Leukemia insights

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*In this month's Leukemia Insights newsletter, written by Naveen Pemmaraju, M.D., Lucia Masarova, M.D., and Prithviraj Bose 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.*

# Clinical Trials for Patients with Myeloproliferative Neoplasms: Spotlight on Polycythemia Vera and Essential Thrombocytosis

There has been notable progress over the past several years in our overall understanding of myeloproliferative neoplasms (MPNs), including for patients with essential thrombocythemia (ET) and polycythemia vera (PV), and also in the development of novel therapeutic approaches for such patients. The majority of patients with MPNs harbor acquired recurrent somatic driver mutations. For instance, essentially all patients with PV will have JAK2 mutations. ET is more molecularly heterogeneous with 1) JAK2V617F mutations as the most commonly found mutation, followed by 2) CALR mutations and, finally 3) MPL mutations. Novel therapies are being designed to target the diseases' fundamental pathogenetic primary or secondary mechanisms or other 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 has been increased focus on deeper and more meaningful disease modification. The recent approval of ropeginterferon, a novel mono-pegylated 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 team aiming for greater MPN disease modification.

### Clinical Trials in Essential Thrombocythemia (ET)

Standard therapy for patients with ET includes cytoreduction for those with high risk or special needs (persistent symptoms,

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uncontrolled counts, etc). There are currently two clinical trials for patients with ET with ropeginterferon, an FDA-approved agent for patients with polycythemia vera (PV) that 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 accruing patients:

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

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

**2) INCB057643 NCT04279847**

INCB057643 is a bromodomain and extra-terminal (BET) protein inhibitor. It is being investigated in patients with myelofibrosis in the LIMBER-103 study, both as monotherapy and in combination with ("added on" to) a stable dose of ruxolitinib in suboptimal responders. The trial now has a separate cohort for patients with ET whose disease is resistant to or who are intolerant of hydroxyurea. Dr. Bose is the principal investigator.

**3) VAC85135MPN10001 NCT05444530**

This is a novel vaccine being studied in patients with CALR- or JAK2-mutated ET or myelofibrosis in combination with either 1 mg/kg or 3 mg/kg of ipilimumab (to augment T-cell responses). This is a finite duration therapy. Very low risk patients with ET are not eligible. Patients with JAK2-mutated disease must be of a certain HLA type. Prior JAK2 inhibitor therapy is not permitted, but prior interferon is. Dr. Bose is the principal investigator.

**4) JNJ-88549968, a T-cell Redirecting Antibody NCT06150157**

This study investigates a first-in-human construct, administered subcutaneously for patients with MPNs with CALR mutations (CALR-mutated MF and ET), the second most common recurring mutation in such patients. This Phase I study with Bayesian Optimal Interval (BOIN) dose-escalation safety design will feature rigorously monitored increasing dose levels of this bi-specific therapy, initially focusing on patients with CALR-mutated myelofibrosis post one prior therapy, then expanding to patients with CALR -mutated ET. The primary objective for Part 1 (dose escalation) is to characterize safety and to determine the putative recommended Phase 2 dose(s) (RP2D) and optimal dosing schedule(s). For Part 2 (cohort expansion), this clinical study will further characterize the safety of JNJ-88549968 at the putative RP2D(s). The secondary objectives are to characterize the PK, assess the immunogenicity, and evaluate the preliminary clinical activity ofJNJ-88549968 in participants with essential thrombocythemia (ET) or myelofibrosis (MF) who have become therapy intolerant or resistant. Dr. Pemmaraju is the principal investigator for this novel study which is enrolling patients.

**Clinical Trials in Polycythemia Vera (PV)**

In higher-risk PV, a "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 phlebotomy need, uncontrolled symptoms, splenomegaly or increased blood counts might need treatment. Standard cytoreductive therapy includes hydroxyurea, pegylated interferon, ropeginterferon, or ruxolitinib (second line post-hydroxyurea intolerance or failure). Clinical

trials are focused on patients on standard therapies with persistent need of phlebotomies or uncontrolled disease.

**1) VERIFY: Rusfertide (PTG-300) for phlebotomy-dependent PV. NCT05210790**

Rusfertide, a 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 phlebotomy-independence, either as monotherapy or in conjunction with the existing PV cytoreductive therapy. Based on the encouraging results observed 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 a 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 enrolling. Dr. Pemmaraju is the principal investigator.

**2) IONIS-TMPRSS6-LRx (Formerly ISIS 702843; Sapablursen) for PV. NCT05143957**

Sapablursen is a liver-targeted, anti-sense oligonucleotide against TMPRSS6, a negative regulator of hepcidin. It leads to increased endogenous hepcidin production from the liver, resulting in sequestration of iron in the reticuloendothelial system and reducing the availability of iron for erythropoiesis. Sapablursen is given subcutaneously (SQ) once every 4 weeks. The IMPRSSION trial is studying sapablursen, alone or in combination with standard cytoreductive therapy, in phlebotomy-dependent patients (≥3 phlebotomies in the preceding 6 months) with PV. This study is enrolling. Dr. Bose is the principal investigator.

**3) ECLIPSE; ropeginterferon in frontline or second-line setting. NCT05481151**

Patients with PV in a need of therapy who are untreated or intolerant/refractory to current treatment are eligible. All patients will receive ropeginterferon, but they will be randomized to one of two arms: the standard slow-dosing, FDA approved schedule vs a 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. Dr. Masarova is the principal investigator.

**Era of CALR-Mutated Directed Therapies Has Begun**

After JAK26V17F, the most common acquired recurrent somatic driver mutation observed in patients with MPNs is CALR. 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. Just over a decade later, the search is on for a method to target this mutation directly, with the ultimate goal of MPN disease modification. A more recent discovery reveals that CALR mutations may have the ability to be targeted via novel immunotherapy/immunomodulatory approaches. It is this very possibility that has opened a potential new era of immunotherapy clinical trials in those with CALR-mutated MPNs, including relapsed/refractory ET and MF. These approaches will include the clinical trials highlighted here, with CALR-mutation-specific vaccines, bi-specific targeting agents, and monoclonal antibody studies, all planned to open soon for first-in-human, Phase I clinical trials.

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 Prithviraj Bose.