Abstract: S302

Title: REDUCED FERRITIN AND INCREASED BONE SPECIFIC ALKALINE PHOSPHATASE IN PARTICIPANTS WITH LOWER-RISK MDS TREATED WITH ELRITERCEPT (KER-050) SUPPORT POTENTIAL TO REBALANCE THE OSTEOHEMATOPOIETIC NICHE

Abstract Type: Oral Presentation

Session Title: Iron metabolism: From basics to the clinic

Background:

Iron overload (IO) in myelodysplastic neoplasms (MDS) contributes to deterioration of the osteohematopoietic niche (OHN) where hematopoietic and osteogenic precursors interact to regulate hematopoiesis and bone metabolism. Excess iron exacerbates ineffective hematopoiesis and bone loss via direct effects on hematopoietic and osteogenic precursors. Iron chelation therapy (ICT) is associated with improved event-free survival in MDS but does not address the underlying cause of IO. Elritercept 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 address ineffective hematopoiesis across multiple lineages. Elritercept has potential to reduce dependence on transfusions and increase iron utilization by promoting erythropoiesis, which could reduce stored iron (ferritin) and mitigate IO. In an ongoing Phase 2 trial in lower-risk (LR) MDS, elritercept treatment resulted in rates of modified IWG 2006 Hematological Improvement-Erythroid (HI-E) and transfusion independence (TI) of 52% and 45%, respectively. Treatment with a research form of elritercept prevented bone loss in a MDS mouse model. Dose-dependent increases in bone specific alkaline phosphatase (BSAP; a marker of osteoblast activity) were also observed in healthy postmenopausal women who received elritercept. Thus, elritercept has potential to provide clinical benefit beyond treating anemia in patients with LR-MDS.

Aims:

To explore potential for elritercept to provide benefit beyond treating anemia in a Phase 2 trial (NCT04419649) of participants with LR-MDS, specifically in multilineage hematopoiesis, iron homeostasis and bone metabolism.

Methods:

Data are presented as of 1 September 2023 for 79 participants who received the recommended Part 2 dose (RP2D) of 3.75-5 mg/kg subcutaneously every 4 weeks.

Results:

The majority of RP2D participants had elevated ferritin (median 822 ng/mL, normal 10-322 ng/mL) at baseline. In 29 (37%) participants with baseline ferritin ≥1000 ng/mL and post-baseline values, a sustained mean decrease in ferritin was observed (Fig 1A), and 14/29 (48%) showed a decrease to <1000 ng/mL while on treatment, including 2 who discontinued ICT. Decreases in ferritin were observed regardless of baseline transfusion burden or erythroid response. Baseline thrombocytopenia (<150 x 109/L) was present in 14 (18%) RP2D participants of whom 5 (36%) achieved a mean increase in platelets over 8 weeks of ≥30 x 109/L with elritercept treatment. Platelet increases were observed in both erythroid responders and non-responders and regardless of baseline transfusion burden. While baseline BSAP levels were generally within normal limits, elritercept treatment was associated with increases in BSAP regardless of baseline transfusion burden or erythroid response (Fig 1B). Among 30 participants with Week 24 data, a mean increase in BSAP of 13% was observed and 6 (20%) participants had an increase ≥30% at Week 24.

Summary/Conclusion:

Sustained reductions in ferritin indicate improved iron utilization and potential to reduce IO while sustained

increases in platelets in participants with baseline thrombocytopenia support potential for elritercept to address ineffective hematopoiesis across multiple lineages. Elritercept may also improve bone metabolism, as supported by the observed increases in BSAP, potentially restoring balance to the OHN. These exploratory analyses and prior clinical and non-clinical observations demonstrate potential for elritercept to address the complex biology of MDS and provide benefit beyond treating anemia.

Figure 1A: Changes in ferritin over time by baseline ferritin levels

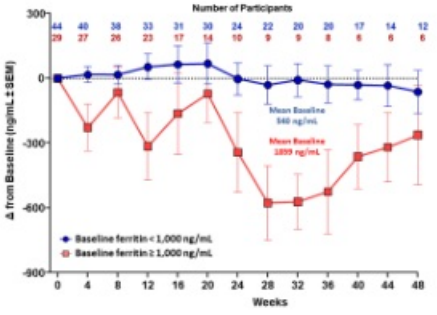
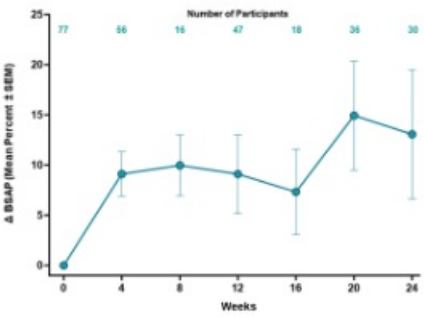


Figure 1B: Changes in BSAP over time



Keywords: Iron overload, Hematopoietic microenvironment, Hematopoiesis, Myelodysplastic syndrome