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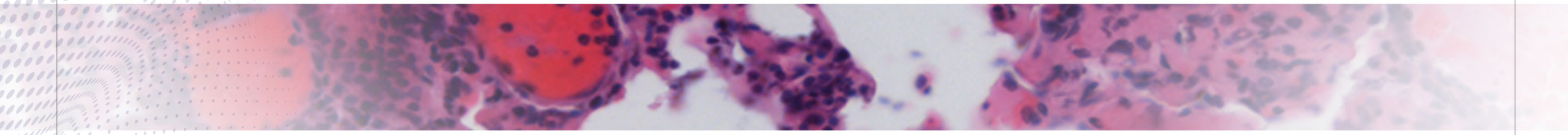
Abstract # 2582



KER-050, a modified ActRIIA ligand trap, alleviates cytopenia arising from multiple etiologies

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Disclosures

All authors are employees of and shareholders of Keros Therapeutics, Inc

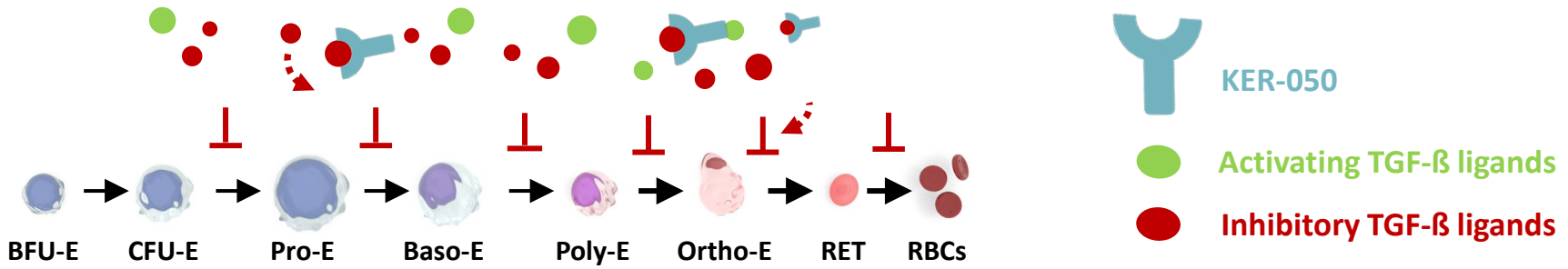
Introduction

- Signaling by the transforming growth factor-beta (TGF-β) superfamily ligands regulates several stages of red blood cell (RBC) maturation. Studies have demonstrated that inhibition of ligands that signal through SMAD2/3 induce RBC production and increase circulating RBCs, hemoglobin, and hematocrit.

- KER-050, a novel, modified ActRIIA ligand trap, has been shown to increase RBCs in rodents and non-human primates, and to increase both RBCs and platelets in healthy participants in a Phase 1 clinical study.

- Murine mechanistic studies determined that a research form of KER-050, stimulates maturation of late-stage erythroid precursors, expands early-stage precursor cell pools and progresses precursors through erythropoiesis (see Abstract #2736).

The objective of these studies is to evaluate the efficacy of KER-050 in alleviating cytopenias caused by multiple conditions such as anemia in the elderly, myelodysplastic syndrome, and anemia due to acute blood loss

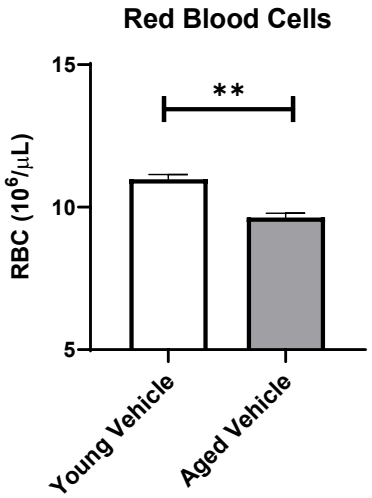


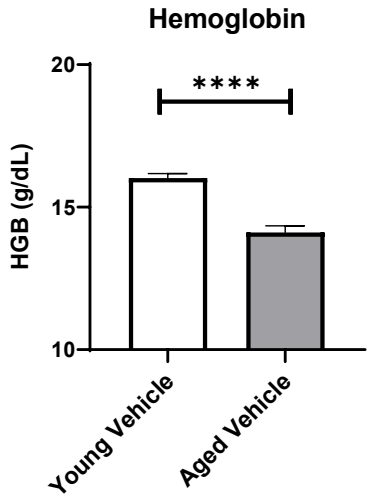
RKER-050 improved anemia in aged animals

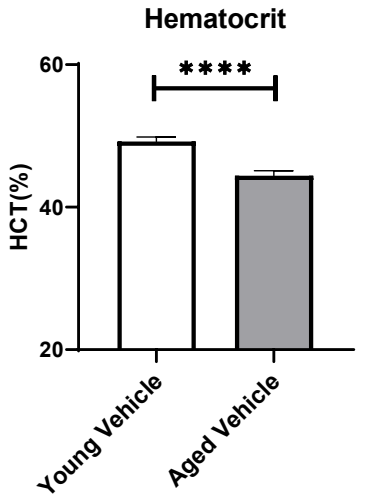
- Anemia is common in aged populations and is often comorbid with disorders of aging such as frailty, leading to significant declines in quality of life.
- To test the efficacy of RKER-050 (a research version of KER-050) in age-related anemia, two-year-old, C57BL/6, female mice (aged) were dosed intraperitoneally (IP) twice weekly for six weeks with either vehicle or 10mg/kg RKER-050. 11-week-old female mice dosed with vehicle (IP, 2x/week for 6 weeks) were included in the study as a young comparator group.

RKER-050 improved anemia in aged animals

N=8-9 Data is shown as mean ± SEM.
Statistical analysis was done by one-way ANOVA with a Dunnett's post test.
**p<0.01 ***p<0.001 ****p<0.0001

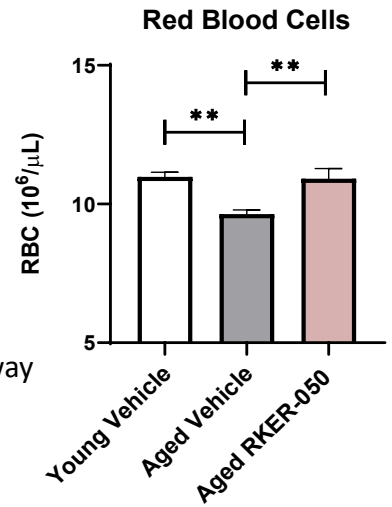


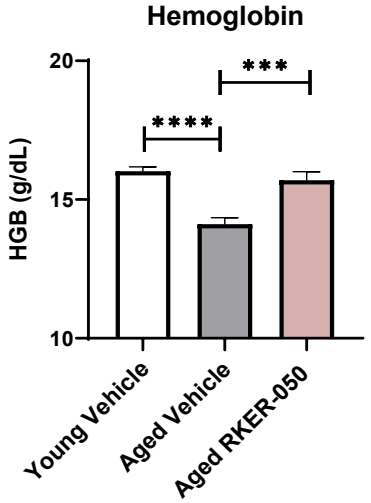


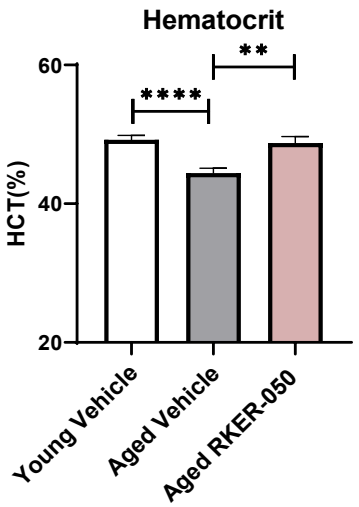


- Age-related anemia was observed in the aged cohort compared to young (11-week-old) female mice, as evidenced by reduced RBCs, hemoglobin and hematocrit.

RKER-050 improved anemia in aged animals







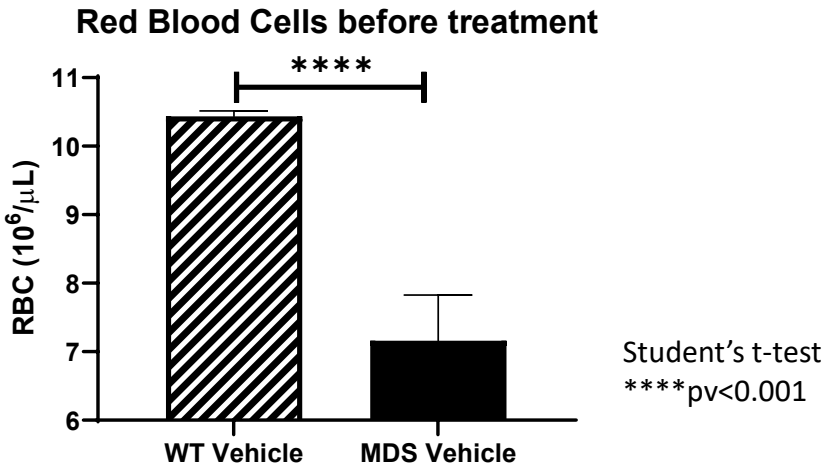
N=8-9 Data is shown as mean ± SEM. Statistical analysis was done by one-way ANOVA with a Dunnett's post test.
**p<0.01 ***p<0.001 ****p<0.0001

- In contrast, treatment with RKER-050 increased red cell parameters; the aged RKER-050 cohort had RBC counts, hemoglobin and hematocrit values that were comparable to young mice.

These data suggest that KER-050 can potentially alleviate age-related anemia

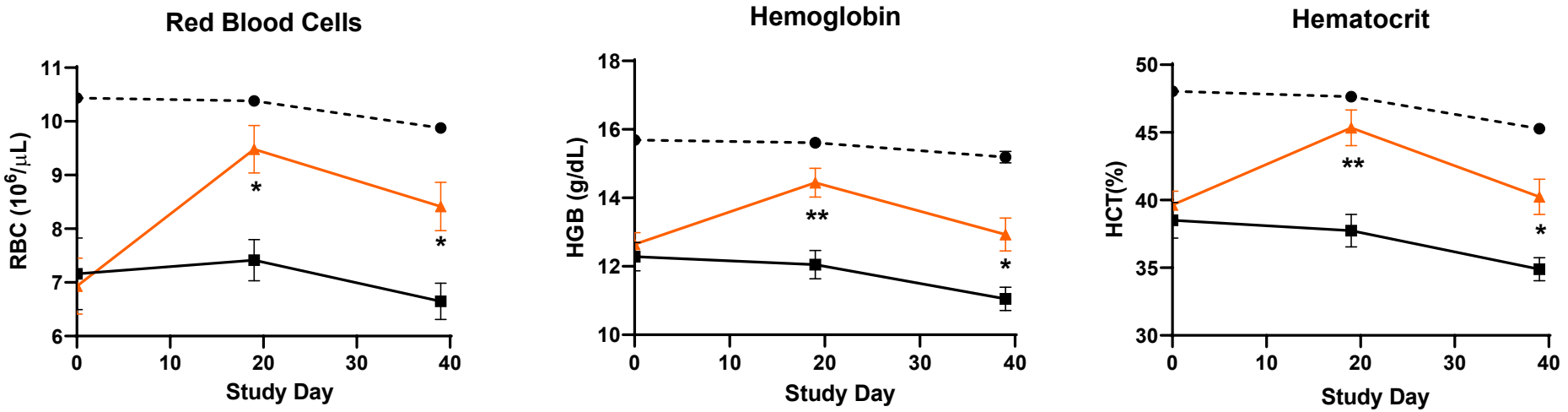
RKER-050 dramatically improved anemia in a mouse model of myelodysplastic syndrome

- Gene fusion of NUP98 and HOXD13, a common mutation resulting in myelodysplastic syndrome (MDS) in humans, was used to model ineffective hematopoiesis due to MDS in mice (MDS mice).
- Six-month-old MDS mice were confirmed as anemic with a 30% lower RBCs than WT mice.
- To test the efficacy of RKER-050 in MDS, mice were dosed with vehicle or RKER-050 at 7.5 mg/kg IP, twice weekly for 5 weeks. WT age-matched control mice were treated with vehicle.



Student's t-test
****pv<0.001

RKER-050 dramatically improved anemia in a mouse model of myelodysplastic syndrome



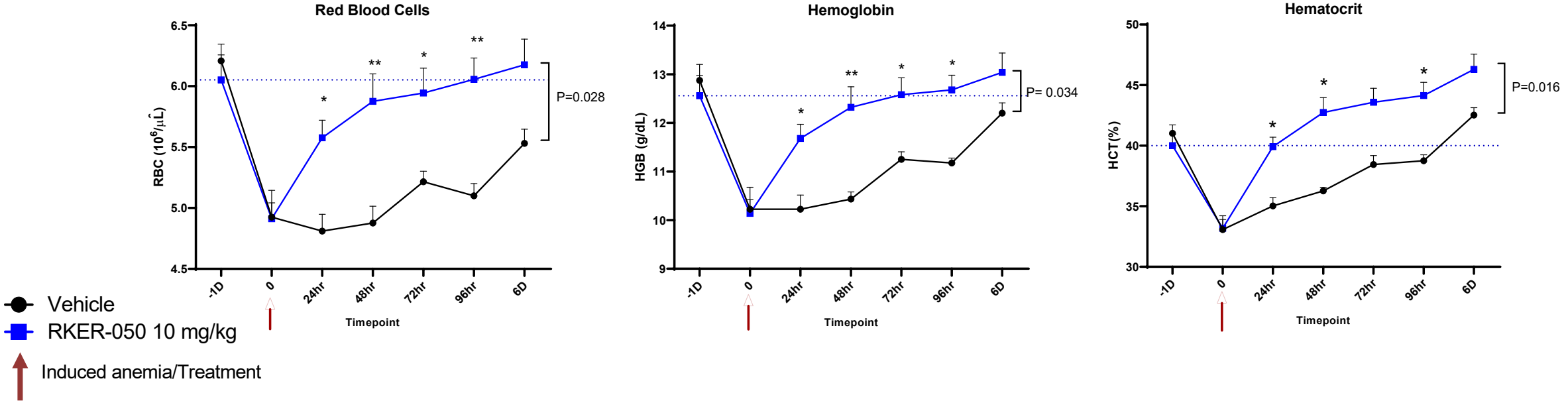
Statistical analysis performed by repeat measures two-way ANOVA. Individual comparisons were calculated with a Sidak post test and shown as *pv<0.05 **pv<0.01. Data is shown as the mean ± SEM.

- Over the treatment period, the vehicle-treated MDS mice remained severely anemic with no improvement in RBCs
- Treatment with RKER-050 resulted in increased RBCs, hemoglobin and hematocrit beginning 19 days after treatment initiation and continuing through to end of study

These data suggest that KER-050 could potentially improve anemia in clinical MDS at a progressive and severely anemic stage of disease

RKER-050 robustly enhanced recovery from acute blood loss induced anemia

- Blood loss anemia can occur in multiple clinical settings, including surgery, gastro-intestinal bleeding and physical trauma.
- To test the efficacy of RKER-050 in increasing RBCs in response to a model of acute blood loss anemia, rats were phlebotomized, given a single dose of RKER-050 at 10mg/kg and hematological parameters assessed every 24hrs.

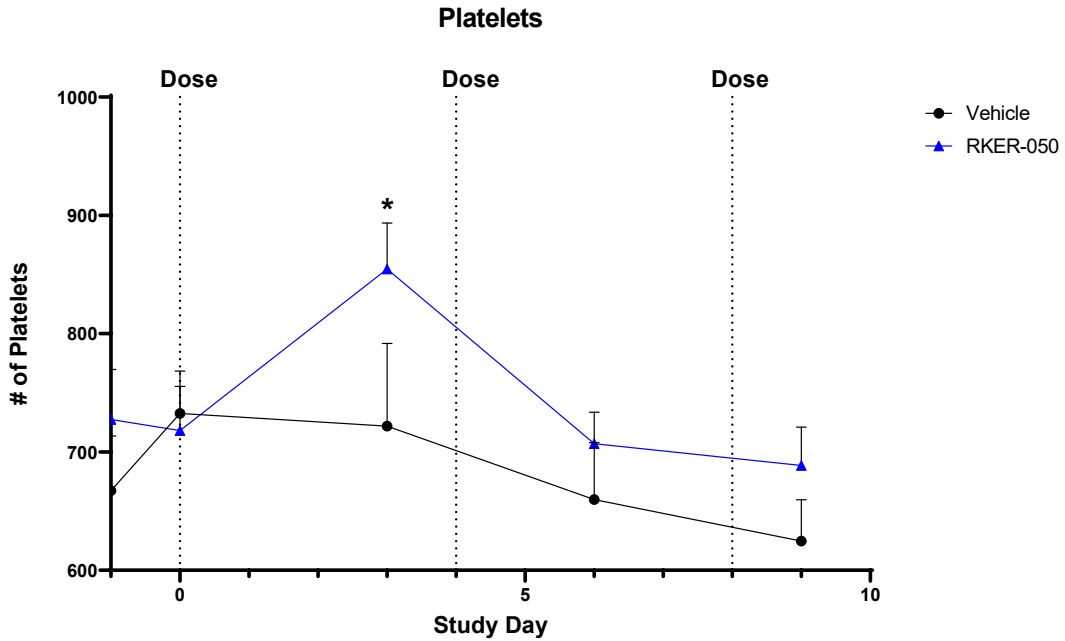


- The phlebotomy was associated with a 20% reduction in circulating RBCs. Over the initial 48hrs, RBCs were not recovered compared to vehicle treated mice. By 6 days, RBC levels had not recovered and were 10.9% below baseline
- In contrast, the RKER-050 treated groups rapidly increased to 7.9% of baseline within 24hrs, with the rats showing a complete recovery within 96hrs.
- Similar recoveries were observed in HGB and HCT.

Acute blood loss was induced in cannulated rats 24 hr prior to first dose by removing 20% of blood volume by body weight. Baseline hematological parameters were measured prior to the bleed on Day -1. N=4 (Vehicle), N=5 (RKER-050). Statistical analysis performed by repeat measures two-way ANOVA. Individual comparisons were calculated with a Sidak posttest and shown as *pv<0.05 **pv<0.01. P values are given for the overall significance between treatments. Data is shown as the mean ± SEM.

RKER-050 increased platelets after phlebotomy in rats

- In our Phase 1 clinical study meaningful increases in platelets in healthy participants were observed in addition to robust increases in RBCs. In this study, we evaluated the effect of RKER-050 on platelets in a rat phlebotomy model.
- In this study, rats had 20% of their blood volume removed and were treated with either vehicle or 10mg/kg RKER-050 (subcutaneous, twice weekly). Blood was sampled every 3 days.



N=5. Data presented as mean ± SEM. Student's t-test of Day 3 time point between vehicle and RKER-050 treated time point was used.

- **RKER-050 increased platelet counts at study day 3 compared to vehicle-treated rats.**
- **These data support that KER-050 has the potential to address both anemia and thrombocytopenia**

Summary and Conclusions

- **KER-050 is a modified ActRIIA ligand trap designed to promote hematopoiesis.**
- **RKER-050 showed efficacy in animal models of:**
  - Age-related anemia
  - Ineffective hematopoiesis in model of myelodysplastic syndrome
  - Anemia due to acute blood loss
- **RKER-050 treatment also showed increase in platelets number in mice.**

These results suggest that KER-050 could be developed for the treatment of anemias and potentially other cytopenias, including thrombocytopenia, arising from a variety of different etiologies.