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POSTER ABSTRACTS

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

Rker-050, a Modified Activin Receptor Type Iia Ligand Trap, Promoted Erythropoiesis in a Murine Model of Myelofibrosis

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Myelofibrosis (MF) is one of several myeloproliferative neoplasms most often associated with anemia due to ineffective hematopoiesis, inflammation, aberrant bone metabolism and progressive fibrosis in the bone marrow (BM). As a compensatory mechanism, extramedullary hematopoiesis is initiated in the spleen, resulting in splenomegaly. Megakaryocyte hyperplasia/dysplasia are thought to be one of the main drivers of MF disease progression. Evidence also suggests that dysregulated TGF-β superfamily activity contributes to ineffective hematopoiesis.

KER-050 and its research form, RKER-050, are investigational modified activin receptor type IIA ligand traps designed to inhibit specific TGF-β superfamily ligands, including activin A, activin B, growth and differentiation factor (GDF) 8 and GDF11, to promote erythropoiesis and thrombopoiesis. Additionally, the KER-050 target ligands promoted fibrosis and bone resorption in preclinical studies. Therefore, by inhibiting these ligands, KER-050 could potentially rebalance the bone marrow microenvironment, including reducing fibrosis, allowing restoration of hematopoiesis and alleviating extramedullary hematopoiesis and associated splenomegaly.

To investigate the potential of RKER-050 to reverse ineffective hematopoiesis in MF, a hypomorphic Gata1 MF mouse model (Gata1Low; MF mice) was utilized which presents similar characteristics to human MF, including ineffective hematopoiesis, cytopenias, extramedullary hematopoiesis, defective bone deposition and BM fibrosis. this study, we also observed aberrant bone growth in the cortex of the hind limb long bones which inappropriately extended into the bone marrow, resulting in limited BM compartment space and demonstrating a severe disease state in these mice.

Anemia status of MF mice was confirmed at the start of the treatment. MF mice showed a 16% reduction in hemoglobin (Hgb) compared to WT control mice. After 12 weeks of treatment, MF+VEH mice continued to exhibit a significant or trending decrease in red blood cells (RBCs; -19%), Hgb (-20%), and hematocrit (Hct; -10%) compared to WT mice. In contrast, MF+050 mice had a significant recovery of RBCs (+31%), Hgb (+24%) and Hct (+20%), compared to MF+VEH mice, demonstrating that RKER-050 reversed anemia in this advanced disease MF model. To assess the mechanism of action of RKER-050, we evaluated erythroid precursor populations in the BM. While MF+VEH mice showed a significant reduction in erythroid progenitors compared to WT mice, These data support increased BM erythropoiesis with RKER-050 treatment. In addition, we evaluated the effect of RKER-050 on thrombopoiesis. MF+VEH mice were severely thrombocytopenic and had significantly increased megakaryocyte progenitors (MkP; +591%) compared to WT mice. Although RKER-050 significantly reduced MkP (-33%; MF+050), suggesting RKER-050 may positively influence the megakaryocyte lineage, this did not translate to improvements in thrombocytopenia, and platelet counts remained similar to MF+VEH.

Additional data will be presented that investigates the potential of RKER-050 treatment in (6-month vs 10-month-old mice, where disease is less severe) to further evaluate the potential to impact cytopenias, extramedullary hematopoiesis and BM fibrosis.

Overall, in the context of severe disease, our results suggest RKER-050 can promote erythropoiesis and reverse anemia in the BM in by rebalancing hematopoiesis in the BM niche. Reestablishing BM hematopoiesis could obviate the need for compensatory extramedullary hematopoiesis in the spleen, the major driver of splenomegaly in MF patients. In conclusion, KER-050 represents a potentially promising approach for patients with MF and other hematological diseases where ineffective hematopoiesis occurs.

Disclosures Moses: *Keros Therapeutics:* Current Employment. **Dills:** *Keros Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Wheeler:** *Keros Therapeutics:* Current Employment. **Todorova:** *Keros Therapeutics:* Current Employment. **Macaluso:** *Keros Therapeutics:* Current Employment. **Damen:** *Keros Therapeutics:* Current Employ-

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