

ASH Meeting Report

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Although there were no major breakthroughs, this year's American Society of Hematology Annual Meeting didn't disappoint. We heard several reports of investigational agents and learned new biological insights into the pathogenesis of the MPNs.

JAK inhibitors: The biggest news from the meeting is that Fedratinib, a JAK inhibitor that had shown promising Phase 3 results but was put on hold by the FDA for possible association with Wernicke's Encephalopathy, is back in the mix. Studies by Dr. Harrison and colleagues suggest that the Encephalopathy is unrelated to the drug. Along with this presentation, Fedratinib was in the news for its acquisition from Impact Biosciences by Celgene. This is a promising development which suggests that this JAK inhibitor will be evaluated by the FDA very soon and may become an approved therapy for myelofibrosis.

Interferon: An exciting presentation by Dr. Gesslinger updated us on the clinical development of the new form of interferon known as Ropeginterferon alfa-2b. This formulation requires less frequent dosing than Pegasys and is under consideration by the European Medicines Agency. Dr. Gesslinger presented two-year data on safety and efficacy in PV. Ropeginterferon was found to have significantly better complete hematologic response (CHR) and also better CHR with improvement in disease burden. The superiority over hydroxyurea (HU) became evident at the 18-month assessment. With respect to safety, Ropeginterferon alfa-2b had a similar profile to HU. These promising data increase the likelihood that this agent will be made available to patients. In addition to Ropeginterferon alfa-2b, there was a presentation by Dr. Mascarenhas on the MPN Research Consortium Global Phase 2 study of Pegasys in high risk PV/ET patients who were intolerant or resistant to HU. The overall response rate at one year was 69% and 60% for PV and ET patients respectively. They also reported that the tolerability was limited due to adverse events. Nevertheless, the outcomes are notable with respect to the advanced nature of the disease in this patient population. This study provides evidence for the efficacy of interferon therapy second line to hydroxyurea and in a subset of patients that can tolerate the medication durable hematologic responses were seen.

Novel agents: Among the clinical studies of novel therapeutic agents, three stood out.

The first was a phase 1 study of RG7388 (Idasanutlin) in PV and ET patients presented on behalf of the MPN-RC by Dr. Mascarenhas. This drug was well tolerated and led to overall response rate of 78%, with more than half the patients achieving >50% reduction in total symptom score. In several patients from the 12 treated with this agent, bone marrow responses and molecular responses were noted. Furthermore, the correlative studies suggested that the drug has the predicted on-target effect on p53 activation. These encouraging results suggest that targeting the p53 pathway will provide benefit to patients. A multicenter phase 2 trial is now underway evaluating this oral agent in high risk PV patients that are intolerant or resistant to hydroxyurea.

A second notable study, presented by Dr. Gangat of the Mayo Clinic, reported data from an ongoing phase I study of the aurora kinase inhibitor Alisertib in PMF. She reported that Alisertib was overall well tolerated and led to >50% reduction in total symptom score in more than half of the patients. The study group also observed a marked improvement in megakaryocyte morphology in the bone marrow of the patients, which is consistent with the pre-clinical data showing that this compound targets these atypical cells in PMF.

Finally, Dr. Bose from MD Anderson presented data from a study of Sotatercept alone or in combination with ruxolitinib in patients with MPN associated myelofibrosis and anemia.

Sotatercept acts to improve anemia through sequestration of TGF- β ligands which can suppress red blood cell production. Of note, 35% of the patients displayed a hemoglobin response. Given the current challenges in improving anemia in this disease, this response rate is promising.

Basic Biology:

One of the more interesting basic science studies was presented by Dr. Elf from Dr. Ann Mullally's laboratory. She provided important new insights into the way that mutant calreticulin protein, common in ET and PMF, activates JAK/STAT signaling. Through a number of basic biochemical experiments, she mapped out the specific parts of the protein that promote signaling and the expanded growth of blood cells. These new insights shed light on possible new strategies to inhibit mutant CALR activity.

Another notable talk was given by Dr. Meyer from Dr. Ross Levine's laboratory. She has been investigating the contributions of an intracellular signaling pathway, named MAPK, to abnormal cell growth in the MPNs, especially in the setting of JAK kinase inhibition. Her pre-clinical studies revealed that combining JAK and MAPK pathway inhibitors gave rise to superior activity in MPN animal models than treatment with either single agent. A clinical trial combining ruxolitinib with a MAPK pathway inhibitor is planned.

Dr. Nieborowaka-Skorska, with Dr. Thomas Skorski and colleagues, presented a study of the use of Olaparib, an inhibitor of PARP (a protein involved in DNA damage repair), in the MPNs. She demonstrated that deficiencies in DNA damage repair caused by ruxolitinib treatment sensitizes tumor cells to the drug, providing rationale for combining these agents in the MPNs.

Conclusions

Based on what we heard at ASH, this coming year may see the approval of new agents to treat the MPNs. Furthermore, successful pre-clinical studies may move into the clinic. Stay tuned to the Foundation's website for important announcements of approvals and new trials.