Luspatercept Response in New Subpopulations of Patients With Lower-Risk Myelodysplastic Syndromes (MDS): Update of the PACE Study

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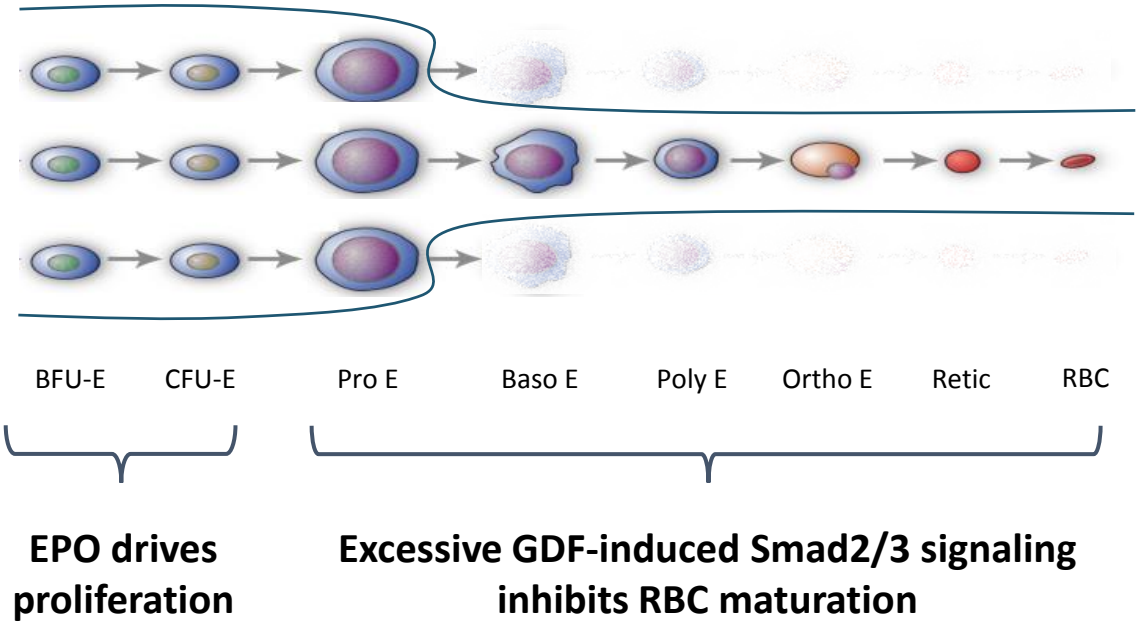
Ineffective Erythropoiesis in MDS

- 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



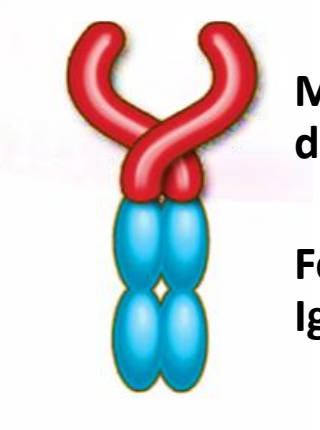
EPO: erythropoietin; ESA: erythropoiesis-stimulating agent; GDF: growth and differentiation factor; RBC: red blood cell

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

Luspatercept (ACE-536) Activity in MDS

- 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

Luspatercept



Modified extracellular domain of ActRIIB receptor

Fc domain of human IgG1 antibody

GDF: growth and differentiation factor; IgG: immunoglobulin G; TGF: transforming growth factor

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

Luspatercept PACE-MDS Phase 2 Clinical Trials Overview

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=89)
3 months → **Extension Study (N=52)**
5 years (ongoing)

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

EPO: erythropoietin; ESA: erythropoiesis-stimulating agent; HI-E: hematologic improvement erythroid; RS: ring sideroblast

Data as of 03 Feb 2017

Luspatercept Lower-Risk MDS Clinical Trials Overview

Phase 2

PACE-MDS

Current Phase 2 study has been expanded to include lower-risk MDS patient subgroups excluded from MEDALIST including ESA-naïve who are:

- RS+ and EPO ≤200 IU/L
- RS- and any EPO level

NCT01749514; NCT02268383

Phase 3

MEDALIST

An ongoing Phase 3 study of lower-risk MDS patients who are:

- Regularly transfused
- RS+
- ESA refractory or ineligible

(ESA-naïve and EPO >200 IU/L)

NCT02631070

EPO: erythropoietin; ESA: erythropoiesis stimulating agent; RS: ring sideroblast

Demographics and Baseline Characteristics

Efficacy Evaluable Population: Patients Treated at Dose Levels ≥ 0.75 mg/kg

Parameter	N=82
Age, yr, median (range)	72 (29-90)
Sex, male, n (%)	52 (63%)
Time since diagnosis, yr, median (range)	2.3 (0-14)
Prior ESA treatment, n (%)	43 (52)
Baseline EPO, n (%)	
<200 IU/L	41 (50%)
200-500 IU/L	19 (23%)
>500 IU/L	22 (27%)
Ring sideroblast (RS) status, n (%)	
RS+ (RS ≥ 15%)	55 (67%)
RS-	25 (31%)
Unknown	2 (2%)
IWG HI-E evaluable	n=82
Hemoglobin, g/dL, median (range)	8.4 (6-10)
Transfusions, units/8 wk, median (range)	2 (0-18)
RBC-TI evaluable	n=56
Hemoglobin, g/dL, median (range)	8.2 (6-10)
Transfusions, units/8 wk, median (range)	4 (2-18)

IWG HI-E evaluable: all efficacy-evaluable patients

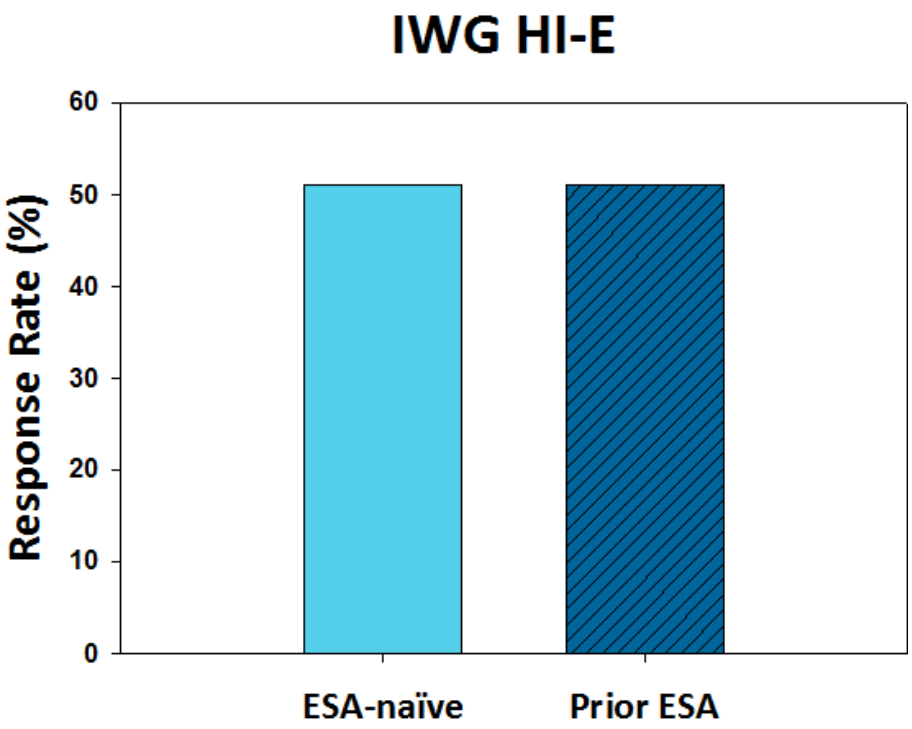
RBC-TI evaluable: efficacy-evaluable patients with ≥ 2 units/8 weeks of RBC transfused at baseline

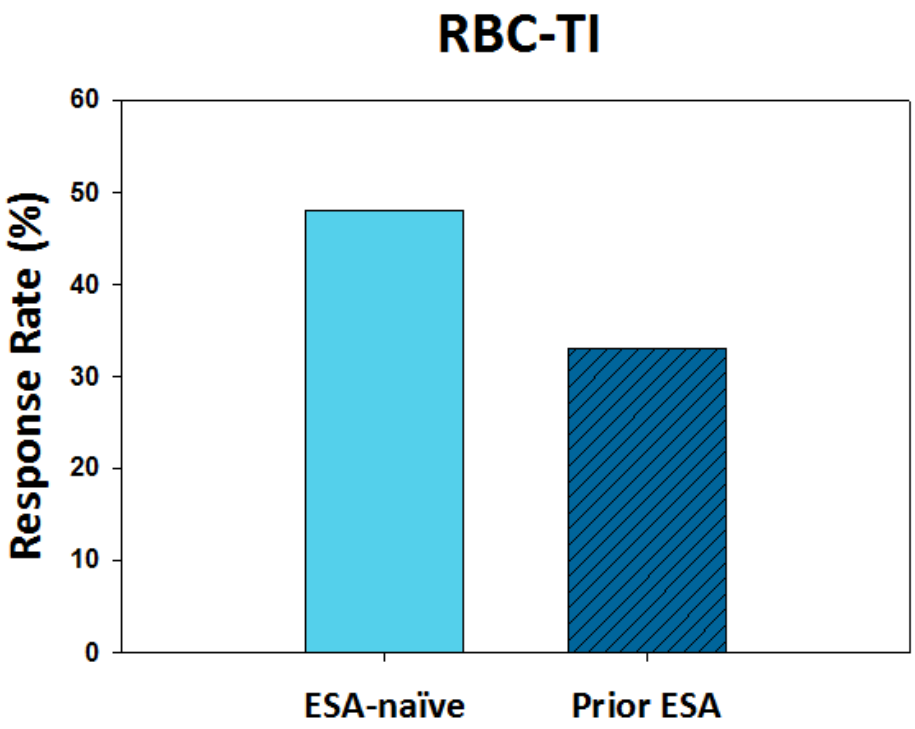
Data as of 03 Feb 2017

Data to be Presented on the Following Subpopulations

- ESA exposure:
  - Naïve
  - Prior treatment
- Baseline EPO levels:
  - < 200 IU/L
  - 200-500 IU/L
  - > 500 IU/L
- Baseline RBC transfusion burden:
  - 0 units/8 weeks
  - ≥ 2 units/8 weeks
- Ring sideroblast (RS) status:
  - RS+
  - RS-

Response Rates in Patients by ESA Exposure

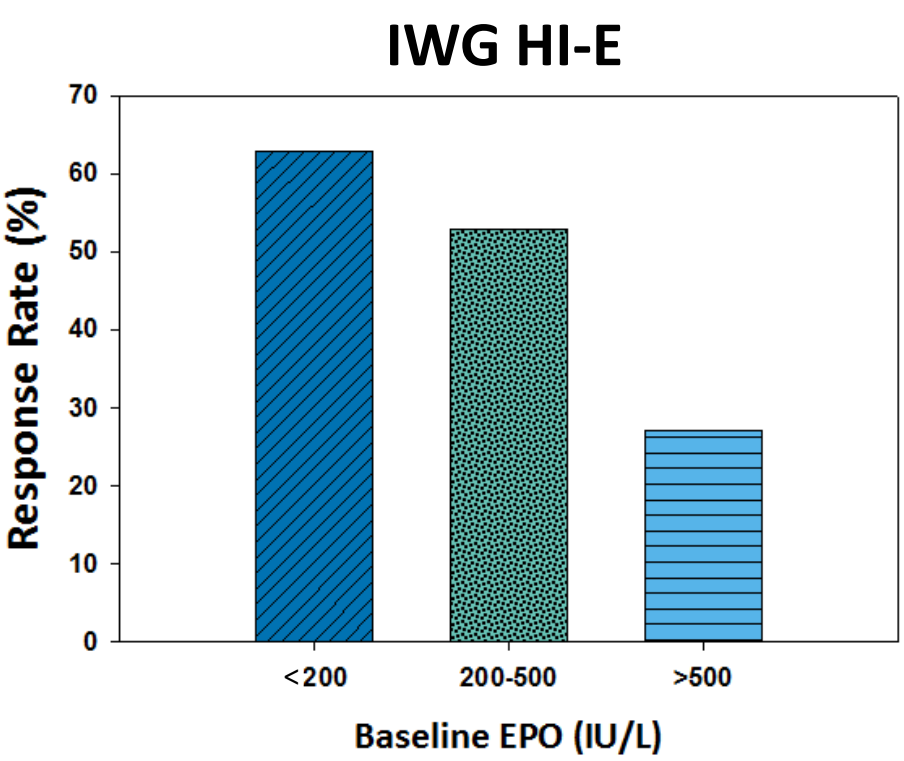


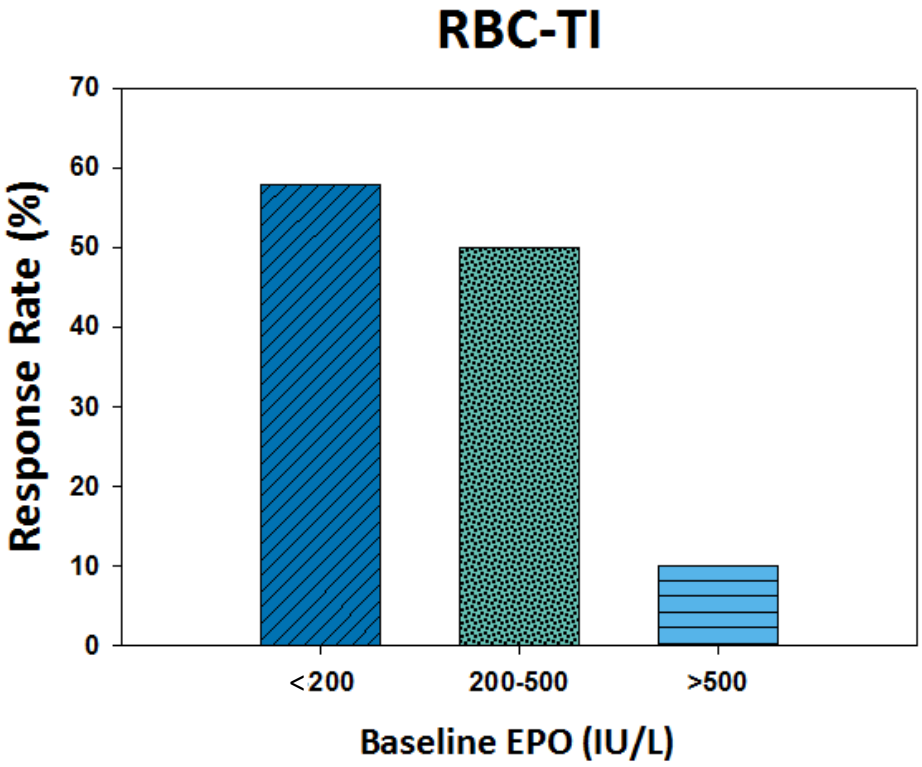


	IWG HI-E, n/N N=82	RBC-TI, n/N N=56
All patients	42/82 (51%)	22/56 (39%)
ESA-naïve	20/39 (51%)	11/23 (48%)
Prior ESA	22/43 (51%)	11/33 (33%)

Data as of 03 Feb 2017

Response Rates in Patients by Baseline EPO Levels





Baseline EPO (IU/L)	IWG HI-E, n/N (%) N=82	RBC-TI, n/N (%) N=56
< 200	26/41 (63%)	14/24 (58%)
200 - 500	10/19 (53%)	6/12 (50%)
> 500	6/22 (27%)	2/20 (10%)

Data as of 03 Feb 2017

Response Rates by Baseline Transfusion Burden in Patients With Baseline EPO ≤ 500 IU/L

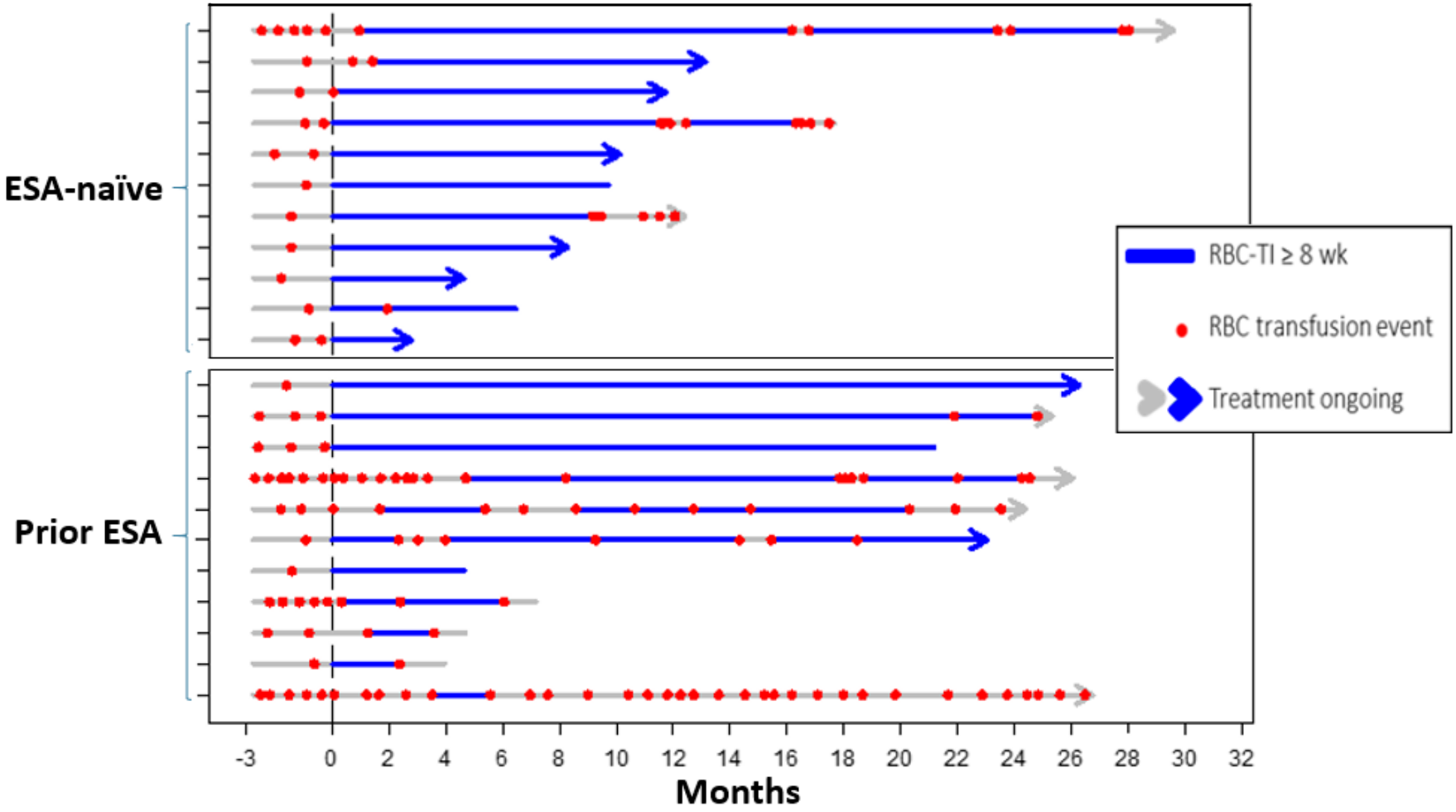
Baseline RBC Transfusion Burden	IWG HI-E, n/N (%)	RBC-TI, n/N (%)
All patients (EPO ≤ 500 IU/L)		
0-1 unit	15/24 (63%)	N/A
≥ 2 units	21/36 (58%)	20/36 (56%)
ESA-naïve (EPO ≤ 500 IU/L)		
0-1 unit	9/15 (60%)	N/A
≥ 2 units	9/13 (69%)	10/13 (77%)
Prior ESA (EPO ≤ 500 IU/L)		
0-1 unit	6/9 (67%)	N/A
≥ 2 units	12/23 (52%)	10/23 (43%)

RBC-TI evaluable: efficacy-evaluable patients with ≥ 2 units of RBC transfused at baseline

Data as of 03 Feb 2017

Pattern of Responses in Patients Achieving at Least 8 Weeks of Transfusion Independence

Patients with Baseline RBC ≥ 2 Units

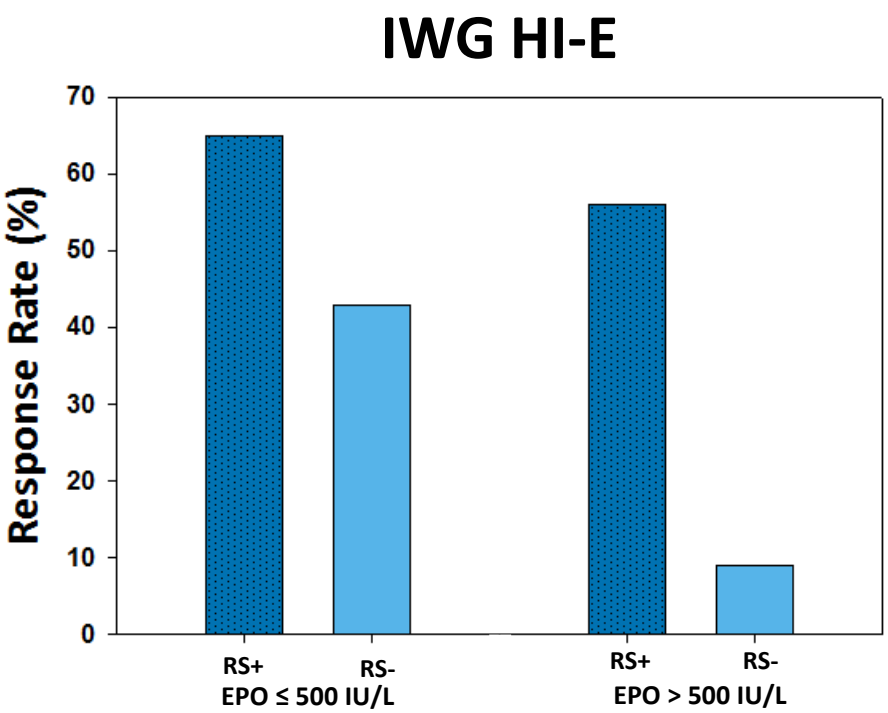


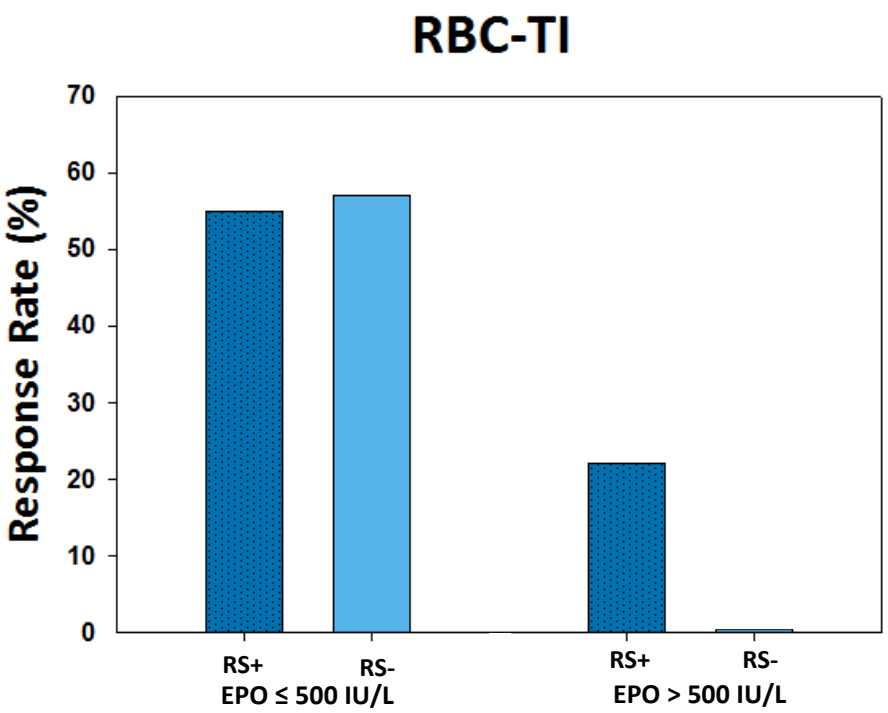
- Median duration of RBC-TI response: 8.7 months, range 2-27 months

RBC-TI: RBC-transfusion independence ≥ 8 weeks

Data as of 03 Feb 2017

Response Rates in Patients by Baseline EPO Level and RS Status Regardless of ESA Exposure





Baseline EPO Level (IU/L)	RS Status	IWG HI-E, n/N (%) N=82	RBC-TI, n/N (%) N=56
EPO ≤ 500	RS+	30/46 (65%)	16/29 (55%)
	RS-	6/14 (43%)	4/7 (57%)
EPO > 500	RS+	5/9 (56%)	2/9 (22%)
	RS-	1/11 (9%)	0/9 (0%)
	Unknown	0/2 (0%)	0/2 (0%)

Data as of 03 Feb 2017

Safety Summary in All Patients

- Majority of adverse events (AEs) were grade 1 or 2
- Six related grade 3 AEs: ascites, blast cell count increase, blood bilirubin increase, hypertension, platelet count increase, pleural effusion
- Two related grade 3 SAEs: general physical health deterioration, myalgia

Preferred Term	Related AEs in > 2 patients, Any Grade, n (%)
Fatigue	6 (6.7)
Headache	6 (6.7)
Hypertension	5 (5.6)
Diarrhea	4 (4.5)
Arthralgia	3 (3.4)
Bone Pain	3 (3.4)
Injection Site Erythema	3 (3.4)
Myalgia	3 (3.4)
Edema peripheral	3 (3.4)

Possibly or probably related
N=89, all patients treated at all dose levels

Data as of 03 Feb 2017

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
- Encouraging responses seen in patients with baseline EPO 0-200 and 200-500 IU/L
  - More favorable RBC-TI responses were observed in ESA-naïve patients
- Emerging data in RS- patients are promising, especially in patients with baseline EPO ≤ 500 IU/L
- Luspatercept was generally well-tolerated for patients on treatment greater than 24 months

The MEDALIST Study

Phase 3 Study of Luspatercept in MDS: NOW ENROLLING

MEDALIST

Patient Population / Study Design	Randomized, double-blind, placebo-controlled study in very low, low, or intermediate risk (IPSS-R) MDS patients with ring sideroblasts (RS+) who require RBC transfusion 210 patients randomized 2:1; luspatercept 1 mg/kg SC every 3 weeks, titration up to 1.75 mg/kg possible
Key Inclusion Criteria	Refractory / intolerant to prior ESA *or* EPO > 200 IU/L RS+; <5% blasts; no prior HMA or lenalidomide ≥ 2 units RBCs transfused / 8 weeks Excluded: del(5q), secondary MDS
Primary Efficacy Endpoint	Proportion of patients who become RBC-transfusion independent (≥ 8 weeks) during the first 24 weeks

Study sponsored by Celgene in collaboration with Acceleron Pharma

NCT02631070

Luspatercept PACE-MDS Study: Acknowledgments

- **German MDS Study Group (D-MDS)**
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