Myelodysplastic Syndromes: Current and Future Management Approaches

Harry P. Erba, MD PhD
Professor, Medicine
Director, Leukemia Program
Division of Hematologic Malignancies and Cellular Therapy
Duke University
Durham, NC

DukeHealth

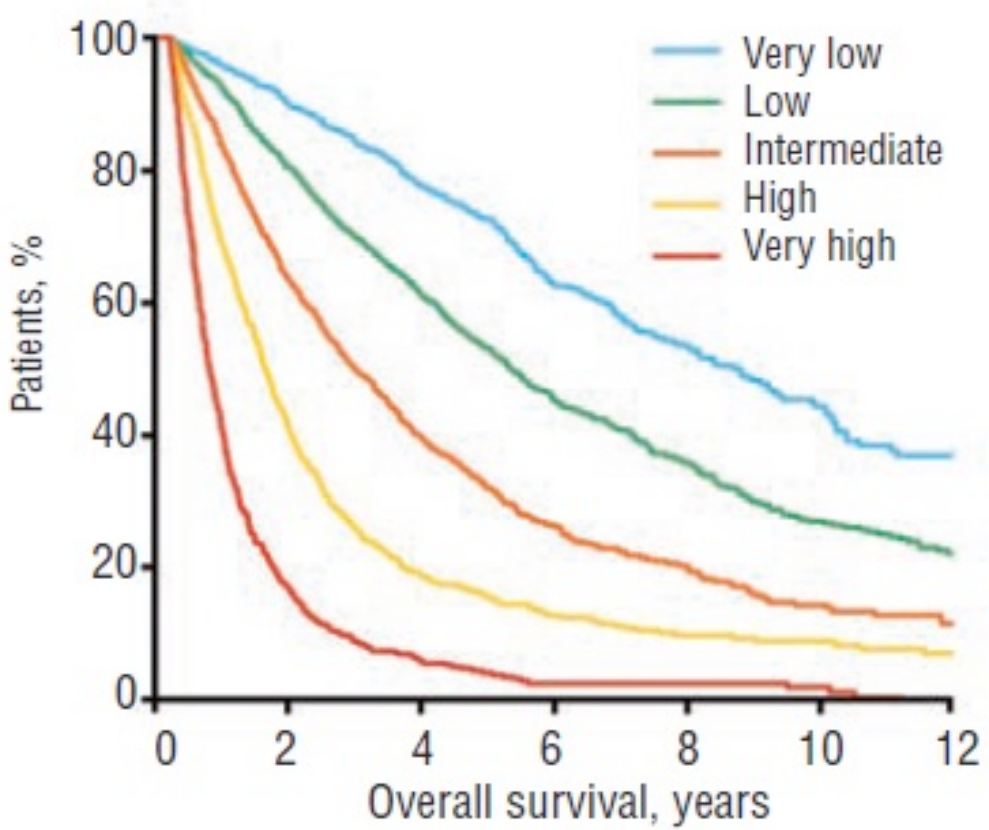
MDS Prognosis: Revised International Prognostic Score

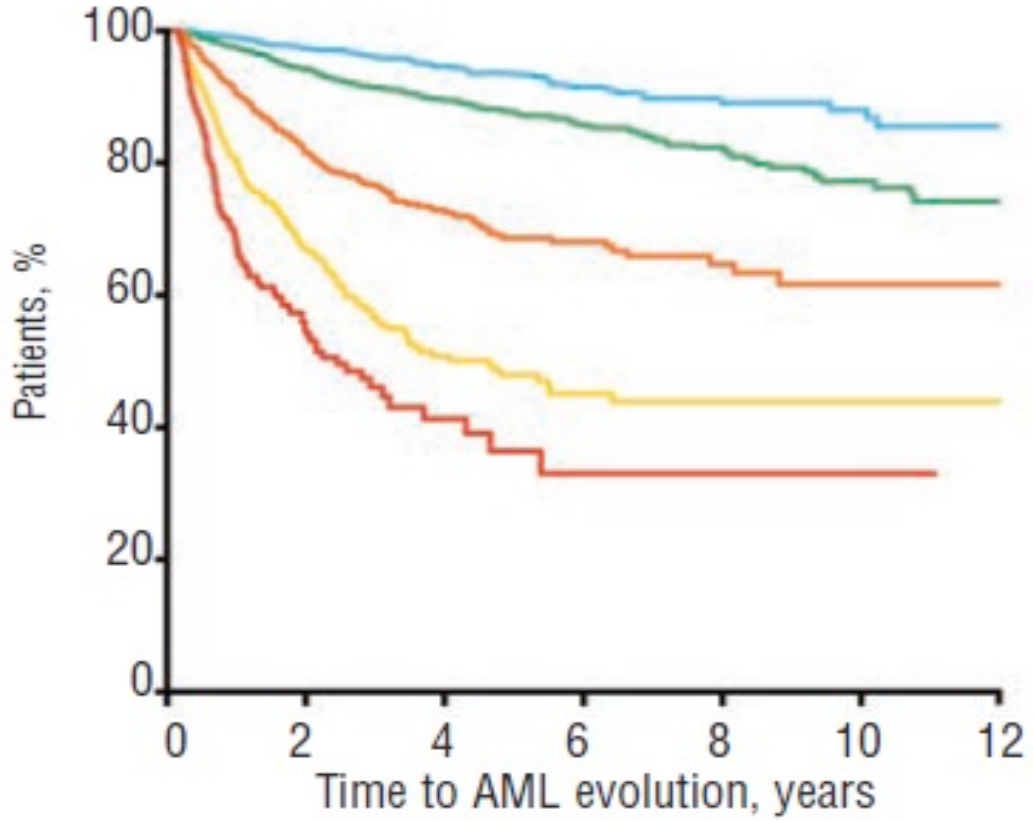
	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
BM blast	≤2%		>2-<5%		5-10%	>10%	
Hemoglobin	≥10		8-<10	<8			
Platelets	≥100	50-<100	<50				
ANC	≥0.8	<0.8					

Risk Group	Risk Score	Median Survival (yrs)
Very Low	≤1.5	8.8
Low	>1.5-3	5.3
Intermediate	>3-4.5	3.0
High	>4.5-6	1.6
Very High	>6	0.8

Greenberg PL, et al. *Blood* 2012; 120(12): 2454-2465

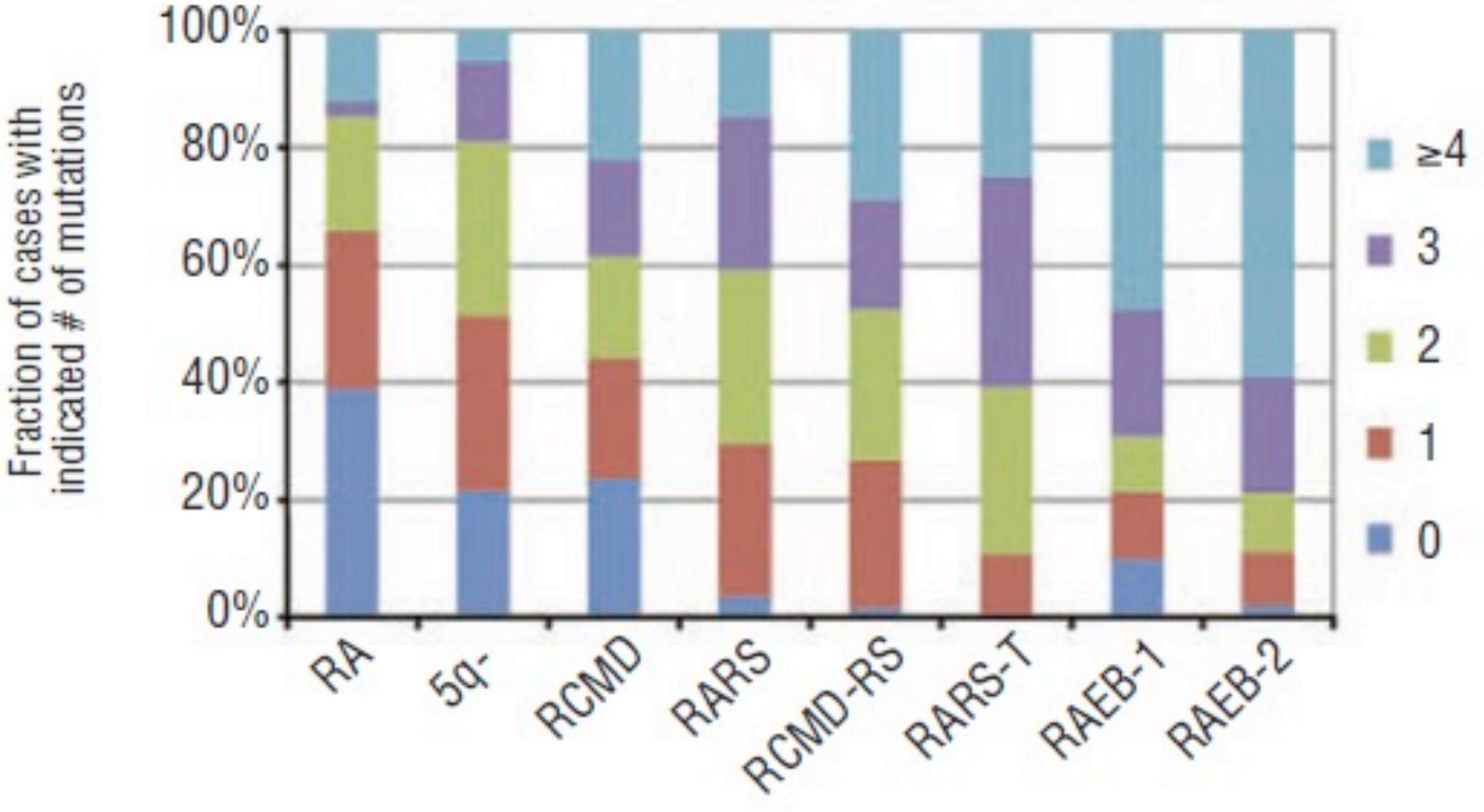
MDS Prognosis: Revised International Prognostic Score





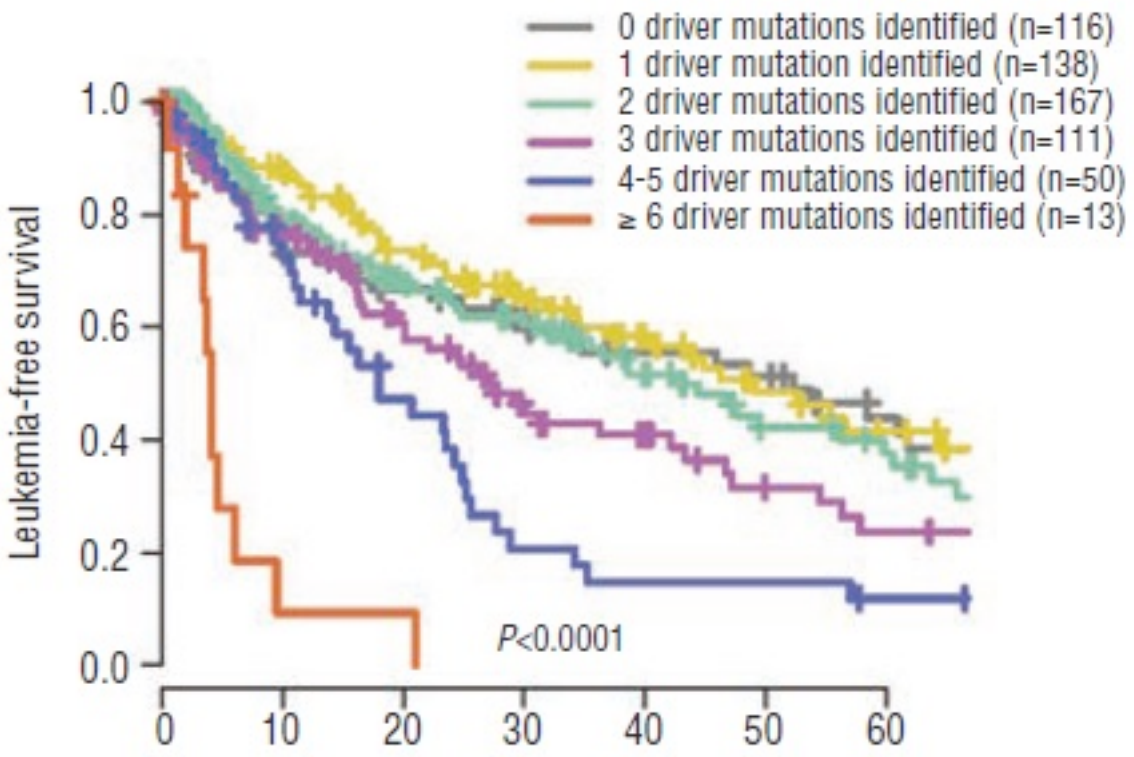
Greenberg PL, et al. *Blood* 2012; 120(12): 2454-2465

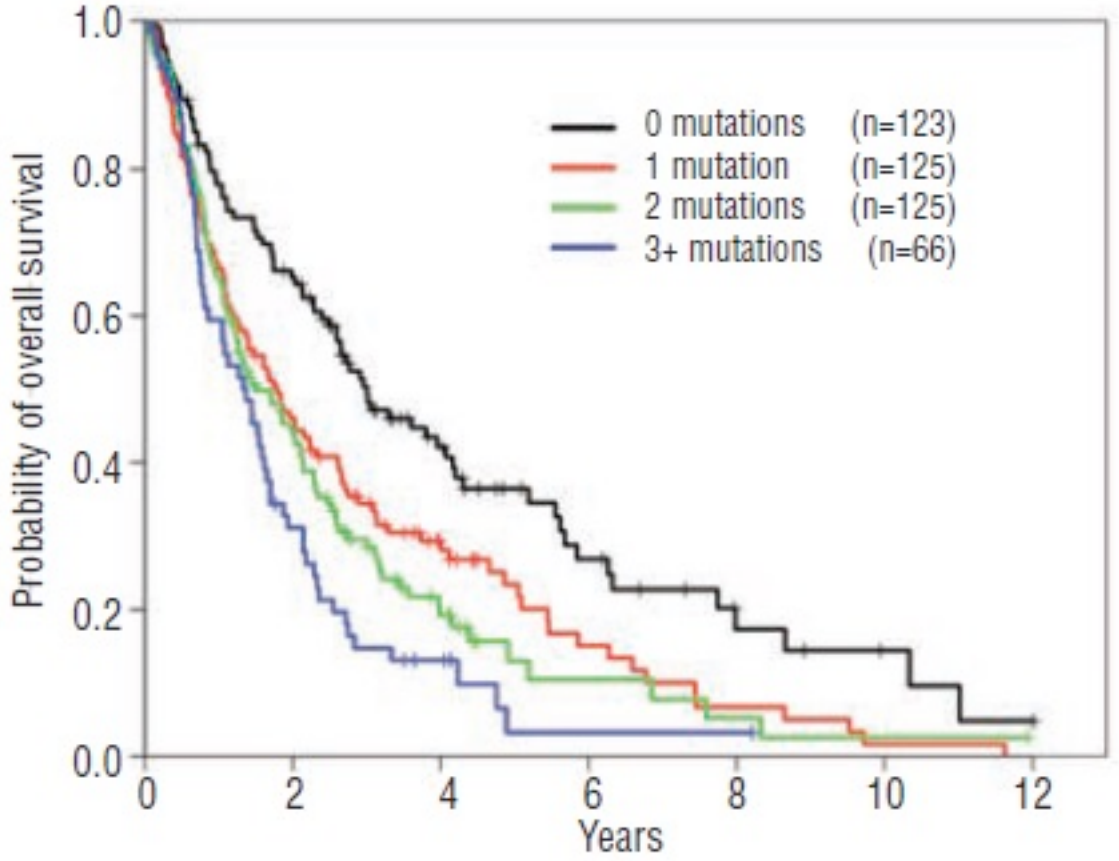
Number of Pathogenic Mutations According to MDS Classification



Haferlach T, et al. *Leukemia* 2014; 28(2): 241-247

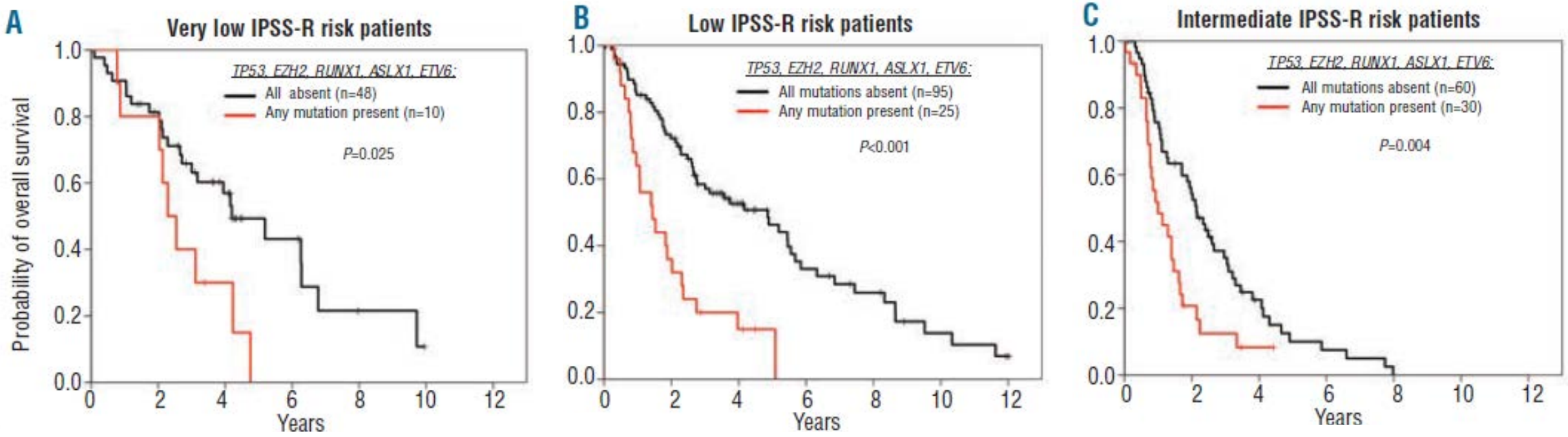
Increasing Number of Pathogenic Mutations are Associated with Inferior Leukemia-free and Overall Survival





Papaemmanuil E, et al *Blood* 2013; 122(22): 3616-3627
Bejar R, et al *Engl J Med* 2011; 364(26): 2496

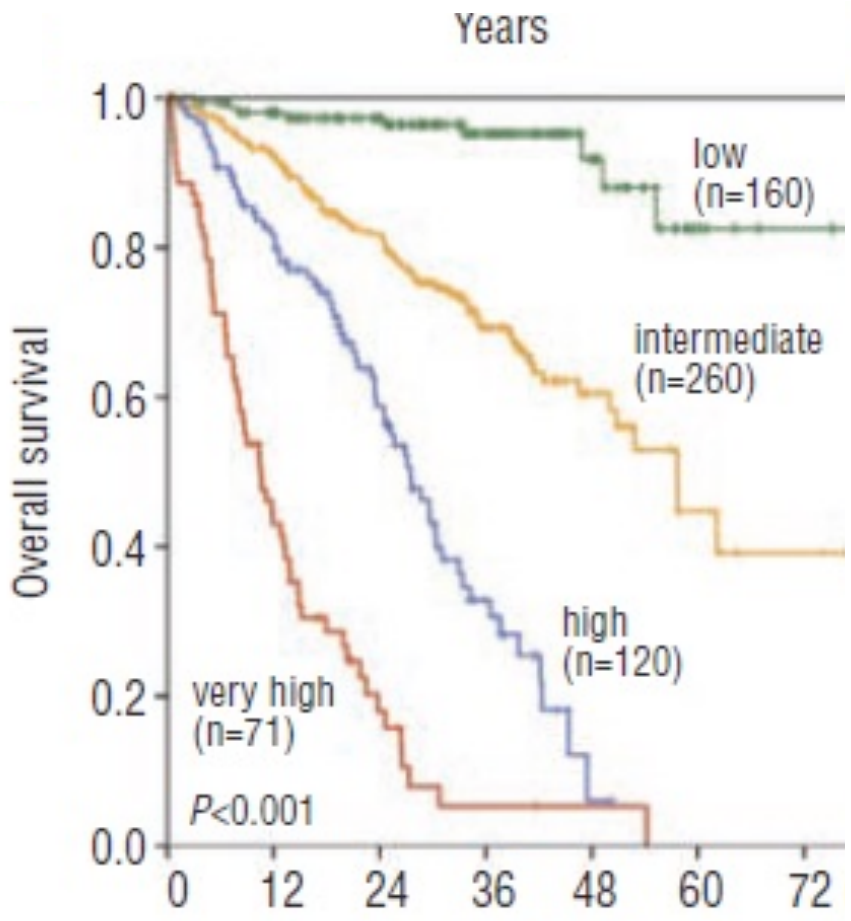
Pathogenic Mutations Can Augment Prognosis based on IPSS-R in Non-High Risk MDS

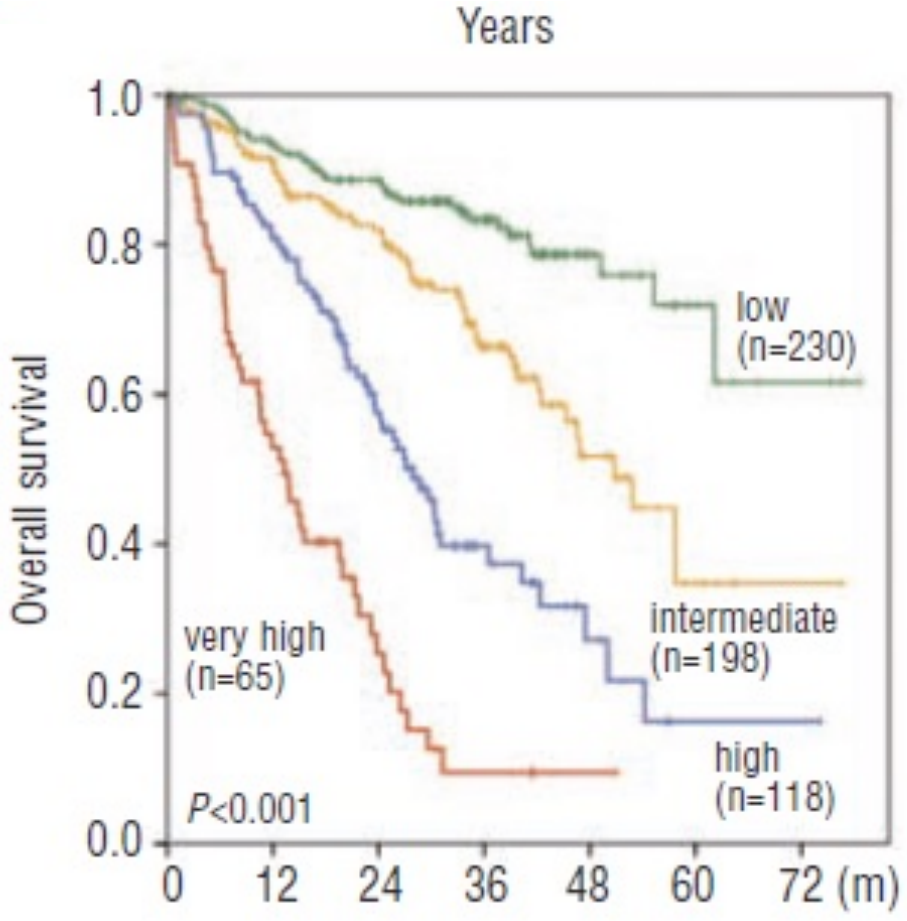


Bejar R, et al *N Engl J Med* 2011; 364(26): 2496

MDS Prognosis: Clinical + Mutational vs Mutational Model Alone

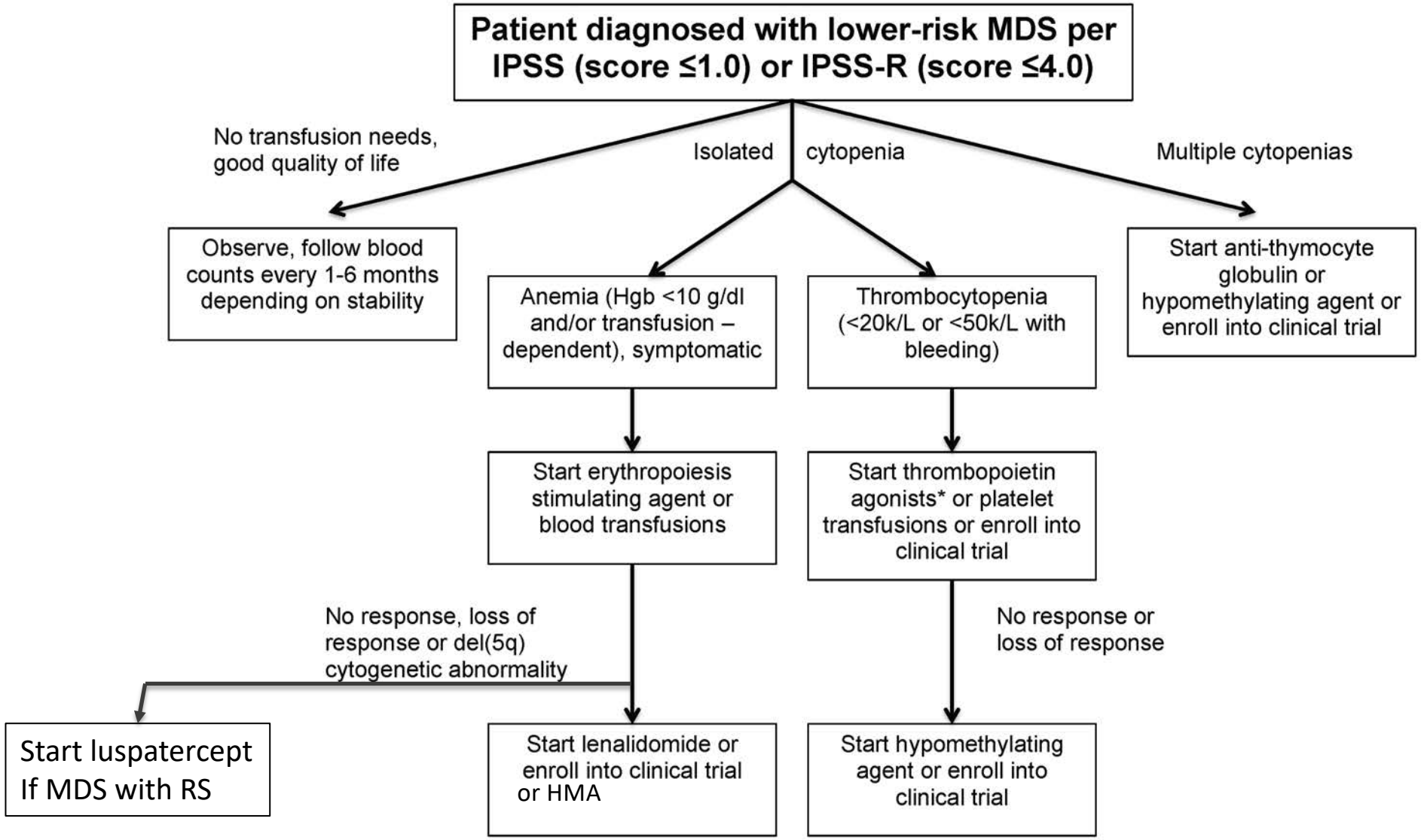
Model
Age
Gender
IPSS-R
14 genes





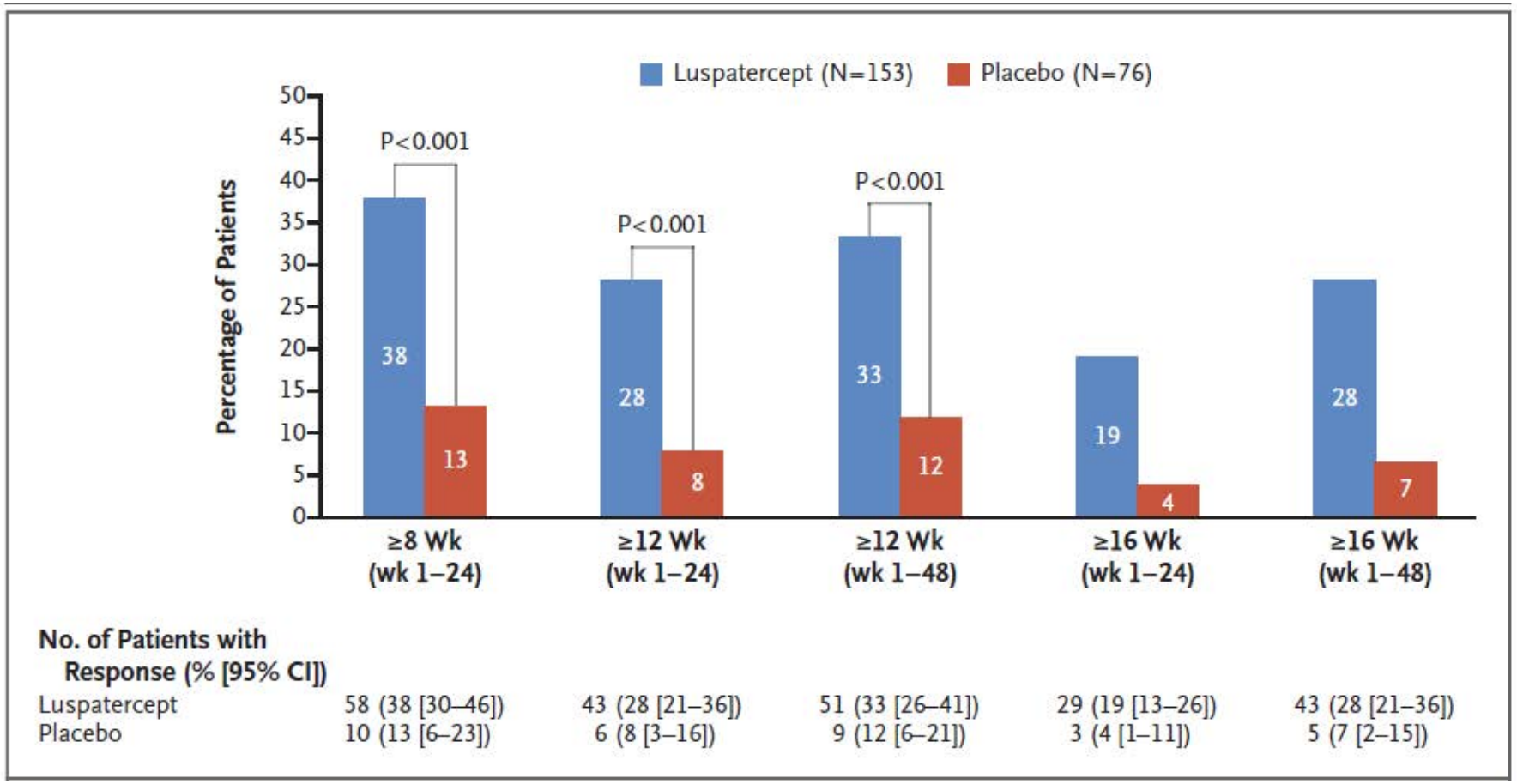
14 Gene Model
ASXL1
CBL
ETV6
EZH2
KRAS
LAMB4
NCOR2
NF1
NPM1
NRAS
PRPF8
RUNX1
TET2
TP53

Haferlach T, et al. *Leukemia* 2014; 28(2): 241-247



Sekeres MA and Gerds AT. ASH Educational Book 2014

Luspatercept vs Placebo in Lower Risk MDS-RS Patients Receiving RBC Transfusion: RBC Transfusion Independence



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; 382140-151.

Luspatercept vs Placebo in Lower Risk MDS-RS Patients Receiving RBC Transfusion: Erythroid Response

Table 2. Erythroid Response and Increase in Mean Hemoglobin Levels.

End Point	Luspatercept (N=153)	Placebo (N=76)
Erythroid response during wk 1–24*		
No. of patients (% [95% CI])	81 (53 [45–61])	9 (12 [6–21])
Reduction of ≥4 red-cell units/8 wk — no./total no. (%)†	52/107 (49)	8/56 (14)
Mean increase in hemoglobin level of ≥1.5 g/dl — no./total no. (%)‡	29/46 (63)	1/20 (5)
Erythroid response during wk 1–48*		
No. of patients (% [95% CI])	90 (59 [51–67])	13 (17 [9–27])
Reduction of ≥4 red-cell units/8 wk — no./total no. (%)†	58/107 (54)	12/56 (21)
Mean increase in hemoglobin level of ≥1.5 g/dl — no./total no. (%)‡	32/46 (70)	1/20 (5)
Mean increase in hemoglobin level of ≥1.0 g/dl — no. (% [95% CI])§		
During wk 1–24	54 (35 [28–43])	6 (8 [3–16])
During wk 1–48	63 (41 [33–49])	8 (11 [5–20])

Fenaux P, et al. *N Engl J Med* 2020; 382140-151.

Luspatercept vs Placebo in Lower Risk MDS-RS Patients Receiving RBC Transfusion: Adverse Events

Event	Luspatercept (N=153)		Placebo (N=76)	
	Any Grade	Grade 3	Any Grade	Grade 3
	number of patients with event (percent)			
General disorder or administration-site condition				
Fatigue	41 (27)	7 (5)	10 (13)	2 (3)
Asthenia	31 (20)	4 (3)	9 (12)	0
Peripheral edema	25 (16)	0	13 (17)	1 (1)
Gastrointestinal disorder				
Diarrhea	34 (22)	0	7 (9)	0
Nausea†	31 (20)	1 (1)	6 (8)	0
Constipation	17 (11)	0	7 (9)	0
Nervous system disorder				
Dizziness	30 (20)	0	4 (5)	0
Headache	24 (16)	1 (1)	5 (7)	0
Musculoskeletal or connective-tissue disorder				
Back pain†	29 (19)	3 (2)	5 (7)	0
Arthralgia	8 (5)	1 (1)	9 (12)	2 (3)
Respiratory, thoracic, or mediastinal disorder				
Dyspnea†	23 (15)	1 (1)	5 (7)	0
Cough	27 (18)	0	10 (13)	0
Infection or infestation				
Bronchitis†	17 (11)	1 (1)	1 (1)	0
Urinary tract infection†	17 (11)	2 (1)	4 (5)	3 (4)
Injury, poisoning, or procedural complication: fall	15 (10)	7 (5)	9 (12)	2 (3)

Fenaux P, et al. *N Engl J Med* 2020; 382140-151.

Oral Cedazuridine/Decitabine vs IV Decitabine: Decitabine AUC

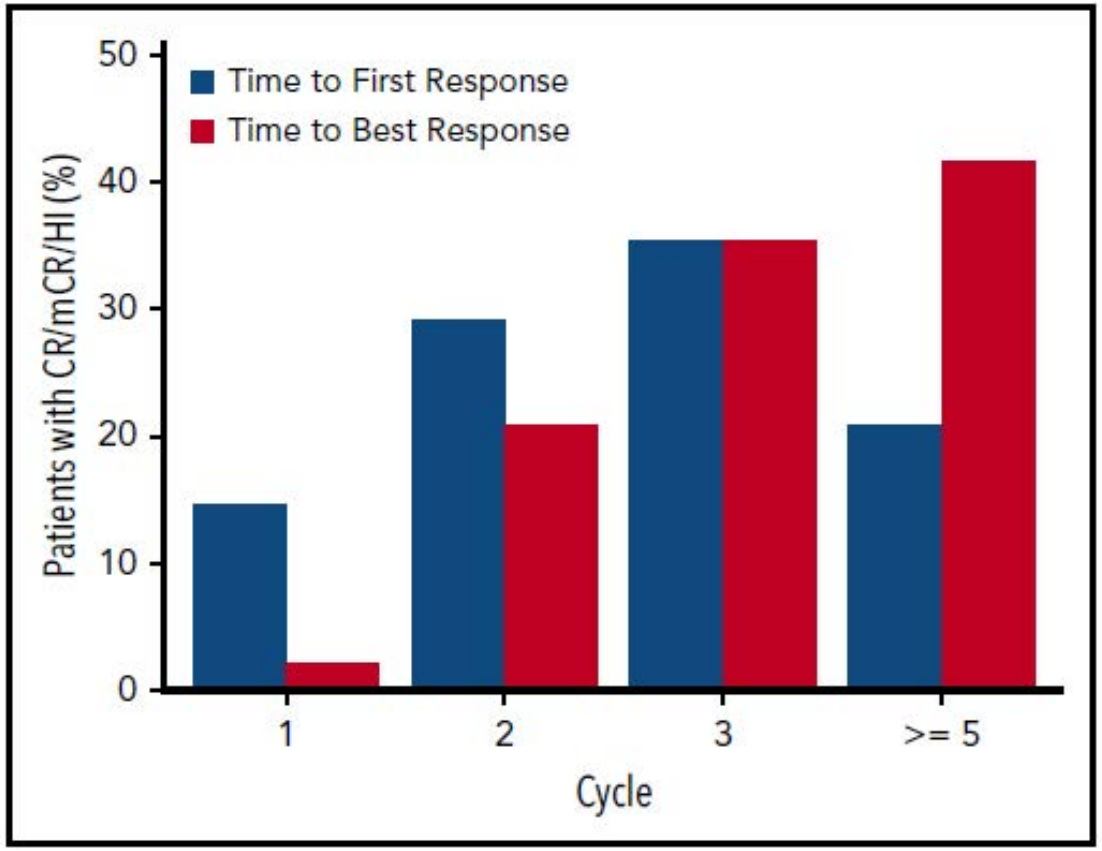
Parameter	IV geometric LSM	Oral geometric LSM	LSM ratio (oral/IV)	80% CI	Intrapatient CV%
Primary paired population					
5-d AUC_{last}, ng × hr per mL (primary end point)					
DC cohort (n = 40)	802.81	750.82	93.52	82.10-106.5	47.0
FDC cohort (n = 24)	745.26	727.29	97.59	80.48-118.3	53.8
Secondary unpaired population					
5-d AUC_{last}, ng × hr per mL					
DC cohort	795.41 (n = 42)	735.62 (n = 48)	92.48	81.37-105.1	48.4
FDC cohort	742.26 (n = 26)	760.43 (n = 28)	102.45	85.35-123.0	52.7
5-d AUC_{24}, h/ng per mL					
DC cohort	794.73 (n = 40)	753.68 (n = 45)	94.83	83.97-107.1	43.5
FDC cohort	696.90 (n = 20)	846.82 (n = 26)	121.51	97.15-152.0	59.1
5-d AUC_{∞}, ng × hr per mL					
DC cohort	794.73 (n = 40)	733.26 (n = 42)	92.27	81.27-104.7	44.6
FDC cohort	687.08 (n = 40)	845.57 (n = 26)	121.30	97.00-151.7	59.1

AUC_{24}, AUC from time 0 to 24 h; AUC_{∞}, AUC from time 0 to ∞; CV, coefficient of variation; DC, dose confirmation (2 separate capsules of cedazuridine and decitabine); FDC, fixed dose combination.

Garcia-Manero G, et al. *Blood* 2020; 136(6): 674-683

Phase 2 of Oral Cedazuridine/decitabine: Response

Type of response	Phase 2 overall (N = 80)	
	n (%)	95% CI
CR	17 (21)	13-32
PR	0	
mCR	18 (22)	14-33
mCR with HI	6 (7)	3-16
HI	13 (16)	9-26
HI-E	8 (10)	4-19
HI-N	2 (2)	0-9
HI-P	11 (14)	7-23
Overall response* (CR + PR + mCR + HI)	48 (60)	48-71
No response	32 (40)	29-52

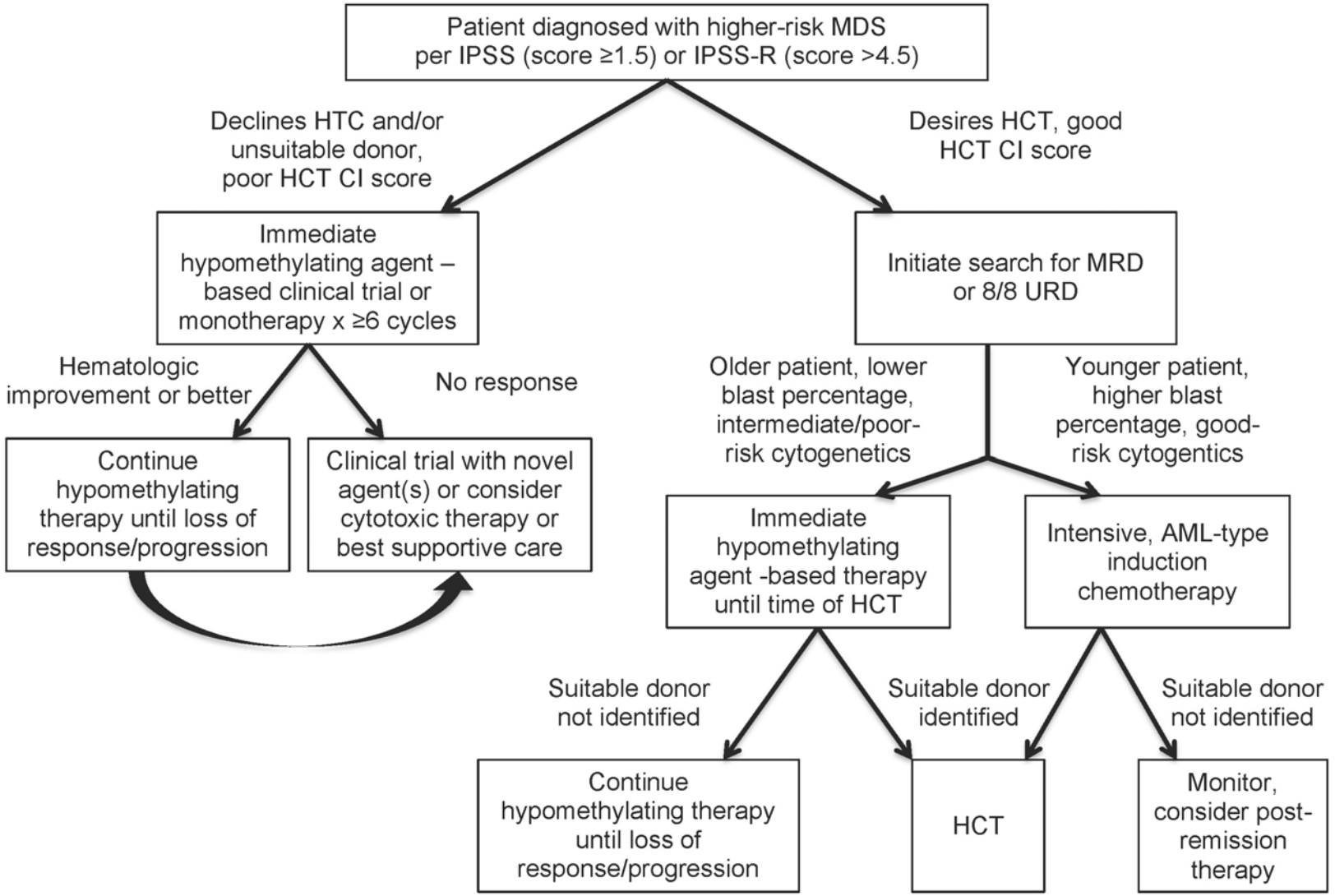


Garcia-Manero G, et al. *Blood* 2020; 136(6): 674-683

Oral Cedazuridine/Decitabine vs IV Decitabine: Similar Rates of TEAE

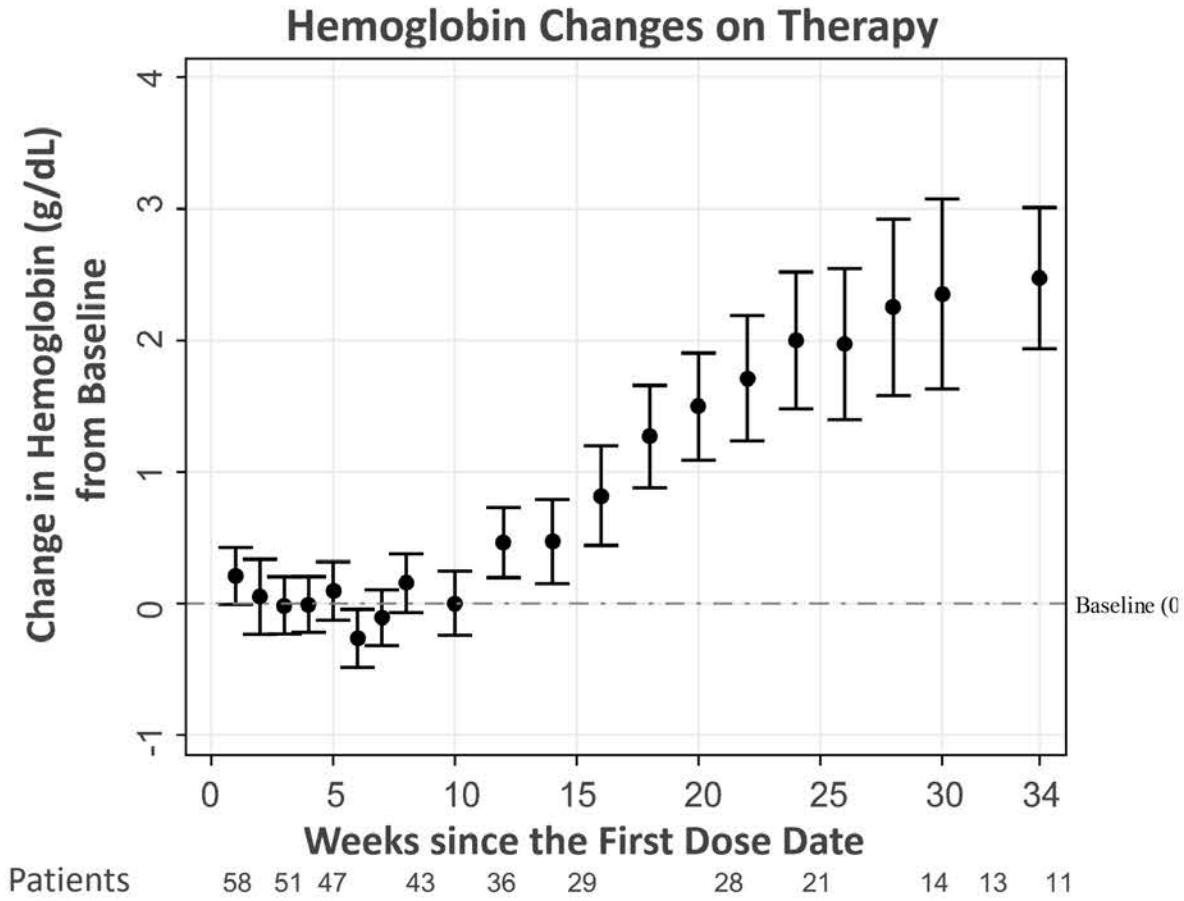
Preferred term, n (%)	IV decitabine cycle 1 or 2 (n = 75)	Oral cedazuridine/ decitabine cycle 1 or 2 (n =78)	All oral cedazuridine/ decitabine cycles (n = 78)
Patients with ≥1 TEAE	69 (92)	72 (92)	75 (96)
Most common TEAEs (≥20% of patients)			
Neutropenia	22 (29)	17 (22)	36 (46)
Thrombocytopenia	24 (32)	23 (29)	34 (44)
Fatigue	10 (13)	15 (19)	26 (33)
Febrile neutropenia	12 (16)	9 (12)	23 (29)
Nausea	11 (15)	13 (17)	22 (28)
Diarrhea	9 (12)	10 (13)	22 (28)
Leukopenia	9 (12)	10 (13)	21 (27)
Dizziness	8 (11)	9 (12)	20 (26)
Anemia	11 (15)	10 (13)	19 (24)
Constipation	12 (16)	14 (18)	19 (24)
Dyspnea	2 (3)	12 (15)	19 (24)
Patients with grade ≥3 TEAEs	44 (59)	45 (58)	65 (83)
Most common grade ≥3 TEAEs (≥10% of patients)			
Neutropenia	20 (27)	16 (21)	36 (46)
Thrombocytopenia	21 (28)	18 (23)	30 (38)
Febrile neutropenia	12 (16)	9 (12)	23 (29)
Leukopenia	8 (11)	7 (9)	19 (24)
Anemia	9 (12)	9 (12)	17 (22)
Pneumonia	5 (7)	7 (9)	10 (13)
Sepsis	1 (1)	4 (5)	8 (10)

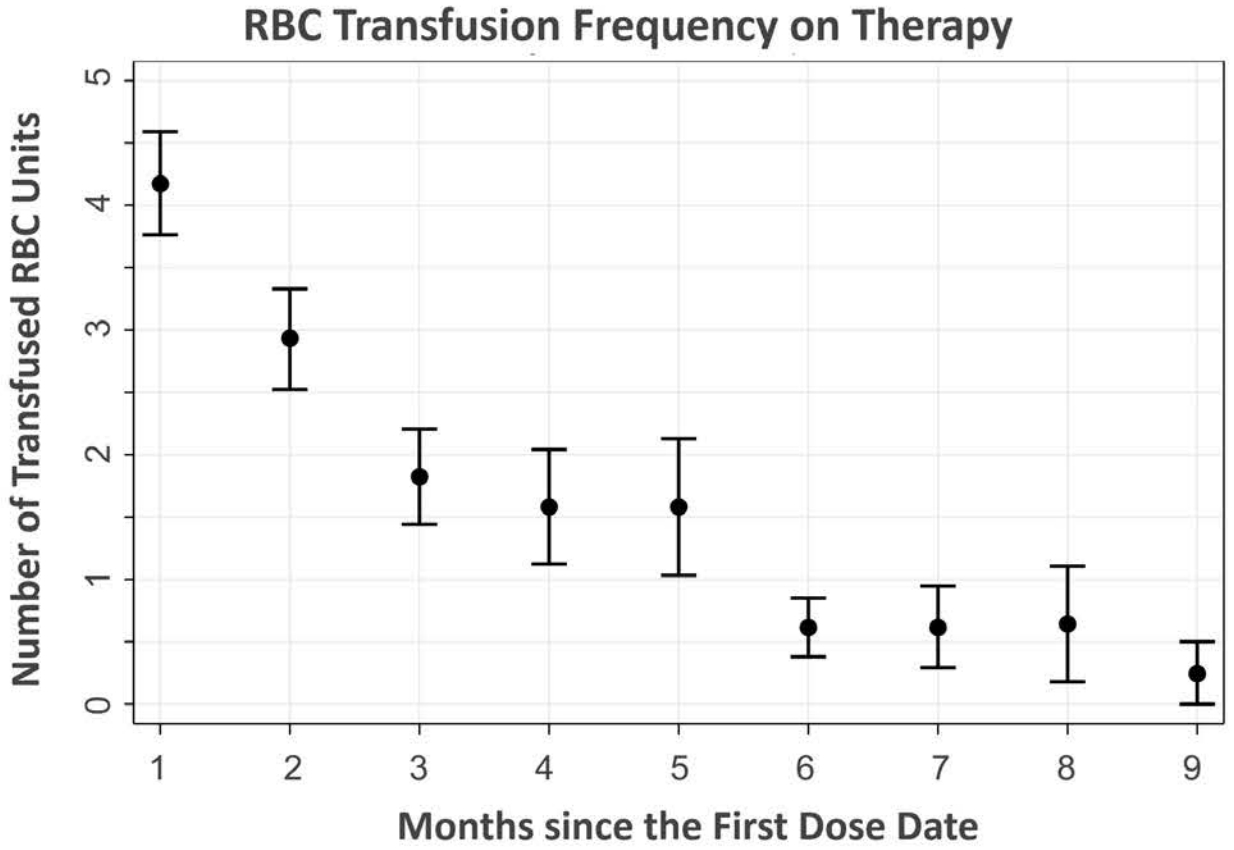
Garcia-Manero G, et al. *Blood* 2020; 136(6): 674-683



Sekeres MA and Gerds AT. ASH Educational Book 2014

On Target Anemia is a Pharmacodynamic Effect and is Mitigated with a Magrolimab Priming and Maintenance Dosing Regimen



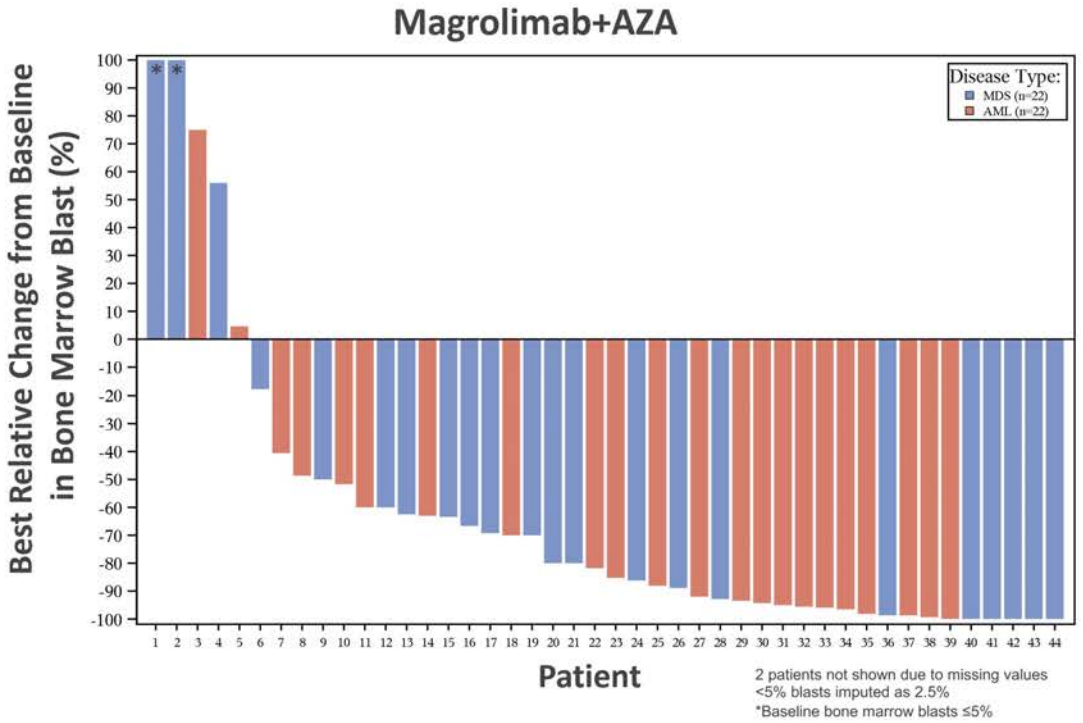


Sallman DA, et al. ASH 2019

Anti-Leukemic Activity is Observed with Magrolimab + AZA in MDS and AML

Best Overall Response	1L MDS N=24	1L AML N=22
ORR	22 (92%)	14 (64%)
CR	12 (50%)	9 (41%)
CRi	-	3 (14%)
PR	0	1 (5%)
MLFS/ marrow CR	8 (33%) 4 with marrow CR + HI	1 (5%)
Hematologic improvement (HI)	2 (8%)	-
SD	2 (8%)	7 (32%)
PD	0	1 (5%)

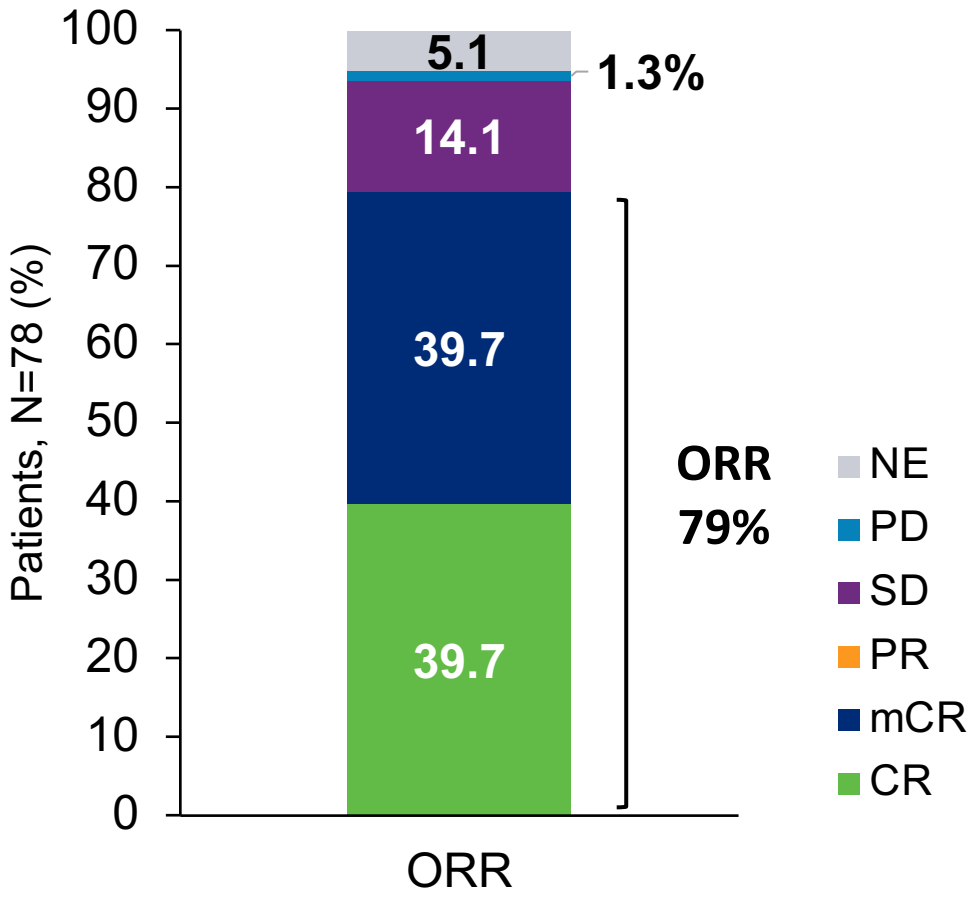
Response assessments per 2006 IWG MDS criteria and 2017 AML ELN criteria; Patients with at least one post-treatment response assessment are shown, all other patients are on therapy and are too early for first response assessment, except for 2 MDS patients not evaluable (withdrawal of consent) and 3 AML (1 AE, 2 early withdrawal)
"-" not applicable



- Magrolimab + AZA induces a 92% ORR (50% CR) in MDS and 64% ORR (55% CR/CRi) in AML
- Median time to response is 1.9 months, more rapid than AZA alone
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy

Sallman DA, et al. ASH 2019

Phase Ib/II Study of Azacitidine and Venetoclax for Higher Risk MDS: Response



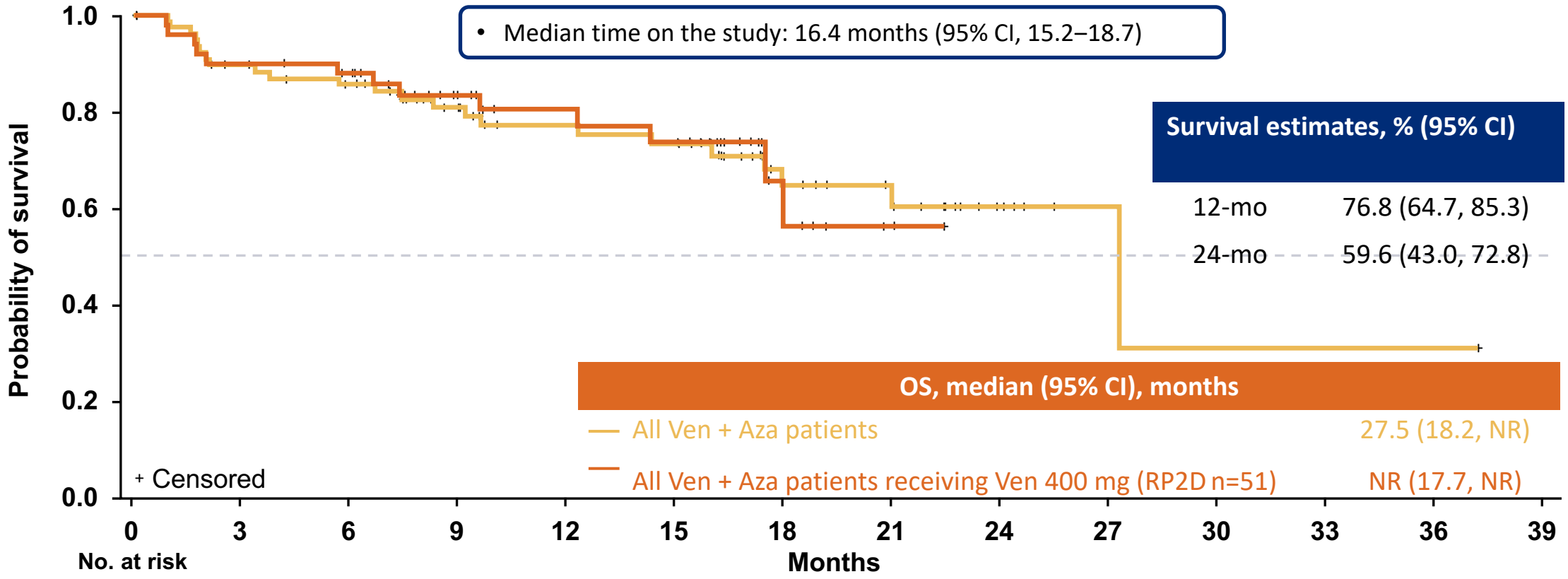
- Median DoR: 12.9 months (min–max, 12.1–16.8)
- Median DoR after CR: 13.8 months (min–max, 6.5–20.9)
- Median time to CR: 2.6 months (min–max, 1.2–19.6)
- For patients receiving Ven 400 mg (RP2D; n=51)[b]
  - 84% of patients achieved ORR[a]
    - 47% achieved ORR by Cycle 2; 78% achieved ORR by Cycle 3
  - 35% of patients achieved CR

Transfusion independence rate	n (% of N=78)
RBC and platelet	51 (65)
RBC	52 (67)
Platelet	60 (77)

- A total of 16 patients (21%) went on to receive poststudy HSCT

Garcia JS et al. ASH 2020; abstract 656

Phase Ib/II Study of Azacitidine and Venetoclax for Higher Risk MDS: Overall Survival



No. at risk														
All Ven + Aza patients	78	66	59	46	38	36	20	15	7	2	1	1	1	0
All Ven + Aza patients receiving Ven 400 mg (RP2D)	51	45	42	31	24	22	7	2	0					

Garcia JS et al. ASH 2020; abstract 656

Phase Ib/II Study of Azacitidine and Venetoclax for Higher Risk MDS: Adverse Events

Any AEs, n (%)	78 (100)
Neutropenia[a]	65 (83)
Febrile neutropenia	38 (49)
Nausea	43 (55)
Constipation	42 (54)
Diarrhea	38 (49)
Thrombocytopenia[b]	38 (49)
Vomiting	32 (41)
Leukopenia[c]	30 (38)
Anemia[d]	23 (29)
Fatigue	20 (26)
Hypokalemia	16 (21)

Grade 3/4 AEs, n (%)	75 (96)
Neutropenia[a]	64 (82)
Febrile neutropenia	38 (49)
Thrombocytopenia[b]	33 (42)
Leukopenia[c]	30 (38)
Anemia[d]	18 (23)

Any SAEs, n (%)	57 (73)
Neutropenia[a]	38 (49)
Febrile neutropenia	35 (45)
Pneumonia	5 (6)
Diverticulitis	4 (5)

Overall, 74 patients (95%) required a cycle delay; median time to delay 15.0 days (range 3–99)

43 patients (55%) had ≥2 Ven dose interruptions

AEs 59 (80%); hematologic toxicity 27 (37%); logistics/scheduling 19 (26%), other 41 (55%)

A total of 35% of patients required ≥1 Ven dose reduction[e]

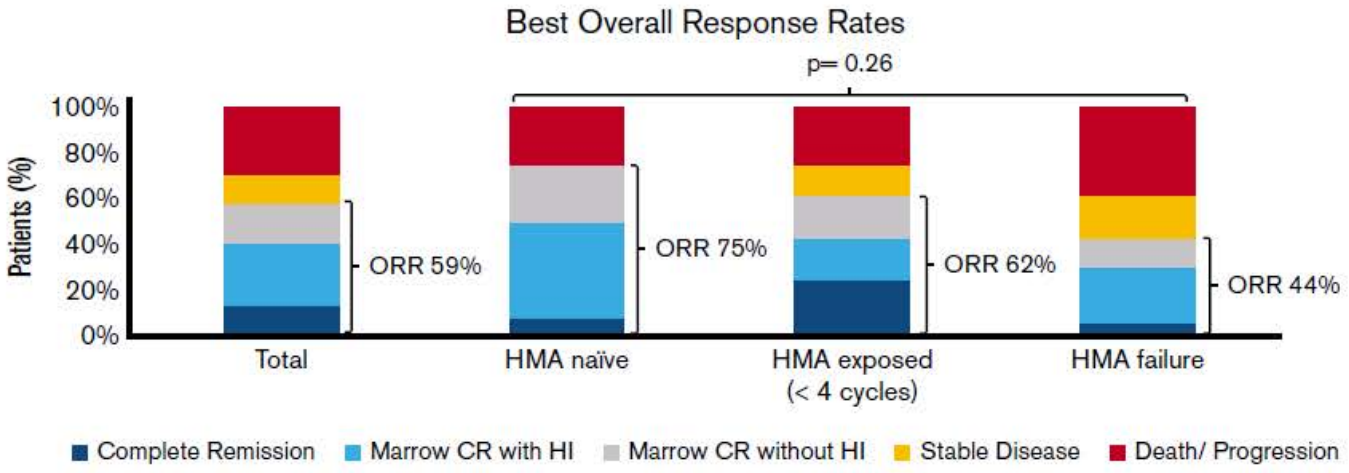
AEs 6 (21%); starting CYP3A inhibitor 20 (71%); other 7 (25%)

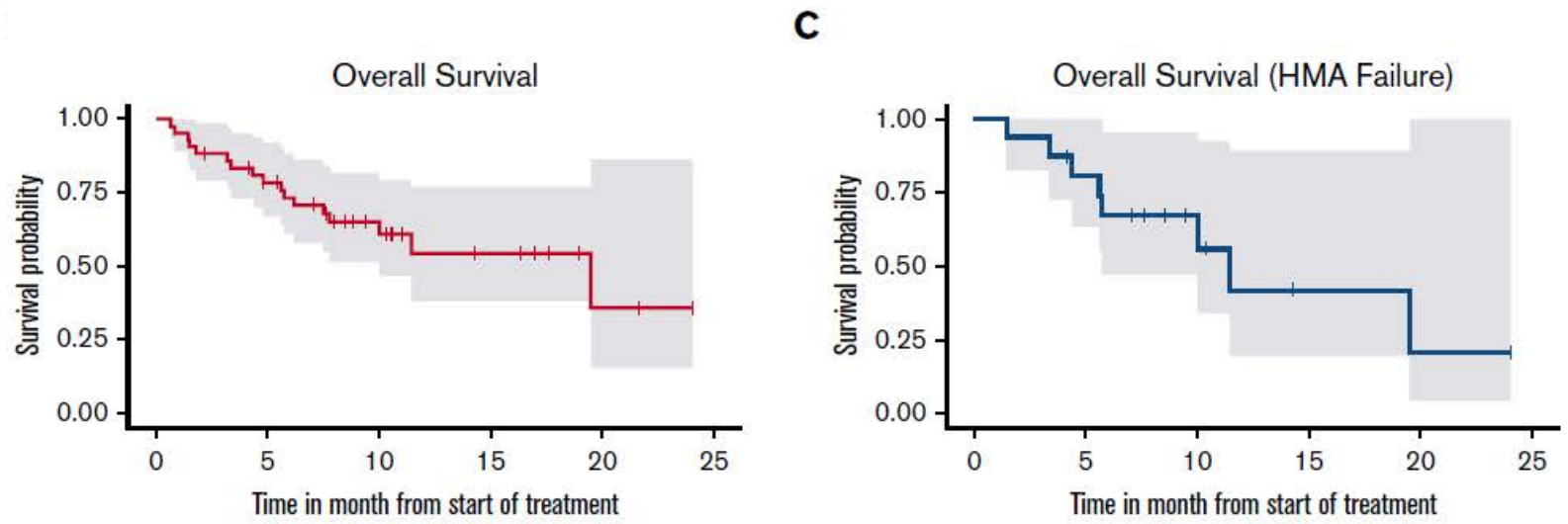
A total of 33% of patients required ≥1 Aza dose reduction[e]

30-day mortality after first dose was 1%

Garcia JS et al. ASH 2020; abstract 656

HMA plus Venetoclax for MDS: Response and Survival





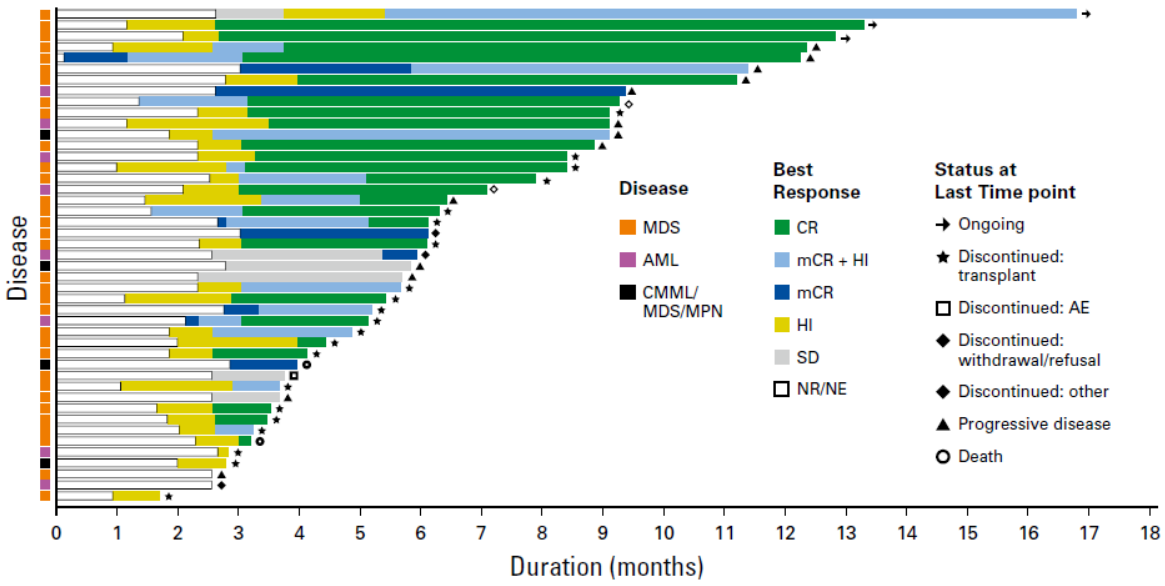
Ball BJ, et al. *Blood Adv.* 2020; 4(13): 2866-2870

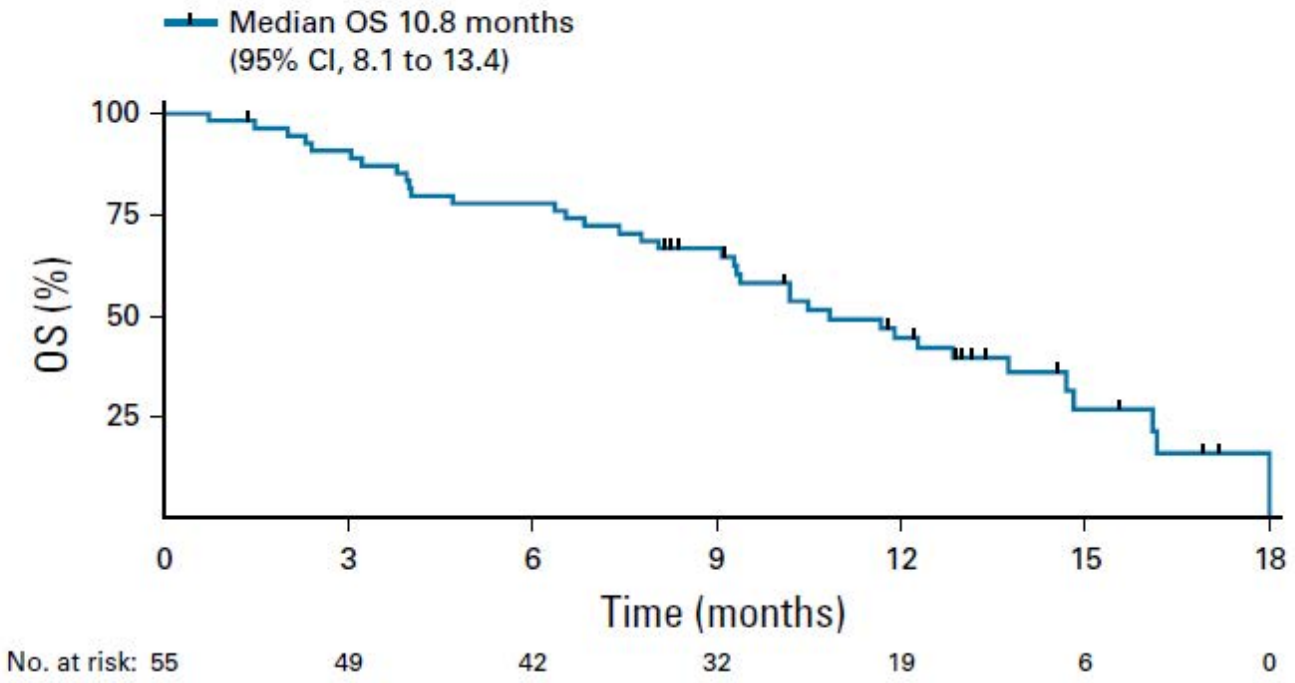
Eprenetapopt plus Azacitidine for TP53-mutated Myeloid Neoplasm

Response	All Patients (N = 55)	MDS (n = 40)	AML (n = 11)	MDS/MPN (n = 4)
ORR (95% CI)[a]	39 (71) [57 to 82]	29 (73) [56 to 85]	7 (64) [31 to 89]	3 (75)[b]
Time to first response, months, median (range)	2.1 (0.1-5.4)	1.9 (0.1-5.4)	2.3 (1.2-3.0)	2.7 (2.0-2.9)
Duration of response, months, median [95% CI][c]	8.0 [6.5 to 11.2]	8.4 [6.5 to 13.2]	7.5 [4.2 to NE]	7.4 [NE to NE]
Best response by IWG, n (%)				
CR	24 (44)	20 (50)	4 (36)	0 (0)
PR	0 (0)	0 (0)	0 (0)	0 (0)
mCR + HI	8 (15)	7 (18)	0 (0)	1 (25)
mCR	4 (7)	1 (3)	2 (18)	1 (25)
HI	3 (5)	1 (3)	1 (9)	1 (25)
SD	4 (7)	2 (6)	1 (9)	1 (25)
NE	10 (18)	7 (18)	3 (27)	0 (0)
PD	2 (4)	2 (4)	0 (0)	0 (0)
CR (95% CI)	24 (44) [30 to 58]	20 (50) [34 to 66]	4 (36) [11 to 69]	0 (0)
Time to CR, months, median (range)	3.1 (2.5-6.1)	3.1 (2.5-6.1)	3.2 (2.8-3.5)	NA
Duration of CR, months, median (95% CI)	7.3 [5.8 to NE]	7.3 [5.8 to NE]	7.0 [3.3 to NE]	NA
Cytogenetic response (95% CI)	26 (47) [34 to 61]	23 (58) [41 to 73]	3 (27) [6 to 61]	0[d]
Partial	8 (15) [7 to 27]	8 (20) [9 to 36]	0 (0) [NE]	
Complete	18 (33) [21 to 47]	15 (38) [23 to 54]	3 (27) [6 to 61]	
TP53				
NGS-negative	21 (38)	17 (43)	4 (36)	0
Serial IHC ≤ 5%	26 (47)	19 (48)	6 (55)	NA

Sallman DA, et al. *J Clin Oncol* 2021; 39: 1584-1594

Eprenetapopt plus Azacitidine for TP53-mutated Myeloid Neoplasm





ITT analysis of 154 patients with TP53-mutated MDS:

Eprenetapopt with AZA: CR 33.3%

AZA alone: CR 22.4% (P = 0.13)

28 DEC 2020

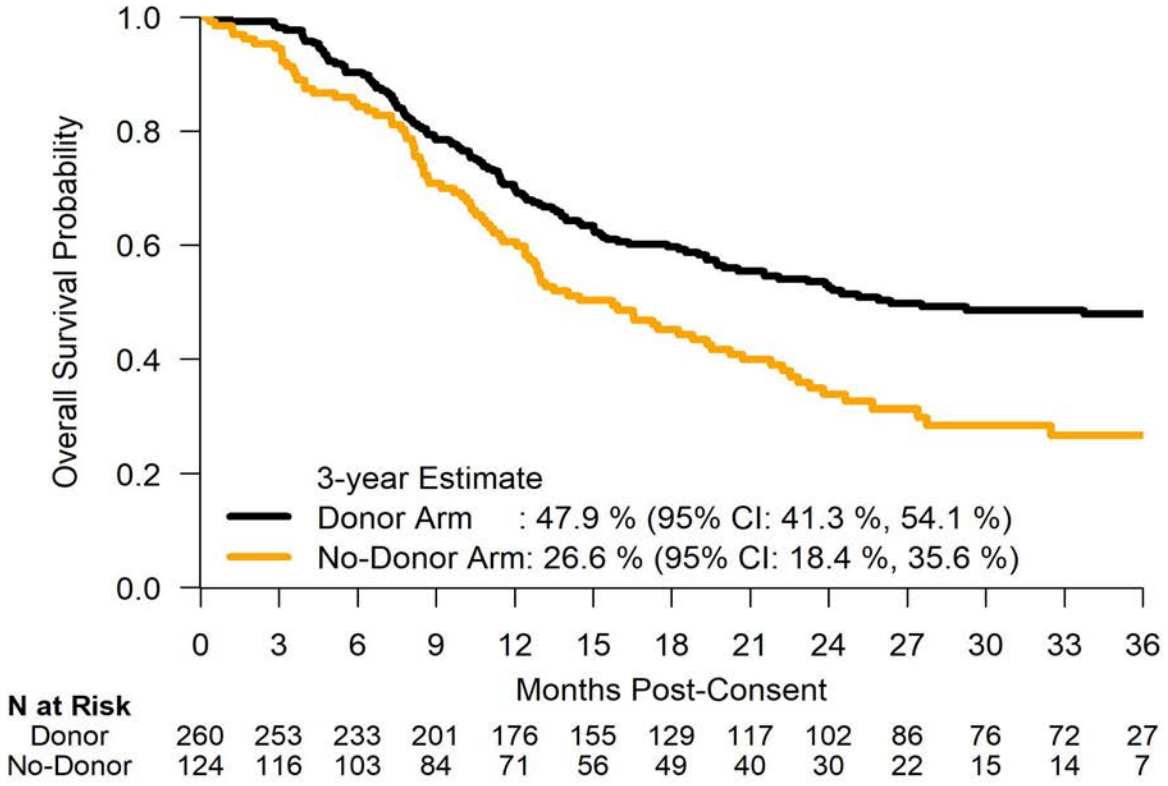
Sallman DA, et al. *J Clin Oncol* 2021; 39: 1584-1594

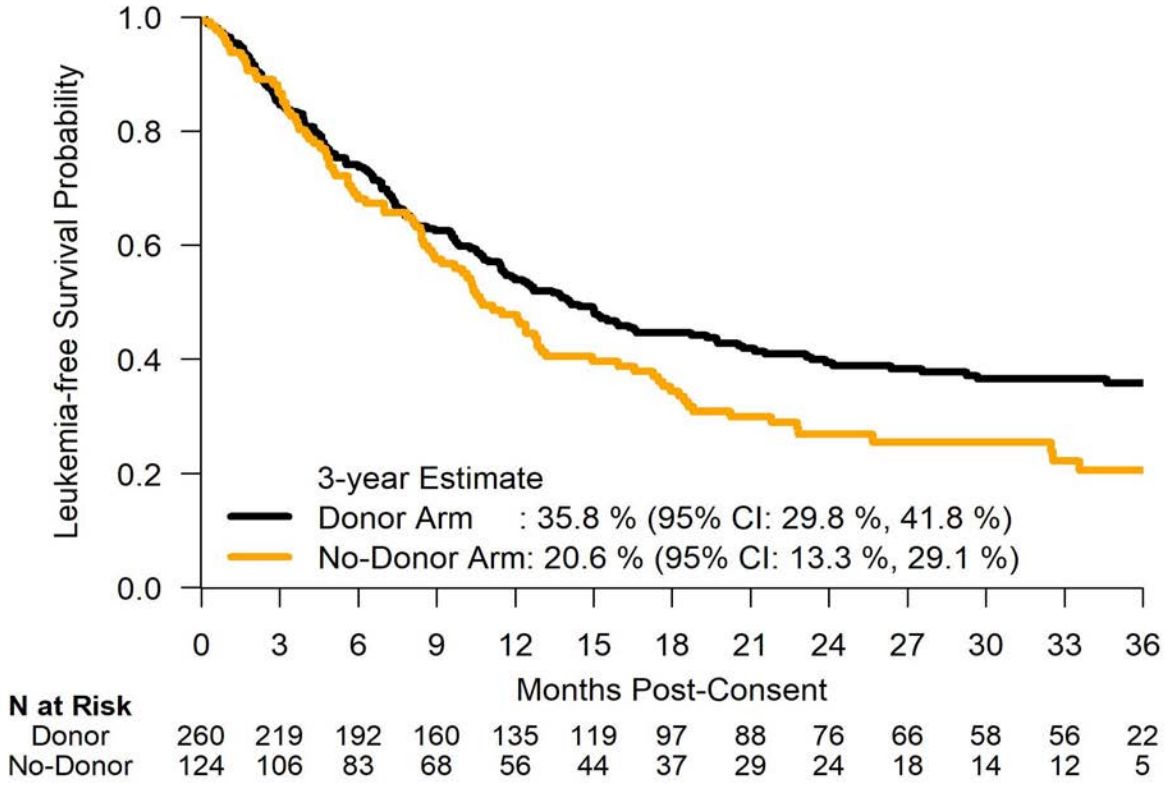
Phase II Study of Enasidenib in *IDH2*-Mutated, Higher Risk MDS

	Response	Arm A (HMA naïve)	Arm B (HMA failure)
	Evaluable (N = 46)	ENA+AZA (N=25)	ENA (N=21)
Overall Response	68%	84%	43%
Complete Remission	24%	24%	24%
Partial Remission	7%	8%	5%
Marrow CR	26%	44%	5%
Hematologic Improvement	9%	8%	10%

Venugopal S, et al. *J Clin Oncol* 2021; 39(15): abstract 7010

Reduced Intensity Allo HSCT vs Hypomethylating Agent or BSC in Patients Ages 50-75 Years with Advanced MDS: ITT

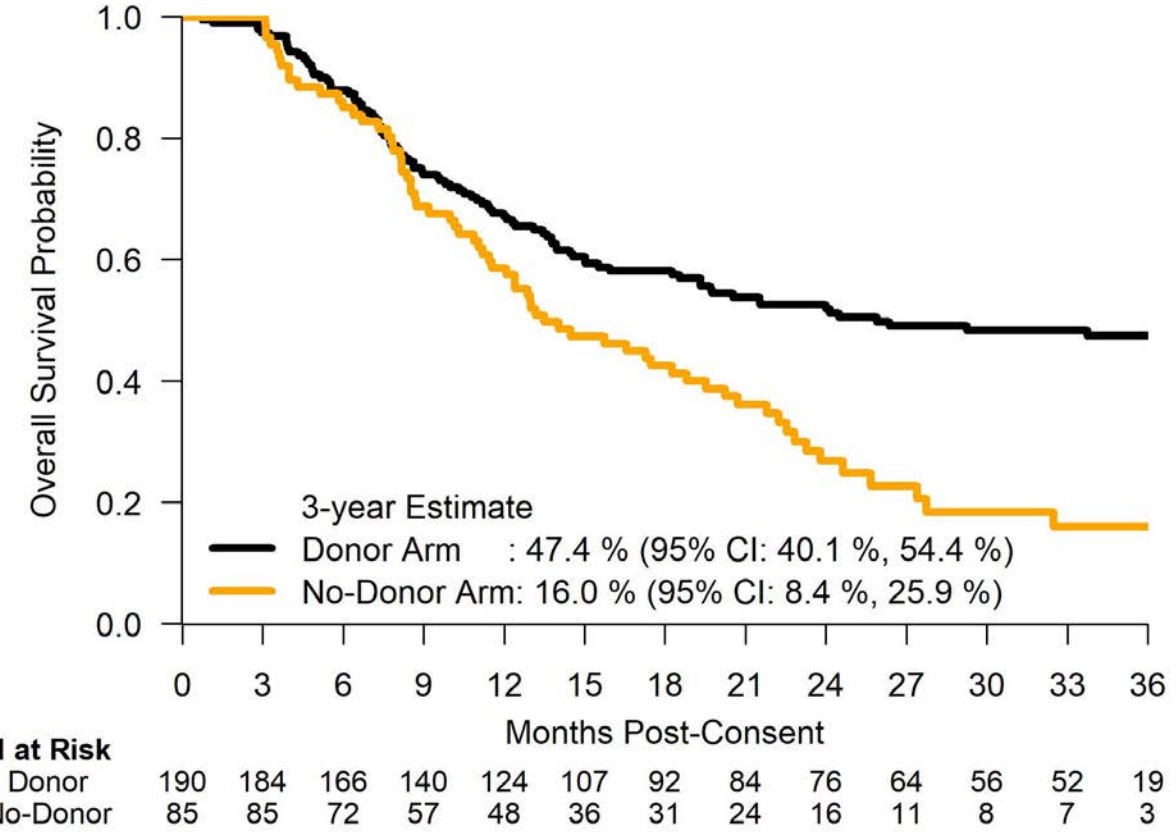


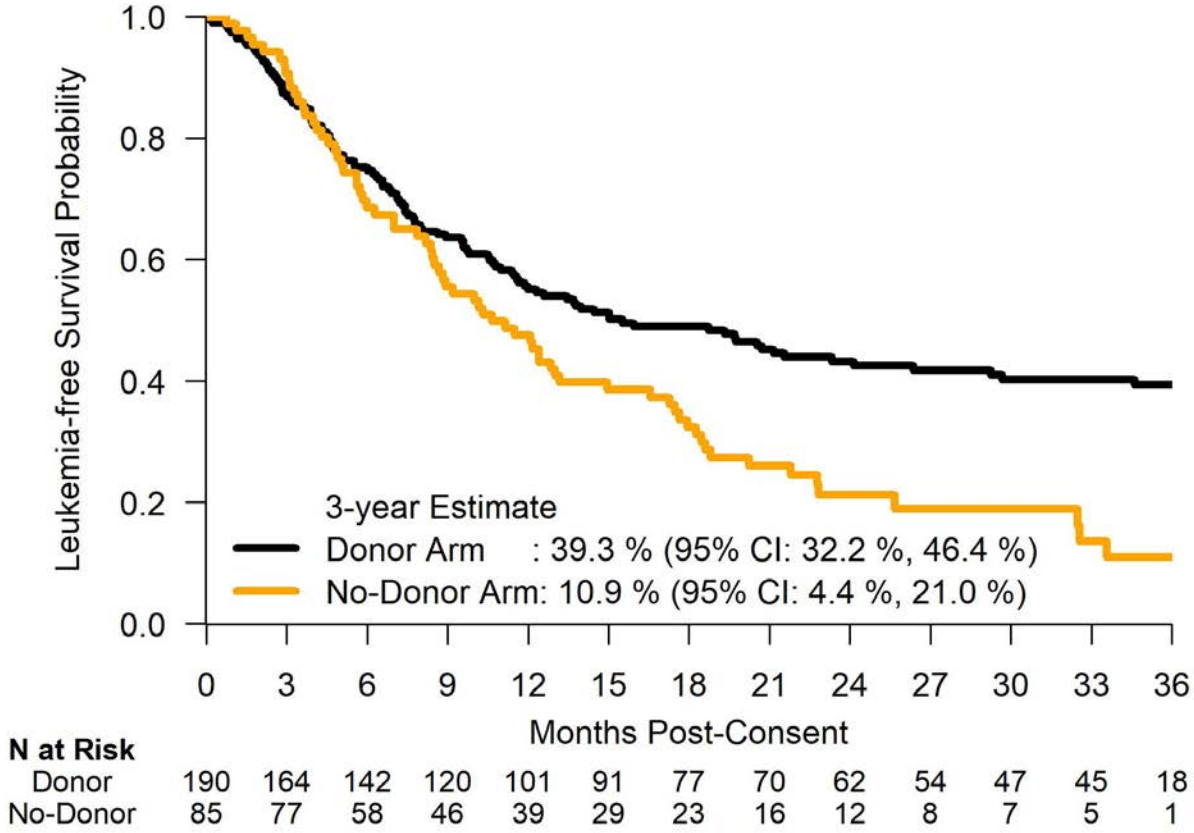


Nakamura R, et al. (BMT CTN 1102). ASH 2020

Reduced Intensity Allo HSCT vs Hypomethylating Agent or BSC in Patients Ages 50-75 Years with Advanced MDS: As Treated

Non-Compliance Rate 26.3%





Nakamura R, et al. (BMT CTN 1102). ASH 2020

Current and Future MDS Therapy

- Goal of therapy is tailored to the patient and to disease risk
- Therapies for lower risk disease generally aim to improve blood counts and quality of life.
- Therapies for higher risk disease aim to improve quality of life and life expectancy.
- Treatment with hematopoietic growth factors and hypomethylating agents alone is frequently disappointing.
- MDS patients should be encouraged to participate in clinical trials evaluating agents that target the pathogenic drivers and the immune environment.