

Patient Spotlight: Linda Ledbetter

Q: When were you first diagnosed with a myeloproliferative neoplasm (MPN) and which subtype, please? Did you first come to MD Anderson to be treated for MPN?

A: The symptom that led to diagnosis of myelofibrosis (MF, one of the MPNs) was itching. I had itching for about 1.5 years before I was diagnosed; itching became intolerable after a shower in summer 2016. I consulted my allergist about the persistent itching, and she suggested to have blood work done. My allergist reviewed the results and together with my hematologist recommended seeing an oncologist. My husband, who was an internal medicine physician and allergist was already being treated for amyloidosis at MD Anderson. The physician who I first consulted in the Department of Lymphoma and Myeloma ordered a bone marrow biopsy and other tests for me. The results led to diagnosis of monoclonal paraproteinemia (or gammopathy) and also indicated an MPN. The physician from the Department of Lymphoma and Myeloma personally called Dr. Verstovsek to refer me. Dr. Verstovsek diagnosed MF. We had a long discussion with Dr. Verstovsek at my first visit. Dr. Verstovsek was very gracious, and he relieved the great burden I had regarding my prognosis.

Q: Has your quality of life improved with treatment?

A: Presently, I have excellent quality of life thanks to the great care I received at MD Anderson. Quality of life is very important to me.



“I consider it my greatest blessing to receive the best medical care and be treated at MD Anderson. I was honored to participate in a clinical trial at MD Anderson, and it would be my privilege to participate in any clinical trials my doctors conduct.”

– Linda Ledbetter

Q: Have you experienced any symptoms since you were diagnosed with MF? Did they improve with the treatment at MD Anderson?

A: A few years ago, I experienced splenomegaly. I also had night sweats, fatigue (low energy). In early 2020, I started taking ruxolitinib due to splenomegaly and worsening of fatigue and itching. At one point, my spleen was enlarged about 3 inches below the ribs on the left side of my abdomen. Treatment with ruxolitinib has improved my symptoms tremendously. Notably, at one of my visits at MD Anderson, in the waiting room, I met another MF patient who had been treated with ruxolitinib for 14 years. Currently, the size of my spleen is normal (not palpable on physical exam), and itching is under control. Lukewarm showers with an anti-allergic body wash, followed by a cold rinse at the end also helped with itchiness. I am allergic and have an allergy shot every month. In the past, I used nasal cromolyn sodium and later, the oral cromolyn solution, which alleviated itchiness considerably. Itchiness has improved a lot since I eliminated dairy from my diet.

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Letter from the Director

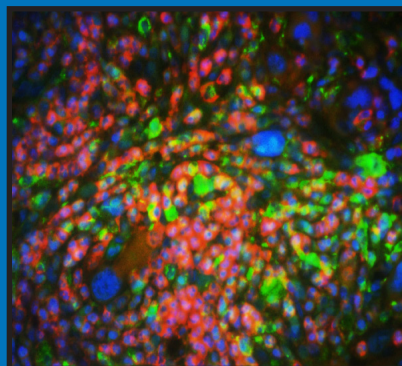
Greetings to All!

It is a very exciting time in research of MPNs, especially for myelofibrosis (MF), because a range of new medications, beyond the cornerstone drug ruxolitinib, are in advanced clinical development. The investigational medications act through a wide array of biological pathways and are evaluated as monotherapies or in combination with ruxolitinib (a JAK inhibitor). With the new agents, we aim to enhance the therapeutic potential of ruxolitinib, improve deficiencies not addressed by JAK inhibitors, such as anemia, or provide options for patients who develop resistance/intolerance to approved JAK inhibitors. We expect to witness major advancements in MPN in the near future.

We are currently leading several highly promising MPN medications, in advanced phase clinical trials, at a global level. Among the medications in pivotal phase 3 randomized clinical trials are the JAK inhibitors **momelotinib** (MOMENTUM trial) and **pacritinib** (PACIFICA trial); the two highly promising JAK inhibitors address major unmet medical needs of specific patients with MF who experience severe anemia or very low platelet counts. Other medications that are being investigated in randomized phase 3 clinical trials at MD Anderson for possible FDA approval include the following: **Luspatercept** is evaluated for anemia benefits and its potential to eliminate the need for blood transfusions in anemic MF patients who are receiving ruxolitinib (INDEPENDENCE trial; comparison to placebo). **CPI-0610** or **pelabresib** (BET inhibitor) appears to enhance the activity of ruxolitinib in improving quality of life and splenomegaly.



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 (MPN). Dr. Verstovsek is an internationally renowned physician-scientist who is fully dedicated to developing novel therapies for MPN and understanding the biology of MPN.



Transfusion-independence was also noted in the current trial. Trial MANIFEST-2 compares the efficacy of CPI-0610 and ruxolitinib to ruxolitinib only in JAK inhibitor-naïve patients. **Navitoclax** (Bcl-xL inhibitor) is evaluated in combination with ruxolitinib in two phase 3 trials in MF patients who relapsed or were refractory to ruxolitinib (TRANSFORM-II; comparison to a physician's therapy of choice) and in the frontline setting (TRANSFORM-I) where the combination of navitoclax with ruxolitinib is compared to ruxolitinib alone.

Imetelstat (telomerase inhibitor) is a pioneering medication in treatment of MF because it appears to significantly prolong survival of MF patients who failed ruxolitinib. The phase 3 study is underway, comparing imetelstat to a physician's therapy of choice in such MF patients.

KRT-232 (HDM2 inhibitor) is evaluated in advanced phase studies, including the phase 3 trial (BOREAS) in MF patients who are refractory/resistant to ruxolitinib (comparison to physician's choice therapy). **Ropeginterferon alpha-2b** is a novel long-acting interferon that is evaluated in ET patients who have resistant or intolerant to hydroxyurea (SURPASS ET trial; comparison to anagrelide).

As always, we are strongly committed to excellent patient care and strive to develop innovative therapeutics that will significantly improve the lives of our patients and ultimately cure them. We remain optimistic that the new medications in clinical development will transform the field of MPN in the near future. •

We wish you all a blessed and pleasant Summer!

Spotlight: Linda Ledbetter

[\[continued from page 1\]](#)

“I have excellent quality of life thanks to the great care I received at MD Anderson. Quality of life is very important to me.” – Linda Ledbetter

Q: What have been your sources of support and optimism during this journey, please?

A: My husband, my daughter and all my doctors have been very supportive. I have been very blessed to receive the best medical care and to be treated at MD Anderson. I consider this my greatest blessing! I have a wonderful group of doctors who are treating me at MD Anderson. I have always had the best medical care; I have been very privileged. My doctors have been fabulous! I know when a doctor is interested and thorough because my husband was a physician for 55 years. He passed away a few years ago. It has been difficult to lose the support and comfort that my husband provided. He was a wonderful doctor and showed personal interest for his patients. His father, grandfather and great-grandfather were all physicians! I have also been impressed with the personal care of the doctors at MD Anderson. For example, recently, I had to see a rheumatologist at MD Anderson. Dr. Verstovsek personally called the physician and informed her about my condition. Experiencing this personal interest made me feel very wonderful, especially since I no longer have my husband’s support. It was very kind and generous of Dr. Verstovsek to do this. Personal interest and care on behalf of the physician are rare to find. I also appreciate the sincerity and expertise of Dr. Verstovsek and his medical team. The fellows who are training with Dr. Verstovsek frequently tell me: “You have the best doctor for MPN treating you!”

My daughter is very special. She has been remarkable and very supportive, especially since my husband passed away a few years ago. She has taken a lot of responsibility regarding my health. She attends my visits with Dr. Verstovsek and



Mrs. Linda and Dr. Abbe Ledbetter, Jr.

asks questions (remotely). My daughter has a medical background because she worked for a pharmaceutical company; she is very informed and interested in my disease. My daughter’s love and support mean so much to me! The community at my Church has also supported me emotionally. I have strong faith and feel so blessed that my illness is not horrible because I can still do 75-80% of the activities I enjoy. I consider it a blessing because I don’t live far from the hospitals. Other people come from all over the world to be treated at MD Anderson.

Q: How did the MF diagnosis impact you? How have you coped with the challenges?

A: At my first appointment, Dr. Verstovsek lifted my spirits with his graciousness and reassurance that my prognosis was not negative as I originally thought. In the past, I occasionally found myself “in the blues”, but I have overcome it. Every time I come to MD Anderson, I see so many people who are very ill, but they are brave. I think about how blessed I am to have such a minor disease. I have had a nearly perfect life regarding my health. Very few people have a perfect life. I have had some challenges but overall, I have been very blessed. I do not like to dwell on the negative aspects of the disease; I focus on the positive aspects. I have had many good years. About 10 years ago, we travelled with my husband from Venice to Greece through Croatia on a cruise ship. The sea was beautiful! We had a spectacular time!

Q: Have you participated in any MPN educational activities?

A: I attended the two *Annual MPN Patient Forums* that Dr. Verstovsek organized at MD Anderson in 2016 and 2017. The Forums were so encouraging and supportive! I loved them. I also enjoy reading the *MPN Focus* newsletters.

Q: If the medications you are taking ceased to be effective, would you consider participating in clinical trials evaluating new promising treatments for MF?

A: If necessary, I would be very pleased to participate in a clinical trial for MF. I participated (as a control patient) in a clinical trial for gammopathy (that may lead to multiple myeloma) for 3 years in the Department of Lymphoma and Myeloma. During the study, I answered many questionnaires. Notably, I completed the program about a year ago. I was honored to participate in this clinical research study at MD Anderson. A few medical experiences that happened to close family members helped me appreciate how important medical research is. Both my mother who was a nurse and my aunt had similar benign brain tumors; my mother died because of the tumor but my aunt’s tumor “disappeared” after she was treated with an investigational steroid! I consider it very important to participate in medical research studies because it is my way to give back to the medical community for all the benefits I have received. I am very pleased with my care and the doctors at MD Anderson, and it would be my privilege to participate in any clinical trials they conduct.

Q: What activities do you enjoy?

A: I have been very active since my childhood. My family always participated in many social and cultural activities. My grandfather was a sculptor in Houston and made the exterior sculptures at Rice University. We had a lot of friends. We entertained many friends with my husband. I look forward to my goddaughter’s wedding, which will take place in New Orleans, in November. I plan to attend all the ceremonies; and go to the gatherings and parties. I look forward to dressing up again. I recently started going to the gym again and playing golf. I have two cats that keep me company and are very affectionate. •

Overview of Myeloproliferative Neoplasms (MPNs)

In our body, we have three major types of blood cells:

Red blood cells (RBCs) are also named erythrocytes. Red blood cells carry oxygen throughout our body. The protein within the RBCs that carries oxygen to the body (with the help of iron ions in heme) is named **hemoglobin** and gives the bright red color to oxygenated blood. All our tissues need oxygen to function normally. The percentage of RBCs in the blood is the **hematocrit** (central figure below). **Anemia** occurs when the number of RBCs decreases.

White blood cells play a major role in fighting infections. When WBCs are low, infections are likely to occur.

Platelets or thrombocytes help control bleeding.

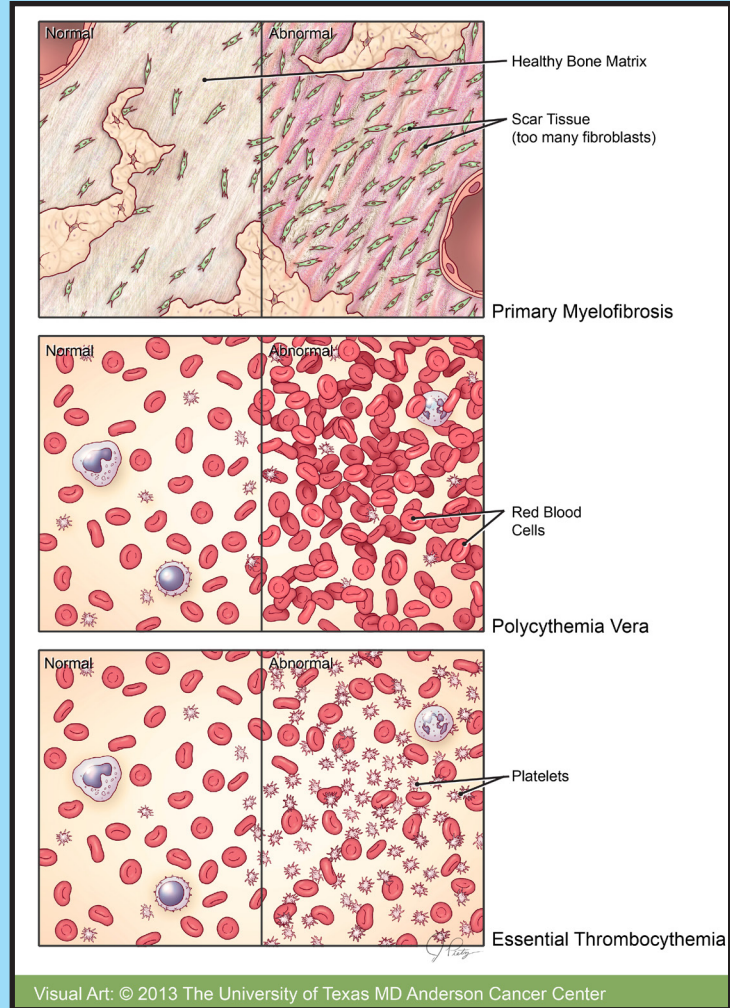
Most of our blood cells are formed in the bone marrow from blood stem cells. **Bone marrow** is the soft, sponge-like tissue in the center of most bones, and it has many blood vessels (figure below). When the bone marrow produces too many myeloid blood cells, a group of chronic blood cancers named **myeloproliferative neoplasms (MPNs)** arise. *Myelo* means "marrow" in Greek, *proliferative* means "uncontrolled", and *neoplasm* is any abnormal growth.

The major MPN subtypes are the following (figure to the right):

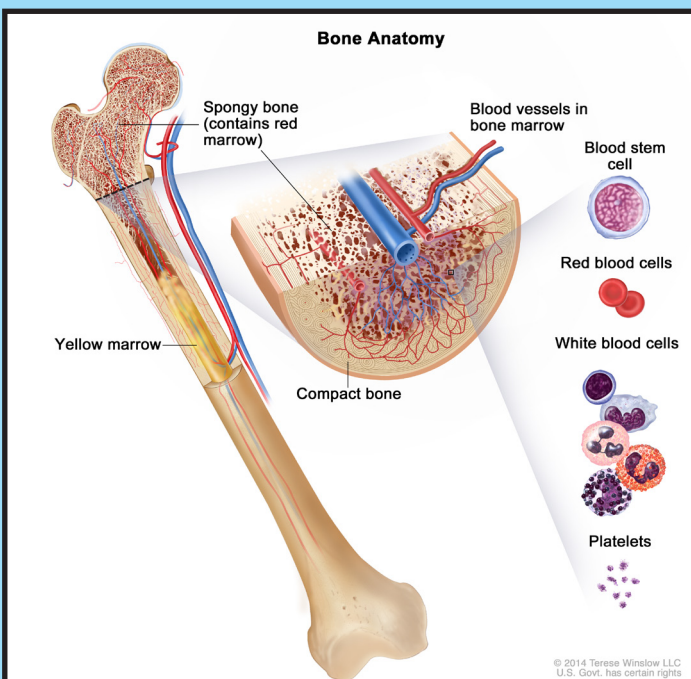
Primary myelofibrosis (PMF) is characterized by bone marrow fibrosis (scarring), namely fibers progressively replace the bone marrow, a process that leads to low counts of the 3 main blood cell types and ultimately failure of the marrow to produce blood. PMF is the most aggressive MPN.

Polycythemia vera (PV) is characterized by an elevated red blood cell mass, leading to a high hematocrit. *Polycythemia* is composed of the Greek words *poly*, which means "many", *cyt* for "cells", and *hemia* from the word *heme* for "blood".

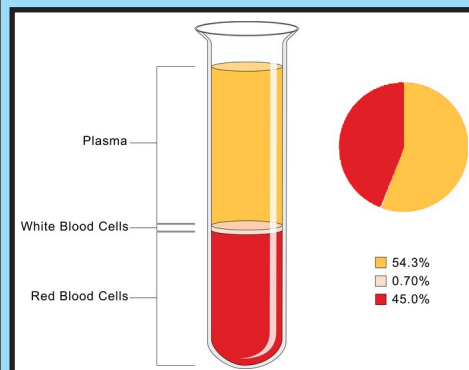
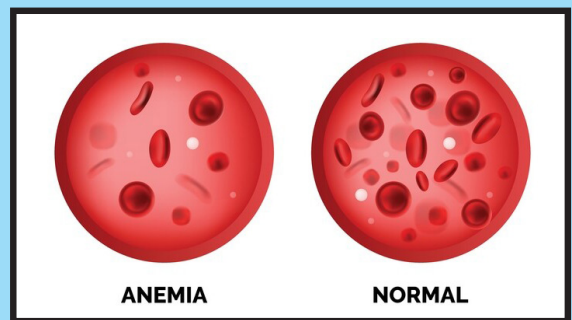
Essential thrombocythemia (ET) is characterized by high platelet (or thrombocyte) counts and megakaryocytes (the precursors of platelets) in the bone marrow. ET is the most indolent MPN and has the best prognosis among MPNs.



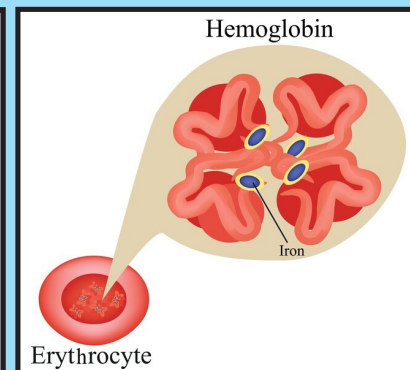
Features of the three main MPN subtypes



Production of the 3 blood cell types in the bone marrow



Hematocrit (red layer)



Hemoglobin with 4 heme units

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-](https://www.mdanderson.org/research/departments-labs-institutes/departments-divisions/leukemia/clinical-trials.html)

[trials.html](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. Early results from this study showed that most patients achieved complete remission.

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: CPI-0610 is an oral medication that inhibits the activity of bromodomain and extraterminal domain (BET) proteins, which have a wide range of functions. Inhibition of BET proteins reduces many other proteins that are important for survival and multiplication of cells, including drivers of bone marrow fibrosis. In this pivotal phase 3 study, CPI-0610 or the placebo is administered in combination with ruxolitinib to MF patients not previously treated with JAK inhibitors. CPI-0610 with ruxolitinib showed enhanced efficacy in the phase 2 MANIFEST trial. The two drugs may work better together than ruxolitinib alone.

Phase 1/2 Study of INCB000928 as Monotherapy or in Combination with 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 alone or in combination with ruxolitinib. INCB000928 is administered by mouth.

To schedule an appointment with a doctor in the
Leukemia Department at MD Anderson, please call:
1-85-LEUKEMIA or 713-563-2000

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 multi-center 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 anti-neoplastic 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.



Phase 1b/2 Study of APG-1252 in Patients with Myelofibrosis Who Progressed after Initial Therapy

Protocol # 2020-0814
clinicaltrials.gov NCT No: 04354727

Principal Investigator:
Naveen Pemmaraju, MD

Study Description: The objective of this study is to evaluate the safety and tolerability of APG-1252 in patients with MF (in chronic or accelerated phase) who are ineligible to receive JAK inhibitor treatment or had inadequate response to ruxolitinib and can receive it with APG-1252. Pelcitoclax (APG-1252) is a novel dual inhibitor of the Bcl-2/Bcl-xL proteins. The trial is based on preclinical data showing that JAK2-mutant cells depend on Bcl-2/Bcl-xL, and the combination of a JAK2 inhibitor with a Bcl-2/Bcl-xL inhibitor overcame cell resistance to a JAK2 inhibitor alone. APG-1252 is administered intravenously.

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) or Reblozyl versus placebo in patients with myelofibrosis-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 RBC transfusion-dependence. Anemia is a critical challenge in MF patients, and at present, there are no approved medications to treat it. Luspatercept increases RBC production. The purpose of adding luspatercept to the treatment regimen of MF patients with anemia is to eliminate the need for blood transfusions when symptoms are responding to JAK2 inhibitors. The phase 3 MEDALIST trial showed that luspatercept was effective and well tolerated in patients with lower-risk myelodysplastic syndromes/MPN and RBC transfusion-dependent anemia; FDA approved luspatercept for treatment of this disease in April 2020. Luspatercept is injected under the skin every three weeks.

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

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

Principal Investigator:
Prithviraj Bose, MD

Study Description: The goal of this clinical research study is to evaluate the safety and efficacy of KRT-232, an orally administered inhibitor of the human double minute 2 (HDM2) protein, in patients diagnosed with myelo-

fibrosis. HDM2 inhibits the function of a very important protein, p53, which plays a critical role in cell survival and death (tumor suppressor). Thus, it is desirable to restore p53 function in patients with myelofibrosis. Patients participating in this clinical trial no longer benefit from treatments with Janus kinase (JAK) inhibitors, such as ruxolitinib. HDM2 inhibitors have a different mechanism of action from JAK inhibitors. The drug 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 over-expressed 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.



[A Randomized, Double-Blind, Phase 3 Study to Evaluate the Activity of Momelotinib versus Danazol in Symptomatic Anemic Patients with Primary MF, Post-PV MF, or Post-ET MF Who Were Previously Treated with JAK Inhibitors \(MOMENTUM trial\)](#)

Protocol #2019-0998
[clinicaltrials.gov NCT No: 04173494](#)

Principal Investigator:
Srdan Verstovsek, MD, PhD

Study Description: Momelotinib is another potent JAK1/2 inhibitor that has the unique ability to improve anemia, which is frequently encountered in MF patients. Momelotinib was evaluated in two phase 2 trials where it consistently demonstrated improvement of anemia and reduction of transfusion-dependence. In this global phase 3 trial (MOMENTUM), the efficacy of momelotinib in improving transfusion dependence, splenomegaly and other MF symptoms will be compared to danazol in patients with primary/secondary MF and anemia. Symptomatic, anemic MF patients who had been previously treated with other JAK inhibitors can be enrolled in the trial. Momelotinib is administered by mouth. The study is open and enrolling patients.

[Phase 1 Study of PRT543 in Patients with Advanced Solid Tumors and Hematologic Malignancies](#)

Protocol # 2019-0113
[clinicaltrials.gov NCT No: 03886831](#)

Principal Investigator:
Srdan Verstovsek, MD, PhD

Study Description: This study aims to evaluate the safety and maximum tolerated dose of PRT543 in patients with relapsed/refractory myelofibrosis who have exhausted available treatment options. PRT543 is a small molecule inhibitor of the protein arginine methyltransferase 5 (PRMT5). PRMT5 catalyzes the transfer of methyl groups to arginine residues in histones (a family of proteins that DNA wraps around to form chromosomes) and is overexpressed in several neoplasms. PRT543 is aimed at cancers that have developed resistance to existing therapies. The drug is administered by mouth. The study is open and enrolling patients.

[A Phase 3 Study \(PACIFICA\) of Pacritinib versus Physician's Choice in Patients with Severe Thrombocytopenia and Primary MF, Post PV MF, or Post-ET MF, Treated with Ruxolitinib](#)

Protocol #2017-0320
[clinicaltrials.gov NCT No: 03165734](#)

Principal Investigator:
Prithviraj Bose, MD

Study Description: Pacritinib is an oral JAK2 and FLT3 inhibitor that does not worsen thrombocytopenia; therefore, it may be a better alternative to treat MF patients with low platelet counts. Pacritinib demonstrated considerable clinical efficacy in the MF patients who were treated in the PERSIST-1 and PERSIST-2 trials. Treatment with pacritinib resulted in durable reductions in splenomegaly and disease-related symptoms in MF patients. In the PACIFICA trial, pacritinib is evaluated in comparison to the physician's choice in patients with advanced MF (previously treated with ruxolitinib) and severe thrombocytopenia (platelet counts < 50,000/ μ L). The enrolled patients will be treated at the optimal dose (200 mg twice a day). Pacritinib is administered by mouth, and gastrointestinal symptoms are manageable.

[Phase 2 Study of Navitoclax Alone or in Combination with Ruxolitinib in Patients with MF](#)

Protocol # 2017-0495
[clinicaltrials.gov NCT No: 03222609](#)

Principal Investigator:
Naveen Pemmaraju, MD

Study Description: The goal of this study is to evaluate the optimum dose and efficacy of navitoclax alone or in combination with ruxolitinib in patients with primary or secondary MF who received at least 12 weeks of continuous ruxolitinib therapy prior to enrollment in the study. 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 data indicate that navitoclax may be effective in treating MF patients who develop resistance to ruxolitinib. Both navitoclax and ruxolitinib are administered by mouth.

[Phase 2 Study of CPI-0610 Taken either with or without Ruxolitinib in Patients with Myelofibrosis](#)

Protocol # 2018-0202
[clinicaltrials.gov NCT No: 02158858](#)

Principal Investigator:
Prithviraj Bose, MD

Study Description: CPI-0610 (Pelabresib) is an oral epigenetic modifier that interferes with the activity of bromodomain and extraterminal 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 study, CPI-0610 is administered alone or in combination with ruxolitinib because the two drugs may work even better together than each drug alone. Interim data on CPI-0610 in patients with myelofibrosis (MANIFEST trial) demonstrated promising clinical activity—namely, significant improvements in spleen volume, anemia, transfusion-dependence, and constitutional symptoms—both as a monotherapy or in combination with ruxolitinib. CPI-0610 in combination with ruxolitinib may become a new standard frontline treatment for 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 assessed 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 for a JAK inhibitor. 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, 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. Ropeginterferon alpha-2b was approved as a treatment for PV patients in the European Union in 2019 and may be approved for PV treatment in the US in 2021.

This phase 3 study 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 ET patients who have 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, an anti-SLAMF7 monoclonal antibody, in patients with MF who are not candidates for JAK inhibitors or have failed JAK inhibitors. Elotuzumab has the potential to improve or reverse bone marrow fibrosis. Elotuzumab is administered by injection.

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 IMbark clinical trial. 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 (excluding JAK inhibitors).



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 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. KRT-232 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. KRT-232 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 (JAK inhibitor, standard first-line therapy for the majority of myelofibrosis patients), relapse, or are not eligible to be treated with JAK inhibitors. TL-895 is a BTK inhibitor, an enzyme important for the growth of cancer cells; thus, malignant cells die with TL-895 treatment. TL-895 has a novel mode of action and is administered by mouth as a pill. •



Highlights of MPN Clinical Trials

Presentations from the 2021 European

Hematology Association (EHA2021)

Virtual Annual Congress

JUNE 9-12, 2021

Navitoclax and Ruxolitinib for Patients with Myelofibrosis and JAK2 Inhibitor Experience: Response Duration in Phase 2 Study

Presenter: Claire Harrison, MD

Navitoclax is a novel small-molecule inhibitor that binds strongly to the B-cell lymphoma 2 (Bcl-2) family of proteins, which prevent the cells from dying. In preclinical studies, ruxolitinib in combination with the non-clinical analog of navitoclax, ABT-737, demonstrated synergism (both drugs were more effective than each one alone) in inducing cell death of JAK2 V617F MPN cell lines.

The efficacy of navitoclax in patients who are taking ruxolitinib but have suboptimal response to it is assessed in the phase 2 clinical trial. Current participants have been on ruxolitinib for a median period of 82 weeks and persistently had an enlarged spleen. Among evaluable patients, after 24 weeks on therapy with navitoclax, about one third achieved 50% or higher improvement in total symptom score and considerable reduction in spleen volume, which lasted, so far, for a median of ~14 months. Several transfusion-dependent patients had a considerable increase in hemoglobin (≥ 2 g/dL) and bone marrow fibrosis improvement. An international phase 3 clinical trial (TRANSFORM-1) evaluating navitoclax/ruxolitinib vs. ruxolitinib alone, is presently enrolling MF patients not previously treated with ruxolitinib, at MD Anderson (protocol # 2020-0743).

Rusfotide (PTG-300) Eliminates the Need for Therapeutic Phlebotomy in Both Low- and High-Risk Polycythemia Vera Patients

Presenter:

Marina Kremyanskaya, MD, PhD

PTG-300 (Rusfotide) is a mimetic of hepcidin, which is a short peptide synthesized by hepatocytes (liver cells) and a key regulator of iron levels and thus, erythropoiesis (production of red blood cells) in the body. PTG-300 is being developed for a broad range of hematologic diseases, including polycythemia vera (PV). PV patients may require periodic therapeutic phlebotomies in order to maintain the hematocrit (percent of red blood cells in the blood) $\leq 45\%$ and decrease thrombotic events.

This phase 2 study (NCT04057040) has 3 parts, and it is evaluating the need for phlebotomies in PV patients who required more than 3 phlebotomies during the 24 weeks before treatment with PTG-300. During the 7 months that the patients were treated with PTG-300, the need for phlebotomies decreased significantly or phlebotomies were eliminated (10 patients did not require phlebotomies for 7 months with PTG-300 treatment); and the hematocrit remained below 45% during the study. PTG-300 appears to be an effective medication for treatment of PV by maintaining the hematocrit below 45% and eliminating the need for phlebotomies.

Imetelstat Demonstrates an Acceptable Safety Profile in Myeloid Malignancies

Presenter: John Mascarenhas, MD

Imetelstat is a potent inhibitor of telomerase, an enzyme that maintains the structural integrity of chromosomes in normal and cancer cells. The clinical efficacy of imetelstat and its possible benefit in prolonging the survival of MF patients relapsed/refractory to JAK inhibitors (for example, ruxolitinib) was evaluated in the phase 2 IMbark trial. After a median follow-up of 42 months, the median overall survival of the MF patients treated with the higher dose of imetelstat was 28 months versus 20 months with the lower dose.

In this presentation, the safety profile of imetelstat in MF patients who were treated with the higher dose was assessed. Among treated patients, 55% had very significant thrombocytopenia (low platelet counts), but it lasted for less than 2 weeks and was reversed in the majority of the patients within 4 weeks with dose modifications. No liver injuries were noted.

Imetelstat is the first medication to be assessed in clinical trials for MF patients regarding its possible ability to prolong survival. A phase 3 randomized clinical trial (IMpactMF), evaluating imetelstat versus best available therapy in JAK inhibitor-refractory MF patients, is currently enrolling patients at MD Anderson (protocol #2020-1141).

Highlights of MPN Clinical Trials (continued)

Presentations from the EHA2021 Virtual Annual Congress

Impact of Ruxolitinib on Survival of Patients with Myelofibrosis in the Real World – Update of ERNEST (European Registry for MPNs) Study

Pres: Paola Guglielmelli, MD, PhD

In this study, the survival data of 1,010 patients with primary and secondary MF from the European Registry (ERNEST) who were treated with ruxolitinib for 5 years or more were analyzed. The MF patients treated with ruxolitinib had significantly longer overall survival compared to hydroxyurea (HU; most commonly used therapy in the past) after matching all parameters (age, gender, MF type): 7.7 years with RUX versus 3.4 years with HU. For high-risk patients, the overall survival was > 2 times longer with RUX vs HU (6.4 vs. 3 years, respectively). Similar to a study in the US, the ERNEST study clearly showed the significant survival benefit that treatment with ruxolitinib confers to MF patients.

Safety and Efficacy of Mepolizumab in Hypereosinophilic Syndrome: An Open-Label Extension Study

Pres: Florence Roufousse, MD, PhD

Hypereosinophilic syndromes (HES) are a group of rare inflammatory disorders that are characterized by an overproduction of white blood cells named eosinophils (the name derives from readily detecting eosinophils with the dye eosin). Mepolizumab is a monoclonal antibody that blocks interleukin-5 (a growth factor for eosinophils) and reduces blood eosinophil counts. Mepolizumab was evaluated in a multicenter phase 3 clinical trial (over 32 weeks) and the extension trial in about 100 patients with HES. In accord with the main study, in the extension study, mepolizumab reduced the mean blood eosinophil counts by

89% compared to baseline; and lowered the mean annual rate of disease flares (symptomatic worsening) to 0.37/year versus 2.7/year with the placebo in patients with HES. The treatment was well tolerated. Mepolizumab is the first newly approved medication for treatment of HES in the last 14 years (approved in September 2020).

Transfusion Independence Is Associated with Improved Overall Survival in Myelofibrosis Patients Receiving Momelotinib

Presenter: Ruben Mesa, MD

Momelotinib is a JAK1/2 inhibitor that has the unique ability among them to significantly improve anemia and eliminate or reduce transfusion-dependence in MF patients due to increasing circulating iron in the body. Momelotinib was evaluated in two phase 2 trials (SIMPLIFY-1 and SIMPLIFY-2), where it consistently demonstrated a suite of anemia benefits besides reducing splenomegaly and symptoms. In these trials, momelotinib also demonstrated long-term survival benefits in anemic MF patients. Further analyses of the data showed significant overall survival advantages in MF patients who achieved transfusion-independence with momelotinib; in SIMPLIFY-1, the 3-year survival was 80%. Currently, momelotinib is being assessed in a phase 3 trial (MOMENTUM) in patients previously treated with a JAK inhibitor, where it is

compared to danazol regarding elimination of red blood cell transfusions and control of MF symptoms.

Efficacy and Safety of Avapritinib in Patients with Advanced Systemic Mastocytosis: Interim Results from the Open-Label, Single-Arm Phase 2 PATHFINDER Study

Presenter: Andreas Reiter, MD

Advanced systemic mastocytosis (advSM) is a rare, aggressive cancer of mast cells, which are a type of white blood cell found in connective tissues and bone marrow. Mast cells play a critical role during inflammation. Avapritinib (BLU-285) is a potent and highly selective inhibitor of the mutant tyrosine kinase protein KIT (mutation D816V). Mutation *KIT* D816V produces an abnormal protein and is the key driver of the disease in 90-95% of SM cases. Avapritinib showed highly promising clinical results in the EXPLORER trial regardless of disease subtype or prior therapy with other drugs, such as the standard medication midostaurin. In the registrational PATHFINDER study, avapritinib elicited profound, rapid and durable responses; and it was well tolerated. Complete remission with full/partial hematologic recovery was noted in ~20% of the patients, and the overall response rate was 75%. Marrow mast cells decreased in 71% of the patients, and disease-related symptoms improved considerably.



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Gifts provide critical support needed to conduct innovative MPN research. Our MPN research teams are dedicated to improving treatments for patients with MPNs. To make a donation by mail, please send gifts to MD Anderson Cancer Center and specify "MPN Clinical Research Center (Dr. Verstovsek)" in the memo line, using the attached envelope.

Highlights of MPN Clinical Trials (continued)

Presentations from the EHA2021 Virtual Annual Congress

Pelabresib (CPI-0610) Improved Anemia Associated with Myelofibrosis: Interim Results from the MANIFEST Phase 2 Study

Presenter:

Srdan Verstovsek, MD, PhD

BET proteins are regulators of key oncogenic, fibrotic, and inflammatory factors in the bone marrow. Pelabresib (CPI-0610) is a novel, selective and potent, small-molecule inhibitor of BET proteins.

In the ongoing, open-label phase 2 trial MANIFEST (protocol # 2018-0202), pelabresib has been evaluated as a monotherapy or in combination with ruxolitinib in anemic MF patients (the study has several arms). Anemia is a significant challenge in MF patients and often leads to ruxolitinib discontinuation. Interim data from the MANIFEST trial showed significant improvements in anemia, including achievement of transfusion-independence and increase in hemoglobin (Hgb). In Arm 2, MF patients with suboptimal response to ruxolitinib received pelabresib as an “add-on” to ruxolitinib. Notably, 36% of the patients in Arm 2 achieved transfusion-independence for a median period of 39 weeks, and Hgb increased by 1.5 g/dL or more in 17% of the patients (transfusion-free for 12 weeks).

Clinical data indicate that pelabresib in combination with ruxolitinib may act synergistically. The randomized phase 3 clinical trial (MANIFEST-2), evaluating pelabresib in combination with ruxolitinib as a frontline treatment, is enrolling patients at MD Anderson (protocol #2020-0739).



Towards A Potential Operational Cure in Patients with Polycythemia Vera? Results from Five-Years’ Ropeginterferon alpha-2b Therapy in a Randomized Setting

Pres: Jean-J. Kiladjan, MD, PhD

Ropeginterferon alpha-2b is a novel, long-acting interferon formulation that can be administered by injection, bimonthly instead of weekly. In the phase 3 randomized PROUD-PV trial and its extension CONTINUATION-PV study, long-term treatment with ropeginterferon alpha-2b was evaluated versus hydroxyurea in patients with polycythemia vera (PV). After treatment for 5 or more years, red blood cell and platelet counts were controlled well in the majority of the patients (87%) treated with ropeginterferon alpha-2b without phlebotomies. Ropeginterferon alpha-2b was considerably superior to hydroxyurea regarding complete hematological (control of red and white blood cells and platelets) and molecular (decrease in *JAK2* V617F allele burden, i.e., number of cells in the sample that has the mutation) responses in PV patients. The mean *JAK2*V617F allele burden decreased below 10% in ~50% of the patients treated with ropeginterferon alpha-2b. After treatment with ropeginterferon alpha-2b for 5 years, the majority of the patients had complete hematological remission. The decrease of *JAK2* in PV patients treated with ropeginterferon alpha-2b for a long time demonstrated the drug’s potential disease-modifying effects. Early initiation of the treatment and baseline *JAK2* <10% were positive prognostic factors for good long-term outcome. In 2019, ropeginterferon alpha-2b was approved in the European Union for PV patients, and the FDA accepted an application for its approval in the US (under review).

Overall and Progression-Free Survival in Patients Treated with Fedratinib as First-Line Myelofibrosis (MF) Therapy and after prior Ruxolitinib (RUX): Results from the JAKARTA and JAKARTA2 Trials

Presenter: Claire Harrison, MD

Fedratinib is an oral, highly selective *JAK2* inhibitor that was approved by the FDA for treatment of patients with intermediate-2 or high-risk MF, in August 2019.

In the phase 3 randomized JAKARTA trial, fedratinib significantly reduced splenomegaly and symptoms in 35-40% of MF patients who had not been previously treated with ruxolitinib. In the phase 2 JAKARTA-2 trial, treatment with fedratinib resulted in 35% reduction in spleen volume and improvement of other symptoms in 25-30% of the patients who had previously received ruxolitinib.

In JAKARTA, the MF patients treated with fedratinib demonstrated a significantly longer median progression-free-survival (23 months) compared to placebo (17.5 months), and more patients remained progression-free with fedratinib. In JAKARTA-2, patients previously treated with ruxolitinib had a median progression-free survival of 13.3 months with fedratinib; and the one-year and 18-month survival rates were 84% and 67%, respectively. These results compare favorably with the results of similar MF patients who discontinued ruxolitinib and did not receive fedratinib. •



MPNFocus

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TEXAS MPN WORKSHOP Second Annual Virtual Meeting



August 19-20, 2021



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We are excited to invite you to attend the **Second Texas MPN Workshop** on August 19-20, 2021. This unique meeting will be a virtual 2-day “workshop” with focused provocative presentations, educational talks, and interactive panels. The meeting aims to foster collaborations and advance the field of MPN. This exciting meeting is open to the broader MPN community, interested physicians, and providers.

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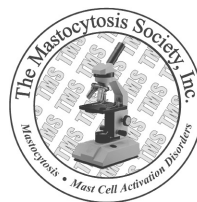


Founded by Ann Brazeau, former vice president of development at **MPN Research Foundation**, **MPN Advocacy & Education International** provides educational programs, materials, and resources for patients, caregivers, physicians, and entire healthcare teams to improve their understanding of MF, PV, and 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.



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



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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.