



62nd ASH Annual Meeting and Exposition

Practice-changing abstracts in myeloproliferative neoplasms (MPN)

December 5–8, 2020

The world-leading experts in MPN shared the top abstracts from ASH 2020 that they believe could have the greatest impact on clinical practice.

In this document, you will find comments from the MPN Hub Steering Committee members on the impact of mutation for MPN development and progression as well as exciting results from studies using novel drugs for the treatment of myelofibrosis and polycythemia vera. Furthermore, the latest data exploring the optimized use of interferon alpha will be featured.



#1 Loss of LKB1/*STK11* Facilitates Leukemic Progression of the Myeloproliferative Neoplasms

“Transformation to acute leukemia is relatively infrequent in patients with PV and ET, but it is reported in up to 20% of patients with MF. The mechanisms underlying transformation to AML are largely unknown, although abnormalities in *TP53* and *JARID2* were reported at the time of AML in some patients. Therefore, there is an urgent need to identify molecular abnormalities associated with AML as premise to identify novel therapeutic targets. By using genetic reprogramming with a CRISPR/Cas9 approach in a murine model of *JAK2*^{V617F}-mutated myeloproliferative disease, loss of *STK11*, a gene encoding for LKB1, an enzyme involved in many intracellular pathways linked to metabolic sensing, was discovered. A role for *STK11* in promoting leukemia in MF was corroborated by additional experiments in mice, and by direct demonstration of reduced LKB1 protein expression in human cells from patients with MPN at the time of AML. These findings make the case for abnormalities of *STK11* as novel molecular mechanisms underlying AML transformation in MPN.”



Alessandro M. Vannucchi

“In this plenary session, investigators were interested in what mutations are responsible for the transformation of MF to blast-phase disease, a terminal condition with dismal therapeutic options. Using a complex screening system, researchers identified *STK11*, the gene that encodes LKB1, as enriched in murine models. LKB1 is an important regulator of cellular energy utilization via AMPK. They conclude that loss of *STK11* may drive aggressive transformation events, mechanistically by mismanagement of oxidative phosphorylation and mitochondrial translation. Identifying *STK11* as a tumor suppressor gene in post-MPN AML will allow for the development of therapeutic options and perhaps for targeted sequencing and early intervention in patients with a high risk for transformation.”



Laura Michaelis

#3082 *CREB3L1* Overexpression Can Reliably Discriminate Ph-MPNs from Reactive Cases

“The topic of this presentation is the identification of a diagnostic marker of Philadelphia chromosome-negative MPN. We found that *CREB3L1* was highly expressed not only in ET but also in PV, PMF, and post-PV/ET MF, and expression levels could accurately discriminate driver-mutation-positive Ph-MPN from reactive hypercytosis, reactive MF, and CML. Surprisingly, some of the patients diagnosed as pathologically triple-negative patients with ET without *CREB3L1* over-expression (*CREB3L1*-negative) achieved spontaneous remission during follow-up. Therefore, if a patient is pathologically diagnosed with ET but the *CREB3L1* expression is negative, a careful consideration should be given to treatment. Results have also been published in *Cancer Science*.”



Norio Komatsu

#LBA-1 Driver Mutation Acquisition *in Utero* and Childhood Followed By Lifelong Clonal Evolution Underlie Myeloproliferative Neoplasms

“In this work, the authors elegantly show that driver mutation acquisition occurs very early in life, even before birth, with life-long clonal expansion. The findings suggest that *JAK2*-mutant clonal expansion rates might determine both if and when clinical manifestations occur. The data could provide opportunities for early interventions to reduce thrombotic risk and target the mutant clone in at-risk individuals.”



Haifa Kathrin Al-Ali

“Completely new understanding of MPN pathophysiology, with first acquisition in very early childhood. Offers new opportunities for early detection and management.”



Steffen Koschmieder

“These fascinating data from researchers at the Wellcome Sanger Institute and the University of Cambridge investigate the origins of driver mutations in samples of patients with MPN. The data from whole-genome sequencing of individual single-cell derived hematopoietic colonies were combined with longitudinal blood samples from ten patients. Somatic mutations were identified and then the chronology of these mutations was outlined, via reconstructed phylogenetic trees. The conclusions are remarkable because they demonstrate that MPN driver mutations occur at much earlier ages than previously anticipated. Despite wide ranging ages of MPN presentation, acquisition of driver mutations occurred *in utero* in some cases and in childhood in others – with a long latency period. Not only are the research methods and findings elegant, but they illuminate a new truth for MPN – that these may not be the result of age-related hematopoietic stem-cell fragility, like other clonal hematopoietic changes, but rather stem from very early mutation acquisition. In the future, one could imagine screening programs or even targeted prophylaxis of disease development.”



Laura Michaelis

Whole-genome sequencing shows driver mutations can be acquired very early in life

“ASH 2020 highlights a robust pipeline of new therapy options, offering hope for many additional treatment options for treating physicians to select from and patients with MPN to benefit from in the near future.”



Ruben Mesa

#346 Potential Disease-Modifying Activity of Imetelstat Demonstrated By Reduction in Cytogenetically Abnormal Clones and Mutation Burden Leads to Clinical Benefits in Relapsed/Refractory Myelofibrosis Patients

“Imetelstat is a first-in-class inhibitor of telomerase. Telomerase is an enzyme involved in maintaining the length of telomeres, the terminal portion of each chromosome, by adding repetitive sequences to those ends. Abnormalities of telomeres are a hallmark of many cancer cells. Imetelstat is an intravenous telomerase inhibitor that is currently in use in clinical trials for different cancers, including MDS and MF. For MF, the completed phase II trial, IMbark, was conducted in patients with intermediate-2 and high-risk MF who were refractory to or had relapsed after treatment with a JAK inhibitor. A phase III trial, ImpactMF, is evaluating the activity of imetelstat compared with BAT in patients with MF who are non-responsive, or refractory, to treatment with a JAK inhibitor. Notably, the study is aimed to measure improvement of OS, the first instance where survival is an endpoint of a clinical trial. In this abstract, referring to data collected in the settings of the IMbark study, it is shown that (1) the drug is clinically active (reduction of splenomegaly and symptom improvement) irrespective of the presence of an abnormal karyotype; (2) the subset of patients with a specific chromosomal abnormality (del 13q-) had at least a 50% reduction of the abnormal clone harboring the cytogenetic abnormality; (3) 46% of the patients receiving the higher dose of imetelstat (9.4 mg/kg) had at least a 20% reduction of the percentage of mutation, and such reduction correlated with clinical responses and prolonged survival. These data suggest that imetelstat may have disease-modifying activity, not only being active on splenomegaly and symptoms, but also potentially targeting the clonal malignant stem cell of the disease, eventually resulting in improved survival.”



Alessandro M. Vannucchi

“This abstract highlights the anticlonal activity of imetelstat with clinical outcome measures such as symptom improvement, spleen reduction, and survival. This importantly endorses that clinical benefit with this telomerase inhibitor is directly a consequence of modulating the malignant clone.”



John Mascarenhas

IMbark phase II study of imetelstat for R/R myelofibrosis: Updates from ASH 2020

#347 Telomerase Activity, Telomere Length and hTERT Expression Correlate with Clinical Outcomes in Higher-Risk Myelofibrosis (MF) Relapsed/Refractory (R/R) to Janus Kinase Inhibitor Treated with Imetelstat

“This important analysis links the on-target engagement of the telomerase inhibitor imetelstat with the observed clinical benefits of spleen, symptom, and bone marrow fibrosis reduction. Additionally, drug exposure was associated with optimal pharmacodynamic effect, and these studies collectively confirm the relevance of telomere biology to MPN pathophysiology and affirm telomerase as a therapeutic target.”



John Mascarenhas

“In the IMbark phase II study in MF, it was shown that an imetelstat dose of 9.4 mg/kg was active against enlarged spleen and disease-associated symptoms, and also resulted in improved OS after a follow-up of 42 months (median, 28.1 months *versus* 19.9 months for the 4.7 mg/kg arm). It would be important to identify biomarkers of drug activity that, beyond providing mechanistic information, would allow early identification of patients who would benefit from treatment. In this study, it is shown that changes in the levels of telomerase activity and human telomerase reverse transcriptase were dose correlated and correlated with clinical responses and improved OS. While reinforcing the idea that the benefits of imetelstat are due to its on-target activity, the results also make the case for using these biomarkers to monitor patients receiving imetelstat.”



Alessandro M. Vannucchi

[IMbark phase II study of imetelstat for R/R myelofibrosis: Updates from ASH 2020](#)

#53 Favorable Overall Survival with Imetelstat Treatment Correlates with Other Clinical Benefits in Intermediate 2 or High Risk Myelofibrosis Relapsed/Refractory to Janus Kinase Inhibitor

“This analysis showed a connection between clinical benefits, such as spleen reduction, symptom improvement, and bone marrow fibrosis reduction, with survival. The importance of establishing this connection demonstrates that imetelstat is affecting the MF clone, which results in key clinical benefits with prolongation of survival nearly twice that reported in multiple separate studies of patients with MF that fail ruxolitinib. Improving multiple facets of MF disease features in combination with prolonging survival meets an unmet need in this second-line setting where the median OS is approximately 12–15 months.”



John Mascarenhas

[IMbark phase II study of imetelstat for R/R myelofibrosis: Updates from ASH 2020](#)

#54 Robust Overall Survival and Sustained Efficacy Outcomes during Long Term Exposure to Mometotinib in JAK Inhibitor Naïve and Previously JAK Inhibitor Treated Intermediate/High Risk Myelofibrosis Patients

“These data demonstrate the potential ability of momelotinib to durably address the unmet needs of patients with intermediate-/high-risk MF. Of particular interest is the median OS of 34.3 months for patients with MF who experienced hematological toxicity during prior ruxolitinib therapy (n = 156) and who were randomized to momelotinib or BAT in the SIMPLIFY-2 trial. This survival compares favorably with previously reported median survival times ranging from 13–30 months in patients who have discontinued ruxolitinib.”



Haifa Kathrin Al-Ali

“Mometotinib is a JAK2 and JAK1 inhibitor that also targets ACVR1, the receptor type 1 for activin, member of the transforming growth factor beta superfamily. Inhibition of ACVR1 has been associated with momelotinib capacity to improve anemia in patients with MF included in the phase III SIMPLIFY (-1, including JAK inhibitor-naïve patients with MF randomized to momelotinib *versus* ruxolitinib; and -2 for patients who had developed hematologic toxicity during previous treatment with ruxolitinib randomized to momelotinib *versus* BAT). This abstract reports on the long-term follow-up of 550 patients included in the core study period of 24 weeks and/or in an extended access protocol, including some patients from the previous phase II study. Thirty percent of inhibitor-naïve patients were still receiving momelotinib at > 144 weeks, indicating durability of dosing; the same figure for ruxolitinib-pretreated patients was remarkably lower at 17%. As regards anemia improvement, the proportion of patients who became transfusion independent at 24 weeks was significantly greater for patients on momelotinib (70% *versus* 54% in Simplify-1 and 44% *versus* 27% in Simplify-2); the median duration of remaining transfusion independent was not reached for inhibitor-naïve patients and it was around 1 year for patients in Simplify-2. OS was similar in the two groups of treatment for inhibitor-naïve patients, while it was 34 months for those coming from previous treatment with ruxolitinib, favorably comparing with 13–30 months reported previously in the literature. In summary, results indicate sustained efficacy and durable advantage on survival in intermediate- and high-risk patients with MF receiving momelotinib.”



Alessandro M. Vannucchi

“Important data for patients with MF who failed ruxolitinib. Very nice survival data with an OS of 35 months in patients receiving momelotinib, which was better than expected.”



Jean-Jacques Kiladjian

“I was very interested to see these data on momelotinib, presented at the recent ASH. Despite the benefits of ruxolitinib and fedratinib, there remain a number of patients in whom these drugs have insufficient efficacy or whose disease grows resistant. Most importantly, patients with anemia often struggle with the anticipated anemia associated with the initiation of ruxolitinib. The ability to achieve or maintain transfusion independence is a substantial clinical need for patients with MF, perhaps as important as addressing splenomegaly and symptoms. The data on transfusion independence for patients on momelotinib were encouraging. In the long-term follow-up of SIMPLIFY-1 (JAK inhibitor-naïve patients with MF randomized 1:1 to momelotinib or ruxolitinib), Week 24 transfusion independence was 67% in the experimental arm compared with 49% in the control arm ($p < 0.001$). Furthermore, the median duration of transfusion independence has not been reached after more than 3 years of follow-up.”



Laura Michaelis

SIMPLIFY-1+2 trial: What is the long-term benefit of momelotinib treatment in R/R MF?

#55 CPI-0610, a Bromodomain and Extraterminal Domain Protein (BET) Inhibitor, in Combination with Ruxolitinib, in JAK-Inhibitor-Naïve Myelofibrosis Patients: Update of MANIFEST Phase 2 Study

“The preliminary data of the ongoing study suggest that the addition of CPI-0610 to ruxolitinib is generally well tolerated and potentially synergistic in JAK inhibitor-naïve patients with MF with a DIPSS score \geq Int-2. The combination treatment seems to have a potential to provide enhanced efficacy as evidenced by higher spleen volume reduction \geq 35% by MRI and improvement in total symptom score rates at Week 24 compared with historical data for ruxolitinib monotherapy.”



Haifa Kathrin Al-Ali

“This arm of the phase II trial of the pan-BET inhibitor CPI-0610 evaluates combination therapy with ruxolitinib in JAK inhibitor-naïve patients with MF and demonstrates that the combo is very active in attaining spleen volume reduction, symptom improvement, BMF reduction, and anemia responses and appears to be more active than historical controls of single-agent ruxolitinib. The MANIFEST-2 is a randomized phase III study of the combination of ruxolitinib + CPI *versus* ruxolitinib + placebo starting across the globe and has the potential to shift the treatment paradigm to combination therapy upfront rather than to wait for failure after single-agent JAK inhibitor treatment.”



John Mascarenhas

[MANIFEST phase II study of ruxolitinib and CPI-0610 in patients with myelofibrosis: An update from Arms 2 and 3](#)

[MANIFEST study: Does the BET inhibitor CPI-0610 show synergy with ruxolitinib in myelofibrosis?](#)

#56 CPI-0610, Bromodomain and Extraterminal Domain Protein (BET) Inhibitor, As “Add-on” to Ruxolitinib, in Advanced Myelofibrosis Patients with Suboptimal Response: Update of MANIFEST Phase 2 Study

“CPI-0610 is an oral inhibitor of a family of proteins, called BET proteins, that bind to chromatin DNA, thereby regulating the transcription of many genes involved in key cellular processes that may be variably altered in tumor cells. MANIFEST is an ongoing phase II clinical trial with CPI-0610 that includes patients with higher-risk MF who showed suboptimal responses to ongoing ruxolitinib and were either red blood cell TI or TD. In the TD cohort, as many as 34% of the patients became TI, 21% had improvement in splenomegaly (> 35% volume reduction compared to baseline), and 46% had significant amelioration in symptom score. The clinical efficacy on splenomegaly and symptom was 22% and 37%, respectively, in the non-TD cohort. Safety was good; the most common side events were anemia and thrombocytopenia, and also mild gastrointestinal events with diarrhea and nausea. These preliminary data indicate substantial efficacy of CPI-0610 added “on-top” of ruxolitinib, particularly for anemia and transfusion dependence improvement.”



Alessandro M. Vannucchi

“A new approach as an add-on treatment (CPI-0610) to ruxolitinib in patients with advanced myelofibrosis achieving suboptimal response with ruxolitinib alone. This combination could restore spleen volume response in about 1/3 of patients, especially those who are not dependent of transfusion. Responses for symptoms were also observed.”



Jean-Jacques Kiladjian

MANIFEST phase II study of ruxolitinib and CPI-0610 in patients with myelofibrosis: An update from Arms 2 and 3

MANIFEST study: Should CPI-0610 be used as an add-on to ruxolitinib in patients with advanced MF?

#52 The Addition of Navitoclax to Ruxolitinib Demonstrates Efficacy within Different High-Risk Populations in Patients with Relapsed/Refractory Myelofibrosis

“A new approach as an add-on treatment (navitoclax) to ruxolitinib in patients with relapsed/refractory myelofibrosis achieving suboptimal response with ruxolitinib. Significant spleen volume reduction, although patients were not responding to ruxolitinib alone.”



Jean-Jacques Kiladjian

Why does adding navitoclax to ruxolitinib induce responses in patients with R/R MF?

#483 Interferon-Alpha (IFN) Therapy Discontinuation Is Feasible in Myeloproliferative Neoplasm (MPN) Patients with Complete Hematological Remission

“These exciting data contribute to setting the frame for future clinical trials evaluating IFN treatment holidays in good-responding patients with MPN. IFN discontinuation was shown to be safe and possible in patients, particularly in those with complete hematological remissions and a driver VAF < 10% at the time of discontinuation.”



Haifa Kathrin Al-Ali

“This observation is noteworthy. It underlines that a fraction of patients with PV on IFN may discontinue the drug and maintain the hematological response. Moreover, it underscores that this result is obtained in patients achieving molecular response.”



Tiziano Barbui

“IFN-alpha is the only drug that, particularly in PV, proved able to induce long-term CHR in a proportion of the patients, being associated with marked reduction, up to disappearance, of the *JAK2*^{V617F} (and calreticulin) mutation burden. The current study included 381 patients who had received ≥ 3 months of IFN, of which 45% PV, 44% ET, and 9% MF. After a median follow-up of 6 years, 34% of the patients were still receiving IFN; the reason for stopping was toxicity in 50%, prolonged CHR in 30%, and failure in 6%. IFN was stopped in 170 patients who were in CHR, and in the 36% who required reintroduction of IFN because of having lost CHR, almost 84% again achieved CHR, indicating the absence of IFN resistance in cases of drug reintroduction. The presence of a mutation burden > 10% at the time of IFN discontinuation was associated with a 3-fold higher likelihood to lose CHR. Information from the study, while reinforcing knowledge about clinical and molecular efficacy of IFN, may be important for optimizing treatment strategies, particularly for identifying the best candidates for IFN discontinuation once reaching CHR.”



Alessandro M. Vannucchi

“In patients where IFN-alpha discontinuation is debated, *JAK2*^{V617F} allele ratio determination may provide additional information.”



Steffen Koschmieder

When can we safely discontinue interferon alpha therapy in patients with MPN?

#480 Interferon in Polycythemia Vera (PV) Yields Improved Myelofibrosis-Free and Overall Survival

“Important long-term data on phlebotomy only, IFN-alpha, and hydroxyurea use in PV favors IFN-alpha. This, together with other studies, may soon change our management of low-risk patients with PV.”



Steffen Koschmieder

“This was an interesting single-institution experience of a large number of patients with PV that were treated with IFN-alpha, hydroxyurea, or therapeutic phlebotomy alone and demonstrated that MFS as well as OS was superior in the IFN-treated subgroup. Although very provocative, these results cannot take the place of a prospective randomized study that eliminates selection bias.”



John Mascarenhas

“This large, retrospective, single-center study found that patients with PV who were given IFN-alpha had an MFS and OS advantage over hydroxyurea or phlebotomy only, and had similar rates of toxicity to hydroxyurea.”



Angela Fleischman

“Data on the role of IFN-alpha in PV. Significant improvements in the risk of myelofibrosis and OS.”



Jean-Jacques Kiladjian

Does interferon alpha prolong survival and prevent progression in patients with PV?

#481 Long-Term Use of Ropeginterferon Alpha-2b in Polycythemia Vera: 5-Year Results from a Randomized Controlled Study and Its Extension

“This study reported the 5-year results from ropeginterferon, a very long-acting IFN-alpha, demonstrating that it effectively controlled hematocrit and minimized the occurrence of thromboembolic events in patients with PV.”



Angela Fleischman

“The results of this study indicate that after 5 years of treatment with ropeginterferon alfa-2b, the response in terms of maintenance of hematocrit on target (< 45%) without phlebotomy and the molecular response are obtained simultaneously in 58.5 % of patients. However, this important finding is not accompanied by a reduction in vascular events—affecting 1.2% patients per year in both the experimental and standard arms.”



Tiziano Barbui

cont. #481 Long-Term Use of Ropeginterferon Alpha-2b in Polycythemia Vera: 5-Year

Results from a Randomized Controlled Study and Its Extension

“Update on the long-term use of ropeginterferon alpha in patients with PV from the PROUD/CONTINUATION trials. Five-year data show that complete hematologic response was maintained in 56% of patients. More importantly, the analysis confirmed the high rate of molecular response, including patients achieving < 10% of *JAK2* mutant allele burden at 5 years of treatment. This threshold may have a value for considering stopping interferon therapy in these patients without any further therapy, and they could stay in so-called operational cure.”



Jean-Jacques Kiladjian

#482 PTG-300 Eliminates the Need for Therapeutic Phlebotomy in Both Low and High-Risk Polycythemia Vera Patients

“PTG-300 is a hepcidin mimetic able to induce iron-restricted erythropoiesis without causing systemic iron deficiency, and in this paper was found to reduce the need of phlebotomy in PV. This is a very interesting observation that could potentially change the clinical practice of treatment in PV.”



Tiziano Barbui

“Hepcidin is a protein, largely produced by liver, that inhibits iron transport through ferroportin, a transport protein that is located on the cell membrane of enterocytes, cells lining the internal walls of intestines. Inhibiting ferroportin results in preventing iron from being released into the blood circulation, making it available for erythropoiesis. PTG-300 is a hepcidin-mimetic that induced dose-related anemia in preclinical studies and is now under investigation in a phase II trial in patients with PV. The abstract reports preliminary results in 13 patients with PV who self-administered the drug at home by weekly subcutaneous injection. The majority of patients showed a progressive decrease in hematocrit levels and no further need of phlebotomies to control raised hematocrit. Therefore, these encouraging data—obviously needing to be substantiated with more patients enrolled—support the potential of PTG-300 as an alternative, safe, and effective treatment to phlebotomies in patients with PV.”



Alessandro M. Vannucchi

“This phase II trial is evaluating a hepcidin analogue that is administered via subcutaneous injection once weekly with the intent to modulate iron distribution and limit the availability of iron for erythropoiesis, thereby controlling hematocrit while avoiding the need for therapeutic phlebotomy and the resultant iron-deficient state. Excellent hematocrit control was achieved in this heterogenous group of patients with PV with this well-tolerated parenteral agent. More data on symptom burden, spleen, and *JAK2*^{V617F} VAF are needed to better understand the full benefit of this novel agent targeting hematocrit control.”



John Mascarenhas



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