THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

EVALUATION OF LENALIDOMIDE (CC-5013) AND PREDNISONE AS A THERAPY FOR PATIENTS WITH MYELOFIBROSIS (MF)
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Study Chair:	Srdan Verstovsek
Additional Contact:	Paula J. Cooley Sandra L. Rood Leukemia Protocol Review Group
Department:	Leukemia
Phone:	713-792-7305
Unit:	428
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(●) The Clinical Research Committee - (CRC)

Protocol Body

Scott Miller
Celgene Corporation
Medical Education Liaison
2104 Vintage Court
McKinney, TX 75070
972-333-0548
1 800 832 4031

EVALUATION OF LENALIDOMIDE (REVLIMID®) AND PREDNISONE AS A THERAPY FOR PATIENTS WITH MYELOFIBROSIS (MF)

University of Texas
MD Anderson Cancer Center
Leukemia Department, Unit 428
Telephone: 713-792-7305

Principal Investigator: Srdan Verstovsek, M.D., Ph.D.

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PROTOCOL BODY

1.0 HYPOTHESIS AND OBJECTIVES

1.1 Hypothesis

Lenalidomide and prednisone in combination are effective and tolerable treatment for patients with myelofibrosis (MF).

1.2 Objectives

Primary: To determine the efficacy of lenalidomide and prednisone in combination in patients with MF, in achieving objective improvements in disease status: complete and partial response, hematological improvement.

Secondary: to determine the safety of lenalidomide and prednisone in combination, in patients with MF.

Tertiary: To examine pertinent morphological, biological, and molecular characteristics of MF in patient samples during therapy with lenalidomide and prednisone.

2.0 BACKGROUND AND RATIONALE

2.1 Myelofibrosis with Myeloid Metaplasia

Myelofibrosis with myeloid metaplasia (MF) is a rare [0.73 per 100,000 person years in males and 0.4 per 100,000 person years in females in the United Kingdom] clonal proliferative disorder of a pluripotent stem cell. This clone subsequently induces fibrogenic cytokines and/or growth factors in the marrow, which stimulate the deposition of extracellular matrix proteins by polyclonal fibroblasts. Megakaryocytic hyperplasia-dysplasia is frequently observed. Invasion of the blood stream and colonization of extramedullary sites ensues, resulting in organomegaly and splenomegaly. Extensive marrow fibrosis and osteosclerosis may be observed in advanced MF, resulting in “dry taps”.

The entity of MF can be either idiopathic (primary or agnogenic myeloid metaplasia), or representative of end-stage myeloproliferative diseases such as polycythemia vera (PV) or essential thrombocythemia (ET). MF occurs in 25% to 50% of patients with PV and in 2% to 3% of patients with ET. In the early cellular phase of MF with minimal marrow fibrosis, the differential diagnosis includes Philadelphia-positive CML, PV, and ET that

must be distinguished, based on cytogenetics and clinicopathologic features. Other entities that can induce myelophthisis include myelodysplastic syndrome (MDS), metastatic malignancies, lymphoma, Hodgkin's disease, and plasma cell dyscrasias. MF must be differentiated from acute megakaryocytic leukemia (AML, M7 of the French-American-British classification) and CML with fibrosis. In acute megakaryocytic leukemia patients usually present with severe constitutional symptoms and pancytopenia but without organomegaly or peripheral blood myelophthisis.

Thus, the clinical picture of MF involves constitutional symptoms (e.g., cachexia, night sweats, fatigue, fever), splenomegaly, anisopoikilocytosis with teardrop erythrocytes, progressive anemia, immature myeloid and erythroid precursors in the peripheral blood, elevated lactate dehydrogenase (LDH) levels, and fibrosis of the marrow (as evaluated by reticulin and trichome [collagen] stains). The leukoerythroblastic picture is postulated to be related to both the intramedullary sinusoidal marrow and splenic hematopoiesis.

The disease generally occurs in adults, with the median age ranging from 54 to 62 years; 70% of the patients are over the age of 50 years. In 40% of the patients, constitutional symptoms are present, including fever, weight loss, nocturnal sweating, pruritus, and bone pain. Splenomegaly is present in 85% to 100% of the patients at diagnosis, and is massive in 10%. Hematologic disease features include anemia in 50% to 70% at diagnosis and 25% will have severe anemia with hemoglobin level < 8.0 gm/dL. Approximately half of the patients present with an elevated white cell count (WBC), 28% with thrombocytosis (platelet count > 500 x 10^9/L, and 37% with thrombocytopenia (platelet count < 150 x 10^9/L). Circulating blast cells are present in one-third of the patients.

Complications of MF are varied. Thrombotic obliteration of intrahepatic veins and splenomegaly may lead to portal hypertension; severe cases may be associated with ascites and/or variceal bleeding. Left upper quadrant pain may herald splenic infarction; episodes are usually self-limited and may persist for several days. Supportive care measures such as analgesics and hydration are usually sufficient; refractory cases may require splenectomy or irradiation. Extramedullary hematopoiesis (EMH) may occur in locations other than the liver or spleen; involvement of such sites may be managed by low-dose irradiation. Liver involvement is associated with increased levels of plasma alkaline phosphatase. Clinical manifestations of EMH include cardiac tamponade, papular skin nodules, pleural effusions, and spinal cord compression.

Autoimmune phenomena have been observed, including Coomb's positive autoimmune hemolytic anemia, nephrotic syndrome, antinuclear antibodies, rheumatoid factor, and lupus-type anticoagulant. Postulated etiologies include clonality of the lymphoid population or activation by abnormal monocyte-macrophage interaction with the immune system.

Adverse prognostic factors for survival include older age and anemia (hemoglobin < 10 gm/dL). The etiology for the latter finding is usually multifactorial and related both to marrow failure and hypersplenism. Poor prognosis has also been correlated with leukocytosis, leukopenia, circulating blasts, increased numbers of granulocyte precursors, thrombocytopenia, abnormal karyotype, and hypercatabolic symptoms.

The course of the disease is highly variable. Median survival from time of diagnosis ranges from 3 to 6 years; survival rates at 2 and 5 years are 68% and 40%, respectively. Progressive marrow failure, transformation into acute myeloid leukemia, and portal hypertension lead to demise.

Various prognostic models have been devised, with only hemoglobin at diagnosis a consistent prognostic factor among several studies. Other parameters included constitutional symptoms, thrombocytopenia, and percentage of WBC precursors.

Lille Scoring System [Hemoglobin < 10 gm/dL, WBC < 4 or > 30 x 10^9/L]

No. of Adverse Prognostic Features	Risk Group	Median Survival (months)
0	Low	93
1	Intermediate	26
2	High	13

Age of the patient and abnormal karyotype are two additional prognostic features. The median survival of young, low-risk patients can range from 13 to 15 years. Overall median survival is estimated between 3 and 6 years with infections, thrombosis and/or hemorrhage, and transformation to leukemic phase frequently leading to death. Patients without any adverse features may survive as long as 10 years, whereas those with any two of these features have an expected survival less than 3 years.

No standard therapy exists for MF. Hydroxyurea is the most commonly used agent in the proliferative phases of the disease. Interferon-alpha had yielded hematologic responses and reductions in splenomegaly (definitions varying among studies) in 30% to 50% of patients, especially those with proliferative phase, however, this agent tends to be poorly

tolerated. Agents used for the management of anemia include androgens and/or erythropoietin. Splenectomy and/or splenic irradiation have been used to manage symptomatic splenomegaly. Splenectomy has been associated with risk of leukemia transformation in some series, and splenic irradiation can result in severe myelosuppression.

No medical therapy has been proven to prolong overall survival for these patients. Patients with an intact quality of life and no threatening hematologic abnormalities, such as erythrocytosis or thrombocytosis, have usually been considered to not require any therapy; however, new therapeutic modalities are currently being considered in determining treatment indications.

In vitro data suggests that cytokines elaborated by megakaryocytes stimulate human bone marrow fibroblasts to divide and secrete collagens. In patients with MF, increased levels of transforming growth factor-beta (TGF-beta) have been observed in circulating peripheral blood mononuclear cells (PBMC) of megakaryocytic lineage.

Increased levels of basic fibroblast growth factor (bFGF) have also been reported in patients with MF. Both TGF-beta and bFGF are members of multifunctional polypeptide families that regulate cell growth and differentiation. In addition to their potent fibrogenic activity, TGF-beta and bFGF regulate hematopoiesis by selective actions on primitive stem cells. Expression of TGF-beta in early CD34+ hematopoietic stem cells negatively regulated the cycle status; this effect could be abrogated by bFGF. In addition, bFGF has been shown to augment the activity of stem cell factor (SCF), interleukin-3 (IL-3), granulocyte-macrophage colony stimulating factor (GM-CSF), or erythropoietin on committed progenitor cells. Other cytokines/proteins that are disregulated in MF include; tumor necrosis factor-alpha (TNF-alpha) and angiogenic agents like vascular endothelial growth factor (VEGF).

Serum interleukin-6 (IL-6) has multiple biological effects, including the regulation of hematopoiesis, immune responses, and acute phase reactions. IL-6 appears to be a potent megakaryocytic maturation factor. Patients with ET appear to have IL-6 levels similar to controls, whereas patients with reactive thrombocytosis have higher IL-6 levels.

2.2 Introduction to Lenalidomide

Lenalidomide is the lead compound in a proprietary class of Celgene compounds known as IMiDs® with immunomodulatory and anti-angiogenic properties that could confer antitumor and antimetastatic effects. It is a derivative of thalidomide, combining higher efficacy and lower toxicity than its parent compound. 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. 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.

Clinical experience in solid tumors with lenalidomide

Twenty patients with varying types of solid tumors (13 with malignant melanoma, 2 each with carcinoma of the pancreas and non-small-cell lung cancer [NSCLC], 1 each with renal carcinoma, breast carcinoma, and carcinoid-unknown primary) were enrolled in a Phase 1 study of lenalidomide conducted at the St. George Hospital, London, UK. This was a non-randomized, open-label with-in patient dose-escalation design, where patients started on 5 mg/day for 7 days and then increased their dose every 7 days to 10 mg/day, 25 mg/day, and 50 mg/day for a total of 4 weeks on therapy. Investigators at the NCI have enrolled 20 patients, including 18 patients with recurrent high-grade gliomas and 2 with other refractory CNS malignancies (1 recurrent atypical meningioma and 1 multiple recurrent spinal hemangioblastomas) into a phase I trial of lenalidomide given on Days 1 through 21 every 28 days. Treatment has been well tolerated with 1 grade 2 myelosuppression as the only toxicity > grade 1.

In an ongoing phase I trial in patients with refractory metastatic cancer conducted through the NCI, 12 patients with metastatic androgen independent prostate cancer have been enrolled. Lenalidomide was administered in daily doses of 5mg (3 patients), 10mg (3 patients) and 20mg (6 patients). Dose limiting toxicity was seen at 20mg/day (1 grade 3 thrombosis and 1 grade 3 hypotension). Stable PSA values for at least 8 weeks were observed in 6 patients.

In a phase III, multi-center, randomized parallel group study comparing two dose regimens of lenalidomide, 293 patients with malignant melanoma were enrolled. Subjects were randomized to receive treatment with lenalidomide at a dose of 5 mg per day orally for 28 days or to 25 mg per day orally for 21 days with a 7 day rest (28 day cycle). Treatment continued until the patient developed disease progression or intolerable adverse events occurred. Interim analysis failed to show an advantage of one regimen over the other with respect to survival. Analysis of response rates is pending. The toxicity profile was similar in both dose groups and the most frequent adverse events were fatigue, seen in 32% of patients, followed by nausea and diarrhea, seen in 24% and 20% of patients respectively. Neutropenia and thrombocytopenia were seen in 2.4% and 2.0% of patients respectively. Grade 3 and 4 toxicities were seen infrequently (<15%).

A second phase III randomized trial compared a lenalidomide dose of 25 mg daily orally for 21 days with a 7 day rest (28 day cycle) to placebo in patients with metastatic melanoma. Three hundred and five patients enrolled on this study and a preplanned interim analysis failed to demonstrate a survival advantage. Response rates are being analyzed. The toxicity profile was favorable and similar to the previous phase III study.

Clinical experience in multiple myeloma with lenalidomide
In 2 phase I studies in multiple myeloma, a total of 41 patients have been treated with lenalidomide. In one study at the University of Arkansas, 15 patients who relapsed or were refractory to high dose melphalan therapy with stem cell transplant were treated for 4 weeks in an open-label safety study and were permitted to continue therapy in an extension phase of the trial. Patient cohorts were treated at the following daily doses: 5mg, 10mg, 25mg, and 50mg. In a similar study at the Dana Farber Cancer Institute, 27 patients with rapidly advancing refractory multiple myeloma were enrolled. Anti-myeloma activity was observed in each of these 2 phase I studies. Decreases in neutrophil and platelet counts were the dose-limiting toxicities associated with lenalidomide. The maximum tolerated dose (MTD) was not reached within 28 days. Due to dose modifications associated with myelosuppression observed beyond Day 28 at the 25mg and 50mg daily dose levels, the dose schedule most widely used in future studies has been lenalidomide on Days 1-21, repeated every 28 days.

Pharmacokinetic analyses were performed on 15 multiple myeloma patients treated in the phase I studies. Absorption was found to be rapid on both Day 1 and Day 28 with time to maximum blood levels ranging from 0.7 to 2.0 hours at all dose levels (5mg, 10mg, 25mg, and 50mg). Plasma lenalidomide declined in a monophasic manner with elimination half-life ranging from 2.8 to 6.1 hours on both Day 1 and 28 at all 4 doses. No plasma accumulation was observed with multiple daily dosing. Peak and overall plasma concentrations were dose proportional over the dosing range of 5mg to 50mg.

A multicenter, randomized, phase II trial compared 2 syncopated dose schedules of lenalidomide used alone or in combination with dexamethasone in the treatment of relapsed or refractory multiple myeloma. All patients were treated on Days 1-21 of a 28-day cycle. Patients treated with 15mg BID experienced more myelosuppression and dose reductions compared with patients treated with 30mg daily. Anti-myeloma activity was observed with each dose and schedule of single agent lenalidomide. The addition of dexamethasone to lenalidomide yielded responses in some patients who had not responded to lenalidomide alone.

A phase I/II trial of Liposomal doxorubicin (Doxil®), vincristine, dexamethasone (DVd) and lenalidomide in heavily pretreated relapsed/refractory multiple myeloma patients is ongoing. The MTD of lenalidomide was 10mg on Days 1-21 in combination with Doxil® 40mg/m2 IVPB on Day 1, vincristine 2mg IVP on Day 1 and dexamethasone 40mg PO on Days 1-4 cycled every 28 days. All patients received amoxicillin, acyclovir and aspirin 81mg prophylactically. The dose limiting toxicity with lenalidomide 15mg on Days 1-21 in combination with DVd was sepsis/septic shock. Additional phase I trials of lenalidomide with chemotherapy in advanced malignancies are in progress.

Celgene Corporation sponsored 2 multicenter, randomized, double-blinded, placebo-controlled phase III trials [1 U.S. (MM-009) and 1 international (MM-010)] in patients with relapsed or refractory multiple myeloma. More than 350 patients were enrolled into each of these studies. All patients had to be considered sensitive to dexamethasone and were treated with dexamethasone 40mg qd, Days 1-4, 9-12 and 17-20. In addition to receiving dexamethasone, patients were randomized to lenalidomide 25mg qd or placebo, Days 1-21. Cycles were repeated every 28 days. After 4 cycles, there was a predetermined reduction of the dexamethasone dose to 40mg daily, Days 1-4 repeated every 28 days.

In both studies, a pre-specified interim analysis conducted by an Independent Data Monitoring Committee demonstrated that subjects receiving the combination of lenalidomide (Len) plus dexamethasone (Dex) had significantly longer times to progression and higher response rates than those treated with single-agent dexamethasone. A New Drug Application (NDA) is currently being prepared for the use of lenalidomide in Multiple Myeloma. Data continue to mature, but the preliminary interim analysis revealed the following results.

	MM-009 Len/Dex	MM-010 Len/Dex	MM-009 Placebo/Dex	MM-010 Placebo/Dex	
CR+PR (%)	61.2	58.0	22.8	21.7	P < 0.001
CR (%)	26.5	13.6	4.1	4.0	
PR (%)	34.7	44.3	18.7	17.7	
SD (%)	28.2	33.5	57.9	64.6	
PD (%)	2.9	2.8	12.3	7.4	
Median TTP	15.0	13.3	5.1	5.1	P <0.000001

(mos)					

Clinical experience in myelodysplastic syndromes (MDS) with lenalidomide

An exploratory trial in 43 MDS patients with transfusion dependent or symptomatic anemia was conducted at the University of Arizona. Patients received lenalidomide at doses of 25mg or 10mg per day, or of 10mg on Days 1-21, repeated every 28 days. All patients had had no response to erythropoietin or had a high endogenous erythropoietin level. Response rates were similar across the 3 dose schedules used. Responses were observed in 24 patients overall (56%) including 21 patients with a major response and 20 patients with sustained transfusion independence. Patients with a major response reached a median hemoglobin level of 13.2 grams per deciliter, with a corresponding 5.3 grams per deciliter median increase from baseline. After a median follow-up of 81 weeks, the median duration of major response had not been reached and was more than 48 weeks. Of 20 patients with karyotypic abnormalities, 10 (50%) patients had a complete cytogenetic remission. The response rate was highest in patients with a clonal interstitial deletion involving chromosome 5q31.1 (10 out of 12, 83%). Neutropenia and thrombocytopenia were the most common adverse events, and resulted in dose delays or reductions in 25 patients (58%).

Celgene Corporation sponsored a multicenter trial (MDS-003) of 148 MDS patients with a clonal interstitial deletion involving chromosome 5q31.1. Lenalidomide was given at a dose of 10mg on Days 1-21, repeated every 28 days, to 44 patients, and at a dose of 10mg daily to the other 104 patients. Transfusion independence was achieved in 93 patients (64%), with a median hemoglobin increase of 3.9g/dl. Cytogenetic response was achieved in 76% of transfusion independent patients with 55% achieving a cytogenetic complete response. Pathologic complete response was documented in 32 out of 110 (29%) evaluable patients. With a median follow-up of 9.3 months, the median response duration had not been reached. Neutropenia (39%) and thrombocytopenia (35%) were the most common adverse events requiring dose delays or reductions.

Another Celgene sponsored trial (MDS-002) in patients with low to intermediate-1 risk MDS enrolled 215 patients, of whom, 166 were documented to have low to intermediate-1 risk MDS. Among the patients with documented low to intermediate-1 risk MDS, 84 patients (51%) responded to treatment. Transfusion independence was achieved in 54 patients (33%) and 30 patients (18%) achieved a minor response, defined as a 50% or greater decrease in blood transfusion requirement. The median duration of transfusion-independence was 41 weeks. The median baseline hemoglobin level was 8.0g/dl, which increased by 3.2g/dl in

responding patients. Among 20 patients evaluable for cytogenetic response, 9 patients (45%) experienced a cytogenetic remission. 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® (lenalidomide) is approved by the FDA. Revlimid® is indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality, with or without additional cytogenetic abnormalities. REVLIMID® in combination with dexamethasone is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy.

Clinical experience in myelofibrosis with myeloid metaplasia with lenalidomide

A Phase II single agent study of lenalidomide in MF was recently performed at MDACC. Forty one patients with platelet count of at least 30 x 10^9/L were treated with 10mg/day oral lenalidomide. Thirty six patients (88%) had received prior treatments, including thalidomide. Twenty patients were evaluable for response and toxicity at the last review. Responses were observed in approximately 50% of the evaluable patients including CR in 2 patients (normalization of hemoglobin and WBC counts), PR in 2 patients (improvement in platelet and hemoglobin, and in splenomegaly), hematologic improvement in 6 patients (improvements in spleen size, platelets and WBC) and transfusion independence in 3 of 13 patients. Common toxicities included rash (29%) and pruritus (20%). Grade $\geq$ 3 toxicities included thrombocytopenia (2 patients), neutropenia (1 patient), rash (1 patient), and fatigue (1 patient).

In another Phase II study of single agent lenalidomide in MF, Tefferi et al reported approximately 20% improvement in anemia. Some of these responses were dramatic and associated with specific cytogenetic abnormalities. In addition, they reported documentation of positive drug effect on constitutional symptoms, LDH, and splenomegaly in patients who did not show early response with anemia, suggesting the likelihood of higher responses with longer duration of therapy.

Adverse Events with Lenalidomide

Most frequently reported adverse events reported during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, UTI, Upper respiratory infection, cellulitis, atrial fibrillation, congestive

heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, tumor lysis syndrome, death not specified and fractures.

Lenalidomide may cause breakdown products of the cancer cells to enter the blood stream, which may lead to heart rate abnormalities, kidney failure, muscle twitching, and/or muscle cramps.

Please refer to lenalidomide package insert or Investigator Brochure for a complete list.

2.3 Prednisone addition to lenalidomide as therapy for MF

Steroid preparations are commonly used as therapy for MF. Furthermore, when used in combination with other medications (e.g. thalidomide) they improve tolerance of those medications and improve results. While there is no experience with lenalidomide and steroids in combination in MF, extensive research has been done in multiple myeloma. The combination has been well tolerated and has demonstrated synergy in the relapsed and refractory multiple myeloma setting. Based on these results, the Eastern Oncology Cooperative Group has recently started a Phase II multicenter trial of the combination of lenalidomide and prednisone in MF, similar to this clinical study. It is expected that the combination will improve the tolerance of lenalidomide with subsequent improvement in the results of therapy.

3.0 BACKGROUND DRUG INFORMATION

3.1 Lenalidomide

Celgene Corporation will supply Revlimid® (lenalidomide) to study participants at no charge through the RevAssist® program. 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 Celgene's RevAssist® program.

Dosage form
Lenalidomide will be supplied as 5 mg capsules for oral administration.

Packaging
Lenalidomide will be shipped directly to the patient through the Celgene's RevAssist® program.

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 RevAssist® program. Per standard RevAssist® requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of Celgene's RevAssist® program. Prescriptions must be filled within 7 days. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

3.2 Prednisone

Prednisone will be used from commercially available supplies.

4.0 PATIENT ELIGIBILITY CRITERIA

4.1 Inclusion criteria

1. Diagnosis of myelofibrosis requiring therapy, including those previously treated and relapsed or refractory, or if newly diagnosed, with intermediate or high risk according to Lille scoring system (risk factors are: Hb < 10 g/dl, WBC < 4 or > 30 x 10^9/L; risk group: 0 factor(s) = low, 1 factor(s) = intermediate, 2 factor(s) = high) or with symptomatic splenomegaly.
2. Understanding and voluntary signing an IRB-approved informed consent form.
3. Age ≥ 18 years at the time of signing the informed consent.
4. Disease-free of prior malignancies for ≥ 2-years with exception of basal cell or squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix or breast.
5. ECOG performance status 0 to 2.
6. Patients must have adequate organ function as demonstrated by the following:
    - Total bilirubin $\leq$ 2.0 mg/dL (unless higher due to MF).
    - Serum creatinine $\leq$ 2.0 mg/dL (unless higher due to MF).
    - Absolute neutrophil count $\geq$ 1 x 10^9/L
    - ALT $\leq$ 3 x upper limit of normal (unless higher due to MF)

7. Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours of starting lenalidomide and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 4 weeks before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a condom during sexual contact with a female of child bearing potential 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 J: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.
8. All study participants must be registered into the mandatory RevAssist® program, and be willing and able to comply with the requirements of RevAssist®.

4.2 Exclusion Criteria

1. Use of any other standard (e.g. hydroxyurea, anagrelide, growth factors) or experimental drug or therapy within 28 days of starting lenalidomide and/or lack of recovery from all toxicity from previous therapy to grade 1 or better.
2. Known prior clinically relevant hypersensitivity reaction to thalidomide, including the development of erythema nodosum if characterized by a desquamating rash.
3. Prior therapy with lenalidomide.
4. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.
5. Suspected Pregnancy, Pregnant or lactating females.
6. 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.
7. Known positive for HIV or infectious hepatitis, type A, B or C.
8. Known prior clinically relevant hypersensitivity to prednisone.
9. Participants with heard rate (HR) of less than or equal to 50, as a HR less than 50 indicates underlying cardiac abnormalities.

† 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).

10. Participants with prior history of thromboembolic disease (i.e. deep venous thrombosis (DVT) or pulmonary embolism (PE) within the last six months, as Lenalidomide has demonstrated a significantly increased risk of DVT or PE.
11. Participant is unwilling or unable to comply with the RevAssist® Program.

5.0 TREATMENT PLAN

The planned dose and schedule of investigation of lenalidomide is 10 mg/day orally (unless blood platelet count is below 100 $x10^9$/L, in which case the starting dose of lenalidomide is 5 mg/day). Lenalidomide will be taken orally in the morning each day on days 1-21, followed by 7 days of no therapy of each 28-day cycle.
Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.
Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately. Twenty eight days is considered one cycle of therapy. Attempts will be made to provide an adequate treatment period of at least 6 months unless significant toxicity observed, to account for delayed time to response observed with biologic agents. Responders will continue therapy for 2 years unless progression of disease or toxicity warranting discontinuation of therapy is observed.

Prednisone will be used orally at the dose of 30 mg/day during cycle 1, 15 mg/day during cycle 2, and 15 mg every other day during cycle 3, and then it will be discontinued.

All patients will be registered on the Patient Data Management System (PDMS) at MD Anderson Cancer Center after the informed consent is signed. Medication will be mailed to participants, per the RevAssist® Program.

5.1 Dose Modification Levels of Lenalidomide

Dose	Actions
Dose Level +3	25 mg on days 1-21 of every 28 day cycle
Dose Level +2	20 mg daily on days 1-21 of every 28 day cycle

Dose	Actions
Dose Level +1	15 mg daily on days 1-21 of every 28 day cycle
Level 0 (starting dose if platelet counts is ≥ $100x10^9$/L)	10 mg on days 1-21 of every 28 day cycle
Dose Level –1 (starting dose if platelet counts is < $100x10^9$/L)	5 mg daily on days 1-21 of every 28 day cycle
Dose Level –2	5 mg every other day x 10 of every 28 day cycle

5.2 **Instructions for Lenalidomide dose modifications or interruption during a cycle**

CTCAE CATEGORY	ADVERSE EVENT	DOSAGE CHANGE
Allergy/Immunology	Allergic reaction/hypersensitivity (including drug fever) Grade 3	Omit lenalidomide for remainder of cycle. Restart at planned start of next cycle at the next lower dose level if adverse event reduces to ≤grade 1.
	Allergic reaction/hypersensitivity (including drug fever) Grade 4	Discontinue Lenalidomide
Blood/Bone Marrow	Neutrophils/granulocytes (ANC/AGC) Grade 4 or grade 3 associated with fever (38.5 degree centigrade or higher)	Omit Lenalidomide for remainder of cycle. Restart at planned start of next cycle at the next lower dose level if ANC ≥1000/μL.
	Platelets ≥Grade 3 if ≥100 x 10^9/L pretherapy or <50% of pretherapy value if <100 x 10^9/L	Omit Lenalidomide for remainder of cycle. Restart at planned start of next cycle at the next lower dose level if platelet is ≥ 50 x 10^9/L if ≥100 x 10^9/L before starting therapy, or at least 50% of the pre-therapy value if <100 x 10^9/L before starting therapy.
Cardiovascular	Sinus bradycardia/other cardiac arrhythmia Grade 2	Omit Lenalidomide for remainder of cycle. Restart at planned start

CTCAE CATEGORY	ADVERSE EVENT	DOSAGE CHANGE
		of next cycle at the next lower dose level if toxicity reduces to grade 1 or lower
	Sinus bradycardia/other cardiac arrhythmia Grade 3 or 4	Discontinue Lenalidomide
	Thrombosis/embolism Grade 3 or 4	Omit Lenalidomide for remainder of cycle and start systemic anticoagulation. Restart at planned start of next cycle at the same dose level at investigator's discretion and only if approved by the PI. (See section 5.5 for anticoagulation recommendations)
Dermatology/Skin	Rash/desquamation Grade 3	Omit Lenalidomide for remainder of cycle. Restart at planned start of next cycle at the next lower dose level if adverse event reduces to ≤grade 1.
	Rash/desquamation Grade 4	Discontinue Lenalidomide
	Rash: Erythema multiforme	Discontinue Lenalidomide
Endocrine	Hyperthyroidism/ Hypothyroidism	Omit Lenalidomide for remainder of cycle. Evaluate etiology, initiate appropriate therapy. Restart at planned start of next cycle at the next reduced dose level.
Other non-hematologic	Grade 3 or 4	Omit Lenalidomide for remainder of cycle. Restart at planned start of next cycle at the next lower dose level if adverse event reduces to ≤ grade 2.

Dose escalation of lenalidomide may be indicated for patients with proliferative disease not controlled with combination of lenalidomide and prednisone after initial cycle of therapy. Dose escalation will only be allowed for patients who have not had any grade 2 or greater clinically relevant drug related non-hematologic toxicity with the prior cycle of therapy. Any other modifications in the dose of lenalidomide can be done if felt to be in the best interest of the patient, and approved by Principal Investigator.

5.3 Prednisone Dose Modifications

Dose modifications/discontinuation for prednisone therapy will be at the discretion of the clinician but must be documented clearly when it happens. Prednisone dose modification/discontinuation will not require withdrawal from the study; the patient may continue taking lenalidomide alone. Treatment of hyperglycemia with either oral hypoglycemic agents or insulin does not necessarily require discontinuation of prednisone if the hyperglycemia is controlled with these medications.

5.4 Initiation of a New Cycle of Therapy

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

- The ANC is ≥ 1,000/μL;
- The platelet count is ≥ $50x10^9$/L if ≥$100x10^9$/L before starting therapy, or at least 50% of the pre-therapy value if <$100x10^9$/L before starting therapy;
- Any lenalidomide-related allergic reaction/hypersensitivity or sinus bradycardia/ other cardiac arrhythmia adverse event that may have occurred has resolved to ≤ grade 1 severity;
- Any other lenalidomide-related adverse event that may have occurred has resolved to ≤ grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of lenalidomide (with/without prednisone after cycle 3) will not be initiated until the toxicity has resolved as described above.

If lenalidomide dosing was omitted for the remainder of the previous cycle or if the new cycle is delayed due to toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction. If the toxicity has not resolved as described above within 4 weeks, the patient will discontinue treatment. In unusual circumstance this rule may be modified by Principal Investigator if felt to be in the best interest of the patient (for example, responding patient with neutropenia or low platelets, that resolve past 4 weeks may be restarted on therapy); this case must be fully documented.

5.5 Concomitant Therapy

All medications (prescription and non-prescription), treatments and therapies taken from the first day of study through the end of study, must be recorded on the source documents.

The use of filgrastim (G-CSF) for subjects in this study is permitted when used to treat neutropenia secondary to therapy. Erythropoietin therapy is not allowed. Subjects should receive full supportive care, including transfusions of

blood products, antibiotics and antiemetics and prophylactic treatment for potential hypersensitivity reactions and tumor lysis syndrome when appropriate.

Prophylactic Anticoagulation:
Lenalidomide increases the risk of thrombotic events in patients who are at high risk or with a history of thrombosis, in particular when combined with other drugs known to cause thrombosis. When lenalidomide is combined with other agents such as steroids (e.g. dexamethasone, prednisone), anthracyclines (Doxil, adriamycin) and erythropoietin the risk of thrombosis is increased. Consideration should be given to the use of aspirin (81 or 325 mg) or some other form of prophylaxis as deemed appropriate. Low molecular weight heparin may be utilized in patients that are intolerant to aspirin. Coumadin should be used with caution and close monitoring of INR is required.

5.6 Treatment Compliance

To monitor treatment compliance, reconciliation of lenalidomide capsules will be done at each visit. Subject diaries will be provided to assist in the collection of dosing information to monitor compliance.

5.7 Pretreatment Evaluation

The mandatory pre-treatment evaluation (within 2 weeks, unless otherwise specified) will be aimed at confirming/establishing the diagnosis. The evaluation will consist of a thorough assessment of the following:

- A complete primary evaluation with physical examination and description of constitutional symptoms
- CBC, differential
- Serum BUN, alkaline phosphatase, creatinine, bilirubin, ALT, sodium, potassium, chloride, carbon dioxide, glucose, lactate dehydrogenase
- Bone marrow aspiration and biopsy (within 3 months if no therapy was given, alternative within one month) to include staining for fibrosis and molecular test for JAK 2 mutation (blood test is acceptable alternative), cytogenetic studies, (within one year).
- CD34+ cell count in blood
- Serum or urine pregnancy test (sensitivity of at least 50 mIU/mL), 10 – 14 days pre therapy and again within 24 hours of initiation of therapy for all females of child bearing potential (FCBP). Counseling for all men about the requirement for latex condom use during sexual contact with females of childbearing potential and the potential risks of fetal exposure must be conducted at a minimum of every 28 days. During counseling, subjects must be reminded to not share study drug and to not donate blood, sperm, or semen. Please refer to Appendix J.
- TSH
- EKG
- Correlative studies (see section 10.0) every 3 months – optional.
- Refer to Appendix K for pre-treatment evaluation schedule.

In addition, the analysis of total and phosphorylated c-Jun protein in peripheral blood will be done. Sample processing will be performed in the laboratory of Dr. Carlos Bueso-Ramos at MD Anderson, while sample analysis will take place at the Celgene Corporation. Samples will be obtained pre-therapy, after 6 and 18 months of therapy. Not all samples might be obtained at all time points. Peripheral blood will be collected into 2 specialized CPT 8 mL vacutainer tubes. Peripheral blood mononuclear cells (PBMC) will be separated, pelleted, lysed, and stored frozen at -70° C until shipping. Samples will be coded so that patient confidentiality will be preserved. They will be

shipped on dry ice to the Celgene Corporation, San Diego. Contact person is: Brydon Bennett, Celgene, *4550 Towne Centre Court, San Diego, CA 92121, Phone: 858 558 7500, Email: bbennett@celgene.com* **(see appendix G)**

5.8 Evaluation During Study

Time parameters for mandatory evaluations during the study are: +/-5 days for blood tests, +/- two weeks for bone marrow exams, and +/-2 weeks for MD Anderson visits. Exception for these rules can be made in unusual circumstances (e.g. long holiday) if approved by Prinicipal Investigator and documented.

- Follow up visits at MD Anderson are required initially monthly (+/- 1 week), with review of constitutional symptoms and physical exam. Following the completion of cycle 3, patients that are on a stable dose of lenalidomide and have no serious drug related side effects, and the physician feels it is in the patients best interest, may return to MDA every three months. Following the completion of cycle 24, patients that are on a stable dose of lenalidomide, have no serious drug related side effects, and the physician feels it is in the patients best interest, may return to MDA every 6 months (+/-2 weeks). Only one, 28 day supply of Lenalidomide may be provided to a patient per monthly cycle. In this case, a monthly phone assessment of toxicity, review of required blood tests (pregnancy test if applicable) and confirmation of the requirements for the initiation of a new cycle must be done.
- CBC with differential every other week x 8, then every 1 month or more frequently as clinically indicated. Following the completion of cycle 24, CBC every 1-3 months while participating on the study.
- Bone marrow aspiration and biopsy every 3 months (to include staining for fibrosis); cytogenetics every 3 months if abnormal prior to therapy; JAK2 mutation analysis every 3 months if mutation present prior to therapy. Following the completion of Cycle 24, bone marrow aspiration and biopsy every year, cytogenetics every year if abnormal prior to therapy; JAK2 every year if mutation present prior to therapy.
- Serum BUN, alkaline phosphatase, creatinine, bilirubin, ALT, sodium, potassium, chloride, carbon dioxide, glucose, lactate dehydrogenase every other week x 6, then every 1 month. Following the completion of cycle 24, complete every 3-6 months while participating on the study
- TSH every 3 months. Following the completion of Cycle 24, TSH every 6 months.
- CD34+ cell counts in blood every 3 months. Following the completion of Cycle 24 CD34+ every year.
- Serum or urine pregnancy test (sensitivity of at least 50 mIU/mL) every week x 4, then monthly for all FCBP with regular menstrual cycles, or every 2 weeks if irregular cycles.
- Correlative studies (see section 10.0) every 3 months – optional. Following the completion of Cycle 24, correlative studies every 6 months-optional.
- Refer to Appendix K for Schedule of Events During Study

5.9 Birth Control Requirements

See Appendix J for detailed procedures.

5.10 Criteria for Removal from the Study

Subjects have the right to withdraw from the study at any time for any reason. An excessive rate of withdrawals can render the study not interpretable; therefore, unnecessary withdrawal of subjects should be avoided. Should a subject decide to withdraw, or is being removed from the study, all efforts will be made by clinical study personnel to complete and report (as a progress note) the observations as thoroughly as possible. The date of discontinuation and reason(s) for patient discontinuation for the study will be recorded in the chart and PDMS. An attempt to complete all evaluations which are required at the final study visit must be conducted for each patient who discontinues treatment, regardless of the reason.

Criteria for discontinuation of therapy include:

- Clearly documented progressive disease, or loss of a response;
- No response within 6 months from the start of therapy;
- Severe toxicities not responding to dose adjustments;
- Major protocol violation (i.e. noncompliance to protocol requirements);
- Development of other conditions for which, in the Investigator's opinion, it is in the subject's best interest to be withdrawn from the study;
- Confirmed or suspected pregnancy;
- Death;
- Lost to follow up;
- Withdrawal of consent.
- Non-compliance with the RevAssist® Program.

6.0 CRITERIA FOR RESPONSE AND TOXICITY

Standard response criteria will be applied in this study. These criterias have been used in all our studies in the last 10years including the lenalidomide single agent study.

CR = Absence of signs or symptoms of the disease.

- WBC between 1 to 10 x 10^9/L with no peripheral blasts, promyelocytes, or myelocytes, and with normalization of bone marrow (< 5% blasts in normocellular or hypercellular marrow, irrespective of marrow fibrosis).

- Resolution of pretreatment cytopenias:
  - ANC $\geq$ 1.5 x 10^9/L without G-CSF or GM-CSF.
  - Hb >12.0 gm/dl (11.0 gm/dl for females) without erythropoietin or transfusion support.
  - PLT > 100 x 10^9/L without growth factor or transfusion support.

- Resolution of pretreatment leukocytosis and/or thrombocytosis: (without the use of hydroxyurea and/or anagrelide).
  - WBC < 10 x 10^9/L without peripheral blasts, promyelocytes, or myelocytes
  - PLT > 100 x 10^9/L but less than 450 x 10^9/L

- Resolution of organomegaly (splenomegaly or hepatomegaly) on physical exam

PR = Improvement in at least 2 of the parameters (if abnormal) listed below:

- Increase of ANC by $\geq$ 50% and to > 1.0 x 10^9/L without G-CSF or GM-CSF
- Increase of Hb by $\geq$ 2 g/dL, if below 10 g/dL before therapy, without erythropoietin or transfusion support.
- Increase of PLT by $\geq$ 50% and to > 30 x 10^9/L without growth factor or transfusion support.
- Resolution of pretreatment leukocytosis to WBC < 10 x 10^9/L, without hydroxyurea
- Resolution of pretreatment thrombocytosis to PLT > 100 x 10^9/L but less than 450 x 10^9/L, without hydroxyurea and anagrelide
- Decrease in transfusion requirements by at least 50% without erythropoietin support.
- Reduction of splenomegaly by $\geq$ 50% by palpation, without hydroxyurea
- Reduction of marrow blasts by $\geq$ 50%, without hydroxyurea
- Reduction of marrow or blood macrocytes by $\geq$ 50%, without hydroxyurea

HI = Improvement in at least 1 of the parameters (if abnormal) listed above under PR

In addition, we will attempt to validate in this study, recently published response criteria developed by the international working group for myelofibrosis. These criteria have not yet been used in any clinical study.

Complete remission (CR): Requires all of the following in the absence of both transfusion and growth factor support;

- Complete resolution of disease-related symptoms and signs including palpable hepatosplenomegaly.
- Peripheral blood count remission defined as hemoglobin > 11 g/dL, platelet count ≥ 100 x 10^9/L, and absolute neutrophil count ≥ 1.0 x 10^9/L.
- Normal leukocyte differential including disappearance of nucleated red blood cells and immature myeloid cells in the peripheral smear, in the absence of splenectomy.*
- Bone marrow histological remission defined as the presence of age-adjusted normocellularity, < 5% myeloblasts, and an osteomyelofibrosis grade of ≤ 1.**

Partial remission (PR): Requires all of the above criteria for CR except the requirement for bone marrow histological remission. However, a repeat bone marrow biopsy is required in the assessment of PR and may or may not show favorable changes that do not however fulfill criteria for CR.

Clinical improvement (CI): Requires one of the following in the absence of both disease progression (as outlined below) and CR/PR assignment *(CI response is validated only if it lasts for ≥ 8 weeks).*

- A ≥ 2 g/dL increase in hemoglobin level or becoming transfusion independent (applicable only for patients with baseline hemoglobin level of < 10 g/dL).§
- Either a ≥ 50% reduction in palpable splenomegaly of a spleen that is ≥ 10 cm at baseline or a spleen that is palpable at > 5 cm at baseline becomes not palpable.§§
- A ≥ 100% increase in platelet count and an absolute platelet count of ≥ 50,000 x 10^9/L. (applicable only for patients with baseline platelet count of < 50 x 10^9/L).
- A ≥ 100% increase in ANC and an ANC of ≥ 0.5 x 10^9/L (applicable only for patients with baseline absolute neutrophil count of < 1 x 10^9/L).

Progressive disease: Requires one of the following;¶

- Progressive splenomegaly that is defined by the appearance of a previously absent splenomegaly that is palpable at > 5 cm below the left costal margin or a ≥ 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a ≥ 50% increase in palpable distance for baseline splenomegaly of > 10 cm.
- Leukemic transformation confirmed by a bone marrow blast count of ≥ 20%.
- An increase in peripheral blood blast percentage of ≥ 20% that lasts for ≥ 8 weeks.

Stable disease: None of the above.

Relapse: Loss CR, PR, and CI. In other words, a patient with CR or PR is considered to have undergone relapse when he or she no longer fulfils the criteria for CI.

**Because of subjectivity in peripheral blood smear interpretation, CR does not require absence of morphological abnormalities of red cells, platelets, and neutrophils.*

*** In patients with CR, a complete cytogenetic response is defined as failure to detect a cytogenetic abnormality in cases with a pre-existing abnormality. A partial cytogenetic response is defined as 50% or greater reduction in abnormal metaphases. In both cases, at least 20 bone marrow- or peripheral blood-derived metaphases should be analyzed. A major molecular response is defined as the absence of a specific disease-associated mutation in peripheral blood granulocytes of previously positive cases. In the absence of a cytogenetic/molecular marker, monitoring for treatment-induced inhibition of endogenous myeloid colony formation is encouraged. Finally, baseline and post-treatment bone marrow slides are to be stained at the same time and interpreted at one sitting by a central review process.*

§*Transfusion dependency is defined by a history of at least 2 units of red blood cell transfusions in the last month for a hemoglobin of < 8.5 g/dL that was not associated with clinically overt bleeding. Similarly, during protocol therapy, transfusions for a hemoglobin of ≥ 8.5 g/dL is discouraged unless it is clinically indicated.*

§§*In splenectomized patients, palpable hepatomegaly is substituted with the same measurements.*

¶*It is acknowledged that worsening cytopenia might represent progressive disease but its inclusion as a formal criterion was avoided because of the difficulty distinguishing disease-associated from drug-induced myelosuppression. However, a decrease in hemoglobin of ≥ 2 g/dL, a 100% increase in transfusion requirement, and new development of transfusion dependency, each lasting for more than 3 months after the discontinuation of protocol therapy can be considered disease progression.*

7.0 ADVERSE EVENTS

As per MDACC and Leukemia phase I-II studies (Appendix C and Appendix F). Toxicity will be scored using CTCAE Version 3.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0. 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

Commented [SM1]: Add appropriate appendix number

Commented [SM2]: Add appropriate appendix number here as well

must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

Myelosuppression and associated complications are expected events during leukemia therapy and are part of the treatment success (marrow emptying of leukemic cells). Therefore, myelosuppression and associated complications such as fever, infections, bleeding and related hospitalizations will not be reported as individual ADRs, but will be summarized in the updated and final reports. Only prolonged myelosuppression, as defined by the new NCI criteria specific for leukemia, i.e., marrow cellularity < 5% on day 42 or later (6 weeks) from start of therapy without evidence of leukemia, will be reported as an ADR and considered in defining the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of particular agents or regimens.

MD Anderson (Sponsor) Reporting Requirements for Serious Adverse Events and Dose Limiting Toxicities:

Serious Adverse Event (SAE) Definition

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

- Results in death
- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is an important medical event[3]
- Suspected positive Pregnancy

[1]"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.

[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[3]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.

Adverse Drug Reaction Reporting

Toxicity will be scored using CTCAE Version 3.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0. 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.

Serious Adverse Events Reporting: The principle investigator has the obligation to report all serious adverse events to the University of Texas M. D. Anderson Cancer Center (MDACC) IRB via the Office of Protocol Research and to Celgene within 24 hours.

In IND studies, all serious adverse events must be reported to the FDA by the investigator through the Office of Research Education & Regulatory Management (ORERM) as required by 21 CFR 312.32. These reports are to be filed utilizing the University of Texas M. D. Anderson Cancer Center Adverse Event Reporting Form. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences.
All other serious adverse events not requiring expedited reporting should be reported to MDACC IRB and ORERM within 5 business days.

All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 24 hours of knowledge regardless of the attribution. SAEs beyond 4 weeks after the end of study drug administration will be reported if thought to be drug related.

NOTE: Instructions concerning procedures and reporting for pregnancies below.

Pregnancies

Pregnancies occurring while the subject is on lenalidomide or within 4 weeks after the subject's last dose of lenalidomide are considered expedited reportable events. If the subject is on lenalidomide, it is to be discontinued immediately and the subject is to be instructed to return any unused portion of lenalidomide to the Investigator. The pregnancy must be reported by the investigator to MDACC IRB and ORERM AND to

Celgene Corporation Worldwide Drug Safety Surveillance (WWDSS) within 24 hours of the Investigator's knowledge of the pregnancy by phone and facsimile using the SAE Form.

The Investigator will follow the subject until completion of the pregnancy, and must notify Celgene Corporation Worldwide Drug Safety Surveillance (WWDSS) of the outcome as specified below. The Investigator will provide this information as a follow-up to the initial SAE.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs (i.e., report the event to Celgene Corporation Worldwide Drug Safety Surveillance (WWDSS) by facsimile within 24 hours of the Investigator's knowledge of the event) and report the event to MDACC IRB and ORERM.

Any suspected fetal exposure to lenalidomide must be reported to Celgene, MDACC IRB AND ORERM within 24 hours of being made aware of the event. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the *in utero* exposure to lenalidomide should also be reported. In the case of a live "normal" birth, Celgene Corporation Worldwide Drug Safety Surveillance (WWDSS), MDACC IRB AND ORERM should be advised as soon as the information is available.

Celgene Drug Safety Contact Information:

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

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

Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA safety reporting requirements. Serious Adverse Events Reporting: The principle investigator has the obligation to report all serious adverse events to the University of Texas M. D. Anderson Cancer

Center (MDACC) IRB via the Office of Protocol Research and also to Celgene within 24 hours.

IND Annual Reports

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed with MD Anderson's ORERM, who will then forward to FDA. An additional copy should be placed in the study's Regulatory Binder and a copy must be sent to Celgene Corporation as a supporter of this study as follows.

Celgene Corporation
Attn: Medical Development
86 Morris Avenue
Summit, NJ 07901
Tel: (908) 673-9000

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

Expedited reporting by Principal Investigator to Celgene

Serious adverse events (SAE) are defined above. The investigator should inform Celgene of any SAE within 24 hours of being aware of the event. The date of awareness should be noted on the report. This must be documented on an MD Anderson SAE form. This form must be completed and supplied to MDACC IRB, ORERM and Celgene within 24 hours/1 business day at the latest on the following working day. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up MD Anderson SAE form. A final report to document resolution of the SAE is required. The Celgene protocol number (RV-MF-PI-0102) should be included on SAE reports to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

Report of Adverse Events to the Institutional Review Board

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

Sponsor Reporting to the FDA

Adverse drug reactions that are **Serious, Unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) in writing by each investigator/physician engaged in clinical research. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

The sponsor shall notify the FDA by telephone or by fax of any unexpected fatal or life threatening experience associated with the use of the drug. As soon as possible, but no later than 7 calendar days after the sponsors initial receipt of the information. Each phone call or fax shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND if applicable.

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.

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.

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.

8.0 Study Monitoring and Auditing

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 into MDACC's PDMS. The Investigator will permit study-related monitoring visits and audits by MDACC's ORERM, 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 monitoring visits 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 MDACC ORERM and the Celgene representative so that the accuracy and completeness may be checked.

Regulatory Considerations / 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.

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.

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; 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.
Premature discontinuation of study

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.

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.

Patients will be given instructions and the M.D. Anderson contact name (principal investigator/MD Anderson Leukemia staff treating physician), phone, and fax numbers. The referring oncologist will be identified, contacted, and the protocol details discussed.

All therapy will be given under the care of MD Anderson Leukemia staff treating physician. The referring oncologist should contact the MD Anderson Leukemia staff treating physician with any questions or problems and the modifications should be initiated only by the MD Anderson Leukemia staff treating physician or principal investigator, and complications will be recorded in a progress note at each follow-up visit.

From past experience, it is recognized collaboration with oncologist outside MD Anderson may occasionally result in some difficulties such as 1) not performing tests as required, 2) not sending results of tests or updates of patient condition, 3) and not informing on toxicities and hospitalizations. Therefore: 1) we will discuss with the referring oncologist about the protocol and doses, 2) we will make significant efforts (contact at least twice and document) to retrieve the information (tests, toxicities, hospitalizations), and 3) we will record in a progress note all the information on follow-up visits. Since information may still be missing in one or more components in some patients (e.g. missing once CBC), these types of difficulties will be collected and documented as protocol deviations.

9.0 STATISTICAL CONSIDERATIONS

The primary objective of phase II of this study is to assess efficacy in terms of the objective response rate (complete and partial response, and clinical improvement) with lenalidomide and prednisone in patients with MF. The MinMax two-stage design proposed by Simon will be implemented. Sample size and decision criteria are chosen to reduce the expected accrual if the treatment

is ineffective in regard to response relative to having no interim stopping rule. The target response rate is 35%. A response rate of 20% or less will be considered unacceptable and treatment with the therapy will be discontinued. Given the response rates stated above, if the probability of inappropriately accepting a poor therapy is 10%, a total sample size of 41 patients will result in 80% power.

In the first stage of the design, a total of 22 patients will be enrolled and the study will be put on hold to assess response. If four or fewer patients respond to the combination therapy, after being treated for 6 months, then the study will be terminated and the therapy will be declared ineffective. However, as soon as 5 or more patients respond to the lenalidomide, an additional 19 patients will be enrolled to complete the study.

After a total of 41 patients have been enrolled into the study, if eleven or fewer patients respond to the therapy, the therapy will be declared ineffective. However, if greater than 11 patients respond to the therapy, the therapy will be considered efficacious. The probability of early termination due to unacceptable response rate is 54%.

Descriptive statistics will be utilized to assess response, time to response, and response duration. Responses will be categorized as the best response achieved during the course of the study. Time to response is defined as the time from start of therapy until the response criteria are fulfilled. Response duration will be defined as the time from response until relapse (progressive disease) or death.

The safety analysis will include subjects who are enrolled to treatment and take at least one dose of study medication. Toxicity will be graded according to the NCI criteria. Descriptive statistics will be used to describe adverse events related to the study drug. Adverse events will be listed and tabulated.

10.0 CORRELATIVE STUDIES

Correlative studies will be done pre-therapy and then every 3 months until patient completes 24 cycles, then every 6 months while on therapy. In the peripheral blood and bone marrow aspirate we will measure the levels of TGF-beta, bFGF, and PDGF. Attempt will be made to collect all samples, but it is possible that some samples might be missed. These tests will be done at M.D. Anderson, in the laboratory of Dr. Bueso-Ramos. For the testing in blood samples, 10cc purple top tube will be obtained and for the testing in bone marrow aspirate samples, 3cc purple top tube will be obtained.

In addition, the analysis of total and phosphorylated c-Jun protein in peripheral blood will be done. Sample processing will be performed in the laboratory of Dr. Carlos Bueso-Ramos at MD Anderson, while sample analysis will take place at

the Celgene Corporation. Samples will be obtained pre-therapy, after 6 and 18 months of therapy. Not all samples might be obtained at all time points. Peripheral blood will be collected into 2 specialized CPT 8 mL vacutainer tubes. Peripheral blood mononuclear cells (PBMC) will be separated, pelleted, lysed, and stored frozen at –70° C until shipping. Samples will be coded so that patient confidentiality will be preserved. They will be shipped on dry ice to the Celgene Corporation, San Diego. Contact person is: Brydon Bennett, Celgene, *4550 Towne Centre Court, San Diego, CA 92121, Phone: 858 558 7500, Email: bbennett@celgene.com (see Appendix I)*

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