Q: When were you first diagnosed with a myeloproliferative neoplasm (MPN) and which one, please?

A: Interestingly, my journey started in 1993. I became dehydrated and ended up in the hospital. The doctor who examined me noticed that my spleen was enlarged. He ordered several tests to figure out what I had but ultimately he could not. I was referred to an oncologist. Between 1993 and 2003, I saw several oncologists, but they did not know much about myeloproliferative neoplasms (MPN). A few used the term “myeloproliferative disorder”, but still not much was known about it. Several oncologists proposed to have a splenectomy but I did not agree. I researched the topic myself, found a team of doctors in Italy and read one of their research articles to learn more about the disease prognosis. At that time, the outlook for patients was not very hopeful. In 2003, I came to MD Anderson for the first time for a consultative visit because my spleen was getting larger every year (I was not experiencing other symptoms). The physician who examined me diagnosed myelofibrosis (MF) but I was not treated and continued the ‘wait-and-see’ approach. I did not see a local oncologist from 2003 to 2008. In 2008, my spleen grew extremely large; I had trouble sleeping, felt fatigued, had night sweats and lost a lot of weight that year. My oncologist told me that he could not help me further, but new drugs were developed so he referred me back to MD Anderson. I came to the Leukemia Department where I was strongly advised to see Dr. Verstovsek who has been my physician since then (January 2009).

Q: Have you participated in clinical trials at MD Anderson since your initial diagnosis? Did you benefit from the medications that you were treated with at MD Anderson?

A: In early 2009, I was enrolled in a clinical trial evaluating an investigational drug but it was not effective. Within one year, I was enrolled in a second clinical trial. Between 2009 and 2017, I have been enrolled in a few clinical trials assessing JAK inhibitors, including momelotinib. The second and third investigational drugs that I received worked better and reduced the size of my spleen. I did not experience many side effects from the drugs I received and generally remained healthy. I was also able to continue working and take great vacations with my family. In 2017, I started treatment with ruxolitinib. My platelets dropped too low on the initial dose so I have been on a low-dose regimen for the last three years. Since I started ruxolitinib, my symptoms stopped, I put on weight and feel healthy. I believe that I benefitted considerably from the treatments I received at MD Anderson.

“My perspective is that regardless of the outcome from my treatment and participation in the clinical studies, I know that I will have helped others. The physicians can apply the feedback and experience from my case to benefit other patients.”

– Nick Pantazis

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Greetings to All!

As 2020 draws to a close, great progress has been made in the clinical arena of myeloproliferative neoplasms (MPN), and we are entering a very auspicious era in the field. We expect to witness further advancements and exponential growth of MPN medications in the near future, acting through a wide array of biological pathways, beyond the success of the cornerstone drug ruxolitinib. We hope that these novel medications, many of which are also currently in clinical development at the Hanns A. Pielenz Research Center for MPN at MD Anderson, will provide additional benefits to our patients and improve challenging aspects of MPN that have not been addressed heretofore.

We are actively engaged, at a global level, in the clinical development of seven novel MPN medications that are in advanced phase 3 randomized clinical trials. Besides the FDA-approved JAK inhibitors ruxolitinib and fedratinib, we are evaluating the efficacy of two other highly promising JAK inhibitors, namely momelotinib and pacritinib, which are particularly advantageous for specific subgroups of myelofibrosis (MF) patients who experience severe anemia and very low platelet counts, respectively.

In addition, we are exploring the efficacy of CPI-0610 (BET inhibitor) and navitoclax (Bcl-xL inhibitor) as monotherapies and in combination with ruxolitinib in patients with MF. The clinical data from ongoing phase 2 open-label studies for the aforementioned drugs are very encouraging.

We are about to launch the pivotal phase 3 randomized trial evaluating imetelstat in patients with refractory MF after the encouraging results of the open-label phase 2 trial (iMbark). Imetelstat (telomerase inhibitor) is the first drug to be assessed in a clinical study for MF patients due to its possible ability to prolong their life.

In June, the FDA accepted a Biologics License Application for ropeginterferon alpha-2b, a long-acting interferon, to treat patients who have polycythemia vera (PV). Ropeginterferon alpha-2b was approved in 2019 as a first-line treatment for PV in the European Union, and we hope this medication will be approved in the US soon. We are also participating in a phase 3 randomized clinical trial to evaluate ropeginterferon alpha-2b in patients with essential thrombocythemia who failed hydroxyurea. We have highlighted the latest clinical developments for several novel MPN medications in the section about the 62nd Annual Meeting of ASH, which was held on December 5-8, 2020.

We have unwavering commitment to excellent patient care and unflagging energy to pursue groundbreaking clinical research studies and develop novel therapeutics to significantly improve the lives of our patients and ultimately cure them. As we are marching into the apogee of MPN medication development, we remain optimistic that the new medications in clinical development will transform the landscape of MPN in the near future.

Happy Holidays! We hope you all stay well and wish you many blessings!

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. 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.
Spotlight: Nick Pantazis

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

A: The positive aspects of my journey have been the following:
1. Living in Houston, near the Medical Center, a fact which gave me the opportunity to come to MD Anderson.
2. Being treated for MF for more than 10 years by Dr. Verstovsek, the best doctor in the world, and his incredible staff!
3. Receiving the best care for my disease. I often think how fortunate I am to live in this day and age. Over the last several years, tremendous progress has been made in medicine, including my disease, and new medications are continuously developed. I consider myself extremely fortunate because if I was diagnosed with MF in the 1970-80s, I would not be around today. I was 30 years old when I had the first symptoms of splenomegaly.

Q: What have been your sources of support through the years?

A: My family has supported me tremendously, especially my wife, my daughters, my sister, and parents. In addition, the Christian Orthodox community and the priests at the Church that I attend have been very supportive. I have personal conversations with the priests; they give me peace of mind. My close friends and the leadership team at my business have been there for me as well. Having an optimistic outlook in life has helped me get through this journey. I make an effort to keep a positive attitude, be resilient, and focus on good things.

Q: What are your future plans regarding your treatment, please?

A: Recently, Dr. Verstovsek noted that my spleen has been getting larger and my platelets were dropping again so I was advised to have a transplant. I plan to have the transplant next year. My dear sister will be the donor. I am nervous about the transplant, but I always remain optimistic. I also know that the support of my family, the Church community and my friends will help me get through it.

Q: Has myelofibrosis affected your daily life and in what ways, please?

A: As I mentioned earlier, since I started treatment, I have not experienced any symptoms except for mild neuropathy in my toes. I have a full life and continue to work full time at my business. I feel healthy, I stay active and have a healthy diet (Mediterranean) thanks to my wife and her vigilance over the years. We go on trips with my wife and daughters and spend time at our property in the country. I also enjoy going horseback riding, river rapids riding, and backpacking with my friends. Of course, I am careful and do not overdo it. Over the years, I have been acutely aware of my disease, but I have not allowed it to become a hindrance in my life and work. I am grateful that I was diagnosed early and that I have been able to receive the best care available. I continue to make plans to keep my business active during the time I am going to have the transplant.

Q: Has the Covid-19 outbreak affected you in any way, please?

A: Covid-19 has not affected us healthwise. We take reasonable precautions: we wear masks and keep social distancing at work. We also spend a lot of time in the country with our miniature donkeys (Clementine in the photo) on weekends.

Q: Have you participated in any MPN educational activities?

A: Yes, I attended in person a couple of patient-centered MPN seminars that Dr. Verstovsek held at MD Anderson and one at Mayo Clinic in Scottsdale, AZ. I also read the MPN Focus newsletter that Dr. Verstovsek publishes, and I keep up with the progress in the field.

“I have not allowed MF to become a hindrance in my life and work. I am grateful that I was diagnosed early and that I have been able to receive the best care available.”

– Nick Pantazis
The Myeloproliferative Neoplasm 10 (MPN10) Total Symptom Score (TSS) Assessment Questionnaire is a valuable and very useful tool to assess and track the symptom status of each patient diagnosed with myeloproliferative neoplasms (MPN).

The questions in the MPN10 Questionnaire are directly correlated to the severity of MPN-related symptoms, which provide a relatively objective way to assess the patient’s quality of life. Therefore, monitoring the score of the MPN10 Questionnaire with time provides the physician with an objective assessment of the patient’s status while being monitored off any therapy, as well as a tool to assess response to treatment. Routine measurement and monitoring of patient-reported symptoms over time guide the physician’s decisions and result in the best possible care for our patients.

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

At MD Anderson Cancer Center, efforts are underway to include the MPN10 Questionnaire and the patients’ answers into current management. The patient will complete the MPN10 TSS Assessment Questionnaire a few days before the appointment at MD Anderson. The patient rates the severity of each symptom in the MPN10 Questionnaire (for example, fatigue, abdominal discomfort, itching) on a scale of 0 to 10 (Figure 1). Each question has a score between 0 and 10. The individual scores marked by the patient for the 10 questions are added, and the MPN10 Total Symptom Score is calculated automatically. The maximum possible total score (TSS) is 100. The individual scores for each question and the total scores are saved in MyChart at each visit, for example, at the beginning and during the course of treatment. The physician can review the scores as a function of time. For example, an increasing score between visits may indicate that the patient is not responding to the treatment and the medication should be changed.

It is important for the patient to report the score for each question so the assessment is objective. For example, fatigue and difficulty with concentration (two points in the questionnaire) may be correlated with anemia, whereas itching and bone pain may be related to uncontrolled myeloproliferation. Early satiety, abdominal discomfort and weight loss may be associated with the severity of splenomegaly, frequently seen in MF patients. We strongly believe that implementation of the MPN10 TSS Assessment Questionnaire will have a great impact on the quality of care provided to our patients.

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**Figure 1. Example of MPN10 Total Symptom Score Assessment Questionnaire**

<table>
<thead>
<tr>
<th>Q</th>
<th>Symptom</th>
<th>Score between 0 and 10 (0 when absent, 10 for worst)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Early satiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Abdominal discomfort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Inactivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Concentration problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Night sweats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Itching</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Bone pain (not arthritis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Fever (&gt;100°F)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Unintentional weight loss</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Total MPN10 Assessment Score | 41 |
Listed below are clinical trials enrolling patients with MPNs at The University of Texas MD Anderson Cancer Center. For more information on these clinical trials, please call the information line toll-free at 1-800-392-1611 or visit: https://www.mdanderson.org/research/departments-labs-institutes/departments-divisions/leukemia/clinical-trials.html and review the MPN section. To find other clinical trials for MPN, please go to clinicaltrials.gov. To schedule an appointment with a doctor in the Leukemia Department at the MD Anderson Cancer Center, please call 713-563-2000 (new patient line).

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

Protocol # 2016-0635  
clinicaltrials.gov NCT No: 03011372  
Principal Investigator: Srdan Verstovsek, MD, PhD  
Study Description: Pemigatinib is a potent oral inhibitor of the enzyme fibroblast growth factor receptor 1 (FGFR1), which plays a key role in cellular proliferation, migration, and survival. In patients with myeloid/lymphoid malignancies and a chromosomal abnormality involving chromosome 8 (specifically 8p11), a protein called FGFR1 is abnormally fused to another protein, and drives the disease. The goal of this study is to evaluate the efficacy of pemigatinib in MPN patients who have the FGFR1 rearrangement, detected by the 8p11 chromosomal abnormality. Early results from this study were extremely encouraging: most patients achieved complete remission.

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

Protocol # 2020-0739  
clinicaltrials.gov NCT No: 04603495  
Principal Investigator: Srdan Verstovsek, MD, PhD  
Study Description: CPI-0610 is an oral medication that inhibits the activity of bromodomain and extraterminal domain (BET) proteins, which have a wide range of functions. Inhibition of BET proteins reduces many other proteins that are important for survival and multiplication of cells, including drivers of bone marrow fibrosis. In this pivotal phase 3 study, either CPI-0610 or the matching placebo is administered in combination with ruxolitinib (a JAK inhibitor, standard first-line therapy for most myelofibrosis patients) because the two drugs may work better together than ruxolitinib alone.

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 30% of MF patients who were irresponsive/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. Potential gastrointestinal side effects can be addressed with supportive care.
Phase 1b Study of PU-H71 in Patients with PMF, Post-PV MF, or Post-ET MF, Treated with Ruxolitinib

Protocol # 2019-0019
clinicaltrials.gov NCT No: 03935555
Principal Investigator: Naveen Pemmaraju, MD

Study Description: The goal of this multi-center phase 1b study is to determine the highest tolerable dose of PU-H71 that can be administered to patients with PMF, post-PV MF, or post-ET MF, in combination with ruxolitinib, a Janus kinase 1/2 (JAK1/2) inhibitor. PU-H71 is an inhibitor of the heat shock protein 90 (HSP90). PU-H71 has demonstrated 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 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. PTG-300 appears to be very promising for treatment of PV. 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.

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

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.

An Open-Label, Phase 2a/2b 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 # 2018-0906
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 Luspatercept (ACE-536), a Selective KIT Mutation Targeted Tyrosine Kinase Inhibitor, in Patients with Advanced Systemic Mastocytosis

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.

Primary MF, Post-PV MF, or Post-ET MF Who Have Failed Prior Treatment with a JAK Inhibitor

Protocol # 2017-0528
clinicaltrials.gov NCT No: 02266204
Principal Investigator: Prithviraj Bose, MD

Study Description: The goal of this clinical trial enrolling patients with MF, post-PV MF, or post-ET MF who have failed prior treatment with a JAK inhibitor is to evaluate the safety and efficacy of SL-401 in patients with primary MF, post-PV MF, or post-ET MF who have failed prior treatment with a JAK inhibitor. SL-401 (also named 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 Who Were Previously Treated with JAK Inhibitors (MOMENTUM trial)

Protocol #2019-0998
clinicaltrials.gov NCT No: 04173494
Principal Investigator:
Srdan Verstovsek, MD, PhD

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

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

Protocol #2019-0113
clinicaltrials.gov NCT No: 03886831
Principal Investigator:
Srdan Verstovsek, MD, PhD

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

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

Protocol #2017-0320
clinicaltrials.gov NCT No: 03165734
Principal Investigator:
Prithviraj Bose, MD

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

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

Protocol #2017-0495
clinicaltrials.gov NCT No: 03222609
Principal Investigator:
Naveen Pemmaraju, MD

Study Description: The goal of this study is to evaluate the optimum dose and efficacy of navitoclax alone or in combination with ruxolitinib in patients with primary or secondary MF who received at least 12 weeks of continuous ruxolitinib therapy prior to enrollment in the study. Navitoclax is a novel small molecule that inhibits the B-cell lymphoma 2 (Bcl-2) family of proteins (primarily Bcl-xL), which are overexpressed in many types of cancer and prevent cancer cells from dying. Preclinical data indicate that navitoclax may be effective in treating MF patients who develop resistance to ruxolitinib. Both navitoclax and ruxolitinib are administered by mouth.

Phase 2 Study of CPI-0610 Taken either with or without Ruxolitinib in Patients with Myelofibrosis

Protocol #2018-0202
clinicaltrials.gov NCT No: 02158858
Principal Investigator:
Prithviraj Bose, MD

Study Description: CPI-0610 is an oral epigenetic modifier that interferes with the activity of bromodomain and extracellular 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 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. Parsaclisib may improve or restore the efficacy of ruxolitinib and have an effect on splenomegaly and other MF symptoms. The drug is administered by mouth.
A Phase 3, Open-Label, Multicenter, Randomized, Active-Controlled Study to Assess Pharmacokinetics and Compare the Efficacy, Safety, and Tolerability of Ropeginterferon alpha-2b (P1101) versus Anagrelide as Second-Line Therapy for Essential Thrombocythemia (ET)

Protocol # 2020-0108
clinicaltrials.gov NCT No: 04285086
Principal Investigator: Srdan Verstovsek, MD, PhD

Study Description: Ropeginterferon alpha-2b is a novel, long-acting interferon formulation that can be administered by injection, bimonthly instead of weekly. Ropeginterferon alpha-2b was approved as a treatment for PV patients in the European Union in 2019 and may be approved for PV treatment in the US in 2021.

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

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

Protocol # 2020-0522
clinicaltrials.gov NCT No: 04517851
Principal Investigator: Prithviraj Bose, MD

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

Phase 3 Study (MYF3001), Evaluating Imetelstat in Adult Patients with Intermediate-2 or High-Risk Myelofibrosis (MF), Refractory to Janus Kinase (JAK) Inhibitors

Protocol # 2020-1141
clinicaltrials.gov NCT No: 04576156
Principal Investigator: Srdan Verstovsek, MD, PhD

Study Description: Imetelstat is a potent inhibitor of telomerase, an enzyme that maintains the structural integrity of chromosomes in normal and cancer cells. Chromosomes are finger-like structures in the nuclei of cells that carry genes. The clinical efficacy of imetelstat and the possible benefit in prolonging survival of patients with myelofibrosis patients relapsed/refractory to ruxolitinib (a JAK inhibitor, standard first-line therapy for most myelofibrosis patients) was evaluated in the IMbark clinical trial. In that 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, comparing imetelstat to standard therapy.

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

Protocol # 2020-0279
clinicaltrials.gov NCT No: 04485260
Principal Investigator: Prithviraj Bose, MD

Study Description: This clinical research study will evaluate the safety and efficacy of ruxolitinib and KRT-232, an orally administered inhibitor of the human double minute 2 (HDM2) protein, in patients with myelofibrosis. HDM2 inhibits the function of a very important protein (p53), which plays a critical role in cell survival and death.
The Addition of Navitoclax to Ruxolitinib Demonstrates Efficacy within Different High-Risk Populations in Patients with Relapsed/Refractory Myelofibrosis

Presenter: Naveen Pemmaraju, MD

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

This phase 2 clinical study is assessing the efficacy of navitoclax and ruxolitinib in patients with relapsed/refractory myelofibrosis. Eligible patients were treated with ruxolitinib for more than 12 weeks and continued to have persistent splenomegaly. Among evaluable patients, about one third had considerable reduction in spleen volume and total symptom score after 24 weeks of treatment. Nearly half of the patients had reduction in driver mutations (JAK2 V617F and CALR). The treatment was well tolerated.

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).

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

Presenter: Marina Kremyanskaya

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 being developed for a broad range of hematologic diseases, including polycythemia vera, associated with dysregulated erythropoiesis and iron metabolism.

Patients with polycythemia (PV) vera may require periodic phlebotomies in order to maintain the hematocrit ≤45% and decrease the risk of thrombosis. This study is evaluating the necessity for phlebotomies in patients with PV who required more than 3 phlebotomies during the 24 weeks before enrollment in the trial and treatment with PTG-300. During the 7-month period that the patients were treated with PTG-300, the hematocrit was controlled below 45% in most patients, and the need for phlebotomies was eliminated. PTG-300 appears to be very promising for treatment of PV. A phase 2 clinical trial, evaluating PTG-300 in patients with phlebotomy-requiring PV is presently open and enrolling patients at the MPN Clinical Research Center at MD Anderson (protocol #2019-0016).

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 was evaluated in the open-label IMbark 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 imetelstat was 28 months versus 20 months with the lower dose, and their symptoms improved; for example, reduction in spleen volume, and more than one degree improvement in bone marrow fibrosis were noted. On the basis of the previous promising results, FDA granted fast track designation to develop imetelstat.

Imetelstat is the first medication to be assessed in a clinical trial for MF patients regarding its possible ability to prolong their life. A phase 3 randomized clinical trial evaluating imetelstat in JAKi-refractory MF patients is currently open and enrolling patients at the MPN Clinical Research Center at MD Anderson (protocol #2020-1141).
Duration of Response to Luspatercept in Patients Requiring Red Blood Cell (RBC) Transfusions with Myelofibrosis (MF) – Updated Data from the Phase 2 ACE-536-MF-001 Study

Presenter: Aaron Gerds, MD

Anemia is a critical complication of myelofibrosis and presents an unmet need in patients diagnosed with this disease. About 60% of the patients with primary or secondary MF develop anemia and require red blood cell (RBC) transfusions. Luspatercept is a recombinant protein that enhances production of red blood cells.

In this presentation, the interim results of luspatercept treatment in 79 patients with MF and anemia, including patients concomitantly treated with ruxolitinib, were reported. Every 21 days, the patients received an injection of luspatercept under the skin for a median of 8 cycles (range, 1–24 cycles).

The updated results from this ongoing study showed that luspatercept had significant and durable clinical activity in a large number of patients with MF-associated anemia, including increase in hemoglobin and more than 50% reduction in the frequency of RBC transfusions over 12 weeks.

A phase 2 clinical trial (protocol #2017-0504), evaluating luspatercept in patients with myelofibrosis and anemia, is currently open and enrolling patients at the MPN Research Center at MD Anderson.

Role of Allogeneic Hematopoietic Cell Transplant in Patients with Myelofibrosis in the JAK Inhibitor Era

Presenter: Dawn Maze, MD

In this study, the outcomes of patients (aged 70 years or less) who had myelofibrosis and received treatment with a JAK inhibitor for a short time (6 months or less) versus MF patients who were treated with a JAK inhibitor for a long time (12 months or more) and did not respond or progressed before having a hematopoietic stem cell transplant (HSCT) were compared. Approximately five hundred MF patients were monitored for 6 years at 8 centers throughout the US and Canada. The patients in the subgroup that received an upfront HSCT had a longer median overall survival (89 months) as compared to the patients who were treated for a long time with a JAK inhibitor before having the HSCT (65 months). However, upfront HSCT was correlated with early mortality, and the benefit of HSCT was evidenced after 5 years. The results of the study suggest that a delayed HSCT strategy may be preferable in MF patients who benefit from JAK inhibitors.

Therapeutic Potential of an Antibody Targeting the Cleaved Form of Mutant Calreticul in Myeloproliferative Neoplasms

Presenter: Yoshihiko Kihara

Essential thrombocythemia (ET) is characterized by many abnormal platelet-forming cells (megakaryocytes) in the bone marrow and high platelet counts. Approximately 20-25% of patients with ET (or PMF) harbor CALR exon 9 mutations. This preclinical study showed that CALR-mutant cells carry a unique sequence in the protein (mutated calreticulin) that can be targeted using immunotherapy. The rat monoclonal antibody B3 recognized the mutant-specific sequence and the cleaved form of mutant CALR expressed on the surface of monocytes in patients harboring the CALR mutation. The authors developed a mouse antibody (B3) and showed that intravenous injection of B3 suppressed thrombocytosis (excess platelets) induced by mutant CALR, which was also associated with a significant reduction in megakaryocytes in the bone marrow. Thus, CALR-targeted antibodies provide a novel promising strategy for treatment of CALR-driven MPN.

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CPI-0610, a Bromodomain and Extraterminal (BET) Protein Inhibitor, in Combination with Ruxolitinib, in JAK Inhibitor (JAKi) Treatment-Naïve Myelofibrosis Patients: Update of the 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 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.

CPI-0610 is a novel, selective and potent small-molecule inhibitor of BET. In the global, open-label 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 that all the patients had at least 30% reduction in spleen volume, and a large proportion had more than 35% reduction at 24 weeks. Significant improvements were observed in anemia, transfusion-dependence, total symptom score (TSS), and bone marrow fibrosis at 24 weeks.

In summary, the preliminary data indicate that the combination of CPI-0610 with ruxolitinib likely is synergistic and may have disease-modifying effects in MF patients who had not been previously treated with ruxolitinib. A phase 3 randomized clinical trial evaluating CPI-0610 in combination with ruxolitinib in patients with MF is open and enrolling patients at the MPN Clinical Research Center at MD Anderson (protocol #2020-0739).

Long-Term Effect of Ruxolitinib (RUX) in Inadequately Controlled Polycythemia Vera (PV) without Splenomegaly: 5-Year Results from the Phase 3 RESPONSE-2 Study

Presenter: Francesco Passamonti, MD

In December 2014, the FDA approved ruxolitinib (JAK1/2 inhibitor) as a second-line treatment for PV patients who are resistant/intolerant to hydroxyurea (HU) based on the results of the RESPONSE trial, which showed the superiority of ruxolitinib vs. HU. The multicenter, randomized phase 3 trial (RESPONSE-2) confirmed the superior efficacy of ruxolitinib vs. HU regarding hematocrit control, complete hematologic response, thromboembolic events and safety after monitoring the PV patients for 5 years (260 weeks). The total number of phlebotomies in the PV group that was treated with ruxolitinib was nearly half (at 260 weeks) versus in the HU-treated group at week 80. In addition, at 260 weeks, the MPN10 Total Symptom Score (TSS) continued to decrease by 50% or more in nearly half of the PV patients treated with ruxolitinib. In accord with the RESPONSE study, the RESPONSE-2 study demonstrated the benefits of treatment with ruxolitinib in HU-intolerant/resistant patients with PV.

Long-Term Use of Ropeginterferon alpha-2b in Polycythemia Vera: 5-Year Results from a Randomized Controlled Study and Its Extension

Presenter: Heinz Gisslinger, MD

Ropeginterferon alpha-2b is a novel, long-acting interferon formulation that can be administered by injection, bimonthly instead of weekly. In the phase 3 randomized PROUD-PV trial and its extension CONTINUATION-PV study, long term treatment with ropeginterferon alpha-2b was evaluated versus hydroxyurea in patients with polycythemia vera (PV). After follow-up at 5 years, the hematocrit remained below 45% in the majority of the patients (82%) who were treated with ropeginterferon alpha-2b compared to the patients who received hydroxyurea. Ropeginterferon alpha-2b was considerably superior to hydroxyurea regarding complete hematological and deep molecular responses in PV patients. The red blood cell and platelet counts were controlled well with ropeginterferon alpha-2b without phlebotomies. The mean JAK2 burden was 5 times lower in the patients treated with ropeginterferon alpha-2b compared to the patients who received hydroxyurea. After treatment with ropeginterferon alpha-2b for 5 years, the majority of the patients had complete hematological remission. Reduction of JAK2 in PV patients who were treated with ropeginterferon alpha-2b for a long time demonstrates the disease-modifying effects of this medication. In 2019, ropeginterferon alpha-2b was approved in the European Union to treat patients with PV, and the FDA accepted a Biologics License Application for ropeginterferon alpha-2b for PV patients. We hope this medication will be approved in the US soon.
Resources for Patients

**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.

**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.

**MPNNET** 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.

**MPN Cancer Connection** 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.

**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 mprresearchfoundation.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, 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.

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