



Weill Cornell Medical College

**A Phase II Study of Daily Alternating Thalidomide and  
Lenalidomide Therapy Plus Rituximab (THRiL) as Initial  
Treatment for Patients with CLL**

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## SCHEMA

<b>PROTOCOL TITLE:</b> A phase II study of daily alternating Thalidomide and Lenalidomide therapy plus rituximab (THRiL) as initial treatment for patients with CLL.	
<b>STUDY DRUGS:</b>	Revlimid®, lenalidomide Thalomid®, thalidomide Rituxan®, rituximab
<b>INDICATION:</b>	Untreated CLL patients
<b>STUDY PHASE:</b>	Phase II
<p><b>BACKGROUND AND RATIONALE:</b></p> <p>While CLL lymphocytes demonstrate impaired apoptosis in vivo, they undergo spontaneous apoptosis ex vivo, even when cultured with cytokines that maintain normal and other malignant B lymphocytes. These data are often taken as evidence of CLL lymphocyte dependency upon cell surface derived signals (either cytokine or cell to cell mediated interactions) for survival. Thalidomide and lenalidomide are proprietary IMiD™ compounds of Celgene Corporation. These immunomodulatory agents are thought to work, in part, through similar mechanisms involving the inhibition of cytokine networks and alteration of adhesion molecules [1-2]. Both thalidomide and lenalidomide have shown activity as single agents and in combination with chemotherapy for the treatment of patients with CLL [3-6]. Treatment with thalidomide, studied first given its earlier development, was limited by its toxicities of neuropathy, sedation, and constipation. While lenalidomide demonstrates increased potency and tolerability compared with thalidomide, its use is complicated by neutropenia, thrombocytopenia, tumor flare, and tumor lysis syndrome [4, 6] and there are ongoing studies addressing these issues.</p> <p>Our hypothesis is that treatment of CLL with an alternating daily dosing schedule of thalidomide and lenalidomide may result in better tolerability by decreasing each agent’s toxicities, while preserving efficacy, and therefore lead to longer duration of therapy and improved responses than has been accomplished with either agent alone. Additionally, the combination of thalidomide and lenalidomide may have additive or synergistic effects therapeutically.</p>	
<p><b>STUDY OBJECTIVES:</b></p> <p><b><u>Primary:</u></b></p> <ul style="list-style-type: none"> <li>• To assess the response rate (overall, complete, and partial) in patients with CLL receiving initial treatment with thalidomide, lenalidomide, and rituximab.</li> </ul> <p><b><u>Secondary:</u></b></p> <ul style="list-style-type: none"> <li>• To determine the safety, tolerability, and feasibility of combining thalidomide, lenalidomide, and rituximab as initial treatment for patients with CLL requiring therapy.</li> <li>• To evaluate duration of response, time to response, progression free survival, and overall survival</li> <li>• To perform correlative studies to determine the potential mechanism of action of how thalidomide and lenalidomide are affecting CLL lymphocytes.</li> </ul>	

**STUDY DESIGN:**

This is an open label, phase II, single arm, and single institution study investigating daily alternating therapy with the IMiD™ compounds, thalidomide and lenalidomide, plus rituximab in untreated CLL patients requiring treatment. In order to obtain correlative samples, patients will receive a two week course of single agent thalidomide or lenalidomide before beginning treatment with the combination regimen. Half of the patients (odd numbered subjects) will start with a two week course of single agent thalidomide and the other half of the patients (even numbered subjects) will start with a two week course of single agent lenalidomide. This will allow the study of correlative samples of monotherapy with either IMiD™ agent. In Cycle -1, half of the patients (odd numbered subjects) will receive thalidomide 50mg PO daily on days 1-14, followed by no treatment days 15-28. The other half of the patients (even numbered subjects) will receive lenalidomide PO daily on days 1-14, followed by no treatment days 15-28. Starting cycle 1, patients will receive thalidomide 50 mg every other day (every odd day on days 1-28: Days 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25 & 27 of a 28 day cycle) alternating with lenalidomide on alternate every other day, dosed based upon current level with stepwise incremental dosing (every even day on days 1-28: Days 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 & 28 of a 28 day cycle). The starting dose of lenalidomide will be based on calculated creatinine clearance and the dose of lenalidomide may be escalated as tolerated to maximal dose of 25 mg (see Section 5 for details). Rituximab 375 mg/m<sup>2</sup> will be administered on days 1, 8, 15 and 22 starting with Cycle 1 and then again on the same weekly x 4 schedule every 6<sup>th</sup> cycle through Cycle 19 (Cycles 7, 13, and 19).

**STUDY ENDPOINTS****Primary:**

- Overall response rate (CR + PR) measured at time of best response

**Secondary:**

- Progression free survival
- Duration of response
- Time to response
- Overall survival
- Toxicity profile
- Correlative studies

**STUDY DURATION:** 3 years**TOTAL SAMPLE SIZE:** 24 patients**DOSING REGIMEN(S):**

**Cycle -1:** thalidomide 50 mg PO daily on days 1-14 or lenalidomide PO daily on days 1-14 of a 28 day cycle (odd numbered subjects will receive thalidomide and even numbered subjects will receive lenalidomide). Days 15-28 no drug treatment.

**Starting on Cycle 1:** Alternating every other day thalidomide 50 mg (every ODD day on days 1-28: Days-1,3,5,7,9,11,13,15,17,19,21,23,25 & 27 of a 28 day cycle) with lenalidomide (every EVEN day on days 1-28: Days-

**STUDY DRUG SUPPLIES:**

Celgene Corporation will supply lenalidomide and thalidomide as capsules for oral administration through the RevAssist® and S.T.E.P.S. programs.

2,4,6,8,10,12,14,16,18,20,22,24,26 & 28 of a 28 day cycle). The starting dose of lenalidomide will be based on calculated creatinine clearance and the dose of lenalidomide may be escalated at the start of any subsequent 28 day cycle beginning with the start of Cycle 2 as tolerated to a maximal dose of 25 mg (see Section 5 for details). Rituximab 375 mg/m<sup>2</sup> will be administered on days 1, 8, 15 and 22) starting with Cycle 1 and then again on the same weekly x 4 schedule every 6<sup>th</sup> cycle through Cycle 19 (Cycles 7, 13, and 19).

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## **1. OBJECTIVES**

### **1.1. Primary Objectives**

- To assess the response rate (overall, complete, and partial) in patients with CLL receiving initial treatment with thalidomide, lenalidomide, and rituximab

### **1.2. Secondary Objectives**

- To determine the safety, tolerability, and feasibility of combining thalidomide, lenalidomide, and rituximab as initial treatment for patients with CLL requiring therapy.
- To evaluate duration of response, time to response, progression free survival and overall survival
- To perform correlative studies to determine the potential mechanism of action of how thalidomide and lenalidomide are affecting CLL lymphocytes.

### **1.3. Primary Endpoint**

- Overall response rate (CR + PR) measured at time of best response

### **1.4. Secondary Endpoints**

- Progression free survival
- Duration of response
- Time to response
- Overall survival
- Toxicity profile
- Correlative studies

## **2. BACKGROUND**

### **2.1 Introduction**

Lenalidomide and thalidomide are proprietary IMiD™ compounds of Celgene Corporation. IMiD™ compounds have both immunomodulatory and anti-angiogenic properties which could confer antitumor and antimetastatic effects. Lenalidomide has been demonstrated to possess anti-angiogenic activity through inhibition of bFGF, VEGF and TNF-alpha induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF [7]. In addition, lenalidomide has a variety of immunomodulatory effects. Lenalidomide stimulates T cell proliferation, and the production of IL-2, IL-10 and IFN-gamma, inhibits IL-1 beta and IL-6 and modulates IL-12

production [8]. Up regulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity [9].

Although the exact antitumor mechanism of action of lenalidomide is unknown, a number of mechanisms are postulated to be responsible for the activity of lenalidomide seen against multiple myeloma. Lenalidomide has been shown to increase T cell proliferation, which leads to an increase in IL-2 and IFN-gamma secretion. The increased level of these circulating cytokines augment natural killer cell number and function, and enhance natural killer cell activity to yield an increase in multiple myeloma cell lysis [10]. In addition, lenalidomide has direct activity against multiple myeloma and induces apoptosis or G1 growth arrest in multiple myeloma cell lines and in multiple myeloma cells of patients resistant to melphalan, doxorubicin and dexamethasone [11].

## 2.2 Indications and Usage

Revlimid® (lenalidomide) is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Revlimid® is also approved in combination with dexamethasone for the treatment of patients with multiple myeloma that have received at least one prior therapy.

Thalomid® (thalidomide) is indicated for the treatment of patients with newly diagnosed multiple myeloma in combination with dexamethasone.

Rituxan® (rituximab) is indicated for the treatment of patients with: Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent, Previously untreated follicular, CD20-positive, B-cell NHL in combination with CVP chemotherapy, Non-progressing (including stable disease), low-grade, CD20-positive B-cell NHL, as a single agent, after first-line CVP chemotherapy and Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens.

## 2.3 Adverse Events

Most frequently reported adverse events reported during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, UTI, Upper respiratory infection, cellulites, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures. Tumor flare reaction (TFR) has been reported frequently in CLL patients treated with lenalidomide. Tumor lysis syndrome (TLS) has been reported in CLL patients treated with lenalidomide. Precautions must be taken to prevent TLS including proper selection of patients with regard to renal function, correction of electrolyte abnormalities, and

TLS prophylaxis and monitoring. Lenalidomide has been shown to increase the level of digoxin in the blood in some patients

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

## 2.4 Overview of CLL

Chronic lymphocytic leukemia (CLL) is the most common leukemia in North America, with an estimated 15,000 new cases diagnosed in the United States in 2007 [12]. CLL is typically a disease of advanced age, with a median age at diagnosis of approximately 65 years, and a male-to-female ratio of 2:1 [13]. CLL is characterized by the clonal expansion of long-lived, mature B lymphocytes that co-express the CD5, CD19, and CD23 surface antigens [14-15]. The malignant cells of CLL are frozen in the G0 stage of the cell cycle, increasing in numbers due more to a lack of apoptosis than augmented proliferation [16-21]. The morbidity and mortality associated with CLL results primarily from the progressive accumulation of lymphocytes in secondary lymphoid tissues and bone marrow. Patients might remain asymptomatic for prolonged periods of time, but most develop disease progression, with 70% of CLL patients dying from causes related to their disease [22].

Overall, patients with CLL have a median life expectancy of almost nine years, but great variability exists depending upon several well described prognostic markers [23]. Traditional prognostic markers include stage [24-25], age [26], gender [26], pattern of bone marrow involvement [27-28], lymphocyte doubling time [29-30], number of circulating prolymphocytes [31-32], and beta-2-microglobulin level [33-34]. More recently, prognostic markers have been identified that are based more on the biological features of the malignant lymphocytes themselves. These novel prognostic markers include: IgVH mutational status [35-36], CD38 expression [36], zap-70 expression [37], and interphase FISH (iFISH) abnormalities [38].

Criteria initially described by the National Cancer Institute Working Group (NCI-WG) on CLL [14], and updated by the International Workshop on CLL (IWCLL) [15], describe the indications for initiation of therapy for patients with CLL as: evidence of progressive marrow failure as evidence by anemia or thrombocytopenia (Rai stage III or IV), massive or symptomatic splenomegaly, massive or symptomatic lymphadenopathy, progressive lymphocytosis with an increase of more than 50% over a 2-month period or a lymphocyte doubling time of less than 6 months, autoimmune cytopenias poorly responsive to corticosteroids, or the presence of B symptoms (fevers greater than 38.0, unintentional weight loss >10% in six months, significant fatigue, or night sweats) [15].

The first chemotherapy treatments proven to be of benefit for patients with CLL were alkylator based regimens, with or without steroids. For untreated patients, response rates range from 50-80%, but these include few complete remissions and a 5-year survival of approximately 50% [39-40] [41] [42-43]. In the late 1980s, the nucleoside analogs, fludarabine [44-49], 2-chlorodeoxyadenosine [50-51], and pentostatin [52-53], emerged as effective therapies for CLL. Based upon the very high response rates apparent in early clinical trials, fludarabine has received the most interest. Fludarabine produces response rates of approximately 70-80% in previously untreated patients, including a complete response rate of up to 30%. In previously treated patients, response rates to fludarabine of 50-70% are seen, including a 67% response rate in patients who received fludarabine as their initial therapy [44-49]. By combining fludarabine with rituximab [54-55] or cyclophosphamide plus rituximab [56-

57], response rates as high as 90-95% can be achieved. Two additionally approved agents for treatment of CLL include alemtuzumab and bendamustine. Alemtuzumab, originally approved for fludarabine refractory CLL with overall response rates of 33% [58], has also received FDA approval in untreated CLL patients with an overall response rate of 83%, including a CR rate of 24% [59]. Bendamustine, approved in 2008 for all lines of treatment of CLL, can generate an overall response rate of 68% and a CR rate of 30% in untreated patients with CLL [60].

Once a patient has progressed on fludarabine, few therapeutic options remain. Fludarabine retreatment offers a possible option for some patients, with overall response rates of 67%, but a CR rate of only 20% [45]. Once a patient becomes refractory to fludarabine, the median overall survival is only nine to ten months [61-62]. Alemtuzumab, initially approved for patients whose disease is refractory to fludarabine, demonstrated 33% response rates, but an overall survival of only 16 months [58]. Ofatumumab, a novel antibody directed against CD20, is currently undergoing testing in these patients, with preliminary overall response rates of 51% in fludarabine-refractory patients that progress after alemtuzumab and 44% in fludarabine-refractory patients with bulky lymphadenopathy that are unlikely to respond to alemtuzumab [63]. Unfortunately, the overall survival for the two groups was 14 and 15 months, respectively.

## 2.5 Rational for Treatment in this Setting

While CLL lymphocytes demonstrate impaired apoptosis *in vivo*, they undergo spontaneous apoptosis *ex vivo*, even when cultured with cytokines that maintain normal and other malignant B lymphocytes. These data are often taken as evidence of CLL lymphocyte dependency upon cell surface derived signals (either cytokine or cell to cell mediated interactions) for survival. Numerous cognate and non-cognate pathways that may play vital roles in CLL cell survival have been identified, including CD40-CD154, VEGF, bFGF, BAFF/BLyS, APRIL, TNF-alpha, IL-4, and IL-10 [64-83]. Agents that alter or inhibit these cytokine networks may be able to play an important role in CLL therapy.

Thalidomide and lenalidomide are immunomodulatory agents that are thought to work, in part, through the inhibition of cytokine networks and alteration of adhesion molecules, including multiple TNF family members [1-2]. One of the early rationales for testing thalidomide as a therapy for CLL were data suggesting a role for TNF-alpha in CLL cell survival [79-81] and the ability of thalidomide to inhibit TNF-alpha production [84]. Subsequent work has demonstrated additional mechanisms of action for thalidomide [85-87]. Clinical studies involving thalidomide, alone and in combination with chemotherapy, confirmed its activity as a therapy for CLL [3, 5]. Unfortunately, treatment with thalidomide was limited by its toxicities of neuropathy, sedation, and constipation.

Lenalidomide, developed by chemically modifying thalidomide, demonstrates improved efficacy and tolerability compared with thalidomide, although its use is still limited by its toxicities of neutropenia, thrombocytopenia, tumor flare, and tumor lysis syndrome [4, 6, 88].

Given the likely similar mechanisms of action for thalidomide and lenalidomide and that the toxicities of both agents are dose related, alternate daily dosing of these agents would provide continuous anti-tumor effect, while utilizing a lower dose of each of the agents. The alternating daily dosing of thalidomide and lenalidomide may result in better tolerability by potentially decreasing each agent's toxicities, lead to longer duration of therapy and result in improved responses than has been accomplished with either agent alone. Additionally, the combination of thalidomide and lenalidomide

may have additive or synergistic effects therapeutically. The tolerability of thalidomide and lenalidomide used in combination has been demonstrated in studies of patients with multiple myeloma [89-90].

The potential tolerability and response rate of a regimen combining thalidomide, lenalidomide, and rituximab make it an ideal treatment for patients with CLL early in the course of their disease. Positioning such a regimen early in the treatment algorithm enables agents with greater toxicities to be delayed until required, helping preserve the patient's quality of life for as long as possible.

This phase II study would investigate the combination of thalidomide, lenalidomide and rituximab in patients with untreated CLL. Patients will remain on the treatment regimen as long as they do demonstrate disease progression or toxicity.

### **3. PATIENT SELECTION**

#### **Screening and Eligibility**

The Investigator is responsible for keeping a record of all subjects who sign an Informed Consent Form for entry into the study. All subjects will be screened for eligibility. Screening procedures are outlined in Section 10, Schedule of Study Assessments and unless otherwise specified, must take place within 28 days prior to initiation of therapy. Approximately 24 subjects with untreated CLL will be screened for enrollment and must meet the eligibility criteria below.

Subjects must meet the following inclusion/exclusion criteria to be eligible for the study.

#### **3.1 Inclusion Criteria**

1. Confirmed diagnosis of CLL or SLL based upon standard criteria as outlined in the IWCLL Update of the 1996 NCI-Working Group criteria for CLL [15]:
  - a) Presence of one of the following:
    1. more than or equal to  $5 \times 10^9$  B lymphocytes/L in the peripheral blood for a duration of at least 3 months. Patients with a B lymphocytosis will be characterized as CLL, while those without will be characterized as SLL
    2. the presence of lymphadenopathy resulting from infiltration with lymphocytes with the phenotype of CLL
    3. bone marrow infiltration with lymphocytes with the phenotype of CLL
  - b) Lymphocytes with the morphologic appearance of small, mature appearing lymphocytes, with  $\leq 55\%$  prolymphocytes (blood or bone marrow)
  - c) Cellular phenotype characterized by the:
    1. co-expression of the CD5, CD20, and CD23 surface antigens
    2. clonal kappa or lambda light chain expression

3. dim surface immunoglobulin expression
2. No prior therapy for CLL, including treatment for autoimmune conditions that have developed since the initial diagnosis of CLL.
3. Active disease requiring therapy as defined by the IWCLL Update of the 1996 NCI-WG guidelines [15]:
  - a) Evidence of progressive marrow failure as manifested by the development of worsening of anemia and / or thrombocytopenia
  - b) Massive, progressive, or symptomatic splenomegaly
  - c) Massive, progressive, or symptomatic lymphadenopathy
  - d) Progressive lymphocytosis with an increase of more than 50% over a 2-month period or a lymphocyte doubling time of less than 6 months.
  - e) Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroids or other standard therapy
  - f) Presence of disease related symptoms: unintentional weight loss of more than 10% within previous six months, significant fatigue, fevers greater than 100.5 F or 38.0 C for 2 or more weeks without evidence of infection, night sweats for more than 1 month without evidence of infection.
4. Understand and voluntarily sign an informed consent form.
5. Age  $\geq 18$  years at the time of signing the informed consent form.
6. Able to adhere to the study visit schedule and other protocol requirements.
7. ECOG performance status of  $\leq 2$  at study entry (see Appendix B).
8. Laboratory test results within these ranges:
  - Absolute neutrophil count  $\geq 1000/\text{mm}^3$
  - Platelet count  $\geq 50,000/\text{mm}^3$
  - Creatinine clearance of  $\geq 30$  mL/min by Cockcroft-Gault formula (see Appendix E). Patients with a baseline creatinine clearance of  $\geq 30$  and  $\leq 60$  mL/min will have a starting dose of lenalidomide 5 mg PO every other day per the defined schedule. Patients with a baseline creatinine clearance of  $\geq 60$  mL/min will have a starting dose of lenalidomide 5 mg PO daily per the defined schedule (see Section 5 for details).
  - Total bilirubin  $\leq 1.5$  times the ULN, unless abnormality is the result of Gilbert's disease or the result of the CLL

- AST (SGOT) and ALT (SGPT)  $\leq 3 \times$  ULN (or  $\leq 5 \times$  ULN if due to the CLL)
9. Disease free of prior malignancies for  $\geq 2$  years with exception of curatively treated basal cell carcinoma, squamous cell carcinoma of the skin, or carcinoma “in situ” of the cervix or breast.
  10. All study participants must be registered into the mandatory Revlimid REMS® and S.T.E.P.S.® ( P-TAP: Protocol Therapy Assistance Program) program(s), and be willing and able to comply with the requirements of Revlimid REMS® and S.T.E.P.S.®.
  11. Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days prior to and again within 24 hours of starting treatment and again within 24 hours before the first dose of lenalidomide AND thalidomide. FCBP 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 and/or thalidomide. Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program . Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Method..
  12. Able to take aspirin 81 or 325 mg daily as prophylactic anticoagulation, unless already on therapeutic anticoagulation. Patients intolerant to ASA may use coumadin or low molecular weight heparin.

### 3.2 Exclusion Criteria

1. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from providing informed consent.
2. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.
3. Evidence of laboratory TLS by Cairo-Bishop Definition of Tumor Lysis Syndrome (see Appendix D). Subjects may be enrolled upon correction of electrolyte abnormalities.
4. Concurrent use of other anti-cancer agents or treatments.

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† A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

5. Prior treatment with thalidomide or lenalidomide.
6. Active serious infection not controlled with antibiotics.
7. Autoimmune hemolytic anemia or thrombocytopenia requiring treatment.
8. Known positive for HIV
9. Active infection with hepatitis B, defined by being positive for HepBsAg or Hep B DNA by PCR, or hepatitis C
10. Pre-existing peripheral neuropathy  $\geq$  grade 2
11. Pregnant or breast feeding females. (Lactating females must agree not to breast feed while taking lenalidomide and/or thalidomide).

#### **4. REGISTRATION PROCEDURES**

##### **Central Patient Registration**

[REDACTED]

[REDACTED]

[REDACTED]

Once a patient is registered onto the trial, they will need to be registered with both the STEPS® (P-TAP) and RevAssist® (RASP) programs in order to receive their thalidomide and lenalidomide. (See Appendix F for instructions.)

#### **5. TREATMENT PLAN**

##### **5.1 Overall design**

This is an open label, phase II, single arm, and single institution study investigating daily alternating IMiD™ agent therapy with thalidomide and lenalidomide plus rituximab in untreated CLL patients requiring treatment as outlined in the IWCLL update of the 1996 NCI-Working Group criteria for CLL [15]. Half of the patients (odd numbered subjects) will start with a two week course of single agent thalidomide and the other half of the patients (even numbered subjects) will start with a two week course of single agent lenalidomide in order to perform correlative studies to elucidate the

mechanisms of action of thalidomide and lenalidomide. Daily alternating IMiD™ agent therapy will begin with cycle 2 as follows:

- Cycle -1: half of the patients (odd numbered subjects) will receive thalidomide 50 mg PO daily on days 1-14, followed by no treatment days 15-28 and the other half of the patients (even numbered subjects) will receive lenalidomide PO daily on days 1-14, followed by no treatment days 15-28. The lenalidomide dose will be based on baseline calculated creatinine clearance\*.
- Cycles 1 and all escalation cycles: Patients will receive thalidomide 50 mg (every **ODD** day on Days 1-28 of a 28 day cycle: Days 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25 & 27) with lenalidomide (every **EVEN** day on Days 1-28 of a 28 day cycle: Days 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 & 28). Each cycle will be 28 days in length. Patients who received lenalidomide during Cycle -1 will receive the same dose of lenalidomide starting with Cycle 1. For patients who did not receive lenalidomide during Cycle -1, lenalidomide will be initiated at a starting dose based on baseline calculated creatinine clearance\*.
- Cycle 1: Patients will also receive rituximab 375 mg/m<sup>2</sup> IV on Days 1, 8, 15 and 22 (+/- 2 days) and then again on the same weekly x 4 schedule every 6<sup>th</sup> cycle through Cycle 19 (Cycle 7, 13, and 19).

\*\*\*\* Rituximab can be given +/- 2days.

\*\*\*\*All correlative work must be drawn prior to Rituximab administration regardless of the day Rituximab is given.

\*The lenalidomide starting dose will be based on baseline calculated creatinine clearance as follows:

<b>Lenalidomide Starting Dose Based on Renal Function at Study Entry</b>	
<b>Baseline Calculated Creatinine Clearance (by Cockcroft-Gault)</b>	<b>Starting Lenalidomide Dose</b>
≥ 60 ml/min	5 mg every <b>EVEN</b> day during Days 1 – 28 of each 28-day cycle**
≥ 30 and < 60 ml/min	5 mg every 2 <sup>nd</sup> <b>EVEN</b> day during Days 1 - 28 of each 28-day cycle**

\*\*For patients who receive lenalidomide during Cycle -1, the lenalidomide dose during Cycle -1 will be at the dose indicated above (5 mg every other day or 5 mg every 2<sup>nd</sup> EVEN day depending on baseline calculated creatinine clearance) taken daily on Days 1 – 14 of the 28-day cycle.

At investigator discretion, the lenalidomide dose may be gradually increased in a step-wise manner (in 5 mg increments) at the start of any subsequent 28-day treatment cycle beginning with the start of Cycle 2, if the patient tolerated the prior treatment cycle without requiring dose modifications, interruptions or delays due to toxicity. For patients who initiate therapy at a lenalidomide 5 mg every 2<sup>nd</sup> EVEN day starting dose, the first dose titration would be to lenalidomide 5 mg every EVEN day, and subsequent dose titrations would be permitted in 5 mg increments. 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. For patients who initiate treatment at lenalidomide 5 mg based on baseline calculated creatinine clearance  $\geq 60$ ml/min, the maximum allowable dose is lenalidomide 25 mg every EVEN day during Days 1-28 of a 28-day cycle. For patients who initiate treatment at lenalidomide 5 mg every 2<sup>nd</sup> EVEN day due to baseline calculated creatinine clearance  $\geq 30$ ml/min but  $< 60$ ml/min, the maximum allowable dose is lenalidomide 15 mg every EVEN day during Days 1-28 of a 28-day cycle.

## 5.2 Investigational Study Drug Combination (THRIL)

### **Starting with Cycle 1:**

#### **A cycle is 28 days:**

Thalidomide 50 mg every ODD day, days 1-28 every 28 days

Lenalidomide every EVEN day, days 1-28 every 28 days at the dose indicated above and with possible dose escalation as described in 5.1.

Rituximab 375 mg/m<sup>2</sup> IV on days 1, 8, 15 and 22 (+/- 2 days) starting with Cycle 1 and then again on the same weekly x 4 schedule every 6<sup>th</sup> cycle through Cycle 19 (Cycles 7, 13, and 19).

Responses will be assessed at monthly intervals using the response criteria outlined by the IWCLL update of the 1996 NCI-Working Group criteria. Patients will remain on treatment until they demonstrate disease progression or unacceptable toxicity. It will be important for the investigator to differentiate disease progression from tumor flare. While no strict criteria can be established for this distinction, rapid changes in clinical status that occur within four weeks of a dose escalation are likely to be tumor flares and should be treated as such.

Tumor flare has been described with both thalidomide and lenalidomide treatment. Therefore, patients should be monitor closely for signs and symptoms of tumor flare for four weeks after each increase in dose. 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  $\geq$  Grade 2 may be treated with corticosteroids. Narcotic analgesics may be added as needed for pain control in subjects experiencing  $\geq$  Grade 2 tumor flare. If corticosteroids are used, the following dosage schedule is

recommended: prednisone 20 mg PO QD x 7 days followed by 10 mg PO QD x 7 days. (See Appendix D: Cairo Bishop Tumor Lysis Definition and Grading Criteria.)

### 5.3 Visit schedule and assessments

Screening Assessments and all on study scheduled visits and assessments are outlined in Section 10 Table of Study Assessments.

At treatment discontinuation, subjects will undergo off study evaluations per the Schedule of Assessments, Section 10. In addition, a safety assessment will be done approximately 28 days post the last dose of study drug. Follow-Up contact with the subjects should occur at a minimum of sixth months.

### 5.4 Drug Administration

#### 5.4.1 Dosing regimen

- Cycle -1: patients will receive thalidomide 50 mg PO daily on days 1-14 or lenalidomide PO on days 1-14, followed by no treatment days 15-28, as described previously in 5.1.
- Cycle 1 and subsequent cycles: Patients will receive thalidomide 50 mg (every **ODD** day on days 1-28 of a 28 day cycle) with lenalidomide (every **EVEN** day on days 1-28 of a 28 day cycle), as described previously. Each cycle will be 28 days in length.
- Cycle 1: Patients will also receive rituximab 375 mg/m<sup>2</sup> IV on Days 1, 8, 15 and 22 and then again on the same weekly x 4 schedule every 6<sup>th</sup> cycle through Cycle 19 (Cycle 7, 13, and 19), as described previously.

Patients unable to tolerate either thalidomide or lenalidomide will be removed from protocol. Patients unable to tolerate rituximab can continue on with protocol treatment without additional rituximab being administered.

Dosing of thalidomide and lenalidomide should be at bedtime in order to allow for the sedative effects of thalidomide to not cause daytime somnolence and to maintain regular dosing intervals. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.** At the start of any non-clinic visit treatment cycles subsequent to Cycle 24, one cycle of study drug will be shipped to the subject.

See Section 5.5 for allopurinol and oral hydration requirements as prophylaxis against tumor lysis syndrome (TLS).

Thalidomide and lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened.

If a dose of thalidomide or 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 thalidomide or 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 (See section 5.6).

#### **5.4.2 Record of administration**

Accurate records will be kept of all study drug administration (including dispensing and dosing) will be made in the source documents. At all times, when dispensing study drug, research center personnel will review the instructions, printed on the packaging, with subjects. Subjects will be asked to maintain a diary to record the drug administration. Subjects will be asked to bring any unused study drug and empty study drug containers to the research center at their next visit. Research personnel will count and record the number of used and unused study drug capsules at each visit and reconcile with the patient diary. At the start of any non-clinic visit treatment cycles subsequent to Cycle 24, the packaging instructions will be reviewed with subjects by telephone call, and study drug and medication log will be shipped to the subject.

### **5.5 General Concomitant Medication and Supportive Care Guidelines**

#### **5.5.1 Recommended Concomitant Therapy**

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, and antiemetics when appropriate. Starting with Cycle -1 and while on study, subjects will receive prophylaxis against *Pneumocystis pneumonia* (with Bactrim DS thrice weekly or equivalent), varicella zoster (with valacyclovir 500 mg daily or equivalent), tumor lysis syndrome (with allopurinol and 8-10 eight ounce glasses of fluid daily), and thrombosis (with aspirin 81 mg daily).

Patients intolerant to or unable to take allopurinol beyond the first 2 cycles and can maintain adequate oral hydration are still eligible to continue to receive treatment on study. Patients who cannot take allopurinol for at least the first 2 cycles are to be removed from study.

Treating physicians must watch for signs of tumor lysis syndrome. It is recommended that all patients with signs of significant tumor lysis syndrome be hospitalized for monitoring, aggressive fluid management, and possible rasburicase.

#### **Hematopoietic Growth Factors**

Myeloid growth factors (G-CSF and pegfilgrastim only) may be used. GM-CSF may not be used given the theoretical impact it might have on CLL disease activity. Erythropoietic Stimulating Agents (ESAs; Aranesp, Procrit) may be used at the discretion of the treating physician and need to be recorded in the medication list.

### **Anticoagulation Considerations**

Patients already on aspirin or other anticoagulation should remain on the current anticoagulation dosing regimen they are on. If they are not on anticoagulation, then they should initiate prophylaxis with aspirin 81 mg or 325 mg daily on Day 1 of Cycle -1. Dose is at the discretion of the Investigator. Coumadin or low molecular weight heparin may be utilized in patients that are intolerant to ASA.

If prophylactic anti-coagulation is used, it should be held for platelet counts < 50,000/mm<sup>3</sup> and then restarted when platelet counts are above this level.

### **Tumor Lysis Syndrome 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.

If patients are intolerant or unable to take allopurinol beyond the first 2 cycles AND can maintain adequate hydration, it will be up to the discretion of the Investigator if patient can continue the treatment plan. Patients who cannot take allopurinol for at least the first 2 cycles are to be removed from study.

Allopurinol 300 mg daily beginning at least 3 days before the start of Cycle -1, continuing through any cycle of lenalidomide escalation and continuing, at least for one additional cycle post escalation as TLS prophylaxis is required for all subjects.

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 fluid each day for the first 14 days of Cycle -1 and Cycle 1 and any subsequent cycle of lenalidomide escalation.

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 treatment, or when treatment 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.

## **Treatment and Dose Modification for Tumor Lysis Syndrome**

All subjects meeting criteria of laboratory TLS or  $\geq$  Grade 1 TLS according to the Cairo-Bishop Definition of Tumor Lysis Syndrome (see Appendix D) 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 D: Cairo-Bishop Definition of Tumor Lysis Syndrome), lenalidomide and thalidomide will be continued at the same dose without interruption or dose reduction. TLS prophylaxis measures outlined in Section 5.5.1 should be continued or re-instituted.
- Subjects with  $\geq$  Grade 2 TLS (see Appendix D: 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 and thalidomide at the current dose with appropriate TLS prophylaxis (Section 5.5.1) after resolution of electrolyte abnormalities to Grade 0.
  - Subsequent episodes: restart lenalidomide and thalidomide with appropriate TLS prophylaxis (Section 5.5.1) after resolution of electrolyte abnormalities to Grade 0. At physician discretion, the doses of lenalidomide and thalidomide may be restarted at the current dose or the dose of lenalidomide and/or thalidomide 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 treatment for 4 consecutive weeks and on Day 3 or 4 following initiation of treatment. See Section 10, Schedule of Study Assessments, for additional specifics regarding serum chemistry and uric acid testing.

## **Tumor Flare Reaction**

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  $\geq$  Grade 2 may be treated with corticosteroids. Narcotic analgesics may be added as needed for pain control in subjects experiencing  $\geq$  Grade 2 tumor flare. If corticosteroids are used, the following dosage schedule is recommended; prednisone 20 mg PO QD x 7

days followed by 10 mg PO QD x 7 days. Given the potential for tumor flares to occur at each escalation of lenalidomide dose, prednisone treatment may be repeated at each occurrence of tumor flare. Patients experiencing tumor flares should not have their dose of lenalidomide escalated the subsequent cycle.

Tumor flare occurring during a cycle when the dose of lenalidomide or thalidomide was escalated should be recorded as an adverse event and not as progressive disease (PD). For tumor flare occurring after the first 2 weeks of any cycle of lenalidomide escalation, it is up to the discretion of the physician to differentiate tumor flare from progression. It is expected that some degree of tumor flare reaction is likely until the patient is on the maximum dose of lenalidomide for more than four weeks. Because of this and the typically indolent nature of CLL, investigators are encouraged to continue escalating a subject's lenalidomide dose if safe and not to determine a patient as having progressive disease until after they have been on the maximum dose of lenalidomide for more than four weeks.

#### **5.5.2 Prohibited concomitant therapy**

Concomitant use other anti-cancer therapies, including radiation, or other investigational agents is not permitted while subjects are receiving study drug during the treatment phase of the study. Corticosteroids may be administered for treatment of a tumor flare reaction as detailed above.

### **5.6 Duration of Therapy and Criteria for Removal From Study**

- Treatment will continue until the occurrence of any of the following events.
- Disease progression (excluding tumor flare)
- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of the treatment regimen.
- Discontinuation of thalidomide or lenalidomide for any reason. (Note, patients who are unable to tolerate rituximab infusions may still continue on the protocol.)
- Major violation of the study protocol.
- Withdrawal of consent
- Lost to follow up
- Death
- Suspected pregnancy or positive pregnancy

### **5.7 Duration of Follow Up**

Subjects who discontinue treatment for any reason will be followed for 30 days. At 28 days post treatment, subjects will undergo a safety assessment. In addition, off study evaluations per the Schedule of Assessments, Section 10 will be done.

## 6. DOSING DELAYS/DOSE MODIFICATIONS

### 6.1 Dose Reduction and Escalation Steps

Doses of the agent believed to be the cause of the AE should be held until resolution of the AE (see Section 6.3 for detailed dose modification instructions).

Table 1 below is used for step-wise dose titration of lenalidomide and for dose reductions of lenalidomide or thalidomide. In all cases, dose modifications should be applied one Dose Level at a time. **Please see Section 5.1 for dose escalation criteria and other details.**

<b>Table 1: Dose Levels</b>	
<b>Lenalidomide</b>	
Dose Level -2*	5 mg every 3 <sup>rd</sup> EVEN day on Days 1-28 of a 28 day cycle*
Dose Level -1***	5 mg every 2 <sup>nd</sup> EVEN day on Days 1-28 of a 28 day cycle
Dose Level 1**	5 mg every EVEN day on Days 1-28 of a 28 day cycle
Dose Level 2	10 mg every EVEN day on Days 1-28 of a 28 day cycle
Dose Level 3	15 mg every EVEN other day on Days 1-28 of a 28 day cycle
Dose Level 4	20 mg every EVEN other day on Days 1-28 of a 28 day cycle
Dose Level 5	25 mg every EVEN other day on Days 1-28 of a 28 day cycle
<b>Thalidomide</b>	
Dose Level -1	50 mg every 2 <sup>nd</sup> ODD day on Days 1-28 of a 28 day cycle
Dose Level 1	50 mg every ODD day on Days 1-28 of a 28 day cycle

Lenalidomide 5 mg every 3<sup>rd</sup> even 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 3<sup>rd</sup> even day may, at the discretion of their physician, have their dose held until toxicity resolves as described in Sections 6.2 and 6.3, and then restart lenalidomide at 5 mg every 3<sup>rd</sup> even day. If the same toxicity recurs at lenalidomide 2.5 mg every second even day, consideration should be given to discontinuing lenalidomide.

\*\* For lenalidomide, Dose Level 1 is the starting dose for patients that have a baseline creatinine clearance  $\geq$  60ml/min (along with thalidomide Dose Level 1).

\*\*\* For lenalidomide, Dose Level -1 is the starting dose for patients that have a baseline creatinine clearance  $\geq$  30ml/min and  $<$  60ml/min (along with thalidomide Dose Level 1).

**Lenalidomide dose escalation is permitted in a step-wise manner per Table 1. Please see Section 5.1 for dose escalation criteria and other details.**

### 6.2 Instructions for Initiation of a New Cycle

A new course of treatment may begin on the scheduled day 1 of a new cycle utilizing the same criteria as outlined for dose modifications in sections 6.3, table 2.

- The ANC is  $\geq 1000/\text{mm}^3$ ; if ANC is between  $500\text{-}1000/\text{mm}^3$  and not associated with fever  $\geq 38.5^\circ\text{C}$ , the new cycle should start as planned and G-CSF or pegfilgrastim may be used to support neutrophil count.
- The platelet count is  $\geq 25,000/\text{mm}^3$ ;
- Any drug-related rash that may have occurred has resolved to  $\leq$  grade 1 severity;
- Any drug-related neuropathy that may have occurred has resolved to  $\leq$  grade 2 in severity;
- Tumor lysis syndrome (TLS) has not exceeded grade 1 severity during previous cycle (see Appendix D: Cairo-Bishop Definition of Tumor Lysis Syndrome);
- If TLS  $\geq$  grade 2 during previous cycle (see Appendix D: Cairo-Bishop Definition of Tumor Lysis Syndrome), electrolyte abnormalities have resolved to  $\leq$  grade 0 severity;
- Any other drug-related adverse events that may have occurred have resolved to  $\leq$  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 the dose of lenalidomide or thalidomide was reduced during the previous cycle, and the cycle was completed without requiring further dose modification, then the next cycle will start at the same doses of lenalidomide and thalidomide as given at the end of the previous cycle. **If lenalidomide or thalidomide dosing was omitted for the remainder of the previous cycle due to toxicity attributed to lenalidomide or thalidomide or if the new cycle is delayed due to lenalidomide-related or thalidomide-related toxicity newly encountered on the scheduled Day 1**, then the new cycle will be started with a one-level dose reduction of lenalidomide or thalidomide based on attribution.

## **Instructions for dose modifications or interruption**

Dose delay and dose reduction rules are as follows and in the table below.

- Lenalidomide and thalidomide dose reduction steps are outlined in Section 6.1.
- For treatment interruptions during a cycle, the 28-day schedule of each cycle will continue to be followed. Missed doses of lenalidomide or thalidomide 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 6.2), the restart day of therapy becomes Day 1 of the next cycle.

Dose re-escalation of lenalidomide following dose reductions due to neutropenia, thrombocytopenia, tumor lysis syndrome, tumor flare, rash, neuropathy, hypothyroidism or hyperthyroidism:

- If the dose of lenalidomide has been reduced for neutropenia, thrombocytopenia, rash, neuropathy, lenalidomide dose re-escalation is permitted if the subject completes one full cycle without experiencing any toxicity that requires dose interruption or reduction. The lenalidomide dose may be increased by one dose level at the initiation of a new cycle of therapy.
- If the dose of lenalidomide has been dose reduced for tumor lysis syndrome, lenalidomide dose re-escalation is permitted if the subject completes one full cycle without experiencing a laboratory TLS or  $\geq$  Grade 1 TLS (see Appendix D: Cairo-Bishop Definition of Tumor Lysis Syndrome), unless the subject requires a dose interruption/reduction for other toxicity.
- If the dose of lenalidomide has been dose reduced for tumor flare, lenalidomide dose re-escalation is permitted if the subject completes one full cycle without experiencing  $\geq$  Grade 1 tumor flare, unless the subject requires a dose interruption/reduction for other toxicity.
- The dose of lenalidomide will be reduced for hypothyroidism or hyperthyroidism as outlined in Table 2.
- Serum chemistry and uric acid should be closely monitored for signs of laboratory or clinical TLS (see Appendix D: Cairo-Bishop Definition of Tumor Lysis Syndrome) following lenalidomide dose re-escalation (see Section 2, Schedule of Study Assessments, for details regarding serum chemistry and uric acid monitoring).
- TLS prophylaxis with allopurinol and hydration as described in Section 5.5.1 should be considered with each dose re-escalation.

### 6.3 Instructions for dose modifications or interruption during a cycle

<b>Table 2: Dose Modifications</b>	
<b>NCI CTC Toxicity Grade</b>	<b>Action</b>
<b>Grade 3 neutropenia associated with fever (temperature <math>\geq 38.5^{\circ}</math> C) or Grade 4 neutropenia</b>	<ul style="list-style-type: none"> <li>• Hold lenalidomide, thalidomide and, if applicable, rituximab dosing. Omitted doses are not made up.</li> <li>• Follow CBC weekly.</li> <li>• Once neutropenia has resolved to <math>\leq</math> grade 3, restart treatment as scheduled. Restart lenalidomide at next lower dose level.* If neutropenia is the only toxicity for which a dose reduction is required, G-CSF or pegfilgrastim may be used in order to allow maintaining the dose of lenalidomide.</li> </ul>
<b>Thrombocytopenia <math>\geq</math> Grade 4 (platelet count <math>&lt; 25,000/\text{mm}^3</math>)</b>	<ul style="list-style-type: none"> <li>• Hold lenalidomide, thalidomide and, if applicable, rituximab dosing. Omitted doses are not made up.</li> <li>• Hold prophylactic anti-thrombotic agents</li> <li>• Follow CBC weekly.</li> <li>• Once thrombocytopenia resolves to <math>\leq</math> grade 3, restart treatment as scheduled. Restart lenalidomide at next lower dose level.*</li> </ul>
<b>Platelet count <math>&lt; 50,000/\text{mm}^3</math></b>	<ul style="list-style-type: none"> <li>• Hold prophylactic anti-coagulation, if applicable.</li> <li>• Restart prophylactic anti-coagulation when platelet count is <math>\geq 50,000/\text{mm}^3</math>.</li> </ul>

<b>Table 2: Dose Modifications</b>	
<b>NCI CTC Toxicity Grade</b>	<b>Action</b>
<p><b>Non-blistering rash</b> <b>Grade 3</b></p>	<ul style="list-style-type: none"> <li>• If Grade 3, hold lenalidomide, thalidomide, and, if applicable, rituximab dosing. Omitted doses are not made up..</li> <li>• Follow weekly.</li> <li>• If rash development is related to a rituximab infusion, restart treatment as scheduled at the previous doses once toxicity resolves to <math>\leq</math> grade 1.</li> <li>• If the development of the rash is not related to a rituximab infusion, and the rash is purpuric, vasculitic, or bullous, or possibly the result of Stevens-Johnson Syndrome or toxic epidermal necrolysis, the patient will be discontinued from the study.</li> <li>• If the development of the rash is not related to a rituximab infusion and inconsistent with Stevens - Johnson syndrome, the clinician may re-institute therapy once the toxicity resolves to <math>\leq</math> grade 1. Re-institute lenalidomide monotherapy at a one dose level reduction. If no recurrence of the rash occurs after one week, then restart thalidomide monotherapy at 50 mg every other day. Further dose escalation of the lenalidomide will be at the discretion of the treating physician per guidelines in Section 6.2.</li> </ul>
<p><b>Grade 4</b></p>	<ul style="list-style-type: none"> <li>• Discontinue treatment and remove patient from study.</li> </ul>
<p><b>Desquamating (blistering) rash- any Grade</b></p>	<ul style="list-style-type: none"> <li>• Discontinue treatment and remove patient from study.</li> </ul>
<p><b>Neuropathy</b> <b>Grade 3</b></p>	<ul style="list-style-type: none"> <li>• Hold lenalidomide and, if applicable, rituximab, and discontinue thalidomide doses. Follow weekly. Omitted doses are not made up..</li> <li>• When toxicity improves to <math>\leq</math> grade 2, restart treatment as scheduled. Restart lenalidomide one dose level lower. Thalidomide will not be re-introduced given its strong association with neuropathy.</li> </ul>
<p><b>Grade 4</b></p>	<ul style="list-style-type: none"> <li>• Discontinue lenalidomide. Remove patient from study.</li> </ul>
<p><b>Venous thrombosis/embolism</b> <b><math>\geq</math> Grade 3</b></p>	<ul style="list-style-type: none"> <li>• Hold lenalidomide, thalidomide, and, if applicable, rituximab, doses and start anticoagulation; restart lenalidomide and thalidomide dosing at investigator's discretion (maintain dose level).</li> <li>• Omitted doses are not made up..</li> </ul>
<p><b>Hyperthyroidism or hypothyroidism</b>  <b>Grade 3</b></p>	<ul style="list-style-type: none"> <li>• Hold thalidomide, lenalidomide and, if applicable, rituximab. Omitted doses are not made up..</li> <li>• Evaluate etiology and initiate appropriate therapy. When toxicity improves to <math>\leq</math> grade 2, restart treatment as scheduled. Restart lenalidomide at one dose level lower and thalidomide at the same dose.</li> </ul>
<p><b>other non-hematologic toxicity <math>\geq</math> Grade 3</b></p>	<ul style="list-style-type: none"> <li>• Hold lenalidomide, thalidomide, and, if applicable, rituximab doses. Follow weekly. Omitted doses are not made up..</li> <li>• Restart lenalidomide, thalidomide, and / or rituximab therapy at discretion of investigator, if the toxicity resolves to <math>\leq</math> grade 2 and consider dose reduction of most likely causative agent.</li> </ul>

\* Lenalidomide 5 mg every 3<sup>rd</sup> even 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 3<sup>rd</sup> even day may, at the discretion of their physician, have their dose held until toxicity resolves as described in Sections 6.2 and 6.3, and then restart lenalidomide 5 mg every 3<sup>rd</sup> even day. If the same toxicity recurs at lenalidomide 5 mg every 3<sup>rd</sup> even day, consideration should be given to discontinuing lenalidomide.

## Treatment Compliance

At all times, when dispensing protocol therapy, research center personnel will review the instructions, printed on the packaging, with subjects. Subjects will be asked to maintain a medication log to record the drug administration. Subjects will be asked to bring any unused drug and empty drug containers to the research center at their next visit. Research personnel will count and record the number of used and unused drug at each visit and reconcile with the patient medication log. Any unused Thalomid® (thalidomide) or Revlimid® (lenalidomide) should be returned to the patient for disposition in accordance with the STEPS® and RevAssist® programs. At the start of any non-clinic visit treatment cycles subsequent to Cycle 24, the packaging instructions will be reviewed with subjects by telephone call, and study drug and medication log will be shipped to the subject.

## 7. ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug under investigation. Safety will be monitored by evaluation of adverse events reported by patients or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

### 7.1 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>).
- **Attribution of the AE:**
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

### 7.2 Recording of Adverse Events

All adverse events will be recorded on a patient specific adverse event log. The AE log will be maintained by the research staff and kept in the patient's research chart.

### 7.3 Serious Adverse Event (SAE) Reporting

#### 7.3.1 Definition of SAE

##### Serious Adverse Event (SAE) Definition

A serious adverse event is one that at any dose (including overdose):

- Results in death
- Is life-threatening<sup>1</sup>
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity<sup>2</sup>
- Is a congenital anomaly or birth defect
- Is an important medical event<sup>3</sup>
- Positively identified pregnancy

<sup>1</sup>“Life-threatening” means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

<sup>2</sup>“Persistent or significant disability or incapacity” means that there is a substantial disruption of a person’s ability to carry out normal life functions.

<sup>3</sup>Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

### 7.3.2 Adverse Event Reporting

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](http://CTEP.INFO.NIH.GOV)). All appropriate 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.

### 7.3.3 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 IP (Investigational Product), or within (insert time-frame which must be at least 28 days

of the subject's last dose of IP), are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent 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, or approved equivalent 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 other appropriate method, 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, or approved equivalent form.

#### **Male Subjects**

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

#### **7.4 Celgene Drug Safety Contact Information:**



## 7.5 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 CFR 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.



All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (e.g. mild, moderate, severe), relationship to study 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.

## 7.6 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), if available. 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 ( [REDACTED] ) 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.

## 7.7 Report of Adverse Events to the Institutional Review Board

All SAEs occurring on this study will be reported to the IRB according to the IRB policy. The IRB requires immediate reporting of all unexpected and study-related (definite or probable) adverse events. The following procedure will be followed for reporting SAE to the IRB:

- Complete the SAE Cover Sheet

- If the event is unexpected AND definitely or probably related to the study, complete the IRB Unexpected, Study-related Adverse Events, Incidents, and Information Reporting Form. This form should be submitted within 24 hours of investigator notification of the event.
- If the event is expected OR possibly or unrelated to the study, only the SAE Cover Sheet must be completed. These events will be reported to the IRB at the time of continuing renewal on the Adverse Event & IND Safety Reporting Cumulative Table.

Forms may also be downloaded from the IRB website at:  
[http://www.med.cornell.edu/research/for\\_pol/ins\\_rev\\_boa.html](http://www.med.cornell.edu/research/for_pol/ins_rev_boa.html)

### 7.8 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 study 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.

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

The Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB/EC, on file (see Section 12.1 for records retention information).

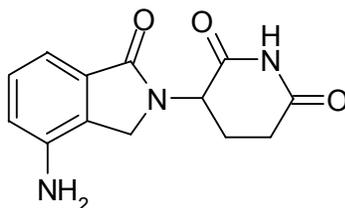
## 8. PHARMACEUTICAL INFORMATION

### 8.1 Lenalidomide

#### 8.1.1 Chemistry

REVLIMID<sup>®</sup> (lenalidomide), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2H-isindol-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<sub>13</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub>, 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.

REVLIMID<sup>®</sup> (lenalidomide) is available in 5 mg and 25 mg capsules for oral administration.

### 8.1.2 **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 (IC<sub>50</sub>s) 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.

### 8.1.3 **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 (C<sub>max</sub>) by 36%. The pharmacokinetic disposition of lenalidomide is linear. C<sub>max</sub> 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.

**Pharmacokinetic Parameters:**

**Distribution:**

In vitro (<sup>14</sup>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.

**8.1.4 Supplier(s)**

Celgene Corporation will supply Revlimid® (lenalidomide) to study participants at no charge through the RASP program (RevAssist® for Study Participants). See Appendix G.

**8.1.5 Dosage form**

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

**8.1.6 Packaging**

Lenalidomide will be shipped on a per subject basis by the contract pharmacy to the clinic site. Bottles will contain a sufficient number of capsules for one cycle of dosing.

**8.1.7 Storage**

Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

**8.1.8 Special Handling Instructions**

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

**8.1.9 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 the Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® program 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 Revlimid REMS® program.

Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

#### 8.1.10 **Pregnancy Testing**

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 for Cycle 1 (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 A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on lenalidomide, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile or email using the Pregnancy Initial Report Form. 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 other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

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

### **Male Subjects**

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

## **8.2 THALOMID® (thalidomide)**

### **8.2.1 Chemistry**

THALOMID®(thalidomide),  $\alpha$ -(N-phthalimido) glutarimide, is an immunomodulatory agent. The empirical formula for thalidomide  $C_{13}H_{10}N_2O_4$  and the gram molecular weight is 258.2. The CAS number of thalidomide is 50-35-1. Thalidomide is off-white to white, nearly odorless, crystalline powder that is soluble at 25°C in dimethyl sulfoxide and sparingly soluble in water and ethanol. The glutarimide moiety contains a single asymmetric center and, therefore, may exist in either of two optically active forms designated S (-) or R (+). THALOMID® (thalidomide) is an equal mixture of the S (-) and R (+) forms and, therefore, has net optical rotation of zero.

Active ingredient: thalidomide. Inactive ingredients: anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

### **8.2.2 Pharmacology and Pharmacokinetics**

Clinical pharmacokinetics studies have shown that thalidomide when administered as a single 200 mg dose, the mean peak plasma concentration is  $1.9 \mu\text{g/ml} \pm 0.5$ , occurring  $3.3 \text{ hours} \pm 1.7$  after dosing. Mean half-life of elimination is  $5.9 \text{ hours} \pm 2.1$ . Single dose, dose proportionality was evaluated over the clinical dose range, i.e., from 50 to 400 mg. The extent of absorption is proportional to dose, however, as the dose increases beyond 200 mg, a flattening of the peak concentration is seen with a delay in the time to the peak concentration. The mean peak plasma concentration following a single 400 mg dose administration was  $2.82 \mu\text{g/ml} \pm 0.80$  occurring by  $4.3 \pm 1.6$  hours after the dose; mean half-life of elimination was  $7.29 \text{ hours} \pm 2.62$ . The rate of absorption was also slower at the highest dose as evidenced by a rate constant

of absorption that was approximately one-half that observed at the lower doses.

### 8.2.3 Human Toxicology

Available data from three clinical pharmacology studies sponsored by Celgene Corporation showed that 38 subjects have been exposed to single doses of thalidomide given either on one occasion or three occasions with one to two week washouts between doses. Two studies were conducted in healthy volunteers and the third study was conducted in patients with Hansen's disease. Thalidomide was administered in a 50 to 400 mg single dose range.

Based on the results of the studies, the most frequently reported adverse experiences were dizziness (31 subjects or 82 %), somnolence (29 subjects or 76%), headache (15 subjects or 39%), and asthenia (12 subjects or 32%). Somnolence and dizziness were reported to occur more frequently at doses of 200 mg and 400 mg than they did at a dose of 50 mg. There was no dose relationship evident for the remaining adverse experiences.

There was no reported severity in intensity of all adverse experiences. All events were mild with the exception of moderate somnolence in 13 subjects, moderate dizziness in 6 subjects, moderate headache in 4 subjects, moderate hypotension in 2 subjects and moderate constipation and moderate pallor in 2 subjects, and a single report of moderate asthenia, diarrhea, leg cramps, nausea and rhinitis. There have been reports of a slowing of the heart rate.

Thalidomide is known to cause nerve damage that may be permanent. Peripheral neuropathy is a common, potentially severe, side effect of treatment with thalidomide that may be irreversible. Peripheral neuropathy generally occurs following chronic use over a period of months, however, reports following short-term use also exist. The correlation with cumulative dose is unclear. Patients should be examined at monthly intervals for the first three months of thalidomide therapy to enable the clinician to detect early signs of neuropathy, which include numbness, tingling or pain in the hands and feet. Patients should be evaluated periodically thereafter during treatment. If symptoms of drug-induced neuropathy develop, thalidomide should be discontinued immediately to limit further damage, if clinically appropriate. Usually treatment with thalidomide should only be reinitiated if the neuropathy returns to baseline status.

Serious dermatologic reactions including toxic epidermal necrolysis and Stevens-Johnson syndrome, which may be fatal, have been reported in association with thalidomide therapy. THALOMID® should be discontinued, if a skin rash occurs and only resumed following appropriate clinical evaluation. If the rash is purpuric, vasculitic, exfoliative, or bullous or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, use of THALOMID® should not be resumed.

The use in Thalidomide in Multiple Myeloma results in an increased risk of venous thromboembolic events, such as deep vein thrombosis and pulmonary embolus. The risk increases significantly when thalidomide is used in combination with standard chemotherapeutic agents including dexamethasone. In one controlled trial the rate of venous thromboembolic events was 22.5% in patients receiving thalidomide in combination with dexamethasone compared to 4.9% receiving dexamethasone alone. Patients and physicians are advised to be observant for signs of thromboembolism. Patients should seek medical attention should they develop symptoms such as shortness of breath, chest pain or leg or arm swelling. Preliminary reports suggest that patients who are appropriate candidates may benefit from concurrent prophylactic anticoagulation or aspirin treatment.

Although not reported from pre-marketing controlled clinical trials, seizures, including grand mal convulsions, have been reported during post-approval use of THALOMID<sup>®</sup> (thalidomide) in clinical practice. Because these events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. Most patients had disorders that may have predisposed them to seizure activity, and it is not currently known whether thalidomide has any epileptogenic influence. During therapy with thalidomide, patients with a history of seizures or with other risk factors for the development of seizures should be monitored closely for clinical changes that could precipitate acute seizure activity.

**THALOMID<sup>®</sup>(thalidomide) can cause severe birth defects in humans. Women and men taking thalidomide must take special precautions and be willing and able to comply with all aspects of the FDA-mandated S.T.E.P.S.<sup>®</sup> program. (see Appendix A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).**

This medicine is for subject use ONLY. IT SHOULD NOT BE SHARED WITH ANYONE. It should be safely stored. It must be kept out of the reach of children and should never be given to women who are able to have children, and used only as directed by the physician.

Subjects should not drink alcohol or take any other medicine that has not been prescribed by the doctor, especially nonprescription drugs that makes the subject sleepy.

#### 8.2.4 **Formulation**

THALOMID<sup>®</sup>(thalidomide) is available in 50 mg capsules for oral administration.

#### 8.2.5 **Storage and Stability**

Thalidomide has been shown to be stable for up to 36 months when stored under

ambient conditions. Over this time period, the capsules show no significant loss in potency and no increase in degradation products. Thalidomide has been shown also to be stable when stored under accelerated conditions (40°C/75% Relative humidity, 3 months). Clinical supplies should be retained in a secure, cool dry place.

#### 8.2.6 **Supplier(s)**

Celgene Corporation will supply Thalomid® (thalidomide) to study participants at no charge through the P-TAP (S.T.E.P.S®) program (see Appendix F).

#### 8.2.7 **Dosage form**

Thalidomide will be supplied as capsules for oral administration.

#### 8.2.8 **Packaging**

Thalidomide will be shipped on a per subject basis by the contract pharmacy to the clinic site. Bottles will contain a sufficient number of capsules for one cycle of dosing.

#### 8.2.9 **Special Handling Instructions**

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

#### 8.2.10 **Prescribing Information**

Patients enrolled into this trial are eligible to participate in Celgene's Protocol Therapy Assistance Program (PTAP). Celgene will provide Thalidomide to study patients free of charge through PTAP. Thalidomide (Thalomid®) will be provided in accordance with the S.T.E.P.S.® program of Celgene Corporation. Per standard S.T.E.P.S.® requirements all physicians who prescribe thalidomide 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 S.T.E.P.S.® program. Prescriptions must be filled within 7 days. Authorization numbers are only valid for 7 days. **Only enough thalidomide for one cycle of therapy will be supplied to the patient each cycle, but no more than a 28 day supply.**

Thalidomide must be prescribed through and in compliance with the S.T.E.P.S.® program of Celgene Corporation. Prescriptions must be filled within 7 days. Authorization numbers are only valid for 7 days. Consideration should be given to prescribing thalidomide 5 to 7 days in advance of Day 1 of each cycle to allow time for required patient and prescriber surveys, and drug shipment to patient. Any unused Thalomid® (thalidomide) should be returned to the patient for disposition in

accordance with the S.T.E.P.S ® program.

**Only enough drug for one 28 day cycle will be supplied at a time.**

#### 8.2.11 **Pregnancy Risk**

Thalidomide is a powerful human teratogen, inducing a high frequency (about 30%) of severe and live-threatening birth defects such as: ectromelia (amelia, phocomelia, hemimelia) of the upper and/or lower extremities, microtia with abnormality of the external acoustic meatus (blind or absent), middle and internal ear lesions (less frequent), ocular lesions (anophthalmia, microphthalmia), congenital heart disease, renal abnormalities. Other less frequent abnormalities have also been described.

Females of childbearing potential (FCBP) 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 4 weeks before starting study drug; 2) while taking study drug; 3) during dose interruptions and 4) for at least 4 weeks after discontinuation of the study drug. The two methods of reliable contraception must include one highly effective method (i.e. intrauterine device (IUD), hormonal [birth control pills, injections, patch or vaginal implants], tubal ligation, partner's vasectomy) and one additional effective (barrier) method (i.e. male condom, diaphragm, cervical cap). The FCBP must be referred to a qualified provider of contraceptive methods if needed.

Combined hormonal contraceptives are not recommended due to the increased risk of venous thrombo-embolic disease. The choice of contraceptive methods should necessitate a risk/benefit discussion between the patient and a qualified physician experienced in the use of contraceptive methods. Effective measures to avoid pregnancy must be taken.

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.

Copper-releasing intrauterine devices are generally not recommended due to the potential risks of infection at the time of insertion and menstrual blood loss which may compromise patients with neutropenia or thrombocytopenia

#### Criteria for females of childbearing potential (FCBP)

Two categories:

1 – Females not of childbearing potential include females who have had a natural menopause for at least 24 consecutive months, a hysterectomy, and/or bilateral oophorectomy

2 – Females of childbearing potential are all other females who are menstruating, amenorrheic from previous medical treatments, under 50 years of age, and/or perimenopausal

#### 8.2.12 **Pregnancy Testing**

Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to prescribing Thalidomide for Cycle 1 (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 thalidomide and at Day 28 post the last dose of thalidomide. 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 thalidomide and at Day 14 and Day 28 post the last dose of thalidomide (see Appendix A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

### 8.3 **Rituximab**

#### 8.3.1 **Chemistry**

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B-lymphocytes. The antibody is an IgG1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effector functions to mediate B-lymphocyte lysis in vitro. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC). The antibody has been shown to induce apoptosis in the DHL-4 human B-cell lymphoma line.

#### 8.3.2 **Pharmacology and Pharmacokinetics**

In prior studies patients treated at the 375 mg/m<sup>2</sup> dose levels exhibited detectable antibody concentrations throughout the treatment period. Most patients exhibited increasing pre-infusion antibody concentrations with each subsequent infusion. In nine patients, the T<sub>1/2</sub> following the first antibody infusion was 59.8 hours (11.1-104.6 hr) with a C<sub>max</sub> of 271 µg/ml. Following the fourth antibody infusion when circulating B cells had been depleted and antigenic sites coated, the T<sub>1/2</sub> was 174 hr (26.4-442.3 hr) and C<sub>max</sub> 496.7 µg/ml.

#### 8.3.3 **Human Toxicology**

No dose-limiting effects were observed in the Phase I/II studies. Reported adverse events including fever, chills, headache, nausea, vomiting, rhinitis, asthenia, and hypotension, occurred primarily during rituximab infusions and typically responded to an interruption of the infusion and resumption at a slower rate.

**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.

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

**Tumor Lysis Syndrome:** Tumor lysis syndrome has been reported and is characterized in patients with a high number of circulating malignant cells ( $\geq 25,000/\text{mm}^3$ ) by rapid reduction in tumor volume, renal insufficiency, hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia.

**Renal Events:** Rituximab has been associated with severe renal toxicity including acute renal failure requiring dialysis, and in some cases has led to death. Renal toxicity has occurred in patients with high numbers of circulating malignant cells ( $\geq 25,000/\text{mm}^3$ ) or high tumor burden who experience tumor lysis syndrome and in patients administered concomitant cisplatin.

**Mucocutaneous Reactions:** Severe bullous skin reactions, including fatal cases of toxic epidermal necrolysis and paraneoplastic pemphigus, have been reported in patients treated with rituximab. The onset of reaction has varied from 1 to 13 weeks following rituximab exposure.

**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 postmarketing reports of prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia.

**Infectious Events:** Rituximab 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.

**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 and demyelinating disease of the brain caused by infection with the JC virus that usually leads to death or severe disability. JC virus infection resulting in PML and death has been reported rarely in patients with hematologic malignancies receiving 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 in patients with systemic lupus erythematosus (SLE) treated with rituximab. These patients with SLE had longstanding disease, history of prior immunosuppressant therapy, and were diagnosed with PML 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.

**Additional Safety Signals:** The following serious adverse events have been reported to occur in patients following completion of rituximab infusions: arthritis, disorders of blood vessels (vasculitis, serum sickness and lupus-like syndrome), eye disorders (uveitis and optic neuritis), lung disorders including pleuritis and scarring of the lung (bronchiolitis obliterans), that may result in fatal outcomes, and fatal cardiac failure.

#### 8.3.4 **Formulation**

Rituximab is commercially available in 10 mL and 50 mL single-use vials containing 100 mg or 500 mg rituximab solution, respectively, at a concentration of 10 mg/mL.

#### 8.3.5 **Storage and Stability**

Intact vials should be stored under refrigeration (2°-8°C). Dilute solutions for infusion (1-4 mg/mL) are stable for 24 hours under refrigeration, and for an additional 24 hours at room temperature. The desired dose of rituximab should be diluted in 0.9% NaCl or D5W to a final concentration of 1-4 mg/mL. The solution should be mixed by gently inverting the bag.

#### 8.3.6 **How Supplied**

Rituximab will be obtained from commercial stock from the non-investigational pharmacy and, along with its administration costs, will be billable to the patient.

#### 8.3.7 **Rituximab Administration**

Rituximab will be administered on days 1, 8, 15 and 22 starting with Cycle 1 and then again on the same weekly x 4 schedule every 6th cycle through Cycle 19 (Cycles 7, 13, and 19). All patients should be premedicated with acetaminophen 650 mg and diphenhydramine 25-50 mg (or equivalent) 30 minutes prior to the rituximab. Rituximab 375 mg/m<sup>2</sup> will be administered by IV infusion starting at a rate of 50 mg/hour. If no infusion related reactions occur, the infusion rate should be escalated in 50 mg/hour increments every 30 minutes to a maximum of 400 mg/hour until the infusion is completed. Vital signs will be monitored every 15 minutes while infusion rate is being escalated.

## 9. CORRELATIVE/SPECIAL STUDIES

See Section 5.1 for specific dosing instructions

**Cycle -1:** Half of the patients will receive 14 days of thalidomide 50 mg PO daily, followed by 14 days off and the other half of the patients will receive 14 days of lenalidomide 5 mg PO daily, followed by 14 days off

**Cycle 1 and beyond:** Alternating thalidomide and lenalidomide continuously

Samples will be collected for correlative studies to be performed in association with the trial. The following samples will be collected:

### 1. CLL Prognostic Profiles\*:

Samples will be analyzed as described in the Schedule of Assessments (Section 10) and will include:

- 1) IgVH Mutation Analysis
- 2) Zap-70 expression by immunohistochemistry
- 3) CD38, CD 5, CD19/CD20, CD 23, sIg
- 4) Interphase FISH for trisomy 12, deletion 17p, deletion 13q14, deletion 11q23 (blood and bone marrow)
- 5) Purified CLL cell interphase FISH (not called Purified on calendar)
- 6) beta-2-microglobulin

### 2. BLyS/BAFF Analysis\*

- 1) Measurement of serum levels of BLyS and APRIL
  - a. day 1 and 15 of cycle -1 (prior to administration of study agents).
  - b. immediately prior to rituximab at cycles 1, 7, 13, and 19, and then prior to the last dose of rituximab (day 22) for that cycle.
- 2) BLyS expression on monocytes:
  - a. day 1 and 15 of cycles -1 (prior to administration of study drug)
  - b. day 1 and 15 of cycle 1 (immediately prior to Rituximab administration)
- 3) BLyS receptor expression on CLL cells:
  - a. Prior to administration of study drug on days 1 and 15 of cycles -1
  - b. Immediately prior to administration of Rituximab on days 1 and 15 of Cycle 1
- 4) BLyS gene polymorphisms: baseline
- 5) MMP-9 activity: baseline

### 3. Impact of IMiD therapy on TNF Family and cox Family mRNA stability\*:

- 1) Impact on p38 MAPK activity: day 1, 15 of cycles -1 and 1 prior to administration of study drugs

- 2) TNF-alpha / cox-2 / BAFF mRNA levels: day 1, 15 of cycles -1 and 1 prior to administration of study drugs
  - 3) Level of HuR binding to TNF-alpha / cox-2 mRNA / BAFF mRNA: day 1, 15 of cycles -1 and 1 prior to administration of study drugs
4. RNA Expression Arrays\*
- Changes in RNA expression resulting from the IMiD therapy will be assessed using RNA expression arrays. Samples to be assessed:
- 1) CLL cells: day 1, 2, and 15 of cycles -1 and 1 prior to administration of study drug
  - 2) T cells: day 1, 2, and 15 of cycles -1 and 1 prior to administration of study drug
  - 3) Monocytes: day 1, 2, and 15 of cycles -1 and 1 prior to administration of study drug
5. Methylation Arrays\*
- Changes in gene methylation patterns resulting from IMiD therapy will be assessed using methylation oligomicroarrays (MOMA) at:
- Day 1 and 15 of cycles -1 and 1 prior to administration of study drug
6. Metabolomics\*: day 1, 15 of cycles -1 and 1 prior to administration of study drug
7. Peripheral Blood Activation Markers\*
- Changes in cell surface markers will be assessed by flow cytometry and will include: CD38, HLA-DR, CD25: Prior to administration of study drug in Cycle -1, 1 and 2 on Days 1 and 15.
8. Peripheral Blood Cell Subset Analysis\*
- Changes in peripheral blood mononuclear cell subsets: baseline; Cycle 1 prior to administration of study drug on days 1 and 15 ; Cycles 2 and 3 prior to administration of study drug on Day 1; every three cycles for Cycle 6 through Cycle 24; followed by every six cycles thereafter.
- Panel to include:
- CD3/CD4/CD8: T cell subsets
  - CD16/CD56: NK cells
  - CD14: monocytes
  - CD3/CD25/FoxP3: regulatory T cells
  - Circulating Endothelial cell precursors
9. VEGF Analysis\* prior to administration of study drug in Cycles -1, 1 and 2 on Days 1 and 8.
- 1) VEGF, bFGF serum levels
  - 2) Changes in VEGF Receptor expression profile

10. Genetic polymorphisms predictive of response\* prior to administration of study drug in Cycles -1, 1 and 2 on Days 1 and 15.

- 1) TNF-alpha
- 2) BAFF

11. T-cell Repertoire Studies: samples will be collected prior to treatment on cycle -1 and prior to cycles 6, 12, and 24 and evaluated for T-cell Repertoire

12. PI 3-Kinase Assessment: samples will be assessed for PI 3-Kinase activity levels prior to cycle -1, day 15 of cycle -1, and day 15 of cycle #1.

\*\*\*\* Rituximab can be given +/- 2days.

\*\*\*\*All correlative work must be drawn prior to Rituximab administration regardless of the day Rituximab is given.

\* See Section 10 for further details

## 10. STUDY CALENDAR

### Schedule of Study Assessments

Procedure	Screening <sup>1</sup>	Cycles -1, 1 and 2							
		24hrs before study drug	Day 1	Day 2	Day 4 (+/- 1)	Day 8	Day 11 (+/- 1)	Day 15	Day 22
Medical history assessment	X								
Interim history			X		X	X	X	X	X
Physical examination, vital signs	X		X		X	X	X	X	X
ECOG performance status, weight	X		X			X		X	X
Lymph node, spleen and liver assessment by physical exam <sup>15</sup>	X		X			X		X	X
CLL Flow Cytometry <sup>16</sup>	X								
interphase FISH (CLL Panel) <sup>2</sup>	X								
Purified CLL cell interface FISH	X								
IgVH Mutation Analysis	X								
BLyS/BAFF Analysis <sup>3</sup>			X <sup>3</sup>					X <sup>3</sup>	X <sup>3</sup>
IMiD™ compound studies and Methylation Arrays <sup>4</sup>			X <sup>4</sup>					X <sup>4</sup>	
RNA Expression Arrays <sup>5</sup>			X		X <sup>5</sup> Day 2			X	
Metabolomics			X <sup>18</sup>					X <sup>18</sup>	
T-cell Repertoire Studies <sup>19</sup>			X <sup>19</sup>						
PI 3-Kinase Assessment <sup>20</sup>			X <sup>20</sup>					X <sup>20</sup>	
Peripheral Blood Activation Markers: CD38, HLA-DR, CD25			X					X	
Peripheral Blood Cell Subset Analysis <sup>6</sup>	X		X <sup>6</sup>					X <sup>6</sup>	
VEGF Analysis			X			X			
Genetic polymorphisms	X								
Bone marrow assessment <sup>12</sup>	X								
CT of the chest / abdomen / pelvis <sup>12</sup>	X								
ECG	X								
Hematology <sup>7</sup>	X		X		X	X	X	X	X
Serum chemistries <sup>8</sup>	X		X		X	X	X	X	X
IFE, beta-2-microglobulin, DAT	X								
Pregnancy testing <sup>9,10</sup>	X	X	X <sup>10</sup>			X <sup>10</sup>		X <sup>10</sup>	X <sup>10</sup>
Register and comply with RevAssist® and S.T.E.P.S.® program	X	X							
Rituximab administration			X <sup>17</sup>			X <sup>17</sup>		X <sup>17</sup>	X <sup>17</sup>
Response assessment <sup>12</sup>									
Record adverse events <sup>13</sup>						X			X
Perform drug accountability			X						
Prescribe and dispense study drugs for next cycle <sup>14</sup>			X						

Procedure	Cycles 3, 4, 5, 6	Cycles 3, 4 and any Cycle where lenalidomide dose is escalated				
	Day 1	Day 4 (or) Day 3	Day 8	Day 11 (or) Day 10	Day 15	Day 22
Medical history assessment						
Interim history	X	X	X	X	X	X
Physical examination, vital signs, weight	X	X	X	X	X	X
ECOG performance status	X		X		X	X
Lymph node, spleen and liver assessment by physical exam <sup>15</sup>	X		X		X	X
Bone marrow assessment <sup>12</sup>						
Peripheral Blood Cell Subset Analysis <sup>6</sup>	X <sup>6</sup>					
CT of the chest / abdomen / pelvis <sup>12</sup>						
Hematology <sup>7</sup>	X	X	X	X	X	X
Serum chemistries <sup>8</sup>	X	X	X	X	X	X
Pregnancy testing <sup>9,10</sup>	X <sup>10</sup>				X <sup>10</sup>	
T-cell Repertoire Studies <sup>19</sup>	X <sup>19</sup>					
Comply with RevAssist® and S.T.E.P.S.® program	X					
Response assessment <sup>12</sup>	X					
Record adverse events <sup>13</sup>	X		X			X
Perform drug accountability	X					
Prescribe and dispense study drugs for next cycle <sup>14</sup>	X					

An unscheduled visit can occur at any time during the study. Source must be maintained for these unscheduled visits. The date for the visit and any data generated must be recorded on the appropriate CRF. Source documents for these unscheduled visits must also be maintained.

Procedure	Rituximab administration Cycles 7, 13, and 19				For all other cycles 8 and beyond <sup>11</sup>	Discontinuation From Protocol therapy
	Day 1	Day 8	Day 15	Day 22	Day 1	
Medical history assessment	X				X	
Interim history	X	X	X	X	X	
Physical examination, vital signs, weight	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X
Lymph node, spleen and liver assessment by physical exam <sup>15</sup>	X	X	X	X	X	
Bone marrow assessment <sup>12</sup>						
BlyS/BAFF Analysis <sup>3</sup>	X				X <sup>3</sup>	
Peripheral Blood Cell Subset Analysis <sup>6</sup>					X <sup>6</sup>	
CD4/CD8/CD56 cell count						X
CT of the chest / abdomen / pelvis <sup>12</sup>	X				X <sup>12</sup>	X
Hematology <sup>7</sup>	X	X	X	X	X	X
Serum chemistries <sup>8</sup>	X	X	X	X	X	X
Pregnancy testing <sup>9,10</sup>	X <sup>10</sup>		X <sup>10</sup>		X <sup>10</sup>	X <sup>10</sup>
Comply with RevAssist® and S.T.E.P.S.® program	X				X	
T-cell Repertoire Studies <sup>19</sup>					X <sup>19</sup>	
IFE, beta-2-microglobulin, DAT	X				X <sup>21</sup>	
Response assessment <sup>12</sup>	X				X <sup>12</sup>	X
Record adverse events <sup>13</sup>	X	X	X	X	X	X <sup>13</sup>
Perform drug accountability	X				X	
Prescribe and dispense study drugs for next cycle <sup>14</sup>	X				X <sup>11</sup>	
Rituximab administration	X <sup>17</sup>	X <sup>17</sup>	X <sup>17</sup>	X <sup>17</sup>		
MRD status – peripheral blood assessment	X				X <sup>12</sup>	
Obtain Follow-Up anti-cancer treatments						F/u phase : Q 3 months
Obtain Follow-Up survival information						F/u phase : Q 3 months

<sup>1</sup> ≤ 28 days from baseline (First day study drug administration)

<sup>2</sup> To include iFISH for trisomy 12, deletion 17p, deletion 13q14, deletion 11q23; should be performed on peripheral blood and bone marrow

<sup>3</sup> BlyS/BAFF Analysis:

- Baseline: BlyS gene polymorphisms, MMP-9 activity
- Cycle -1 and 1; Days 1 & 15 prior to administration of study drug: serum levels of BlyS & APRIL, BlyS expression on monocytes, BlyS receptor expression on CLL cells
- Cycle 1, 7, 13, and 19 –immediately prior to Rituximab: serum levels of BlyS & APRIL

<sup>4</sup> IMiD™ compound Studies and Methylation Arrays:

- Cycle -1 and 1: Days 1 & 15 prior to administration of study drug: p38Mark activity, TNF-alpha/cox-2/BAFF mRNA levels, level of HuR binding to TNF-alpha/cox-2 mRNA/BAFF mRNA
- Cycle -1 and 1: Days 1 & 15 prior to administration of study drug: Changes in gene methylation patterns resulting from IMiD therapy by MOMA

<sup>5</sup> RNA Expression Arrays:

- Cycle -1 and 1: Days 1, 2 & 15 prior to administration of study drug: CLL cells, T cells, Monocytes

<sup>6</sup> Peripheral Mononuclear cell subsets

- **Prior to administration of study drug Days:** 1 and 15 of Cycle 1; Day 1 of Cycles 2 and 3; q 3 cycles through Cycle 24(cycle 6, 9, 12, etc.); then q 6 cycles thereafter: CD3/CD4/CD8-T cell subsets;

CD16/CD56- NK cells; CD14- monocytes; CD3/CD25/FoxP3-regulatory T cells; Circulating Endothelial cell precursors

- <sup>7</sup> To include WBC, differential, hemoglobin, hematocrit, platelets. Hematology profiles are required weekly during Cycle -1 of lenalidomide-containing therapy, and during any cycle in which the dose of lenalidomide is escalated or re-escalated. For subjects who are on a stable lenalidomide dose (without escalation or interruption) for  $\geq 1$  cycle of treatment, hematology profiles are required on Days 1 and 15 of the cycle.
- <sup>8</sup> To include Na, K, Cl, CO<sub>2</sub>, BUN, Cr, glu, Ca, phos, uric acid, LDH, alkaline phosphatase, total bilirubin, ALT, AST, albumin, total protein. 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 3 or 4 of Cycle -1. 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, 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. 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.
- <sup>9</sup> Pregnancy tests required 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).
- <sup>10</sup> Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to initiation of lenalidomide and thalidomide. 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/thalidomide and at day 28 post the last dose of lenalidomide/thalidomide. 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/thalidomide and at day 14 and day 28 post the last dose of lenalidomide/thalidomide (see Appendix A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).
- <sup>11</sup> After cycle 24, clinic visits (and the corresponding assessments) are only required every 3<sup>rd</sup> cycle (e.g. Cycle 24, 27, 30, etc.). For any non-clinic visit treatment cycles (e.g. Cycle 25, 26, 28, 29, etc.), subjects must still meet all requirements for the initiation of a new treatment cycle, including compliance with the RevAssist® and S.T.E.P.S.® programs, and all pregnancy testing and pregnancy risk counseling requirements. Hematology assessment (see number 7) will be done locally as required for the initiation of a new treatment cycle.
- <sup>12</sup> CT scans should be done every six months for three years, and every twelve months thereafter. Response assessment and MRD assessment should be performed every six months subsequent to Cycle 24. Patients whose blood counts meet criteria of a CR should undergo a CT scan within 4 weeks. If CT scan supports a response of CR, then bone marrow examination and peripheral blood MRD assessment should be performed within 4 weeks.
- <sup>13</sup> An additional safety assessment will be done 28 days (+/- 2 days) following the last dose of study drug.
- <sup>14</sup> Only enough thalidomide and lenalidomide for 1 cycle of therapy may be provided to the patient each cycle. For non-clinic visit treatment cycles subsequent to Cycle 24 (e.g. Cycle 25, 26, 28, 29, etc.), study drug will be shipped to the subject at the start of each cycle.
- <sup>15</sup> Physical examination of lymphadenopathy, spleen and liver will be performed on Days 1, 8, 15, and 22 of Cycles -1, 1, 2, 3,4 and 5 to assess for tumor flare reaction, and on Day 1 of subsequent cycles starting with cycle 5 to assess response.
- <sup>16</sup> CLL Flow Cytometry should include markers for diagnosis and prognosis: CD5, CD19/CD20, CD23, CD38, sIg, and zap-70, by immunohistochemistry. Also IgVH Mutation Analysis, Purified CLL cell interphase FISH, beta 2 microglobulin
- <sup>17</sup> Rituximab administration starting with Cycle 1 and then every 6<sup>th</sup> cycle through Cycle 19 (i.e. 7, 13, and 19) on Days 1, 8, 15 and 22.
- <sup>18</sup> Metabolimics on Days 1 and 15 prior to study drug administration for Cycles -1 and 1.
- <sup>19</sup> T-cell Repertoire Studies: samples will be collected prior to treatment on cycle -1 and prior to cycles 6, 12, and 24 and evaluated for T-cell Repertoire
- <sup>20</sup> PI 3-Kinase Assessment: samples will be assessed for PI 3-Kinase activity levels prior to cycle -1, day 15 of cycle -1, and day 15 of cycle #1.
- <sup>21</sup> After Cycle 19, IFE, beta-2-microglobulin, DAT assessment will be done every 6 cycles starting with Cycle 24.

\*\*\*\* Rituximab can be given +/- 2days.

\*\*\*\*All correlative work must be drawn prior to Rituximab administration regardless of the day Rituximab is given.

## 11. MEASUREMENT OF EFFECT

Baseline lesion assessments must occur within  $\leq 28$  days of study drug administration or as indicated in Section 10, Schedule of Study Assessments.

Efficacy assessments are scheduled to occur every four weeks. It should be noted that signs and symptoms of a tumor flare may appear similar to disease progression. Investigators should decide whether apparent increases in disease are indicative of a tumor flare or disease progression. If the increases in lymphadenopathy, tenderness, leukocytosis, or cytopenias occur within four weeks of a dose escalation, then it is possible the changes are indicative of a disease flare. If these changes begin more than four weeks after a dose increase, then the changes are likely disease progression. These are guidelines to help investigator in making their decision, but the decision regarding classifying their disease as progression or flare remains ultimately with the investigator.

Response and progression will be evaluated in this study using the International Workshop on CLL (IWCLL) update of the 1996 NCI-Working Group criteria for CLL [15].

11.1 **Complete response:** requires all of the following conditions to be met:

1. Absence of clonal lymphocytes in the peripheral blood by flow cytometry.
2. Blood counts above the following values:
  - a) neutrophil count  $> 1500/ \text{mm}^3$ , without the use of growth factors
  - b) hemoglobin  $> 11 \text{ gm/dL}$ , untransfused (men and women)
  - c) platelet count  $> 100,000/ \text{mm}^3$ , untransfused
3. Absence of lymphadenopathy on CT examination of the neck, chest, abdomen, and pelvis (lymph nodes  $< 1.5 \text{ cm}$  in diameter).
4. Absence of hepatomegaly or splenomegaly by CT examination
5. Absence of constitutional symptoms.
6. Bone marrow biopsy and aspirate demonstrating normal cellularity for the age of the patient and free of clonal CLL cells by conventional (not 4-color) flow cytometry and / or immunohistochemistry. If lymphoid nodules are present (formerly nPR), they should be assessed by immunohistochemistry to determine whether they are composed of CLL cells. If the lymphoid nodules are not CLL cells, then the patient will be considered a CR. If the lymphoid nodules are composed of CLL cells, then the patient will be categorized as a PR. If the bone marrow is found to be hypocellular, a repeat marrow biopsy should be performed after 4-6 weeks.
7. Patients who fulfill all of the criteria for CR, including marrow examination, but who have persistent anemia or thrombocytopenia, or neutropenia unrelated to CLL but related to drug toxicity will be characterized as CR with incomplete marrow recovery (CRi). These patients will be followed in order to determine whether their prognosis differs from

patients in CRs or PRs.

11.2 **Partial response:** any response less than a complete response but still meeting the following criteria:

1. 50% decrease in peripheral blood lymphocytes from the pre-treatment value.
2. 50% reduction in lymph node size by CT examination as measured by the sum of the products of up to 6 lymph nodes, or in one lymph node diameter if only a single lymph node is present.
3. No increase in the size of any lymph node, and no new enlarged lymph nodes, by CT examination.
4. 50% reduction in the size of the liver and / or spleen by CT examination
5. Blood counts must show one of the following:
  - a) neutrophil count  $\geq 1500/\text{mm}^3$  or 50% improvement over baseline without the use of growth factors.
  - b) hemoglobin  $> 11.0 \text{ gm/dL}$  or 50% improvement over baseline without transfusions or erythropoietin support.
  - c) platelet count  $> 100,000/\text{mm}^3$  or 50% improvement over baseline without transfusions.

11.3 **Progressive disease:** any of the following characteristics:

1. Progressive lymphadenopathy, as defined by:
  - a) Appearance of any newly enlarged lymph nodes to  $> 1.5 \text{ cm}$ .
  - b) An increase by 50% or more in greatest diameter of any previous site of disease. For a lymph node of 1 to 1.5 cm must increase by at least 50% to a size greater than 1.5 cm. A lymph node greater than 1.5 cm in diameter must increase to more than 2.0 cm in diameter.
  - c) An increase of 50% or more in the sum of the products of diameters of multiple lymph nodes.
2. An increase in liver or spleen size by 50% or more or the appearance of new hepatomegaly or splenomegaly.
3. An increase in the number of blood lymphocytes by 50% or more with at least 5000 B lymphocytes  $/\text{mm}^3$ .
4. Transformation to a more aggressive histology.
5. Occurrence of cytopenias attributable to CLL, excluding those related to therapy or autoimmune phenomenon. The progression of any cytopenia is defined by:

- a) decrease in Hb by more than 2 g/dL or to less than 10 g/dL.
- b) decrease in platelet counts by more than 50% or to less than 100,000/ mm<sup>3</sup>.

11.4 **Stable disease:** patients who have not achieved a CR or a PR, and who have not exhibited progressive disease, will be considered to have stable disease.

11.5 **Relapse:** patients who has previously achieved a CR or PR, but after a period of 6 or more months, demonstrate evidence of disease progression.

11.6 **Refractory disease:** disease progression within 6 months of the last treatment.

11.7 **Duration of response definitions:**

1. **Duration of response:** from the end of the last treatment until evidence of progressive disease.
2. **Time to response:** interval from the first treatment day to the date response first identified.
2. **Progression-free survival:** interval between the first treatment day and the first sign of disease progression.
3. **Event-free survival:** interval between the first treatment day to the first sign of disease progression, treatment for relapse, or death, whichever occurs first.
4. **Survival duration:** interval between the first day of treatment and death

## 12. DATA REPORTING / REGULATORY CONSIDERATIONS

### 12.1 Protocol amendments

Any amendment to this protocol must be agreed to by the Principal Investigator and reviewed by Celgene. Amendments should only be submitted to IRB/EC after consideration of Celgene review. Written verification of IRB/EC approval will be obtained before any amendment is implemented.

### 12.2 Protocol deviations

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be made only for that subject. A decision will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study. The subject's medical records will completely describe the deviation from the protocol and state the reasons for such deviation. In addition, the Investigator will notify the IRB/EC in writing of such deviation from protocol.

Non-emergency minor deviations from the protocol will be permitted with approval of the Principal Investigator.

### **12.3 Data Safety Monitoring Board**

The role of the Data Safety Monitoring Board (DSMB) will be fulfilled by the Weill Cornell Medical College DSMB. The purpose of the Data Safety Monitoring Board (DSMB) is to advise on serious safety considerations, lack of efficacy and any other considerations within the charge to the Committee. Data will be analyzed and submitted to the DSMB annually in order to allow for assessments of response and toxicities.

The DSMB may request additional meetings or safety reports as deemed necessary upon discussion with Celgene and its representatives. The DSMB may stop the study following review of results from each interim analysis. Appropriate efficacy and safety data summaries will be provided to the DMC after each interim analysis.

### **12.4 Data Collection**

The data collection plan for this study is to utilize the HemOnc database to capture all treatment, toxicity, and efficacy data for all enrolled patients.

### **12.5 Regulatory Considerations**

All protocol amendments and consent form modifications will be made by the Principal Investigator. Celgene Corporation will have the opportunity to review and approve the changes prior to submission of these changes to the local IRB and distribution to participating sites.

### **12.6 Investigator responsibilities**

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

Investigators must enter study data onto CRFs or other data collection system. The Investigator will permit study-related audits by Celgene or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

The Investigator, or a designated member of the Investigator's staff, must be available at some time during audits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each visit and be made available to the Celgene representative so that the accuracy and completeness may be checked.

### **12.7 Institutional Review Board/Ethics Committee approval**

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the

performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of IRB/EC approval must be submitted by the Investigator to the IRB/EC for approval. The Investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB/EC prior to use.

#### **12.8 Informed consent**

The Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files.

#### **12.9 Subject confidentiality**

Celgene affirms the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

## 12.10 Study records requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

## 12.11 Premature discontinuation of study

### 12.11.1 Single center

The responsible local clinical Investigator, as well as Celgene, have the right to discontinue this study at any time for reasonable medical or administrative reasons in any single center. Possible reasons for termination of the study could be but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality.
- Inaccurate or incomplete data collection.
- Falsification of records.
- Failure to adhere to the study protocol.

### 12.11.2 Study as a whole

Celgene reserves the right to terminate this clinical study at any time for reasonable medical or administrative reasons.

Any possible premature discontinuation would be documented adequately with reasons being stated, and information would have to be issued according to local requirements (e.g., IRB/EC, regulatory authorities, etc.).

## 13. STATISTICAL CONSIDERATIONS

### 13.1 Overview

Sample size recommendations for the phase II design are determined according to Simon's two-stage Minimax design [91]. We project an overall response proportion (CR + PR) of 60%, below which the response will be unacceptable, and an overall response proportion of 80% above which the regimen will be considered worthy of further exploration. The null hypothesis that the overall response proportion is less than or equal to 60% will be tested against the alternative hypothesis that the overall response proportion is greater than or equal to 80%. For the purpose of these statistical analyses, responses will be assessed starting after cycle #6 of treatment and then every cycle thereafter.

The sample size computations were performed assuming a 10% level of significance and 80% power. In the first stage, 11 patients will enter the study. If 6 or fewer patients respond, the study will be terminated early and declared to have a negative result. If 7 or more patients respond, enrollment will be extended to 24 patients. At Stage 2, the treatment will be declared effective and worthy of further testing if 18 or more patients respond among the 24 patients entered. This two-stage design yields a  $\geq 0.80$  probability of a positive result if the true percentage of overall responders is  $\geq 80\%$ . It yields a  $\geq 0.90$  probability of a negative result if the true percentage of overall responders is  $\leq 60\%$ .

Table A. Numbers of observed overall responders required to accept or reject  $H_0$  at each stage. Under this design,  $H_0$  will not be rejected at Stage 1

	N	Accept $H_0$	Reject $H_0$
Stage 1	11	$\leq 6$	---
Stage 2	24	$\leq 17$	$\geq 18$

### 13.2 Datasets to be analyzed

Primary Endpoint:

- Overall response rate (CR + PR)

Secondary Clinical Endpoints:

- Progression Free Survival
- Duration of response
- Time to response
- Overall survival
- Toxicity profile

### 13.3 Statistical Methodology

Primary Endpoint:

- The primary endpoint of response rate (overall, CR, PR) will be estimated and a 95% confidence interval will be estimated via binomial proportions

Secondary Endpoints:

- With adequate follow-up time, progression-free survival (PFS) will be assessed by Kaplan-Meier survival analysis and 95% confidence intervals will be calculated using Greenwood's formulae. PFS will be defined as the time from the first treatment day until objective or symptomatic progression (or until date of last follow-up if no progression).
- Duration of Response: from the end of the last treatment until evidence of progressive disease.
- Time to Response
- Overall Survival
- The frequency of subjects experiencing toxicities will be tabulated. Toxicities will be assessed and graded according to CTCAE v4.0 terminology. Exact 95% confidence intervals around the toxicity proportions will be calculated to assess the precision of the obtained estimates.

#### 13.4 Safety evaluation

Data from all subjects who receive any drug while on study will be included in the safety analyses. Subjects enrolled on to the study but who did not take any study drugs, will not be evaluated for safety.

The severity of the toxicities will be graded according to the NCI CTCAE v4.0 whenever possible (Appendix C).

#### 13.5 Interim analyses

##### 13.5.1 Interim analysis strategy

Accrual will not be put on hold during the study in order to perform an interim analysis given the preliminary clinical data already generated demonstrating activity for lenalidomide in CLL. Efficacy and safety data will be analyzed after the first eleven patients reach cycle four. Data will be analyzed subsequently every four months in order to allow for assessments of response and toxicities. For the purpose of performing the interim analysis, responses will be assessed starting after cycle #6 of treatment and then every cycle thereafter.

In the first stage, 11 patients will enter the study. If 6 or fewer patients respond, the study will be terminated early and declared to have a negative result. If 7 or more patients respond, enrollment will be extended to 24 patients.

## 14.0 REFERENCES

1. Anderson, K.C., *Lenalidomide and thalidomide: mechanisms of action--similarities and differences*. *Semin Hematol*, 2005. **42**(4 Suppl 4): p. S3-8.
2. Knight, R., *IMiDs: a novel class of immunomodulators*. *Semin Oncol*, 2005. **32**(4 Suppl 5): p. S24-30.
3. Chanan-Khan, A., K.C. Miller, K. Takeshita, A. Koryzna, K. Donohue, Z.P. Bernstein, A. Mohr, D. Klippenstein, P. Wallace, J.B. Zeldis, C. Berger, and M.S. Czuczman, *Results of a phase I clinical trial of thalidomide in combination with fludarabine as initial therapy for patients with treatment-requiring chronic lymphocytic leukemia (CLL)*. *Blood*, 2005. **106**(10): p. 3348-52.
4. Chanan-Khan, A., K.C. Miller, L. Musial, D. Lawrence, S. Padmanabhan, K. Takeshita, C.W. Porter, D.W. Goodrich, Z.P. Bernstein, P. Wallace, D. Spaner, A. Mohr, C. Byrne, F. Hernandez-Ilizaliturri, C. Chrystal, P. Starostik, and M.S. Czuczman, *Clinical Efficacy of Lenalidomide in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia: Results of a Phase II Study*. *J Clin Oncol*, 2006.
5. Furman, R.R., J.P. Leonard, S.L. Allen, M. Coleman, T. Rosenthal, and J.L. Gabilove, *Thalidomide alone or in combination with fludarabine are effective treatments for patients with fludarabine-relapsed and refractory CLL*. *J Clin Oncol*, 2005. **23**(16S): p. 595s, abs 6640.
6. Ferrajoli, A., S. O'Brien, S. Faderl, W. Wierda, D. Davis, B. Lee, J. Reuben, E. Schlette, H. Kantarjian, and M. Keating, *Lenalidomide induces complete and partial responses in patients with relapsed and treatment-refractory chronic lymphocytic leukemia (CLL)*. *Blood*, 2006. **108**(11): p. 94a, abs #305.
7. Dredge, K., R. Horsfall, S.P. Robinson, L.H. Zhang, L. Lu, Y. Tang, M.A. Shirley, G. Muller, P. Schafer, D. Stirling, A.G. Dalglish, and J.B. Bartlett, *Orally administered lenalidomide (CC-5013) is anti-angiogenic in vivo and inhibits endothelial cell migration and Akt phosphorylation in vitro*. *Microvasc Res*, 2005. **69**(1-2): p. 56-63.
8. Corral, L.G., P.A. Haslett, G.W. Muller, R. Chen, L.M. Wong, C.J. Ocampo, R.T. Patterson, D.I. Stirling, and G. Kaplan, *Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha*. *J Immunol*, 1999. **163**(1): p. 380-6.
9. Schafer, P.H., A.K. Gandhi, M.A. Loveland, R.S. Chen, H.W. Man, P.P. Schnetkamp, G. Wolbring, S. Govinda, L.G. Corral, F. Payvandi, G.W. Muller, and D.I. Stirling, *Enhancement of cytokine production and AP-1 transcriptional activity in T cells by thalidomide-related immunomodulatory drugs*. *J Pharmacol Exp Ther*, 2003. **305**(3): p. 1222-32.
10. Davies, F.E., N. Raje, T. Hideshima, S. Lentzsch, G. Young, Y.T. Tai, B. Lin, K. Podar, D. Gupta, D. Chauhan, S.P. Treon, P.G. Richardson, R.L. Schlossman, G.J. Morgan, G.W. Muller, D.I. Stirling, and K.C. Anderson, *Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma*. *Blood*, 2001. **98**(1): p. 210-6.

11. Hideshima, T., D. Chauhan, Y. Shima, N. Raje, F.E. Davies, Y.T. Tai, S.P. Treon, B. Lin, R.L. Schlossman, P. Richardson, G. Muller, D.I. Stirling, and K.C. Anderson, *Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy*. Blood, 2000. **96**(9): p. 2943-50.
12. Jemal, A., R. Siegel, E. Ward, T. Murray, J. Xu, and M.J. Thun, *Cancer statistics, 2007*. CA Cancer J Clin, 2007. **57**(1): p. 43-66.
13. Rozman, C. and E. Montserrat, *Chronic lymphocytic leukemia [published erratum appears in N Engl J Med 1995 Nov 30; 333(22):1515]*. N Engl J Med, 1995. **333**(16): p. 1052-7.
14. Cheson, B.D., J.M. Bennett, M. Grever, N. Kay, M.J. Keating, O.B. S, and K.R. Rai, *National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment*. Blood, 1996. **87**(12): p. 4990-7.
15. Hallek, M., B.D. Cheson, D. Catovsky, F. Caligaris-Cappio, G. Dighiero, H. Dohner, P. Hillmen, M.J. Keating, E. Montserrat, K.R. Rai, and T.J. Kipps, *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. **111**(12): p. 5446-56.
16. Andreeff, M., *Cell kinetics of leukemia*. Semin Hematol, 1986. **23**(4): p. 300-14.
17. Defoiche, J., C. Debacq, B. Asquith, Y. Zhang, A. Burny, D. Bron, L. Lagneaux, D. Macallan, and L. Willems, *Reduction of B cell turnover in chronic lymphocytic leukaemia*. Br J Haematol, 2008. **143**(2): p. 240-7.
18. Damle, R.N., S. Temburni, C. Calissano, S. Yancopoulos, T. Banapour, C. Sison, S.L. Allen, K.R. Rai, and N. Chiorazzi, *CD38 expression labels an activated subset within chronic lymphocytic leukemia clones enriched in proliferating B cells*. Blood, 2007. **110**(9): p. 3352-9.
19. Messmer, B.T., D. Messmer, S.L. Allen, J.E. Kolitz, P. Kudalkar, D. Cesar, E.J. Murphy, P. Koduru, M. Ferrarini, S. Zupo, G. Cutrona, R.N. Damle, T. Wasil, K.R. Rai, M.K. Hellerstein, and N. Chiorazzi, *In vivo measurements document the dynamic cellular kinetics of chronic lymphocytic leukemia B cells*. J Clin Invest, 2005. **115**(3): p. 755-64.
20. Gottardi, D., A. Alfarano, A.M. De Leo, A. Stacchini, L. Bergui, and F. Caligaris-Cappio, *Defective apoptosis due to Bcl-2 overexpression may explain why B-CLL cells accumulate in G0*. Curr Top Microbiol Immunol, 1995. **194**: p. 307-12.
21. McConkey, D.J., J. Chandra, S. Wright, W. Plunkett, T.J. McDonnell, J.C. Reed, and M. Keating, *Apoptosis sensitivity in chronic lymphocytic leukemia is determined by endogenous endonuclease content and relative expression of BCL-2 and BAX*. J Immunol, 1996. **156**(7): p. 2624-30.
22. Diehl, L.F., L.H. Karnell, and H.R. Menck, *The American College of Surgeons Commission on Cancer and the American Cancer Society. The National Cancer Data Base report on age, gender, treatment, and outcomes of patients with chronic lymphocytic leukemia*. Cancer, 1999. **86**(12): p. 2684-92.
23. Molica, S. and D. Levato, *What is changing in the natural history of chronic lymphocytic leukemia?* Haematologica, 2001. **86**(1): p. 8-12.

24. Rai, K.R., A. Sawitsky, E.P. Cronkite, A.D. Chanana, R.N. Levy, and B.S. Pasternack, *Clinical staging of chronic lymphocytic leukemia*. Blood, 1975. **46**(2): p. 219-34.
25. Binet, J.L., A. Auquier, G. Dighiero, C. Chastang, H. Piguët, J. Goasguen, G. Vaugier, G. Potron, P. Colona, F. Oberling, M. Thomas, G. Tchernia, C. Jacquillat, P. Boivin, C. Lesty, M.T. Duault, M. Monconduit, S. Belabbès, and F. Gremy, *A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis*. Cancer, 1981. **48**(1): p. 198-206.
26. Catovsky, D., J. Fooks, and S. Richards, *Prognostic factors in chronic lymphocytic leukaemia: the importance of age, sex and response to treatment in survival. A report from the MRC CLL 1 trial. MRC Working Party on Leukaemia in Adults*. Br J Haematol, 1989. **72**(2): p. 141-9.
27. Rozman, C., E. Montserrat, J.M. Rodriguez-Fernandez, R. Ayats, T. Vallespi, R. Parody, A. Rios, D. Prados, M. Morey, F. Gomis, and et al., *Bone marrow histologic pattern--the best single prognostic parameter in chronic lymphocytic leukemia: a multivariate survival analysis of 329 cases*. Blood, 1984. **64**(3): p. 642-8.
28. Pangalis, G.A., V.A. Boussiotis, and C. Kittas, *B-chronic lymphocytic leukemia. Disease progression in 150 untreated stage A and B patients as predicted by bone marrow pattern*. Nouv Rev Fr Hematol, 1988. **30**(5-6): p. 373-5.
29. Montserrat, E., J. Sanchez-Bisono, N. Vinolas, and C. Rozman, *Lymphocyte doubling time in chronic lymphocytic leukaemia: analysis of its prognostic significance*. Br J Haematol, 1986. **62**(3): p. 567-75.
30. Vinolas, N., J.C. Reverter, A. Urbano-Ispizua, E. Montserrat, and C. Rozman, *Lymphocyte doubling time in chronic lymphocytic leukemia: an update of its prognostic significance*. Blood Cells, 1987. **12**(2): p. 457-70.
31. Melo, J.V., D. Catovsky, W.M. Gregory, and D.A. Galton, *The relationship between chronic lymphocytic leukaemia and prolymphocytic leukaemia. IV. Analysis of survival and prognostic features*. Br J Haematol, 1987. **65**(1): p. 23-9.
32. Vallespi, T., E. Montserrat, and M.A. Sanz, *Chronic lymphocytic leukaemia: prognostic value of lymphocyte morphological subtypes. A multivariate survival analysis in 146 patients*. Br J Haematol, 1991. **77**(4): p. 478-85.
33. Di Giovanni, S., G. Valentini, P. Carducci, and P. Giallonardo, *Beta-2-microglobulin is a reliable tumor marker in chronic lymphocytic leukemia*. Acta Haematol, 1989. **81**(4): p. 181-5.
34. Hallek, M., L. Wanders, M. Ostwald, R. Busch, R. Senekowitsch, S. Stern, H.D. Schick, I. Kuhn-Hallek, and B. Emmerich, *Serum beta(2)-microglobulin and serum thymidine kinase are independent predictors of progression-free survival in chronic lymphocytic leukemia and immunocytoma*. Leuk Lymphoma, 1996. **22**(5-6): p. 439-47.
35. Hamblin, T.J., Z. Davis, A. Gardiner, D.G. Oscier, and F.K. Stevenson, *Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia*. Blood, 1999. **94**(6): p. 1848-1854.

36. Damle, R.N., T. Wasil, F. Fais, F. Ghiotto, A. Valetto, S.L. Allen, A. Buchbinder, D. Budman, K. Dittmar, J. Kolitz, S.M. Lichtman, P. Schulman, V.P. Vinciguerra, K.R. Rai, M. Ferrarini, and N. Chiorazzi, *Ig V Gene Mutation Status and CD38 Expression As Novel Prognostic Indicators in Chronic Lymphocytic Leukemia*. *Blood*, 1999. **94**(6): p. 1840-1847.
37. Crespo, M., F. Bosch, N. Villamor, B. Bellosillo, D. Colomer, M. Rozman, S. Marce, A. Lopez-Guillermo, E. Campo, and E. Montserrat, *ZAP-70 expression as a surrogate for immunoglobulin-variable-region mutations in chronic lymphocytic leukemia*. *N Engl J Med*, 2003. **348**(18): p. 1764-75.
38. Dohner, H., S. Stilgenbauer, A. Benner, E. Leupolt, A. Krober, L. Bullinger, K. Dohner, M. Bentz, and P. Lichter, *Genomic aberrations and survival in chronic lymphocytic leukemia*. *N Engl J Med*, 2000. **343**(26): p. 1910-1916.
39. Sawitsky, A., K.R. Rai, O. Glidewell, and R.T. Silver, *Comparison of daily versus intermittent chlorambucil and prednisone therapy in the treatment of patients with chronic lymphocytic leukemia*. *Blood*, 1977. **50**(6): p. 1049-59.
40. Keller, J.W., W.H. Knospe, M. Raney, C.M. Huguley, Jr., L. Johnson, A.A. Bartolucci, and G.A. Omura, *Treatment of chronic lymphocytic leukemia using chlorambucil and prednisone with or without cycle-active consolidation chemotherapy. A Southeastern Cancer Study Group Trial*. *Cancer*, 1986. **58**(6): p. 1185-92.
41. Montserrat, E., A. Alcala, R. Parody, A. Domingo, J. Garcia-Conde, J. Bueno, C. Ferran, M.A. Sanz, M. Giralt, D. Rubio, and et al., *Treatment of chronic lymphocytic leukemia in advanced stages. A randomized trial comparing chlorambucil plus prednisone versus cyclophosphamide, vincristine, and prednisone*. *Cancer*, 1985. **56**(10): p. 2369-75.
42. Raphael, B., J.W. Andersen, R. Silber, M. Oken, D. Moore, J. Bennett, H. Bonner, R. Hahn, W.H. Knospe, J. Mazza, and et al., *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 Oncol*, 1991. **9**(5): p. 770-6.
43. *Is the CHOP regimen a good treatment for advanced CLL? Results from two randomized clinical trials. French Cooperative Group on Chronic Lymphocytic Leukemia*. *Leuk Lymphoma*, 1994. **13**(5-6): p. 449-56.
44. Keating, M.J., S. O'Brien, H. Kantarjian, W. Plunkett, E. Estey, C. Koller, M. Beran, and E.J. Freireich, *Long-term follow-up of patients with chronic lymphocytic leukemia treated with fludarabine as a single agent*. *Blood*, 1993. **81**(11): p. 2878-84.
45. Keating, M.J., S. O'Brien, S. Lerner, C. Koller, M. Beran, L.E. Robertson, E.J. Freireich, E. Estey, and H. Kantarjian, *Long-term follow-up of patients with chronic lymphocytic leukemia (CLL) receiving fludarabine regimens as initial therapy*. *Blood*, 1998. **92**(4): p. 1165-71.
46. O'Brien, S., H. Kantarjian, M. Beran, T. Smith, C. Koller, E. Estey, L.E. Robertson, S. Lerner, and M. Keating, *Results of fludarabine and prednisone therapy in 264 patients with chronic lymphocytic leukemia with multivariate analysis-derived prognostic model for response to treatment [see comments]*. *Blood*, 1993. **82**(6): p. 1695-700.

47. Hiddemann, W., R. Rottmann, B. Wormann, A. Thiel, M. Essink, C. Ottensmeier, M. Freund, T. Buchner, and J. van de Loo, *Treatment of advanced chronic lymphocytic leukemia by fludarabine. Results of a clinical phase-II study*. Ann Hematol, 1991. **63**(1): p. 1-4.
48. Montserrat, E., J.L. Lopez-Lorenzo, F. Manso, A. Martin, E. Prieto, J. Arias-Sampedro, M.N. Fernandez, F.J. Oyarzabal, J. Odriozola, A. Alcala, J. Garcia-Conde, R. Guardia, and F. Bosch, *Fludarabine in resistant or relapsing B-cell chronic lymphocytic leukemia: the Spanish Group experience*. Leuk Lymphoma, 1996. **21**(5-6): p. 467-72.
49. Gjedde, S.B. and M.M. Hansen, *Salvage therapy with fludarabine in patients with progressive B-chronic lymphocytic leukemia*. Leuk Lymphoma, 1996. **21**(3-4): p. 317-20.
50. Saven, A. and L.D. Piro, *2-Chlorodeoxyadenosine: a newer purine analog active in the treatment of indolent lymphoid malignancies*. Ann Intern Med, 1994. **120**(9): p. 784-91.
51. Saven, A., R.H. Lemon, M. Kosty, E. Beutler, and L.D. Piro, *2-Chlorodeoxyadenosine activity in patients with untreated chronic lymphocytic leukemia*. J Clin Oncol, 1995. **13**(3): p. 570-4.
52. Ho, A.D., J. Thaler, P. Stryckmans, B. Coiffier, M. Luciani, P. Sonneveld, K. Lechner, S. Rodenhuis, M.E. Peetermans, F. deCataldo, and et al., *Pentostatin in refractory chronic lymphocytic leukemia: a phase II trial of the European Organization for Research and Treatment of Cancer*. J Natl Cancer Inst, 1990. **82**(17): p. 1416-20.
53. Catovsky, D., *Clinical experience with 2'-deoxycoformycin*. Hematol Cell Ther, 1996. **38**(Suppl 2): p. S103-7.
54. Byrd, J.C., B.L. Peterson, V.A. Morrison, K. Park, R. Jacobson, E. Hoke, J.W. Vardiman, K. Rai, C.A. Schiffer, and R.A. Larson, *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**(1): p. 6-14.
55. Byrd, J.C., K. Rai, B.L. Peterson, F.R. Appelbaum, V.A. Morrison, J.E. Kolitz, L. Shepherd, J.D. Hines, C.A. Schiffer, and R.A. Larson, *Addition of rituximab to fludarabine may prolong progression-free survival and overall survival in patients with previously untreated chronic lymphocytic leukemia: an updated retrospective comparative analysis of CALGB 9712 and CALGB 9011*. Blood, 2005. **105**(1): p. 49-53.
56. Keating, M.J., S. O'Brien, M. Albitar, S. Lerner, W. Plunkett, F. Giles, M. Andreeff, J. Cortes, S. Faderl, D. Thomas, C. Koller, W. Wierda, M.A. Detry, A. Lynn, and H. Kantarjian, *Early Results of a Chemoimmunotherapy Regimen of Fludarabine, Cyclophosphamide, and Rituximab As Initial Therapy for Chronic Lymphocytic Leukemia*. J Clin Oncol, 2005.
57. Wierda, W., S. O'Brien, S. Wen, S. Faderl, G. Garcia-Manero, D. Thomas, K.A. Do, J. Cortes, C. Koller, M. Beran, A. Ferrajoli, F. Giles, S. Lerner, M. Albitar, H. Kantarjian, and M. Keating, *Chemoimmunotherapy With Fludarabine, Cyclophosphamide, and Rituximab for Relapsed and Refractory Chronic Lymphocytic Leukemia*. J Clin Oncol, 2005.

58. Keating, M.J., I. Flinn, V. Jain, J.L. Binet, P. Hillmen, J. Byrd, M. Albitar, L. Brettman, P. Santabarbara, B. Wacker, and K.R. Rai, *Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study*. *Blood*, 2002. **99**(10): p. 3554-61.
59. Hillmen, P., A.B. Skotnicki, T. Robak, B. Jaksic, A. Dmoszynska, J. Wu, C. Sirard, and J. Mayer, *Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia*. *J Clin Oncol*, 2007. **25**(35): p. 5616-23.
60. Knauf, W.U., T. Lissichkov, A. Aldaoud, R. Herbrecht, A.M. Liberati, J. Loscertales, G. Juliusson, C. Dittrich, and K. Merkle, *Bendamustine versus chlorambucil in treatment-naive patients with B-cell chronic lymphocytic leukemia (B-CLL): results of an international phase III study*. *Blood*, 2007. **110**(11): p. abs 2043.
61. Tam, C.S., S. O'Brien, S. Lerner, I. Khouri, A. Ferrajoli, S. Faderl, M. Browning, A.M. Tsimberidou, H. Kantarjian, and W.G. Wierda, *The natural history of fludarabine-refractory chronic lymphocytic leukemia patients who fail alemtuzumab or have bulky lymphadenopathy*. *Leuk Lymphoma*, 2007. **48**(10): p. 1931-9.
62. Keating, M.J., S. O'Brien, D. Kontoyiannis, W. Plunkett, C. Koller, M. Beran, S. Lerner, and H. Kantarjian, *Results of first salvage therapy for patients refractory to a fludarabine regimen in chronic lymphocytic leukemia*. *Leuk Lymphoma*, 2002. **43**(9): p. 1755-62.
63. Osterborg, A., T.J. Kipps, J. Mayer, S. Stilgenbauer, C.D. Williams, A. Hellmen, T. Robak, R.R. Furman, P. Hillmen, M. Trneny, M.J. Dyer, S. Padmanabhan, T. Kozak, G. Chan, R.L. Davis, N. Losic, C.A. Russell, M. Piotrowska, J. Wilms, and W.G. Wierda, *Ofatumumab (HuMax-CD20), a novel CD20 monoclonal antibody, is an active treatment for patients with CLL refractory to both fludarabine and alemtuzumab or bulky fludarabine-refractory disease: results from the planned interim analysis of an international pivotal trial*. *ASH Annual Meeting Abstracts*, 2008. **112**(11): p. 328.
64. Grdisa, M., *Influence of CD40 ligation on survival and apoptosis of B-CLL cells in vitro*. *Leuk Res*, 2003. **27**(10): p. 951-6.
65. Willimott, S., M. Baou, K. Naresh, and S.D. Wagner, *CD154 induces a switch in pro-survival Bcl-2 family members in chronic lymphocytic leukaemia*. *Br J Haematol*, 2007. **138**(6): p. 721-32.
66. van Kooten, C., I. Rensink, L. Aarden, and R. van Oers, *Cytokines and intracellular signals involved in the regulation of B-CLL proliferation*. *Leuk Lymphoma*, 1993. **12**(1-2): p. 27-33.
67. Castejon, R., J.A. Vargas, Y. Romero, M. Briz, R.M. Munoz, and A. Durantez, *Modulation of apoptosis by cytokines in B-cell chronic lymphocytic leukemia*. *Cytometry*, 1999. **38**(5): p. 224-30.
68. Decker, T., T. Flohr, P. Trautmann, M.J. Aman, W. Holter, O. Majdic, C. Huber, and C. Peschel, *Role of accessory cells in cytokine production by T cells in chronic B-cell lymphocytic leukemia*. *Blood*, 1995. **86**(3): p. 1115-23.
69. Mainou-Fowler, T. and A.G. Prentice, *Modulation of apoptosis with cytokines in B-cell chronic lymphocytic leukaemia*. *Leuk Lymphoma*, 1996. **21**(5-6): p. 369-77.

70. Farahani, M., A.T. Treweeke, C.H. Toh, K.J. Till, R.J. Harris, J.C. Cawley, M. Zuzel, and H. Chen, *Autocrine VEGF mediates the antiapoptotic effect of CD154 on CLL cells*. *Leukemia*, 2005.
71. Ferrajoli, A., T. Manshouri, Z. Estrov, M.J. Keating, S. O'Brien, S. Lerner, M. Beran, H.M. Kantarjian, E.J. Freireich, and M. Albitar, *High levels of vascular endothelial growth factor receptor-2 correlate with shortened survival in chronic lymphocytic leukemia*. *Clin Cancer Res*, 2001. **7**(4): p. 795-9.
72. Gora-Tybor, J., J.Z. Blonski, and T. Robak, *Circulating vascular endothelial growth factor (VEGF) and its soluble receptors in patients with chronic lymphocytic leukemia*. *Eur Cytokine Netw*, 2005. **16**(1): p. 41-6.
73. Till, K.J., D.G. Spiller, R.J. Harris, H. Chen, M. Zuzel, and J.C. Cawley, *CLL, but not normal, B cells are dependent on autocrine VEGF and alpha4beta1 integrin for chemokine-induced motility on and through endothelium*. *Blood*, 2005. **105**(12): p. 4813-9.
74. Lee, Y.K., N.D. Bone, A.K. Strege, T.D. Shanafelt, D.F. Jelinek, and N.E. Kay, *VEGF receptor phosphorylation status and apoptosis is modulated by a green tea component, epigallocatechin-3-gallate (EGCG), in B-cell chronic lymphocytic leukemia*. *Blood*, 2004. **104**(3): p. 788-94.
75. Molica, S., G. Vitelli, D. Levato, G.M. Gandolfo, and V. Liso, *Increased serum levels of vascular endothelial growth factor predict risk of progression in early B-cell chronic lymphocytic leukaemia*. *Br J Haematol*, 1999. **107**(3): p. 605-10.
76. Molica, S., G. Cutrona, G. Vitelli, R. Mirabelli, M. Molica, G. Digiesi, D. Ribatti, M. Ferrarini, and A. Vacca, *Markers of increased angiogenesis and their correlation with biological parameters identifying high-risk patients in early B-cell chronic lymphocytic leukemia*. *Leuk Res*, 2007. **31**(11): p. 1575-8.
77. Konig, A., T. Menzel, S. Lynen, L. Wrazel, A. Rosen, A. Al-Katib, E. Raveche, and J.L. Gabrilove, *Basic fibroblast growth factor (bFGF) upregulates the expression of bcl-2 in B cell chronic lymphocytic leukemia cell lines resulting in delaying apoptosis*. *Leukemia*, 1997. **11**(2): p. 258-65.
78. Nishio, M., T. Endo, N. Tsukada, J. Ohata, S. Kitada, J.C. Reed, N.J. Zvaifler, and T.J. Kipps, *Nurselike cells express BAFF and APRIL, which can promote survival of chronic lymphocytic leukemia cells via a paracrine pathway distinct from that of SDF-1{alpha}*. *Blood*, 2005.
79. Adami, F., A. Guarini, M. Pini, F. Siviero, R. Sancetta, M. Massaia, L. Trentin, R. Foa, and G. Semenzato, *Serum levels of tumour necrosis factor-alpha in patients with B-cell chronic lymphocytic leukaemia*. *Eur J Cancer*, 1994. **30A**(9): p. 1259-63.
80. Cordingley, F.T., A. Bianchi, A.V. Hoffbrand, J.E. Reittie, H.E. Heslop, A. Vyakarnam, M. Turner, A. Meager, and M.K. Brenner, *Tumour necrosis factor as an autocrine tumour growth factor for chronic B-cell malignancies*. *Lancet*, 1988. **1**(8592): p. 969-71.
81. Foa, R., M. Massaia, S. Cardona, A.G. Tos, A. Bianchi, C. Attisano, A. Guarini, P.F. di Celle, and M.T. Fierro, *Production of tumor necrosis factor-alpha by B-cell chronic lymphocytic leukemia cells: a possible regulatory role of TNF in the progression of the disease*. *Blood*, 1990. **76**(2): p. 393-400.

82. Kay, N.E., L. Han, N. Bone, and G. Williams, *Interleukin 4 content in chronic lymphocytic leukaemia (CLL) B cells and blood CD8+ T cells from B-CLL patients: impact on clonal B-cell apoptosis*. Br J Haematol, 2001. **112**(3): p. 760-7.
83. Kitabayashi, A., M. Hirokawa, and A.B. Miura, *The role of interleukin-10 (IL-10) in chronic B-lymphocytic leukemia: IL-10 prevents leukemic cells from apoptotic cell death*. Int J Hematol, 1995. **62**(2): p. 99-106.
84. Sampaio, E.P., E.N. Sarno, R. Galilly, Z.A. Cohn, and G. Kaplan, *Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes*. J Exp Med, 1991. **173**(3): p. 699-703.
85. Paravar, T. and D.J. Lee, *Thalidomide: mechanisms of action*. Int Rev Immunol, 2008. **27**(3): p. 111-35.
86. Majumdar, S., B. Lamothe, and B.B. Aggarwal, *Thalidomide suppresses NF-kappa B activation induced by TNF and H2O2, but not that activated by ceramide, lipopolysaccharides, or phorbol ester*. J Immunol, 2002. **168**(6): p. 2644-51.
87. Yagy, T., H. Kobayashi, H. Matsuzaki, K. Wakahara, T. Kondo, N. Kurita, H. Sekino, K. Inagaki, M. Suzuki, N. Kanayama, and T. Terao, *Thalidomide inhibits tumor necrosis factor-alpha-induced interleukin-8 expression in endometriotic stromal cells, possibly through suppression of nuclear factor-kappaB activation*. J Clin Endocrinol Metab, 2005. **90**(5): p. 3017-21.
88. Andritsos, L.A., A.J. Johnson, G. Lozanski, W. Blum, C. Kefauver, F. Awan, L.L. Smith, R. Lapalombella, S.E. May, C.A. Raymond, D.S. Wang, R.D. Knight, A.S. Ruppert, A. Lehman, D. Jarjoura, C.S. Chen, and J.C. Byrd, *Higher doses of lenalidomide are associated with unacceptable toxicity including life-threatening tumor flare in patients with chronic lymphocytic leukemia*. J Clin Oncol, 2008. **26**(15): p. 2519-25.
89. Palumbo, A., A. Larocca, P. Falco, G. Sanpaolo, A.P. Falcone, V. Federico, L. Canepa, M. Crugnola, M. Genuardi, V. Magarotto, M.T. Petrucci, and M. Boccadoro, *Lenalidomide, melphalan, prednisone and thalidomide (RMPT) for relapsed/refractory multiple myeloma*. Leukemia, 2010. **24**(5): p. 1037-42.
90. Mark, T., M. Coleman, D.S. Jayabalan, R. Pearse, F. Zafar, S. Ely, M.C. Manco, M. Crann, J.P. Leonard, S. Chen-Kiang, and R. Niesvizky, *T-Bird (thalidomide, clarithromycin/[Biaxin(R)], lenalidomide/[Revlimid(R)], Dexamethasone) Therapy for Upfront Use in Symptomatic Multiple Myeloma*. ASH Annual Meeting Abstracts, 2009. **114**(22): p. 1861-.
91. Simon, R., *Optimal two-stage designs for phase II clinical trials*. Control Clin Trials, 1989. **10**(1): p. 1-10.
92. Cairo, M.S. and M. Bishop, *Tumour lysis syndrome: new therapeutic strategies and classification*. Br J Haematol, 2004. **127**(1): p. 3-11.

## **Appendix A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods**

## **Risks Associated with Pregnancy**

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

All study participants must be registered into the mandatory RevAssist® and S.T.E.P.S programs, and be willing and able to comply with the requirements of RevAssist® and S.T.E.P.S.

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

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

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

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 and/or thalidomide 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 and/or thalidomide study therapy):

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

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 and/or thalidomide study therapy):

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

### Contraception

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

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

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)

- Tubal ligation
- Partner’s vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

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

### Pregnancy testing

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

### **Before starting study drug**

#### *Female Patients:*

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

#### *Male Patients:*

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

### **During study participation and for 28 days following study drug discontinuation**

#### *Female Patients:*

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and

then every 14 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation.

- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a study patient, study drug must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

#### Male Patients:

- Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to lenalidomide must be conducted at a minimum of every 28 days.
- 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.

## Appendix B: ECOG Performance Status Scale

<b>SCORE</b>	<b>DESCRIPTION</b>
<b>0</b>	Fully active, able to carry on all pre-disease performance without restriction.
<b>1</b>	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.
<b>2</b>	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
<b>3</b>	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
<b>4</b>	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
<b>5</b>	Dead.

## **Appendix C: NCI CTCAE Version 4.0**

Toxicity will be scored using NCI CTCAE 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 CTCAE Version 4.0.

## Appendix D: Cairo-Bishop Definition of Tumor Lysis Syndrome [92]

**Table: Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome**

Uric Acid	$\geq 476 \mu\text{mol/l}$ ( $\geq 8.0 \text{ mg/dl}$ ) or 25% increase from baseline
Potassium	$\geq 6.0 \text{ mmol/l}$ ( $\geq 6.0 \text{ mEq/l}$ ) or 25% increase from baseline
Phosphorous	$\geq 1.45 \text{ mmol/l}$ ( $\geq 4.5 \text{ mg/dl}$ ) or 25 % increase from baseline
Calcium	$\leq 1.75 \text{ mmol/l}$ ( $\leq 7.0 \text{ mg/dl}$ ) or 25% decrease from baseline
<p>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 (<math>\pm</math> alkalinization) and a hypouricaemic agent(s).</p>	

**Table: Cairo-Bishop Definition of Clinical TLS**

<b>The presence of laboratory TLS and one or more of the following criteria:</b>
<ol style="list-style-type: none"> <li>1. Creatinine: <math>\geq 1.5 \text{ ULN}</math> (age &gt; 12 years or age adjusted)</li> <li>2. Cardiac arrhythmia / sudden death</li> <li>3. Seizure*</li> </ol>

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	-	$\leq 1.5 \times \text{ULN}$	None	None
1	+	$1.5 \times \text{ULN}$	Intervention not indicated	None
2	+	$> 1.5 - 3.0 \times \text{ULN}$	Non-urgent medical intervention indicated	One brief generalized seizure; seizure(s) well controlled or infrequent; focal motor seizures not interfering with ADL
3	+	$> 3.0 - 6.0 \times \text{ULN}$	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	+	$> 6.0 \times \text{ULN}$	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 E: Cockcroft-Gault estimation of CrCl

Cockcroft-Gault estimation of creatinine clearance (CrCl):

(Cockcroft, 1976; Luke 1990)

**(Males)**

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})}$$

**(Females)**

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \times 0.85$$

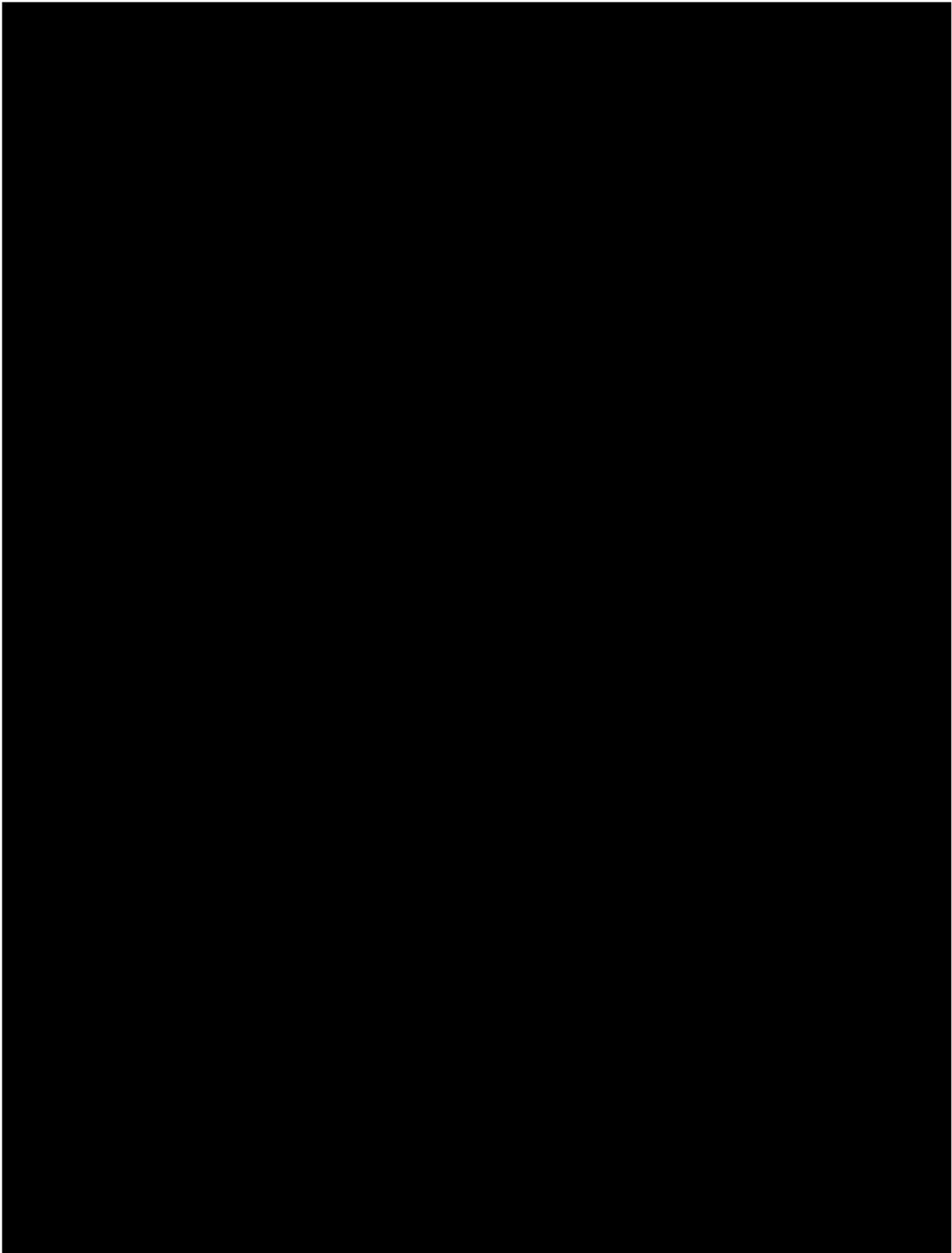
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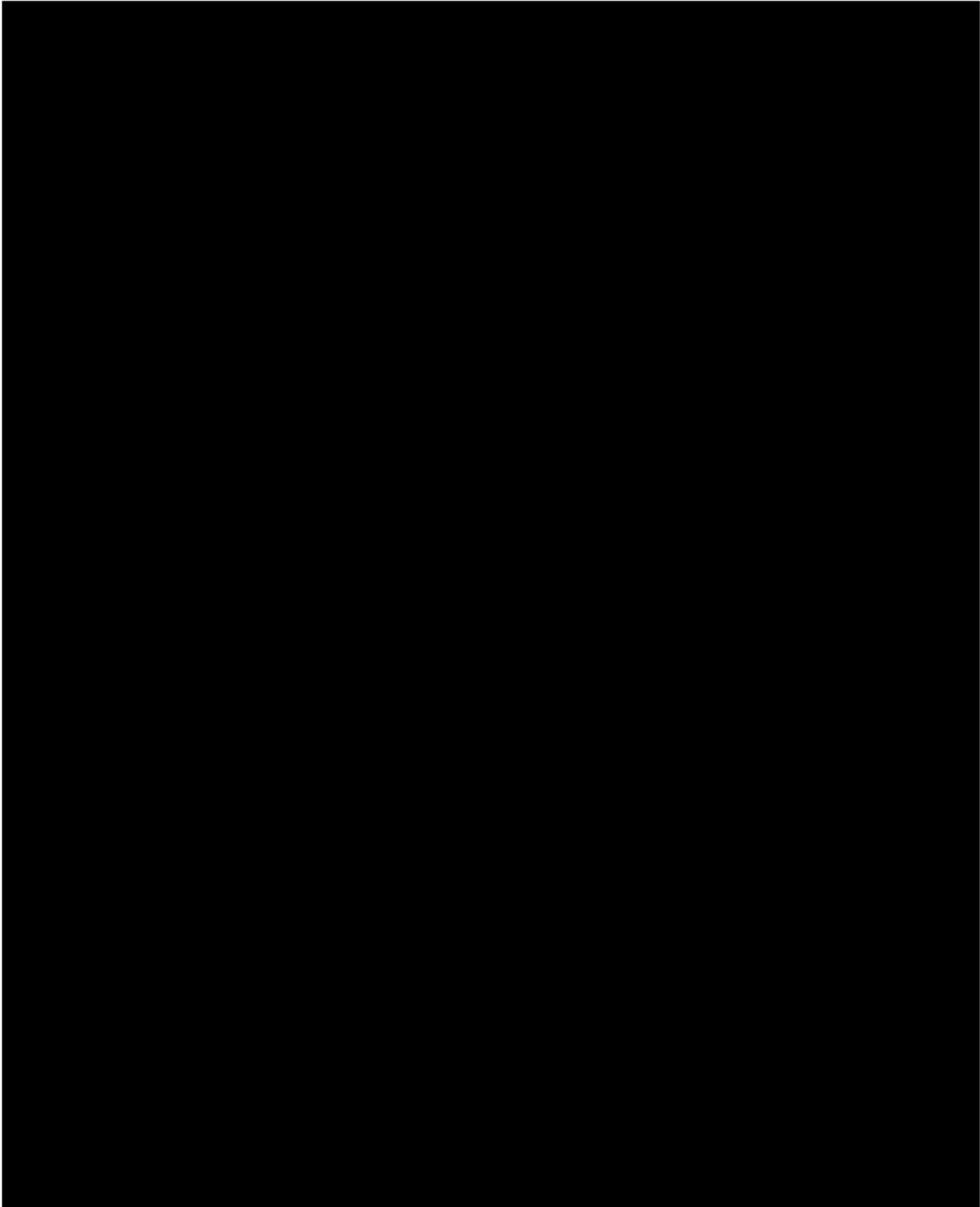
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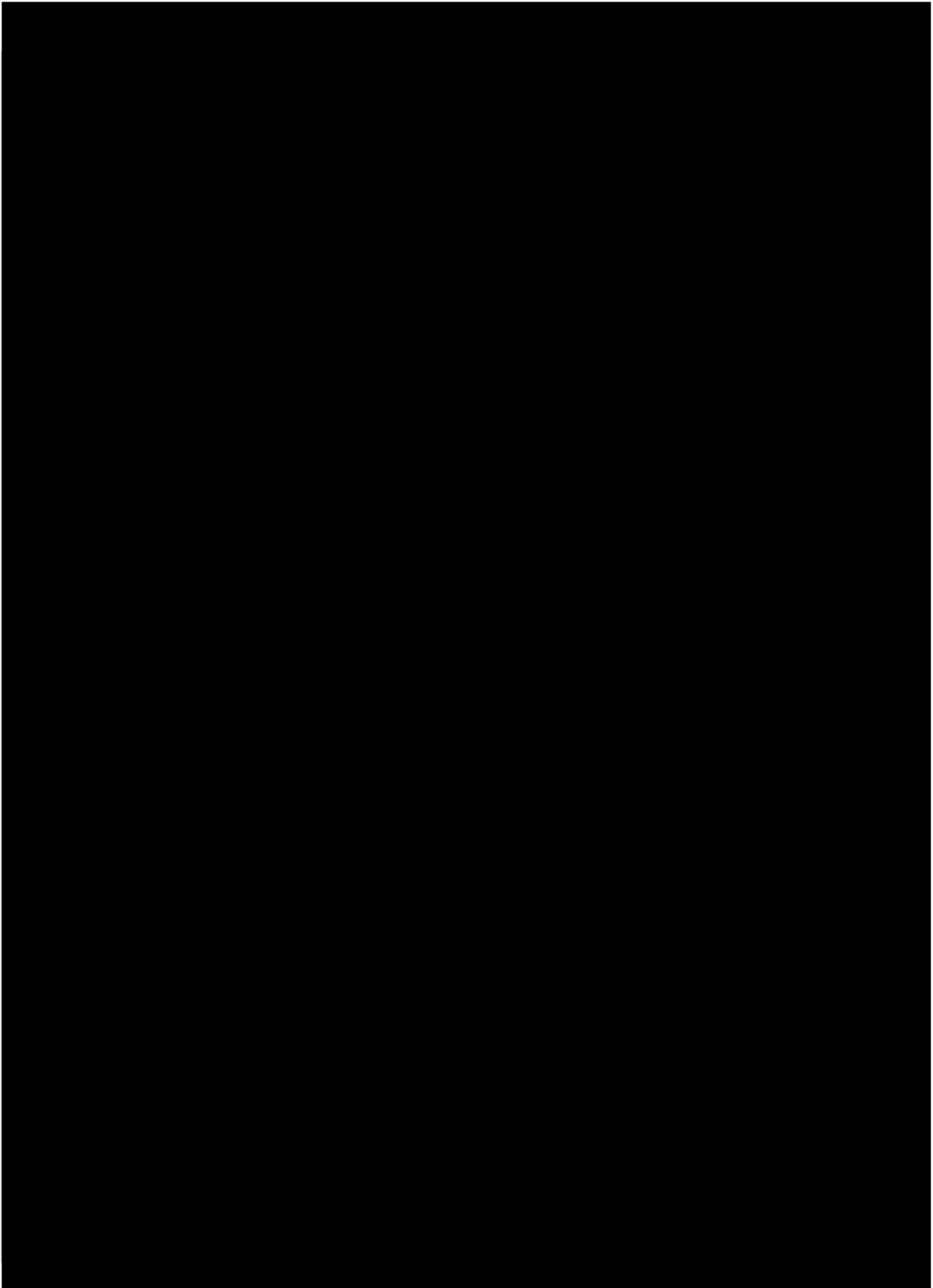
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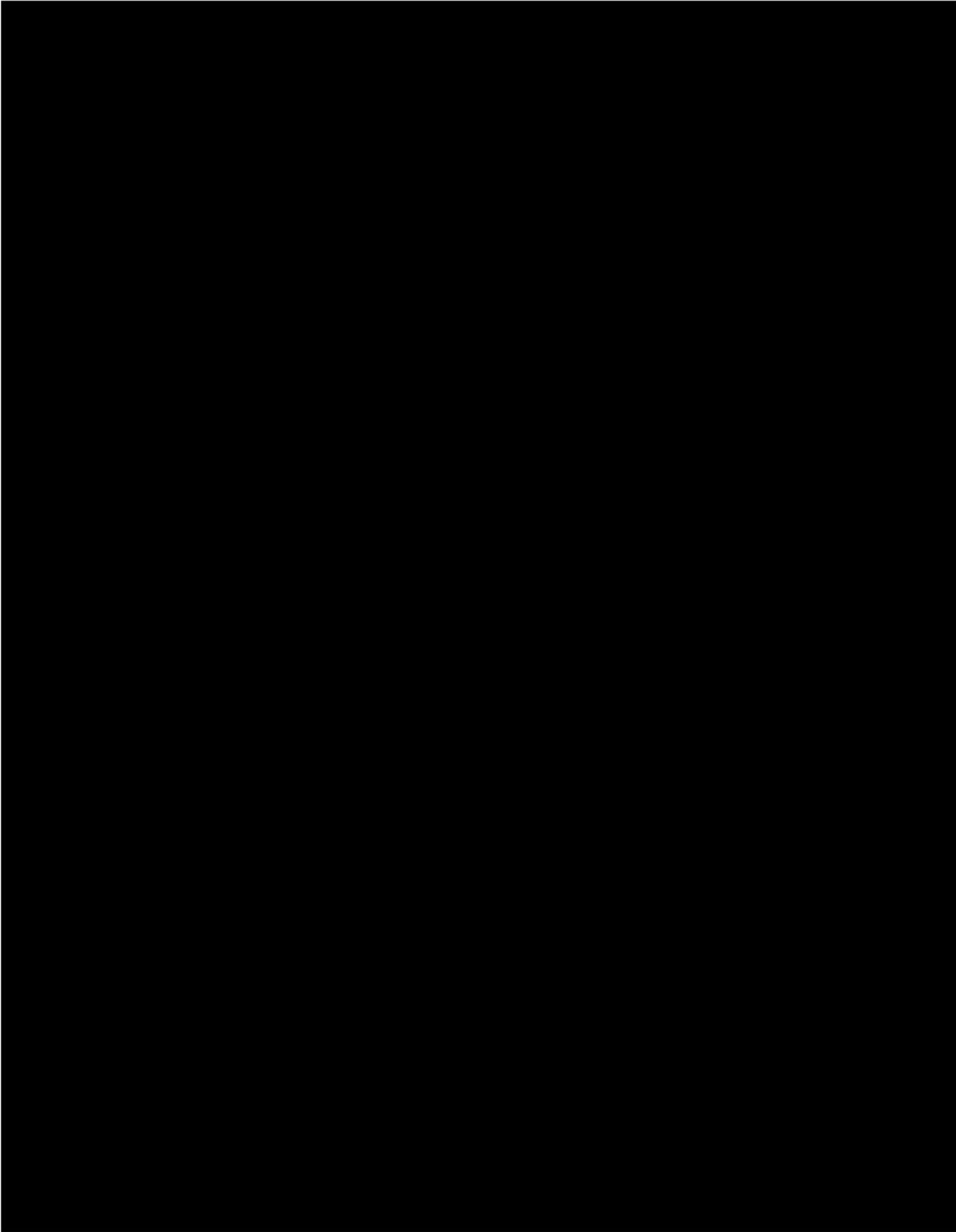
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## Appendix H: Summary of Changes from Protocol Version 2 dated September 23, 2013

The protocol has been amended to discontinue rituximab after Cycle 19 and reduce the frequency of subject visits to every three cycles subsequent to Cycle 24.

List of substantive changes [relevant sections]:

- Treatment with rituximab will be discontinued after Cycle 19.  
*[Schema, Sections 5.1, Section 5.2, Section 5.4.1, Section 8.3.7, Section 10]*
- Subsequent to Cycle 24, clinic visits are required every three cycles. At the start of non-clinic visit treatment cycles, subjects must still meet all the requirements for the initiation of a new treatment cycle, including compliance with the RevAssist® and S.T.E.P.S.® programs, and all pregnancy testing and pregnancy risk counseling requirements. Hematology assessment will be done locally as required for the initiation of a new treatment cycle. Study drug will be shipped to subjects at the start of non-clinic visit cycles.  
*[Section 5.4.1, Section 5.4.2, Section 6.3, Section 10]*
- The provision of Lenalidomide and Thalidomide has been corrected to state that both drugs are shipped on a per subject basis by the contract pharmacy to the clinic site, rather than direct-to-patient.  
*[Section 8.1.6, Section 8.2.8]*
- BLYS/BAFF Analysis will be discontinued after the last cycle of Rituximab treatment.  
*[Section 9, Section 10]*
- Peripheral Blood Cell Subset Analysis will now be done every six cycles subsequent to Cycle 24.  
*[Section 9, Section 10]*
- CT scans will be done every six months for three years, and every twelve months thereafter. Response assessment and MRD assessment should be performed every six months subsequent to Cycle 24.  
*[Section 10]*
- IFE, beta-2-microglobulin, DAT assessment will be done every 6 cycles starting with Cycle 24.  
*[Section 10]*
- The DSMB concluded at the 8/11/2016 meeting that the data and safety review schedule be changed from quarterly to annual.  
*[Section 12.3]*