Luspatercept significantly reduces red blood cell transfusion burden, regardless of gene mutation frequency, spectrum, and prognostic significance, among patients with lower-risk myelodysplastic syndromes enrolled in the MEDALIST trial

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Introduction

- There are few treatment options for the majority of patients with Revised International Prognostic Scoring System (IPSS-R)-defined lower-risk, red blood cell (RBC) transfusion-dependent myelodysplastic syndromes (MDS) who are refractory, intolerant, or ineligible/unlikely to respond (serum erythropoietin > 200 U/L) to erythropoiesis-stimulating agents (ESAs)[1]
- Luspatercept is a first-in-class erythroid maturation agent that binds several TGF-β superfamily ligands to decrease Smad2/3 signaling and enhance late-stage erythropoiesis[2]
- The phase 3 MEDALIST trial evaluated luspatercept in patients with IPSS-R defined Very low-, Low-, and Intermediate-risk MDS with ring sideroblasts (RS+) requiring regular RBC transfusions who were refractory, intolerant, unlikely to respond to, or ineligible for ESAs[3]

Objective

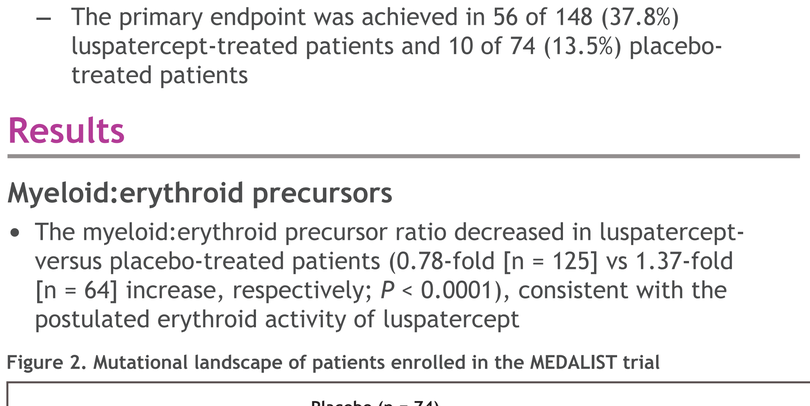
- To explore the association between MDS-relevant gene mutations and response to luspatercept, as well as the dynamics of gene mutations on therapy in MEDALIST patients

Methods

Study design

- MEDALIST is a phase 3, randomised, double-blind, placebo-controlled trial (NCT02631070)
- Eligible patients were randomised 2:1 to receive luspatercept (starting dose 1.0 mg/kg, titration allowed to 1.75 mg/kg) or placebo subcutaneously every 3 weeks for ≥ 24 weeks (**Figure 1**)

Figure 1. MEDALIST trial study design



Data cutoff: May 8, 2018. Includes last patient randomised + 48 weeks.
[a]≥ 2 units/8 weeks for ≥ 16 weeks prior to randomisation with no consecutive 56-day transfusion-free period during the preceding 16 weeks.
AML, acute myeloid leukaemia; ESA, erythropoiesis-stimulating agent; HMA, hypomethylating agent; iMID, immunomodulatory drug; IPSS-R, Revised International Prognostic Scoring System; IWG, International Working Group; MDS, myelodysplastic syndromes; RBC, red blood cell; RS, ring sideroblast; s.c., subcutaneously; sEPO, serum erythropoietin; WHO, World Health Organization.

Mutational and cytogenetic analysis

- DNA was isolated from bone marrow mononuclear cells (BMMCs) from 222 of 229 patients (148 luspatercept and 74 placebo) enrolled in the study at screening and, when available, every 24 weeks following treatment (137 luspatercept and 69 placebo)
- Next-generation sequencing of 23 MDS-relevant genes was performed
  - Mean coverage was 1,000-fold and the variant allele frequency (VAF) cutoff was ≥ 1%
- Bone marrow cell populations were analyzed by cytomorphology
- Correlative analyses were carried out using the primary response criterion of RBC transfusion independence (RBC-TI) ≥ 8 weeks within the first 24 weeks of treatment
  - The primary endpoint was achieved in 56 of 148 (37.8%) luspatercept-treated patients and 10 of 74 (13.5%) placebo-treated patients

Results

Myeloid:erythroid precursors

- The myeloid:erythroid precursor ratio decreased in luspatercept- versus placebo-treated patients (0.78-fold [n = 125] vs 1.37-fold [n = 64] increase, respectively; $P < 0.0001$), consistent with the postulated erythroid activity of luspatercept

Figure 2. Mutational landscape of patients enrolled in the MEDALIST trial

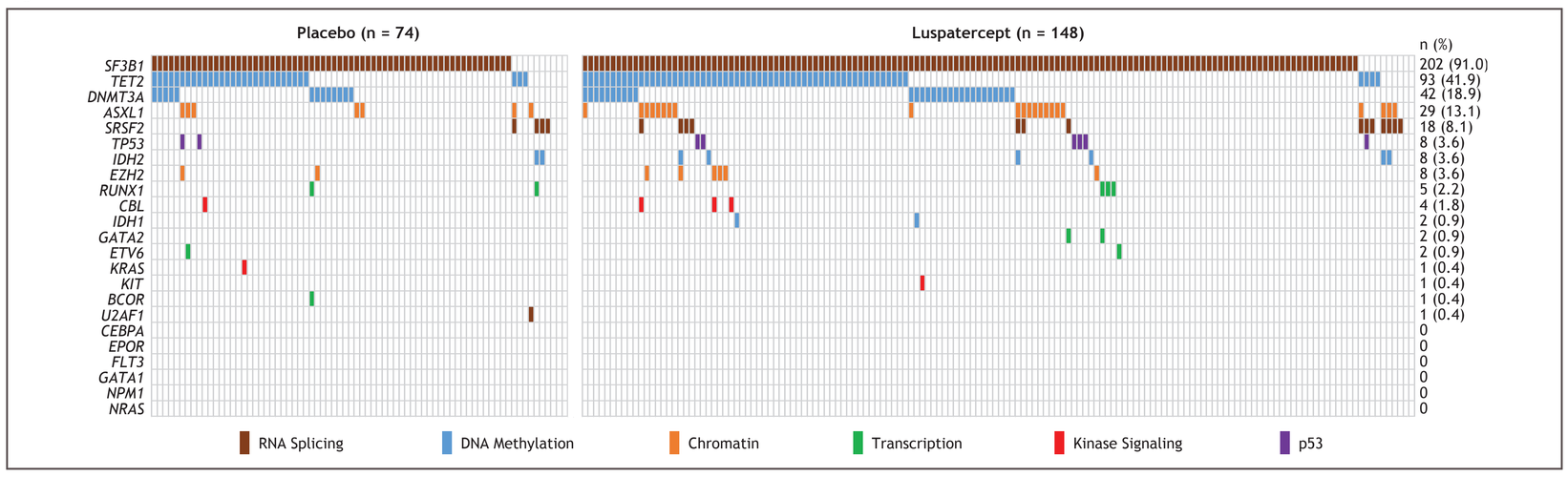
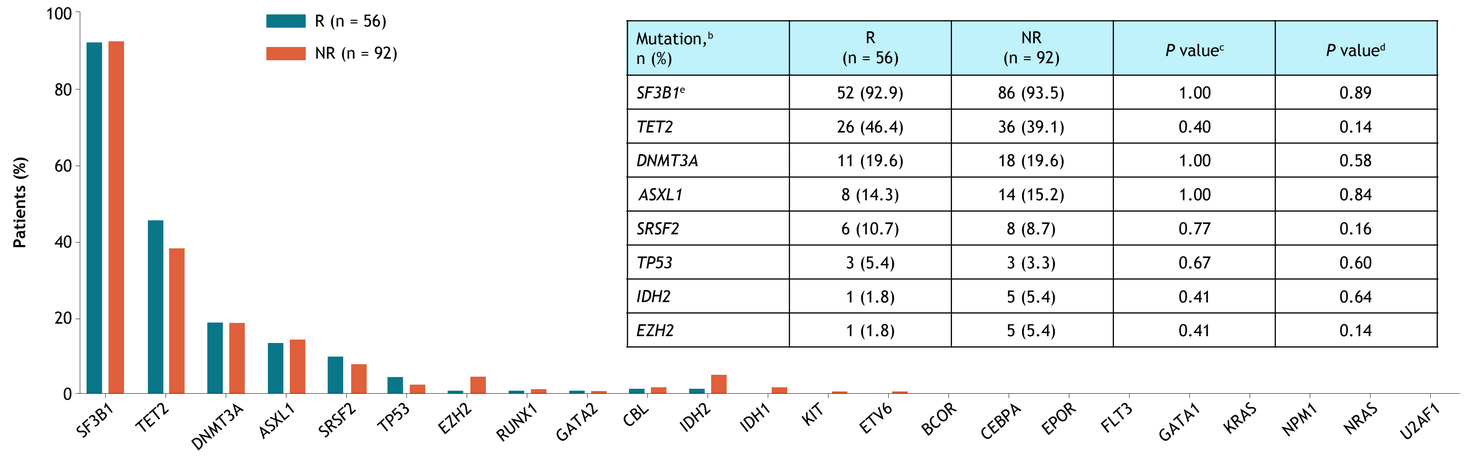


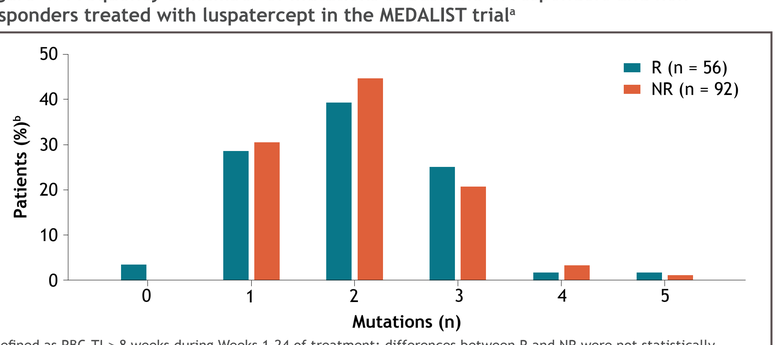
Figure 3. Frequency of mutations at baseline for patients treated with luspatercept in the MEDALIST trial, classified by response[a]



Mutation,[b] n (%)	R (n = 56)	NR (n = 92)	*P* value[c]	*P* value[d]
SF3B1[e]	52 (92.9)	86 (93.5)	1.00	0.89
TET2	26 (46.4)	36 (39.1)	0.40	0.14
DNMT3A	11 (19.6)	18 (19.6)	1.00	0.58
ASXL1	8 (14.3)	14 (15.2)	1.00	0.84
SRSF2	6 (10.7)	8 (8.7)	0.77	0.16
TP53	3 (5.4)	3 (3.3)	0.67	0.60
IDH2	1 (1.8)	5 (5.4)	0.41	0.64
EZH2	1 (1.8)	5 (5.4)	0.41	0.14

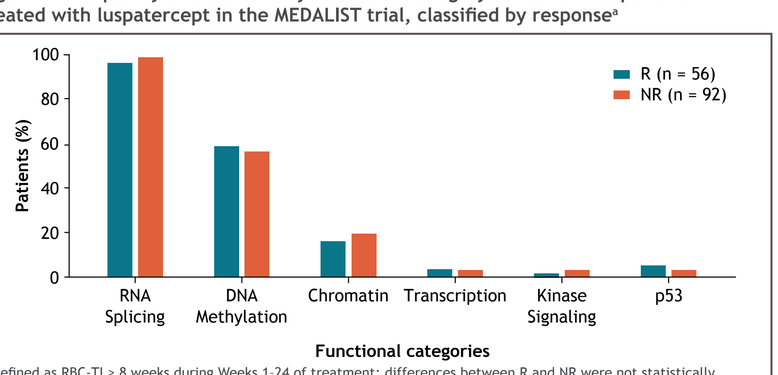
[a]Defined as RBC-TI ≥ 8 weeks during Weeks 1-24 of treatment. [b]Only mutations present in ≥ 5 patients are shown. [c]Fisher's exact test. [d]Multifactor ANOVA; *P* values were derived adjusting for baseline demographic and cellular composition status. [e]Response rates were also similar regardless of baseline *SF3B1* variable allele frequency (R: 43%, NR: 42%; $P = 0.11$).
ANOVA, analysis of variance; NR, non-responder; R, responder; RBC-TI, red blood cell transfusion independence.

Figure 4. Frequency of number of mutations at baseline in responders and non-responders treated with luspatercept in the MEDALIST trial[a]



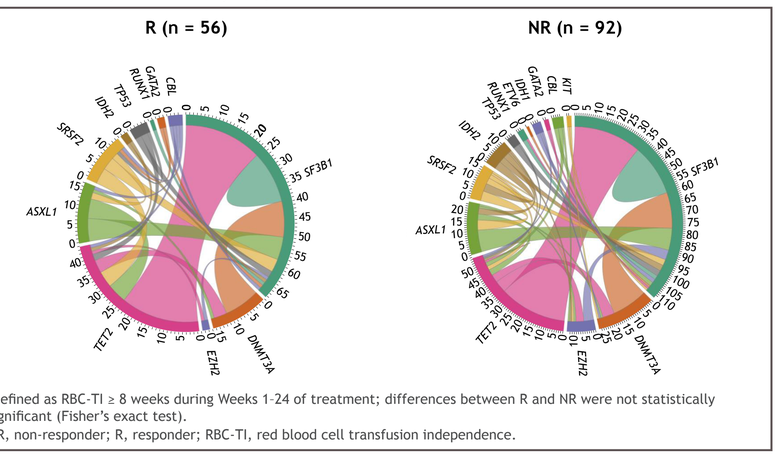
[a]Defined as RBC-TI ≥ 8 weeks during Weeks 1-24 of treatment; differences between R and NR were not statistically different. [b]Frequencies were calculated separately for R and NR. Frequencies were calculated as the percentage of R or NR patients with the indicated number of mutations of the total number of R or NR, respectively.
NR, non-responder; R, responder; RBC-TI, red blood cell transfusion independence.

Figure 5. Frequency of mutations by functional category at baseline of patients treated with luspatercept in the MEDALIST trial, classified by response[a]



[a]Defined as RBC-TI ≥ 8 weeks during Weeks 1-24 of treatment; differences between R and NR were not statistically significant in any category (Fisher's exact test).
NR, non-responder; R, responder; RBC-TI, red blood cell transfusion independence.

Figure 6. Co-occurrence of mutations for patients treated with luspatercept in the MEDALIST trial, classified by response[a]

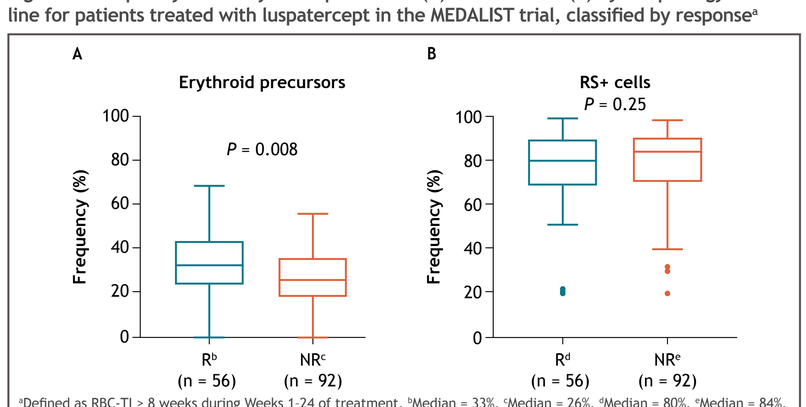


[a]Defined as RBC-TI ≥ 8 weeks during Weeks 1-24 of treatment; differences between R and NR were not statistically significant (Fisher's exact test).
NR, non-responder; R, responder; RBC-TI, red blood cell transfusion independence.

Table 1. Acquisition and loss of mutations by Week 25

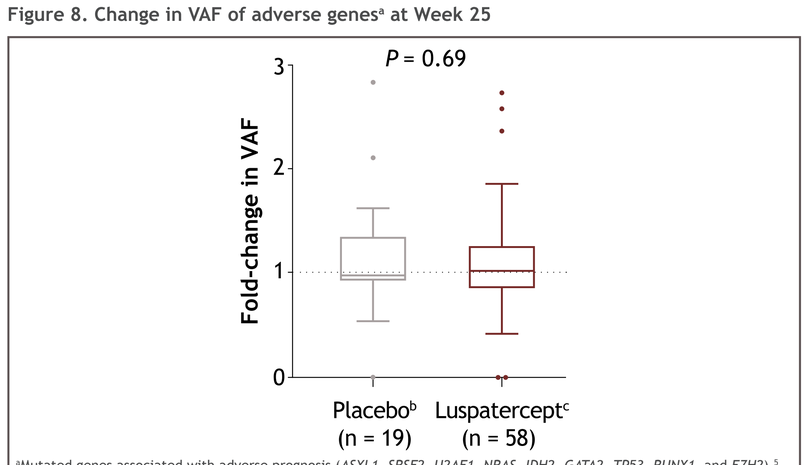
Patients with change in mutation status, n (%)	Luspatercept (n = 126)	Placebo (n = 64)	*P* value
Acquisition of mutations	13 (10.3)	8 (12.5)	0.63
Loss of mutations	4 (3.2)	5 (7.8)	0.16

Figure 7. Frequency of BM erythroid precursors (A) and RS+ cells (B) by morphology at baseline for patients treated with luspatercept in the MEDALIST trial, classified by response[a]



[a]Defined as RBC-TI ≥ 8 weeks during Weeks 1-24 of treatment. [b]Median = 33%. [c]Median = 26%. [d]Median = 80%. [e]Median = 84%.
BM, bone marrow; NR, non-responder; R, responder; RBC-TI, red blood cell transfusion independence; RS, ring sideroblasts.

Figure 8. Change in VAF of adverse genes[a] at Week 25



[a]Mutated genes associated with adverse prognosis (*ASXL1*, *SRSF2*, *U2AF1*, *NRAS*, *IDH2*, *GATA2*, *TP53*, *RUNX1*, and *EZH2*).[5] [b]Median 0.95-fold change. [c]Median 1.01-fold change.
VAF, variant allele frequency.

Conclusions

- Patients enrolled in the MEDALIST study had mutation profiles consistent with RS+ MDS,[6] with a preponderance of *SF3B1* mutations
- RBC-TI responses with luspatercept were achieved regardless of the presence of individual mutations, number of mutations, mutations in various functional categories, or co-mutations at baseline
- At baseline, bone marrow erythroid precursors were higher in luspatercept-treated responders versus non-responders, whereas levels of RS+ cells were similar, indicating that the relative proportion of RS+ erythroid cells is not associated with response to luspatercept
- No difference was observed between luspatercept and placebo-treated patients in the frequency of acquisition or loss of mutations, or changes in VAF for genes associated with adverse prognosis

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Acknowledgments

- The study was supported by Celgene, a Bristol-Myers Squibb Company in collaboration with Acceleron Pharma
- All authors contributed to and approved the presentation; writing and editorial assistance were provided by James O'Reilly, PhD, of Excerpta Medica, funded by Bristol-Myers Squibb Company

Disclosures

G.J.M.: Celgene (now BMS) - research funding. P.V., O.I.: no conflicts to disclose. G.G-M.: Astex, BMS, Helsinn - consultancy; AbbVie, Amphivena, Astex, BMS, Celgene (now BMS), H3Bio, Helsinn, Merck, Novartis, Onconova - grant/research support. R.B.: Celgene (now BMS) - consultancy; Celgene (now BMS), Otsuka - research funding; Celgene (now BMS) - honoraria. V.S.: Celgene (now BMS), J&J, Novartis - honoraria; Acceleron, Amgen, Celgene (now BMS), Menarini, Novartis - membership on an entity's board of directors or advisory committee. M.D-C.: Celgene (now BMS), Novartis - consultancy; Celgene (now BMS), Novartis - research funding; Celgene (now BMS) and Novartis - membership on an entity's board of directors or advisory committee. C.F.: Celgene (now BMS), Janssen, Novartis - consultancy; Celgene (now BMS) - research funding; Celgene (now BMS), Janssen, Novartis - speakers bureau. M.A.S.: Celgene (now BMS), Millennium, Syros - membership on an entity's board of directors or advisory committee. R.S.K.: AbbVie, Agios, Celgene (now BMS), DSI, Incyte, Pfizer - consultancy; AbbVie, Agios, Jazz Pharmaceuticals - speakers bureau. A.M.Z.: AbbVie, Acceleron Pharma, Boehringer-Ingelheim, elgene (now BMS), Epizyme, Incyte, Ionis, Otsuka, Pfizer, Takeda, Trovagene - consultancy; AbbVie, Acceleron Pharma, ADC Therapeutics, Boehringer-Ingelheim, Celgene (now BMS), Incyte, Medimmune/AstraZeneca, Otsuka, Pfizer, Takeda, Trovagene - research funding; AbbVie, Acceleron Pharma, Agios, Ariad, Astellas, BeyondSpring, Boehringer-Ingelheim, Cardinal Health, Celgene (now BMS), Daiichi-Sankyo, Epizyme, Incyte, Ionis, Jazz Pharmaceuticals, Novartis, Otsuka, Pfizer, Seattle Genetics, Takeda, Trovagene - honoraria; Ionis - advisory board. A.V.: Celgene (now BMS), Janssen - research funding; Acceleron Pharma, Celgene (now BMS), Stelexis -honoraria; Stelexis - equity ownership. D.R.D., A.L.: BMS - former employment, equity ownership. P.G.L.: Acceleron Pharma - former employment, equity ownership; Abbott Laboratories, Inc., Fibrogen, Inc., - equity ownership. A.F.L.: Acceleron Pharma, Aileron Therapeutics, Celgene (now BMS), Cellular Biomedicine Group, International Personalized Cancer Center Advisory Committee - membership on a board of directors or advisory committees; Celgene (now BMS), Cellular Biomedicine Group - travel, accommodations, expenses; Thousand Talent Award - other; Aileron Therapeutics, Celgene (now BMS), Cellular Biomedical Group - honoraria; Celgene (now BMS) - research funding. P.F.: Aprea, Astex, Celgene (now BMS), Jazz Pharmaceuticals - research funding; Astex, Celgene (now BMS), Jazz Pharmaceuticals - honoraria. U.P.: AbbVie, Celgene (now BMS), Novartis - consultancy; AbbVie, Celgene (now BMS), Novartis - honoraria.

Presented at the 60th Annual Scientific Meeting of the British Society for Haematology (BSH); 9-14 November 2020.