2026

DEBATES AND DIDACTICS in Hematology and Oncology

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Disclosures

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The Role of BCL-2 Inhibitors in the Treatment of Higher-Risk MDS

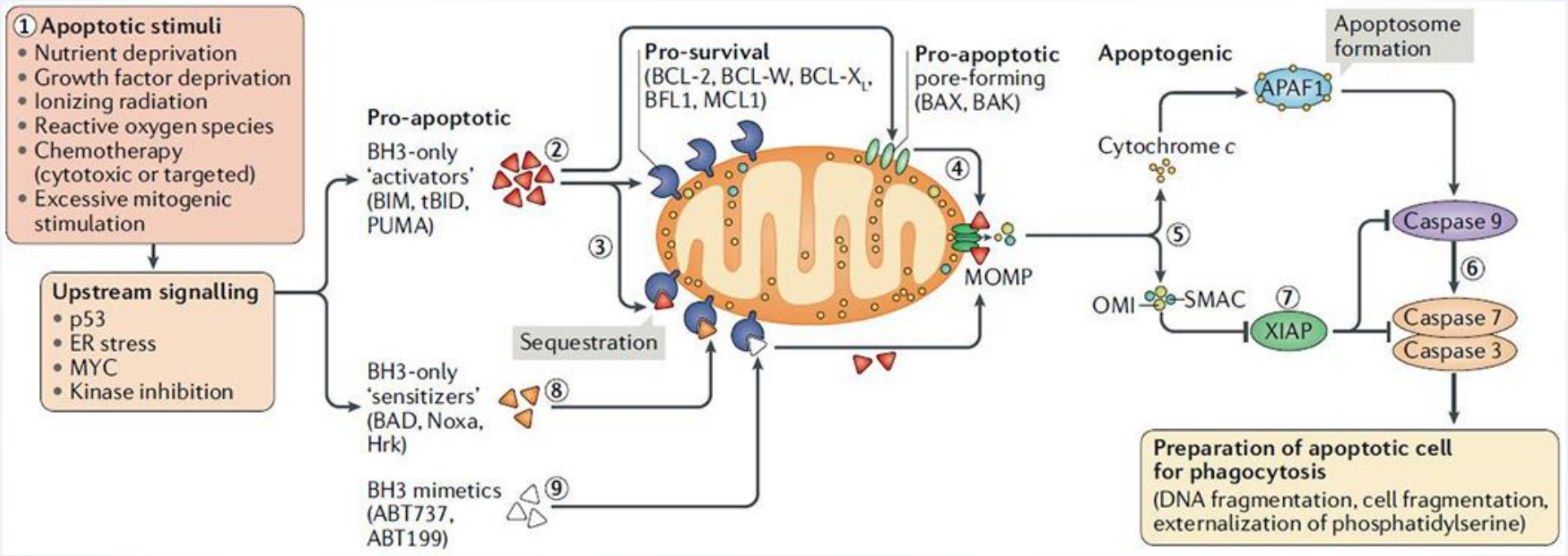
Michael J. Hochman, MD

Assistant Professor of Hematology

Winship Cancer Institute of Emory University

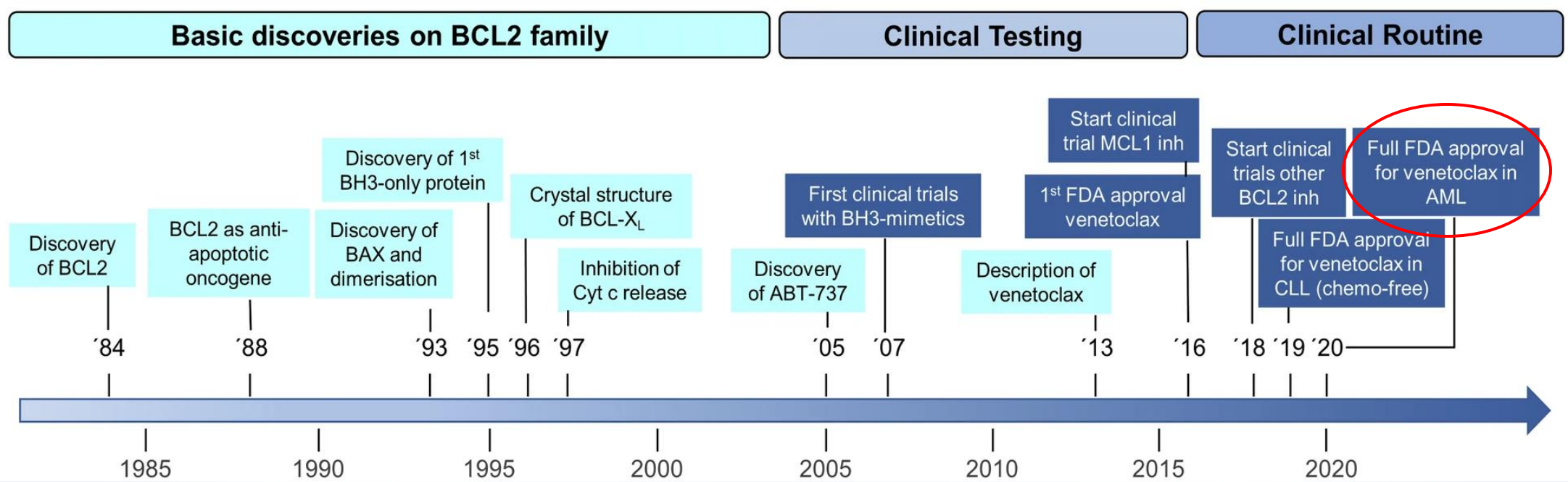
Thursday, July 23rd

B-Cell Lymphoma (BCL)-2 is a Pro-Survival BH3 Peptide



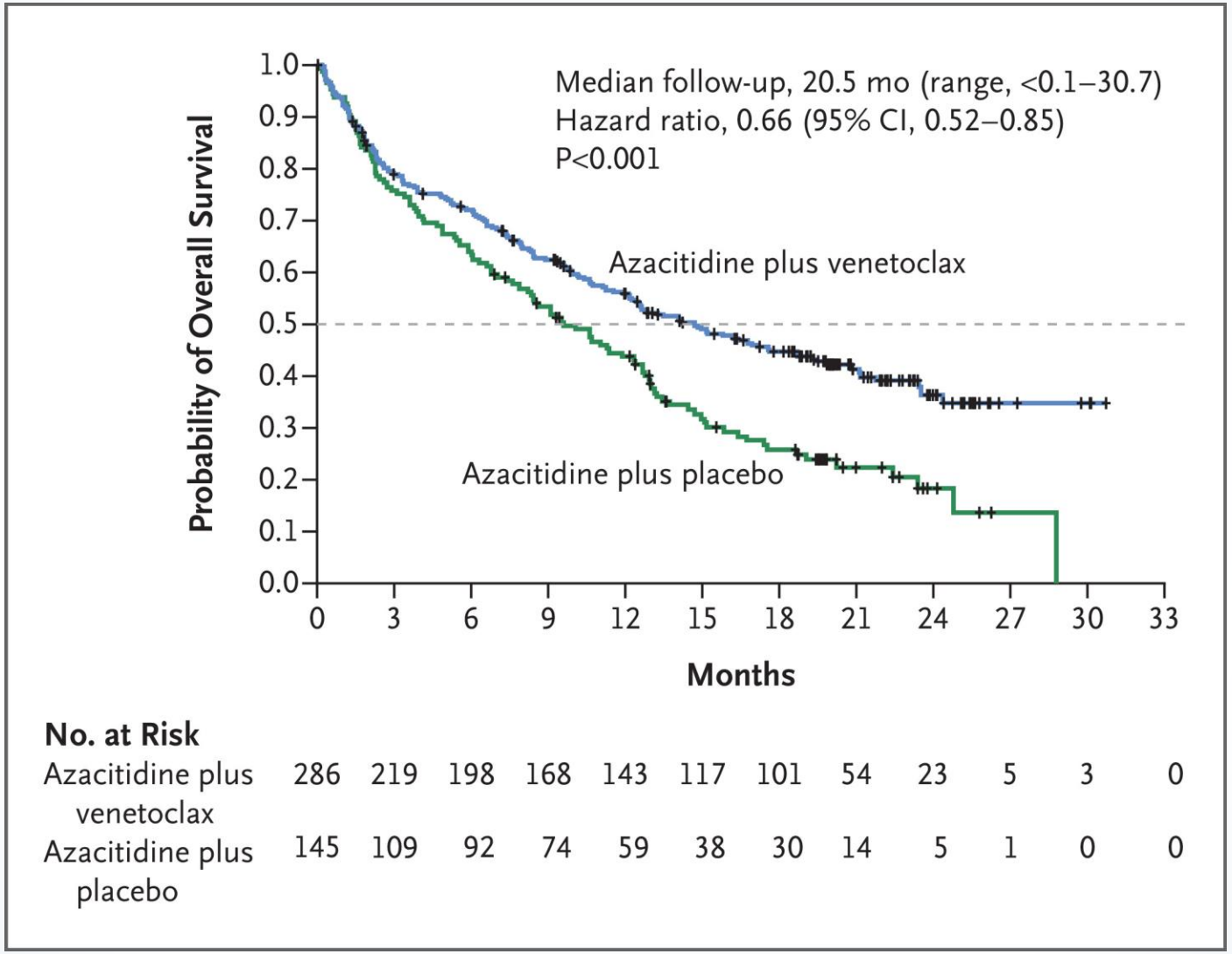
Singh R, Letai A, Sarosiek K. *Nat Rev Mol Cell Biol*. 2019. doi:10.1038/s41580-018-0089-8

BCL-2 Inhibition Permits Triggering of Apoptosis in Myeloblasts



Vogler, M., Braun, Y., Smith, V.M. et al. *Sig Transduct Target Ther* 2025. https://doi-org.proxy.library.emory.edu/10.1038/s41392-025-02176-0

Azacitidine plus Venetoclax Prolongs Survival in Acute Myeloid Leukemia

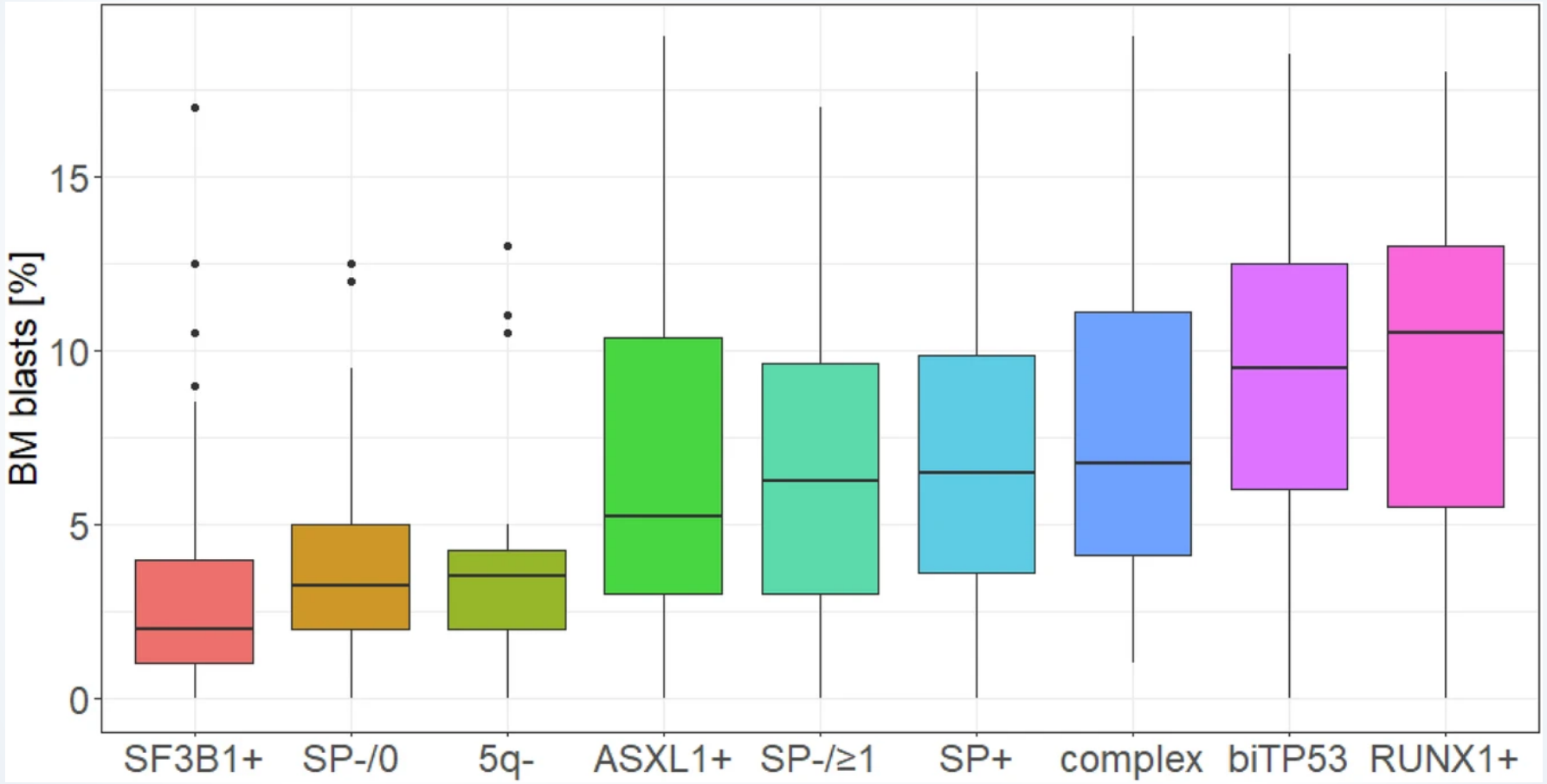


DiNardo CD, Jonas BA, Pullarkat V, et al. *N Engl J Med*. 2020. doi:10.1056/NEJMoa2012971

Trial name	Phase	Investigational arm	Control arm*	Patient population	Eligibility	Primary endpoint	Results of primary endpoint	Secondary endpoint	Reference #
SWOG S1117	2	azacitidine + lenalidomide (10 mg/day days 1–21)	azacitidine	HR-MDS/CMML	Blasts ≥5%; IPSS ≥1.5	↑ ORR 20% (CR/PR/HI)	49% vs 38% ($P = 0.16$)	No improvement in OS	[27]
SWOG S1117	2	azacitidine + vorinostat (300 mg twice daily on days 3–9)	azacitidine	HR-MDS/CMML	Blasts ≥5%; IPSS ≥1.5	↑ ORR 20% (CR/PR/HI)	27% vs 38%; ($P = 0.16$)	11.6 versus 16.7 months ($p=0.74$)	[27]
E1905 Study	2	azacitidine + entinostat (4 mg/m²/day on days 3 and 10)	azacitidine	Therapy-related MDS/AML	Any IPSS	CR, PR, or trilineage HI	17% vs 46%	OS versus 13 months	[28]
FUSION-AML-001 (MDS Cohort)	2	azacitidine + durvalumab (1500 mg IV q 4 weeks)	azacitidine	Int to very high MDS	IPSS-R int to very high	ORR (CR, mCR, HI)	61.9% vs 47.6% ($P = 0.18$)	No Increase PDL1 on BM Blasts	[29]
SUPPORT	3	azacitidine + eltrombopag (200 mg/day, up to 300 mg/day)	azacitidine	Int to HR-MDS	int-1, int-2, high IPSS	Platelet transfusion-free interval	16% vs 31% ($P = 0.001$)	ORR 20% vs 35%	[25]
NCT02610777	2	azacitidine + pevonedistat (20 mg/m² IV days 1,3,5)	azacitidine	HR-MDS/CMML/ oligoblastic AML	IPSS-R int to very high	OS	21.8 vs 19.0 months ($P = 0.334$)	EFS 20.2 vs 14.8 months ($p = 0.045$) for HR-MDS	[34]
NCT03745716	3	azacitidine + eprenetapopt (4.5 g IV days 1–4)	azacitidine	*TP53* mutant HR-MDS	IPSS-R int to very high	CR	34.6% vs 22.4%; $P = 0.13$	NA	NA
PANTHER	3	azacitidine + pevonedistat (20 mg/m² IV days 1,3,5)	azacitidine	HR-MDS/CMML/ oligoblastic AML	IPSS-R int to very high	EFS	17.7 months vs 15.7 months ($P = 0.447$)	OS 21.6 vs17.5 (0.293) in HR-MDS	[26]
STIMULUS-MDS1	2	azacitidine/decitabine + sabatolimab (400 mg day 8 and 22)	azacitidine/ decitabine	Int to very high MDS	IPSS-R int to very high	CR and PFS	PFS 11.1 vs 8.5 months ($P = 0.102$); CR 21.5% vs 17.7% ($P = 0.769$)	Lower risk and <10% blasts with improved PFS	[30]
STIMULUS-MDS2	3	azacitidine + sabatolimab (800 mg day 8)	azacitidine	Int to very high MDS/CMML-2	IPSS-R int to very high	OS			
ENHANCE	3	azacitidine + magrolimab (priming/loading over C1–2; C3+30 mg/kg days 1 and 15)	azacitidine	Int to very high MDS	IPSS-R int to very high	CR and OS			
VERONA	3	azacitidine + venetoclax (400 mg days 1–14)	azacitidine	Int to very high MDS; excludes t-MDS	IPSS-R int to very high	OS			

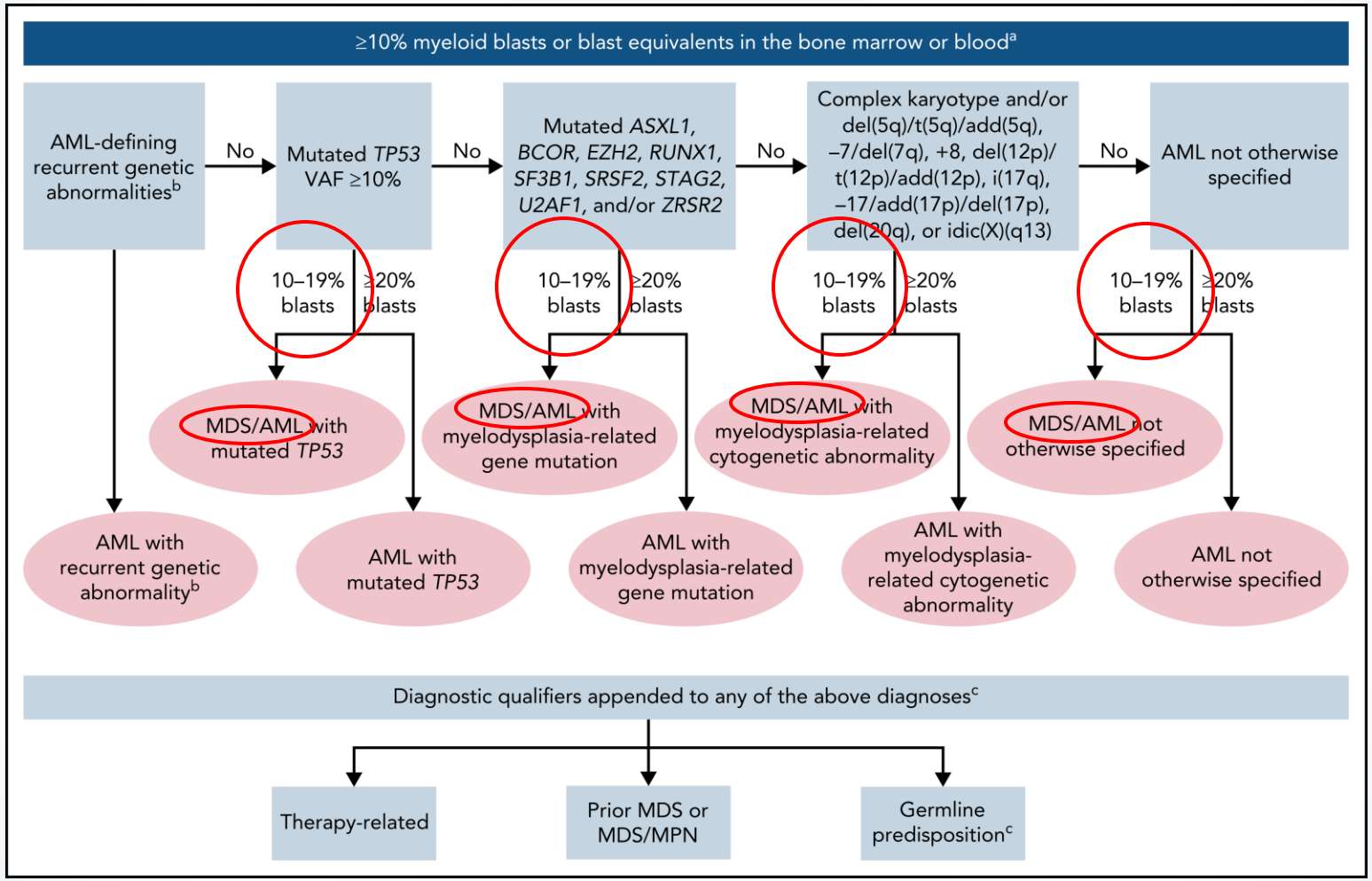
Sallman DA, Xie Z. *Hematology Am Soc Hematol Educ Program*. 2023. doi:10.1182/hematology.2023000421

Bone Marrow Blast Percentage Correlates with MDS Genetic Subgroup Classification



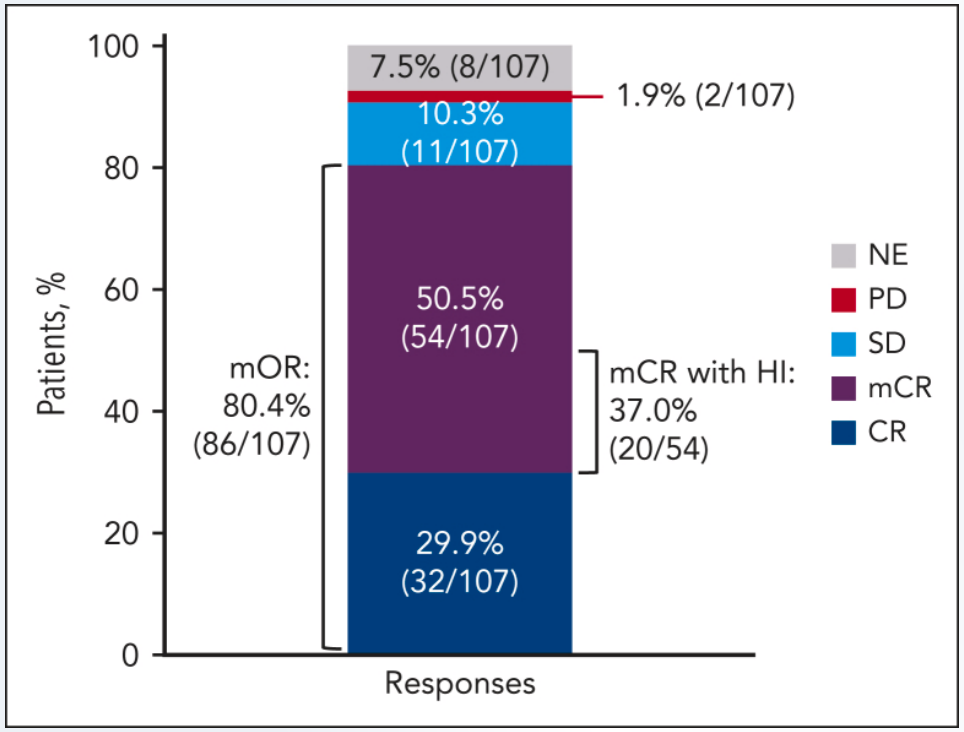
Huber S, Haferlach T, Hutter S, Hoermann G, Kern W, Haferlach C. 2025. doi:10.1038/s41375-024-02484-4

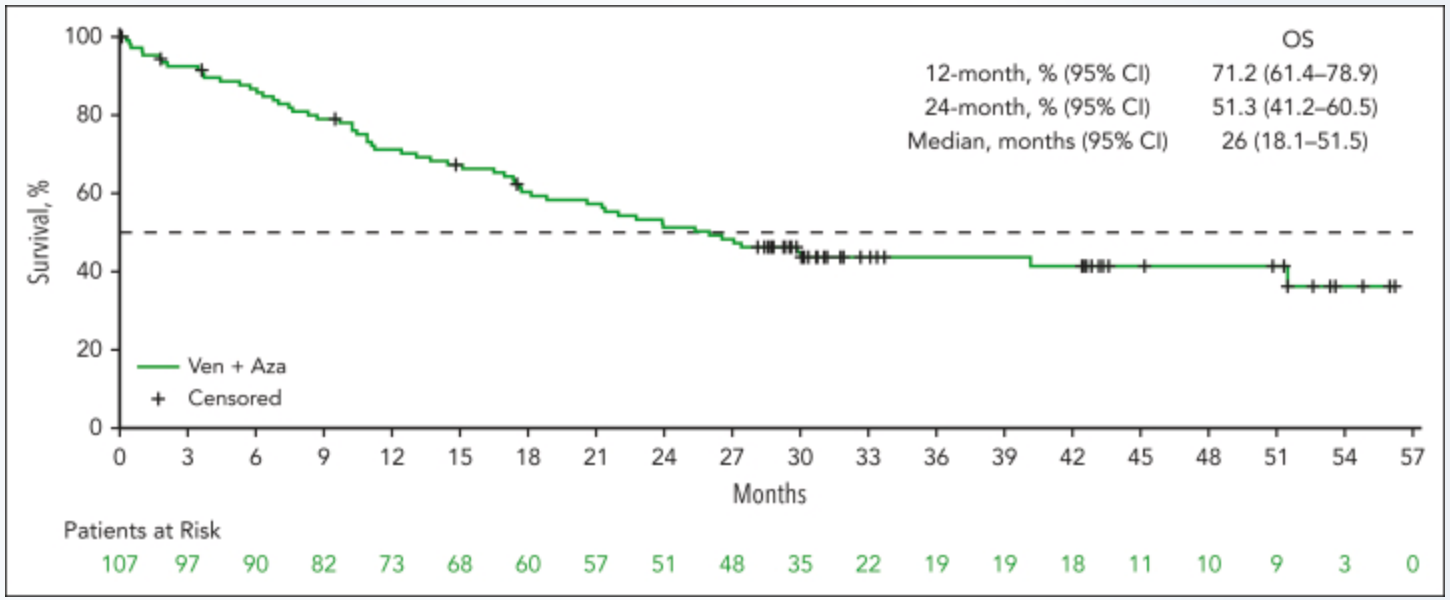
MDS with Excess Blasts-2 is Reclassified as "MDS/AML" per the International Consensus Classification



Arber DA, Orazi A, Hasserjian RP, et al. *Blood*. 2022.
Döhner H, Wei AH, Appelbaum FR et al. *Blood* 2022.

Azacitidine plus Venetoclax Shows Promising Results in Phase 1b Investigation





Garcia JS, Platzbecker U, Odenike O, et al. *Blood*. 2025. doi:10.1182/blood.2024025464

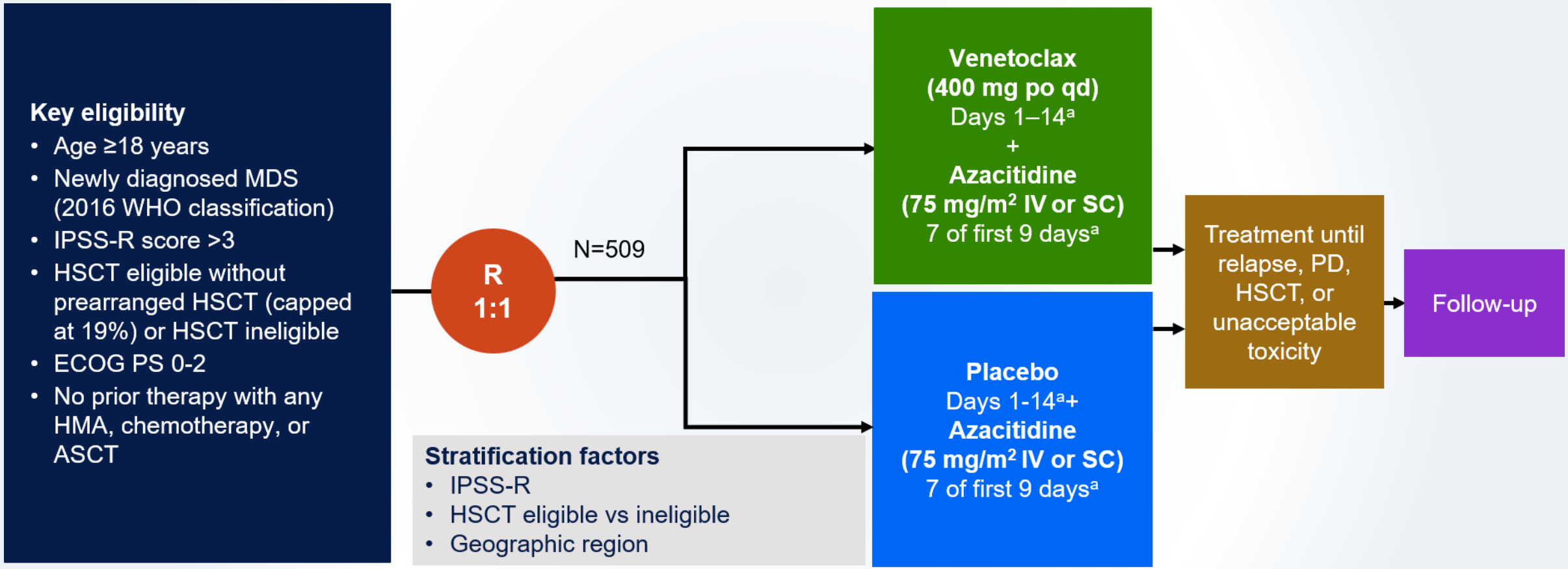
VERONA: Similar Survival Seen with Treatment Using Azacitidine plus Venetoclax vs. Azacitidine plus Placebo in Higher-Risk MDS

	Pbo + Aza (N=253)
	21.68 (17.81–23.79)
	.733–1.126)
	ank[b], *P* value=0.38

[a]Overall survival was defined as the number of months from the date of the first dose of study drug to the date of death. The data were censored at the date the patient was last known to be alive on or before the cutoff date.
[b]Stratified by IPSS-R (intermediate, high, very high) and HSCT eligibility (eligible, ineligible) from IVRS/IWRS. OS, overall survival.

Garcia-Manero et al. SOHO 2025. Slides Courtesy of Jacqueline Garcia, MD.

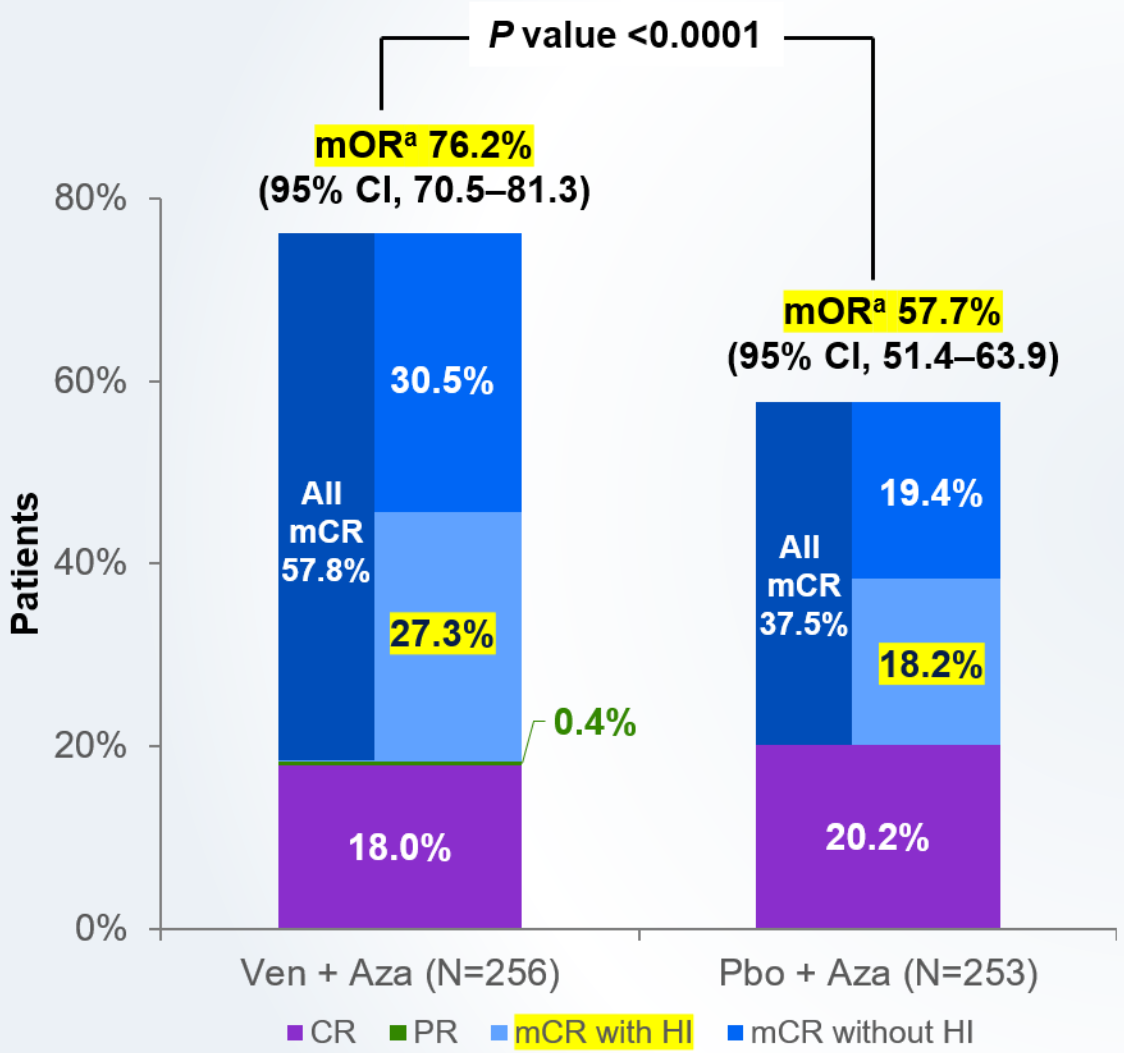
Study Design of VERONA Trial



- **Primary endpoint:** Overall survival
- Key secondary endpoints: mOR (CR + PR + mCR),[b] overall hematologic improvement, complete remission, red blood cell and platelet transfusion independence,[c] PROs, OR (CR + PR), and safety

Garcia-Manero et al. SOHO 2025. Slides Courtesy of Jacqueline Garcia, MD.

Azacitidine + Venetoclax Resulted in Higher Overall Response than Azacitidine + Placebo

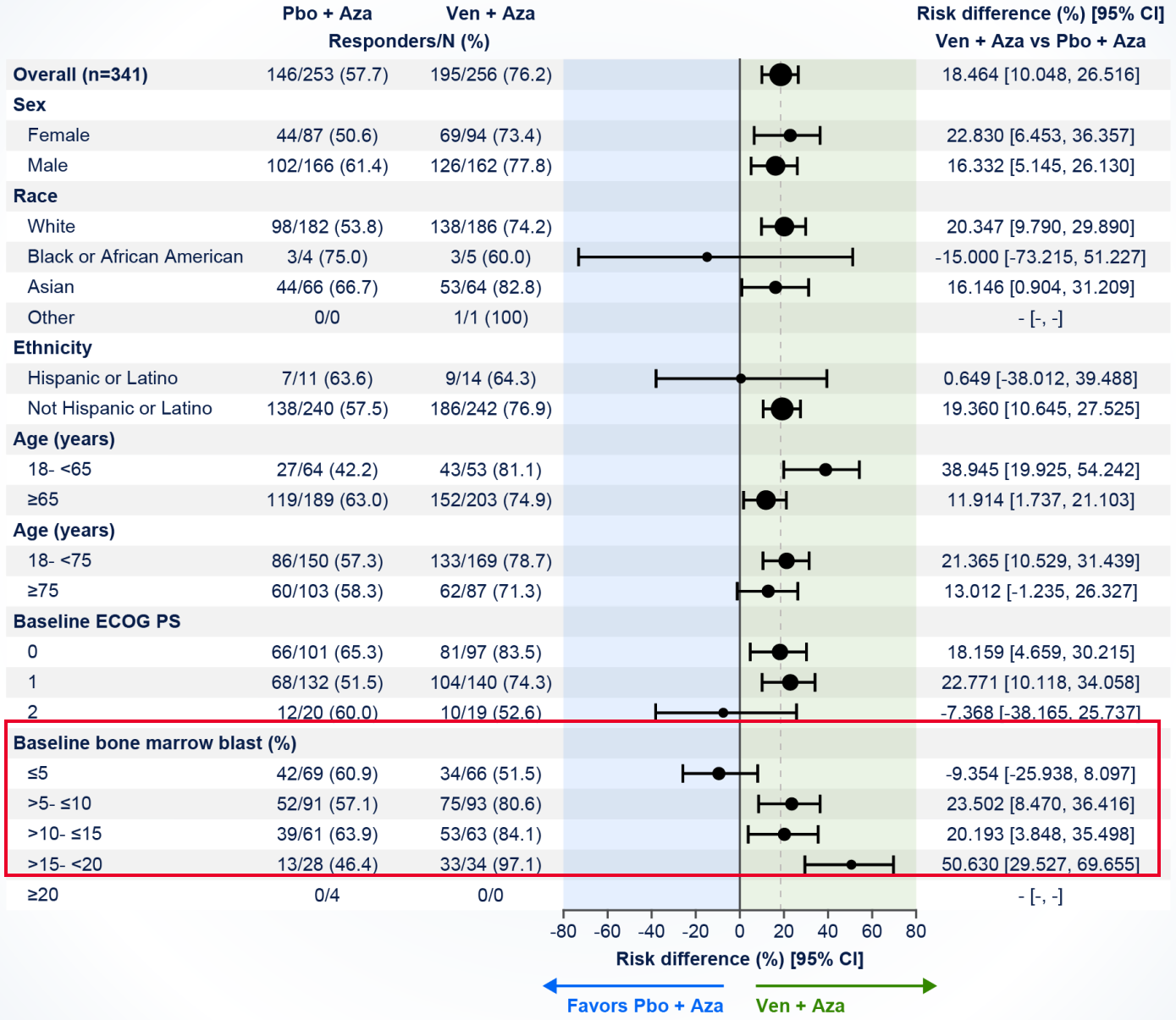


	Ven + Aza (N=256)	Pbo + Aza (N=253)
Overall hematological improvement,[b] % (95% CI)	49.4 (43.0–55.8)	41.2 (35.0–47.6)
P value	0.0723	
Transfusion independence rate,[c] % (95% CI)	55.7 (47.1–64.1)	33.6 (25.7–42.1)
P value	0.0003	
Median duration of transfusion independence,[c] days (range)	183 (56-1396)	294 (59-1408)

All *P* values are nominal. [a]CR+PR+mCR. [b]Based on investigator response assessment; erythroid + platelet + neutrophil responders. [c]Per the modified IWG 2006 criteria; based on patients having red blood cell or platelet transfusion within 8 weeks prior to or on first dose of study drug (red blood cell and/or platelet transfusion dependent at baseline). HI, hematological improvement.

Garcia-Manero et al. SOHO 2025. Slides Courtesy of Jacqueline Garcia, MD.

Response Rate Higher in Patients with MDS with Increased Blasts



	Pbo + Aza Responders/N (%)	Ven + Aza Responders/N (%)	Risk difference (%) [95% CI] Ven + Aza vs Pbo + Aza
Overall (n=341)	146/253 (57.7)	195/256 (76.2)	18.464 [10.048, 26.516]
Sex			
Female	44/87 (50.6)	69/94 (73.4)	22.830 [6.453, 36.357]
Male	102/166 (61.4)	126/162 (77.8)	16.332 [5.145, 26.130]
Race			
White	98/182 (53.8)	138/186 (74.2)	20.347 [9.790, 29.890]
Black or African American	3/4 (75.0)	3/5 (60.0)	-15.000 [-73.215, 51.227]
Asian	44/66 (66.7)	53/64 (82.8)	16.146 [0.904, 31.209]
Other	0/0	1/1 (100)	- [-, -]
Ethnicity			
Hispanic or Latino	7/11 (63.6)	9/14 (64.3)	0.649 [-38.012, 39.488]
Not Hispanic or Latino	138/240 (57.5)	186/242 (76.9)	19.360 [10.645, 27.525]
Age (years)			
18- <65	27/64 (42.2)	43/53 (81.1)	38.945 [19.925, 54.242]
≥65	119/189 (63.0)	152/203 (74.9)	11.914 [1.737, 21.103]
Age (years)			
18- <75	86/150 (57.3)	133/169 (78.7)	21.365 [10.529, 31.439]
≥75	60/103 (58.3)	62/87 (71.3)	13.012 [-1.235, 26.327]
Baseline ECOG PS			
0	66/101 (65.3)	81/97 (83.5)	18.159 [4.659, 30.215]
1	68/132 (51.5)	104/140 (74.3)	22.771 [10.118, 34.058]
2	12/20 (60.0)	10/19 (52.6)	-7.368 [-38.165, 25.737]
Baseline bone marrow blast (%)			
≤5	42/69 (60.9)	34/66 (51.5)	-9.354 [-25.938, 8.097]
>5- ≤10	52/91 (57.1)	75/93 (80.6)	23.502 [8.470, 36.416]
>10- ≤15	39/61 (63.9)	53/63 (84.1)	20.193 [3.848, 35.498]
>15- <20	13/28 (46.4)	33/34 (97.1)	50.630 [29.527, 69.655]
≥20	0/4	0/0	- [-, -]

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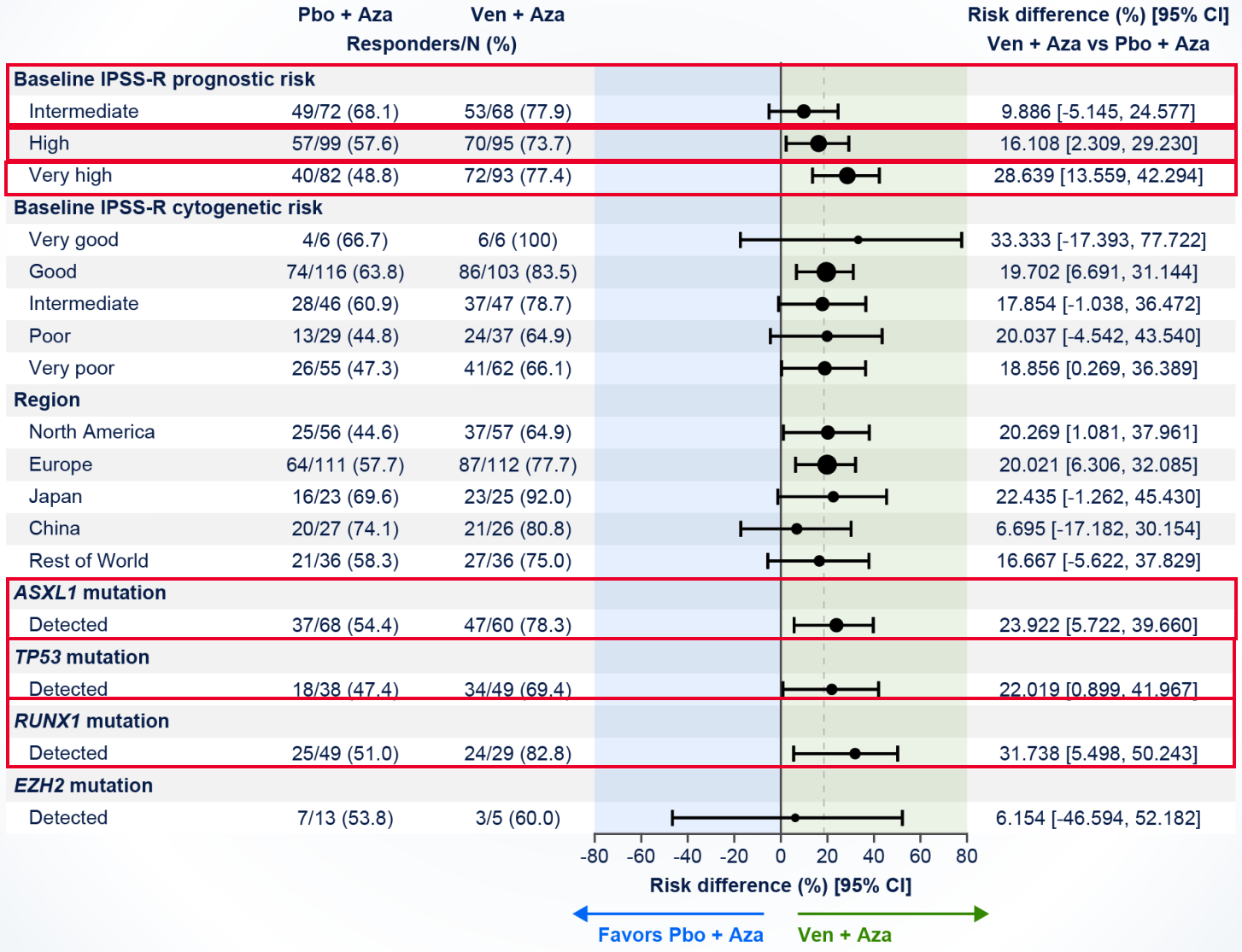
Response Rates Higher in Patients with Mutations in *ASXL1*, *RUNX1*, and *TP53*



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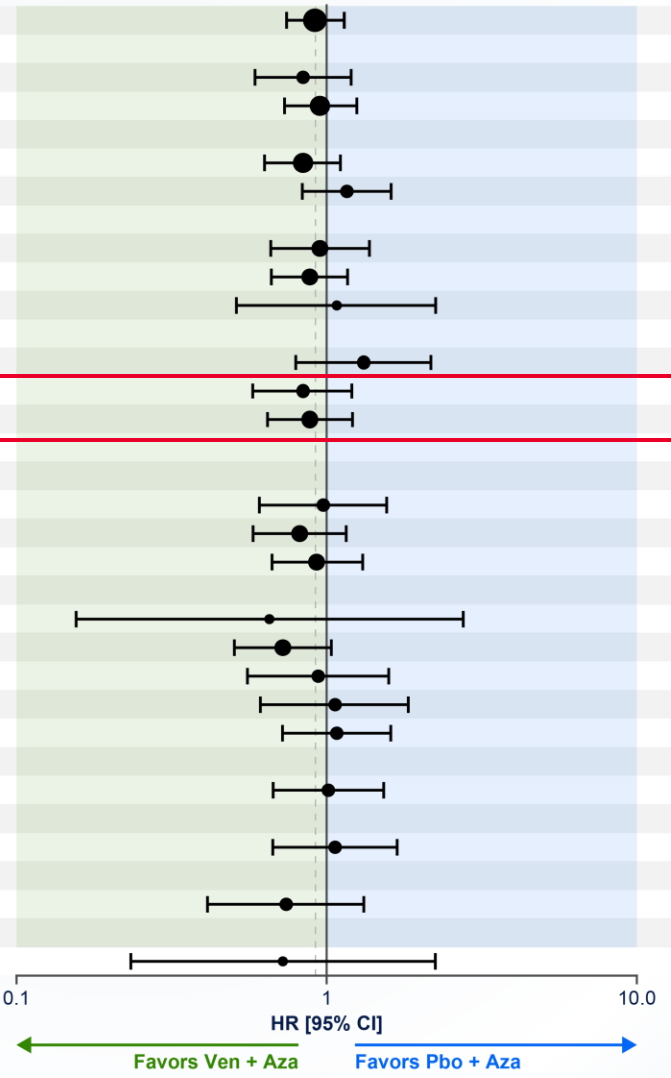
Higher Baseline Bone Marrow Blast Percentage did not Trend with Increased Survival When Treated with Ven + Aza

	Pbo + Aza Events/N (%)	Ven + Aza Events/N (%)	HR [95% CI] Ven + Aza vs Pbo + Aza
Overall	169/253 (66.8)	167/256 (65.2)	0.920 [0.743, 1.139]
Sex			
Female	59/87 (67.8)	63/94 (67.0)	0.839 [0.587, 1.199]
Male	110/166 (66.3)	104/162 (64.2)	0.956 [0.731, 1.250]
Age (years)			
18- <75	95/150 (63.3)	99/169 (58.6)	0.835 [0.630, 1.107]
≥75	74/103 (71.8)	68/87 (78.2)	1.160 [0.834, 1.613]
Baseline ECOG PS			
0	59/101 (58.4)	56/97 (57.7)	0.952 [0.660, 1.373]
1	94/132 (71.2)	98/140 (70.0)	0.880 [0.663, 1.168]
2	16/20 (80.0)	13/19 (68.4)	1.072 [0.512, 2.246]
Baseline bone marrow blast (%)			
< 5%	28/48 (58.3)	34/48 (70.8)	1.313 [0.795, 2.169]
≥ 5% - < 10%	61/93 (65.6)	54/83 (65.1)	0.834 [0.577, 1.205]
≥ 10% - < 20%	76/108 (70.4)	79/125 (63.2)	0.884 [0.645, 1.211]
≥ 20%	4/4 (100)	0/0	- [-, -]
Baseline IPSS-R prognostic risk from EDC			
Intermediate	35/72 (48.6)	34/68 (50.0)	0.973 [0.607, 1.561]
High	70/99 (70.7)	60/95 (63.2)	0.818 [0.579, 1.156]
Very high	64/82 (78.0)	73/93 (78.5)	0.933 [0.667, 1.306]
Baseline IPSS-R cytogenetic risk from EDC			
Very good	5/6 (83.3)	3/6 (50.0)	0.655 [0.156, 2.755]
Good	68/116 (58.6)	53/103 (51.5)	0.722 [0.504, 1.035]
Intermediate	29/46 (63.0)	27/47 (57.4)	0.938 [0.555, 1.585]
Poor	23/29 (79.3)	29/37 (78.4)	1.059 [0.611, 1.833]
Very poor	43/55 (78.2)	54/62 (87.1)	1.077 [0.721, 1.609]
***ASXL1* mutation**			
Detected	50/68 (73.5)	42/60 (70.0)	1.013 [0.672, 1.527]
***TP53* mutation**			
Detected	31/38 (81.6)	44/49 (89.8)	1.064 [0.670, 1.688]
***RUNX1* mutation**			
Detected	36/49 (73.5)	17/29 (58.6)	0.737 [0.413, 1.317]
***EZH2* mutation**			
Detected	13/13 (100)	4/5 (80.0)	0.724 [0.234, 2.240]



Garcia-Manero et al. ASH 2025. Slides Courtesy of Jacqueline Garcia, MD.

Adverse Events Leading to Treatment Discontinuation, Dose Reduction Differed Between Groups

AEs, n (%)	Ven + Aza (N=255)	Pbo + Aza (N=246)
Serious AEs	167 (65.5)	135 (54.9)
AEs leading to		
Treatment discontinuation		
Ven/Pbo	106 (41.6)	136 (55.3)
Aza	106 (41.6)	136 (55.3)
Dose interruption		
Ven/Pbo	201 (78.8)	167 (67.9)
Aza	201 (78.8)	165 (67.1)
Dose reduction		
Ven/Pbo	32 (12.5)	17 (6.9)
Aza	124 (48.6)	67 (27.2)
AEs leading to death[a]	18 (7.1)	20 (8.1)
Disease progression	4 (1.6)	2 (0.8)
Septic shock	3 (1.2)	2 (0.8)
Sepsis	1 (0.4)	2 (0.8)
AML transformation	1 (0.4)	2 (0.8)
Cardiac arrest	1 (0.4)	3 (1.2)
Multiple organ dysfunction syndrome	1 (0.4)	2 (0.8)
Deaths	167 (65.5)	169 (68.6)
Most common cause[b]		
Disease progression	100 (39.2)	100 (40.7)
AEs	27 (10.6)	28 (11.4)
≤30 days after last dose	19 (7.5)	21 (8.5)
>30 days after last dose	147 (57.6)	147 (59.8)

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Patients More Frequently Went to HSCT after Ven + Aza Compared to Placebo + Aza

	Ven + Aza (n=256)	Pbo + Aza (n=253)
HSCT		
Overall HSCT, n (%)[a]	43 (16.8)	33 (13.0)
Median time to HSCT (range), months	5.6 (2.9–18.1)	6.7 (2.2–33.9)
HSCT without intervening therapy, n (%)[b]	39 (15.2)	23 (9.1)
Additional post-study treatment prior to HSCT n (%)[c]	4 (9.3)	10 (30.3)
Venetoclax	0	5 (15.2)
Best response on study treatment prior to HSCT, n (%)		
CR	11 (25.6)	9 (27.3)
mCR	26 (60.5)	11 (33.3)
SD	6 (14.0)	13 (39.4)
Subsequent therapy after study treatment		
All post-study therapy, n (%)	**73 (28.5)**	**98 (38.7)**
Venetoclax	27 (10.5)	53 (20.9)

[a]Includes all patients who reported poststudy HSCT, including those who received other treatments prior to transplant. [b]Includes patients who received HSCT immediately after study treatment. [c]Percentage based on the number of patients who did not go directly to HSCT out of all patients who underwent HSCT.
SD, stable disease.

Garcia-Manero et al. ASH 2025. Slides Courtesy of Jacqueline Garcia, MD.

Why was VERONA a Negative Study?

1. MDS Biology is Inherently Different than AML
2. Inclusion of Patients without Excess Blasts
3. Dose Reductions of Azacitidine Backbone Limited Treatment Effect
4. More Treatment Delays in Venetoclax Arm
5. *TP53*-Mutant MDS was Overrepresented
6. Study Design Factors
7. To Be Determined

Is there a role for venetoclax now in HR-MDS?

2024 European LeukemiaNet: Genetic Risk Classification for Adults with AML Receiving Less-Intensive Therapies

Risk category	Genetic abnormality
Favorable	Mutated *NPM1* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) Mutated *IDH2* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) Mutated *IDH1*∗ (*TP53*^{wt}) Mutated *DDX41*† Other cytogenetic and/or molecular abnormalities‡ (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})
Intermediate	Other cytogenetic and molecular abnormalities‡ (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})
Adverse	Mutated *TP53*

This classification does not apply to patients who have received prior treatment with an HMA.

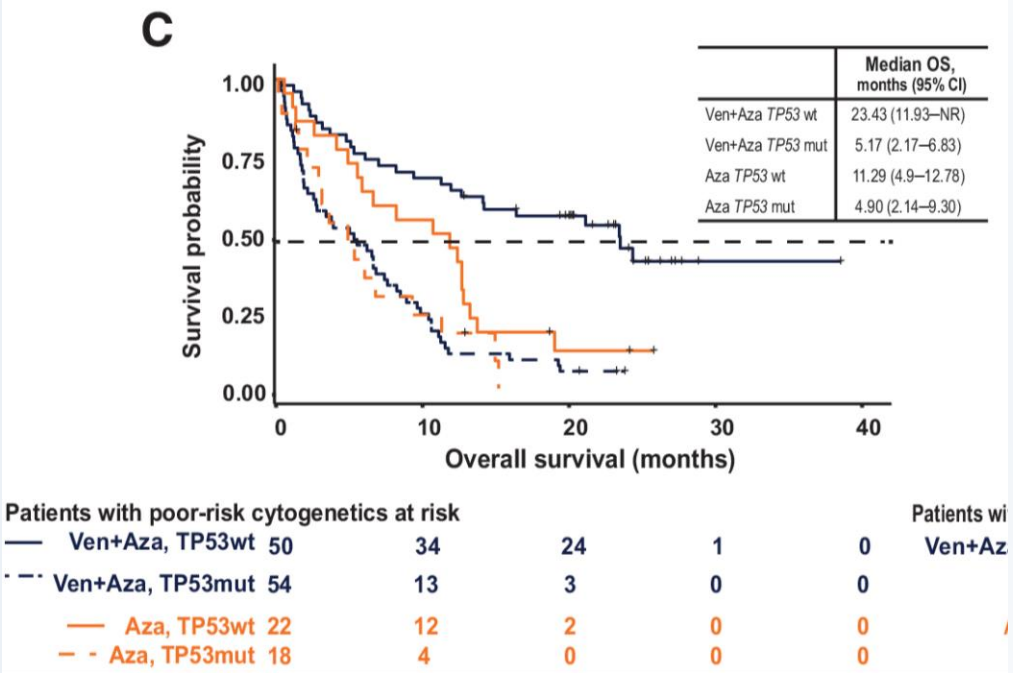
∗Favorable risk applies specifically to patients treated with AZA + IVO, irrespective of the presence of activating signaling gene mutations.

†Identification of a *DDX41* mutation at near-heterozygous frequency should prompt consideration of germ line *DDX41* mutation.

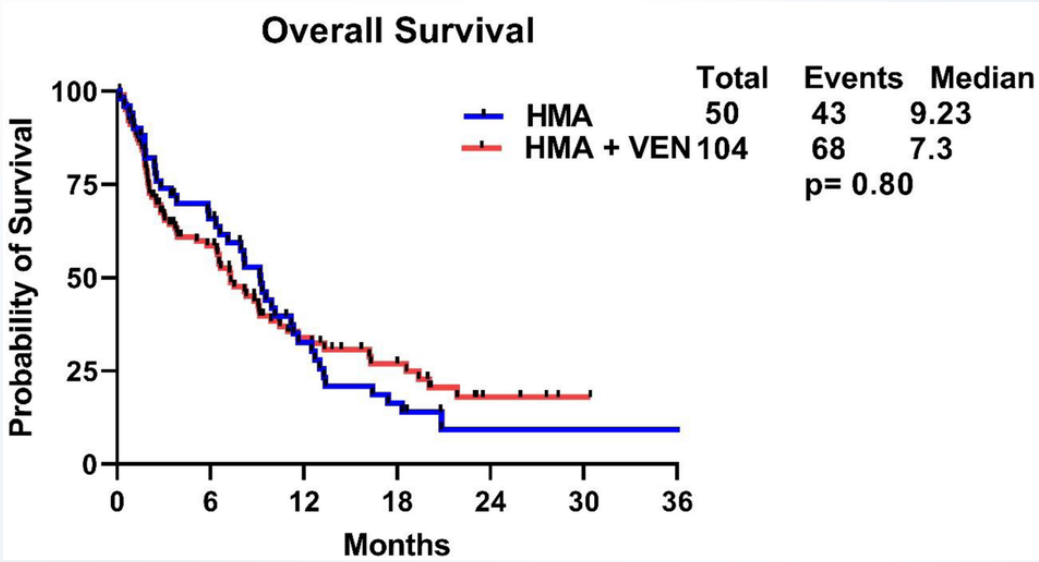
‡For many cytogenetic and molecular abnormalities, single or as coaberrations, no data are currently available; they are tentatively categorized as favorable and intermediate-risk depending on the absence or presence of activating signaling gene mutations.

Döhner H, DiNardo CD, Appelbaum FR, et al. *Blood*. 2024. doi:10.1182/blood.2024025409

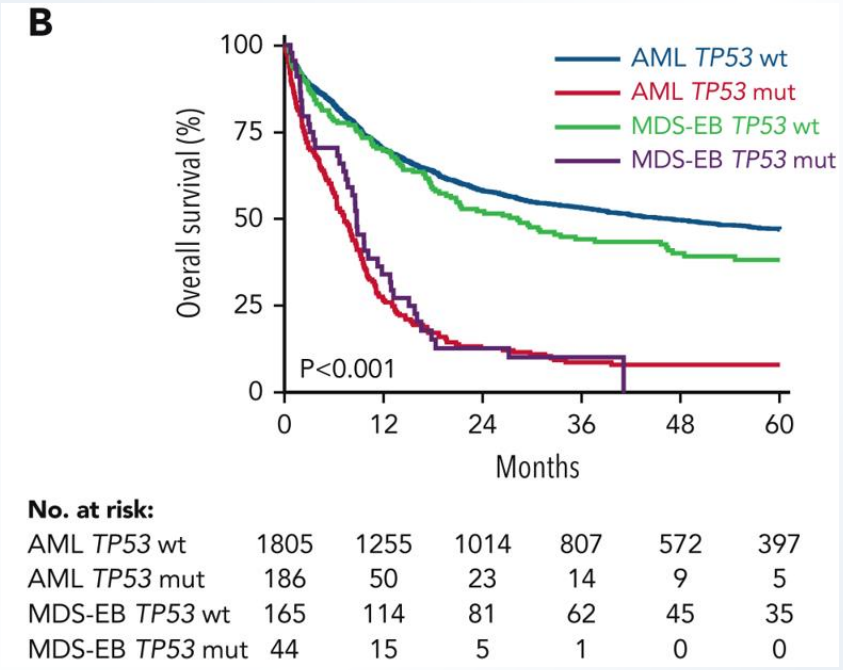
Data Suggests that *TP53*-Mutant AML Does not Have Improved Survival with Venetoclax



Pollyea DA, Pratz KW, Wei AH, Pullarkat V et al. *Clin Cancer Res* 2022 doi: 10.1158/1078-0432.CCR-22-1183.

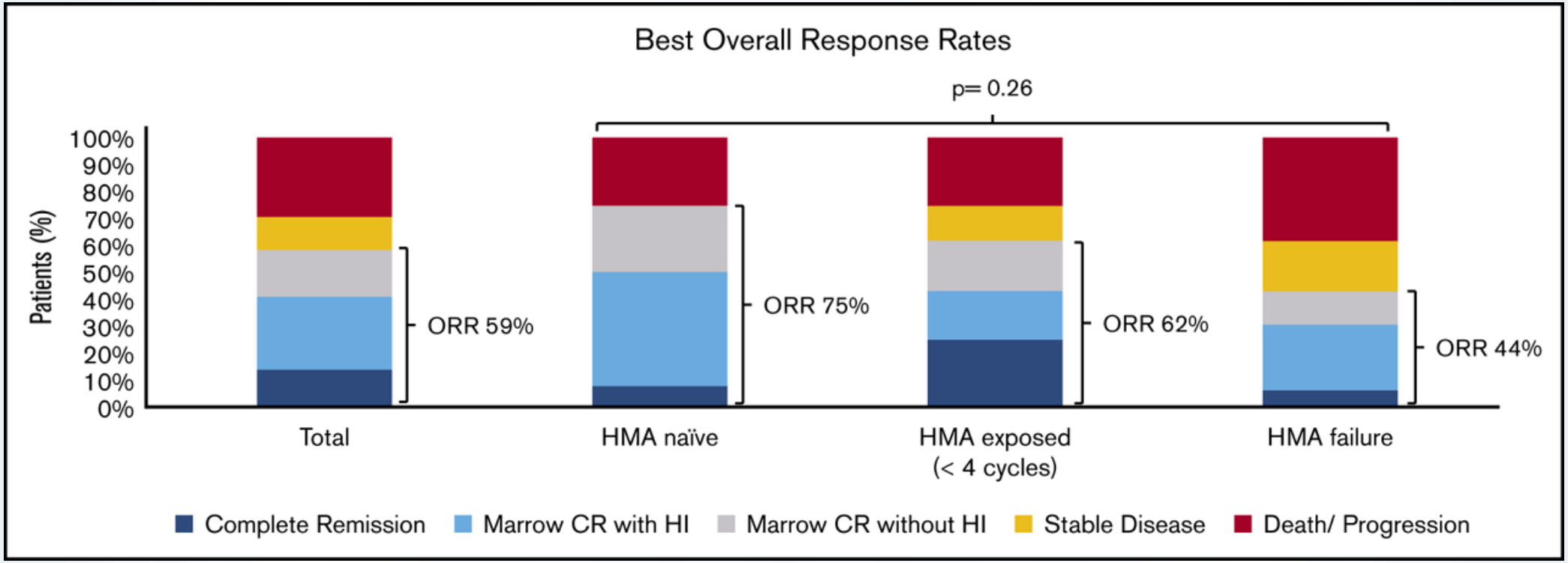


Badar T, Nanaa A, Atallah E, Shallis R et al. *Blood Cancer Journal* 2024 doi: 10.1158/1078-0432.CCR-22-1183.



Grob T, Al Hinai ASA, Sanders MA, et al. *Blood*. 2022. doi:10.1182/blood.2021014472

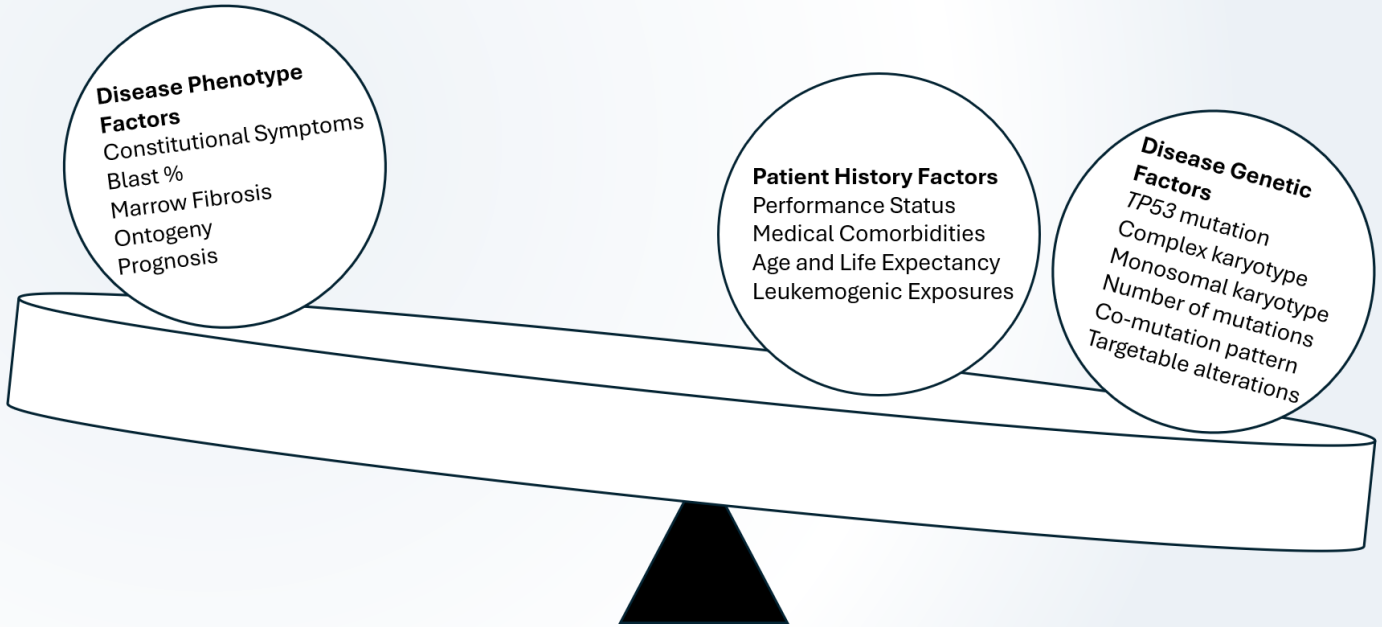
Complete Remission Rate Lower in Patients with HMA Failure MDS



Ball BJ, Famulare CA, Stein EM, et al. *Blood Advances*. 2020. doi:10.1182/bloodadvances.2020001482

Factors to Weigh in Considering Venetoclax in Higher-Risk MDS

1. Clinical Trial Availability
2. Baseline Blast Percentage
3. Prior HMA Exposure
4. Transplant Candidacy
5. *TP53* Mutation, Allelic Status
6. Cytogenetic Risk
7. Signaling Mutations
8. *ASXL1* Mutation Status



Hochman MJ, DeZern AE. ASCO Daily News 2024.

Other BCL-2 Inhibitors in Development for Hematologic Malignancies

Drug Name	Company	Diseases under Study	Unique Features	Studies in Myeloid Neoplasms
Sonrotoclax / BGB11417	BeOne Medicines	CLL/SLL MCL WM	Binds BCL-2 with higher affinity than VEN Can inhibit G101V BCL-2 variant	Phase 1b/2 BGB-11417-103 (NCT04771130)
Lisfatoclax/ APG-2575	Ascentage Pharma Group	CLL/SLL AML, MDS	Less DDIs and faster cellular uptake than VEN, some evidence of activity in VEN-resistant MN	Phase 3 (Registrational) “GLORA-4” (NCT06641414)
Lacutoclax / LP-108	Newave Pharmaceuticals	CLL/SLL AML, MDS, CMML	Comparable or more potent BCL-2 inhibition than VEN	Phase 1 Monotherapy and combo (NCT04139434)
TQB3909	Chia Tai Tianqing Pharmaceutical Group	AML, MF NHL, MCL Breast Cancer		Phase 1b/2 TQB3909-Ib/II-03 (NCT07011186)

Adopted from Vogler, M., Braun, Y., Smith, V.M. et al. *Sig Transduct Target Ther* 2025. https://doi-org.proxy.library.emory.edu/10.1038/s41392-025-02176-0

Parting Thoughts on Role of BCL-2i in HR-MDS

1. VERONA failed to meet its primary endpoint of improved overall survival for AZA/VEN versus AZA in HR-MDS.
2. VERONA showed increased ORR in patients with increased blasts (especially if >10-15%) and specific mutations (*ASXL1*, *RUNX1*).
3. Patients with *TP53*-mutant HR-MDS (especially biallelic hits) are least likely to benefit from VEN.
4. Patients with increased blasts are most likely to benefit from venetoclax in terms of treatment response.
5. Patients with HR-MDS who are not transplant candidates should be prioritized for clinical trials.
6. Venetoclax may be most reasonable in patients who need blast clearance prior to allogeneic stem cell transplant.
7. **Integrating patient- and disease-related factors to make shared decisions with patients is critical.**

Q&A