Leukemia insights

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In this month's Leukemia Insights newsletter, written by Naveen Pemmaraju, M.D., and Lucia Masarova, M.D., and sponsored in part by the Charif Souki Cancer Research Fund, we outline clinical trials offered for patients with myeloproliferative neoplasms. Learn more about our Leukemia program.

Myeloproliferative Neoplasm Clinical Trials: Focus on Polycythemia Vera and Essential Thrombocytosis

Remarkable progress has been made in the past several years in our overall understanding and in the development of novel therapeutic approaches for patients with myeloproliferative neoplasms (MPNs), including essential thrombocythemia (ET) and polycythemia vera (PV). The majority of patients with MPNs acquire recurrent somatic driver mutations. For example, almost all patients with PV have JAK2 mutations. ET is more molecularly heterogeneous with 1) JAK2V617F mutations most commonly, followed by 2) CALR mutations and, finally 3) MPL mutations. Novel therapies are being designed to attack the diseases' pathogenetic mechanisms or hallmark features, such as impaired iron metabolism in PV. Historically, therapy goals were primarily to mitigate thrombotic and bleeding risks and control blood counts and symptoms; more recently, there is increased focus on deeper and more meaningful disease modification. The recent approval of ropeginterferon, a novel monopegylated interferon alfa-2b, for patients with PV, and emerging data showing some bone marrow responses and its effect on malignant clones at the molecular level, has opened up an era of targeting deeper disease modification and investigating it in other MPNs. Other agents, such as the new class of agents known as hepcidin mimetics, aim to help patients with PV restore more normal hematocrit levels and become phlebotomy-free. At our center, we prefer to treat patients with novel agents on clinical trials and strive to deliver an optimized targeted treatment approach with a multidisciplinary MPN team.

Clinical Trials in Essential Thrombocythemia (ET)

Standard therapy for patients with ET includes cytoreduction for those with high risk or special needs (persistent symptoms, uncontrolled counts etc). There are currently two clinical trials with ropeginterferon for patients with ET.

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CONTACT OUR STAFF

Mary Alma Welch - Editor
Lisa Palacios - Publishing Editor
Leukemia@mdanderson.org

It is an FDA-approved agent for patients with polycythemia vera (PV) and is showing promising efficacy on the natural course of the disease in addition to symptoms and features (high counts, thrombotic risk). Ropeginterferon is an injectable agent that can be self-administered every 2 to 4 weeks. Both clinical trials below are open and accruing patients.

1. **SURPASS ET; second-line setting (ropeginterferon vs anagrelide), NCT04285086**

In this trial, patients with previously treated ET with hydroxyurea are blindly randomized to either ropeginterferon or anagrelide, oral agent used as a standard next line of therapy. Patients will be monitored for the rate of response, including deep molecular remission, and safety. Ropeginterferon is provided free of charge.

2. **ExceedET; frontline or second-line setting (ropeginterferon), NCT05482971**

Patients with ET in need of therapy and regardless of previous treatment are eligible for this trial. All patients are treated with ropeginterferon that is provided free of charge. This study is exploring a faster dose-escalating strategy of ropeginterferon, which could particularly benefit patients with higher disease burden.

Clinical Trials in Polycythemia Vera (PV)

In higher-risk polycythemia vera (PV), a so-called "triple therapy" approach is recommended: phlebotomy (goal HCT <45) , baby aspirin in those who can tolerate/no contraindications, and some sort of cytoreductive therapy (recommended for all patients over the age of 60 years and/or those with previous history of thrombosis, either of which is deemed as "higher-risk" category). Additionally, patients with high needs for phlebotomies, uncontrolled symptoms, splenomegaly or increased blood counts might need treatment. Standard cytoreductive therapy includes hydroxyurea, pegylated interferon, ropeginterferon, and ruxolitinib (second line post-hydroxyurea intolerance or failure). Clinical trials are focused on patients with persistent need of phlebotomies on standard approach or uncontrolled disease.

1. **Rusfertide (PTG-300) for patients with phlebotomy-dependent PV. NCT05210790.** This novel hepcidin mimetic agent has shown safety and efficacy in the phase 2 REVIVE study. Given as a self-administered, once-weekly injection, the primary goal is to help the patient achieve phlebotomy-independence, either as monotherapy or in conjunction with patient's existing PV cytoreductive therapy previously unsuccessful in controlling HCT. Based on the encouraging results observed thus far from the phase 2 study, there is now a global, double-blind placebo-controlled randomized phase 3 VERIFY study. With a goal to randomize 250 patients with PV across 100 sites, this clinical trial randomizes in 1:1 fashion, featuring patients with ongoing therapy + rusfertide vs ongoing therapy + placebo in Part 1 of the study. Then in Part 1b (weeks 32-52) patients are moved to ongoing rusfertide therapy. A built-in Part 2 of the study aims to measure long-term safety with follow-up planned for weeks 52-156 with ongoing PV therapy + rusfertide. This study is open and enrolling.

2. **IONIS-TMPRSS6-LRx (Formerly ISIS 702843; Sapablursen) for patients with PV. NCT05143957.** Sapablursen is a newer agent in the MPN field. It is a ligand-conjugated antisense medicine that aims to decrease the production of the so-called "transmembrane protease, serine 6" (TMPRSS6) in patients with PV. TMPRSS6 is a protein produced in the liver that plays an important role in the production of the iron regulatory hormone hepcidin. Hepcidin reduces iron absorption from the gut and iron re-cycling in the body. Overall, increased hepcidin production reduces the number of red blood cells produced and represents a novel treatment strategy for polycythemia vera. Results from preclinical studies confirm that sapablursen controls excessive red blood cell production in a PV model. This study is open and enrolling.

3. **ECLIPSE; frontline or second-line setting (ropeginterferon), NCT05481151.** Patients with PV in a need of therapy who are previously untreated or intolerant/refractory to current treatment are eligible. All patients will be

treated with ropeginterferon, but they will be randomized to two arms: standard slow-dosing currently FDA approved schedule vs faster dose-escalating strategy. The faster schedule might render faster responses and thus protect patients from breakthrough events until they achieve drug steady state. Ropeginterferon is provided free of charge.

Upcoming clinical trials in CALR-mutated MPNs: Focus on Novel Immunotherapy Approaches

After JAK26V17F, the most common acquired recurrent somatic driver mutation that is observed in patients with MPNs is the CALR mutation. As elucidated by Nangalia and Klampfel more than a decade ago in NEJM, CALR mutations are present in approximately 20-30%+ of all patients with ET and MF. A more recent discovery reveals that those with CALR mutations might have a more neoepitope/immunomodulatory profile and therefore may have the ability to be targeted via Immunotherapy approaches. This possibility has opened up a potential new era of modern immunotherapy clinical trials in those with CALR-mutated MPNs, which will include relapsed/refractory ET. These approaches will include upcoming clinical trials with CALR mutation-specific vaccines, bi-specific immune agents, and monoclonal antibody studies, all planned to open for first-in-human, phase I clinical trials by the end of 2023 and by early 2024.

Follow the online conversation in MPNs at our hashtag #MPNSM. If you have any questions, please reach out to our MPN Team experts: Drs. Naveen Pemmaraju, Lucia Masarova and Prithvi Bose.

Leukemia Faculty Contacts

Completing these studies in a timely manner will allow us to move quickly on positive leads. We appreciate referrals and will make every effort, once a patient is enrolled on a study, to continue as much of the care as possible through the referring oncologist. We also will keep you apprised of the patient's progress. View our faculty roster.

Clinical Faculty

Kantarjian, Hagop	*Department Chair*	(713) 792-7026
Garcia-Manero, Guillermo	*Deputy Chair, Chief, Section of Translational Research, Chief, Section of Myelodysplastic Syndromes (MDS), and Director, Leukemia Clinical Fellowship Program*	(713) 745-3428
Wierda, William	*Deputy Chair, Chief, Section of Chronic Lymphocytic Leukemia (CLL), and Leukemia Center Medical Director*	(713) 745-0428
Andreeff, Michael	*Chief, Section of Molecular Hematology and Therapy, Center Medical Director, Bone Marrow Aspiration Clinic*	(713) 792-7261
Borthakur, Gautam	*Chief, Section of Developmental Therapeutics*	(713) 563-1586
Daver, Naval	*Director, Leukemia Research Alliance Program*	(713) 794-4392
DiNardo, Courtney D.	*Co-Leader, Section of Acute Myeloid Leukemia (AML), Co-Leader, Section of Developmental Therapeutics Leader, Hereditary Hematologic Malignancy Clinic*	(734) 358-1053
Ferrajoli, Alessandra	*Leukemia Center Associate Medical Director*	(713) 792-2063
Issa, Ghayas “Gus"	*Co-Leader, Section of Chronic Myeloid Leukemia (CML)*	(713) 745-8432
Jabbour, Elias	*Chief, Section of Acute Lymphoblastic Leukemia (ALL)*	(713) 792-4764
Jain, Nitin	*Director, Cellular Therapy Program*	(713) 745-6080
Kadia, Tapan	*Co-Leader, Section of Acute Myeloid Leukemia (AML), Co-Leader, Section of Developmental Therapeutics, Co-Leader, Leukemia Clinical Fellowship Program*	(713) 563-3534
Montalban Bravo, Guillermo	*Director, Chronic Myelomonocytic Leukemia (CMML) Program*	*(713) 792-4956*
Pemmaraju, Naveen	*Director, Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) Program*	*(713) 794-3604*
Ravandi, Farhad	*Chief, Section of Acute Myeloid Leukemia (AML)*	(281) 216-7806
Sasaki, Koji	*Co-Leader, Section of Chronic Myeloid Leukemia (CML)*	(713) 745-2882

Leukemia Faculty Contacts (continued)

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Clinical Faculty

Abbas, Hussein	(713) 745-8433
Alvarado, Yesid	(713) 794-4364
Bose, Prithviraj	(713) 792-7747
Burger, Jan	(713) 563-1487
Chien, Kelly	(713) 745-7584
Kornblau, Steven	(713) 794-1568
Haddad, Fadi	(346) 234-4135
Hammond, Danielle	
Maiti, Abhishek	(346) 725-0901
Masarova, Lucia	(832) 750-4211
Montalban Bravo, Guillermo	(713) 794-3604
Ohanian, Maro	(713) 792-0091
Pemmaraju, Naveen	(713) 792-4956
Reville, Patrick	
Short, Nicholas	(713) 563-4485
Swaminathan, Mahesh	(832) 728-8778
Takahashi, Koichi	(713) 745-4613
Thompson, Philip	(713) 792-7430
Yilmaz, Musa	(713) 745-9945

Research Faculty

Battula, Venkata	(713) 563-2227
Bhalla, Kapil N.	(713) 563-8619
Burks, Jared K.	(713) 792-7640
Carter, Bing Z.	(713) 794-4014
Chang, Kyung Hee	(713) 792-4694
Colla, Simona	(713) 794-5223
Estrov, Zeev	(713) 794-1675
Fiskus, Warren	(713) 563-5901
Ganan_Gomez, Irene	(713)-792-7828
Ishizawa, Jo	(713) 792-7640
Keating, Michael	(713) 745-2376
Piya, Sujan	(713) 792-7305
Post, Sean	(713) 794-1458
Pourebrahimabadi, Rasoul	(713) 792-7305
Rytting, Michael E.	(713) 792-4855
Wei, Yue	(713) 792-9854
Zeng, Zhinhong	(713) 792-7640
Zhang, Weiguo	(713) 794-4085