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(S220) PELABRESIB PLUS RUXOLITINIB COMBINATION THERAPY IN JAK INHIBITOR-NAIVE PATIENTS WITH MYELOFIBROSIS IN THE MANIFEST-2 STUDY: PRELIMINARY EVIDENCE OF BONE MARROW RECOVERY

Topic: 15. Myeloproliferative neoplasms - Biology & translational research

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Background:

Bromodomain and extraterminal (BET) proteins are key drivers of myelofibrosis (MF) pathogenesis and disease progression through modulation of the expression of key genes. Pelabresib (PELA), an investigational, oral small molecule BET inhibitor, is being evaluated in the Phase 3 MANIFEST-2 study (NCT04603495) in combination with the standard of care Janus kinase inhibitor (JAKi) ruxolitinib (RUX), vs placebo + RUX (PBO+RUX), in JAKi-naïve patients (pts) with MF. Results show the potential of PELA+RUX to improve the four hallmarks of MF, with significantly reduced splenomegaly, improved symptom score, improved anemia, and reduced bone marrow (BM) fibrosis at Week (Wk) 24 (Rampal et al, ASH 2023; Abstract 628).

Aims:

To further investigate the impact of PELA+RUX combination on BM microenvironment and its association with clinical outcomes.

Methods:

Mutational analyses were conducted from peripheral whole blood samples obtained pre-treatment and at Wk 48 by targeted next-generation sequencing. Proinflammatory cytokine (CK) levels were measured by bead-based multiplex assay from plasma obtained pre-treatment and at Wk 24. Using tissue samples from BM biopsies obtained pre-treatment and at Wk 24, BM immunohistochemistry staining was conducted for reticulin fiber density (RFD), CD61+ megakaryocytes (MKs), and CD71+ erythrocyte progenitor cells (EPCs), and assessed by digital pathology. Informed consent was obtained from enrolled pts.

Results:

In total, 41.3% (19/46) vs 37.8% (14/37) of pts treated with PELA+RUX vs PBO+RUX, respectively, had ≥20%*JAK2* variant allele fraction (VAF) reduction at Wk 48; mean % change in *JAK2* VAF was -26.2% vs -17.0% at Wk 48. Reduction in *JAK2* VAF was associated with the primary endpoint of SVR35 (≥35% spleen volume reduction from baseline [BL]; p<0.001) at Wk 24. A greater reduction in proinflammatory CK levels was observed at Wk 24 with PELA+RUX (NF-κB–

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regulated CK set: -33.9% [CI -36.5, -31.1]) vs PBO+RUX (-20.8% [CI -23.7, -17.9]; p<0.001), and decreased CK levels were associated with SVR35 (p<0.001) and TSS50 (≥50% improvement in total symptom score from BL; p=0.005) responses at Wk 24. BM assessment at Wk 24 showed significantly greater reduction in RFD in pts treated with PELA+RUX (-5.2 arbitrary units; [CI -6.9, -3.5]) vs PBO+RUX (-1.0; [CI -6.6, -1.7]; p<0.001). Greater reductions in MKs were reported for PELA+RUX vs PBO+RUX (-54.5 cells/mm2 [CI -70.8, -38.3] vs -27.4 cells/mm2 [CI -42.9, -11.9]; p=0.012); and, in contrast to an observed increase in EPC proportions from BL with PELA+RUX, a decrease was observed with PBO+RUX (11.4% [CI -2.4, 27.2] vs -9.8% [CI -20.6, 2.5]; p=0.019) (Fig 1A). In addition, pts who did not require red blood cell transfusions showed a greater increase in the proportion of EPCs at Wk 24 (Fig 1B).

Summary/Conclusion:

Results from pts treated with PELA+RUX in MANIFEST-2 indicate a potential for PELA to enhance clinical responses to RUX by further reducing mutational burden and decreasing inflammation, which was associated with SVR35 and TSS50 responses. Additionally, PELA+RUX resulted in improvement of the BM microenvironment as evidenced by a reduction in fibrosis, a decrease of MK density, and maturation of EPCs associated with amelioration of anemia. Consistent with previous findings, correlation between improvement in BM microenvironment and clinical outcome suggests that PELA+RUX could lead to more profound and durable clinical responses in pts with MF.

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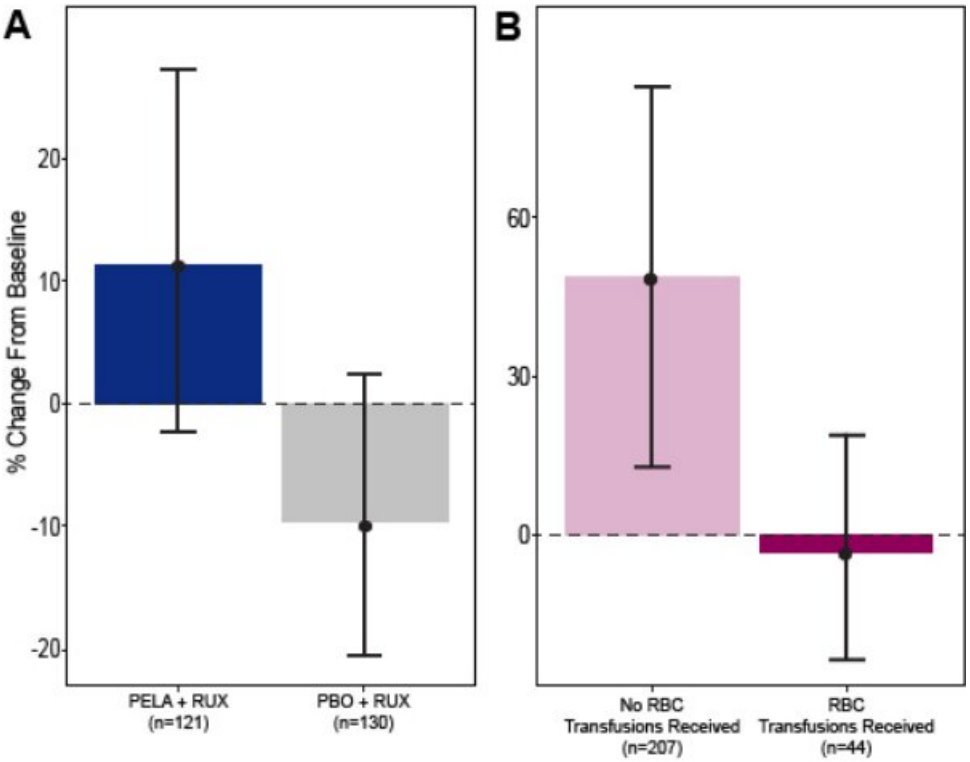
CH and JM contributed equally.

Figure 1: (A) Change in Erythrocyte Progenitor Cells From Baseline. (B) Change in Erythrocyte Progenitor Cells According to RBC Transfusion Status at Week 24



PBO, placebo; PELA, pelabresib; RBC, red blood cell; RUX, ruxolitinib.

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