SUMMARY OF CHANGES

NCI Protocol #: 8834
Local Protocol #: OSU 10156

NCI Version Date: March 15, 2024
Protocol Date: March 15, 2024
Summary of Changes Initiated by OSU:

#	Section	Page(s)	Change	Rationale
1.	Throughout (Headers/Title Page)	All	Update version date to March 15, 2024.	This is an amendment protocol so updated the version date to reflect the changes
2.	Throughout	Throughout	Minor administrative changes	Minor administrative changes to correct grammar, spelling, and formatting.
3.	6.3.1	28	Adverse events of White Blood Cell Decreased and Lymphocyte Count Decreased added as exception for dose modifications.	These events are an expected therapeutic outcome of treatment with Lenalidomide.
4.	9	52	Research sample collection to be discontinued upon approval of Amendment 24.	Study endpoints have been met.
5.	10	57	Visit windows specified for	Added to allow for more

			visits Cycle 7+ and during follow-up.	flexibility in visit schedule.
6.	10	60	Study calendar footnote O updated to clarify end of treatment requirements.	Updated for clarity

NCI PROTOCOL #: 8834

Local Protocol #: OSU 10156

Phase II study of lenalidomide to repair immune synapse response and humoral immunity in early-stage, asymptomatic chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) with high-risk genomic features

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Amendment 16 / Version 1 / July 14, 2017
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Amendment 21 / Version 1 / September 5, 2018
Amendment 22 / Version 1 / August 23, 2019
Amendment 23 / Version 1 / June 9, 2021
Amendment 24 / Version 1 / March 15, 2024

SCHEMA

Patient Eligibility

Histologically confirmed, asymptomatic CLL/SLL with at least one high-risk genomic feature
Age ≥18 years and ≤ 80 years
ECOG performance status ≤ 2
Non-pregnant and/or using adequate birth control
No previous treatment for CLL/SLL
No history of AIHA/ITP
No VTE events within 6 months
Estimated life expectancy ≥24 months

Required Laboratory Values

ANC ≥ 1500/μL
Platelets ≥ 100,000/μL
Bilirubin ≤ 1.5 x ULN
AST/ALT ≤ 2.5 x ULN
Creatinine clearance ≥60 mL/min

Treatment Plan

Arm A: Concurrent

Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8+
		V		**V**			
L	**L**	**L**	**L**	**L**	**L**	**L**	**L**

Arm B: Sequential

Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8+
V		**V**					
			L	**L**	**L**	**L**	**L**

V = PCV13 pneumococcal vaccine administration; **L** = lenalidomide

Patients will be randomized to receive concurrent lenalidomide and pneumococcal vaccine (Arm A) or sequential pneumococcal vaccine alone followed by lenalidomide (Arm B). Since the primary endpoint is to determine the change in anti-pneumococcal antibody titer levels, this endpoint will be evaluated in each arm about one month after the booster (2^{nd}) vaccination is administered. In Arm A, this will be evaluated at the beginning of cycle 6. In Arm B, this corresponds to the beginning of cycle 4. Secondary aims will include response, progression free survival, and immunologic response to primary tumor cells.

Lenalidomide treatment will be administered on a continuous basis. For the sake of convenience of dose-modification and response and toxicity monitoring, one cycle will be defined as 28 days. Treatment will be administered at 2.5 mg/day during the first cycle to minimize risk for tumor flare and/or tumor lysis. If tolerated, the dose will be increased to 5 mg/day beginning in the second cycle. Treatment will continue for at least 24 cycles (approximately 2 years) in the absence of disease progression or irreversible Grade ≥ 3 hematologic or non-hematologic toxicities.

Patients will receive 2 doses of 13-valent protein-conjugated pneumococcal vaccine (Prevnar 13, PCV13) administered 2 months apart. In Arm A, the vaccine will be administered at the beginning of Cycles 3 and 5. In Arm B, the vaccine will be administered at the beginning of Cycles 1 and 3.

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To determine the proportion of early-stage, high-risk CLL patients achieving a response (≥ 4-fold increase from baseline and/or antibody concentrations ≥0.35 μg/mL in 6 of 7 type-specific anti-pneumococcal antibody levels) after 2 doses of pneumococcal 13-valent conjugated vaccine (Prevnar 13, PCV13) administered concurrent with versus sequential to low-dose lenalidomide

1.2 Secondary Objectives

1.2.1 To determine the complete response (CR) rate after 2 years of lenalidomide therapy

1.2.2 To determine the time to first treatment (TFT), defined as the time from diagnosis to first non-lenalidomide therapy for progressive CLL as described by IWCLL 2008 criteria[1].

1.2.3 To determine the incidence of infection and invasive pneumococcal infections following treatment with the PCV13 vaccine and either concurrent or sequential lenalidomide.

1.2.4 To determine the frequency of humoral and cellular immune response to CLL tumor antigens following treatment with the PCV13 vaccine and either concurrent or sequential lenalidomide.

1.2.5 To determine the safety and toxicity associated with long-term lenalidomide exposure

1.2.6 To perform correlative pharmacodynamic and pharmacokinetic studies and correlate these with vaccine/tumor immunologic and disease response.

2. BACKGROUND

2.1 Chronic Lymphocytic Leukemia (CLL/SLL)

2.1.1 CLL and infection risk

Chronic lymphocytic leukemia (CLL) is the most frequently diagnosed form of leukemia in the western world. It was initially defined as a generalized, self-perpetuating neoplastic proliferation of lymphoid tissue, particularly of small lymphocytes.[1.a.i.2] It is now recognized as a clinically heterogeneous disease originating from B lymphocytes that may differ in activation, maturation state, or cellular subgroup.[1.a.i.3] Accordingly, CLL displays a marked survival heterogeneity, ranging from months to over 20 years (SEER data). One of its clinically defining features is the predisposition to infectious complications. That predisposition continue to be one of the principal causes of morbidity and mortality in patients with this disease, accounting for 30 to 50% of deaths.[1.a.i.4] The immune defect in CLL is characterized by both humoral and cellular deficits.

Hypogammaglobulinemia is often present at diagnosis and typically increases in incidence as disease progresses such that 75% of patients are ultimately affected.[5] Impaired immunoglobulin production significantly increases the risk for bacterial infection, particularly those caused by encapsulated organisms such as *Streptococcus pneumoniae*. Cellular immune defects are characterized by alterations in the number and function of T cell subsets.[6-8] Studies in both murine models of human CLL and in patients demonstrate the CLL cells are very immunosuppressive[7,9,10]. Defects in both cellular and humoral immunity likely account for the poor response to vaccination in CLL patients, and developing strategies to enhance vaccine response represents an important area in CLL research.

2.1.2 **Vaccination in patients with CLL**

CLL patients typically respond poorly to vaccines, particularly pneumococcal polysaccharide and influenza vaccines. This is especially true in patients with advanced disease stage. In 1960, a series of 42 previously untreated CLL patients was challenged with antigens to mumps, diphtheria, influenza, and typhoid. While there was some correlation between the level of gamma-globulin deficiency and response to antigenic stimulation, this response did not reach that of normal controls, even in patients with normal gamma-globulin levels. In observing these patients over the next year, the patients with the best response to vaccines had the fewest number of bacterial infections.[11] A subsequent study evaluated the responses of patients with hematologic malignancies to influenza vaccines. Eight of the thirteen patients with lymphoproliferative disorders failed to have a four-fold increase in antibody titer with vaccination. Stiver and colleagues demonstrated a 4-fold increase in antibody titer in 36% of patients to influenza A and 32% of those to influenza B. Four patients included in this study had received chemotherapy, and none of these patients had a 4-fold rise in antibody titer in response to vaccination.[12] A correlation between immunologic response to vaccine and absolute numbers of CD4+/CD45RA+ naïve T cells has been identified, which may suggest a role of this subset of cells in antibody response.[13] With a booster, response rates increased from 5% to 15% for influenza A and from 15% to 30% for influenza B, but this did not have a significant impact on protection rates.[14] This poor response was confirmed in an open, randomized study, where the response rates in two doses compared to one was 18% vs 22% for H1N1, 26% vs 14% for H3N2, and 25% vs 22% for influenza B. The results in patients with previous versus current chemotherapy were not statistically different, and patients who had received monoclonal antibody therapy were uniformly poor responders. Of seven patients, there was only one who had a response to influenza B, and no patients responded to H1N1 or H3N2.[15]

Purified polysaccharide antigens result in T cell-independent type-2 antibody formation. In conjugated vaccines, the polysaccharide antigen is conjugated to a toxoid as a carrier protein, resulting in antibody responses to the polysaccharide antigens in a T cell-dependent way. T cell-dependent antigens induce immunological memory, resulting in the possibility of booster vaccinations. Recent studies have indicated that conjugation of polysaccharides may render the antigen more immunogenic in the CLL population, and there is evidence that patients with CLL have a more significant immune response to

Haemophilus influenzae b conjugate than to plain polysaccharide antigen. A statistically significant response to *H. influenza* has been described, where 6 of 28 patients developed a protective antibody level, but no patients in this series had a response to the polysaccharide pneumococcal vaccine. This same study demonstrated a much more robust response to immunizations in control populations than in CLL patients. However, age, disease stage, and IgG levels all play a role in the degree of response to immunization, as illustrated in the study by Hartkamp et al.[16] This study showed poor responses to immunization with both the polysaccharide pneumococcal vaccine, as well as the protein-conjugated *H. influenza* vaccine overall. However, a significant correlation was demonstrated with less advanced disease stage and absence of hypogammaglobulinemia, as well as higher levels of total IgG, IgG2, and IgG4 subclasses and lower levels of soluble CD23 (sCD23). Sinsalo *et al* have since reported that 39% of patients achieved a significant response to administration of a 7-valent conjugated pneumococcal vaccine. Responding patients had Binet stage A and had not yet received chemotherapy or developed hypogammaglobulinemia. Responses in more advanced stage of disease were only 5%.[17]

2.1.3 **Agents used to augment vaccine response**

Histamine acts as a mediator of immune and inflammatory reactions, has a direct inhibitory effect on immunoglobulin production by B-cells in vitro through histamine H2 receptors, and acts as an immune regulatory factor, which can be modulated by histamine type-2 receptor antagonists.[18] Histamine is seen in higher levels in patients with CLL.[19] The theory that responses to vaccines may be further enhanced by adjuvant treatment with H2-blocker, however, is not well-supported by clinical evidence. In a study by Jurlander and colleagues, antibody to *Hib* conjugated with a tetanus-toxioid increased to protective levels in 90% of patients vaccinated with adjuvant ranitidine. On the other hand, the use of ranitidine to help mount antibody responses resulted in no significant difference in the response to vaccination against influenza types A and B.[19] Patients in this study tended to be younger, lower stage, and minimally treated, though. A more recent study by Van der Velden et al confirmed that administration of ranitidine increases levels of anti-*Hib* antibody and anti-tetanus toxoid antibody when compared with case-controls, but no significant improvements were noted with pneumococcal antibody responses.[20]

Co-administration of granulocyte-macrophage colony-stimulating factor (GM-CSF) is another method that has been tried to augment immune response. GM-CSF has been demonstrated to expand the myeloid subset of dendritic cells, inducing high levels of Th2 cytokines. Mice studies showed a significant increase in titers to ovaalbumin vaccine antibodies when those antibodies were coadministered with GM-CSF, specifically in IgG1 titers.[21] Administration of GM-CSF with the 23-valent polysaccharide vaccine did not improve response. A 4-fold rise in IgG was seen in less than 10% of patients given multiple dose levels of GM-CSF.[22]

2.2 **Lenalidomide**

2.2.1 **Lenalidomide activity in relapsed and treatment-naïve CLL**

Lenalidomide is a potent immunomodulatory analogue of thalidomide and has been demonstrated to possess anti-angiogenic activity through inhibition of bFGF, VEGF and TNF-alpha induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF.[23] In addition, lenalidomide has a variety of immunomodulatory effects including stimulation of T cell proliferation and the production of IL-2, IL-10 and IFN-γ, as well as inhibition of IL-1 beta and IL-6 production, and modulation of IL-12 production.[24] Upregulation of T cell derived IL-2 production is achieved, at least in part, through increased AP-1 activity.[25] Although the exact mechanism of lenalidomide anti-tumor activity is unknown, a number of mechanisms are postulated for this agent's activity against multiple myeloma. Lenalidomide increases T cell proliferation, which leads to an increase in IL-2 and IFN-γ secretion. The increased level of these circulating cytokines augment natural killer cell number and function, and enhance natural killer cell activity to yield an increase in multiple myeloma cell lysis.[26] In addition, lenalidomide has direct activity against multiple myeloma and induces apoptosis or G1 growth arrest in multiple myeloma cell lines and in multiple myeloma cells of patients resistant to melphalan, doxorubicin and dexamethasone.[27]

Lenalidomide has demonstrated promising activity in both untreated and relapsed/refractory CLL, including patients with high-risk genomic features such as del(17p) and del(11q).[28-32] In refractory disease, overall and complete response rates of 37% and 7%, respectively have been reported. At the doses employed in those studies (10-25mg/day), however, higher than expected rates of tumor flare response were observed.[28,29] Ferrajoli and colleagues have recently updated their experience treating 60 previously untreated CLL patients over the age of 65 with single-agent lenalidomide. Lenalidomide was initiated at 5mg/day on a continuous schedule with dose-escalation to 25 mg allowed, although the average tolerated dose was 10mg. At median follow-up of 15.5 months, 3 patients had achieved CR, 7 patients nPR (12%), and 22 patients PR (36%) for an ORR of 53%.[32] Importantly, most CR and nPR responses were achieved between 9 and 15 cycles of treatment and have thus far proved durable with continuation of therapy. While the optimal dose has yet to be established, lenalidomide appears to be highly active at even lower doses. Chen reported an overall response rate of 65% among 25 previously untreated patients. Safety and tolerability were improved with an initial dose of 2.5 mg/day slowly escalated to no more than 10mg/day.[31] In our institution's own phase I study, MTD was established at 2.5 mg/day escalated to 5 mg/day continuously administered, at which dose both biological and clinical activity were noted.[30]

2.2.2 **Low-dose lenalidomide can potentially reverse the immune deficiency of CLL**

Our group has reported the case of a relapsed CLL patient with high-risk disease (unmutated IgVH, complex karyotype including del17p) treated with low-dose lenalidomide (5mg/day continuously) who demonstrated gradual reduction of lymph node volume and peripheral blood lymphocytosis over 5 months of therapy. A polyclonal hypergammoglobulinemia (IgM, IgG, and IgA expansion) was observed concomitant with

disease response.[33] Badoux and colleagues have since reported an increase in immunoglobulin levels in elderly patients treated with lenalidomide. They found that IgG levels increased by a median 140 g/dL, most typically observed between 3 and 9 cycles of therapy.[34] Further, that group noted an early kinetic T-cell response with increases in the absolute number and proportion of CD3+, CD4+, and CD8+ T-cells concurrent with decreases in the peripheral blood absolute lymphocyte count. Over time this promoted normalization of CD4+/CD8+ T-cell ratios in both peripheral blood and bone marrow.

2.2.3 Lenalidomide can break humoral tumor tolerance in CLL

The exact mechanism by which lenalidomide induces these effects remains uncertain, but the drug has been reported to promote both cellular and innate immune activation and interference with the tumor cell microenvironment. Co-culture of CLL cells and autologous T-cells with lenalidomide can reverse the T cell immune synapse defect present in this disease, and lenalidomide effectively increases the co-stimulatory molecules CD40, CD80, and CD86 on CLL cells.[7] Previously, it has been shown that transduction of human CD154 (the surface ligand of CD40) into primary CLL cells likewise promotes expression of co-stimulatory molecules on bystander CLL cells.[35,36] In those experiments, residual normal B cells demonstrated improvement in both hypogammaglobulinemia and development of antibodies to the CLL-specific antigen ROR1. Our group has now shown that extended duration lenalidomide treatment promotes a similar CD154 gene therapy phenotype through PI3-kinase dependent activation of NF-κB mediated transcriptional activation and post-transcriptional mRNA stabilization of CD154.[33] Increases in CD154 mRNA were observed in serial samples from lenalidomide treated patients (at 2.5-5 mg/day). Further, in a subject who had not received prior therapy with the B-cell depleting agent rituximab prior to lenalidomide, there was evidence of increased titers of ROR1 antibody following lenalidomide treatment as well as increases in polyclonal IgG production. These findings suggest the potential benefit of administering lenalidomide much earlier in the disease course, when both humoral and cellular immune mechanisms are more likely to remain intact.

2.3 Protein-conjugated Pneumococcal Vaccines

2.3.1 Prevnar (Pneumococcal 7-valent conjugate vaccine, PCV7*)* in Immunocompromised Patients

Pneumococcal 7-valent conjugate vaccine, or Prevnar, is a solution of saccharides of the capsular antigens of *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F individually conjugated to diphtheria CRM_{197} protein. It is typically administered in childhood as a 3-dose primary series with a booster given in the second year of life. It has been studied in several immunocompromised patient populations, such as transplant recipients, in an attempt to improve rates of invasive pneumococcal disease over the polysaccharide 23-valent vaccine. Many anti-rejection medications are designed to impair T cell function. However, many of the current immunosuppressive regimens affect both T and B cell function. The American Academy of Pediatrics recommends immunization with sequential pneumococcal vaccines for pediatric solid organ recipients based on data from

the sickle cell population with two doses of the 7-valent conjugate pneumococcal vaccine (PCV7) and a single dose of 23V given at two months apart. This has been found to be safe, but the efficacy of the second dose of PCV7 or the dose of 23V was unknown. Significant increases in antibody titer were seen by Lin *et al* in response to the first dose of PCV7, but only moderate, and not significant, increases were seen after the second dose.[37] There has been evidence since published that the administration of 23V following immunization with PCV7 results in a rapid rise in IgG, consistent with a booster effect, followed by a rapid decline, suggesting the induction of suppressor cells or tolerance.[38] Vaccination with PCV7 has been demonstrated to be safe and efficacious in several immunocompromised adult populations, including the elderly, patients with COPD, stem cell transplant recipients, those with specific antibody deficiency, and patients with HIV, although an optimal dosing strength or schedule has not been clearly identified.[39-44] A recently published study evaluating PCV7 to prevent recurrent invasive pneumococcal infections in patients with HIV demonstrated a statistically significant reduction in the episodes of infection caused by the serotypes included in the vaccine with an efficacy of 74% when two doses of PCV7 were administered within a 28 to 56 day window.[45]

The widespread use of PCV7 in children has changed the epidemiology of invasive pneumococcal disease among adults over the past decade. The incidence of invasive pneumococcal disease declined overall from 40.8 cases/100,000 among adults over the age of 50 in 1998-1999 to 29.4 cases/100,000 in 2002-2003, with a decline of 55% in disease caused by the 7 serotypes included in PCV7. In contrast, disease caused by the 16 serotypes included only in the polysaccharide vaccine did not change, and disease not caused by serotypes included in either vaccine increased.[46] The proportion of adults who are colonized with PCV7-type pneumococci has decreased, as well; however, the proportion of isolates with intermediate susceptibility to penicillin has increased.[47] A recent study of 175 HIV-positive patients, all but one of whom had received vaccination with the polysaccharide vaccine, revealed colonization with pneumococci in a total of 6 (3.4%) patients, reflecting a relatively low incidence of colonization. Five of the isolates were serotypes not included in PCV7.[48] Due to herd immunity and serotype replacement effects in the general population, this suggests that there may be a need for a more expansive vaccination strategy in immunocompromised adults.

2.3.2 **Prevnar 13 (Pneumococcal 13-valent conjugate vaccine, PCV13)**

Prevnar 13 (PCV13) is a 13-valent pneumococcal conjugate vaccine that was recently licensed by the Food and Drug Administration (FDA) for prevention of invasive pneumococcal disease (IPD) caused by the 13 pneumococcal serotypes covered by the vaccine and for prevention of otitis media caused by the serotypes in PCV7. Dosing recommendations and safety profile are identical to those for PCV7. PCV13 contains polysaccharides of the capsular antigens of *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, individually conjugated to a nontoxic diphtheria CRM_{197} (CRM, cross-reactive material) carrier protein. A 0.5 ml PCV13 dose contains approximately 2 μg of polysaccharide from each of 12 serotypes and approximately 4 μg of polysaccharide from serotype 6B.[49] For the 7 common serotypes, PCV13 and PCV7

elicited comparable responses, with a similar percent of previously unimmunized infants achieving the 0.35 μg/ml IgG threshold required for response; while the IgG level was lower among patients receiving PCV13, functional response as measured by serotype-specific opsonophagocytic assays (OPAs) were comparable.[50] It is estimated that adding these 6 serotypes will increase coverage for prevention of IPD to 80-92% globally. The addition of 6A and 19A, in particular, is an important advance, as these serotypes mediate a substantial proportion of IPD worldwide, and 19A has emerged as a serotype that is resistant to penicillin.[51] While the Advisory Committee on Immunization Practices (ACIP) has not made recommendations for vaccination with PCV13 in patients over the age of 6 years, the recommended dosing schedule for children over the age of 12 months with an immunocompromising condition who have not been previously vaccinated against *S. pneumoniae* is 2 doses with a minimum interval of 8 weeks between doses.

2.3.3 Lenalidomide as an adjuvant to Prevnar in Multiple Myeloma

A study by Noonan et al in patients with multiple myeloma administered Prevnar before or concurrently with lenalidomide [52]. Response to vaccine included pneumococcal serotype titres as well as CRM-197 T cell responses quantified the B and T cell responses to Prevnar vaccination. All patients had measurable T cell and antibody responses to Prevnar. T cell responses to CRM-197 were significantly higher in the concurrent arm. Vaccination primed serotype humoral responses were noted in both treatment arms but an enhanced response to the booster vaccine was only noted in the patients receiving concurrent lenalidomide suggesting augmentation of a T-cell dependent response. DTH responses to Candida were examined to determine systemic immunity where concurrent lenalidomide demonstrated up to a 78-fold increase in induration compared to no change with sequentially administered prevnar followed by lenalidomide. An increase in T cell activation was also noted in the concurrent arm of prevnar and lenalidomide. Unexpectadly, the overall response rate was also higher in the concurrent arm (57%) as compared to sequential treatment (10%). Collectively, the preliminary findings of this study suggest synergy between the immunomodulatory effects of lenalidomide and vaccines. Although preliminary, the authors hypothesized that the increased anti-tumor effect observed in the concurrent arm might support the hypothesis of lenalidomide-induced vaccine-mediated epitope spreading. However, no direct anti-tumor immunologic response was observed in this study.

2.4 Rationale for Study Drug and Population

Notwithstanding the potential benefits accruing to lenalidomide treatment early in the natural history of disease, routine treatment for patients with early-stage CLL at diagnosis has previously not been considered beneficial. The standard of care remains to treat only patients progressing to symptomatic disease, sparing patients with early stage disease from toxicity.[1.a.i.1,53] Accumulating data, however, suggests that there exists an identifiable high-risk subgroup for whom the likelihood of early progression and subsequent death from their disease is great. Genomic and molecular features of the CLL clone explain much of the variation in prognosis and can identify higher-risk subpopulations meriting

consideration for risk-adapted intervention.[54,55] Patients with CLL demonstrating unmutated immunoglobulin heavy chain genes (IgV_H), complex karytotype (≥3 abnormalities), and FISH-detected deletions of chromosomes 11q22.3 and 17p13.1 demonstrate a shorter treatment-free interval and impaired survival.[56-60]

While initially described in a heterogeneous (early-/late-stage) population, more recent prospective studies have validated the independent prognostic value of these markers in early-stage (Rai 0/1, Binet A) disease.[61-63] Preliminary evidence suggests that these markers may also characterize a group among monoclonal B-cell lymphocytosis patients more likely to require treatment.[64] Recent studies assessing the benefit of treatment in early-stage disease, including the recently closed U.S. intergroup "early intervention" study (CALGB 10501), have targeted a similarly defined high-risk population.[65]

The preliminary data summarized above support the contention that treatment with the immunomodulatory agent lenalidomide, when initiated early in the disease course, can potentially change the natural history of not only the disease itself but also the immunological derangements responsible for its chief morbidities. We hypothesize that low-dose lenalidomide can enhance the efficacy of vaccination for infectious diseases as measured by antibody response to pneumonia vaccination with conjugated 13-valent pneumococcal vaccine. Correlative studies will evaluate parameters of immune reconstitution (quantitative immunoglobulins, T-cell subsets) and explore postulated mechanisms of lenalidomide activity. We further hypothesize that initiation of low-dose lenalidomide in asymptomatic patients with high genomic risk CLL can induce complete remissions with continued exposure to the drug.

2.5 Correlative Studies Background

2.5.1 **Serum immunoglobulin levels**: Quantitative serum immunoglobulin levels (IgG, IgA, IgM) will be obtained at baseline and every 2 months thereafter. Improvement in immunoglobulin levels over time will be correlated with the ability of lenalidomide to up-regulate CD154 on CLL cells and pharmacokinetics of lenalidomide. We have observed that CD154 up-regulation occurs in approximately 75% of CLL patients treated with lenalidomide [66].

2.5.2 **B-, T-, and NK-cell subsets and activation status**: Changes in subsets and activation status of B-, T-, and NK lymphocytes in peripheral blood following lenalidomide therapy will be evaluated using multiparametric flow cytometry. Lymphocyte CD4, CD8, T-regulatory, and NK cell subsets will be enumerated and markers of activation status will be characterized for each. Recent un-published data from our laboratory has demonstrated that lenalidomide can increase CD4 expression of IL21 which will be assessed by real time PCR from RNA isolated from these cells and serial plasma cytokine measurement. Activation of T- and NK-cells will be correlated with both up-regulation of CD154 on CLL cells and pharmacokinetics of lenalidomide.

2.5.3 **CLL cell activation**: B-cell activation will be further characterized by upregulation of CD154 as the primary measure (based upon our data), along with CD40, CD80, CD86. CD154, CD40, CD80, CD86 expression will be analyzed by flow cytometry on gated CLL cells. Additionally, we will measure serial changes in different cytokine receptor expression on CLL cells that could contribute to cytoxicity and immunogeneticity. Concurrent with such receptor measurement we will also assess serum cytokines and cellular cytokine production by accessory immune cells. Change in CD154 expression will be correlated with pharmacokinetics and immune response.

2.5.4 **Anti-ROR1 antibody levels**: Tumor-specific anti-ROR1 antibody titers will be determined by ELISA in plasma at baseline and every 6 months thereafter. Development of ROR1 antibodies will be correlated with the ability to up-regulate CD154 on CLL cells and pharmacokinetics of lenalidomide.

2.5.5 **Anti-CLL tumor antibody levels**: Tumor-specific antibody titers will be determined by an adapted flow cytometry assay from plasma at baseline and every 6 months thereafter. Development of anti-CLL antibodies will be correlated with the ability to up-regulate CD154 on CLL cells and pharmacokinetics of lenalidomide In patients developing such antibodies, normal B-cells derived from these patients will be isolated for identification of relevant target antigens. This work will be performed in collaboration with Christoph Rader at the intramural program of the NCI.

2.5.6 **Anti-pneumococcal antibody levels:** Serum antibody levels to specific pneumococcal antigens will be assessed at baseline, 2 months following initiation of lenalidomide therapy (cycle 3 day 1), 2 months after initial vaccination (cycle 5 day 1) and 1 month after second vaccination (cycle 6 day 1) and every 6 months thereafter for patients remaining in follow-up for patients in Arm A. For those in Arm B, titers will be assessed at baseline, 2 months after initial vaccination (cycle 3 day 1), 1 month after second vaccination (cycle 4 day 1), and every 6 months thereafter starting with cycle 7 day 1. ELISA will be used to quantitate anti-capsular polysaccharide antibodies against serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. Development of increasing pneumococcal titers will be correlated with the ability to up-regulate CD154 on CLL cells, T-cell activation, and pharmacokinetics of lenalidomide.

2.5.7 **Epigentic changes in CLL cells**: Histone modifications have been reported following treatment with lenalidomide. We will assess for modification of histone proteins by liquid chromatography and mass spectrometry. These histone changes will be correlated with response and pharmacokinetics of lenalidomide in an exploratory fashion.

2.5.8 **Expression of MDR1 on CLL and immune cells**: Our group has recently demonstrated that lenalidomide is an MDR1 substrate. Given that CLL cells express this transporter to varying degrees, we will assess baseline expression of this and correlate it with CLL cell activation.

2.5.9 **Pharmacokinetic studies**: Pharmacokinetic studies will be performed to correlate Pk features with measures of B-cell activation and other pharmacodynamic studies.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically identified chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) as defined by the WHO classification of hematopoietic neoplasms.

3.1.2 CLL/SLL cells must demonstrate one or more of the following high-risk genomic features:

- Del(17p13.1) as detected by fluorescence in-situ hybridization (FISH) in >20% of cells
- Del(11q22.3) as detected by FISH in >20% of cells
- Complex karyotype (≥3 cytogenetic abnormalities on stimulated karyotype)
- Unmutated IgVH (≥98% sequence homology compared with germline sequence)

3.1.3 Patients cannot meet any of the following consensus criteria for initiating treatment:

- Progressive splenomegaly and/or lymphadenopathy identified by physical examination or radiographic studies
- Progressive lymphocytosis with total WBC ≥ 300,000/µL
- Anemia (<11 g/dL) or thrombocytopenia (<100,000/µL) due to bone marrow involvement
- Presence of unintentional weight loss > 10% over the preceding 6 months
- NCI CTCAE grade 2 or 3 fatigue
- Fevers > 100.5° or night sweats for > 2 weeks without evidence of infection
- Progressive lymphocytosis with an increase of > 50% over a 2 month period or an anticipated doubling time of < 6 months

3.1.4 No prior therapy for CLL/SLL, including chemotherapy, radiotherapy, and/or immunotherapy will be allowed.

3.1.5 Age ≥ 18 years and ≤ 80 years (or with justification if older than 80 years due to the higher risk of toxicity in patients older than 80 years). CLL is rare in children and likely represents a different disease process. As a result, children are excluded from this study but may be eligible for future pediatric phase 2 combination trials.

3.1.6 Estimated life expectancy of greater than 24 months.

3.1.7 ECOG performance status ≤ 2 (Karnofsky ≥ 60%; see Appendix A).

3.1.8 Patients must have normal organ and marrow function as defined below:

▪ Total bilirubin	≤ 1.5 x ULN unless secondary to Gilbert's disease
▪ AST(SGOT)/ALT(SGPT)	≤ 2.5 X institutional upper limit of normal
▪ Creatinine clearance	≥ 60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal according to the Cockcraft-Gault formula
▪ Absolute neutrophil count	≥ 1,500/μL
▪ Platelet count	≥ 100,000/μL

3.1.9 Able to swallow capsules without difficulty and no history of malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.

3.1.10 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 starting lenalidomide. Further, they 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 starting 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. A FCBP 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). All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. (See **Appendix C**: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods, and also **Appendix D**: Education and Counseling Guidance Document).

3.2 Exclusion Criteria

3.2.1 Patients who have had any treatment for their CLL/SLL, including but not limited to chemotherapy, radiotherapy, or immunotherapy, prior to entering the study.

3.2.2 No corticosteroid use will be permitted within two weeks prior to study, except for maintenance therapy for a non-malignant disease. Maintenance therapy dose may not exceed 20 mg/day prednisone or equivalent.

3.2.3 Patients who meet consensus criteria for the treatment of CLL/SLL as defined in **3.1.3** above.

3.2.4 Patients may not be receiving any other investigational agents.

3.2.5 Patients with a recent history (within 6 months of study entry) of DVT/PE are not eligible. Patients with a distant history (greater than 6 months before study entry) of venous thromboembolic disease are eligible, but should receive prophylactic aspirin or low molecular weight heparin. (See **5.2.3** below)

3.2.6 History of allergic reactions attributable to compounds of similar chemical or biologic composition to thalidomide, lenalidomide or any component of PCV7 or PCV13, including the diphtheria toxoid.

3.2.7 Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, or other cancer from which the subject is considered by his or her physician to have a 2 year survival expectation.

3.2.8 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements..

3.2.9 Pregnant women are excluded from this study because lenalidomide is an immunomodulatory agent (IMID) with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with lenalidomide, breastfeeding should be discontinued if the mother is treated with lenalidomide.

3.2.10 HIV-positive patients on combination antiretroviral therapy will be eligible if they otherwise meet required hematologic parameters and are not receiving an antiviral agent with known or potential interaction with lenalidomide. Because the primary aim of this study is to measure the immune response to pneumococcal vaccination, only patients with CD4 cell counts ≥ 200 and viral load < 50 will be eligible.

3.2.11 Patients who have been treated for autoimmune hemolytic anemia or autoimmune thrombocytopenia within the last 6 months or are direct antiglobulin test/Coomb's test or indirect antiglobulin test positive at the time of screening.

3.2.12 Patients who have developed erythema nodosum characterized by a desquamating rash while taking thalidomide or similar drugs in the past are excluded.

3.2.13 Because of the potential for H2-blockers to modulate antibody response to pneumococcal vaccine, patients must discontinue treatment with H2-blockers (cimetidine, ranitidine, etc.) prior to beginning protocol therapy.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

3.4 Accrual Targets

Ethnic Category	Sex/Gender				
	Females		Males		Total
Hispanic or Latino	2	+	2	=	4
Not Hispanic or Latino	22	+	22	=	44
Ethnic Category: Total of all subjects	24 (A1)	+	24 (B1)	=	48 (C1)
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	1	+	1	=	2
Black or African American	2	+	2	=	4
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	21	+	21	=	42
Racial Category: Total of all subjects	24 (A2)	+	24 (B2)	=	48 (C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

Accrual Rate: 3 pts/month

Total Expected Accrual: 44 Min 48 Max

Projected Start Date of Study: 01/01/2011

4. REGISTRATION PROCEDURES

Each site must have two trained counselors available for counseling all patients receiving lenalidomide supplied by the Division of Cancer Treatment and Diagnosis. Trained counselors must complete training using the online program provided free by Celgene, the Celgene Pregnancy Prevention Counseling Program (CPPCP). Registration for CPPCP is done by completing the form found in Appendix C and following the directions provided in the email notification. After the training is complete, the counselors must generate a training certificate and provide it to PMB (fax number 240-276-7893; Attention CPPCP) for documentation. Sites may not order lenalidomide until documentation for two trained counselors is provided to the appropriate office.

5. TREATMENT PLAN

5.1 Agent Administration

Patients will be randomized to one of the following two treatment arms: Arm A (Concurrent PCV13 + lenalidomide) or Arm B (Sequential PCV13 + lenalidomide). (See **Table 1**). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. Treatment will be administered on an outpatient basis.

Table 1: Treatment Overview

Arm A: Concurrent

Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8+
		V		**V**			
L	**L**	**L**	**L**	**L**	**L**	**L**	**L**

Arm B: Sequential

Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8+
V		**V**					
			L	**L**	**L**	**L**	**L**

V = PCV13 pneumococcal vaccine administration; **L** = lenalidomide

All patients will be instructed on how to use a medication diary documenting each dose of medication (**Appendix B**). At monthly visits the patient will bring the medication calendar to the clinic. All bottles of study medication should be brought to each clinic visit for comparison with the medication calendar. The medication calendar for the previous month will be reviewed, and a new medication calendar will be given to the patient with each new lenalidomide supply.

5.1.1 Lenalidomide

Lenalidomide treatment will be administered on a continuous basis. However, for convenience of dose-modification, response, and toxicity monitoring, the treatment period will be divided into cycles of 28-day length. Lenalidomide will be dispensed in no more than one 28-day supply. Before each supply is released, each patient's medication calendar from the previous cycle will be reviewed to assess compliance. Patients will also be required to review the Lenalidomide Information Sheet (**Appendix E**) and the Education and Counseling Guidance Documents (**Appendix D**) prior to receiving each monthly supply of lenalidomide.

Table 2: Lenalidomide Dosing and Administration

Treatment Arm	Cycle	Dose	Ancillary Medications	Schedule	Cycle Length
A Concurrent	1	2.5 mg/day	Allopurinol 300 mg/day beginning 3 days prior to lenalidomide and continuing through at least the end of Cycle 1 Dexamethasone may be given for up to 7 days during Cycles 1 and 2 for symptomatic tumor flare	Days 1-28 continuous	28 days
	2+	5 mg/day			

B Sequential	1-3	No lenalidomide	Allopurinol 300 mg/day beginning 3 days prior to lenalidomide and continuing through at least the end of Cycle 4 Dexamethasone may be given for up to 7 days during Cycles 4 and 5 for symptomatic tumor flare	Days 1-28 continuous	
	4	2.5 mg/day			
	5+	5 mg/day			

Lenalidomide dosing and administration are summarized in **Table 2**. Lenalidomide treatment will be administered at 2.5 mg/day during the first cycle of treatment (Arm A: Cycle 1; Arm B: Cycle 4) to minimize risks for tumor flare and/or tumor lysis. The dose of lenalidomide will be increased to 5 mg/day beginning as early as the second cycle of therapy (Arm A: Cycle 2; Arm B: Cycle 5) if all of the following criteria are met on Day 1:

- No clinically significant Grade 3 or greater non-hematologic toxicities attributable to lenalidomide during the preceding cycle.
- Any hematologic toxicity is resolved to ≤ Grade 1.
- Maintained platelet count >50K at all times during the previous cycle.
- Maintained ANC >1K at all times during the preceding cycle.
- Any other drug-related adverse events have resolved to Grade ≤ 1 severity.

During the first cycle of lenalidomide exposure, and any cycle in which the dose is subsequently escalated, patients are seen on Days 1 and 8 for laboratory evaluation (CBC, chemistries), history, and physical examination to evaluate for tumor lysis and/or tumor flare, respectively. Management of tumor flare response is detailed in **5.2.1** below.

Patients not meeting criteria for dose escalation upon beginning the second cycle of lenalidomide can be re-evaluated for dose escalation at the start of subsequent cycles, at which time the same criteria will apply. However, dose escalation beyond 5 mg/day will not be permitted so as to limit the risk in this patient population who would not otherwise be receiving therapy. Criteria for removal from study (**Section 5.5**), dose modifications for toxicity (**Section 6.1**), and guidelines for intrasubject dose escalation (**Section 6.4**) are further discussed below. Management of biochemical and clinical tumor lysis is described in **6.3.9** and **6.3.10** below.

Lenalidomide can be taken without regard to meals. If a patient misses a dose of lenalidomide, the patient should take it as soon as he or she remembers that day. If the patient does not remember until the next day, the patient should skip the missed dose. Patients should NOT take two doses the same day. Missed doses will not be made-up, and the resulting remainder of study drug should be returned with the bottle at the next follow-up visit.

5.1.2 Protein-conjugate 13-valent pneumococcal vaccine

PCV13 administration is summarized in **Table 3** below. Patients will receive 2 doses of PCV13 administered 8 weeks apart. In Arm A (Concurrent), vaccine will be administered on Day 1 of cycles 3 and 5. In Arm B (Sequential), patients will be vaccinated on Day 1 of cycles 1 and 3. Each 0.5 mL dose of vaccine will be given intramuscularly in the deltoid muscle of the upper arm. PCV13 should not be administered intravenously, intradermally, or subcutaneously.

Table 3: Dosing and Administration of PCV13

Treatment Arm	Cycle	Dose	Schedule	Cycle Length
A Concurrent	3	0.5 mL IM	Cycle 3 Day 1	28 days
	5	0.5 mL IM	Cycle 5 Day 1	
B Sequential	1	0.5 mL IM	Cycle 1 Day 1	
	3	0.5 mL IM	Cycle 3 Day 1	

5.1.3 Other modality(ies) or procedures

N/A

5.2 General Concomitant Medication and Supportive Care Guidelines

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, and antiemetics when appropriate. All concomitant medications, including the reason(s) for treatment, dosage, and the dates of treatment, should be recorded on the flow sheets.

5.2.1 **Corticosteroids for tumor flare:** Swelling, erythema, and tenderness of lymph nodes (especially pathologically involved lymph nodes), with/without fever and rash, are expected effects of treatment with lenalidomide. First line treatment is analgesics (e.g. NSAIDs, acetaminophen, oral narcotics) or corticosteroids at the discretion of the treating physician. If the treating physician believes steroids are indicated, administration of dexamethasone (recommended dose = 4mg/day x 7 days) during the first two cycles of lenalidomide treatment is permitted. Steroid administration beyond 7 days can be considered after consultation with the principal investigator.

5.2.2 **Allopurinol**: All patients, unless allergic, should receive allopurinol 300 mg orally daily starting 3 days prior to initiating lenalidomide therapy and continuing through at least the end of the first cycle of treatment as tumor lysis syndrome prophylaxis. This coincides with Cycle 1 in Arm A and Cycle 4 in Arm B. Allopurinol may be continued through the second cycle of lenalidomide treatment and beyond at the discretion of the treating physician. If the patient is allergic to allopurinol, this drug will be omitted.

5.2.3 **Thromboprophylaxis:** Lenalidomide increases the risk of thrombotic events in patients who are at high risk or with a history of thrombosis, in particular when combined with other drugs known to cause thrombosis. When lenalidomide is combined with other agents such as corticosteroids, anthracyclines and erythropoeitic stimulating agents, the risk of thrombosis is increased. Consequently, concurrent use of ESAs will not be permitted. Prophylactic aspirin (recommended dose = 81 mg/day) or low molecular weight heparin (e.g enoxaparin 40 mg/day SQ) are to be given to patients with a high risk of developing DVT/PE or arterial thromboses unless otherwise contraindicated. High risk will be defined as a history of DVT/PE, significant family history, performance status ≥ 2, smoking history, or use of oral contraceptives. Patients with diabetes mellitus or coronary artery disease are considered to be at high risk for arterial thromboembolic events. All patients will be counseled to discontinue smoking and to seek appropriate cardiovascular risk reduction consistent with good medical practice. Patients requiring anticoagulation for something other than a history of thrombosis (i.e. prophylaxis for atrial fibrillation or mechanical heart valve) will not be excluded from the study. If warfarin is used, close monitoring of the INR is recommended. If anticoagulation becomes necessary for any reason other than a thrombotic event during the study period, patients may continue on the study provided that they are appropriately monitored. In the unexpected event that a patient develops severe thrombocytopenia (platelet count <50K), thromboprophylaxis should be held, irrespective of the indication, unless the treating physician, in consultation with the principal investigator, believes the benefit to the patient otherwise outweighs the risks.

5.2.4 **Transfusion**: Cytopenias requiring transfusion are not an expected complication of treatment on this study. If necessary, however, all blood products should be irradiated and leukoreduced to prevent transfusion-associated graft versus host disease.

5.2.5 **Antibiotics**: Routine antimicrobial prophylaxis will not be permitted. Antibiotics given for other indications should be carefully documented.

5.2.6 **Colony stimulating factor use**: Myeloid growth factors will not be permitted except for the treatment of febrile neutropenia as outlined in **6.3.2.** below. Erythropoetic stimulating agents (ESAs) will not be permitted for any indication.

5.2.7 **CYP inhibitors:** Lenalidomide has not been demonstrated to be a substrate, inhibitor, or inducer of the CYP group of enzymes and clinically relevant pharmacokinetic drug-drug interactions are unlikely to occur between lenalidomide and co-administered CYP substrates or inhibitors

5.2.8 **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.

5.2.9 **Concomitant medications:** Study flow sheets and/or case report forms must capture the concurrent use of all other drugs, over-the-counter medications, supplements, or alternative therapies on a monthly basis.

5.3 Duration of Therapy

Patients demonstrating clinical benefit, defined as achievement of an objective response (CR, CRi, or PR) or stable disease (SD), may continue therapy for up to 24 cycles (approximately 2 years) of treatment with lenalidomide. Therapy beyond 24 cycles may be considered after discussion with the principal investigator and consultation with the study sponsor.

Investigators are encouraged to keep patients experiencing clinical benefit on study unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk. If the subject meets any 1 of the following criteria, withdrawal from treatment is mandatory:

- Disease progression meeting 2008 IWCLL consensus criteria for treatment.
- Intercurrent illness that prevents further lenalidomide administration.
- Any treatment-related Grade 4 non-hematologic toxicity.
- Unacceptable and/or unmanageable Grade ≥ 3 toxicity attributable to lenalidomide.
- Any treatment-related hematologic or non-hematologic toxicity delaying treatment more than 14 days.

- Development of autoimmune hemolytic anemia (AIHA) or immune-mediated thrombocytopenia (ITP)
- Subject elects to withdraw from study or becomes pregnant.
- General or specific changes in the patient's condition rendering the patient unacceptable for further treatment in the judgment of the investigator.
- Subject is noncompliant with study procedures and/or scheduled evaluations.
- Investigator considers withdrawal to be in the best interest of the subject.
- Diagnosis of new or secondary malignancies after initiating treatment

Subjects with inadequate study drug compliance (i.e. ≤ 80% of planned doses administered) may be replaced.

5.4 Duration of Follow Up

Each subject should be followed for at least 30 (±7) days after his or her last dose of lenalidomide (i.e. the "safety follow-up period") to monitor for resolution or progression of AEs and to document the occurrence of new events unless the subject receives a new CLL therapy within this time frame.

Subjects who withdraw consent should still be encouraged to complete the safety follow-up assessments, but these assessments cannot be mandated once consent is withdrawn. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Beyond the safety follow-up period, patients no longer receiving protocol therapy will continue to be evaluated at 3 month intervals for the first year and every 6 months thereafter until they receive a new CLL therapy, withdraw consent, or expire. Patients may remain in follow-up if disease progression occurs. Required historical, laboratory, and physical examination procedures at each follow-up visit are detailed in the **Study Table** (**Section 10**).

5.5 Criteria for Removal from Study

Patients will be removed from treatment when any of the criteria listed in **Section 5.3** applies. Irreversible or unacceptable treatment-related toxicities that are Grade ≥ 3 as listed in **Section 5.3** necessitate discontinuation from study treatment. A patient with a treatment-related Grade ≥ 3 adverse event that resolves to Grade ≤ 1 within 14 days may continue treatment with appropriate dose reductions as outlined in **Section 6**. Any Grade 4 toxicity attributable to lenalidomide will require discontinuation from study treatment. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

5.6 Criteria for Halting the Study

If there are ≥ 2 treatment-related Grade 4 non-hematologic events in the first 10 patients or any grade 5 events, enrollment in the study will be temporarily halted pending review by the PI and the study sponsors regarding the need for modifications to the protocol or consent.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Dose Modifications due to Toxicity

Because this study assesses the benefits of treating early-stage, asymptomatic CLL/SLL patients who would not otherwise be receiving therapy, the definition of "unacceptable" toxicity will be defined as any treatment-related Grade 4 non-hematologic toxicity or any treatment-related Grade ≥ 3 toxicity deemed unmanageable or unacceptable by the patient, his or her treating physician, or the study chair. As described, in **Section 5.3** and **Section 5.5**, unacceptable toxicity will require discontinuation of protocol therapy.

Subjects will be evaluated for adverse events at each visit with the NCI CTEP CTCAE version 5 used as a guide for grading of severity for both hematologic and non-hematologic toxicity.

6.2 Criteria for Starting a New Cycle

A new course of treatment may begin on the scheduled day 1 of a new cycle if:

- All lenalidomide-related hematologic toxicity has resolved to Grade ≤ 1 severity.
- Any lenalidomide-related rash or neuropathy that may have occurred has resolved to Grade ≤ 1 severity.
- Any other drug-related adverse events that may have occurred have resolved to Grade ≤ 1 severity.

6.3 Criteria for Dose Reductions

Dose modifications of lenalidomide may be made at any time during treatment if lenalidomide is held for toxicity or at the start of a new cycle if the previous dose was not well-tolerated. Lenalidomide dose levels are displayed in **Table 4**. No dose reductions below dose level -1 (2.5 mg every other day) will be permitted. Specific criteria for holding and/or modifying the dose of lenalidomide are further detailed in this section.

Table 4. Lenalidomide Dose Levels

Dose Level	Lenalidomide Dose
1	5 mg daily
0	2.5 mg daily
-1	2.5 mg every other day

If a toxicity requiring dose reduction is experienced, appropriate measures will be taken as described below (**6.3.1**), and when therapy with the study drug resumes it will be considered the next day of the patient's current cycle. For example, if drug is held prior to the daily dose on day 8 for a toxicity, and the toxicity resolves to allow lenalidomide resumption after 7 days, it would then be considered day 8 of the current cycle.

6.3.1 Hematologic Toxicity

- In the instance of Grade ≥ 3 lenalidomide-related hematologic toxicity on day 1 of a cycle, delay lenalidomide therapy and monitor CBC at least weekly. If toxicity resolves to Grade ≤1 within 2 weeks, then resume lenalidomide at the next lower dose level.

- If Grade ≥ 3 lenalidomide-related hematologic toxicity occurs during a cycle, delay lenalidomide therapy and monitor CBC at least weekly. If toxicity resolves to Grade ≤1 within 2 weeks, then resume lenalidomide at the next lower dose level.

- If treatment is delayed for more than 2 weeks, discontinue protocol therapy.

- WBC colony stimulating factors may not be used to avoid dose reductions but can be used in the treatment of febrile neutropenia as outlined in **6.3.2** below.

- Because of the potential to increase the risk for venous thromboembolic disease, the use of erythropoetic stimulating agents (ESAs) will not be permitted.

- Because a decrease in absolute lymphocyte count (and thus WBC count) is an expected therapeutic outcome of treatment with Lenalidomide, no dose modification is required for the AEs of White Blood Cell Decreased or Lymphocyte Count Decreased.

6.3.2 Febrile Neutropenia

- In the event of febrile neutropenia occurring at any time during a cycle, hold lenalidomide therapy and administer G-CSF until recovery (ANC ≥1500/μL + absence of fever). If the patient recovers within 2 weeks, then resume lenalidomide at the next lower dose level.

- If treatment is delayed for more than 2 weeks, discontinue protocol therapy

6.3.3 **Allergic Reaction**

- Patients experiencing an IgE-mediated allergic reaction (including anaphylaxis, hives, or asthma) attributable to lenalidomide should discontinue treatment immediately and be removed from further protocol therapy.

- In the instance of any other Grade 2 allergic reaction attributable to lenalidomide, hold lenalidomide therapy and monitor toxicity at least weekly. If toxicity resolves to Grade ≤ 1 within 2 weeks, then resume lenalidomide at the next lower dose level.

- In the instance of any Grade ≥ 3 allergic reaction to lenalidomide, remove patient from protocol therapy.

- For any Grade ≥ 3 allergic reaction to Prevnar 13 vaccine, further vaccination must be discontinued. Further treatment with lenalidomide, however, can be continued.

6.3.4 **Dermatologic and Skin Toxicity**

- For any grade bullous, hemorrhagic, or desquamating rash (i.e. TEN), remove patient from protocol therapy.

- For any grade erythema multiforme, remove patient from protocol therapy.

- For other Grade ≥ 3 non-desquamating rash, hold lenalidomide therapy and monitor toxicity at least weekly. If toxicity resolves to Grade ≤ 1 within 2 weeks, then resume lenalidomide at the next lower dose level.

6.3.5 **Autoimmune Hemolytic Anemia or Thrombocytopenic Purpura**

Lenalidomide will be discontinued in patients developing autoimmune hemolytic anemia or autoimmune thrombocytopenia.

6.3.6 **Cardiac Toxicity**

- For lenalidomide-related grade 2 toxicity, hold lenalidomide and follow at least weekly. If toxicity resolves to Grade ≤ 1 within 2 weeks, then resume lenalidomide at the next lower dose level.

- For lenalidomide-related Grade ≥ 3 toxicity, discontinue lenalidomide.

6.3.7 **Venous Thromboembolic Disease**

For any grade deep venous thrombosis, arterial thrombosis, or embolism, discontinue lenalidomide.

6.3.8 **Tumor Flare**

- Swelling, erythema, and tenderness of lymph nodes (especially pathologically involved lymph nodes) are expected effects of treatment with lenalidomide. First line treatment is analgesics (e.g. NSAIDs, acetaminophen, oral narcotics) or corticosteroid therapy at the discretion of the treating physician. Suggested corticosteroid dosing is detailed in **5.2.1** above.

- Symptomatic tumor flare alone will not require that lenalidomide be held unless:
  - Symptomatic tumor flare persists beyond 3 days of corticosteroid treatment
  - Treating physician believes it is in the patient's best interest.

- If lenalidomide is held, therapy should be resumed when tumor flare resolves, or at the principal investigator's discretion.

6.3.9 **Tumor Lysis Syndrome (NCI CTCAE Grade > 2)**

- Hold (interrupt) lenalidomide dose.

- First episode: When attributable electrolyte abnormalities resolve to Grade ≤ 1, restart lenalidomide at the current dose with appropriate TLS prophylaxis. .

- Subsequent episodes at the same dose level: When attributable electrolyte abnormalities resolve to Grade≤ 1, restart lenalidomide at the next lowest dose level with appropriate TLS prophylaxis.

- Subjects should be closely monitored for signs of TLS after resuming treatment. To monitor for TLS, serum chemistry and uric acid tests should be performed on Day 3 or Day 4 following re-initiation of lenalidomide and at least every week following re-initiation of lenalidomide for 4 consecutive weeks.

6.3.10 **Infection**

It is imperative that accurate reporting of infectious events occur not only as a secondary endpoint of the study, but also so prophylactic therapies (if needed) can be included for future patients enrolled. Infectious toxicity (particularly Grade ≥2 severity) needs to be recorded and graded in a standard fashion both during treatment and at least every three months following completion of protocol therapy for patients remaining on study. The following information related to all infections must be documented: site of infection (lungs, sinus, skin, blood, urine, fever of unknown origin, etc.), causative agent (type of bacteria, fungus, virus, etc.) if any identified, specific therapeutic interventions. All herpes simplex and varicella zoster cases should be reported and noted as infectious (not skin) toxicities.

- Because infections are an expected complication of CLL, infections occurring in the absence of hematologic toxicity (i.e those not meeting criteria for neutropenic fever) will not require dose reductions.

- For Grade ≥ 3 infection, hold lenalidomide and administer medically appropriate therapy. If toxicity resolves to Grade ≤ 2 within 2 weeks, then resume lenalidomide at the same dose level.

- Lenalidomide therapy can continue during an episode of Grade ≤ 2 infection, so long as infection is adequately controlled.

6.3.11 Abnormal Menstruation or Pregnancy Test

If a female study patient misses a period, or for abnormal menstrual bleeding or abnormal pregnancy test, obtain a serum pregnancy test. Hold lenalidomide therapy until pregnancy is excluded. Discontinue protocol therapy if pregnancy test is positive. See **Section 7.7** for further information regarding management and reporting requirements pertaining to pregnancy occurring during lenalidomide treatment.

6.3.12 Other Non-Hematologic Toxicity

- In the instance of Grade ≥ 2 lenalidomide-related non-hematologic toxicity on day 1 of a cycle, delay lenalidomide therapy and monitor at least weekly. If toxicity resolves to Grade ≤ 1 within 2 weeks, then resume lenalidomide at the next lower dose level.

- If Grade ≥ 2 lenalidomide-related non-hematologic toxicity occurs during a cycle, delay lenalidomide therapy and monitor at least weekly. If toxicity resolves to Grade ≤ 1 within 2 weeks, then resume lenalidomide at the next lower dose level.

- If treatment is delayed for more than 2 weeks, discontinue protocol therapy

6.4 Intrasubject Escalation

As described previously in **5.1.1**, the dose of lenalidomide may be increased to 5 mg/day beginning as early as the second treatment cycle if all of the following criteria are met:

- No clinically significant Grade 3 or greater non-hematologic toxicities attributable to lenalidomide during the preceding cycle.
- Any lenalidomide-associated hematologic toxicity has resolved to Grade ≤ 1 severity.
- Maintained platelet count >50K at all times during the previous cycle.
- Maintained ANC >1K at all times during the preceding cycle.
- Any other drug-related adverse events have resolved to Grade ≤ 1 severity.

Patients not meeting criteria for dose escalation upon beginning the second cycle of

lenalidomide can be re-evaluated for dose escalation at the start of subsequent cycles, at which time the same criteria will apply. Dose escalation beyond 5 mg/day will not be permitted so as to limit the risk in this patient population who would not otherwise be receiving therapy.

If the lenalidomide dose has been reduced for toxicity, dose re-escalation is permitted if the patient has tolerated the reduced dose for greater than one cycle. The patient will then be re-evaluated for dose escalation at the beginning of each subsequent cycle of therapy according to the parameters detailed above. If the patient subsequently develops toxicity requiring dose reduction, no further attempts at dose escalation will be permitted.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (**07.1.1**) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited (via CTEP-AERS) reporting **in addition** to routine reporting.

7.1 CAEPR for Lenalidomide

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

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 4081 patients.* Below is the CAEPR for Lenalidomide (CC-5013).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.8, June 27, 2019[1]

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Blood and lymphatic system disorders - Other (pancytopenia)		
	Febrile neutropenia		
	Hemolysis		
CARDIAC DISORDERS			
		Atrial fibrillation	
		Heart failure	
		Myocardial infarction[2]	
EAR AND LABYRINTH DISORDERS			
	Vertigo		
ENDOCRINE DISORDERS			
		Hyperthyroidism	
	Hypothyroidism		***Hypothyroidism (Gr 3)***
EYE DISORDERS			
	Blurred vision		
	Cataract		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
Constipation			***Constipation (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		
	Dyspepsia		
	Nausea		***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema limbs		***Edema limbs (Gr 3)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 3)***
	Generalized edema		
	Non-cardiac chest pain		
	Pain		
HEPATOBILIARY DISORDERS			
		Hepatic failure	
		Hepatobiliary disorders - Other (cholestasis)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
		Anaphylaxis	
		Immune system disorders - Other (angioedema)	
		Immune system disorders - Other (graft vs. host disease)[3]	
INFECTIONS AND INFESTATIONS			
	Infection[4]		***Infection[4] (Gr 3)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Bruising		
	Fall		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		
	Blood bilirubin increased		
	GGT increased		
	Investigations - Other (C-Reactive protein increased)		
		Lipase increased	
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		
	Hyperglycemia		
	Hyperuricemia		
	Hypocalcemia		
	Hypokalemia		
	Hypomagnesemia		
	Hyponatremia		
	Hypophosphatemia		
	Iron overload		
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
	Bone pain		
	Generalized muscle weakness		
	Muscle cramp		***Muscle cramp (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		
		Rhabdomyolysis[5]	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy[6]	
		Myelodysplastic syndrome[6]	

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor flare)[7]	
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (second primary malignancies)	
		Treatment related secondary malignancy[6]	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Depressed level of consciousness		
	Dysesthesia		
	Dysgeusia		
	Headache		
	Paresthesia		
	Peripheral motor neuropathy		
	Peripheral sensory neuropathy		
		Stroke[2]	
	Syncope		
	Tremor		
PSYCHIATRIC DISORDERS			
	Depression		
	Insomnia		***Insomnia (Gr 2)***
	Psychiatric disorders - Other (mood altered)		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Epistaxis		
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
		Erythema multiforme	
	Hyperhidrosis		***Hyperhidrosis (Gr 2)***
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
		Skin and subcutaneous tissue disorders - Other (drug reaction with eosinophilia and systemic symptoms [DRESS])	
	Skin and subcutaneous tissue disorders - Other (pyoderma gangrenosum)		
		Stevens-Johnson syndrome	

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Toxic epidermal necrolysis	
SURGICAL AND MEDICAL PROCEDURES			
		Surgical and medical procedures - Other (impaired stem cell mobilization)[8]	
VASCULAR DISORDERS			
	Hematoma		
	Hypertension		
	Hypotension		
	Peripheral ischemia		
	Thromboembolic event[9]		***Thromboembolic event[9] (Gr 3)***
	Vasculitis		

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

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

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

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

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

[6]There has been an increased frequency of secondary malignancies (SPM) including ALL, AML, and MDS, and certain other types of cancers of the skin and other organs in multiple myeloma (MM) patients being treated with melphalan, prednisone, and lenalidomide post bone marrow transplant. The use of lenalidomide in cancers other than MM, shows that invasive SPMs occurred in a small number of patients. Patients treated with lenalidomide should be closely followed for the occurance of SPMs.

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

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

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

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

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

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

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

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

NOTE: In a trial of first line treatment of patients with chronic lymphocytic leukemia (CLL), single agent lenalidomide (CC-5013) increased the risk of death as compared to control arm (chlorambucil).

NOTE: In two randomized trials of patients with multiple myeloma (MM), the addition of MK-3475 (pembrolizumab) to a thalidomide analog plus dexamethasone, resulted in increased mortality. Treatment of patients with MM with a PD-1 or PD-L1 blocking antibody, such as MK-3475 (pembrolizumab), in combination with a thalidomide analog, such as lenalidomide, is not recommended outside of controlled clinical trials.

NOTE: In a clinical trial in patients with Mantle cell lymphoma (MCL), there was an increase in early deaths (within 20 weeks); 12.9% in the lenalidomide (CC-5013) arm vs. 7.1% in the control arm.

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (monocytosis); Disseminated intravascular coagulation; Eosinophilia
CARDIAC DISORDERS - Atrial flutter; Atrioventricular block first degree; Cardiac arrest; Cardiac disorders - Other (cardiovascular edema); Cardiac disorders - Other (ECG abnormalities); Chest pain - cardiac; Left ventricular systolic dysfunction; Palpitations; Pericarditis; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
ENDOCRINE DISORDERS - Cushingoid
EYE DISORDERS - Dry eye; Flashing lights; Retinopathy
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal mucositis; Ascites; Colonic perforation; Dysphagia; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (Crohn's disease aggravated); Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (pale feces); Gastrointestinal hemorrhage[10]; Gastrointestinal obstruction[11]; Ileus; Mucositis oral; Pancreatitis; Rectal mucositis; Small intestinal mucositis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Malaise; Multi-organ failure
HEPATOBILIARY DISORDERS - Cholecystitis
INFECTIONS AND INFESTATIONS - Conjunctivitis; Infections and infestations - Other (opportunistic infection associated with >=Grade 2 Lymphopenia); Myelitis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture; Hip fracture; Vascular access complication

INVESTIGATIONS - Activated partial thromboplastin time prolonged; Cholesterol high; Creatinine increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (hemochromatosis)
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypoglycemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Chest wall pain; Joint effusion; Muscle weakness lower limb; Neck pain; Osteonecrosis of jaw[12]
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Dysphasia; Edema cerebral; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Leukoencephalopathy; Memory impairment; Nervous system disorders - Other (hyporeflexia); Spinal cord compression; Seizure; Somnolence; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Psychosis
RENAL AND URINARY DISORDERS - Urinary frequency; Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (hypogonadism); Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Atelectasis; Bronchopulmonary hemorrhage; Hypoxia; Laryngeal mucositis; Pharyngeal mucositis; Pleural effusion; Pulmonary hypertension; Respiratory failure; Tracheal mucositis; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Nail loss; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome); Urticaria
VASCULAR DISORDERS - Hot flashes; Phlebitis; Vascular disorders - Other (hemorrhage NOS)

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

7.1.1 Adverse event list for PCV13

- Administration site conditions: injection site dermatitis, injection site urticaria, injection site pruritus, redness, inflammation or skin discoloration, mass, or local hypersensitivity reactions

- Blood and lymphatic system disorders: lymphadenopathy localized to the region of the injection site

- Immune system disorders: hypersensitivity reaction including fevers, face edema, dyspnea, generalized urticaria, bronchospasm; anaphylactic/anaphylactoid reaction including shock

- Skin and subcutaneous tissue disorders: angioneurotic edema, erythema multiforme

- Respiratory: apnea

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade**: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only. 'Expected' AEs (the ASAEL) are ***bold and italicized*** in the CAEPR (**07.1.1**).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

Expedited AE reporting for this study must use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These requirements are briefly outlined in the table below (**7.3.1**).

A 24-hour notification is to be made to CTEP by telephone at 301-897-7497, only when internet connectivity is disrupted. Once internet connectivity is restored, an AE report submitted by phone in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.1 **Expedited reporting guidelines** – CTEP-AERS Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Last Dose of the Investigational Agent on Phase 2 and 3 Trials

Phase 2 and 3 Trials									
	Grade 1	**Grade 2**	**Grade 2**	**Grade 3**		**Grade 3**		**Grades 4 & 5[2]**	**Grades 4 & 5[2]**
	Unexpected and Expected	**Unexpected**	**Expected**	**Unexpected with Hospitalization**	**Unexpected without Hospitalization**	**Expected with Hospitalization**	**Expected without Hospitalization**	**Unexpected**	**Expected**
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**
CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events
- Pregnancy of a female subject or the female partner of a male subject occurring while the subject is on lenalidomide or within 4 weeks after the subject's last dose of lenalidomide are considered expedited reportable events. If the subject is on lenalidomide, it is to be discontinued immediately and the subject is to be instructed to return any unused portion of lenalidomide to the Investigator. The pregnancy must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge of the pregnancy.

  The Investigator will follow the pregnant female until completion of the pregnancy, and must report via CTEP-AERS the outcome as specified below. The Investigator will provide this information as a follow-up to the initial SAE.

  If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting the event via CTEP-AERS within 24 hours of the Investigator's knowledge of the event).

  Any suspected fetal exposure to lenalidomide must be reported via CTEP-AERS within 24 hours of being made aware of the event. The pregnant female should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

  All neonatal deaths that occur within 30 days of birth should be expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC. In addition, any infant death after 30 days that the Investigator suspects is related to the in utero exposure to lenalidomide should also be reported.

  In the case of a live "normal" birth, the outcome should be reported via CTEP-AERS as soon as the information is available.

CTEP-AERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

December 15, 2004

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

- All new or secondary malignancies including solid tumors (this includes non-melanoma skin malignancies), hematologic malignancies, Myelodysplastic Syndrome (MDS)/Acute Myelogenous Leukemia (AML) and *in situ* tumors that occur during study treatment and/or during protocol specified follow-up periods must be reported via CTEP-AERS regardless of attribution.

- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

7.3.2 Protocol-specific expedited adverse event reporting exclusions

None

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must also be reported in routine study data submissions.**

7.5 OSU Institutional Safety Monitoring and Reporting Requirements

7.5.1 OSU Comprehensive Cancer Center Data and Safety Monitoring Plan

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data and patient safety at their regular Disease Group meetings (at least monthly) and the discussion will be documented in the minutes. The PI of the trial will review toxicities and responses of the trial where applicable at these disease center meetings and determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the PI and compared to what is known about the agent/device from other sources; including published literature, scientific meetings and discussions with the sponsors, to determine if the trial should be terminated before completion. Serious adverse events and responses will also be reviewed by the OSUCCC Data and Safety Monitoring Committee (DSMC). The PI will also submit a progress report biannually for Phase II and quarterly for Phase I) that will be reviewed by the committee per the DSMC plan. All reportable Serious Adverse Events (SAE) will also be reported to the IRB of record as per the policies of the IRB.

7.5.2 OSU Cancer IRB reporting requirements

7.5.2.1 Reporting procedures

All adverse events will be noted in the study forms. Any unexpected adverse events or adverse events Grade ≥2 will be reported immediately to the principal investigator. All adverse events will be reported on Form FDA 3500 A (i.e. Med Watch Form).

7.5.2.2 Reporting to the OSU Cancer IRB

Reporting of adverse events to the OSU Cancer IRB will be performed in accordance with FDA regulations. Details are described below. The OSU Event Reporting Form should be used to report untoward events that may affect participants in research approved by an OSU IRB. Events requiring prompt reporting include adverse events, protocol deviations, and other unforeseen problems or findings that suggest participants, research staff, or others are placed at greater risk by the research than previously expected. These events, classified broadly as unanticipated problems involving risks to the subjects or others, must be reported promptly to the IRB. Unanticipated problems can occur in any type of research and may involve physical, psychological, social, legal, or economic harms.

7.5.2.3 Events requiring prompt reporting

Events that may represent unanticipated problems involving risks to subjects or others and therefore require prompt reporting include the following:

- Adverse events or injuries that are serious, unexpected, and related
- Events requiring prompt reporting according to the protocol or sponsor

- Data and Safety Monitoring Board (DSMB) reports, interim analyses, or other oversight committee/monitoring reports altering the risk/benefit profile
- These events should be promptly reported (see below), regardless of whether they occur during the study, after study completion, or to a participant who has withdrawn from or completed study participation

7.5.2.4 Time frame for reporting

All internal events (those occurring in research at OSU or at a site under an OSU IRB's jurisdiction) as described above should be reported within 10 days of the Investigator's or research staff member's learning of the event. Events resulting in temporary or permanent interruption of study activities by the Investigator or sponsor to avoid potential harm to participants should be reported immediately (within 48 hours) whenever possible.

7.5.2.5 Additional information

Related adverse events and other problems involving risk that do not meet the reporting requirements and do not represent potential unanticipated problems involving risks to subjects or others should be reported in summary form at the time of continuing IRB review. However, any problem or adverse event that an investigator believes could influence the safe conduct of the research should be reported promptly.

7.6 Celgene Drug Safety Contact Information

Celgene Corporation
Worldwide Drug Safety Surveillance (WWDSS)
86 Morris Avenue
Summit, N.J. 07901

Toll Free:	(800)-640-7854
Phone:	(908) 673-9667
Fax:	(908) 673-9115
e-mail:	drugsafety@celgene.com

7.7 Pregnancy

- Pregnancy Reporting:

Females of Childbearing Potential:

- Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or the partner of a male subject occurring while the subject is on lenalidomide or within 28 days after the subject's last dose, are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected

pregnancy, or positive pregnancy test must be reported via CTEP-AERS as a **grade 4** event under: SOC pregnancy, puerperium and perinatal conditions; adverse event: **pregnancy, puerperium and perinatal conditions-other, fetal exposure.**

- *The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.*

- The Investigator will follow the female subject until completion of the pregnancy, and must make an amendment to the initial pregnancy report immediately regarding the outcome of the pregnancy and neonatal status (either normal or abnormal outcome).
- If the outcome of the pregnancy was abnormal (including spontaneous or therapeutic abortion, fetal demise and congenital abnormalities), the Investigator should report the abnormal outcome as an amendment to the initial pregnancy report as soon as the as the Investigator has knowledge of the outcome.
- All neonatal deaths and neonatal complications that occur within 28 days of birth should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC., as an amendment to the initial pregnancy report. In addition, any infant death after 28 days that the Investigator suspects is related to the *in utero* exposure to the lenalidomide should also be reported as an amendment within 24 hours of the Investigator's knowledge of the event.

Male Subjects

- If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

NOTE:
Before lenalidomide is dispensed, patients must have 1) a negative pregnancy test (if applicable) and 2) be counseled by a trained counselor. Pharmacists may be trained counselors (see Lenalidomide Counselor Program Site Counselor Identification Form in the protocol). The counseling requirements for investigational-use lenalidomide are separate from the RevAssist program. Only a 28-day supply may be dispensed to a patient at one time.

8.1 Lenalidomide (Revlimid, CC-5013 NSC#703813)

Lenalidomide, 3-(4'aminoisoindoline-1'-one)-1-piperidine-2, 6-dione, is an immunomodulatory agent. The Chemical Abstract Service (CAS) registry number for lenalidomide is 191732-72-6. Lenalidomide is also known by the earlier clinical code names CC-5013 and CDC-501. Lenalidomide has an empirical formula of $C_{13}H_{13}N_3O_3$ and a molecular weight of 259.25. It is an off-white to pale-yellow solid.

8.1.1 **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.

8.1.2 **How Supplied:** Celgene supplies and CTEP, NCI, DCTD distributes lenalidomide 2.5 mg (size 4) and 5 mg (size 2) hard gelatin capsules in tamper-evident, child-resistant, opaque, high density polyethylene (HDPE) bottles with HDPE caps. Bottles contain 100 capsules per container.

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

8.1.3 **Storage:** The capsules should be stored at room temperature (15-30°C) away from moisture and direct sunlight. At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access.

8.1.4 **Stability:** Refer to the package labeling for expiration date. Lenalidomide stability is adequate for at least 28 days after transferring to a pharmacy vial.

8.1.5 **Route of Administration:** Take lenalidomide by mouth with or without food. Do not crush, chew or open capsules.

8.1.6 **Dispensing:** Only a 28-day supply may be dispensed at one time. Sites may not mail lenalidomide to patients.

Patient Care Implications and Counseling: <u>Risks Associated with Pregnancy</u>
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

Definition of female of childbearing potential (FCBP)
This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Before starting study drug:
Female Subjects:

- FCBP must have two negative pregnancy tests (minimum sensitivity of 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The subject may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.

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.

All Subjects:

- Only enough lenalidomide for one cycle of therapy may be dispensed with each cycle of therapy.

- 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.

Counseling

- In investigational studies where lenalidomide is supplied by the NCI, patients will be counseled by a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). Two healthcare professionals at each site will be trained by Celgene in requirements specific to counseling of subjects (investigators cannot counsel patients as part of this requirement). Refer to specific protocol sections for more information about training requirements.

- Once trained, these healthcare staff will counsel subjects prior to medication being dispensed to ensure that the subject has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the subject understands the risks associated with lenalidomide. This step

will be documented with a completed Lenalidomide Education and Counseling Guidance Document (Appendix D) and no drug will be dispensed until this step occurs. Counseling includes verification with the female patient that required pregnancy testing was performed and results were negative. A Lenalidomide Information Sheet (Appendix E) will be supplied with each medication dispense.

8.1.7 **Females of childbearing potential should not handle the clinical dosage forms unless they are wearing gloves.**

8.1.8 **Drug dispensing requirements**

In investigational studies, lenalidomide will be dispensed by a healthcare professional. The healthcare professional will counsel subjects prior to medication being dispensed to ensure that the subject had complied with all requirements including use of birth control and pregnancy testing. This step will be documented with a completed Education and Counseling Guidance Document (**Appendix D**), and no drug will be dispensed until this step occurs. Counseling includes verification with the patient that required pregnancy testing was preformed and results were negative. A Lenalidomide Information Sheet (**Appendix E**) will be supplied with each medication dispense.

8.1.9 **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.

8.1.10 **Eligibility and screening**
The Investigator is responsible for keeping a record of all subjects who sign an Informed Consent Form for entry into the study. All subjects will be screened for eligibility. Screening procedures are outlined in Section 2, Schedule of Study Assessments and unless otherwise specified, must take place within 14 days prior to initiation of therapy. Screening pregnancy tests (sensitivity of at least 25 mIU/mL) for women of child-bearing potential must occur 10 to 14 days prior and again ≤ 24 hours from initiation of therapy.

8.1.11 **Agent ordering**
NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP,

DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.1.12 **Agent accountability**

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.13 **Investigator Brochure Availability**

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.1.14 **Adverse events with lenalidomide**

The most frequently reported adverse events reported during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, UTI, Upper respiratory infection, cellulitis, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures.

Complete and updated adverse events are available in the Investigational Drug Brochure and the IND Safety Letters.

8.1.15 **Useful Links and Contacts**

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

8.2 13-valent Protein-Conjugated Pneumococcal Vaccine (Prevnar 13, PCV13)

8.2.1 Supplier(s)

PCV13 is manufactured by Wyeth Pharmaceuticals and is commercially available.

8.2.2 Description

PCV13 is a sterile suspension of saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, individually linked to non-toxic diphtheria CRM_{197} protein. Each serotype is grown in soy peptone broth. The individual polysaccharides are purified through centrifugation, precipitation, ultrafiltration, and column chromatography. The polysaccharides are chemically activated to make saccharides, which are directly conjugated by reductive amination to the protein carrier CRM_{197}, to form the glycoconjugate. CRM_{197} is a nontoxic variant of diphtheria toxin isolated from cultures of *Corynebacterium diphtheriae* strain C7 (β197) grown in a casamino acids and yeast extract-based medium. CRM_{197} is purified through ultrafiltration, ammonium sulfate precipitation, and ion-exchange chromatography. The individual glycoconjugates are purified by ultrafiltration and column chromatography and analyzed for saccharide to protein ratios, molecular size, free saccharide, and free protein.

The individual glycoconjugates are compounded to formulate PCV13. Potency of the formulated vaccine is determined by quantification of each of the saccharide antigens and by the saccharide to protein ratios in the individual glycoconjugates. Each 0.5 mL dose of the vaccine is formulated to contain approximately 2.2 µg of each of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F saccharides, 4.4 µg of 6B saccharides, 34 µg CRM_{197} carrier protein, 100 µg polysorbate 80, 295 µg succinate buffer, and 125 µg aluminum as aluminum phosphate adjuvant.

8.2.3 **Packaging**

PCV13 is supplied as 0.5 mL single-dose pre-filled syringes for intramuscular injection, with 10 doses per package (NDC 0005-1971-02). The vial stopper and the tip cap and rubber plunger of the pre-filled syringe do not contain latex.

8.2.4 **Storage and stability**

The product is a suspension containing an adjuvant and should be vigorously shaken prior to use. Unopened containers should be stored at 2-8ºC and unused portions discarded. PCV13 should not be frozen and should be discarded if frozen.

8.2.5 **Contraindications**

Known hypersensitivity to PCV7, PCV13, or to any of the components of the conjugate vaccine.

8.2.6 **Adverse effects**

Local reactions include erythema, induration, and tenderness. Other adverse reactions include fever, irritability, drowsiness, restless sleep, decreased appetite, vomiting, diarrhea, urticaria-like rash, lymphadenopathy localized to the region of the injection site, hypersensitivity reactions including face edema, dyspnea, bronchospasm, and anaphylactoid reactions, angioneurotic edema, and erythema multiforme.

8.2.7 **Administration guidelines**

Since this product is a suspension containing an adjuvant, it should be vigorously shaken immediately prior to use to obtain a homogenous, white suspension in the vaccine container. If it cannot be resuspended, the product should not be used. It should not be used if particulate matter or discoloration is found on visual inspection. It should not be mixed with any other vaccines/products in the same syringe. A 0.5 ml dose is given intramuscularly in the deltoid muscle of the upper arm. It should not be administered intravenously, intradermally, or subcutaneously. Patients will receive 2 doses of PCV13 administered 8 weeks apart. In Arm A (Concurrent), vaccine will be administered on Day 1 of cycles 3 and 5. In Arm B (Sequential), patients will be vaccinated on Day 1 of cycles 1 and 3.

9. CORRELATIVE/SPECIAL STUDIES

The rich biology associated with lenalidomide administration in CLL offers the opportunity to perform detailed correlative studies. These studies are outlined below. Outside of studies outlined in **Section 9.1** which are related to the study primary endpoint, collection times or samples may be deleted or altered (with no excess draws or collection from this baseline) if deemed to be impractical. If this occurs, an amendment will be

submitted related to this but accrual to the study will not be interrupted while this is under review.

Study end points have been met, therefore all research sample collection will cease upon approval of protocol version 24. Given the low number of patients continuing to receive treatment additional research samples will not be of scientific interest.

9.1 Anti-pneumococcal Antibody Levels

Specimens collected for anti-pneumococcal antibody levels will be processed in the OSU CLL Experimental Therapeutics Laboratory prior to shipment to a contract laboratory (Mayo Medical Laboratories, Rochester, MN) where type-specific antibody levels will be measured.

9.1.1 Collection of Specimens

In Arm A (Concurrent), serum antibody levels specific to each of 7 pneumococcal antigens contained in the PCV13 vaccine will be assessed at Cycle 1 Day 1 (baseline), 2 months following initiation of lenalidomide therapy (Cycle 3 Day 1), 2 months after initial vaccination (Cycle 5 Day 1) and 1 month after second vaccination (Cycle 6 Day 1) and every 6 months thereafter for patients remaining in follow-up. For those in Arm B, titers will be assessed at Cycle 1 Day 1(baseline), 2 months after initial vaccination (Cycle 3 Day 1), 1 month after second vaccination (Cycle 4 Day 1), and every 6 months thereafter.

9.1.2 Handling of Specimens

One 5 mL of blood will be collected in plain red top tubes, mixed 5 times and allowed to clot 30 minutes. Samples will then be spun at 1,200 x g for 10 minutes to isolate serum. Serum in three separate vials will be stored in -80°C freezer. Each sample will be labeled with the protocol number, patient number, reference time point relative to the protocol, date and time the sample was obtained, and date and time the sample was placed in the -80°C freezer until further analysis. 0.5 mL of refrigerated serum sent to the Mayo Medical Laboratories, Rochester, MN, as outlined in the laboratory manual. Additional serum remaining may be used for other tests related to understanding mechanism of action/response of lenalidomide or biology of CLL.

9.1.3 Sample and Data Analysis.

IgG antibodies to *Streptococcus pneumoniae* serotypes are measured by microsphere photometry. Purified pneumococcal polysaccharides coupled covalently to polystyrene microspheres bind IgG antibodies in patients' sera during the first incubation. After incubation, the microspheres are washed and incubated with phycoerythrin conjugated antihuman IgG antibody. The concentration of IgG antibodies to each polysaccharide is determined by comparison to dose-response curves calculated from serial dilutions of a serum pool from immunized adults with known concentrations of antibodies to each polysaccharide (secondary standard). The secondary standard is traceable to a standard reference preparation (FDA 89-SF) that contains known concentrations of IgG antibodies to 23 different *Streptococcus pneumoniae* serotypes. Dose-response curves prepared from

serial dilutions of the secondary standard parallel the dose-response curves of the primary reference preparation for all polysaccharides. (Jacob GL, Homburger HA: Simultaneous Quantitative Measurement of IgG Antibodies to *Streptococcus Pneumoniae* Serotypes by Microsphere Photometry. Poster Presentation; AAAAI 60th Annual Meeting, March 19-23, 2004. San Francisco, CA. J Allergy Clin Immunol, Vol. 113, No 2, [Abstract 1049, pS288] 2004; Plikaytis BD, Holder PF, Pais LB, et al: Determination of parallelism and nonparallelism in bioassay dilution curves. J Clin Microbiol 1994;2441-2447; Plikaytis BD, Goldblatt D, Frasch CE, et al: An analytical model applied to a multicenter pneumococcal enzyme-linked immunosorbent assay study. J Clin Microbiol 2000;38:2043-2050)

9.2 Pharmacodynamic Studies: Immunoglobulins and Anti-Tumor Antibodies

Pharmacodynamic studies concerning serum immunoglobulin and anti-tumor antibody levels will be performed at the OSU CLL Experimental Therapeutics Laboratory in collaboration with Dr. Christoph Rader of the NCI intramural research program.

9.2.1 Collection of Specimens

For patients treated on Arm A (patients who receive lenalidomide beginning Cycle 1, collection of blood samples will occur on Days 1 (baseline), and Day 1 of 3, 5, 7 and every 6 months subsequently. For patients treated on Arm B (patients who receive lenalidomide beginning with Cycle 4), samples will be collected at Day 1 of Cycle 1 (baseline), Day 1 of Cycles 4, 5, 7, and every 6 months subsequently.

9.2.2 Handling of Specimens

Two x 5 mL of blood will be collected in plain Red top tubes, mixed 5 times and allowed to clot 30 minutes. Samples will then be spun at 1,200 x g for 10 minutes to isolate serum. Serum in three separate vials will be stored in -80°C freezer. Each sample will be labeled with the protocol number, patient number, reference time point relative to the protocol, date and time the sample was obtained, and date and time the sample was placed in the -80°C freezer until further analysis.

9.2.3 Sample and Data Analysis.

The samples will be analyzed in batches to assess quantitative total and vaccine specific immunoglobulin levels as outlined below. Levels of immunoglobulin levels over time will be correlated with the ability of lenalidomide to up-regulate CD154 on CLL cells and pharmacokinetics of lenalidomide.

- **Anti-IgG1, IgG2, IgG3, IgG4, IgM, and IgA** will be determined from serum at baseline and every 6 months thereafter on select patients for whom reversal of hypogammaglobulinemia occurs.
- **Anti-ROR1 antibody levels**: Tumor-specific anti-ROR1 antibody titers will be determined by ELISA in serum at baseline and every 6 months thereafter. Development of ROR1 antibodies will be correlated with the ability to up-regulate CD154 on CLL cells and pharmacokinetics of lenalidomide
- **Anti-CLL tumor antibody levels**: Tumor-specific antibody titers will be determined

by an adapted flow cytometry assay from serum at baseline and every 6 months thereafter. Development of anti-CLL antibodies will be correlated with the ability to up-regulate CD154 on CLL cells and pharmacokinetics of lenalidomide In patients developing such antibodies, normal B-cells derived from these patients will be isolated for identification of relevant target antigens. This will be done in collaboration with Dr. Christoph Radar.

9.3 Lenalidomide Pharmacokinetics

Pharmacokinetic evaluations for lenalidomide will be conducted in collaboration with the Pharmacoanalytical Shared Resource at OSU.

9.3.1 Collection of Specimens.

Arm A: For patients treated on Arm A (patients who will receive lenalidomide during cycles 1 and 2), pharmacokinetic assessments of lenalidomide will occur during days 1 and 2 of cycle 2. Samples will be collected at the following time points: prior to dosing (time 0), 0.5, 1, 2, 3, 4.5, and 6 hours after dose administration on day 1 of cycle 2. An additional sample will be obtained prior to lenalidomide ingestion on day 2 of cycle 2 (i.e. 24 hours after the dose is ingested on day 1).

Arm B: For patients in Arm B (patients who receive lenalidomide beginning in cycle 4) PK sampling will occur during days 1 and 2 of cycle 5. The sampling times will be consistent with those in Arm A and comprise the following time points: prior to dosing (time 0), 0.5, 1, 2, 3, 4.5, and 6 hours after dose administration on day 1 of cycle 5. An additional sample will be obtained prior to lenalidomide ingestion on day 2 of cycle 5 (i.e. 24 hours after the dose is ingested on day 1).

9.3.2 Handling of Specimens.

Four mL of blood will be collected in EDTA (purple top) tubes, placed on ice and immediately centrifuged at 1,200 x g for 10 minutes to isolate plasma. Plasma will be frozen in two separate vials and stored in a -20°C freezer. Each sample will be labeled with the protocol number, patient number, reference time point relative to the protocol, date and time the sample was obtained, and date and time the sample was placed in the -20°C freezer.

9.3.3 Sample and Data Analysis.

The samples will be analyzed in batches to assess plasma drug concentrations, the plasma drug concentration-time profile (AUC), volume of distribution (Vss), clearance (CL), and half-life using liquid chromatographic/mass spectrometry (LC/MS) according to previously described methods.[67] Comparisons of PK data from patients treated on Arm A

vs. Arm B will be made to assess possible PK alterations due to PCV13 administration. Additional comparisons will be made between patients who received dexamethasone treatment on cycles 1 (Arm A) or 5 (Arm B) to identify potential interactions between lenalidomide and dexamethasone due to steroid-induced induction of MDR1 or other lenalidomide clearance mechanisms.

9.4 Pharmacodynamics: Cytokines

9.4.1 **Collection of Samples:** For patients treated on Arm A (patients who receive lenalidomide beginning Cycle 1), collection of blood samples will occur on Days 1 (baseline), 3 and 8 of the Cycle 1 and Day 1 of Cycles 2, 3, 5, 7 and every 6 months subsequently. For patients treated on Arm B (patients who receive lenalidomide beginning with Cycle 4) samples will be collected at Day 1 of Cycle 1 (baseline), Day 1 of Cycles 4, 5, 7 and every 6 months subsequently.

9.4.2 **Handling of Samples:**

Venous whole blood (approximately 10 mL) should be drawn into two 5-mL potassium EDTA (lavender-top) vacutainers. Samples will then be spun at 1,200 x g for 10 minutes to isolate plasma. Plasma in three separate vials will be stored in -80°C freezer. Each sample will be labeled with the protocol number, patient number, reference time point relative to the protocol, date and time the sample was obtained, and date and time the sample was placed in the -80°C freezer until further analysis.

9.4.3 **Sample and Data Analysis:**

The samples will be analyzed in batches to assess cytokine (such as IL-6, TNF-α, VEGF, bFGF) and soluble chemokines will be examined by a multiplex flow cytometry assay or ELISA. Other cytokines, chemokines, or soluble factors may be assessed on residual material not used for these studies. These studies will be done in the CLL experimental Therapeutics Laboratory

9.5 Flow Cytometry B-, T-, and NK-cell subsets and activation status

These studies will be performed at the OSU CLL Experimental Therapeutics Laboratory.

9.5.1 **Collection of Specimens**

For patients treated on Arm A (patients who receive lenalidomide beginning Cycle 1), collection of blood samples will occur on Days 1 (baseline), 3 and 8 of the Cycle 1 and Day 1 of Cycles 3, 5, 7 and every 6 months subsequently. For patients treated on Arm B (patients who receive lenalidomide beginning with Cycle 4) samples will be collected at Day 1 of Cycle 1 (baseline), Day 1, 3, and 8 of Cycle 4, Day 1 of Cycle 5, 7, and every 6 months subsequently.

9.5.2 **Handling of Specimens**

One x 5mL of blood will be collected in sodium heparin containing green top tube (Flow cytometry). Each sample will be labeled with the protocol number, patient number, reference time point relative to the protocol, date and time the sample was obtained. The heparin green top tube will be transported at room temperature to the flow cytometry laboratory.

9.5.3 **Sample and Data Analysis.**

Changes in subsets and activation status of B-, T-,and NK lymphocytes in peripheral blood following lenalidomide therapy will be evaluated using multiparametric flow cytometry immune modulation panel at OSU. Lymphocyte CD4, CD8, T-regulatory, and NK cell subsets will be enumerated and markers of activation status will be characterized for each.

CLL cell activation studies: B-cell activation will be further characterized by upregulation of CD154 as the primary measure (based upon our data), along with CD40, CD80, CD69, and CD86 by flow cytometry. Additionally, we will measure serial changes in IL-21 receptor expression on CLL cells which we recently have shown is up-regulated by lenalidomide. Change in CD154 expression will be correlated with pharmacokinetics, immune, and clinical response.

9.6 Pharmacodynamic Studies: T-cell Function and Epigenetic Changes in CLL Cells

9.6.1 **Collection of Specimens**

For patients treated on Arm A (patients who receive lenalidomide beginning Cycle 1), collection of blood samples will occur on Days 1 (baseline), 3 and 8 of the Cycle 1 and Day 1 of Cycles 2, 3, 5, 7 and every 6 months subsequently. For patients treated on Arm B (patients who receive lenalidomide beginning with Cycle 4) samples will be collected at Day 1 of cycle 1 (baseline), Day 1, 3, and 8 of cycle 4, Day 1 of cycle 5, 6, 7, and every 6 months subsequently.

9.6.2 **Handling of Specimens**

Two x 10mL of blood will be collected in sodium heparin containing green top tube (Flow cytometry). Each sample will be labeled with the protocol number, patient number, reference time point relative to the protocol, date and time the sample was obtained.

9.6.3 **Sample and Data Analysis.**

T-cell Functional activation studies: CRM197 specific T cells numbers and frequency will be evaluated by flow cytometry. CD4 cell production of specific cytokines will be assessed. Other T-cell dependent activation studies toward primary tumor cells will be performed including ELISPOT and T-cell synapse studies as previously reported.[7] These will be done in the CLL experimental Therapeutics Laboratory.

Activation and Epigenetic Changes in CLL Cells: Activation and epigenetic studies will be performed in the OSU CLL Experimental Therapeutics Laboratory. Tumor cells will be isolated from peripheral blood by ficoll density gradient centrifugation using Rosette-Sep reagent (Stem Cell Technologies, Vancouver BC). Cells will be washed and counted, and histones acid-extracted from $5x10^7$ cells as we described previously.[68] Histones will be analyzed by mass spectrometry according to our published procedures [69] Activation studies will be performed using methods previously published by our group.[70] Other studies related to understanding mechanism of action of lenalidomide, CLL biology, or predicting response to lenalidomide may be performed on remaining material.

9.7 Correlative Studies Prioritization

Studies 9.1-9.4 rely upon serum or plasma for their analyses. Adequate sample volume has been requested to perform the studies outlined. Studies 9.5 and 9.6 rely upon adequate tumor and immune cell subsets. Priority will be given to the immune subset analysis by flow cytometry; next activation studies, then T cell function, and epigenetics changes based upon the number of CLL cells available at each sample time point.

10. STUDY CALENDAR

Screening evaluations including history and physical examination and all laboratory studies are to be conducted within 14 days prior to the start of protocol therapy. CT scans of the chest, abdomen and pelvis will be completed within 6 weeks and bone marrow biopsy and aspirate (optional) are to be completed within 12 weeks prior to the start of therapy and should include evaluation for myelodysplasia. Visits Cycle 7+ have a +/- 7 day visit window. Follow-Up visits have a +/- 14 day visit window. Additional required data are summarized in the study calendar.

Schedule of Study Assessments: Arm A (Concurrent)

Procedure	Screening	Cycle 1 & 2				Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7+	End of Therapy[o]	Follow-Up[p]
		W1	W2	W3	W4							
Clinical Assessment												
Informed Consent	X											
Physical Examination[a]	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status[b]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Interval infection history[c]		X	X	X	X	X	X	X	X	X	X	X
Record adverse events		X	X	X	X	X	X	X	X	X	X	
Perform Drug Accountability[d]	X	X	X	X	X	X	X	X	X	X		
Education and Counseling [e]		X				X	X	X	X	X		
Response assessment[n]						X		X		X[n]	X	X
Laboaratory Studies and Procedures												
ECG	X											
Complete blood count[m]	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistries[f]	X	X	X	X	X	X	X	X	X	X		X
Urinalysis	X											
Quantitative serum immunoglobulins	X					X		X		Every 6 mo	X[q]	X
Direct and indirect antiglobulin test	X											
TSH	X										X	
Pregnancy testing[g]	X	X	X	X	X	X	X	X	X	X	X	
Bone marrow biopsy[h]	Optional										X	
Risk stratification studies[i]	X											
CT scans [r]	X											
Anti-pneumococcal antibody titers		X				X		X	X			
Treatment												
Allopurinol[j]		X	X	X	X							
Thromboprophylaxis[k]		X	X	X	X	X	X	X	X	X		
Dispense Lenalidomide[l]		X				X	X	X	X	X		
Lenalidomide		X	X	X	X	X	X	X	X	X		
PCV13 administration						X		X				
Correlative Studies												
Pharmacokinetic Studies[s]		C2 D1,2										
Pharmacodynamic Studies[t]	X	C1 D1,3 C2 D1	C1 D8			X		X				

Schedule of Study Assessments: Arm B (Sequential)

Procedure	Screening	Cycle 1	Cycle 2	Cycle 3	Cycle 4 & 5				Cycle 6	Cycle 7+	End of Therapy[o]	Follow-Up[p]
					W1	W2	W3	W4				
Clinical Assessment												
Informed Consent	X											
Physical Examination[a]	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status[b]	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	
Interval infection history[c]		X	X	X	X	X	X	X	X	X	X	
Record adverse events		X	X	X	X	X	X	X	X	X	X	
Perform Drug Accountability[d]	X				X	X	X	X	X	X	X	
Education and Counseling [e]					X				X	X	X	
Response assessment[n]					C5					X[n]	X	X
Laboaratory Studies and Procedures												
ECG	X											
Complete blood count[m]	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistries[f]	X	X	X	X	X	X	X	X	X	X		X
Urinalysis	X											
Quantitative immunoglobulins	X	X		X	X					Every 6 mo	X[q]	X
Direct and indirect antiglobulin test	X											
TSH	X										X	
Pregnancy testing[g]	X				X[g]	X	X	X	X	X	X	
Bone marrow biopsy[h]	Optional										X	
Risk stratification studies[i]	X											
CT scans[r]	X										X	
Anti-pneumococcal antibody titers		X		X	X							
Treatment												
Allopurinol[j]					X	X	X	X				
Thromboprophylaxis[k]					X	X	X	X	X	X		
Dispense Lenalidomide[l]					X	X	X	X	X	X		
Lenalidomide					X	X	X	X	X	X		
PCV13 administration		X		X								
Correlative Studies												
Pharmacokinetic Studies[s]					C5 D1,2							
Pharmacodynamic Studies[t]	X	X			C4 D1,3 C5 D1	C4 D8			X			

a. Physical examination should include vitals signs, weight, general physical examination (including neurologic examination), measurement of liver and spleen span in centimeters below the costal margin in the anterior axillary line, and bi-dirmensional measurement of cervical, supraclavicular, axillary, and inguinal nodes.
b. See **Appendix A**.
c. See **6.3.10** for required information to be documented for each episode of infection.
d. Patient medication diary is reviewed to assess patient compliance on the first day of each cycle in which lenalidomide is administered.
e. The Lenalidomide Education and Counseling Guidance Document (Appendix D) must be completed and signed by a trained counselor at the participating site prior to each dispensing of lenalidomide treatment. A copy of this document must be maintained in the patient records. The Lenalidomide Information Sheet (Appendix E) will be given to each patient receiving lenalidomide treatment. The patient must read this document prior to starting lenalidomide study treatment and each time they receive a new supply of study drug.
f. Serum chemistries should include: comprehensive metabolic panel, phosphate, uric acid, and LDH.
g. Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to initiation of lenalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on study treatment (including breaks in treatment); 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 study treatment (including breaks in treatment), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix C: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).
h. Unilateral bone marrow biopsy and aspirate will be obtained at end of treatment. In addition to routine pathology, aspirate samples should be studied for, interphase cytogenetics, standard CLL FISH panel, CpG stimulated karyotype, and flow cytometry. If patients decline bone marrow biopsy at end of study , these same studies should be done on peripheral blood. If patients demonstrate anti-ROR1 antibody response, a research bone marrow aspirate may be done every 6 months to isolate normal B-cells for correlative studies.
i. Risk stratification studies will include serum β2-microglobulin in addition to tests performed on the screening bone marrow biopsy specimen: IgV_H mutational analysis (unless already known), interphase cytogenetics, stimulated karyotype and standard CLL FISH panel.
j. Allopurinol should be administered beginning 3 days before first lenalidomide administration and continued through the first cycle of lenalidomide treatment in its entirety. Allopurinol can be continued during subsequent cycles at the treating physician's discretion.
k. Thromboprophylaxis should begin with lenalidomide in patients at high-risk for venous or arterial thromboembolism (see **5.2.3**).
l. Only enough lenalidomide for 28 days or one cycle of study treatment (whichever is shorter) may be provided to the patient each cycle.
m. CBC is checked on D1 and D8 during the first cycle of lenalidomide exposure and during the second cycle and/or any subsequent cycle in which the dose of lenalidomide has been escalated. CBC should be checked weekly during any subsequent cycle in which the dose of lenalidomide has been reduced for hematologic toxicity.
n. Response is assessed clinically (CBC, physical examination) after every 2 cycles of lenalidomide treatment beginning with Cycle 3 (Arm A) or Cycle 5 (Arm B), respectively. For patients meeting clinical criteria for CR for ≥ 2 months, bone marrow biopsy and CT scans should be performed to confirm response.
o. The End of Therapy visit is defined as that occurring after 24 cycles. Patients discontinuing treatment at other times secondary to toxicity, progression, or preference only need the clinical assessment (except informed consent and education and counseling) and a complete blood count. Patients discontinuing for any reason are followed for at least 30 days to ensure resolution of any adverse events; however, these patients will still be followed for outcome until meeting criteria outlined in footnote "p" below.
p. Patients no longer receiving active treatment are followed every 3 months during the first year and every 6 months thereafter until the patient receives a new CLL therapy, withdrawal of consent, or death.
q. Unless completed within the last month.
r. CT scans of the chest, abdomen, and pelvis.

s. For patients treated on **Arm A** (patients who will receive lenalidomide during cycles 1 and 2), pharmacokinetic assessments of lenalidomide will occur during days 1 and 2 of cycle 2. Samples will be collected at the following time points: prior to dosing (time 0), 0.5, 1, 2, 3, 4.5, and 6 hours after dose administration on day 1 of cycle 2. An additional sample will be obtained prior to lenalidomide ingestion on day 2 of cycle 2 (i.e. 24 hours after the dose is ingested on day 1). For patients in **Arm B** (patients who receive lenalidomide beginning in cycle 4) PK sampling will occur during days 1 and 2 of cycle 5. The sampling times will be consistent with those in Arm A and comprise the following time points: prior to dosing (time 0), 0.5, 1, 2, 3, 4.5, and 6 hours after dose administration on day 1 of cycle 5. An additional sample will be obtained prior to lenalidomide ingestion on day 2 of cycle 5 (i.e. 24 hours after the dose is ingested on day 1).

t. Blood for pharmacodynamic studies is obtained on the first day of each cycle indicated unless stated otherwise. Details regarding specimen collection and handling are found in **Sections 9.1-9.6** above.

11. MEASUREMENT OF EFFECT

11.1 Response Criteria.

All patients will be evaluated for response. Response will be characterized according to the 2008 International Workshop on CLL (IWCLL) guidelines for the diagnosis and treatment of CLL[7], which include clinical, hematologic, and bone marrow features as outlined below.

11.2 Complete Response

Requires all of the following for a period of at least two months from completion of therapy:

- Absence of adenopathy on physical exam.
- No hepatomegaly or splenomegaly on physical exam.
- Absence of constitutional symptoms.
- Normal CBC as exhibited by polymorphonuclear leukocytes ≥ 1500/μL, platelets > 100,000/μL, hemoglobin > 11.0 g/dL (untransfused), and lymphocyte count < 5,000/ μL.
- Bone marrow aspirate and biopsy must be normocellular for age with < 30% of nucleated cells being lymphocytes. Lymphoid nodules must be absent. If the marrow is hypocellular, a repeat determination should be performed in one month.
- Patients who otherwise fulfill the criteria for CR after induction, with the exception of a persistent cytopenia that is believed to be treatment related, will be considered a partial response. Additionally, patients who fulfill the criteria for CR with exception of having bone marrow lymphoid nodules will be considered a partial response.
- Flow cytometry will be used to further characterize patients who achieve a CR by the above criteria. Those without evidence of marrow disease by this technique will be identified as such in analysis of treatment-free survival.

11.3 Partial Response

Requires > 50% decrease in peripheral lymphocyte count from pre-treatment value, > 50% reduction in lymphadenopathy, and/or > 50% reduction in Splenomegaly or hepatomegaly for a period of at least two months from completion of therapy. All lymph nodes will be measured bi-dimensionally and the sums of these added to determine if 50% or greater reduction has occurred. Patients may have bone marrow lymphoid nodules and persistent cytopenias. Additionally, these patients must have one of the following:

- Polymorphonuclear leukocytes ≥ 1500/μL or 50% improvement from pre-treatment value.

- Platelets > 100,000/μL or 50% improvement from pre-treatment value.

- Hemoglobin > 11.0 g/dL (untransfused) or 50% improvement from pre-treatment value.

11.4 Stable Disease

Patients who do not fulfill the criteria for complete or partial response as defined above but do not exhibit progressive disease will be considered as having stable disease.

11.5 Progressive Disease

Characterized by any one of the following events:

- ≥ 50% increase in the products of at least two lymph nodes on two consecutive determinations two weeks apart (at least one lymph node must be ≥2 cm); appearance of new palpable lymph nodes.

- ≥ 50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin; appearance of palpable hepatomegaly or splenomegaly, which was not previously present.

- ≥ 50% increase in the absolute number of circulating lymphocytes to at least 5,000/μL.

- Transformation to a more aggressive histology (i.e. Richter's syndrome or prolymphocytic leukemia with > 55% prolymphocytes).

- Patients not fulfilling the above criteria for progressive disease but demonstrating a decrease in hemoglobin > 2 g/dl or a decrease ≥ 50% in platelet or granulocyte count, will not be rated as progressive disease because these may occur as both a consequence of therapy and of underlying CLL. A bone marrow biopsy in such settings is strongly encouraged.

11.6 Duration of response

11.6.1 Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease that smallest measurements recorded since treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

11.6.2 Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since treatment started.

11.7 Progression Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of disease progression or death secondary to any cause.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/cdus.htm). **Note**: **All** adverse events that have occurred on the study, including those reported through CTEP-AERS, must be reported via CDUS.

12.1.2 Responsibility for Data Submission

N/A

12.2 CTEP Multicenter Guidelines

N/A

12.3 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, Agent-CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following

obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http:// ctep.cancer.gov/industry) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data".):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used, and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 CFR Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for

Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Suite 7111
Bethesda, Maryland 20892
FAX 301-402-1584
Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13. STATISTICAL CONSIDERATIONS

13.1 Study Overview

This is a randomized phase II trial designed to evaluate the impact of lenalidomide given concurrently with the conjugated 13-valent pneumococcal vaccine (PCV13) versus when PCV13 is administered first and then followed by lenalidomide. We will evaluate serotype-specific antibody responses along with PK and PD markers in each of the treatment arms.
In addition, we will evaluate the clinical efficacy of lenalidomide when given with PCV13 in terms of whether or not a complete response (CR) is achieved in the first two years along with progression-free survival (PFS), incidence of infection, and general toxicity and tolerability of this regimen in this patient population.

13.2 Primary Endpoint:

The primary endpoint for evaluation and comparison in this study is the proportion of patients who achieve an antibody response. Following the definitions used by the WHO for serotype-based response as well as recent definitions of antibody response in the literature for multi-valent pneumococcal conjugate vaccine, we will define an antibody response in the context of this trial as achieving at least a four-fold increase in post-vaccination serotype-specific IgG titers or serotype-specific IgG concentrations of ≥ 0.35 μg/mL for 6 of 7 serotypes measured by a standard ELISA assay. These will be measured as changes from baseline compared to repeat assessment 1 month after the second (booster) dose of PCV13.

13.3 Study Design

In this trial, patients will be randomized in a 1:1 allocation to receive lenalidomide with PCV13 up front concurrently (Arm A) vs. PCV13 up front and then subsequent administration of lenalidomide (Arm B). In this study we will compare the proportion of patients in each arm who achieve a significant antibody response as defined above. While it is not typical to employ a direct comparison of primary endpoints in the phase II setting, we believe that a randomized phase II design will better control for cohort and sampling variability necessary to assess the primary endpoint. In addition, in a secondary manner, we will also evaluate the clinical efficacy of treatment with lenalidomide in these patients vaccinated with PCV13, where clinical efficacy will be primarily determined through the proportion of patients who achieve a CR within two years (see Analysis Plan for more details).

Randomization will be stratified on exposure to pneumococcal vaccination in the previous 5 years. Those patients who have previously received a polysaccharide pneumococcal vaccine will not be excluded. If a patient drops out of the study prior to administration of a 2nd (booster) pneumococcal vaccination, they will not be considered evaluable for the primary endpoint and will be replaced on the study. However, the patient will be included in analyses of efficacy and tolerability as appropriate.

Assuming that vaccine success in each arm is binomially distributed, we will use a two-sided chi-square test to compare the difference in proportions. We will constrain the Type I error rate in the comparison of vaccine response rates to 0.10. Using a two-sided test, we will have at least 90% power to detect a difference of 0.40 between the two rates (0.20 vs. 0.60) with a total of 44 evaluable patients (22 in each arm). Comparing these two vaccine success rates, if $p_A \neq p_B$ and the resulting p-value < 0.10, we will consider the arm with the higher antibody response rate to have a significantly higher rate of vaccine success than the other arm. This design also allows for an interim analysis to be conducted after 11 patients have been accrued to each treatment arm (i.e. 50% of total planned accrual). Under a Lan-DeMets alpha spending function to constrain the Type I error rate, we will consider it sufficient evidence that one arm has a significantly higher antibody response rate than the other arm if the observed p-value <0.0056 (design generated using East version 5.3).

Independent of the comparison of vaccine-related efficacy, we will also formally evaluate

clinical efficacy using the two-year CR rate. Previous experience with lenalidomide suggests that late responses may be observed. Therefore, to effectively capture evidence of regimen efficacy (beyond the primary endpoint analysis) we will assess the CR rate in a pooled analysis across both arms since the main component of the regimen is lenalidomide therapy. If we find that one arm has shown to be superior to another in terms of antibody response rate as described above, then we will also compare the CR rates between these two arms in an exploratory manner. For the purposes of this trial, if a patient has a documented CR on at least two consecutive evaluations during the first two years, they will deemed a clinical success. Given the extended time required to observe this clinical endpoint in these patients, we will use a one-stage design. With 44 patients, we will have at least 90% power and a Type I error of 0.10 to be able to detect a 25% or greater true CR rate versus the null hypothesis that the true CR rate is at most 10%. If 8 or more patients are deemed a clinical success as defined above, then we will consider this evidence of efficacy and worth pursuing further. Otherwise, if at most 7 of these 44 evaluable subjects have a CR at the end of two years of follow-up, then we will consider this insufficient clinical activity and may look to modify the treatment regimen to build on observed vaccine response.

13.4 Sample Size/Accrual Rate

We expect that at most 10% will potentially drop out prior to administration of the 2nd vaccination, which translates to a total maximum sample size of 22+2=24 in each arm for a total of 48 patients. With an anticipated accrual rate of about 3 patients per month, we expect that this trial will be fully accrued in at most 16 months.

13.5 Analysis of Secondary Endpoints

In addition to evaluating the proportion of patients who have a vaccine-related antibody response to PCV13, we will also evaluate the seroconversion rates and antibody titre levels for each of the serotypes of the 13-valent pneumococcal vaccine. These markers will be summarized using descriptive statistics by treatment arm. We will graphically evaluate changes in these serotype-specific markers between the two arms, and we will also use the nonparametric Mann-Whitney rank sum test to compare the geometric mean concentrations.

Secondary endpoints will also include the CR rate following 2 years of lenalidomide treatment. Assuming that the number of CRs is binomially distributed, then we will also generate corresponding 95% confidence intervals for the CR rate estimate. If there is also a significant difference between the arms in terms of the vaccine response to PCV13, then we will also compare the CR rates between the two arms in an exploratory manner, although we will only be able to detect a large differential in CR rates (10% vs. 40%) with at least 80% power and a Type I error rate of 10%. In addition, we will evaluate time to event outcomes such as time to first treatment (TFT) and overall survival (OS). TFT will be defined as the time from study entry to first therapy for progressive CLL as defined by IWCLL 2008 criteria.[1] To evaluate this endpoint, patients will be followed even after discontinue therapy, where we will document date of subsequent treatment and/or progressive disease. Survival will also be evaluated, although we do not expect

many events in this early stage, asymptomatic group of patients. Time to event outcomes will be summarized and explored between treatment arms using Kaplan-Meier methods. Formal comparison of these endpoints between the two arms will not be done due to lack of statistical power to do so. In a very exploratory manner, we will also assess time to treatment in relation to the results reported by Shanafelt et al (2009); in an exploratory manner, we will utilize their prognostic scoring to identify an expected versus observed time to treatment.[64,65]

In each arm, we will evaluate the overall and complete response rates after two years, the proportion of patients in each arm who are progression-free at 2 years, and safety and tolerability of each regimen. Adverse events will be summarized by and across treatment arms, where we will summarize the type, severity, and perceived attribution to study treatment according to NCI's CTCAE (version 5). The rates of severe (grade 3+) toxicity (at least possibly related to treatment) and non-hematologic toxicity will be summarized; assuming the incidence of severe toxicity is binomially distributed, 95% confidence intervals will be calculated. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine the toxicity patterns. In addition, we will assess time to treatment failure, defined as the time from study entry to discontinuation of treatment; we will also summarize reasons patients discontinue study treatment.

Descriptive statistics (i.e. means, standard deviations, 95% confidence intervals for continuous variables and frequencies for discrete data) will be computed for all correlative laboratory parameters. Given the small sample size in this phase II trial, a total of 44 patients may limit our ability to perform inferential tests. Still, we will graphically evaluate these PK and PD markers within and across arms to assess potential patterns and relationships. Where model assumptions are met, we will also utilize repeated measures models (linear or nonlinear mixed models, generalized estimating equation models) to explore relationships with the various markers and clinical outcomes of interest.

13.6 Reporting and Exclusions

13.6.1 Evaluation of toxicity

All patients will be evaluable for toxicity from the time of their first treatment with lenalidomide.

13.6.2 Evaluation of response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B MEDICATION CALENDAR

SUBJECT DIARY

Site #	8834	PI Name:	Dr. Kerry Rogers	Subject #:	

Instructions: The study drug is stored at room temperature. Please do not freeze or refrigerate the study drug. The study drug must be taken by mouth once a day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact. Do not open capsules or dissolve them in water.

Each dose should be taken at approximately the same time each day with or without food. If a dose is missed, it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If it has been more than 6 hours, the dose should be skipped and you must take the next dose at the scheduled time the next day. The missed dose will not be made up and all the capsules from the missed dose must be returned to the clinic or hospital at the next visit.

Please complete the form below EVERY DAY to keep track of your doses. The purpose of this form is to help you remember to take the study drug once a day. For each day, complete the **date and time** (including circling "am" or "pm") for when you took the study drug, and the **number of capsules** you took. If you experienced any **symptoms** that you feel might have been related to the study drug, write those down as well. Always take this form with you when you attend your visits with the clinic or hospital.

CYCLE_____(fill in cycle #)

DAY	DATE	TIME	# CAPSULES	SYMPTOMS
1		am pm		
2		am pm		
3		am pm		
4		am pm		
5		am pm		
6		am pm		
7		am pm		
8		am pm		
9		am pm		
10		am pm		
11		am pm		
12		am pm		
13		am pm		
14		am pm		
15		am pm		
16		am pm		
17		am pm		
18		am pm		

19		am pm		
20		am pm		
21		am pm		
22		am pm		
23		am pm		
24		am pm		
25		am pm		
26		am pm		
27		am pm		
28		am pm		

28 DAYS IS THE END OF THE CYCLE. YOUR STUDY DOCTOR WILL LET YOU KNOW IF YOU CAN CONTINUE WITH THE NEXT CYCLE.

APPENDIX C RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Counseling

For a female of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

The investigator must ensure that for females of childbearing potential:

- Complies with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females NOT of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

Traces of lenalidomide have been found in semen. Male patients taking lenalidomide must meet the following conditions (i.e., all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential

Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) during dose interruptions; and 4) for at least 28 days after study treatment discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

[*Because of the increased risk of venous thromboembolism in patients 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 to 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.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting study drug

Female Patients:

FCBP must have two negative pregnancy tests (minimum sensitivity of 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10 to 14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The patient may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

Male Patients:

Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Female Patients:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a study patient, study drug must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study treatment must be discontinued during this evaluation.

- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male Patients:

- Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to lenalidomide must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Female patients should not donate blood during treatment and for at least 28 days following discontinuation of lenalidomide.
- Male patients should not donate blood, semen or sperm during treatment or for at least 28 days following discontinuation of lenalidomide.
- Only enough study drug for 28 days or one cycle of therapy (whichever is shorter) may be dispensed with each cycle of therapy.

APPENDIX D LENALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT

Protocol Number: _____

Patient Name (Print): _____ DOB: _____/_____/_____ (mm/dd/yyyy)

(Check the appropriate box to indicate risk category)

Female: □

If female, check one:

- □ FCBP (Female of childbearing potential): sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months)
- □ NOT FCBP

Male: □

□

Do Not Dispense study drug if:

- **The patient is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The patient states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual intercourse) [at least 28 days prior to treatment, during treatment, and during dose interruption].**

1. I verified that the required pregnancy tests performed are negative.
2. I counseled FCBP regarding the following:
   - Potential risk of fetal exposure to lenalidomide: If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking lenalidomide. The teratogenic potential of lenalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking lenalidomide.
   - Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual contact [at least 28 days prior to treatment, during treatment, during dose interruption and 28 days after discontinuation of lenalidomide].
   - That even if she has amenorrhea she must comply with advice on contraception

- Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:
  - Highly effective methods:
    - Intrauterine device (IUD)
    - Hormonal (birth control pills, injections, implants)
    - Tubal ligation
    - Partner's vasectomy
  - Additional effective methods:
    - Male condom
    - Diaphragm
    - Cervical Cap
- Pregnancy tests before, during, and after treatment, even if the patient agrees not to have reproductive heterosexual contact. Two pregnancy tests will be performed prior to receiving study drug, one within 10 to 14 days and the second within 24 hours of the start of study drug.
- Frequency of pregnancy tests to be done:
  - Every week during the first 28 days of this study and a pregnancy test every 28 days during the patient's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
  - If the patient missed a period or has unusual menstrual bleeding.
  - When the patient is discontinued from the study and at day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after study drug discontinuation.

– Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.

– NEVER share study drug with anyone else.

– Do not donate blood while taking study drug and for 28 days after stopping study drug.

– Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.

– Do not break, chew, or open study drug capsules.

– Return unused study drug to the study doctor.

3. Provide Lenalidomide Information Sheet to the patient.

FEMALE NOT OF CHILDBEARING POTENTIAL (NATURAL MENOPAUSE FOR AT LEAST 24 CONSECUTIVE MONTHS, A HYSTERECTOMY, OR BILATERAL OOPHORECTOMY):

4. I counseled the female NOT of child bearing potential regarding the following:
   - Potential risks of fetal exposure to lenalidomide (Refer to item #2 in FCBP)
   - NEVER share study drug with anyone else.
   - Do not donate blood while taking study drug and for 28 days after stopping study drug.
   - Do not break, chew, or open study drug capsules
   - Return unused study drug capsules to the study doctor.
5. Provide Lenalidomide Information Sheet to the patient.

MALE:

6. I counseled the Male patient regarding the following:
   - Potential risks of fetal exposure to lenalidomide (Refer to item #2 in FCBP).
   - To engage in complete abstinence or use a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or a female of childbearing potential, while taking study drug, during dose interruptions and for 28 days after stopping study drug.
   - Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking study drug should be advised to call their healthcare provider immediately if they get pregnant.
   - NEVER share study drug with anyone else.
   - Do not donate blood, semen or sperm while taking study drug and for 28 days after stopping study drug.
   - Do not break, chew, or open study drug capsules.
   - Return unused study drug capsules to the study doctor.
7. Provide Lenalidomide Information Sheet to the patient.

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____

Maintain a copy of the Lenalidomide Education and Counseling Guidance Document in the patient records.

Celgene Corporation	**Celgene Pregnancy Prevention & Counseling Program** **Site Counselor Identification Form** **for NCI Studies** **NCI Protocol #: _____** Principal Investigator: _____ Institution Name: _____

- **Please identify at least two (2) counselors and fax back to 888-314-2392**
- **Use one form per counselor.**
- **Identified counselors must be licensed healthcare professionals (e.g. RN, PA, RPh, PhD, LPN, CNP, or MD) and must not be the principal investigator.**
- **If you have any questions, please email (coop_ma@celgene.com)**

Counselor Information

CTEPpersonID: _____ CTEPsiteID: _____

First Name: _____ Middle Initial:_____ Last Name: _____

License Type: (circle one) MD PhD PA CNP RN LPN RPh Other:_____

Email Address: _____

Phone: _____ Fax: _____

Institution Street Address: _____

City: _____ State/Region: _____

Zip/Post Code: _____ Country: _____

Previously approved as a Counselor? □ No □ Yes

If no, please list all the protocols #(s), corresponding CTEPsiteID(s) and institution names(s) that you *plan to provide* counseling for:

If yes, please list the protocols #(s), corresponding CTEPsiteID(s) and institution names(s) *for protocols Celgene has already associated you with*:

Protocol#:	CTEPsiteID	Institution

APPENDIX E: LENALIDOMIDE INFORMATION SHEET

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Lenalidomide Information Sheet before you start taking study drug and each time you get a new supply. 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?

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. **Findings from a monkey study indicate that lenalidomide caused birth defects in the babies of female monkeys who received the drug during pregnancy.**

If you are a woman 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
- **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)
- **Stop taking study drug if you become pregnant during treatment**

- If you suspect you are pregnant at any time during the study, you must stop lenalidomide immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to the National Cancer Institute and the pharmaceutical collaborator, Celgene Corporation**.**

- **Do not breastfeed while taking study drug**
- The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not of childbearing potential:

In order to ensure that an unborn baby is not exposed to lenalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a man:

Lenalidomide is detected in trace quantities in human semen. The risk to the fetus in females of child bearing potential whose male partner is receiving lenalidomide is unknown at this time.

- Men (including those who have had a vasectomy) must either abstain from sexual intercourse or use a condom during sexual contact with a pregnant female or a female that can become pregnant:
  - While you are taking lenalidomide
  - During dose interruptions of lenalidomide
  - For 28 days after you stop taking lenalidomide
- **Men should not donate sperm or semen** while taking study drug and for 28 days after stopping lenalidomide.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to the National Cancer Institute and the pharmaceutical collaborator, Celgene Corporation. Your partner should call their healthcare provider immediately if she gets pregnant.**

Restrictions in sharing lenalidomide and donating blood:

- **Do not share lenalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.**
- **Do not donate blood** while you take lenalidomide and for 28 days after stopping study drug.
- **Do not break, chew, or open study drug capsules.**
- You will get no more than a 28-day supply of lenalidomide at one time.
- Return unused study drug capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.