KER-050, an inhibitor of TGF-β superfamily signaling, observed to have a rapid, dynamic, and durable effect on erythropoiesis

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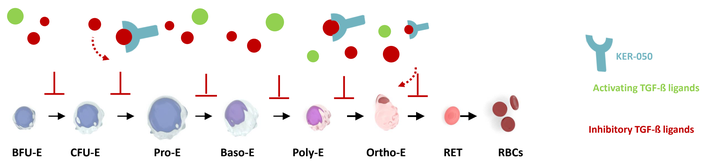
INTRODUCTION

Erythropoiesis, the multi-stage differentiation process of hematopoietic stem cells to red blood cells (RBCs), is a tightly regulated process required to maintain adequate blood supply. Ineffective erythropoiesis, such as in myelodysplastic syndromes (MDS) or myelofibrosis (MF), can result from defects at any stage in the pathway and can result in anemia. However, current treatments target distinct stages of erythropoiesis, resulting in some patients being unresponsive to treatment; targeting multiple stages of erythropoiesis may provide a better treatment option.

The TGF-β superfamily regulates erythropoiesis by maintaining a balance between progenitor quiescence and differentiation. KER-050, a modified ActRIIA ligand trap, is designed to promote erythropoiesis through inhibition of TGF-β ligands that signal though SMAD2/3, including activins and GDFs. In a Phase 1 clinical study, administration of KER-050 to healthy volunteers led to a robust, rapid, and sustained increase in RBCs and hemoglobin (HGB)*.



* Ordonez, C. *et.al*. **Administration of KER-050, A Novel ACTRIIA Ligand Trap, To Healthy Participants Elicited Robust and Sustained Increases in Hemoglobin and Platelets** (EHA congress, 2020)

Aim: Determine the durability of effect and mechanism of action of KER-050 on erythropoiesis

METHODS

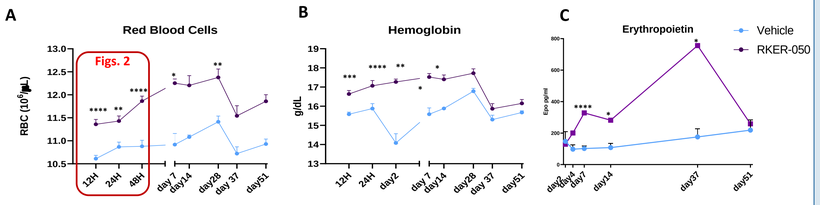
C57BL/6 male mice (11-week-old) were treated with a single dose of either vehicle or a research form of KER-050 (RKER-050). Peripheral blood was evaluated for reticulocytes (RET), RBCs, and HGB. Bone marrow (BM) erythroblasts were analyzed by flow cytometry, at multiple time points from 12 hours (hr) through day 51.

Erythropoietin (Epo) levels were measured in serum at mentioned timepoints. Red blood cell life span was measured via in vivo labeling with EZ-link Sulfo-NHS-Biotin. Biotinylated RBCs in circulation were measured by flow cytometry at designated time points.

N=10-20, Two-way ANOVA with Sidak multiple comparison or Student's t-test were used for statistical analysis *p ≤0.05 **p ≤0.01 ***p ≤0.005 ****p ≤0.001.

RESULTS

Figure 1: RKER-050 treatment resulted in rapid and sustained increases in RBCs, HGB, as well as erythropoietin

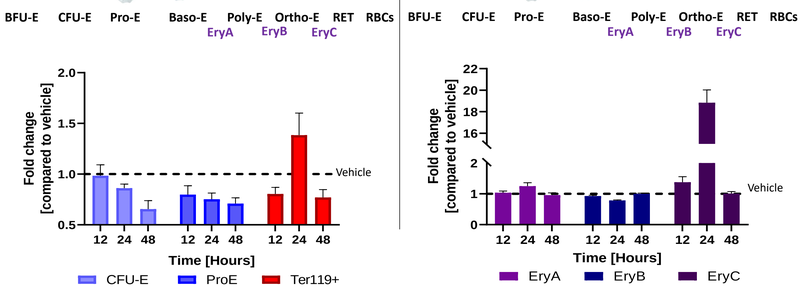


- Treatment with RKER-050 resulted in rapid and sustained increases in RBCs and HGB from 12hr through day 51 post-treatment (A+B)
- Surprisingly, erythropoietin (EPO) levels were significantly increased starting day 7, potentially allowing for the long-lasting increase in RBCs (C)
- The early increases in RBCs preceded the change in EPO, demonstrating this effect is EPO-independent
- Increased EPO could be contributing to the increase in the early progenitor populations at day 14 (Figure 3)

Figure 2: RKER-050 treatment resulted in a dynamic mobilization of erythroblasts from the bone marrow into the circulation

A. Observed reductions in CFU-E and Pro-E corresponded to increased Ter119+ population, supporting differentiation of early progenitors

B. EryC represented the majority of the increased Ter119+ cells with continuous maturation of EryB to the later stage EryC population



C. Maturing erythroblasts provided a continuous supply of reticulocytes to the circulation resulting in a rapid increase in RBCs. The transient decrease in reticulocytes is replenished by continuous flux of maturing EryCs from the bone marrow

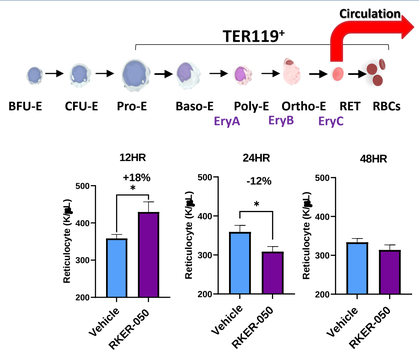
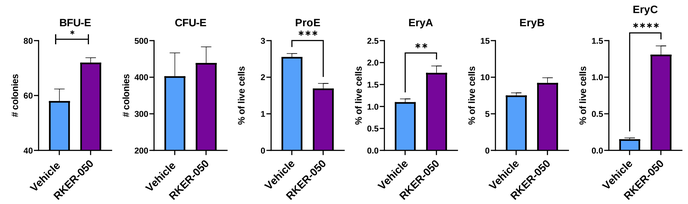
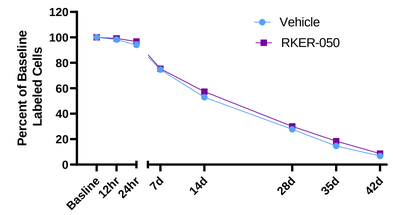


Figure 3: A single dose of RKER-050 treatment increased erythropoietic tone for at least 14 days



Observed increases in early and late-stage progenitors at day 14 post-single dose demonstrate that treatment with RKER-050 expanded the early progenitor pool that continues to mature and contributes to the overall upregulation of erythropoiesis

Figure 4: RKER-050 treatment did not affect RBC life span



Biotin labeled RBCs treated with vehicle or RKER-050 were cleared from circulation at a similar rate

SUMMARY AND CONCLUSION

Our studies demonstrate that RKER-050:

- ***Resulted in rapid and sustained increases on RBC and Hgb***
- ***Increased erythropoietin levels***
- ***Potentially affects erythropoiesis at several stages:***
  - ***Mobilized the early-stage precursor population that differentiate to replenish the late-stage erythroblast pools***
  - ***Stimulated terminal maturation of late-stage erythroid precursors and increased the outflux of late-stage reticulocytes into circulation***
- ***Did not affect RBC life span***

These studies demonstrate the rapid, but also durable, effect of RKER-050 on erythropoiesis. These multiple dynamic effects of KER-050 on early and late-stage erythroblast maturation and Epo make KER-050 a potential treatment for diseases exhibiting defects in different stages of erythropoiesis such as MDS and MF.