



## Protocol Page

# EVALUATION OF RUXOLITINIB AND LENALIDOMIDE COMBINATION AS A THERAPY FOR PATIENTS WITH MYELOFIBROSIS

2011-0269

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### Core Protocol Information

<b>Short Title</b>	Ruxolitinib and Lenalidomide for patients with Myelofibrosis
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#### Which Committee will review this protocol?

- The Clinical Research Committee - (CRC)

## Protocol Body



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**EVALUATION OF RUXOLITINIB AND LENALIDOMIDE COMBINATION AS A  
THERAPY FOR PATIENTS WITH MYELOFIBROSIS**

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## 1.0 HYPOTHESIS AND OBJECTIVES

### Hypothesis

Ruxolitinib (also known as INCB018424), a JAK1/2 inhibitor, and lenalidomide (immunomodulatory inhibitory drug; IMiD) are effective and tolerable treatments for patients with myelofibrosis (MF). Combination of these agents in patients with MF can improve the overall clinical response to therapy without causing excessive toxicity.

### Objectives

Primary:

- to determine the efficacy of the combination of INCB018424 with lenalidomide in patients with MF, in achieving objective improvements in disease status

Secondary:

- to determine the safety of the combination in patients with MF

Exploratory:

- to explore time to response and duration of response
- to explore the effect of the combination on anemia and transfusion dependence in patients with MF
- to explore changes in JAK2V617F allele burden

## 2.0 BACKGROUND AND RATIONALE

### 2.1 Myelofibrosis with Myeloid Metaplasia

Myelofibrosis with myeloid metaplasia (MF) is a rare 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 about 25% 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 MDS with fibrosis. In acute megakaryocytic leukemia patients usually present with severe constitutional symptoms and pancytopenia but without organomegaly or peripheral blood myelophthisis.

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% 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<sup>9</sup>/L, and 37% with thrombocytopenia (platelet count < 150 x 10<sup>9</sup>/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 5 to 6 years. Progressive marrow failure, transformation into acute myeloid leukemia, and portal hypertension lead to demise.

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) 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.

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 dysregulated in MF include; tumor necrosis factor-alpha (TNF-alpha) and angiogenic agents like vascular endothelial growth factor (VEGF).

## **2.2 INCB018424**

### **Rationale**

JAKs play an important role in signal transduction following cytokine and growth factor binding to their receptors. In addition, JAKs activate a number of downstream pathways implicated in the proliferation and survival of malignant cells including the STATs (signal transducers and activators of transcription), a family of important latent transcription factors. Aberrant activation of JAKs has been associated with increased malignant cell proliferation and survival in patients with Philadelphia chromosome negative MPD. The finding that peripheral blood from myeloproliferative disease (MPD) patients is capable of forming erythroid and megakaryocyte colonies in the absence of exogenous factors (which signal through JAKs) suggests that cells from these patients are intrinsically different than normal cells. Indeed, work from a number of laboratories led to the identification of multiple somatic mutations in genes associated with cytokine and growth factor signaling. These include a mutation in the pseudo-kinase domain of JAK2V617F (amino acid 617, valine to phenylalanine) that results in constitutive activation of JAK2 and downstream STATs. This mutation was found in > 90% of all PV patients and in approximately 50% of all ET and Myelofibrosis with Myeloid Metaplasia

(MMM) patients. More recently, other mutations have been identified in MPD patients lacking the JAK2V617F mutation. For instance, additional activating mutations in JAK2, as well as a mutation in the thrombopoietin receptor (MPL), result in constitutive ligand-independent JAK activation. Importantly, ectopic expression of each of these mutant genes has been demonstrated to be sufficient to cause MPD-like syndromes in mice. Moreover, even in MPD patients lacking a confirmed JAK2 mutation, the detection of STAT activation suggests dysregulated JAK activity. In fact, regardless of the mutational status of JAK2, the malignant cells expectedly retain their responsiveness to JAK activating cytokines and/or growth factors; hence, they may benefit from JAK inhibition. These findings, in addition to the limited life span of these patients and lack of beneficial therapies for the treatment of PMF and post-PV/ET MF, clearly support the evaluation of JAK inhibitor in these diseases. INCB018424 phosphate is an inhibitor of the Janus kinase family of protein tyrosine kinases (JAKs) that is currently under development for treatment of myeloproliferative disorders (MPD).

### **Clinical Experience**

We conducted a phase 1–2 trial of INCB018424 in patients with *JAK2* V617F–positive or *JAK2* V617F–negative primary myelofibrosis, post–essential thrombocythemia myelofibrosis, or post–polycythemia vera myelofibrosis. A total of 153 patients received INCB018424 for a median duration of more than 14.7 months. The initial dose-escalation phase established 25 mg twice daily or 100 mg once daily as maximum tolerated doses, on the basis of reversible thrombocytopenia. A dose-dependent suppression of phosphorylated signal transducer and activator of transcription 3 (STAT3), a marker of JAK signaling, was demonstrated in patients with wild-type *JAK2* and in patients with the *JAK2* V617F mutation. We studied additional doses and established that a 15-mg twice-daily starting dose, followed by individualized dose titration, was the most effective and safest dosing regimen. At this dose, 17 of 33 patients (52%) had a rapid objective response ( $\geq 50\%$  reduction of splenomegaly) lasting for 12 months or more, and this therapy was associated with grade 3 or grade 4 adverse events (mainly myelosuppression) in less than 10% of patients. Patients with debilitating symptoms, including weight loss, fatigue, night sweats, and pruritus, had rapid improvement. Clinical benefits were associated with a marked diminution of levels of circulating inflammatory cytokines that are commonly elevated in myelofibrosis.

### **2.3 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 myelofibrosis with lenalidomide**

Two similarly designed but separate phase 2 studies involving single-agent lenalidomide in a total of 68 patients with symptomatic myelofibrosis were reported in one paper. Protocol treatment consisted of oral lenalidomide at 10 mg/d (5 mg/d if baseline platelet count < 100 x 10<sup>9</sup>/L) for 3 to 4 months with a plan to continue treatment for either 3 or 24 additional months, in case of response. Overall response rates were 22% for anemia, 33% for splenomegaly, and 50% for thrombocytopenia. Response in anemia was deemed impressive in 8 patients whose hemoglobin level normalized from a baseline of either transfusion dependency or hemoglobin level lower than 100 g/L. Additional treatment effects in these patients included resolution of leukoerythroblastosis (4 patients), a decrease in medullary fibrosis and angiogenesis (2 patients), and del(5)(q13q33) cytogenetic remission accompanied by a reduction in JAK2(V617F) mutation burden (1 patient). Grade 3 or 4 adverse events included neutropenia (31%) and thrombocytopenia (19%). Authors concluded that lenalidomide engenders an intriguing treatment activity in a subset of patients with MF that includes an unprecedented effect on peripheral blood and bone marrow abnormalities.

To investigate the safety and efficacy of the combination of lenalidomide and prednisone in patients with MF, 40 patients were treated. Therapy consisted of lenalidomide 10 mg/d (5 mg/d if baseline platelet count < 100 x 10<sup>9</sup>/L) on days 1 through 21 of a 28-day cycle for six cycles, in combination with prednisone 30 mg/d orally during cycle 1, 15 mg/d during cycle 2, and 15 mg/d every other day during cycle 3. Lenalidomide therapy was continued indefinitely in patients exhibiting clinical benefit. The median follow-up was 22 months (range, 6 to 27). Responses were recorded in 12 patients (30%) and are ongoing in 10 (25%). The median time to response was 12 weeks (range, 2 to 32). According to the International Working Group for Myelofibrosis Research and Treatment consensus criteria, three patients (7.5%) had partial response and nine patients (22.5%) had clinical improvement durable for a median of 18 months (range, 3.5 to 24+). Overall response rates were 30% for anemia and 42% for splenomegaly. Moreover, 10 of 11 assessable responders who started therapy with reticulin fibrosis grade 4 experienced reductions to at least a score of 2. All eight JAK2<sup>V617F</sup>-positive responders experienced a reduction of the baseline mutant allele burden, which was greater than 50% in four, including one of whom the mutation became undetectable. Grade 3 to 4 hematologic adverse events included neutropenia (58%), anemia (42%), and thrombocytopenia (13%). The combination of lenalidomide and prednisone induced durable clinical, molecular, and pathologic responses in MF.

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 of adverse events).

### **3.0 BACKGROUND DRUG INFORMATION**

#### **3.1 Ruxolitinib (INCB018424) (Refer to Investigator's Brochure)**

INCB018424 phosphate, referred to herein as INCB018424, is a substituted pyrrolopyrimidine compound that acts as a potent and selective inhibitor of the Janus kinase family of enzymes. INCB018424 is a novel, potent, and selective inhibitor of the JAKs with modest selectivity for JAK2. INCB018424 potently (IC<sub>50</sub> values < 5 nM) inhibits JAKs, yet it does not significantly inhibit (<30% inhibition) a broad panel of 26 other kinases when tested at 200 nM (approximately 100 times the average IC<sub>50</sub> value for JAK enzyme inhibition). Moreover, in cell-based assays relevant to the pathogenesis of MPDs, such as JAK-STAT signaling and the growth of cytokine-dependent lines, INCB018424 demonstrated excellent potency (IC<sub>50</sub> values of 80-141 nM). This effect was not due to general cytotoxicity, because INCB018424 (up to 25 μM) had no significant effect on the growth of cytokine-independent cell lines transformed by the Bcr-Abl oncogene. In addition, INCB018424 inhibited JAK/STAT signaling and growth of a cell line expressing the JAK2 mutant variant (JAK2V617F) that has been implicated in the pathogenesis of the majority of Philadelphia chromosome negative MPD. Additional details as to the *in vitro* pharmacology of INCB018424 may be found in the Clinical Investigator's Brochure (CIB).

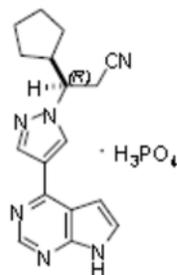
INCB018424 was evaluated in two mouse models where either a cytokine-dependent multiple myeloma cell line, INA-6, or a cell line, BaF3, engineered to express JAK2V617F was inoculated. The ability of INCB018424 to inhibit JAK pathway signaling as well as tumor cell survival and growth was assessed *in vivo*. *In vitro* cell biology experiments have demonstrated that the potency of INCB018424 is very similar between the cytokine-dependent INA-6 myeloma cells, with wild type JAKs, and the BaF3 cells expressing a clinically relevant mutant JAK2. As such, the *in vivo* studies described herein characterize the ability of INCB018424 to inhibit wildtype JAK2 (using the INA-6 xenograft model) and MPD-related mutant JAK2 (using a mouse model of splenomegaly driven by cells expressing the mutant JAK2V617F).

Treatment of mice with orally administered INCB018424 resulted in a dose-dependent suppression of STAT3 phosphorylation and tumor growth in the cytokine-dependent INA-6 xenograft model at doses ≥ 10 mg/kg BID. Moreover, oral administration of INCB018424 inhibited the dramatic splenomegaly in mice resulting from intravenous inoculation of the BaF3-JAK2V617F cells. Additional details as to the *in vivo* pharmacology of INCB018424 may be found in the Clinical Investigator's Brochure

(CIB). In summary, pharmacological data obtained in both *in vitro* and *in vivo* model systems support the potential utility of orally administered INCB018424 in the treatment of malignancies, including MPD such as PMF and Post-PV/ET MF.

The chemical name of INCB018424 phosphate is (*R*)-3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate (Figure 1). INCB018424 phosphate has a molecular formula of C<sub>17</sub>H<sub>21</sub>N<sub>6</sub>O<sub>4</sub>P and a molecular weight of 404.36. INCB018424 phosphate drug substance is a white to off-white powder, and is referred to herein as INCB018424.

#### INCB018424 Phosphate Structural Formula



INCB018424 drug product will be provided as 5 mg and 25 mg strength tablets. The tablet formulation contains the active ingredient along with commonly used excipients. All excipients are of compendial grade. The medication will be provided for free to participants in this study by the manufacturer, Incyte Inc. The 5 mg tablets are stable for six months at 40C/75% RH and at least 24 months at 25C/60% RH. The 25 mg tablets are stable for six months at 40C/75% RH and at least 36 months at 25C/60% RH.

### 3.2 Lenalidomide

Lenalidomide will be supplied as 5 mg capsules for oral administration. Lenalidomide will be shipped directly to the patient through the Celgene's RevAssist® program. Lenalidomide will not be provided for free to participants in this study, but will be provided upon insurance approval through commercial supply. 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.

### 3.3 Prednisone

Prednisone will be used from commercially available supplies.

## 4.0 PATIENT ELIGIBILITY CRITERIA

### Inclusion criteria

1. Diagnosis of myelofibrosis (either primary or post essential thrombocythemia/polycythemia vera) requiring therapy, including those previously treated and relapsed or refractory, or if newly diagnosed, with intermediate-1 or -2 or high risk according to International Working Group (IWG) criteria.
2. Understanding and voluntary signing an IRB-approved informed consent form.
3. Age  $\geq$  18 years at the time of signing the informed consent.
4. Disease-free of prior malignancies for  $\geq$  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:
  - Direct bilirubin  $\leq$  2.0 mg/dL
  - Serum creatinine  $\leq$  2.0 mg/dL.
  - SGPT  $\leq$  3 x upper limit of normal
7. Females of childbearing potential (FCBP)<sup>†</sup> 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®.
9. Platelets  $\geq$  100000/uL
10. ANC  $\geq$  1000/uL

### Exclusion Criteria

1. Use of any other standard (e.g. hydroxyurea, anagrelide, growth factors) or experimental drug or therapy within 14 days or 5-half lives, whichever is longer, of starting study therapy 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 or INCB018424.
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.

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<sup>†</sup> 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).

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 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.
10. Known to have a hypercoagulability syndrome (eg: antithrombin III, deficiency, anticardiolipin syndrome etc...)
11. Concurrent use of strong inducers or strong inhibitors of CYP3A4 (strong inducers are rifampin and St. John's Worth, carbamazepine, phenytoin, and barbiturates such as phenobarbital; strong inhibitors are HIV-antivirals, clarithromycin, itraconazole, ketoconazole, nefadozone, and telithromycin).
12. Incarcerated persons are excluded from the protocol.

## **5.0 TREATMENT PLAN**

Four weeks on therapy is considered one cycle of therapy. INCB018424 and lenalidamide will be given orally in an outpatient setting. INCB018424 will be given continuously daily in 28-day cycles, and lenalidamide will be given on days 1-21 of 28 day cycles. Dosage for cycles can be reduced, increased or delayed based assessment of efficacy and on adverse events, if any occur, as described below. Delays of a maximum of 8 weeks are allowed from scheduled next cycle.

Subjects will be asked to maintain a diary to record drug administration. Subjects will be asked to bring any unused study drug to the research center at their next visit. Research personnel will count and record the number of used and unused study drug capsules/tablets (both ruxolitinib and lenalidomide) at each visit and reconcile with the subject diary. The study coordinator will question the patient regarding adherence to the dosing regimen, record the number of capsules/tablets and strengths returned in the carton, the date returned and determine treatment compliance before dispensing new medication to the study patient. Compliance below 80% will require counseling of the patient by study site personnel.

The planned dose and schedule of investigation of INCB018424 is 15 mg orally twice daily (BID), continuously in 28-day cycles. Lenalidomide will be taken orally 5 mg/day in the morning each day on days 1-21, followed by 7 days of no therapy of each 28-day cycle; medication will be mailed to participants, per the RevAssist® Program.

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 6 years unless progression of disease or toxicity warranting discontinuation of therapy is observed.

Prednisone will be added for patients who have not responded after 3 cycles of therapy. It will be dosed orally at the dose of 30 mg/day during cycle 4, 15 mg/day during cycle 5, and 15 mg every other day during cycle 6, and then it will be discontinued.

All patients will be registered in the Clinical Oncology Research system(CORE) at MD Anderson Cancer Center after the informed consent is signed.

## 5.1 Dose Modification

Dose Level mg BID	INCB018424 (Days 1-21 Q 4 weeks)	Lenalidomide QD
Dose Level +3	25	15
Dose Level +2	20	10
Dose Level +1	20	5
Level 0	15	5
Dose Level -1	10	5
Dose Level -2	10	5 mg every other day x 10
Dose Level -3	5	5 mg every other day X 10

If drug-related grade 3 or 4 non-hematologic toxicity is attributable to one or both of the drugs, dose interruption of that particular drug(s) is mandatory. Patient who experience grade 3 drug related non-hematological toxicity may be given a subsequent course one dose level below the previous course, but the patient must have recovered to grade  $\leq 1$  before institution of the next course. If a patient has drug-related grade 4 non-hematologic toxicity, he/she may receive a subsequent courses at one reduced dose level after resolution of toxicity to grade  $\leq 1$ , only if approved by the Principal Investigator based on the clinical significance of the toxicity and only if patient has had derived a benefit from the therapy. The dose of therapeutic agents can be decreased during a cycle, at the discretion of treating physician, for chronic grade 2 non-hematologic toxicity. In specific circumstances, after discussion with the Principal Investigator, one of the two medications can be discontinued for safety. Documentation of the reason(s) study drug is discontinued is required. Other dose modifications may be considered as clinically indicated with documentation and approval of the PI

During a cycle of therapy, dosing of INCB018424 and lenalidomide will be discontinued for platelet counts  $\leq 35 \times 10^9/L$  OR for ANC  $\leq 500/uL$ . Dosing of INCB018424 may resume at 5mg QD if the platelet count increases  $> 35 \times 10^9/L$  AND ANC  $> 500/uL$ , and can be increased to 5mg BID for the remainder of the cycle once platelet count is  $> 50 \times 10^9/L$  AND ANC  $> 1000/uL$ . Lenalidomide will not be restarted during this cycle.

Patients who experience platelet count  $\leq 35 \times 10^9/L$  or ANC  $\leq 500/uL$  during a cycle of therapy, will have a dose reduction of therapy by one dose level for subsequent

cycles. A reduction of 2 dose levels may be considered if the myelosuppression was deemed severe and life threatening by the treating physician, and if it is in the patient's best interest. Reductions in dosing for therapy related anemia can be done at the discretion of the investigator.

Patients may be escalated to the next higher dose level if ALL of the following criteria are met (for the study drug being dose escalated). (Applicable also for patients receiving only one study drug)

1. no dose reductions due to toxicity were required in the prior 2 cycles
2. no dose interruptions due to toxicity were required in the prior 2 cycles
3. the prior cycle was not delayed due to toxicity
4. the current cycle is not delayed due to toxicity
5. Platelet count  $\geq 100 \times 10^9/L$  AND ANC  $\geq 1000/uL$
6. The patient has sub-optimal benefit defined as a failure to reduce palpable spleen length by at least 50% and/or suboptimal improvement in MF related symptoms as assessed by the investigator, and/or failure to improve cytopenia
7. no development of new onset transfusion dependency

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. 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.

## **5.2 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  $\geq 1,000/\mu L$ ;
- The platelet count is  $> 50 \times 10^9/L$ ,
- Any drug-related grade 3-4 adverse event that may have occurred has resolved to  $\leq$  grade 1 severity;

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle will not be initiated until the toxicity has resolved as described above. If drug dosing was interrupted during 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 when the criteria above are met AND with at least a one-level dose reduction. Treatment with INCB018424 may continue at 5mg QD so long as  $ANC > 500/uL$  AND platelets  $> 35 \times 10^9/L$  or at 5mg BID so long as  $ANC \geq 1000/uL$  AND platelets  $> 50 \times 10^9/L$  while waiting to initiate a new cycle. If after a 4 week delay, the platelet count remains  $> 50 \times 10^9/L$  but  $\leq 75 \times 10^9/L$ , the next cycle therapy may begin with INCB018424 dosed at 5mg BID and the dose of lenalidomide reduced by at least 1 dose level from the prior cycle. If the prior cycle was at dose level -2 or -3 then lenalidomide (and prednisone if started) must be discontinued and the patient may continue therapy with INCB018424 alone following dosing rules.

If the toxicity has not resolved as described above within 8 weeks of the scheduled start date for the cycle, the patient will discontinue treatment. In unusual circumstances this rule may be modified by the 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 6 weeks may be restarted on therapy); this case must be fully documented.

### **5.3 Concomitant Therapy**

All supportive measures consistent with optimal subject care will be given throughout the study. Concomitant medications will be captured in the CRF beginning at screening. Packed red blood cell or platelet transfusions are allowed when necessary. Growth factor use (including erythropoietin) is not allowed with the exception of the use of filgrastim (G-CSF) or pegfilgrastim, which is permitted ONLY when used to treat febrile neutropenia or in patients who have prolonged (one week or more) grade 3-4 neutropenia, after approval from Principal Investigator. Concomitant use of cytotoxic chemotherapeutic agents (e.g. hydroxyurea), or other experimental drug or therapy for myelofibrosis while the subject is on study is prohibited. Concurrent use of strong inducers or strong inhibitors of CYP3A4 (strong inducers are rifampin and St. John's Wort; strong inhibitors are HIV-antivirals, clarithromycin, itraconazole, ketoconazole, nefazodone, and telithromycin) is prohibited.

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 100 mg) as prophylaxis as deemed appropriate (through commercial supply, not provided by the Incyte or Celgene companies). When the platelet count falls below  $35 \times 10^9/L$ , aspirin prophylaxis should be discontinued until the platelet count is  $> 35 \times 10^9/L$  and stable (not less than prior measurement) or increasing on two consecutive measurements at least 4 days apart.

### **5.4 Pharmacokinetic Assessment**

Blood samples will be collected for pharmacokinetic (PK) analysis at three different time points. Patient medical number will be changed to a code that could only be deciphered by the principal investigator, thus preserving patient confidentiality. This collection will involve an additional procedure (a needle stick) at these time points. Time of the dose taking and PK sample draw time will be recorded in the draw sheets that are part of patients' medical records. Blood samples will be centrifuged to obtain plasma and stored at  $-20^{\circ} C$  until shipment to Incyte Corp., who will perform the testing.

### **5.5 Pretreatment Evaluation**

- History and physical exam including vital signs, body weight and height, and spleen and liver measurements. This also includes a transfusion history for 3 months prior to day 1 and concomitant medication notation (within 14 days of study day 1)

- CBC and differential, electrolytes (Na, K, Cl HCO<sub>3</sub>), creatinine, uric acid, BUN, glucose, total bilirubin, and SGPT, PT/PTT, INR (within 14 days of study day 1).
- Bone marrow biopsy and aspirate (within 3 months of study day 1) with cytogenetics (if not done before) and JAK2V617F status and allele burden.
- Urinalysis (within 14 days of study day 1)
- ECG (within 14 days of study day 1)
- Pregnancy test (for FCBP only) with a sensitivity of at least 50 mIU/mL, within 10 – 14 days prior to and again within 24 hours of starting lenalidomide.
- Myelofibrosis Symptom Assessment Form (MFSAF) questionnaire and MDASI (MD Anderson Symptom Inventory) questionnaire (within 3 days of study day 1)

## 5.6 Evaluation During Study

- Directed history and physical examination including vital signs, body weight, and spleen and liver measurements prior to each cycle for the first 3 cycles then every 3 to 6 cycles. This also includes a transfusion history for previous cycle of therapy and concomitant medication notation.
- CBC and differential, electrolytes (Na, K, Cl HCO<sub>3</sub>), creatinine, BUN, glucose, total bilirubin, and SGPT weekly for 2 cycles, then every 2 weeks while on therapy. Those responding patients continuing therapy past 6 cycles and on a stable dose level without interruption or delay for 4 cycles may have blood tests done monthly)
- Bone marrow aspiration with cytogenetics (if abnormal pre-therapy), JAK2V617F allele burden (if JAK2V617F mutation present pre-therapy) after cycle 3,6,9,12 and then as determined appropriate by the investigator.
- Response assessment (IWG-MRT) monthly for first 3 cycles, then every 3 to 6 cycles
- Pregnancy test, urine or blood, (sensitivity of at least 50 mIU/mL) every week x 4, then every 4 weeks for all FCBP with regular menstrual cycles, or every 2 weeks if irregular cycles.
- Optional blood samples (20-50cc) on day 1 of cycle 2 for pharmacokinetics (PK) at approximately 0.5-1 hour, 2-4 hours, and 4-8 hours post ruxolitinib dose (3 time points). Not all research samples may be collected at all time points.
- Collect any unused study drug and review patient study drug dosing diary for compliance;
- Assessment of AEs using the NCI CTEP CTCAE, version 4.0 (published 28 May 2009)
- Myelofibrosis Symptom Assessment Form (MFSAF) questionnaire every cycle x3, then every 3 to 6 cycles
- MDASI (MD Anderson Symptom Inventory) questionnaire administration: patients will complete the paper or tablet PC version of the MDASI at every cycle x3, then every 3 to 6 cycles. Patients will be instructed in the use of an Interactive Voice Response (IVR) system that will be used to assess symptoms with the MDASI weekly for first 3 cycles of therapy when patients do not have clinic appointments. If patients do not respond to an IVR call, the research coordinator will attempt to personally contact the patient by telephone to complete the MDASI.

## **Outside Physician Participation During Treatment**

- MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician.  
This will be documented in the patient record
- A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (Appendix L)
- Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.
- Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.
- A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.
- Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.
- The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.
- Patients will return to MDACC every 2 weeks during Cycles 1 and 2, monthly for 2 cycles, then every 3 to 6 months as long as on the study for evaluation.

The patient will be contacted by the PI and his staff 30 days and 60 days after discontinuation of protocol +/-7 days to assess for AE's, unless the patient receives further cytotoxic chemotherapy treatment.

### **5.7 Criteria for Removal from the Study**

Treatment with study drugs is to be discontinued when any of the following occurs:

- Lack of therapeutic effect (any effort should be made to provide therapy to the patient in a safe way for at least 3-6 cycles for proper assessment of potential efficacy)
- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug.
- Withdrawal of consent
- Lost to follow up
- Death
- Suspected pregnancy

## 6.0 CRITERIA FOR RESPONSE

Best overall response will be categorized according to the International Working Group Criteria:

**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  $\geq 100 \times 10^9/L$ , and absolute neutrophil count  $\geq 1.0 \times 10^9/L$ .
- 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  $\leq 1$ .\*\*

**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  $\geq 8$  weeks*).

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

**Progressive disease:** Requires one of the following:<sup>¶</sup>

- 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  $\geq 100\%$  increase in palpable distance for baseline splenomegaly of 5-10 cm or a  $\geq 50\%$  increase in palpable distance for baseline splenomegaly of > 10 cm.
- Leukemic transformation confirmed by a bone marrow blast count of  $\geq 20\%$ .
- An increase in peripheral blood blast percentage of  $\geq 20\%$  that lasts for  $\geq 8$  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. §Transfusion dependency is defined by a history of at least 2 units of red blood cell transfusions in the last month for hemoglobin of < 8.5 g/dL that was not associated with clinically overt bleeding. Similarly, during protocol therapy, transfusions for 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 REGULATORY AND REPORTING REQUIREMENTS**

### **7.1 Serious Adverse Event Reporting (SAE) for M. D. Anderson-Sponsored IND Protocols**

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical 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 (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events**, that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

### **Reporting to FDA:**

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

**It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical**

**Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.**

## **7.2 Expedited reporting by investigator to Incyte and Celgene**

Serious adverse events (SAE) are defined above. The investigator will inform Incyte and/or Celgene of any SAE within 24 hours of being aware of the event via email and/or fax. Respective companies will to be informed based on the attribution of a given SAE:

1. Due to INCB018424 alone – These SAEs will only to be reported to INCYTE.
2. Due to the Lenalidomide – These SAEs will only be reported to CELGENE.
3. Due to both the INDB018424 and the Lenalidomide – These SAEs will be reported to INCYTE and CELGENE.
4. All pregnancies will be reported to both companies.

If the investigator can't associate causality with one or the other alone then causality needs to be associated with the combination of the products. These SAEs will go to both INCYTE and CELGENE.

Adverse events will be documented in the medical record and entered into the case report form. PDMS/ CORE will be used as the electronic case report form for this protocol. Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial. SAEs must be documented on MDACC "Internal SAE Report Form for Prompt Reporting". This form must be completed and supplied to Incyte and/or 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 MDACC SAE reporting form.

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or the female partner of a male subject occurring while the subject is on study drug, or within 60 days of the subject's last dose of study drug, are considered immediately reportable events. Study drug is to be discontinued immediately in a female patient and the patient instructed to return any unused portion of the study drug to the investigator(s). The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Incyte and Celgene immediately by phone and facsimile using the MDACC AE report form. The female should be referred to an obstetrician-gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The Investigator(s) will follow the female subject until completion of the pregnancy, and must notify Incyte and Celgene of the outcome of the pregnancy as a follow-up to the initial AE report. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the Investigator(s) should follow the procedures for reporting SAEs (i.e., report the event to Incyte and Celgene within 24 hours of the Investigator's knowledge of the event). In the case of a live "normal" birth, Incyte and Celgene should be advised within 24 hours of the Investigator's knowledge of the event. 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(s) suspects is related to the in utero exposure to the study drug should also be reported to Incyte and Celgene within 24 hours of the Investigators' knowledge of the event. If the female is found not to be pregnant, any determination regarding the subject's continued participation in the study will be determined by the principal investigator.

## **8.0 STATISTICAL CONSIDERATIONS**

All subjects meeting the eligibility criteria that have signed a consent form and have begun treatment will be evaluable for response. This is a two stage, phase II trial designed to assess the effect of therapy in subjects with Primary, Post Polycythemia Vera, or Post Essential Thrombocythemia Myelofibrosis (PMF, post-PV MF, or post-ET MF). Secondary objective is to determine the safety of therapy in this population.

The primary objective of this study is to assess efficacy in terms of the objective response rate (complete and partial response, and clinical improvement by IWG-MRT) in patients with MF. The Min-Max 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 50%. A response rate of 35% 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% ( $\alpha=0.1$ ), a total sample size of 49 patients will result in 80% power ( $\beta=0.2$ ).

In the first stage of the design, a total of 31 patients will be enrolled and the study will be put on hold to assess response. If 10 or fewer patients respond to the combination therapy, after being treated for 6 months or discontinued due to excessive toxicity or lack of efficacy, then the study will be terminated and the therapy will be declared ineffective. Those patients who stopped receiving one of the two study drugs due to safety reasons will be counted as failures in the efficacy analysis. However, if 11 or more patients respond, up to an additional 18 patients will be enrolled to complete the study.

After a total of 49 patients have been enrolled into the study, if 21 or fewer patients respond to the therapy, the therapy will be declared ineffective. However, if greater than 21 patients respond to the therapy, the therapy will be considered efficacious. The probability of early termination due to unacceptable response rate is 46% under the null hypothesis.

Data from all subjects who receive any study drug will be included in the safety analyses. Subjects who entered the study and did not take any of the study drug and had this confirmed, will not be evaluated for safety.

The severity of the toxicities will be graded according to the NCI CTCAE v4.0 whenever possible. We will follow standard reporting guidelines for adverse events (Appendix C; Leukemia-specific Adverse Event Recording and Reporting Guidelines).

Descriptive statistics will be utilized to assess time to response and response duration.

**Duration of response:** duration of response is defined as the date at which the subject's objective status is first noted to be a CR, PR or CI to the date progression (no longer meeting criteria for either CR, PR or CI) is documented (if one has occurred). Patients who continue to respond as of the data cut-off date will be censored as of the date of their last assessment documenting continued response.

**Time to response:** The time to response is defined as the time from study registration to the first date at which the subject's objective status was classified as a response (CR, PR or CI). In subjects who do not achieve a response, time to response will be censored at the subject's last evaluation date. The distribution for each of these event-time variables (duration of response and time to response) will be estimated by Kaplan-Meier curves.

**Anemia:** Descriptive statistics will be used to explore improvements in anemia and transfusion dependence. The following outcomes will be summarized: mean changes in hemoglobin at monthly intervals. The proportion of transfusion independent patients not requiring transfusions on study who experience an increase of 2 g/dL in their hemoglobin relative to baseline, the proportion of transfusion dependent patients (defined as requiring a transfusion of 2 units PRBCs monthly for 3 months (12 weeks) prior to starting the trial) who become transfusion independent (not requiring a transfusion of PRBCs over a period of 3 months (12 weeks) while on study), the proportion of transfusion dependent patients who become transfusion independent and have a 1 g/dL increase in hemoglobin relative to baseline, and the proportion of transfusion independent patients requiring a transfusion while on study.

**JAK2V617F Allele burden:** Change in JAK2V617 allele burden from baseline to each visit where it is measured.

This phase II clinical trial will have a stopping rule based on toxicity defined as an adverse events considered to be at least possibly related to treatment. In particular, accrual to the study will be temporarily suspended if: a) 2 or more among the first 10 subjects treated on this trial experiences a Grade 4 non-hematologic toxicity or a

serious adverse event that is felt to be drug related. b) 20% or more of subjects (when more than 10 subjects have been accrued) experience a Grade 4 non-hematologic toxicity or serious adverse event that is felt to be drug related. After consideration by the study team (study chair, statistician), a decision will be made as to whether accrual can resumed after approval of the appropriate IRB.

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## APPENDIX I: SCHEDULE OF ASSESSMENTS

Procedure	Screening Period ≤14 days from Day 1 (first day of study drug administration)	Cycle 1 <sup>9</sup> and 2				Cycle 3 <sup>9</sup> Every 28 days	After Cycle 3 or at discontinuation <sup>9</sup> Every 3 to 6 Cycles (84 to 168 days)
		Day 1 <sup>5</sup>	Day 8	Day 15	Day 22		
Informed Consent signing	X						
Medical History (including prior MF-directed therapies)	X						
Physical examination <sup>1</sup>	X	X		X		X	X
Vital Signs and Weight, Height <sup>11</sup>	X	X		X		X	X
Transfusion History <sup>2</sup>	X <sup>2</sup>					X	X
MFSAF and MDASI questionnaires		X				X	X
Pregnancy test (for FCBP only) <sup>3</sup>	X	X	X	X	X	X	X
CBC and differential <sup>6</sup>	X	X	X	X	X	X <sup>6</sup>	X <sup>6</sup>
Serum Chemistry <sup>4</sup>	X	X	X	X	X	X <sup>6</sup>	X <sup>6</sup>
12-Lead ECG and urinalysis	X						
Bone Marrow Aspirate and Biopsy <sup>7</sup>	X						X <sup>8</sup>
Correlative studies for PK: Peripheral blood sample x3	-	X <sup>10</sup>					
Assess and Record adverse events	X	X		X		X	X
Record concomitant therapies/procedures	X	X		-		X	X
Response Assessment					X	X	X

<sup>1</sup> Includes measurement of spleen and liver.

<sup>2</sup> Subjects must have 3 months documented transfusion history prior to Day 1.

<sup>3</sup> Pregnancy test, urine or blood, with a sensitivity of at least 50 mIU/mL, within 10 – 14 days prior to and again within 24 hours of starting lenalidomide; then every week x 4, then monthly for all FCBP with regular menstrual cycles, or every 2 weeks if irregular cycles.

<sup>4</sup> sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, total bilirubin, alanine aminotransferase, and glucose. Uric Acid, PT/PTT and INR need be done only pre-therapy.

<sup>5</sup> If not done within 3 days of Day 1.

<sup>6</sup> CBC with differential and serum chemistries will be done weekly for 2 cycles, then every 2 weeks while on therapy. Those responding patients continuing therapy past 6 cycles and on a stable dose level without interruption or delay for 4 cycles may have blood tests done monthly.

<sup>7</sup> Bone Marrow Aspirate and Biopsy (can be done within 3 months) includes standard cytogenetic analysis and JAK2 mutation testing (quantitative PCR for allele burden). Cytogenetic test and JAK2 mutation test do not need to be repeated during the study in patients with known normal chromosomes or without mutation. BM collected after Cycle 3,6,9,12 and then as determined appropriate by the investigator.

<sup>8</sup> May be omitted if so decided by the treating physician. Should be done to confirm complete response and when clinically indicated.

- <sup>9</sup>. All scheduled visits will have a +/- 7 days window unless otherwise stated. In between required MD Anderson visits, mandatory visits may be done at the local referring doctor's office at minimum every 28 days (+/- 7 days);, this will also include phone contact by the study staff. The discontinuation visit will be considered as such on the date the patient is taken off the protocol. The patient will be contacted by the PI 30 days and 60 days after discontinuation of protocol +/-7 days to assess for AE's.
- <sup>10</sup>. on day 1 of cycle 2 for pharmacokinetics (PK) at approximately 0.5-1 hour, 2-4 hours, and 4-8 hours post Ruxolitinib dose (3 time points).
- <sup>11</sup>. Height at screening only

## APPENDIX II

International Working Group for Myelofibrosis Research and Treatment Prognostic scoring system

<b>Risk group</b>	<b>No. of factors</b>	<b>Median survival (mo; 95% CI)</b>	<b>Proportion of deaths, %</b>
Low	0	135 (117-181)	32
Intermediate-1	1	95 (79-114)	50
Intermediate-2	2	48 (43-59)	71
High	3 or more	27 (23-31)	73

Risk factors include: age >65 years, constitutional symptoms, hemoglobin <10g/dL, white blood cell count >25x10<sup>9</sup>/L, Blood blasts ≥ 1%.