

13.4 Evaluation of the best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note: Patients with a global deterioration of their health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration.” Every effort should be made to document objective progression, even after discontinuation of treatment.



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In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

13.5 Duration of response

13.5.1 Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented. If stem cell transplant is planned after achieving CR, these patients will be censored at the time of beginning the preparative regimen for transplant.

13.5.2 Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

13.5.3 Progression-Free Survival

Mean and median durations of response, progression-free survival, event-free survival and overall survival will be calculated from the observed study durations. If the study evaluation is performed before all data have reached their respective end-points, right-censored data for all duration estimates will be treated as independent censoring and Kaplan-Meier survival estimates will be employed. Time-to-progression analyses will treat patient withdrawals and interventions for reasons other than progression or death as independent censoring. If stem cell transplant is planned after achieving a response, these patients will be censored at the time of beginning the preparative regimen for transplant.

13.5.4 Time to progression is defined as the start of treatment to the first documented progression or death.

13.5.5 Event free survival is defined as the time of enrollment to the first documented event, with events defined as: death, relapse, progressive disease, secondary malignancy, or toxicity attributed to therapy and requiring removal from study.

13.5.6 Time to death is defined from the start of treatment to the date of death.



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14.0 CRITERIA FOR REMOVAL FROM STUDY

Termination of Treatment and/or Study Participation

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

The investigator or Millennium Pharmacovigilance may discontinue the clinical research study if they determine that the study or treatment offers little or no future benefit, or the supply of medication ceases to be available, or other causes prevent continuation of the clinical research study. If at any time the treating physician feels that continuing in the study is not beneficial for a given patient, or if a patient is unable to follow the treatment plan, treatment may be stopped. If there is progression of disease despite this therapy, it will be stopped. If the investigator is in doubt as to whether progression has occurred, particularly with respect to non target lesions and the appearance of a new lesion, it is advisable to continue treatment for up to one additional cycle until formal evaluation of response has been completed. Every effort should be made to complete this evaluation before the end of the next cycle.

15.0 BIOSTATISTICS

15.1 Study Design/Endpoints

For the weekly schedule, the MTD doses of bortezomib (1.8 mg/m^2) and cyclophosphamide (1000 mg/m^2) will be brought forward to the phase II portion. For the twice-weekly schedule, the 1.3 mg/m^2 dose of bortezomib will be used. Each treatment arm will be evaluated separately. The study will employ a Simon two stage design in the analysis of the Phase II portion in each arm separately. For indolent lymphomas and MCL, a 60% response rate is considered promising, whereas, a 40% is considered not promising. Assuming Type I and Type II errors are 0.10 and 0.20 respectively, then 17 patients will be accrued to the first stage of each arm. If 7 or fewer patients in either treatment arm respond, no additional patients will be enrolled in that treatment arm and the regimen will be considered not promising in this cohort of patients. If 8 or more patients respond in either treatment arm, then an additional 13 patients (for a total of 30) will be enrolled in that arm.

We will use the “pick the winner” format based on the randomized phase II clinical trials approach proposed by Simon et al.(Simon, Wittes et al. 1985). If both regimens are efficacious without significant differences in toxicity, then we plan to pick the winner as follows: If the number of patients who respond in one arm is at least 16 and it exceeds by at least 1 patient the number of responders in the other arm, then the arm with the higher response rate (RR) would be declared the winner. If neither arm had at least 16 responses, the regimens in both arms would be considered unworthy of further evaluation. No formal statistical comparison between the two arms is planned.



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Upon completion of the trial, if objective responses are observed in 16 patients or more in either arm, this new regimen will be declared to have promising activity. Based on this two stage design, the probability of completing the trial and declaring the new regimen effective is 80% when the true response rate is at least 60%. Although this sample size will not allow for statistical comparisons between arms, differences between the arms (such as toxicity or convenience, in addition to response) may generate hypotheses that can be tested in future studies.

15.2 Sample Size/Accrual Rate

Approximately 1 to 2 patients will be accrued per month. It is expected that the duration of the entire study should be approximately 30-60 months. 60 patients total will take part in Phase II of this study at Memorial Sloan-Kettering Cancer Center, The Cancer Institute of New Jersey, Robert Wood Johnson Medical School, Columbia University Medical Center, and the Winship Cancer Institute at Emory University. About 42 patients are expected to be treated at MSKCC; the remainder will be accrued by the subsites.

15.3 Stratification Factors

Patients will be randomized between the twice-weekly and weekly bortezomib treatment schedules at the time of enrollment. Each treatment arm will be analyzed independently from the other. As such, each treatment arm will accrue patients following the Simon two stage design.

15.4 Analysis of Secondary Endpoints

The following secondary endpoints will also be investigated in the phase II portion of the trial:

15.4.1 Progression-free survival, mean and median durations of response, event-free survival, and overall survival will be calculated from the observed durations. The Kaplan-Meier curves will be generated.

15.4.2 The primary safety endpoint is to determine toxicity based on NCI Common Terminology Criteria for Adverse Events version 4.0. The frequencies of toxicities will be tabulated for each arm separately.

15.5 Reporting and Exclusions

15.5.1 Evaluation of toxicity. All patients will be assessable for toxicity from the time of their first treatment with bortezomib. Patients who do not receive at least one dose of bortezomib will be excluded from this analysis and replaced.

15.5.2 Evaluation of response. All patients who meet eligibility criteria and are included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: (1) complete response, (2) partial



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response, (3) stable disease, (4) progressive disease, (5) early death from malignant disease, (6) early death from toxicity, (7) early death because of other cause, or (9) unknown (not assessable, insufficient data).

15.5.3 An incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

All conclusions should be based on all eligible patients except as outlined above. Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub-analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

16.0 RESEARCH PARTICIPANT REGISTRATION PROCEDURES

16.1 Research Participant Registration

Only individuals designated as consenting professionals on the facesheet of this protocol may obtain patient informed consent.

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. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed by MSKCC staff only. The completed signature page of the written consent/verbal script and a completed Eligibility Checklist must be faxed to PPR.

Patient registration must be initiated at Memorial Sloan Kettering Cancer Center ***within 48 hours of the patient signing the informed consent.***

16.1.1 For Participating Sites

Central registration for this study will take place at Memorial Sloan Kettering Cancer Center (MSKCC).



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To complete registration and enroll a patient from another institution, the study staff at that site must contact the designated research staff at MSKCC to notify him/her of the participant registration. The site staff then needs to fax registration/eligibility documents to the **Multicenter Trials Core** at MSKCC at **646-227-2482**.

The following documents must be sent for each enrollment **within 24 hours** of the informed consent being signed:

- The completed or partially completed MSKCC eligibility checklist
- The signed informed consent and signed HIPAA Authorization form (Research Authorization)
- Supporting source documentation for eligibility questions (laboratory results, pathology report, radiology reports, MD notes, Physical exam sheets, medical history, prior treatment records, and EKG report)

Upon receipt, the research staff at MSKCC will conduct an interim review to confirm documents are received to complete registration.

If the eligibility checklist is not complete, the patient will be registered PENDING and the site is responsible for sending a completed form within 30 days of the consent.

If the eligibility checklist is complete, the patient meets all criteria, all source documentation is received, the participating site IRB has granted approval for the protocol, and the site is in good standing with MSKCC, the MSKCC research staff will send the completed registration documents to the MSKCC Protocol Participant Registration (PPR) Office to be enrolled as stated in section 16.1. The participant will be registered.

Once eligibility has been established and the participant is registered, the participant will be assigned an MSKCC Clinical Research Database (CRDB) number (protocol participant number). This number is unique to the participant and must be written on all data and correspondence for the participant. This protocol participant number will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.

17.0 PROTECTION OF HUMAN SUBJECTS

Three copies of the MSKCC informed consent will be signed and dated by the patient or the patient's legally authorized representative, and by the physician obtaining informed consent before drug will be administered. Physicians qualified to obtain informed consent are the Investigators listed on the cover page of the protocol. One copy will be given to the patient, one copy will be filed in the patient's medical record, and one copy will be retained in the Protocol Participant Registration Office, Office of Clinical Research.



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Risks in Relation to Anticipated Benefit: All four drugs used in this protocol are active in B-cell lymphoproliferative disorders, and it is anticipated that the benefit derived from disease suppression will outweigh the risks of toxicity.

Provisions for Adverse Events: Anti-emetics will be prescribed to all patients in order to minimize nausea and vomiting. Infections will be treated with appropriate antimicrobial therapy. Blood and platelet transfusions will be given as clinically indicated.

Protocol Amendments and Study Termination: All protocol amendments will be reviewed and approved by Millennium Pharmaceuticals, Inc. before they are submitted to the Institutional Review Board of Memorial Hospital for approval and implementation.

Alternative Treatments: Patients with B-cell lymphoproliferative disorders not treated on this protocol could be treated with a conventional approach, or offered participation in another study, as appropriate. Many different chemotherapeutic regimens, radioimmunotherapies and stem cell transplant modalities have shown activity in these diseases.

Incentives: No incentives will be offered to patient/subjects for participation in this study. Participation is voluntary.

Costs: Most costs associated with the procedures specified in this protocol reflect those associated with the typical care provided to patients with B-cell lymphoproliferative disorders. Bortezomib will be provided free of charge, as will any other costs related to the protocol that are not considered standard of care. The patient will be responsible for the costs of standard medical care, including complications of treatment.

Eligibility Exceptions: There will be no exceptions to the eligibility requirements for this protocol without the authorization of the Institutional Review Board and the Privacy Board of Memorial Sloan-Kettering Cancer Center.

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.

17.2 Serious Adverse Event (SAE) Reporting

From the time the patient signs consent until he or she is 30 days post treatment, all SAEs must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org containing the following information:



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Fields populated from the CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- 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
- 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 information:
 - 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

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

17.3 Adverse events, regulatory and reporting requirements

17.3.1 Definitions

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.

Serious Adverse Event definition

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

- Results in death.



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- Is life-threatening. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, ie, 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. Hospital 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.

17.3.2 Procedures for AE and SAE reporting

17.3.2.1 It is the responsibility of the principal investigator and his/her research team to identify, review and report all necessary adverse events to the institutional IRB, Millennium Pharmacovigilance and governmental agencies (i.e., NCI and/or FDA) as appropriate. Adverse events should be identified through standard, routine protocol review and clinical assessment of each subject participating in the



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clinical trial. This review should be timely in order to meet the requirements for adverse event reporting defined below. All unexpected or serious adverse events (SAE), regardless of the type of research study, phase or sponsor must be reported to the MSKCC IRB (see section 19.2).

17.3.2.2 All serious adverse events (SAEs) (regardless of expectedness, causality, and whether commercial or investigational bortezomib is used) must be reported to Millennium Pharmacovigilance. See Section 19.3.5 for the reporting of SAEs. The sponsor-investigator is responsible to meet all regulations and requirements applicable to the sponsor-investigator.

17.3.3 Millennium Reporting Guidelines

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 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. Planned hospital admissions or surgical procedures for an illness or disease that existed *before the patient was enrolled in the trial* are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

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

Sponsor-investigator must report all SAEs, regardless of expectedness or relationship with any study drug, to Millennium Pharmacovigilance as soon as possible, but no later than 5 calendar days of the sponsor-investigator's observation or awareness of the event. For external sites, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Millennium Pharmacovigilance from all sites participating in the study. Subinvestigators 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 subinvestigator(s). Millennium Pharmacovigilance may request follow-up information to a reported SAE, which the sponsor-investigator will be responsible for providing to Millennium Pharmacovigilance.

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

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



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

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

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

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

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

Procedures for Reporting Drug Exposure during Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and must permanently discontinue study drug(s). All pregnancies and suspected pregnancies must be reported to Millennium Pharmacovigilance immediately. The pregnancy must be followed for the final pregnancy outcome (ie, delivery, still birth, miscarriage) and Millennium Pharmacovigilance will request this information from the sponsor-investigator.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to Millennium Pharmacovigilance immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome



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17.3.4 Serious Adverse Event (SAE) Reporting for Participating Sites

Responsibility of Participating Sites

- Participating sites are responsible for reporting all SAEs to the MSKCC PI via fax or e-mail within 3 calendar days of learning of the event.
- Participating sites should notify the MSKCC PI of any grade 5 event immediately
- Participating sites should use the SAE Report Template (Appendix A) to report SAEs to MSKCC.

SAE contact information for the Coordinating Center is listed below:

**Multicenter Trials Core
Study Coordinator
e-Fax: 646-227-2482**

Responsibility of MSKCC

- The MSKCC Research Staff is responsible for submitting all SAEs to the MSKCC IRB/PB as specified in 19.2 (and to the funding entity as described in 19.3.3)
- The MSKCC PI is responsible for informing all participating sites about unexpected SAEs as they occur within 30 days of receiving the stamped SAE from the MSKCC IRB/PB.
- Any report pertaining to a grade 5 event will be distributed to the participating sites as soon as possible

17.4 Safety Reports

- MSKCC will distribute outside safety reports to the participating sites immediately upon receipt.
- MSKCC must submit safety reports to the MSKCC IRB/PB according to institutional guidelines.
- Participating sites must submit safety reports to their institution's IRBs within 30 days of receipt from MSKCC or per participating site guidelines.

17.5 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).

17.6 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. Millennium Pharmaceuticals, Inc. 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 Europe. The pregnancy must be followed through delivery for SAEs.



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17.7 Inclusion of Children in Research

This protocol/project does not include children because the number of children is limited and because the majority are already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

18.0 DATA MANAGEMENT ISSUES

18.1 Data Management

Data

Standardized Case Report Forms (CRFs), directions for use and sign off requirements have been generated for this study. Blank case report forms will be sent to the study staff at each participating site for use. The participating Site PI is responsible for ensuring these forms are completed accurately, legibly and in a timely manner.

Source Documentation

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into CRFs. Relevant source documentation to be submitted throughout the study includes:

- Baseline measures to assess pre-protocol disease status (ex. CT, bone marrow)
- Treatment records
- Grade 3-5 toxicities/adverse events not previously submitted with SAE Reports
- Response designation

Data and Source Documentation Submission for Participating Sites

Participating sites should fax CRFs and source documentation to MSKCC to the contact provided below. Submissions should include a cover page listing all CRFs enclosed per participant.

FAX to the attention of:

Multicenter Trials Core

e-Fax: 646-227-2482

Data Review and Queries for Participating Site Data

Data and source documentation to support data should be transmitted to MSKCC according to chart below. Research staff at MSKCC will review data and source documentation as it is submitted. Data will be monitored against source documentation and discrepancies will be sent as queries to the participating sites. Queries will be sent by MSKCC Research staff twice a month.

Participating sites should respond to data queries within 14 days of receipt.



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Data and Source Submission Requirements and Timelines for Therapeutic Studies

	Baseline	Cycle 1	Cycle 2	Cycle 3	Cycle 4	SAE	Off Study
SUBMISSION SCHEDULE							
Source Documentation	Within 24 hours	within 14 days of end of cycle (until Cycle 8 if needed)				Within 3 days of event; updates to be submitted as available	Within 14 days of visit
CRFs	Within 7 days of visit						
Required Forms							
Demographics Form	X						
Medical History Form	X						
Concomitant Medications Form	X	X	X	X	X		X
Physical Exam Form	X	X	X	X	X		X
Treatment Form		X	X	X	X		X
Laboratory Form	X	X	X	X	X		X
Lesion/EOD Form					X ¹		X
Adverse Event Form		X	X	X	X	X	X
Serious Adverse Event Form						X	
Off Study Form							X

¹Lesion/EOD form should be provided after 4 cycles, and every restaging point thereafter.



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18.2 Quality Assurance

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 and 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 once a year or more frequently if indicated.

18.2.1 Quality Assurance for Participating Sites

Each site participating in the accrual of participants to this protocol will be audited by the staff of the MSKCC study team for protocol and regulatory compliance, data verification and source documentation. Audits may be accomplished in one of two ways: (1) selected participant records can be audited on-site at participating sites or (2) source documents for selected participants will be sent to MSKCC for audit. Audits will usually be determined by participant accrual numbers and rate of accrual, but can also be prompted by reported SAEs or request of MSKCC PI.

Audits will be conducted at least once shortly after initiation of participant recruitment at a site, annually during the study (or more frequently if indicated), and at the end or closeout of the trial. The number of participants audited will be determined by available time and the complexity of the protocol.

The audit will include a review of source documentation to evaluate compliance for:

- Informed consent documents and procedures
- Adherence to eligibility criteria
- Protocol defined treatment
- Required baseline, on study and follow-up protocol testing
- IRB documents (submitted amendments, annual continuing review reports, SAEs)
- Required specimen submission
- Pharmacy review, if applicable
- Case Report Form submissions to MSKCC: timing and accuracy

A wrap-up session will be conducted at the participating site and preliminary findings will be discussed with the participating site PI and research team. The preliminary results will be sent to the MSKCC PI.

Each audit will be summarized and a final report will be sent to the PI at the audited participating site within 30 days of the audit. The report will include a summary of findings, participant by participant case review, specific recommendations on any performance and/or shortcomings and request for corrective action, when necessary.



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When corrective action is required, the participating site must reply within 45 days of receipt of audit report with their corrective action plan.

A copy of the audit report and corrective action plan (if applicable) submitted by the participating site must be sent to the MSKCC IRB/PB, CRQA and maintained in the department's protocol regulatory binder.

18.2.2 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.

18.2.3 Response Review

Since therapeutic efficacy is a stated primary objective, all sites patient's responses are subject to review by MSKCC's Therapeutic Response Review Committee (TRRC). Radiology, additional lab reports and possibly bone marrow biopsies and/or aspirates will need to be obtained from the participating sites for MSKCC TRRC review and confirmation of response assessment. These materials must be sent to MSKCC promptly upon request.



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18.3 Regulatory Documentation

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC Institutional Review Board/Privacy Board (IRB/PB). Prior to implementing this protocol at the participating sites, approval for the MSKCC IRB/PB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to MSKCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, MSKCC will formally contact the site and grant permission to proceed with enrollment.

18.4 Amendments

Each change to the protocol document must be organized and documented by MSKCC and first approved by the MSKCC IRB/PB. Upon receipt of MSKCC IRB/PB approval, MSKCC will immediately distribute amendments to the participating sites, for submission to their local IRBs.

Participating sites must obtain approval for all non expedited amendments from their IRB within 90 calendar days of MSKCC IRB/PB approval. If the amendment is the result of a safety issue, sites will not be permitted to continuing enrolling new participants until the participating site IRB approval has been granted.

The following documents must be provided to MSKCC for each amendment within the stated timelines:

- Participating Site IRB approval
- Participating Site IRB approved informed consent form and HIPAA authorization



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18.5 Additional IRB Correspondence

Continuing Review Approval

The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to MSKCC within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of study activities.

Deviations and Violations

A protocol deviation on this study is defined as a request to treat a research participant who does not meet all the eligibility criteria, pretreatment evaluation, or who requires alteration in their study plan. If a deviation from this protocol is proposed for a potential or existing participant at MSKCC or a participating site, approval from the MSKCC IRB/PB is required prior to the action. Participating sites should contact the MSKCC PI who will in turn seek approval from the MSKCC IRB/PB.

A protocol violation is anything that occurs with a participant, which deviated from the protocol without prior approval from the MSKCC IRB/PB. For protocol violations that are identified after they occur, the participating site should report to MSKCC as soon as possible. The MSKCC PI will in turn report the violation to the MSKCC IRB/PB.

Participating sites should report deviations and violations to their institution's IRBs as soon as possible per that site's institutional guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations and violations should be submitted to MSKCC as received.

Other correspondence

Participating sites should submit other correspondence to their institution's IRB according to local guidelines, and submit copies of that correspondence to MSKCC.

Document maintenance

The MSKCC PI and the Participating Site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

The participating sites will ensure that all participating site IRB correspondence (IRB approval letters referencing protocol version date and amendment number, IRB approved protocol, appendices, informed consent forms, deviations, violations, and approval of continuing reviews) is maintained in the regulatory binder on site and sent to MSKCC.

A regulatory binder for each site will also be maintained at MSKCC; this binder may be paper or electronic.



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After study closure, the participating site will maintain all source documents, study related documents and CRFs for 7 years.

18.6 Noncompliance

If a participating site is noncompliant with the data and regulatory requirements set forth in section 18.0-18.2, accrual privileges may be suspended and/or contract payments may be withheld (if applicable), until the outstanding issues have been resolved.

19.0 RANDOMIZATION

19.1 Randomization for MSKCC

Patients will be randomized to a treatment schedule with bortezomib given on a weekly (Arm A) vs. twice-weekly (Arm B) schedule. After eligibility is established and immediately after consent is obtained, patients will be registered in the Protocol Patient Registrar (PPR) system and randomized using the Clinical Research Database (CRDB). To register and randomize, MSKCC staff will call PPR at (646) 735-8000 between the hours of 8:30 am and 5:30 pm, Monday – Friday. Randomization will be accomplished by the method of random permuted block.

19.2 Randomization for Non-MSKCC Participating Sites

Randomization to a treatment schedule with bortezomib given on a weekly (Arm A) vs. twice-weekly (Arm B) schedule for this study will take place at Memorial Sloan Kettering Cancer Center (MSKCC) immediately following registration. Protocol Patient Registrar (PPR) system should only be contacted by MSKCC research staff, and randomization results will be promptly reported to the participating site staff by MSKCC research staff via e-mail, along with the patient registration number.

20.0 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.



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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.

20.1 For Participating Sites

The investigators listed on the protocol cover page and their qualified designees at each participating site may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines.

Signed copies of the informed consent should be distributed as follows: One copy will be given to the participant to be retained for their personal records. One copy will be maintained on file at the MSKCC. The third copy will be confidentially maintained by the participating institution.

A note will be placed in the medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

21.0 CORRELATIVE STUDIES

21.1 Tissue Microarray: Pretreatment paraffin-embedded histologic samples will be obtained from all MSKCC patients, when possible. TMA blocks will be subjected to immunohistochemical staining targeting cell markers that will give insight into biological features predicted to relate to prognosis or response to treatment. TMA staining will be correlated with treatment outcome in each patient. We will then look for trends that would suggest baseline biological characteristics that correlate with ultimate response to bortezomib treatment. This correlative study will not require the harvesting of any additional tissue samples from the patients enrolled. Participating outside sites will not be asked to partake in these correlative studies.

21.2 DNA Sequencing, real-time PCR, and Gene Expression Studies: Funding is being sought for genetic studies. Once funding is obtained the informed consent will be revised to request patient permission for fine needle aspirate. DNA and RNA will be isolated from FNA samples collected from consenting patients to understand the roles of specific



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genes in disease pathogenesis and response to the treatment protocol. Genomic DNA will be subjected to sequencing to detect mutations and loss of heterozygosity, and to real-time PCR to detect gene amplifications and deletions. RNA will be used to generate cDNA through RT-PCR for analysis of gene expression. Samples for these studies will require additional FNA procedures but will not require any additional biopsy procedures than what's outlined in the other sections. Patients who participate will undergo 2 FNA procedures. Both will be Research Non-Billable and funded by Geoffrey A. Beene Cancer Center Grant and start-up funds from Sloan Kettering Institute. This optional correlative study will only be open to follicular lymphoma patients. Participating outside sites will not be asked to partake in these correlative studies.

22.0 ADMINISTRATIVE REQUIREMENTS

22.1 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 sponsor-investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations. This is the responsibility of the sponsor-investigator.

22.2 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 the protocol and informed consent documents be reviewed by Millennium prior to IRB/IEC submission.

22.3 Patient Information and Informed Consent

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



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22.4 Institutional Review

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

22.5 Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The sponsor-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.

22.6 Protocol Compliance

The sponsor-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 sponsor-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.

22.7 On-site Audits

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

22.8 Drug Accountability

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



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Any unused or expired commercially labeled bortezomib must be returned to Millennium. Bortezomib destruction at any study site is not allowed for commercially labeled product that is associated with this Investigator Initiated Study.

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

22.9 Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the sponsor-investigator or Millennium, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the sponsor-investigator or Millennium by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

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

22.10 Record Retention

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



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23.0 APPENDICES

APPENDIX A: SAE Template (attached as a separate protocol document)

APPENDIX B: Karnofsky Performance Status Scale

The following table presents the Karnofsky performance status scale:

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

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

Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH. The use of nitrogen mustards in the palliative treatment of cancer. *Cancer* 1948; 1(4):634-656.

Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM, ed. *Evaluation of Chemotherapeutic Agents*. New York: Columbia University Press, 1949, 19 1-205.



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APPENDIX C: Body Surface Area and Creatinine Clearance Calculations

Body surface area (BSA) should be calculated using a standard nomogram that yields the following results in meters squared (m²):

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

or

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

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

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

For females use 85% of calculated CrCl value.

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



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**APPENDIX D: NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION OF
CARDIAC DISEASE**

The following table presents the NYHA classification of cardiac disease:

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

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

APPENDIX E: Common Terminology Criteria for Adverse Events Version 4.0

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



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APPENDIX F: FACT/GOG-Neurotoxicity Questionnaire, Version 4.0



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IRB Protocol

IRB#: 05-103 A(14)

NEUROTOXICITY ASSESSMENT TOOL

Patient Name _____ Visit Date _____

Instructions for Patients

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

	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have numbness or tingling in my hands	0		2	3	4
I have numbness or tingling in my feet	0		2	3	4
I feel discomfort in my hands	0		2	3	4
I feel discomfort in my feet	0		2	3	4
I have joint pain or muscle cramps	0		2	3	4
I feel weak all over	0			3	4
	0			3	4
	0			3	4
	0			3	4
	0		2	3	4
	0		2	3	4

Instructions for Health Care Professionals

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

NCI Common Toxicity Criteria for Peripheral Neuropathy and Neuropathic Pain³

Peripheral Sensory Neuropathy (NCI CTC Grade)

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

Neuropathic Pain (NCI CTC Grade)

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

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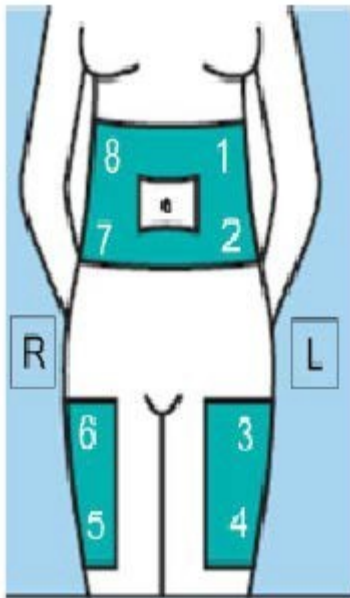
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APPENDIX H: BORTEZOMIB INJECTION SITE TOOL

Bortezomib S for IRB #05-103: A Phase II Study of the Novel Proteasome Inhibitor Bortezomib in Combination with Rituximab, Cyclophosphamide and Prednisone in Patients with Relapsed/Refractory Indolent B-Cell Lymphoproliferative Disorders and Mantle Cell Lymphoma (MCL)

Instructions (Per Protocol section 4.1.2): Bortezomib will be administered as a subcutaneous (SC) injection administered at a concentration of 2.5 mg/mL normal [0.9%] saline. SC injection sites are the thighs or abdomen. Injection sites will be rotated for subsequent injections within a cycle (see figure below).



	<i>To Be Completed By Nurse</i>
Date	
Cycle Number	
Day Number	
Previous Site of Injection (#)	
Today's Site of Injection (#)	

RN Signature: _____

Date: _____

Comments: _____



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