Targeted therapy in low-risk MDS

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Disclosures

	No, nothing to disclose
X	Yes, please specify:

Company Name	Honoraria/ Expenses	Consulting/ Advisory Board	Funded Research	Royalties/ Patent	Stock Options	Ownership/ Equity Position	Employee	Other (please specify)
Celgene/BMS	x	X	x					
Novartis	x		x					
Curis			x					
Jazz	x		x					
Amgen			x					

Off-Label Product Use

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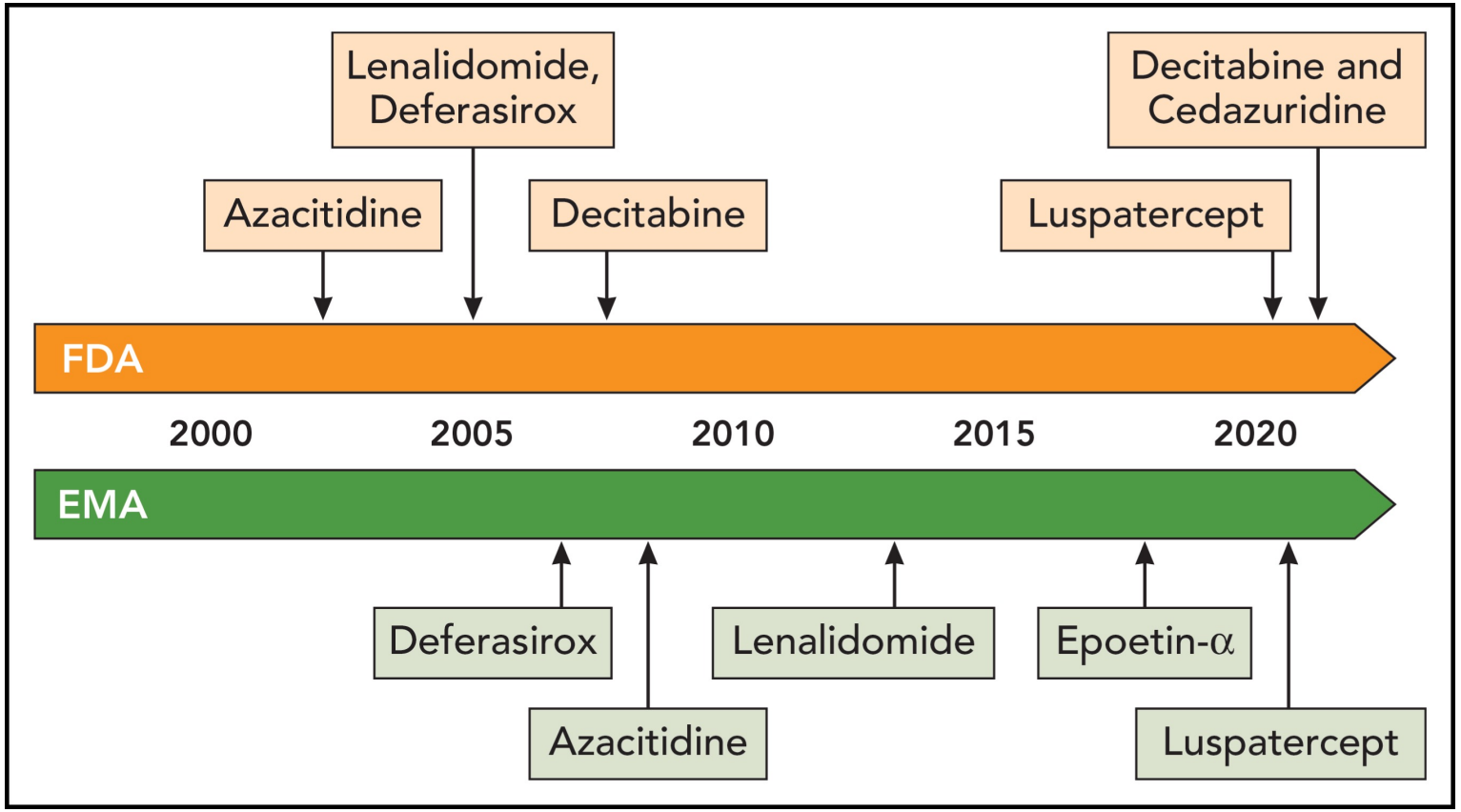
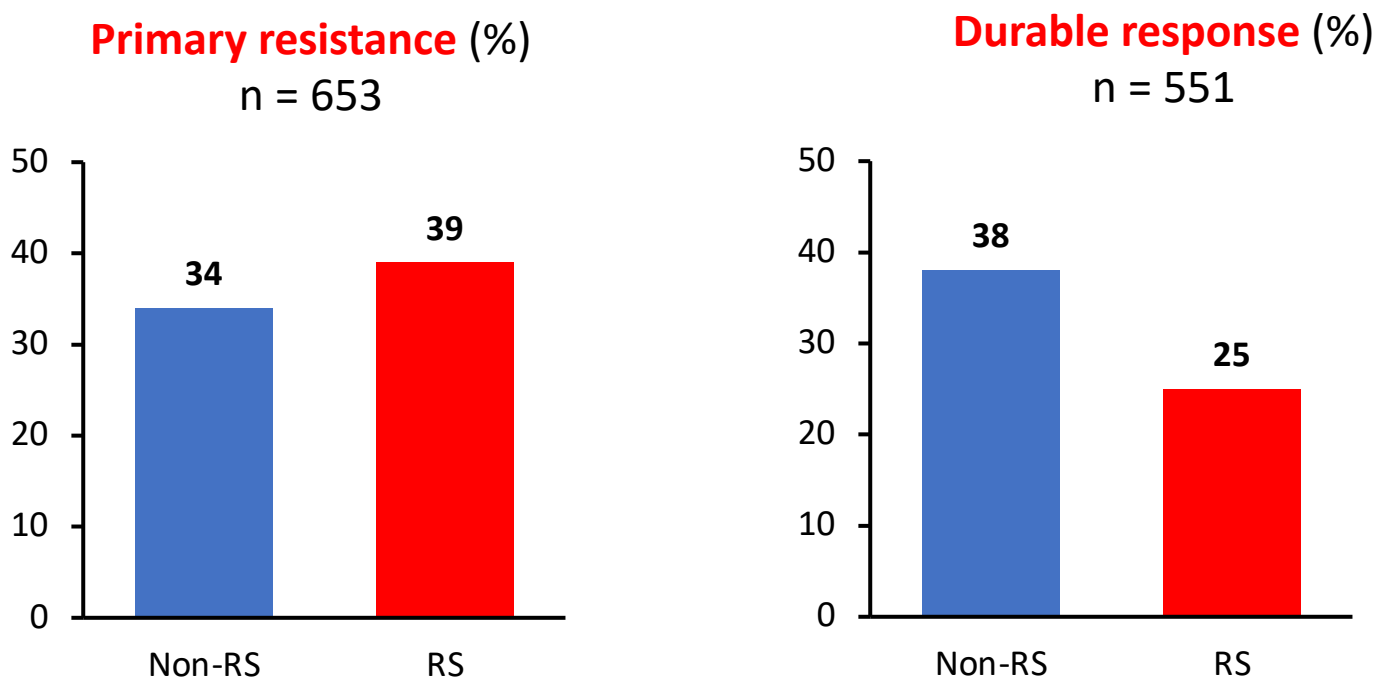
x	Yes (but this will be highlighted)

Do we need novel therapies in MDS?



Kubasch, Fenaux, Platzbecker. Blood Adv 2021

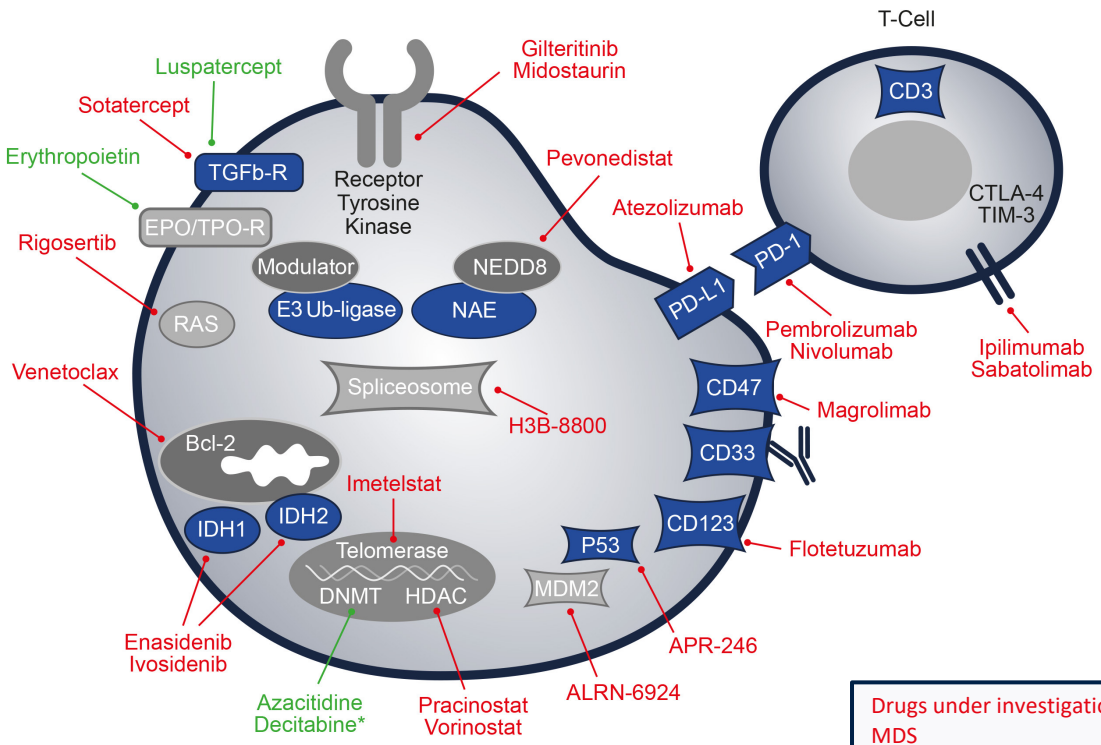
Response to erythropoiesis-stimulating agents (ESA) and ring sideroblasts



- n=1698 IPSS low/int-1
- ORR 61.5% median 17 m

Park et al. J Clin Oncol 2017

Current and future treatment options for patients with MDS



***Only approved for the treatment of MDS in the US and Canada**

Bcl, B-cell lymphoma; CD, cluster of differentiation; CTLA, cytotoxic T-lymphocyte antigen; DNMT, DNA methyl transferase; EPO, erythropoietin; HDAC, histone deacetylase; IDH, isocitrate dehydrogenase; MDM, Mouse double minute; MDS, myelodysplastic syndromes; NAE, NEDD8 activating enzyme; NEDD8, neural precursor cell expressed developmentally downregulated protein; PD, programmed cell death; PD-L, programmed cell death-ligand; TGFb-R, transforming growth factor beta-receptor; TIM, T cell immunoglobulin and mucin domain-containing protein; TPO-R, thrombopoietin receptor

Ad

adapted from Platzbecker U. Blood 2019

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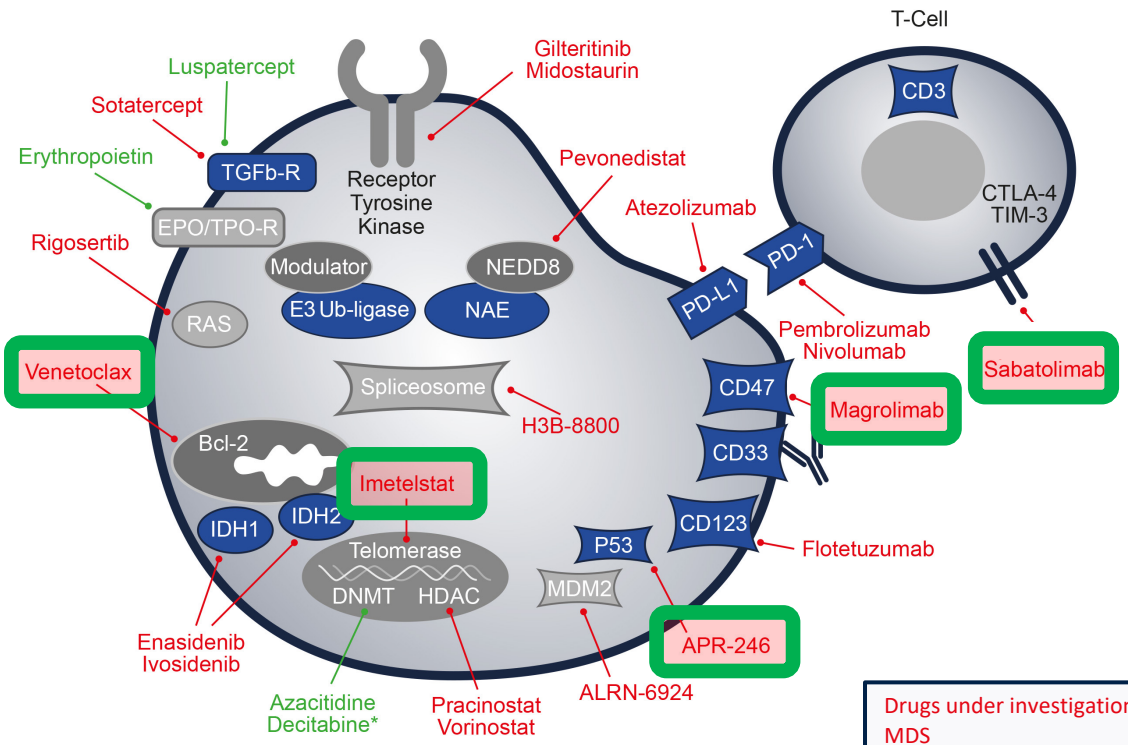

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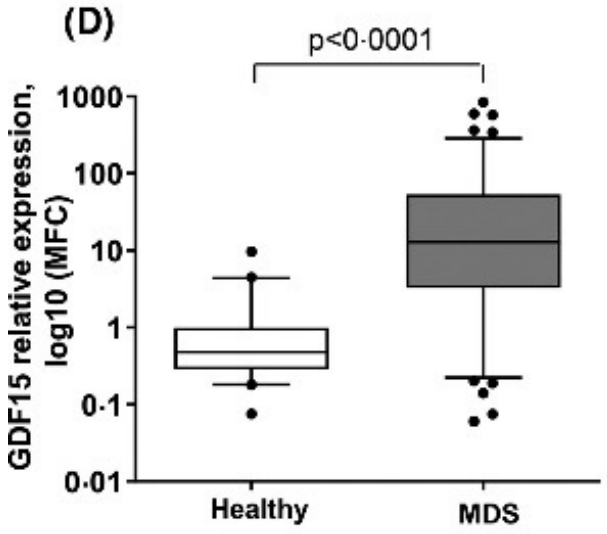
Ad

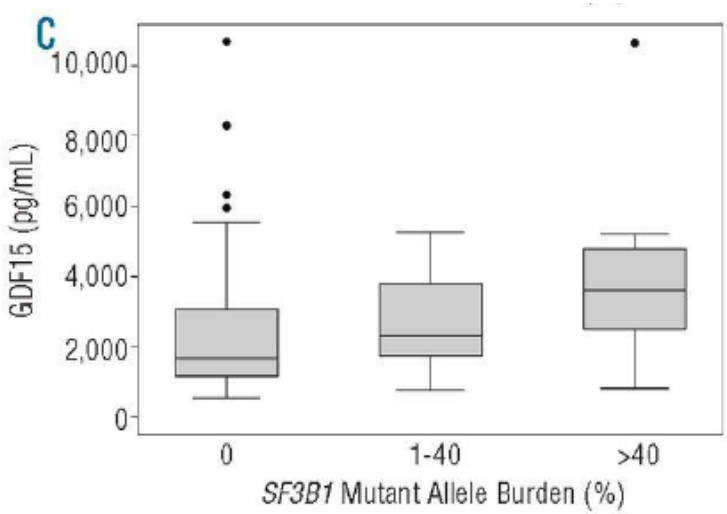
adapted from Platzbecker U. Blood 2019

GDF-15 in MDS

on erythroblasts

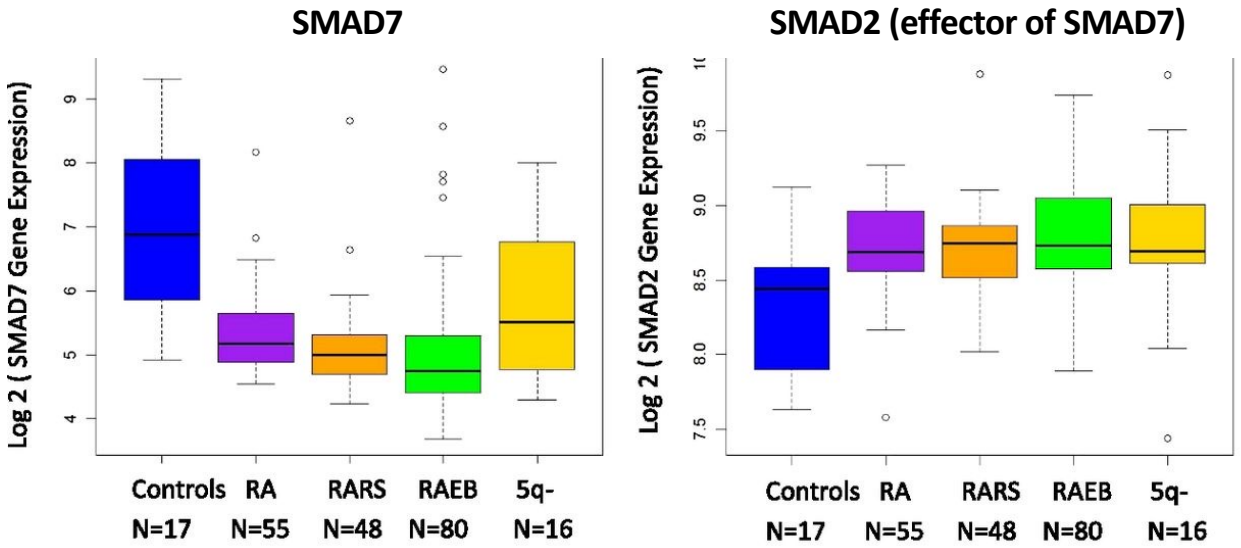


plasma



Santini et al. PLOS 2011, Ambaglio et al. Haematologica 2013, Riabov et al. BJH 2021

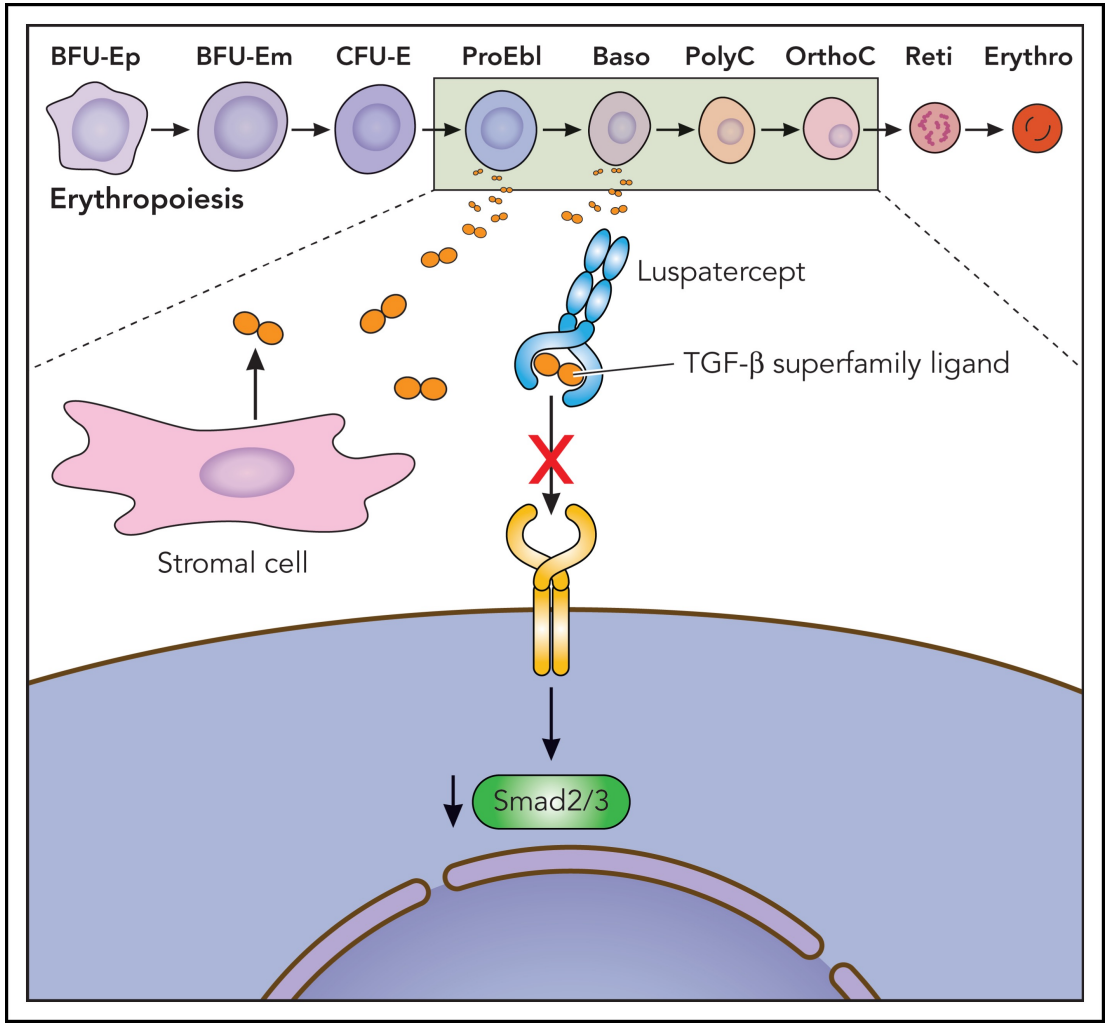
TGF-β and SMAD2/7 in MDS



- *SMAD7*, a negative regulator of TGF-β receptor-I kinase, is markedly reduced in MDS, and leads to ineffective haematopoiesis
- Increased levels of microRNA-21 are seen in MDS and reduce *SMAD7* levels, thus overactivating TGF-β signalling

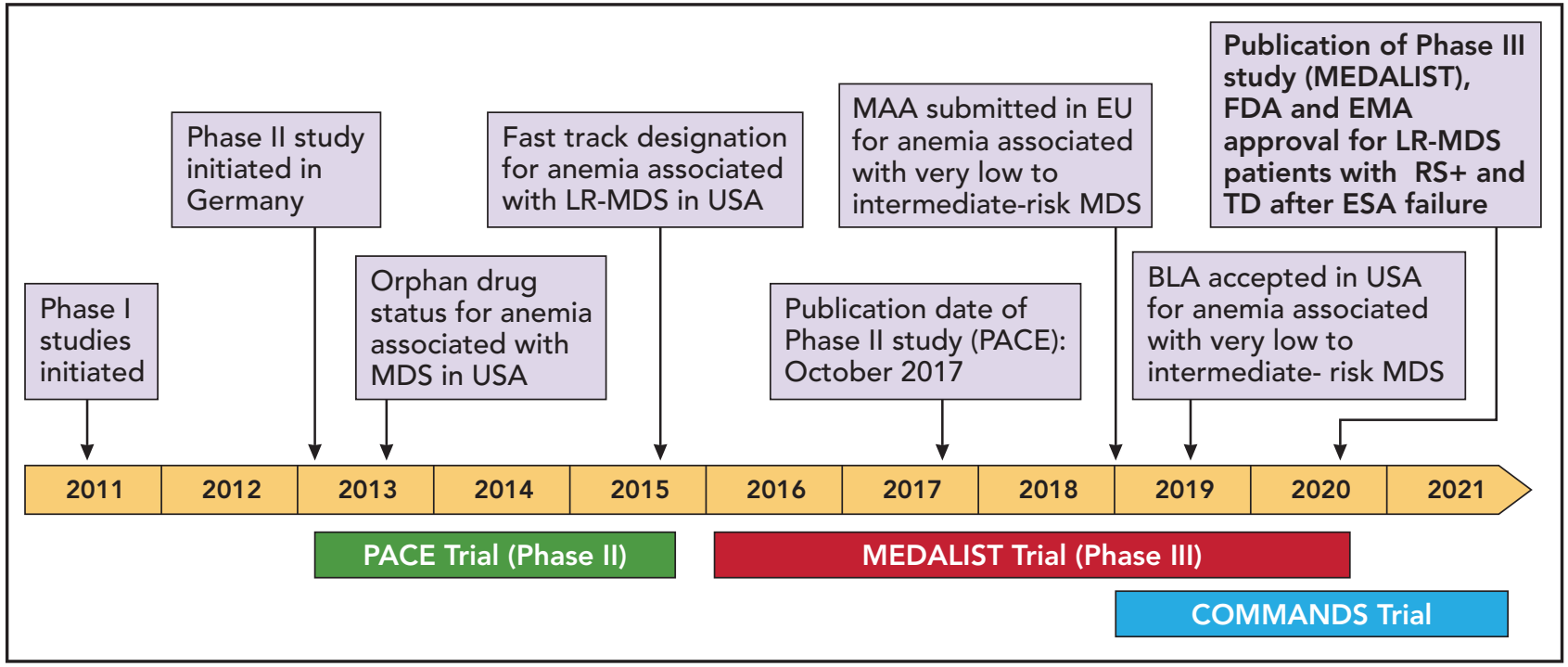
Bhagat et al. Blood 2013

Ligand-trap to modulate ineffective hematopoiesis



Kubasch, Fenaux, Platzbecker. Blood Adv 2021

Luspatercept development



Kubasch, Fenaux, Platzbecker. Blood Adv 2021

PACE Trial

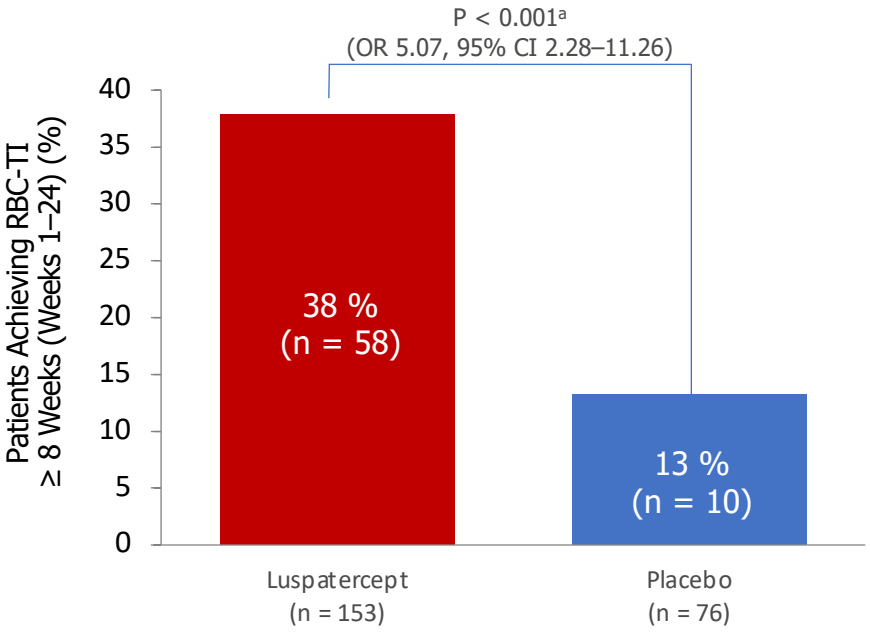
Response by Subgroup

n/N (%)	IWG HI-E[a]	RBC-TI[b]
All patients	32/51 (63)	16/42 (38)
Transfusion burden		
LTB (< 4 RBC units/8 weeks)	11/17 (65)	6/8 (75)
HTB (≥ 4 RBC units/8 weeks)	21/34 (62)	10/34 (29)
Prior use of ESAs		
Yes	21/34 (62)	11/29 (38)
No	11/17 (65)	5/13 (39)
Prior use of lenalidomide		
Yes	5/8 (63)	1/8 (13)
No	27/43 (63)	15/34 (44)
Serum erythropoietin level		
< 200 IU/L	19/25 (76)	10/19 (53)
≥ 200 to ≤ 500 IU/L	7/12 (58)	4/9 (44)
> 500 IU/L	6/14 (43)	2/14 (14)
RS status		
Positive (≥ 15% RS)	29/42 (69)	14/33 (42)
Negative (< 15% RS)	3/7 (43)	2/7 (29)
Unknown	0/2	0/2

[a] For LTB patients, IWG HI-E is defined as ≥ 1.5 g/dL Hb increase over 8 weeks; for HTB patients, IWG HI-E is defined as a reduction of ≥ 4 RBC units over 8 weeks;
[b] Patients with a baseline transfusion burden of ≥ 2 RBC units/8 weeks were included in the RBC-TI evaluable population.
Platzbecker et al., Lancet Oncol 2017. DOI: http://dx.doi.org/10.1016/S1470-2045(17)30615-0.

MEDALIST Trial

RBC-TI Response by Primary Endpoint



n (%)	Luspatercept (n = 153)	Placebo (n = 76)
Primary endpoint responders[b]	58 (37.9)	10 (13.2)
Responders with 1 response	22 (14.4)[c]	6 (7.9)
Responders with 2 responses	**23 (15.0)**	4 (5.26)
Responders with ≥ 3 responses	13 (8.5)	0

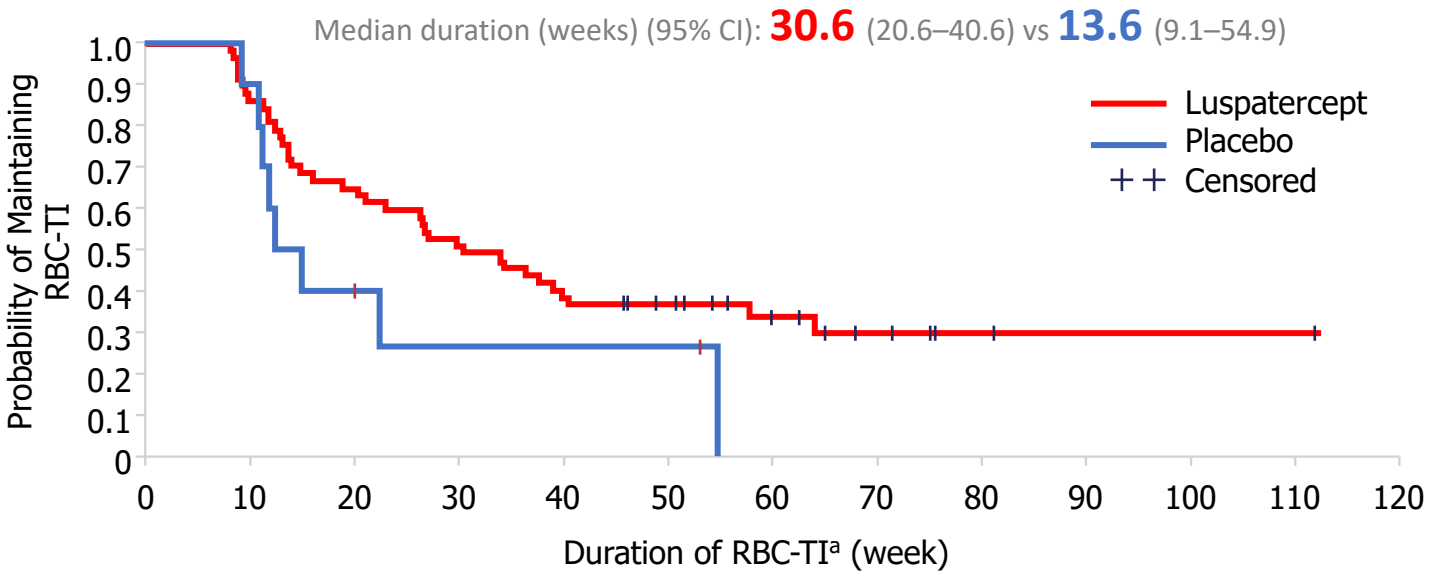
Response rates were similar regardless of SF3B1 allelic burden and total number of baseline somatic mutations.

[a] Determined using a Cochran–Mantel–Haenszel test stratified for average baseline RBC transfusion requirement (≥ 6 vs. < 6 units/8 weeks) and baseline IPSS-R score (Very low or Low vs. Intermediate). [b] Defined as the absence of any red blood cell transfusion during any consecutive 56-day period during weeks 1–24. [c] Eleven patients were transfusion-free during the entire post-treatment period.

Fenaux & Platzbecker et al. NEJM 2020, ASH 2020

MEDALIST Trial

Duration of RBC-TI Response in Primary Endpoint Responders



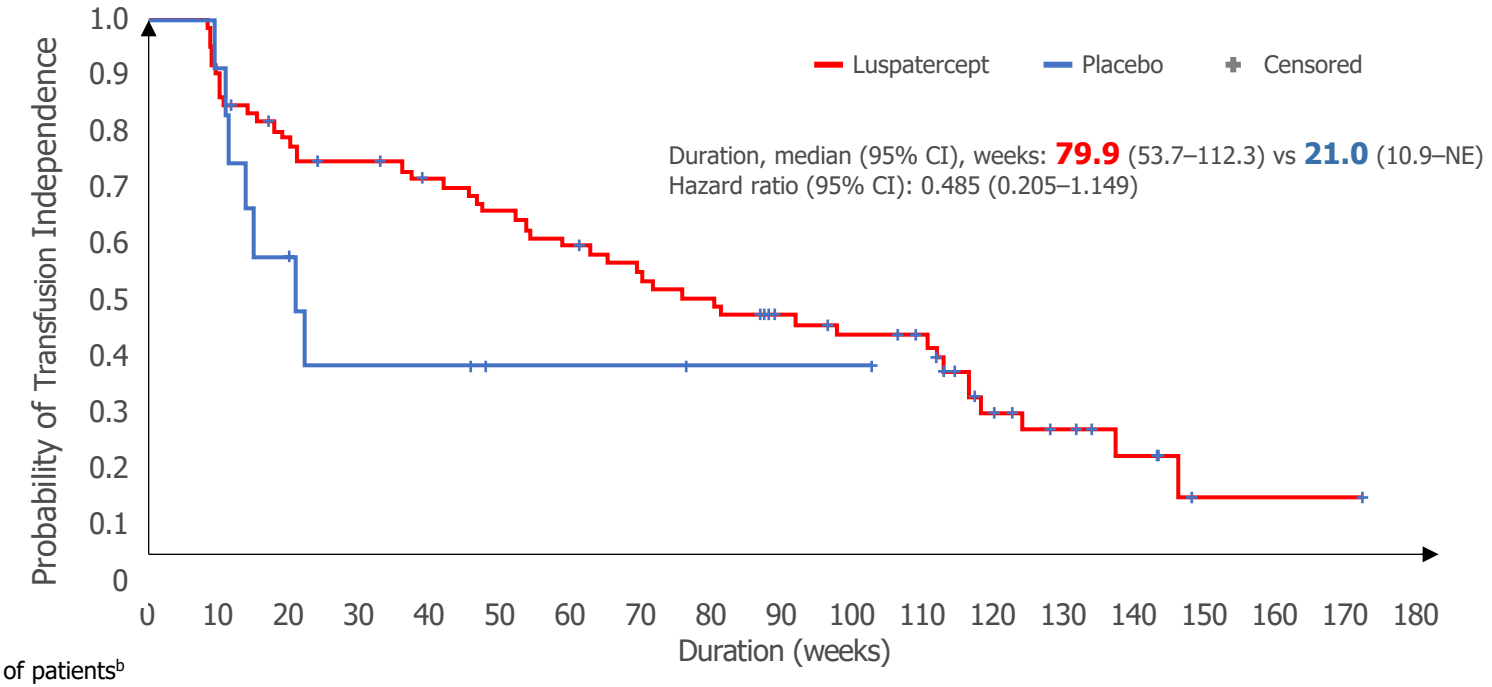
Number of patients													
Luspatercept	58	49	37	29	22	18	10	6	3	2	1	1	0
Placebo	10	9	3	2	2	2	0						

[a] During indicated treatment period. Patients who maintained RBC-TI at the time of analysis are censored.

Fenaux & Platzbecker et al. NEJM 2020

MEDALIST Trial

Cumulative Duration of RBC-TI Response



Number of patients[b]																	
Luspatercept	73	63	55	52	48	44	40	35	32	27	24	22	11	8	5	1	1	1
Placebo	12	11	7	4	4	2	2	2	1	1	1							

[a] Cumulative duration of RBC-TI ≥ 8 weeks is defined as the sum of all durations of RBC-TI for patients achieving RBC-TI ≥ 8 weeks during the entire treatment phase.
[b] In the intent-to-treat population; patients who maintained response were censored from the analysis.
NE = not estimable. Data cutoff: July 1, 2019.

Fenaux et al. ASH 2019

MEDALIST Trial

Safety

All Grade TEAE (≥ 10 % Incidence in Either Treatment Arm), n (%)	Luspatercept (n = 153)	Placebo (n = 76)
Fatigue	41 (27)	10 (13)
Asthenia	31 (20)	9 (12)
Edema peripheral	25 (16)	13 (17)
Diarrhea	34 (22)	7 (9)
Nausea[a]	31 (20)	6 (8)
Constipation	17 (11)	7 (9)
Dizziness	30 (20)	4 (5)
Headache	24 (16)	5 (7)
Back pain[a]	29 (19)	5 (7)
Arthralgia	8 (5)	9 (12)
Dyspnea[a]	23 (15)	5 (7)
Cough	27 (18)	10 (13)
Bronchitis[a]	17 (11)	1 (1)
Urinary tract infection[a]	17 (11)	4 (5)
Fall	15 (10)	9 (12)

Incidence of TEAEs in patient receiving luspatercept generally decreased over time.

[a] ≥ 1 event was reported as serious.

Fenaux & Platzbecker et al. NEJM 2020

MEDALIST Trial

Response by Subgroup

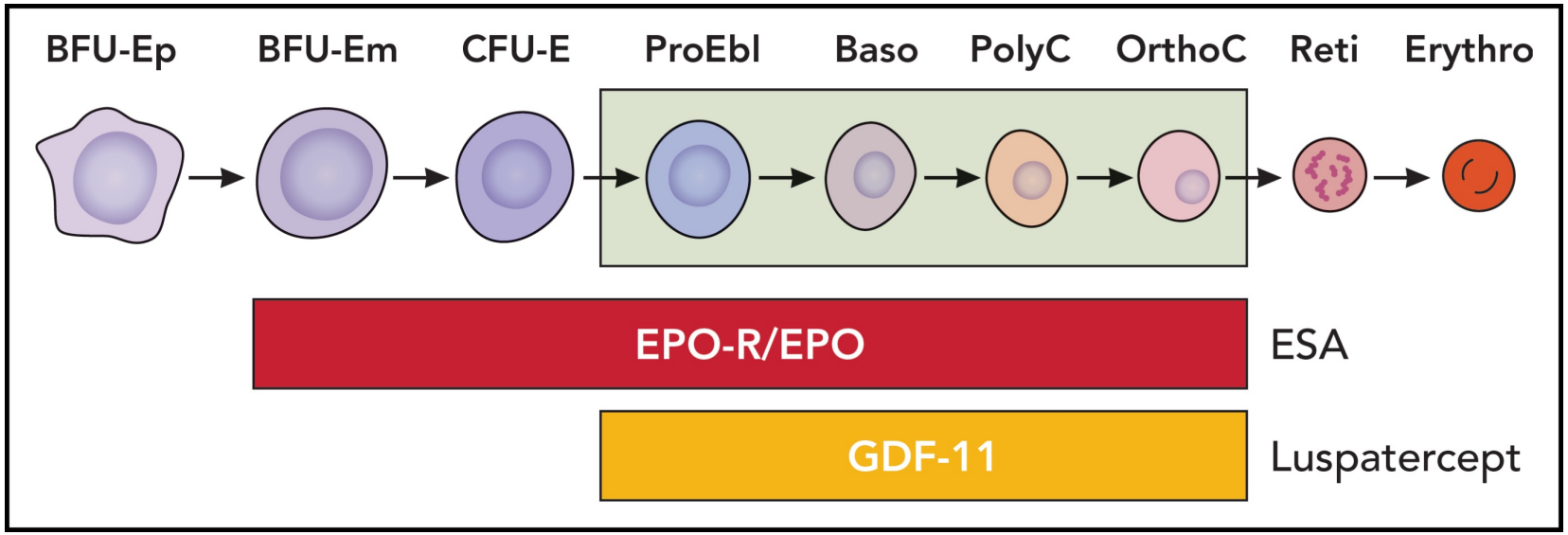
Baseline erythroid biomarkers by clinical benefit (CB) response

Biomarker	Luspatercept (N = 153)		
	CB (n = 89)	No CB (n = 64)	*P* value
Transfusion burden,[a] mean (SD), RBC units	n = 89 10.404 (5.96)	n = 64 11.906 (4.74)	0.08520
Hemoglobin, mean (SD), g/L	n = 83 89.78 (9.78)	n = 62 87.59 (11.70)	0.23526
Serum EPO, mean (SD), IU/L	n = 85 184.24 (252.44)	n = 64 248.92 (262.97)	0.13297
≤ 100	n = 47 58.70 (24.04)	n = 18 51.93 (30.94)	0.41029
> 100 to ≤ 200	n = 18 144.15 (24.18)	n = 21 141.01 (22.62)	0.68019
> 200	n = 20 515.35 (352.01)	n = 25 481.39 (291.27)	0.73074
BM EP, mean (SD), %	n = 87 31.31 (14.35)	n = 63 26.53 (12.22)	0.02975
Serum ERFE, mean (SD), ng/mL	n = 80 21.36 (12.26)	n = 57 20.22 (8.62)	0.52414
Serum sTfR1, mean (SD), nM	n = 82 31.45 (18.81)	n = 61 31.79 (18.57)	0.59966
Reticulocyte count, mean (SD), $\times 10^9$/L	n = 75 36.75 (19.14)	n = 60 31.65 (13.30)	0.07091

Data cutoff: July 1, 2019.
[a]Transfusion burden during the 16 weeks prior to randomization.
EP, erythroid precursor; ERFE, erythroferrone; SD, standard deviation; sTfR1, soluble transferrin receptor-1.

Platzbecker et al. ASH 2020

Ligand-trap to modulate ineffective hematopoiesis

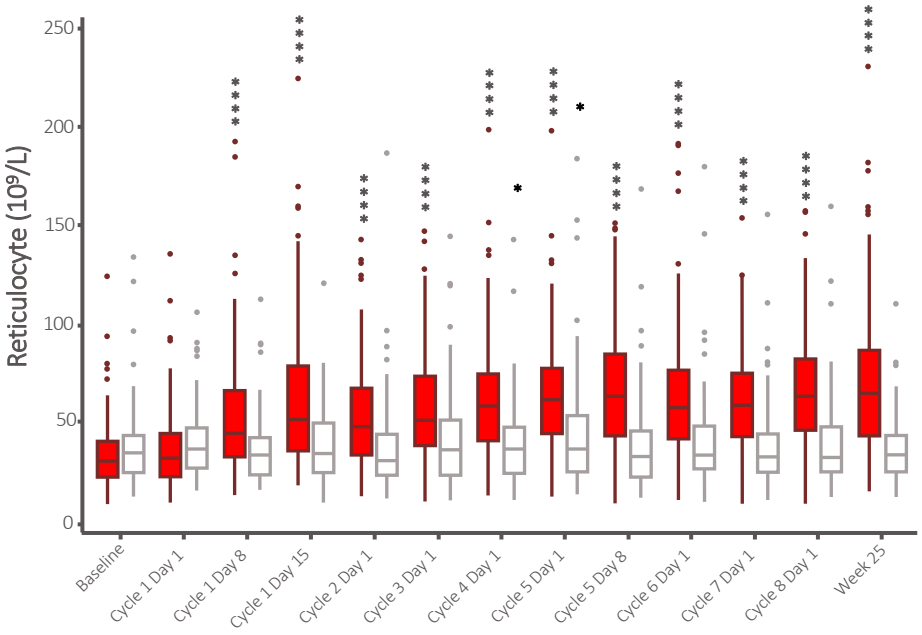


Kubasch, Fenaux, Platzbecker. Blood Adv 2021

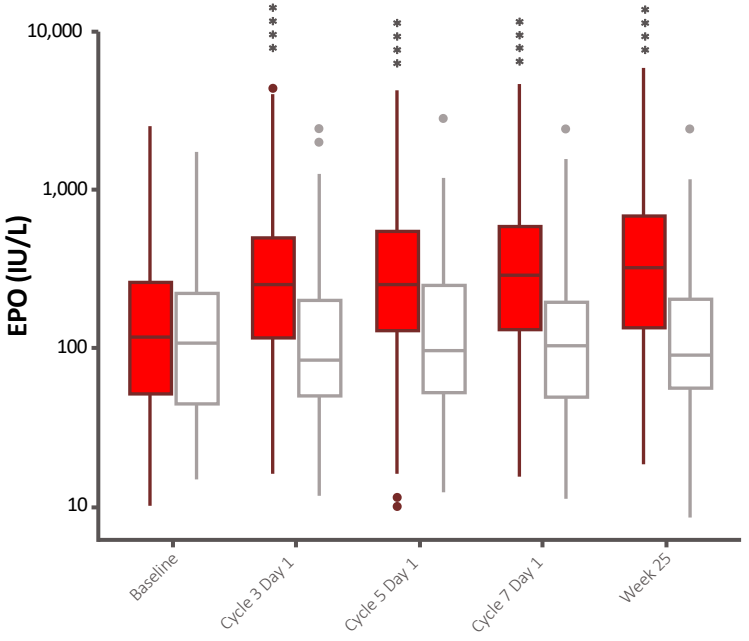
MEDALIST Trial

Retics and EPO levels

Reticulocyte count at baseline and during primary treatment phase (Weeks 1-24)



Serum EPO at baseline and during primary treatment phase (Weeks 1-24)



Data cutoff: July 1, 2019.
* $P < 0.05$ **** $P < 0.0001$ vs. Baseline

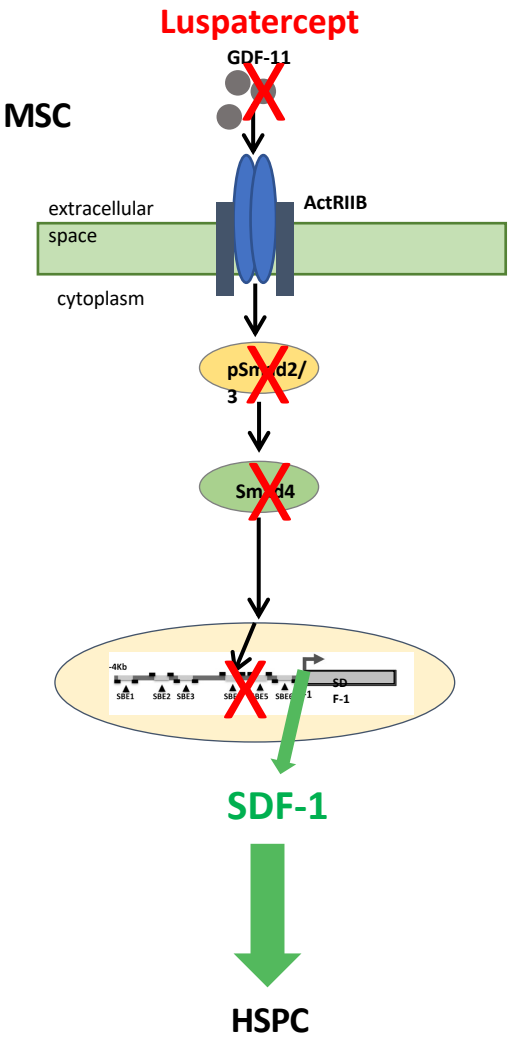
Luspatercept

Placebo

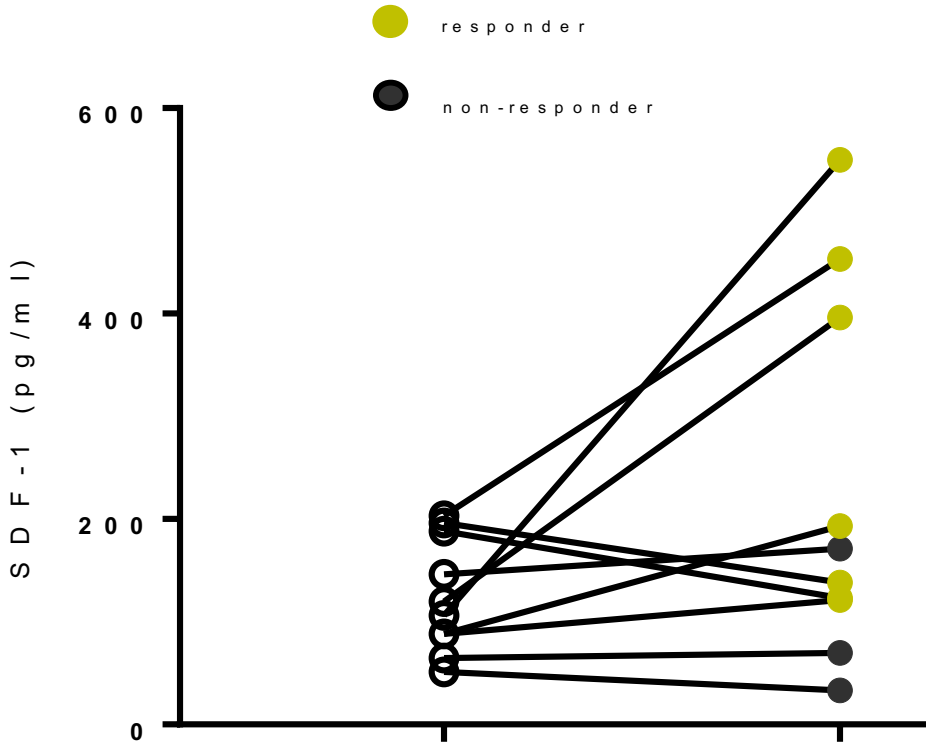
Platzbecker et al. ASH 2020

Luspatercept MoA

SDF-1 and stromal cells



- interaction with stromal cells
- phenotype
- clonogenic potential
- migratory potential



Effect of Luspatercept treatment on SDF-1

Wobus et al. Leukemia in press

PACE Trial

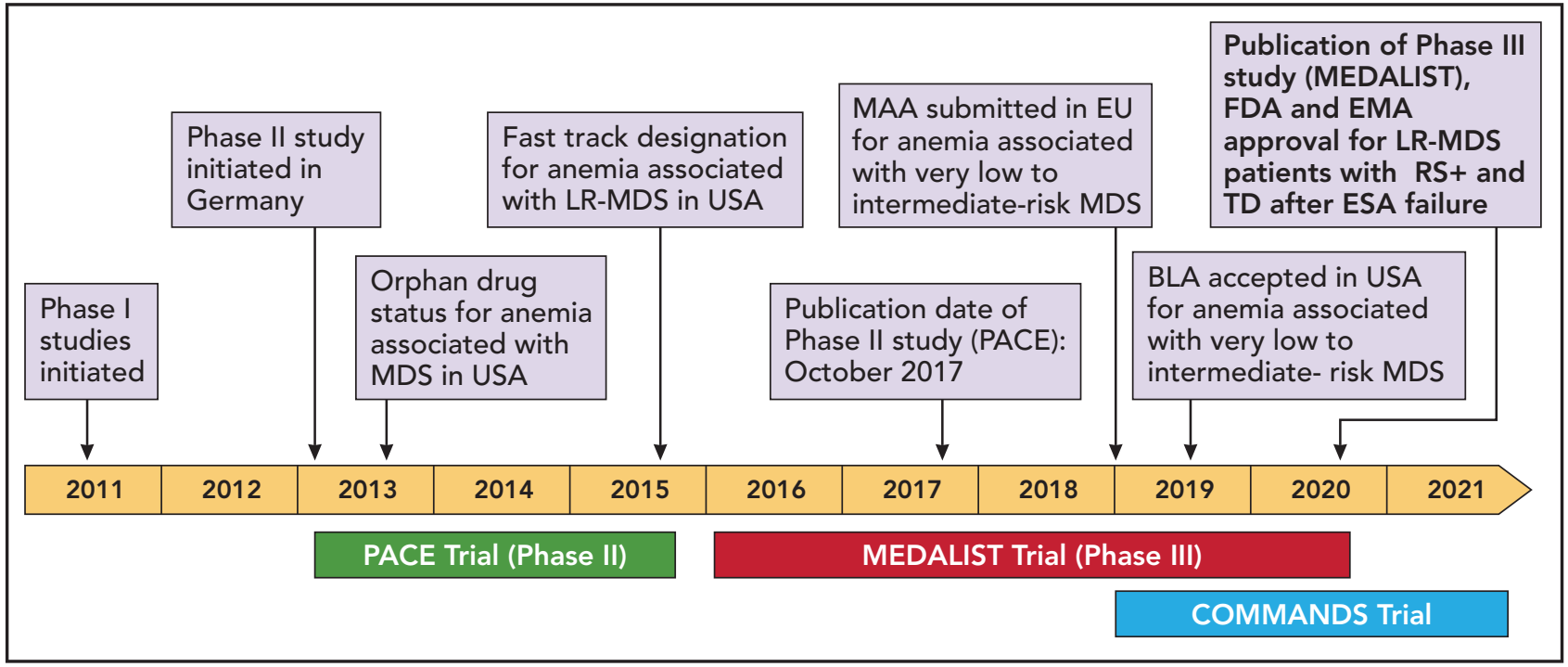
LUSP in RS+ and RS-

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

Platzbecker et al. SOHO 2020

Luspatercept development



Kubasch, Fenaux, Platzbecker. Blood Adv 2021

HMA in early LR-MDS

3d DAC vs. 3d AZA q4w

- N=113
- 85% INT by IPSS-R
- 19% ESA pre-treatment
- Median time from diagnosis: 5 weeks

- **HI: 18%**
- Median response duration: 18 months

Jabbour et al. Blood 2017

HMA in late LR-MDS

Oral AZA vs. PBO

- IPSS int-1
- RBC-TI: **31%** vs. **11%** of patients, (*P*=0.0002)
- median durations of **11.1** and **5.0** months
- Platelet response: **24.3%** *vs.* **6.5%**

Garcia-Manero et al. JCO 2021

Imetelstat Trial in ESA Failure MDS

Response

Parameters	N = 38
8-week TI, n (%)	16 **(42)**
Time to onset of 8-week TI, weeks, median (range)	8.3 (0.1-40.7)
Duration of TI, weeks, median (95% CI)[a]	**88.0** (23.1 – 140.9*)
Cumulative duration of TI ≥ 8 weeks[b], median (95% CI)[a]	92.3 (42.9, 140.9)
Hb rise ≥ 3.0 g/dL during TI[c], n (%)	12 (32)
24-week TI, n (%)	12 **(32)**
Hb rise ≥ 3.0 g/dL during TI[c], n (%)	11 (29)
1-year TI, n (%)	11 **(29)**

[a] Kaplan Meier method; [b] Cumulative Duration of TI ≥ 8 weeks is defined as the sum of all periods of TI ≥ 8 weeks during the treatment; [c] Maximum Hb rise of ≥ 3g/dL from pretreatment level (pretreatment level defined as mean Hb / 8 weeks).
CI, confidence interval; Hb, hemoglobin

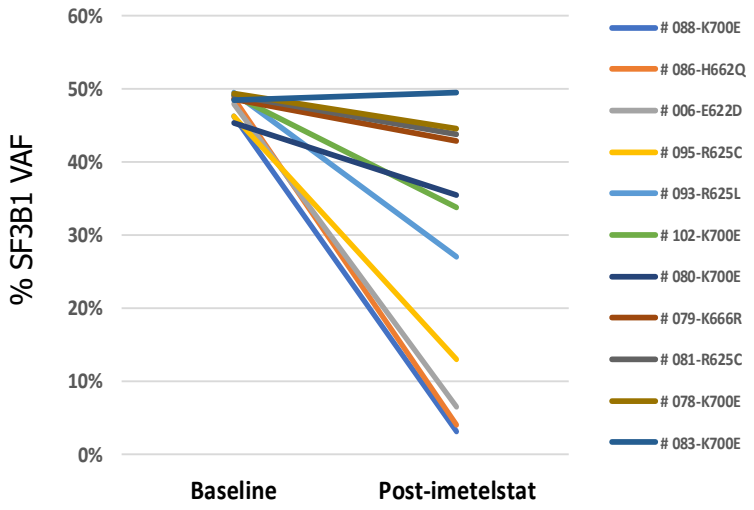
*Longest TI > 2.7 years

Steensma et al. JCO 2021

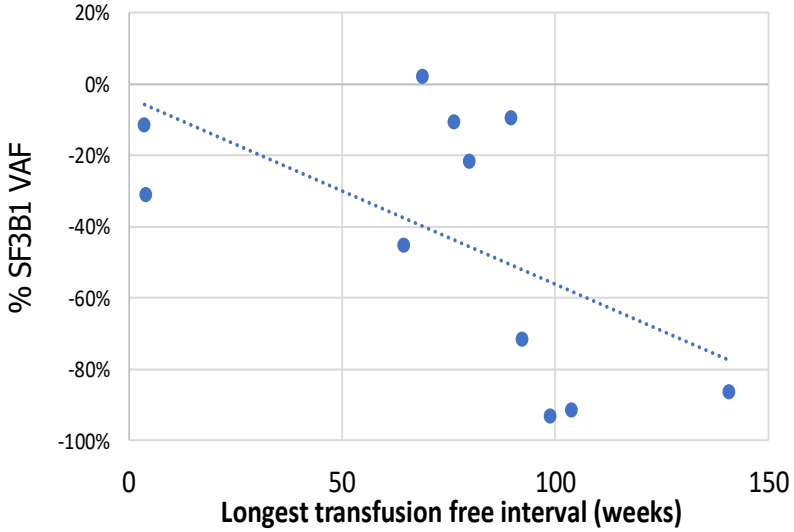
Imetelstat Trial in ESA Failure MDS

On target effects

A.



B.



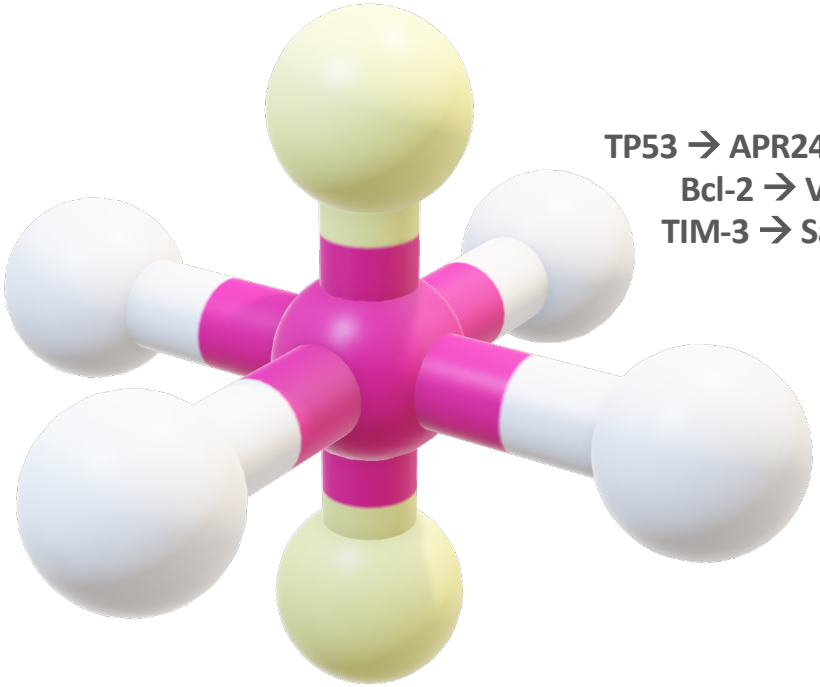
Steensma et al. JCO 2021

Treatment Stratification 4.0 – On the way to precision medicine?

IDH1/2 Mutation → IDH1/2 Inhibitors (not approved)

Ferritin levels → Iron chelation
EPO → ESA treatment

TP53 → APR246, Magrolimab (not approved)
Bcl-2 → Venetoclax (not approved)
TIM-3 → Sabatolimab (not approved)

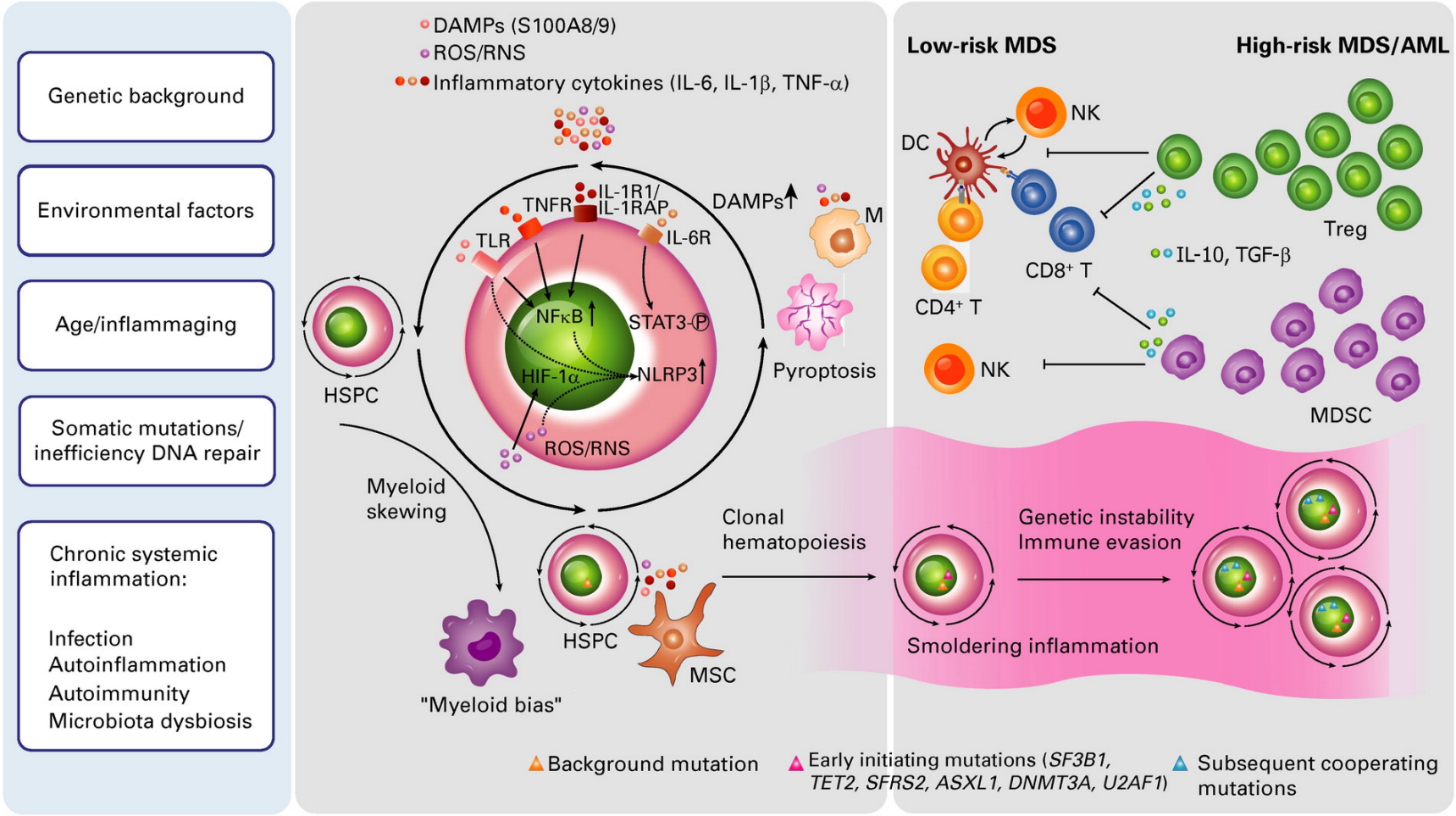


del(5q) → Lenalidomide

Inflammasome activation
→ Anti-Inflammatory Therapy

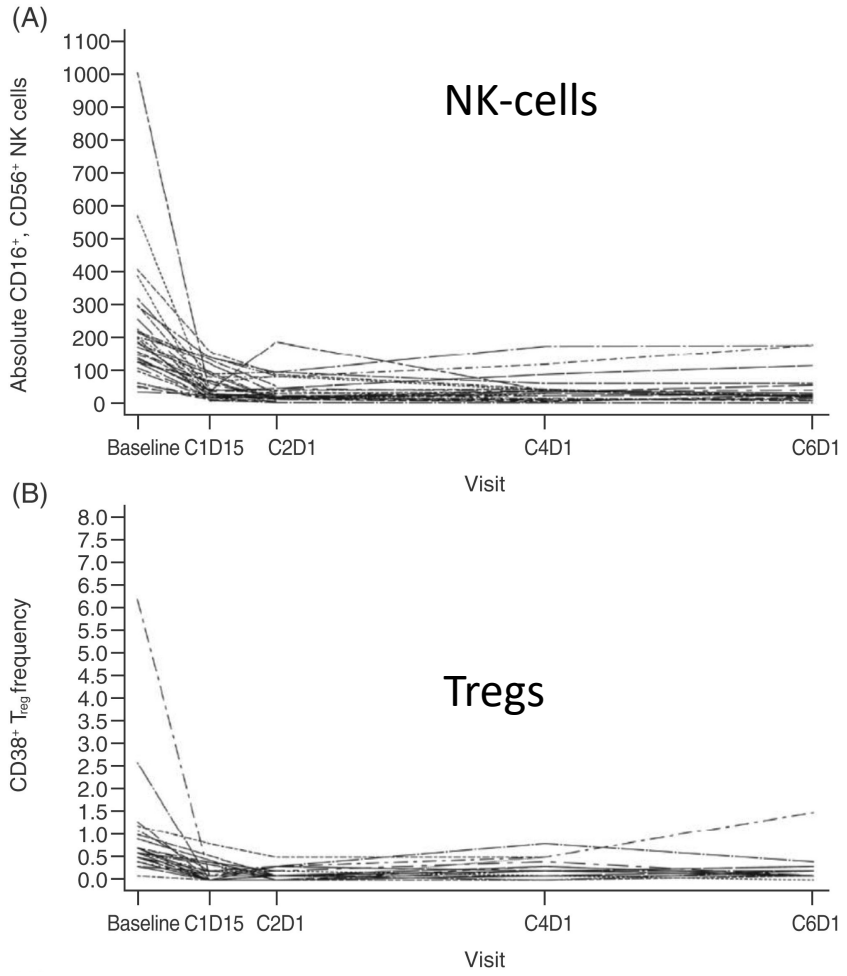
RS+ → Luspatercept
Spliceosome mutation → spliceosome modulators (not approved)

The “Immunome” in MDS: Culprit and Target or Bystander ?



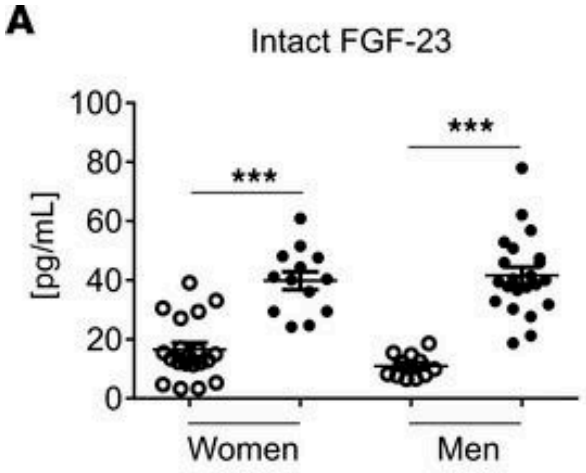
Winter et al. Journal of Clinical Oncology 2020

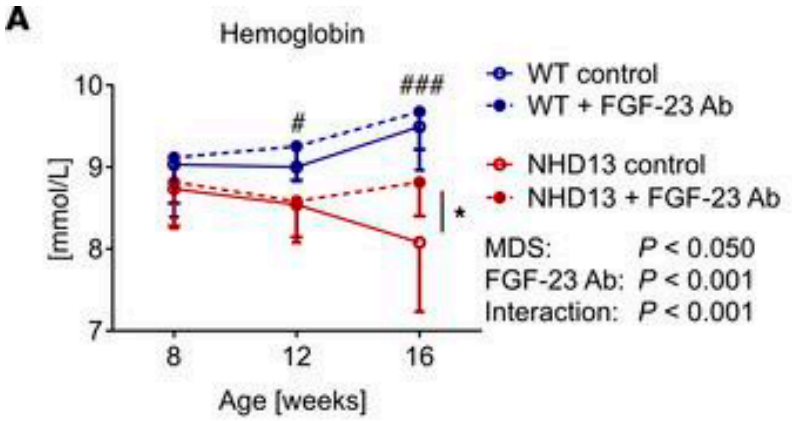
Daratumomab in LR-MDS



Garcia-Manero et al. AJH 2021

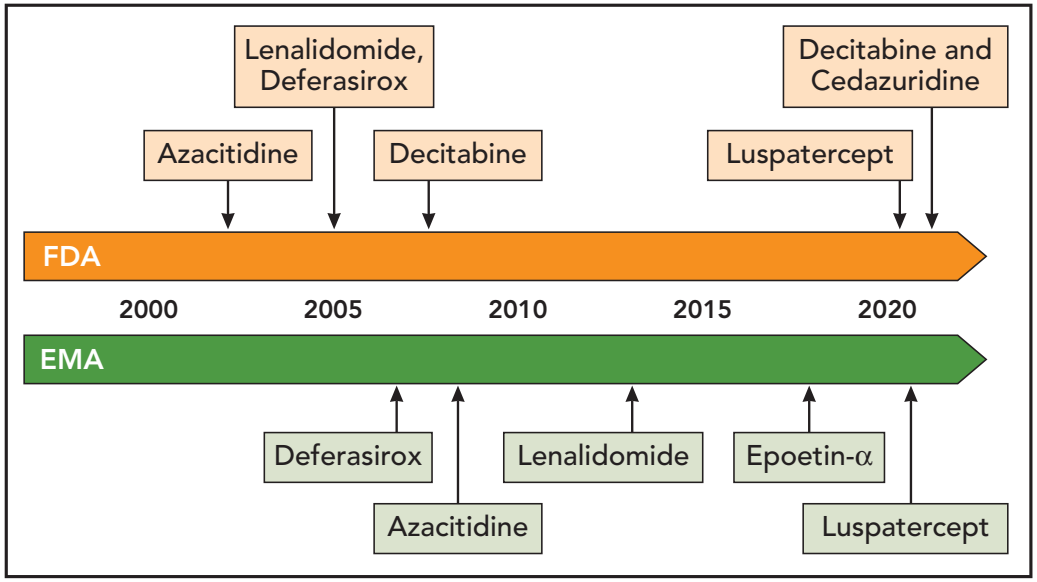
Increased FGF-23 levels are linked to ineffective erythropoiesis and impaired bone mineralization in myelodysplastic syndromes





Weidner et al. JCI Insight 2020

Summary



- Era of „targeted“ therapy in LR-MDS is about to start
- Luspatercept effective in RS-MDS
- „Late 1st line“ studies are ongoing in RS-/RS+

- Novel approaches: Imetelstat, anti-inflammatory agents

EMSCO MYELODYSPLASTIC SYNDROMES

D·MDS Deutsche MDS-Studiengruppe