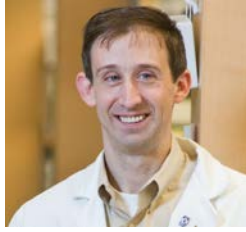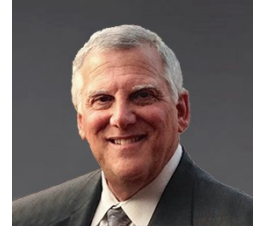# 2018 ASH Report

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Once again, the annual ASH meeting was full of interesting science and clinical updates. This year there was an emphasis on advanced clinical studies of interferon, combination studies of investigational agents with ruxolitinib, and new potential therapeutic targets for the MPNs.

INTERFERON

There were three notable presentations regarding interferon testing in the MPNs, including two on interferon alpha-2 and one on ropeginterferon alfa-2b. Dr. Mascarenhas presented the results of the MPN-RC phase 3 randomized trial of pegylated interferon alfa 2a (PEG) versus hydroxyurea (HU) for the treatment of high-risk PV and ET. The study revealed that the complete remission rates were similar for PEG and HU at 1 and 2 years, but that PEG was associated with a higher rate of grade 3/4 toxicity. In patients with significant baseline MPN symptom burden, both HU and PEG therapy had a beneficial impact on the symptom burden with different patterns of efficacy and toxicity reported between HU and PEG. Results of the three-year Daliah Phase 3 trial of PEG in PV were presented by Dr. Knudsen. The study showed that the clinicohematologic response rate was higher, although not significantly, with interferon compared to HU. Moreover, the median reduction in JAK2V617F allele burden was greater with interferon therapy. Finally, Dr. Gisslinger presented the three-year clinical data from the PROUD and CONTI-PV studies of Ropgeinteferon, reporting on efficacy, safety and molecular response. This study revealed that Ropeginteferon provided durable hematologic responses and symptom control, was well tolerated, and had a striking effect on the mutant allele burden, with 66% of patients achieving molecular remission for JAK2 as well as a reduction in other disease associated genes such as TET2.

NOVEL SINGLE AGENT CLINICAL STUDIES

PRM-151 is a natural human protein that has been shown to reverse fibrosis in pre-clinical studies. Dr. Verstovsek provided an update on the status of 18 patients who had been treated in a phase 1/2 study for up to 140 weeks. Overall, PRM-151 was well tolerated and the treatment was associated with a reduction in spleen volume and symptom burden in a subset of patients, but most notably a reduction in the fibrosis grade in the majority of patients on

study. The results of the phase 1 study of the aurora kinase A inhibitor alisertib, presented by Dr. Gangat, were similar in that alisertib was well tolerated, resulted in a reduction in spleen size and symptom burden in a subset of patients, and notably reduced the degree of fibrosis in 5 of 7 patients for whom sequential marrows were available. These two agents thus represent potential anti-fibrotic agents. Another novel agent reported was LCL161, which is an antagonist of inhibitor of apoptosis proteins that results in increased cell death. Results from a phase 2 study, presented by Dr. Pemmaraju, demonstrated an objective response rate of 30% which included a number of anemia and symptom responses. Finally, Dr. Pemmaraju also presented a poster featuring results from an ongoing Phase 1/2 clinical trial of Tagraxofusp (SL-401) in patients with intermediate or high risk relapsed/refractory MF. Tagraxofusp is a novel targeted therapy directed to the interleukin-3 receptor-α (CD123), a target expressed in some myeloid malignancies including MF. While this study is still enrolling patients, Tagraxofusp monotherapy has demonstrated improvements in splenomegaly, with a manageable safety profile in this patient population.

COMBINATION THERAPIES

A major effort continues to be the search for a drug that will increase the effectiveness of JAK inhibition and potentially cure patients. Among the combinations, notable ones included thalidomide, a PI3K pathway inhibitor, and 5-azacytidine. There was also an interesting presentation of the combination of ruxolitinib with pegylated interferon alpha 2a, referred to as the Ruxopeg study. In each case, there appeared to be promising preliminary efficacy signals, although further study will be required to determine just how much each of the new therapies enhances JAK inhibition.

NOVEL PRE-CLINICAL TARGETS AND NEW BASIC BIOLOGY INSIGHTS

One of the most interesting presentations came from the work of Dr. Constantinescu and colleagues who wondered whether mutant CALR protein was secreted from cells, and if so, whether it had any tumor inducing properties. This study revealed that indeed mutant CALR protein is released from cells where it is then free to induce JAK/STAT signaling in nearby cells. Interestingly, the cells that already harbor a CALR mutation were more sensitive to the secreted CALR than normal cells. This study shows that mutant CALR can act as a "rogue cytokine" to presumably potentiate the growth of the tumor. Another interesting study presented by Dr. Maslah described the rationale for and preliminary results of a pre-clinical study of the combination of interferon alpha and arsenic. Although interferon has significant anti-tumor activity and the ability to reduce the JAK2V617F mutant allele burden, the addition of arsenic significantly enhanced this effect and also led to a profound loss of tumor initiating cells. The results suggest that combining these approved agents is worthy of further investigation. Other pre-clinical abstracts identified new potential therapeutic modalities including inhibitors of PIM kinase and a protein named PRMT5, which modifies other proteins in cells to regulate their activity. Inhibition of these two proteins effectively reduced JAK2V617F MPN in animal models and support further investigation of these pathways in MPN patients. Additional preclinical studies presented support the potential clinical utility of inhibitors of Axl kinase (with BGB324),

SHP2 (with SHP-099) and the NFkB pathway (with pevonedistat) in combination with JAK inhibition. Lastly, Dr. Kralovics presented his work on an MPN tumor cell neoantigen discovery platform as a means to ultimately develop personalized vaccines and/or adoptive cell-based therapies. He was able to identify a rich source of neoantigens in about 60% of the patients tested, in particular those with mutations in CALR, MPL and SF3B1.

DISEASE PROGNOSIS AND PROGRESSION

There was no shortage of presentations addressing MPN disease prognosis and the factors that contribute to disease progression. It was great to see so many major academic centers, both US and abroad, contributing to this area of research. Prognostic scoring systems for the MPNs continue to evolve with the introduction of additional patient, hematologic, karyotypic and gene mutational analyses to further enhance predictions of disease progression and overall survival. One example to highlight is the mutation enhanced international prognostic scoring system for ET and PV developed by Dr. Tefferi (Mayo Clinic) and Dr. Vannucchi (University of Florence). By looking at the factors that led to fibrotic and leukemic progression and overall survival in a large cohort of patients, a simplified system of 4 risk factors has been created to predict low, intermediate and high-risk groups of patients. These studies and others have suggested that spliceosome mutations enhance survival prediction in ET and PV and identify those at risk for fibrotic progression, and that *TP53* mutations may predict leukemic transformation in ET. Mutations in *AXL1*, *EZH2*, *IDH1*, *IDH2*, *RAS* pathway gene and elevated IL-8 serum levels have been associated with disease progression and adverse outcomes in patients with MPNs. The majority of studies in this area of research are retrospective, so additional large patient prospective studies are still needed to truly understand the specific causative role of these mutations in MPN progression. The time may soon be approaching when genomic based classification systems predicting differences in disease outcomes may transcend the original MPN diagnosis. This information will allow for better patient selection for more aggressive therapies, those more likely to respond to traditional therapies, e.g. JAK inhibitors and interferon, and potentially open the pathway for early disease treatment and prevention strategies.