LUSPATERCEPT INCREASES HEMOGLOBIN AND REDUCES TRANSFUSION BURDEN IN PATIENTS WITH LOW OR INTERMEDIATE-1 RISK MYELODYSPLASTIC SYNDROMES (MDS): PRELIMINARY RESULTS FROM A PHASE 2 STUDY

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Faculty Disclosure

X	Yes

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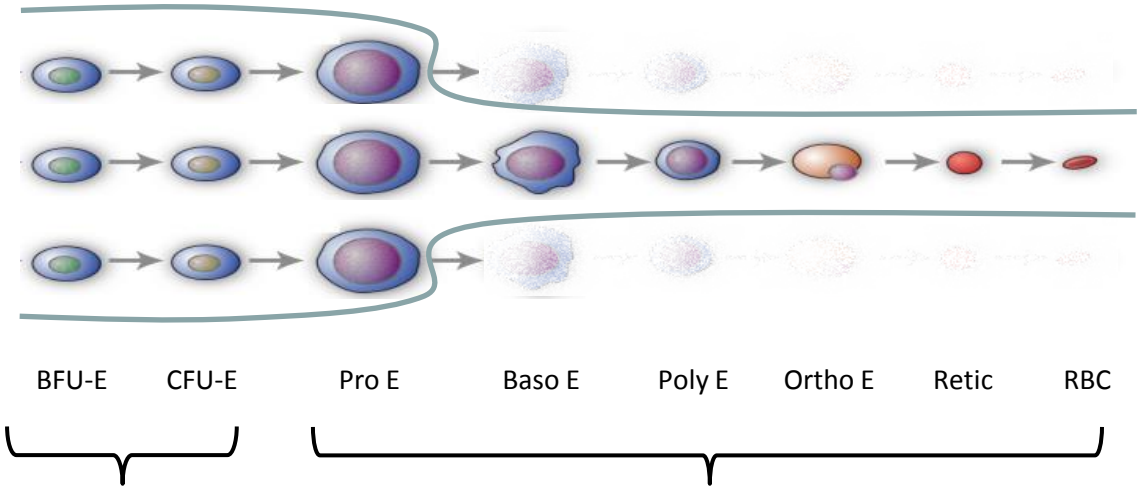
Will you be presenting or referencing off-label or investigational use of a therapeutic product?		
X	Yes	Clinical trial results for investigational product luspatercept

Ineffective Erythropoiesis in MDS

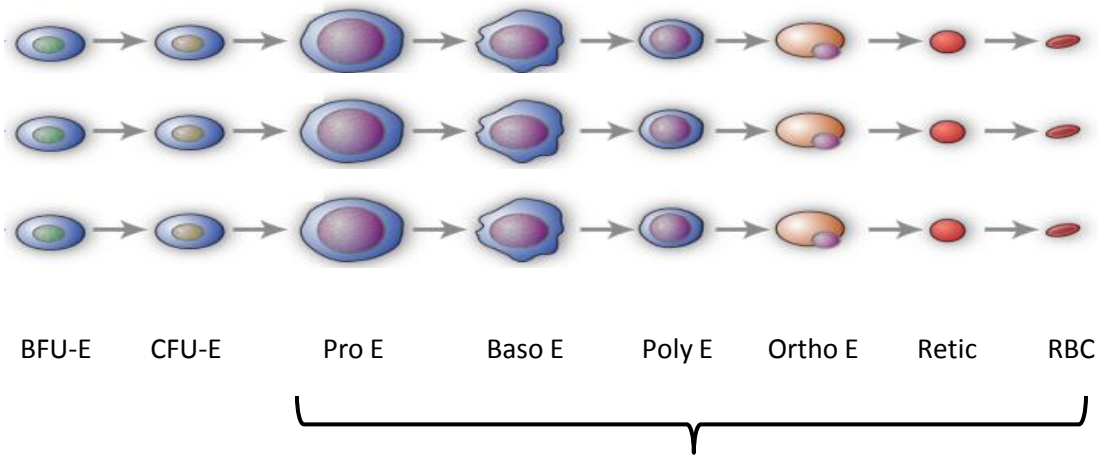
- Anemia, a hallmark of MDS, is challenging to treat, particularly after failure of ESAs[1]
- Defects in maturation of erythroid precursors (ineffective erythropoiesis) lead to erythroid hyperplasia and anemia
- Ineffective erythropoiesis is driven by excessive Smad2/3 signaling[2]



1. Fenaux P, et al. Blood. 2013;121:4280
2. Zhou L, et al. Blood 2008;112:3434

Luspatercept Activity in MDS

- Luspatercept, a modified activin receptor type IIB (ActRIIB) fusion protein, acts as a ligand trap for GDF11 and other ligands of the TGF-β superfamily to suppress Smad2/3 activation; increases Hgb in healthy volunteers[1]
- In a murine model of MDS, RAP-536 (murine ortholog of luspatercept) corrects ineffective erythropoiesis, reduces erythroid hyperplasia and increases hemoglobin[2]



Luspatercept promotes differentiation and maturation by trapping Smad2/3 activating ligands

1. Attie, K et al. Am J Hematol 2014;89:766
2. Suragani R et al., Nat Med 2014;20:408

Luspatercept PACE-MDS Study Overview

- Phase 2, multicenter, open-label, dose-finding, 3-month treatment study in IPSS low/int-1 MDS
- Eligibility criteria: nonresponsive/refractory to ESA or EPO >500 U/L; no prior azacitidine or decitabine; no current lenalidomide, ESA, G-CSF
- **Primary efficacy endpoint:**
  - Low transfusion burden (LTB, <4U RBC/8 weeks, Hgb <10 g/dL): Hemoglobin increase of ≥ 1.5 g/dL for ≥ 2 weeks
  - High transfusion burden (HTB, ≥4U RBC/8 weeks): Reduction of ≥4U or ≥50% units transfused over 8 weeks
- Luspatercept administered SC every 3 weeks x 5 doses in the study
  - Patients may be eligible for additional 12 months treatment in extension study (data not shown)

NCT01749514
EudraCT 2012-002523-14

Dosing Cohorts

- **Enrollment complete (N=58)**
  - **Dose Escalation, N=27, completed**
    - 7 sequential cohorts, n=3-6 each, luspatercept dose ranging from 0.125 to 1.75 mg/kg
  - **Expansion Cohort, N=31, ongoing**
    - Starting dose 1.0 mg/kg, individual dose titration up to 1.75 mg/kg
    - 17 patients had at least 4 cycles of treatment or discontinued early, and were included in the analysis as of 23 Feb 2015
  - **Preliminary results for 44 patients are presented**

	Dose Escalation							Expansion
Dose Level (mg/kg)	0.125	0.25	0.50	0.75	1.0	1.33	1.75	1.0[a]
No. of patients	3	3	3	6	3	6	3	17

[a]Starting dose level; dose level increased to 1.33 mg/kg in 5 patients and to 1.75 mg/kg in 1 patient

Data as of 23 Feb 2015

Baseline Characteristics (1 of 2)

	N = 44	
Age, yr, median (range)	71 (27-88)	
Sex, males (%)	25 (57%)	
Prior ESA treatment, n (%)	27 (61%)	
Prior lenalidomide treatment, n (%)	9 (21%)	
Time since diagnosis, yr, median (range)	2.5 (0.2-13.6)	
Hemoglobin, g/dL, LTB patients, median (range)	9.0 (6.8-10.1) (n=15)	
Units RBC transfused/8 weeks in patients who received transfusions, median (range)	LTB (n=6) 2 (2-2)	HTB (n=29) 6 (4-14)

Data as of 23 Feb 2015

Baseline Characteristics (2 of 2)

Patient Subgroup	N = 44 n (%)
IPSS	
Low	22 (50%)
Int-1	20 (46%)
Int-2	2 (4%)
IPSS-R	
Very Low	2 (4%)
Low	25 (57%)
Intermediate	14 (32%)
High	3 (7%)
Ring Sideroblast (RS)	**N=43**
RS positive (≥15% of cells)	35 (81%)
RS negative (<15% of cells)	8 (19%)
Splicing Mutation SF3B1	**N=43**
SF3B1 mutation present	25 (58%)
SF3B1 mutation absent	18 (42%)

Data as of 23 Feb 2015

Erythroid Response and Transfusion Independence

Response Criteria	Lower Dose Groups 0.125-0.5 mg/kg N=9 n (%)	Higher Dose Groups 0.75-1.75 mg/kg N=35 n (%)
Primary efficacy endpoint	3 (33%)	22 (63%)
IWG HI-E	2 (22%)	19 (54%)
Transfusion independence (Patients who received at least one transfusion)	1/7 (14%)	10/28 (36%) LTB 4/6 HTB 6/22

Primary efficacy endpoint: For LTB patients: Hemoglobin increase ≥ 1.5 g/dL for ≥ 2 weeks
For HTB patients: ≥ 4 Unit or ≥ 50% reduction in transfusions over 8 weeks

IWG HI-E: International Working Group, Hematologic Improvement – Erythroid Response
For LTB patients: Hemoglobin increase ≥ 1.5 g/dL for ≥ 8 weeks
For HTB patients: ≥ 4 Unit reduction in transfusions over 8 weeks

Transfusion Independence: Transfusion-free for ≥ 8 weeks on treatment

Data as of 23 Feb 2015

Transfusion Independence
Higher Dose Groups (0.75-1.75 mg/kg)

Transfusion Independence (TI)

- 10/28 (36%) patients achieved transfusion independence

Onset of TI

- 9 of the 10 TI patients had onset within the first 6 weeks of treatment

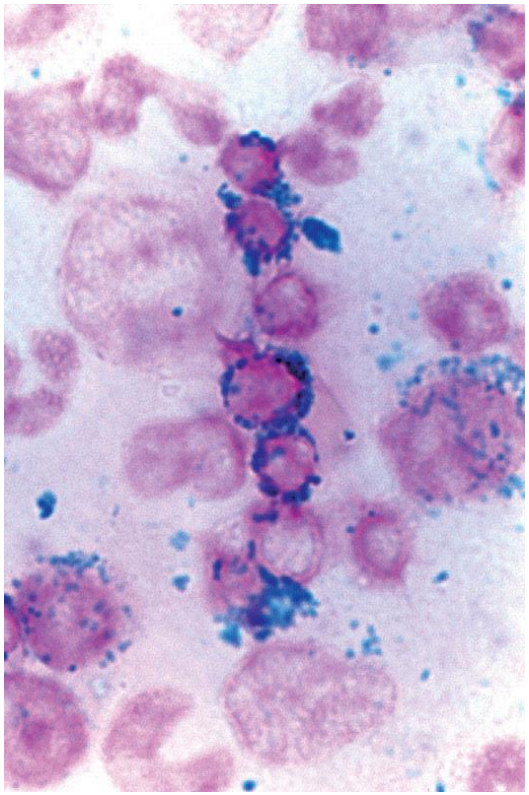
Duration of TI

- All 10 achieved transfusion independence for ≥10 weeks in this 3-month treatment study

Transfusion Independence: Transfusion-free for ≥ 8 weeks on treatment for patients who received at least one transfusion

Data as of 23 Feb 2015

Ring Sideroblasts, Somatic Mutations and Ineffective Erythropoiesis



- Ring sideroblasts (RS) are abnormal erythroid precursors with perinuclear siderotic granules
- Approximately 30% of all MDS (WHO) patients, and a greater proportion of lower risk patients, are RS positive and demonstrate ineffective erythropoiesis[1]
- Nearly all MDS patients with dominant mutations in splicing factor 3B1 (SF3B1) are RS positive[2]
- Knock-in mutation of SF3B1 (K700E) in mice causes ineffective erythropoiesis by blocking maturation of late-stage erythroid precursors[3]
- Luspatercept corrects ineffective erythropoiesis by promoting late-stage erythroid differentiation and maturation[4]

1. Haferlach T et al. Leukemia 2014;28:241, Germing U et al. Haematologica 2006;91:1596
2. Cazzola M et al. Blood 2013;122:4021
3. Obeng E et al. Abstract 828, ASH 2014
4. Suragani R et al., Nat Med 2014;20:408

Erythroid Response in RS+, mSF3B1 Patients
Higher Dose Groups (0.75-1.75 mg/kg)

Patient Population	IWG HI-E
All Patients (n=35)	19 (54%)
RS positive (n=30)	19 (63%)
RS negative (n=4)	0 (0%)
SF3B1 mutation present (n=22)	16 (73%)
SF3B1 mutation absent (n=13)	3 (23%)

IWG HI-E: For LTB patients: Hemoglobin increase ≥ 1.5 g/dL for ≥ 8 weeks
For HTB patients: ≥ 4 Unit reduction in transfusions over 8 weeks

- 39% (9/23) of RS positive patients achieved transfusion independence (TI)

Data as of 23 Feb 2015

Safety Summary

Adverse events (all grades) reported in ≥ 4 patients, regardless of causality

Preferred Term n (%)	0.125 mg/kg (N=3)	0.25 mg/kg (N=3)	0.50 mg/kg (N=3)	0.75 mg/kg (N=6)	1.0 mg/kg (N=3)	1.33 mg/kg (N=6)	1.75 mg/kg (N=3)	Exp 1.0 mg/kg (N=17)	Overall (N=44)
Diarrhea	0	1 (33)	1 (33)	1 (17)	0	1 (17)	0	2 (12)	6 (14)
Nasopharyngitis	0	1 (33)	0	2 (33)	0	0	0	3 (18)	6 (14)
Myalgia	0	1 (33)	1 (33)	0	1 (33)	0	0	2 (12)	5 (11)
Bone pain	0	0	1 (33)	0	2 (67)	0	0	1 (6)	4 (9)
Bronchitis	0	0	0	0	1 (33)	0	0	3 (18)	4 (9)
Headache	0	0	0	1 (17)	0	1 (17)	0	2 (12)	4 (9)
Muscle spasms	0	0	2 (67)	0	1 (33)	0	1 (33)	0	4 (9)

- Majority of adverse events (AEs) were grade 1 or 2
- Two possibly related serious adverse events (SAEs): grade 3 muscle pain (onset day 90); grade 3 worsening of general condition (onset day 46, recurred day 66, unrelated)
- One possibly related non-serious grade 3 AE of blast cell count increase

Data as of 23 Feb 2015

Luspatercept PACE-MDS Study: Conclusions

- In this 3 month study, lower risk MDS patients treated with luspatercept ≥ 0.75 mg/kg demonstrated a robust hematologic improvement (54% achieved IWG HI-E)
- A greater response rate was achieved in RS positive patients in the higher dose groups
  - 63% achieved IWG HI-E
  - 39% achieved transfusion independence
- Luspatercept was generally safe and well-tolerated
- These results support pivotal, controlled studies of luspatercept in patients with lower-risk MDS

Luspatercept PACE-MDS Study: Acknowledgements

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