Hackensack University Medical Center
John Theurer Cancer Center

Trial Title

PHASE II CLINICAL PROTOCOL FOR THE TREATMENT OF PATIENTS WITH PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA WITH FOUR OR SIX CYCLES OF FLUDARABINE AND CYCLOSPHOSPHAMIDE WITH RITUXIMAB PLUS LENALIDOMIDE FOLLOWED BY LENALIDOMIDE CONSOLIDATION/MAINTENANCE

Trial ID Numbers
Celgene Reference No.: RV_CLL_PI_0530

Trial Drug
Lenalidomide (Revlimid®)

IND #: 112004

Support Provided By
Celgene Corp.

Sponsor Investigator
Andre Goy, MD
John Theurer Cancer Center
Hackensack University Medical Center
92 Second Street
Hackensack NJ 07601

Medical Monitor & Sponsor Contact:
Andre Goy, MD Phone # 551-996-3033

Primary Research Nurse Coordinator: Marisa Valentinetti, RN
Contact Phone # 551-996-8073

Regulatory Contact:
William Marrero BS, CCRP wmarrero@hackensackUMC.org

Data Management contact:
Mary Morin marymorin@hackensackUMC.org

Final Protocol Versions/ Dates:
May 11, 2011 Original
September 14, 2011 Amendment 1
December 18, 2011 Amendment 2
March 2, 2012 Amendment 3
April 2, 2012 Amendment 4
June 22, 2012 Amendment 5
March 14, 2014 amendment 6 PI change only

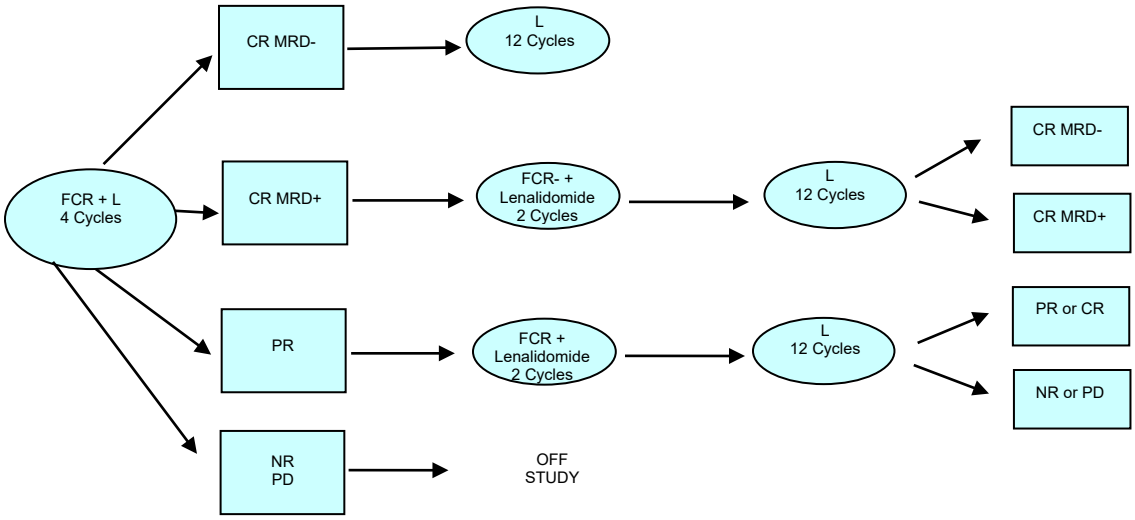
Protocol Synopsis

PROTOCOL TITLE: PHASE II CLINICAL PROTOCOL FOR THE TREATMENT OF PATIENTS WITH PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA WITH FOUR OR SIX CYCLES OF FLUDARABINE AND CYCLOSPHOSPHAMIDE WITH RITUXIMAB PLUS LENALIDOMIDE FOLLOWED BY LENALIDOMIDE CONSOLIDATION/MAINTENANCE	
DATE PROTOCOL FINAL:	June 22, 2012
INDICATION:	Untreated CLL
STUDY PHASE:	2
BACKGROUND AND RATIONALE: In previously-untreated subjects with CLL, fludarabine and rituximab with or without cyclophosphamide (FR or FCR) produces complete responses (CR) of 40-80%. The objective of this study is to evaluate the minimal residual disease (MRD) complete response rate (using the 2008 IWCLL guidelines) after 4 cycles of FCR plus lenalidomide in subjects with previously untreated CLL. Lenalidomide is active in frontline treatment of CLL as well as in patients with refractory disease. MRD has been demonstrated to be a sensitive surrogate marker for progression-free survival. If patients are MRD negative complete responders (CR) they will stop at 4 cycles of FCR followed by the lenalidomide consolidation/maintenance arm of the study. If they have a MRD positive CR or partial response (PR) they will continue with 2 additional cycles of FCR plus lenalidomide followed by lenalidomide consolidation/maintenance. They will be re-tested for MRD after the 6th cycle of FCR- and after 6 and 12 months of lenalidomide monotherapy. If they have no response (NR) or progressive disease (PD) following 4 cycles of FCR- plus lenalidomide they will be removed from the study.	
STUDY OBJECTIVES: Primary: The primary objective is to evaluate the complete response rate following 4 cycles of FCR plus lenalidomide in previously untreated patients with CLL. Secondary: The first secondary objective is to evaluate the toxicity of patients with previously untreated CLL treated with FCR plus lenalidomide, followed by lenalidomide. The second is to evaluate the overall response rate and overall survival of patients with previously untreated CLL treated with FCR plus lenalidomide followed by lenalidomide. The third is to determine if two additional cycles of FCR plus lenalidomide after 4 cycles will convert patients with a PR to CR and patients with a CR MRD + to CR MRD -. The fourth objective is to determine whether adding lenalidomide as a consolidation/maintenance therapy will eliminate bone marrow minimal residual disease in CR patients and whether	

patients who have a PR after 6 cycles of FCR plus lenalidomide will respond to 12 months of lenalidomide. The final objective is to determine whether the expression of ZAP-70, CD38, and chromosomes correlate with response rate, duration of response, and survival for previously untreated patients with CLL.

STUDY DESIGN:

2-stage phase 2 study-design. 19 subjects are treated in stage-1 with FCR plus 5mg lenalidomide increasing to 10mg and 15mg in subsequent cycles depending on toxicity. If there are at least 5 CRs after 4 cycles of FCR plus lenalidomide the study will accrue an additional 35 subjects (see statistical section). A secondary objective of this study will be to determine if MRD positive patients will become MRD negative with lenalidomide consolidation/maintenance and whether PR patients will convert to CRs. Lenalidomide will begin 2 months after the last dose of FCR in all subjects with CR. It may begin as soon as 1 month after FCR plus lenalidomide in subjects with PR. Lenalidomide is given in 28 d cycles increasing the dose from 5 mg/d to 10 mg/d in cycle 2 and to 15mg in cycles 3-6 if well- tolerated (no grade-3 or -4 toxicity). Patients with creatinine clearance ≥30ml/min and <60ml/min will start at 5 mg every other day increasing to 5 and 10mg daily in subsequent cycles . Reduction to the prior dose is allowed for grade-3/-4 toxicity. MRD will be studied by flow cytometry from bone marrow and peripheral blood samples following 4 and 6 cycles of FCR- and after 6 and 12 months of lenalidomide in CR patients.



STUDY ENDPOINTS

Primary:

Analysis of the Primary Endpoint: The complete responses will be estimated by the number of patients with CR divided by the total number of evaluable patients. Ninety-five percent confidence intervals for the true CR will be calculated.

Toxicity:

All toxicities that were determined to be possibly, probably or definitely related to the treatment will be tabulated according to grade and type (according to the NCI Common Toxicity Criteria, Version 4.0). The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns.

Secondary:

Analysis of the other Secondary Endpoints: The overall response rate will be estimated by the number of patients with complete and partial responses divided by the total number of evaluable patients. Ninety-five percent confidence intervals

for the true success proportion will be calculated. Responses will be evaluated after 4 and 6 cycles of FCR plus lenalidomide and after 6 and 12 cycles of lenalidomide consolidation/maintenance. The overall survival (OS) is defined as the time interval between the treatment starting date and the documented date of death. For a surviving patient, OS is censored at the last follow-up date when the patient is documented to be alive. Progression-free survival (PFS) is defined as the time interval between the treatment starting date and the documented date of disease progression or death, whichever occurs first. For an alive and progression free patient, PFS is censored at the last follow-up date when patient is documented to be progression free. The OS and PFS will be estimated by the Kaplan-Meier method. The median survival and the corresponding 95% confidence interval will also be reported. However, given the small sample size, these estimates will be largely exploratory in nature. The relation of these endpoints to the expression of ZAP-70, CD38, IgVH status and chromosomes will be explored by standard group comparison methods or proper regression methods.

Monitoring:

The principal investigator(s) and the study statistician will review the study periodically to identify accrual, toxicity, and any endpoint problems that might be developing. This study will be monitored according to the data and safety monitoring plan that is currently in place, and if necessary will report to the HUMC Data and Safety Monitoring Board for review.

STUDY DURATION: 24 months

TOTAL SAMPLE SIZE: 54

Stage 1: 19

Stage II: 35

DOSING REGIMEN(S):

Induction Phase: (28 day cycles)

NOTE: Lenalidomide starting dose recommendations for Cycle 1 for calculated creatinine clearance ≥30ml/min and <60ml/min*

Cycle 1	Fludarabine	20mg/m^2 IV days 2-4
	Cyclophosphamide	150mg/m^2 IV days 2-4
	Rituximab	375mg/m^2 IV day 1
	Rituximab	500 mg/m^2 IV day 14 +/- 2 days
	Pegylated G-CSF*	6mg ≥ 24 hours after last dose of chemotherapy
	Lenalidomide	5mg po days 8 – 28
Cycle 2	Fludarabine	20mg/m^2 IV da□s 1-3
	Cyclophosphamide	150mg/m^2 IV days 1-3
	Rituximab	500mg/m^2 IV day 1 & 14 +/- 2 days
	pegylated G-CSF	6mg 24 hours after last dose of chemotherapy
	Lenalidomide	10mg days 8-28 if no grade 3 or 4 toxicity at the 5mg dose. Dose may be adjusted down for grade 3/4 toxicity

DRUG SUPPLIES:

For study participants, Celgene Corporation will provide lenalidomide at no charge through RevAssist Program.

Cycle 3-6	Fludarabine	20mg/m^2 IV days 1-3
	Cyclophosphamide	150mg/m^2 days 1-3
	Rituximab	500mg/m^2 day 1 & 14 +/- 2 days
	Pegylated G-CSF	6mg 24 hours after last dose of chemotherapy
	Lenalidomide	15mg days 8-28 if no grade 3 or 4 toxicity at the 10mg dose. Dose may be adjusted down for grade 3/4 toxicity

Consolidation Phase for CR only Begins 2 months after last dose of FCR plus lenalidomide in all CR patients (MRD– after 4 cycles FCR, MRD+ after 6 cycles) Maximum of 12 cycles NOTE: Lenalidomide starting dose recommendations for Cycle 1 for calculated creatinine clearance ≥30ml/min and <60ml/min*		
Cycle 1	Lenalidomide	5mg PO days 1-28 of 28 day cycle
Cycle 2	Lenalidomide	10mg PO days 1-28 of 28 day cycle if no grade 3/4 toxicity in cycle 1, Dose may be adjusted down for grade 3/4 toxicity
Cycles 3-12	Lenalidomide	15mg PO days 1-28 of 28 day cycle if no grade 3/4 toxicity in cycle 2, Dose may be adjusted down for grade 3/4 toxicity

Consolidation Phase for PR only Begins 1-3 months after last dose of FCR plus lenalidomide in all PR patients Maximum of 12 cycles NOTE: Lenalidomide starting dose recommendations for Cycle 1 for calculated creatinine clearance ≥30ml/min and <60ml/min*		
Cycle 1	Lenalidomide	5mg PO days 1-28 of 28 day cycle

Cycle 2	Lenalidomide	10mg PO days 1-28 of 28 day cycle if no grade 3/4 toxicity in cycle 1 Dose may be adjusted down for grade 3/4 toxicity
Cycle 3-12	Lenalidomide	15mg PO days 1 – 28 of 28 day cycle if no grade 3/4 toxicity in cycle 2. Dose may be adjusted down for grade 3/4 toxicity

*** Dosing of lenalidomide will begin at 5 mg every other day, days 8-28 in cycle 1 for patients with creatinine clearance of ≥ 30 ml/min and ≤ 60 ml/min. Dose increase to 5mg daily, days 8-28 in cycle 2 and 10mg daily, days 8-28 in cycles 3-12 if no grade 3/4 toxicity. Dose may be adjusted down for grade 3/4 toxicity. During induction, lenalidomide schedule is days 8-28, and during consolidation, lenalidomide schedule is days 1-28.**
****an alternative to pegylated G-CSF is filgrastim 5 mcg/kg sc (see paragraph 6.3.1)**

1.0 INTRODUCTION

1.1. Disease Background

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in the Western world. It is generally considered to be incurable with conventional doses of chemotherapy. Until recently there has been little enthusiasm for more aggressive approaches to this often indolent disease. However, with the advent of purine analogues and the high complete remission rates they bring, new interest has been kindled in the management of this disorder.

The annual incidence of CLL in the United States is approximately 10,000 cases/year (1). CLL is considered to be a disease of advanced age. The median age of patients at diagnosis is 72. However, increasingly younger patients are being diagnosed with this disorder (2). CLL is more common in males than in females (3). With the advent of “routine” blood tests, many patients are now being diagnosed while still asymptomatic. The most common complaints of symptomatic patients are fatigue, weight loss, fevers, frequent bacterial and viral infections, and increased tendency to bleed. On physical examination lymphadenopathy and splenomegaly are often found. Laboratory evaluation reveals an excess of mature appearing lymphocytes in the peripheral blood. These leukemic cells have a phenotypically abnormal, but characteristic, B cell immunophenotype. The patient may also have thrombocytopenia and anemia.

The diagnosis of CLL is made by a combination of morphologic and immunophenotypic criteria. Different diagnostic criteria have been set forth by several organizations. The National Cancer Institute-sponsored working group produced guidelines for CLL clinical protocols. Their diagnostic criteria require that leukemic cells appear mature (morphologically resembling small lymphocytes) and that no more than 55% be prolymphocytes. The leukemic cells express an abnormal phenotype characteristic of CLL: co-express B cell antigens, such as CD19 and CD20, with CD5 the T-cell antigen and have low density CD20 and slg on the cell surface. Other criteria include a minimal absolute lymphocyte count of 5,000/mm3, a bone marrow aspirate demonstrating ~ 30% of all nucleated cells are lymphoid, and the exclusion of other lymphoproliferative disorders (4).

The Rai staging criteria, as originally proposed, grouped patients on the presence or absence of lymphadenopathy (Stage I), splenomegaly and/or hepatomegaly (Stage II), anemia (Stage III), or thrombocytopenia (Stage IV). Patients

with only a lymphocytosis were classified Stage 0 (5). The original Rai system was later modified to reduce the number of stages from five to three, without altering its prognostic capabilities (6).

Patients with a good prognosis (Rai Stage 0) have a median survival of more than 12.5 years while intermediate risk patients (Rai Stage I and II) have worse prognosis with a median survival of less than 8 years. High risk patients (Rai Stage III and IV) have an expected survival of between 1.5 and 2.5 years (5, 7).

Other prognostic indicators include: absolute blood lymphocyte count, bone marrow histological patterns, cytogenetics, lymphocyte doubling time (LDT), lactate dehydrogenase levels, beta-2 microglobulin, lymphocyte morphological subtypes, age, sex, and response to treatment (8, 9). Patients with LDT of 12 months or less have a significantly worse prognosis than patients with a longer LDT (10). Somatic hypermutation of immunoglobulin heavy chain variable region (IgVH) genes is seen in about 50% of patients and have a more favorable prognosis compared to patients who have leukemic cells with unmutated IgVH genes (11-14). Expression of ZAP-70 is associated with IgVH mutations , with ZAP-70 expression often correlated with unmutated IgGVH, and may also be an independent prognostic marker (15). Trisomy 12 and 17p (p53) chromosomal deletion also correlated with poor prognosis (16-18). Expression of CD38 on CLL cells has also been associated with a poor prognosis(19).

While partially related to stage, the pattern of infiltration of the bone marrow reflects the total burden of disease. Patients with a diffuse pattern (vs. nodular or interstitial) have a less favorable prognosis (20, 21). A high absolute blood lymphocyte count, high LDH, older age, male gender, increased percentage of prolymphocytes, and poor response to treatment also portend a poor prognosis. These prognostic indicators are more useful in early stage disease where there appears to be a subgroup of patients who have prolonged periods without disease progression. Efforts have been made to define a group of patients with “smoldering CLL” who have a prognosis that approximates that of the general population. Criteria that have been identified include peripheral blood lymphocyte doubling time greater than 12 months; non-diffuse bone marrow infiltration; absolute lymphocyte count <30 x 109/mm3 and hemoglobin >13 g/dL (8, 22).

1.2. Treatment

As CLL remains largely an incurable disease, treatment will usually be initiated with palliative intent, and therefore, should not necessarily begin at the time of diagnosis. Studies to date have not demonstrated an improvement in survival with early intervention when compared to treating later in the course of the disease (23). In general, treatment should begin when the patient becomes symptomatic or there is evidence of frank progression of disease. As outlined above, symptoms include fever, excessive fatigue, weight loss, and symptomatic enlargement of either lymph nodes or spleen. These symptoms are all relative indications for treatment and the urgency for initiating therapy will depend on the magnitude of the symptoms. For instance, minor well-tolerated lymphadenopathy does not mandate treatment. Infections are common in CLL and, consequently, may not necessarily be an indication to start cytotoxic therapy. In fact, patients having difficulty with recurrent infections as a consequence of disease-induced hypogammaglobulinemia may benefit from infusional therapy with intravenous gamma globulin. However, impaired bone marrow function, as evidenced by anemia, thrombocytopenia, or granulocytopenia caused by marrow infiltration by malignant cells definitely warrants specific treatment. Other life-threatening events include lymphadenopathy that compromises vital organs, autoimmune destruction of either platelets or red cells, and transformation of the CLL to a more aggressive malignancy. Finally, if patients are considering enrollment in an investigational therapeutic trial (e.g., bone marrow transplantation following cytotoxic therapy), treatment might be initiated earlier.

Previously, chlorambucil has been considered the standard treatment for CLL. This choice has come about after initial studies demonstrated improved response rates but no improvement in survival for chlorambucil and prednisone over single agent chlorambucil alone. Subsequent trials comparing chlorambucil and prednisone to other forms of combination chemotherapy (COP, CVP, CMP, CHOP) failed to demonstrate a significant improvement in survival with these more intensive and toxic regimens, even though they were able to demonstrate improved response rates (10, 22, 24, 25-27). The standard treatment recommendations are again being challenged with the advent of the nucleoside analogues.

Fludarabine appears the most promising of this new class of drugs. Fludarabine monophosphate is the 2-fluoro, 5’-phosphate derivative of the anti-leukemic agent 9-B-D-arabinofuranosyl adenine (ara-A). Its intracellular metabolic product F-ara-ATP suppresses DNA synthesis by inhibiting ribonucleotide reductase and DNA polymerase alpha.

Grever et al. demonstrated the activity of fludarabine in previously treated CLL patients. Greater than 50% of the patients showed clinical improvement (28). Subsequent reports confirmed the activity of this agent in CLL (29). Response rates in previously untreated patients approximate 70% (29, 30). In addition, a preliminary report of a randomized clinical trial comparing chlorambucil with fludarabine indicates a superior complete response rate with fludarabine (27% vs. 3%) but was not associated with improved survival (31).

There is limited experience of multidrug combination therapies involving fludarabine in CLL. While the addition of prednisone to chlorambucil may increase the response rates when compared to the single agent, there was no advantage to adding prednisone to fludarabine (32). There is also a report of an increase in atypical infections, predominantly listeriosis or Pneumocystis carinli pneumonia (PCP), in patients treated with fludarabine in combination with prednisone (32, 33). These infections have not been noted to the same extent in patients who were treated with fludarabine alone.

There is laboratory data to suggest that fludarabine and cyclophosphamide is a worthwhile combination with synergistic tumor killing when leukemia cells taken from patients with CLL are exposed to this combination in vitro (NCI Consensus conference). In a thymidine uptake assay, these investigators have demonstrated that the DNA repair that normally occurs after exposure to cyclophosphamide is blocked by the fludarabine. Fludarabine is known to inhibit DNA polymerase which is needed for DNA repair. Studies have shown enhanced cytotoxicity of alkylating agents and decreased DNA repair with other nucleoside analogs (34, 35). Clinical stuides have documented activity of FC (36, 37).

Rituximab as a single agent has modest activity in CLL (38-42). No dose-limiting effects were observed in Phase I/II studies. Reported adverse events including fever, chills, headache, nausea, vomiting, rhinitis, and mild hypotension, occurred primarily during rituximab infusions and typically responded to an interruption of the infusion and resumption at a slower rate. Other adverse events included neutropenia, thrombocytopenia and asthenia.

Patients with preexisting cardiac conditions, including arrhythmia and angina, have had recurrences of these cardiac events during rituximab infusions. Although rare, tumor lysis syndrome has been reported in postmarketing studies and is characterized in patients with a high number of circulating malignant cells (>25,000 ul) by rapid reduction in tumor volume, renal insufficiency, hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia. In rare cases, severe and fatal cardiopulmonary events, including hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock have occurred (4-7/10,000 patients or 0.04-0.07%.) Nearly all fatal infusion-related events occurred in association with the first infusion. The following immune serious adverse events have been reported to occur rarely (<0.1%) in patients following completion of rituximab infusions: arthritis, disorders of blood vessels (vasculitis, serum sickness and lupus-like syndrome), lung disorders including pleuritis and scarring of the lung (bronchiolitis obliterans), eye disorders (uveitis and optic neuritis), and severe bullous skin reactions (including toxic epidermal necrolysis and pemphigus) that may result in fatal outcomes. Patients may have these symptoms alone or in combination with rash and polyarthritis.

Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of rituximab and approximately one month after the last dose. A direct causal relationship between rituximab and HBV viral reactivation has not been established.

The combination of fludarabine and rituximab demonstrated excellent responses in a phase 2 randomized study of 104 patients. There were 28% and 47% complete responses in the sequential and combined arms respectively (58). Combining rituximab with fludarabine and cyclophosphamide suggest that the three drug combination has ever greater activity in patients with CLL than the combination of fludarabine and cyclophosphamide or fludarabine and rituximab. Data from the M. D. Anderson Cancer Center report complete responses of 58% and overall responses of 94% (59). These data were confirmed by the German CLL Study Group (GCLLSG) and FCR was approved by the US FDA for the treatment of CLL in the front line setting and for patients with relapsed/refractory disease (60). Recent data published by Foon *et al,* suggest that low dose fludarabine and cyclophosphamide can be combined with rituximab to minimize hematologic toxicity with a comparable response rate and duration of response to standard dose FCR (74).

Lenalidomide, a thalidomide analogue, is an immunomodulating drug with antitumor activity approved by the USFDA for the treatment of myelodysplastic syndrome and multiple myeloma.(43-47) Lenalidomide downregulates tumor necrosis factor-ά(48), alters tumor microenvironment(49), activates T cells(50, 51), enhances antibody-dependent cytotoxicity(50, 52), and upregulates select tumor suppressor genes.(53) Forty-five relapsed/refractory CLL patients were treated with 25mg of daily oral lenalidomide days 1 through 21 of a 28 day cycle.(54) The overall response rate was 47% with 9% complete responses. Grade 3/4 fatigue, thrombocytopenia and neutropenia were seen in 10%, 45% and 70% of patients, respectively. A flare reaction consisting of pain, swelling and erythema at the sites of disease was seen in 58% of patients and was grade 3/4 in 8%. Onset was typically within 24 hours of the first dose with a median duration of 14 days. In another study, 44 relapsed/refractory patients were treated with lenalidomide at 5mg daily with dose escalation up to 25mg daily.(55) An overall response rate of 32% with 7% complete remissions. Myelosuppression was the most common toxicity with grade 3/4 neutropenia in 41% of courses and grade 3/4 thrombocytopenia in 16% of courses. Tumor flare reactions were seen in 10% of courses which responded to a 6 day course of steroids. In another study four patients with relapsed CLL treated with lenalidomide at 25mg/day had unacceptable toxicity with severe tumor flare in 3 patients and sepsis and renal failure in the fourth.(56) Lenalidomide has also been studied in previously untreated CLL patients. Two preliminary reports initiated single agent therapy at 5 and 5mg daily with dose escalation to 25mg daily for 21 days of a 28 day cycle.(56, 57) Partial responses were reported in 65% of patients in one study (57) and 54% in the other study(56). Toxicity were manageable myelosuppression and tumor flare in both studies.

Due to activity demonstrated in the relapsed / refractory setting as well as its proposed novel mechanisms of activity, lenalidomide has been studied in combination in the relapsed/refractory and front line settings with promising results. Lenalidomide has been studied in combination with fludarabine and rituximab in two recent studies. In one study toxicity was excessive when lenalidomide began on day 1 of chemo-immunotherapy (61) however in another Phase I/II study when the lenalidomide was initiated on day 8 of the cycle, toxicity was acceptable (62) and activity was notable. When lenalidomide was initiated on day 8 of therapy in combination with FR the ORR was 83% in 6 patients. Lenalidomide has also been studied in combination with cyclophospamide and fludarabine in the relapsed setting (FCL). Using the FCL regimen, lenalidomide was given on days 1-14 of each cycle with an ORR of 67% and a maximum tolerated dose of lenalidomide of 5mg (63) per day.

Our expectations of therapy in CLL have increased because the more active regimens have shown that CR with eradication of MRD is possible. MRD-negative remissions have been observed after auto-HSCT, (64) alemtuzumab (65) and chemotherapy (66). In all of these series, MRD-negative patients survive longer than MRD- positive patients.

Quantitative assessment of MRD in 471 patients in the CLL8 trial receiving FC or FCR has provided additional insight into the clinical significance of MRD (67). Four-color flow cytometry showed that a low MRD was correlated with longer PFS regardless of treatment. The FCR regimen had lower median MRD compared with FC, resulting in longer PFS. Several clinical studies have also suggested that eradication of MRD may improve PFS, treatment-free survival and possibly OS (59,66,68),

Another issue that has not been addressed is length of treatment required with the FCR regimen. Two trials have addressed dose of FCR suggesting that lower doses may be better tolerated and maintain efficacy (69, 70). Decreasing the cycles of FCR may be possible with similar efficacy. In this trial we will decrease the cycles of FCR from 6 to 4 in patients who are in CR and are MRD negative after 4 cycles.

In this proposed trial to minimize the potential for hematologic toxicity, FCR will be combined with lenalidomide using the schedule proposed by Foon *et al* (74). Cycle 1 will include rituximab given slowly on day 1 at 375 mg/m^2 and 500 and 500 mg/m^2 on day 14 while fludarabine will be given at 20 mg/m^2 and cyclophosphamide at 150 mg/m^2 on days 2-4. The fludarabine and cyclophosphamide will be given at the above doses every four weeks on days 1-3, immediately preceded by rituximab. Additionally rituximab will be administered at 500 mg/m^2 (cycle 2-6) with subsequent cycles. Based on previous work, lenalidomide will begin in cycle 1 days 8 – 28 at a 5mg dose to be escalated to 10mg in cycle 2 and a maximum of 15mg in cycles 3 - 6 if there was no grade 3 or 4 toxicity at the prior dose. Following FCR patients will receive 12 months of lenalidomide. FISH panel will include the common recurrent CLL genetic abnormalities including 11q, 6q, trisomy 12, 13q, and 17p (p53). All patients will have bone marrow aspirations and biopsies to determine bone marrow infiltration for prognosis. Flow cytometry will be used to study bone marrow and peripheral blood for minimal residual disease.

2.0 RATIONALE

We and others have used 6 cycles of chemoimmunotherapy for previously untreated CLL patients (59, 68, 69). There exists no data regarding reducing the cycles of chemoimmunotherapy to reduce exposure to cytotoxic agents and minimum data combining lenalidomide sequentially in the induction therapy. All of the patients who entered a CR responded quickly yet none of the studies to date have carefully evaluated patients for response prior to the completion of 6 cycles. We believe that many patients will enter a CR after only 4 cycles of FCR plus lenalidomide, and we expect that many of these patients will be bone marrow MRD negative.

The secondary objective of this study is the effect of lenalidomide following FCR plus lenalidomide. For patients who enter a CR they will have bone marrow MRD multi-color flow cytometry after completing FCR plus lenalidomide. If they are CR MRD negative after 4 cycles of FCR they will receive 12 cycles of lenalidomide. If they are CR MRD+ they will have two more cycles of FCR plus lenalidomide followed by repeat bone marrow & peripheral blood MRD studies followed by 12 cycles of lenalidomide. One month after the 6th and 12th cycles of lenalidomide they will be retested for MRD. For patients who are PRs after 4 cycles of FCR plus lenalidomide they will receive 2 additional cycles of FCR plus lenalidomide. They may begin lenalidomide as soon as 1 month post FCR and lenalidomide and may receive up to 12 cycles at the discretion of the investigator. We expect lenalidomide will eradicate MRD in MRD+ CR patients and a proportion of the PR patients should respond to lenalidomide. The International Workshop on CLL criteria for treatment initiation and evaluation of response will be used in this study (71).

3.0 OBJECTIVES

3.1. Primary:
To evaluate the complete response rate after 4 cycles of FCR plus lenalidomide in patients with previously untreated CLL.

3.2. Secondary:

3.2.1. To determine whether an additional 2 cycles of FCR plus lenalidomide will eliminate bone marrow minimal residual disease detected by 4 color flow cytometry.

3.2.2. To determine whether 12 cycles of lenalidomide consolidation/maintenance will eliminate MRD in MRD+ CR patients.

3.2.3. To determine whether patients who have a PR following 4 cycles of FCR- plus lenalidomide improve their responses after 2 additional cycles of FCR plus lenalidomide.

3.2.4. To determine if patients with a PR will respond to lenalidomide consolidation/maintenance after 6 cycles of FCR plus lenalidomide.

3.2.5. To evaluate overall response rate, progression-free survival and overall survival of patients with previously untreated CLL treated with FCR and lenalidomide followed by lenalidomide.

3.2.6. To evaluate the toxicity of patients with previously untreated CLL treated with FCR and lenalidomide followed by lenalidomide.

3.2.7. To determine whether the expression of ZAP-70, CD38, and chromosomes, correlate with response rate, duration of response, and survival for previously untreated patients with CLL.

3.2.8. To determine whether lenalidomide will enhance immune recovery following FCR plus lenalidomide.

3.2.9. To determine the transfusion requirement for patients while receiving this regimen.

3.2.10. To determine the frequency of second malignancies among patients receiving this regimen.

4.0 TRIAL POPULATION

Between 19 and 54 previously untreated CLL subjects will participate in this trial. All subjects must meet the following criteria for eligibility; no waivers for this protocol will be provided for eligibility

4.1. Inclusion Criteria

4.1.1. **Patients must have diagnosis of CLL (as defined by the NCI Criteria below:**

- Patients must have peripheral blood absolute lymphocyte count of >5,000/mm^3 obtained within 2 weeks prior to start of study.
- The lymphocytosis must consist of small, mature lymphocytes, with ≤55% (not greater than 55%) prolymphocytes.
- Patients must have phenotypically characterized CLL as defined as:
  - **a)** The predominant population of cells share B-cell antigens with CD5 in the absence of other pan-T-cell markers (CD3, CD2, etc.);
  - **b)** Surface immunoglobulin (slg) and CD20 with low-cell surface density expression.
  - **c)** **If surface immunoglobulin can be demonstrated, the leukemic cells are restricted to expression of either kappa or lambda.**
- Splenomegaly, hepatomegaly or lymphadenopathy are not required for the diagnosis of CLL.

4.1.2. Patients must require chemotherapy. Indications for chemotherapy are listed below-

4.1.2.1. one or more of the following disease related symptoms are required :

- **a)** Weight loss >10% within the previous 6 months
- **b)** Fevers of greater than 100.0° F for 2 weeks without evidence of infection.
- **c)** Night sweats without evidence of infection. Evidence of progressive marrow failure as manifested by the development of or worsening of anemia (<10g/dL) and/or thrombocytopenia (< 100,000/mm^3).
- **d)** Massive (i.e., > 6 cm below left costal margin) or progressive splenomegaly
- **e)** Massive nodes or clusters (i.e., >5cm in longest diameter) or progressive adenopathy. Progressive lymphocytosis with an increase of >50% over 2 month period, or an anticipated doubling time of less than 6 months.

4.1.3. Patients must not have received prior treatment cytotoxic, immunotherapy or investigational therapy.

4.1.4. Patients must not have history of corticosteroid treatment for CLL, Autoimmune thrombocytopenia, or autoimmune hemolytic anemia.

NOTE: Marked hypogammaglobulinemia or the development of a monoclonal protein in the absence of any of the above criteria for active disease are not sufficient for protocol therapy.

4.1.5. Calculated creatinine clearance ≥30ml/min by Crockcroft-Gault formula (see Appendix VI)

4.1.6. Bilirubin must be ≤1.5mg/dl, unless secondary to tumor, obtained within 2 weeks prior to registration.

4.1.7. Platelets ≥75x10^9/L, unless due to CLL involvement of bone marrow (within 2 weeks of registration).

4.1.8. Neutrophils ≥1.5x10^9/L, unless due to CLL involvement of bone marrow (within 2 weeks of registration).

4.1.9. AST or ALT < 2x upper limit of normal, unless related to CLL (within 2 weeks of registration).

4.1.10. Age ≥18 years.

4.1.11. ECOG performance status 0-2

4.1.12 Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days and again within 24 hours prior to starting Cycle 1 of lenalidomide (prescriptions must be filled within 7 days as required by RevAssist) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. . See Appendix: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

4.1.13. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. See Appendix: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

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

4.1.15. Subject must provide written informed consent.

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

4.2. Exclusion Criteria

4.2.1. Patients with autoimmune hemolytic anemia or autoimmune thrombocytopenia are not eligible.

4.2.2. No prior immunotherapy, investigational or cytotoxic chemotherapy.

4.2.3. Patients with a history of steroid treatment for CLL/SLL autoimmune hemolytic anemia, or autoimmune thrombocytopenia are not eligible

4.2.4. Patients with active infections requiring oral or intravenous (IV) antibiotics until resolution of the infection and completion of therapeutic antibiotics.

4.2.5. Women of childbearing potential and sexually active males who both refuse to use an accepted and effective method of contraception or women who are breastfeeding.

4.2.6. Patients with a second malignancy other than basal cell carcinoma or squamous cell carcinoma of the skin or *in situ* carcinoma of the cervix are not eligible unless the tumor was treated with curative intent at least two years previously.

4.2.7. History of known HIV

4.2.8. History or presence CNS disease (CLL)

4.2.9. History or presence of any comorbidity or psychiatric condition that, in the opinion of the investigator, would make compliance with the protocol difficult or place the subject at undue risk.

4.2.10. New York Heart Classification III or IV heart disease.

4.2.11. Hepatitis BsAg or Hepatitis C positive. Patients who are seropositive because of hepatitis B virus vaccine are eligible.

4.2.12. Known hypersensitivity to thalidomide.

4.2.13. Evidence of laboratory TLS by Cairo-Bishop definition of Tumor Lysis Syndrome (see Appendix V). Subjects may be enrolled upon correction of electrolyte abnormalities.

4.2.14. Patients must not have received prior treatment cytotoxic, immunotherapy or investigational therapy.

4.2.15. Patients must not have history of corticosteroid treatment for CLL, Autoimmune thrombocytopenia, or autoimmune hemolytic anemia.

5.0 REGISTRATION

After informed consent has been obtained patients will be registered at Hackensack University Medical Center.

Once eligibility has been confirmed by site, eligibility worksheets must be completed prior to initiating therapy.

6.0 TRIAL DESIGN

A cycle is defined as 28 days. Patients will receive treatment as outlined in section 6.1.

6.1. Treatment Plan

Induction: *One cycle = 28 days*

Cycle	Day	Dosing
Cycle 1	Day 1	Rituximab IV 375mg/m^2 this dose may be given in divided doses; 50mg/m^2 on day 1, 100mg/m^2 on day 2, and 225mg/m^2 on day 3
	Day 14 +/- 2 days	Rituximab IV 500mg/m^2
	Days 2-4	Cyclophosphamide IV 150 mg/m^2 followed by fludarabine IV 20 mg/m^2
	Day 5	Neulasta SQ 6mg
	Days 8 - 28	Lenalidomide 5mg PO
Cycle 2	Day 1 & 14 +/- 2 days	Rituximab IV 500 mg/m^2
	Day 1-3	Cyclophosphamide IV 150 mg/m^2 followed by fludarabine IV 20 mg/m^2
	Day 4	Neulasta SQ 6mg
	Days 8 - 28	Lenalidomide 10mg PO (if no grade 3/4 toxicity is observed in cycle 1)
Cycle 3-6	Day 1 & 14 +/- 2 days	Rituximab IV 500mg/ m^2
	Day 1 – 3	Cyclophosphamide IV 150mg/ m^2 followed by fludarabine IV 20mg/ m^2
	Day 4	Neulasta SQ 6 mg
	Day 8-28	Lenalidomide 15mg PO (if no grade 3/4 toxicity is observed in cycle 2)
No dose adjustments will be permitted for Rituximab. *Note: Cycle 1 starting dose recommendations and escalations guidelines after Cycle 1 for calculated creatinine clearance ≥30ml/min and <60ml/min.*		

COMPLETE RESPONSE (CR)

Consolidation/Maintenance: *Begins 2 months after last dose of FCR plus lenalidomide*

Cycle	Day	Dosing
Cycle 1	Day 1-28	Lenalidomide 5mg PO
Cycle 2	Day 1-28	Lenalidomide 10mg PO (if no grade 3/4 toxicity is observed in cycle 1)
Cycles 3-12	Day 1-28	Lenalidomide 15mg PO (if no grade 3/4 toxicity is observed in cycle 2)

Note: Cycle 1 starting dose recommendations and escalations guidelines after Cycle 1 for calculated creatinine clearance ≥30ml/min and <60ml/min.

PARTIAL RESPONSE (PR)
Consolidation/Maintenance: *Begins 1-3 months after last dose of FCR plus lenalidomide in PR patients for a total of 12 cycles.*

Cycle	Day	Dosing
Cycle 1	Day 1-28	Lenalidomide PO 5mg
Note: Cycle 1 starting dose recommendations and escalations guidelines after Cycle 1 for calculated creatinine clearance ≥30ml/min and <60ml/min.		
Cycle 2	Day 1-28	Lenalidomide 10mg PO days (if no grade ¾ toxicity is observed in cycle 1)
Cycles 3-12	Day 1-28	Lenalidomide 15mg PO (if no grade 3/4 toxicity is observed in cycle 2)
Note: Lenalidomide dose may be adjusted down for grade 3 or 4 toxicity, see section 12.0 for dose modification guidelines. No dose adjustments will be permitted for Rituximab. If dose is not tolerable treatment should be discontinued.		

6.2. **Lenalidomide Starting Dose Modifications Based on Renal Function within 28 days prior to starting Lenalidomide and Rituximab or Single Agent Lenalidomide**

Baseline Calculated Creatinine Clearance (by Cockcroft-Gault)	Starting Lenalidomide Dose
≥ 60 ml/min	Follow treatment plan in Section 6.1
≥ 30 and < 60 ml/min	All treatment plans: Cycle 1 only 5mg every other day of a 28 day-cycle

Patients started with a reduced 5mg every other day lenalidomide dose due to baseline calculated creatinine clearance ≥ 30ml/min but < 60ml/min within 28 days prior to starting lenalidomide may, at investigator discretion, have their lenalidomide dose increased at the start of subsequent treatment cycles, if they tolerated the prior treatment cycle without requiring dose modifications, interruptions or delays due to toxicity. For patients who initiate therapy at a 5mg every other day lenalidomide dose may increase to 5mg daily in cycle 2 and 10mg daily in cycles 3-12 if no grade 3/4 toxicities are observed in prior cycles.

The lenalidomide dose may only be increased at the start of a new cycle of therapy, may only be increased once every 28 days (or less frequently), and may only be increased if the prior treatment cycle was completed without requiring dose modifications, interruptions or delays due to toxicity. The maximum allowable dose is lenalidomide 15mg daily on Days 1-28 of a 28-day cycle or 10 mg daily for patients with cc ≥ 30 ml/min and ≤ 60 ml/min.

6.3. **Supportive Care**
All supportive measures consistent with optimal patient care will be given throughout the study; modifications to supportive care medications outlined below are at the discretion of the treating physician and will not be considered protocol deviations.

6.3.1. Filgrastim, SC or peg-filgrastim should be initiated at least 24 hours following the completion of chemotherapy. Filgrastim should be continued until post-nadir counts are 10,000/mm^3. Filgrastim must be stopped 48 hours prior to the next cycle of chemotherapy regardless of the ANC.

6.3.2. PCP prophylaxis: Trimethoprim/sulfamethoxazole DS, one p.o. b.i.d can be given on Monday, Wednesday, and Friday starting with the first dose of chemotherapy and ending 6 months after last dose of chemotherapy. Pentamidine 4mg/kg IV q month is a suitable alternative to trimethoprim/sulfamethoxazole. Dapsone 100 mg daily is a suitable alternative to trimethoprim/sulfamethoxazole. To be started cycle 1 day 4.

6.3.3. Allopurinol 300mg PO daily for 14 days should be given starting seven days prior to the first dose of chemotherapy during the first and second cycle of chemotherapy and lenalidomide. This may be administered during subsequent cycles at the discretion of the treating physician.

6.3.4. Antiemetics: Prophylactic antiemetic medications such as granisetron 2 mg P0 30 minutes prior to fludarabine and cyclophosphamide infusions are recommended and are to be administered at the discretion of the treating physician.

6.3.5. Zoster prophylaxis (Acyclovir 400mg BID or equivalent) can be given from the start of therapy until 6 months after completing chemotherapy. To be started cycle 1 day 4.

6.3.6. Premedications: for Rituximab, Fludaraibine, and Cyclophosphamide should be given as per your institutional standard of care.

6.3.7. Candidiasis prophylaxis (fluconazole 200 mg daily PO or equivalent) can be given from the start of therapy until 6 months after completing chemotherapy. To be started cycle 1 day 4.

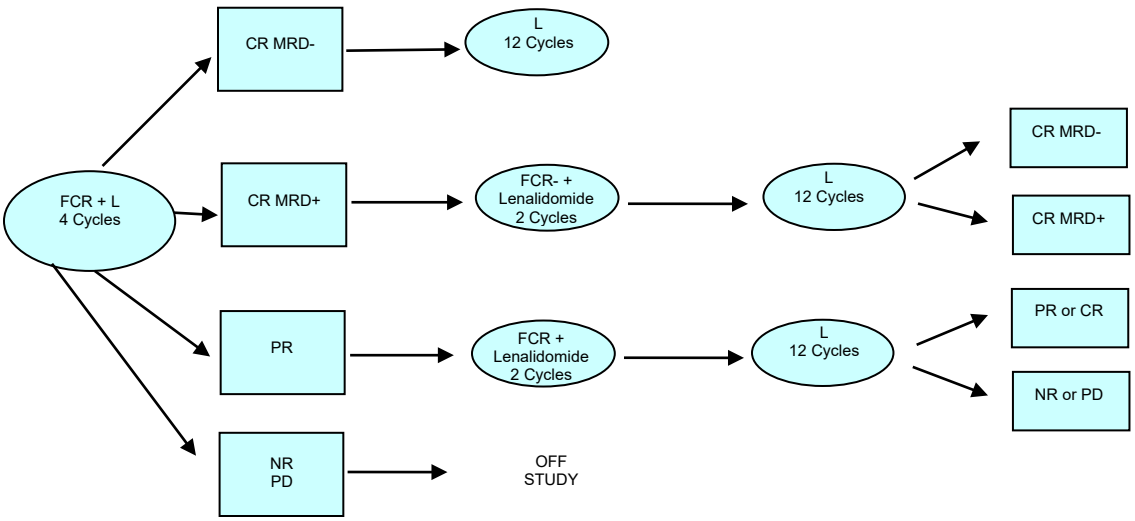
6.3.8. Ciprofloxacin 500mg BID for ten days or equivalent should be given for prophylactic neutropenic fever.

6.3.9. Rasburicase can be given at the discretion of the investigator.

6.3.10. DVT prophylaxis should be started on cycle 1 day 8 (aspirin 81mg PO daily unless contraindicated. If ASA is contraindicated use other DVT prophylaxis according to hospital guidelines.

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

6.4. Schema



7.0 STUDY DRUG

7.1. Rituximab

Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration. Rituximab is supplied at a concentration of 5mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for intravenous administration in 9.0 mg/mL sodium chloride, 7.35mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Sterile Water for injection. The pH is adjusted to 6.5.

7.1.1. Stability & Storage: Rituximab vials are stable at 2° to 8°C (36° to 46°F). Do not use beyond expiration date stamped on carton. Rituximab vials should be protected from direct sunlight.

The sponsor-investigator of the trial is responsible for the maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all trial drug in accordance with Code of Federal Regulations, institutional standard operating procedures and Genentech requirements.

7.1.2. Dosage & Administration:

Usual Dose: The approved and accepted dosage of rituximab is 500mg/m^2 given as an IV infusion once weekly for four doses (days 1, 8, 15, and 22). In this study rituximab is given at 375 mg/m^2 for only the day 1 dose and thereafter will be given at 500 mg/m^2. Refer to protocol section 6.0 for treatment design details. Rituximab may be administered in an outpatient setting. DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

Preparation for Administration: Use appropriate aseptic technique. Withdraw the necessary amount of rituximab and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride USP or 5% Dextrose in Water USP. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Rituximab solutions for infusion are stable at 2° to 8°C (36° to 46°F) for 24 hours and at room temperature for an additional 12 hours. No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

Administration: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Hypersensitivity reactions may occur. Premedications, consisting of acetaminophen and diphenhydramine, should be considered before each infusion of rituximab. Premedication may attenuate infusion-related events. Since transient hypotension may occur during rituximab infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to rituximab infusion.

Administration Guidelines for Adult Patient Population

First Infusion: The rituximab solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

Rituximab infusion should be interrupted for severe reactions. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100mg/hr to 50mg/hr) when symptoms have completely resolved. Treatment of infusion-related symptoms with diphenhydramine and acetaminophen is recommended. Additional treatment with bronchodilators or IV saline may be indicated. Most patients who have experienced non-life-threatening infusion-related reactions have been able to complete the full course of rituximab therapy. Epinephrine, antihistamines and corticosteroids should be available for immediate use in the event of a hypersensitivity reaction to rituximab (e.g., anaphylaxis).

Subsequent Infusions: Subsequent rituximab infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr as tolerated.

7.1.3. Over dosage

There has been no experience with over dosage in human clinical trials. Single doses higher than 500mg/m2 have not been tested in controlled studies.

7.1.4. Safety Profile

No dose-limiting effects were observed in the Phase I/II studies. Reported adverse events including fever, chills, headache, nausea, vomiting, rhinitis, and mild hypotension, occurred primarily during rituximab infusions and typically responded to an interruption of the infusion and resumption at a slower rate. Other adverse events included neutropenia, thrombocytopenia, asthenia, other hematologic events, cardiac and cardiopulmonary events, and tumor lysis syndrome.

Fatal Infusion Reactions: Severe and fatal cardiopulmonary events, including angioedema, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock, have been reported. These severe reactions typically occurred during the first infusion with time to onset of 30-120 minutes.

Mucocutaneous Reactions: Severe bullous skin reactions, including fatal cases of toxic epidermal necrolysis, have been reported rarely in patients treated with rituximab. Paraneoplastic pemphigus has been reported very rarely in NHL and CLL patients undergoing chemotherapy plus rituximab treatment. The onset of reaction has varied from 1 to 13 weeks following rituximab exposure.

Cardiac Events: Patients with preexisting cardiac conditions, including arrhythmia and angina, have had recurrences of these cardiac events during rituximab infusions.

Cardiopulmonary Events: In rare cases, severe and fatal cardiopulmonary events, including hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock, have occurred (4-7/10,000 patients or 0.04-0.07%.) Nearly all fatal infusion-related events occurred in association with the first infusion.

Renal Events: Rituximab has been associated with severe renal toxicity including acute renal failure requiring dialysis, and in some cases has lead to death. Renal toxicity has occurred in patients with high numbers of circulating malignant cells (>25,000/mm^2) or high tumor burden who experience tumor lysis syndrome.

Hematologic Events: In clinical trials, Grade 3 and 4 cytopenias were reported in 48% of patients treated with rituximab; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following Rituximab therapy were reported.

In addition, there have been a limited number of post marketing reports of prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia (defined as occurring 40 days after the last dose of rituximab) in patients with hematologic malignancies. In reported cases of late onset neutropenia (NCI-CTC Grade 3 and 4), the median duration of neutropenia was 10 days (range 3 to 148 days). Documented resolution of the neutropenia was described in approximately one-half of the reported cases; of those with documented recovery, approximately half received growth factor support. In the remaining cases, information on resolution was not provided. More than half of the reported cases of delayed onset neutropenia occurred in patients who had undergone a prior autologous bone marrow transplantation. In an adequately designed, controlled, clinical trial, the reported incidence of NCI-CTC Grade 3 and 4 neutropenia was higher in patients receiving rituximab in combination with fludarabine as compared to those receiving fludarabine alone (76% [39/51] vs. 39% [21/53]).

Tumor Lysis Syndrome: Although rare, tumor lysis syndrome has been reported in post marketing studies and is characterized in patients with a high number of circulating malignant cells (>25,000 ul) by rapid reduction in tumor volume, renal insufficiency, hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia.

Infectious Events: Rituxan induced B-cell depletion in 70% to 80% of patients with NHL and was associated with decreased serum immunoglobulins in a minority of patients; the lymphopenia lasted a median of 14 days (range, 1-588 days). Infectious events occurred in 31% of patients: 19% of patients had bacterial infections, 10% had viral infections, 1% had fungal infections, and 6% were unknown infections. Serious infectious events (Grade 3 or 4), including sepsis, occurred in 2% of patients.

Immunization: Response rates may be reduced with non live vaccines.

Hepatitis B Reactivation: Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately four months after the initiation of rituximab and approximately one month after the last dose.

Other Serious Viral Infections: The following additional serious viral infections, either new, reactivated or exacerbated, have been identified in clinical studies or postmarketing reports. The majority of patients received Rituxan in combination with chemotherapy or as part of a hematopoietic stem cell transplant. These viral infections included JC virus, progressive multifocal leukoencephalopathy [PML]), cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. In some cases, the viral infections occurred up to one year following discontinuation of Rituxan and have resulted in death.

Progressive Multifocal Leukoencephalopathy (PML): PML is a rare disease caused by the reactivation of latent JC virus in the brain. Immunosuppression allows reactivation of the JC virus which causes demyelination and destruction of oligodendrocytes resulting in death or severe disability. Rare cases of PML, some resulting in death, have been reported in patients with hematologic malignancies who have received rituximab. The majority of these patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Cases of PML resulting in death have also been reported following the use of rituximab for the treatment of autoimmune diseases. The reported cases had multiple risk factors for PML, including the underlying disease and long-term immunosuppressive therapy or chemotherapy. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab.

Physicians should consider PML in any patient presenting with new onset neurologic manifestations. Consultation with a neurologist, brain MRI, and lumbar puncture should be considered as clinically indicated. In patients who develop PML, rituximab should be discontinued and reductions or discontinuation of any concomitant chemotherapy or immunosuppressive therapy should be considered.

Bowel Obstruction and Perforation: Abdominal pain, bowel obstruction and perforation, in some cases leading to death, were observed in patients receiving Rituxan in combination with chemotherapy for DLBCL. In post-marketing reports, which include both patients with low-grade or follicular NHL and DLBCL, the mean time to onset of symptoms was 6 days (range 1−77) in patients with documented gastro-intestinal perforation. Complaints of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.

Immunogenicity: Patients may develop a human anti-chimeric antibody (HACA) response with rituximab treatment. The clinical significance of this is unclear.

Pregnancy: B-cell lymphocytopenia generally lasting less than 6 months can occur in infants exposed to rituximab in utero.

Additional Safety Signals: The following immune serious adverse events have been reported to occur rarely (<0.1%) in patients following completion of rituximab infusions: arthritis, disorders of blood vessels (vasculitis, serum sickness and lupus-like syndrome), lung disorders including pleuritis and scarring of the lung (bronchiolitis obliterans), eye disorders (uveitis and optic neuritis), and severe bullous skin reactions (including toxic epidermal necrolysis and pemphgus) that may result in fatal outcomes. Patients may have these symptoms alone or in combination with rash and polyarthritis.

See the rituximab Investigator Brochure for additional details regarding safety experience with rituximab.

7.2. Fludarabine Phosphate

7.2.1. Other names

Fludara®, fludarabine, 2-fluoro-adenine arabinoside-5-phosphate, 2-fluoro-ARA AMP, FAMP, NSC#312887.

7.2.2. Classification

Purine antimetabolite

7.2.3. Mode of Action

Fludarabine is rapidly phosphorylated *in vivo* to 2-fluoro-ARA-A, incorporated into cells and converted to the active triphosphate form, which inhibits DNA polymerase and ribonucleotide reductase, thus inhibiting DNA synthesis. Fludarabine is also incorporated into DNA.

7.2.4. Storage and Stability

Unreconstituted vials should be stored in the refrigerator. At a concentration of 25 mg/mL and following dilution in normal saline or 5% dextrose to a concentration of 1 mg/mL the drug is chemically stable for at least 16 days at room temperature under normal laboratory light. Solutions of 0.04 mg/ml in 5% dextrose or normal saline in glass bottles or PVC bags are chemically stable for at least 48 hours at room and refrigerated temperatures.

7.2.5. Preparation

Fludarabine, 50 mg/vial, is reconstituted with 2 ml of sterile water, resulting in a 25 mg/mi solution. The desired dose is further diluted to concentrations of 0.04 - 1 mg/mi in normal saline or 5% dextrose (100- 125 ml). The dose on this trial is 20 mg/m^2.

7.2.6. Administration

Administer by IV infusion over 30 minutes or longer.

7.2.7. Incompatibilities

No information available.

7.2.8. Availability

Fludarabine, 50 mg/vial, is commercially available.

7.2.9. Side Effects

7.2.9.1. Hematologic: Leukopenia, primarily lymphopenia and granulocytopenia, and thrombocytopenia, dose-related; may be cumulative, dose-limiting; anemia.

7.2.9.2. Dermatologic: Alopecia (uncommon, mild); rash (rare); dermatitis (rare)

7.2.9.3. Gastrointestinal: Nausea and vomiting are relatively uncommon and preventable with standard antiemetic drugs; anorexia; stomatitis (rare with conventional doses); rare; diarrhea, constipation, abdominal cramps.

7.2.9.4. Hepatic: Increased SGOT, mild and transient.

7.2.9.5. Neurologic: Somnolence, fatigue; peripheral neuropathy (paresthesias), rare and usually transient; delayed demyelinating central nervous system toxicities, including mental status changes, cortical blindness, severe somnolence and coma have occurred, usually with high doses (e.g. 150-200 mg/m^2 x 5); seizures (rare).

7.2.9.6. Pulmonary: Hypersensitivity reactions characterized by dyspnea, cough, interstitial pulmonary infiltrate have been reported.

7.2.9.7. Cardiovascular: Edema (frequent); pericardial effusion, hypotension chest pain (rare).

7.2.9.8. Other: Metabolic acidosis and lactic acidemia due to rapid tumor lysis; muscle weakness (rare); fever (rare).

7.2.10. Nursing Implications

It is recommended that the following precautions be taken:

- Check CBC and platelet counts, particularly with cumulative drug doses.
- Premedicate with antiemetics.
- Monitor for stomatitis, refer for oral health assessment if indicated.
- Observe patient for CNS toxicity (vision changes, confusion, etc.).
- Anticipate tumor lysis syndrome in patients with bulky disease.
- Monitor pulmonary function, especially in patients who have received chlorambucil.

7.3. Cyclophosphamide

7.3.1. Other names

Cytoxan, CTX, CPM, Neosar.

7.3.2. Classification

Alkylating agent.

7.3.3. Mode of Action

Cyclophosphamide prevents cell division primarily by cross-linking DNA strands. The cell continues to synthesize other cell constituents (RNA and protein), an imbalance occurs and the cell dies. Cyclophosphamide is considered cell cycle phase non-specific.

7.3.4. Storage and Stability

Tablets and injectable powder are stored at room temperature. The temperature is not to exceed 90°F. Reconstituted parenteral solutions are stable for 24 hours at room temperature or 14 days if refrigerated.

7.3.5. Preparation

Dissolve the 100 mg, 200 mg, 500 mg, I gm, and 2 gm vials in 5, 10, 25, 50, and 100 ml of sterile water, respectively, resulting in a solution of 20 mg/ml. Shake vials vigorously and warm slightly in lukewarm water to facilitate dissolution. The lyophilized form is more easily solubilized.

7.3.6. Administration

IV infusion over 1 hour

7.3.7. Compatibilities

7.3.7.1. Barbiturates, phenytoin, and chloral hydrate may increase the rate of hepatic conversion of cyclophosphamide to active metabolites, although the clinical importance of these interactions has not been established.

7.3.7.2. Corticosteroids may inhibit metabolism and reduce the effect of cyclophosphamide, although the clinical importance of this interaction has not been established.

7.3.7.3. May prolong the neuromuscular blocking activity of succinylcholine.

7.3.7.4. Imipramine and phenothiazines may reduce cyclophosphamide metabolism, increasing bone marrow suppression.

7.3.7.5. Possible potentiation of doxorubicin and daunorubicin cardiotoxicity.

7.3.7.6. Cyclophosphamide (6-8 mg/ml) and doxorubicin (0.4-0.6 mg/ml) are compatible for 7 days at room temperature

7.3.8. Availability

Commercially available.

7.3.9. Side Effects

- Hematologic: Leukopenia, with nadirs about 8-14 days after administration and recovery in 18-25 days; spares platelets.
- Dermatologic: Alopecia.
- Gastrointestinal: Nausea and vomiting (begins 6-10 hours after administration).
- Hepatic: Increased AST, ALT.
- Neurologic: Headache, dizziness.
- Pulmonary: Rarely Interstitial pulmonary fibrosis.
- Cardiovascular: Cardiac necrosis with high-dose cyclophosphamide.
- Renal: Hemorrhagic cystitis (onset of cystitis may be delayed from 24 hours to several weeks); SIADH, dose related, more common with single large doses greater than 2 gm/m^2.
- Other: Metallic taste during injection; nasal congestion; testicular atrophy, amenorrhea, may be long-term; rarely, anaphylaxis; teratogenic; may cause secondary neoplasms.

7.3.10. Nursing Implications

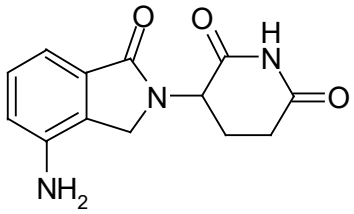
It is recommended that the following precautions be taken:

- Monitor CBC, platelet counts.
- Assess hydration and fluid balance. Patients receiving larger doses should force fluids up to 2 liters/day for 72 hours after administration. Patient should void q 2-3 hours to facilitate emptying of bladder.
- A baseline 12 lead ECG may be obtained prior to high-dose therapy.
- Premedicate with antiemetics.
- Advise patient of potential “metallic taste.” Hard candy with a strong flavor may alleviate this side effect.

7.4. Lenalidomide

REVLIMID® (lenalidomide), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:

Chemical Structure of Lenalidomide



3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

7.5. Clinical Pharmacology

Mechanism of Action:

The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory and antiangiogenic properties. Lenalidomide inhibited the secretion of pro-inflammatory cytokines and increased the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibited cell proliferation with varying effectiveness (IC50s) in some but not all cell lines. Of cell lines tested, lenalidomide was effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5) but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions. Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 in vitro.

7.6. Pharmacokinetics and Drug Metabolism:

Absorption:

Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose.

Co-administration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration (Cmax) by 36%. The pharmacokinetic disposition of lenalidomide is linear. Cmax and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Pharmacokinetic sampling in myelodysplastic syndrome (MDS) patients was not performed. In multiple myeloma patients maximum plasma concentrations occurred between 0.5 and 4.0 hours post-dose both on Days 1 and 28. AUC and Cmax values increase proportionally with dose following single and multiple doses. Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

Distribution:

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

Metabolism and Excretion:

The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.

7.7. Suppliers

Celgene Corporation will supply lenalidomide to study participants at no charge through the RevAssist® program.

7.8. Dosage form

Lenalidomide will be supplied as 5mg and 25 mg capsules for oral administration.

Lenalidomide will be shipped to the pharmacy at the study site in individual bottles. Bottles will contain a sufficient number of capsules to last for one cycle of dosing. Lenalidomide must be dispensed in the original packaging with the label clearly visible. **Only enough lenalidomide for 1 cycle of therapy may be provided to the patient each cycle.**

7.9 Packaging

Lenalidomide will be shipped directly to patients or to the clinic site for IND studies. Bottles will contain a sufficient number of capsules for one cycle of dosing.

7.10 Labeling

Lenalidomide investigational supplies are dispensed to the patients in individual bottles of capsules. Each bottle will identify the contents as study medication. In addition, the label will bear the name of Celgene Corporation, quantity contained and the standard caution statement as follows: Caution: New drug - Limited by Federal law to investigational use. The drug label must be clearly visible. Additional labels must not cover the Celgene label.

7.10.1 Prescribing Information

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with accordance with the RevAssist® program of Celgene Corporation. Per standard RevAssist® requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the RevAssist® Program. Prescriptions must be filled within 7days for females of childbearing potential and 14 days for all risk categories. Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site for IND studies. **Only enough Lenalidomide for one cycle of therapy will be shipped to the patient each cycle.**

7.11 Unused lenalidomide supplies

Any unused lenalidomide must be returned as instructed through RevAssist program.

7.12 Storage

At the study site, lenalidomide will be stored in a locked, safe area to prevent unauthorized access. Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

7.13 Unused lenalidomide supplies

7.14

Drug dispensing requirements

In investigational studies, lenalidomide will be dispensed through a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). These healthcare professionals will be trained by Celgene in requirements specific to counseling of subjects. Once trained these healthcare staff will counsel subjects prior to medication being dispensed to ensure that the subject has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the subject understands the risks associated with lenalidomide.

Counseling includes verification with the patient that required pregnancy testing was preformed and results were negative. A Lenalidomide Information Sheet (see Appendix IV) will be supplied with each medication dispense.

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

Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to initiation of Cycle 1 of lenalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on lenalidomide therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on lenalidomide therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).
[7]

All patients must be counseled about pregnancy precautions, risks of fetal exposure and other risks. The counseling must be done on Day 1 of each cycle (or at a minimum of every 28 days) throughout the entire duration of lenalidomide treatment, including dose interruptions, and at lenalidomide discontinuation.

7.15 Dosing Regimen

The dosing schedule is outlined in Section 6.1. Dosing will be in the morning at approximately the same time each day. Prescriptions must be filled within 7 days. .

If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

Subjects experiencing adverse events may need study treatment modifications

7.16 Special Handling Instructions

Females of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves.

7.17 Pregnancy Prevention Risk Management Plans

7.16.1 Lenalidomide Pregnancy Prevention Risk Management Plan

7.16.2 Lenalidomide Pregnancy Risk Minimisation Plan for Celgene Clinical Trials

Appendix II, III, IV applies to all patients receiving lenalidomide therapy. The following Pregnancy Risk Minimisation Plan documents are included in this appendix:

1) Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods (Appendix II);

    1. The Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Appendix II) provides the following information:

        - Potential risks to the fetus associated with lenalidomide exposure
        - Definition of Female of Childbearing Potential
        - Pregnancy testing requirements for patients receiving Lenalidomide who are females of childbearing potential
        - Acceptable birth control methods for both female of childbearing potential and male patients receiving Lenalidomide in the study

- Requirements for counseling of all study patients receiving Lenalidomide about pregnancy precautions and the potential risks of fetal exposure to lenalidomide

8.0 PATIENT CONSENT & PEER JUDGEMENT

The protocol and informed consent document for this study must be approved in writing by the appropriate Institutional Review Board (IRB) prior to any patient being registered on this study. Changes to the protocol, as well as a change of principal investigator, must also be approved by the Board. Any advertisements used to recruit subjects must also be reviewed and approved by the IRB. Records of the Institutional Review Board review and approval of all documents pertaining to this study must be kept on file by the investigator (housed in the Clinical Trials Office) and are subject to FDA inspection at any time during the study. Periodic status reports must be submitted to the Institutional Review Board at least yearly, as well as notification of completion of the study and a final report within 3 months of study completion or termination.

9.0 DATA FORMS & SUBMISSION SCHEDULE

Study data will be collected and stored in Velos or Paper CRF's. Velos is a web based comprehensive cancer clinical trial software system which uses an Oracle database to store all data.

10.0 RECORD RETENTION

All documentation, including source documents, supporting documentation, administrative records, study drug inventory and accountability, must be retained by the Investigator for a minimum of 2 years after market approval or at least 2 years after formal discontinuation of the study. If any investigator retires, relocates, or withdraws from the investigation after the conduct of the study, the responsibility of maintenance of study records may be transferred to another person (coordinating site or other investigator).

11.0 STUDY PARAMETERS & CALENDAR

11.1. Screening Procedures: A complete list of baseline procedures can be found in the study calendar.

11.1.1. Any scans, x-rays, and baseline bone marrow biopsies used to document measurable or evaluable disease should be done within 8 weeks prior to initiating therapy.

11.1.2. Pre-study CBC (with differential and platelet count) should be done ≤ 2 weeks before initiating therapy.

11.1.3. All required pre-study chemistries, including sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST/SGOT, ALT/SGPT, LDH, and uric acid should be done ≤4 weeks before initiating therapy, unless specifically required on day 1 as per protocol.

11.1.4. Hepatitis B surface antigen, surface antibody, and core antibody and Hepatitis C testing will be done ≤2 weeks before initiating therapy.

11.1.5. Pregnancy testing (urine or serum) is required for all females of child bearing potential (FCBP) as defined by a sexually mature female who 1) has not undergone hysterectomy or bilateral oophorectomy or 2) has not been naturally post menopausal (absence of menses) for 24 consecutive months.

11.1.5.1. For FCBP with regular or no menses:
testing is to be done with 10-14 days of first cycle of lenalidomide, within 24 hours before prescribing lenalidomide, weekly for the first 28 days, and every 4 weeks while receiving lenalidomide (including breaks in therapy), at discontinuation of lenalidomide and 28 days post treatment.

11.1.5.2. For FCBP with irregular menses: testing is to be done with 10-14 days of first cycle of lenalidomide, within 24 hours before prescribing lenalidomide, weekly for the first 28 days, and every 2 weeks while receiving lenalidomide (including breaks in therapy), at discontinuation of lenalidomide and days 14 and 28 days post treatment.

11.2. **Study Calendar**

	INDUCTION				CONSOLIDATION/ MAINTENANCE		POST CONSOLIDATION/MAINTENANCE		FOLLOW-UP	
	Baseline	(C1D1) Before Each Cycle[1< 8]	(C3D1) After Second Cycle[8]	After Fourth and Sixth Cycle[8]	Entry for Consolidation /maintenance	Day 1 All Revlimid Cycles	1 month after consolidation	3 months after consolidation/maintenance	Follow-Up (Stable/ PD)[6]	Follow-Up (PR/CR)[6]
Informed Consent	X									
Medical History & Height[2]	X									
Physical Exam	X	X		X	X	X	X	X		X
Vital signs, weight & Performance status	X	X		X				X		
Education and Counseling guidance		X[8]								
CBC with Differential	X[1]	Weekly			X	Every 2 weeks		X		X
Chemistry[3]	X	X		X		See footnote 3	X	X		X
Beta-2 microglobulin	X			X			X	X		X
Hepatitis B and C	X[1,3]									
Serum creatinine[2]	X	X		X			X	X		X
CT of neck, chest, abdomen & pelvis[5]	X			X	See footnote 5					Annual
Pregnancy test[4]	X				X[4]	X[4]				
Bone marrow biopsy and aspirate with routine flow cytometry, cytogenetic and CLL FISH panel Zap-70 and mutational status of IgVH	X									
Flow cytometry of bone marrow for minimal residual CLL				X		X[7]	X[7]			Annual
Flow cytometry of peripheral blood for minimal residual CLL				X	X	X[7]	X[7]	X		Annual
Quantitative immunoglobulins	X			X			X	X		X
Direct & indirect Coombs	X									
Palpable tumor measurement	X		X	X				X		X
Survival Follow-up & Anti-cancer therapy									X	X

FOOTNOTES:	
1	Baseline Studies to be performed within 28 days of start of treatment do not need to be repeated on C1D1. Day 1 procedures should be done within 2 days of the start of treatment cycle.
2	Height needed only at baseline. Obtain creatinine clearance if serum creatinine> 1.5 mg/dl.
3	Chemistry includes sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST/SGOT, ALT/SGPT, LDH, and uric acid. Testing for Hepatitis B includes: Hepatitis B surface antigen, surface antibody, and core antibody At a minimum, for tumor lysis syndrome (TLS) monitoring purposes, subjects will have chemistry assessments weekly during at least the first 2 cycles of lenalidomide-containing treatment as well as on Day 10 or 11 of Cycle 1 during induction and Day 3 or 4 during consolidation of lenalidomide-containing treatment. In addition, because the risk for TLS may be elevated when lenalidomide is re-started after treatment interruptions or when the lenalidomide dose is escalated, in any cycle in which the lenalidomide dose is escalated or re-escalated or treatment is interrupted for more than 1 week, subjects will have weekly chemistry assessments performed for at least 4 consecutive weeks as well as an additional chemistry assessment on day 3 or 4 during the first week of escalating, re-escalating or re-initiating lenalidomide therapy. For subjects who do not experience any abnormalities in serum chemistry assessments for 2 consecutive cycles while on a stable lenalidomide dose (without escalation or interruption) throughout these 2 cycles, the timing of chemistry assessments may be reduced to Day 1 and Day 15 in subsequent cycles. See section 12.3.3 for tumor lysis prophylaxis guidance.
4	Urine/serum pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide (prescriptions must be filled within 7 days). FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).
5	CTs should be performed within 8 weeks prior to initiating therapy and every 6 months during consolidation until disease progression
6	All PR or CR subjects will have follow-up exams every 3 months for year 1, every 6 months for years 2-5. Patients who begin subsequent anti-cancer treatments will be followed for survival only until death. After year 5, PR & CR subjects will be followed annually until death for survival and new anti-cancer therapy only. Stable & PD subjects will be followed every 3 months for year one then annually until death for survival and new anti-cancer therapy.
7	MRD will be tested from peripheral blood and bone marrow prior to cycle 7 of consolidation and after cycle 12.
8	All patients must be counseled about pregnancy precautions, risks of fetal exposure and other risks. The counseling must be done on Day 1 of each cycle (or at a minimum of every 28 days) and at drug discontinuation. See The Appendix C: Education and Counseling Guidance Document must be completed by a trained Counselor (a consenting professional or designated nurse who has completed training).

12.0 DOSE MODIFICATION & TOXICITY MANAGEMENT

12.1. Dose Modification for Fludarabine and Cyclophosphamide

The dose modifications listed below refer to both fludarabine and cyclophosphamide. It is important to remember the following stipulations.

A. Dose re-escalation after downward modification will not be permitted.
B. The investigator should grade and report adverse events according to the Common Toxicity Criteria (version 4.0).

12.1.1. Hematologic Toxicity

Dose modifications should be based on the nadir of the patient's platelet count and/or absolute neutrophil count (mature polys + bands) obtained immediately prior to the next planned treatment. There will be no dosage reduction for decreases in hemoglobin concentration.

Adjustments for changes in the platelet count.

Platelet Count (/mm^3)	Dosage Adjustment (% reduction is relative to dose delivered during the first course)
≥75,000 (after first treatment)	No dose modification

<75,000 (after first treatment)	Delay treatment and repeat the platelet count weekly, If repeat counts ≥75,000 proceed with next treatment at 25% dose reduction If required delay in treatment is > 2 weeks, discontinue protocol treatment
<75,000 (after first dose reduction)	Delay treatment and repeat the platelet count weekly, If repeat counts ≥75,000 proceed with next treatment at 50% dose reduction. If required delay in treatment is > 2 weeks, discontinue protocol treatment.

Absolute Neutrophil Count (mm^3)	Dose Adjustment (% reduction is relative to dose delivered during the first course)
≥ 1500 (after first treatment)	No dose modification
<1500 (after first planned treatment)	Delay treatment and repeat WBC weekly, if repeat ANC ≥ 1500, proceed with next treatment with a 25% dose reduction If required delay in treatment is > 2 weeks, discontinue protocol treatment.
<1500 (after first dose reduction)	Delay treatment and repeat the ANC weekly, If repeat ANC ≥1,500 proceed with next treatment at 50% dose reduction. If required delay in treatment is > 2 weeks, discontinue protocol treatment.

12.1.2. Gastrointestinal Toxicity

Patients who develop grade 2 gastrointestinal (GI) toxicity except nausea and vomiting without sufficient prophylaxis should receive 75% of fludarabine and cyclophosphamide. Patients who develop grade 3 gastrointestinal toxicity should receive 50% of fludarabine and cyclophosphamide. Patients who develop grade 4 GI toxicity should discontinue protocol treatment.

12.1.3. Infections

Patients who develop grade 4 infection will discontinue protocol treatment.

12.1.4. Genitourinarv Toxicity

Patients who develop grade 2 GU toxicity should receive 75% of fludarabine and cyclophosphamide. Patients who develop grade 3 GU toxicity should receive 50% of fludarabine and cyclophosphamide. Patients who develop grade 4 GU toxicity should discontinue protocol treatment.

12.1.5. Pulmonary Toxicity

Patients who develop grade 3 or 4 fludarabine-related pneumonitis should discontinue protocol treatment.

12.1.6. Cardiac Toxicity

Patients who develop irreversible grade 4 cardiac toxicity should discontinue protocol treatment.

12.1.7. Autoimmune Toxicity

Patients who develop autoimmune hemolytic anemia, autoimmune thrombocytopenia, or other autoimmune disorders should discontinue protocol treatment.

12.1.8. Other Toxicity

Patients who develop any other grade 3 toxicities not listed above, should receive 75% of fludarabine and cyclophosphamide. Patients who develop any other grade 4 toxicity should discontinue study treatment.

12.2. Dose Modification for Rituximab

The dose of Rituximab generally remains constant throughout the trial. If rapid tumor lysis occurs, Rituximab should be stopped. It may be restarted after symptoms and laboratory abnormalities have resolved. In the event of severe or life-threatening anaphylaxis or hypersensitivity reaction, discontinue the patient from the treatment phase. Do not retreat with Rituximab.

Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis throughout their study participation.

Hematologic Events: In clinical trials, Grade 3 and 4 cytopenias were reported in 48% of patients treated with RITUXAN; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range 1 to 588 days) and of neutropenia was 13 days (range 2 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following RITUXAN therapy were reported.

In addition, there have been a limited number of post marketing reports of prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia (defined as occurring 40 days after the last dose of RITUXAN) in patients with hematologic malignancies. In reported cases of late onset neutropenia (NCI-CTC Grade 3 and 4), the median duration of neutropenia was 10 days (range 3 to 148 days). Documented resolution of the neutropenia was described in approximately one-half of the reported cases; of those with documented recovery, approximately half received growth factor support. In the remaining cases, information on resolution was not provided. More than half of the reported cases of delayed onset neutropenia occurred in patients who had undergone prior autologous bone marrow transplantation. In an adequately designed, controlled, clinical trial, the reported incidence of NCI-CTC Grade 3 and 4 neutropenia was higher in patients receiving RITUXAN in combination with fludarabine as compared to those receiving fludarabine alone (76% [39/51] vs. 39% [21/53]).[43]

See warning section of the Package insert for language for management of first infusion reactions.

12.3. Dose Modification for Lenalidomide

Doses will escalate from 5mg daily day 8-28 of the first 28 day cycle to 10mg day 8-28 in cycle 2 and to 15mg day 8-28 in cycles 3-6 in the induction phase or 3-12 in the consolidation phase. Dose de-escalation from 15mg to 10mg to 5mg will be allowed for grade 3/4 toxicity at any time during cycles 1-12.

Table 1: Lenalidomide Dose Modification Steps

Current Lenalidomide Dose	One Level Dose Reduction
15 mg (days 8-28 or 1-28)	10 mg (days 8-28 or 1-28)
10 mg (days 8-28 or 1-28)	5 mg (days 8-28 or 1-28)
5 mg (days 8-28 or 1-28)	5 mg every other day (days 8-28 or 1-28)
5 every other day (days 8-28 or 1-28)	See * below

*Lenalidomide 5 mg every other day is the minimum lenalidomide dose. Lenalidomide will be discontinued in patients who cannot tolerate this dose. However, patients who experience toxicity requiring dose reduction while receiving lenalidomide 5 mg every other day may, at the discretion of their physician, have their dose held until toxicity resolves as described below and then restart lenalidomide 5 mg every other day. If the same toxicity recurs at lenalidomide 5 mg every other day, consideration should be given to discontinuing lenalidomide.

Instructions for initiation of a New Cycle in all consolidation Cycles
A new course of treatment may begin on the scheduled Day 1 of a new cycle if:

- The ANC is ≥ 1500/mm³;
- The platelet count is ≥ 75,000/mm³;
- Any drug-related rash or neuropathy that may have occurred has resolved to ≤ grade 1 severity;
- No evidence of laboratory TLS by Cairo-Bishop Definition of Tumor Lysis Syndrome (see Appendix V). Subjects may be started on consolidation therapy with the combination of lenalidomide and rituximab upon correction of electrolyte abnormalities;
- Any other drug-related adverse events that may have occurred have resolved to ≤ grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above. If a lenalidomide dose reduction was taken during the previous cycle, and the cycle was completed without requiring further dose modification, then the next cycle will start at the same reduced dose of lenalidomide. **If lenalidomide dosing was omitted for the remainder of the previous cycle due to toxicity attributed to lenalidomide or if the new cycle is delayed due to lenalidomide-related toxicity newly encountered on the scheduled Day 1**, then the new cycle will be started with a one-level dose reduction of lenalidomide.

Instructions for dose modifications or interruption
For treatment interruptions during a cycle, the 28-day schedule of each cycle will continue to be followed. Missed doses of lenalidomide are not made up. For treatment interruptions that delay the scheduled start of a new cycle, when toxicity has resolved as required to allow the start of a new cycle (Section 8.3), the restart day of therapy becomes Day 1 of the next cycle.

Table 2: Dose Modifications for Lenalidomide

NCI CTC Toxicity Grade	Dose Modification Instructions
Grade 3 neutropenia associated with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia	• Hold (interrupt) lenalidomide dose. Omitted doses are NOT made up. • Follow CBC weekly. • First episode: If neutropenia resolves to ≤ grade 3 without fever prior to the scheduled end of the current cycle, restart lenalidomide at the current dose level and continue through the scheduled end of the current cycle. Otherwise, omit for remainder of cycle and restart lenalidomide at the current dose level at the start of the next cycle. • Second and subsequent episodes: If neutropenia resolves to ≤ grade 3 without fever prior to the scheduled end of the current cycle, restart lenalidomide at the next lower dose level* and continue through the scheduled end of the current cycle. Otherwise, omit for remainder of cycle and restart lenalidomide at the next lower dose level* at the start of the next cycle.
Thrombocytopenia ≥Grade 4 (platelet count < 25,000/mm³)	• Hold (interrupt) lenalidomide dose. Omitted doses are NOT made up. • Follow CBC weekly. • **NOTE**: Consider criteria (perhaps based on platelet count) for holding and then resuming prophylactic anti-coagulation, if applicable. • If thrombocytopenia resolves to ≤ grade 3 prior to the scheduled end of the current cycle, restart lenalidomide at next lower dose level* and continue through the scheduled end of the current cycle. Otherwise, omit for remainder of cycle and restart lenalidomide at the next lower dose level* at the start of the next cycle.

Table 2: Dose Modifications for Lenalidomide	
NCI CTC Toxicity Grade	**Dose Modification Instructions**
Platelet count < 50,000/mm³	• Hold prophylactic anti-coagulation, if applicable. • Restart prophylactic anti-coagulation when platelet count is ≥ 50,000/mm³.
Tumor Lysis Syndrome (TLS) ≥Grade 2 (see Section 8.3.1 and Appendix: Cairo-Bishop Definition of TLS)	• Hold (interrupt) lenalidomide dose. Omitted doses are NOT made up. • First episode: after resolution of electrolyte abnormalities to Grade 0, restart lenalidomide at the current dose with appropriate TLS prophylaxis (Section 8.3.1). • Subsequent episodes: after resolution of electrolyte abnormalities to Grade 0, restart lenalidomide with appropriate TLS prophylaxis (Section 8.4.6). At physician discretion, the lenalidomide dose may be restarted at the current dose or lenalidomide may be reduced by 1 dose level*. • First or subsequent episodes: subjects should be closely monitored for signs of TLS after resuming treatment. To monitor for TLS, serum chemistry and uric acid tests should be performed at least every week following initiation of lenalidomide for 4 consecutive weeks and on Day 3 or 4 following initiation of lenalidomide. See Section 2, Schedule of Study Assessments, for additional specifics regarding serum chemistry and uric acid testing.
Non-blistering rash **Grade 3** **Grade 4**	• If Grade 3, hold (interrupt) lenalidomide dose. Follow weekly. • If the toxicity resolves to ≤ grade 1 prior to the scheduled end of the current cycle, restart lenalidomide at next lower dose level* and continue through the scheduled end of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level* at the start of the next cycle. Omitted doses are not made up. • If Grade 4, discontinue lenalidomide. Remove patient from study.
Desquamating (blistering) rash- any Grade	• Discontinue lenalidomide. Remove patient from study.
Neuropathy **Grade 3** **Grade 4**	• If Grade 3, hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to the scheduled end of the current cycle, restart lenalidomide at next lower dose level* and continue through the scheduled end of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level* at the start of the next cycle. Omitted doses are not made up. • If Grade 4, discontinue lenalidomide. Remove patient from study.
Venous thrombosis/embolism ≥ Grade 3	• Hold (interrupt) lenalidomide and start therapeutic anticoagulation, if appropriate • Restart lenalidomide at investigator's discretion (maintain dose level). • See Anticoagulation Consideration (Section 5.6.1.2).
Hyperthyroidism or hypothyroidism	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level*.

Table 2: Dose Modifications for Lenalidomide	
NCI CTC Toxicity Grade	**Dose Modification Instructions**
other non-hematologic toxicity ≥ Grade 3	• Hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 prior to the scheduled end of the current cycle, restart lenalidomide and continue through the scheduled end of the current cycle. Otherwise, omit for remainder of cycle. Omitted doses are not made up. For toxicity attributed to lenalidomide, reduce the lenalidomide dose by 1 dose level* when restarting lenalidomide.

12.3.1. **Tumor Lysis Syndrome**

- All subjects meeting criteria of laboratory TLS or ≥ Grade 1 TLS according to the Cairo-Bishop Definition of Tumor Lysis Syndrome (see Appendix) should receive vigorous intravenous hydration and should be considered for rasburicase therapy as needed to reduce hyperuricemia, until correction of electrolyte abnormalities.
- In cases of laboratory TLS and Grade 1 TLS (see Appendix: Cairo-Bishop Definition of Tumor Lysis Syndrome), lenalidomide will be continued at the same dose without interruption or dose reduction. TLS prophylaxis measures outlined in Section 8.4.6 should be continued or re-instituted.
- Subjects with ≥ Grade 2 TLS (see Appendix: Cairo-Bishop Definition of Tumor Lysis Syndrome) will be managed as follows in addition to intravenous hydration and consideration for rasburicase therapy (above).
    - Hold (interrupt) treatment.
    - First episode: restart lenalidomide at the current dose with appropriate TLS prophylaxis (Section 8.4.6) after resolution of electrolyte abnormalities to Grade 0.
    - Subsequent episodes: restart lenalidomide with appropriate TLS prophylaxis (Section 8.4.6) after resolution of electrolyte abnormalities to Grade 0. At physician discretion, the lenalidomide dose may be restarted at the current dose or lenalidomide may be reduced by 1 dose level.
    - First or subsequent episodes: subjects should be closely monitored for signs of TLS after resuming treatment. To monitor for TLS, serum chemistry and uric acid tests should be performed at least every week following initiation of lenalidomide for 4 consecutive weeks and on Day 3 or 4 following initiation of lenalidomide. See Section 10.3 Schedule of Study Assessments, for additional specifics regarding serum chemistry and uric acid testing.

12.3.2. **Tumor Flare Reaction (TFR):**

Prophylaxis for (TFR) is not recommended. Grade 1 TFR may be treated with NSAIDs (i.e. ibuprofen 400-600 mg orally every 4-6 hours as needed). TFR ≥ Grade 2 may be treated with corticosteroids. Narcotic analgesics may be added as needed for pain control in subjects experiencing ≥ Grade 2 tumor flare. If corticosteroids are used, the following dosage schedule is recommended; prednisone 20mg PO daily x 7 days followed by 5mg PO daily x 7 days.

Tumor flare occurring during the first 2 weeks of Cycle 1 should be recorded as an adverse event and not as progressive disease (PD). For tumor flare occurring after the first 2 weeks of Cycle 1, differentiate tumor flare from progression.

12.3.3. **Tumor Lysis Syndrome (TLS) Prophylaxis (allopurinol and hydration)**

Tumor lysis syndrome (TLS), characterized by hyperkalemia, hyperuricemia, and hyperphosphatemia resulting from the rapid release of potassium, uric acid, and phosphate, has been reported in CLL patients treated with lenalidomide necessitating TLS prophylaxis including allopurinol and oral hydration. The risk of TLS is highest during the first cycle of therapy and may be elevated when lenalidomide is re-started after treatment interruptions or when the lenalidomide dose is escalated.

Allopurinol 300mg po daily beginning at least 3 days before the start of lenalidomide therapy and continuing through at least the end of Cycle 2 as TLS prophylaxis is required for all subjects.

Within the first 3 cycles of therapy, additional allopurinol should be given concurrent with any dose escalation (or re-escalation, if permitted) of lenalidomide. In these instances, allopurinol should be started concurrent with (or if feasible, 3 days prior to) the escalation of lenalidomide, and continued through at least the end of the cycle. A similar course of allopurinol should be considered when lenalidomide is restarted after having been held for any reason within the first 3 cycles of therapy.

Subjects should be instructed to maintain adequate hydration and maintain urinary output as an additional measure to prevent TLS. To maintain fluid intake, subjects should be instructed to drink 8 to 10 eight ounce glasses of water each day for the first 14 days of Cycle 1. Hydration levels should be adjusted according to age and clinical status, and lowered if the subject's cardiovascular status indicates the possibility of volume overload. Within the first 3 cycles of therapy, additional oral hydration should be considered concurrent with any dose escalation (or re-escalation, if permitted) of lenalidomide, or when lenalidomide is restarted after having been held for any reason.

Based on a patient's reaction and laboratory parameters, TLS prophylaxis may be continued or restarted as needed at the Investigator's discretion, see section 12.3.1 for guidance.

12.3.4. **Anticoagulation Consideration**

Lenalidomide increases the risk of thrombotic events in patients who are at high risk or with a history a thrombosis, in particular when combined with other drugs known to cause thrombosis. When lenalidomide is combined with other agents such as steroids (e.g. dexamethasone, prednisone), anthracyclines (Doxil, Adriamycin) and erythropoietin the risk of thrombosis is increased.

All patients should receive prophylactic anti-coagulation. Aspirin (81 or 325 mg) is the recommended agent for anti-coagulation prophylaxis. Low molecular weight heparin may be utilized in patients that are intolerant to ASA. Coumadin should be used with caution and close monitoring of INR.

Prophylactic anti-coagulation should be held for platelet counts < 50,000mm^3 and then restarted when platelet counts are above this level.

Full therapeutic anti-coagulation should be considered for patients who have a history of venous thromboembolism. Whether therapeutic anti-coagulation is used or not, patients with a history of venous thromboembolism should be closely monitored throughout the study, especially during periods of fluctuating platelet counts.

13.0 CRITERIA FOR TREATMENT DISCONTINUATION & REMOVAL FROM STUDY

13.1. **Treatment Discontinuation**

- Progressive disease
- Subjects who meet toxicity criteria for discontinuation
- Subjects who wish to discontinue therapy
- Physician discretion that the treatment is no longer in the best interest of the patient.
- Pregnancy
- Development of HBV infection or hepatitis during treatment.

13.2. **Study Discontinuation**

- Withdraw of consent
- If the study ends or is stopped by the sponsor-investigator
- Non-compliance

- Subjects who are lost to follow-up. Lost to follow-up is defined as three (3) consecutive failed attempts to contact the patient or three (3) consecutive missed protocol required follow up assessment appointments. Such instances should be well documented in the source documents.
  Every effort should be made to continue to follow patients according to schedule of events once treatment has ceased, however, patients that are unwilling or unable to comply with follow up schedule should, at the discretion of the investigator, be removed from the study.

14.0 EVALAUTION OF RESPONSE

14.1. Assessment of Clinical Response (2008 NCIWG Guidelines, 63)

The major criteria for determination of the response to therapy in patients with CLL include physical examination and evaluation of peripheral blood and bone marrow. It is recommended that the laboratory and clinical studies which are abnormal pre-study be repeated to document the degree of maximal response.

14.2. **Complete Remission (CR)**

Complete remission requires **ALL** of the following for a period of at least 2 months:

- Absence of lymphadenopathy by physical examination and CT
- No hepatomegaly or splenomegaly by CT
- Absence of constitutional symptoms
- Normal CBC as exhibited by:
  - Polymorphonuclear leukocytes ≥1 500/mm^3.
  - Platelets> 100,000/mm^3.
  - Hemoglobin> 11.0 gm/dl (un-transfused).
  - Peripheral blood lymphocytes <4000/mm^3

    One marrow aspirate and biopsy should be performed 2 months after clinical and laboratory evidence of a CR to document that a complete remission has been achieved. The marrow sample must be at least normocellular with < 30% of nucleated cells being lymphocytes. If it is hypocellular, a repeat determination should be made in 1- 2 months. Samples will be submitted for pathology review and the presence of small lymphoid nodules, without definitive phenotypic evidence of persistent disease, noted, although not included in the current definition of CR. A patient who is in CR, but has small lymphoid nodules, will be considered to have nodular PR & recorded separately.
- Any other laboratory assays (i.e., quantitative immunoglobulins, PCR for unique immunoglobulin rearrangement) will not be used currently as an index for response but will be recorded for clinical correlations.
- Bone marrow 3 months after last dose of FCR- showing no evidence of cells with an abnormal, CLL-like, phenotype.

14.3. **Partial Response (PR)**

In addition to the parameters listed below, the presence or absence of constitutional symptoms will be recorded.

To be considered a partial response, the patient must exhibit all of the following for at least 2 months:

- ≥50% decrease in peripheral blood lymphocyte count from the pretreatment baseline value
- ≥50% reduction in lymphadenopathy
- ≥50% reduction in size of liver and/or spleen (if abnormal prior to therapy)

AND

One or more of the following remaining features for at least 2 months:

- Polymorphonuclear leukocytes ≥1500/mm^3 or 50% improvement over baseline.
- Platelets> 100,000/mm^3 or 50% improvement over baseline.
- Hemoglobin > 11.0 gm/dl or 50% improvement over baseline without transfusions.

14.4. **Progressive Disease (PD)**

PD will be characterized by at least one of the following:

- 50% increase in the sum of the products of at least 2 lymph nodes on 2 consecutive examinations 2 weeks apart (at least 1 node must be 2 cm).Appearance of new palpable lymph nodes.
- 50% increase in the size of liver and/or spleen as determined by measurement below the respective costal margin; appearance of palpable hepatomegaly or splenomegaly which was not previously present.
- 50% increase in the absolute number of circulating lymphocytes.
- In the absence of progression as defined above, the presence of a > 2 gm/dl decrease in hemoglobin, or> 50% decrease in platelet count and/or absolute granulocyte count will not exclude a patient from continuing on study. Bone marrow aspirate and biopsy are strongly encouraged to better define the cause of the suppressed counts.
- Transformation to a more aggressive histology (e.g., Richter's syndrome or prolymphocytic leukemia with > 55% prolymphocytes).

14.5. **Stable Disease (SD)**

Patients who have not achieved a CR or a PR, or who have not exhibited findings consistent with Progressive Disease will be considered as having Stable Disease.

15.0 REPORTING OF ADVERSE EVENTS

15.1. **Adverse Event Reporting definitions**

In the event of an adverse event, the first concern will be for the safety of the subject. Each participating center will report adverse events to their IRB per local guidelines. In addition, Investigators are required to report to Dr. Anthony Mato, who will submit to the Hackensack University Medical Center IRB any serious adverse event, whether expected or unexpected, and which is assessed by the investigator to be reasonably or possibly related to or caused by study drugs. All events meeting these criteria will be reported for the time period beginning first dose of study drug(s) through the protocol-defined follow-up period. Serious criteria, definitions, and guidance for reporting follow.

An adverse event (AE) is any untoward medical occurrence in a subject participating in an investigational trial or protocol regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

Serious Adverse Event (SAE) Definition

Serious adverse events (SAE) are adverse events occurring at any dose which meet one or more of the following serious criteria and **MUST BE REPORTED WITHIN 24HOURS AFTER SITE'S INITIAL RECEIPT OF INFORMATION**:

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

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

Sponsor-Investigator shall use his/her judgment to determine the relationship between the Serious Adverse Drug Experience and the Study Drug.

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose per se will not be reported as an AE/SAE).

"Lack of efficacy" or "failure of expected pharmacological action" will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

All adverse events that meet these criteria **are** to be reported.

Events that **do not** meet the definition of an AE include:

- Any clinically significant abnormal laboratory finding or other abnormal safety assessments that is associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

Laboratory and Other safety assessment abnormalities as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator **are** to be recorded as AEs or SAEs.

ALT levels of greater than 3 times the upper limit of normal (ULN) and simultaneous bilirubin levels of greater than 2 times ULN (>35% direct bilirubin; bilirubin fractionation required) **are** to be recorded as SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression) does not need to be reported as an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject or if the investigator considers that there was a causal relationship between treatment with investigational product or protocol design/procedures and the disease progression, then this must be reported as an SAE.

Time Period and Frequency of Detecting AEs and SAEs

All SAEs regardless of relationship to investigational product will be collected from the first dose of investigational product to 6 months after the last dose of investigational product.

From the time a subject consents to participate in and completes the study, all SAEs assessed **as related to study participation** (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or will be reported to the sponsor-investigator, and local IRB, if applicable.

Any pre-existing condition or signs and symptoms present prior to investigational product will be recorded as medical history.

Any SAE brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to investigational product must be promptly reported.

Adverse Event Reporting:
The following adverse reactions must be reported in the manner described below.

All serious adverse events (SAE) regardless of causality must be reported to the PI, and Celgene (within 24 hours) or Co-PI and the protocol coordinator for notification of Hackensack University Medical Center's IRB. See section 15.2 for specific reporting criteria for adverse events associated with rituximab. See section 15.3 for specific reporting criteria for adverse events associated with lenalidomide.

	Unexpected, fatal or life-threatening, and associated with study drug	**Unexpected, of moderate or greater severity (but not fatal or life-threatening) and are associated with the research intervention**	**Serious, unexpected event that is associated with the study drug**
Call to HUMC within 24 hours	X		
Notify IRB within 24 hours	X		
Notify Celgene within 24 hours	X	X	X
Notify DSMB promptly & local IRB within 10 days		X	
Notify FDA within 15 days	X		

- An adverse reaction is considered serious if it is fatal or life-threatening; requires or prolongs hospitalization; produces a disability; or results in a congenital anomaly/birth effect.
- An adverse reaction is considered to be of moderate or greater severity if it requires medical evaluation (such as additional laboratory testing) and/or medical treatment; or if it is a serious adverse reaction.
- An adverse reaction is considered to be unexpected if it is not identified in nature, severity, or frequency in the current IRB-approved research protocol or informed consent document.
- An adverse reaction is considered to be associated with the research intervention if there is a reasonable possibility that the reaction may have been caused by the research intervention (i.e., a causal relationship between the reaction and research intervention cannot be ruled out by the investigator(s).

HUMC requires SAEs to be reported on the MedWatch form and on the HUMC IRB adverse event form. The treating investigator must sign the HUMC Adverse event form. (This only applies to the John Theurer Cancer Center, all other participating sites will follow their own IRB guidelines and submit all SAE's on a MedWatch form to Dr. Anthony Mato at fax number **551-996-0751 or via email to Amato@hackensackUMC.org**

15.2. Reporting Adverse Events Associated with Lenalidomide

Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

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 (insert time-frame which must be at least 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.. 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. 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 email within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent 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
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

Investigator Reporting Responsibilities
The conduct of the study will comply with all FDA safety reporting requirements.

IND Annual Reports
If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Celgene Corporation as a supporter of this study as follows.

IND Annual Reports
Celgene Corporation
Attn: Medical Affairs Operations
Connell Corporate Park
400 Connell Drive Suite 700
Berkeley Heights, NJ 07922

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (e.g. mild, moderate, severe), relationship to drug (e.g. probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for “serious” and as defined above are present. The investigator is responsible for reporting adverse events to Celgene as described below.

Expedited reporting by investigator to Celgene
Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form 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_CLL_PI_0530) 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.

Report of Adverse Events to the Institutional Review Board
The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

Trial Coordination Center Reporting Guidelines

All Serious Adverse Events (SAE) will be reviewed by the principal investigator to determine if they meet the Hackensack University Medical Center's Institutional Review Board guidelines for reporting. The Hackensack Research staff will submit any reportable SAE reports to the IRB as per their guidelines, and report to other sub-sites, if applicable.

15.3. **MedWatch 3500 Reporting Guidelines:**

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500 form:

- Protocol description (and number, if assigned)
- Description of event, onset date, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information:

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500 report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500 form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

15.4. **Trial Drug Relationship**

The investigator will determine which events are associated with the use of trial drug. For reporting purposes, an AE should be regarded as possibly related to the use of the investigational product if the investigator believes:

- There is a clinically plausible time sequence between onset of the AE and trial drug administration; and/or
- There is a biologically plausible mechanism for trial drug causing or contributing to the AE; and
- The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.

Trial drug relationship will be assessed to rituximab and lenalidomide separately and specified on SAE form.

15.5. **Adverse event updates/IND safety reports**

Celgene shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of drug in this study or in other studies that is both serious and unexpected.

- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

It is the sponsor-investigator's responsibility to ensure safety information is disseminated to any affiliate or sub-sites.

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects in accordance with their IRB policy.

The Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB/EC, on file.

16.0 STATISTICAL CONSIDERATIONS

16.1. Overview

This study is designed to assess the toxicity and complete response rate of FCR- plus lenalidomide followed by lenalidomide in patients with previously untreated CLL. The patients will be evaluated for response and toxicity using a two-stage, phase II study design.

16.1.1. Primary Endpoint: The primary endpoint of this trial is CR after 4 cycles of FCR- in patients with previously untreated CLL.

16.1.2. Secondary Endpoint: Secondary endpoints are MRD measured by four-color flow cytometry and response to lenalidomide overall survival, toxicity, duration of response, and the expression of ZAP-70, CD38, IgV_H status, and chromosomes.

16.1.3. Sample Size and Accrual: Nineteen patients will be accrued in the first stage. If the study continues to the second stage, an additional 35 patients will be accrued. Accrual is expected to occur at a rate of 2-3 patients per month.

16.1.4. Analysis population:

Safety population: All enrolled patients who received at least one dose of the combination drug will be included in the safety population.

Evaluable population: All enrolled patients who complete the 1 cycle of treatment and follow-up examination and evaluation will be included in the analysis of clinical response.

16.2. Statistical Considerations for the Clinical Trial

16.2.1. Decision Rule, Power and Significance: This study is designed to evaluate the CR rate of FCR- following four cycles of therapy in patients with previously untreated CLL. The patients will be evaluated using an optimum two stage phase 2 study design. Patients who meet the entry criteria and have completed at least one cycle of FCR- will be evaluated for response. All enrolled patients who received at least one does of the study therapy will be included in the safety population.

In the proposal for patients with untreated CLL we are interested in excluding an unfavorable CR of 20% versus a 40% CR rate under the alternative hypothesis. Assuming a significance level of 0.05 and 90% power, we need sample sizes in 2 stages as n1=19, and n2=35 (total maximum sample size = 54). In the first stage, 19 evaluable patients will be accrued.

If fewer than 5 patients have a CR, the study will terminate. If at least 5 CRs are observed, the study will continue to accrue an additional 35 patients. After the second stage, if the total number of CRs is at least 16, the treatment will be deemed worthy of further study. Conversely, if the study terminates at the first stage, or if the CRs total 15 or fewer, the FCR- therapy will not be recommended for further study. Additionally if 5 patients experience a grade 3-4 non-hematologic treatment-related events during the first stage, we will terminate the protocol based on unacceptable toxicity.

The MRD elimination rate will be estimated by the number of patients whose MRD is eliminated after lenalidomide treatment divided by the total number of CR patients with MRD who begin lenalidomide treatment. The 95% exact-binomial confidence interval for the MRD elimination rate will be estimated using the Clopper-Pearson method. Assuming the FCR- CR rate is 40% and that 50% of the patients experiencing a CR have MRD, then we would expect the MRD elimination rate to be estimated based on approximately 11 patients.

16.2.2. Analysis of Endpoint: The complete responses will be estimated by the number of patients with CR divided by the total number of evaluable patients. Ninety-five percent confidence intervals for the true CR will be calculated.

Analysis of the other Secondary Endpoints: The overall response rate will be estimated by the number of patients with complete and partial responses divided by the total number of evaluable patients. Ninety-five percent confidence intervals for the true success proportion will be calculated. The overall survival (OS) is defined as the time interval between the treatment starting date and the documented date of death. For a surviving patient, OS is censored at the last follow-up date when the patient is documented to be alive. Progression-free survival (PFS) is defined as the time interval between the treatment starting date and the documented date of disease progression or death, whichever occurs first. For an alive and progression free patient, PFS is censored at the last follow-up date when the patient is documented to be progression free. The OS and PFS will be estimated by the Kaplan-Meier method. The median survival and the corresponding 95% confidence interval will also be reported. However, given the small sample size, these estimates will be largely exploratory in nature. The relation of these endpoints to the expression of ZAP-70, CD38, IgVH status and chromosomes will be explored by standard group comparison methods or proper regression methods.

16.2.3. Toxicity: All toxicities that were determined to be possibly, probably or definitely related to the treatment will be tabulated according to grade and type (according to the NCI Common Toxicity Criteria, Version 4.0). The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns.

16.2.4. Monitoring: The principal investigator(s) and the study statistician will review the study periodically to identify accrual, toxicity, and any endpoint problems that might be developing. This study will be monitored according to the data and safety monitoring plan that is currently in place, and if necessary will report to HUMC Data Safety Monitoring Board for review monthly.

16.3. Data Safety Plan

Monitoring and Quality Assurance:

This trial will be monitored by the same monitoring process in effect for all HUMC Investigator Initiated Trials. **It is the responsibility of the PI (or designee) to monitor the safety data for this study. At minimum local safety data should be reviewed by corresponding investigator on a monthly basis**. All SAEs will be reported according to section 15.0, section 15.1, section 15.2 and section 15.6. Major deviations are sent to the IRB per their requirements. All investigators are required to submit quarterly safety meeting minutes to HUMC Data Safety Monitoring Board.

All study safety data from all patients, irrespective of enrolling center, will be monitored by the DSMB on a monthly basis for accrual, patient safety, and data quality. All study participants on study are reviewed on a recurring basis for any toxicity or other untoward events. The Clinical Research Monitoring Coordinator (CRMCO) will track patient consent and enrollment. The principal investigator, study statistician, and CRMCO will monitor safety data for all patients, including adverse events (AE's) for all grades and attributions, serious adverse events (SAE's), and study drug administration.

If any literature becomes available which suggests that conducting this trial is no longer ethical, the study will be terminated and the IRB will be notified of the new findings. Any modifications necessary to ensure patient safety are discussed and modifications will be submitted to the IRB. Modifications to this study will not be implemented until approved by the IRB. The IRB will be notified of any changes in the risk/benefit ratio, which would affect whether the study should continue.

All patients will be monitored by the CRMCO routinely for accrual, patient safety and data quality. This monitoring will be done by comparing source documentation to the case report forms (CRF's). Source documents may be requested from sites for remote monitoring. Any variation between the two data sets will be discussed and/or queried.

The first level of ongoing oversight is carried out by the principal investigator, Dr. Mato, primary research nurse and the study data coordinator. These individuals meet at least monthly with each cycle to review recently acquired data, stopping rules and adverse events. The data recorded within the research charts and protocol database is compared with the actual data that is available from the medical record and clinical histories. All investigators in the protocol have received formal training in the ethical conduct of human research.

Additionally, institutional support of trial monitoring is provided in accordance with HUMC Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, protocols are reviewed at least monthly by the Data Safety Monitoring Board. and yearly IRB. The Data Safety Monitoring Board (DSMB) will be composed of medical and statistical independent reviewers and will meet to review the efficacy and safety data and determine a risk/benefit analysis in this subject population. The purpose of the DSMB is to advise on serious safety considerations, lack of efficacy and any other considerations within the charge to the Committee. The DSMB may request additional meetings or safety reports as deemed necessary. The DSMB may stop the study following review of results from each interim analysis. The first interim analysis will examine only safety information; the second interim, conducted when the database is more mature, will examine both safety and efficacy. Appropriate efficacy and safety data summaries will be provided to the DSMB after each interim analysis.

16.4. Correlative Analysis

Median duration of response and overall survival will be estimated and Kaplan-Meier curves will be presented for all subjects who begin protocol treatment. The mean, median and range of the duration of response and survival will be cross-tabulated against expression of ZAP-70, CD38, IgV_H status and MRD measured by multi-color flow cytometry. Clinical response will also be tabulated against these laboratory endpoints.

17.0 REFERENCES

1. Rai KR, Patel DV. Chronic Lymphocytic Leukemia, in Hoffman R, Benz E, Shattil 5, Furie B, Cohen H, Silberstein L (eds): Hematology: Basic Principles and Practice, New York, Churchill Livingstone, 1995, p. 1308.

2. Linet MS, Cartwright RA. Chronic lymphocytic leukemia: epidemiology and etiologic findings. Nouv Rev Fr Hematol 1988; 30:353.

3. Jaksic B, Vitale B, Hauptmann E, Planinc-Peraica A, Ostojic 5, Kusec R. The roles of age and sex in the prognosis of chronic leukemias. A Study of 373 Cases. Cancer 1991; 64:345.

4. Hallek M, Cheson BD, Catovsky D, Caligaris-Capplo F, Dighiero G, Dohner H, Hillmen P, Keating MJ, Montserrat E, Rai KR, Kipps TJ. 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 2008; 1111:5446

5. Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. Blood 1975; 46:219.

6. Rai KR, Sawitsky A. A review of the prognostic role of cytogenetic, phenotypic, morphologic, and immune function characteristics in chronic lymphocytic leukemia. [Review]. Blood Cells 1987; 12:327.

7. Montserrrat E, Rozman C. Bone marrow biopsy in chronic lymphocytic leukemia: a review of its prognostic importance. [Review]. Blood Cells 1987; 12:315.

8. Montserrat E, Rozman C. Chronic lymphocytic leukaemia: prognostic factors and natural history. Bailliere's Clinical Haematology 1993; 6:849.

9. Han T, Bhargava A, Henderson ES, et al. Prognostic significance of beta-2-microglobulin (-2m) in chronic lymphocytic leukemia (CLL) and non-Hodgkin's lymphoma (NHL). Proc Amer Soc Clin Oncol 1989; 8:270 (abstr 270).

10. Montserrat E, Alcala A, Parody R, Domingo A, Garcia-Conde J, Bueno J, Ferran C, Sanz MA, Giralt M, Rubio D, Anton I, Estape J, Rozman C. Treatment of chronic lymphocytic leukemia in advances stages. Cancer 1985; 56:2369.

11. Fais F,Ghiotto F, Hashimoto S, et al. Chronic lymphocytic leukemia B cells express restricted sets of mutated and unmutated antigen receptors. J Clin Invest 1998; 102:1515.

12. Damle RN, Wasil T, Fais F, et al. Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. Blood 1999; 94:1840.

13. Oscier DG, Thompsett A, Zhu D, Stevenson FK. Differential rates of somatic hyper mutation in V(H) genes among subsets of chronic lymphocytic leukemia defined by chromosomal abnormalities. Blood 1997; 89:4153.

14. Hamblin TJ, Davis Z, Gardiner A, Oscier DG, Stevenson FK. Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood 1999; 94:1848.

15. Crespo M, Bosch F, Villamor N. Bellosillo B, Colomer D, Rozman M, Marcé S, López-Guillermo A, Campo E, Montserrat E. ZAP-70 expression as a surrogate for immunoglobulin-variable-region mutations in chronic lymphocytic leukemia. N Engl J Med 2003; 348:1764.

16. Lin K, Sherrington PD, Dennis M, Matrai Z, Cawley JC, Pettitt AR. Relationship between p53 dysfunction, CD38 expression, and IgV(H) mutation in chronic lymphocytic leukemia. Blood 2002; 100:2291.

17. Gahrton G, Juliusson G. Clinical implication of chromosomal aberrations in chronic b-lymphocytic leukaemia cells. Nouv Rev Fr Hematol 1988; 30:389.

18. Bird ML, Ueshima Y, Rowley JD, Haren JM, Vardiman JW. Chromosome abnormalities in B cell chronic lymphocytic leukemia and their clinical correlations. Leukemia 3:1989.

19. Kröber A, Seiler T, Benner Z, Bullinger L, Brückle E, Lichter P, Döhner H, Stilgenbauer S. V_H mutation status, CD38 expression level, genomic aberrations, and survival in chronic lymphocytic leukemia. Blood 2002;100:1410.

20. Rozman C, Montserrat E. Bone marrow biopsy in chronic lymphocytic leukaemia. Nouv Rev Fr Hematol 1988; 30:369.

21. Pangalis GA, Boussiotis VA, Kitttas C. B-Chronic lymphocytic leukemia. Nouv Rev Fr Hematol, 1988; 30:373.

22. Montserrat E, Vinolas N. Reverter JC, Rozman C. Natural history of chronic lymphocytic leukemia: on the progression and prognosis of early clinical stages. Nouv Rev Fr Hematol 1988; 30:359.

23. Shustik C, Mick R, Silver R, Sawitsky A, Rai K. Shapiro L. Treatment of early chronic lymphocytic leukemia: intermittent chlorambucil versus observation. Hematological Oncology 1988; 6:7.

24. Liepman M. Votaw ML. The treatment of chronic lymphocytic leukemia with COP chemotherapy. Cancer 1978; 41:1664.

25. Oken MM, Kaplan ME. Combination of chemotherapy with cyclophosphamide, vincristine, and prednisone in the treatment of refractory chronic lymphocytic leukemia. Cancer Treatment Reports 1979; 63:441.

26. Hansen MM, Andersen E, Christensen BE, Christansen I, Geisler C, Kristensen D, Jensen KB, Junker P. CHOP versus prednisolone + chlorambucil in chronic lymphocytic leukemia (CLL): preliminary results of a randomized multicenter study. Nouv Rev Fr Hematol 1988; 30:433.

27. Raphael b. Andersen JW, Silber R, Oken M, Moore D, Bennet J, Bonner H, Hahn R, Knospe WH, Mazza J, Glick J. Comparison of chlorambucil and prednisone versus cyclophosphamide, vincristine, and prednisone as initial treatment for chronic lymphocytic leukemia: long-term follow-up of an eastern cooperative oncology group randomized clinical trial J Clin Onc 1991; 9:770.

28. Grever MR, Kopecky KJ, Coltman CA, Files JC,Greenberg BR, Hutton JJ, Talley R, Von Hoff DD, Balcerzak SP. Fludarabine monophosphate: a potentially useful agent in chronic lymphocytic leukemia. Nouv Rev Fr Hematol 1988; 30:457.

29. Keating MJ, Kantarjian H, Talpaz M, Redman J, Koller C. Barlogie B, Velasquez W, Plunkett W, Freireich EJ, McCredie KB. Fludarabine: a new agent with major activity in chronic lymphocytic leukemia. J Clin Onc 1991; 9:44.

30. Keating MJ, Kantarjian H, O'Brien S, Koller C, Talpaz M, Schachner J, Child CC, Freireich EJ, McCredie KB. Fludarabine: a new agent with marked cytoreductive activity in untreated chronic lymphocytic leukemia. J Clin Onc

1991; 9:44.

31. Rai KR, Peterson BL, Appelbaum FR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. Lancet 1996; 347:1432.

32. O'Brien S, Kantarjian H, Beran M, Smith T, Koller C, Estey E, Robertson LE, Lerner S, Keating M. Results of fludarabine and prednisone therapy in 264 patients with chronic lymphocytic leukemia with multivariate analysis-derived prognostic model for response to treatment. Blood 1993; 82:1695.

33. Anaissie E, Kontoylannis DP, Kantarjian H, Elting L, Robertson LE, Keating M. Listeriosis in patients with chronic lymphocytic leukemia who were treated with fludarabine and prednisone. Ann In Med 1992; 117:466.

34. Johnston JB, Verburg L, Shore T, Williams M, Israels LG, Begleiter A. Combination therapy with nucleoside analogs and alkylating agents. Leukemia 8 Suppl 1994; 1:S140.

35. Begleiter A, Pugh L. Israels LG,Johnston JB. Enhanced cytotoxicity and inhibition of DNA damage repair in irradiated murine L5178Y lymphoblasts and human chronic lymphocytic leukemia cells treated with 2'-deoxycoformycin and deoxyadenosine *in vitro*. Cancer Res 1988; 48:3981.

36. O'Brien SM, Kantarjian HM, Cortes J, et al. Results of the fludarabine and cyclophosphamide combination regimen in chronic lymphocytic leukemia. J Clin Oncol 2001; 19:1414.

37. Flinn IW, Byrd JC, Morrison C, et al. Fludarabine and cyclophosphamide with filgrastim support in patients with previously untreated indolent lymphoid malignancies. Blood 2000; 96:71.

38. Hainsworth JD, Litcy S, Barton JH, Houston GA, Hermann RC, Bradof JE, Greco FA. Single-agent rituximab as first-line and maintenance treatment for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: A phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol 2003; 21:1746.

39. O'Brien SM, Kantarjian H, Thomas DA, Giles FJ, Freireich EJ, Cortes J, Lerner S, Keating MJ. Rituximab dose-escalation trial in chronic lymphocytic leukemia. J Clin Oncol 2001;19:2165.

40. Byrd JC, Murphy T, Howard RS, Lucas MS, Goodrich A, Park K, Pearson M, Waselenko JK, Ling G, Grever MR, Grillo-Lopez AJ, Rosenberg J, Kunkel L, Flinn IW. Rituximab using a thrice weekly dosing schedule in B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma demonstrates clinical activity and acceptable toxicity. J Clinic Oncol 12001; 9:2153.

41. Ladetto M, Bergui L, Ricca I, Campana S, Pileri A, Tarella C. Rituximab anti-CD20 monoclonal antibody induces marked but transient reductions of peripheral blood lymphocytes in chronic lymphocytic leukaemia patients. Medical Oncology 2000; 17:203.

42. Huhn D, von Schilling c, Wilhelm M, Ho AD, Hallek M, Kuse R, Knauf W, Riedel U, Hinke A, Srock S, Serke S, Peschel c, Emmerich B, for the German Chronic Lymphocytic Leukemia Study Group. Rituximab therapy of patients with B-cell chronic lymphocytic leukemia. Blood 2001; 98:1326.

43. List A, Kurtin S, Roe DJ, et al: Efficacy of lenalidomide in myelodysplastic syndromes. N Engl J Med 352:549-557, 2005.

44. List A, Dewald G, Bennet J, et al: Lenalidomide in myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med 355:1456-1465, 2006.

45. Richardson PG, Schlossman RL, Weller E, et al: Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in pateints with relapsed multiple myeloma. Blood 100:3063-3067, 2002.

46. Richardson PG, Mitsiades CS, et al: A randomized phase 2 study o f lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma. Bllod 108: 3458-3464, 2006.

47. Rajkumar SV, Hayman SR, Lacy MQ, et al: Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. Blood 106:4050-4053, 2005.

48. Marritt JB, Clarke IA, Dredge K, et al: Thalidomide and it analogues have distinct and opposing effects on TNF-alpha and TNFR2 during co-stimulation of both CD4(+) and CD8(+) cells. Clin Exp Immunol 130:75-84, 2002.

49. Mnagianeli DP, Blansfield JA, Kachala S, et al: Combination therapy targeting the tumor microenvironment is effective in a midel of human ocular melanoma. J Transl Med 5:38-46, 2007.

50. Tai YT, Li XF, Catley L, et al: Immunimodulatory drug lenalidomide (CC-5013, IMiD3) augments anti-CD40 SGN-40-induced cytotxoicity in human multiple myeloma: Clinical implication. Cancer Res 65:11712-11720, 2005.

51. LeBlanc R, Hideshima T, Catley LP, et al: Immunomodulatory drug costimulates T cells via the B7-CD28 pathway. Blood 103:1787-1790, 2004.

52. Hernandez-Ilizaliturri FJ, Reddy N, Holkova B, et al: Immunomodulatory drug CC-5013 or CC-4047 and rituximab enhance antitumor activity in a severe combined immunodeficient mouse lymphoma model. Clin Cancer Res 11:5984-5992, 2005.

53. Pellatti A, Jadersten M, Forsblom AM, et al: Lenalidomide inhibits the malignant cloneand upregulated the SPARC gene mapping to the commonly deleted region in 5q-syndrome patients. Proc Natl Acad Sci USA 104:11406-11411, 2007.

54. Chanan-Kan A, Miller KC, Musial L, et al: Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase II study. J Clin Oncol 24:5343-5349, 2006.

55. Ferrajoli A, Lee B-N, Schlette EJ, et al: Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia. Blood 111:5291-5297, 2008.

56. Andritsos LA, Johnson AJ, Lozanski G, et al: Higher doses of lenalidomide are associated with unacceptable toxicity including life-threatening tumor flare in patients with chronic lymphocytic leukemia. J Clin Oncol 26:2519-2525, 2008.

57. Chen C, Paul H, Xu W, et al: A phase II study of lenalidomide in previously untreated, symptomatic chronic lymphocytic leukemia (CLL). Blood 112:23, 2008 (abstr 44).

58. Byrd JC, Peterson BL, Morrison VA, Park K, Jacobson R, Hoke E, Vardiman JW, Rai K, Schiffer CA, Larson RA. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia; results from Cancer and Leukemia Group B 9712 (CALGB 9712). Blood 2003; 101:6.

59. Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. J Clin Onc 2005; 23:4079-4088.

60. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia. Lancet 2010; 376: 1164-74

61. A phase I study of lenalidomide in combination with fludarabine and rituximab in previously untreaed CLL/SLL. Leukemia (2010), 1-3

62. Flinn I, Berdeja Jesus G, Waselenko Jamie K, et al. Preliminary Results from a Phase I/II Study of Fludarabine, Rituximab, and Lenalidomide in Untreated Patients with Chronic Lymphocytic Leukemia (CLL). ASH 2010 (abst 2461)

63. Francesca M, Armiento D, Orlando S, et al. Fludarabine, Cyclophosphamide and Lenalidomide (FCL) for Previously Treated Patients with Chronic Lymphocytic Leukemia (CLL); Results of the Dose-Finding Phase of the GIMEMA LLC606 Study. ASH 2010 (abst 1377)

64. Provan D, Bartlett-Pandite L, Zwicky C, Neuberg D, Maddocks A, Corradini P et al. Eradication of polymerase chain reaction-detectable chronic lymphocytic leukemia cells is associated with improved outcome after bone marrow transplantation. Blood 1996; 88: 2228-2235

65. Moreton P, Kennedy B, Lucas G, et al. Eradication of minimal residual disease in B-cell chronic lymphocytic leukemia after alemtuzumab therapy is associated with prolonged survival. J. Clin Oncol 2005; 23: 2971-2979.

66. Bosch F, Ferrer A, Lopez-Guillermo A, Giné E, Bellosillo B, Villamor N et al. Fludarabine, cyclophosphamide and mitoxantrone in the treatment of resistant or relapsed chronic lymphocytic leukaemia. Br J Haematol 2002; 119: 976-984

67. Boettcher S, Fischer K, Stilgenbauer S, Busch R, Fingerle-Rowson G, Fink AM et al. Quantitative MRD assessments predict progression-free survival in CLL patients treated with fludarabine and cyclophosphamide with or without rituximab – a prospective analysis in 471 patients from the randomized GCLLSG CLL8 trial. Blood 2008; 112: 11, abstract 326)

68. Kay NE, Geyer SM, Call TG, Shanafelt TD, Zent CS, Jelinek DF et al. Combination chemoimmunotherpay with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia. Blood 207; 109: 405-411

69. Foon KA, Boyiadzis M, Land SR, et al: Chemoimmunotherapy with low-dose fludarabine and cyclophosphamide and high dose rituximab in previously untreated patients with chronic lymphocytic leukemia. J Clin Onc 2009; 27(4):498-503.

70. Smolej L, Spacek M, Brychtova Y, et al. Low-Dose Fludarabine and Cyclophosphamide Combined with Rituximab in the Treatment of Elderly/Comorbid Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL): Preliminary Results of Project Q-Lite by Czech CLL Study Group. ASH 2010 (abst 2466)

71. Hallek M, Cheson B, Catovsky D, et al: Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from International Workshop on Chronic Lymphocytic Leukemia update the National Cancer Institute – Working Group 1996 guidelines. Blood. 2008: 111:5446-5456.

72. Simon R., Optimal two-stage designs for phase II clinical trial. Controlled Clinical Trials 10:1-10, 1989.

73. Dufy DE, Santner TJ, Confidence intervals for binomial parameter based on multistage tests. Biometrics 43:81-93, 1987.

74. Foon et al. Chemoimmunotherapy with low dose fludarabine and cyclophosphamide and high dose rituximab in previously untreated patients with chronic lymphocytic leukemia. JCO 27 (4) 498-503, 2009.

Appendix I

PROTOCOL SIGNATURE PAGE

PHASE II CLINICAL PROTOCOL FOR THE TREATMENT OF PATIENTS WITH PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA WITH FOUR OR SIX CYCLES OF A COMBINATON OF FLUDARABINE, CYCLOSPHOSPHAMIDE AND RITUXIMAB FOLLOWED BY LENALIDOMIDE CONSOLIDATION/MAINTENANCE

Investigator:

Signature of Principal Investigator	Date
Printed Name of Investigator	

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

Appendix II: Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods)

Risks Associated with Pregnancy

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

Criteria for females of childbearing potential (FCBP)

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

Counseling

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

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol (Section **Error! Reference source not found.**)
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

The investigator must ensure that for females of childbearing potential:

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

For a female NOT of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females NOT of childbearing potential must be counseled

concerning the following risks and requirements prior to the start of lenalidomide study therapy):

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

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

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

Contraception

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

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

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

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

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Pregnancy testing

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

Before starting study drug

Female Patients:

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

Male Patients:

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

During study participation and for 28 days following study drug discontinuation

Female Patients:

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

Male Patients:

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

Additional precautions

- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Female patients should not donate blood during therapy and for at least 28 days following discontinuation of study drug.
- Male patients should not donate blood, semen or sperm during therapy or for at least 28 days following discontinuation of study drug.
- Only enough study drug for one cycle of therapy may be dispensed with each cycle of therapy.
- Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to lenalidomide must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Female patients should not donate blood during therapy and for at least 28 days following discontinuation of study drug.
- Male patients should not donate blood, semen or sperm during therapy or for at least 28 days following discontinuation of study drug.
- Only enough study drug for one cycle of therapy may be dispensed with each cycle of therapy.
- Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:
  - Highly effective methods:
    - Intrauterine device (IUD)

    - Hormonal (birth control pills, injections, implants)
    - Tubal ligation
    - Partner's vasectomy
  - Additional effective methods:
    - Male condom
    - Diaphragm
    - Cervical Cap
- Pregnancy tests before and during treatment, even if the patient agrees not to have reproductive heterosexual contact. Two pregnancy tests will be performed prior to receiving study drug, one within 10 to 14 days and the second within 24 hours of the start of study drug.
- Frequency of pregnancy tests to be done:
  - Every week during the first 28 days of this study and a pregnancy test every 28 days during the patient's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
  - If the patient missed a period or has unusual menstrual bleeding.
  - When the patient is discontinued from the study and at day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after study drug discontinuation.
- Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.
- NEVER share study drug with anyone else.
- Do not donate blood while taking study drug and for 28 days after stopping study drug.
- Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.
- Do not break, chew, or open study drug capsules.
- Return unused study drug to the study doctor.

1. Provide Lenalidomide Information Sheet to the patient.

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

1. I counseled the female NOT of child bearing potential regarding the following:
   - Potential risks of fetal exposure to lenalidomide (Refer to item #2 in FCBP)
   - NEVER share study drug with anyone else.
   - Do not donate blood while taking study drug and for 28 days after stopping study drug.

- Do not break, chew, or open study drug capsules
- Return unused study drug capsules to the study doctor.

2. Provide Lenalidomide Information Sheet to the patient.

MALE:

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

Investigator/Counselor Name (Print): _____

(circle applicable)

Investigator/Counselor Signature: _____ Date: _____/_____/_____

(circle applicable)

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

Appendix III – ECOG Performance Status Scale

SCORE	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix IV – NCI CTC Version 4.0

TOXICITY WILL BE SCORED USING NCI CTC VERSION 4.0 FOR TOXICITY AND ADVERSE EVENT REPORTING. A COPY OF THE NCI CTC VERSION 4.0 CAN BE DOWNLOADED FROM THE CTEP HOMEPAGE: (**HTTP://CTEP.INFO.NIH.GOV**). ALL APPROPRIATE TREATMENT AREAS HAVE ACCESS TO A COPY OF THE CTC VERSION

Appendix V: Cario-Bishop Tumor Lysis Criteria

(Cairo MS et al. Br J Haematol 2004)

Table: Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome (LTLS)

Uric Acid	≥ 476 µmol/l (≥ 8.0 mg/dl) or 25% increase from baseline
Potassium	≥ 6.0 mmol/l (≥ 6.0 mEq/l) or 25% increase from baseline
Phosphorous	≥1.45 mmol/l (≥ 4.5 mg/dl) or 25 % increase from baseline
Calcium	≤ 1.75 mmol/l (≤ 7.0 mg/dl) or 25% decrease from baseline
Laboratory tumor lysis syndrome (LTLS) is defined as either a 25% change or level above or below normal, as defined above, for any two or more serum values of uric acid, potassium, phosphate, and calcium within 3 days before or 7 days after the initiation of chemotherapy. This assessment assumes that a patient has or will receive adequate hydration (± alkalinization) and a hypouricaemic agent(s).	

Table: Cairo-Bishop Definition of Clinical TLS

The presence of laboratory TLS and one or more of the following criteria:
1. Creatinine: ≥ 1.5 ULN (age > 12 years or age adjusted) 2. Cardiac arrhythmia / sudden death 3. Seizure*

ULN, Upper limit of normal

*Not directly attributable to a therapeutic agent

Table: Cairo-Bishop Grading System for TLS

Grade	LTLS	Creatinine	Cardiac Arrhythmia	Seizure
0	-	≤ 1.5 x ULN	None	None

Grade	LTLS	Creatinine	Cardiac Arrhythmia	Seizure
1	+	1.5 x ULN	Intervention not indicated	None
2	+	> 1.5 – 3.0 x ULN	Non-urgent medical intervention indicated	One brief generalized seizure; seizure(s) well controlled or infrequent; focal motor seizures not interfering with ADL
3	+	> 3.0 – 6.0 x ULN	Symptomatic and incompletely controlled medically or controlled with device	Seizure in which consciousness is altered; poorly controlled seizure disorder; breakthrough generalized seizures despite medical intervention
4	+	> 6.0 x ULN	Life-Threatening	Seizures of any kind that are prolonged, repetitive, or difficult to control
5	+	Death*	Death*	Death*

LTLS, laboratory tumor lysis syndrome; ULN, upper limit of normal; ADL, activities of daily living

*Probably or definitely attributable to clinical TLS

Appendix VI: Cockcroft-Gault Formula for Calculated Creatinine Clearance

For serum creatinine concentration in mg/dL:

CrCl= [(140-age) x (wt in kg)]□÷□ [72 x serum creatinine (mg/dL)] (x 0.85 for females)

For serum creatinine concentration in mg/dL:

CrCl= [(140-age) x (wt in kg)]□□□ [0.81 x serum creatinine (μmol/L)] (x 0.85 for females)

Source: Cockcroft and Gault 1976

Appendix VII: Sample Consent Form