MC138E

Celgene Protocol #RV-CL-CLL-PI-003938

Mayo Clinic Cancer Center

Impact of Short Term Lenalidomide on Immune Response to Prevnar 13® in Individuals with Chronic Lymphocytic Leukemia (CLL), Small Lymphocytic Leukemia (SLL), and Monoclonal B Cell Lymphocytosis (MBL)

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Drug Availability
Commercial Supply: *Prevnar 13® (IND# 123373)*
Drug Company Supplied via Revlimid REMS®: Lenalidomide

√ Study contributor(s) not responsible for patient care.
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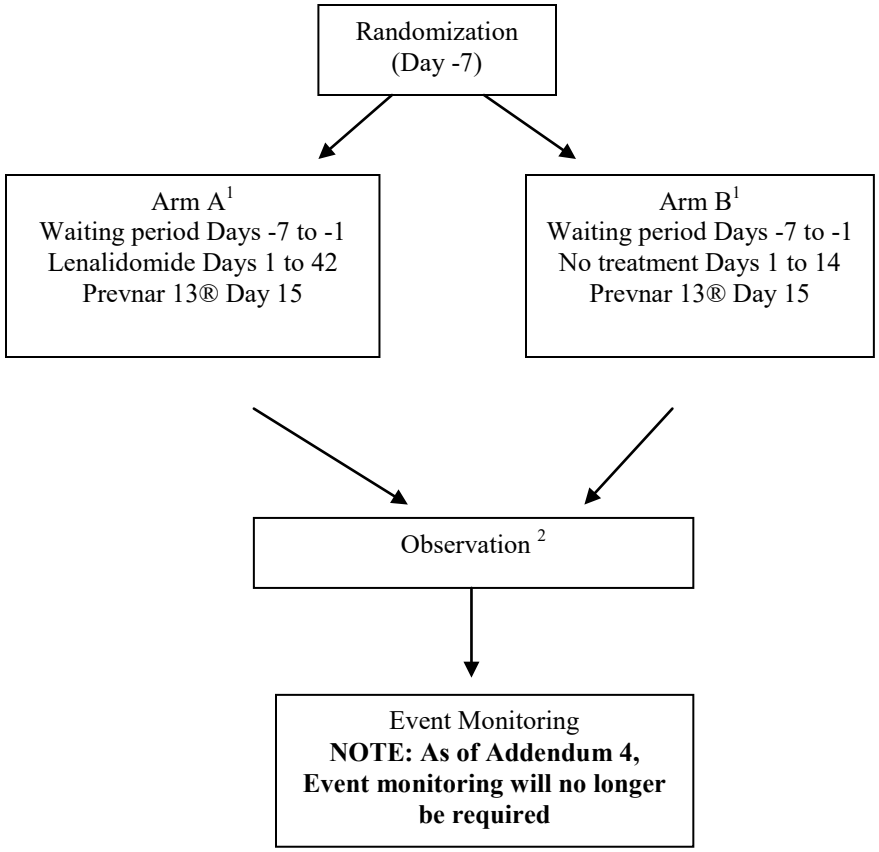
Index

SCHEMA:



[1] Cycle 1 = 50 Day Cycle (Days -7 to 43). Registration on Day -7 allows time for lenalidomide to be ordered through the Revlimid REMS®. Treatment with lenalidomide should begin on Day 1 for Arm A and Prevnar 13® should be given on Day 15 for both Arms.
[2] Cycle 2 (Observation) = 28 days (+/- 10 days)

Generic name: Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein) Brand name: Prevnar 13® Mayo abbreviation: PREVNAR13 Availability: Commercial supply	Generic name: Lenalidomide Brand name(s): Revlimid® Mayo Abbreviation: CC5013 Availability: Celgene supplied through the Revlimid REMS® program

1.0 Background

1.1 Infection and Survival in Patients with CLL and MBL

Chronic lymphocytic leukemia (**CLL**) is one of the most common lymphoid malignancies, accounting for ~11% of all hematologic neoplasms.[1] Over the last decade, the precursor state to CLL termed monoclonal B-cell lymphocytosis (**MBL**) has been defined. MBL is characterized by the presence of a small ($<5 \times 10^9$/l) population of clonal B cells in the peripheral blood in the absence of lymphadenopathy, cytopenias or autoimmune disease. In most patients with MBL, immunophenotype of the clonal B-cells is identical to chronic lymphocytic leukemia (CLL).[2] Although screening studies indicate that 3–12% of adults over age 40 have MBL, only a fraction of these MBL cases come to clinical attention (now designated as **clinical or high count MBL**), which is typically identified when patients are found to have mild lymphocytosis identified on a complete blood count obtained for other reasons.[2,3] The risk of progression from clinical MBL to CLL requiring chemotherapy treatment is ~1%/year.[4,5] Accordingly, given the typical age when clinical MBL is identified, most individuals with clinically recognized MBL will never require treatment for CLL. Despite their low risk of progressing to require CLL treatment, these patients are now recognized as at risk for serious infections (see below).

In addition to having a life expectancy that is substantially shorter than that of age-matched individuals in the general population, the 100,000 individuals in the United States living with CLL must also deal with an increased risk of infections. Strikingly, 30–50% of all deaths in patients with CLL are attributed to infections or infectious complications.[6] The increased rates of infection observed in patients with CLL even prior to receiving treatment suggested to us that this immunodeficiency state may be present among individuals with the precursor state to the disease. Recent evidence indicates that patients with clinically recognized MBL are also at increased risk of infection and suggest the risk of serious infection in individuals with clinical MBL is substantially greater than the risk they will ever progress to require treatment for CLL.[7] The increased susceptibility to infection in CLL patients results from a complex immunodeficiency state that includes defects in both humoral and cell mediated immunity that predate exposure to chemotherapy. Thus the immunodeficiency of CLL is multifactorial and is likely related to hypogammaglobulinemia, B- and T-cell dysfunction, and defects in innate immunity. [6,8,9] The mechanisms of decreased immune competence in MBL are poorly elucidated but surely are important ones to overcome and reverse.

1.2 Efforts to Reduce Infection in CLL and MBL:

CLL-The high rate of death from infection among patients with CLL has generated interest in strategies to reduce infection risk including vaccination strategies. Unfortunately, even prior to administration of chemotherapy, patients with CLL have decreased or suboptimal response to vaccinations. [10-12] Influenza seroconversion rates have ranged from 5-15% for influenza A and B,[11] as opposed to the 80-90% seroconversion rates typically seen in healthy adults. Responses to the polysaccharide pneumococcal vaccine (Pneumovax) have also been remarkably low, with responses ranging from 10-22%.[13,14]

Since CLL patients are truly immunocompromised even in early stage disease, it is not surprising that conventional vaccinations given to these patients are found to be

suboptimal. The exact etiologies are yet unclear but certainly relate to deficient immunoglobulin production, the impact of age, and, of course, the immunosuppressive effect of recent chemotherapies or chemoimmunotherapy (CIT). Efforts to enhance vaccine responses have been studied including the use of H2 Blockade and GM-CSF but have to date been unimpressive. Ranitidine as an adjuvant for influenza and pneumococcal vaccines led to no improvement for either influenza[15] or pneumococcal responses.[16] GM-CSF also demonstrated no ability to augment pneumococcal vaccine response.[14]

***MBL*-There are no published data on vaccine responses in patients with MBL.** However, given that we have found that patients with MBL have increased risk for serious infections similar to patients with CLL, [7] which is likely a result of immune dysfunction, we hypothesize that MBL patients will also have suboptimal responses to vaccination.

1.3 **Lenalidomide:** Lenalidomide is a proprietary IMiD® compound of Celgene Corporation. IMiD® compounds have both immunomodulatory and anti-angiogenic properties which could confer antitumor and anti-metastatic effects. Lenalidomide 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.{Dredge, 2005 #663} In addition, lenalidomide has a variety of immunomodulatory effects. Lenalidomide stimulates T cell proliferation, and the production of IL-2, IL-10 and IFN-gamma, inhibits IL-1 beta and IL-6 and modulates IL-12 production.{Corral, 1999 #664} Upregulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity.{Schafer, 2003 #665}

Although the exact antitumor mechanism of action of lenalidomide is unknown, a number of mechanisms are postulated to be responsible for lenalidomide's activity against multiple myeloma. Lenalidomide has been shown to increase T cell proliferation, which leads to an increase in IL-2 and IFN-gamma 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{Davies, 2001 #666}. 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{Wu, 2004 #675}.

<u>Current Indications and Usage of Lenalidomide:</u>
Revlimid® (lenalidomide) is indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Revlimid® is also approved in combination with dexamethasone for the treatment of patients with multiple myeloma that have received at least one prior therapy.

<u>Adverse Events with Lenalidomide:</u>
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, 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.

According to researchers, patients with cancer have a higher risk of developing a second new cancer when compared to people without cancer. In clinical studies of newly diagnosed multiple myeloma, a higher number of second cancers were reported in patients treated with lenalidomide as induction therapy (treatment for several cycles to reduce number of cancer cells) and/or bone marrow transplant followed by lenalidomide for a long period of time compared to patients treated with induction therapy and/or bone marrow transplant then placebo (a capsule containing no lenalidomide). Patients should make their doctors aware of their medical history and any concerns they may have regarding their own increased risk of other cancers.

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

1.4 **Lenalidomide and Immune Reconstitution:**

Lenalidomide is an immunomodulatory drug that is FDA approved for the treatment of multiple myeloma and myelodysplasia. Lenalidomide also has clinical activity in a number of other hematologic malignancies, including CLL.[17-20] In CLL, lenalidomide is thought to mediate its anti-tumor activity through modulation of the tumor microenvironment rather than a direct cytotoxic effect on the leukemic cells. [19,21,22] Immunomodulatory mechanisms include disrupting pro-tumor cytokines, anti-angiogenic signaling and activation of adaptive humoral and T-cell immunity.[19,21,22] Notably, both *in vitro and in vivo* data suggest that oral lenalidomide can repair defects in the T-cell immune synapse and reduce T regulatory levels in patients with CLL. In addition, there are reports that serum immunoglobulin levels can be enhanced with exposure to lenalidomide.

Notably, previous studies in patients with multiple myeloma also suggest that lenalidomide may improve the immune response to pneumococcal vaccination.[23] A "window of opportunity" study evaluated the immune response in patients with multiple myeloma receiving lenalidomide treatment. The first cohort received an initial dose of the pneumococcal 7-valent conjugate vaccine (PCV) prior to the initiation of lenalidomide and a second vaccination while on lenalidomide. The second cohort received both vaccinations while on lenalidomide. The PCV-specific humoral and cellular responses were greater in the second cohort suggesting lenalidomide augmented the vaccine response of these patients.[23]

1.5 **Strategic Concept:**

Most CLL patients are >age 65 and will have already received the 23 valent pneumococcal vaccine (Pneumovax). As noted, the response to pneumococcal vaccine in patients with CLL, however, is poor ranging from 10-22%.[13,14] In 2012, the Center for Disease Control recommended that, in addition to the Pneumovax, immunocompromised patients (such as those with CLL) also received the Pneumococcal 13-valent Conjugate

Vaccine (Prevnar 13) once during their lifetime to boost immunity to pneumococcal infection. This recommendation is primarily based on expert opinion with no data that it increases immunity in patients with CLL who typically have a poor response to vaccines in general.

In this study, we will conduct a pilot study evaluating the ability of a brief course of low dose lenalidomide to augment the response to the pneumococcal conjugate vaccination Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein)(Prevnar 13®) in patients **naïve to Prevnar 13** with clinical MBL and previously untreated, early stage CLL.

The rationale for this study is that lenalidomide has been shown to mediate much of its clinical activity through the immunomodulation of the microenvironment, including enhancement of the host immune system and evidence from patients with multiple myeloma that lenalidomide can augment vaccine response.[23] Thus, even though MBL and CLL patients will only have a short duration exposure to lenalidomide in this trial, **we hypothesize that there will be significant improvement in immune response to Prevnar 13® for patients receiving lenalidomide, whereby the immune response to PCV vaccination will be enhanced and that both T cell repertoire and T cell synapse levels will be improved.**

Sixty patients who have not previously received the Prevnar 13® (PCV13) vaccine will be enrolled in the study. All enrolled patients will receive a dose of PCV13 approximately 2 weeks after registration. Half of the study participants will be randomized to receive a brief course of low dose lenalidomide (2.5 mg dose for 2 weeks followed by 5 mg dose for 4 weeks) while remaining patients will receive only the vaccinations (see Schema). Correlative studies will evaluate immune function and response to Prevnar 13 vaccine immune parameter assessments at entry to the trial and following vaccination.

2.0 Goals

2.1 Primary

2.11 To assess the ability of a 6 week course of low dose lenalidomide to improve the proportion of patients with MBL and CLL who develop an immune response to pneumococcal vaccination as measured by the proportion of patients with ≥ 4-fold rise from pre-vaccine (day 15) for ≥ 2 of the 3 serotypes measured at 28 days post-vaccination by opsonophagocytic activity (OPA) of antibodies from sera.

2.2 Secondary

2.21 Evaluate disease status by physical exam and complete blood counts in patients participating in each arm of the study at the time of the 6 week assessment of immune response.

2.22 Evaluate time to treatment for progressive CLL for patients on each study arm.

2.23 Evaluate the adverse events profile in each study arm.

2.3 Correlative Research

2.31 To assess the immune response to pneumococcal vaccination as measured by fold-change from pre-vaccine (day 15) to 28 days post-vaccination in opsonophagocytic activity (OPA) GMT of antibodies from sera.

2.32 To assess the immune response to pneumococcal vaccination as measured by fold-change from pre-vaccine (day 15) to 28 days post-vaccination in quantitative *Streptococcus pneumoniae* immunoglobulin G (IgG) GMT of antibodies from sera.

2.33 Evaluate the effect of 6 weeks of low dose lenalidomide on global immune function including T-cell repertoire, T-cell immune synapse, serum immunoglobulin levels, and absolute numbers of T-cell and NK cells.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Diagnosis of:
a. CLL according to the NCI criteria (Hallek 2008)[24] or
b. SLL according to the WHO criteria (Harris, 1999)[25] or
c. MBL according to the consensus criteria (Marti 2006)[26]

This includes **previous** documentation of:

- Biopsy-proven small lymphocytic lymphoma (Harris, 1999)
  or
- Diagnosis of CLL[24] or MBL[26] as evidenced by all of the following:

  - ✓ Clonal B-cell population in the peripheral blood with immunophenotyping consistent with CLL defined as:
    - The population of lymphocytes share both B-cell antigens [CD19, CD20 (typically dim expression), or CD23] as well as CD5 in the absence of other pan-T-cell markers (CD3, CD2, etc.)
    - Clonality as evidenced by κ (kappa) or λ (lambda) light chain expression (typically dim immunoglobulin expression) or other genetic method (e.g. IGHV analysis)

    NOTE: Splenomegaly, hepatomegaly, or lymphadenopathy are not required for the diagnosis of CLL

  - ✓ Patients with a peripheral blood B-cell lymphocyte count of $<5 \times 10^9$/L and no evidence of lymphadenopathy or organomegaly will be classified as MBL. Patients with a peripheral blood B-cell lymphocyte count of $<5 \times 10^9$/L who have evidence of lymphadenopathy will be classified as SLL. Patients with a peripheral blood B-cell lymphocyte count $\geq 5 \times 10^9$/L will be considered to have CLL.

- ✓ Before diagnosing MBL, CLL or SLL, mantle cell lymphoma must be excluded by demonstrating a negative FISH analysis for t(11;14)(IgH/CCND1) on peripheral blood or tissue biopsy or negative immunohistochemical stains for cyclin D1 on involved tissue biopsy.

3.12 CLL or SLL patients only (does not apply to MBL patients): Rai Stage 0-1 (both CLL and SLL patients can be staged using the Rai system).

3.13 Patients must not previously have received the Prevnar 13 pneumococcal vaccination. NOTE: Previous vaccination with Pneumovax (PCV23) is permitted but must have been at least 365 days prior to registration.

3.14 Patients must be previously untreated (see note) and **must NOT** have any of the following indications for chemotherapy:

- Evidence of progressive marrow failure as manifested by the development of or worsening anemia (≤11 g/dL) and/or thrombocytopenia (≤ 100 x 10^9/L) not due to autoimmune disease
- Symptomatic or progressive lymphadenopathy, splenomegaly or hepatomegaly.
- One or more of the following disease-related symptoms:
  - Weight loss ≥ 10% within the previous 6 months
  - Extreme fatigue attributed to CLL
  - Fevers >100.4°F for 2 weeks without evidence of infection
  - Drenching night sweats without evidence of infection

Note:
1. Prior chemotherapy or monoclonal antibody based therapy for treatment of CLL or SLL will be considered prior therapy. Nutraceutical treatments with no established benefit in CLL (such as epigallocatechin gallate or EGCG, found in green tea or other herbal treatments) will not be considered "prior treatment".
2. Prior corticosteroid therapy for an indication other than CLL/SLL will not be considered "prior treatment". Previous use of corticosteroids for treatment of autoimmune complications of CLL/SLL does not constitute prior therapy for CLL/SLL.

3.15 Age ≥18 years.

3.16 ECOG Performance Status (PS) 0 or 1 (Appendix III).

3.17 The following laboratory values obtained ≤ 14 days prior to registration.

- Absolute neutrophil count (ANC) ≥1000/mm^3
- Platelet count ≥ 100,000/mm^3
- Hemoglobin ≥11.0 g/dL
- Total bilirubin ≤1.5 x upper limit of normal (ULN) unless due to Gilbert's disease. If total bilirubin is >1.5 x ULN, a direct bilirubin should be performed and must be <1.5 mg/dL for Gilbert's to be diagnosed.
- Aspartate transaminase (AST) ≤3 x ULN
- Calculated creatinine clearance must be ≥ 50 ml/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:

Creatinine clearance for males = $\dfrac{(140 - \text{age})(\text{weight in kg})}{(72)(\text{serum creatinine in mg/dL})}$

Creatinine clearance for females = $\dfrac{(140 - \text{age})(\text{weight in kg})(0.85)}{(72)(\text{serum creatinine in mg/dL})}$

3.18 Provide informed written consent.

3.19a Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.19b All study participants must be willing to be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the REMS® program. NOTE: Actual registration in the Revlimid REMS® program may occur after the patient is randomized since this requirement only applies to patients randomized to Arm A.

3.19c Females of reproductive potential must be willing to adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program. NOTE: This requirement only applies to patients randomized to Arm A.

3.19d Able to take aspirin (81 or 325 mg) daily as prophylactic anticoagulation (patients intolerant to ASA may use warfarin or low molecular weight heparin).

3.19e Willing to provide blood samples for correlative research purposes (see Sections 6.12 and 14.0).

3.2 Exclusion Criteria

3.21 Palpable lymph nodes >3 cm in maximal dimension.

3.22 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant women
- Nursing women

- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.23 Any of the following comorbid conditions:
- New York Heart Association classification III or IV cardiovascular disease (Appendix I).
- Recent myocardial infarction (≤ 30 days)
- Uncontrolled infection

3.24 Immunocompromised patients and patients known to be HIV positive and currently receiving antiretroviral therapy. NOTE: Patients known to be HIV positive, but without clinical evidence of an immunocompromised state, are eligible for this trial.

3.25 Other active primary malignancy requiring treatment or limiting survival to ≤2 years prior to registration.

3.26 Any radiation therapy ≤28 days prior to registration.

3.27 Any major surgery ≤ 28 days prior to registration.

3.28 Current use of corticosteroids. EXCEPTION: Low doses of steroids (≤ 10 mg of prednisone or equivalent dose of other steroid) used for treatment of non-hematologic medical conditions. NOTE: Previous use of corticosteroids is allowed.

3.29a Active hemolytic anemia requiring immunosuppressive therapy or other pharmacologic treatment. NOTE: Patients who have a positive Coombs test but no evidence of hemolysis are NOT excluded from participation.

3.29b History of deep venous thromboses or pulmonary embolism ≤ 365 days prior to registration.

3.29c Co-existent diffuse large B-cell lymphoma (Richters Transformation)

4.0 Test Schedule

	Active Monitoring Phase				
Tests & Procedures	Days Prior to Registration ≤14 days	Day 15 (+/- 3 days)	Day 28 (+/- 7 days)	Day 43 (+/- 4 days)	Observation: 28 days after end of first cycle (Day 72 +/- 10 days)
Medical history	X				
Adverse event assessment	X	X		X	X
Physical exam, including PS, weight and vital signs	X			X	X
Height	X				
Register in the REVLIMID REMS® program (Arm A only)	X[8]				
Counseling for the REVLIMID REMS® program (Arm A only)			X		
Tumor measurement by physical exam	X[1]			X[1]	
Peripheral blood immunophenotyping by flow cytometry	X[2]				
CBC with differential and reticulocytes	X	X		X	X
Serum pregnancy test	X[3]	X[3]	X[3]	X[3]	
Chemistry group (SGOT [AST], SGPT [ALT], total bilirubin, serum creatinine, calcium, alkaline phosphatase, uric acid, LDH, potassium)	X	X		X	
Glucose	X				
Direct bilirubin	X[7]				
CD38	X[2]				
ZAP-70	X[2]				
IGHV	X[4]				
CD49d	X[4]				
Serum protein electrophoresis	X			X	
Beta-2-microglobulin	X				
Peripheral blood CLL FISH panel	X[6]				
Serum quantitative immunoglobulins (IgG, IgA, IgM)	X			X	
Coombs test (monospecific direct coombs IgG and C3)	X				
ECG	X				
Quantitative T & B cells, peripheral blood	X			X	

Prevnar 13 pneumococcal vaccination		X			
Research blood specimens (see Section 14.0)	X[5,R]	X[5,R]		X[5,R]	

1. Physical exam should measure the spleen and liver noting the maximal distance below the respective costal margins and should record the bidimensional diameter of the largest palpable node in each area of involvement including the following sites: left neck (sub-mandibular, cervical, supra-clavicular), right neck (sub-mandibular, cervical, supra-clavicular), left axillary, right axillary, left groin (inguinal, femoral) and right groin (inguinal, femoral).
2. May be waived for patients who have previously had full flow immunophenotyping consistent with CLL performed at Mayo Clinic. Similarly, if the patient has previously had CD38 and/or ZAP-70 testing performed at Mayo Clinic, repeat assay is elective after discussing with the study chair.
3. For women of childbearing potential only. Must follow pregnancy testing requirements as outlined in the Revlimid REMS® program material.
4. If patient has previously had done clinically at Mayo Clinic, this does not need to be repeated.
5. Blood specimens will be collected and submitted at baseline, Day 15 and Day 43. Kits are required.
6. This can be waived if patient has had a clinical FISH performed at Mayo Clinic ≤ 365 days prior to registration.
7. Only needed if total bilirubin is > 1.5 x ULN.
8. Actual registration in the Revlimid REMS® program will occur after the patient is randomized and may fall outside of this window.

R Research funded (see Section 19.0). Will be charged to study and not to patient's account.

5.0 Stratification Factors:

5.1 Age: <65 vs. ≥65

5.2 Rai stage: MBL or 0 vs. I

5.3 Previous Pneumovax: Yes vs. no

6.0 Registration/Randomization Procedures

6.1 Registration Procedures

6.11 To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page (http://ccswww.mayo.edu/training/) and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted]. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.12 Correlative Research

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19e and 14.0).

6.13 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: [redacted]). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.14 Prior to accepting the registration, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.15 At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research of CLL at Mayo.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.

6.16 Treatment on this protocol must commence at Mayo Clinic Rochester, Mayo Clinic Arizona, or Mayo Clinic Florida institution under the supervision of a medical oncologist or hematologist.

6.17 Treatment cannot begin prior to registration and must begin ≤ 21 days after registration.

6.18 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.19a All required baseline symptoms (see Section 10.6) must be documented and graded.

6.19b Study drug (Prevnar 13®) is available on site.

6.2 Randomization Procedures

6.21 The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.

6.22 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups (35).

- Arm A (lenalidomide + Prevnar 13®
- Arm B (Prevnar 13®)

7.0 Protocol Treatment

7.1 Treatment Schedule

Arm	Agent	Dose Level	Route	Day
A	lenalidomide	2.5 mg	Oral	1-14
	lenalidomide	5 mg*	Oral	15-42
	Aspirin	325 mg	Oral	1-42
	Prevnar 13®**	1 dose	IM	15
B	Prevnar 13®**	1 dose	IM	15

* Unless dose reduced for adverse events, see Section 8.0

** Prevnar 13® vaccination should be administered on day 15 regardless of lenalidomide toxicity unless treating physician determines it should be held. If Prevnar 13® held, it should be administered as soon as deemed appropriate by treating physician.

7.2 For this protocol, the patient must return to the consenting institution for evaluation on Day 15 (+/-3 days) and Day 43 (+/-4 days) of the study.

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed.

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

8.1 **ARM A**: Dose Levels (Based on Adverse Events in Tables 8.*2*).

Dose Level	**Lenalidomide Days 1-14**	**Lenalidomide Days 15-42**
0	2.5 mg p.o. once daily	5 mg p.o once daily
-1	2.5 mg p.o. every other day	2.5 mg p.o. once daily
-2	2.5 mg p.o. Mondays and Thursdays	2.5 mg p.o. every other day

* Dose level 0 refers to the starting dose.

8.2 Lenalidomide Dose Modifications

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION
Days 1-42			
Blood and lymphatic system disorders	Anemia ≥ Grade 3		Transfuse red blood cells at physician discretion. Continue current dose level. For repeat episodes of anemia related to lenalidomide, dose may be reduced at physician's discretion.
	Anemia ≤ Grade 2		Transfuse red blood cells at physician discretion. Continue current dose level.
Cardiac disorders	Sinus bradycardia or Ventricular arrhythmia Grade 2		Omit lenalidomide (interrupt dose). Re-evaluate toxicity weekly. When symptoms resolve to ≤grade 1, decrease lenalidomide by 1 dose level and restart lenalidomide at the discretion of the treating physician. If symptoms do not resolve to ≤grade 1 by Day 35, discontinue lenalidomide treatment.
	Sinus bradycardia or Ventricular arrhythmia ≥Grade 3		Discontinue lenalidomide treatment.
Endocrine disorders	Hyperthyroidism ≥ Grade 2		Omit lenalidomide (interrupt dose). Initiate appropriate therapy. Reassess in 2 weeks. If symptoms resolve to ≤grade 1 decrease lenalidomide by 1 dose level and resume treatment. If symptoms do not resolve to ≤grade 1 by Day 35, discontinue lenalidomide.
	Hypothyroidism ≥ Grade 2		Omit lenalidomide (interrupt dose). Initiate appropriate therapy for hypothyroidism. Reassess in 2 weeks. If symptoms resolve to ≤grade 1 decrease lenalidomide by 1 dose level and resume treatment. If symptoms do not resolve to ≤grade 1 by Day 35, discontinue lenalidomide.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION
Days 1-42			
Investigations	Platelet count decreased ≥ Grade 3		Omit lenalidomide (interrupt dose). Omit anti-coagulant or Aspirin while platelet count <50 x 10^9/liter. May re-initiate when platelet count >75 x 10^9/liter (must re-initiate at time lenalidomide restarted). Recheck CBC with platelet count weekly. If platelet count increases to >75 x 10^9/liter, decrease lenalidomide by 1 dose level and restart treatment. If platelet count does not increase to >75 x 10^9/liter by Day 35, discontinue lenalidomide.
	Neutrophil count decreased ≥ Grade 3		Omit lenalidomide (interrupt dose). Recheck neutrophil count weekly. If neutrophil count > 1.0 x 10^9/liter, decrease lenalidomide by 1 dose level and restart treatment. If neutrophil count does not increase to > 1.0 x 10^9/liter by Day 35, discontinue lenalidomide. Growth factor support may be administered at the discretion of the treating physician. See Section 9.2.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Tumor pain ≥ Grade 3		Note: Differentiate tumor flare from disease progression. Treat with naproxen 500 mg p.o. BID. Continue lenalidomide during flare reaction. If patient does not experience adequate relief after 2 days of naproxen, add prednisone 20 mg p.o. daily. Steroids should be tapered as tolerated at the discretion of the treating physician.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION
Days 1-42			
Nervous system disorders	Peripheral motor neuropathy or Peripheral sensory neuropathy Grade 3		Omit lenalidomide (interrupt dose). Re-evaluate toxicity weekly. When symptoms resolve to ≤grade 1, decrease lenalidomide by 1 dose level and resume treatment. If symptoms do not resolve to ≤grade 1 by Day 35, discontinue lenalidomide.
	Peripheral motor neuropathy or Peripheral sensory neuropathy Grade 4		Discontinue lenalidomide
Skin and subcutaneous tissue disorders	Rash maculo-papular Grade 3		Omit lenalidomide (interrupt dose). Initiate supportive care measures as appropriate. Re-evaluate toxicity weekly. When symptoms resolve to ≤grade 1, decrease lenalidomide by 1 dose level and resume treatment. If symptoms do not resolve to ≤grade 1 by Day 35, discontinue lenalidomide.
	Stevens-Johnson syndrome ≥ Grade 3		Discontinue lenalidomide
	Erythema multiforme ≥ Grade 3		Discontinue lenalidomide.
Vascular disorders	Thromboembolic event ≥ Grade 3		Discontinue lenalidomide. Initiate anti-coagulation as appropriate.
Other non-hematologic	≥ Grade 3 as per NCI Common Terminology Criteria for Adverse Events v4.0 that does **NOT** respond to supportive care measures		Omit lenalidomide (interrupt dose). Re-evaluate toxicity weekly. When symptoms resolve to ≤grade 1, decrease lenalidomide by 1 dose level and restart treatment at the discretion of the treating physician. If symptoms do not resolve to ≤grade 1 by Day 35, discontinue lenalidomide treatment.

8.3 Prevnar 13 will be given per protocol regardless of whether or not lenalidomide dose reduced or omitted.

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

NOTE: If the patient experiences a significant adverse event requiring a dose reduction, then the dose will remain lowered through day 42.

NOTE: Adverse events requiring a dose-reduction step for lenalidomide beyond the two dose-reduction steps (levels –1 and –2) will be at the discretion of the treating physician, if the decision is made for the patient to be kept on study. These dose reductions must be clearly recorded in reported clinical data.

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetics may be used at the discretion of the attending physician.

9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the : ASCO 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline Journal of Clinical Oncology 2006;24:3187-3205.

9.3 Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, and antiemetics when appropriate. **Any blood transfusions administered must be irradiated blood products to reduce risk of transfusion mediated graft versus host disease in CLL patients receiving T-cell suppressive therapy. Leukocyte reduction of all blood products for patients on protocol is also required.** All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.4 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.5 DVT prophylaxis: As indicated in section 7.0, all patients receiving lenalidomide (Arm A) will be required to take aspirin 325 mg/day for DVT Prophylaxis during the study as long as they are on lenalidomide. Patients who are intolerant or allergic to aspirin may use low molecular weight heparin at prophylactic dose level.

9.6 Treatment of Tumor Flares: Patients experiencing a tumor flare during lenalidomide therapy will be treated with naproxen 500 mg p.o. BID until symptoms resolve. Study medications will be continued through flare symptoms if tolerated by patient. If patient does not experience adequate relief after 2 days of naproxen therapy, add prednisone 20 mg p.o. each day. Steroids should be tapered as tolerated at the discretion of the treating physician.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 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 for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether the event must be reported as an expedited report (see Section 10.4). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). Grade is an essential element of the Guidelines and, in general, relates to **severity** for the purposes of regulatory reporting to NCI.

NOTE: A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

10.2 **Expected vs. Unexpected Events**

- The determination of whether an AE is expected is based on agent-specific information provided in Section 15.0 of the protocol and the study specific consent form.

- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of the protocol and the study specific consent form.

NOTE: "Unexpected adverse experiences" means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 **Assessment of Attribution**

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.31 **AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the <u>SAME</u> Arm**

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the entire combination (arm) is then considered an investigational intervention for reporting.

<u>Routine Reporting</u>

- Routine AE reporting for Phase 1 and Phase 2 clinical studies using an investigational agent /intervention in combination with a commercial agent is stated in the protocol. See Section 10.6.

<u>Expedited Reporting</u>

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for investigational agents/interventions in Section 10.4, and where indicated, an expedited report must be submitted.

- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report. Refer to Section 10.4 for specific AE reporting requirements or exceptions.

- Commercial agent expedited reports must be submitted to the FDA via MedWatch or Celgene SAE form.

- An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity, expedited reporting is required. The clinical investigator must determine severity.

10.4 Expedited Reporting Requirements for IND/IDE Agents

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in Section 10.41 of the protocol.
Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:
- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:
- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional instructions:

1. The investigator must inform Celgene in writing using a MEDWATCH 3500A or Celgene SAE form (see Forms Packet).

(http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm) of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (RV-CL-CLL-PI-003938) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

Contact Celgene Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
[redacted]

Expedited Reporting by Investigators to Celgene: For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events of being related to lenalidomide based on the Investigator Brochure. In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

2. Use paper MEDWATCH 3500A or Celgene SAE form. Submit to Celgene (see above for contact information).

Mayo Clinic Cancer Center (MCCC) Institutions: Provide copies, along with the UPIRTSO cover sheet, by fax (507-538-7164) to the MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist who will determine and complete IRB reporting. The RAU will submit to the MCCC SAE Coordinator and the MCCC IND Coordinator to determine if FDA submission is needed.

10.41 Special Situations for Expedited Reporting

Exceptions to Expedited Reporting: EXPECTED Serious Adverse Events

An expedited report may not be required for specific Grade 1, 2, 3 and 4 Serious Adverse Events where the AE is **EXPECTED**. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will supercede the standard Expedited Adverse Event Reporting Requirements. Note: These adverse events must still be reported through the routine reporting mechanism [i.e. Nadir/Adverse Events Form]; see footnote 1.

CTCAE Category	Adverse Event	Grade	Attribution	Comments
Blood and lymphatic system disorders	Anemia	3 or 4	All	This frequent event in patients with CLL will be reported through the routine reporting mechanism
Investigations	Platelet count decreased	3 or 4	All	This frequent event in patients with CLL will be reported through the routine reporting mechanism
	Neutrophil count decreased	3 or 4	All	This frequent event in patients with CLL will be reported through the routine reporting mechanism
	Lymphocyte count decreased	3 or 4	All	This frequent event in patients with CLL will be reported through the routine reporting mechanism
	White blood cell decreased	3 or 4	All	This frequent event in patients with CLL will be reported through the routine reporting mechanism

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

10.5 Other Required Reporting

10.51 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.52 Death

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE be reported. Three options are available to describe the event:
    - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
    - Myelodysplastic syndrome (MDS)
    - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.55 Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on lenalidomide, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile or email using the Pregnancy Initial Report Form (see Forms Packet). 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 notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form (see Forms Packet). If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

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 their healthcare provider immediately.
Celgene Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
[redacted]

10.6 Required Routine Reporting

Adverse events to be graded at each evaluation (e.g. day 15, day 43, and observation) and pretreatment symptoms/conditions to be evaluated at baseline per Common Terminology Criteria for Adverse Events (CTCAE) v4.0 grading unless otherwise stated:

System Organ Class (SOC)	Adverse Event/Symptoms	Baseline	Day 15, Day 43, and Observation
Investigations	Platelet count decreased**	X	X
General disorders and administration site conditions	Fever	X	X
	Fatigue	X	X
Blood and lymphatic system disorders	Febrile neutropenia	X	X
	Anemia**	X	X
Skin and subcutaneous tissue disorders	Rash maculo-papular	X	X
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Tumor pain*		X

* Tumor flare reactions will be classified under tumor pain and graded based on CTCAE v4.0.
** Grading will be performed by the study statisticians at the time of analysis based on the CLL toxicity grading scale for blood counts in Appendix IV. CTCAE grades for platelet count decreased and anemia will also be recorded for reporting purposes.

10.61 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.611 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.612 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.613 Grade 5 AEs (Deaths)

10.6131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6132 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.62 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation

11.1 Response to Prevnar 13® Vaccine

The goal of this study is to determine response to Prevnar 13® vaccine. The two most common serologic methods for quantifying and evaluating the function of antibodies induced by pneumococcal vaccination are quantification of *Streptococcus pneumoniae* IgG antibodies and measurement of opsonophagocytic activity (OPA) of antibodies from sera of vaccinated individuals. The OPA assay is a functional antibody assay that is important for the evaluation of candidate vaccines and is a requirement for the licensure of new pneumococcal conjugate vaccine formulations. OPA reflects *in vivo* mechanisms of defense against pneumococcal infection. **The measurement of functional antibodies has been shown to better correlate with protection in infant populations and it is also likely to be a better indicator for elderly populations than the measurement of antibodies specific to the capsular polysaccharides by ELISA assay.**[27] While there is no defined correlate of protection for pneumococcal vaccines, it is thought that OPA titers are associated with protection against invasive pneumococcal disease. The primary endpoint for Prevnar 13® adult clinical trials that led to the FDA approval of Prevnar 13® relied on immunogenicity endpoints of OPA geometric mean titer (GMT) and proportion achieving at least 4-fold increase in OPA titer.[28] Nevertheless, even when assessing OPA titers, most vaccine trials also measure and report quantitative IgG antibodies specific to *Streptococcus pneumoniae* serotypes.

Accordingly, the Primary outcome for vaccine immunogenicity in this trial will be: OPA titers against 3 pneumococcal serotypes (4, 9V, 23F) included PCV13 vaccine will be measured at pre-vaccine (day 15) and 28 days after immunization (e.g. at the day 43 evaluation; fold change from pre-vaccination sera responses).

- Overall Prevnar 13® response will be defined as ≥ 4-fold rise from pre-vaccine (day 15) for ≥ 2 of the 3 serotypes measured at 28 days post-vaccination.

11.2 CLL/SLL Disease Status:

This study does not intend to treat patients' underlying CLL/SLL. Accordingly, the protocol does not require bone marrow biopsies or CT imaging and response assignment according to the IWCLL/NCI criteria is therefore not possible. Patients "disease status" based on physical exam and complete blood counts, however, will be assessed at the time of the day 43 visit.

11.21 CLL/SLL: Disease status will be classified as one of the following using the criteria below which are based on the IWCLL criteria without the bone marrow biopsy results[24]:

- progressive disease
- stable disease
- partial response
- clinical complete response (or clinical complete response with incomplete marrow recovery)

11.22 MBL: Disease status will be classified as one of the following criteria based on the IWCLL criteria for progressive disease:

- progressive disease
- not progressive disease

11.3 For the purposes of this study, patient's disease status will be evaluated at the time of the day 43 evaluation. Although the patient will be periodically seen Days 1 - 42, response evaluations will not occur on those dates.

NOTE: Information from CT scans is not considered in the standard classification of response.

11.4 Definitions

The NCI Working Group criteria (Hallek, 2008) will be used to assess response to therapy.

11.41 <u>COMPLETE CLINICAL RESPONSE (CCR)</u> requires <u>all</u> of the following at the Day 43 evaluation:

11.411 Absence of lymphadenopathy (e.g. lymph nodes >1.5 cm) by physical examination.

11.412 No hepatomegaly or splenomegaly by physical examination.

11.413 Absence of constitutional symptoms.

11.414 CBC demonstrating:

- Peripheral blood lymphocytes <4000/μL.
- Neutrophils >1500/μL
- Platelets >100,000/ μL (untransfused).
- Hemoglobin >11.0 g/dL (untransfused).

Note: Patients who fulfill all criteria for a CCR but who have a persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity rather than residual CLL will be classified as **CCR with incomplete marrow recovery (CCRi)** according to the international criteria (Hallek, 2008).

11.42 PARTIAL RESPONSE (PR): PR requires the patient exhibits at least two of the features in Sections 11.421, 11.422, and 11.423 below (**if** abnormal prior to therapy) as well as one or more of the remaining features (Sections 11.424, 11.425, 11.426) at the day 43 evaluation. For patients with Rai stage 0 disease (e.g. no palpable nodes or organomegaly) and those with MBL a 50% reduction in lymphocytosis will be considered to represent a PR. In addition to the parameters listed below, the presence or absence of constitutional symptoms will be recorded.

11.421 ≥ 50% decrease in peripheral blood lymphocyte count from the pretreatment baseline value.

11.422 ≥ 50% reduction in the sum of the products of the maximal perpendicular diameters of the largest measured node or nodal masses in the right and left cervical, axillary, and inguinal lymph node regions on physical examination.

11.423 ≥ 50% reduction in size of liver and/or spleen as measured by physical exam noting the maximal distance below the respective costal margins of palpable hepatosplenomegaly during rest.

11.424 Neutrophils >1500/ul or 50% improvement over baseline.

11.425 Platelets >100,000/ul or 50% increase over baseline.

11.426 Hemoglobin >11.0 gm/dl or 50% increase over baseline without transfusions.

11.43 PROGRESSION (PD): Patients will be considered to have PD according to the NCI criteria[24] if they experience any of the following:

11.431 ≥ 50% increase in the sum of the products of at least 2 lymph nodes (at least one node must be ≥2 cm) or the appearance of new palpable lymph nodes >1.5 cm not due to a tumor flare. Enlargements or the appearance of new nodes due to a tumor flare do NOT qualify as progression. If there is uncertainty as to whether lymph node enlargement at the Day 43 evaluation represents tumor flare, repeat examination 2-4 weeks after the protocol specified discontinuation of lenalidomide can be used to help make this determination.

11.432 ≥ 50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin on 2 consecutive determinations 2 weeks apart and with a minimum of a ≥ 2 cm increase in size from baseline; or appearance of hepatomegaly or splenomegaly which was not previously present at baseline and not due to a tumor

flare. If there is uncertainty as to whether an increase in liver/spleen size at the Day 43 evaluation represents tumor flare, repeat examination 2-4 weeks after the protocol specified discontinuation of lenalidomide can be used to help make this determination.

11.433 Transformation to a more aggressive histology (e.g. Richter's transformation).

NOTE: If a patient develops DLBCL at any time, it will be considered progressive disease. If the patient develops any other hematological malignancy while on study, it will not be considered progressive disease.

11.434 ≥ 50% increase in the absolute number of circulating lymphocytes NOT due to infection or tumor flare (taking as reference for progressive disease the smallest absolute lymphocyte count recorded since the treatment started).

11.435 Cytopenias due to lenalidomide toxicity will **not** be considered to represent disease progression. In the absence of progression as defined by 11.431, 11.432, 11.433, 11.434 above, the presence of a ≥ 2 g/dL decrease in HGB, or ≥ 50% decrease in platelet count, or absolute neutrophil count will NOT be considered progression. Work-up of such decreases to exclude auto-immune hemolytic anemia, pure red cell aplasia, or idiopathic thrombocytopenic purpura (ITP) should be considered.

11.44 STABLE DISEASE (SD): Patients who do not meet criteria for CCR (or CCRi), PR, or PD will be classified as having "stable disease".

11.45 Not progressive disease (Not PD): The patient did not meet the criteria for progression per section 11.43 (MBL patients only).

11.5 Summary Definition of objective response for patients with B–CLL

	CCR[1]	CCRi[2]	PR[3]	PD[4]
PHYSICAL EXAM				
Nodes[5]	None	None	≥50% ↓	≥50% ↑, new nodes
Liver/spleen[6]	Not palpable	Not palpable	≥50% ↓	≥50% ↑, newly palpable
Symptoms	None	None	N/A	N/A
PERIPHERAL BLOOD				
ANC	>1500/µL	See footnote 2	>1500/µL	See footnote 4
Platelets	>100,000/µL	See footnote 2	>100,00/µL	See footnote 4
Hemoglobin	>11.0 g/dL without transfusion	See footnote 2	>11.0 g/dL	See footnote 4
Lymphocytes	<4000/µL	<4000/µL	≥50% ↓	≥50% ↑ to at least 5,000/µL
BONE MARROW	N/A	N/A	N/A	N/A

1. Clinical complete response (CCR) requires fulfillment of all physical exam and peripheral blood criteria as noted in the table above. No bone marrow biopsy is required to call a patient a CCR.
2. Patients who fulfill all criteria for a CCR but who have a persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity rather than residual CLL will be classified as CCR with incomplete marrow recovery (CCRi).
3. Partial response (PR) requires fulfillment of at least two of the above-noted decrease in circulating lymphocytes, regression in adenopathy and regression in hepatosplenomegaly, and at least one other parameter listed above for a duration of >2 months after the completion of treatment. See Section 11.42.
4. Progression: Fulfilling the criteria as noted in section 11.43.
5. Measurement of lymphadenopathy will be determined on physical exam by adding the sum of the products of the maximal perpendicular diameters of measured lesion(s). For purposes of determining CCR all nodes on physical exam need to be ≤ 1.5 cm in maximal dimension or documented to be free of CLL by biopsy. NOTE: Information from CT scans scans regarding lymphadenopathy is not considered in the standard classification of response.
6. Measurement of hepatosplenomegaly will be determined by noting the maximal distance below the respective costal margins of palpable hepatosplenomegaly during rest (e.g., not during deep inspiration). NOTE: Information from CT scans regarding hepatosplenomegaly is not considered in the standard classification of response.

12.0 Descriptive Factors

12.1 $CD38^+$ expression: Positive (≥30%) vs. negative (<30%).

12.2 Chromosomal anomalies as detected by FISH: 13q- vs. 12+ vs. 11q- vs. 17p- vs. other abnormality vs. normal karyotype.

12.3 *IGHV* mutation status: Mutated (≥2%) vs. unmutated (<2%) vs. indeterminate.

12.4 ZAP-70 expression: Positive (≥20%) vs. negative (<20%).

12.5 CD49d expression: Positive (≥45%) vs. negative (<45%).

13.0 Treatment/Follow–up Decision at Evaluation of Patient

NOTE: As of Addendum 4, Event monitoring will no longer be required

13.1 After completion of the Day 43 response to vaccine evaluation, patients will discontinue treatment and enter one cycle of OBSERVATION (28 days after end of first cycle +/- 10 days) and then enter EVENT MONITORING.

13.2 If Lenalidomide is discontinued due to patient refusal or noncompliance, unacceptable toxicity, or intercurrent illness that makes treatment assessment difficult and the patient received the Prevnar 13 vaccine, they will receive their Day 43 response to vaccine evaluation at which point they will then enter one cycle of OBSERVATION (28 days after end of first cycle +/- 10 days) and then enter EVENT MONITORING.

13.3 If a patient on Arm A does not receive the Prevnar 13 vaccine, they will discontinue treatment and go directly to event monitoring per Section 18.0 of the protocol. If a patient on Arm B does not receive the Prevnar 13 vaccine, they will be deemed a cancel and will be removed from the study per Section 13.6 of the protocol.

13.4 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry.

- If the patient received treatment, the patient will go directly to event monitoring. All data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

Note: Due to the nature of the disease, if the patient is diagnosed with DLBCL within the first cycle of treatment, it will be assumed that the DLBCL was present at registration. The patient will be deemed ineligible per Sec 3.29c.

13.5 A patient is deemed a *major violation*, if protocol requirements regarding Lenalidomide treatment during Days 1-42 are severely violated such that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation

must be submitted. The patient will go directly to the event-monitoring phase of the study. Event monitoring will be required per Section 18.0 of the protocol.

13.6 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any Lenalidomide (Arm A) or Prevnar (Arm B) is given . On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.7 A patient will be deemed a *flagr* if they received Lenalidomide and then failed to receive the Prevnar 13 vaccine (Arm A). Patients classified as a flagr will not be evaluable for response and will be replaced.

14.0 Body Fluid Biospecimens

14.1 The collection of blood/blood products is **mandatory** for the translational/pharmacologic research component of this study. Summary Table of Research Blood and Body Fluid Specimens to be Collected for this Protocol

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Baseline	Day 15 visit	Day 43 visit	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
T cell immune function (repertoire, synapse) and plasma cytokine profile (14.21)	Mandatory	Whole Blood	Sodium heparin (green)	10 mL (5)	X	X	X	No	Refrigerate/ Cold pack.
Specific immune response to Prevnar 13 vaccination (*Streptococcus pneumoniae* IgG antibodies,, OPA)(14.22)	Mandatory	Serum	(red top)	10 mL (2)	X	X	X	No	Refrigerate/ Cold pack.

14.2 Background and Methodology

14.21 Global immune changes in CLL T cell function.

a) *T cell repertoire:* T lymphocytes recognize complexes of major histocompatibility complex gene products and bound, processed peptides through T cell receptors (TcRs) that are heteroduplexes of alpha and beta subunits. T lymphocyte populations are characterized by diverse TcR repertoires that have been hypothesized to be essential for effective T lymphocyte responses to large numbers of pathogens. The importance of diversity in T lymphocyte populations for maintenance of robust immune responses relevant to human health has driven the development of methods to quantitate TcR repertoire diversity. We have developed a novel method to analyze diversity of murine TcR beta transcripts[29] designated as the BV:BJ matrix method. This is based on amplification in real-time PCRs using 252 combinations of BV (beta variable) and BJ (beta-joining)-specific primer pairs that derive from 21 BV and 12 BJ genes. This method is able to reliably analyze TcR repertoire diversity in total populations of T lymphocytes. Our studies and others in CLL patients have shown significant deficits in repertoire along with individual T cell populations that have major expansions.

Processing: Peripheral blood mono-nuclear cells will be isolated by Ficoll-hypaque separation and frozen in liquid nitrogen. Malignant $CD19^+$ CLL B-cells will be positively selected while $CD3^+$ T-cells will be negatively selected using MACS cell isolation kits with an autoMACS™ Pro Separator (Miltenyi Biotec, Auburn, CA).

Total RNA will be extracted, and residual genomic DNA will be removed with an RNase-Free DNase Set (Qiagen) and used to assess T-cell repertoire. Extracted RNA levels from 10^6 $CD3^+$ T-cells will typically range anywhere from 2-4 µg.

Assessment of T-cell repertoire using a BV-BJ Matrix Method: In brief, this method is designed to generate a single estimate of repertoire diversity and increase the success of identifying and sequencing transcripts that are expressed by expanded T-cell clonotypes. Since BV and BJ genes belong to relatively closely related families, BV- and BJ-specific primers are rigorously selected to ensure specificity and comparable efficiency.[29,30]

b) *T regulatory cells:* In addition, a relative increase of circulating regulatory CD4+ T cells (T-regs) and their function has been observed in CLL, providing yet another explanation for increased infections and diminished responses to vaccinations.

Processing: T-cells isolated by magnetic bead sort (outlined above), will undergo immunophenotyping by flow cytometry.

c) *T cell synapse:* In CLL leukemic B cells inhibit normal T lymphocytes through the impairment of the formation of the immunologic synapse in a

contact-dependent manner. Because of the leukemic nature of CLL, these inhibiting cell contacts can occur ubiquitously. The resulting state of cellular immunodeficiency offers a plausible explanation for the frequent infections and secondary cancers seen in CLL. We have just reported on the administration of a 6 month course of lenalidomide in CLL patients following chemoimmunotherapy (CIT) where we found enhanced T cell synapse levels for the responding patients.[31]

Processing: T-cell: APC immune synapse bioassays: The ability of $CD3^+$ T-cells to interact (% conjugation) with APCs (baseline fluorescently labeled CLL cells pulsed with superantigen, sAg) and assemble signaling complexes to the immune synapse site will be visualized and quantified using combined multi-color high-resolution imaging flow cytometry (ImageStream) and confocal (Zeiss) Imagestream/Axiovision quantitative image analysis software will characterize and analyze the functional organization of T-cell synapses including the receptor layer (CD4, CD8, co-signaling molecules), the signaling layer and the cytoskeletal layer as previously described.[32,33] Granzyme B^+ will act as a biomarker for CTL lytic synapses. These data will then be exported for statistical analysis to generate mean values at each treatment time-point using the published approach.[32,33]

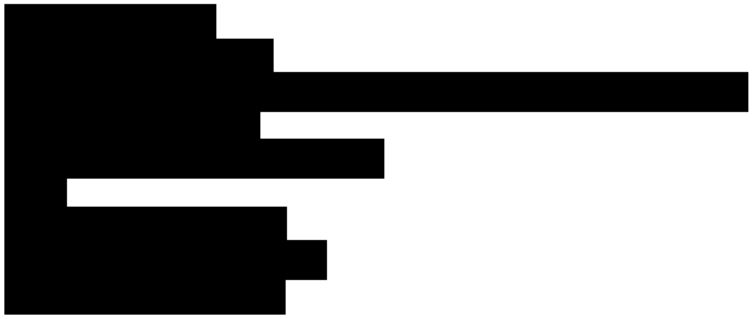
14.22 *Specific immune response to Prevnar 13® vaccination*:

Immunity following pneumococcal disease is directed primarily against the capsular polysaccharide of the bacteria serotype involved. Antibody mediated killing of *Streptococcus pneumoniae* by phagocytes is an important mechanism of protection. The two most common serologic methods for quantifying and evaluating the function of antibodies induced by pneumococcal vaccination are IgG quantification by enzyme-linked immunosorbent assay (ELISA) and measurement of opsonophagocytic activity (OPA) of antibodies from sera of vaccinated individuals. The OPA assay is a functional antibody assay that is important for the evaluation of candidate vaccines and is a requirement for the licensure of new pneumococcal conjugate vaccine formulations. OPA reflects *in vivo* mechanisms of defense against pneumococcal infection. **The measurement of functional antibodies has been shown to better correlate with protection in infant populations and it is also likely to be a better indicator for elderly populations than the measurement of antibodies specific to the capsular polysaccharides by ELISA assay.[27]** While there is no defined correlate of protection for pneumococcal vaccines, it is thought that OPA titers are associated with protection against invasive pneumococcal disease. The primary endpoint for Prevnar 13® adult clinical trials that led to the FDA approval of Prevnar 13® relied on immunogenicity endpoints of OPA geometric mean ratio (GMT) and proportion achieving at least 4-fold increase in OPA titer.[28] Nevertheless, even when assessing OPA titers, most vaccine trials also measure and report quantitative IgG antibodies specific to *Streptococcus pneumoniae* serotypes.

- We will report pre-vaccination (baseline) and Day 28 post-vaccination OPA GMTs for each serotype (4, 9V, 23F) in vaccine group and vaccine group + lenalidomide.

- We will report pre-vaccination (baseline) and Day 28 post-vaccination *Streptococcus pneumoniae* serotype specific IgG GMTs for each serotype (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 19A, and 23) in vaccine group and vaccine group + lenalidomide.
- Correlative endpoints for vaccine immunogenicity will include comparison of fold change in OPA GMT for each serotype (4, 9V, 23F) between vaccine group and vaccine + lenalidomide group and comparison of fold change in *Streptococcus pneumonia*e quantitative IgG level for each serotype (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 19A, and 23) between vaccine group and vaccine + lenalidomide group.

We plan to send serum specimens to the Bacterial Respiratory Pathogen Reference Laboratory at University of Alabama Birmingham for pneumococcal opsonophagocytic assays. This laboratory is directed by Moon Nahm, MD, Professor of Pathology. Samples will be stored at Mayo until batch shipped to UAB.



14.3 Blood Products Handling

14.31 **Kits are required for this study for non-Mayo Rochester sites.**

The kit contains supplies and instructions for collecting, processing, and shipping specimens.

Participating institutions may obtain kits by e-mailing [redacted]. E-mail requests should include the site address, contact information and number of kits being requested.

Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. **Allow 3 to 4 business days to receive the kits.**

14.32 Label specimen tubes with protocol number, patient initials (last name, first name), study patient ID number (if available) and date of collection.

14.33 Collect all peripheral blood according to specific kit instructions (see Appendix VI) and table above.

14.34 Shipping

Specimens must be shipped the same day they are drawn.

Ship in their respective Styrofoam boxes; a cold pack is required. Avoid freezing of specimens. The Fed Ex airbill is pre-addressed.

Ship specimens via Priority Overnight service on **Monday – Thursday Preferred** (Friday only if you must) directly to:

[redacted]

Please email [redacted] or call [redacted] to notify the laboratory when specimens are being shipped. The message should include the study name, sample type, Fed Ex airbill tracking number, contact name and telephone number.

Shipping costs will be covered by the study if these kits and Fed Ex airbills are used for shipping specimens. Each kit contains the required tubes.

15.0 Drug Information

15.1 Lenalidomide (Revlimid®, CC-5013, CDC-501)

Please consult the most current Investigator's Brochure and package insert for complete drug information.

15.11 **Background**: Lenalidomide has a wide range of effects, including the inhibition of hematopoietic tumor cell proliferation, the enhancement of T cells and natural killer (NK) cell activity, the modulation of stem cell differentiation, the inhibition of angiogenesis, and the inhibition of inflammation.

15.12 **Formulation**: For clinical study, lenalidomide is provided as 1.25-, 2.5-, 5-, 10-, 15-, 20-, and 25-mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

Placebo capsules for the 1.25-, 2.5-, 5-, 10-, 15-, 20-, and 25-mg lenalidomide capsules are available for use in blinded studies. Each placebo capsule visually matches the drug product.

The lenalidomide and placebo capsules are supplied in push-through blister foil or tamper-evident, child-resistant, opaque, high-density polyethylene (HDPE) containers with HDPE caps.

15.13 **Preparation and storage**: Lenalidomide should be stored at room temperature, between 59 and 86ºF (15-30ºC). Store drug away from direct sunlight.

15.14 **Administration:** Capsules are administered by mouth daily with water. Patients should not break, chew or open the capsules.

15.15 **Pharmacokinetic information**:
a) Absorption – Lenalidomide is rapidly absorbed following oral administration to subjects with multiple myeloma or MDS, with maximum plasma concentrations occurring between 0.5 and 1.5 hours post-dose. Co-administration with a high-fat and high-calorie meal in healthy subjects reduced the extent of absorption, resulting in an approximately 20% decrease in AUC and 50% decrease in C_{max} in plasma.

In the pivotal MM and MDS registration trials where the efficacy and safety were established for lenalidomide, the drug was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Multiple dosing (up to 100 mg BID) did not cause marked drug accumulation.

b) Distribution – In vitro (^{14}C)-lenalidomide binding to plasma proteins is approximately 30%.

c) Metabolism – Lenalidomide undergoes limited metabolism. Unchanged lenalidomide is the predominant circulating component in humans. Two identified metabolites are hydroxy-lenalidomide and N-acetyl-lenalidomide; each constitutes less than 5% of parent levels in circulation.

d) Excretion – Elimination is primarily renal. Approximately 65% to 85% of lenalidomide is eliminated unchanged through urinary excretion in subjects with normal renal function. The half-life of elimination is approximately 3 to 4 hours (2 to 3 hours in patients 5 to 21 years) at the clinically relevant doses (5 to 50 mg/day). Steady-state levels are achieved within 4 days.

15.16 **Potential Drug Interactions**: In vitro studies demonstrate that lenalidomide is not a substrate of CYP enzymes. In addition, lenalidomide shows little inhibitory or induction potential towards the CYP enzymes in vitro. Hence, coadministration of CYP substrates, inhibitors, or inducers with lenalidomide is not likely to result in clinically relevant drug-drug interactions in humans.

In vitro, lenalidomide is not a substrate of BCRP, MRP1, MRP2, MRP3, OAT1, OAT3, OATP1B1, OCT1, OCT2, MATE1, OCTN1, or OCTN2. Thus, it is unlikely that substrates or inhibitors of these transporters would affect lenalidomide disposition in humans.

Lenalidomide is not an inhibitor of BSEP, BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2. Thus, lenalidomide is not anticipated to cause any significant drug-drug interactions due to inhibition of these transporters.

Lenalidomide is not an inhibitor of UGT1A1 and is not anticipated to cause any significant drug-drug interactions due to UGT1A1 inhibition.

In vitro, lenalidomide is a weak substrate, but not an inhibitor of P-glycoprotein (P-gp).

Erythropoietic agents or other agents that may increase the risk of thrombosis, such as hormone replacement therapy and oral contraceptives, should be used with caution in patients with multiple myeloma receiving lenalidomide with dexamethasone.

Periodic monitoring of digoxin plasma levels is recommended due to increased C_{max} and AUC with concomitant lenalidomide therapy. Close monitoring of PT and INR is recommended in multiple myeloma patients taking concomitant warfarin.

15.17 **Known potential toxicities**:

Pregnancy Warning: 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, a teratogenic effect of lenolidomide in humans cannot be ruled out. Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception.

Very Common AEs (≥ 10%): anemia, leukopenia, neutropenia, thrombocytopenia, cataracts, blurred vision, abdominal pain, constipation, diarrhea, dyspepsia, nausea, vomiting, asthenia, chills, edema including peripheral, fatigue, pyrexia, abnormal liver function tests, bronchitis, nasopharyngitis, pneumonia, rhinitis, upper respiratory tract infection, urinary tract infection weight decreased, decreased appetite, hyperglycemia, hypocalcemia, hypokalemia, arthralgia, back pain, bone pain, muscle spasms, musculoskeletal pain, myalgia, pain in extremity, dizziness, dysgeusia, headache, hypoesthesia, neuropathy peripheral, neuropathy, tremor, depression, insomnia, cough, dyspnea, epistaxis, pharyngitis, pulmonary embolism, dry skin, pruritus, rash, and deep vein thrombosis.

Common (≥ 1% and < 10%): febrile neutropenia, granulocytopenia, hemolytic anemia, lymphopenia, pancytopenia, acute myocardial infarction, atrial fibrillation, cardiac failure, congestive heart failure, myocardial ischemia, tachycardia, vertigo, upper abdominal pain, dry mouth, , toothache, chest pain, fall, , cholestasis, bacteremia, erysipelas, gastroenteritis, herpes simplex, herpes zoster, influenza, lower respiratory infection, respiratory infection, sinusitis, sepsis, contusion, alanine aminotransferase increased, c-reactive protein increased, gamma-glutamyltransferase increased, dehydration, diabetes mellitus, gout, hyperuricemia, hypophosphatemia, hypomagnesemia, hyponatremia, iron overload, muscular weakness, acute myeloid leukemia, basal cell carcinoma, Myelodysplastic syndrome, squamous cell carcinoma of skin, tumor flare, tumor lysis syndrome, cerebrovascular accident, lethargy, paresthesia, peripheral sensory neuropathy, syncope, mood altered, renal failure, respiratory distress,

erythema, hyperhidrosis, night sweats, hematoma, hypertension, hypotension, peripheral ischemia, thrombosis, and vasculitis.

Uncommon, limited to important or life-threatening (< 1%): hypersensitivity, Graft vs. Host Disease

The following additional adverse reactions have been reported in Celgene-sponsored clinical studies and are considered by the company to be at least possibly related to the administration of lenalidomide: pneumonitis, transient abnormal liver laboratory tests, hyperthyroidism, , TLS, TFR, rhabdomyolysis, and allergic conditions, including angioedema, SJS, and toxic epidermal necrolysis. These reactions are reported voluntarily from a population of uncertain size, so it is not possible to reliably estimate their frequency.

Lenalidomide may have minor or moderate influence on the ability to drive and use machines. Fatigue, dizziness, somnolence, vertigo and blurred vision have been reported with the use of lenalidomide. Therefore, caution is recommended when driving or operating machines.

Please refer to the Investigator's Brochure for a more comprehensive list of treatment-emergent adverse events.

15.18 **Drug procurement:** Lenalidomide (Revlimid®) will be provided directly to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers in accordance with the REVLIMID REMS™ program. Per standard requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the Celgene REVLIMID REMS™ program. Prescriptions must be filled within 7 days. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.**

Any unused lenalidomide should be returned for disposition in accordance with the REVLIMID REMS™ program.

15.19 **Nursing Guidelines:**

15.191 Myelosuppression is dose-dependent and reversible with treatment interruption and/or dose reduction. Monitor CBC w/diff regularly. Instruct patient to report any unusual bruising or bleeding (thrombocytopenia); signs and symptoms of infection (neutropenia); and energy conserving lifestyle (anemia).

15.192 Lenalidomide can have thrombotic adverse events (i.e DVT and PE). Instruct patient to report any limb swelling or pain, and to seek medical attention for shortness of breath or chest pain.

15.193 Because of the potential for birth defects patients should be instructed in effective methods of birth control. Female patients should use 2 forms of birth control during treatment and for 4 weeks after discontinuing

therapy. Males must be instructed to use a latex condom during any sexual contact with a woman of child bearing potential (even if they have had a vasectomy), because it is unknown if lenalidomide is present in semen.

15.194 Patents may experience pruritus, rash and dry skin. Because of the rare risk of Steven's Johnson Syndrome, patients should immediately report any rash to their provider.

15.195 Drug may cause hyperglycemia. Patients with diabetes or impaired fasting glucose may need to have their glucose levels monitored more closely.

15.196 Gastrointestinal side effects (diarrhea, constipation, nausea, dyspepsia, anorexia, etc) are commonly seen. Manage patient symptomatically and monitor for effectiveness.

15.197 Patients may experience myalgias, arthralgias, and other generalized pain. Administer analgesics as ordered and monitor for their effectiveness.

15.198 Upper respiratory symptoms (nasopharyngitis, cough, epistaxis, etc.) can be seen. Manage symptomatically and monitor for effectiveness.

15.199 Agent may cause fatigue, dizziness, vertigo, or blurred vision. Instruct patients to use caution when driving or operating machines.

15.2 Pneumococcal 13-valent Conjugate Vaccine (Prevnar 13®)

15.21 **Background**: Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein), is a sterile solution 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.

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.

15.22 **Formulation:** Supplied as ready-to-use prefilled syringes (10 x 0.5-mL prefilled syringes per package). Pneumococcal 13-valent Conjugate Vaccine is manufactured as a liquid preparation for intramuscular injection. 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.

15.23 **Preparation and storage**: Pneumococcal 13-valent Conjugate Vaccine is stored at refrigerated temperatures of 2ºC to 8ºC (36ºF to 46ºF) away from freezer compartment. DO NOT FREEZE. Discard if frozen.

15.24 **Administration:** Shake vigorously immediately prior to use to obtain a uniform suspension in the vaccine container. The vaccine should not be used if it cannot be resuspended. After shaking, the vaccine is a homogeneous, white suspension. Do not mix the vaccine with other products in the same syringe.

The dose is 0.5 mL to be given intramuscularly. ***Do not inject intravenously***, intradermally or subcutaneously**.** The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk and/or blood vessel. Before injection, the skin at the injection site should be cleansed and prepared with a suitable germicide. After insertion of the needle, aspirate and wait to see if any blood appears in the syringe, which will help avoid inadvertent injection into a blood vessel. If blood appears, withdraw the needle and prepare for a new injection at another site.

15.25 **Potential Drug Interactions**: Patients receiving therapy with immunosuppressive agents (large amounts of corticosteroids, antimetabolites, alkylating agents, cytotoxic agents) may not respond optimally to active immunization.

As with other intramuscular injections, Pneumococcal 13-valent Conjugate Vaccine should be given with caution to patients on anticoagulant therapy.

See complete prescribing information for information regarding co-administration of Pneumococcal 13-valent Conjugate Vaccine with other vaccines.

15.26 **Known potential toxicities**: There is no safety data available in the adult patient population. Please see Prevnar 13® prescribing information for comprehensive toxicity data.

The following systemic events were noted within 2-3 days of the Pneumococcal 13-valent Conjugate Vaccine injection in pediatric patients: fever, irritability, drowsiness, restless sleep, decreased appetite, vomiting, diarrhea, and urticaria-like rash. The following local reactions occurred within 3 days of immunization pediatric patients: erythema, induration, tenderness and interference with limb movement.

15.27 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.28 **Nursing Guidelines:**

15.281 Monitor for injection site reaction. Local reaction is usually seen within 3 days of vaccination, including erythema, induration and tenderness. Treat symptomatically and monitor for signs on infection.

15.282 Patients may experience mild fever. Acetaminophen can be used symptomatically. Monitor for effectiveness.

15.283 Patients may experience "flu-like" symptoms (fever, irritability, decreased appetite, vomiting and diarrhea). Treat symptomatically.

16.0 Statistical Considerations and Methodology

16.1 Overview:
This is a randomized Phase II study designed to compare the response rate of the control arm (Prevnar 13 alone) to the experimental arm (Prevnar 13 plus lenalidomide).

16.11 Primary Endpoint:
The primary endpoint of this trial is the rate of response to the Prevnar 13 vaccine, which will be compared between the two arms. A response will be defined as a four-fold rise from pre-vaccine (day 15) to 28 days after immunization (day 43) for ≥ 2 of the 3 serotypes studied by opsonophagocytic activity (OPA) of antibodies from sera. Throughout Section 16.0, response will be considered synonymous with "success", unless specified otherwise. All patients meeting the eligibility criteria who have signed a consent form and, received the Prevnar 13 vaccine will be evaluable for response, with the exception of patients who are determined to be a major treatment violation or flagr.

16.2 Statistical Design:

16.21 Decision Rule:

It has been shown that CLL patients have poor response to vaccines. In previous studies, responses to the polysaccharide pneumococcal vaccine (Pneumovax) have been remarkably low, with responses ranging from 10-22%.[13,14] Similar responses are expected with the Prevnar 13 vaccine. The addition of lenalidomide is expected to increase response rates to Prevnar 13 vaccine.

A randomized trial comparing the experimental arm (Prevnar 13 plus lenalidomide) against the control arm (Prevnar 13 alone) will be conducted as described by Rubinstein[34]. We will enter 26 evaluable patients on each arm of the study using a 1:1 randomization scheme utilizing the Pocock and Simon dynamic allocation procedure[35], where patients are stratified based on age (<65 vs. ≥65), Rai stage (MBL or 0 vs. I), and previous Pneumovax (yes vs. no). A sample size of 26 patients per arm provides 80% power to detect an improvement in response rate from 10% to 30%, using a one-sided test at a significance level of 0.16 (EAST 6.2).

The z-score will be calculated for testing the null hypothesis that the difference of response rates between the two arms is equal to zero, based on the normal approximation with pooled variance of standardized test statistics.

16.211 Final Decision Rule: The final analysis will take place after all 52 evaluable patients have completed the response evaluation at 43 days.

The response rates will be compared between the two arms using EAST6. If the response rate is higher in the experimental arm, where the z-score is greater than 0.988 (p-value < 0.162), this will be considered sufficient evidence that the experimental arm may be recommended for further testing in subsequent studies. Otherwise, we will conclude that there is not statistical evidence of superiority of the experimental regimen.

16.212 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.33.

16.22 Sample Size:
The randomized phase II study design to be used is fully described in section 16.21. A maximum of 52 evaluable patients (26 in each arm) will be accrued onto this phase II study unless undue toxicity is encountered. We anticipate accruing an additional 6 patients (3 in each arm) to account for ineligibility, cancellation, major treatment violation, or failure to receive the Prevnar 13vaccine. Maximum projected accrual is 58 patients.

16.23 Accrual Rate and Study Duration:
The anticipated accrual rate is approximately 3-4 patients per month. Therefore, the accrual period for this phase II study is expected to be about 1.5 years. The final analysis can begin approximately 1.75 years after the trial begins, i.e. as soon as the final patient accrued to this trial has completed the response evaluation at 43 days and data entry has been completed.

16.24 Power and Significance Level: Assuming that the responses are binomially distributed in each arm, the operating characteristics of the current design can be tabulated according to various true differences of the proportions, including the probabilities that the experimental regimen is superior to the control regimen.

If the true difference is proportions is	0	0.10	0.20	0.30
Then the probability of declaring that the experimental regimen warrants further studies is….	0.16	0.51	0.80	0.95

16.25 Other Considerations: Toxicity, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.3 Analysis Plan: The analysis for this trial will commence at planned time points (see 16.2) and at the time the patients have become evaluable for the primary endpoint. Such a decision will be made by the Statistician and Study Chair, in accord with CCS Standard Operating Procedures, availability of data for secondary endpoints (eg, laboratory correlates), and the level of data maturity. It is anticipated that the earliest date in which

the results will be made available via manuscript, abstract, or presentation format is when last patient has been followed for at least 2 months.

16.31 Primary Endpoint:

16.311 Definition: The primary endpoint of this trial is the rate of response to the Prevnar 13 vaccine, which will be compared between the two arms. A response will be defined as a four-fold rise from pre-vaccine (day 15) to 28 days after immunization (day 43) for ≥ 2 of the 3 serotypes studied by opsonophagocytic activity (OPA) of antibodies from sera. Patients who are not evaluated for the OPA titers at both pre-vaccine (day 15) and day 43 due to a missed blood draw or other reasons will be considered a non-responder. All patients meeting the eligibility criteria who have signed a consent form and received the Prevnar 13 vaccine will be evaluable for response, with the exception of patients who are determined to be a major treatment violation or flagr.

16.312 Estimation: The proportion of successes will be estimated in each arm by the number of successes divided by the total number of evaluable patients. Ninety-five percent confidence intervals for the true success proportion will be calculated in each arm based on the normal approximation. Comparison of response rates between the two treatment groups will be performed using a one-sided z-test (based on normal approximation with pooled variance of standardized test statistics) at significance level 0.16.

16.32 Secondary Endpoints:

16.321 Disease status by physical exam and complete blood counts will be evaluated in each patient. For CLL, each patient will be classified as CCR, CCRi, PR, SD, or PD per Section 11.2 at the time of the 6 week assessment of immune response. The distribution of disease status will be evaluated in each arm and will be summarized descriptively. Patients will be classified as responders (CCR, CCRi, PR) vs. non-responders (SD, PD). For MBL, patients will be classified as Not PD vs. PD. Differences in disease status response will be compared between the two arms using Fisher's exact test.

16.322 Time to treatment for progressive CLL will be defined as the time from the date of registration to the date of initiation of treatment for progressive CLL. The distribution of time to treatment will be estimated in each arm using the method of Kaplan-Meier. Time to treatment will be compared between the two arms using log-rank statistics.

16.323 Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). Platelets and hemoglobin will be graded according to the Grading Scale for Hematologic Adverse Events in CLL Studies in Appendix IV. The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed for each arm to determine

patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.33 Correlative Analyses:

16.331 Pre-vaccination (day 15) and day 28 post-vaccination OPA GMTs for each serotype (4, 9V, 23F) will be reported in the vaccine and vaccine + lenalidomide groups. The fold-change in OPA GMT from baseline to 28 days post-vaccination will be evaluated for each serotype, where two-sample t-tests will be used to compare GMTs between the vaccine and vaccine + lenalidomide groups.

16.332 Pre-vaccination (day 15) and day 28 post-vaccination *Streptococcus pneumoniae* serotype specific IgG GMTs for each serotype (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 19A, and 23) will be reported in the vaccine and vaccine + lenalidomide groups. The fold-change in quantitative IgG GMT from pre-vaccine (day 15) to 28 days post-vaccination will be evaluated for each serotype, where two-sample t-tests will be used to compare GMTs between the vaccine and vaccine + lenalidomide groups.

16.333 Measures of global immune function including T-cell repertoire, T-cell immune synapse, serum immunoglobulin levels, and absolute numbers of T-cell and NK cells will be evaluated at both baseline and after 6 weeks of low dose lenalidomide. Values over time will be summarized graphically and descriptively. Changes from baseline to 6 weeks will be evaluated using paired t-tests. Two sample t-tests will be used to compare each measure between the vaccine and vaccine + lenalidomide groups.

16.34 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals.

16.35 <u>Data & Safety Monitoring</u>

16.351 The principal investigator(s) and the study statistician will review the study at least every quarter to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.352 Adverse Event Stopping (applies to each arm independently): The stopping rule specified below is based on the knowledge available at study development. We note that the rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatments under investigation.

The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to <u>both arms</u> if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy either of the following:

- if 4 or more patients in the first 15 treated patients in either arm experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.
- if after the first 15 patients have been treated, 25% of all patients in either arm experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.
- Any grade 5 event related to treatment

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.353 Enhanced Safety Monitoring Rule: If at any time after the first 12 patients have been treated on the experimental arm, the rate of grade 3 or 4 non-hematologic adverse events in the experimental arm is ≥ 25%higher than the rate in the control arm, the study team will review the adverse events profile in each arm. Accrual may be temporarily suspended to evaluate the types of adverse events and the relation to study treatment.

16.4 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 1.75 years after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the last patient registered has completed the response evaluation at 43 days.

16.5 <u>Inclusion of Women and Minorities</u>

16.51 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.52 There is no information currently available regarding differential effects of this regimen in subsets defined by race or gender, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.53 The geographical region served by Mayo, has a population which includes approximately 3% minorities. Based on prior Mayo studies involving similar disease sites, we expect about 3-5% of patients will be classified as minorities by race and about 30% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	1	1
Not Hispanic or Latino	17	40	57
Ethnic Category: Total of all subjects	17	40	58
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	0	1	1
Native Hawaiian or other Pacific Islander	0	0	0
White	17	40	57
Racial Category: Total of all subjects	17	41	58

Ethnic Categories:
Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
Not Hispanic or Latino

Racial Categories:
American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."
Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens: None.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
On-Study	≤2 weeks after registration
Adverse Event - Baseline	
Measurement - Baseline	
Research Blood Submission (see Section 14.0)	
Other Laboratory Results	
OPA Titers	
Quantitative IgG Levels	
FISH Results - Baseline	
Quantitative Flow Cytometry	
Immunophenotyping Reports including CD38, CD49d, and ZAP-70[1, 2]	
IgVH Mutation Analysis Report[1]	
CLL FISH Report[1]	
End of Active Treatment/Cancel Notification	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

1. Submit copy of the report, Attention: [redacted].
2. For patients who previously had full flow immunophenotyping performed and at pre-study workup had limited repeat flow immunophenotyping, submit a copy of both reports.

Test Schedule Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation
Evaluation/Treatment [2]		X	
Evaluation/Observation [1]			X
Nadir/Adverse Event		X	X
Measurement		X	X
Research Blood Submission		X (see Section 14.0)	
Other Laboratory Results		X	
Interval Laboratory		X	
OPA Titers		X	
Quantitative IgG Levels		X	
Quantitative Flow Cytometry		X	
End of Active Treatment/Cancel Notification		X	
ADR/AER	At each occurrence (see Section 10.0)		

1. Complete at each evaluation during Observation (see Section 4.0).
2. Complete at each evaluation during Active Treatment (see Section 4.0).

Follow-up Material(s)

CRF	**Event Monitoring Phase[1]**				
	q. 6 months until PD or subsequent treatment for CLL[2]	At PD or subsequent treatment for CLL[2]	q. 12 mos. after PD or subsequent treatment for CLL	Death	New Primary
Event Monitoring	X	X	X	X	At each occurrence

1. If a patient is still alive 2 years after registration, no further follow-up is required.
   NOTE: As of Addendum 4, Event monitoring will no longer be required
2. Submit copy of documentation of response or progression, Attention: [redacted].

19.0 Budget

19.1 Costs charged to patient: routine clinical care and Prevnar 13® vaccine.

19.2 Tests to be research funded: Research bloods and associated correlative studies (see Section 14), and lenalidomide will be research funded.

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Appendix I

NYHA Classification

Class I: NO Symptoms with ordinary activity

Class II: Symptoms with ordinary activity

Class III: Symptoms with minimal activity

Class IV: Symptoms at rest

Appendix II

Rai Classification

0	lymphocytosis (> 5 x 10^9/L)
I	lymphocytosis and lymphadenopathy
II	lymphocytosis and splenomegaly +/- lymphadenopathy
III	anemia (Hgb < 11 g/dL)
IV	thrombocytopenia (platelets < 100 x 10^9/L)

Appendix III
ECOG Performance Status Scale

Grade	***Descriptions***
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix IV
Grading Scale for Hematologic Toxicity in CLL Studies[1]

Decrease from Pretreatment value (%)	Grade[2]	
	Platelets[3, 5]	Hemoglobin[4, 5]
No change - 10%	0	0
11-24%	1	1
25-49%	2	2
50-74%	3	3
≥ 75%	4	4

1. A decrease in circulating granulocytes is not being considered since it is not a reliable index in CLL.
2. Grades: 1–mild; 2–moderate; 3–severe; 4–life–threatening. Grade 5 (fatal) toxicity can potentially occur at any level of decrease from pretreatment values and will be recorded as such.
3. If, at any level of decrease the platelet count is <20,000/μL, this will be considered grade 4, unless the initial platelet count was ≤ 20,000 μL in which case the patient is inevaluable for toxicity referable to platelet counts.
4. Baseline and subsequent hemoglobin determinations must be immediately prior to any given transfusions.
5. If, at any level of decrease from the baseline value the platelet and/or hemoglobin counts are within normal limits, this will be considered a grade 0.

* Hallek BD, et al.: Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer-Institute- Working Group 1996 guidelines: Blood 111:54465456, 2008.

Appendix V
PATIENT MEDICATION DIARY

Patient Instructions

- Take at the same time each day with or without food.
- Please indicate on the calendar below *every* day that you take your study medication by placing the dose taken on the line under the date.
- If you miss a dose, place a check "**0**" under the date, but remember to take your prescribed dose at the next regularly scheduled time.
- Bring ***all*** bottles and any unused study medication along with this diary when you return for your next appointment.
- Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened.

Medication(s)	Dose
Lenalidomide	**Days 1-14:** 2.5 mg **Days 15-42:** 5 mg (unless dose is reduced due to adverse events)

Study Drug	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Date							
Lenalidomide							

Study Drug	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**
Date							
Lenalidomide							

Study Drug	**Day 15**	**Day 16**	**Day 17**	**Day 18**	**Day 19**	**Day 20**	**Day 21**
Date							
Lenalidomide							

Study Drug	**Day 22**	**Day 23**	**Day 24**	**Day 25**	**Day 26**	**Day 27**	**Day 28**
Date							
Lenalidomide							

Study Drug	**Day 29**	**Day 30**	**Day 31**	**Day 32**	**Day 33**	**Day 34**	**Day 35**
Date							
Lenalidomide							

Study Drug	**Day 36**	**Day 37**	**Day 38**	**Day 39**	**Day 40**	**Day 41**	**Day 42**
Date							
Lenalidomide							

Date:_____ Participant's Signature_____

Appendix VI – Kit Instructions

Impact of Short Term Lenalidomide on Immune Response to Prevnar 13® in Individuals with Chronic Lymphocytic Leukemia (CLL), Small Lymphocytic Leukemia (SLL), and Monoclonal B cell Lymphocytosis (MBL)

Blood Collection Kit Mayo Clinic CLL Laboratory
Specimen Checklist and Shipping Instructions

**** PLEASE AVOID DRAWING OR SENDING SPECIMENS ON FRIDAYS AND HOLIDAYS****

Kit Contents:

- 5 lb Styrofoam box and cardboard mailing sleeve
- Patient Information Form
- FedEx Airbill with pre-printed return address
- Five 10ml Sodium Heparin (green top) collection tubes
- Two 10ml Red Top collection tubes
- Absorbent tube holder
- Zip lock specimen bag
- (1) Kool-PAK. Place the ice pack in the freezer for at least 24 hours prior to specimen shipment. Allow the frozen ice pack to thaw at room temperature for 2-3 hours **before** preparing the specimen for shipment.

Packing and Shipping Instructions:

1. Collect the following specimens:
   - Peripheral blood – Draw:
     - 50ml in five (5) Sodium Heparin tubes **(All Time Points)**
     - 20ml in two (2) Red Top tubes **(Baseline and Day 43 *visit*)**
2. Label specimens with protocol number MC138E, patient's initials (last name, first name), study patient ID number (if available) and date of collection.
3. Place the slightly thawed Kool-PAK in bottom of Styrofoam container.
4. Place absorbent toweling on top of Kool-PAK.
5. Place the tubes in the absorbent holder and seal in the zip lock specimen bag.
6. Wrap the filled specimen bag in paper toweling and place in the Styrofoam container. Do not place the specimens directly on the ice pack.
7. Place the Styrofoam container and the completed Patient Information Form within the cardboard mailing sleeve.
8. Prepare the package for shipping, applying packing tape as needed. Complete the sender portion of the return FedEx Airbill. Ship specimens priority overnight delivery the same day as collected.
9. Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location. **Please e-mail [redacted] or call [redacted] to notify the laboratory when specimens are being shipped.** The samples in prepared kits should be shipped to the following:

[redacted]

Patient Information Form

Specimen Date: / /
Institution/Affiliate:
Physician:
Patient Initials (last name, first name):
Hospital ID:
Study Number #: MC138E

Contact Person:
Institution:
Address:
City State Zip
Phone #:
FAX #:

Please circle the time-point being shipped at this time:

1. Baseline
2. Day 15 *visit*
3. Day 43 *visit*

Any questions concerning these samples or to obtain blood collection kits for the MC138E study, please contact:

[redacted]

Affiliates who anticipate participating in this study should please call in advance for kits