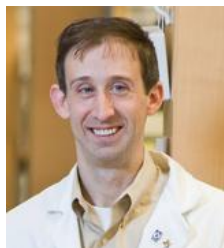


ASH MEETING MPN REPORT

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This report focuses on four areas from the ASH presentations:

- JAK inhibitor Clinical Updates
- New Mechanisms of Action, Clinical Updates
- Combination Studies
- Notable Basic Science Reports

We write these with the patient in mind, so that you can be an involved participant in your care. When you're finished reading this report, we would love to hear your feedback. Send us your comments at info@mpnresearchfoundation.org

JAK INHIBITOR CLINICAL STUDY UPDATES

Pacritinib (CTI Biopharma): Dr. Vannucchi presented an update on the Phase 3 PERSIST-1 trial of this JAK2/FLT3 inhibitor in myelofibrosis. The most striking finding was that pacritinib resulted in consistent reductions in spleen volume and the total symptom scores across subgroups of patients with low platelet counts. The PERSIST-2 trial of pacritinib in primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis is currently enrolling. The company plans to seek approval from the FDA for this drug in late 2016.

Momelotinib (Gilead): This JAK1/2 inhibitor is currently in a Phase 3 clinical trial for treatment of myelofibrosis. In Phase 1 and 2 studies, it has been shown to reduce spleen size and symptom score and to provide an anemia benefit.

NS-018 (NS Pharma): Dr. Verstovsek and colleagues reported the results of a phase 1/2 study of NS-018, a selective JAK2 inhibitor, in patients with primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis. 56% of patients treated with a 300mg dose achieved a 100% reduction in palpable spleen size. There was an overall improvement in all assessed symptoms by 4 weeks, with a maintained improved at 12 weeks for most symptoms. NS-018 was similarly effective in patients who previously received JAK inhibitor treatment. The

Phase 2 part of the study is ongoing in patients who have received prior JAK inhibitor treatment.

NEW MECHANISMS OF ACTION CLINICAL UPDATES

PRM151 (Promedior): Dr. Verstovsek reported on the efficacy and safety of PRM151 in 13 patients who completed at least 72 weeks of treatment with PRM151. This drug is form of a natural human protein named pentraxin-2, which acts to suppress fibrosis at sites of tissue damage. PRM-151 was well tolerated and led to improvements in hemoglobin levels and platelet counts as well as constitutional symptoms and spleen size. The phase 2 study of PRM-151 is ongoing.

What is a “mechanism of action”?

A mechanism of action is a molecular target to which a drug binds, such as an enzyme or receptor. The JAK2 mutation is an example of a mechanism of action.

Imetelstat (Janssen): Imetelstat is a drug that targets telomerase, an enzyme complex that maintains the structure at the ends of chromosomes. It is currently being studied in patients with intermediate risk-2 or high-risk myelofibrosis. While there were no updates on the trial, there were several abstracts pertaining to the drug and its activity. In one presentation, Dr. Tefferi reported that imetelstat may offer clinical benefits to patients with refractory anemia with ringed sideroblasts (RARS). This small study was based on the prior observation that myelofibrosis patients with splicing mutations, which are common in RARS, tended to have a better response to imetelstat.

COMBINATION STUDIES

Ruxolitinib clearly provides a therapeutic benefit to patients, but is not a cure. Therefore, a number of investigators are testing ways to improve the activity of ruxolitinib by combining with other therapies. Many of these combinations show clinical activity, but the extent to which the benefit is beyond that of ruxolitinib alone is unclear.

5-azacytidine (AZA): AZA is a DNA methyltransferase inhibitor approved for treatment of myelodysplastic syndrome. Dr. Verstovsek and colleagues assessed the activity of the combination of AZA with ruxolitinib in patients with a variety of myeloid neoplasms, including myelofibrosis. About half of the 24 enrolled patients showed a response, with the majority of the myelofibrosis cohort achieving a significant reduction in spleen size. The main toxicity was myelosuppression. Further studies with this combination are warranted.

What is “myelosuppression”? It is the suppression of the bone marrow's production of blood cells and platelets.

Interferon- α 2 (IFNa2): Since treatment with interferon is associated with inflammation, Hasselbach and colleagues investigated whether the addition of ruxolitinib, which is effective at suppressing inflammation, would benefit patients, particularly those who are intolerant to IFNa2. A study of 30 patients showed that the combination was well tolerated and effective in a majority of patients, with reductions in symptoms, spleen volume and allele burden. This preliminary study of the combination of IFNa2 and

ruxolitinib suggests that it is effective in PV and hyperproliferative myelofibrosis. In particular, the ability of the combination to ameliorate symptoms while simultaneously reducing the allele burden is very promising.

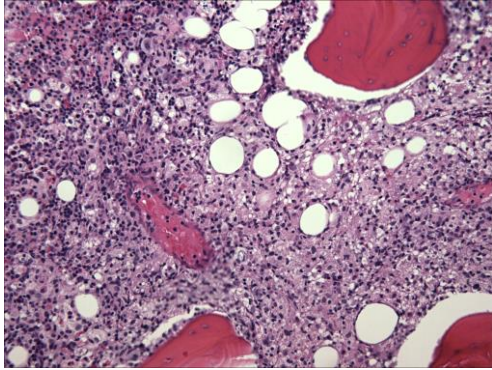
Sonidegib: This is a small molecule inhibitor of the hedgehog signaling pathway, which controls cell growth. Sonidegib is approved for treatment of basal cell carcinoma, a form of skin cancer. A previous pre-clinical study demonstrated that the combination of sonidegib and ruxolitinib improved splenomegaly and bone marrow fibrosis better than ruxolitinib alone. Dr. Gupta presented data from a Phase 1b/2 study of the combination in patients with myelofibrosis. Twelve of 27 patients achieved $\geq 35\%$ spleen volume reduction by week 24. There was a decrease in allele burden (9% median decrease) and reduction in fibrosis in 2 patients.

Pomalidomide: Previous studies by Dr. Tefferi have suggested that this immunomodulatory drug may improve anemia and thrombocytopenia in a subset of MF patients. Dr. Stegelmann presented data from a Phase 1b/2 study of ruxolitinib with pomalidomide in myelofibrosis. A subset of patients achieved clinical improvement, with reductions in symptoms and spleen size some displayed increased hemoglobin, while still others showed stable disease.

Buparlisib: This drug is an inhibitor of another important signaling pathway named PI3K. Preliminary studies have suggested that inhibition of this pathway has beneficial effects in myelofibrosis. Dr. Durrant presented data from the HARMONY phase Ib study of the combination of buparlisib with ruxolitinib in MF. Over 80% of patients achieved greater than 50% reduction in spleen size at any point in time during the study, with this effect seen even in some patients who failed ruxolitinib monotherapy. Side effects included thrombocytopenia, anxiety and depression

NOTABLE BASIC SCIENCE REPORTS

1 - Calreticulin (CALR) activates JAK/STAT signaling in an MPL dependent manner. In an exciting late breaking abstract presentation, Dr. Elf from the Mullally laboratory presented new insights into the mechanism by which CALR mutations contribute to ET and PMF. Until recently, the connection between CALR, which is a protein chaperone, and activated JAK/STAT signaling was unknown. Dr. Elf reported that expression of CALR mutants in mice led to an MPN phenotype with prominent megakaryocyte expansion and thrombocytosis. She also showed that activation of JAK/STAT signaling by the mutant CALR proteins requires the thrombopoietin reception MPL, and that the pathway activation could be suppressed by ruxolitinib. These results help explain why CALR mutant cells are responsive to JAK inhibition. The Vainchenker, Kralovics and Constantinescu laboratories recently reported similar findings in the journal *Blood*. Both Dr. Mullally and Dr. Kralovics are funded by the MPNRF.



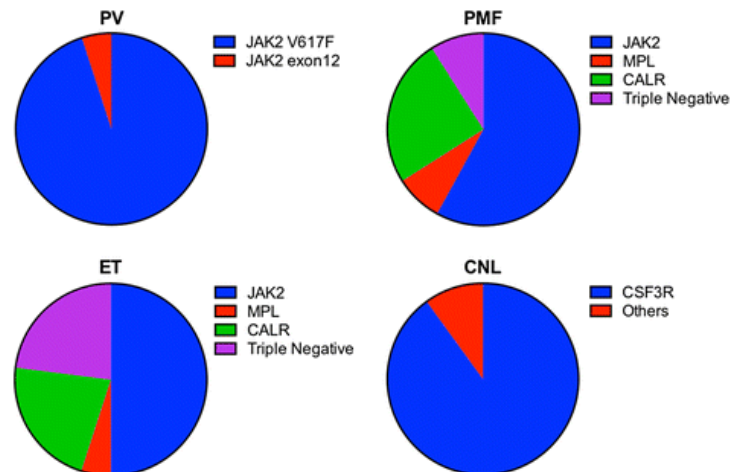
2 - Elimination of fibrosis may not be enough. Is bone marrow fibrosis a cause or effect of PMF?

Two studies asked whether suppressing the cytokine TGF- β could reduce bone marrow fibrosis and subsequently ameliorate the disease. Presentations by Dr. Yue and Suragani reported surprising effects of TGF- β inhibition in animal models of myelofibrosis. The Yue study assessed the activity of the TGF- β inhibitor galunisertib in the JAK2V617F and MPLW515L mouse models of the

MPNs. The treatment led to reductions in collagen expression and TGF- β signaling that were associated with a striking decrease in bone marrow fibrosis. Galunisertib also decreased the peripheral white blood cell count, but it did not significantly reduce the spleen size. Similarly, the study presented by Dr. Suragani, which assayed the activity of a TGF- β antibody RAP-1332 in the JAK2V617F mouse model, revealed that blocking this pathway significantly reduced bone marrow fibrosis. However, it only led to modest decreases in spleen weight and erythroid hyperplasia, little change in the megakaryocyte burden, and no significant improvements in peripheral blood counts. Together the studies suggest that controlling bone marrow fibrosis on its own may only yield modest therapeutic benefit.

3 - Understanding the link between genetics and prognosis. Two

presentations by Dr. Tefferi examined the relationship between mutations in non-driver mutations (driver mutations being *JAK2*, *MPL* and *CALR*), and prognosis. In the first talk, Dr. Tefferi reported that more than 80% of PMF cases had at least one non-driver mutation. He revealed that the presence of an *ASXL1*, *CBL*, *RUNX1* or *SRSF2* mutation confers a worse outcome. In his second talk, he applied a similar method to investigate the relevance of non-driver mutations to PV and ET. Nearly half the patients harbored non-driver mutations, and the number and or nature of these mutations may predict overall survival, risk to progression to MF or acute leukemia. Overall, these studies suggest that incorporating DNA sequencing data into prognosis scoring may help identify which patients face a worse disease.



SUMMARY

In summary, the 2015 ASH meeting provided important updates to novel therapies and biologic studies in the MPNs. A large number of studies are investigating the ability of novel agents to cooperate with ruxolitinib to improve its efficacy. So far, though, it is difficult to discern the added benefit of the second agents: more studies are needed.

With respect to science, we now have a much better understanding of the biological effect of the *CALR* mutations on blood cells as well as new insights into the relationship between secondary genetic mutations and outcome. Next year's ASH promises to have important new updates on the next generation of JAK inhibitors and novel agents, as they are rapidly moving through the clinical trials.