Luspatercept Increases Hemoglobin and Reduces Transfusion Burden in Patients with Low-Intermediate Risk Myelodysplastic Syndromes (MDS): Long-Term Results from Phase 2 PACE-MDS Study

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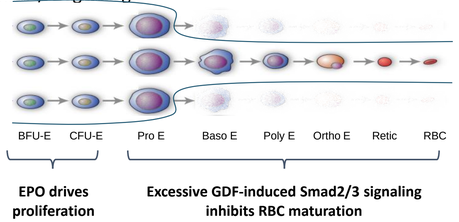
Introduction

- Anemia, a hallmark of MDS, is a significant clinical challenge to treat, particularly after failure of ESAs. Defects in maturation of erythroid precursors (ineffective erythropoiesis) lead to erythroid hyperplasia and anemia. Ineffective erythropoiesis leading to erythroid hyperplasia and RBC apoptosis in the bone marrow is associated with excessive Smad2/3 signaling.[1,2]



- 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, promotes late-stage RBC maturation, and increased hemoglobin levels in MDS mice and healthy human volunteers.[3,4]

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 (ESA refractory/ineligible or EPO > 500 U/L; no prior HMA; no current ESA, G-CSF, IMiD)

Efficacy endpoints (extension study):

- **LTB:** Low transfusion burden (<4U/8wk, Hb<10 g/dL):
  IWG HI-E: Hb increase ≥ 1.5 g/dL for all values over 8 weeks
- **HTB:** High transfusion burden (≥4U/8wk):
  IWG HI-E: ≥ 4 unit decrease over 8 weeks

Other efficacy endpoints: RBC transfusion independence (TI), time to/duration of HI-E response

Treatment: Luspatercept administered SC every 3 weeks

Follow-up: Patients followed for 2 months post-last dose

Base Study (N=73)
3 months treatment
NCT01749514
- Dose escalation: 0.125, 0.25, 0.5, 0.75, 1.0, 1.33, 1.75 mg/kg
- Expansion: starting dose level 1.0 mg/kg, titration up to 1.75 mg/kg

→

Extension Study (N=42)
up to 5 years (ongoing)
NCT02268383
- 1.0 -1.75 mg/kg

Preliminary Data as of 09 Sept 2016

Baseline Characteristics

Table 1. Demographics and Baseline Characteristics

Parameter	Base Study N=73	Extension Study N=42
Age, yr, median (range)	72 (27-90)	72 (29-90)
Sex, male, n (%)	40 (55)	25 (60)
Time since diagnosis, yr, median (range)	2.3 (0-14)	2.9 (0-14)
Prior lenalidomide treatment, n (%)	10 (14)	6 (14)
Prior ESA treatment, n (%)	39 (53)	21 (50)
Baseline EPO, n (%)		
<200 U/L	37 (51)	26 (62)
200-500 U/L	16 (22)	9 (21)
>500 U/L	20 (27)	7 (17)
RS+ (ring sideroblast ≥ 15%), n (%)	52 (71)	36 (86)
LTB Patients	n=32	n=22
Hemoglobin, g/dL, median (range)	8.6 (6.4-10.1)	8.6 (6.4-10.1)
HTB Patients	n=41	n=20
Transfusions, units/8 wk, median (range)	6 (4-18)	6 (4-14)

Table 2. Baseline MDS Categories

Category n (%)	Base Study N=73	Extension Study N=42
WHO Subtypes		
RARS	14 (19)	9 (21)
RCMD-RS	33 (45)	22 (52)
RCMD	8 (11)	3 (7)
RAEB-1	8 (11)	5 (12)
Other (RAEB-2, del(5q), MDS/MPN)	9 (12)	2 (5)
Missing	1 (1)	1 (2)
IPSS		
Low	34 (47)	24 (57)
Int-1	38 (52)	18 (43)
Int-2	1 (1)	0
IPSS-R		
Very Low	12 (16)	8 (19)
Low	33 (45)	21 (50)
Intermediate	24 (33)	12 (29)
High	3 (4)	1 (2)
Very High	1 (1)	0

Safety

- Majority of adverse events (AEs) were grades 1 or 2
- Four possibly/probably related grade 3/serious AEs as of 28 Nov 2016: blast cell count increase, myalgia, worsening of general condition, progression to AML

Table 3. Adverse Events (Related/All Grades) in ≥ 2 Patients

Preferred Term	N (%)
Diarrhea	4 (6)
Fatigue	4 (6)
Headache	4 (6)
Hypertension	4 (6)
Arthralgia	3 (4)
Bone Pain	3 (4)
Injection Site Erythema	3 (4)
Myalgia	3 (4)
Edema peripheral	2 (3)

Erythroid Response

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

Baseline EPO (U/L)	RS Status	IWG HI-E, n/N (%) Base N=64	IWG HI-E, n/N (%) Extension N=42	RBC-TI, n/N (%) Base N=49	RBC-TI, n/N (%) Extension N=28
<200	RS+	18/29(62)	19/23(83)	13/19(68)	10/14(71)
	RS-	2/5(40)	3/3(100)	1/4(25)	1/2(50)
≥200 to ≤500	RS+	5/11(46)	7/8(88)	3/9(33)	3/5(60)
	RS-	0/3(0)	0/1(0)	2/2(100)	1/1(100)

Table 5. Response Rates in ESA Naïve/EPO ≤ 500 U/L Subpopulations
Patients Treated at Dose Levels ≥ 0.75 mg/kg

Transfusion Burden	IWG HI-E, n/N (%) Base N=64	IWG HI-E, n/N (%) Extension N=42	RBC-TI, n/N (%) Base N=49	RBC-TI, n/N (%) Extension N=28
All	12/20 (60)	13/16(81)	9/12 (75)	8/10(80)
LTB	6/13 (46)	8/11(73)	5/5 (100)	5/5(100)
HTB	6/7 (86)	5/5(100)	4/7 (57)	3/5(60)

Figure 1. Increase in Mean Hemoglobin in LTB Patients in Extension Study

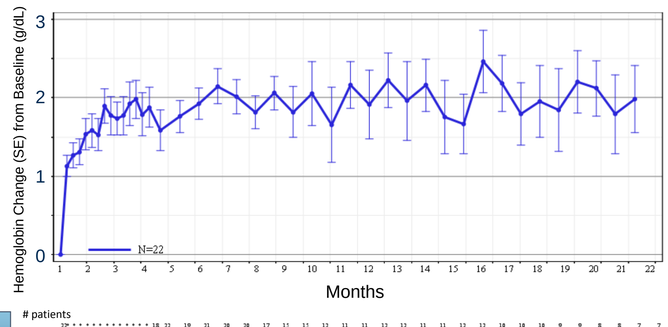
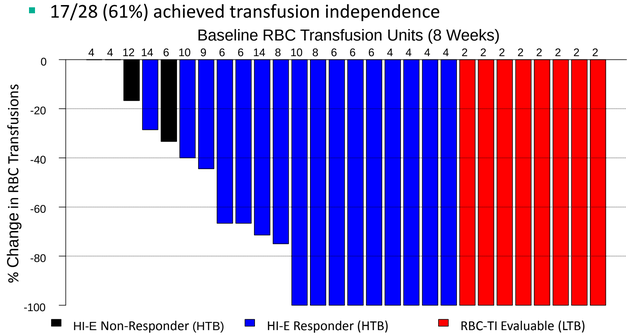


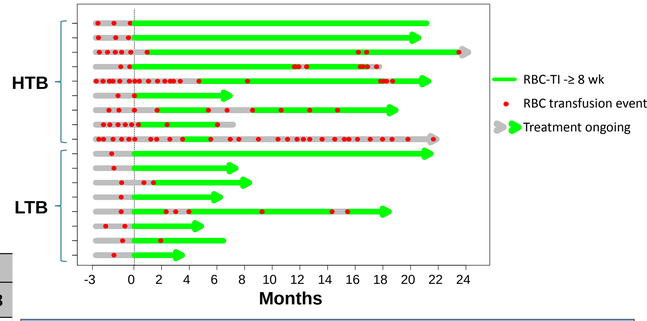
Figure 2. Reduction in Transfusion Burden in Extension Study

- 17/28 (61%) achieved transfusion independence



Erythroid Response

Figure 3. Duration of Transfusion Independence in RBC-TI Responders in Extension Study



Summary/Conclusions

- Lower-risk MDS patients treated with luspatercept demonstrated robust and sustained increases in hemoglobin and decreases in transfusion burden (per IWG HI-E) and a high rate of RBC transfusion independence
- In patients with EPO levels < 200, response rates were similar in both RS+ and RS- patients
- In patients with EPO levels ≥200 to ≤500, response rates were higher in RS+ compared to RS- patients
- These data support the initiation of Phase 3 studies of luspatercept in lower-risk MDS (MEDALIST NCT 02631070)

Acknowledgments/References

German MDS Study Group (D-MDS)
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