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

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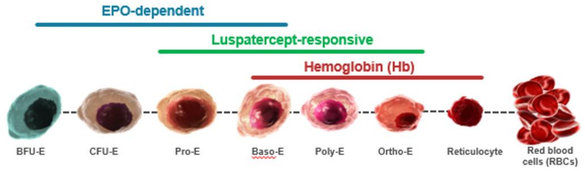
Abstract 2982

Introduction

- Luspatercept promotes 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; increased hemoglobin in healthy volunteers
- In a murine model of MDS, murine analog RAP-536 corrected ineffective erythropoiesis, reduced erythroid hyperplasia, and increased hemoglobin

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=106; NCT01749514; Platzbecker U, et al. Lancet Oncol 2017; 18:1338-47)
  - Extension study 5 years (ongoing) (N=70; 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: 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

Safety

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

Table 1. Adverse Events (Related/All Grades) in > 2 Patients

Preferred Term	N (%)
Headache	8 (7.5%)
Hypertension	7 (6.6%)
Fatigue	6 (5.7%)
Bone Pain	5 (4.7%)
Diarrhea	5 (4.7%)
Arthralgia	4 (3.8%)
Injection Site Erythema	4 (3.8%)
Myalgia	3 (2.8%)
Edema peripheral	3 (2.8%)

N=106, all patients treated at all dose levels

Preliminary data as of 08 Sept 2017

Baseline Characteristics

Table 2. Demographics and Baseline Characteristics
Patients Treated at Dose Levels ≥ 0.75 mg/kg

Parameter	N=99
Age, yr, median (range)	73 (29-90)
Sex, male, n (%)	65 (66%)
Time since diagnosis, yr, median (range)	1.9 (0.1-13.6)
Prior ESA treatment, n (%)	46 (47%)
Baseline EPO, n (%)	
<200 IU/L	52 (53%)
200-500 IU/L	22 (22%)
>500 IU/L	25 (25%)
Ring sideroblast (RS) status, n (%)	
RS+ (RS ≥ 15%)	62 (63%)
Non-RS	35 (35%)
Unknown	2 (2%)
IWG HI-E evaluable	n=99
Hemoglobin, g/dL, median (range)	8.4 (6-10)
Transfusions, units/8 wk, median (range)	2 (0-18)
RBC-TI evaluable	n=67
Transfusions, units/8 wk, median (range)	4 (2-18)
Mutation evaluable	n=89

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

Table 3. Mutated Genes Per Patient at Baseline
Patients Treated at Dose Levels ≥ 0.75 mg/kg; Mutation Evaluable Population

	0	1-2	3-5
RS+ (n=58)	7%	66%	28%
Non-RS (n=29)	38%	41%	21%
RS Unknown (n=2)	50%	50%	0%
ESA-naïve (n=49)	25%	53%	22%
Prior ESA (n=40)	10%	63%	28%
EPO <200 U/L (n=49)	22%	61%	16%
EPO 200-500 U/L (n=20)	5%	60%	35%
EPO >500 U/L (n=20)	20%	45%	35%
<4 units RBCs/8 wks baseline (n=53)	25%	57%	19%
≥4 units RBCs/8 wks baseline (n=36)	8%	58%	33%

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

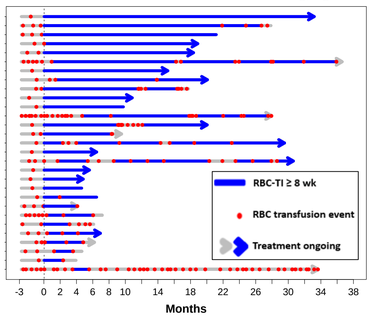
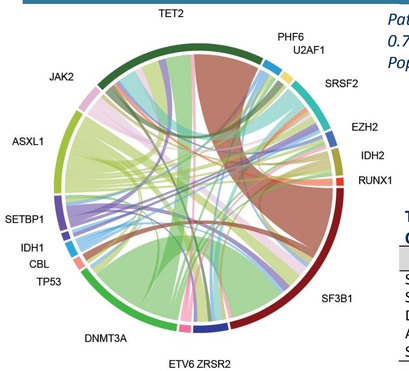


Table 4. IWG HI-E Response Rate by Mutation
Patients Treated at Dose Levels ≥ 0.75 mg/kg; Mutation Evaluable Population

Mutation	Response Rate n/N (%)
SF3B1	33/46 (72%)
TET2	17/29 (59%)
DNMT3A	11/18 (61%)
ASXL1	6/13 (46%)
SRSF2	3/9 (33%)

NOTE: NRAS, KIT, MPL and NPM1 were also evaluated and were not found mutated in any patients

Mutational Status



Patients Treated at Dose Levels ≥ 0.75 mg/kg; Mutation Evaluable Population

Figure 2. Frequency of Co-Mutations

Table 5. Most Frequent Co-Mutations

Co-Mutations	%
SF3B1 and TET2	20%
SF3B1 and DNMT3A	17%
DNMT3A and TET2	8%
ASXL1 and TET2	6%
SRSF2 and TET2	6%

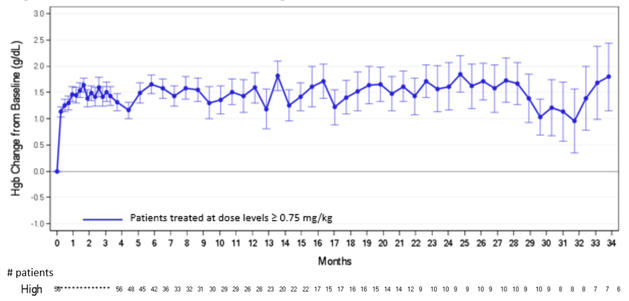
Individual patients may have mutations in other genes or count towards multiple pairs

Response

Table 6. IWG HI-E and RBC-TI Response by ESA, EPO, RS Status
Patients Treated at Dose Levels ≥ 0.75 mg/kg

Response Rates	IWG-HI-E, n/N (%) (N=99)	RBC-TI, n/N (%) (N=67)
All patients	52/99 (53%)	29/67 (43%)
ESA-naïve	28/53 (53%)	17/31 (55%)
Prior ESA	24/46 (52%)	12/36 (33%)
Baseline EPO <200 U/L		
RS+	25/39 (64%)	16/24 (67%)
Non-RS	7/13 (54%)	3/7 (43%)
Baseline EPO 200-500 U/L		
RS+	10/14 (71%)	4/9 (44%)
Non-RS	4/8 (50%)	3/5 (60%)
RS Status		
RS+	40/62 (65%)	22/42 (52%)
Non-RS	12/35 (34%)	7/23 (30%)
Unknown	0/2 (0%)	0/2 (0%)

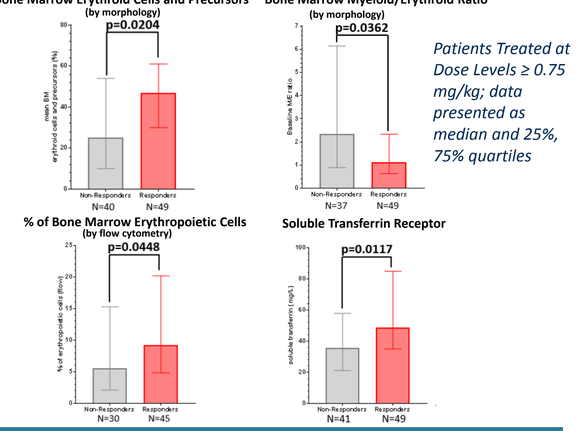
Figure 3. Increase in Mean Hemoglobin in Low Transfusion Burden Patients



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

Response

Figure 4. Response Rate by Cellular and Morphologic Parameters



Patients Treated at Dose Levels ≥ 0.75 mg/kg; data presented as median and 25%, 75% quartiles

Summary/Conclusions

- Lower-risk MDS patients 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
  - HI-E responders had increased levels of bone marrow erythroid cells/precursors and soluble transferrin receptor and lower baseline myeloid/erythroid ratios
- Treatment benefit similar in ESA-naïve and prior ESA-treated patients and benefit is observed in both RS+ and non-RS patients
- The majority of patients had at least one mutation in the genes analyzed; co-mutations in SF3B1 and TET2 and in SF3B1 and DNMT3A were the most common

Acknowledgements/References

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