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Protocol Title

A Phase I/II trial of Bendamustine in Combination with Bortezomib and Pegylated Liposomal Doxorubicin in Patients with Relapsed or Refractory Multiple Myeloma: Hoosier Cancer Research Network MM08-141

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Trial Supported by

Cephalon Oncology (Investigator Initiated Study)

Investigational New Drug (IND) Application

IND exempt

Initial Protocol Version Date: **25SEP2009**
Amendment # 1: Amended Protocol Version Date: 06APR2010
Amendment #2: Amended Protocol Version Date: 16MAR2012
Amendment #3: Amended Protocol Version Date: 04APR2013
Amendment #4: Amended Protocol Version Date: 21AUG2014

PROTOCOL SIGNATURE PAGE

A Phase I/II trial of Bendamustine in Combination with Bortezomib and Pegylated Liposomal Doxorubicin in Patients with Relapsed or Refractory Multiple Myeloma: **Hoosier Cancer Research Network MM08-141**

VERSION DATE: 21AUG2014

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to Hoosier Cancer Research Network and keep a copy for your files.

_____ _____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator Title

_____

Name of Facility

_____

Location of Facility (City and State)

_____ ❑ Not Submitting to IRB

Expected IRB Approval Date

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STUDY SYNOPSIS

TITLE	A Phase I/II trial of Bendamustine in Combination with Bortezomib and Pegylated Liposomal Doxorubicin in Patients with Relapsed or Refractory Multiple Myeloma: Hoosier Cancer Research Network MM08-141
STUDY PHASE	Phase I/II
OBJECTIVES	**Primary Objective:** • Determine the maximum tolerated dose of bendamustine in association with bortezomib and pegylated liposomal doxorubicin in patients with relapsed or refractory MM. • Assess the overall response rate (CR+PR) of bendamustine in association with bortezomib and pegylated liposomal doxorubicin in patients with relapsed or refractory MM. **Secondary Objective:** • Describe the toxicity of the combination of bendamustine with bortezomib and pegylated liposomal doxorubicin. • Evaluate the time to progression, overall survival, progression free survival, and duration of response of MM patients treated with bendamustine, bortezomib and pegylated liposomal doxorubicin. • Correlate bendamustine pharmacokinetics parameters (C_{max}, t1/2, and AUC) at cycle 1 (and cycle 2) with patients' responses and correlate the DNA damage/repair at day 1 of cycle 1 and day 4 of cycle 2 with patients' responses.
STUDY DESIGN	This will be an open label phase I/II trial to determine the safety and the biologic activity of the bendamustine, bortezomib and pegylated liposomal doxorubicin combination.
NUMBER OF PATIENTS	A total of up to 69 patients will be enrolled. Up to 18 patients will be enrolled on the Phase I portion. Up to 51 patients will be enrolled on the Phase II portion.
ELIGIBILITY	• Written informed consent, HIPAA authorization for release of personal health information, ability to understand the requirements of the study, abide by the study restrictions, and agree to return for the required assessments. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately. • Age ≥ 18 years at the time of consent. • ECOG Performance Status of 0-2 within 21 days prior to registration for protocol therapy. • A histologically established diagnosis of multiple myeloma with evidence of relapse or refractory disease. **NOTE:** Relapsed myeloma is defined in patients as at least a 25% increasing monoclonal (M)-protein in serum or urine or in the size of a plasmacytoma compared to a best response reached after a previous therapy. **NOTE:** Refractory myeloma is defined as failure to achieve at least a minor response (patient achieved stable disease as his/her best response) or progression of disease on current therapy or within 60 days of last dose of current therapy. • Must have a detectable serum or urine M-Protein by protein electrophoresis that is at least 500 mg/dL (serum) or 1 gm/24 hours (urine), respectively, or serum free light chain level >100 mg/l for the involved free light chain. **NOTE:** Patients with non-secretory myeloma or plasmacytoma only will be excluded.

	• Must have received at least one (1) prior line of systemic treatment that has included either lenalidomide or thalidomide. **NOTE:** Patients may have undergone prior autologous stem cell transplantation (stem cell transplant with high dose induction chemotherapy with/without planned maintenance therapy will be considered one line of therapy). Patients who have received prior bortezomib, pegylated liposomal doxorubicin, or the combination are eligible. Patients who have received prior bendamustine for the treatment of MM are also eligible if this was not combined with bortezomib or pegylated liposomal doxorubicin. • Must not have received an excessive cumulative dose of anthracycline. **NOTE:** Permissible prior exposure is doxorubicin ≤ 240 mg/m^2 (or anthracycline equivalent calculated as 1 mg doxorubicin = 1 mg Doxil = 1.8 mg epirubicin = 0.25 idarubicin = 0.3 mg mitoxantrone) • Females of childbearing potential and males must be willing to use an effective method of contraception (hormonal or barrier method of birth control; abstinence) from the time consent is signed until 30 days after treatment discontinuation. • Females of childbearing potential must have a negative pregnancy test within 7 days prior to prior to registration for protocol therapy. **NOTE:** Females are considered not of child bearing potential if they are surgically sterile (they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months. • Females must not be breastfeeding. • Must be willing to provide correlative blood samples. • No ≥ grade 2 peripheral neuropathy. • No cytotoxic chemotherapy within 30 days prior to registration for protocol therapy. **NOTE:** This interval may be reduced to 14 days for thalidomide, lenalidomide, bortezomib, or corticosteroids, provided other entry criteria are met. • No autologous stem cell transplant within 6 months prior to registration for protocol therapy • No prior radiation therapy to > 25% of bone marrow forming bones (i.e., pelvis) within 30 days prior to registration for protocol therapy. See Study Procedures Manual to calculate percent of prior radiation. • No current corticosteroid therapy in doses greater than 10 mg daily of prednisone (or equivalent) if given for management of co-morbid conditions. • No known central nervous system involvement by myeloma. • No poorly controlled intercurrent illness including, but not limited to, ongoing or active infection, poorly controlled diabetes, symptomatic congestive heart failure, cardiac arrhythmia, or psychiatric illness/social climate that in the opinion of the investigator would limit compliance with study requirements. • No unstable angina pectoris or recent myocardial infarction (within 6 months). • No patients known to be positive for HIV, or active Hepatitis A, B, or C. • No major surgery within 30 days prior to registration for protocol therapy. Placement of a venous access device within 30 days prior to registration for protocol therapy is allowed. **NOTE**: Organ and marrow function must be assessed within 21 days prior to registration for protocol therapy.

<table>
<tr><td></td><td>

- Absolute neutrophil count (ANC) ≥ 1.2 x K/mm^3 (without G-CSF support in the previous 14 days)
- Platelets ≥ 75 x K/mm^3 (without platelet transfusion in the previous 14 days)
- LVEF >45% corrected by MUGA scan or echocardiogram.
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
- AST ≤ 2.5 x ULN
- ALT ≤ 2.5 x ULN
- Serum creatinine < 3.0 mg/dL

</td></tr>
<tr><td>EVALUATION CRITERIA</td><td>

Responses will be based on a modified International Myeloma Working Group criteria[18], and defined as outlined below:

<table>
<tr><th>Response*</th><th>Definition</th></tr>
<tr><td>Complete Response (CR)</td><td>Negative for monoclonal protein by immunofixation on the serum and urine, <u>and</u>
Disappearance of any soft tissue plasmacytomas, <u>and</u>
<5% plasma cells in bone marrow</td></tr>
<tr><td>Stringent complete response (sCR)</td><td>CR as defined above, <u>plus</u>
Normal free light chain ratio, <u>and</u>
Absence of clonal cells in bone marrow by flow-cytometry</td></tr>
<tr><td>Near complete response (nCR)</td><td>Meeting criteria for CR, <u>except</u> with persistence of original monoclonal protein by IF while absence by serum or urine protein electrophoresis.</td></tr>
<tr><td>Very good partial response (VGPR)</td><td>90% or more reduction in serum M-protein <u>plus</u>
urine M-component <100 mg/24 hours</td></tr>
<tr><td>Partial response (PR)</td><td>50% or more reduction in serum M-protein <u>and</u>
90% or more reduction in urine M-protein or to <200 mg/24hours

If serum and urine M-protein are immeasurable, a 50% or more reduction in free light chain level is required in place of M-protein criteria.

In addition to the above criteria, if present at baseline, a 50% or more reduction in the size of soft tissue plasmacytomas is required.

For patients with free light chains as their only measurable disease, a 50% or greater decrease in the difference between involved and uninvolved free light chain levels.</td></tr>
<tr><td>Minimal response (MR)</td><td>25-49% reduction in serum M-protein, <u>and</u>

If present, a 50-89% reduction in 24 hour light chain excretion, which exceeds 200 mg/24 hours, <u>and</u>

No increase in the size or number of lytic bone lesions</td></tr>
</table>

</td></tr>
</table>

		(development of compression fracture does not exclude response)
	Stable disease (SD)	Not meeting criteria for CR, VGPR, MR, PR or progression of disease.
	Progressive disease (PD)	Any one of the following criteria: - Increase of 25% or more in serum or urine M-protein from baseline. - Serum M-protein and/or the absolute increase must be ≥0.5 g/dL - Urine M-protein and/or absolute increase must be ≥200 mg/24 hours - Development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas - Development of hypercalcemia (corrected serum Ca^{++} >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disease. In patients who have achieved CR or sCR: - Reappearance of serum or urine M-protein by IF or electrophoresis. - Development of 5% or more clonal plasma cells in the bone marrow - Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesions, or hypercalcemia).
	* All response categories require two consecutive assessments made any time before the institution of any new therapy. Repeat of radiographic studies and bone marrow evaluation are not required to satisfy these responses.	

STATISTICAL CONSIDERATIONS

Although bendamustine has been combined with mitoxantrone, etoposide, and Idarubicin with acceptable toxicity, there is currently no data of its appropriate dosing in combination with pegylated liposomal doxorubicin and bortezomib. Therefore, we will investigate the combination in two phases:

Phase I component

The primary objective in the phase I component is to determine the MTD of bendamustine in combination with bortezomib and pegylated liposomal doxorubicin (with growth factor support) to gain a better idea of safe dosing before proceeding with the second phase to assess efficacy.

A standard 3 + 3 design will be used to determine the MTD. Three patients will be enrolled at dose level 1. If no patient experiences dose limiting toxicities (DLTs), escalation to the next dose level will occur. If 1 of 3 patients at any dose level experiences a DLT, 3 additional patients will be enrolled at that dose level. If only 1 of 6 patients experiences a DLT, dose escalation will be permitted. If 2 or more patients at any dose level experienced a DLT, then the previous dose with at most 1 out of 6 DLT will be considered the maximum tolerated dose (MTD). If myelosuppression is dose limiting, we will add an additional dose level at the MTD with growth factor (G-CSF;

filgrastim) support (dose level +3). Dose escalation will not occur beyond level 3. Therefore, we will need at most 18 patients in phase I.

Phase II component

The primary objective in the Phase II component is to determine the overall response (CR+PR) at the MTD of bendamustine in combination with bortezomib and pegylated liposomal doxorubicin. Note that here CR includes all categories of sCR, CR, nCR and PR includes all categories of VGPR and PR defined in Section 8.1. A min/max optimal two-stage design will be followed. Patients will be considered evaluable for response if they have received at least 2 cycles of therapy or if they have had disease progression before 2 cycles are completed. If a patient does not finish at least 2 cycles (except for disease progression), we will recruit a new patient to replace him/her. An overall response rate of 60% or more will be acceptable, while an overall response rate of less than 40% will be considered unacceptable. In statistical terms, we will test the null hypothesis H0: $p0<0.4$ versus the alternative hypothesis H1: $p1>0.6$, where p is the probability of overall response. Type I and type II errors will be both set at 0.1. In the first stage, we will enroll 28 evaluable patients. If less than 12 patients respond, the trial will be stopped and we will conclude in favor of the null hypothesis. If 12 or more patients respond, we will proceed with the second stage by enrolling an additional 13 evaluable patients for a maximum sample size of 41 evaluable patients. If more than 20 patients achieve at least a partial response, we will conclude in favor of H1: $p1> 0.6$. The probability of early termination under the null hypothesis is 0.55. We expect only 80% of enrolled patients to be evaluable. Therefore, overall, we will have to enroll 51 patients if the stage 2 is conducted to achieve 41 evaluable samples.

Analysis

- **Phase I Component**

  Patients' characteristics will be summarized using mean, median, and standard deviation for continuous variables, and tables for discrete variables. Toxicity profile (for all patients) will be presented by rate of overall toxicity and rates of grade 3 or 4 toxicities analyzed separately and combined. Adverse events will be summarized in phase I and accompanied by 95% confidence intervals using binomial distribution. Response rates will be summarized.

- **Phase II Component**

  Descriptive analysis of patients' characteristics will be summarized in a similar way as Phase I.

  <u>Primary analysis</u>

  The primary objective in phase II is to assess the overall response rate (CR+PR) of treatment at the MTD level found in phase I. Overall response rate will be evaluated and accompanied by 95% confidence intervals using the binomial distribution. Response rate by categories will be calculated with 95% confidence intervals.

  <u>Secondary analysis</u>

  Toxicity profile (for all phase II patients) will be presented by rate of overall toxicity and rates of grade 3 or 4 toxicities analyzed separately and combined. The toxicity analysis may also be performed for the patients with and without

autologous stem cell transplantation separately due to the potential higher hematological toxicity in transplanted patients. Time to progression will analyzed using Kaplan-Meier survival analysis and accompanied with 95% confidence interval. Similar analysis will be applied to the progression-free survival, duration of response, and overall survival. Median survival time will be calculated with 95% confidence interval for each of the time-to-event outcome.

Correlative analysis

The bendamustine pharmacokinetics parameters (C_{max}, t1/2, and AUC) at cycle 1 (and cycle 2) will be correlated with response by comparing their means between the responders (CR +PR) and those respond (non-responders) otherwise using two-sample t tests. Appropriate transformation of the pharmacokinetics parameters will be done to fit the normal distribution assumption. Similar analysis will be used to correlate them with toxicity (grade 3-4).
The DNA damage/repair at day 1 of cycle 1 and day 4 of cycle 2 will be compared using a paired t test. AUC for the extent of DNA damage will be correlated with response by comparing their means between responders and non-responders. AUC will be correlated with response duration using a proportional hazards model, and plasma AUC using Pearson's correlation coefficient.

Modifications in the August 2014 amendment

The amendment introduces a lower dose level of bendamustine, which if passing the study will be the recommended dose level for future studies. This low dose will be used for the remaining first stage, and second stage. The same rule will be used for the first stage. For the second stage, the response rate at the low dose will be evaluated first. If this rate is no less than the response rate of the high dose by 10% and no less than 50%, the two dose levels will be combined in analyses following the original rule, i.e. if more than 20 patients achieve at least a partial response, we will conclude in favor of H1: $p1 > 0.6$. Otherwise, the response rate will be evaluated and its 95% confidence intervals will be calculated separately for the two dose levels. It is argued from the scientific point of view that the low dose will have at least the same or even higher response rate as the high dose. Consequently, the power level will be at least the same as the original designed. For the secondary and correlative analyses, they will be performed both separately for the two dose levels and in the combined manner.

Confidential

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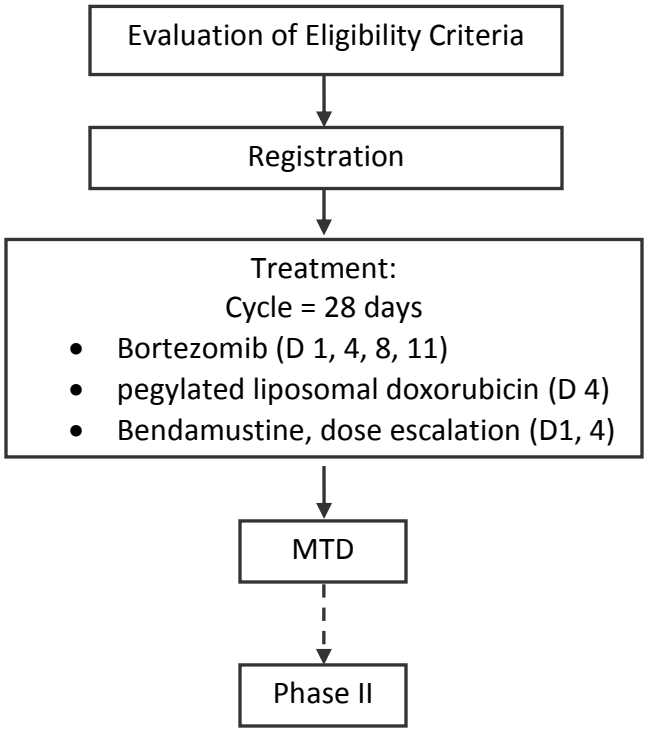
SCHEMA

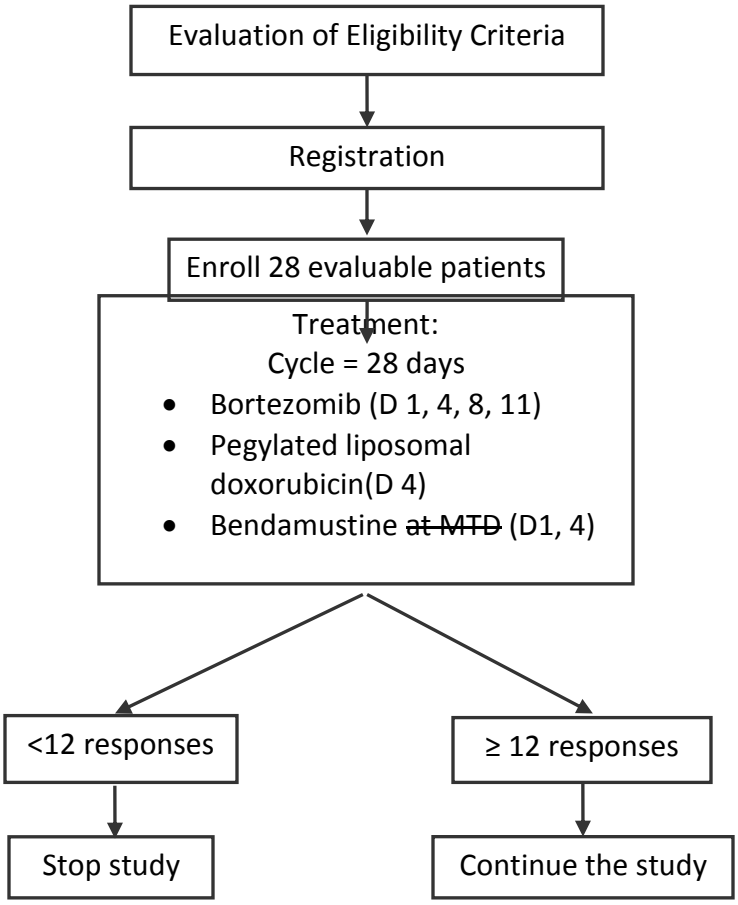
A Phase I/II trial of Bendamustine in Combination with Bortezomib and Pegylated Liposomal Doxorubicin in Patients with Relapsed or Refractory Multiple Myeloma: Hoosier Cancer Research Network MM08-141

Phase I



Protocol therapy may continue for up to 8 cycles in the absence of disease progression or unacceptable toxicity.

Phase II



Protocol therapy may continue for up to 8 cycles in the absence of disease progression or unacceptable toxicity.

1.0 BACKGROUND & RATIONALE

Multiple myeloma is a clonal disorder affecting terminally differentiated B-cells, with accumulation of plasma cells in the bone marrow. The annual incidence of MM is approximately 4 per 100,000, and is particularly common in the elderly population with a median age of 65 years; only 3% of patients with MM are < 40 years old.

Therapy for MM remains unsatisfactory and is essentially palliative. Although cytotoxic chemotherapy prolongs the survival of symptomatic patients, the prognosis of treated patients with MM remains poor. While high-dose chemotherapy with stem cell support increases the proportion of complete responses, the effect on prolongation of overall survival remains relatively modest, and all patients invariably relapse[1,2]. Intensifying treatment with tandem cycles of high-dose alkylating agents (with or without total body radiation) have improved outcome in some[3,4], but not all studies[5]. For patients who progress after primary chemotherapy therapy, including autologous stem cell transplantation, further chemotherapy is generally of limited benefit. Overall, the results of conventional cytotoxic chemotherapy in MM suggest that a plateau has been reached, indicating the need for novel therapies.

Recently, the novel agents, thalidomide, lenalidomide, and bortezomib have been investigated with promising results[6,7]. In recent trials, a further improvement in response rates and time to progression is observed when these agents are combined with corticosteroids and conventional cytotoxic agents[8,9,10]. The novel regimen of bortezomib and pegylated liposomal doxorubicin (PLD) has recently been shown to result in a complete response (CR) rate of 36%, overall response of 73%, and a time to progression (TTP) of 9.3 months in patients with relapsed and refractory MM[11]. Furthermore, the regimen was shown to be superior to bortezomib alone in a phase III trial[12], supporting the preclinical studies indicating synergism between bortezomib and DNA damaging agents[13]. In spite of the excellent outcomes reported, the majority of patients still relapse indicating a need to continue to develop novel regimens. The bortezomib and pegylated liposomal doxorubicin regimen represents a good platform on which to combine other active and non-cross-reactive agents.

1.1 Bendamustine

Bendamustine is a DNA alkylating agent with a unique mechanism of action, including the ability to cause cross-linking between DNA and proteins and proteins alone. With short exposure, bendamustine also induces the onset of apoptosis as well as ATP depletion, and these effects are sustained. Experiments have demonstrated that bendamustine has only partial cross resistance with other alkylating agents and has *in vitro* activity in cells that are resistant to a variety of anti-tumor agents. In preclinical studies, bendamustine toxicity was predominantly bone marrow suppression, gastrointestinal toxicity, fever, dermal hypersensitivity reactions, glomerulitis, prostatic atrophy, and alopecia.

Bendamustine has been shown to be clinically efficacious in non-Hodgkin's lymphoma, CLL, breast cancer, and MM. In a phase III trial comparing bendamustine (150 mg/m^2 on days 1 and 2) plus prednisone (BP) and melphalan (15 mg) plus prednisone (MP) in

patients with MM, BP resulted in significantly more patients achieving complete remission (CR) (32% vs. 11%, P=0.009), and longer remission duration (18 months vs. 12 months, P=0.017)[14]. Bendamustine has been investigated in combination with a number of classic cytotoxic agents, including etoposide, Idarubicin, and mitoxantrone in a variety of lymphoid disorders with acceptable toxicity and tolerability.

However, one published study using lymphoma cell lines has suggested that the combination of bendamustine with doxorubicin (or mitoxantrone) is antagonistic *in vitro*[15], discouraging the investigation of bendamustine/ doxorubicin combination therapy in MM. To establish whether similar antagonism occurs in MM cells and study the effect of addition of bendamustine (B) to doxorubicin (D) and bortezomib (V), we (Farag Laboratory, Indiana University School of Medicine) evaluated cellular cytotoxicity using the different drug combinations in H929 and MM1R myeloma cell lines using the MTS ([3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt) assay. The effect of the combination in terms of additive, antagonistic, or synergistic activity was assessed by Valeriote and Lin's method[16]. In repeated experiments, bendamustine alone induced MM cell death in a time and dose-dependent manner, with a bendamustine concentration that was lethal to 50% of cells (LC_{50}) of 34.9± 3.4 μg/ml after 48 hours of drug exposure. Further, when combined with doxorubicin, bendamustine showed no antagonistic effect. Indeed, the measured cell survival for the combination of B+D was similar to the calculated expected cell survival based on individual drug activity, indicating an additive effect (Figure 1). In addition, bendamustine showed an additive effect when combined with bortezomib, and as previously shown doxorubicin and bortezomib (D+V) were synergistic (Figure 1). To test the effect of the combination of all three drugs, cells were cultured with bendamustine (15 μg/ml) and doxorubicin (0.03 μg/ml) for 48 hours, and bortezomib (2.5 nmol/l) was added in the last 24 hours, and cytotoxicity was assayed. The expected cell survival for the combination of B+(D+V) is lower than the product of the effects of B and D+V, indicating a synergistic effect of bendamustine when combined added to the combination of doxorubicin and bortezomib (Figure 1). These results provide pre-clinical rationale for clinically testing the efficacy of combining bendamustine with the established combination of pegylated liposomal doxorubicin and bortezomib, which may be a highly effective regimen in the treatment for MM.

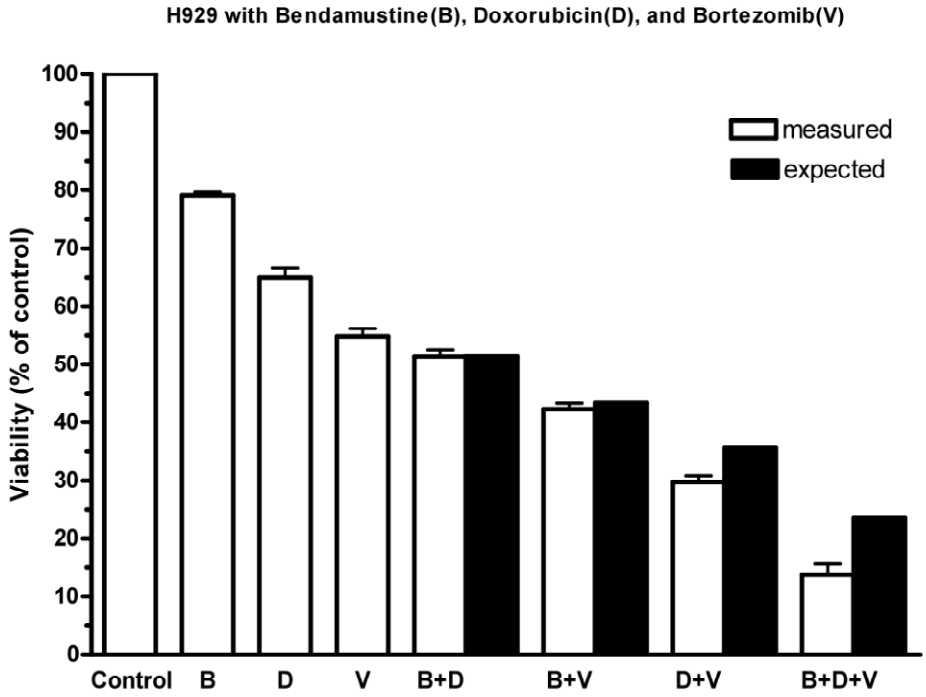


Figure 1. Representative experiment showing synergistic cytotoxic activity of bendamustine when combined with doxorubicin and bortezomib in H929 cells. *B, 15μg/ml bendamustine; D, 0.03μg/ml doxorubicin; V, 2.5nmol/L bortezomib; B+D, 15μg/ml bendamustine and 0.03μg/ml doxorubicin; B+V, 15μg/ml bendamustine and 2.5nmol/L bortezomib; D+V, 0.03μg/ml doxorubicin and 2.5nmol/L bortezomib; B+D+V, the combination of 15μg/ml bendamustine with 0.03μg/ml doxorubicin and 2.5nmol/L bortezomib. Synergy of the drug combination was defined when the measured cell survival was lower than the product of the effect of each single drug.*

In humans, bendamustine follows first order pharmacokinetics over a wide range of doses (120 to 280 mg/m^2)[14]. Following a 30-minute IV infusion, C_{max} is achieved in 30-35 minutes; elimination from plasma occurs in a biphasic fashion with a distribution half life of approximately 10 minutes and an elimination half-life of about 30-36 minutes[14]. About 20% of bendamustine is excreted in the urine, mainly as bendamustine HCl, γ-hydroxy bendamustine, the relatively inactive mono- and di-2-chloroethyl amine bendamustine derivatives, and as yet to be identified polar metabolites[14]. A small amount (8.7%) of bendamustine HCl is excreted via bile. Importantly, in patients with hepatic tumor involvement or with renal dysfunction (including those requiring dialysis) the clearance of bendamustine is not significantly different than clearance in subjects with none of these findings[14]. Therefore, bendamustine is quite suitable for use in MM patients where renal insufficiency is not uncommon due to disease progression.

In phase I clinical trials in human, the maximum tolerated dose (MTD) of a single intravenous infusion of bendamustine was established as 215 mg/m^2, with non-hematological dose-limiting toxicity (DLT) being predominantly anti-cholinergic effects, including dry mouth, cardiac tachyarrhythmia, somnolence and constipation[17]. None of these DLTs overlap with those of those of bortezomib and pegylated liposomal doxorubicin.

As bendamustine appears to be non-cross resistant to other alkylating agents, has potent anti-myeloma activity, and has DLT that is not overlapping with bortezomib and

pegylated liposomal doxorubicin, we postulate that the combination of bendamustine into the bortezomib and pegylated liposomal doxorubicin regimen may be an effective, well-tolerated preparative regimen for MM patients. While an increase in myelosuppression is a possibility, this may be mitigated successfully with myeloid growth factors.

1.2 Rationale for study

As reviewed above, the combination of bortezomib and pegylated liposomal doxorubicin has been shown to have synergistic activity against myeloma cells, and has also been shown to be a clinically effective regimen in MM patients compared to bortezomib alone in a randomized phase III trial. We have also shown that the addition of bendamustine to the combination of bortezomib and doxorubicin shows further synergy against MM cell lines in pre-clinical studies, providing pre-clinical rationale to test the three drug combination clinically.

Although bendamustine has been combined with mitoxantrone, etoposide, and idarubicin with acceptable toxicity, there is currently no data of its appropriate dosing in combination with pegylated liposomal doxorubicin and bortezomib. Therefore, we will investigate the combination in two phases:

(1) In the first phase, we will perform a limited phase I study to determine the MTD of bendamustine in combination with bortezomib and pegylated liposomal doxorubicin to gain a better idea of safe dosing before proceeding with the second phase to assess efficacy. As myelosuppression may be a dose-limiting effect that could be overcome with growth factor support, we will also test the MTD of the combination with myeloid growth factor support.

(2) At the MTD, we will expand to a phase II trial to assess efficacy of the combination in terms of overall response rate (complete and partial responses).

1.3 Rational for MTD reduction in Phase II

In the course of the phase II portion of the study, an excess of cumulative myelotoxicity was observed that occurred beyond the first cycle. Of 22 patients treated, 8 patients came off study because of prolonged grade 3-4 myelotoxicity (neutropenia and/or thrombocytopenia), which occurred beyond the third cycle of treatment. As patients came off study, the planned course of treatment was not delivered which could have compromised the potential maximal response. As this was not observed in the first cycle, it was not evident in the phase I component of the trial when the MTD was determined. Based on this observation, the study is amended to dose reduce bendamustine and allow longer period for recovery of counts before patients came off study provided clinical benefit is observed (see Sections 5.2 and 6.2).

2.0 OBJECTIVES

2.1 Primary Objectives:

2.1.1 Determine the maximum tolerated dose of bendamustine in association with bortezomib and pegylated liposomal doxorubicin in patients with relapsed or refractory MM.

2.1.2 Assess the overall response rate (CROP) of bendamustine in association with bortezomib and pegylated liposomal doxorubicin in patients with relapsed or refractory MM.

2.2 Secondary Objectives:

2.2.1 Describe the toxicity of the combination of bendamustine with bortezomib and pegylated liposomal doxorubicin.

2.2.2 Evaluate the time to progression, overall survival, progression free survival, and duration of response of MM patients treated with bendamustine, bortezomib and pegylated liposomal doxorubicin.

2.2.3 Correlate bendamustine pharmacokinetics parameters (C_{max}, t1/2, and AUC) at cycle 1 (and cycle 2) with patients' responses and correlate the DNA damage/repair at day 1 of cycle 1 and day 4 of cycle 2 with patients' responses.

3.0 ELIGIBILITY CRITERIA

3.1 Written informed consent, HIPAA authorization for release of personal health information, ability to understand the requirements of the study, abide by the study restrictions and agree to return for the required assessments.
NOTE: HIPAA authorization may be included in the informed consent or obtained separately.

3.2 Age $\geq$ 18 years at the time of consent.

3.3 ECOG Performance Status of 0-2 within 21 days prior to registration for protocol therapy.

3.4 A histologically established diagnosis of multiple myeloma with evidence of relapse or refractory disease.

NOTE: Relapsed myeloma is defined in patients as at least a 25% increasing monoclonal (M)-protein in serum or urine or in the size of a plasmacytoma compared to a best response reached after a previous therapy.

NOTE: Refractory myeloma is defined as failure to achieve at least a minor response (patient achieved stable disease as his/her best response) or progression of disease on current therapy or within 60 days of last dose of current therapy.

3.5 Must have a detectable serum or urine M-Protein by protein electrophoresis that is at least 500 mg/dL (serum) or 1 gm/24 hours (urine), respectively. For patients without measurable disease by serum or urine protein electrophoresis as defined above, patients who have detectable serum free light chain >100 mg/l will be eligible.
NOTE: Patients with non-secretory myeloma or plasmacytoma only will be excluded.

3.6 Must have received at least one (1) prior line of systemic treatment that has included either lenalidomide or thalidomide.
NOTE: Patients may have undergone prior autologous stem cell transplantation (stem cell transplant with high dose induction chemotherapy with/without planned maintenance therapy will be considered one line of therapy). Patients who have received prior bortezomib, pegylated liposomal doxorubicin, or the combination are eligible. Patients who have received prior bendamustine for the treatment of MM are also eligible if this was not combined with bortezomib or pegylated liposomal doxorubicin.

3.7 Must not have received an excessive cumulative dose of anthracycline.
NOTE: Permissible prior exposure is doxorubicin ≤ 240 mg/m^2 (or anthracycline equivalent calculated as 1 mg doxorubicin = 1 mg Doxil = 1.8 mg epirubicin = 0.25 idarubicin = 0.3 mg mitoxantrone)

3.8 Females of childbearing potential and males must be willing to use an effective method of contraception (hormonal or barrier method of birth control; abstinence) from the time consent is signed until 30 days after treatment discontinuation.

3.9 Females of childbearing potential must have a negative pregnancy test within 7 days prior to registration for protocol therapy.
NOTE: Females are considered not of child bearing potential if they are surgically sterile (they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months.

3.10 Females must not be breastfeeding.

3.11 Must be willing to provide correlative blood samples.

3.12 No ≥ grade 2 peripheral neuropathy.

3.13 No cytotoxic chemotherapy within 30 days prior to registration for protocol therapy.
NOTE: This interval may be reduced to 14 days for thalidomide, lenalidomide, bortezomib, or corticosteroids, provided other entry criteria are met.

3.14 No autologous stem cell transplant within 6 months prior to registration for protocol therapy.

3.15 No prior radiation therapy to ≥ 25% of bone marrow forming bones (i.e., pelvis) within 30 days prior to registration for protocol therapy. See Study Procedures Manual to calculate percent of prior radiation.

3.16 No current corticosteroid therapy in doses greater than 10 mg daily of prednisone (or equivalent) if given for management of co-morbid conditions.

3.17 No known central nervous system involvement by myeloma.

3.18 No poorly controlled intercurrent illness including, but not limited to, ongoing or active infection, poorly controlled diabetes, symptomatic congestive heart failure, cardiac arrhythmia, or psychiatric illness/social climate that in the opinion of the investigator would limit compliance with study requirements.

3.19 No unstable angina pectoris or recent myocardial infarction (within 6 months).

3.20 No patients known to be positive for HIV, or active Hepatitis A, B, or C.

3.21 No major surgery within 30 days prior to registration for protocol therapy. Placement of a venous access device within 30 days prior to registration for protocol therapy is allowed.

NOTE: Organ and marrow function must be assessed within 21 days prior to registration for protocol therapy.

3.22 Absolute neutrophil count (ANC) $\geq$ 1.2 x K/mm^3 (without G-CSF support in the previous 21 days)

3.23 Platelets $\geq$ 75 x K/mm^3 (without platelet transfusion in the previous 21 days)

3.24 LVEF >45% corrected by MUGA scan or echocardiogram.

3.25 Total bilirubin $\leq$ 1.5 x upper limit of normal (ULN)

3.26 AST $\leq$ 2.5 x ULN

3.27 ALT $\leq$ 2.5 x ULN

3.28 Serum creatinine < 3.0 mg/dL

4.0 PATIENT REGISTRATION

4.1 All patients must be registered through the Hoosier Cancer Research Network's database system.

Patients must be registered prior to starting protocol therapy and begin therapy within 5 working days of registration.

4.2 Blinding

The study treatment is not blinded to the patient or the investigator

5.0 TREATMENT PLAN

The protocol and treatment plan will be conducted in two components:

1) A dose-escalation, phase I study to determine the MTD of bendamustine in combination with bortezomib and pegylated liposomal doxorubicin.
2) A phase II study at the MTD of bendamustine to assess efficacy of the combination in terms of overall response rate.

5.1 Phase I component

The primary objective is to determine the MTD of bendamustine when combined with bortezomib and pegylated liposomal doxorubicin. All patients will receive the same doses of bortezomib and pegylated liposomal doxorubicin. The dose of bendamustine will be escalated in successive cohorts of patients. Using a standard dose escalation design, successive cohorts of 3 patients will be treated with escalating doses of bendamustine as outlined in Section 5.1.1 (see also dose-escalation rules Section 5.1.3). At the MTD (or highest dose-level if the MTD is not reached), patients will then be treated on the Phase II component of the study.

5.1.1 Treatment schedule

After informed consent and collection of baseline tests and samples, patients will receive study drugs according to the following schedule. The order of administration will be left to the investigator's discretion. Each cycle will be 28 days. Patients will continue treatment for a total of 8 cycles.

Table 1: Phase I Treatment Administration

REGIMEN DESCRIPTION				
Agent	**Dose**	**Route**	**Schedule**	**Cycle length**
Bortezomib	1.3 mg/m^2	IV bolus	Days 1, 4, 8, and 11	28 days
Pegylated liposomal doxorubicin	30 mg/m^2	IV over 1 hour	Day 4	
Bendamustine*	escalating cohorts	IV over 1 hour	Days 1 and 4	

*** NOTE**: The dose of bendamustine will be escalated in phase I of the protocol in successive cohorts according to the following dose levels:

Table 2: Phase I Dose levels

Cohort	n	Bendamustine (mg/m^2)	Bortezomib (mg/m^2)	Pegylated liposomal doxorubicin (mg/m^2)	Filgrastim
–1	**3-6**	**60**	**1.3**	**30**	**-**
+1 (start)	**3-6**	**90**	**1.3**	**30**	**-**
+2	**3-6**	**120**	**1.3**	**30**	**-**
+3	**3-6**	**120 (or MTD)**	**1.3**	**30**	**5 µg/kg**

Patients will initially be enrolled on dose level +1 (i.e., bendamustine 90 mg/m^2).

At any dose level, three (3) patients will be treated. If no dose-limiting toxicity [DLT] is observed (see Section 5.1.2 for definition), the next cohort of three (3) patients is treated at the next higher dose level. If 1 of the 3 patients demonstrates DLT in a given dose level, an additional 3 patients are treated at that dose level. If only 1 of the 6 shows DLT, the next cohort of three patients is entered at the next dose level. If 2 or more of the 6 demonstrate DLT at the first dose level, we will deescalate to dose level –1. At subsequent dose levels, the MTD is defined as the previous dose level where no more than 1 of 6 patients experiences DLT.

5.1.1.1 Dose Level +3:

If only myelosuppression is dose limiting at any given dose level, we will add an additional dose level at the MTD with growth factor (G-CSF; filgrastim) support (dose level +3).

Filgrastim will be administered as 5 µg/kg/day SC starting day 6 until neutrophil recovery to ANC ≥1000.

Dose escalation will occur only when all patients in the given cohort have completed the first cycle. The MTD will be based on DLT in the first cycle. Patients can continue with repeated cycles at the same dose level of the drugs until progression up to a maximum of 8 cycles. Dose modification in subsequent cycles will be performed according to toxicity.

5.1.2 Dose-Limiting Toxicity (DLT) in Phase I Component of Trial

The National Cancer Institute Common Terminology Criteria for Adverse events (CTCAE) version 3.0 (http://ctep.cancer.gov) will used to characterize toxicities.

DLT is defined as adverse events (AE) related to study treatment occurring in the first cycle of treatment with an attribution of possible, probably, or definite and fulfilling one of the following criteria:

- Grade 4 neutropenia and thrombocytopenia that persists for greater than 7 days, and which is not due to underlying disease.
- Grade 4 fatigue or a two-point decline in ECOG performance status.

- Any grade 3 or 4 non-hematologic/organ toxicity (except rash, alopecia, nausea and vomiting controllable with anti-emetic therapy, and correctable biochemical abnormalities).
- Treatment delays exceeding 14 days due to toxicity during the first cycle of treatment will constitute DLT.

5.1.3 Maximum Tolerated Dose (MTD) and Dose Escalation Rules in Phase I Component

To define the Maximum Tolerable Dose (MTD), patients will be evaluated for DLT in the first cycle of treatment. The MTD is the dose level at which less than 2 out of 6 patients experience DLT. The MTD becomes the recommended dose for the phase II component of the study.

Patients will initially be enrolled onto dose level +1 (see Section 5.1.1). Three to six patients will be enrolled at each dose level. All patients assigned to a dose level must be followed at least until day 28 before dose escalation to the next cohort level can begin. The following rules will be followed:

Table 3: Dose Escalation Rules

Number of patients with DLT at given dose level	**Escalation decision**
0 out of 3	Enter 3 patients at the next dose level
≥ 2 out of 3	Dose escalation will be stopped. This dose level will be declared the **maximum administered dose**. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that next lowest dose level.
1 out of 3	Enter at least 3 more patients at this dose level • If 0 of these additional 3 patients experience DLT, proceed to next dose level. • If 1 or more of these additional 3 patients experience DLT, then dose escalation is stopped, and this dose is declared the maximum administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤ 1 out of 6 at highest dose level below the maximum administered dose	This will be defined as the MTD. This dose level will be expanded to enrolment as the Phase II component of the study.

5.1.4 Second Cycle and Subsequent Cycles

Patients may continue receiving treatment in the absence of disease progression or unacceptable toxicity for a total of 8 cycles. Filgrastim may be used at the investigator's discretion. Dose modifications will be made according to section 6.0.

5.2 Phase II component

NOTE: Based on the participant rate of myelosuppression observed in the first 20 number of participants in the Phase II part of this study, the MTD established during the

Phase I is reduced from 120mg/ m^2 to 90mg/ m^2. Please refer to Section 1.3 **Rational for MTD reduction in Phase II.**

The phase II component will determine the response rate to the combination**.** Patients will receive study drugs according to the following schedule:

Table 4: Phase II Treatment Administration

REGIMEN DESCRIPTION				
Agent	**Dose**	**Route**	**Schedule**	**Cycle length**
Bortezomib	1.3 mg/m^2	IV bolus or SQ injection*	Days 1, 4, 8, and 11	28 days
Pegylated liposomal doxorubicin	30 mg/m^2	IV over 1 hour	Day 4	
Bendamustine	90mg/ m^2	IV over 1 hour	Days 1 and 4	

*Reconstitution volumes for IV and SQ injection should be:

INTRAVENOUS:

Route of Administration	Bortezomib (mg/vial)	Diluent (0.9% sodium chloride)	Final Concentration
Intravenous	3.5mg	3.5mL	1.0mg/ml

SUBCUTANEOUS:

Route of Administration	Bortezomib (mg/vial)	Diluent (0.9% sodium chloride)	Final Concentration

Subcutaneous	3.5mg	1.4 mL	2.5mg/ml

INTRAVENOUS AND SUBCUTANEOUS ROUTE OF ADMINISTRATION HAVE DIFFERENT RECONSTITUTED CONCENTRATIONS. CAUTION SHOULD BE USED WHEN CALCULATING THE VOLUME TO BE ADMINISTERED.

Each cycle will be 28 days. Patients will continue treatment for up to 8 cycles.

NOTE:

- In the absence of excessive toxicity, patients will receive a minimum of 2 cycles of therapy before being evaluated for response/progression. Patients whose disease has progressed (>25% increase in serum or urine M protein) will be taken off therapy and failure of therapy declared. Patients whose disease has not progressed will be eligible to continue therapy.
- Patients will continue treatment until disease-progression, development of unacceptable toxicity, or for up to 8 cycles.
- Dose modifications will be made according to the guidelines in Sections 6.1 and 6.2
- Patients will be evaluated for toxicity after each cycle.
- Patients will be evaluated for response/disease progression every 2 cycles (i.e., every 6 weeks) or earlier if clinically indicated.

5.3 Duration of Therapy in Phase II component

Patients will remain on study for up to 8 cycles as long as there is no grade 3 or 4 non-hematological toxicity (see below), and there is no progression of disease as assessed by evaluation after a minimum of 2 cycles.

Patients will be removed from study if they are not able to comply with treatment, if the patient withdraws consent, or if the investigator or agencies involved in the study administration discontinue the study.

5.4 Supportive care

5.4.1 Prophylactic antiemetic therapy will be left to the discretion of the treating physician and/or institutional guidelines.

5.4.2 Bisphosphonates may be used at the discretion of the treating physician.

5.4.3 Erythropoietin preparations may be used for anemia at the discretion of the treating physician.

5.4.4 Palliative radiation therapy may be employed at the discretion of the treating physician for the treatment of intractable pain due to myeloma, pathological fracture, or compressive lesions caused by plasmacytomas.

5.4.5 Other medications and supportive measures to maintain the patient's baseline condition or to treat intercurrent conditions may be administered at the discretion of the investigator.

5.4.6 It is recommended that patients receive prophylaxis for herpes zoster infection (e.g., acyclovir, valacyclovir)

5.4.7 Premedication with antihistamines, antipyretics, and/or corticosteroids for patients with a previous grade 1 or 2 infusion reaction to bendamustine should be considered.

NOTE: Dosing on Days 1 & 4 may be critical for efficacy of the combination. All efforts should be made to maintain the treatment schedule. However, Day 1 infusions may be given ±3 days for reasons such as observed holidays, inclement weather, scheduling conflicts, etc. This should be clearly documented in patient's chart and case report forms.

5.4.8 Filgrastim or pegfilgrastim is strongly encouraged and may be used at the discretion of the treating physician unless deemed necessary per section 6.2.1.

6.0 DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 will be used to grade adverse events.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in section 7.0

Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

Patients who complete 8 cycles of treatment or who discontinue for reasons other than disease progression (but haven't started another treatment) will be evaluated at least 30 days after the last dose of study drug.

If patients require discontinuation of ***any*** drug due to adverse event (as described below) patients should be taken of study.

6.1 Phase I component

6.1.1 No dose modification of any of the drugs will be made during cycle 1 of treatment in the phase I component of the study.

6.1.2 In second and subsequent cycles, the guidelines outlined for dose adjustments for the phase II component of the protocol should be followed (Section 6.2)

6.2 Phase II component

Patients will be monitored for toxicity. Appropriate adjustment of dose, delay or discontinuation of drugs will be made as outlined below for each drug:

6.2.1 Hematological Toxicity

- A cycle of treatment should not start unless the absolute neutrophil count (ANC) is ≥1.0 x K/mm^3 and the platelet count is ≥75 x K/mm^3 at least 28 days after the start of the previous cycle. If blood counts are below these levels, treatment should be delayed for 1 week. After 1 week, the peripheral blood counts are reassessed and treatment again delayed for an additional week if the ANC is <1.2 x K/mm^3 and the platelet count is <75 x K/mm^3. If counts have recovered, filgrastim or pegfilgrastim is strongly recommended and should then be used prophylactically in subsequent cycles if this has not been used in cycle 1 (i.e., level 3 dosing; see section 5.1.1).

- If marrow recovery (ANC is ≥1.2 x K/mm^3, platelet count is ≥75 x K/mm^3) does not occur after a two-week delay, the patient should be taken off study treatment. However, **if responding** to treatment and treatment delayed > 2 weeks due to myelosuppression only, the patient may remain on study treatment with pegylated liposomal doxorubicin and bendamustine reduced by 33%. If > 4 week delay is required the patient should be taken off study treatment.
- If grade 4 neutropenia and/or thrombocytopenia occurred in the previous cycle and/or treatment delayed > 1 week in spite of filgrastim or pegfilgrastim, the doses of pegylated liposomal doxorubicin and bendamustine should be reduced by 33% in subsequent cycles.

- If grade 4 neutropenia (ANC <0.5x K/mm^3) lasting 5 days or more, or neutropenic fever has occurred with a cycle of therapy even if delay in subsequent dosing has not occurred, filgrastim or pegfilgrastim should be used prophylactically with the next cycle of treatment (if it has not been used in cycle 1; i.e., level 3 dosing; see section 5.1.1).

6.2.2 Dose reduction for pegylated liposomal doxorubicin (PLD)

- The dose of pegylated liposomal doxorubicin should be reduced by 33% for myelosuppression that occurs in spite of growth factor support (see Section 6.2.1)

- The dose of pegylated liposomal doxorubicin should be reduced by 50% if the total **bilirubin** is 1.2 to 3 mg/dL, and by 75% if the bilirubin is >3 mg/dL (in the absence of proven hemolysis). Subsequently, the dose should be increased to the original dose if hepatic function improves (bilirubin <1.2 mg/dL). If the patient does not improve after the initial dose reduction, there will be no further reductions.

- The dose will not be modified for renal impairment.

- For patients developing signs of significant cardiac toxicity (ECG voltage criteria; clinically significant arrhythmias) or cardiac failure, pegylated liposomal

doxorubicin should be discontinued. **Patients requiring discontinuation of pegylated liposomal doxorubicin will be removed from protocol.**

- **Palmar-plantar erythrodysesthesia (PPE) syndrome.** Treatment with pegylated liposomal doxorubicin is associated with higher risk of PPE. The following grading of PPE and dose adjustment of pegylated liposomal doxorubicin will be used:

Table 5: Dose Adjustments for Palmar-Plantar syndrome

PALMAR - PLANTAR ERYTHRODYSESTHESIA SYNDROME	
Toxicity Grade	*Dose Adjustment*
1 (mild erythema, swelling, or desquamation not interfering with daily activities)	**Redose unless patient has experienced previous Grade 3 or 4 toxicity.** If so, delay up to 2 weeks and decrease dose by 25%. Return to original dose interval.
2 (erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter.)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** If after 2 weeks there is no resolution pegylated liposomal doxorubicin should be discontinued and patient removed from protocol.
3 (blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution pegylated liposomal doxorubicin should be discontinued and patient removed from protocol.
4 (diffuse or local process causing infectious complications, or a bed ridden state or hospitalization)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, pegylated liposomal doxorubicin should be discontinued and patient removed from protocol.

- **Stomatitis.** The dose of pegylated liposomal doxorubicin should be adjusted as follows for stomatitis:

Table 6: Dose Adjustments for Stomatitis

STOMATITIS	
Toxicity Grade	**Dose Adjustment**
1 (painless ulcers, erythema, or mild soreness)	**Redose unless patient has experienced previous Grade 3 or 4 toxicity.** If so, delay up to 2 weeks and decrease dose by 25%. Return to original dose interval.
2 (painful erythema, edema, or ulcers, but can eat)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** If after 2 weeks there is no resolution, pegylated liposomal doxorubicin should be discontinued and patient removed from protocol.
3 (painful erythema, edema, or ulcers, and cannot eat)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, pegylated liposomal doxorubicin should be discontinued and patient removed from protocol.
4 (requires parenteral or enteral support)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, pegylated liposomal doxorubicin should be discontinued and patient removed from protocol.

6.2.3 Bortezomib

NOTE: Patients with prior thalidomide therapy and persistent peripheral neuropathy are at increased risk for development of grade 2-3 peripheral neuropathy when treated with bortezomib, although this is not a contraindication to treatment with bortezomib.
The dose of bortezomib should be reduced for development of peripheral neuropathy as follows:

Table 7: Dose Adjustments for Peripheral Neuropathy

PERIPHERAL NEUROPATHY	
Toxicity Grade	**Dose Adjustment**
Grade 1: Paresthesia without pain or loss of function	No dose change
Grade 1 with pain, or Grade 2 interfering with function but not activities of daily living	Reduce to 1 mg/m^2
Grade 2 with pain, or Grade 3 interfering with activities of daily living	Discontinue bortezomib and remove patient from protocol

6.2.4 Bendamustine

- The dose of bendamustine should be reduced by 33% for myelosuppression that occurs in spite of growth factor support (see Section 6.2.1)

7.0 STUDY CALENDAR & EVALUATIONS

Study Day	Pre-study		Cycles[3]				End of treatment visit[4]	Follow up[5]
	-21 days	-7 days	Day 1	Day 4	Day 8	Day 11	(30 ± 7 days post last treatment)	
REQUIRED ASSESSMENTS								
Medical history	X							
Height	X							
Physical examination	X		X				X	
BP, weight	X							
ECOG performance status	X		X				X	
ECG	X							
MUGA or Echo	X							
CBC with differential	X		X	X	X	X	X	
Complete metabolic panel[1]	X		X	X	X	X	X	
Pregnancy test		X						
Adverse event and concomitant medication assessment	X		X				X	
DISEASE ASSESSMENT								
Serum β_2-microglobulin	X							
Serum immunoglobulins (IgG, IgA, IgM)	X		Every 2 cycles or as clinically indicated				X	
Serum protein electrophoresis (SPEP) and immunofixation (IF)[2]	X		Every 2 cycles or as clinically indicated				X	
Serum free light chains[2]	X		Every 2 cycles or as clinically indicated				X	
24-hour urine for M-protein[2]	X		Every 2 cycles or as clinically indicated				X	
Skeletal survey	X[6]		If progression is suspected					
Bone marrow aspirate and core biopsy	X[7]		For confirmation of complete remission or as clinically indicated[10]				X[11]	
TREATMENT								
Bortezomib			X	X	X	X		
Pegylated Liposomal Doxorubicin				X				
Bendamustine			X	X				
CORRELATIVE STUDIES - Mandatory								
Pharmacokinetics (PK)			X[8]					
Pharmacodynamics (PD)			X[9]	X[9]				
FOLLOW- UP								
Survival								X
Disease progression								X

[1] Complete metabolic panel (CMP) to include creatinine, BUN, albumin, AST, ALT, alkaline phosphatase and total bilirubin.

[2] SPEP, IF, serum free light chains, and 24-hour urine for M-protein are performed every 2 cycles (i.e., before cycle 3, 5, 7, etc.) to assess disease response/progression, and when the patient is taken off treatment (see footnote #4) if not performed in the previous 4 weeks. Disease evaluation may also be performed at other times as clinically indicated if disease progression is suspected.

[3] Dosing on Days 1 & 4 may be critical for efficacy of the combination. All efforts should be made to maintain the treatment schedule. However, Day 1 infusions may be given ±3 days for reasons such as observed holidays, inclement weather, scheduling conflicts, etc.

[4] All patients, including those who discontinue protocol therapy early, should be evaluated 30 ± 7 days post last dose for the end of treatment visit. End of treatment evaluation of disease status will be performed only for patients who complete 8 cycles of treatment or who discontinue for reasons other than disease progression (but haven't started another treatment). See section 7.4.

[5] All patients who receive study drug will be followed for disease progression and survival every 3 months for 2 years from registration for protocol therapy, every 6 months for years 3 - 5, and annually thereafter.

[6] Skeletal survey: If not performed within 3 months prior to registration for protocol therapy.

[7] Bone marrow aspirate and core biopsy: If not performed within 6 months prior to registration for protocol therapy.

[8] Mandatory PK studies for bendamustine will be performed only in cycles 1 and 2. Blood will be drawn (5-8 ml) at baseline (i.e., before drug administration and 24-hours after the start of the infusion. Please see the Study Procedure Manual for collection, processing and shipping instructions.

[9] Mandatory PD studies will be performed in cycles 1 and 2 only. In cycle 1, blood (15 ml) will be drawn at baseline (i.e., before drug administration and 24 hours after the start of the infusion on day 1 (i.e., bendamustine and bortezomib). In cycle 2, blood will be drawn at baseline (i.e., before drug administration and 24 hours after the start of the infusion on Day 4. Please see the Study Procedure Manual for collection, processing and shipping instructions.

[10] A bone marrow aspirate and core biopsy should be performed (including flow cytometry) to confirm complete remission.

[11] End of treatment bone marrow aspirate and core biopsy will be performed only as clinically indicated.

7.1 BASELINE/SCREENING

7.1.1 Within 21 days prior to registration for protocol therapy:

- History and Physical examination, and assessment of ECOG performance status
- Height, blood pressure, weight
- Twelve-lead ECG
- Cardiac ejection fraction (by MUGA scan or echocardiography).
- Adverse event and concomitant medication assessment
- Serum protein electrophoresis (SPEP) and quantification of M-protein, and immunofixation
- 24-hour urine for protein electrophoresis and immunofixation
- Serum free light chains
- Serum immunoglobulins (IgG, IgA, IgM)
- Serum β_2-microglobulin
- CBC and differential
- Complete metabolic panel (CMP) to include creatinine, BUN, albumin, AST, ALT, alkaline phosphatase and total bilirubin.
- Skeletal survey (if not performed within previous 3 months)
- Bone marrow aspirate and core biopsy (including cytogenetics and FISH studies) if not performed in the previous 6 months.

7.1.2 Within 7 days of registration for protocol therapy:

- Pregnancy test for women of childbearing potential

7.2 ON TREATMENT

7.2.1 Day 1 of each cycle (within 3 days prior):

Note: Cycle 1 Day 1 testing need not be repeated if completed within 7 days of starting protocol therapy.

- History and Physical examination, and assessment of ECOG performance status
- CBC with differential
- Complete metabolic panel (CMP) to include creatinine, BUN, albumin, AST, ALT, alkaline phosphatase and total bilirubin. .
- Adverse event and concomitant medication assessment
- Bortezomib administration
- Bendamustine administration

Day 1 of Cycle 1 and 2 only:

- Mandatory PK studies: Blood will be collected at baseline (i.e., before drug administration) and 24-hours after the start of the infusion.

Day 1 of Cycle 1 only:

- Mandatory PD studies: Blood will be collected at baseline (i.e., before drug administration) and 24 hours after the start of the infusion on day 1 (i.e., bendamustine and bortezomib).

7.2.2 Day 4 of each cycle (within 1 day prior):

- CBC with differential
- Complete metabolic panel (CMP) to include creatinine, BUN, albumin, AST, ALT, alkaline phosphatase and total bilirubin.
- Bortezomib administration
- pegylated liposomal doxorubicin administration
- Bendamustine administration

Day 4 of Cycle 2 only:

- Mandatory PD studies: Blood will be collected at baseline (i.e., before drug administration) and 24 hours after the start of the infusion on day 4.

7.2.3 Day 8 of each cycle (within 1 day prior):

- CBC with differential
- Complete metabolic panel (CMP) to include creatinine, BUN, albumin, AST, ALT, alkaline phosphatase and total bilirubin.
- Bortezomib administration

7.2.4 Day 11 of each cycle (within 1 day prior):

- CBC with differential
- Complete metabolic panel (CMP) to include creatinine, BUN, albumin, AST, ALT, alkaline phosphatase and total bilirubin.
- Bortezomib administration

7.2.5 Disease Assessment

Every 2 cycles or as clinically indicated:

- Serum protein electrophoresis (SPEP) and immunofixation (IF)
- Serum free light chains
- 24 hour urine for M-protein

If progression is suspected:

- Skeletal survey
- Serum protein electrophoresis (SPEP) and immunofixation (IF)
- Serum free light chains
- 24 hour urine for M-protein

For confirmation of complete remission or as clinically indicated:

- Bone marrow aspirate and core biopsy (including flow cytometry)

7.3 TREATMENT DISCONTINUATION

A patient will be discontinued from the treatment under the following circumstances:

- If there is evidence of progressive disease.
- If the attending physician thinks a change of therapy would be in the best interest of the patient.
- If the patient requests discontinuation.
- If the drug(s) exhibit(s) unacceptable adverse event.
- If a patient becomes pregnant.

- Treatment interruption for greater than (or equal to) 14 days due to treatment related adverse event, except in the case of patient responding and myelosuppression causing delay of > 2 weeks but < 4 weeks. Please see Section 6.0 for additional information.
- Patients can stop participating at any time. However, if they decide to stop participating in the study, patients will continue to be followed for disease progression and survival (if haven't withdrawn consent).

7.4 END OF TREATMENT EVALUATIONS: 30 days post last dose of study therapy (± 7 days)

All patients, including those who discontinue protocol therapy early, should be evaluated 30 days post last dose for the end of treatment visit. The end of treatment evaluations should not be performed prior to 21 days after the last dose.

End of Treatment evaluations will include:

- History and Physical examination, and assessment of ECOG performance status
- Adverse event and concomitant medication assessment
- CBC with differential
- Complete metabolic panel (CMP) to include creatinine, BUN, albumin, AST, ALT, alkaline phosphatase and total bilirubin.
- Evaluation of disease status will be performed only for patients who complete 8 cycles of treatment or who discontinue for reasons other than disease progression (but haven't started another treatment). Disease assessment will include: SPEP and IF, serum free light chains, 24-hour urine evaluation for M-protein and bone marrow biopsy (as clinically indicated; see Section 7.0).

7.5 FOLLOW-UP:

All patients who receive study drug will be followed for disease progression and survival every 3 months for 2 years from registration for protocol therapy, every 6 months for years 3 - 5, and annually thereafter.

Completion of the off-study eCRF in the database is required once follow-up is completed.

8.0 CRITERIA FOR DISEASE EVALUATION

Responses will be based on a modified International Myeloma Working Group criteria[18], and defined as outlined below:

8.1 Definitions

Table 8: Response Criteria

Response*	Definition
Complete Response (CR)	Negative for monoclonal protein by immunofixation on the serum and urine, **and** Disappearance of any soft tissue plasmacytomas, **and** <5% plasma cells in bone marrow
Stringent complete response (sCR)	CR as defined above, **plus** Normal free light chain ratio, **and** Absence of clonal cells in bone marrow by flow-cytometry
Near complete response (nCR)	Meeting criteria for CR, **except** with persistence of original monoclonal protein by IF while absence by serum or urine protein electrophoresis.
Very good partial response (VGPR)	90% or more reduction in serum M-protein **plus** urine M-component <100 mg/24 hours
Partial response (PR)	50% or more reduction in serum M-protein **and** 90% or more reduction in urine M-protein or to <200 mg/24hours If serum and urine M-protein are immeasurable, a 50% or more reduction in free light chain level is required in place of M-protein criteria. In addition to the above criteria, if present at baseline, a 50% or more reduction in the size of soft tissue plasmacytomas is required. For patients with free light chains as their only measurable disease, a 50% or greater decrease in the difference between involved and uninvolved free light chain levels.
Minimal response (MR)	25-49% reduction in serum M-protein, **and** If present, a 50-89% reduction in 24 hour light chain excretion, which exceeds 200 mg/24 hours, **and** No increase in the size or number of lytic bone lesions (development of compression fracture does not exclude response)
Stable disease (SD)	Not meeting criteria for CR, VGPR, MR, PR or progression of disease.

Progressive disease (PD)	Any one of the following criteria: - Increase of 25% or more in serum or urine M-protein from baseline. - Serum M-protein and/or the absolute increase must be ≥0.5 g/dL - Urine M-protein and/or absolute increase must be ≥200 mg/24 hours - Development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas - Development of hypercalcemia (corrected serum Ca^{++} >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disease. In patients who have achieved CR or sCR: - Reappearance of serum or urine M-protein by IF or electrophoresis. - Development of 5% or more clonal plasma cells in the bone marrow - Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesions, or hypercalcemia).

* All response categories require two consecutive assessments made any time before the institution of any new therapy. Repeat of radiographic studies and bone marrow evaluation are not required to satisfy these responses.

9.0 BIOLOGICAL CORRELATIVES

Please see the Study Procedure Manual for collection, processing and shipping instructions.

The following laboratory correlative studies will be performed:

9.1 Bendamustine pharmacokinetics.

Blood levels of bendamustine will be assayed only after the first dose (day 1) of cycles 1 and 2 of treatment. The maximum concentration (C_{max}), half-life (t1/2), and area under the curve (AUC) will be determined according to standard techniques and correlated with response to treatment, grades 3-4 toxicities, and pharmacodynamic activity (see below). Mandatory samples will be collected at baseline and at 24 hours after start of infusion.

9.2 Pharmacodynamic activity.

It has been previously shown that DNA repair is an important mechanism mediating resistance to alkylator therapy in MM[19]. Furthermore, the measurement of DNA adduct formation/repair in peripheral blood mononuclear cells (PBMC) is a valid surrogate tissue for evaluating alkylator therapy in MM[20]. In this protocol, we will investigate the extent of DNA damage and kinetics of repair in PBMC as a possible predictor of response in patients treated with bendamustine in combination with bortezomib and pegylated liposomal doxorubicin.

Specifically, we will compare the molecular endpoints of DNA damage/repair in PBMC after receiving bendamustine with bortezomib (day 1 of cycle 1) and after receiving bendamustine, pegylated liposomal doxorubicin, and bortezomib (day 4 of cycle 2), and correlate the AUC for the extent of DNA damage associated with each assessment with response and response duration, and with plasma AUC of drug.

Mandatory blood samples will be collected at baseline in cycle 1 and 2. In cycle 1, blood samples will be also collected at 24 hours after the start of the infusion on day 1 to assess the effect of bendamustine and bortezomib. In cycle 2, blood samples will be collected at 24 hours after the start of the infusion on day 4 to assess the effect of the bendamustine, pegylated liposomal doxorubicin and bortezomib combination. The following molecular endpoints will be measured:

- Total amount of DNA damage over time as measured using the COMET assay and the ARP assay kits (Kamiya Biomedical, Seattle, WA), and represented by the AUC during 0-24 hours of blood sampling in each of cycles 1 and 2 as described above. The AUC of DNA damage/repair will be calculated using an adaptation of previously reported methods[20,21,22,23].

The assays will be performed in Dr. Farag's laboratory.

The AUC for DNA damage/repair following bendamustine and bortezomib will be compared to that following bendamustine, pegylated liposomal doxorubicin, and bortezomib to evaluate any incremental effect on DNA damage when the three drugs are utilized in vivo. In addition, the AUC for DNA damage/repair in responders and non-responders will be compared, and correlated with PK parameters of C_{max} and AUC of plasma levels of bendamustine.

10.0 CTM INFORMATION & ADVERSE EVENTS MANAGEMENT

10.1 Bortezomib (Velcade™)

Classification: Proteasome inhibitor

Mode of Action: Bortezomib inhibits proteasomes, enzyme complexes that regulate protein homeostasis within the cell. Specifically, it reversibly inhibits chymotrypsin-like activity at the 26S proteasome, leading to activation of signaling cascades, cell-cycle arrest and apoptosis.

Pharmacodynamic/kinetics:
Protein binding: ~83%
Metabolism: Hepatic via CYP 1A2, 2C9, 2C19, 2D6, 3A4; forms metabolites (inactive)
Half-life elimination: 9-15 hours

Formulation: Bortezomib is supplied as a powder for reconstitution (preservative free): 3.5 mg per vial (contains mannitol 35 mg). See Section 5.2 for specifications regarding reconstitution volume for IV vs. subcutaneous injection.

Administration: Rapid IV push (i.e., 3-5 seconds) or subcutaneous injection

Dosing: The dose of Bortezomib in this protocol is 1.3 mg/m^2 with dose adjustment as outlined in Section 6.2. There are no specific guidelines available for dosing in patients with renal impairment, although MM patients with renal failure have been successfully treated without significant toxicity. Studies, however, did not include patients with Creatinine clearance <13 ml/min and patients on hemodialysis.
Specific guidelines are not available for patients with liver impairment, although the clearance of the drug may be decreased.

Side effects and toxicity:
The following adverse events have been reported to occur with bortezomib:

Most Common side effects:
The most common risks are those that have occurred in greater than or equal to 30% of patients who have received bortezomib:

- Feeling weak, tired, and generally uncomfortable
- Gastrointestinal effects such as constipation, diarrhea, nausea, vomiting, and loss of appetite. These may result in dehydration and/or weight loss.
- Fever commonly with shaking chills
- Painful feelings or numbness and tingling in hands and feet (neuropathy), which may not get better after stopping bortezomib. Uncommonly, the nerves that control things like heart rate, gut movement and urinary bladder may be affected.
- Lowered platelets; this may increase the chance of bleeding
- Lowered red cells or anemia which may result in feeling tired

Very Common side effects:
The very common risks are those that have occurred in 10-29% of patients who have received bortezomib:

- Lowered white blood cells called neutrophils that may increase risk of infection and is uncommonly associated with fever; commonly patients may have lowered white blood cells called lymphocytes or have lowered red blood cells, white blood cells and platelets at the same time
- Flu-like symptoms and other upper respiratory tract infections, such as chills, sore throat, and runny nose and sinus and throat infections
- Abdominal (belly) pain
- Aches and pains in muscles and joints pain in bones and in arms and legs
- Swelling or fluid build-up in the arms and legs, and feeling dizzy and weight gain. Patients should not drive or operate any dangerous tools or machines if they have these or any other symptoms
- Cough, feeling short of breath, lung infections including pneumonia and commonly bronchitis
- Headache
- Skin rash with itching and redness. An uncommon risk is a severe, life-threatening or deadly rash with skin peeling and mouth sores.

- 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.
- Feeling anxious
- Problems sleeping (insomnia)

Common side effects:
Common risks are those that have occurred in 1-9% of patients who have received bortezomib:

- Lowered blood pressure that can commonly cause feelings of light headedness or fainting when standing up
- Changes in heart rate and heart beat that can feelings of light-headedness, dizziness, fainting, shortness of breath, and/or chest pain. This may also cause patients to feel confused. An uncommon risk is a possible life threatening abnormal heart beat
- New or worsening heart failure, which can show up as feeling short of breath, swelling in the legs, and/or chest pain, or decreased heart function and can uncommonly, be severe. If patients have heart failure or other diseases that put them at risk of getting heart failure, they should tell their doctor.
- Fluid buildup around the lungs
- Infection and/or inflammation of the eye or eyelids
- Blurred vision
- 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.
- Nosebleeds
- Kidney function that gets worse
- Infections of the bladder, sinuses, throat, stomach and intestines (gut), skin and at the area of skin where the catheter is placed
- Fungal infections in the mucous membrane such as the mouth and throat and uncommonly in the skin and nails
- Life-threatening infections in the blood (sepsis)
- Changes in blood sugar have been reported in a few diabetic patients who took oral anti-diabetic medicine. If patients are taking oral anti-diabetic medicines they may need blood sugar levels watched more closely.
- Blood in the urine
- Feeling confused
- Changes in the way things taste
- Abnormal liver tests and decreased protein in the blood
- Lowered amount of potassium and sodium in the blood and increase in the amount of calcium in the blood
- Muscular weakness
- Redness at injection site
- Itching at injection site

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

- Inflammation and fluid buildup in the lungs, or pus build up between the layers surrounding the lungs that may cause breathing 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 cause breathing problems and can be life-threatening.
- Inflammation of the layers surrounding the heart or collection of fluid around the heart may cause chest pain or breathing problems and can be life-threatening or lead to death.
- Hepatitis and liver failure (in patients who also got many drugs and had other serious medical problems).
- Pain, redness, swelling and infection in the area of the skin where bortezomib is injected into the vein
- Pain in the mouth and throat when swallowing
- Loss of hearing
- Intestinal obstruction (blockage in the gut) that may get better on its own and not need surgery and inflammation of the intestines, pancreas or stomach
- Coughing up blood
- Bleeding in the brain and subdural hematoma which is bleeding between the skull and your brain
- Fast 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
- Severe muscle weakness and paralysis (not being be able to move the arms and legs)
- Changes to the brain that may cause convulsions and confusion
- Posterior reversible encephalopathy syndrome (PRES) affects the brain and may cause headaches, changes in vision, changes in mental status, or seizures (fits), 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 the body at the time of treatment onset. Persons with a weakened immune system may develop PML. PML can result in death or severe disability. Monitor for symptoms that include: 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.

Contraindications: Hypersensitivity to bortezomib, boron, mannitol, or any component of the formulation.
Pregnancy: Adverse effects were observed in animal studies. There are no adequate and well-controlled studies in pregnant women. Effective contraception is recommended for women of childbearing potential.

Lactation: Excretion in breast milk is unknown and breast feeding is not recommended.
Drug Interactions:

CYP3A4 inhibitors: Serum level and/or toxicity of bortezomib may be increased. Inhibitors include amiodarone, cimetidine, clarithromycin, erythromycin, delavirdine, diltiazem, disulfiram, fluoxetine, fluvoxamine, grapefruit juice, nefazodone, nevirapine, propoxyphene, quinupristin/dalfopristin, verapamil, zafirlukast, zileuton.

CYP3A4 inducers: Serum levels and/or efficacy of bortezomib may be decreased. Some common inducers include amiodarone, carbamazepine, nevirapine, phenobarbital, phenytoin, rifampin.

Warnings/Precautions: The U.S. Food and Drug Administration (FDA) currently recommends that procedures for proper handling and disposal of antineoplastic agents be considered. Bortezomib may cause peripheral neuropathy, risk may be increased with previous use of neurotoxic agents or pre-existing peripheral neuropathy; adjustment of dose and schedule may be required. May cause orthostatic/postural hypotension; use caution with dehydration, history of syncope or medications associated with hypotension. Use caution with hepatic or renal impairment. Safety and efficacy have not been established in pediatric patients.

Procurement: Commercial supplies for bortezomib will be used in this study and billed to third party payers or the patient. Bortezomib is approved by the FDA for patients with relapsed MM.

10.2 Doxorubicin HCL liposome injection (Doxil®)

Classification: Doxil® (doxorubicin HCl liposome injection) is doxorubicin hydrochloride (HCl) encapsulated in long-circulating STEALTH® liposomes for intravenous administration. The active ingredient of Doxil® is doxorubicin HCl, a cytotoxic anthracycline antibiotic isolated from *Streptomyces peucetius* var. *caesius*. STEALTH® Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The STEALTH® liposomes of Doxil® are formulated with surface-bound methoxypolyethylene glycol (MPEG), a process often referred to as pegylation, to protect liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time.

Mode of Action: The mechanism of action of doxorubicin HCl is related to its ability to bind DNA and inhibit nucleic acid synthesis. Cell structure studies have demonstrated rapid cell penetration and perinuclear chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, and induction of mutagenesis and chromosomal aberrations.

Formulation: Doxil® (doxorubicin HCl liposome injection) is supplied as a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, single use vials. Each 10-mL vial contains 20 mg doxorubicin HCl at a concentration of 2 mg/ml. Each 30-mL vial contains 50 mg doxorubicin HCl at a concentration of 2 mg/ml.

Drug Storage and Stability: Refrigerate unopened vials of Doxil® at 2°C to 8°C (36°F to 46°F). Avoid freezing. Prolonged freezing may adversely affect liposomal drug products; however, short-term freezing (less than 1 month) does not appear to have a deleterious effect on Doxil®. Caution should be exercised in the handling and preparation of Doxil®. The use of gloves is required.

Administration: The appropriate dose of Doxil®, up to a maximum of 90 mg, must be diluted in 250 ml of 5% Dextrose Injection, USP prior to administration. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in Doxil®. Diluted Doxil® should be refrigerated at 2°C to 8°C (36°F to 46°F) and administered within 24 hours.
Doxil® should be considered an irritant and precautions should be taken to avoid extravasation. With intravenous administration of Doxil®, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation occur, the infusion should be immediately terminated and restarted in another vein. The application of ice over the site of extravasation for approximately 30 minutes may be helpful in alleviating the local reaction. Doxil® must not be given by the intramuscular or subcutaneous route.

Dosing: In this protocol, Doxil® should be administered intravenously at a dose of 30 mg/m^2 (doxorubicin HCl equivalent) at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion-related reactions are observed, the rate of infusion can be increased to complete administration of the drug over one hour. If Doxil® comes into contact with skin or mucosa, immediately wash thoroughly with soap and water. The dose of Doxil® should be reduced based on toxicity according to the guidelines in Section 6.2.2.

Side Effects and Toxicity: The major toxic effects of doxorubicin are nausea and vomiting, alopecia, mucositis, and phlebitis at the site of drug administration. In addition, the following toxicities may occur:

Myelosuppression, predominantly neutropenia, occurs with a nadir at 10-14 days, with recovery in 21 days. Patients with obstructive liver disease have more severe myelosuppression due to impaired drug excretion, and dose reduction is usually required (see Section 6.2). Renal excretion is minimal, although is sufficient to turn the urine color red. Renal impairment does not result in increased toxicity, and no dose reductions are required.

Radiation recall reactions may occur patients who have received prior or are receiving concurrent radiation therapy with reactivation or exacerbation of radiation dermatitis.

Cardiac toxicity, manifested as acute left ventricular failure, congestive heart failure due to cardiomyopathy, arrhythmia, or rarely sudden death, occurs predominantly in patients who receive cumulative doses in excess of 550 mg/m^2.
Other side effects are much less common and include fever on the day of administration, chills, facial flushing, anaphylaxis, conjunctivitis, and lacrimation.

Procurement: Commercial supplies of Doxil® will be used in this study and billed to third party payers or the patient. Doxil® in combination with Bortezomib is approved by the FDA for use in patients with relapsed MM.

10.3 Doxorubicin Hydrochloride Liposome (Lipo-Dox®)

Clasification: doxorubicin hydrochloride encapsulated in long circulating pegylated Liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The pegylated Liposomes of doxorubicin are formulated with surface bound methoxypolyethylene glycol (MPEG), a process often referred to as pegylation, to protect liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time. Pegylated liposomes have a half-life of approximately 55 hours in humans. They are stable in blood and direct measurement of liposomal doxorubicin shows that at least 90% of the drug remains liposome encapsulated during circulation. It is hypothesized that because of their small size and persistence in the circulation, the pegylated doxorubicin liposomes are able to penetrate the altered and often compromised vasculature of tumors. Once the pegylated liposomes distribute to the tissue compartment, the encapsulated doxorubicin HCL becomes available. The exact mechanism of release is not understood.

Mode of Action: The exact mechanism of the antitumor activity of doxorubicin is not known. It is generally believed that inhibition of synthesis of DNA, RNA and protein is responsible for the majority of the cytotoxic effects. Liposomal doxorubicin penetrates the cells rapidly, binds to chromatin and inhibits nucleic acid synthesis by intercalation between adjacent base pairs of the DNA double helix thus preventing their unwinding for Replication.

Formulation: Each Lipo-Dox® vial contains pegylated liposomal doxorubicin HCl 2 mg/ml and delivers 10ml (20mg) in a concentrate for single dose intravenous infusion and is presented as a sterile, translucent, and red suspension. The active ingredient of Lipo-Dox® is doxorubicin HCl, a cytotoxic anthracycline antibiotic obtained from Streptomyces peucetius var. caesius

Drug Storage and Stability: Refrigerate unopened vials at 2°C to 8°C. Avoid freezing. After dilution with Dextrose 5% in Water, the diluted Lipo-Dox® solution should be used immediately or stored at 2°C to 8°C for not longer than 24 hours. Discard the partially used vials.

Administration: The appropriate dose of liposomal doxorubicin up to a maximum of 90 mg must be diluted in 250 ml of 5% Dextrose Injection USP prior to administration. Doses exceeding 90 mg should be diluted in 500 ml of 5% dextrose injection USP prior to administration. Aseptic technique must be strictly observed since no preservative or bacteriostatic agents are present in LipoDox. Diluted liposomal doxorubicin should be refrigerated at 2°C to 8°C and administered within 24 hours. LipoDox should not be used with in line filters and should not be mixed with other drugs. It should not be used with any other diluent other than Dextrose injection 5%. Partially used vials should be discarded.

Dosing: LipoDox should be administered 2 intravenously at a dose of 30 mg/m^2 at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion related adverse events are observed, the rate of infusion can be increased to complete administration of the drug over one hour.

Side effects and Toxicity: It is recommended that all patients receiving liposomal doxorubicin routinely undergo frequent ECG monitoring. Transient ECG changes such as, T-wave flattening, S-T segment depression and benign arrhythmias are not considered mandatory indications for the suspension of liposomal doxorubicin therapy. However, reduction of the QRS complex is considered more indicative of cardiac toxicity. If this change occurs, the most definitive test for anthracycline myocardial injury i.e., endomyocardial biopsy, must be considered. Acute infusion related reactions characterized by flushing, shortness of breath, facial swelling, headache, chills, chest pain, back pain, tightness in the chest and throat, fever, tachycardia, pruritus, rash, cyanosis, syncope, bronchospasm, asthma, apnea and/or hypotension have been reported with liposomal doxorubicin. In most patients, these reactions resolve over the course of several hours to a day once the infusion is terminated or when the rate of infusion is slowed.

Liposomal doxorubicin should be administered at the initial rate of 1 mg/min to minimize the risk of infusion reactions.
Moderate and reversible myelosuppression has been observed in ovarian and breast cancer patients who received liposomal doxorubicin with anemia being the most common hematologic adverse event followed by leucopenia, thrombocytopenia and neutropenia.
Dosage should be reduced in patients with impaired hepatic function. Prior to liposomal doxorubicin administration evaluation of hepatic function is recommended using conventional clinical laboratory tests such as SGOT, SGPT, alkaline phosphatase and bilirubin.
Radiation induced toxicity to the myocardium, mucosae, skin and liver have been reported to be increased by the administration of doxorubicin HCl.

10.4 Bendamustine (Treanda®)

Classification: Alkylating agent.

Mode of Action: Bendamustine is a DNA alkylating agent with a unique mechanism of action, including the ability to cause cross-linking between DNA and proteins and proteins alone. With short exposure, bendamustine also induces the onset of apoptosis as well as ATP depletion, and these effects are sustained. Bendamustine has only partial cross-resistance with other alkylating agents and has *in vitro* activity in cells that are resistant to a variety of anti-tumor agents.

Bendamustine's active metabolites, gamma-hydroxy bendamustine (M3) and N-desmethylbendamustine (M4) are formed via cytochrome P450 CYP1A2. Inhibitors of CYP1A2 (e.g., fluvoxamine, ciprofloxacin) have potential to increase plasma concentration of bendamustine and decrease plasma concentrations of active metabolites. Inducers of CYP1A2 (e.g., omeprazole, smoking) have potential to decrease plasma

concentrations of bendamustine and increase plasma concentrations of its active metabolites. Caution should be used, or alternative treatments considered if concomitant treatment with CYP1A2 inhibitors or inducers is needed.

Formulation: Bendamustine is available as powder in 100 mg vials for reconstitution.

Drug Storage and Stability: Bendamustine is stable in normal saline (NS), and Dextrose 2.5 in ½ NS.

Administration: Bendamustine is infused over 60 minutes in this protocol. Premedication with antihistamines, antipyretics, and/or corticosteroids for patients with a previous grade 1 or 2 infusion reaction to bendamustine should be considered.

Dosing: The dose of Bendamustine should be reduced based on toxicity according to the guidelines in Section 6.2.

Side Effects and Toxicity:

Tumor Lysis Syndrome:
Tumor lysis syndrome associated with bendamustine treatment has been reported in patients in clinical trials and in spontaneous reports. The onset tends to be within the first treatment cycle of bendamustine and, without intervention, may lead to acute renal failure and death. Preventive measures include maintaining adequate volume status, and close monitoring of serum chemistry, particularly potassium and uric acid levels. Allopurinol has also been used prior to or at the beginning of bendamustine therapy. However, there may be an increased risk of severe skin toxicity when bendamustine and allopurinol are administered concomitantly.

Skin Reactions:
Skin reactions have been reported in clinical trials and postmarketing spontaneous reports. These events have included rash, toxic skin reactions, and bullous exanthema. Some events occurred when bendamustine was given in combination with other anticancer agents, so the precise relationship of the skin reactions to bendamustine treatment is uncertain.

In a study of bendamustine (90 mg/m2) in combination with rituximab (study SDX-105-02), 1 case of TEN occurred. TEN has been associated with treatment with rituximab. Spontaneous reports of SJS and TEN, some fatal, have been reported when bendamustine was administered concomitantly with allopurinol and other medications known to cause these syndromes. The relationship to bendamustine cannot be determined.
When skin reactions occur, they may be progressive and increase in severity with further treatment. Therefore, patients with skin reactions should be monitored closely. If skin reactions are severe or progressive, bendamustine treatment should be withheld or discontinued.

The following side effects and toxicities have been reported to occur in >10% of patients:
Hypersensitivity/infusion reactions: Infusion reactions, which may include chills, fever, pruritus, and rash, are common. Rarely, anaphylactic and anaphylactoid reactions have

occurred particularly with the second or subsequent cycle(s). In general, patients who experienced grade 3 or 4 allergic reactions were not rechallenged in previously reported clinical trials. Consider premedication with antihistamines, antipyretics and/or corticosteroids for patients with a history of grade 1 or 2-infusion reaction. Discontinue for severe allergic reaction; consider discontinuation with grade 3 or 4 infusion reaction.

Cardiovascular: Peripheral edema (≤13%)

Central nervous system: Fatigue (9% to 57%), fever (24% to 34%), headache (≤21%), chills (6% to 14%), dizziness (≤14%), insomnia (≤13%)

Dermatologic: Rash (8% to 16%; grades 3/4: ≤3%)
Endocrine & metabolic: Dehydration (≤14%)

Gastrointestinal: Nausea (20% to 75%), vomiting (16% to 40%), diarrhea (9% to 37%), constipation (≤29%), anorexia (≤23%), weight loss (7% to 18%), stomatitis (≤15%), abdominal pain (5% to 13%), appetite loss (≤13%), dyspepsia (≤11%)

Hematologic: Myelosuppression (nadir: in week 3), lymphopenia (68% to 99%; grades 3/4: 47% to 94%), leukopenia (61% to 94%; grades 3/4: 28% to 56%), anemia (88% to 89%; grades 3/4: 11% to 13%), thrombocytopenia (77% to 86%; grades 3/4: 11% to 25%), neutropenia (75% to 86%; grades 3/4: 43% to 60%)

Hepatic: Bilirubin increased (≤34%; grades 3/4: 3%)

Neuromuscular & skeletal: Back pain (≤14%), weakness (8% to 11%)

Respiratory: Cough (4% to 22%), dyspnea (≤16%)

The following toxicities have been reported to occur in 1% to 10% of patients:
Cardiovascular: Tachycardia (≤7%), hypotension (≤6%), chest pain (≤6%), hypertension aggravated (≤3%)

Central nervous system: Anxiety (≤8%), depression (≤6%), pain (≤6%)

Dermatologic: Pruritus (5% to 6%), dry skin (≤5%)

Endocrine & metabolic: Hypokalemia (≤9%), hyperuricemia (≤7%; grades 3/4: 2%), hyperglycemia (grades 3/4: ≤3%), hypocalcemia (grades 3/4: ≤2%), hyponatremia (grades 3/4: ≤2%)

Gastrointestinal: Gastroesophageal reflux disease (≤10%), xerostomia (9%), taste alteration (≤7%), oral candidiasis (≤6%), abdominal distention (≤5%)

Genitourinary: Urinary tract infection (≤10%)

Hematologic: Febrile neutropenia (3% to 6%)

Hepatic: ALT increased (grades 3/4: ≤3%), AST increased (grades 3/4: ≤1%)

Local: Infusion site pain (≤6%), catheter site pain (≤5%)

Neuromuscular & skeletal: Arthralgia (≤6%), bone pain (≤5%), limb pain (≤5%)

Renal: Creatinine increased (grades 3/4: ≤2%)

Respiratory: Upper respiratory infection (10%), sinusitis (≤9%), pharyngolaryngeal pain (≤8%), pneumonia (≤8%), nasopharyngitis (6% to 7%), wheezing (≤5%), nasal congestion (≤5%)

Miscellaneous: Herpes infection (3% to 10%), infection (≤6%; grades 3/4: 2%), hypersensitivity (≤5%; grades 3/4: 1%), diaphoresis (≤5%), night sweats (≤5%)

Rare important or life-threatening toxicities, reported in <1% of patients include: Acute renal failure, alopecia, anaphylaxis, bullous exanthema, cardiac failure, dermatitis, erythema, hemolysis, infusion reaction, injection/infusion site reaction (irritation, pruritus, swelling), malaise, mucosal inflammation, myelodysplastic syndrome, pulmonary fibrosis, sepsis, septic shock, skin necrosis, somnolence, toxic epidermal necrolysis, toxic skin reactions, tumor lysis syndrome.

Procurement: Cephalon, Inc. will provide bendamustine at no cost in this protocol.

11.0 REPORTING ADVERSE EVENTS & SERIOUS ADVERSE EVENTS

11.1 Definitions of Adverse Events

11.1.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered an investigational product and which does not necessarily have a causal relationship with the treatment. An adverse event (AE) can, therefore, be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

11.1.2 Serious Adverse Event (SAE)

"Serious Adverse Event or Adverse Drug Reaction (AE/ADR)" means any AE/ADR occurring at any dose that results in any of the following outcomes:

a) Death
b) A life-threatening AE/ADR (i.e., the patient/subject was, in the view of the initial reporter/investigator, at immediate risk of death from the AE/ADR as it occurred. It does not refer to an AE/ADR that hypothetically might have caused death if it were more severe);

c) Inpatient hospitalization or prolongation of existing hospitalization (i.e., hospitalization was required to treat or diagnose the AE/ADR; excludes hospitalization for unrelated reasons);
d) A persistent or significant disability or incapacity (*disability* here means that there is a substantial disruption of a person's ability to conduct normal life functions);
e) A congenital anomaly/birth defect
f) An important medical event (i.e., AEs/ADRs that might not be immediately life-threatening, or result in death or hospitalization might be considered serious when, based upon appropriate medical and scientific judgment, they might jeopardize the patient/subject or might require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above).
g) Any suspected transmission via a medicinal product of an infectious agent

11.1.3 Unexpected Adverse Event

An adverse event not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the Investigator's Brochure or package insert.

11.2 Adverse Event (AE) Reporting

Adverse events (AEs) will be recorded from the time of consent and for at least 30 days after treatment discontinuation, regardless of whether or not the event(s) are considered related to trial medications. All AEs considered related to trial medication will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

11.3 Serious Adverse Event (SAE) Reporting

11.3.1 Study Center (Site) Requirements for Reporting SAEs

Investigators and other site personnel must report any SAEs occurring during the course of the study **within one business day** of discovery of the event. This includes events both related and unrelated to the investigational product.

The definition of "related" being that there is a reasonable possibility the drug caused the adverse experience. Sponsor-Investigator shall use his/her judgment to determine the relationship between the Serious Adverse Drug Experience and the Study Drug.

Table 9: Definition or Relationship of AE to Study Medication

Unrelated	The Adverse Event is *clearly not related* to the investigational agent(s)
Unlikely	The Adverse Event is *doubtfully related* to the investigational agent(s)
Possible	The Adverse Event *may be related* to the investigational agent(s)
Probable	The Adverse Event is *likely related* to the investigational agent(s)
Definite	The Adverse Event is *clearly related* to the investigational agent(s)

The completed SAE Report Form (see Study Procedure Manual) must be faxed to Hoosier Cancer Research Network within 1 business day of discovery of the event. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

11.3.2 Death and Immediately Life-Threatening Events

Any death and immediately life-threatening event from any cause while a patient is receiving trial treatment on this protocol or up to 30 days after the last dose of trial treatment, or any death and immediately life-threatening event occurring more than 30 days after trial treatment has ended but which is felt to be treatment related must be reported **within one business day** of discovery of the event. All deaths must be reported primarily for the purposes of SAE reporting; however, deaths due unequivocally to progression are not SAEs.

The site's local IRB should be notified and the local reporting procedures followed. The completed SAE Reporting Form should be faxed to Hoosier Cancer Research Network **within one business day** of discovery of the event.

11.3.3 HCRN Requirements for Reporting SAEs

Institution (HCRN) shall notify Cephalon within one (1) business day, by facsimile, upon learning of the occurrence during the Study of:

(a) All Serious AE/ADRs, regardless of causality;
(b) Any exposure of a pregnant Study participant to the Study Drug within thirty (30) days of exposure;
(c) A female partner of a male Study participant becoming pregnant within thirty (30) days of exposure;
(d) Any medical event which may reasonably be believed to impair the integrity, validity or ongoing viability of the Study.

The Hoosier Cancer Research Network will report any SAE to Cephalon, Inc. (from the time of first dose until 30 days post discontinuation) within one business day of receipt of the SAE Transmittal Form and will report to regulatory authorities (FDA) per federal guidelines.

All such occurrences listed in this section shall be reported to Cephalon using the SAE Transmittal Form provided by Cephalon.

The Hoosier Cancer Research Network will fax the SAE Transmittal Form to Cephalon and will provide follow-up information as reasonably requested.

Cephalon, Product Safety:
Fax: 610-738-6396

All HCRN Institutional Participants shall notify their IRB, as appropriate as per institutional policy.

In the event the IRB requests additional safety information from Sponsor Investigator, Institution shall notify Cephalon of such request within one (1) business day.

11.4 IND Safety Reports Unrelated to This Trial

IND safety reports not occurring on this trial but involving the study intervention (outside SAEs) received from outside sources will be reviewed by the Sponsor Investigator and will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines.

12.0 STATISTICAL CONSIDERATIONS

Although bendamustine has been combined with mitoxantrone, etoposide, and Idarubicin with acceptable toxicity, there is currently no data of its appropriate dosing in combination with pegylated liposomal doxorubicin and bortezomib. Therefore, we will investigate the combination in two phases:

12.1 Phase I component

The primary objective in the phase I component is to determine the MTD of bendamustine in combination with bortezomib and pegylated liposomal doxorubicin (with growth factor support) to gain a better idea of safe dosing before proceeding with the second phase to assess efficacy.

A standard 3 + 3 design will be used to determine the MTD. Three patients will be enrolled at dose level 1. If no patient experiences dose limiting toxicities (DLTs), escalation to the next dose level will occur. If 1 of 3 patients at any dose level experiences a DLT, 3 additional patients will be enrolled at that dose level. If only 1 of 6 patients experiences a DLT, dose escalation will be permitted. If 2 or more patients at any dose level experienced a DLT, then the previous dose with at most 1 out of 6 DLT will be considered the maximum tolerated dose (MTD). If myelosuppression is dose limiting, we will add an additional dose level at the MTD with growth factor (G-CSF; filgrastim) support (dose level +3). Dose escalation will not occur beyond level 3. Therefore, we will need at most 18 patients in phase I.

12.2 Phase II component

The primary objective in the Phase II component is to determine the overall response (CR+PR) at the MTD of bendamustine in combination with bortezomib and pegylated liposomal doxorubicin. Note that here CR includes all categories of sCR, CR, nCR and PR includes all categories of VGPR and PR defined in Section 8.1. A min/max optimal two-stage design will be followed. Patients will be considered evaluable for response if they have received at least 2 cycles of therapy or if they have had disease progression before 2 cycles are completed. If a patient does not finish at least 2 cycles (except for disease progression), we will recruit a new patient to replace him/her. An overall response rate of 60% or more will be acceptable, while an overall response rate of less than 40% will be considered unacceptable. In statistical terms, we will test the null hypothesis H0: $p0<0.4$ versus the alternative hypothesis H1: $p1>0.6$, where p is the probability of overall response. Type I and type II errors will be both set at 0.1. In the first stage, we will enroll 28 evaluable patients. If less than 12 patients respond, the trial will be stopped and we will conclude in favor of the null hypothesis. If 12 or more patients respond, we will proceed with the second stage by enrolling an additional 13 evaluable patients for a maximum sample size of 41 evaluable patients. If more than 20 patients achieve at least a partial response, we will conclude in favor of H1: $p1> 0.6$.

The probability of early termination under the null hypothesis is 0.55. We expect only 80% of enrolled patients to be evaluable. Therefore, overall, we will have to enroll 51 patients if the stage 2 is conducted to achieve 41 evaluable samples.

12.3 Analysis

12.3.1 Phase I Component

Patients' characteristics will be summarized using mean, median, and standard deviation for continuous variables, and tables for discrete variables. Toxicity profile (for all patients) will be presented by rate of overall toxicity and rates of grade 3 or 4 toxicities analyzed separately and combined. Adverse events will be summarized in phase I and accompanied by 95% confidence intervals using binomial distribution. Response rates will be summarized.

12.3.2 Phase II Component

Descriptive analysis of patients' characteristics will be summarized in a similar way as Phase I.

Primary analysis

The primary objective in phase II is to assess the overall response rate (CR+PR) of treatment at the MTD level found in phase I. Overall response rate will be evaluated and accompanied by 95% confidence intervals using the binomial distribution. Response rate by categories will be calculated with 95% confidence intervals.

Secondary analysis

Toxicity profile (for all phase II patients) will be presented by rate of overall toxicity and rates of grade 3 or 4 toxicities analyzed separately and combined. The toxicity analysis may also be performed for the patients with and without autologous stem cell transplantation separately due to the potential higher hematological toxicity in transplanted patients. Time to progression will analyzed using Kaplan-Meier survival analysis and accompanied with 95% confidence interval. Similar analysis will be applied to the progression-free survival, duration of response, and overall survival. Median survival time will be calculated with 95% confidence interval for each of the time-to-event outcome.

Correlative analysis

The bendamustine pharmacokinetics parameters (C_{max}, t1/2, and AUC) at cycle 1 (and cycle 2) will be correlated with response by comparing their means between the responders (CR +PR) and those respond (non-responders) otherwise using two-sample t tests. Appropriate transformation of the pharmacokinetics parameters will be done to fit the normal distribution assumption. Similar analysis will be used to correlate them with toxicity (grade 3-4).

The DNA damage/repair at day 1 of cycle 1 and day 4 of cycle 2 will be compared using a paired t test. AUC for the extent of DNA damage will be correlated with response by comparing their means between responders and non-responders. AUC will be correlated with response duration using a proportional hazards model, and plasma AUC using Pearson's correlation coefficient.

12.4 Time to event endpoint

12.4.1 Time to progression (TTP)

The time from the start of treatment (i.e., first dose) to disease progression, with disease progression and death due to disease progression as events and deaths due to causes other than progression as censored. Censoring date will be the last disease evaluation date for patient without progression/death or date of death due to other diseases for patients' deaths due to other causes.

12.4.2 Progression-free survival (PFS)

The time from the start of treatment to disease progression or death (regardless of cause of death), whichever comes first. Censoring date will be the last disease evaluation date.

12.4.3 Duration of response (DOR)

Duration from first date of at least partial response to the time of progression or death due to disease progression as events, with disease progression and death due to disease progression as events and deaths due to causes other than progression as censored. Censoring date will be the last disease evaluation date or date of death due to other causes as appropriate.

12.4.4 Overall survival (OS)

The time from the start of treatment to death from any cause with last date known alive as censoring date.

12.5 Modifications in the August 2014 amendment

This amendment introduces a lower dose level of bendamustine, which if passing the study will be the recommended dose level for future studies. This low dose will be used for the remaining first stage, and second stage. The same rule will be used for the first stage. For the second stage, the response rate at the low dose will be evaluated first. If this rate is no less than the response rate of the high dose by 10% and no less than 50% in general, the two dose levels will be combined in analyses following the original rule, i.e. if more than 20 patients achieve at least a partial response, we will conclude in favor of H1: $p1 > 0.6$. Otherwise, the response rate will be evaluated and its 95% confidence intervals will be calculated separately for the two dose levels. It is argued from the scientific point of view that the low dose will have at least the same or even higher response rate as the high dose. Consequently, the power level will be at least the same as the original designed. For the secondary and correlative analyses, they will be performed both separately for the two dose levels and in the combined manner.

13.0 TRIAL MANAGEMENT

13.1 Quality Controls and Quality Assurance

13.1.1 Study Monitoring

Monitoring visits to the trial sites will be made periodically during the trial, to ensure all aspects of the protocol are followed. Source documents will be reviewed for verification

of agreement with data as submitted via the data collection system. The investigator/institution guarantee access to source documents by HCRN or its designee and appropriate regulatory agencies.

The trial site may also be subject to quality assurance audit by Cephalon, Inc. or its designee as well as inspection by appropriate regulatory agencies.

It is important for the investigator and their relevant personnel to be available during the monitoring visits and possible audits and for sufficient time to be devoted to the process.

13.1.2 Data and Safety Monitoring Plan

HCRN data safety monitoring activities include:

- Review of clinical trial conducted for progress and safety
- Review of all adverse events requiring expedited reporting as defined in the protocol
- Review of reports generated by data quality control review process
- Notification of the Sponsor Investigator of recommended action
- Notification of sites coordinated by the HCRN of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications

13.1.3 Data/Safety Monitoring and Reporting Guidelines

The HCRN will compile data summary reports for this trial and submit these reports to the Sponsor-investigator. The HCRN will submit data summary reports to the Indiana University Simon Cancer Center (IUSCC) Clinical Trial Monitoring Committee (CTMC) for review per the HCRN's standard operating procedures (SOP) and the study-specific data monitoring plan (DMP).

13.2 Data Handling and Record Keeping

13.2.1 Case Report Forms

An electronic case report form (eCRF) is required and must be completed for each included patient. The completed dataset is the sole property of HCRN and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from HCRN.

13.2.2 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all eCRFs, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the investigator in compliance with regulations.

During data entry, range and missing data checks will be performed on-line. The checks to be performed will be documented in the Data Monitoring Plan for the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site

and the site monitor. Corrections will be made by the study site personnel. This will be done on an ongoing basis.

13.3 Changes to the Protocol

Study procedures will not be changed without the mutual agreement of the Sponsor Investigator, Hoosier Cancer Research Network, and Cephalon, Inc.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (amended protocol) will be generated by the Hoosier Cancer Research Network and must be approved by each IRB, Cephalon, Inc., and if applicable, also the local regulatory authority. Local requirements must be followed.

If a protocol amendment requires a change to the Written Informed Consent Form, then the IRB must be notified. Approval of the revised Written Informed Consent Form by the IRB is required before the revised form is used.

The principal investigator is responsible for the distribution of these documents to his or her IRB, and to the staff at his or her center. The distribution of these documents to the regulatory authority will be handled according to local practice.

Cephalon's willingness to supply study drug is predicated upon the review of the protocol. The Hoosier Cancer Research Network agrees to provide written notice to Cephalon, Inc. of any modifications to the protocol or informed consent.

13.4 Ethics

13.4.1 Ethics Review

The final study protocol, including the final version of the Written Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB. The investigator must submit written approval to the HCRN office before he or she can enroll any patient into the study.

The principal investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB annually, as local regulations require.

Progress reports and notifications of serious unexpected adverse drug reactions will be provided to the IRB according to local regulations and guidelines.

The investigator is also responsible for providing the IRB with reports of any serious adverse drug reactions from any other study conducted with the investigational product. Cephalon, Inc. will provide this information to the Sponsor Investigator. These reports will be reviewed by the Sponsor Investigator and those considered unexpected and possibly related to protocol therapy plus all deaths within 30 days of discontinuing treatment will be forwarded to participating sites for submission to their Institutional

Review Boards per their guidelines. All other events will be held and submitted to the sites for continuing review.

13.4.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki, which are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

13.5 Written Informed Consent

The investigator will ensure the patient is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Patients must also be notified they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The investigator must store the original, signed Written Informed Consent Form. A copy of the signed Written Informed Consent Form must be given to the patient.

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