

In this month's Leukemia Insights newsletter, written by [Prithviraj Bose, M.D.](#), and [Srdan Verstovsek, M.D., Ph.D.](#), and sponsored in part by the Charif Souki Cancer Research Fund, we provide a summary of clinical trials for patients with polycythemia vera, essential thrombocythemia, systemic mastocytosis and myeloid/lymphoid neoplasms with eosinophilia. Learn more about our [program](#).

## Clinical Trials Update: Myeloproliferative Neoplasms

Development of novel therapeutics for the myeloproliferative neoplasms (MPN) has led to explosive growth in the past several years. The US Food and Drug Administration (FDA) has approved four agents since 2019: fedratinib for higher-risk myelofibrosis (MF) and baseline platelets  $\geq 50 \times 10^9/L$ ; avapritinib for advanced systemic mastocytosis (SM) with baseline platelets  $\geq 50 \times 10^9/L$ ; ropeginterferon alfa-2b for polycythemia vera (PV); and pacritinib for myelofibrosis (MF) with baseline platelets  $< 50 \times 10^9/L$ . Approval of momelotinib for patients with MF is widely anticipated this year ([Verstovsek, Lancet 2023](#)), and a number of other agents and combinations are being tested in Phase 3 trials. Here, we summarize the clinical trials for patients with MPN currently available or soon to open at MD Anderson.

### Trials for PV:

#### 1. *Rusfertide*.

Rusfertide is a hepcidin mimetic administered subcutaneously weekly. Mimicking the action of hepcidin, rusfertide sequesters iron in the reticuloendothelial system (RES), restricting its availability for erythropoiesis. In the Phase 2 REVIVE study ([NCT04057040](#)), rusfertide led to elimination of phlebotomy requirements in 84% of patients in the first 28 weeks of treatment ([Hoffman, ASH 2021](#)). Symptom benefits and improvement/normalization of iron parameters were also observed. The Phase 3, pivotal VERIFY trial ([NCT05210790](#)) compares rusfertide to placebo in patients with PV who have required  $\geq 3$  phlebotomies in the preceding 6 months. Patients may continue the cytoreductive agents they are on at study entry. This trial is open.

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## 2. Sapablursen.

Sapablursen is a liver-directed, antisense oligonucleotide against TMPRSS6, which is a negative regulator of hepatic hepcidin production. Thus, sapablursen would be expected to increase endogenous hepcidin production. It is also administered subcutaneously, but, unlike rusfertide, only once every 4 weeks. Two doses of sapablursen are being compared in an open-label, Phase 2 trial ([NCT05143957](#)) in patients with PV who have required at least 3 phlebotomies in a 6-month period. As in the VERIFY study, both patients who are and who are not on cytoreductive therapy are eligible. This trial is open.

## 3. Ropeginterferon alfa-2b.

Ropeginterferon alfa-2b (BESREMI™) is approved in the US for patients with PV and has been studied in both high- and low-risk patients. A Phase 3b, open-label, randomized study ([NCT05481151](#), ECLIPSE-PV) aims to study optimal dosing and dose escalation of this active agent in patients with PV. This trial will open soon.

## **Trials for ET:**

### 1. Ropeginterferon alfa-2b.

The phase 3, registration SURPASS-ET trial ([NCT04285086](#)) compares ropeginterferon alfa-2b, administered subcutaneously every 2 weeks, to anagrelide in patients with ET who have failed hydroxyurea (HU), either because of resistance or intolerance. A WBC count  $\geq 10 \times 10^9/L$  at study entry is required, as is a platelet count  $\geq 450 \times 10^9/L$ . This study is open. Ropeginterferon alfa-2b is also being explored in a Phase 2, open-label trial ([NCT05482971](#), EXCEED-ET) in interferon-naïve patients with ET, regardless of prior exposure to HU and/or anagrelide. This trial will open soon.

## **Trials for SM:**

### 1. Bezuclastinib.

Bezuclastinib is a highly selective and potent small-molecule inhibitor of *KIT* D816V, the driver mutation found in up to 95% of patients with SM. Additionally, bezuclastinib only minimally penetrates the blood-brain barrier (BBB), and spares related kinases, such as platelet derived growth factor receptor kinases A and B. For these reasons, cognitive effects and hemorrhagic events such as intracranial bleeds, known toxicities of avapritinib, are not expected and have not been reported to date. Bezuclastinib is being studied in the APEX trial ([NCT04996875](#)) in patients with advanced SM (aggressive SM, SM with an associated hematologic neoplasm, or mast cell leukemia), with preliminary results in 16 patients demonstrating high efficacy similar to avapritinib (*DeAngelo*, ASH 2022) and minimal toxicity. This agent is also being studied in the SUMMIT trial ([NCT05186753](#)) in patients with indolent and smoldering SM. Both trials are assessing different doses of bezuclastinib; the SUMMIT trial also has a placebo arm with early crossover (after 3 cycles). Prior *KIT* inhibitor therapy is permitted on the APEX trial but not currently on the SUMMIT trial. Both trials are open.

### 2. Elenestinib

Like bezuclastinib, elenestinib (formerly BLU-263) also is a potent and selective inhibitor of *KIT* D816V with minimal penetration of the BBB. The Phase 2/3 HARBOR study ([NCT04910685](#)) is enrolling patients with indolent SM. The dose-finding part 1 of this study compares different doses of elenestinib against placebo, while part 2 compares the recommended phase 2 dose identified in part 1 against placebo, followed by an open-label part 3 in which all patients receive elenestinib. This trial is open.

## **Trials for MF:**

### **“Add-on” trials for patients with an insufficient/suboptimal response to ruxolitinib**

#### **1. Navtemadlin.**

Navtemadlin is an oral, small-molecule human double minute 2 (HDM2) antagonist that has shown promising single-agent activity in the setting of JAK inhibitor failure (*Al-Ali*, EHA 2020; *Vachhani*, ASH 2021). HDM2 is overexpressed in MPN, particularly in *JAK2*-mutated MPN. This Phase 2 trial ([NCT04485260](#)) evaluates the addition of navtemadlin in patients with a suboptimal response after  $\geq 18$  weeks of ruxolitinib (at a stable dose for at least the preceding 8 weeks). Because of the mechanism of action of HDM2 inhibitors, patients must not have *TP53*-mutated disease. This trial is open.

#### **2. TL-895.**

TL-895 is an oral, second-generation Bruton tyrosine kinase (BTK) inhibitor similar to acalabrutinib and zanubrutinib. The mechanisms of action of BTK inhibitors in MF include down-regulation of nuclear factor kappa B (NF- $\kappa$ B) and mobilization of CD34<sup>+</sup> cells from marrow niches. This Phase 2 trial ([NCT04655118](#)) assesses TL-895 in an “add-on” fashion in patients with a suboptimal response to ruxolitinib monotherapy after at least 12 weeks ( $\geq 8$  weeks of stable dose preceding study entry). This trial is open.

#### **3. INCB057643**

INCB057643 is an oral bromodomain and extra-terminal (BET) protein inhibitor. BET proteins are epigenetic readers that control the transcription of several critical oncogenes, such as *c-Myc*, *Bcl-2*, *NF- $\kappa$ B*, etc. Encouraging results have been reported with pelabresib, a pan-BET inhibitor, in combination with ruxolitinib, especially in the upfront setting. Pelabresib is currently in a fully accrued, pivotal, placebo-controlled Phase 3 trial in combination with ruxolitinib, the results of

which are awaited. INCB057643 is being studied both as monotherapy in patients with advanced, myeloid malignancies, including MF, and as an “add-on” therapy in MF patients on a stable dose of ruxolitinib, but with a suboptimal response to the latter, in this Phase 1/2 trial ([NCT04279847](#)). Notably, this trial does not exclude patients with MF in the accelerated phase (blasts in the peripheral blood or bone marrow of 10-19%). This trial is open.

#### **4. Regulatory T cells.**

CK0804, representing the first foray into cellular therapy in MF, is an allogeneic, umbilical cord blood-derived regulatory T cell (T-regs) product. CK0804 is combined with ruxolitinib and evaluated in a Phase 1b trial ([NCT05423691](#)) in MF patients with measurable splenomegaly, anemia or symptoms. CK0804 is infused IV in the outpatient setting. This trial is open.

## **Trials for patients failing JAK inhibitor therapy**

#### **1. Imetelstat.**

Prognosis after ruxolitinib discontinuation is poor, with median survival reported in several studies to be 11-14 months. In a Phase 2 study ([NCT02426086](#)), the telomerase inhibitor imetelstat, administered IV every 3 weeks at a dose of 9.4 mg/kg in patients who failed JAK inhibitor therapy, yielded a median survival of 29.9 months (*Mascarenhas*, JCO 2021). This agent is now being compared to best available therapy (BAT, excluding JAK inhibitors) in the Phase 3 IMPactMF trial ([NCT04576156](#)) with overall survival as the primary endpoint. It is the first pivotal trial in MF to use this outcome measure as its primary endpoint. This trial is open.

#### **2. Navtemadlin.**

The phase 3 BOREAS trial ([NCT03662126](#)) compares navtemadlin, 240 mg daily on days

1-7 of a 28-day cycle, to BAT (excluding JAK inhibitors) in patients with MF that is refractory or resistant to JAK inhibition. JAK inhibitor-intolerant patients are not eligible to participate in this registrational trial. A 28-day washout from prior JAK inhibitor therapy is required. This trial is recruiting participants.

3. *Ilginatinib*. Ilginatinib (formerly NS-018) is an oral, small-molecule inhibitor of JAK2 that is more selective for mutant JAK2 (V617F) and less myelosuppressive than the first two marketed JAK inhibitors (ruxolitinib, fedratinib). Ilginatinib is being evaluated in comparison to BAT, which can be pacritinib, in JAK inhibitor-exposed (only 1 prior JAK inhibitor is permitted) patients with MF and severe thrombocytopenia (platelet counts  $<50 \times 10^9/L$ ) in a randomized Phase 2 study ([NCT04854096](#)). This trial is open.

4. *PXS-5505*. PXS-5505 is an oral, small-molecule, pan-lysyl oxidase (LOX) inhibitor. LOX promotes the formation of networks of collagen fibers and is elevated in the bone marrow of MF patients, thereby promoting fibrosis. This open-label, Phase 1/2a clinical trial ([NCT04676529](#)) is evaluating the safety and tolerability of PXS-5505 in MF patients who have relapsed on, are refractory to, or intolerant of ruxolitinib. This trial is open and accepts patients with baseline platelets  $<50 \times 10^9/L$ .

5. *GB-2064*. GB-2064 is an oral inhibitor of LOX like-2 (LOXL2), which belongs to a family of enzymes driving cross-linking of collagen and elastin fibers. LOXL2 is overexpressed in the bone marrow of patients with primary MF. This phase 2 study ([NCT04679870](#)) is evaluating GB2064 in patients with MF who are ineligible for, or whose disease has relapsed on or was refractory to JAK inhibitors. A baseline platelet count of at least  $50 \times 10^9/L$  and a minimum absolute neutrophil count of  $1.5 \times 10^9/L$  are required for eligibility. This trial is open.

6. *TL-895*. In this phase 2 clinical trial ([NCT04655118](#)), TL-895 (second-generation

BTK inhibitor) is being studied as a single agent in MF patients who are ineligible for, intolerant of, or whose disease has progressed on/been refractory to treatment with JAK inhibitors (for example, ruxolitinib). This trial is open and accepts patients with baseline platelets  $<50 \times 10^9/L$ .

## **Trials for patients who are not candidates for JAK inhibitors**

### *1. Elotuzumab.*

Elotuzumab is an anti-SLAMF7 monoclonal antibody that targets SLAMF7-expressing monocytes that are the precursors of fibrocytes, the cells that engender bone marrow fibrosis in MF. This Phase 2 investigator-sponsored trial ([NCT04517851](#)) studies elotuzumab as an anti-fibrotic agent in patients who are not candidates for JAK inhibitor therapy in the judgment of the treating physician. Prior JAK inhibitor therapy is permitted. Elotuzumab is administered IV weekly during the first 2 cycles (8 weeks) and every 4 weeks thereafter. This trial is open.

### *2. VAC85135.*

This Phase 1 study ([NCT05444530](#)) investigates VAC85135, a novel vaccine against mutant *CALR* as well as mutant *JAK2*, in combination with the anti-CTLA4 antibody, ipilimumab. Patients must not have low-risk disease and must be JAK inhibitor-naïve (i.e., those who are not candidates for or who refuse JAK inhibitors). Patients with *JAK2*-mutated MF must express HLA-A0201. Patients with ET who are not at “very low risk” for thrombosis are also eligible. This trial will open soon.

## **Trials for MF-associated anemia**

### *1. Luspatercept.*

The activin receptor ligand trap, luspatercept, is an erythroid maturation agent approved for the treatment of anemia in patients with

myelodysplastic neoplasms with ring sideroblasts (RS), as well as those with myelodysplastic/myeloproliferative neoplasms with RS and thrombocytosis. In a Phase 2 trial in anemic patients with MF, luspatercept led to promising responses, including transfusion independence (TI), particularly in patients who were on a stable dose of ruxolitinib and required PRBC transfusions (*Gerds*, ASH 2019, 2020). These findings led to the pivotal, placebo-controlled, Phase 3 trial (INDEPENDENCE, [NCT04717414](#)) of luspatercept, administered subcutaneously every 3 weeks at a starting dose of 1.33 mg/kg, in patients with MF on a stable dose of a JAK inhibitor who require PRBC transfusions. Crossover is not permitted. This trial is open.

#### *Zilurgisertib.*

Zilurgisertib is an oral, small-molecule inhibitor of activin receptor type 1 (ACVR1, also known as ALK2). Inhibition of ACVR1/ALK2 leads to

down-regulation of hepatic hepcidin production, leading to iron becoming more available for erythropoiesis. The anemia benefits of momelotinib (*Oh, Blood Adv* 2020) and, more recently, pacritinib (*Oh, ASH* 2022) have been attributed to this mechanism. In this Phase 1/2 trial ([NCT04455841](#)), zilurgisertib is being studied both alone and as an “add-on” to a stable dose of ruxolitinib in patients with MF and anemia. This trial is open.

#### *DISC-0974.*

DISC-0974 is an antibody directed against hemojuvelin, a positive regulator of hepcidin production – this is, thus, another mechanism of down-regulating hepcidin, distinct from that of the ACVR1/ALK2 inhibitors. This agent is being studied, both as monotherapy and in “add-on” fashion, in anemic MF patients on a stable dose of a JAK inhibitor or HU, in a Phase 2 trial ([NCT05320198](#)). This trial is open.

## Leukemia Faculty Contacts

*Completing these studies in a timely manner will allow us to move quickly on positive leads. We appreciate referrals and will make every effort, once a patient is enrolled on a study, to continue as much of the care as possible through the referring oncologist. We also will keep you apprised of the patient's progress. [View our faculty roster.](#)*

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