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POSTER ABSTRACTS

631.CHRONIC MYELOID LEUKEMIA: BIOLOGY AND PATHOPHYSIOLOGY, EXCLUDING THERAPY

Fedratinib Treatment Reduces the Inflammatory Cytokine Profile and Decreases Exhausted T Cells Correlating with Clinical Response in Patients with Myelofibrosis: Biomarker Analysis from the Phase 3 FREEDOM2 Trial

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Introduction: Myelofibrosis (MF) is a clonal myeloproliferative neoplasm (MPN) characterized by a hyperactive JAK-STAT pathway, splenomegaly, and constitutional symptoms. JAK inhibitors (JAKi) have been the mainstay in MF treatment over the past decade. Pro-inflammatory cytokines, the levels of which have prognostic value (Tefferi et al. J Clin Oncol 2011), have been shown to be upregulated in MF. However, there is paucity of data on chronic immune dysregulation in pathogenesis of MF. Here, we report the multiplatform biomarker analysis including immune changes from phase 3 (FREEDOM2) trial in patients with MF previously exposed to ruxolitinib (Rux) and treated with fedratinib vs. best available therapy (BAT) (primary efficacy: 35.8% vs 6% responders at the end of cycle 6 (EOC6) in fedratinib vs BAT, respectively). Of note, 78% of the patients on BAT continued RUX therapy until EOC6, allowing direct comparison between RUX and fedratinib.

Methods: In the FREEDOM2 trial, patients (N=201) were randomized into two arms, fedratinib (400 mg/day) or BAT in a 2:1 ratio, respectively. The primary endpoint was the proportion of patients with ≥35% reduction of spleen volume (SVR35) on MRI at the end of cycle 6 (EOC6). In the FREEDOM2 biomarker cohort, mutational analysis was performed in enriched CD66b+ cells using the MLL myeloid panel targeting 74 genes. Rules-Based Medicine's (RBM) HumanMAP v2.0 panel targeting 85 cytokines was used to measure changes in serum cytokine levels from C1D1 to EOC6. Custom Q2 immune panels to detect myeloid and lymphoid subsets were used for immunophenotyping of peripheral blood samples.

Results: Baseline mutations in FREEDOM2 were commonly found MPN mutations that include JAK2 V617F (71%), ASXL1 (43%), CALR (22%), TET2 (22%) and MPL (11%). However, baseline mutation status was not a predictor of response.

Patients receiving fedratinib demonstrated significant down-regulation of several pro-inflammatory cytokines including CRP, ENRAGE, IL-18, IL-16, TIMP-1, and increase of anti-inflammatory cytokines including adiponectin, MMP2, and CEA (Wilcoxon signed rank test, BH adjusted p <0.001) at EOC6 vs C1D1. In addition, the change in levels of many cytokines correlated with the clinical endpoint (SVR35) demonstrating that the therapeutically relevant changes were mediated by fedratinib (Pearson rho $P<0.05$) (Figure 1). Importantly, fedratinib was superior to the BAT in its ability to alter levels of key cytokines (p <0.05) at EOC6.

PD-1 expression has been shown to be upregulated in CD4+ and CD8+ T cells in MF patients and is associated with poor overall survival. However, RUX did not have a significant effect on PD1+ T cells (Veletic et al. *Haematologica* 2021). Interestingly, flow cytometric analysis revealed that fedratinib decreased exhausted CD8+ T cells (PD1+) up to 40% (Δ median change -11.4%,p<0.001)) (figure 2). Importantly, the reduction in exhausted T cells correlated with the reduction in spleen volume with fedratinib treatment (R= -0.51, P=0.00011; Figure 2). Consistent with this, we also observed median increases in NK (+3%, p<0.001) and NK-T (+13.8%, p<0.001) populations when compared to the BAT arm.

Conclusions: To our knowledge, this is the first comprehensive study detailing cytokine and immune changes in patients with MF in a clinical trial. In addition, our data for the first time demonstrates the impact of fedratinib on the immune system and its ability to reduce exhausted T cells, highlighting the immune modulatory mechanism of fedratinib. Notably, the cytokine and immune changes correlated with the primary endpoint and were not observed in the BAT arm demonstrating superior

efficacy of fedratinib in previously RUX exposed patients. Furthermore, since majority of the patients in the BAT arm continued to receive RUX, these findings highlight the mechanistic differences between fedratinib and RUX on clinical response in MF (SVR35). Overall, our data highlight multiple novel avenues to achieve therapeutic efficacy in MF and positions fedratinib as an effective therapy with a distinctive mechanism of action. Additional analyses on the effect of fedratinib treatment on myeloid immune subsets and transcriptomic changes are underway to gain comprehensive mechanistic understanding.

Disclosures Jeyaraju: *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Hayati:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Wang:** *Bristol Myers Squibb:* Current Employment. **Harrison:** *AOP:* Honoraria, Speakers Bureau; *Galecto:* Honoraria, Speakers Bureau; *GSK:* Honoraria, Speakers Bureau; *CTI:* Honoraria, Speakers Bureau; *Novartis:* Honoraria, Research Funding, Speakers Bureau; *BMS:* Honoraria, Speakers Bureau; *Abbvie:* Honoraria, Speakers Bureau; *Morphosys:* Honoraria, Speakers Bureau. **Kiladjian:** *Incyte Corporation:* Membership on an entity's Board of Directors or advisory committees; *BMS:* Membership on an entity's Board of Directors or advisory committees; *AOP Orphan Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *AbbVie, AOP Health, Bristol-Myers Squibb, GlaxoSmithKline, Incyte, Novartis, Pharmaessentia.:* Consultancy. **Hernandez:** *BMS:* Current Employment, Current equity holder in publicly-traded company. **Brown:** *Bristol Myers Squibb:* Current Employment, Current holder of *stock options* in a privately-held company. **Lopes De Menezes:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company, Patents & Royalties: Patents filed/pending. **Gandhi:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company. **Suragani:** *Bristol Myers Squibb:* Current Employment, Current equity holder in publicly-traded company.

Figure 1. Fedratinib treatment reduces the inflammatory cytokines in patients with MF: Heat map shows change in cytokine levels in patients in the fedratinib arm with paired C1D1 and EOC6 data (n=70). Left/middle annotation bar plots show the Pearson rho correlation of FC (in soluble markers' abundance) and %SVR (with *P* value <0.05 highlighted in green). The bar plots on the right show Wilcoxon signed-rank test for paired analysis of C1D1 vs EOC6 biomarkers concentration (with significant adjusted *P*<0.001 colored in green). Annotations above show JAK2, MPL, and CALR mutation status at C1D1, as well as SVR ≥25% and SVR ≥35 % at EOC6.

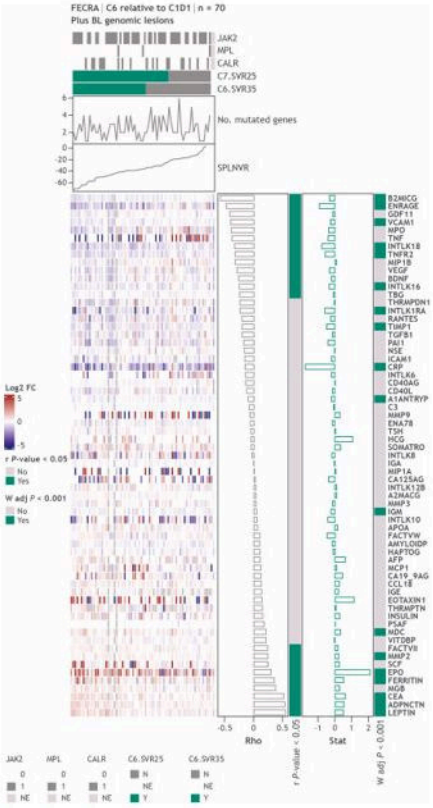

Figure 2. Correlation of change in exhausted CD8+ T cells and primary response to Fedratinib. Scatter plot shows change in % of exhausted CD8 T-cells (CD3+CD4-CD8+CD279+) on the X axis and % spleen volume reduction on the Y axis with Fedratinib. Green spheres indicate patients who achieved SVR35 at the EOC6 and grey ones indicate patients that did not achieve SVR35 at EOC6. Numbers indicate Pearson rho and p value.

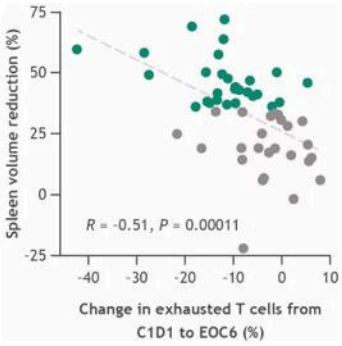

Figure 1

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