A Sequential Two-Stage Dose Escalation Study to Evaluate the Safety and Efficacy of Ruxolitinib for the treatment of Chronic Myelomonocytic Leukemia (CMML): A Phase 2 Expansion

NCT03722407

Version 5

August 20, 2020

MCC 19727 Study Title: A Sequential Two-Stage Dose Escalation Study to Evaluate the Safety and Efficacy of Ruxolitinib for the treatment of Chronic Myelomonocytic Leukemia (CMML): A Phase 2 Expansion.

Sponsor:	Moffitt Cancer Center
Funding:	INCYTE
***Principal Investigator:**	Eric Padron, MD Moffitt Cancer Center 12902 Magnolia Drive Tampa, FL 33612 Telephone: 813-745-8264 e-mail address: Eric.Padron@moffitt.org
SubInvestigators	Rami Komrokji, MD Jeffrey E Lancet, MD Kendra Sweet, MD Bijal Shah, MD David Sallman, MD Chetasi Talati, MD Andrew Kuykendall, MD Timothy Kubal, MD
Statistician:	Quincy Mo, PhD
Previous Version: **Date:**	**4** **01/30/2020**
Version: **Date:**	**5** **08/20/2020**

Protocol Synopsis

Title: A Sequential Two-Stage Dose Escalation Study to Evaluate the Safety and Efficacy of Ruxolitinib for the treatment of Chronic Myelomonocytic Leukemia (CMML): A Phase 2 Expansion.

Study Objectives	Primary Objectives: 1. To determine overall response rates as measured by the international working group MDS/MPN criteria. Secondary Objectives: 1. To determine the time to AML transformation of patients on ruxolitinib. 2. To determine the median overall survival. 3. To determine the duration of response achieved as in secondary endpoint one. 4. To determine the change in symptom score from baseline to week 16. 5. To determine the change in spleen volume at 16 weeks. 6. To determine if a correlation exist between the presence of the known recurrent mutations (JAK2, c-CBL, N-RAS, K-RAS, RUNX-1, TET2, SRSF2, EZH2, ASXL1, and DNMT3a) and response to ruxolitinib. 7. To determine if a correlation exists between inflammatory cytokine secretion in the peripheral blood and response to ruxolitinib in CMML patients.
Study Endpoints	Primary: 1. Proportion of subject achieving clinical benefit defined as hematologic improvement, complete remission, partial remission, or stable disease by the IWG MDS/MPN criteria at week 16 Secondary 1. Acute myeloid leukemia (AML) transformation according to WHO criteria. 2. Overall survival (OS). 3. Duration of response. 4. The Myeloproliferative Neoplasms Symptom Assessment Form (MPN-SAF TSS Total Symptom Score at baseline and at week 16. 5. ≥35% decrease in splenic volume as measured by CT Scan if applicable 6. Mutational status in our CMML patients by sanger sequencing of JAK2, c-CBL, N-RAS, K-RAS, RUNX-1, TET2, SRSF2, EZH2, ASXL1, and DNMT3a (pretreatment and progression). 7. Changes in cytokine secretion of peripheral blood at baseline and week 16 as previously described[1].

Eligibility Criteria	**Inclusion Criteria:** 1. Confirmed diagnosis of CMML using the World Health Organization (WHO) classification (appendix D). 2. Age >18 years at the time of obtaining informed consent. 3. Must be able to adhere to the study visit schedule and other protocol requirements. 4. Patients must be able to provide adequate BM aspirate and biopsy specimens for histopathological analysis and standard cytogenetic analysis during the screening procedure. 5. An Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 is required. 6. Women of childbearing potential must have a negative pregnancy test at time of screening and baseline visits and must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse 1) for at least 28 days before starting study drug; 2) while participating in the study; and 3) for at least 28 days after discontinuation from the study. The two methods of reliable contraception must include one highly effective method (i.e. intrauterine device [IUD], hormonal [birth control pills, injections, or implants], tubal ligation, partner's vasectomy) and one additional effective (barrier) method (i.e. latex condom, diaphragm, cervical cap). 7. Must understand and voluntarily sign an informed consent form. 8. Must have a life expectancy of greater than 3 months at time of screening. 9. Must have symptomatic splenomegaly and/or an MPN-SAF TSS>17. **Exclusion Criteria:** 1. Any of the following lab abnormalities: • Platelet count of less than 35,000/uL • Absolute Neutrophil Count (ANC) less than 250/uL • Serum Creatinine ≥ 2.0 • Serum total bilirubin >1.5x ULN 2. Use of cytotoxic chemotherapeutic agents, or experimental agents (agents that are not commercially available) for the treatment of CMML within 28 days of the first day of study drug treatment. 3. Prior history of metastatic malignancy in past 2 years 4. Any serious medical condition or psychiatric illness that will prevent the subject from signing the informed consent form or will place the subject at unacceptable risk if he/she participates in the study. 5. Concurrent use of GM-CSF. G-CSF could be used for the short-term management of neutropenic infection. Stable doses of erythropoietin stimulating agents that were started >8 weeks from first ruxolitinib dose or corticosteroids that were being administered prior to screening are allowed. 6. Uncontrolled current illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. 7. Pregnant women are excluded from this study because ruxolitinib has not been studied in pregnant patients. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ruxolitinib, breastfeeding should be discontinued if the mother is treated with ruxolitinib.
Baseline Assessment (within 4 weeks of starting treatment)	1. Medical history including: a. Disease characteristics such as first diagnosis of CMML, WHO/FAB subtype, IPSS score, MD Anderson Scoring System (MDASC), prior treatments. b. ECOG performance status. c. The Myeloproliferative Neoplasms Symptom Assessment Form (MPN-SAF TSS). d. Concurrent medication review. 2. Routine physical examination to include vital signs, height and weight.

	3. Bone marrow examination, including cytomorphology, cytogenetic assessment, and flow cytometry analysis. 4. Laboratory assessments: • Hematology to include platelet count, hemoglobin, hematocrit, white blood cells (WBC) and WBC differential (including: neutrophils, eosinophils, basophils, lymphocytes and monocytes), INR, PT, PTT, and reticulocyte count. • Clinical chemistries including BUN/urea, creatinine, calcium, chloride, glucose, sodium, potassium, bicarbonate, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, total protein, LDH, and albumin. • Urine or serum pregnancy test for females of childbearing potential will be performed at Screening or on Day 1, prior to first dose of study medication. 5. Review and record any blood and blood supportive care products for the prior 8 weeks. 6. CT scan of the abdomen to measure splenic volume.
Treatment plan	Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 11. Appropriate dose modifications for ruxolitinib are described in Section 10. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's CMML. Ruxolitinib will be supplied by INCYTE as 5mg tablets. . Ruxolitinib will be self-administered as a twice-daily oral dose for a continuous treatment cycle. Ruxolitinib tablets will be taken approximately 12 hours apart (morning and night). Patients will not take the morning dose of ruxolitinib at the first regularly scheduled visit.. On all other days corresponding to study visits, patients will take the morning dose of study drug prior to the visit, and will note on the subject reminder card the time that medications were taken. Patients will also be instructed to take ruxolitinib without respect to food, as previous data demonstrate no change in drug kinetics or absorption. **All patients will be given 40 mg/day divided in equal BID doses.** A maximum of 29 patients will be treated at the MTD identified in phase I of 20mg BID. See study calendar for assessment on study.
Dose delay/modif-ications	Dose delays/modifications are allowed for those patients enrolled in phase II as described in section 6.
Duration of Therapy	Patients will be treated for a total of 16 weeks. For patients responding at week 16, treatment may continue until one of the following criteria applies: • Intercurrent illness that prevents further administration of treatment. • Unacceptable adverse event(s). • Patient decides to withdraw from the study. • General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator. • Evidence of disease progression by the IWG MDS/MPN criteria.
Duration of Follow-Up	Patients will be followed as per calendar on treatment for 17 weeks. After 17 weeks, patients who continue on study will be followed monthly. Off study data on AML transformation and overall survival will be updated every 6 months or until death, whichever occurs first. Patients removed from the study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. <u>Criteria for Removal from Study</u> Study drug treatment can continue for patients receiving clinical benefit per IWG criteria, unless: one or more withdrawal criteria are met, or at the subject's discretion, or if the study is terminated. *Subject Completion

	A subject will be considered to have completed the study if the subject meets at least 1 of the following criteria: - The subject has completed 16 weeks of treatment with study medication with no improvement. - The subject died during the study. - The subject experienced an adverse event (AE) that lead to withdrawal from the study. *Subject Withdrawal from Study A subject may voluntarily withdraw from study medication or withdraw consent from the study at any time. The investigator may also, at his or her discretion, discontinue a subject from participating in the study at any time. The investigator will record the date and the reason for subject withdrawal from the study.8/ *Subject Withdrawal from Study Medication If the subject is permanently withdrawn from treatment with study medication, but does not withdraw consent, the investigator must make every effort to have the subject complete all withdrawal assessments at the time of withdrawal, and complete all scheduled follow-up visits. **Treatment: with study medication must be discontinued if (Withdrawal Criteria):** • No clinical benefit has been attained after 16 weeks of treatment. • Evidence of Disease progression according to IWG MDS/MPN criteria. • A subject becomes pregnant. • A subject is significantly non-compliant with the requirements of the protocol. • A subject has an adverse experience that would, in the investigator's judgment, make continued participation in the study an unacceptable risk.
Follow up on study	See calendar page 36
Statistics	**Study Design:** This will be a two stage Simon's phase 2 design. After testing the treatment dose on 10 patients in the first stage, the trial will be terminated if 1 or fewer achieve a clinical benefit. If the trial goes on to the second stage, a total of 29 patients will be studied. If the total number responding is less than or equal to 5, the drug is rejected. Sample Size/Accrual Rate The first phase of the stage II will recruit 10 patients at 20mg BID ruxolitinib. If more than 1 response are seen by 17 weeks on ruxolitinib, then a total of 29 patients will be accrued at 20mg BID to determine efficacy.
Laboratory Correlates	**Phases 1 and 2** Peripheral blood and Bone Marrow Aspirate will be collected and processed in the lab of Eric Padron in the Stabile Research Building (SRB) at the Moffitt Cancer and Research Institute as described in section 16.

1 OBJECTIVES

1.1 Primary Objective:

To determine overall response rates as measured by the international working group MDS/MPN criteria.

1.2 Secondary Objectives:

1.2.1 To determine the time to AML transformation of patients on ruxolitinib.

1.2.2 To determine the median overall survival.

1.2.3 To determine the duration of response achieved as in secondary endpoint one.

1.2.4 To determine the change in symptom score from baseline to week 16.

1.2.5 To determine the change in spleen volume at 16 weeks.

1.2.6 To determine if a correlation exist between the presence of the known recurrent mutations (JAK2, c-CBL, N-RAS, K-RAS, RUNX-1, TET2, SRSF2, EZH2, ASXL1, and DNMT3a) and response to ruxolitinib.

1.2.7 To determine if a correlation exists between inflammatory cytokine secretion in the peripheral blood and response to ruxolitinib in CMML patients.

2 BACKGROUND

2.1 Chronic Myelomonocytic Leukemia

Chronic Myelomonocytic Leukemia (CMML) is a clonal malignancy characterized by cytopenias with or without leukocytosis, marrow dysplasia, monocytosis, splenomegaly, and a propensity to transform to acute myeloid leukemia[2]. Prior to 2001, the World Health Organization (WHO) classified CMML as a subtype of the myelodysplastic syndromes (MDS)[3]. However because CMML exhibits clinical and pathologic features of a MDS and of a Myeloproliferative Neoplasm (MPN), it was reclassified by the WHO as a member of the Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) highlighting its nosologic complexity. CMML shares this WHO designation with atypical Chronic Myeloid Leukemia (aCML), Refractory Anemia with Ringed Sideroblasts and Thrombocytosis (RARS-T), and the pediatric counterpart of CMML, Juvenile Myelomonocytic Leukemia (JMML)[4]. JMML is a

lethal pediatric malignancy with clinical features similar to CMML and hallmarked by selective hypersensitivity to GM-CSF[5]. The reclassification of CMML has been substantiated by next generation sequencing techniques that have allowed for the massive genetic sequencing of myeloid malignancies[6,7]. The occurrence of recurrent mutations in CMML and MDS are now known to be different in both type and/or frequency suggesting that these diseases represent distinctly different entities. The clinical behavior of CMML is unique in that it displays features of an MDS and of an MPN within the same patient. However, CMML patients can display the predominant features of an MDS-like or MPN-like disease. The French-American-British (FAB) group was first to subdivide CMML patients into an MDS variant and MPN variant based on a white blood cell (WBC) count greater than 20K/dL[8]. The WHO later favored subdivisions based on a myeloblast percentage greater than 10% in the bone marrow aspirate because of its prognostic value[4]. Irrespective of these subdivisions, recent genomic advances have yet to translate to effective, CMML specific therapies and thus the current standard-of-care in CMML remains the use of drugs developed for MDS.

For instance, in 2009, Fenaux and colleges reported the results of a randomized phase III trial that demonstrated a survival advantage (24.5mo vs 15mo) for 5-azacitidine, a DNA methyltransferase (DNMT) inhibitor, when compared with induction chemotherapy, low dose cytarabine, or best supportive care in patients with higher risk MDS and CMML. However, only 22 CMMLs were included in this study and unequal randomization did not allow for subset analysis of these patients[9]. Despite this, 5-azacitidine gained FDA approval for the treatment of CMML and has become the first line therapy of choice. Subsequent retrospective reports have suggested that the rates of hematologic improvement in CMML are similar to MDS but that this similarity is lost when analyzing the myeloproliferative variant of CMML alone. The myeloproliferative variant appears to be have response rates on the order of 10-15%[10].

Chronic Myelomonocytic Leukemia (CMML) is a rare disease with an incidence of

approximately 0.3 per 100,000. The prognosis is poor with a median overall survival ranging between 12 and 20 months that is not known to be improved by 5-azacitidine[11]. Allogeneic stem cell transplant (ASCT) remains the only potential curative therapy. However, most patients are ineligible secondary to age related exclusion. Those that can undergo transplant face a high degree of morbidity and unacceptable transplant related mortality with only a small fraction of patients alive at 5 years[12]. From an economic perspective, an ASCT is costly as are the prophylactic antibiotics necessary to prevent life threatening infection and the immuno-suppressants needed to control graft versus host disease as a result of the transplant. To make matters worse, there are very few clinical trials available in CMML relative to other hematologic malignancies. This, in combination with its dismal prognosis and lack of standard therapies makes the outlook of patients with CMML quite grim. There is a clear need for new CMML-specific therapies in this orphaned disease.

2.2 GM-CSF signaling and Chronic Myelomonocytic Leukemia

GM-CSF hypersensitivity, as defined by increased hematopoietic colony formation in methylcellulose when exposed to low dose GM-CSF, has been a known feature of JMML for over a decade[5]. The obvious clinical similarities between JMML and CMML have lead to studies, including our own, investigating the nature of GM-CSF signaling in CMML. The first such study in 2002, Ramshaw and colleges showed that spontaneous hematopoietic colony growth could be achieved in CMML patient samples and that this was inhibited by E21R, a GM-CSF specific antagonist, suggesting that autocrince or paracrine production of GM-CSF was important to *in vitro* CMML cell proliferation and differentiation. They also performed transplantation experiments in a NOD/SCID murine model that was transgenically modified to secrete human GM-CSF or not. Only those CMML cells transplanted in the GM-CSF transgenic mouse engrafted demonstrating an *in vivo* requirement for proliferation[13]. In the next study, Kotecha and colleges explored the downstream signals elicited by the GM-CSF receptor in JMML. Despite the fact that JMML is predominantly a RAS-mediated disease, Kotecha and colleges demonstrated that it was STAT5 and not ERK that was hyperphosphorylated in the presence of GM-CSF.

This phenomenon was not seen in normal controls or other pediatric MPNs but was seen in five CMML patient samples[14].

Our laboratory has confirmed these results by demonstrating that CMML primary samples are sensitive to very low doses of GM-CSF as measured by STAT5 phosphorylation (n=20)[15]. We have also shown that GM-CSF inhibition is important to CMML viability by introducing KB-003, a highly specific monoclonal antibody to GM-CSF developed by KaloBios pharmaceuticals. Despite the molecular and clinical heterogeneity observed in CMML, all samples tested (n=10) showed decrease proliferation and viability when exposed to GM-CSF blockade and the vast majority of samples tested (n=20) showed GM-CSF dependent STAT5 activation (Yp) at lower doses of GM-CSF compared to controls and compared to other cytokines within the CMML patients. Further it was the immature monocytes (CD33+/CD14+) that seemed most sensitive to this inhibition, leaving the rest of the bone marrow unaffected.

2.3 **Ruxolitinib**

Ruxolitinib is an FDA-approved agent for the treatment of myelofibrosis. It is a potent inhibitor of JAK1 and JAK2 (nM IC50) that has been tested in a wide array of JAK/STAT dependent processes. In JAK/STAT dependent cell lines, ruxolitinib demonstrates IC50 values of 80-300 nM and can inhibited JAK/STAT signaling and growth in cell lines expressing the constitutively active JAK2 mutant (JAK2V617F) that is present in approximately 15% of CMML patients[6]. The JAK2V617F abnormality has been broadly implicated in the pathogenesis of the majority of Philadelphia chromosome negative MPNs. It is because of this that INCYTE, the makers of ruxolitinib, have targeted MPNs in its initial drug development. To this end, *in vivo* studies have demonstrated that ruxolitinib improves splenomegaly and survival in a murine JAK/STAT dependent MPN model after only 3 weeks of treatment. Treatment with ruxolitinib also reduced inflammatory cytokines and pSTAT3 levels in these mice suggesting an *in vitro* and *in vivo* effect in JAK/STAT dependent malignancies[16].

Safety

During the Phase I and Phase II development program, ruxolitinib was assessed in healthy volunteers, patients with various degrees of renal or hepatic impairment, in patients with rheumatoid arthritis, prostate cancer, multiple myeloma, myelofibrosis (MF), polycythemia vera (PV) and essential thrombocythemia (ET). The aggregate safety database for ruxolitinib included 679 patients treated in 6 studies. Hematologic events were the most frequently reported adverse events (AE)s however, the majority of these were of Grades 1-2, seldom leading to study drug discontinuation (<1% of patients). Increased rates of anemia did result in an increase in packed red blood cell (PRBC) transfusion requirements for some ruxolitinib-treated patients but platelet transfusions while on ruxolitinib were rare. No Grade 4 events as it relates to biochemistry laboratory abnormalities of alanine aminotransferase (ALT), aspartate aminotransferase (AST) or cholesterol were reported. The Phase III safety dataset in MF patients shows that it was appropriate to individually adjust doses for patients according to their tolerability and efficacy. However, 124 patients (41.2%) required no dose reduction, indicating the starting dose of 15mg or 20mg BID was appropriate for these individuals. Of the 177 patients who had dose reduction, 91 patients (51%) had only one. Interruptions of dosing were less frequent than dose reductions, with 215 patients (71.4%) requiring no dose interruption. Of the 86 patients who had dose interruptions, 59 patients (19.6%) had only one dose interruption. The Phase III safety dataset in MF patients showed that the only notable imbalances (ruxolitinib versus placebo or best available therapy [BAT]) in AEs related to hemorrhagic events were in Grade 1-2 skin and soft tissue bruising which did not lead to dose reduction or discontinuation. Similarly, the only notable imbalances (ruxolitinib versus placebo or BAT) in AEs related to infections were urinary tract infections and herpes zoster infections. A thorough QT study was conducted in 50 healthy patients. There was no indication of a QT/QTc prolonging effect of ruxolitinib in single doses up that exceeded those proposed in this study[17].

Efficacy

In two large phase 3 clinical trials, ruxolitinib has demonstrated efficacy in patients with high-risk myelofibrosis. The first trial randomly assigned patients to receive

15mg twice daily of ruxolitinib (155 patients) or placebo (154 patients). The primary endpoint of the study was defined as the proportion of patients with a reduction in spleen volume of 35% or more at 24 weeks by means of magnetic resonance imaging (MRI). The primary end point was reached in 41.9% of patients in the ruxolitinib group as compared with 0.7% in the placebo group (P<0.001). A reduction in spleen volume was durable as 67.0% of the patients with a response had the response for 48 weeks or more. There was an improvement of 50% or more in the total symptom score, a myelofibrosis specific quality-of-life scoring system, at 24 weeks in 45.9% of patients who received ruxolitinib as compared with 5.3% of patients who received placebo (P<0.001)[18]. The second trial randomly assigned patients to the same dose of ruxolitinib or best available therapy (BAT) defined by the treating physician. The primary end point was the percentage of patients with at least a 35% reduction in spleen volume at week 48 by MRI or computed tomography. A total of 28% of the patients in the ruxolitinib group met the primary endpoint as compared with 0% in the group receiving the best available therapy (P<0.001). At 48 weeks, the mean palpable spleen length had decreased by 56% with ruxolitinib but had increased by 4% with the best available therapy. The median duration of response with ruxolitinib was not reached, with 80% of patients still having a response at a median follow-up of 12 months[19].

2.4 Rationale for Ruxolitinib in CMML

GM-CSF signaling is both dysregulated and important for CMML survival *in vitro* and *in vivo* (see section 2.2). Although GM-CSF signaling is hallmarked by cytokinepleotropy, it appears that STAT5 is preferentially activated in the CMML disease phenotype. Our laboratory has shown that targeting GM-CSF activation leads to decreased viability in primary CMML patient samples. In the late 1990s, efforts were made to target this pathway. Frankel and colleges developed a GM-CSF molecule fused to diphtheria toxin that was highly toxic to CMML myeloid progenitors in 16/20 patient samples tested[20]. This led to a phase I clinical trial in relapsed/refractory acute leukemias. Unfortunately, unacceptable hepatoxicity was seen, even at moderate doses of compound, that did not allow for dose escalation[21].

This hepatotoxicity is now thought to be Kupffer cell mediated.

The JAK kinases are the sentinel kinases responsible for the key phosphorylation event in many cytokine receptors, including GM-CSF. Parganas and colleges developed a JAK2 deficient murine model that showed that JAK2 is required to elicit GM-CSF mediated signaling[22]. Considering this, our laboratory explored JAK1/2 pharmacologic inhibition with SD1029 in primary CMML cells. SD-1029 is a selective JAK1/JAK2 (μM IC50) inhibitor that is not available for clinical use and has a similar JAK inhibition profile to ruxolitinib. In 3 CMML patient samples tested, SD-1029 increased apoptosis and decreased viability by ANNEXIN-V and DAPI staining in a dose dependent fashion. None of these patients tested harbored a JAK2V617F mutation. Lastly, Ravandi and colleges recently published the results of a phase 2 trial using ruxolitinib in refractory leukemias. In this cohort, 4 CMML patients were enrolled to take BID ruxolitinib (dose not available). It is reported that 2/4 CMML patients demonstrated some degree of clinical benefit[23]. Although the nature of the benefit was not expounded upon, it provides further proof-of-principle that JAK inhibition may indeed result in responses in this disease. Our preliminary data, in addition to the extensive data demonstrating the role of GM-CSF in CMML, provides compelling evidence to explore JAK1/2 inhibition with ruxolitinib as a therapeutic target in CMML.

2.5 A phase 1/2 clinical study of ruxolitinib in CMML

We have performed a phase 1/2 study of ruxolitinib in CMML. This study included any patient with a WHO diagnosis of CMML irrespective of therapy. This phase 1 study identified 20mg PO BID as the maximally tolerated dose of ruxoltinib in CMML and accrued 20 patients[24]. This study demonstrated broad range activity that was enriched in patients with splenomegaly and disease related symptoms. This was confirmed in the phase 2 study which accrued 29 patients and has presented in abstract form. Therefore, this phase 2 expansion will explore efficacy in only those CMML patients with either symptomatic splenomegaly and/or disease related symptoms defined by a Total Symptom Score of $\geq$17.

3 STUDY ENDPOINTS

3.1 Primary

3.1.1 Proportion of subject achieving clinical benefit defined as hematologic improvement, complete remission, partial remission, or stable disease by the IWG MDS/MPN criteria at week 16 (see section 14)

3.2 Secondary

3.2.1 Acute myeloid leukemia (AML) transformation according to WHO criteria.

3.2.2 Overall survival (OS).

3.2.3 Duration of response.

3.2.4 The Myeloproliferative Neoplasms Symptom Assessment Form (MPN-SAF TSS) Total Symptom Score at baseline and at week 16.

3.2.5 ≥35% decrease in splenic volume as measured by CT Scan if applicable

3.2.6 Mutational status in our CMML patients by sanger sequencing of JAK2, c-CBL, N-RAS, K-RAS, RUNX-1, TET2, SRSF2, EZH2, ASXL1, and DNMT3a (pretreatment and progression).

3.2.7 Changes in cytokine secretion of peripheral blood at baseline and week 16 as previously described[1].

4 PATIENT SELECTION / Eligibility Criteria

4.1 **Inclusion criteria**

4.1.1 Confirmed diagnosis of CMML using the World Health Organization (WHO) classification (appendix D).

4.1.2 Age >18 years at the time of obtaining informed consent.

4.1.3 Must be able to adhere to the study visit schedule and other protocol requirements.

4.1.4 Patients must be able to provide adequate BM aspirate and biopsy specimens for histopathological analysis and standard cytogenetic analysis during the screening procedure.

4.1.5 An Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 is required.

4.1.6 Women of childbearing potential must have a negative pregnancy test at time of screening and baseline visits and agree to use two reliable forms of contraception

simultaneously or to practice complete abstinence from heterosexual intercourse 1) for at least 28 days before starting study drug; 2) while participating in the study; and 3) for at least 28 days after discontinuation from the study. The two methods of reliable contraception must include one highly effective method (i.e. intrauterine device [IUD], hormonal [birth control pills, injections, or implants], tubal ligation, partner's vasectomy) and one additional effective (barrier) method (i.e. latex condom, diaphragm, cervical cap).

4.1.7 Must understand and voluntarily sign an informed consent form.

4.1.8 Must have a life expectancy of greater than 3 months at time of screening.

4.1.9 Must have symptomatic splenomegaly and/or an MPN-SAF TSS >17.

4.2 **Exclusion Criteria**

4.2.1 Any of the following lab abnormalities:

4.2.1.1 Platelet count of less than 35,000/uL

4.2.1.2 Absolute Neutrophil Count (ANC) of less than 250 cells/uL

4.2.1.3 Serum Creatinine ≥2.0

4.2.1.4 Serum total bilirubin >1.5 x ULN

4.2.2 Use of cytotoxic chemotherapeutic agents, or experimental agents (agents that are not commercially available) for the treatment of CMML within 28 days of the first day of study drug treatment.

4.2.3 Any serious medical condition or psychiatric illness that will prevent the subject from signing the informed consent form or will place the subject at unacceptable risk if he/she participates in the study.

4.2.4 Concurrent use of GM-CSF. G-CSF could be used for the short-term management of neutropenic infection. Stable doses of erythropoietin stimulating agents that were started >8 weeks from first ruxolitinib dose or corticosteroids that were being administered prior to screening are allowed.

4.2.5 Uncontrolled current illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

4.2.6 History of metastatic malignancy in the preceding 2 years.

4.2.7 Pregnant women are excluded from this study because ruxolitinib has not been studied in pregnant patients. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ruxolitinib, breastfeeding should be discontinued if the mother is treated with ruxolitinib.

4.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

5 STUDY DESIGN

This is a phase 2, Simon's two stage design. A total of 10 patients will be treated during the first stage of phase 2 (stage 1) at 20mg BID. The trial will be terminated if 1 or fewer respond. If the trial goes on to the second stage, a total of 29 patients will be studied to determine efficacy in phase 2.

6 TREATMENT PLAN

6.1 Ruxolitinib administration

All patients will self-administer ruxolitinib twice daily, 12 hours apart as an outpatient. On all days corresponding to study visits, patients will take the morning dose of study drug prior to the visit, and will note on the subject reminder card the time that medications were taken. Reported adverse events and potential risks are described in Section 11. Appropriate dose modifications for ruxolitinib are described in Section 10. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's CMML.

6.1.1 Ruxolitinib will be supplied by INCYTE as tablets that will be self-administered BID orally, with or without food approximately 12 hours apart (morning and night).

6.1.2 The dosage strength is 5 mg/tablet ruxolitinib phosphate (free base equivalent). Administration instructions will be provided at Study Visits. The administration instructions will state that medication is "For Investigational Use Only". Ruxolitinib 5 mg tablets are packaged as 60 count in high-density

polyethylene (HDPE) bottles. The bottles will include labeling "New Drug - Limited by Federal (USA) Law to Investigational Use. The bottles of tablets should be stored at room temperature, 15°C to 30°C (59°F to 86°F).

6.2 General Concomitant Medication and Supportive Care Guidelines

All concomitant medications and medication history for 2 weeks MUST be recorded in the eCRF, and include: drug name, dose, frequency of administration, start and stop dates, and indication. All prior medications used to treat CMML will be recorded regardless of when they were received by the subject. Information collected for these medications will include dates of use, best treatment response (e.g., disease improvement, stabilization of disease or no improvement/disease progression), and reasons for stopping therapy. Any change in dosage of any concomitant medication (change in dose or frequency) MUST be recorded in the eCRF, to include: drug name, dose, frequency of administration, start and stop dates and indication.

6.3 Permitted Medications

6.3.1.1 Growth Factors

Erythropoiesis-stimulating agents (ESAs) are allowed for anemia during the study as per accepted standards in the treatment of CMML as long as the ESA was initiated >8 weeks prior to the first dose of ruxolitinib. Patients who enter the study on ESAs should continue at the same dose schedule until the optimal dose of study medication has been established. G-CSF is allowed during the study for patients with severe neutropenia and recurrent infections. Patients who enter the study on G-CSF should continue at the same dose schedule until the optimal dose of study medication has been established. GM-CSF is not permitted at any time during the study as preclinical evidence suggests that GM-CSF may be important for CMML proliferation and survival.

6.3.1.2 Systemic corticosteroids

Systemic corticosteroid doses greater than the equivalent of 10 mg prednisolone per day is not permitted, unless use is part of an ruxolitinib-dose tapering strategy. (see section 7 Optional Dose Tapering Strategy).

6.3.1.3 Aspirin

Aspirin in doses exceeding 162 mg per day is not permitted. Low dose aspirin (≤ 162 mg/day) and non-steroidal anti-inflammatory agents (acetaminophen, Ibuprofen) may be used.

6.3.1.4 Medications that are inhibitors of CYP3A4

When concomitant administration of a potent systemic inhibitor of CYP3A4 metabolizing enzymes (ketoconazole, clarithromycin, itraconazole, nefazodone and telithromycin, see section 7) that is required for subject management, the dose of ruxolitinib tablets must be adjusted as described in section 7. Based on the low overall bioavailability of topical ketoconazole, with very low systemic levels seen following topical administration, no dose adjustment of ruxolitinib is needed for use with topical ketoconazole.

6.3.1.5 Blood Products

The use of blood products to include packed red blood cells (PRBCs) and platelet transfusions are permitted and to be given at the discretion of the treating physician. Recommended guidelines for transfusion include a platelet threshold of 10,000/L for platelet transfusion and a hemoglobin threshold of 8g/dL for PRBC transfusion.

6.4 Prohibited Medications

Patients must abstain from using prohibited prescription or non-prescription drugs within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study medication and until completion of follow-up procedures (Exclusion Criteria).

The following medications are prohibited during the study:

• Any prior or concomitant use of another JAK inhibitor.

• Any investigational medication other than the study drugs.

• Use of the potent inducers of CYP3A4, rifampin and St John's Wart, is not permitted at any time during participation in the study.

• The GM-CSF growth factor receptor agonists must not be used. Preclinical evidence suggests that it is important for CMML proliferation and survival and it is directly upstream for JAK2, the target of ruxolitinib. GM-CSF must not have been used for at least 28 days prior to receiving the first dose of study drug.

7 Duration of Therapy

Patients will be treated for a total of 16 weeks. For patients responding at week 16, treatment may continue until one of the following criteria applies:

7.1 Inter-current illness that prevents further administration of treatment,

7.2 Unacceptable adverse event(s),

7.3 Patient decides to withdraw from the study, or

7.4 General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

7.5 Evidence of disease progression by the IWG MDS/MPN criteria.

8 Duration of Follow-Up

Patients will be followed as per calendar on treatment for 17 weeks. After 17 weeks patient who continue on study will be followed monthly. Off study data on AML transformation and overall survival will be updated every 6 month or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

9 Criteria for Removal from Study

9.1 Subject Completion

A subject will be considered to have completed the study if the subject meets at least 1 of the following criteria:

9.1.1 The subject has completed 16 weeks of treatment with study medication with no improvement.

9.1.2 The subject died during the study.

9.1.3 The subject experienced an AE that lead to withdrawal from the study.

9.2 Subject Withdrawal from Study

A subject may voluntarily withdraw from study medication or withdraw consent from the study at any time. The investigator may also, at his or her discretion, discontinue a subject from participating in the study at any time. The investigator will record the date and the reason for subject withdrawal from the study.

9.3 Subject Withdrawal from Study Medication

If the subject is permanently withdrawn from treatment with study medication, but does not withdraw consent, the investigator must make every effort to have the

subject complete all withdrawal assessments at the time of withdrawal, and complete all scheduled follow-up visits. Treatment with study medication must be discontinued if:

- The subject withdraws consent.
- Further participation would be injurious to the subject's health or well-being in the Investigator's medical judgment.
- The study is terminated.
- The subject becomes pregnant
- The patients exhibits leukemic transformation (as evidenced by bone marrow blast counts of at least 20%, or peripheral blast counts of at least 20% lasting at least 8 weeks.
- No clinical benefit has been attained after 16 weeks of treatment.
- Evidence of Disease progression according to IWG MDS/MPN criteria.
- a subject is significantly non-compliant with the requirements of the protocol.
- a subject has an adverse experience that would, in the investigator's judgment, make continued participation in the study an unacceptable risk.

Patients withdrawing from study can be tapered off of ruxolitinib over a 4 week period at the discretion of the investigator

10 DOSING DELAYS/MODIFICATIONS

All patients enrolled in the phase 2 portion may have the following dose delays/modifications once the MTD has been defined.

Ruxolitinib may be held by the Investigator at any time if there is concern about subject safety. Dosing must be halted immediately if either of the following occurs:

• Platelet counts fall below 10,000/μL and/or a life-threatening bleeding event

• Febrile neutropenia

Dosing may be reinstated following dose interruption using the re-start schema detailed in below.

10.1 **Dose Adjustments**:

In order to provide sufficient data to make the dose adjustment decisions, it is recommended that hematology parameters be obtained weekly and at least two times weekly for platelet count < 25,000/μL or ANC < 500/μL. In the event that any subject

permanently discontinues the study drug, regardless of reason, reasonable efforts should be made to have the subject return for an early termination visit. If the drug discontinuation is being contemplated for a reason other than low platelet count or low ANC, the use of a tapering strategy should be considered (see below). The date the subject discontinued the study drug and the specific reason for discontinuation will be recorded in the eCRF; eg, reasons such as discontinued due to inadequate efficacy or withdrawn due to adverse event. This information will be used to summarize the reasons for study discontinuation. Efforts will be made to follow patients who discontinue from the study in order to determine overall survival and leukemia free survival. Investigators will contact patients every 6 months to determine if patients have undergone leukemic transformation, or death, and for the latter, the cause of death.

10.2 **Dose Adjustments in Ruxolitinib Tablets for Safety:**

Dosing must be held if platelet counts decline below 10,000/μL or if a life-threatening bleed occurs with a platelet count below 20,000/μL. Doses must be decreased for platelet count values that decline greater than 50% of baseline **and** are **greater** than 25,000/μL to 75% of the defined MTD. Doses must be decreased for platelet count values that decline greater than 50% of baseline **and** are **below** 25,000/μL to 50% of the defined MTD. The dosing scheduled should be maintained at BID dosing to assure appropriate pharmacokinetics. Dose reductions should be executed by decreasing the individual dose and not the frequency of administration. In order to provide sufficient data to make the dose adjustment decisions, it is recommended that hematology parameters be obtained as defined in section 10.1. Dosing may be restarted or increased following recovery of platelet counts to acceptable levels. The following is the **recommended** dose restart/increase strategy:

In patients whom drug was held, ruxolitinib may be restarted at 50% of the MTD after platelet count has improved to pre-ruxolitinib baseline levels and/or febrile neutropenia has resolved for at least 2 weeks. In patients whom drug dose was decreased, ruxolitinib may be increased to the previous dose (MTD) after platelet count has improved to pre-ruxolitinib baseline levels and/or febrile neutropenia has resolved for at least 2 weeks. If criteria is met for discontinuation/dose modification

then ruxolitinib must be discontinued with no potential for restart. The objective for restarting or escalating after a reduction for safety is to find the highest safe dose of ruxolitinib for each subject, with increases in dose generally not more than in increments of 5 mg BID and not more often than every 2 weeks.

Dose Reductions for Concomitant CYP Inhibitor Usage

Ruxolitinib is metabolized in the liver by the cytochrome (CYP) P450 metabolizing enzyme system, predominantly by the 3A4 isozyme. With concomitant dosing of potent CYP3A4 inhibitors such as systemic ketoconazole (see Appendix B), plasma exposure of ruxolitinib increases approximately 2-fold. Thus, a dose reduction of ~ 50% for ruxolitinib is appropriate for patients who take systemic ketoconazole or other potent CYP3A4 inhibitors systemically as concomitant medication. BID doses will be decreased to the corresponding once daily dose as follows:

- If dose is 20 mg BID, change dose to 20 mg **QD**
- If dose is 15 mg BID, change dose to 15 mg **QD**
- If dose is 10 mg BID, change dose to 10 mg **QD**
- If dose is 5 mg BID, change dose to 5 mg **QD**
- If dose is 5 mg QD, no dose change is required.

Potent inhibitors of CYP3A4 include systemic ketoconazole, clarithromycin, itraconazole, nefazodone and telithromycin. NOTE: once the course of therapy using a CYP3A4 inhibitor has been completed, the subject should resume his/her prior BID dose regimen of study drug beginning the next day.

10.3 **Dose Reductions for Hepatic Impairment**

Hepatic impairment will be classified by the NCI Organ Dysfunction Working Group criteria. Any hepatic dysfunction classified as moderate or severe will require the treating physician to hold study drug until two weeks after hepatic dysfunction can be classified as mild or normal by NCI criteria. Ruxolitinib may be restarted at 50% of the MTD. If moderate or severe hepatic impairment occur a second time in the same subject, ruxolitinib will be discontinued.

11 ADVERSE EVENTS: REPORTING REQUIREMENTS

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or serious adverse event (SAE).

To ensure patient safety, each SAE must be reported to the coordinating site and to Incyte (SafetyReporting@incyte.com) on the Incyte form provided within 24 hours of being made aware of the event. Moffitt Cancer Center and all participating sites will report SAEs by completing an SAE report in OnCore, the electronic data capture system. The SAE must be reported by email (affiliate.research@moffitt.org) to the External Site Coordination (ESC) office within 24 hrs. If applicable, the site should also follow protocol guidelines for additional reporting to government agencies.

11.1 Definition of an AE

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose per se will not be reported as an AE/SAE). "Lack of efficacy" or "failure of expected pharmacological action" per se within the duration of initial ruxolitinib treatment/exposure of 16 weeks will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

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

• Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.

• Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

• The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

• Death due to the disease being studied.

11.2 **Definition of an SAE**

A serious adverse event is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

NOTE: The term "life-threatening" the definition refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- Requires hospitalization or prolongation of existing hospitalization.

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in disability/incapacity

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may

interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- All treatment related grade 4 non-hematologic laboratory abnormalities assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.0.

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

11.3 Relationship to Investigational Product

It is a regulatory requirement for investigators to assess relationship to investigational product based on information available. The assessment should be reviewed on receipt of any new information and amended if necessary. “A reasonable possibility” is meant to convey that there are facts/evidence or arguments to suggest a causal relationship. Facts/evidence or arguments that may support “a reasonable possibility” include, e.g., a temporal relationship, a pharmacologically-predicted event, or positive dechallenge or rechallenge. Confounding factors, such as concomitant medication, a concurrent illness, or relevant medical history, should also be considered.

11.4 Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline should be recorded as per the NCI-CTC AE criteria. However, these laboratory results are to be recorded as AEs or SAEs if deemed clinically significant in the medical and scientific judgment of the

investigator or treating physician. Any clinically significant safety assessments that are associated with the underlying disease are **not** to be reported as AEs or SAEs, except for findings judged by the investigator or treating physician to be more severe than expected for the subject's condition or death. Data will be collected for typical disease-related events such as anemia, leukocytopenia or worsening of thrombocytopenia. All infections experienced during the study are to be recorded as AEs or SAEs.

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

During the study period, the following conditions will not qualify as an AE or SAE provided they are not considered attributable to study medication:

• Cases of disease progression.

11.6 Pregnancy

Any pregnancy that occurs during study participation must be reported. To ensure subject safety, each pregnancy must be reported to the FDA with CC notification to INCYTE SafetyReporting@incyte.com within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to the pharmacovigilance group at the H. Lee Moffitt Cancer Center. In addition, the investigator must attempt to collect pregnancy information on any female partners of male study patients who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to the H. Lee Moffitt Cancer Center as described above.

11.7 Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. AEs will be collected from the start of Investigational Product and through the follow-up contact. SAEs will be collected

over the same time period as stated above for AEs. However, any SAEs assessed **as related** to study participation (e.g., investigational product, protocol mandated procedures, invasive tests, or change in existing therapy) will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to INCYTE SafetyReporting@incyte.com within 24 hours, as indicated.

11.8 Prompt Reporting of Serious Adverse Events and Other Events to the FDA with notification to INCYTE

Any serious adverse events which occur during the clinical study or within 30 days of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the investigator. In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported. SAEs brought to the attention of the investigator at any time after cessation of ruxolitinib and considered by the investigator to be related or possibly related to ruxolitinib must be reported to FDA with notification to INCYTE SafetyReporing@incyte.com if and when they occur. Additionally, in order to fulfill international reporting obligations, SAEs that are related to study participation (e.g., procedures, invasive tests, change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until he/she is discharged.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours*	"SAE" data collection tool	24 hours*	Updated "SAE" data collection tool
Pregnancy	2 Weeks*	Pregnancy Notification Form	2 Weeks*	Pregnancy Follow-up Form

- From the time point when the SAE or pregnancy became known to reporter.

11.9 Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator to the FDA (and INCYTE SafetyReporting@incyte.com) is essential so that legal obligations and ethical responsibilities towards the safety of patients are met. The sponsor-investigator has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The sponsor-investigator will comply with specific regulatory requirements relating to safety reporting to the regulatory authority, /Institutional Review Board (IRB), the FDA, notification to INCYTE, and sub-investigators. Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and those policies set forth by the FDA and are forwarded to investigators and INCYTE as necessary. An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from the H. Lee Moffitt Cancer Center will file it with the CIB and will notify the IEC /IRB, if appropriate according to local requirements.

12 PHARMACEUTICAL INFORMATION

12.1 Packaging and Labeling

Ruxolitinib 5 mg tablets are packaged as 60 counts in high-density polyethylene (HDPE) bottles. The bottles will include labeling “New Drug - Limited by Federal (USA) Law to Investigational Use.

12.2 Preparation

Tablets will be provided to the site and no specific preparation of study medication is required prior to administration.

12.3 Handling and Storage

Investigational product must be dispensed or administered according to procedures described herein. Only patients enrolled in the study may receive investigational product, in accordance with all applicable regulatory requirements. Only authorized site staff may supply or administer investigational product. All investigational products must be stored in a secure area with access limited to the investigator and authorized site staff and under physical conditions that are consistent with investigational product-specific requirements. The bottles of tablets should be stored

at room temperature, 15°C to 30°C (59°F to 86°F). Any unused investigational product will be returned to INCYTE for destruction or destroyed at the institution per institutional policy (if allowable).

13 Study Calendar

All screening evaluations will be performed within 4 weeks prior to the start of ruxolitinib treatment. Patients must have a bone marrow biopsy and aspirate (including cytogenetics) performed within 4 weeks prior to the start of treatment. All transfusion and pre-transfusion Hgb or platelet count must be recorded for the 8 weeks prior to initiation of study treatment. Strict adherence to the visit schedule is required. In the event that a visit or test cannot be scheduled on the exact visit day, a window of ± 7 days is allowable. Bone marrow aspiration and biopsy exams can be done within a 14 day window of the allotted date.

13.1 **Baseline Assessment**: within 4 weeks of starting treatment

- Medical history including:
  - Disease characteristics such as date of diagnosis of CMML, WHO/FAB subtype, IPSS score, MD Anderson Scoring System (MDASC), prior treatments.
  - ECOG performance status.
- Concurrent medication review.
- Red blood cell and platelets transfusion past 8 weeks.
- Routine physical examination to include vital signs, height and weight.
- Bone marrow examination, including cytomorphology, cytogenetic assessment, and flow cytometry analysis. Possibly include NGS myeloid panel (it is not considered a deviation if cytogenetic, flow cytometry and NGS myeloid panel is not completed).
- Laboratory assessments:
  - Hematology to include platelet count, hemoglobin, hematocrit, white blood cells (WBC) and WBC differential (including: neutrophils, eosinophils,

basophils, lymphocytes and monocytes), INR, PT, and PTT and reticulocyte count.

- Clinical chemistries including BUN/urea, creatinine, chloride, sodium, potassium, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, bicarbonate, calcium, chloride, glucose, LDH, total protein, and albumin.
- Urine or serum pregnancy test for females of childbearing potential will be performed at Screening or on Day 1, prior to first dose study medication.

•Symptom Score using the Myeloproliferative Neoplasms Symptom Assessment Form (MPN-SAF). (See Appendix C).

• CT scan of the abdomen to evaluate spleen volume.

•Review and record any blood and blood supportive care products for the prior 8 weeks.

Re-screening

Bone marrow biopsy and CT scan of the abdomen may not need to be repeated for a re-screening process if they are completed within 3 months from the time of consenting on the study. Although, all the other procedures including labs, Myeloproliferative Neoplasms Symptom Assessments, research labs (research lab exclude aspirate) will be performed during the re-screening process within 4 weeks prior to the start of the study treatment.

Patient can be re-screened and start the first day of treatment on the same day if patient meets the eligibility criteria on the study.

13.2 **Treatment Period** (weeks 1-16):

13.2.1 Ruxolitinib will be administered as a twice daily oral dose for a 4-week treatment cycle. Patients will have a CBC with leukocyte differential performed weekly for the first 16 weeks. Serum chemistry will be performed weekly for first 4 weeks and then every 2 weeks through week 16. A BM aspirate and biopsy with cytogenetic analysis will be performed after cycle 2 and 4 (at the end of week8 and week16) to assess pathologic response, cytogenetic response and disease progression. For patients who achieve CR, marrow CR, or PR a confirmation bone marrow aspirate and biopsy should be obtained 4 to 8 weeks after documentation of CR, marrow CR, or PR.

13.3 **End of C4/ Week 16 Response Assessment:** Patients will complete a response assessment (see Section 14) within one week after their last administration of ruxolitinib. . Physical exam, vital signs, concomitant medication, adverse event reporting, CBC, CT scan of the abdomen, serum chemistry and BM aspirate and biopsy with cytogenetic analysis will be performed.

13.4 **Continuation Phase**: After completing cycle 4 response assessments, responders may continue to receive ruxolitinib and the final week 16 dose in the absence of DLT or disease progression. Bone marrow biopsy and aspirate will be

repeated after every 6 cycles (For patients who achieve CR, marrow CR, or PR a confirmation a one-time bone marrow aspirate and biopsy should be obtained 4 to 8 weeks after documentation of CR, marrow CR, or PR). A CBC will be obtained and complete metabolic profile as per standard of care. The End of Treatment assessment should be done within a week off treatment.

13.5 **End Of Treatment:** Patients discontinuing study early or any time after completing End of C4/Week 16 Response Assessment visit should complete their end of treatment visit within two weeks after their last dose of investigational product. Physical exam, vital signs, concomitant medication, adverse event reporting, CBC, CT scan of the abdomen, blood chemistry and BM aspirate and biopsy with cytogenetic analysis will be performed during the end of treatment visit. CT scan abdomen and BM aspirate and biopsy during EOT can be performed at the discretion of Coordinating Center PI.

13.6 **Off Treatment assessment**: includes best response achieved, date of first response, date of loss of response, reason for discontinuation.

13.7 **Off study evaluation**: include vital status, date of death/last contact, transformation to AML and the date of transformation to AML if applicable. This Evaluation will be updated every 6 month for 2 years.

Study Calendar	**Pre-Study**	**C1/ Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**C2/ Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**C3/ Wk 9**	**Wk 10**	**Wk 11**	**Wk 12**	**C4/ Wk 13**	**Wk 14**	**Wk 15**	**Wk 16**	**End of C4 Response Assessmnet**	**Biweekly (every 2 weeks, after End of C4 response assessmemt)**	**Continuation Phase- Every 4 weeks (if response)**	**Off-Study or EOT-**
Ruxolitinib Dispense[a]		X				X				X				X				X		Xa1	
Informed consent	X																				
Demographics	X																				
Medical history	X					X				X				X				X		X	X
Physical exam to include spleen assessment	X					X				X				X				X		X	X
Vital signs	X					X				X				X				X		X	X
Height[1]	X																				
Weight	X					X				X				X				X		X	X
Performance Status	X					X				X				X				X		X	X
Concurrent medication review	X																				
CBC w/diff, plts,	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Retic Count	X					X				X				X				X			
Serum chemistry[b]	X	X	X	X	X		X		X		X		X		X		X	X	X[b1]	X	X
INR, PT, and PTT	X																				
Adverse event evaluation		X ---------- Adverse events will be summarized and reported prior to each cycle. ---------- X																			
Bone marrow	X									X								X			

biopsy/aspirate[d] ***																					
B-HCG [c]	X																				
Lab. Correlates [e]	X					X				X				X				X			
Prior CMML Treatments	X																				
CT scan Abdomen[h]	X																	X			X
Transfusion Log	X					X				X				X				X		X	X
Response Assessments										X								X		X	X
Symptom Score Scale [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Off-treatment Assessment/Off -Study Follow-up/ CMML Summary Form																		X			X

a. Dose as assigned for cohort in phase 1, dose assigned as MTD in phase 2. Ruxolitinib dispensing will take place on day 1 of each 4 week cycle. Any lost study drug may be re-dispensed as needed.

b. Albumin, alkaline phosphatase, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, potassium, total protein, AST, ALT, sodium, and total bilirubin.

b1. Biweekly Serum chemistry is optional after the completion of End of C4 Response Assessment; however, it is mandatory to complete serum chemistry every cycle (monthly serum chemistry is required on the study protocol).

c. Serum or urine pregnancy test (if women of childbearing potential).

d. In addition to specimen required for pathologic review, and additional aspirate will be collected (goal volume of 30cc). BM biopsy will occur at screening, end of Week 8, and Week 16. Week 8 and Week 16 BM biopsies have a window of +/- 14 days. In the event patient has CR or PR see Section 13.2.1 for additional one time BM biopsy.

e. In addition to specimen required for routine labs, 6 green top vials, 1 red top vial.

f. The Myeloproliferative Neoplasms Symptom Assessment Form (MPN-SAF TSS) using ERT's DiaryPro done by the patient. Data upload and device maintenance will occur at each scheduled visit through Week 16. Patient cannot be enrolled on the study protocol without ERT's DiaryPro registration. No waiver on the ERT handheld device will be given in any circumstances.

g. BM aspirate and biopsy includes mutational panel should be performed every 6 cycles (window of +/- 14days) after completion of week 16 on the treatment.

h. CT scan abdomen may be completed with/without contrast.
i. Height is preferred to be recorded as a baseline; however, missing height during the screening process will not be a deviation on the study protocol.

*End of C4/ Week 16 Response Assessmnet and End of Treatment: Patients will complete a response assessment within one week after their last administration of ruxolitinib. Patients discontinuing study early should complete their end of treatment visit within two weeks after their last dose of investigational product. Physical exam, vital signs, concomitant medication, adverse event reporting, CBC, and serum chemistry and BM aspirate and biopsy with cytogenetic analysis will be performed.

**Continuation Phase: After completing cycle 4 response assessments, HI-platelet responders may continue to receive ruxolitinib and the final week 16 dose in the absence of DLT or disease progression. Bone marrow biopsy and aspirate will be repeated after every 6 cycles. A CBC will be obtained and complete metabolic profile as per standard of care.
The off treatment assessment should be done within a week off treatment.
For patients who achieve CR, marrow CR, or PR a confirmation bone marrow aspirate and biopsy should be obtained 4 to 8 weeks after documentation of CR, marrow CR, or PR.
***Off Treatment assessment: includes best response, date of first response, date of loss of response, reason for discontinuation.

****Off study follow up: include vital status, date of death/last contact, transformation to AML and the date of transformation to AML if applicable. This evaluation will be updated every 6 month for 2 years.

*****Myeloproliferative Neoplasms Symptom Assessment Form: The Myeloproliferative Neoplasms Symptom Assessment Form (MPN-SAF TSS) can be completed on paper in case an electronic assessment on ERT is not available on the day of screening and rescreening visits. In the event there is a discrepancy of MPN assessment score on paper and electronic assessment, the treating physician will determine which assessment will be used for eligibility purposes on the study.

*****All dates are entered into the database (Oncore) in +/- one week from the date of visit complete

****** During the pandemic or any contrary circumstances, monthly visits may me a zoom/virtual visit per Investigator discretion only after the completion of week 16 on the study protocol. However, patient have to complete all the safety labs and study-related procedures/tests on the study protocol. Any missed procedures will be a deviation excluding vital signs and physical exam.

14 MEASUREMENT OF EFFECT

Definitions:

Response and progression will be assessed according to modified International Working Group (IWG) MDS/MPN criteria (see section 14).

Complete Response (CR)

1. Bone Marrow:
    a. ≤5% myeloblasts and promonocytes
    b. ≤ grade 1 reticulin fibrosis
2. Peripheral Blood:
    a. WBC ≤ 10 x 10^9 cells/L
    b. Hgb ≥ 11g/dL
    c. Platelets ≥ 100 x 10^9 cells/L
    d. Blasts 0%
    e. Neutrophil precursors ≤ 2%
    f. Monocytes ≤ 1 x 10^9 cells/L
3. Extramedullary Disease
    a. Complete resolution of extramedullary disease present before therapy including palpable hepatosplenomegaly

Complete Cytogenetic Response

Resolution of previously present chromosomal abnormalities as seen on G band cytogenetics.

Partial Response

Normalization of peripheral counts and hepatosplenomegaly with bone marrow myeloblasts reduced by 50% but remaining >5% of cellularity except in cases of MDS/MPN with ≤ 5% bone marrow blasts at baseline

Marrow Response

Optimal marrow response: Presence of all CR marrow criteria without normalization of peripheral blood indices.

Partial marrow response: Bone marrow blasts reduced by 50% but remaining >5% of cellularity **or** reduction in grading of reticulin fibrosis from baseline on at least 2 bone marrow evaluations at least 2 months apart.

Clinical Benefit

Requires 1 of the following in the absence of progression or CR/partial response and independent of marrow response to be considered clinical benefit.

1. Erythroid Response: a)Hgb increase by ≥2.0 g/dL b)TI for ≥8 wk for patients requiring at least 4 packed red blood cell transfusions in the previous 8 wk
   Only red blood cell transfusions given based on physician's judgment for a pretreatment Hgb of ≤8.5 g/dL will count in the red blood cell TI response evaluation
2. Platelet response: a) Transfusion independence when previously requiring platelet transfusions of at least a rate of 4 platelet transfusions in the previous 8 wk. b) Pretreatment ≤20 3 10^9/L: increase from <20 x 10^9/L to >20 x10^9/L and by at least 100% c) Pretreatment >20 x 10^9/L but ≤ 100 x 10^9/L: absolute increase of ≥30 x

10^9/L

3. Neutrophil response: a) Pretreatment ≤0.5 x 10^9/L at least 100% increase and an absolute increase >0.5x 10^9/L b) Pretreatment > .0.5 x 10^9/L and ≤1.0 x 10^9/L. At least 50% increase and an absolute increase ≥0.5 x 10^9/L
4. Spleen response: A ≥ 35% reduction in spleen volume as measured by CT-scan from baseline at week 16.
5. Symptom response: Improvement in symptoms as noted by decrease of ≥50% as per the MPN-SAF TSS scoring in those with a MPN-SAF TSS≥17 (modified from original MDS/MPN-IWG).

Pathologic Response: Pathologic response is categorized as per the modified MDS/MPN IWG. Response parameters in the peripheral blood and/or bone marrow must be sustained for at least 4 weeks. See section 14.

Symptom Assessment in CMML

Symptoms of CMML will be assessed using the MPN-SAF TSS (see Appendix C). Patients will be issued a hand-held device (eDiary) on which to record symptoms of CMML. The subject will be instructed to complete the eDiary each night beginning on Day -4 or earlier of the screening phase (eg, 4 days prior to Cycle 1 Day 1) through treatment discontinuation. Patients will bring the device to the study site at each study visit so that the device charging can be verified and accumulated data can be downloaded, as applicable. The device will then be returned to the subject at these same visits for continued use each night. The subject will return the device and the docking station for the final time at the EOT visit so that the data can be archived. Detailed directions for the administration of the eDiary will be provided in the Study Reference Manual.

15 STATISTICAL CONSIDERATIONS

15.1 Study Design

This will be a two stage Simon's phase 2 design. After testing the treatment dose on 10 patients in the first stage, the trial will be terminated if 1 or fewer achieve a clinical benefit. If the trial goes on to the second stage, a total of 29 patients will be studied. If the total number responding is less than or equal to 5, the drug is rejected.

15.2 Sample Size/Accrual Rate

The Simon's optimal two-stage design will be employed to test the null hypothesis that response rate (RR) is less than 10% versus the alternative that RR greater or equal to 30%. If the treatment is actually not effective, there is a 0.05 probability of concluding that it is. If the drug is actually effective, there is a 0.19 probability of concluding that it is not. The probability of early terminating the trial at the end of first stage under the null is 0.74. After testing the treatment dose on 10 patients in the first stage, the trial will be terminated if 1 or fewer desired respond. If the trial goes on to the second stage, a total of 29 patients will be studied. If the total number responding is less than or equal to 5, the drug is rejected. A sample size of 29 from Phase 2 produces a two-sided 95% CI with a width equal to 0.38 (±19) when the sample proportion is 0.50 that is the maximum width for a CI with an given sample sizes.

15.3 Statistical Analysis Methods

Demographic and clinical variables for the study patients will be summarized using descriptive statistics (mean, standard deviation, median, inter-quartile range, range, and frequency counts and percentages). Safety and efficacy data will be analyzed overall as well as separately for each dose cohort when appropriate.

15.4 Safety Analysis

This analysis will include all patients who have received any protocol treatment, regardless of patient eligibility. The number (%) of patients with adverse events, serious adverse events, and adverse events leading to treatment discontinuation will be reported. Adverse events summary will be reported by type and severity. Laboratory parameters will also be summarized using descriptive statistics. The number and proportion of patients with DLTs will be summarized.

15.5 Efficacy Analysis: ITT

This analysis will include all patients who have received any protocol treatment, regardless of patient eligibility or duration of treatment. Those who have no response assessment data due to reasons such as drop out of the study, withdrawal consent, or lost to follow-up will be treated as non-responders for various response evaluations. The proportion of patients achieving a response will be

summarized. A 95% exact binomial confidence interval of the proportion will also be provided for all participants treated at the 20mg BID. In addition, a second analysis of evaluable patients will be performed. Evaluable patients are defined as those who complete at least 8 weeks of therapy and complete their first treatment bone marrow biopsy and aspirate to evaluate study drug response.

16 Laboratory Correlates

Unless otherwise specified, all laboratory correlates will be performed in the laboratory of Eric Padron.

H.LEE MOFFITT CANCER CENTER
CC: ERIC PADRON
STABILE RESEARCH BUILDING
SRB 23234
12902 MAGNOLIA DR TAMPA FL 33612

16.1 Sample Collection

At screening (see section 13.2) and weeks 5, 9, 13, and 17, 6 green tops and 1 red top vial will be collected. Designated study personnel will collect the sample from the laboratory draw area. Peripheral blood will be collected in 6 green top (hepranized) 10 ml tubes and 1 red top (clot activator or no additive) 10 ml tube for a total of seven tubes and 70cc of peripheral blood. At screening, week 8 and end of week 16 (see study calendar), bone marrow aspirate will be collected in three lavender (EDTA) 10 ml tubes or a 60 ml heparinized syringe for a total of 30cc. These will be shipped to the laboratory as directed above within 24hrs and will be processed using RBC lysis buffer to remove RBC and debris at the H. Lee Moffitt Cancer Center. They will be additionally processed by centrifugation (1700rpm for 20 minutes) with FICOLL to collect the mononuclear cellular layer. This layer will be cryopreserved as previously described and stored in liquid nitrogen for later use labeled with a unique identifier that corresponds to each patient known only to the investigator and study personnel. The red top samples will be processed by centrifugation and the supernatant (serum) collected and cryopreserved for later use labeled with a unique identifier that corresponds to each patient known only to the investigator and study personnel.

16.2 **Genomic Studies**

Using portion of cryopreserved bone marrow aspirates, 100ug of DNA will be isolated as previously described. Next, a comprehensive sequencing of patients by NextGen sequencing of JAK2, c-CBL, N-RAS, K-RAS, RUNX-1, TET2, SRSF2, EZH2, ASXL1, and DNMT3a will be done in with pretreatment samples and end of study **or** progression. The isolated DNA will be sent to the laboratory of Dr. Omar Abdel-Waheb located on the campus of Memorial Sloan Kettering Cancer Center. Dr Abdel-Waheb has is a nationally recognized expert in the genomics of myeloid malignancies and has sequenced many patients for this comprehensive panel of gene mutations.

17 REGULATORY CONSIDERATIONS

This research will be done in compliance with the applicable State and Federal laws and regulations and in compliance with ICH guidelines. The study description will be posted on the www.clinicaltrials.gov website in compliance with current regulations. The data and safety plan will be executed in accordance with ICH guidelines and in compliance with policy and procedures at the H. Lee Moffitt Cancer Center and Research Institute. The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

17.1 Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Patients (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

17.2 Use of Specimens For Research

The patient is free at any time in the future to decide not to provide specimens or to withdraw his/her specimens from further scientific research. Such a decision will have UnoU impact on his/her treatment or other aspects of participation in this study.

17.3 Institutional Review

This study must be approved by an appropriate institutional review committee as defined by

Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Patients (Code of Federal Regulations 45 CFR 46).

17.4 Drug Accountability

For each drug supplied for a study, an accountability ledger containing current and accurate inventory records covering receipt, dispensing, and the return of study drug supplies must be maintained. Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions. During the course of the study, the following information must be noted on the accountability ledger; the identification code of the subject to whom drug is dispensed, the date(s) and quantity of drug dispensed to the subject, and the date(s) and quantity of drug returned by the subject; patients should return empty containers to the investigator, with the return noted on the ledger. These Accountability Forms must be readily available for inspection and are open to FDA inspection at any time.

17.5 RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

17.6 Study Monitoring**:**

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain and have available for monitoring adequate case records (accurate source documents and CRFs) for the patients treated under this protocol. In addition, the Investigator agrees to maintain all administrative documents, eg, IRB/IEC correspondence, investigational product and supplies shipment manifests, monitoring logs, or Moffitt Cancer Center/designee correspondence. The PI will be primarily responsible for monitoring of adverse events, protocol violations, and other immediate protocol issues. The study coordinator will collect information of patients

enrolled at Moffitt and other institutions through the use of electronic or paper AE forms, CRF forms, End of Study forms, and Informed Consent forms.

Internal Monitoring

Data will be captured in Oncore, Moffitt's Clinical Trials Database. Regulatory documents and Case Report Forms will be reviewed/monitored internally by Moffitt's Internal Monitors, periodically, throughout the conduct of the trial. The monitoring will include source data verification, utilizing research patients' medical records.
It will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly to verify data is accurate, complete, and verifiable from source documents; and the conduct of the trial is in compliance with the currently approved protocol/amendments, Good Clinical Practice (GCP), and applicable regulatory requirements.
To obtain access to OnCore, the External Site Coordination (ESC) office Coordinator will supply forms required to be completed by the site staff. Once the completed forms are received, the site coordinator will receive DUO access, logon/password, and information on how to access OnCore. The ESC office will provide OnCore training to the site once initial access is granted and on an ongoing basis, as needed.

On-site Audits

The Investigator should promptly notify Moffitt Cancer Center or its authorized representative of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to Moffitt Cancer Center or its authorized representative.

Data & Safety Monitoring Plan

Identification of oversight responsibility:

The PI has primary responsibility.

The MCC Protocol Monitoring Committee (PMC);

The PMC meets monthly and reviews accrual, patterns and frequencies of all adverse events, protocol violations and when applicable, internal audit results.

Description of internal (PI) safety review and monitoring process:

Responsible for identifying and reviewing adverse events biweekly:

Principal Investigator

Study team

To be reviewed:

Adverse events by grade (Gr. 3 or above using CTCAE v4.0) and attribution (expected or unexpected)

Relationship to study drug/intervention

Application of dose finding escalation/de-escalation rules

Application of study designed stopping/decision rules

Whether the study accrual pattern warrants continuation/action

Protocol violations

AEs will be reported along with all other data in the Oncore database. The PI or PI designate will report all adverse events to the Clinical Research Office (CRO). The CRO will report all SAEs to INCYTE, and all reportable SAEs to the IRB. AE information will be entered into the CRO database. AE information will be managed by the CRO and will be made available to the PMC or appropriate monitoring body by designated members of the PMC or the study statisticians.

17.7 Registration Procedures:

All subjects must be registered with the External Site Coordination (ESC) office to be able to participate in a trial. The participating site must fax on 813-745-5666 or email the completed study specific eligibility checklist and registration forms, supporting documents and signed informed consent to the Coordinating Center. Unsigned or incomplete forms will be returned to the site. Once documents are received, the ESC Research Coordinator will review them to confirm eligibility and to complete the registration process. If eligibility cannot be confirmed, the research coordinator will query the site for clarification or additional documents as needed. Subjects failing to meet all study eligibility requirements will not be registered and will be unable to participate in the trial.

Upon completion of registration, the ESC Research Coordinator will provide the participating site with the study sequence number and randomization information, if

indicated. Within 24-48 hours after registration, it is the site's responsibility to:

- Enter the demographic and on-study patient information into the Oncore database.
- Order investigational agent(s) if indicated per protocol.

It is the responsibility of the participating Investigator or designee to inform the subject of the research treatment plan and to conduct the study in compliance with the protocol as agreed upon with Moffitt Cancer Center and approved by the site's IRB.

To register a patient send the completed signed eligibility checklist along with the patient registration form and supporting documentation to the ESC via email at affiliate.research@moffitt.org or via fax at 813-745-5666, Monday through Friday between 8:00AM and 5:00PM (EST).

Required Documentation

Before the study can be initiated at any site, the site will be required to provide regulatory documentation to the External Site Coordination (ESC) office at Moffitt Cancer Center. Sites must provide a copy of their informed consent to the ESC office for review and approval prior to submission of any documents to the site's IRB. Any changes requested by the site's IRB must be provided to the ESC staff for review and approval prior to resubmission to the IRB.

The ESC office must receive the following trial specific documents either by hardcopy, fax, or email before a site can be activated for any trial:

1. IRB Approval Letter that includes the protocol version and date
2. FDA Related Forms 1572/1571/310 as appropriate
3. Signed Protocol Title Page
4. IRB Approved Consent Form
5. Site Delegation of Authority Log
6. Signed Financial Interest Disclosure Forms (principal and sub investigators)
7. Updated Investigator/Personnel documents (CVs, licenses, GCP and HSP training certificates, etc.) as needed.
8. Updated Laboratory Documents (certifications, normal ranges, etc.) as needed.

9. Signed protocol specific Task Order

A study initiation teleconference will be held prior to the start of any study related activity at the site. Attendance is required for:

- The site PI and appropriate research staff
- Moffitt PI and ESC research coordinator

The requirements of the protocol and all associated procedures and processes will be reviewed and agreed upon prior to the activation of the study. The ESC utilizes the EDC system, OnCore. OnCore training will be scheduled, if indicated, with the appropriate staff from the site.

18. REFERENCES

1. Niyongere S, Lucas N, Sansil S, et al. Comprehensive Inflammatory Cytokine Profiling Identifies IL-8/CXCL8 As Elevated, Associated with Proliferative Features, and Independently Prognostic in Chronic Myelomonocytic Leukemia (CMML): Am Soc Hematology; 2016.
2. Emanuel PD. Juvenile myelomonocytic leukemia and chronic myelomonocytic leukemia. *Leukemia*. 2008;22(7):1335-1342.
3. Vardiman J, Harris N, Brunning R. The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood*. 2002;100(7):2292.
4. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood*. 2009;114(5):937-951.
5. Emanuel P, Bates L, Castleberry R, Gualtieri R, Zuckerman K. Selective hypersensitivity to granulocyte-macrophage colony-stimulating factor by juvenile chronic myeloid leukemia hematopoietic progenitors. *Blood*. 1991;77(5):925.
6. Kohlmann A, Grossmann V, Klein H-U, et al. Next-generation sequencing technology reveals a characteristic pattern of molecular mutations in 72.8% of chronic myelomonocytic leukemia by detecting frequent alterations in TET2, CBL, RAS, and RUNX1. *Journal of Clinical Oncology*. 2010;28(24):3858-3865.
7. Jankowska AM, Makishima H, Tiu RV, et al. Mutational spectrum analysis of chronic myelomonocytic leukemia includes genes associated with epigenetic regulation: UTX, EZH2, and DNMT3A. *Blood*. 2011;118(14):3932-3941.
8. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the acute leukaemias. French-American-British (FAB) co-operative group. *Br J Haematol*. 1976;33(4):451-458.
9. Fenaux P, Mufti G, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *The Lancet Oncology*.

2009;10(3):223-232.
10. Costa R, Abdulhaq H, Haq B, et al. Activity of azacitidine in chronic myelomonocytic leukemia. *Cancer*. 2010.
11. Rollison DE, Howlader N, Smith MT, et al. Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001-2004, using data from the NAACCR and SEER programs. *Blood*. 2008;112(1):45-52.
12. Lim Z, Brand R, Martino R, et al. Allogeneic Hematopoietic Stem-Cell Transplantation for Patients 50 Years or Older With Myelodysplastic Syndromes or Secondary Acute Myeloid Leukemia. *Journal of Clinical Oncology*. 2010;28(3):405-411.
13. Ramshaw H, Bardy P, Lee M. Chronic myelomonocytic leukemia requires granulocyte-macrophage colony-stimulating factor for growth in vitro and in vivo. *Experimental …*. 2002.
14. Kotecha N, Flores N, Irish J, et al. Single-cell profiling identifies aberrant STAT5 activation in myeloid malignancies with specific clinical and biologic correlates. *Cancer Cell*. 2008;14(4):335-343.
15. Padron E, Painter JS, Mailloux AW, et al. GM-CSF Signaling Abnormalities in Chronic Myelomonocytic Leukemia. *ASH Annual Meeting Abstracts*. 2011;118(21):1713-.
16. Quintas-Cardama A, Vaddi K, Liu P, et al. Preclinical characterization of the selective JAK1/2 inhibitor INCB018424: therapeutic implications for the treatment of myeloproliferative neoplasms. *Blood*. 2010;115(15):3109-3117.
17. INCYTE. Ruxolitinib Investigator's Broshure. 2012.
18. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med*. 2012;366(9):799-807.
19. Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med*. 2012;366(9):787-798.
20. Frankel AE, Lilly M, Kreitman R, et al. Diphtheria toxin fused to granulocyte-macrophage colony-stimulating factor is toxic to blasts from patients with juvenile myelomonocytic leukemia and chronic myelomonocytic leukemia. *Blood*. 1998;92(11):4279-4286.
21. Frankel A, Powell B, Hall P, Case L, Kreitman R. Phase I trial of a novel diphtheria toxin/granulocyte macrophage colony-stimulating factor fusion protein (DT388GMCSF) for refractory or relapsed acute myeloid leukemia. *Clinical cancer research*. 2002;8(5):1004.
22. Parganas E, Wang D, Stravopodis D, et al. Jak2 is essential for signaling through a variety of cytokine receptors. *Cell*. 1998;93(3):385-395.
23. Eghtedar A, Verstovsek S, Estrov Z, et al. Phase II study of the JAK kinase inhibitor ruxolitinib in patients with refractory leukemias, including post myeloproliferative neoplasms (MPN) acute myeloid leukemia (AML). *Blood*. 2012.
24. Padron E, Dezern A, Andrade-Campos M, et al. A Multi-Institution Phase 1 Trial of Ruxolitinib in Patients with Chronic Myelomonocytic Leukemia (CMML). *Clin Cancer Res*. 2016.

18 APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

19 APPENDIX B: CYP3A4 Strong Inhibitors

HIV Antivirals:
-indinavir
-boceprevir
-lopinavir/ritonavir
-ritonavir
-telaprevir
-nelfinavir
-saquinavir

Others:
-clarithromycin
-conivaptan
-grapefruit juice
-mibefradil
-posaconazole
-voriconazole
-itraconazole
-ketoconazole
-nefazodone
-telithromycin

* Dose reductions as in section 7 are required for strong inhibitors of the CYP3A4.

20 APPENDIX C: Myeloproliferative Neoplasms-Symptom Assesment Form (MPN-SAF)

The Myelofibrosis Symptom Assessment Form (MPN-SAF) Validation Survey.

Instructions: Please fill out all questions, as best able, until the STOP instruction toward the end of the packet.

Brief Fatigue Inventory ©

Instructions: Please fill out all questions, as best able, reflecting how these symptoms affected you over the **LAST WEEK** unless directed otherwise. Complete forms until the STOP instruction toward the end of the packet.

Symptom	1 to 10 (0 if absent) ranking* 1 is most favorable and 10 least favorable
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your	
• General activity	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
• Mood	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
• Walking ability	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
• Normal work (includes work both outside the home and daily chores)	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
• Relations with other people	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
• Enjoyment of life	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)

© MD Anderson Cancer Center

Figure 1.The Myelofibrosis Symptom Assessment Form (MPN-SAF) Validation Survey.

Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) ©

Circle the one number that describes how, during the past Week how much difficulty you have had with each of the following symptoms	
Filling up quickly when you eat (Early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal pain	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with headaches	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration - Compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Dizziness/ Vertigo/ Lightheadedness	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Numbness/ Tingling (in my hands and feet)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Difficulty sleeping	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Depression or sad mood	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with sexual desire or Function	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Cough	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
What is your overall quality of life?	(As good as it can be) 0 1 2 3 4 5 6 7 8 9 10 (As bad as it can be)

21 APPENDIX D: WHO CLASSIFICATION FOR CMML

WHO Subtype	Peripheral Blood	Bone Marrow
Chronic Myelomonocytic Leukemia *CMML-0 *CMML-1 ***CMML-2	*<2 percent blasts **<5 percent blasts ***5-19 percent blasts persistant monocytosis >1000/ul +/- cytopenias Leukocytosis frequent	*<5% myeloblasts **<5-9% myeloblast ***10-19% blasts >10% dysplasia in affected lineage ***Auer Rods The absence of the Philadelphia chromosome of bcr-abl fusion gene.