MPN and MDS: Targeting red cells and platelets– **09-June-2023**

KER-050 Treatment Improved Markers of Erythropoietic Activity and Hematopoiesis Over Six Months Which Resulted in Hematological Responses Across a Broad Lower-Risk MDS Population

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s417 MPN and MDS: Targeting red cells and platelets

DISCLOSURES

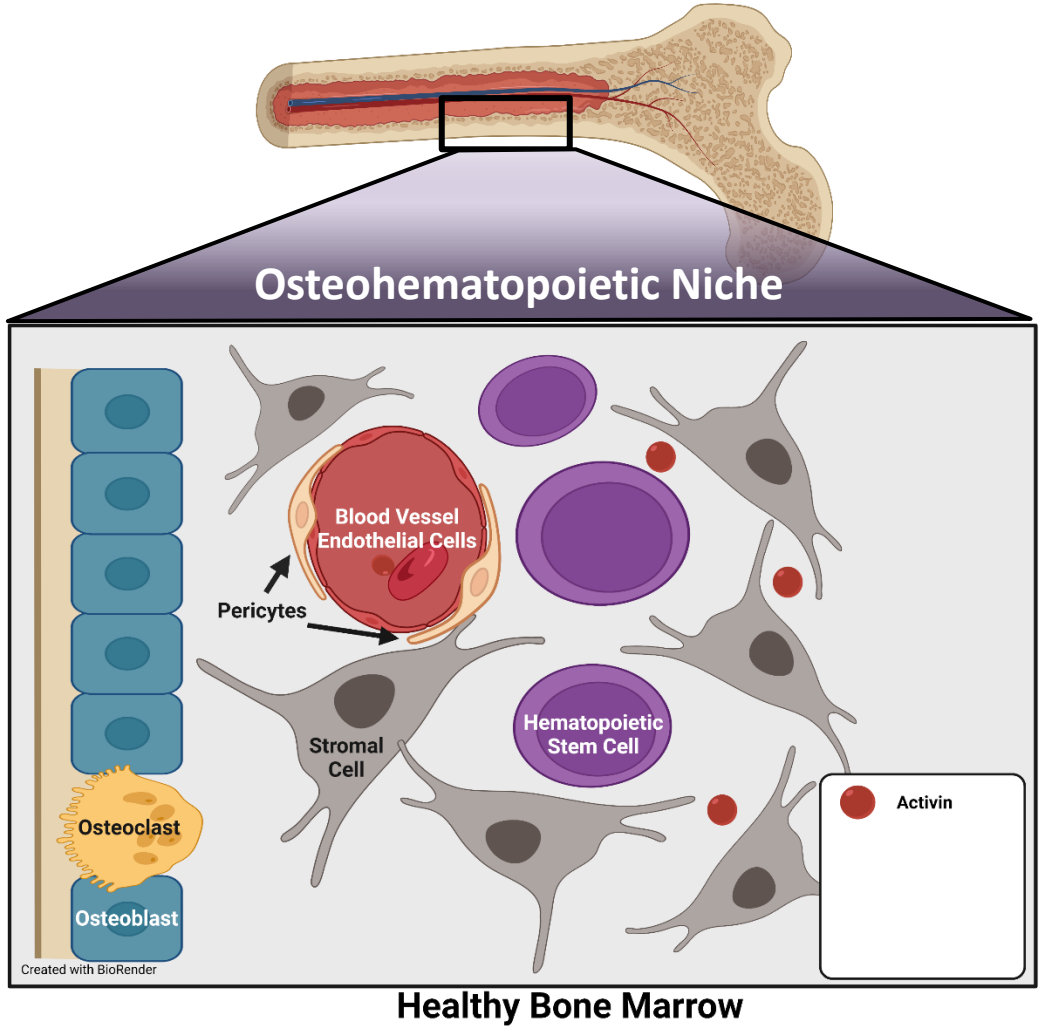
Keros Corporation (Advisory board)
Geron (Advisory board)
Novartis (Honoraria)
BMS (Advisory board)
I adore my wife, my children and Uwe Platzbecker

Spelling and pronounciation (SPAP) disclosure

In the upcoming talk, I will use the following pronounciation of medical terms:

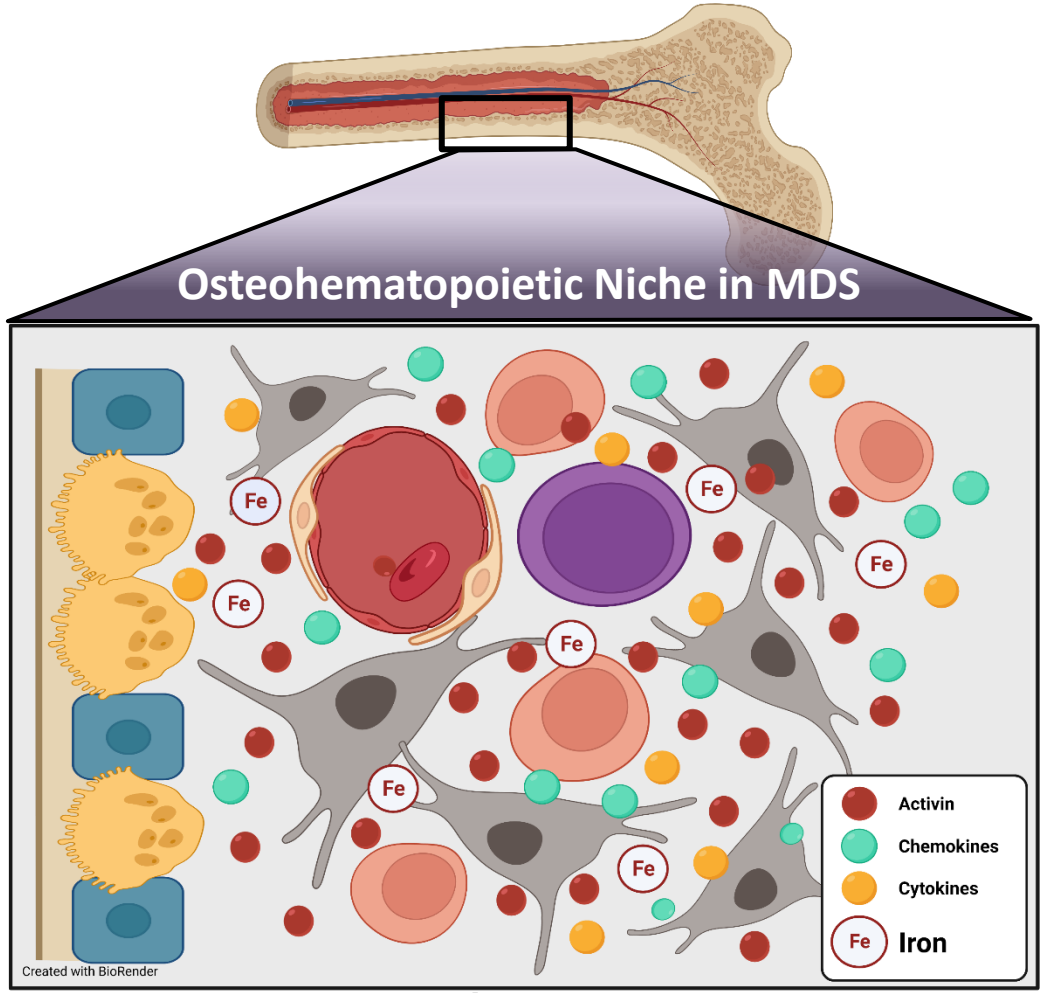
Term	Pronounciation	IPA transcropt
Ligand	liggaend	ˈlɪg.ənd
Niche	Neesh	niːʃ
Pleiotropic	Plahy-o-trow-pic	ˌplī-ə-ˈtrō-pik
Homeostasis	Homee-oh-staysis	həʊ.mi.əʊˈsteɪ.sɪs
Lineage	Linn-i-dj	ˈlɪn.i.ɪdʒ
Leukemic	Loo-keemic	luːˈkiː.mi.k

Complications of MDS Arise from a Dysregulated Bone Marrow Microenvironment



Healthy Bone Marrow

Complications of MDS Arise from a Dysregulated Bone Marrow Microenvironment



MDS and Progression to AML

Dysregulated signaling within OHN creates hostile environment for functional hematopoiesis:

- Dysregulated TGF-β signaling including activin A[1,2,3]
- Accumulation of iron[2]
- Increases in inflammatory cytokines[1,2]

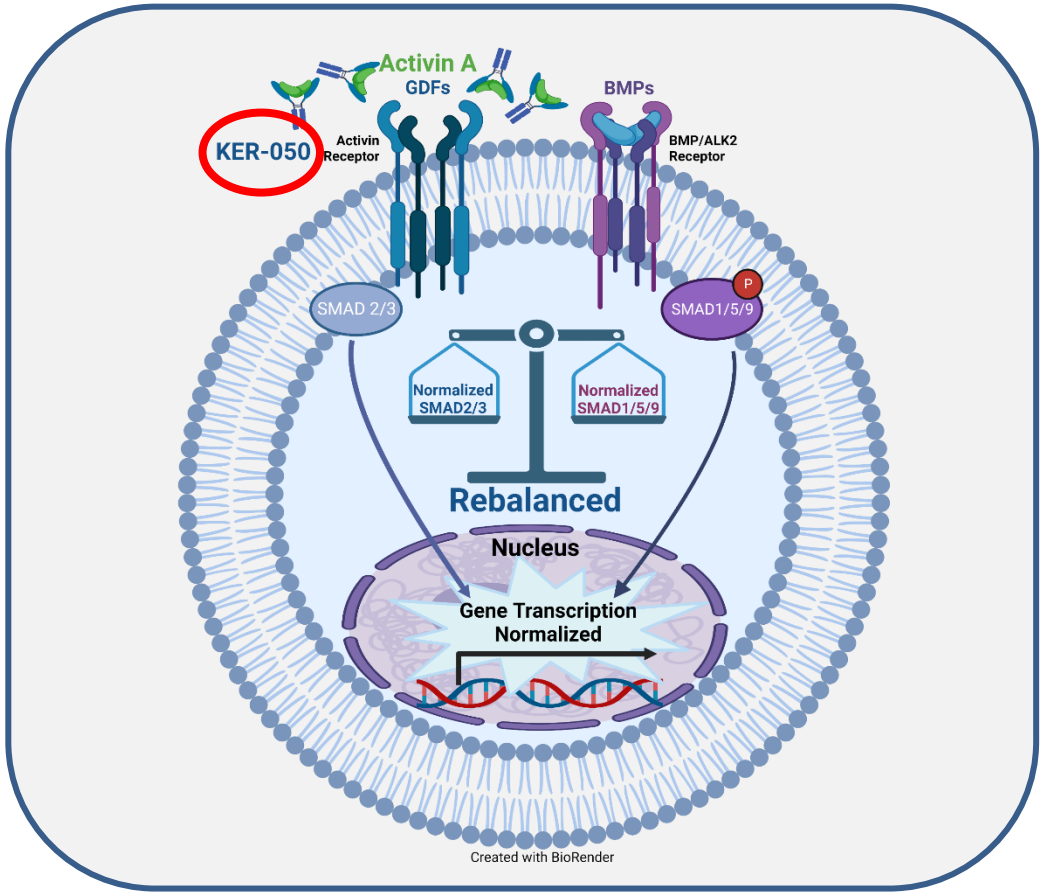
Consequences include:

- Progressive cytopenias
- RBC transfusion dependence
- Tissue iron overload
- Clonal proliferation and leukemic transformation

1. Portale F, et al., Haematologica. 2019; 2. Bulycheva E, et al., Leukemia. 2015; 3. Ottewell P, J Bone Onc. 2016

KER-050 as a Potential Treatment for MDS

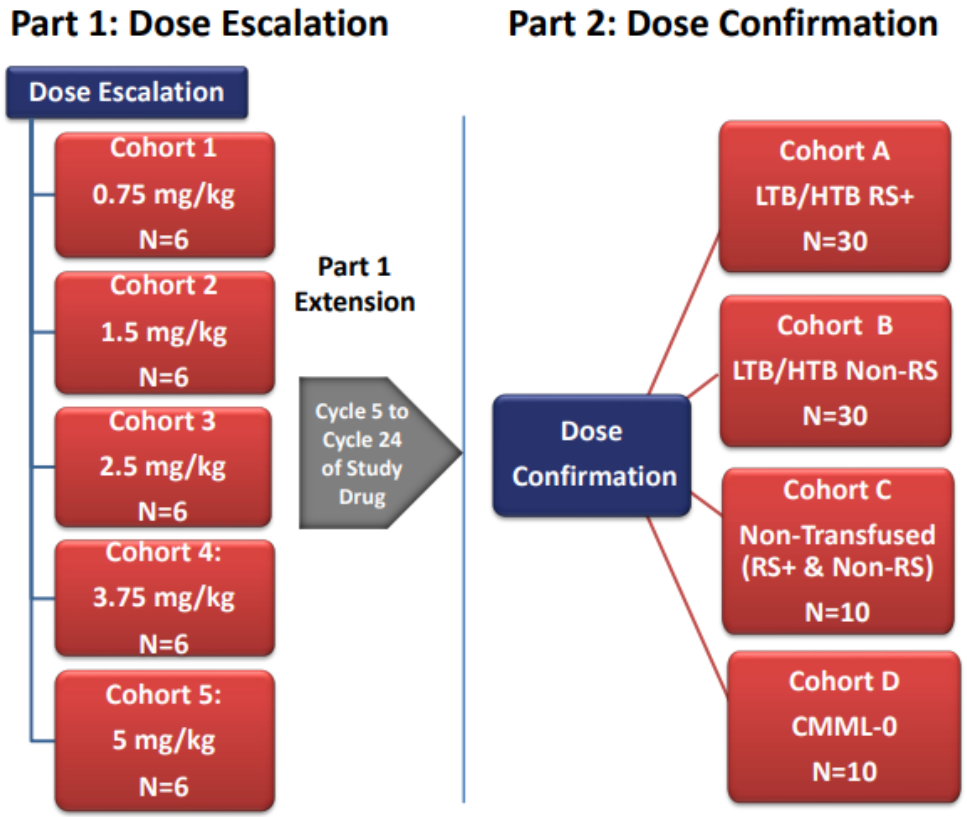
- Investigational modified activin receptor type IIA ligand trap
- KER-050 is designed to:
  - Bind and inhibit select TGF-β superfamily ligands, including:
    - **Activin A** and Activin B
    - GDF-8 and GDF-11
- KER-050 has the potential to:
  - Rebalance SMAD 2/3 and SMAD 1/5/9 signaling within bone marrow cells[1]
  - Restore the OHN to a state that promotes growth and differentiation of erythroid cells and megakaryocytes[1,2,3]
  - Promote iron utilization by increasing red blood cell production[2]



1. *Portale F, et al., Haematologica. 2019.; 2. Chee L, et. al. Am Soc Hematol Annual Meeting and Exposition, 2022 (#3656)*
3. *Moses B and Materna C, et. al., Am Soc Hematol Annual Meeting and Exposition, 2022 (#4387)*

KER050-MD-201: A Phase 2 Study to Assess KER-050 in Low- to Intermediate-Risk MDS

KER050-MD-201 (NCT04419649) Design and Dose Levels Tested



- **Primary Objective:**
  - Assess safety and tolerability of KER-050
- **Secondary Endpoints include:**
  - Hematological Improvement- Erythroid (modified IWG 2006 HI-E)
  - Transfusion Independence (TI) ≥8 weeks
- **Ongoing Study – Status as of 03-April-2023:**
  - Part 1 Dose Escalation completed (N=31); Part 1 Extension ongoing
  - RP2D: 3.75 mg/kg w/titration to 5 mg/kg Q4W
  - Part 2 Dose Confirmation enrolling

  - **RP2D-Experienced Participants: N=59**
    - 25 participants from Part 1
    - 34 participants from Part 2

RP2D = Recommended Part 2 Dose

Data are presented as of a data cutoff date of 03-April-2023

RP2D Population Included Difficult-to-Treat Patients With High Disease Burden

Parameter	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 Status, n (%)	
RS Positive	42 (71.2)
Non-RS	17 (28.8)
IPSS-R Risk Category, n (%)	
Very Low	8 (13.6)
Low	39 (66.1)
Intermediate	11 (18.6)
Missing	1 (1.7)
MDS WHO 2016 Classification, n (%)	
MDS	2 (3.4)
MDS-MLD	12 (20.3)
MDS-RS-MLD	29 (49.2)
MDS-RS-SLD	5 (8.5)
Missing	11 (18.6)
Prior ESA	13 (22.0)
Concurrent Iron Chelator	17 (28.8)

- Most required transfusions at baseline
  - Over half were High Transfusion Burden (HTB; ≥4 RBC units/8 wks)
  - Among HTB participants, 12/31 (38.7%) received ≥8 RBC units/8 wks
- Majority were Ring Sideroblast positive (RS+)
- Majority had multi-lineage dysplasia (MLD)

Data are presented as of a data cutoff date of 03-April-2023

Opportunity to Evaluate Longer-Term Exposure to KER-050

Exposure of overall MDS RP2D Population as of the data cutoff date:

- 59 participants received ≥1 dose of KER-050 (included in safety population)
- Median duration of treatment = 225 days (≈32 weeks)
  - Range 6 to 649 days (≈1 to 93 weeks)
- Median doses received = 6
  - Range 1 to 22
    - 14 (23.7%) participants received ≥12 doses
    - 15 (25.4%) participants received <3 doses

Hematological response and markers of hematopoiesis are presented from exploratory analyses of RP2D participants with at least 6 months of KER-050 treatment or who have discontinued (n=37)

KER-050 Was Generally Well-Tolerated

- Most frequent TEAEs (in ≥ 15% of participants) regardless of causality were:
  - Fatigue, n=13 (22%)
  - Nausea and Diarrhoea, n=11 each (18.6%)
  - Epistaxis, n=10 (16.9%)
  - COVID-19 and Dyspnoea, n=9 each (15.3%)
- 1 treatment-related TESAE (Gr 2 Injection site reaction)
- 2 fatal TEAEs (Cardiac failure and Myocardial infarction); both determined to be unrelated to study treatment by the investigator
- No participants progressed to AML

Category	RP2D (N=59) n (%)
Any TEAE	53 (89.8)
Any treatment-related TEAE	19 (32.2)
Any TE serious AE (TESAE)	20 (33.9)
Any treatment-related TESAE	1 (1.7)
Any TEAE leading to death	2 (3.4)
Any TEAE leading to IMP Discontinuation[a]	6 (10.2)

[a] Related TEAEs leading to IMP discontinuation = injection site reaction; unrelated TEAEs = nodular melanoma, COPD and cardiac failure congestive (both in 1 participant), dyspnoea, cardiac failure, and myocardial infarction

TEAE = Treatment Emergent Adverse Event
TESAE = Treatment Emergent Serious Adverse Event
IMP = Investigational Medicinal Product
AML = Acute Myeloid Leukemia

KER-050 Treatment Resulted in Hematological Response Across a Broad Population of Patients with Lower-Risk MDS

Response Endpoint	RP2D Participants[a]	
	All Evaluable	HTB Evaluable
Overall Response[b]	19/37 (51.4)	11/22 (50)
Modified IWG 2006 HI-E[c]	19/37 (51.4)	11/22 (50)
TI ≥ 8 weeks[d] RS+ Non-RS	11/26 (42.3) 8/19 (42.1) 3/7 (42.9)	9/22 (40.9) 6/17 (35.3) 3/5 (60)

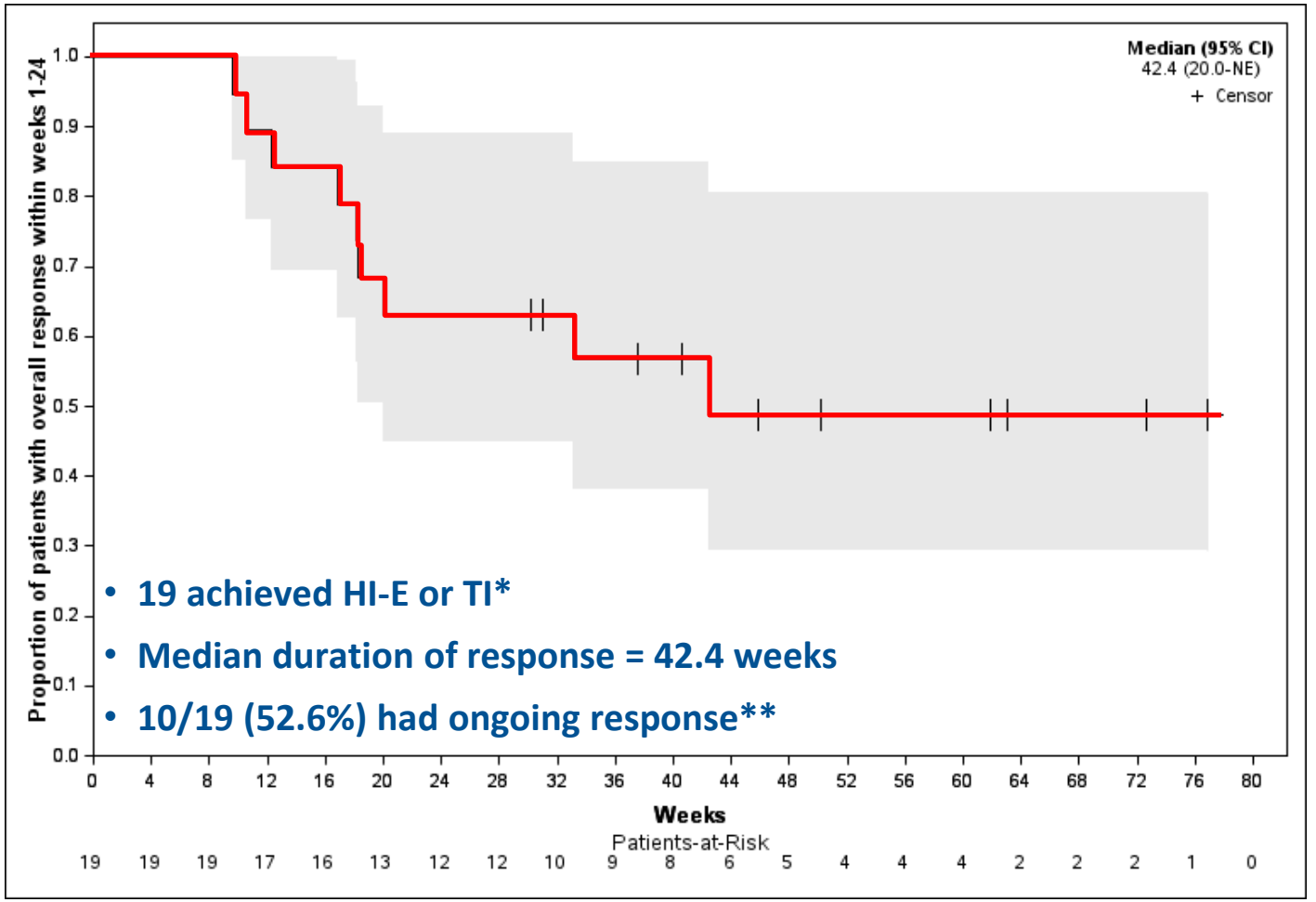
[a] Includes data for weeks 0-24 in RP2D participants with ≥24 weeks of treatment or who discontinued
[b] Defined as achieving modified IWG 2006 HI-E and/or TI
[c] Modified HI-E = mean increase in hemoglobin ≥1.5 g/dL (NT+LTB) or reduction in transfusion of ≥4 RBC units (HTB) over 8 weeks on-treatment compared to 8-week pre-treatment period
[d] TI-evaluable participants received at least 2 RBC units in the 8 weeks prior to treatment initiation

- Similar rates of HI-E and TI observed regardless of transfusion burden or RS status
- 44.1%* of participants show a ≥30 x 10^9/L increase from baseline in platelet count sustained over at least 8 weeks

*Percentage based on 34 patients who had at least 24 weeks of treatment or discontinued AND had both baseline and 8 weeks of post-baseline platelet data

Data are presented as of a data cutoff date of 03-April-2023

Data Suggest KER-050 Elicited a Durable Response



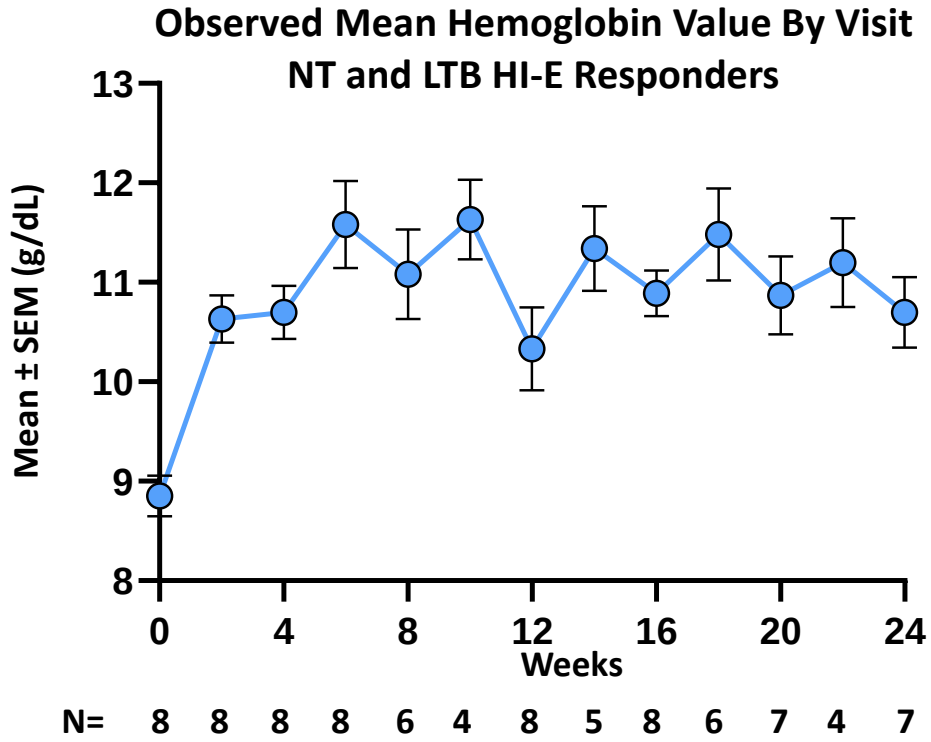
* During weeks 0-24 in RP2D participants with ≥24wk of treatment or who discontinued

**Participants with ongoing response censored at time of cutoff, denoted by vertical lines

Data presented as of a data cutoff date of 03-April-2023;

Note: "Patients-at-Risk" = number of responders at risk of losing response (ie still maintaining a response) at each timepoint

Sustained Increases in Hemoglobin Observed Over 6 Months of KER-050 Treatment

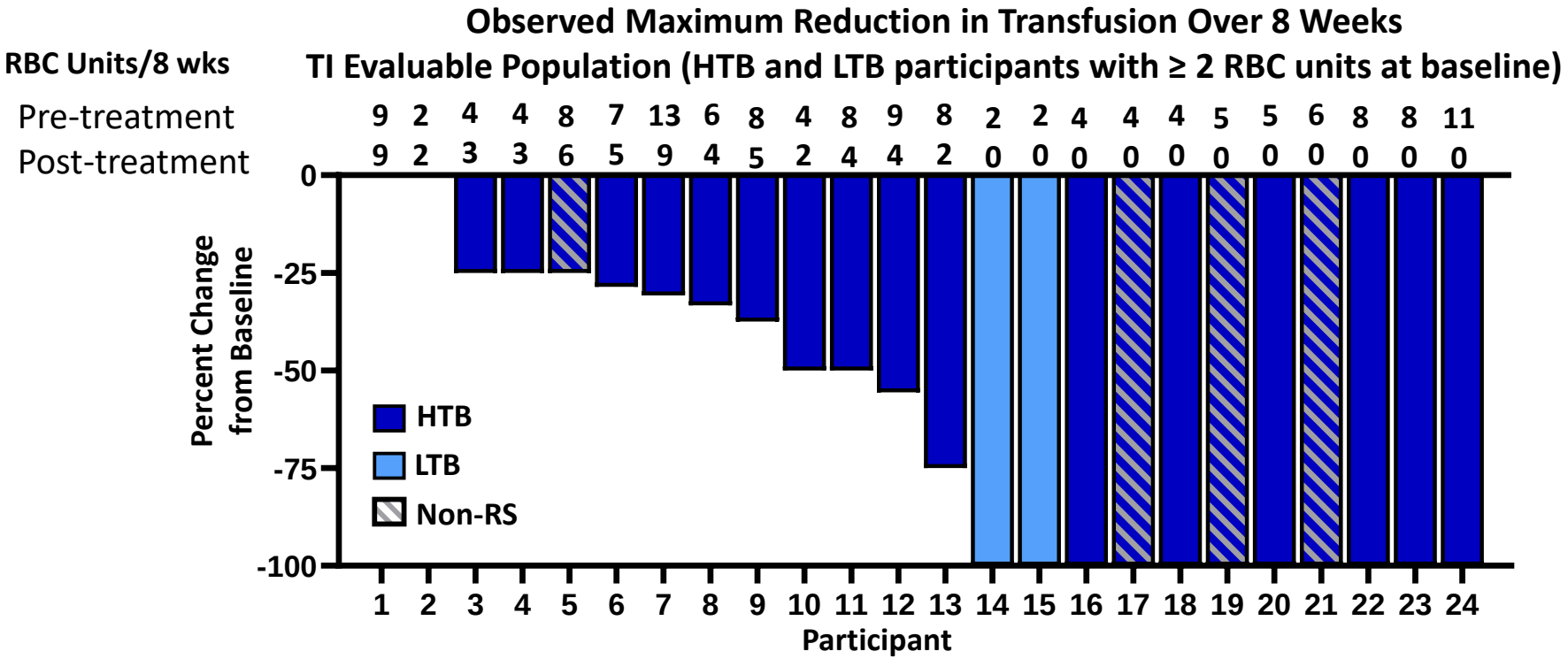


8/15 (53.3%) NT and LTB participants with ≥6 months of treatment (or discontinued) achieved HI-E response in first 24 weeks of treatment

Observed sustained increases in hemoglobin support durable response with KER-050

Data are presented as of a data cutoff date of 03-April-2023. Baseline hemoglobin calculated as average over 8-week pre-treatment period. Hemoglobin values within 14 days following a transfusion censored except for pre-transfusion values. Per protocol, KER-050 dose must be held at Hgb levels ≥12 g/dL.

Reductions in Transfusion Burden Observed with KER-050 Treatment

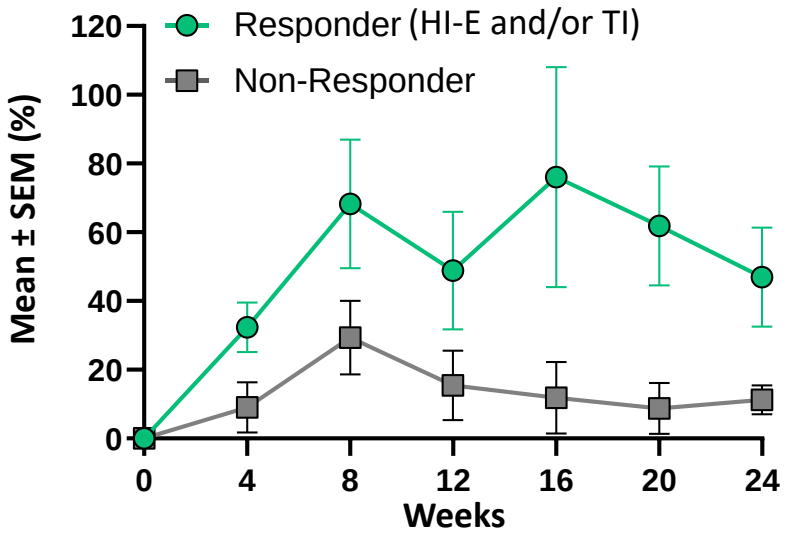


- Reduced transfusion burden observed in majority of LTB and HTB participants
- TI observed in both RS+ and non-RS participants
- TI achieved in participants with baseline TB ranging from 2 to 11 units/8 weeks

Data are presented as of a data cutoff date of 03-April-2023. Note: 2 participants discontinued with insufficient data to determine 8-week transfusion reduction, and are not included in this plot

Data Suggest Enhanced Erythropoiesis and Potential to Reduce Iron Overload

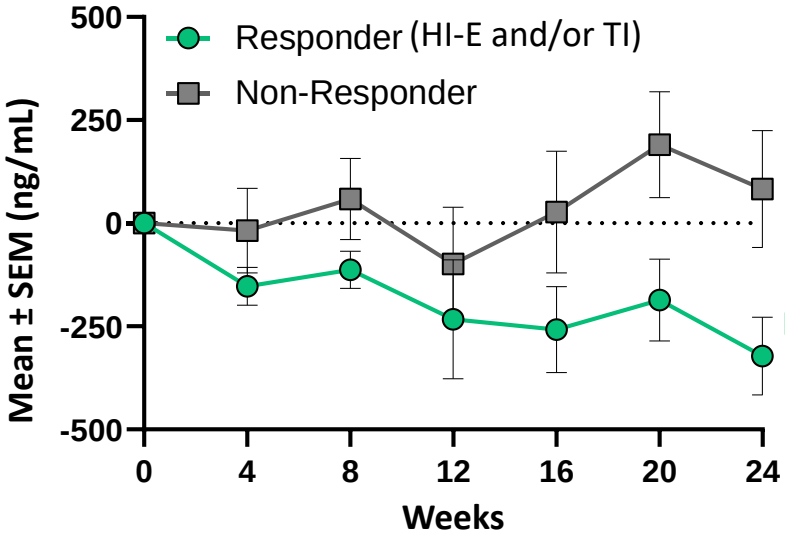
Observed Percent Change from Baseline In Soluble Transferrin Receptor (sTfR)



N=							
Responder (HI-E and/or TI)	19	16	10	16	11	17	15
Non-Responder	17*	15	7	11	7	9	7

*One participant was missing a baseline sTfR assessment.

Observed Change from Baseline In Ferritin



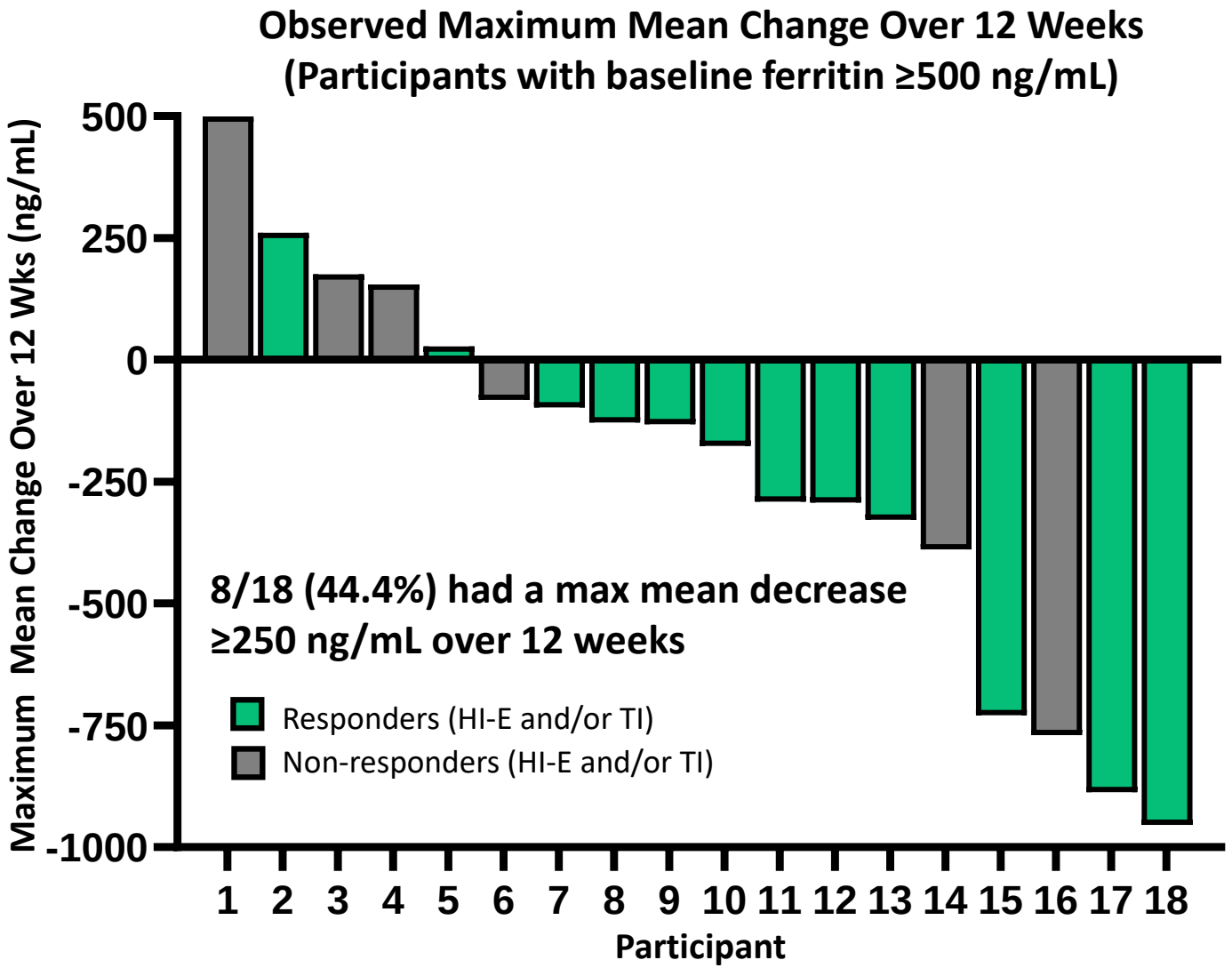
Mean Δ at week 24
-322 ng/mL

N=							
Responder (HI-E and/or TI)	19	17	17	17	18	17	16
Non-Responder	18	17	14	13	13	11	9

Observed Reductions in Serum Ferritin with KER-050 Treatment

Iron overload is a serious clinical complication in MDS

- A serum ferritin >1000 ng/mL is associated with 3x greater risk of death in MDS patients[1]
- Baseline ferritin in this analysis population (n=37):
  - Mean = 1026 ng/mL
  - Range = 86.3 to 5,829 ng/mL
  - 18 participants ≥500 ng/mL



[1]*A. Waszczuk-Gajda et al. Adv Clin Exp Med. 2016.*

Data are presented as of a data cutoff date of 03-April-2023

Conclusions

As of the 03 April 2023 data cutoff date:

- KER-050 was generally well-tolerated; safety profile was consistent to that previously reported for this trial
- Durable hematological responses were observed in a broad, lower-risk MDS population including those with HTB and/or non-RS disease
- Observed decreases in serum ferritin, a marker of iron overload, may reflect:
  - Reduced iron overload due to reduced transfusion burden
  - Improved iron utilization with increased erythropoiesis

Study KER050-MD-201 amended to further evaluate the potential of KER-050 to reduce serum ferritin in MDS patients with iron overload

Thank You

Special thanks to investigators, clinical staff, study participants and their caregivers