Leukemia insights

JULY 2022

MONTHLY EDITION

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

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*In this month's Leukemia Insights newsletter, written by Helen T. Chifotides, Ph.D., and Srdan Verstovsek, M.D., Ph.D., and sponsored in part by the Charif Souki Cancer Research Fund, we overviewed novel treatments in clinical development for myelofibrosis, currently evaluated in clinical trials at the Hanns A. Pielenz Clinical Research Center for Myeloproliferative Neoplasms (MPNs) at the MD Anderson Cancer Center. Learn more about MPNs, our MPN research program, and our Leukemia program*

# Novel strategies in development for treatment of myelofibrosis

The accelerated regulatory approval of the relatively non-myelosuppressive JAK inhibitor pacritinib in early 2022 as a treatment for patients with intermediate- or high-risk myelofibrosis (MF) and severe thrombocytopenia (baseline platelet count below $50x10^9$/L) was an important advancement in the field of myeloproliferative neoplasms (MPN). Prior to pacritinib's approval, patients with MF and thrombocytopenia, who have a relatively poor prognosis, had limited treatment options because the other two approved JAK2 inhibitors (ruxolitinib, fedratinib) can exacerbate myelosuppression. However, a major unmet medical need remains for patients with MF and anemia, a suboptimal response or resistance to ruxolitinib, and patients who progress to acute myeloid leukemia (AML). In this issue, we review the MF agents in clinical development at the MD Anderson Cancer Center (Table 1).

## Synergistic ruxolitinib-based combinations and monotherapies in the frontline setting

**1. Pelabresib (MANIFEST-2** trial**; NCT04603495):**
Inhibitors of bromodomain and extra-terminal (BET) proteins (epigenetic "reader" proteins) in combination with JAK2 inhibitors have shown synergism in preclinical models of MF. In the phase 2 MANIFEST trial in JAK inhibitor-naïve patients, **pelabresib** (formerly CPI-0610; oral BET inhibitor) in combination with ruxolitinib demonstrated notable clinical efficacy. Based on the promising results of the MANIFEST trial, the combination of pelabresib with ruxolitinib is currently being assessed in comparison to placebo plus ruxolitinib in the randomized phase 3 MANIFEST-2 trial, which is open to JAK inhibitor-naïve MF patients.

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## CONTACT OUR STAFF

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**2. Navitoclax(TRANSFORM-1;NCT04472598):** This predecessor of venetoclax inhibits the anti-apoptotic Bcl-2 family of proteins (primarily Bcl-xL). The non-clinical analog of navitoclax in combination with ruxolitinib demonstrated synergism in preclinical models of *JAK2* V617F-driven MF. The promising results that navitoclax elicited in combination with ruxolitinib in JAK inhibitor-naïve patients (Phase 2 study) support evaluation of the combination (navitoclax with ruxolitinib vs. placebo with ruxolitinib) in a phase 3 trial (TRANSFORM-1) in JAK inhibitor-naïve patients with MF. Navitoclax and ruxolitinib are administered orally. This trial is open.

**3. Navtemadlin (formerly KRT-232) or TL-895 (NCT04878003):** Human double minute 2 (HDM2), the physiologic antagonist of the tumor suppressor p53, is overexpressed in MF; therefore, HDM2 inhibition would restore expression of the tumor suppressor protein p53 and mediate apoptosis of malignant cells. Navtemadlin is a first-in-class, potent, bioavailable inhibitor of HDM2. TL-895 is a highly selective, irreversible oral Bruton's tyrosine kinase (BTK) inhibitor that acts on bone marrow kinase, an enzyme that has an important role in NF-kB activation and induction of pro-inflammatory cytokines. Navtemadlin or TL-895 (both administered orally) are currently assessed in a phase 2 trial in MF patients who had not been previously treated with JAK inhibitors. The trial is open.

## "Add-on" agents to ruxolitinib for suboptimal responders

**1. Navtemadlin (NCT04485260):** The oral HDM2 inhibitor navtemadlin (described above) is also studied in the "add-on" setting in patients with suboptimal response to ruxolitinib. This phase 1b/2 trial is open.

**2. PU-H71 (NCT03935555):** PU-H71 is an orally administered inhibitor of the chaperone protein, heat shock protein 90 (HSP90). HSP90 inhibition can degrade JAK2, thus circumventing resistance to JAK2 inhibitors. In preclinical MPN models, PU-H71 demonstrated synergism in combination with ruxolitinib. PU-H71 is being studied in the "add-on" setting in patients with a suboptimal response to ruxolitinib. The trial is open.

## New monotherapies in the second-line setting

**1. Navtemadlin (BOREAS; NCT03662126):** As previously noted, there is a strong biologic rationale to test HDM2 inhibition as a therapeutic strategy in MF. In the phase 2 part of the study, navtemadlin showed clinical efficacy in *TP53*-wild type patients with MF who relapsed or were refractory to ruxolitinib. The open phase 3 study, called BOREAS, compares navtemadlin to best available therapy (excluding JAK inhibitors) in *TP53*-wild type patients with MF who relapsed or are refractory/resistant to JAK inhibitors.

**2. TL-895 (NCT04655118):** Besides being evaluated in the first line setting (as previously described), TL-895, a highly selective oral BTK inhibitor, is assessed in a phase 2 study in MF patients who relapsed or were refractory or intolerant to JAK inhibitors. The trial is open.

**3. GB2064 (MYLOX1 trial; NCT04679870):** It is an oral inhibitor of lysyl oxidase like-2 (LOXL2), which belongs to the family of enzymes driving cross-linking of collagen and elastin fibers. Lysyl oxidase is overexpressed in the bone marrow of patients with primary MF, thereby promoting fibrosis. The phase 2 study, which evaluates GB2064 in patients with MF who relapsed or were refractory to JAK inhibitors, is open.

**4. Imetelstat (IMpactMF; NCT04576156):** This telomerase inhibitor was evaluated in the phase 2 trial in patients who were refractory or relapsed to JAK inhibitors and elicited a notable median overall survival of 29 months. The randomized phase 3 trial IMpactMF on imetelstat was designed for patients who relapsed or are refractory to JAK inhibitors. The comparator arm is best available therapy, excluding JAK inhibitors. Overall survival benefit is the primary endpoint of this trial, which is unprecedented for MF clinical trials.

## Therapies for those intolerant/ resistant/refractory or not candidates for JAK inhibitors

**Elotuzumab (NCT04517851):** Studies conducted by investigators at MD Anderson and in Japan showed that the cells that make up bone marrow fibrosis (fibrocytes) are derived from monocytes, a type of white blood cells. Monocytes express a protein called the signaling lymphocytic activation molecule F7 (SLAMF7) on the surface. Elotuzumab is a SLAMF7-targeting monoclonal antibody (administered by injection) that was approved for multiple myeloma and may improve or reverse bone marrow fibrosis in MF patients. As a potential antifibrotic agent in MF, elotuzumab may improve anemia and thrombocytopenia. The phase 2 study is open.

## Patients with MF and anemia

**1. Luspatercept (INDEPENDENCE trial; NCT04717414)** is an activin receptor ligand trap; this novel class of fusion proteins ameliorates anemia of diverse etiologies by sequestering ligands of the TGF-β superfamily that bind to the activin receptor to suppress terminal erythroid differentiation. Luspatercept was assessed for anemia benefits in MF patients in a phase 2 trial (NCT03194542); the agent demonstrated promising results, particularly in transfusion-dependent patients receiving ruxolitinib. The pivotal phase 3 study, evaluating the addition of luspatercept to ruxolitinib versus adding placebo, in transfusion-dependent patients with MF (on a stable dose of ruxolitinib), is open. Luspatercept in administered subcutaneously.

**2. Pelabresib (MANIFEST; NCT02158858):** As previously noted, the BET inhibitor pelabresib is an active agent in MF. The monotherapy arm (pelabresib only; it is administered orally) of this multiple arm study for transfusion-dependent MF patients who no longer are on ruxolitinib continues to accrue patients.

**3. INCB000928 (NCT04455841):** This potent orally bioavailable type 1 activin receptor (ACVR1) or activin receptor-like kinase-2 (ALK2) inhibitor decreases hepcidin expression in human liver cells and rodent models of anemia. Hepcidin is a small peptide hormone that functions as a master regulator of iron homeostasis. Suppression of hepcidin secretion restores iron homeostasis, stimulates erythropoiesis; and thereby increases hemoglobin and significantly improves anemia and transfusion dependence. INCB000928 is being studied, both as a monotherapy and in combination with ruxolitinib ("add-on" setting), in anemic patients with MF, in a phase 1/2 trial that is currently open and enrolling patients.

## Table 1: Selected Clinical Trials on Agents in Clinical Development for MF at MD Anderson

| Investigational Agent | Mechanism of Action | Clinical Trial Identifier | Enrolled Patients | Phase | Clinical Setting |
|---|---|---|---|---|---|
| **Pelabresib (+Ruxolitinib)** | BET inhibitor | MANIFEST-2 (NCT04603495) | MF patients who are JAK inhibitor-naive | 3 | First-line |
| **Navitoclax (+Ruxolitinib)** | Bcl-2/Bcl-xL inhibitor | TRANSFORM-1 (NCT04472598) | MF patients who are JAK inhibitor-naive | 3 | First-line |
| **Navtemadlin or TL-895** | HDM2 inhibitor or BTK inhibitor | NCT04878003 | Patients with MF who are JAK inhibitor-naive | 2 | First-line |
| **Navtemadlin** | HDM2 inhibitor | NCT04485260 | *TP53*-wild type MF patients who had a suboptimal response to ruxolitinib after ≥18 weeks of treatment with a stable dose for ≥8 weeks | 1b/2 | "Add-on" to Ruxolitinib |
| **PU-H71** | HSP90 inhibitor | NCT03935555 | MF patients treated with ruxolitinib for ≥3 months and had persistent/worsening symptoms | 1 | "Add-on" to Ruxolitinib |
| **Navtemadlin** | HDM2 inhibitor | BOREAS (NCT03662126) | *TP53*-wild type MF patients who relapsed or are refractory/resistant to JAK inhibitors | 2/3 | Second-line |
| **TL-895** | BTK inhibitor | NCT04655118 | MF patients who relapsed after or were refractory/ intolerant of JAK inhibitor therapy | 2 | Second-line |
| **GB2064** | LOXL2 inhibitor | MYLOX1 (NCT04679870) | Patients with MF relapsed/ refractory to JAK inhibitor therapy | 2 | Second-line |
| **Imetelstat** | Telomerase inhibitor | IMpactMF (NCT04576156) | Patients with intermediate-2 or high-risk MF who failed JAK inhibitor therapy | 3 | Second-line |
| **Elotuzumab** | Anti-SLAMF7 monocloncal antibody | NCT04517851 | Patients with *JAK2* V617F-mutated MF who are not candidates for JAK inhibitors | 1 | First-line and second-line |
| **Luspatercept** | Activin receptor IIB ligand trap | INDEPENDENCE (NCT04717414) | MF patients with anemia who are on a stable dose of ruxolitinib, requiring 4-12 red blood cell transfusions in the 12 weeks before randomization | 3 | "Add-on" to Ruxolitinib |
| **Pelabresib** | BET inhibitor | MANIFEST (NCT02158858; Arm 1) | Transfusion-dependent MF patients and those who are not; patients discontinued ruxolitinib or were ineligible for JAK inhibitors | 2 | Second-line |
| **INCB00928** | ACVR1/ALK2 inhibitor | NCT04455841 | MF patients with anemia (Hb<10 g/dL) previously treated with JAK inhibitors for ≥12 weeks | 1/2 | Monotherapy or "add-on" to Ruxolitinib |

## 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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## Announcements

**Texas MPN Workshop (TMW) 2022.** The 3rd Annual Workshop and Meeting, hosted by the Mays Cancer Center, home to UT Health San Antonio MD Anderson, will be held at the Westin Riverwalk, San Antonio, TX, on August 26-27, 2022. Leaders of the MPN community and key investigators will present many novel research and therapeutic strategies in clinical development for MPNs. To register, please visit: TMW 2022 registration.

**10th Annual Society of Hematologic Oncology (SOHO) Meeting.** The tenth annual meeting of the Society of Hematologic Oncology (SOHO 2022) is scheduled to take place from September 28 to October 1, 2022, at the Hilton Americas in Houston, Texas. Hematology/oncology specialists from around the world will gather at the event. As a hybrid event, SOHO 2022 offers in-person and virtual attendance options. Click the following link to begin the secure registration process: www.soho.click/2022