LUSPATERCEPT INCREASES HEMOGLOBIN AND REDUCES TRANSFUSION BURDEN IN PATIENTS WITH LOW OR INTERMEDIATE-1 RISK MYELODYSPLASTIC SYNDROMES (MDS): PRELIMINARY RESULTS FROM A PHASE 2 STUDY

Uwe Platzbecker, MD

U Platzbecker[1], U Germing[2], A Giagounidis[3], K Goetze[4], P Kiewe[5], K Mayer[6], O Ottman[7], M Radsak[8], T Wolff[9], D Haase[10], M Hankin[11], D Wilson[11], A Laadem[12], M Sherman[11] and K Attie[11]

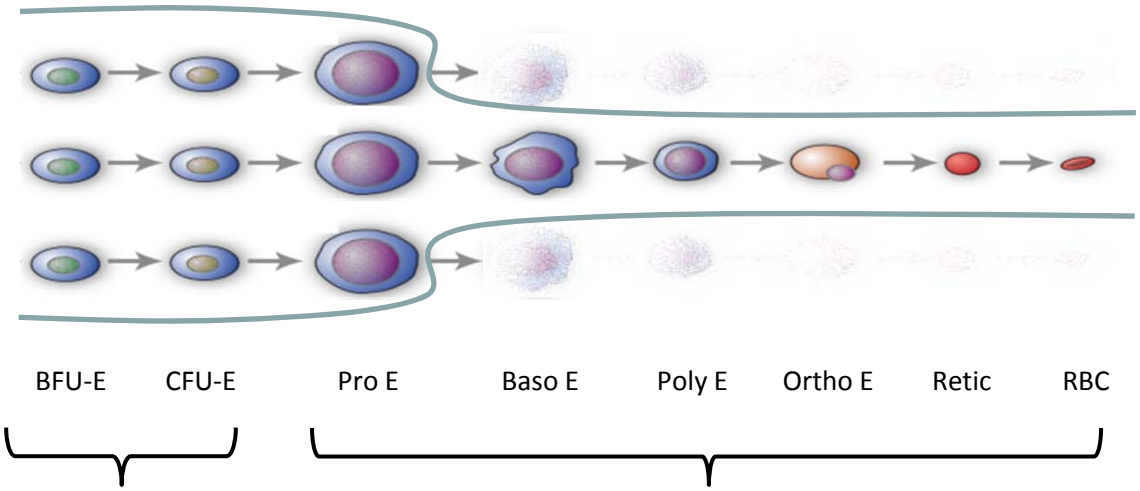
[1]Universitätsklinikum Carl Gustav Carus, Dresden; [2]Universitätsklinikum Düsseldorf; [3]Marien Hospital Düsseldorf; [4]Technical University of Munich; [5]Onkologischer Schwerpunkt am Oskar-Helene-Heim, Berlin; [6]Universitätsklinikum Bonn; [7]Klinikum der J.W. Goethe-Universität Frankfurt; [8]University Medical Center - Johannes Gutenberg-Universität, Mainz; [9]OncoResearch Lerchenfeld UG, Hamburg; [10]Department of Hematology and Medical Oncology, University Medicine of Göttingen, Germany; [11]Acceleron Pharma, Cambridge, MA; [12]Celgene Corporation, Summit, NJ, USA

Study supported by Acceleron and Celgene

D·MDS
Deutsche MDS-Studiengruppe

Ineffective Erythropoiesis in MDS

- Anemia, a hallmark of MDS, is challenging 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]



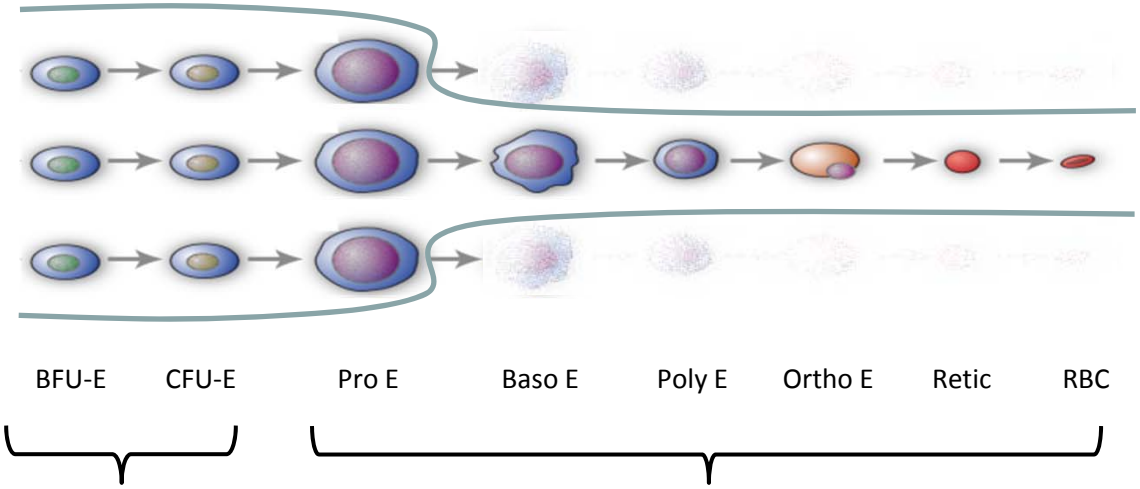
High EPO levels drive proliferation

Excessive GDF-induced Smad2/3 signaling inhibits RBC maturation

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

Luspatercept Activity in MDS

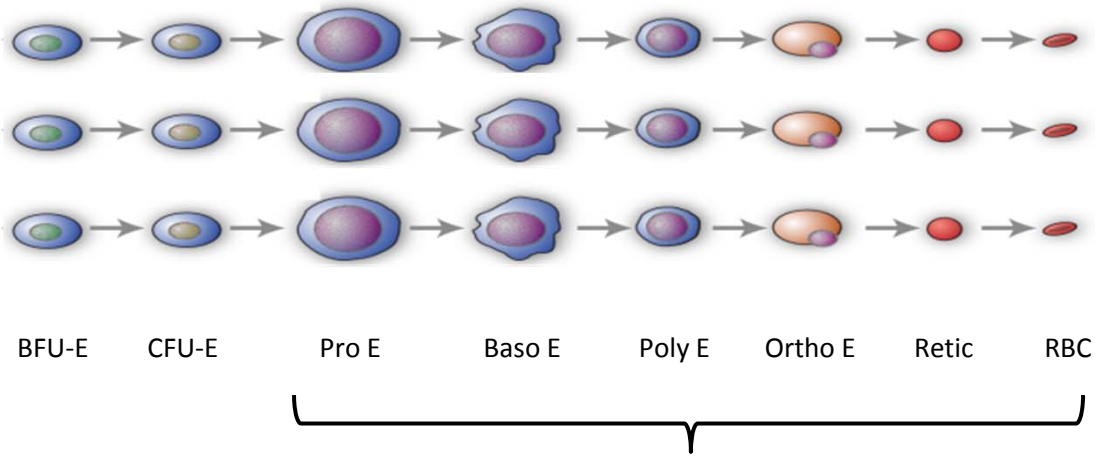
- Luspatercept, a modified activin receptor type IIB (ActRIIB) fusion protein, acts as a ligand trap for GDF11 and other ligands of the TGF-β superfamily to suppress Smad2/3 activation and increases Hgb in healthy volunteers[1]
- In a murine model of MDS, RAP-536 (murine analog of luspatercept) corrects ineffective erythropoiesis, reduces erythroid hyperplasia and increases hemoglobin[2]



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

Luspatercept Activity in MDS

- Luspatercept, a modified activin receptor type IIB (ActRIIB) fusion protein, acts as a ligand trap for GDF11 and other ligands of the TGF-β superfamily to suppress Smad2/3 activation and increases Hgb in healthy volunteers[1]
- In a murine model of MDS, RAP-536 (murine analog of luspatercept) corrects ineffective erythropoiesis, reduces erythroid hyperplasia and increases hemoglobin[2]



Luspatercept promotes differentiation and maturation by trapping Smad2/3 activating ligands

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

Luspatercept PACE-MDS 3-Month Treatment Study Overview

- Phase 2, multicenter, open-label, dose-finding, 3-month treatment study in IPSS low/int-1 MDS
- Key eligibility criteria:
  - Nonresponsive/refractory to ESA or EPO >500 U/L
  - 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

NCT01749514
EudraCT 2012-002523-14

3-Month Treatment Study Enrollment

- Enrollment in the dose escalation and expansion is complete (N=58)
  - **Dose escalation, N=27,** in 7 sequential cohorts, n=3-6 each, luspatercept dose level ranging from 0.125 to 1.75 mg/kg, subcutaneously, every 3 weeks
  - **Expansion, N=31,** starting dose 1.0 mg/kg, individual dose titration up to 1.75 mg/kg
- Preliminary results for 49 patients (N=27 dose escalation, N=22 expansion) are presented

	Dose Escalation							Expansion
Dose Level (mg/kg)	0.125	0.25	0.50	0.75	1.0	1.33	1.75	1.0*
No. of patients	3	3	3	6	3	6	3	22

* Starting dose level; dose level increased to 1.33 mg/kg in 8 patients and to 1.75 mg/kg in 2 patients

Data as of 17 Apr 2015

Baseline Characteristics (1 of 2)

	N=49	
Age, yr, median (range)	71 (27-88)	
Sex, male, n (%)	27 (55%)	
Prior ESA treatment, n (%)	30 (61%)	
Prior lenalidomide treatment, n (%)	9 (18%)	
Time since diagnosis, yr, median (range)	2.8 (0.2-13.6)	
Hemoglobin, g/dL, LTB patients, median (range)	8.7 (6.8-10.1) (n=17)	
Units RBC transfused/8 weeks in patients who received transfusions, median (range)	LTB (n=6) 2 (2-2)	HTB (n=32) 6 (4-14)

Data as of 17 Apr 2015

Baseline Characteristics (2 of 2)

Patient Subgroup	N = 49 n (%)
IPSS	
Low	27 (55%)
Int-1	21 (43%)
Int-2	1 (2%)
IPSS-R	
Very Low	2 (4%)
Low	30 (61%)
Intermediate	14 (29%)
High	3 (6%)
Ring Sideroblast (RS)	**N=48**
RS positive (≥15% of cells)	40 (83%)
SF3B1 mutation present*	29 (73%)
SF3B1 mutation absent	10 (25%)
RS negative (<15% of cells)	8 (17%)

* One patient was not evaluable for SF3B1

Data as of 17 Apr 2015

Dose-Dependent Erythroid Response and Transfusion Independence

Response Criteria	0.125-0.5 mg/kg N=9 n (%)	0.75-1.75 mg/kg N=40 n (%)
Primary efficacy endpoint	3 (33%)	23 (58%)
IWG HI-E	2 (22%)	19 (48%)
Transfusion independence (TI)	1/7 (14%)	11/30 (37%) LTB 4/6 HTB 7/24

- 10 of the 11 TI patients in the higher dose groups had onset within the first 6 weeks of treatment

Transfusion Independence: Transfusion-free for ≥ 8 weeks on treatment for patients who received at least 2 RBC units pre-treatment

Data as of 17 Apr 2015

Enriched Response in RS+ and mSF3B1 Sub-groups in Higher Dose Groups

Patient Population	IWG HI-E
All Patients	19/40 (48%)
RS* positive	19/35 (54%)
EPO < 200	14/23 (61%)
EPO ≥ 200	5/12 (42%)
RS negative	0/4 (0%)
SF3B1 mutation* present	16/26 (62%)
SF3B1 mutation absent	3/13 (23%)

RS: Ring sideroblast; positive if ≥15% of erythroid precursors in bone marrow
Epo: Serum erythropoietin (mU/mL)
SF3B1: Splicing factor 3B1
Higher Dose Groups: 0.75-1.75 mg/kg

* One patient not evaluable

Data as of 17 Apr 2015

Safety Summary for 3-Month Treatment Study

Adverse events (all grades) reported in ≥ 4 patients, regardless of causality

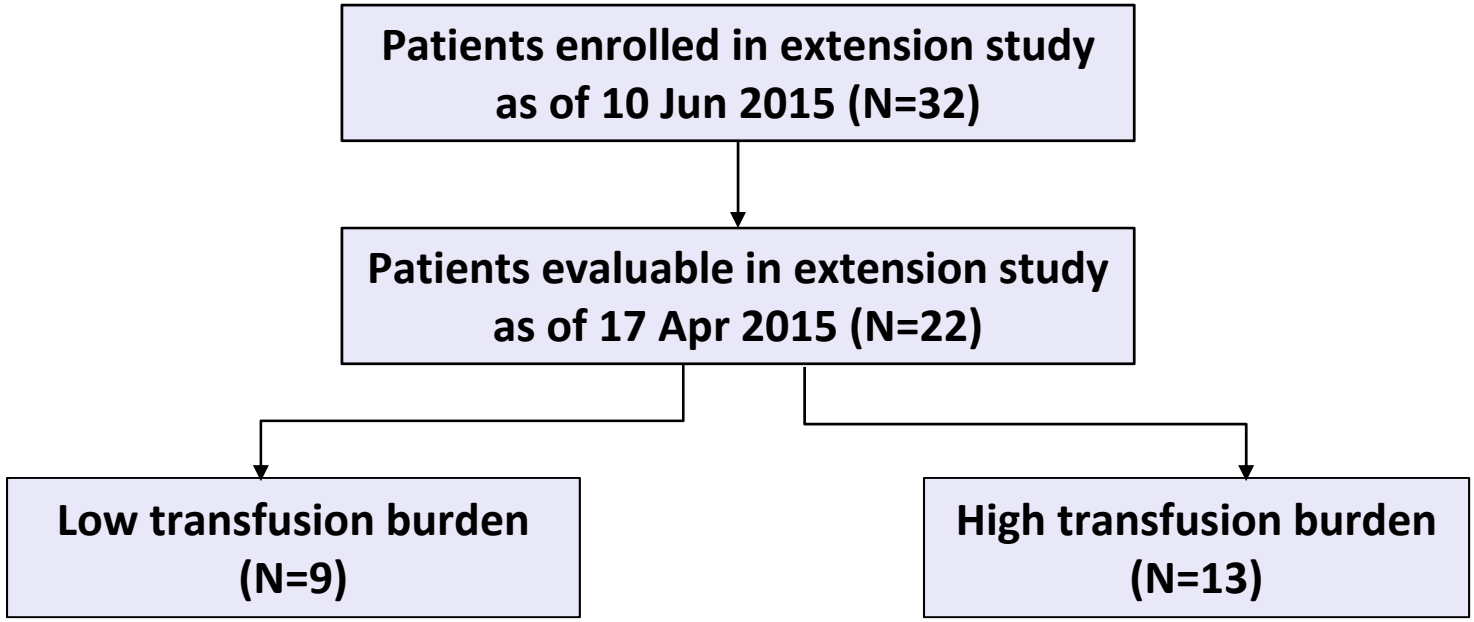
Preferred Term n (%)	0.125-0.5 mg/kg N=9 n (%)	0.75-1.75 mg/kg N=40 n (%)	Overall (N=49)
Myalgia	2 (22)	5 (13)	7 (14)
Diarrhea	2 (22)	4 (10)	6 (12)
Nasopharyngitis	1 (11)	5 (13)	6 (12)
Headache	0	5 (13)	5 (10)
Abdominal pain upper	1 (11)	3 (8)	4 (8)
Bone pain	1 (11)	3 (8)	4 (8)
Bronchitis	0	4 (10)	4 (8)
Fatigue	0	4 (10)	4 (8)
Hypertension	0	4 (10)	4 (8)
Muscle spasms	2 (22)	2 (5)	4 (8)

- Majority of adverse events (AEs) were grade 1 or 2
- Two possibly related serious adverse events (SAEs): grade 3 muscle pain (onset day 90); grade 3 worsening of general condition (onset day 44, recurred day 66, unrelated)
- One possibly related non-serious grade 3 AE of blast cell count increase

Data as of 17 Apr 2015

Luspatercept PACE-MDS 12-Month Treatment Extension Study - Overview

- Patients who complete the initial 3-month treatment study may have been eligible to enroll in a 12-month extension study
  - For patients with interval between studies >3 months, starting dose level is 1.0 mg/kg
  - For patients without interval between studies, current dose level is continued

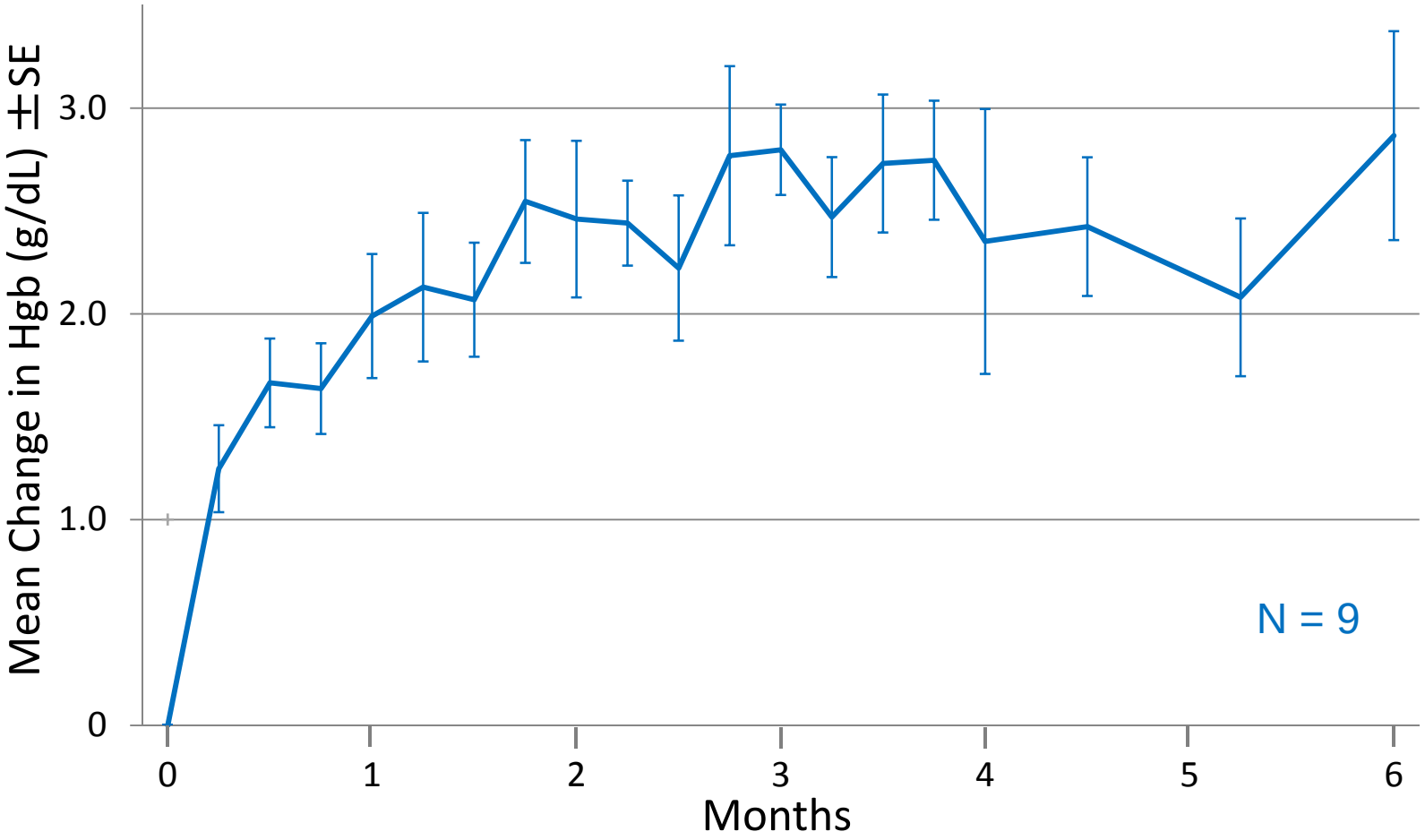


NCT02268383
EudraCT 2014-001280-13

Data as of 17 Apr 2015

Durable Hemoglobin Response in LTB Patients

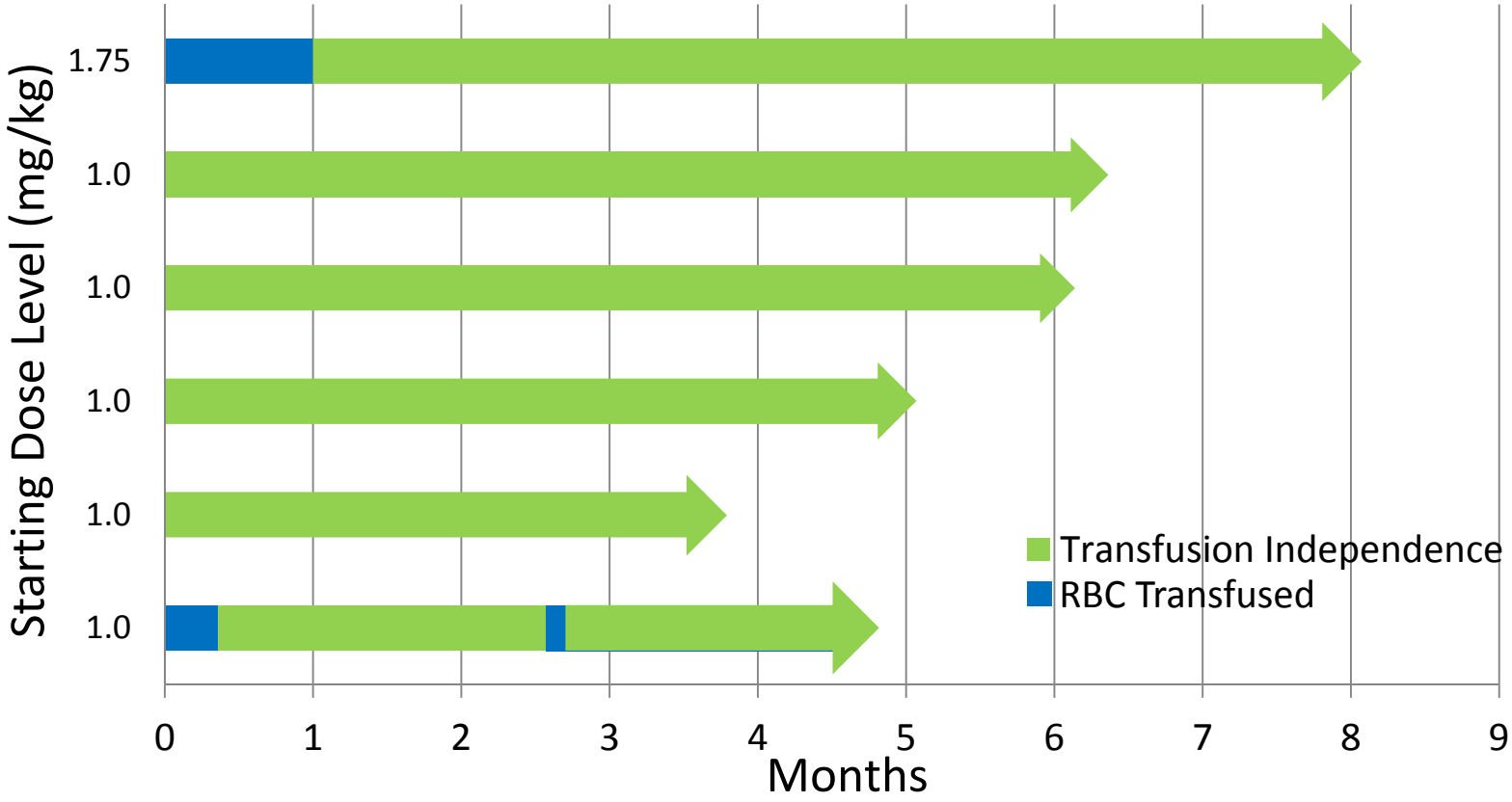
- All 9 LTB patients in the extension study were evaluated for hemoglobin response
- 89% (8/9) patients achieved IWG HI-E response for hemoglobin increase
- All patients are ongoing as of the data cutoff



Data as of 17 Apr 2015

Durable Transfusion Independence

- 43% (6/14*) patients in the extension study achieved transfusion independence
- All 6 responding patients are ongoing as of the data cutoff



* Includes 1 LTB patient also evaluable for transfusion independence
All patients had a baseline transfusion burden of 2-8 units over 8 weeks
Transfusion Independence: Transfusion-free for ≥ 8 weeks on treatment for patients who received at least 2 RBC units pre-treatment

Data as of 17 Apr 2015

Luspatercept PACE-MDS Study: Conclusions

- Lower risk RS+ MDS patients treated with luspatercept ≥ 0.75 mg/kg demonstrated a robust hematologic improvement per IWG HI-E and transfusion independence
- Luspatercept was generally safe and well-tolerated
- Longer-term treatment demonstrated sustained increases in hemoglobin and maintained transfusion-independence
- Based on these results, pivotal, controlled studies of luspatercept in patients with lower-risk MDS are planned

Data as of 17 Apr 2015

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. Ottman, M. Radsak, T. Wolff
  - 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
- Acceleron: K. Attie, M. Sherman, M. Hankin, D. Wilson, 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, L. Alexander, G. Hahn
- Central Labs: CRL, ICON, Genoptix, ILS
- Central Labs (Bone Marrow): A. Giagounidis, D. Haase, H. Kreipe, U. Oelschlägel
- Sponsored by: Acceleron Pharma and Celgene

D·MDS
Deutsche MDS-Studiengruppe