Advancing Frontiers in Myeloproliferative Neoplasms

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THE 30th EUROPEAN Hematology Association (EHA) Congress marked a pivotal year in advancing the treatment and understanding of myeloproliferative neoplasms (MPN). Breakthroughs in novel therapies, disease biology, and molecular risk stratification highlighted EHA 2025 Congress as a key event shaping the future of MPN care. Herein are the main takeaways from pivotal presentations.

NEW THERAPEUTIC HOPE IN MYELOFIBROSIS

Two major studies presented at EHA 2025 brought promising news for patients with myelofibrosis (MF).

RESTORE Trial[1]

Timothy Devos, University Hospitals Leuven, Belgium, presented data showing that elritercept, an activin receptor ligand trap, provided both haematological and clinical benefits in patients with MF. Treatment led to reductions in splenomegaly and improved symptom control. Notably, elritercept significantly improved anaemia, demonstrating efficacy both as a standalone therapy and in combination with ruxolitinib, suggesting its potential as a disease-modifying agent.

MANIFEST-2 72-Week Update[2]

Alessandro Vannucchi, University of Florence and AOU Careggi, Florence, Italy, presented updated results from the MANIFEST-2 trial, which assessed pelabresib, a bromodomain and extraterminal domain (BET) inhibitor, in combination with ruxolitinib in patients with JAK inhibitor-naïve MF. The regimen demonstrated sustained improvements in spleen volume and symptom burden at 72 weeks, alongside a favourable safety profile, supporting its role as a potential first-line treatment. Although an early imbalance in leukaemic transformation was noted in the pelabresib arm compared to placebo, the incidence over time aligned with expected rates for the MF population.

NOVEL AGENTS TARGETING *CALR* MUTATIONS AND T CELL REDIRECTION

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INCA035784[3]

Beth Psaila, Imperial College London, UK, introduced a T cell-redirecting bispecific antibody that targets *CALR* mutations, showing early signs of immune activation and tumour targeting in preclinical and early-phase clinical testing. This approach opens a new chapter for immunotherapy in MPNs.

INCA33989[4]

John Mascarenhas, Icahn School of Medicine at Mount Sinai, New York, USA, presented first-in-human data on INCA33989, a monoclonal antibody specifically targeting mutant *CALR*. In patients with essential thrombocythaemia (ET), the therapy demonstrated a favourable safety profile and encouraging early clinical activity. Most patients experienced rapid and sustained normalisation of blood counts, along with a reduction in mutant *CALR* variant allele frequency. Notably, 25% of patients achieved early partial molecular remission, suggesting the potential for true disease modification and supporting a new precision medicine approach in *CALR*-mutant ET.

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INTERFERON INNOVATION: ROPEGINTERFERON ALFA-2B STANDS OUT

Ropeginterferon alfa-2b, a long-acting interferon, took centre stage with several abstracts presented across the Congress.

SURPASS-ET Trial[5]

Harry Gill, The University of Hong Kong, Hong Kong SAR of China, delivered a presentation that compared ropeginterferon alfa-2b versus anagrelide in second-line ET. Ropeginterferon alfa-2b demonstrated superior haematologic and molecular responses, alongside a better safety profile.

Pre-Fibrotic Myelofibrosis Use[6]

In lower-risk and early-stage MF, ropeginterferon alfa-2b showed disease control and JAK2V617F allele burden reduction, suggesting utility in early intervention.

Low-Polycythaemia Vera Rollover Cohort[7]

Data showed deep molecular responses even at fixed low doses in polycythaemia vera (PV), indicating sustained disease modulation with less toxicity.

Resistance Mechanisms

Jihyun Song, University of Utah, USA, revealed molecular pathways linked to resistance, paving the way for personalised treatment optimisation.

MYELOFIBROSIS BEYOND JAK INHIBITION

Several abstracts presented at EHA2025 emphasised the requirement to address unmet needs such as anaemia and post-JAK failure.

Nuvisertib[9]

Lindsay Rein, Duke University Medical Center, Durham, North Carolina, USA, presented early-phase results of nuvisertib, a selective proviral integration site for Moloney murine leukemia virus 1 (PIM1) inhibitor, demonstrating clinical activity across spleen volume reduction, symptom improvement, and haematological response. The treatment also modulated inflammatory cytokines, indicating a potential mechanism of action. These findings offer a promising therapeutic option for patients with MF who are refractory to JAK inhibitor therapy.

Momelotinib Studies[10,11]

Francesca Palandri, IRCCS S. Orsola-Malpighi Hospital, Bologna, Italy, explored momelotinib, which uniquely targets anaemia through activin A receptor type I (ACVR1) inhibition. Post hoc analyses of SIMPLIFY-1 and MOMENTUM trials showed improved survival in patients achieving dual spleen and transfusion responses, reinforcing its disease-modifying potential.[12,13]

Anaemia-Related Outcomes[14]

Pankit Vachhani, University of Alabama at Birmingham, USA, emphasised the benefits of combining erythropoiesis-stimulating agent or danazol with ruxolitinib in patients with MF who are anaemic. This approach maintained spleen and symptom responses comparable to the broader JUMP cohort and allowed most patients to tolerate higher ruxolitinib doses while keeping haemoglobin levels stable.[15] The findings support integrated anaemia management to sustain treatment intensity and improve outcomes.

GENOMIC RISK STRATIFICATION AND BIOMARKERS

Precision medicine was also a recurring theme throughout the Congress, highlighted by two key presentations delivered by Barbara Mora, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, and Elisa Rumi, University of Pavia, Italy.

Genomic Profiling in Post-Polycythaemia Vera and Post-Essential Thrombocythaemia Myelofibrosis[16]

Mora highlighted the role of next-generation sequencing in guiding treatment transitions in secondary MF, particularly in determining transplant eligibility and identifying high-risk clones.

Germline Genetics[17]

Rumi's work on familial and early-onset MPNs revealed the germline variants contributing to pathogenesis, suggesting a need for genetic counselling and earlier screening.

Does clone size matter? Debate

There was a lively discussion led by Harrison regarding the allelic burden of driver mutations in MPNs, how this impacts thrombotic risk and event-free survival in MPNs, but also how it is still not included in the tools currently used for risk stratification and therapeutic decision-making.

EMERGING MECHANISTIC INSIGHTS AND TARGETS

Tyrosine Kinase 2 Activation in *CALR*-Mutant MPNs[18]

Nicolas Chatain, University Hospital RWTH Aachen, Germany, showed that tyrosine kinase 2 (TYK2), not JAK2, is a key downstream effector in *CALR*-mutant disease, challenging traditional assumptions and pointing to new druggable targets.

Bone Marrow Microenvironment[19]

Martina Crysandt, University Hospital RWTH Aachen, Germany, presented a study that mapped stromal and immune

cell interactions in the myelofibrotic niche, suggesting the potential for combination strategies targeting the tumour microenvironment.

Neutrophil-to-Lymphocyte Ratio[20]

Tiziano Barbui, Fondazione per la Ricerca Ospedale di Bergamo ETS, Bergamo, Italy, proposed the neutrophil-to-lymphocyte ratio as a simple surrogate marker for JAK2V617F suppression, closely reflecting variant allele frequency dynamics and correlating with event-free survival in PV.

POLYCYTHAEMIA VERA AND ESSENTIAL THROMBOCYTHAEMIA: NEW INSIGHTS

Divesiran[21]

Marina Kremyanskaya, Icahn School of Medicine at Mount Sinai, New York, USA, discussed early-phase results of divesiran, a small interfering RNA targeting *ALAS2*, which showed potential in reducing haematocrit and controlling disease activity in PV.

> **EHA2025 represented a significant milestone in MPN research**

MPL-Mutant Essential Thrombocythaemia[22]

Steffen Koschmieder, RWTH Aachen University, Germany, led an international study of 312 patients with *MPL*-mutant ET, revealing distinct thrombotic risk and survival patterns compared to *JAK2*- or *CALR*-mutated cases. The findings highlight the need for tailored risk scores and management strategies for this unique MPN subgroup.

CONCLUSION: A TRANSFORMATIVE YEAR FOR MYELOPROLIFERATIVE NEOPLASMS

EHA2025 represented a significant milestone in MPN research. Novel therapies, including calreticulin (CALR)-targeted immunotherapies, momelotinib, and elritercept, are expanding the treatment landscape beyond JAK inhibitors. Advances in genomic profiling, interferon therapy, and biomarker development are bringing the field closer to personalised medicine. Collectively, these developments are not only broadening therapeutic options, but also prompting a re-evaluation of disease mechanisms and treatment strategies, signalling a future of greater precision and hope for patients with MPN.

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