EFFECTS OF KER-050 ON IRON METABOLISM: EXPLORATORY ANALYSES FROM AN ONGOING PHASE 2 STUDY IN PATIENTS WITH MYELODYSPLASTIC SYNDROMES

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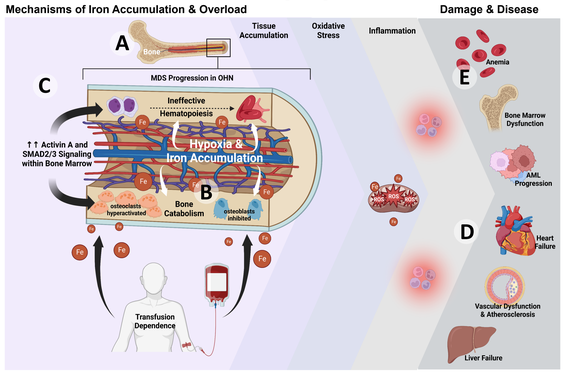
INTRODUCTION

- Iron overload (IO) is a negative consequence of red blood cell (RBC) transfusions in myelodysplastic syndromes (MDS) and is associated with poor prognosis[1,2] (**Figure 1**)
  - For patients with high transfusion burden (HTB), there are limited effective treatment options to improve anemia, reduce transfusion dependence, and reduce IO[2]
  - Symptomatic iron chelation is efficacious in managing IO but is associated with toxicities[2,3]
- In addition to the systemic complications (**Figure 1, D**), IO disrupts the osteohematopoietic niche (OHN, **Figure 1, A**), leading to accelerated bone marrow failure (**Figure 1, E**)
  - Oxidative stress resulting from excess iron in erythroid precursors reduces colony-forming ability and has been associated with impaired erythroid development[4,5]
  - Activation of osteoclasts and inhibition of osteoblasts disrupts the bone marrow microenvironment, impairing hematopoietic stem and progenitor cell regulation[1] (**Figure 1, B**)
  - Upregulated activin A signaling contributes to these processes (**Figure 1, C**)
- KER-050
  - KER-050 is an investigational modified activin receptor type IIA ligand trap that is designed to inhibit TGF-β superfamily ligands, including activin A, activin B, and growth differentiation factors 8 and 11
  - KER-050 is designed to promote differentiation of hematopoietic precursors and rebalance bone turnover, restoring a healthy OHN that supports effective hematopoiesis
    - Preclinical data demonstrated pro-osteoblast and anti-osteoclast effects consistent with the potential to rebalance osteogenic activity in the OHN[6]
    - Clinical data to date demonstrate that KER-050 has the potential to promote hematopoiesis and reduce transfusion burden in participants with MDS, including those with HTB[7]
- Here, we present additional preliminary results from an ongoing phase 2 study of KER-050 in patients with MDS, including:
  - Updated safety and efficacy data from long-term evaluation of KER-050 in participants with experience at the recommended Part 2 dose (RP2D) range of 3.75-5.0 mg/kg administered every 4 weeks (**Figure 2, right; results shown in blue**)
  - Exploration of KER-050 impacts on markers of IO in the 16-week Part 1 Dose Escalation (**Figure 2, left; results shown in red**)

Figure 1. Mechanisms and Consequences of Iron Accumulation and Overload in MDS, and Potential Role of Activin and SMAD2/3 Signaling



AML: acute myeloid leukemia; Fe: iron; MDS: myelodysplastic syndromes; OHN: osteohematopoietic niche; ROS: reactive oxygen species; SMAD: mothers against decapentaplegic homologs.

RESULTS

Evaluation of Long-Term Treatment With KER-050: A Safety and Efficacy Update From Participants Receiving the RP2D (3.75-5.0 mg/kg Every 4 Weeks)

Table 1. Baseline Characteristics of Participants Treated at the RP2D of 3.75-5.0 mg/kg

Parameter	RP2D Dataset n=36
Age, years, median (range)	74.5 (61-88)
Male, n (%)	20 (55.6)
RS status, n (%)	
RS+	23 (63.9)
Non-RS	13 (36.1)
WHO MDS classification, n (%)	
MDS-MLD	12 (33.3)
MDS-MLD-RS	20 (55.6)
MDS-SLD	0
MDS-SLD-RS	1 (2.8)
Unclassifiable	2 (5.6)
Unknown/missing	1 (2.8)

Parameter	RP2D Dataset n=36
IPSS risk category, n (%)	
Very low	2 (5.6)
Low	28 (77.8)
Intermediate	6 (16.7)
Prior ESA therapy, n (%)	6 (16.7)
Iron chelator therapy, n (%)	11 (30.6)
RBC transfusion status, units per 8 weeks, n (%)	
NT, 0 units	10 (27.8)
LTB, <4 units	6 (16.7)
HTB	20 (55.6)
4 to <8 units	11 (30.6)
≥8 units	9 (25.0)

ESA: erythropoiesis-stimulating agent; HTB: high transfusion burden; IPSS: International Prognostic Scoring System; LTB: low transfusion burden; MDS: myelodysplastic syndromes; MLD: multiple lineage dysplasia; NT: nontransfused; RBC: red blood cell; RP2D: recommended Part 2 dose; RS: ring sideroblast; SLD: single lineage dysplasia; WHO: World Health Organization.

Analysis Populations, Exposure, and Disposition as of 1-Oct-2022 Data Cutoff Date

- Safety (n=36): All participants who had received a dose of KER-050
- Efficacy (n=29): HI-E evaluable: ≥8 weeks postbaseline hemoglobin assessments (NT and LTB) or transfusion assessments (HTB); TI evaluable: ≥8 (or ≥12) weeks postbaseline transfusion assessments with ≥2 units RBC transfusion at baseline
- Mean duration of treatment in the safety population was 196 days (range 34-465 days)
  - 80.6% of participants received ≥3 doses
  - 47.2% of participants received ≥6 doses
  - 25.0% of participants received ≥12 doses
- Treatment was ongoing in 79.3% of the efficacy evaluable population as of the data cutoff date

Table 2. Treatment-Emergent Adverse Events

Category	Participants Reporting, n (%), n=36
Any TEAE	33 (91.7)
Any treatment-related TEAE	11 (30.6)
Any serious TEAE	12 (33.3)
Any treatment-related serious TEAE	1 (2.8)
Any TEAE leading to death	1 (2.8)
Any TEAE leading to IMP discontinuation	4 (11.1)

IMP: investigational medicinal product; TEAE: treatment-emergent adverse event.

Safety (as of Data Cutoff Date): KER-050 Was Generally Well Tolerated in Participants With RP2D Experience

- No dose-limiting toxicities and no progression to acute myeloid leukemia
- 1 fatal TEAE of cardiac failure occurred and was determined to be unrelated to study treatment (**Table 2**)
- 2 TEAEs led to treatment discontinuation: injection-site reaction (related); dyspnea (unrelated)
- Most common TEAEs that occurred in >5 participants were diarrhea (22.2%), fatigue (19.4%), dyspnea (16.7%), and nausea (16.7%)

Efficacy

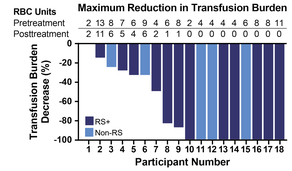
- Findings continue to support that KER-050 has the potential to restore hematopoiesis and reduce transfusion burden in a broad patient population, including those who are HTB, RS+, and non-RS

Table 3. Efficacy Summary of 8- and 12-Week Endpoints in Participants With RP2D Experience

Response Summary	Response Rate, n/m (%)	
	All Evaluable	HTB Evaluable
Overall erythroid response (HI-E or TI)	15/29 (51.7%)	10/16 (62.5%)
IWG 2006 HI-E	15/29 (51.7%)	10/16 (62.5%)
TI ≥8 weeks	9/18 (50%)	8/16 (50%)
RS+	6/12 (50%)	5/11 (45.5%)
Non-RS	3/6 (50%)	3/5 (60%)
TI ≥12 weeks	8/16 (50%)	7/14 (50%)

HI-E response criteria: ≥1.5 g/dL increase in hemoglobin (NT and LTB) or ≥4-unit reduction from baseline in transfused RBCs (HTB) over ≥8 weeks.
HI-E: hematologic improvement–erythroid; HTB: high transfusion burden; IWG: International Working Group; LTB: low transfusion burden; NT: nontransfused; RS: ring sideroblast; RP2D: recommended Part 2 dose; TI: transfusion independent.

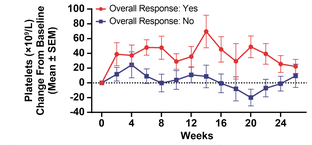
Figure 3. Treatment With KER-050 Resulted in HI-E and TI in Transfusion-Dependent Non-RS and RS+ Participants



Improvements in transfusion burden were seen across participants with low transfusion burden (LTB) and HTB; 8 out of 16 HTB participants and 1 out of 2 LTB participants achieved transfusion independence with KER-050 treatment

HI-E: hematologic improvement–erythroid; HTB: high transfusion burden; RBC: red blood cell; RS: ring sideroblast; TI: transfusion independent.

Figure 4. Sustained Increase in Platelets Observed in Participants Achieving HI-E or TI With KER-050 Treatment

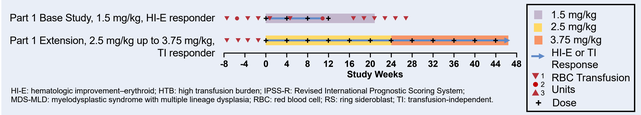


Increases in platelets for HI-E and TI responders support a differentiated mechanism of action that promotes hematopoiesis across multiple cell lineages

Altered visit schedules for participants re-baselined in Part 1 Extension following treatment gap contribute to fluctuating Ns across visits.
HI-E: hematologic improvement–erythroid; TI: transfusion independent.

Case Study Highlighting Clinical Response With Long-Term KER-050 Treatment

Characteristics: Male, age 72, non-RS, MDS-MLD, HTB, baseline IPSS-R score=2.0 (low), concomitant iron chelation therapy



HI-E: hematologic improvement–erythroid; HTB: high transfusion burden; IPSS-R: Revised International Prognostic Scoring System; MDS-MLD: myelodysplastic syndrome with multiple lineage dysplasia; RBC: red blood cell; RS: ring sideroblast; TI: transfusion-independent.

- This participant achieved an initial HI-E response when treated with KER-050 1.5 mg/kg in Part 1 Dose Escalation (top bar)
- The participant was rescreened and initiated in Part 1 Extension (bottom bar) following a 112-day gap between the last dose in Dose Escalation and first dose in the Extension
- The participant then achieved TI and remained TI as of the data cutoff date (>40 weeks)

Summary: Safety and Efficacy Update From Long-Term Evaluation of Participants Receiving RP2D

- As of 1-Oct-2022, participants included in the long-term RP2D population are primarily transfusion dependent (TD) with MLD
- KER-050 continues to be generally well tolerated in participants receiving long-term treatment at the RP2D as of the data cutoff date
- HI-E ≥8 weeks was achieved by 51.7% of all evaluable participants and 62.5% of evaluable HTB participants
- TI ≥8 and ≥12 weeks occurred in 50% of evaluable HTB and LTB participants
  - TI responses were observed in both RS+ and non-RS participants
- Increases in platelets in HI-E or TI responders support the potential of KER-050 as a treatment for multilineage cytopenias

By restoring multilineage hematopoiesis and reducing transfusion burden, KER-050 may show potential to attenuate IO, particularly in patients receiving frequent RBC transfusions

Exploratory Analyses of KER-050 Impact on Markers of IO: Part 1 Dose Escalation

Table 4. Baseline Characteristics

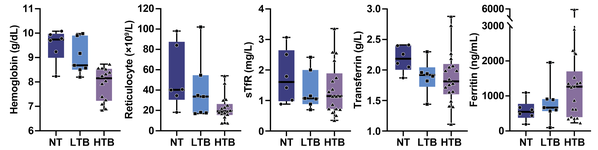
Parameter	NT	LTB	HTB	All
n (%)	6 (19.4)	7 (22.6)	18 (58.1)	31 (100)
Age, median, years (range)	70.0 (61-78)	74.0 (64-88)	74.5 (55-88)	73.3 (55-88)
Male, n (%)	3 (50.0)	4 (57.1)	12 (66.7)	19 (61.3)
RS status, n (%)				
RS+	4 (66.7)	3 (42.9)	10 (55.6)	17 (54.8)
Non-RS	2 (33.3)	4 (57.1)	8 (44.4)	14 (45.2)
RBC transfusion status, units per 8 weeks, mean (range)	0	1.9 (1-3)	6.5 (4-16)	4.2 (0-16)
Iron chelator therapy, n (%)	0	0	8 (44.4)	8 (25.8)

HTB: high transfusion burden; LTB: low transfusion burden; NT: nontransfused; RBC: red blood cell; RS: ring sideroblast.

Observed differences in baseline biomarkers suggest the following for TD vs non-TD participants:

- Greater deficits in erythropoiesis: lower levels of hemoglobin, reticulocytes, and soluble transferrin receptor (sTfR) (**Figure 5**)
- More severe IO: lower levels of transferrin and elevated serum ferritin, especially among participants with HTB

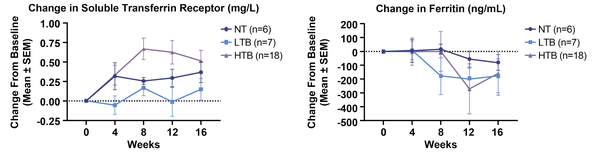
Figure 5. Baseline Values in Markers of Hematopoiesis and Iron Metabolism



HTB: high transfusion burden (n=18); LTB: low transfusion burden (n=7); NT: nontransfused (n=6); sTfR: soluble transferrin receptor.

- Observed increases in sTfR, particularly in HTB participants, suggest increased erythropoietic activity (**Figure 6, left**)
- Observed decreases in ferritin suggest reduction of IO, especially in TD participants (**Figure 6, right**)

Figure 6. Treatment With KER-050 Resulted in Biomarker Changes Supporting Increased Erythropoiesis and Attenuated IO

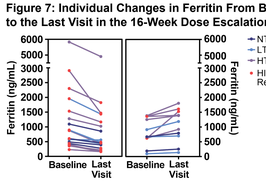


HTB: high transfusion burden; IO: iron overload; LTB: low transfusion burden; NT: nontransfused.

- Most participants achieving hematological response (HI-E or TI) showed decreases in ferritin (**Figure 7, left**) vs increases (**Figure 7, right**)
- Decreases were most pronounced for participants with baseline ferritin >500 ng/mL, suggesting reduction of IO in the most impacted participants

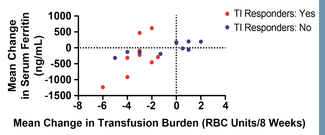
In general, reductions in transfusion burden were associated with reductions in serum ferritin, especially for participants achieving transfusion independence (**Figure 8**)

Figure 7: Individual Changes in Ferritin From Baseline to the Last Visit in the 16-Week Dose Escalation



HI-E: hematologic improvement–erythroid; HTB: high transfusion burden; LTB: low transfusion burden; NT: nontransfused; TI: transfusion-independent.

Figure 8. Reduction in Transfusion Burden[a] Associated With Reduction in Serum Ferritin



[a]Units per 8 weeks over 16 weeks in Part 1 Dose Escalation. TI evaluable population includes LTB and HTB participants with at least 2 units of RBC transfusion at baseline and at least 8 weeks of postbaseline transfusion records.
HTB: high transfusion burden; LTB: low transfusion burden; RBC: red blood cell; TI: transfusion-independent.

Summary: KER-050 and Markers of IO

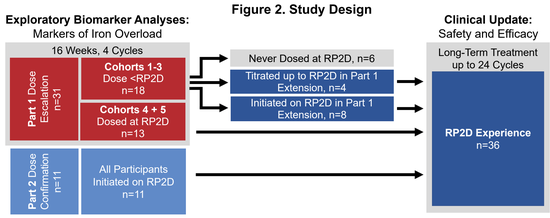
- Differences observed in baseline biomarkers suggest greater deficits in erythropoiesis and more severe IO among TD participants vs NT participants
  - These trends were especially pronounced in HTB participants, potentially reflecting a more disrupted OHN
- Increases in sTfR and decreases in serum ferritin support that KER-050 has the potential to restore erythropoietic activity and potentially attenuate IO over a relatively short duration

Together, the preliminary findings presented here suggest that KER-050 has the potential to improve hematopoiesis, reduce transfusion burden, and reduce IO, a serious clinical complication impacting survival of patients with MDS

METHODS

- This ongoing, 2-part, phase 2 study is evaluating KER-050 in participants with very low- to intermediate-risk MDS who have anemia (hemoglobin ≤10 g/dL or receiving transfusions) (NCT04419649)
- As of 1-Oct-2022, Part 1 Dose Escalation was completed; Part 2 Dose Confirmation was initiated, and 11 participants were enrolled
  - The RP2D was defined as 3.75-5.0 mg/kg every 4 weeks
  - Part 1 Extension provides the opportunity for long-term treatment with KER-050 and escalation up to the RP2D for participants who completed Part 1 Dose Escalation
- Long-term evaluation of KER-050 will focus on study participants who have been dosed at the RP2D (**Figure 2, right**)
  - Clinical updates on safety and efficacy endpoints are provided for these participants
- Exploratory analyses evaluating the impact of KER-050 on indices of IO are presented from the 16-week Part 1 Dose Escalation (**Figure 2, left**)

Figure 2. Study Design



RP2D: recommended Part 2 dose.

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