Abbreviated Title: EPOCH-R-B +/- B Maintenance in MCL
CC Protocol #: 05-C-0170 P
Version Date: 09/06/2018
NCT Number: NCT00114738

Randomized Phase II Study of Dose-Adjusted EPOCH-Rituximab-Bortezomib Induction Followed by Bortezomib Maintenance versus Observation in Untreated Mantle Cell Lymphoma with Microarray Profiling and Proteomics

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Investigational Agents: None

Commercial Agents: Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin, Rituximab, Bortezomib, Filgrastim

PRÉCIS

Background:

- Mantle cell lymphoma (MCL) presents a clinical challenge because it is aggressive and incurable with chemotherapy. Therefore, novel treatment approaches are needed.
- MCL has overexpression of NF-kappa B (NF-κB), a transcription factor that affects cell growth and survival, and cyclin D1 that affects cell cycle and growth. These proteins appear to be involved in the pathogenesis of MCL.
- Bortezomib, a proteasome inhibitor that inhibits NF-κB and cyclin D1, has demonstrated activity in patients with relapsed or refractory MCL.
- Dose-adjusted-EPOCH-R has excellent activity in MCL, with a complete response (CR) rate of 92%, but patients eventually relapse.

Objective:

- Determine the PFS and OS of DA-EPOCH-RB followed by bortezomib maintenance versus observation

Eligibility:

- Diagnosis of mantle cell lymphoma
- No prior treatment except for local radiation or a short course of steroids for control of symptoms,
- Age $\geq$ 18 years old
- Adequate major organ function unless impairment is due to lymphoma.

Study Design:

- To assess the clinical activity and biological effects of bortezomib, patients will initially receive one cycle of bortezomib alone with sequential tumor biopsies for microarray analysis.
- All patients will then receive Dose-adjusted (DA)-EPOCH-RB for 6 cycles, and if they have at least a PR, this will be followed by randomization to either immediate bortezomib maintenance x 18 months, or to observation, followed by bortezomib if progression occurs. This study has as a primary goal, to describe progression free survival (PFS) and overall survival of early bortezomib maintenance versus observation following induction with bortezomib followed by DA-EPOCH-RB. Important secondary goals are to assess response and toxicity to bortezomib alone or DA-EPOCH-RB, to evaluate time to progression after receiving bortezomib following progression on an observation arm, and to assess the biological effects of bortezomib on untreated MCL.

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary

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1.1.2 Secondary

- Determine response to bortezomib pre-DA-EPOCH-RB in "window of opportunity"
- Determine response and toxicity of DA-EPOCH-RB
- Determine response and PFS of bortezomib at disease progression in the observation arm
- Compare time to non-protocol treatment in the maintenance versus observation arms
- Assess effects of bortezomib on mantle cell lymphoma by microarray, proteomics and genomic methylation microarrays
- Correlate microarray, genomic methylation and proteomic findings with clinical outcomes

1.1.3 Exploratory

- Explore molecular and genomic studies in tissue that may predict response and outcomes

1.2 BACKGROUND AND RATIONALE

Hypothesis: Mantle cell lymphoma (MCL), an aggressive B-cell neoplasm, has only recently been recognized as a distinct biologic entity and compromises approximately 2.5 to 4% of all NHL in the U.S. It occurs more commonly in the elderly, has a male predominance and typically presents at an advanced stage. The clinical behavior of MCL tends to be aggressive but can vary from relatively indolent to very aggressive. Although the disease responds to chemotherapy, it is usually incurable and responses are of short duration with a median survival of 3 – 4 years. [1] Studies looking at various chemotherapy regimens in untreated mantle cell lymphoma have demonstrated event-free survivals ranging from 8 to 19 months and disease-free survivals ranging from 19 to 25 months, depending on the series (Table 1).

Series	n	PR (%)	CR (%)	Median DFS (months)	Median PFS (months)	Median Survival (months)
G.A. Velder[1,2]	41	---	32	25	---	24
W.Hiddenmann[3]	45	52	17	---	8	28
H. Samaha[4]	121	28	68	---	---	38
I. Teodorovic[5]	65	---	52	20	19	45
E. Zucca[6]	26	---	50	19	---	33
J. Armitage[7]	83	---	---	---	---	32

The use of autologous stem cell transplantation and high dose therapy in the treatment of newly diagnosed mantle cell lymphoma is controversial. Khouri et al tested an aggressive regimen of hyper-CVAD and high-dose methotrexate/cytarabine followed by stem cell transplantation in patients with relapsed or previously untreated mantle cell lymphoma.[8] Among the 25 previously untreated patients, the overall survival (OS) and event-free survival (EFS) at 3 years were 92% and 72% respectively. In contrast, the EFS at 3 years was 17% in the previously treated patients. Although the results are impressive in the untreated group, the results from the previously treated group suggest that this combination approach can salvage few if any patients and is therefore unlikely to be curative in the untreated group. A recent study published by Mangel et al. prospectively evaluated intensive chemotherapy and high-dose chemotherapy plus rituximab for newly diagnosed advanced stage mantle cell lymphoma. Of 20 patients treated, 17 remain in remission at a median of 30 months from diagnosis.[9] However, longer follow-up is required to assess the impact of this strategy on PFS and OS. Other studies have shown little evidence that high-dose treatment with transplant is potentially curative. Freedman et al treated 28 MCL patients with high-dose chemo-radiotherapy and anti-B-cell monoclonal antibody purged autologous bone marrow transplantation.[10] Twenty patients had received prior regimens before transplant, and 8 were in first CR/PR following CHOP. Nineteen (68%) patients relapsed at a median of 21 months, and of 8 patients in first CR/PR, 5 had relapsed. With a median follow-up of 24 months, DFS and OS were estimated to be 31% and 62%, respectively, at 4 years, indicating that high dose chemotherapy with autologous stem-cell support cures few if any patients.

Thus, with anthracycline based chemotherapy or high dose chemotherapy, MCL is largely incurable and therefore new treatment approaches are needed. Dose-adjusted EPOCH in combination with rituximab has good activity in mantle cell lymphoma with a CR rate of 92%. However, most patients eventually have disease relapse and thus additional approaches to treatment of this disease are worth investigating with the hope of improving time to treatment failure and curability rates.

MCL is characterized by t (11; 14) (q13; q32) resulting in over-expression of cyclin D1 which is involved in regulation of the cell cycle - it controls G1 progression and G1 – S transition. NF-κB, a transcription factor involved in immune and inflammatory cellular responses affecting both cell growth and survival, appears to have an important role in the pathogenesis of aggressive lymphoid malignancies including MCL.[11] Therefore, therapeutic strategies that target NF-κB, such as proteasome inhibition by Bortezomib, possibly in combination with conventional chemotherapy, are worthwhile investigating.

In eukaryotic cells, the ubiquitin proteasome pathway plays an essential role in the degradation of most intracellular proteins. The 26 S proteasome degrades regulatory proteins involved in cell cycle control. Some targets of this degradation are p53, p21, NF-κB, IκB and bcl-2. The NF-κB/Rel transcription factors integrate diverse intracellular signaling pathways that are activated during normal cellular differentiation and during immune responses. [12-15] NF-κB dependent transcriptional activity is mediated by dimers of NF-κB family members (p50/105, p52/100, p65/RelA, RelB, or c-Rel), and is regulated by members of the IκB family of inhibitors, principally IκBα, which binds to NF-κB dimers and retains them in the cytoplasm. Upon phosphorylation by the IKK complex, IκBα is targeted for ubiquitination and proteasomal degradation, and released NF-κB dimers can translocate to the nucleus and activate transcription of target genes.[13] NF-κB target genes encode diverse mediators of immune responses as well as

regulators of cellular proliferation and apoptosis. The expression of these target genes varies, in part, with the cell type in which NF-κB is activated. NF-κB activity is also critical for normal B cell development and survival.[16] NF-κB activation by mitogenic stimuli is normally self-limited, but constitutive nuclear NF-κB has been found in several types of cancers, raising the possibility that NF-κB may contribute to malignant transformation or progression[11,17]. For example, in cell lines and Hodgkin's disease, mutations of IκBα gene result in its functional inactivation and the accumulation of p50/RelA heterodimers in the nucleus.[17-21] In other types of lymphoid malignancies, constitutive NF-κB activity can occur occasionally due to translocations involving the NF-κB2 gene that disrupt its carboxy terminus,[22,23] or by amplification of the *c-rel* locus.[24,25] Of interest is evidence that NF-κB transcriptionally activates bcl-2.

The ability of NF-κB to inhibit responses to cancer therapeutic agents may contribute to the poor outcome of MCL, and inhibition of NF-κB can synergize with chemotherapy to kill tumor cells.[11] P21 and p27, two cdk inhibitory proteins and members of the INK-4 family are important for cell cycle regulation.[26] MCL cells often have low levels of p21 and p27, and low p27 levels have been associated with a poor prognosis.[27] Both p21 and p27 are up regulated in MCL cells after Bortezomib treatment.[28] Two recently published studies [28,29] have demonstrated that inhibition of the proteasome induces cell cycle arrest and apoptosis in MCL lines. In the first of these,[28] it is demonstrated that inactivating NF-κB in MCL lines with the proteasome inhibitor Bortezomib or the PIκBα inhibitor Bay 11, blocks MCL cell growth leading to tumor cell death. The mechanism of blocking cell growth was via cell cycle arrest and induction of cell death, both of which involve inhibition of constitutive NF-κB activation. This cell cycle arrest was associated with inhibition of cyclin D1 expression. A second study [11] looked at proteasome inhibition in MCL lines that closely resembled blastic MCL with deletion of p15 and p16 (Granta 519) and mutation of P53 (NCEB)). In this study, cell cycle arrest and apoptosis were accompanied by accumulation of the cdk inhibitor p21 in both cell lines. These results suggest that inhibition of NF-κB, through proteasome inhibition by Bortezomib, may induce tumor cell apoptosis or decrease bcl-2 associated drug resistance.

Two studies, recently presented in abstract form, have demonstrated good activity of Bortezomib in the setting of relapsed and refractory mantle cell lymphoma. In the first of these,[30] the dose of Bortezomib was 1.5mg/m^2 IV on days 1, 4, 8 and 11 every 21 days. Of 15 evaluable patients, 8/15 patients responded with 3 CRs and 5 PRs (RR 53%). In the second study,[31] using a dose of 1.3mg/m^2 IV twice weekly for 2 out of every 3 weeks, there was a PR rate of 38.5% (5 of 13 evaluable patients).

1.2.1 Bortezomib 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. Bortezomib is a dipeptidyl boronic acid derived from leucine and phenylalanine, which is a potent and reversible inhibitor of the proteasome. The ubiquitin-proteasome pathway is essential for the degradation of most short- and long-lived intracellular proteins in eukaryotic cells. The 26S proteasome, universally present and abundant in all eukaryotic cells, is an ATP-dependent multicatalytic protease that is central to the degradative pathway. The 26S proteasome functions not only in a housekeeping role to eliminate damaged or misfolded proteins but also as a critical regulator of multiple cellular processes by virtue of the many regulatory proteins governing the cell cycle, transcription factor activation, apoptosis, and cell trafficking that are substrates for

proteasome-mediated degradation. The proteasome is the final degradative enzyme involved in an important catabolic pathway for many intracellular regulatory proteins including NF-κB, p53, and the cyclin-dependent kinase inhibitors p21 and p27. Notably, Bortezomib induces apoptosis in cells that over express bcl-2, a genetic trait that confers unregulated growth and resistance to conventional chemotherapeutics. Targeting the proteasome has emerged as a novel approach to cancer therapy. Bortezomib is currently approved by the United States Food and Drug Administration (US FDA) and it is registered in Europe for the treatment of multiple myeloma patients who have received at least one prior therapy and have demonstrated disease progression on the last therapy.

1.2.2 Bortezomib 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

1.2.3 Clinical Pharmacokinetics and Pharmacodynamics of Bortezomib

The clinical pharmacology characterization of bortezomib has been determined from phase 1 studies in subjects with solid tumors and hematological malignancies, and confirmed in phase 2 studies in subjects with multiple myeloma. In solid tumor subjects, the mean terminal elimination half-life of bortezomib was 9.06 hours. The mean area under the curve $(AUC)_{(0\text{-}24)}$ after the first dose (1.3 mg/m^2) of bortezomib was 48.2 hr*ng/mL. The average clearance of bortezomib following a single 1.3 mg/m^2 dose was 49.0 L/hr. However, the AUC increased to 81.0 hr*ng/mL after the third dose in the first cycle as a result of a reduction in systemic clearance to 28.2 L/hr with a consequent increase in elimination half-life to 54.0 hours. Clinical experience has shown that the change in clearance does not result in overt toxicity from accumulation in this multidose regimen in humans. The overall disposition of bortezomib is consistent with a 2-compartment PK model, although the existence of a third compartment cannot be excluded at this time due to the lack of supportive steady-state PK data in humans. In

subjects with advanced malignancies, the maximum pharmacodynamic effect (inhibition of 20S activity) occurred within 1-hour post dose. At the therapeutic dose of 1.3 mg/m^2 in subjects with multiple myeloma, the mean proteasome inhibition at 1-hour post dose was approximately 61%.

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

The relationship between bortezomib plasma concentrations and proteasome inhibition can be described by a maximum effect (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.

1.2.4 Clinical Experience with Bortezomib

It is estimated that as of June 2005, more than 24,000 patients have been treated with bortezomib, including patients treated through Millennium-sponsored clinical trials, Investigator-Initiated Studies, the US NCI Cancer Therapy Evaluation Program (CTEP), and with commercially available drug. Bortezomib has been commercially available since 13 May 2003.

The overall goal of the Millennium phase 1 program was to determine the MTD and dose-limiting toxicity (DLT) of bortezomib in a number of therapeutic settings involving subjects with various advanced malignancies. In a Phase I trial in patients with refractory hematologic malignancies, the MTD for a twice weekly for 4 weeks of a 42-day cycle was 1.04 mg/m^2/dose, with DLTs of thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise (Orlowski et al., 2002). The toxicity was greatest during the third and fourth weeks of therapy. In the 3-week schedule of bortezomib monotherapy (4 doses, given on Days 1, 4, 8, and 11 of a 21-day treatment cycle), the DLT occurred at 1.56 mg/m^2/dose (3 subjects with Grade 3 diarrhea and 1 with peripheral sensory neuropathy). Therefore, the MTD at this schedule was 1.3 mg/m^2/dose. In a 35-day treatment cycle with 4 weekly doses of bortezomib monotherapy, the MTD was 1.6 mg/m^2/dose and DLT included hypotension, tachycardia, diarrhea, and syncope.

In phase 1 clinical studies, anti-tumor activity was reported in subjects with NHL, multiple myeloma, Waldenström's Macroglobulinemia, squamous cell carcinoma of the nasopharynx, bronchoalveolar carcinoma of the lung, renal cell carcinoma, and prostate cancer. The safety and efficacy of bortezomib in subjects with multiple myeloma were investigated in two phase 2 clinical studies, studies M34100-024 (subjects with first relapse) and M34100-025 (subjects with second or greater relapse and refractory to their last prior therapy). In M34100-025, 202 heavily pre-treated subjects with refractory multiple myeloma after at least 2 previous treatments received bortezomib 1.3 mg/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 (Blade et al., 1998) were utilized to determine disease response. CRs were observed in 4% of subjects, with an additional 6% of patients meeting all criteria for CR but having a positive immunofixation test. PR or better was observed in 27% of subjects, and the overall

response rate (CR, PR and minor response [MR] combined) was 35%. Seventy percent of subjects experienced stable disease or better.

The phase 3 study (M34101-039), also referred to as the APEX study, was designed to determine whether bortezomib provided benefit (time to progression [TTP], response rate, and survival) to patients with relapsed or refractory MM relative to treatment with high-dose dexamethasone. The study was also designed to determine the safety and tolerability of bortezomib relative to high-dose dexamethasone, and whether treatment with bortezomib was associated with superior clinical benefit and quality of life relative to high-dose dexamethasone. A total of 669 patients were enrolled and 663 patients received study drug (bortezomib: 331; dexamethasone: 332). Patients randomized to bortezomib received 1.3 mg/m^2 I.V. push twice weekly on days 1, 4, 8, and 11 of a 3-week cycle for up to eight treatment cycles as induction therapy, followed by 1.3 mg/m^2 bortezomib weekly on days 1, 8, 15, and 22 of a 5-week cycle for three cycles as maintenance therapy. Patients randomized to dexamethasone received oral dexamethasone 40 mg once daily on days 1 to 4, 9 to 12, and 17 to 20 of a 5-week cycle for up to four treatment cycles as induction therapy, followed by dexamethasone 40 mg once daily on days 1 to 4 followed of a 4-week cycle for five cycles as maintenance therapy. The European Group for Blood and Marrow Transplant (EBMT) response criteria, as described by Blade (Blade et al., 1998) were utilized to determine disease response. There was a 78% increase in TTP for the bortezomib arm. Median TTP was 6.2 months for the bortezomib arm and 3.5 months for the dexamethasone arm (*P*<.0001). CR (complete response) + PR (partial response) was 38% with bortezomib vs. 18% with dexamethasone (*P*<.0001). CR was 6% with bortezomib vs. <1% with dexamethasone (*P*<.0001). The CR + nCR rate was13% with bortezomib vs. 2% with dexamethasone. In patients who had received only one prior line of treatment (bortezomib: 132; dexamethasone: 119), CR + PR was 45% with bortezomib vs. 26% with dexamethasone (*P*=.0035). With a median 8.3 months of follow-up, overall survival was significantly longer (*P*=.0013) for patients on the bortezomib arm vs. patients on the dexamethasone arm. The probability of survival at one year was 80% for the bortezomib arm vs. 66% for the dexamethasone arm, which represented a 41% decreased relative risk of death in the first year with bortezomib (*P*=.0005). In patients who had received only one prior line of treatment, the probability of survival at one year was 89% for the bortezomib arm vs. 72% for the dexamethasone arm, which represented a 61% decreased relative risk of death in the first year with bortezomib (*P*=.0098). (Richardson et al., 2005)

The optimal schedule for bortezomib is unclear. To further investigate the schedule, a study was recently presented at the American Society of Hematology in 2005.

Patients were indolent lymphoma were randomized to bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 of a 21-day cycle (Arm A) or 1.6 mg/m^2 on days 1, 8, 15, and 22 of a 35-day cycle (Arm B) for up to 15 weeks (5 and 3 cycles in arms A and B, respectively). Starting from day 1, rituximab 375mg/m^2 was administered weekly for 4 weeks. In this study, 81 patients were enrolled. At data reporting 46 (23 each arm) had received study drug, and 42 (20 Arm A, 22 Arm B) were evaluable for response. The median bortezomib dose received was 15.9 mg/m^2 (61% of max. expected) in Arm A, and 19.0 mg/m^2 (99% of max. expected) in Arm B. Overall response rates were similar in both arms with 50% Arm A and 45% Arm B. Treatment was tolerated in both arms with grade ≥3 AEs in 10 patients in Arm A and 5 patients in Arm B. The most common grade ≥3 AEs were gastrointestinal toxicities, neutropenia, thrombocytopenia and peripheral neuropathy, but no grade ≥3 thrombocytopenia or neutropenia were observed in Arm B. These

results suggest that weekly dosing is less toxic. However, it is unclear if it is as effective because rituximab was administered in both arms and may have obscured differences in outcome. Because the twice weekly schedule has been shown to be effective in mantle cell lymphoma, it will be used in the maintenance arm of this study. Because this is a maintenance and not treatment schedule, patients will receive bortezomib 1.3 mg/m^2 weekly on days 1, 4, 8 and 11 of an 8-week treatment cycle.

1.2.5 DA-EPOCH-bortezomib background

We recently commenced a study, using bortezomib in combination with DA-EPOCH in patients with relapsed or refractory diffuse large B-cell NHL. To reach the optimal dose of Bortezomib used in conjunction with DA-EPOCH, there was an accelerated dose escalation of Bortezomib with doses of 0.5, 1, 1.5 and 1.7 mg/m^2. On the basis of tolerability and feasibility, the 1.5mg/m^2 dose was the dose selected for Phase II evaluation with DA-EPOCH and was administered on days 1 and 4 of a 21-day cycle. Thus far, the toxicities of this combination have included nausea/vomiting, stomatitis, diarrhea, constipation, thrombocytopenia, neutropenia, fever and neutropenia and neuropathy.

Preliminary experience with DA-EPOCH-RB has been obtained in the first 5 patients on the current study. Of these patients, bortezomib doses were reduced or discontinued in all 5 patients due to at least grade 2 neuropathy. These results indicate that the acceptable phase II dose of bortezomib with DA-EPOCH-R should be reduced to 1.3 mg/m^2. The apparent higher toxicity in the current study compared to our previous study may in part be due to the administration of Part A where patients receive bortezomib 1.5 mg/m^2 on days 1, 4, 8, 11 for analysis of translational endpoints and response. Because bortezomib neurotoxicity is cumulative, neurotoxicity during DA-EPOCH-RB will be higher due to bortezomib exposure on Part A. Hence, to reduce neurotoxicity, Part A will administer bortezomib at 1.3 mg/m^2 for days 1 and 4 only (times during which translational endpoints are obtained). As noted above, maintenance bortezomib will be administered using the standard dose and schedule (bortezomib 1.3 mg/m^2 days 1, 4, 8, 11) but will be repeated at 8-week intervals.

Toxicity of DA-EPOCH-B from our phase I study are shown in the table below.

Toxicity Profiles :DA -EPOCH-Bortezomib*

	Grade			
Adverse Event	2	3	4	**≥ Grade 2 %**
Nausea/vomiting	**2**	**1**	**-**	**8**
Stomatitis	**10**	**-**	**-**	**26**
Constipation	**4**	**-**	**-**	**10**
Diarrhea	**3**	**1**	**-**	**10**
Hematological				
Thrombocytopenia	**7**	**14**	**-**	**54**
Transfusion platelets	**-**	**7**	**2**	**23**
Neutropenia	**3**	**7**	**21**	**79**
Infectious				
Fever and neutropenia	**-**	**6**	**-**	**15**
Neuropathy * *	**1**	**-**	**-**	
Cardiac	**-**	**2**	**-**	**5**

*** * Toxicity is by patient and not cycle** *** Based on 39 cycles**

1.2.6 DA-EPOCH-R background

DA-EPOCH-Rituximab (DA-EPOCH-R) is a novel combination of chemotherapy and the CD-20 monoclonal antibody, rituximab. DA-EPOCH in combination with rituximab has produced a 92% complete remission rate in patients with newly diagnosed mantle-cell lymphoma.[33]

This study sets out to evaluate the combination of EPOCH-Rituximab-Bortezomib induction followed by either early or delayed Bortezomib maintenance in untreated MCL. We plan to accrue 80 patients on this study. This design will allow an assessment of the efficacy of maintenance Bortezomib on time to treatment failure and will provide additional information on the efficacy of Bortezomib at the time of relapse, if this were to occur. In a recent study of EPOCH-R followed by idiotype vaccine in 26 untreated MCL patients, 92% achieved a complete remission following EPOCH-R alone.[33] Additionally, there was 24-month median response duration and 100% survival, indicating that EPOCH-R is a highly effective treatment platform. However, despite the high CR rate, 40% of patients on the study have progressed, suggesting that this approach will not be curative in most patients. Based on the biology of MCL, the addition of Bortezomib to EPOCH-R may further increase the cytotoxicity of the regimen. Additionally, given the over-expression of cyclin D1 in MCL, which is believed crucial in driving cells from the G1 to the S phase, it is worthwhile targeting this pathway through long-term proteasome inhibition. Hence, we propose using maintenance Bortezomib for 18 months following induction with EPOCH-R-Bortezomib. Maintenance therapy has previously been shown to be highly effective in recurrent Hodgkin's lymphoma and provides different kinetics of cell kill compared to cyclic treatment. We plan to incorporate micro-array analysis of tissue from patients with MCL and correlate gene expression signatures to other molecular and histological markers and to survival and response. This will be achieved by taking advantage of a "window of opportunity" in which all patients will receive a single cycle of Bortezomib before induction with paired

tumor samples for microarray and CT scan assessment of tumor response. Recent work by Louis Staudt's group has shown that the proliferation gene expression signature is a quantitative integrator of oncogenic events that predicts survival in MCL and may provide an important prognostic tool in addition to discovering new molecular predictors of outcome using this novel approach.[34] Furthermore, there is little information on the biological effects of Bortezomib in mantle cell lymphoma. Paired samples for analysis by microarray and proteomics will permit further characterization of the potential mechanisms of Bortezomib. These results will be correlated with clinical outcome as a secondary objective.

1.2.7 Microarray Profiling and Proteomics Background

Gene expression profiling on microarrays. We aim to perform gene expression profiling on Affymetrix whole genome arrays in both biopsies from all patients enrolled in the study. We chose gene expression profiling to assess the molecular changes induced by a proteasome inhibitor because gene expression profiling provides a comprehensive and highly quantitative overview of tumor biology and can be carried out even from small amounts of tissue. Gene expression signatures that relate to specific cellular functions or to the activity of distinct signaling pathways can be reproducibly monitored and can identify subsets of patients with distinct tumor biology, different prognosis or differential response to therapy. For example, Rosenwald et al have recently identified a proliferation gene expression signature in a retrospective study in MCL biopsies profiled on the Lymphochip[34]. This proliferation signature integrates different oncogenic events and confers powerful prognostic information. Therefore, we will use the proliferation signature to determine the effect of proteasome inhibition on proliferation rate in vivo and to test whether our proposed combination therapy is able to overcome the adverse prognostic impact of high tumor proliferation. In addition to monitoring changes in gene expression induced by bortezomib, we will use the pre-treatment gene expression profile to develop a molecular predictor of treatment responsiveness. In the second biopsy on bortezomib monotherapy we will use gene expression profiling to characterize sequelae of proteasome inhibition in vivo **to** better define MCL pathobiology and to identify predictors of treatment response. The mechanisms of bortezomib induced cell death and the reason for its apparent tumor selectivity are currently incompletely understood. In vitro data provide a number of hypotheses including inhibition of the NF-kB pathway, activation of caspases, down regulation of cyclin D1 or upregulation of cell cycle inhibitors such as $p21^{cip}$ and $p27^{kip-1}$. The gene expression profiles from the paired biopsies will be helpful in testing whether some of these in vitro observations translate into clinical reality. For instance, we will be able to follow changes in NF-kB regulated genes and thereby estimate the relative importance of this signaling pathway for MCL.

The genetic aberrancies which characterize lymphoma are manifested functionally by changes at the protein level and result in modulation of critical cell signaling pathways such as those involving apoptosis. The technology to profile these protein pathways has evolved through the development of reverse phase protein microarrays (RPPMs)[35-37]. This approach allows not only quantitation of proteins of interest, but also determination of their activation state, regulated through post-translational modifications such as phosphorylation or cleavage.

The small molecule inhibitor of the proteasome, bortezomib, promotes apoptosis; this effect appears to be due in part to prevention of NF-κB activation, but the precise mechanisms have not been fully established[38]. Furthermore, the proteasome degrades proteins with a wide variety of cellular functions other than regulation of apoptosis (e.g. cell cycle proteins). While previous

studies have shown clinical promise of bortezomib in lymphoma, including MCL[39], the key signaling pathways modulated in responders and non-responders have not been characterized. Because bortezomib acts by inhibiting proteasomal degradation, its principal effects are expected to be observed at the protein level.

In this portion of the study we will profile the activation status of cell signaling pathways in MCL before and after bortezomib therapy using RPPMs. Tissue biopsies will be processed by freezing tissue (approximately 0.5 cm^3 for open biopsies or 1 core for needle biopsies) in OCT. Tumor lysates will be immobilized in serial dilutions on a solid phase. Antibodies will be applied in solution phase and binding will be detected by secondary tagging and amplification. Over 400 such antibodies, including those specific for post-translational modifications such as phosphorylation, have been validated for use in RPPMs by the NCI-FDA Clinical Proteomics Program. The precision, sensitivity and linearity of this protocol have been validated using clinical specimens[35]. Bioinformatic analysis of the data can identify significant proteins or combinations, including the hierarchical clustering typical of microarrays[35]. The Center for Cancer Research, National Cancer Institute, currently has open clinical trials for other diseases that incorporate this method of RPPMs to evaluate protein expression in pre- and post-treatment tissue biopsies.

The goal of these analyses will be (1) to identify protein profiles (including activation status of specific signaling pathways) from pre-treatment specimens that correlate with response to bortezomib in MCL; and (2) to determine differences between pre- and post-treatment protein profiles that correlate to response. These data will be helpful in:

(1) Development of future clinical trials of individualized therapy, including:
    a. Selective use of bortezomib in patients with appropriate pre-treatment protein profiles.
    b. Selective continuation of bortezomib (vs. change in therapy) based on proteomic correlates of response.

(2) Identification of activation of undesirable (e.g. anti-apoptotic) pathways as an inadvertent effect of proteasome inhibition, particularly in non-responders. This information could be used to:
    a. Suggest targeted therapies which might be used successfully in combination with bortezomib.
    b. Direct development of novel, more selective, proteasome inhibitors.

1.2.8 Genomic Methylation Analysis Background

Epigenetic changes including aberrant methylation of gene promoters and acetylation of histones have been shown to regulate gene transcription in normal and cancer cells. Gene expression profiling has identified groups of genes associated with resistance to the proteasome inhibitor Bortezomib (BZM), a promising novel therapy for Mantle Cell Lymphoma(MCL). We have developed in-house, a high resolution, comprehensive global methylation assay called HELP (HPA II Enzyme Ligation mediated PCR amplification). Briefly, genomic DNA is digested using 2 restriction enzymes (HPAII and MSP1) that are iso-schizomers of each other, the resulting products amplified using ligation-mediated PCR and hybridized onto a custom-designed promoter array using the Nimblegen platform. Preliminary data comparing MCL cell line specimens to Naïve B cells using HELP shows abnormal methylation of several key genes like p53 and NPM1. We hypothesize that aberrant epigenetic silencing may regulate genes

associated with Bortezomib resistance in MCL. Integrative genomic approaches combining array- based comparative genomic hybridization (CGH) and gene expression have identified novel deletions involving key molecules in MCL biology. We will determine the aberrantly methylated genes involved in MCL pathogenesis by comparing these results with normal mantle zone B cells from routine tonsillectomy specimens. Moreover, by correlating methylation profiles to clinical response in this study we will develop a prediction model for BZM resistance, which could be used in future large scale clinical trials to individualize therapy in MCL. Leftover genetic material (gDNA) will be used to confirm the HELP results at individual genomic loci using MassArray, which is a high throughput Robotic Mass-spectrometric analysis system specifically designed for measuring small amounts of DNA and RNA.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Diagnosis of mantle cell lymphoma (confirmed at NCI). All variants are eligible.

2.1.2 Age ≥ 18 years.

2.1.3 No prior treatment except for local radiation or a short course of steroids for control of symptoms. 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.

2.1.4 All stages of disease.

2.1.5 ECOG performance status ≤ 3.

2.1.6 Adequate major organ function (serum creatinine ≤1.5 mg/dl or creatinine clearance > 50 ml/min; bilirubin ≦ 1.5 mg/dl (total) except < 5 mg/dl in patients with Gilbert's syndrome as defined by > 80% unconjugated; ANC > 1000 and platelets > 75,000) unless impairment due to organ involvement by lymphoma.

2.1.7 No myocardial infarction within 6 months prior to enrollment or New York Hospital Association (NYHA) Class III or IV heart failure, 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.

2.1.8 No grade 2 ≥ peripheral neuropathy within 14 days before enrollment.

2.1.9 Ability to give voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.

2.1.10 HIV antibody negative.

2.1.11 Female subject is either post-menopausal at least 1 year before the Screening visit or surgically sterilized or if they are of childbearing potential, agree to practice 2 effective methods of contraception (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) at the same time, 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. Female subject is not

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

2.1.12 Male subject even if surgically sterilized (i.e., status post vasectomy) must agree 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.

2.1.13 No invasive tumors within the last 5 years unless confined to an organ (e.g. prostate or thyroid cancer) and treated with curative therapy (e.g. surgery and/or radiation). Please note, there must be no evidence of the prior malignancy using standard criteria to evaluate the specific prior malignancy.

2.1.14 No known involvement of central nervous system by lymphoma

2.1.15 No history of hypersensitivity to bortezomib, boron or mannitol.

2.1.16 Patient has not received other investigational drugs with 14 days before enrollment.

2.1.17 No serious medical or psychiatric illness likely to interfere with participation in this clinical study.

2.1.18 Exclusion for FDG scan is anyone exceeding the weight limit of the scanner (350 lb).

2.2 EVALUATION PRE-TREATMENT

To be done within 4 weeks of commencing treatment; 2.2.5 must be done within one week of commencing treatment:

2.2.1 Complete History and Physical examination

2.2.2 CBC, differential, PT, PTT, AST, ALT, LDH, alkaline phosphatase, bilirubin, albumin, calcium, phosphate, uric acid, creatinine (24-hour creatinine clearance if serum creatinine > 1.5 mg/dl), electrolytes, urinalysis, immunoglobulin free light chains and serum protein electrophoresis. Type & screen, and isohemagglutinin titer.

2.2.3 HIV antibody, Anti-HCV antibody, & hepatitis B surface antigen.

2.2.4 HLA typing (A,B, Cw) and Anti-varicella zoster virus IgG ELISA

2.2.5 HCG (serum) in women of childbearing potential.

2.2.6 Electrocardiogram

2.2.7 MUGA or echocardiogram in patients with history of MI or CHF.

2.2.8 Staging: CT scan of chest, abdomen and pelvis; PET (fluorine 18-FDG) scan, bone marrow biopsy. Imaging of head and CSF analysis if clinical suspicion of CNS

involvement. Colonoscopy recommended if not performed in previous 2 months and/or known to be positive.

2.2.9 Peripheral blood flow cytometry

3 PATIENT REGISTRATION AND RANDOMIZATION

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and faxed to 301-480-0757. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

Randomization takes place after Cycle 6 restaging is completed (weeks 0-12 after completion of cycle 6 of DA-EPOCH-RB). Only patients who have achieved a PR or CR will be eligible for randomization.

4 STUDY IMPLEMENTATION

4.1 STUDY DESIGN

Part A: Bortezomib on days 1, 4, 8 & 11 with sequential tumor sampling. Part A is completed on day 21-28. In patients with leukemic MCL, timed blood samples may be obtained throughout the first course, typically pre and at 6 hours and 24 hours after the first dose and before and 24 hours after the second dose. Select patients without leukemic disease may have serial blood draws during Part A to serve as a comparison group. In patients with nodal disease two lymph node biopsies will be obtained if nodal disease is safely accessible: one pre-treatment and the second 12-24 hours after the 2nd bortezomib dose. On treatment bone marrow aspirate or lymphapheresis to obtain lymphoma cells may be substituted for the lymph node biopsy in select patients.

If Platelet Count <25 K/mcL and impairment is due to organ involvement by lymphoma, proceed to Part B. If a patient has advanced disease that requires urgent treatment with chemotherapy, proceed to Part B.

Part B: Induction: DA-EPOCH-RB x 6 cycles

Part C: Randomization to bortezomib maintenance versus observation for patients who have achieved PR or CR. Randomization will occur within 12 weeks after completion of Part B (Post-cycle 6 of DA-EPOCH-RB). Patients with disease progression in the observation arm will be offered bortezomib treatment. Patients cannot be randomized to maintenance if they have any grade of toxicity which forbids bortezomib administration. Toxicity must resolve to a lower grade (that allows administration of bortezomib) within 12 weeks of completing DA-EPOCH-RB to be eligible for randomization. If toxicity does not resolve to this level within 12 weeks, the patient is not eligible for randomization.

4.2 DRUG ADMINISTRATION

- **Part A: Bortezomib x 1 cycle (21 days)**

Agent	Dose	Route	Duration	Schedule
Bortezomib	1.3 mg/m^2	IV injection	Bolus (3-5 sec)	Days 1, 4, 8, 11

- **Part B: DA-EPOCH-Rituximab-Bortezomib. (Begin after part A day 21 to 28).**

  All patients initiate therapy at Dose Level 1 of DA-EPOCH-RB shown below. Doses are based on actual body weight for all patients. Future dose adjustments based on hematological toxicity as shown below.

Drugs	**Dosages & Administration/Schedule**
Bortezomib	1.3 mg/m^2 per dose for 2 doses on day 1 (before rituximab) and day 4 (between etoposide+doxorubicin+vincristine bag exchanges)
Prednisone	60 mg/m^2 PO BID days 1-5 (first dose at least 60 min before starting rituximab)
Rituximab	375 mg/m^2 day 1 (before etoposide+doxorubicin+vincristine infusion begins; see Section **12.2** for administration instructions)
Etoposide	50 mg/m^2/day CIV days 1- 4 (96 hour infusion)
Doxorubicin	10 mg/m^2/day CIV days 1-4 (96 hour infusion)
Vincristine	0.4 mg/m^2/day CIV days 1-4 (96 hour infusion)
Cyclophosphamide	750 mg/m^2 IV day 5 over 30-60 mins
Filgrastim	Body weight <75 kg: 300 mcg/dose Body weight ≥75 kg: 480 mcg/dose Doses are given once daily by subcutaneous injection on days 6 to 15 or ANC > 5000/mcL after the leukocyte nadir.
Cycle Length	Repeat cycle every 21 days

- Repeat cycles every 21 days. Delay cycle until ANC > 1000/mcL or platelets >75,000/mcL. Use filgrastim to increase ANC and begin next cycle as soon as ANC recovers. If no recovery after 2 weeks, contact study Chair for guidance.

4.2.1 Dose Adjustments Based on Hematological Toxicity for DA-EPOCH-RB

Doses for doxorubicin, etoposide and cyclophosphamide will be based on measurements of the previous cycle ANC or platelet nadir whichever is lower. **Dose adjustment is based on measurements of <u>twice weekly CBC only</u>, even if additional CBCs are obtained. Twice weekly CBCs must be at least 3 days apart.**

- If Nadir ANC ≥ 500/mcL on all measurements: ↑ One level above last cycle
- If Nadir ANC < 500/mcL on 1 or 2 measurements: Same level as last cycle
- If Nadir ANC < 500/mcL ≥ 3 measurements: ↓ One level below last cycle

Or

- If nadir platelet < 25,000/mcL on ≥ 1 measurement: ↓ One level below last cycle

4.2.2 Dose Levels

Adjustments apply only to etoposide, doxorubicin and cyclophosphamide. Levels below 1 only involve 20% reductions in cyclophosphamide.

Drugs	Drug Doses per Dose Levels							
	-2	-1	**1**	2	3	4	5	6
Doxorubicin (mg/m^2/day)	10	10	**10**	12	14.4	17.3	20.7	24.8
Etoposide (mg/m^2/day)	50	50	**50**	60	72	86.4	103.7	124.4
Cyclophosphamide (mg/m^2)	480	600	**750**	900	1080	1296	1555	1866

4.2.3 Part C: Bortezomib maintenance versus observation (followed by bortezomib if progression occurs).

Patients must have achieved at least a PR after DA-EPOCH-RB to be randomized on Part C. Randomization takes place when patient is eligible after Cycle 6 restaging is completed. Patients cannot be randomized to maintenance if they have any grade of toxicity which forbids bortezomib administration. Toxicity must resolve to a lower grade (that allows administration of bortezomib) within 12 weeks of completing DA-EPOCH-RB to be eligible for randomization. If toxicity does not resolve to this level within 12 weeks, the patient is not eligible for randomization.

4.2.4 Maintenance bortezomib arm

Begin maintenance 8-12 weeks after completion of DA-EPOCH-RB (e.g. Day 77 of last cycle). Bortezomib 1.3 mg/m^2 days 1, 4, 8 and 11 every 56 days (i.e. q8 weeks) for 18 months (10 cycles) or until disease progression, whichever comes first. After maintenance, begin follow-up as described in Section **4.5.2**.

Agent	Dose	Route	Duration	Schedule
Bortezomib	1.3 mg/m^2	IV injection	Bolus (3-5 sec)	Days 1, 4, 8, 11 Repeat q 56 days

4.2.5 Observation (followed by bortezomib if progression occurs) arm

Observation continues for 18 months or until disease progression, whichever comes first. If disease progression occurs on the observation arm, begin bortezomib. Bortezomib 1.3 mg/m^2 days 1, 4, 8, and 11 every 28 days (i.e. q4 weeks). Continue treatment for 18 months or until disease progression, whichever comes first. After completion of observation or treatment begin follow-up as described in Section **4.5.2**.

Agent	Dose	Route	Duration	Schedule
Bortezomib	1.3 mg/m^2	IV injection	Bolus (3-5 sec)	Days 1, 4, 8, 11 Repeat q 28 days

4.3 TREATMENT MODIFICATIONS

4.3.1 Part A: Bortezomib toxicity reasonably ascribed to treatment

4.3.1.1 Hematological Toxicity

Day 1 platelets < 25,000/mcL	Proceed to Part B with DA-EPOCH-RB.

Day 4 platelets < 25,000/mcL	Stop bortezomib and proceed to Part B with DA-EPOCH-RB 10-14 days after last bortezomib dose

4.3.1.2 Diarrhea Toxicity

At first loose stool, start loperamide 2 mg po q 2 h while awake and q 4 h while sleeping. Continue around the clock until 12 h diarrhea free. If diarrhea free > 12 h, stop loperamide. If new episode, retreat as outlined. Please note the manufacturer's recommended maximum daily dose of loperamide is 16 mg. If grade 3 diarrhea accompanied by mucus or dehydration, stop bortezomib and proceed to Part B with DA-EPOCH-RB 10-17 days after last bortezomib dose

4.3.2 Part B: DA-EPOCH-RB toxicity reasonably ascribed to treatment

4.3.2.1 Hematologic Toxicities

See Section **4.2.1** Part B Dose Adjustments for EPOCH-RB

4.3.2.2 Ileus and Constipation

Symptomatic ileus/constipation may occur. Because the severity of constipation is dose related, it is usually unnecessary to stop the vincristine altogether. Every effort should be made to not unnecessarily reduce vincristine doses. Ileus/constipation is usually worse on the first cycle, so prophylactic bowel care is essential. If vincristine dose is reduced for this toxicity, it can often be increased to full dose on subsequent cycles without recurrence of severe ileus/constipation. If ileus or constipation requires hospitalization, reduce vincristine 25%. If symptoms resolve after vincristine reduction, increase dose to previous level on subsequent cycles.

4.3.2.3 Neurological Toxicity

Sensory or Motor Neuropathy

Neurotoxicity Grade	**Vincristine mg/m^2/day**	**Bortezomib mg/m^2/day**
1 without neuropathic pain	0.4 mg/m^2/day	1.3 mg/m^2/day
1 with neuropathic pain	0.2 mg/m^2/day	1.3 mg/m^2/day
2 without neuropathic pain	0	1.3 mg/m^2/day
≥ 2 with neuropathic pain	0	0

If neuropathy resolves to a lower grade, doses for that lower grade may be reinstituted at investigator discretion. If the grade of neuropathy increases after being re-escalated, doses must be reduced for the appropriate toxicity grade and may not be re-escalated, even if neuropathy resolves again to a lower grade.

4.3.2.4 Hepatic Toxicity

Patients with mild hepatic impairment (bilirubin ≤ 1.5 x ULN) do not require a starting dose adjustment. Please note that patients with bilirubin levels > 1.5 ULN are excluded from enrollment in this protocol. If a patient develops moderate or severe hepatic impairment with bilirubin ≥ Grade 2 (> 1.5 -3.0 X ULN) while on study, the investigator should hold bortezomib until the toxicity returns to < Grade 2. Restarting bortezomib at the next lower dosed level could be considered at the Investigator's discretion and following exclusion of bortezomib-induced

liver impairment and careful consideration of liver disease due to other causes, such as, but not limited to, active infection and mantle cell-related liver disease.

No doxorubicin dose modifications for increased bilirubin. Pharmacokinetic data from our group has shown no significant effect of bilirubin on doxorubicin clearance. The following are the dose reductions that apply to vincristine for hyperbilirubinemia due to disease. NOTE: INCREASE VINCRISTINE TO FULL DOSE AFTER BILIRUBIN NORMALIZES

Total bilirubin on day 1	**Vincristine mg/m^2/day**
1.5-3 mg/dL	0.3 mg/m^2/day
> 3.0 mg/dL	0.2 mg/m^2/day

4.3.2.5 Diarrhea Toxicity

Diarrhea treatment ascribed to Bortezomib: At first loose stool: Start loperamide 2 mg p.o. q 2 h while awake and q 4 h while sleeping. Continue around the clock until 12 h diarrhea free. If diarrhea free > 12 h, stop loperamide. If new episode, retreat as outlined. If grade 3 diarrhea accompanied by mucus or dehydration, hold doses of bortezomib (if applicable) and hydrate.

Diarrhea management for next cycle dosing:

Diarrhea Grade	**Bortezomib mg/m^2/day**
≥ grade 3 or associated with mucus or dehydration	1 mg/m^2/day

4.3.2.6 Other Non-Hematological Toxicity

Toxicity Grade	**Management**
≥ grade 3	Hold bortezomib until ≤ grade 1. Restart bortezomib at: 1 mg/m^2/day. If recurrence of ≥ grade 3 toxicity, hold bortezomib until ≤ grade 1. Restart bortezomib at 0.75 mg/m^2/day. If recurrence of ≥ grade 3 toxicity, discontinue bortezomib during DA-EPOCH-RB.

4.3.2.7 Infusion Related Toxicity

Side effects of rituximab may be infusion rate related and may be reduced by slower administration or premedication. Thus, dose reductions of rituximab will not be made. Rituximab will be discontinued for the duration of the cycles in patients with grade 4 allergic reactions. At the discretion of the PI, rituximab may be administered on the following cycles using slower infusion rates and pretreatment with diphenhydramine using standard medical practice.

4.3.3 Part C. Maintenance Bortezomib or Treatment after Observation toxicity reasonably ascribed to treatment

Patients cannot be randomized to maintenance if they have any grade of toxicity which forbids bortezomib administration. Toxicity must resolve to a lower grade (that allows administration of

bortezomib) within 12 weeks of completing DA-EPOCH-RB to be eligible for randomization. If toxicity does not resolve to this level within 12 weeks, the patient is not eligible for randomization. The dose modifications apply to the first and all subsequent maintenance cycles.

4.3.3.1 Hematological Toxicity

Day 1 platelets < 25,000/mcL	Delay until recovery above this level
*Days 4, 8 or 11 platelets < 25,000/mcL	Hold dose for cycle.

*Draw CBC on these days only if day 1 platelets <50, 000/mcL or as clinically indicated.

4.3.3.2 Diarrhea Toxicity

Diarrhea treatment during cycle: At first loose stool: Start loperamide 2 mg po q 2 h while awake and q 4 h while sleeping. Continue around the clock until 12 h diarrhea free. If diarrhea free > 12 h, stop loperamide. If new episode, retreat as outlined. Please note the manufacturer's recommended maximum daily dose of loperamide is 16 mg. If grade 3 diarrhea accompanied by mucus or dehydration, hold doses of Bortezomib and hydrate.

Diarrhea management for next cycle dosing:

Diarrhea Grade	**Bortezomib mg/m^2/day**
≥ grade 3 or associated with mucus or dehydration	1 mg/m^2/day

4.3.3.3 Neurotoxicity

Sensory or Motor Neuropathy

Neurotoxicity Grade	**Bortezomib Management**
Grade 1	Bortezomib 1.3 mg/m^2
Grade 2 without pain (interfering with function but not with activities of daily living).	Bortezomib 1 mg/m^2
Grade 2 with pain or grade 3 (interfering with activities of daily living)	Hold bortezomib until ≤ grade 2 without pain. Reduce bortezomib to 1 mg/m^2 and administer cycles every 12 weeks. If toxicity ≥ grade 2 with pain after 12 weeks, discontinue bortezomib.
Grade 4 (disabling)	Discontinue bortezomib

If neuropathy resolves to lower grade, doses for that lower grade may be reinstituted at investigator discretion. If the grade of neuropathy increases after being re-escalated, doses must be reduced for the appropriate toxicity grade and may not be re-escalated, even if neuropathy resolves again to a lower grade.

4.3.3.4 Other Non-Hematological Toxicity

Toxicity Grade	**Management**

≥ grade 3	Hold bortezomib until ≤ grade 1. Restart bortezomib at 1 mg/m^2/day. If recurrence of ≥ grade 3 toxicity, hold bortezomib until ≤ grade 1. Restart bortezomib at 0.75 mg/m^2/day. If recurrence of ≥ grade 3 toxicity, discontinue bortezomib.

4.4 ON STUDY EVALUATION

4.4.1 Part A: Bortezomib alone

Studies	Pre-therapy[A]	Day -1 or day 1 of cycle	Day 5 (12-24 hours after second bortezomib dose	Day 4 of cycle
Hx; PE; VS; PS	x			
Tumor Measurement	x			
CBC/diff	x	x	x	x
Electrolytes, Creatinine, BUN, ALT, AST, Bilirubin, LDH, Ca^{++}, Phos, Mg	x	x	x	x
EBV viral load	x			
Immunoglobulin Free Light Chains, Serum Protein Electrophoresis, Isohemagglutinin titer, Type & Screen	x			
TBNK, 24 cc red & green CPT tubes	x			
HLA typing, Anti-varicella zoster virus	x			
CT chest/abd/pelvis, PET scan[D]	x			
Research PET scan			x[E]	
Bone marrow biopsy & aspirate, peripheral blood flow cytometry	x			
Colonoscopy[B]	x			
Optional Tumor biopsy, timed blood collections and/or apheresis[C]	x		x[C]	
10 cc red top for serum storage	x			

A- Initial assessment is to be performed within 4 weeks prior to starting treatment.

B- Colonoscopy is recommended pre-treatment unless prior colonoscopy within 2 months or known to be positive or medically contra-indicated.

C- Biopsies will be obtained in all patients (who agree to the optional biopsy) with safely accessible lymph nodes. Snap freeze and store tissue biopsies for translational studies. In patients with leukemic MCL treated at the NCI, up to 8 additional blood samples (typically 6 and 24 hrs post dose 1, and pre and 24 hours post dose 2 of bortezomib) of 20-40cc each may be obtained to collect lymphocytes for analysis of gene expression on microarray and proteomic analysis. In these patients a cbc/diff will be obtained at the time of research blood collection. The amount of blood that may be drawn from adult patients for research purposes shall not exceed 10.5 mL/kg

or 550 mL, whichever is smaller, over any eight week period. Lymphapheresis may be performed pre-treatment in all patients with leukemic MCL at the NCI and may be repeated 12-24 hours after the first or second bortezomib dose instead of the timed blood draws. Tissue samples are to be stored at -80º C and shipped on dry ice.

D- Clinical PET scans may be performed at other time points throughout this protocol if the investigator deems it medically necessary.

E- If research biopsies are obtained, research PET scan will be within 24 hours of the second biopsy. If no research biopsies are obtained, the PET scan may be omitted. If a patient has evidence of tumor reduction between day 8 and 21, a repeat PET scan may be done at the end of Part A cycle.

4.4.1.1 Microarray and Proteomic analysis

The pretreatment lymph node biopsy (optional) will be used to perform all standard diagnostic tests. In addition we will extract RNA and protein for research studies. The second biopsy (optional) obtained during Bortezomib monotherapy will be used for research studies only. In cases where there is peripheral blood involvement by mantle cells, timed blood collections or apheresis may be carried out in addition to a lymph node biopsy. Standard diagnostic tests will be sent and samples will be taken for microarray analysis as above. Microarray and proteomic analysis may be performed on lymph node biopsies, serum, whole blood samples and apheresis collected for research. In protein extracts of tumor cells pre and during therapy we aim to determine activity of key regulatory proteins such as components of the NF-kappa B signal transduction pathway, the levels of cell cycle inhibitors such as $p21^{cip}$ and $p27^{kip-1}$ and the p53 stress response. In addition, we may determine serum levels of proteins that play a role in lymphocyte function including chemokines and cytokines. Where possible we may initiate studies that aim at characterizing changes in protein levels on a global scale

4.4.1.2 Timing of the second biopsy

The optimal timing for the on-treatment biopsy can only be estimated at this time. Experiments in cell lines indicate that after 6 hours of proteasome inhibition there are many highly significant changes in gene expression. On the other hand, in a recent study on the effect of Fludarabine on chronic lymphocytic leukemia cells maximal effects required at least 24 hours to develop and the most robust response was observed between 48 and 96hours from start of therapy (Rosenwald, 2004). Thus, the optimal time point to detect changes in response to bortezomib could range from 6 hours after the initial infusion to days after the second infusion. We will perform the second biopsy 12-24 hours after the first or second infusion for several reasons: first, the relatively long time interval will make it likely that we will be able to detect effects of proteasome inhibition on signaling pathways such as the NF-kB pathway that may not be immediately interrupted by bortezomib; second, we will be better able to detect cumulative changes in protein levels and third, scheduling the second biopsy at these time points minimizes interference with an orderly treatment cycle. We plan to analyze a first set of biopsies to determine whether there are any changes in gene expression detectable in these samples. If there are no or only minimal changes in gene expression we will move the biopsy time point. From the timed blood samples in patients with leukemic MCL we will derive a better understanding of the kinetics of molecular changes in the tumor cells on bortezomib therapy. This data will help determine the optimal time point for lymph node biopsies.

4.4.1.3 Tissue immunohistochemistry

- Tumor tissue will be analyzed by immunohistochemistry. RT-PCR may be performed on tumor samples to correlate changes in gene expression.
- Tumor tissue may be stored for future research assays which are related to this study and do not pose an increase in patient risk.

4.4.1.4 Genome–wide Methylation Analysis

Genomic DNA (gDNA) will be prepared and digested using HPAII and MSPI enzymes from coded tumor samples from enrolled MCL patients. Digested DNA products are then amplified using ligation mediated PCR and hybridized to a custom high density oligonucleotide Microarray. Methylation array testing will be done in duplicate and analyzed using an extensive quality control, primary analysis and normalization pipeline based on the R statistical package and developed by statisticians and bio-informaticians of the Einstein Epigenomics program. Data from all patients will be analyzed by supervised clustering to determine differentially methylated genes in MCL and any correlation for promoter methylation to response to bortezomib. We will confirm results at individual loci by mass spectrometric analysis using the MassArray machine.

4.4.1.5 Biopsy Procedure

Standard techniques will be used for pre-treatment and post-treatment percutaneous biopsies which may include CT and / or ultrasound guided biopsy. In some cases, such biopsies may be expedited and facilitated with the use of navigation tools such as an automated laser angle selector connected to CT scan, or a standard needle guide connected to a protractor to determine which exact angle the biopsy needle will be inserted.

These guiding techniques may occur as maneuvers to facilitate the biopsy, which will take place in the usual conventional fashion, with standard, disposable, conventional spring-loaded biopsy equipment. Such guiding techniques may add to the reliability of tissue acquisition from specific spatial coordinates of a tumor target. Accurate spatial tissue acquisition may lead to more reliable, accurate and precise tissue characterization, which in turn should be more reproducible. When performing sequential biopsies, the knowledge of sampling location within a tumor may actually help avoid multiple needle punctures or repeat procedures, as might occur when samples are obtained from necrotic regions or regions without high quality mRNA (cDNA) for microarrays or sufficient protein for proteomics analysis.

Sequential biopsy has been used routinely at the NCI as a research and prognostic tool, as well as pathway to surrogate biological markers for tumor response, prognosis, or susceptibility to specific targeted agents. Sequential biopsies are usually performed under the assumption that all tumor is created equal (mRNA and proteins) at a given time point, which is clearly an oversimplification with broad ramifications. Precision biopsy techniques might normalize some of the spatial heterogeneity inherent to tumors. Such normalization (as occurs when repeat biopsies are taken from precisely the same location of tumors) could minimize the added noise from the interpretation of already voluminous and noisy data (as in the case of the gene microarrays).

The correlation and anatomic mapping of tumor biology to multiparametric imaging may improve the search for reliable imaging surrogates for tumor biology or behavior. Image fusion

with CT/PET or image registration with electromagnetic tracking allows for the biopsies to be performed with multimodality guidance. This allows PET scans or functional dynamic MRI to provide the guidance for biopsy needle placement, such that biopsies may be taken from specific areas of tumor that have higher metabolic activity on FDG PET for example.

We will use precision techniques like automated laser pointers, to facilitate being able to reliably sample a tumor from precisely the same region on repeated biopsies. This should maximize our chances of detecting significant alterations in tumor biology and protein or gene expression signatures (such as the proliferation signature or upregulation of cell cycle inhibitors).

4.4.2 Part B: DA-EPOCH-RB

Studies	Pre-therapy [A]	Day -1 or Day 1 of cycles 2-6	Twice weekly each cycle [F]	End of cycle 4 and 6 (+/- 1 day)	End of cycle 6 (+/- 2 days)
Hx; PE; VS; PS	X	x			
Tumor Measurement	X			x	
CBC/diff	X	x	x		
Electrolytes, Creatinine, BUN, ALT, AST, Bilirubin, LDH, Ca^{++}, Phos, Mg	X	x			
Isohemagglutinin titer, Immunoglobulin Free Light Chains, Serum Protein Electrophoresis,	X				X
EBV viral load					x
TBNK, 24 cc red & green CPT tubes	X				x
Anti-varicella zoster virus					x
CT chest/abd/pelvis	X			x	
Clinical PET scan					x
Peripheral blood flow cytometry, Bone marrow biopsy & aspirate[B]	X				X[B]
Colonoscopy[C]					x
10 cc whole blood for storage[D]	X[E]				x
10 cc red top for serum storage	X	X			X

A. Pre-DA- EPOCH-R-B evaluation.

B. If patient proceeds directly to Part B, without Part A, then peripheral blood flow cytometry and bone marrow biopsy are to be performed pre-treatment. Repeat both tests if positive at diagnosis.

C. Repeat colonoscopy after cycle 6 if positive at initial diagnosis (or not performed) and not medically contraindicated.

D. 10 cc whole blood for DNA extraction. Draw blood in 10 cc tube with EDTA as preservative. Call Dr. Adrian Wiestner's lab for pick-up: 301-451-7135.

E. May be requested in patients who presented with leukemic MCL.

F. Twice weekly (e.g., on Monday & Thursday or Tuesday & Friday to assure that counts are checked every three to four days).

4.4.3 Part C: Bortezomib maintenance versus observation with treatment at progression.

Studies	Pre-Cycle 1	Day 1(+/- 1 day) each cycle	Day 4, 8 and 11 of each cycle[A]	Every 4 months in both arms[B]	Follow up[E, F]
Hx; PE; VS; PS		x		x	x
Tumor Measurement				x	
CBC/diff		x	x	x	x
Electrolytes, Creatinine, BUN, ALT, AST, Bilirubin, LDH, Ca^{++}, Phos, Mg		x		x	x
Immunoglobulin Free Light Chains, Serum Protein Electrophoresis,					x
TBNK, 24 cc red & green CPT tubes[G]				x	
CT chest/abd/pelvis	x[H]			x	x
Colonoscopy[C]					
Bone marrow biopsy & aspirate[C]					
Tumor biopsy and/or apheresis[D]					
10 cc red top for serum storage		x		x	x

A- For patients undergoing treatment on the maintenance arm or in patients with progression on the observation arm. Draw CBC on these days only if Day 1 platelets <50, 000/mcL or as clinically indicated.

B- Restage every 4 months (+/- 1 week) in patients undergoing treatment and in patients on observation during treatment or observation period.

C- A repeat bone marrow biopsy and colonoscopy may be done in patients who progress. Repeat if patients receive bortezomib after progression on the observation arm and only if they achieved a second CR by CT scan or at end of treatment.

D- When possible, a repeat lymph node biopsy and/or lymphapheresis will be obtained in patients who progress after DA-EPOCH-RB.

E- Patients who are not randomized to treatment or observation, follow-up to occur every 4 months (+/- 2 weeks) for 2 years, then every 6 months (+/- 2 weeks) for 2 years, and then yearly (+/- 4 weeks) thereafter. Patients who are randomized to treatment or observation on Part C will proceed to follow-up after completion of treatment or observation. Follow-up to occur every 6 months (+/- 2 weeks) for 2 years, and then yearly (+/- 4 weeks) thereafter.

F- After the sixth year, patients may be followed by local oncologist who agrees to send office visit notes and lab results to Research Team. Records should be sent via fax to Research Nurse Office 301.480.1105, attention Dr. Wyndham Wilson. Patients who are not randomized to treatment or observation on part C will proceed directly to follow up. Patients who are taken off-study will continue to be followed for survival using publicly available information, such as the Social Security Death Index.

G- This test to be done only up to 2 years s/p the end of Part B.

H- Pre-Cycle 1 CT scan may be done up to 2 weeks before beginning Part C.

4.5 POST-TREATMENT EVALUATIONS

4.5.1 Patients who are not randomized to treatment or observation on Part C will proceed directly to follow up. Follow-up to occur every 4 months (+/- 2 weeks) for 2 years, then every 6 months (+/- 2 weeks) for 2 years, and then yearly (+/- 4 weeks) thereafter.

4.5.2 Patients who are randomized to treatment or observation on Part C will proceed to follow-up after completion of treatment or observation. Follow-up to occur every 6 months (+/- 2 weeks) for 2 years, and then yearly (+/- 4 weeks) thereafter.

4.5.3 For all groups: after the sixth year, patients may be followed by local oncologist who agrees to send office visit notes and lab results to Research Team. Records should be sent via fax to Research Nurse Office 301.480.1105, attention Dr. Wyndham Wilson. Adverse event data that occurs during the follow-up period that is unrelated to study treatment will not be reported. Patients who are taken off-study will continue to be followed for survival using publicly available information, such as the Social Security Death Index.

4.5.4 Patients who are taken off-study will continue to be followed for survival using publicly available information, such as the Social Security Death Index.

4.6 OFF TREATMENT CRITERIA

- Completion of protocol therapy
- Progressive disease requiring non-protocol therapy
- Participant requests to be withdrawn from active therapy
- Investigator discretion

4.7 OFF STUDY CRITERIA

- Voluntary withdrawal
- Institution of non-protocol treatment
- Non-compliance which affects safety or endpoints of the study
- Death
- Physician's determination that withdrawal is in the patient's best interest

4.8 OFF PROTOCOL THERAPY AND OFF-STUDY PROCEDURE

Authorized staff must contact the Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off-study. A Participant Status Updates Form from the website (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

5 SUPPORTIVE CARE

5.1 PROPHYLAXIS OF PNEUMOCYSTIS JIROVECI (FORMERLY, CARINII)

All patients will receive prophylaxis for Pneumocystis during EPOCH chemotherapy. Trimethoprim/sulfamethoxazole 1 DS P.O. QD for three days each week. Monday, Wednesday,

Friday is the preferred schedule. Patients allergic to either component may receive other standard treatments.

5.2 PROPHYLAXIS FOR HEPATITIS B REACTIVATION.

Patients who are positive for Hepatitis B core antibody (anti-HBc) and not acutely infected are at varying risk for reactivation of Hepatitis B. These patients will have quantitative PCR testing performed for Hepatitis B virus. Additionally, patients at high and moderate risk will receive appropriate prophylaxis for hepatitis B reactivation, e.g., lamivudine 100mg PO daily to continue until 8 weeks after last chemotherapy with repeat quantitative PCR performed 4-8 weeks after stopping prophylaxis.

anti-HBc	HBsAg	Anti-HBs	Risk	HBV PCR	Prophylaxis
+ or −	+	+ or −	High	pre-tx, post 2, 4, 6 cycles	Yes
+	−	−	Moderate	pre-tx, post 2, 4, 6 cycles	Yes
+	−	+	Low	pre-tx, post 3, 6 cycles	No, if PCR neg

5.3 PROPHYLAXIS FOR HERPES SIMPLEX AND/OR HERPES ZOSTER

All patients will receive prophylaxis for Herpes Simplex and/or Herpes Zoster virus infection during Part B EPOCH chemotherapy, using ValAcyclovir 500 mg twice daily, Acyclovir 400 mg twice daily or Famciclovir 500 mg twice daily.

5.4 RECOMMENDATIONS FOR MANAGEMENT OF GASTROINTESTINAL ISSUES:

5.4.1 Prevention and/or treatment of nausea and vomiting prior to and during chemotherapy:

- Ondansetron 24 mg PO x1 dose 30–60 min prior to Cyclophosphamide, followed by Ondansetron 8 mg every 12 hours for 3 more days (5 or 6 doses)
- Prochlorperazine 10 mg PO every 6 hours PRN for nausea or vomiting

5.4.2 Prevention of symptoms of gastroesophageal reflux disease (GERD) and other conditions caused by excess stomach acid:

- Omeprazole 20 mg PO once daily

5.4.3 Prevention and/or treatment of constipation:

- Docusate Sodium 50 mg + Sennosides 8.6 mg 1 tablet PO twice daily.
- Lactulose 10-20 grams (15–30 mL) PO every 6 hours PRN for constipation

6 BIOSPECIMEN COLLECTION

6.1 PROCEDURES FOR COLLECTING TUMOR BIOPSIES AND/OR PERIPHERAL BLOOD CELLS

1. Orders for tumor biopsies, research blood samples and lymphapheresis collections should be placed in CRIS (Clinical Research Information System, Clinical Research Center, NIH, Bethesda, MD)

2. Tumor biopsies will be submitted in native condition to the Department of Pathology, CCR, NIH and handled according to routine procedures. Material released for research studies will be documented on form NIH 2803-1. Initial processing of samples for research will depend on the size of the tumor biopsy. For core biopsies, the research sample will typically consist of 2 cores in a microcentrifuge vial snap frozen on dry ice. Surgical lymph node biopsies may in addition be processed for single cell suspension, additional vials of snap frozen tissue and OCT embedded tissue.
3. Lymphapheresis is performed in the Department of Transfusion Medicine, and blood will be collected in the phlebotomy suite, on a clinical ward, or in an outpatient clinic of the CRC, NIH. Samples will be transferred to the research laboratory at room temperature. Cells will be separated by Ficoll density gradient centrifugation and only mononuclear cells will be harvested, processed, analyzed, and stored.
4. Tumor and normal blood cells may be viably frozen, typically at concentrations of 20-100x10^6/mL in FCS with 10% DMSO using a temperature controlled freezing process to optimize sample viability. Samples will be transferred to Nitrogen tanks for long term storage.
5. Tumor and normal blood cells can be further processed. Additional purification may be carried out by selection with magnetic beads binding to appropriate surface molecules, typically CD19. For analysis cells may be lysed to obtain RNA (using Qiagen manufactured kits are similar) or proteins (salt and/or triton containing buffers with addition of protease and phosphatase inhibitors). Integrity of RNA is monitored by gel electrophoresis and concentration of RNA or protein is measured spectrophotometrically.
6. Research sample inventory and storage. All research samples are assigned a unique number and cataloged. Viably frozen cells are stored in a temperature controlled, alarm secured Nitrogen tank. Tumor biopsies and processed biologic material (RNA, protein) is stored at -80ºC in a temperature controlled, alarm secured -80ºC freezer.

6.2 CORRELATIVE STUDIES

6.2.1 Molecular and Genomic Studies

Samples will be analyzed to assess the effects of treatment on molecular and genetic changes within the cancer genome, and to correlate these with clinical outcomes (e.g., microarray, proteomics, and other genetic and/or mutational analyses). Although direct analysis of germline DNA is not planned, normal genome could be analyzed for comparison with other testing or inadvertently analyzed within other samples, or as part of future analyses.

NOTE: Effective with Amendment O, the option for exploratory genetic testing was added and this protocol amended accordingly, including revised informed consent/procedures.

6.2.2 Methylation/Epigenetic Testing

Coded samples consisting of extracted DNA or cellular material from either frozen blood cells or lymph node biopsies will be sent to Samir Parekh, MD for genome-wide methylation analysis and epigenetic testing. The address to send the samples to is:

Samir Parekh, M.D.
Department of Oncology Hoffheimer 1

Montefiore Medical Center
111 East 210th Street, Bronx, NY 10467
Phone: 718.920.4826

6.2.3 Circulating Tumor DNA

Coded, de-identified frozen or formalin fixed and paraffin embedded (FFPE) human tissue and serum and/or plasma samples will be sent to Adaptive Biotechnologies Corp. It is of research interest to determine if circulating tumor DNA before, during or after therapy is predictive of long-term disease survival. Adaptive Biotechnologies Corp will assess whether immune repertoire data (B-cell immunoglobulin receptor sequences) from the Human Material can be used as biomarkers that correlate with disease-free survival. Adaptive Biotechnologies Corp will use a proprietary method, Immune Cell Receptor Sequencing (ICRS) platform, for amplifying and analyzing immune cell receptor sequences, allowing unprecedented sensitivity and specificity. Data from experiments conducted by Adaptive Biotechnologies Corp using the Human Material will be provided to NCI and such data provided by Adaptive Biotechnologies Corp to NCI may be used by NCI for any purpose. The address to send the samples to is:

Adaptive Biotechnologies Corp
1551 Eastlake Ave E
Suite 200
Seattle, WA 98102

6.3 SAMPLE STORAGE, TRACKING AND DISPOSITION

All specimens obtained in the protocol are used as defined in the protocol. Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without IRB notification and an executed MTA.

6.3.1 Procedures for stored specimens

- The Clinical Support Laboratory, Leidos Biomedical Research, Inc.-Frederick, processes and cryopreserves samples in support of IRB-approved, NCI clinical trials. All laboratory personnel with access to patient information annually complete the NIH online course in Protection of Human Subjects. The laboratory is CLIA certified for anti-IL15 and certain cytokine measurements, and all laboratory areas operate under a Quality Assurance Plan with documented Standard Operating Procedures that are reviewed annually. Laboratory personnel are assessed for competency prior to being permitted to work with patient samples. Efforts to ensure protection of patient information include:
- The laboratory is located in a controlled access building and laboratory doors are kept locked at all times. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.
- Hard copy records or electronic copies of documents containing patient information are kept in the locked laboratory or other controlled access locations.
- An electronic database is used to store information related to patient samples processed by the laboratory.
- The database resides on a dedicated program server that is kept in a central, locked computer facility.

- The facility is supported by two IT specialists who maintain up to date security features including virus and firewall protection.
- Program access is limited to specified computers as designated by the laboratory director. Each of these computers has a password restricted login screen.
- The database sample entry program itself is accessed through a password protected entry screen.
- The database program has different levels of access approval to limit unauthorized changes to specimen records and the program maintains a sample history.
- Upon specimen receipt each sample is assigned a unique, sequential laboratory accession ID number. All products generated by the laboratory that will be stored either in the laboratory freezers or at a central repository facility are identified by this accession ID.
- Inventory information will be stored at the vial level and each vial will be labeled with both a sample ID and a vial sequence number.
- Vial labels do not contain any personal identifier information.
- Samples are stored inventoried in locked laboratory freezers and are routinely transferred to the NCI-Frederick repository facilities for long term storage.
- Access to stored clinical samples is restricted. Investigators establish sample collections under "Source Codes" and the investigator responsible for the collections, typically the protocol Principal Investigator, specifies who has access to the collection. Specific permissions will be required to view, input or withdraw samples from a collection. Sample withdrawal requests submitted to approved laboratory staff by anyone other than the repository source code owner are submitted to the source code owner for approval. The repository facility will also notify the Source Code holder of any submitted requests for sample withdrawal.
- It is the responsibility of the Source Code holder (generally the NCI Principal Investigator) to ensure that samples requested and approved for withdrawal are being used in a manner consistent with IRB approval.
- The Clinical Support Laboratory does perform testing services that may be requested by clinical investigators including, but not limited to, immunophenotyping by flow cytometry and cytokine testing using ELISA or multiplex platforms.
- When requests are submitted by the NCI investigator for shipment of samples outside of the NIH it is the policy of the laboratory to request documentation that a Material Transfer Agreement is in place that covers the specimen transfer. At a minimum, the lab needs confirmation that one has been executed or an exception was granted from an office authorized to make such exceptions, e.g. NCI Technical Transfer Center. The laboratory does not provide patient identifier information as part of the transfer process but may, at the discretion of the NCI investigator, group samples from individual patients when that is critical to the testing process.
- The NCI investigator responsible for the sample collection is responsible for ensuring appropriate IRB approvals are in place and that a Material Transfer Agreement has been executed prior to requesting the laboratory to ship samples outside of the NIH.

6.3.2 Study Completion, Future Use and Sample Destruction

The study will remain open so long as sample or data analysis continues. Following completion of the planned analyses, samples will remain in storage as detailed above.

Tissue specimens and derived tissue lysates, RNA and DNA collected in the course of this research project may be banked and used in the future to investigate new scientific questions related to this study that are not expressly stated in the present protocol. However, this research may only be done if the risks of the new questions and the proposed research have undergone prospective IRB review and approval. If new risks are associated with the research the Principal Investigator must amend the protocol and obtain informed consent from all research subjects.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved; additionally, the samples will be destroyed (or returned to the patient, if so requested) and reported as such to the IRB.

Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (e.g., broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB, the NCI Clinical Director, and the office of the CCR, NCI, as appropriate.

6.4 GENETIC/GENOMIC ANALYSIS

6.4.1 Description of the scope of genetic/genomic analysis

At any point in the analyses, normal genome could be analyzed for comparison with other testing (e.g., mutational analyses, cancer genome).

6.4.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized

Confidentiality for genetic samples will be maintained as described (Sections **6.3.1** and **6.4.2**). In addition, a Certificate of Confidentiality has been obtained for this study.

6.4.3 Management of Results

Subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists).

6.4.4 Genetic Counseling

Subjects who remain on the study will be contacted with a request to provide a blood sample to be sent to a CLIA certified laboratory. If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH to have genetic education and counseling to explain this result; at the time of any such event(s), these activities will be funded by the NCI/CCR in consideration of the specific circumstances. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense).

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

7 DATA COLLECTION AND EVALUATION

7.1 DATA COLLECTION

7.1.1 Principal Investigator/Research Team

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of at least possibly related to the agent/intervention should be recorded and reported as per sections **8.2** and **8.3**.

All data will be collected in a timely manner and reviewed by the PI, the study chairman or a lead associate investigator for toxicity. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be reported, as appropriate.

The principal investigator will review adverse events and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

End of study procedures: Data will be stored according to HHS, FDA and NIH Intramural Records Retention Schedule regulations as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

7.1.2 Data Collection Clarifications

7.1.2.1 Abnormal Laboratory Values

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact

- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

7.2 DATA SHARING PLANS

7.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

_X_ Coded, linked data in an NIH-funded or approved public repository.

_X_ Identified data in BTRIS (automatic for activities in the Clinical Center)

How and where will the data be shared?

Data will be shared through:

_X_ An NIH-funded or approved public repository: ClinicalTrials.gov.

_X_ Another public repository: dbGaP.

_X_ BTRIS (automatic for activities in the Clinical Center)

_X_ Publication and/or public presentations.

When will the data be shared?

_X_ At the time of publication or shortly thereafter.

7.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

7.3 EVALUATION OF CT SCAN MEASUREMENTS

CT Scans are used to assess baseline tumor burden and to determine tumor response. The following measurement guidelines are intended to ensure that tumor measurements and assessments of response are conducted consistently throughout the study.

7.3.1 Part A

Baseline (Pre-treatment) tumor measurements will be obtained using the CT Scan performed prior to the initiation of any Protocol Therapy. These pre-treatment baseline measurements will be recorded and used as the cumulative baseline product when restaging post Part A on cycle 1 Day 21 after the administration of single agent Bortezomib

7.3.2 Part B

The Cumulative Product which was calculated after completion of Cycle 1 Part A will become the baseline tumor measurement for Pre-Part B. This product also serves as the Cumulative Baseline Product for subsequent restaging CT Scans for Part B, i.e. post cycle 4 and Cycle 6.

If it is determined that the patient is to bypass Part A and proceed directly to Part B, then pre-treatment baseline measurements will be obtained and recorded as stated in Part A.

7.3.3 Part C

The Cumulative Product which was calculated after completion of Cycle 6 Part B will become the baseline tumor measurement for Pre-Part C. The CT scan for Pre Part C will be performed when the patient is evaluated for Randomization to Bortezomib maintenance versus observation occurs. This occurs approximately 12 weeks after the completion of Part B. The tumor measurements obtained at this time point will serve as the Cumulative Product for Pre-Part C and subsequent Cumulative baseline products for further treatment and restaging CT Scan evaluations.

7.4 RESPONSE CRITERIA

7.4.1 Response criteria for lymphomas

Responses must last for at least 4 weeks off treatment.

1.1.1.2 Complete response (CR)

Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities (e.g. LDH) definitely assignable to the lymphoma. All lymph nodes must have regressed to normal size (≤ 1.5 cm in greatest diameter if > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in greatest diameter must have decreased to ≤ 1 cm or by more than 75% in the sum of the products of the greatest diameters (SPD). Spleen, if considered to be enlarged before therapy, must have regressed in size and not be palpable on physical examination. The bone marrow must show no evidence of disease by histology. Lymphocyte aggregates within the bone marrow must be negative for B-cell markers (e.g. L26).

Flow cytometric, molecular or cytogenetic studies will not be used to determine response.

1.1.1.3 Complete response unconfirmed (CRu)

As per CR criteria except that if a residual node is > 1.5 cm, it must have regressed by > 75% in SPD. Lymphocyte aggregates within the bone marrow must be negative for B-cell markers (e.g. L26).

1.1.1.4 Partial response

≥ 50% decreased in SPD of 6 largest dominant nodes or nodal masses. No increase in size of nodes, liver or spleen and no new sites of disease. Splenic and hepatic nodules must regress by ≥ 50% in the SPD. Bone marrow is irrelevant for determination of a PR.

1.1.1.5 Definition of progressive disease (PD):

Defined by at least one of the following: ≥50% increase in the sum of the products of at least two lymph nodes appearance of new lymph nodes, ≥50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin, appearance of new palpable hepatomegaly or splenomegaly that was not previously present, ≥50% increase in the absolute number of circulating lymphocytes.

1.1.1.6 Definition of stable disease

(SD) will be characterized by not meeting any of the criteria outlined above.

7.5 TOXICITY CRITERIA

The NCI Common Toxicity Criteria version 3.0 will be used for toxicity and adverse event reporting. A copy of the CTC version 3.0 can be downloaded from http:/ctep.cancer.gov/reporting/ctc.html. Dose limiting toxicity is defined in section **4.3**.

8 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

8.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

8.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

8.1.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

8.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

8.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

8.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

8.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to
  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.2 NCI-IRB AND CLINICAL DIRECTOR (CD) REPORTING

8.2.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report to the NCI-IRB:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

8.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
   - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
   - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
   - All Grade 5 events regardless of attribution;
   - All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

8.2.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

8.3 PROCEDURES FOR AE AND SAE REPORTING TO MANUFACTURER

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. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. AEs which are serious must be reported to Millennium Pharmacovigilance (or designee) from the first dose of bortezomib up to and including 30 days after administration of the last dost of bortezomib. Any SAE that occurs at any time after completion of bortezomib treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to 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).

Since this is an investigator-initiated study, the principal investigator Dr. Wyndham Wilson, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB. Regardless of expectedness or causality, all SAEs must also be reported 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. See below for contact information for the reporting of SAEs to Millennium Pharmacovigilance.

As the study sponsor, Dr. Wilson will be the single point of contact with Millennium for safety reporting. Dr. Wilson will require all local physicians operating under the protocol for all patients (i.e., those from the NCI study site) to report SAEs to Dr. Wilson immediately. Dr. Wilson will be responsible for ensuring that all local physicians are aware of SAE reporting requirements and that they send such reports to Dr. Wilson.

The sponsor-investigator should fax the SAE Form within five calendar days after becoming aware of the event. Follow-up information on the SAE may be requested by Millennium. 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. Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

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

SAE and Pregnancy Reporting Contact Information (North America Reporting)

Millennium Pharmacovigilance
SAE and Pregnancy Reporting Contact Information
FAX Number: 1-800-963-6290
Email: TakedaOncoCases@cognizant.com

8.4 PROCEDURES FOR REPORTING DRUG EXPOSURE DURING PREGNANCY AND BIRTH EVENTS

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must fax a completed Pregnancy Form (Section **0**) to the Millennium Department of Pharmacovigilance or designee (see Section **8.3**). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form (Section **0**) to the Millennium Department of Pharmacovigilance or designee (see Section **8.3**). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

All SAEs that are reported to Millennium must also be forwarded to the Regulatory Affairs Branch, CTEP via email to ctepsupportae@tech-res.com.

9 STATISTICAL CONSIDERATIONS

The primary objective of this study is to determine in a small, randomized study whether there could be a statistically significant difference in progression free survival between patients with mantle cell lymphoma who are randomized to receive EPOCH-RB followed by maintenance Bortezomib versus observation alone.

In order to detect a difference in progression free survival with a two-tailed 0.05 alpha level, simulations were performed to determine the sample size. The following assumptions were made:

Accrual will take place over 24 months. It will be assumed that greater than 90% of patients who enter the trial will experience a PR or CR and hence be eligible for randomization. The observation arm will be assumed to have a median progression free survival of approximately 24 months, and will follow an exponential failure distribution with a 0.0289 hazard rate throughout.

This was based on results obtained from the single arm trial of EPOCH-R + vaccine in mantle cell lymphomas in which the median progression free survival of 26 patients was approximately 24 months, and assuming that the observation arm will have similar results. It will be assumed that the maintenance therapy progression free survival curve will decrease less rapidly than the observation curve, and then plateau. For purposes of calculation, the maintenance therapy curve will be assumed to have an exponential failure rate of ½ that of the other curve for the first 24 months (lambda=0.0144), resulting in approximately 71% PFS at 24 months. It will further be assumed that the curve will flatten out such that it attains 51% PFS by 48 months (lambda=0.0137 from 24 to 48 months) and finally levels out to 50% PFS at 72 months (lambda=0.0008 from 48 to 72 months). Under these assumptions, using 10000 simulations with nQuery Advisor, with 36 patients per arm (total 72), there is 81% power to detect the differences as stated above with a two-tailed 0.05 alpha level test. In order to enroll 72 patients who are able to be randomized, the accrual ceiling will be set at 80 patients, and could be expanded by amendment if necessary to enroll 72 randomized subjects.

The primary evaluation will be a Kaplan-Meier analysis with a two-tailed log rank test. Since accrual is expected to take place rapidly for this trial, and progression free survival probabilities well past 2 years will be of interest to examine, there will be no formal provision for early termination of this trial. Also, because the two arms differ mainly in the use of maintenance therapy vs. standard duration of agents and then observation, it is not expected that there will be differences in toxicity between the two arms. Furthermore, the study will not be blinded and is of limited size. Thus, there will not be a need for formal DSMB evaluation of this study. The PI will monitor the trial in conjunction with the study statistician and will report all adverse events in a timely fashion to the IRB.

Overall survival (OS) will also be determined for both randomized arms of the trial and compared beginning at the date of randomization. Because this is a relatively indolent disease, statistically significant differences in OS will be difficult to observe with only 72 randomized subjects. However, the results obtained will be reported, along with appropriate 95% confidence intervals.

Secondary evaluations will include, but not be limited to the following: Clinical response will be evaluated on all 80 patients who receive the initial cycle of Bortezomib alone, and a 95% confidence interval will be formed about the observed response proportion. Biopsies taken pre-treatment and post this single cycle of Bortezomib will yield gene expression data and microarray data that can be evaluated both to determine if pre-treatment expression levels or gene patterns can be found which differ according to degree of clinical response noted (CR vs. <CR, or CR+PR vs. SD+PD), or to see if changes in expression levels or changes in microarray patterns can be used to predict response to DA-EPOCH-RB. With a total of up to 80 subjects having this data available, even with 90% of patients responding and 10% not responding, there would be over 80% power to detect a 1.2 standard deviation difference between response categories in an individual gene with its expression level evaluated, using a 0.05 alpha level two tailed t-test. Since a large number of such tests may be performed, the power to detect individual differences at that level may be reduced, but since these analyses will be done with exploratory intent, the results obtained will be used to guide future research. Analyses will tend to focus on cell cycle regulatory genes to see if changes in their expression levels and patterns are associated with clinical response, PFS, and OS.

In addition, response and clinical toxicity to DA-EPOCH-RB will be determined and reported descriptively, and a 95% confidence interval about the observed fraction of patients who have a CR or a CR+PR will be formed. As well, time to progression after progressing on the observation arm will be determined using the Kaplan-Meier method. This will be reported descriptively, using appropriate 95% confidence intervals. With 24 months to accrue 80 patients, in order to yield 72 randomized subjects, approximately 3 patients per month are expected to enroll in an average month.

10 COLLABORATIVE AGREEMENTS

10.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)

The agent(s) (hereinafter referred to as "Agent(s)"), PS-341, used in this protocol is provided to the NCI under a CRADA with Millennium (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment, Diagnosis and Centers. Therefore, the following obligations/guidelines apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and should be maintained as such by the investigators.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different CTAs or CRADAs, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data."):
    a. NCI must provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational agent.
3. The NCI encourages investigators to make data from clinical trials fully available to Collaborator(s) for review at the appropriate time (see #5). The NCI expects that clinical trial data developed under a CTA or CRADA will be made available exclusively to Collaborator(s), and not to other parties.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for cooperative group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. An additional 30 days may be requested in order to ensure that confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts should be provided to Collaborator(s) for courtesy review following submission, but prior to presentation at the meeting or publication in the proceedings. Copies of any manuscript and/or abstract should be sent to the following address and the Regulatory Affairs Branch will then distribute them to Collaborator(s):

   Regulatory Affairs Branch, CTEP, DCTDC, NCI
   9609 Medical Center Drive
   Bethesda, MD 20892
   email: info@ctep.nci.nih.gov

10.2 MATERIAL TRANSFER AGREEMENTS (MTA)

10.2.1 Adaptive Biotechnologies Corp

An MTA has been executed to allow the samples described in Section **6** to be shipped to Adaptive Biotechnologies Corp. (MTA #33895)

10.2.2 Montefiore Medical Center

An MTA has been executed to allow the samples described in Section **6** to be shipped to Montefiore Medical Center. (MTA #25660)

11 HUMAN SUBJECTS PROTECTIONS

11.1 RATIONALE FOR SUBJECT SELECTION

Non-Hodgkin's lymphomas affect all races and genders. However, males are more likely than females to be affected and this will be reflected in the gender distribution of our cases. We have selected mantle cell lymphomas for inclusion in this trial because they are considered to be incurable with chemotherapy. Thus, they would potentially benefit from the use of a novel agent like Bortezomib combined with a chemotherapy regimen like EPOCH-R. Additionally, the administration of maintenance Bortezomib therapy could result in an improved clinical outcome. Patients under the age of 18 are excluded because mantle cell lymphoma is rare in young patients, and the inclusion of an occasional younger patient will not provide generalizable information that would justify their inclusion on this phase II study. Additionally, patients with HIV infection will be excluded due to the severe immunosuppression of this therapy, and pregnant or nursing mothers are excluded because of the potential teratogenic effects of therapy.

11.2 PARTICIPATION OF CHILDREN

Subjects under the age of 18 are excluded because mantle cell lymphoma is rare in young patients; and the inclusion of an occasional younger patient will not provide generalizable information that would justify their inclusion on this study

11.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent were excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is the prospect of direct benefit to subjects from treatment, including ongoing follow-up for detection of early relapse and to allow for the return of incidental findings of genetic testing (Sections **6.4.3** and **11.5)** all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation".

Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects meeting the above criteria that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MAS Policy 87-4 and NIH HRPP SOP 14E for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney (DPA), will be followed.

11.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

Patients may or may not obtain direct benefit from treatment with Bortezomib combined with EPOCH-R. Results from a phase I/II study of Bortezomib in combination with EPOCH shows the combination to have tolerable side effects.

The potential risks of genetic testing are as outlined in the informed consent document (included/revised with Amendment O; version date: 09/29/2017). This study has a Certificate of Confidentiality, which helps to protect patient's research information. The researchers involved in this study cannot be forced to disclose the identity or any information collected in this study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the patient or the researcher may choose to voluntarily disclose the protected information under certain circumstances. Furthermore, federal agencies may review patient's records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others. The procedures involved in this protocol, with their attendant risks and discomforts and potential benefits will be carefully explained to the patient.

11.5 RISKS/BENEFITS ANALYSIS

Patients may derive direct benefit from DA-EPOCH-R based on prior research results. Bortezomib with DA-EPOCH, may increase this benefit because it can inhibit a pathway associated with drug resistance. The potential toxicity of this combination is reasonable in relation to the potential benefit to this group of patients who have treatable diseases. Additionally, the knowledge that will be gained from this trial is potentially important and may be of direct benefit to patients.

Adults who become unable to consent are included in this protocol because the protocol offers a prospect of direct benefit. The risks and benefits of participation for adults who become unable to consent are no different than those described for less vulnerable patients.

11.6 CONSENT PROCESS AND DOCUMENTATION

Informed consent will be obtained in all patients on this trial. There will be no minors enrolled < 18 years old so that assent is unnecessary. The attached informed consent contains all elements required for consent. In addition, the Principle Investigator or his designee will provide oral consent and will be available to answer all patient questions.

11.6.1 Telephone re-consent

The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator.

12 PHARMACEUTICAL INFORMATION

12.1 BORTEZOMIB

12.1.1 Supply

Bortezomib is being supplied by Millennium Pharmaceuticals, Inc. directly to the Clinical Center Pharmacy. Dr. Wilson, as sponsor of the study, will be responsible for complete study drug accountability in accordance with good clinical practices and ensuring that the study drug is labeled for clinical trial use only.

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

12.1.2 Storage and Stability

Vials containing lyophilized BORTEZOMIB for Injection should be stored according to the label requirements. For the United States, store at USP Controlled Room Temperature which is 25ºC (77ºF); storage temperature excursions are 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 the sponsor will notify the investigator should this information be revised during the conduct of the study.

12.1.3 Preparation and Administration

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

The drug will be prepared under the supervision of a pharmacist, or appropriately qualified and trained personnel. The amount (in mg) of drug to be administered will be determined based on body surface area. Body surface area is to be calculated based on body weight using a standard calculation. The dose should be calculated on Day 1 of each cycle; the dose administered should remain the same throughout each cycle but should be recalculated at the start of the next cycle. If a patient experiences a notable change in weight within a cycle, as determined by an unscheduled weight assessment, then the patient's dose should be recalculated at that time based on clinical judgment.

The appropriate amount of bortezomib will be drawn from the injection vial and administered as an 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 bortezomib.

12.1.4 Product Destruction

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

12.1.5 Potential Risks of Bortezomib

To date, more than 436,000 patients have been treated with bortezomib in both clinical trials investigating its use in hematological malignancies and solid tumors, and in patients who were treated with commercially available bortezomib.

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

The known anticipated risks of bortezomib therapy are presented in Table 11-1 and Table 11-2. These risks are grouped according to the combined frequency observed in an integrated analysis of AEs in sponsored clinical studies of single-agent bortezomib dosed at 1.3 mg/m2 twice weekly on a 21-day schedule, in patients with multiple myeloma and mantle cell lymphoma.

12.1.6 Precautions and Restrictions

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

Female patients must meet 1 of the following:

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

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

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

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 (i.e., status post-vasectomy) must agree to 1 of the following:

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

Table 12-1 Known Anticipated Risks of BORTEZOMIB by MedDRA System Organ Class, Observed Incidence, and Preferred Term	
System Organ Class **Observed Incidence**	**Preferred Term**
Blood and Lymphatic System Disorders	
Most common	Thrombocytopenia*, anemia*
Very common	Neutropenia*
Common	Lymphopenia, pancytopenia*, leukopenia*, febrile neutropenia
Cardiac Disorders	
Common	Tachycardia, atrial fibrillation, palpitations, cardiac failure congestive*
Uncommon	Cardiogenic shock*, atrial flutter, cardiac tamponade*±, bradycardia, atrioventricular block complete, arrhythmia, cardiac arrest*, cardiac failure, arrhythmia, pericardial effusion, pericarditis, pericardial disease±, cardiopulmonary failure±
Ear and Labyrinth Disorders	
Uncommon	Deafness, hearing impaired
Eye Disorders	
Common	Blurred vision, conjunctivitis, conjunctival hemorrhage
Gastrointestinal Disorders	
Most common	Constipation, diarrhea*, nausea, vomiting*
Very common	abdominal pain (excluding oral and throat)
Common	Dyspepsia, pharyngolaryngeal pain, gastroesophageal reflux, abdominal distension, gastritis, stomatitis, mouth ulceration, dysphagia, gastrointestinal hemorrhage*, lower gastrointestinal hemorrhage*± rectal hemorrhage
Uncommon	Eructation, gastrointestinal pain, tongue ulceration, retching, upper gastrointestinal hemorrhage*, hematemesis*, oral mucosal petechiae, ileus paralytic*, ileus, odynophagia, enteritis, colitis, esophagitis, enterocolitis, diarrhea hemorrhagic, acute pancreatitis*, intestinal obstruction
General Disorders and Administration Site Conditions	
Most common	Fatigue, pyrexia
Very common	Chills, edema peripheral, asthenia
Common	Neuralgia, lethargy, malaise, chest pain, mucosal inflammation*
Uncommon	Injection site pain, injection site irritation, injection site phlebitis, general physical health deterioration*, catheter-related complication
Hepatobiliary Disorders	
Uncommon	Hyperbilirubinemia, hepatitis*±
Immune System Disorders	
Uncommon	Drug hypersensitivity, angioedema
Infections and Infestations	

Table 12-1 Known Anticipated Risks of BORTEZOMIB by MedDRA System Organ Class, Observed Incidence, and Preferred Term	
System Organ Class Observed Incidence	**Preferred Term**
Very common	Upper respiratory tract infection, nasopharyngitis, pneumonia*, Herpes zoster*
Common	Lower respiratory tract infection*, sinusitis, pharyngitis, oral candidiasis, urinary tract infection*, sepsis∗, bacteremia*, cellulitis∗, Herpes simplex, bronchitis, gastroenteritis*, infection
Uncommon	Septic shock*, catheter-related infection*, skin infection*, Herpes zoster disseminated*, lung infection∗, infusion site cellulitis, catheter site cellulitis, infusion site infection, urosepsis*, Aspergillosis*, tinea infection, Herpes zoster ophthalmic, Herpes simplex ophthalmic, meningoencephalitis herpetic±, varicella, empyema±, fungal esophagitis±
Injury, Poisoning, and Procedural Complications	
Common	Fall
Uncommon	Subdural hematoma
Investigations	
Common	Weight decreased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood alkaline phosphatase increased, liver function test abnormal, blood creatinine increased*
Uncommon	Gamma-glutamyltransferase (GGT) increased, oxygen saturation decreased*, blood albumin decreased, ejection fraction decreased*
Metabolism and Nutritional Disorders	
Very common	Decreased appetite, anorexia, dehydration*
Common	Hyperglycemia, hypoglycemia, hyponatremia, hypokalemia, hypercalcemia*
Musculoskeletal and Connective Tissue Disorders	
Very common	Bone pain, myalgia, arthralgia, back pain
Common	Muscular weakness
Uncommon	Limb discomfort
Neoplasms, Benign, Malignant, and Unspecified (including cysts and polyps)	
Uncommon	Tumor lysis syndrome*
Nervous System Disorders	
Most common	Peripheral neuropathy (including all preferred terms under the MedDRA High-level term Peripheral neuropathy NEC)
Very common	Paresthesia, dizziness excluding vertigo, headache
Common	Polyneuropathy, syncope, dysesthesia, dysgeusia, postherpetic neuralgia
Uncommon	Convulsion, loss of consciousness, ageusia, encephalopathy, paralysis*,autonomic neuropathy, reversible posterior leukoencephalopathy syndrome±, posterior reversible encephalopathy syndrome ♦

Table 12-1 Known Anticipated Risks of BORTEZOMIB by MedDRA System Organ Class, Observed Incidence, and Preferred Term	
System Organ Class **Observed Incidence**	**Preferred Term**
Psychiatric Disorders	
Very common	Anxiety, insomnia
Common	Confusional state
Uncommon	Delirium
Renal and Urinary Disorders	
Common	Renal impairment*, renal failure*, hematuria
Uncommon	Micturition disorder
Respiratory, Thoracic, and Mediastinal Disorders	
Very common	Cough, dyspnea
Common	Epistaxis, dyspnea exertional, pleural effusion*, rhinorrhea, hypoxia*, pulmonary edema*
Uncommon	Hemoptysis*, acute respiratory distress syndrome*, respiratory failure*, pneumonitis*, lung infiltration, pulmonary alveolar hemorrhage*, interstitial lung disease*, pulmonary hypertension*, pleurisy, pleuritic pain
Skin and Subcutaneous Tissue Disorders	
Very common	Rash
Common	Rash pruritic, rash erythematous, urticaria, petechiae
Uncommon	Cutaneous vasculitis, leukocytoclastic vasculitis±
Vascular Disorders	
Common	Hypotension*, orthostatic hypotension
Uncommon	Cerebral hemorrhage*
Source: VELCADE® Investigator's Brochure Edition 16. 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. ♦ Effective MedDRA update to version 14.0, the term 'reversible posterior leukoencephalopathy syndrome' updated to 'posterior reversible encephalopathy syndrome (PRES)'.	

Table 112-2 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	
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	

Table 112-2 Reports of Adverse Reactions From Postmarketing Experience	
System Organ Class Preferred Term	**Observed Incidence[a]**
Acute febrile neutrophilic dermatosis	Unknown
Toxic epidermal necrolysis	Unknown
Source: VELCADE® Investigator's Brochure Edition 16. 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 bortezomib include hepatic failure and QT prolongation. Fatal outcomes have been reported.
Women of childbearing potential should avoid becoming pregnant while being treated with bortezomib. Genotoxicity testing has shown that bortezomib is negative in the in vitro Ames assay and in the in vivo micronucleus assay, but it is a clastogen in the in vitro chromosomal aberration assay.

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

12.1.7 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
1-866-835-2233 (US and International)

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 **8.3**).

Bortezomib should be given prior to the rituximab infusion.

12.2 RITUXIMAB

Refer to the FDA approved package insert for complete product information.

12.2.1 Supply

Commercially available in single-use vials containing 10 mL (100 mg) or 50 mL (500 mg) of rituximab solution at a concentration of 10 mg/mL.

12.2.2 Storage

Rituximab vials should be stored in a secure refrigerator at 2º to 8°C.

12.2.3 Preparation

Rituximab will be diluted to a final volume of 0.9% Sodium Chloride or 5% Dextrose Injection to prepare a standard product with concentration of 2 mg/ml. Caution should be taken during the preparation of the drug, as shaking can cause aggregation and precipitation of the antibody.

12.2.4 Stability

After dilution, rituximab is stable at 2-8 degrees C (36-46 degrees F) for 24 hours and for an additional 24 hours at room temperature.

12.2.5 Administration

A peripheral or central intravenous line will be established. During rituximab infusion, a patient's vital signs (blood pressure, pulse, respiration, temperature) should be monitored according to the standard of care. Medications readily available for the emergency management of anaphylactoid reactions should include: epinephrine (1:1000, 1 mg/mL) for subcutaneous injection, diphenhydramine hydrochloride for intravenous injection, and resuscitation equipment.

Prophylaxis against hypersensitivity and infusion-related reactions associated with rituximab will include acetaminophen 650 mg and diphenhydramine hydrochloride 50-100 mg administered 30 to 60 minutes prior to starting rituximab. Patients will also receive their first dose of prednisone 60 mg/m^2 (or a glucocorticoid equivalent dose of an alternative steroid) at least 60 minutes before rituximab treatment commences.

Rituximab will be administered as an intravenous infusion at 375 mg/m^2 on day 1 of each cycle of EPOCH after bortezomib (when both drugs are given on the same day) and before starting etoposide + doxorubicin + vincristine administration. Rituximab infusions will be administered to patients primarily in an outpatient clinic setting.

First dose:

The initial dose rate at the time of the first rituximab infusion should be 50mg/hour (25 mL/hr) for the first 30 minutes. If no toxicity is seen, the dose rate may be escalated gradually in 50 mg/hour (25 mL/h) increments at 30 minute intervals) to a maximum of 400 mg/hour (maximum rate = 200 mL/h).

Second and Subsequent Doses (select the appropriate administration timing):

90-minute Administration

If the first dose of rituximab was well tolerated, subsequent doses may be administered over 90 minutes with 20% of the total dose given in the first 30 minutes, and remaining 80% of the total dose administered over the subsequent 60 minutes; e.g.:

Two-Step Rate Escalation	Volume to administer (X mL)

1st portion (0 – 30 minutes)	$\frac{\text{Total Dose (mg)}}{2} \leftrightarrow 0.2 = \text{X mL (over 30 min)}$
2nd portion (30 – 90 minutes)	$\frac{\text{Total Dose (mg)}}{2} \leftrightarrow 0.8 = \text{X mL (over 60 min)}$

Special Note: The 90-minute infusion scheme is not recommended for patients with clinically significant cardiovascular disease or high circulating lymphocyte counts (≧5000/mcL).

Standard Administration for Second & Subsequent Infusions

Patients who tolerate initial treatment without experiencing infusion-related adverse effects but for whom the 90-minute infusion scheme during subsequent treatments is considered inappropriate, may receive subsequent rituximab doses at the Standard Rate for Subsequent Infusions, which is as follows:

Begin at an initial rate of 100 mg/hour (50 mL/h) for 30 minutes. If administration is well tolerated, the administration rate may be escalated gradually in 100-mg/hour (50-mL/h) increments at 30-minute intervals to a maximum rate of 400 mg/hour (maximum rate = 200 mL/h).

CAUTION: DO NOT ADMINISTER RITUXIMAB AS AN INTRAVENOUS PUSH OR BOLUS.

12.2.6 Toxicities

Common toxicities include fever, chills, nausea, asthenia, headache, angioedema, pruritis and rash. Leukopenia occurs in approximately 10% but grade 3 or 4 neutropenia is uncommon. Hypotension occurred in 10% of patients during rituximab infusion, and serious bronchospasm and urticaria associated with rituximab infusion each occurred in fewer than 10% of patients. Less common toxicities include abdominal pain, vomiting, thrombocytopenia, anemia, myalgia, arthralgia, dizziness, and rhinitis. Recently, in patients receiving Rituximab, there have been reports of hepatitis B virus reactivation with fulminant hepatitis, hepatic failure and death in some patients with hematological malignancies.

12.3 CYCLOPHOSPHAMIDE

12.3.1 Supply

Commercially available as a lyophilized powder for reconstitution in vials containing 100 mg, 200 mg, 500 mg, 1gm, and 2 gm of cyclophosphamide.

12.3.2 Storage and preparation

Intact vials should be stored at room temperature (not to exceed 30ºC). Reconstitute with appropriate amounts of 0.9% NaCl to produce a final concentration of 20 mg/ml. Discard solution after 24 hours at room temperature. Stable up to 6 days if refrigerated (2º-8°C).

12.3.3 Administration

Cyclophosphamide will be diluted in D5W or 0.9% NaCl and administered as an intravenous infusion over 30minutes. Patients will be instructed to drink an adequate amount of fluids and empty their bladders frequently during cyclophosphamide administration.

12.3.4 Hydration Guidelines

All patients should receive 0.9%NS at the following volumes (based on cyclophosphamide dose levels) and rates with half the specified volume given before starting cyclophosphamide administration and half the volume given after completing the cyclophosphamide administration.

Cyclophosphamide Dosage Levels	Fluid Volume and Administration Rate
1 & 2	1000 mL 0.9%NS @ 300 – 500 mL/h
Levels 3, 4, & 5	2000 mL 0.9%NS @ 300 – 500 mL/h
Levels ≥6	2500 mL 0.9%NS @ 300 – 500 mL/h

12.4 DOXORUBICIN

Refer to the FDA approved package insert for complete product information.

12.4.1 Supply

Commercially available as a lyophilized powder for reconstitution in 10, 20, 50, and 100 mg vials. Also available as 2 mg/ mL solution for injection in 10, 20, 50, and 200 mg vials.

12.4.2 Preparation and stability

Intact vials of doxorubicin solution for injection should be stored in the refrigerator (2º-8ºC). Intact vials of doxorubicin lyophilized powder for reconstitution should be stored at room temperature (not to exceed 30ºC).

Reconstitute vials of doxorubicin powder with appropriate amounts of 0.9% NaCl to produce a final concentration of 2 mg/ml. Reconstituted solutions are stable for 7 days at room temperature and 15 days under refrigeration when protected from light.

12.4.3 Toxicities

Myelosuppression, stomatitis, alopecia, nausea and vomiting, and acute and chronic cardiac toxicity, manifested as arrhythmias or a congestive cardiomyopathy, the latter uncommon at total cumulative doses less than 500 mg/m^2. The drug causes local necrosis if infiltrated into subcutaneous tissue. Please refer to the package insert for a complete listing of all toxicities.

12.5 VINCRISTINE

Refer to the FDA approved package insert for complete product information.

12.5.1 Supply

Commercially available as a 1 mg/mL solution for injection in 1 mg, 2 mg, and 5 mg vials.

12.5.2 Stability

Vials should be stored at 2º-8ºC and should be protected from light.

12.5.3 Toxicities

Peripheral neuropathy, autonomic neuropathy, alopecia. Local necrosis if injected subcutaneously. Please refer to the package insert for a complete listing of all toxicities.

12.6 ETOPOSIDE

12.6.1 Supply

Commercially available as a concentrate for parenteral use in 100 mg vials; each ml contains 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80, 650 mg of polyethylene glycol 300, and 30.5% alcohol.

12.6.2 Toxicities

Myelosuppression, nausea, vomiting, anaphylactoid reactions, alopecia, and hypotension if infusion is too rapid. Please refer to the package insert for a complete listing of all toxicities.

12.7 ADMINISTRATION OF VINCRISTINE/DOXORUBICIN/ETOPOSIDE

Stability studies conducted by the Pharmaceutical Development Section, Pharmacy Department, NIH Clinical Center, have demonstrated that admixtures of vincristine, doxorubicin, and etoposide in 0.9% Sodium Chloride Injection, USP (0.9%NS) at concentrations, respectively, of 1, 25, and 125 mcg/mL; 1.4, 35, and 175 mcg/mL; 2, 50, and 250 mcg/mL; and 2.8, 70, 350 mcg/mL are stable for at least 36 hours at room temperature when protected from light. Also, admixtures containing vincristine, doxorubicin, and etoposide concentrations of 1.6, 40, and 200 mcg/mL are stable for at least 30 hours at 32°C.

For this study, etoposide, doxorubicin, and vincristine comprising a daily dose (a 24-hour supply) will be diluted in 0.9%NS. Product containers will be replaced every 24 hours to complete the planned duration of infusional treatment. Product volumes will be determined by the amount of etoposide present in a 24-hour supply of medication. For daily etoposide doses ≤130 mg, admixtures will be diluted in approximately 500 mL 0.9%NS. For daily etoposide doses >130 mg, admixtures will be diluted in approximately 1000 mL 0.9%NS.

Etoposide + doxorubicin + vincristine admixtures will be administered by continuous IV infusion over 96 hours with a suitable rate controller pump via a central venous access device.

Temporary PICC lines or permanent lines may be used. Extravasation of these diluted agents has not caused local tissue damage due to their low concentrations in the solution.

12.8 PREDNISONE

12.8.1 Supply

Commercially available in a large number of oral dosage strengths including pills and liquid formulations.

12.8.2 Storage

Tablets should be stored in well-closed containers at temperatures between 15-30^{o}C.

12.8.3 Administration

Prednisone utilization will be simplified by using only 20- and 50-mg tablets to produce individual doses and by stratifying prednisone doses by a patient's body surface area (BSA), according to the chart below. These are recommendations and not requirements.

BSA (m^2)	Each Dose
1.25 – 1.49	80 mg

1.5 – 1.83	100 mg
1.84 – 2.16	120 mg
2.17 – 2.41	140 mg
2.42 – 2.6	150 mg
2.61-2.69	160 mg
2.7 – 3	170 mg

12.8.4 Toxicities

Proximal muscle weakness, glucose intolerance, thinning of skin, redistribution of body fat, Cushingoid facies, immunosuppression, propensity to gastrointestinal ulceration. Please refer to the package insert for a complete listing of all toxicities.

12.9 FILGRASTIM (G-CSF/NEUPOGEN[R])

Refer to the FDA approved package insert for complete product information.

12.9.1 Supply

Commercially available in single use vials containing 300 mcg (1 mL/vial) and 480 mcg/vial (300 mcg/ml, 1.6 mlvial).

12.9.2 Storage

Should be stored at 2º-8ºC (do not freeze and do not shake) and is stable for at least 1 year at this temperature.

12.9.3 Administration

Filgrastim will be given by subcutaneous injection; patient or other caregiver will be instructed on proper injection technique.

10.8.2 Toxicities

Rare anaphylactic reactions with the first dose; bone pain at sites of active marrow with continued administration. Local reactions at injection sites. Constitutional symptoms, increased alkaline phosphatase, LDH, uric acid; worsening of pre-existing inflammatory conditions. Please refer to the package insert for a complete listing of all toxicities.

13 ADMINISTRATIVE REQUIREMENTS

13.1 GOOD CLINICAL PRACTICE

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

13.2 ETHICAL CONSIDERATIONS

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

13.3 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).

13.4 PATIENT CONFIDENTIALITY

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by name and/or 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.

13.5 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.

13.6 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.

13.7 DRUG ACCOUNTABILITY

Accountability for the drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at

the site (if applicable), use by each patient, and return to Millennium or disposal of the drug (if applicable and if approved by Millennium) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers. All material containing bortezomib will be treated and disposed of as hazardous waste in accordance with governing regulations.

13.8 RECORD RETENTION

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

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15 APPENDIX A: PROCEDURE FOR SERUM SEPARATION

This procedure is for use with blood tubes or syringes containing no anticoagulant. In some cases the blood will be received in vacutainer tubes containing a serum separator. Use of these serum separator tubes (SST) simplifies the recovery of serum after centrifugation since the gel separator will be found between the cell layer and the serum.

Complete all required data entry. Prepare transmittal form to accompany sample. Assign each sample a unique Sample Accession Number. Contact the Clinical Support Laboratory at (301) 846-5125 to receive one or more Sample Accession Numbers for use. Laboratory staff can also be contacted by email:

To: Theresa Burks – burkst@mail.nih.gov
CC: Helen Rager (Supervisor) – ragerh@mail.nih.gov
CC: Dr. Mingzhu Zhu (Lab Head) – zhum@mail.nih.gov

The sample should be allowed to clot at room temperature for approximately 30 minutes. If possible the sample should be processed immediately after clotting. If it is not possible to proceed immediately the sample should be refrigerated or placed in a sealed bag on wet ice until processing can be performed. Both the draw time and time when processing was completed should be recorded.

Set the centrifuge temperature to 4°C. Centrifuge the sample for 10 minutes at 2000 rpm (approx. 1170 x g) in the RC-3B centrifuge with no brake (2300 rpm Sorvall RT6000B). The centrifugation time does not include the time required for the rotor to reach the target speed. To determine centrifugation speed for different centrifuge/rotor combinations see the centrifuge manual or visit the following website:
http://researchlink.labvelocity.com/tools/conversionTools/CentrifugationTool.jhtml

Prior to initiating sample processing or during the centrifugation step label 2 ml Nunc cryovials (NUNC 368632 1.8 ml round bottom cryovial or equivalent) with the sample Accession Number. If multiple blood tubes have been received for a single patient/timepoint also label a 15 or 50 ml polypropylene tube depending on expected recovery volume.

Carefully remove the serum layer (*the translucent first layer of fluid)* without disturbing the clot. Do not attempt to recover serum from the side of the retracted clot as doing so will result in contamination of the serum. If it is noted that the serum has not been cleanly removed transfer the recovered serum to a 15 ml polypropylene tube and repeat centrifugation.

If only a single tube of blood was received for serum recovery aliquot directly to the labeled Nunc cryovials at 1ml per vial (1 10ml tiger top (SST) or red top vacutainer = approximately 4 vials, 2 tubes = >6 vials).

If multiple blood tubes are received for a single patient/timepoint, transfer the serum from each tube into a single 15 or 50 ml centrifuge tube. Mix the contents by repeated pipetting or by replacing the lid and inverting the tube at least 6 times prior to aliquoting.

Transfer filled vials to the -70°C freezer. If the laboratory does not have access to a -70°C freezer (or colder storage such as vapor phase LN2) the serum should be frozen solid on dry ice before transfer to the -20°C freezer. If samples are held at temperatures outside the range of –60 to -86°C please note the storage temperature on the transmittal form.

Include any comments concerning adequacy of the specimen (e.g., gross hemolysis) on the transmittal form.

16 APPENDIX B: EPOCH ADMIXTURES: PREPARATION AND ADMINISTRATION

Preparation

All 3-in-1 admixtures dispensed from the Pharmacy will contain a 24-hour supply of etoposide, doxorubicin, and vincristine, *PLUS* 40 mL overfill (excess) fluid and a proportional amount of drug to compensate for volume lost in parenteral product containers and administration set tubing.

Etoposide Dose	**Volume of Fluid Containing a Daily Dose**	**Volume of Overfill** (fluid + drug)	**Total Volume in the Product** (including overfill)
≤ 130 mg	528 mL	40 mL	568 mL
> 130 mg	1056 mL	40 mL	1096 mL

Before dispensing 3-in-1 admixtures, Pharmacy staff will:

[1] Purge all air from the drug product container,
[2] Attach an administration set appropriate for use with a portable pump,
[3] The set will be primed close to its distal tip, and
[4] The set will be capped with a Luer-locking cap.

Pre-printed product labeling will identify the 'Total Volume To Infuse' and the 'Volume of Overfill (fluid + drug)'.

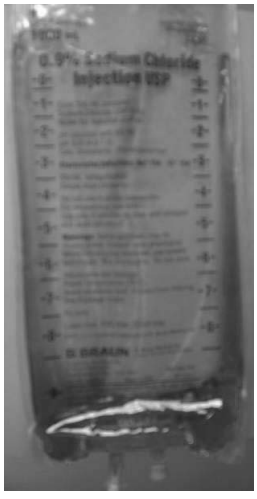
Bags will be exchanged daily for four consecutive days to complete a 96-hour drug infusion (unless treatment is interrupted or discontinued due to un-anticipated events).

Administration

Portable pumps used to administer etoposide + doxorubicin + vincristine admixtures will be programmed to deliver one of two fixed volumes at one of two corresponding fixed rates based on the amount of etoposide and fluid that is ordered (see the table, below).

Etoposide Dose	**Total Volume to Infuse per 24 hours**	**Volume of Overfill** (drug-containing fluid)*	**Administration Rate**
≤ 130 mg	528 mL	40 mL	22 mL/hour
> 130 mg	1056 mL	40 mL	44 mL/hour

*DO NOT attempt to infuse the overfill.



At the end of an infusion, some residual fluid is expected because overfill (excess fluid and drug) was added; however, nurses are asked to return to the Pharmacy for measurement any drug containers that appear to contain a greater amount of residual drug than expected.

Example at right: The amount of fluid remaining in a bag after completing a 24-hour infusion (1056 mL delivered).

17 APPENDIX C: PREGNANCY REPORTING FORM

Pregnancy Form

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: ___/___/_____ (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: _____

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

e-Pregnancy Form (27 November 2013)

MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

Pregnancy Form

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: _____

e-Pregnancy Form (27 November 2013)

INSTITUTE: National Cancer Institute

STUDY NUMBER: 05-C-0170 PRINCIPAL INVESTIGATOR: Wyndham H. Wilson, M.D., Ph.D.

STUDY TITLE: Randomized Phase II Study of Dose-Adjusted EPOCH-Rituximab-Bortezomib (EPOCH-R-B) Induction Followed by Bortezomib Maintenance versus Observation in Untreated Mantle Cell Lymphoma with Microarray Profiling and Proteomics

Continuing Review Approved by the IRB on 10/29/18
Amendment Approved by the IRB on 10/17/18 (P) Date posted to web: 11/08/18

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

This is a clinical research study to test a new investigational approach using VELCADE® (Bortezomib) For Injection with EPOCH-R chemotherapy to treat your mantle cell lymphoma. VELCADE® (bortezomib) for Injection is a drug under development by Millennium Pharmaceuticals, Inc. VELCADE has received FDA approval for the treatment of multiple myeloma patients who have received at least one prior therapy and have demonstrated disease progression on the last therapy. Additionally, in October 2014, VELCADE received FDA approval for the treatment of Mantle Cell Lymphoma. VELCADE is still currently under

investigation for other indications. VELCADE is the type of drug known as a "proteasome inhibitor." It has been studied in about 9000 patients with various types of cancer. VELCADE enters cells and affects the way they divide. VELCADE interferes with a substance found inside cells in your body. Mantle cell lymphoma is a form of cancer of the white blood cells called lymphocytes. In mantle cell lymphoma, the abnormal lymphocytes multiply and accumulate in lymph nodes and elsewhere. Standard treatment with chemotherapy can often control the mantle cell lymphoma for a period of time but in most patients, the disease does not go entirely away or comes back. In this study, we are testing VELCADE® in combination with EPOCH-R chemotherapy.

We hope that this is also the case in newly diagnosed mantle cell lymphoma and that the addition of this drug to EPOCH-R will lead to better cure rates. EPOCH (each letter stands for one of the drugs used in the combination) uses standard chemotherapy drugs and has been shown to have a high degree of effectiveness in lymphomas. Recent evidence indicates that the effects of chemotherapy may be improved by the use of a new drug called Rituximab. In fact, we recently carried out a study using EPOCH-Rituximab in newly diagnosed mantle cell lymphoma and found that 92% of the patients had a complete remission after this combination. We hope that by adding VELCADE, the results will be as good if not better. Once chemotherapy is finished, we will assign patients by chance to receive VELCADE or not. For patients who are not assigned to receive this, they will be offered VELCADE, if their disease returns. Our hope is that this so called 'maintenance therapy' will improve the overall cure rate and increase the amount of time before the disease returns.

Why are you being asked to take part in this study?

You have been invited to participate in this study because you have mantle cell lymphoma.

Description of Research Study

The study is divided into 3 parts. Before being enrolled in the study, you will undergo a series of tests to determine if you are eligible for the study and to determine the extent (called stage) of your lymphoma. If you are found not to be eligible for the study, you will be referred back to your home physician. If you are eligible, we will ask you to undergo a lymph node biopsy before you start any treatment. In the first part of the study, you will receive VELCADE by itself. We will repeat the biopsy after you have received the second dose of the drug. Both of these biopsies are optional; we will ask you later if you agree to have the biopsies. In the second part of the study, you will receive a series of treatments with EPOCH-R-Bortezomib. It usually takes 18 weeks to complete this part of the study. In the third part, you will be assigned by chance to receive or not to receive VELCADE. If you are assigned to receive it, you will receive 4 doses of VELCADE every 8 weeks approximately. You will continue receiving VELCADE for up to 18 months. If before the end of 18 months, your disease returns, then the VELCADE will stop. If you have been assigned not to receive the VELCADE, you will be offered VELCADE if the disease returns.

What will happen if you take part in this research study?

Part A: VELCADE alone

You will first receive VELCADE alone. You will receive 1 cycle in total – that will be 4 doses of the drug given over 2 weeks. The VELCADE will be given by injection into the vein. This is given in approximately 30 seconds. Then 3 to 4 weeks from starting Part A, you will begin treatment with EPOCH-R and VELCADE. If your mantle cell lymphoma is too advanced, your doctor may decide to skip this part and have you start treatment in Part B.

Part B: EPOCH-R-B treatment

Each chemotherapy treatment period is called a cycle. The cycle is repeated every three weeks and the chemotherapy drugs are administered only during the first five days of every cycle. EPOCH-R-B consists of prednisone by mouth on days 1 to 5, and etoposide, doxorubicin, and vincristine as an infusion over days 1 to 5 (total of 96 hours), and cyclophosphamide on day 5 by vein. You will receive the infused drugs as an outpatient through a lightweight, portable infusion pump, about the size of a portable tape recorder. The pumps deliver the therapy through an intravenous catheter which is placed in your vein beforehand. You will be taught about the use and care of the pump and what to do if it stops working. The rituximab will be given by vein over several hours on day 1, immediately before the chemotherapy infusion begins, and the VELCADE will be given by vein over 30 seconds before the rituximab on day 1 and again on day 4. Cyclophosphamide will be given by intravenous injection over about 15 minutes on day 5, immediately after the chemotherapy infusion is completed. Each cycle lasts 3 weeks: 5 days of chemotherapy followed by 16 days of no chemotherapy. You will receive 6 cycles of EPOCH-R-B. If your lymphoma grows, however, EPOCH-R-B will be discontinued. After each EPOCH-R-B treatment, we give another drug, G-CSF, to help your normal bone marrow cells recover from the chemotherapy and produce normal white cells. You will be taught how to inject the G-CSF under your skin (like an insulin shot) each day beginning on day 6 of each cycle and continuing for 10 days. If your white blood cell count is still very low on the day treatment is due to begin again, the chemotherapy may be delayed and the G-CSF restarted until recovery of the white count. Because several of the chemotherapy drugs can lower your resistance to infection, you will receive an antibiotic called Bactrim for three days each week while you are on chemotherapy. If you are allergic to this antibiotic, you will receive a different drug that has the same function.

Part C: VELCADE alone

After you have completed the EPOCH-R-B therapy, you will be assigned by chance to receive or not to receive VELCADE alone. If you are assigned by chance to not receive it and your disease relapses, you will be offered it at this time. If you are assigned to receive VELCADE after EPOCH-R-B, the VELCADE will be given every 56 days, as 4 doses over 11 days. There will then be a break of 45 days before the next cycle. If you are not assigned

to receive VELCADE but your disease relapses, you will be offered VELCADE as 4 doses over 11 days with a break of 17 days before the next cycle. The time over which you receive the 4 doses and the break before the next 2 doses is called a cycle. You will continue to receive cycles like this for a period of up to 18 months or until your disease comes back or progresses. The VELCADE will be given by vein over 30 seconds.

Research Tests

Research studies will be performed on your blood, bone marrow, tumor tissue or other fluids to look at different genes and proteins that may be involved in the development of your lymphoma or the reaction of the immune system. We plan to do a tissue biopsy before you start treatment and a further biopsy a day after treatment has begun. Both of these biopsies are optional; we will ask you later if you agree to have the biopsies. Biopsies requiring major surgery (e.g., in the chest or the abdomen) will not be performed for research purposes alone but only if absolutely necessary for your medical care. The progress of your response will be followed by CT scans of your body and blood tests.

As part of your clinical evaluation and follow up we will use CT scans and Positron Emission Tomography (PET) scan to determine the extent of your disease and response to treatment. In addition we will do one CT scan and up to two PET scans for research purposes to look for any early effect of the VELCADE you will receive. Some patients may also undergo up to two biopsies under CT guidance for research purposes. This radiation is for research purposes only and is not necessary for your medical care. Positron emission tomography (PET) uses a radioactive sugar molecule called fluorodeoxyglucose, or FDG for short. This sugar is similar to glucose, an ordinary form of sugar that the body uses for fuel. The FDG is labeled with a type of radioactive element, an isotope, called Fluorine-18 (F-18) that emits particles called positrons that can be detected by a special camera and viewed on a computer screen. The FDG used for the research PET scans is an FDA approved agent.

You will not be eligible for the PET scan if:

- You weigh more than 350 lbs. Weight in excess of 350 pounds will exceed the weight limit for the scanner table.
- You need conscious sedation in order to perform the research PET scan
- Technical problems with the scanner would significantly delay your treatment

In addition, if you are a woman of childbearing potential, you must have a negative pregnancy test.

The FDG-PET scan will be done in the Nuclear Medicine or PET Department of the NIH Clinical Center. Prior to the test you will not be allowed to eat (including mints, sugar containing medicine or gum) or drink anything but water for 6 h. If possible you should drink 2 to 3 glasses of water before the test. The FDG will be injected into the vein after which you will

rest quietly in a room for 1 hr after which the PET scan will be performed. Just before the initial scan, you will be asked to empty the bladder.

The PET camera is shaped like a doughnut and looks like a CT scanner. You will be asked to lie very still on a table within the machine and flat on the back with the arms over the head or to the side. Your head will lie on a soft cradle. For about 11/2 hour the picture-taking process will take place depending on your height. As part of the PET scan we will do a "transmission scan" with the same scanner or using a CT to determine your body thickness and to align any abnormalities seen on the FDG scan with anatomical findings on CT. A PET technologist will be present at all times and a physician will be available throughout the procedure. If for any reason you feel that cannot continue, the scanning can be stopped and you can be removed from the scanner immediately. However, the information from the scan may be lost at that time. After the scan is finished, you will be asked to empty the bladder again every 1 1/2 hours for 6 hours to eliminate the radioactive sugar. One blood sample may be drawn during the PET scan to determine the blood sugar levels.

Additional Research Testing

What tests will be done on my samples?

Your blood and tissue that is collected will be used to look for specific changes in the DNA in tumors that could be used to develop new ways of diagnosing and treating cancer, and to understand more about lymphoma. DNA (also called deoxyribonucleic acid) are the molecules inside cells that carry genetic information and pass it from one generation of cells to the next – like an instruction manual. Normal tissue contains the DNA (instructions) that you were born with, DNA in tumor cells has changed – or mutated – and we think that change in the DNA is what causes tumors to form and to grow, forming the cancer genome or DNA. In order to determine which parts of the DNA have mutated, we will compare the DNA in your tumor cells to DNA from your normal cells. When we are examining these pieces of your DNA, it is possible that we could identify possible changes in other parts of your DNA that are not related to this research. These are known as "incidental medical findings".

These include:

- Changes in genes that are related to diseases other than cancer
- Changes in genes that are not known to cause any disease. These are known as normal variations.
- Changes in genes that are new and of uncertain clinical importance. This means that we do not know if they could cause or contribute to a disease or if they are normal variations.

However, the analyses that we perform in our laboratory are for research purposes only; they are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing. Changes that we observe unrelated to our research may or may not

be valid. Therefore, we do not plan to inform you of the results of testing on your tissue and blood that is performed in our research lab. However, in the unlikely event that we discover a finding believed to be clinically important based on medical standards at the time we first analyze your results, we will contact you. This could be many years in the future. We will ask you to have an additional tube of blood drawn to verify the findings we have seen in our lab. If the results are verified, you will be re-contacted and offered the opportunity to come to NIH to have genetic education and counseling to explain this result. If you do not want to come to NIH, a referral to a local genetic healthcare provider will be provided and the consultation will be at your expense.

Who else besides the investigators on this study will know the results of my sample testing?

Once we obtain any of the samples listed above, the investigators take all your personal information off those samples and label them with a study code number. Only the investigators on this study know who the sample came from. The key linking your personal information with the code number is kept in a secure computer data base, with access only to key research staff who will be discussing this study with you. Once the sample has been labeled with a code, it is sent to a variety of NIH laboratories for storage and testing. No one testing your samples will be able to link the results to you personally. Specimens obtained during your participation in this study may be sent for testing to investigators outside of NCI or the NIH. All samples will be coded to protect your privacy and no personal information will be included. Other investigators on this study will have access to limited clinical and biologic data such as age, gender and disease status.

Your individual genomic data and health information will be put in a controlled-access database. This means that only researchers who apply for and get permission to use the information for a specific research project will be able to access the information. Your genomic data and health information will not be labeled with your name or other information that could be used to identify you. Researchers approved to access information in the database have agreed not to attempt to identify you.

How long will your samples be stored?

The samples collected during this study will be stored for as long as the study is open. When this study is closed, we will keep the samples for future research.

When you are finished taking the drugs (treatment)

This depends on how you have responded to the therapy. If all evidence of disease has disappeared, we will schedule periodic visits to the Clinical Center for follow-up examination and tests. If the disease does not disappear entirely or if it should recur after having disappeared for a period of time, then you may need further therapy. At that time you will be given the opportunity of participating in additional research protocols that may be appropriate for you. If no such protocols are available, you will be returned to the care of your local physician. It is

important to stress that participation in this protocol does not constitute a promise of long-term medical care here at the Clinical Center. It is conceivable that participation in this study may make you ineligible to participate in certain other research protocols because the requirements for entry onto these protocols may not allow patients who have already been treated with certain drugs or who have had certain side effects from previous treatment. You may decide now not to receive treatment on this protocol, or you may choose at any point in time to stop the treatment and withdraw from the protocol; in either case you will be returned to the care of your referring physician.

Risks or Discomforts of Participation

In order to determine whether this study is suitable for you, a number of tests will have to be done. Some or all of these tests will be repeated during and after the chemotherapy at different times. Depending on the tests you had before coming here, these may include blood and urine tests, studies of lung function, CAT or MRI scans, colonoscopy with biopsies, radioisotope scans, and biopsies of tumor tissue, bone marrow, liver, or other sites. Biopsies will, when possible, be done under local anesthesia. The risks associated with bone marrow biopsies include pain, bleeding, and local infection. Risks of biopsies include pain, bleeding, infection, and the risks to the particular area undergoing surgery.

General anesthesia itself is generally very safe but has a very small risk of major complications such as heart attack or stroke. The surgical and anesthetic risks will be explained to you in more detail at the time of surgery, if this is needed. Risks of colonoscopy with biopsies include discomfort and bleeding from the rectum; rarely the colon may be punctured and if this occurs, it is serious and may require surgery. A separate consent describing all of the complications and side effects of colonoscopy with biopsies will be obtained from you. Your blood will be tested for your HLA type. This test is to identify surface groups of proteins which are unique to each person.

Radiation Risks

This research study involves exposure to radiation from two FDG-PET/CT scans and up to three CT scans. Please note that this radiation exposure is not necessary for your medical care and is for research purposes only. If you are an adult, the total amount of radiation you will receive in this study is from 30-millicurie mCi of FDG.

Using the standard way of describing radiation dose, from participating in this study for adults receiving the PET scan and the CT scans will receive a total of 14 rem to your urinary bladder, 12 rem to your heart, and 19 rem to your thyroid. All other organs will receive smaller amounts of radiation. Although each organ will receive a different dose, the amount of radiation exposure you will receive from these procedures is equal to a uniform whole-body exposure of 7.4 rem. This calculated value is known as the "effective dose" and is used to relate the dose received by each organ to a single value. The amount of radiation received in this study is slightly higher than the guideline established by the NIH Radiation Safety Committee for research subjects.

The guideline is for an effective dose not to exceed 5 rem received per year in adults. The NIH Radiation Safety Committee, a group of experts in radiation matters, has reviewed the use of radiation in adults in this research study and has approved this use as involving acceptable risk and necessary to obtain the research information desired.

For comparison, the average person in the United States receives a radiation exposure of 0.3 rem per year from natural background sources, such as from the sun, outer space, and from radioactive materials that are found naturally in the earths air and soil. The dose that you will receive from this research study is about the same amount you would normally receive in 25 years from these natural sources. If you would like more information about radiation and examples of exposure levels from other sources, please ask the investigator for a copy of the pamphlet called, *An Introduction to Radiation for NIH Research Subjects.*

The effects of radiation exposure on humans have been studied for over 60 years. In fact, these studies are the most extensive ever done of any potentially harmful agent that could affect humans. In all these studies, no harmful effect to humans has been observed from the levels of radiation you will receive by taking part in this research study. However, scientists disagree on whether radiation doses at these levels are harmful. Even though no effects have been observed, some scientists believe that radiation can be harmful at any dose - even low doses such as those received during this research.

One possible effect that could occur at these doses is a slight increase in the risk of cancer. Please be aware that the natural chance of a person getting a fatal cancer during his/her lifetime is about 1 out of 4 (or 25 percent). The increase in the chance of getting a fatal cancer, as a result of the radiation exposure received from this research study, is estimated at 0.3 percent. Therefore, the total risk of fatal cancer may be estimated to increase from 25 percent to up to 25.3 percent. This change in risk is small and cannot be measured directly. Compared with other everyday risks, such as flying in an airplane or driving a car, this increase is considered slight.

Please tell your doctor if you have taken part in other research studies or received any medical care at the NIH or other places/hospitals that used radiation. This way we can make sure that you will not receive too much radiation. Consider x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

If you would like more information about radiation and examples of exposure levels from other sources, please ask the investigator for a copy of the pamphlet called, An Introduction to Radiation for NIH Research Subjects.

If you are pregnant or breast feeding, you may not participate in this research study. It is best to avoid radiation exposure to unborn or nursing children since they are more sensitive to radiation than adults. There are no expected toxicities associated with the intravenous injection of small quantities of FDG.

In order to receive EPOCH-R-B therapy you will need to have an intravenous catheter placed.

This catheter is usually placed in the arm, chest or neck area into a major vein inside your chest. We usually remove the catheter after each cycle but on occasion it can be left in for several cycles. The catheter is necessary for infusion of chemotherapy and for the drawing of blood. It is usually inserted under local anesthesia. The risks associated with the procedure include pain, bleeding, infection, and puncture of the underlying lung. Lung puncture can result in lung collapse, which might require that a chest tube be placed into the chest cavity (usually for a day or two) to help the lung reinflate. The long-term risks of the catheter include infection and clotting of the vein in which the catheter sits. If these occur, it may be necessary to remove the catheter. These risks will be explained to you in more detail at the time of the insertion.

You may have side effects while on the study. Every one taking part in the study will be watched carefully for any side effects. However doctors do not know all the side effects that may happen. Side effects may be mild or serious. Your health care team may give you medicines to help lessen side effects. In some cases, side effects can be serious or long-lasting or may never go away. There is also the risk of death from either the treatment or your/your child's disease.

You should talk to your doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the treatment are identified below.

Study Treatment Risks

Side effects of Velcade alone

VELCADE should not be taken if you are overly sensitive to bortezomib (VELCADE), boron or mannitol. You face some risks or discomforts when you are treated with the study drug, VELCADE. You are at risk of experiencing all, some, or none of these symptoms and they may vary in severity. The severity may be mild, moderate or severe, up to and including death. Any symptoms or conditions that you have before you start study drug may worsen. Also, there is always a chance that a rare or previously unknown risk may occur. If any of these symptoms occur, you must tell your doctor who may give you other drugs to ease any discomfort you experience. Your doctor may decrease or withhold the dose of VELCADE. Other drugs and supplements may affect the way VELCADE works. Tell your doctor about all drugs and supplements you are taking while participating in this study. In addition, if a severe reaction to the study drug occurs, your doctor may permanently stop the study treatment.

Most Common VELCADE Risks:

The most common risks are those that have occurred in greater than or equal to 30% of patients who have received VELCADE:

- weakness, fatigue, and general discomfort
- gastrointestinal effects such as constipation, diarrhea, nausea and vomiting
- fever very commonly with shaking chills
- painful sensations or numbness and tingling in hands and feet which may not get better

after stopping VELCADE. Uncommonly, the nerves that control things like your heart rate, gut movement and urinary bladder may be affected.
- lowered platelets that may increase the chance of bleeding
- lowered red cells or anemia which may make you feel tired

Very Common VELCADE Risks:

The very common risks are those that have occurred in 10-29% of patients who have received VELCADE:
- decrease in white blood cells called neutrophils or lymphocytes that may increase your risk of infection and is uncommonly associated with fever.
- You may have lowered white blood cells or have lowered red blood cells at the same time
- loss of appetite, which may result in dehydration and/or weight loss
- abdominal pain
- symptoms of flu and other upper respiratory tract infections, such as chills, sore throat, and runny nose
- aches and pains in muscles and joints; and back pain
- skin rash
- cough, feeling short of breath, lung infections including pneumonia and commonly bronchitis
- headache
- dizziness
- Herpes virus such as shingles (herpes zoster) that can sometimes cause local pain that does not go away for a while and herpes simplex virus. Shingles can sometimes spread over large parts of the body. Both may also affect the eyes or brain, but this is uncommon.
- problems sleeping and feeling anxious

Common VELCADE Risks:

Common risks are those that have occurred in 1-9% of patients who have received VELCADE:
- changes in heart rate and heart beat that can cause you to possibly feel light-headed, dizzy, faint, short of breath, and/or have chest pain. This may also cause you to feel confused. An uncommon risk is a possible life threatening abnormal heart beat.
- new or worsening heart failure (which may appear as shortness of breath, swelling in the legs, and/or chest pain) or decreased heart function that can uncommonly be severe. If you have heart failure or other diseases that put you at risk of getting heart failure, you should tell your doctor.
- lowered blood pressure that can commonly cause you to feel dizzy or faint when you stand up. You should not drive or operate any dangerous tool or machines if you have these symptoms.
- accumulation of fluid in and around the lungs

- decreased level of oxygen in the blood
- infection and/or inflammation of the eyes or eyelids
- painful sores of the mouth and/or throat, which may make swallowing difficult
- heartburn, acid reflux and stomach bloating
- severe bleeding, including bleeding in the stomach and intestines (gut) that may be linked with low platelet counts, and blood clotting changes. Uncommonly, this bleeding may cause bloody diarrhea and/or bloody vomit.
- skin rash with itching and redness. An uncommon risk is a severe, life-threatening or deadly rash with skin peeling and mouth sores.
- swelling in the arms and legs, and weight gain
- nosebleeds
- deterioration in kidney function
- infections of the bladder, sinuses, throat, stomach and intestines, and skin and the area of skin where your catheter is placed
- nerve pain after herpes infection
- severe muscle weakness and paralysis (not being able to move your arms and legs)
- changes in blood sugar have been reported in a few diabetic patients receiving medicine for diabetes. If you are taking medicines for diabetes you may need close monitoring of your blood sugar levels.
- blood in the urine
- confusion
- abnormal liver tests. Uncommon risks are hepatitis, and liver failure in patients who got many other drugs and had other serious medical problems.
- reduction in white blood cell count
- lowered amount of potassium and sodium in your blood and increase in the amount of calcium in your blood.
- muscular weakness
- blurred vision
- changes in the way things taste

Uncommon VELCADE Risks:

Uncommon risks are those that have occurred in less than 1% of patients who have received VELCADE:

- pain, redness, swelling and infection in the area of the skin where VELCADE is injected into the vein.
- pain in the mouth and throat when swallowing
- decrease in or loss of hearing
- intestinal obstruction (blockage of the gut) that may get better on its own and not need surgery
- inflammation of the intestines, pancreas or stomach

- fungal infections in the mucous membranes such as the mouth and throat, and uncommonly in the skin and nails
- life-threatening infections in the blood (sepsis)
- coughing up blood
- bleeding in the brain and subdural hematoma, which is bleeding between the skull and your brain
- inflammation of the layers surrounding your heart or collection of fluid around the heart may cause chest pain or breathing problems and can be life-threatening or lead to death. If you have new or worsening chest pain or breathing problems you should tell your doctor.
- rapid death of cancer cells that may let toxins into the blood and injure organs, such as the kidneys
- allergic reactions that may include skin swelling and/or swelling of the face or throat and could be severe or life threatening
- inflammation and fluid build up in the lungs, or pus build up between the layers surrounding the lungs that may cause bleeding problems, and can be life-threatening or lead to death. Increased blood pressure in the lungs, called pulmonary hypertension, has also been reported. This can also cause breathing problems, and can be life-threatening. If you have new or worsening breathing problems you should tell your doctor.
- changes in the brain that may cause convulsions and confusion
- A syndrome called "posterior reversible leukoencephalopathy syndrome" that affects the brain and may cause headaches, changes in your vision, changes in your mental status, or seizures, but is usually reversible.
- loss of some to all vision affecting one or both eyes, which may be caused by damage to the nerve in the eye. Loss of vision may or may not be reversible.
- Progressive multifocal leukoencephalopathy (PML); PML is a rare, serious infection of the brain that is caused by a virus already in your body at the time of treatment onset. Persons with a weakened immune system may develop PML. PML can result in death or severe disability. Tell your study doctor immediately if you have any of the following symptoms or if anyone close to you notices these symptoms: confusion or problems thinking, loss of balance or problems walking, difficulty speaking, decreased strength or weakness on one side of your body, blurred vision or loss of vision.

Side Effects of EPOCH-R-B

Likely:

- Lowered white blood cell count that may lead to infection
- Lowered platelets which may lead to an increase in bruising or bleeding
- Lowered red blood cells which may cause anemia, tiredness, or shortness of breath
- Should low counts occur, they can be treated with blood products (transfusions), antibiotics, and there may be a reduction in the amount of drug given to you

- Constipation
- Fatigue or tiredness
- Painful tingling and numbness of fingers and/or toes
- Hair loss
- Fever and/or chills
- Time away from work
- Urine colored red for a day or two after the doxorubicin infusion
- Fingernail and toenail changes
- Tearing or dry eyes
- Runny nose
- Bony pain

Less Likely:

- Nausea and/or vomiting
- Loss of appetite, change in taste and weight loss
- Temporary shortness of breath or dizziness while receiving rituximab
- Headaches
- Muscle aches and muscle weakness
- Hoarseness or pain in the jaw
- Elevated blood sugar levels
- Elevated or decreased blood pressure
- Confusion
- Mouth & throat sores. Temporary irritation to the mouth may lead to mouth ulcers (similar to canker sores). Medications to numb the mouth may ease the mouth discomfort.
- Stomach ulcers
- Skin rashes and/or dry skin
- Loss of control of muscles or reflexes
- Abnormalities in blood results such as elevated liver enzymes, low blood protein and low blood calcium
- Mood changes such as agitation or depression
- Trouble sleeping

Rare, But Serious:

- Severe constipation may result in abdominal pain and cramping
- Bladder irritation with painful and bloody urine
- Damage to the heart muscle
- Skin rash that may be serious and life-threatening
- Allergic reaction that may be severe or life-threatening. Symptoms may include difficulty breathing, low blood pressure, fast heart rate, and sweating.

- Severe hepatitis (liver infection) in those patients who are carriers of the hepatitis virus. Patients who may have had prior exposure to the hepatitis B and C virus may be at an increased risk of recurrence of the virus that may lead to severe liver damage that can be life-threatening. You doctor will screen you for the hepatitis virus before beginning treatment on this study. If you test positive for the virus, you will be closely monitored for signs of the infection, and you will be treated, if appropriate, by your doctor.

Other Study Treatment Risks

Infection and bone marrow risks: It is important to emphasize that when you have a decreased white blood cell count from the VELCADE alone or the EPOCH-R-B combination treatment, you are at risk of infection. Such infections can be very serious and can even cause death if not quickly and properly treated. Therefore, if you have a temperature greater than 38.3o C (101o F), you must call your doctor immediately. Chemotherapy may also cause your platelets to fall; since platelets are the blood elements that permit blood to clot, this may place you at increased risk of serious bleeding. It may be necessary to give you transfusions of platelets if your platelet counts reach very low levels. There is a small chance that damage to the normal bone marrow may eventually result in bone marrow failure, leading to a serious shortage of one or more kinds of cells in the blood, or to leukemia. Because this is a relatively new combination of drugs, it is always possible that unanticipated side effects may occur, including death.

Reproductive risks: Many of the drugs used in this treatment program are toxic to the cells in the ovary and testicle and may produce sterility. Recovery of normal fertility is not well studied although we know that some patients treated with this combination have remained fertile after the therapy has been completed. For this reason, men who are about to receive this treatment should, if they wish to have children in the future, consider sperm banking before start of the treatment. These drugs may also be very toxic to an unborn child. Therefore, adequate birth control measures (such as the contraceptive pill, condoms, diaphragm with contraceptive foam or ointment, contraceptive sponge, etc.) should be used by participants or their sexual partners while receiving treatment on this study. Women of childbearing age will have a pregnancy test, which must be negative at the time of study entry. This test requires that blood be drawn from a vein one or two days prior to the study. The results of the pregnancy test will be made available to you prior to the initiation of the study. In addition, you must not be breastfeeding a baby during this study. Your physicians will watch you closely for side effects and will stop treatment if any side effects become a serious threat to your life or well-being. Your physicians will also stop the treatments if it becomes clear that the treatment is not successfully controlling your disease.

If you or your partner becomes pregnant while in this study you must tell the study doctor immediately. The doctor will advise you of the possible risks to your unborn baby and discuss options for managing the pregnancy with you. Because of possible risks to your unborn baby, the study drug will be stopped permanently.

Risks of blood transfusions: Rarely, patients may develop a dangerous side effect from blood transfusions called graft versus host disease (GVH). This disease is caused by white cells from the blood transfusion that can attack your normal tissues and cause death. GVH is preventable by radiating the blood before you receive it. It is important to emphasize that you will not receive any radiation from the blood and the radiation procedure done on the donated blood will not harm you. If you require a blood transfusion at the NIH during this study, you will receive blood that has been radiated. However, if your local physician gives you a blood transfusion, it is important that you make sure the blood has been radiated.

Psychological or Social Risks Associated with Loss of Privacy

The following general points are indirectly related to your participation in the research study:

1. Unanticipated medical information: During the course of this investigation, it is possible (although not likely) that we will obtain unanticipated information about your health or genetic background.
2. Release of genetic information:

- Your privacy is very important to us and we will use many safety measures to protect your privacy. However, in spite of all of the safety measures that we will use, we cannot guarantee that your identity will never become known. Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them.
- While the controlled-access databases developed for this project will not contain information that is traditionally used to identify you, such as your name, address, telephone number, or social security number, people may develop ways in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a blood relative) in another database and be able to identify you (or your blood relative). It also is possible that there could be violations to the security of the computer systems used to store the codes linking your genetic and medical information to you.
- Since some genetic variations can help to predict the future health problems of you and your relatives, this information might be of interest to health providers, life insurance companies, and others. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives. Therefore, your genetic information potentially could be used in ways that could cause you or your family distress, such as by revealing that you (or a blood relative) carry a genetic disease.
- There also may be other privacy risks that we have not foreseen.

Since some genetic variations can help to predict future health problems for you and your relatives, this information might be of interest to health care providers, life insurance companies, and others. However, Federal and State laws provide some protections against discrimination based on genetic information. For example, the Genetic Information Nondiscrimination Act (GINA) makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. However, GINA does not prevent companies that sell life insurance, disability insurance, or long-term care insurance from using genetic information as a reason to deny coverage or set premiums. GINA also does not apply to members of the United States military, individuals covered by the Indian Health Service, or veterans obtaining health care through the Veteran's Administration. Lastly, GINA does not forbid insurance medical underwriting based on your current health status though the Affordable Care Act limits consideration of pre-existing conditions by insurers.

Potential Benefits of Participation

Most patients will have tumor shrinkage with chemotherapy. However, we do not know if the addition of VELCADE will add to this benefit and do not know if you will be cured of your lymphoma. We do not know if you will receive personal, medical benefit from taking part in this study. We do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

Alternative Approaches or Treatments

It should be emphasized that we do not know at this point whether VELCADE combined with EPOCH-R with or without maintenance VELCADE is superior, inferior, or equivalent to standard combination chemotherapy for your disease. Alternative procedures that could be used to treat your disease include:

1. Other combination drug regimens and other schedules of the same drugs used in this study. For example, a chemotherapy called CHOP given in the conventional manner would be suitable standard therapy for your condition. You could also receive CHOP-R or EPOCH-R as standard treatment.
2. Treatment with single drugs. This is known to produce brief responses of a few months' duration in many patients but to have little beneficial effect in long-term control of the disease.
3. Radiation (X-ray) treatments. This can stop tumor growth in particular locations, such as bone, abdomen, and other sites but is not successful in controlling the disease overall unless the disease is very localized at the start of therapy.
4. Surgery. As with radiation, surgery can be successful in removing tumor from particular locations but cannot be used successfully to remove all lymphoma cells from the body, since the disease is almost always present in multiple locations. Also, surgery cannot be used against tumor in some of the organs most commonly involved by lymphoma, such as the liver or the lungs.

5. Watching and waiting may be an option for select patients without symptoms.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Will your medical information be kept private?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board
- Millennium Pharmaceuticals, Inc., which is providing VELCADE, its collaborators and designees;
- Some of the specimens and/or data obtained may be sent to researchers outside of the National Cancer Institute to perform additional research studies designed to help us better understand lymphoma.

A description of this clinical trial will be available on http://www.Clinicaltrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most the Web site will include a summary of the results. You can search this Web site at any time.

Millennium Pharmaceuticals, Inc is collaborating with us on this study. Thus, Millennium and its designees will have access to your research records and data which may include:

- results from procedures conducted to find out if you are eligible for the study;

- information that is created or collected from you during the study, such as the results of any tests or procedures performed during the study;
- information about your medical history and treatment included in your medical records.

The above information and materials may identify you by name, address, telephone number, social security number, health plan number, study number, date of birth, dates relating to various medical procedures, or other identifying information. You cannot participate in this study if you do not sign this form, authorizing the uses and disclosures of your information described below.

You will be informed of any new findings related to the development or safety of VELCADE that may affect your willingness to continue to take part in this study.

Early Termination

You will be discontinued from this study for any of the following reasons:

- You may be withdrawn from the study if you do not comply with the study requirements.
- Your doctors do not feel it is in your medical best interests to be continued on this study.
- You have had unacceptable toxicity which does not permit safe continuation on the study
- You require another treatment.

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to Millennium Pharmaceuticals, Inc. or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases cannot be recalled and destroyed.

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

You should also know that there are several circumstances in which the Certificate does not provide coverage. These include when information:

- will be used for auditing or program evaluation internally by the NIH; or
- must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA).
- is necessary for your medical treatment and you have consented to this disclosure;
- is for other research.

In addition, identifiable, sensitive information protected by this Certificate cannot be admissible as evidence or used for any purpose in any action, suit, or proceeding without your consent.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

Millennium Pharmaceuticals, Inc. is providing VELCADE for this study to NIH without charge. No NIH investigator involved in this study receives payments or other benefits from any company whose drug, product or device is being tested. However, there are some non-NIH collaborators on this study who may receive payments or benefits, limited by the rules of their workplace.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the

information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect, use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used.

Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future. If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Wyndham Wilson, M.D., Ph.D.; Building 10, Room 4N115, Telephone: 240-760-6092. If you have any questions about the use of your specimens and data for future research studies, please contact the Office of the Clinical Director, Telephone: 240-760-6070.

You may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM OCTOBER 29, 2018 THROUGH NOVEMBER 12, 2019.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____