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E2408

# A 3-Arm Randomized Phase II Trial of Bendamustine-Rituximab (BR) Followed by Rituximab vs Bortezomib-BR (BVR) Followed by Rituximab vs BR Followed by Lenalidomide/Rituximab in High Risk Follicular Lymphoma


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***STUDY PARTICIPANTS***

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Addendum #6 – 9/13
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Addendum #8 – 9/14
Addendum #9 – 9/14
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Lenalidomide (NSC# 703813) Supplied by Celgene
Bendamustine (NSC# 138783) Supplied by Teva Oncology

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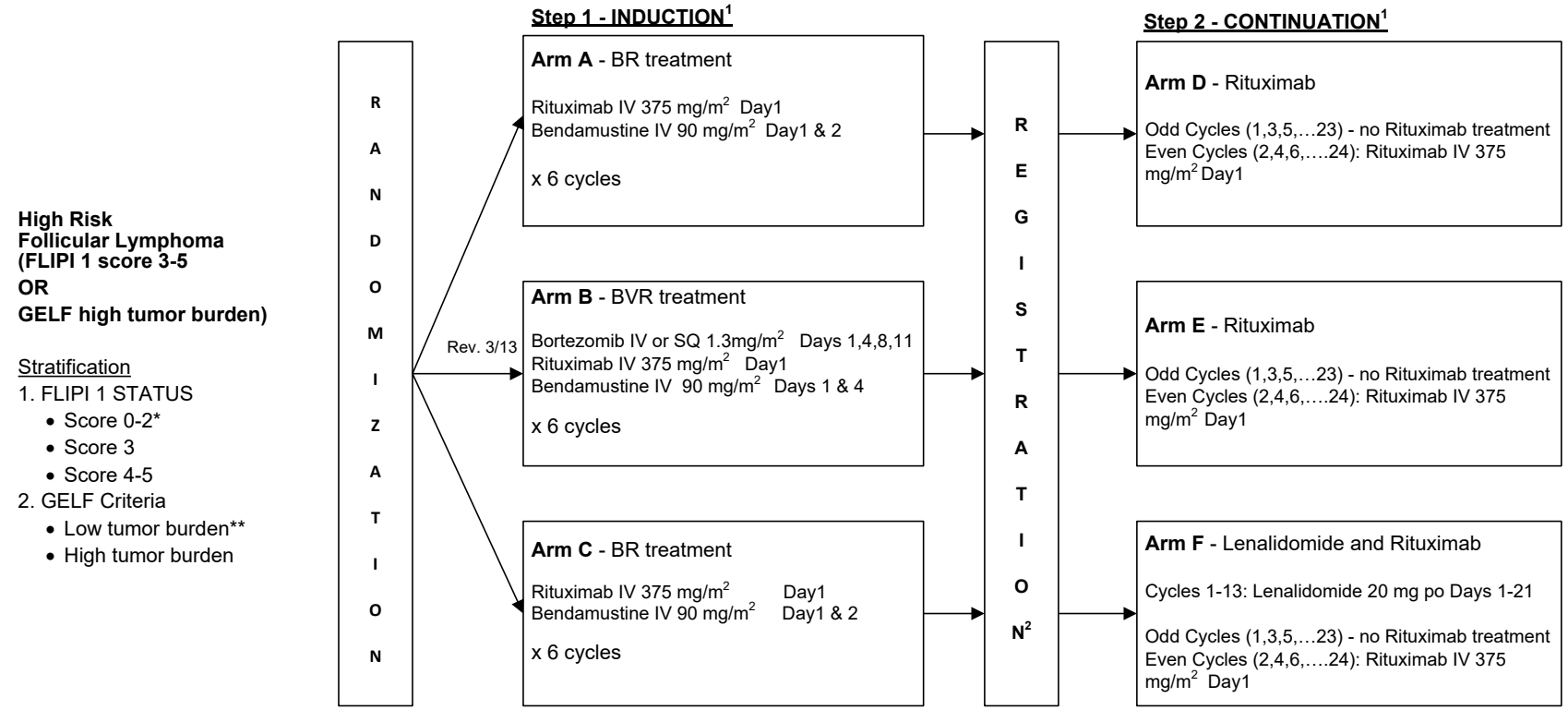
## Schema




Rev. 4/13

Rev. 9/14

Accrual goal = 286 total patients

Cycle length is 28 days (4 weeks)

* Requires High tumor burden per GELF criteria (see Section 3)

** Requires FLIPI Status of 3 or higher (per FLIPI 1 criteria)

1. At time of restaging, if disease progresses, patient discontinues protocol therapy. Restaging for induction and continuation will take place after every three (3) Rituximab treatments. See Section 5.1.5 for treatment and restaging schedules.
2. For patients who have stable disease or better at time of post-induction restaging.

# 1. Introduction

## 1.1 Natural History of Indolent Lymphoma

According to the American Cancer Society, it is estimated that approximately 66,000 individuals were diagnosed with non-Hodgkin's lymphoma (NHL) and over 19,000 men and women died of the disease in 2008 (1). Cases of follicular lymphoma (FL) comprise more than 70% of "low-grade" histologies and 22% of all cases of NHL, second only to diffuse large B-cell lymphoma (2,3). The survival rates for patients with indolent non-Hodgkin's lymphoma (NHL) remained unchanged from the 1950s through the early 1990s, but recent evidence suggests that outcomes are improving (4-6). Indolent NHL is a particular challenge because it is an incurable disease requiring multiple treatments yet relatively long survivals elevate the importance of quality of life associated with treatment. Advanced stage high tumor burden patients have shorter survivals and, even in the rituximab era, high risk patients have significantly shorter PFS.

## 1.2 Treatment for Indolent Lymphoma

### 1.2.1 Background

Traditional treatment options for low-grade NHL have included expectant observation for asymptomatic low tumor burden disease and multi-agent cytotoxic chemotherapy for patients who have symptomatic, high tumor burden or progressive disease. Biologic therapy has become an integral part of therapy and includes agents that specifically target B-lymphocytes such as monoclonal anti-CD20 antibodies and radiolabled anti-CD20 antibodies. Though treatment response is high to cytotoxic and biologic therapies initially, relapse is inevitable and response rate and duration decline whereas cumulative toxicities increase with subsequent treatments. With a better understanding of malignant lymphocyte biology at the cellular level, novel agents that target key molecular and cell signaling pathways are under investigation. Investigating new combinations of novel agents with biologic and cytotoxic therapies provide the opportunity to improve outcomes for patients with indolent NHL.

### 1.2.2 Induction Therapy

Several randomized phase III trials comparing varied chemotherapy combinations (i.e., cyclophosphamide, vincristine, prednisone (CVP), cyclophosphamide, adriamycin, vincristine, prednisone (CHOP), mitoxantrone, chlorambucil, prednisone) plus rituximab with chemotherapy alone in previously untreated patients have been reported and updated (Table 1) (7-18). The overall response rate (ORR) and either median time to treatment failure (TTF) or median event-free survival (EFS) were superior in the chemoimmunotherapy arm for both chemotherapy-naïve patients and those who have been previously treated. Moreover, overall survival (OS) improvements for the chemoimmunotherapy arms (versus chemotherapy without immunotherapy) are becoming apparent.

The ECOG 1496 study randomized responding patients induced with CVP to either maintenance rituximab or observation (7). The median PFS for patients receiving rituximab maintenance was 5.6 years versus 1.8 years for those receiving no maintenance (P=0.0000003; hazard ratio, 0.4 [0.3-0.6]), and estimated OS at 3 years was 92% versus 83% (P=0.03; one-sided log rank test), favoring the rituximab maintenance arm. The German Lymphoma Study Group randomized 428 patients over age 60 with untreated, advanced-stage FL to CHOP alone or CHOP combined with rituximab (R-CHOP) for 6 to 8 cycles (10). After a median observation time of 18 months, TTF (P<0.001) and OS (P=0.016) were superior in the R-CHOP arm. Patients younger than 60 years achieving a partial remission (PR) or complete remission (CR) after CHOP or R-CHOP were then randomized to long-term interferon or autologous stem cell transplant. Interestingly, the benefit of R-CHOP was much less apparent among the patients who received autologous stem cell transplant (SCT), and transplantation did not seem to add to R-CHOP. An updated reported showed improved 4-year progression free survival (PFS) and OS for patients who received chemoimmunotherapy (14).

1.2.3 A new standard induction chemotherapy regimen for high tumor burden follicular lymphoma: bendamustine-based therapy.

A pivotal randomized phase III trial was recently reported by Rummel et al that compared bendamustine/rituximab induction chemotherapy vs R-CHOP for patients with high tumor burden follicular lymphoma (157). Bendamustine is an alkylating agent which contains a bifunctional mechlorethamine derivative, a benzimidazole heterocyclic ring, and a butyric acid substituent. Mechlorethamine and its derivatives develop electrophilic alkyl groups, which form covalent bonds resulting in interstrand crosslinks. Bendamustine has demonstrated clinical activity in multiple tumor types including chronic lymphocytic leukemia (CLL), Hodgkin's lymphoma, NHL, multiple myeloma, breast cancers, and small-cell lung cancers (148). Bendamustine has been marketed in Germany for over 30 years, and was formally re-approved in 2005 in Germany by the Federal Institute for Drug and Medical Devices (BfArM), for the treatment of patients with indolent NHL, CLL, or multiple myeloma. Bendamustine subsequently received approval in the United States of America (USA) in 2008 by the Food and Drug Administration (FDA) for the first-line treatment of patients with CLL, and for the treatment of patients with advanced indolent B-cell NHL that progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen.

Bendamustine has been shown to be a potent, selective, cytotoxic agent against B lymphocytes with synergism between bendamustine and rituximab observed in both CD20+ lymphoma cell lines and on ex vivo cells from patients with B-CLL or B-cell lymphomas (149). In preliminary studies, the efficacy of bendamustine alone and in combination with rituximab, has been seen with both a high response rate and improved duration of response in patients with advanced

indolent NHL which progressed during or after treatment with rituximab or a rituximab-containing regimen (151). In these studies, bendamustine was well tolerated, with a manageable toxicity profile in the setting of fairly durable responses.

A multicenter Phase 2 study was conducted by the Study Group Indolent Lymphomas, Germany (StiL), of patients (n=63) with either relapsed/refractory indolent lymphoma (n=47) or mantle cell lymphoma (n=16) who were treated with rituximab at 375 mg/m2 on day 1 and bendamustine at 90 mg/m2 on days 2 and 3 every 28 days for 4 cycles (155). The overall response rate (ORR) was 90%, the CR rate was 60%, and the median PFS was 24 months. Bendamustine was well tolerated in this study. Leukopenia was the most common hematologic adverse event with World Health Organization (WHO) grade 3 or grade 4 events occurring in 35 (16%) of 216 cycles. Other less frequent grade 3 or grade 4 hematologic adverse events included thrombocytopenia (3%) and anemia (1%). Growth factors were not administered and no evidence of cumulative myelosuppression was observed. The most common nonhematologic toxicity was grade 1 nausea reported in 43% of cycles. A second multicenter Phase 2 study in a similar population of lymphoma patients receiving the same combination therapy had comparable results (154). Patients (n=67) with either relapsed/refractory indolent lymphoma (n=51) or mantle cell lymphoma (n=16) were treated with rituximab at 375 mg/m2 on day 1 and bendamustine at 90 mg/m2 on days 2 and 3 of each 28-day cycle for 4 to 6 cycles. Patients also received a dose of 375 mg/m2 of rituximab 7 days before the first 28-day cycle and 28 days after the last cycle of the combination treatment. The ORR was 92% and the CR rate was 42%.

The pivotal, multicenter, randomized Phase 3 study, conducted by the StiL, enrolled 549 patients with advanced indolent NHL or MCL to treatment with either bendamustine in combination with rituximab (BR) or standard R-CHOP in the first-line setting (156,157). Entry criteria included stage III or IV disease, a defined need for treatment in all patients (except those with mantle cell lymphoma), and no prior treatment. The primary objective was to prove non-inferiority of the BR regimen compared with the R-CHOP regimen, defined as a difference of less than 15% (amended to 10%) in PFS after 3 years but with an improved safety profile. Patients in the BR group were treated with rituximab at 375 mg/m$^2$ on day 1 and bendamustine at 90 mg/m$^2$ on days 1 and 2 of each 28-day treatment cycle. Patients in the R-CHOP group were treated with rituximab at 375 mg/m$^2$, cyclophosphamide at 750 mg/m$^2$, doxorubicin The first interim analysis of 273 evaluable patients was reported at the American Society of Hematology (ASH) meeting in December 2007 (156). The 2-drug combination (BR) appeared as effective as the 5-drug combination (R-CHOP) with an ORR of 94% for the BR group (n=139) compared with 93% for the R-CHOP group (n=134) in this preliminary analysis. The CR rates were also similar, slightly favoring the BR combination over R-CHOP, with a CR of 51% for BR, compared with 40% for R-CHOP. In terms of toxicity, R-CHOP was more toxic compared with BR. R-CHOP was

more frequently associated with serious adverse events (SAE) and overall toxicity compared with BR.

In December 2009, Rummel et al presented the final analysis of the randomized phase III STiL study. (157) A median number of 6 cycles was given in both treatment arms each (82% of BR pts and 86% of CHOP-R patients received 6 cycles. Among all patients, response was similar between the two patient groups with an ORR for BR of 92.7% for BR and 91.3% for R-CHOP; however, CR rate was improved for BR (40%) compared with R-CHOP (31%). Among all patients, BR was associated with a superior PFS compared with R-CHOP (BR: 54.9 vs CHOP-R: 34.8 months (median), HR = 0.57 (95% CI: 0.43 - 0.76; p = 0.00012) as was the time to next treatment (BR: not reached vs CHOP-R: 37.5 months (median), R = 0.52 (95% CI: 0.38 - 0.70), p = 0.00002). No differences in OS were noted. Of 513 evaluable patients, 179 were high tumor burden follicular lymphoma. BR was associated with significantly improved PFS among FL patients: BR: not reached vs CHOP-R: 46.7 months (median), HR = 0.63 (95% CI: 0.42 - 0.95), p = 0.0281. Among salvage treatments, approximately 40% of BR patients received R-CHOP, while 38% of R-CHOP patients received BR.

In terms of toxicity, significant differences in hematologic toxicities were observed for neutropenia grade 3+4 occurring in 46.5% of R-CHOP patients vs 10.7% with BR (p< 0.0001). This was despite more GCSF use in R-CHOP (20%) compared with BR (4.0%). Other toxicities that were significantly increased with R-CHOP compared with BR included: Alopecia (all vs <2% patients, p< 0.0001), paresthesias (73 vs 18, < 0.0001), stomatitis (47 vs 16, <0.0001), infectious complications (127 vs 96, p=0.0025), sepsis (8 vs 1 pt, p=0.0190). The only side effects more frequent with BR compared with R-CHOP were skin/erythema (42 vs 23 p=0.0122) and allergic reaction (skin) (40 vs 15, p= 0.0003). In this final analysis, the combination of BR improved PFS and CR rates, while showing a better tolerability profile. These results strongly suggest that BR may be the new standard first-line treatment for patients with high tumor burden FL.

**Table 1.** Randomized Trials Comparing Chemoimmunotherapy With Chemotherapy in Follicular Lymphoma

| Series | Year | No. Patients | Arms | Conclusions |
|---|---|---|---|---|
| Hochster (7,15) | 2005 | 401 | CVP vs CVP with rituximab post-induction maintenance | Improved PFS (median with rituximab 5.6 years vs 1.8 with no maintenance, P=0.0000003) and OS (88% vs 72%, p0.03) with post-induction rituximab |
| Hiddeman (10) and Buske (14) | 2005 and 2006 | 428 | 8 cycles each CHOP vs R-CHOP (all patients then randomized to interferon maintenance vs autologous HSCT) | 4-year PFS: CHOP 28% vs R-CHOP 62% (p< 0.0001) 4-year OS: CHOP 81 % vs. R-CHOP 90% versus (p=0.039) |
| Marcus (11,12) | 2006 | 321 | 8 cycles each CVP vs R-CVP | At 53-month median follow up, median TTF: CVP 15 months vs R-CVP 34 months; OS improved for R-CVP (p=0.029, log rank; hazard ratio 0.60) |
| Foussard (18) and Salles (8) | 2006 | 358 | CHVP x 12 cycles over 18 months vs. 6 cycles R-CHVP over 6 months (both arms treated with concurrent interferon-alpha x 18 months) | Median 5-year follow-up, EFS: CHVP 37% vs. R-CHVP 53% (p<0.0001); Median OS: CHVP 79% vs. R-CHVP 84% (p=not significant) |
| Herold (13) | 2007 | 358 | 8 cycles each of MCP vs R-MCP (both followed by interferon-alpha) | Median EFS (p=0.001) and median OS (p=0.0096) improved with R-MCP |
| Forstpointner (16) | 2006 | 125 (relapsed) | 4 cycles each FCM vs R-FCM with 2nd randomization of rituximab maintenance (4 weekly doses at 3 and 9 months) vs observation | Response duration significantly prolonged by R-maintenance after R-FCM |
| Van Oers (17) | 2006 | 465 (relapsed) | 6 cycles each CHOP vs R-CHOP induction followed by 2nd randomization to rituximab maintenance (one dose q3 months x 24 months) vs observation | Improved PFS with R maintenance after CHOP induction (HR, 0.30; P < .001) and R-CHOP induction (HR, 0.54; P 0.004) |
| Rummel (157) | 2009 | 564 | 6 cycles each of R-CHOP vs bendamustine/rituximab (BR) | Significantly improved PFS with BR induction (BR: not reached vs CHOP-R: 46.7 months (median), HR = 0.63 (95% CI: 0.42 - 0.95), p = 0.0281) and significantly less toxicity with BR compared with R-CHOP |

### 1.2.4 Post-Induction (Continuation) CD20 Antibody Therapy

To improve the response rate, duration of response, and potentially prolong OS, additional doses of rituximab have been administered as post-remission or "maintenance therapy." Median EFS has been shown to be prolonged with this approach, following chemotherapy induction (15-17) or after rituximab alone therapy (19,20). Two of the most commonly applied maintenance (or continuation) rituximab approaches following "induction" are the following: 1) rituximab given as a single dose every 2 to 3 months (17,19) and 2) 4 weekly doses of rituximab given every 6 months for 2 years (7, 16, 20).

Prior pharmacokinetic data have shown that the administration of a single dose of rituximab every 3 to 4 months maintains effective blood levels (21), while preliminary pharmacokinetic data from an ECOG trial in lymphoma patients with low tumor burden who received single rituximab dose every 3 months showed that 47% of patients had rituximab blood levels ≤ 25 mcg/mL at 12 weeks (22). Therefore, rituximab maintenance therapy may have to be administered at more frequent intervals (e.g., every 2 months).

### 1.2.5 Importance of Achieving Complete Remission (CR)

The achievement of a CR with induction therapy in low-grade NHL is important, especially if the ultimate goal is to administer post-remission therapy (e.g., monoclonal antibody) that is likely to be most effective in the presence of quantitative t(14;18). In order to study the importance of induction treatment for untreated low-grade lymphoma, a recent meta-analysis analyzed the clinical outcome of patients with a focus on CR rate and its relation to disease progression. Thirty-two induction/treatment regimens from 25 publications (2001-2006) with 2,421 patients were studied by Saville et al (23). Therapies were induction and/or consolidation therapy, excluding trials with rituximab maintenance. Treatment categories were chemotherapy combinations without fludarabine, rituximab as a single-agent or in combination with chemotherapy, fludarabine as a single-agent or in combination, and ibritumomab tiuxetan or tositumomab as single agents or in combination. There was a highly significant linear correlation between the CR rate and event rate for disease progression with all treatments (rho= -0.79; 95% CI: -0.57 to -0.91; *P*<0.001). The analysis showed that a higher CR rate correlated with a lower hazard of disease progression.

As discussed above in Section 1.2.2 (and Table 1), the ECOG 1496 low-grade lymphoma randomized trial showed a significant advantage for patients who received maintenance rituximab (MR) after CVP induction with a median PFS of 5.6 years versus 1.8 years for those who did not receive maintenance (P=0.0000003; hazard ratio, 0.4 [0.3-0.6]) (7). In terms of *prognostic analysis* for patients who received MR following CVP induction (n=158), several factors were examined in univariate and Cox proportional hazard models. There was a significantly better outcome/benefit with MR for patients who had *quantitative t(14;18)* after CVP induction compared with gross

disease (quantitative t(14;18) defined as <10% marrow involvement, no lymph node >2 cm, and reduction of a bulky nodal mass by >75%). Median PFS was not reached for minimal disease MR patients compared to 3 years for those with gross disease after CVP (HR=0.4, [0.2,0.6], p=0.001). In addition to quantitative t(14;18), CR rate (p=0.04) also predicted for longer PFS (96% v 71% at 2 years). In multivariate analysis for PFS, only quantitative t(14;18) after CVP was significant (RR 0.5, p=0.009). For OS there was a strong trend favoring MR among high tumor burden patients (one-sided p=0.03).

Therefore, an *important strategy* in the current randomized trial is to incorporate novel therapeutic approaches in an attempt to achieve quantitative t(14;18) with increased CR rate following induction therapy and through continuation therapy immediately following induction.

## 1.3 Defining High-Risk Follicular Lymphoma

### 1.3.1 High-Risk Follicular Lymphoma

We hypothesize that alternate methods of defining tumor burden and response to treatment are superior to current clinical methods, such as the FLIPI score and Revised Response Criteria, in predicting high risk lymphoma. High risk lymphomas have shorter lower complete response rates and lower disease-free survival rates, and, most importantly, shorter progression-free and overall survivals. Currently, there is no gold standard to define high risk follicular lymphoma, although a number of methods are in clinical use including the FLIPI risk score, the original (33,34) and revised Groupe D'Etude des Lymphomes Follicularies (GELF) criteria, (8) British National Lymphoma Investigation (BNLI) criteria (35), the German Lymphoma Study Group (10), the East German Study Group Criteria (13), and the M.D. Anderson tumor score (36). Advanced stage and higher initial tumor burden have long been recognized to confer inferior prognosis in cancer. Notably, these criteria are rather crude in NHL, with an Ann Arbor staging system more than 40 years old. Further, the enumeration of nodal sites and definition of bulk is inconsistent.

#### 1.3.1.1 Groupe D'Etude des Lymphomes Follicularies (GELF) Tumor Burden

The GELF criteria were established in the late 1990's as clinical criteria that separated follicular lymphoma patients into low and high tumor burden (33,34). The criteria were used to define patient populations who warranted initiation of cytotoxicic chemotherapy based on symptoms attributable to their disease/lymphoma or high risk features (e.g., compression of vital organs) (34) vs asymptomatic patients with low-risk features who were included in "watch and wait" (no immediate cytotoxics) randomized trials (33,35). Further, several of the criteria, such as size of nodes (bulky disease) and number of nodal sites, have been shown to be associated with increased risk of relapse (36). The original GELF criteria included stage II, III, or IV

patients with the presence of at least one of the following signs: any nodal or extranodal tumor mass with a diameter of greater than 7 cm; involvement of at least three nodal sites, each with a diameter of greater than 3 cm; any B symptom; splenic enlargement with inferior margin below the umbilicus line; compression syndrome (ureteral, orbital, gastrointestinal) or pleural or peritoneal serous effusion (irrespective of cell content); leukemia (> 5.0 x $10^9$/L circulating malignant cells) or cytopenia (polymorphonuclear leukocytes <1.0 x $10^9$/L and/or platelets <100 x $10^9$/L). Over the past decade, lymphoma groups around the world have used similar, but slightly modified criteria (8,10, 53,35-38).

1.3.1.2 Follicular Lymphoma International Prognostic Index (FLIPI)

The FLIPI was developed in order to predict prognosis of patients with newly diagnosed follicular lymphoma (FL). The five original FLIPI criteria were: age > 60 years, Ann Arbor stage III-IV, hemoglobin level < 12 gm/dL, >4 nodal areas, and serum LDH level above normal. The original FLIPI discriminated between 3 major subgroups of patients with FL with regard to OS, carrying a low (0-1 risk factors), intermediate (2 risk factors), or high risk (3-5 risk factors) (39). However despite the data being derived from FL patients who were treated in different treatment regimens on varied multicenter study group protocols, none of the regimens/patients were treated with rituximab therapy. An updated report examined the importance of the FLIPI prognostic score among rituximab-based treated patients (9). Buske et al showed that among 362 patients treated with R-CHOP, a modified definition of FLIPI risk groups may be warranted of 1 or 2 risk factors (55% of the patients), 3 risk factors (27%), and patients with 4 or 5 risk factors (18%). This resulted in a separation of 3 distinct risk groups (2-year TTF 90% vs 74% vs 57%, respectively; *P* <0.001).

1.3.2 Quantitative t(14;18) in Follicular Lymphoma.

In follicular lymphomas, about 70% of patients have t (14;18) cells in the blood and marrow compartments that can be detected and quantified by application of the polymerase-chain reaction (PCR) for major and minor breakpoints. Numerous studies have demonstrated that patients who achieve quantitative t(14;18), defined as the absence of detectable t(14;18) cells, enjoy longer PFS (40-45). This is true with chemotherapy (40, 42, 46), high dose therapy and transplantation (41, 43, 45), and in the rituximab era including radioimmunotherapy (42, 44-46). Importantly, a higher proportion of patients (~75%) are able to achieve quantitative t(14;18) with chemo-immunotherapy, suggesting that the rate of decline of PCR-positive cells may be a more precise predictor. Further, the cumulative body of data indicate that the marrow aspirate is a somewhat more sensitive

compartment for establishment of quantitative t(14;18), such that decline in circulating PCR-positive cells should be a convenient and reliable way to determine rate of change whereas a marrow sample is optimal for establishing absolute quantitative t(14;18) at the end of treatment. Because the distribution of FL is variable among patients, with some manifesting relatively bulky disease with no or minimal marrow disease and others manifesting smaller, widespread adenopathy with greater marrow disease, the determination of quantitative t(14;18) could vary by disease pattern. Despite the wealth of data regarding PCR status in FL, associations with disease pattern have largely not been done. Further, there is an observation that the marrow compartment, which was often the last to clear in the rituximab era, is more susceptible to rituximab and, in fact, the ability to achieve quantitative t(14;18) has increased substantially. These observations indicate the need to complement the t (14;18) analyses with sensitive imaging of the lymph node compartments.

## 1.4 Bortezomib

### 1.4.1 Bortezomib Background

The ubiquitin proteasome pathway has become an attractive target for pharmacological blockade in the treatment of lymphoproliferative malignancies because it plays a central regulatory role in cell survival, cell-cycle progression, and cell homeostasis in eukaryotic cells. Through the degradation of intracellular proteins, the ubiquitin-proteasome pathway regulates key signaling pathways such as transcription activation, apoptosis, and pathways that direct angiogenesis, cell trafficking, and metastasis (47). Specific proteins degraded by the proteasome include the growth regulatory proteins p21 and p27, the p53 tumor suppressor, and the transcription factor nuclear factor kappa B (NF-*k*B) (48-52). Preclinical models have demonstrated that inhibition of the ubiquitin-proteasome pathway induces apoptosis in a variety of tumor-derived cell lines (53-55). Proteasome inhibition is of particular interest in NHL due to its mitigating effects on nuclear factor kappa B (NF-*k*B) through degradation of the NF-*k*B inhibitor protein, I*k*B. NF-*k*B activates pro-survival genes and proteins such as bcl-2, an anti-apoptotic protein that is over-expressed in follicular lymphoma. Preclinical data has shown that proteasome inhibition results in phosphorylation and the subsequent cleavage and inactivation of bcl-2 (56).

### 1.4.2 Single-agent Bortezomib Lymphoma Clinical Trials

Bortezomib is a potent, selective, and reversible proteasome inhibitor that was first approved by the FDA for the treatment of relapsed and refractory multiple myeloma and for patients with myeloma who have received at least one prior therapy (57,58). Bortezomib was also approved for the treatment of newly diagnosed multiple myeloma in the United States as of June 2008. In December 2006, bortezomib received FDA approval for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy (59-

61). Two single-agent phase 2 bortezomib lymphoma studies included small numbers of indolent non-Hodgkin lymphoma (NHL). Goy and colleagues (60) treated 27 patients with B-cell lymphomas (including diffuse large B-cell lymphoma (DLBCL) and indolent NHLs) of which only 4 attained a response (1 complete remission (CR), 1 CR unconfirmed (CRu), 2 partial remissions (PR)). The one CRu occurred in a patient with follicular lymphoma (FL), while the CR was in a patient with small lymphocytic lymphoma (SLL), and the PRs in one patient with DLBCL, and one in Waldenstroms. Interestingly, the response in FL occurred only after a protocol amendment allowing more protracted schedules of administration, following earlier protocol versions that required patients to be removed from study after two cycles if they had no response. In a study by Straus and colleagues (62), 11 FL were assessed. Two of the 11 patients responded to therapy (18%), which interestingly occurred 3 months after the end of treatment. This study, like the one reported by Goy et al (60), also removed patients from study for absence of response after 1 or 2 cycles of therapy. It is has been shown that responses to bortezomib therapy in indolent lymphoma can be delayed.

In the largest single-agent bortezomib indolent lymphoma study conducted to date, O'Connor and colleagues showed an overall response rate (ORR) of 50% in the subset of patients with FL (63,64). In a 33 patient multicenter study, patients with relapsed or refractory FL, marginal zone lymphoma SLL, and Waldenstroms were eligible and patients continued on treatment if no progression of disease occurred. The median number of prior therapies for all patients was 3. The ORR for the entire population was 39% (35% on an intention to treat) including 4 CRs. Of the 18 patients with FL, four achieved a CR and 5 achieved PR for an ORR of 50%. The median time to response for patients with FL was 11 to 12 weeks, while the median time to treatment response for patients with MCL was 4 weeks. Interestingly, among all responding patients, the progression-free survival (PFS) with bortezomib was equivalent to the PFS seen with the line of chemotherapy given prior to study (12.3 months for both), which was identical for patients with FL alone.

This single-agent response rate of 50% for FL is among the highest reported for a non-chemotherapeutic drug in the relapsed/refractory setting. Further, preliminary data is available from David and colleagues in a multicenter study using rituximab/bortezomib therapy in untreated "high tumor burden" indolent lymphoma (65). Expected ORR using single-agent rituximab in "low tumor burden" FL is 72%-73% (with 20%-36% CR) (37,66). Investigators at Northwestern University are conducting a Simon 2-stage phase II trial for untreated "high tumor burden" indolent lymphoma and reported on the pre-planned interim analysis (65). All patients were required to have "high tumor burden" as defined by GELF criteria. Twenty-seven pts have enrolled, of whom 17 were in the first stage. Fourteen patients had FL, 2 MZL, and 1 SLL. The median Follicular Lymphoma International Prognostic Index (FLIPI) was 3, while the median follow-up was 12 months (range 1-24 months). Induction therapy consisted of 3 cycles:

bortezomib given at 1.6 mg/m$^2$ days 1, 8, 15, and 22 q35 days for 3 cycles and rituximab at 375 mg/m$^2$ x 4 weekly doses for cycle 1, then day 1 only for cycles 2 and 3. Abbreviated consolidation therapy was subsequently given with 1 dose of each drug q2 months x 8 months. After cycle 1, the ORR was only 29% (no CRs) with 71% stable disease (SD). The best ORR, seen after 3 cycles of induction and 8 months of maintenance therapy was 71% (with CR 35%) in this high tumor burden patient population. According to histology, the best ORR among FL patients was 86% (CR 42%). Therapy was overall well tolerated. The *conversion* of ORR of 29% (CR 0%) following 4 weeks of rituximab/bortezomib to an ORR of 86% (CR 42%) is suggestive of clinical benefit from bortezomib therapy.

1.4.3 Bortezomib/Rituximab Lymphoma Clinical Data

Two bortezomib/rituximab treatment regimens were evaluated in a randomized phase II study for patients with relapsed, refractory low grade NHL (67). Treatment Arm A treated patients with bortezomib 1.3 mg/m$^2$ twice weekly on days 1, 4, 8, and 11 of a 21-day cycle in combination with 4 doses of rituximab 375mg/m$^2$ given on days 1, 8, and 15 of cycle 1 and day 1 of cycle 2. Patients on Treatment Arm B receive bortezomib 1.6mg/m$^2$ weekly on days 1, 8, 15, and 22 of a 35-day cycle with 4 doses of rituximab 375mg/m$^2$ weekly on days 1, 8, 15, and 22 of cycle 1. Study end points include ORR, time to progression, and safety and tolerability data. To date, 81 patients have enrolled on the study, and preliminary safety data are available for 60 patients. Grade 3 or 4 adverse events have occurred in 54% of patients on Arm A (twice weekly bortezomib), and 18% of patients on Arm B (weekly bortezomib), with no grade 4 events on Arm B. The most common grade 3 or 4 adverse events included nausea and/or vomiting (15% Arm A, 3% Arm B), diarrhea (4% Arm A, 9% Arm B), peripheral neuropathy (8% Arm A, 3% Arm B) and fatigue (4% Arm A, 6% Arm B). Based on preliminary data the response rate is 51% in Arm A and 54% in Arm B.

1.4.4 Bortezomib/Chemotherapy Data

Preclinical data has shown that bortezomib induced synergistic apoptosis when combined with rituximab and cyclophosphamide in lymphoma cells in vitro and in vivo SCID mice (68). This cell death occurred through caspase-dependent mechanisms. Clinically, bortezomib has also been combined with combination chemotherapy programs such as CHOP and CVP. Gerecitano et al incorporated bortezomib into R-CVP replacing oncovin (vincristine) of CVP with bortezomib (R-CBP) for 16 pts with relapsed or refractory FL, CLL/SLL, marginal zone lymphoma, WM, or MCL (69). Bortezomib was escalated from 1.1 to 1.8 mg/m$^2$ given days 2 and 8 with escalating cyclophosphamide from 750 mg/m$^2$ to 1,000 mg/m$^2$ given day 1. Therapy was overall well tolerated and no dose limiting toxicity had been reached at bortezomib 1.8 mg/m$^2$ and cyclophosphamide of 1,000 mg/m$^2$. Of 12 evaluable patients ORR is 58% with 2 CRs (17%, including 1 MCL, 1 FL) and 5 PRs (42%, including 2 FL, 1 MCL, 1 MALT, and 1 MZL transformed).

1.4.5 Bortezomib/BR (BVR) Lymphoma Combination Clinical Trials

Data has been presenting from 2 prospective clinical trials combining bortezomib with BR (BVR) for the treatment of lymphoma. Fowler et al reported results on 49 patients with relapsed/refractory FL (150). Patients received therapy as 35-day cycles with bortezomib dosed at 1.6 mg/m$^2$ (days 1, 8, 15, 22), bendamustine 90 mg/m$^2$ (days 1, 2), and rituximab 375 mg/m$^2$ (days 1, 8, 15, 22, cycle 1; d 1, cycles 2–5) for up to 5 cycles. They showed that BVR had an ORR of 84% with a CR rate of 47%. Overall BVR was well tolerated. Non-hematologic grade 3/4 AEs that occurred in more than one patient included syncope (n=2; 3%) and peripheral neuropathy. Grade 3/4 neutropenia, thrombocytopenia, and anemia were seen in 25%, 6%, and 3% of pts, respectively. Treatment-related serious AEs were reported in 17 (27%) patients, including 3 (5%) with febrile neutropenia and 1 (2%) with grade 3 herpes zoster who did not receive antiviral prophylaxis and discontinued therapy. Of the 17 (27%) patients with treatment-related peripheral neuropathy, only 4 (6%) had grade 3 (2 discontinued therapy; no grade 4); peripheral neuropathy has resolved in 5 (29%) patients to date.

Friedberg et al reported results using the same combination therapy (i.e., BVR), but they used a different treatment schedule (152). Treatment consisted of bendamustine 90 mg/m$^2$ days 1 and 4; rituximab 375 mg/m$^2$ day 1 and bortezomib 1.3 mg/m$^2$ day 1, 4, 8, 11. Six 28-day cycles of therapy were planned. Thirty-one patients were enrolled; median age was 64 yrs (range 44-84). Histology included 16 FL, 7 MCL, 3 marginal zone NHL, 3 SLL and 2 lymphoplasmacytic NHL. Patients were heavily pretreated with a median of 4 prior regimens, including anthracycline containing chemotherapy (n=19), purine analog chemotherapy (n=6), stem cell transplant (n=6), and radioimmunotherapy (n=9). Of 25 patients evaluable for response, ORR was 84%. Best response following therapy was CR/CRu: 13 (52%); PR: 8 (32%); SD: 1(4%); PD: 3 (12%). Interestingly, 11/11 patients with FL responded to treatment (including 7 (64%) CR/CRu). Common expected toxicities included thrombocytopenia, fatigue, fever, anemia, neutropenia and infusion reactions. Peripheral neuropathy was reported in 18 patients, including 2 with grade 3 neurotoxicity; additionally 14 patients reported constipation. There were 5 patients who developed varicella zoster reactivation (no prophylaxis given). These resulted were deemed promising and warranting additional evaluation of this B-RB regimen in *de novo* disease. A randomized trial would be necessary to determine the degree to which bortezomib adds efficacy to the BR combination.

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1.4.6 Subcutaneous bortezomib.

A randomized Phase 1 pilot study in 24 subjects with multiple myeloma demonstrated that both the IV and SC routes of VELCADE administration have similar systemic drug exposure and proteasome inhibition. Importantly, SC and IV administration of VELCADE 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 VELCADE, when administered at 1 mg/mL concentration[1].

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. 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. The ORR (CR+PR) after 4 cycles of treatment was 42 % in both the SC and IV treatment groups for the response-evaluable population. The ORR after 4 cycles in the IV arm was consistent with what was observed in historical single-agent VELCADE trials with relapsed multiple myeloma subjects. The study met the noninferiority objective (p-value for the noninferiority hypothesis was 0.00201).

The median TTP (Kaplan-Meier estimate) was 10.4 months in the SC treatment group and 9.4 months in the IV treatment group. The hazard ratio was 0.839 with 95% CI (0.564, 1.249), and the p=0.3866 (stratified log-rank test), indicating similar results between the SC and IV arm. The median PFS (Kaplan-Meier estimate) was 10.2 months in the SC treatment group and 8.0 months in the IV treatment group. After a median follow-up of 11.8 months, the 1-year survival rate was 72.6% in the SC arm and 76.7% in the IV arm. The p-value for the difference in 1-year survival rate was 0.5037, indicating similar results between the SC and IV arm. The median time to first response (Kaplan-Meier estimate) was 3.5 months for both the SC and IV treatment groups. Among the responders, the median duration of response (Kaplan-Meier estimate) was 9.7 months in the SC treatment group, compared with 8.7 months in the IV treatment group. Overall, similar efficacy results were observed in the SC and IV treatment groups, and the study demonstrated that VELCADE SC administration is not inferior to VELCADE IV administration.

From a safety standpoint, the safety profile between the SC and IV treatment groups in general was comparable in most System Organ Classes (SOCs), a difference in incidence in certain safety parameters in favor of the SC treatment group was noted. One hundred and forty (95%) subjects in the SC treatment group and 73 (99%) subjects in the IV treatment group reported at least 1 treatment-emergent adverse event. In the SC treatment group, there was a lower incidence of Grade $\geq$3 adverse events as compared with the IV treatment group (57% vs. 70%, respectively); a lower incidence of adverse events leading to treatment discontinuations (22% in the SC treatment group and 27% in the IV treatment group); and a lower incidence of adverse events leading to dose modifications in the SC group: dose reduction (33% in the SC treatment group compared with 45% in the IV treatment group); dose withholding (30% in the SC treatment group compared with 39% in the IV treatment group); or

cycle delay (20% in the SC treatment group compared with 34% in the IV treatment group). Serious adverse events were similar between the 2 treatment groups (36% in the SC treatment group and 35% in the IV treatment group).

The SC treatment group reported a lower incidence in several adverse events associated with VELCADE toxicity. The incidence of peripheral neuropathy events (all Grades) was 38% in the SC treatment group and 53% in the IV treatment group; the incidence of Grade ≥2 peripheral neuropathy events was 24% in the SC treatment group and 41% in the IV treatment group; and the incidence of Grade ≥3 peripheral neuropathy event was 6% in the SC treatment group and 16% in the IV treatment group. There also appeared to be a trend towards lower incidence in gastrointestinal adverse events (37% for SC and 58% for IV, predominantly due to differences in Grade 1-2 abdominal pain, diarrhea, and dyspepsia); as well as a ≥5% difference in incidence of Grade 3 and 4 hematology laboratory results in the SC treatment group compared with the IV treatment group for WBC (8% in the SC treatment group compared with 18% in the IV treatment group), neutrophil count (22% in the SC treatment group compared with 28% in the IV treatment group) and platelets (18% in the SC treatment group compared with 23% in the IV treatment group).

Local tolerability of SC administration was acceptable. Nine (6%) subjects reported a local reaction to SC administration as an adverse event. Eighty-five (58%) subjects in the SC treatment group reported at least 1 local injection site reaction. The most common local injection site reaction was redness, which was reported in 84 (57%) subjects. The majority of subjects with worst injection site reactions were assessed as mild (38%) or moderate (18%). Only 2 (1%) subjects were reported as having severe injection site reactions. All local site reactions resolved completely and rarely led to treatment modifications.

In conclusion, the SC administration of VELCADE has good local tolerance. The systemic safety profile for the SC administration of VELCADE was associated with a lower incidence of Grade ≥3 adverse events, and treatment modifications (discontinuations and dose reductions). In particular, there was a lower incidence of peripheral neuropathy NEC reported.

## 1.5 Lenalidomide

### 1.5.1 Background

Lenalidomide is a member of a class of pharmaceutical agents known as immunomodulatory drugs. It offers potential benefit over the first commercially available immunomodulatory compound, thalidomide, in terms of both safety and efficacy in human subjects (72). The key to its therapeutic potential lies in the fact that it has multiple mechanisms of action, which act to produce both anti-inflammatory and anti-tumor effects. These effects are thought to be contextual in that they depend on both the cell type and the triggering stimulus. To date, lenalidomide

has been associated with TNF-α inhibitory, T-cell costimulatory, and antiangiogenic activities (72). Lenalidomide is marketed in the United States for the treatment of subjects with transfusion-dependent anemia due to low- or intermediate-1-risk Myelodysplastic Syndrome (MDS) associated with a deletion 5-q cytogenetic abnormality with or without additional cytogenetic abnormalities and in combination with dexamethasone for subjects with previously treated multiple myeloma. Lenalidomide is also approved and marketed, in combination with dexamethasone, for the treatment of patients with multiple myeloma who had been treated with at least one prior therapy.

Lenalidomide is being investigated as treatment for various hematological and oncologic indications. It is also being explored as a treatment for inflammatory conditions, including chronic regional pain syndrome. While many of the studies are ongoing, results from controlled and uncontrolled studies in subjects with multiple myeloma and MDS are available. Lenalidomide as well as thalidomide have demonstrated activity in multiple myeloma, another B cell malignancy. Increased angiogenesis has been described in NHL (72-75). Immunomodulatory drugs such as lenalidomide directly kill certain types of tumor cells or induce cell-cycle arrest. They also possess potent anti-angiogenic activity in vitro and this is likely to contribute to their anti-tumor effects. Immunomodulatory drugs help to minimize metastasis by reducing the expression of pro-angiogenic cytokines, such as vascular endothelial growth factor, decreasing blood vessel cytokines, density and affecting cell adhesion molecules. In addition, immunomodulatory drugs co-stimulate T-cells and enhance antitumor immunity, which is mediated by T-helper-1 type cytokines, such as interferon-γ and interleukin-2 (IL-2). Immunomodulatory drugs also co-stimulate T-cells and enhance other innate immune cells such as natural killer cells, which can enhance tumor cell death (76,77). In addition, a recent manuscript demonstrated remarkable activity of thalidomide when combined with rituximab for relapsed mantle cell NHL (78). Preclinical experiments have noted that in the Burkitt lymphoma derived Namalwa cells, single agent lenalidomide inhibits proliferation in a concentration dependent manner (~30% inhibition at 30 mM). Single agent dexamethasone also inhibits Namalwa cell growth in a concentration dependent manner with IC50 >1000 nM. When used in combination with lenalidomide (10~100 mM), the IC50 for dexamethasone is 2.0-6.3 nM, indicating an additive effect of Lenalidomide and dexamethasone. Furthermore, in mouse models/studies, significant enhancement of rituximab-mediated ADCC was seen when used in combination with lenalidomide (79). This was associated with recruitment of NK cells and stimulation of dendritic cells. In addition, an antiangiogenic effect was seen following lenalidomide/rituximab treatment in these studies.

### 1.5.2 Single-Agent Lymphoma Clinical Data

Witzig and colleagues reported data on 43 patients with relapsed/refractory indolent lymphoma using single-agent Lenalidomide (80). Patients received lenalidomide 25 mg orally once

daily on days 1-21 on a 28-day cycle and continued therapy for 52 weeks as tolerated or until disease progression. The median age of patients was 63 years (range, 43–89) and the median number of prior treatment regimens was 3 (range, 1–15). Histology included SLL (n=18), FL (n=22), nodal marginal B-cell lymphoma (n=2) and extranodal marginal zone B-cell lymphoma of MALT type (n=1). Eleven of the 43 patients (26%) exhibited an objective response (2 CR, 1 CRu, 8 PR), 15 had SD, while 13 had PD (4 not evaluable). Responses included 4/18 SLL (22%) and 7/22 FL (32%), while median time to response was 3.6 months for all patients (range 1.7–4.1). PFS was 4.6 months for all patients and 7.7+ months (range 4.4-13.5+) for responding patients and ongoing. Therapy was well tolerated with the most common grade 4 adverse event being neutropenia (14%) and the most common grade 3 adverse events of neutropenia (21%) and thrombocytopenia (12%).

Data from two phase II studies of single-agent lenalidomide in patients with relapsed or refractory aggressive NHL have been presented (81,82). In the first trial, 49 patients received lenalidomide 25 mg orally once daily on days 1 to 21 on a 28-day cycle (82). Histology included DLBCL (n=26), FL grade 3 (n=5), MCL (n=15) and transformed DLBCL (n=3). Median time from original diagnosis was 2.7 years (range, 0.4-32 years) and median number of prior treatment regimens was 4 (1-8). Nearly all patients had received prior rituximab and 63% were rituximab-refractory. Seventeen patients (35%) exhibited an objective response (2 CR, 4 CRu and 11 PR). Response was the similar for patients who were refractory to rituximab or not. The median duration of response was 10.4 months. Multivariate analysis identified only time since last rituximab and tumor burden as correlated with response. A follow-up phase II study was recently reported following accrual of 83 patients with relapsed/refractory aggressive lymphoma with the same treatment plan as above (81). Histology included 22 MCL, 49 DLBCL, 6 FL grade 3, and 6 transformed DLBCL. Median age was 63 years (range, 21-86) with median time from original diagnosis of 2.2 years (0.4-12), median time from last therapy of 4.2 months (range, 1.2-66), and median prior treatment regimens of 3 (range, 1-13). An objective response was documented in 24/83 patients (29%) with 5 CR/CRu, 19 PR, and 16 SD. Therapy was overall well tolerated with the most common grade 3/4 adverse events were neutropenia (24%), thrombocytopenia (16%), leukopenia (9%), anemia (6%), dehydration (5%), and fatigue (5%).

Habermann et al reported on the safety of lenalidomide through the combined analyses of 2 phase II clinical trials of patients with relapsed/refractory aggressive NHL (NHL-002 and NHL-003) (83). Lenalidomide monotherapy was shown to have a favorable safety profile. Using the intent-to-treat population, 136 patients were studied. The most common (≥10%) adverse events were fatigue, neutropenia, rash, thrombocytopenia, constipation, anemia, diarrhea, pyrexia, nausea, peripheral edema, decreased white blood cell count, anorexia, and cough. The most common grade 3/4 adverse events

were neutropenia (21%) and thrombocytopenia (15%), while serious adverse events (≥ 2% of patients) were disease progression, febrile neutropenia, pyrexia, and pneumonia in 4%, and back pain, deep vein thrombosis, dehydration, and diarrhea in 2%. No events of tumor lysis syndrome were reported.

1.5.3 Combined Lenalidomide/Rituximab Lymphoma Data

Wang et al reported the results of a phase I/II examining dose escalation of lenalidomide days 1-21 on a 28 day cycle (starting dose 5mg orally qd) in combination with rituximab 375 mg/m$^2$ weekly for 4 weeks for patients with relapsed/refractory MCL (84). Fifteen patients were treated on a 3+3 Fibonacci design with median age 73 and 12/15 had received prior rituximab-hyperCVAD/MA therapy. Two dose limiting toxicities (DLT's) that occurred at 25mg lenalidomide; one patient had grade 3 hypercalcemia and the other had grade 4 neutropenic fever and died of sepsis (G5) during the first cycle. Therefore maximal tolerated dose with rituximab in this patient population was determined to be 20mg. In terms of response, no responses were seen at 10mg or 15mg. However of 10 evaluable patients, 3 PR's and 3 CR's were documented at 20mg.

The above pre-clinical and clinical trial data support the study schema adding lenalidomide consolidation therapy following R-chemotherapy induction. Consolidation therapy consists of lenalidomide 20 mg orally days 1-21 of a 28 day cycle for 1 year, given with rituximab 375 mg/m$^2$ given one dose every 2 months for 2 years. This will be compared with the standard treatment arm of single agent rituximab 375 mg/m$^2$ one dose every 2 months for 2 years.

1.5.4 Lenalidomide Consolidation/Maintenance Clinical Data

Lenalidomide has been well studied in multiple myeloma as a part induction therapy as well as consolidative and maintenance treatment (i.e., post-induction) (85-88). Palumbo et al recently reported on 86 patients who received 4 cycles of induction chemotherapy (bortezomib, liposomal doxorubicin, dexamethasone), followed by 2 cycles of high-dose cyclophosphamide for stem cell collection, and then 2 autologous stem cell transplants (i.e., tandem); patients then received lenalidomide-based consolidation and maintenance therapy. After the 2$^{nd}$ transplant, patients received lenalidomide 25 mg/day (days 1-21 on 28-day cycle) combined with prednisone 50mg qod for 4 cycles. This was followed by long-term lenalidomide maintenance treatment (10mg daily) (85). Overall, lenalidomide post-induction therapy was well tolerated with one DVT seen and one patient who discontinued therapy.

Zonder et al evaluated lenalidomide-based post-induction therapy in a randomized phase III trial for 198 patients with newly diagnosed multiple myeloma (86). Patients were randomized to dexamethasone alone induction followed by dexamethasone alone maintenance therapy vs combined dexamethasone with lenalidomide (25mg daily on 28 of 35 days) x 3 cycles followed by maintenance with dexamethasone with lenalidomide (25mg daily days 21 of 28).

Lenalidomide-based maintenance was given until disease progression. The trial was stopped early due to improved clinical benefit for lenalidomide/dexamethasone arm. Toxicities were manageable, including increased thrombosis in the combined arm vs dexamethasone alone (27% and 9%, respectively) and grade 3-4 neutropenia (14% and 2%, respectively), and grade 3-5 infections (51% and 28%, respectively). Of note, the incidence of thrombosis related to immunomodulatory drugs has been shown to be increased when combined with steroids and/or chemotherapy (89).

Anderson et al studied lenalidomide-based maintenance among 43 patients with relapsed/refractory multiple myeloma (88). After 8 cycles of induction therapy (lenalidomide 15mg, days 1-14, bortezomib 1.0mg/m$^2$, days 1, 4, 8, 11, and dexamethasone 10/20mg (cycles 1-4 and 5-8) on days of and after bortezomib), stable or responding disease patients received maintenance therapy with: lenalidomide days 1-14, bortezomib days 1 and 8 (at doses tolerated at end of cycle 8) along with dexamethasone 10 mg, d ays 1, 2, 8, and 9. Toxicities were reported to be consisting mainly of grade 1-2 myelosuppression. Attributable non-hematologic toxicities included DVT (2 patients), grade 3 peripheral neuropath (1 patient), and grade 3 atrial fibrillation (2 patients).

In addition, Coleman et al studied immunomodulatory drugs in combination with rituximab for patients with relapsed/refractory CLL, SLL, and MCL (90). They administered rituximab weekly x 4 every 6 months along with daily alternating thalidomide (50mg) and lenalidomide (10mg). Overall therapy was tolerated well. No significant neurologic toxicity or thromboembolic events were seen and cytopenias were modest. The above pre-clinical and clinical trial data support the study schema adding lenalidomide consolidation therapy following rituximab-chemotherapy induction. Post-induction therapy will consist of lenalidomide at 20mg orally days 1-21 on 28-day cycles for 12 months along with rituximab 375 mg/m$^2$ given one dose every 2 months for 24 months. This will be compared with the standard treatment arms of rituximab alone 375 mg/m$^2$ one dose every 2 months for 24 months.

## 1.6 Quality of Life in Lymphoma

### 1.6.1 Background and Significance

Few clinical trials have examined quality of life in NHL, especially indolent disease (91). This protocol provides an opportunity to prospectively examine the trajectory of treatment-emergent symptoms, the impact of novel treatment approaches on patients' well-being and functional status, and symptom palliation from treatment for patients who are likely to have several physical symptoms due to their disease in addition to a high level of subjective distress associated with their long-term prognosis. The assessment of health-related quality of life (HRQL) among patients with indolent lymphoma has been infrequently examined in prospective clinical trials. ECOG, in a recent phase III study for patients with untreated

low tumor burden indolent lymphoma, integrated HRQL analyses as a key component of correlative studies (E4402, the RESORT trial). This group of low tumor burden patients largely have few physical symptoms associated with their illness; therefore the focus of quality of life studies had emphasis on subjective distress, psychological functioning, and physical and functional wellbeing.

We are seeking to build on ECOG-ACRIN's experience with measuring HRQL among adults with lymphoma by including HRQL endpoints in the proposed trial, thus expanding this research to include NHL patients with high tumor burden. Given the paucity of HRQL among adults with lymphoma, we anticipate that these findings will represent a major contribution to clinical research through enhancing our understanding of patients' functioning and well-being throughout treatment.

Prior quality of life research in lymphoma has demonstrated an association between diagnosis, treatment, relapse and disease progression with impairments in HRQL (physical, functional, emotional and social well-being) and increased anxiety (92-94). A prospective quality of life analysis was performed in elderly Italian patients with aggressive lymphoma treated with different anthracycline-containing chemotherapy regimens (93). They showed that baseline quality of life correlated with IPI score and with anemia. They found that at the end of treatment that no functional scale was worse and that a significant improvement was seen for sleep, appetite, pain, and global health. Moreover, when comparing the quality of life results for patients in CR versus PR or less, only patients in CR had a benefit with respect to emotional state (0.10), role function (0.05), constipation (0.04), and global quality of life (0.05). While patients in PR or less had no quality of life parameter that was significantly improved at the end of therapy. The majority of other quality of life lymphoma data has been collected through uncontrolled studies. In a retrospective analysis, Webster and Cella showed that diagnosis and disease recurrences were associated with a negative psychological impact (91). While Montgomery and colleagues showed that among a variety of leukemia and lymphoma patients that 51% had clinically significant anxiety, 27% reported poor mental adjustment to their illness, 51% had moderate distress, and 14% had severe distress (95,96).

### 1.6.2 Quality of Life Design

We will prospectively measure HRQL (physical, functional, emotional and social well-being) using the Functional Assessment of Cancer Therapy – General (FACT-G) (67). Disease-related symptoms and concerns specific to lymphoma will be assessed using the FACT-Lymphoma subscale (FACT-Lym) (97-99). While limited research has examined HRQL among patients with NHL, emotional function is significantly impacted and is therefore an important endpoint for this trial. Fatigue and neurotoxicity are anticipated to be the most commonly experienced side effects from bortezomib and lenalidomide. Treatment-emergent symptoms will be assessed using

the FACT-Fatigue subscale and neurotoxicity will be assessed using the FACT/GOG-Neurotoxicity subscale.

1.7 Rationale and Importance of Current Study

Despite unchanged survival rates for patients with indolent NHL from the 1950s through the 1990s, several recent randomized phase III clinical trials have shown significantly improved PFS as well improved OS rates, especially with the incorporation of rituximab monoclonal antibody therapy (7,10,11,13,16,18). We intend to build off of this recent clinical success by incorporating the novel targeted therapeutic agents, bortezomib and lenalidomide, both with known single-agent efficacy and safety in NHL (see Sections 1.3 and 1.4 above).

We will achieve maximal cytoreduction in higher risk (increased tumor burden) follicular NHL through improved CR rates with bortezomib incorporated into chemoimmunotherapy induction and through the addition of lenalidomide to rituximab post-induction therapy. This hypothesis is based on strong prior clinical trial data (E1496), which showed that the significant benefit of post-induction rituximab therapy was most effective in patients with quantitative t(14;18) following induction treatment (see Section 1.2.4 above). Better cytoreduction will result in improved PFS and, potentially, OS for patients with high tumor burden indolent NHL. In addition, we will collect specimens for future investigations for biomarkers for response and survival and also examine the importance and impact of different induction chemoimmunotherapy induction regimens and rituximab-based consolidation /maintenance therapy among patients' HRQL.

1.8 Gender and Ethnicities Statement

As there is no a priori reason to expect different treatment effects by gender or ethnicity, entry to this study is not restricted to these categorizations. Subgroup analyses will be conducted to detect any gender and/or ethnicity treatment effects, and any interactions between treatment and these factors. On a recent ECOG trial in low-grade lymphoma (E1496), 56% of the patients are male and 5% are members of minority ethnic groups. It is anticipated that a similar proportion of patients on this study will be males and members of minority ethnic groups.

1.9 Overall Summary/Hypothesis

Our hypothesis is that enhanced induction therapy and/or improved continuation treatment (post-induction) will improve tumor cytoreduction as assessed by achievement of increased CR rates and prolonged DFS for patients with high tumor burden low-grade lymphoma. Furthermore, these new novel therapeutic combinations will be safe and well tolerated among this patient population. This hypothesis is based on our own strong prior clinical trial data (E1496), which showed that the benefit of post-remission rituximab therapy was most significant in patients with quantitative t(14;18) following induction therapy and the achievement of quantitative t(14;18) was the only significant factor for PFS in multivariate analysis. Further, achievement of CR with CVP on the E1496 trial resulted in significantly different PFS at two years (96% v 71%). An important strategy in the current randomized trial is to incorporate novel therapeutic approaches in an attempt to achieve quantitative t(14;18) with increased CR rate following induction therapy and through consolidative therapy immediately following induction. Our hypothesis will be tested in a 3-arm randomized phase II

clinical trial comparing standard therapy of BR induction followed by rituximab continuation vs BVR induction followed by rituximab continuation and vs BR induction followed by lenalidomide/rituximab continuation.

## 2. Objectives

### 2.1 Primary Objectives

2.1.1 To compare the complete remission (CR) rate of BR versus BVR as induction therapy.

2.1.2 To compare the 1-year post-induction disease-free survival (DFS) rate with rituximab plus lenalidomide to rituximab alone as continuation therapy.

### 2.2 Secondary Objectives

2.2.1 To determine the 3-year progression-free survival (PFS) and the 5-year overall survival (OS) with BR, BVR, lenalidomide plus rituximab, and rituximab alone.

2.2.2 To evaluate patient-reported outcomes at baseline and during treatment to determine differences in symptom palliation, treatment-related symptoms and overall health-related quality of life (HRQL) according to treatment arm.

2.2.3 To examine the association between baseline FLIPI information and outcome (CR, DFS, PFS, and OS).

2.2.4 To examine the association between baseline and end-of-treatment patient co-morbidities assessed by the Cumulative Illness Rating Scale (CIRS) and outcome (CR, DFS, PFS, and OS).

2.2.5 To create an image and tissue bank including serial PET/CT scans, diagnostic paraffin-embedded tissue, germline DNA, and serial blood and bone marrow samples sufficient to support proposed and future studies of tumor and host characteristics that may predict for clinical outcome, including treatment arm effects, and enhance existing prognostic indices.

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2.2.6 To evaluate the rate of peripheral neuropathy associated with subcutaneous and intravenous VELCADE (bortezomib).

## 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.

3.1 Randomization to Induction (Step 1)

_____ 3.1.1 Patient must have a histologically confirmed (biopsy-proven) diagnosis of follicular B-cell non-Hodgkin lymphoma (World Health Organization classification: follicular center grades 1, 2, and 3a), with no evidence of transformation to large cell histology.

Patients having ***both*** diffuse and follicular architectural elements will be considered eligible if the histology is predominantly follicular (i.e. ≥ 50% of the cross-sectional area), and there is no evidence of transformation to a large cell histology. If the interval since tissue diagnosis of low-grade malignant lymphoma is > 24 months, diagnostic confirmation using either core needle or excisional lymph node biopsy is required to confirm that the histology remains in one of the eligible categories. Bone marrow biopsy alone is not acceptable.

_____ 3.1.2 Patient must meet criteria for High Tumor Burden (higher risk) as defined by **either** the Groupe D'Etude des Lymphomes Folliculaires (GELF) criteria **OR** the follicular lymphoma international prognostic index (FLIPI):

_____ 3.1.2.1 To meet GELF criteria, a patient must have at least one criterion (please answer yes or no for each criterion):

_____ 3.1.2.1.1 Nodal or extranodal mass > 7 cm (please also document here the largest/longest single nodal or extranodal mass diameter).

Largest size:_____

_____ 3.1.2.1.2 At least 3 nodal masses: all > 3.0 cm in diameter.

_____ 3.1.2.1.3 Systemic symptoms due to lymphoma or B symptoms.

_____ 3.1.2.1.4 Splenomegaly with spleen > 16 cm by CT scan.

_____ 3.1.2.1.5 Evidence of compression syndrome (e.g., ureteral, orbital, gastrointestinal) or pleural or peritoneal serous effusion due to lymphoma (irrespective of cell content).

_____ 3.1.2.1.6 Leukemic presentation (> 5.0 x $10^9$/L malignant circulating follicular cells).

_____ 3.1.2.1.7 Cytopenias (polymorphonuclear leukocytes < 1.0 X $10^9$/L, hemoglobin < 10gm/dL, and/or platelets <100 x $10^9$/L).

**OR**

_____ 3.1.2.2 To meet FLIPI criteria (see Appendix IV for lymph node diagram), a patient must have a score of 3, 4, or 5 (per FLIPI-1, one point each for below criterion; please answer yes or no for each criterion):

_____ 3.1.2.2.1 Age > 60 years

_____ 3.1.2.2.2 Ann Arbor stage III-IV

_____ 3.1.2.2.3 Hemoglobin level < 12 mg/dL

_____ 3.1.2.2.4 > 4 nodal areas (see Appendix IV for nodal diagram)

_____ 3.1.2.2.5 Serum LDH level above normal

_____ 3.1.3 Patient must have stage II, III or IV disease (Modified Ann Arbor Staging – see Appendix XI).

_____ 3.1.4 Baseline measurements and evaluations (PET and CT) must be obtained within 6 weeks of randomization to the study. Combined PET/CT will be sufficient if the PET/CT is performed with oral and intravenous contrast; if PET/CT is without oral and intravenous contrast, then **separate** CTs (in addition to PET/CT) must be obtained. Patient must have at least one objective measurable disease parameter. Measurable disease in the liver is required if the liver is the only site of lymphoma. Please see Section 6 for definition of measurable disease.

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**NOTE:** CTs of neck, chest, abdomen and pelvis must be obtained **≤ 6 weeks** prior to randomization. PET scans must be done ≤ 8 weeks prior to randomization.

_____ 3.1.5 Patient must have had no prior chemotherapy, radiotherapy or immunotherapy for lymphoma. For purposes of this trial, prednisone or other corticosteroids used for non-lymphomatous conditions will not be considered as prior chemotherapy. In addition, a prior/recent short course (< 2 weeks) of steroids for symptom relief of lymphoma-related symptoms will not make a patient ineligible.

_____ 3.1.6 HIV positive patients are not excluded, but to enroll, must meet all of the below criteria:

3.1.6.1 HIV is sensitive to antiretroviral therapy

3.1.6.2 Must be willing to take effective antiretroviral therapy if indicated

3.1.6.3 No history of CD4 prior to or at the time of lymphoma diagnosis < 300 cells/$mm^3$

3.1.6.4 No history of AIDS-defining conditions

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

3.1.6.6 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/$mm^3$, which ever occurs later.

_____ 3.1.7 Patient must have no recent history of malignancy except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the patient has been disease-free for at least 2 years.

_____ 3.1.8 Patient must have adequate organ function as measured by the following criteria, obtained without growth factor and/or transfusion, within 4 weeks of randomization:

3.1.8.1 ANC > 1500 /$mm^3$ (includes neutrophils and bands)

ANC: _____ Date of Test: _____

3.1.8.2 Platelet count > 100,000 /$mm^3$.

Platelet count: _____ Date of Test: _____

**NOTE:** Patients with documented marrow involvement (with lymphoma) at the time of randomization are not required to meet the above hematologic parameters.

3.1.8.3 AST and ALT < 5 x the upper limit of normal.

AST: _____ Date of Test: ____ ULN: ____

ALT: _____ Date of Test: ____ ULN: ____

3.1.8.4 Alkaline phosphatase < 5 x the upper limit of normal.

Alkaline phosphatase: ____ Date of Test: ____ ULN: ____

3.1.8.5 Total bilirubin < 1.5 x the upper limit of normal.

Total Bilirubin: ____ Date of Test: ____ ULN: ____

**NOTE:** Patients with known Gilbert's disease should contact the study PI.

3.1.8.6 Creatinine < 2.0 mg/dL. Creatinine: _____ Date of Test: _____

**NOTE:** Determination of renal function classified by either measured CLcr, or CLcr estimated by Cockcroft-Gault method.

_____ 3.1.9 ECOG performance status 0-2. ECOG PS status: ____

_____ 3.1.10 Patient must have no active, uncontrolled infections (afebrile for > 48 hours off antibiotics).

_____ 3.1.11 Patients must not have ≥ Grade 2 neuropathy.

_____ 3.1.12 Patient must not have myocardial infarction within 6 months prior to registration or have New York Heart Association (NYHA) Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to randomization entry, any ECG abnormality at screening has to be documented by the investigator as not medically relevant.

_____ 3.1.13 Patient must not have serious medical or psychiatric illness likely to interfere with participation in this clinical study

_____ 3.1.14 Patients must not have known hypersensitivity to boron or mannitol.

_____ 3.1.15 Patients must be tested for hepatitis B surface antigen within 6 weeks of randomization. Patients who are chronic carriers of Hepatitis B Virus with + Hepatitis surface antigen (HBsAg +) are excluded, as chemotherapy and B-cell depleting therapy have been associated with virus reactivation and fulminant hepatitis.

Date of Test _____ Result _____

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**NOTE:** Patients with prior history of Hepatitis B infection, but immune, with <u>only</u> IgG Hepatitis core antibody + (HBcAb +) must receive anti-viral prophylaxis (e.g., lamivudine 100mg po daily) for at least 1 week prior to cycle 1 and throughout induction and continuation therapy and for at least 12 months after the last rituximab dose. In addition, consultation with a hepatologist is recommended.

_____ 3.1.16 Age 18 years or older.

_____ 3.1.17 Patient agrees that if randomized to Arm C and proceed onto Arm F they must register into the mandatory RevAssist® program, and be willing and able to comply with the requirements of RevAssist®.

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_____ 3.1.18 For patients randomized to Arms A and B- Women must not be pregnant or breast-feeding due to the use of chemotherapy and/or other therapeutic agents used 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. A female of childbearing potential 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).

Female? _____ (Yes or No)
Date of blood test or urine study: _____

Rev. 10/11 _____ 3.1.19 For patients randomized to Arms A and B- Women of childbearing potential and sexually active males must be strongly advised to use an accepted and effective method of contraception.

_____ 3.1.20 Patients randomized to Arm C and proceeding to Arm F

Rev. 10/11 _____ 3.1.20.1 Women must not be pregnant or breast-feeding due to use of chemotherapy and experimental treatment agents in this protocol. 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 VII - Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

Female of childbearing potential?___ (Yes or No)

Date of blood or urine study?_____

_____ 3.1.20.2 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/lenalidomide: 1) for at least 28 days before starting lenalidomide; 2) while participating in the study; 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.

_____ 3.1.20.3 Women must agree to abstain from donating blood during study participation and for at least 28 days after discontinuation from protocol treatment. 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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_____ 3.1.20.4 Patients must be willing to take DVT prophylaxis as all patients randomized to the lenalidomide/rituximab continuation arm will be required to have deep vein thrombosis (DVT) prophylaxis. Subjects with 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. Subjects without a history of a thromboembolic event are required to take a daily aspirin (81 mg 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.

3.2 <u>Registration to Continuation Therapy (Step 2)</u>

_____ 3.2.1 Patient must have improved their response or have had no interval change in their tumor measurements with restaging from Induction cycle 3 to 6 as determined at Cycle 6 restaging.

_____ 3.2.2 Patient must have adequate organ function as measured by the following criteria, obtained without growth factor and/or transfusion, within 4 weeks of registration:

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3.2.2.1 ANC > 1000/mm$^3$ (includes neutrophils and bands)

ANC: _____ Date of Test: _____

3.2.2.2 Platelet count > 100,000 /mm$^3$.

Platelet count: _____ Date of Test: _____

**NOTE:** Patients with documented marrow involvement (with lymphoma) at the time of registration are not required to meet the above hematologic parameters.

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3.2.2.3 AST and ALT < 5 x the upper limit of normal.

AST: _____ Date of Test: ____ ULN: ____

ALT: _____ Date of Test: ____ ULN: ____

3.2.2.4 Alkaline phosphatase < 5 x the upper limit of normal.

Alkaline phosphatase: ____ Date of Test: ____ ULN: ____

3.2.2.5 Total bilirubin < 1.5x the upper limit of normal.

Total Bilirubin: ____ Date of Test: ____ ULN: ____

**NOTE:** Patients with known Gilbert's disease should contact the study PI.

3.2.2.6 Creatinine < 2.0 mg/dL. Creatinine: _____ Date of Test: _____

**NOTE:** Determination of renal function classified by either measured CLcr, or CLcr estimated by Cockcroft-Gault method.

_____ 3.2.3 ECOG performance status 0-2. ECOG PS status: ____

_____ 3.2.4 Patient must have no active, uncontrolled infections (afebrile for > 48 hours off antibiotics).

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_____ 3.2.5 Patients must not have ≥ Grade 2 neuropathy (Arm F only).

_____ 3.2.6 Patients with prior history of Hepatitis B infection, but immune, with only IgG Hepatitis core antibody + (HBcAb +) must receive anti-viral prophylaxis (e.g., lamivudine 100mg po daily) for at least 1 week prior to cycle 1 and throughout induction and continuation therapy and for at least 9 months after the last rituximab dose. In addition, consultation with a hepatologist is recommended.

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_____ 3.2.7 Additional Requirements for Arm C Induction patients registering to Step 2 (Arm F Lenalidomide/Rituximab):

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_____ 3.2.7.1 Patients must be willing to take deep vein thrombosis (DVT) prophylaxis. Subjects with 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. Subjects without a history of a thromboembolic event are required to take a daily aspirin (81 mg 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.

_____ 3.2.7.2 Women must not be pregnant or breast-feeding due to use of chemotherapy and experimental treatment agents in this protocol. 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

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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 VII - Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

Female of childbearing Potential?___ (Yes or No)

Date of blood or urine study?_____

_____ 3.2.7.2.1 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).

_____ 3.2.7.3 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/lenalidomide: 1) for at least 28 days before starting lenalidomide; 2) while participating in the study; 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.

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

_____ 3.2.7.4 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 the cycles of continuation therapy of which lenalidomide are taken and for at least 28 days after discontinuation/stopping lenalidomide.

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

_____ 3.2.7.5 Patients registering to Arm F must register into the mandatory RevAssist® program, and be willing and able to comply with the requirements of RevAssist®.

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## 4. Registration and Randomization Procedures

### CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

### CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

### CTSU Registration Procedures

**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. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU**

**members' web site by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.**

**Requirements for E2408 site registration:**

- **CTSU IRB Certification**
- **CTSU IRB/Regulatory Approval Transmittal Sheet**

**Submitting Regulatory Documents**

Submit completed forms along with a copy of your IRB Approval *and Model Informed Consent* to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

**CTSU Regulatory Office**
**1818 Market Street, Suite 1100**
**Philadelphia, PA 19103**
**PHONE: 1-866-651-2878**
**FAX: (215) 569-0206**
**EMAIL: CTSURegulatory@ctsu.coccg.org** (for regulatory document submission only)

**Required Protocol Specific Regulatory Documents**

**1. CTSU Regulatory Transmittal Form.**

**2. 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.**

**3. 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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**4. Pharmacy License and Investigator Statement (Appendix XV)**

In order to ship bendamustine, E2408 has a protocol-specific requirement to collect a site pharmacy license. For sites who do not utilize a pharmacy, a signed Investigator Statement (see Appendix XV) is required. This form only

needs to be submitted by the Principal Investigator at each institution, it does not have to be submitted for each sub-investigator.

Before submission of the Investigator Statement, confirm the following:

- All fields are complete
- The form has been signed by the Principal Investigator

**Checking Your Site's Registration Status:**

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- 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 at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

**Patients must not start protocol treatment prior to randomization.**

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**Treatment should start within seven working days after randomization.**

**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://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

**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. 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.**

**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.**

**NOTE: To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol specific funding page on the CTSU members' website for**

**additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.**

**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.**

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**Treatment should start within seven 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. A confirmation of registration will be forwarded by the ECOG-ACRIN Operations Office - Boston.

4.1.5 Classification/Stratification Factors

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4.1.5.1 FLIPI-1score (3 groups): 0 or 1 or 2 factors vs. 3 factors vs. 4 or 5 factors.

4.1.5.2 GELF tumor burden: low vs high.

4.1.6 Additional Requirements

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

**NOTE:** Copies of the consent are not collected by the ECOG-ACRIN Operations Office - Boston.

4.1.6.2 PET/CT and CT scans must be submitted for central review as outlined in Section 11.

4.1.6.3 Quality of life forms are to be submitted as indicated in Section 6.1.2.

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4.1.6.4 Pathology materials must be submitted for central review per Section 10.

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4.1.6.5 Additional specimens are to be submitted for laboratory 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 10.4

4.1.6.6 **Arm C female patients of child-bearing potential:** At the start of cycle 6 of induction therapy, female patients of child-bearing potential are to initiate abstinence from or utilize adequate contraception methods during heterosexual intercourse.

**4.1.6.7 RevAssist® Program**

Lenalidomide will be provided to patients on Arm F 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 RevAssist® program of Celgene Corporation. Per standard RevAssist® requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects randomized to Arm C who then proceed on to Arm F of this trial, must be registered in and comply with all requirements of the RevAssist® program. Refer to Section 8.4.9 of the protocol for complete information on the RevAssist® Program.

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 E2408 Forms Packet. Document the reason for not starting protocol treatment on the off-treatment form. Also report the date and type of the first non-protocol treatment that the patient receives.

## 4.2 Registration (Step 2)

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

**Treatment should start per instructions in Section 5.**

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**NOTE:** Patients for arms D and E should register to step 2 prior to cycle 1, even though no treatment is scheduled for that time period.

The following information will be requested at time of randomization:

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. A confirmation of registration will be forwarded by the ECOG-ACRIN Operations Office - Boston.

4.2.5 Classification Factors

4.2.5.1 Induction Treatment: Arm A vs. Arm B vs. Arm C

4.2.6 Additional Requirements

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4.2.6.1 PET/CT and CT scans must be submitted for central review as outlined in Section 11.

4.2.6.2 Quality of life forms are to be submitted as indicated in Section 6.1.2.

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4.2.6.3 Additional specimens are to be submitted for laboratory studies and/or banking as indicated in Sections 10 and 11, per patient content.

**NOTE:** Submitted scans and specimens must be entered and tracked via the ECOG-ACRIN Sample Tracking System (STS). See Section 10.4.

4.2.6.4 Arm C/Arm F patients must enroll in *RevAssist*® and agree to comply with the *requirements* of the *RevAssist*® *program.* It is recommended that patients register for the program no later than the beginning of Cycle 6 of Induction.

4.2.6.5 RevAssist® Program

Lenalidomide will be provided to patients on Arm F 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 RevAssist® program of Celgene Corporation. Per standard RevAssist® requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects randomized to Arm C who then proceed on to Arm F of this trial, must be registered in and comply with all requirements of the RevAssist® program. Refer to Section 8.4.9 of the protocol for complete information on the RevAssist® Program.

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 E2408 Forms Packet. Document the reason for not starting protocol treatment on the off-treatment form. Also report the date and type of the first non-protocol treatment that the patient receives.

## 4.3 Investigator's Drug Brochure and Safety Alerts

The Investigator Drug Brochures (IDBs) for bortezomib , lenalidomide and bendamustine are available for download from the ECOG webpage. The IDBs provide relevant and current scientific information about the investigational product. The IDBs 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 E2408 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 E2408 study files.

4.4 IND Status

When used in this protocol, bortezomib, lenalidomide and bendamustine are each 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 bortezomib, lenalidomide and bendamustine in this protocol is exempt from the requirements of an IND and described under Title 21 CFR 312.2(b).

## 5. Treatment Plan

**NOTE:** Please refer to Section 5.1.5, Table 2 for a detailed outline of the treatment schedule for each of the three study arms: (i) R-bendamustine induction followed by rituximab continuation OR (ii) RB-bendamustine induction followed by rituximab continuation OR (iii) R-bendamustine induction followed by lenalidomide/rituximab continuation.

**NOTE:** Patients with prior history of Hepatitis B infection, but immune, with only Hepatitis core antibody + (HBcAb +) (i.e., HBsAg and HBV DNA testing must be negative) are allowed to receive treatment on this trial. Additionally, these patients must receive anti-viral prophylaxis (e.g., lamivudine 100mg po daily) for at least 1 week prior to cycle 1 and throughout induction and continuation therapy and for 12 months beyond the last dose of rituximab. In addition, consultation with a hepatologist is recommended.

**NOTE:** See Section 5.4.1 for dose modifications for Rituximab.

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**NOTE:** PET/CT scan imaging requirements for central review are outlined in Section 11.1 and Appendix VI.

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**NOTE:** For all drugs and continuing cycles of therapy, BSA does not need to be re-calculated unless there is a greater than 5% change in weight.

### 5.1 Arm A - BENDAMUSTINE-RITUXIMAB (BR) INDUCTION FOLLOWED BY RITUXIMAB CONTINUATION (ARM D)

#### 5.1.1 Arm A - BR Induction

| Agent | Dose | Route | Day | Cycle Length** |
|---|---|---|---|---|
| Rituximab* | 375 mg/m$^2$ | IV | 1 | Every 28 days |
| Bendamustine | 90 mg/m$^2$ | IV | 1 and 2 | Every 28 days |

All doses are based on actual body weight.

* Rituximab may be rounded to the nearest 50 mg.

** Cycle length may be altered to 26 days (-2 days) or to 31 days (+3 days), for holidays or other extenuating scheduling situations.

**NOTE:** Prophylactic filgrastim or pegfilgrastim may be used in any cycle according to ASCO guidelines (101).

##### 5.1.1.1 Premedication

5.1.1.1.1 Acetaminophen (650 or 1000 mg orally) and diphenhydramine (25 or 50 mg oral or intravenous) 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.

5.1.1.1.2 Standard anti-emetic therapy may be given to patients prior to administration of each

BR treatment: including 5-HT3 serotonin receptor antagonists (e.g., ondansetron 8-16 mg) +/– steroids (e.g., dexamethasone).

5.1.1.2 Administration Schedule

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

5.1.1.2.1 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.

5.1.1.2.2 Bendamustine 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 will be administered to patients after the administration of rituximab.

**NOTE:** See Sections 5.5 and 5.6 regarding supportive care recommendations (for HIV negative and HIV positive patients).

**NOTE:** Dose modifications – BR See Section 5.4.2 for dose modifications (due to toxicity).

5.1.1.3 Restaging and Length of Therapy

5.1.1.3.1 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.

5.1.1.3.2 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 improved their response or have had no interval change in their tumor measurements with restaging from cycle 3 to 6 will then proceed to continuation therapy. Patients who have progressive disease (PD) will discontinue protocol treatment.

5.1.1.4 Arm D -Rituximab Continuation

| Agent | Dose | Route | Day | Cycle Length |
|---|---|---|---|---|
| Rituximab* | 375 mg/m$^2$ | IV | 1 | Every 8 weeks (56 days)** |

Dosing is based on actual body weight.

* The first dose of rituximab continuation should be given **8 weeks** after the start of cycle 6 of induction (i.e., to start week 29 as in Section 5.1.5). The first dose of rituximab must not be delayed longer than 4 weeks from the scheduled time point.

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** May be given +/- 1 week (i.e., at 7 or 9 week interval).

5.1.1.4.1 Premedication

5.1.1.4.1.1 Acetaminophen (650 or 1000 mg) and diphenhydramine (25 or 50 mg) is to be administered 30 to 60 minutes prior to starting each infusion of rituximab.

5.1.1.4.1.2 Since transient hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to rituximab infusion.

5.1.1.4.2 Administration Schedule

Rituximab 375 mg/m$^2$ IV Day 1. The rituximab dose may be rounded to the nearest 50 mg.

**NOTE:** The first dose/infusion of rituximab continuation should be given **8 weeks** after the start of cycle 6 of induction.

5.1.1.5 Length of Therapy

Repeat rituximab dosing every 8 weeks for 2 years (a total of 12 rituximab doses).

5.1.1.6 Dose Modifications: Toxicity Grading

All toxicities should be graded according to the Common Terminology Criteria for Adverse Events.

5.1.1.7 Dose Modifications – Rituximab

See Section 5.4.1.

5.1.2 Arm B - BENDAMUSTINE, RITUXIMAB-BORTEZOMIB (BVR) INDUCTION FOLLOWED BY RITUXIMAB CONTINUATION (ARM E)

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5.1.2.1 Arm B - BVR Induction

| Agent | Dose | Route*** | Days | Cycle Length** |
|---|---|---|---|---|
| Rituximab* | 375 mg/m$^2$ | IV | d 1 | Every 28 days |
| Bortezomib | 1.3 mg/m$^2$ | IV or SQ | d 1, 4, 8, and 11 | Every 28 days |
| Bendamustine | 90 mg/m$^2$ | IV | d 1 and 4 | Every 28 days |

All doses are based on actual body weight.

* Rituximab may be rounded to the nearest 50 mg vial.

** Cycle length may be altered to 26 days (-2 days) or to 31 days (+3 days), for holidays or other extenuating scheduling situations.

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*** See Section 8.3 for key differences between IV and SQ administration.

**NOTE:** Prophylactic filgrastim or pegfilgrastim may be used according to ASCO guidelines (101).

**NOTE:** Anti-viral prophylactic therapy (e.g., acyclovir 400 mg orally BID or valacyclovir 500 mg orally QD) is strongly recommended throughout induction on Arm B and continuing for at least 6 weeks after the last cycle.

5.1.2.1.1 Premedication

5.1.2.1.1.1 Acetaminophen (650 or 1000 mg) and diphenhydramine (25 or 50 mg) 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.

5.1.2.1.1.2 Standard anti-emetic therapy should be given to patients prior to administration of each BVR treatment: including 5-HT3 serotonin receptor antagonists (e.g., ondansetron 8-16 mg) +/– steroids (e.g., dexamethasone).

5.1.2.2 Administration Schedule

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

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5.1.2.2.1 Bortezomib 1.3 mg/m$^2$ IV or SQ Days 1, 4, 8, and 11 (four total doses per cycle).

5.1.2.2.2 Rituximab 375 mg/m$^2$ IV Day 1. The rituximab dose may be rounded to the nearest 50 mg. See Section 5.4.1 regarding rituximab infusion rates.

5.1.2.2.3 Bendamustine will be administered to patients by IV infusion on days 1 and 4 of each 28-day cycle. The infusions are given over a 60-minute period and on day 1 will be administered to patients after the administration of rituximab.

**NOTE:** See Sections 5.5 and 5.6 regarding supportive care recommendations (for HIV negative and HIV positive patients).

**NOTE:** Dose Modifications – BVR: See Section 5.4.3 for dose modifications (due to toxicity).

5.1.2.3 Restaging and length of therapy

5.1.2.3.1 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.

5.1.2.3.2 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 improved their response or have had no interval change in their tumor measurements with restaging from cycle 3 to 6 will then proceed to rituximab continuation as below in Section 5.1.2.4. Patients who have progressive disease (PD) will discontinue protocol treatment.

5.1.2.4 Arm E - Rituximab Continuation

| Agent | Dose | Route | Day | Cycle Length |
|---|---|---|---|---|
| Rituximab* | 375 mg/m$^2$ | IV | 1 | Every 8 weeks (56 days)** |

Dosing is based on actual body weight.

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* The first dose of rituximab continuation should be given **8 weeks** after the start of cycle 6 of induction (i.e., to start week 29 as in Section 5.1.5). The first dose of rituximab must not be delayed more than 4 weeks from the scheduled time point.

** May be given +/- 1 week (i.e., at 7 or 9 week interval).

5.1.2.4.1 Premedication

Acetaminophen (650 or 1000 mg) and diphenhydramine (25 or 50 mg) 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.

5.1.2.4.2 Administration Schedule

Rituximab 375 mg/m$^2$ IV Day 1. The rituximab dose may be rounded to the nearest 50 mg.

**NOTE:** The first dose/infusion of rituximab continuation should be given **8 weeks** after the start of cycle 6 of induction.

5.1.2.4.3 Length of Therapy

Repeat rituximab dosing every 8 weeks for 2 years (a total of 12 rituximab doses).

5.1.2.4.4 Dose Modifications: Toxicity Grading

All toxicities should be graded according to the Common Terminology Criteria for Adverse Events (version 4.0).

5.1.2.4.5 Dose Modifications – Rituximab

See Section 5.4.1.

5.1.3 Arm C - BENDAMUSTINE-RITUXIMAB (BR) INDUCTION FOLLOWED BY LENALIDOMIDE AND RITUXIMAB CONTINUATION (ARM F)

5.1.3.1 Arm C - BR Induction

| Agent | Dose | Route | Day | Cycle Length** |
|---|---|---|---|---|
| Rituximab* | 375 mg/m$^2$ | IV | 1 | Every 28 days |
| Bendamustine | 90 mg/m$^2$ | IV | 1 and 2 | Every 28 days |

All doses are based on actual body weight.

* Rituximab may be rounded to the nearest 50 mg vial.

** Cycle length may be altered to 26 days (-2 days) or to 31 days (+3 days), for holidays or other extenuating scheduling situations.

**NOTE:** Prophylactic filgrastim or pegfilgrastim may be used according to ASCO guidelines (101).

5.1.3.2 Premedication

5.1.3.2.1 Acetaminophen (650 or 1000 mg) and diphenhydramine (25 or 50 mg) 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.

5.1.3.2.2 Standard anti-emetic therapy may be given to patients prior to administration of each

treatment: including 5-HT3 serotonin receptor antagonists (e.g., ondansetron 8-16 mg) +/– steroids (e.g., dexamethasone).

5.1.3.3 Administration Schedule

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

5.1.3.3.1 Rituximab 375 mg/m$^2$ IV Day 1. The rituximab dose may be rounded to the nearest 50 mg. See Section 5.4.1 regarding rituximab infusion rates.

5.1.3.3.2 Bendamustine 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 will be administered to patients after the administration of rituximab.

**NOTE:** See Sections 5.5 and 5.6 regarding supportive care recommendations (for HIV negative and HIV positive patients).

**NOTE:** Dose Modifications – BR: See Section 5.4.2 for dose modifications (due to toxicity).

5.1.3.4 Restaging and Length of Therapy

5.1.3.4.1 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.

5.1.3.4.2 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 improved their response or have had no interval change in their tumor measurements with restaging from cycle 3 to 6 will then proceed to continuation therapy. Patients who have progressive disease (PD) will discontinue protocol treatment.

5.1.4 Arm F - Lenalidomide/Rituximab Continuation

| Agent | Dose* | Route | Day | Cycle Length |
|---|---|---|---|---|
| Lenalidomide** | 20 mg | PO | 1 through 21 | Every 28 days |
| Rituximab*** | 375 mg/m$^2$ | IV | 1 | Every 8 weeks (56 days) |

All doses are based on actual body weight.

* See Section 5.4.4 regarding dose reductions of lenalidomide.

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** The first cycle of Lenalidomide should start **4 weeks** after the start of cycle 6 of induction (i.e., to start week 25 as in Section 5.1.5). Also, please see Appendix V for the pill diary that must be filled out for each cycle/dose of lenalidomide therapy. The first dose of lenalidomide must not be delayed more than 6 weeks from the scheduled time point.

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*** The first dose of rituximab continuation should be given **8 weeks** after the start of cycle 6 of induction (i.e., to start week 29 as in Section 5.1.5). Rituximab therapy will be given every 8 weeks (every 56 days) "on schedule" regardless of potential delay or withdrawal of lenalidomide. In addition, rituximab may be given +/- 1 week (i.e., at 7 or 9 week interval). The first dose of rituximab must not be delayed more than 4 weeks from the scheduled time point.

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For a patient that discontinues lenalidomide after undergoing all three dose reductions, they are able to remain on-study and continue with rituximab maintenance. In addition, if a patient is unable to tolerate lenalidomide and the treating physician discontinues lenalidomide prior to undergoing all three dose reductions, they may stay on study and continue with rituximab maintenance, however this must be discussed with the study PI.

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**NOTE:** Missed or delayed doses of lenalidomide will not be given or made up. Any missed or delayed dose should be recorded in the patient pill diary as missed or delayed.

5.1.4.1 Lenalidomide fertility instructions

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

**Before starting study drug:**

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All study participants must be registered into the mandatory RevAssist® program, and be willing and able to comply with the requirements of RevAssist®. 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 VIII: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

**NOTE:** 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).

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5.1.4.2 Anticoagulation

All subjects randomized to lenalidomide/rituximab continuation therapy will be **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 Coumadin 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 Coumadin treatment or another accepted full anticoagulation regimen.

Of note, if platelets decline to < 50,000/mm$^3$, prophylactic anti-coagulation should be stopped (in addition to holding lenalidomide as below in Section 5.7.5). 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.

5.1.4.3 Rituximab Premedication.

- Acetaminophen (650 or 1000 mg) and diphenhydramine (25 or 50 mg) 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.

5.1.4.4 Administration Schedule

a. Lenalidomide 20mg PO days 1 through 21 on a 28-day cycle.

**NOTE:** The first cycle of Lenalidomide will start **4 weeks** after the start of cycle 6 of induction. See Table in Section 5.1.5.

**NOTE:** Prior to starting lenalidomide continuation, 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).

**NOTE:** Creatinine clearance should be calculated prior to the first dosing of lenalidomide.

**NOTE:** See Appendix V for the lenalidomide pill diary that must be filled out for each cycle/dose of lenalidomide therapy.

b. Rituximab 375 mg/$m^2$ IV Day 1. The rituximab dose may be rounded to the nearest 50 mg.

**NOTE:** The first dose of rituximab continuation should be given **8 weeks** after the start of cycle 6 of induction.

**NOTE:** All patients receiving Lenalidomide based continuation therapy must complete the Lenalidomide pill diary for each cycle/dose of Lenalidomide (see Appendix V).

5.1.4.5 Length of Therapy

5.1.4.5.1 Repeat rituximab dosing every 8 weeks for 2 years (a total of 12 rituximab doses).

5.1.4.5.2 Lenalidomide therapy is given every 4 weeks for a total of 13 cycles.

5.1.4.6 Dose Modifications: Toxicity Grading

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

5.1.4.7 Dose Modifications- Rituximab

See Section 5.4.1

5.1.4.8 Dose Modifications- Lenalidomide

See Section 5.4.4

5.1.5 Overall Treatment Plan

**Table 2 Treatment schedule/timing**

**NOTE:** Restage after every three (3) Rituximab treatments.

| | | | | |
|---|---|---|---|---|
| Rev. 4/13 | **RANDOMIZATION (STEP 1)** stratification factors: GELF tumor burden (Low vs High) and FLIPI (0-2 vs. 3 vs. 4-5) | | | |
| | | **BR Induction (Arm A)** | **BVR Induction (Arm B)** | **BR Induction (Arm C)** |
| | *6 cycles of Induction* | *BR Induction* | *BVR Induction* | *BR Induction* |
| | Cycle = 28 days 1: Wk 1-4 | *BR* #1 | *BVR* #1 | *BR* #1 |
| | 2: wk 5-8 | *BR* #2 | *BVR* #2 | *BR* #2 |
| | 3: wk 9-12 | *BR* #3 | *BVR* #3 | *BR* #3 |
| | | RESTAGE #1 | | |
| | 4: wk13-16 | *BR* #4 | *BVR* #4 | *BR* #4 |
| | 5: wk17-20 | *BR* #5 | *BVR* #5 | *BR* #5 |
| | 6: wk21-24 | *BR* #6 | *BVR* #6 | *BR* #6 |
| | | RESTAGE #2 | | |
| Rev. 4/13 | **REGISTRATION (STEP 2)*** Prior to Week 25 | | | |
| | *Year 1 of Continuation (52 weeks)* | **Rituximab Continuation (Arm D)** | **Rituximab Continuation (Arm E)** | **Lenalidomide/Rituximab Continuation (Arm F)** |
| | Cycle = 28 days C1: w 25-28 | No treatment | No treatment | Lenalidomide #1 |
| | 2: wk29-32 | Rituximab #1 | Rituximab #1 | Rituximab #1 and Lenalidomide #2 |
| | 3: wk33-36 | No treatment | No treatment | Lenalidomide #3 |
| | 4: wk37-40 | Rituximab #2 | Rituximab #2 | Rituximab #2 and Lenalidomide #4 |
| | 5: wk41-44 | No treatment | No treatment | Lenalidomide #5 |
| | 6: wk45-48 | Rituximab #3 | Rituximab #3 | Rituximab #3 and Lenalidomide #6 |
| | 7: wk49-52 | No treatment | No treatment | Lenalidomide #7 |
| Rev. 4/13 | | RESTAGE #3 Prior to Week 53 | | |
| | 8: wk53-56 | Rituximab #4 | Rituximab #4 | Rituximab #4 and Lenalidomide #8 |
| | 9: wk57-60 | No treatment | No treatment | Lenalidomide #9 |
| | 10: wk61-64 | Rituximab #5 | Rituximab #5 | Rituximab #5 and Lenalidomide #10 |
| | 11: wk65-68 | No treatment | No treatment | Lenalidomide #11 |
| | 12: wk69-72 | Rituximab #6 | Rituximab #6 | Rituximab #6 and Lenalidomide #12 |
| | 13: wk73-76 | No treatment | No treatment | Lenalidomide #13 |
| Rev. 4/13 | | RESTAGE #4 After Week 76 | | |
| | *Year 2 of Continuation* | *Rituximab (alone) continuation- all patients* | | |
| | Cycles 14-18 | Rituximab to continue every 8 weeks for 3 doses (given Cycles 14, 16, 18) Odd Cycles: no Treatment | | |
| Rev. 4/13 | | RESTAGE #5 Prior to start of Cycle 20 | | |
| | **Cycles 20-24** | **Rituximab to continue every 8 weeks for 3 doses (given Cycles 20, 22, 24) Odd Cycles: no Treatment** | | |
| | | RESTAGE #6 | | |

*Rituximab therapy to be given every 8 weeks "on schedule" regardless of potential delay (or withdrawal) of Lenalidomide. Rituximab may be given +/- 1 week (i.e., at 7 or 9 week interval).

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## 5.2 Adverse Event Reporting Requirements

### 5.2.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (please refer to the E2408 Forms Packet for the list of forms with directions for routine adverse event reporting). Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. The following sections provide information about expedited reporting.

### 5.2.2 Determination of Reporting Requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event; 3) the phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

**Steps to determine if an adverse event is to be reported in an expedited manner:**

Step 1: *Identify the type of event:* The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

Step 2: *Grade the event using Version 4.0 of the NCI CTCAE*.

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial).* Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event*. *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 only, when either the type of event or the severity of the event is **NOT** listed in:

- **Arm A, B, C, D, E, and F** – the drug package insert, Investigator Brochure, or protocol

Step 5: *Review Section 5.2.6 for E2408 and/or ECOG-ACRIN specific requirements for expedited reporting of specific adverse events that require special monitoring.*

**NOTE:** For general questions regarding expedited reporting requirements, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497.

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5.2.3 Reporting Methods

**Arms A, B, C, D, E and F**- This study requires that expedited adverse event reporting use 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

- the FDA (800-332-1088) and
- the AE Team at ECOG-ACRIN (617-632-3610)

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

**Supporting and follow up data**: Any supporting or follow up documentation must be faxed to ECOG-ACRIN (617-632-2990), Attention: AE 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 When to Report an Event in an Expedited Manner

When an adverse event requires expedited reporting, submit a full CTEP-AERS report within the timeframes outlined in Section 5.2.6

**NOTE:** Adverse events that meet the reporting requirements in Section 5.2.6 and occur within 30 days of the last dose of protocol treatment must be reported on an expedited adverse event report form (using CTEP-AERS). For any adverse events that occur more than 30 days after the last dose of treatment, only those that have an attribution of possibly, probably, or definitely AND meet the reporting requirements in Section 5.2.6 must be reported on an expedited adverse event report form (using CTEP-AERS).

5.2.5 Other Recipients of Adverse Event Reports

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

Adverse events determined to be reportable 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.

A drug supporter representative may call a site for additional 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.

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### 5.2.6 Expedited Reporting for Commercial Agents

Commercial reporting requirements are provided below. The commercial agents used in arms Arm A, B, C, D, E, and F of this study are Rituximab, Bortezomib, Lenalidomide and Bendamustine.

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only – Arms A, B, C, D, E, and F

| 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 | d |

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

**a** This includes all deaths within 30 days of the last dose of treatment regardless of attribution. **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.

Rev. 2/14

**Pregnancy:**

Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) occurring while the subject is onprotocol treatment, or within 28 days of the subject's last dose of protocol treatment, are considered immediately reportable events. **The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge.**

Rev. 9/14

**Please refer to Appendix XVI for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.**

Rev. 5/11

### 5.2.7 Reporting Second Primary Cancers

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. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at:

ECOG-ACRIN Operations Office - Boston
FSTRF
900 Commonwealth Avenue
Boston, MA 02215

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. Submit a copy of the pathology report to ECOG-ACRIN and NCI/CTEP confirming the diagnosis.
4. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG-ACRIN and 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.

## 5.3 Comprehensive Adverse Events and Potential Risks List (CAEPR)

Rev. 5/12, 9/14

### 5.3.1 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Bortezomib

Rev. 5/12, 9/13, 9/14

The Comprehensive Adverse Events and Potential Risks List (CAEPR) provides a thorough and single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. The CAEPRS 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 2.5, June 30, 2014**[1]

| **Adverse Events with Possible Relationship to PS-341 (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 | | |
| INFECTIONS AND INFESTATIONS | | |
| Infection[4] | | |
| INVESTIGATIONS | | |
| | Neutrophil count decreased | |
| Platelet count decreased | | |
| | Weight loss | |
| METABOLISM AND NUTRITION DISORDERS | | |
| Anorexia | | |
| | Dehydration | |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | |
| | Arthralgia | |

| | | |
|---|---|---|
| | Back pain | |
| | Bone pain | |
| | Musculoskeletal and connective tissue disorder - Other (muscle spasms) | |
| | Myalgia | |
| | Pain in extremity | |
| NERVOUS 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]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

**Also reported on PS-341 (bortezomib, Velcade) trials but with the relationship to PS-341 (bortezomib, Velcade) still undetermined:**

**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** - Hepatic failure; Hepatobiliary disorders - Other (hepatitis); 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; Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; 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; GGT increased; INR increased; Investigations - Other (albumin); 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); Tumor lysis syndrome

**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:** PS-341 (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.

Rev. 10/11, 9/13
10/14, 7/16

### 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 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 4081 patients. Below is the CAEPR for lenalidomide (CC-5013).

**Version 2.6, December 24, 2015**[1]

| **Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 4.0 Term) [n= 4081]** | | |
|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | |
| Anemia | | |
| CARDIAC DISORDERS | | |
| | | Myocardial infarction[2] |
| ENDOCRINE DISORDERS | | |
| | Hypothyroidism | |
| GASTROINTESTINAL DISORDERS | | |
| Constipation | | |
| Diarrhea | | |
| | Nausea | |
| | | Pancreatitis |
| | Vomiting | |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | |
| | Chills | |
| | Edema limbs | |
| Fatigue | | |
| | Fever | |
| HEPATOBILIARY DISORDERS | | |
| | | Hepatic failure |
| IMMUNE SYSTEM DISORDERS | | |
| | | Anaphylaxis |
| | | Immune system disorders - Other (graft vs. host disease)[3] |
| INFECTIONS AND INFESTATIONS | | |
| | Infection[4] | |
| INVESTIGATIONS | | |
| | | Lipase increased |
| | Lymphocyte count decreased | |
| Neutrophil count decreased | | |
| Platelet count decreased | | |
| | Weight loss | |
| | White blood cell decreased | |

| | | |
|---|---|---|
| METABOLISM AND NUTRITION DISORDERS | | |
| | Anorexia | |
| | | Tumor lysis syndrome |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | |
| | Arthralgia | |
| | Back pain | |
| | Musculoskeletal and connective tissue disorders - Other (muscle cramp/muscle spasm) | |
| | Myalgia | |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) | | |
| | | Leukemia secondary to oncology chemotherapy[5] |
| | | Myelodysplastic syndrome[5] |
| | | Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor flare)[6] |
| | | Treatment related secondary malignancy[5] |
| NERVOUS SYSTEM DISORDERS | | |
| | Dizziness | |
| | Headache | |
| | | Stroke[2] |
| | | Leukoencephalopathy |
| PSYCHIATRIC DISORDERS | | |
| | Insomnia | |
| RENAL AND URINARY DISORDERS | | |
| | | Acute kidney injury |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | |
| | Cough | |
| | Dyspnea | |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | |
| | | Erythema multiforme |
| | Hyperhidrosis | |
| | Pruritus | |
| | Rash maculo-papular | |
| | Skin and subcutaneous tissue disorders - Other (pyoderma gangrenosum) | |
| | | Stevens-Johnson syndrome |
| | | Toxic epidermal necrolysis |
| SURGICAL AND MEDICAL PROCEDURES | | |
| | | Surgical and medical procedures - Other (impaired stem cell mobilization)[7] |
| VASCULAR DISORDERS | | |
| | Thromboembolic event[8] | |

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

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

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

[8] 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.

[9] 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.

[10] 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.

[11] 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 (eosinophilia); Blood and lymphatic system disorders - Other (monocytosis); Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Febrile neutropenia; Hemolysis; Spleen disorder

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

**EAR AND LABYRINTH DISORDERS** - Tinnitus

**ENDOCRINE DISORDERS** - Cushingoid; Hyperthyroidism

**EYE DISORDERS** - Blurred vision; Conjunctivitis; Dry eye; Flashing lights; Retinopathy

**GASTROINTESTINAL DISORDERS** - Abdominal distension; Abdominal pain; Anal mucositis; Ascites; Colonic perforation; Dry mouth; Dyspepsia; Dysphagia; Flatulence; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (Crohn's disease aggravated); Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other

(pale feces); Gastrointestinal hemorrhage[9]; Gastrointestinal obstruction[10]; Ileus; Mucositis oral; Rectal mucositis; Small intestinal mucositis

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - General disorders and administration site conditions - Other (edema NOS); Malaise; Multi-organ failure; Non-cardiac chest pain; Pain

**HEPATOBILIARY DISORDERS** - Cholecystitis

**IMMUNE SYSTEM DISORDERS** - Allergic reaction; Immune system disorders - Other (angioedema)

**INFECTIONS AND INFESTATIONS** - Infections and infestations - Other (Opportunistic infection associated with >=grade 2 lymphopenia)

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

**INVESTIGATIONS** - Activated partial thromboplastin time prolonged; Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Cholesterol high; Creatinine increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (hemochromatosis)

**METABOLISM AND NUTRITION DISORDERS** - Acidosis; Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia

**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Arthritis; Bone pain; Chest wall pain; Generalized muscle weakness; Joint effusion; Muscle weakness lower limb; Musculoskeletal and connective tissue disorders - Other (rhabdomyolysis); Neck pain; Osteonecrosis of jaw[11]; Pain in extremity

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

**NERVOUS SYSTEM DISORDERS** - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysgeusia; Dysphasia; Edema cerebral; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Memory impairment; Myelitis; Nervous system disorders - Other (hyporeflexia); Nervous system disorders - Other (spinal cord compression); Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Syncope; Transient ischemic attacks; Tremor

**PSYCHIATRIC DISORDERS** - Agitation; Anxiety; Confusion; Depression; 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; Epistaxis; Hypoxia; Laryngeal mucositis; Pharyngeal mucositis; Pleural effusion; Pneumonitis; Pulmonary hypertension; Respiratory failure; Tracheal mucositis; Voice alteration

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

**VASCULAR DISORDERS** - Hot flashes; Hypertension; Hypotension; 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.

### 5.3.3 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Rituximab (NSC 687451)

The Comprehensive Adverse Event 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. They are developed and continuously monitored by the CTEP Investigational Drug Branch (IDB). The information listed in the CAEPR(s) below, as well as the other resources described in the 'Determination of reporting requirements' part of the Adverse Event Reporting section in this 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 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] | |
| | 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 | |
| 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.

## 5.4 Dose Modifications

All toxicities should be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

### 5.4.1 Dose Modifications – Rituximab

**NOTE:** There is no dose reduction for rituximab, only infusion rate adjustment or discontinuation.

#### 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.

Rituximab should be administered intravenously through a dedicated line at an initial rate of 50 mg/hr. 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).

**Table 3. 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. If there are no complications after one hour of observation, the intravenous line may be discontinued. If/once the patient is transitioned to rapid rituximab infusion (i.e. 90 minute infusion), vital signs, observation and related care may be done according to institutional standards.

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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 – BR

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**NOTE:** Bendamustine-related infusion reactions can be treated according to the appropriate standard of care.

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) must resolve to grade 0 or 1 or the grade at baseline before beginning the next treatment cycle. Toxicity is measured using the National Cancer Institute Common Terminology Criteria for Adverse Events.

5.4.2.2 Hematologic

At the start of each cycle, ANC must be at least 1000/$mm^3$ and platelet count must be at least 75000/$mm^3$ to proceed with treatment (unless the patient has documented marrow involvement with lymphoma suppressing bloodcounts). Routine granulocyte-colony stimulating factor (G-CSF) support is not required but in the case of severe or life threatening (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 BR to be administered (eg, ANC > 1 x $10^9$/L, platelets > 75 x$10^9$/L).

5.4.2.3 Dose Reductions

5.4.2.3.1 If thrombocytopenia of grade 2 or higher or neutropenia of grade 3 or higher persists for 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.

5.4.2.3.2 Patients who experience bendamustine-related grade 4 hematologic 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 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 study-drug-related grade 4 hematologic toxicity, grade 3 or 4 nonhematologic toxicity, or grade 2 or greater thrombocytopenia or 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 3 or 4 non-hematologic toxicity+ | Reduce dose to 75 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 3 or 4 non-hematologic toxicity+ | Reduce dose to 60 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 3 or 4 non-hematologic toxicity+ | Reduce dose to 45 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 3 or 4 non-hematologic toxicity+ | Stop bendamustine |
| | 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.

\+ Due to bendamustine; and excluding grade 3 nausea/vomiting

5.4.3 Dose Modifications – BVR

5.4.3.1 BR component

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

5.4.3.2 Bortezomib

5.4.3.2.1 Grade 4 hematologic toxicity and/or Grade 2 or greater thrombocytopenia and/or grade 3 or higher neutropenia that requires a dose delay of 2 weeks: if patient is receiving bendamustine at 90 mg/m2, then only bendamustine will be reduced as in Table 4.

If any of these toxicities re-occur (at a bendamustine dose of 75 mg/m$^2$ or lower), and if the toxicity returns to Grade 1 or better, and bortezomib is to be restarted, the dose must be reduced by approximately 25% as follows (for all days):

| Dose Level | Dosage |
|---|---|
| 0 | 1.3 mg/m$^2$ |
| -1 | 1 mg/m$^2$ |
| -2 | 0.7 mg/m$^2$ |
| -3 | Contact the study chair |

5.4.3.2.2 For grade 3 or grade 4 non-hematologic toxicity (besides neurotoxicity- see Section 5.4.3.2.3 and Table 5) 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 resolved 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 approximately 25% as follows (for all days):

| Dose Level | Reduce dose to: |
|---|---|
| 1.3 mg/m$^2$ | 1 mg/m$^2$ |
| 1 mg/m$^2$ | 0.7 mg/m$^2$ |
| 0.7 mg/m$^2$ | Contact the study chair |

If the patient was receiving 0.7 mg/m$^2$, the case should be discussed with the study chair.

5.4.3.2.3 Neurotoxicity

Follow the table immediately below when assessing neurotoxicity. Bortezomib dose reductions apply to all days (1, 4, 8, and 11) dosing of this drug. 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) in the E2408 Forms packet. This is an important tool for determining the presence and intensity of neuropathic pain and/or peripheral neuropathy from the patients' perspective. Neuropathic symptoms are more prominent than abnormalities on the clinical examination. After the patient completes the neurotoxicity-direct 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.

5.4.3.2.4 Hepatic Impairment

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

**NOTE:** Patients with bilirubin levels greater than 1.5 ULN

(> 1.5) are excluded from enrollment in this protocol.

**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 and/or loss of reflexes) without pain or loss of function | No action |
| Grade 1 with pain | Reduce by one dose level (see Table 6) |
| Grade 2 without pain (Moderate symptoms; limiting instrumental ADL) | Hold* bortezomib therapy until toxicity improves to grade 1 or resolves. When toxicity improves/resolves, re-initiate with a reduction by 1 dose level and change treatment schedule to once per week (see Table 6) |
| Grade 2 with pain or Grade 3 (Severe symptoms; limiting self care ADL) | Hold* bortezomib therapy until toxicity improves to grade 1 or resolves. When toxicity improves/resolves, re-initiate with a reduction by two dose levels and change treatment schedule to once per week (see Table 6) |
| Grade 4 (Life-threatening consequences; urgent intervention indicated) | Discontinue bortezomib (permanently) |

ADLs = activities of daily living

***Hold:** Interrupt bortezomib for up to 3 weeks until the toxicity returns to Grade 1 or resolves.

**Activities of Daily Living (ADL):** Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

**Table 6. Dose level reductions of bortezomib.**

| | |
|---|---|
| **One dose level** | 1.3 to 1* |
| **Two dose levels** | 1.3 or 1* to 0.7 mg/m$^2$/dose |
| **Schedule change** | Change from twice per week (days 1,4,8, and 11) to once per week (days 1 and 8);** |

* If the patient is receiving 1 mg/m$^2$/dose biweekly and experiences repeat grade 1 with pain then patient should have schedule change to once per week. If grade 1 pain re-occurs on weekly dosing, then contact the Principal Investigator.

** If patient is receiving once weekly bortezomib dosing and experiences grade 1 with pain or repeat grade 2 or more toxicity, contact the Principal Investigator.

5.4.4 Dose Modifications- Lenalidomide

Subjects will be evaluated for adverse events at each visit with the revised NCI CTCAE version 4.0 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 5.1.4 for

dose reduction instructions for lenalidomide (including fertility instructions).

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Any missed or delayed doses of lenalidomide will not be given or made up. Any missed or delayed dose should be recorded in the patient pill diary as missed or delayed. In addition, rituximab should be given "on schedule" regardless of missed lenalidomide doses.

Rev. 9/14

For a patient that discontinues lenalidomide after undergoing all three dose reductions, they are able to remain on-study and continue with rituximab maintenance. In addition, if a patient is unable to tolerate lenalidomide and the treating physician discontinues lenalidomide prior to undergoing all three dose reductions, they may stay on study and continue with rituximab maintenance, however this must be discussed with the study PI.

**Table 7. Dose Modifications for Lenalidomide.**

| NCI CTCAE Toxicity Grade | Action Required |
|---|---|
| Sustained (≥ 7 days)<br>Grade 3 **neutropenia** or > any Grade 3 neutropenia associated with fever (temperature > 38.5° C) or any Grade 4 neutropenia | Hold (interrupt dosing)<br>Follow CBC every seven days<br>If neutropenia has resolved to ≤ Grade 2 restart at next lower dose level<br>Use of growth factors (filgrastim, pegfilgrastim) is permitted at the discretion of the investigator |
| **Thrombocytopenia**<br>≥ Grade 3 (platelet count <50,000 cells/$mm^3$ [50 X $10^9$/L]) | Hold (interrupt dosing) lenalidomide.<br>Hold prophylactic anti-coagulation.<br>Follow CBC weekly every seven days<br>If thrombocytopenia resolves to ≤ Grade 2 restart at next lower dose level (and restart prophylactic anti-coagulation) |
| **Allergic reaction or hypersensitivity***<br>Grade 2 | Hold (interrupt) dose. Follow at least every seven days<br>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. |
| Grade 3-4 | Discontinue Lenalidomide. |
| Desquamating (blistering) rash- any Grade | Discontinue Lenalidomide. |
| Venous thrombosis/embolism<br>> Grade 3 | • Hold (interrupt) lenalidomide and start anticoagulation; restart lenalidomide at investigator's discretion (maintain dose level).<br>Omit lenalidomide for remainder of cycle. See Anticoagulation Consideration (Section 5.1.4.2) |
| Other non-hematologic toxicity > Grade 3** | • Hold (interrupt) lenalidomide dose. Follow at least weekly.<br>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 below section regarding modifications for renal insufficiency.

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

- The ANC is ≥ 1,000 cells/$mm^3$ (1.0 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 study chair must be notified.

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 20 mg daily on Days 1-21 every 28 days.

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

| Dose level | Dosage |
|---|---|
| 0 | 20 mg daily on Days 1-21, every 28 days |
| Level –1 Dose | 15 mg daily on Days 1-21, every 28 days |
| Level –2 Dose | 10 mg daily on Days 1-21, every 28 days |
| Level –3 Dose* | 5 mg daily on 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.

5.4.4.2 Renal insufficiency: Lenalidomide dosing

Patients with creatinine clearance of ≥ 60 mL/min will be started at lenalidomide 20mg daily on Days 1-21 of each 28-day cycle as above. No dose adjustments are required for patients with CLcr >/= 60 mL/min.

Patients with creatinine clearance of ≥ 30 mL/min but < 60 mL/min will be started at lenalidomide 10mg daily (Dose modification calculated at 50% rounded down) 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 will occur at the start of a cycle). For these patients who start on 10mg daily, de-escalation of one dose level will be allowed to 5mg. Further dose de-escalation will be allowed to 5mg every other day. 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 should be started at lenalidomide 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. Once a subject's dose has been reduced, no dose re-escalation is permitted.

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

5.5 Supportive Care (non-HIV)

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

5.5.2 Filgrastim (Neupogen) or Pegfilgrastim (Neulasta) granulocyte colony stimulating factors (G-CSFs) 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.

5.5.3 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). Some authorities recommend, that patients receive pneumocystis prophylaxis during all chemotherapy (e.g., Bactrim DS on Mondays, Wednesdays, and Fridays or Dapsone 50 mg orally twice daily for subjects allergic to Bactrim) as well as prophylaxis for oral thrush (e.g, fluconazole 100 mg daily or oral nystatin).

5.5.4 Anti-viral prophylactic therapy (e.g., acyclovir 400mg orally BID or valacyclovir 500mg orally QD) is strongly recommended for patients who are randomized to receive BVR induction therapy (i.e., Arm B). All other patients should be administered treatment at the discrection of the treatment physician, but it is recommended for patients with recent history of zoster or other HSV infection.

5.6 Supportive care therapy for HIV positive patients.

5.6.1 HAART (highly active anti-retroviral therapy): In general, HIV-positive patients who are on a stable HAART regimen should continue HAART while receiving chemotherapy. However, for patients who are newly diagnosed with HIV, it is preferable to defer starting HAART until after chemotherapy is completed. HAART regimens containing zidovudine

and stavudine should be avoided during chemotherapy due to concerns for overlapping toxicity with chemotherapy. In addition, the protease inhibitor atazanavir (Rayataz™) can cause a physiologically unimportant hyperbilirubinemia; however, in the setting of chemotherapy, some experts suggest switching that drug for another equally effective one. If HAART is withheld during chemotherapy, it should be resumed promptly after conclusion of the last cycle of chemotherapy.

5.6.2 Bactrim (one double strength tablet twice daily three days per week) should be given for Pneumocystis and Toxoplasmosis prophylaxis to HIV-positive patients during induction chemotherapy (all study arms). Dapsone (50 mg orally twice daily), atovaquone, or aerosolized pentamidine may be substituted for Pneumocystis prophylaxis in subjects allergic to Bactrim. Pneumocystis prophylaxis should be continued until the CD4 cells are over 200/mcL.

5.6.3 Fluconazole, 100 mg daily, should be given for antifungal prophylaxis for patients during induction chemotherapy (all study arms). Itraconazole, 200 mg daily, should be substituted for fluconazole for histoplasmosis prophylaxis if the CD4 count falls below 150/mcL and if the patient lives in an endemic area.

5.6.4 Anti-viral prophylactic therapy (e.g., acyclovir 400mg orally BID or valacyclovir 500mg orally QD) should be administered at the discretion of the treatment physician, but it is recommended for patients with recent history of zoster or other HSV infection and is strongly recommended for patients randomized to Induction BVR therapy (i.e., arm B).

5.6.5 Azithromycin, 1,200 mg PO, once weekly, should be given for prophylaxis against Mycobacterium avium complex if the CD4 count falls below 50/mcL.

5.6.6 Administration of granulocyte growth factors (filgrastim, pegfilgrastim, sargramostim) is recommended in HIV+ patients during induction chemotherapy (e.g. 5 mcg/kg subcutaneously of filgrastim daily) until the leukocyte count has recovered to > 1 x $10^9$/L.

5.7 Duration of Therapy

Patients will receive protocol therapy unless:

5.7.1 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 instructions in the E2408 Forms Packet.

5.7.2 Patient withdraws consent.

5.7.3 Progressive disease.

5.7.4 Unacceptable toxicity.

5.7.5 Suspected pregnancy.

## 5.8 Duration of Follow-up

5.8.1 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-Hodgkins Lymphoma Response Criteria

**NOTE:** These criteria are based upon the criteria from the Revised Response Criteria for Malignant Lymphoma (158).

**NOTE:** PET-CTs will be reviewed centrally for quality assurance purpose. Please see Section 11.2 and Appendix VI for further details regarding QARC central review.

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.
- Measurements for all dominant nodes and extranodal masses will be reported at baseline. Measurements on non-dominant nodes are not required.
- 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, 2.1cm, 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.

### 6.1 Complete Response

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

6.1.1 For lymphomas for which 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.

6.1.2 If the 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.

No new sites of disease.

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).

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

6.3.3 For variably FDG-avid lymphomas/FDG-avidity unknown: 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 < 1 x < 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 > 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 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

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 or the first date of unscheduled new anti-lymphoma treatment.

6.8 Time to Progression

Time to progression (TTP) is defined as the time from study entry until lymphoma progression or death due to lymphoma. In TTP, deaths from other causes are censored either at the time of death or at an earlier time of assessment, representing a random pattern of loss from the study. TTP is not as useful as PFS unless the majority of deaths on a study are unrelated to the lymphoma due to the efficacy of the treatment and/or prolonged follow-up.

6.9 Time to Treatment Failure

Time to treatment failure (event-free survival) is measured from the time from study entry to any treatment failure including discontinuation of treatment for any reason, such as disease progression, toxicity, patient preference, initiation of new treatment without documented progression, or death. This composite endpoint is generally not encouraged by regulatory agencies because it combines efficacy, toxicity and patient withdrawal.

6.10 Disease-Free Survival

Disease-free survival is measured from the time of occurrence of disease-free state (e.g., the adjuvant setting following surgery or radiation therapy) or attainment of a complete remission) to disease recurrence or death from lymphoma or acute toxicity of treatment. This definition may be complicated by deaths that occur during the follow-up period that are unrelated to the lymphoma and there is controversy as to whether such deaths should be considered as events or censored at the time of occurrence. Whereas it is often possible to

identify those deaths related to the lymphoma, there is the potential for bias in the attribution of deaths.

6.11 Disease-Specific Survival

Disease-specific survival (e.g., lymphoma-specific survival, cause-specific survival) is potentially subject to bias because the exact cause of death is not always easy to ascertain. To minimize the risk of bias, the event should be recorded as death from lymphoma, or from toxicity from the drug. Death from unknown causes should be attributed to the drug. For certain trials, time to next lymphoma treatment may be of interest, defined as time from the end of primary treatment until the initiation of the next therapy.

6.12 Quality of Life Measurement

6.12.1 Quality of life materials must be submitted at the time points listed below. Please refer to the table below and see the E2408 Forms Packet. Failure to submit materials may render the patient unevaluable.

6.12.2 Hypothesis

We hypothesize that HRQL will provide a meaningful comparison of the different induction and continuation therapies in this randomized phase III study and that HRQL data will complement the standard assessment of treatment-related toxicity. Please see Section 1.6 above for more detailed background/significance and hypothesis discussion.

Prospective data will be informative to clinicians and patients in providing descriptive data on what to expect with regard to these domains during and following treatment. Long-term follow-up will provide valuable descriptive data on patients' HRQL as they transition from active treatment to survivorship. In addition, these results will be used to identify the most relevant endpoints for follow-up phase III trials, to calculate power estimates to adequately address follow-up HRQL questions, and to establish minimally important differences to evaluate clinically meaningful changes over time and between treatment arms.

6.12.3 Study Design

We will prospectively measure HRQL (physical, functional, emotional and social well-being) using the Functional Assessment of Cancer Therapy – General (FACT-G) (97). Disease-related symptoms and concerns specific to lymphoma will be assessed using the FACT-Lymphoma subscale (FACT-Lym) (97-99). The FACT-Lym used in this study will encompass of the parameters of the FACT-G.While limited research has examined HRQL among patients with NHL, emotional function is significantly impacted and is therefore an important endpoint for this trial.

Fatigue and neurotoxicity are anticipated to be the most commonly experienced side effects from bortezomib and lenalidomide. Treatment-emergent symptoms will be assessed using the FACT-

Fatigue subscale and neurotoxicity will be assessed using the FACT/GOG-Neurotoxicity subscale.

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**Table 9. Quality of Life Studies.**

| QOL Form | Baseline | Induction | Continuation |
|---|---|---|---|
| FACT-Lym and FACT-Fatigue | X | At response assessment #1 (prior to cycle 4) | On day 1 (at start) of continuation;<br>at 6 months of continuation;<br>at 12 months of continuation;<br>at 24 months (end) of continuation |
| FACT/GOG Neurotoxicity | X | Prior to each induction cycle (starting at cycle 2) | At the start of each rituximab cycle for the first year of continuation. Every 4 months for the second year. |

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6.12.4 Quality of Life Studies to be Performed

(1) FACT-Lymphoma subscale (FACT-Lym) - 42 items.

(2) FACT-Fatigue scale - 13 items.

(3) FACT/GOG-Neurotoxicity scale - 11 items.

6.12.5 Administration Instructions

6.12.5.1 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.

6.12.5.2 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.

6.12.5.3 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.

6.12.5.4 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.

6.12.5.5 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.

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

# 7. Study Parameters

## 7.1 Therapeutic Parameters

1. Prestudy scans and x-rays used to assess all measurable or non-measurable sites of disease must be done ≤ **6 weeks** prior to randomization. PET scan may be ≤ **8 weeks** prior to randomization. Rev. 4/13

2. If the patient had a bone marrow within the previous 12 months positive for lymphoma then the patient does not need a repeat bone marrow performed (besides the correlative study bone aspirate with consent- See Section 11.1.2). All other patients should have a restaging bone marrow biopsy and aspirate **≤ 8 weeks** prior to registration. Rev. 9/14

3. Prestudy CBC (with differential and platelet count) should be done ≤ **4 weeks** before randomization.

4. All required prestudy chemistries, should be done ≤ **4 weeks** before randomization – unless specifically required on Day 1 as per protocol.

5. History & Physical, adverse events, performance status, tumor assessment by physical exam, FLIPI and GELF assessment, and Co-morbidity assessments should be done **≤ 2 weeks** before randomization. Rev. 9/14

See Section 7.2 below regarding biologic sample submissions.

**Table 10. Study Parameters**

| | | Induction (BR or BVR) | | Continuation (rituximab or lenalidomide/rituximab) | | Post-Therapy Follow-up |
|---|---|---|---|---|---|---|
| **Parameter** | **Pre-study** | **Cycles[1]** | **Restaging** | **Cycles[2]** | **Restaging** | |
| Assignment of FLIPI scores[3] | X | | | | | |
| Notation of GELF criteria[3] | X | | | | | |
| History and Physical examination | X | Every cycle | | X | | X[18] |
| Performance Status | X | Every cycle | | X | | X[18] |
| Tumor Measurements by Physical Exam (if applicable) | X | Every cycle | X | X | X | X[18] |
| CBC and Differential[4] | X[4] | Every cycle | | X | | X[18] |
| Serum Chemistries (electrolytes, SGOT, SGPT, total bilirubin, direct bilirubin,[5] LDH, creatinine, glucose, alkaline phos, and calcium) | X | Every cycle | | X | | X[18] |
| Beta-2-microglobulin | X | | | X (prior to 1st dose) | | |
| Uric acid | X | | | | | |
| Rev. 10/11 Rev. 9/14 Bone marrow aspirate biopsy[16] | X[16] | | After cycle 6[6] | | | |
| Pregnancy test (for women of child-bearing potential)[7] | X | | | X[8] | | |
| Hepatitis B surface antigen and core antibody testing | X[9] | | | | | |
| Rev. 1/15 TSH | X | | | X[14] | Every 6 months during continuation and at completion of continuation | |
| CD4 count and HIV viral load (HIV + patients only) | X | After cycle 3 and after 6 | | X[19] | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Creatinine clearance | X[10] | | | | | |
| Rev. 5/12 | CT Neck, Chest, Abdomen, and Pelvis[12] | X[11] | | After cycle 3 and after 6[11,12] | After cycles 7, 13, 18, 24 | X[12,19] | X[18] |
| Rev. 2/14 | PET/CT Scan[12] | X[11] | | After cycle 3 and after 6[11,12] | | | |
| | Quality of life studies[13] | X | See Section 6.12 | See Section 6.12 | See Section 6.12 | See Section 6.12 | |
| | Co-morbidity assessment[15] | X | | | | | X[15] |
| | Registration to RevAssist[17] | See section 8.4.9 | | | | | |
| Rev. 10/11 | Biological Sample Submissions | See Section 7.2 | | | | | |

1. Cycles are every 28 days. Patients may be evaluated in the office more frequently, if needed, at physician discretion.
2. Rev.4/13, 9/14 Rev. 2/14 Cycles are every 28 days for all arms in continuation therapy, however patients treated in arms D and E of continuation do not need to be seen in clinic (or have blood tests/labs done) q 28 days unless clinically warranted.. All patients should be seen in clinic on the first cycle of continuation for H&P and completion of HRQL forms. Please refer to treatment schedule in Section 5.1.5. If a delay occurs in lenalidomide, rituximab treatment should still be continued "on time." Any missed or delayed doses of lenalidomide should be recorded in the patient diary as missed or delayed.
3. Yes/No should be entered for each criterion of GELF and FLIPI, as well as absolute calculation of FLIPI-1 and FLIPI-2. (See Section 3.1.2 and Appendix IV).
4. At baseline: please record the absolute lymphocyte count.
5. Direct bilirubin is required only if total bilirubin is elevated.
6. Repeat biopsy/core and aspirate only if positive at baseline. Bone marrow biopsy and aspirate should also be obtained at time of relapse.
7. Within 10-14 days prior to start of induction treatment. See Section 3.1.18 for definition of female of childbearing potential.
8. For patients randomized to Arm C and registered to Arm F, pregnancy tests 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 (see Appendix VIII: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).All patients should receive the Lenalidomide Information Sheet (Appendix XIV) each time lenalidomide is dispensed.

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 (e.g., lamuvidine 100mg po QD) 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 continuation therapy starts - especially for patients randomized to lenalidomide therapy (see Section 5.4), and then repeated thereafter as clinically indicated.
11. Rev. 2/14 Combined PET/CT scan will be sufficient if the PET/CT is performed with intravenous and oral contrast; if PET/CT is without oral and intravenous contrast (it is OK to avoid IV contrast when clinical scenario dictates), then separate/dedicated CTs of neck/chest/abdomen/pelvis (in addition to PET/CT) must be obtained. PET/CTs and CTs will be reviewed centrally for quality assurance purposes. Please see Section 11.2 and Appendix VI (FDG-PET/CT and CT IMAGING) for further details regarding QARC central review guidelines.
12. Rev. 9/14 It is acknowledged that due to particular circumstances, there may be situations for follow-up scans that both dedicated CT scans with contrast and a PET/CT scans will not be able to be obtained; in this circumstance, PET/CTs are the preferred imaging modality. Notably however, once a patient enters complete remission, then only CT's (chest/abdomen/pelvis) should be obtained (not both PET/CT and dedicated CTs).
13. See Section 6.12 and the E2408 Forms Packet for appropriate timing and required forms.
14. Rev. 9/14 Should be drawn prior to 1st treatment. Further thyroid evaluation/testing (e.g., T3, T4, T3 uptake) to be completed as clinically indicated at the discretion of treating physician.
15. See Section 9.2.3 and Appendix X for further details/methods for completion. Obtain once at baseline (pre-treatment) and then repeat once at the end of continuation therapy (at the end of 2 years of continuation).
16. Rev. 10/11, 9/14 Bilateral bone marrow biopsies are strongly recommended, but not required. If the patient had a bone marrow biopsy within the previous 12 months that was positive for lymphoma, then the patient does not need a repeat bone marrow performed. However, the correlative pre-study study bone aspirate with consent is still recommended (See Section 7.2 and Section 11)
17. After randomization to Arm C and registration to Arm F. Please see Section 8.4.9 for more information.
18. Rev. 10/11, 9/14 Patients in follow-up will follow this schedule:

    For scans

    - Every 6 months if the patient is between 2 and 5 years from the study entry.
    - After 5 years from study entry, at physician discretion.

    For disease progression and survival

    - Every 6 months if the patient's between 2 and 5 years from study enrty.
    - Every 12 months if the patient is between 5 and 15 years from the study entry.
19. Refer to Section 5.1.5 for restaging schedule.

## 7.2 Biological Sample Submissions

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**NOTE:** Submitted scans and specimens must be entered and tracked via the the ECOG-ACRIN Sample Tracking System (STS). See Section 10.4.

**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.

| | Baseline | Induction, Cycle 2 | Induction, Post -Cycle Three (3) Restaging | Prior to Start of Continuation[2] | After Twelve (12) Months of Continuation[2] | End of Continuation[2] | Relapse | Ship to: |
|---|---|---|---|---|---|---|---|---|
| **MANDATORY** for Central Review | | | | | | | | |
| Rev. 1/15 Diagnostic Tumor Biopsy[6] | X | | | | | | | CBPF (Section 10 |
| PET/CT and CT Scans[3] | X | | X | X[7,8] | | X | X | QARC (Section 11.1.1) |
| **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.*" | | | | | | | | |
| Tumor Tissue | Any on study biopsy[5] | | | | | | | CBPF (Section 10) |
| Peripheral Blood (red top tubes) | X[1] | X | | X | X | X | | Mayo Clinic Lymphoma Laboratory (Section 11.1.2) |
| Rev. 9/14 Peripheral Blood (EDTA purple top tubes)[9] | X[1] | X | | X | X | X | | |
| Rev. 5/12 Bone Marrow Aspirate (EDTA purple top tubes) | X[4,5,10] | | | X[5] | | | | |

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1. Baseline blood should be collected after randomization, prior to treatment. Collect three (3) 10mL EDTA tubes and one (1) 10mL red top tube at each time point.
2. Specimens may be collected at time of restaging assessments. Blood specimens may also be collected the day of but prior to the next administration of the study drugs, if given.
3. The clinical PET/CTs and CTs performed to determine eligibility and to monitor disease are to be submitted as outlined in Section 11.1 and Appendix VI (FDG-PET/CT and CT IMAGING) for further details regarding QARC central review guidelines. Scans will be reviewed centrally for quality assessment purposes.

4. Bone marrow from the pre-study assessment may be submitted prior to randomization on the day of collection. Any amount of bone marrow will be accepted. However, for patients with an inaspirable bone marrow ("dry tap"), or if bone marrow has been done previously and the patient refuses to have another aspiration done, call Kim Henderson at (507) 284-3805 to discuss the case and the possibility for submitting peripheral blood only.

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5. Samples are to be submitted from patients who consent to participate in the laboratory research studies OR who answer "Yes" to "I agree to provide additional specimens for research."
6. 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.
7. Once a patient enters complete remission, then only CT's (chest/abdomen/pelvis) will be obtained (no further restaging PET scanning); if a patient is not in complete remission at the completion of induction (i.e., stable disease or partial remission), then restaging PET scans will be continued (see Table 10).
8. After six (6) cycles.
9. Draw 30mL of blood at baseline and 20mL for all other time points.
10. Patient must sign consent before submission of bone marrow aspirate. If submitting initial bone marrow aspirate prior to patient enrollment to the trial, please use the Generic Specimen Submission Form (#2981) when sending the bone marrow and label with patient identifiers. Once the patient has been randomized please call Kim Henderson (507) 284-3805 with the ECOG-ACRIN patient sequence number and enter the information into the ECOG-ACRIN Sample Tracking System.

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## 8. Drug Formulation and Procurement

### IND Status

When used in this protocol, bortezomib, lenalidomide and bendamustine are each 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 bortezomib, lenalidomide and bendamustine in this protocol is exempt from the requirements of an IND and described under Title 21 CFR 312.2(b).

8.1 Bendamustine (NSC 138783)

For complete information, please refer to the Investigator Brochure or the package insert.

8.1.1 Other Names

Bendamustine hydrochloride, CEP-18083), TREANDA.

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

Description of Drug Substance and Formulation

Bendamustine (TREANDA) for injection, 100 mg/vial, is a sterile, non-pyrogenic lyophilized product for intravenous administration. Bendamustine (TREANDA) for injection, 100 mg/vial, contains 100 mg of bendamustine (active ingredient) and 170 mg of mannitol. Mannitol is a bulking excipient which yields a physically stable and readily re-dissolvable lyophilized product.

Intact vials may be stored up to $25^0$C with excursion permitted up to $30^0$C. Vials should be retained in the original package until time of use to protect from light.

Admixture Stability: Bendamustine (TREANDA) contains no antimicrobial preservative. The admixture should be prepared as close as possible to the time of patient administration.

Once diluted with either 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 36-47°F) or for 3 hours when stored at room temperature (15-30°C or 59-86°F) and room light. Administration of bendamustine (TREANDA) must be completed within this period.

8.1.5 Dose Specifics

Bendamustine will be administered as a 60-minute IV infusion at a dose of 90 mg/m$^2$ on days 1 and 4 of each 28-day cycle.

8.1.6 Dosage in Renal or Hepatic Failure

In a population pharmacokinetic analysis of bendamustine in patients receiving 120 mg/m2 there was no meaningful effect of renal impairment (CrCL 40 - 80 mL/min, N=31) on the pharmacokinetics of bendamustine. Bendamustine has not been studied in patients with CrCL < 40 mL/min. These results are however limited, and therefore bendamustine should be used with caution in patients with mild or moderate renal impairment. Bendamustine should not be used in patients with CrCL < 40 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

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.

8.1.8 Administration

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.

8.1.9 Compatibilities

No incompatibilities are known (no data is available).

8.1.10 Availability

**Drug Orders:**

**Initial Orders:** Following submission of the required documents and patient randomization, a supply of Bendamustine may be ordered from Teva Oncology. Institutions must fax the completed E2408 Bendamustine Drug Request Form (Appendix XIII and available on the ECOG Web Site) to Teva Oncology at 610-727-2030.

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Please indicate the number of vials needed on the E2408 Bendamustine Drug Request Form (Appendix XIII). **Please note that vials are packaged in multiples of 10. Each vial is equal to 100 mg of bendamustine.**

**No Starter Supplies are available for this protocol.**

Institutions should allow 3 business days for receipt of the Bendamustine from the date the drug request is received by Teva Oncology. Shipments will be made from Teva Oncology Monday through Thursday for delivery onsite Tuesday through Friday.

**There will be no weekend or holiday delivery of drugs.**

**Reorders**: Institutions should keep in mind that shipments take 3 business days from the date the drug request is received by Teva Oncology. Reorders using the E2408 Bendamustine Drug Request Form (Appendix XIII) should be faxed to Teva Oncology at 610-727-2030. Once approved by Teva Oncology, the drug will be received on site within 3 business days. Shipments will be made from Teva Oncology on Monday through Thursday for delivery onsite Tuesday through Friday. **Please note that vials are packaged in multiples of 10. Each vial is equal to 100 mg of bendamustine.**

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**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:**

At the completion of the patient's treatment at your institution, all unused drugs, partially used, or empty containers must be destroyed at the site according to the institution's policy for drug destruction. Please maintain appropriate records of the disposal, including dates and quantities. Sites are required to complete the Certificate of Drug Destruction of Clinical Trials located in Appendix VII – Bendamustine Reconciliation. A copy of this form should be faxed to Teva Oncology at 610-756-2030.

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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

- 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

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

8.1.12.1.1 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.

8.1.12.1.2 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.

8.1.12.1.3 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/mm³ and increased risk of bleeding with platelet counts less than 20,000 cells/ mm³. 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 with antiemetics.
5. Observe for possible phlebitis at injection site.
6. Administer antiemetics as indicated.

8.1.14 References

Bertoni F, Zucca E. Bendamustine in lymphomas: More to combine? Leukemia & Lymphoma 2007;48(7):1264-6.

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 continuation).

### 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. 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. If there are no complications after one hour of observation, the intravenous line may be discontinued. Oral pre-medication (2 tablets, 650 to 1000 mg, of acetaminophen and 25 to 50 mg diphenhydramine) 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 strongly advised 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.

**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).

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. If there are no complications after one hour of observation, the intravenous line may be discontinued.

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 the CAEPR in Section 5.3.3.

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) should be used in patients with bulky tumor masses (> 10cm). Patients should be provided IV hydration and administered allopurinol. 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. It is unlikely that TLS will be seen in this study of stages 1 and 2 diffuse large cell disease.

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 (NSC 681239)

For complete information, please refer to the Investigator Brochure or the package insert.

### 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, PS-341

### 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 Arm B, a supply of Bortezomib may be ordered from UVI, Inc. Institutions must electronically submit the completed E2408 Bortezomib Drug Request Form (Appendix XII and available on the ECOG Web Site) to UVI, Inc at mdubois@uintavision.com.

When ordering Bortezomib for Arm B, please see below for the recommended time table for drug requests. A total of 2 shipments are recommended for patients on Arm B. 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 E2408 Bortezomib Drug Request Form (Appendix XII). **NOTE**: A supply of individual vials of bortezomib is currently available for distribution through UVI, Inc. Once this supply is depleted, 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.

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**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 Arm B. 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 E2408 Bortezomib Drug Request Form (Appendix XII) should be emailed to UVI, Inc, at mdubois@uintavision.com. **NOTE**: A supply of individual vials of bortezomib is currently available for distribution through UVI, Inc. Once this supply is depleted, 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.

Rev. 12/10

Rev. 12/10

**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 E2408 Clinical Trial Material Return Request Form (Appendix XII, page 2) to 1-866-422-4797. 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.

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8.3.8 Preparation

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

INTRAVENOUS: 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. 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.

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

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

Bortezomib will be given at a dose of 1.3 mg/m² on days 1, 4, 8, and 11 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.

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8.3.11 Route of Administration

Intravenous OR Subcutaneous

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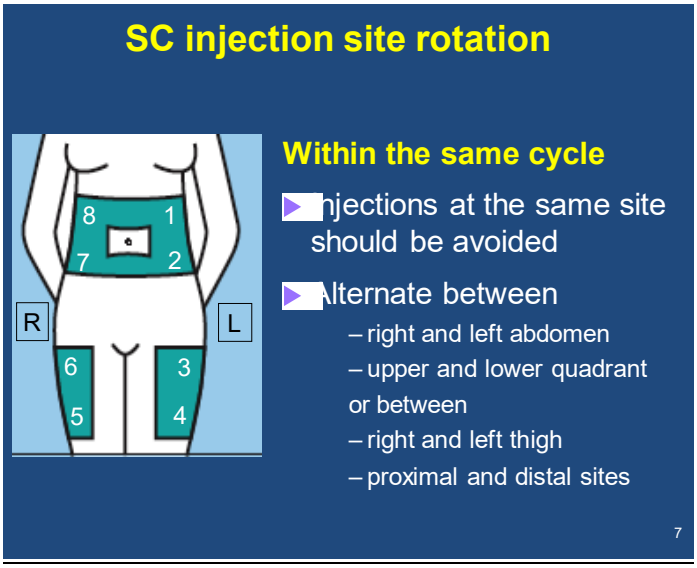
8.3.12 Method of Administration

For intravenous administration: IV push over 3-5 seconds

For subcutaneous administration: The drug quantity contained in one vial (3.5 mg) may exceed the usual dose required. Caution should be used in calculating the dose to prevent overdose. When administered subcutaneously, sites for each injection (thigh or abdomen) should be rotated as noted in the below diagram.

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 VELCADE administration subcutaneously, a less concentrated VELCADE solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously. Alternatively, the IV route of administration should be considered.

In clinical trials of VELCADE IV, local skin irritation was reported in 5% of patients, but extravasation of VELCADE was not associated with tissue damage. In a clinical trial of subcutaneous VELCADE, a local reaction was reported in 6% of patients as an adverse event, mostly redness.




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 5.3.1.

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.

8.3.17 References

Bortezomib Investigator Drug Brochure. Millennium Pharmaceuticals. Version 13.

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 complete information, please refer to the Investigator Brochure or the 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

How Supplied: Lenalidomide is supplied as 5 mg, 10 mg, or 15 mg hard gelatin capsules for oral administration in tamper evident, child-resistant, opaque, high density polyethylene (HDPE) bottles with HDPE caps. Bottles will contain a sufficient number of capsules for one cycle of dosing.

The capsules also contain anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

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

Stability: Shelf life surveillance of the intact containers is on-going. The intact bottles of 5 mg, 10 mg, and 15 mg capsules are stable for at least 36 months when stored at controlled room temperature (15-30°C).

8.4.5 Dose Specifics

Patients will receive lenalidomide at 20mg orally on days 1 through 21 on 28 day cycles (i.e., days 22 to 28 to stop/not take lenalidomide) during continuation 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 < 60 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 -1), and then 5mg every other day (dose level -2). Once a subject's dose has been reduced, no dose re-escalation is permitted.

8.4.6 Patients with creatinine clearance of < 30 mL/min by Cockroft-Gault formula should be started at lenalidomide 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 -1). Once a subject's dose has been reduced, no dose re-escalation is permitted.

8.4.7 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.

8.4.8 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.

8.4.9 Availability

**Drug Orders:**
**RevAssist® Program**

Lenalidomide will be provided to patients on Arm F 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 RevAssist® program of Celgene Corporation. Per standard RevAssist® requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects randomized to Arm C who then proceed on to Arm F of this trial, must be registered in and comply with all requirements of the RevAssist® 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 Arm C. These steps register the patient and physician into the RevAssist program. Once it is determined the patient is eligible to proceed on to Arm F 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 RevAssist® 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 20mg, given to patients on Arm F, 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 20 mg, you may order **one** of the following combinations per cycle:

| Capsule Strength | Quantity needed for one cycle |
|---|---|
| 10mg | 42 pills |
| **OR** | |
| 5mg<br>**Plus**<br>15mg | 21 pills<br>**Plus**<br>21 pills |
| **OR** | |
| 5mg | 84 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 Arm C. These steps register the patient and physician into the RevAssist program. Once it is determined the patient is eligible to proceed on to Arm F 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 RevAssist® program by either calling 1-888-423-5436 or registering through www.REVLIMID.com.
2. Patient must be randomized to Arm C and eligible to proceed on to Arm F.
3. Prescribing physician assists patient to enroll in the RevAssist® program by obtaining and signing a Patient-Physician Agreement Form (PPAF) either through calling Celgene Customer Care at 1-888-423-5436 or via www.REVLIMID.com
4. Patient signs the appropriate PPAF and agrees to follow all the procedures of the commercial RevAssist® Program. The prescribing physician will then fax the completed PPAF to Celgene at 1-888-432-9325
5. Patient and prescriber complete the phone surveys as required by the RevAssist® Program by calling Celgene Customer Care at 1-888-423-5436 or utilizing the RevAssist online® access.
6. At the completion of the survey, the prescribing physician is given a RevAssist® authorization number. They complete the RevAssist® for Study Participants Clinical Trial Prescription Form

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(Appendix IX and available on the ECOG Web Site) and faxes it to Biologics, Inc. at 919-256-0794.

7. Prescribing physician advises the patient that a representative from a RevAssist® contract pharmacy will contact them by phone within 24 hours.
8. RevAssist® contract pharmacy calls patient to conduct patient education.
9. RevAssist® contract pharmacy calls Celgene Customer Care for confirmation number.
10. RevAssist® 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 RevAssist® Program by calling Celgene Customer Care at 1-888-423-5436 or utilizing the RevAssist online® access.
2. At the completion of the survey, the prescribing physician is given a RevAssist® authorization number. They complete the RevAssist® for Study Participants Clinical Trial Prescription Form (Appendix IX and available on the ECOG Web Site) and faxes it to Biologics, Inc. at 919-256-0794.

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3. Prescribing physician advises the patient that a representative from a RevAssist® contract pharmacy will contact them by phone within 24 hours.
4. RevAssist® contract pharmacy calls patient to conduct patient education.
5. RevAssist® contract pharmacy calls Celgene Customer Care for confirmation number.
6. RevAssist® 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 RevAssist® 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.

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**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.

8.4.10 Side Effects

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Please refer to the CAEPR in Section 5.3.2.

8.4.11 Nursing/ Patient Implications

1. Ensure women of childbearing potential 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 Coumadin 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 Coumadin treatment or another accepted full anticoagulation regimen.
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. 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.
9. 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.

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 2 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.

# 9. Statistical Considerations

## 9.1 Primary Endpoints

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The study is a randomized three arm trial at 1:2:2 ratios to the control arm (Arm A: BR+R) and two experimental arms (Arm B: BVR+R and Arm C: BR+R/L). Patients will be randomized to the three arms stratified on patient follicular lymphoma international prognostic index (0-2 vs 3 vs 4-5 risk factors) and GELF tumor burden (low vs. high). With 250 patients accrued over 25 months (10 patients per month) and a projected 5% ineligible rate, the study will have 236 eligible patients with 48 on the control arm and 94 on each of the experimental arms.

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At the Fall 2013 DSMC meeting, 185 out of 250 patients have enrolled to the study. We observed a 9% ineligible or inevaluable rate, which is higher than the 5% rate projected in the original design. In addition, 23% patients did not registered for step 2 continuation after step 1 treatment. The non-enrollment rate was 17% after BR induction for arm A and C, and was 33% after BVR induction for arm B.

After discussion with NCI, the study team decided to increase the accrual to arms A and C in order to preserve the power for the second primary analysis of the lenalidomide question, while closing arm B once the original accrual goal is met. Assume a 9% ineligibility rate and 17% non-enrollment rate (percentage of patients that will not register for step 2 continuation) after BR induction, 24% (1-0.91*0.83) of initial enrollment will not be available for the analysis of the secondary primary endpoint (1-year DFS after BR induction). Therefore, the accrual goal is increased from 250 to 286. The additional 36 patients will be randomized at 1:2 ratios to the control arm (Arm A+D: BR+R) and the experimental arm Arm C+F: BR+R/L. This increase in accrual will ensure around 48 patients on the Arm A+D (BR+R) and 94 patients on arm C+F (BR+R/L) registered for step 2 and available for the analysis of the second primary endpoint. The calculation used an average drop-off rate from two BR induction arms (arm A and C), we consider that the impact on power of uneven drop-off rate between these two arms is small.

### 9.1.1 The first primary endpoint

The first primary objective is to compare the complete remission (CR) rate after induction with BVR vs BR. The definition of complete remission (CR) is based upon the criteria from the Revised Response Criteria for Malignant Lymphoma (158). It is expected that the CR rate for the BR arm will be 50% based on a compilation of data in the literature. The study will target a 16% increase in CR rate to 66% for the BVR arm. With 142 patients on BR (Arms A +C) and 94 patients on BVR, the trial will have 90% power, at the one-sided 0.15 significance level, to detect a difference in CR rate of 16% or more between the BVR and BR arms (Fisher's exact test). The primary analysis will be performed using Cochran-Mantel-Haenszel (CMH) test, stratified on the FLIPI (scores of 3 vs 4,5) and GELF (low vs high) criteria. In case few FLIPI 0-2 patients enter the study; they will

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be included into the group of FLIPI 3.

9.1.2 The second primary endpoint

The second primary objective is to compare the 1-year post-induction disease-free survival (DFS) rate of rituximab/lenalidomide (R/L) with rituximab (R) alone continuation following BR induction. DFS rate is defined as the percentage of patients that are alive and in complete remission (CR). The proportion of patients achieving CR during induction or consolidation and maintaining CR at 1 year after induction completion will be determined. As above, the expected CR rate for BR is 50%. Assuming 95% of induction patients proceed to continuation (CR=50%, PR/SD=45%), we expect about 18% of PR/SD of patients, or about 8% of all continuation patients, to improve response to CR after 1-year of standard rituximab continuation. We also expected that about 8% of continuation patients will progress during this period of time (16% of induction CR patients). Therefore, the expected 1-year post-continuation DFS rate for the rituximab continuation following standard BR induction therapy is 50%. With 48 patients on BR+R (Arm A) and 94 patients on BR+R/L (Arm C), the trial will have 87% power, at the one-sided 0.15 significance level (Fisher's exact test), to detect a difference in DFS rate of 20% or more between the rituximab-alone arm (Arm A) and the rituximab + lenalidomide arm (Arm C) following BR induction. This difference corresponds to an improvement in DFS rate from 50% in the rituximab-alone consolidation therapy to 70% in the combination of rituximab and lenalidomide arm (Arm C). A per-protocol analysis will be performed including all patients registered to step 2 continuation. Sensitivity analysis will also be conducted by treating patients that do not continue on treatment beyond induction (e.g., progressed on induction therapy) as not being in disease-free status 1 year after induction.

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9.2 Secondary Endpoints

The secondary endpoints include progression-free survival (PFS) and overall survival (OS). With 48 patients on BR+R and 94 patients on both BR+R/L and BVR+R, the trial will have 84% power to detect a 15% difference in 3-yr PFS rate from 75% on R-bendamustine+R to 90% on BR+R/L and BVR +R, and a 15% difference in 5-yr OS rate from 75% on BR+R to 90% on BR+R/L and BVR +R, at one-sided 0.15 significance level.

As part of the in-depth analysis, we will assess the effect of continuation therapy (DFS, PFS and OS rate) in converting partial response (PR) or stable disease (SD) from induction into complete remission (CR). Descriptive statistics (mean and 95% confidence interval) will be used to summarize the conversion rate for each of the three arms. Potential prognostic factors will be correlated with conversion status by Fisher's exact test or Chi-square test, logistic regression will be used to assess the effect on conversion from the combination of multiple factors. We will also evaluate the effect of continuation therapy in maintaining disease-free status for patients who achieve CR after induction, summary statistics will be used to report 1-yr DFS, 3-yr PFS and 5-yr OS rate for induction CRs for each of the three arms.

We will also examine the association of the original FLIPI score (FLIPI-1) and the recently reported FLIPI-2 score that was recently reported (132). We will also determine the relationship between FLIPI-2 score and outcome (CR, DFS, PFS, and OS). For binary outcomes, logistic regression will be used to assess this relationship; for time-to-event outcomes, the method of Kaplan and Meier and the logrank test, as well as Cox proportional hazards models, will be used to assess the relationship with FLIPI score.

9.2.1 Image and Tissue Bank

To explore the potential of metabolic tumor burden to predict clinical outcome and enhance existing prognostic indices, we will centrally archive PET/CT scans at baseline and after 3 and 6 cycles of induction therapy. Patients who do not enter complete remission after the completion of induction (i.e. stable disease or partial remission), will have restaging PET scans continued during the continuation phase of treatment (see Table 10). This inventory can be used to support exploratory analyses of new methods for quantitative imaging such as measurement of metabolic tumor burden (MTB). MTB can be correlated with clinical outcomes in the E2408 study (CR rate, DFS rate, PFS, OS), conventional prognostic indices (FLIPI, GELF), and host and tumor biomarkers in future studies.

Another measure of tumor burden with high potential to better predict clinical outcome is the quantitative assessment of t(14;18)-containing cells. To allow future exploration of this biomarker in the context of E2408, we will obtain blood samples at baseline; after 1, 3 and 6 cycles of induction; and after 12 and 24 months continuation. Bone marrow samples will be obtained at baseline and upon restaging after 12 and 24 months continuation. Collection of these samples will allow correlations of this biomarker with MTB and FLIPI score, and absolute values and changes in quantitative t(14;18) PCR can be correlated the clinical endpoints of the E2408 study. As the combination of MTB (above) and quantitative t(1418) assessment may emerge as a better predicter of treatment efficacy, banking of both image and biospecimens will afford studies of all E2408 participants and analyses within each treatment arm. PET scans will be obtained at baseline and after 3 and 6 cycles of induction therapy. All subsequent scheduled restaging scans will be CTs only, unless a patient has not entered complete remission as discussed above. In addition, bone marrow aspirates will be performed only at baseline and prior to continuation.

In 2009, both the follicular lymphoma tumor and the tumor microenvironment in the host appear to play major roles in prognoses. Establishing a tumor bank of paraffin-embedded tissues and host DNA positions us to study the best available markers at the conclusion of E2408. In this endeavor, we will be led by funded, ongoing correlative research including gene expression profiling, microarray analyses, and single nucleotide polymorphism studies in ECOG's completed E1496 and E4402 studies. The resources of E2408 can be used to validate findings from these prior studies as

well as providing specimens for discovery particular to the treatment arms of E2408. Among these are measures of T and NK cell activation markers potentially related to the immunomodulatory activities of lenalidomide and changes in TNF-alpha and proteasome levels related to bortezomib.

We anticipate approximately 2/3 of patients will have a measurement of metabolic tumor burden (MTB) by PET/CT scan and a measurement of molecular tumor burden by quantitative assessment of t(14;18)-containing cells, at baseline and at one or more time points through the treatment. We propose to pool patients from all three arms based on the hypothesis that MTB combined with quantitative t(14;18) measurement at varied time points may better predict treatment efficacy regardless of actual treatment received. (There are data in Ladetto et al. Blood 2008 that support the similar predictive ability of t(14;18)+ cells despite highly significant differences in treatment efficacy) (45). For both the absolute value and log rate of change with respect to baseline at each follow-up time point, two-sample Wilcoxon rank test will be used to correlate MTB and molecular tumor burden measurement with dichotomized clinical outcomes, such as with or without CR at the end of induction, FLIPI 1-3 versus 4-5 and DFS status 1-year post induction; Spearman correlation metric will be used to correlate the two measurements at each time point. We propose to use regression analysis to evaluate the potentially prognostic value of MTB and/or measurement in addition to standard clinical assessments (e.g. FLIPI, GELF score). The methods include logistic regression model for dichotomized outcomes (disease-free or not) and Cox proportional hazard model for time to event outcomes (DFS, PFS). In addition, the classification and regression trees (CART) method can be used to select important prognostic factors to classify patient disease or progression status at the landmark time points. As knowledge is moving quickly in biomarker field, the actual analysis plan to correlate MTB and molecular tumor burden measurement with host tumor microenvironment characterized by series markers will be determined based on the state-of-the-art biomarker knowledge at the conclusion of patient accrual.

#### 9.2.2 Quality of Life (QOL)

Patient-reported outcomes measures will be administered to assess overall HRQL, disease-related symptoms, distress (anxiety and depression) and treatment-related symptoms. Overall HRQL (physical, functional, emotional and social well-being) will be prospectively measured using the 42-item FACT-Lymphoma subscale (FACT-Lym) throughout trial participation and at follow-up. This will also capture disease-related symptoms and concerns. Treatment-related symptoms, specifically fatigue and neurotoxicity, will be measured using the 13-item FACT-Fatigue scale and the 11-item FACT/GOG-Neurotoxicity scale. The patient self-report assessment will include a total of 66 items.

This assessment will be administered at six time points:

1. Baseline (pre-treatment)
2. Mid-way through induction (after cycle 3)
3. End of induction (before continuation).
4. At 6 months of continuation (s/p 6 cycles of lenalidomide)
5. End of 1st year of continuation.
6. End of 2nd year of continuation.

The timing of these assessments will allow us to examine symptom palliation within a several weeks of treatment initiation (2nd time point) and throughout induction treatment where bortezomib will be added to BR therapy. Since bortezomib is known to cause neurotoxicity, the FACT/GOG-neurotoxicity scale will be collected prior to each induction cycle for patients randomized to BVR therapy. Time points were also selected to assess treatment-related symptoms following maximum exposure to treatment agents (3rd and 5th time points). Assessment at the end of continuation (6th time point) will provide us with important data on patients' well-being and functional status as they transition from active treatment to survivorship.

Scores from assessment instruments will be examined at each time point for differences between treatment arms (induction or continuation) on overall HRQL, disease-related symptoms, distress, and treatment-related symptoms. Data will also be examined to identify differences between treatment arms (induction or continuation) on change scores over time. The impact of disease-related symptoms and treatment-related symptoms on overall HRQL will be examined to establish the extent to which symptom palliation and treatment-induced symptoms impact functioning and well-being.

The standard deviation of the physical and functional well-being domains are approximately 6 and the standard deviation of the FACT-G is approximately 16. Differences which can be detected with 80% power between two arms in the change of scores from baseline (pre-treatment) are computed 1) allow for slightly less and more variability for the scales without data (standard deviation of 4,6,8,16,20), 2) assuming correlation between repeated scores of 0.4, 0.6, 0.8, 3) assuming equal percentage of patients completed assessment in the two arms at any time point, 4) using a two-sided t-test with a 0.05 significance level. Assuming that 90%, 80%, 60% or 40% of patients have completed assessment at both time points (lower completion rate at later time point), Table 12 shows the difference between that can be detected with 80% power. Power calculations are base on the number of complete cases, and therefore are conservative.

**Table 12. Difference that can be detected in the change in domain score at each time point from baseline between two arms using two-sided t-test at significance level of 0.05 for various**

**standard deviations of the scores, correlation between repeated measures and number of patients with complete assessments.**

| Standard deviation | Correlation | Standard Deviation of change | Difference detected with 80% power | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Induction | | | Continuation | | |
| | | | 90% (N=128, 85) | 80% (N=114, 75) | 60% (N=85, 56) | 80% (N=75, 38) | 60% (N=56, 29) | 40% (N=38 , 19) |
| 4 | 0.4 | 4.38 | 1.73 | 1.83 | 2.13 | 2.47 | 2.84 | 3.51 |
| | 0.6 | 3.58 | 1.41 | 1.50 | 1.73 | 2.02 | 2.32 | 2.87 |
| | 0.8 | 2.53 | 1.00 | 1.06 | 1.23 | 1.42 | 1.64 | 2.03 |
| 6 | 0.4 | 6.57 | 2.59 | 2.75 | 3.19 | 3.70 | 4.26 | 5.26 |
| | 0.6 | 5.37 | 2.12 | 2.25 | 2.61 | 3.02 | 3.48 | 4.30 |
| | 0.8 | 3.79 | 1.49 | 1.59 | 1.84 | 2.13 | 2.46 | 3.04 |
| 8 | 0.4 | 8.76 | 3.45 | 3.67 | 4.26 | 4.93 | 5.68 | 7.02 |
| | 0.6 | 7.16 | 2.82 | 3.00 | 3.48 | 4.03 | 4.64 | 5.74 |
| | 0.8 | 5.06 | 1.99 | 2.12 | 2.46 | 2.85 | 3.28 | 4.05 |
| 16 | 0.4 | 17.5 | 6.90 | 7.33 | 8.50 | 9.85 | 11.34 | 14.02 |
| | 0.6 | 14.3 | 5.63 | 5.99 | 6.95 | 8.05 | 9.27 | 11.45 |
| | 0.8 | 10.1 | 3.98 | 4.23 | 4.91 | 5.69 | 6.54 | 8.09 |
| 20 | 0.4 | 21.9 | 8.63 | 9.18 | 10.64 | 12.33 | 14.19 | 17.54 |
| | 0.6 | 17.9 | 7.05 | 7.50 | 8.70 | 10.08 | 11.60 | 14.34 |
| | 0.8 | 12.6 | 4.96 | 5.28 | 6.12 | 7.09 | 8.16 | 10.09 |

For induction question (BR vs. BVR), patients from BR+R and BR+R/L will be combined together (total 142 patients) to compare with that from BVR +R arm (94 patients). And for continuation questions comparing the effect of R/L and R-alone, only patients under treatment of BR+R (48 patients) and BR+R/L (94 patients) will be included. It is nature to anticipate higher percentage of complete cases in early phase of the study and the proportion decreases as study pursue, therefore we anticipate as much as 90% complete cases in the induction phase and 80% complete case in continuation phase. For example, assuming the standard deviation of the FACT-G is 16, there is at least 80% power to detect a difference in the change of the total FACT-G score of 5.63-6.95 between the two induction treatments, or 8.05-11.45 between two continuation treatments after BR induction, if the correlation is 0.6 and 3.98-4.91 or 5.69-8.09 if the correlation is 0.8.

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The additional patients enrolled will be included in the analysis of quality of life. However, it should not affect power for step 2 analysis due to the non-enrollment rate. It will increase power for step 1 analysis, but the effect is anticipated to be small.

Besides comparing QOL scores between arms 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 through time. Patient variation will be treated as random

effect in modeling the longitudinal data (QOL score) with linear mixed models. Data with and without missing data imputation will be analyzed and results will be compared. Imputations will be done by fitting informative censoring model using EM algorithm (38, 101). These methods consider informative missing by jointly modeling longitudinal response (QOL score) and the time to dropout. Frequency, descriptive statistics will be utilized to summarize and understand the quality of life data for this population.

9.2.3 Co-Morbidity

We will collect the number of co-morbidities for each patient at baseline and at the end of therapy (i.e., at the end of 2 years of continuation therapy) utilizing the Cumulative Illness Rating Scale and assess the relationship between CIRS score and outcome (CR, DFS, PFS). Van Sprousen and colleagues reported that the prevalence of a serious co-morbidity of non-Hodgkin lymphoma patients aged 60-69 years and >70 years was 43% and 61%, respectively (133). The most common co-morbid conditions were patients 60–69 years and ≥ 70 years were cardiovascular disease (15% and 22%, respectively), hypertension (14% and 14%, respectively), diabetes mellitus (8 and 10%, respectively), and COPD (6% and 10% respectively). Van de Schans and colleagues recently validated the original FLIPI score (i.e., FLIPI-1) in a cohort of 353 FL patients (134). Furthermore, they examined the impact of co-morbidity with survival in these same patients. Interestingly, they found that a survival model that included age in three categories (≤60, 61–70 and >70 years) and presence of cardiovascular disease resulted in a better prognostic index than the standard FLIPI-1. Examining cardiovascular disease (CVD) alone, presence of CVD predicted for significantly inferior 5-year and 10-year overall survival (48% and 24%, respectively) vs patients without history of CVD (71% and 56%, respectively; $p<0.0001$).

The comprehensive geriatric assessment (CGA) has been developed as a procedure to assess the objective health status of elderly persons (135-139). The CGA is considered to be more effective than standard medical evaluation for the care of the elderly. Initially, use of a CGA was based on its ability to predict morbidity and mortality in the general geriatric population, although accumulating data show the benefits of using the CGA specifically in patients with cancer (135,138,139). Comorbidity is an essential part of the CGA. Several comorbidity scales have been used in research, although the Cumulative Illness Rating Scale (CIRS) is one of the more prominent tools utilized in geriatrics (135,140). The CIRS measures chronic medical illness burden while taking into account the severity of chronic diseases. The CIRS has been revised to reflect common problems of elderly people and was renamed the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (141); this version has subsequently been validated (142). Furthermore, several recent cancer related studies have validated the relevance of the CIRS to define comorbidities among oncology patient populations, some of which correlated with survival (143-144).

For binary outcomes such as CR, logistic regression will be used to assess the relationship with CIRS score; for time-to-event outcomes, the method of Kaplan and Meier and the logrank test, as well as Cox proportional hazards models, will be used to assess the association with co-morbidity.

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### 9.2.4 Peripheral Neuropathy

As of amendment #5, the study allows subcutaneous administration of bortezomib for patients that are randomized to Arm B (BVR arm). In a report by Moreau et al (2011) in multiple myeloma patients, peripheral neuropathy of any grade was observed in 38% vs 53%, respectively, of grade 3 or worse was observed in 6% vs 16% patients, respectively,with subcutaneous vs intravenous bortezomib administration. We will report percent patients that experience peripheral neuropathy of any grade and of grade 3 or higher, with 90% confidence interval. Based on current accrual and the expected activation time for amendment #5, we anticipate that 65% of patients, respectively, will received intravenous bortezomib and 35% will receive subcutaneous bortezomib.

Out of 94 eligible patients, the estimate leads to 61 and 33 patients with intravenous and subcutaneous bortezomib, respectively. Thus, the width of 90% confidence interval will be no wider than 22% and 30% for intravenous and subcutaneous bortezomib, respectively.

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## 9.3 Gender and Ethnicity

Based on previous data from E1496 the anticipated accrual in subgroups defined by gender and race is:

Follicular Patients (Accrual goal = 286)

**Table 13.**

| **Ethnic Category** | **Gender** | | |
|---|---|---|---|
| | **Females** | **Males** | **Total** |
| Hispanic or Latino | 5 | 12 | 17 |
| Not Hispanic or Latino | 121 | 148 | 269 |
| **Ethnic Category: Total of all subjects** | 126 | 160 | 286 |
| **Racial Category** | | | |
| American Indian or Alaskan Native | 0 | 1 | 1 |
| Asian | 0 | 1 | 1 |
| Black or African American | 2 | 10 | 12 |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 |
| White | 124 | 148 | 272 |
| **Racial Category: Total of all subjects** | 126 | 160 | 286 |

## 10. Pathology Review

**NOTE:** ECOG-ACRIN requires that all biological samples submitted be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). An STS shipping manifest form must be generated and shipped with the sample submissions. See Section 10.4.

Rev. 10/11 **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 Submitting Diagnostic Material

Rev. 10/11 Diagnostic material from the original diagnostic tumor biopsy must be submitted for review and classification and laboratory studies. Diagnostic materials from additional biopsies performed while on study should be submitted for use in the laboratory studies and/or banking.

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 Materials Required For This Protocol

#### 10.2.1 Forms (Submit with every pathology submission)

- ECOG-ACRIN Generic Specimen Submission Form (#2981). 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
- Immunologic studies, if available
- Sample Tracking System Shipping Manifest Form

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

#### 10.2.2 Biological Sample Submissions:

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**NOTE:** If unable to submit blocks contact the ECOG-ACRIN CBPF for alternatives at 844-744-2420 or eacbpf@mdanderson.org.

##### 10.2.2.1 MANDATORY

- Tumor block from the original diagnostic biopsy sample.

**NOTE:** Submission of pathology materials for diagnostic review is mandatory in order for the patient to be considered evaluable. Failure to submit pathology materials may render the case unevaluable.

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

10.2.2.2 From patients who answer "Yes" to participation in the laboratory research studies or to "I agree to provide additional specimens for research."

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

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## 10.3 Shipping Procedures

Access to the shipping account for shipments to the ECOG-ACRIN CBPF at MD Anderson Cancer Center 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.

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

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

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

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Log the samples into the ECOG-ACRIN Sample Tracking System (STS) prior to shipping. An STS shipping manifest form must be generated and shipped with all sample submissions. If STS is unavailable, follow the instructions in Section 10.4 regarding alternative form requirements.

## 10.4 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:** 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 must be generated and shipped with all sample submissions.**

Please direct your questions or comments pertaining to the STS to ecog-acrin.tst@jimmy.harvard.edu.

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10.4.1 Study Specific Notes

An Generic Specimen Submission Form (#2981) will be required only if STS is unavailable at time of sample submission or if baseline samples are submitted prior to randomization to the treatment trial (patient **must** sign consent prior to collection). Indicate the appropriate Lab on the submission form:

- ECOG-ACRIN Central Biorepository and Pathology Facility

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- Mayo Clinic Lymphoma Laboratory
- QARC

Retroactively enter all collection and shipping information when STS is available.

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10.5 Central Biorepository and Pathology Facility: Sample Processing and Routing

- Slides will be cut from the original diagnostic blocks and initial materials will be forwarded to Randy Gascoyne, M.D. for review.
- Shavings from all submitted blocks will be forwarded to Randy Gascoyne, M.D. for use in the optional laboratory studies outlined in Section 11.
- Blocks from patients who consented to 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 Randy Gascoyne, M.D.

10.6 Banking

TMAs and residual material from the blocks/slides submitted will be retained at the ECOG-ACRIN Central Repository for possible use in future ECOG-ACRIN 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

Creation of an image and tissue bank for correlative studies is an important aspect of modern clinical research. We plan to develop such a resource from the E2408 study in order to pursue the most promising state-of-the-art investigations at the study's conclusion. At this time, we have organized our ideas regarding correlative studies in two areas: 1) improved assessment of tumor burden with imaging and molecular biomarkers, and 2) evaluation of the heterogeneity in tumor characteristics and the host immune system.

What follows (Section 11.2) is an outline of our current thinking and background/rationale for funding applications. However, we acknowledge that the pace of current scientific developments may necessitate following alternative or new avenues when the E2408 study is fully accrued. In fact, foremost among emerging study data, are the funded correlative assessment of E1496 samples for gene expression, SNP analyses, and immunohistochemical markers and the SNP and TMA assays of E4402, both prior ECOG-led follicular lymphoma studies.

### 11.1 Submission of Scans and Biological Materials

ECOG-ACRIN requires that all scans and 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 10.4.

Submission of PET/CT and CT scans are outlined in Section 11.1.1. Submission of blood and bone marrow are outlined in Section 11.1.2.

#### 11.1.1 Centralized Review of FDG-PET/CT and CT Scans (MANDATORY)

An important secondary objective of this study is to create an image and tissue bank including serial PET/CT scans. Separate CT's of the neck/chest/abdomen/pelvis will be required in addition to the PET/CT if the PET/CT is performed without intravenous and oral contrast (see Appendix VI: FDG-PET/CT and CT IMAGING).

The imaging archived in this bank will be centrally read by the E2408 Nuclear Medicine physician on the Study Committee.

**NOTE:** For purposes of treatment decision, the local reading will be used. The central review is for the establishment of the image bank and will not be returned to the site.

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##### 11.1.1.1 Required Scan Submissions

Combined clinical PET/CT scans and clinical CTs performed to determine patient eligibility and monitoring of disease must be submitted from the following time points:

- Pretreatment
- Restaging after cycle three (3) of induction
- Restaging after completion of induction prior to start of continuation (after 6 cycles)
- Restaging after following completion of continuation*

- At relapse*

**NOTE:** Combined PET/CT scan will be sufficient if the PET/CT is performed with intravenous and oral contrast; if PET/CT is without oral and intravenous contrast, then separate/dedicated CTs of neck/chest/abdomen/pelvis (in addition to the PET/CT) must be obtained and submitted at the same time points as above.

**NOTE:** For patients who do not enter complete remission at the completion of induction, restaging FDG-PET/CT scans are done during the continuation phase (see Table 10 in Section 7.1)

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11.1.1.2 FDG-PET/CT and CT with Infusion Scan Submissions

To ensure the highest standards and consistency between different centers, **all** FDG-PET scans must be submitted to the Quality Assurance Review Center (QARC) in Lincoln, RI, for centralized review (**see** Appendix VI**: FDG-PET/CT and CT IMAGING). All FDG-PET/CT and CT scans with intravenous contrast should be submitted to QARC. QARC will transmit the scans to the ECOG-ACRIN central reviewer, Dr. Andrew Quon (Stanford University).**

Borderline metabolism in a lesion will be considered negative as determined by the international harmonization conference. Details of submission of FDG-PET/CT scans to QARC for centralized review and on the performance and recommended scoring/interpretation of FDG-PET/CT scans are outlined in Appendix VI**: FDG-PET/CT and CT IMAGING.**

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For questions please contact ECOG-ACRIN Study Manager at QARC at the ph: (401) 753-7600 or by e-mail: ECOG@QARC.org.

11.1.1.3 Shipping Guidelines

Scans must be sent in DICOM format via CD via overnight delivery, or submitted electronically via SFTP to the Quality Assurance Review Center (QARC).

**NOTE:** Instructions on how to obtain an SFTP can be found on the QARC website: www.QARC.org

CD's should be submitted to the address below. Multiple studies for the same patient may be submitted on one CD, however, please submit only one patient per CD.
Quality Assurance Review Center (QARC)

640 George Washington Highway
Suite 201
Lincoln, RI 02865
Phone: 401-753-7600
Fax: 401-753-7601

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Log the scans into the ECOG-ACRIN Sample Tracking System (STS) prior to shipping. An STS shipping manifest form must be generated and shipped with all sample submissions. If the STS is unavailable, follow the instructions in Section 10.4 regarding alternative form submission.

For each patient, study data acquisition information and patient information must be recorded on the PET acquisition form (Appendix VI) and forwarded to QARC. **Image data must be transferred to QARC at the same time as the completed FDG-PET/CT acquisition form.**

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#### 11.1.2 Submission of Blood and Bone Marrow

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Samples are to be submitted 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."

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##### 11.1.2.1 Sample Submission Schedule

Samples should be shipped on the day they are drawn at room temperature. 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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Please contact Kim Henderson **prior to** the collection of the samples for the air bills in order ship the samples.

A. **Bone marrow aspirate (3-5 mL requested)** to be submitted at the following time points:

- Baseline (if submitted prior to randomization or if the biopsy was performed previously and another will not be done, contact the receiving laboratory)
- Restaging after completion of induction therapy (prior to start of continuation)

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**NOTE:** Samples may be submitted from patients who answer "Yes" to "I agree to provide additional specimens for research."

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B. **Peripheral blood** to be collected at the five (5) following time points:

- Baseline (after randomization, prior to treatment)
- Prior to the administration of any cycle two (2) treatment
- Prior to the start of continuation therapy* (prior to administration of first rituximab (Arms A and B) or Lenalidamide (Arm C) treatment)
- At twelve (12) months of continuation*
- At twenty-four (24) months of continuation* (end of continuation)

* May be collected at time of restaging assessments. If collected on a day of treatment, collect prior to administration of any study drugs.

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11.1.2.2 Sample Preparation Guidelines

The following CBC information must be entered into STS with each time point: WBC and lymphocyte count.

Samples should be shipped the day they are drawn. Samples from multiple patients can be shipped together, but must be placed in separately labeled tubes and bags.

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Please contact Kim Henderson (507-284-3805 or Henderson.Kimberly@Mayo.edu) **prior to** the collection of the samples for the air bills in order ship the samples.

Sample tubes must be clearly labeled with the ECOG-ACRIN protocol number (E2408), the patient's ECOG-ACRIN sequence number (if available), the patient's initials (last name, first name), the date and time the sample was collected, and the sample type (PB, BM).

- Peripheral blood, no anticoagulant, red top tubes: Draw approximately 10mL of whole blood into the red top tubes at each time point.

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- Peripheral blood, EDTA purple top tubes:
  - BASELINE: draw approximately 30mL of whole blood into three (3) 10mL EDTA purple top tubes
  - All other time points: draw approximately 20mL of whole blood into two (2) 10mL EDTA purple top tubes

- EDTA (purple top tube) bone marrow aspirate (while 3-5mL is recommended, any amount is acceptable).

**NOTE:** **For patients with an inaspirable bone marrow ("dry tap"),** or if bone marrow has been done previously and the patient refuses to have another aspiration done, call Kim Henderson (Mayo Clinic Lymphoma Laboratory) at (507) 284-3805 to discuss the case and the possibility for submitting peripheral blood only. Be prepared to report the WBC count and the blast count in the peripheral blood at the time of the call.

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#### 11.1.2.3 Shipping Procedures

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Please contact Kim Henderson (507-284-3805 or Henderson.Kimberly@Mayo.edu) **prior to** the collection of the samples for the air bills in order ship the samples.

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. 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 samples in individual plastic bags and place them in the Styrofoam container and close the lid.
- 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.

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- Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

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If your shipment was not logged into the ECOG-ACRIN STS please call Kim Henderson at (507) 284-3805 or e-mail Henderson.Kimberly@mayo.edu to notify the laboratory when samples are being shipped. Indicate the ECOG-ACRIN protocol number and

the name of the contact person and phone number. The samples should be shipped to the following:

Ship to:

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Kim Henderson
Mayo Clinic Lymphoma Laboratory
613 Stabile
200 First Street Southwest
Rochester, MN 55905

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Log the samples into the ECOG-ACRIN Sample Tracking System (STS) prior to shipping. An STS shipping manifest form must be generated and shipped with all sample submissions. If STS is unavailable or if baseline samples are being submitted prior to randomization to the treatment trial, follow the instructions in Section 10.4 regarding alternative form requirements.

## 11.2 Identification of Relevant Biomarkers for Comparison of Treatment Effects

### 11.2.1 Assessment of tumor burden with imaging and molecular biomarkers

Tumor burden at diagnosis is prognostic in follicular lymphoma, forming the basis of the GELF tumor burden score (high or low).[33, 34] Likewise, in our prior E1496 study, GELF tumor burden was prognostic in both standard and maintenance rituximab arms.[7] FLIPI risk score has also been associated with PFS in the modern immunochemotherapy era.[9] However, these systems of tumor burden and disease risk are categorical rather than quantitative and also fail to incorporate the diversity of disease presentations. *We hypothesize that the integration of quantitative imaging data and a molecular indicator of tumor burden with standard clinical assessments at presentation and post-treatment will better predict disease risk and clinical outcome.*

Positron emission tomography (PET) scans will be centrally reviewed at baseline and indicated timepoints and the imaging features of each lesion (semantic type, location, axial dimensions/area/volume, and standard uptake value [SUV]) will be recorded with a calculation of overall volume and metabolic tumor burden, using an open source software framework built on caBIG technologies (Dr. Rubin). Quantitative imaging results at baseline will be evaluated to determine value added to standard clinical criteria. Accuracy of standard clinical prognostic criteria (number of nodal sites, number of nodal sites >3 cm, and masses >7 cm) will be assessed. Metabolic tumor burden at presentation will be correlated with DFS and PFS endpoints and value added to FLIPI and GELF will be determined. Quantitative metabolic tumor burden during and after therapy will also be compared to International Harmonization Criteria in the assessment of response to treatment and correlated with DFS and PFS. Quantitative imaging may serve as a biomarker of response to newer therapeutics (ie RB-bendamustine) with the potential to shorten or adapt clinical trials.

Molecular assessment of t(14;18)-positive cells in the blood and marrow compartments has been studied over the past two decades in FL, sometimes with mixed results. In the chemotherapy era, half or fewer follicular lymphoma patients achieved quantitative t(14;18) after a full course of treatment. With more than 10 years of follow-up, autologous transplantation results in follicular lymphoma continue to demonstrate the prognostic significance of achieving quantitative t(14;18) in both the patient and the transplanted cells assessed ex vivo.[114,115] Although some early data suggested that quantitative t(14;18) assessment in the rituximab era was less predictive, the results of three randomized clinical trials demonstrated the prognostic significance of achieving quantitative t(14;18) and the higher rate of quantitative t(14;18) achieved with chemotherapy plus rituximab.[45,116,130] Notably, the Italian trial reported that achievement of quantitative t(14;18) neutralized the marked PFS difference in the treatment arms. Because ~75-85% of patients treated with a full course of modern therapy such as R- bendamustine clear the marrow and circulating compartment of t(14-18)+ cells as assessed by real-time quantitative PCR, the log clearance or rate of reduction may be more predictive of DFS and PFS.[116] Varied methods in the study of t(14;18)+ cells have contributed to lack of reproducibility across a range of international laboratories.[117] Recent technologic advances include an international effort to standardize quantitative t(14;18) assessment in European lymphoma clinical trials (C. Pott personal communication) and the enhancement of detection of t(14;18) with probes covering additional Bcl-2 breakpoint regions.[118] Coordination with the international community and use of probes expanded to cover additional Bcl-2 breakpoint regions is important for current clinical trials. It will be key, in addition, to view quantitative t(14;18) results in context and with appreciation for the diversity of anatomic presentations of FL. *Thus, we hypothesize that quantitative t(14;18) analyses will significantly add to standard determinants of tumor burden and clinical response, and that quantitative t(14;18) combined with quantitative imaging may better predict treatment efficacy as determined by DFS and PFS.* In the context of this study, we will correlate baseline quantitatative t(14;18) (blood, marrow) with quantitative metabolic tumor burden and FLIPI score, and DFS and PFS endpoints. Quantitative t(14;18) will be measured after cycle 1 (blood, marrow), cycle 6 (blood, marrow) and months 1, 12, and 24 (blood) of continuation. The association of log change in quantitative t(14;18) and absolute values with DFS and PFS will be determined.

11.2.2 Tumor and host characteristics and treatment arm

We hypothesize that variation in response to treatment is attributable to heterogeneity in tumor characteristics and the host immune system and that these attributes contribute to response of specific therapeutic interventions. Molecular profiling of follicular lymphoma demonstrated the significance of the tumor microenvironment and engendered

interest in the interaction between the malignant B-cells and bystander cells (T cells, dendritic cells, fibroblasts, and macrophages) in lymph node or bone marrow infiltrates. Two immune response signatures, one with favorable and one with unfavorable prognostic significance, in the chemotherapy era have been proposed. [105] Although the more favorable expression signature IR1 is enriched for genes expressed in various T-cell subsets, whereas the unfavorable IR2 signature harbors genes expressed in macrophages and dendritic cells, the biological conclusions are not straightforward. These signatures appear to capture a picture of intricate interactions between the neoplastic B cells with their microenvironment rather than the presence of particular cell types in the lymphoma infiltrate. This may explain the somewhat contradictory studies correlating the number or distribution of various cells of the microenvironment, such as macrophages (CD68) or T-cell subsets (CD4, CD8, and Treg) with the clinical course of follicular lymphoma.[106,107,108,110] In addition, the therapeutic intervention must also be considered in the context of its impact on the FL cells and their microenvironment.

Three recent papers published data on the prognostic impact of macrophages, FoxP3 positive T-cell and mast cells in FL patients treated with CHOP chemotherapy with or without the addition of rituximab.[107,119,131] Remarkably, the prognostic impact of these cell populations was lost or reversed in patients treated with rituximab, supporting the notion that specific therapeutics influence the impact of the microenvironment in FL. For instance, fludarabine has a rather specific effect on FoxP3-positve regulatory T-cells in B-CLL patients, impacting inhibitory function as well as cell numbers.[120] Very low-dose radiotherapy (2 Gray x 2) provides another example of effect on the microenvironment through the induction of activation of cytotoxic T-cells and macrophages.[129] Lenalidomide has emerged as a interesting promising new agent in FL based on efficacy in clinical trials and the potential immunomodulatory effects on the microenvironment. Contact between FL B-cells and T-cells results in an immunologic defect, including creation of T-regulatory cells. [121]Lenalidomide abolished or markedly inhibited the suppressive function of T regulatory cells in pre-clinical studies, downregulating FoxP3 expression.[122,123] In a recent elegant study, Gribben and colleagues showed that lenalidomide repairs suppressed T-cell immunological synapse formation in FL.[124] The Gribben lab was able to show that lenalidomide repaired in part the suppressed recruitment of integrin LFA-1, Lck, Itk, Rab27A and filamin-A to the synapse in subsequent T cell:APC interactions. Further, they validated the expression of Itk, Rab27A and filamin-A in FL tissue microarrays (TMA) and reported that elevated expression of intrafollicular Rab27A (mediator of targeted secretion of CD8 T cell cytolytic granules) was a favorable prognostic marker. Together, these data suggest that lenalidomide offers the exciting prospect of repairing T-cell suppression in FL and that the observed variability in the microenvironment by immunohistochemical analysis of TMA may

correlate with clinical outcomes and impact of lenalidomide. We therefore plan to build a TMA of all E2408 cases and evaluate the staining patterns of the microenvironment in the context of clinical outcomes and treatment.

In the current study, lenalidomide will be combined with rituximab, a circumstance in which its additional immunomodulatory activities should prove beneficial. In particular, the ability of lenalidomide to enhance natural killer (NK) cell and monocyte-mediated antibody dependent cellular cytotoxicity (ADCC). In vitro, lenalidomide-enhanced rituximab efficacy was associated with increased granzyme B and Fas ligand expression and could be inhibited by a granzyme B inhibitor.[125] We plan to measure T and NK subsets and determine expression of CD107a (LAMP-1), a marker for degranulation of NK and activated CD8+ T cells.[126] Recent data in children treated with lenalidomide demonstrate the feasibility of this approach; NK numbers and activation status were statistically increased upon treatment.[127]

The host immune system may also play an important role upon combination of rituximab and bortezomib, as rituximab efficacy has already been linked to the Fc$\gamma$ receptor status of host immune cells.[112,113] In addition, a recent analysis of mantle cell patients treated with bortezomib suggests that plasma biomarkers may relate to efficacy,[62] while an analysis in multiple myeloma showed that peripheral blood proteasome levels predicted response to bortezomib therapy.[128] Accordingly, we plan to collect tissue and serum specimens to measure TNF-alpha and proteasome levels at baseline and after the first cycle of chemotherapy. Results will be correlated with the quality of response and also with the change in measured t(14;18) circulating cells determined at the same time points. A variety of markers including CTAG1B, EEF2, CFLAR and GAS5 are being tested in ongoing bortezomib trials. We will have the opportunity to test those of interest at a later date on the TMA generated from the E2408 study.

A major area of interest relates to the potential toxicity issues as well as efficacy in the investigational arms of our study. We plan to bank germline DNA from the peripheral blood for potential future studies of interest related to single nucleotide polymorphisms. This effort will afford the opportunity to evaluate the interventions in the current study and, theoretically, can be combined with ~500 samples collected in the preceding E4402 study with regard to immune response polymorphisms that may predict survival in FL.[109]

In summary, the essential nature of our correlative studies is acquisition of baseline tumor and peripheral blood at strategic time points in order to study the characteristics of the FL and host response that best describe clinical outcomes for standard and investigational therapeutics in the E2408 trial. We recognize that knowledge is moving quickly and that it is likely that some studies proposed at this time will be outdated while new studies will emerge as important at the conclusion of this trial. Therefore, it is essential to

collect the relevant biospecimens in preparation for state-of-the-art biomarker studies at the conclusion of patient accrual.

11.3 Banking

Upon completion of the analysis, the residuals and/or derivatives of the bone marrow and blood collected for the laboratory studies will be retained in 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.

11.4 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 on a monthly basis or upon request by any laboratory holding and/or using any specimens associated with this study.

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11.5 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. The quarterly cut-off dates are March 31, June 30, September 30, and December 31.

## 12. Records to Be Kept

Please refer to the E2408 Forms Packet for the forms submission schedule and copies of all forms. The E2408 Forms Packet may be downloaded by accessing the ECOG World Wide Web Home Page (http://www.ecog.org). Forms must be submitted to the ECOG-ACRIN Operations Office - Boston, FSTRF, 900 Commonwealth Avenue, Boston, MA 02215 (ATTN: DATA).

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.

### 12.1 Records Retention

This study is being conducted under an IND exemption and is not intended to support any FDA-related filings. However, ECOG-ACRIN requires clinical investigators to retain all trial-related documentation, including source documents, for at least one year from the posting of the final technical report of the outcome of this trial to support any publication of the data.

Please contact the ECOG-ACRIN Operations Office - Boston prior to destroying any source documents.

## 13. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

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**A 3-Arm Randomized Phase II Trial of Bendamustine-Rituximab (BR) Followed by Rituximab vs Bortezomib-BR (BVR) Followed by Rituximab vs BR Followed by Lenalidomide/Rituximab in High Risk Follicular Lymphoma**

**Appendix I**

**Informed Consent Template for Cancer Treatment Trials (English Language)**
**[Deleted in Addendum #5]**

# INFORMED CONSENT INTENTIONALLY REMOVED FROM PROTOCOL DOCUMENT

**Appendix I was removed from the protocol document in Addendum #5 and is posted as a separate document on the ECOG website. This was removed from the protocol to comply with NCI formatting guidelines.**

**A 3-Arm Randomized Phase II Trial of Bendamustine-Rituximab (BR) Followed by Rituximab vs Bortezomib-BR (BVR) Followed by Rituximab vs BR Followed by Lenalidomide/Rituximab in High Risk Follicular Lymphoma**

## Appendix II

## Pathology Submission Guidelines

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 E2408.

Rev. 1/15

4. ECOG-ACRIN Generic Specimen Submission Form (#2981)

## Guidelines for Submission of Pathology Materials

Rev. 1/15

The following items should always be included when submitting pathology materials to the ECOG-ACRIN Central Biorepository and Pathology Facility:

- Institutional Surgical Pathology Report
- Pathology materials (see attached List of Required Material)
- ECOG-ACRIN Generic Specimen Submission Form (#2981)

Instructions:

1. Provide the following information to the pathologist. "*" indicate information to be provided with the submitted materials
   * Patient's name (last, first)
   * Protocol number
   * Protocol case number (the patient's ECOG-ACRIN sequence number

     Patient's hospital number
   * Institution and

     Affiliate (if appropriate)
   * The submitted materials must be labeled with the institution's specimen specific assession number
2. Complete blank areas of the pathologist's instructional memo and forward it, along with the List of Required Material to the appropriate pathologist.
3. The pathologist should return the required pathology samples and surgical pathology reports, along with the completed ECOG-ACRIN Generic Specimen Submission Form (#2981); if used. If any other reports are required, they should be obtained from the appropriate department at this time.
4. Keep a copy of the ECOG-ACRIN Generic Specimen Submission Form (#2981) or STS-shipping manifest for your records.
5. Double-check that ALL required forms, reports and pathology samples are included in the package to the Central Biorepository and Pathology Facility. (See appropriate List of Required Material.)

   **Pathology specimens submitted WILL NOT be processed by the Central Biorepository and Pathology Facility until all necessary items are received.**
6. Mail pathology materials to:

   ECOG-ACRIN Central Biorepository and Pathology Facility
   MD Anderson Cancer Center
   Department of Pathology, Unit 085
   Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
   1515 Holcombe Blvd
   Houston, TX 77030

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 ECOG-ACRIN Central Biorepository and Pathology Facility by telephone 844-744-2420 or by email: eacbpf@mdanderson.org.

## List of Required Material

| | |
|---|---|
| E2408 | A 3-Arm Randomized Phase II Trial of Bendamustine-Rituximab (BR) Followed by Rituximab vs Bortezomib-BR (BVR) Followed by Rituximab vs BR Followed by Lenalidomide/Rituximab in High Risk Follicular Lymphoma |

Baseline (submit within one month of patient randomization)

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1. ECOG-ACRIN Generic Specimen Submission Form (#2981).
2. Institutional pathology report ***(must be included with EVERY pathology submission)***.
3. Required Pathology Materials:
    - Tumor block from the original diagnostic biopsy sample.

**NOTE:** Submission of pathology materials for diagnostic review is mandatory in order for the patient to be considered evaluable. Failure to submit pathology materials may render the case unevaluable.

During Treatment (submit within one month of collection)

1. ECOG-ACRIN Generic Specimen Submission Form (#2981).
2. Institutional pathology report ***(must be included with EVERY pathology submission)***.
3. Pathology Materials:
    - Tissue blocks from any diagnostic biopsies performed while on study.

**NOTE** If unable to submit blocks contact the ECOG-ACRIN CBPF for alternatives at 844-744-2420 or eacbpf@mdanderson.org.

**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.

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
ECOG-ACRIN Laboratory Science and Pathology Committee

Rev. 9/14
Rev.1/15

**DATE:**

**SUBJECT:** Submission of Pathology Materials for A 3-Arm Randomized Phase II Trial of Bendamustine-Rituximab (BR) Followed by Rituximab vs Bortezomib-BR (BVR) Followed by Rituximab vs BR Followed by Lenalidomide/Rituximab in High Risk Follicular Lymphoma

The patient named on the attached request has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for pathology review and laboratory studies and banking.

Keep a copy of the submission for your records. Forward 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 ECOG-ACRIN Central Biorepository and Pathology Facility.

Blocks and/or slides submitted for this study will be retained at the ECOG-ACRIN Central Repository for future studies. Blocks will be returned for purposes of patient management upon request.

***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 Central Biorepository and Pathology Facility at 844-744-2420 or eacbpf@mdanderson.org.

## ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3



**Institution Instructions:** This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time-point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

**Protocol Number** _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

**Date Shipped** _____ **Courier** _____ **Courier Tracking Number** _____

**Shipped To (Laboratory Name)** _____ **Date CRA will log into STS** _____

**FORMS AND REPORTS:** Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

| **Required fields for all samples** | | | | **Additional fields for tissue submissions** | | | | **Completed by Receiving Lab** |
|---|---|---|---|---|---|---|---|---|
| **Protocol Specified Timepoint:** | | | | | | | | |
| **Sample Type** (fluid or fresh tissue, include collection tube type) | **Quantity** | **Collection Date and Time 24 HR** | | **Surgical or Sample ID** | **Anatomic Site** | **Disease Status** (e.g., primary, mets, normal) | **Stain or Fixative** | **Lab ID** |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |

| **Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.** | | | | | |
|---|---|---|---|---|---|
| **Leukemia/Myeloma Studies:** | **Diagnosis** | **Intended Treatment Trial** | **Peripheral WBC Count (x1000)** | **Peripheral Blasts %** | **Lymphocytes %** |
| | | | | | |
| **Study Drug Information:** | **Therapy Drug Name** | **Date Drug Administered** | **Start Time 24 HR** | **Stop Time 24HR** | |
| | | | | | |
| **Caloric Intake:** | **Date of Last Caloric Intake** | | **Time of Last Caloric Intake 24HR** | | |
| | | | | | |

**CRA Name** _____ **CRA Phone** _____ **CRA Email** _____

**Comments**

9/12/14

**A 3-Arm Randomized Phase II Trial of Bendamustine-Rituximab (BR) Followed by Rituximab vs Bortezomib-BR (BVR) Followed by Rituximab vs BR Followed by Lenalidomide/Rituximab in High Risk Follicular Lymphoma**

## 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. 9/14

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, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

# A 3-Arm Randomized Phase II Trial of Bendamustine-Rituximab (BR) Followed by Rituximab vs Bortezomib-BR (BVR) Followed by Rituximab vs BR Followed by Lenalidomide/Rituximab in High Risk Follicular Lymphoma

## Appendix IV

## Follicular Lymphoma International Prognostic Index (FLIPI)

### FLIPI 1

Each patient should be assessed for the presence or absence of the following 5 adverse prognostic factors (adverse factor in italics): FLIPI 1

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1) Age (> *60 years* vs. ≤ 60 years)
2) Ann Arbor stage (*III-IV* vs I-II)
3) Hemoglobin level (< *120 g/L* vs 120 g/L or higher)
4) Number of nodal areas (> *4* vs 4 or less; see figure below please)
5) Serum LDH level (*above normal* vs normal or below).

Each patient should then be assigned into one of the following 3 risk groups:

- low risk (0-1 adverse factor)
- intermediate risk (2 factors)

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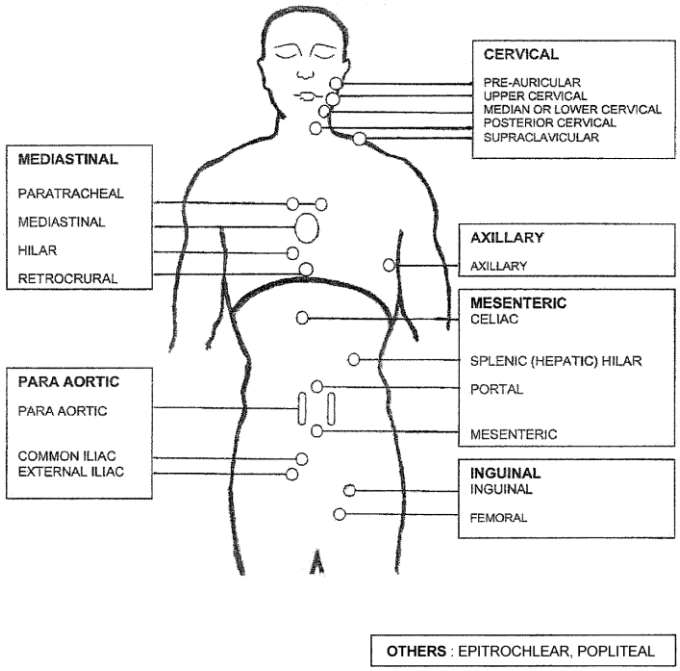
**Figure.** Nodal map according to FLIPI model. (Bilateral involvement = 2)

- high risk (3 or more adverse factors)




Solal-Celigny P, et al. Blood 2004; 104:1258-1265; and Buske C, et al. Blood. 2006;108:1504-1508.

## FLIPI-2

An updated analysis of the FLIPI was reported (FLIPI-2). This analysis was completed on 832 follicular lymphoma patients treated from 2003 through 2005, of who the majority received rituximab-based therapy. Five clinical factors were identified as being correlated with survival. Three of the parameters were different than the original FLIPI (FLIPI-1), while two were similar (i.e., anemia and older age).

Each patient treated in E2408 should be further assessed for the presence or absence of the following 5 adverse prognostic factors (adverse factor in italics):

1) Age (> *60 years* vs 60 years or less)
2) Hemoglobin level (< *120 g/L* vs 120 g/L or higher)
3) β2-microglobulin (*above normal* vs normal or below)
4) Largest involved lymph node (> *6 cm* vs 6cm or lower)
5) Bone marrow (*involved* vs not involved)

Federico M, et al. J Clin Oncol 2009; 27:1-9.

**A 3-Arm Randomized Phase II Trial of Bendamustine-Rituximab (BR) Followed by Rituximab vs Bortezomib-BR (BVR) Followed by Rituximab vs BR Followed by Lenalidomide/Rituximab in High Risk Follicular Lymphoma**

## Appendix V

## Patient Pill Diary for Lenalidomide

Patient Name_____

Dates: _____ through _____

**Lenalidomide 20 mg PO (by mouth) Days 1 to 21, every 28 days (If dose other than 20mg: _____)**

| DAY | Date | Number of capsules taken | Aspirin (or other anticoagulant) | Comments |
|---|---|---|---|---|
| Day 1 | | | | |
| Day 2 | | | | |
| Day 3 | | | | |
| Day 4 | | | | |
| Day 5 | | | | |
| Day 6 | | | | |
| Day 7 | | | | |
| Day 8 | | | | |
| Day 9 | | | | |
| Day 10 | | | | |
| Day 11 | | | | |
| Day 12 | | | | |
| Day 13 | | | | |
| Day 14 | | | | |
| Day 15 | | | | |
| Day 16 | | | | |
| Day 17 | | | | |
| Day 18 | | | | |
| Day 19 | | | | |
| Day 20 | | | | |
| Day 21 | | | | |
| Day 22 | | | | |
| Day 23 | | | | |
| Day 24 | | | | |
| Day 25 | | | | |
| Day 26 | | | | |
| Day 27 | | | | |
| Day 28 | | | | |

Additional Instructions for Patients

- Bring the diary to every appointment
- Record doses as you take them and do not batch entries at a later time
- Correct errors if they occur by crossing them out and writing in the correct information
- Do not open, crush or chew lenalidomide capsules
- If you miss a dose, take it as soon as you remember on the same day. If you miss taking your dose for the entire day, take your regular dose the next scheduled day. Do NOT double your regular dose to make up for the missed dose.
- If you take more than the prescribed dose of lenalidomide you should seek emergency medical care if needed and contact study staff immediately.

**A 3-Arm Randomized Phase II Trial of Bendamustine-Rituximab (BR) Followed by Rituximab vs Bortezomib-BR (BVR) Followed by Rituximab vs BR Followed by Lenalidomide/Rituximab in High Risk Follicular Lymphoma**

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## Appendix VI

## FDG-PET IMAGING

FDG-PET/CT scans with $^{18}$Fluorine- fluorodeoxyglucose (FDG) will be performed at baseline, after three (3) cycles of induction chemotherapy, at completion of induction chemotherapy (i.e., after six (6) cycles of induction chemotherapy) and at relapse. FDG-PET/CT will then be repeated until a patient achieves CR status, then only CTs will be obtained.

**NOTE:** Scan data must be submitted to QARC at each time point, i.e. after baseline, interim response, final response, continuation, and relapse.

**Baseline FDG-PET/CT scan:**

All patients should have a pre-treatment FDG-PET/CT scan as a baseline to compare with subsequent scans to assess response. This should be performed no more than six (6) weeks before starting chemotherapy.

**Interim Response FDG-PET/CT scan:**

To assess the response to the first thee (3) cycles of chemotherapy, an interim PET/CT scan will be performed after cycle three (3) of induction chemotherapy. Scan data must be submitted to QARC.

**Final Response Assessment FDG-PET/CT scan:**

To assess the final response after completion of all therapy, patients should have repeat whole body PET/CT scans and diagnostic quality, contrast-enhanced CT scans of the chest, abdomen, and pelvis (and neck, if done at baseline), 30 days after completion of the last dose of induction chemotherapy.

**Continuation:**

Rev. 2/14 Re-staging will be repeated after 7, 13, 18, and 24 months of continuation. Once a patient achieves CR status, then FDG-PET/CT will not be performed (i.e., only CT with contrast). Patients not in CR at start of continuation should have <u>both</u> contrast CT and FDG-PET/CT performed- until CR is achieved.

**Scans should also be submitted at relapse.**

**<u>Scanning Facilities</u>**

- Only full-ring integrated FDG-PET/CT scanners are acceptable (coincidence cameras are not acceptable). The CT of the FDG-PET/CT is used for attenuation correction of PET data and anatomic localization. CT settings should follow institutional guidelines.
- Scans must be sent in DICOM format via CD via overnight delivery or electronically via SFTP to the Quality Assurance Review Center (QARC). See central review section below for further requirements.
    - Instructions to obtain an sFTP are found on the QARC website: www.QARC.org

- CD's should be submitted to the address below. Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD.

  Quality Assurance Review Center (QARC)
  640 George Washington Highway
  Suite 201
  Lincoln, RI 02865
  Phone: 401-753-7600
  Fax: 401-753-7601

- For questions please contact ECOG-ACRIN Study Manager at QARC at the phone number above or by e-mail: ECOG@QARC.org

## Scanning Protocol

### Patient preparation

Non-diabetic patients should fast for at least 8 hours prior to the scan. Plain (unflavored water) should be taken during the period of fasting and the uptake period to ensure good hydration.

Diabetic patients should ideally be given a morning appointment. They should take their usual antidiabetic medication (oral or insulin) and eat a light meal (lighter than they normally would) on that morning. The time interval between that morning meal and PET/CT scan should be approximately 3-4 hours.

Oral diazepam or beta blockers may be given if desired to reduce brown fat uptake one hour prior to tracer injection.

Oral diluted contrast (e.g., Gastografin or 2% barium sulfate) may be administered, according to institutional guidelines. Intravenous contrast may also be administered, provided this is done in a technique that avoids deterioration of the CT images by streak artifacts from high-concentration intravenous contrast bolus.

### Detailed scanning protocol

1. Administer 260 - 555 MBq (7-15mCi) $^{18}$F- FDG
2. Emission part of the scan should start no earlier than 60 and no later than 90 minutes after injection.
3. The exact same period of uptake must be used for staging and response scans – within 15 minutes.
4. Perform attenuation corrected PET-CT scan to cover the area from the base of the skull to mid-thigh. This should be done with the arms above the head.
5. Perform a separate head and neck scan, with arms down, ONLY IF this is the only site of disease.
6. Attenuation correction of PET emission data will be based on the low dose CT from the FDG-PET/CT.

Acquisition should be performed using the institution's standard protocol, i.e. with regard to time per bed position, 2D or 3D, CTAC parameters, reconstruction parameters etc. Images should be reconstructed using OSEM or a similar iterative reconstruction algorithm. Both attenuation-corrected and non attenuation-corrected images should be reconstructed. The proposed data acquisition/reconstruction protocol (including details of all the parameters above) must be agreed with the core lab prior to the start of the study.

## Image data transfer

**Image data must be transferred to QARC at the same time as the completed FDG-PET/CT acquisition form.**

**The following DICOM files are required (save screens, post-processed movies, static DICOM re-renderings of images or similar files are NOT adequate for interpretation):**

- Attenuation corrected images (skull base to mid thigh)
- Non-attenuation corrected half body images
- CT scan (skull base to mid thigh)
- Attenuation corrected view of head and neck (if performed)
- Non-attenuation corrected view of head and neck (if performed)
- Head and neck CT scan (if performed)

Projection images (MIPs) are not required.

**NOTE:** For PET/CT imaging, the transferred imaging data should include uncorrected and attenuation-corrected PET projection data, as well as the reconstructed PET or PET/CT images used by the institution to achieve a response assessment. The imaging data submitted for central review must allow the study to be reconstructed and displayed in transaxial, sagittal and coronal formats using standard reconstruction techniques. Reconstructed MPEG clips and similar types of reconstructions will not be accepted.

**Central Review.**

Response determinations and treatment decisions will NOT be based on the centralized review. The central review is for the establishment of an image bank.

**Reporting.**

Visual interpretation will be used. The PET response scans will be scored with reference to sites of presumed lymphomatous involvement on the PET staging scan.

**Negative**

**1 no uptake**

**2 uptake ≤ mediastinum**

**3 uptake > mediastinum but ≤ liver**

**Positive**

**4 uptake > liver in some sites even if uptake ≤ liver or mediastinum at other sites**

**5 uptake > liver in over 90% of sites or development of new uptake consistent with progressive disease**

For the purpose of this study, scores 1, 2, 3 with uptake in sites abnormal on the staging scan equal or less than liver uptake will be regarded as 'negative' for disease and scores 4, 5 with uptake greater than liver will be regarded as 'positive' for disease. A separate analysis will be performed on patients with a score of 3 whose scan findings are analogous to the concept of 'minimal residual disease' (MRU) referred to in earlier published data on the use of PET in lymphoma. However for the purposes of treatment, patients with a score of 3 on the interim PET scan will be regarded as negative for disease.

**Absolute and relative standard uptake values (SUVs) will be recorded for research purposes but SHOULD NOT be used to determine scan positivity (because of inter-institution variations in scan performance and the acknowledged lack of standardization for SUV values).**

Standard uptake values (SUVs) will be used to quantify tracer uptake, and response to therapy will be determined by the change in SUV for scans acquired before and after therapy. The change in SUV will be correlated with actual prognosis to test the possibility of defining "quantitative response categories" which may have prognostic value. SUV numbers will be used in a post hoc analysis and the most appropriate measure to be used will be determined. The use of SUVmax and variations of SUVmax will be used in this analysis.

SUVs will be measured either by using a volumetric region of interest (ROI) that clearly encompasses a given lesion (carefully avoiding areas of higher normal activity in the vicinity, such as kidneys or bladder), or with a circular ROI. If a circular ROI is used, this needs to be done in several slices to assure that the recorded SUV is indeed the highest SUV within a given lesion. SUV max will be reported, normalized to body weight. A total of 6 lesions will be measured in this protocol.

**Radiation Dosimetry**

The whole body dose for FDG is about 0.10 rad/mCi, and the effective dose equivalent about 0.10 rem/mCi (0.03mSv/MBq). For the suggested activity range of 7-15mCi, the effective dose equivalent will be 0.7-1.5 rem (7.8 – 16.6mSv) (ARSAC Notes for Guidance 2006). The target organ is the urinary bladder wall, which will receive 0.22rad/mCi with a realistic one hour voiding interval (ICRP Publication 53). The dose from a low dose (140kV, 80mA) CT as part of a PET/CT is about 0.9 rad (rem) or 9mSv (Wu et al. Eur J Nucl Med Mol Imaging 31:38-43, 2004).

## E2408 ACQUISITION DATA FOR FDG-PET/CT SCAN

(To be completed by PET scanning facility. Please submit the scans along with the corresponding radiology reports for the scans to QARC)

**PET-CT Scan acquired at** _____

Patient's initials: _____

Patient's ECOG-ACRIN sequence number: _____

Referring Consultant: _____

Consultant telephone number: _____

Consultant fax number: _____

Hospital name and address: _____

_____

_____

Date of PET scan: _____

Time of administration of activity (hour:min) _____

Site of tracer administration and state left or right _____

Patient height (cm) _____

Patient weight (kg) _____

| | START TIME | NO OF BED POSITIONS | DURATION PER BED POSITION | TOTAL SCAN DURATION |
|---|---|---|---|---|
| Skull Base-Thighs | | | | |
| HEAD & NECK SCAN (if acquired) | | | | |

**RESULT OF INTERIM PET-CT SCANS** (AFTER CYCLE 3 AND AFTER CYCLE 6 OF INDUCTION CHEMOTHERAPY AND DURING CONTINUATION IF CR IS NOT ACHIEVED AND AT RELAPSE) according to 5 point scale:

1 : no uptake
2 : uptake ≤ mediastinum
3 : uptake > mediastinum but ≤ liver
4 : uptake > liver at some sites even if uptake ≤ liver or mediastinum at other sites
5 : uptake > liver in > 90% of initial sites or development of new sites consistent with progressive disease

---

**Local Report**

**Score** **1** **2** **3** **4** **5** (please circle)

List sites of residual uptake (score 4 and 5):

……
…….

Comments e.g. positive sites elsewhere in the body:

Name:…… Date:

Signature:

**WHEN COMPLETED, SEND BOTH SHEETS WITH IMAGE DATA FILES (SEE PROTOCOL) TO QARC AND RETAIN FIRST COPY FOR FDG-PET/CT CENTER RECORDS**

**SUV ANALYSIS**

The study will rely on visual interpretation only. However data will be collected for post hoc analysis to determine whether visual interpretation can be refined and semi-quantitative measures used to subgroup patients further into 'tighter' quantitative response categories which may have prognostic value. A scheme for analysis of semi-quantitative data is suggested below.

The 'hottest' lesions at staging will be chosen for SUV analysis but if subsequently the response scan shows residual activity at sites different from the 'hottest' lesions at staging, these sites will be used as the index lesions instead. Uptake in up to 6 lesions will be documented. The maximum SUV within the lesion will be calculated using decay corrected administered dose and body weight. The maximum SUV will be selected using a region of interest placed on the axial PET slice with the highest uptake. The maximum CT diameter of the mass will be recorded on the axial slice with the greatest CT diameter. Note the PET and CT axial slices may not match as the maximum SUV may occur within the lesion in a different axial plane to the maximum size on CT. If this occurs and the entire lesion shows at least some degree of FDG uptake, the maximum CT diameter in transaxial dimension should be recorded. However, if only a section of a large residual mass shows residual FDG uptake on the interim scan, then the CT diameter should be measured on the slice where that residual FDG uptake occurs.

**Initial staging CT scan (with intravenous contrast)**

| Index lesion | Site e.g. left supraclavicular | SUV max | PET axial slice | CT max transverse diameter (mm) | CT axial slice |
|---|---|---|---|---|---|
| 1 | | | | | |
| 2 | | | | | |
| 3 | | | | | |
| 4 | | | | | |
| 5 | | | | | |
| 6 | | | | | |

**Response CT scans (with intravenous contrast) after primary chemotherapy**

Correlate with staging scan index lesions and note any additional lesions with higher uptake

| Index lesion | Site e.g. left supraclavicular | SUV max | PET axial slice | CT max transverse diameter (mm) | CT axial slice |
|---|---|---|---|---|---|
| 1 | | | | | |
| 2 | | | | | |
| 3 | | | | | |
| 4 | | | | | |
| 5 | | | | | |
| 6 | | | | | |

Rev. 10/11

FORM COMPLETED BY:

**A 3-Arm Randomized Phase II Trial of Bendamustine-Rituximab (BR) Followed by Rituximab vs Bortezomib-BR (BVR) Followed by Rituximab vs BR Followed by Lenalidomide/Rituximab in High Risk Follicular Lymphoma**

Rev. 9/14

## Appendix VII

## Bendamustine Reconciliation

Certificate of Destruction of Clinical Trial Drugs

*Instructions:* *Complete this form when patient's treatment is completed at your institution. All unused drugs, partially used, or empty containers must be destroyed according to institutional policy for drug destruction. A copy of this form should emailed to Teva Oncology at carolyn.paugh@tevapharm.com or faxed to 610-756-2030. A copy should be maintained with the drug accountability records for this protocol.*

Rev. 4/13

| | |
|---|---|
| **Sponsor:** | Teva Oncology/ECOG-ACRIN |
| **ECOG-ACRIN Study No.** | E2408 |
| **DPM:** | Carolyn Paugh |

| | |
|---|---|
| **Investigator Name:** | |
| **Investigator Number:** | |
| **Investigator Address:** | |

| Drug Name | Lot Number | Expiry Date | Amount Used | Amount Unused | Number of Bottles destroyed at site |
|---|---|---|---|---|---|
| Bendamustine | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

**Reason for destruction:** _____

**Method & Location of destruction:** _____

**Date of Destruction:** _____

***I confirm the above material has been destroyed in a safe and appropriate manner.***

**Name and Title:** _____

**Date:** _____

**Signature:** _____

**PI Signature:** _____

**A 3-Arm Randomized Phase II Trial of Bendamustine-Rituximab (BR) Followed by Rituximab vs Bortezomib-BR (BVR) Followed by Rituximab vs BR Followed by Lenalidomide/Rituximab in High Risk Follicular Lymphoma**

## Appendix VIII

## Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. The risks to a fetus are not known. However, because lenalidomide is related to thalidomide, and thalidomide is known to cause severe birth defects, the following requirements must be observed.

All study participants must be registered into the mandatory RevAssist® program, and be willing and able to comply with the requirements of RevAssist®.

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: 1) for at least 28 days before starting lenalidomide; 2) while participating in the study; and 3) for at least 28 days after discontinuation from the study. 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.

- Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective method listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.
- 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.

**Before starting lenalidomide:**

Rev. 10/11

Female Subjects:

- FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to prescribing lenalidomide. The first pregnancy test must be performed within 10-14 days prior to prescribing lenalidomide and the second pregnancy test must be performed within 24 hours prior to prescribing lenalidomide (prescriptions must be filled within 7 days). The subject may not receive lenalidomide until the Investigator has verified that the results of these pregnancy tests are negative.

† A female of childbearing potential is a sexually mature woman 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).

*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.

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

*All Subjects:*

- 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.

*Female Subjects:*

- 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 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.
- 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.

*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.

# A 3-Arm Randomized Phase II Trial of Bendamustine-Rituximab (BR) Followed by Rituximab vs Bortezomib-BR (BVR) Followed by Rituximab vs BR Followed by Lenalidomide/Rituximab in High Risk Follicular Lymphoma

Rev. 2/14

## Appendix IX

## RevAssist for Study Participants

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 Num RV-E24082804

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

**A 3-Arm Randomized Phase II Trial of Bendamustine-Rituximab (BR) Followed by Rituximab vs Bortezomib-BR (BVR) Followed by Rituximab vs BR Followed by Lenalidomide/Rituximab in High Risk Follicular Lymphoma**

## Appendix X

## Modified Cumulative Illness Rating Scale (CIRS)

**The Modified Cumulative Illness Rating Scale (CIRS).**

| | Body system | Score | | | | |
|---|---|---|---|---|---|---|
| 1. | Cardiac (heart only) | 0 | 1 | 2 | 3 | 4 |
| 2. | Hypertension (rating is based on severity; organ damage is rated separately) | 0 | 1 | 2 | 3 | 4 |
| 3. | Vascular (blood, blood vessels and cells, bone marrow, spleen, lymphatics) | 0 | 1 | 2 | 3 | 4 |
| 4. | Respiratory (lungs, bronchi, trachea below the larynx) | 0 | 1 | 2 | 3 | 4 |
| 5. | EENT (eye, ear, nose, throat, larynx) | 0 | 1 | 2 | 3 | 4 |
| 6. | Upper GI (esophagus, stomach, and duodenum; pancreas; do not include diabetes) | 0 | 1 | 2 | 3 | 4 |
| 7. | Lower GI (intestines, hernias) | 0 | 1 | 2 | 3 | 4 |
| 8. | Hepatic (liver and biliary tree) | 0 | 1 | 2 | 3 | 4 |
| 9. | Renal (kidneys only) | 0 | 1 | 2 | 3 | 4 |
| 10. | Other GU (ureters, bladder, urethra, prostate, genitals) | 0 | 1 | 2 | 3 | 4 |
| 11. | Muscolo-skeletal-integumentary (muscle, bone, skin) | 0 | 1 | 2 | 3 | 4 |
| 12. | Neurological (brain, spinal cord, nerves, do not include dementia) | 0 | 1 | 2 | 3 | 4 |
| 13. | Endocrine-Metabolic (includes diabetes, thyroid; breast; systemic infections; toxicity) | 0 | 1 | 2 | 3 | 4 |
| 14. | Psychiatric/Behavioral (includes dementia, depression, anxiety, agitation/delirium, psychosis) | 0 | 1 | 2 | 3 | 4 |

## PHILOSOPHY AND DEVELOPMENT OF THE SCALE

Compiling and quantifying medical problems in the elderly population will allow meaningful comparison of medical burden and treatment outcomes in elderly patients with variable and complex medical problems.

The Cumulative Illness Rating Scale (CIRS) was initially developed by Linn et al. and published in JAGS 1968 (1); it appeared immediately a user friendly but comprehensive review of medical problems by organ systems, based on a 0 thru 4 rating, yielding a cumulative score. This scale was successively revised by Miller et al. to reflect common problems of the elderly with an emphasis on morbidity using specific examples and was renamed CIRS for Geriatrics (CIRS-G) (2); moreover, Miller and Towers provided also a manual of guidelines for scoring their version (3).

Then, in 1995, Parmelee et al. validated a Modified CIRS version, based on a 1 thru 5 rating and with some differences in categories, in a geriatric residential population (4). Finally, Mistry et al. used this latter Modified CIRS version with a 0 thru 4 rating to measure medical burden in psychogeriatric participants of the UPBEAT program, showing that inclusion of acute medical conditions did not undermine the usefulness of the CIRS (5). Based on the version of Miller and Towers, current guidelines were adapted to the Modified CIRS version and updated.

## RATING SUGGESTIONS (GENERAL PRINCIPLES)

Every single disease must be classified in the appropriate system. If there are several problems in the same system, only the most severe is rated. Example: for a patient suffering from mild diet-controlled diabetes (Grade 1) and hyperthyroidism in pharmacologic treatment (Grade 2), only the higher rated condition would be scored in the Endocrine system (e.g. rating is 2).

The spread of a cancer may lead to rate the condition in more than one category. For example, lymphoma with bone involvement treated with nonsteroidal anti-inflammatory drugs (NSAID) is Rated 4 in Respiratory and 2 in Musculoskeletal.

### General rules for severity rating:

0 - No problem affecting that system or past problem without clinical relevance.
1 - Current mild problem or past significant problem.
2 - Moderate disability or morbidity and/or requires first line therapy.
3 - Severe problem and/or constant and significant disability and/or hard to control chronic problems (complex therapeutic regimen).
4 - Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment.

### LEVEL 0

No problem or healed minor injuries; past childhood illnesses (chickenpox); minor surgery (carpal tunnel completely healed, caesarean); uncomplicated healed fractures; other past problems healed without sequel, residual or complication (pneumonia).

### LEVEL 1

Any current medical problem that causes mild discomfort or disability, or has occasional exacerbations, having only minor impact on morbidity (asthma controlled with PRN bronchodilators, occasional heartburn relieved with PRN antiacids). Medical problems that are not currently active but were significant problems in the past (passage of a kidney stone) or required major surgery (hysterectomy, cholecystectomy, appendectomy).

### LEVEL 2

Medical conditions that require daily treatment or first line therapy (asthma controlled with inhaled steroids, gastro-esophageal reflux treated with daily medication, osteoarthritis requiring daily NSAID, etc.) and/or have moderate disability or morbidity.

### LEVEL 3

Chronic conditions that are not controlled with first line therapy (asthma needing continuous corticosteroid therapy, symptomatic angina despite medical regimes, heart failure with symptoms or uncontrolled hypertension despite complex therapeutic regimen) and/or constant significant disability, but not severe disability.

### LEVEL 4

Any acute condition that requires immediate treatment or hospitalization (unstable angina, acute myocardial infarction, stroke, but also bladder outlet obstruction) and/or extremely severe

problems; organ failure (end-stage renal disease needing dialysis, oxygen-dependent chronic obstructive pulmonary disease, terminal heart failure); severe sensory impairment (almost complete blindness or deafness, being wheelchair bound) and/or severely affected quality of life, severe impairment in function; delirium by medical (organic) conditions.

## ORGAN SPECIFIC CATEGORIES

The following organ specific categories will attempt to provide guidelines for consistent rating of comparable severity. Common conditions will be stressed with the focus on the "judgement strategy" that can be applied to other problems not listed.

If there are several problems in the same system, only the most severe is rated.

## HEART

In this category only heart and coronary disease have to be considered (not vascular): coronary arteries disease, heart failure, valvular heart diseases, heart disease secondary to hypertension, endocardities, miocardities, pericardities, arrhythmias (extrasystoles, bundle-branch blocks, atrial fibrillation, PMK placement), heart malignancies. Functional impact must be considered too, e.g. NYHA II heart failure has different value between dependent and independent persons.

0. No problems
1. Remote MI (>5 years ago); occasional [exertion] angina; asymptomatic valvular disease
2. CHF compensated with meds (NYHA I-II); daily anti-angina meds; left ventricular hypertrophy; atrial fibrillation, bundle branch block, daily anti-arrhythmic drugs (even for prophylaxis); PMK placement for asymptomatic bradycardia (relieved by Holter EKG monitoring); valvular disease requiring medical treatment
3. Previous MI (<5 years ago); abnormal stress test; status post (previous) percutaneous coronary angioplasty, coronary artery bypass graft surgery or other cardiac surgery (valve replacement); moderate CHF (NYHA II-III) or complex medical treatment; bifascicular block; PMK placement for cardiogenic syncope; pericardial effusion or pericarditis
4. Acute coronary syndrome, unstable angina or acute MI; intractable CHF (NYHA III-IV acute or chronic); marked restriction to the normal activity of daily living secondary to cardiac status

## HYPERTENSION

Consider only hypertension severity; organ damage (complications) should be considered into the respective categories.

0. Normotension
1. Borderline hypertension; hypertension compensated with salt restriction and weight loss, drug free (when drug therapy is indicated, but the patient does not take meds, the score is at least 2)
2. Daily antihypertensive meds: hypertension controlled by 1 pill therapy (even fixed doses combinations)
3. Hypertension requiring two or more pills for control
4. Malignant hypertension, or hypertension non controlled by complex therapeutic regimen

## VASCULAR-HEMATOPOIETIC

Artery disease: carotid atherosclerosis, peripheral arteries disease (PAD), aneurysms (every site);
Venous disease: venous insufficiency, varices, deep venous thrombosis (DVT), pulmonary embolism, primary pulmonary hypertension;
Hematopoietic disease: anemia, leucopenia, thrombocytopenia, hematological malignancy;
Lymphopoietic disease: chronic lymphatic edema, lymphoma, spleen and thymus disease;

Immunologic disease: systemic lupus erythematosus, systemic sclerosis (scleroderma), sarcoidosis, hypersensitivity

0. No problem
1. Venous insufficiency, varices, lymphedema; carotid stenosis < 70%; hemoglobin 10-12 g/dl (in females), 12-14 g/dl (in males); anemia of chronic "inflammatory" disease
2. Previous DVT; one symptom of atherosclerosis disease (claudication, bruit, amaurosis fugax, absent pedal pulses) or daily meds (e.g. anti-platelets drugs); PAD IIa-IIb by Fontaine; carotid stenosis > 70%; aortic aneurysm < 4 cm; hemoglobin 8-10 g/dl (in females), 10-12 g/dl (in males); anemia secondary to iron, B12 vitamin or folate deficiency, or to chronic renal failure; total white blood cell (WBC) 2000-4000/mmc; mild thrombocytopenia (50000-150000/mmc)
3. DVT or recent DVT (< 6 months ago); two or more symptoms of atherosclerosis (see above); PAD Fontaine III or recent/previous angioplasty (with or without stenting); hemoglobin <8g/dl (in females), < 10 g/dl (in males); dyserythropoietic anemia; WBC < 2000/mmc; severe thrombocytopenia (< 50000/mmc)

Pulmonary embolism (acute or recent/previous); atherosclerosis requiring surgical intervention (e.g. aortic aneurysm > 4 cm, symptomatic carotid stenosis >70%, PAD Fontaine IV or amputation for vascular causes, etc.); recent/previous vascular surgery; any hematological or vascular malignancy (including multiple myeloma)

In case of immunological disease, score should be assigned by considering blood abnormalities, stadium of organ damage and/or functional disability (2: symptoms controlled by daily meds; 3: symptoms not well controlled; 4: symptoms impossible to be controlled or short time poor prognosis).

**RESPIRATORY**

In this category we consider COPD, asthma, emphysema, restrictive pulmonary interstitial lung diseases, malignancies of lung and pleura, pneumonia, and smoking status too.

0. No problem
1. Recurrent episodes of acute bronchitis; currently treated asthma with prn inhalers when required; cigarette smoker > 10 but < 20 pack years

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2. Instrumental diagnosis of COPD or pulmonary interstitial disease (x-ray, TC, spirometry); daily prn inhalers (≤ 2 pharmacological classes); two or more episodes of pneumonia in the last 5 years; cigarette smoker > 20 but < 40 pack years
3. exertion dyspnea secondary to limited respiratory capacity, not well controlled by daily meds; required oral steroids for lung disease; daily prn inhalers (3 pharmacological classes); acute pneumonia treated as an outpatient
4. Chronic supplementation of oxygen; respiratory failure requiring assisted ventilation, or previous (at least one episode); any lung or pleural neoplasm; acute pneumonia requiring hospitalization

Smoking is an important respiratory and cardiovascular risk, so it is considered as a disease, and it is rated according to *lifetime pack years*:

Number of cigarette packs smoked per day X Number of years smoked in their lifetime

e.g. 1 pack year = 20 cigarettes/die (1 pack) X 1 year

Ex-smokers should be rated too, but those who have been smoke free for the most recent 20 years would merit a lower rating than currently smoking

Examples:

A. Patient smoking 20 cig/die (1 pack) for 25 years = 25 pack years - CIRS score: 2

B. Patient smoking 40 cig/die (2 packs) for 25 years = 50 pack years – CIRS score: 3

C. Ex-smoker of 20 cig/die (1 pack) for 25 years, he stopped 5 years ago – CIRS score: 2

D. Ex smoker of 20 cig/die (1 pack) for 25 years, he stopped 20 years ago – CIRS score: 1

Classification of COPD could be more specific when instrumental data (objective evidence) are available: blood gases, forced expiratory volume in 1 second (FEV1), etc.

## EYES, EARS, NOSE & THROAT, and LARYNX

To simplify the potential complexity of this category it was decided to score according to the severity of the disability created by sensory diseases (degree of limited autonomy and communication), and avoid rating each type of pathology. Sensory impairments should be rated **after** instrumental correction (corrective lenses, hearing aid, etc.).
Eyes: glaucoma, cataracts, macular degeneration (diabetic/hypertensive retinopathy), any other pathology
Ears: otitis, dizziness, any cause of hearing impairment
Nose & Throat: rhinitis, pharyngitis, nasal polyps, sinusitis, malignancies
Larynx: dysphonia, acute and chronic laryngitis, malignancies

0. No problems
1. Corrected vision with glasses; mild hearing loss; chronic sinusitis
2. Difficulty in reading newspaper or drive although glasses; required hearing aid; chronic sinonasal complaints requiring medication; vertigo/dizziness requiring daily meds
3. Severe low vision, partially blind (required an escort to venture out, unable to read newspaper); severe ear impairment (conversational heading still impaired with hearing aid); laryngeal dysphonia (not neurological dysarthria)
4. Functional blindness/deafness: unable to read, recognize a familiar face, unable to conversational heading, even if “organically” he is not completely blind or deaf; laryngectomy (every cause, especially malignancies); required surgical intervention for vertigo; aphonia secondary to laryngeal impairment.

## UPPER GASTROINTESTINAL SYSTEM

This category is comprehensive of the intestinal tract from esophagus to duodenum, and pancreatic trees: dysphagia, GERD, hiatal hernia, esophageal diverticula, any type of gastritis (consider also H. Pylori eradication or not), gastric/duodenal ulcer, acute or chronic pancreatitis, malignancies (comprehensive of gastric lymphoma).
*Pay attention that type 1 diabetes is rated under “metabolic”.*

0. No problem
1. Hiatal hernia, GERD or gastritis requiring prn meds; previous ulcer (>5 years ago); previous H. Pylori eradication therapy (> 5 years ago)
2. Daily proton pump inhibitor/anti-acid meds; documented gastric or duodenal ulcer or H.P. eradication therapy within 5 years
3. Active gastric or duodenal ulcer; positive fecal occult blood test; any swallowing disorder or dysphagia; chronic pancreatitis requiring supplemental pancreatic enzymes for digestion; previous episode of acute pancreatitis
4. Any type of malignancies (see “*Rating Malignancies*”); previous gastric surgery because of cancer; history of perforated ulcer (gastric surgery not because of cancer, ulcorrhaphy); melena/heavy bleeding from upper GI source; acute pancreatitis

## LOWER GASTROINTESTINAL SYSTEM

Comprehensive of the rest of the G.I. system, from small bowel to anus: Whipple's disease, diverticulosis, irritable bowel, malignancies. Constipation is rated, too, by type and frequency of laxatives required, or by history of impaction.

0. No problems, previous appendectomy, previous hernia repair (without complications)
1. Constipation managed with prn meds; active hemorrhoids; intestinal hernia requiring surgery; previous hernia repair with complications (intestinal adherences, laparocele, etc.); irritable bowel syndrome (few symptoms)
2. Constipation requiring daily bulk laxatives (psyllium, policarbophil, sterculia, guar gum, etc.), or stool softeners; diverticulosis (previous diverticulitis); inflammatory bowel disease in remission with meds (> 5 years ago)
3. Bowel impaction/diverticulitis within the last year; daily use of stimulant (irritant) or osmotic laxatives (bysacodil, senna, glycerol, sodium docusate; lactulose, polyethylene glycol) or enemas; chronic bowel inflammation in remission with meds (< 5 years ago)
4. Diverticulitis flare up; active inflammatory disease; current impaction; hematochezia/active bleeding from lower GI source; bowel carcinoma

## LIVER AND BILIARY TREES

Comprehensive of liver, gallbladder, biliary trees, portal system: acute and chronic hepatitis (viral, alcoholic, toxic, autoimmune, idiopathic), cirrhosis, portal hypertension, hemochromatosis, primary biliary cirrhosis, cholelithiasis, cholangitis, primary malignancies. As the hepato-biliary system is difficult to assess through the physical examination, therefore, laboratory results must be used.

0. No problem
1. History of hepatitis (actually normal values of transaminases); cholecystectomy
2. Cholelithiasis; chronic hepatitis or previous hepatitis (< 5 years ago) or any other liver disease (hemochromatosis, primary biliary cirrhosis) with mildly elevated transaminases (within 3-times normal values); heavy alcohol use within 5 years (to rate in "psychiatric", too)
3. Chronic hepatitis or any other liver disease with marked elevation of transaminases (> 3-times normal values); elevated bilirubin
4. Acute cholecystitis; any biliary obstruction; active hepatitis/liver cirrhosis; any liver or biliary tree carcinoma

## RENAL

This category is exclusive of kidney: kidney stones, acute/chronic renal failure, glomerulonephritis; nephrosic/nephritic syndrome; active/chronic pyelonephritis, diabetic or hypertensive nephropathy (albuminuria/proteinuria), renal carcinoma.
*Bence-Jones proteinuria in multiple myeloma should not be considered.*

0. No problem
1. Asymptomatic kidney stone; kidney stone passage within the last ten years; pyelonephritis within 5 years; kidney cysts without hematuria
2. Serum creatinine > 1.5 but < 3 mg/dl without diuretic or antihypertensive medication (particularly ACE-inhibitors or SRAA blockers); kidney calculi requiring daily meds
3. Serum creatinine > 3 mg/dl or > 1.5 mg/dl in conjunction with diuretics, antihypertensive, or bicarbonate therapy; active pyelonephritis; nephrosic syndrome; colic symptoms treated as an outpatient
4. Required dialysis; renal carcinoma; colic symptoms requiring hospitalization

**GENITOURINARY**

Ureters, bladder, urethra.
Genitals, prostate, testicles, penis, seminal vesicles.
Uterus, ovaries. *Mammary gland is rated under "metabolic".*
This category is comprehensive of all GU tract impairments: ureteral or bladder stones, benign prostate hypertrophy (BPH), urinary tract infections (UTI's), prolapses, etc. Urinary incontinence and indwelling catheter should also be considered.

0. No problem
1. Stress incontinence; BPH without urinary symptoms; hysterectomy or ovariectomy (uterine fibroma, benign neoplasm)
2. Pathological pap smear (or 2 consecutives abnormal); frequent UTI's (3 or more in the past year) in female or current UTI's; urinary incontinence (not stress) in females; BPH with urinary symptoms (frequency, urgency, hesitancy); status post TURP; any urinary diversion procedure; indwelling catheter; bladder calculi
3. Prostatic cancer in situ (e.g. incidentally found during TURP); vaginal bleeding; cervical carcinoma in situ; hematuria (any cause); urinary incontinence (not stress) in males; bladder polyps
4. Acute urinary retention; current urosepsis; any GU malignancies except as above

**MUSCULOSKELETAL/INTEGUMENT**

This is a very wide category, including: osteoarthritis, osteoporosis, any bone fracture; primary neoplasm (bone, muscle, connective tissue, skin), distinguishing melanoma from other localized skin cancers; rheumatoid arthritis and polymyalgia rheumatica; muscular injuries (rotator cuff, long head of the biceps); pressure sores; any dermatological disease.
The scores of this category are strictly correlated to the disability they cause; for the evaluation of the level of disability, refer to BADL and IADL.

**NOTICE**: score the severity of each illness according to the level of disability caused by the same illness in this category, without considering the disability caused by other diseases. For example: a patient affected both by osteoarthritis and hemiplegia from a previous stroke has a high level of disability, but you have to score 2 for disability by osteoarthritis (in this category) and 4 for disability by stroke (in the neurological category); for a patient with both a deforming rheumatoid arthritis and a previous stroke without remaining outcomes you have to score 4 for disability from arthritis (in this category) and 2 for disability from stroke (in the neurological category).

0. No problem
1. Requires PRN meds for osteoarthritis (NSAID) or has mildly limited IADL from joint pathology; excised skin cancers (except melanoma); skin infections requiring antibiotics within a year
2. Daily anti-osteoarthritis meds (NSAID) or use of assisitive devices or little limitation in ADL (previous arthroprosthesis or treated fracture with a low level of remaining disability); osteoporosis without vertebral fractures; daily meds for chronic skin diseases (even local, as psoriasis or pressure sores); non metastatic melanoma; daily meds for rheumatoid arthritis (except steroids) with a low level of disability
3. Osteoarthritis with a moderate level of disability in ADL; requires chronic treatment with steroids for arthritic conditions or joints' deformities or severely impaired; osteoporosis with vertebral compression fractures

4. Wheelchair bound for osteomuscular disease; severe joint deformities or severely impaired usage; osteomyelitis; any bone or muscle or connective tissue neoplasm (see "Rating Malignancies"); metastatic melanoma.

Fractures and/or arthroprosthesis (both recent and old) have to be scored according to the level of disability they cause (considering outcomes too), in order to avoid confusion about possible classifications of different fractures or joints. The same for muscular diseases.

**CENTRAL AND PERIPHERAL NERVOUS SYSTEM**

This category includes the "somatic" pathologies of the central and peripheral nervous system: any kind of stroke, neurodegenerative diseases (Parkinson's disease and parkinsonism, multiple sclerosis, amyotrophic lateral sclerosis, etc.), myelopathies, traumas with neurological outcomes, primary or secondary epilepsy, neuropathies (diabetic, alcoholic, any other etiology), primary tumors, chronic headaches (migraine), insomnia, etc. It must carefully estimate the severity and prognosis of the illness but also the functional impairment that the illness causes.

0. No problem (or fewer convulsions in childhood)
1. Frequent headaches requiring PRN meds without impairment in Advanced ADL; previous TIA (one event); previous epilepsy, actually not treated, without crisis since more than 10 years ago.
2. Chronic headache requiring daily meds (even for prophylaxis) or with regularly functional impairment in Advanced ADL (bed rest, job withdrawal, etc.); actual TIA or more than one previous TIA; previous stroke without significant residual; mild severity neurodegenerative diseases (see above), treated and well controlled; epilepsy controlled with drugs.
3. Previous stroke with mild residual dysfunction (hemiparesis, dysarthria); any neurosurgical procedure; moderate severity neurodegenerative diseases (see above), not well controlled by meds; epilepsy in treatment but with periodic crisis.
4. Acute stroke or previous stroke with severe residual dysfunction (hemiplegia, aphasia, severe vascular dementia) or more than one previous stroke (multi-infarct encephalopathy); severe neurodegenerative diseases (see above) causing disability in ADL; neurological coma.

**Alzheimer's disease and dementia should not be rated into this category** (Psychiatric and behavioral diseases): Alzheimer's disease should be listed only under psychiatric disorders; if dementia stems from vascular and/or mixed dementia and/or other neurological condition (e.g. Parkinson's Disease), both "neurologic" and "psychiatric" categories should be endorsed at the appropriate level for severity, considering in this category the stroke and the multi-infarct encephalopathy responsible for the cognitive impairment (score 3 for stroke with remaining outcomes, score 4 for multi-infarct encephalopathy).

**ENDOCRINE-METABOLIC SYSTEM AND BREAST (systemic infections and poisonings too)**

Type 1 and type 2 diabetes (organ damage should be considered into the respective categories, like for hypertension), obesity and dyslipidemia (hypercholesterolemia) represent the core of this category; it includes also hypo- and hyper-thyroidism, hypo- and hyper-parathyroidism, adrenal pathologies (Cushing' or Addison' disease), hypogonadism, hypopituitarism, etc. Malignancies of these glands, both benignant (like thyroid nodules) and malignant (like thyroid or adrenal cancer, vipoma, etc.) are included too.

Even if it is an exocrine gland, breast was included in this category because the authors didn't find a more appropriate one; so it includes the breast cancer too.
Moreover, it includes: electrolyte disorders, sepsis, systemic infections (like tuberculosis, syphilis, AIDS) scored according to their severity and the functional impairment they cause (see general indications) and poisonings (chronic by metals or acute by pesticides or carbon monoxide).

0. No problem
1. Diabetes and/or dyslipidemia compensated with diet; mild obesity (BMI 30-35 kg/m$^2$); hypothyroidism in replacement therapy (L-thyroxin); hyperthyroidism caused by Plummer' adenoma surgically treated.
2. Diabetes compensated with oral hypoglycemic drugs or insulin (hemoglobin A1c <7%); dyslipidemia well controlled by daily meds (c-LDL lower than the recommended target according to the individual global cardiovascular risk); moderate obesity (BMI 35-45 kg/m$^2$); hyperthyroidism (Basedow, Plummer) in pharmacologic treatment; asymptomatic or surgically treated hyperparathyroidism; fibrocystic breast disease.
3. Diabetes not well compensated by therapy (hemoglobin A1c 7-8.5%, presence of complications); dyslipidemia not well controlled (c-LDL higher than the recommended target according to the individual global cardiovascular risk; for instance, c-LDL>100 mg/dl in patients with previous myocardial infarction or stroke); severe obesity (BMI >45 kg/m$^2$); symptomatic hyperparathyroidism (for instance, hypercalcaemia); replacement therapy for adrenal failure; any electrolytes disorder requiring hospitalization.
4. Uncontrolled diabetes (hemoglobin A1c >8.5%) or one diabetic ketoacidosis or nonketotic hyperosmolar coma during the past year; genetic uncontrolled dyslipidemia; acute adrenal failure during hormonal replacement therapy; any neoplasm of thyroid, breast, adrenal gland (see "Rating Malignancies").

**NOTICE**: when the patient is not treated with drug therapy for diabetes or dyslipidemia but he should be for the optimal control of the pathology (for instance, hemoglobin A1c > 7%, total cholesterol > 250 mg/dl), score the pathology according to the laboratory values, which really define its severity.

## PSYCHIATRIC AND BEHAVIORAL DISEASES

This category includes both dementia and related behavioral disorders (psychosis, anxiety, depression, agitation) and all the pre-existing and/or not related to dementia psychiatric disorders. Since this is the only item analyzing patient's mental status (all the others refer to physical status), it is very important to evaluate it considering carefully further information derived from the Comprehensive Geriatric Assessment (MMSE; Geriatric Depression Scale, Neuro-Psychiatric Inventory if available) (8, 9).

0. No psychiatric problem or history thereof
1. Minor psychiatric condition or history thereof: previous (occasional) psychiatric treatment without hospitalization; major depressive event and/or use of antidepressants more than 10 years ago without hospitalization; occasional use of minor tranquilizers (e.g. BDZ; even if as hypnotherapy for insomnia); mild cognitive impairment (MMSE 25-28).
2. A history of major depression (according to DSM-IV criteria) within the last 10 years (treated or untreated); mild dementia (MMSE 20-25); previous admission to Psychiatric Department for any reason; history of substance abuse (more than ten years ago, including alcoholism).
3. Current major depression (according to DSM-IV criteria) or more than two previous major depression episodes in the past 10 years; moderate dementia (MMSE 15-20); current and usual usage of daily anti-anxiety meds (even as hypnotherapy for insomnia); current or within

the past ten years substance abuse or dependence (according to DSM-IV criteria); requires daily antipsychotic medication; previous attempt at suicide.

4. Current mental illness requiring psychiatric hospitalization, institutionalization, or intensive outpatient management (psychiatric emergency, as attempt at suicide or severe depression with suicide purpose, acute psychosis or acute decompensation of chronic psychosis, severe substance abuse; severe agitation from dementia); severe dementia (MMSE <15); **delirium** (acute confusion or altered mental status for medical (organic) reasons: in this case you have to codify also the medical cause in its own category with the appropriate level of severity).

It could be requested psychiatric consult for this category; dementia and depression, the most frequent diseases in the elderly, can be scored in details using the MMSE and GDS. The severity of any mental disorder (dementia, depression, anxiety, psychosis, substance abuse and all the others) has to be scored according to the level of functional impairment or disability they cause.

***DRUG LIST***

**Medical history**

1. *Drugs list (*fundamental*), including laxatives and tranquilizers (drug doses not needed- but list of each medication here):*

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**A 3-Arm Randomized Phase II Trial of Bendamustine-Rituximab (BR) Followed by Rituximab vs Bortezomib-BR (BVR) Followed by Rituximab vs BR Followed by Lenalidomide/Rituximab in High Risk Follicular Lymphoma**

## Appendix XI

## 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 XII

## Bortezomib Drug Ordering Form

| | | |
|---|---|---|
| Rev. 12/10 | **Section I (To be completed by Site)**<br>**All shaded areas must be completed before forwarding the drug request to UVI, Inc.** | |
| ECOG-ACRIN Protocol Number: **E2408** | | Millennium Protocol Number: **X05341** |
| **Delivery Address**<br>**Institution Name:**<br>**CTEP ID:**<br>**Attention To:**<br>**Street Address:**<br>**City, State, Zip Code:** | | **Shipment Must Reach Destination By:**<br>**(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:**<br>**Principal Investigator Address:** | | **PATIENT SEQUENCE NUMBER:**<br>**ARM RANDOMIZED TO:** |
| **STUDY DRUG:** | **BORTEZOMIB** | |
| **BORTEZOMIB QUANTITY:** | **SHIPMENT #**<br>**See below or Section 8.3.7 for Shipment Time Points**<br>**(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:** | | |
| **UVI Personnel Name:** | **Signature:** | **Date:** |

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## E2408 CLINICAL TRIAL MATERIAL RETURN REQUEST FORM

**Section I (*To be completed by Site*)**

**Instruction – How to Return Commercial Velcade (bortezomib) 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 Barbara Franklin 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 barbara.franklin@takeda.com

| | |
|---|---|
| **RETURN PICK UP ADDRESS**<br>**(*Address the VELCADE will be picked up from):*** | **TOTAL Amount of VELCADE Vials to Be Returned:**<br><br>**_____vials** |
| **Contact Name:** | **LOT NUMBER(s):** |
| **Phone:** | |
| **Fax:** | |
| **Email Address:** | **Reason for Return:** |
| **Principal Investigator Name:**<br>**Sub-Investigator Name (*if applicable*):** | **Millennium Protocol Number:** |

**Section II (*To be completed by Millennium*)**

**Millennium Approval (Commercial Operations):**

_____

**Printed name** **Signature** **Date**

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## Appendix XIII

## Bendamustine Drug Ordering Form

Pharmaceuticals

# ECOG 2408 (C18083/6248)
# REQUEST FOR DRUG SHIPMENT

COMPLETE AND EMAIL TO:
Carolyn.Paugh@tevapharm.com or
Fax completed form to +1-610-756-2030

Instructions for completion: Please allow for at least 3 days for delivery. Clearly type or print information in all sections below. For any questions related to drug shipment or completion of this form please contact Carolyn Paugh at Carolyn.Paugh@tevapharm.com or (610-727-6360).

---

Product name: Treanda (Bendamustine HCL) 100 mg vials

Number of vials needed (vials are shipped in multiples of 10): ___ vials

Patient Number:_____

Initial order or resupply? : _____

Date shipment needed: _____

---

**DRUG SHIPMENT ADDRESS AND CONTACT INFORMATION**

Institution name:
Street address:
City/state/zip:
Attn to:

Pharmacy phone number:

Requester name:
Requester phone number:

Requestor fax number:

Investigator name:

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## Appendix XIV

## 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 as outlined in Section 5.2.6 of the protocol.

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

## Investigator Statement

In order to ship bendamustine, E2408 has a protocol-specific requirement to collect a site pharmacy license. For sites who do not utilize a pharmacy, a signed statement by the investigator is required as follows:

1. I have read and understand the storage and dispensing requirements related to the investigational inventory of bendamustine being supplied for use in this clinical trial. I acknowledge that this research site has appropriate facilities to provide adequate and secure storage of this agent. As Principal Investigator for this trial, it is my responsibility to ensure that a current record of investigational product receipt, storage and disposition is maintained and all records of drug accountability comply with applicable regulations.

**ACKNOWLEDGED AND AGREED**

Signature: _____

Investigator's Name (printed): _____

Address: _____

Telephone: (  ) _____

Date: _____

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## Appendix XVI

## 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 protocol treatment, or within 28 days of the patient's last dose of protocol treatment 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?**

The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP'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 assistance in recording the grade or category of these events, please contact the CTEP AEMD Help Desk at 301-897-7497 or aemd@tech-res.com, for it will need to be discussed on a case by case basis.

**Reporting a Fetal Death**

A fetal death 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, puerperium and perinatal conditions - Other (pregnancy loss)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions".

A fetal death should NOT be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death.

**Reporting a Neonatal Death**

A neonatal death is defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" 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 protocol treatment must also be reported via CTEP-AERS.

It must be reported via CTEP-AERS as Grade 4 "General disorders and administration - Other (neonatal loss)"under the System Organ Class (SOC) "General disorder and administration".

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)