ELSEVIER

Blood 142 (2023) 196–198

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Durable Clinical Benefit with Ker-050 Treatment: Findings from an Ongoing Phase 2 Study in Participants with Lower-Risk MDS

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Background: In myelodysplastic syndromes (MDS), defects occur at multiple stages of hematopoiesis. Available Erythropoiesis Stimulating or Erythroid Maturation Agents (ES/EMAs) target early or late stages of erythropoiesis, respectively, and are only effective in subsets of patients. For patients with high transfusion burden (HTB) who have diminished erythropoietic capacity and a worse prognosis, ES/EMAs show limited efficacy and durability of response (DOR). 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) that is being evaluated in diseases with ineffective hematopoiesis (IH), including MDS and myelofibrosis. Preclinical studies demonstrated that KER-050 increased erythropoiesis and thrombopoiesis and acted on early- and late-stage erythropoietic and megakaryocyte progenitors. By eliciting effects on hematopoiesis across multiple differentiation stages and cell lineages, KER-050 has the potential to address the complex nature of IH and to provide robust and sustained hematological improvement in patients with MDS who have limited treatment options, including those with HTB or non-ring sideroblast (RS) MDS.

Methods: Analyses evaluating KER-050 at the recommended Part 2 dose (RP2D; 3.75 - 5 mg/kg q4wk) in participants with lower-risk (LR), RS+ or non-RS MDS from an ongoing Phase 2 study (NCT04419649) are presented as of a data cutoff date of April 3, 2023. The primary endpoint evaluates the safety and tolerability of KER-050. Secondary endpoints of modified IWG 2006 Hematological Improvement-Erythroid (HI-E) and transfusion independence (TI) ≥8 weeks are presented for participants who received ≥24 weeks of treatment or discontinued. DOR and changes in hematological parameters for participants with ongoing TI are presented for the first time.

Results: At baseline, most participants receiving KER-050 at the RP2D (74.6%) required regular transfusions (≥2 RBC units/8 weeks); 52.5% of RP2D participants had HTB (≥4 RBC units/8 weeks) and 20.3% had ≥8 RBC units/8 weeks (Table 1). The median treatment duration was 166 days (range 6 to 649). Most participants (89.8%) had at least 1 treatment-emergent adverse event (TEAE), and 32.2% had TEAEs considered treatment-related (Table 1). The most frequently observed TEAEs in ≥15% of participants were fatigue (22.0%), nausea and diarrhea (18.6% each), epistaxis (16.9%), and COVID-19 and dyspnea (15.3% each). A minority of participants (10.2%) had TEAEs that led to treatment discontinuation. Consistent with prior data, rates of TI for ≥8 weeks were similar regardless of baseline transfusion burden or RS status (Table 1). Among TI responders, 72.7% maintained TI for ≥24 weeks (data not shown), and the median DOR was not yet evaluable as more than half (6/11) had ongoing TI as of the cutoff date (Figure 1). Five of the 6 (83.3%) participants with ongoing TI had HTB at baseline, including one participant with a baseline transfusion burden of 11 RBC units/8 weeks, and all 3 responders with ongoing TI for >60 weeks.

One participant with HTB and non-RS MDS had ongoing TI for >72 weeks with a steady increase in hemoglobin from 8.4 to 11.8 g/dL. Erythroid responses were not at the expense of other cell lineages, as levels of platelets and neutrophils generally did not decrease (Figure 1). In fact, 44.1% of participants overall experienced a sustained (≥8 weeks) mean increase in platelet count of $\geq 30 \times 10^9$ within the first 24 weeks. Sustained decreases in ferritin were observed in parallel with increases in soluble transferrin receptor (Table 1), and for 3 participants, iron chelator therapy (ICT) was able to be discontinued. Investigation into changes in serum ferritin and ICT with KER-050 treatment will continue as cohorts of participants with MDS and iron overload are enrolled.

Summary: Updated findings from this ongoing Phase 2 study in LR MDS continue to show that KER-050 is generally well-tolerated and has potential to elicit sustained hematological improvements in a broad population of participants with LR MDS, including those with HTB. New data reveal an encouraging DOR, with observed preservation or improvement of multilineage hematopoiesis and sustained decreases in ferritin manifesting clinically with discontinuation of ICT. The study is ongoing and an update with the latest data will be provided at the time of presentation.

Disclosures 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; *GSK:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees. **Ross:** *Keros:* Consultancy; *Takeda:* Membership on an entity's Board of Directors or advisory committees; *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; *Menarini:* Membership on an entity's Board of Directors or advisory committees; *Celgene/BMS:* Honoraria, Research Funding. **Giagounidis:** *Curis:* Consultancy; *Keros Pharmaceuticals:* Consultancy; *Amgen:* Consultancy; *Novartis:* Consultancy; *BMS:* Consultancy. **Tan:** *Keros Therapeutics:* Research Funding. **Cluzeau:** *Incyte:* Speakers Bureau; *Servier:* Consultancy, Speakers Bureau; *Keros:* Speakers Bureau; *Syros:* Speakers Bureau; *Jazz Pharma:* Consultancy, Speakers Bureau; *Abbvie:* Consultancy, Speakers Bureau; *Novartis:* Consultancy, Speakers Bureau; *BMS:* Consultancy, Speakers Bureau. **Chee:** *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Keros Therapeutics:* Honoraria; *Otsuka:* 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. **Feng:** *Keros Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Jiang:** *Keros Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Bobba:** *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. **Grayson:** *BioCryst Pharmaceuticals:* Ended employment in the past 24 months; *Keros Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Cooper:** *Keros Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Salstrom:** *Keros Therapeutics:* Current Employment, Current equity holder in publicly-traded company.

https://doi.org/10.1182/blood-2023-180974

Table 1. Baseline, Safety, and Response Parameters for Participants Dosed at the RP2D (3.75-5 mg/kg)

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)
High Transfusion Burden (HTB), ≥4 units	31 (52.5)
≥8 units	12 (20.3)
Ring Sideroblast (RS) Status, n (%)	
RS Positive	42 (71.2)
Non-RS	17 (28.8)
Prior ESA, n (%)	13 (22.0)
Concurrent Iron Chelator, n (%)	17 (28.8)
Safety	**RP2D (N=59)**
Any Treatment Emergent Adverse Event (TEAE), n (%)	53 (89.8)
Any treatment-related TEAE, n (%)	19 (32.2)
Any TE serious AE (TESAE), n (%)	20 (33.9)
Any treatment-related TESAE, n (%)	1 (1.7)
Any TEAE leading to death, n (%)	2 (3.4)
Any TEAE leading to IMP Discontinuation, n (%)	6 (10.2)

Hematological Response	RP2D mITT24[a] (N=37)	
	All Evaluable	HTB Evaluable
Overall Response, n/m[b] (%)	19/37 (51.4)	11/22 (50)
Modified IWG 2006 HI-E[c], n/m (%)	19/37 (51.4)	11/22 (50)
TI ≥ 8 weeks, n/m[d] (%)	11/26 (42.3)	9/22 (40.9)
RS+	8/19 (42.1)	6/17 (35.3)
non-RS	3/7 (42.9)	3/5 (60)

Observed Biomarker Changes	TI Responders (N=11)	
	Week 24	Week 48
Soluble Transferrin Receptor, mean % change	59.4% (n=9)	52.9% (n=6)
Ferritin, mean change (ng/mL)	-357 (n=10)	-351 (n=6)

ESA = erythroid stimulating agent; IMP = Investigational Medicinal Product; IWG HI-E = International Working Group Hematological Improvement – Erythroid; RBC = red blood cell; TI = Transfusion Independence.

[a] mITT24 = modified intent to treat, 24 weeks: participants are included if they have ≥24 weeks of treatment or discontinued.

[b] Defined as achieving modified IWG 2006 HI-E and/or TI over the first 24 weeks of treatment; n = number of participants meeting response criteria, m = number of evaluable

[c] Modified HI-E = mean increase in hemoglobin ≥1.5 g/dL (NT+LTB) or reduction in transfusion of ≥4 RBC units (HTB) over 8 weeks on-treatment compared to 8-week pre-treatment period (within the first 24 weeks)

[d] TI-evaluable participants received at least 2 RBC units in the 8 weeks prior to treatment initiation

Figure 1. Participants with Ongoing Transfusion Independence as of the Data Cutoff Date (03-April-2023)

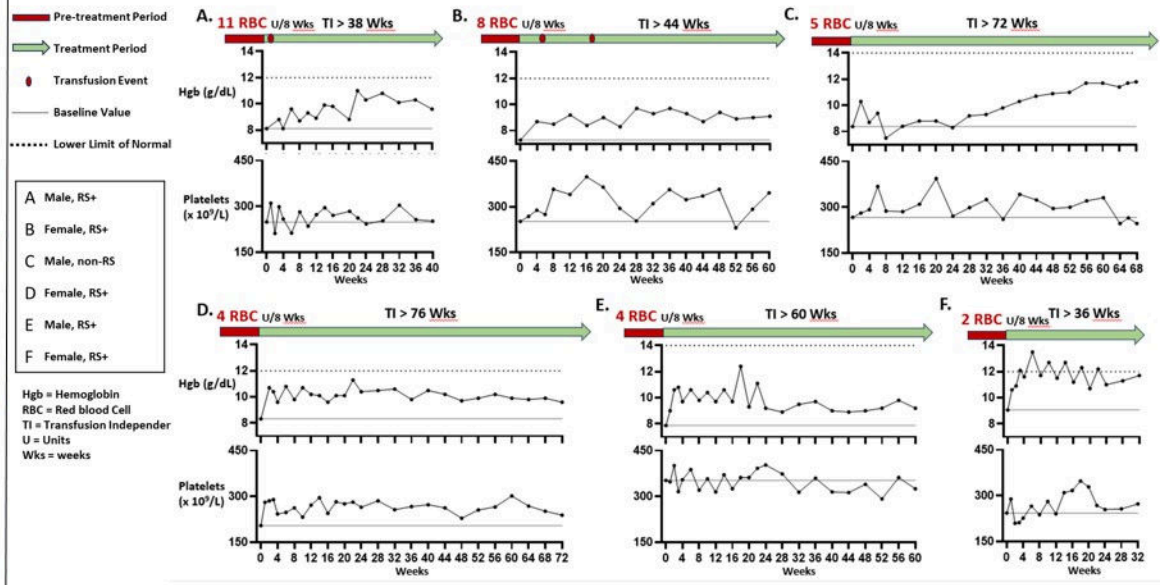

Figure 1