CITY OF HOPE NATIONAL MEDICAL CENTER
1500 E. DUARTE ROAD
DUARTE, CA 91010

DEPARTMENT OF Hematology/HCT

TITLE: A PHASE II STUDY OF WEEKLY MAINTENANCE BORTEZOMIB AND RITUXIMAB IN MANTLE CELL LYMPHOMA S/P AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION

CITY OF HOPE PROTOCOL NUMBER/VERSION: IRB # 10137 VERSION: 16

DATE(S)/ OF AMENDMENT(S)/REVISION(S):

COH Initial Submission	12/13/10	Version 00
COH DSMB Corrections	12/28/10	Version 00
COH IRB Corrections	02/23/11	Version 00
COH Amend 01	03/31/11	Version 01
COH Amend 02	08/11/11	Version 02
COH Amend 03	01/25/12	Version 03
COH Amend 04	07/05/12	Version 04
COH Amend 05	11/26/12	Version 05
COH Amend 06	01/15/13	Version 06
COH Amend 07	(Protocol dated 10/04/13, Revised DSMP)	Version 07
COH Amend 08	Personnel Change dated 12/17/13	Version 08
COH Amend 09	(Protocol dated 06/11/14, Revised Study Calendar)	Version 09
COH Amend 10	(Adding Drs. Aldoss and Pullarkat)	Version 10
COH Amend 11	(Adding Drs. Cao, Zain, & Mei)	Version 11
COH Amend 12	(Title Page - Personnel Change 9/15/14)	Version 12
COH Amend 13	(Protocol dated 11/18/2014)	Version 13
COH Amend 14	(Protocol dated 04/09/2015)	Version: 14
COH Amend 15	(Protocol dated 10/21/2015)	Version: 15
COH Amend 16	(Protocol dated 12/13/18)	Version: 16

DISEASE SITE: Mantle Cell Lymphoma
STAGE: Maintenance
MODALITY(IES): Chemotherapy
TYPE: Phase II

PRINCIPAL INVESTIGATOR: Matthew Mei, M.D.

PARTICIPATING CLINICIANS: Stephen Forman, M.D., Ravi Bhatia, M.D., Amrita Krishnan, M.D., Auayporn Nademanee, M.D., Ryotaro Nakamura, M.D., Margaret O'Donnell, M.D., Pablo Parker, M.D., Leslie Popplewell, M.D., David Snyder, M.D., Anthony Stein, M.D., Eileen Smith, M.D., Chatchada Karanes, M.D., Leonard Farol, M.D., Firoozeh Sahebi, M.D., Ricardo Spielberger, M.D., Ji-Lian Cai, M.D., Tanya Siddiqi, M.D., Samer Khaled, M.D., Myo Htut, M.D., Nitya Nathwani, M.D., Michael Rosenzweig, M.D., Ahmed Aribi, M.D, Haris Ali, M.D., Amandeep Salhotra, M.D., Ibrahim Aldoss, M.D., Vinod Pullarkat, M.D., Thai Cao, M.D., Jasmine Zain, M.D., Alex Herrera, MD, Monzr Al Malki, MD and Elizabeth Budde, MD

PARTICIPATING SITES:

Fred Hutchinson Cancer Center	Leona A. Homberg

A phase II study of weekly maintenance bortezomib and rituximab in mantle cell lymphoma post autologous hematopoietic cell transplantation

X05337

Protocol Version:	Date of Protocol:
Original	9/16/10
Revised for CPRMC	11/22/10
Revised for DSMB	12/13/10
Revised for DSMB	12/28/10
Revised for IRB	02/23/11
Amendment 01	03/31/11
Amendment 02	08/11/11
Amendment 03	01/25/12
Amendment 04	07/05/12
Amendment 05	11/26/12
Amendment 06	01/15/2013
Amendment 07	10/04/2013
Amendment 08 (title page only)	12/17/2013
Amendment 09	06/11/2014
Amendment 10 (title page only)	8/18/2014
Amendment 11 (title page only)	9/09/2014
Amendment 12 (title page only)	9/15/2014
Amendment 13	11/18/2014
Amendment 14	04/09/2015
Amendment 15 (Administrative)	10/21/2015
Amendment 16 (PI Change)	12/13/2018

Investigator & Study Center:

Matthew Mei, MD

City of Hope National Medical Center

1500 E. Duarte Rd,

Duarte, CA 91010

Telephone: (626) 256-4673, ext 64762

Additional Investigator and Study Center

Leona A. Holmberg, M.D.

Fred Hutchinson Cancer Research Center

1100 Fairview Ave N

Seattle, WA 98109

Telephone: (206) 667-4832

Study Sponsor, Monitor and Data Coordinating Center:

City of Hope

Study Sponsor:

Millennium Pharmaceuticals, Inc.

PROTOCOL SUMMARY

Title: A phase II study of weekly maintenance bortezomib and rituximab in mantle cell lymphoma post autologous hematopoietic cell transplantation

Objectives

The primary objective of this study is to:

- Determine anti-tumor activity as assessed by disease-free survival (DFS). Estimate the two year DFS rate in mantle cell lymphoma patients treated with bortezomib + rituximab after autologous hematopoietic stem cell transplantation.

The secondary objectives of this study are to:

- To estimate the overall survival rate and evaluate time to treatment failure/remission duration.
- To describe non-relapse death events and the toxicity profile.
- Evaluate the biological markers of mantle cell lymphoma patients treated with bortezomib + rituximab after autologous hematopoietic stem cell transplantation.

Patient population

Refer to specific inclusion and exclusion criteria detailed in protocol.

Number of patients

36

Study design and methodology

Phase II, (Efficacy) clinical trial

Treatments administered

1) Bortezomib will be administered at a dose of 1.3 mg/m2 on D1, 8, 15, and 22 every 3 month for a total of 8 cycles.
2) Rituximab will be administered at a dose of 375mg/m2 on D1, 8, 15, 22 every 6 month for a total of 4 cycles.

Efficacy data collected

The following evaluations will be conducted to assess the efficacy of bortezomib + rituximab

- CT/PET or CT of neck, chest, abdomen, and pelvis will be performed every 6 months for the 1st two years and then yearly for the 3rd, 4th and 5th years.

- Bone marrow biopsy will be performed every 6 months for the 1st two years, then yearly thereafter

Correlative studies collected to be done at City of Hope site only

- Peripheral blood samples will be collected at baseline and day 1 of every cycle, then every 6 months for 1st two years and then yearly for 3 years to examine CCND1 mRNA and isomer expression.
- Bone marrow sample will be collected at baseline, every 6 months for the 1st two years, then yearly for 3 years to examine CCND1 mRNA and isomer expression.
- Diagnostic lymph node samples will be examined for CCND1 mRNA, isomer expression, and Ki-67.
- Please see section (3.5.2) for details on correlatives studies

Safety data collected

- Specific safety measurements are detailed in section 3.6.3 and section 4.

Statistical procedures

Specific statistical procedures are detailed in section 5.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES IN THE TEXT

Tables

ABBREVIATIONS LIST

Abbreviation	Definition
°C	degrees Celsius
μM	micromolar
20S	20S proteasome subunit
AE	adverse event
ANC	absolute neutrophil count
Bc1-2	B-cell lymphoma-2; a gene that inhibits apoptosis
BSA	body surface area
CAM	cell adhesion molecules
cm	centimeter
CR	Complete Response
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
dL	deciliter
DLT	Dose Limiting Toxicity
DNA	deoxyribonucleic acid
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ht	height
IκB	I kappa B kinase; cytokine response kinase that activates transcription factor NF-kappa b at serine 32 and 36
ICAM-1	intercellular adhesion molecule 1
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous
IκBα	I kappa B alpha-associated protein kinase
kg	kilogram
Ki	inhibitory constant
lbs	pounds

Abbreviation	Definition
m^2	square meters
mg	milligram
min	minute
mL	milliliter
mm^3	cubic millimeters
mmol	millimole
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NF-κB	nuclear factor-κB
ng	nanogram
nM	nanomole
p21	p21(ras) farnesyl-protein transferase
p27	cyclin-dependent kinase inhibitor
p53	tumor suppressor protein with molecular weight of 53 kDa
SAE	serious adverse event
US	United States
USP	United States Pharmacopeia
VCAM-1	vascular cell adhesion molecule 1
w/w	weight-to-weight ratio
wt	weight

INTRODUCTION AND STUDY RATIONALE

1.1 Overview of the Disease

Mantle cell lymphoma (MCL) is a subtype of non-Hodgkin lymphoma (NHL) accounts for up to 8000 newly diagnosed NHL cases in US and EU each year[1-2]. Its hallmark is the t(11;14)(q13;q32) chromosomal translocation of the cyclin D1 gene (CCND1). This results in overexpression of CCND1 and increases cell proliferation[3]. CCND1 is a regulator of cell cycle and mediates G1 to S phase progression[4]. Although CCND1 has been found to be over expressed in other tumor types (breast, neuroblastoma, pancreas, multiple myeloma), the mechanism of over expression by the t(11;14)(q13;32) translocation is only found in MCL[5]. It has been assumed that CCND1 not only promotes oncogenesis but also induces chemoresistance since MCL has a worse prognosis when compared to follicular lymphoma or diffuse large B cell lymphoma. Indeed, standard chemotherapy regimens such as R-CHOP that can achieve complete remission (CR) in other NHL can only achieve CR in 34% of MCL[6]. Also, MCL has a much higher relapse rate even if complete remission can be achieved. Clinically, MCL typically presents with advanced stage disease. The sites of disease include the lymph nodes, Bone marrow, spleen, peripheral blood, and the GI tract. Patients can present with stage I (13%), stage II (7%), stage III (9%), or stage IV (71%). The median age at presentation is 63 years old, and this disease favors men over women at a 3:1 ratio[2]. Majority of the patients are elderly male patients with stage IV disease.

There is no standard therapeutic regimen for MCL. One treatment approach is the R-hyperCVAD regimen which includes 8 cycles of aggressive chemotherapy. The CR/CRu rate is 87%, the 3 year FFS is 64%, and recent updates show 5 year FFS of 48%[7]. The disadvantages of this regimen include high toxicity profile, inability of patients to complete the full 8 cycles of therapy (30% of patients did not finish), and late relapses occur without a plateau effect. Another treatment approach is to use autologous hematopoietic stem cell transplantation (AHCT) as consolidation to reduce relapse. The data ranges from 5 year EFS of 39%, 3 year PFS of 93%, 54 month EFS of 79%, and 5 year EFS of 35%[8-12]. The results are disappointing since relapses still occur after AHCT. It is evident that some form of maintenance therapy needs to be given to try to prolong the PFS after AHCT.

Bortezomib is a small molecule proteasome inhibitor that can affect multiple signaling pathways. The anti-neoplastic effect of bortezomib likely involves several distinct mechanisms, including inhibition of cell growth and survival pathways, induction of apoptosis, and inhibition of expression of genes that control cellular adhesion, migration and angiogenesis. Thus, the mechanisms by which bortezomib elicits its antitumor activity may vary among tumor types, and the extent to which each affected pathway is critical to the inhibition of tumor growth could also differ. Indeed it has been shown to downregulate CCND1 expression in MCL in vitro. It also has activity against MCL as a single agent therapy and is FDA approved therapy for relapsed MCL. See section 1.2 for details on bortezomib.

RITUXAN (rituximab) is a chimeric IgG monoclonal antibody targeting the CD20 surface antigen present on both normal lymphocytes and B-cell lymphomas. The activity of this agent is multi-faceted, in that it leads to direct lysis by complement activation as well as antibody dependant cell mediated cytotoxicity, triggers apoptosis, and may lead to various signaling pathway changes in targeted cells (Cartron 2004). It also appears to act as a chemosensitizer by blocking IL-10 binding, leading to decreased intracellular bcl-2 (Demidem, 1997). It has been showed to have strong activity in vitro against MCL. This agent also has

clinical activity in relapsed MCL and is a standard upfront agent for all Non-Hodgkin's Lymphoma. See section 1.3 for details on RITUXAN.

The combination of bortezomib + rituximab has been proven to be efficacious in the in vitro setting in MCL cell lines. Alinari et al. showed that the addition of rituximab to bortezomib activated AKT pathways, decreased nuclear NF kappa B levels, induces apoptosis, and causes cell cycle arrest (Alinari 2009). There is no true phase I data of combining rituximab and bortezomib. Both agents have been studied extensively in the phase I setting alone. The toxicities are minimal and many investigators moved on to phase II study. This particular combination also has been tried in Waldenstrom Macroglobulinemia and marginal zone lymphoma and was found to be safe and efficacious (Ghobrial 2010, de Vos 2009.) Dev Vos et al studied this combination in a phase II trial in marginal zone lymphoma. He actually used a higher dose of 1.6 mg/m2 weekly with rituximab 375 mg/m2 weekly. His study was published in JCO 2009 and showed strong efficacy and minimal toxicities. Ghobrial also used a once week dosing of 1.6 mg/m2 weekly with rituximab 375 mg/m2 weekly to treat Waldenstrom Macroglobulinemia. Her study is published in American journal of Hematology 2010 and also showed strong efficacy and minimal toxicities. Since our study is on for the use of maintenance after patients achieve CR, we elect to use a lower dose of 1.3 mg/m2 rather than 1.6 mg/m2. Since rituxan and bortezomib target different pathways in MCL, the combination would lead to synergy against tumor resistant pathways. Also the toxicity profiles of these agents are low and relatively non interactive, which makes this combination ideal for study in the maintenance setting.

1.2 Bortezomib for Injection

1.2.1 Scientific Background

Bortezomib for Injection is a small molecule proteasome inhibitor developed by Millennium Pharmaceuticals, Inc., (Millennium) as a novel agent to treat human malignancies. Bortezomib is currently approved by the United States Food and Drug Administration (US FDA) for the treatment of patients with multiple myeloma (MM). It is also indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy. In the European Union (EU), bortezomib in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated MM who are not eligible for high-dose chemotherapy with bone marrow transplant. Bortezomib is indicated as monotherapy for the treatment of progressive MM in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation.

By inhibiting a single molecular target, the proteasome, bortezomib affects multiple signaling pathways. The anti-neoplastic effect of bortezomib likely involves several distinct mechanisms, including inhibition of cell growth and survival pathways, induction of apoptosis, and inhibition of expression of genes that control cellular adhesion, migration and angiogenesis. Thus, the mechanisms by which bortezomib elicits its antitumor activity may vary among tumor types, and the extent to which each affected pathway is critical to the inhibition of tumor growth could also differ. Bortezomib has a novel pattern of cytotoxicity

in National Cancer Institute (NCI) in vitro and in vivo assays (Adams et al., 1999). In addition, bortezomib has cytotoxic activity in a variety of xenograft tumor models, both as a single agent and in combination with chemotherapy and radiation (Steiner et al., 2001; Teicher et al., 1999; Cusack et al., 2001; LeBlanc et al., 2002; Pink et al., 2002). Notably, bortezomib induces apoptosis in cells that over express bcl-2, a genetic trait that confers unregulated growth and resistance to conventional chemotherapeutics (McConkey et al., 1999).

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

1.2.2 Nonclinical Pharmacology

Pharmacokinetic (PK) and pharmacodynamic studies were conducted in the rat and cynomolgus monkey. Upon intravenous (IV) bolus administration, bortezomib displays a rapid distribution phase ($t_{1/2\alpha}$ <10 minutes) followed by a longer elimination phase ($t_{1/2\beta}$ 5–15 hours). Bortezomib has a large volume of distribution (range 5–50 L/kg). The plasma PK profile is well described by a 2-compartment model.

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

1.2.3 Nonclinical Toxicity

Single-dose IV toxicity studies were conducted with bortezomib in the mouse, rat, dog, and monkey to establish the single-dose maximum tolerated dose (MTD). The MTDs were 0.25 mg/kg (1.5 mg/m^2) and 0.067 mg/kg (0.8 mg/m^2) in the 2 most sensitive species, rat and monkey, respectively.
Repeat-dose multi-cycle toxicity studies of 3 and 6 months in the rat and 9 months in the monkey, each with 8-week recovery periods, were conducted to characterize the chronic toxicity of bortezomib when administered by the clinical route and regimen of administration. The MTD in the 6-month rat study was 0.10 mg/kg (0.6 mg/m^2) and the key target organs were the gastrointestinal (GI) tract, hematopoietic and lymphoid systems. The MTD in the 9-month monkey study was 0.05 mg/kg (0.6 mg/m^2) and the key target organs were the GI tract, hematopoietic and lymphoid systems, peripheral nervous system, and kidney. Full or partial reversibility was observed for each of the toxicities described to date.

In general, the nature of the toxicity of bortezomib is similar across species, and target organs of toxicity in animals have been largely predictive of human toxicity. The toxicity of bortezomib in animals is characterized by a steep dose-response with mortality seen at dosages above the MTD. The cause of

death at acutely lethal dosages is considered to be related to indirect cardiovascular (CV) effects of hypotension and vascular changes with secondary bradycardia and the cause of death in long-term studies has been attributed to GI or hematologic toxicity. The pharmacologic effects of bortezomib on the CV system have been extensively characterized and have demonstrated that indirect effects on CV function occur only at acutely lethal dosages and are abrogated by routine supportive care.
Additional detailed information regarding the nonclinical pharmacology and toxicology of bortezomib may be found in the 2006 Investigator's Brochure

1.2.4 Clinical Pharmacokinetics and Pharmacodynamics

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

Bortezomib demonstrates multi-compartmental pharmacokinetics. Following intravenous administration of 1.0 mg/m^2 and 1.3 mg/m^2 dose, the mean first-dose maximum observed plasma concentrations of bortezomib were 57 and 112 ng/mL, respectively in 11 patients with multiple myeloma and creatinine clearance values >50 mL/min participating in a pharmacokinetics study. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1.0 mg/m^2 dose and 89 to 120 ng/mL for the 1.3 mg/m^2 dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours. Bortezomib is eliminated more rapidly following the first dose. Mean Total Body Clearances were 102 and 112 L/h following the first dose for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1.0 and 1.3 mg/m^2, respectively. Clinical experience has shown that the change in clearance does not result in overt toxicity from accumulation in this multidose regimen in humans.
In subjects with advanced malignancies, the maximum pharmacodynamic effect (inhibition of 20S activity) occurred within 1-hour post dose. At the therapeutic dose of 1.3 mg/m^2 in subjects with multiple myeloma, the mean proteasome inhibition at 1-hour post dose was approximately 61%.

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

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

1.2.5 Clinical Experience

It is estimated that as of January 2009, more than 100,000 patients have been treated with bortezomib, including patients treated through Millennium-sponsored clinical trials, Investigator-Initiated Studies, the US NCI Cancer Therapy Evaluation Program (CTEP), and with commercially available drug. Bortezomib has been commercially available since 13 May 2003.

The overall goal of the Millennium phase 1 program was to determine the MTD and dose-limiting toxicity (DLT) of bortezomib in a number of therapeutic settings involving subjects with various advanced malignancies. In a phase 1 trial in patients with refractory hematologic malignancies, the MTD for a twice weekly dosing for 4 weeks of a 42-day cycle was 1.04 mg/m^2/dose, with DLTs of thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise.[1] The toxicity was greatest during the third and fourth weeks of therapy. In the 3-week schedule of bortezomib monotherapy (4 doses, given on Days 1, 4, 8, and 11 of a 21-day treatment cycle), the DLT occurred at 1.56 mg/m^2/dose (3 subjects with Grade 3 diarrhea and 1 with peripheral sensory neuropathy). Therefore, the MTD at this schedule was 1.3 mg/m^2/dose. In a 35-day treatment cycle with 4 weekly doses of bortezomib monotherapy, the MTD was 1.6 mg/m^2/dose and DLT included hypotension, tachycardia, diarrhea, and syncope.

In phase 1 clinical studies, antitumor activity was reported in subjects with Non-Hodgkin's Lymphoma (NHL), MM, Waldenström's Macroglobulinemia, squamous cell carcinoma of the nasopharynx, bronchoalveolar carcinoma of the lung, renal cell carcinoma, and prostate cancer.[2,3,4,5]

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)[6] and M34100-025 (subjects with second or greater relapse and refractory to their last prior therapy).[7] In M34100-025, 202 heavily pretreated subjects with refractory MM after at least 2 previous treatments received bortezomib, 1.3 mg/m^2 on Days 1, 4, 8, and 11 of a 21-day treatment cycle. The European Group for Blood and Marrow Transplant (EBMT) response criteria, as described by Blade[8] were utilized to determine disease response. Complete responses (CRs) were observed in 4% of subjects, with an additional 6% of patients meeting all criteria for CR but having a positive immunofixation test. Partial response (PR) or better was observed in 27% of subjects, and the overall response rate (CR, PR, and minor response [MR] combined) was 35%. Seventy percent of subjects experienced stable disease or better.

The phase 3 study (M34101-039)[9], also referred to as the APEX study, was designed to determine whether bortezomib provided benefit (time to progression [TTP], response rate, and survival) to patients with relapsed or refractory MM relative to treatment with high-dose dexamethasone. The study was also designed to determine the safety and tolerability of bortezomib relative to high-dose dexamethasone, and whether treatment with bortezomib was associated with superior clinical benefit and quality of life relative to high-dose dexamethasone. A total of 669 patients were enrolled and 663 patients received study drug (bortezomib: 331; dexamethasone: 332). Patients randomized to bortezomib received 1.3 mg/m^2 IV push twice weekly on Days 1, 4, 8, and 11 of a 3-week cycle for up to 8 treatment cycles as induction therapy, followed by 1.3-mg/m^2 bortezomib weekly on Days 1, 8, 15, and 22 of a 5-week cycle for 3 cycles as maintenance therapy. Patients randomized to dexamethasone received oral dexamethasone 40 mg once daily on Days 1 to 4, 9 to 12, and 17 to 20 of a 5-week cycle for up to 4 treatment cycles as

induction therapy, followed by dexamethasone 40 mg once daily on Days 1 to 4 of a 4-week cycle for 5 cycles as maintenance therapy. The EBMT response criteria were utilized to determine disease response. There was a 78% increase in TTP for the bortezomib arm. Median TTP was 6.2 months for the bortezomib arm and 3.5 months for the dexamethasone arm ($p < 0.0001$). CR + PR was 38% with bortezomib versus 18% with dexamethasone ($p < 0.0001$). CR was 6% with bortezomib versus < 1% with dexamethasone ($p < 0.0001$). The CR + nCR (near CR) rate was 13% with bortezomib versus 2% with dexamethasone. In patients who had received only 1 prior line of treatment (bortezomib: 132; dexamethasone: 119), CR + PR was 45% with bortezomib vs 26% with dexamethasone ($p = 0.0035$). With a median 8.3 months of follow-up, overall survival was significantly longer ($p = 0.0013$) for patients on the bortezomib arm versus patients on the dexamethasone arm. The probability of survival at 1 year was 80% for the bortezomib arm versus 66% for the dexamethasone arm, which represented a 41% decreased relative risk of death in the first year with bortezomib ($p = 0.0005$). In patients who had received only 1 prior line of treatment, the probability of survival at 1 year was 89% for the bortezomib arm versus 72% for the dexamethasone arm, which represented a 61% decreased relative risk of death in the first year with bortezomib ($p = 0.0098$). Updated response rates and survival data were reported for M34101-039.[10] The updated CR + PR rate was 43% with bortezomib. The CR + nCR rate was 16% with bortezomib. With a median 22 months of follow-up, overall survival was significantly longer for patients on the bortezomib arm versus patients on the dexamethasone arm. The median overall survival was 29.8 months (95% CI: 23.2, not estimable) for the bortezomib arm vs 23.7 months (95% CI: 18.7, 29.1) for the dexamethasone arm (hazard ratio = 0.77, $p = 0.0272$). The probability of survival at 1 year was 80% for the bortezomib arm versus 67% for the dexamethasone arm ($p = 0.0002$).

The safety and efficacy of bortezomib in relapsed or refractory mantle cell lymphoma (MCL) were investigated in an international, phase 2, multicenter study M34103-053, also referred to as the PINNACLE study.[11] The single-arm study was designed to evaluate the response rates, duration of response (DOR), TTP, overall survival (OS), and safety of bortezomib treatment in patients with relapsed or refractory mantle cell lymphoma. For 141 evaluable patients, the response rate was 31% (8% CR/unconfirmed CR [Cru]). Median time to response was 40 days (range 31-204 days). The median number of cycles administered across all patients was 4; in responding patients, the median number of cycles was 8. The median DOR by algorithm was 9.2 months and 13.5 months in patients with CR/CRu. Median TTP for both groups was 6.2 months. With a median follow-up of 13.4 months, overall survival had not been reached. The most commonly reported adverse events (AEs) were fatigue, peripheral neuropathy, and gastrointestinal events. A time-to-event update to the PINNACLE study[12] was reported after a median follow-up of 26.4 months. TTP was 6.7 months for all patients, 12.4 months in all responders. The median DOR was 9.2 months in all responders and had not been reached in patients achieving CR/Cru. Overall survival was 23.5 months in all patients and 36 months in patients with CR/Cru. Survival at 12 months was 69% overall and 91% in responding patients.

The phase 3 study (MMY 3002) known as the VISTA study, evaluated the safety and efficacy of the combination of bortezomib, melphalan, and prednisone in previously untreated multiple myeloma patients who were not candidates for stem cell transplant.[13] The study was designed to determine the benefit of adding bortezomib to MP (melphalan and prednisone) as assessed by TTP. Patients (682) were

randomized to receive nine 6-week cycles of melphalan 9mg/m^2 and prednisone 60 mg/m^2 on Days 1 to 4, alone or in combination with bortezomib 1.3 mg/m^2 by IV bolus on Days 1, 4, 8, 11, 22, 25, 29, and 32 during Cycles 1 to 4, and on Days 1, 8, 22, and 29 during Cycles 5 to 9. Response was evaluated every 3 weeks using the EBMT criteria. At a preplanned interim analysis, the independent data monitoring committee recommended that the study be stopped since the prespecified statistical boundary end point of TTP had been crossed. Response rates were 30% with 4% CR. The rates of partial response or better were 71% in the bortezomib (VMP) group compared to 34% in the MP group ($p = 0.001$). With follow-up of 16.3 months, the TTP for the VMP group was 24 months compared to 16.6 months in the MP group ($p = 0.000001$) and was associated with a 52% reduced time to progression. The median DOR was 19.9 months in the VMP group and 13.1 months in the MP group. Overall survival had not been reached in either group. Hematologic toxicity was similar in both groups. The incidence of peripheral sensory neuropathy and gastrointestinal symptoms was higher in the VMP group. The incidence of herpes zoster was 3% in patients in the VMP group who received antiviral prophylaxis. Fifteen percent of patients in the VMP group discontinued therapy due to AEs compared to 14% in the MP group.

The VISTA study update after extended follow-up of 25.9 months,[14] confirmed a survival benefit for the VMP group. Overall survival was not reached in either group: VMP group (75) deaths, 3 year OS 72%; MP group (111) deaths, 3 year OS 59% ($p = 0.0032$). Patients on VMP were less likely to start second-line therapy (VMP 38% vs MP 57% at the time of data cut-off) with a longer time to next therapy (TNT) and treatment free interval (TFI). Of the MP patients who received subsequent therapy, 43% went on to receive bortezomib.

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

In the VISTA study, VMP was associated with prolonged TTP, TNT, TFI, and OS. Patients were successfully treated with subsequent IMiD-based therapy and retreated with bortezomib. After 36.7 months follow-up, OS continued to be superior for VMP. The OS for VMP had not yet been reached compared to MP (43.1 months).[15]

1.2.6 Potential Risks of Bortezomib

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

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

The known anticipated risks of bortezomib therapy are presented in Table 0-1 and Table 0-12. These risks are grouped according to the combined frequency observed in an integrated analysis of AEs in sponsored clinical studies of single-agent bortezomib dosed at 1.3 mg/m^2 twice weekly on a 21-day schedule, in patients with multiple myeloma and mantle cell lymphoma.

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

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

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

System Organ Class Observed Incidence	Preferred Term
Hepatobiliary Disorders	
Uncommon	Hyperbilirubinaemia, hepatitis*±
Immune System Disorders	
Uncommon	Drug hypersensitivity, angioedema
Infections and Infestations	
Very common	Upper respiratory tract infection, nasopharyngitis, pneumonia*, Herpes zoster*
Common	Lower respiratory tract infection*, sinusitis, pharyngitis, oral candidiasis, urinary tract infection*, sepsis*, bactaeremia*, cellulitis*, Herpes simplex, bronchitis, gastroenteritis*, infection
Uncommon	Septic shock*, catheter-related infection*, skin infection*, Herpes zoster disseminated*, lung infection*, infusion site cellulitis, catheter site cellulitis, infusion site infection, urosepsis*, Aspergillosis*, tinea infection, Herpes zoster ophthalmic, Herpes simplex ophthalmic, meningoencephalitis herpetic±, varicella, empyema±, fungal oesophagitis±
Injury, Poisoning, and Procedural Complications	
Common	Fall
Uncommon	Subdural haematoma
Investigations	
Common	Weight decreased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood alkaline phosphatase increased, liver function test abnormal, blood creatinine increased*
Uncommon	Gamma-glutamyltransferase (GGT) increased, oxygen saturation decreased*, blood albumin decreased, ejection fraction decreased*
Metabolism and Nutritional Disorders	
Very common	Decreased appetite, anorexia, dehydration*
Common	Hyperglycaemia, hypoglycaemia, hyponatraemia, hypokalaemia, hypercalcaemia*
Musculoskeletal and Connective Tissue Disorders	
Very common	Bone pain, myalgia, arthralgia, back pain
Common	Muscular weakness
Uncommon	Limb discomfort
Neoplasms, Benign, Malignant, and Unspecified (including cysts and polyps)	
Uncommon	Tumour lysis syndrome*

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

System Organ Class Observed Incidence	Preferred Term
Nervous System Disorders	
Most common	Peripheral neuropathy (including all preferred terms under the MedDRA High-level term Peripheral neuropathy NEC)
Very common	Paresthesia, dizziness excluding vertigo, headache
Common	Polyneuropathy, syncope, dysesthesia, dysgeusia, postherpetic neuralgia
Uncommon	Convulsion, loss of consciousness, ageusia, encephalopathy, paralysis*,autonomic neuropathy, reversible posterior leukoencephalopathy syndrome±
Psychiatric Disorders	
Very common	Anxiety, insomnia
Common	Confusional state
Uncommon	Delirium
Renal and Urinary Disorders	
Common	Renal impairment*, renal failure*, haematuria
Uncommon	Micturition disorder
Respiratory, Thoracic, and Mediastinal Disorders	
Very common	Cough, dyspnoea
Common	Epistaxis, dyspnoea exertional, pleural effusion*, rhinorrhea, hypoxia*, pulmonary oedema*
Uncommon	Hemoptysis*, acute respiratory distress syndrome*, respiratory failure*, pneumonitis*, lung infiltration, pulmonary alveolar haemorrhage*, interstitial lung disease*, pulmonary hypertension*, pleurisy, pleuritic pain
Skin and Subcutaneous Tissue Disorders	
Very common	Rash
Common	Rash pruritic, rash erythematous, urticaria, petechiae
Uncommon	Cutaneous vasculitis, leukocytoclastic vasculitis±
Vascular Disorders	
Common	Hypotension*, orthostatic hypotension
Uncommon	Cerebral haemorrhage*

Source: BortezomibInvestigator's Brochure Edition 14.

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

* Fatal outcomes have been reported.

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

Table 0-2 Reports of Adverse Reactions From Postmarketing Experience

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

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

System Organ Class Observed Incidence	Preferred Term
Skin and subcutaneous system disorders	
Acute febrile neutrophilic dermatosis	Unknown
Toxic epidermal necrolysis	Unknown
Eye Disorders	
Ophthalmic herpes	Rare
Optic neuropathy	Rare
Blindness	Rare

Source: Bortezomib Investigator's Brochure Edition 14.

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

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

Other medical events of interest that are considered not causally related to 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.

1.2.7 Subcutaneous administration of Bortezomib

Subcutaneous administration of has been investigated in two clinical trials in MM (multiple myeloma), including MMY-3021, a phase III, randomized, open-label, prospective study of subcutaneous (SC) vs. intravenous (IV) administration of bortezomib in patients with relapsed MM. Subcutaneous administration of bortezomib has not been approved by the FDA.

Moreau et al published a phase I trial of SC vs. IV bortezomib in relapsed MM in Hematologicae 2008. 93(12):1908-11. This trial showed the response rate was similar between the IV vs. SC arm and area under the curve was also similar.

In 2008, Moreau et al. first described the subcutaneous administration of bortezomib in a group of patients with multiple myeloma (MM). At the 2010 annual meeting of the American Society of Hematology (ASH), this group presented data from a phase III randomized controlled trial comparing intravenous and subcutaneous routes of administration of bortezomib with or without dexamethasone in patients with MM. Randomized, 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. 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 (range one to ten) in both groups.

ORR after four cycles was 42% in both groups (61 patients in subcutaneous group and 31 in intravenous group; ORR difference -0·4%, 95% CI -14·3 to 13·5), showing non-inferiority (p=0·002). After a median follow-up of 11·8 months (IQR 7·9-16·8) in the subcutaneous group and 12·0 months (8·1-15·6) in the intravenous group, there were no significant differences in time to progression (median 10·4 months, 95% CI 8·5-11·7, vs 9·4 months, 7·6-10·6; p=0·387) and 1-year overall survival (72·6%, 95% CI 63·1-80·0, vs 76·7%, 64·1-85·4; p=0·504) with subcutaneous versus intravenous bortezomib.

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.

Subcutaneous bortezomib offered non-inferior efficacy to standard intravenous administration, with an improved safety profile.

1.2.8 Precautions and Restrictions

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

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or

- Surgically sterile, or

- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing the informed consent form through 30 days after the last dose of bortezomib, or agree to completely abstain from heterosexual intercourse.

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

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

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

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

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

1.3 RITUXIMAB (rituximab) for Injection

1.3.1 Scientific background:

Rituximab is a chimeric IgG monoclonal antibody targeting the CD20 surface antigen present on both normal lymphocytes and B-cell lymphomas. The activity of this agent is multi-faceted, in that it leads to direct lysis by complement activation as well as antibody dependant cell mediated cytotoxicity, triggers apoptosis, and may lead to various signaling pathway changes in targeted cells (Cartron 2004). It also appears to act as a chemosensitizer by blocking IL-10 binding, leading to decreased intracellular bcl-2 (Demidem, 1997). This suggests that rituximab may synergize with bortezomib. It is reasonable to combine the two agents, bortezomib and rituximab, in MCL.

This combination has already been used in previous phase II trials for relapsed MCL with good results. It was well tolerated for MCL patients.

1.3.2 Pharmacology:

Kinetics: In prior studies patients treated at the 375mg/m2 dose levels exhibited detectable antibody concentrations throughout the treatment period. Most patients exhibited increasing pre-infusion antibody concentrations with each subsequent infusion. In nine patients, the T1/2 following the first antibody infusion was 59.8 hours (11.1-104.6 hr) with a C max of 271g/ml. Following the fourth antibody infusion when circulating B cells had been depleted and antigentic sites coated, the T1/2 was 174 hrs (26.4-442.3 hr) and C max 496.7 g/ml.

1.3.3 Formulation:

Rituximab antibody will be provided in 100 mg (10ml) and 500 mg (50 ml) vials at a concentration of 10.0 mg of protein per mL.

1.3.4 Storage and stability:

Stored at 2-8. Reconstituted antibody is stable for 24 hours upon refrigeration followed by 12 hours at room temperature.

1.3.5 Preparation:

Diluted with normal saline to a concentration of 1-4 mg/ml. Shaking can cause aggregation and precipitation fo the antibody and should be avoided.

1.3.6 Route of Administration:

Intravenous

1.3.7 Availability and Accountability:

Rituximab is commercially available in 10 mL (100mg) and 50 mL (500mg) single-use vials at a concentration of 10mg/mL. Use of rituximab is considered standard care for this indication, and will not be provided by Millennium.

1.3.8 Incompatibilities

Do not mix or dilute rituximab with other drugs. No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

1.3.9 Side effects

1. Infusion related symptoms: Fever, chills, rigors, hypotension, anaphylaxis or hypersensitivity reactions, arrhythmia, dyspnea, bronchospasm, angioedema. In rare cases, severe and fatal cardiopulmonary events, including hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock, have occurred. (4-7/10,000 patients or 0.04-0.07%). Nearly all fatal infusion-related events occurred in association with the first infusion. Patients with pre-existing cardiac conditions, including arrhythmia and angina, have had recurrences of these cardiac events during rituximab infusions.
2. Gastrointestinal: Nausea, vomiting.
3. Hematologic: Leukopenia, anemia, thrombocytopenia. In clinical trials, NCI CTC Grade 3 and 4 cytopenias were reported in 48% of patients treated with rituximab; these include: lymphopenia (40%), neutropenia (6%), leucopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2-116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following rituximab therapy was reported.

4. Dermatologic: Rash, pruritus, urticaria, and rarely severe mucocutaneous reactions
5. Infectious: Reactivation of hepatitis B; reactivation of other viral infections or increased susceptibility to other infections. Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to diagnosis of hepatitis was approximately four months after the initiation of rituximab and approximately one month after the last dose.

1.4 Study rationale and selection of drug doses

Doses of RITUXAN given is 375 mg/m2 give weekly x 4 weeks given every 6 month for 4 cycles. This is the standard maintenance dosing regimen used for follicular lymphoma and for mantle cell lymphoma.

Doses of bortezomib given is 1.3 mg/m2 weekly x 4 weeks given every 3 month x 8 cycles. Doses of 1.3 mg/m2 is based on prior pharmacokinetics study. Dosing schedule is changed from D1, 4, 8, 11 to D 1, 8, 15, and 22 to allow for recovery of normal healthy tissues in post transplant patients to avoid toxicity since this will be a maintenance study. Prior studies have also combined bortezomib + RITUXAN and proved no additional toxicities[13-14]. We have chosen to use the subcutaneous route of administration instead of intravenous route because of increased convenience for patients (this is a maintenance study and patients will likely prefer subcutaneous administration due to less time spent in clinic). Also based on the ASH 2010 presentation there appears to be less grade $\geq$ 3 AEs and peripheral neuropathy associated with SC administration.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the two year disease free survival in MCL patients treated with bortezomib + rituximab after HSCT

2.2 Secondary Objectives

Evaluate the toxicity profile, safety, overall survival, time to treatment failure, remission duration, and biological markers of mantle cell lymphoma patients treated with bortezomib + rituximab after autologous hematopoietic stem cell transplantation.

3 INVESTIGATIONAL PLAN

3.1 Overall Design and Plan of the Study

This is an open label, phase II study of maintenance bortezomib + RITUXAN in patients with mantle cell lymphoma s/p autologous hematopoietic stem cell transplantation (AHCT). Patients must have achieved engraftment by D60-180 as evidenced by ANC >1000 and Plt > 80K. Patients also must not have greater than grade 1 peripheral neuropathy at the time of starting bortezomib. Patients will start the screening process at D60 to D180 after AHCT to make sure they qualify for study. Patients need to be in complete remission by D60 to D180 as evidenced by either CT scan of the neck, chest, abdomen, and pelvis, or by CT/PET scan, and by bone marrow biopsy. Patients will then start treatment with bortezomib + RITUXAN as maintenance therapy within D60-D180 after AHCT. Bortezomib will be given at a dose of 1.3 mg/m2 on D1, 8, 15, 22 in a 28 day period every 3 months for a total of 8 cycles. RITUXAN will be given at dose of 375 mg/m2 on D1, 8, 15, 22 in a 28 day period every 6 months for a total of 4 cycles.

The primary efficacy endpoint of this study is two year disease free survival. This is a phase II efficacy trial. Response will be assessed according to modified criteria for malignant lymphoma, based on (Cheson et al 1999) and (Cheson, et al 2007). For the 1st two years of treatment, assessments will be performed at every cycle. After treatment period, assessments will be performed every 6 months for three additional years. Patients will then undergo end of treatment assessment at year five. Clinical suspicion of disease relapse at any time will require a physical examination and radiological confirmation to be performed promptly, rather than waiting for the next scheduled radiological assessment.

3.2 Selection of Patients

The total number of patients to be enrolled on this study is 36. (25 from COH and 11 at Fred Hutchinson Cancer Research Center)

Enrollment is defined as the first day of bortezomib treatment (i.e., Day 1 of Cycle 1).

3.2.1 Inclusion Criteria

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

- Patients must have histological documented or cytological confirmed Mantle Cell Lymphoma. Cyclin D1 must be present as evidenced by either FISH or Immunohistochemical staining.
- Patients must have undergone AHCT and achieved engraftment by D60-180 as evidenced by ANC >1000/mcL and Plt > 75,000/mcL.
- Patients must be in complete remission at D60-180 after AHCT as evidenced by CT scan of the neck/chest/abd/pelvis or CT/PET scans.
- 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.
- Female subject is either post-menopausal or surgically sterilized or willing to use an acceptable method of birth control (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) for the duration of the study.

- Male subject agrees to use an acceptable method for contraception for the duration of the study.
- Age > 18 years old. Because no dosing or adverse event data are currently available on the use of bortezomib in patients < 18 years of age, children are excluded from this study but will be eligible for future pediatric single-agent trials, if applicable.
- Life expectancy of greater than 3 months.
- Karnosfsky > 60%.
- Patients must have normal organ and marrow function as defined below:
    - ANC > 1000/mcL
    - Plts > 75,000/mcL
    - Total bilirubin within normal institutional limits, patients with elevation of unconjugated bilirubin alone, as in Gilbert's disease, are eligible.
    - AST/ALT < 2.5 X institutional upper limit of normal.
    - Creatinine up to and including 2 mg/dL.

3.2.2 Exclusion Criteria

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

- Patient has ≥Grade 2 peripheral neuropathy within 14 days before enrollment and at D60-180 after AHCT. Patients who had ≥ Grade 2 peripheral neuropathy within 14 days before enrollment but resolves to grade 1 or lower peripheral neuropathy at D60-D180 after AHCT can be enrolled at this time.
- Patient has >1.5 x ULN Total Bilirubin unless history of Gilbert's syndrome.
- Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure (see section 8.4), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at Screening has to be documented by the investigator as not medically relevant.
- Patient has hypersensitivity to bortezomib, boron or mannitol.
- Female subject is pregnant or breast-feeding. Confirmation that the subject is not pregnant must be established by a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women.
- Patient has received other investigational drugs with 14 days before treatment of treatment with bortezomib + rituximab
- Serious medical or psychiatric illness likely to interfere with participation in this clinical study.
- Diagnosed or treated for another malignancy within 3 years of enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy.
- Patients with other active malignancies (no evidence of other cancer or life expectancy greater than 5 years) are ineligible for this study.

- HIV positive patients or Hepatitis B or C positive patients due to risk of reactivation from marrow-suppressive therapy and Rituximab.
- Patients with active CNS disease or history of brain mets are excluded from study.
- Prior exposure to either bortezomib or rituximab is not an exclusion criteria.

Eligible patients will be given the opportunity to participate in the study. The goals of the study will be described and the patient will be given a copy of the informed consent to review. The interested patient will sign the consent form and retain a copy.

3.3 Registration Processes

Registration Process (City of Hope patients)

- **Registrations for this protocol must be made through the CTO office at the City of Hope between the hours of 8:30 a.m. to 4:30 p.m., Monday through Friday (except holidays).**
- **Patients must be registered prior to initiation of protocol therapy.**
- **A patient failing to meet all protocol requirements may not be registered. If you have any questions regarding eligibility, contact (626) 256-4673 ext. 62468 and ask for the CRA in charge of this study.**
- **Prestudy laboratory tests, scans and x-rays must be completed prior to registration according to the study calendar.**
- **Patients must sign an informed consent prior to registration.**
- **Confirm that the patient meets all inclusion and exclusion eligibility criteria for the protocol.**
- **Completion of the Eligibility Checklist (per institutional guidelines).**
- **Verify that all required prestudy tests were performed.**
- **Fax the completed Eligibility Checklist and the signed, dated informed consent to CTO. The FAX number is (626) 301-8393.**
- **Call CRA at (626) 256-4673 x 62468 to confirm the FAX arrival. If the CRA is not in the office, have him/her paged.**
- **If the patient qualifies, the CRA will assign the patient's study ID number.**
- **Once a patient has been registered, CRA will confirm registration of the patient.**

The outside institution patient registration process will be handled by the Department of Clinical Research Information Support (CRIS) Data Coordinating Center (DCC) at City of Hope. Documentation of current IRB approval must be on file with the DCC prior to registration of patients on this study for participating institutions.

The steps below are to be taken when registering a **patient at a participating institution**:

Registration Process (Participating Institutions)

- **The participating institution's research staff must assure they have the most current and updated version of the protocol and informed consent prior to enrolling a patient. If a question arises, please contact the Data Coordinating Center at 626-256-4673 extension 63968 or via pager at 626-423-6486.**
- **The participating institution must assure that all prestudy laboratory tests, scans and x-rays have been completed prior to registration according to the study calendar.**
- **The participating institution must assure that the patient has signed an approved informed consent prior to registration, including Experimental Subject Bill of Rights (if applicable) and appropriate HIPAA authorization.**
- **The participating institution must confirm that the patient meets all inclusion and exclusion eligibility criteria for a protocol. The eligibility checklist must be completed in its entirety.**
- **A patient failing to meet all protocol requirements may not be registered. Patients must be registered prior to initiation of protocol therapy.**
- **Once a patient is eligible, all the pre-study requirements have been fulfilled, and the informed consent obtained, the research nurse or the data manager (study coordinator) at the participating center will inform the Data Coordinating Center (626-256-4673, ext 63968; pager 626-423-6486) and FAX (fax number 626-301-8422) a copy of the signed informed consent, patients' Bill of Rights, signed HIPPA consent, completed eligibility checklist and corresponding source documentation confirming eligibility (including pathology reports, lab reports, x-ray reports, etc.).**

<u>The City of Hope Data Coordinating Center will:</u>

- **Review all materials received to ensure the patient is eligible.**
- **Ensure the consent form is valid and is signed correctly by all parties. If additional information is needed or should there be any questions, the Data Coordinating Center will immediately contact the participating institution and registration will not occur until all issues are resolved. No exceptions will be granted.**
- **The patient will be registered centrally at City of Hope.**
- **Confirmation of Registration will be emailed/faxed to the participating institution noting study number as well as assigning the dose (if applicable) within 24 hours via fax or email.**
- **The Data Coordinating Center will call the research nurse or data manager (study coordinator) at the participating site and verbally confirm registration.**
- **If a patient does not receive protocol therapy following registration, the patient's registration on the study may be cancelled. The Data Coordinating Center should be notified of cancellations as soon as possible.**

3.4 Procedures for On-Study and Treatment Deviations

Any amendments to the study protocol need to be approved by the IRB at the study sponsor site, City of Hope, and then at the participating center. All deviations or single subject exceptions to the study protocol must be reported to the primary IRB of the participating site, and to Dr. Matthew Mei, the study PI at the sponsor institution.

3.5 Study Treatments

3.5.1 Clinical Trial Materials

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

Rituximab antibody will be provided in 100 mg (10ml) and 500 mg (50 ml) vials at a concentration of 10.0 mg of protein per mL.

3.5.2 Preparation, Handling, and Storage of Drugs

Bortezomib

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

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

Subcutaneous administration.

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

Intravenous administration

Drug is available in sterile, single use vials containing 3.5 mg of bortezomib. ~~x~~ Each vial of bortezomib for Injection should be reconstituted under a laminar flow biological cabinet (hood) within eight hours before dosing with **3.5 mL** of normal (0.9%) saline, Sodium Chloride Injection USP, so that the reconstituted solution contains bortezomib at a concentration of **1 mg/mL** for intravenous administration.

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. 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.

Rituximab is stored at 2-8. Reconstituted antibody is stable for 24 hours upon refrigeration followed by 12 hours at room temperature. It needs to be diluted with normal saline to a concentration of 1-4 mg/ml. Shaking can cause aggregation and precipitation of the antibody and should be avoided. The route of administration is intravenous. Rituximab is commercially available in 10 mL (100mg) and 50 mL (500 mg) single-use vials at a concentration of 10mg/ml. Use of rituximab is considered standard of care for this indication, and will not be provided by Millennium. Do not mix or dilute rituximab with other drugs. No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

Bortezomib Destruction

Investigational bortezomib (expired or end of study) should be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

3.5.3 Drug administration and dosage schedule

Table 3.5. Treatment Schema

	Pre-Study	Day 1	Day 8	Day 15	Day 22	
bortezomib		X	X	X	X	Repeat every 3 month x 8 cycles
rituximab		X	X	X	X	Repeat every 6 month x 4 cycles

Bortezomib will be administered on D1, 8, 15, and 22 every 3 month for a total of 8 cycles. Bortezomib dosing will be 1.3 mg/m2

Rituximab will be administered on D1, 8, 15, 22 every 6 month for a total of 4 cycles. Rituximab dosing will be 375 mg/m2

Bortezomib Administration

Intravenous and subcutaneous route of administration have different reconstituted concentration. Caution should be used when calculating the volume to be administered.

SUBCUTANEOUS ADMINISTRATION

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

Subcutaneous Administration Precautions

- The drug quantity contained in one vial (3.5 mg) may exceed the usual dose required. Caution should be used in calculating the dose to prevent overdose.
- When administered subcutaneously, sites for each injection (thigh or abdomen) should be rotated.
- New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, erythematous, or indurated.

- If local injection site reactions occur following bortezomib administration subcutaneously, a less concentrated bortezomib solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously. **Alternatively, the IV route of administration should be considered.**
- In clinical trials of bortezomib IV, local skin irritation was reported in 5% of patients, but extravasation of bortezomib was not associated with tissue damage. In a clinical trial of subcutaneous bortezomib, a local reaction was reported in 6% of patients as an adverse event, mostly redness.

INTRAVENOUS ADMINISTRATION

Drug is available in sterile, single use vials containing 3.5 mg of bortezomib. Each vial of bortezomib for Injection should be reconstituted under a laminar flow biological cabinet (hood) within eight hours before dosing with **3.5 mL** of normal (0.9%) saline, Sodium Chloride Injection USP, so that the reconstituted solution contains bortezomib-at a concentration of **1 mg/mL** for intravenous administration.

Drug will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Patients may be treated on an out-patient basis, if possible.

The pharmacist will prepare the drug under aseptic conditions. The amount (in mg) of drug to be administered will be determined based on body surface area. Body surface area is to be calculated based on body weight using a standard nomogram (see section 8.3). The dose should be calculated on Day 1 of each cycle; the dose administered should remain the same throughout each cycle but should be recalculated at the start of the next cycle. If a patient experiences a notable change in weight (e.g., loss or gain of ≥8 lbs or 3.6 kg) within a cycle, as determined by an unscheduled weight assessment, then the patient's dose should be recalculated at that time.

The appropriate amount of bortezomib will be drawn from the injection vial and administered as an IV push over 3 to 5 seconds. Vials are for single use administration. There must be at least 72 hours between each dose of bortezomib.

Rituximub administration
Rituximab will be administered only to eligible patients under the supervision of the investigator or identified sub-investigators. Patients may be treated on an out-patient basis, if possible. The pharmacist will prepare the drug under aseptic conditions. The amount (in mg) of the drug to be administered will be determined based on body surface area. Body surface area is to be calculated based on body weight using a standard nomogram (see section 8.3). The dose should be calculated on Day 1 of each cycle; the dose administered should remain the same throughout each cycle but should be recalculated at the start of the next cycle. If a patient experiences a notable change in weight (e.g., loss or gain of > 8 lbs or 3.6 kg) within a cycle, as determined by an unscheduled weight assessment, then the patient's dose should be recalculated at that time.

3.5.4Dose Modification and Delay

Dose escalation will not be allowed in any patient.

There will not be any dose modification for rituximab or dose delay.

Table 3.2 Dosing Level Schema

	Bortezomib	rituximab
Level 1	1.3 mg/m2	375 mg/m2
Level -1	1.0 mg/m2	375 mg/m2
Level -2	0.7 mg/m2	375 mg/m2

Before each drug dose, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

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

If the patient experiences febrile neutropenia, a Grade 4 hematologic toxicity (including a platelet count $<50 \times 10^9$/L) or any ≥Grade 3 non-hematologic toxicity considered by the investigator to be related to bortezomib, then drug is to be held.

For non-hematologic toxicities, bortezomib is to be held for up to 2 weeks until the toxicity returns to Grade 1 or better. For infection toxicities, bortezomib can be held up for 3 weeks until toxicity returns to grade 2 or better.

For hematologic toxicities, bortezomib is to be held for up to 2 weeks until the patient has a hemoglobin value of 9 , platelet value of 75,000 , and absolute neutrophil value of >1000. Growth factors, packed red blood cell and plt transfusions may be given as needed.
Dose interruption or study discontinuation is **not** required for lymphopenia of any grade.

If, after bortezomib has been held, the toxicity does not resolve, or improve to grade 1, as defined above, then drug must be discontinued. For infection toxicities, if after the bortezomib has been held for 3 weeks, and the toxicity does not resolve or improve to grade 2, then the drug must be discontinued.

If the toxicity resolves, as defined above, and bortezomib is to be restarted, the dose must be reduced by approximately 25% for this cycle as follows:

1. If the patient was receiving 1.3 mg/m^2, reduce the dose to 1.0 mg/m^2.
2. If the patient was receiving 1.0 mg/m^2, reduce the dose to 0.7 mg/m^2.
3. If the patient was receiving 0.7 mg/m^2, discontinue drug
4. If the patient received a reduced dose of bortezomib without return of toxicities, then the patient can receive the prior dose of drug without the 25% dose reduction at the next cycle.
5. No dose adjustment is necessary for rituximab.
6. Premedication such as Benadryl, Tylenol, and hydrocortisone can be given to treat and prevent infusion related reactions from rituximab.

Patients who experience bortezomib -related neuropathic pain and/or peripheral sensory neuropathy are to be managed as presented in Table 3.1 Management of Patients with bortezomib -Related Neuropathic Pain and/or Peripheral Sensory Neuropathy. **Once the dose is reduced for peripheral neuropathy, the dose may not be re-escalated.**

Table 3-4 Management of Patients with bortezomib-Related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy (Mandatory With Adjustments as Necessary)

Recommended Dose Modification for bortezomib related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy	
Severity of Peripheral Neuropathy Signs and Symptoms	**Modification of Dose and Regimen**
Grade 1 (paresthesias, weakness and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce **bortezomib** to 1.0 mg/m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold* **bortezomib** therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of **bortezomib** at 0.7mg.m^2 and change treatment schedule to once per week.*
Grade 4 (Sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue **bortezomib**
Grading based on NCI Common Terminology Criteria CTCAE v4.0 NCI Common Terminology Criteria website - http://ctep.info.nih.gov/reporting/ctc.html	

ADL = activities of daily living

*Key:

Reduce by one dose level:	**bortezomib** dose reduction from 1.3 to 1.0, or 1.0 to 0.7 mg/m^2/dose.
Hold:	Interrupt **bortezomib** for up to 2 weeks until the toxicity returns to Grade 1 or better.
Schedule change:	There is no schedule changes

The neurotoxicity-directed questionnaire (see section 8.7) is a useful tool for determining the presence and intensity of neuropathic pain and/or peripheral neuropathy from the patient's perspective. Neuropathic symptoms are more prominent than abnormalities on the clinical examination. After the patient completes the neurotoxicity-directed questionnaire, the questionnaire should be reviewed to assist with the evaluation of the onset and intensity of peripheral neuropathy and other neurotoxicities that may possibly require intervention or dose modification.

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

3.5.5 Blinding, Packaging, and Labeling

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

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

3.5.6 Concomitant Treatment

Required Concurrent Therapy

The following medications/supportive therapies can be used during study participation, as applicable:

G-CSF

Platelets transfusions

Packed red blood cell transfusions

Antibiotic therapy

Prednisone

Investigators should consider using antiviral prophylaxis in subjects being treated with bortezomib

Prohibited Concurrent Therapy

- Any investigational agent other than bortezomib

3.5.7 Treatment Compliance

All drugs will be administered to eligible patients under the supervision of the investigator or identified sub-investigator(s). The pharmacist will maintain records of drug receipt (if applicable), drug preparation, and dispensing, including the applicable lot numbers, patients' height, body weight, and body surface area (see section 8.3), and total drug administered in milliliters and milligram. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.

3.6 Duration of Treatment and Patient Participation

In the absence of treatment delays dues to adverse events, treatment should continue for 4 cycle of rituximab and 8 cycles of bortezomib.

Screening period is between D 60 to D 180 after HSCT. Patients will be on treatment for 2 years durations and be followed for 3 additional years for a total of 5 year follow up.

Termination of Treatment and/or Study Participation

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

Intercurrent illness

Occurrence of an unacceptable adverse event

A treatment cycle delay or bortezomib interruption of >2 weeks or missing three of four bortezomib
doses within a treatment cycle because of toxicity

Patient request

Protocol violations

Non-compliance

Administrative reasons

Failure to return for follow-up

General or specific changes in the patient's condition unacceptable for further treatment in the judgment of the investigator

Progressive disease at any time

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.

3.7 Efficacy, Pharmacodynamic/Pharmacogenomic/Correlative studies, and Safety Measurements

3.7.1 Efficacy Measurements

Patients will be undergoing CT/PET scans or full body CT scans every 6 months for assessment of disease. The imaging needs to be obtained within 1-2 weeks prior to dosing of each subsequent cycle of bortezomib or Rituximab. After 2 years of treatment, CT/PET or full body CT scans can be spaced to once a year until a follow up of 5 years is reached.

Patients will have bone marrow biopsy done as baseline of study. Bone marrow biopsy will be performed every 6 month during 1st two years of study then yearly. It will also be performed at the time of relapse or suspected relapse.

Disease response will be assessed and defined by the revised Cheson Criteria (Cheson 2007)

Complete response (CR):

Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease related symptoms if present before therapy.

All lymph nodes and masses must regress to normal size (< 1.5 cm in greatest transverse diameter if > 1.5 cm prior to treatment) or become PET negative.

If bone marrow was involved by lymphoma, it must be cleared as documented by biopsy at the same location.

Progressive disease (PD): Appearance of any new lesion during or at the end of therapy.

Survival: defined as the time form registration to time of death due to any cause. If a patient is not known to have died, survival time is censored at the time of last follow-up. Patients will be followed till death.

Progression free survival: Defined as the time from registration to the first observation of disease progression or death due to any cause. If a patient has not progressed or died, progression-free survival is censored at the time of last follow-up.

3.7.2 Pharmacokinetic/Pharmacodynamic/Pharmacogenomic/Correlative Studies--Correlative Studies will be done at City of Hope only.

Patients will have bone marrow biopsy done as baseline of study. Bone marrow biopsy will be performed every 6 months during 1st two years of study then yearly. It will also be performed at the time of relapse or suspected relapse.

Patients will have peripheral blood samples done at baseline, and every 3 months during 1st and 2nd year of study and then yearly. It will also be performed at the time of relapse or suspected relapse.

Paraffin block from the representative diagnostic section or 12 unstained paraffin slides will be obtained from diagnostic material and the time of relapse. These can be from fresh or fixed tissue.

We will examine CCND1 expression, CCND1 mRNA expression, and its isomer expression in peripheral blood, bone marrow samples, and lymph nodes samples (from diagnostic sample). We will also examine proliferation markers such as Ki-67 and others by immunohistochemistry. All samples will be analyzed at Beckman Research Institute under Dr. John Rossi laboratory.

There are two sets of biomarkers that will be evaluated in this study. The 1st set of biomarkers to be tested is Ki-67 expression and CCND1 truncated isomer expression. This biomarker would be examined in primary tumor tissue, including lymph nodes (from diagnostic sample) and bone marrow and peripheral blood specimens. Ki-67 expression and CCND1 truncated isomer has been shown in previous study to predict for prognosis in a retrospective pattern. However, it has not been evaluated in a prospective trial. We will be looking to see if maintenance treatment with

bortezomib + rituximab after AHCT would be able to overcome the poor prognosis predicted by high Ki-67 expression (30% or higher) or the presence of the truncated CCND1 isomer.

The second set of biomarkers to be evaluated is CCND1 mRNA expression in bone marrow and peripheral blood. Although MCL is the only lymphoma that expresses CCND1, normal tissues such as GI tract can also produce CCND1 mRNA. It has not been used as an early marker for relapse due to background noise from normal tissue. In this study, we hope to evaluate the expression of CCND1 mRNA in the bone marrow and peripheral blood longitutionally from serial measurements. We hope to correlate an increase in CCND1 mRNA from baseline with relapse.

Blood sample collection and storage for DNA and RNA analysis:

Prior to drug administration on Day 1 of each cycle then every 6 months through year two and yearly thereafter to five years.

25 ml of blood will be obtained in EDTA (lavender-topped) tubes to measure CCND1 mRNA. The blood for isolation of cells may be drawn from a central line or peripherally.

Samples will be stored in the Beckman Research Institute Rossi laboratory. Following completion of this study, samples will remain in storage. If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed and reported as such to the IRB. Existing data from samples already distributed or analyzed will be retained and may be published without identification of individual patients.

Any new use of these samples will require prospective IRB review and approval; any loss or destruction of samples and the planned disposition of samples after the protocol is terminated will be reported to the IRB.

Bone Marrow Aspirate sample collection and storage for DNA/RNA analysis.

Each time a bone marrow aspiration is obtained for clinical management of the patient, additional aspirate will be obtained and transferred into a BD vacutainer CPT tube with sodium heparin.

3.7.3 Safety Measurements

Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events, the regular monitoring of hematology, serum chemistry, routine monitoring of vital

signs (heart rate, blood pressure, and body temperature) and physical condition. Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, Version 4.0.

4 STATISTICAL PROCEDURES

4.1 Sample Size Estimation

The aim of this study is to examine the anti-tumor activity/efficacy of this maintenance regimen in eligible patients. The City of Hope historical rate of DFS is 60%, which is a consistent with what is reported in literature. This is an efficacy study. We expect a disease-free survival rate (DFS) (primary endpoint) to improve by 20% with this maintenance therapy. To achieve a DFS of 80% at two years, we need a sample size of 36 evaluable patients. (alpha=0.05, 1-beta=0.80). With adequate follow-up time, the endpoints of DFS, overall survival (OS), and time to treatment failure will be assessed by Kaplan-Meier survival analysis and 95% confidence intervals will be calculated using Greenwood's formula. Based on the current referral patterns to the City of Hope, it is expected that approximately 5 patients per year will be enrolled in this study; approximately five years of accrual will be required.

While early stopping rules have been incorporated into the study for excessive toxicity; there will be no interim analysis for efficacy. Toxicities will be recorded using the NCI CTCAE 4.0 Scale. The table below will be consulted as relevant toxicities are encountered.

Early Stopping Criteria: For each adverse outcome, stop if the cumulative number of patients reaches or exceeds the following limits:

Table of Early Stopping Criteria

# of patients treated	# of patients expired due to treatment related causes that would stop the study*	# of patients with ≥grade 3 toxicities that would require an evaluation for safety** and ***	Probability that the early stopping rule will be invoked given a failure rate of:		
			10%	15%	20%
12	3	3	0.11	0.26	0.45
18	5	5	0.12	0.27	0.47
24	6	6	0.12	0.31	0.53
30	8	8	0.13	0.31	0.53
36	9	9	0.13	0.32	0.55

* Note: The stopping rules are not statistically based; expected treatment related mortality should not to exceed 25%.
** Note: For hematologic toxicities: Any grade 4 neutropenia associated with fever or infection and lasting beyond three weeks, or grade 4 neutropenia lasting for more than 28 days per CTCAE 4.0 toxicity criteria should be counted toward the early stopping rule.

***Note: For infection toxicities, only grade 3 that does not resolve within 3 weeks or any grade 4 events would require an evaluation for safety. As these patients are post AHCT and start onto study within a year post AHCT, their immune system has not recovered to normal and grade 3 infection events can occur even without maintenance treatment.

Any patient who receives treatment will be evaluable for toxicity. Each patient will be assessed periodically according to the treatment schedule for the development of any toxicity. The toxicity rule for safety will be assessed as each patient reaches day +90 post initiation of bortezomib. If more than the specified number of patients (noted in the table above) have significant treatment related toxicities, then the safety of the study will be evaluated. Based on this evaluation the study will either be amended to reduce the dose/adjust schedule or will be closed.

4.2 Randomization and Stratification

Randomization/stratification will not be used in this study

4.3 Populations for Analysis

MCL lymphoma patients s/p autologous hematopoietic stem cell transplantation

4.4 Statistical Methods

The toxicities observed will be summarized in terms of type (e.g. organ affected or ANC) severity (by NCI CTCAE v4.0 and nadir or maximum values for the laboratory measures), date of onset, duration, reversibility, and attribution. Tables will be created to summarize these toxicities and side effects. Baseline information (e.g., the extent of prior therapy) and demographic information will be presented for all study patients.

In accordance with the primary study objectives, we will perform descriptive statistical analyses on these data after the study is complete. With adequate follow-up time, the endpoints of DFS, overall survival (OS), and time to treatment failure will be assessed by Kaplan-Meier survival analysis and 95% confidence intervals will be calculated using Greenwood's formula. DFS will be defined as the time from first treatment day until objective or symptomatic relapse or death as a result of lymphoma or acute toxicity of treatment. OS will be defined as the time from first treatment day until death.

4.5 Protocol Deviations

4.5.1 Deviation Policy

Brief interruptions and delays may occasionally be required due to travel delays, airport closure, inclement weather, family responsibilities, security alerts, government holidays, etc. This can also extend to complications of disease or unrelated medical illnesses not related to disease progression. These delays of up to three days will not be considered protocol deviations.

Planned deviations may be permitted in accordance with the COH policy on "Clinical Research Protocol Planned Deviations and Single Subject Exception." These planned deviations, considered Single Subject Exceptions, are considered an Amendment to the Protocol. In addition, if contractually obligated, the sponsor must also approve any planned deviations.

4.5.2 Reporting of Unplanned Deviations

All unplanned deviations will be reported to the COH DSMB who will forward to the IRB following review.

4.5.3 Resolving Disputes

If there is a dispute among the persons involved in the provision of research treatment, in regard to whether a treatment deviates from the protocol, resolution will be resolved in accordance with the Clinical Research Protocol Planned Deviations and Single Subject Exceptions policy.

4.6 Results Reporting

The COH, as sponsor of IND #112273, will submit reports annually to the FDA within 60 days of the anniversary date that the IND went into effect in accordance with 21 CFR 312.33.

5 HUMAN SUBJECTS PROTECTION

5.1 Data and Safety Monitoring

a) **Definition of Risk Level**

This is a Risk Level 4 study, as defined in the "City of Hope Data and Safety Monitoring Plan", http://www.coh.org/dsmc/Pages/forms-and-procedures.aspx involving COH as IND holder and is a phase II study of weekly maintenance using bortezomib and rituximab for mantle cell lymphoma.

b) **Monitoring and Personnel Responsible for Monitoring**

The Protocol Management Team (PMT) consisting of the PI, Collaborating Investigator, CRA/protocol nurse, and statistician is responsible for monitoring the data and safety of this study, including implementation of the stopping rules for safety and efficacy.

Table 1: City of Hope PMT Reporting Timelines for the DSMC

Risk Level	Phase	Standard Reporting Requirement
RL 1, RL2, and Expanded Access Studies	No reports required	
3	I	Every 3 months from activation date, as indicated in MIDAS
3	Pilot, Feasibility, II-IV	Every 6 months from activation date, as indicated in MIDAS
4	Pilot, Feasibility, I-IV	Every 3 months from activation date, as indicated in MIDAS

Data and safety will be reported to the COH DSMC using the PMT report and submitted quarterly from the anniversary date of activation . Protocol specific data collection will include the following items: hematological response, toxicities of treatment, and survival. The planned endpoints is two years DFS.

5.2 Definitions

Adverse event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Unexpected Adverse Event [21 CFR 312.32 (a)] – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Serious Adverse Event (SAE) **[21 CFR 312.32] - defined as *any expected or unexpected adverse event* that results in any of the following outcomes:**

- Death
- Is life-threatening experiences (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization equal or greater than 24 hours)) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Secondary malignancy
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem (UP) - Any incident, experience or outcome that **meets all three** of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**

Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

5.3 Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems - Most unanticipated problems must be reported to the COH DSMC and IRB **within 5 calendar days** according to definitions and guidelines at http://www.coh.org/policy/Policies%20and%20Procedures/REVIEWING_AND_REPORTING_UNANTICIPATED_PROBLEMS.pdf. Any unanticipated problem that occurs during the study conduct will be reported to the DSMC and IRB by submitting electronically in iRIS (http://iris.coh.org).

Serious Adverse Events - **All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to definitions and guidelines at http://www.coh.org/policy/Policies%20and%20Procedures/REVIEWING_AND_REPORTING_UNANTICIPATED_PROBLEMS.pdf and Table 2 below. Those SAEs that require expedited reporting will be submitted electronically in iRIS (http://iris.coh.org).**

Adverse Events - Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of *serious* OR are not unanticipated problems will be reported only in the continuation reports and PMT reports (see Table 2 below).

DSMC Risk Level 3 and Risk Level 4 Protocol Reporting Timelines

Required Reporting Timeframe to the DSMC		
Attribution	**Unexpected**	**Expected**
Death while on active treatment or within 30 days of last day of treatment		
Possibly, Probably, Definitely	5 calendar days	
Unlikely, Unrelated		
Death after 30 days of last active treatment/therapy		
Possibly, Probably, Definitely	5 calendar days	No reporting required
Unlikely, Unrelated	No reporting required	No reporting required
Within 30 days of last active treatment/therapy		
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	5 calendar days	10 calendar days
	Grades 1 and 2 AND resulting in "hospitalization"	

Required Reporting Timeframe to the DSMC		
Attribution	**Unexpected**	**Expected**
Possibly, Probably, Definitely	10 calendar days	10 calendar days
Unlikely, Unrelated	10 calendar days	10 calendar days
After 30 days of last active treatment/therapy		
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	10 calendar days	10 calendar days
Unlikely, Unrelated	No reporting required	No reporting required
	Grades 1 and 2 AND resulting in "hospitalization"	
Possibly, Probably, Definitely	10 calendar days	10 calendar days
Unlikely, Unrelated	No reporting required	No reporting required

DSMC Risk Level 1 and Risk Level 2 Protocol Reporting Timelines

Required Reporting Timeframe to DSMC		
Attribution	**Unexpected**	**Expected**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	5 calendar days	5 calendar days
Unlikely, Unrelated	No reporting required	No reporting required
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days	No reporting required
Unlikely, Unrelated	No reporting required	No reporting required
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	No reporting required	No reporting required
	Grades 1 and 2 AND resulting in "hospitalization"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	No reporting required	No reporting required

COH IRB Adverse Event Reporting Timelines

Required Reporting Timeframe to COH IRB		
Attribution	**Unexpected**	**Expected**
	Death while on active treatment/therapy or within 30 days of the last day of active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days[1]	Annual
Unlikely, Unrelated	Annual	Annual
	Grades 3 and 4	
Possibly, Probably, Definitely	5 calendar days[1]	Annual
Unlikely, Unrelated	Annual	Annual
	Grade 1 and 2	
Possibly, Probably, Definitely	5 calendar days[1]	Annual[2]
Unlikely, Unrelated	Annual[2]	Annual[2]

[1] These events must be reported in the time frame if they meet the definition of an unanticipated problem.
[2] For studies that are not first in human, Phase I and first in pediatric trials, only grades 3-5 must be reported at annual review.

ADDITIONAL REPORTING REQUIREMENTS

SAEs meeting the requirements for expedited reporting to the FDA, as defined in 21 CFR 312.32, will be

reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting which can found at: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

The PI or designee will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the following:

- any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]

- any adverse experience associated with use of the drug that is both serious and unexpected must be submitted no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]

- any follow-up information to a study report shall be reported as soon as the relevant information becomes available. [21 CFR 312.32(d)(3)]

In addition to reporting to COH DSMC and IRB, SAEs must be reported to Millennium Pharmacovigilance. The procedures are as follows:

AEs which are serious must be reported to Millennium Pharmacovigilance (or designee) from first dose of bortezomib up to and including 30 days after administration of the last dose of bortezomib. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Any SAE that occurs at any time after completion of bortezomib treatment or after the designated follow-up period that the investigator and/or sub-investigator considers to be related to any study drug must be reported to the Millennium Pharmacovigilance (or designee). Planned hospital admissions or surgical procedures for an illness or disease that existed *before the patient was enrolled in the trial* are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

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

Sponsor-investigator must report all SAEs, regardless of expectedness or relationship with any study drug, to Millennium Pharmacovigilance (or designee) as soon as possible, but no later than 5 calendar days of the sponsor-investigator's observation or awareness of the event. In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Millennium Pharmacovigilance (or designee) from all sites participating in the study. Sub investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her

foregoing reporting obligations to Millennium Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and sub investigator(s). Millennium Pharmacovigilance (or designee) may request follow-up information to a reported SAE, which the sponsor-investigator will be responsible for providing to Millennium Pharmacovigilance (or designee).

Millennium will provide a sample SAE Report Form representative of the information Millennium Pharmacovigilance may request in follow-up (see Appendix 9.7).

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

5.3 Millennium Definitions:

Adverse Event - Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

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

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

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

Clarification should be made between the terms *serious* and *severe* because they ARE NOT the same. The term *severe* is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical

significance (such as a severe headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but may not be considered an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Safety Reporting Requirements and Timelines – Participating Sites

The guideline is to provide a procedure for accurate and timely reporting of unanticipated problems and/or adverse events meeting reporting criteria as defined in Section 5.2 of this protocol for participating sites. The participating site, including the participating Principal Investigator and/or study coordinators are responsible for reporting all unanticipated problems and/or adverse events immediately (within 24 hours after learning of the event) to their local IRB, the Principal Investigator at City of Hope, and the Data Coordinating Center at COH.

The participating Principal Investigator must report each unanticipated problem and/or adverse event, regardless of attribution, to the City of Hope Principal Investigator, Dr. Matthew Mei and to the Data Coordinating Center at City of Hope within 24 hours of learning of the occurrence. In the event that the participating site Principal Investigator and/or staff does not become aware of the unanticipated problem and/or adverse event immediately (e.g., participant sought treatment elsewhere), the participating site is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the unanticipated problem and/or adverse event.

Report to City of Hope all unanticipated problems and/or serious adverse events (meeting criteria as defined in Section 5.2) by telephone (to Dr. Matthew Mei and the DCC) and send via scan/email and fax a copy of the following forms:

- Notification of Unanticipated Problem/Serious Adverse Event Form (located at end of the protocol). This is a coversheet for all reports submitted as required.
- Participating sites internal serious adverse event form. This is the form/report that participating sites submit to their IRB of record.
- Millennium Serious Adverse Event Form (located at end of the protocol)

SAE Notification Contact Numbers:

Dr. Matthew Mei **Phone: 626-256-4673x82405** **Fax: 626-301-8116**
Data Coordinating Center **Phone: 626-256-4673x63968** **Email: dcc@coh.org**
(Please use #secure# in the subject line)

The Data Coordinating Center at City of Hope, after review of all information and documents provided by the participating site, and in collaboration with the City of Hope Principal Investigator, will submit to the appropriate committees/company as follows:

- City of Hope IRB and DSMC and the Office of IND Development and Regulatory Affairs (as applicable) using the City of Hope's electronic submission system (IRIS)
- Millennium Pharmacovigilance, using the Millennium Serious Adverse Event Form

Any supporting documentation to the reports (i.e., laboratory, pathology, progress notes, discharge summary, autopsy, etc.) explaining the adverse event should also be submitted to the Data Coordinating Center at City of Hope. The Data Coordinating Center will then submit to our COH committees (using IRIS) as well as submit to Millennium in a timely manner.

5.4 Participation of Children

Participants under the age of 18 will be excluded from study because no dosing or adverse event data are currently available for the use of bortezomib + rituximab in participants < 18 years of age.

5.5 Evaluation of benefits and Risks/Discomforts

There may or may not be any clinical benefit to a patient from participation in this trial. Their participation will benefit future cancer patients. Potential risks include the possible occurrences of any of a range of side effects that are listed in the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients as described in protocol Section 6.3. If patients suffer any physical injury as a result of participation in this study, immediate medical treatment is available. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which participants are entitled under applicable regulations.

5.6Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and must permanently discontinue study drug(s). All pregnancies and suspected pregnancies must be reported to Millennium Pharmacovigilance (or designee; see Section 6.10 for contact information) immediately. The pregnancy must be followed for the final pregnancy outcome (ie, delivery, still birth, miscarriage) and Millennium Pharmacovigilance will request this information from the investigator.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to Millennium Pharmacovigilance (or designee) immediately (see Section 6.10 for contact information). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

6 ADMINISTRATIVE REQUIREMENTS

6.1 Good Clinical Practice

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

6.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (see section 8.5). The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator. Millennium requests that informed consent documents be reviewed by Millennium or designee prior to IRB/IEC submission.

6.3 Patient Information and Informed Consent

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

6.4 Patient Confidentiality

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

6.5 Protocol Compliance

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

The investigator will submit all protocol modifications to Millennium and the regulatory authority(ies) in accordance with the governing regulations.
Any departures from the protocol must be fully documented in the source documents.

6.6 On-site Audits

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

6.7 Drug Accountability

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

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

6.8 Premature Closure of the Study

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

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

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

6.9 Record Retention

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

6.10 Product Complaints

A product complaint is a verbal, written, or electronic expression which implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see the following) and

report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium quality representative**.**

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

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

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, an SAE form should be completed and sent to PPD (refer to Section 4.2).

7 REFERENCES

1. Campo E, Raffeld M, Jaffe ES. Mantle-cell lymphoma. Semin Hematol. 1999;36:115-127

2. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin. 2007;57:43-66.

3. Witzig T. Current treatment approaches for mantle-cell lymphoma. JCO 2005; 23: 6409-6414.

4. Resnitzky D, Gossen M, Bujard H, Reed SI. Acceleration of the G1/S phase transition by expression of cyclins D1 and E with an inducible system. Mol Cell Biol. 1994;14:1669-1679.

5. Knudsen KE, Diehl JA, Haiman CA, Knudsen ES. Cyclin D1: polymorphism, aberrant splicing and cancer risk. Oncogene. 2006; 25:1620-1628.

6. Lenz G, Dreyling M, Hoster E, et al. Immunotherapy with rituximab and cyclphosphamide, doxorucibin, vincristine, prednisone significant improves response and time to treatment failure, but not long term outcomes in patients with previously untreated mantle cell lymphoma. JCO 2005; 23:1984-92.

7. Romaguera JE, Fayad L, Rodriguez MA. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol. 2005; 23:7013-23.

8. Dreyling M, Lenz G, Hoster E, et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network. Blood 2005; 105:2677-84.

9. Till BG, Gooley TA, Crawford N, et al. Effect of remission status and induction chemotherapy regimen on outcome of autologous stem cell transplantation for mantle cell lymphoma. Leuk Lymphoma 2008; 29:1-12.

10. Gianni AM, Magni M, Martelli M, et al. Long-term remission in mantle cell lymphoma following high-dose sequential chemotherapy and in vivo rituxmiab-purged stem cell autografting (R-HDS regimen). Blood 2003; 102:749-55.

11. Popplewell LL, Nademanee A, Carter N, et al. Autologous vs allogeneic cell transplantation for mantel cell lymphoma (MCL): outcomes over a 10-year period at city of hope (abstract). Blood 2004; 104:255a.

12. Vandenberghe E, Ruiz de Elvira C, Isaacson P, et al. Does transplantation improve outcome in mantle cell lymphoma (MCL)? : a study from the EBMT. Blood 2000; 96:482a.

13. De Vos S, Goy A, Dakhil SR, et al. Multicenter randomized phase II study of weekly or twice weekly bortezomib plus rituxan in patients with relapsed or refractory follicular or marginal zone B cell lymphoma. JCO 2009; 27: 5023-30.

14. Ghobrial M, Hong F, Padmanabhan S, et al. Phase II trial of weekly bortezomib in combination with rituxan in relapsed or refractory waldenstrom's macroglobulinemia. JCO 2010; Feb 9.

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

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. Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000; 18 (12):2354-62.

19. 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.

20. Jagannath S, Barlogie B, Berenson J et al. A Phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. Br J Haematol 2004: 127:165-172

21. 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.

22. Lightcap ES, McCormack TA, Pien CS, Chau V, Adams J, Elliott PJ. Proteasome inhibition measurements: clinical application. Clin Chem 2000; 46 (5):673-83.

23. 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. 7th Annual Genitourinary Oncology Conference, 1999; Houston, TX. Abstract

24. 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.

25. Papandreou C, Daliani D, Millikan RE, Tu S, Pagliaro L, Adam J. Phase I Study of Intravenous (I.V.) Proteasome Inhibitor PS-341 in Patients (Pts) with Advanced Malignancies. Proc Am Soc Clin Oncol, 2001. Abstract 340

26. Pink MM, Pien CS, Ona VO, Worland P, Adams J, Kauffman MG. PS-341 enhances chemotherapeutic effect in human xenograft models. Proc Am Assoc Cancer Res, 2002; San Francisco, CA. Abstract 787

27. Richardson PG, Barlogie B, Berenson J et al. A Phase II study of Bortezomib in Relapsed, Refractory Myeloma. N Engl J Med 2003; 348:2609-2617

28. Richardson et al, Bortezomib Continues to Demonstrate Superior Efficacy Compared With High-Dose Dexamethasone in Relapsed Multiple Myeloma: Updated Results of the APEX Trial. Blood, 2005; 106: Abstract 2547.

29. Steiner P, Neumeier H, Lightcap E, Sadis S, Pien C, Pink M et al. Adaptation of Human Tumor Cell Lines to PS-341. AACR-NCI-EORTC International Conference, 2001; Miami Beach, FL. Millennium Pharmaceuticals, Inc., 75 Sidney Street, Cambridge, MA 02139. Abstract

30. 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.

31. VELCADE (bortezomib) [package insert]. Cambridge, MA: Millennium Pharmaceuticals, Inc.; 2003.

32. Moreau P, Coiteux V, Hulin C, et al. Prospective comparision of subcutaneous versus intravenous adminstration of bortezomib in patients with multiple myeloma. Hematologicae 2008; 93(12): 1908-11.