Biomarkers of Ineffective Erythropoiesis Predict Response to Luspatercept in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS): Final Results from the Phase 2 PACE-MDS Study

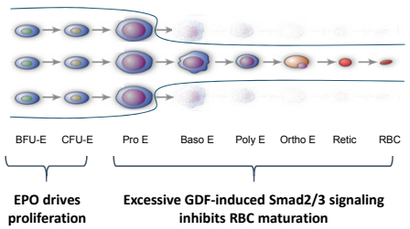
Uwe Platzbecker, MD[1], Ulrich Germing, MD[2], Aristoteles Giagounidis, MD, PhD[3], Katharina Götze, MD[4], Philipp Kiewe, MD[5], Karin Mayer, MD[6], Oliver Ottmann, MD[7], Markus Radsak, MD[8], Thomas Wolff, MD[9], Detlef Haase, MD[10], Monty Hankin[11], Dawn Wilson[11], Xiaosha Zhang[11], Abderrahmane Laadem, MD[12], Matthew L. Sherman, MD[11] and Kenneth M. Attie, MD[11]

[1]Universitätskliniken Carl Gustav Carus, Dresden, [2]Universitätskliniken Düsseldorf, [3]Marien Hospital Düsseldorf, [4]Technical University of Munich, [5]Onkologischer Schwerpunkt am Oskar-Helene-Heim, Berlin, [6]University Hospital Bonn, [7]Universitätskliniken Frankfurt, Goethe Universität, Frankfurt/Main, [8]Johannes Gutenberg-Universität, Mainz, [9]OncoResearch Lerchenfeld UG, Hamburg, [10]Universitätsmedizin Göttingen, Germany, [11]Acceleron Pharma, Cambridge, MA, [12]Celgene Corporation, Summit, NJ, USA

ASH 2015
Abstract 2862

Introduction

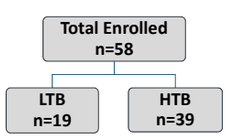
- Anemia, a hallmark of MDS, is challenging to treat, particularly after failure of ESAs. Ineffective erythropoiesis leading to erythroid hyperplasia and RBC apoptosis in the bone marrow is associated with excessive Smad2/3 signaling.[1]



- Luspatercept is a modified activin receptor type IIB-IgG Fc fusion protein that binds ligands of the TGF-β superfamily, inhibits Smad2/3 signaling, promotes late-stage RBC maturation and increased hemoglobin levels in MDS mice and healthy human volunteers.[2,3]
- Splicing factor mutations in MDS, notably in SF3B1 gene, correlate with ring sideroblasts in bone marrow and ineffective erythropoiesis.

Study Design

- A phase 2, multicenter, open-label, dose escalation study in adults with lower-risk MDS (ESA refractory/ineligibile or EPO >500 U/L; no prior HMA; no current ESA, G-CSF, IMiD)
- **Primary efficacy endpoint:** Erythroid response, defined as
  - **LTB:** Low transfusion burden (<4U/8wk, Hb<10): Hb increase ≥ 1.5 g/dL
  - **HTB:** High transfusion burden (≥4U/8wk): 4U or 50% decrease U/8wk
- **Secondary endpoints:** Safety, RBC transfusion independence (TI), IWG HI-E, HI-N, HI-P, serum ferritin, HR-QoL
- **Treatment:**
  Base study (n=58): Up to 5 doses administered SC q 3 weeks
  - Dose escalation (n=27): 0.125, 0.25, 0.5, 0.75, 1.0, 1.33, 1.75 mg/kg
  - Expansion cohort (n=31): starting dose 1.0 , titration up to 1.75 mg/kg
- *Extension study (n=32)*: additional 24 months of treatment (study ongoing, *see abstract #92*)
- **Analysis of RBC-TI:** Includes 39 HTB and 8 LTB patients



clinicaltrials.gov
NCT01749514

Baseline Characteristics

Table 1. Demographics and Baseline Characteristics.

	0.125-0.5 mg/kg, N=9	0.75-1.75 mg/kg, N=49	Overall N=58
Age, yr, median (range)	72 (27-88)	71 (30-90)	72 (27-90)
Sex, male, n (%)	1 (11%)	33 (67%)	34 (59%)
Prior ESA treatment, n (%)	3 (33%)	35 (71%)	38 (66%)
Prior lenalidomide, n (%)	2 (22%)	8 (16%)	10 (17%)
Time since Dx, yr, med (range)	4.6 (0.9-10.0)	2.3 (0.2-13.6)	2.4 (0.2-13.6)
LTB (n=19): Hb, g/dL, med (range)	8.7 (8.3-9.0)	8.7 (6.4-10.1)	8.7 (6.4-10.1)
HTB (n=39): Transfusions, U/8 wk, median (range)	8 (4-8)	6 (4-18)	6 (4-18)

Table 2. Baseline Categories, Biomarkers

Category n (%)	Overall N=58	Biomarker Mean (SD)	0.75-1.75 mg/kg RS+	0.75-1.75 mg/kg RS-
WHO Subtypes	**n (%)**		**N=40**	**N=7**
RARS	11 (19%)	RBC (10^{12}/L)	2.8 (0.5)	3.2 (0.5)
RCMD-RS	29 (50%)	Hemoglobin (g/dL)	8.1 (1.1)	8.6 (0.7)
RCMD	6 (10%)	Reticulocytes(10^9/L)	35.7 (28.7)	26.0 (14.5)
RAEB-1	8 (14%)	MCV (fL)	93.0 (8.5)	93.6 (6.8)
Other (RAEB- 2, del(5q), MDS/MPN)	4 (7%)	% Erythroid (bone marrow nucleated cells)	45.8 (17.9)	17.6 (20.9)
IPSS	**n (%)**	GDF11 (pg/mL)	114 (123) n=10	64 (6) n=2
Low	27 (47%)	GDF15 (pg/mL)	8364 (7793)	3071 (2897)
Int-1	30 (52%)	EPO (IU/L)	299 (402)	775 (635)
Int-2	1 (2%)	Ferritin (µg/L)	1547 (922)	1534 (1415)
IPSS-R	**n (%)**			
Very Low	2 (3%)	**Flow Cytometry:**	**N=24**	**N=4**
Low	31 (53%)	Pro-E (%)	11.0 (11.4)	16.5 (12.4)
Intermediate	21 (36%)	Baso (%)	3.9 (4.0)	5.9 (6.4)
High	3 (5%)	Polychrom (%)	26.2 (11.9)	20.8 (3.3)
Very High	1 (2%)	Ortho (%)	47.5 (14.1)	45.9 (12.4)

Safety

- Majority of adverse events (AEs) were grade 1 or 2
- One possibly related grade 3 AE: blast cell count increase
- Two possibly related serious AEs: grade 3 myalgia; grade 3 worsening of general condition

Table 3. Adverse Events (All Grade/Any Cause) in ≥ 4 Patients

Preferred Term n (%)	0.125-0.5 mg/kg N=9	0.75-1.75 mg/kg N=49	Overall N=58
Diarrhea	2 (22%)	5 (10%)	7 (12%)
Myalgia	2 (22%)	5 (10%)	7 (12%)
Nasopharyngitis	1 (11%)	6 (12%)	7 (12%)
Fatigue	0	6 (12%)	6 (10%)
Abdominal pain upper	1 (11%)	4 (8%)	5 (9%)
Bone pain	1 (11%)	4 (8%)	5 (9%)
Bronchitis	0	5 (10%)	5 (9%)
Headache	0	5 (10%)	5 (9%)
Hypertension	0	5 (10%)	5 (9%)
Anemia	0	4 (8%)	4 (7%)
Muscle spasms	2 (22%)	2 (4%)	4 (7%)

Erythroid Response/Biomarkers

Table 4. Hemoglobin and Transfusion Response

Response Criteria (over 8 weeks)	0.125-0.5 mg/kg N=9, n (%)	0.75-1.75 mg/kg N=49, n (%)
LTB (< 4U/8wk)		
IWG HI-E, Hb increased ≥ 1.5 g/dL	0/2 (0%)	8/17 (47%)
RBC transfusion independent	0/0 (0%)	6/8 (75%)
HTB (≥ 4U/8wk)		
IWG HI-E (≥ 4U reduction)	2/7 (29%)	16/32 (50%)
RBC transfusion independent	1/7 (14%)	8/32 (25%)
HTB + LTB pts with ≥ 2U/8 wk		
RBC transfusion independent	1/7 (14%)	14/40 (35%)

- Neutrophil responses (IWG HI-N) were seen in 4 of 8 (50%) patients with baseline neutrophil count < 1.0 X 10^9/L

Figure 1. Mean Change in Hemoglobin in LTB patients (N=19)

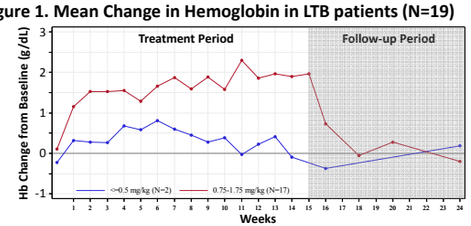


Table 5. Biomarkers / Response in Higher Dose Groups

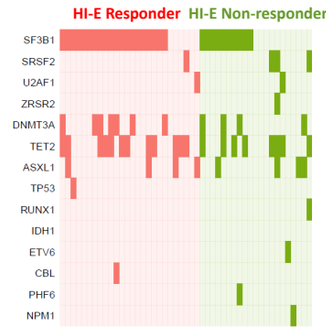
Subgroup N (%)	IWG HI-E Response Rate	RBC-TI Response Rate
All	**24/49 (49%)**	**14/40 (35%)**
RS+	22/40 (55%)	12/31 (39%)
RS-	2/7 (29%)	2/7 (29%)
SF3B1 mutation	18/30 (60%)	9/24 (38%)
Any splicing factor mutation	20/36 (56%)	13/29 (45%)
EPO < 200 U/L	16/25 (64%)	10/18 (56%)
EPO 200-500 U/L	4/11 (36%)	3/9 (33%)
EPO > 500 U/L	4/13 (31%)	1/13 (8%)
Prior ESA	16/35 (46%)	10/29 (35%)
ESA Naïve	8/14 (57%)	4/11 (36%)

Table 6. Baseline Biomarkers by IWG HI-E Response in High Dose Groups

Baseline Biomarker Mean (SD)	HI-E Responders N=24	HI-E Non-Responders N=25
RBC (10^{12}/L)	2.87 (0.5)	2.81 (0.5)
Hemoglobin (g/dL)	8.2 (1.1)	8.2 (1.0)
Reticulocytes (10^9/L)	33.7 (31.5)	32.0 (23.0)
BM Erythroid Cells (%)	44.6 (21.7)	36.9 (21.0)
GDF11 (pg/mL)	78.2 (38.8) n=5	125.6 (146.0) n=7
GDF15 (pg/mL)	6546 (5186)	8378 (9001)
EPO (IU/L)	324 (504)	508 (579)
Ferritin (µg/L)	1543 (912)	1608 (1106)
Flow Cytometry:	**N=15**	**N=13**
Pro-erythroblasts (%)	9.5 (7.8)	14.8 (14.5)
Basophilic normoblasts (%)	3.8 (3.7)	4.7 (5.1)
Polychromatic (%)	27.5 (12.9)	23.0 (8.9)
Orthochromatic (%)	46.0 (12.6)	48.7 (15.1)

Erythroid Response/Biomarkers

Figure 2. IWG HI-E Response in Higher Dose Groups by Mutation



Each column represents one patient, showing mutations present at baseline

Summary/Conclusions

- Lower risk MDS patients treated with luspatercept at ≥ 0.75 mg/kg achieved hematologic improvement and reduced RBC transfusion burden / independence
- Higher response rates were observed in patients with ring sideroblasts and SF3B1 mutations
- Similar response rates were observed in ESA-naïve vs ESA-experienced, and approximately 1/3 of patients with EPO 200-500 U/L responded
- Luspatercept was generally safe and well-tolerated
- These data support initiation of Phase 3 studies of luspatercept in lower-risk MDS (MEDALIST)

Acknowledgments/References

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
Acceleron: C. Rovaldi, B. O'Hare, T. Akers, J. Desiderio, T. Sacco, S. Ertel
Celgene: S. Ritland, J. Zhang, N. Chen **Chiltern:** C. Lanza, F. VanderSchueren
Central Labs: CRL, ICON, Genoptix, ILS, A. Giagounidis, D. Haase, H. Kreipe, U. Oelschlägel

References:
1. Zhou L, et al. Blood 2008;112:3434
2. Suragani R et al., Nat Med 2014;20:408
3. Attie, K et al. Am J Hematol 2014;89:766

Study supported by Acceleron and Celgene

Disclosures: Platzbecker: *Celgene, Novartis:* Honoraria, Research Funding; *Boehringer:* Research Funding. **Goetze:** *Celgene, Novartis:* Honoraria. **Ottmann:** *BMS:* Honoraria, Research Funding; *Novartis:* Consultancy. **Hankin, Wilson, Zhang, Sherman, Attie:** *Acceleron:* Employment. **Laadem:** *Celgene Corp:* Employment.