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

MPNFocus

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

SUMMER 2020

Patient Spotlight: Jan Cammack

Q: What myeloproliferative neoplasm (MPN) were you diagnosed with and approximately how long ago? How did your journey begin, please?

A: I was diagnosed with myelofibrosis (MF) 21 years ago. At the time, MF diagnosis was considered a death sentence because MF had a grim prognosis. My first local hematologist could not help me so I immediately searched the internet to understand the results of my bone marrow biopsy. From my research, I learned that I had a blood malignancy. I also communicated with an MPN patient, Ms. Joyce Niblack (she formed the MPN-NET support group), and she advised me to come to MD Anderson. At the same time, a second local oncologist who I consulted also referred me to MD Anderson because he adhered to his father's advice (also a doctor) who believed that "If you can't help the patient, you should refer the patient to someone who can." Despite the fact that I had young children at the time, I made arrangements and came to MD Anderson with my husband. For the initial appointments, we came together but later, I came to MD Anderson on my own, and my husband took care of our children. When I was diagnosed with MF, one of my children was 27 years old and married, one was seven years old, and the youngest was three. At present, my younger children are 29 and 24 years old. Since my diagnosis, my two younger children were married, and I have three grandchildren and a great-grandchild. I have been very blessed.

"It is very comforting for me to know that my doctor is constantly researching new MPN treatments because if the medication I am taking does not work, there will be another one that may be effective."

– Jan Cammack

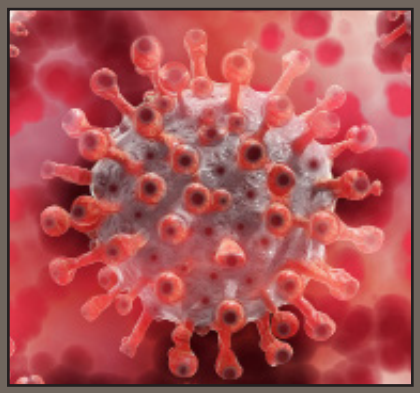
Q: How did the initial diagnosis of myelofibrosis impact you and how did you cope with it?

A: I believe that the Lord had prepared me for this disease because other events had happened in my life and had made me strong. As soon as I was diagnosed with MF, I fell on my hands and knees and fervently prayed to the Lord. I asked God to extend my life as He did for King Hezekiah in the Old Testament. According to the Bible narrative, King Hezekiah became ill and was at the point of death. Prophet Isaiah notified King Hezekiah that the Lord said, "Put your house in order because you are going to die, you will not recover." Hezekiah prayed fervently to God and asked Him to heal him, and extend his life. God hearkened to his prayer and answered Hezekiah (through Prophet Isaiah and the supernatural sign of the sundial) that He would heal him and add 15 years to his life. God granted 15 years to King Hezekiah (2 Kings 20:1-11, Isaiah 38:1 and 38:8).

About 15 years after I was diagnosed with MF, I told my dentist that when I was diagnosed with MF, I prayed to God and asked Him to extend my life, as King Hezekiah did, but I had not received word if He would. My dentist said, "We can assume that God did not say 'no' to your prayers!" I often bring to mind the verse from the Book of Job, "Thou [God] shall call, and I will answer Thee; Thou will long for the creature Thy hands have made (Job 14:15)." I know that my time is not determined by me or the drugs but by my Creator. How can I not have confidence and hope when I

Letter from the Director

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 Neoplasm. Dr. Verstovsek is an internationally recognized physician–scientist who is not only dedicated to understanding the biology of MPN, but also to developing new therapies for MPN.



Greetings to All!

As we are entering a new dynamic and highly promising era in the field of myeloproliferative neoplasms (MPN), it has been extremely exciting to be heavily involved and witness the rapid advances and expansion of the therapeutic arsenal of MPN medications. A slew of clinical trials, evaluating novel medications that act through a broad range of mechanisms, are underway (again) at the *Hanns A. Pielenz Clinical Research Center for MPN*. The clinical trials have been detailed in the relevant section of the newsletter. We have also highlighted the latest findings regarding clinical developments in the MPN abstracts from the international 25th Congress of the European Hematology Association (EHA25) that was held in June 11-14, 2020.

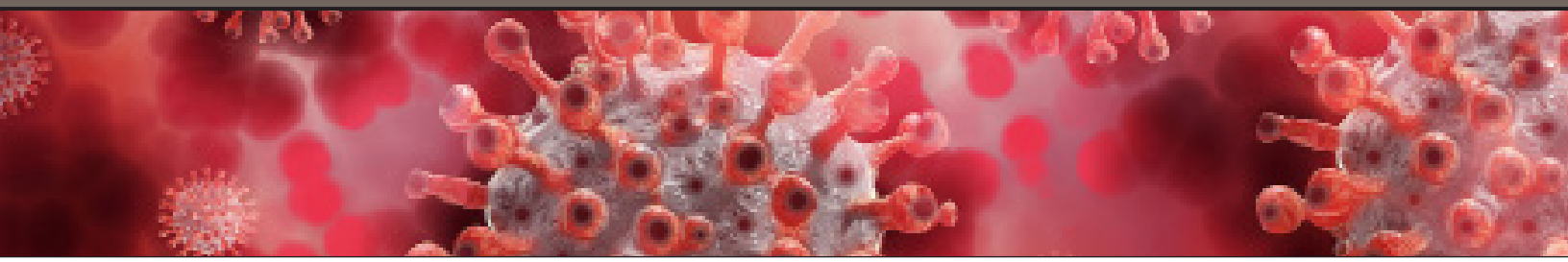
Along with the advancements in MPN treatments, during the last few months, we all experienced the extraordinary challenges of the Covid-19 outbreak. You may have had to postpone your appointments at the MPN Clinic. Presently, we have resumed outpatient appointments, and we can also arrange virtual appointments via telemedicine if you are unable to come to the MD Anderson Cancer Center.

As your physician, I would like to address potential concerns regarding Covid-19 and convey to you the guidelines that were developed for MPN patients, on the basis of the recent experience of hematologists worldwide, and were endorsed by the American Society of Hematology (ASH). Our general advice for MPN patients is to adhere to treatment and management as it was prior to the Covid-19 outbreak and concomitantly take precautions to minimize exposure to the virus.

Notwithstanding the higher susceptibility that patients with advanced MF and other comorbidities may have to be infected with Covid-19, treatment with a JAK inhibitor, for example, may impart an advantage to MF patients. As a JAK2 inhibitor, ruxolitinib exerts an anti-inflammatory effect on the "cytokine storm" that is activated in MF patients. Early studies demonstrated that a similar Covid-19-associated "cytokine storm" (severe over-reaction of the immune system) is triggered in advanced stages of Covid-19 infection. For this reason, a global, randomized phase 3 clinical trial evaluating the efficacy of Ruxolitinib, a JAK inhibitor, in treatment of Covid-19 patients is underway. For patients with PV and ET, we also recommend strict compliance with disease treatment and management prior to the Covid-19 outbreak, aimed at keeping the blood cell counts under control and preventing the risk of thrombosis or bleeding. We recommend consultation of a hematologist for complex cases with high risk of thrombosis or bleeding and Covid-19 infection. For a more detailed discussion on the topic, you may visit the *Patient Power* web page: https://patientpower.info/myeloproliferative-neoplasms/living-with-myeloloproliferative-neoplasms/what-do-mpn-patients-need-to-know-about-covid-19.

We are strongly committed to pursuing excellence in patient care and clinical research. As we continue to be at the forefront of research in MPN, the care and safety of our patients remains our top priority. We are here to serve you all with indomitable dedication and resilience, regardless of the challenges, and provide you with leading treatments and excellent care in MPN. •

We hope you all stay well and safe and wish you many blessings!



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know that such great issues of life are in God's hands! And, I know why I am still here! Over the course of the years I have been coming to MD Anderson, I had the opportunity to encourage other patients and the staff by discussing my experiences.

Q: You have been a patient at the MPN clinical research program at MD Anderson for many years. How has your participation in the MPN clinical trials affected the course of your disease? Do you believe that you have benefited from participating in the MPN clinical trials at MD Anderson?

A: I have a progressive disease, and you have to be progressive and aggressive in order to treat it successfully. For this reason, it is necessary to have excellent guidance from your doctor who will advise you which trial(s) seem best to enroll in. The patient needs to establish a partnership with the doctor.

Through the course of my disease, I have participated in six clinical trials. I was treated with one of the drugs (revlimid or lenalidomide) for 9.5 years. I was one of the few patients that benefited tremendously from lenalidomide. When I stopped responding to lenalidomide, I had to try other drugs. Even though I have the classic characteristics of MF (splenomegaly and JAK2-positive mutation), Janus kinase (JAK) inhibitors, such as ruxolitinib, were not very effective in my case. Currently, I am treated with a novel medication, which is a bromodomain and extraterminal (BET) protein inhibitor that has a different mechanism of action from JAK inhibitors. I have been on it for over a year. I have not had any blood transfusions for the last 9 months. To the contrary, in the past, my hemoglobin was very low. I was transfusion-dependent for two years and needed a blood transfusion every three weeks. I am very grateful that it worked for me. The doctors at MD Anderson are remarkably humble. Dr. Verstovsek had the humility to admit that there are unknown aspects of the disease (MF), and that he did not know why JAK inhibitors did not work in my case when I asked him this question. Dr. Verstovsek is a practical and honest person besides being a great doctor. God partners well with good doctors and good medicines. As we read in the Old Testament: "Honor a physician for his services...," "Healing comes from the Most High," and "There is a time when success is also in their hands." (Ecclesiasticus 38:1-2, and 38:13).

Q: What were the positive aspects of your journey through the years?

A: A very important aspect has been the opportunity I had to participate in clinical trials and try new medications that worked very well for me. Throughout the course of the disease, I have experienced more improvement than regression. It has been a continuous path towards stability because progression of this disease has been slowed down by the investigational drugs (in clinical development). Because of my participation in the clinical trials and the good medications I received, I never had to stay for too long in a symptomatic state, for example being anemic or thrombocytopenic. My outcome has been very positive thanks to my faith in the Lord, my excellent doctors and the effective treatments that I received at MD Anderson.

It is very comforting for me to know that my doctor (Dr. Verstovsek) is constantly researching new treatments for myeloproliferative neoplasms (MPN) because, if the medication I am taking does not work, there will be another one that may be effective. My experience has demonstrated that just because one receives a terrible diagnosis, it does not mean that the outcome is going to be terrible. Sometimes, the medication in clinical development does not work. If this happens, one should not let the disappointment last for too long because there are other medications to try and perhaps, they will work, as it happened in my case.

I would also like to point out the critical impact of the ongoing clinical research in MPN. For example, in my case, the medications that I have been taking were not in clinical development when I was diagnosed with MF. The speed and momentum of new drug development are remarkable.

"A very important aspect has been the opportunity I had to participate in clinical trials and try new medications that worked very well for me. Throughout the course of the disease, I have experienced more improvement than regression. It has been a continuous path towards stability because progression of this disease has been slowed down by the medications in clinical development."

– Jan Cammack

Q: What have been your sources of support through this journey?

A: As I mentioned earlier, my faith in the Lord has been extremely important in my journey. I keep my hope and trust in the Lord and believe that if God wants me to be here, I will be. I cannot take any credit for my outcome. God is a good God. I have been very blessed and I have a wonderful life despite the fact that there are some days when I may not feel very well. When I met Dr. Verstovsek, I could tell that the Lord was going to use him in big ways to help me! The doctors, the clinical nurses and staff at MD Anderson are "my people"!

Importantly, my husband, my children and my friends have been very supportive through the years. Now that our children have grown up and my husband retired, he once again accompanies me to MD Anderson Cancer Center. My husband is such an encourager and helper!

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– Jan Cammack

Q: What were the challenges that you faced because of the disease through the years, please?

A: The main challenge has been that my appearance does not reveal my disease and everyone says that I do not look sick. I take the comment graciously but one cannot judge the book by the cover. While a healthy appearance is wonderful, my friends and family members may have a false impression of well-being.
At the beginning, I sailed along very well. I only had splenomegaly but my blood counts were normal. When I developed anemia (about 15 years ago), I started feeling fatigue. At times, it is difficult for me to keep up with the activities because my energy level is low. However, I have been transfusion-independent after I started a new treatment a year ago. Another challenge I have had since diagnosis has been splenomegaly (for 21 years). After having it for so long, I feel that it has become part of me, and it is managed with the medications to an extent. I was always very active but I had to restrict some of my activities after I was diagnosed with MF. However, I did not want my children to think that I was an invalid so it was a challenge to give up a few activities that I enjoyed. For example, I could no longer go snow skiing, snow tubing (because of the splenomegaly) or get on the trampoline. I have learned that one has to constantly look forward (and be hopeful) and not look back at what one had to give up because that is a very lonely road. I have also experienced neuropathy (my hands and feet are numb). I take a medication and a supplement for the neuropathy. Finally, a few MF medications have side effects (primarily gastrointestinal) but they are manageable.

Q: Has the Covid-19 outbreak affected you and in what ways? Were you able to pursue your treatment at MD Anderson and how did this work out, please?

A: I believe that Covid-19 may restrict us physically but it should not affect us mentally. Covid-19 may be with us for a while. It took me about a month to get over the shock of being quarantined and the seriousness of the illness. I stayed at home most of the time. For the first time, I realized that I am fragile and elderly. Now, I go out for a walk, and I am wise about it because everyone likes to greet me warmly. I had to cancel my appointments at MD Anderson due to the situation with Covid-19. However, I communicated with Dr. Verstovsek via teleconference to meet protocol standards and had my blood work done locally, so I did not feel that my healthcare was restricted because of Covid-19.

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– Jan Cammack

Q: Have you pursued any educational and research activities related to MPN through the years? Have these activities been helpful to you and in what ways, please?

A: I have the approach of a patient-researcher and I like to keep up with the progress in the field of MPN. I read the *MPN Focus* newsletter that Dr. Verstovsek publishes, and I am a member of three MPN support communities. I read the abstracts and case studies on MPN that are posted by the American Society of Hematology (ASH), and I earmark the posts if they apply to me. Dr. Verstovsek also provides me with a lot of medical information about my disease. In the past, I attended the presentations that Dr. Verstovsek delivered on MPN, in Scottsdale, AZ and Texas. Moreover, I frequently monitor the new studies and reports on the efficacy of the medications that I am treated with. This is my life, and I like to stay informed about the progress made regarding new medications.

It has been very exciting for me because I was among the first MPN patients who participated in one of the important studies that reported on the *JAK2* V617F mutation as a key player and therapeutic target in a significant proportion of MPN patients. In the early 2000s, I provided a blood sample for the study, in response to an internet recruitment that one of the MPN support groups had posted. I was among the patients that were *JAK2* V617-positive. This is another example of how I, as a patient, can contribute to a large community of patients and doctors in the field of MPN. •

MPN Clinical Trials

Listed below are clinical trials enrolling patients with MPNs at The University of Texas MD Anderson Cancer Center. For more information on these clinical trials, please call the information line toll-free at 1-800-392-1611 or visit: https://www.mdanderson.org/research/departments-labs-institutes/departments-divisions/leukemia/clinical-trials.html and review the MPN section. To find other clinical trials for MPN, please go to clinicaltrials.gov. To schedule an appointment with a doctor in the Leukemia Department at 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 through genetic rearrangement, and drives the disease process. The goal of this study is to evaluate the efficacy of pemigatinib in MPN patients who have the FGFR1 rearrangement, as detected by the 8p11 chromosomal abnormality. Early results from this study are extremely encouraging, with the majority of patients achieving complete remission.

Phase 3b Study of Fedratinib in Patients with DIPSS Intermediate or High-Risk Primary MF, Post-PV MF, or Post-ET MF and Previously Treated with Ruxolitinib (FREEDOM trial)

Protocol # 2018-1167
clinicaltrials.gov NCT No: 03755518

Principal Investigator:
Srdan Verstovsek, MD, PhD

Study Description: Fedratinib (Inrebic®) is a highly selective JAK2 inhibitor that the FDA approved in August 2019 for treatment of patients with intermediate-2 or high-risk MF. In the JAKARTA2 study, fedratinib exhibited 35% reduction in spleen size and improved quality of life in about one third of the MF patients who did not respond or were intolerant to ruxolitinib. The FREEDOM trial will evaluate the efficacy and safety of fedratinib in MF patients who were previously treated with ruxolitinib for three months or more and did not respond. The drug is administered by mouth, and potential gastrointestinal side effects can be addressed with supportive care and dose reduction.

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 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, bone marrow fibrosis, anemia, transfusion-dependence, and constitutional symptoms– both as a monotherapy or in combination with ruxolitinib. The trial is open and enrolling patients.

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

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

Principal Investigator:
Naveen Pemmaraju, MD

Study Description: The goal of this multicenter phase 1b study is to determine the highest tolerable dose of PU-H71 that can be administered to patients with PMF, post-PV MF, or post-ET MF, in combination with ruxolitinib, a Janus kinase 1/2 (JAK1/2) inhibitor. PU-H71 is an inhibitor of the heat shock protein 90 (HSP90). PU-H71 has demonstrated antineoplastic activity in many types of cancer. Among its other activities, HSP90 stabilizes several proteins involved in tumor growth, for example JAK2; therefore, Hsp90 inhibitors are investigated as anticancer agents. In this clinical trial enrolling patients with MF, concurrent treatment with PU-H71 and ruxolitinib is expected to enhance the activity of ruxolitinib owing to the mechanisms of action of the two drugs (this is supported by preclinical studies). PU-H71 is administered by mouth. The study is open and enrolling patients.

Phase 2 Study of the Hepcidin Mimetic PTG-300 in Patients with Phlebotomy-Requiring Polycythemia Vera

Protocol # 2019-0016
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 PTG-300 in patients diagnosed with PV that are phlebotomy-dependent. PTG-300 is a mimetic of hepcidin, which is a short peptide synthesized by hepatocytes and a key regulator of iron levels in the body. PTG-300 is developed for a broad range of hematologic diseases, including polycythemia vera, associated with dysregulated erythropoiesis and iron metabolism. The study is open and enrolling patients. PTG-300 is injected under the skin.

Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Luspatercept (ACE-536) in Patients with MPN-Associated Myelofibrosis and Anemia with and without Red Blood Cell Transfusion Dependence

Protocol # 2017-0504
clinicaltrials.gov NCT No: 03194542

Principal Investigator:
Prithviraj Bose, MD

Study Description: The goal of this multicenter clinical study is to evaluate the safety and efficacy of luspatercept (ACE-536). The study will also assess the drug's potential to increase hemoglobin or reduce red blood cell (RBC) transfusion-dependence in patients with MPN-associated myelofibrosis because anemia is a critical complication of this disease. Luspatercept is a recombinant fusion protein that increases RBC production. Preliminary data on treatment with luspatercept from the MEDALIST trial showed that the drug is effective and well tolerated in patients with lower-risk myelodysplastic syndromes and anemia. 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 myelofibrosis. 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.

An Open-Label, Single Arm, Phase 2 Study to Evaluate the Efficacy and Safety of Avapritinib (BLU-285), a Selective *KIT* Mutation Targeted Tyrosine Kinase Inhibitor, in Patients with Advanced Systemic Mastocytosis

Protocol # 2018-0943
clinicaltrials.gov NCT No: 03580655

Principal Investigator:
Prithviraj Bose, MD

Study Description: This study aims to evaluate the efficacy and safety of avapritinib (BLU-285) in adult patients with advanced systemic mastocytosis (SM). SM is a rare cancer of mast cells, which play a critical role in inflammation. Avapritinib is a potent and highly selective inhibitor of the mutant protein KIT D816V. The mutation *KIT* D816V produces an abnormal protein and is the key driver of the disease in 90-95% of SM cases. Current treatments do not eradicate the mutation *KIT* D816V; therefore, there is a great medical need to find new drugs. Avapritinib showed very promising clinical results in the EXPLORER trial regardless of prior therapy or disease subtype: 77% overall response rate as well as profound and durable improvements on measures of mast cell burden and symptoms in advanced SM. The drug is given by mouth and is well tolerated.

Phase 2 of SL-401 in Advanced, High-Risk Myeloproliferative Neoplasms

Protocol # 2014-0976
clinicaltrials.gov NCT No: 02268253

Principal Investigator:
Naveen Pemmaraju, MD

Study Description: The goal of this study is to evaluate the safety and efficacy of SL-401 (also named tagraxofusp) in patients diagnosed with relapsed/refractory myelofibrosis. This treatment is based on a different mechanism from other therapeutics. Tagraxofusp is a recombinant fusion protein targeting the cell-surface interleukin-3 (IL-3) receptor or CD123, which is overexpressed in many hematologic malignancies. Tagraxofusp is administered intravenously, and requires inpatient hospitalization for three days in most patients.

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 That 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. Mometotinib 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 symtoms will be compared to danazol in patients with primary/secondary MF and anemia. Symtomatic, 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

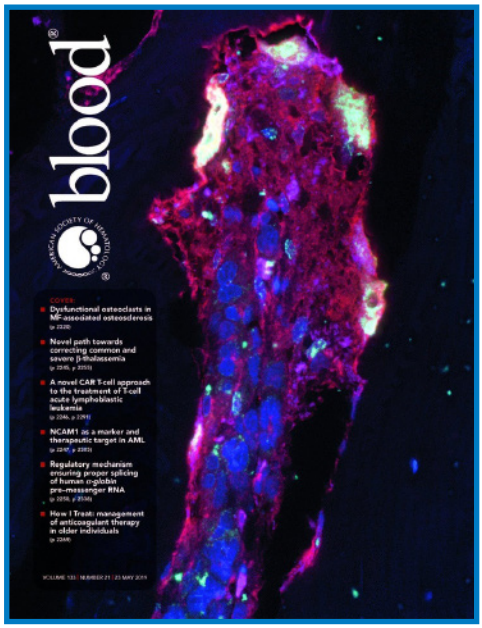
Study Description: This study aims to evaluate the safety and maximum tolerated dose of PRT543 in patients with relapsed/refractory myelofibrosis who have exhausted available treatment options. PRT543 is a small molecule inhibitor of the protein arginine methyltransferase 5 (PRMT5). PRMT5 catalyzes the 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.

Phase 2 Study of Navitoclax Alone or in Combination with Ruxolitinib in Patients with Myelofibrosis

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.



Bone marrow from patient with myelofibrosis. Image featured on the cover of the May 2019 issue in the prestigious journal *Blood*. Veletic I, Manshouri T, Multani AS, Yin CC, Chen L, Verstovsek S, Estrov Z. Myelofibrosis osteoclasts are clonal and functionally impaired. *Blood.* 2019;133(21):2320-2324.

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/μL). The enrolled patients will be treated at the optimal dose (200 mg twice a day). Pacritinib is administered by mouth, and gastointestinal symptoms are manageable.

Phase 2 Study of Parsaclisib in Combination with Ruxolitinib in Patients with Myelofibrosis

Protocol # 2016-0233
clinicaltrials.gov NCT No: 02718300

Principal Investigator: Naval Daver, MD

Study Description: In this study, the efficacy and highest tolerable dose of parsaclisib (INCB050465) in combination with ruxolitinib (JAK1/2 inhibitor) will be determined in patients with MF. Patients can be enrolled in this clinical trial if they were treated with ruxolitinib for at least 6 months, on a stable dose during the preceding 8 weeks, and had suboptimal response. Parsaclisib is a highly selective and potent inhibitor of the phosphoinositide-3 kinase (PI3K)-δ isoform, an enzyme primarily expressed in hematopoietic cells. PI3K-δ plays a key role in cell signaling and growth, survival, and multiplication of cancer cells. Parasaclisib may improve or restore the efficacy of ruxolitinib and have an effect on splenomegaly and other MF symptoms. The drug is administered by mouth. •

The Case for Personalized, Patient-Centered Communication in Rare Blood Cancers: Incorporation of Social Media/Twitter for the Patient and Caregiver Facing MPNs: #MPNSM

Naveen Pemmaraju, MD, Associate Professor, Leukemia Department

In our continued focus on patients with the most rare blood cancers, Dr. Verstovsek and I and our MPN group have always strived to provide patients and their families with the latest in cutting edge research. There are many ways to do this. Each platform and various types of media allow patients and caregivers to digest and absorb medical information in their own personalized ways. Newsletters, such as this one, focused on a specific topic, such as MPN clinical research (trials), are an amazing resource for those who are interested in getting the latest information in the fields of rare blood diseases.

Over time, several new online and social media outlets have gained widespread acceptance and usage among the majority of Americans. Simple online searches, while straightforward, may not yield, in all cases, the most relevant or even the latest research findings on topics of interest, particularly with respect to rare disease. Sometimes, the latest information, directly from experts themselves, can only be ascertained on social media sources, where these scientists and researchers are able to provide their own thoughts with a direct connection to the rest of the world with follow-up questions, discussions, and links to key articles and posts from scientific meetings. Most of these social media or interactive media formats are familiar to our readers – Facebook, Twitter, Instagram, YouTube, LinkedIn, to name a few. For many of us in the medical hematology/oncology fields, including MPNs, Twitter has become the social media platform of choice for creating new content, sharing the latest research findings, and having debates and discussions, including those around the time of our major medical meetings on the newest topics that will be of interest to our patients.

Along with my co-founders, I had the honor to start a grassroots Twitter medical community known as **#MPNSM** (Myeloproliferative Neoplasms on Social Media; the symbol # shows a category or topic on Twitter that can be archived/searched). This hashtag disease-specific group was created for all stakeholders involved in the MPN field, including diverse parties, ranging from patients and caregivers to advocacy groups and practicing physicians, and research scientists. Created in 2014-2015, **#MPNSM** really started to take off and foster increased engagement near the time of one of our major medical meetings, held by the American Society of Hematology (ASH) in 2015. This experience has led to our own research analyses of the first several years, showing sustained interest and increase in the total number of new users each year since then.

The discussions and information have led to new research collaborations, patient referrals, improved understanding, and learning about MPNs. The dissemination of knowledge on new therapies and clinical trials for our patients with MPNs occurs in an unprecedented, real-time manner, with the ability to reach out directly to key opinion leaders and researchers in the field, in a genuine, unfiltered way. As with any form of media, patient privacy, dignity and respect are of highest importance to keep in mind as we embark in this modern era of communication.

Texas MPN Workshop (TMW) 2020

Dr. Verstovsek and Dr. Pemmaraju are excited to invite you to attend the First Texas MPN Workshop on August 27-28, 2020. This unique meeting will be a virtual 2-day "workshop" with focused provocative 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.

Registration is free for all!

To register, please visit: https://mayscc.eventsair.com/texasmpn/regpage/Site/Register

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Highlights of MPN Clinical Trials

Presentations from the 25th European Hematology Association (EHA25) Virtual Annual Congress

JUNE 11-14, 2020

Navitoclax in Combination with Ruxolitinib in Patients with Primary or Secondary Myelofibrosis: A Phase 2 Study

Presenter: Claire N. 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 (the two drugs together are more effective than each one alone) in inducing apoptosis (cell death) of *JAK2* V617F MPN cell lines.

This phase 2 multicenter clinical study is assessing the safety and efficacy of navitoclax combined with ruxolitinib in patients with primary and secondary myelofibrosis. Eligible patients had been treated with ruxolitinib for at least 12 weeks and continued to have persistent splenomegaly. Among the enrolled patients, 43% had considerable reduction in spleen volume (more than 35%), and 25% showed improvement of the bone marrow fibrosis by one grade or more. The treatment was well tolerated, and symptoms improved in the majority of the patients. The phase 2 clinical trial evaluating navitoclax as monotherapy or in combination with ruxolitinib in MF is presently open and enrolling patients at the MPN Clinical Research Center at MD Anderson (protocol #2017-0495).

KRT-232, A First-in-Class, Human Double Minute 2 Inhibitor (HDM2i), for Myelofibrosis Relapsed or Refractory to Janus-Associated Kinase Inhibitor (JAKi) Treatment

Presenter:
Srdan Verstovsek, MD, PhD

Hematopoietic stem/progenitor cells in patients with myelofibrosis overexpress human double minute 2 (HDM2), which is a key negative regulator of the tumor suppressor p53. KRT-232 is a novel, potent, small-molecule inhibitor of HDM2.

In a global phase 2 study that is underway at our institution, KRT-232 showed promising efficacy and tolerability in patients with intermediate to high-risk myelofibrosis (MF). The patients had been previously treated with ruxolitinib for a median time of 15 months and did not respond to the treatment. The safety and efficacy of KRT-232 are dose-dependent; KRT-232 induced a significant reduction in spleen volume in a proportion of the patients.

The phase 2 clinical trial, evaluating KRT-232 in ruxolitinib-resistant MF patients, is presently open and enrolling patients at the MPN Clinical Research Center at MD Anderson (protocol #2018-0906).

Favorable Overall Survival with Imetelstat Treatment Correlates with Other Clinical Benefits in Intermediate-2 or High-Risk Myelofibrosis Relapsed/Refractory to Janus Kinase Inhibitor

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 the possible benefit in prolonging survival in intermediate-2 to high-risk myelofibrosis (MF) relapsed/refractory to JAK inhibitors (ruxolitinib) was evaluated in the IMbark clinical trial. After a median follow-up of 42 months, the median overall survival of the MF patients who were treated with the higher dose of imetelsat (9.4 mg/kg) was 28 months versus 20 months with the lower dose (4.7 mg/kg), and the symptoms improved; for example, reduction in spleen volume, and more than one degree improvement in bone marrow fibrosis.

On the basis of the previous promising results, FDA granted fast track designation to develop imetelstat. We will lead a pivotal phase 3 trial to evaluate imetelstat in JAK-refractory MF patients.

A phase 3 trial has been planned at the MPN Clinical Research Center at MD Anderson in late 2020. Imetelstat is the first medication that may prolong survival in MF patients.

Highlights of MPN Clinical Trials (continued)

Presentations from the EHA25 Virtual Annual Congress

Phase II Randomized Clinical Trial Comparing Ropeginterferon versus Phlebotomy in Low-Risk Patients with Polycythemia Vera. Results of the Pre-Planned Interim Analysis

Presenter: Tiziano Barbui, MD

Low-risk PV patients may only need periodic phlebotomies (cytoreductive therapy) to keep the hematocrit ≤ 45% and reduce the risk of thrombosis. In this randomized study, the effect of ropeginterferon alpha-2b versus phlebotomy was assessed in low-risk PV patients after follow-up at one year. Notably, the hematocrit remained less than 45% in the majority of the patients who were treated with ropeginterferon alpha-2b every 2 weeks compared to the patients who had cytoreductive therapy. No disease progression was noted in the patients treated with ropeginterferon alpha-2b. Conversely, a proportion of the patients who didn't receive treatment showed progression, and the need for phlebotomies was higher. The patients treated with ropeginterferon alpha-2b experienced a significant reduction in symptoms, including splenomegaly, and platelet counts were significantly reduced.

Avapritinib Induces Responses in Patients with Advanced Systemic Mastocytosis (advSM), Regardless of Prior Midostaurin

Presenter: Jason R. Gotlib, MD

Advanced systemic mastocytosis (advSM) is a rare, aggressive cancer of mast cells, which are migrant cells of connective tissue and play a critical role in inflammation. Avapritinib (BLU-285) is a potent and highly selective inhibitor of the mutant tyrosine kinase protein KIT (mutation D816V) that has demonstrated remarkable results in the treatment of SM. The 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 midostaurin. Specifically, the overall response rate was 77%. Avapritinib induced profound, rapid and durable improvements in measures of mast cell burden, for example, *KIT* decreased below detection levels in the majority of the patients. The improvements were correlated with reduction in symptoms related to SM.

The phase 2 clinical trial evaluating avapritinib in advMS is open and enrolling patients at the MPN Clinical Research Center at MD Anderson (protocol #2018-0943).

Addition of Parsaclisib, a PI3Kδ Inhibitor, in Patients with Suboptimal Response to Ruxolitinib: A Phase 2 Study in Patients with Myelofibrosis

Presenter:
Abdulraheem Yacoub, MD

Parsaclisib is a highly selective and potent oral inhibitor of the delta isoform of phosphatidylinositol-3-kinase (PI3K). PI3K is an enzyme primarily expressed in hematopoietic cells and plays a key role in cell signaling and growth, survival, and multiplication of cancer cells. Persistent activation of the PI3K-AKT pathway, due to JAK2 activation, may cause suboptimal response of MF patients to ruxolitinib treatment. In this trial, patients who had primary or secondary MF and received ruxolitinib for more than 6 months (stable dose for more than 8 weeks) were treated with the combination of parsaclisib and ruxolitinib. The combination of the two drugs was efficacious, primarily in the subgroup that was treated with ruxolitinib and 5 mg of parsaclisib twice daily; this cohort experienced a considerable change in palpable spleen length at 12 weeks, and reduction of symptoms. Parsaclisib had an acceptable safety profile.

The phase 2 study, assessing parsaclisib in combination with ruxolitinib in patients with myelofibrosis, is presently open and enrolling patients at the MPN Clinical Research Center at MD Anderson (protocol #2016-0233).

Efficacy and Safety of Mepolizumab in Hypereosinophilic Syndrome: A Phase 3, Randomized, Placebo-Controlled Trial

Presenter: Florence Roufosse, MD

Hyperoesinophilic 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. Mepolizumab was evaluated in a multicenter phase 3 clinical trial in adolescent children and adults (12 years or older) that had HES.

Mepolizumab reduces the blood eosinophil counts; thereby, it lowered the annual rate of flares and the occurrence of the first flare by 66% compared to the placebo in patients with HES, during the 32-week study. The drug was well tolerated. Mepolizumab will be the first medication for treatment of HES if it receives FDA approval.

Highlights of MPN Clinical Trials (continued)

Presentations from the EHA25 Virtual Annual Congress

CPI-0610, a Bromodomain and Extraterminal (BET) Protein Inhibitor, in Combination with Ruxolitinib, in JAK Inhibitor (JAKi) Treatment-Naïve Myelofibrosis Patients: Update from MANIFEST Phase 2 Study

Presenter: John Mascarenhas, MD

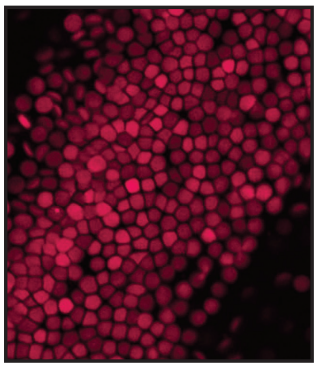
We have been studying combinations of ruxolitinib (JAK1/2 inhibitor) with new drugs, such as bromodomain and extra-terminal (BET) inhibitors, in many clinical trials because patients can have inadequate response to ruxolitinib or relapse. BET proteins are regulators of the transforming growth factor beta, which is an important driver of fibrosis. Preclinical studies demonstrated synergism between ruxolitinib and a BET inhibitor in reducing spleen volume and bone marrow fibrosis. CPI-0610 is a selective and potent small-molecule inhibitor of BET.

In the international, multicenter MANIFEST phase 2 trial, CPI-0610 has been evaluated in combination with ruxolitinib in anemic patients with intermediate-2 myelofibrosis (MF) who had not been treated with ruxolitinib. Interim data from the trial showed significant reduction in spleen volume. At 24 weeks, all the patients had at least 30% reduction in spleen volume, and a large proportion had more than 35% reduction. Significant improvements were observed in anemia, transfusion-dependence, total symptom score, and bone marrow fibrosis, indicating that CPI-0610 may have disease-modifying effects in MF patients. The phase 2 clinical trial evaluating CPI-0610 as monotherapy or in combination with ruxolitinib in MF is open and enrolling patients at the MPN Clinical Research Center at MD Anderson (protocol #2018-0202).

Real-World Survival in Elderly Patients with Myelofibrosis in the United States: Ruxolitinib-Exposed versus Unexposed

Presenter: Srdan Verstovsek, MD, PhD

We searched the Medicare Fee-for-Service (FFS) claims database to identify the patients (1,399), aged 65 years or more (median age 77 years), that had been diagnosed with intermediare-1 or higher risk myelofibrosis (for less than 12 months), from January 2012 to December 2017. We stratified the patients in ruxolitinib-exposed (over 1,000) and ruxolitinib-unexposed (272) groups on the basis of ruxolitinib prescriptions in the follow-up period. The survival rates for the ruxolitinib-exposed subgroup were higher than the ruxolitinib-unexposed subgroup. At one year, the survival rate was 11% higher for the ruxolitinib-treated subgroup versus the subgroup that was not treated with ruxolitinib. At two years, the ruxolitinib-treated group had a 15% higher survival rate compared to the non-treated subgroup. Importantly, the risk of mortality was 39% lower in the patients that had been exposed to ruxolitinib versus those who had not. The study clearly showed the survival benefit that treatment with ruxolitinib confers to myelofibrosis patients.



Red blood cells, PRINT Technology; Courtesy of National Cancer Institute.

Ropeginterferon alpha-2b Is Efficacious and Reduces Variant *TET2* Alelle Burden in Patients with Polycythemia Vera and *TET2* Mutation: Genetic Analysis of Phase III PROUD-PV/ CONTINUATION-PV Studies

Presenter: Robert Kralovics, 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 PROUD-PV trial and its extension CONTINUATION-PV study, which is ongoing, ropeginterferon alpha-2b was evaluated in patients with polycythemia vera (PV).

After follow-up at 3 years, ropeginterferon alpha-2b was found to be considerably superior to hydroxyurea regarding complete hematological and molecular responses in PV patients. The red blood cell and platelet counts were controlled better with ropeginterferon alpha-2b. *JAK2* decreased below the detection limit in a number of the patients treated with ropeginterferon alpha-2b. After *JAK2, TET2* is the next most frequent mutation in PV patients. After treatment with ropeginterferon alpha-2b for 36 months, the majority of the patients had complete hematological remission. Reduction of both JAK2 and *TET2* in PV patients who were treated with ropeginterferon alpha-2b for a long time demonstrates the disease-modifying effects of this medication.

In late 2018, ropeginterferon alpha-2b was approved in Europe to treat patients with PV without symptomatic splenomegaly. In early June, the FDA accepted a Biologics License Application (BLA) for ropeginterferon alpha-2b as a treatment for PV patients without symptomatic splenomegaly.•

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

MPNFocus

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.

Writer and Editor: Helen Chifotides, Ph.D.
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Resources for Patients

MPN ADVOCACY & EDUCATION INTERNATIONAL

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

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

Founded in 1994 by patient advocate, Robert Tollen, the 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 or email 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.

MPN EDUCATION FOUNDATION

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 formed in 1994 by patient Joyce Niblack. In May of 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, in May 1996. You can subscribe to MPN-NET on the Foundation's homepage at mpninfo.org.

Apfed
American Partnership for Eosinophilic Disorders

APFED is a non-profit patient advocacy organization established to assist and support patients and their families coping with eosinophil-associated diseases (EADs), including eosinophil-associated gastrointestinal disorders, hypereosinophilic syndrome, and Churg-Strauss Syndrome. For more information, go to apfed.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.

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

MPN 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, visit mpncancerconnection.org.

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.