THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Pacritinib Prior to Transplant for Patients with Myeloproliferative Neoplasms (MPN) 2014-0786

Core Protocol Information

Short Title	Pacritinib before transplant for MPN
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Which Committee will review this protocol?

(●) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

Primary Objective:
To compare the progression-free survival of adding Pacritinib prior to standard of care allogeneic stem cell transplantation (SOC Allo TP) conditioning with Fludarabine and Busulfan AUC of 4000 microMol-min per day to historical controls in patients with myelofibrosis.

Secondary Objectives:
To evaluate safety and efficacy of this therapy as determined by:

1.1 Neutrophil and platelet engraftment.
1.2 Non-relapse mortality at one year post transplant.
1.3 Overall survival at one year post transplant.
1.4 Liver and spleen response to Pacritinib.
1.5 Immune recovery.
1.6 Quality of life and symptom score.
1.7 Primary and secondary graft failure.
1.8 Complete remission.
1.9 Relapse.

To evaluate the use of marrow specific quantitative MRI (qMRI) sequences in assessment of disease burden, including:

1.10 Diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADP) maps
1.11 Marrow fat quantification sequences

2.0 Background

2.1. Overview of the myeloproliferative disorders:
The myeloproliferative disorders (MPD) are chronic hematological malignancies originating at the level of pluripotent hematopoietic stem cells.[1,2] The discovery that JAK2 mutations are found in virtually all patients with PV and approximately 50 percent of those with either ET or PMF, has refined current diagnostic criteria in classic MPN

- Polycythemia vera (PV) is considered to be present when an otherwise unexplained increased hematocrit/red blood cell mass is accompanied by the presence of a JAK2 mutation along with a decreased erythropoietin level

- Primary myelofibrosis (agnogenic myeloid metaplasia, chronic idiopathic myelofibrosis) is characterized by the presence of bone marrow fibrosis that cannot be attributed to another myeloid disorder such as CML, PV, ET, or MDS.

- Essential thrombocythemia (ET) is a diagnosis of exclusion, representing clonal or autonomous thrombocytosis not classifiable as PV, PMF, CML, or MDS.

<u>The concepts common to these disorders are:</u>

1) Clonal hematopoiesis
2) Transformation to acute leukemia (AL): Up to 10% of PV & ET patients develop AL.

3) Progression to myelofibrosis: Up to 10% of patients with ET and PV progress to myelofibrosis with development of massive hepatosplenomegaly, cytopenias and transfusion dependency. Patients who have progressed to myelofibrosis and/or to acute leukemia have a poor prognosis.

2.2. Idiopathic Myelofibrosis:
Idiopathic myelofibrosis (IM) (agnogenic myeloid metaplasia, myelofibrosis with myeloid metaplasia) is a clonal myeloproliferative disorder due to an acquired somatic mutation of a hematopoietic progenitor cell, resulting in clonal erythrocytes, platelets, granulocytes, monocytes and their precursors. These malignant megakaryocytes and monocytes secrete fibrogenic cytokines – TGF, PDGF, FGF, which cause polyclonal fibroblast proliferation, collagen and reticulin deposition, and eventual bone marrow fibrosis, the hallmark of the disease. This process progresses to bone marrow failure and extramedullary hematopoiesis.[1,3,4]

The annual incidence of IM ranges from 0.5 –1.5 per 100,000, while the median age at diagnosis is 55-65 years. Most patients with IF present with anemia, marked splenomegaly, early satiety and constitutional symptoms. During the clinical course, most experience progressive anemia requiring frequent blood transfusions, and death occurs eventually due to bone marrow failure or leukemic transformation. Current treatment of IM is palliative, consisting of supportive care with blood transfusions, splenectomy 5, splenic radiation, hydroxyurea, and more recently thalidomide.[6-9] None of these therapies alters the natural history of this disease.

The median survival is 6.5 years from diagnosis[10], but varies from 2 years to greater than 10 years depending on presence or absence of well-defined prognostic indicators. A simple but widely accepted scoring system using two of these factors, namely Hb <10 gm/dl and WBC >30,000/l or <4,000/l separates patients into three groups with low (0 factor), intermediate (1 factor), and high (2 factors) risks, associated with a median survival of 93, 26, and 13 months. A more recent study that included anemia (Hb < 10 gm/dl), advanced age (> 64), constitutional symptoms (fever, night sweats, weight loss), leukocytosis (>25,000/l), circulating blasts (≥ 1%), thrombocytopenia, need for blood transfusion and high-risk cytogenetic abnormalities outlines 4 prognostic group with a median survival of 185, 78, 35, and 16 months respectively.[4,11-13] Stem cell transplantation is an appropriate option for later two groups. Molecular studies have shown that mutations are present in 31 - 44% patients with myelofibrosis in *ASXL1, EZH2, SRSF2, IDH 1 and 2*, genes. These also have prognostic value independent of International prognostic scoring system with a median survival of 2.6, 7.0, and 12.3 years of 2 or more mutations, 1 mutation, and no mutation in these 5 genes again identifying a poor prognostic subgroup suitable for stem cell transplantation.[14,15]

2.3. Allogeneic stem cell transplantation:
Allogeneic hematopoietic cell transplantation by eradicating the malignant clone and restoring normal hematopoiesis is expected to alter the natural history of IM.

Table 1: Allogeneic Transplantation for Myelofibrosis.

Study	N	Median Age	NRM	Median Follow up	OS
Guardiola et al[16]	55	42	27%	36 months	47%
Bacigalupo et al[17]	46	51	24%	44 months	45%
Robin et al[18]	147	53	39%	35 months	39%
Patriarca et al[19]	100	49	43%	34 months	42%

Balen et al[20]	289	47	35%/50%	41/46 months	37%/30%
Lussana et al[21]	250	56	28%	13 months	55%*
Kroger et al[22]	103	55	16%	33 months	67%
Ditschkowsk[23]	76	45	36%	55 months	53%
Scott[24]	170	51	34%	5.9 years	57%
Gupta[25]	233	55	24%	50 months	47%
Rondelli et al[26]	66	54	22%/59%	24/12 months	75%/32%
Popat et al[27]	46	59	13%	25 months	69%

*outcomes for related and unrelated donors respectively, NRM non-relapse mortality, OS overall survival

Due to the uncommon occurrence of this disease and older age at disease onset, majority of studies are small and those that included more than 40 patients are summarized in Table 1.[16,28-31]

Transplantation in patients with myelofibrosis is a challenging task. Extramedullary hematopoiesis results in massive hepatosplenomegaly and impaired organ function, making these patients particularly at high risk of graft rejection and treatment related mortality. A special problem area is the treatment of older or debilitated patients. Guardiola published a series of 55 patients demonstrating inferior results for older patients: Five year survival of 14% in patients older than 45 years compared to the 5 year survival of 62% in younger patients[16]. These inferior results in older patients and patients with comorbidity who comprise majority of patients with this disease make myeloablative transplantation a promising but not suitable therapy for most patients with myelofibrosis. Best results of myeloablative transplant using mainly Busulfan and cyclophosphamide regimen in patients with median age of 51 show NRM of 38% and OS of 57%.[24]

Another approach would be to use a reduced intensity or a nonmyeloablative conditioning regimen, which have been reported to extend allogeneic transplant to older patients and patients with other co-morbid medical conditions. We, and others, have shown that reduced intensity stem cell transplantation can be safely utilized in older patients and those with comorbidities in other hematological malignancies.[32-37] Rondelli et al and Kroger et al have reported encouraging data in multi-institutional small studies of reduced intensity transplantation in older patients with myelofibrosis.[30,31] In these retrospective studies with a median age of 54 years, a non-relapse mortality of 10% - 16% and 3 year overall survival of 84% - 85% was reported. Based on these data multiple centers studied reduced intensity allogeneic transplantation in myelofibrosis. Recent analysis of worldwide experience reported to CIBMTR registry showed NRM of 24% and OS of 47%[25]. Outcome was significantly inferior with unrelated donor. Similarly high NRM of 53% was reported with unrelated donors in a prospective study done by MPD research consortium.[38] Best results to date with reduced intensity regimen were reported by Kroger et al. NRM was 16% and OS 67% with Busulfan and Fludarabine regimen; however 17% of patients had low risk disease and hence expected to have better outcome. Moreover, 13% of patients needed stem cell boost for graft failure or weak graft or declining chimerism.[31]

2.4 Allogeneic transplantation for Myelofibrosis: M D Anderson data:

At MDACC based on encouraging early data,[30,31] we did a prospective study to evaluate the role of allogeneic stem cell transplantation using reduced intensity conditioning regimen of

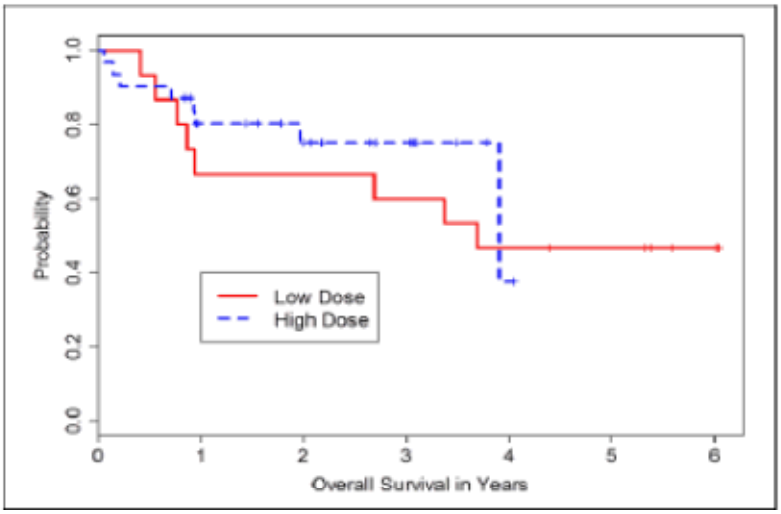
Fludarabine and Busulfan in patients with myelofibrosis (2005-0726). We used the regimen that we were using at that time for chronic myeloid leukemia.[39] The regimen was well tolerated with very low NRM of 15% even with unrelated donors in contrast to NRM of up to 50% seen in some studies. However, the relapse rate was high in the initial cohort of 15 patients. We therefore increased the intensity of conditioning regimen for subsequent patients, giving a higher dose of Busulfan after pharmacokinetic analysis. We hypothesized that increased dose intensity delivered with PK guidance will reduce relapse rate without increasing non-relapse mortality (NRM), thereby improving overall outcome.[27]

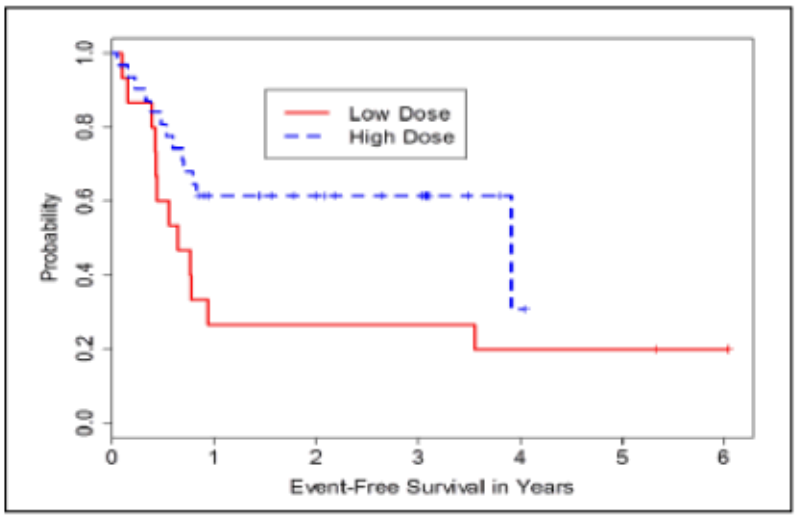
23 males and 23 females with a median age of 58 years (27-74) were enrolled. They had intermediate (25) or high-risk (21) disease. Median peripheral blood CD 34 count was 52/μl (range 1-16430/μl). Donors were matched sibs (19), matched unrelated (23), or mismatched unrelated (4). With a median follow up of 2.1 years (range 0.1-6 years), 3 year overall survival(OS), event-free survival (EFS), cumulative incidence (CI) of non-relapse mortality (NRM), and CI of relapse were 69%, 50%, 13%, and 37%, respectively. Multivariate Cox regression analysis showed that Bu-high dose (HR 0.41; p=0.04) and peripheral blood CD 34 count (HR 1.7; p=0.03) were significantly associated with EFS, and high CD-34 count was significantly associated with OS (HR 1.87; p=0.04). Table 2 shows details of 3 year outcomes of low dose and high dose group (Figure 1).

Table 2

@ 3 years	Bu-High (N=31)	B-Low (N=15)
Overall Survival	75%	60%
Event Free Survival	61%	27%
CI of Relapse	29%	53%
CI of NRM	10%	20%

Figure 1





For this protocol, therefore we will use this regimen of PK guided Busulfan (daily AUC 4000 µMol.min) and Fludarabine. We will compare the results of our current study with this historic cohort.

Major impediments to stem cell transplant in myelofibrosis:

Myelofibrosis results in extramedullary hematopoiesis, massive hepatosplenomegaly and fibrosis in the marrow and there are several major issues unique to it from transplant perspective. These include high incidence of graft failure and weak graft after transplant necessitating use of stem cell boost[22] and organ dysfunction - particularly involving liver - leading to a high incidence of veno-occlusive disease and non-relapse mortality.[40] A safe agent that can reduce organomegaly and disease burden pretransplant may improve transplant outcome by improving engraftment, reducing organ toxicity and lowering relapse risk. Furthermore, it may allow more patients to become eligible for transplant by improving their performance status. A Jak 2 inhibitor might be the answer.

Jak 2 inhibitors and stem cell transplantation:

Discovery of Jak2 V617F mutation, which makes kinase constitutionally active in patients with myeloproliferative disorders led to development several targeted agents including Pacritinib to inhibit this pathway. Jak 2 is mutated in up 60% of patients with ET and MF and 98% of patients with PV.[41-43] Even in patients without this mutation, this pathway is overactive. Ruxolitinib, a Jak2 inhibitor, is licensed by FDA for MF reduces splenomegaly, improves constitutional symptoms, and improves survival[44,45] both in patients with and without Jak 2 V617F. Early data on its usage pre-transplant are conflicting[22,46 47] with excellent outcome reported in some studies, but a possible higher complication rate reported in other study. This later study presented as an abstract is difficult to interpret, because complications reported are hard to differentiate from usual complications seen post-transplant. Pacritinib causes less myelosuppression than Ruxolitinib and may be superior to ruxolitinib as a pre-transplant agent to reduce organomegaly and to reduce the disease burden.

Pacritinib:

Pacritinib, a Jak2/Flt 3 inhibitor, has activity in myeloid and lymphoid malignancies. Currently it is in Phase 3 studies in patients with myelofibrosis. Details of this molecule are in the attached investigator brochure and a brief summary follows. It is a potent selective inhibitor of mutant as well as normal Jak2 kinase. Preclinical studies showed its activity in suppressing Jak 2 mediated tumors. PK studies in clinical trials showed slow absorption (Tmax 4-6 hours) and dose related increase in systemic exposure up to 400 mg per day. Terminal elimination half-life was 47 hours. Food did not impair absorption. At 100 mg/day dose steady state levels exceeded IC50 values for inhibition of Jak2/Flt3 kinase. Phase I studies identified 400 mg daily as dose for further studies. Dose limiting toxicity included grade 3 QTc prolongation, grade 3 diarrhea and grade 2 dizziness and blurred vision. Most common adverse events occurring in more than 20% were diarrhea, nausea, vomiting, constipation, dyspnea, fatigue and edema. Most events were mild to moderate severity. Only grade 3 or higher adverse event occurring in more than 10% of patients were anemia or thrombocytopenia (16%). MRI showed ≥ 25% spleen volume reduction in 55% of patients. An improvement in all symptoms relevant to myelofibrosis was seen. Thus, Pacritinib is very safe and highly effective therapy for patients with myelofibrosis and we would like study its role pre-transplant to improve transplant outcomes.

Correlative Research Studies (optional):

To evaluate the effect of the JAK2 inhibitor Pacritinib on immune recovery and graft-versus-host disease post-transplant

Janus kinase-2 (JAK2) conveys receptor-binding signals by several inflammatory cytokines, via phosphorylation of STAT3. Selective inhibition of JAK2 was shown to induce tolerance to allo-antigens, while preserving de novo responses to pathogens 48. Selective JAK2 inhibition was also shown to preserve Treg numbers through preservation of the IL-15/JAK3/pSTAT5 pathway.

Signaling through IFNγ-receptor, mediated by JAK1/JAK2 and STAT1, has been shown to result in increased surface expression of CXCR3, a key chemokine receptor involved in T-cell trafficking to sites of inflammation. A recent study in a murine model of GVHD, showed that pharmacologic inhibition of IFNγR signaling with inhibitors of JAK1/JAK2 resulted in decreased expression of CXCR3 associated with reduced GVHD, mediated by altered trafficking of effector T cells to GVHD target organs,[49] providing another mechanism through which selective JAK2 inhibition could influence GVHD.

We *hypothesize* that the Jak 2 inhibitor, Pacritinib will reduce the risk of GVHD in patients with myelofibrosis undergoing allogeneic stem cell transplantation, resulting in improved survival.

To test this hypothesis we propose the following aims:

Aim 1: To determine how Pacritinib affects the balance of Treg/Th1/Th2/Th17 cells. T cells collected at multiple time points before and during therapy (as outlined below) will be activated via CD3/TCR and CD28 ligation and differentiated according to their cytokine profile into Th1 (CD4+IFN-γ+), Th2 (CD4+IL-4+), Th17 (CD4+IL-17+) and Tr1 (CD4+IL-10+). Naturally occurring Tregs will be defined as CD4+CD25hiFoxp3+CD127lo.

Aim 2: To determine how Pacritinib influences the expression of chemokine receptors on the surface of T cells, including CXCR2, CXCR3, CXCR4, CXCR5, CCR3, CCR4, CCR5, CCR6,

CCR7, and CCR9

Aim 3: To determine how Pacritinib influences the pathogen-specific immune responses.

We will conduct analyses of T cell phenotype, estimate antigen-specific T cell precursor frequencies (by intracellular cytokine flow cytometry and peptide/dextramer staining) and determine antigen-specific cytokine production capacity (cytokine bead array assay). We will perform:

1) Immunophenotypic recovery of naive, stem-like memory, central and effector memory CD4+ and CD8+ T cells, using a 10 color flow cytometry panel (CD3, CD4, CD8, CD45RA, CD45RO, CCR7, CD62L, CD95, IL-7Rα, IL-2Rα);

2) The number and function of recovering CMV, T cells capable of responding functionally to in vitro stimulation with overlapping pools of peptide by intracellular cytokine detection.[3,5,6]

Aim 4: To determine how Pacritinib influences the phenotype and function of dendritic cells (DCs).

We will characterize DC subsets in PB collected at multiple time points before and during therapy (as outlined below) by:

1) Analysis of DC subsets, myeloid/plasmacytoid and immature/mature, based on expression of CD3, CD4, CD14, CD123, CD11c, CD1a, CD1c and CD141;

2) Determining the expression of DC co-stimulatory molecules involved in APC function (HLA-DR, CD80, CD83, and CD86) and chemokine receptors involved in DC homing (CCR4, CCR5, CXCR3, CCR10).

Serum samples collected from patients will be assayed for cytokine levels using the BD Cytometric Bead Array for Th1/Th2 cytokines (IL-2, IL-4, IL-5, IL-6, IL-10, TNF, IFN-γ) and for inflammation (IL-8, IL-1β, IL-6, IL-10, TNF, IL-12p70).

3.0 Patient Eligibility

Inclusion Criteria:

1. Patients with Idiopathic Myelofibrosis or Myelofibrosis secondary to Polycythemia Vera or Essential Thrombocythemia.
2. Patients 18 to less than or equal to 70 years.
3. Patients wanting to pursue transplant.
4. Patients must have a Zubrod PS equal or less than 2.
5. Calculated creatinine clearance greater than 50ml/min. using the Cockcroft-Gault equation.
6. Ejection fraction equal or above 40%.
7. Serum direct bilirubin less than 1 mg/dl (unless due to Gilbert's syndrome or hemolysis).
8. SGPT equal or less than 4 x normal values.
9. Corrected DLCO equal or above 50% of expected.
10. Negative Beta HCG test in a woman with childbearing potential defined as not post-menopausal for 12 months or no previous surgical sterilization) and if fertile, males and females must agree to use contraceptives.

Exclusion Criteria:

1. Patients with low risk myelofibrosis (Appendix J:DIPSS plus criteria).
2. Uncontrolled life-threatening infections.
3. HIV positive.
4. Patients with active viral hepatitis.
5. Prior treatment with Pacritinib.
6. Prior stem cell transplant.
7. QTc greater than 450 ms.
8. CYP3A4 strong or moderate inhibitors/inducers in the past 7 days.

4.0 Treatment Plan

4.1 <u>The investigational agent for this study is Pacritinib.</u>

4.1.1 Patients will start Pacritinib 200 mg po bid.

4.1.2 Patients can proceed to transplant after 60 days of starting Pacritinib but not more than 180 days.

4.1.3 Pacritinib will be stopped 21 days prior to starting preparative regimen for SOC Allo TP.

4.1.4 If for whatever reason a patient cannot pursue or receive SOC Allo TP, they will be able to continue treatment with Pacritinib until there is evidence of disease progression.

4.1.5 A patient will still be able to proceed to SOC ALLO TP if for any reason they cannot complete 60 days of treatment prior to transplant.

4.1.6 If a patient vomits or misses a dose, will continue treatment with the next scheduled dose. Missed doses and reason for non-compliance will be recorded.

4.1.7 Every effort should be made to avoid CYP3A4 inducers or inhibitors (see Appendix H) while patients are on pacritinib. If concomitant therapy with CYPsA4 inhibitors or inducers is medically necessary and there are no available or suitable substitutes, this should be documented in the patient's medical record and extreme caution taken with their continued use during the study duration.

4.1.8 Patients will document compliance of taking medication on a patient diary.

4.2 <u>Treatment Interruption:</u>

Safety parameters including AEs, hematology, and serum chemistry will be monitored according to the protocol. Pacritinib treatment may be withheld for up to 4 weeks due to drug-related toxicities. A longer recovery period may be allowed based on the toxicity, but must be agreed upon between the investigator and medical monitor. After treatment interruption, patients may resume the pacritinib treatment at the same dose level or at a reduced dose level. No dose re-escalation is allowed.

4.3 <u>Pacritinib Dose Management Guidelines for Pacritinib-Related Nonhematologic Toxicities:</u>

4.3.1 A maximum of 2 dose reductions is allowed. The first dose reduction will be a 100 mg reduction from the original dose. The dose will be reduced to 200 mg Q AM and 100 mg Q PM.

4.3.2 The second dose reduction will be another 100 mg reduction and the dose will be reduced to 100 mg BID.

4.3.3 Once the dose is reduced, no re-escalation is allowed.

4.3.4 Dose management for nonhematologic toxicities is summarized in Table 3.

Table 3 Treatment Toxicity and Dose Management: Pacritinib-Related Nonhematologic Toxicities	
CTCAE Toxicity Grade	**Management/ Action**
1 or 2	No change.
3	▪ Hold treatment. ▪ If the toxicity resolves to grade ≤ 1 or to the baseline grade within 7 days, treatment may be resumed at the same level or the next lower dose, at the discretion of the investigator after discussion with the sponsor. ▪ Toxicity that does not resolve to grade ≤ 1 or to the baseline grade within 7 days requires dose reduction to the next lower dose level.
4	▪ Hold treatment. ▪ If the toxicity resolves to grade ≤ 1 or to the baseline grade within 7 days, treatment may be resumed, but dose will be reduced by one dose level from the level at which the toxicity was observed. ▪ If grade 4 toxicity occurs at the lowest dose of 200 mg/day, the patient should be discontinued from the study.

4.3.6 The lowest dose of pacritinib used in the study will be 200 mg/day. If toxicity persists despite dose reduction to 200 mg/day, the patient should be discontinued from treatment.

4.4 <u>Dose Management Guidelines for Hematologic Toxicities:</u>

4.4.1 Myelosuppression is an expected event in patients with MF. However, myelosuppression with associated complications such as fever, infection, or bleeding or myelosuppression that worsens during treatment (based on local laboratory values) must be reported as an AE.

4.4.2 Patients with myelosuppression may receive supportive care including transient use of granulocyte colony stimulating factor for the treatment of febrile neutropenia and transfusion as clinically indicated.

4.4.3 Patients receiving pacritinib are not allowed to receive hematopoietic growth factors such as erythropoietin for the treatment of anemia.

4.4.4 Patients with clinically significant worsening of myelosuppression (as judged by the investigator and based on local laboratory values) for more than 7 days or myelosuppression associated with infection or bleeding should have pacritinib dosing interrupted. Pacritinib may be restarted at a reduced dose once the toxicity has resolved to grade ≤ 2 or to the baseline grade and the complications of myelosuppression such as infection or hemorrhage have resolved.

4.5 <u>Allogeneic graft</u>:

Peripheral blood (PB) or bone marrow (BM) progenitor cells may be used in this study peripheral blood will be preferred.

4.6 <u>Preparative Regimen</u>:

SOC transplant conditioning with Fludarabine and Busulfan AUC of 4000 microMol-min per day providing that pharmacokinetic can be done, otherwise Busulfan dose will be given as a fixed dose of 100 mg/m^2 daily for four days. A SOC treatment plan and informed consent will be used for this.

4.7 GVHD Prophylaxis and Supportive Care as per standard practice in patients receiving allogeneic transplant:

Recipients of matched related and unrelated donors will receive tacrolimus and Mini Methotrexate as per institutional standard.

Recipients of matched or one antigen mismatched unrelated donors will receive anti thymocyte globulin (ATG) tacrolimus and Mini Methotrexate as per institutional standard. Patients who do not have a suitable related or unrelated donor and who are going to undergo transplant from a haploidentical donor will come off study.

4.8 Data Confidentiality Plan

Patients registered in this protocol will be de-identified by using a unique identifier number that is automatically generated in BMTWeb, linkage to patient sensitive information is not possible outside BMTWeb.

Access to the database is only available to individuals within the department and with authorize access. Data gathered for this study will not be reused or disclosed to any other person or entity, or for other research.

5.0 Evaluation During Study

5.1 Disease Assessment Prior to Start of Pacritinib (baseline):

a) Patient medical history and physical examination including measurement of liver and spleen size by physical examination or imaging (MRI or CT or ultrasound if possible) with addition of marrow-specific MRI sequences.
b) CBC, differential and platelet count
c) Bone marrow aspiration and biopsy
d) Chemistry panel
e) Serology for CMV, HBV, HCV and HIV
f) B-HCG in women of childbearing potential
g) 2 D echo, EKG
i) Pulmonary function tests with DLCO
j) Chest x-ray
k) MF symptoms questionnaire (Appendix D.)
l) Fact BMT questionnaire (Appendix E.)
m) Blood for immunological profile if patient agrees to consent to optional study.

5.2 Follow up each month while on Pacritinib:

Patients will come to MDACC once each month to pick-up the next month's Pacritinib and have the following done. The monthly visits will continue as long as patient is taking Pacritinib.

a) Medical history and physical examination
b) CBC, differential and platelet count
c) Chemistry panel
d) EKG

Cycle 1 only: Day 14 (+/- 2 days) CBC, differential and platelet count and chemistry panel. These can be drawn locally and results sent to MDACC. The PI/treating physician must review outside lab results, determine clinical significance, sign and date the outside lab results.

Cycle 1 only: During week 2, study personnel will call patient about any new symptoms.

Patients treated on this protocol may require supportive care treatment (concomitant medications). These medications are considered standard of care and have no scientific contribution to the protocol; therefore no data will be captured on various medications needed or their side effects.

5.3 Within about 7 days after completion of Pacritinib (but before transplant):

1) Physical examination including measurement of liver and spleen size by physical examination or imaging (MRI or CT or ultrasound if possible).
2) EKG
3) Bone marrow aspiration and biopsy

5.4 Post-transplant Evaluations:

5.4.1 Post-transplant evaluations will follow our standard practice and are done to monitor engraftment and disease status.

5.4.2 Additional post-transplant follow-up specific to this study at approximately 1, 3, 6, and 12 months post-transplant:

1) At around 3 months:
    a) Measurement of liver and spleen size by physical examination or imaging (MRI or CT or ultrasound if possible).
    b) Bone marrow aspiration and biopsy

   At around 12 months:
    a) Repeat measurement of liver and spleen size, if liver and spleen were still enlarged at 3 months post-transplant.
    b) Bone marrow biopsy aspiration and biopsy
2) Blood for immunological profile if patient agrees to consent to optional study.
3) MF symptoms questionnaire (Appendix D.)
4) Fact BMT questionnaire (Appendix E.)
5) Participant Follow-up Assessment questionnaire (Global Impression of Change Scale, Appendix F.)

5.5 Correlative Research Studies (Optional):

60 cc of blood (5 green top tubes and 1 purple top tube) will be collected before the first dose of pacritinib, after the last dose of pacritinib (before transplant), and at approximately 1, 3, 6, and 12 months post-transplant.

This research blood will be sent to Dr. Katy Rezvani's laboratory at MD Anderson. Studies to be conducted are described in Section 2.4.

6.0 Statistical Considerations

General

This will be a single-arm, Phase II study of pacritinib, fludarabine, and busulfan as a preparative

regimen in allogeneic stem cell transplantation in patients with myelofibrosis. The primary endpoint is progression-free survival (PFS) in patients undergoing matched related or at least 7/8 matched unrelated donor transplant. We will enroll at least 21 evaluable patients, defined as patients who undergo transplant with a matched related or at least 7/8 matched unrelated donor. Patients who do not have a suitable related or unrelated donor will come off study and may receive a transplant from a haploidentical donor. For this reason and because some patients may decide not to undergo transplant after starting the drug, we may need to enroll up to 40 patients to ensure that 21 are evaluable for our primary endpoint.

Endpoints

6.1 Primary End Point (Progression-Free Survival):

Progression-free survival is defined as the time of stem-cell transplant to the time of death or disease progression.

6.2 Secondary End Points:

Neutrophil Engraftment is defined as a sustained ANC $\geq$ 0.5 x 10^9/L for 3 consecutive days and evidence of donor chimerism by D+28 (the first chimerism study will be done 3-4 weeks post-transplant).

Platelet Engraftment is defined as a sustained first of three consecutive laboratory values of platelet ≥ 20x109/L with no platelet transfusions administered for 7 consecutive days.

Non-relapse mortality is defined as death without disease progression.

Liver response will be defined by the change in the size of the liver measured below the coastal margin in the mid-clavicular line by palpitation.

Spleen response will be defined by the change in the size of the spleen measured below the coastal margin in the mid-clavicular line by palpitation.

Quality of life will be measured by the QOL FACT BMT.

Symptom score will be measured by the MPD symptom score.

Immune recovery will be measured by various cell subsets and cytokine levels.

Primary Graft Failure is defined as failure to achieve an ANC $\geq$ 0.5 x 10^9/L for 3 consecutive days by day 28, with <10% cellularity on bone marrow biopsy and no evidence of donor chimerism.

Secondary graft failure is defined as a sustained declined of ANC <0.5 x 10^9/L for 3 consecutive days after initial documented engraftment with no evidence of disease progression.

Complete remission is defined as per response criteria defined by European Myelofibrosis network (Appendix G.).

Relapse will be recorded by the day of detection.

Overall Survival is defined as the interval between day of transplant and day of death.

Sample Size and Power
The historical 1-year PFS rate in this population is 61%. Our goal is to improve this to 80%. We expect to enroll patients over a 3-year period and follow all patients for 1 year after enrollment is complete. Under these assumptions, assuming exponentially -distributed PFS times, and using a one-sided exponential MLE test with a 5% Type I error rate, we will need 21 patients to have 80% power to detect an increase in 1-year PFS to 80%. We will provide the 1-year PFS rate along with a corresponding 95% interval and test the hypothesis that it is greater than 61% using an exponential MLE test. Only patients who undergo transplant with a matched related or at least 7/8 matched unrelated donor will be include in this analysis.

Secondary Analyses
We will use the Kaplan-Meier method to estimate the distribution of secondary time-to-event (TTE) endpoints overall survival, time to neutrophil engraftment, and time to platelet engraftment. We will use Cox regression analysis will be used to assess the association between TTE endpoints (including PFS) and clinical and disease covariates of interest. We will assess the cumulative incidence of non-relapse mortality (NRM) and disease relapse in a competing risks framework and use the method of Fine and Gray to fit regression models to these endpoints.

Liver and spleen response to pacritinib will be measured by the change in the size of each organ measured below the coastal margin in the mid-clavicular line by palpation and imaging.

Quality of life (QOL) will be assessed using the QOL FACT BMT, and symptom score will be assessed by the MPD symptom score. Changes in these over time will be analyzed by a generalized linear mixed model (GLMM) approach to account for intra-patient correlation.

For the immune studies, various cell subsets and cytokine levels will be assessed at several timepoints. GLMM or other appropriate statistical models will be fit to assess changes over time in these parameters and relationships with other endpoints.

We will use descriptive statistical methods to tabulate safety parameters such as the rate of adverse events. Only patients who undergo transplant with a matched related or at least 7/8 matched unrelated donor will be include in these analyses.

We will separately summarize safety and other data for patients who receive pacritinib but who do not undergo stem cell transplant.

We will perform a descriptive statistical analysis of the Participant Follow-up Assessment questionnaire (Global Impression of Change Scale, Appendix F.) data collected at approximately 1, 3, 6, and 12 months post-transplant.

7.0 Criteria for Removal from the Study

7.1 Any toxicity that is deemed unacceptable by the study PI.
7.2 Disease progression.
7.3 Lack of compliance with the requirements of the study.
7.4 Withdrawal of consent.
7.5 After one year of transplant.

7.6 No matched related or less than 7/8 matched unrelated donor.

8.0 Adverse Events and Reporting Requirements

8.1 AEs during Pacritinib phase

The severity of the adverse events (AEs) will be graded according to the Common Terminology Criteria v4.0 (CTCAE). We will not capture expected Grade 1 and Grade 2 AEs. Grade 3 and 4 AEs will be collected and recorded in the medical record. Only Pacritinib-related adverse events and protocol specific data will be entered into PDMS/CORe. PDMS/CORE will be used as the electronic case report form for this protocol.

Events not included in the CTCAE chart will be scored as follows:
General grading:

Grade 2: Moderate: discomfort present with some disruption of daily activity, require treatment.

Grade 3: Severe: discomfort that interrupts normal daily activity, not responding to first line treatment.

Grade 4: Life Threatening: discomfort that represents immediate risk of death

Causality Assessment

For the purpose of this study, events known to be caused by Pacritinib will be assessed as definitely related.

Events known to be caused by components of the transplant package and its direct consequences as well as those events known to be related to drugs used for the treatment of GVHD, infections and supportive treatment will be scored as unrelated.

When the relationship of the adverse event cannot be ruled out with certainty the AE may be considered possibly related.

The PI will be responsible for assessing the causality and will be final arbiter. Documentation of grade, onset/resolution date and attribution will be entered into the patient's medical record and signed by the PI.

Collection of adverse events

Collection of adverse events will reflect the onset and resolution date and maximum grade. Intermittent events should be labeled as such and followed until resolution. If a patient is taken off study while an event still ongoing, this will be followed until resolution unless another therapy is initiated. Pre-existing medical conditions will be recorded only if an exacerbation occurs during the active treatment period. Co-morbid events will not be scored separately.

Adverse events related to Pacritinib will be collected and recorded for the duration of active treatment plus 14 days.

List of expected adverse events related to Pacritinib:
Occurring in >10% include:
1. Nausea, vomiting, diarrhea, dehydration

2. Anemia, thrombocytopenia
3. Fatigue

Treatment Duration Definitions:
Active Treatment: patients receiving Pacritinib.

Last day of "Active Treatment": is the last day of Pacritinib.

Reporting Requirement:
Serious Adverse Event Reporting (SAE) Language

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

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

The investigator will inform CTI Biopharma of any SAE within 24 hours of being aware of the event via email and/or fax.

Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

Serious adverse events will be captured from the time of the first protocol-specific intervention, until 14 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

Additionally, any serious adverse events that occur after the 14 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

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

Adverse events known to be related to SOC ALLO TP will not be recorded in PDMS.

<u>List of most common expected adverse events related to SOC ALLO TP:</u>

1. Infections in the presence or absence of neutropenia: fungal, bacterial and or viral infections.
2. Fever: Non-neutropenic or neutropenic without infection
3. Acute graft versus host disease (aGVHD): most commonly manifested by skin rash, diarrhea and abnormal liver function tests could also present with some degree of fever, upper gastrointestinal symptoms (nausea and vomiting) mucositis and eye dryness.
4. Gastrointestinal (GI tract): the GI tract manifestations could be not only due
5. to direct damage from the preparative regiment but also be a manifestation of GVHD or infections. Therefore, the time course and its presentation are crucial when assessing these as adverse events. Nausea/vomiting, mucositis, diarrhea when presented within first 7 to 10 days most likely will be related to the preparative regimen.
6. Skin rash: not related to GVHD could be caused by chemotherapy used for the preparative regimen or antibiotics used a supportive treatment.
7. Transaminitis: liver function test elevation.
8. Pulmonary events: not related to CHF most likely caused by drug injury or infection. These could present with a pneumonitis pattern manifested with shortness of breath, pulmonary infiltrates on chest radiograph, sometimes accompanied by fever and cough and progress to acute respiratory insufficiency and a diffuse bilateral alveolar pattern.
9. Cytokine Storm/ engraftment syndrome: most likely caused by released cytokines.
10. Hemorrhagic cystitis: not related to chemotherapy agents used in the proposed preparative regimen is most likely caused by viral infection.
11. Thrombotic thrombocytopenic purpura (TTP).
12. Veno-occlusive Disease of the Liver (VOD): could be caused by Busulfan. Some antimicrobial agents have been also incriminated in its development.
13. Fluid overload due to hydration required for conditioning regimen, blood product transfusions and or IV alimentation
14. Graft failure.
15. Chronic GVHD.

16. For the purpose of this study, the following events would not be considered adverse events and would not be recorded in the database:
    a. Flu-like symptoms not associated with infection
    b. Abnormal laboratory findings considered associated to the original disease
    c. Isolated changes in laboratory parameters such as electrolyte, magnesium and metabolic imbalances, uric acid changes, elevations of ALT, AST, LDH and alkaline phosphatase.

9.0 Background Drug Information

9.1 Pharmacologic Class of Pacritinib: JAK2-FLT3 inhibitor

9.2 Formulation

For use in clinical studies as an oral agent, pacritinib is supplied as size #0 hard gelatin capsules with gray bodies and red caps. Capsules contain 100 mg pacritinib (free base) and the following inactive ingredients: microcrystalline cellulose NF, polyethylene glycol 8000 (PEG 8000) NF, and magnesium stearate NF. The capsule gelatin is bovine derived.

Pharmacies at investigational sites will receive bottles with child-resistant closures containing 100 capsules (100 mg).

9.3 Storage Conditions

Drug product should be stored in the pharmacy, hospital, clinic, or warehouse at controlled room temperature, 20°C to 25°C (68°F to 77°F), with excursions allowed between 15°C to 30°C (59°F to 86°F). Patients should be instructed that storage temperatures for pacritinib in the home should be below 30°C (86°F). Unused or expired Pacritinib will be disposed per MDACC Investigational Drug policy,

9.4 Observed Risks

The adverse effects observed in toxicity studies, as well as data from phase 1 and 2 clinical studies in patients with advanced MF, AML, and lymphoma:

- **Hematologic**: Reversible myelosuppression; leukopenia, neutropenia, thrombocytopenia, and anemia have been observed; these events are common in hematologic malignancies and may not be related to pacritinib administration. Thrombocytopenia, anemia, neutropenia, and leukopenia ADRs were more common in lymphoid than myeloid patients. Patients participating in clinical trials of pacritinib will be monitored frequently for myelosuppression. Provisions for interruption of treatment and dose reduction in the event of myelosuppression are outlined in clinical trial protocols.
- **Gastrointestinal**: Treatment with pacritinib is associated with dose-related diarrhea and nausea. Vomiting, abdominal pain, abdominal distension, anorexia, and constipation have also been reported to be related to pacritinib administration. Diarrhea and vomiting ADRs were more common in myeloid studies than lymphoid studies, but the reverse was true for constipation. Nausea was the same in both populations. Antiemetic and antidiarrheal medications should be prescribed prophylactically to control symptoms. Fluid and electrolytes should be replaced as needed to prevent dehydration. Pre-existing nausea, vomiting, and diarrhea should be adequately controlled before beginning therapy. Patients

with significant GI symptoms despite optimal supportive care may have study drug interrupted or have the dose of study drug reduced per protocol.

- **Cardiac**: QTc prolongation has been reported in association with pacritinib therapy. A post-hoc review of the patients in the phase 1-2 Studies SB1518-2007-001 and SB1518-2008-003 identified 9 patients with at least one reported QTc exceeding 500 ms; all but one were treated at a pacritinib dose of ≥ 400 mg QD. Therapy was continued in most of these patients for extended periods of time after the observations of QTc prolongation. In addition, pre-study cardiac history was noted in 7 patients, and 8 patients were taking concomitant medications associated with QTc prolonga-tion. Other cardiac TEAEs and ADRs were rare in all pacritinib-treated populations. Based on these observations, investigators are advised to exclude any patient with a baseline QTc > 450 ms and to perform routine ECG monitoring during treatment. For patients with identified changes in treatment-emergent ECG abnormalities or other cardiac events, study drug may be interrupted or the dose may be reduced per protocol.
- **Hepatic**: Animal studies suggest that pacritinib treatment may cause dose-related hepatotoxicity. There has been little evidence of hepatotoxicity in clinical trials to date. Significant increases in aminotransferases have been observed infrequently and have not been accompanied by concomitant increases in bilirubin. Most reported hepatic toxicities were seen in the myeloid population. No instances of hepatic dysfunction meeting Hy's Law criteria have been observed. Hepatic function (AST/SGPT, ALT/SGOT, alkaline phosphatase, and total bilirubin) will continue to be assessed at frequent intervals during treatment with pacritinib.
- **Renal**: Animal studies suggest that treatment may cause dose-related renal toxicity. To date, little impact on renal function has been observed in human clinical trials. Assessment of renal function (creatinine, BUN, sodium, potassium) will be undertaken frequently in patients participating in clinical trials of pacritinib.
- **General**: Additional adverse effects commonly reported during pacritinib administration have included infections, fatigue, asthenia, peripheral edema, pyrexia, and rash. Infectious ADRs were more common in lymphoid patients, while the other adverse effects were more common in myeloid patients. Bleeding and bruising complications have been reported, most of which were low grade and generally more common in the myeloid population than in the lymphoid population. Patients participating in clinical trials of pacritinib will be monitored closely for these adverse effects.

No reproductive or developmental toxicity studies have been performed; therefore, the effects of pacritinib on female and male fertility are unknown. If fertile, both males and females must agree to use effective birth control. Women of childbearing potential must use highly effective methods of birth control for the duration of study treatment and for 12 months after last dose of study drug. The contraceptive methods considered highly effective are intrauterine devices and hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices, or injections with prolonged release).

No drug-drug interaction studies have been conducted with pacritinib. In vitro studies indicate that pacritinib has no significant potential to inhibit or induce CYP450 isozymes and has no significant involvement with p-glycoprotein mediated transport. Pacritinib is believed to be metabolized by CYP3A4. Therefore, caution is advised when considering the coadministration of potent inhibitors of CYP3A4 in conjunction with pacritinib. Specific exclusions are outlined in the protocols for human clinical trials of pacritinib.

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