Luspatercept Treatment Leads to Long Term Increases in Hemoglobin and Reductions in Transfusion Burden in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS): Preliminary Results from the Phase 2 PACE-MDS Extension Study

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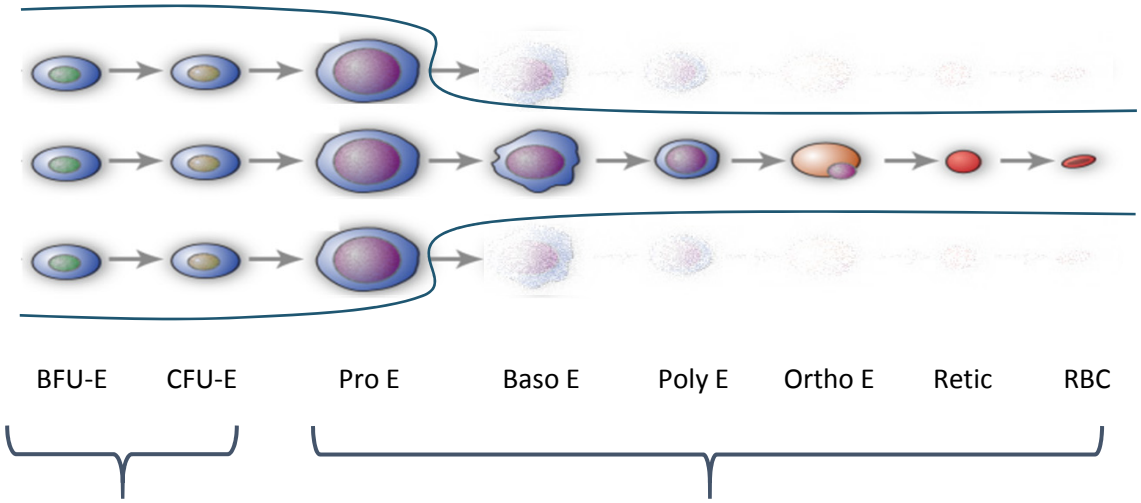
Ineffective Erythropoiesis in MDS

- Anemia, a hallmark of MDS, is a significant clinical challenge to treat, particularly after failure of ESAs[1]
- Defects in maturation of erythroid precursors (ineffective erythropoiesis) lead to erythroid hyperplasia and anemia
- Ineffective erythropoiesis is driven by excessive Smad2/3 signaling[2]



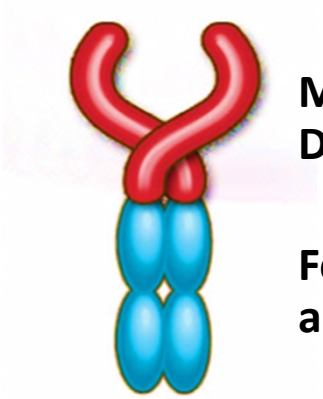
ESA: erythropoiesis stimulating agent; EPO: erythropoietin; GDF: growth and differentiating factor; RBC: red blood cell

1. *Fenaux P, et al. Blood. 2013;121:4280*
2. *Zhou L, et al. Blood 2008;112:3434*

Luspatercept (ACE-536) Activity in MDS

- Luspatercept, a modified activin receptor type IIB (ActRIIB) fusion protein, acts as a ligand trap for GDF11 and other TGF-β family ligands to suppress Smad2/3 activation; increased Hb in healthy volunteers[1]
- In a murine model of MDS, murine analog RAP-536 corrected ineffective erythropoiesis, reduced erythroid hyperplasia and increased Hb[2]

Luspatercept



Modified Extracellular Domain of ActRIIB receptor

Fc domain of human IgG_1 antibody

GDF: growth and differentiating factor; TGF: transforming growth factor
Hb: hemoglobin

1. *Attie, K et al. Am J Hematol 2014;89:766*
2. *Suragani R et al., Nat Med 2014;20:408*

Luspatercept Lower-Risk MDS Phase 2 Extension Study

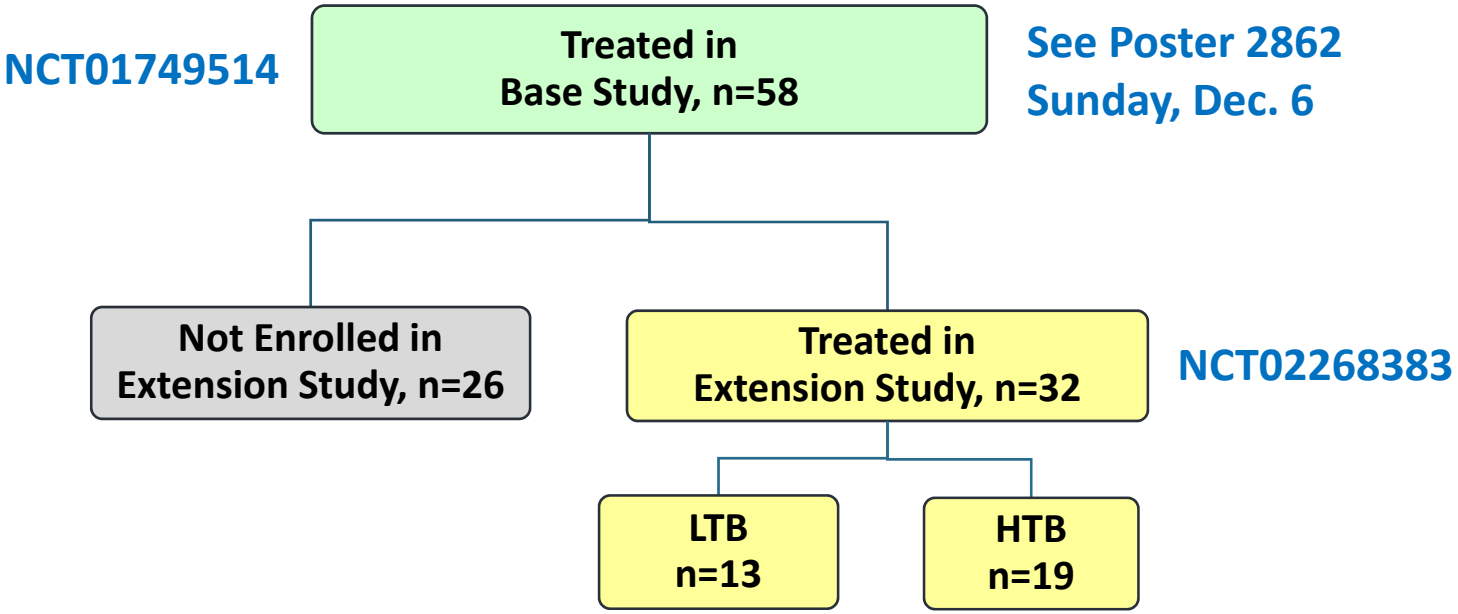
A phase 2, multicenter, open-label, 3-month dose escalation study in adults with lower-risk MDS, followed by a 24-month extension study

- **Eligibility**
  - EPO >500 U/L or ESA refractory/intolerant/unavailable
  - No prior azacitidine or decitabine
  - No current ESA, G-CSF, GM-CSF, lenalidomide
- **Efficacy endpoints (extension study)**
  - **LTB:** Low transfusion burden patients (< 4 Units/8 wk, Hb < 10 g/dL): **IWG HI-E:** Hb increase ≥ 1.5 g/dL for 8 weeks
  - **HTB:** High transfusion burden patients (≥ 4 Units/8 wk): **IWG HI-E:** ≥4 Unit decrease Units over 8 weeks
- **Other efficacy endpoints**
  - **RBC-TI:** RBC transfusion independence ≥ 8 weeks
  - Time to/duration of HI-E response
  - HI-N, HI-P, HR-QoL (FACT-An), PD and iron biomarkers

EPO: erythropoietin, ESA: erythropoiesis stimulating agent; G(M)-CSF: granulocyte (macrophage) colony-stimulating factor; HI-E/N/P: hematologic improvement erythroid/neutrophils/platelets; HR-QoL: health-related quality of life; PD: pharmacodynamic

Luspatercept Lower-Risk MDS Phase 2 Extension Study

- Subcutaneous (SC) injection every 3 weeks
- **Base study (n=58):** 3 months of treatment
  - Dose escalation phase (n=27): 0.125, 0.25, 0.5, 0.75, 1.0, 1.33, 1.75 mg/kg
  - 1st Expansion cohort (n=31): starting dose 1.0, titration up to 1.75 mg/kg
- **Extension study (n=32):** additional 24 months of treatment (ongoing)
  - Starting dose 1.0 mg/kg or current dose, titration up to 1.75 mg/kg



LTB: Low transfusion burden patients (< 4 Units/8 wk, Hb <10 g/dL)

HTB: High transfusion burden patients (≥ 4 Units/8 wk)

Data as of 31 Aug 2015

Baseline Characteristics – Patients in Extension Study

Parameter	N=32
Age, yr, median (range)	71.5 (29-90)
Sex, male, n (%)	22 (69%)
Time since diagnosis, yr, median (range)	2.9 (0-14)
Prior lenalidomide treatment, n (%)	6 (19%)
Prior ESA treatment, n (%)	19 (59%)
Baseline EPO	
<200 U/L	20 (63%)
200-500 U/L	7 (22%)
>500 U/L	5 (16%)
RS+ (ring sideroblast ≥ 15%)	29 (91%)
SF3B1 mutation	23 (72%)
LTB Patients (n=13)	
Hemoglobin, g/dL, median (range)	8.5 (6.4-10.1)
HTB Patients (n=19)	
Transfusions, Units/8 wk, median (range)	6 (4-14)

LTB: Low transfusion burden patients (< 4 Units/8 wk, Hb <10 g/dL)

HTB: High transfusion burden patients (≥ 4 Units/8 wk)

Data as of 31 Aug 2015

Baseline Characteristics – WHO, IPSS(-R)

Category	N=32 n (%)
WHO Subtypes	
RARS	8 (25%)
RCMD-RS	19 (59%)
RCMD	2 (6%)
RAEB-1	3 (9%)
IPSS	
Low	22 (69%)
Int-1	10 (31%)
IPSS-R	
Very Low	9 (28%)
Low	14 (44%)
Intermediate	8 (25%)
High	1 (3%)

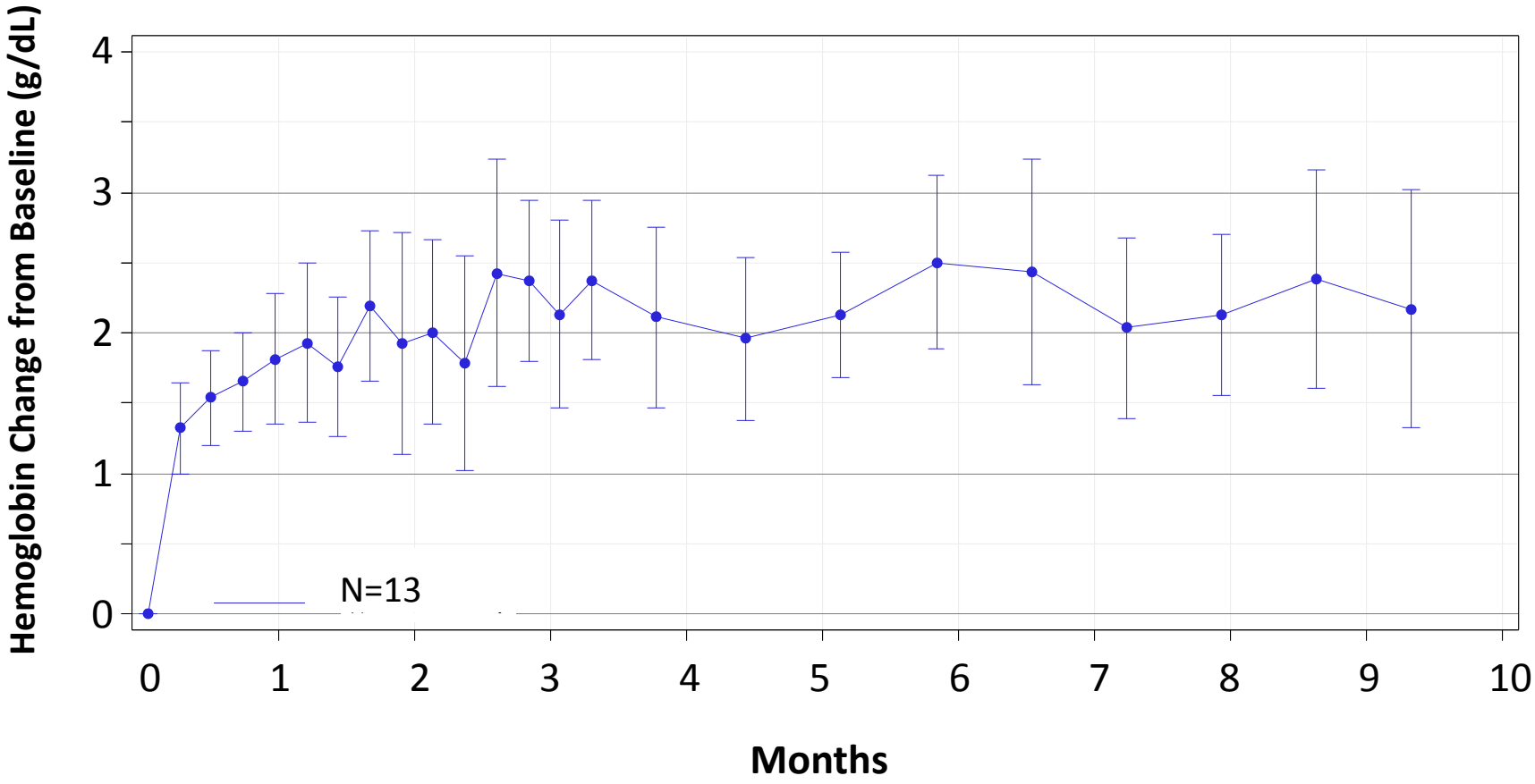
LTB: Low transfusion burden patients (< 4 Units/8 wk, Hb <10 g/dL)

HTB: High transfusion burden patients (≥ 4 Units/8 wk)

Data as of 31 Aug 2015

Increase in Mean (SE) Hemoglobin in LTB Patients

- 69% (9/13) LTB patients achieved IWG HI-E response for mean Hb increase



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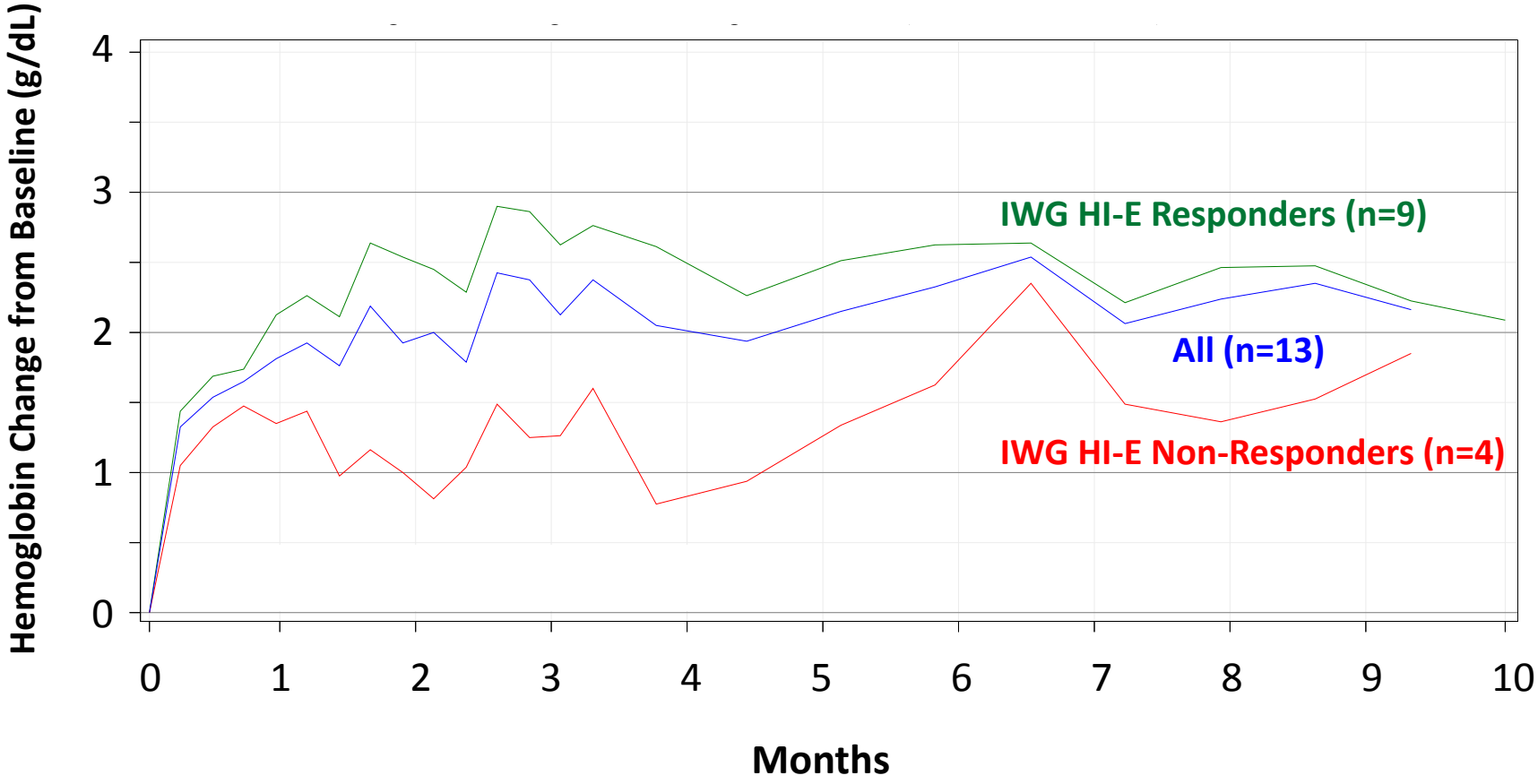
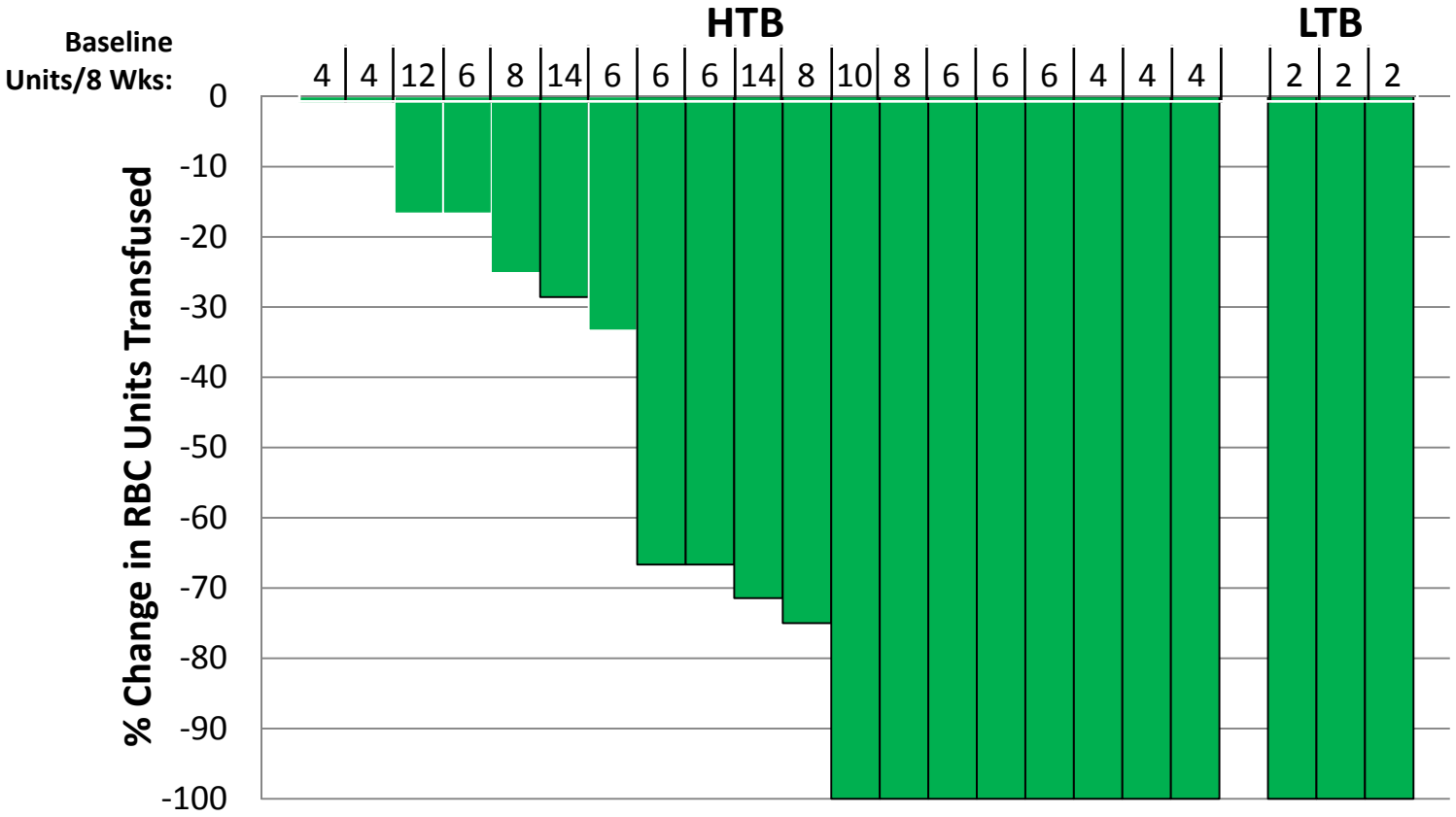


LTB: Low transfusion burden patients (< 4 Units/8 wk, Hb < 10 g/dL)

Data as of 31 Aug 2015

Reduction in Transfusion Burden in HTB Patients

- 68% (13/19) HTB patients achieved IWG HI-E
- 42% (8/19) HTB patients achieved RBC transfusion independence (TI)
  - An additional 3/3 (100%) LTB patients with 2 Units/8 wks achieved RBC-TI



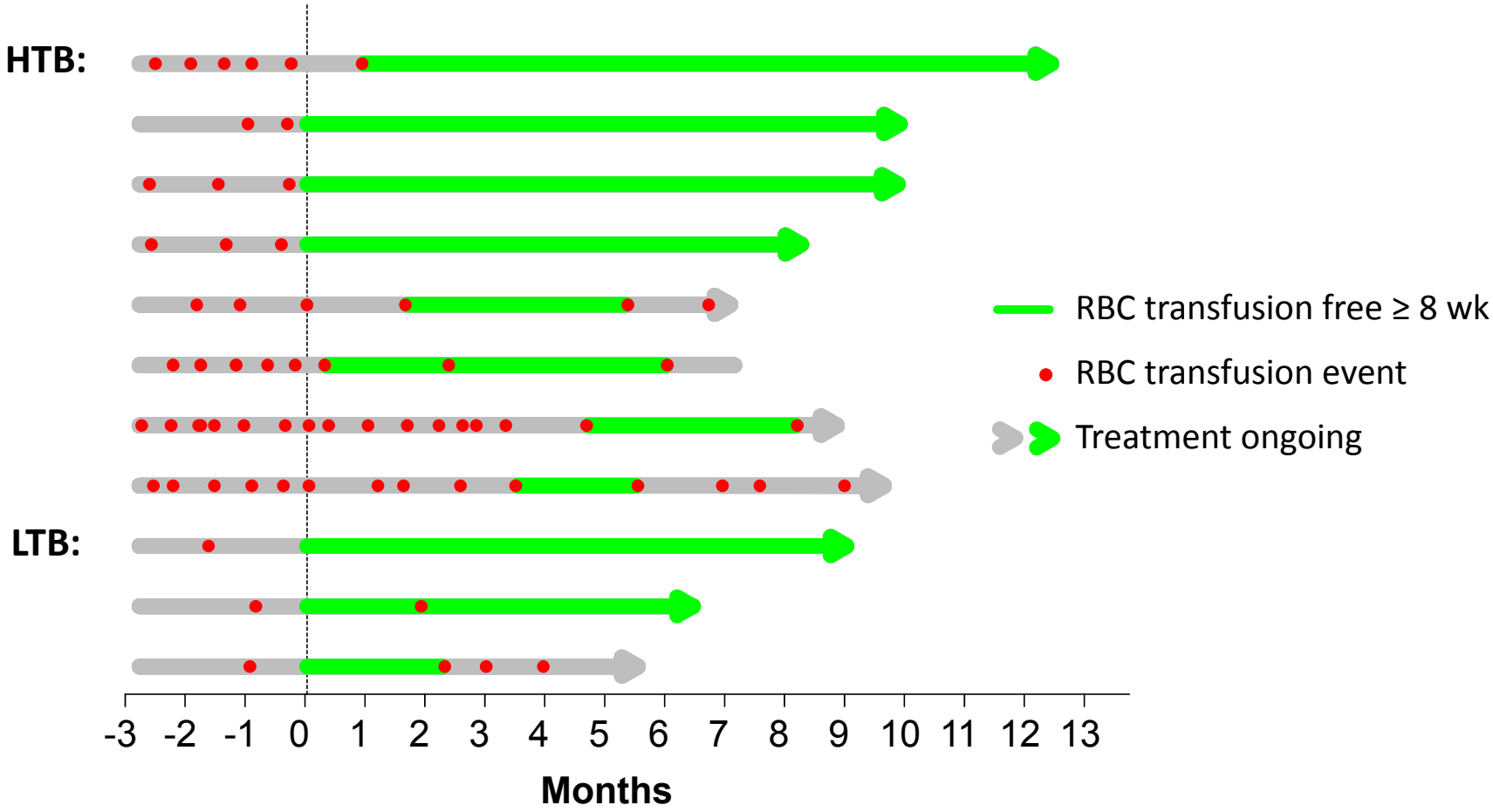
LTB: Low transfusion burden patients (< 4 Units/8 wk, Hb <10 g/dL)

HTB: High transfusion burden patients (≥ 4 Units/8 wk)

Data as of 31 Aug 2015

Duration of Transfusion Independence in RBC-TI Responders

- 50% (11/22*) patients who were transfused prior to study achieved RBC transfusion independence (TI) ≥ 8 weeks (range 9-50+ weeks)



* Includes 19 HTB patients and 3 LTB patients evaluable for transfusion independence

Data as of 31 Aug 2015

Response Rates by Baseline Characteristics

- Majority of patients in extension study were RS+; ≥ 50% patients responded to luspatercept who had EPO up to 500 I/U or prior ESA treatment

n (%)	IWG HI-E N=32	RBC-TI* N=22
All Patients	22/32 (69%)	11/22 (50%)
RS positive	21/29 (72%)	10/19 (53%)
Baseline EPO		
< 200 U/L	16/20 (80%)	7/13 (54%)
200-500 U/L	5/7 (71%)	2/4 (50%)
> 500 U/L	1/5 (20%)	2/5 (40%)
Prior ESA Treatment		
Yes	12/19 (63%)	7/14 (50%)
No	10/13 (77%)	4/8 (50%)

* **RBC-TI:** RBC transfusion independent ≥ 8 weeks; includes 19 HTB patients and 3 LTB patients evaluable for transfusion independence (at least 2 Units over 8 weeks pre-treatment)

Data as of 31 Aug 2015

Safety Summary - Patients in Extension Study

- No serious or grade 3 or 4 adverse events related to study drug reported during the extension study
- 7/32 (22%) patients discontinued early: patient request (n=3), lack of effect (n=2), progression (n=1), death (n=1)

Adverse events at least possibly related to study drug during the extension study (N=32)

Preferred Term	No. Patients (%)
At least 1 related AE	3 (9.4)
Bone pain	1 (3.1)
Headache	1 (3.1)
Hypotonia	1 (3.1)
Myalgia	1 (3.1)
Nausea	1 (3.1)

Data as of 31 Aug 2015

Conclusions

- Lower risk MDS patients treated with luspatercept demonstrated a robust hematologic improvement per IWG HI-E and reduced transfusion burden
- Luspatercept was generally safe and well-tolerated
- Treatment for up to 1 year demonstrated sustained increases in hemoglobin and prolonged transfusion independence
- Patients who were refractory to prior ESA or had serum EPO up to 500 U/L responded particularly well to luspatercept treatment
- These results support the initiation of Phase 3 studies of luspatercept in patients with lower-risk MDS (MEDALIST)

Data as of 31 Aug 2015

The MEDALIST Study

Phase 3 Study of Luspatercept in MDS

Patient Population / Study Design	Randomized, double-blind, placebo-controlled study in very low, low or intermediate risk (IPSS-R) MDS patients with ring sideroblasts (RS+) who require RBC transfusion 210 patients randomized 2:1; luspatercept 1 mg/kg SC every 3 weeks, titration up to 1.75 mg/kg possible
Key Inclusion Criteria	Refractory / intolerant to prior ESA *or* EPO > 200 U/L RS+; <5% blasts; no prior HMA or lenalidomide ≥ 2 units RBCs transfused / 8 weeks Excluded: del(5q), secondary MDS
Primary Efficacy Endpoint	Proportion of patients that become RBC-transfusion independent (≥ 8 weeks) during the first 24 weeks

Sponsored by Celgene

Luspatercept PACE-MDS Study: Acknowledgements

- **German MDS Study Group (D-MDS)**
  - Principal Investigators: U. Platzbecker, U. Germing, A. Giagounidis, K. Goetze, P. Kiewe, K. Mayer, O. Ottmann, M. Radsak, T. Wolff, J. Chromik
  - Sub-Investigators: K. Sockel, K. Trautmann-Grill, J. Middeke, C. Müller-Thomas, F. Crespo, S. Gröpper, G. Bug, F. Lang, L. Wunderle, V. Janzen, J. Alt, J. Beck, G. Heß, T. Kindler, T. Wehler, D. Sasca, A. Kündgen, J. Neukirchen, O. Knigge, A. Kirsch, V. Böhme, A. Mohr, U. Brandl, J. Heiders, D. Leven-Tietze
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