Mutational and Subgroup Analyses of Lower-Risk Myelodysplastic Syndromes (MDS) Patients Treated with Luspatercept: Phase 2 PACE-MDS Study

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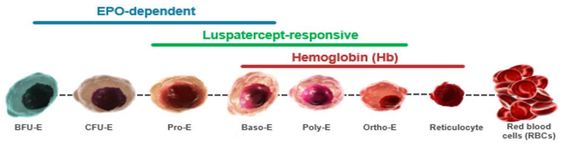
Abstract PF498 [1]Universitätsklinikum Carl Gustav Carus, Dresden, [2]Marien Hospital Düsseldorf, Düsseldorf, [3]Onkologischer Schwerpunkt am Oskar-Helene-Heim, Berlin, [4]Universitätsklinikum Düsseldorf, Düsseldorf, [5]III. Department of Medicine, Hematology and Medical Oncology, Technical University of Munich, Klinikum rechs der Isar, Munich, [6]University Hospital Bonn, Bonn, [7]Johannes Gutenberg-Universität, Mainz, [8]OncoResearch Lerchenfeld UG, Hamburg, [9]Universitätsklinikum Frankfurt, Goethe Universität , Frankfurt/Main, Germany; [10]Acceleron Pharma, Cambridge, MA, [11]Celgene Corporation, Summit, NJ, USA

Introduction

- Many serious hematologic diseases such as MDS are associated with an erythroid maturation defect, leading to erythroid hyperplasia, anemia, and morbidity
- Diseases characterized by defective late-stage erythropoiesis may not respond or have suboptimal response to ESA, e.g. EPO therapy
- Luspatercept acts as an erythroid maturation agent (EMA) by promoting terminal differentiation of erythroblasts in late-stage erythropoiesis



EPO: erythropoietin; ESA: erythropoiesis-stimulating agent

- 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, resulting in increased hemoglobin in healthy volunteers
- In a murine model of MDS, the murine analog RAP-536 corrected ineffective erythropoiesis, reduced erythroid hyperplasia, and increased hemoglobin levels
- Platzbecker U, et al. Lancet Oncol 2017 reported on 58 lower-risk MDS patients; presented here is a further analysis of flow and bone marrow biomarkers

Study Design

- A Phase 2, multicenter, open-label, 3-month dose-escalation study in adults with lower-risk MDS, followed by a 5-year extension study
  - Base study 3 months (N=108; NCT01749514)
  - Extension study 5 years (ongoing) (N=71; NCT02268383)
- Key eligibility criteria: low to int-risk (IPSS) MDS including non-transfusion dependent and transfusion dependent; ESA-naïve and prior ESA; range of baseline EPO; RS+ and non-RS patients
- Treatment: luspatercept 0.125 – 1.75 mg/kg (base study); 1.0 – 1.75 mg/kg (extension); SC q3 weeks; 2-month follow-up
- Endpoints: IWG (2006) HI-E: Hemoglobin (Hgb) increase ≥ 1.5 g/dL over 8 weeks for patients with < 4 units/8 wk and Hgb < 10 g/dL; ≥ 4 RBC unit decrease over 8 weeks for patients with ≥ 4 units/8 wk; RBC-TI: RBC-transfusion independence ≥ 8 weeks; time to/duration of HI-E response
- Baseline bone marrow and blood samples were analyzed by central morphology and flow cytometry according to ELN guidelines for evaluation of erythroid precursors and soluble transferrin receptor.

Preliminary data as of 06 April 2018

Baseline Characteristics

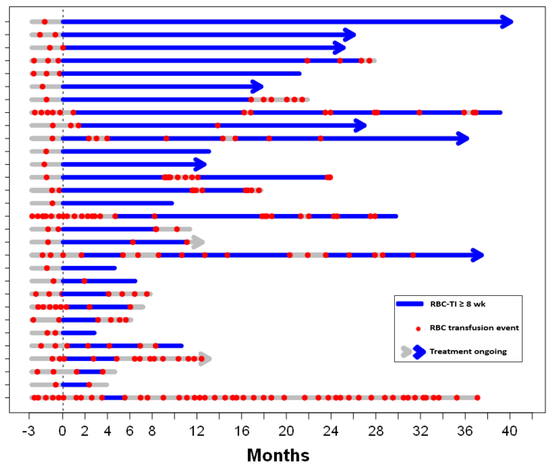
Table 1. Demographics and Baseline Characteristics

Parameter	N=101
Age, yr, median (range)	73 (29-90)
Sex, male, n (%)	67 (66%)
Time since diagnosis, yr, median (range)	1.8 (0.0-13.6)
Prior ESA treatment, n (%)	46 (46%)
Baseline EPO, n (%)	
<200 IU/L	53 (53%)
200-500 IU/L	23 (23%)
>500 IU/L	25 (25%)
Ring sideroblast (RS) status, n (%)	
RS+ (RS ≥ 15%)	62 (61%)
Non-RS	37 (37%)
Unknown	2 (2%)
IWG HI-E evaluable	n=101
Hemoglobin, g/dL, median (range)	8.4 (6-10)
Transfusions, units/8 wk, median (range)	2 (0-18)
RBC-TI evaluable	n=68
Transfusions, units/8 wk, median (range)	4 (2-18)

Patients treated at dose levels ≥ 0.75 mg/kg
IWG HI-E evaluable: all patients
RBC-TI evaluable: ≥2U/8 wks of RBC transfused at baseline

Response

Figure 1. Duration of Transfusion Independence in RBC-TI Responders



Patients treated at dose levels ≥ 0.75 mg/kg with baseline RBC ≥ 2U/8 wks

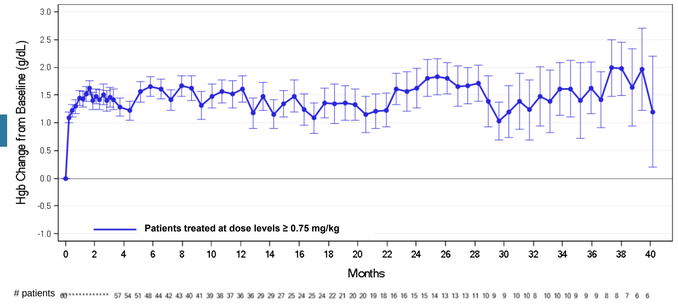
Response

Table 2. IWG HI-E and RBC-TI Response by ESA, EPO, RS Status

Response Rates	IWG HI-E, n/N (%) (N=101)	RBC-TI, n/N (%) (N=68)
All patients	55/101 (55%)	30/68 (44%)
ESA-naïve	31/55 (56%)	18/32 (56%)
Prior ESA	24/46 (52%)	12/36 (33%)*
Baseline EPO		
≤ 500 IU/L	49/76 (65%)	27/46 (59%)
> 500 IU/L**		
RS+	5/9 (56%)	2/9 (22%)*
Non-RS	1/14 (7%)	1/11 (9%)

Patients treated at dose levels ≥ 0.75 mg/kg
*Median baseline transfusion burden ≥ 4 units
**2 pts with EPO > 500 IU/L had unknown RS status

Figure 2. Sustained Increase in Mean Hemoglobin in Low Transfusion Burden Patients



Low-transfusion-burden patients: < 4 units/8 wk, Hb <10 g/dL

Table 3. IWG HI-E Responder Characteristics

	SF3B1 mutated N=46		non-SF3B1 mutated N=42*	
HI-E Response Rate, n/N (%)	35/46 (76%)		16/42 (38%)	
EPO < 500 IU/L	31/40 (78%)		15/29 (52%)	
EPO ≥ 500 IU/L	4/6 (67%)		1/13 (8%)	
	R	NR	R	NR
n	35	11	16	26
Erythroid cells and precursors (%, bone marrow morphology)	50 (10, 78)	30 (15, 80)	30 (1, 70), n=11	22 (1, 80), n=25
M/E ratio (bone marrow morphology)	1.00 (0.28, 9)	2.33 (0.25, 5.67)	2.33 (0.43, 99) n=11	3.77 (0.25, 100) n=22
Erythroid precursors (%, flow cytometry)	13.24 (1.07, 39.10) n=29	8.43 (1.24, 24.03) n=8	6.61 (0.21, 28.69) n=12	4.46 (0.10, 43.59) n=16
Soluble transferrin receptor (nmol/L)	63.6 (15.6, 181.1) n=34	54.1 (10.4, 108.5)	34.4 (11.3, 136.1) n=15	35.6 (8.8, 249.7) n=21

Patients treated with ≥ 0.75 mg/kg with evaluable mutational data
Data presented as median (min, max); NR=non-responder; R=responder
*Non-SF3B1 group includes RS+ patients without an SF3B1 mutation

Safety

- Majority of adverse events (AEs) were grade 1 or 2
- Eight possibly related grade 3 non-serious AEs (in 1 patient each unless noted): ascites, blood bilirubin increase, bone pain, hypertension (in 2 patients), mucosal inflammation, platelet count increase, transformation to AML
- Four possibly related SAEs (in 3 patients): general physical health deterioration (1 patient), muscular weakness & musculoskeletal pain (1 patient), and myalgia (1 patient)

Table 4. Adverse Events (Related/All Grades) in > 2 Patients

Preferred Term	n (%)
Headache	8 (7.4%)
Hypertension	7 (6.5%)
Fatigue	6 (5.6%)
Arthralgia	5 (4.6%)
Bone Pain	5 (4.6%)
Diarrhea	5 (4.6%)
Injection Site Erythema	4 (3.7%)
Myalgia	3 (2.8%)
Edema peripheral	3 (2.8%)

N=108, all patients treated at all dose levels

Summary/Conclusions

- Lower-risk MDS patients with and without the SF3B1 mutation with EPO < 500 IU/L treated with luspatercept continue to demonstrate sustained increases in hemoglobin and decreases in transfusion burden (per IWG HI-E) and a high rate of RBC transfusion independence.
- Additional analyses are ongoing to understand the role of other biomarkers such as mutation status and how they may impact the biology and influence response.
- As there is not one distinct profile of responder characteristics, this may suggest the possibility that luspatercept may work as an erythroid maturation agent (EMA) in a broad range of genotypes and phenotypes.

Acknowledgements/References

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