MYELODYSPLASTIC SYNDROME

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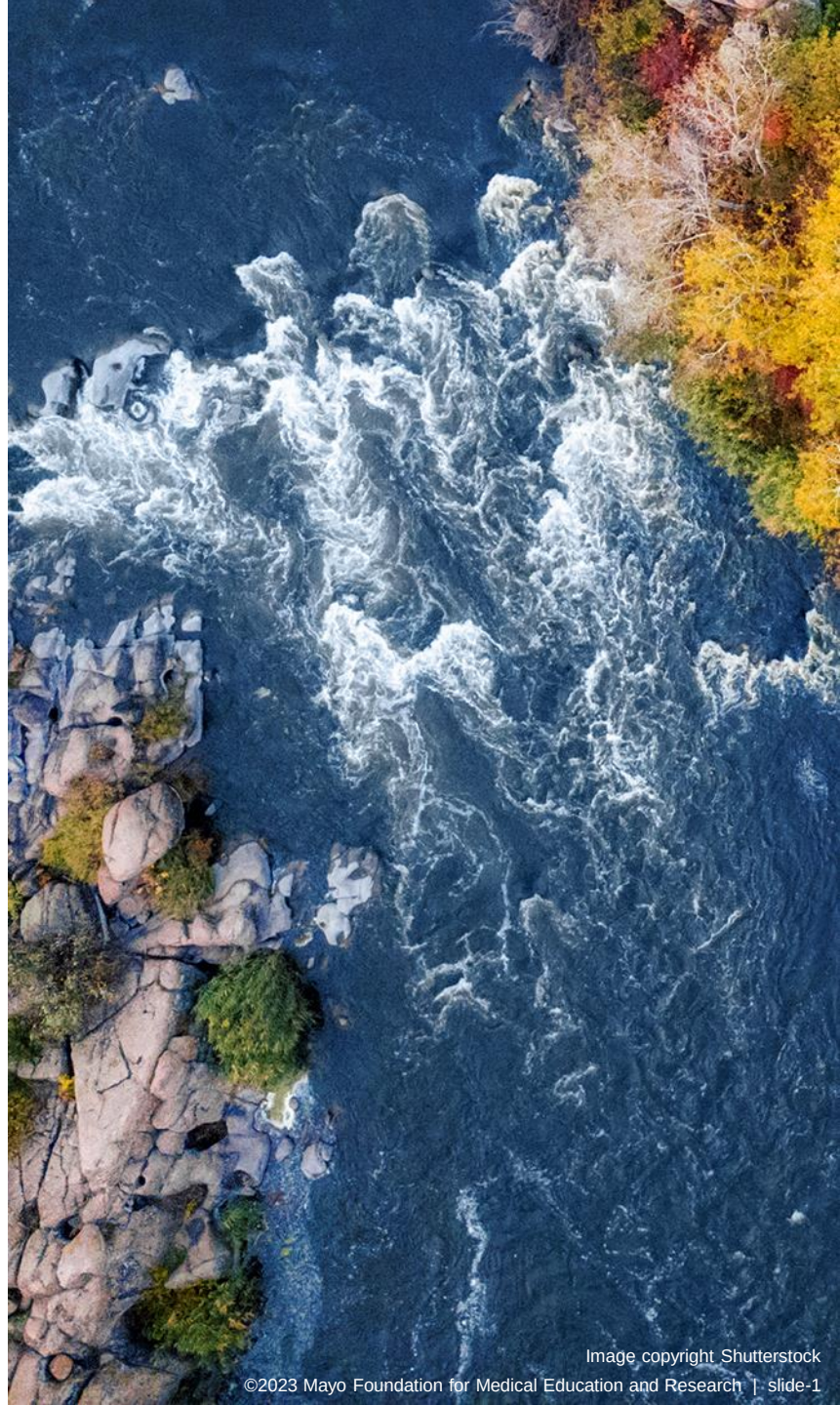
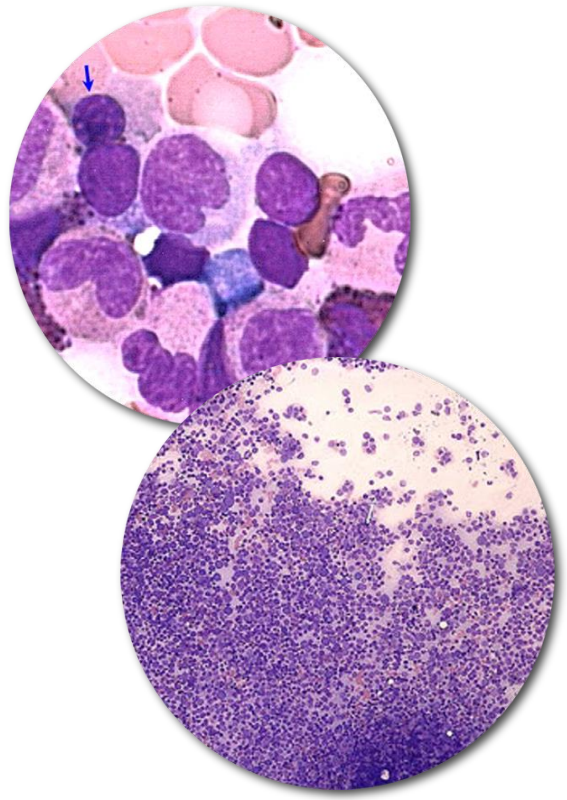


MYELODYSPLASTIC SYNDROMES

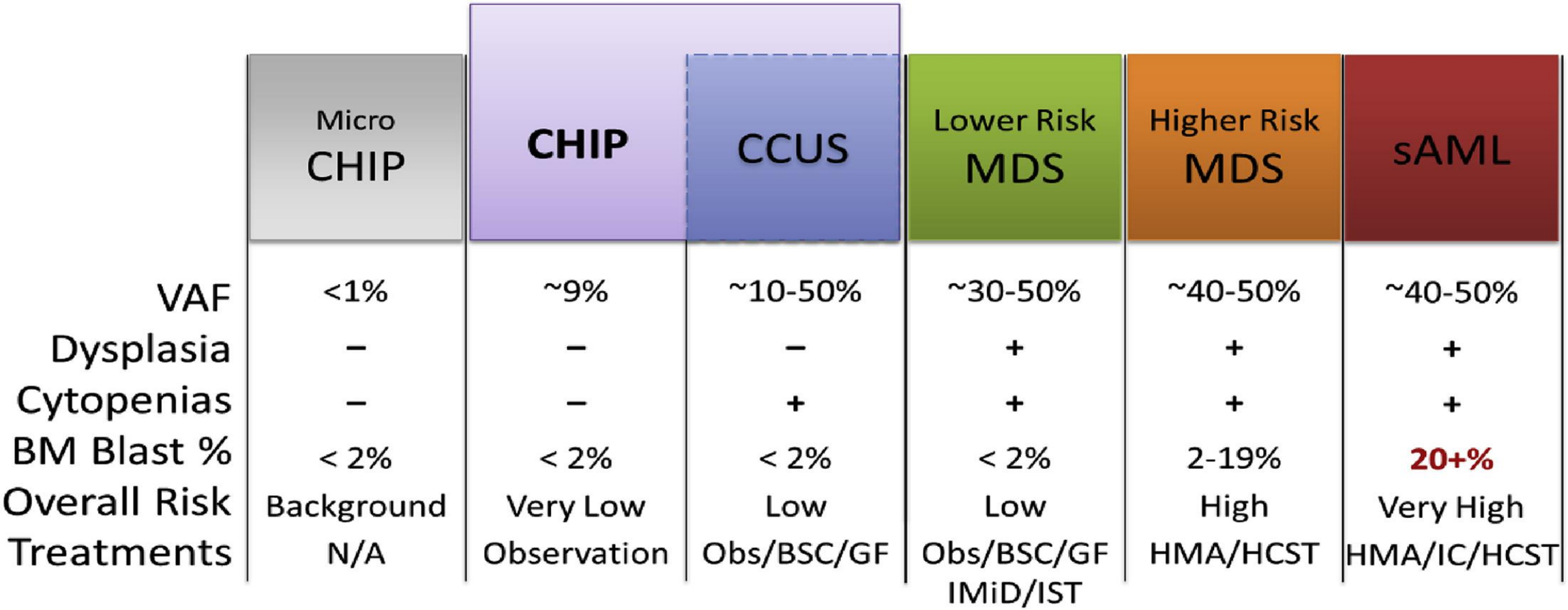
- Heterogenous group of clonal malignant hematopoietic disorders sharing an ineffective production of one or more myeloid cell lines (accelerated apoptosis)
- Typically discrepancy between cellular marrow and peripheral cytopenias
- 10-30,000 cases per year in US
- Median age 76; M>F
- Ineffective hematopoiesis
  - Bleeding, anemia, infections
- Risk of transformation to AML
- Variable clinical course- need for prognostication



Bennett J, et al. The myelodysplastic syndromes. In: Abeloff MD, et al, editors. Clinical oncology. New York NY: Churchill Livingstone; 2004. pp. 2849-2881.

PATHOGENESIS OF MDS

- Arise from mutations in hematopoietic stem cells
- Genetic/ hematologic conditions
- Extrinsic factors
  - T cell dysregulation, stromal cell abnormalities, inflammasome/ inflammatory cytokines
- Familial MDS
  - Germline mutations
    - R*UNX1*, *ANKRD26*, *CEBPA*, *DDX41*, *ETV6*, *TERC*, *TERT*, *SRP72*, and *GATA2*
- Clonal hematopoiesis of indeterminate potential (CHIP)
  - mutations assc. with MDS present, but no dysplasia, cytopenias



R. Bejar Best Prac and Research Clin Haem Dec 2018

PREDISPOSITIONS/ RISK FACTORS FOR MDS

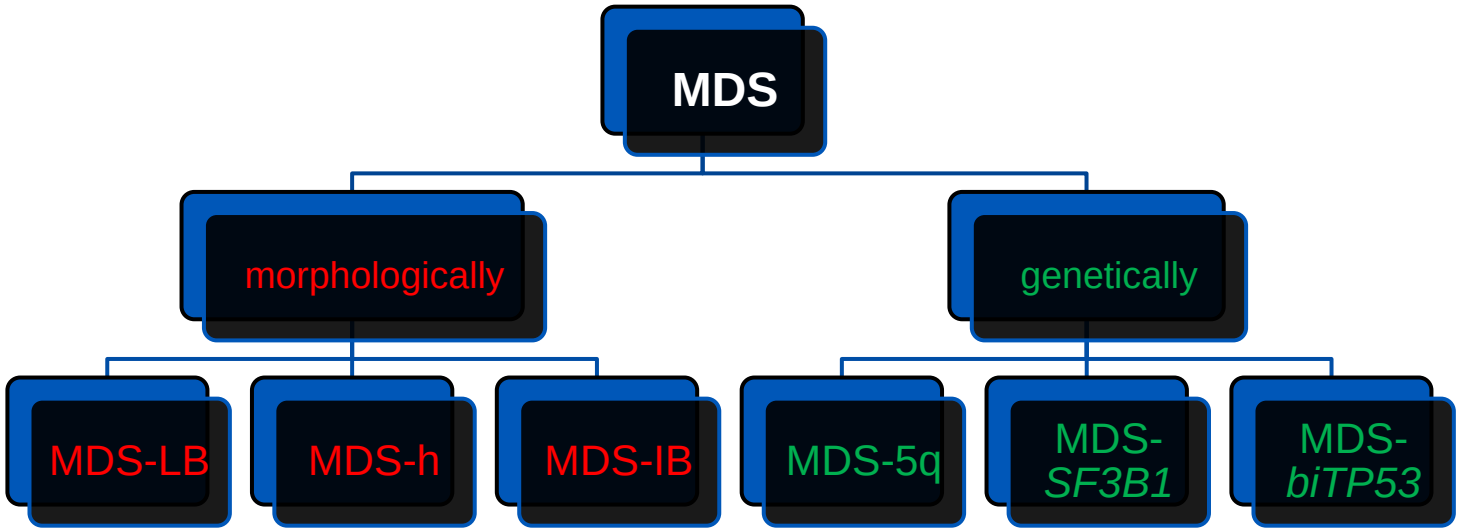
- Age
  - Incidence increases with age
  - Uncommon Age <50
  - Most cases age 70’s, 80’s
- Sex (M>f)
- Prior chemotherapy/ radiotherapy
- Tobacco use
- Environmental
  - benzene
- Other heme disorders
  - Aplastic Anemia, PNH
- Genetic
  - Fanconi anemia
  - Shwachman-diamond syndrome
  - Diamond Blackfan anemia
  - Severe congenital neutropenia
  - Dyskeratosis congenita
- Familial MDS (rare)

MDS PRESENTATION

- Symptoms
  - Many present asymptomatic
  - Fatigue
  - Weakness
  - Frequent Infection
  - Bruising
- Physical signs
  - Eccymosis
  - Pallor
- CBC
  - Anemia
  - Macrocytic (MCV >100)
  - Neutropenia
    - Pelger-huet cells
  - Thrombocytopenia

MDS WHO 2022

- Genetically defined
  - MDS-5q
  - MDS-*SF3B1m*
  - MDS-*biTP53*
- Morphologically defined
  - MDS-LB low blasts
  - MDS-h hypocellular
  - MDS-IB increased blasts
    - IB-1: 2-4% PB blasts, 5-9% BM blasts
    - IB-2: 5-19% PB blasts, 10-19% blasts or Auer rods
    - Fibrosis: 2-19% PB blasts, 5-19% BM blasts



RISK STRATIFICATION

Factors	Values
• CBC	• Single lineage vs multiple
• Blasts%	• <5% vs ≥ 5%
• Cytogenetics	• Complex/-5/-7/-17
• NGS	• TP53, MLL-PTD
• models	• IPSS-molecular

R-IPSS OUTCOMES

IPSS-R Prognostic Score Values*

Prognostic Variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
BM Blast %	<=2		>2-<5%		5-10%	>10%	
Hemoglobin	=>10		8-<10	<8			
Platelets	=>100	50-< 100	<50				
ANC	=>0.8	<0.8					

IPSS-R Cytogenetic Risk Groups*,**

Cytogenetic Prognostic Subgroups	Cytogenetic Abnormalities
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 or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities
Very Poor	Complex: >3 abnormalities

IPSS-R: Prognostic Risk Category Clinical Outcomes*

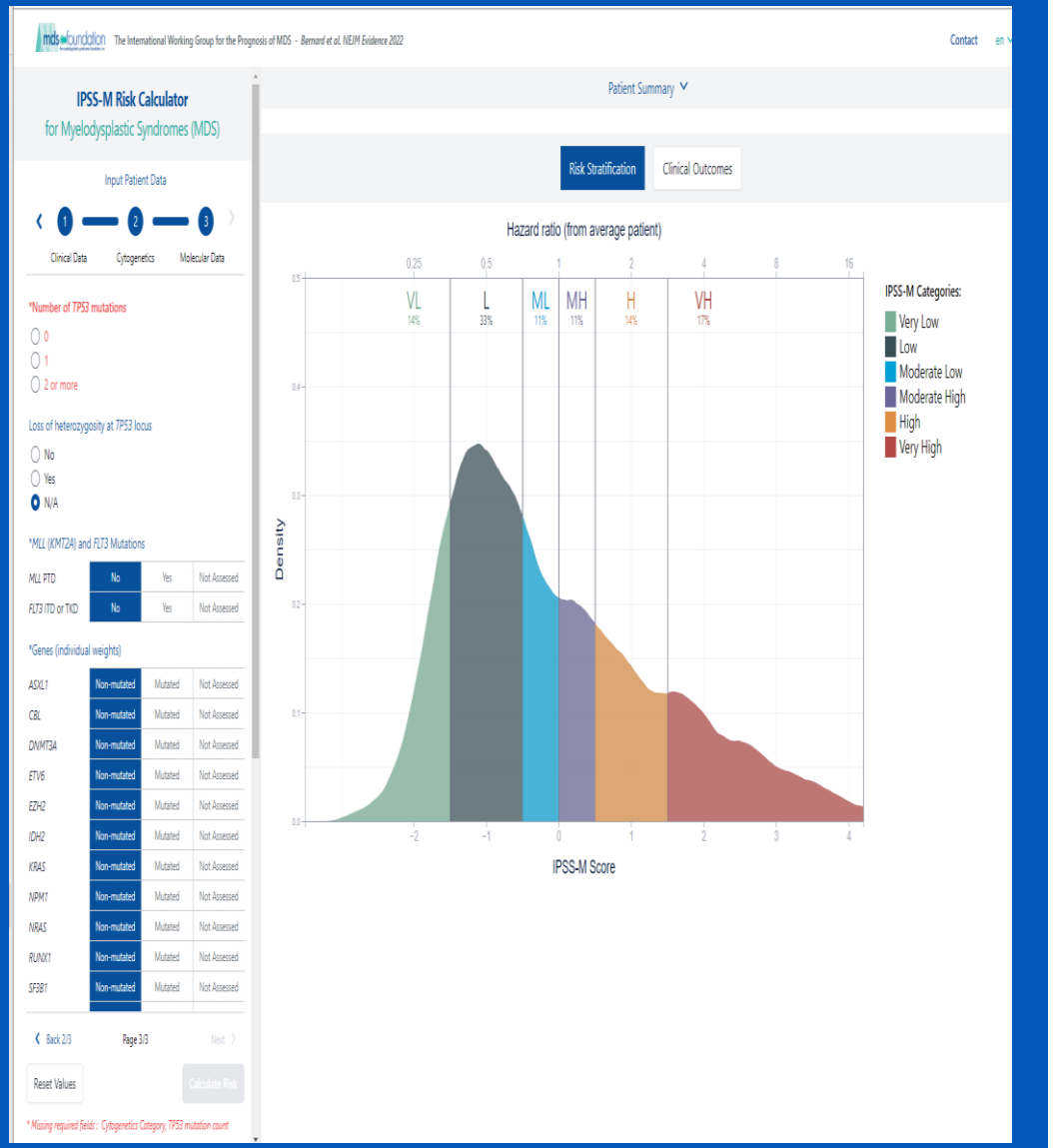
	No. Pts	Very Low	Low	Intermediate	High	Very High
Risk Score		≤1.5	>1.5-3	>3-4.5	>4.5-6	>6
Patients (%)	7012	19%	38%	20%	13%	10%
Survival***		8.8	5.3	3.0	1.6	0.8
AML/25%***,^		NR	10.8	3.2	1.4	0.7

Peter L. Greenberg et al. Blood 2012;120:2454-2465

MUTATIONS TIPS

Gene	Correlation	Rx
SF3B1	Ring sideroblast	luspatercept
IDH1	Cbc ~	Ivosidenib, HMA+VEN
IDH2	Cbc ~	Enasidenib, HMA+VEN
FLT3	AML transformation	Gilteritinib
NPM1	AML-defining	CTX vs HMA+VEN
RUNX1	AML transformation	HMA+VEN
DDX41	Germline ?, cbc ~	HMA+VEN, LEN
STAT3	LGL	ISA
PIGA1	PNH	Complement inhibitor
UBA1	VEXAS	HMA,, JAKi
TP53	T-MN	? PO DAC

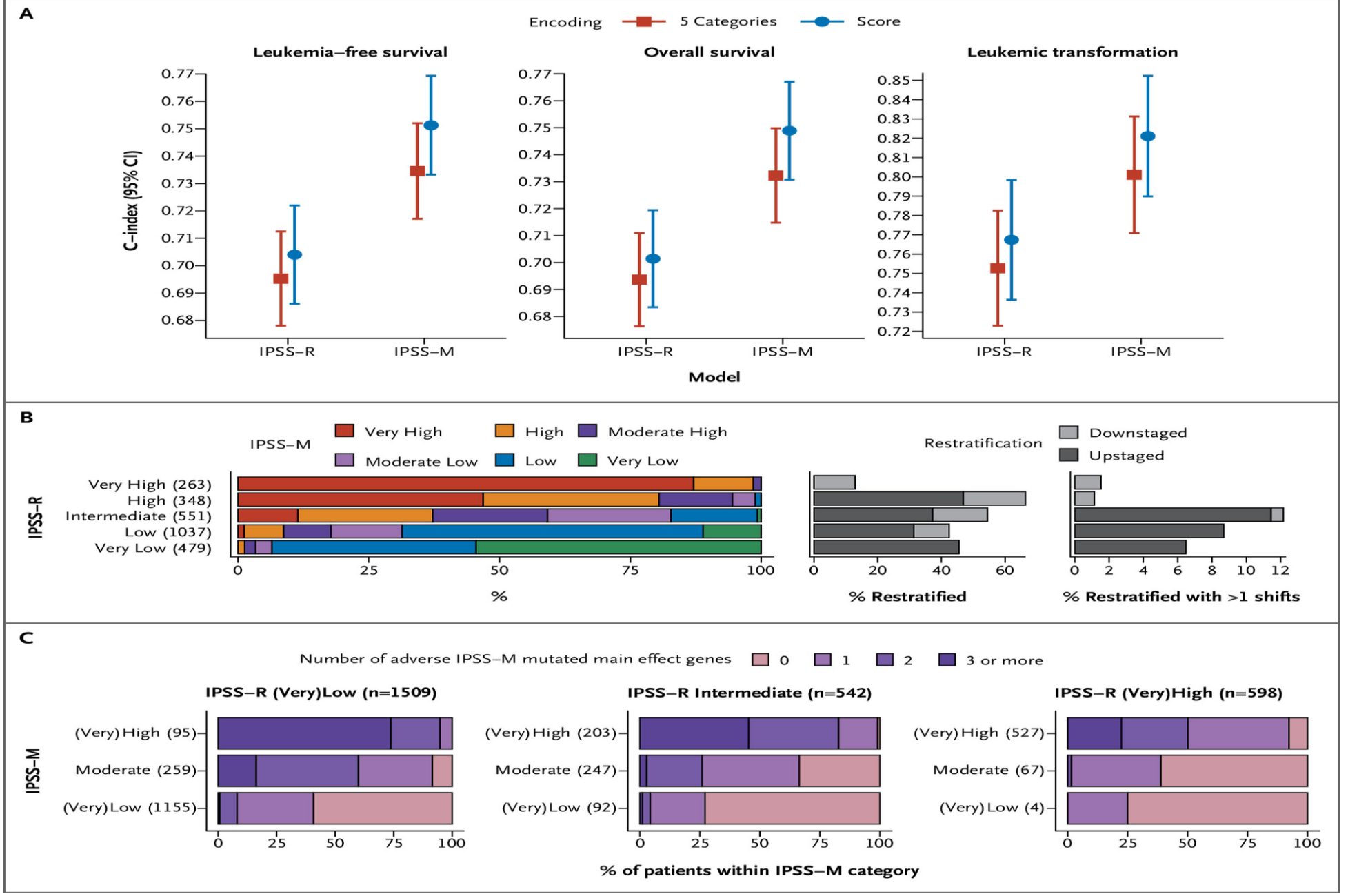
@AlkaliDr



MOL-IPSS

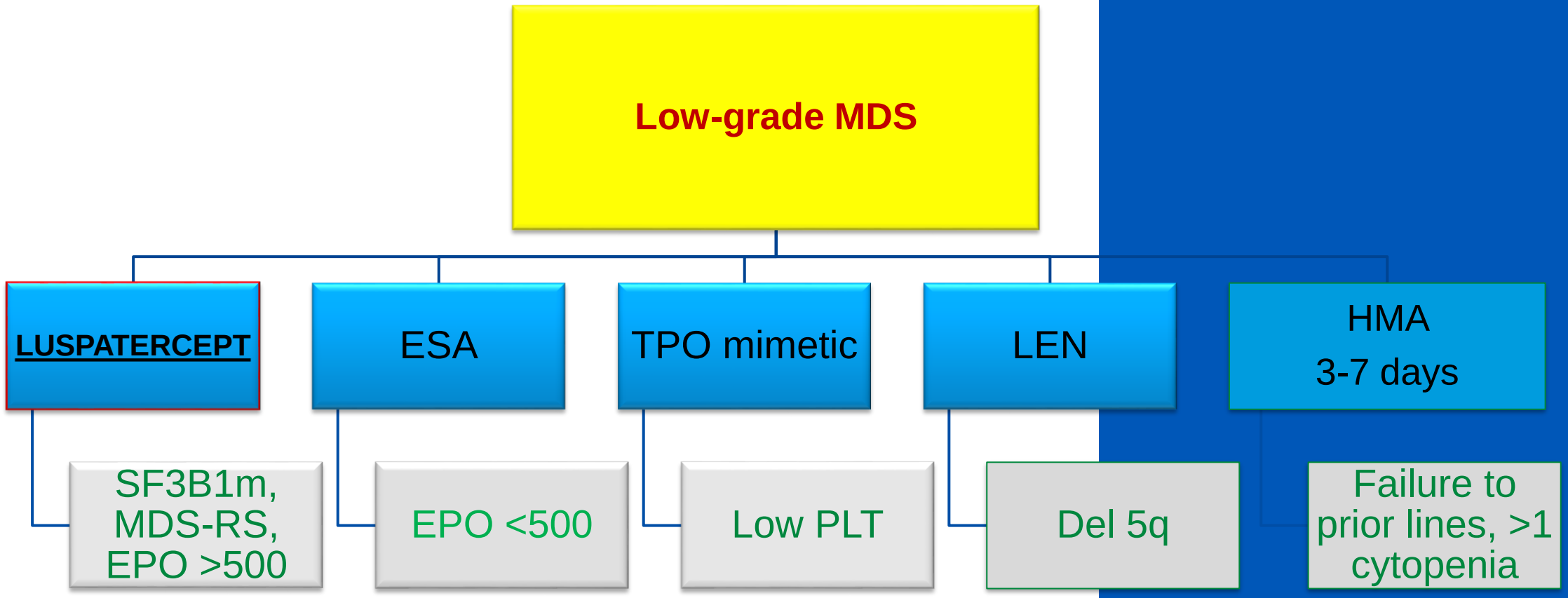
- Clinical-molecular prognostic model (IPSS-Molecular [IPSS-M]), pretreatment diagnostic or peridiagnostic samples from 2957 patients with MDS were profiled for mutations in 152 genes
- *TP53*$^{\text{multihit}}$, *FLT3* mutations, and *MLL*$^{\text{PTD}}$ top genetic predictors of adverse outcomes.
- *SF3B1* mutations were associated with favorable outcome
- Compared with the IPSS-R, the IPSS-M improved prognostic discrimination across all clinical end points and restratified 46% of patients

Online calculator: mds-risk-model.com



Molecular International Prognostic Scoring System for Myelodysplastic Syndromes, Volume: 1, Issue: 7, DOI: (10.1056/EVIDoa2200008)

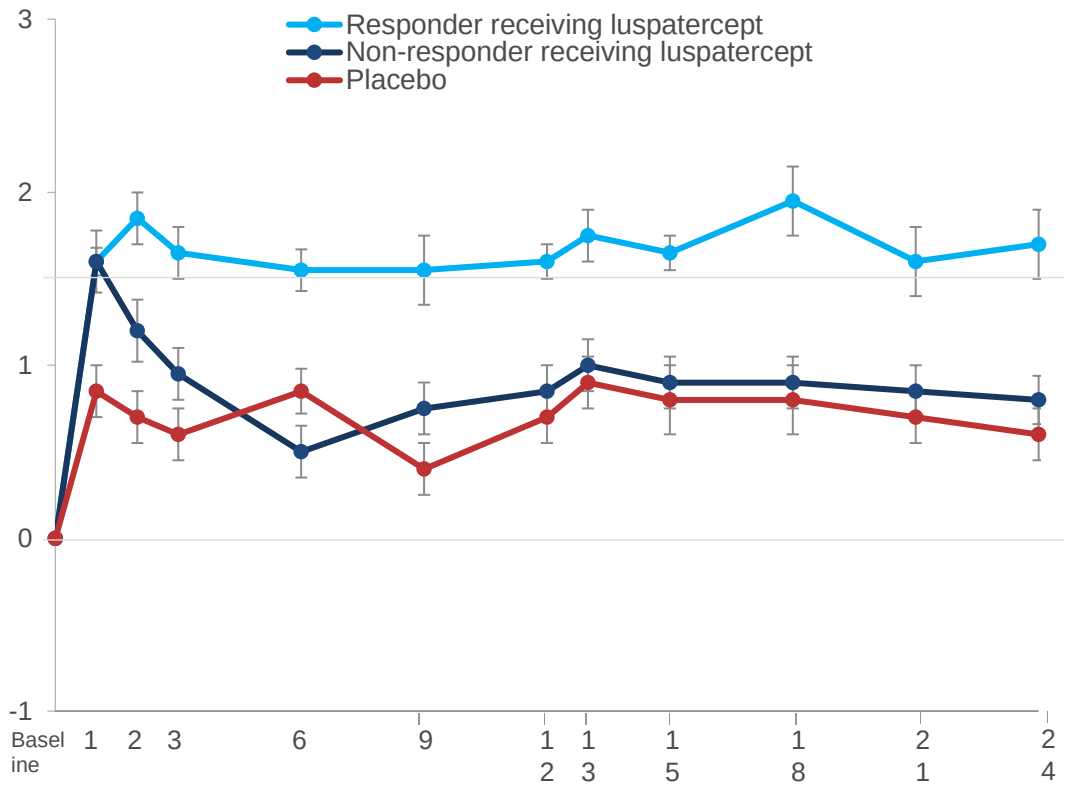
E Bernard et al. NEJM Evidence 2022;1:EVIDoa2200008.



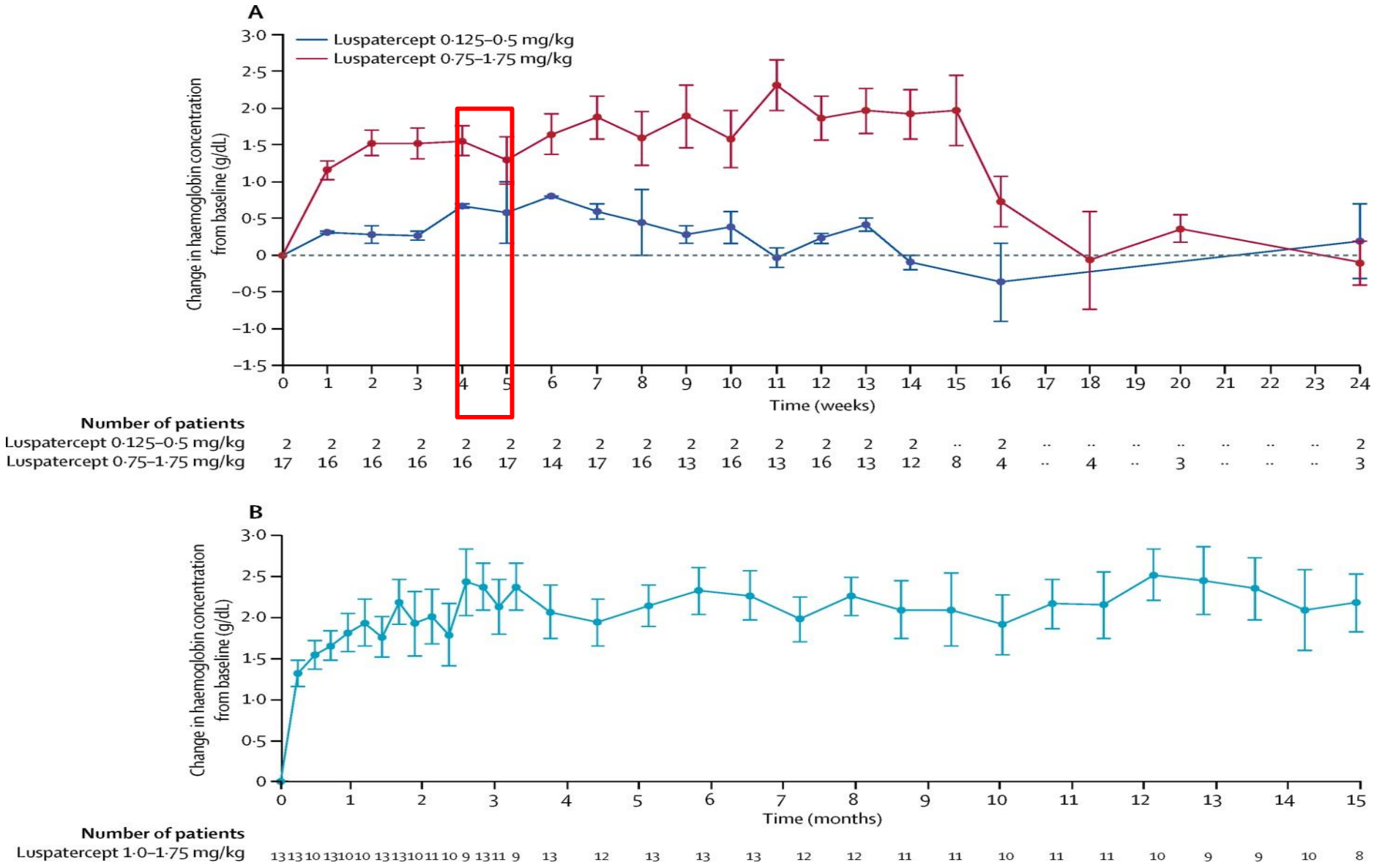
@AlkaliDr

LUSPATERCEPT

- TGFb ligand and Smad Fusion protein inhibitor
- In lower-risk, Ring sideroblast -positive MDS:
  - Lupsatercept better in reducing rbc transfusion
    - More transfusion independence
    - Better Hb increase than placebo
  - Erythroid responses were durable, with approximately 40% of patients achieving RBC-TI sustained at 12 months of treatment
  - Well tolerated in this patient population
- FDA approved for thalassemia, MDS



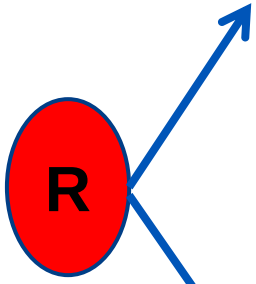
Courtesy Alan List



The Lancet Oncology 2017 18, 1338-1347DOI: (10.1016/S1470-2045(17)30615-0)

MDS MEDALIST

- MDS-RS*
- >18 years
- IPSS-R:
  - VL, L, Int-1
- **TD** (2/8wks)
- ESA
  - Failure* or
  - not likely to respond



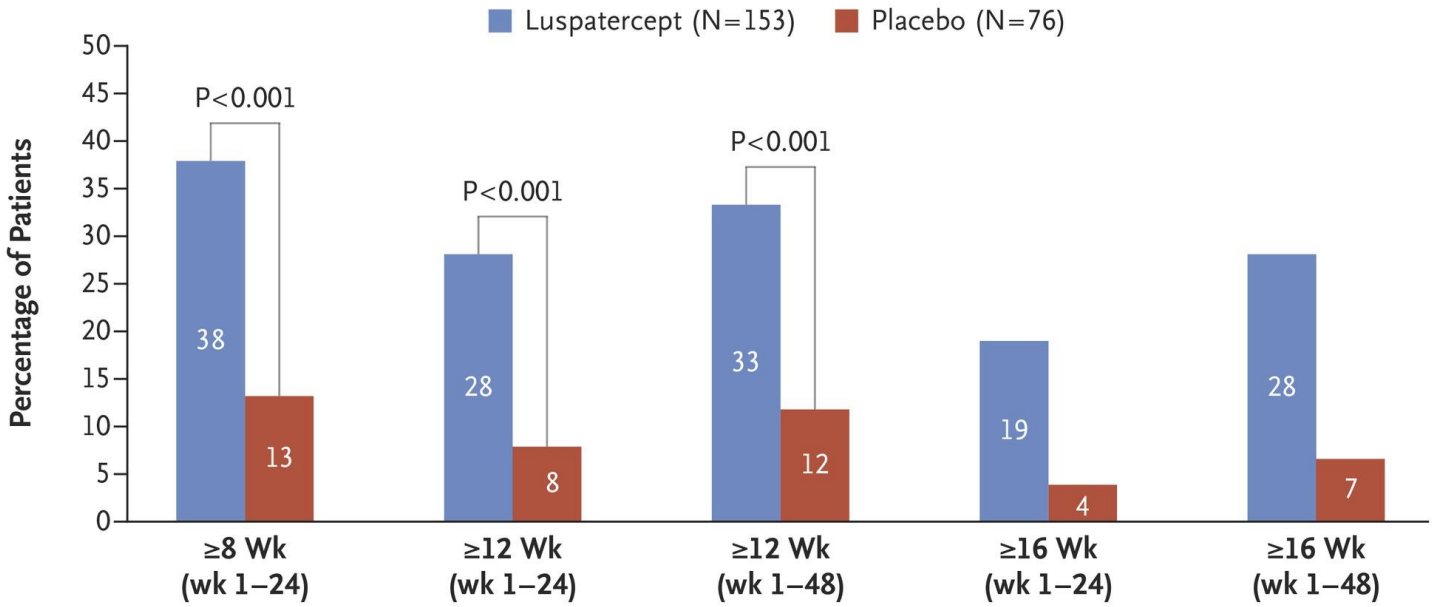
Luspatercept SC 1mg/Kg q 21 days
N=153

Placebo SC q 21 days
N= 76

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

The NEW ENGLAND JOURNAL of MEDICINE

MDS MEDALIST



No. of Patients with Response (% [95% CI])	≥8 Wk (wk 1–24)	≥12 Wk (wk 1–24)	≥12 Wk (wk 1–48)	≥16 Wk (wk 1–24)	≥16 Wk (wk 1–48)
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])

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

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The COMMANDS study

The COMMANDS study (NCT03682536) is a phase 3, global, open-label, randomized trial comparing the efficacy and safety of luspatercept versus epoetin alfa for the treatment of anemia due to IPSS-R LR-MDS in ESA-naive patients who require RBC transfusions

Key eligibility criteria

- ≥ 18 years of age
- IPSS-R very low-, low, or intermediate-risk MDS (with or without RS) by WHO 2016, with < 5% blasts in bone marrow[a]
- Required RBC transfusions (2-6 pRBC units/8 weeks for a minimum of 8 weeks immediately prior to randomization)
- Endogenous sEPO < 500 U/L
- ESA-naive

Patients stratified by:

- Baseline sEPO level
- Baseline RBC transfusion burden
- RS status

Randomized 1:1

Luspatercept (N = 178)
1.0 mg/kg s.c. Q3W
titration up to 1.75 mg/kg

Epoetin alfa (N = 178)[b]
450 IU/kg s.c. QW
titration up to 1050 IU/kg

Response assessment at day 169 and every 24 weeks thereafter

End treatment
Due to lack of clinical benefit[c] or disease progression per IWG criteria

Post-treatment safety follow-up

- Monitoring for other malignancies, HR-MDS or AML progression, subsequent therapies, survival
- For 5 years from first dose or 3 years from last dose, whichever is later

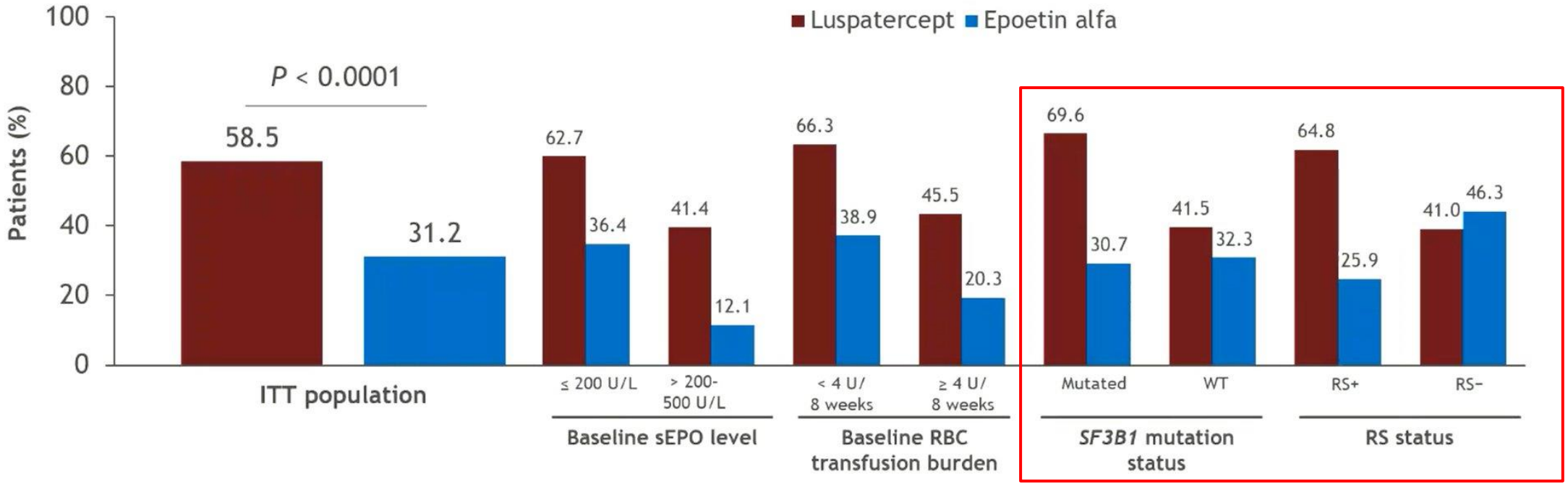
The primary endpoint : RBC transfusion independence for at least 12 weeks with a concurrent mean Hg increase of at least 1·5 g/dL (weeks 1-24)

[a]MDS with del(5q) were excluded. [b]2 patients randomized to the epoetin alfa arm withdrew consent prior to receiving their first dose; [c]Clinical benefit defined as transfusion reduction of ≥ 2 pRBC units/8 weeks versus baseline; AML, acute myeloid leukemia; ESA, erythropoiesis-stimulating agent; IPSS-R, Revised International Prognostic Scoring System; IWG, International Working Group; LR-MDS, lower-risk MDS; MDS, myelodysplastic syndromes; pRBC, packed RBC; QW, once weekly; Q3W, every 3 weeks; RBC, red blood cell; RS, ring sideroblasts; s.c., subcutaneously; sEPO, serum erythropoietin; WHO, World Health Organization.

Della Porta MG, et al. EHA 2023 [Abstract #S102]

Primary endpoint: luspatercept superior to epoetin alfa

- Of 301 pts included in the efficacy analysis, 86 (58.5%) patients receiving luspatercept and 48 (31.2%) epoetin alfa achieved the primary endpoint
  - Achievement of the primary endpoint favored luspatercept or was similar to epoetin alfa for all subgroups analyzed



This prespecified interim analysis included 301 patients who had either completed 24 weeks of treatment or discontinued prior to completing 24 weeks of treatment.

Della Porta MG, et al. EHA 2023 [Abstract #S102]

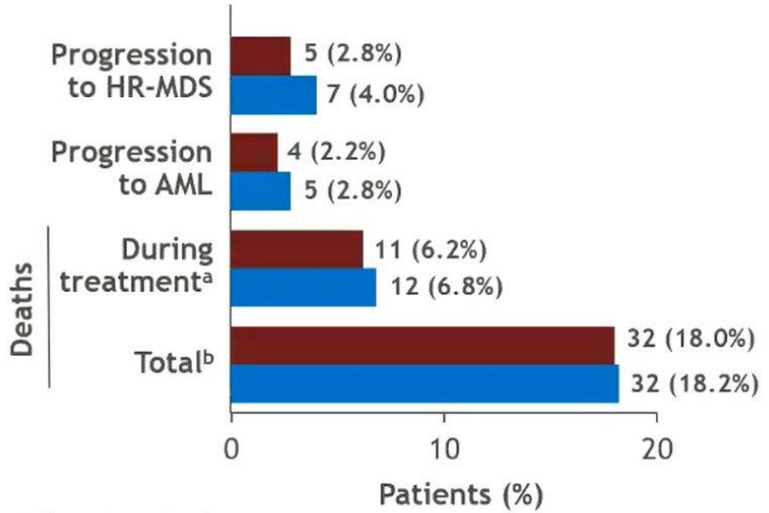
Safety profile of luspatercept manageable and comparable to previous studies

- Exposure to luspatercept was ~2 times longer compared with epoetin alfa, providing a longer reporting period for AEs

Patients, n (%)	Luspatercept (N = 178)		Epoetin alfa (N = 176)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Heme-related TEAEs				
Anemia	17 (9.6)	13 (7.3)	17 (9.7)	12 (6.8)
Thrombocytopenia	11 (6.2)	7 (3.9)	3 (1.7)	1 (0.6)
Neutropenia	9 (5.1)	7 (3.9)	13 (7.4)	10 (5.7)
Leukocytopenia	2 (1.1)	0	3 (1.7)	0
TEAEs of interest				
Fatigue	26 (14.6)	1 (0.6)	12 (6.8)	1 (0.6)
Diarrhea	26 (14.6)	2 (1.1)	20 (11.4)	1 (0.6)
Peripheral edema	23 (12.9)	0	12 (6.8)	0
Asthenia	22 (12.4)	0	25 (14.2)	1 (0.6)
Nausea	21 (11.8)	0	13 (7.4)	0
Dyspnea	21 (11.8)	7 (3.9)	13 (7.4)	2 (1.1)
TEE	8 (4.5)	5 (2.8)	5 (2.8)	1 (0.6)

TEAEs of any grade
164 (92.1%) luspatercept
150 (85.2%) epoetin alfa

Treatment duration, median (range), weeks
41.6 (0-165) luspatercept
27.0 (0-171) epoetin alfa



Safety data are not exposure-adjusted.
[a]11 deaths in each arm led to treatment discontinuation. One additional death occurred in the epoetin alfa arm after treatment discontinuation due to an AE; the death occurred during the 42-day safety follow up, which was considered a death during treatment but not counted as a death leading to treatment discontinuation. [b]Deaths during treatment period and post-treatment period. TEE, thromboembolic event.

Della Porta MG, et al. EHA 2023 [Abstract #S102]

LUSPATERCEPT

- SC Q21 days
- Adjust dose based on response
- Hold if Hg >11.5
- FDA approved
- Works more if
  - Frontline
  - RS+
  - *SF3B1*+
  - Thrombocytosis+
  - LT

IMELSTAT

- First-in-class telomerase inhibitor
  - Targets cells with high telomerase activity and human telomerase reverse transcriptase expression, both of which have been reported in MDS
- IMERGE- global phase 2 clinical trial on LR-MDS resistant to ESA
  - Treatment with imetelstat achieved >1 year transfusion independence in 29% of RBC TD, ESA-R/R LR-MDS patients who were non-del(5q) and lenalidomide/HMA-naïve.
  - 24-week TI predicted a likelihood to achieve TI >1 year
-

Platzbecker et al ASH Annual meeting 2022; abs 459

IMERGE PHASE 3: STUDY DESIGN

- International, double-blind, randomized phase III trial

Patients with low-risk or intermediate 1–risk MDS (IPSS-R); R/R to ESA or EPO >500 mU/mL (ESA ineligible); RBC transfusion dependent (≥4 U/8 wk over 16 wk prestudy); non-del(5q); no prior lenalidomide or HMAs

(N = 178)

2:1

Imetelstat
7.5 mg/kg IV Q4W
(n = 118)

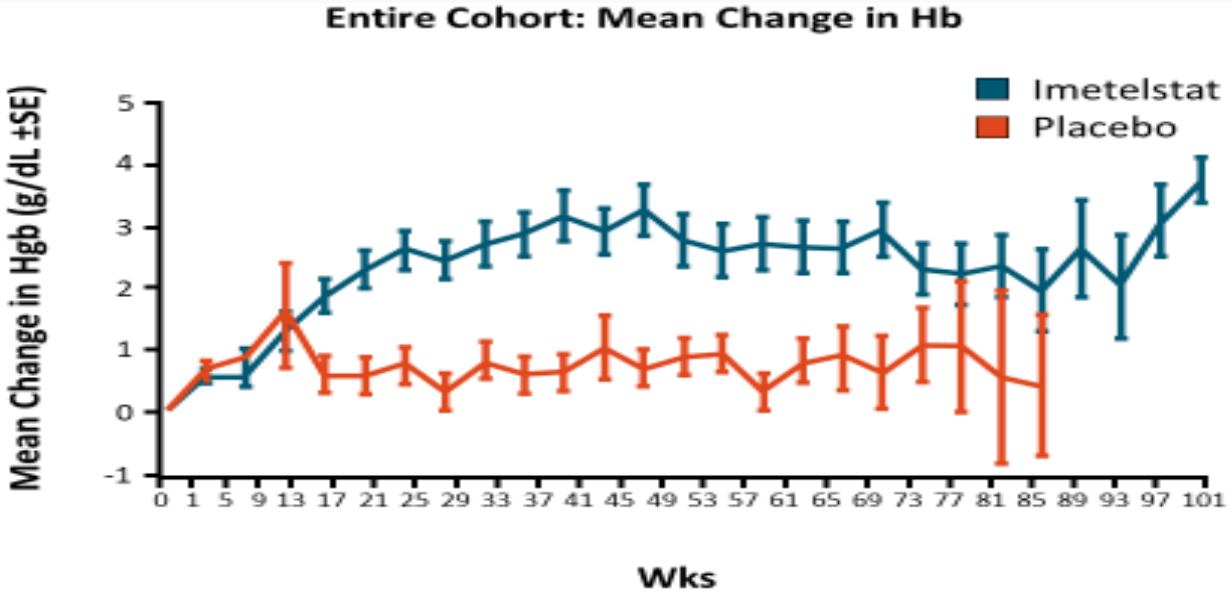
Placebo
(n = 60)

- **Primary endpoint:** 8-wk RBC-TI
- **Key secondary endpoints:** 24-wk RBC-TI, TI duration, HI-E, safety
- **Key exploratory endpoints**: changes in VAF, PRO (FACIT-Fatigue)

Zeidan. ASCO 2023. Abstr 7004.

IMERGE3

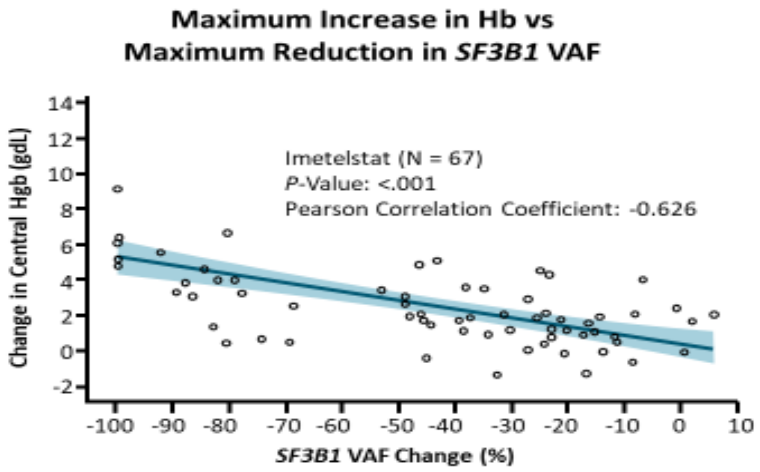
Measure, n (%)	Imetelstat N=118	Placebo N=60	P[a]
8-wk TI	47 (39.8)	9 (15.0)	<0.001
TI duration, median wks (95% CI)[b]	51.6 (26.9–83.9)	13.3 (8.0–24.9)	<0.001[d]
24-wk TI	33 (28.0)	2 (3.3)	<0.001
HI-E[c]	50 (42.4)	8 (13.3)	<0.001

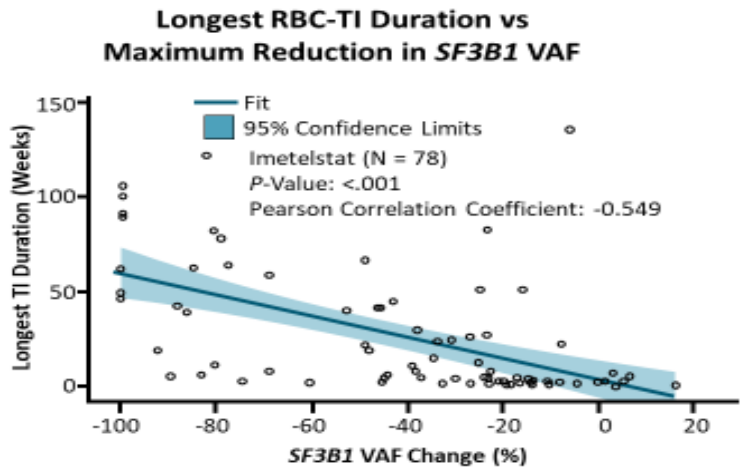


- No new safety signals were identified.
- The most common Grade 3/4 AEs were thrombocytopenia and neutropenia, with similar rates of Grade ≥3 bleeding and infections on imetelstat and placebo.
- In pts treated with imetelstat, cytopenias were manageable, of short duration, and >80% were reversible to Grade ≤2 within 4 wks.

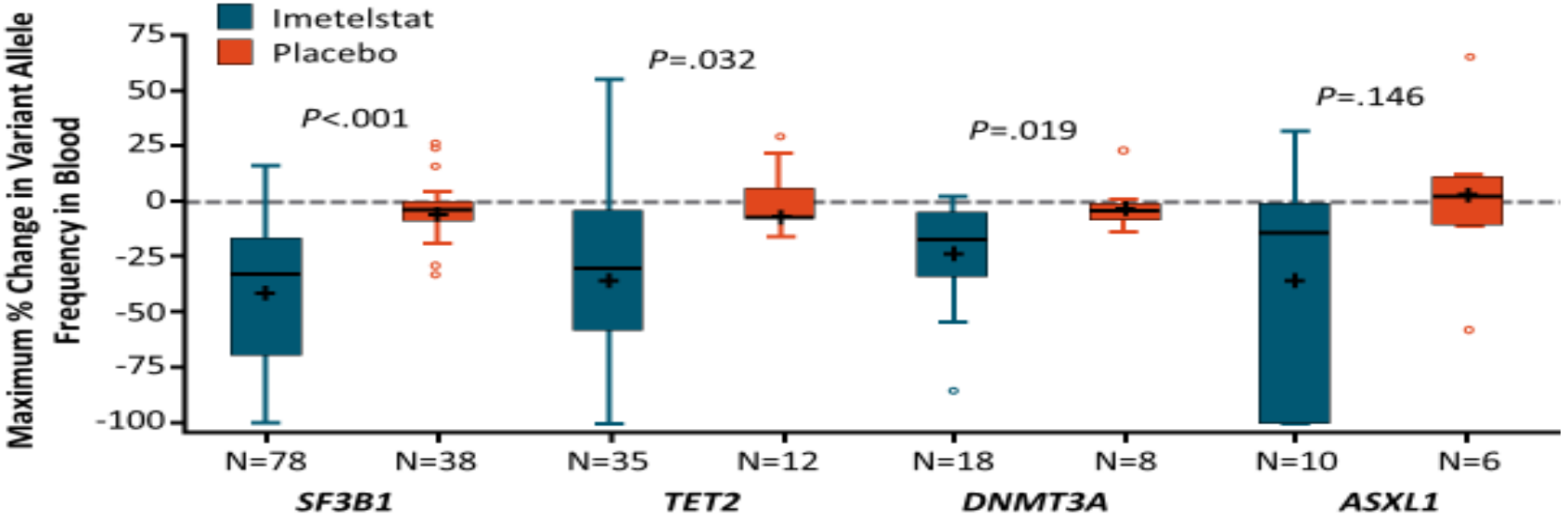
Zeidan. ASCO 2023. Abstr 7004.

IMPACT OF TREATMENT ON REDUCTION OF VAF



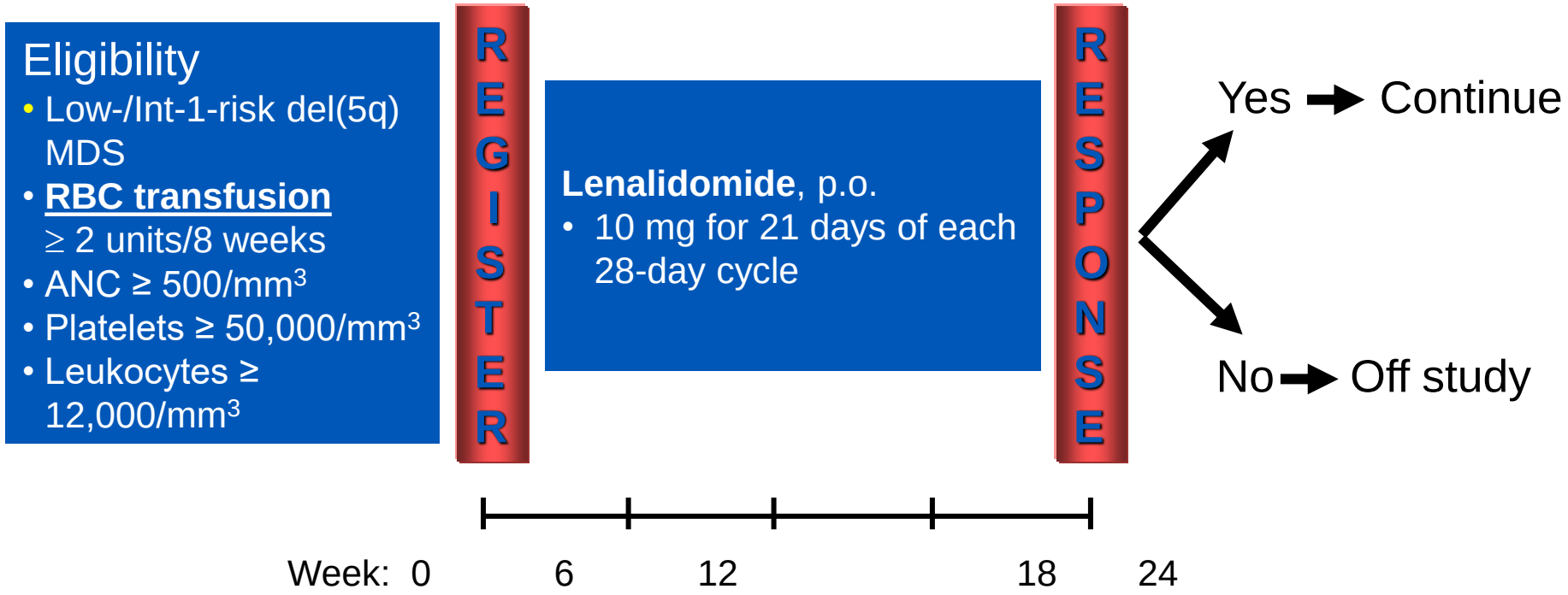


TET2, DNMT3A, or *ASXL21* VAF reductions correlated with longer RBC-TI duration



Zeidan. ASCO 2023. Abstr 7004.

MDS-003: STUDY DESIGN



Primary objective: erythroid response* (RBC-TI)
Secondary objectives: RBC-TI duration, cytogenetic response, tolerability

*As defined by the IWG 2000 criteria: Cheson BD, et al. Blood 2000;96:3671–4. ANC, absolute neutrophil count; p.o., orally; RBC, red blood cell; TI, transfusion independence.

List A, et al. N Engl J Med 2006;355:1456–65.

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MDS-003: ERYTHROID RESPONSE AT 24 WEEKS

Variable	N = 148 (ITT)
Erythroid response, n (%)	
RBC-TI (≥ 56 consecutive days without transfusion and Hb levels rose by 1 g/dL)	**99 (67)**
≥ 50% decrease in transfusions	**13 (9)**
Total (RBC-TI + ≥ 50% decrease in transfusions)	**112 (76)**
Median Hb increase, g/dL (range)	**5.4 (1.1–11.4)**
Median time to response, weeks (range)	**4.6 (1–49)**

- **RBC-TI achieved by 67% of lenalidomide-treated del(5q) patients**

List A, et al. N Engl J Med 2006;355:1456–65.

LEN IN MDS 5Q TP53+

Table 1. Patient characteristics of all patients analyzed for *TP53* mutations

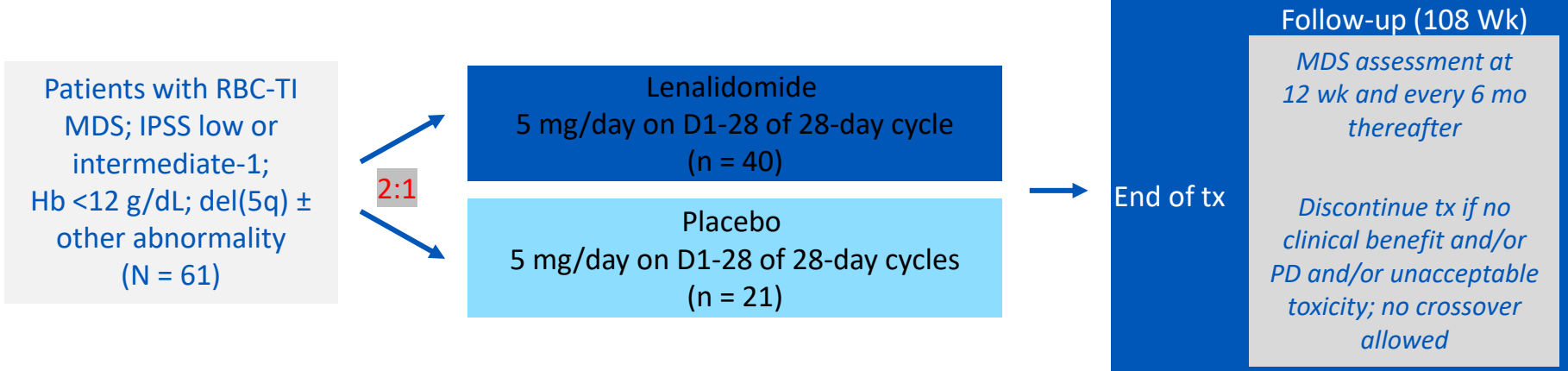
	All	*TP53*^{WT}	*TP53*^{Mut}	
Number of patients	67	59	8	
Gender, n *(%)*				
Male	13 (18)	11 (19)	2 (25)	NS
Female	54 (82)	48 (81)	6 (75)	
Median age (range)	70 (40–87)	70 (40–84)	74 (55–87)	NS
WHO subtype, n *(%)*				
MDS-U	2 (3)	2 (3)	0	NS
RCUD (RA, RT)	13 (19)	12 (20)	1	
RCMD	43 (64)	37 (63)	6 (75)	
RCMD-RS	9 (13)	8 (14)	1	
FAB subtypes, n *(%)*				
RA	55 (77)	47 (80)	7 (88)	NS
RARS	9 (13)	8 (13)	1 (12)	
Missing	4 (6)	4 (7)	0	
IPSS risk groups, n *(%)*				
Low	42 (63)	35 (59)	7 (87)	NS
Intermediate-1	21 (31)	20 (34)	1 (13)	
Missing	4 (6)	4 (7)	0	
IPSS-R risk groups, n *(%)*				
Very low	8 (10)	6 (10)	2 (25)	NS
Low	49 (73)	44 (75)	5 (62)	
Intermediate	6 (9)	5 (8)	1 (13)	
Missing	4 (6)	4 (7)	0	
Mean blood counts (s.d.)				
Hb (g /dl)	8.9 (1.3)	8.9 (1.3)	9.2 (1.5)	NS
ANC (1×10^9/l)	3.12 (3.1)	3.11 (3.1)	3.65 (2.9)	NS
Platelets (1×10^9/l)	333 (265)	311 (192)	501 (575)	NS
Ferritin (µg/l)	1381 (1306)	1405 (1394)	1227 (683)	NS
Mean medullary blast count, % (Std)	2.0 (1.4)	2.3 (1.3)	1.6 (1.6)	NS
Median number of PRBC transfusions 8 weeks before enrollment, *n* (range)	2 (0–10)	2 (0–8)	5 (0–10)	NS
Median time from first diagnosis to treatment, months (range)	30 (1–181)	22 (1–181)	14 (2–39)	NS
Median number of Len cycles, *n* (range)	15 (1–49)	16 (1–49)	6 (1–28)	NS

	TP53 wt	TP53 mu	P value
N	59	8	
Median cycles	16	6	0.38
TI	75%	50%	0.2
TTR	4 months	4 months	
event	25%	63%	0.045
progression	15%	25%	0.6
Median time to 25% AML	NR	18 m	
OS, months	NR	43.2	0.002

Oblander J et al. Leukemia 2016: 1956-9.

SINTRA-REV: STUDY DESIGN

- Multicenter, randomized, double-blind, placebo-controlled phase III trial

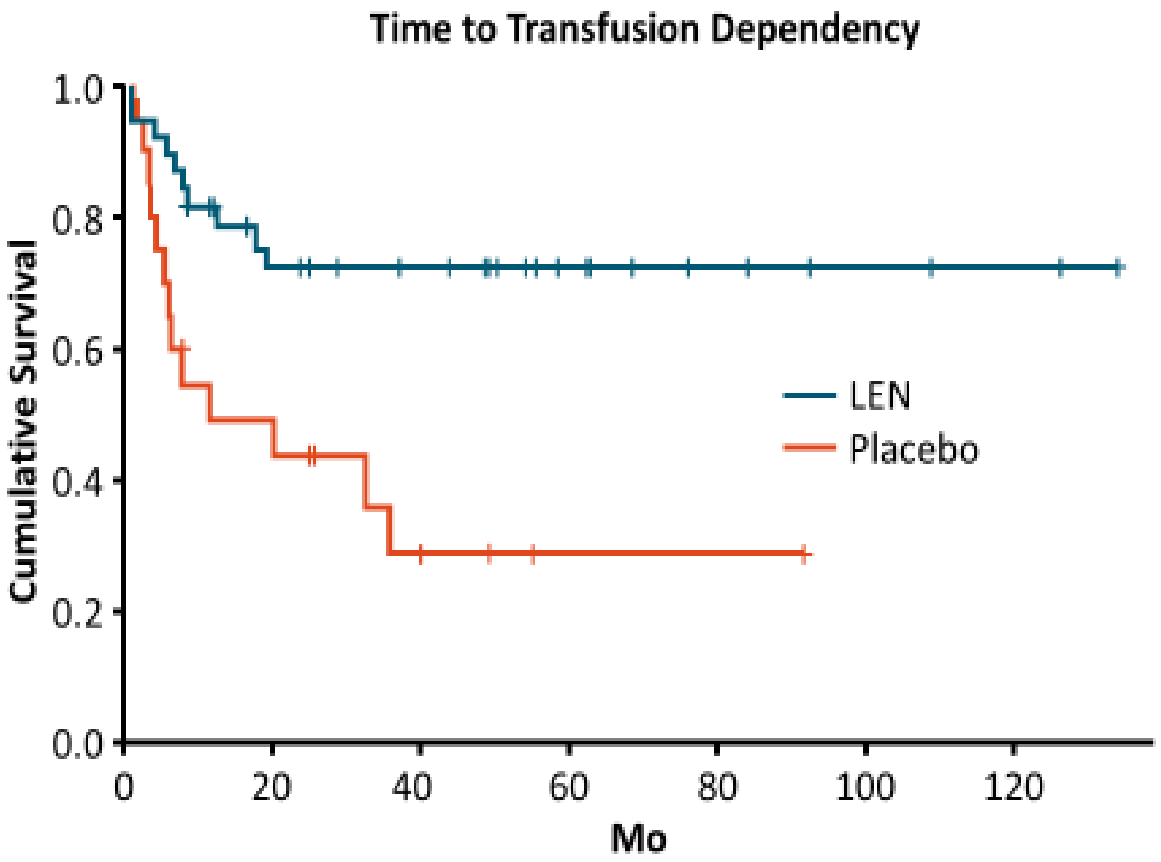


Primary endpoint: time to transfusion dependence

Secondary endpoints: erythroid response, cytogenetic response, duration of RBC-TI, change in Hb, bone marrow response, neutrophil/platelet changes, safety, OS, EFS, AML transformation, clonal evolution

Cadenas. ASH 2022. Abstr 460.

SINTRA-REV: TIME TO TRANSFUSION DEPENDENCY IN ITT POPULATION (PRIMARY ENDPOINT)

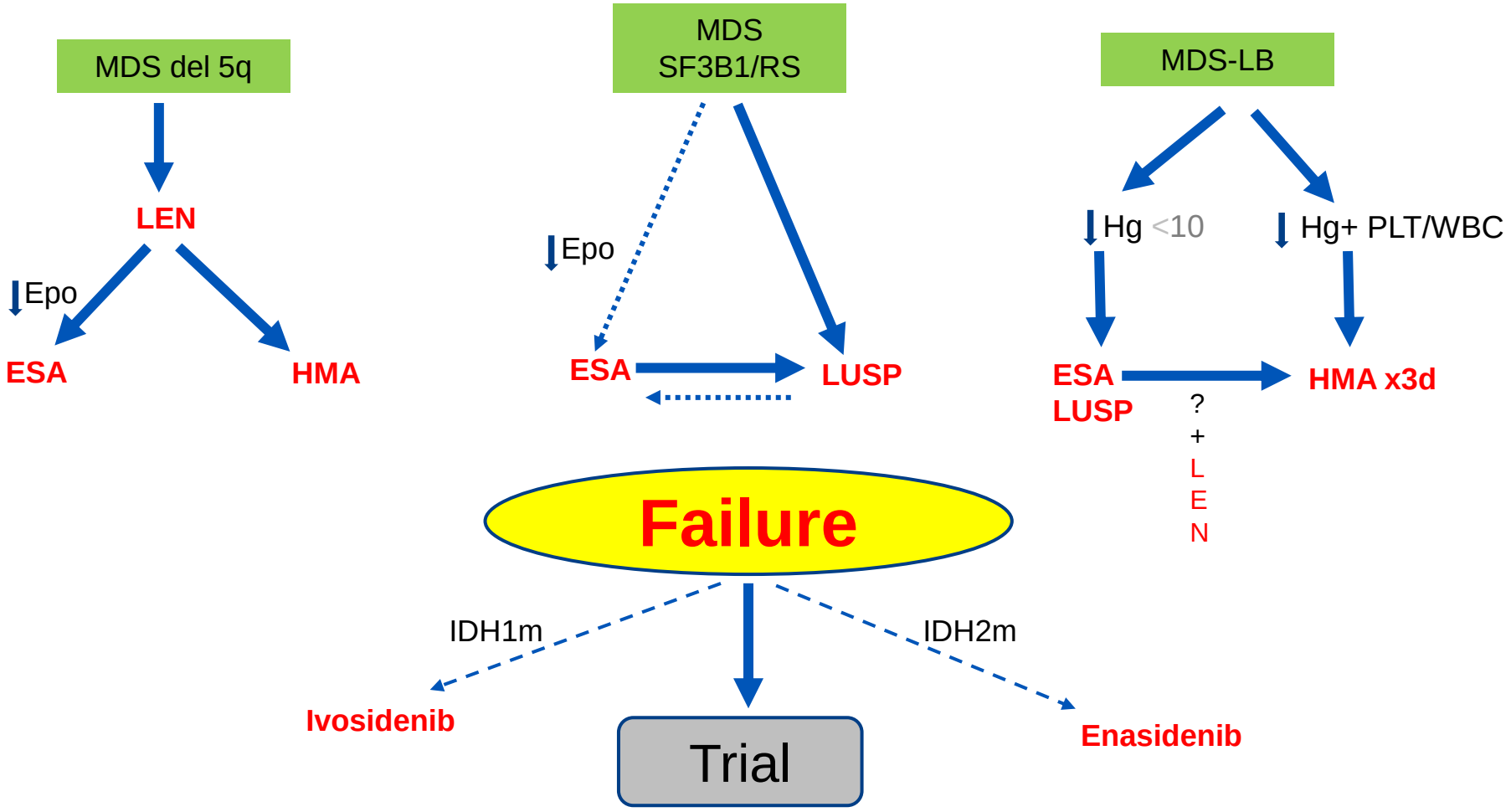


	Len (n = 40)	Placebo (n = 21)	*P*
Events, n (%)	10 (25)	13 (65)	.005
HR (95% CI)	0.302 (0.132-0.692)		
Median time to TD, mo	NR	11.6	.003

- Median follow-up: 5.05 yr (range: 0.3-11)

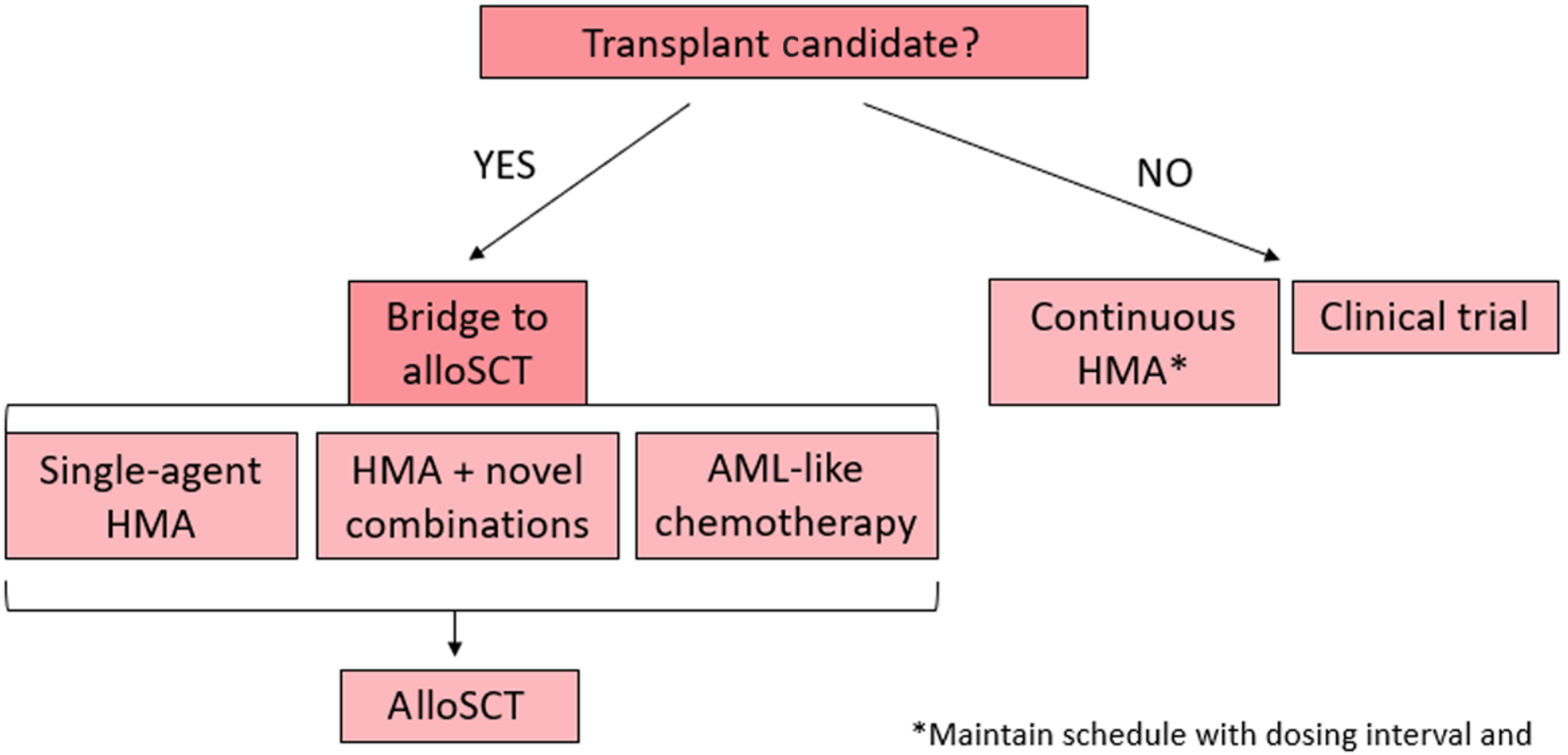
Cadenas. ASH 2022. Abstr 460. Reproduced with permission.

Low grade MDS



@AlkaliDr

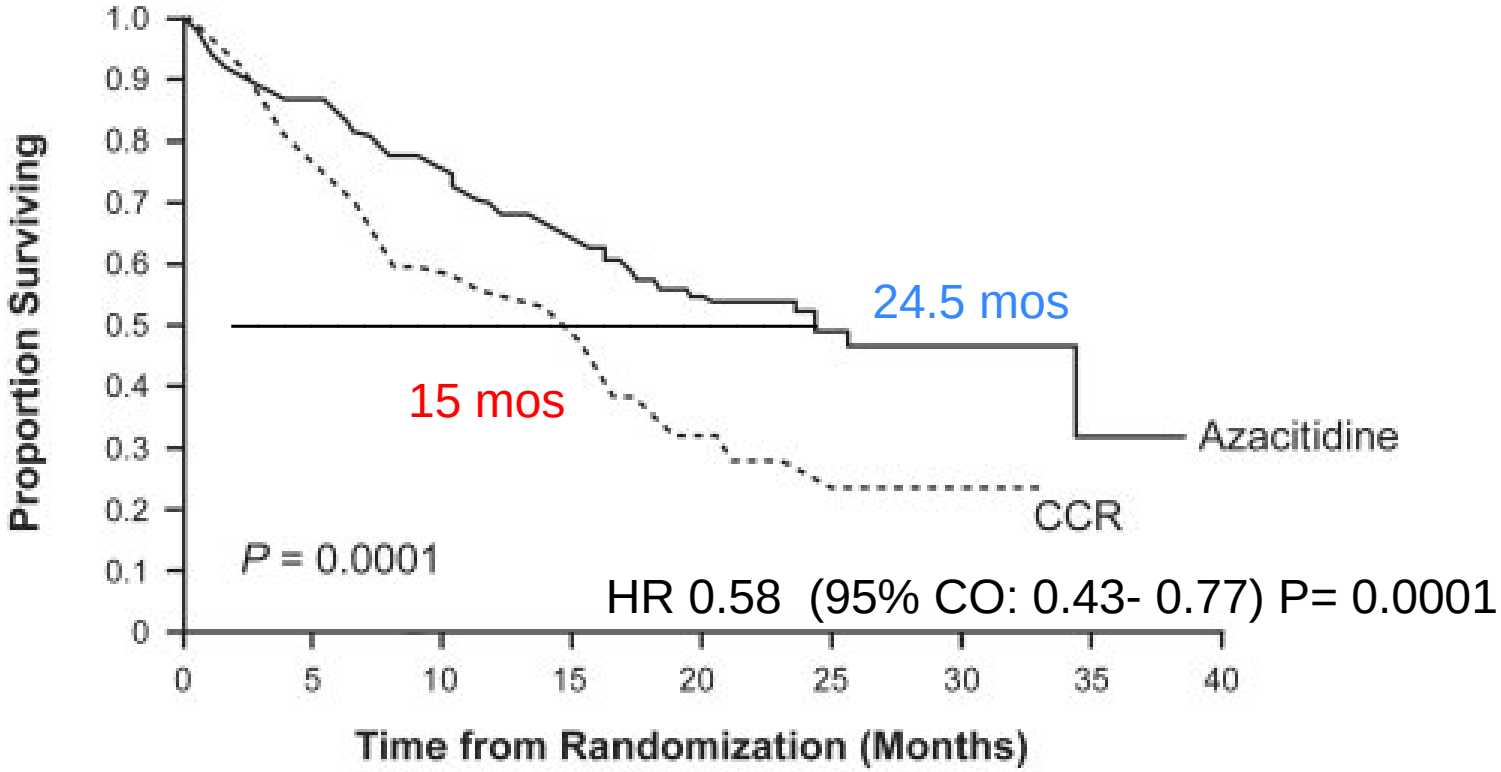
Current Treatment Algorithm in HR-MDS



*Maintain schedule with dosing interval and intensity for first 4-6 cycles for maximum benefit

Kristin L. Koenig,Uma Borate, New investigational combinations for higher-risk MDS, Hematology Am Soc Hematol Educ Program, 2022, Figure 2.

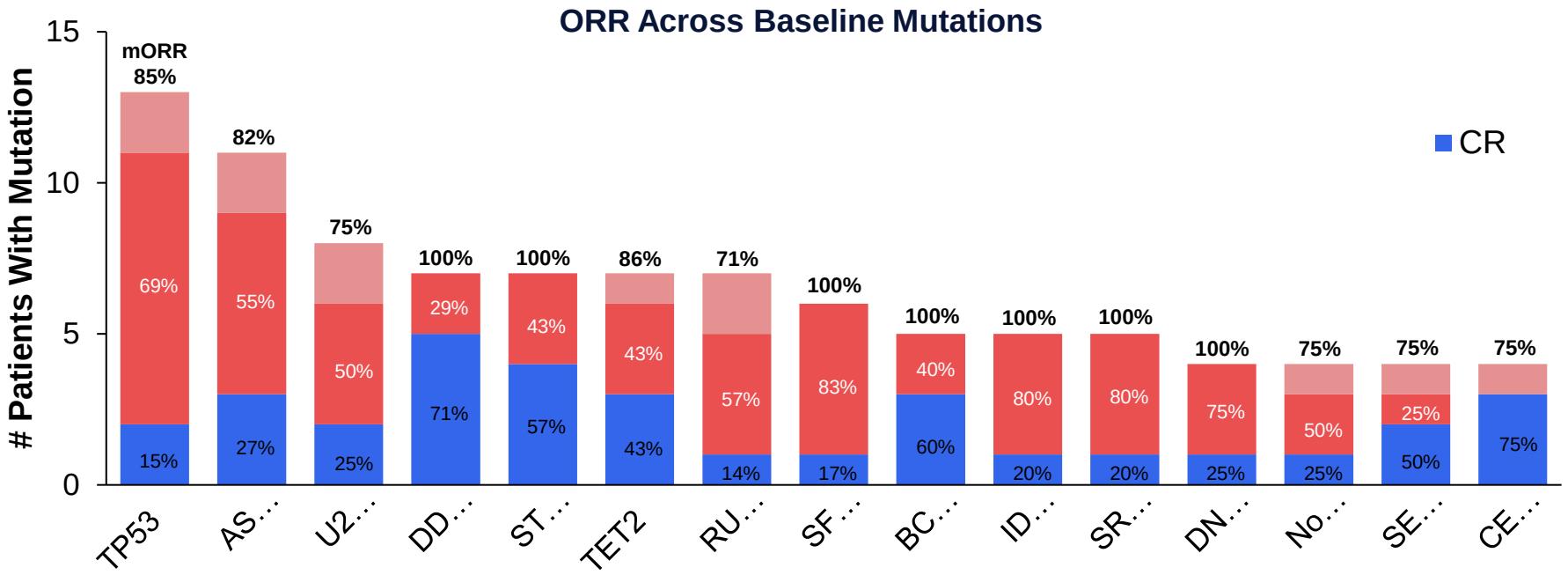
AZA vs CCR in high risk MDS



CCR: 7+3, LDAC, BSC

Fenaux et al Lancet Oncology 2009

Azacitidine and Venetoclax in HR-MDS



Garcia J et al. ASH Annual Meeting 2021, Atlanta GA. Abstract 241

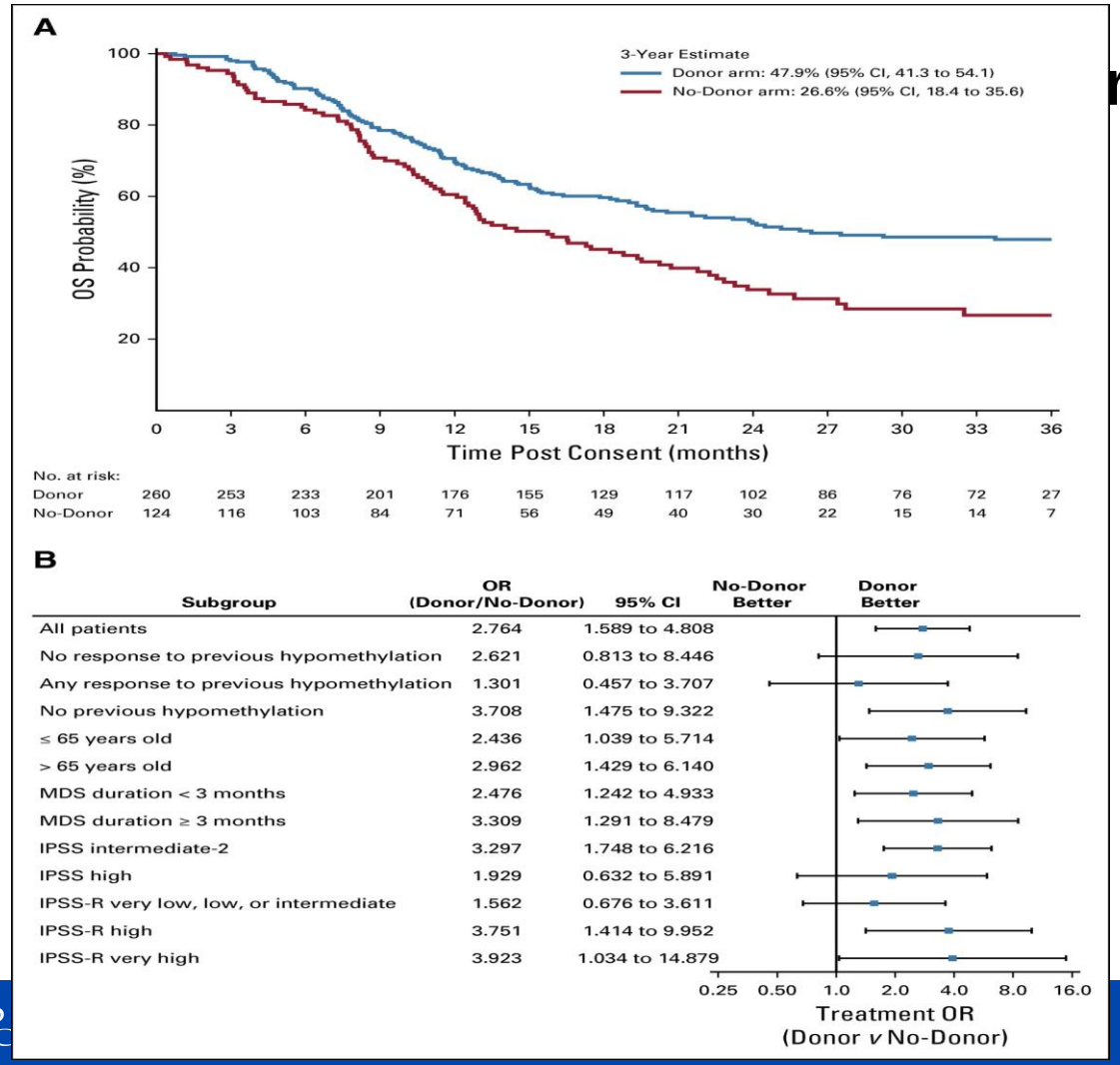
To transplant or not……

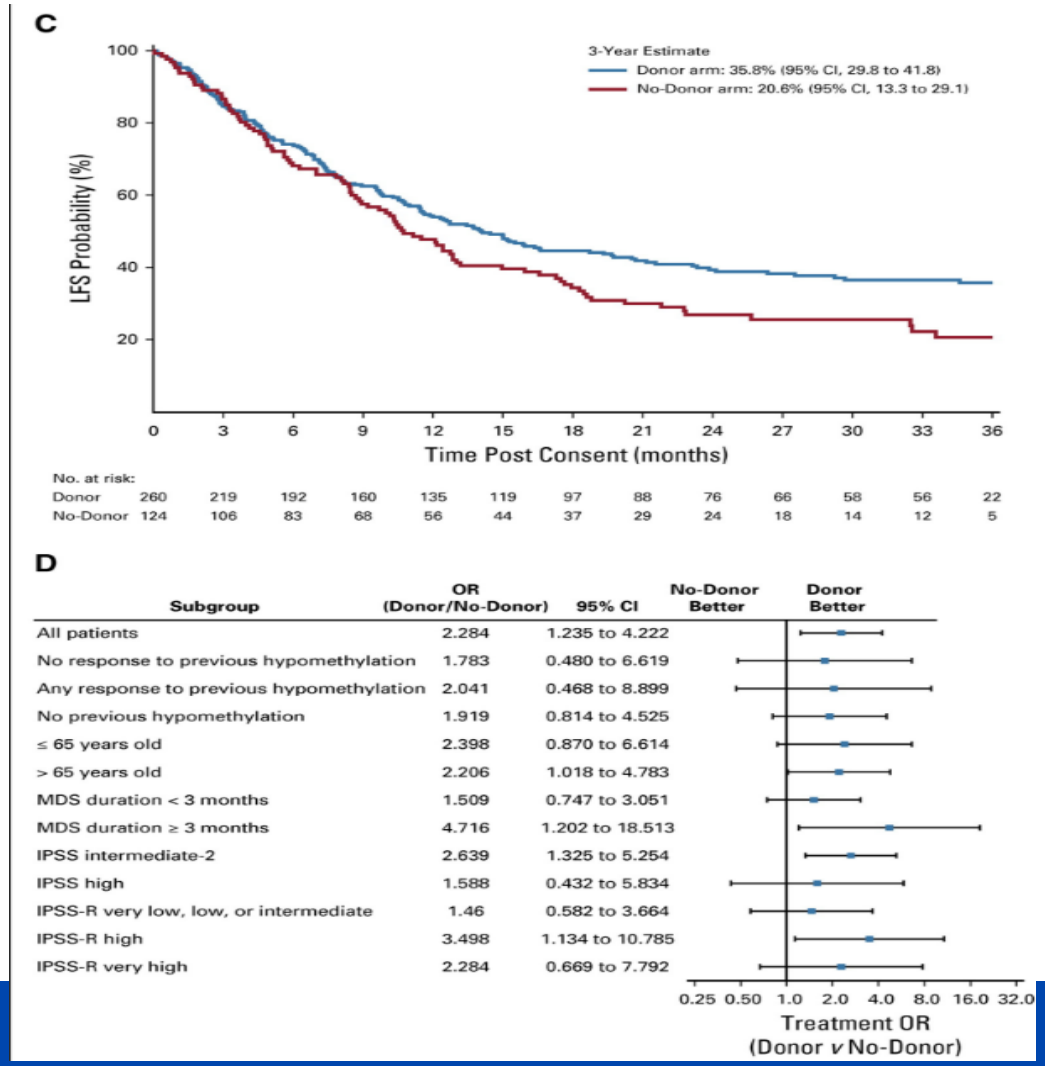
Biologic Assignment Trial of Reduced-Intensity Hematopoietic Cell Transplantation Based on Donor Availability in Patients 50-75 Years of Age With Advanced Myelodysplastic Syndrome

Ryotaro Nakamura, MD[1]; Wael Saber, MD, MS[2]; Michael J. Martens, PhD[2]; Alyssa Ramirez, BS[3]; Bart Scott, MD[4]; Betul Oran, MD[5]; Eric Leifer, PhD[6]; Roni Tamari, MD[7]; Asmita Mishra, MD[8]; Richard T. Maziarz, MD[9]; Joseph McGuirk, DO[10]; Peter Westervelt, MD, PhD[11]; Sumithira Vasu, MBBS[12]; Mrinal Patnaik, MBBS[13]; Rammurti Kamble, MD[14]; Stephen J. Forman, MD[1]; Mikkael A. Sekeres, MD, MS[15]; Frederick Appelbaum, MD[4]; Adam Mendizabal, PhD[3]; Brent Logan, PhD[2]; Mary Horowitz, MD, MS[2]; and Corey Cutler, MD, MPH[16]; on behalf of the Blood and Marrow Transplant Clinical Trials Network

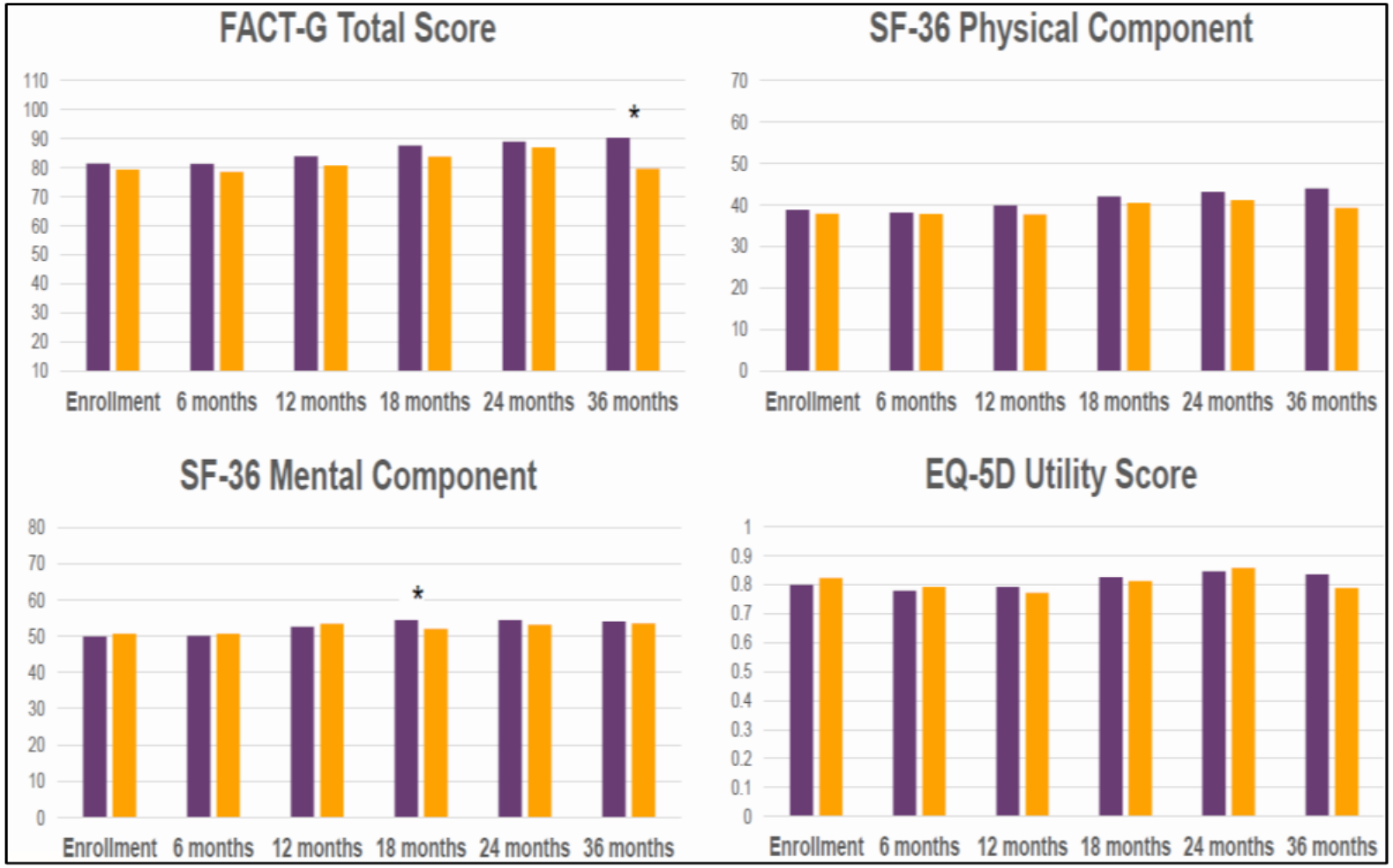
J Clin Oncol 00.

Clinical outcomes
(Donor arm=260 and No donor arm=124 patients)





Quality of life similar in both groups

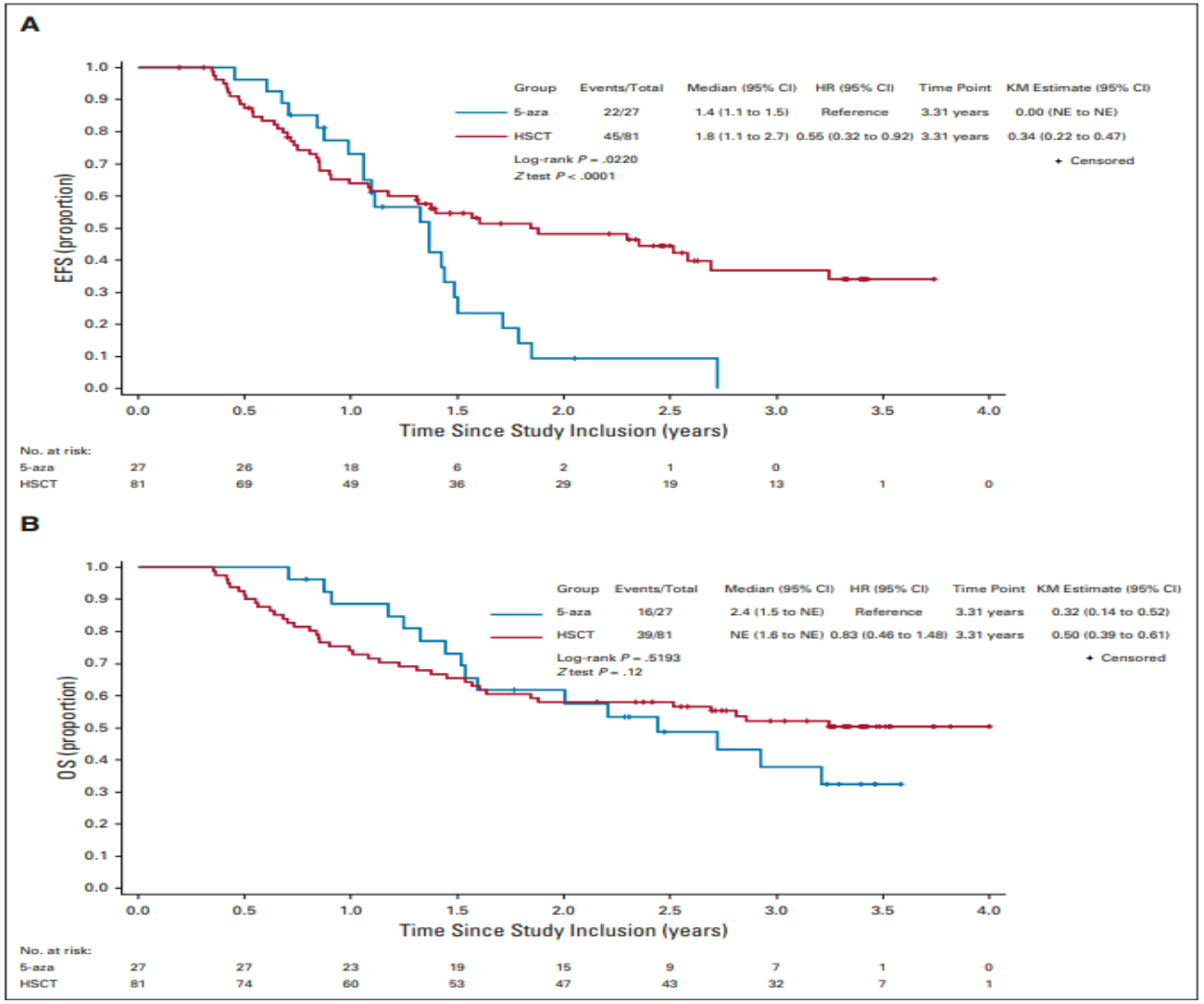


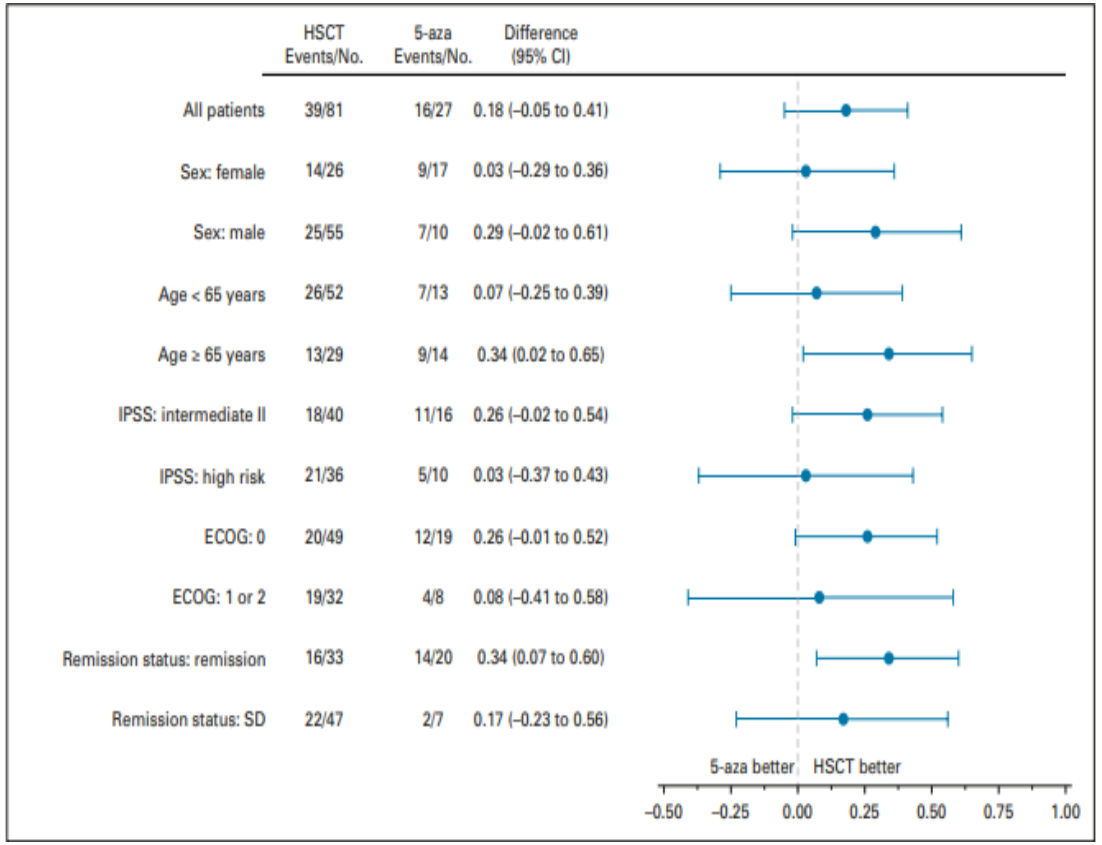
Comparison Between 5-Azacytidine Treatment and Allogeneic Stem-Cell Transplantation in Elderly Patients With Advanced MDS According to Donor Availability (VidazaAllo Study)

Nicolaus Kröger, MD[1]; Katja Sockel, MD[2]; Christine Wolschke, MD[1]; Wolfgang Bethge, MD[3]; Richard F. Schlenk, MD[4,5]; Dominik Wolf, MD[6,7,8]; Michael Stadler, MD[9]; Guido Kobbe, MD[10]; Gerald Wulf, MD[11]; Gesine Bug, MD[12]; Kerstin Schäfer-Eckart, MD[13]; Christof Scheid, MD[14]; Florian Nolte, MD[15]; Jan Krönke, MD[16]; Matthias Stelljes, MD[17]; Dietrich Beelen, MD[18]; Marion Heinzelmann[1]; Detlef Haase, MD[11]; Hannes Buchner, PhD[19]; Gabriele Bleckert, PhD[19]; Aristoteles Giagounidis, MD[20]; Uwe Platzbecker, MD[2,21]; on behalf of the German MDS Study Group and the German Cooperative Transplant Study Group

J Clin Oncol 39:3318-3327.

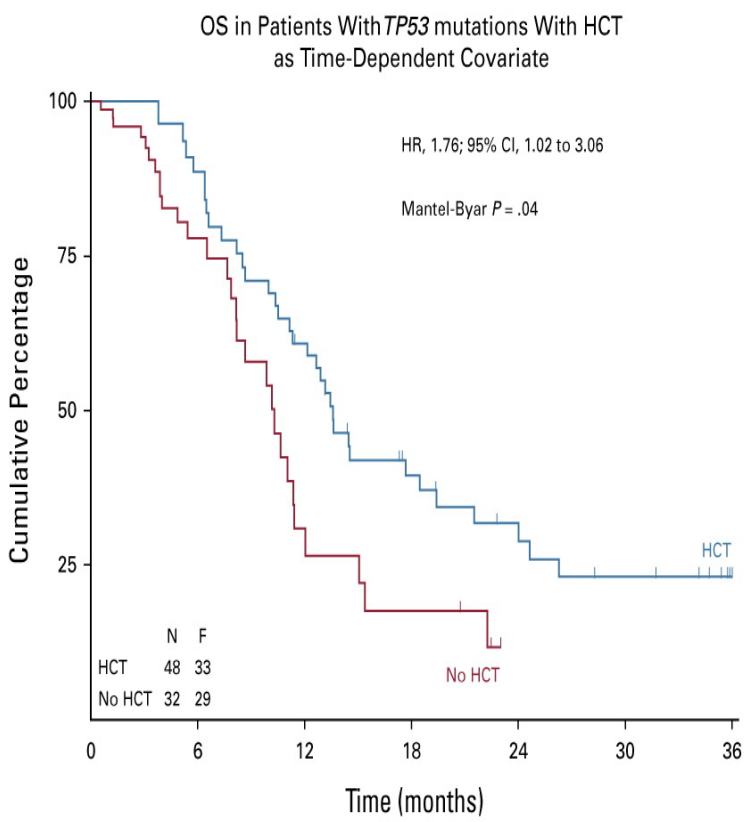
Clinical outcomes
(HCT arm=81 and continuous 5-Aza arm=27)

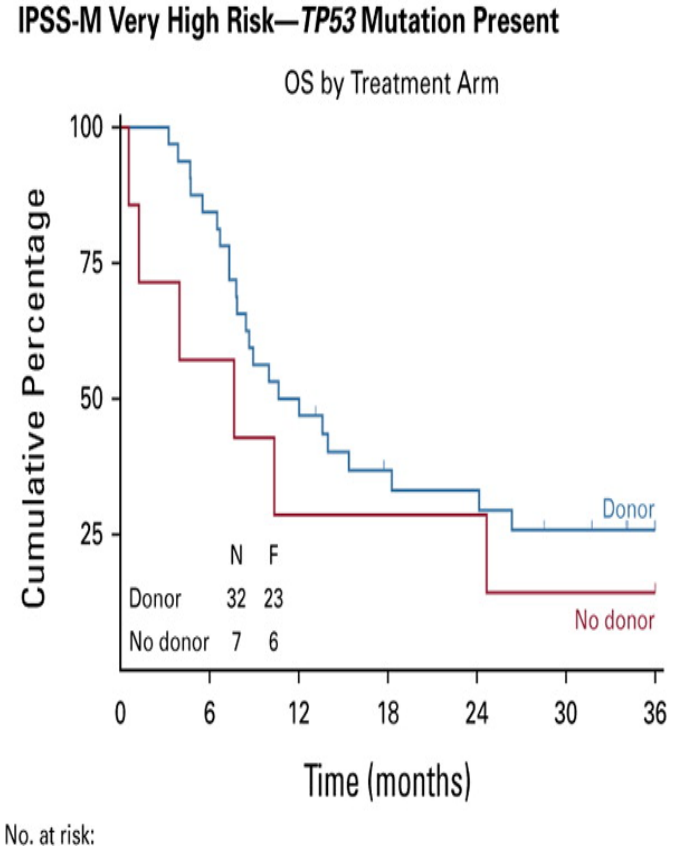


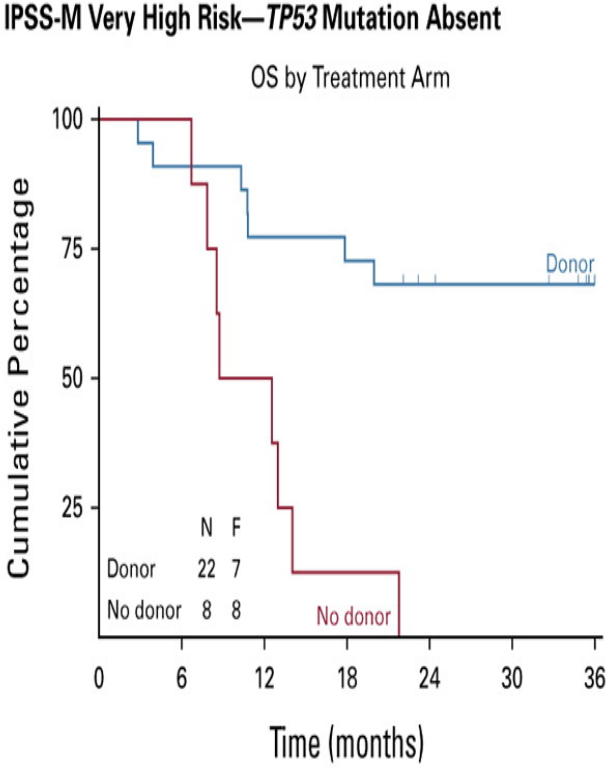


Kroger et al. JCO 2021

Does transplant work even with high risk mutations such as TP53?







No. at risk:

Versluis et al. JCO 2023

Eprenetapopt (APR-246) + HMA following Allo-hct

- 33 patients (14 AML, 19 MDS)
- Median age was 65 (range, 40-74) years.
- median number of eprenetapopt cycles was 7 (range, 1-12).
- With a median follow-up of 14.5 months, the
  - median RFS was 12.5 months
  - 1-year RFS probability was 59.9% (95% CI, 41 to 74).
  - median follow-up of 17.0 months,
  - median overall survival (OS) was 20.6 months (95% CI, 14.2 to not estimable)
  - 1-year OS probability was 78.8% (95% CI, 60.6 to 89.3).

MAYO CLINIC

A Mishra et al JCO December 2022

Conclusions

- Many recent advances in Prognostication and Treatment of MDS
  - M-IPSS
  - CHIP, CCUS
- New indications/ therapies for LR-MDS
  - Luspatercept, Imelstat
- Allo-hct with proven survival benefit in HR-MDS in older adults
  - Effective strategy even in TP53 myeloid neoplasm

Allo-HCT for high risk MDS (BMT CTN 1102)

- Allo-HCT with reduced intensity conditioning (RIC) in patients 50 to 75 years old with HR-MDS comparing patients with and without a (HLA)-matched donor.
- 384 total patients
  - 67.7% (260 patients) had a matched donor and
  - 32.3% (124 patients) did not have a matched donor and instead received HMA and/or supportive care
  - HLA-matched donor experienced
    - increased OS (absolute improvement in 3-year OS was 21.3% [95% CI, 10.2-31.8; *P* = .0001])
    - improved leukemia-free survival (absolute improvement in 3-year LFS was 15.2% [95% CI, 13.3-29.1; *P* = .003])
- Interestingly, OS was significantly shorter in patients without response to HMA prior to alloSCT (HR, 1.64; *P* = .0097)

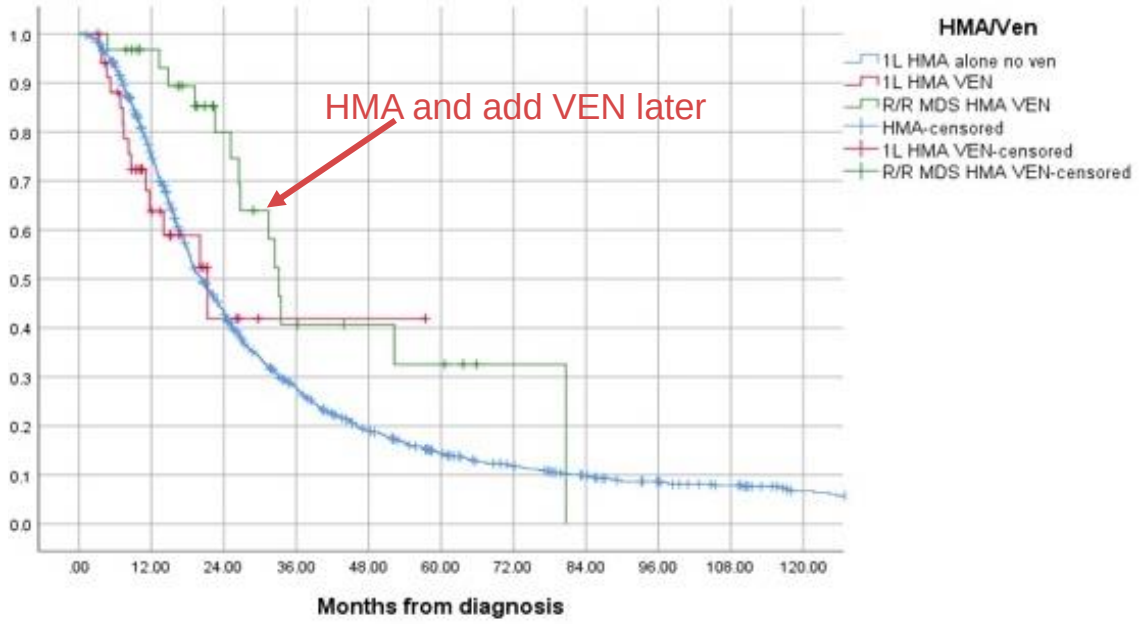
Nakamura R, , Saber W , Martens MJ , et al. JCO 2021 ;39 (30):3328 -3339

Assessing the Role of Venetoclax in Combination with Hypomethylating Agents in Higher Risk Myelodysplastic Syndromes

- Higher risk MDS at Moffitt Cancer Center (INT, H, VH)
- Compare: first line single agent HMA, first line HMA/Ven combination, HMA, but add Ven after HMA failure (R/R MDS HMA/Ven)

Table-1 Baseline characteristics comparing HMA alone versus HMA Ven first line therapy in higher risk MDS

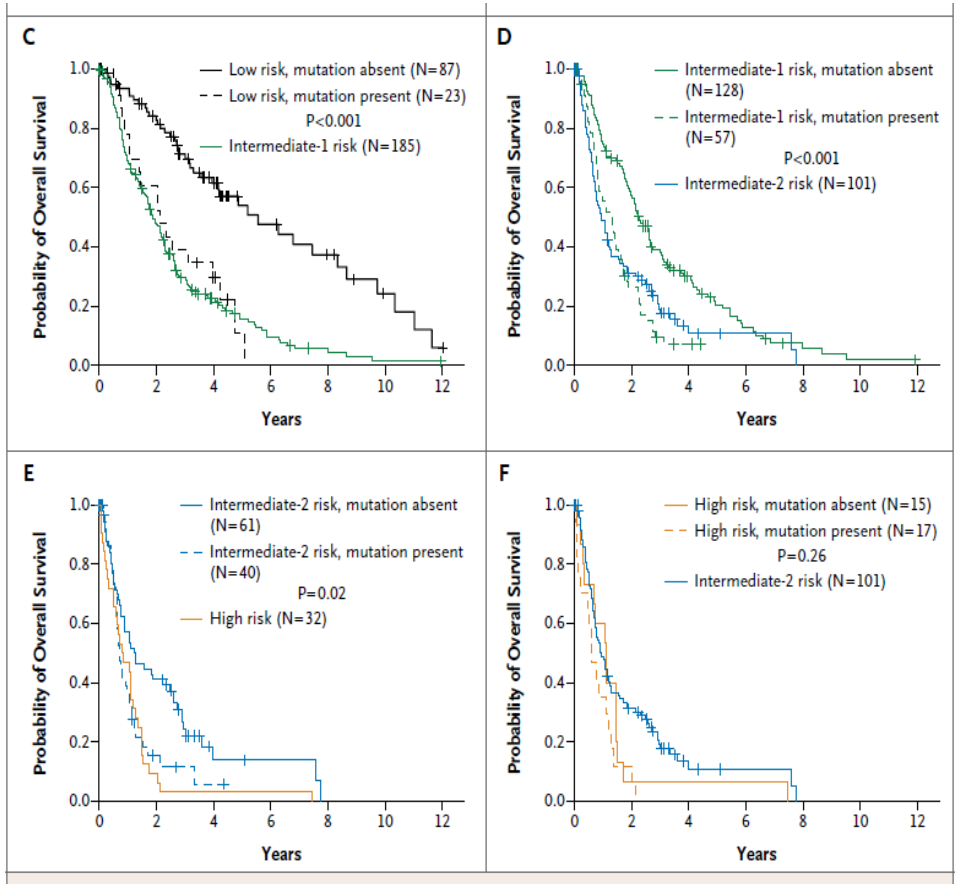
		HMA IL	HMA/Ven 1L	P value
n		1127	35	
Age	mean	68.4	67.8	.76
Gender	Male	66%	71%	.5
Race	White	90%	97%	.66
t-MDS		24%	23%	.86
WHO 2016	MDS-SLD/MLD	18%	4%	.04
	MDS-RS	6%	4%	
	MDS-EB1	33%	9%	
	MDS-EB2	39%	78%	
R-IPSS	Intermediate	31%	17%	.22
	High	31%	37%	
	Very High	38%	46%	
Myeloblasts	Mean (%)	8	13	< .005
Hgb	Mean (g/dl)	9	9	1.0
WBC	Mean	4	10.6	< .005
ANC	Mean	1.8	4.1	<.005
platelets	platelets	96	100	.8
Somatic Mutations	*SF3B1*	5%	0	.3
(n= 546 sequenced)	*TET-2*	16%	23%	.3
	IDH-1	3%	3%	.7
	IDH-2	5%	14%	.056
	ASXL-1	21%	46%	.002
	TP53	27%	34%	.6
	NRAS	4%	11%	.07



Komrokji R et al. Blood Cancer journal 2022

TP53 Mutations Predict Prognosis in MDS

- p53 is a critical tumor suppressor protein that responds to cellular stress by inducing cell cycle arrest, senescence and/or apoptosis to eliminate precancerous and tumor cells.
- Mutations in the *TP53* gene (m*TP53*) are found in 5-10% of MDS and AML patients and predict for the most inferior OS (median OS 6-12 months).
- Confers poor prognosis in allo-SCT



Bejar R, et al. *NEJM*. 2011.

Thank you