Luspatercept (ACE-536) Increases Hemoglobin and Reduces Transfusion Burden in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS): Preliminary Results from a Phase 2 Study

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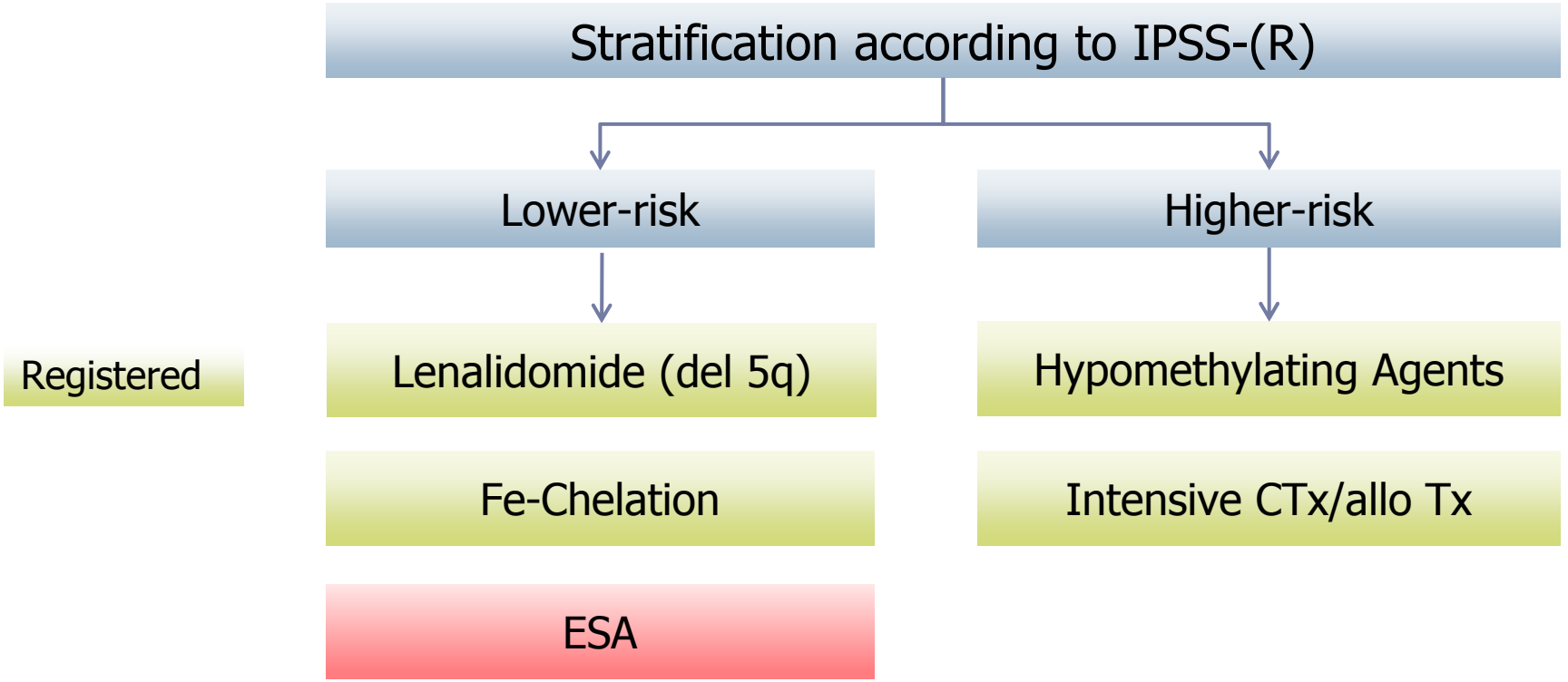
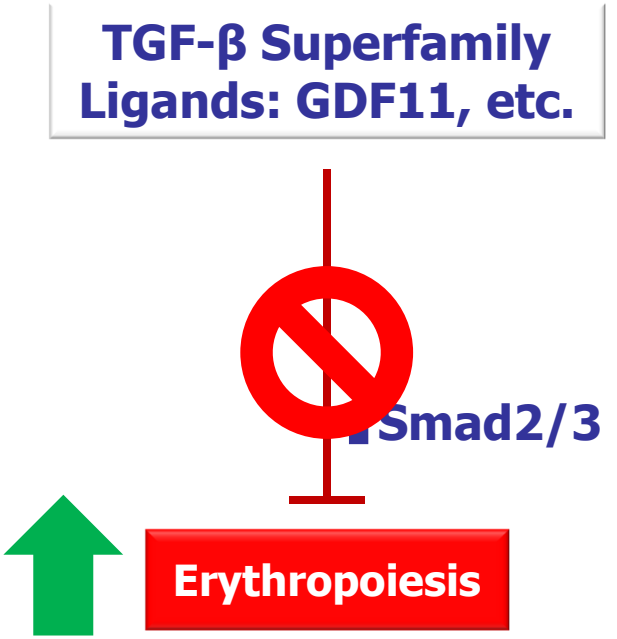
Limited Therapeutic Options in MDS



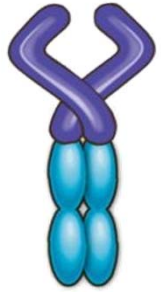
- 80–90% of MDS patients become dependent on RBC transfusions
- Many patients unresponsive/refractory to ESAs
- Need for novel disease-specific therapeutics to treat anemia

Luspatercept in MDS: Background



Luspatercept

Fusion protein containing modified activin receptor type IIB (ActRIIB)



Activin Receptor Domain

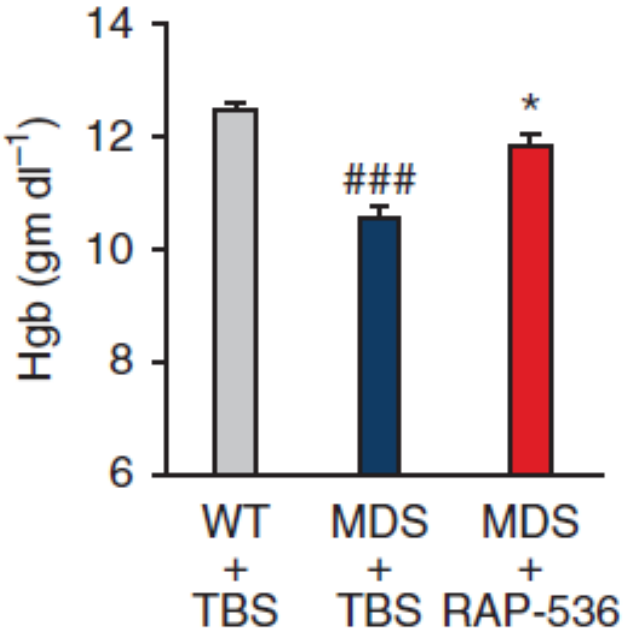
Human IgG Fc Domain

- Mechanism is distinct from erythropoietin
- Acts on late-stage erythropoiesis to increase mature RBCs in the circulation

Suragani R, et al. Nature Med 2014
Zhou L, et al., Blood 2008

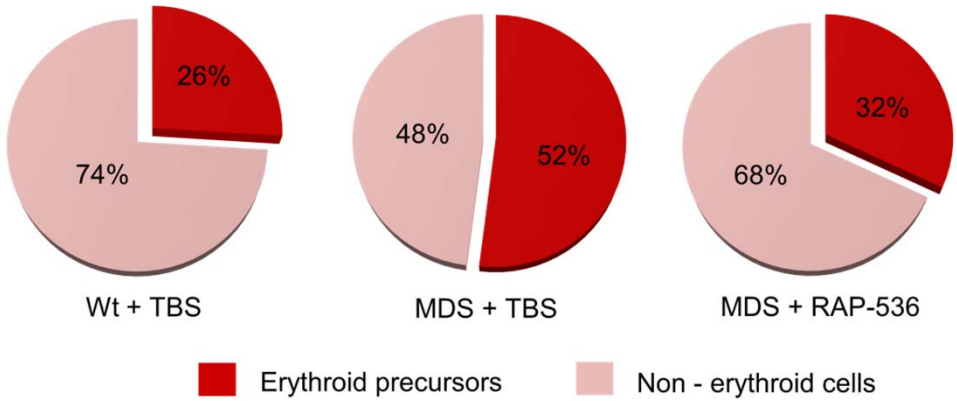
Effects in MDS Mouse Model

Increases Hemoglobin

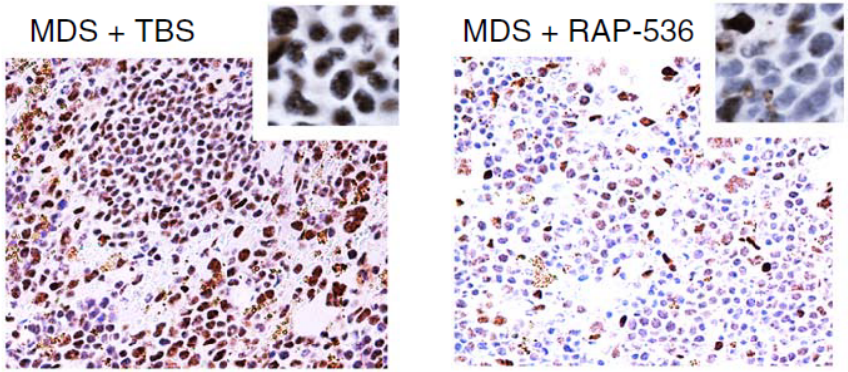


###p< 0.001 vs WT+TBS
*p< 0.05 vs MDS+TBS

Normalizes M:E Ratio in BM



Inhibits Smad2/3 Signaling

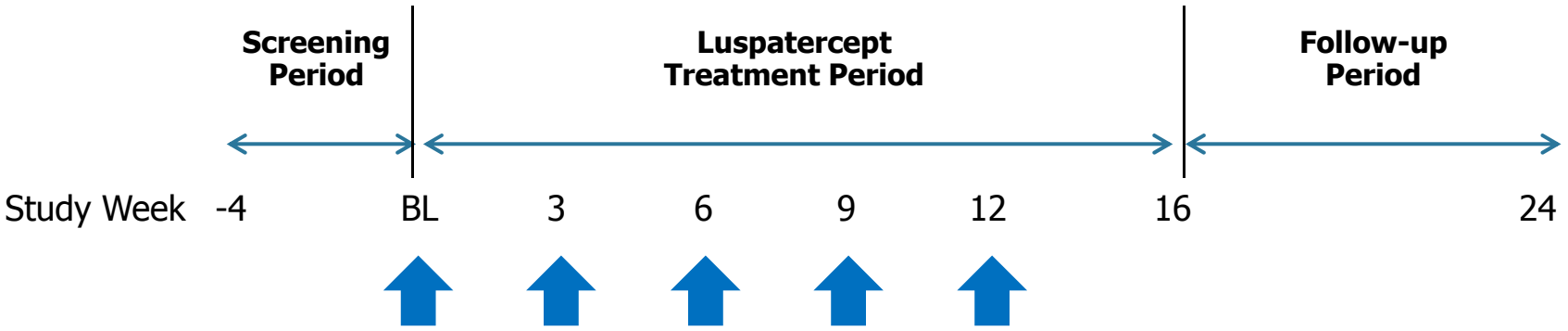


Studies using RAP-536, murine analog of luspatercept

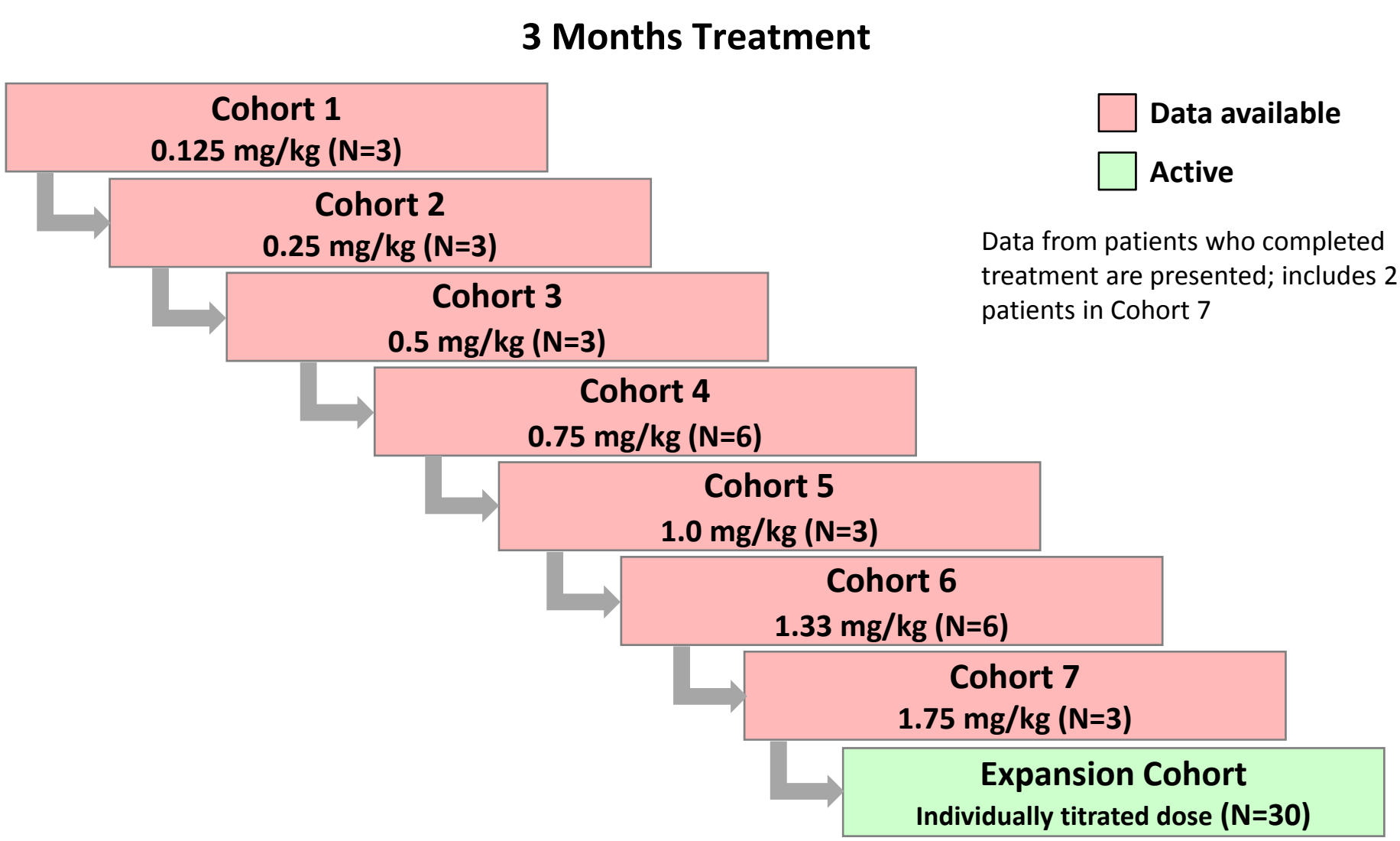
Suragani R et al., Nature Med 2014

Luspatercept PACE-MDS Study Overview

- Phase 2, multicenter, open-label, dose-finding study in IPSS low/int-1 MDS
- **Eligibility criteria:** EPO >500 U/L or nonresponsive/refractory to ESA; no prior azacitidine or decitabine; no current lenalidomide, ESA, G-CSF
- **Primary efficacy endpoints**
  - Low Transfusion Burden (LTB, <4U RBC/8 weeks, Hgb <10 g/dL): Hemoglobin increase of ≥ 1.5 g/dL for ≥ 2 weeks
  - High Transfusion Burden (HTB, ≥4U RBC/8 weeks): Reduction of ≥4U or ≥50% units transfused over 8 weeks
- Luspatercept administered SC every 3 weeks for 3 months



Luspatercept PACE-MDS Study Design



Patients completing base study can enroll into a 12-month extension study

Baseline Characteristics

All Patients	**N = 26**
Age, yr, median (range)	71 (27-88)
Sex, males (%)	13 (50%)
Prior ESA treatment, n (%)	14 (54%)
Prior lenalidomide treatment, n (%)	5 (19%)
Low Transfusion Burden (LTB)	**N = 7 (27%)**
Hemoglobin, g/dL, median (range)	9.1 (8.3-9.7)
Units RBC/8 weeks, median (range)	0 (0-2)
High Transfusion Burden (HTB)	**N = 19 (73%)**
Units RBC/8 weeks, median (range)	6 (4-13)

Data as of 03 Oct 2014

Baseline MDS Characteristics

Classification	N = 26 n (%)
WHO Subtype	
RARS	4 (15%)
RCMD-RS	11 (42%)
RCMD	5 (19%)
RAEB-1*	4 (15%)
del (5q)	2 (8%)
IPSS	
Low	12 (46%)
Int-1	12 (46%)
Int-2	2 (8%)
IPSS-R	
Low	15 (58%)
Intermediate	8 (31%)
High	3 (12%)

*Includes 2 patients with ≥15% RS

Data as of 03 Oct 2014

Pharmacokinetic and Safety Summary

Pharmacokinetics

- Dose-dependent increase in Cmax and area under curve (AUC)
- Mean half-life (t½) is approximately 14 days, supporting Q3W dosing

Safety

- No drug-related serious adverse events (AEs)
- One possibly related grade 3 AE of blast cell count increase
- Majority of adverse events were grade 1 or 2

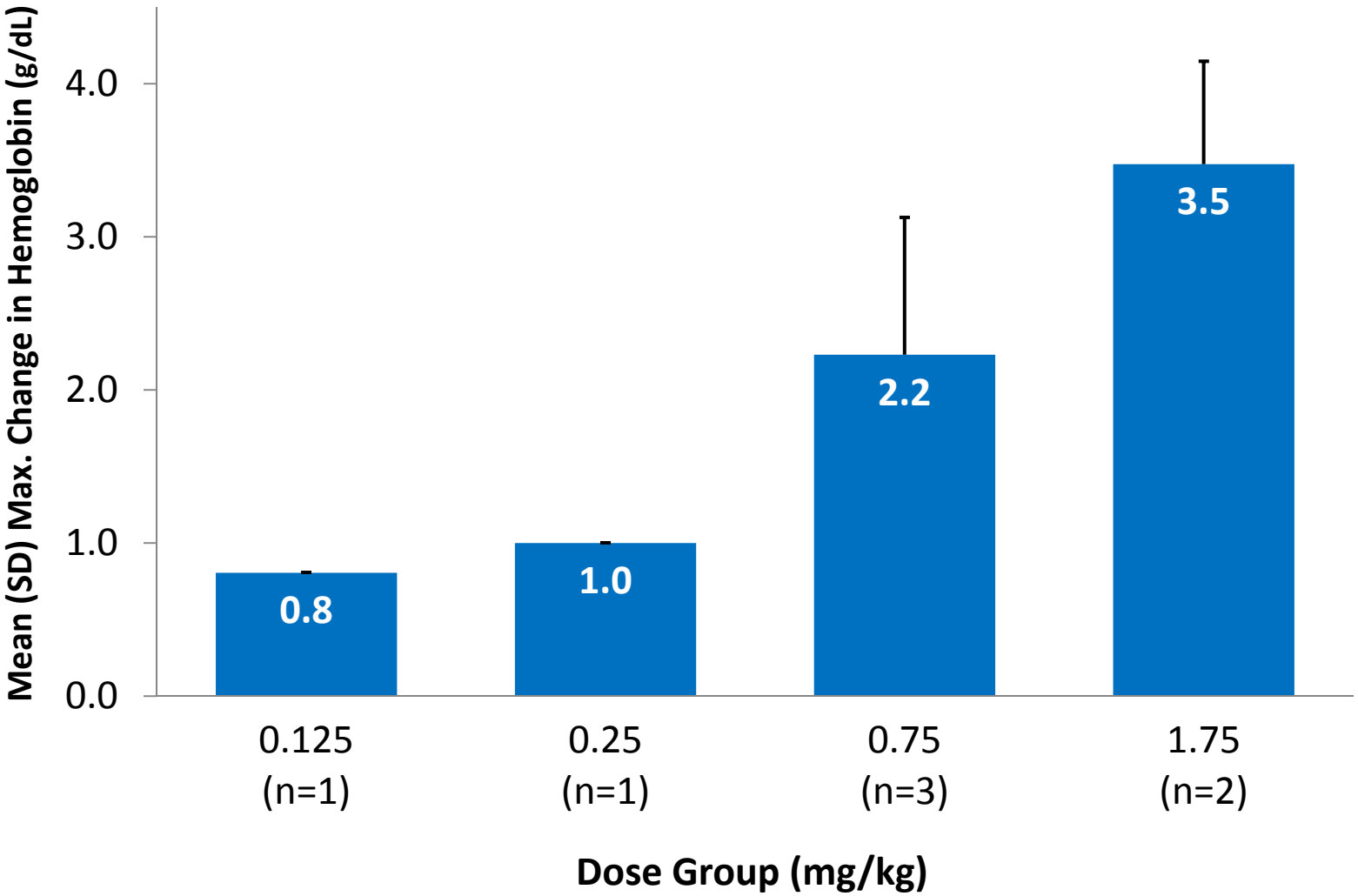
Adverse Events in ≥ 10% of Patients (Regardless of Causality):

Preferred Term n (%)	0.125 mg/kg (N=3)	0.25 mg/kg (N=3)	0.50 mg/kg (N=3)	0.75 mg/kg (N=6)	1.0 mg/kg (N=3)	1.33 mg/kg (N=6)	1.75 mg/kg (N=2)	Overall (N=26)
Diarrhea	0	1	1	1	0	1	0	4 (15%)
Muscle Spasms	0	0	2	0	1	0	1	4 (15%)
Bone Pain	0	0	1	0	2	0	0	3 (12%)
Fatigue	0	0	0	0	0	3	0	3 (12%)
Myalgia	0	1	1	0	1	0	0	3 (12%)
Nasopharyngitis	0	1	0	2	0	0	0	3 (12%)

Data as of 03 Oct 2014

Low Transfusion Burden (LTB) Patients

Maximum Hemoglobin Increase in LTB Patients



LTB, low transfusion burden

Data as of 03 Oct 2014

LTB Patients: Hemoglobin Response

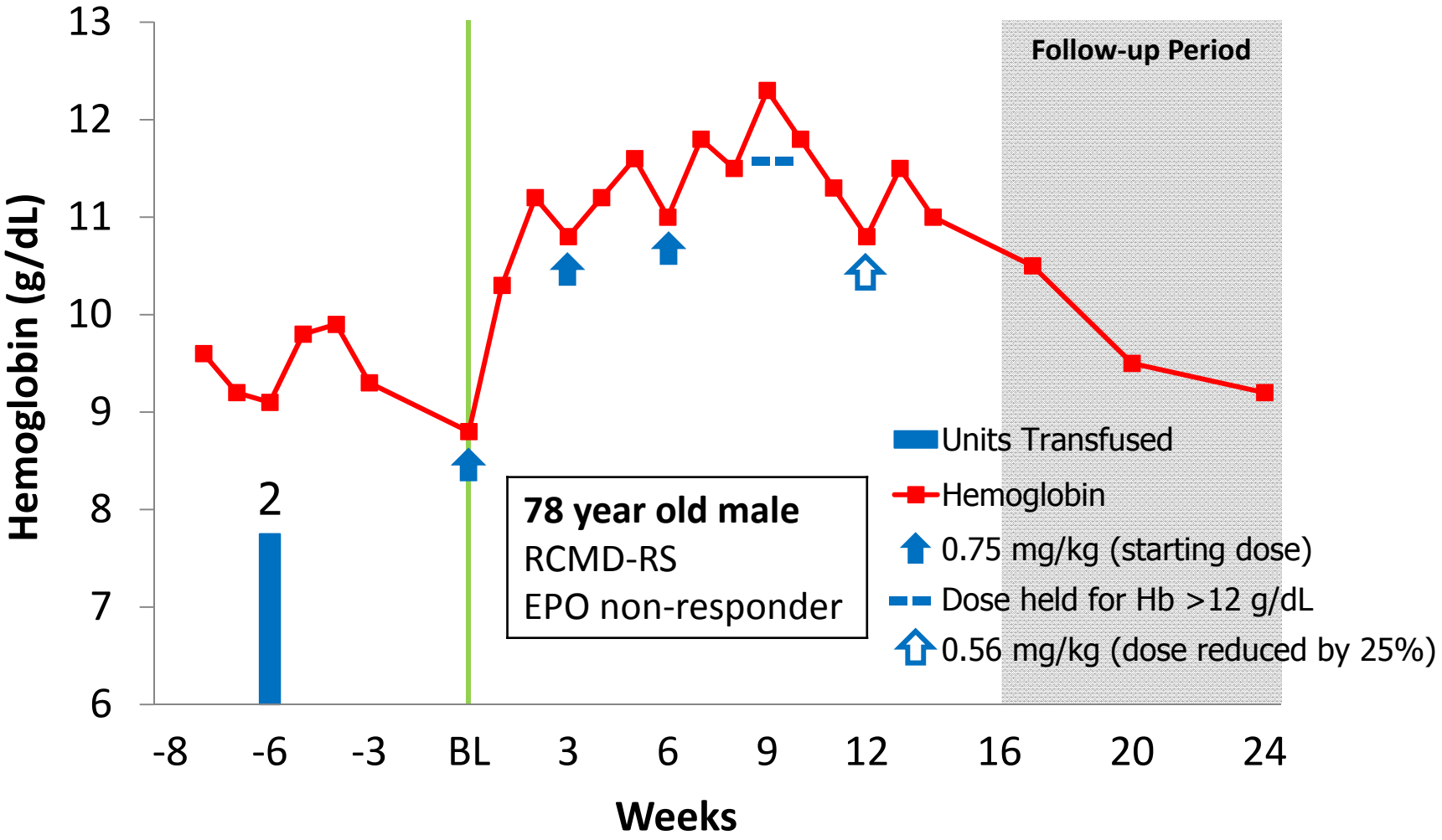
- All 5 patients at the higher dose levels had prior ESA treatment
- No patients received prior lenalidomide treatment

Response Criteria	0.125-0.5 mg/kg N=2 n (%)	0.75-1.75 mg/kg N=5 n (%)
Hemoglobin increase ≥1.5 g/dL for ≥2 weeks	0	**4 (80%)**
Hemoglobin increase ≥1.5 g/dL for ≥8 weeks (HI-E)	0	**2 (40%)**

LTB, low transfusion burden

Data as of 03 Oct 2014

LTB Responder (HI-E): Hemoglobin



LTB, low transfusion burden

Data as of 03 Oct 2014

High Transfusion Burden (HTB) Patients

HTB Patients: Transfusion Response

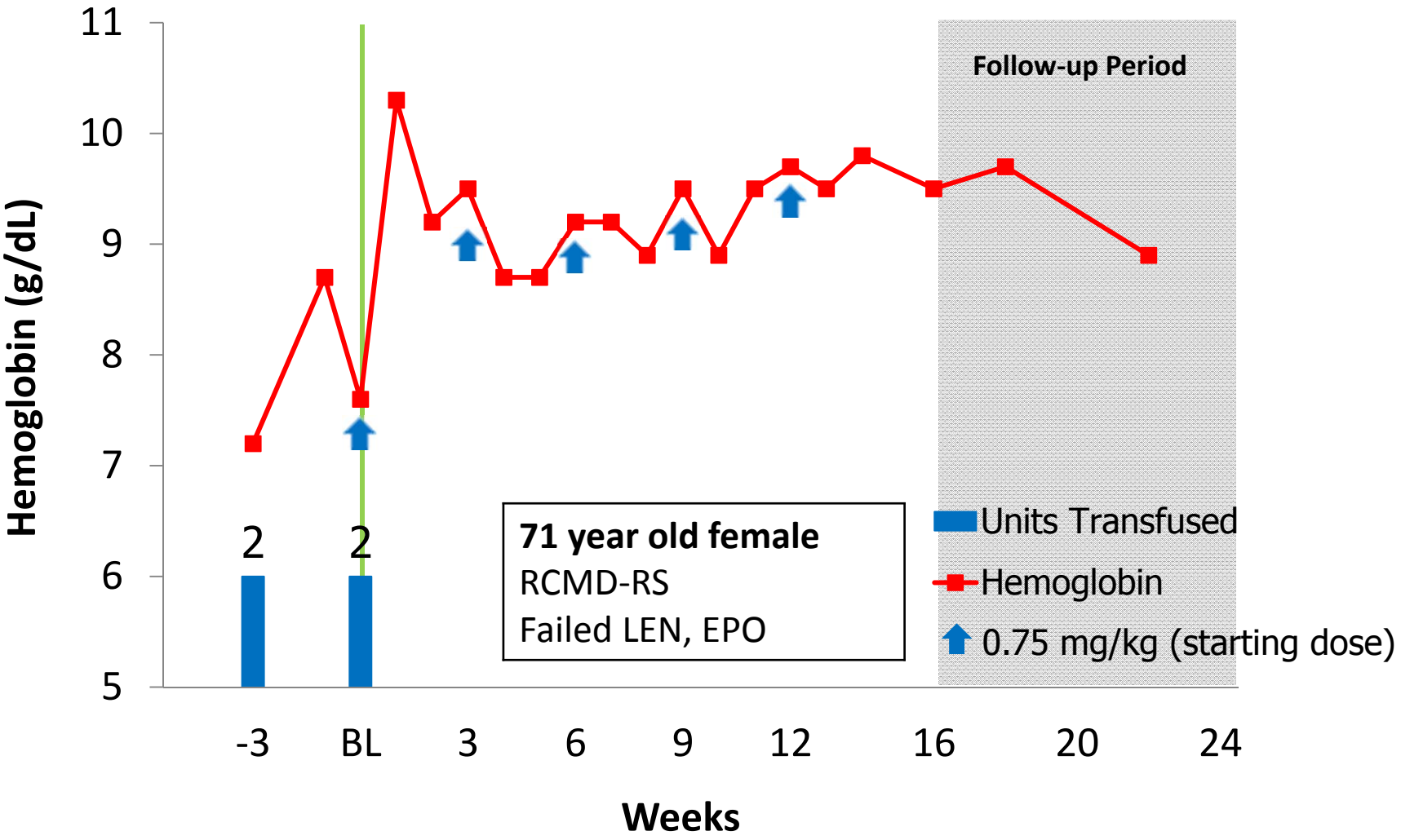
- 9/19 (47%) of patients received prior ESA treatment
- 5/19 (26%) of patients received prior lenalidomide treatment

RBC Transfusion Reduction over 8 Weeks	0.125-0.5 mg/kg N=7 n (%)	0.75-1.75 mg/kg N=12 n (%)
≥4 Units or ≥50%	3 (43%)	**5 (42%)**
≥4 Units (HI-E)	2 (29%)	**5 (42%)**
Transfusion Independence (TI)	1 (14%)	**3 (25%)**

HTB, high transfusion burden

Data as of 03 Oct 2014

HTB Responder (HI-E):d RBC Transfusions



HTB, high transfusion burden

Data as of 03 Oct 2014

Efficacy Summary: HI-E Response Rate

Patient Subgroup	0.125-0.5 mg/kg (N=9) n (%)	0.75-1.75 mg/kg (N=17) n (%)
LTB patients (N=7)	0/2 (0%)	**2/5 (40%)**
HTB patients (N=19)	2/7 (29%)	**5/12 (42%)**
All patients (N=26)	2/9 (22%)	**7/17 (41%)**

HI-E (IWG):
LTB: Hemoglobin increase ≥1.5 g/dL for ≥8 weeks
HTB: Reduction of ≥4 units RBCs transfused over 8 weeks

HI-E, hematologic improvement-erythroid
IWG, International Working Group
LTB, low transfusion burden; HTB, high transfusion burden

Data as of 03 Oct 2014

HI-E Response Rate by Ring Sideroblast Morphology, SF3B1 Mutation

Response Rate at Higher Dose Levels (0.75-1.75 mg/kg)

Baseline Status	Response Rate (HI-E) n (%)
All Patients (N=17)	7 (41%)
Ring Sideroblasts	
RS ≥15% (N=13)	7 (54%)
RS <15% (N=4)	0 (0%)
SF3B1 Mutation	
SF3B1 Mutation Present (N=9)*	6 (67%)**
SF3B1 Mutation Absent (N=8)	1 (13%)

* All 9 patients with SF3B1 mutation present had RS ≥15%
** Includes all 3 patients who became transfusion independent

Data as of 03 Oct 2014

Luspatercept PACE-MDS Study: Conclusions

- Luspatercept was safe and well tolerated for 3 months of treatment
- Erythroid response (HI-E, IWG) was achieved in 41% of patients treated at ≥0.75 mg/kg
  - Erythroid response (HI-E, IWG) was achieved in 67% of ring sideroblast (+) patients with SF3B1 mutations
- These data strongly support further evaluation of luspatercept in patients with lower-risk MDS

Luspatercept PACE-MDS Study: Acknowledgements

- German MDS Study Group (DMDS)
  - Principal Investigators: U. Platzbecker, U. Germing, A. Giagounidis, K. Goetze, P. Kiewe, K. Mayer, O. Ottman, M. Radsak, T. Wolff
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