VELCADE* (bortezomib) for Injection

Millennium Pharmaceuticals, Inc

STUDY PROTOCOL
Protocol Number <X05165>
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Phase I/II study of bortezomib (VELCADE®) plus rituximab-hyperCVAD alternating with bortezomib plus rituximab-high dose methotrexate/cytarabine in patients with untreated aggressive mantle cell lymphoma

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PROTOCOL

Abbreviations List

Abbreviation	Definition
°C	degrees Celsius
°F	degrees Fahrenheit
mM	micromolar
20S	20S proteasome subunit
AE	adverse event
ALC	Absolute lymphocyte count
ANC	absolute neutrophil count
AUC	area under the curve
Bc1-2	B-cell lymphoma-2; a gene that inhibits apoptosis
BSA	body surface area
BUN	Blood urea nitrogen
CAM	cell adhesion molecules
CBC	Complete blood count
cm	centimeter
CR	Complete Response
CTC	(NCI) Common Toxicity Criteria
CTEP	Cancer Therapy Evaluation Program
CV	cardiovascular
DIFF	diffuse
dL	deciliter
DLT	Dose Limiting Toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FSS	Failure Free Survival
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
Hct	Hematocrit
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
ht	height
Hyper-CVAD	Cyclophosphamide, vincristine doxorubicin, prednisone
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 Harmonisation
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
LDH	Lactate dehydrogenate
LLN	Lower limit of normal
m^2	square meters
mcg	microgram
MCL	Mantle Cell Lymphoma
mg	milligram
min	minute
mL	milliliter
mm^3	cubic millimeters
mmol	millimole
MR	Minor response
MTD	Maximum Tolerated Dose
MTX	methotrexate
NCI	National Cancer Institute
NF-κB	nuclear factor-κB
ng	nanogram
NHL	Non-Hodgkin Lymphoma
NOD	nodular
OS	Overall survival
nM	nanomole
p21	p21(ras) farnesyl-protein transferase
p27	cyclin-dependent kinase inhibitor
p53	tumor suppressor protein with molecular weight of 53 kDa
PD	Progressive disease
PG	Pharmacogenomics
PI	Principle investigator
PK	Pharmacokinetics
PLT	Platelet
PR	Partial response
PS	Performance statue
PSF	Progression-free survival
RBC	Red blood cell count
SAE	serious adverse event
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TTF	Time to treatment failure
TTP	Time to progression
US	United States
USP	United States Pharmacopeia
VCAM-1	vascular cell adhesion molecule 1
WBC	White blood cell count

w/w	weight-to-weight ratio
wt	weight

INTRODUCTION AND STUDY RATIONALE

1.1 Overview of the Disease

DEFINITION AND CLINICAL COURSE OF MANTLE CELL LYMPHOMA

Mantle cell lymphoma (MCL) is a clinicopathologic entity whose cell of origin is a CD5 antigen expressing B-cell lymphoma derived from a subpopulation of B-lymphocytes residing in the mantle zone of the lymphoid follicle (1). Three variants have been described including mantle zone (MZ); diffuse MCL (DIFF), and nodular MCL (NOD) (2, 3). A blastoid (4) cytologic variant has been described when cells present with more finely dispersed chromatin, evenly distributed, reminiscent of that seen in lymphoblasts and typically associated with p53 mutation (5), high proliferation rate and worse outcome. Phenotypically, the malignant cells lack CD10 and CD23 (5) which helps distinguish them from follicular and small lymphocytic lymphomas, respectively. The lambda light chain subtype is seen more often than in other lymphomas (4, 6) and cytogenetic analysis demonstrates at (11; 14) (q13; q32) translocation, which juxtaposes the Bcl-1 oncogene located on chromosome 11q13 with the immunoglobulin heavy chain gene located on chromosome 14q32 (7), resulting in dysregulation and overexpression of cyclin D1. The typical presentation of MCL includes generalized lymphadenopathy as well as involvement of the spleen, bone marrow, blood (leukemic phase), and gastrointestinal tract (4, 6, 8-10).

MCL is currently considered one of the most refractory lymphomas to treatment and has the worse outcome of all non-Hodgkin's lymphomas, with a complete remission (CR) rate of 20-40%, a median progression-free survival (PFS) of 12-16 months, and a median overall survival (OS) of only 3 years after CHOP-based therapy. In a review of 46 previously untreated patients with MCL at UT MD Anderson Cancer Center (UTMDACC) who received an anthracycline-based chemotherapy (11), 72% of patients with the MZ pattern of MCL achieved a complete remission (CR), versus only 20% of those with diffuse or nodular histologies. The 3 year OS by histology pattern was: MZ 100%, DIFF 52%, and NOD 23.9%. Only 20% of patients with DIFF MCL, by far the most common of the histological presentations of MCL, remained free from progression at 3 years of median follow up. Similar dismal results were obtained by Vose et al (12), where the 5 year OS and FFS for DIFF MCL were 26% and 11%, respectively. Patients with blastic histology had a median survival of 22 months in a previously published report (4).

Bortezomib

Bortezomib is the first of a new class of targeted therapy which specifically inhibits the proteasome (14). The proteasome is involved in the recycling and editing process of the majority of intracellular proteins. It degrades abnormal or mutated proteins as well as short lived proteins, most of which are involved in cell cycle, cell growth, cell survival and differentiation. By nature proteasome inhibitors affect many pathways including the two main apoptosis pathways and the NFKB pathway. NFKB appears as an important target in this setting: typically NFKB is trapped in the cytosol bound to IKB. In cell stress situations (such as anoxia, chemotherapy or radiation), IKB gets phosphorylated leading to the release of NFKB, which can then translocate into the nucleus and induce the transcription of factors preventing apoptosis, allowing cell growth and survival and making NFKB an important factor of chemoresistance. In addition several of the proteins affected by proteasome inhibition are relevant for the biology of MCL, including p21, p27, ATM, and p53 (5, 15, 16). The activity of bortezomib seen in preclinical

models including in cell lines (17), has been confirmed by several phase I and II trials in NHL. In those studies bortezomib was found to be highly effective in relapsed/refractory mantle cell lymphoma with a response rate of 41% when given at a dose of 1.5 mg/m2 on days 1, 4, 8, and 11 (18). Additional mechanisms recently shown suggest distinct changes in MCL cells after proteasome inhibition and involve an increase in MCL1 counterbalanced by a rapid increase in NOXA protein in a p53-independent manner (19)

Synergism/additive effects

The inhibition of NFKB, as well as the disruption of several other pathways, provides a rationale to combine bortezomib with other DNA damaging agents. This has been verified in the laboratory where bortezomib has shown additive effect when given concurrently with rituximab (20) or synergistic effect in cell lines when given after 4HC (21), Cytarabine (22), doxorubicin and vincristine (23). It also enhances the sensitivity of leukemic cells when given prior to administration of glucocorticoids (24). This synergism is schedule-dependent, as giving the drug before doxorubicin or vincristine has no synergistic or additive effect (25)

Toxicity alone and in combination chemotherapy

The principal toxicity of bortezomib when given alone at our institution was thrombocytopenia (18), partly due to the acceptance of patients with less than 100,000 platelet count/mm3 to the trial. This thrombocytopenia has been described to be of short duration regardless of the dose employed and does not appear to be associated with an effect on hematopoiesis but rather with a reversible inhibition of megakaryocytic budding, which appears to be an NFKB dependent mechanism (26, 27). In a recent phase I-II study (28), the use of bortezomib with an intense regimen comprising rituximab plus dose-adjusted etoposide, prednisone, infusional vincristine, cyclophosphamide, and infusional doxorubicin (BR-DAEPOCH)] there was a doubling of the incidence of grade 3 thrombocytopenia when compared to historical R-DAEPOCH. However, there were no increased complications related to this. Larger studies in multiple myeloma have shown that bortezomib can be given even in patients with < 10,000 platelets/mm^3 and has been well tolerated. Another reported side effect of bortezomib has been neurotoxicity, specially sensory neuropathy and neuropathic pain. In the same R-DAEPOCH phase I-II trial there was no worsening of neuropathy from doses up to 1.5 mg/m2 (bortezomib being given on days 1 and 4 only in this combination). However neuropathy was the dose limiting toxicity at the maximally tolerated dose (MTD) of 1.7 mg/m2. Bortezomib at a dose of 1.3 mg/m^2 has been tested with rituximab-HyperCVAD and found not to increase neurotoxicity after the first 3 cycles (Dr.Brad Kahl, personal communication)

1.2 VELCADE (bortezomib) for Injection- information

1.2.1 Scientific Background

VELCADE® (bortezomib) for Injection is a small molecule proteasome inhibitor developed by Millennium Pharmaceuticals, Inc., (Millennium) as a novel agent to treat human malignancies. VELCADE is currently approved by the United States Food and Drug Administration (US FDA) and it is registered in Europe for the treatment of multiple myeloma patients who have received at least one prior therapy.

By inhibiting a single molecular target, the proteasome, bortezomib affects multiple signaling pathways. The anti-neoplastic effect of bortezomib likely involves several distinct mechanisms, including inhibition of cell growth and survival pathways, induction of apoptosis, and inhibition of expression of genes that control cellular adhesion, migration and angiogenesis. Thus, the mechanisms by which bortezomib elicits its antitumor activity may vary among tumor types, and the extent to which each affected pathway is critical to the inhibition of tumor growth could also differ. Bortezomib has a novel pattern of cytotoxicity in National Cancer Institute (NCI) in vitro and in vivo assays (30). 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 (33, 34, 43, 44, 32, 36, 40, and 41). Notably, bortezomib induces apoptosis in cells that over express bcl-2, a genetic trait that confers unregulated growth and resistance to conventional chemotherapeutics (38).

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 (35).

1.2.2 Non-clinical Pharmacology

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

The pharmacodynamic action of bortezomib is well established and can be measured through an ex vivo assay (20S proteasome activity) (37). 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 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 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 June 2011 more than 300,000 patients have been treated with VELCADE, including patients treated through Millennium-sponsored clinical trials, Investigator-Initiated Studies, the US NCI Cancer Therapy Evaluation Program (CTEP), and with commercially available drug. VELCADE 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 VELCADE in a number of therapeutic settings involving subjects with various advanced malignancies. In a Phase I trial in patients with refractory hematologic malignancies, the MTD for a twice weekly for 4 weeks of a 42 day cycle was 1.04 mg/m^2/dose, with DLTs of thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise (39). The toxicity was greatest during the third and fourth weeks of therapy. In the 3-week schedule of VELCADE 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 VELCADE monotherapy, the MTD was 1.6 mg/m^2/dose and DLT included hypotension, tachycardia, diarrhea, and syncope.

In phase 1 clinical studies, anti-tumor activity was reported in subjects with NHL, multiple myeloma, Waldenström's Macroglobulinemia, squamous cell carcinoma of the nasopharynx, bronchoalveolar carcinoma of the lung, renal cell carcinoma, and prostate cancer.

The safety and efficacy of VELCADE in subjects with multiple myeloma were investigated in two phase 2 clinical studies, studies M34100-024 (subjects with first relapse) (Jagannath et al, 2004) and M34100-025 (subjects with second or greater relapse and refractory to their last prior therapy). (Richardson et al, 2003) In M34100-025, 202 heavily pre-treated subjects with refractory multiple myeloma after at least 2 previous treatments received VELCADE, 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 (31) were utilized to determine disease response. CRs were observed in 4% of subjects, with an additional 6% of patients meeting all criteria for CR but having a positive immunofixation test. PR or better was observed in 27% of subjects, and the overall response rate (CR, PR and minor response [MR] combined) was 35%. Seventy percent of subjects experienced stable disease or better.

The phase 3 study (M34101-039), also referred to as the APEX study, was designed to determine whether VELCADE 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 VELCADE relative to high-dose dexamethasone,

and whether treatment with VELCADE 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 (VELCADE: 331; dexamethasone: 332). Patients randomized to VELCADE received 1.3 mg/m^2 I.V. push twice weekly on days 1, 4, 8, and 11 of a 3-week cycle for up to eight treatment cycles as induction therapy, followed by 1.3 mg/m^2VELCADE weekly on days 1, 8, 15, and 22 of a 5-week cycle for three cycles as maintenance therapy. Patients randomized to dexamethasone received oral dexamethasone 40 mg once daily on days 1 to 4, 9 to 12, and 17 to 20 of a 5-week cycle for up to four treatment cycles as induction therapy, followed by dexamethasone 40 mg once daily on days 1 to 4 followed of a 4-week cycle for five cycles as maintenance therapy. The European Group for Blood and Marrow Transplant (EBMT) response criteria, as described by Blade (31) were utilized to determine disease response. There was a 78% increase in TTP for the VELCADE arm. Median TTP was 6.2 months for the VELCADE arm and 3.5 months for the dexamethasone arm (*P*<.0001). CR (complete response) + PR (partial response) was 38% with VELCADE vs. 18% with dexamethasone (*P*<.0001). CR was 6% with VELCADE vs. <1% with dexamethasone (*P*<.0001). The CR + nCR rate was13% with VELCADE vs. 2% with dexamethasone. In patients who had received only one prior line of treatment (VELCADE: 132; dexamethasone: 119), CR + PR was 45% with VELCADE vs. 26% with dexamethasone (*P*=.0035). With a median 8.3 months of follow-up, overall survival was significantly longer (*P*=.0013) for patients on the VELCADE arm vs. patients on the dexamethasone arm. The probability of survival at one year was 80% for the VELCADE arm vs. 66% for the dexamethasone arm, which represented a 41% decreased relative risk of death in the first year with VELCADE (*P*=.0005). In patients who had received only one prior line of treatment, the probability of survival at one year was 89% for the VELCADE arm vs. 72% for the dexamethasone arm, which represented a 61% decreased relative risk of death in the first year with VELCADE (*P*=.0098). (42)Updated response rates and survival data were reported for M34101-039 (Richardson ASH, 2003). The updated CR (complete response) + PR (partial response) rate was 43% with VELCADE. The CR + nCR rate was 16% with VELCADE. With a median 22 months of follow-up, overall survival was significantly longer for patients on the VELCADE arm vs. patients on the dexamethasone arm. The median overall survival was 29.8 months (95% CI: 23.2, not estimable) for the VELCADE 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 one year was 80% for the VELCADE arm vs. 67% for the dexamethasone arm (*P*=0.0002).

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

1.2.6 Potential Risks of VELCADE

To date, more than 300,000 patients have been treated with VELCADE in both clinical trials investigating its use in hematological malignancies and solid tumors, and in patients who were treated with commercially available VELCADE.

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

The known anticipated risks of VELCADE therapy are presented in Table 0-1 and Table 0-2. These risks are grouped according to the combined frequency observed in an integrated analysis of AEs in sponsored clinical studies of single-agent VELCADE 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 VELCADE 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*,

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

System Organ Class Observed Incidence	Preferred Term
	intestinal obstruction
General Disorders and Administration Site Conditions	
Most common	Fatigue, pyrexia
Very common	Chills, oedema peripheral, asthenia
Common	Neuralgia, lethargy, malaise, chest pain, mucosal inflammation*
Uncommon	Injection site pain, injection site irritation, injection site phlebitis, general physical health deterioration*, catheter-related complication
Hepatobiliary Disorders	
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	

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

System Organ Class Observed Incidence	Preferred Term
Common	Weight decreased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood alkaline phosphatase increased, liver function test abnormal, blood creatinine increased*
Uncommon	Gamma-glutamyltransferase (GGT) increased, oxygen saturation decreased*, blood albumin decreased, ejection fraction decreased*
Metabolism and Nutritional Disorders	
Very common	Decreased appetite, anorexia, dehydration*
Common	Hyperglycaemia, hypoglycaemia, hyponatraemia, hypokalaemia, hypercalcaemia*
Musculoskeletal and Connective Tissue Disorders	
Very common	Bone pain, myalgia, arthralgia, back pain
Common	Muscular weakness
Uncommon	Limb discomfort
Neoplasms, Benign, Malignant, and Unspecified (including cysts and polyps)	
Uncommon	Tumour lysis syndrome*
Nervous System Disorders	
Most common	Peripheral neuropathy (including all preferred terms under the MedDRA High-level term Peripheral neuropathy NEC)
Very common	Paresthesia, dizziness excluding vertigo, headache
Common	Polyneuropathy, syncope, dysesthesia, dysgeusia, postherpetic neuralgia
Uncommon	Convulsion, loss of consciousness, ageusia, encephalopathy, paralysis*,autonomic neuropathy, reversible posterior leukoencephalopathy syndrome±, posterior reversible encephalopathy syndrome □
Psychiatric Disorders	
Very common	Anxiety, insomnia

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

System Organ Class Observed Incidence	Preferred Term
Common	Confusional state
Uncommon	Delirium
Renal and Urinary Disorders	
Common	Renal impairment*, renal failure*, haematuria
Uncommon	Micturition disorder
Respiratory, Thoracic, and Mediastinal Disorders	
Very common	Cough, dyspnoea
Common	Epistaxis, dyspnoea exertional, pleural effusion*, rhinorrhea, hypoxia*, pulmonary oedema*
Uncommon	Hemoptysis*, acute respiratory distress syndrome*, respiratory failure*, pneumonitis*, lung infiltration, pulmonary alveolar haemorrhage*, interstitial lung disease*, pulmonary hypertension*, pleurisy, pleuritic pain
Skin and Subcutaneous Tissue Disorders	
Very common	Rash
Common	Rash pruritic, rash erythematous, urticaria, petechiae
Uncommon	Cutaneous vasculitis, leukocytoclastic vasculitis±
Vascular Disorders	
Common	Hypotension*, orthostatic hypotension
Uncommon	Cerebral haemorrhage*

Source: VELCADE® Investigator's Brochure Edition 15.

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.

φEffective MedDRA update to version 14.0, the term 'reversible posterior leukoencephalopathy syndrome' updated to 'posterior reversible encephalopathy

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

System Organ Class Observed Incidence	Preferred Term
syndrome (PRES)'.	

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
Optic neuropathy	Rare
Blindness	Rare
Gastrointestinal Disorders	
Acute pancreatitis	Rare
Ischemic colitis	Rare
Hepatobiliary disorders	
Hepatitis	Uncommon
Liver failure	Unknown
Infections and infestations	
Herpes meningoencephalitis	Rare
Septic shock	Rare
Progressive multifocal leukoencephalopathy	Very Rare
Immune System Disorders	
Angioedema	Rare
Nervous System Disorders	

Table 0-2 Reports of Adverse Reactions From Postmarketing Experience

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

Source: VELCADE® Investigator's Brochure Edition 15.

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 VELCADE include hepatic failure and QT prolongation. Fatal outcomes have been reported.

Women of childbearing potential should avoid becoming pregnant while being treated with VELCADE. 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 VELCADE may be found in the Investigator's Brochure.

1.2.7 Potential Risks of Rituximab

Contraindications

There are no contraindications listed in the manufacturer's labeling.

Warnings/Precautions

Boxed warnings:

• Infusion reactions: See "Concerns related to adverse effects" below.

• Mucocutaneous reactions: See "Concerns related to adverse effects" below.

• Progressive multifocal leukoencephalopathy: See "Concerns related to adverse effects" below.

• Tumor lysis syndrome: See "Concerns related to adverse effects" below.

Concerns related to adverse effects:

• Bowel obstruction/perforation: Have been reported, with an average onset of symptoms of ~6 days; complaints of abdominal pain should be evaluated, especially if early in the treatment course.

• Infusion reactions: Severe (occasionally fatal) infusion-related reactions have been reported, usually with the first infusion; fatalities have been reported within 24 hours of infusion; monitor closely and discontinue with grades 3 or 4 infusion reactions. Reactions usually occur within 30-120 minutes and may include hypotension, angioedema, bronchospasm, hypoxia, urticaria, and in more severe cases pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and/or anaphylaxis. Risk factors associated with fatal outcomes include chronic lymphocytic leukemia, female gender, mantle cell lymphoma, or pulmonary infiltrates. Closely monitor patients with a history of prior cardiopulmonary reactions or with pre-existing cardiac or pulmonary

conditions and patients with high numbers of circulating malignant cells (>25,000/mm3). Discontinue infusion for severe reactions and serious or life-threatening cardiac arrhythmias; subsequent doses should include cardiac monitoring during and after the infusion. Medications for the treatment of hypersensitivity reactions (eg, bronchodilators, epinephrine, antihistamines, corticosteroids) should be available for immediate use; treatment is symptomatic. Mild-to-moderate infusion-related reactions (eg, chills, fever, rigors) occur frequently and are typically managed through slowing or interrupting the infusion. Infusion may be resumed at a 50% infusion rate reduction upon resolution of symptoms. Due to the potential for hypotension, consider withholding antihypertensives 12 hours prior to treatment.

• Mucocutaneous reactions: Severe and sometimes fatal mucocutaneous reactions (lichenoid dermatitis, paraneoplastic pemphigus, Stevens-Johnson syndrome, toxic epidermal necrolysis and vesiculobullous dermatitis) have been reported, occurring from 1-13 weeks following exposure. Discontinue in patients experiencing severe mucocutaneous skin reactions; the safety of re-exposure following mucocutaneous reactions has not been evaluated.

• Progressive multifocal leukoencephalopathy: Progressive multifocal leukoencephalopathy (PML) due to JC virus infection has been reported with rituximab use. Cases were reported in patients with hematologic malignancies receiving rituximab either with combination chemotherapy, or with hematopoietic stem cell transplant. Cases were also reported in patients receiving rituximab for autoimmune diseases who had received concurrent or prior immunosuppressant therapy. Onset may be delayed, although most cases were diagnosed within 12 months of the last rituximab dose. Evaluate any neurological change promptly; consider neurology consultation, brain MRI and lumbar puncture for suspected PML. Discontinue rituximab in patients who develop PML; consider reduction/discontinuation of concurrent chemotherapy or immunosuppressants.

• Renal toxicity: May cause renal toxicity in patients with hematologic malignancies; consider discontinuation with increasing serum creatinine or oliguria.

• Tumor lysis syndrome: Tumor lysis syndrome leading to acute renal failure requiring dialysis may occur 12-24 hours following the first dose. Hyperkalemia, hypocalcemia, hyperuricemia, and/or hyperphosphatemia may occur. Consider prophylaxis (allopurinol, hydration) in patients at high risk (high numbers of circulating malignant cells ≥25,000/mm3 or high tumor burden).

• Viral infections: Rarely, reactivation of hepatitis B (with fulminant hepatitis and hepatic failure) has been reported in association with use; screen high-risk patients prior to therapy initiation. Other serious and potentially fatal viral infections, either new or reactivated, associated with use include

cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. Viral infections may be delayed; occurring up to 1 year after discontinuation of therapy.

Disease-related concerns:

• Cardiovascular disease: Use with caution in patients with pre-existing cardiovascular disease or prior cardiopulmonary events.

• Respiratory disease: Use with caution in patients with pre-existing pulmonary disease, or prior cardiopulmonary events.

Concurrent drug therapy issues:

• Biologic agents: Safety and efficacy of rituximab in combination with biologic agents have not been established.

• Disease-modifying antirheumatic drugs (DMARD): Safety and efficacy of rituximab in combination DMARD other than methotrexate have not been established.

• Immunizations: Live vaccines should not be given concurrently with rituximab; there is no data available concerning secondary transmission of live vaccines with or following rituximab treatment. RA patients should be brought up to date with nonlive immunizations (following current guidelines) before initiating therapy; evaluate risks of therapy delay versus benefit (of nonlive vaccines) for NHL patients.

Special populations:

• Elderly: Use with caution in the elderly; higher risk of cardiac (supraventricular arrhythmia) and pulmonary adverse events (pneumonia, pneumonitis).

• Pediatrics: Not approved for use in children.

• Rheumatoid arthritis (RA) patients: Monitor closely RA patients during and after each infusion; increased risk of cardiovascular events. Safety and efficacy of retreatment for RA have not been established.

Pregnancy Risk Factor

C

Pregnancy Considerations

Animal studies have demonstrated adverse effects including decreased (reversible) B-cells and immunosuppression. There are no adequate and well-controlled studies in pregnant women. IgG molecules are known to cross the placenta (rituximab is an engineered IgG molecule) and rituximab has been detected in the serum of infants exposed in utero. B-Cell lymphocytopenia lasting <6 months may occur in exposed infants. Use during pregnancy only if clearly needed.

Lactation

Excretion in breast milk unknown/not recommended

Breast-Feeding Considerations

It is not known if rituximab is excreted in human milk. However, human IgG is excreted in breast milk, and therefore, rituximab may also be excreted in milk. The manufacturer recommends discontinuing breast-feeding until circulating levels of rituximab are no longer detectable.

Adverse Reactions

>10%:

Central nervous system: Fever (5% to 53%), chills (3% to 33%), headache (19%), pain (12%)

Dermatologic: Rash (15%; grades 3/4: 1%), pruritus (5% to 14%), angioedema (11%; grades 3/4: 1%)

Gastrointestinal: Nausea (8% to 23%), abdominal pain (2% to 14%)

Hematologic: Cytopenias (grades 3/4: ≤48%; may be prolonged), lymphopenia (48%; grades 3/4: 40%; median duration 14 days), leukopenia (14%; grades 3/4: 4%), neutropenia (14%; grades 3/4: 6%; median duration 13 days), thrombocytopenia (12%; grades 3/4: 2%)

Neuromuscular & skeletal: Weakness (2% to 26%)

Respiratory: Cough (13%), rhinitis (3% to 12%)

Miscellaneous: Infusion-related reactions (lymphoma: first dose 77%; decreases with subsequent infusions; may include angioedema, bronchospasm, chills, dizziness, fever, headache, hyper-/hypotension, myalgia, nausea, pruritus, rash, rigors, urticaria, and vomiting; reactions reported are

lower [first infusion: 32%] in RA); infection (31%; grades 3/4: 4%; bacterial: 19%; viral 10%; fungal: 1%), night sweats (15%)

1% to 10%:

Cardiovascular: Hypotension (10%), peripheral edema (8%), hypertension (6% to 8%), flushing (5%), edema (<5%)

Central nervous system: Dizziness (10%), anxiety (2% to 5%), agitation (<5%), depression (<5%), hypoesthesia (<5%), insomnia (<5%), malaise (<5%), nervousness (<5%), neuritis (<5%), somnolence (<5%), vertigo (<5%), migraine (RA: 2%)

Dermatologic: Urticaria (2% to 8%)

Endocrine & metabolic: Hyperglycemia (9%), hypoglycemia (<5%), hypercholesterolemia (2%)

Gastrointestinal: Diarrhea (10%), vomiting (10%), dyspepsia (3%), anorexia (<5%), weight loss (<5%)

Hematologic: Anemia (8%; grades 3/4: 3%)

Local: Pain at the injection site (<5%)

Neuromuscular & skeletal: Back pain (10%), myalgia (10%), arthralgia (6% to 10%), paresthesia (2%), arthritis (<5%), hyperkinesia (<5%), hypertonia (<5%), neuropathy (<5%)

Ocular: Conjunctivitis (<5%), lacrimation disorder (<5%)

Respiratory: Throat irritation (2% to 9%), bronchospasm (8%), dyspnea (7%), upper respiratory tract infection (RA: 7%), sinusitis (6%)

Miscellaneous: LDH increased (7%)

Postmarketing and/or case reports: Acute renal failure, anaphylactoid reaction/anaphylaxis, angina, aplastic anemia, ARDS, arrhythmia, bowel obstruction, bronchiolitis obliterans, cardiac failure, cardiogenic shock, disease progression (Kaposi's sarcoma), fatal infusion-related reactions, fulminant hepatitis, gastrointestinal perforation, hemolytic anemia, hepatic failure, hepatitis, hepatitis B reactivation, hyperviscosity syndrome (in Waldenström's macroglobulinemia), hypogammaglobulinemia, hypoxia, interstitial pneumonitis, lichenoid dermatitis, lupus-like syndrome, marrow hypoplasia, MI, neutropenia (late-onset occurring >40 days after last dose), optic neuritis,

pancytopenia (prolonged), paraneoplastic pemphigus (uncommon), pleuritis, pneumonia, pneumonitis, polyarticular arthritis, progressive multifocal leukoencephalopathy (PML), pure red cell aplasia, renal toxicity, serum sickness, Stevens-Johnson syndrome, supraventricular arrhythmia, systemic vasculitis, toxic epidermal necrolysis, tumor lysis syndrome, urticaria, uveitis, vasculitis with rash, ventricular fibrillation, ventricular tachycardia, vesiculobullous dermatitis, viral reactivation (includes JC virus, cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C)

Emetic Potential

Very low (<10%)

Monitoring Parameters

CBC with differential and platelets, peripheral CD20+ cells; HAMA/HACA titers (high levels may increase the risk of allergic reactions); renal function, fluid balance; vital signs; monitor for infusion reactions, cardiac monitoring during and after infusion in rheumatoid arthritis patients and in patients with pre-existing cardiac disease or if arrhythmias develop during or after subsequent infusions

Screen for hepatitis B in high-risk patients prior to initiation of rituximab therapy (the NCCN NHL guidelines recommend screening all NHL patients prior to therapy). In addition, carriers and patients with evidence of recovery from prior hepatitis B infection should be monitored closely for clinical and laboratory signs of HBV infection during therapy and for up to a year following completion of treatment. High-risk patients should be screened for hepatitis C (per NCCN guidelines).

Complaints of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment. Signs or symptoms of progressive multifocal leukoencephalopathy (focal neurologic deficits, which may present as hemiparesis, visual field deficits, cognitive impairment, aphasia, ataxia, and/or cranial nerve deficits). If PML is suspected, obtain brain MRI scan and lumbar puncture.

Nursing: Physical Assessment/Monitoring

Assess patient history with mouse antibodies prior to beginning therapy. Assess other pharmacological or herbal products patient may be taking for potential interactions (eg, anything that may increase hypotensive effects of this drug). Evaluate results of laboratory tests prior to, during, and following therapy. Patient must be monitored closely during and following each infusion; severe infusion reactions

can occur. Pretreatment with acetaminophen and diphenhydramine is recommended (corticosteroid when used to treat RA). Emergency equipment and medications (epinephrine, antihistamines, corticosteroids) should be immediately available during infusion. In the event of severe infusion reaction, infusion should be stopped and prescriber notified immediately. Evaluate patient response closely after each dose and following discontinuation of therapy (eg, abdominal pain [bowel obstruction and perforation], hyper-/hypertension, CNS changes, hyper-/hypoglycemia, rash); bowel obstruction and perforation can occur early in therapy; acute tumor lysis syndrome leading to acute renal failure can occur 12-24 hours after first dose; severe mucocutaneous reactions can occur from 1-13 weeks following treatment; and new or reactivated serious viral infection may occur up to one year following discontinuation of therapy. Teach patient possible side effects/appropriate interventions and importance of reporting adverse reactions.

Monitoring: Lab Tests

CBC with differential and platelets, peripheral CD20+ cells. Patients with elevated HAMA/HACA titers may have an allergic reaction when treated with rituximab or other antibodies from a mouse genetic source.

1.3 Combination of Velcade with rituximab-HyperCVAD and rituximab-high dose methotrexate/cytarabine

1.3.1 Scientific Background: Experience with R-HCVAD

Because of the poor response to treatment, new chemotherapeutic combinations are under investigation. We have evaluated at MDACC the use of rituximab-HCVAD, where cyclophosphamide was given at a higher and hyperfractionated schedule, doxorubicin and vincristine were given as in the regular CHOP regimen doses, and prednisone was substituted by high dose dexamethasone. This regimen was alternated with rituximab plus high doses of methotrexate and Ara-C (13). With this regimen, patients $\leq$ 65 years old achieved an 89% CR rate and, with a median follow-up of 40 months, a 3-year FFS of 75%. The curve, however, shows a pattern of late relapses suggesting persistence of minimal residual disease due to resistance to the regimen.

1.3.2 Potential Risks of rituximab-hyperCVAD and rituximab-high dose methotrexate/cytarabine

The principal toxicity was hematologic but the rate of neutropenic infections (13%) and mortality (5% from acute toxicity) was expected for the intensity of the regimen. Twenty-nine percent of patients did not finish their intended number of cycles because of toxicity, and of these patients, 80% belonged to the group of patients scheduled to receive eight cycles of therapy. The distribution of patients who did not finish the intended number of cycles was similar by age group. The principal toxicity in the study was hematologic. The hematologic toxic effects were 28-51% grade 4 neutropenia and 2-17% grade 4 thrombocytopenia for the rituximab plus hyper-CVAD part of the regimen and 55-68% grade 4

neutropenia with 28-50% cumulative thrombocytopenia for the rituximab plus high-dose methotrexate/cytarabine regimen. Neutropenic fever occurred after 15% of the 602 courses administered. There were five toxic deaths during therapy, of which three were a result of neutropenic sepsis. One of these septic episodes was caused by Staphylococcus aureus infection, and two were caused by a levofloxacin-resistant Gram-negative organism (both patients ≤60 years old and already in CR). After a change from levofloxacin to ciprofloxacin, no other cases of resistant Gram-negative sepsis occurred. A fourth patient died of pulmonary hemorrhage during the nadir of cycle two, presumably related to scarring from recently treated pulmonary aspergillosis. The fifth patient, who also was less than 60 years old, died of unknown causes before the start of the second cycle and after an uneventful first cycle.

1.3.3 Study rationale and selection of drug doses

Bortezomib is the first of a new class of targeted therapy, which specifically inhibits the proteasome (14). The proteasome is involved in the recycling and editing process of the majority of intracellular proteins. It degrades abnormal or mutated proteins as well as short live proteins, most of which are involved in cell cycle, cell growth, cell survival and differentiation. By nature proteasome inhibitors affect many pathways including the two main apoptosis pathways and the NFKB pathway. NFKB appears as an important target in this setting: typically NFKB is trapped in the cytosol bound to IKB. In cell stress situations (such as anoxia, chemotherapy or radiation), IKB gets phosphorylated leading to the release of NFKB, which can then translocate into the nucleus and induce transcription of a variety of factors preventing apoptosis, allowing cell growth and survival and making NFKB an important factor of chemoresistance. In addition several of the proteins affected by proteasome inhibition are relevant for the biology of MCL, including p21, p27, ATM, and p53 (5, 15, 16). Additional mechanisms recently shown suggest distinct changes in MCL cells after proteasome inhibition and involve an increase in MCL1 counterbalanced by a rapid increase in NOXA protein in a p53 independent manner (17).

The activity of bortezomib seen in preclinical models including in cell lines (18), has been confirmed by several phase I and II trials in NHL. In those studies bortezomib was found to be highly effective in relapsed/refractory mantle cell lymphoma with a response rate of 41% when given at a dose of 1.5 mg/m2 on days 1, 4, 8, and 11 (19, 20).

Synergism/additive effects

The inhibition of NFKB, as well as the disruption of several other pathways, provides a rationale to combine bortezomib with other DNA damaging agents. This has been verified in the laboratory where bortezomib has shown additive effect when given concurrently with rituximab (21) or synergistic effect in cell lines when given after cyclophosphamide (22), Cytarabine (23), doxorubicin and vincristine (24). It also enhances the sensitivity of leukemic cells when given prior to administration of glucocorticoids (25).

The principal toxicity of bortezomib when given alone at our institution was thrombocytopenia (19) partly due to the acceptance of patients with less than 100,000 platelet count/mm3 to the trial. This thrombocytopenia has been described to be of short duration regardless of the dose employed and does not appear to be associated with an effect on hematopoiesis but rather with a reversible inhibition of

megakaryocytic budding, which appears to be an NFKB dependent mechanism (26, 27). In a recent phase I-II study (28), the use of bortezomib with an intense regimen comprising rituximab plus dose-adjusted etoposide, prednisone, infusional vincristine, cyclophosphamide, and infusional doxorubicin (BR-DAEPOCH)] there was a doubling of the incidence of grade 3 thrombocytopenia when compared to historical R-DAEPOCH. However, there were no increased complications related to this. Another reported side effect of bortezomib, neurotoxicity (specially sensory neuropathy and neuropathic pain) in the same R-DAEPOCH phase I-II trial there was no worsening of neuropathy from doses up 1.7 mg/m2 (bortezomib being given on days 1 and 4 only in this combination). However neuropathy was the dose limiting toxicity at the maximally tolerated dose (MTD) of 1.7 mg/m2.

Bortezomib in combination with rituximab-hyperCVAD and in combination with rituximab-high dose methotrexate/cytarabine

We plan to add bortezomib to our intense regimen because of the above-described in-vitro synergism/additive effect documented between bortezomib and most of the drugs used in the regimen.

We will monitor toxicity. Two major areas of monitoring will be sensory neuropathy when given with the hyperCVAD regimen because of the use of vincristine but with the experience with EPOCH and its 4-day infusion of vincristine where the sensory neurotoxicity was less, we are confident our trial will not see a significant increase in sensory neuropathy. Recent data using bortezomib in combination with R-hyperCVAD given twice per cycle and in a schedule similar to ours and with a dose of bortezomib of 1.3 mg/m2 showed neurotoxicity after the fourth cycle (Brad Kahl, personal communication), In this study, no rituximab-methotrexate-cytarabine was used. The other area of monitoring will be the thrombocytopenia and duration of, but we are expecting no major change in the delivery of treatment because, over the last 10 years, the dose adjustment decision in our regimen has not been based on hematologic nadir, but rather on delay to the next cycle of more than 1 week and, as explained above, bortezomib is not expected to affect stem cells or recovery time of blood counts, in particular the platelet counts.

In addition, recent data shows good tolerance when IV bolus bortezomib is given on same day with IV bolus doxorubicin and vincristine (personal communication, Brad Kahl). In our study, the dose of bortezomib given with the R-HCVAD portion of the intense therapy is not being explored. Only the dose of bortezomib given with R-MTX/Cytarabine will be tested in a phase I cohort format (52).

Tissue Studies:

The proteasome is involved in the recycling and editing process of the majority of intracellular proteins. It degrades abnormal or mutated proteins as well as short live proteins, most of which are involved in cell cycle, cell growth, cell survival and differentiation. By nature proteasome inhibitors affect many pathways including the two main apoptosis pathways and the NFKB pathway. NFKB appears as an important target in this setting: typically NFKB is trapped in the cytosol bound to IKB. In cell stress situations (such as anoxia, chemotherapy or radiation), IKB gets phosphorylated leading to the release of NFKB, which can then translocate into the nucleus and induce the transcription of factors preventing apoptosis, allowing cell growth and survival and making NFKB an important factor of chemoresistance.

In addition several of the proteins affected by proteasome inhibition seem to berelevant for the biology of MCL, including p21, p27, ATM, and p53 (5, 15, 16).

2. STUDY OBJECTIVES

2.1 Primary Objective of Phase I

The primary objective is:

Determine the safety and the maximum tolerated (MTD) of bortezomib when added to the combination of rituximab, methotrexate and cytarabine alternating with bortezomib, rituximab-hyperCVAD in patients with untreated aggressive mantle cell lymphoma.

2.2 Secondary Objectives of Phase I

The secondary objective is:

- Evaluate overall response rate, complete response rate (CR), overall survival, and duration of remission.

2.3 Primary Objective of Phase II

The primary objective of Phase II study is:
To evaluate the response and failure-free survival (FFS) rates following therapy with bortezomib plus rituximab-hyperCVAD alternating with bortezomib plus rituximab-high dose methotrexate/cytarabine in patients between 18 and 79 years old with untreated aggressive mantle cell lymphoma.

2.4 Secondary Objectives of Phase II

The secondary objectives of Phase II are to:

- Evaluate overall response rate, overall survival, and duration of remission.
- Evaluate toxicity of the combination regimen
- Correlate outcome with pretreatment markers

3.0 INVESTIGATIONAL PLAN

3.1 Overall Design and Plan of the Study

General: This is a prospective phase I/II open-label study at 2 institutions: UT MD Anderson Cancer Center and Hackensack University Medical Center. Phase I will take place over one year period and Phase II will take place over 3 years. All patients shall be registered with the Clinical Oncology Research System (CORe) at www.oncologyresearch.org prior to receiving treatment. Patients from MD Anderson will be registered according to the standing CORe registration procedure. Patients from the Hackensack, New Jersey site will be given study-specific identifiers through CORe for registration purposes. All patients will be registered when consent has been obtained and eligibility has been confirmed. There will be no individual site registration and patient lists will reflect the order in which patients are registered, regardless of participating site.

A data quality management plan (DQMP) has been created for this study (see Appendix N) and will be utilized throughout the course of this project.

Patients will be treated with bortezomib-rituximab-hyperCVAD alternating with bortezomib-rituximab-high dose methotrexate/cytarabine starting with bortezomib-rituximab-HCVAD for 6-8 cycles. Rituximab will be delivered on day 1 of each course of chemotherapy. Rituximab will not be given for patients with leukemic presentations until this has resolved (typically by the end of cycle 1). Leukemic presentation will be defined for this purpose as >1000 lymphoma cells/mm^3 as determined by flow cytometry studies performed in peripheral blood.

An attempt will be made to acquire tissue before the start of treatment. Patients may be treated for odd cycles (Bortezomib, Rituxan, cyclophosphamide, Vincristine, Doxorubicin) either on an inpatient or outpatient basis. It is strongly suggested that treatment for even numbered cycles (Rituximab, Bortezomib, Methotrexate, and Cytarabine) should be administered on an inpatient basis.

The other participating site will fax their signed (by the PI) eligibility checklist as well the signed informed consent to the protocol chair or designated staff as outlined in the DQMP prior to enrollment and/or dosing of protocol therapy. These documents will be collected by the study personnel at MDACC and filed in the regulatory binder under correspondence.

3.2 Selection of Patients

Number of patients to be enrolled
Phase I = 20
Phase II = 90
Total = 110

3.2.1 Inclusion Criteria

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

- Confirmed diagnosis of previously untreated nodular or diffuse mantle cell lymphoma and their blastoid cytologic variant.
- ECOG Performance status of 0, 1, or 2 (see appendix 8.7).
- Serum bilirubin <1.5 mg/dl and serum creatinine < 2.0 mg/dl within 14 days before enrollment (unless higher levels are due to lymphoma)
- Platelet count >100,000/$mm^3$and absolute neutrophil count (ANC) > 1,000/mm^3 within 14 days before enrollment (unless due to lymphoma).
- Cardiac ejection fraction $\geq$ 50% by ECHO or MUGA.
- Age 18 years to 79 years.
- Voluntary written IRB-approved 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 for at least 1 year before the screening test or surgically sterilized or if they are of childbearing potential, agree to practice 2 effective methods of birth control at the same time (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) from the time of signing the informed

consent through 30 days after the last dose of study treatment, or agree to completely abstain from heterosexual intercourse.

- Male subject even if surgically sterilized (ie, status post vasectomy) agrees to practice effective barrier contraception during the entire study treatment period and through 30 days after the last dose of study treatment, or agree to completely abstain from heterosexual intercourse.

3.2.2 Exclusion criteria:

- HIV infection.
- CNS involvement.
- Co-morbid medical or psychiatric illnesses that preclude treatment with intense dose chemotherapy.
- Concurrent or previous malignancy with < 90% probability of survival at 5 years.
- Patient has ≥ Grade 2 peripheral neuropathy within 14 days before enrollment.
- Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure (see Appendix 8.3), 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.
- Participation in clinical trials with other investigational agents not included in this trial,14 days of the start of this trial and throughout the duration of this trial.
- Radiation therapy within 3 weeks before randomization. Enrollment of subjects who require concurrent radiotherapy (which must be localized in its field size) should be deferred until the radiotherapy is completed and 3 weeks have elapsed since the last date of therapy.

3.3 Study Treatments

3.3.1 Clinical Trial Materials

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

3.3.2 Preparation, Handling, Storage and Destruction of Drugs

VELCADE (bortezomib)

Vials containing lyophilized VELCADE 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.

VELCADE is cytotoxic. As with all cytotoxic drugs, caution is required when preparing and handling VELCADE 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.

Drug is available in sterile, single use vials containing 3.5 mg of VELCADE. Each vial of VELCADE 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 VELCADE at a concentration of 1 mg/mL. Prior to reconstitution the vials should remain in the cartons to protect them from light. Dissolution is completed in approximately 10 seconds. The reconstituted solution is clear and colorless, with a final pH of 5 to 6. Reconstituted VELCADE 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.

3.3.3 Drug administration and dosage schedule

General: All patients shall be registered online with the Clinical Oncology Research System (CORE) at www.oncologyresearch.org prior to receiving treatment. Treatment will be with cycles of bortezomib-rituximab-hyperCVAD alternating with bortezomib-rituximab-high dose methotrexate/cytarabine starting with rituximab-HCVAD for 6-8 cycles.

VELCADE 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 drug will be prepared under the supervision of a pharmacist, or appropriately qualified and trained personnel.
The amount (in mg) of drug to be administered will be determined based on body surface area. Body surface area is to be calculated based on body weight using a standard nomogram (see APPENDIX 8.2). 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 (eg, 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 based on clinical judgment.

The appropriate amount of VELCADE will be drawn from the injection vial and administered as an intravenous (IV) push over 3 to 5 seconds followed by a standard saline flush or through a running IV line. Vials are for single use administration.

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

VELCADE Destruction

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

Rituximab will be delivered on day 1 of each course of chemotherapy. Rituximab will not be given for patients with leukemic presentations until this has resolved (typically does by the end of cycle 1). Leukemic presentation will be defined for this purpose as >1000 lymphoma cells/mm^3 as determined by flow cytometry studies in peripheral blood.

Phase I Treatment Schedule:

Patients may be either inpatient or outpatient.

CYCLE 1, 3, 5, and, if needed, 7 (bortezomib plus rituximab-hyperCVAD, 21-day cycle) given ± 3 business days of target date of administration. See section 3.3.4 for dose modifications.

1. Rituximab 375 mg/m^2 (given per institutional standard of care, day 1 of chemotherapy)

2. Premedicate with antiemetics of choice

3. a. Cyclophosphamide 300 mg/m^2/per dose IV over 3h Q 12h x 6 doses to be given after infusion of rituximab. If Rituximab is not given on Day 1, Cyclophosphamide will begin on day 1.

   b. Mesna 600 mg/m/dose IV daily over 24h by continuous infusion.
   Begin 1-4 hours prior to first dose of cyclophosphamide and complete by 8-12 hours after last dose of cyclophosphamide.

   c. Bortezomib 1.3 mg/m^2 IVPB over 3-5 seconds given at any time between 1st and second dose of cyclophosphamide.

   d. Vincristine 1.4 mg/m^2 (maximum 2 mg) IVPB on day 5 (~~12 hours~~ after last cyclophosphamide) and on day 12.

e. Doxorubicin 50 mg/ m^2/day IVPB after Last dose of cyclophosphamide. Order of infusion of vincristine and doxorubicin irrelevant.

f. Bortezomib 1.3 mg/m^2 IVPB over 3-5 seconds after the two drugs (vincristine and doxorubicin) are infused.

g. Decadron* 40 mg IV or P.O. daily x 4 on Days 2-5 and 12-15

h. G-CSF 5-10 mcg/kg SQ rounded to 480 mcg daily starting 24 – 36 hours after and of doxorubicin infusion until granulocytes are more than 4 x 10^3/dl.

i. Prescriptions to start 24 – 36hours of after end of chemotherapy:
   i) Ciprofloxacin 500 mg po BID starting one day after the end of chemotherapy
   ii) Fluconazole 100 mg po daily starting day 1 after chemotherapy times 10 days.
   iii) Valacyclovir 500 mg po daily until 30D past last bortezomib dose
   iv) Compazine 10 mg po Q 4-6 hours PRN n/v
   v) Allergies to any of these medicines will require appropriate substitution and documentation. The number of days on antibiotics may increase if patients have persistent neutropenia.

*If a patient exhibits sensitivity to decadron, based on the physician's determination and with the approval of the PI, it may be removed from this portion of the chemotherapy.

Any medication that must be administered in the outpatient setting on a weekend or holiday may be administered within ± three (3) business days of the day due and not be considered a deviation or violation of the intent of the protocol.

Patient compliance regarding oral prescriptions will be documented by exception. Documentation will be written if the patient states he did not take a medication for any reason.

CYCLE 2 (bortezomib plus rituximab-Mtx/Ara-c, 21-day cycle) Patients should receive the bortezomib portion of this regimen as inpatient. The rituximab portion can be given as inpatient or outpatient.

1. a. Rituximab 375 mg/m^2 (given per institutional standard of care, day 1 of chemotherapy)
   b. Bortezomib IVPB over 3-5 seconds given after rituximab.
   Cohort #1 (for first 3 patients only):
   Bortezomib 0.7 mg/m2 after rituximab and 24-36 hrs after last dose of cytarabine on cycles 2, 4, 6, 8
   Cytarabine - Administer IV at -1 dose level, according to age. (See section 3.3.4 D) over 2-3 hours, Q10-12 hours after methotrexate infusion for cycle 2 only. 3 patients treated sequentially for cycle 2 and each assessed before start of 1st cycle with Methotrexate/Cytarabine and after 14d for pulmonary toxicity. If no pulmonary toxicities occur cycles 4, 6, and 8 can be at standard Cytarabine Administer IV at 0 dose level, according to age. (See section 3.3.4 D)

Methotrexate starting after rituximab infusion, 200 mg/m2 IV over 2 hours, then 800 mg/m2 IV over 22 . Patients with a serum creatinine > 1.5 mg/dl will get 50% dose methotrexate (adjust dose according to section 3.3.4)

Subsequent patients:
CYCLES 2,4,6,8 (21-day cycle)
Rituximab 375 mg/m^2 (given per institutional standard of care, day 1 of chemotherapy
Bortezomib
Cohort 2: 0.7mg/m2 Day 1 and 24-36 hrs after last cytarabine infusion(with dose level 0 cytarabine)
Cohort 3: 1.0 mg/m2 Day 1 and 24-36 hrs after last cytarabine infusion
Cohort 4: 1.3 mg/m2 Day 1 and 24-36 hrs after last cytarabine infusion
Cytarabine - Administer IV at 0 dose level, according to age. (See section 3.3.4 D) over 2hours, Q12 hours starting after end of methotrexate infusion.

2. Premedicate with antiemetics of choice
a. Methotrexate starting after rituximab infusion, 200 mg/m^2 IV over 2 hours, then 800 mg/m^2 IV over 22 hours Patients with a serum creatinine > 1.5 mg/dl will get 50% dose methotrexate (adjust dose according to section 3.3.4)

b. IV fluids daily continuous infusion days 2-5.

c. Cytarabine Dose level 0, according to age. (See section 3.3.4) (except for as stated in 1b above) IV over 2 hours Q12 hours x 4 doses starting after methotrexate infusion

d. Bortezomib IVPB as described in 1b above over 3-5 seconds given 24-36 hrs after last cytarabine dose
e. Citrovorum rescue 50 mg po 12 hours after methotrexate infusion is completed followed by 15 mg p.o. Q6 hours x 8

f. Check serum creatinine daily. Check methotrexate levels 24h and 48h post completion of methotrexate-if > 1 micromolar at 24hrs or > 0.1 micromolar at 48 hours, increase citrovorum rescue to 50 mg (or as per clinician's discretion), IV Q6 hrs and continue daily check of methotrexate levels until methotrexate < 0.1 micromolar.

g. G-CSF 5-10 mcg/kg SQ rounded to 480 mcg daily starting 24 - 36 hours after last dose of Cytarabine once methotrexate levels have cleared and until granulocytes more than 4 x 10^3/dl.

h. Additional prescriptions
i) Na bicarbonate 650 mg x 2 po BID x days 2-6 of cycle
ii) Ciprofloxacin 500 mg po BID starting day 1 after chemotherapy times 10 days. Give if Methotrexate level is less than 0.1 microMoles/L.
iii) Fluconazole 100 mg po daily starting day 1 after chemotherapy times 10 days
iv) Predforte 2 gtts each eye QID days 3-9 of cycle, Starting 12 hours before 1st cycle of cytarabine dose.

v) Valacyclovir 500 mg po QD until 30days after last dose of bortezomib
vi) Allergies to any of these medicines will require appropriate substitution and documentation. The number of days on antibiotics may increase if patients have persistent neutropenia.

Any medication that must be administered in the outpatient setting on a weekend or holiday may be administered within plus or minus three business days of the day due, with the approval of the PI, and not be considered a deviation or violation of the intent of the protocol.

Patient compliance regarding oral prescriptions will be documented by exception. Documentation will be written if the patient states he did not take a medication for any reason.

Phase II Treatment Schedule:

CYCLE 1, 3, 5, and, if needed, 7 (bortezomib plus rituximab-hyperCVAD, 21-day cycle)) given ± 3 business days of target date of administration. See section 5.3 for dose modifications)

1. Rituximab 375 mg/m^2 (given per institutional standard of care, day 1 of chemotherapy). Rituximab may be given at the end of cycle 1 if the patient presents in the leukemic phase or has large tumor burden.
2. Premedicate with antiemetics of choice
   a. Cyclophosphamide 300 mg/m^2/per dose IV over 3h Q 12h x 6 doses b. Mesna 600 mg/m/dose IV daily over 24h continuous infusion. Begin 1-3 our prior to the start time of cyclophosphamide and complete by 10-12 hours after last dose of cyclophosphamide.
   c. Bortezomib 1.3 mg/m^2 IVPB over 3-5 seconds given between the first and second infusion of cyclophosphamide
   d. Vincristine 1.4 mg/m^2 (maximum 2 mg) IVPB after infusion of cyclophosphamide and again on day 12.
   e. Then Doxorubicin 50 mg/ m^2/day IVPB After infusion of cyclophosphamide. Either vincristine or doxorubicin can be given first. Bortezomib 1.3 mg/m^2 IVPB over 3-5 seconds following infusion of the 2 drugs (vincristine and doxorubicin)

CYCLE 2 (21-day cycle) Patients should receive the bortezomib portion of this regimen as inpatient.

The rituximab portion can be given as inpatient or outpatient.

Rituximab 375 mg/m^2 (given per institutional standard of care, day 1 of chemotherapy
   a. Bortezomib 1.3 mg/m^2 IVPB over 3-5 seconds at end of infusion of rituximab

Bortezomib 1.3 mg/m^2 IVPB over 3-5 seconds after rituximab
Premedicate with antiemetics of choice

a. Methotrexate starting after rituximab and bortezomib, 200 mg/m^2 IV over 2 hours, then 800 mg/m^2 IV over 22 hours. Patients with a serum creatinine > 1.5 mg/dl will get 50% dose methotrexate (adjust dose according to section 5.3.1)

b. IV fluids daily continuous infusion

c. Cytarabine 3g/m^2 IV over 2-3 hours Q12 hours x 4 doses after methotrexate infusion (only 1 gram/m^2 if older than 60 years or with a pre-treatment serum creatinine of > normal. Document the start and stop times of these drugs.

d. Bortezomib 1.3 mg/m^2 over 3-5 seconds 24-36 hrs following the last dose of cytarabine

e. Citrovorum rescue 50 mg po 10-12 hours after methotrexate infusion is completed followed by 15 mg p.o. Q6-8 hours x 8

f. Check serum creatinine on days 2, 4. Check methotrexate levels at 24h and 48h post completion of methotrexate-if > 1 micromolar at 24 hrs or > 0.1 micromolar at 48 hours, increase citrovorum rescue to 50mg IV Q6 hrs and continue daily check of methotrexate levels until methotrexate < 0.1 micromolar.

g. G-CSF 5 mcg/kg SQ rounded to 480 mcg daily starting 24 – 36 hours after last dose of Ara-C until granulocytes more than 4 x 10^3/dl.

h. Additional prescriptions

i) Na bicarbonate 650 mg x 2 po BID x days 2-6 of cycle
ii) Ciprofloxacin 500 mg po BID starting 24 to 36 hours after the last dosage of chemotherapy and continuing for 10 days
iii) Fluconazole 100 mg po daily starting 24 to 36 hours after the last dosage of chemotherapy and continuing for 10 days.
iv)Predforte 2 gtts each eye QID starting 24 to 36 hours after the last dosage of chemotherapy and continuing for 10 days
v) Valacyclovir 500 mg po QD starting 24 to 36 hours after the last dose of chemotherapy and continuing throughout the entire course of chemotherapy.
vi)Allergies to any of these medicines will require appropriate substitution and documentation. The number of days on antibiotics may increase if patients persist neutropenic. Substitution of Neulasta for Neupogen will be made at the discretion of the investigator only.

Any medication that must be administered in the outpatient setting on a weekend or holiday may be administered within plus or minus three business days of the day due, with the approval of the PI, and not be considered a deviation or violation of the intent of the protocol.

Patient compliance regarding oral prescriptions will be documented by exception. Documentation will be written if the patient states he did not take a medication for any reason.

If a patient exhibits sensitivity to decadron, based on the physician's determination and with the approval of the PI, decadron may be removed from this portion of the chemotherapy.

3.3.4 Dose Modifications

A. For age and Special Circumstances
   a. Bilirubin
      i) 1.2 -3.0 mg/dl- Reduce doxorubicin by 50%
      ii) 3.1 -5.0 mg/dl-Reduce doxorubicin by 75%
      iii) > 1.5-3.0 mg/dl- Reduce vincristine by 50%
      iv) > 3.0 mg/dl- Omit vincristine

   Serum creatinine > 1.5 mg/dl or clearance < 60 cc/min.- decrease methotrexate dose by 50% and decrease Cytarabine (Ara-C) dose to 0.75 gm/m^2 per dose. If serum creatinine 2 mg/dl or more, do not give Cytarabine.

   b. SGOT
      i) 60-180mg/dl – Administer 50% of vincristine dose
      ii) > 180mg/dl – Omit vincristine

   c. Additional methotrexate adjustments-
      i) If severe mucositis with previous dose, reduce MTX by 25% (1 dose level; see section 3.3.4 D)
      ii) If pleural effusion or ascites, or third space fluid collection, hold MTX and repeat HCVAD-R cycle.
      iii) Check methotrexate levels at 24 and 48 hours: if > 1 micromolar at 24h or >0.1 micromolar at 48h respectively, give citrovorum rescue 50mg (or as per clinician's discretion) IV Q6h till methotrexate levels < 0.1 micromolar.
      iv) If bilirubin is 3.1-5 mg/dl, Administer 75% of methotrexate dose.
      v) If bilirubin > 5mg/dl, Omit methotrexate
      vi) If SGOT >180mg/dl, Administer 75% of methotrexate dose.

   d. Additional Cytarabine adjustments -
      i) If grade 3-4 central nervous system toxicity with previous dose, decrease Cytarabine by 1 dose level.
      ii) If during MTX/Cytarabine infusion, serum creatinine increases by >/= 50% over baseline values, hold cytarabine and contact physician.

B. Dose Reduction for Hematologic Toxicity

Toxicities are to be assessed according to the NCI Common Toxicity Criteria (CTC), Version 3.0 (see Appendix 8.5).

Because of expected grade 4 neutropenia and thrombocytopenia with the regimen, there will be no dose adjustments based on nadir of counts. Instead, a delay of recovery of counts will determine the need to reduce doses.

	Toxicity	Dose Modification
Day 21:	ANC>1000/mm^3 and Platelets>100,000/mm^3	No Change
Day 21:	ANC 750-1000/mm^3 and Platelets <75,000/mm^3	Delay therapy*until ANC > 1K, and Plt 100,000
Day 21:	ANC < 750/mm^3 and Platelets < 75,000/mm^3	Delay therapy*until ANC > 1K, plat > 100K and decrease 1 level for cyclophosphamide, doxorubicin, and bortezomib,cytarabine
	Delay > 2 weeks	Discuss with Chairman
	Neutropenic Fever	Decrease l level for cyclophosphamide, doxo-rubicin and bortezomib (see Table 3.3.4D)
	Serious Infection or Bleeding	Discuss with Chairman

C. Dose Reductions for non-hematologic toxicity (see Table 3.3.4 D)

Grade	Dose Modification
0-2	No Change
3	Decrease one dose level for offending drug
4	Discuss with Chairman

Dose limiting toxicity is defined as a decrease from baseline DLCO (pulmonary function tests) by more than 25% and with no other possible causes after the first complete cycle of this regimen. If not deemed critical in phase I portion of the study, pulmonary toxicities will not be evaluated in Phase II.

Table 3.3.4 D Dose Modification During Treatment

Drug	-2	-1	0
Cyclophosphamide mg/m^2 IV over 3 hrs q 12 hrs x 6	192	240	300
Vincristine mg/m^2 IV days 5 and 12	0	1mg total dose	1.4 mg (maximum 2 mg)
Doxorubicin mg/m^2 IVPB day 5	32 mg	40 mg	50 mg
Bortezomib mg/m^2 IVPB cycles 1, 3, 5, 7	0.7 mg	1.0 mg	1.3 mg
Methotrexate mg/m^2 as per instructions	500 mg	750 mg	1000 mg (1 gram)
Cytarabine g/m^2 as per instructions-patients $\leq$ 60 yrs (60 years of age or less)	1 gm (1000 mg)	2 gm 2000 mg	3 gm (3000 mg) (-1 dose level for first 3 patients, first methotrexate/cytarabine cycle in Phase I patients only)
Cytarabine g/m^2 patients > 60 yrs (61 to 79 years of age)	0.5 gm (500 mg)	0.75 gm (750 mg)	1 gm (1000 mg) (-1 dose level for first 3 patients, first methotrexate/cytarabine dose in Phase I patients only)
Mesna (mg/M2)	384 mg	480 mg	600 mg

Dose escalation will not be allowed in any patient. There must be at least 72 hours between doses of bortezomib.

Before each drug dose, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI Common Toxicity Criteria (CTC), Version 3.0 (see Appendix 8.5).

i) Myelosuppression and its associated complications are part of the successful treatment of aggressive mantle cell lymphoma. Therefore, infections, bleeding and hospitalizations due to this will not be reported as adverse drug reactions unless there is a documented sepsis or atypical infection.

ii) Readmission day 0-30 post chemotherapy to receive parenteral narcotics for pain relief of mucositis for parenteral control of nausea/vomiting, to receive blood or platelet transfusions, or for supportive measures such as hydration and symptom control.

iii) Electrolyte disturbances will not be reported unless they are part of tumor lysis syndrome or cytokine release syndrome. Grade 3-4 CNS or renal toxicity is rare enough that we would like to have report on.

Additional Dose Modification for bortezomib:

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 $<25 \times 10^9$/L) or any ≥Grade 3 non-hematologic toxicity considered by the investigator to be related to VELCADE, 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 Phase I participants, dose limiting toxicity is defined as a grade 3-4 non-hematologic toxicity that can not be ameliorated, prevented, or controlled with standard prophylactic therapy such as, but not limited to, nausea, vomiting, fatigue, diarrhea, constipation, low electrolyte levels, or tumor pain. Particular attention will be drawn to a decrease from baseline DLCO (pulmonary function tests) by more than 25% and with no other possible cause after the first complete cycle of rituxan-bortezomib-methotrexate cytarabine of this regimen for the first 3 enrolled patients of each new dose level of bortezomib. In addition, if the DLCO drops below 60% predicted, this will be considered a dose limiting toxicity. Grade 4 hematologic toxicity and neutropenic fever are high after therapy with our aggressive chemotherapy regimen (63% grade 4 neutropenia, 42% grade 4 thrombocytopenia, and 20% neutropenic fevers with rituximab-methotrexate/cytarabine) and will not be considered for dose-limiting toxicity.

For neuro-toxicities, VELCADE is to be held for up to 2 weeks until the toxicity returns to Grade 1 or better. For hematologic toxicities, VELCADE is to be held for up to 2 weeks until the patient has platelet value of 100,000, and neutrophil value of 1.0 on day 1 of therapy.

Dose interruption or study discontinuation is not required for lymphopenia of any grade.
Chemotherapy will be held until the ANC is $>1000/mm^3$ or the Platelets$>100,000/mm^3$ unless due to involvement by lymphoma. The primary physician, in consultation with the PI, will determine when the patient must be removed from study due to delay of chemotherapy.

If, after VELCADE has been held, the toxicity does not resolve, as defined above, then drug must be discontinued.
If the patient was receiving 0.7 mg/m^2, discontinue drug, unless patient is responding, in which case this should be discussed with the PI. Dose reductions below 0.7 mg/m^2 should be avoided, but will be considered if patient is having a good response.

Patients who experience bortezomib-related neuropathic pain and/or peripheral sensory neuropathy are to be managed as presented in Table 3.3.4 E

Table 3.3.4 E Management of Patients with Bortezomib-Related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy Recommended Dose Modification for VELCADE-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 by one dose level*
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold* VELCADE therapy until toxicity resolves. When toxicity resolves reinitiate with a reduction by two dose levels and change treatment schedule to once per week.*
Grade 4 (Permanent sensory loss that interferes with function)	Discontinue VELCADE
Grading based on NCI Common Terminology Criteria for Adverse Events CTCAE v3.0 NCI Common Terminology Criteria website - http://ctep.info.nih.gov/reporting/ctc.html	

ADL = activities of daily living

*Key:

For Phase I and Phase II Patients:

Hold: Interrupt VELCADE for up to 2 weeks until the toxicity returns to Grade 1 or better.

Reduce by one dose level: VELCADE dose reduction from 1.3 to 1.0, or 1.0 to 0.7 mg/m^2/dose.

Reduce by two dose levels: VELCADE dose reduction from 1.3 or 1.0 to 0.7 mg/m^2/dose

For Phase II Patients:

Hold: Interrupt VELCADE for up to 2 weeks until the toxicity returns to Grade 1 or better

Reduce by one dose level: VELCADE dose reduction from 1.3 to 1.0, 1.0 to 0.7 mg/m^2/dose.

The neurotoxicity-directed questionnaire (see Appendix 8.6) 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.

3.3.5 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.

3.3.6 Concomitant Treatment

Required Concurrent Therapy

The following medications/supportive therapies are required during study participation, as applicable:

G-CSF 5 mcg/kg SQ rounded to the nearest of 300 or 480 mcg daily starting 24 - 36 hours after last dose of Cytarabine until granulocytes more than 4 x 10^3/dL . Only on unique occasions will Neulasta be allowed as a substitute for patients with financial or physical issues precluding treatment with Neupogen. These variances will be determined by the Investigator on an individual basis.

Additional prescriptions

i) Na bicarbonate 650 mg x 2 po BID x days 2-6 of cycle
ii) Ciprofloxacin 500 mg po BID starting 24 to 36 hours after the last dosage of chemotherapy and continuing for 10 days
iii) Fluconazole 100 mg po daily starting 24 to 36 hours after the last dosage of chemotherapy and continuing for 10 days.
iv) Predforte 2 gtts each eye QID starting 24 to 36 hours after the last dosage of chemotherapy and continuing for 10 days
v) Valacyclovir 500 mg po QD starting 24 to 36 hours after the last dose of chemotherapy and continuing throughout the entire course of chemotherapy.
vi) Allergies to any of these medicines will require appropriate substitution and documentation. The number of days on antibiotics may increase if patients persist neutropenic. Substitution of Neulasta for Neupogen will be made at the discretion of the investigator only.

Allergies to any of these medicines will require appropriate substitution and documentation. The number of days on antibiotics may increase if patients have persistent neutropenia.

If a patient exhibits sensitivity or allergy to decadron or an antibiotic/antifungal/antiviral required by the protocol, it may be removed from this portion of the chemotherapy or a suitable replacement may be prescribed.

Prohibited Concurrent Therapy

- Participation in clinical trials with other investigational agents not included in this trial, within 14 days of the start of this trial and throughout the duration of this trial.

3.3.7 Treatment Compliance

All drug 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 Appendix 8.2), and total drug administered in milliliters and milligrams and date and time of administration. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.

Each site will be responsible for ordering and maintaining inventory.

Precautions and Restrictions

It is not known what effects VELCADE 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 VELCADE, 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.

3.4 Staging and Duration of Treatment and Patient Participation Treatment plan

a. Staging after first 2 cycles of bortezomib-intense chemotherapy (one bortezomib-rituximab-hyper-CVAD, one rituximab-high-dose methotrexate/cytarabine):
   i) If complete response, continue X 4 more cycles and stop therapy

ii) If partial response, continue for 2 more cycles and re-evaluate
iii) If minor or no change or progressive disease, off protocol

b. Staging after 4 cycles of bortezomib-intense chemotherapy:

i) If complete response, give 4 more cycles and stop therapy.
ii) If improved response (MR or PR from cycle 2), give 2 more cycles and re-stage.
iii) If stable disease – biopsy. If positive, remove from study. If negative, give 2 more cycles; if progressive disease, off protocol.
iv). If continued response, give 2 more cycles and re-stage.

c. Staging after 6 cycles:

i) If complete response, give 2 more and stop therapy.
ii) If < CR, off study.

3.5 EVALUATION BEFORE, DURING, AND AFTER INTENSIVE CHEMOTHERAPY

Response will be assessed using the Cheson criteria (29). Failure will be defined as disease progression or relapse, or death due to any cause, or initiation of alternate antineoplastic therapy.

See Appendix 8.1

3.6 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 VELCADE interruption of >2 weeks or missing three of four VELCADE 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

The primary reason for a patient's withdrawal from the study is to be recorded in the source documents.

4 ADVERSE EVENTS

All serious adverse events (SAEs) (regardless of expectedness, causality, and whether commercial or investigational VELCADE is used) must be reported to Millennium Pharmacovigilance (or designee). See Section 4.2 for the reporting of SAEs.

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

Adverse events will be reported according to M. D. Anderson established reporting requirements. It is expected that patients who enroll in this study will have pre-existing conditions. Although a pertinent positive finding identified on baseline assessment is not an adverse event, it is to be documented at baseline using CTC/CTCAE terminology and grade. An adverse event report is not required if a patient is entered on a protocol with a pre-existing condition (e.g., anemia, fatigue). The baseline adverse event must be re-assessed throughout the trial and changes must be noted. Whenever the grade changes from baseline, the change must be entered in PDMS. Toxicities of all grades, including changes in baseline toxicities, which occur after the onset of therapy, will be collected for statistical purposes in the medical history section of the patient database system.

4.1 Definitions

4.1.1 Adverse Event Definition

An adverse event (AE) is 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 the treatment. An adverse event can be any unfavorable and unintended sign (eg, including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event or 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.

4.1.2 Serious Adverse Event Definition

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

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

- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a persons' ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs, 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" since they ARE NOT synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as "serious," which is based on patient/event outcome or action criteria described above and are usually associated with events that pose a threat to a patient's life or functioning. A severe adverse event does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

4.1.3 Procedures for AE and SAE Reporting

Adverse events (AEs) may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. AEs which are serious must be reported to Millennium Pharmacovigilance (or designee) from first dose of VELCADE up to and including 30 days after administration of the last dose of VELCADE. 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 VELCADE 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 Dr. Romaguera, (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.

4.2 Procedures for AE and SAE Reporting

Sponsor-investigator- must report all (SAE) 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. All 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 subinvestigator(s). All SAE's must be reported within 24 hours of acknowledgement by the way of fax to Dr. Jorge Romaguera (713) 794-5656. Any patient death while the patient is on study must be reported to Dr. Jorge Romaguera (713) 745-4246 or (713) 404-3854 within 24 hours. Millennium Pharmacovigilance (or designee) may request follow-up information to a reported SAE, which the sponsor-investigator will be responsible for providing to Millennium Pharmacovigilance (or designee).

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

Intensity for each SAE, including any lab abnormality, will be determined by using the NCI CTCAE, version 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 sponsor-investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

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

i) Myelosuppression and its associated complications are part of the successful treatment of aggressive mantle cell lymphoma. Therefore, infections, bleeding and hospitalizations due to this will not be reported as adverse drug reactions unless there is a documented sepsis or atypical infection.

ii) Readmission day 0-30 post chemotherapy to receive parenteral narcotics for pain relief of mucositis for parenteral control of nausea/vomiting, to receive blood or platelet transfusions, or for supportive measures such as hydration and symptom control.

iii) Electrolyte disturbances will not be reported unless they are part of tumor lysis syndrome or cytokine release syndrome. Grade 3-4 CNS or renal toxicity is rare enough that we would like to have report on.

4.3 Monitoring of Adverse Events and Period of Observation

Adverse events, both serious and non-serious, and deaths that occur during the patient's study participation will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).There will be scheduled teleconferences that will include the physician investigators from each institution and led by Dr. Romaguera. These teleconferences will take place prior to each dose escalation or in the event of a dose limiting toxicity or as needed to ensure communication between sites. The primary aim of the teleconference is to ensure patient safety throughout the conduct of this phase I study. At a minimum Dr. Romaguera and Dr. Goy must be represented at the teleconference(s). It is recommended that the research nurse, study coordinator or data coordinator also join the conference call(s).

There must be written documentation, of the conference call(s) and this documentation will be filed in the regulatory binder at each site. This note should provide cohort information including cohort, dose and slot allocation.

4.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects she is pregnant while participating in this study, she must inform the investigator immediately and must permanently discontinue drug therapy. Millennium must also be contacted immediately by faxing a completed Pregnancy Form (APPENDIX 8.8) other approved equivalent form to the Millennium Pharmacovigilance or designee (see Section 4.2). The pregnancy must be followed through outcome (i.e. delivery, still birth, miscarriage) and Millennium Pharmacovigilance will request this information from the investigator.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, Millennium must also be contacted immediately by faxing a completed Pregnancy Form (Appendix 8.8) to the Millennium Pharmacovigilance or designee (see Section 4.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

5 STATISTICAL PROCEDURES

5.1 Sample Size Estimation

Sample Size and Power

A total of 20 patients will be enrolled in Phase I of the study at the accrual rate of 2 patients per month. Patients from MD Anderson will be registered according to the standing CORe registration procedure. Patients from the Hackensack, New Jersey site will be given study-specific identifiers for registration purposes. All patients will be registered when consent has been obtained and eligibility has been confirmed. There will be no individual site registration and patient lists will reflect the order in which patients are registered, regardless of participating site. Upon completion of an analysis of the Phase I portion of the protocol, Phase II will be implemented.

The primary objective of Phase I is to determine the maximum tolerated dose (MTD) of bortezomib that can be safely added to the rituximab-methotrexate-cytarabine treatment combination in this regimen. The secondary objectives include overall response rate, complete remission, duration of response, and overall survival (OS). FFS is defined as time from the initiation of induction chemotherapy until failure as defined in Response Criteria or until the last follow-up visit.

The primary objective of Phase II is to evaluate Time to failure (TTF) following therapy with bortezomib plus rituximab-hyperCVAD alternating with bortezomib plus rituximab-high dose methotrexate/cytarabine in patients <= 79 years old with untreated aggressive mantle cell lymphoma when treated at the MTD determined at Phase I of the trial.

5.2 Statistical Methods for Phase II

Sample Size and Power

In this phase II study, the primary endpoint is time to failure (TTF). Failure is defined as recurrence/progression of disease or death from either disease or toxicity. It is hypothesized that bortezomib plus rituximab-hyperCVAD alternating with bortezomib plus rituximab-high dose methotrexate/cytarabine in patients <= 79 years old with untreated aggressive mantle cell lymphoma will prolong the median TTF from 4.7 years (standard treatment) to 8.8 years. A maximum of 90 patients will be enrolled at an estimated accrual rate of 2.5 patients per month for 3 years. Patients will be followed for an additional 2 years after completion of the treatment. Given that the median time to treatment failure of 4.7 years for the null hypothesis, two-sided type I error rate of 0.05, accrual rate of 30 patients per year, the sample size of 90 patients will enable the trial to detect a median time to failure of 8.8 years with at least 83% of power.

Bayesian toxicity monitoring schema will be used to monitor severe toxicity profile in the combined therapy. “Severe toxicity” per patient is defined as at least two episodes of neutropenic fever during treatment courses, or grade 3-4 neuropathy during the course of the patient’s treatment. The severe toxicity monitoring will start after enrolling 10 patients. We will denote the probability of severe toxicity for the combined therapy as θ. The trial will be stopped early if

$$Pr[\theta > 0.15 \mid data\ ] > 0.90.$$

In other words, the therapy will be stopped if there is a greater than 90% chance to observe more than 15% severe toxicity. We assume that the prior distribution of θ follows a Beta(0.15, 0.85), which implies that the prior toxicity rate is 15%. Based on this rule, we will consider stopping the trial if number of patients with severe toxicities in total number of patients treated is >= 6/20-22, 7/23-27, 8/28-33, 9/34-38, 10/39-43, 11/44-49, 12/50-54, 13/55-60, 14/61-65, 15/66-71, 16/72-77, 17/78-82, 18/83-88, 19/89. The operating characteristics are summarized in the Table 2, based on 5,000 simulations. When the true rate for severe toxicity is 0.10, there is a 3.6% chance that the trial will be stopped early. On the other hand, if the true severe toxicity rate is 0.20 or 0.30, the chance of stopping the trial early is 66.7% and 99.4%, respectively.

Table 1. Probability of stopping the trial early due to severe toxicities

True severe toxicity rate	Prob(stop treatment early)
0.10	0.036
0.15	0.251
0.20	0.667
0.30	0.994

Analysis Plans

Patients' demographic information at baseline will be analyzed. The student t-test or the Wilcoxon rank sum test will be used to compare continuous variables between two different patient groups. The chi-square test or the Fisher's exact test will be applied to assess the association between two categorical variables. Logistic regression will be utilized to assess the effect of patient prognostic factors on the response rate.

Time-to-event outcomes, including TTF, response duration, and overall survival, will be estimated using Kaplan-Meier method. The log-rank test will be performed to test the difference in time-to-event distributions between patient groups. Cox proportional hazards model will be utilized to evaluate the effects of covariates on the time-to-event analysis.

Toxicity data will be summarized by frequency tables.

For the efficacy endpoint, intend-to-treat analysis will be applied to the eligible patients. For the toxicity endpoint, per-treated analysis will be used to include any patient who received the treatment – regardless of the eligibility or the duration or dose of the treatment received.

Analysis Plan

The phase I trial will follow a standard 3+3 algorithm with a single exception as described below. Bortezomib in the rituximab-methotrexate treatment combination will be evaluated at three dose levels, 1) 0.7 mg/m^2, 2) 1.0 mg/m^2, and 3) 1.3 mg/m^2. Up to 18 evaluable patients will be treated on this protocol based on the intent to treat principle. Any patient who receives any part of the proposed treatment regimen who is otherwise eligible will be considered evaluable for toxicity.

The MTD is defined as the highest dose of bortezomib in which 2 or fewer patients in 6 treated experiences a dose limiting toxicity (DLT) among the dose levels tested. Dose limiting toxicity is defined as a grade 3-4 non-hematologic toxicity that can not be ameliorated, prevented, or controlled with standard prophylactic therapy such as, but not limited to, nausea, vomiting, fatigue, diarrhea, constipation, low electrolyte levels, or tumor pain. Particular attention will be drawn to a decrease from baseline DLCO (pulmonary function tests) by more than 25% when comparing a pre-treatment with a day 21 of treatment pulmonary function test after the first cycle of rituximab-methotrexate/cytarabine and with no other possible explanation for it. In addition, if the DLCO drops below 60% predicted, this will be considered a dose limiting toxicity. Grade 4 hematologic toxicity and neutropenic fever are high after therapy with our aggressive chemotherapy regimen (63% grade 4 neutropenia, 42% grade 4 thrombocytopenia, and 20% neutropenic fevers with rituximab-methotrexate/cytarabine) and will not be considered for dose-limiting toxicity. Patients will be enrolled in cohorts of 3 patients. For the first three patients at the lowest starting dose level, each patient enrolled must not experience a DLT for at least 14 days before the subsequent patients can be enrolled. The initial dose of bortezomib is 0.7 mg/m^2. If no (0) DLT's are observed in the first 3 patients treated, the next cohort of 3 patients will be treated at the next dose level. If 1 DLT is observed in the first 3 patients treated, an additional cohort of patients will be treated at the same dose level. The MTD will be exceeded if 2 or more DLT's are experienced in 3 or 6 patients treated at a given dose level. If the MTD is exceeded at the first dose level, this regimen will be considered too toxic for subsequent implementation. The dose of bortezomib can be escalated only if 0 in 3 or 2 in 6 patients experience a DLT. Six patients must be treated and evaluated, with 2 or fewer DLT's, to declare a candidate dose the MTD.

There will be no intra-patient dose escalation of bortezomib. In the first cohort of three patients with the lowest dose of bortezomib, a dose of cytarabine of 2 grams/M^2/dose will be used for the first cycle of rituximab-methotrexate/cytarabine and, if well tolerated, will increase in the same patients for the additional 2 cycles of bortezomib with rituximab-methotrexate/cytarabine to the standard 3 g/m^2. No patients will be enrolled in the next dose level until all toxicities are fully assessed in the previous cohort. Toxicity evaluation will be completed when all patients in a cohort have completed one cycle of rituximab-methotrexate/cytarabine therapy.

The analysis of data from this protocol will be largely descriptive. Categorical variables (e.g., gender, DLT) will be summarized in frequency tables. Continuous variables (e.g., age, cumulative dose) will be summarized using the mean (s.d.) and median (range). Graphical analysis (e.g., BLiP plots, boxplots, and others) will be used to depict the distribution of data by dose level. Logistic regression analysis will be used to model the dose-toxicity relationship as well as nonparametric smoothing procedures.

For the Phase II portion of the study, the MTD will be used for dosing. For the Analysis, the Patients' demographic information at baseline will be analyzed. The student t-test or the Wilcoxon rank sum test

will be used to compare continuous variables between two different patient groups. The chi-square test or the Fisher's exact test will be applied to assess the association between two categorical variables. Logistic regression will be utilized to assess the effect of patient prognostic factors on the response rate.

Time-to-event outcomes, including FFS, response duration, and overall survival, will be estimated using Kaplan-Meier method. The log-rank test will be performed to test the difference in time-to-event distributions between patient groups. Cox proportional hazards model will be utilized to evaluate the effects of covariates on the time-to-event analysis.
Toxicity data will be summarized by frequency tables.
For the efficacy endpoint, intend-to-treat analysis will be applied to the eligible patients. For the toxicity endpoint, per-treated analysis will be used to include any patient who received the treatment – regardless of the eligibility or the duration or dose of the treatment received.

For the Phase II Portion of the Study, the following will be used for the Efficacy and Safety Analysis.

5.3 Efficacy Analysis
Kaplan-Meier estimates of times-to-event will be constructed for each endpoint. Median FFS/OS/duration of response and corresponding 95% confidence intervals will be reported. Additionally, a Cox proportional hazards regression model will be fit to assess the effect of other potential prognostic factors on FFS/OS/duration of response. Descriptive statistics such as cross-tabulations will be used to summarize the efficacy and toxicity data.

5.4 Safety Analysis
Bayesian toxicity monitoring schema will be used to monitor severe toxicity profile in the combined therapy. "Severe toxicity" is defined as at least two episodes of neutropenic fever or grade 3-4 neuropathy during treatment courses. The severe toxicity monitoring will start after enrolling 10 patients. We will denote the probability of severe toxicity for the combined therapy as θ. The trial will be stopped early if

$$\Pr[\theta > 0.15 \mid \text{data}] > 0.90.$$

In other words, the therapy will be stopped if there is a greater than 90% chance to observe more than 15% severe toxicity. We assume that the prior distribution of θ follows a Beta(0.15, 0.85), which implies that the prior toxicity rate is 15%. Based on this rule, we will consider stopping the trial if number of patients with severe toxicities in total number of patients treated is >= 6/20-22, 7/23-27, 8/28-33, 9/34-38, 10/39-43, 11/44-49, 12/50-54, 13/55-60, 14/61-65, 15/66-71, 16/72-77, 17/78-82, 18/83-88, 19/89. The operating characteristics are summarized in the Table 2, based on 5,000 simulations. When the true rate for severe toxicity is 0.10, there is a 3.6% chance that the trial will be stopped early. On the other hand, if the true severe toxicity rate is 0.20 or 0.30, the chance of stopping the trial early is 66.7% and 99.4%, respectively.

Table 1. Probability of stopping the trial early due to severe toxicities

True severe toxicity rate	Prob(stop treatment early)

True severe toxicity rate	Prob(stop treatment early)
0.10	0.036
0.15	0.251
0.20	0.667
0.30	0.994

Correlative studies
The following studies will be conducted at the 2 institutions in the tissue specimens collected and correlated with outcome:
NfkB, p53, p21, p27, p14, p16, proteosome, GSTpi, Ki-67, ATM.

Interim Analysis
Safety - Please see Bayesian toxicity tables above.
Procedures for Reporting Deviations to Original Statistical Analysis Plan
See Bayesian toxicity tables above.

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 Appendix 8.4). 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). The participating site will fax a copy of the signed informed consent to Dr. Jorge Romaguera (713) 794-5656, prior to study enrollment along with an eligibility checklist signed by the PI at the participating site.

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. Each site will be responsible for ordering and maintaining investigational drug inventory. Any unused or expired commercially labeled bortezomib must be returned to Millennium. Bortezomib destruction at any study site is not allowed for commercially labeled product that is associated with this Investigator Initiated Study.

All material containing VELCADE 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:

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

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

6.9 Record Retention

All samples for correlative studies will be sent to MDACC for further evaluation.
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 below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium quality representative.

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

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

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

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APPENDIX: 8.1 Study Flow Chart

Evaluation	Screening (within 6 wks before 1st dose of bortezomib)	Prior to 1st cycle of MTX/ Cyta-rabine	Staging After Cycle 2 of intense chemot herapy	Staging After Cycle 4 with intense chemot herapy	Staging After Cycle 6 of intense chemot herapy	Staging After Cycle 8 of intense chemot herapy	Every 3 Mos X 1 Yr Post-treat ment ± 1 mont h	Every 4 Mos X 2nd Yr Post-treatm ent ± 1 month	Every 6 Mos X 3-4Yrs Post-treatm ent ± 2 month s	Long-term F/U Yearly ± 3 months
Informed consent	X									
Inclusion & exclusion criteria	X									
Demographics	X									
Tissue diagnosis	X[a, d]									
Medical history	X						X	X	X	X
Physical examination with neuro-assessment (sensory)*	X	X	X	X	X	X	X	X	X	X

ECOG performance status	X	X	X	X	X	X				
Vital signs	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X
Height	X	X								
Chest X-ray	X[c]		X	X	X	X	X	X	X	X
CT Head and Neck	X[c]		X[h]	X	X	X	X	X	X	X
CT Chest, Abdomen and Pelvis	X[c]		X[h]	X	X	X	X	X	X	X
PET(optional)	X[b]			X[j] (Phase I)	X[k] (Phase I)					
EKG	X									
ECHO or MUGA	X									

Bilateral or unilateral BM biopsy and Unilateral aspirate	X[d]		X[d,h]	X[d,h]	X[d,h]	X[d,h]	X[d,h]	X[d,h]	X[d,h]	X[d,h]
Colonoscopy[l]			X[h] (Phase I & II)	X[j] (Phase I & II)	X[k] (Phase I & II)					
Serum B-HCG Pregnancy test	X[f]									
HIV test	X									
Hematology[e]	X	1-3 x wk during tx.[g]	1-3 x wk during tx.[g]	1-3 x wk during tx.[g]	1-3 x wk during tx.[g]	1-3 x wk during tx.[g]	X	X	X	X
Chemistry [e]	X	X	X	X	X	X	X	X	X	X
Serum LDH[e]	X	X	X	X	X	X	X	X	X	X
Lymphoma Markers	X [d]		X	X	X	X	X	X	X	X
Cytogenetics	X [d]									
Molecular studies	X[d]									

Complete pulmonary function tests		X[i] (Phase I only)	X[i] (Phase I only)							
Optional tissue Studies	X[d]									

*Neurological assessment will be done q 3 weeks (every cycle).

[a] All patients should have a lymph node biopsy whenever possible. The PI can override this if MCL has been diagnosed by other means, or if there is no lymph node to biopsy. Send collected tissue for correlative studies outlined in footnote d.

[b] PET scan is desirable at Screening, but not mandatory.

[c] Other radiologic imaging studies can be done as deemed necessary by the clinical presentation.

[d] Send any blood, bone marrow aspirate/biopsy, lymph node tissue, or any body cavity tissue collected for cytogenetics, lymphoma markers, and molecular studies (mRNA cyclin D1 by RT-PCR, DNA for MTC by PCR.). The following studies will be conducted at MD Anderson with the tissue specimens: NfkB, p53, p21, p27, p14, p16, proteasome, GSTpi, Ki-67, and ATM. All of these are desirable but not mandatory. Send peripheral blood for lymphoma markers. The pathologist is Dr. Ruth Katz (office number: 713-794-5623; office location: G3.3753; laboratory location: G 3. 3628, Assistant: Cassandra [ext. 4-5625]). Adam Naig, Jr. should be contacted to expedite process (ext. 3-5277, pager 404-9176). Samples of each of these sites should also be sent to the lymphoma tissue bank under the direction of Dr. Sattva Neelapu (contact Elham Ghonimi at pager 713-606-3764 or Joyce Jackson at pager 713-404-4113).

[e] Testing required for every cycle D1± 3 days: CBC with differential and platelet count, β_2 microglobulin level (Phase I screening visit only), serum albumin, alkaline phosphatase, bilirubin, BUN, calcium, creatinine, glucose, inorganic phosphorus, SGPT, SGOT, electrolytes, total protein, uric acid, sodium, potassium, chloride, CO^2, and LDH.

[f] Pregnancy testing is not required for post-menopausal or surgically sterilized women.

[g] During chemotherapy cycles: CBC differential and platelets 1-3 times per week or as often as determined by treating physician

[h] After Cycle 2 of the bortezomib chemotherapy regimens: bilateral BM biopsy and unilateral aspirate, if initially positive. CT scans of the chest abdomen and pelvis. Repeat CT head and neck, if initially positive. If CT scans and BM negative, perform colonoscopy with random biopsies.

[i] For Phase I only, the first 3 patients entered in the study on a new cohort will have pulmonary function tests performed prior to the start of the first bortezomib-rituximab-methotrexate/cytarabine cycle and again repeated on day 21 of the second cycle (14 days after

the dose of bortezomib on day 6). For the lowest bortezomib dose level, the first patient enrolled must not experience a DLT for at least 14 days before the second and third patient is enrolled.

[j] After Cycle 4: If no change and persistent mass, consider PET/biopsy. If BM and CT's negative and evidence of disease in the colon after cycle #2, repeat colonoscopy with random biopsies.

[k] After Cycle 6: PET strongly recommended if initially positive. Colonoscopy with random biopsies if still positive after cycle # 4.

l. At any time, colonoscopy to be done at next cycle if patient shown to be in complete remission by CT and BM.

APPENDIX 8.2 Body Surface Area and Creatinine Clearance Calculations

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

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

or

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

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

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

For females use 85% of calculated CrCl value.

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

APPENDIX 8.3 New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease:

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

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

APPENDIX 8.4 Declaration of Helsinki

World Medical Association Declaration of Helsinki:

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000.

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving

consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
11. The subjects must be volunteers and informed participants in the research project.
12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that

prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

APPENDIX 8.5 Common Terminology Criteria for Adverse Events Version 3.0

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

APPENDIX 8.6 FACT/GOG-Neurotoxicity Questionnaire, Version 4.0

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

ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
I have numbness or tingling in my hands……	0	1	2	3	4
I have numbness or tingling in my feet……	0	1	2	3	4
I feel discomfort in my hands…….	0	1	2	3	4
I feel discomfort in my feet……	0	1	2	3	4
I have joint pain or muscle cramps……	0	1	2	3	4
I feel weak all over……	0	1	2	3	4
I have trouble hearing……	0	1	2	3	4
I get a ringing or buzzing in my ears……	0	1	2	3	4
I have trouble buttoning buttons……	0	1	2	3	4
I have trouble feeling the shape of small objects when they are in my hand……	0	1	2	3	4
I have trouble walking……	0	1	2	3	4

Sources: Cella DF, Tulsky DS, Gray G, Sarafian B, Lloyd S, Linn E, et al. The functional assessment of cancer therapy (FACT) scale: development and validation of the general measure. J Clin Oncol 1993;11(3):570-79

APPENDIX 8.7 Eastern Cooperative Oncology Group (ECOG) Performance Status Criteria

EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG)
PERFORMANCE STATUS CRITERIA

Grade	Scale
0	Fully active, able to carry on all pre-disease performance without restriction (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, i.e., light housework, office work (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours (Karnofsky 30-40)
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair (Karnofsky 10-20)
5	Dead

APPENDIX 8.8 Pregnancy Reporting Form

MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

Pregnancy Form v03Nov2008 (IIS)

Report Type: ❒ Initial ❒ Follow-up	Date of Report: ___/___/_____ DD MM Yr

REPORTER INFORMATION: (Please forward if an alternative physician is more appropriate)		
Reporter name: _____	Title: _____	
Address: _____	Telephone No.: _____	Fax No. _____
City, State/Province: _____	Postal Code: _____	Country: _____

FATHER'S INFORMATION ❒ Father Unknown	
Initials: _____ Date of Birth: ___/___/_____ DD MM Yr or Age: _____years	
Participating in an MPI clinical study? ❒ No ❒ Yes *If no*, what company product was taken: _____ *If yes, please provide:* Study drug: _____ Protocol No: _____ Center No: _____ Patient No: _____	
Medical / Familial / Social History (i.e. Include chronic illnesses: specify, familial birth defects/genetic/chromosomal disorders; habitual exposure: specify, alcohol/tobacco; drug exposure: specify, substance abuse and medication use. Please include drug treatment prior to or around the time of conception and/or during pregnancy) _____ _____	Race: _____ Occupation: _____ Number of children: _____

MOTHER'S INFORMATION:

Initials: _____ Date of Birth: ___/___/_____ or Age: _____years
DD MM Yr

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

Race: _____
Occupation: _____

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

_____
_____
_____

Number of previous pregnancies: Full term ____ Pre-term _____
Outcomes of previous pregnancies:
(Please indicate number of occurrences)
- Spontaneous abortion:_____
- Therapeutic abortion:_____
- Elective abortion:_____
- Other: _____
- Normal live birth:_____
- Children born with defects:____
- Stillbirth:_____
- Outcome unknown:_____

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

Product Name	Dosage	Route administered to patient	Date of first use (DD/MM/Yr)	Date of end treatment (DD/MM/Yr)	Indication	Contraindicated to pregnancy
			(__/__/__)	(__/__/__)		❒Yes ❒No ❒Unk
			(__/__/__)	(__/__/__)		❒Yes ❒No ❒Unk
			(__/__/__)	(__/__/__)		❒Yes ❒No ❒Unk
			(__/__/__)	(__/__/__)		❒Yes ❒No ❒Unk

CURRENT PREGNANCY INFORMATION

Period at exposure: _____ weeks Trimester (1) (2) (3)
Date of last menstrual period: ____/____/_____ ❒ Unknown
DD MM Yr

Pregnancy Status

❒ Pregnancy Ongoing
Estimated date of delivery: ___/___/_____
DD MM Yr
❒ Live Birth
❒ Stillbirth
❒ Early Termination
- ❒ Spontaneous abortion*
- ❒ Therapeutic abortion*
- ❒ Elective abortion*
- ❒ Other*:_____

If box is checked, please note reason in "Additional Details" section below

Fetal/Neonatal Status

❒ Normal
❒ Birth defect (structural/chromosomal disorder)*
❒ Other (non-structural, premature birth, intrauterine death/stillbirth)*

If box is checked, please note details in "Additional details" section below

Additional Details:

Is there evidence of a defect from a prenatal test? ❒Yes ❒No

If yes, indicate which test(s) showed evidence of birth defect:

❒Ultrasound ❒Amniocentesis ❒Maternal Serum-Alpha-Fetoprotein

❒Chorionic Villi Sampling ❒Human Chorionic Gonadotropin ❒Other:_____

Please specify details of defect(s), disorder(s), and/or other anomaly(ies): _____

_____

What are the defect(s) attributed to:_____

Infant Information:

Gestational weeks at birth or at termination: _____weeks

Date of birth or termination: ____/____/_____
DD MM Yr

If multiple births (e.g. twins), indicate number: _____
(Please complete separate form for each child)

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

Breast-fed: ❒Yes ❒ No ❒ Unk

Method of delivery: ❒ Normal vaginal ❒ Caesarean section
❒ Other: _____

Sex: ❒ Male ❒ Female ❒ Unk

Length: _____ ❒ cm ❒ in

Weight: _____ ❒ g ❒ lbs

Head circumference: _____ ❒ cm ❒ in

Apgar score (0-10) at 1 minute: ____ ❒ Unk

Apgar score (0-10) at 5 minute: ____ ❒ Unk

Resuscitation required: ❒ Yes ❒ No ❒ Unk

Admission to intensive care required:
❒ Yes ❒ No ❒ Unk

Additional Notes:

_____

_____

_____

Please attach RELEVANT LABORATORY TESTS AND PROCEDURES (e.g. results of ultrasounds, amniocentesis, chorionic villi sampling, or miscellaneous testing as applicable). In the case of an abnormal evolution or outcome, please send copies of results of all relevant laboratory testing and procedures, including pathology results of products of conception and or autopsy reports if applicable. Please submit any additional relevant information on a separate sheet.

Investigator signature: _____ Date: ___/___/_____
DD MM Yr

Investigator Name: _____