

VIEWPOINTS

Promising Findings in Myeloproliferative Neoplasms and AL Amyloidosis

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MOMENTUM: Clinically meaningful benefits with JAK1/2 inhibition coupled with ACVR1 receptor blockade in patients with myelofibrosis

Janus kinase 1/2 (JAK1/2) inhibitors have been successfully used for the treatment of cancer and inflammatory diseases.^{1,2} In fact, JAK1/2 inhibitors have been in focus for the treatment of myelofibrosis (MF), a debilitating condition with poor overall survival.³ There are two ways in which JAK1/2 inhibition can be improved and utilized in this indication; they include the inhibition of an additional receptor or the combination with another drug.

The phase III MOMENTUM study investigated the response rate of momelotinib, an oral JAK1/2 and activin A receptor, type 1 (ACVR1) inhibitor, versus danazol in patients with anemia and symptomatic MF previously treated with a JAK inhibitor.⁴ Momelotinib is the first and only JAK1/2 inhibitor that decreases hepcidin, an important iron-regulating peptide, that is elevated in primary and secondary MF, leading to a reduction of serum iron, anemia and a reduction of erythropoiesis, all of which are common in MF patients.⁵

The trial included 195 patients, who were treated with a JAK inhibitor (JAKi), with tapering and washout of JAKi for ≥ 21 days, and were then randomized in a 2:1 fashion to receive either momelotinib (200 mg, daily) plus placebo or danazol (600 mg, daily) plus placebo during the 24-week double-blind period. This was followed by an open-label/crossover period where all patients received momelotinib. The primary endpoint of this study was the total symptom score (TSS) response rate at week 24. Secondary endpoints included the transfusion independence (TI) rate and splenic response rate (SRR), both at week 24.

In the momelotinib group, 24.6% (32/130) of patients achieved the primary endpoint of Myelofibrosis Symptom Assessment Form (MFSAF) TSS response rate at week 24 compared with 9.2% (6/65) of patients in the danazol group.⁴ Concerning the key secondary endpoints, 40% (52/130) of patients in the momelotinib group achieved a 25% reduction in SRR

at week 24 compared with 6.2% (4/65) of patients in the danazol group. Notably, a 35% reduction in SRR was recorded in 23.1% of patients in the momelotinib group versus 3.1% of patients in the danazol group. There was an increase in mean hemoglobin over time with the introduction of momelotinib treatment, while the transfusion independence rate at week 24 in the momelotinib group was 31% versus 20% in the danazol group ($p=0.0064$). No statistically significant difference was observed in the overall survival (OS) between the two groups, but there was a trend towards an improved OS with momelotinib treatment.

In conclusion, momelotinib leads to a significant improvement in symptoms, spleen size and anemia in MF patients with a trend towards an improved OS.

REFINE: JAK1 inhibitor plus BCL inhibitor was well tolerated and showed clinical benefits in JAK inhibitor-naïve patients with myelofibrosis

The phase II REFINE study evaluated the safety and efficacy of navitoclax, a first-in-class, oral B-cell lymphoma (BCL)-2/BCL-X_L inhibitor, in combination with ruxolitinib, a JAK1/2 inhibitor, in JAKi-naïve patients with myelofibrosis.⁶ Navitoclax is a small molecule that binds with a high affinity to pro-survival proteins (BCL-2, BCL-X_L and BCL-W), promoting the release of pro-apoptotic factors, ultimately leading to the apoptosis of myeloproliferative neoplasm (MPN) cells.⁷ The study consisted of four patient cohorts; however, the presentation at EHA2022 focused on Cohort 3, which included patients who were naïve to JAK2 inhibitor and bromodomain and extra-terminal motif (BET) inhibitor.⁸

Patients in Cohort 3 received navitoclax 100 mg or 200 mg once daily (if the baseline platelet count was $\leq 150 \times 10^9/L$ or $>150 \times 10^9/L$, respectively). Additionally, ruxolitinib was orally administered twice daily at a starting dose based on the baseline platelet count per local ruxolitinib label.⁸ The primary endpoint was a reduction in the spleen volume of $\geq 35\%$ (SVR₃₅) from baseline at week 24. Key secondary endpoints included a $\geq 50\%$ reduction in total symptom score (TSS50), a change in grade of bone marrow fibrosis from baseline, anemia response rate and overall safety. All patients enrolled in the study experienced a reduction in splenic volume, 63% (20/32) of whom met the primary endpoint. In terms of the secondary endpoints, there was a reduction in bone marrow fibrosis of ≥ 1 grade from baseline in 27% of patients by week 24; moreover, there was a 40% change in baseline in the anemia response at any time post-baseline.

In summary, the combination of navitoclax and ruxolitinib in JAK inhibitor-naïve patients with MF was well-tolerated and demonstrated a clinical benefit. However, these results will need to be confirmed by the ongoing phase III TRANSFORM-1 study.⁹

MANIFEST: JAK inhibitor plus BET inhibitor demonstrated a robust reduction in splenic volume and total symptom score in JAK inhibitor-naïve patients with myelofibrosis and in those with a suboptimal response to ruxolitinib

The ongoing global phase II MANIFEST study is investigating the safety and efficacy of pelabresib, a BET inhibitor, that downregulates the expression of genes that contribute to the heterogeneous pathology of MF, as monotherapy or in combination with ruxolitinib in patients with myelofibrosis and essential thrombocythemia.¹⁰

The trial consists of four treatment arms; however, the results presented at EHA2022 focused on the preliminary data for Arm 2 (second-line MF, suboptimal response or MF progression on ruxolitinib) and Arm 3 (first-line MF, with Dynamic International Prognostic Scoring System [DIPSS] Int-2/High). Patients in Arm 2 were treated with ruxolitinib and the addition of pelabresib (“add on”) and were further divided between Arm 2A (n=59, transfusion-dependent [TD]) and Arm 2B (n=27, Non-TD). Patients in Arm 3 (n=84) with higher risk MF received the combination of ruxolitinib and pelabresib first-line.

The primary endpoint for treatment Arms 2B and 3 was SVR₃₅, and the achievement of transfusion independence in Arm 2A. The key secondary endpoint for all treatment arms was TSS50, and for Arm 2A it was additionally SVR₃₅.¹⁰ In Arm 2, SVR₃₅ at week 24 was achieved by 20% of patients, and TSS50 at week 24 was achieved by 37% of patients. There was a modest effect on transfusion dependence in Arm 2A. In Arm 3 at week 24, SVR₃₅ and TSS50 were achieved in 68% and 56% of patients, respectively. Furthermore, the spleen volume reduction in both treatment arms appeared to be durable and deepened over time. The most common treatment-emergent adverse events (TEAEs) were low-grade, including anemia and thrombocytopenia, as well as diarrhea, nausea and abdominal pain. Serious TEAEs reported in ≥3 patients in Arm 2 included anemia (6 patients), respiratory tract infections (4 patients) and urinary tract infections (3 patients). In Arm 3, serious TEAEs reported in ≥3 patients included 6 patients with respiratory tract infection and 3 patients with pyrexia. At week 24, 26% of patients in Arm 2 achieved a ≥1 grade improvement in bone marrow fibrosis versus 28% of patients in Arm 3.

Following these promising results, the currently open for enrollment phase III MANIFEST-2 study was initiated, which is investigating the efficacy and safety of pelabresib plus ruxolitinib versus placebo plus ruxolitinib in JAK inhibitor-naïve MF patients.¹¹

Final results from the PROUD-PV/CONTINUATION-PV studies: Ropeginterferon alfa-2b potentially lowers the risk of progression from polycythemia vera to myelofibrosis or acute leukemia

Final results from the PROUD-PV/CONTINUATION-PV studies after six years of therapy with ropeginterferon alfa-2b in early polycythemia vera (PV) patients were discussed at EHA2022.¹² Typical patient-centered treatment goals in PV include ameliorating of symptom burden, minimizing the risk of progression to myelofibrosis or acute leukemia and preventing thromboembolic complications.

Ropeginterferon alfa-2b is mono-pegylated interferon that is administered every 2–4 weeks and is approved for all lines of treatment of PV by the European Medicines Agency (EMA),¹³ and the Food and Drug Administration (FDA).¹⁴ It is also approved by Swissmedic as monotherapy for the treatment of adult patients with PV without symptomatic splenomegaly and for whom cytoreductive therapy is indicated.¹⁵

During the initial PROUD-PV study, treatment-naïve patients and hydroxyurea (HU) pre-treated patients (<3 years, not full responders) were randomized 1:1 either to ropeginterferon alfa-2b or HU.¹⁶ After 1 year of treatment, patients were included in the CONTINUATION-PV study, where ropeginterferon alfa-2b-treated patients continued their treatment, while patients with prior HU were moved onto best available therapy (BAT) for another 5 years.

In the 6th year of treatment, 81.4% of patients in the ropeginterferon alfa-2b arm were free from phlebotomies to maintain the hematocrit <45% compared with 60.0% of patients in the control arm ($p=0.005$).¹² Moreover, ropeginterferon alfa-2b potentially has a disease-modifying effect, as there is a reduction in *JAK2* V617F allele burden of <1% in 20.7% of patients in the ropeginterferon alfa-2b arm versus 1.4% in the control arm ($p=0.0001$); this effect may lower the risk of disease progression. Event-free survival (EFS) was statistically significantly higher in the ropeginterferon alfa-2b arm compared with the control arm as risk events (death, disease progression, and thromboembolic events) were reported in 5/95 versus 12/74 patients, respectively ($p=0.04$).

In conclusion, ropeginterferon alfa-2b should be used in an early-stage PV population as it is not very active in patients with pronounced splenomegaly.

Thematic debate: Should low-risk polycythemia vera patients and low-risk myelofibrosis patients be treated?

During a thematic debate at EHA2022, there was a discussion regarding the evidence and the need for treating low-risk PV or low-risk MF patients. Conventional prognostic factors in PV include age >60 years and a history of thrombosis. There are several molecular risk factors with regard to OS (*SRSF2*, *IDH2*), leukemia-free survival (*IDH2*, *RUNX1*) and myelofibrosis-free survival (*U2AF1*), which have not been integrated into routine clinical practice. Updated recommendations from the European Leukemia Net (ELN) 2021 suggest that patients with PV with symptomatic or progressive splenomegaly, persistent leukocytosis (>11G/l, >15G/l ?) or poor tolerance to phlebotomy should be treated with cytoreductive drugs. With regard to patients with MF, there are numerous risk stratification scores for primary (International Prognostic Scoring System [IPSS], Dynamic IPSS [DIPSS], mutation-enhanced IPSS [MIPSS-70]) and secondary myelofibrosis (MYelofibrosis SECondary to PV and essential thrombocytopenia prognostic model [MYSEC-PM]), including peripheral blood values, clinical and genetic data.

During the thematic debate, Prof. Christen Lykkegaard Andersen (Copenhagen, Denmark) represented the part in favor of treating low-risk patients with PV and MF, while Prof. Claire Harrison (London, UK) represented the opponents.

With regards to low-risk PV, interferon (IFN) treatment can lead to both longstanding molecular and histological remissions in some patients, and the best treatment response is in low-risk patients.¹⁶ However, the reduction in *JAK2* V617F allele burden <1% is only seen in about 20% of patients. There is some evidence that treating low-risk PV patients may help to avoid the first thrombotic complication and to minimize the risk of progression to myelofibrosis and acute leukemia. On the other hand, there is a lack of prospective data regarding survival benefit and the fact that IFN-treated patients are usually younger with a smaller risk of acute leukemia might be a bias. It is known that the level of variant allele frequency (VAF) and leukocytes are linked and that a high level of VAF is therefore worrisome; therefore, it might be advisable to initiate treatment according to VAF and not according to leukocytes, although such data are presently lacking. It can be argued that both the PROUD-PV and the CONTINUATION-PV studies demonstrated a benefit for the use of IFN treatment in clinically relevant aspects; however, since the median EFS for such patients is about 25 years anyway, data for long-term follow-up are required.

Focusing on low-risk MF, Prof. Andersen stated that treatment with IFN should be given independent of driver mutations, whereas Prof. Harrison indicated that the data on the use of IFN in patients with *CALR* mutations are less strong and that there are no data to support early intervention with

JAK inhibitors in such patients. The potency of IFN is certainly worse if a second mutation occurs, and our therapeutic options in patients developing anemia and progressive splenomegaly are very limited; thus, preemptive treatment with IFN might be justified. Conversely, clinical and laboratory follow-up every 4–6 months with yearly abdominal ultrasound to evaluate spleen size could be used instead in order to monitor these patients for disease progression and to initiate treatment at that time. The performance of next-generation sequencing at diagnosis (single nucleotide polymorphism [SNP] arrays are slightly more sensitive) outside clinical studies remains a matter of dispute, and it might be advisable to look for high-molecular risk mutations (*ASXL1*, *EZH2*, *SRSF2* or *IDH1/2*) as those have the potential of altering the clinical management. Young patients with low-risk MF typically respond better to IFN therapy, but there are no sufficient data on disease modification with IFN in patients with low-risk MF. However, ruxolitinib at later stages of MF and at higher risk, respectively, probably has disease-modifying properties by, among others, reduction of inflammation.

In conclusion, there is no clear answer on whether or not patients with low-risk PV or low-risk MF should be preemptively treated, exceeding the ELN 2021 recommendations. The ultimate treatment decision is, therefore, at the discretion of the physician taking into account the disease characteristics and wishes of a well-informed patient.

EMN22 study: Daratumumab monotherapy induced rapid and deep hematological responses in newly diagnosed patients with AL amyloidosis and cardiac stage IIIb

Patients with immunoglobulin light-chain (AL) amyloidosis and cardiac stage IIIb are notoriously difficult to treat and have a median overall survival of just about four months.¹⁷ The phase III ANDROMEDA study, which investigated the efficacy of daratumumab in combination with bortezomib, cyclophosphamide, and dexamethasone in newly diagnosed AL amyloidosis, excluded patients with advanced cardiac stage IIIb.¹⁸ Currently, there are no approved drugs for treating patients with newly diagnosed AL amyloidosis and cardiac stage IIIb.

The phase II EMN22 study by the European Myeloma Network (EMN) is investigating the efficacy and safety of daratumumab monotherapy in an off-label setting in newly diagnosed patients with AL amyloidosis and cardiac stage IIIb.¹⁹ Of the 27 patients in the intention-to-treat (ITT) population, only 8 (30%) patients are continuing treatment at the cut-off date, while 16 patients (59%) discontinued treatment (6 patients due to progressive disease, 7 patients due to a safety event, 2 patients due to death, 1 patient due to withdrawal of consent). The remaining 3 patients (11%) had completed treatment as per protocol.

The overall response rate (ORR) was 66.7%, while the response was fast with a median time to first response of 7 days (range 6–114). The median duration of daratumumab monotherapy was 7 months (range <1–24). The median OS in this study was 9 months [95% CI: 3–not reached], which compared favorably to the historical data of 4 months as mentioned above.²⁰ Regarding safety, 18 patients (66.7%) experienced ≥ 1 non-serious TEAEs grade 3 or 4, peripheral edema, dyspnea and atrial fibrillation being the most common. There were 20 patients (74.1%) with ≥ 1 serious TEAEs, the majority of which were cardiac disorders, with cardiac failure/congestive cardiac failure (9 patients) and sudden cardiac death (3 patients) being the most common.

In summary, daratumumab monotherapy induced rapid and deep hematological responses without new safety signals, with a prolongation of the median OS to 9 months. This multinational, open-label study aims to enroll 40 newly diagnosed patients with AL amyloidosis and cardiac stage IIIb.

Conflict of interest

The author has taken part in advisory boards organized by Amgen, BMS/Celgene, Janssen-Cilag, Novartis, OrPha Swiss and Takeda. These funding entities did not play a role in the development of the manuscript and did not influence its content in any way.

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Author contributions

The author has created and approved the final manuscript.



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