LUSPATERCEPT INCREASES HEMOGLOBIN AND REDUCES TRANSFUSION BURDEN IN PATIENTS WITH LOW-INTERMEDIATE RISK MYELODYSPLASTIC SYNDROMES (MDS): LONG-TERM RESULTS FROM PHASE 2 PACE-MDS STUDY

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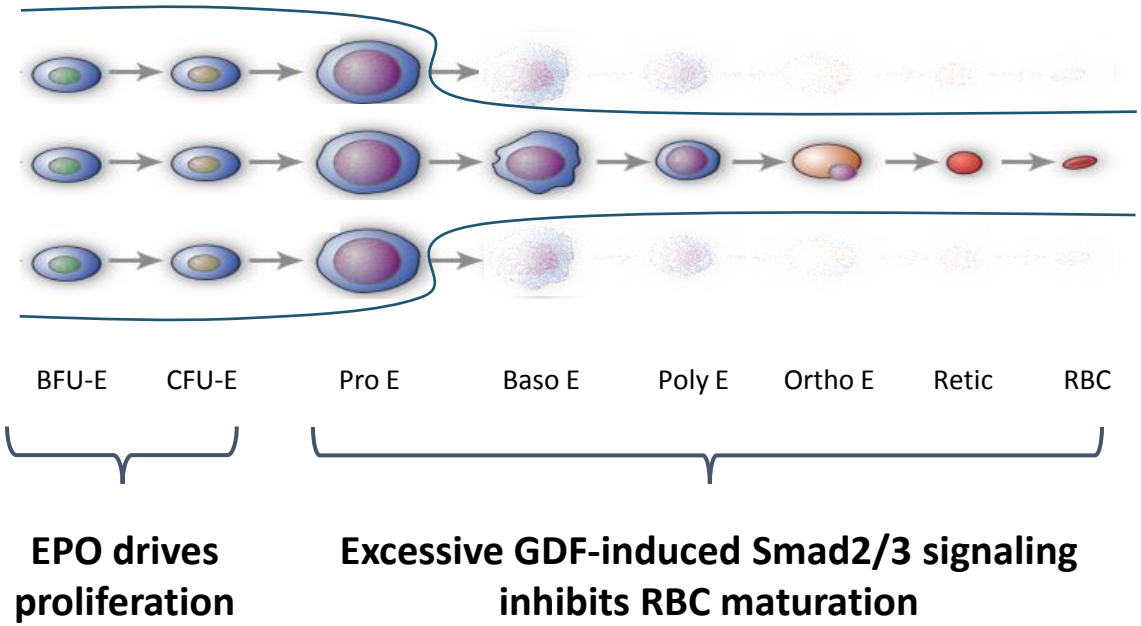
Ineffective Erythropoiesis in MDS

- 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]



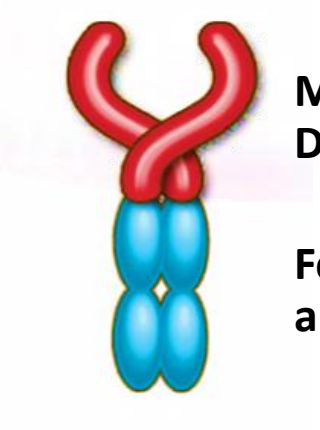
ESA: erythropoiesis stimulating agent; EPO: erythropoietin; GDF: growth and differentiating factor; RBC: red blood cell

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 signaling; increased hemoglobin in healthy volunteers[1]
- In a murine model of MDS, murine analog RAP-536 corrected ineffective erythropoiesis, reduced erythroid hyperplasia and increased hemoglobin[2]

Luspatercept



Modified Extracellular Domain of ActRIIB receptor

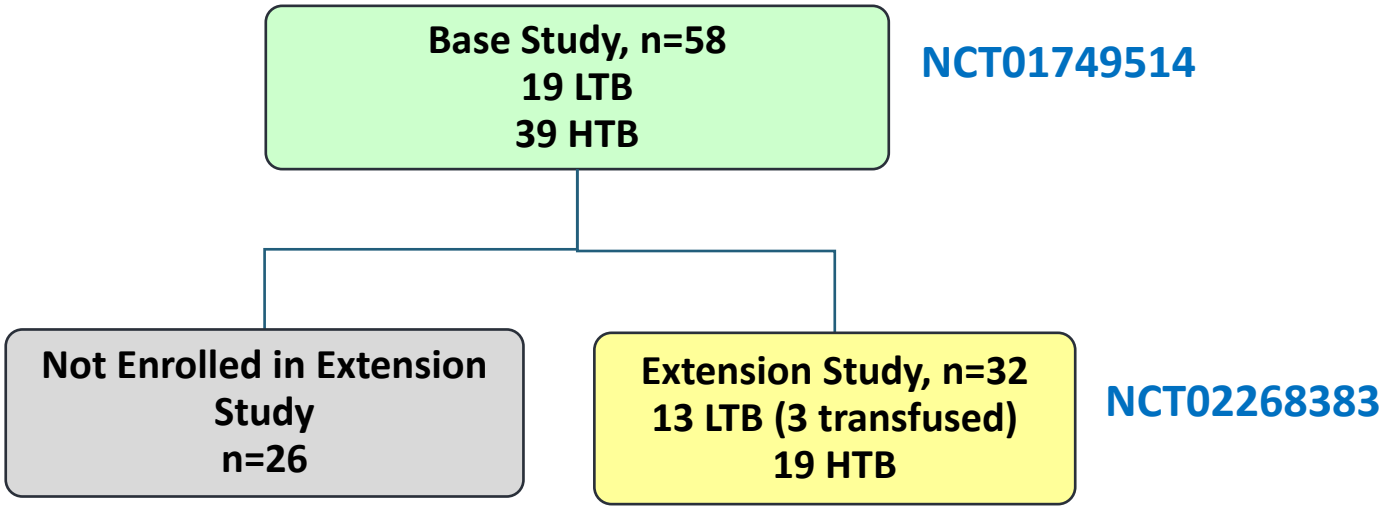
Fc domain of human IgG_1 antibody

GDF: growth and differentiating factor
TGF: transforming growth factor

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

- Subcutaneous (SC) injection every 3 weeks
- **Base study (n=58):** 3 months of treatment
  - Dose escalation phase (n=27)
    - Lower dose levels: 0.125, 0.25, 0.5 mg/kg
    - Higher dose levels: 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): 1.0-1.75 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 04 Mar 2016

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
  - Completed 3-month base study
- **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 all values over 8 weeks
  - **HTB:** High transfusion burden patients (≥ 4 Units/8 wk):
    IWG HI-E: ≥ 4 Unit decrease 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; HI-E/N/P: hematologic improvement erythroid/neutrophils/platelets; HR-QoL: health-related quality of life; PD: pharmacodynamic

Demographics and Baseline Characteristics

Parameter	Base Study N=58	Extension Study N=32
Age, yr, median (range)	71.5 (27-90)	71.5 (29-90)
Sex, male, n (%)	34 (59%)	22 (69%)
Time since diagnosis, yr, median (range)	2.4 (0-14)	2.9 (0-14)
Prior lenalidomide treatment, n (%)	10 (17%)	6 (19%)
Prior ESA treatment, n (%)	38 (66%)	19 (59%)
Baseline EPO		
<200 U/L	28 (48%)	19 (59%)
200-500 U/L	13 (22%)	7 (22%)
>500 U/L	17 (29%)	6 (19%)
RS+ (ring sideroblast ≥ 15%)	45 (78%)	29 (91%)
SF3B1 mutation	33 (57%)	23 (72%)
LTB Patients	**n=19**	**n=13**
Hemoglobin, g/dL, median (range)	8.7 (6.4-10.1)	8.5 (6.4-10.1)
HTB Patients	**n=39**	**n=19**
Transfusions, Units/8 wk, median (range)	6 (4-18)	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 04 Mar 2016

Baseline MDS Categories – WHO, IPSS(-R)

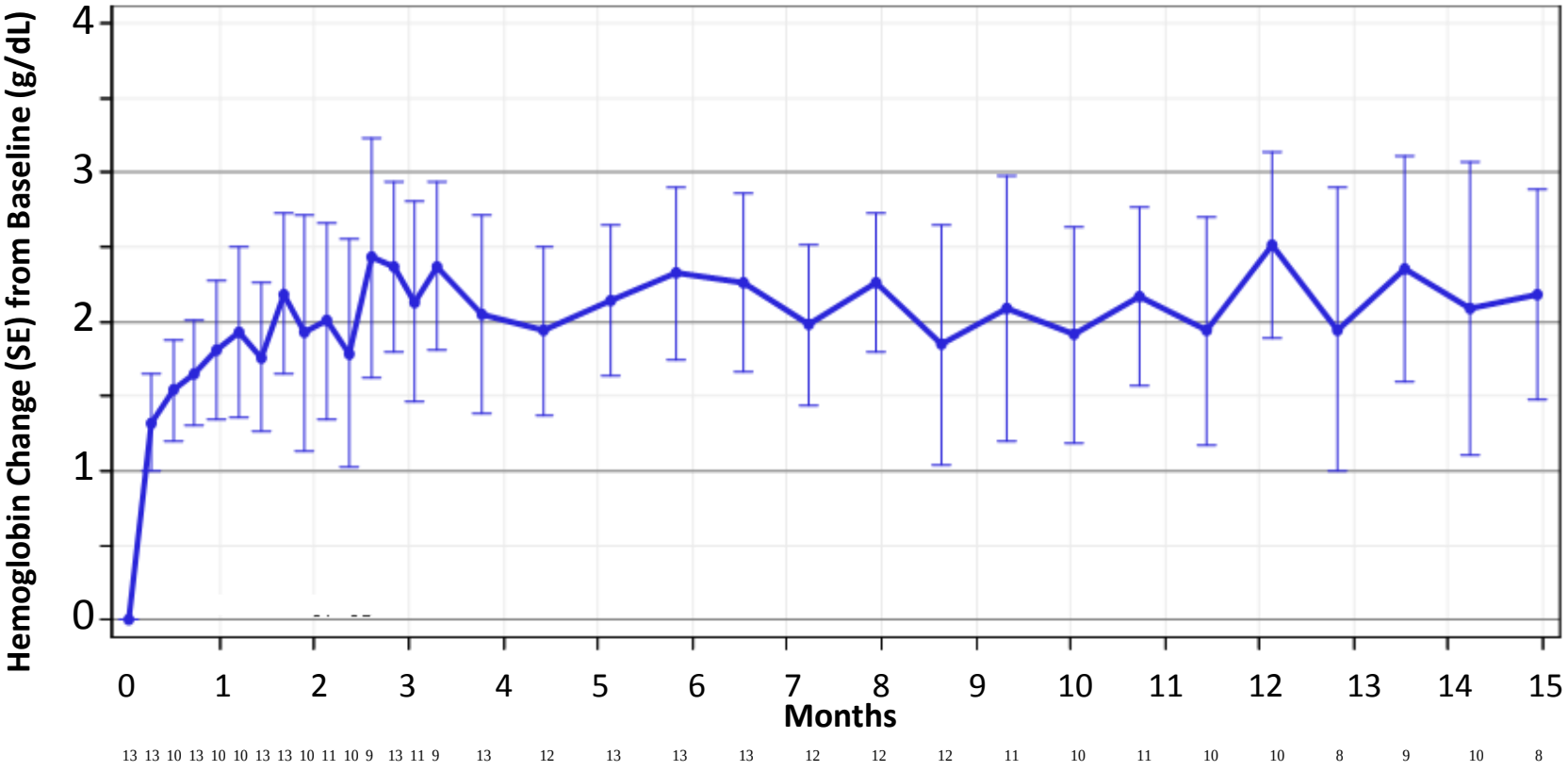
Category n (%)	Base Study N=58	Extension Study N=32
WHO Subtypes		
RARS	11 (19%)	6 (19%)
RCMD-RS	29 (50%)	21 (66%)
RCMD	6 (10%)	2 (6%)
RAEB-1	8* (14%)	3** (9%)
Other (RAEB-2, del(5q), MDS/MPN)	4 (7%)	0
IPSS		
Low	27 (47%)	18 (56%)
Int-1	30 (52%)	14 (44%)
Int-2	1 (2%)	0
IPSS-R		
Very Low	1 (2%)	1 (3%)
Low	31 (53%)	20 (63%)
Intermediate	22 (38%)	10 (31%)
High	3 (5%)	1 (3%)
Very High	1 (2%)	0

* 5 patients RS+

**2 patients RS+

Data as of 04 Mar 2016

Increase in Mean Hemoglobin in LTB Patients with > 3 Months of Treatment (Extension Study)

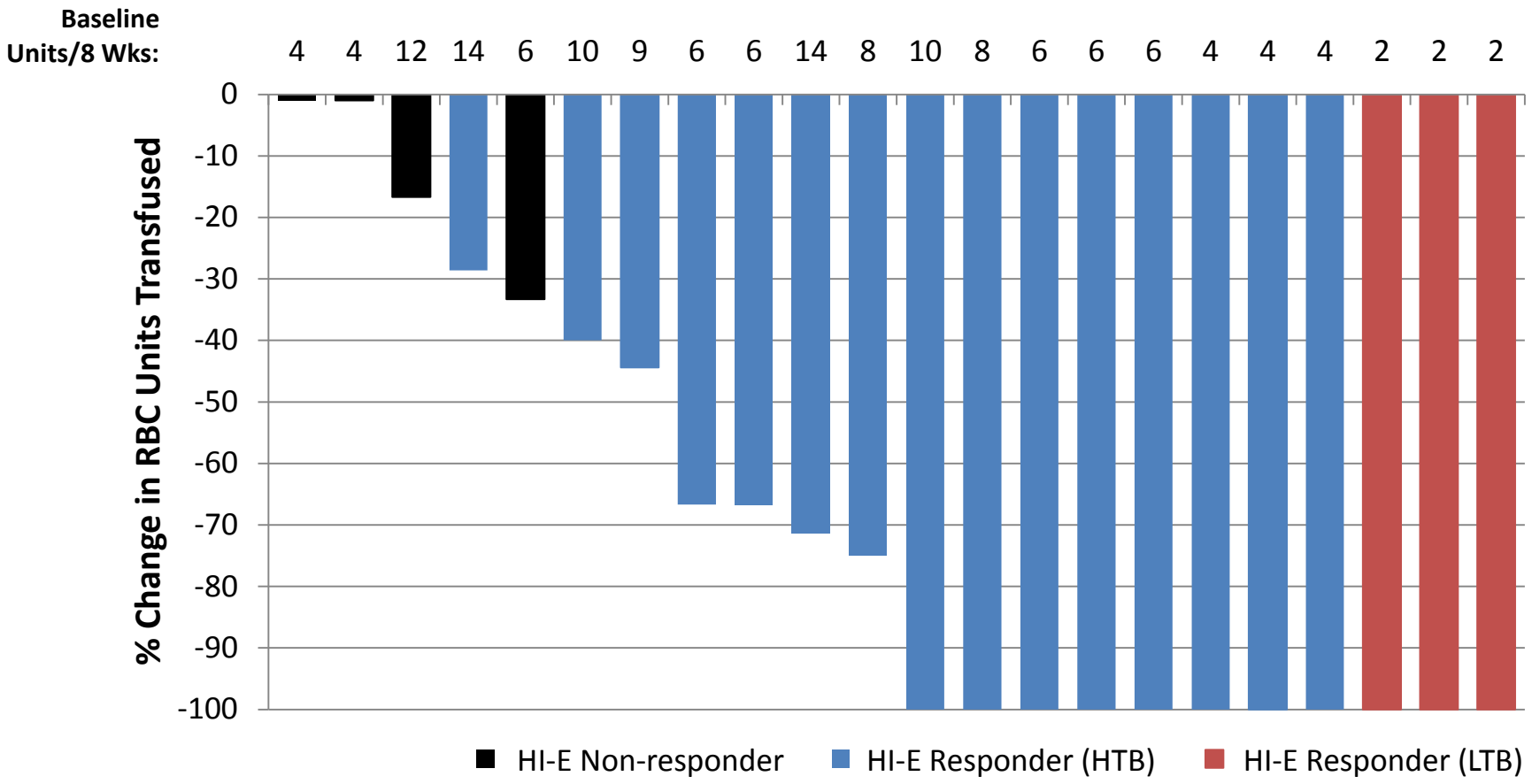


- 11/13 (85%) HI-E responders; median time to response: 6 weeks

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

Data as of 04 Mar 2016

Reduction in Transfusion Burden in Patients with > 3 Months of Treatment (Extension Study, N=22)



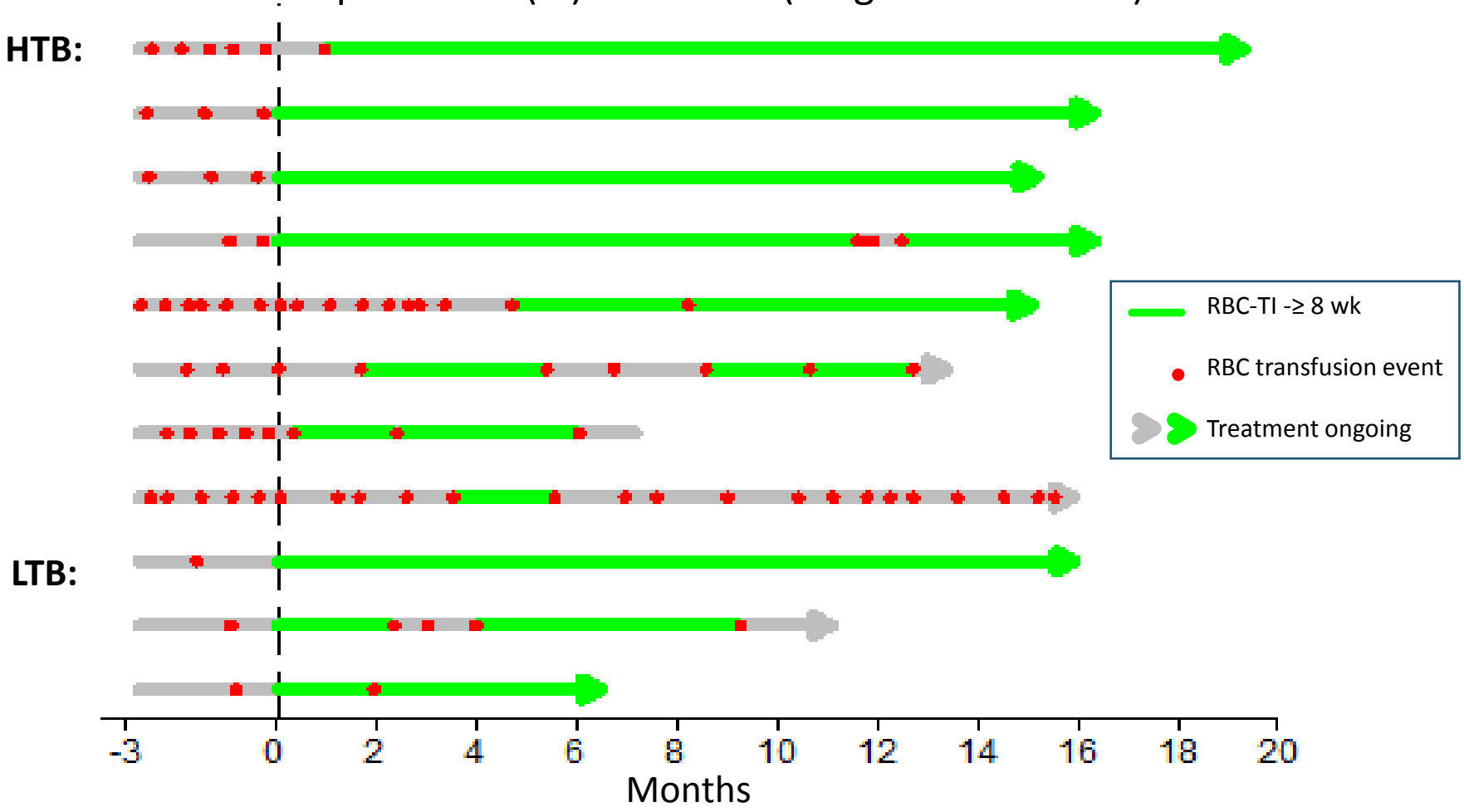
- 15/19 (79%) HTB patients were HI-E responders (≥ 4 unit decrease /8 wk)

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 04 Mar 2016

Duration of Transfusion Independence in RBC-TI Responders with > 3 Months Treatment (Extension Study, N=11/22)

- 50% (11/22*) patients who were transfused prior to study achieved RBC transfusion independence (TI) ≥ 8 weeks (range 9-80+ weeks)



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

Data as of 04 Mar 2016

Erythroid Response by IWG HI-E

Category	IWG HI-E (n, % of Patients) Patients treated at higher dose levels	
	Base Study N=49	Extension Study N=32
All Patients	**25/49 (51%)**	**26/32 (81%)**
RS positive	23/40 (58%)	24/29 (83%)
Baseline EPO		
< 200 U/L	17/25 (68%)	17/19 (90%)
200-500 U/L	4/11 (36%)	6/7 (86%)
> 500 U/L	4/13 (31%)	3/6 (50%)
Prior ESA Treatment		
Yes	17/35 (49%)	15/19 (79%)
No	8/14 (57%)	11/13 (85%)

Data as of 04 Mar 2016

RBC Transfusion Independence (RBC-TI)

Category	RBC-TI* (n, % of Patients) Transfused patients treated at higher dose levels	
	Base Study N=40	Extension Study N=22
All Patients	**14/40 (35%)**	**11/22 (50%)**
RS positive	12/31 (39%)	10/19 (53%)
Baseline EPO		
< 200 U/L	10/18 (56%)	7/12 (58%)
200-500 U/L	3/9 (33%)	2/4 (50%)
> 500 U/L	1/13 (8%)	2/6 (33%)
Prior ESA Treatment		
Yes	10/29 (35%)	7/14 (50%)
No	4/11 (36%)	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 04 Mar 2016

Safety Summary – Adverse Events
Base and Extension Studies, All Patients

- Majority of adverse events (AEs) were grade 1 or 2
- Three related* grade 3 AEs: blast cell count increase, myalgia, worsening of general condition
- Favorable safety profile for luspatercept in patients with MDS was maintained in long-term extension study

Related* adverse events in ≥ 2 patients, (N=58)

Preferred Term	No. Patients (%)
Fatigue	4 (7%)
Bone pain	3 (5%)
Diarrhoea	3 (5%)
Myalgia	3 (5%)
Headache	2 (3%)
Hypertension	2 (3%)
Injection site erythema	2 (3%)

*Possibly or probably related

Data as of 04 Mar 2016

Conclusions

- Lower risk MDS patients treated with luspatercept demonstrated a robust hematologic improvement per IWG HI-E and a high rate of transfusion independence
- Luspatercept was generally safe and well-tolerated in these studies
- Patients demonstrated sustained increases in hemoglobin and durable transfusion independence
- Responses observed regardless of prior ESA status and across a range of baseline EPO levels
- These results supported the initiation of a Phase 3 study of luspatercept in patients with lower-risk MDS (MEDALIST)

Data as of 04 Mar 2016

The MEDALIST Study

Phase 3 Study of Luspatercept in MDS: NOW ENROLLING

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

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NCT02631070

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, J. Chromik, M. Radsak, T. Wolff, J. Chromik
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- **Acceleron:** K. Attie, M. Sherman, M. Hankin, D. Wilson, E. Donovan, X. Zhang, C. Rovaldi, B. O'Hare, T. Akers, J. Desiderio, T. Sacco, S. Ertel
- **Celgene:** A. Laadem, S. Ritland, J. Zhang, N. Chen
- **Chiltern:** C. Lanza, F. VanderSchueren
- **Central Labs:** CRL, ICON, Genoptix, ILS
- **Central Labs (Bone Marrow):** A. Giagounidis, D. Haase, H. Kreipe, U. Oelschlägel

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