Leukemia insights

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Making Cancer History®

*In this month's Leukemia Insights newsletter, written by Srdan Verstovsek, M.D., Ph.D., and Helen T. Chifotides, Ph.D., and sponsored in part by the Charif Souki Cancer Research Fund, we highlight novel promising treatments for myelofibrosis in clinical trials at the **Hanns A. Pielenz Clinical Research Center for Myeloproliferative Neoplasms (MPNs)** at MD Anderson Cancer Center. Several regimens are in advanced Phase 3 clinical trials. Learn more about **MPNs**, our **MPN research program**, and our **Leukemia program**.*

Promising Novel Treatments in Clinical Development for Myelofibrosis

Studies for Newly Diagnosed Patients

1. **MANIFEST-2 (NCT04603495):** Bromodomain and extra-terminal (BET) inhibitors in combination with JAK inhibitors have shown synergism in preclinical myelofibrosis (MF) models. On the basis of the promising efficacy that was noted in the phase 2 MANIFEST trial in JAK inhibitor-naïve patients (67% response rate in spleen size reduction and 59% response rate in improvement of symptoms at 24 weeks; Kremyanskaya, EHA 2021), the combination of ruxolitinib and the oral BET inhibitor **pelabresib** (formerly CPI-0610) is compared to ruxolitinib plus placebo in this pivotal phase 3 trial open for JAK inhibitor-naïve MF patients.
2. **TRANSFORM-1 (NCT04472598): Navitoclax**, the predecessor of venetoclax, inhibits both anti-apoptotic proteins Bcl-2 and Bcl-xL. Bcl-xL may be particularly important for malignant cell survival in the context of *JAK2* V617F mutations. Moreover, synergism has been demonstrated between ruxolitinib and navitoclax in preclinical models of MF. Based on promising results achieved with the addition of navitoclax to the regimen of patients with a "suboptimal" response to ruxolitinib (phase 2 REFINE trial; Harrison, EHA 2021) regarding spleen and symptom responses, this phase 3 trial will compare the combination of ruxolitinib with navitoclax to ruxolitinib plus placebo in JAK inhibitor-naïve MF patients. This trial is open.
3. **PACIFICA (NCT03165734): Pacritinib** is a relatively non-myelosuppressive JAK2/IRAK1/FLT3 inhibitor that may be particularly effective in MF patients with a

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"cytopenic" phenotype (characterized by smaller spleen size, anemia and thrombocytopenia). This oral agent is being studied in patients with platelet counts below 50,000/μL at baseline; these patients have a dismal prognosis, and no guidance on dosing is available for either ruxolitinib or fedratinib. This pivotal phase 3 trial is enrolling JAK inhibitor-naïve patients as well as those with a limited exposure to ruxolitinib. Patients are randomized 2:1 to receive pacritinib or physician's treatment of choice (low dose ruxolitinib, danazol, or corticosteroids). This trial is open.

4. **TL-895 or navtemadlin (NCT04878003):** TL-895 is a highly selective, irreversible oral Bruton's tyrosine kinase inhibitor that inhibits bone marrow kinase, an enzyme that has an important role in NF-kB activation and induction of pro-inflammatory cytokines. Human double minute 2 (HDM2), the physiologic antagonist of p53, is overexpressed in MF; thus, HDM2 inhibition would restore expression of the tumor suppressor protein p53. TL-895 or the oral HDM2 inhibitor navtemadlin (formerly KRT-232) are assessed in a phase 2 trial in JAK inhibitor naïve patients. If response is not seen within a few months of therapy, patients are then treated with a JAK inhibitor. The trial is open.

"Add-on" Studies for Patients with Suboptimal Responses to JAK2 Inhibitors

1. **Navitoclax (NCT03222609):** *JAK2* V617F activates Bcl-xL, and the combination of ruxolitinib with the non-clinical analog of navitoclax (ABT-737) showed synergism in preclinical models of *JAK2* V617F-driven myeloproliferative neoplasms (MPNs). Promising clinical efficacy was noted in terms of spleen and symptom responses in this ongoing phase 2 trial (REFINE) in the "add-on" setting (Harrison, EHA 2021). This trial is open.
2. **Navtemadlin (NCT04485260):** *JAK2* V617F and transforming growth factor beta (TGF-β) lead to overexpression of HDM2, the physiologic antagonist of p53, in MF. *TP53* mutations are rare in chronic phase MF, making HDM2 inhibition an attractive therapeutic target. The oral HDM2 inhibitor navtemadlin (formerly KRT-232) is active in patients with relapsed/refractory MF and is presently studied in the "add-on" setting in patients with a suboptimal response to ruxolitinib. This phase 1b/2 trial is open.
3. **PU-H71 (NCT03935555):** PU-H71 is an oral inhibitor of the chaperone protein heat shock protein 90 (HSP90). HSP90 inhibition can degrade JAK2, thus circumventing resistance to JAK2 inhibitors. PU-H71 is being studied in the "add-on" setting in MF patients with a suboptimal response to ruxolitinib. This trial is open.

Studies for Patients Who Have Failed JAK Inhibitors

1. **BOREAS (NCT03662126):** As previously noted, there is a strong biologic rationale to test HDM2 inhibition as a therapeutic strategy in MF. The phase 2 part of the study assessing **navtemadlin** in MF patients who relapsed or were refractory to ruxolitinib was completed; in this study, the optimal daily dose was determined and shown to be active (Al-Ali, EHA 2020). In the phase 3 portion of the study, navtemadlin will be compared to best available therapy (excluding JAK inhibitors) in MF patients who are refractory/resistant to JAK inhibitors. This trial is open.

2. **IMpactMF (NCT04576156):** The telomerase inhibitor **imetelstat** was evaluated in the phase 2 trial IMbark (NCT02426086) in patients who were refractory or relapsed to JAK2 inhibitors. In this trial, the higher dose of imetelstat (9.4 mg/kg administered intravenously every 3 weeks) conferred a median overall survival of 29.9 months (Mascarenhas, *J. Clin. Oncol*. 2021). On the basis of these results, which compare favorably to historical survival data of relapsed/refractory MF patients, the phase 3 trial IMpactMF in patients who relapsed or are refractory to JAK inhibitors will start enrolling participants at MD Anderson soon; survival benefit is the primary endpoint of this trial, which is unprecedented for MF clinical trials.
3. **PRT543 (NCT03886831):** A novel epigenetic target of interest in the MPNs is the protein arginine N-methyltransferase 5, PRMT5. PRT543 is an oral inhibitor of PRMT5 that is being studied in a phase 1 trial in patients with advanced solid tumors or hematologic malignancies, including MF. The escalation portion of the study showed promising data, and the study is now in the expansion phase. PRT543 in combination with ruxolitinib demonstrated synergism in a *JAK2* V617F MF model. The expansion study comprises several cohorts enrolling patients with intermediate- and high-risk MF, MF with blasts ≥ 10% (including post-MPN acute myeloid leukemia [AML]), myelodysplastic syndromes (MDS), MDS/MPN overlap syndromes, and relapsed/refractory AML; for all cohorts, eligible patients must harbor spliceosome mutations. This study is open.
4. **TL-895 (NCT04655118):** This Bruton's tyrosine kinase 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.
5. **GB2064 (NCT04679870):** This is an inhibitor of lysyl oxidase like-2, which belongs to the family of enzymes driving cross-linking of collagen and elastin fibers. A phase 2 study evaluating GB2064 in MF patients who relapsed or were refractory to JAK inhibitors is open.

Studies for Patients with Anemia

1. **Luspatercept** 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 recently approved for treatment of anemia in β-thalassemia and MDS with ring sideroblasts. Luspatercept was also 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 (Gerds, ASH 2020). The pivotal phase 3 study evaluating luspatercept in combination with ruxolitinib versus placebo plus ruxolitinib in transfusion-dependent MF patients (INDEPENDENCE;NCT04717414) will open at MD Anderson soon.
2. **MANIFEST (NCT02158858):** As previously noted, dual inhibition of BET proteins and JAK2 has been found to be synergistic in MPN models. In the "add-on" arm of the phase 2 MANIFEST study, **pelabresib** (formerly CPI-0610) was added to the regimen of patients with a suboptimal response to ruxolitinib; the combination afforded encouraging responses in transfusion-dependent patients, a number of whom achieved transfusion independence (Verstovsek, EHA 2021). This cohort has been expanded and, along with the monotherapy arm (pelabresib), continues to accrue patients.

3. **INCB000928 (NCT04455841):** This is an oral ACVR1/ALK2 inhibitor that decreased hepcidin expression in human liver cells and rodent models of anemia. INCB000928 is studied both as a montherapy and in combination with ruxolitinib in anemic MF patients. This phase 1/2 trial is open.

A Study for Patients Who Have Failed or Are Not Candidates for JAK Inhibitors

Studies conducted by investigators at MD Anderson (Verstovsek et al., *J. Exp. Med*. 2016) and a Japanese group (Maekawa et al., *Blood* 2019) showed that fibrocytes leading to bone marrow fibrosis in MF are derived from monocytes, which express the signaling lymphocytic activation molecule F7 (SLAMF7). **Elotuzumab** is a SLAMF7-targeting monoclonal antibody approved for the treatment of multiple myeloma. This phase 2 study (**NCT04517851**) is open.

Announcements

A Tribute to Emil J Freireich, M.D.
Recognized as a founding father of modern clinical cancer research, Emil J Freireich, M.D., pioneered the development of groundbreaking combination therapies to treat childhood leukemia. He is credited for curing thousands of children over the course of his 60-year career, but his revolutionary work in leukemia led to therapeutic breakthroughs for other types of cancers and continues to save countless lives to this day. In honor of his enduring legacy as a trailblazing oncologist, teacher and mentor, MD Anderson celebrates Freireich's life and career in a virtual tribute event. **mdanderson.org/FreireichTribute**

Bridging Oncology and Primary Care Education Series
MD Anderson Cancer Center is featuring an online educational series for all health care provider specialties. This series will feature specialized presentations covering: Gastroenterology, Internal Medicine, Dermatology/Melanoma, Hematology, Breast, Gynecologic Oncology, Immunology, Thoracic and Head & Neck, COVID Related Topics and Hot Topics. The modules are pre-recorded and will be available through July 15, 2021–February 1, 2022. To view more details or register, go to http://mdanderson.org/ccc21.

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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