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

MPNFocus

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

WINTER 2020

Patient Spotlight: Claudette Bartlett

Q: Could you please tell us, in brief, about your diagnosis of myeloproliferative neoplasms and how it is being treated?

A: I was diagnosed with essential thrombocythemia (ET) more than 20 years ago, and later it progressed to myelofibrosis (MF). In 2002, my local doctor referred me to MD Anderson Cancer Center because he could no longer help me. At MD Anderson, I was offered the opportunity to participate in different clinical studies because standard therapy did not work anymore.

Initially, I was enrolled in the clinical trial studying the medication called sotatercept because of the anemia I had. Unfortunately, I didn't respond to the treatment, so Dr. Verstovsek advised me to enroll in the clinical trial studying LCL161. This is another investigational agent that may possibly help me with my problem with anemia.

I haven't been on LCL161 for a long time, but I feel better since I started the treatment. Every week, I have blood work done. My local physician monitors my lab results, and my local health care team sends my lab results to the coordinator at MD Anderson. My local health care team has been collaborating very well with the personnel at MD Anderson since I started participating in the clinical trials. My local oncologist keeps up with the latest in his field, and has been a valuable member of the team that is trying to help me. He believes that I will greatly benefit from participating in the clinical trials conducted at MD Anderson Cancer Center.

"My participation in clinical trials gives me a good reason to be optimistic."

"I also think that if the clinical trials do not help me, they will help someone else."

– Claudette Bartlett

Q: How important do you think it is for your family to be involved in your treatment?

A: My husband's involvement has been crucial. He has been extremely supportive, and takes very good care of me. He drives me back and forth to Houston every time we come to MD Anderson (the drive is 6 hours each way). I would not be able to come to MD Anderson and participate in the clinical trials if it were not for my husband. He is always aware of my blood counts as much as I am. Thanks to my husband who has been so involved, we haven't had to ask our children to help us. It would be difficult for them to help us because they are working.

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Featured News

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

Greetings to all!

In this issue, we highlight select, clinically relevant presentations on myeloproliferative neoplasms (MPNs) from the international 61st Annual Meeting of the American Society of Hematology (ASH), which was held in Orlando, FL, in December 2019. We joined more than 30,000 hematology/oncology professionals who hailed across the globe. We presented and discussed the most significant developments that have emerged in the biology and treatment of hematological malignancies, including MPNs. Here, we are sharing the latest clinical findings in myeloproliferative disease to educate our patients, their families and caregivers, and the community at large.

In addition to our educational efforts, we are continuing our endeavors in clinical research. A brief summary of the clinical trials at MD Anderson Cancer Center that are currently enrolling MPN patients has been included in this issue. As you are aware, the ongoing clinical trials conducted at the ***Hanns A. Pielenz Clinical Research Center for MPN*** aim to provide innovative therapeutic options that can significantly benefit our patients.

Preliminary results for a few ongoing clinical trials at the MPN research center are highlighted in the section with the ASH 2019 presentations. It is our pleasure to share the progress in the burgeoning field of MPN research. Our driving spirit is to provide exceptional care and support to all our patients and their families through pivotal research studies, leading to important advancements and novel treatments against MPNs.

We are committed to developing new drugs and effective strategies to treat MPNs, improving treatment outcomes for our patients, and ultimately curing them.

As we continue to make great strides in clinical and laboratory MPN research, we are optimistic that novel therapies, with the highest positive impact on the lives of our patients, will be developed and become available soon.

Wishing you all many blessings. •

Support for Patients in Texas

Founded by MPN patient and advocate Charlie Nielsen, the South Texas support group meets several times a year to discuss issues associated with living with an MPN.

The North Texas support group is led by Andrea Spica and meets quarterly.

Both groups provide an opportunity to meet and share with others who have a similar diagnosis.

To find out more information or join either group, please contact them either by e-mail or through their Facebook pages:

North Texas,
Dallas/Ft. Worth
Andrea926@SBCGlobal.net

South Texas,
Houston
CharlieNielsen@aol.com

Facebook
Facebook.com/groups/
MPNSupportTX

Spotlight

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Q: What are the positive aspects of your journey?

A: The positive aspects of my journey are the great support that I have from my husband, and the fact that I see excellent doctors who have extensive knowledge and expertise.

Q: What expectations do you have from your participation in the clinical trials at MD Anderson?

A: Of course, I hope that my condition will improve because currently, I am transfusion-dependent. Being able to participate in clinical trials gives me hope. It is important for me to focus on the positive aspects of my life and enjoy each day that I feel well. Since I started the new treatment, for example, I feel well most of the time. I hope that my blood counts will be better because I have been feeling better.

"I feel better since I started the treatment."

– Claudette Bartlett

Q: How has your participation in clinical trials affected your life? How have your daily activities changed since your diagnosis, and how do you cope with the challenges?

A: Both my husband and I have retired. We lead a simple life; we don't travel a lot. We arrange our schedule around our next trip to Houston. We work around my illness. The most important point is that both my husband and I are strongly committed to doing the best for my well-being, and hope that my health will improve with my participation in the clinical trials. I believe that as long as you have hope, you can keep trying.

Q: Did you have any symptoms of ET prior to your initial diagnosis?

A: When I had routine blood work done (before the ET diagnosis), my platelet counts were very high. My physician advised me to see a local oncologist (he passed away since then). I have been seeing another local oncologist for many years; he is a wonderful doctor. Initially, I was treated with hydroxyurea and anagrelide, and I had a good response for a long time.

"I believe that as long as you have hope, you can keep trying."

– Claudette Bartlett

Q: Was it difficult for you to cope with the diagnosis of ET? Your disease has changed to MF after several years. What did that mean for you? Did you understand what that change in diagnosis meant?

A: My diagnosis with ET was not difficult to cope with because my doctors were able to control my blood counts until it progressed to MF. Coping with ET had become a way of life. I was accustomed to ET. I was feeling well when I had ET and I responded well to the drugs for a long time. However, diagnosis with MF has introduced a new twist in my journey. MF seems more serious to me. Initially, I didn't know much about MF but I know a little more about it now. I am learning more each day.

Q: Did you know about the clinical trials on myelofibrosis conducted at MD Anderson, before your first visit?

A: I did not know about the clinical trials conducted at MD Anderson until I was advised to join one. I am grateful to my local doctor who referred me to MD Anderson in 2002. My participation in the clinical trials gives me a good reason to be optimistic. I also think that if the clinical trials do not help me, they will help someone else.

Q: Have you pursued any educational activities regarding myelofibrosis and if so, how have they helped you manage the difficulties you have encountered?

A: I have not pursued any educational activities. I just take things day by day. I don't search the internet. Sometimes, searching the internet can make you feel gloomy. I may have to deal with some challenges in the future but currently, I take one day at a time. I do read the newsletter that the MPN Clinical Research Center publishes at MD Anderson. •

MPN RESEARCH

You Can Make a Difference

Gifts provide critical support needed to conduct innovative MPN research. Our MPN clinical and laboratory research team is dedicated to improving treatment outcomes for patients with MPNs.

To make a donation by mail, please send gifts to The University of Texas MD Anderson Cancer Center and specify "MPN Clinical Research Center" in the memo line using the attached envelope.

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 go to mdanderson.org/mpnclinicaltrials.com

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 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.

Importantly, MD Anderson Cancer Center announced the results of another multicenter clinical trial on tagraxofusp (clinicaltrials.gov NCT No: 02113982), in April 2019. The study showed that tagraxofusp had an overall response rate of 90% as a first line treatment for blastic plasmacytoid dendritic cell neoplasm (BPDCN), a deadly type of cancer with no prior available therapies.

Phase 2 Study of CPI-0610 either Taken 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 therapeutic agent that interferes with the activity of bromodomain proteins, which have a wide range of cell functions. Inhibiting bromodomain 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. The interim data for CPI-0610 in patients with myelofibrosis (MANIFEST trial) showed promising clinical activity–significant improvements in spleen volume, bone marrow fibrosis, anemia, transfusion-dependence, and constitutional symptoms– both as 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 required for tumor growth; 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 1/2 Studies of DCC-2618 (KIT D618V Inhibitor) in Patients with Advanced Systemic Mastocytosis

Protocol #2015-0621
clinicaltrials.gov NCT No: 02571036

Principal Investigator:
Filip Janku, MD, PhD

Study Description: The novel KIT inhibitor ripretinib or DCC-2618 is being evaluated in regard to its safety and tolerability in patients with advanced systemic mastocytosis (SM). In the vast majority of cases, advanced SM is characterized by the presence of an abnormality in the gene named *KIT*. The *KIT* D816V mutation produces an abnormal protein that is important for disease persistence and progression. This drug is a potent and selective inhibitor of the abnormal KIT protein.

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, 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 Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis 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.

A Two-Part, Randomized, Open-Label, Multicenter, Phase 2a/2b Study of the Efficacy, Safety, and Pharmacokinetics of KRT-232 Compared to Ruxolitinib in Patients with Phlebotomy-Dependent Polycythemia Vera (PV)

Protocol #2018-0907
clinicaltrials.gov NCT No: 03669965

Principal Investigator:
Prithviraj Bose, MD

Study Description: The goal of this multicenter clinical trial, which has two parts, is to study the efficacy and safety of KRT-232 in patients that have phlebotomy-dependent PV. As detailed in protocol 2018-0906, KRT-232 is an inhibitor of the human double minute 2 (HDM2) protein, and has a different mechanism of action from JAK inhibitors. The study is open and enrolling patients that have failed therapy with hydroxyurea. KRT-232 is administered by mouth.

MPN Clinical Trials (continued)

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 Study of Sotatercept to Treat Patients with MPN-Associated MF and Anemia

Protocol #2012-0534
clinicaltrials.gov NCT No: NCT01712308

Principal Investigator:
Prithviraj Bose, MD

Study Description: The goal of this clinical research study is to assess the improvement of MPN-associated anemia in patients who are treated with sotatercept alone or in combination with ruxolitinib. The latter patients must have already been on ruxolitinib therapy for at least six months, receiving a stable dose for the preceding two months. Sotatercept is injected under the skin every three weeks and is well tolerated.

An Open-Label, Phase 1/2, Dose-Escalation/Dose-Expansion Safety Study of INCB059872 in Patients with Advanced Malignancies

Protocol #2016-0556
clinicaltrials.gov NCT No: 02712905

Principal Investigator:
Gautam Borthakur, MD

Study Description: The purpose of this multicenter study is to evaluate the safety and tolerability of INCB059872– an oral therapeutic that inhibits an enzyme named lysine-specific demethylase 1 (LSD1)– in patients with myelofibrosis and other advanced malignancies. LSD1 makes epigenetic modifications to histones, and is overexpressed in several types of cancer. Patients with myelofibrosis are eligible to participate if they have failed or are not good candidates for standard approved treatments.

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.

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1-85-LEUKEMIA (toll-free) or 713-563-2000

MPN Clinical Trials (continued)

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 phase 1 multicenter 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

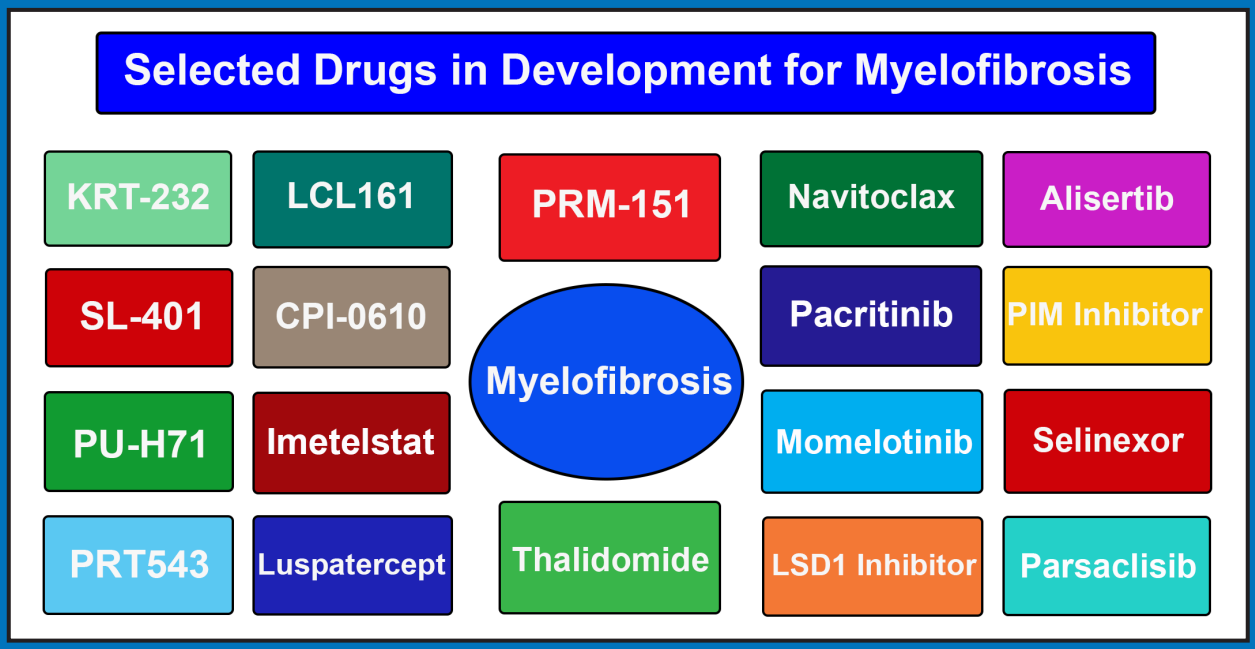
Study Description: The goal of this study is to evaluate the optimum dose and efficacy of navitoclax alone or in combination with ruxolitinib in patients with primary or secondary MF who received at least 12 weeks of continuous ruxolitinib therapy prior to enrollment in the study. Navitoclax is a novel 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.

Phase 2 Study of INCB050465 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 INCB050465 (parsaclisib) in combination with the JAK1/2 inhibitor ruxolitinib 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. INCB050465 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. INCB050465 may improve or restore the efficacy of ruxolitinib and have an effect on splenomegaly and other MF symptoms. The drug is administered by mouth. •



Highlights of MPN Clinical Trials

Presentations from the 61st Annual Meeting American Society of Hematology

DECEMBER 7-10, 2019 • ORLANDO, FL

Ruxolitinib Induced Meaningful and Directional Changes in the Bone Marrow Microenvironment of Patients with Myelofibrosis Enrolled in the COMFORT-I Study

Presenter:
Srdan Verstovsek, MD, PhD

The goal of this analysis was to evaluate the long term effects in the bone marrow – primarily fibrosis (scarring) and osteosclerosis (hardening of the bone or marrow), which are hallmarks of the disease) in a cohort of 57 patients with intermediate-2 or high-risk primary or secondary myelofibrosis; the patients were treated with ruxolitinib (JAK1/2 inhibitor) in the phase 3 COMFORT-I study. The bone marrow specimens were independently reviewed by three expert pathologists.

The analysis showed that bone marrow fibrosis improved or was stable in 40% and 67% of the patients, whereas osteosclerosis improved or remained stable in 21% and 63% of the patients, respectively. Furthermore, the majority of the patients (71%) demonstrated a decrease in inflammation of the bone marrow microenvironment (cytokine-producing megakaryocytes, macrophages, and abnormal plasma cells). The disease-modifying effects of ruxolitinib in MF are likely attributed to its dual ability to decrease myeloproliferation through inhibition of JAK2 and inflammation through inhibition of JAK1.

Results of PAC203: A Randomized Phase 2 Dose-Finding Study and Determination of the Recommended Dose of Pacritinib

Presenter: John Mascarenhas, MD

Pacritinib is a dual inhibitor of Janus kinase 2 (JAK2) and FMS-like receptor tyrosine kinase 3 (FLT3) that demonstrated clinical benefit in patients with MF in two previous clinical trials (PERSIST-1 and PERSIST-2). The PAC203 phase 2 study was conducted to determine the optimum recommended dose of pacritinib in MF patients who were intolerant or failed to benefit from ruxolitinib. The study included 161 patients with a median age 69 years old. Forty three percent of the patients had platelet counts below 50,000/mL, and 71% were anemic (Hgb<10 g/dL). Two doses of pacritinib were evaluated in the study: 100 or 200 mg administered by mouth twice a day. The best results in reduction of spleen volume (≥35%) and total symptom score improvement (≥ 50%) were noted with the higher dose. The improvement with the higher dose was substantially greater than with the lower one. The higher dose was well tolerated and efficacious, especially in patients with low platelet counts. The phase 3 study (PACIFICA) will compare the results of pacritinib (200 mg twice a day) versus the physician's choice in MF patients who have severe thrombocytopenia and are either naïve to or received prior JAK2 inhibitor therapy.

A Phase 2 Study of Luspatercept in Patients with Myelofibrosis-Associated Anemia

Presenter:
Srdan Verstovsek, MD, PhD

Anemia is a critical complication of myelofibrosis and presents an unmet need in patients diagnosed with this disease. About two thirds of the patients with primary or secondary MF have 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 74 patients with MF and anemia (median concentration of hemoglobin was 8.6-8.8 g/dL at study entry), including patients concomitantly treated with ruxolitinib, were reported. Every 21 days, the patients received an injection of luspatercept under the skin at a starting dose of 1.0 mg/kg, in doses that increased up to 1.75 mg/kg, for a median of 8 cycles (range, 1–24 cycles). The preliminary results from this ongoing study showed that luspatercept had significant clinical activity in a large number of patients with MF-associated anemia, including increase in Hgb ≥ 1.5 g/dl and ≥ 50% reduction in the frequency of RBC transfusions. The phase 2 clinical trial evaluating luspatercept in patients with myelofibrosis and anemia is currently open and enrolling patients at the MPN Research Center at MD Anderson (protocol #2017-0504).

Highlights of MPN Clinical Trials (continued)

Presentations from the 61st Annual Meeting of ASH

Ruxolitinib for Patients with Polycythemia Vera: Responders versus Non-Responders as Defined in the RESPONSE Trial

Presenter:

Srdan Verstovsek, MD, PhD

The phase 3 RESPONSE trial compared treatment with ruxolitinib (JAK1/2 inhibitor) versus best available therapy in phlebotomy-dependent patients with polycythemia vera (PV) that were intolerant or resistant to hydroxyurea.

The primary analysis of the study showed that 60% of the patients treated with ruxolitinib achieved hematocrit control (< 45%) at 8 months. Strict control of the hematocrit is critical in PV to prevent thromboembolic events.

The present analysis of the RESPONSE trial evaluated the long-term efficacy (up to 5 years) of ruxolitinib in patients who did not have hematocrit below 45% at 8 months.

The analysis showed that PV patients who were treated with ruxolitinib achieved control of their hematologic parameters (hematocrit, white blood cells, and platelets) over the course of the study, regardless of whether they reached hematocrit control at 32 weeks.

Between 80 and 256 weeks, 91% and 68% of the evaluable patients that were treated with ruxolitinib remained phlebotomy-independent, for responders and non-responders to hematocrit control, respectively. After 8 months, the average spleen volume reduction was approximately 35% and 50% compared to baseline, for responders and non-responders to hematocrit control (<45%), respectively.

In addition, the *JAK2* V617F mutation burden was reduced by approximately 25% in the responders and by 30% in the non-responders to hematocrit control, at week 256 versus baseline. The results from the present analysis clearly show that the benefits of treatment with ruxolitinib in PV patients are long term (up to 5 years) and are not limited to patients who achieve hematocrit control.

Thromboembolic Risk Reduction and High Rate of Complete Molecular Response with Long-Term Use of Ropeginterferon alpha-2b in Polycythemia Vera: Results from a Randomized Controlled Study

Presenter:

Jean-Jacques Kiladjian, MD, PhD

The goals of cytoreductive therapy in polycythemia vera (PV) patients are to prevent cardiovascular/thrombotic events, arising from high red blood cell counts, and alleviate symptoms. Ropeginterferon-alpha-2b (ropegIFN) is a novel, long-acting interferon formulation that can be administered by injection, bimonthly instead of weekly.

The study comprises two major phases, the PROUD-PV and CONTINUATION-PV trials. In the first phase, 257 patients with PV were treated with ropegIFN or hyroxyurea for 12 months. In the second phase, the long-term response to treatment with ropegIFN was compared with standard cytoreductive therapy regarding thromboembolic and other adverse events as well as hematological and molecular parameters in patients with PV over a 4-year period.

The PROUD-PV trial demonstrated the non-inferiority of ropegIFN to hydroxyurea after treatment for 12 months. The 4-year ongoing CONTINUATION-PV study, however, clearly demonstrated that treatment with ropegIFN was superior with respect to both hematological and molecular responses compared to hydroxyurea.

After three years, 61% of the patients treated with ropegIFN achieved and continuously maintained complete hematological remission (control of red blood cell and platelet counts) compared with 43% of the patients in the hydroxyurea arm. In line with the high rate of complete hematological remission, very few major thromboembolic adverse events were observed in the ropegIFN arm versus the control (hydroxyurea).

Additionally, a higher rate of molecular responses was noted in the group treated with ropegIFN (67%) versus hydroxyurea (26%). Complete molecular remissions (*JAK2* V617F allele burden below 1% detection limit) were only noted in the cohort treated with ropegIFN. In the patients treated with ropegIFN, the median *JAK2* V617F allele burden decreased from 37% at baseline to 10%, whereas it increased from 38% to 43% in the control group, over four years.

The minimization of thromboembolic events and the deep molecular responses that were noted in PV patients with long-term treatment underscore the disease-modifying potential of ropegIFN. In late 2018, ropegIFN was approved in Europe to treat patients with PV. We look forward to positive developments and approval of ropegIFN in the US.

Highlights of MPN Clinical Trials (continued)

Presentations from the 61st Annual Meeting of ASH

Fedratinib Induces Spleen Responses and Reduces Symptom Burden in Patients with Myeloproliferative Neoplasm (MPN)-Associated Myelofibrosis (MF) and Low Platelet Counts That Were either Ruxolitinib-Naïve or Were Previously Treated with Ruxolitinib

Presenter: Ruben A. Mesa, MD

Fedratinib is an oral, highly selective JAK2 inhibitor that was approved by the FDA for treatment of patients with intermediate-2 or high-risk primary or secondary MF, including post-polycythemia vera or post-essential thrombocythemia MF, in August 2019.

The phase 3 JAKARTA and phase 2 JAKARTA-2 trials were conducted to assess the clinical activity of fedratinib in patients with intermediate-2 to high-risk MF who had low platelet counts and were intolerant or did not respond to ruxolitinib. In the JAKARTA-2 trial– it had more stringent criteria for MF patients that were refractory or intolerant to ruxolitinib– treatment of 97 patients with fedratinib resulted in 35% reduction in spleen volume and improvement of other symptoms in about 30% of the patients. Besides JAK2, fedratinib is an inhibitor of the FMS-like receptor tyrosine kinase 3 (FLT3), which explains why the treated patients experienced adverse gastrointestinal events that are not noted with ruxolitinib; however, these symptoms could be managed with dose modification and supportive care.

Patients with MF who enrolled in JAKARTA or JAKARTA2 with platelet counts $<100\times10^9$/L had similar reduction rates of spleen volume and symptoms, in both frontline and second-line (post-ruxolitinib) settings. Fedratinib was well tolerated in patients with very low platelet counts at baseline. The phase 3 clinical trial assessing fedratinib in patients with intermediate- or high-risk myelofibrosis who are resistant or intolerant to ruxolitinib (FREEDOM trial) is currently open and enrolling patients at the MPN Research Center at MD Anderson (protocol #2018-1167).

Safety and Efficacy of Combined Ruxolitinib and Thalidomide in Patients with Myelofibrosis: A Phase II Study

Presenter: Raajit Rampal, MD, PhD

Ruxolitinib effectively eases constitutional symptoms and reduces spleen size in myelofibrosis (MF) patients. Concurrent treatment of MF with ruxolitinib and a second drug can be more efficacious in certain cases. Previous studies showed that anemia and platelet counts improved in MF patients treated with thalidomide- a known drug with immunomodulatory activity.

The goal of this ongoing phase 2 study is to evaluate the efficacy of treatment with ruxolitinib in combination with thalidomide in patients with primary, post-polycythemia vera, or post-essential thrombocythemia myelofibrosis. Prior to enrollment, the patients have to be treated with ruxolitinib for at least 3 months, and be on a stable dose for a minimum of 4 weeks. The preliminary results of the study demonstrated promising efficacy and good tolerability of the drug combination. An overall response, including both clinical improvement (higher hemoglobin and platelet levels) and decreased symptom burden, was recorded in 60% (9/15) of the patients. In particular, platelet counts increased by 75% in six out of eight patients who enrolled in the trial with thrombocytopenia, and the response was maintained in the majority of the patients for six months after initiation of treatment with the drug combination. The treatment was well-tolerated. These results are particularly important given that treatment modalities are lacking for thrombocytopenia in primary and secondary MF.

Final Analysis at 5 Years Follow-up of Patients with MPN-Associated Splanchnic Vein Thrombosis Treated with Ruxolitinib in a Phase 2 Study

Presenter:

Alessandro M. Vannucchi, MD

In many cases, the underlying cause of splanchnic vein thrombosis is a myeloproliferative neoplasm (MPN). In this presentation, the investigators reported the long-term (5.5 years) results of a phase 2 study assessing the safety and effectiveness of ruxolitinib, a JAK1/2 inhibitor, in reducing spleen size in patients with MPN-associated splanchnic vein thrombosis.

Eighteen patients entered the extension phase of the trial: eight were diagnosed with primary myelofibrosis (MF), five with polycythemia vera (PV), four with essential polycythemia (ET), and one with post-ET MF.

Among eight patients who exhibited spleen response after 72 weeks, four had a complete response, and four had greater than 50% spleen reduction. The *JAK2* V617F mutation burden was reduced more than 50% in 40% of the patients.

In summary, the long-term study showed that ruxolitinib was safe in patients with MPN-associated

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splanchnic vein thrombosis and efficacious against splenomegaly in one third of the patients. Sustained reduction in spleen size may contribute to decreasing the upstream venous system pressure in these patients.

Results from a Phase 2 Study of Navitoclax in Combination with Ruxolitinib in Patients with Primary or Secondary Myelofibrosis

Presenter: Claire N. Harrison, MD

Navitoclax is a novel small molecule inhibitor that binds with high affinity to the B-cell lymphoma 2 (Bcl-2) family of proteins (mostly Bcl-xl), which prevent the cells from dying. Preclinical studies showed that navitoclax has cytotoxic activity against MPN-derived cell lines.

In this presentation, the preliminary results of the phase 2 multicenter clinical study, assessing the efficacy and safety of navitoclax combined with ruxolitinib in patients with primary and secondary myelofibrosis were reported. Eligible patients had received prior continuous treatment with ruxolitinib for at least 12 weeks.

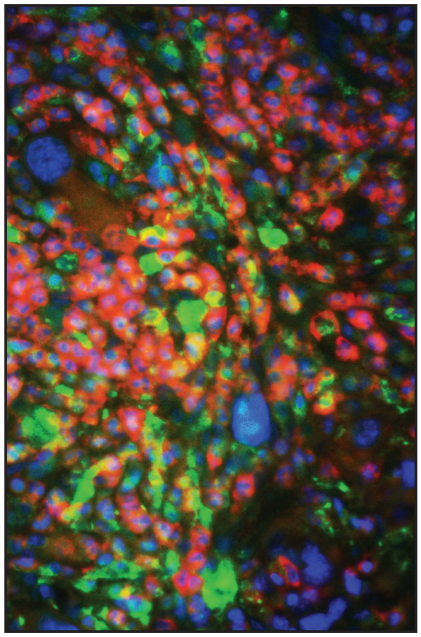
Among the enrolled patients with MF, six (25%) showed improvement of the bone marrow by one grade or more, and 10 (42%) had considerable reduction of spleen volume (≥ 35%). The treatment was well tolerated and improved the total symptom score.

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 Research Center at MD Anderson (protocol #2017-0495).

Preliminary Report of MANIFEST, a Phase 2 Study of CPI-0610, a Bromodomain and Extraterminal (BET) Domain Inhibitor, in Combination with Ruxolitinib, in JAK Inhibitor (JAKi) Treatment Naïve Myelofibrosis Patients

Presenter: Claire N. Harrison, MD

Many clinical trials are studying combinations of ruxolitinib (JAK1/2 inhibitor) with new drugs, such as bromodomain and extra-terminal (BET) inhibitors, because patients can have inadequate response to ruxolitinib or relapse. Apart from regulating other oncogenic pathways, BET proteins are transcriptional regulators of the transforming growth factor beta (TGFβ), an important driver of fibrosis. The results of preclinical studies demonstrated synergism (the two drugs together are more effective than each one alone) between ruxolitinib and a BET inhibitor in reducing spleen volume and bone marrow fibrosis.



In the international, multicenter MANIFEST phase 2 trial, CPI-0610 – a selective and potent small molecule inhibitor of BET– is evaluated in combination with ruxolitinib, in patients with myelofibrosis (MF). The MANIFEST trial comprises three Arms (parts). In Arm 1 of the study, CPI-0610 is evaluated as monotherapy. In Arm 2, CPI-0610 is assessed in combination with ruxolitinib in MF patients who had been previously treated with ruxolitinib and didn't respond or were intolerant.

Preliminary data from Arm 1 and Arm 2 of the study showed that the treatment was well tolerated. Hemoglobin levels increased, whereas the spleen volume, bone marrow fibrosis and the number of transfusions, and pro-inflammatory cytokine levels decreased.

In Arm 3, anemic patients with MF who had not been treated with JAK inhibitors (JAKi naïve patients) in the past, received CPI-0610 in combination with ruxolitinib. At the cutoff date (June 2019), among the 11 treated patients, 4 who had been on treatment for 12 weeks or more achieved greater than 35% reduction in spleen volume, and more than 50% improvement in total symptom score.

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.

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 Research Center at MD Anderson (protocol #2018-0202). •

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

MPNFocus

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

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Resources for 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 not-for-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 go to mpnsupport.org or email listserv@listserv.icors.org with "subscribe mpdsupport" in the body of the email. To join the Facebook group, 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-centric organization, the group has nearly 2,900 members from around 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

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.

MPN RESEARCH FOUNDATION
CHANGE YOUR PROGNOSIS

Founded by patients for patients, the **MPN Research Foundation** is a catalyst for research funding in pursuit of new treatments – and eventually a cure – for MPNs. To date, the Foundation has funded numerous laboratory and clinical projects related to MPN research. 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.