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BET INHIBITOR PELABRESIB DECREASES INFLAMMATORY CYTOKINES, IMPROVES BONE MARROW FIBROSIS AND FUNCTION, AND DEMONSTRATES CLINICAL RESPONSE IRRESPECTIVE OF MUTATION STATUS IN MYELOFIBROSIS PATIENTS

Topic: 16. Myeloproliferative neoplasms - Clinical

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Background: Myelofibrosis (MF) is characterized by abnormal megakaryopoeisis and overproduction of pro-inflammatory cytokines (Ck), which lead to bone marrow (BM) fibrosis, progressive anemia, and extramedullary hematopoiesis resulting in hepatosplenomegaly. Driver and high molecular risk mutations are well characterized and impact survival of MF patients (pts). Bromodomain and extraterminal domain (BET) proteins regulate neoplastic myeloproliferation and pro-inflammatory Ck expression mediated by nuclear factor kappa B (NF-κB), serving as a rational target for drug development in MF. Pelabresib (CPI-0610) is a potent, selective BET inhibitor under investigation in the ongoing Phase 2 MANIFEST trial (NCT02158858), given as a monotherapy to ruxolitinib (rux) intolerant/refractory MF pts in arm 1; as an 'add-on' to rux in MF pts who have suboptimal or lost response to rux in arm 2; and as combination therapy with rux in JAK inhibitor naïve MF pts in arm 3. Pelabresib demonstrated reductions in spleen volume and symptoms, improvements in hemoglobin levels, and conversions to transfusion independence.

Aims:

Evaluation of translational studies from MANIFEST Phase 2 trial.

Methods:

We assessed pharmacodynamic (PD) activity of pelabresib including changes in inflammatory Ck in blood, improvement of BM biology, including fibrosis (BMF), erythroid (Ery) progenitor and megakaryocyte (Mk) histotopography, and impact of mutations status on clinical response.

Results:

Rapid PD response was demonstrated by 55% median reduction of blood *IL8* mRNA level compared to baseline (BL) 4 hours post the 1st dose of pelabresib in 101 pts, with similar reduction across arms. Elevated blood Ck levels were observed at BL across arms, consistent with prior MF studies. Reduction of NF-κB and non-NF-κB regulated inflammatory Ck was observed on cycle 1 day 14 (C1D14) across arms and maintained at C5D1 and C9D1.

BMF grading was assessed by local pathologists for BL and post-treatment (most at 24 weeks) biopsies available from 116 evaluable pts. Relative BMF improvement of ≥1 grade was observed in 33% (38/116) of all pts, with 21% (6/29) in arm 1, 41% (16/39) in arm 2 and 33% (16/48) in arm 3. BMF grade worsening was observed in only 6%

(7/116) of pts. Exploratory analysis of Ery and Mk lineages by immunohistochemistry staining for CD71 and CD61 were conducted centrally on BM biopsy pairs collected at BL and week 24 for 37 pts. Semi-quantitative analysis revealed an increase in Ery progenitors in 59% (22/37) of pts. Tight clusters of Mk, characteristic in MF BM, were observed at BL, and improvement in Mk histotopography was observed in 65% (24/37) of pts.

Mutation analysis revealed similar mutation profiles at BL across arms, with *JAK2* (65%) and *ASXL1* (47%) as the most frequently mutated genes. The 14 most frequently mutated genes at BL were assessed for correlation with spleen volume reduction by ≥35% (SVR35) or ≥50% reduction of total symptom score (TSS50) at 24 weeks. SVR35 and TSS50 at 24 weeks were similar in pts regardless of mutational status for each of the 14 genes analyzed.

Summary/Conclusion:

Our interim translational data demonstrate a robust PD effect of pelabresib in MF pts, indicate broad clinical responses of pelabresib monotherapy and combination with rux irrespective of mutation status, including *ASXL1*, and suggest at a disease-modifying potential of pelabresib by improving BM histotopography and function. MANIFEST-2; a global, randomized, double-blind phase 3 trial (NCT04603495) is currently underway evaluating combination of pelabresib with rux versus placebo with rux in JAK inhibitor treatment naïve MF pts.

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