The Hanns A. Pielenz Clinical Research Center for Myeloproliferative Neoplasm Newsletter

MPNFocus

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

SPRING 2022

Patient Spotlight: Calliope Kriticos Kalfas

Q: How were you first diagnosed with an MPN? Did you have any symptoms or was the MPN incidentally diagnosed?

A: In December 2018, my primary care doctor referred me to a hematologist because she was concerned that my platelet and white blood cell counts were high during a routine check-up. I went to the appointment and was in total shock when I realized that this doctor was an oncologist. I had no clue as to why she would refer me to an oncologist. I was in shock. The initial appointment was cancelled. *I* was glad! I did not want to see an oncologist. *I was not sick!!! I did not have any symptoms!* Grudgingly, I rescheduled the appointment a few months later because my primary care doctor insisted. I was diagnosed with polycythemia vera (in 2016). The doctor prescribed a high daily dose of hydroxyurea (HU). HU made me feel very tired and lethargic. I took it for 3 months and then, I was switched to anagrelide to decrease the risk of blood clots. After 3 days on anagrelide, I stopped it on my own because the doctor's office delayed calling me back and anagrelide caused terrible body pain. I did not sleep for 48 hours; I was nauseous, had fever, and cried from the pain. In Feb. 2019, I visited a second doctor who diagnosed essential thrombocythemia and prescribed HU, but at a much lower dose, which I could tolerate. I saw the second doctor monthly. At the third appointment, the doctor told me that I was fine and suggested seeing him in six months. Both my son Konstantinos and I decided that I would not go back to see this doctor.

"My belief in God and knowing that I walk on this earth doing His Will gives me the courage to carry on every day and continue healing. Every day is a lesson in trust: trusting God, your doctors, your body, yourself."

– Calliope Kalfas

Featured News

Q: Were you referred to the Clinical Research Center for MPNs or did you find it on your own, please? What was your MPN diagnosis at MD Anderson?

A [*continued from the previous question*]**:** At this point, the search began! I was on the internet day and night learning everything I could about myeloproliferative neoplasms (MPNs). During my search, I found the website named Clinical Research Center for MPNs at MD Anderson. It was through this site that I was introduced to Dr. Srdan Verstovsek. However, Dr. Verstovsek was at MD Anderson. *And I did not have cancer nor did I want to have cancer!*

But the more I read about my two previous diagnoses, the more I knew that the first two oncologists I had seen simply were not experts in these rare diseases. So, I pulled myself up by the bootstraps and called MD Anderson for an appointment with Dr. Verstovsek in September 2019. Within two weeks, I met with Dr. Verstovsek. Previously, I had arranged to have all my medical records, including a bone marrow biopsy, forwarded to Dr. Verstovsek. I had another bone marrow biopsy and other tests done at MD Anderson. Finally, I was correctly diagnosed with myelofibrosis in fall 2019. My tests showed that I harbor the *JAK2*V617F mutation and have diploid cytogenetics (normal). Initially, Dr. Verstovsek prescribed HU to decrease my platelet counts, but he gradually increased the dosing so that I could tolerate it, and I did not have a problem.

Letter from the Director

Greetings to All!

The beginning of 2022 was marked with a major advancement in the treatment of myelofibrosis.

On February 27, the Federal Drug Administration (FDA) granted accelerated approval to **pacritinib** (JAK2 inhibitor) for treatment of adults with intermediate or high-risk primary or secondary myelofibrosis and severe thrombocytopenia (platelet count below $50x10^9$/L; platelets are blood cells that are involved in clotting). Receiving FDA-approval for pacritinib is a very important advancement because until recently, there was a critical unmet need for thrombocytopenic patients with myelofibrosis; these patients have a poor prognosis and cannot be treated with the other JAK2 inhibitors (ruxolitinib and fedratinib) because these medications can further exacerbate low platelet counts. In previous phase 3 clincal trials, patients with myelofibrosis and low platelet counts achieved notable spleen and symptom responses when they were treated with pacritinib, regardless of platelet counts.

Dr. Srdan Verstovsek, Professor of Medicine in the Department of Leukemia at The University of Texas MD Anderson Cancer Center, serves as the Director of the Hanns A. Pielenz Clinical Research Center for Myeloproliferative Neoplasms (MPNs).
Dr. Verstovsek is an internationally renowned physician–scientist who is fully dedicaed to developing novel therapies for MPNs and understanding the biology of MPNs.

Furthermore, we are currently leading a very promising medication (momelotinib) in advanced clinical development for patients who have myelofibrosis and moderate/severe anemia. **Momelotinib** is unique among JAK1/2 inhibitors because it also inhibits ACVR1. ACVR1 is a protein receptor on the surface of hepatic (liver) cells that is a key regulator of hepcidin production. Hepcidin is a small peptide hormone that is the master regulator of iron metabolism in the body. Inhibition of ACVR1 results in suppression of hepcidin excretion, which leads to stimulation of red blood cell production and significant improvement of anemia, including the elimination of red blood cell transfusions. Previous phase 2 and 3 clinical trials showed the marked anemia benefits of momelotinib. Currently, we are leading the ongoing pivotal phase 3 trial MOMENTUM, which has already demonstrated promising preliminary results. Momelotinib may be approved in 2023 for myelofibrosis patients who have anemia. We eagerly look forward to several advancements for our patients!

Spotlight: Calliope Kalfas

[continued from page 1]

Q: Were you diagnosed with any other type of cancer besides MF? When were you diagnosed with it and how is it managed now?

A: Yes, I have chronic lymphocytic leukemia (CLL). I also had HR-positive/HER2-negative metastatic breast cancer to the femur/hip that was diagnosed in September 2020 (27 years after having breast cancer). I had a radical resection of the left femur and hip replacement in the Orthopedics department. I am treated with Ibrance and letrozole for metastatic breast cancer to the bones. I also had six months of physical therapy and occupational therapy. I had to learn to walk again. To make things even more interesting, prior to my hip/femur surgery, I was recovering from a torn rotator cuff. Painful? Very! And of course, everything was on the left side. Left femur/hip – left rotator cuff. Made rehabilitation extremely interesting. The physical and occupational therapists are the *best*!!! They pushed me just hard enough. Today, I walk exceptionally well. I use a cane when I am out in public, just to put everyone on notice that I am still a little fragile. My daughter laughs at me because I am usually carrying my cane instead of using it. There are not enough words to say how much I appreciate everyone in the Department of Rehabilitation.

Q: How has your MF been treated since you came to MD Anderson?

A: I was treated with HU in the past, but I don't take it now. Presently, I take Ibrance with letrozole for metastatic breast cancer. Ibrance has helped normalize my blood counts without the need to take HU. I was very happy when Dr. Verstovsek eliminated HU from my regimen. So far, Ibrance has worked wonders with my metastatic breast cancer, and the great surprise for me is that it also helps control my blood counts (platelets and white blood cells). Very importantly, I have not had side effects from Ibrance whereas I had to build up tolerance to HU.

Mrs. Kalfas (center) with her daughter Dimitra and her son Konstantinos.

"You cannot afford the luxury of one negative thought! When negative thoughts begin to crop into my mind, I immediately stop and say 'no' to myself. Not going there!"

– Calliope Kalfas

Q: Have you engaged in any educational activities on MPNs? Do you enjoy them, and have you benefited from them?

A: Yes, I definitely have. They have been very informative for me, especially when I was first diagnosed with MF. It was very scary for me, when not one but two doctors were really not too familiar with the MPN subtypes. I educated myself with the webinars and videos sponsored by MPN Education Foundation. Since I have been treated by Dr. Verstovsek, I read the MPN Focus newsletters, which I enjoy reading and find very informative.

Q: What have been the positive aspects of your journey?

A: I have become more aware of the little things. I enjoy every day. I enjoy the little precious moments that many times I previously brushed over. I love to walk in nature and look at her beauty. I love to talk with friends and family, offering hope when necessary; advice when asked; praise when deserved; and LOVE, always!!! I also found strength I never knew was there, especially when I had surgery during the COVID-19 outbreak. I was in the hospital for 3 weeks, and no one could visit me. I can say that the nursing staff at MD Anderson are absolutely fabulous! *They* became my family. They were so kind and compassionate. I still remember one of my nurses singing to me when I was so ready to leave the hospital and come home. She would sing to me – at the top of her lungs, just to make me laugh. And *that* she did!!!

Q: What have been your sources of support and encouragement?

A: There are no words that can express what I felt when I first met Dr. Verstovsek! After my "less than acceptable" encounters with doctors that were not familiar with my disease, it was so comforting to know that I was in the hands of an expert. Dr. Verstovsek is absolutely one of the humblest doctors I have ever met! His mere presence exudes comfort. There have been many times when just him laying his hand on my arm gave me courage in the face of my battle. Even behind the mask, I knew that he was smiling at me. They say that the eyes are windows to the soul; his eyes are kind, comforting, understanding, and wise.

Besides my wonderful MPN doctor and his team, my two children have been there with me during this entire adventure. I call it an adventure, because I have traveled the depths of my soul, the depths of my spirituality, and the depths of my family history. *My two wonderful children, my son Konstantinos and my daughter Dimitra, were there with me every step of the way!!!*

My belief in GOD and knowing that I walk on this earth doing His Will gives me the courage to carry on every day and continue healing. Every day is a lesson in trust: trusting GOD, trusting your doctors, trusting your body, trusting yourself. One of my favorite phrases is: "*You can't afford the luxury of one negative thought.*" *Whenever negative thoughts begin to crop in my mind, I immediately stop and say "no" to myself. "Not going there!!!"*

Q: Since you were diagnosed with MF, have you had any symptoms that affected your daily activities?

A: The main symptom that I have experienced is fatigue. I was 72 years old when I was diagnosed; today, I am 76. I smile and give myself permission to take a nap when I am tired. This seems to work every time. *Is it age? Or is it fatigue? It doesn't matter.* I still enjoy that nap, and without *any* quilt.

Q: Have you benefited from the treatments you received at MD Anderson?

A: I am alive and walking today because of the treatments I received at MD Anderson. Had I not made the decision to make that appointment with Dr. Verstovsek, I dare not think about where I would be today. It was because of him that I trusted in MD Anderson when I was diagnosed with metastatic breast cancer.

"I am alive and walking today because of the treatments that I received at MD Anderson. Had I not made the decision to make that appointment with Dr. Verstovsek, I dare not think about where I would be today. It was because of him that I trusted in MD Anderson when I was diagnosed with metastatic breast cancer." – *Calliope Kalfas*

Q: Have you participated in any clinical trials for MF or any other type of clinical research?

A: I have given permissions to Dr. Verstovsek (for MPN research) and the physicians who treat me in the departments of Orthopedics and Breast Medical Oncology to conduct clinical research on my blood specimens. My blood specimens are valuable resources for research because not only do I have myelofibrosis, which is a rare disease, but I also had HR-positive/HER2-negative metastatic breast cancer, which was diagnosed in 2020 (27 years after my first diagnosis of breast cancer in 1993). I have not participated in any clinical trials.

Q: Currently, you are treated with Ibrance (palbociclib) for HR-positive metastatic breast cancer; and the same medication concurrently improves your blood counts, which were high due to the MF in the past. Another medication (abemaciclib) that acts similarly to Ibrance will be studied in a clinical trial for MF at MD Anderson in the near future. What are your thoughts about this prospect?

A: I think this is wonderful! As I mentioned earlier, Ibrance has helped control my high blood cell counts (platelets and white blood cells); this indicates that this type of medications (CDK4/6 inhibitors) may be promising for the treatment of myelofibrosis besides HR-positive metastatic breast cancer. •

"I have become more aware of the little things. I enjoy every day. I enjoy the little precious moments that many times I previously brushed over. I love to walk in nature and look at her beauty. I love to talk with friends and family, offer hope when necessary; advice when asked; praise when deserved; and love, always!"

– *Calliope Kalfas*

Myeloproliferative Neoplasm 10 (MPN10) Total Symptom Score (TSS) Questionnaire

The Myeloproliferative Neoplasm 10 (MPN10) Total Symptom Score (TSS) Questionnaire is a valuable and very useful tool to assess and track the severity of MPN-related symptoms and the quality of life for each patient.

Monitoring the TSS derived from the MPN10 Questionnaire as a function of time provides the physician with an objective assessment of the patient's status while being off any therapy and in response to treatment. Routine measurement and monitoring of patient-reported symptoms over time guide the physician's decisions and result in the best possible care for our patients.

The importance and great value of the MPN10 Questionnaire is demonstrated by the fact that it has been validated and endorsed by the National Comprehensive Cancer Network (NCCN). The MPN10 Questionnaire is recommended in the NCCN Guidelines for MPN and is used globally for patients treated with both approved and investigational medications that are studied in clinical trials. NCCN comprises 30 leading cancer centers in the US, represented by global experts who aim to promote high-quality patient cancer care, research, and education.

At MD Anderson Cancer Center, the MPN10 Questionnaire was implemented in *Epic* in April 2022. All MPN patients will receive notification to complete the MPN10 Questionnaire 3 days before their appointment at MD Anderson. The patient will rate the severity of each symptom in the MPN10 Questionnaire (for example, fatigue, abdominal discomfort, itching) on a scale of 0 to 10.

Please review an example of the MPN10 Questionnaire in Figure 1. Each question has a score between 0 and 10. Zero corresponds to absence of the symptom, and 10 is the score for the worst symptom status. The individual scores that the patient marks for the 10 questions are added, and the MPN10 Total Symptom Score will be calculated automatically. The maximum possible TSS is 100. Higher TSS scores correspond to more severe symptoms. The individual scores for each question and the total scores are saved in *MyChart* at each visit, for example, at the beginning and during the course of treatment. The physician can review the scores as a function of time. For example, an increasing score between visits may indicate that the patient is not responding to treatment and the medication should be changed.

It is important for the patients to report the score for each question objectively. For example, early satiety, abdominal discomfort and unintentional weight loss may be associated with the severity of splenomegaly, frequently seen in patients with myelofibrosis. Fatigue and difficulty in concentrating may be correlated with anemia. Itching and bone pain may be related to uncontrolled myeloproliferation. Implementation of the MPN10 Questionnaire will positively impact our patients' quality of care. •

Q	Symptom	Score between 0 and 10 (0 when absent,10 for worst)	Score
		0 1 2 3 4 5 6 7 8 9 10	
1	Fatigue		7
2	Early satiety		8
3	Abdominal discomfort		6
4	Inactivity		5
5	Concentration problems		5
6	Night sweats		4
7	Itching (pruritus)		5
8	Bone pain (not arthritis)		3
9	Fever (>100°F)		2
10	Unintentional weight loss		6
		Total MPN10 Score	51

Figure 1. Example of MPN10 Total Symptom Score Questionnaire

Bone Marrow & MPN

Bone Anatomy. The bone comprises three tissues: compact bone, spongy bone, and bone marrow. Compact bone makes up the outer bone layer whereas spongy bone is located at the ends of the bones. **Bone marrow** is the soft, spongy tissue that is located at the center of most bones and has many blood vessels. There are two types of bone marrow: red and yellow. **Red bone marrow** contains blood stem cells that become red blood cells, white blood cells, and platelets (Figure 2).

Bone marrow aspiration and biopsy. After numbing a small area of skin, a hollow needle (bone marrow needle) is inserted into the patient's hip bone (Figure 3). A small amount of bone marrow, blood, and/or a small piece of bone with marrow are removed for examination under the microscope.

The bone marrow specimen that is removed during the procedure is sent to the pathology and cytogenetics/molecular laboratories. An expert pathologist examines the specimens under the microscope and characterizes the morphology and the appearance of the cells and the bone marrow. The pathology results together with the clinical findings lead the physician to the correct MPN diagnosis, for example, essential thrombocythemia (ET), polycythemia vera (PV), prefibrotic/early myelofibrosis, or myelofibrosis (MF).

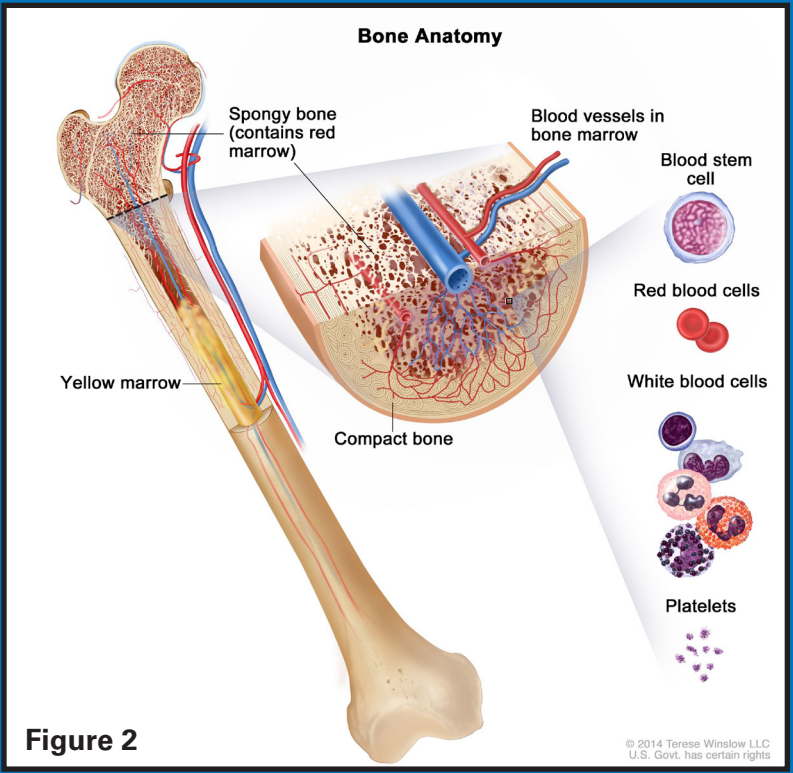


Figure 2

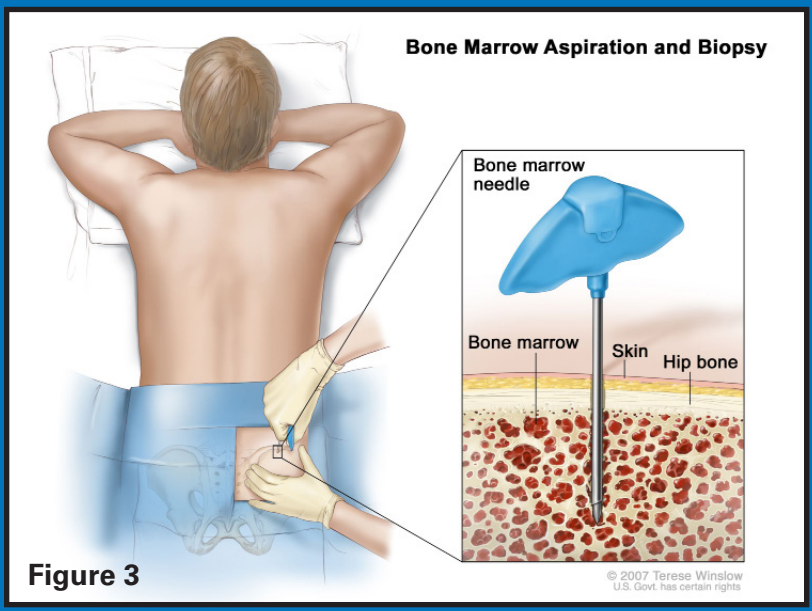


Figure 3

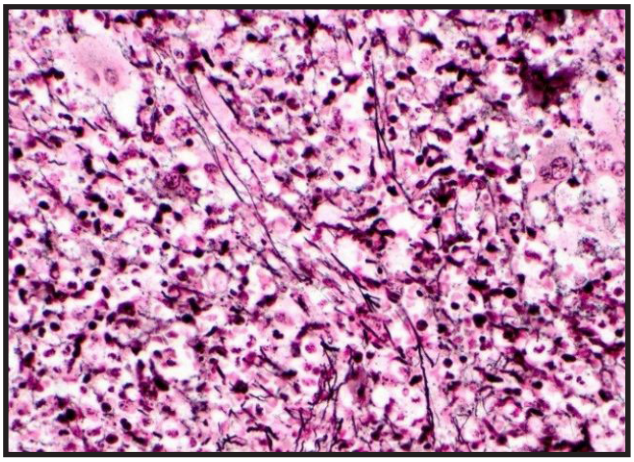
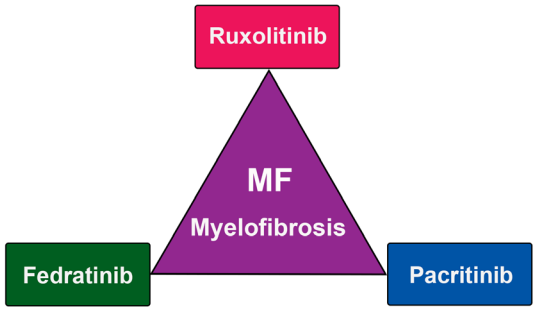


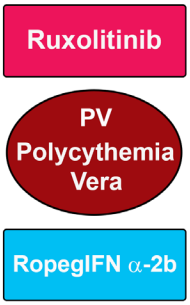
Figure 4. Bone marrow of patient with PMF and fibrosis

Other important tests that can be done on the bone marrow include cytogenetic analysis and genes that have been mutated; **mutation** is a change in the DNA sequence that may lead to disease development (along with other factors). In MPNs, *JAK2* mutations (usually V617F) are detected in the vast majority of patients (95%) who have PV and about 50-60% of the patients with primary MF or ET. *CALR* is mutated in about 20-30% of MF and ET patients; and *MPL* is mutated in approximately 10-20% of MF and ET patients. *JAK2*, *CALR* and *MPL* are named **driver mutations** because they make malignant cells grow out of control in the bone marrow.

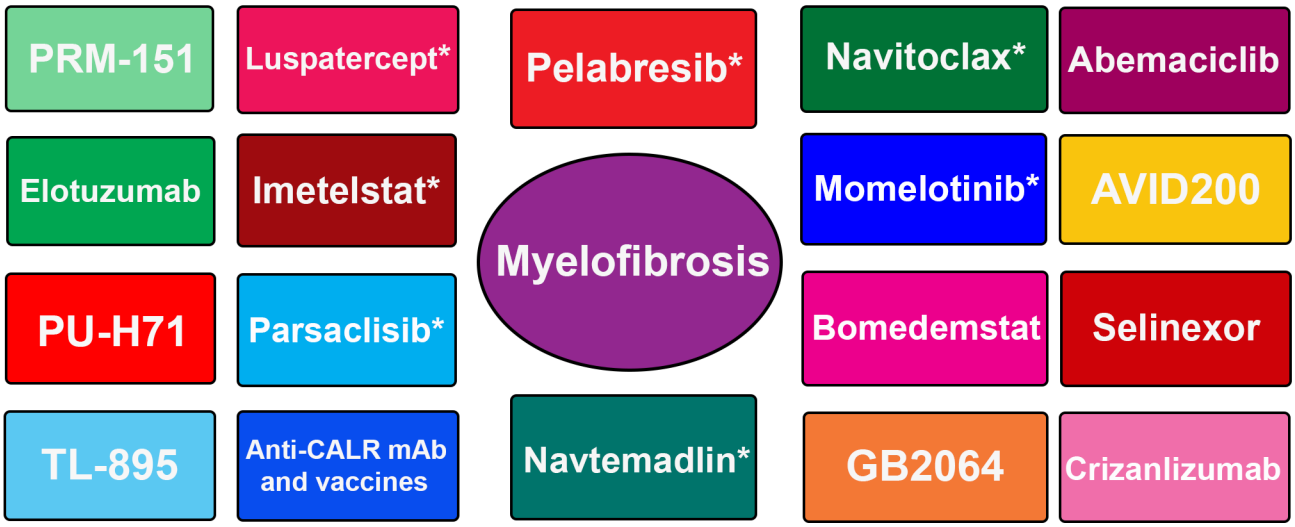
Approved Drugs for Myelofibrosis



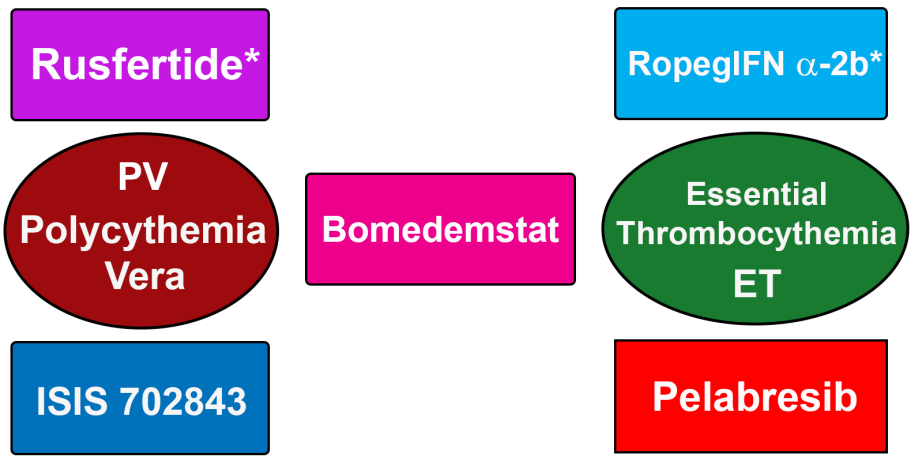
Approved Drugs for Polycythemia Vera



Selected Drugs in Development for Myelofibrosis



Drugs in Development for Polycythemia Vera and Essential Thrombocythemia



*Medications in phase 3 clinical trials

MPN Clinical Trials

Listed below are clinical trials enrolling patients with MPNs at The University of Texas MD Anderson Cancer Center. For more information on these clinical trials, please call the information line toll-free at 1-800-392-1611 or visit: https://www.mdanderson.org/research/departments-labs-institutes/departments-divisions/leukemia/clinical-trials.html and review the MPN section. To find other clinical trials for MPN, please go to clinicaltrials.gov. To schedule an appointment with a doctor in the Leukemia Department at the MD Anderson Cancer Center, please call 713-563-2000 (new patient line).

Phase 2 Study of Pemigatinib (INCB054828) in Patients Having Myeloid/Lymphoid Hematologic Malignancies with FGFR1 Rearrangement (8p11 Chromosomal Abnormality)

Protocol # 2016-0635

clinicaltrials.gov NCT No: 03011372

Principal Investigator:
Srdan Verstovsek, MD, PhD

Study Description: Pemigatinib is a potent oral inhibitor of the enzyme fibroblast growth factor receptor 1 (FGFR1), which plays a key role in cellular proliferation, migration, and survival. In patients with myeloid/lymphoid malignancies and a chromosomal abnormality involving chromosome 8 (specifically 8p11), a protein called FGFR1 is abnormally fused to another protein, and drives the disease. In this study, the efficacy of pemigatinib in MPN patients who have the FGFR1 rearrangement is evaluated. Pemigatinib showed very high rates of complete and partial responses, which were also durable.

Phase 3 Study (VERIFY) of the Hepcidin Mimetic Rusfertide (PTG-300) in Patients with Phlebotomy-Requiring Polycythemia Vera (PV)

Protocol # 2022-0005
clinicaltrials.gov NCT No: 05210790
Principal Investigator:
Srdan Verstovsek, MD, PhD

Study Description: The objective of this study is to evaluate the safety and efficacy of rusfertide compared to placebo in patients diagnosed with PV who required phlebotomies to maintain the hematocrit < 45% (with or without concurrent cytoreductive therapy). Rusfertide is a mimetic of hepcidin, which is a short peptide synthesized by hepatocytes (liver cells). Rusfertide is a key regulator of iron levels in the body, and therefore, it affects the production of red blood cells. In the phase 2 trial, patients required ≥3 phlebotomies before rusfertide treatment; rusfertide treatment essentially eliminated phlebotomies in all the patients. Rusfertide is injected under the skin.

Phase 1/2 Study of INCB000928 as Monotherapy Ruxolitinib in Participants with Anemia due to Myeloproliferative Disorders

Protocol # 2020-0409

clinicaltrials.gov NCT No: 04455841

Principal Investigator:

Srdan Verstovsek, MD, PhD

Study Description: In this study, the safety and tolerability of INCB000928 will be assessed in participants with myelofibrosis (post-polycythemia vera MF and post-essential thrombocythemia MF) who are transfusion-dependent or present with symptomatic anemia (hemoglobin <10 g/dL). The main goals of the study are to assess the efficacy of INCB000928 in improving anemia, the duration of anemia response, and the rate of transfusion-independence in MF patients with anemia. INCB000928 will be administered as monotherapy. INCB000928 is administered by mouth.

Phase 1b Study of PU-H71 in Patients with PMF, Post-PV MF, or Post-ET MF, Treated with Ruxolitinib

Protocol # 2019-0019
clinicaltrials.gov NCT No: 03935555

Principal Investigator:
Naveen Pemmaraju, MD

Study Description: The goal of this multicenter phase 1b study is to determine the highest tolerable dose of PU-H71 that can be administered to patients with PMF, post-PV MF, or post-ET MF, in combination with ruxolitinib, a Janus kinase 1/2 (JAK1/2) inhibitor. PU-H71 is an inhibitor of the heat shock protein 90 (HSP90). PU-H71 has demonstrated antineoplastic activity in many types of cancer. Among its other activities, HSP90 stabilizes several proteins involved in tumor growth, for example JAK2; therefore, HSP90 inhibitors are investigated as anticancer agents. In this clinical trial enrolling patients with MF, concurrent treatment with PU-H71 and ruxolitinib is expected to enhance the activity of ruxolitinib owing to the mechanisms of action of the two drugs (this is supported by preclinical studies). PU-H71 is administered by mouth. The study is open and enrolling patients.

A Phase 3 Study of Luspatercept (ACE-536) versus Placebo in Subjects with Myeloproliferative Neoplasm-Associated Myelofibrosis on Concomitant JAK2 Inhibitor Therapy and Who Require Red Blood Cell Transfusions (INDEPENDENCE trial)

Protocol # 2020-1010
clinicaltrials.gov NCT No: 04717414

Principal Investigator:
Srdan Verstovsek, MD, PhD

Study Description: The goal of this pivotal phase 3 clinical study is to evaluate the efficacy of luspatercept (ACE-536) versus placebo in patients with MF-associated anemia who are receiving concomitant JAK2 inhibitors and require red blood cell (RBC) transfusions. The study will assess the drug's potential to increase hemoglobin and eliminate the necessity for red blood cell transfusions. Anemia is a critical challenge in MF patients. Luspatercept increases RBC production. Adding luspatercept to the treatment of MF patients with anemia can eliminate the need for blood transfusions when symptoms are responding to JAK2 inhibitors.

An Open-Label, Phase 2a/2b Study of KRT-232 (Navtemadlin) in Patients with Primary MF, Post-PV MF or Post-ET MF Who Have Failed Prior Treatment with a JAK Inhibitor (BOREAS trial)

Protocol # 2018-0906
clinicaltrials.gov NCT No: 03662126

Principal Investigator:
Prithviraj Bose, MD

Study Description: The goal of this study is to evaluate the safety and efficacy of navtemadlin (formerly KRT-232) in patients diagnosed with MF. Navtemadlin is an inhibitor of protein human double minute 2 (HDM2). HDM2 inhibits the function of p53, an important protein that plays a critical role in cell survival and death (tumor suppressor). The phase 2 part of the study, evaluating navtemadlin in MF patients who relapsed or were refractory to ruxolitinib, was completed, and the optimal daily dose was determined. The phase 2 study was amended to the phase 3 study in which navtemadlin will be compared to best available therapy (excluding JAK inhibitors) in MF patients who are refractory/resistant to JAK inhibitors. The phase 3 part of the study (BOREAS) has been launched and is accruing patients. Navtemadlin is administered by mouth.

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Navitoclax in Combination with Ruxolitinib versus Ruxolitinib in Patients with Myelofibrosis (TRANSFORM-1)

Protocol # 2020-0743
clinicaltrials.gov NCT No: 04472598

Principal Investigator:
Naveen Pemmaraju, MD

Study Description: In this phase 3 study, the efficacy of navitoclax in combination with ruxolitinib versus ruxolitinib and placebo will be assessed in patients with intermediate-2 or high-risk myelofibrosis who have not been previously treated with a JAK inhibitor. The main goals of the study are to measure the percentage of patients who achieve spleen volume reduction of 35% or more and the percentage that achieves at least 50% reduction in Total Symptom Score (TSS) at 24 weeks. Navitoclax is a novel small molecule that inhibits the B-cell lymphoma 2 (Bcl-2) family of proteins (primarily Bcl-xL), which are overexpressed in many types of cancer and prevent cancer cells from dying. Preclinical studies demonstrated that inhibition of both Bcl-1/Bcl-xL and JAK2 has the potential to enhance death of malignant cells. Both navitoclax and ruxolitinib are administered by mouth.

Phase 2 Clinical Study of the Safety, Efficacy, Pharmacokinetic, and Pharmacodynamic Profiles of Bezuclastinib (CGT9486) in Patients with Advanced Systemic Mastocytosis (APEX trial)

Protocol # 2021-0587
clinicaltrials.gov NCT No: 04996875

Principal Investigator:
Prithviraj Bose, MD

Study Description: In mastocytosis, the body makes too many mast cells. In this phase 2 study, the safety and efficacy of bezuclastinib will be evaluated in patients with advanced systemic mastocytosis. Bezuclastinib is an oral small-molecule differentiated inhibitor of the KIT kinase and has unique selectivity to the mutation *KIT* D816V, which drives the growth of mast cells (type of white blood cells). Bezuclastinib is administered by mouth.

Study of CPI-0610 (Pelabresib) in Patients with Essential Thrombocythemia Who Are Intolerant or Refractory to Hydroxyurea

Protocol #2018-0202
clinicaltrials.gov NCT No: 02158858

Principal Investigator:
Prithviraj Bose, MD

Study Description: Pelabresib (formerly CPI-0610) inhibits the activity of bromodomain and extra-terminal domain (BET) proteins, which have a wide range of cell functions, including the bone marrow. The MANIFEST trial had three Arms in which pelabresib alone or in combination with ruxolitinib was evaluated in patients with myelofibrosis. This study constitutes a new arm that was added to the MANIFEST trial. The goal of this new study is to explore the efficacy of pelabresib in patients with high-risk essential thrombocythemia (ET) who are intolerant of or refractory to hydroxyurea. ET is considered high-risk when the patient's age is 60 years and higher or they have prior history of thrombosis. In this study, the potential of pelabresib to decrease proliferation of megakaryocytes in the bone marrow and platelets in the peripheral blood along with thrombotic events will be evaluated. Pelabresib is administered by mouth as a pill.

Randomized Phase 2 Clinical Study of the Safety and Efficacy, of Bezuclastinib (CGT9486) in Patients with Indolent or Smoldering Systemic Mastocytosis (SUMMIT trial)

Protocol # 2021-0880
clinicaltrials.gov NCT No: 05186753

Principal Investigator:
Prithviraj Bose, MD

Study Description: In mastocytosis, the body makes too many mast cells (mast cells respond to allergic and immune reactions). In this phase 2 study, the safety and efficacy of bezuclastinib vs. placebo will be evaluated in patients with indolent (non-advanced) systemic mastocytosis. Bezuclastinib is an oral small-molecule differentiated inhibitor of the KIT kinase and has unique selectivity to the mutation *KIT* D816V, which drives the growth of mast cells. Bezuclastinib is administered by mouth.

Phase 3 Randomized, Double-Blind Active-Control Study of CPI-0610 (Pelabresib) and Ruxolitinib vs. Placebo and Ruxolitinib in JAK-Inhibitor Treatment-Naïve MF Patients (MANIFEST-2 trial)

Protocol #2020-0739
clinicaltrials.gov NCT No: 04603495

Principal Investigator:
Srdan Verstovsek, MD, PhD

Study Description: Pelabresib (formerly CPI-0610) is an oral epigenetic modifier that interferes with the activity of bromodomain and extra-terminal domain (BET) proteins, which have a wide range of cell functions. Inhibition of BET proteins reduces the levels of many other proteins that are important for survival and multiplication of cells, including drivers of bone marrow fibrosis. In this pivotal phase 3 study, pelabresib is administered in combination with ruxolitinib to MF patients not previously treated with JAK inhibitors. In the MANIFEST trial, pelabresib alone or in combination with ruxolitinib showed promising clinical activity– namely, significant improvements in spleen volume reduction, hemoglobin levels, red blood cell transfusion burden, and reduction in bone marrow fibrosis and symptoms. Treatment with pelabresib may have disease-modifying potential in MF.

An Open-Label, Phase 2a Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Oral GB2064 (LOXL2 Inhibitor) in Participants with Myelofibrosis

Protocol # 2020-1217
clinicaltrials.gov NCT No: 04679870

Principal Investigator:
Srdan Verstovsek, MD, PhD

Study Description: In this study, the safety and efficacy of GB2064 will be evaluated in patients with myelofibrosis (intermediate- or high-risk) who are not currently taking a JAK inhibitor (e.g., ruxolitinib or fedratinib) and are refractory, intolerant or ineligible. It has been shown that the enzyme lysyl oxidase (LOX) promotes formation of a network of collagen fibers and is elevated in the bone marrow of mice and MF patients, thereby promoting fibrosis (scarring). In preclinical studies, small-molecule inhibitors of LOX showed promising results in slowing down the progression of myelofibrosis. GB2064 is administered by mouth.

Phase 3 Clinical Study Evaluating Imetelstat vs. BAT in Adult Patients with Intermediate-2 or High-Risk Myelofibrosis (MF), Refractory to Janus Kinase (JAK) Inhibitors (IMpactMF)

Protocol # 2020-1141
clinicaltrials.gov NCT No: 04576156

Principal Investigator:
Srdan Verstovsek, MD, PhD

Study Description: Imetelstat is a potent inhibitor of telomerase, an enzyme that maintains the structural integrity of chromosomes in normal and cancer cells. Chromosomes are finger-like structures in the nuclei of cells that carry genes. The clinical efficacy of imetelstat and the possible benefit in prolonging survival of patients with myelofibrosis patients relapsed/refractory to ruxolitinib (a JAK inhibitor, standard first-line therapy for most myelofibrosis patients) was evaluated in the phase 2 trial (IMbark). In the IMbark study, the higher dose of imetelstat was possibly associated with a prolonged survival (vs. what one would expect), and this dose will be administered intravenously every 21 days in the pivotal phase 3 trial (IMpactMF), that will compare imetelstat to best available therapy (BAT), excluding JAK inhibitors.

Phase 2 Study Assessing the Safety and Efficacy of KRT-232 or TL-895 in JAK Inhibitor Treatment-Naïve Myelofibrosis

Protocol # 2021-1335
clinicaltrials.gov NCT No: 04878003

Principal Investigator:
Srdan Verstovsek, MD, PhD

Study Description: This open-label phase 2 study is evaluating the safety and efficacy of navtemadlin (formerly KRT-232) or TL-895 in MF patients who had not been previously treated with JAK inhibitors. Navtemadlin is an inhibitor of human double minute 2 (please see protocol #2020-0279). TL-895 is a Bruton's tyrosine kinase (BTK) inhibitor. TL-895 plays a key role in activating NF-κB, a protein that controls DNA transcription, cytokine production and cell survival. Both medications are administered by mouth.

Phase 3 (SURPASS ET), Open-Label, Multicenter, Randomized, Active-Controlled Study to Assess Pharmacokinetics and Compare the Efficacy, Safety, and Tolerability of Ropeginterferon alpha-2b (P1101) versus Anagrelide as Second-Line Therapy for Essential Thrombocythemia (ET)

Protocol # 2020-0108
clinicaltrials.gov NCT No: 04285086

Principal Investigator:
Srdan Verstovsek, MD, PhD

Study Description: Ropeginterferon alpha -2b is a novel, long-acting interferon formulation that can be administered by injection, bi-monthly instead of weekly. In February 2019, ropeginterferon alpha-2b was approved as a treatment for PV patients who require phlebotomies in the European Union and in the US in November 2021.

This phase 3 study (SURPASS ET) will assess the efficacy (platelets and white blood cells, disease symptoms, hemorrhagic or thrombotic events), safety and tolerability of ropeginterferon alpha-2b compared to anagrelide (a medicine that reduces platelets), after 12 months of treatment, as a second-line therapy for high-risk ET patients who had a suboptimal response or failed hydroxyurea (standard first line therapy).

Phase 1 Study of Elotuzumab in the Treatment of *JAK2*-Mutated Primary Myelofibrosis, Post-PV MF, or Post-ET MF

Protocol # 2020-0522
clinicaltrials.gov NCT No: 04517851

Principal Investigator:
Prithviraj Bose, MD

Study Description: The goal of this pilot study is to assess the efficacy (improvements in blood cell counts and bone marrow fibrosis grade, splenomegaly, and disease-related symptoms), safety and tolerability of elotuzumab in patients with MF who are not candidates for JAK inhibitors or have failed JAK inhibitors. Elotuzumab is an anti-SLAMF7 monoclonal antibody that has the potential to improve or reverse bone marrow fibrosis. Elotuzumab is administered by injection.

An Open-Label, Multicenter, Phase 1b/2 Study of the Safety and Efficacy of KRT-232 Combined with Ruxolitinib in Patients with PMF, Post-PV MF, or Post-ET MF Who Have a Suboptimal Response to Ruxolitinib

Protocol # 2020-0279
clinicaltrials.gov NCT No: 04485260

Principal Investigator:
Prithviraj Bose, MD

Study Description: This clinical research study will evaluate the safety and efficacy of ruxolitinib and navtemadlin (formerly KRT-232), an orally administered inhibitor of the human double minute 2 (HDM2) protein, in patients with myelofibrosis. HDM2 inhibits the function of a very important protein (p53), which plays a critical role in cell survival and death. Navtemadlin in combination with ruxolitinib may show synergistic efficacy and disease modification through a complementary mechanism promoting death of malignant cells. Patients participating in this clinical trial should be on a stable dose of ruxolitinib and have suboptimal response to it. Navtemadlin is administered by mouth as a pill.

Phase 2 Open-label, Multicenter Study of TL-895 in Patients with Relapsed/Refractory Myelofibrosis, Janus Kinase Inhibitor-Intolerant Myelofibrosis and Janus Kinase Inhibitor Treatment-Ineligible Myelofibrosis

Protocol # 2020-0738
clinicaltrials.gov NCT No: 04655118

Principal Investigator:
Srdan Verstovsek, MD, PhD

Study Description: This study aims to evaluate the efficacy of TL-895 in myelofibrosis patients who do not respond to ruxolitinib. Ruxolitinib (JAK1/2 inhibitor) is the standard first-line therapy for the majority of myelofibrosis patients. Patients who relapse or are not eligible to be treated with JAK inhibitors can also be enrolled in this study. TL-895 is a Bruton's tyrosine kinase (BTK) inhibitor that plays a key role in activating NF-κB. NF-κB is a protein that controls DNA transcription, cytokine production, and cell survival. BTK activity is important for the growth of cancer cells; malignant cells die when they are treated with TL-895. TL-895 has a novel mode of action and is administered by mouth. •

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MPN Focus

MPN Focus is a periodic newsletter published by The Hanns A. Pielenz Clinical Research Center for Myeloproliferative Neoplasm at MD Anderson Cancer Center. MPN Focus provides the members of the MPN community with information on current research and treatments.

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Resources for Physicians & Patients

MPN Advocacy & Education International

Founded by Ann Brazeau, former vice president of development at **MPN Research Foundation, MPN Advocacy & Education International** provides educational programs, materials, and resources for patients, caregivers, physicians, and entire healthcare teams to improve their understanding of MF, PV, and ET. Information on 2019 Patient Education Symposia, hosted by MPN Advocacy & Education International, can be found at http://mpnadvocacy.com/events/. For more information, visit mpnadvocacy.com or contact Ann Brazeau at 517-889-6889 or abrazeau@mpnadvocacy.com.

MPNforum – the MPN community's publication – is a non-profit online magazine, founded by Zhenya Senyak (MPN patient). MPNforum (mpnforum.com) publishes articles and stories focused on patients diagnosed with an MPN. Founded in 1994 by patient advocate, Robert Tollen, the MPDSupport.org website and email list offers interesting information on MPNs. All are welcome to subscribe, and all archives are available. Robert, who was diagnosed with PV in 1990, has created a closed Facebook group with more than 1500 members. For more information or to join the listserve, please go to mpnsupport.org or email listserv@listserv.icors.org with "subscribe mpdsupport" in the email.

MPN Education Foundation

Formed in 2004, the **MPN Education Foundation** aims to bring information and support to MPN patients and their loved ones all over the world via the website mpninfo.org, by convening a conference every 2 years and via the email-based group MPN-NET.

MPN-NET is an email-based support group that was formed in 1994 by patient Joyce Niblack. In May 1996, the group became a member of the Association of Cancer Online Resources, distributing email via a listserv platform. Although MPN-NET remains a US-centered organization, the group has nearly 2,900 members across the globe. All discussions are archived and available to all members since its inception (May 1996). You can subscribe to MPN-NET on the Foundation's homepage at mpninfo.org.

The Patient Story

The Patient Story was initiated by Stephanie Chuan to help cancer patients. Stories of cancer patients and expert interviews are posted. For MPNs, please visit: https://www.thepatientstory.com/medical-experts/oncologist/srdan-verstovsek/

Apfed
American Partnership for Eosinophilic Disorders

APFED is a non-profit patient advocacy organization established to assist and support patients and their families coping with eosinophilic disorders, including eosinophil-associated gastrointestinal disorders, hypereosinophilic syndrome, and Churg-Strauss Syndrome. For more information, visit Apfed.org.

MPN Cancer Connection

MPN Cancer Connection, also founded by David Wallace, is a non-profit "patient-focused" organization that helps educate and empower MPN patients by providing the necessary resources and funding for PV Reporter. For more information or to subscribe to their newsletter, please visit mpncancerconnection.org.

The Mastocytosis Society, Inc.

The Mastocytosis Society, Inc. is a non-profit organization dedicated to supporting patients with mastocytosis and mast cell activation disorders, as well as their families, caregivers and physicians through research, education and advocacy. Please visit tmsforacure.org.

PV Reporter

PV Reporter.com is a comprehensive, easy-to-navigate, patient-focused website for MPNs developed by David Wallace, "an aspiring web designer, publisher, writer, patient advocate," who was diagnosed with polycythemia vera in 2009. PV Reporter.com was created to provide "easy access" to pertinent information on PV, ET, and MF. For more information, please visit pvreporter.com.

MPN Research Foundation
Change Your Prognosis

Founded by patients for patients, the **MPN Research Foundation** is a catalyst for research funding, in pursuit of new treatments – and eventually a cure – for MPNs. The Foundation has funded numerous laboratory and clinical projects related to MPN research to date. The Foundation is also dedicated to helping patients change their prognosis by serving as a valuable source of education and resources in the MPN community. For more information, please visit mpnresearchfoundation.org.