A Phase 2 Trial of Bortezomib in KRAS-Mutant Non-Small Cell Lung Cancer in Never Smokers or Those with KRAS G12D

PROTOCOL FACE PAGE FOR

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Title: A Phase 2 Trial of Bortezomib in *KRAS*-Mutant Non-Small Cell Lung Cancer in Never Smokers or Those with *KRAS* G12D

Objectives

The primary objective of this study is:

to determine the efficacy of single-agent subcutaneous bortezomib in patients with advanced (stage IIIB/IV) *KRAS*-mutant non-small cell lung cancer (NSCLC) in never-smokers (<100 lifetime cigarettes) or patients with a G12D mutation. The primary endpoint will be best objectiveresponse rate (CR+PR) at any time prior to progression by RECIST v1.1.

The secondary objectives of this study are to evaluate:

1. progression-free survival
2. overall survival
3. 8-week stable disease
4. toxicity (NCI-CTCAE v4.0)

Patient Population: patients with advanced (stage IIIB/IV) KRAS-mutant non-small cell lung cancer (NSCLC) who either are never-smokers (<100 lifetime cigarettes) or have a G12D mutation

Number of Patients: 25 patients evaluable for response.

Study Design and Methodology: This will be a single-institution, open label, two-stage, single agent trial of subcutaneous bortezomib in patients with advanced (stage IIIB/IV) *KRAS*-mutant NSCLC with a never-smoking history or a G12D mutation.

Treatments Administered: Bortezomib (1.3 mg/m^2/dose) will be administered by subcutaneous injection on days 1, 4, 8, and 11 of a 21-day cycle. Cycles will be repeated until disease progression or unacceptable toxicity.

Efficacy Data Collected: The following evaluations will be conducted to assess the efficacy of bortezomib - radiographic response rate by RECIST v1.1, progression-free survival, and overall survival.

Safety Data Collected: The following evaluations will be conducted to assess the safety of bortezomib - toxicity assessments by NCI-CTCAE v4.0.

Statistical Design: Stage II minimax design testing the null hypothesis of 10% objective response rate (ORR) against alternative of 30% ORR. In the first stage, 16 evaluable patients will be accrued- if 2/16 have a response, 9 additional patients will be accrued in the second stage. Bortezomib will be considered worthy of further study if 5/25 patients respond.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

The primary objective of this study is:

To determine the efficacy of single-agent subcutaneous bortezomib in patients with advanced (stage IIIB/IV) KRAS-mutant non-small cell lung cancer (NSCLC) who either are never-smokers (<100 lifetime cigarettes) or have a G12D mutation. The primary endpoint will be best objective response rate (ORR,= PR+CR) at any time prior to progressionby RECIST v1.1.

HYPOTHESIS: The use of subcutaneous bortezomib in patients with advanced (stage IIIB/IV) KRAS-mutant non-small cell lung cancer (NSCLC) who either are never-smokers (<100 lifetime cigarettes) or have a G12D mutation will result in improved efficacy in this patient population, as determined by overall response rates.

The secondary objectives of this study are to evaluate:

1. progression-free survival
2. overall survival
3. 8-week stable disease
4. toxicity (NCI-CTCAE v4.0).

3.0 BACKGROUND AND RATIONALE

3.1 Proteasome Inhibition in *KRAS*-Mutant Lung Cancer

Lung Cancer and *KRAS* Mutations: Lung cancer is the most common cause of cancer death in the U.S. and worldwide. Approximately 215,020 new lung cancer cases are diagnosed in the U.S. each year,[1] and approximately 1.44 million new lung cancer cases are diagnosed worldwide.[2] Of patients who are diagnosed with lung cancer, more than 80% eventually succumb to the disease. Histologically, the vast majority of patients with lung cancer have non-small cell lung cancer (NSCLC). Platinum doublet chemotherapy is the standard first-line treatment for NSCLC, and single agent chemotherapy or erlotinib provides clinical benefit in second-line patients.[3] The overall survival for patients with lung adenocarcinomas who receive standard first line therapy is approximately 12 months with an overall survival of 2% and 13% at 5 years for clinically-staged and pathologically-staged disease, respectively. Thus, despite the advances in the treatment of NSCLC over the past decade, there remains a high unmet medical need for new treatments for lung cancer.

Point mutations in *KRAS* are the most common oncogene driver mutations in NSCLC, and occur in approximately 25% of adenocarcinomas of the lung. In the United States alone, this molecularly selected cohort accounts for an approximate incidence of 22,000 patients a year. *KRAS* mutations have been shown to confer resistance to epidermal growth factor receptor (EGFR)-targeted therapies in colorectal cancer[4] and emerging data suggest that lung cancer patients with mutations of the *KRAS* oncogene are similarly resistant to the EGFR-tyrosine kinase inhibitors (TKIs), erlotinib and gefitinib.[5] Some data also suggest that NSCLC patients with *KRAS* mutations may not respond to adjuvant platinum-based chemotherapy,[6] although subsequent analyses have shown conflicting results. Finally, some studies have shown that the presence of *KRAS* mutations represents a negative prognostic factor for patients with NSCLC.[7] Taken together, there is a need for new medical treatments for patients with *KRAS*-mutant NSCLC.

Never-smokers and *KRAS* G12D: Although *KRAS* mutations were classically thought to occur in smokers, an evaluation of nearly 500 patients from Memorial Sloan Kettering noted a 15% incidence of *KRAS* mutations in lung adenocarcinomas from never-smokers.[8] Furthermore, *KRAS* transition mutations were noted more commonly in never-smokers, compared to transversions that occurred more frequently in former or current smokers. In this cohort, G12D was the most common *KRAS* mutation in never-smokers and the second most common mutation overall. Never-smokers on the whole, are thought to have tumors that are genetically less complex than tumors in smokers[9], making the use of targeted therapy in the former more attractive.

KRAS Mutants Rely on NF-kB: NF-kB forms a family of transcription factors that participates in a number of essential biological processes such as inflammation, the immune response, development, cell growth, and survival.[10] Preclinical evidence suggests that patients with *KRAS* mutations are highly dependent on the NF-kB pathway. Barbie *et al*[11] employed a systematic RNA interference (RNAi) screen to detect synthetic lethal partners of oncogenic *KRAS*. Knockdown of the non-canonical IkB kinase, TKB1, resulted in apoptosis in *KRAS* mutant human cell lines. TKB1 was found to activate NF-kB signaling and subsequent pro-survival signals such as BCL-XL and cREL. In a separate paper, Meylan *et al* demonstrated that the introduction of a nonphosphorylatable NF-kB super repressor, IkB, in *KRAS* G12D-mutant murine tumors resulted in loss of cell viability secondary to apoptosis.[12]

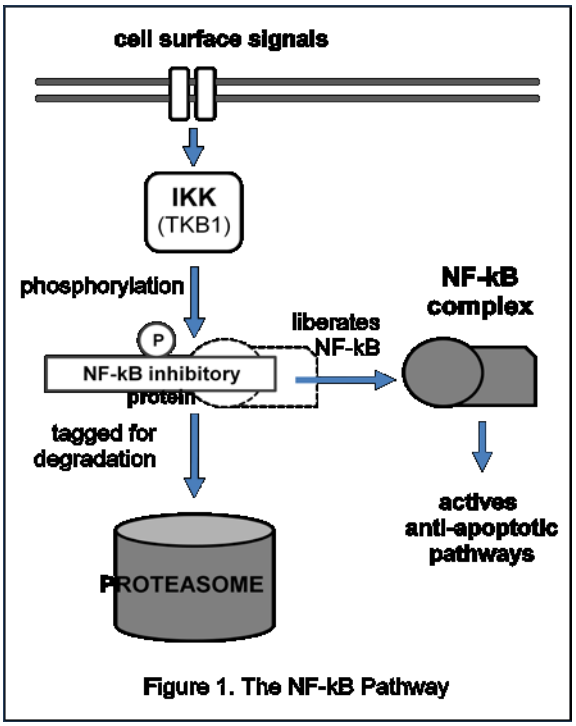

Figure 1. The NF-kB Pathway

Proteasome Inhibition Downregulates NF-kB and Induces *KRAS*-Mutant Tumor Regression: The fact that *KRAS* mutant tumors are dependent on NF-kB signaling provides a strong rationale for the use of targeted therapy with proteasome inhibitors. These drugs have been shown to result in downregulation of the NF-kB pathway via prevention of the degradation of NF-kB inhibitory proteins such as IkB.[13] In a separate genome-wide RNAi screen, Luo *et al* demonstrated a diverse set of proteins with synthetic lethal interactions with oncogenic *KRAS*. Among these, knockdown of proteasome subunits such as PSMA5, PSMB5, and PSMB6 was shown to result in accumulation of *KRAS* mutant cells in prometaphase and subsequent death. Furthermore, two structurally distinct small molecule inhibitors of the proteasome, bortezomib and MG132 exhibited synthetic lethality in RAS mutant cells in the study, again secondary to a profound prometaphase block.[14] In $KRAS^{LSL\text{-}G12D/wt}$;$p53^{flox/flox}$ mice (G12D-mutant), bortezomib induced *in-vivo* tumor regression of lung adenocarcinoma. Taken together, these observations provide a strong biologic rationale for the use of proteasome inhibition with bortezomib in the treatment of *KRAS*-mutant NSCLC.

Our clinical experience at MSKCC supports the hypothesis that proteasome inhibition results in synthetic lethality in *KRAS*-mutant lung cancers. We have seen impressive reductions in tumor volume (near complete responses) with bortezomib in two patients at our center, one in each of two separate trials. We conjectured that the individuals might harbor a similar genetic signature and

subjected their tumors to mutational analysis. Genotyping revealed that both samples harbored a *KRAS* G12D mutation

At MSKCC, an average of 2-3 patients with G12D-mutant advanced adenocarcinoma alone are seen per month based on LC-MAP data. In addition, 64 patients with G12D mutations have already been identified at MSKCC as of 2011. The target accrual for this protocol is 25 patients. Based on our *KRAS* G12D volume alone (not taking into account our never-smoker *KRAS*-mutant population which represents 15% of all *KRAS* mutations), we expect to fully accrue within 12-18 months of study initiation.

3.2 Bortezomib: Mechanism of Action

Bortezomib for Injection is a small-molecule proteasome inhibitor developed by Millennium Pharmaceuticals, Inc., (Millennium) as a novel agent to treat human malignancies. Bortezomib is currently approved by the United States Food and Drug Administration (US FDA) for the treatment of patients with multiple myeloma (MM). It is also indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy.

By inhibiting a single molecular target, the proteasome, bortezomib affects multiple signaling pathways. The antineoplastic effect of bortezomib likely involves several distinct mechanisms, including inhibition of cell growth and survival pathways, induction of apoptosis, and inhibition of expression of genes that control cellular adhesion, migration, and angiogenesis. Thus, the mechanisms by which bortezomib elicits its antitumor activity may vary among tumor types, and the extent to which each affected pathway is critical to the inhibition of tumor growth could also differ. Bortezomib has a novel pattern of cytotoxicity in National Cancer Institute (NCI) in vitro and in vivo assays.[15] 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.[16,17,18,19,20,21,22,23,24,25,26,27,28] Notably, bortezomib induces apoptosis in cells that over express bcl-2, a genetic trait that confers unregulated growth and resistance to conventional chemotherapeutics.[29]

The mechanisms of action leading up to apoptosis have been more clearly defined and include initiation of the unfolded protein response and direct/indirect effects on various molecular targets including cell cycle control proteins p27 and p21, cyclins, signal transduction molecules, transcription factors c-jun and HIF1-α, tumor suppressor protein p53, angiogenesis factors, and many others. Bortezomib is thought to be efficacious in multiple myeloma via its inhibition of nuclear factor κB (NF-κB) activation, its attenuation of interleukin-6 (IL-6)-mediated cell growth, a direct apoptotic effect, and possibly anti-angiogenic and other effects.[30,31,32,33,34,35,36,37]

3.3 Bortezomib: Clinical Experience

It is estimated that as of June 2011, more than 300,000 patients have been treated with bortezomib, including patients treated through Millennium-sponsored clinical trials, Investigator-Initiated Studies, the US NCI Cancer Therapy Evaluation Program (CTEP), and with commercially available drug. Bortezomib has been commercially available since 13 May 2003. For further details regarding the drug, please refer to the Investigator's Brochure.

3.3.1 Intravenous Administration

In a phase 1 trial in patients with refractory hematologic malignancies, the MTD for a twice weekly dosing for 4 weeks of a 42-day cycle was 1.04 mg/m^2/dose, with DLTs of thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise.[38] The toxicity was greatest during the third and fourth weeks of therapy. In the 3-week schedule of bortezomib monotherapy (4 doses, given on Days 1, 4, 8, and 11 of a 21-day treatment cycle), the DLT occurred at 1.56 mg/m^2/dose (3 subjects with Grade 3 diarrhea and 1 with peripheral sensory neuropathy). Therefore, the MTD at this schedule was 1.3 mg/m^2/dose. Antitumor activity was reported in subjects with Non-Hodgkin's Lymphoma (NHL), MM, Waldenström's Macroglobulinemia, squamous cell carcinoma of the nasopharynx, bronchoalveolar carcinoma of the lung, renal cell carcinoma, and prostate cancer.[39,40,41,42]

The safety and efficacy of bortezomib in subjects with MM were investigated in two phase 2 clinical studies, studies M34100-024 (subjects with first relapse)[43] and M34100-025 (subjects with second or greater relapse and refractory to their last prior therapy).[44] In M34100-025, 202 heavily pretreated subjects with refractory MM after at least 2 previous treatments received bortezomib, 1.3 mg/m^2 on Days 1, 4, 8, and 11 of a 21-day treatment cycle. Complete responses (CRs) were observed in 4% of subjects, with an additional 6% of patients meeting all criteria for CR but having a positive immunofixation test. Partial response (PR) or better was observed in 27% of subjects, and the overall response rate (CR, PR, and minor response [MR] combined) was 35%. Seventy percent of subjects experienced stable disease or better.

The phase 3 study (M34101-039)[45], also referred to as the APEX study, was designed to determine whether bortezomib provided benefit (time to progression [TTP], response rate, and survival) to patients with relapsed or refractory MM relative to treatment with high-dose dexamethasone. The study was also designed to determine the safety and tolerability of bortezomib relative to high-dose dexamethasone, and whether treatment with bortezomib was associated with superior clinical benefit and quality of life relative to high-dose dexamethasone. A total of 669 patients were enrolled and 663 patients received study drug (bortezomib: 331; dexamethasone: 332). Bortezomib resulted in an increase in response rates, TTP, and OS. Updated response rates and survival data were reported for M34101-039.[46] The phase 3 study (MMY 3002) known as the VISTA study, evaluated the safety and efficacy of the combination of bortezomib, melphalan, and prednisone in previously untreated multiple myeloma patients who were not candidates for stem cell transplant.[47] The study was designed to determine the benefit of adding bortezomib to melphalan and prednisone as assessed by TTP. The addition of bortezomib resulted in improvements in response rate, TTP, time to next therapy, treatment-free interval, and OS with a higher incidence of peripheral sensory neuropathy and GI symptoms in the VMP group despite similar hematologic toxicities.

3.3.2. Subcutaneous Administration

After a randomized Phase 1 trial demonstrated similar drug exposure, proteasome inhibition, and efficacy and safety profiles between VELCADE IV and SC, a Phase 3 study compared the efficacy and safety of subcutaneous versus intravenous bortezomib at the approved 1.3 mg/m^2 dose and twice per week schedule in patients with relapsed multiple myeloma.[33] Subcutaneous bortezomib was shown to offfer non-inferior efficacy to standard intravenous administration, with an improved safety profile.

222 patients were randomly assigned to receive subcutaneous (n=148) or intravenous (n=74) bortezomib. The response-evaluable population consisted of 145 patients in the subcutaneous group and 73 in the intravenous group. Patients received a median of eight cycles in both groups. ORR after four cycles was 42% in both groups showing non-inferiority (p=0·002). After a median follow-up of 11.8 months in the subcutaneous group and 12.0 months in the intravenous group, there were no significant differences in time to progression and 1-year overall survival.

Grade 3 or worse adverse events were reported in 84 (57%) patients in the subcutaneous group versus 52 (70%) in the intravenous group; the most common were thrombocytopenia (19 [13%] vs 14 [19%]), neutropenia (26 [18%] vs 13 [18%]), and anaemia (18 [12%] vs six [8%]). Peripheral neuropathy of any grade (56 [38%] vs 39 [53%]; p=0.044), grade 2 or worse (35 [24%] vs 30 [41%]; p=0.012), and grade 3 or worse (nine [6%] vs 12 [16%]; p=0.026) was significantly less common with subcutaneous than with intravenous administration. Subcutaneous administration was locally well tolerated. In conclusion, the SC administration of VELCADE has good local tolerance. The systemic safety profile for the SC administration of VELCADE was associated with a lower incidence of Grade ≥3 adverse events, and treatment modifications (discontinuations and dose reductions). In particular, there was a lower incidence of peripheral neuropathy reported. Additional information regarding bortezomib is available in the current Investigator's Brochure.

3.3.3 Potential Risks with Bortezomib

To date, more than 300,000 patients have been treated with bortezomib in both clinical trials investigating its use in hematological malignancies and solid tumors, and in patients who were treated with commercially available bortezomib. The known anticipated risks of bortezomib therapy are presented in Appendix A. These risks are grouped according to the combined frequency observed in an integrated analysis of AEs in sponsored clinical studies of single-agent bortezomib dosed at 1.3 mg/m^2 twice weekly on a 21-day schedule, in patients with multiple myeloma and mantle cell lymphoma.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a single-institution, open label, one-arm Simon minimax two-stage phase II clinical trial of subcutaneous bortezomib in patients with advanced (stage IIIB/IV) KRAS-mutant non-small cell lung cancer (NSCLC) who either are never-smokers (<100 lifetime cigarettes) or have a G12D mutation.

A maximum of 25 patients will be enrolled in this trial in a two-stage design. Stage 1 involves a preliminary determination of efficacy of the drug in a total of 16 patients. If zero to one responses are observed , the drug would be considered unworthy of study with consequent trial termination.

However, if 2 or more responses are observed in this cohort by RECIST v1.1 criteria, the trial would then proceed to an expanded cohort in Stage 2. Stage 2 involves accrual of an additional 9 patients. Bortezomib would be considered worthy of further study in this population if 5 or more patients out of the total 25 enrolled have an objective response.

4.2 Intervention

Bortezomib will be administered by subcutaneous injection twice weekly for 2 weeks (Days 1, 4, 8, and 11) at 1.3 mg/m^2/dose followed by a 10-day rest period for a 21 day cycle. Dose modifications are permitted as per a prescribed algorithm. Acyclovir at 400mg daily is recommended as prophylaxis for herpes zoster.

Restaging scans, with evaluation of response, will be done every 2 cycles (6 weeks of treatment ± 7 days). Treatment will continue until clinical disease progression, unacceptable toxicity, treatment delay > 2 weeks, or at the discretion of the treating physician or patient.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1. Preparation, Handling, Storage, and Destruction

Bortezomib (VELCADE) is available in sterile, single use vials containing 3.5 mg of VELCADE with a 1:10 ratio of bortezomib to mannitol.

SUBCUTANEOUS: Each vial of VELCADE for Injection should be reconstituted under a laminar flow biological cabinet (hood) within eight hours before dosing with 1.4 mL of normal (0.9%) saline, Sodium Chloride Injection USP, so that the reconstituted solution contains VELCADE at a concentration of 2.5 mg/mL for subcutaneous administration. For injection site reactions, a more dilute concentration of 1 mg/mL can be used.

Vials containing lyophilized VELCADE® (bortezomib) for Injection should be stored according to the label requirements. For the United States, store at USP Controlled Room Temperature which is 25ºC (77ºF); for Europe, do not store above 30ºC (86ºF); excursions permitted from 15 to 30ºC (59-86ºF). To date, stability data indicate that the lyophilized drug product is stable for at least 18 months when stored under the recommended conditions. Stability studies are ongoing, and Millennium Pharmaceuticals, Inc. will notify the investigator should this information be revised during the conduct of the study.

INTRAVENOUS (used ONLY in the event of intolerable subcutaneous toxicity e.g. injection site reactions, see Section 5.3): Prior to IV administration, the contents of each vial must be reconstituted with 3.5 mL of normal (0.9%) saline (sodium chloride injection). The reconstituted product should be a clear and colorless solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If any discoloration or particulate matter is observed, the reconstituted product should not be used.

Bortezomib contains no antimicrobial preservative. When reconstituted as directed, bortezomib may be stored at 25ºC (77ºF). Reconstituted VELCADE should be administered within 8 hours of preparation. The reconstituted material may be stored in the original vial and/or the syringe prior to administration. The product may be stored for up to 8 hours in a syringe; however, total storage time for the reconstituted material must not exceed 8 hours when exposed to normal indoor lighting.

Bortezomib is cytotoxic. As with all cytotoxic drugs, caution is required when preparing and handling bortezomib solutions. Cytotoxic drugs should only be handled by staff specially trained in the safe handling of such preparations. The use of gloves and other appropriate protective clothing is recommended. In case of skin contact, wash the affected area immediately and thoroughly with soap and water for at least 15 minutes. If product contacts eye, immediately flush eye thoroughly with water for at least 15 minutes. Always contact a physician after any form of body contact. All materials that have been used for preparation should be disposed of according to standard practices. A log must be kept of all disposed materials.

Prior to reconstitution the vials should remain in the cartons to protect them from light. Dissolution is completed in approximately 10 seconds. The reconstituted solution is clear and colorless, with a final pH of 5 to 6. Reconstituted bortezomib should be administered promptly and in no case more than 8 hours after reconstitution.

5.2. Dispensing and Administration

Drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients may be treated on an outpatient basis, if possible.The drug will be prepared under the supervision of a pharmacist, or appropriately qualified and trained personnel. The amount (in mg) of drug to be administered will be determined based on body surface area. Body surface area is to be calculated based on body weight using a standard nomogram or calculation (Appendix D). The dose should be calculated prior to Cycle 1 Day 1 based on weight measured at screening. Dose should be recalculated at the start of a cycle only if a significant change in weight has occurred (>10%). If a patient experiences a notable change in weight within a cycle, as determined by an unscheduled weight assessment, then the patient's dose should be recalculated at that time based on clinical judgment. There must be at least 72 hours between each dose of bortezomib.

IMPORTANT NOTE: Intravenous and subcutaneous route of administration have different reconstituted concentrations. Caution should be used when calculating the volume to be administered. For administration:

> SUBCUTANEOUS: Administer subcutaneously – for subsequent doses, administer at least 1 inch from an old site and never administer to tender, bruised, erythematous, or indurated sites. If injection site reaction occurs, the more dilute 1 mg/mL concentration may be used subcutaneously (Section 5.1).
>
> INTRAVENOUS (used ONLY in the event of intolerable subcutaneous toxicity e.g. injection site reactions, see Section 5.3): Administer the appropriate dose via rapid I.V. push (approximately 3-5 seconds).

5.3. Precautions for Subcutaneous Administration

- 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. If local injection site reactions occur following VELCADE administration

subcutaneously, a less concentrated VELCADE solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously. Alternatively, the IV route of administration can be considered at the investigator's discretion. In clinical trials of VELCADE IV, local skin irritation was reported in 5% of patients, but extravasation of VELCADE was not associated with tissue damage. In a clinical trial of subcutaneous VELCADE, a local reaction was reported in 6% of patients as an adverse event, mostly redness. Should IV bortezomib be used, the dosing and monitoring schedule for patients is identical to that of SQ administration (Section 9.1 and Section 9.2.1 for dose reductions)

5.4. Binding, Packaging, Labeling

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

5.5. Drug Destruction

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

5.6. Product Complaints

A product complaint is a verbal, written, or electronic expression which implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see the following) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium quality representative. For Product Complaints, call MedComm Solutions at: **+1-866-835-2233**

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Pathologic or cytologic evidence of non-small cell lung cancer (NSCLC)
2. Documented *KRAS* mutation
3. History of smoking < 100 cigarettes (never-smoker) OR patient with a *KRAS* G12D mutation regardless of smoking history
4. Clinical stage IIIB/IV or recurrent/medically inoperable NSCLC
5. Age ≥ 18 years
6. Three (3) weeks since last chemotherapy, and three (3) weeks since prior radiation therapy and recovered from treatment
7. Karnofsky performance status ≥ 70%
8. Adequate hematologic and/or hepatic function

a. WBC ≥ 3,000/ul or absolute neutrophil count ≥ 1,000/ul
b. Hemoglobin ≥ 9.0 g/dl
c. Platelet count ≥ 100,000/ul
d. AST ≤ 2.0 X ULN (upper limit of normal)
e. Total bilirubin ≤1.5 x ULN

9. Measurable indicator lesions by RECIST v1.1 criteria.
10. Voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.
11. 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.
12. Male subjects 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

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

1. Uncontrolled central nervous system metastases defined as any lesion which is either
   a. symptomatic, or
   b. requiring escalating doses of corticosteroids
2. Significant medical history or unstable medical condition such as
   a. uncontrolled diabetes
   b. myocardial infarction within 6 months prior to enrollment
   c. New York Heart Association Class III or IV heart failure (Appendix E)
   d. severe uncontrolled ventricular arrythmias
   e. uncontrolled angina
   f. ECG evidence of acute ischemia or active conduction system abnormalities
3. Baseline ≥ grade 2 peripheral neuropathy by CTCAE v 4.0 (Appendix B)
4. Known hypersensitivity to boron or mannitol
5. Female patients who are pregnant/lactating or have a positive serum or urine β-hCG pregnancy test

6. Serious medical or psychiatric illness likely to interfere with participation in this clinical study.
7. No active concurrent malignancy, with the exception of
   a. *in-situ* malignancy
   b. completely resected basal cell carcinoma or squamous cell carcinomas of the skin
   c. low-risk prostate cancer after curative therapy
8. 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

7.0 RECRUITMENT PLAN

Eligible patients with *KRAS*-mutant advanced NSCLC will be recruited from the Thoracic Oncology Service at MSKCC. Testing for *KRAS* mutations is performed routinely for all adenocarcinomas of the lung. Every attempt will be made to recruit women and minorities in this study. Participation is voluntary. The consenting physician will inform patients of their diagnosis and current treatment options including standard treatment, and the risks, benefits and experimental nature of this treatment program. There are no gender or racial restrictions. Patients under the age of 18 are excluded because this disease rarely affects patients in this age group.

8.0 PRETREATMENT EVALUATION

Patients will undergo baseline screening after informed consent is obtained. This includes the following, to be completed within 14 days of starting treatment, except for imaging which can be completed within 30 days of treatment initiation, unless otherwise stated:

(1) medical history
(2) baseline evaluation of symptoms and detailed medication list
(3) physical examination
(4) evaluation for weight loss and performance status (Appendix C)
(5) height (anytime prior to treatment), weight, and vital signs
(6) blood work
   (a) complete blood count
   (b) comprehensive metabolic panel
(7) pregnancy test (for women of child-bearing potential, pregnancy testing is not required for postmenopausal or surgically-sterilized women)
(8) baseline electrocardiogram
(9) baseline imaging (within 30 days of treatment initiation)
   (a) computed tomography and/or MRI of the chest, abdomen, and pelvis
   (b) MRI of the brain only if judged by investigator to be indicated

9.0 TREATMENT/INTERVENTION PLAN

9.1 Schedule and Dose Administration

Bortezomib is to be administered subcutaneously in 21-day cycles at a dose of 1.3 mg/m^2/dose on days 1, 4, 8, and 11. Treatment will only be initiated once eligibility criteria have been met and the appropriate pretreatment evaluations performed.

Antiviral prophylaxis with 400 mg of acyclovir daily is recommended for all patients as herpes zoster can occur commonly in patients who receive bortezomib without prophylaxis. For sexually-active patients, it is recommended that either 1 highly effective method of contraception or 2 effective methods of contraception be used as detailed in Appendix F.

Bortezomib will be continued until:

(1) disease progression
(2) unacceptable toxicity
(3) treatment delay >2 weeks, or
(4) at the discretion of the patient or treating physician

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

9.2 Toxicity-Based Dose and Schedule 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 Toxicity Criteria for Adverse Events (CTCAE v4.0, Appendix B). Should significant local reaction occur due to subcutaneous administration, a switch to the IV formulation at the same dose and schedule can be considered but only at the investigator's discretion.

9.2.1. General Algorithm

In general, all previously established or new toxicities observed any time are to be managed as described in the following table:

Table 9.1. Toxicity Management

Toxicity	Grade	Action
Lymphopenia	Any	None
Nonhematological toxicity*	3	Hold bortezomib up to 2 weeks or until toxicity returns to grade 1 or better
	4	Discontinue bortezomib
Hematological Toxicity	4	Hold bortezomib up to 2 weeks or until all of the following: • Hgb ≥ 8g/dL (grade 2 or better) • Platelets ≥ 75 K/mcL (grade 1 or better) • ANC ≥ 1000 K/mcL (grade 2 or better)

*excludes neuropathy & hepatic toxicities: management of these toxicities discussed subsequently

DOSE MODIFICATION LEVELS FOR BORTEZOMIB

all doses given on D1, 4, 8, and 11 of a 21-day cycle

Starting dose	**1.3 mg/m^2**
Dose Level -1	**1.0 mg/m^2**
Dose Level -2	**0.7 mg/m^2**

If bortezomib has been held:

i) If the toxicity does not resolve within ≤ 2 weeks, bortezomib must be discontinued
ii) If the toxicity resolves as described in the table above, bortezomib can be restarted, however dose must be reduced by approximately 25% as follows:

(1) If the patient was receiving 1.3 mg/m^2, reduce to **Dose Level -1**.

(2) If the patient was receiving 1 mg/m^2, reduce to **Dose Level -2**

(3) if the patient was receiving 0.7 mg/m^2, discontinue drug unless patient is responding, in which case, drug continuation at the discretion of the principal investigator.

If the drug is discontinued, every effort will be made to have patients evaluated for response at the planned time. If this is not possible, the patient will be considred a non-responder. Please refer to the Investigator's Brochure for information regarding the rationale behind the dose for each dose modification level as based on previous experience with bortezomib.

Once bortezomib is reduced for any toxicity, the dose may not be re-escalated.

9.2.2. Neurologic Toxicities

Patients who experience bortezomib-related neuropathic pain or peripheral sensory neuropathy are to be managed as presented in the following table:

Table 9.2. Management of Patients With 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 without pain or loss of function	No action
Grade 1 with pain or Grade 2	Reduce bortezomib by one dose level; if already at at **Dose Level -2**, discontinue drug
Grade 2 with pain or Grade 3	Withhold bortezomib therapy until toxicity resolves. When toxicity resolves reinitiate at **Dose Level -2** and change treatment schedule to once per week. If already at **Dose Level -2**, discontinue drug.
Grade 4	Discontinue bortezomib

Source: VELCADE (bortezomib) for Injection Investigator's Brochure Edition 14.
Grading based on NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0

9.2.3. Hepatic Impairment

Patients with bilirubin ≤ 1.5 x ULN (grade 1) do not require a starting dose adjustment. Please note that patients with bilirubin levels > 1.5 ULN (grade 2 or worse) are excluded from enrollment.

If a patient develops grade 2 or worse hyperbilirubinemia (>1.5 ULN) while on study, the investigator should hold bortezomib for 2 weeks or until the toxicity returns to grade 1 or better.

Restarting bortezomib at the next lower dose level (see DOSE MODIFICATION LEVELS above) could be considered at the investigator's discretion and following exclusion careful consideration of liver disease due to other causes, such as, but not limited to, active infection and lung cancer-related liver disease. If already at **Dose Level -2**, discontinue drug.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Treatment will be initiated once criteria for study inclusion have been fully met. Restaging scans, with evaluation of response, will be done every 2 cycles (during week 3 of second cycle, ± 7 days). Treatment will continue until clinical disease progression, unacceptable toxicity, treatment delay > 2 weeks, or at the discretion of the treating physician or patient.

Table 10.1. Study Treatment Schedule and Evaluations

		CYCLE 1					CYCLE 2					CYCLES 3 and 4, and onwards…									
	Baseline	Wk* 1		Wk 2		Wk 3	Wk 1		Wk 2		Wk 3	Wk 1		Wk 2		Wk 1		Wk 2		Wk 3	Off Study[d]
		D 1	D 4	D 8	D 11		D 1	D 4	D 8	D 11		D 1	D 4	D 8	D 11	D 1	D 4	D 8	D 11		
Bortezomib IV (1.3 mg/m2/day)		X**	X**	X**	X**		X**	X**	X**	X**		X**	X**	X**	X**	X**	X**	X**	X**		
Informed Consent	X																				
Obtain pathology specimen for KRAS	X																				
Medical History	X																				
Physical Exam	X	X*		X*		X*	X*		X*			X*		X*		X*		X*			X
Concurrent medications	X	X*		X*		X*	X*		X*			X*		X*		X*		X*			X
Vital signs	X	X*	X*	X*	X*	X*	X*	X*	X*	X*		X*	X*	X*	X*	X*	X*	X*	X*		X
Performance status	X	X*		X*		X*	X*		X*			X*		X*		X*		X*			X
CBC	X	X*	X*	X*	X*	X*	X*	X*	X*	X*		X*	X*	X*	X*	X*	X*	X*	X*		X
CMP	X	X*		X*		X*	X*		X*			X*				X*					X
EKG	X																				
Adverse event evaluation	X	X*		X*		X*	X*		X*			X*		X*		X*		X*			X
Radiologic tumor assessments	X[c]										X[a]									X[a]	
MRI	X																				
Pregnancy test	X[b]																				

Wk: week, D: day

*: **± 3 day window** for on-study evaluations (Physical exam, concurrent medications, vital signs, performance status, CBC, CMP, EKG, adverse event evaluation

: **± 1 day window for treatment with Bortezomib

a: **± 7 days**, imaging will be performed after every 2 cycles of therapy

b: **± 7 days**, serum qualitative/urine, not required for postmenopausal or surgically-sterilized women

c: **± 30 days** of Week 1 Day 1.

d: The off-study visit should be completed 30 days after the end of treatment (**+/- 14 days**)

11.0 TOXICITIES/SIDE EFFECTS

11.1. Anticipated Toxicities

A detailed list of anticipated side-effects from bortezomib treatment are included in Appendix A and discussed in the Investigator's Brochure. In general, the risks and side-effects of bortezomib as detailed in the informed consent include those which are:

Likely (occurring in ≥30% of patients)

- Fatigue
- Constipation, diarrhea, nausea, vomiting, and loss of appetite (may result in dehydration or weight loss)
- Fever commonly with shaking chills
- Pain or numbness and tingling in the hands and feet
- Low platelets increasing the likelihood of bleeding
- Low red blood cell count leading to fatigue

Less Likely (occurring in 10-29% of patients)

- Low white cell count increasing the likelihood of infections (such as those of the upper and lower respiratory tract including sinusitis, bronchitis and pneumonia)
- Flu-like symptoms such as sore throat, runny nose, and chills
- Abdominal pain
- Aches and pains in the muscles, joints, and arm and leg bones
- Fluid retention with swelling in the arms and legs (may result in weight gain and dizziness with standing)
- Cough or shortness of breath
- Headache
- Skin rash with itching and redness
- Herpes virus infections such as shingles
- Anxiety and insomnia

Rare but serious (<10% of patients)

- Low blood pressure with light-headedness or fainting
- Irregular heart beat and cardiac arrest
- New or worsening heart failure
- Fluid build-up in the lungs and respiratory failure
- Gastrointestinal bleeding or obstruction
- Bleeding in the brain
- Infections in the blood or sepsis
- Allergic reactions
- Confusion and/or seizures from a brain syndrome called reversible posterior encephalopathy
- Loss of vision or hearing

11.2. Adverse and Serious Adverse Event Definitions

Adverse event (AE): any untoward medical occurrence in a patient or subject administered subcutaneous bortezomib.

- The untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of bortezomib whether or not it is related to the bortezomib.
- This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.
- For this protocol an abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

Serious Adverse Event (SAE): any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening
  - refers to an AE in which the patient was at risk of death at the time of the event
  - does not refer to an event which hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of an existing hospitalization
- Results in persistent or significant disability or incapacity
  - Disability is defined as a substantial disruption of a person's ability to conduct normal life functions
- Is a congenital anomaly/birth defect.
- Is a medically important event.
  - refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment
    - may jeopardize the patient
    - require medical or surgical intervention to prevent one of the outcomes listed above, or
    - involves suspected transmission via a medicinal product of an infectious agent (any organism, virus, or infectious particle e.g., prion protein transmitting Transmissible Spongiform Encephalopathy, whether pathogenic or non-pathogenic)
  - examples 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

As far as possible, each adverse event should be evaluated to determine:

- severity grade via CTCAE v4.0
- relationship to study drug
- duration (start and end dates)
  action taken
- whether or not it constitutes an SAE

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The primary endpoint of the study is tumor response; this will be evaluated according to the RECIST v1.1 criteria. Secondary endpoints of progression free survival, 8-week stable disease, and overall survival will be evaluated according to RECIST v.1.1 criteria as well.

Once patients discontinue study treatment secondary to progression of disease, overall survival (OS) status will be followed by standard death registries and by calling the patient and/or his or her primary care physician twice a year. For patients who continue to receive care at MSKCC, biannual chart reviews will be conducted by the research staff. For patients who choose to receive further care at an outside facility, every attempt to contact the patient and/or his/her treating physician will be made on a biannual basis as well. OS will be measured from the time of study treatment initiation. Patients who discontinue treatment secondary to toxicity will continue to be followed on study until evidence of resolution of toxicity to grade 1 or better and evidence of disease progression. The

12.1. Objective Response

Objective responses are defined according to RECIST v1.1 criteria.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.2. "Best" Response

The Best Objective Response is recorded from the start of treatment until disease progression. In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Note that Objective Response and progression free survival (PFS) are clinical endpoints.

13.0 CRITERIA FOR REMOVAL FROM STUDY

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 for any of the following reasons that represent grounds for study discontinuation:

- Progressive disease at any time
- Occurrence of an unacceptable adverse event
- A significant treatment cycle delay or bortezomib interruption, at the investigator's discretion (as detailed in Section 9.1).
- Intercurrent illness
- Protocol violations
- Noncompliance
- Administrative reasons
- Failure to return for follow-up
- General or specific changes in the patient's condition unacceptable for further treatment in the judgment of the investigator

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

14.0 BIOSTATISTICS

The primary endpoint of this single-arm phase II trial will be best objective response rate (ORR) to Bortezomib (partial+complete responses) by RECIST criteria v1.1, evaluated at any time between treatment initiation and documented progression of disease. A Simon two-stage minimax design will be used to test the null hypothesis of 10% response rate against the desired alternative of a 30% ORR, with a one-sided type I error (probability of falsely accepting a non-promising therapy) of 10% and power of 90%. The null hypothesis is based on historical data of best objective response of non-small cell lung carcinomas to cytotoxic chemotherapy after failure of first-line chemotherapy (range from 8-10%). In the first stage of this design, 16 patients will be accrued. If zero to one responses are observed, then the study will be terminated and declared negative. If at least 2 responses are observed, then an additional 9 patients will be accrued to the second stage. At the end of the study, if 5 or more patients respond out of a total of 25 patients enrolled, the treatment will be considered worthy of further investigation in this patient population. Under this design, the expected sample size is 25, and the probability of early termination is 51%.

Patients who receive at least one dose of the drug will be evaluable for response. For patients who discontinue the drug before the documented progression via RECIST v1.1, every effort will be made to have a final evaluation scan. If this is not possible, they will be considered non-responders.

With an expected accrual rate at MSKCC of 1-2 patients a month for this selected cohort, we expect to complete accrual within 8 months (if study will be stopped after the first stage) or 12-18 months (if patients will be accrued for both stages).

Progression-Free (PFS) and overall survival (OS) will be calculated using Kaplan-Meier estimators starting from the time of treatment initation. Patients will be followed-up until progression of disease or death (for PFS) or until death (for OS). Patients who do not experience the event of interest during the study time will be censored at the time of the last available follow-up.

Eight-week stable disease will be summarized using descriptive statistics.

Toxicities will be assessed through the NCI-Common Terminology Criteria for Adverse Events version 4.0 and presented individuall and using descriptive statistics. Dose modifications will be permitted as per a prescribed algorithm.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

Randomization is not performed in this study.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team. The data collected for this study will be entered into the Clinical Research Database (CRDB).

16.1 Quality Assurance

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.

16.1.2. Protocol Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Millennium and written IRB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB 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. The investigator will submit all protocol modifications to Millennium and the regulatory authority(ies) in accordance with the governing regulations. Any departures from the protocol must be fully documented in the source documents.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: *http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1*.

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://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf

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 or risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industry sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

16.3. On-Site Audits

Regulatory authorities 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.

16.4. Premature Closure of 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

16.5. Record Retention

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

17.0 PROTECTION OF HUMAN SUBJECTS

Good Clinical Practice: The study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The 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.

Ethical Considerations: The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The Institutional Review Board (IRB) 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 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 by the investigator. Millennium requests that the protocol and informed consent documents be reviewed by Millennium prior to IRB submission.

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 (IRB/PB).

In order to maintain patient privacy, all data capture records, drug accountability records, study reports, and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from Millennium or its

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

17.2 Serious Adverse Event (SAE) Reporting

Any SAE 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. The report should contain the following information:

Fields populated from 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
    - 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.

17.2.1. Adverse Event Reporting to Millenium Pharmacovigilance

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 must be reported to Millennium Pharmacovigilance (or designee). SAEs will be reported using the Clinical Research Database (CRDB) reporting form.

SAEs must be reported to Millennium Pharmacovigilance (or designee) from first dose of bortezomib up to and including 30 days after administration of the last dose of bortezomib. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Any SAE that occurs at any time after completion of bortezomib treatment or after the designated follow-up period that the investigator and/or sub-investigator considers to be related to any study drug must be reported to the Millennium

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

This is an investigator-initiated study. The principal investigator Gregory J. Riely, 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 (or designee) as soon as possible, but no later than 5 calendar days of the sponsor-investigator's observation or awareness of the event. 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 (or designee) may request follow-up information to a reported SAE, which the sponsor-investigator will be responsible for providing to Millennium Pharmacovigilance (or designee).

The SAE report must include event term(s), serious criteria, and the investigator's or sub-investigator's determination of both the intensity of the event(s) and the relationship of the event(s) to study drug administration. Intensity for each SAE, including any lab abnormality, will be determined by using the NCI CTCAE, version used at your institution, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html. Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

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

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 per institution's policy. Sponsor-investigator will be responsible for forwarding such reports to any sub-investigator(s).

17.2.2. Reporting Drug Exposure: Pregnancy and Birth Events

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

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to Millennium Pharmacovigilance (or designee) immediately.

18.0 INFORMED CONSENT PROCEDURES

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

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

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

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

19.0 REFERENCES

[1] Jemal A, Siegel R, Ward E, Muray T, Xu J, Thun, MJ.Cancer Statistics,2007. CA:Cancer for Clin.2007; 57:43-66.

[2] Parkin DM, Bray F, Ferlay J, Pisani P. Global Cancer Statistics 2002. CA:Cancer for Clin. 2005; 55:74-108.

[3] NCCN: National Comprehensive Cancer Network 13. NCCN clinical practice guidelines in oncology™: non-small cell lung cancer

[4] Amado RG, Wolf M, Peeters M, VanCutsem E, Siena S, Freeman D, et al. Wild-typeKRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol.2008; 26:1626-1634.

[5] Winton T, Livingston R, Johnson D, Rigas J, Johnston M, Butts C, Cormier Y, Goss G, Inculet R, Vallieres E, Fry W, Bethune D, Ayoub J, Ding K, Seymour L, Graham B, Tsao MS, Gandara D, Kesler K, Demmy T, Shepherd F. Vinorelbine plus cisplatin vs observation in resected non-small cell lung cancer. NEJM 2005:23;352(25)2589-97.

[6] Zhu C-Q, Santos G, Ding K, Sakurada A, Cutz JC, Liu N. Role of KRAS and EGFR as biomarkers of response to erlotinib in national cancer institute of Canada clinical trials group study BR.21. J Clin Oncol. 2008; 26:4268-4275.

[7] Mascaux C, Iannino N, Martin B, Paesmans M, Berghmans T, Dusart M et al. The role of RAS oncogene in survival of patients with lung cancer: a systematic review of the literature with meta-analysis. Brit J of Cancer. 2005: 92:131-139.

[8] Riely GJ, Kris MG, Rosenbaum D, et al. Frequency and distinctive spectrum of KRAS mutations in never smokers with lung adenocarcinoma. *Clin Cancer Res.* Sep 15 2008;14(18):5731-5734.

[9] Powell CA, Spira A, Derti A, et al. Gene expression in lung adenocarcinomas of smokers and nonsmokers. *Am J Respir Cell Mol Biol.* Aug 2003;29(2):157-162.

[10] Sun SC. Non-canonical NF-kappaB signaling pathway. *Cell Res.* Jan 2011;21(1):71-85.

[11] Barbie DA, Tamayo P, Boehm JS, et al. Systematic RNA interference reveals that oncogenic KRAS-driven cancers require TBK1. *Nature.* Nov 5 2009;462(7269):108-112.

[12] Meylan E, Dooley AL, Feldser DM, et al. Requirement for NF-kappaB signalling in a mouse model of lung adenocarcinoma. *Nature.* Nov 5 2009;462(7269):104-107.

[13] Escobar M, Velez M, Belalcazar A, Santos ES, Raez LE. The role of proteasome inhibition in nonsmall cell lung cancer. *J Biomed Biotechnol.* 2011;2011:806506.

[14] Luo J, Emanuele MJ, Li D, et al. A genome-wide RNAi screen identifies multiple synthetic lethal interactions with the Ras oncogene. *Cell.* May 29 2009;137(5):835-848.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[48]Moreau P, Coiteux V, Hulin C, Leleu X, van de Velde H, Acharya M, Harousseau JL. Prospective comparison of subcutaneous versus intravenous administration of bortezomib in patients with multiple myeloma. Haematologica. 2008 Dec;93(12):1908-11. Epub 2008 Sep 2.

20.0 APPENDICES

APPENDIX A: Anticipated Side-Effects of Bortezomib

Known Anticipated Risks of bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Blood and Lymphatic System Disorders	
Most common	Thrombocytopenia*, anemia*
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 hemorrhage
Gastrointestinal Disorders	
Most common	Constipation, diarrhea*, nausea, vomiting*
Very common	abdominal pain (excluding oral and throat)
Common	Dyspepsia, pharyngolaryngeal pain, gastroesophageal reflux, abdominal distension, gastritis, stomatitis, mouth ulceration, dysphagia, gastrointestinal hemorrhage*, lower gastrointestinal hemorrhage*± rectal hemorrhage
Uncommon	Eructation, gastrointestinal pain, tongue ulceration, retching, upper gastrointestinal hemorrhage*, hematemesis*, oral mucosal petechiae, ileus paralytic*, ileus, odynophagia, enteritis, colitis, esophagitis, enterocolitis, diarrhea hemorrhagic, acute pancreatitis*, intestinal obstruction
General Disorders and Administration Site Conditions	
Most common	Fatigue, pyrexia
Very common	Chills, edema peripheral, asthenia
Common	Neuralgia, lethargy, malaise, chest pain, mucosal inflammation*
Uncommon	Injection site pain, injection site irritation,

Known Anticipated Risks of bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
	injection site phlebitis, general physical health deterioration*, catheter-related complication
Hepatobiliary Disorders	
Uncommon	Hyperbilirubinemia, 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∗, bacteremia*, 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 esophagitis±
Injury, Poisoning, and Procedural Complications	
Common	Fall
Uncommon	Subdural hematoma
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	Hyperglycemia, hypoglycaemia, hyponatremia, hypokaliemia, hypercalcemia*

Known Anticipated Risks of bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
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	Tumor lysis syndrome*
Nervous System Disorders	
Most common	Peripheral neuropathy (including all preferred terms under the MedDRA High-level term Peripheral neuropathy NEC)
Very common	Paresthesia, dizziness excluding vertigo, headache
Common	Polyneuropathy, syncope, dysesthesia, dysgeusia, postherpetic neuralgia
Uncommon	Convulsion, loss of consciousness, ageusia, encephalopathy, paralysis*, autonomic neuropathy, reversible posterior leukoencephalopathy syndrome±
Psychiatric Disorders	
Very common	Anxiety, insomnia
Common	Confusional state
Uncommon	Delirium
Renal and Urinary Disorders	
Common	Renal impairment*, renal failure*, hematuria
Uncommon	Micturition disorder
Respiratory, Thoracic, and Mediastinal Disorders	
Very common	Cough, dyspnea
Common	Epistaxis, dyspnea exertional, pleural effusion*, rhinorrhea, hypoxia*, pulmonary edema*
Uncommon	Hemoptysis*, acute respiratory distress syndrome*, respiratory failure*, pneumonitis*, lung infiltration, pulmonary alveolar hemorrhage*, 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

Known Anticipated Risks of bortezomib by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
	vasculitis±
Vascular Disorders	
Common	Hypotension*, orthostatic hypotension
Uncommon	Cerebral hemorrhage*

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.

Reports of Adverse Reactions From Postmarketing Experience

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

Reports of Adverse Reactions From Postmarketing Experience

Acute respiratory distress syndrome (ARDS)	Rare
Interstitial pneumonia	Rare
Lung infiltration	Rare
Pneumonitis	Rare
Pulmonary hypertension	Rare
Skin and subcutaneous system disorders	
Acute febrile neutrophilic dermatosis	Unknown
Toxic epidermal necrolysis	Unknown

Source: VELCADE® (bortezomib) for Injection Investigator's Brochure Edition 14.
a Incidence is assigned using the following convention: very common (≥ 1/10); common (≥ 1/100 and < 1/10); uncommon (≥ 1/1000 and < 1/100); rare (≥ 1/10,000 and < 1/1000); very rare (< 1/10,000, including isolated reports).
b Acute diffuse infiltrative pulmonary disease is a MedDRA Lower Level Term which corresponds to a Preferred Term of Interstitial lung disease.

ADDITIONAL NOTES:

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

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

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

APPENDIX B: Common Terminology Criteria for Adverse Events

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting: http://ctep.cancer.gov/reporting/ctc.html

APPENDIX C: 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. Cancer1948; 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, l9 1-205.

APPENDIX D: Body Surface Area and Creatinine Clearance Calculations

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

$$BSA = (W^{0.425} \times H^{0.725}) \times 0.007184$$

where the weight is in kilograms and the height is in centimeters.

DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Medicine. 1916; 17:863-71

Creatinine clearance (CrCl) can be calculated using the Cockroft-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 Cockroft-Gault formula will tend to overestimate the creatinine clearance. (Adipose tissue tends to contribute little creatinine requiring renal clearance.)

APPENDIX E: New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

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

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

APPENDIX F: Pregnancy and Effective Methods of Contraception

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

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

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

Highly effective methods	Other effective methods (barrier methods)
Intra-uterine devices (IUD) Hormonal contraceptives (birth control pills/oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants)	Latex condom 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 (i.e., status post vasectomy) must agree to 1 of the following:

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

APPENDIX G: Pregnancy Reporting Form

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MILLENNIUM
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PregnanCY Form v03Nov2008(llS) Pagel of 4

Report Type: IJ Initial D Follow-up Date of Report: / / DO MM Yr

REPORTER INFORMATION: (Please forward rf an alternative Physician is more appropriate!		
Reporter name:	n ue:	
Address:	Te ephone No.:	Fax No_
Cily, State{Province:	Postal Code:	Country:

FATHER'S INFORMATION		O Father Unknown
Initials:	Date of Birth: ___/___/___ DO MM Yr	or Age: years

Participatn g in an MPIclinical study? O No O Yes
If no, w hat company product w as taken:
If yes, please provide: Study drug: ProtocolNo:
Center No: Patient No:

Medicall/ Famli a l /Soc all History

Qe. Include chron c illnesses: specify, famitial birth defeclslgenetic/chromosom: l di sorders; habitual exposure: specify., al cohol llobacco; drug exposure: specify, substance abuse ard med cation use. Please i nclude drug treatment
prior to or around the time of conception and/or duringpregnancy)

Race:
Occupation:
Number of children:

Takeda /AVA\ MILLENNIUM
THE TAK50A OHCXILOCW t.OMPAN'II'

Pregnancy Form v03Nov200S (1lS)

MOTHER'S INFORMATION:

Initials: _____ Date of Birth: ___/___/_____ (DO MM Yr) or Age: _____years

Participating in an MPI clinical study? O No D Yes
If no, what company product was taken: _____
If yes, please provide: Study drug: _____ Protocol No: _____
Center No: _____ Patient No: _____

Race: _____
Occupation: _____

Medical / Familial / Social History
(i.e. Include alcohol/tobacco and substance abuse; complications of past pregnancy, labor/delivery, fetus/baby; illnesses during this pregnancy; assisted conception: specify; other disorders including familial birth defects/genetic/chromosomal disorders; method of diagnosis consanguinity, etc.)

Number of previous pregnancies: Full term ____ Pre-term ____

Outcomes of previous pregnancies:
(Please indicate number of occurrences)

- Spontaneous abortion:
- Therapeutic abortion:
- Elective abortion: _____
- Other:
- Normal live birth: _____
- Children born with defects: ____
- Stillbirth: _____
- Outcome unknown:

MOTHER'S DRUG EXPOSURE INFORMATION
Please include medical prescriptions, vaccinations, medical devices, OTC products, pregnancy supplements (such as folic acid, multivitamins)

Product Name	Dosage	Route administered to patient	Date of first use (DD MM/Yr)	Date of end treatment (DD MM/Yr)	Indication	Contraindicated to pregnancy
			(/ /)	(/ /)		DYes ONo DUnk
			(/ /)	(/ /)		DYes ONo DUnk
			(/ /)	(/ /)		DYes ONo DUnk
			(/ /)	(/ /)		DYes ONo DUnk

Tab.da 11\YA\
MELLENNIUM
THE TAKEIIIA ONC'.OI.OGY (J'>MPANY

Pregnancy Form v03Nov2008 (US)

CURRENT PREGNANCY 11\JFORMATION

Period at exposure: weeks Trimester (1) (2) (3)
Date of last mensbl.Jal period: ___/___/___ t:J Unknown
DO IMM Yr

g IJiJD Sliltu
[] Pregnancy Ongoing
Estimated date Of delivery: / /
D!) MM :tr
LJ Live Birth
LJ StDbirth
LJ Early Tem1nation
t:J Spontaneous abortion*
t:J Therapeutic abortion*
t:J Elective abortion•
t:J Other": _____
"ff box is checked , ple-ase no r:eason m "Additional Deu ls:" section below

Fet.altNeonatalStatus
a Norma'l
LJ Birth defect (strucwral/chromosomal disorder)*
LJ Other (non-structura , premature birth,intrauterine death/stil birth)*

"If box is cheCked. please note tails ;,. "Additional derails" ection beklw

Additi iill c lili! i
Is there evidence of a defect from a prenatal test? t:JYes LINo
If yes,indicate w hich test(s) showed evidence of birth detect:
t:JUltrasound OAmn ocentes s LIMaternal Serum-Aipha-Fetoprotein []Chorionic ViiJi Sampling c:JHuman Chorionic Gonadotropin f:JOther: P ease specify detas of defecf{s), disorder(s), and/or ofher arnoma.ly(i es):

What are the defed(s) attributed to:

Takeda /AVA\ MILLENNIUM
THIE TAKEDA <mr.OLOGV ('.OMPANY

Pregnancy Form v03Nov200S (DS)

Infant Infonnatjgn;

Gestational weeks at birth or at termination: _____ weeks

Date of birtf'l or termfnation: __/ /--:=---
Ill> MM Yr

If mul tiple birtlls (e.g. twins), ndicate number: ___
(Please complete separate form for each child)

Birth Order (1, 2,3, etc.) ____

Breast-fed: DYes D No D Unk

Method of delivery: D Normal vaginal a Caesarean section

Sex: O Male D Female D Unk

Length: _____D em D in

Weight: _____D g D lbs

Head circumference: D em D in

Apgar S()ore (0-10) at 1 mmute: ___ D Unk

Apgar S()ore (0-10) at 5 minute: ___ a Unk

Resuscitation required: O Yes D No a Unk

Admiss1on to intensive care requ red:
D Yes D No D Unk

AdcUt jonal Nptes;

Please attach RELEVANT LABORATORY TESTS A:ND PROCEDURES (e. g. results of ultrasounds, amniocentesis, cllorionic vii lb mpfing, or misce0a.neous testing a.s appl cable). In the case of an abnormal evolulion or 0\Jtcome_please send co p es of results of a0
reevantl aboratory te-sting and procedure-s. includ ng p.alhology results of produas of conception and or autopsy reports if appJcable. Please submit 1311Y additionall relevantl information on a separate sheet.

Investigator signature: _____ Date: oo r:JA 1---:::::---
Yr

Investigator Name: _____