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# NEWSLETTER

## Clinician Update: Myelofibrosis

## Myelofibrosis Treatment: What Lies Ahead?

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# Myelofibrosis Treatment: What Lies Ahead?

Janus kinase (JAK) inhibitors have become a mainstay therapy for various cancers, including myelofibrosis. Three JAK inhibitors are approved by the Food and Drug Administration (FDA) for treating this blood cancer: ruxolitinib (*Jakafi*), fedratinib (*Inrebic*), and pacritinib (*Vonjo*). These therapies have demonstrated benefits for this patient population in terms of reduction of spleen volume and symptom control. However, many patients are unable to tolerate, do not respond, or develop resistance to these and other current treatments. What's more, no existing therapy reduces the risk for transformation to acute leukemia. (Allogeneic hematopoietic stem cell transplantation is the only curative therapy for myelofibrosis, but not an option for most patients due to high associated mortality risk.)

Clearly there is a significant unmet need for new treatments for this challenging disease. Here's a look at what may lie ahead for the management of myelofibrosis.

**Novel JAK inhibitors:** Pacritinib (approved in January 2022) and momelotinib (under review by the U.S. Food and Drug Administration; see page 4) are JAK inhibitors that target additional pathways related to myeloproliferative changes. Both are designed to fill the unmet need of patients with disease- and treatment-related cytopenias.

**BET inhibitors:** This new class of drugs blocks the bromodomain and extra-terminal domain (BET) protein, which prevents epigenetic changes involved in cell cycle regulation, apoptosis, and production of pro-fibrotic cytokines. Mouse models have demonstrated a reduction in pro-inflammatory cytokines and bone marrow fibrosis reversal. Pelabresib (as monotherapy and in combination with ruxolitinib) is in advanced-stage trials.

**BLCT inhibitors:** One inhibitor of the BLCT-2 protein (which regulates apoptosis), venetoclax (*Venclexta*) is approved for CLL/SLL and acute myeloid leukemia. A new BLCT-2 inhibitor, navitoclax, is currently in trials for treatment of myelofibrosis (see page 5).

**MDM2-targeted therapies:** Murine double minute 2 (MDM2) is an oncogene associated with several cancers. Early-stage trials of navtemadlin, a potent inhibitor of MDM2, are underway, as monotherapy and in combination with ruxolitinib, as well as with TL-895, an experimental BTK inhibitor.

**Telomerase therapies:** Telomerase (an enzyme that adds telomeres to DNA strands) is upregulated in up to 90% of cancers, potentially disturbing apoptosis and promoting uncontrolled cell growth. Imetelstat, which inhibits human telomerase reverse transcriptase (hTERT) activity, is in a phase 2 trial involving myelofibrosis patients who are refractory to or relapsed on a JAK inhibitor.

Other potential new strategies for treating advanced myelofibrosis in clinical trials include PI3 kinase inhibitors, bomedemstat therapies, SMAC mimetics, recombinant proteins, and immunotherapies. Massive Bio can match your patients with clinical trials of cutting-edge treatments for myelofibrosis and other blood cancers. If you have a patient who you believe is a candidate for a clinical trial, contact Massive Bio at (646) 867-7200 or referrals@massivebio.com.

*Source:* Waksal J and Mascarenhas J. "Novel Therapies in Myelofibrosis: Beyond JAK Inhibitors," Current Hematologic Malignancy Reports, August 19, 2022.

# Clinical Trial News

## In the Pipeline: Momelotinib for Myelofibrosis

The U.S. Food and Drug Administration (FDA) has accepted a New Drug Application (NDA) for momelotinib, a novel therapy for myelofibrosis. Momelotinib was developed by Sierra Oncology, which was recently acquired by GSK. The drug has the potential for sales of over $1 billion a year, according to PharmaPhorum. That's largely because momelotinib appears to have a reduced risk for causing anemia, the major reason myelofibrosis patients cease treatment.

The NDA is supported by data from the phase III MOMENTUM trial, which compared momelotinib to danazol. Participants included 195 symptomatic and anemic subjects who had previously been treated with a JAK inhibitor. (Enrollment criteria included an MFSAF v4.0 Total Symptom Score of ≥ 10 at screening and anemia with Hgb < 10 g/dL.) Patients were randomly assigned 2:1 to receive an oral daily dose of either momelotinib or danazol for 24 weeks, when patients receiving danazol were given the opportunity to switch to momelotinib.

At 24 weeks, patients receiving momelotinib achieved an average reduction in baseline total symptoms score of -9.36, compared to -3.13 in the danazol arm. Patients in the momelotinib arm were more likely to go at least 12 weeks without requiring a red blood cell transfusion (30.8% versus 20.0%) and less likely to develop anemia (8% versus 11%). Spleen volume reduction was significantly greater in the momelotinib arm, too. Treatment discontinuation due to adverse events was lower among patients given momelotinib (18% versus 23%).

Momelotinib inhibits the JAK1 and JAK2 signaling pathways, as well as activin A receptor type 1 (ACVR1). The latter inhibition may explain lower rates of anemia. The FDA has stated that it will release its approval decision for momelotinib by June 2023.

**Navitoclax Shows Promise in Phase II Study**
Adding navitoclax to ruxolitinib improves management of myelofibrosis, suggests the results of a phase 2 study published in the *Journal of Clinical Oncology* in May 2022. Preclinical data suggested that ruxolitinib and navitoclax work synergistically. Ruxolitinib attenuates navitoclax capacity to promote apoptosis, while navitoclax appears to overcome resistance by resensitizing myeloid cells to JAK2 inhibition. In a phase 2, open-label trial that included 34 adult patients with intermediate- to high-risk myelofibrosis who were experiencing disease progression or had suboptimal response on a stable ruxolitinib dose (≥ 10 mg twice daily). Patients received additional therapy of navitoclax at a starting dose of 50 milligrams once daily, which was escalated to a maximum of 300 milligrams.

The primary end point of ≥ 35% spleen volume reduction from baseline was achieved by 26.5% of patients at week 24, and by 41%, at any time during the study. Additionally, 50% reduction of total symptom score was achieved by 30% (6 of 20) of patients at week 24, and bone marrow fibrosis improved by 1 to 2 grades in one third (11 of 33) of evaluable patients. Further trials of navitoclax for myelofibrosis are ongoing.

# For Your Patients: Where To Turn for Support

## The Leukemia & Lymphoma Society

Patients with myelofibrosis and other blood cancers can find support, information, and other resources at the Leukemia & Lymphoma Society (LLS). The LLS traces its roots to 1949, when New Yorkers Rudolph and Antoinette de Villiers, the parents of a teen who succumbed to leukemia five years earlier, established a fundraising and education organization in his name, known as the Robert Roesler de Villiers Foundation. The organization has changed names several times over the years, but has always been guided by the conviction that blood cancers are curable diseases. Today, LLS not only funds research on cures, but also provides a variety of services for patients, such as support groups and financial assistance. Learn more at lls.org.

**MPN Forum Live**

MPN Forum Live is a podcast for patients with and caregivers of people with myeloproliferative neoplasms, or MPNs, including myelofibrosis, polycythemia vera, and essential thrombocythemia. The podcast, which is hosted by Jeremy Smith, frequently presents patient stories, as well as interviews with experts on managing and treating MPNs.