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E1411

Intergroup Randomized Phase II Four Arm Study In Patients With Previously Untreated Mantle Cell Lymphoma Of Therapy With: Arm A = Rituximab+ Bendamustine Followed By Rituximab Consolidation (RB → R); Arm B = Rituximab + Bendamustine + Bortezomib Followed By Rituximab Consolidation (RBV→ R), Arm C = Rituximab + Bendamustine Followed By Lenalidomide + Rituximab Consolidation (RB → LR) or Arm D = Rituximab + Bendamustine + Bortezomib Followed By Lenalidomide + Rituximab Consolidation (RBV → LR)

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STUDY PARTICIPANTS	***ACTIVATION DATE***
US Sites Only	May 22, 2012
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	Addendum #2 – Incorporated Prior to Activation
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	Addendum #5 – 2/14
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	Addendum #11 – 7/16
	Addendum #12 – 1/17
	Addendum #13
	Addendum #14

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

Rev. 12/13, 4/14, Add13

For regulatory requirements:	**For patient enrollments:**	**Submit study data**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions (i.e. patient eligibility or treatment-related) Contact the Study PI of the Coordinating Group		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or electronic data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

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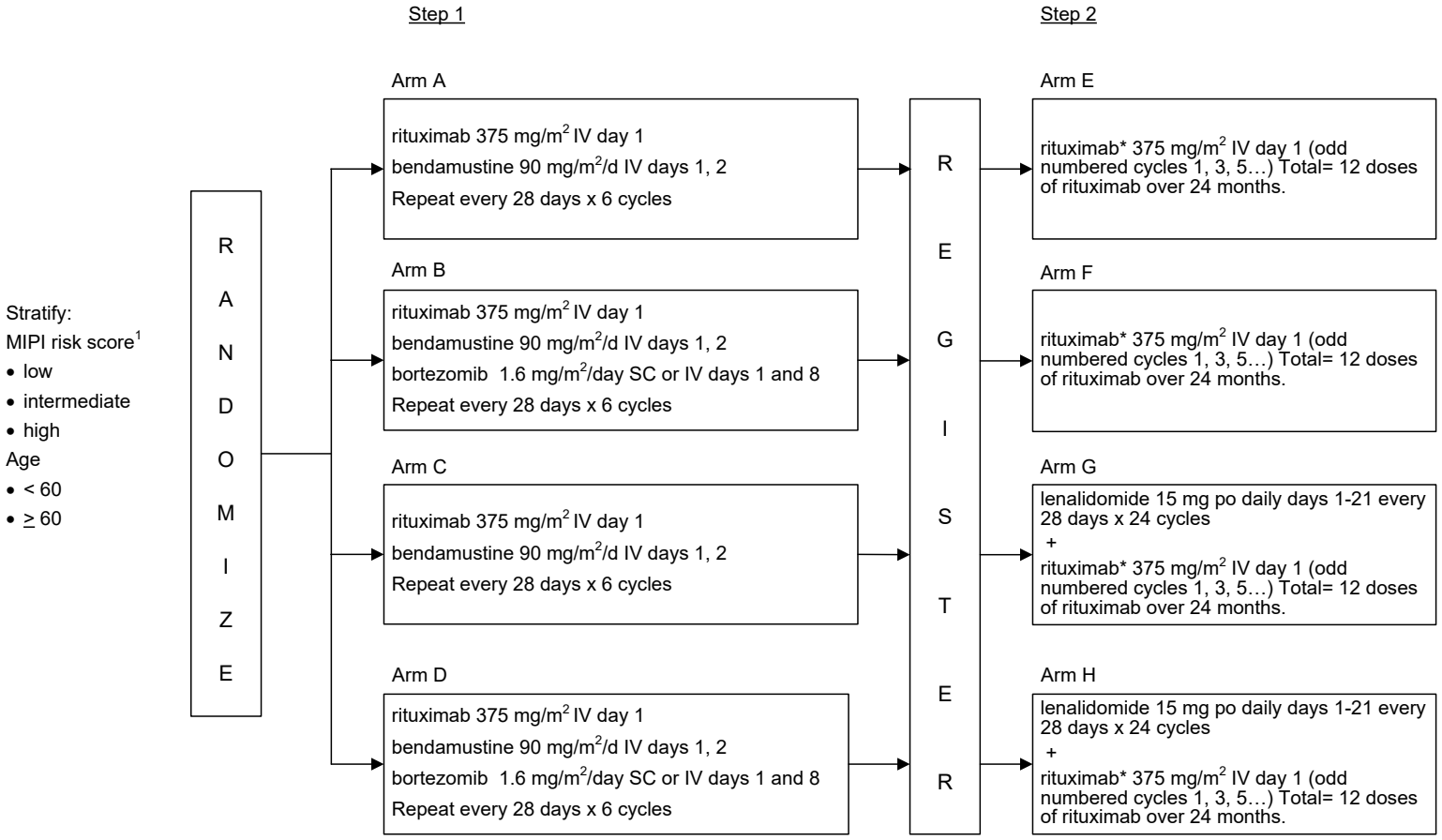
Rev. Add13

Schema



Accrual = 372
Cycle = 28 days

1. See Section 4.1.5.1 for MIPI calculator link

* Rituximab 375 mg/m2 IV can be replaced by Rituxan Hycela (rituximab and hyaluronidase human) 1400 mg/23,400 Units SC after at least one dose of rituximab IV has been administered.

1. Introduction

1.1 Overview of Mantle Cell Lymphoma (MCL)

Mantle cell lymphoma is a difficult disease to treat as it is incurable, like indolent lymphoma, but has a shorter median survival. The usual estimate for overall survival in MCL has been 3-5 years in the pre-rituximab era[1]. Recent analysis of survival in sequential eras demonstrated survival ~2.5 years in 1975-1986, but almost 5 years in 1996-2004 for patients treated with MCP, CHOP or R-CHOP[2]. Retrospective analysis of all MCL patients seen from 1997-2007 at one center reported median survival > 7 years[3]. Thus, while MCL is clearly a difficult disease to treat, its prognosis may not be as dismal as generally thought.

Median age at diagnosis of MCL is in the 7th decade, while median age in two recent ECOG trials has been 60-62. Age is an important variable in MCL, having prognostic importance in the IPI and MIPI. Age and co-morbidities also factor into treatment decisions regarding treatment intensity, e.g. risk-benefit balance for R-HyperCVAD-M/A[4] or high dose chemotherapy with stem cell support (HDC/SCT) [5-7]. Clinical trials that use more intensive therapeutic options generally have lower median age, as well as upper age limits[5-7]. Thus, treatment strategies vary with age.

Many previous studies in MCL are relatively small Phase II trials, often either with age restrictions or analyzed retrospectively for effects of age. In order to meet the challenges in MCL of completing clinical trials of adequate size in timely fashion utilizing strategies suitable for patients stratified by age and co-morbidities, an intergroup strategy has emerged. Initial treatment of patients with MCL will be divided by age and comorbidities. Older patients (≥ 60) will be treated with novel combinations. Younger (< 65) patients who are fit will be offered treatment with a more aggressive, generally HDC/SCT based, regimen when such a study is available. They may be treated on this less intensive treatment study based on physician or patient preference, when HDC/SCT is not planned, or when a more intensive trial is not available. Here we present the proposed trial for the older age group, also open to younger patients as described above.

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1.2 Treatment of MCL

The current benchmark for comparison of treatment outcomes in lymphoma, including MCL, is often R-CHOP. Data, however, for benefit of anthracyclines in MCL is not strong, with an older relatively small trial showing no clear benefit[8]. Nonetheless, initial therapy for untreated MCL with R-CHOP yields high response rates (RR), although remissions are not durable. Howard et al[9] reported a 96% response rate and median progression free survival (PFS) of 16 months. Lenz et al reported 92% RR and with consolidation treatment a 28 month PFS[10].

Treatment Approaches Applicable to Young, Fit Patients

One approach to improving these results is to achieve better cytoreduction with more intensive induction therapy. R-Hyper-CVAD alternating with R-high dose methotrexate/cytarabine (M/A)[4] was reported to have longer failure-free survival, 5 years for those 65 or under, but only 3 years for those over 65. A multicenter SWOG trial of this regimen [11] had slow accrual, perhaps indicating selection bias, and a median age of 57 with upper limit of 70. This trial confirmed a high rate of

CR/CRu of 58%, however, many patients could not complete therapy and PFS with short follow-up appears shorter than the single center data. An Italian study[12] similarly found that many patients could not complete this regimen. Thus, while it remains to be seen whether the prolonged PFS will be reproduced in younger patients, it is generally accepted that this therapy cannot be safely administered in patients over 60 or in poor performance status patients.

An alternative approach to improving on results with R-CHOP is to build on the high response rate with R-CHOP by consolidating the remission. In a randomized trial, 4-6 cycles of a CHOP- like regimen were followed by interferon or HDC/SCT. HDC/SCT significantly prolonged PFS (median 3.5 years), but not overall survival, perhaps because crossover, i.e. HDC/SCT at relapse, was permitted [5], and HDC/SCT is not curative[5, 6].

A logical extension of the above approaches, combining intensified induction followed by consolidation, has encouraging results. Initial treatment of patients age $\leq$ 65 with MCL (median age = 56) with addition of rituximab and high dose cytarabine (HDAC) cycles toR-CHOP to intensify induction, and then consolidating with HDC/SCT, led to prolonged PFS and a suggestion of a plateau, although late relapses continue to occur[7]. Again, this intensity of treatment is not generally applicable to most MCL patients, in whom median age at diagnosis is > 60.

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Treatment Approaches Applicable to Older Patients or Those with Comorbidities

Approaches more generally applicable to the majority of patients with MCL will need to be less intensive. Since remissions, but not cure, can be obtained in a high percentage of MCL patients, an attractive concept is remission induction followed by remission consolidation to try to eradicate residual lymphoma cells. Several new biologically targeted agents have demonstrated activity in MCL and present opportunities for novel combination approaches, both for induction and consolidation. The previous two ECOG trials of initial therapy of MCL tested novel consolidation (E1499) and induction (E1405) approaches. E1499 tested consolidation with RIT (^{90}Y-ibritumomab tiuxetan) after initial therapy of MCL with 4 cycles of R-CHOP. In this study, RIT improved quality of response and led to a median PFS of 27 months overall, and 25 months for those > 65. This is encouraging for a brief, well-tolerated regimen, however, no plateau in PFS is apparent[13]. In E1405, bortezomib, approved in the U.S. as a single agent in relapsed MCL, was incorporated into a modified R-HyperCVAD regimen and response rates are > 95% with > 70% complete responses[14].

Many agents are currently under investigation in MCL with documented activity. Bortezomib[15-19] is being studied alone and in combination regimens, as in E1405. Single agent, and in some cases combination, activity has been reported for a range of drugs including the mTOR inhibitors temsirolimus[20] and everolimus[21], nucleoside analogs fludarabine[22] and cladribine[23], immune modulating agents thalidomide[24] and lenalidomide [25, 26], as well as bendamustine [27].

Bendamustine in MCL:

Bendamustine is an alkylating agent that structurally also contains a purine-like benzimidazole ring. It is approved in the U.S. for treatment of CLL and for indolent B cell lymphoma progressing during or within 6 months of rituximab or a rituximab containing regimen. Based on in vitro data suggesting synergy between

rituximab and bendamustine (RB), much of the data on efficacy of bendamustine in MCL comes from combination studies of RB. Rummel et al[27] reported a Phase II trial RB (90 mg/m^2) in relapsed/refractory NHL. This study included 16 patients with MCL, 7 resistant to their last therapy, with responses in 12/16 (75%), including 8 (50%) CR. Robinson et al [28] reported a confirmatory US study of this RB regimen that included 12 patients with MCL, with 11 of 12 (92%) RR including 5 (42%) CR and 2 (17%) CRu. Median duration of response was 19 months. As initial therapy, a randomized trial in Europe comparing R-CHOP with R-bendamustine (RB)[29] has included about 100 patients with MCL among its 500 patients. Overall, RB appears non-inferior to R-CHOP with less myelosuppression and without the risk of cardiac toxicity. Based on these data, as well as activity of bendamustine (with or without rituximab) in indolent lymphoma, there is interest in exploring RB as initial therapy in MCL, perhaps as a platform to achieve high response rates with less toxicity allowing additional agents to be added.

Bortezomib in MCL:

Bortezomib is a potent, selective and reversible inhibitor of the proteasome. Bortezomib [15-19] is approved in the U.S. as a single agent in relapsed MCL, with a RR of 47% (8% CR) and PFS in responders of almost 8 months[30]. Bortezomib has been studied in combination with rituximab with no unexpected toxicities. It is also feasible to combine this agent with chemotherapy regimens such as modified R-hyperCVAD[31] and R-CHOP[32]. ECOG has recently completed accrual to a trial in mantle cell lymphoma (E1405) based on modified hyper-CVAD + bortezomib (VcR-CVAD), with dose modifications for neuropathy due to concomitant vincristine, demonstrating feasibility in the cooperative group setting[14]. Outcome results require further follow-up. Given the single agent activity in relapsed MCL, and ability to administer with largely non-overlapping toxicity profiles with standard chemotherapy and rituximab, bortezomib warrants further investigation in initial combination therapy of MCL.

A randomized Phase 1 pilot study in 24 subjects with multiple myeloma demonstrated that both the IV and subcutaneous (SC) routes of bortezomib administration have similar systemic drug exposure and proteasome inhibition[71]. Importantly, SC and IV administration of bortezomib appeared to result in similar efficacy profiles (ie, response rate) and similar safety profiles. The pilot study also provided preliminary evidence of good local tolerance for SC injection of bortezomib, when administered at 1 mg/mL concentration. The data from the Phase 1 pilot study formed the basis of the design of a randomized, Phase 3 study that compared the efficacy and safety of subcutaneous versus intravenous bortezomib at the approved 1.3 mg/m(2) dose and twice per week schedule in patients with relapsed multiple myeloma[72]. 222 patients were randomly assigned in a 2:1 ratio to receive either subcutaneous (n=148) or intravenous (n=74) bortezomib. The response-evaluable population consisted of 145 patients in the subcutaneous group and 73 in the intravenous group. Patients received a median of eight cycles (range one to ten) in both groups. Overall, similar efficacy results were observed in the SC and IV treatment groups, and the study demonstrated that bortezomib SC administration is not inferior to bortezomib IV administration.

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Rituximab-bendamustine-bortezomib:

Based on the above discussion, RB may be a base upon which to build improved treatment regimens in MCL. Bortezomib has activity in lymphoma and is approved for relapsed MCL. It has a largely non-overlapping toxicity profile with RB. RBV has been investigated in a phase I/II trial in lymphoma, including a few patients with MCL (Friedberg JW, Vose JM, Kelly JL, Young F, Bernstein SH, Peterson D, Rich L, Blumel S, Proia NK, Liesveld J, Fisher RI, Armitage JO, Grant S, Leonard JP. The combination of bendamustine, bortezomib, and rituximab for patients with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma. Blood, 117: 2807-2812 2011). R was given day 1, bendamustine at 90 mg/m^2/d on days 1 and 4 along with bortezomib at standard dose and schedule of 1.3 mg/m^2 days 1, 4, 8 and 11 of a 28 day cycle for a planned 6 cycles. This dose and schedule was tolerable with main toxicity being thrombocytopenia in about ½ of patients, and neuropathy. The VERTICAL trial used rituximab day 1, the usual bendamustine schedule days 1 and 2 and bortezomib weekly x 4 every 35 days[33]. No data using a day 1 and 4 schedule of single agent bendamustine exists.

Lenalidomide in MCL:

Lenalidomide is an immunomodulatory agent whose precise mechanism of anti-lymphoma activity remains unclear. It has activity in a range of lymphoma histologies, including indolent and aggressive lymphoma and CLL. Specifically looking at MCL, two trials of lenalidomide in relapsed/refractory aggressive lymphoma included some patients with MCL. In one study, of 15 patients with relapsed MCL[25] 8 (53%) responded, including 3 (20%) CR. The other trial[26] had

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39 MCL patients with 41% RR (13% CR). Lenalidomide was approved in the U.S. in 2013 for patients with relapsed MCL based on data showing a 28% response rate in heavily pre-treated patients (ref Goy A et al, JCO 2013). Recent data combining lenalidomide and rituximab in indolent lymphoma and CLL, based in part on potential for synergy through mechanisms such as enhanced ADCC, are encouraging and do not indicate any unexpected toxicities.

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Rationale for choice of induction regimens:

This trial will accrue mostly patients who are ≥ 60. Thus, the regimen needs to be tolerable in this group. While R-CHOP is one possible standard in such patients, based on the RB vs R-CHOP data the RB regimen is non-inferior and less toxic, making it an attractive option upon which to build. Bortezomib is active in MCL and can be added to this regimen, but its effect on efficacy and toxicity in this patient population requires study. Thus, this randomized Phase II trial will compare the results of each induction regimen in previously untreated patients with MCL.

To ensure optimal drug therapy, and minimize other variables, we have selected a standard RB dose and schedule of rituximab 375 mg/m^2 day 1 and bendamustine 90 mg/m^2/day days 1 and 2 every 4 weeks. The RBV regimen will use the same RB dose and schedule. Originally, the standard bortezomib schedule of 1.3 mg/m^2/d on days 1, 4, 8 and 11, also every 28 days, was selected to maximize the possibility of demonstrating benefit of this agent. The study is amended to use the weekly schedule of 1.6 mg/m^2/d on days 1 and 8 of each 28 day cycle as it appears to be equivalent, less toxic and requires fewer

patient visits. As bortezomib has been approved for SC administration, either IV or SC route of bortezomib is permitted.

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Rituximab ± Lenalidomide Consolidation Therapy:

It is reasonable to investigate use of additional therapy following initial therapy of MCL, which has a high response rate but disappointing duration of response. Such additional therapy has included HDC/SCT in younger patients, interferon, rituximab or radioimmunotherapy (E1499). While the benefit of rituximab in MCL has been modest, recently randomized trial data has become available demonstrating significant prolongation of response duration following R-CHOP induction in MCL when rituximab was compared with interferon maintenance (Kluin-Nelemans, H. C., E. Hoster, et al. (2012). "Treatment of older patients with mantle-cell lymphoma." N Engl J Med **367**(6): 520-531.), In addition, attention has been given to use of lenalidomide consolidation in lymphoma and myeloma. Lenalidomide is an immunomodulatory agent whose precise mechanism of anti-lymphoma activity remains unclear. Nonetheless, it is active in indolent and aggressive lymphoma including MCL, as well as in CLL. In CLL tumor lysis has been observed, suggesting that use with lower tumor burden, as in the maintenance setting, may be safer. Lenalidomide consolidation of remission in follicular lymphoma is currently being studied in an ECOG trial. Rituximab maintenance is part of the treatment in the previous ECOG trial E1405. Lenalidomide may enhance rituximab killing through ADCC. This study will use rituximab every 2 months for 2 years, based on this schedule being used in the PRIMA trial of indolent lymphoma to demonstrate prolongation of PFS, prolongation of duration of response following R-CHOP induction in MCL in the European Mantle cell Lymphoma network trial (Kluin-Nelemans, H. C., E. Hoster, et al. (2012). "Treatment of older patients with mantle-cell lymphoma." N Engl J Med **367**(6): 520-531.), and ECOG 4402 in which a significant percentage of patients treated every 3 months had sub-therapeutic trough levels. Lenalidomide will be administered at 15 mg orally daily for 21 days of a 28 day cycle for the same 2 year period.

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Quality of Life

Quality of Life in Mantle Cell Lymphoma: Background and Significance

Quality of life among patients with mantle cell lymphoma has not commonly been assessed. Because MCL is not curable, the goal of treatment is to induce remission. Mantle cell lymphoma is a difficult disease to treat given the lack of curative treatment options, the shorter overall median survival compared to indolent lymphoma [59-61], and the older median age at diagnosis which requires consideration of comorbidities and age-related health risks in evaluating the risk-benefit balance with regard to treatment [62-64]. Patient-reported outcomes data on improvement of initial symptoms from treatment, treatment-emergent symptoms, and overall health-related quality of life (HRQL) is needed to accurately evaluate the trade-off between treatment-induced impairments to HRQL versus disease-related symptom control and survival benefits. In the absence of curative therapy, the balance of treatment-related symptom improvement versus treatment-related toxicity will be an important parameter in deciding which treatment is “optimal.”

This protocol provides the unique opportunity to assess symptom burden introduced by the addition of bortezomib and lenalidomide to standard therapy for MCL among a cohort of older adults with MCL. Neurotoxicity is anticipated to be

the most commonly experienced side effect from bortezomib. Lenalidomide is associated with hematologic adverse events and fatigue. Accordingly, treatment-emergent symptom assessment will include targeted assessment of neuropathy and fatigue. The severity of fatigue associated with lenalidomide and associated impairments in HRQL are important to measure because the duration of treatment is 24 months. If observed, improvements in progression-free survival must be considered in light of potential long-term effects on HRQL, particularly given median survival for this population. This protocol will also provide the opportunity to assess improvements in disease-related symptoms associated with treatment. Last, this protocol provides the opportunity to collect longitudinal data among MCL patients during treatment and once treatment has been completed, which will provide data from the patient perspective on HRQL during survivorship. Given the paucity of patient-reported outcomes data among patients with MCL, we anticipate these findings will provide a major contribution to our understanding of patient well-being throughout and subsequent to treatment.

Our quality of life hypotheses are: (1) Patients receiving bortezomib during induction therapy (Arms B and D) will report more neuropathy symptoms at the conclusion of induction therapy than patients who do not receive bortezomib (Arms A and C). (2) Patients receiving lenalidomide + rituximab during consolidation therapy (Arms G and H) will report more fatigue during and at the conclusion of consolidation therapy than patients receiving rituximab only (Arms E and F). (3) Patients receiving bortezomib during induction therapy and lenalidomide during consolidation therapy (Arm B or D followed by Arm G or H) will report greater reduction in overall HRQL compared to pre-treatment than patients on other treatment arms. Additional descriptive analyses will provide information on reduction in lymphoma-specific symptoms during treatment, the longitudinal trajectory of neuropathy, the longitudinal trajectory of fatigue, and overall HRQL during and following treatment.

Quality of Life Design

Quality of life is an important secondary endpoint for this trial. The QOL study design has been developed based on prior ECOG trials with QOL endpoints which have established a precedent, and the QOL design will allow us to address the QOL objectives outlined in the next section. The ECOG protocol E2408 is a 3-arm randomized phase II trial to evaluate response among adults with follicular lymphoma receiving induction bendamustine-rituximab +/- bortezomib followed by rituximab +/- lenalidomide. The QOL design for E2408 is designed to answer the same questions we have set forth in this protocol, specifically the response of disease-related symptoms to treatment, treatment-emergent symptoms associated with bortezomib and lenalidomide, and the trajectory of HRQL on a longitudinal basis.

Trial participants will complete a patient-reported outcomes (PRO) assessment to measure lymphoma-specific symptoms, treatment-emergent symptoms, and overall health-related quality of life. The Functional Assessment of Cancer Therapy – Lymphoma, FACT-Lym subscale will be administered to assess disease-related symptoms, specifically this scale will be used to evaluate improvement of disease-related symptoms in response to treatment [59, 61, 63]. The FACT-Lym includes 15 items that assess the most common concerns among adults with lymphoma and has been administered to participants from two ECOG

Lymphoma protocols (E4402, E2408). Treatment-emergent neurotoxicity will be assessed using the 11-item FACT/GOG-Neurotoxicity scale (FACT/GOG-Ntx). The FACT/GOG-Ntx has been used to assess bortezomib-related neuropathy among myeloma patients [62] and is being administered to participants on ECOG trial E2408 to assess bortezomib-related neuropathy. Fatigue will be assessed using the 13-item FACT-Fatigue scale [64]. The FACT-Fatigue scale has been administered to participants on ECOG trials for various types of cancer and is being administered to E2408 participants to assess fatigue associated with disease and associated with lenalidomide. Overall health-related quality of life will be assessed using the FACT-General, FACT-G [60], a 27-item scale which measures physical, functional, social and emotional well-being.

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Trial participants will complete PRO assessment at the time of randomization, at the conclusion of induction therapy, after 6 cycles of consolidation therapy, at the conclusion of consolidation therapy, and annually for 5 years. The assessment at the conclusion of induction therapy will allow us to measure bortezomib-induced neuropathy, HRQL, and any changes in lymphoma symptoms since baseline. PRO assessment after 6 cycles of consolidation therapy will allow us to examine the extent of fatigue and associated impairments in HRQL associated with lenalidomide and to evaluate additive toxicities and HRQL among participants who have received bortezomib and lenalidomide in addition to standard therapy. PRO assessment at the conclusion of consolidation therapy will allow us to quantify the cumulative effects of 24 months of treatment with lenalidomide on fatigue and HRQL, in comparison to participants receiving rituximab alone. Rituximab has not been associated with significant symptom burden, therefore we anticipate the PRO assessments during and post-consolidation therapy will allow us to better understand lenalidomide-associated fatigue and HRQL impairments. In addition PRO assessments will allow us to examine changes in lymphoma-specific concerns throughout the course of treatment and during follow-up. PRO assessments annually at follow-up (months 36, 48, 60) will provide the unique opportunity to prospectively assess HRQL in this rare population. Participants who go off protocol for progression will complete PRO assessment at the time of progression to allow us to quantify differences in PRO domains between participants who progress and those who continue on protocol. This data will help to inform statistical analyses to manage missing data due to attrition.

1.3 FDG PET Imaging in MCL

The clinical course of MCL is heterogeneous and encompasses a clinical spectrum of indolent forms and rapidly progressive malignancy, with a poor prognosis. Although median survival of MCL has historically been in the range of 3-4 years, the emergence of dose-intensified regimens, and salvage treatments

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using novel therapies has recently led to a gain of 2-3 years in overall survival[2,3]. Notwithstanding the new developments in management there is still a need to further understand prognostic factors, determinants of therapy efficacy to develop better predictive markers for response. Because of the considerable variability in disease course, it is essential to identify patient subsets that are most likely to respond to distinct therapeutic approaches. Computed tomography (CT) has been the mainstay of initial evaluation and response assessment which is the recognized modality of choice by standardized International Workgroup Criteria (IWG) (Cheson et al 1999). More recently, the introduction of [18F]-Fluorine-

Deoxyglucose Positron Emission Tomography (FDG-PET),and its proven superior predictive value in curable subtypes of lymphoma, mainly, in Hodgkin lymphoma (HL), has led to the development of Revised IWC criteria incorporating PET into the response scheme which significantly altered response assessment in HL and DLBCL (Cheson et al 2007). However, the role of FDG PET remains under-investigated in MCL.

There are only a limited number of studies utilizing PET in the management of MCL, and the available literature mostly consists of subset analyses within a mixed group of NHL patients (Tsukamoto et al 2007, Elstrom et al 2003, Karam et al 2009, Brepoels et al 2008). Only two retrospective FDG-PET series reported results exclusively in MCL (Karam et al 2009, Brepoels et al 2008). MCL presents with a broad histological spectrum, and the prognosis of various morphological subtypes is still under investigation. Most authors agree that the blastoid-variant of MCL has an even more aggressive clinical behavior with a very poor prognosis (Weigert et al 2007, Bosch et al 1997, Watanabe et al 2010.). The published results of PET studies show significant variability in FDG-uptake, with higher FDG uptake obtained in more aggressive subtypes suggesting that pre-treatment FDG PET may identify patients with an unfavorable prognosis. Brepoels et al reported a high sensitivity for FDG PET for the detection of MCL (100%) but 20 % of these patients had very low grade FDG uptake (Brepoels et al 2008). A higher FDG-uptake was shown in patients with the more aggressive blastoid and large-cellular variants of MCL variant of MCL, which are known to have a more aggressive disease course compared to common MCL. This finding confirms the results of Karam et al, who have shown a more aggressive disease course in patients with high FDG uptake compared to those with low FDG uptake (Karam et al 2009). In support of these findings, in a mixed group of 36 untreated NHL patients (26 aggressive, 2 mantle, 8 indolent), a positive correlation was observed between the SUVmax at the biopsy site and the MIB-1 labeling index ($r = 0.69$, $p < 0.001$) (Watanabi et al 2010). Consequently, there is some evidence that SUVmax may stratify patients with more aggressive disease course, although it is unproven whether or not FDG-PET may be useful to diagnose high-grade MCL.

Although assessment of response is important in lymphoma, it is not yet clear how response evaluation should be effectively performed in MCL. In a retrospective study of 37 MCL patients, after either front line (CHOP or RCHOP) or 2nd or 3rd line therapy, the investigators found no difference between CT-based or PET-based evaluations with respect to response; similar outcomes were reported for PR and CR determined by revised IWC employing FDG-PET (Brepoels 2008). In a more recent prospective study, in 49 patients with relapsed or refractory follicular lymphoma (FL) or MCL (n=10), the percent reduction in SUVmax (70% vs 29%) and maximum perpendicular diameter (78% vs 48%) after completion of therapy were significantly greater in patients with complete response than in patients with non-CR ($P<0.0001$). The positive and negative predictive value of SUVmax at a threshold of 61% was 77% and 78%, respectively (Tateishi et al 2011). Bodet-Milin et al, retrospectively reported a positive and negative predictive value of 62.5 and 100%, respectively, for revised IWC with PET for identifying relapse at one year in a multicenter study involving seven centers and 44 MCL patients (Bodet-Milin et al 2010). With a median follow-up of 21 months, only the revised IWC criteria were accurate to identify patients with high risk for early relapse. Prognostic Index (IPI) and revised IWC

criteria modified both event-free survival (EFS) (p = .02 and .0001, respectively) and overall survival duration (p = .03 and .05, respectively). Combining mantle cell prognostic index (MIPI) (Hoster et al 2008) and SUVs may provide a better means as a predictive measure of outcome but this hypothesis should be proven by further prospective investigations (Bodet-Milin et al 2010). Consequently, there are limited data in patients with MCL using FDG-PET and the existing studies have reported mixed results and mixed patient populations, currently making it very difficult to extract useful and uniform information.

Measuring chemosensitivity early during therapy as a predictor of response has been reported in a two-center retrospective cohort study although the results of this study have not been formally published (Mato et al 2010). In this study of 82 advanced stage MCL patients undergoing HDT/SCT, FDG-PET post-2 cycles and post-3 cycles were positive in 34% and 18% of patients, respectively. With a median follow-up of 23 months, interim PET status was not found to be associated with PFS or OS (p=0.8). In corroboration with prior studies, post treatment PET status was statistically significantly associated with PFS (p=.001) and trended towards significance for OS (p=0.1). Post treatment PET status remained an independent predictor of PFS in a multivariate analysis that included MIPI score, blastoid variant and Ki-67. (Mato et al 2010). Although these data do not support the prognostic utility of an interim, a prospective multicenter trial using a standardized approach towards PET protocol and interpretation is still warranted to prove or refute its role. Due to the inherent nature of the frequent relapses, early detection of persistent disease may lead to more aggressive management. However, it is also conceivable that MCL patients will always have some residual disease early during therapy that it may not be useful segregating patients into different response categories. It is an unknown whether or not there is a significant difference between PET-CR and PET-PR patients with respect to survival. In this regard, the persistence or resolution of the metabolic activity at completion of therapy may be more valuable for stratifying different response groups with respect to chemo-resistance. It is also possible that PET may complement the predictive value of serum molecular markers since eradication of all remaining viable lymphoma cells in the blood may not parallel responses at the nodal or extranodal sites. For example, in a prior study, at the completion of rituximab and CHOP therapy, 36% of patients had no evidence of PCR-detectable disease, however, only 44% of these patients who were in molecular remission had clinical, radiologic, or pathologic CR/CRu therapy; the remaining 56% of molecular responders achieved only a PR at completion of induction therapy (Howard et al 2002).

Consequently, prospective investigations are necessary in further evaluating disease biology as well as the relevance of assessment of metabolic response both in the interim and post therapy setting, particularly in those patients undergoing front-line therapy.

1.4 Summary

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Our hypotheses are that: (1) a novel combination of RB or RBV as initial therapy for MCL will be generally applicable MCL, particularly in older patients not considered candidates for more aggressive HyperCVAD and SCT based regimens, achieve a higher rate of CR and be as tolerable as R-CHOP; and (2) consolidation with lenalidomide-rituximab in these patients will be tolerable, increase overall and complete response rates, as well as prolong PFS compared with rituximab consolidation alone.

At this point, given the range of questions that need to be answered and current resources, in particular the number of MCL patients available, as well as the lack of an accepted standard initial therapy, we believe that a series of smaller Phase II trials will be more informative than large randomized phase 3 trials. This randomized Phase II induction plus consolidation approach is designed to select the optimal regimen(s), on the basis of efficacy (primary endpoint of PFS), safety, and impact on patient-reported quality of life to take forward in subsequent trials. Secondary endpoints of overall and complete response rates at the end of induction therapy, conversion to complete response during consolidation and toxicity will be factored into this decision. Concurrent European trials of RB followed by scheduled rituximab will help inform these decisions as well.

2. Objectives

2.1 Primary Objectives

2.1.1 To determine whether the addition of bortezomib (RBV) to an induction regimen of rituximab-bendamustine (RB) improves progression-free survival (PFS) compared to RB alone in patients with previously untreated mantle cell lymphoma. Rev. 12/13

2.1.2 To determine whether the addition of lenalidomide to a consolidation regimen of rituximab following an induction regimen of RB or RBV improves PFS compared to consolidation rituximab alone in this patient population.

2.2 Secondary Objectives

2.2.1 To determine whether the addition of bortezomib to induction therapy improves the PET-documented complete response rate compared to RB alone.

2.2.2 To determine the objective response rate (ORR) for RB and RBV.

2.2.3 Among patients who do not have PET-documented CR at the end of induction, to determine whether the addition of lenalidomide to consolidation therapy improves CR and ORR compared with rituximab alone.

2.2.4 To determine overall survival (OS) in the treatment arms.

2.2.5 To determine safety, with attention to the addition of bortezomib in the induction regimen and lenalidomide-rituximab as consolidation therapy.

2.3 Laboratory Correlative Studies

2.3.1 To collect paraffin embedded tissue for creation of tissue microarray.

2.3.2 To collect and bank serum and blood mononuclear cells for future studies.

2.3.3 To collect formalin fixed paraffin embedded (FFPE) tissue to analyze potential prognostic factors:

2.3.3.1 Ki-67 proliferation index by immunohistochemistry and correlation with proposed 5 gene set of proliferation markers analyzed by RNA PCR.

2.3.3.2 SOX 11 expression by immunohistochemistry.

2.3.3.3 Micro-RNA levels by microarray.

2.4 Quality of Life Objectives

2.4.1 Using patient-reported outcomes data, to determine the extent and severity of neuropathy associated with the addition of bortezomib to induction treatment.

2.4.2 Using patient-reported outcomes data, to determine the extent and severity of fatigue associated with the addition of lenalidomide to consolidation treatment.

2.4.3 To evaluate the effects of the addition of bortezomib and lenalidomide on patient-reported health-related quality of life.

2.4.4 To evaluate the effects of bortezomib-related neuropathy on patient-reported health-related quality of life.

2.4.5 To evaluate the response of lymphoma-specific symptoms to treatment.

2.4.6 Using longitudinal patient-reported outcomes data, to describe the trajectory of lymphoma symptoms, neuropathy, fatigue and overall health-related quality of life prior to, during and following treatment among older adults with MCL.

2.5 Imaging Correlative Studies

2.5.1 To assess the proportion of patients up and down staging when FDG-PET/CT is added to standard Ann Arbor staging.

2.5.2 To assess the ability of pre-treatment FDG-PET/CT semi quantitative parameters including SUVmax and metabolic measurements to predict response rate and PFS.

2.5.3 Among patients with interim FDG-PET/CT imaging, to assess the correlation of interim FDG-PET/CT imaging with response rate and PFS both during induction and consolidation therapy.

2.5.4 To assess standard FDG-PET/CT metrics including SUVmax, tumor metabolic burden, total tumor burden, and association with pathology features (blastoid variant vs. other, and Ki67) in the setting of MCL.

2.5.5 To assess differences in overall and complete response rates when using Deauville vs. International Harmonization Project FDG-PET/CT interpretation criteria.

2.5.6 To determine whether there is a correlation between FDG-PET/CT response and residual disease assessment by molecular and/or flow cytometric techniques.

2.6 Residual Disease Assessment by Molecular and Flow Cytometric Techniques

2.6.1 To determine whether the number of malignant cells in circulation predict the number of cells in marrow

2.6.2 To determine whether the number of malignant cells in circulation/in marrow at the end of induction correlate with CR and 2 year PFS.

2.6.3 To determine whether there is a higher rate of minimal residual disease (MRD) negativity among patients randomized to RBV as compared with RB, and among patients treated with LR maintenance compared with R.

2.6.4 To compare the two methods of MRD detection - molecular techniques and flow cytometry as prognostic markers for outcome

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

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NOTE: **There is no provision for stem cell collection in this study, but there is also no prohibition of stem cell collection. If the treating physician feels collection is warranted, the following guidelines must be followed:**

- **Stem cell collection may only be performed after cycle 6 of step 1**
- **Mobilization should begin around Day 21 of cycle 6, or coming off cycle 6**
- **Only growth factors may be used; no chemotherapy, for mobilization**
- **There must be 14 days from last growth factor to start of step 2 therapy.**

3.1 Step 1 Registration

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_____ 3.1.1 MIPI score must be calculated and entered in OPEN (see Section 4.1.5.1).

NOTE: For this calculation WBC 7,500/mm^3 = 7,500/uL = 7.5 x 10^9/L should be entered as 7500.

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_____ 3.1.2 Age ≥ 18 years.

_____ 3.1.3 Females of childbearing potential must not be pregnant or breast-feeding due to risk of fetal harm by the chemotherapeutic agents prescribed in this protocol.

All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy.

Female? _____ (Yes or No)

Date of blood test or urine study: _____

A female of childbearing potential (FCBP) is any woman, regardless of sexual orientation or whether they have undergone tubal ligation,

who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

_____ 3.1.4 Women of childbearing potential and sexually active males must be strongly advised to use an accepted and effective method of contraception.

_____ 3.1.5 Patients must have measurable disease as defined in Section 6.

_____ 3.1.6 Histologically confirmed untreated mantle cell lymphoma, with documented cyclin D1 (BCL1) by immunohistochemical stains and/or t(11;14) by cytogenetics or FISH.

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Rev. 2/14 _____ 3.1.7 Patients must have at least one objective measurable disease parameter. Baseline measurements and evaluations must be obtained within 4 weeks of registration to the study. Abnormal PET scans will not constitute evaluable disease, unless verified by CT scan or other appropriate imaging. Measurable disease in the liver is required if the liver is the only site of lymphoma. If the only radiographically assessable disease is splenomegaly (without discrete measurable nodules), the patient can be enrolled, but for such patients CR cannot be differentiated from PR (per Section 6.1.3), while the spleen will be considered nodal with respect to criteria for PD (see Section 6.4.5).

_____ 3.1.8 ECOG performance status between 0-2.

_____ 3.1.9 Hematologic parameters (unless due to marrow involvement) obtained within 4 weeks prior to registration.

3.1.9.1 ANC $\geq$ 1500/ mm^3 (1.5 x 10^9/L)

3.1.9.2 Platelets $\geq$ 100,000/ mm^3 (100 x 10^9/L)

_____3.1.10 Liver/Renal function, obtained within 4 weeks prior to registration

_____ 3.1.10.1 AST/ALT $\leq$ 2 x upper limit of normal (ULN)

_____ 3.1.10.2 Total bilirubin $\leq$ 2 x upper limit of normal (ULN) or, if total elevated, direct bilirubin $\leq$ 2 x upper limit of normal (ULN)

_____ 3.1.10.3 Calculated creatinine clearance by Cockroft-Gault formula $\geq$ 30 ml/min

Rev. 12/13 _____ 3.1.11 No evidence of prior malignancy except: adequately treated non-melanoma skin cancer, adequately treated in situ carcinoma, low grade prostate carcinoma (Gleason grade ≤ 6) managed with observation that has been stable for at least 6 months, or any malignancy treated with curative intent continuously disease free for $\geq$ 3 years so as not to interfere with interpretation of radiographic response.

_____ 3.1.12 No prior therapy for MCL, except: < 2 weeks of steroid therapy for symptom control or local radiation therapy for symptom control if there is measurable disease outside the radiation portal. Patients may be on chronic steroids for non-malignant disease if on a stable dose equivalent to ≤ 20 mg prednisone per day.

Rev. 12/13 _____ 3.1.13 Patient must have no known CNS involvement.

Rev. 12/13, 2/14 _____ 3.1.14 Patient agrees that if randomized to Arms C or D, and proceeding onto Arms G or H, they must register into the mandatory RevAssist program, and be willing and able to comply with the requirements of RevAssist.

Patients must have no medical contra-indications to, and be willing to take, DVT prophylaxis as all patients registering to the lenalidomide/rituximab Arms G and H will be required to have deep vein thrombosis (DVT) prophylaxis. Patients randomized to Arms G or H who have a history of a thrombotic vascular event will be required to have full anticoagulation, therapeutic doses of low molecular weight heparin or warfarin to maintain an INR between 2.0 – 3.0, or any other accepted full anticoagulation regimen (e.g. direct thrombin inhibitors or Factor Xa inhibitors) with appropriate monitoring for that agent. Patients on Arms G and H without a history of a thromboembolic event are required to take a daily aspirin (81 mg or 325 mg) for DVT prophylaxis. Patients who are unable to tolerate aspirin should receive low molecular weight heparin therapy or warfarin treatment or another accepted full anticoagulation regimen.

Ways to minimize risk of DVT should be discussed with patients, including, but not limited to, avoiding smoking, minimizing pro-thrombotic hormone replacement, avoiding prolonged periods of inactivity (e.g. uninterrupted long car or plane trips).

_____ 3.1.15 HIV positive patients are <u>not</u> excluded, but to enroll, must meet <u>all</u> of the below criteria:

3.1.15.1 HIV is sensitive to antiretroviral therapy.

3.1.15.2 Must be willing to take effective antiretroviral therapy if indicated.

Rev. 5/16 3.1.15.3 CD4 count at screening ≥ 300 cells/mm^3.

3.1.15.4 No history of AIDS-defining conditions.

3.1.15.5 If on antiretroviral therapy, must not be taking zidovudine or stavudine.

Must be willing to take prophylaxis for Pneumocystis jiroveci pneumonia (PCP) during therapy and until at least 2 months following the completion of therapy or until the CD4 cells recover to over 250 cells/mm^3, whichever occurs later.

_____ 3.1.16 Patients must not have grade 2 or greater peripheral neuropathy.

_____ 3.1.17 Patients must not have NYHA Class III or IV heart failure, uncontrolled angina severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia.

_____ 3.1.18 Patients must not have hypersensitivity to bortezomib, boron or mannitol.

_____ 3.1.19 Patients must not have a serious medical or psychiatric illness likely to interfere with study participation.

Rev. 12/13 _____ 3.1.20 Patients must not be participating in any other therapeutic clinical trial or taking any other experimental medications within 14 days prior to registration.

3.2 Step 2 Registration

_____ 3.2.1 ECOG performance status between 0-2

_____ 3.2.2 CR, PR or SD after Step 1.

_____ 3.2.3 Prior to beginning consolidation, patients must meet the following criteria:

Hematologic parameters:

_____ 3.2.3.1 ANC ≥ 1000 cells/mm^3 (1.0 x 10^9/L)

_____ 3.2.3.2 Platelets ≥ 75,000 cells/mm^3 (75 x 10^9/L)

_____ 3.2.3.3 AST/ALT ≤ 2 x upper limit of normal (ULN)

Rev. 8/15 _____ 3.2.3.4 Total bilirubin ≤ 2 x upper limit of normal (ULN) or, if total elevated, direct bilirubin ≤ 2 x upper limit of normal (ULN)

_____ 3.2.3.5 Calculated creatinine clearance by Cockroft-Gault formula ≥ 30 ml/min

Rev. 12/13
Rev. 5/16 _____ 3.2.4 Patient agrees that if randomized to Arms C or D, and proceeding onto Arms G or H, they must register into the mandatory REMS program, and be willing and able to comply with the requirements of REMS.

_____ 3.2.4.1 Pregnancy tests must occur within 10 - 14 days and again within 24 hours prior to initiation of Cycle 1 of lenalidomide. *Females of childbearing potential (FCBP)* with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on lenalidomide therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on lenalidomide therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix VI: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 - 14 days and again within 24 hours prior to starting Cycle 1 of lenalidomide and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to

use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix VI: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods, AND also Appendix XIV: Lenalidomide Information Sheet.

*A female of childbearing potential is any sexually mature female, regardless of sexual orientation of whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female of childbearing Potential? _____ (Yes or No)

Date of blood or urine study? _____

_____ 3.2.4.2 Females of childbearing potential (FCBP) must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study/lenaliomide: 1) for at least 28 days before starting lenalidomide; 2) while participating in the study including interruptions in therapy; and 3) for at least 28 days after discontinuation/stopping lenalidomide. The two methods of reliable contraception must include one highly effective method (i.e. intrauterine device (IUD), hormonal [birth control pills, injections, or implants], tubal ligation, partner's vasectomy) and one additional effective (barrier) method (i.e. latex condom, diaphragm, cervical cap). FCBP must be referred to a qualified provider of contraceptive methods if needed.

_____ 3.2.4.3 Women must agree to abstain from donating blood during study participation and for at least 28 days after discontinuation from protocol treatment.

_____ 3.2.4.4 Males must agree to abstain from donating blood, semen, or sperm during study participation and for at least 28 days after discontinuation from protocol treatment.

All males, regardless of whether they have undergone a successful vasectomy, must agree to use a latex condom during sexual contact with a female of childbearing potential, or to practice complete abstinence from heterosexual intercourse with any female of childbearing potential during all cycles of study treatment and for at least 28 days following discontinuation of protocol treatment

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_____ 3.2.4.5 Patients must have no medical contra-indications to, and be willing to take, DVT prophylaxis as all patients registering to the lenalidomide/rituximab Arms G and H will be required to have deep vein thrombosis (DVT) prophylaxis. Patients randomized to Arms G or H who have full anticoagulation, a history of a thrombotic vascular event will be required to have therapeutic doses of low molecular weight heparin or warfarin to maintain an INR between 2.0 – 3.0, or any other accepted full anticoagulation regimen (e.g. direct thrombin inhibitors or Factor Xa inhibitors) with appropriate monitoring for that agent. Patients on Arms G and H without a history of a thromboembolic event are required to take a daily aspirin (81 mg or 325 mg) for DVT prophylaxis. Patients who are unable to tolerate aspirin should receive low molecular weight heparin therapy or warfarin treatment or another accepted full anticoagulation regimen.

Ways to minimize risk of DVT should be discussed with patients, including, but not limited to, avoiding smoking, minimizing pro-thrombotic hormone replacement, avoiding prolonged periods of inactivity (e.g. uninterrupted long car or plane trips).

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Physician Signature _____ Date _____

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

4. Randomization Procedures

CTEP Registration Procedures

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Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>. For questions, please contact the RCR Help Desk by email at <RCRHelpDesk@nih.gov>.

CTSU Registration Procedures

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This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

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Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization

- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572

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- An active status on a participating roster at the registering site.

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Downloading Site Registration Documents:

Site registration forms may be downloaded from the **E1411** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the **ECOG-ACRIN** link to expand, then select trial protocol **E1411**
- Click on LPO Documents, select the Site Registration Documents link, and download and complete the forms provided.

Requirements for E1411 site registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

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Submitting Regulatory Documents

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Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

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Required Protocol Specific Regulatory Documents

1. Copy of IRB Informed Consent Document.

NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

2. A. CTSU IRB Certification Form.

Or

B. Signed HHS OMB No. 0990-0263 (replaces Form 310)

Or

C. IRB Approval Letter

NOTE: The above submissions must include the following details:

- **Indicate all sites approved for the protocol under an assurance number.**
- **OHRP assurance number of reviewing IRB**
- **Full protocol title and number**
- **Version Date**
- **Type of review (full board vs. expedited)**
- **Date of review.**
- **Signature of IRB official**

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Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

NOTE: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

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Patient Enrollment

Patients must not start protocol treatment prior to randomization.

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Treatment should start within ten working days after registration.

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at <https://ctepcore.nci.nih.gov/iam>) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a

transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN site staff should verify the following:

- **All eligibility criteria has been met within the protocol stated timeframes.**
- **All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).**

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.1 Randomization (Step 1)

Patients must not start protocol treatment prior to randomization.

Rev. 12/13 Treatment should start within ten working days after registration.

The following information will be requested at time of randomization:

4.1.1 Protocol Number

4.1.2 Investigator Identification

4.1.2.1 Institution and affiliate name (Institution CTEP ID)

4.1.2.2 Investigator's name (NCI number)

4.1.2.3 Cooperative Group Credit

4.1.2.4 Credit Investigator

4.1.2.5 Protocol specific contact information

4.1.3 Patient Identification

4.1.3.1 Patient's initials (first and last)

4.1.3.2 Patient's Hospital ID and/or Social Security number

4.1.3.3 Patient demographics

4.1.3.3.1 Gender

4.1.3.3.2 Birth date

4.1.3.3.3 Race

4.1.3.3.4 Ethnicity

4.1.3.3.5 Nine-digit ZIP code

4.1.3.3.6 Method of payment

4.1.3.3.7 Country of residence

4.1.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1. An eligibility checklist has been appended to the protocol.

4.1.5 Classification/Stratification Factors

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4.1.5.1 Mantle cell lymphoma IPI (MIPI) score: low, intermediate, or high (65).

MIPI score = 0.03 535 × age (y) + 0.6978 (if ECOG-ACRIN > 1) + 1.367 × $\log_{10}$(LDH/ULN) + 0.9393 × $\log_{10}$(WBCs per mm^3).

NOTE: MIPI calculator can be accessed using the European MCL Network website.

http://www.european-mcl.net/en/clinical_mipi.php

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4.1.5.2 Age (< 60 years vs ≥ 60 years)

4.1.6 Additional Requirements

4.1.6.1 Patients must provide a signed and dated, written informed consent form.

4.1.6.2 PET/CT scans must be submitted for central review as outlined in Section 10.1.

4.1.6.3 Pathology materials must be submitted for central review per Section 10.2.

4.1.6.4 Additional specimens are to be submitted for laboratory research studies and/or banking as indicated in Sections 10 and 11 per patient consent.

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4.1.6.5 Data collection for this study will be done exclusively in Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at <https://ctepcore.nci.nih.gov/iam>) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator)) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the

"accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com

NOTE: Submitted scans and specimens must be entered and tracked via the ECOG-ACRIN Sample Tracking System (STS). See Section 10.3.

4.1.7 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted according to the instructions in the E1411 Completion Guidelines.

4.2 Step 2 Registration

Patients should not start protocol treatment prior to step 2 registration.

Treatment should start per instructions in Section 4. The following information will be requested at time of registration

4.2.1 Protocol Number

4.2.2 Investigator Identification

4.2.2.1 Institution and affiliate name (Institution CTEP ID)

4.2.2.2 Investigator's name (NCI number)

4.2.2.3 Cooperative Group Credit

4.2.2.4 Credit Investigator

4.2.2.5 Protocol specific contact information

4.2.3 Patient Identification

4.2.3.1 Patient's initials (first and last)

4.2.3.2 Patient's Hospital ID and/or Social Security number

4.2.3.3 Patient demographics

4.2.3.3.1 Gender

4.2.3.3.2 Birth date

4.2.3.3.3 Race

4.2.3.3.4 Ethnicity

4.2.3.3.5 Nine-digit ZIP code

4.2.3.3.6 Method of payment

4.2.3.3.7 Country of residence

4.2.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.2. An eligibility checklist has been appended to the protocol.

4.2.5 Classification Factors

4.2.5.1 Induction Treatment on Step 1.

4.2.6 Additional Requirements

4.2.6.1 PET/CT scans must be submitted for central review as outlined in Section 10.1.

4.2.6.2 Additional specimens are to be submitted for laboratory research studies and/or banking as indicated in Sections 10 and 11 per patient consent.

NOTE: Submitted scans and specimens must be entered and tracked via the ECOG-ACRIN Sample Tracking System (STS). See Section 10.3.

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4.2.6.3 REMS® Program

Lenalidomide will be provided to patients on Arms G and H for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the REMS® program of Celgene Corporation. Per standard REMS® requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects randomized to Arms C or D who then proceed on to Arms G or H of this trial, must be registered in and comply with all requirements of the REMS® program. Refer to Section 8.4.8 of the protocol for complete information on the REMS® Program.

4.2.6.4 Data collection for this study will be done exclusively in Medidata Rave. Prior to beginning data entry in Rave, study staff must be registered in Medidata and complete the required training modules. Study staff will receive an invitation to join the study in Rave after evidence of IRB approval is submitted to RSS.

4.2.7 Instructions for Patients Who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, follow-up data will still be collected and must be submitted according to the instructions in the E1411 Completion Guidelines.

4.3 Investigator's Drug Brochure and Safety Alerts

The Investigator Drug Brochure (IDB) for lenalidomide and bortezomib are available for download from the ECOG webpage. The IDB provides relevant and current scientific information about the investigational product. The IDB should be submitted to your IRB/EC according to GCP regulations. The IDB and any correspondence to the Institutional Review Board (IRB)/Ethics Committee (EC) should be kept in the E1411 regulatory files.

Should any SAE report on this study qualify as a safety alert report requiring expedited reporting, the SAE report will be sent by the respective pharmaceutical company to regulatory authorities globally (including the FDA) and ECOG-ACRIN. If applicable, ECOG-ACRIN will disseminate these safety alert reports to all ECOG-ACRIN investigators in the bimonthly group mailings. These reports should be forwarded to your IRB/EC within 90 days of receipt for review. Reporting instructions are provided with each safety alert. These safety alerts and any correspondence to your IRB/EC should be maintained in your E1411 study files.

4.4 IND Status

When used in this protocol lenalidomide and bortezomib are classified as an "unapproved use of an approved agent" and by definition considered investigational agents. However, while it is not an indication currently approved by the FDA, the use of lenalidomide and bortezomib in this protocol are exempt from the requirements of an IND and described under Title 21 CFR 312.2(b).

5. Treatment Plan

5.1 Administration Schedule

5.1.1 ARM A/ARM E

5.1.1.1 Step 1 Induction (Arm A)

Rituximab 375 mg/m^2 IV day 1

Bendamustine 90 mg/m^2/day IV days 1 and 2

Repeat cycles every 4 weeks for a total of 6 cycles

Rev. 12/13

NOTE: Rituximab dose may be rounded to the nearest 50 mg

Other agents may be rounded ± 5%

Rev. 12/13

NOTE: Cycle length may be altered to 25 days (-3 days) or to 31 days (+3 days), for holidays or other extenuating scheduling situations.

Rev. 8/15

NOTE: Prophylactic Neupogen or Neulasta (or an approved biosimilar agent) may be used according to ASCO guidelines.

NOTE: Dose Modifications – See Section 5.4.

Premedication

Rev. 12/13

- Acetaminophen (650 or 1000 mg) and diphenhydramine (25 or 50 mg) or equivalent is to be administered 30 to 60 minutes prior to starting each infusion of rituximab. Since transient hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to rituximab infusion.
- Standard anti-emetic therapy may be given to patients prior to administration of each RB treatment: including 5-HT3 serotonin receptor antagonists and steroids (e.g., dexamethasone).

Administration Schedule

Rev. 8/15

The following are to be administered, preferably in the order indicated (1 cycle = 28 days).

- Rituximab 375 mg/m^2 IV Day 1. The rituximab dose may be rounded to the nearest 50 mg. See Section 5.4.1.1 regarding rituximab infusion rates.
- See Section 5.4.1.1 for patients felt to be at risk for, or who have had, infusion reactions.

Rev. 12/13

- Bendamustine 90 mg/m^2/day will be administered to patients by IV infusion on days 1 and 2 of each 28-day cycle. The infusions are given over a 60-minute period

and on day 1 it is preferable that it be administered to patients after the administration of rituximab.

NOTE: See Section 5.5 regarding supportive care recommendations.

Restaging and Length of Therapy

- Repeat cycles every 28 days for a total of 6 cycles. Patients may be evaluated in the office more frequently if needed at physician discretion.
- Patients will be restaged after 3 cycles of therapy. Patients who are in at least stable disease (SD, PR, or CR) after 3 cycles will receive 3 subsequent cycles. Patients who have progressive disease (PD) at restaging will be discontinued from study treatment.

Rev. 8/15

5.1.1.2 Step 2 (Arm E)

Patients who have improved their response or have had no interval change in their tumor measurements with restaging from cycle 3 to 6 on Arm A will then proceed to Step 2 on Arm E.

Rev. 12/13
Rev. Add13

Rituximab 375 mg/m^2 IV or Rituxan Hycela (rituximab and hyaluronidase human) 1400 mg/23,400 Units SC every 8 weeks for 12 doses.

Rev. 12/13
Rev. 5/16

NOTE: The first dose of rituximab consolidation should be given 8 weeks (± 3 working days if needed for scheduling) after the start of cycle 6 of induction (this will be the start of week 29). In the event of a treatment delay, the first dose of rituximab may be given up to 16 weeks after the start of cycle 6 of induction.

Rev. 12/13
Rev. Add13

NOTE: Rituximab IV dose may be rounded to the nearest 50 mg

NOTE: There are no prescribed dose modifications for rituximab. If, however, a patient has grade 3 or 4 neutropenia in the absence of other grade 3 or 4 cytopenias, consider the possibility of "late-onset neutropenia" associated with rituximab. Manage per institutional standards. Often, myeloid growth factor is administered and per investigator's choice rituximab may be administered on schedule or delayed by 1 week intervals with repeat CBC to ensure resolution of neutropenia, and then start the new cycle. If not recovered by 4 weeks despite growth factor, patient will be removed from treatment.

NOTE: If there have been no dose delays or reductions during step 2 for 4 consecutive cycles, the

patient may be seen every other cycle for subsequent cycles.The patient should be contacted by phone at the time of the even numbered cycle to assess clinical status and toxicities and still requires every 8 week blood draws. The phone contact and lab data must be documented.

Rev. 1/17

Rev. Add13

NOTE: If using Rituxan Hycela, patients must receive at least one full dose of a rituximab product IV before receiving Rituxan Hycela SC. Please refer to the commercial package insert.

5.1.2 ARM B/ARM F

5.1.2.1 Step 1 Induction (Arm B)

Rev. 12/13

Bortezomib 1.6 mg/m^2/day SC or IV on days 1 and 8

Rituximab 375 mg/m^2 IV day 1

Bendamustine 90 mg/m^2/day IV days 1 and 2

Repeat cycles every 4 weeks for a total of 6 cycles

NOTE: Rituximab dose may be rounded to the nearest 50 mg.

Rev. 12/13

Other agents may be rounded ± 5%

NOTE: Cycle length may be altered to 25 days (-3 days) or to 31 days (+3 days), for holidays or other extenuating scheduling situations.

Rev. Add13

NOTE: Prophylactic Neupogen or Neulasta (or an approved biosimilar agent) may be used according to ASCO guidelines.

NOTE: Prophylactic acyclovir 400-800 po BID or per institutional standard dosing, or valacyclovir 1,000 once a day (or 500 twice a day) until at least one month post-treatment with Bortezomib.

<u>Premedication</u>

Rev. 12/13

- Acetaminophen (650 or 1000 mg) and diphenhydramine (25 or 50 mg) or equivalent is to be administered 30 to 60 minutes prior to starting each infusion of rituximab. Since transient hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to rituximab infusion.
- Standard anti-emetic therapy should be given to patients prior to administration of each RBV treatment: including 5-HT3 serotonin receptor antagonists and steroids (e.g., dexamethasone).

Rev. 8/15

Administration Schedule

The following are to be administered, preferably in the order indicated (1 cycle = 28 days)

Rev. 12/13

- Bortezomib 1.6 mg/m^2 SC or IV Days 1 and 8 (two total doses per cycle).
- Rituximab 375 mg/m^2 IV Day 1. The rituximab dose may be rounded to the nearest 50 mg. See Section 5.4.1.1 regarding rituximab infusion rates.

Rev. 12/13

- Bendamustine 90 mg/m^2/day will be administered to patients by IV infusion on days 1 and 2 of each 28-day cycle. The infusions are given over a 60-minute period and on day 1 it is preferable that it be administered to patients after the administration of rituximab.

NOTE: See Section 5.5 regarding supportive care recommendations.

NOTE: Dose Modifications – See Section 5.4.

Restaging and length of therapy

- Repeat cycles every 28 days for a total of 6 cycles. Patients may be evaluated more frequently if needed at physician discretion.
- Patients will be restaged after 3 cycles of therapy. Patients who are in at least stable disease (SD, PR, or CR) after 3 cycles will receive 3 subsequent cycles. Patients who have progressive disease (PD) at restaging will be discontinued from study treatment.

Rev. 8/15

5.1.2.2 Step 2 (Arm F)

Patients who have improved their response or have had no interval change in their tumor measurements with restaging from cycle 3 to 6 on Arm B will then proceed to Step 2 on Arm F.

Rev. 12/13
Rev. Add13

Rituximab 375 mg/m^2 IV or Rituxan Hycela (rituximab and hyaluronidase human) 1400 mg /23,400 Units SC every 8 weeks for 12 doses.

Rev. 12/13
Rev. 5/16

NOTE: The first dose of rituximab consolidation should be given 8 weeks (± 3 working days if needed for scheduling) after the start of cycle 6 of induction (this will be the start of week 29). In the event of a treatment delay, the first dose of rituximab may be given up to 16 weeks after the start of cycle 6 of induction.

NOTE: There are no prescribed dose modifications for rituximab. If, however, a patient has grade 3 or 4 neutropenia in the absence of other grade 3 or 4 cytopenias, consider the possibility of “late-

onset neutropenia" associated with rituximab. Manage per institutional standards. Often, myeloid growth factor is administered and per investigator's choice rituximab may be administered on schedule or delayed by 1 week intervals with repeat CBC to ensure resolution of neutropenia, and then start the new cycle. If not recovered by 4 weeks despite growth factor, patient will be removed from treatment.

NOTE: If there have been no dose delays or reductions during step 2 for 4 consecutive cycles, the patient may be seen every other cycle for subsequent cycles.The patient should be contacted by phone at the time of the even numbered cycle to assess clinical status and toxicities and still requires every 8 week blood draws. The phone contact and lab data must be documented.

Rev. 1/17

Rev. Add13

NOTE: If using Rituxan Hycela, patients must receive at least one full dose of a rituximab product IV before receiving Rituxan Hycela SC. Please refer to the commercial package insert.

5.1.3 ARM C/ARM G

5.1.3.1 Step 1: Induction (Arm C)

Rituximab 375 mg/m^2 IV day 1

Bendamustine 90 mg/m^2/day IV days 1 and 2

Repeat cycles every 4 weeks for a total of 6 cycles

NOTE: Rituximab dose may be rounded to the nearest 50 mg.

Rev. 12/13

Other agents may be rounded ± 5%

NOTE: Cycle length may be altered to 25 days (-3 days) or to 31 days (+3 days), for holidays or other extenuating scheduling situations.

Rev. 8/15

NOTE: Prophylactic Neupogen or Neulasta (or an approved biosimilar agent) may be used according to ASCO guidelines.

For premedication and administration schedules for Arm C Step 1 (Induction), follow instructions for Arm A, Step 1 (Induction).

5.1.3.2 Step 2 (Arm G)

Patients who have improved their response or have had no interval change in their tumor measurements with restaging from cycle 3 to 6 on Arm C will then proceed to Step 2 on Arm G.

Lenalidomide 15 mg po daily days 1-21 every 28 days x 24 cycles

Lenalidomide may begin either the same day as, or up to 2 days after, rituximab on cycles in which rituximab is administered

Rev. 12/13

Rev. Add13

Rituximab 375 mg/m^2 IV or Rituxan Hycela (rituximab and hyaluronidase human) 1400 mg/23,400 Units SC once every 8 weeks for 12 doses

NOTE: Dose modifications see Section 5.4.

Administration Schedule for Step 2 (Arm G)

- Lenalidomide 15 mg PO days 1 through 21 on a 28-day cycle.

Rev. 12/13

NOTE: The first cycle of lenalidomide will start **8 weeks** (± 3 working days if needed for scheduling) after the start of cycle 6 of induction (this will be the start of week 29). Patients who, due to unacceptable lab values or other reasons, are unable to start consolidation within 16 weeks after the start of Cycle 6 of induction will be withdrawn from study treatment and followed as per step 2 guidelines.

Rev. 8/15

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Rev. Add13

NOTE: Rituximab IV may be rounded to the nearest 50 mg.

Rev. 12/13

NOTE: Lenalidomide may begin either the same day as, or up to 2 days after, rituximab on cycles in which rituximab is administered.

Rev. 5/16

NOTE: Prior to initiating any lenalidomide cycle, the ANC must be ≥ 1000 cells/mm^3 (1.0 x 10^9/L) and the platelet count must be ≥ 75,000 cells/mm^3 (75 x 10^9/L). See Section 5.4.4.1 for dose modifications.

NOTE: Creatinine clearance (CrCl) should be calculated prior to the first dosing of lenalidomide. If CrCl ≥ 30 ml/min but < 50 ml/min, lenalidomide dose should be decreased to 10 mg (see Section 5.4.4.2).

If CrCl < 30 ml/min, or for patients on dialysis, lenalidomide should not be given.

Rev. 5/16

NOTE: All patients receiving lenalidomide based consolidation therapy must complete the lenalidomide pill diary for each cycle/dose of lenalidomide (see Appendix IV).

Rev. 8/15

Rev. 1/17

NOTE: If there have been no dose delays or reductions during step 2 for 4 consecutive cycles, the patient may be seen every other cycle for

subsequent cycles. The patient should be contacted by phone at the time of the even numbered cycle to assess clinical status and toxicities and still requires every 4 week blood draws prior to prescribing lenalidomide. The phone contact and lab data must be documented. The pill diary must still be collected for each cycle.

Rev. Add13

- Rituximab 375 mg/m^2 IV or Rituxan Hycela (rituximab and hyaluronidase human) 1400 mg/23,400 Units SC Day 1. The rituximab IV dose may be rounded to the nearest 50 mg

Rev. 5/16

NOTE: The first dose of rituximab consolidation should be given **8 weeks** (± 3 working days if needed for scheduling) after the start of cycle 6 of induction (this will be the start of week 29).

Rev. 12/13

NOTE: In the event of a treatment delay, the first dose of rituximab may be given up to 16 weeks after the start of cycle 6 induction.

NOTE: Rituximab therapy will be given every 8 weeks (every 56 days) "on schedule" regardless of potential delay or withdrawal of lenalidomide except if a patient has grade 3 or 4 neutropenia in the absence of other grade 3 or 4 cytopenias, consider the possibility of "late-onset neutropenia" associated with rituximab. Administer myeloid growth factor. Delay treatment by 1 week intervals with repeat CBC to ensure resolution of neutropenia and then start the new cycle.If not recovered by 4 weeks despite growth factor, patient will be removed from treatment.

Rev. 8/15

Rev. Add13

NOTE: If using Rituxan Hycela, patients must receive at least one full dose of a rituximab product IV before receiving Rituxan Hycela SC. Please refer to the commercial package insert.

Length of Therapy

- Repeat rituximab dosing every 8 weeks for a total of 12 doses.
- Lenalidomide therapy is given every 4 weeks for a total of 24 cycles.

Rev. 2/14

Anticoagulation

Rev. 5/16

All subjects randomized to lenalidomide/rituximab consolidation therapy will be **required** to have deep vein thrombosis (DVT) prophylaxis every day during lenalidomide therapy. Subjects with a history of a

thrombotic vascular event are required to have full anticoagulation, therapeutic doses of low molecular weight heparin or warfarin to maintain an INR between 2.0–3.0, or any other accepted full anticoagulation regimen (e.g. direct thrombin inhibitors or Factor Xa inhibitors) with appropriate monitoring for that agent. All subjects without a history of a thromboembolic event are required to take a daily aspirin (81mg or 325 mg) for DVT prophylaxis. Subjects who are unable to tolerate aspirin should receive low molecular weight heparin therapy or warfarin treatment or another accepted full anticoagulation regimen.

Of note, if patients' platelets decline to < 50,000/mm^3 (50 x 10^9/L), prophylactic anti-coagulation should be stopped (in addition to holding lenalidomide as below in Section 5.4.4). If/when lenalidomide is restarted (with return of platelet toxicity to ≤ Grade 2 as in Table 7 in Section 5.4.4), then prophylactic anti-coagulation should also be restarted.

5.1.3.2.1 Lenalidomide Fertility Instructions

NOTE: Please also see Appendix VI "Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods."

Before starting study drug:

Rev. 5/16

All study participants must be registered into the mandatory REMS program, and be willing and able to comply with the requirements of REMS. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days prior to and again within 24 hours of prescribing lenalidomide (prescriptions must be filled within 7 days) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. See Appendix VI: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

NOTE: A female of childbearing potential (FCBP) is any sexually mature female, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

5.1.4 ARM D/ARM H

5.1.4.1 Step 1 Induction (Arm D)

Rev. 12/13

Bortezomib 1.6 mg/m^2/day SC or IV on days 1 and 8

Rituximab 375 mg/m^2 IV day 1

Bendamustine 90 mg/m^2/day IV days 1 and 2

Repeat cycles every 4 weeks for a total of 6 cycles

NOTE: Rituximab may be rounded to the nearest 50 mg.

Rev. 12/13

Other agents may be rounded ± 5%

Rev. 12/13

NOTE: Cycle length may be altered to 25 days (-3 days) or to 31 days (+3 days), for holidays or other extenuating scheduling situations.

Rev. 8/15

NOTE: Prophylactic Neupogen or Neulasta (or an approved biosimilar agent) may be used according to ASCO guidelines.

NOTE: Prophylactic acyclovir 400-800 po BID or per institutional standard dosing, or valacyclovir 1,000 once a day (or 500 twice a day) until at least one month post-treatment with Bortezomib.

<u>Restaging and Length of Therapy</u>

- Repeat cycles every 28 days for a total of 6 cycles. Patients may be evaluated more frequently if needed at physician discretion.
- Patients will be restaged after 3 cycles of therapy. Patients who are in at least stable disease (SD, PR, or CR) after 3 cycles will receive 3 subsequent cycles. Patients who have progressive disease (PD) at restaging will be discontinued from study treatment.

For premedication and administration schedules for Step 1 Induction (Arm D), follow instructions for Step 1 Induction (Arm B).

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5.1.4.2 Step 2 (Arm H)

Patients who have improved their response or have had no interval change in their tumor measurements with restaging from cycle 3 to 6 on Arm D will then proceed to Step 2 on Arm H.

Lenalidomide 15 mg po daily days 1-21 every 28 days x 24 cycles.

Lenalidomide may begin either the same day as, or up to 2 days after, rituximab on cycles in which rituximab is administered

Rev. Add13

Rituximab 375 mg/m^2 IV or Rituxan Hycela (rituximab and hyaluronidase human) 1400 mg/23,400 Units SC once every 8 weeks for 12 doses.

Rev. 12/13

NOTE: Dose modifications see Section 5.4

Administration Schedule for Step 2 (Arm H)

- Lenalidomide 15 mg PO days 1 through 21 on a 28-day cycle.

NOTE: The first cycle of lenalidomide will start **8 weeks** (± 3 working days if needed for scheduling) after the start of cycle 6 of induction (this will be the start of week 29). Patients who, due to unacceptable lab values or other reasons, are unable to start consolidation within 16 weeks after the start of Cycle 6 of induction will be withdrawn from study treatment and followed as per step 2 guidelines.

Rev. 12/13

NOTE: Lenalidomide may begin either the same day as, or up to 2 days after, rituximab on cycles in which rituximab is administered

NOTE: Prior to initiating any lenalidomide cycle, the ANC must be ≥ 1000 cells/mm^3 (1.0 x 10^9/L) and the platelet count must be ≥ 75,000 cells/mm^3 (75 x 10^9/L). See Section 5.4.4.1 for dose modifications.

NOTE: Creatinine clearance (CrCl) should be calculated prior to the first dosing of lenalidomide. If CrCl ≥ 30 ml/min but < 50 ml/min, lenalidomide dose should be decreased to 10 mg (see Sec 5.4.4.2).

If CrCl < 30 ml/min, or for patients on dialysis, lenalidomide should not be given.

For administration schedules and anticoagulation for Step 2 Arm H, follow instructions for Step 2 Arm G.

NOTE: All patients receiving lenalidomide based consolidation therapy must complete the lenalidomide pill diary for each cycle/dose of lenalidomide (see Appendix IV).

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Rev. Add13

NOTE: If there have been no dose delays or reductions during step 2 for 4 consecutive cycles, the patient may be seen every other cycle for subsequent cycles. The patient should be contacted by phone at the time of the even numbered cycle to assess clinical status and toxicities and still requires every 4 week blood draws prior to prescribing lenalidomide. The phone contact and lab data must be documented. The pill diary must still be collected for each cycle. Rituximab 375 mg/m^2 IV or Rituxan Hycela (rituximab and hyaluronidase human) 1400 mg/23,400 Units SC Day 1. The rituximab IV dose may be rounded to the nearest 50 mg

NOTE: The first dose of rituximab consolidation should be given **8 weeks** (± 3 working days if needed for scheduling) after the start of cycle 6 of induction (this will be the start of week 29).

NOTE: In the event of a treatment delay, the first dose of rituximab may be given up to 16 weeks after the start of cycle 6 induction.

NOTE: Rituximab therapy will be given every 8 weeks (every 56 days) “on schedule” regardless of potential delay or withdrawal of lenalidomide except if a patient has grade 3 or 4 neutropenia in the absence of other grade 3 or 4 cytopenias, consider the possibility of “late-onset neutropenia” associated with rituximab. Administer myeloid growth factor. Delay treatment by 1 week intervals with repeat CBC to ensure resolution of neutropenia and then start the new cycle.If not recovered by 4 weeks despite growth factor, patient will be removed from treatment.

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NOTE: If using Rituxan Hycela, patients must receive at least one full dose of a rituximab product IV before receiving Rituxan Hycela SC. Please refer to the commercial package insert.

Length of Therapy

- Repeat rituximab dosing every 8 weeks for a total of 12 doses.
- Lenalidomide therapy is given every 4 weeks for a total of 24 cycles.

Anticoagulation

All subjects randomized to lenalidomide/rituximab consolidation therapy will be **required** to have deep vein thrombosis (DVT) prophylaxis every day during lenalidomide therapy. Subjects with a history of a thrombotic vascular event are required to have full anticoagulation, therapeutic doses of low molecular weight heparin or warfarin to maintain an INR between 2.0–3.0, or any other accepted full anticoagulation regimen (e.g. direct thrombin inhibitors or Factor Xa inhibitors) with appropriate monitoring for that agent. All subjects without a history of a thromboembolic event are required to take a daily aspirin (81mg or 325 mg) for DVT prophylaxis. Subjects who are unable to tolerate aspirin should receive low molecular weight heparin therapy or warfarin treatment or another accepted full anticoagulation regimen.

Of note, if patients' platelets decline to < 50,000/mm^3 (50 x 10^9/L), prophylactic anti-coagulation should be stopped (in addition to holding lenalidomide as below in Section 5.4.4). If/when lenalidomide is restarted (with return of platelet toxicity to ≤ Grade 2 as in Table 7 in Section 5.4.4), then prophylactic anti-coagulation should also be restarted.

5.1.4.2.1 Lenalidomide Fertility Instructions

NOTE: Please also see Appendix VI "Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods."

Before starting study drug:

All study participants must be registered into the mandatory REMS program, and be willing and able to comply with the requirements of REMS. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days prior to and again within 24 hours of prescribing lenalidomide (prescriptions must be filled within 7 days) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one

highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. See Appendix VI: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

NOTE: A female of childbearing potential (FCBP) is any sexually mature female, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

5.1.5 Study Table

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RANDOMIZATION stratification factor: MIPI low, intermediate, or high AGE < 60 or ≥ 60 yrs

6 cycles of Induction *Cycle = 28 days*	***Step 1, Arm A*** ***Rituximab/Bendamustine***	***Step 1, Arm B*** ***Rituximab/Bendamustine/*** ***Bortezomib(V)***	***Step 1, Arm C*** ***Rituximab/Bendamustine***	***Step 1, Arm D*** ***Rituximab/Bendamustine/*** ***Bortezomib(V)***
1: wk 1-4	*#1*	*#1*	*#1*	*#1*
2: wk 5-8	*#2*	*#2*	*#2*	*#2*
3: wk 9-12	*#3*	*#3*	*#3*	*#3*
RESTAGE ALL ARMS ***(CT or PET/CT)***				
4: wk13-16	*#4*	*#4*	*#4*	*#4*
5: wk17-20	*#5*	*#5*	*#5*	*#5*
6: wk21-24	*#6*	*#6*	*#6*	*#6*
RESTAGE ALL ARMS ***(PET/CT)***				
24 months *Cycle = 28 days* *For all arms, every 4 week evaluations C1-6*	***STEP 2 Arm E*** ***Rituximab*** ***Odd Numbered cycles 1, 3, 5,…***	***STEP 2 Arm F*** ***Rituximab*** ***Odd Numbered cycles 1, 3, 5,…***	***STEP 2 Arm G*** ***Lenalidomide/Rituximab*** ***Consolidation***	***Step 2 Arm H*** ***Lenalidomide/Rituximab***
C1:wk29-32	***Rituximab***	***Rituximab***	*Lenalidomide and Rituximab*	*Lenalidomide and Rituximab*
2: wk33-36			*Lenalidomide*	*Lenalidomide*
3: wk37-40	***Rituximab***	***Rituximab***	*Lenalidomide and Rituximab*	*Lenalidomide and Rituximab*
4: wk41-44			*Lenalidomide*	*Lenalidomide*
5: wk45-48	***Rituximab***	***Rituximab***	*Lenalidomide and Rituximab*	*Lenalidomide and Rituximab*
6: wk49-52			*Lenalidomide*	*Lenalidomide*
RESTAGE ALL ARMS ***(CT or PET/CT, except*** ***PET/CT if last PET+)***				
If there have been no dose delays/reductions in step 2 C1-6, patient may be seen every other cycle				
7: wk53-56	***Rituximab***	***Rituximab***	*Lenalidomide and Rituximab*	*Lenalidomide and Rituximab*
8: wk57-60			*Lenalidomide*	*Lenalidomide*
9: wk61-64	***Rituximab***	***Rituximab***	*Lenalidomide and Rituximab*	*Lenalidomide and Rituximab*
10: wk65-68			*Lenalidomide*	*Lenalidomide*

11: wk69-72	***Rituximab***	***Rituximab***	*Lenalidomide and Rituximab*	*Lenalidomide and Rituximab*
12: wk73-76			*Lenalidomide*	*Lenalidomide*
RESTAGE ALL ARMS (CT or PET/CT)				
13: wk 77-80	***Rituximab***	***Rituximab***	*Lenalidomide and Rituximab*	*Lenalidomide and Rituximab*
14: wk 81-84			*Lenalidomide*	*Lenalidomide*
15: wk85-88	***Rituximab***	***Rituximab***	*Lenalidomide and Rituximab*	*Lenalidomide and Rituximab*
16: wk 89-92			*Lenalidomide*	*Lenalidomide*
17: wk 93-96	***Rituximab***	***Rituximab***	*Lenalidomide and Rituximab*	*Lenalidomide and Rituximab*
18: wk 97-100			*Lenalidomide*	*Lenalidomide*
RESTAGE ALL ARMS (CT or PET/CT)				
19: wk 101-104	***Rituximab***	***Rituximab***	*Lenalidomide and Rituximab*	*Lenalidomide and Rituximab*
20: wk105-108			*Lenalidomide*	*Lenalidomide*
21: wk 109-112	***Rituximab***	***Rituximab***	*Lenalidomide and Rituximab*	*Lenalidomide and Rituximab*
22: wk 113-116			*Lenalidomide*	*Lenalidomide*
23:wk 117-120	***Rituximab***	***Rituximab***	*Lenalidomide and Rituximab*	*Lenalidomide and Rituximab*
24: wk 121-124			*Lenalidomide*	*Lenalidomide*

RESTAGE After completion of treatment, or when a patient comes off treatment. (CT or PET/CT)

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5.1.5.1 QOL Questionnaire

If a patient misses an appointment on the scheduled date, the questionnaires may be completed by telephone on the appointed date or they may be completed at the time the appointment is rescheduled. If the missed scheduled date is on a treatment date, the quality of life assessment will be done when the patient comes for the rescheduled treatment.

If a patient cannot complete the questionnaire because he/she is too sick, this should be documented on the Assessment Compliance Form.

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5.2 Adverse Event Reporting Requirements

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

- **Routine reporting**: Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave.
- **Expedited reporting**: In addition to routine reporting, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

5.2.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is ***clearly NOT related*** to treatment
Unlikely	The AE is ***doubtfully related*** to treatment
Possible	The AE ***may be related*** to treatment
Probable	The AE is ***likely related*** to treatment
Definite	The AE is ***clearly related*** to treatment

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Expectedness:** Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes, when either the type of event or the severity of the event is NOT listed in the protocol or drug package.

5.2.3 Reporting Procedure

This study requires that expedited adverse event reporting use the CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

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- the AE Team at ECOG-ACRIN (857-504-2900) and
- the FDA (1-800-332-1088)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

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Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the FDA (800-332-0178) in the same timeframe."

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.2.4 Determination of Reporting Requirements

Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both

- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- the relationship to the study treatment (attribution)
- the expectedness of the adverse event

Using these factors, the instructions and tables in the following sections have been customized for protocol E1411 and outline the specific expedited adverse event reporting requirements for study E1411.

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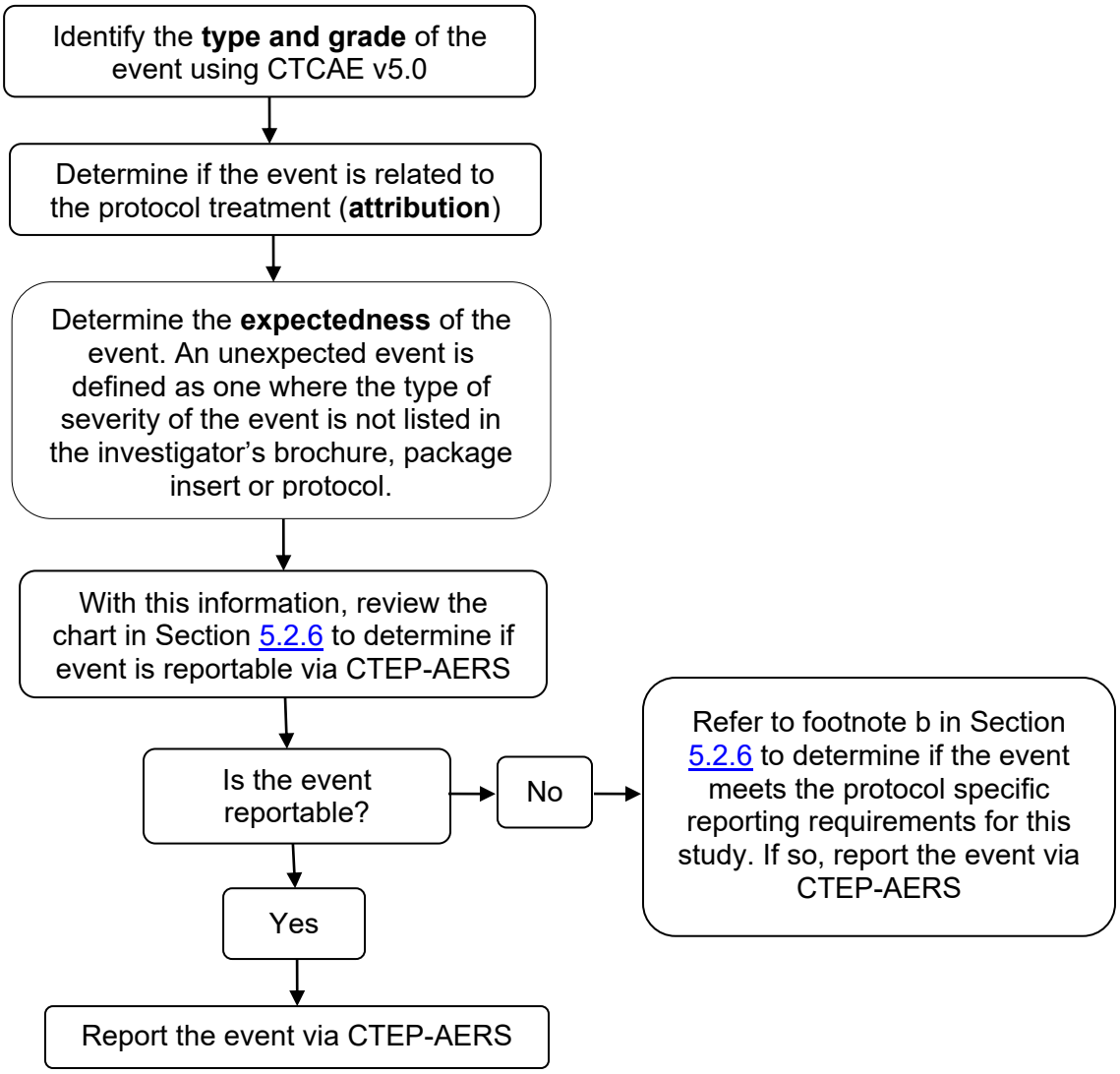
5.2.5 Steps to Determine if an Adverse Event is to be Reported in an Expedited Manner



5.2.6 Expedited Reporting Requirements for Arms A, B, C, D, E, F, G, and H on protocol E1411

Commercial Agents: Rituximab and Bendamustine

IND Exempt Agents: Lenalidomide and Bortezomib

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Expedited reporting requirements for adverse events experienced by patients on arms with using the commercial reporting requirements (Arms A, B, C, D, E, F, G, and H)

Attribution	Grade 4		Grade 5[a]		ECOG-ACRIN and Protocol-Specific Requirements
	Unexpected	Expected	Unexpected	Expected	See footnote (b) for special requirements.
Unrelated or Unlikely			7 calendar days	7 calendar days	
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

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a A death occurring while on study or within 30 days of the last dose of treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided

NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

NOTE: Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported via CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

Pregnancies (Arms G and H only):

Female Subjects of Childbearing Potential

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Pregnancies and suspected pregnancies (including a positive/inconclusive pregnancy test regardless of age or disease state) occurring while the subject is on lenalidomide, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events. **The pregnancy, suspected pregnancy, or positive/inclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge. Please refer to Appendix XVIII for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.**

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5.2.7 Other Recipients of Adverse Event Reports and Supplemental Data

ECOG-ACRIN will forward CTEP-AERS reports to the appropriate regulatory agencies and pharmaceutical company, if applicable.

A drug supporter representative may call a site for additional or supplemental information regarding a serious adverse event. Any additional written AE information requested by the drug supporter MUST be submitted to BOTH ECOG-ACRIN and the drug supporter.

Adverse events determined to be reportable via CTEP-AERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.2.8 Second Primary Cancer Reporting Requirements – Arms A, B, C, D, E, and F

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave.

- **A <u>second</u> malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A <u>secondary</u> malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form within 2 weeks via Medidata Rave.
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
  3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-

ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form

5.2.9 Second Primary Cancer Reporting Requirements – Arms G and H (Lenalidomide arms)

All cases of second and secondary malignancies including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), regardless of attribution, that occur following treatment on NCI-sponsored trials must be reported as follows:

1. Complete a Second Primary Form in Medidata Rave within 14 days.
2. Report the diagnosis via CTEP-AERS, regardless of attribution, at http://ctep.cancer.gov

   Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, c.) treatment related secondary malignancy, or d.) Neoplasm Other, malignant (grade 3 or 4)
3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: **All new malignant tumors must be reported through CTEP-AERS whether or not they are thought to be related to either previous or current treatment.** All new malignancies should be reported including solid tumors (including non-melanoma skin malignancies), hematologic malignancies, Myelodysplastic Syndrome (MDS)/Acute Myelogenous Leukemia (AML), and *in situ* tumors.

Whenever possible, the CTEP-AERS report should include the following:

- Tumor pathology
- History of prior tumors

- Prior treatment/current treatment including duration
- Any associated risk factors or evidence regarding how long the tumor may have been present
- When and how the tumor was detected
- Molecular characterization or cytogenetics or the original tumor (if available) and of any new tumor
- Tumor treatment and outcome (if available).

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

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5.3 Comprehensive Adverse Events and Potential Risks Lists

5.3.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Rituximab (NSC 687451)

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The Comprehensive Adverse Events and Potential Risks List (CAEPR) provides a thorough and detailed list of reported and/or potential adverse events associated with the agent below. The information listed in the CAEPR below, as well as the investigator's brochure, package insert or protocol can be used to determine expectedness of an event when evaluating if the event is reportable via CTEP-AERS.Please refer to the package insert for more information. *Frequency is provided based on 986 patients.* Below is the CAEPR for Rituximab.

Version 2.1, March 19, 2010[1]

Adverse Events with Possible Relationship to Rituximab (CTCAE 4.0 Term) [n= 986]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
	Blood and lymphatic system disorders - Other (Hyperviscosity: Waldenstrom's)	
	Febrile neutropenia	
CARDIAC DISORDERS		
	Myocardial infarction	
	Sinus tachycardia	
	Supraventricular tachycardia	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Diarrhea	
	Nausea	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Chills		
	Edema limbs	
	Fatigue	
Fever		
Infusion related reaction		
	Pain	
IMMUNE SYSTEM DISORDERS		
	Allergic reaction	
		Anaphylaxis
	Serum sickness	
INFECTIONS AND INFESTATIONS		
	Infection[2]	

Adverse Events with Possible Relationship to Rituximab (CTCAE 4.0 Term) [n= 986]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Infections and infestations - Other (Activation of Hepatitis B, C, CMV, parvovirus B19, JC virus, varicella zoster, herpes simplex, West Nile virus)	
	Infections and infestations - Other (Infection in HIV Positive Patients)	
INVESTIGATIONS		
Lymphocyte count decreased		
	Neutrophil count decreased	
	Platelet count decreased	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Hyperglycemia	
	Hypocalcemia	
	Hypokalemia	
		Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Myalgia	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
	Tumor pain	
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Headache	
	Lethargy	
		Nervous system disorders - Other (progressive multifocal leukoencephalopathy)
	Seizure	
RENAL AND URINARY DISORDERS		
	Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
		Adult respiratory distress syndrome
	Allergic rhinitis	
	Bronchospasm	
	Cough	
	Dyspnea	
	Hypoxia	
	Pneumonitis	
	Sore throat	

Adverse Events with Possible Relationship to Rituximab (CTCAE 4.0 Term) [n= 986]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
		Erythema multiforme
	Hyperhidrosis	
	Pruritus	
	Rash maculo-papular	
	Skin and subcutaneous tissue disorders - Other (angioedema)	
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis
	Urticaria	
VASCULAR DISORDERS		
	Flushing	
	Hypertension	
	Hypotension	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[3]Gastrointestinal obstruction includes Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, and Small intestinal obstruction under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

Also reported on rituximab trials but with the relationship to rituximab still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Hemolysis
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac disorders - Other (cyanosis); Left ventricular systolic dysfunction; Sinus bradycardia; Ventricular fibrillation
EYE DISORDERS - Conjunctivitis; Eye disorders - Other (ocular edema); Uveitis; Watering eyes
GASTROINTESTINAL DISORDERS - Constipation; Dyspepsia; Dysphagia; Gastrointestinal obstruction[3]; Gastrointestinal perforation[4]; Mucositis oral
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (Opportunistic infection associated with >=Grade 2 Lymphopenia)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture
INVESTIGATIONS - Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Cardiac troponin I increased; Cardiac troponin T increased; Creatinine increased; Investigations - Other (hyperphosphatemia); Investigations - Other (LDH increased); Weight loss

METABOLISM AND NUTRITION DISORDERS - Anorexia; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hyperuricemia; Hypoglycemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis
NERVOUS SYSTEM DISORDERS - Nervous system disorders - Other (Cranial Neuropathy NOS); Peripheral motor neuropathy; Peripheral sensory neuropathy; Pyramidal tract syndrome; Reversible posterior leukoencephalopathy syndrome; Syncope
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Depression; Insomnia
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Epistaxis; Pharyngolaryngeal pain; Pleural effusion; Pulmonary edema; Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Skin and subcutaneous tissue disorders - Other (paraneoplastic pemphigus)
VASCULAR DISORDERS - Phlebitis; Thromboembolic event; Vasculitis

NOTE: Rituximab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

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5.3.2 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Lenalidomide (CC-5013, NSC 703813)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. The information listed in the CAEPR below, as well as the investigator's brochure, package insert or protocol can be used to determine expectendess of an event when evaluating if the event is reportable via CTEP-AERS. Frequency is provided based on 4081 patients. Below is the CAEPR for lenalidomide (CC-5013).

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Version 2.7, March 14, 2018[1]

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		
	Blood and lymphatic system disorders - Other (pancytopenia)	
	Febrile neutropenia	
	Hemolysis	
CARDIAC DISORDERS		
		Atrial fibrillation
		Heart failure
		Myocardial infarction[2]
EAR AND LABYRINTH DISORDERS		
	Vertigo	
ENDOCRINE DISORDERS		
		Hyperthyroidism
	Hypothyroidism	
EYE DISORDERS		
	Blurred vision	
	Cataract	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
Constipation		
Diarrhea		
	Dry mouth	
	Dyspepsia	
	Nausea	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
	Edema limbs	
Fatigue		
	Fever	
	Generalized edema	

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Non-cardiac chest pain	
	Pain	
HEPATOBILIARY DISORDERS		
		Hepatic failure
		Hepatobiliary disorders - Other (cholestasis)
IMMUNE SYSTEM DISORDERS		
		Allergic reaction
		Anaphylaxis
		Immune system disorders - Other (angioedema)
		Immune system disorders - Other (graft vs. host disease)[3]
INFECTIONS AND INFESTATIONS		
	Infection[4]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Bruising	
	Fall	
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Alkaline phosphatase increased	
	Aspartate aminotransferase increased	
	Blood bilirubin increased	
	GGT increased	
	Investigations - Other (C-Reactive protein increased)	
		Lipase increased
	Lymphocyte count decreased	
Neutrophil count decreased		
Platelet count decreased		
	Weight loss	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Dehydration	
	Hyperglycemia	
	Hyperuricemia	
	Hypocalcemia	
	Hypokalemia	
	Hypomagnesemia	
	Hyponatremia	
	Hypophosphatemia	
	Iron overload	

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Bone pain	
	Generalized muscle weakness	
	Muscle cramp	
	Pain in extremity	
		Rhabdomyolysis[5]
	Myalgia	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
		Leukemia secondary to oncology chemotherapy[6]
		Myelodysplastic syndrome[6]
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor flare)[7]
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (second primary malignancies)
		Treatment related secondary malignancy[6]
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Depressed level of consciousness	
	Dysesthesia	
	Dysgeusia	
	Headache	
	Paresthesia	
	Peripheral motor neuropathy	
	Peripheral sensory neuropathy	
		Stroke[2]
	Syncope	
	Tremor	
PSYCHIATRIC DISORDERS		
	Depression	
	Insomnia	
	Psychiatric disorders - Other (mood altered)	
RENAL AND URINARY DISORDERS		
		Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea	

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Epistaxis	
		Pneumonitis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Dry skin	
		Erythema multiforme
	Hyperhidrosis	
	Pruritus	
	Rash maculo-papular	
		Skin and subcutaneous tissue disorders - Other (drug reaction with eosinophilia and systemic symptoms [DRESS])
	Skin and subcutaneous tissue disorders - Other (pyroderma gangrenosum)	
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis
SURGICAL AND MEDICAL PROCEDURES		
		Surgical and medical procedures - Other (impaired stem cell mobilization)[8]
VASCULAR DISORDERS		
	Hematoma	
	Hypertension	
	Hypotension	
	Peripheral ischemia	
	Thromboembolic event[9]	
	Vasculitis	

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Myocardial infarction and cerebrovascular accident (stroke) have been observed in multiple myeloma patients treated with lenalidomde and dexamethasone.

[3] Graft vs. host disease has been observed in subjects who have received lenalidomide in the setting of allo-transplantation.

[4] Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[5] The rare adverse event of rhabdomyolysis has been observed with lenalidomide. The reports of rhabdomyolysis were confounded by concurrent use of statins and dexamethasone, concurrent viral and bacterial infections, trauma, and serotonin syndrome. Statins, infections, trauma, and serotonin syndrome are known risk factors for rhabdomyolysis.

[6] There has been an increased frequency of secondary malignancies (including ALL, AML, and MDS) in multiple myeloma patients being treated with melphalan, prednisone, and lenalidomide post bone marrow transplant.

[7] Serious tumor flare reactions have been observed in patients with chronic lymphocytic leukemia (CLL) and lymphoma.

[8] A decrease in the number of stem cells (CD34+ cells) collected from patients treated with >4 cycles of lenalidomide has been reported.

[9] Significantly increased risk of deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis has been observed in patients with multiple myeloma receiving lenalidomide with dexamethasone.

[10] Gastrointestinal hemorrhage includes: Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[11] Gastrointestinal obstruction includes: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, and Small intestinal obstruction under the GASTROINTESTINAL DISORDERS SOC.

[12] Osteonecrosis of the jaw has been seen with increased frequency when lenalidomide is used in combination with bevacizumab, docetaxel (Taxotere®), prednisone, and zolendronic acid (Zometa®).

NOTE: While not observed in human subjects, lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception.

Adverse events reported on lenalidomide (CC-5013) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that lenalidomide (CC-5013) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (monocytosis); Disseminated intravascular coagulation; Eosinophilia

CARDIAC DISORDERS - Atrial flutter; Atrioventricular block first degree; Cardiac arrest; Cardiac disorders - Other (cardiovascular edema); Cardiac disorders - Other (ECG abnormalities); Chest pain - cardiac; Left ventricular systolic dysfunction; Palpitations; Pericarditis; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular tachycardia

EAR AND LABYRINTH DISORDERS - Tinnitus

ENDOCRINE DISORDERS - Cushingoid

EYE DISORDERS - Dry eye; Flashing lights; Retinopathy

GASTROINTESTINAL DISORDERS - Abdominal distension; Anal mucositis; Ascites; Colonic perforation; Dysphagia; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (Crohn's disease aggravated); Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (pale feces); Gastrointestinal hemorrhage[10]; Gastrointestinal obstruction[11]; Ileus; Mucositis oral; Pancreatitis; Rectal mucositis; Small intestinal mucositis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Malaise; Multi-organ failure

HEPATOBILIARY DISORDERS - Cholecystitis

INFECTIONS AND INFESTATIONS - Conjunctivitis; Infections and infestations - Other (opportunistic infection associated with >=Grade 2 Lymphopenia); Myelitis

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture; Hip fracture; Vascular access complication

INVESTIGATIONS - Activated partial thromboplastin time prolonged; Cholesterol high; Creatinine increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (hemochromatosis)

METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypoglycemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Chest wall pain; Joint effusion; Muscle weakness lower limb; Neck pain; Osteonecrosis of jaw[12]

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Dysphasia; Edema cerebral; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Leukoencephalopathy; Memory impairment; Nervous system disorders - Other (hyporeflexia); Spinal cord compression; Seizure; Somnolence; Transient ischemic attacks

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Psychosis

RENAL AND URINARY DISORDERS - Urinary frequency; Urinary incontinence; Urinary tract pain

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (hypogonadism); Vaginal hemorrhage

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Atelectasis; Bronchopulmonary hemorrhage; Hypoxia; Laryngeal mucositis; Pharyngeal mucositis; Pleural effusion; Pulmonary hypertension; Respiratory failure; Tracheal mucositis; Voice alteration

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Nail loss; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome); Urticaria

VASCULAR DISORDERS - Hot flashes; Phlebitis; Vascular disorders - Other (hemorrhage NOS)

NOTE: Lenalidomide (CC-5013) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

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5.3.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Bortezomib (PS-341, NSC 681239)

The Comprehensive Adverse Events and Potential Risks List (CAEPR) provides a thorough and detailed list of reported and/or potential adverse events associated with the agent below. They are developed and continuously monitored by the CTEP Investigational Drug Branch (IDB). The information listed in the CAEPR below, as well as the investigator's brochure, package insert or protocol can be used to determine expectedness of an event when evaluating if the event is reportable via CTEP-AERS. Frequency is provided based on 2084 patients. Below is the CAEPR for bortezomib (PS-341).

Version 2.6, May 25, 2017[1]

Adverse Events with Possible Relationship to Bortezomib (Velcade) (CTCAE 4.0 Term) [n= 2084]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		
CARDIAC DISORDERS		
		Heart failure
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
Constipation		
Diarrhea		
	Dyspepsia	
	Gastrointestinal hemorrhage[2]	
		Gastrointestinal perforation[3]
	Ileus	
Nausea		
Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
	Edema limbs	
Fatigue		
Fever		
HEPATOBILIARY DISORDERS		
		Hepatic failure[4]
		Hepatobiliary disorders - Other (hepatitis)[4]
INFECTIONS AND INFESTATIONS		
Infection[5]		
INVESTIGATIONS		
		Alanine aminotransferase increased[4]
		Alkaline phosphatase increased[4]
		Aspartate aminotransferase increased[4]
		Blood bilirubin increased[4]
		GGT increased[4]
		INR increased[4]

Adverse Events with Possible Relationship to Bortezomib (Velcade) (CTCAE 4.0 Term) [n= 2084]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Investigations - Other (albumin)[4]
	Neutrophil count decreased	
Platelet count decreased		
	Weight loss	
METABOLISM AND NUTRITION DISORDERS		
Anorexia		
	Dehydration	
		Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Bone pain	
	Musculoskeletal and connective tissue disorder - Other (muscle spasms)	
	Myalgia	
	Pain in extremity	
NERVOU S SYSTEM DISORDERS		
	Dizziness	
	Headache	
		Leukoencephalopathy
	Neuralgia	
	Paresthesia	
Peripheral motor neuropathy		
Peripheral sensory neuropathy		
		Reversible posterior leukoencephalopathy syndrome
PSYCHIATRIC DISORDERS		
	Anxiety	
	Insomnia	
RENAL AND URINARY DISORDERS		
		Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
		Adult respiratory distress syndrome
	Cough	
	Dyspnea	
	Pharyngeal mucositis	
		Pulmonary hypertension
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Rash maculo-papular	
VASCULAR DISORDERS		
	Hypotension	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage,

Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[3] Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[4] Cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic reactions include hepatitis, increases in liver enzymes, and hyperbilirubinemia.

[5] Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on bortezomib (Velcade) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that bortezomib (Velcade) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (hematocrit low); Blood and lymphatic system disorders - Other (lymphadenopathy); Disseminated intravascular coagulation; Febrile neutropenia; Hemolytic uremic syndrome; Leukocytosis

CARDIAC DISORDERS - Acute coronary syndrome; Asystole; Atrial fibrillation; Atrial flutter; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (cardiac amyloidosis); Cardiac disorders - Other (cardiomegaly); Chest pain - cardiac; Left ventricular systolic dysfunction; Mobitz type I; Myocardial infarction; Palpitations; Pericardial effusion; Pericardial tamponade; Pericarditis; Right ventricular dysfunction; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular arrhythmia; Ventricular fibrillation; Ventricular tachycardia

EAR AND LABYRINTH DISORDERS - External ear inflammation; Hearing impaired; Tinnitus

ENDOCRINE DISORDERS - Hypothyroidism

EYE DISORDERS - Blurred vision; Conjunctivitis; Dry eye; Extraocular muscle paresis; Eye disorders - Other (chalazion); Eye disorders - Other (choroidal effusion); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (retinal hemorrhage with bilateral vision impairment); Keratitis; Watering eyes

GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Bloating; Colitis; Dry mouth; Duodenal ulcer; Dysphagia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (colonic wall thickening); Gastrointestinal disorders - Other (early satiety); Gastrointestinal disorders - Other (eructation); Gastrointestinal disorders - Other (ileitis); Gastrointestinal disorders - Other (ischemic bowel); Gastrointestinal disorders - Other (mouth/tongue ulceration); Gastrointestinal disorders - Other (retching); Gastrointestinal pain; Gingival pain; Hemorrhoids; Mucositis oral; Oral pain; Pancreatitis; Small intestinal obstruction; Typhlitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (catheter related complication); General disorders and administration site conditions - Other (hepato-renal syndrome); Hypothermia; Injection site reaction; Malaise; Multi-organ failure; Non-cardiac chest pain; Pain; Sudden death NOS

HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (portal vein thrombosis); Hepatobiliary disorders - Other (VOD)

IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Cytokine release syndrome

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Fall; Fracture; Vascular access complication

INVESTIGATIONS - Activated partial thromboplastin time prolonged; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Cardiac troponin I increased; Cardiac troponin T increased; Cholesterol high; Creatinine increased; Ejection fraction decreased; Investigations - Other (BUN); Investigations - Other (low chloride); Investigations - Other (pancytopenia); Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Metabolism and nutrition disorders - Other (hypoproteinemia)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Avascular necrosis; Buttock pain; Chest wall pain; Generalized muscle weakness; Joint range of motion decreased; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (cramping); Osteonecrosis of jaw

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain

NERVOUS SYSTEM DISORDERS - Acoustic nerve disorder NOS; Akathisia; Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Edema cerebral; Encephalopathy; Facial muscle weakness; Facial nerve disorder; Hypersomnia; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Memory impairment; Nervous system disorders - Other (autonomic neuropathy); Nervous system disorders - Other (Bell's palsy); Nervous system disorders - Other (cranial palsy); Nervous system disorders - Other (dysautonomia); Nervous system disorders - Other (L sided facial droop); Nervous system disorders - Other (paralysis); Nervous system disorders - Other (polyneuropathy); Nervous system disorders - Other (spinal cord compression); Nervous system disorders - Other (tongue paralysis); Presyncope; Seizure; Somnolence; Stroke; Syncope; Tremor; Vasovagal reaction

PSYCHIATRIC DISORDERS - Agitation; Confusion; Delirium; Depression; Personality change; Psychosis

RENAL AND URINARY DISORDERS - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Hematuria; Proteinuria; Renal and urinary disorders - Other (bilateral hydronephrosis); Renal and urinary disorders - Other (calculus renal); Renal and urinary disorders - Other (glomerular nephritis proliferative); Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract pain

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Aspiration; Atelectasis; Bronchopulmonary hemorrhage; Bronchospasm; Epistaxis; Hiccups; Hypoxia; Laryngeal edema; Mediastinal hemorrhage; Pharyngolaryngeal pain; Pleural effusion; Pleuritic pain; Pneumonitis; Postnasal drip; Pulmonary edema; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (obstructive airways disease); Respiratory, thoracic and mediastinal disorders - Other (pleurisy); Respiratory, thoracic and mediastinal disorders - Other (respiratory distress); Respiratory, thoracic and mediastinal disorders - Other (tachypnea); Tracheal mucositis; Tracheal stenosis; Voice alteration

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Bullous dermatitis; Dry skin; Erythema multiforme; Erythroderma; Hyperhidrosis; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (angioedema); Skin and subcutaneous tissue disorders - Other

(leukoclastic vasculitis); Skin and subcutaneous tissue disorders - Other (skin lesion NOS); Urticaria

VASCULAR DISORDERS - Capillary leak syndrome; Flushing; Hematoma; Hypertension; Thromboembolic event; Vascular disorders - Other (trach site); Vasculitis

NOTE: Bortezomib (Velcade) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent

5.4 Dose Modifications

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All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

5.4.1 Dose Modifications – Rituximab

5.4.1.1 Hypersensitivity and Infusion Reactions and Rituximab Infusion Rates

Available at the bedside prior to rituximab administration will be epinephrine for subcutaneous injection, diphenhydramine hydrochloride for IV injection, and resuscitation equipment for the emergency management of anaphylactoid reactions.

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Rituximab should be administered intravenously through a dedicated line at an initial rate of 50 mg/hr, or slower if clinically indicated. Rituximab administration schedules should be followed as per the standard of care at each institution. In general, if hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 300 mg/hr. If hypersensitivity or infusion-related events develop, the infusion should be temporarily slowed or interrupted. The patient should be treated according to the appropriate standard of care. The infusion can be continued at one-half the previous rate when symptoms abate. Subsequent rituximab infusions can be administered at an initial rate of 100 mg/hr, and increased at 30-minute intervals by 100 mg/hr increments to a maximum of 400 mg/hr.

NOTE: In addition, alternative rituximab infusion rates (i.e., “rapid rituximab infusion”) can be used per institutional guidelines as long as the total number of milligrams of rituximab is the same and that “rapid infusion” is not administered with the patients first rituximab cycle. Further, a rituximab infusion time should never be given over less than 90 minutes (common infusion time for “rapid infusion” is 20% of the bag volume over 30 minutes, and then 80% of the remaining bag volume over 60 mintues).

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NOTE: If in the clinical judgement of the treating physician it may be safer for the patient, or if required by persistent infusion reactions to rituximab, rituximab infusion may be divided over days 1 and 2. In such cases, bendamustine should be administered at the end of each daily rituximab infusion if possible.

Table 3 Rituximab Infusion Rate Adjustments

Infusion Rate	Fever		Rigors		Mucosal Congestion/ Edema		Hypotension
	(or)	→	(or)	→		→	
Decrease ½	>38ºC		Mild		Mild		Mild
Interrupt	>39ºC		Moderate		Moderate		Mild to Moderate

Rev. 8/15

During the rituximab infusion, the patient's vital signs (blood pressure, pulse, respiration, temperature) should be monitored per institutional standards, generally at least every 15 minutes x 4 and then hourly until the infusion is discontinued.

5.4.1.2 Cardiovascular

Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of rituximab. Patients with preexisting cardiac conditions including arrhythmias and angina have had recurrences of these events during rituximab therapy and should be monitored throughout the infusion and immediate post-infusion period.

5.4.1.3 Tumor Lysis Syndrome

Rituximab rapidly decreases benign and malignant CD20 positive cells. Tumor lysis syndrome has been reported to occur within 12 to 24 hours after the first rituximab infusion in patients with high numbers of circulating malignant lymphocytes. Patients with high tumor burden (bulky lesions) may also be at risk. Patients at risk of developing tumor lysis syndrome should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should be provided for patients who develop tumor lysis syndrome.

5.4.2 Dose Modifications – Bendamustine

5.4.2.1 Bendamustine treatment modifications, ie, dose delays and dose reductions, are permitted for patients who are unable to tolerate the protocol-specified dosing schedule. Dose modifications will be made according to the guidelines described below. All toxicity (both hematologic and nonhematologic, excluding hemoglobin and ALC) must resolve to grade 0 or 1 (except ANC ≥ 1 x 10^9/L) or the grade at baseline before beginning the next treatment cycle. Toxicity is measured using the National Cancer

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Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI CTCAE v5.0).

See Section 8.1.11.

5.4.2.2 Hematologic

5.4.2.2.1 At the start of each cycle, ANC must be at least 1000/mm^3 (ANC ≥ 1 x 10^9/L) and platelet count must be at least 75000/mm^3 (≥ 75 x 10^9/L) to proceed with treatment (unless the patient has documented marrow involvement with lymphoma). Routine granulocyte-colony stimulating factor (G-CSF) support is not required but in the case of grade 3 or 4 neutropenia, G-CSF is recommended. It is recommended that cycles be delayed in 1-week increments for a maximum of 4 weeks until hematologic parameters allow the next cycle of RB to be administered (eg, ANC ≥ 1 x 10^9/L, platelets ≥ 75 x10^9/L).

5.4.2.3 Dose Reductions

5.4.2.3.1 If thrombocytopenia or neutropenia of grade 3 or higher requiring a dose delay of 2 weeks, a reduction in the dose of bendamustine will be required (as described below) and will be implemented for all subsequent cycles once the neutrophil and platelet counts return to an acceptable level.

NOTE: If there is a delay of more than 28 days due to bendamustine-related toxicity, treatment with bendamustine should be discontinued.

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5.4.2.3.2 Patients who experience bendamustine-related grade 4 hematologic (neutropenia or thrombocytopenia only) or grade 3 or 4 non-hematologic toxicity at a dose of 90 mg/m^2 (except for alopecia or grade 3 nausea or vomiting) will have their dose of bendamustine decreased to 75 mg/m^2/day. Similarly, patients who experience grade 2 or greater thrombocytopenia or grade 3 or greater neutropenia who require a dose delay of 2 weeks at 90 mg/m^2/day will have their dose of bendamustine decreased to 75 mg/m^2/day in the subsequent cycle (Table 4).

NOTE: In the case of neutropenia only, G-CSF support should be used before considering a dose reduction. G-CSF should be administered to the patient according to local and ASCO guidelines (see http://www.asco.org). If neutropenia occurs despite G-CSF support, then a dose reduction of bendamustine should be implemented. The patient should receive further G-CSF support for all subsequent treatment cycles.

5.4.2.3.3 If a patient again experiences bendamustine–related grade 4 hematologic toxicity, grade 3 or 4 nonhematologic toxicity, or grade 2 or greater thrombocytopenia or grade 3 or greater neutropenia (with G-CSF support) requiring another dose delay of 2 weeks of bendamustine at 75 mg/m^2/day, the dose will be further reduced to 60 mg/m^2 (Table 4).

Table 4. Bendamustine Dose Reduction Schedule

Dose	Toxicity	Action
90 mg/m^2	Grade 4 hematologic toxicity	Reduce dose to 75 mg/m^2
	Grade 2 or greater thrombocytopenia or grade 3 or higher neutropenia* that requires a dose delay of 2 weeks	Reduce dose to 75 mg/m^2
75 mg/m^2	Grade 4 hematologic toxicity	Reduce dose to 60 mg/m^2
	Grade 2 or greater thrombocytopenia or grade 3 or higher neutropenia that requires a dose delay of 2 weeks	Reduce dose to 60 mg/m^2
60 mg/m^2	Grade 4 hematologic toxicity	Reduce dose to 45 mg/m^2
	Grade 2 or greater thrombocytopenia or grade 3 or higher neutropenia that requires a dose delay of 2 weeks	Reduce dose to 45 mg/m^2
45 mg/m^2	Grade 4 hematologic toxicity	Stop bendamustine
	Grade 2 or greater thrombocytopenia or grade 3 or higher neutropenia that requires a dose delay of 2 weeks	Stop bendamustine

* In the case of neutropenia only, G-CSF support should occur before considering dose reduction.

5.4.3 Dose Modifications – Bortezomib

5.4.3.1 RB Component

5.4.3.1.1 Hematologic and non-hematologic (besides neurotoxicity): see Section 5.4.1 and 5.4.2.

5.4.3.2 Bortezomib (Velcade)

5.4.3.2.1 For hematologic toxicities, there is no planned adjustment of bortezomib dose; see Table 4 above regarding adjustments of bendamustine. If a day 8 CBC is obtained and platelets are < 30,000/mm^3 (< 30 x 10^9/L), document if the dose is not given based on treating physician clinical judgement and patient safety. It would be skipped, not to be "made up" later.

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5.4.3.2.2 For grade 3 or grade 4 non-hematologic toxicitiy (besides neurotoxicity) that is considered by the investigator to be likely or definitely related to bortezomib, then drug is to be held. For non-hematologic toxicities, bortezomib may be held for up to 3 weeks until the toxicity returns to Grade 1 or better.

If, after bortezomib has been held, the toxicity does not resolve as defined above, then the drug must be discontinued. If the toxicity returns to Grade 1 or better, and bortezomib is to be restarted, the dose must be reduced by as follows (for all days):

- If the patient was receiving 1.6 mg/m^2, reduce dose to 1.3 mg/m^2.
- If the patient was receiving 1.3 mg/m^2, reduce dose to 1 mg/m^2.
- If the patient was receiving 1 mg/m^2, reduce dose to 0.7 mg/m^2.
- If the patient was receiving 0.7 mg/m^2, the case should be discussed with the Principal Investigator.

5.4.3.2.3 Local Reactions to SC Administration

Sites for each injection (thigh or abdomen) should be rotated. New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, erythematous, or indurated. If local injection site reactions occur following bortezomib administration subcutaneously, a less concentrated bortezomib solution (1

mg/mL instead of 2.5 mg/mL) may be administered subcutaneously. Alternatively, the IV route of administration should be considered.

5.4.3.2.4 Neurotoxicity

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Follow the table immediately below when assessing neurotoxicity. Bortezomib dose reductions apply to doses on both days 1 and 8 of each cycle. All dose modification will be permanent and no dose re-escalations will be attempted. Please contact the study chair if uncertainties arise regarding the application of Tables 5 and 6 below. Please also see the neurotoxicity-directed quality of life form (FACT-GOG neurotoxicity). This is an important tool for determining the presence and intensity of neuropathic pain and/or peripheral neuropathy from the patient's perspective. Neuropathic symptoms are more prominent than abnormalities on the clinical examination. After the patient completes the neurotoxicity-directed questionnaire, the questionnaire should be reviewed to assist with the evaluation of the onset and intensity of peripheral neuropathy and other neurotoxicities that may possibly require intervention or dose modification.

Table 5. Dose modification for bortezomib-related neuropathic pain and/or peripheral sensory neuropathy.

Severity of Peripheral Neuropathy Signs and Symptoms	**Modification of Dose and Regimen**
Grade 1 (paresthesias) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (limiting instrumental ADL)	Reduce by one dose level (see Table 6)
Grade 2 with pain or Grade 3 (limiting self care ADL)	Hold* bortezomib therapy until toxicity improves/resolves. When toxicity improves /resolves, re-initiate with a reduction by two dose levels (see Table 6)
Grade 4 (life-threatening consequences; urgent intervention indicated)	Discontinue bortezomib (permanently)

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ADLs = activities of daily living

***Hold:** Interrupt bortezomib for up to 2 weeks until the toxicity returns to Grade 1 or resolves.

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Table 6. Dose level reductions of bortezomib.

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One dose level	1.6 to 1.3, or 1.3 to 1.0, or 1.0 to 0.7 mg/m^2/dose*
Two dose levels	1.6 to 1.0, or from either 1.3 or 1 reduce to 0.7 mg/m^2/dose*

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*If the patient is receiving 0.7 mg/m^2/dose and experiences repeat grade 1 with pain or grade 2 (or worse), discontinue bortezomib.

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5.4.4 Dose Modifications- Lenalidomide

NOTE: See Section 5.4.4.2 for dosing in renal insufficiency.

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Subjects will be evaluated for adverse events at each visit with the NCI CTCAE v.5.0 used as a guide for the grading of severity. The dose of lenalidomide for each subject will be interrupted and modified following toxicity as described below. Refer to the table below for instructions on dose modifications and Section 5.4.4.1 for dose reduction instructions for lenalidomide.

Table 7. Dose Modifications for Lenalidomide.

Toxicity Grade	Action Required
Grade ≥ 3 neutropenia at the beginning of a cycle. Or if any of the following occur during a cycle: Sustained (≥ 7 days) Grade 3 neutropenia or ≥ any Grade 3 neutropenia associated with fever (temperature ≥ 38.5° C) or any Grade 4 neutropenia	Hold (interrupt dosing) Follow CBC every seven days If neutropenia has resolved to ≤ Grade 2 restart at next lower dose level Use of growth factors (Neupogen, Neulasta) is permitted at the discretion of the investigator
Thrombocytopenia ≥ Grade 2 at the beginning of a cycle (<75,000 cells/mm^3) or Grade ≥ 3 on a CBC done during a cycle (platelet count < 50,000 cells/mm^3 [50 X 10^9/L])	Hold (interrupt dosing) lenalidomide. Hold prophylactic anti-coagulation. Follow CBC weekly every seven days If thrombocytopenia resolves to ≤ Grade 1 restart at next lower dose level (and restart prophylactic anti-coagulation)
Allergic reaction or hypersensitivity* Grade 2 Grade 3-4	 Hold (interrupt) dose. Follow at least every seven days Rash should resolve to ≤ grade 1 prior to starting the next cycle of therapy. When the toxicity resolves to ≤ Grade 1, restart at next lower dose level. Discontinue lenalidomide study drug
Desquamating (blistering) rash- any Grade	Discontinue lenalidomide.

Toxicity Grade	Action Required
Venous thrombosis/embolism ≥ Grade 3	Hold (interrupt) lenalidomide and start anticoagulation; restart lenalidomide at investigator's discretion (maintain dose level). Omit lenalidomide for remainder of cycle. See Anticoagulation Consideration (Section 5.5.4)
Other non-hematologic toxicity ≥ Grade 3**	Hold (interrupt) lenalidomide dose. Follow at least weekly. If the toxicity resolves to ≤ grade 2 prior to Day 21, restart lenalidomide and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle. Omitted doses are not made up. For toxicity attributed to lenalidomide, reduce the lenalidomide dose by 1 dose level when restarting lenalidomide.

* These measures should be taken only for those reactions attributed to lenalidomide.

** See Section 5.4.4.2 regarding modifications for renal insufficiency.

The next cycle of treatment may begin on the scheduled Day 1 if:

- The ANC is ≥ 1,000 cells/mm^3 (1 X 10^9/L);
- The platelet count is ≥ 75,000 cells/mm^3 (75 X 10^9/L);
- Lenalidomide-related allergic reaction or hypersensitivity not requiring discontinuation have resolved to ≤ Grade 1 severity;
- Any other lenalidomide-related AE not requiring discontinuation has resolved to ≤ Grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated once every seven days and a new cycle of lenalidomide will not be initiated until the toxicity has resolved as described above. If a new cycle is delayed for more than 28 days, the Principal Investigator must be notified.

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If lenalidomide is held on day 1 or during a cycle, dosing will restart when toxicity has resolved as per Table 7, but missed doses will not be "made up". This will maintain cycle length. Rituximab will be administered as scheduled every 8 weeks.

If lenalidomide dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle. There will be no more than one dose reduction from one cycle to the next.

5.4.4.1 Lenalidomide Dose Reduction

The daily oral dose of lenalidomide may be reduced successively by one level from the starting dose of 15 mg daily on Days 1-21 every 28 days.

Table 8. Dose Reduction Steps for Adverse Events Related to Lenalidomide.

Starting Dose	15 mg daily on Days 1-21, every 28 days
Level –1 Dose	10 mg daily on Days 1-21, every 28 days

Level –2 Dose	5 mg daily on Days 1-21, every 28 days
Level –3 Dose*	5 mg on alternate days from Days 1-21, every 28 days

NOTE: Once a subject's dose has been reduced, no dose re-escalation is permitted.

*Subjects who cannot tolerate Dose Level –3 are to have lenalidomide discontinued permanently.

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5.4.4.2 Renal Insufficiency: Lenalidomide dosing

Patients with creatinine clearance of ≥ 50 mL/min should be started at lenalidomide 15 mg daily on Days 1-21 of each 28-day cycle as above. No dose adjustments are required for patients with CrCl ≥ 50 mL/min. Patients with creatinine clearance of ≥ 30 mL/min but < 50 mL/min should be started at lenalidomide 10 mg daily on Days 1-21 of each 28-day cycle (these patients could be escalated once to 15 mg daily on Days 1-21 of each 28-day cycle if they are tolerating lenalidomide well – the escalation should occur at the start of a cycle). For these patients who start on 10 mg daily, de-escalation will be allowed to 5 mg (dose level -2), and then 5 mg every other day (dose level -3). Once a subject's dose has been reduced, no dose re-escalation is permitted.

Patients with a CrCl < 30 mL/min and those on dialysis will be excluded.

5.5 Supportive Care

5.5.1 All supportive measures consistent with optimal patient care will be given throughout the study.

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5.5.2 Filgrastim (Neupogen) or Pegfilgrastim (Neulasta) granulocyte colony stimulating factors (G-CSFs), or approved biosimilar agents, are not recommended for routine use in this study. It is recommended that investigators follow the most recent ASCO guidelines (101). In the event of neutropenic fever, infection, and/or dose delay or reduction, please see Sections 5.4.2 or 5.4.3 regarding further instructions.

Prophylactic antibiotic therapy (e.g. levofloxacin) during induction chemotherapy to prevent febrile neutropenia is at the discretion of the treating physician as discussed above (Sections 5.4.2 and 5.4.3).

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Anti-viral prophylactic therapy (e.g., acyclovir, famciclovir) should be administered for patients on Arm B or Arm D; for Arms A and C, anti-viral prophylactic therapy should be administered at the discretion of the treating physician, but it is recommended for patients with recent history of zoster or other HSV infection.

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5.5.3 For patients on lenalidomide/rituximab consolidation (step 2), pregnancy testing should be repeated within 2 weeks of the start of treatment. See Section 3.1.3 for definition of female of childbearing potential (FCBP). Before starting lenalidomide: FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL). The first

pregnancy test must be performed within 10-14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the Investigator has verified that the results of these pregnancy tests are negative. Female subjects will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure. During study participation and for 28 days following discontinuation from the study: FCBP with regular cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following discontinuation from the study. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following discontinuation from the study. In addition to the required pregnancy testing, the Investigator must confirm with FCBP at each visit that she is continuing to use two reliable methods of birth control. Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days. During counseling, subjects must be reminded to not share study drug and to not donate blood. Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide treatment must be discontinued during this evaluation. If pregnancy or a positive pregnancy test does occur in a study subject or the partner of a male study subject during study participation, lenalidomide must be immediately discontinued.

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5.5.4 Patients must have no medical contra-indications to, and be willing to take, DVT prophylaxis as all patients registering to the lenalidomide/rituximab Arms G and H will be required to have deep vein thrombosis (DVT) prophylaxis. Patients randomized to Arms G or H who have a history of a thrombotic vascular event will be required to have full anticoagulation, therapeutic doses of low molecular weight heparin or warfarin to maintain an INR between 2.0 – 3.0, or any other accepted full anticoagulation regimen (e.g. direct thrombin inhibitors or Factor Xa inhibitors) with appropriate monitoring for that agent. Patients on Arms G and H without a history of a thromboembolic event are required to take a daily aspirin (81 mg or 325 mg) for DVT prophylaxis. Patients who are unable to tolerate aspirin should receive low molecular weight heparin therapy or warfarin treatment or another accepted full anticoagulation regimen.

Ways to minimize risk of DVT should be discussed with patients, including, but not limited to, avoiding smoking, minimizing pro-thrombotic hormone replacement, avoiding prolonged periods of inactivity (e.g. uninterrupted long car or plane trips).

5.6 Duration of Therapy

Patients will receive protocol therapy unless:

5.6.1 Extraordinary medical circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the schedule in the E1411 Forms Completion Guidelines.

5.6.2 Patient withdraws consent.

5.6.3 Patient has progressive disease

5.6.4 Patient experiences unacceptable toxicity.

5.6.5 Non-protocol therapies are administered.

5.6.6 Suspected or documented pregnancy occurs

5.7 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 15 years from the date of registration. All patients must also be followed through completion of all protocol therapy.

6. Measurement of Effect

Non-Hodgkin Lymphoma Response Criteria

NOTE: These criteria are based on the Revised Response Criteria for Malignant Lymphoma, (Cheson et al.), Journal of Clinical Oncology, 2007, Vol. 25:579-586.

The criteria use the following categories of response: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Relapse and Progression (PD). In the case of stable disease, follow-up assessments must have met the SD criteria at least once after study entry at a minimum interval of six weeks.

The following guidelines are to be used for establishing tumor measurements at baseline and for subsequent comparison:

- The six largest dominant nodes or extranodal masses must be identified at baseline.
- If there are 6 or fewer nodes and extranodal masses, all must be listed as dominant
- If there are more than 6 involved nodes or extranodal masses, the 6 largest dominant nodes or extranodal masses should be selected according to the following features: a) they should be clearly measurable in at least two perpendicular measurements; b) they should be from as disparate regions of the body as possible; and c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- Rev. 8/15 Measurements on non-dominant nodes are not required. They will be assessed subsequently as “resolved” or “not-resolved.”
- The lymph nodes or extranodal masses selected for measurement should be measured in two perpendicular diameters, one of which is the longest perpendicular diameter. The lymph nodes should be measured in centimeters to the nearest one tenth of a centimeter (e.g. 2.0 cm, 2.1 cm, 2.2 cm, etc.)
- The two measured diameters of each lymph node site or extranodal mass should be multiplied giving a product for each nodal site or extranodal mass. The product of each nodal site should be added, yielding the sum of products of the diameters (SPD). The SPD will be used in determining the definition of response for those who have less than a complete response.

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6.1 Complete Response (CR)

Complete disappearance of all detectable clinical evidence of disease, and disease-related symptoms if present prior to therapy.

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6.1.1 In patients with no pre-treatment PET scan, or if the PET scan was positive prior to therapy: a post-treatment residual mass of any size is permitted as long as it is PET-negative.

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6.1.2 In a pretreatment PET scan was negative: all lymph nodes and extranodal masses must have regressed on CT to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm prior to therapy). Previously involved nodes that were 1.1-1.5 cm in their long axis and > 1.0 cm in their short axis prior to treatment must have decreased to ≤ 1 cm in their short axis after treatment.

6.1.3 The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination, and nodules related to lymphoma should disappear. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size and involvement. For instance, a spleen considered normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma, but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes.

6.1.4 If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but demonstrating a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

NOTE: Complete Remission/unconfirmed (CRu): Using the above definition for CR and that below for PR eliminates the category of CRu.

6.2 Partial Response (PR)

The designation of PR requires all of the following:

6.2.1 A ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or extranodal masses. These nodes or masses should be selected according to the following: (a) they should be clearly measurable in at least 2 perpendicular dimensions; if possible, they should be from disparate regions of the body; (b) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

6.2.2 No increase in the size of other nodes, liver or spleen.

6.2.3 Bone marrow assessment is irrelevant for determination of a PR if the sample was positive prior to treatment. However, if positive, the cell type should be specified, e.g. large-cell lymphoma or small cleaved cell lymphoma.

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6.2.4 No new sites of disease.

6.2.5 If there was was PET-positive prior to therapy, the post-treatment PET should be positive at any previously involved sites.

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6.2.6 If a pretreatment PET scan was negative, CT scan criteria should be used.

6.2.7 Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.

6.2.8 When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

6.3 Stable Disease (SD)

6.3.1 Failing to attain the criteria needed for a PR or CR, but not fulfilling those for progressive disease (see below).

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6.3.2 The PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

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6.3.3 For patients without a pretreatment PET scan or if the pre-treatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

6.4 Progression (PD) and Relapse

For determination of relapsed and progressive disease, lymph nodes should be considered abnormal if the long axis is more than 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if the short axis is more than 1 cm. Lymph nodes $\leq$ 1 x $\leq$ 1 cm will not be considered as abnormal for relapse or progressive disease.

Treatment decisions in patients with presumed refractory, relapsed or progressive disease should not be made solely on the basis of a single PET scan without histologic confirmation.

6.4.1 Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size.

Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

6.4.2 At least a 50% increase from nadir in the SPD of any previously involved nodes or extranodal masses, or in a single involved node or extranodal mass, or the size of other lesions (e.g. splenic or hepatic nodules). To be considered progressive disease, a lymph node or extranodal mass with a diameter of the short axis of less than 1.0 cm must increase by $\geq$ 50% and to a size of 1.5 cm x 1.5 cm or more than 1.5 cm in the long axis.

6.4.3 At least a 50% increase in the longest diameter of any single previously identified node or extranodal mass more than 1 cm in its short axis.

6.4.4 Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

6.4.5 Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these response criteria, the

spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

6.5 Duration of Response

This is measured from the documented beginning of response (CR or PR) to the time of relapse. This is measured in responders.

6.6 Survival

Overall survival is defined as the date of study entry to the date of death.

6.7 Progression-Free Survival

Progression-free Survival (PFS) is defined as the time from entry onto study until lymphoma progression or death from any cause. PFS is often considered the preferable endpoint in lymphoma clinical trials, especially those involving incurable histologic subtypes (e.g., follicular and low grade, mantle cell lymphoma). PFS reflects tumor growth and, therefore, occurs prior to the endpoint of overall survival. In addition, PFS is not confounded by the administration of subsequent therapy. Whether a prolongation of PFS represents direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the risk-benefit ratio of the therapy under investigation. Unlike survival, the precise date of progression is generally unknown. It may be defined as the first date of documentation of a new lesion or enlargement of a previous lesion, or the date of the scheduled clinic visit immediately after radiologic assessment has been completed. Where there is missing information, censoring of the data may be defined as the last date at which progression status was adequately assessed.

6.8 PRO Assessment: Symptom Burden and HRQL

6.8.1 Neurotoxicity

Neurotoxicity associated with bortezomib will be assessed using the 11-item FACT/GOG-Ntx subscale. Administration of the FACT/GOG-Ntx prior to, during and following treatment will yield valuable information on the longitudinal trajectory of this symptom. The FACT/GOG-Ntx includes items that assess severity of neurotoxicity and associated functional impairments.

6.8.2 Fatigue

Fatigue associated with disease, induction therapy, and the addition of lenalidomide to consolidation therapy will be assessed using the 13-item FACT-Fatigue subscale. The FACT-Fatigue includes items that assess severity of fatigue and functional interference.

6.8.3 Lymphoma-specific Concerns

The 15-item FACT-Lymphoma subscale will be used to assess lymphoma-specific concerns, including symptoms and uncertainty about the future due to disease. Longitudinal administration of the

FACT-Lymphoma subscale will provide the opportunity to assess symptom response to treatment and the trajectory of lymphoma symptoms among older adults with this rare disease. Administration of the FACT-Lymphoma at the time of progression for participants who progress before protocol completion will allow us to examine symptoms associated with progression as a secondary question.

6.8.4 Overall Health-Related Quality of Life (HRQL)

The 27-item FACT-General will be administered to assess overall health-related quality of life. The FACT-G includes four subscales: physical, functional, emotional and social well-being. The FACT-G will provide data from the patient perspective on quality of life and functional status throughout treatment and post-treatment during survivorship.

6.9 Quality of Life Administration Schedule

6.9.1 Assessment Schedule

Participants will complete a patient-reported outcomes assessment to measure the following:

Symptom/Domain	Measure	Number of items
Neurotoxicity	FACT/GOG-Ntx subscale	11
Fatigue	FACT-Fatigue subscale	13
Lymphoma-specific concerns	FACT-Lymphoma subscale	15
Overall health-related quality of life	FACT-General	27

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Please complete QOLs at the following time points from initial registration to the study

- Baseline Step 1
- 6 Months (± 28 days)
- 12 Months (± 28 days)
- 30 Months (± 28 days)
- 36 Months (± 28 days)
- 48 Months (± 28 days)
- 60 Months (± 28 days)

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If the patient ends step 1 treatment early, for any reason (including progression), complete an end of induction QOL then continue with the above schedule (if the next scheduled QOL is within 90 days of the end of induction QOL, the next scheduled QOL is not required).

If the patient ends step 2 treatment early complete an end of consolidation QOL then continue with the above schedule (if the next scheduled QOL is within 90 days of the 12-month QOL or within 180 days of the end of consolidation QOL, the next scheduled QOL is not required).

6.9.2 PRO Administration Instructions

6.9.2.1 The questionnaires must be administered at the timepoints listed above. The patient should be instructed to respond to the questionnaires in terms of his/her experience during the time frame specified on each questionnaire.

6.9.2.2 The patient should be asked to read the instructions at the beginning of each questionnaire and complete all the items. It is permissible to assist the patient with the completion of the questionnaires as long as the staff person does not influence the patient's responses.

6.9.2.3 The questionnaires must be reviewed by the protocol nurse or research coordinator as soon as the patient completes them to ensure all items were marked appropriately. If more than one answer was marked, the patient should be asked to choose the answer which best reflects how he/she is feeling. If a question was not answered, the patient should be asked if he/she would like to answer it. The patient should always have the option to refuse. If the patient refuses, it should be indicated on the questionnaire that he/she declined to answer the item.

6.9.2.4 If the patient cannot complete a questionnaire, or if the patient refuses to complete the questionnaire, the reason should be noted on the Assessment Compliance Form.

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7. Study Parameters

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7.1 Therapeutic Parameters

1. Prestudy scans and x-rays used to assess all measurable or non-measurable sites of disease must be done ≤ **4 weeks** prior to randomization.

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2. Patients must have a staging bone marrow biopsy and aspirate prior to randomization. The bone marrow biopsy and aspirate should be completed **≤ 8 weeks** prior to registration.

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3. History and Physical Exam and PS should be done ≤ **4 weeks** before randomization.

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4. All required prestudy blood tests, should be done ≤ **4 weeks** before randomization – unless specifically required on Day 1 as per protocol, or pregnancy test as per footnote 7.
5. See Section 7.2 below regarding biological sample submissions.

		Induction (RB or RBV)		Consolidation (rituximab or lenalidomide/rituximab)		Post-Therapy Follow-up
Parameter	**Pre-study**	**Cycles[1] (± 3 days)**	**Restaging**	**Cycles[2] (± 3 days)**	**Restaging Every 24 weeks and at completion of consolodation**	
Assignment of MIPI scores[3]	X					
History and Physical examination	X	Every cycle	X	X		
Performance Status	X	Every cycle	X	X		X[15]
Tumor Measurements by Physical Exam (if applicable)	X		X		X	X[15]
CBC and Differential[4]	X[4]	Every cycle	X	X[20]		X[15]
Serum Chemistries (electrolytes, SGOT, SGPT, total bilirubin, direct bilirubin,[5] LDH, creatinine, glucose, alkaline phos, and calcium)	X	Every cycle	X	X[20]		X[15]
Beta-2-microglobulin	X		After cycle 6			X[15]
Uric acid	X		X			
Bone marrow aspirate biopsy	X[16]		After cycle 6[6]			
Pregnancy test (for women of child-bearing potential)[7,8]	X			X[8]		
Hepatitis B surface antigen and core antibody testing[9]	X[9]					
TSH	X		X		X	
CD4 count and HIV viral load (HIV + patients only)	X		X[18]		X[18]	

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Creatinine clearance (calculated by Cockcroft-Gault)	X[10]		After cycle 6	X[10]		
CT Neck, Chest, Abdomen, and Pelvis	X[11]		After cycle 3[11]		X[11, 12]	X[15]
FDG-PET/CT Scan	X[11]		After cycle 6[11]		1st restaging, if positive end of induction	
Quality of life studies[13]	X	X[14]		X[14]		X[14]
Registration to REMS[17]	X[17]			X[17]		
Research Blood Samples (see Section 7.2)	X[19]		X[19] After cycles 3 and 6		X[19] After step 2 cycles 4, 8, 12, 18 and 24	

1. Cycles are every 28 days. Patients may be evaluated in the office more frequently, if needed, at physician discretion.
2. Refer to treatment schedule Section 5 If a delay occurs in lenalidomide, rituximab treatment should still be continued "on time."

Rev. 2/14 3. Value should be entered for MIPI score. See Section 4.1.5.1 for the MIPI Calculator link.

4. At baseline: please record the absolute lymphocyte count.
5. Direct bilirubin is required only if total bilirubin is elevated.

Rev. 2/14 6. Repeat biopsy/core and aspirate only if positive at baseline and otherwise is in CR. Bone marrow biopsy and aspirate should also be
Rev. 12/13 obtained at time of relapse. If baseline marrow is positive only by flow cytometry, the aspirate and flow cytometry should be repeated

7. Within 10-14 days prior to start of induction treatment. See Section 3 for definition of female of childbearing potential.
8. For patients randomized to Arms C and D, who proceed to Arms G and H, pregnancy tests are needed for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female regardless of sexual orientation or whether she has undergone a tubal ligation who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide (prescriptions must be filled within 7 days). FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide.
9. Patients must be tested for hepatitis B surface antigen within 6 weeks of randomization. Liver function tests and quantitative PCR assay for HBV levels in serum to be performed monthly until 6 months following last rituximab dose, for HBcAb positive patients who receive rituximab. Further, consideration should be given to treat patients with anti-viral prophylaxis prior to, during, and for 6 months after completion of the last dose of rituximab. Patients who are positive for HBsAg (surface antigen) are not allowed to enroll on study.
10. Calculate at baseline before induction, and then calculate again at baseline before consolidation therapy starts for patients continuing to lenalidomide therapy, and then repeated thereafter as clinically indicated.

Rev. 12/13 11. PET/CT scan is preferred at baseline. Diagnostic CT scans of the neck/chest/abdomen/pelvis must be performed if PET/CT scan cannot be obtained at baseline due to timing constraints, insurance or reimbursement issues, or other reasons, and must be documented in the patient's chart. Either PET/CT or diagnostic CT scans are required after cycle three (3) of induction therapy to document response, PET/CT scan is required upon completion of induction therapy. Staging scans will be done during consolidation after cycle 6 (week 52 ± 1 week),

cycle 12 (week 76 ± 1 week), cycle 18 (week 100 ± 1 week) and at completion of consolidation. If the end of induction PET scan is not negative, the first restaging scan at consolidation week 24 should be a repeat of the PET scan. Otherwise, these scans during and at the end of consolidation can be either PET or diagnostic CT, though it is highly recommended the same modality be used in an individual patient. If PET negative at the end of induction, no further PET imaging is required. PET/CTs and CTs will be reviewed centrally for quality assurance purposes. If the baseline PET/CT study is performed combined with the intravenous and oral contrast, then all subsequent PET/CT studies should be performed following the same methodology to avoid variability in SUV max among the PET/CT studies with the same patient. PET/CT scans are to be sent to the CALGB imaging core laboratory as outlined in Section 10.1 and Appendix IX.

12. Refer to Section 5.1.5 for restaging schedule.
13. See Section 6.8
14. See Section 6.9 for administration schedule.
15. Patients in follow-up will follow this schedule until disease progression:

Rev. 12/13 For history, physical and blood tests

- Every 3 months if the patient is less than 2.5 years from end of consolidation.
- Every 6 months if the patient is between 5 and 10 years from the study entry.

Rev. 12/13 For imaging

- CT chest/abdomen/pelvis annually (± 1 month) until 5 years from end of consolidation, then as clinically indicated

Rev. 12/13 For disease progression and survival

- Every 12 months if the patient is between 10 and 15 years from the study entry.
- Once patients have documented disease progression (Sec 5.6; 5.7) they are followed only for survival every 6 months for the first 5 years and then every 12 months until study completion.

Rev. 12/13 16. Patients must have a staging bone marrow biopsy and aspirate **≤ 8 weeks** prior to randomization
17. After registration to Arm C and D, and prior to registration to Arms G and H. See Section 8.4.8 for information on the REMS program.
18. At the time of restaging for Induction (after cycles 3 and 6). At the time of restaging during consolidation treatment. Please refer to the treatment table 5.1.5 for the restaging schedule.
19. For patients who have consented to research sample collection, see Sec 7.2 for schedule of blood and marrow submissions.

Rev. 1/17 20 Patients on Arms E and F only, these labs may be completed every 8 weeks.

7.2 Biological Sample Submissions

NOTE: Submitted scans and specimens must be entered and tracked via the ECOG-ACRIN Sample Tracking System (STS). See Section 10.3.

NOTE: An informed consent must be signed prior to the submission of any samples including mandatory diagnostic reviews, laboratory studies and/or banking. Samples for laboratory studies and/or banking should be submitted only from patients who have given written consent for the use of their samples for these purposes.

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	Baseline	Post Cycle Three	Post Cycle Six (End of Induction)	Every Four (4) Months During First Year of Maintenance	Every Six (6) Months During Second Year of Maintenance	Twelve (12) Months After Completion of Maintenance	Ship to:
MANDATORY for *Central Review*							
Diagnostic Tumor Biopsy	X	Any on study biopsy[5]					ALLIANCE Biorepositiry at Ohio State (Section 10.2/ Appendix II)
Submissions Based on Additional Patient Consent							
Peripheral Blood, ACD (yellow top tubes)[3,6]	X[1]	X	X				Mayo Clinic Lymphoma Laboratory (Section 11.1)
Peripheral Blood, EDTA (purple top tube)[3,5]	X[1]	X	X				
Peripheral Blood, red top tube[3,5]	X[1]	X	X				
Peripheral Blood, EDTA (purple top tube)[3,6]	X[1]	X	X	X	X	X	Sequenta, Inc. (Section 11.2)
Bone Marrow Aspirate, EDTA (purple top tube)[3,6]	X[7]		X[4]				

1. Baseline blood should be collected after randomization, prior to treatment.

Rev. 12/13 2. [Deleted in Addendum #2]

3. Kits are available for the collection and shipment of the blood and bone marrow samples. See Section 11.1.2 for instructions.
4. Patients in CR only.
5. Submit from patients who answer *"Yes"* to *"I agree to provide additional specimens/blood for research."*
6. Submit from patients who answer *"Yes"* to *"I agree to participate in the laboratory research studies that are being done as part of this clinical trial."*

Rev. 12/13, 8/15 7. Patient must sign consent before submission of optional bone marrow aspirate (this should be from the bone marrow biopsy done prior to enrollment, do not have repeat bone marrow biopsy collected for research only). If submitting initial bone marrow aspirate to Sequenta prior to patient enrollment to the trial, please call Kim Henderson at Mayo Clinic (507) 284-3805 to obtain an interim patient number. Do not label the

tube with any patient identifiers aside from the number given by Kim. Please use the ECOG-ACRIN Generic Specimen Submission Form (#2981) when sending the bone marrow to Sequenta. Once the patient has been randomized please call Kim with the ECOG-ACRIN patient sequence number and enter the information into the ECOG-ACRIN Sample Tracking System. If patient has had marrow done prior to signing consent, submit the blood samples, but do not repeat the marrow simply for research purposes.

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8. Drug Formulation and Procurement

IND Status

When used in this protocol lenalidomide and bortezomib are classified as an "unapproved use of an approved agent" and by definition considered investigational agents. However, while it is not an indication currently approved by the FDA, the use of lenalidomide and bortezomib in this protocol are exempt from the requirements of an IND and described under Title 21 CFR 312.2(b).

8.1 Bendamustine

CAUTION: There are currently two different preparations of bendamustine commercially available; the lyophilized preparation of bendamustine under the trade name of Treanda® requiring reconstitution and described under Section 8.1 and a new preparation of a ready-to-dilute solution under the trade name of Bendeka™. Both preparations are given at the same dose and schedule and have the same expected toxicity and dose modifications as described in the protocol. However, the preparation, rate of infusion and stability between the two products are significantly different. Either commercially available agent may be used for E1411. However, please exercise caution and indicate which preparation was used to alert personnel administering the infusion whether a 10 minute or a 60 minute infusion time is to be used.

8.1.1 Other Names

Bendamustine hydrochloride, CEP-18083), TREANDA, BENDEKA.

8.1.2 Classification

Bendamustine hydrochloride (herein bendamustine) is an alkylating agent, which contains a bifunctional mechlorethamine derivative, a benzimidazole heterocyclic ring, and a butyric acid substituent.

8.1.3 Mode of Action

Mechlorethamine and its derivatives develop electrophilic alkyl groups and form covalent bonds with electron-rich nucleophilic moieties, which result in interstrand deoxyribonucleic acid (DNA) crosslinks. The bifunctional covalent linkage leads to cell death via several pathways; however, the exact mechanism of action of bendamustine remains unknown.

8.1.4 Storage and Stability

8.1.4.1 TREANDA

Reconstituted parenteral solutions are stable for 3 hours at room temperature, and for 24 hours if refrigerated.

8.1.4.2 BENDEKA

BENDEKA (bendamustine hydrochloride) Injection contains no antimicrobial preservative. The admixture should be prepared as close as possible to the time of patient administration.

If diluted with 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, the final admixture is stable for 24 hours when stored refrigerated (2-8°C or 36-46°F) or for 6 hours when stored at room temperature (15-30°C or 59-86°F) and room light. Administration of diluted BENDEKA (bendamustine hydrochloride) Injection must be completed within this period of time.

In the event that 5% Dextrose Injection, USP is utilized, the final admixture is stable for 24 hours when stored refrigerated (2-8°C or 36-46°F) or for only 3 hours when stored at room temperature (15-30°C or 59-86°F) and room light. Administration of diluted BENDEKA must be completed within this period of time.

Retain the partially used vial in original package to protect from light and store refrigerated (28°C or 36-46°F) if additional dose withdraw from the same vial is intended.

Stability of Partially Used Vials (Needle Punched Vials)

BENDEKA™ (bendamustine hydrochloride) Injection is supplied in a multiple-dose vial. Although it does not contain any antimicrobial preservative, BENDEKA is bacteriostatic. The partially used vials are stable for up to 28 days when stored in its original carton under refrigeration (2-8°C or 36-46°F). Each vial is not recommended for more than a total of six (6) dose withdrawals.

After first use, the partially used vial should be stored in the refrigerator in the original carton at 2°C to 8°C or 36-46°F and then discarded after 28 days.

8.1.5 Dose Specifics

8.1.5.1 TREANDA

TREANDA will be administered as a 60-minute iv infusion at a dose of 90 mg/m^2 on days 1 and 2 of each 28-day cycle.

8.1.5.2 BENDEKA

BENDEKA will be admistered as a 10-minute iv infusion at a dose of 90 mg/m^2 on days 1 and 2 of each 28-day cycle.

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8.1.6 Dosage in Renal or Hepatic Failure

In a population pharmacokinetic analysis of bendamustine in patients receiving 120 mg/m^2 there was no meaningful effect of renal impairment (CrCL 40 - 80 mL/min, N=31) on the pharmacokinetics of bendamustineThese results are, however, limited, and therefore bendamustine should be used with caution in patients with mild or moderate renal impairment. Bendamustine has not been studied in

patients with CrCL < 40 mL/min, so the package insert states that bendamustine should not be used in patients with CrCL < 40 mL/min. Bendamustine is not renally excreted to a significant degree, however, and clinical experience does not suggest any excess toxicity when bendamustine is administered with CrCL 30-40. Thus, the lower limit for CrCL in eligibility criteria for this study, as well as for ongoing cycles durig step 1, is 30 mL/min.

In a population pharmacokinetic analysis of bendamustine in patients receiving 120 mg/m^2 there was no meaningful effect of mild (total bilirubin ≤ ULN, AST ≥ ULN to 2.5 x ULN, and/or ALP ≥ ULN to 5.0 x ULN, N=26) hepatic impairment on the pharmacokinetics of bendamustine. Bendamustine has not been studied in patients with moderate or severe hepatic impairment. These results are however limited, and therefore bendamustine should be used with caution in patients with mild hepatic impairment. Bendamustine should not be used in patients with moderate (AST or ALT 2.5 - 10 x ULN and total bilirubin 1.5 - 3 x ULN) or severe (total bilirubin > 3 x ULN) hepatic impairment.

8.1.7 Preparation

8.1.7.1 TREANDA

It will be reconstituted with 20 mL of only Sterile Water for Injection, USP. The volume needed of the reconstituted bendamustine should be aseptically withdrawn for the required dose (based on 5-mg/mL concentration) and immediately transferred to an infusion bag of 0.9% Sodium Chloride Injection, USP (normal saline). As an alternative to 0.9% Sodium Chloride Injection, USP (normal saline), an infusion bag of 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, may be considered. The resulting final concentration of bendamustine in the infusion bag should be within 0.2 and 0.6 mg/mL. For a dose of bendamustine in the 50- to 180-mg range, a 250-ml infusion bag may be used. For a dose of bendamustine in the 100- to 360-mg range, a 500-ml infusion bag should be used. The reconstituted solution must be transferred to the infusion bag within 30 minutes of reconstitution. After transferring, thoroughly mix the contents of the infusion bag. The admixture should be a clear and colorless to slightly yellow solution.

8.1.7.2 BENDEKA

BENDEKA™ (bendamustine hydrochloride) Injection, for intravenous use is a clear, and colorless to yellow ready-to-dilute solution supplied as 100 mg/4 ml multiple-dose vials. Allow vial to reach room temperature. If particulate matter is observed, the product should not be used.

Aseptically withdraw the volume needed for the required dose from the 25 mg/mL solution and immediately transfer

the solution to a 50 mL infusion bag of one of the following diluents:

− 0.9% Sodium Chloride Injection, USP; or

− 2.5% Dextrose/0.45% Sodium Chloride Injection, USP;

OR

− 5% Dextrose Injection, USP.

The resulting final concentration of bendamustine hydrochloride in the infusion bag should be within 1.85 mg/mL – 5.6 mg/mL. After transferring, thoroughly mix the contents of the infusion bag. The admixture should be a clear, and colorless to yellow solution.

No other diluents have been shown to be compatible. The 5% Dextrose Injection, USP, offers a sodium-free method of administration for patients with certain medical conditions requiring restricted sodium intake.

8.1.8 Administration

8.1.8.1 TREANDA

Drug should be administered as an IV infusion over 60 minutes. If medical conditions necessitate, e.g., fluid management issues or infusion reactions, the infusion may be given over a longer period of time. However, the entire infusion time should be < 120 minutes. In–line filters are not required for administration. Prime the infusion line with drug solution and accurately record infusion start and stop times as part of your source documentation. Unless there are extenuating circumstances, all of the drug should be administered to the patient with the exception of what remains in the line. Be sure to document any problems you may encounter with the infusion. If for any reason the drug cannot be entirely administered, please measure the remaining volume in the infusion bad and record on your source documentation.

8.1.8.2 BENDEKA

The prepared infusion is **administered intravenously over 10-minutes** at the dose and schedule described by the protocol.

8.1.9 Compatibilities

For specific details refer to handbook on injectable drugs by Lawrence A. Trissel.

8.1.10 Availability

Bendamustine is commercially available. See Package Insert for further information.

8.1.11 Side Effects

The adverse events specified below are also likely to be of clinical importance and may result in bendamustine dose delays or dose reductions, as outlined in Section 5.4.2.

- Infection and pneumonia: Infection, including pneumonia and sepsis, has been reported and, in rare cases, infection has been associated with hospitalization, septic shock, and death. Patients with myelosuppression following bendamustine treatment are susceptible to infections and should be advised to contact a physician if they have symptoms or signs of infection, including fever or respiratory symptoms.
- Infusion reactions and anaphylaxis: Infusion reactions with bendamustine have occurred commonly in clinical studies with symptoms that are generally mild and include fever, chills, pruritus, and rash. In rare instances, severe infusion reactions, described as anaphylactic and anaphylactoid reactions, have occurred, particularly in the second and subsequent cycles of therapy. Patients should be asked about symptoms suggestive of infusion reactions after their first cycle of therapy. Measures to prevent severe reactions, including antihistamines, antipyretics, and corticosteroids should be considered in subsequent cycles in patients who have previously experienced infusion reactions.
- Tumor lysis syndrome: Tumor lysis syndrome has been reported with bendamustine, with onset typically within the first treatment cycle. Tumor lysis syndrome may lead to acute renal failure and death without appropriate medical intervention. Preventive measures include maintaining adequate volume status, close monitoring of blood chemistry (particularly potassium and uric acid levels), and the use of allopurinol during the first 1 to 2 weeks of bendamustine treatment.
- Skin reactions: Skin reactions have been reported with the use of bendamustine, including non-specific rash, toxic skin reactions, and bullous exanthema. The relationship of skin reactions to bendamustine administration is often unclear as bendamustine is frequently administered with other anti-cancer therapies. A case of fatal TEN has been reported in 1 patient treated with a combination of bendamustine and rituximab. The TEN was considered possibly related to either agent. The relationship of this adverse event to bendamustine remains uncertain as TEN has also been reported with single-agent rituximab. When skin reactions occur, they may be progressive and increase in severity with further treatment. If skin reactions are severe or progressive, bendamustine should be withheld or discontinued.
- Other malignancies: Development of premalignant and malignant disorders following treatment with bendamustine has been reported. The reports are limited and included development of myelodysplastic syndromes, myeloproliferative disorders, acute myeloid leukemia, and bronchial carcinoma. Because of

confounding effects of other previous chemotherapy in these patients, the relationship to bendamustine could not be determined.

8.1.12 Drug Interactions

Bendamustine is a substrate for the cytochrome P450(CYP) 1A2 isoenzyme.

8.1.12.1 Bendamustine is metabolized to minimally active metabolites by CYP1A2. Concurrent administration of a CYP1A2 inhibitor such as atazanavir, cimetidine, ciprofloxacin, fluvoxamine, mexiletine, tacrine, thiabendazole, zileuton, norfloxacin, and/or ethinyl estradiol may *increase* bendamustine concentrations in plasma. Caution should be exercised, or alternative treatments considered, when coadministering bendamustine with a CYP1A2 inhibitor.

8.1.12.2 Bendamustine is metabolized to minimally active metabolites by CYP1A2. Concurrent administration of a CYP1A2 inducer such as barbiturates, carbamazepine, and/or rifampin may cause a decrease in bendamustine plasma concentrations and a potential *decrease* in cytotoxicity. The parent compounds are believed to be primarily responsible for the cytotoxicity of this agent. Caution should be exercised, or alternative treatments considered, when coadministering bendamustine with a CYP1A2 inducer.

8.1.12.3 Bendamustine is metabolized to minimally active metabolites by CYP1A2. Smoking tobacco has been shown to induce CYP1A2, and may cause a *decrease* in bendamustine plasma concentrations and a potential decrease in cytotoxicity. The parent compound is believed to be primarily responsible for the cytotoxicity of this agent. Caution should be exercised, or smoking cessation considered, when coadministering bendamustine with a CYP1A2 inducer.

8.1.13 Nursing /Patient Implications

1. Monitor CBC, platelet count. Advise patients of increased risk of infection with absolute neutrophil count less than 500 cells/mm^3 and increased risk of bleeding with platelet counts less than 20,000 cells/mm^3. Advise patients to call the clinic if they develop a fever above 101ºF or notice any easy bruising, petechiae (pinpoint red spots on skin), or prolonged bleeding.
2. Advise patient of possible alopecia, although this is very uncommon with bendamustine therapy.
3. Assess hydration and fluid balance. Patients should be encouraged to have at least 1 liter of fluids per day for 72 hours after administration.

4. Consider premedication with antiemetics.
5. Observe for possible phlebitis at injection site.
6. Administer antiemetics as indicated.

8.1.14 References

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Chow KU, Sommerlad WD, Boehrer S, Schneider B, Seipelt G, Rummel MJ, et al. Anti- CD20 antibody (IDEC-C2B8, rituximab) enhances efficacy of cytotoxic drugs on neoplastic lymphocytes in vitro: role of cytokines, complement, and caspases. Haematologica 2002;87(1):33-43.

Friedberg J, Cohen P, Chen L, Robinson K, Forero-Torres A, La Casce A, et al. Bendamustine in patients with rituximab-refractory indolent and transformed non- Hodgkin's lymphoma: Results form a Phase II multicenter, single-agent study. J Clin Oncol 2008;26(2):204-10.

Robinson K, Williams M, Cohen P, Tulpule A, van der Jagt R, Herst J, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent Bcell and mantle cell non-Hodgkin's lymphoma. J CLin Oncol [serial online] 2008;17.001v1:[Epub].

Rummel MJ, Al-Batran SE, Kim SZ, Welslau M, Hecker R, Kofahl-Krause D, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. J Clin Oncol 2005;23(15):3383-9.

8.2 Rituximab

8.2.1 Other Names

IDEC-C2B8, Chimeric anti-CD20 monoclonal antibody, Rituxan.

8.2.2 Classification

Antibody.

8.2.3 Mode of Action

Rituximab is a chimeric murine/human gamma 1 kappa monoclonal antibody (Chinese hamster ovary [CHO] transfectoma). It recognizes the CD20 antigen expressed on normal B cells and most malignant B-cell lymphomas. It binds with high affinity to CD20-positive cells, performs human effector functions *in vitro*, and depletes B cells *in vivo*. The Fab domain of rituximab binds to the CD20 antigen on B-lymphocytes and the Fc domain recruits immune effector functions to mediate Bcell lysis *in vitro.* The biological effect is manifested by B-cell depletion in peripheral blood, lymph nodes, and bone marrow.

8.2.4 Storage and Stability

Intact vials of rituximab are stored at refrigerated temperatures of 2 degrees to 8 degrees Celsius (36 degrees to 46 degrees Fahrenheit).

Protect vials from direct sunlight. Once diluted to a concentration of 1 to 4 mg/mL in polyvinylchloride or polyolefin IV bags containing normal saline or 5% dextrose, the product is stable for up to 24 hours at 2 degrees to 8 degrees Celsius, and at room temperature for an additional 12 hours after refrigeration (for a maximum period of 36 hours) if protected from light.

8.2.5 Dose Specifics

Rituxumab will be administered at 375 mg/m² intravenously throughout each aspect of this trial (induction and consolidation).

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8.2.6 Preparation

Withdraw the necessary amount of rituximab and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride or 5% Dextrose in Water. Gently invert the bag to mix the solution. Caution should be taken during the preparation of the drug, as shaking can cause aggregation and precipitation of the antibody.

8.2.7 Administration

Rituximab is administered intravenously. An in-line filter is not required. The initial rate is 50 mg/hr for the first hour, or slower if clinically indicated. If no toxicity is seen, the rate may be escalated gradually in 50 mg/hour increments at 30-minute intervals to a maximum of 300mg/hr. If the first dose is well tolerated, the initial rate for subsequent dose is 100mg/hr, increased gradually in 100 mg/hr increments at 30-minute intervals, not to exceed 400 mg/hr. If the patient experiences fever and rigors, the antibody infusion is discontinued. The severity of the side effects should be evaluated. If the symptoms improve, the infusion is continued initially at one-half the previous rate. Following the antibody infusion, the intravenous line should be maintained for medications as needed. Oral pre-medication (650 to 1000 mg of acetaminophen and 25 to 50 mg diphenhydramine) or equivalent will be administered 30 to 60 minutes prior to starting each infusion of rituximab. The patient should be treated according to the best available local practices and procedures. In patients with detectable circulating lymphoma cells, it is often recommended that the initial infusion rate be reduced to 25 mg/hr; these patients may experience more frequent and severe transient fever and rigors, shortness of breath, and hypotension.

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NOTE: In addition, alternative rituximab infusion rates (i.e., “rapid rituximab infusion”) can be used per institutional guidelines as long as the total number of milligrams of rituximab is the same and that “rapid infusion” is not administered with the patient’s first rituximab cycle. Further, a rituximab infusion should never be given over <u>less than</u> 90 minutes (common infusion time for “rapid infusion” is 20% of the bag volume over 30 minutes, and then 80% of the remaining bag volume over 60 mintues).

8.2.7.1 Hypersensitivity and Infusion Reactions

Available at the bedside prior to rituximab administration will be epinephrine for subcutaneous injection, diphenhydramine hydrochloride for IV injection, and resuscitation equipment for the emergency management of anaphylactoid reactions.

Rituximab should be administered intravenously through a dedicated line at an initial rate of 50 mg/hr. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 300 mg/hr. If hypersensitivity or infusion-related events develop, the infusion should be temporarily slowed or interrupted. The patient should be treated according to the appropriate standard of care. The infusion can be continued at one-half the previous rate when symptoms abate. Subsequent rituximab infusions can be administered at an initial rate of 100 mg/hr, and increased at 30-minute intervals by 100 mg/hr increments to a maximum of 400 mg/hr.

Rituximab Infusion Rate Adjustments

Infusion Rate	Fever		Rigors		Mucosal Congestion/ Edema		Hypotension
	(or)	→	(or)	→		→	
Decrease ½	>38.0ºC		Mild		Mild		Mild
Interrupt	>39.0ºC		Moderate		Moderate		Mild to Moderate

During the rituximab infusion, the patient's vital signs (blood pressure, pulse, respiration, temperature) should be monitored at least every 15 minutes x 4 and then hourly until the infusion is discontinued. Following the antibody infusion, the intravenous line should be maintained for medications as needed.

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8.2.7.2 Cardiovascular

Infusions should be discontinued in the event of serious or life threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of rituximab. Patients with preexisting cardiac conditions including arrhythmias and angina have had recurrences of these events during rituximab therapy and should be monitored throughout the infusion and immediate post-infusion period.

8.2.7.3 Tumor Lysis Syndrome

Rituximab rapidly decreases benign and malignant CD20 positive cells. Tumor lysis syndrome has been reported to occur within 12 to 24 hours after the first rituximab infusion in patients with high numbers of circulating malignant lymphocytes. Patients with high tumor burden (bulky lesions) may also be at risk. Patients at risk of developing tumor lysis syndrome should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should be provided for patients who are at risk for, or who develop, tumor lysis syndrome.

8.2.8 Compatibility/Incompatibilities

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

8.2.9 Availability

Commercially available:

Preservative-free injection 10mg/mL, in 10 and 50 mL single-unit vials.

Please see Package Insert for further information.

8.2.10 Side Effects

Please refer to CAEPR in Section 5.3.1.

8.2.11 Nursing /Patient Implications

1. Monitor blood pressure, pulse, respiration, and temperature every 15 minutes x 4 or until stable and then hourly until the infusion is discontinued.
2. Have epinephrine for subcutaneous injections, diphenhydramine for intravenous injection, and resuscitation equipment for emergency management of anaphylactoid reactions available.
3. Monitor and alter infusion rates in the presence of toxicities.
4. Carriers of hepatitis B virus should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis throughout study participation.
5. Due to the risks of bowel obstruction and bowel perforation, patients should be monitored for complaints of abdominal pain, especially early in the course of treatment.
6. Patients with concurrent RA should be monitored throughout the infusion and rituximab ahould be discontinued in the event of a serious or life-threatening cardiac event.

Rituximab shows no significant effect on bone marrow reserve and no apparent increased rate of infections in heavily pretreated, relapsed lymphoma patients. Prophylaxis for Tumor Lysis Syndrome (TLS)

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should be used in patients with bulky tumor masses (> 10cm). Patients should be provided IV hydration and administered allopurinol or similar agent. Precautionary hospitalization should be made available for patients who experience severe infusional symptoms which do not resolve after discontinuation or completion of the infusion. Hospitalization is not mandated for these patients. This will be left to the discretion of the investigator.

8.2.12 References

Product Information: rituximab. IDEC Corporation, December, 1998.

Reff ME *et al.* Depletion of B cell *in vivo* by a chimeric mouse human monoclonal antibody to CD20. Blood 1994; 83:435-45.

Demidem A *et al.* Chimeric anti-CD20 antibody (IDEC-C2B8) is apoptic and sensitizes drug resistant human B cell lymphomas and AIDS related lymphomas to the cytotoxic effect of CDDP, VP-16, and toxins. FASEB 1995; J9:A206.

Maloney DG *et al.* Phase I clinical trial using escalating single dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2D8) in patients with recurrent B-cell Lymphoma. Blood 1993; 82(Suppl 1):445a.

Maloney DG *et al.* Initial report in a phase I/II multiple dose clinical trial of IDEC-C2B8 (chimeric anti-CD20) in relapsed B-cell lymphoma. Proc Am Soc Clin Oncol 1994; 13:993.

8.3 Bortezomib (Velcade) PS-341, NSC 681239

Please see Package Insert for further information.

8.3.1 Chemical Name or Amino Acid Sequence

N-Pyrazinecarbonyl-L-phenylalanine-L-leucine boronic acid

8.3.2 Other Names

MLN341, LDP-341, Velcade®, bortezomib

8.3.3 Classification

Proteasome Inhibitor

8.3.4 CAS Registry Number

179324-69-7

8.3.5 Molecular Formula

$C_{19}H_{25}BN_4O_4$

8.3.6 Mechanism of Action

Inhibitors of the 26S proteasome act through multiple mechanisms to suppress tumor survival pathways, arrest tumor growth, tumor spread, and angiogenesis. By inhibiting the proteasome, bortezomib affects a combination of cellular regulatory mechanisms thereby providing a novel therapeutic approach to cancer treatment. This multiple

mechanistic approach potentially represents a more effective anticancer strategy compared to the antitumor activity afforded by conventional chemotherapy. The mechanisms of anti-tumor activity that have been established for bortezomib involve many pathways thought to be integral to cancer treatment strategies. The following observations were made in in vitro and in vivo experiments:

- Directly induces apoptosis of tumor cells.
- Inhibits activation of NF-KB in cells and in tumor microenvironment.
- Reduces adherence of myeloma cells to bone marrow stromal cells.
- Blocks production and intracellular signaling of IL-6 in myeloma cells.
- Blocks production and expression of pro-angiogenic mediators.
- Overcomes defects in apoptotic regulators, such as Bcl-2 overexpression and alterations (i.e., mutations) in tumor suppressor p53 and loss of Apaf-1.
- In MM, bortezomib is directly cytotoxic to myeloma cells and also modulates the micro-environment via inhibition of NF-KB.

8.3.7 How Supplied

Drug Orders:

Drug is available in sterile, single use vials containing 3.5 mg of bortezomib. Please refer to Section 8.3.8 for instructions on preparing the drug for injection.

Initial Orders:

Following submission of the required documents and patient randomization to Arms B or D, a supply of Bortezomib may be ordered from UVI, Inc. Institutions must electronically submit the completed E1411 Bortezomib Drug Request Form (Appendix XV and available on the ECOG Web Site, www.ecog.org) to UVI, Inc at mdubois@uintavision.com.

When ordering Bortezomib for Arms B and D, please see below for the recommended time table for drug requests. A total of 2 shipments are recommended for patients on Arm B and D. Recommended time points for drug requests are as follows:

Shipment #	Patient Treatment Time Point
1	Cycles 1-3
2	Cycles 4-6

Please indicate the number of vials needed on the E1411 Bortezomib Drug Request Form (Appendix XV).

NOTE: Vials of bortezomib must be ordered in multiples of 4.

Institutions should allow 3 business days for receipt of the Bortezomib from the date the drug request is received by UVI, Inc. Shipments will be made from UVI, Inc. Drug orders received by 2PM EST Monday through Thursday will be processed for shipment that day. Approved orders will be delivered onsite Tuesday through Friday.

There will be no weekend or holiday delivery of drugs.

Reorders: See table above for recommended time points for submitting drug requests for patients on Arms B and D. Institutions should keep in mind that shipments take 3 business days from the date the drug request is received by UVI, Inc. Reorders using the E1411 Bortezomib Drug Request Form (Appendix XV) should be emailed to UVI, Inc, at mdubois@uintavision.com.

NOTE: A supply of individual vials of bortezomib must be ordered in multiples of 4. Once approved by UVI, Inc, the drug will be received on site within 3 business days. Shipments will be made from UVI, Inc. Drug orders received by 2PM EST Monday through Thursday will be processed for shipment that day. Approved orders will be delivered onsite Tuesday through Friday.

There will be no weekend or holiday delivery of drugs.

Drug Inventory Records: Investigational Product Records at Investigational Site(s): It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines.

Drug Destruction and Return:

All unused bortezomib must be returned to Millennium. Sites are advised to fax a completed E1411 Clinical Trial Material Return Request Form (Appendix XV) to 617-444-1477. Millennium will provide a call tag for free pick up of the bortezomib to be returned, as well as instructions on preparing the package for pick up.

Please maintain appropriate records of the return, including dates and quantities.

8.3.8 Preparation

Drug is available in sterile, single use vials containing 3.5 mg of bortezomib. Each vial of bortezomib for Injection should be reconstituted under a laminar flow biological cabinet (hood) within eight hours before dosing with 3.5 mL of normal (0.9%) saline, Sodium Chloride Injection USP, so that the reconstituted solution contains bortezomib at a concentration of 1 mg/mL. For SC use, reconstitute with 1.4 mL of normal (0.9%) saline, Sodium Chloride Injection USP, so that the reconstituted solution contains bortezomib at a concentration of 2.5 mg/mL for subcutaneous administration. Prior to reconstitution the vials should remain in the cartons to protect

them from light. Dissolution is completed in approximately 10 seconds. The reconstituted solution is clear and colorless, with a final pH of 5 to 6. Reconstituted bortezomib should be administered promptly and in no case more than 8 hours after reconstitution. All materials that have been used for preparation should be disposed of according to standard practices. A log must be kept of all disposed materials.

8.3.9 Storage

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

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

8.3.10 Dose Specifics

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Bortezomib will be given at a dose of 1.6 mg/m² on days 1 and 8 of each cycle for patients randomized to receive BVR induction. Dose escalation is not allowed in any patient, and there must be at least 72 hours between each dose of bortezomib.

8.3.11 Route of Administration

Intravenous or subcutaneous (SC). Note different reconstitution methods, concentration and volume of administration for the different routes.

8.3.12 Method of Administration

IV push over 3-5 seconds.

SC, thigh or abdomen.

8.3.13 Incompatibilities

Bortezomib is metabolized by cytochrome P-450 CYP3A4 and CYP2D6 and may interact with other drugs which are either inducers or inhibitors of these isoenzymes. Examples of enzyme-inducing

agents - phenytoin, carbamazepine, phenobarbital, rifampin and rifabutin - may decrease serum concentrations of bortezomib, thereby diminishing the therapeutic efficacy. Enzyme-inhibiting drugs such as erthromycin, clarithromycin, ketoconazole, itraconazole, voriconazole, fluconazole, diltiazem and cyclosporine may increase serum concentrations of bortezomib, thereby increasing the risk of toxicity. Specialized references should be consulted when attempting to predict drug interactions. To date, there are no clinical studies to address drug interactions with bortezomib.

8.3.14 Special Handling

Shelf life surveillance of the intact vials is ongoing. The solution as reconstituted is stable for 43 hours at room temperature.

CAUTION: The single-use lyophilized dosage form contains no antibacterial preservatives. Therefore, it is advised that the reconstituted product be discarded 8 hours after initial entry.

8.3.15 Side Effects

Please refer to the CAEPR in Section 5.3.3.

8.3.16 Nursing/Patient Implications

Patients and nurses should share side-effects with treating clinician so they can be treated if appropriate.

1. Monitor for signs of myelosuppression such as infection, bleeding or shortness of breath.
2. Evaluate for gastrointestinal toxicity providing antiemetics as appropriate and monitor bowel habits.
3. Counsel the patient regarding the risk of peripheral neuropathy and that it is likely to be dose-related. Patients who have received neurotoxic chemotherapy in the past (e.g. Vinca alkaloids, taxanes, etc.) may be at higher risk for this complication.
4. Have patient promptly report any vision changes.
5. Assess SC injection sites for signs of inflammation.

8.3.17 References

Bortezomib Investigator Drug Brochure. Millennium Pharmaceuticals. 2003.

Richardson P, Barlogie B, Berenson J, et al. A Phase II multicenter study of the proteasome inhibitor bortezomib (Velcade, formerly PS341) in multiple myeloma patients with relapsed/refractory disease. Proc Am Soc Hematology 2002 #385.

Chris Fausel, Pharm.D. 317-278-3402

8.4 Lenalidomide (NSC 703813)

For further information on lenalidomide, please refer to the approved package insert.

8.4.1 Other names

IMiD™ compound CC-5013, Revlimid® (formerly Revimid™)

8.4.2 Classification

Immunomodulatory drug

8.4.3 Mode of Action

Lenalidomide, a thalidomide analog, is an immunomodulatory agent with a spectrum of activity that is not fully characterized. In vitro, it inhibits secretion of the pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 and increases secretion of the anti-inflammatory cytokine IL-10. It also induces T-cell proliferation, IL-2 and IFN-γ production in vitro.

8.4.4 Storage and Stability

Storage: The capsules should be stored at room temperature (15-30°C) away from moisture and direct sunlight.

Stability: Refer to package labeling for expiration date.

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8.4.5 Dose Specifics

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Patients on Arm G and H will receive lenalidomide at 15 mg orally on days 1 through 21 on 28 day cycles (i.e., days 22 to 28 to stop/not take lenalidomide) during consolidation therapy. Only enough lenalidomide for 1 cycle of therapy may be provided to the patient each cycle. Dose reductions (for adverse events) are discussed in Section 5.4.4.1 and Table 8).

Patients with creatinine clearance of ≥ 30 mL/min but < 50 mL/min should be started at lenalidomide 10mg daily on Days 1-21 of each 28-day cycle (these patients could be escalated once to 15mg daily on Days 1-21 of each 28-day cycle if they are tolerating lenalidomide well – the escalation should occur at the start of a cycle). For these patients who start on 10mg daily, de-escalation will be allowed to 5mg (dose level -2), and then 5mg every other day (dose level -3). Once a subject's dose has been reduced, no dose re-escalation is permitted.

Patients with creatinine clearance of < 30 mL/min by Cockroft-Gault formula at registration to step 2 will not be given lenalidomide. If, however, this develops while on step 2 treatment, lenalidomide dose should be decreased to 5mg daily on Days 1-21 of each 28-day cycle (these patients could be escalated once to 10mg daily on Days 1-21 of each 28-day cycle if they are tolerating lenalidomide well – the escalation should occur at the start of a cycle). For these patients who start on 5mg daily, de-escalation will be allowed to 5mg every other day (dose level -3). Once a subject's dose has been reduced, no dose re-escalation is permitted.

8.4.6 Route of Administration

Oral. Clinical studies have shown that lenalidomide administration coincident with food intake appears to delay absorption to some degree, although the extent of absorption is not altered. Therefore, lenalidomide can be taken with or without food.

8.4.7 Potential Drug Interactions

Periodic monitoring of digoxin levels is recommended during coadministration with lenalidomide. Digoxin levels were slightly higher when digoxin was administered with lenalidomide in a clinical study. There was no effect on lenalidomide pharmacokinetics.

Warfarin and lenalidomide may be co-administered without additional monitoring. No pharmacokinetic or pharmacodynamic interactions were observed between lenalidomide and warfarin.

Nonclinical in vitro metabolism studies suggest that lenalidomide is not likely to result in metabolic drug interactions in humans. In vitro, lenalidomide did not significantly inhibit marker enzyme activities for CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4. In rats, no induction of any CYP450 enzymes was observed. Administration of lenalidomide in monkeys showed no effects on the activities of CYP1A, CYP2B, CYP2C, CYP2E, CYP3A, or CYP4A.

8.4.8 Availability

Drug Orders:

REMS Program

Lenalidomide will be provided to patients on Arms G and H for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the REMS program of Celgene Corporation. Per standard REMS requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects randomized to Arms C and D who then proceed on to Arms G and H of this trial, must be registered in and comply with all requirements of the REMS™ program.

Scheduling Considerations:

Lenalidomide cannot be shipped to patients until all of the steps outlined below have been completed. Due to the multiple steps involved in ordering lenalidomide we ask that sites allow adequate time for order processing to ensure patient treatment is not delayed.

For initial orders, steps 1 through 4 can be completed anytime after randomization to Arms C or D. These steps register the patient and physician into the REMS program. Once it is determined the patient is eligible to proceed on to Arms G or H sites can complete the remaining steps. Step 5 begins the prescription process and all subsequent steps must be completed within 7 days.

Sites should educate patients that they must register in and comply with all requirements of the REMS™ program including the patient survey and patient education in order for drug orders to be approved.

Shipments will be made from Biologics, Inc. Monday through Thursday for delivery Tuesday through Friday. Upon approval of drug orders, patients will receive lenalidomide via FedEx in 1-2 business days. **Please note that lenalidomide will be shipped directly to patients.**

There will be no weekend or holiday delivery of drugs.

Prescriptions must be filled within 7 days and only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

No Starter Supplies are available for this protocol.

Strengths Available and Order Recommendations:

Lenalidomide is available as a 5mg, 10mg or 15 mg capsule for oral administration. For this study, the maximum daily dose of lenalidomide is 15mg, given to patients on Arms G and H, on days 1 through 21 of each cycle. Only enough lenalidomide for one cycle of therapy will be supplied to the patient at a time.

If the patient is dosed at 15 mg, you may order **one** of the following combinations per cycle:

Capsule Strength	**Quantity needed for one cycle**
15mg	21 pills
OR	
5mg **Plus** 10mg	21 pills **Plus** 21 pills
OR	
5mg	63 pills

Initial Orders:

Please note that lenalidomide cannot be shipped to patients until all of the following steps have been completed. Steps 1 through 4 can be completed at anytime after randomization to Arms C or D. These steps register the patient and physician into the REMS program. Once it is determined the patient is eligible to proceed on to Arms G or H sites can complete the remaining steps. Step 5 begins the prescription process and all subsequent steps must be completed within 7 days.

1. Prescribing physician registers in the REMS program by completing the Prescriber Enrollemnt Form and submit this form electronically through www.CelgeneRiskManagement.com or fax to 1-888-423-9325
2. Patient must be randomized to Arms C or D and eligible to proceed on to Arms G or H.

3. Prescribing physician assists patient to enroll in the REMS program by obtaining and signing a Patient-Physician Agreement Form (PPAF) online at www.CelgeneRiskManagement.com or by calling the Celgene Customer Care Center for assistance at1-888-423-5436
4. Patient signs the appropriate PPAF and agrees to follow all the procedures of the commercial REMS Program. The prescribing physician will then submit the PPAF to the Celgene Customer Care Center via mail (86 Morris Avenue, Summit, NJ 07901), email (customercare@celgene.com), fax (1-888-432-9325), or online (www.celgeneriskmanagement.com)
5. Patient and prescriber complete a surveys as required by the REMS Program by calling Celgene Customer Care at 1-888-423-5436 or utilizing the REMS online® access at www.CelgeneRisk Management.com.
6. At the completion of the survey, the prescribing physician is given a REMS authorization number. They complete the REMS for Patient Prescription Form (Appendix XIII and available on the ECOG Web Site) and fax it to one of the Celgene Certified Pharamacy Network participants (List available at www.celgene.com/PharmacyNetwork).
7. Prescribing physician advises the patient that a representative from a REMS contract pharmacy will contact them by phone within 24 hours.
8. REMS contract pharmacy calls patient to conduct patient education.
9. REMS contract pharmacy calls Celgene Customer Care for confirmation number.
10. REMS contract pharmacy approves the order and ships lenalidomide and FDA-approved Medication Guide directly to the patient. Once the order is approved, patient will receive lenalidomide via FedEx in 1-2 business days.

Reorders:

Please note that lenalidomide cannot be shipped to patients until all of the following steps have been completed:

1. Patient and prescriber complete the phone surveys as required by the REMS Program by calling Celgene Customer Care at 1-888-423-5436 or utilizing the REMS online access.
2. At the completion of the survey, the prescribing physician is given a REMS authorization number. They complete the REMS for PatientPrescription Form (Appendix XIII and available on the ECOG Web Site) and fax it it to one of the Celgene Certified Pharamacy Network participants (List available at www.celgene.com/PharmacyNetwork).

3. Prescribing physician advises the patient that a representative from a REMS contract pharmacy will contact them by phone within 24 hours.
4. REMS contract pharmacy calls patient to conduct patient education.
5. REMS contract pharmacy calls Celgene Customer Care for confirmation number.
6. REMS contract pharmacy approves the order and ships lenalidomide and FDA-approved Medication Guide directly to the patient. Once the order is approved, patient will receive lenalidomide via FedEx in 1-2 business days.

Scheduling Considerations:

Lenalidomide cannot be shipped to patients until all of the steps above have been completed. Due to the multiple steps involved in ordering lenalidomide we ask that sites allow adequate time for order processing to ensure patient treatment is not delayed.

Sites should educate patients that they must register in and comply with all requirements of the REMS™ program including the patient survey and patient education in order for drug orders to be approved.

Shipments will be made from Biologics, Inc. Monday through Thursday for delivery Tuesday through Friday. Upon approval of drug orders, patients will receive lenalidomide via FedEx in 1-2 business days. **Please note that lenalidomide will be shipped directly to patients.**

There will be no weekend or holiday delivery of drugs.

Prescriptions must be filled within 7 days and only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

Drug Inventory Records:

Investigational Product Records at Investigational Site(s): It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines.

Drug Destruction and Return:

Sites are to instruct patients to return any unused lenalidomide to Celgene for destruction. Instructions for return of drug are included with each shipment of lenalidomide and instruct patients to call Celgene Customer Care at 1-888-423-5436 to begin the return process. Once notified, Celgene will provide patients with a pre-paid UPS label to return unused lenalidomide to the company.

8.4.9 Side Effects

Please refer to the CAEPR in Section 1.1.1.

8.4.10 Nursing/ Patient Implications

1. Ensure women of childbearing age are not pregnant and sexually active women and men are abstaining or are using an effective form of contraception while taking lenalidomide. This should be discussed prior to each course of treatment.
2. Caution patient not to drive or use hazardous machinery until the potential sedative effects of the drug are known in the patient.
3. Caution patient to report leg swelling or shortness of breath, because of the risk of thrombosis/embolism

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4. All subjects who receive lenalidomide are **required** to have deep vein thrombosis (DVT) prophylaxis during lenalidomide therapy. Subjects with a history of a thrombotic vascular event are required to have full anticoagulation, therapeutic doses of low molecular weight heparin or warfarin to maintain an INR between 2.0–3.0, or any other accepted full anticoagulation regimen (e.g. direct thrombin inhibitors or Factor Xa inhibitors) with appropriate monitoring for that agent. All subjects without a history of a thromboembolic event are required to take a daily aspirin (81mg or 325 mg) for DVT prophylaxis. Subjects who are unable to tolerate aspirin should receive low molecular weight heparin therapy or warfarin treatment or another accepted full anticoagulation regimen. Refer to Section 5.5.4.
5. Counsel patient to report abnormal sensations in hands or feet, such as decreased sensation or dysesthesia. Paresthesias are often noted early before neuropathy develops.
6. Advise patient to immediately report rashes or fever.
7. Advise patient to take dose at the same time each day.

8.4.11 Lenalidomide Fertility Instructions

Before starting study drug:

Female Subjects

- Females of childbearing potential (FCBP) must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The subject may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.
- Will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure.
- Must agree to abstain from donating blood during study participation and for at least 28 days after discontinuation from the study.

Male Subjects

- Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.
- Will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure.
- Must agree to abstain from donating blood, semen, or sperm during study participation and for at least 28 days after discontinuation from the study.

During study participation and for 28 days following discontinuation from the study:

All Subjects

- No more than a 28-day supply of study drug will be dispensed at a time.
- Lenalidomide capsules should be swallowed whole and should not be broken, chewed or opened.
- If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.
- Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

Female Subjects

- Pregnancy tests must occur within 10-14 days prior to the start of the study drug and again within 24 hours prior to initiation of the first cycle of lenalidomide.
- FCBP with regular cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following discontinuation from the study. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following discontinuation from the study.
- In addition to the required pregnancy testing, the Investigator must confirm with FCBP that she is continuing to use two reliable methods of birth control at each visit.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days. During counseling, subjects must be reminded to not share study drug and to not donate blood.

- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after discontinuation from the study

Male Subjects

- Counseling about the requirement for latex condom use during sexual contact with females of childbearing potential and the potential risks of fetal exposure must be conducted at a minimum of every 28 days. During counseling, subjects must be reminded to not share study drug and to not donate blood, sperm, or semen.
- If pregnancy or a positive pregnancy test does occur in a study subject or the partner of a male study subject during study participation, study drug must be immediately discontinued.
- Men should continue pregnancy precautions for at least 2 months after stopping drug (lenalidomide).

8.4.12 References

Richardson PG, Schlossman RL, Weller E, et al. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed Multiple Myeloma. Blood 2002; 100:3063-7.

Richardson P, Jagannath S, Schlossman R, et al. A Multi-center, Randomized, Phase II Study to Evaluate the Efficacy and Safety of 2 CDC-5013 Dose Regimens When Used Alone or in Combination with Dexamethasone (Dex) for the Treatment of Relapsed or Refractory Multiple Myeloma (MM). Blood 2003; 102:235a.

Zangari M, Tricot G, Zeldis J, Eddlemon P, Saghafifar F, Barlogie B. Results of Phase I Study of CC-5013 for the Treatment of Multiple Myeloma (MM) Patients Who Relapse after High Dose Chemotherapy (HDCT). Blood 2001:775a (A3226).

Davies FE, Raje N, Hideshima T, et al. Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in Multiple Myeloma. Blood 2001; 98:210-6.

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8.5 Rituxan Hycela

NOTE: Please note that Rituxan Hycela (rituximab and hyaluronidase human) injection for SC use will be allowed during step 2 of this study (arms E-H). Please see the package insert for more information.

8.5.1 Description

Rituxan Hycela (rituximab and hyaluronidase human) is a colorless to yellowish, clear to opalescent solution.

8.5.2 Storage and Stability

Rituxan Hycela should be stored in the refrigerator at 2°C–8°C (36°F–46°F) in the original carton to protect from light. Do not freeze.

Once transferred from the vial into the syringe, if not used immediately, store the solution of rituximab/hyaluronidase in the refrigerator at 2°C–8°C (36°F–46°F) up to 48 hours and subsequently for 8 hours at room temperature up to 30°C (86°F) in diffuse light.

8.5.3 Dose Specifics

Rituxan Hycela injection for SC use may be administered for rituximab maintenance at 1400mg/23,400 Units SC every 8 weeks (+/- 1 week). However, patients must receive at least one full dose of Rituximab by IV infusion prior to receiving Rituxan Hycela SC. Please refer to the commercial package insert.

8.5.4 Route of Administration

Inject Rituxan Hycela into the subcutaneous tissue of the abdomen over approximately 5-7 minutes and never inject into areas where the skin is red, bruised, tender or hard, or areas where there are moles or scars. No data are available on performing the injection at other sites of the body.

NOTE: Please note that Rituxan Hycela (rituximab and hyaluronidase human) is ready to use for SC injection only.

Please see Package Insert for further information.

8.5.5 Availability

Commercially available:

Injection: 1400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL (120mg/2,000 Units per mL) in a single-dose vial.

Injection: 1600 mg rituximab and 26,800 Units hyaluronidase human per 13.4 mL (120mg/2,000 Units per mL) in a single-dose vial.

8.5.6 Side Effects

Please see Package Insert for further information.

8.5.7 Nursing/Patient Implications

Rituximab/hyaluronidase is compatible with polypropylene and polycarbonate syringe material and stainless-steel transfer and injection needles.

To avoid clogging the needle, attach the injection needle to the syringe immediately prior to administration.

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9. Statistical Considerations

9.1 Primary Endpoints

The goals of the study are to determine if either bortezomib (Velcade, V,) added to an induction regimen of rituximab/ bendamustine (RB) or lenalidomide (L) added to rituximab (R) maintenance is associated with improved outcome in patients with MCL and to identify arms suitable for evaluation in the Phase 3 setting. 372 patients, of whom 360 are expected to be eligible and treated, will be stratified for balancing purposes according to MIPI risk status (low risk vs.
Rev. 12/13 intermediate vs. high risk) and age (< 60 vs. ≥ 60), and enrolled over 45 months and equally randomized to one of four arms:

Arm A: RB –> Arm E: R
Arm B: RBV -> Arm F: R
Arm C: RB -> Arm G: LR
Arm D: RBV-> Arm H: LR

Induction Analysis of Progression-Free Survival

We hypothesize that patients treated with RB->R will have a 2-year PFS rate of 70%. (estimated from R-CHOP -> R data, (Dreyling personal communication).

Rev. 12/13 Patients will be stratified according to MIPI risk status, age, and consolidation treatment assignment. PFS for patients randomized to RB induction (Arms A and C) will be compared to PFS for patients randomized to RBV (Arms B and D). With an anticipated 23 additional months of follow-up after the end of accrual, there will be adequate power (93.8%) to detect a 37.4% reduction in the hazard, corresponding to 2-year PFS of 80%, using a stratified logrank test with 1-sided Type I error of 10%. Full information will exist when 149 patients have progressed or died.

Consolidation Analysis of Progression-Free Survival

The impact of lenalidomide on consolidation will be examined among all eligible patients beginning consolidation therapy. Patients who withdraw before starting consolidation will be excluded. A recent analysis after 36 months of patient accrual showed that only about 80.5% of patients begin consolidation treatment compared to the 90% initially assumed. Therefore, the sample size has been
Rev. 12/13 increased to adjust for this. For this analysis, PFS will be defined as the time from the start of consolidation treatment to the earliest of disease progression or death. Patients will be stratified according to MIPI risk status and age at the study entry and induction treatment assignment. PFS for patients registered to R consolidation (Arms E and F) will be compared to PFS for patients randomized to LR consolidation (Arms G and H).

Given 290 eligible, treated patients in the analysis, there will be 89.4% power to detect the same 37.4% reduction in the hazard as for the induction comparison, using a stratified logrank test with 1-sided Type 1 error of 10%. Full information will exist when 120 eligible, treated patients have progressed or died.

Sensitivity Analysis

As a sensitivity analysis, an intent-to-treat (ITT) analysis will be performed to evaluate PFS for the consolidation therapy. All randomized patients including

those who drop out before consolidation therapy will be included in the analysis. Patients will be stratified according to MIPI risk status at study entry and induction treatment assignment. PFS for patients randomized to Arms A and B will be compared to PFS for patients randomized to Arms C and D. For purposes of this analysis, PFS will be counted as time from randomization.

The purpose of the sensitivity analysis is to detect potential bias if there is a difference in dropout rates between the induction arms. If different results are obtained from the ITT analysis, the results of the primary analysis may need to be interpreted with caution.

Interim Analysis

Both phases of the study (induction and consolidation) will be monitored by the ECOG-ACRIN Data Monitoring Committee (DMC) for early stopping for harm and futility. The 'harm' analysis will be performed at 25% information. If the lower bound of a 95% confidence interval for the hazard ratio is above 1, the DMC may recommend dropping bortezomib in the RBV induction arms (so all patients will be treated with RB induction) or dropping lenalidomide in the LR consolidation arms (so all patients will be treated with R consolidation), and the study will continue with two arms for that phase. The futility analyses will be performed at 50% and 75% information. If the estimated hazard ratio for either the induction or consolidation comparison is greater than 1, the DMC may recommend dropping bortezomib in the RBV arms or dropping lenalidomide in the LR arms, and the study will continue with two arms for that phase. These analyses will be done separately for induction and consolidation comparisons. The effect of the interim analyses on the operating characteristics is fairly small.

9.2 Secondary Endpoints

Analysis of PET-documented Complete Response

PET-documented CR (complete disappearance of enhancing regions) will be assessed first at the end of induction. Information from patients on the two RB arms and on the two RBV arms will be pooled for comparing the CR rate between the two induction regimens. This analysis will be conducted using Fisher's exact test with 10% one-sided Type I error adjusting for MIPI risk status. With 180 patients per treatment group, there will be 93.4% power to detect an improvement in the PET-documented CR rate from 50% to 65% with the addition of bortezomib.

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Patients who did not achieve PET-documented CR (PET positive) at the end of induction and begin consolidation therapy will continue to be followed for the emergence of PET-documented CR after 6 cycles of consolidation therapy. Information from patients on the two LR arms and on the two R arms will be pooled for comparing the proportion of patients converting to PET-documented CR after 6 cycles of consolidation therapy between the two consolidation regimens. This analysis will include patients with PET-documented residual disease after induction who proceed to consolidation therapy. Assuming 50% will have induction CRs and another 19.5% will not proceed to consolidation because of progression and other reasons, we expect 30.5% of patients (27.5 per arm for each of the 4 arms) will have a PET scan after 6 cycles of consolidation therapy. With 64 patients in each group (LR vs. R), there will be 88% power to detect an improvement in the proportion of patients converting to PET-documented CR

from 15% to 35% with the addition of lenalidomide, using Fisher's exact test with 10% one-sided Type I error adjusting for MIPI risk status at study entry and induction treatment assignment.

Rev. 12/13 Section 9.4 and Section 9.6 outline statistical considerations for toxicity and QOL objectives. All other secondary objectives will primarily be descriptive.

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9.3 Subset Analysis for Patients Aged 60 Years and Older

A subset analysis of the primary and secondary endpoints will be done for patients aged 60 years and older. We anticipate approximately 80% (N=288) of patients will be ≥ 60 years old. For the induction analysis, PFS will be compared between RB induction (Arms A and C) and RBV induction (Arms B and D), stratified according to MIPI risk status, age and consolidation treatment assignment. Using the same hypotheses as for the whole population, there will be 89.2% power to detect the same 37.4% reduction in the hazard, using a stratified logrank test with 1-sided Type 1 error of 10%. Full information will exist when 119 patients have progressed or died. For the consolidation analysis, PFS will be compared between R consolidation (Arms A and B) and LR consolidation (Arms C and D), stratified according to MIPI risk status at the study entry, age and induction treatment assignment. Assuming 232 patients started consolidation treatment and are included in the analysis, there will be 83.7% power to detect 37.4% reduction in the hazard, using a stratified logrank test with 1-sided Type 1 error of 10%. Full information will exist when 96 eligible, treated patients have progressed or died.

PET-documented complete response and other secondary endpoints will also be evaluated in this subset of patients.

9.4 Toxicity

Toxicity will be continuously monitored throughout the study. All patients who receive treatment, regardless of eligibility, will be assessed for toxicity. Assuming that toxicity data is available on all 93 treated patients per arm, the 90% confidence interval for the true probability of observing a toxicity of Grade 4 or higher will be no wider than 18%. Below are probabilities of observing at least one rare toxicity in patients under different true underlying toxicity rates.

True Rare Toxicity Rate	Probability of Observing at least One Occurrence
.01	0.61
.02	0.85
.03	0.94
.04	0.98
.05	0.99

9.5 Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Monitoring Committee (DMC). The DMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double

blind studies, the DMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DMC. Any DMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DMC Policy can be obtained from the ECOG-ACRIN Operations Office – Boston.

9.6 Quality of Life

Patient-reported quality of life, as measured by the FACT-General scale, the FACT-lymphoma subscale, the FACT-Fatigue subscale and the FACT/GOG-Ntx neurotoxicity subcale, will be assessed at baseline, at the end of induction therapy, after 6 cycles of consolidation therapy, at the conclusion of consolidation therapy, at time of progression, and annually for 5 years.

9.6.1

To evaluate the extent and severity of neuropathy associated with the addition of bortezomib to induction treatment, the change in FACT/GOG-Ntx score from baseline to the end of induction will be examined in patients treated with RB (Arms A+C) and patients treated with RBV (Arms B+D), respectively. The table below shows the mean change of the score from baseline that can be detected with 90% power using a two-sided Wilcoxon signed rank test with Type I error of 5%, assuming different proportions of patients who complete the questionnaires at both time points. Assuming 80% of eligible, treated patients will have measurements at both time points, there will be 90% power to detect a 0.28 SD change from baseline to the end of induction within each group.

% of patients who complete the QOL questionnaires at both time points	Number of patients in each treatment group (RB or RBV)	Change from baseline that can be detected with 90% power in each group in terms of standard deviation (SD)
90%	162	0.26 SD
80%	144	0.28 SD
70%	126	0.30 SD
60%	108	0.32 SD

If statistically significant changes from baseline to the end of induction are noted in either treatment group, the difference in change of the score from baseline between patients treated with RBV and RB will be examined. The table below shows the differences in change of the score that can be detected with 90% power using a two-sided Wilcoxon rank sum test with Type I error of 5%, assuming different proportions of patients who complete the questionnaires at both time points. Assuming 80% of eligible, treated patients will have measurements at both time points, there will be 90% power to detect a 0.40 SD difference between groups.

% of patients who complete the QOL questionnaires at both time points	Number of patients in each treatment group (RB or RBV)	Difference between groups that can be detected with 90% power in terms of standard deviation (SD)
90%	162	0.37 SD
80%	144	0.40 SD
70%	126	0.43 SD
60%	108	0.46 SD

Strategies to minimize the impact of missing assessments will include a prospective reminder system through which enrolling sites will be notified in advance of patients' upcoming assessment schedules.

9.6.2 To evaluate the extent and severity of fatigue associated with the addition of lenalidomide to consolidation treatment, the FACT-Fatigue score will be examined. To ensure patients are comparable at the beginning of consolidation, we will first examine the change in the FACT-Fatigue score in the induction phase. If there are no significant changes in FACT-Fatigue score from baseline to the end of induction in either treatment group (RB or RBV), and no significant differences in FACT-Fatigue score at the end of induction between arms, the patients treated with LR consolidation will be pooled and those treated with R consolidation will be pooled (otherwise, each arm will be analyzed individually). The change in FACT-Fatigue score from the end of induction to after 6 cycles of consolidation will be examined in patients treated with R consolidation and patients treated with LR consolidation, respectively. Considering that about 19.5% of patients will not begin consolidation therapy, and the proportion of patients who complete questionnaires usually decreases over the course of the study, we assuming 60% of patients will have measurements at both time points. There will be 87.0% power to detect a 0.34 SD change from end of induction to after 6 cycles of consolidation within each group, using a two-sided Wilcoxon signed rank test with Type I error of 5%. Similarly, the change in FACT-Fatigue score from the end of induction to the end of consolidation will be examined.

If statistically significant changes are noted in either treatment group at either time point, the change in the score from the end of induction between patients treated with R and LR consolidation will be compared. Assuming 60% patients per arm with change scores and using a two-sided Wilcoxon rank sum test with Type I error of 5%, there will be about 87.0% power to detect a 0.48 SD difference between the groups.

If there are differences between groups in QOL at the end of induction, each arm may be considered individually in the evaluation of QOL during consolidation. In this case, assuming 60% of patients with repeated measurements, there will be adequate (77.080%) power to detect a 0.42 SD change from the end of induction within each arm.

9.6.3 To evaluate the effects of the addition of bortezomib and lenalidomide on global patient-reported health-related quality of life, the FACT-General score will be examined at baseline, at the end of induction, after 6 cycles of consolidation and at the end of consolidation. The analysis will be similar to the one outlined in 9.5.1 and 9.5.2.

9.6.4 To evaluate the effects of bortezomib-related neuropathy on global patient-reported health-related quality of life, the FACT-General scores will be compared between patients with and without neuropathy. First, median of the FACT/GOG-Ntx score at the end of induction will be calculated among patients treated with RBV. Patients with FACT/GOG-Ntx scores above median will be categorized into 'neuropathy' group and those with scores below median will be categorized into 'no neuropathy' group. The FACT-General scores at the end of induction will then be compared between groups with and without neuropathy, using a two-sided Wilcoxon rank sum test with Type I error of 5%. In addition, the FACT-General scores at later times (following 6 cycles of consolidation therapy etc) will be compared between the two groups to assess the long term effects of neuropathy on QOL. The comparisons will be stratified by consolidation treatment assignment. Repeated measures analysis techniques will also be utilized.

9.6.5 To evaluate the response of lymphoma-specific symptoms to treatment, the FACT-lymphoma scores will be examined at each time point, and compared between different treatment groups. The analysis will be similar to the one outlined in 9.5.1 and 9.5.2.

9.6.6 To describe the trajectory of overall health-related quality of life, lymphoma symptoms, neuropathy, and fatigue prior to, during and following treatment, the FACT-General score, the FACT-lymphoma score, the FACT-Fatigue score and the FACT/GOG-Ntx score will be examined at each time point. Besides comparing these QOL scores between treatment groups at each time point, repeated measures analysis techniques will also be utilized to examine the treatment effect, time effect, and potential interaction on QOL score over time. The method of Schluchter for jointly modeling QOL scores and survival will be explored in an attempt to account for the possibility of informative missingness (66).

9.7 Selection of Optimal Regimen(s)

There were no power or sample calculations for this section.

9.8 Imaging Correlative Studies

Imaging by FDG-PET will be done pretreatment (PET-0), after cycle 3 (PET-3), and after cycle 6 (PET-6).

9.8.1 There were no power or sample size calculations for this section.

9.9 Lab Correlative Studies (FFPE tissues)

We assume that lab data will be available from 90% of patients (n=324). We will consider a transformation of Ki67 data to improve the normality and variance stabilization of its distribution.

9.9.1 A Cox regression model will be fitted to predict PFS by the expression levels of the five genes of proliferation markers that were discovered by Hartmann et al (2008) (55). The association between Ki-67 proliferation index and the risk score from the fitted prediction model will be assessed by scatter plot and correlation coefficient estimate. A regression analysis with a two-sided alpha=5% will have 95% power to detect a Pearson correlation of 0.2.

9.9.2 Ki67 index will be associated with PFS by Cox regression method. Suppose that the whole patient population has 75% 2-year PFS with exponential distribution. With 324 patients accrued for 40 months and 2 years of additional follow-up, with two-sided alpha=5%, Cox regression has 90% power to detect a hazard ratio of 1.35 between two patient groups with Ki67 index values of one standard deviation away. We will conduct multivariate analysis to investigate if Ki67 is a prognostic factor independent of MIPI. The analysis will be conducted when 117 events (progressions or deaths) are observed. Similar analyses will be conducted to associate Ki67 index with CR and OR using two-sample t-test for univariate analysis and logistic regression for multivariate analysis. Treatment assignment will also be included in the multivariate analyses if it is significant on the clinical outcomes.

9.9.3 Expression of SOX11 by IHC will be correlated with OR and PFS similarly as Ki67 index. miRNA profiling will be associated with response and PFS using prediction-validation method based on 10-fold cross validation. The gradient lasso algorithm (Sohn et al 2009) will be used to fit a prediction model based on Cox regression model (67). This algorithm will reduce the number of genomic markers. A prediction model for OR will be estimated by replacing the objective function of the gradient lasso algorithm for the likelihood function of logistic regression. The validity of the fitted prediction model will be assessed by calculating the p-value using permutation method.

9.10 Minimal Residual Disease (MRD) Correlative Studies

There are several analysis steps of the samples. First, DNA sequences that are likely to be uniquely present in a particular patient's cells based on the sequencing of B cell rearrangements will be identified from samples in which cancer cells are found at high levels, such as bone marrow aspirate or diagnostic biopsy. After identifying patient specific malignant clones, numbers of cells that are likely to be of tumor origin in circulation and in marrow at baseline and subsequent timepoints will be identified by molecular counting techniques.

To determine whether the number of malignant cells in circulation predict the number of cells in marrow, graphic display and Spearman's rank correlation coefficient will be used. MRD status will be assigned for blood and bone marrow separately for each paired sample, and the concordance will be assessed. The analysis will be done at diagnosis, and at follow up assessment.

To determine whether the number of malignant cells in circulation or in marrow at the end of induction correlate with CR or 2-year PFS, the number of malignant cells will be compared between CR vs. non-CR, and between those who are progression-free at 2 years vs. those who are not, using Wilcoxon rank-sum tests with one-sided Type I error of 10%. We expect that blood samples will be collected in approximately 90% of patients at baseline, and 90% of these patients will have blood samples at the end of induction (292 samples). For bone marrow samples, we expect 80% of patients with positive marrow initially and 40% with follow-up bone marrow biopsies. That will give us an approximately 144 bone marrow samples at the end of induction. Assuming 50% of patients will achieve CR after induction, we will have adequate power (90%) to detect an effect size of 0.31 (0.31 standard deviation difference) in number of malignant cells between CR and non-CR with 292 blood samples, and an effect size of 0.44 with 144 bone marrow samples. Assuming 70% of patients will be progression-free at 2 years, we will have adequate power (90%) to detect an effect size of 0.34 in number of malignant cells between those who are progression-free at 2 years vs. those who are not, with 292 blood samples, and an effect size of 0.48 with 144 bone marrow samples.

The association between MRD level and progression-free survival will be evaluated using Cox proportional hazards models, adjusting for important clinical covariates. If an association is identified, recursive partitioning and/or maximum likelihood methods will be used to identify a useful cut point for distinguishing patients with good/poor PFS outcomes. A similar analysis will be done for flow cytometry outcomes. Positive predictive value (PPV) and negative predictive value (NPV) of these tests will be estimated. Since PPV and NPV are estimated from a data selected classification, cross validation will be performed to adjust for the bias from optimizing the classification rule.

To determine whether there is a lower level of residual disease among patients randomized to RBV as compared with RB, the number of malignant cells in circulation and in marrow at the end of induction will be compared between these two treatment groups, using Wilcoxon rank-sum test with one-sided Type I error of 10%. We will have adequate power (90%) to detect an effect size of 0.31 in number of malignant cells between the RBV group and RB group with 292 blood samples, and an effect size of 0.44 with 144 bone marrow samples. To determine whether there is a higher rate of MRD- among patients randomized to RBV as compared with RB, MRD status in circulation and in marrow will be assessed at the end of induction for patients in each treatment group. Assuming overall rate of MRD- is 30%, with 292 blood samples (146 each group), we will have 90% power to detect a difference in MRD- rate between RBV group and RB group from 22% to 38%, using Fisher's exact test with one-sided Type I error of 10%. The following table summarizes differences in MRD- rate between groups that can be detected with 292 blood samples and 144 bone marrow samples assuming different overall rate of MRD-.

Overall rate of MRD-	Differences in MRD- rate that can be detected with 292 blood samples (146 each group)	Differences in MRD- rate that can be detected with 144 marrow samples (72 each group)
20%	13% vs. 27%	10% vs. 30%
30%	22% vs. 38%	19% vs. 41%
40%	31% vs. 49%	28% vs. 52%
50%	41% vs. 59%	37% vs. 63%

Similarly, the number of malignant cells and proportion of MRD- will be compared between patients treated with LR maintenance and those treated with R maintenance, using Wilcoxon rank-sum test and Fisher's exact test respectively with one-sided Type I error of 10%.

To compare the two methods of MRD detection - molecular techniques and flow cytometry as prognostic markers for outcome, the predictive value of the MRD for CR and for 2-year PFS will be analyzed using receiver operating characteristics (ROC) curves for different cut-off values. The areas under the ROC curves (AUC) for these two methods will be compared using the method of Delong et al (1988) (69).

To explore whether MRD relapse signals clinical relapse and in what time frame, patients who are MRD- at the end of induction will be identified. Time to MRD relapse will be calculated from the end of induction to the time when patients become MRD+. Time to clinical relapse will also be calculated from the end of induction. The associations between time to MRD relapse and time to clinical relapse will be investigated using an estimator of Kendall's τ under bivariate censoring.

An interim analysis of MRD assay is planned per agreement between ECOG-ACRIN and Sequenta. The concordance between MRD level in peripheral blood (and marrow when possible) as measured by the Sequenta assay and the level obtained using flow cytometry will be evaluated after the first 100 patients have undergone induction therapy and been measured for MRD by both Sequenta and Mayo Clinic Lymphoma Lab. Also, the association between MRD level and PFS will be evaluated after the first 100 patients have been followed for 2 years. These analyses will be pooled over treatment arm, so no results by treatment will be included. The study investigators have agreed in principle to the release of these results while the study is ongoing. However, to assure that results of this analysis do not unintentionally compromise the primary objectives of the study, the release of the analyses must be approved by the DMC and the investigators will be given the opportunity to review and approve any abstracts, presentations or manuscripts prior to release.

9.11 Gender and Ethnicity

Based on previous data, the anticipated accrual in subgroups defined by gender and race is shown in the following table. Mantle cell lymphoma is more common in males, and based on published research (Armitage et al, 1998) and accrual to previous studies, we expect accrual to reflect this higher prevalence.

Gender and Minority Accrual Estimates for Proposed Study (Accrual Goal=372)

	Sex/Gender		
	Females	**Males**	**Total**
Ethnic Category			
Hispanic or Latino	9	10	19
Not Hispanic or Latino	145	208	353
Ethnic Category: Total of all subjects	154	218	372
Racial Category			
American Indian or Alaskan Native	1	2	3
Asian	1	2	3
Black or African American	8	11	19
Native Hawaiian or other Pacific Islander	1	2	3
White	143	201	344
Racial Category: Total of all subjects	154	218	372

10. Centralized Review

NOTE: Submitted scans and specimens must be entered and tracked via the ECOG-ACRIN Sample Tracking System (STS). See Section 10.3.

NOTE: Details on data and image acquisition, and processing and evaluation of FDG-PET/CT scans are outlined in Appendix IX (FDG-PET/CT IMAGING).

NOTE: An informed consent must be signed prior to the submission of any samples including mandatory diagnostic reviews, laboratory studies and/or banking. Samples for laboratory studies and/or banking should be submitted only from patients who have given written consent for the use of their samples for these purposes.

10.1 FDG-PET/CT Scan Imaging

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10.1.1 PET/CT Imaging Time Points

The following PET/CT scans will be collected digitally:

- *Baseline*

  NOTE: The baseline PET/CT scan must be obtained ≤ 28 days prior to randomization.

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  NOTE: Diagnostic CT scans of the neck/chest/abdomen/pelvis must be performed if PET/CT scan cannot be obtained at baseline due to timing constraints, insurance or reimbursement issues, or other reasons, and must be documented in the patient's chart.

- *Post Cycle Three (3)*

  NOTE: The interim FDG-PET/CT scan (if and when available) after three (3) cycles of induction therapy will be obtained at least 12 days after the administration of the 3rd cycle of induction therapy.

- *Post Cycle Six (6) – End of Induction*

  NOTE: The post completion of induction therapy FDG-PET/CT scan will be obtained at least 3 weeks after the administration of the last dose of induction therapy.

- *After Cycle Six (6) (week 24 ± 1 week) of Consolidation (if PET (+) at end of induction)*
- *After Cycle Twelve (12) (week 48 ± 1 week) of Consolidation*
- *After Cycle Eighteen (18) (week 72 ± 1 week) of Consolidation*
- *End of Consolidation*

10.1.2 Evaluation of PET/CT Data

All images will be read centrally by the CALGB Imaging Core Laboratory.

To ensure the highest standards and consistency between different centers, all FDG-PET scans (baseline, interim [when available], end of

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induction therapy (post six cycles), and six months into consolidation therapy) must be submitted to the CALGB Imaging Core Laboratory at Ohio State University Medical Center for centralized review.

Centralized review will be performed by a member of a team of PET/CT readers. There will be an adjudicator from the same pool of reviewers in the case of disagreement. There will be one reviewer, Dr. Nathan Hall, who will provide back-up PET/CT reviewer services within the CALGB Imaging Core Laboratory. The CALGB Imaging Core Laboratory will transmit the scans to the expert reviewers and then will transmit the results to the CALGB Statistical Center.

Questions concerning the FDG imaging procedure, interpretation of FDG-PET/CT scans and the definition of PET positivity should be directed to:

Lale Kostakoglu, MD, MPH
E1411 Imaging Co-Chair
Tel: (212) 241-6319
Fax: (212) 831-2851
lale.kostakoglu@mssm.edu

10.1.3 PET/CT Data Submission

The complete PET and CT studies must be electronically submitted to the CALGB Imaging Core Laboratory in digital DICOM format; any other formats such as Bitmap, JPG, hardcopy files, or scanned films are unacceptable. De-identify the patient data using institutional procedures to remove the patient name and medical record number while preserving the patient study ID number and protocol number separately.

Imaging data shall be submitted to the CALGB Imaging Core Laboratory within no more than three (3) business days once the image acquisition is completed at the site.

Images may be electronically transferred by either Web-based (a PC with internet access is needed) or FTP-based (a PC with both internet access and any FTP software installed is needed) transfer approaches. The standard and secure online access information will be provided separately through the specific trial e-mail E1411@ImagingCoreLab.com, per the request by participating sites before their first data submission.

Once the electronic imaging data submission is done, send an e-mail to the CALGB Imaging Core Laboratory at E1411@ImagingCoreLab.com to inform them that the study has been completely uploaded from the institution. Please include the basic information of submitted data sets as follows:

1) E1411 patient study ID number and protocol number
2) Scan time point
3) Date of scans

4) Date of first day of protocol treatment

5) Institution name

Institutions must send an ECOG-ACRIN 1411 PET/CT Adjunctive Data Sheet (Appendix XVI) to the CALGB Imaging Core Laboratory.

NOTE: An STS shipping manifest form must be generated and shipped with all sample submissions.

10.2 Pathology Review

Pathology materials from the original diagnostic tumor biopsy must be submitted for review and classification and laboratory studies. Pathology materials from tumor biopsies performed while on study should be submitted for banking for future use.

The clinical investigator and the submitting pathologist have the responsibility for submitting representative diagnostic material for review and classification. Refer to Appendix II (Pathology Submission Guidelines).

10.2.1 Materials Required For This Protocol

10.2.2 Forms (Submit with every pathology submission)

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- CALGB Pathology Material Submission Form (#3467), Parts A & B completed. Please identify the clinical status of the submitted material (i.e., pretreatment as opposed to remission and relapse).
- A copy of the surgical pathology report
- Immunophenotypic studies, if available
- Sample Tracking System Shipping Manifest Form

In addition to the surgical pathology report, if immunophenotypic studies have been performed at the home institution, it is necessary that these be forwarded as well.

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10.2.3 Biological Material Submissions:

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If blocks cannot be submitted, 12 unstained slides, two or more 4mm mega cores and an H&E are required. The Alliance Biorepository at Ohio State does provide institutions with the dermal punch coring instruments needed to extract the cores required for this study. Please contact the Alliance Biorepository at Ohio State to order the kit.

If your institutions' pathologist requires further instruction, has questions regarding coring, or in the event there is not enough tissue to fulfill the alternative submission, please contact the Alliance Biorepository at Ohio State at (614) 293-7073 or path.calgb@osumc.edu

10.2.3.1 MANDATORY

- Paraffin embedded tumor block from the original biopsy

NOTE: Submission of pathology materials for central review is mandatory in order for the patient to be considered evaluable. Failure to submit

pathology materials may render the case unevaluable.

NOTE: The original tumor biopsy submitted at baseline will also be used for the optional laboratory studies outlined in Section 11 for those patients who have consented to participate.

10.2.3.2 From patients who answer "Yes" to "I agree to provide additional specimens for research."

- Tumor blocks from any diagnostic biopsies performed while on study.

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10.2.4 Shipping Procedures

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ECOG-ACRIN and SWOG Sites:

Access to the shipping account for shipments to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF) at MD Anderson can now be obtained by logging onto fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org.

Alliance sites will be reimbursed for shipping costs from Alliance.

Ship at ambient temperature, using a cool pack during warmer months.

10.2.4.1 Submission Schedule

- The required initial pathology materials must be submitted within one month of patient randomization.
- Additional tumor biopsies should be submitted within one month of collection.

Shipping Address:

Alliance Biorepository at Ohio State
The Ohio State University
Innovation Center
2001 Polaris Parkway, Lab #1315
Columbus, OH 43240-2000
Ph: (614) 293-7073
Fax: (614) 293-7967

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Ship pathology samples Monday-Thusday, no Friday shipments, by overnight courier.

An STS shipping manifest form must be generated and shipped with all sample submissions.

10.2.4.2 Pathology Coordinating Office: Sample Processing and Routing

- Slides will be cut from the original diagnostic tumor blocks and forwarded to Dr. David Yang for review.
- Pathology samples will be routed for laboratory studies as outlined in Sections 11.3 and 11.4.
- Blocks from patients who consented to the laboratory studies and/or banking of residuals for future studies: Four 3 mm cores will be taken from each block and placed into tissue microarrays (TMA). The regions of interest will be designated by Dr. David Yang.
- Sections/slides will be forwarded to Sequenta, Inc. for molecular MRD analysis for those cases with no bone marrow.

10.3 ECOG-ACRIN Sample Tracking System

It is **required** that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst

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Important: Any case reimbursements associated with sample submissions will not be credited if samples are not logged into STS. Additionally, please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html Please take a moment to familiarize yourself with the software prior to using the system.

A shipping manifest form must be generated and shipped with all sample submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu

10.3.1 Study Specific Notes

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A Generic Specimen Submission Form (#2981) will be required only if STS is unavailable at the time of sample submission, along with the Patient Information Form (Appendix XVII). Indicate the appropriate Lab ID # on the submission form:

- 0104 = Mayo Clinic Lymphoma Laboratory
- 0148 = Alliance Biorepositiry at Ohio State
- 0162 = CALGB Imaging Core Laboratory
- 0163 = Sequenta, Inc.

Retroactively enter all collection and shipping information when STS is available.

10.4 Banking

TMAs and residual material from the blocks/slides submitted will be retained at the Central Repository for possible use in future approved studies. Any residual blocks will be available for purposes of individual patient management on specific written request. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

11. Correlative Studies

NOTE: ECOG-ACRIN requires that all biological samples submitted be entered and tracked via the online ECOG-ACRIN Sample Tracking System. An STS shipping manifest form must be generated and shipped with the submissions. See Section 10.3.

11.1 Submission of Blood to Mayo Clinic

Blood samples should be shipped the day they are drawn. If you have any questions concerning sample collection and shipment, please contact Kim Henderson at (507) 284-3805 or Henderson.Kimberly@mayo.edu at the Mayo Clinic Lymphoma Laboratory.

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11.1.1 Sample Submission Schedule

Blood samples are being collected for Flow Cytometry for Minimal Residual Disease (MRD) to be performed by investigators at Mayo Clinic. Submit from patients who answer *"Yes"* to *"I agree to participate in the laboratory research studies that are being done as part of this clinical trial."*

Peripheral blood from ACD (yellow top tubes) should be collected at the following time points:

- Baseline (after randomization, prior to treatment)
- Post Cycle Three (3)
- Post Cycle Six (6) [End of Induction]

Blood samples are also being collected for banking for possible future research studies. Submit from patients who answer *"Yes"* to *"I agree to provide additional blood for research."*

Peripheral blood from EDTA (purple top tube) and red top tube should be collected at:

- Baseline (after randomization, prior to treatment)
- Post Cycle Three (3)
- Post Cycle Six (6) [End of Induction]

11.1.2 Sample Preparation Guidelines

Kits are available to order for the collection of the samples, and will contain the supplies and instructions for collecting, processing, and shipping the samples. To order kits contact Kim Henderson at (507) 284-3805 or Henderson.Kimberly@mayo.edu. Include the name of the contact person, phone number, and address where the kits should be shipped, ECOG-ACRIN protocol number, the number of kits needed, and if the kits need to be shipped priority overnight, otherwise kits will arrive in three to four working days.

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The following CBC information must be entered into STS with each time point: WBC and lymphocyte count.

Blood samples should be shipped the day they are drawn at room temperature (do not freeze). Samples from multiple patients can be shipped together, but must be placed in separately labeled tubes and bags.

All samples must be clearly labeled with the ECOG-ACRIN protocol number E1411, the patient's initials (last name, first name), the patient's ECOG-ACRIN sequence number (If available), date of collection, and type of sample (PB).

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- Peripheral blood: Draw 7mL of whole blood into each of three (3) ACD yellow top tubes (provided in the kit) at each time point. Ship day of collection.
- Peripheral blood: Draw 10mL of whole blood into one (1) EDTA purple top tube (provided in the kit) at each time point. Ship day of collection.
- Peripheral blood: Draw 10mL of whole blood into one (1) red top tube (provided in the kit) at each time point. Ship day of collection.

11.1.3 Shipping Procedures

Blood samples should be mailed the day they are obtained and shipped overnight to arrive during normal working hours. The laboratory is open to receive shipments Monday through Friday. Follow packing guidelines listed in the kit. If samples are sent late in the week and will arrive on the weekend, please note "Saturday Delivery" on the Federal Express form.

FRIDAY AND PRE-HOLIDAY SHIPMENTS SHOULD BE AVOIDED.

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- Place the tubes in the absorbent holder and seal in the zip lock specimen bag.
- Place the filled specimen bag in the Styrofoam container.
- Loosely pack with paper toweling.
- Place the Styrofoam container and the Sample Tracking System Shipping Manifest Form within the cardboard mailing sleeve.
- Prepare the package for shipping, applying packing tape as needed. Complete the sender portion of the return FedEx Air Bill and adhere to the exterior lid of the box. Ship samples priority overnight delivery the same day collected.
- Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

Rev. 12/13 Please e-mail Kim Henderson at Henderson.Kimberly@mayo.edu to notify the Mayo Clinic Lymphoma Laboratory when samples are being
Rev. 12/13 shipped. Indicate the ECOG-ACRIN protocol number, the FedEx tracking number, and the name and phone number of the contact person. The blood samples in prepared kits should be shipped to the following:

Rev. 12/13
Kim Henderson
Mayo Clinic Lymphoma Laboratory
613 Stabile
200 First Street Southwest
Rochester, MN 55905

An STS shipping manifest form must be generated and shipped with all sample submissions.

Blood samples from the ACD tubes will be forwarded to Dr. Curtis Hanson at Mayo Clinic for MRD analysis by flow as outlined in Section 11.5 and to Dr. Sandeep Dave at Duke University for the laboratory studies outlined in Section 11.4.

11.2 Submission of Blood and Bone Marrow to Sequenta, Inc.

Blood and bone marrow samples are being collected for Molecular Minimal Residual Disease (MRD) studies as outlined in Section 11.6. Submit from patients who answer *"Yes"* to *"I agree to participate in the laboratory research studies that are being done as part of this clinical trial."*

11.2.1 Sample Submission Schedule

Rev. 12/13 Blood and bone marrow samples should be shipped the day they are drawn. If you have any questions concerning sample collection and shipment, please contact Kim Henderson at (507) 284-3805 or Henderson.Kimberly@mayo.edu at the Mayo Clinic Lymphoma Laboratory.

Rev. 12/13 Draw 10mL of peripheral blood into one (1) EDTA (purple top tube) at the following time points:

- Baseline (prior to treatment)
- Post Cycle Three (3)
- Post Cycle Six (6) [End of Induction]
- Every Four (4) Months During the First Year of Maintenance
- Every Six (6) Months During the Second Year of Maintenance
- Twelve (12) Months After Completion of Maintenance

Rev. 12/13 Draw 3-5mL of 'redirect' bone marrow aspirate into one (1) EDTA (10 mLpurple top tube) at the following time points:

- Baseline (prior to treatment)
- Post Cycle Six (6) [End of Induction, Patients in CR Only]

11.2.2 Sample Preparation Guidelines

Kits are available to order for the collection of the samples, and will

contain the supplies and instructions for collecting, processing, and shipping the samples. Ordering instructions are outlined in Section 11.1.2.

The following CBC information must be entered into STS with each time point: WBC and lymphocyte count.

Blood and bone marrow samples should be shipped the day they are drawn at room temperature (do not freeze). Samples from multiple patients can be shipped together, but must be placed in separately labeled tubes and bags.

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All samples must be clearly labeled with the ECOG-ACRIN protocol number E1411, the patient's initials (last name, first name), the patient's ECOG-ACRIN sequence number (If available), Sequenta sequence number, date of collection, and type of sample (PB,BM).

- Peripheral blood: Draw 10mL of whole blood into one (1) EDTA purple top tube (provided in the kit) at each time point. Ship day of collection. Invert the tube eight times prior to shipment.
- Bone Marrow Aspirate: One (1) EDTA purple top tube (provided in the kit) at each time point (while 3-5mL is recommended, any amount is acceptable). Ship day of collection.

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11.2.3 Shipping Procedures

Blood and bone marrow samples should be mailed the day they are obtained and shipped overnight to arrive during normal working hours. The laboratory is open to receive shipments Monday through Friday. Follow packing guidelines listed in the kit and in Section 11.1.3.

FRIDAY AND PRE-HOLIDAY SHIPMENTS SHOULD BE AVOIDED.

Please e-mail the Sequenta ECOG-ACRIN Study Coordinator at ECOGE1411@sequentainc.com to notify the laboratory when samples are being shipped. Indicate the ECOG-ACRIN protocol number, the FedEx tracking number, and name and phone number of the contact person.

The blood and bone marrow samples in prepared kits should be shipped to the following:

Sequenta, Inc.

Attn: ECOG-ACRIN Study Coordinator
400 East Jamie Court, Suite #301
South San Francisco, CA 94080
Phone: (650) 243-3900

An STS shipping manifest form must be generated and shipped with all sample submissions.

11.3 Ki67 Proliferation Index and SOX11 Expression

We will prospectively assess two promising biomarkers that may provide important prognostic information in MCL. The proliferation signature has been demonstrated by gene expression profiling (GEP) to be of prognostic value in

MCL, independent of other clinical factors.[36] While assessment of this signature is difficult in routine practice, a global assessment of proliferation using an immunohistochemical stain for the Ki67 antigen confirms this concept. Indeed Ki67 index has been shown to add value to the mantle cell international prognostic index (MIPI) and has been assessed retrospectively in multiple large patient cohorts treated with modern therapy with consistent results.[37-40] Indeed high Ki67 predicts poor outcome in patients undergoing autologous stem cell transplantation.[41] Recently, the transcription factor SOX11 has been reported to be expressed in the majority of MCL. The function of SOX11 is poorly understood. It is expressed in embryonic neuronal progenitors and in mesenchymal cells in many developing organs and its absence appears lethal in knock out mouse experiments. It is also highly expressed in MCL nuclei, a pattern that appears relatively specific in B-cell lymphoma.[42,43] The prognostic significance of SOX11 is uncertain; however, GEP studies now suggest that lack of SOX11 is associated with favorable outcome and indolent behavior in MCL.[11]

We will assess Ki67 and SOX11 in tissue microarrays (1mm dia. cores) via immunohistochemistry using automated immunostainers as described previously.[41,45] Staining will be assessed by image analysis using the Aperio slide scanner and analysis software for nuclear staining quantitation.

11.4 miRNA Profiling

We will further assess the role of microRNAs as prognostic markers in patients with mantle cell lymphoma. MicroRNAs are 18-22 nucleotide-long RNA molecules that regulate the expression of genes. There is an increasing recognition of the role of microRNAs in malignancies.[46-48] Lymphoma is among the few malignancies known to be causally associated with microRNA deregulation[3]. MicroRNAs have also shown promise as diagnostic and prognostic biomarkers in a variety of malignancies.[46,49] Intact microRNAs can be isolated from tissues preserved using standard paraffin-embedded methods[50,51], making it easier to translate to clinical use.

We have recently elucidated the microRNA transcriptome of normal and malignant B cells[52] and identified over 200 new microRNAs. We have developed a custom microarray that comprises all the known microRNAs from every species (virus to human), as well as the 279 microRNAs that we discovered. Thus, our microarray provides a comprehensive platform for the identification of microRNA expression in lymphomas. We will assess the expression of microRNAs and their relationship to prognosis in patients with mantle cell lymphoma. Available cases will be divided into equal sized training and validation sets. Small RNAs from the biopsy tissue will be labeled and hybridized to the microarray, the images scanned, normalized and log2- transformed using methods well-established in our laboratory. We will evaluate the association of progression-free and overall survival using methods similar to those we have described previously[53]. We will develop a multivariate predictor based on microRNA expression based on the training set cases and only the optimal model will be validated using the independent test set cases.

Additional exploratory studies will be performed on the same tissue to help determine the mechanistic basis of microRNA expression and the associated target genes. Polymorphisms have been shown to be an important cause of altered microRNA expression and target interaction[54]. We will use standard

methods such as Northern Blot, real-time PCR, immunohistochemistry and sequencing for these studies to identify the role of polymorphisms on microRNA and target expression. We will also analyze the association of the identified polymorphisms with overall and progression-free survival, in conjunction with microRNA expression.

The end-result of this study would be a comprehensive identification of microRNAs that are associated with response to treatment and potential mechanistic insights into the deregulation of microRNA and its target gene expression.

This work will require the equivalent of one core biopsy and a tube of blood (ACD, yellow top tube) from patients.

These assays will be performed by Sandeep Dave, M.D. at Duke University.

11.5 6-Color Flow Cytometry for Minimal Residual Disease

This is a commercial assay that requires 6mL of ACD blood. The technique detects minimal residual disease. It has been demonstrated to be comparable to molecular techniques in CLL but has not been tested in MCL. The assay will use antibody to kappa, lambda, CD5, CD20, CD45, and CD19. The results will be read by Dr. Curtis Hanson of Mayo Hematopathology and results sent to ECOG-ACRIN where they will be merged with clinical data and compared with molecular techniques performed by Sequenta, Inc. The technique provides a quantitative result.

11.6 Molecular Minimal Residual Disease

This is an assay that detects the cancer-specific IgH rearrangement by deep sequencing. For each patient the cancer-specific IgH rearrangement can be identified through the assessment of a diagnostic sample. The diagnostic sample can be the positive lymph node (frozen or archived FFPE), bone marrow (aspirate or clot), or Peripheral Blood Mononuclear Cell (PBMC) preparation. In E1499 and E1405, circulating MCL cells were detectable in 88% of samples in the central flow cytometry laboratory (Dr. E. Paietta; unpublished data). All the IgH sequences are amplified from the diagnostic samples and the product is subjected to DNA sequencing. The cancer-specific sequence is expected to be present at high frequency (>10%) in contrast to most other sequences present at very low level (<0.1%). The cancer-specific sequence is then readily identified for each patient. Minimal residual disease in follow up samples can then be assessed by determining the level of that sequence in the sample. This is done by amplifying all the IgH sequences from the relevant samples and subjecting the product to deep sequencing (1M reads or more). The level of the cancer-specific sequence can then be determined at very high sensitivity and specificity.

11.7 Banking

Upon completion of the analysis, the residuals and/or derivatives of blood and bone marrow samples collected for the laboratory studies will be retained at an ECOG-ACRIN designated repository for possible use in ECOG-ACRIN approved future studies. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

11.8 Sample Inventory Submission Guidelines

Inventories of all samples collected, aliquoted, and used on the above mentioned laboratory studies and/or banking will be submitted electronically by secure web application to the ECOG-ACRIN Operations Office – Boston upon request by any laboratory holding and/or using any samples associated with this study.

11.9 Lab Data Transfer Guidelines

The data collected or generated on the above mentioned laboratory studies will be submitted electronically by secure web application to the ECOG-ACRIN Operations Office – Boston on a quarterly basis.

12. Electronic Data Capture

Please refer to the E1411 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

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13. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

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Appendix I

Informed Consent Template for Cancer Treatment Trials (English Language)
[Deleted in Addendum #3]

INFORMED CONSENT INTENTIONALLY REMOVED FROM PROTOCOL DOCUMENT

Appendix I was removed from the protocol document in Addendum #3 and is posted as a separate document on the ECOG website. This was removed from the protocol to comply with NCI formatting guidelines.

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Appendix II

Pathology Submission Guidelines

The following items are included in Appendix II:

1. Guidelines for Submission of Pathology Materials
   (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. List of Required Materials for E1411

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4. CALGB Pathology Submission Form (#3467)

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Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG-ACRIN Pathology Coordinating Office:

- Institutional Surgical Pathology Report
- Pathology materials (see attached List of Required Material)
- CALGB Pathology Material Submission Form (#3467)

Instructions:

1. Rev. 12/13 Place the Patient ID label provided by the ECOG-ACRIN Operations Office – Boston in Part A of the CALGB Pathology Material Submission Form (#3467).

   If a label is not available, **TYPE or PRINT** the following information in **Part A** of the form:

   Patient's name (last, first)
   Protocol number
   Protocol case number (the patient's ECOG-ACRIN sequence number; for intergroup studies, include both the ECOG-ACRIN and other group's sequence numbers)
   Patient's hospital number
   Institution
   Affiliate (if appropriate)

2. Rev. 12/13 Complete blank areas of the pathologist's instructional memo and forward it, along with the List of Required Material and the CALGB Pathology Material Submission Form (#3467), to the appropriate pathologist.

3. Rev. 12/13 The pathologist should return the required pathology samples and surgical pathology reports, along with the completed CALGB Pathology Material Submission Form (#3467) (Part B completed). If any other reports are required, they should be obtained from the appropriate department at this time.

4. Rev. 12/13 Keep a copy of the CALGB Pathology Material Submission Form (#3467) for your records. (The original should be sent to the Alliance Biorepository at Ohio State.)

5. Double-check that ALL required forms, reports and pathology samples are included in the package to the Alliance Biorepository at Ohio State. (See appropriate List of Required Material.)

   Pathology specimens submitted WILL NOT be processed by the Alliance Biorepository at Ohio State until all necessary items are received.

6. Mail pathology materials to:

   Alliance Biorepository at Ohio State
   The Ohio State University
   Department of Pathology
   Innovation Centre
   2001 Polaris Parkway
   Columbus, OH 43240
   Phone: (614) 293-7073
   Fax: (614) 293-7967
   Email: path.calgb@osumc.edu

If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the Alliance Biorepository at Ohio State by telephone (614) 293-7073 or by fax (614) 293-7697.

LIST OF REQUIRED MATERIAL

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E1411: Intergroup Randomized Phase II Four Arm Study In Patients With Previously Untreated Mantle Cell Lymphoma Of Therapy With: Arm A = Rituximab+ Bendamustine Followed By Rituximab Consolidation (RB → R); Arm B = Rituximab + Bendamustine + Bortezomib Followed By Rituximab Consolidation (RBV→ R), Arm C = Rituximab + Bendamustine Followed By Lenalidomide + Rituximab Consolidation (RB → LR) or Arm D = Rituximab + Bendamustine + Bortezomib Followed By Lenalidomide + Rituximab Consolidation (RBV → LR)

Baseline (MANDATORY)

Rev. 12/13 *1.* CALGB Pathology Material Submission Form (#3467) – Parts A & B completed. *[or appropriate pathology submission form]*

2. Institutional pathology report ***(must be included with EVERY pathology submission)***.

Rev. 8/15 3. Required Pathology Materials:

- Paraffin embedded tumor block from the original biopsy

NOTE: Submission of pathology materials for central review is mandatory in order for the patient to be considered evaluable. Failure to submit pathology materials may render the case unevaluable.

NOTE: The original tumor biopsy submitted at baseline will also be used for the optional laboratory studies for those patients who have consented to participate. Since blocks are being used for laboratory studies, in some cases the material may be depleted and, therefore, the block may not be returned.

Rev. 12/13 **NOTE:** If blocks cannot be submitted, 12 unstained slides, two or more 4mm mega cores and an H&E are required. The Alliance Biorepository at Ohio State does provide institutions with the dermal punch coring instruments needed to extract the cores required for this study. Please contact the Alliance Biorepository at Ohio State to order the kit.

If your institutions' pathologist requires further instruction, has questions regarding coring, or in the event there is not enough tissue to fulfill the alternative submission, please contact the Alliance Biorepository at Ohio State at (614) 293-7073 or path.calgb@osumc.edu

On Study Tumor Biopsies (from consenting patients)

Rev. 12/13 1. CALGB Pathology Material Submission Form (#3467) – Parts A and B completed. [or appropriate pathology submission form]

2. Institutional pathology report ***(must be included with EVERY pathology submission)***.

3. Pathology Materials:

- Tumor blocks from any diagnostic biopsies performed while on study.

ECOG-ACRIN
cancer research group
Reshaping the future of patient care

Robert L. Comis, MD, and Mitchell D. Schnall, MD, PhD
Group Co-Chairs

MEMORANDUM

TO: _____

(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
Rev. 12/13 ECOG-ACRIN Laboratory Science and Pathology Committee

DATE:

SUBJECT: *Submission of Pathology Materials for E1411:* Intergroup Randomized Phase II Four Arm Study In Patients With Previously Untreated Mantle Cell Lymphoma Of Therapy With: Arm A = Rituximab+ Bendamustine Followed By Rituximab Consolidation (RB → R); Arm B = Rituximab + Bendamustine + Bortezomib Followed By Rituximab Consolidation (RBV→ R), Arm C = Rituximab + Bendamustine Followed By Lenalidomide + Rituximab Consolidation (RB → LR) or Arm D = Rituximab + Bendamustine + Bortezomib Followed By Lenalidomide + Rituximab Consolidation (RBV → LR)

Rev. 12/13, 8/15 The patient named on the attached CALGB Pathology Material Submission Form (#3467) has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for pathology review, laboratory studies and banking for future research.

Please complete PART B of the Submission Form. Keep a copy for your records and return the completed Submission Form, the surgical pathology report(s), the slides and/or blocks and any other required material (see List of Required Material) to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the Alliance Biorepository at Ohio State.

Blocks and/or slides submitted for this study will be retained at the Central Repository for future studies. Blocks will be returned upon written request for purposes of patient management.

Please note: Since blocks are being used for laboratory studies, in some cases the material may be depleted, and, therefore, the block may not be returned.

If you have any questions regarding this request, please contact the Alliance Biorepository at Ohio State at (614) 293-7073 or by fax (614) 293-7697. The ECOG-ACRIN CRA at your institution is:

Name: _____

Address:_____

Phone: _____

Thank you.

Rev. 12/13 Form #3467

CALGB DIAGNOSTIC PATHOLOGY MATERIAL SUBMISSION FORM

Instructions: **This form is a required part of pathology submission.** Please complete and submit along with all pathology materialand corresponding pathology reports requested by the protocol. See list of required materials as specified in EACH protocol.

Tel. 614-293-7073 **Fax 614-293-7967**

PART A: To Be Completed By Data Manager/CRA

DO NOT USE INITIALS – Submit Patient's FULL Name
(The Patient has authorized the use of PHI.)

Date sample sent to CALGB _____/_____/_____ (M,D,Y)

Data Manager_____

Address _____

_____

Telephone No. ( ) _____

Fax No. ( ) _____

Email address _____

Patient's Name:

Last_____ First _____

ECOG Prot. No. _____ ECOG Patient Seq. No. _____

Participating Group Prot. No. _____ Participating Group Patient ID No._____

Group _____ Institution_____ PI_____

Step No. _____ Affiliate _____

ECOG-ACRIN Parent Prot. No. __ Seq. No._____

PART B: TO BE COMPLETED BY DATA MANAGER/CRA AND SUBMITTING PATHOLOGIST

	Status* (See Below)	Date Specimen Collected (M/D/Y)	Disease Site	Number of Slides/Vials	Specimen ID Numbers	Type of Stain	
Complete for Slides/Vials		/ /					
		/ /					
	Status* (See Below)	**Date Specimen Collected (M/D/Y)**	**Disease Site**	**Number of Blocks/Punch**	**Specimen ID Numbers**	**Fixative**	
Complete for Blocks/Punch		/ /					
		/ /					

***Status:** Please identify the clinical status of the sample.
List ***all*** that apply:

1. Original diagnostic material
2. AML/MDS diagnosis
3. Pre-protocol treatment biopsy/tissue
4. Post-protocol treatment biopsy/tissue
5. Post-surgery biopsy/tissue
6. Relapse/recurrence
7. Remission/response
8. Other, specify: _____

Submitting Pathologist _____

Telephone No. ( ) _____

Address _____

_____

Did the patient consent to participate in the storage of samples for future research? Yes No

MATERIAL RETURN (All materials will be retained by the ECOG PCO unless return is requested here.)

Does the submitting institution's policy require the return of any submitted material (blocks, H&E slides, etc.)? Yes No

If so, please indicate which materials must be returned _____

All materials will be returned to the **submitting pathologist** unless an alternate address is indicated here _____

If materials were not able to be submitted for this protocol and its correlative studies, please circle the reason for non-submission.

Federal/State Regulations ____ Hospital/Institutional Policy _____ Insufficient Tissue _____ Other_____ (Specify) _____

Pathologist or Investigator's Signature _____

Investigator: Keep a copy for your files and submit original form to the destination specified in protocol. 2/05

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Appendix III

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Rev. 4/14

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we will improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and the ECOG-ACRIN Cancer Research Group" throughout, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

Rev. 12/13

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Appendix IV

Patient Pill Calendar

Pill Calendar Directions

1. Take your scheduled dose of each pill.
2. If you forget, the missed pills will not be taken later.
3. Please bring the empty bottle or any leftover tablets and your pill calendar to your next clinic visit.

Patient Pill Calendar for Lenalidomide

This is a calendar on which you are to record the time and number of tablets you take each day. You should take your scheduled dose of each pill. **Note the times and the number of tablets that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed pill calendar to your doctor's visits.

DAY	Date			Time pills taken		Number of pills taken		Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
	Month	Day	Year	AM	PM	AM	PM	
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
16								
17								
18								
19								
20								
21								
22	No lenalidomide dose on this day							
23	No lenalidomide dose on this day							
24	No lenalidomide dose on this day							
25	No lenalidomide dose on this day							
26	No lenalidomide dose on this day							
27	No lenalidomide dose on this day							
28	No lenalidomide dose on this day							

Patient. Signature: _____ Date: _____

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Appendix V

ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

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Appendix VI

Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

All study participants must be registered into the mandatory RMES® program, and be willing and able to comply with the requirements of REMS®.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Counseling

For a female of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

The investigator must ensure that for females of childbearing potential:

- Complies with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females NOT of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

Traces of lenalidomide have been found in semen. Male patients taking lenalidomide must meet the following conditions (i.e., all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) dose interruptions; and 4) for at least 28 days after study treatment discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting study drug

Female Patients:

FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10 to 14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The patient may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

Male Patients:

Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Female Patients:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a study patient, study drug must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male Patients:

- Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to lenalidomide must be conducted at a minimum of every 28 days.

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- If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

Additional precautions

- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Female patients should not donate blood during therapy and for at least 28 days following discontinuation of study drug.
- Male patients should not donate blood, semen or sperm during therapy or for at least 28 days following discontinuation of study drug.

- Only enough study drug for one cycle of therapy may be dispensed with each cycle of therapy.

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Appendix VII

Mantle Cell Lymphoma International Prognostic Index (MIPI)

Rev. 2/14

A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma bloodjournal.hematologylibrary.org. See Section 4.1.5.1 for MIPI Calculator link.

Using data of 455 advanced stage MCL patients treated within 3 clinical trials, we examined the prognostic relevance of IPI and FLIPI and derived a new prognostic index (MCL international prognostic index, MIPI) of overall survival (OS).

According to the MIPI, patients were classified into

- **low risk** (44% of patients, median OS not reached),
- **intermediate risk** (35%, 51 months), and
- **high risk groups** (21%, 29 months),

based on the 4 independent prognostic factors:

- **age**,
- **performance** status,
- **lactate dehydrogenase** (LDH), and
- **leukocyte** count.
- Cell proliferation (Ki-67) was exploratively analyzed as an important biologic marker and showed strong additional prognostic relevance.

The MIPI is the first prognostic index particularly suited for MCL patients and may serve as an important tool to facilitate risk-adapted treatment decisions in patients with advanced stage MCL.

Reference:

(Blood. 2008;111: 558-565)
Using data of 455 advanced stage MCL patients treated within 3 clinical trials, we examined the prognostic relevance of IPI and FLIPI and derived a new prognostic index (MCL international prognostic index, MIPI) of overall survival (OS). Statistical methods included Kaplan-Meier estimates and the log-rank test for evaluating IPI and FLIPI and multiple Cox regression for developing the MIPI. IPI and FLIPI showed poor separation of survival curves. According to the MIPI, patients were classified into low risk (44% of patients, median OS not reached), intermediate risk (35%, 51 months), and high risk groups (21%, 29 months), based on the 4 independent prognostic factors: age, performance status, lactate dehydrogenase (LDH), and leukocyte count. Cell proliferation (Ki-67) was exploratively analyzed as an important biologic marker and showed strong additional prognostic relevance. The MIPI is the first prognostic index particularly suited for MCL patients and may serve as an important tool to facilitate risk-adapted treatment decisions in patients with advanced stage MCL

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Appendix VIII

Modified Ann Arbor Staging System

Stage I	Involvement of a single lymph node region.
Stage II	Involvement of 2 or more lymph node regions on the same side of the diaphragm.
Stage III	Involvement of lymph node regions on both sides of the diaphragm.
Stage IV	Diffuse or disseminated involvement of one or more extra lymphatic organs or tissues, with or without associated lymph node involvement.

The subscript E (e.g., IIE or IIIE) is used to denote involvement of an extra lymphatic site primarily or by direct extension, rather than hematogenous spread, as in the case of a mediastinal mass extending to involve the lung.

The presence of (B) or absence of (A) fever, night sweats, and/or unexplained loss of 10% or more body weight in the 6 months prior to admission are denoted by the corresponding suffix letters B and A.

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Appendix IX

FDG-PET Imaging, Interpretation, PET and CT Data Submission, and Semi-quantitative Analysis

PET/CT Imaging Timelines

The following PET/CT and IC contrast CT scans will be collected digitally for archival:

- The baseline PET/CT scan and the diagnostic CT scan must be obtained ≤ 28 days prior to registration. In the case of a patient who already had a baseline FDG-PET/CT scan at an outside facility, the quality of the PET/CT scan must be approved by the CALGB Imaging Core Lab before the enrollment of the patient to E1411. Furthermore, these patients will not be included in the quantitative evaluations. The FDG PET/CT study can be performed by combining the intravenous contrast enhanced diagnostic CT study into one PET/CT study.
- The interim FDG-PET/CT scan (if and when available) after 3 cycles of induction therapy will be obtained at least 12 days after the administration of the 3rd cycle of induction therapy (post 3 cycles). If the baseline PET/CT study is performed using a protocol combining the intravenous contrast enhanced diagnostic CT into one study then all subsequent PET/CT studies should be performed following the same methodology to avoid variability in SUVmax among FDG PET/CT studies within the same patient.
- The post completion of induction therapy FDG-PET/CT scan and diagnostic CT scan will be obtained at least 3 weeks after the administration of the last dose of induction therapy (post 6 cycles). If the baseline PET/CT study is performed using a protocol combining the intravenous contrast enhanced diagnostic CT into one study then all subsequent PET/CT studies should be performed following the same methodology to avoid variability in SUVmax among FDG PET/CT studies within the same patient.

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- The interim consolidation FDG-PET/CT scan (if PET (+) at end of treatment) should be obtained six (6) months into consolidation. If the baseline PET/CT study is performed using a protocol combining the intravenous contrast enhanced diagnostic CT into one study then all subsequent PET/CT studies should be performed following the same methodology to avoid variability in SUVmax among FDG PET/CT studies within the same patient.

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- The final FDG-PET/CT scan should be obtained at the completion of consolidation. If the baseline PET/CT study is performed using a protocol combining the intravenous contrast enhanced diagnostic CT into one study then all subsequent PET/CT studies should be performed following the same methodology to avoid variability in SUVmax among FDG PET/CT studies within the same patient.
    - All interim (when available) and post-therapy PET/CT and IV contrast CT scans should be performed on the same scanner with the same specifications as those performed at baseline. Ideally, the IV contrast CT scan should be done on the same

day following the PET/CT scan. Alternatively, if the baseline FDG PET/CT was done with a protocol combining the IV contrast CT into the FDG PET/CT protocol (namely, FDG PET/CT is performed with IV contrast on board with a diagnostic CT), then the interim PET/CT study should be done using the same protocol. However, if the IV contrast CT is obtained on a separate day, the time difference between PET/CT and IV contrast CT should not exceed 15 days at baseline and should not exceed 7 days after any cycle of therapy. In the case of a patient who already had a baseline FDG-PET/CT scan at an outside facility, the quality of the PET/CT scan must be approved by the CALGB Imaging Core Lab before the enrollment of the patient to E1411. Furthermore, these patients will not be included in the quantitative evaluations.

- For reproducible and accurate results, post-therapy PET/CT scans should be acquired using the same FDG uptake time (post-injection interval) as the pre-therapy scan. The difference in waiting period after injection of FDG between the baseline and interim (when available) or post-therapy PET/CT scans should not exceed 10 minutes for maintaining consistency and ensuring accuracy for quantitative studies.
- Patient CT scans should follow institutional standards for oral and IV contrast. Scans of the chest, abdomen, and pelvis should be obtained at all time points, and scans of the neck should be obtained if it is deemed involved at baseline.

PET/CT Data Acquisition

All data acquisitions and reconstructions will be performed on a PET/CT system. A phantom study will be performed to standardize all PET/CT systems prior to the initiation of the protocol.

- Prior to FDG Injection and During Uptake Period

  Patients must fast for at least four hours before the PET/CT scan. Oral hydration is strongly encouraged prior to and during injection of 18F-FDG (250-500mL water can be given PO during the uptake period) and during the uptake period after administration of 18F-FDG. IV furosemide (10 mg) may be administered (but is not mandatory) to increase urinary elimination of the tracer and minimize image artifacts caused by urinary stasis in the abdomen and pelvis. Intravenous fluids containing dextrose or parenteral feeding should be withheld for at least 6 hours prior to the injection of 18F-FDG. No steroid administration is allowed for at least 7 days prior to FDG-PET imaging. Active exercise should be discouraged for at least 24 hours prior to the study. Muscle stress, tension, chewing, and movement during the uptake period should be minimized to decrease muscle uptake. Patients should not speak during the injection and uptake period. Interviews with the patient should be withheld until after completion of the imaging study.

  The blood glucose level should be checked before the 18F-FDG injection. Blood sugar (measured by glucometer) must be less than 200 mg/dL at the time of the FDG-PET/CT study. If the blood glucose level is greater than 200 mg/dL, the FDG-PET/CT imaging should be rescheduled. If the blood glucose level still exceeds 200 mg/dL on the following scheduled day for PET scanning, the patient will not be included in the trial. Insulin administration immediately before the PET/CT study to reduce the glucose levels is not allowed. Patients with diabetes should continue to adhere to their oral agents or insulin routines. These medications should not be administered near the 18F-FDG injection time. In insulin-dependent patients, insulin should be administered at least 5 hours prior to the 18F-FDG injection. Patients with diabetes who are on diabetic medication should take their medication 4-5 hours prior to the test. If blood sugar

exceeds 150 mg/dL (but less than 200 mg/dL), a note should be made in on the case report form.

Metallic objects should be removed from the patients whenever possible. Patients should be kept in a warm waiting room prior to 18F-FDG injection to avoid brown adipose tissue uptake. In anxious and claustrophobic patients, administration of oral diazepam (0.06-0.10 mg/kg) is recommended 30-40 minutes prior to the initiation of the imaging study.

Weight (kg), height (cm), blood glucose (mg/dL), and the date and time of chemotherapy and colony stimulating administration (e.g., GCSF, GMCSF) will be recorded prior to the injection of 18F-FDG.

5-20 mCi of 18F-FDG will be administered (depending on the PET/CT scanner and the manufacturer's recommendations) IV, depending on the manufacturer's recommendation. A 10-20mL saline flush is recommended in reducing the venous retention of 18F-FDG. The patient must wait for at least 60 minutes prior to the initiation of the PET/CT acquisition for all PET/CT scans (both pre-and post-therapy scans). The wait period should be kept within a maximum of **10 minutes** among patients. The wait period must not exceed 80 minutes at baseline. **It is NOT acceptable to start imaging with wait periods of less than 60 minutes and longer than 80 minutes for both pre- and post-therapy PET/CT scans.** The time difference between baseline and other PET studies should **not** be > 10 minutes. A time difference of > 15 minutes between PET/CT studies is **NOT** acceptable.

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The imaging will start after voiding the bladder. 150-200mL of water must be given to the patient immediately prior to the study acquisition before they are positioned on the table to distend stomach and avoid physiologic stomach uptake.

PET/CT Image Acquisition

Patients will be positioned on the table in a headfirst, supine position with arms elevated above the head to reduce beam-hardening artifacts at the level of the liver. A separate head and neck imaging will be pursued for those whose primary disease site is in the neck with the arms positioned along the side. The use of oral contrast is at the discretion of each facility. However, IV-contrast dedicated CT acquisition should follow PET imaging with non-contrast low-dose CT to avoid variations in FDG uptake in the blood pool and the tumor that is caused by the IV contrast agent. The low dose CT associated with PET should be acquired using a current of not less than 80 mA/second. Nonetheless, if the baseline PET/CT study is performed using a protocol combining the intravenous contrast enhanced diagnostic CT into one study then all subsequent PET/CT studies should be performed following the same methodology to avoid variabilities in SUVmax among FDG PET/CT studies within the same patient.

It is critical that all post-therapy PET/CT scans be performed in an identical way to the baseline scan with the same scanner, same scanning direction (skull to thighs or thighs to skull) and consistent arm positioning.

For PET imaging, six to seven contiguous volumes will be chosen, depending on the patient's height, to ensure data acquisition of the entire region of interest (ROI), the level of the skull base to the 1/3 proximal femurs. The time/bed position should be in accordance with the manufacturer's recommendations for optimal imaging. Adjacent fields of view should share overlapping slices.

PET/CT Image Processing

Follow the manufacturer's recommendation for image reconstruction. The emission data will be corrected for scatter, random coincidence events, and system dead-time using provided software. An iterative reconstruction (ordered subsets expectation maximization) and CT-based attenuation correction will be used for the PET images. Reconstructions should be archived both with and without attenuation correction to resolve issues arising from potential artifacts generated by the CT-based attenuation correction procedure.

Evaluation of PET/CT Data

All images will be read centrally by the CALGB Imaging Core Laboratory.

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To ensure the highest standards and consistency between different centers, all FDG-PET scans must be submitted to the CALGB Imaging Core Laboratory at Ohio State University for centralized review. Response determinations must be based on the centralized review of the FDG-PET scan and NOT on scan assessments by local physicians.

Centralized review will be performed by a member of a team of PET/CT readers. There will be an adjudicator from the same pool of reviewers in the case of disagreement. There will be one reviewer, Dr. Nathan Hall, who will provide back-up PET/CT reviewer services within the CALGB Imaging Core Laboratory. The CALGB Imaging Core Laboratory will transmit the scans to the expert reviewers for response determination and then will transmit the results to the CALGB Statistical Center.

Determination of FDG-PET positivity or negativity will be performed using a 5-point scoring system on guidelines established by an international PET harmonization conference convened in London in May 2007 (See Appendix X). According to these guidelines, scans will be judged to be positive if lesions are more hypermetabolic than the liver by visual, qualitative inspection. Borderline metabolism in a lesion will be considered negative in concordance with the policies of Gallamini and Hutchings whose studies established the value of early interim FDG-PET imaging (Bernard et al 2001, Watanabe et al 2010, Tateishi et al 2011).

Objectives/Endpoint: Definition of Response by Metabolic Criteria

The primary endpoints are OR, CR, and PFS in PET-6 positive and PET-6 negative groups (at the end of 6 cycles of induction therapy) in both the R-B-V and R-B arms of induction therapy, using London criteria provided in Appendix X.

Negative PET Scan (Metabolic Responders)

Upon qualitative evaluation, tumor FDG uptake that is less than or equal to the liver in target or non-target tumors, regardless of their location, the absence of new lesions that are deemed to be tumor, and the absence of non-target tumors will be considered negative for the presence of residual lymphoma (Appendix X).

Positive PET Scan

Upon qualitative evaluation, diffuse or focal uptake exceeding that seen in the liver in target or non-target tumors, regardless of their location, will be considered positive for residual tumor.

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Semi-quantitative Analysis

In patients with multiple tumor sites, the six sites with the highest uptake will be designated as the target sites. For these lesions, SUV measurements and metabolic volumes will be determined at baseline, after cycle 3 (when available), at completion of induction therapy (post 6 cycles), as outlined below.

At baseline, a 3D volume of interest (VOI) will be taken over the tumor on axial, sagittal, and coronal multi-planar reformatting (MPR) views that visually show the most prominent uptake. Maximum SUV body weight (SUVbw), will be obtained over the lesion.

Using receiver operator curves (ROC), most optimal cutoff for absolute decrease in metabolic volumes and maximum SUVbw, absolute uptake in the tumor/s and relative uptake in tumor/s versus various reference anatomic sites (liver, mediastinal blood pool, and background), as well as various cutoffs for post-therapy maximum SUVbw metabolic volumes, will be determined and compared after cycle 3 of induction and following cycle 6 of induction (for PET negative patients).

In patients with multiple tumor sites, the six sites correlating with the PET target lesions will be designated as the target sites. In each lymph node region the lesions with the highest uptake will be chosen. If there is any lesion that demonstrates uptake after therapy other than the designated target lesions, they will be non-target lesions and will be evaluated in the same fashion as target lesions. For all designated lesions, volumetric vs. 2 dimensional (2-D) measurement changes between baseline and after cycle 3 of induction and following cycle 6 of induction therapy will be determined from dedicated CT scans. Using receiver operator curves (ROC), the most optimal cutoff for absolute decrease and percent decrease will be determined. A combinatorial analysis will be performed incorporating the changes from PET data and dedicated CT data to determine if this approach increases the predictive value of both tests combined compared to each test alone.

Qualitative and semi quantitative FDG-PET findings/changes, CT size changes, and combinatorial analyses (PET + dedicated CT data) will be compared with molecular parameters, and conventional parameters, including IPS in the prediction of response and PFS.

Post-Induction Therapy

At any point after therapy, the decision for biopsy of any lesion is at the discretion of the treating physician. After completion of induction treatment, during consolidation therapy, if any PET/CT data are available during or after completion of consolidation phase of therapy, central evaluation of PET response and PET-based prediction of survival will also be considered using the same objectives and evaluation strategy designed for the induction phase of the protocol.

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Appendix X

Deauville Criteria

Negative Scan

- Score 1 no uptake
- Score 2 uptake ≤ mediastinum
- Score 3 update > mediastinum and ≤ liver

Positive Scan

- Score 4 moderately ↑ > liver
- Score 5 markedly ↑ uptake > > liver

Score X:

New areas of update unlikely to be related to lymphoma.

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Appendix XI

[Deleted in Addendum #2]

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Appendix XII

E1411 Imaging Site Personnel Form

Responsible CRA Contact Complete Address E-mail Phone Number Fax Number	**Radiology Department Contact** Complete Address E-mail Phone Number Fax Number

Please provide the information requested above. Provide the middle initial for individuals who commonly use them. Also, please add or correct the degree/title as necessary. This information will be retained by the CALGB Imaging Core Laboratory.

Once completed, you may send this form to:

CALGB Imaging Core Laboratory
Attn: E1411
Wright Center of Innovation
The Ohio State University
395 West 12th Avenue, Room 414
Columbus, OH 43210
Fax: (614) 293-9275

Call the CALGB Imaging Core Laboratory at (614) 293-9151 with any questions. Thank you for your assistance.

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Appendix XIII

RevAssist for Study Participants Clinical Trial Prescription Form

Print Form

RevAssist® for Study Participants
Clinical Trial Prescription Form

REVLIMID® (lenalidomide) Patient Prescription Form for Study Participants

Today's Date: ____/____/____ (mm dd yyyy)

Date Rx Needed: ____/____/____ (mm dd yyyy)

Patient Last Name (Print): _____

Patient First Name (Print): _____

Social Security Number: _____

Home Phone Number: ( ) _____

Other Phone Number: ( ) _____

Home Address: _____

_____

City: _____ State: _____ Zip: _____

Shipping Address if Different from Home Address: _____

_____

City: _____ State: _____ Zip: _____

Date of Birth: ____/____/____ (mm dd yyyy)

Language Preference:
English ☐ Spanish ☐ Other: _____

Best Time to Call Patient:

AM _____ PM _____

Prescriber Name (Print): _____

Prescriber Phone Number: ( ) _____ Ext. _____

Physician State License Number: _____

Physician DEA Number: _____

Fax Number: ( ) _____

Prescriber Address: _____

_____

City: _____ State: _____ Zip: _____

Office Contact: _____

Office Contact Phone Number: ( ) _____ ext. _____

Patient Type From Patient Physician Agreement Form
(Check One)

- ☐ Adult Female - NOT of Childbearing Potential
- ☐ Adult Female - Childbearing Potential
- ☐ Adult Male
- ☐ Female Child - NOT of Childbearing Potential
- ☐ Female Child - Childbearing Potential
- ☐ Male Child

TAPE PRESCRIPTION HERE PRIOR TO FAXING
OR COMPLETE THE FOLLOWING:

REVLIMID®

- ☐ 5 mg capsule -- Quantity: _____
- ☐ 10 mg capsule -- Quantity: _____
- ☐ 15 mg capsule -- Quantity: _____
- ☐ 25 mg capsule -- Quantity: _____

Directions:

_____

_____

NO REFILLS ALLOWED (Maximum Quantity = 28 days)

Prescriber Signature: _____

Date: ____/____/____ (mm dd yyyy)

Authorization # _____
(To be filled in by healthcare provider)

Pharmacy Confirmation # _____
(To be filled in by pharmacy)

Protocol Information

Protocol #: RV -NHL-ECOG-0491

ECOG Ref Number: RV-E2804

Patient Study ID: _____

FAX the Prescription Form to:

Biologics, Inc.

Clinical Trial Services

FAX Number: 919-256-0794

Phone Number: 800-693-4906

Attn: Clinical Trial Project Manager

For further information on Revlimid®, please refer to the full prescribing information.

August 24, 2007, Revised: 8/09

IMPORTANT INFORMATION ABOUT RevAssist®

- To avoid fetal exposure REVLIMID®(lenalidomide) is only available under a special restricted distribution program called RevAssist®
- Only prescribers registered with RevAssist® can prescribe REVLIMID® (lenalidomide)
- Only RevAssist® contract pharmacies can dispense REVLIMID® (lenalidomide)
- In order to receive REVLIMID® (lenalidomide), patients must enroll in RevAssist® and agree to comply with the requirements of the RevAssist® program
- Information about REVLIM®(lenalidomide) and the RevAssist® program can be obtained by calling the Celgene Customer Care Center toll-free at 1-888-423-5436, or at www. REVLIMID.com

How to Fill a REVLIMID® (lenalidomide) Prescription

1. Healthcare provider (HCP) instructs patient to complete patient survey
2. HCP completes survey
3. HCP completes patient prescription form
4. HCP obtains RevAssist® authorization number
5. HCP provides authorization number on patient prescription form
6. HCP faxes form, including prescription
7. HCP advises patient that a representative from a RevAssist® contract pharmacy will contact them
8. RevAssist® contract pharmacy conducts patient education
9. RevAssist® contract pharmacy calls for confirmation number
10. RevAssist® contract pharmacy ships REVLIMID® to patient with the FDA-approved MEDICATION GUIDE

August 24, 2007

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Appendix XIV

E1411 Lenalidomide Information Sheet

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Lenalidomide Information Sheet before you start taking lenalidomide and each time you get a new supply, since there may be new information. This Lenalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about lenalidomide?

1. Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby. Lenalidomide is similar to the medicine thalidomide. It is known thalidomide causes life-threatening birth defects. Lenalidomide has not been tested in pregnant women but may also cause birth defects.

   If you are a female who is able to become pregnant:

   - Do not take lenalidomide if you are pregnant or plan to become pregnant
     - for 28 days before starting lenalidomide
     - while taking lenalidomide
     - during dose interruptions of lenalidomide
     - for 28 days after stopping lenalidomide
   - Stop taking lenalidomide if you become pregnant during lenalidomide treatment
   - Do not breastfeed while taking lenalidomide
   - You must have pregnancy testing done at the following times:
     - within 10 – 14 days and again 24 hours prior to the first dose of lenalidomide
     - weekly for the first 28 days
     - every 28 days after the first month or every 14 days if you have irregular menstrual periods
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of lenalidomide (14 and 28 days after the last dose if menstrual periods are irregular)
   - You must practice complete abstinence or use two reliable, separate forms of effective birth control at the same time:
     - for 28 days before starting lenalidomide
     - while taking lenalidomide
     - during dose interruptions of lenalidomide
     - and for 28 days after stopping Lenalidomide

- Study doctors and healthcare providers are instructed to report all cases of pregnancy

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If you are a male**:**

It is not known if lenalidomide passes into semen.

- Male patients, including those who have had a vasectomy, must use a latex condom during sexual intercourse with a pregnant female or a female that can become pregnant:
  - While you are taking lenalidomide
  - for 28 days after you stop taking lenalidomide
  - Male patients should not donate sperm or semen while taking lenalidomide and for 28 days after stopping lenalidomide.

2. Lenalidomide may cause a reduction in the number of white blood cells and platelets**.** This can lead to increased risk of infection and bleeding. You may need a blood transfusion or certain medicines if your blood counts drop too low. You will have blood tests done as part of the clinical research trial in which you are participating. This is discussed in the informed consent document.

3. Lenalidomide may cause an increased chance for blood clots in the veins and in the lungs**.** Call your study doctor or get emergency medical care right away if you get the following signs or symptoms:

- shortness of breath
- chest pain
- arm or leg swelling

4. Lenalidomide restrictions in sharing lenalidomide and donating blood:

- Do not share lenalidomide with other people
- Do not give blood while you take lenalidomide and for 28 days after stopping lenalidomide
- You will get no more than a 28-day supply of lenalidomide at one time

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

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Appendix XV

E1411 Bortezomib Drug Request Form

Section I (To be completed by Site)

All shaded areas must be completed before forwarding the drug request to UVI, Inc.

ECOG-ACRIN Protocol Number: **E1411**	Millennium Protocol Number:
Delivery Address **Institution Name:** **CTEP ID:** **Attention To:** **Street Address:** **City, State, Zip Code:**	**Shipment Must Reach Destination By:** **(MM/DD/YY)-** ***Deliveries are not made on Mondays, weekends or holidays)***
Pharmacy Contact Name:	**Pharmacy Contact Phone:**
Pharmacy Contact Fax:	**Pharmacy Contact E Mail:**
Principal Investigator Name: **Principal Investigator Address:**	**PATIENT SEQUENCE NUMBER:** **ARM RANDOMIZED TO:**

STUDY DRUG:	**BORTEZOMIB**	
BORTEZOMIB QUANTITY: **(Quantities are 4 Vials Per Carton)**	**SHIPMENT #** **See below or Section 8.3.7 for Shipment Time Points** **(Place check mark below)**	**SHIPMENT TIME POINT**
		#1, Cycles 1-3
		#2, Cycles 4-6

Drug is being provided at no charge. Site may not submit any claims or receive any reimbursement for any source (whether public or private) for Drug and may not be returned to Millennium (or its distributor) for a refund or credit. Drug must be used solely pursuant to the Protocol. All other uses are strictly prohibited.

By: _____
(Signature//Title)

Name (Print): _____

PLEASE EMAIL THIS DRUG REQUEST AS AN ATTACHMENT TO mdubois@uintavision.com		
Section II (To be completed by UVI, Inc)		
UVI, Inc. Approval: **Confirm Patient on Arm B or D:**		
UVI Personnel Name:	**Signature:**	**Date:**

Section I (*To be completed by Site*)

Instruction – How to Return Commercial Velcade for Investigational Use Only :

1. Complete form below and fax to # **1-866-422-4797** for Millennium approval
2. Once form is received, you will receive a Return Authorization number and call tag for free pick up of the VELCADE to be returned, as well as instructions on preparing your package for pick up.
3. Upon pick up of your package, please notify your CRA/M that the Return Request has been completed.

NOTE: Please ensure that the VELCADE vials are adequately protected when packaging to prevent breakage.

If you have any questions, please contact Barbara Franklin at phone #: 617-551-8985 or franklin@mpi.com.

RETURN PICK UP ADDRESS (*Address the VELCADE will be picked up from):*	**TOTAL Amount of VELCADE Vials to Be Returned:** **_____vials**
Contact Name:	**LOT NUMBER(s):**
Phone:	
Fax:	
Email Address:	**Reason for Return:**
Principal Investigator Name:	**Millennium Protocol Number:**
Sub-Investigator Name (*if applicable*):	

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Appendix XVI

E1411 PET/CT Adjunctive Data Sheet

ECOG-ACRIN1411 protocol requires PET scans to start at **[60-80] min** post FDG injection. This exact same wait period of uptake must be used consistently for follow-ups with **no more than 10 min difference from the baseline**, and the wait period should be kept within **a maximum of 10 minutes difference among patients**.

1. ECOG-ACRIN Patient ID: _____ Patient Initials: _____
2. Institution/Affiliate: _____

   ECOG-ACRIN Institution ID: _____
3. Date of PET/CT Scan (MM/DD/YYYY): _____/_____/_____

   Time point of the study (Mark the time period on the left side and provide required date on the right side):
   - __ Baseline (**≤ 28 days** before randomization)
     Date of Registration: _____/_____/_____
   - __ Interim (> **C3D12** of induction administration)
     Date of C3D1: _____/_____/_____
   - __ Final (> **3wks** after admin of last induction dose)
     Date of last dose of induction: _____/_____/_____
   - Interim (> **C6** of consolidation administration) Rev. 12/13
     Date of C6D1: _____/_____/_____
   - __ Interim (> **C12** of consolidation administration) Rev. 12/13
     Date of C12D1: _____/_____/_____
   - Final (> **3wks** after admin of last consolidation dose) Rev. 12/13
     Date of last dose of consolidation: _____/_____/_____
4. Patient had been fasting for ____**hours;** Patient blood glucose level was _____ **mg/dL** or ____ **mmol/L**
5. Patient weight prior to dosing _____**kg** or _____**lbs;** Patient height ____ **cm** or ____**ft** ____ **in**.

6. Location of injection side (Circle one):

   Right / **Left** Antecubital **Right** / **Left** Wrist **Other**, specify: _____

7. Effective FDG Dose injected: ____ **mCi** or ____ **MBq** at the Time of Injection: ____**hh**: _____**mm**

   Pre-injection FDG-Syringe Dose: ____ **mCi** or ____ **MBq** at the Time of Pre-Calibration: ____**hh**: _____**mm**

   Post-injection Residual Dose assay: ____ **mCi** or ____ **MBq** at the Time of Syringe Empty: ____**hh**:____**mm**

8. PET scan started at _____ minutes post FDG injection.

9. CT of PET/CT for PET Attenuation Correction: **kVp** _____ **mA/mAs**_____

   Additional diagnostic CT was performed? **Yes** / **No**

10. Was Oral contrast used during CT scan? **Yes** / **No**

    Was IV contrast used during CT scan? **Yes** / **No**

11. In the past 4 weeks, has the patient received colony stimulating factors?

    No / **Yes** (then mark all that apply):

    Filgrastim (Neupogen®) ___ Epoetin (Aranesp®, Epogen®, Procrit®) ___

    Pegfilgrastim(Neulasta®)___ Other _____

12. **Model** of the PET/CT scanner used for this study: _____

    Same as the baseline? **Yes / No / N/A**

13. Was the PET imaging completed according to protocol?

    Yes / **No** If not, please explain:

    _____ _____

14. Site treating physician:_____ E-Mail: _____ Telephone: _____

15. Site Primary Contact:_____ E-Mail: _____ Telephone: _____

16. Completed by: _____ Date of the form completed: _____/_____/_____

Reminder - This Form should be submitted to the CALGB Imaging Core Lab via:

Email: ECOG1411@imagingcorelab.com

Fax: 614-293-9275

FTP: Contact Imaging Core Lab at the trial email

Mail: Imaging Core Lab, The Ohio State University, Rm#414, 395 W 12th Ave, Columbus, OH 43210

ICL Contact Telephone: 614-293-2929

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Intergroup Randomized Phase II Four Arm Study In Patients With Previously Untreated Mantle Cell Lymphoma Of Therapy With: Arm A = Rituximab + Bendamustine Followed By Rituximab Consolidation (Rb → R); Arm B = Rituximab + Bendamustine + Bortezomib Followed By Rituximab Consolidation (RBV → R), Arm C = Rituximab + Bendamustine Followed By Lenalidomide + Rituximab Consolidation (RB → LR) or Arm D = Rituximab + Bendamustine + Bortezomib Followed By Lenalidomide + Rituximab Consolidation (RBV → LR)

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Appendix XVII

Blood Collection Kit Mayo Clinic Lymphoma Laboratory Specimen Checklist and Shipping Instructions

**** PLEASE AVOID DRAWING OR SENDING SPECIMENS ON FRIDAYS AND HOLIDAYS****

Kit Contents:

- Small Styrofoam box and cardboard mailing sleeve
- Patient Information Form
- FedEx Air bill with pre-printed return address
- 7ml ACD (yellow top) collection tubes
- 10ml EDTA (purple top) collection tube
- 10ml Red Top collection tube
- Absorbent tube holder
- Zip lock specimen bag

Packing and Shipping Instructions:

1. Collect the following specimens:
   1 Peripheral blood – Draw:
   - 21ml into three (3) ACD tubes
   - 10ml in one (1) EDTA tube
   - 10ml in one (1) Red Top tube
2. All specimens are to be clearly labeled with the protocol number E1411, the patient's initials (last, first, middle), ECOG-ACRIN sequence number (if available) and date of collection.
3. Place the tubes in the absorbent holder and seal in the zip lock specimen bag.
4. Place the filled specimen bag in the Styrofoam container.
5. Loosely pack with paper toweling.
6. Place the Styrofoam container and the Sample Tracking System manifest form within the cardboard mailing sleeve.
7. Prepare the package for shipping, applying packing tape as needed. Complete the sender portion of the return FedEx Air bill and adhere to the exterior lid of the box. Ship specimens via priority overnight delivery (next day delivery by 10am) the same day collected.
8. Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

IMPORTANT: If these are baseline sample submissions being shipped prior to patient enrollment please call Kim Henderson at (507) 284-3805 at the Mayo Clinic

Lymphoma Laboratory for a "Sequenta Sequence Number". This number will be the only patient identifier on the paperwork and baseline sample submissions to Sequenta.

Please e-mail Kim Henderson at Henderson.Kimberly@mayo.edu to notify the laboratory when samples are being shipped. Indicate the ECOG-ACRIN protocol number, the FedEx tracking number, name and phone number of the contact person. The blood samples in prepared kits should be shipped to the following:

Kim Henderson
Mayo Clinic Lymphoma Laboratory
613 Stabile
200 First Street Southwest
Rochester, MN 55905

Patient Information Form

It is required that samples submitted from patients participating in E1411 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (see Section 10.3). This form is used only in the event that the STS is inaccessible and then the shipments are to be logged in retroactively, indicating the actual dates of collection and shipment.

Specimen Date: / /

Institution/Affiliate: _____

Physician: _____

Patient Initials (last name, first name): _____

Hospital ID or Social Security #: _____

ECOG-ACRIN Protocol #: E1411

ECOG-ACRIN Patient Sequence #: _____

Contact Person: _____

Institution: _____

Address: _____

City State Zip

Phone #: _____

FAX #: _____

Please indicate which samples are being shipped at this time:

1. Baseline
2. Post Cycle Three
3. Post Cycle Six (End of Induction)

Any questions concerning these samples or to obtain blood collection kits for the E1411 study, please contact:

Kim Henderson
Mayo Clinic Lymphoma Laboratory
(507) 284-3805
Henderson.Kimberly@mayo.edu

Affiliates who anticipate participating in this study should please call in advance for kits.

Intergroup Randomized Phase II Four Arm Study In Patients With Previously Untreated Mantle Cell Lymphoma Of Therapy With: Arm A = Rituximab + Bendamustine Followed By Rituximab Consolidation (Rb → R); Arm B = Rituximab + Bendamustine + Bortezomib Followed By Rituximab Consolidation (RBV → R), Arm C = Rituximab + Bendamustine Followed By Lenalidomide + Rituximab Consolidation (RB → LR) or Arm D = Rituximab + Bendamustine + Bortezomib Followed By Lenalidomide + Rituximab Consolidation (RBV → LR)

Rev. 12/13

Appendix XVIII

Instructions for Reporting Pregnancies on a Clinical Trial

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on lenalidomide, or within 28 days of the patient's last dose of lenalidomide must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

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The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via NCI's Adverse Event Reporting System (CTEP-AERS) (http://ctep.cancer.gov)

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERS report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERS report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status via CTEP-AERS.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN Operations Office – Boston. Please contact the ECOG-ACRIN Operations Office – Boston to ask for a conference call to be set up with the appropriate individuals.
- It is recommended the female subject be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an *amendment* to the initial CTEP-AERS report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if the outcome of the pregnancy occurred on a subsequent cycle, a *new* CTEP-AERS report should be initiated reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For
Rev. 4/14 assistance in recording the grade or category of these events, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497for it will need to be discussed on a case by case basis.

Rev. Add13 ***Reporting a Pregnancy Loss***

A pregnancy loss is defined in CTCAE as "*A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation.*"

It must be reported via CTEP-AERs as Grade 4 "*Pregnancy Loss*" under the System Organ Class (SOC) "*Pregnancy, puerperium and perinatal conditions"*.

A pregnancy loss should **NOT** be reported as a Grade 5 event as currently CTEP-AERs recognizes this event as a patient's death.

Rev. Add13 ***Reporting a Neonatal Death***

A neonatal death is defined in CTCAE as "*A death occurring during the first 28 days after birth*" that is felt by the investigator to be at least possibly due to the investigational agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, must be reported via CTEP-AERs AND any infant death after 28 days that is suspected of being related to the *in utero* exposure to lenalidomide must also be reported via CTEP-AERs.

It must be reported via CTEP-AERs as Grade 4 "*Death neonatal*" under the System Organ Class (SOC) "General disorder and administration site conditions".

A neonatal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERs recognizes this event as a patient's death.

Additional Required Forms:

When submitting CTEP-AERs reports for pregnancy, pregnancy loss, or neonatal loss, the **CTEP *'Pregnancy Information Form'*** must be completed and faxed along with any additional medical information to CTEP (301-230-0159). This form is available on CTEP's website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf)