Long-term Efficacy and Safety of Luspatercept in Lower-Risk Myelodysplastic Syndromes (MDS): Phase 2 PACE-MDS Study

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Introduction

- Patients with lower-risk myelodysplastic syndromes (LR MDS) develop anemia due to ineffective erythropoiesis, leading to red blood cell (RBC) transfusion dependence[1,2]
- Diseases characterized by defective late-stage erythropoiesis may not respond or may have suboptimal response to erythropoiesis-stimulating agents, e.g. EPO therapy
- Luspatercept is a first in class erythroid maturation agent that binds to select transforming growth factor-β superfamily ligands to diminish Smad2/3 signaling and enhance late-stage erythropoiesis[3]
- Luspatercept has been approved by the US Food and Drug Administration for the treatment of anemia in adult patients failing an erythropoiesis-stimulating agent and requiring ≥ 2 RBC units over 8 weeks with IPSS-R very low-to-intermediate-risk MDS with ring sideroblasts (RS) or with myelodysplastic/ myeloproliferative neoplasm with RS and thrombocytosis[4]
- Luspatercept has been investigated in patients with LR MDS and RS[5], in an ongoing Phase 3 trial regardless of RS status (COMMANDS, NCT03682536), and as previously reported in this Phase 2 trial of luspatercept which includes subtypes of LR MDS with and without RS, regardless of prior ESA exposure, and various baseline transfusion burden and EPO levels[6]
- Here we present the final results of the long-term (5 year) extension study; all eligible patients have rolled into a follow-up study (NCT04064060)

Study Design

- A Phase 2, multicenter, open-label, 3-month dose-escalation plus 5-year extension in adults with lower-risk MDS
- Key eligibility criteria: IPSS low to int-risk MDS including non-transfusion dependent and transfusion dependent; ESA-naïve and prior ESA; range of baseline EPO; RS+ and non-RS (RS negative) 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 included:
  - 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
  - Duration of response

Data cut off date 20 May 2020

Baseline Characteristics

Table 1. Demographics and Baseline Characteristics

Parameter	N=108
Age, yr	72 (29-90)
Sex, male, n (%)	72 (67%)
Time since diagnosis, yr	1.8 (0.0-13.6)
Prior ESA treatment, n (%)	47 (44%)
Baseline EPO, n (%)	
<200 IU/L	58 (54%)
200-500 IU/L	25 (23%)
>500 IU/L	25 (23%)
Ring sideroblast (RS) status, n (%)	
RS+ (RS ≥ 15%)	62 (57%)
Non-RS	44 (41%)
Unknown	2 (2%)
Transfusion burden, n (%)	
< 4U RBC/8 weeks	63 (58%)
Hemoglobin, g/dL	8.7 (6-10)
≥ 4U RBC/8 weeks	45 (42%)
Transfusions, units/8 wk	6 (4-18)

Patients treated at dose levels ≥0.75 mg/kg
Median (range) unless otherwise noted

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 (in 2 patients), 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 2. Adverse Events (Related/All Grades) in ≥ 2 Patients

Preferred Term	n (%)
Fatigue	8 (7.0%)
Headache	8 (7.0%)
Hypertension	7 (6.1%)
Arthralgia	5 (4.3%)
Bone Pain	5 (4.3%)
Diarrhea	5 (4.3%)
Injection Site Erythema	4 (3.5%)
Myalgia	3 (2.6%)
Edema peripheral	3 (2.6%)

N=115, all patients treated at all dose levels

Response

Table 3. IWG HI-E and RBC-TI Response by Baseline Characteristics

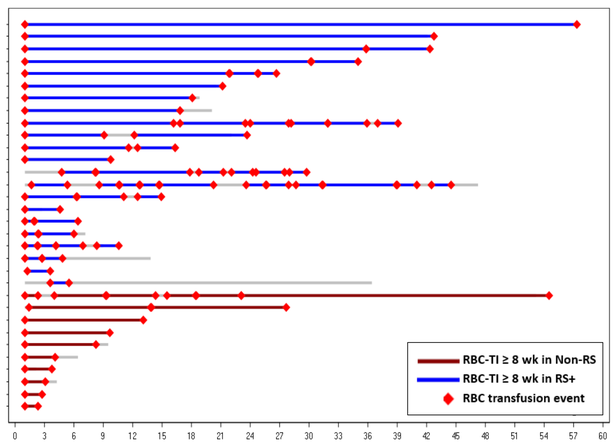
Response Rates	IWG HI-E, n/N (%) (N=108)	RBC-TI, n/N (%) (N=73)
All patients	58/108 (54%)	32/73 (44%)
ESA exposure		
ESA-naïve	33/61 (54%)	20/37 (54%)
Prior ESA	25/47 (53%)	12/36 (33%)
RS status*		
RS+	42/62 (68%)	22/42 (52%)
Non-RS	16/44 (36%)	10/29 (35%)
Baseline EPO		
< 200 IU/L	39/58 (67%)	21/35 (60%)
200-500 IU/L	13/25 (52%)	8/16 (50%)
> 500 IU/L	6/25 (24%)	3/22 (14%)
Transfusion burden		
< 4U RBC/8 weeks	34/63 (54%)	20/28 (71%)
≥ 4U RBC/8 weeks	24/45 (53%)	12/45 (27%)

*2 patients with unknown RS status
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

Median (range) duration of treatment (N=108): 10.4 (0.7-63.6) months

Response

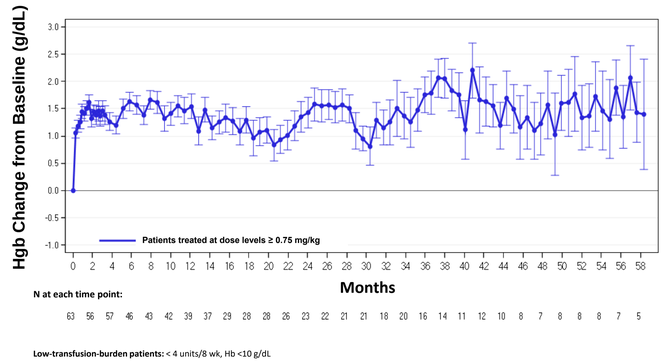
Figure 1. Duration of Transfusion Independence in RBC-TI Responders



Patients treated at dose levels ≥ 0.75 mg/kg with baseline RBC ≥ 2 units/8 weeks

Response

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



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

Summary/Conclusions

- Consistent with previous reports, data from the 5-year Phase 2 study of luspatercept in LR MDS continue to show robust efficacy across subgroups
  - Notably, efficacy continues to be seen regardless of RS status and across a range of EPO levels, including EPO < 200 IU/L
- The safety profile remains consistent with previous reports on this study and in the Phase 3 MEDALIST trial[5,6]

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