Current and Future Treatment Considerations for Patients with Myelodysplastic Syndromes (MDS)

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MDS

- A group of clonal hematopoietic stem cell diseases characterized by cytopenia(s), dysplasia in one or more of major myeloid cell lines, ineffective hemopoiesis and increased risk of development of AML – WHO: Classification of hematopoietic and Lymphoid Tissues: 2008: 4th Edition.

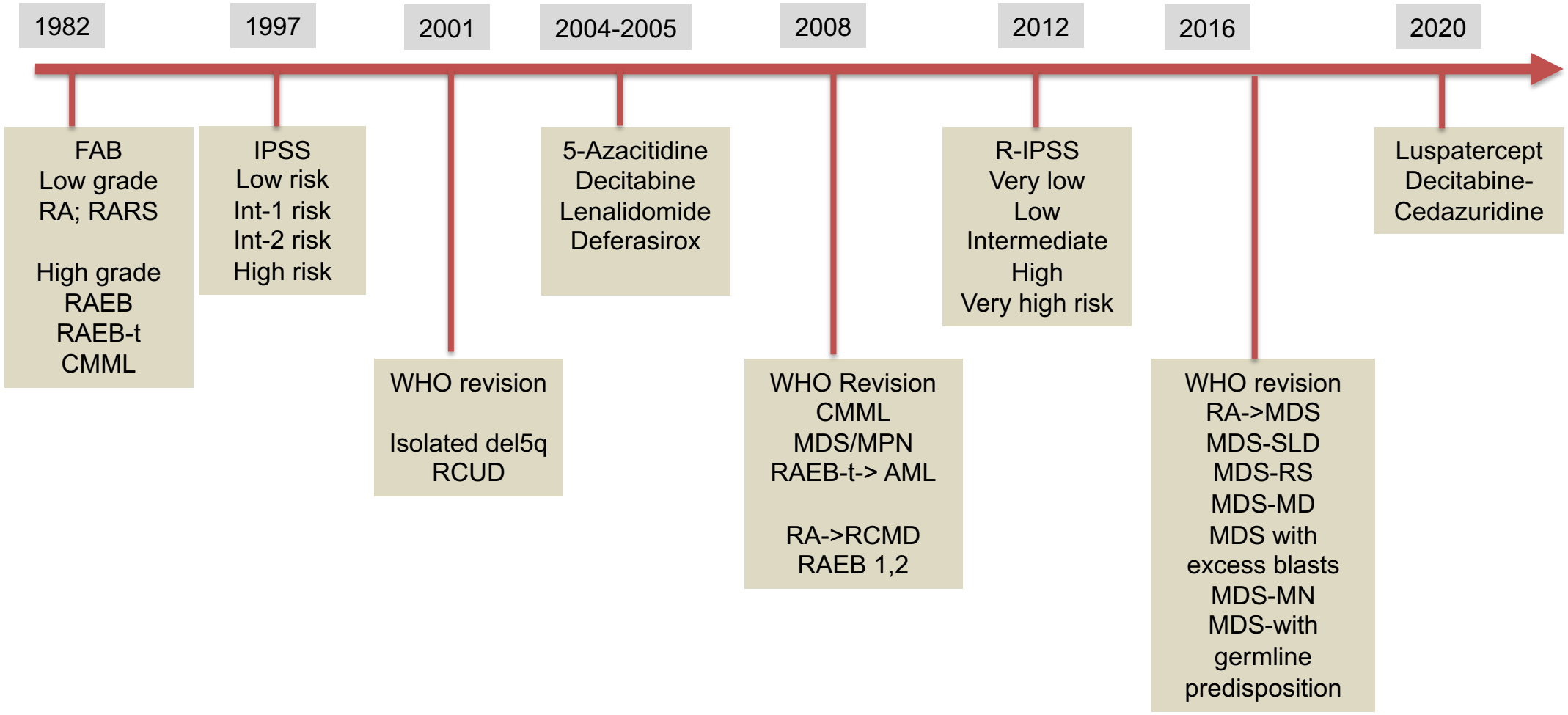
- A group of clonal bone marrow neoplasms characterized by ineffective hematopoiesis, manifested by morphologic dysplasia in hematopoietic cells and by peripheral cytopenia(s).- WHO: 2016 revision.

- Incidence: 4.5 cases per 100,000 people/year and goes higher with age with among 70-79 years and ≥80 years age 26.9 and 55.4 per 100,000 people/year respectively; Around 15,000 cases per year. Men>Women; Whites> non-white.

- Risk factors: Age, DNA damage, environmental, PNH/AA or hereditary causes.

D A Arber et al. WHO 2016 revision

Timeline in MDS



IPSS and IPSS-R

Score values					
Prognostic variable	0	0.5	1.0	1.5	2.0
Marrow blast %	<5	5-10%	-	11-20	21-30
Karyotype	Good	Intermediate	Poor	-	-
Cytopenia	0/1	2/3			

IPSS risk category	Overall Score	Median survival in the absence of therapy	25% AML progression in the absence of therapy
Low	0	5.7	9.4
Int-1	0-5-1.0	3.5	3.3
Int-2	1.5-2.0	1.1	1.1
High	≥2.5	0.4	0.2

Cytogenetics: Good=normal, -Y alone, del(5q) alone, del (20q) alone, poor=complex≥3 abnormalities) or chromosome 7 anomalies; Intermediate=other abnormalities [excludes t(8;21); inv(16); t(15;17)]

Cytopenia: ANC<1800/mcL, Platelets <100,000/mcL, Hb <10 g/dL.

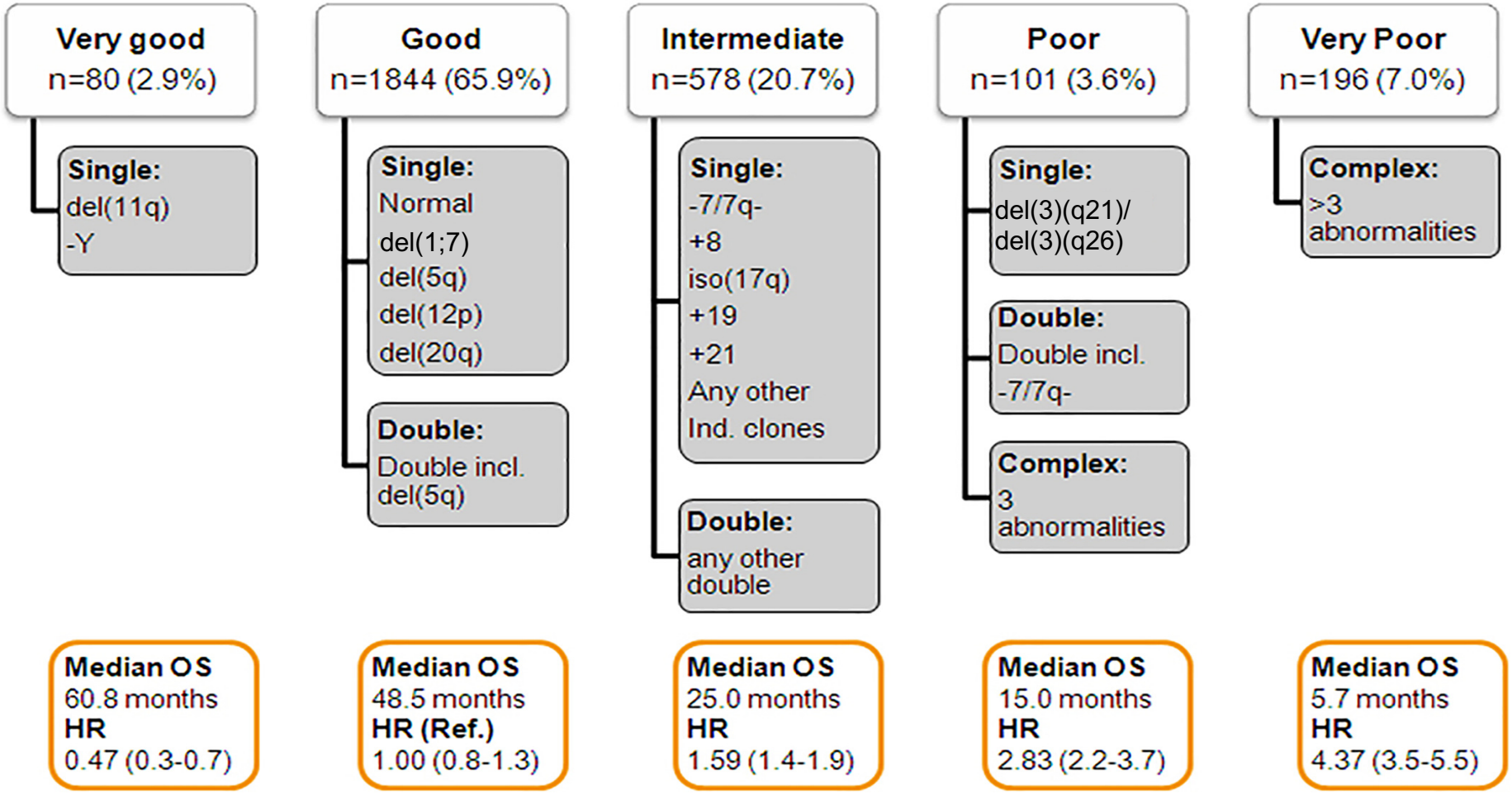
Greenberg P et al, Blood 1997; 89:2079-2088
Greenberg P et al, Blood 2012; 120:2454-2465

Score values							
Prognostic variable	0	0.5	1	1.5	2	3	4
CyG	Very good	-	Good	-	Interme diate	Poor	Very poor
Marrow blasts%	≤2	-	>2-<5	-	5-10	>10	-
Hemoglobi n	≥10	-	8-<10	<8	-	-	-
Platelets	≥100	50-<100	<50	-	-	-	-
ANC	≥0.8	<0.8	-	-	-	-	-

IPSS_R; Risk category	Overall score	Median survival in the absence of therapy	25% progression risk to AML
Very low	≤1.5	8.8	NR
Low	>1.5-≤3.0	5.3	10.8
INT	>3-≤4.5	3	3.2
High	>4-≤6.0	1.6	1.4
Very high	>6.0	0.8	0.7

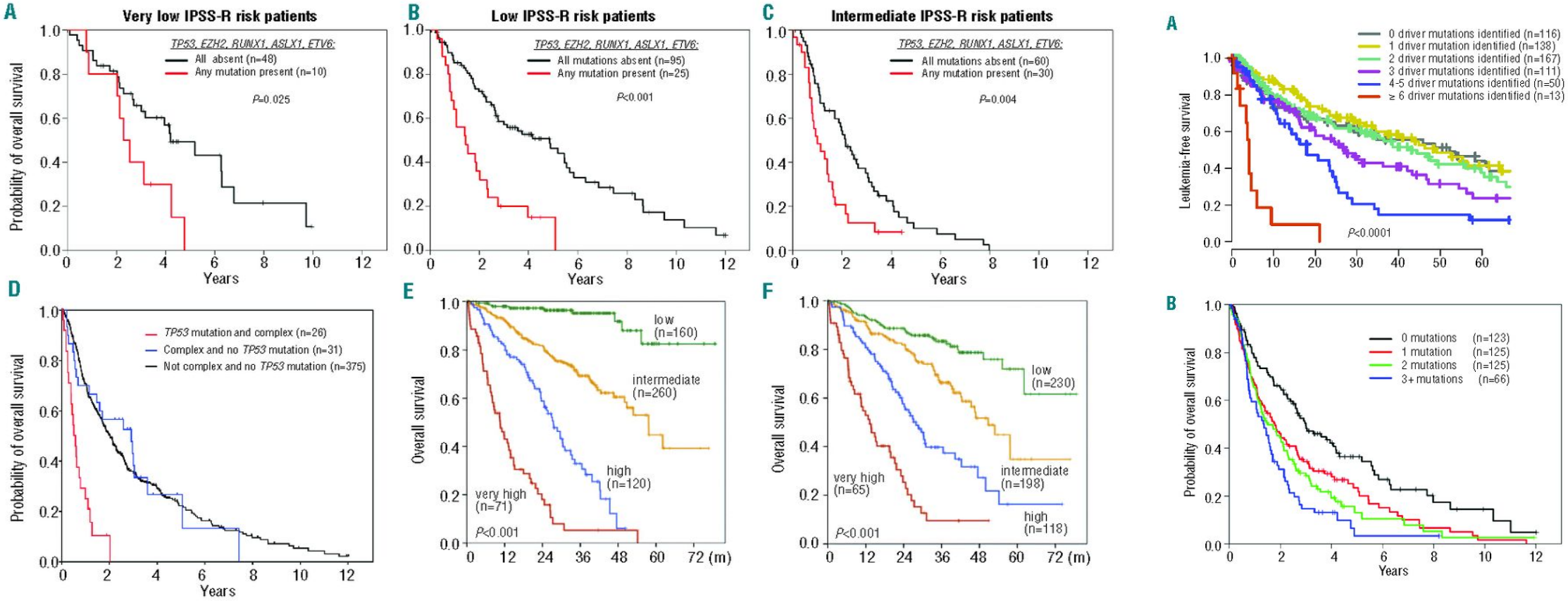
Cytogenetics: Very good=-Y, del(11q); Good: normal, del(5q), del(12p), del(20q), double including del(5q); Intermediate=del(7q), +8, +19, i(17q), any other single of double clones; Poor=-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: ≤3 abnormalities; Very complex=>3 abnormalities.

IPSS-R



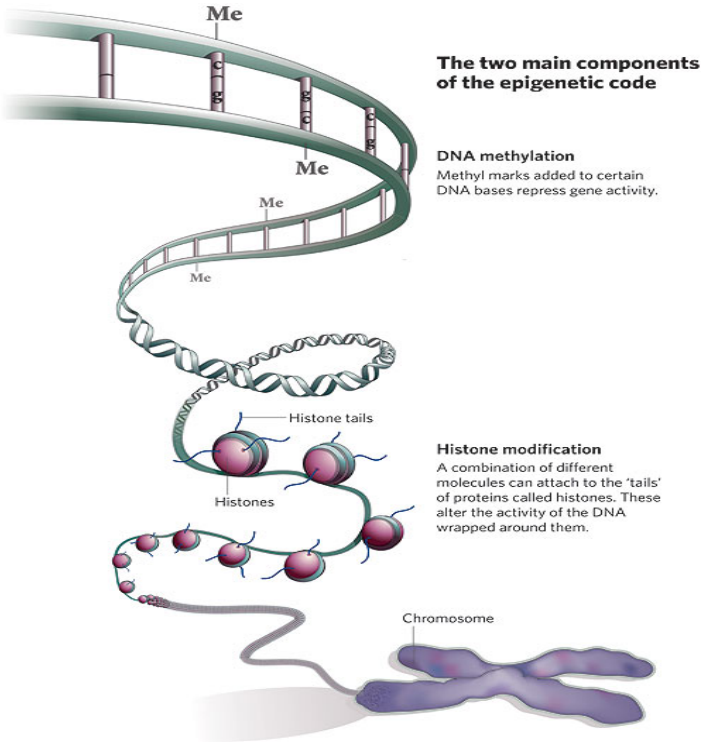
Schanz J et al. JCO 2012;30(8):820-829.

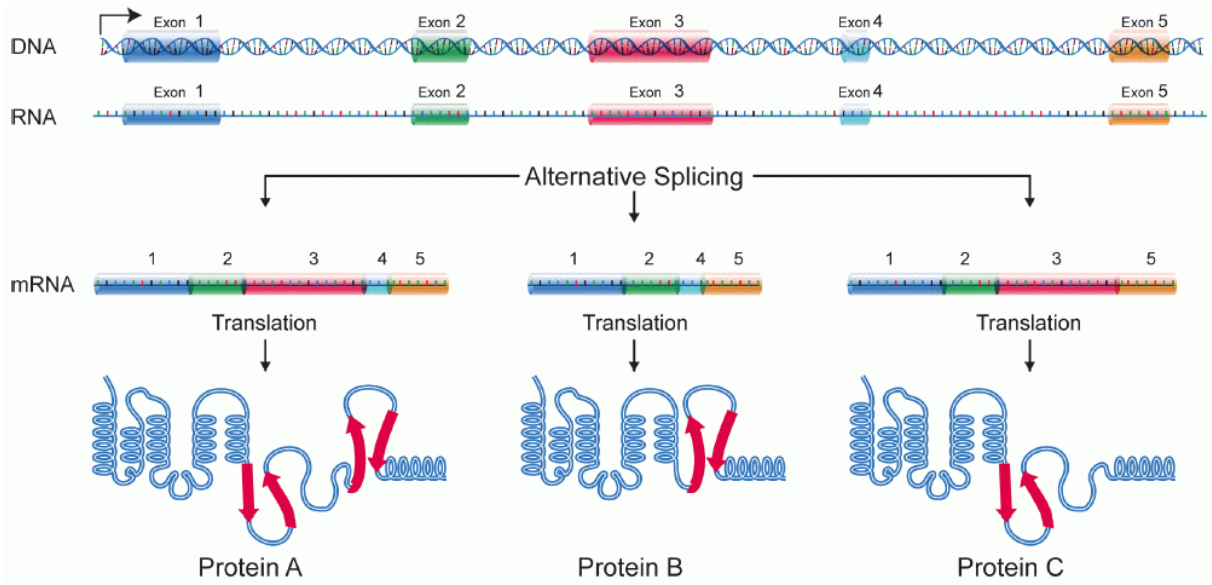
Impact of mutations



Bejar R Haematologica Vol. 99 No. 6 (2014): June, 2014

Recurrent Mutations in Myelodysplastic Syndromes		
Spliceosome genes	*U2AF1, SRSF2, ZRSR2,SR3B1*	
Epigenetic modifiers	*TET2, DNMT3A, EZH2, ASXL1, IDH1/2*	*"OFF" factor: DNA methylation, Histone modification*
Transcription factors	*RUNX1,ETV6, WT1, GATA2*	*"ON" factor*
Activated signaling	*NF1, NRAS, CBL, PTPN11, JAK2*	
Tumor suppressor	*TP53*	
Cohesin factors	*STAG2, SMC3*	



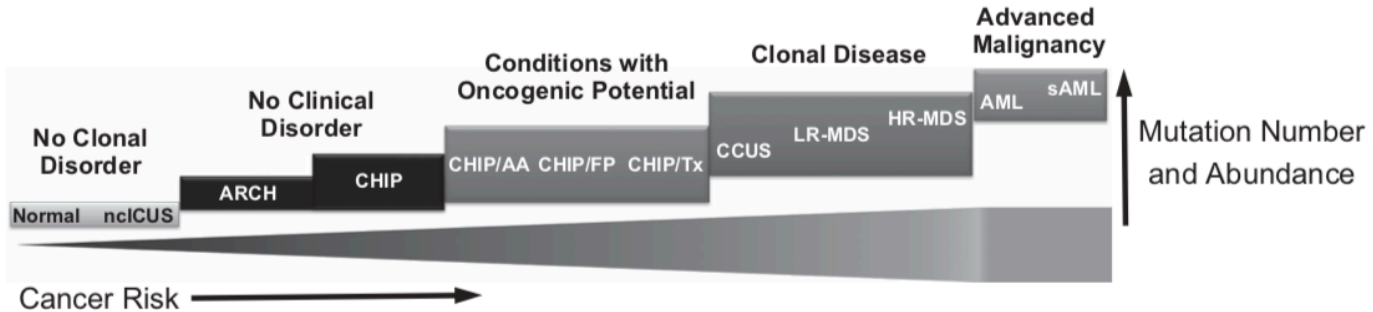


Transcription factors: Facilitate DNA transcription to RNA

R Bejar and P. Greenberg. J Natl Compr Canc 2017;15:131-135
J Qiu, Nature: volume 441, pages143–145 (2006)
National Human Genome Genome Research Institute

Novel terms

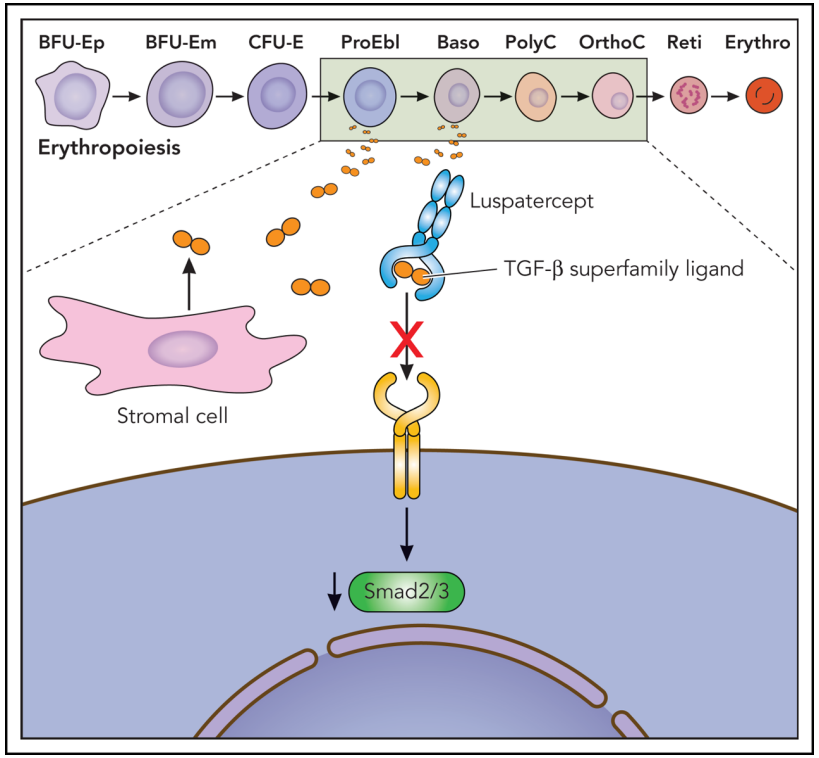
Acronym	*Condition*	*Description/Definition*
ARCH	Aging related clonal hematopoiesis	Describes the presence of detectable, benign clonal hematopoiesis (defined by the presence of somatic mutations in the blood or bone marrow) whose incidence increases with age. No formal definition involving clonal abundance or types of mutations. No clinical significance is implied.
CHIP	Clonal hematopoiesis of indeterminate potential	Defined by somatic mutations of myeloid malignancy-associated genes in the blood or bone marrow present at $\geqslant$ 2% variant allele frequency in individuals without a diagnosed hematologic disorder.
CHOP	Clonal hematopoiesis of oncogenic potential	Describes clonal hematopoiesis in a clinical context where it is associated with a significant likelihood of progressing to a frank malignancy.
IDUS	Idiopathic dysplasia of undetermined significance	Individuals with unexplained morphologic dysplasia of blood cells who are not cytopenic. Can occur with or without clonal hematopoiesis.
ICUS	Idiopathic cytopenia of undetermined significance	Patients with one or more unexplained cytopenias who do not meet diagnostic criteria for myelodysplastic syndrome or another hematologic disorder. Can occur with or without clonal hematopoiesis although often used to refer to cytopenias without evidence of clonal hematopoiesis.
CCUS	Clonal cytopenia of undetermined significance	Patients with one or more unexplained cytopenias who do not meet diagnostic criteria for myelodysplastic syndrome or another hematologic disorder, but who have somatic mutations of myeloid malignancy-associated genes in the blood or bone marrow present at $\geqslant$ 2% variant allele frequency. Can be considered as the intersection between CHIP and ICUS.



R Bejar. Leukemia (2017) 1869 – 1871

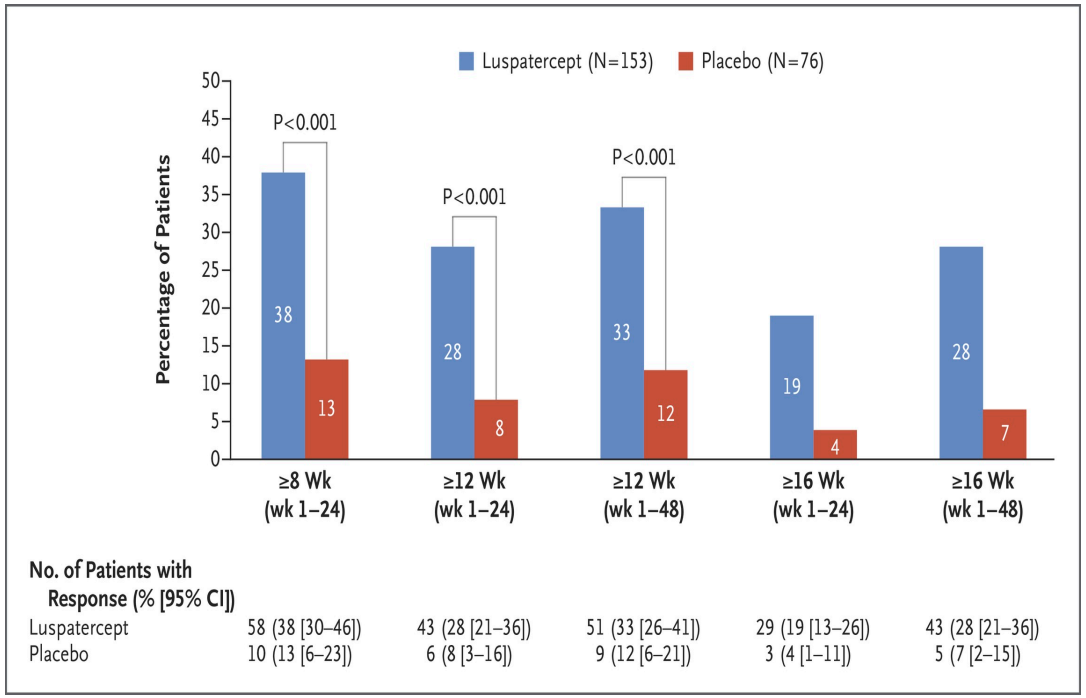
Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes MEDALIST trial

- Luspatercept is a fusion protein aimed at binding TGF-β family members(ligand trap) and reducing SMAD2 and SMAD3 signaling in patients with myelodysplasia with ring sideroblasts leading to erythroid maturation.
- A Phase III, double-blind, 2:1 randomized trial comparing ACE-536 Vs. Placebo in transfusion dependent very low, low and intermediate risk MDS by R-IPSS with MDS-RS or MDS with SF3B1 mutation, ESA refractory or serum EPO>200 U/L.
- **Results:** In patients with lower-risk disease, transfusion independence for 8 weeks or longer occurred in 38% of patients in the luspatercept group and 13% of those in the placebo group($p<0.0001$).
- **Toxicities:** Most common AEs were fatigue, headache, musculoskeletal pain, arthralgia, dizziness/vertigo, nausea, diarrhea, cough, abdominal pain, dyspnea and hypersensitivity.



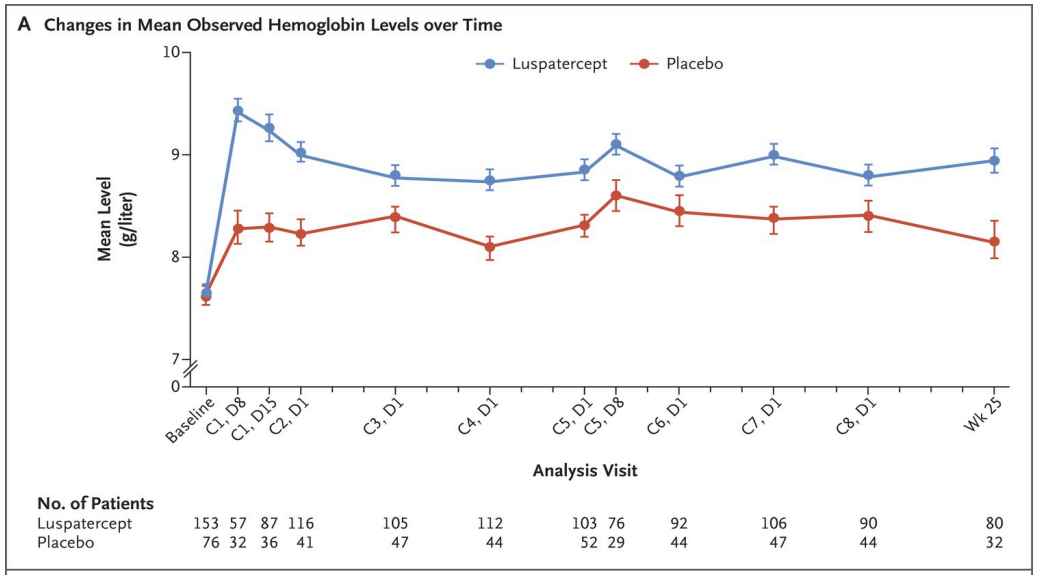
Fenaux P et al. N Engl J Med 2020;382:140-151
AS Kubasch et al. Blood Adv (2021) 5 (5): 1565–1575.

MEDALIST: Independence from Red-Cell Transfusion and changes in mean haemoglobin over time



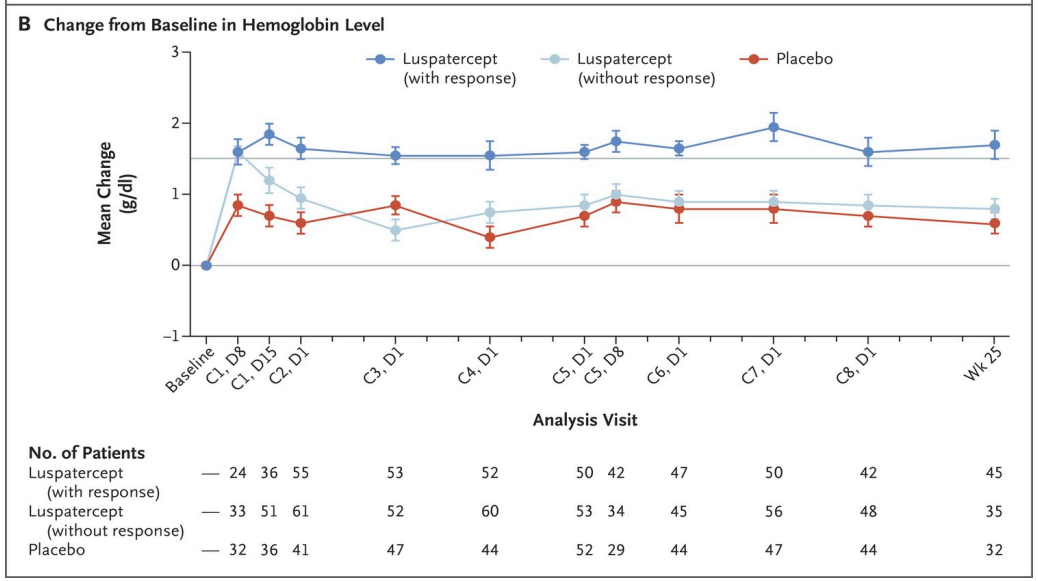
No. of Patients with Response (% [95% CI])

Luspatercept	58 (38 [30–46])	43 (28 [21–36])	51 (33 [26–41])	29 (19 [13–26])	43 (28 [21–36])
Placebo	10 (13 [6–23])	6 (8 [3–16])	9 (12 [6–21])	3 (4 [1–11])	5 (7 [2–15])



No. of Patients

Luspatercept	153	57	87	116	105	112	103	76	92	106	90	80
Placebo	76	32	36	41	47	44	52	29	44	47	44	32



No. of Patients

Luspatercept (with response)	—	24	36	55	53	52	50	42	47	50	42	45
Luspatercept (without response)	—	33	51	61	52	60	53	34	45	56	48	35
Placebo	—	32	36	41	47	44	52	29	44	47	44	32

Fenaux P et al. N Engl J Med 2020;382:140-151

MEDALIST: Demographic and Disease Characteristics of the Patients and Mutations at baseline

Table 1. Demographic and Disease Characteristics of the Patients at Baseline.*

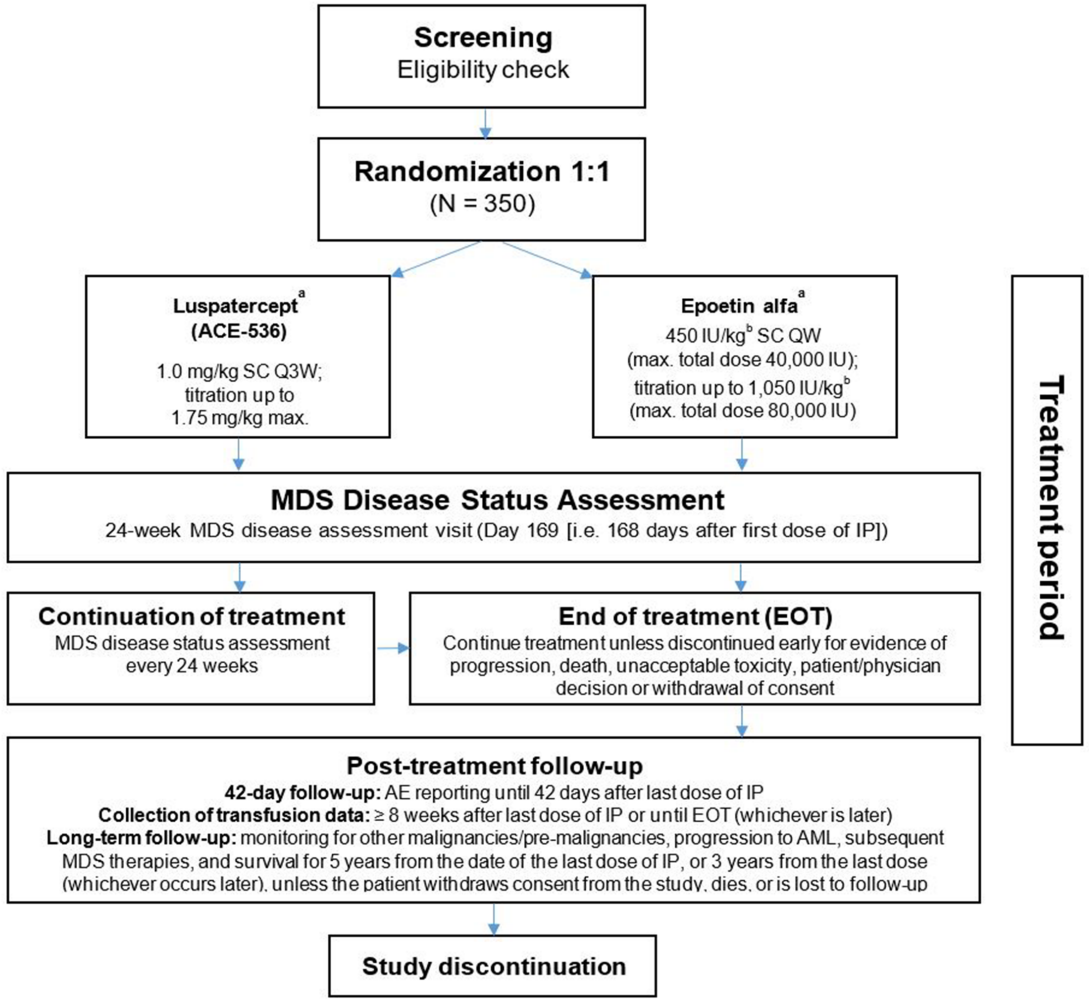
Characteristic	Luspatercept (N = 153)	Placebo (N = 76)	Total (N = 229)
Median age (range) — yr	71 (40–95)	72 (26–91)	71 (26–95)
Male sex — no. (%)	94 (61)	50 (66)	144 (63)
Median time since original diagnosis of MDS (range) — mo	44.0 (3–421)	36.1 (4–193)	41.8 (3–421)
WHO classification of MDS — no. (%)†			
MDS with refractory anemia with ring sideroblasts	7 (5)	2 (3)	9 (4)
MDS with refractory cytopenia with multilineage dysplasia‡	145 (95)	74 (97)	219 (96)
IPSS-R risk category — no. (%)§			
Very low	18 (12)	6 (8)	24 (10)
Low	109 (71)	57 (75)	166 (72)
Intermediate	25 (16)	13 (17)	38 (17)
Median serum erythropoietin level (range) — U/liter¶	156.9 (12–2454)	130.8 (29–2760)	153.2 (12–2760)
Serum erythropoietin level category — no. (%)			
<100 U/liter	51 (33)	31 (41)	82 (36)
100 to <200 U/liter	37 (24)	19 (25)	56 (24)
200 to 500 U/liter	43 (28)	15 (20)	58 (25)
>500 U/liter	21 (14)	11 (14)	32 (14)
Missing data	1 (1)	0	1 (<1)
Mutated *SF3B1* — no./total no. (%)‖	138/148 (93)	64/74 (86)	202/222 (91)
Median red-cell transfusion burden (range) — no. of units/8 wk over period of 16 wk**	5 (1–15)	5 (2–20)	5 (1–20)
Red-cell transfusion-burden category — no. (%)			
≥6 units/8 wk	66 (43)	33 (43)	99 (43)
4 to <6 units/8 wk	41 (27)	23 (30)	64 (28)
<4 units/8 wk	46 (30)	20 (26)	66 (29)
Median pretransfusion hemoglobin level (range) — g/dl††	7.6 (6–10)	7.6 (5–9)	7.6 (5–10)
Received ESA previously — no. (%)	148 (97)	70 (92)	218 (95)
Disease refractory to ESA — no./total no. (%)	144/148 (97)	69/70 (99)	213/218 (98)
Discontinued previous ESA-containing regimen owing to an adverse event — no./total no. (%)	4/148 (3)	1/70 (1)	5/218 (2)
Previous iron chelation therapy — no. (%)	71 (46)	40 (53)	111 (48)
Median platelet count (range) — 10^{-9}/liter	235.0 (59–892)	222.5 (60–689)	234.0 (59–892)

* Percentages may not total 100 because of rounding. ESA denotes erythropoiesis-stimulating agent, IPSS-R Revised International Prognostic Scoring System, MDS myelodysplastic syndrome, and WHO World Health Organization.
† One patient in the luspatercept group had locally diagnosed MDS with ring sideroblasts with multilineage dysplasia.
‡ All the patients were classified as having refractory cytopenia with multilineage dysplasia with ring sideroblasts because they were required to have ring sideroblasts according to the inclusion criteria.
§ MDS in one patient (1%) in the luspatercept group was classified as IPSS-R high-risk. This case was a protocol violation, and the patient entered the trial in error.
¶ The baseline erythropoietin level was defined as the highest erythropoietin value within 35 days before the first dose.
‖ The analysis included only patients with available baseline gene mutation data.
** The analysis included data only within the 16 weeks before randomization.
†† The pretransfusion hemoglobin level was defined as the last value measured on or before the date and time of the first dose.

No. — %	Luspatercept (n = 148)	Placebo (n = 74)
SF3B1	138 (93.2)	64 (86.5)
TET2	62 (41.9)	31 (41.9)
DNMT3A	29 (19.6)	13 (17.6)
ASXL1	22 (14.9)	7 (9.5)
SRSF2	14 (9.5)	4 (5.4)
TP53	6 (4.1)	2 (2.7)
EZH2	6 (4.1)	2 (2.7)
IDH2	6 (4.1)	2 (2.7)
RUNX1	3 (2.0)	2 (2.7)
CBL	3 (2.0)	1 (1.4)
IDH1	2 (1.4)	0
GATA2	2 (1.4)	0
KIT	1 (0.7)	0
ETV6	1 (0.7)	1 (1.4)
KRAS	0	1 (1.4)
BCOR	0	1 (1.4)
U2AF1	0	1 (1.4)
NPM1	0	0
EPOR	0	0
GATA1	0	0
NRAS	0	0

Fenaux P et al. N Engl J Med 2020;382:140-151

The COMMANDS Trial: A Phase 3 Study of the Efficacy and Safety of Luspatercept Versus Epoetin Alfa for the Treatment of Anemia Due to IPSS-R Very Low-, Low-, or Intermediate-Risk MDS with or without Ringed Sideroblasts in Erythropoiesis Stimulating Agent-Naive Patients Who Require RBC Transfusions (NCT03682536)

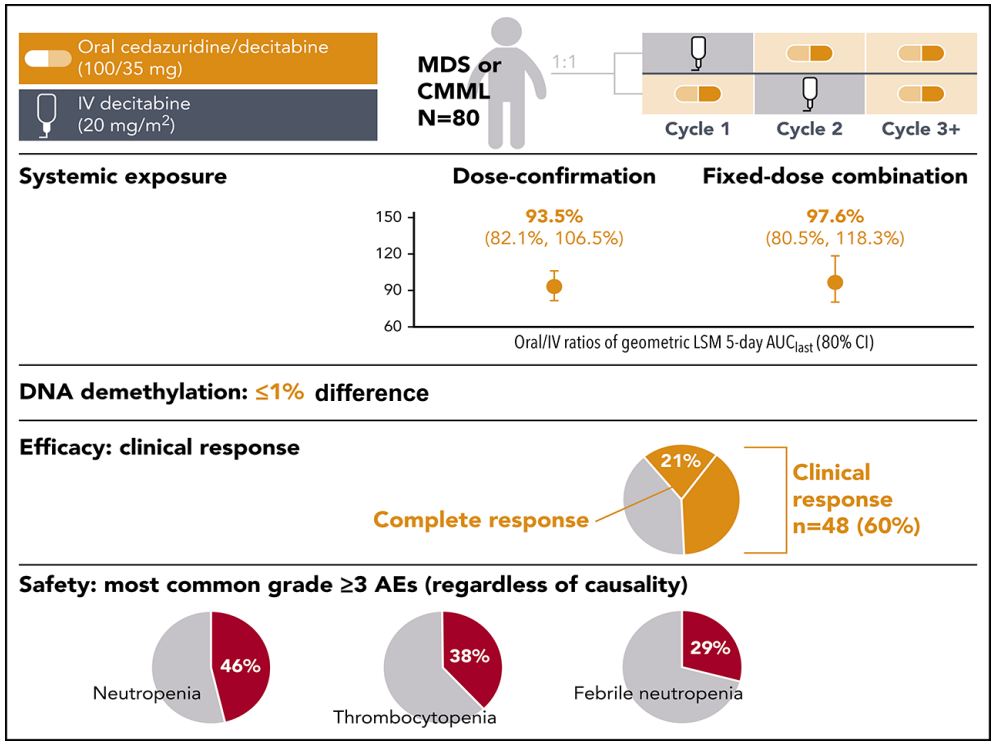


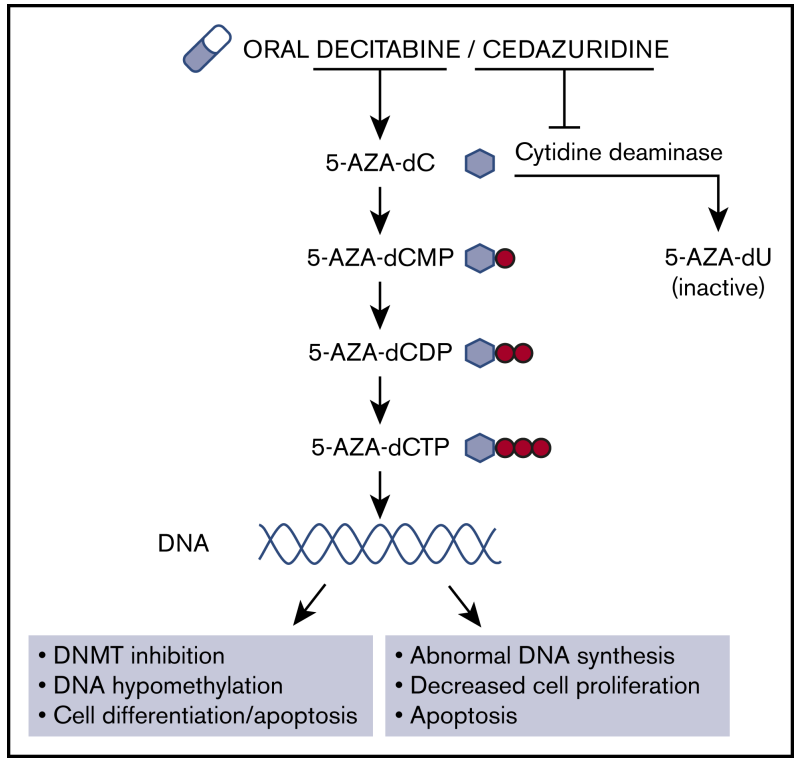
Exclusion criteria: Prior use of ESAs, granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF), disease-modifying agents (like lenalidomide), or hypomethylating agents; and presence of del(5q) cytogenetic abnormality.

The **primary endpoint** is the proportion of patients who achieve RBC-TI for 12 weeks within the first 24 weeks on study, with a concurrent mean hemoglobin (Hb) increase of ≥ 1.5 g/dL compared with baseline. Key secondary endpoints include duration of RBC-TI, change in Hb levels, achievement of HI-E response per International Working Group (IWG) 2006 criteria, and safety.

ASH 2020: Abstract 636: Blood (2020) 136 (Supplement 1)

Cedazuridine/decitabine





- In both **Phase II ASTX727-01-B** and **Phase III randomized (1:1) ASTX727-02 (ASCERTAIN)** study patients with de novo and secondary MDS or CMML or Int-1, Int-2 and high risk by IPSS were studied.
- Exposure by PK and safety during first 2 cycles measured.
- The overall safety profile is similar to IV decitabine.

Patel AA et al, Blood Adv (2021) 5 (8): 2264–2271.
Garcia-Manero G et al. Blood (2020) 136 (6): 674–683.
Savona M et al. Blood (2020) 136 (Supplement 1): 37–38.

Outcomes of phase II and III trials of decitabine and cedazuridine

Characteristic	Phase 2 (NCT02103478) ASTX727-01-B[45]	Phase 3 (NCT03306264) ASTX727-02[46,47]
Total patients, N	80	133
Mean age (range), y	71 (32-90)	71 (44-88)
MDS (intermediate-1), n (%)	35 (44)	11 (8)
MDS (intermediate-2), n (%)	19 (24)	85 (64)
MDS (high risk), n (%)	9 (11)	21 (16)
CMML, n (%)	17 (21)	16 (12)
Median number of cycles (range)	7 (1-29)	8 (1-18)
Oral/IV ratio of geometric LSM 5-d AUC, %	97.6	98.9
Difference (oral-IV) in mean maximum LINE-1 demethylation, %	0.017-1.079	0.7-0.8
Patients with CR, n (%)	17 (21)	29 (22)
Patients with PR, n (%)	0	0
Patients with mCR, n (%)	18 (22)	43 (32)
Overall response (CR + PR + mCR + HI), n (%)	48 (60)	82 (62)
Median follow-up, mo	24	24.7
Median overall survival, mo	18.3	NR
Most common grade ≥3 TEAEs, %	Neutropenia: 46 Thrombocytopenia: 38 Febrile neutropenia: 29 Leukopenia: 24 Anemia: 22 Pneumonia: 13 Sepsis 10	Neutropenia: 52 Thrombocytopenia: 50 Anemia: 40 Febrile neutropenia: 26 Leukopenia: 21 Pneumonia: 12

TEAEs, treatment-emergent adverse events.

Patel AA et al, Blood Adv (2021) 5 (8): 2264–2271.

Venetoclax

- **NCT02966782:** Phase 1b open-label multicenter study: R/R MDS: Safety and Efficacy of Venetoclax monotherapy (n=22) or Ven + Azacitidine (n=38). Monotherapy: Median follow up: 4.7 months. 7% ORR and 75% stable disease. Ven+Aza; Combination: Median follow up 6.8 m, 12-month estimated OS was 65% and 40% ORR (CR+mCR).

- **NCT02942290:** Phase 1b, open-label, dose escalation Ven+Aza for treatment naïve high risk MDS. 57 patients with median follow up of 13 months, ORR 77% with median duration of response of 14.8 m. Median PFS = 17.5 months

- Serious grade 3 AE: Febrile neutropenia or thrombocytopenia.

Figure: Outcomes of Patients With RR-MDS Treated with Ven+Aza Who Achieved CR/mCR

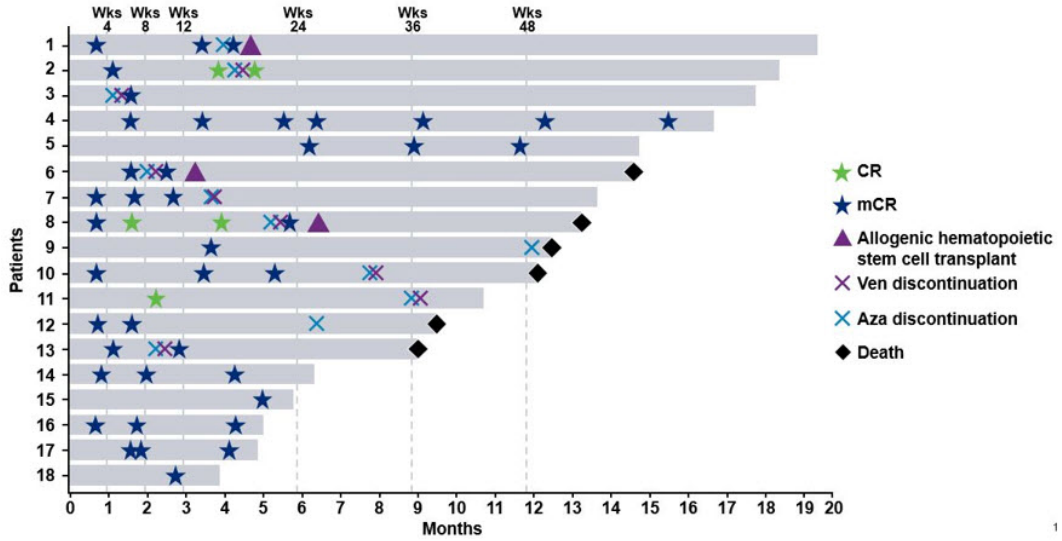
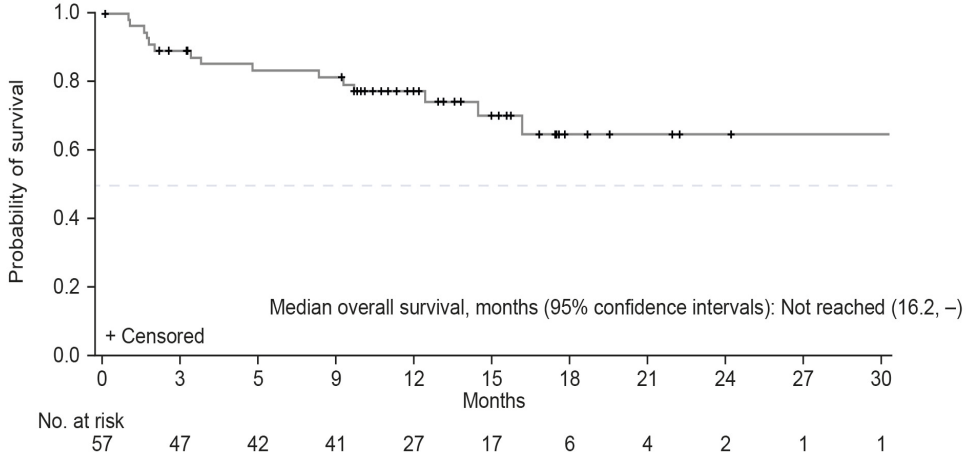


Figure 1. Kaplan–Meier Curve for Overall Survival of All Patients



Zeiden AM et al. ASH 2019: Abstract 637
Zeiden AM et al. ASH 2020: Abstract 3109
Garcia JS et al. ASH 2020: Abstract 656

Breakthrough Therapy Designation Granted for Venetoclax for Patients with Higher-Risk MDS

Press Release: July 21, 2021

"The U.S. FDA granted a Breakthrough Therapy Designation to venetoclax in combination with azacitidine for the potential treatment of adult patients with previously untreated intermediate-, high- and very high-risk myelodysplastic syndromes (MDS) based on revised International Prognostic Scoring System (IPSS-R).

This Breakthrough Therapy Designation underscores the need for more treatment options for these patients and the utility of venetoclax to potentially treat different forms of blood cancer.

This designation is supported by data from the Phase Ib M15-531 study.

In addition to the Phase Ib M15-531 study, venetoclax is being investigated in combination with azacitidine for the treatment of MDS in the Phase Ib M15-522 study in patients with relapsed or refractory disease, and the Phase 3 randomized VERONA study in patients with newly diagnosed higher-risk MDS."

https://news.abbvie.com/news/press-releases/venetoclax-venclexta-granted-us-fda-breakthrough-therapy-designation-btd-in-higher-risk-myelodysplastic-syndrome-mds.htm

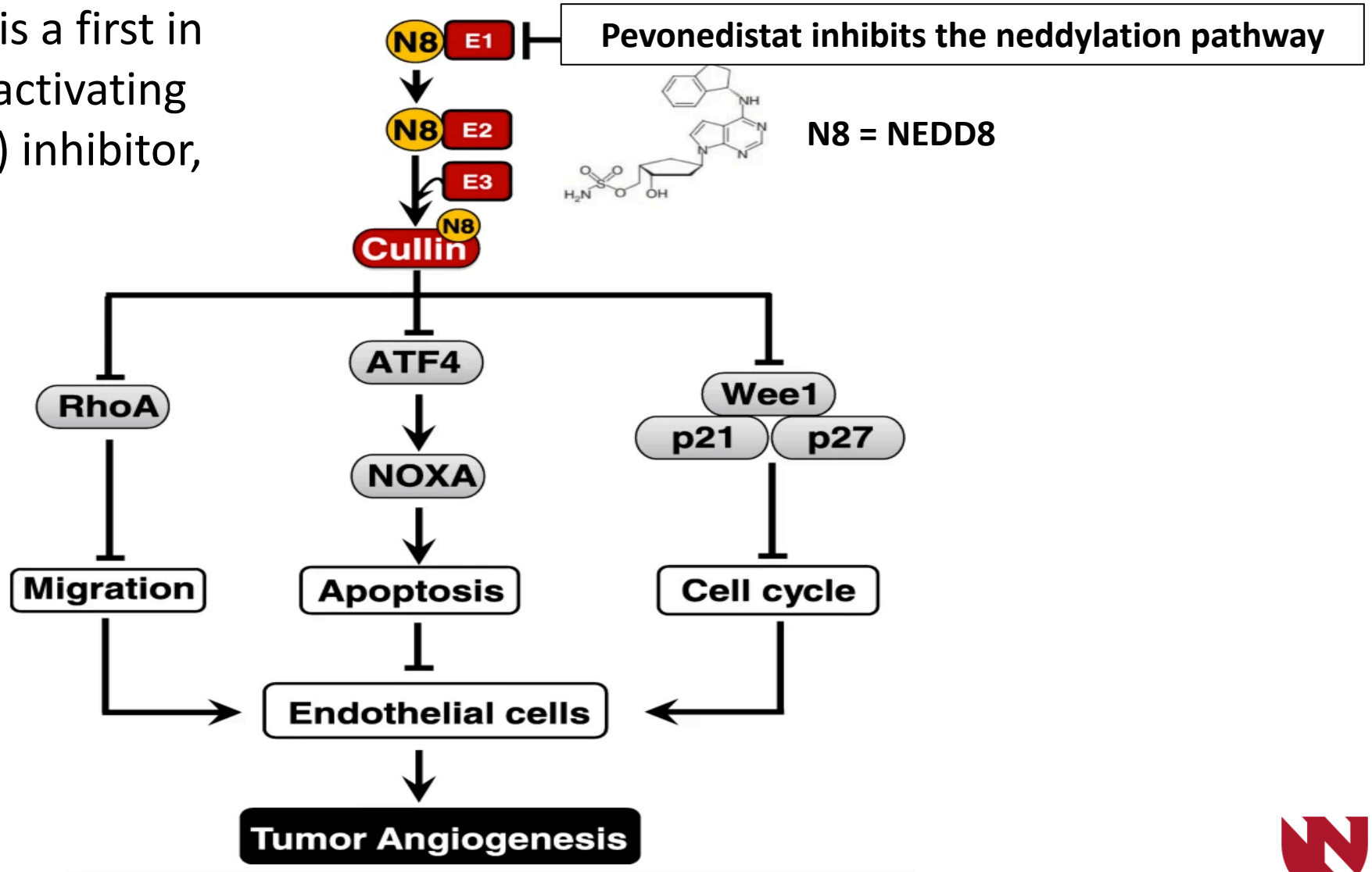
IDH1/2 inhibitors (Ivosidenib/Enasidenib)

- IDH1/2 mutations occur in 5-12% of MDS
- In the **phase 1b dose escalation study with Ivosidenib** in HMA failed R/R MDS with IDH1 mutation: 11 of 12 had ORR (91.7%) and 5 with CR (41.7%). Dose 500 mg PO QD.
- **Enasidenib:** phase 1-2 open-label R/R or ineligible for standard therapy. Median follow up 11 months; 17 patients with IDH2 mutation. ORR 53% with median duration of response 9.2 mo, event free survival 11 mo.
    - Most common AE: Diarrhea (53%), indirect hyperbilirubinemia (35%), pneumonia(29%), Thrombocytopenia (24%), TLS(18%).
- **Phase II study of enasidenib/Aza:** 46 patients evaluable with IDH2 mutation, ORR of 68%, treatment naïve IDH2 positive MDS (n=25): ENA+Aza: ORR 84% with CR 24% and PR+mCR: 52%; HMA failure (n=21): ENA single-agent (100 mg daily): 43% ORR with CR 24%, PR+mCR 10%. Median OS of 32.2 months in ENA+AZA group and 21.3 mo in ENA group.
    - Most common treatment related AE: cytopenia and infection.

DiNardo CD et al. N Engl J Med 2018; 378:2386-2398; Lancet Haematol. 2020 Apr;7(4):e309-e319; Venugopal S et al. JCO Vol 39; 15 suppl (ASCO 2021)

Pevonedistat: Mechanism of Action

Pevonedistat is a first in class NEDD8-activating enzyme (NAE) inhibitor,



Zhou L et al. Molecular Cancer 2019;18(1):77.

Pevonedistat

- Small molecule inhibitor of NEDD8-activating enzyme.
- Phase II: high risk MDS/CMML: 120 patients randomized 1:1 to Pev+HMA IV day 1,3,5 + Aza day 1-7 (n=58) Vs. Aza alone (n=62). 67 patients with high-risk MDS intent-to-treat EFS: 21 vs 16.6 m, ORR (79% vs 57%), Median duration of response 34.6 m vs 13.1 mo. Transfusion independence 69 vs 47% with 23.3 vs 11.6 months of median transfusion independence.
- Responses seen even in patients with high-risk mutations.

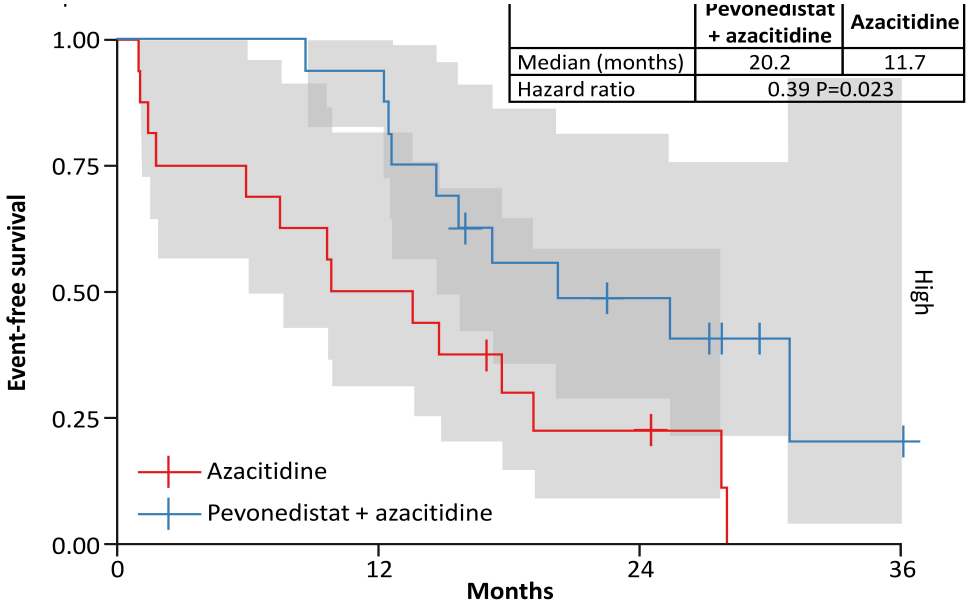
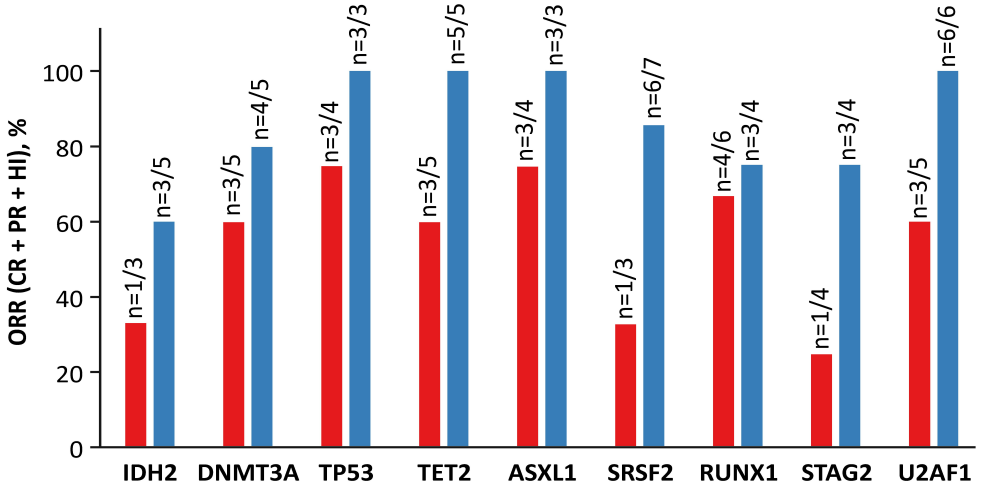


Figure 2. Clinical activity was observed with pevonedistat + azacitidine in patients with higher-risk myelodysplastic syndrome harboring poor-prognostic mutations. CR, complete remission; HI, hematologic improvement; ORR, overall response rate; PR, partial remission.



Sekeres M et al. ASH 2020: Abstract # 653

Breakthrough Therapy Designation Granted for Pevonedistat for Patients with Higher-Risk (HR) MDS

Press Release: July 30, 2020

- The U.S. FDA granted Breakthrough Therapy Designation for the investigational drug pevonedistat for the treatment of patients with HR-MDS. Pevonedistat could be the first novel treatment for HR-MDS patients in more than a decade, expanding treatment options that have so far been limited to hypomethylating agent (HMA) monotherapy alone.
- The Breakthrough Therapy Designation is based on the final analysis of the Pevonedistat-2001 Phase 2 study, which evaluated pevonedistat plus azacitidine versus azacitidine alone in patients with rare leukemias, including HR-MDS.
- The FDA considered a number of endpoints, including OS, EFS, complete remission and transfusion independence, as well as the adverse event profile. This designation signals a potential advancement in addressing the needs of people living with HR-MDS.

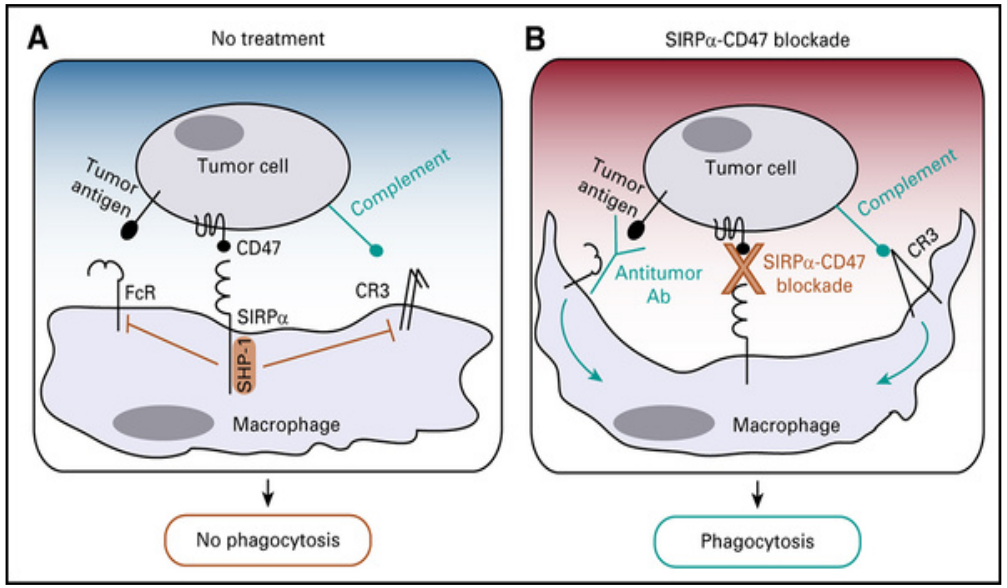
Ongoing Phase III Trials of Pevonedistat in AML/MDS

- **PANTHER trial** of Pevonedistat plus Azacitidine versus Single-Agent Azacitidine as First-Line Treatment for Patients With HR-MDS, Chronic Myelomonocytic Leukemia, or Low-Blast Acute Myelogenous Leukemia
- **PEVOLAM Trial** comparing Pevonedistat plus Azacitidine versus Azacitidine in Older/Unfit Patients With Newly Diagnosed Acute Myeloid Leukemia who are Ineligible for Standard Induction Chemotherapy

https://www.takeda.com/newsroom/newsreleases/2020/takeda-announces-u.s.-fda-breakthrough-therapy-designation-granted-for-pevonedistat-for-the-treatment-of-patients-with-higher-risk-myelodysplastic-syndromes-hr-mds/
Clinicaltrials.gov (Accessed in August 2021)

Magrolimab: The “eat me” signal promotor

- CD47 upregulated in blasts/leukemic stem cells(LCS).
- Induces tumor phagocytosis and eliminates LCS.
- Phase 1b: intermediate – very high risk MDS by R-IPSS. Magrolimab + AZA, in 33 evaluable patients with 91% ORR and 42% CR, 24%mCR. Median time to response is 1.9 months with median follow up of 5.8 m. Median response duration not reached. Median OS and response duration not reached with 6 months estimated OS of 100%.
- Common AE: anemia(44%), fatigue, Infusion reactions, neutropenia and thrombocytopenia.
- **ENHANCE,** a randomized Phase III Magrolimab vs Placebo + AZA is underway.
- Very good responses in TP53 mutated AML



Sallman D et al. EHA Annual congress: 2020: Abstract S187
Veillette A et al: JCO. 37(12):1012-1014, April 20, 2019.

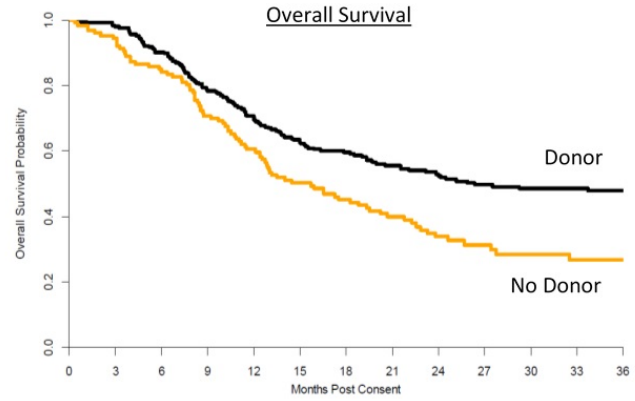
Early phase studies summary

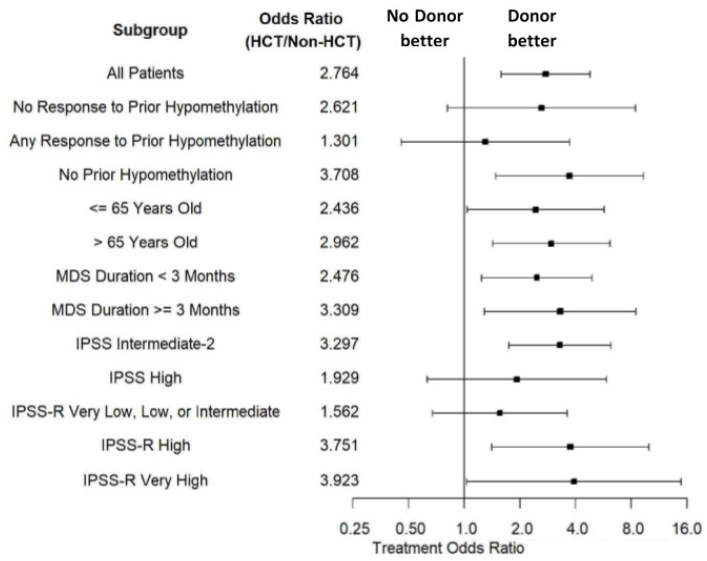
Drug	Phase	ORR*	CR	Median OS/PFS	Response duration	Common Adverse events
Decitabine/ cedazuridine	2/3	~60%	20-22%	18 m-NR	7.5 m	Cytopenia, febrile neutropenia, infections
Venetoclax monotherapy	1b	7%		3.4 m		
Ven+Aza (R/R)	1b	40%		65%		Cytopenia, febrile neutropenia, infections, constipation or diarrhea
Ven+Aza (naïve)	1b	77%	42%	17.5 m	14.8 m	Same
Ivosidenib (IDH1+)	1b	92%	42%			Fatigue, nausea, dyspnea, prolonged QTc, leukocytosis, cough, diarrhea, constipation.
Enasidenib (IDH2 +):R/R	1b	53%		16.9 m (OS)	9.2 m	Diarrhea, hyperbilirubinemia, pneumonia, thrombocytopenia, tumor lysis.
Enasidenib +Aza (naïve)	2	84%	24%	32.2 m		Differentiation syndrome (12%), cytopenia, infections
Pevonedistat +Aza (naïve)	2	79%	52%	21 m	34.6 m	
Magrolimab +Aza	1b	91%	42%	NR(>6 m)	NR	Fatigue, infusion reactions, cytopenia.

*ORR: CR+ PR+ marrow CR+ Hematological improvement.

A Multi-Center Biologic Assignment Trial Comparing Reduced Intensity Allogeneic Hematopoietic Cell Transplantation to Hypomethylating Therapy or Best Supportive Care in Patients Aged 50-75 with Advanced Myelodysplastic Syndrome: Blood and Marrow Transplant Clinical Trials Network Study 1102

	Donor Arm (N=260) N (%)	No Donor Arm (N=124) N (%)	Total (N=384) N (%)
Age (years)			
Mean (SD)	65.6 (5.6)	66.0 (5.9)	65.7 (5.7)
Median (Range)	66.3 (50.1, 75.3)	67.3 (50.7, 75.1)	66.7 (50.1, 75.3)
65 or Older	155 (59.6%)	80 (64.5%)	235 (61.2%)
Gender			
Female	95 (36.5%)	48 (38.7%)	143 (37.2%)
Male	165 (63.5%)	76 (61.3%)	241 (62.8%)
Ethnicity			
Hispanic or Latino	11 (4.2%)	9 (7.3%)	20 (5.2%)
Not Hispanic or Latino	233 (89.6%)	108 (87.1%)	341 (88.8%)
Unknown	9 (3.5%)	7 (5.6%)	16 (4.2%)
NA	7 (2.7%)	0 (0.0%)	7 (1.8%)
Karnofsky Performance Status			
90 - 100	99 (55.0%)	35 (41.7%)	134 (50.8%)
< 90	81 (45.0%)	49 (58.3%)	130 (49.2%)
MDS Subtype			
RCUD	5 (1.9%)	1 (0.8%)	6 (1.6%)
RARS	5 (1.9%)	2 (1.6%)	7 (1.8%)
RAEB-1	61 (23.5%)	31 (25.0%)	92 (24.0%)
RAEB-2	132 (50.8%)	63 (50.8%)	195 (50.8%)
RCMD	36 (13.8%)	14 (11.3%)	50 (13.0%)
Isolated del(5q)	6 (2.3%)	7 (5.6%)	13 (3.4%)
Unclassifiable	15 (5.8%)	6 (4.8%)	21 (5.5%)
MDS Duration from Diagnosis to Enrollment (months)			
Mean (SD)	8.4 (21.6)	11.0 (27.1)	9.2 (23.5)
Median (Range)	2.5 (0.2, 182.3)	2.2 (0.3, 211.6)	2.3 (0.2, 211.6)
Highest IPSS Score			
Intermediate-2 (1.5-2.0)	173 (66.5%)	81 (65.3%)	254 (66.1%)
High Risk (=2.5)	87 (33.5%)	43 (34.7%)	130 (33.9%)
Response to Hypomethylating Therapy			
Complete Response	10 (3.8%)	7 (5.6%)	17 (4.4%)
Partial Response	46 (17.7%)	23 (18.5%)	69 (18.0%)
No Response	79 (30.4%)	42 (33.9%)	121 (31.5%)
Never had therapy	88 (33.8%)	33 (26.6%)	121 (31.5%)
Unknown	37 (14.2%)	19 (15.3%)	56 (14.6%)
Number of Distinct Cytogenetic Abnormalities			
1	43 (28.5%)	28 (34.6%)	71 (30.6%)
2	31 (20.5%)	19 (23.5%)	50 (21.6%)
3	20 (13.2%)	14 (17.3%)	34 (14.7%)
=4	52 (34.4%)	20 (24.7%)	72 (31.0%)
Missing	5 (3.3%)	0 (0.0%)	5 (2.2%)





ASH 2020- Abstract 75: Nakamura et al.

Case 1

- 84 year old man was followed by primary care physician at least since 2005 to have macrocytosis without anemia. Hemoglobin 14.3 gm/dL, MCV 103-105 fL (82-98 fL), WBC 8900/mcL, ANC 6800/mcL, Platelet: 240,000/mcL.
- Normal vitamin B12, folic acid and no liver disease
- Progressively had worsened macrocytosis and mild anemia around 2016-2018 (Hemoglobin 11-12 gm/dL with MCV around 110-115 fL, WBC 3900/mcL, ANC 1900/mcL. Progressive fatigue with hemoglobin around 10-11 gm/dL and ECHO showed severe aortic stenosis.
- Normal Copper or zinc levels.
- Patient declined bone marrow at this time. Myeloid mutation panel from peripheral blood sample showed SF3B1, ASXL1 mutation.

Case 1 Continued

- Underwent TAVR in 2019 without improvement in fatigue and shortness of breath.
- Worsened anemia in 2019-2020; Bone marrow biopsy performed February 2020 showed hypercellular bone marrow (80%) with MDS-RS and multilineage dysplasia (erythroid and megakaryocytic). Marrow blasts not increased. CBC: WBC 3100/µL, ANC 1800/µL, Hemoglobin 7.8 gm/dL, MCV 120fL, Platelet count 295,000/µL, Cytogenetics 45, X,-Y[4]/46,XY[15] and started to need PRBC transfusions.
- Serum erythropoietin level 184 U/L

Case 1 Continued

- Let us calculate the R-IPSS:
- Cytogenetics: Very good(0); Marrow blasts not increased (0); Hemoglobin (1.5); Platelet count (0); ANC (0) - Low risk (1.5 total score).
- Started Darbepoetin alfa 150 mcg with response to hemoglobin and transfusion independent which lasted for 6-7 months. Started to have hemoglobin around 8-9 gm/dL in spite of increased dose.
- Started Luspatercept around February 2021 at a dose of 1 mcg/kg SC Q 3 weeks. Hemoglobin improved to a range of 10-11 gm/dL and had sustained these responses.
- He continues to maintain the response now.