Luspatercept Increases Hemoglobin and Reduces Transfusion Burden in Patients With Lower-Risk Myelodysplastic Syndromes (MDS): Long-Term Results From the Phase 2 PACE-MDS Study

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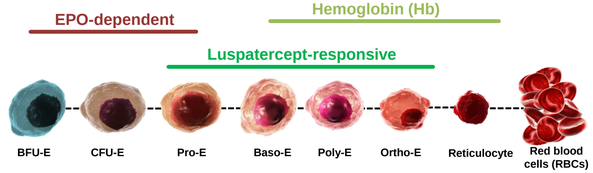
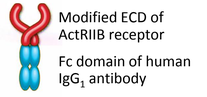
Abstract P666

Introduction

- Anemia, a hallmark of MDS, is a significant clinical challenge to treat, particularly after failure of erythropoiesis-stimulating agents (ESAs)
- Defects in maturation of erythroid precursors (ineffective erythropoiesis) lead to erythroid hyperplasia and anemia
- Diseases characterized by defective late-stage erythropoiesis may not respond to erythropoietin (EPO) or ESA therapy[1]
- Luspatercept promotes terminal differentiation of erythroblasts in late-stage erythropoiesis[2]





- 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[3]
- In a murine model of MDS, murine analog RAP-536 corrected ineffective erythropoiesis, reduced erythroid hyperplasia, and increased hemoglobin[1]

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 (N=95) 3 months NCT01749514 → Extension Study (N=57) 5 years (ongoing) NCT02268383

Eligibility	Efficacy Endpoints

• Prior cohorts: RS+/RS-
  • EPO > 500 IU/L
  • EPO ≤ 500 IU/L and ESA refractory, intolerant, or ineligible
• New ESA-naïve cohorts:
  • RS+, EPO ≤ 200 IU/L
  • RS-, any EPO level
	• IWG (2006) HI-E:
	  • Hb increase ≥ 1.5 g/dL for all values over 8 weeks for patients with < 4 units/8 wk and Hb < 10 g/dL
	  • ≥ 4 RBC unit decrease over 8 weeks for patients with ≥ 4 units/8 wk

Treatment	**Other Efficacy Endpoints**
• Luspatercept 0.125 – 1.75 mg/kg (base study); 1.0 – 1.75 mg/kg (extension); SC q3 weeks • All patients followed up for 2 months post last dose or early discontinuation	• RBC-TI: RBC-transfusion independence ≥ 8 weeks • Time to/duration of HI-E response

Data cut off as of 13 Apr 2017

Baseline Characteristics

Table 1. Demographics and Baseline Characteristics
Patients Treated at Dose Levels ≥ 0.75 mg/kg

Parameter	N=88
Age, yr, median (range)	72 (29-90)
Sex, male, n (%)	56 (64%)
Time since diagnosis, yr, median (range)	2.0 (0.1-13.6)
Prior ESA treatment, n (%)	45 (51%)
Baseline EPO, n (%)	
<200 IU/L	43 (49%)
200-500 IU/L	20 (23%)
>500 IU/L	25 (28%)
Ring sideroblast (RS) status, n (%)	
RS+ (RS ≥ 15%)	56 (64%)
RS-	29 (33%)
Unknown	3 (3%)
IWG HI-E evaluable	n=88
Hemoglobin, g/dL, median (range)	8.3 (6-10)
Transfusions, units/8 wk, median (range)	2 (0-18)
RBC-TI evaluable	n=60
Transfusions, units/8 wk, median (range)	4 (2-18)

IWG HI-E evaluable: treated at dose levels ≥ 0.75 mg/kg
RBC-TI evaluable: treated at dose levels ≥ 0.75 mg/kg with ≥ 2 units/8 weeks of RBC transfused at baseline

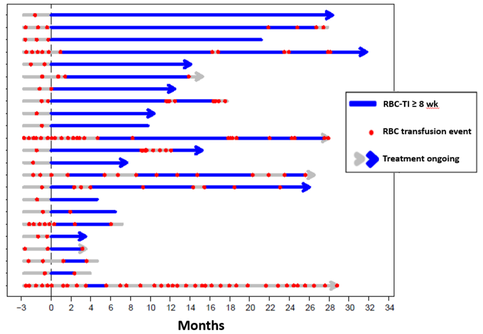
Table 2. Baseline MDS Categories
Patients Treated at Dose Levels ≥ 0.75 mg/kg

Category, n (%)	N=88		N=88
WHO 2006 Subtypes		**IPSS**	
RCMD-RS	30 (34%)	Low	37 (42%)
RARS	15 (17%)	Int-1	49 (56%)
RCMD	13 (15%)	Int-2	2 (2%)
RAEB-1	11 (13%)	**IPSS-R**	
CMML or MDS/MPN	7 (8%)	Very Low	2 (2%)
del(5q)	5 (6%)	Low	54 (61%)
RA	3 (3%)	Intermediate	25 (28%)
RAEB-2	1 (1%)	High	6 (7%)
Missing	3 (3%)	Very High	1 (1%)

Erythroid Response

Figure 1. Duration of Transfusion Independence in RBC-TI Responders *Patients Treated at Dose Levels ≥ 0.75 mg/kg with Baseline RBC ≥ 2 Units*

- Median duration of treatment for RBC-TI responders: 14.7 months (range 2.8-32.4 months, ongoing)



RBC-TI: RBC-transfusion independence ≥ 8 weeks

Erythroid Response

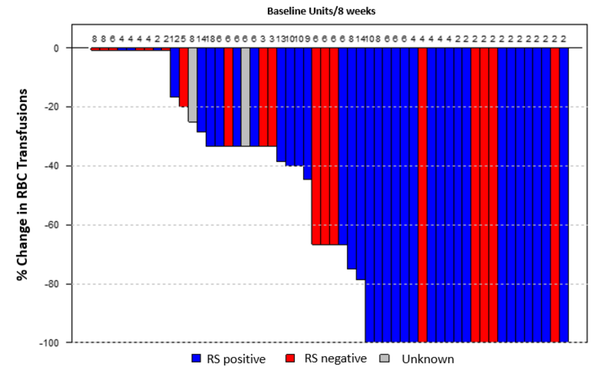
Table 3. Response Rates by ESA Exposure
Patients Treated at Dose Levels ≥ 0.75 mg/kg

ESA Status	IWG HI-E, n/N (%) N=88	RBC-TI, n/N (%) N=60
All patients	44/88 (50%)	23/60 (38%)
ESA-naïve	21/43 (49%)	12/25 (48%)
Prior ESA	23/45 (51%)	11/35 (31%)

Table 4. Response Rates by Baseline EPO and RS Status
Patients Treated at Dose Levels ≥ 0.75 mg/kg

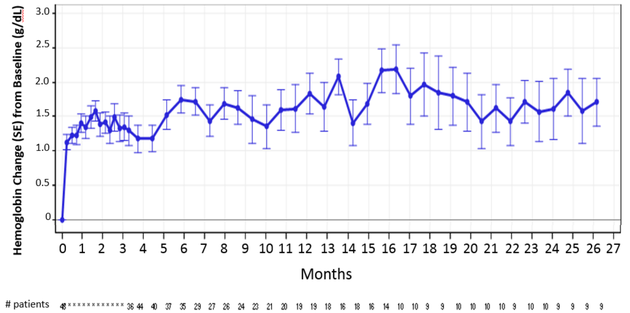
Baseline EPO (IU/L)	RS Status	IWG HI-E, n/N (%) N=88	RBC-TI, n/N (%) N=60
<200	RS+	23/35 (66%)	13/21 (62%)
	RS-	4/8 (50%)	1/4 (25%)
200 - 500	RS+	7/12 (58%)	3/8 (38%)
	RS-	4/8 (50%)	3/5 (60%)
>500	RS+	5/9 (56%)	2/9 (22%)
	RS-	1/13 (8%)	1/11 (9%)
	Unknown	0/3 (0%)	0/2 (0%)

Figure 2. Reduction in Transfusion Burden
Patients Treated at Dose Levels ≥ 0.75 mg/kg



1 patient with insufficient post-baseline transfusion data not shown; 5 patients with transfusion burden increase by 2 units each not shown

Figure 3. Increase in Mean Hemoglobin in Low-Transfusion Burden Patients *Patients Treated at Dose Levels ≥ 0.75 mg/kg*



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

Safety Summary

- Majority of adverse events (AEs) were grade 1 or 2
- Seven possibly related grade 3 non-serious AEs (in 1 patient each): ascites, blast cell count increase, blood bilirubin increase, bone pain, hypertension, platelet count increase, pleural effusion
- Four possibly related SAEs as of 15 June 2017: ataxia, general physical health deterioration, muscle weakness, and myalgia

Table 5. Possibly or Probably Related Adverse Events (Any Grade) in > 2 Patients

Preferred Term	n (%)
Headache	7 (7.4%)
Fatigue	6 (6.3%)
Hypertension	5 (5.3%)
Bone Pain	4 (4.2%)
Diarrhea	4 (4.2%)
Arthralgia	3 (3.2%)
Injection Site Erythema	3 (3.2%)
Myalgia	3 (3.2%)
Edema Peripheral	3 (3.2%)

N=95, all patients treated at all dose levels

Summary/Conclusions

- Lower-risk MDS patients treated with luspatercept continue to demonstrate robust increases in hemoglobin and decreases in transfusion burden (per IWG HI-E) and a high rate of RBC transfusion independence
  - Encouraging response rates observed across all baseline EPO levels
  - Response rates similar in patients who received prior ESA to those who are ESA naïve
  - IWG HI-E response rates similar in RS+ and RS- patients except when EPO > 500
- Luspatercept was generally well tolerated
- Data continue to support initiating a new Phase 3 trial in first-line patients

Acknowledgments/References

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