

## Patient Spotlight: Jo Hallila

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**Q:** Which type of MPN do you have and when were you diagnosed?

**A:** I was diagnosed with myelofibrosis in March 2019. I could feel my spleen below my ribs. After a CT scan showed possible bone scarring, I was referred to Dr. Verstovsek at MD Anderson Cancer Center. The blood work and bone marrow biopsy confirmed the diagnosis of myelofibrosis.

**“I am deeply thankful to the men and women who work tirelessly to improve the lives of patients they may have never met. This includes physicians and their staff, researchers, patients in clinical trials, and philanthropists who help us afford the medications. Patients with MPN, including myself, are surrounded by a broad supporting community!”**

– Jo Hallila



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**“Importantly, I believe in Jesus Christ. I trust my days and my future in Him. He has given me deep, unexplainable joy every day.”**

– Jo Hallila

# Letter from the Director

## Greetings to All!

The end of 2021 and the beginning of the new year come with major advancements and great aspirations in MPN treatments.

In mid-November 2021, the Federal Drug Administration (FDA) approved **ropeginterferon alpha-2b (ropegIFN)** for treatment of patients with polycythemia vera (PV) in the US. **RopegIFN** is a novel long-acting interferon formulation that can be administered by injection, bimonthly or even monthly instead of weekly. **RopegIFN** was approved for PV treatment in the European Union in 2019. In the phase 3 PROUD-PV trial and its extension CONTINUATION-PV trial, the hematocrit was controlled very well (below 45%) in the vast majority of the patients, and the *JAK2V617F* mutation burden decreased with **ropegIFN**. Approval of **ropegIFN** represents a critical advancement in PV as the medication not only manages symptoms and short-term complications but it may also help reduce the risk of disease progression over time.

In June 2021, the FDA also approved **avapritinib** to treat advanced systemic mastocytosis.



*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 dedicated to developing novel therapies for MPNs and understanding the biology of MPNs.*

Advanced systemic mastocytosis is a rare myeloid malignancy driven by the *KITD816V* mutation (please see pages 4-5). **Avapritinib** induced profound reductions in mast cells, significantly reduced enlarged spleen, improved symptoms and quality of life; and was well tolerated.

As we enter 2022, we await another major advancement in MF. There is a high unmet need for thrombocytopenic MF patients because they cannot be treated with the approved JAK2 inhibitors as they can further exacerbate low platelet counts. Patients who have myelofibrosis and low platelet counts attained notable spleen and symptom responses when treated with the investigational JAK2 inhibitor **pacritinib**. **Pacritinib** is expected to receive approval from the FDA by the end of February 2022.

As we are witnessing an apogee in the development of new MPN medications, we remain highly optimistic that the quality of life and the outcomes of our MPN patients will continue to improve dramatically. We eagerly look forward to a novel and great MPN era in the very near future!

**Happy Holidays!  
Blessed and Happy New Year!**





## Spotlight: Jo Hallila

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**Q:** What were your symptoms and did you begin any treatment right away?

**A:** Splenomegaly was my only symptom, so Dr. Verstovsek and his team monitored the size of my spleen every few months. In November 2020, Dr. Verstovsek informed me that my spleen had increased in size to the point that he advised starting ruxolitinib. He explained the different factors in the decision in simple terms that made sense, so I started taking ruxolitinib right away. Dr. Verstovsek reviewed my blood counts and checked the size of my spleen each month. It took a couple of increments in the dosage, but within a few months my spleen went back to normal size, and my blood counts have remained steady. This happened a year ago, and everything has been stable since then. I am very grateful to everyone involved in developing ruxolitinib.

**Q:** What have been your sources of support?

**A:** I have a huge circle of support! First, everyone at MD Anderson, from the very first day, was organized and very patient to explain everything and answer our endless questions! That evening, we left feeling very encouraged and safe. I am grateful to Dr. Verstovsek and appreciate his gracious, kind and positive demeanor in the midst of a difficult diagnosis. I am blessed to be under his care.

Second, I have been encouraged by my husband and my family. My daughter-in-law set up a notebook for me so I could keep all the papers from the first day organized! Before the Covid-19 outbreak, my husband came to every appointment and has always listened, supported and helped me process this new normal.



**Mrs. Hallila and Lucy, her dear granddaughter.**

Our two sons regularly express deep appreciation to me for being their mother. Our granddaughter is a constant encouragement, too. I love spending time with her, creating lasting memories. We also have many friends from our church community who send notes and reminders of their care and prayers. Of course we are praying for breakthroughs in research to improve the patients' quality of life and find cures!

**Q:** What are your plans for the future?

**A:** I plan to travel with my husband and spend time with my family, especially my granddaughter. My younger son just got married in November. I am very thankful I was healthy to be present at his wedding; this was very important to me.

**Q:** What was the most difficult part of your diagnosis?

**A:** By far, the most difficult part was telling our sons. It was early in the process, of course, so we did not know the positive developments in treatment, how severe my situation would be determined to be, or quite frankly, how long I might live. This is hard news to deliver to your sons. But they also are men of faith, and after the initial shock, they have done well. In fact, we may be closer as a family because we do not take days for granted.

**Q:** Do you participate in any educational activities on MPN?

**A:** I read the *MPN Focus* newsletter cover to cover. I love the clear educational visuals, which help me understand MPNs and their symptoms. Reading about the clinical trials is informative and encouraging. It makes me appreciate the commitment and dedication of everyone involved in the rigorous research to develop new therapies and ultimately a cure for myeloproliferative neoplasms.

**“We are praying for breakthroughs in research to improve the quality of life and find cures!”** – Jo Hallila

**Q:** How do you remain so positive?

**A:** Of course I was shaken when such a serious health issue was being discussed. But my referring physician kept saying, “It is not time to panic yet.” Then, by the time I received the official diagnosis, I had met Dr. Verstovsek, his PA, and his nurse. Their calm, reassuring, positive attitude comforted my soul. Also, and actually most importantly, I believe in Jesus Christ. I trust my days and my future in Him. He has given me deep, unexplainable joy every day. So, despite my diagnosis, I never panicked!

**Q:** Do you have anything else you would like to share?

**A:** I am deeply thankful to the men and women who work tirelessly to improve the lives of patients they may have never met. This includes physicians and their staff, researchers, patients in clinical trials, and philanthropists who help us afford the medications. Patients with myeloproliferative neoplasms, including myself, are surrounded by a broad community of support! •

# Mastocytosis

**Mastocytosis** is a hematologic neoplasm in which the body produces too many abnormal mast cells.

**Mast cells** are a type of white blood cell that is part of the body's immune system. Mast cells are found in connective tissues throughout the body, especially under the skin, near blood vessels and lymph vessels, in the bone marrow, the lungs, and the gastrointestinal tract. Mast cells have small sacs containing different substances that are released when mast cells are activated (please see Figure 1). During allergic reactions and certain immune responses, mast cells release chemicals such as histamine, cytokines, and growth factors, which activate the body's response to allergens (for example, certain foods, insect venoms, pollen), medications or pathogens.

According to the latest classification of the World Health Organization (WHO), there are three variants of mastocytosis: skin or **cutaneous mastocytosis**, **systemic mastocytosis** and **mast cell sarcoma**, which is a rare, aggressive, localized mast cell tumor.

**Cutaneous mastocytosis** is a relatively benign disease, characterized by patches of itchy, red/brown skin lesions.

Cutaneous mastocytosis is predominantly encountered in children, and it often resolves on its own when the child reaches adolescence. In adults, mastocytosis is most often systemic, namely it involves one or more internal organs and the bone marrow; however, the skin can also be involved. A major diagnostic criterion for systemic mastocytosis is the formation of aggregates with mast cells (over 15) in the involved tissue besides the skin (Figures 2, 3).

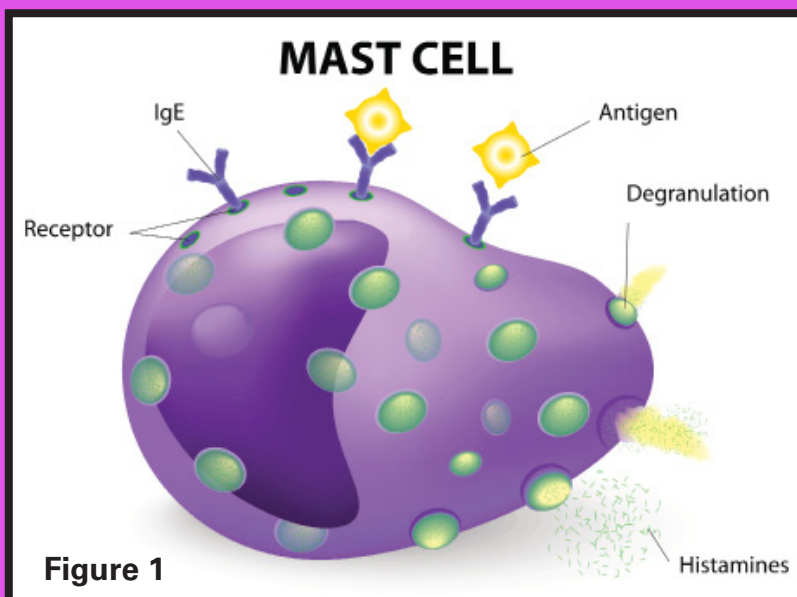
Among several types of **systemic mastocytosis**, the vast majority of patients belong to the **indolent systemic mastocytosis** or **advanced systemic mastocytosis** group.

**Indolent systemic mastocytosis** is the most common form of the disease. It does not affect organ function, but may cause many symptoms and poor quality of life. In general, it does not affect life expectancy and hardly ever progresses to an aggressive form. Symptoms may include skin swelling, hives, flushing, headaches, low blood pressure, itching, nausea, fainting, shortness of breath, and body aches. Most cases of indolent systemic mastocytosis can be treated with antihistamines and by avoiding dietary and

environmental triggers. Prednisone, cromolyn sodium (mast cell stabilizer) or other types of anti-allergic medications may help control the symptoms.

**Advanced systemic mastocytosis** is characterized by organ damage due to the infiltration of neoplastic mast cells (for example, Figure 2). Advanced systemic mastocytosis is further subcategorized in 3 subtypes: **aggressive systemic mastocytosis**, **systemic mastocytosis with an associated hematologic neoplasm**, and **mast cell leukemia**.

Aggressive systemic mastocytosis is characterized by the infiltration of internal organs by mast cells, resulting in organ dysfunction; this may significantly affect life expectancy. Systemic mastocytosis with an associated hematologic neoplasm is the most common type of advanced systemic mastocytosis. In this case, patients have two bone marrow neoplasms, mastocytosis and another form of non-mast cell hematologic neoplasm (including MPN, for example). Mast cell leukemia is a very rare entity, which is suspected when there are abnormal mast cells in the blood; mast cell leukemia is associated with a very shortened survival.



Professor Verstovsek presented a series of excellent MPN educational videos for MPN patients. To view the videos, please visit the **MD Education** web page: <https://mpnpatientus.md-education.com/>



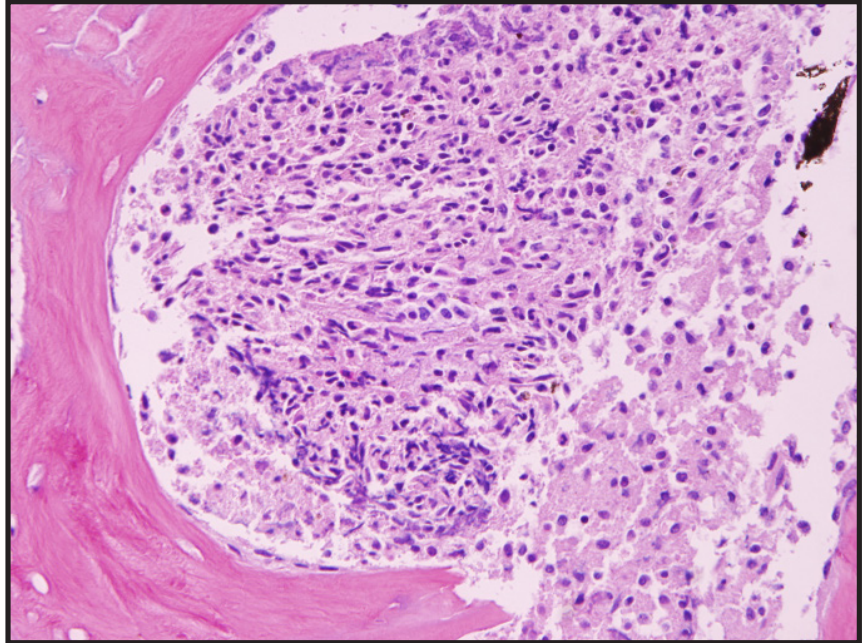
# Mastocytosis

The vast majority of patients (about 95%) who have mastocytosis harbor a mutation in the *KIT* gene (called *KITD816V* mutation), encoding a tyrosine kinase, an enzyme. The mutated tyrosine kinase is an abnormal protein in mast cells driving their growth. Detection of *KIT* mutation(s) in the bone marrow or other extra-cutaneous organs is a hallmark of the disease and is considered a minor diagnostic criterion for systemic mastocytosis. Presence of mutation *KITD816V* in malignant mast cells serves as a target for development of new therapies.

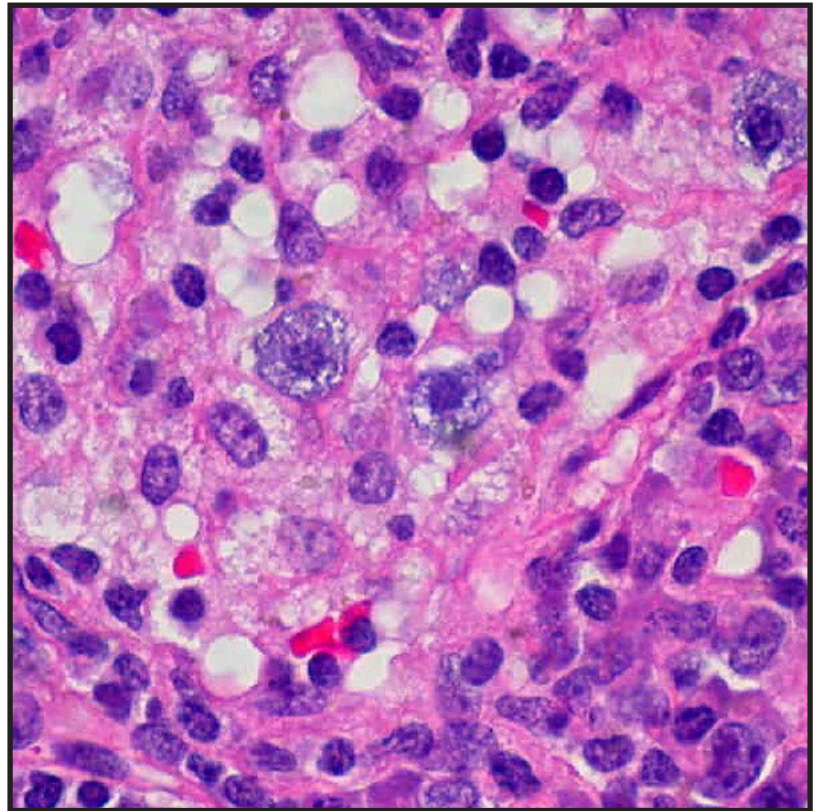
**Midostaurin** was the first medication that the Food and Drug Administration (FDA) approved for the treatment of advanced systemic mastocytosis patients based on its ability to affect mutant *KITD816V* protein; approval took place in 2017. Midostaurin preferentially inhibits the activity of mutated *KITD816V* protein (versus normal *KIT* protein) and therefore, it has direct effect on malignant mast cells by decreasing their growth and release of histamine. This leads to clinically important improvements in patients' symptoms and organ function.

In June 2021, the FDA approved **avapritinib** (formerly BLU-285) as a therapy for advanced systemic mastocytosis. Approval was based on the high response rates recorded in recent clinical trials. Avapritinib is a potent and highly selective inhibitor of mutant *KITD816V*. Treatment with avapritinib resulted in profound reductions in the number of mast cells in the bone marrow. Clinical benefits included significant reductions in enlarged spleen, and improvement in anemia and patients' quality of life. Therapy with avapritinib may last for several years.

The presence of other mutations besides *KIT* (for example, *SRSF2*, *ASXL1*, and *RUNX1*) contributes to the complexity of the disease, cause resistance to targeted therapies, and may have adverse prognostic significance.



**Fig. 2.** Bone marrow biopsy from a patient with systemic mastocytosis showing the infiltration of mast cells in the bone marrow.



**Figure 3.** Stained mast cells.

# 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](http://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](http://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 2 Study of the Hepcidin Mimetic Rusfertide (PTG-300) in Patients with Phlebotomy-Requiring Polycythemia Vera (PV)

**Protocol # 2019-0016**  
[clinicaltrials.gov](http://clinicaltrials.gov) NCT No: 04057040  
**Principal Investigator:**  
**Srdan Verstovsek, MD, PhD**

**Study Description:** The objective of this study is to evaluate the safety and efficacy of rusfertide in patients diagnosed with PV who required therapeutic phlebotomies (bloodletting) to maintain the hematocrit below 45% and decrease thrombotic events. 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 erythropoiesis (production of red blood cells). Patients required  $\geq 3$  phlebotomies before taking rusfertide; rusfertide treatment essentially eliminated phlebotomies in all the patients. The study is open and enrolling 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](http://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.

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](https://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.



## 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](https://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 hemo-

globin 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](https://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 accrues 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](https://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.

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

**Protocol # 2021-0587**

[clinicaltrials.gov](https://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 bezucastinib will be evaluated in patients with advanced systemic mastocytosis. Bezucastinib 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 (please review pages 4-5 on mastocytosis). Bezucastinib 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](https://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.

## Phase 1 Study of PRT543 in Patients with Advanced Solid Tumors and Hematologic Malignancies

**Protocol # 2019-0113**

[clinicaltrials.gov](https://clinicaltrials.gov) NCT No: **03886831**

**Principal Investigator:**  
**Srdan Verstovsek, MD, PhD**

**Study Description:** In the expansion study, PRT543 is evaluated in a few cohorts. One group includes patients who have chronic MF and splicing mutations. The second group includes patients with accelerated or blast phase MPN who harbor splicing mutations, and the third cohort includes MF patients who will receive PRT543 as an "add-on" to ruxolitinib regardless of having splicing mutations. PRT543 is a small molecule inhibitor of PRMT5. PRMT5 catalyzes the transfer of methyl groups to arginine residues in histones (DNA wraps around histones to form chromosomes), and it is overexpressed in several neoplasms. The drug is administered by mouth.

## 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](https://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/ $\mu$ L). The enrolled patients are 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](https://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 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](https://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 myelofibrosis.

## 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](https://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](https://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. Ropeginterferon alpha-2b was approved for PV treatment in the US in November 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](https://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](https://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 (BAT), 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](https://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 Study Assessing the Safety and Efficacy of KRT-232 or TL-895 in JAK Inhibitor Treatment-Naïve Myelofibrosis

**Protocol # 2021-1335**  
[clinicaltrials.gov](https://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 previous 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 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](https://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 63<sup>rd</sup> Annual Meeting

### American Society of Hematology

DECEMBER 11-14, 2021 • ATLANTA, GA

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#### Pelabresib (CPI-0610) Monotherapy in Patients with Myelofibrosis—Update of the Clinical and Translational Data from the Ongoing MANIFEST Trial

**Presenter: Marina Kremyanskaya, MD, PhD**

Pelabresib (formerly CPI-0610) is a selective and potent small-molecule inhibitor of bromodomain and extra-terminal (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 arm of the phase 2 open label MANIFEST trial, pelabresib is evaluated as a monotherapy in patients with advanced myelofibrosis (MF) who are intolerant or refractory to ruxolitinib; this group of patients generally has few therapeutic options. Interim data from this trial showed significant spleen volume reduction in about one third of the patients after 24 weeks of therapy. Significant improvements were also observed in MF-related symptoms, bone marrow fibrosis, and hemoglobin levels. In addition, pelabresib decreased the plasma levels of cytokines, which are proteins elevated in MF patients and are associated with inflammation. The phase 3 clinical trial evaluating pelabresib in combination with ruxolitinib is enrolling MF patients at the MPN Clinical Research Center at MD Anderson (protocol # 2020-0739).

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#### Rusfertide (PTG-300) Controls Hematocrit and Essentially Eliminates Phlebotomy Requirement in Polycythemia Vera Patients

**Presenter: Ronald Hoffman, MD**

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

This phase 2 study is evaluating the need for phlebotomies in PV patients who required 3 or more phlebotomies during the 24 weeks before starting rusfertide. Phlebotomies were essentially eliminated in all the patients (even in those receiving hydroxyurea, interferon or ruxolitinib, which are standard therapies for PV). Treatment with rusfertide consistently maintained the hematocrit below 45% and improved symptoms in a number of the patients. The phase 2 study (protocol 2019-0016) is open and enrolling patients, and the phase 3 trial will be launched soon at MD Anderson Cancer Center.

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#### Final Results of a Phase 2 Study of Sotatercept (ACE-011) for Anemia of MPN-Associated Myelofibrosis

**Presenter: Prithviraj Bose, MD**

Sotatercept (formerly ACE-011) is a protein that traps different proteins and prevents their binding to cells (specifically, it is called activin receptor ligand trap). Sotatercept stimulates erythropoiesis (production of red blood cells) likely by interfering with suppressive activity of transforming growth factor (TGF)- $\beta$ .

Our MPN team conducted a phase 2 clinical trial (NCT01712308) in which sotatercept was studied as a monotherapy and in combination with ruxolitinib in MF patients. The patients had anemia that did not require red blood cell transfusions or they were red blood cell transfusion-dependent. Sotatercept was injected under the skin every three weeks.

About one third of the MF patients treated with sotatercept alone or with the combination sotatercept/ruxolitinib had anemia responses. The patients who responded to sotatercept either achieved red blood cell transfusion independence or their hemoglobin levels increased by  $\geq 1.5$  g/dL compared to baseline for  $\geq 12$  weeks. A similar medication called luspaterecept is also in clinical development for MF patients. The phase 3 clinical trial evaluating luspaterecept in MF patients requiring RBC transfusions is enrolling patients at MD Anderson (protocol # 2020-1010).



# Highlights of MPN Clinical Trials (continued)

## Presentations from the 63<sup>rd</sup> Annual Meeting of ASH

### Treatment of Myelofibrosis Patients with the TGF- $\beta$ 1/3 Inhibitor AVID200 (MPN-RC 118) Induces a Profound Effect on Platelet Production

**Presenter: John Mascarenhas, MD**

AVID200 is a medication that traps transforming growth factor (TGF)- $\beta$  1/3, a cytokine in the blood that promotes bone marrow fibrosis and thus myelofibrosis. AVID200 is evaluated in patients with advanced MF who were intolerant/resistant or ineligible to receive ruxolitinib, had bone marrow fibrosis grade 2/3, and platelet counts  $\geq 25 \times 10^9/L$ . AVID200 was administered intravenously every 21 days. Treatment with AVID200 resulted in limited responses regarding spleen volume reduction and symptom improvement. However, it significantly improved thrombocytopenia; and the medication was well tolerated. No existing therapy for MF improves platelet counts well. Therefore, AVID200 could possibly be used in the future in combination with other medications in patients with advanced MF.

### A Retrospective Head-to-Head Comparison between Pacritinib and Ruxolitinib in Patients with Myelofibrosis and Moderate to Severe Thrombocytopenia

**Presenter: John Mascarenhas, MD**

Pacritinib has been in clinical development for MF patients who have low platelet counts (thrombocytopenia). In this retrospective study, pacritinib was compared head-to-head with ruxolitinib in cohorts of MF patients who had very low platelets, similar clinical features (age, hemoglobin, DIPSS score, transfusions) and had not been previously treated with JAK inhibitors. The patients had participated in the phase 3 randomized PERSIST-2 trial. Patients treated with pacritinib exhibited 3 times higher rates of spleen volume reduction and 4 times

higher symptom responses compared to ruxolitinib. The patients on ruxolitinib received mean doses starting at 10 mg/day only due to low platelet counts; the low dosage is a possible reason why ruxolitinib was not very effective. Pacritinib was administered at full dose over time. MF patients with thrombocytopenia currently have an unmet medical need, but pacritinib is expected to receive FDA approval in early 2022.

### Phase 2 Study (FIGHT-203) of Pemigatinib (INCB054828) in Patients with Myeloid/Lymphoid Neoplasms (MLNs) with FGFR1 Rearrangement (MLN<sup>FGFR1</sup>)

**Presenter: Jason Gotlib, MD, MS**

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 MLNs and a chromosomal abnormality involving chromosome 8 (specifically 8p11), a protein called FGFR1 is abnormally fused to another protein, and drives the disease; it is a rare disease. This phase 2 study is evaluating the efficacy of pemigatinib in patients with MLN<sup>FGFR1</sup>. Pemigatinib showed very high rates of complete and partial responses, which were also durable. Pemigatinib is the first medication to confer such benefits and may provide a long term option for patients with MLN<sup>FGFR1</sup> or facilitate transition to hematopoietic stem cell transplantation in eligible patients.

### Efficacy of Avapritinib in Patients with Advanced Systemic Mastocytosis: Hematologic and Bone Marrow Responses from the Phase 2 Open-Label, Single-Arm PATHFINDER Study

**Presenter: Tracy George, MD**

Advanced systemic mastocytosis is a rare, aggressive cancer of mast cells, which are a type of white blood cell found in connective tissues and the bone marrow.

Avapritinib is a potent and highly selective inhibitor of the mutant tyrosine kinase protein KIT (mutation *KIT*D816V). Mutation *KIT*D816V produces an abnormal protein and is the key driver of the disease in 90-95% of cases.

Avapritinib showed highly promising clinical results in the phase 1 EXPLORER trial regardless of disease subtype or prior therapy with other drugs, such as the standard medication midostaurin.

In the phase 2 PATHFINDER study, avapritinib elicited profound, rapid and durable responses; and it was well tolerated. The overall response rate was 75%. Bone marrow mast cells decreased in the majority of the patients, and disease-related symptoms improved considerably. The Federal Drug Administration recently approved avapritinib for treatment of advanced systemic mastocytosis. •



## MPN RESEARCH You Can Make a Difference

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.

# 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



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](http://mpnadvocacy.com) or contact Ann Brazeau at 517-889-6889 or [abrazeau@mpnadvocacy.com](mailto:abrazeau@mpnadvocacy.com).

**MPNforum** – the MPN community’s publication – is a non-profit online magazine, founded by MPN patient Zhenya Senyak. MPNforum ([mpnforum.com](http://mpnforum.com)) publishes articles and stories focused on patients suffering from an MPN.

Founded in 1994 by patient advocate, Robert Tollen, the [MPDSupport.org](http://MPDSupport.org) website and email list has offered interesting information on MPNs. Anyone is welcome to subscribe, and all archives are available. Robert, who was diagnosed with PV in 1990, has also created a closed Facebook group with more than 1500 members. For more information or to join the listserve, please go to [mpnsupport.org](http://mpnsupport.org) or email [listserv@listserv.icors.org](mailto:listserv@listserv.icors.org) with “subscribe mpdsupport” in the body of the email. To join the Facebook group, please go to [facebook.com/groups/375525335856981](https://facebook.com/groups/375525335856981).



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 the website [mpninfo.org](http://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](http://mpninfo.org).



**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](http://Apfed.org).



**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](http://mpncancerconnection.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](http://tmsforacure.org).



**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](http://PV Reporter.com) was created to provide “easy access” to pertinent information on PV, ET, and MF. For more information, please visit [pvreporter.com](http://pvreporter.com).



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](http://mpnresearchfoundation.org).