RKER-050 RESCUED RUXOLINITIB (RUX)-INDUCED REDUCTION IN RED BLOOD CELL PARAMETERS

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INTRODUCTION

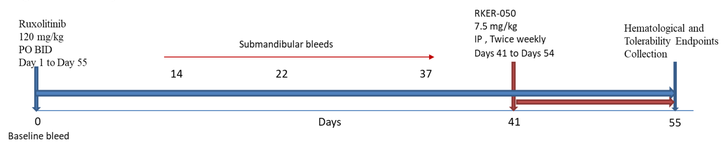
Myelofibrosis (MF) is characterized by the dysfunctional Janus kinase/signal transducers and activators of transcription signaling (JAK/STAT) pathways leading to progressive proliferation of granulocytic and megakaryocytic cells in the bone marrow at the expense of other hematopoietic lineages. Clinical signs of MF include cytopenias, splenomegaly and transformation to acute leukemia[1]. Current treatment options to address anemia in diseases of ineffective hematopoiesis, such as MF, target discreet stages in erythropoiesis, whereas defects leading to ineffective hematopoiesis can occur throughout the pathway. Ruxolitinib (rux), a JAK2 inhibitor and a therapeutic for MF, functions to impair the activating mutations that cause the expansion of megakaryocytic precursors. However, JAK2 also transduces signals of the erythropoietin receptor, thrombopoietin receptor, and the granulocyte colony-stimulating factor receptor. Therefore, individuals being treated with rux have treatment-associated anemia and thrombocytopenia, leading to a lack of tolerability as well as being dose-limiting[2].

The TGF-β superfamily plays a vital role in the regulation of hematopoiesis; specifically, SMAD2/3 activation results in cell quiescence and inhibits precursors from progressing through later stages of hematopoiesis. KER-050, a modified ActRIIA ligand trap, is designed to inhibit SMAD2/3 signaling and promote erythropoiesis by mobilizing both early and late-stage erythroid precursors. In a Phase 1 clinical study, administration of KER-050 to healthy volunteers led to sustained increases in RBCs and hemoglobin (HGB) along with increases in platelets.

- **In this study, we evaluated whether the activity of RKER-050, a research form of KER-050, requires JAK signaling and whether adding RKER-050 to rux treatment could reverse rux-related reduction in hematological parameters.**

METHODS

Study Design: We first established anemia in C57Bl/6 mice by dosing with rux before administering RKER-050. Mice were dosed with vehicle or 120 mg/kg rux via oral gavage, twice daily (BID) for approximately 37 days. Whole blood samples were taken via submandibular bleed throughout the study in order to observe any hematological changes using a Hematrue analyzer. On day 41, mice from each rux group received vehicle (TBS) or RKER-050 (7.5 mg/kg) intraperitoneally (IP) twice weekly for a total of five doses accompanying BID treatment with rux.
Statistics: Data were analyzed with Prism 9 (GraphPad Software, San Diego, CA, USA) using a one-way ANOVA Error bars= Mean/SEM.



RESULTS

Treatment with Ruxolitinib led to reductions in RBC, HGB, and HCT

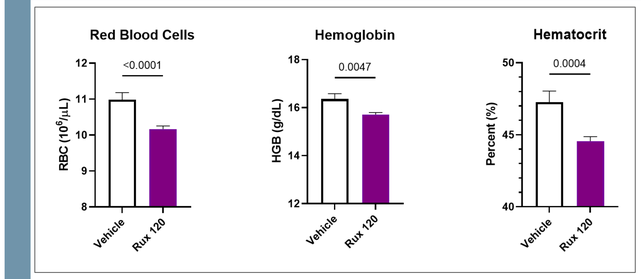


Figure 1: After 37 days of treatment, from baseline, with rux at 120 mg/kg via oral gavage was sufficient to significantly reduce RBC, HGB, HCT. This protocol was used to evaluate the effect of RKER-050 on rux-induced anemia.

RKER-050 therapy reversed rux-induced reduction in RBC, HGB, and HCT

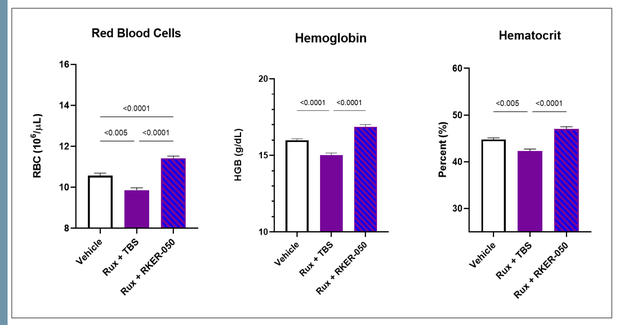


Figure 2: Mice receiving rux alone continued their decline in RBCs and, on day 55, continued to have significant reductions in RBC, HGB and HCT levels compared to the control group. These findings are consistent with the progressive effect of JAK2 inhibition on suppressing erythrocyte maturation and production. Treatment with RKER-050 abated the observed rux-associated reductions in RBCs, HGB, and HCT, with observed significant increases when compared to the rux-vehicle group.

There are no adverse clinical observations during co-treatment with RKER-050

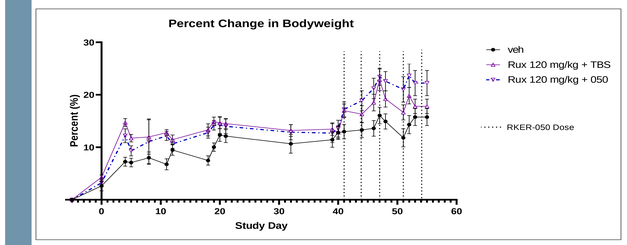


Figure 3: The rux-RKER-050 cohort also had significantly increased body mass, measured between day 41 and day 55 versus the rux-vehicle group. This demonstrates that rux+050 combination therapy did not have a negative effect on bodyweight, a common marker of tolerability.

CONCLUSIONS

- These data demonstrate that rux treatments reduced red blood cell number, hemoglobin and hematocrit.
  - **Coadministration of RKER-050 reversed rux-associated reductions in red blood cell parameters, indicating RKER-050 functions independently of JAK/STAT pathway. Therefore, KER-050 could be a potential treatment option for ineffective hematopoiesis resulting from defective JAK/STAT signaling in MF patients.**
- Treatment with KER-050 has the potential to mitigate the dose limiting effects of rux and enhance duration of therapy in MF patients.
- RKER-050 also increased body weight through its anabolic effect on muscle, a potential benefit in elderly MF patients.

REFERENCES

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ACKNOWLEDGEMENTS

Thank you to the Keros Research Team

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