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POSTER ABSTRACTS

102.IRON HOMEOSTASIS AND BIOLOGY

Ker-050 Treatment Reduced Iron Overload and Increased Bone Specific Alkaline Phosphatase in Participants with Lower-Risk MDS Supporting Potential to Restore Balance to the Osteohematopoietic Niche

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Background: Iron overload (IO) in myelodysplastic syndromes (MDS) contributes to the deterioration of the osteohematopoietic niche (OHN), where hematopoietic and osteogenic precursors interact to regulate hematopoiesis and bone metabolism. Excess iron exacerbates ineffective hematopoiesis, inflammation, and bone loss via direct effects on resident hematopoietic and osteogenic precursors. Iron chelation therapy (ICT) is associated with improved event-free survival in patients with MDS but does not address the underlying cause of IO and introduces patient burden due to tolerability and cost. KER-050 is an investigational, modified activin receptor type IIA ligand trap designed to inhibit select TGF-β superfamily ligands (activins A, B, GDFs 8, 11) and promote differentiation and maturation of erythroid and megakaryocytic precursors. KER-050 has potential to reduce dependence on red blood cell transfusions and increase iron utilization via erythropoiesis, possibly mitigating IO at its source. As previously reported from an ongoing Phase 2 study (NCT04419649), KER-050 treatment in participants with lower-risk (LR) MDS resulted in rates of modified IWG 2006 Hematological Improvement-Erythroid (HI-E) and transfusion independence (TI) of 51.4% and 42.3%, respectively, with a mean decrease in ferritin (322 ng/mL at Week 24) among HI-E and/or TI responders. KER-050 treatment also demonstrated effects on osteogenic precursors, including prevention of bone loss in a mouse model of MDS and dose-dependent increases in bone specific alkaline phosphatase (BSAP), a marker of bone formation, observed in healthy postmenopausal women. Thus, KER-050 has potential to address the multifaceted pathogenesis of MDS, including IO. Here, we present new data from the ongoing Phase 2 study in MDS, exploring the potential of KER-050 to provide benefit beyond hematologic responses and to ameliorate IO in MDS.
Methods: This ongoing Phase 2 study is evaluating KER-050 in participants with LR MDS. Data from exploratory assessments of markers of IO, hematopoiesis, and bone turnover are presented as of a cutoff date of April 3, 2023, for all participants who had received the recommended Part 2 dose (RP2D; 3.75-5 mg/kg q4wks).
Results: Baseline ferritin levels in RP2D participants (N=59) were generally elevated, while levels of mean corpuscular hemoglobin and reticulocyte hemoglobin were in the normal range (Table 1). After KER-050 treatment, sustained decreases in serum ferritin were observed among participants with baseline levels ≥1000 ng/mL (Figure 1), likely driven in part by reduced transfusion burden in responders. Concomitant increases observed in soluble transferrin receptor (sTfR; Figure 1) suggest that increased erythropoiesis may also have contributed. Mean decreases in ferritin observed in non-transfused (NT) participants (-228 ng/mL at Week 24, n=7) indicate potential for KER-050 to affect iron homeostasis by mechanisms other than transfusion reduction. In 1 NT participant receiving ICT, the baseline ferritin of 1632 ng/mL decreased to <500 ng/mL over 32 weeks, leading to ICT discontinuation and coinciding with an increase in hemoglobin (Hgb) from 9.2 g/dL at baseline to 11.3 g/dL

over the same period. In another NT participant not receiving ICT, ferritin decreased from 1094 ng/mL at baseline to 884 ng/mL and 583 ng/mL at Weeks 24 and 68, respectively, while Hgb gradually increased from 9.94 g/dL at baseline to 10.7 and 12.2 g/dL at Weeks 24 and 68. KER-050 treatment was also associated with increases in BSAP, a new finding in this MDS population that is consistent with prior observations in preclinical and healthy volunteer studies. Despite some heterogeneity, mean increases of 8.47% (n=23) and 10.4% (n=13) were observed at Weeks 24 and 48, respectively; 3 participants with erythroid responses had increases in BSAP of ≥30% at these time points.

Summary: Exploratory data indicate potential for KER-050 to drive meaningful decreases in ferritin in participants with LR MDS, particularly among those with IO. While transfusion reduction likely contributes, observations in NT participants highlight the potential for enhancement of erythropoiesis to improve IO, irrespective of transfusions. Observed changes in BSAP suggest that KER-050 is also acting on osteogenic precursors, with the potential to provide functional improvements within the OHN. Updated results will be provided at the presentation.

Disclosures Chee: *Keros Therapeutics:* Honoraria; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Otsuka:* Membership on an entity's Board of Directors or advisory committees. **Ross:** *Imago BioSciences, Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA:* Research Funding; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Takeda:* Membership on an entity's Board of Directors or advisory committees; *Celgene/BMS:* Honoraria, Research Funding; *Keros:* Consultancy; *Menarini:* Membership on an entity's Board of Directors or advisory committees. **Cluzeau:** *BMS:* Consultancy, Speakers Bureau; *Novartis:* Consultancy, Speakers Bureau; *Abbvie:* Consultancy, Speakers Bureau; *Jazz Pharma:* Consultancy, Speakers Bureau; *Syros:* Speakers Bureau; *Keros:* Speakers Bureau; *Servier:* Consultancy, Speakers Bureau; *Incyte:* Speakers Bureau. **Tan:** *Keros Therapeutics:* Research Funding. **Giagounidis:** *Keros Pharmaceuticals:* Consultancy; *Amgen:* Consultancy; *Curis:* Consultancy; *BMS:* Consultancy; *Novartis:* Consultancy. **Diez-Campelo:** *BMS/Celgene:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Advisory board fees; *Gilead Sciences:* Other: Travel expense reimbursement; *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *GSK:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Graham:** *Keros Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **McGinty:** *Keros Therapeutics:* Current Employment. **Ross:** *Keros Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Bobba:** *Keros Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Feng:** *Keros Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Jiang:** *Keros Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Hankin:** *Keros Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Rovaldi:** *Keros Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Cooper:** *Keros Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Grayson:** *BioCryst Pharmaceuticals:* Ended employment in the past 24 months; *Keros Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Salstrom:** *Keros Therapeutics:* Current Employment, Current equity holder in publicly-traded company.

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Table 1. Baseline Disease Characteristics and Lab Parameters

Baseline Characteristics	RP2D (N=59)
Median Age, years (range)	74.0 (53, 89)
Sex, n (%) Male	34 (57.6)
RBC Transfusion Status, units per 8 weeks, n (%)	
Non-transfused (NT), 0 units	12 (20.3)
Low Transfusion Burden (LTB), <4 units	16 (27.1)
<2 units	3 (5.1)
≥2 to <4 units	13 (22.0)
High Transfusion Burden (HTB), ≥4 units	31 (52.5)
≥8 units	12 (20.3)
Concurrent Iron Chelator	17 (28.8)
Median Ferritin, ng/mL (range)	770.8 (86.3, 5289.1)
NT	486.4 (190.0, 1632.0)
LTB	731.0 (250.6, 1182.5)
HTB	1052.1 (86.3, 5289.1)
Proportion of participants with	
<500, n (%)	19 (32.2)
≥500 to < 1000, n (%)	18 (30.5)
≥1000, n (%)	22 (37.3)
- Concurrent Iron Chelator, n/m[a] (%)	9 /22 (40.9)
Median MCH, pg/cell (range)	33.0 (26, 41)
Median CHr, pg/cell (range)	34.4 (29.4, 34.7)
Median sTfR, mg/L (range)	1.59 (0.29, 7.14)
Median BSAP, µg/L (range)	13.7 (7.0, 60.7)

[a]n=number of participants with baseline ferritin ≥1000 ng/mL and concurrent iron chelator, m=number of participants with baseline ferritin ≥1000 ng/mL; BSAP=bone specific alkaline phosphatase; CHr=reticulocyte hemoglobin content; MCH=mean corpuscular hemoglobin; sTfR=soluble transferrin receptor

Figure 1. Change from Baseline in Ferritin and Percent Change from Baseline in Soluble Transferrin Receptor by Baseline Ferritin Levels (≥1000 ng/mL vs <1000 ng/mL)

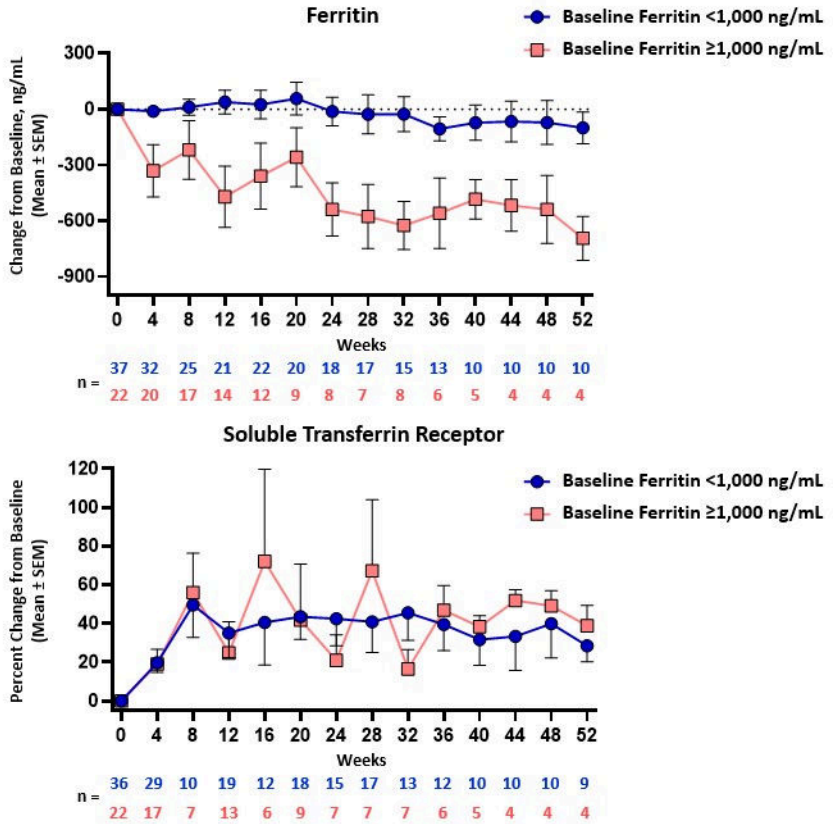

Figure 1