

# Higher-Risk MDS: Treatment Landscape in 2026

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# Disclosures

I disclose the following financial relationship(s):

- Agios, Advisory Board or Panel,
- Servier, Advisory Board or panel
- Jazz, Grants/Research Support
- Incyte, Speaker's Bureau
- Novartis Advisory Board or Panel,
- Abbvie, Advisory Board of Panel,
- Intellia – Advisory Board or Panel
- BMS – Advisory Board or Panel
- Janssen – Steering Committee/Advisory Board
- Curis – Advisory Board or Panel
- Shattuck Labs – Advisory Board or Panel
- Aprea – Research Support
- Gilead – Advisory Board or Panel, Steering Committee
- Syros – Advisory Board or Panel
- Syndax – Consulting
- Akesobio – Consulting



**Selected historical RCTs**

- AZA+Lenalidomide vs. AZA+ Vorinostat vs. AZA (SWOG S1117)
- AZA+ Durvalumab vs. AZA
- AZA+ Eltrombopag vs. AZA
- AZA + Pevonedistat vs. AZA (PANTHER)
- AZA+ APR-246 vs. AZA
- AZA+ Sabatolimab vs. AZA
- AZA vs. Conventional care

**MDS classifications:**

- WHO (prior versions)
- WHO (2022)
- ICC (2022)

**Risk stratification models:**

- IPSS (1997)
- IPSS-R (2002)
- IPSS-M (2022)

**MDS IWG response criteria:**

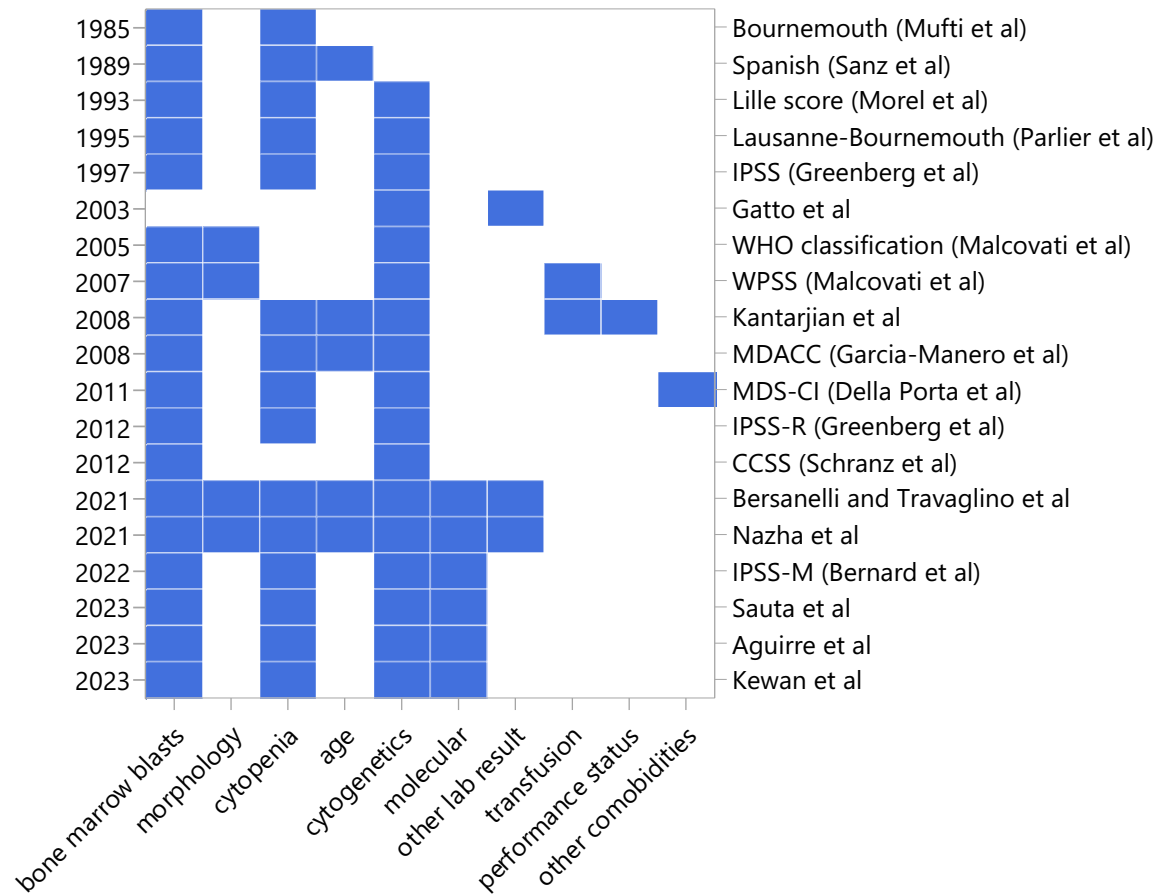
- 2000
- 2006 for HR-MDS
- 2018 for LR-MDS
- 2023 for HR MDS

**Phase 3 RCTs:**

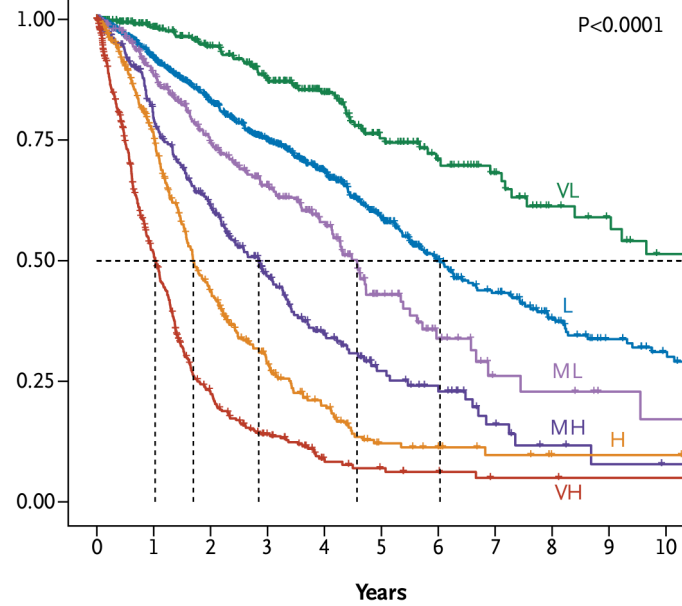
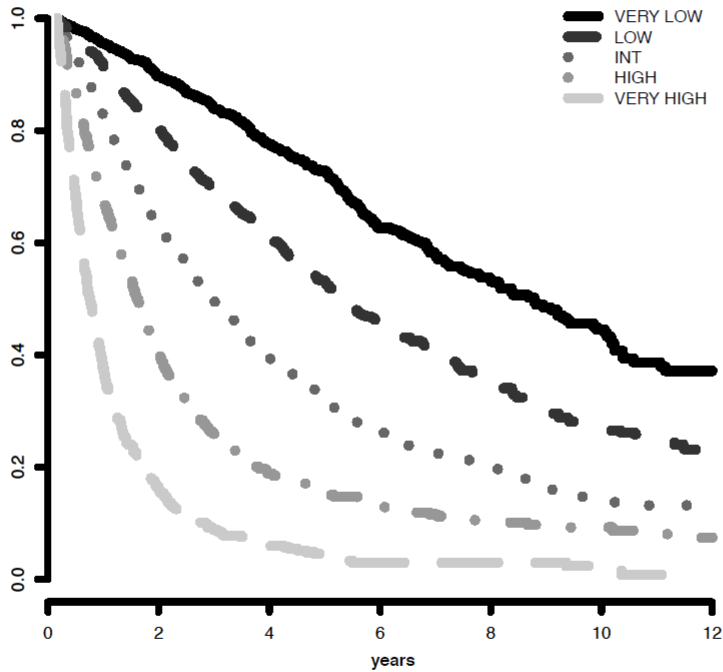
- AZA+Venetoclax
- AZA+ ~~Sabatolimab~~
- AZA+ ~~Magrolimab~~
- AZA+ ~~Tarlatamab~~

Two decades history of HR-MDS

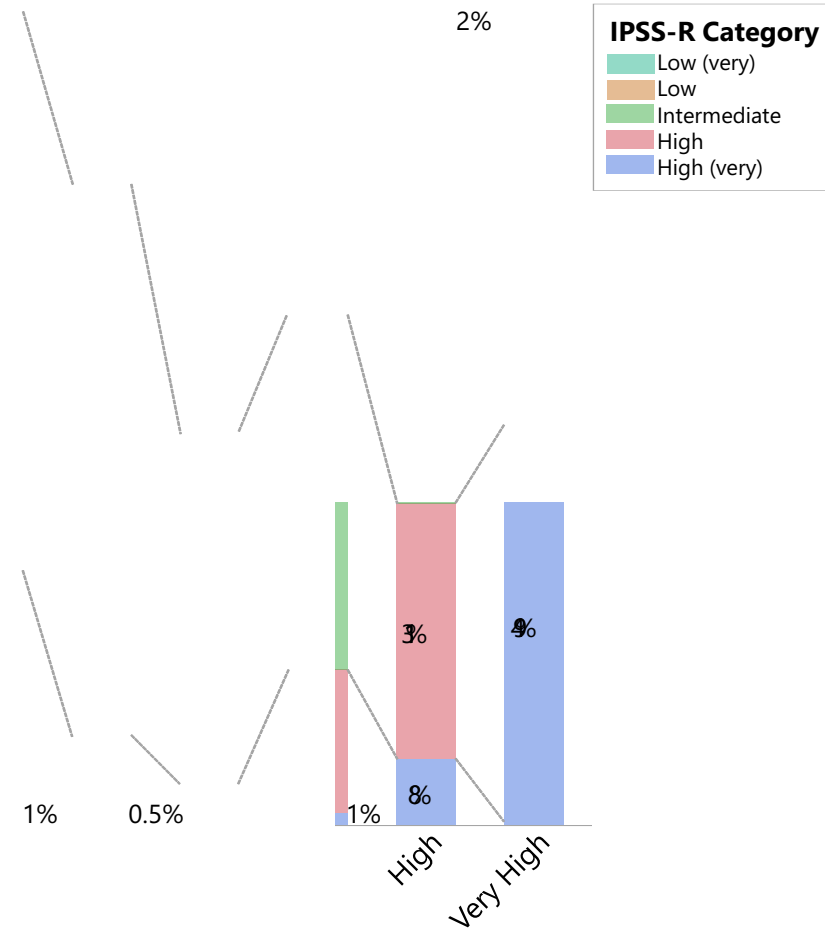
# Prognostic Models in MDS



# IPSSM Reclassifies a Significant Proportion of Patients



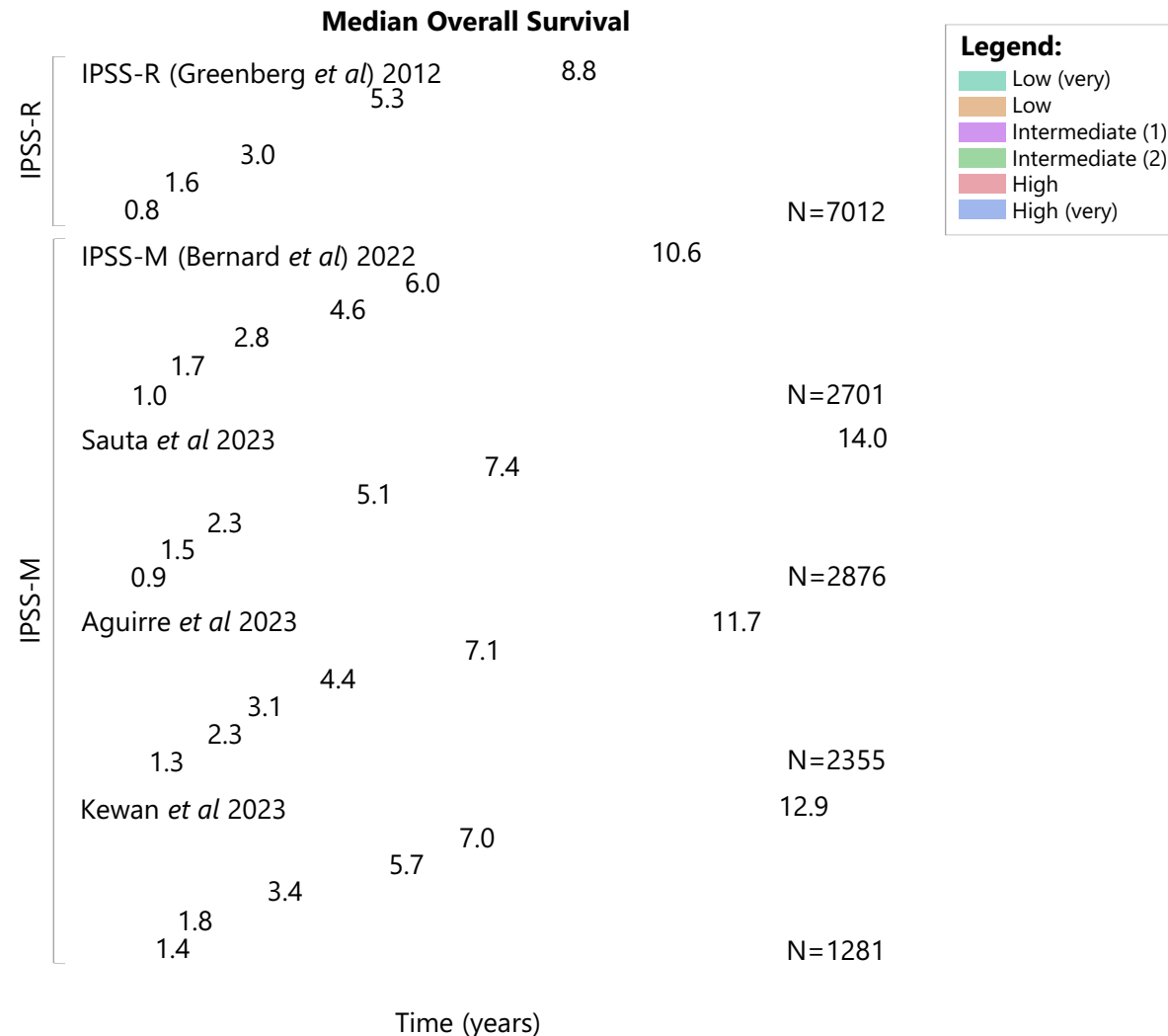
Prior IPSS-R Classification



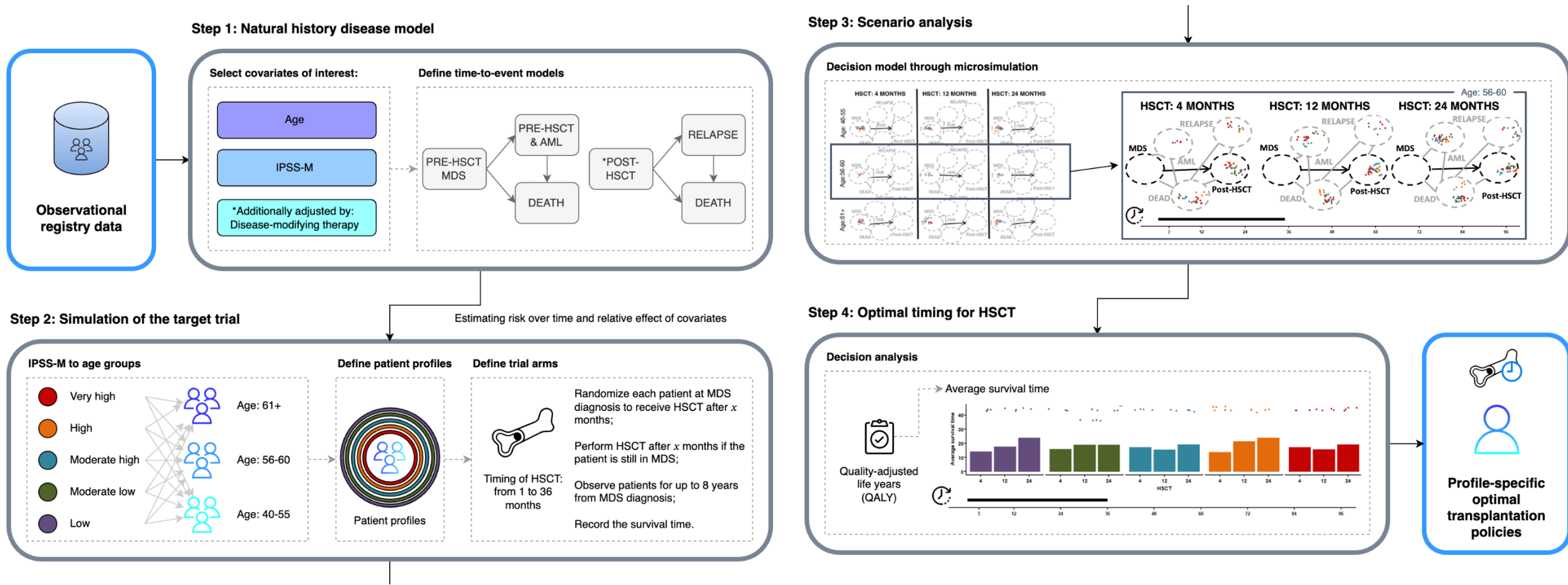
IPSS-M Classification

<https://mds-risk-model.com/> and free app  
C-index improved by 5%

# IPSS-M has been well Validated by Multiple Groups

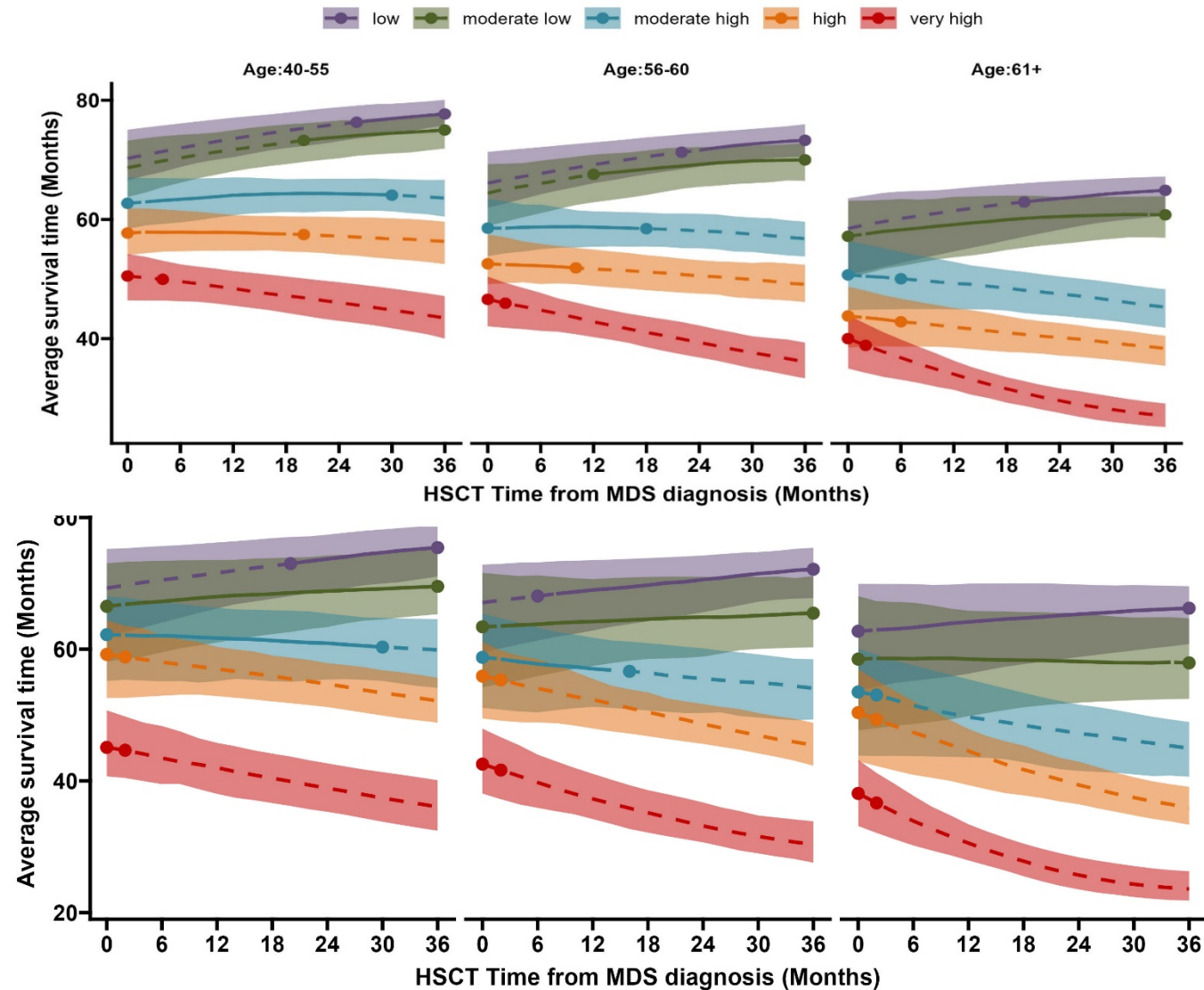


# Decision Support System to define optimal timing of HSCT in patients with MDS stratified according to IPSS-M criteria

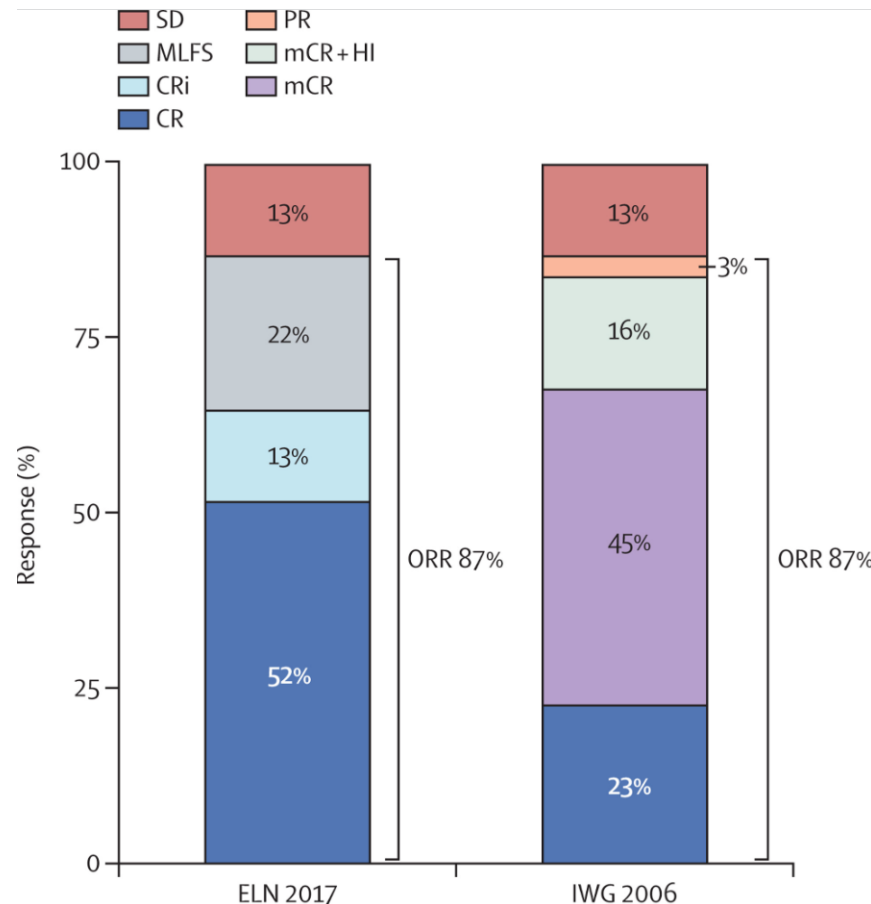


# IPSS-M Higher Risk MDS Patients benefit from an Early Transplant Approach

- 13% of patient's early transplant by IPSS-R benefit from a delayed strategy
- 32% of delayed transplant by IPSS-R would benefit from early transplant
- Ultimately both result in a significant gain of life expectancy (restricted mean survival time;  $P=0.001$ )



# CPX-351 for Frontline Treatment of HR-MDS



Parallel Study in US with similar data (Jacoby M et al., ASH 2021, manuscript in preparation)

Azacitidine outcomes show equivalence with CR/CRh (Brunner A et al., Blood Cancer J 2022)

# Updated IWG Response Criteria

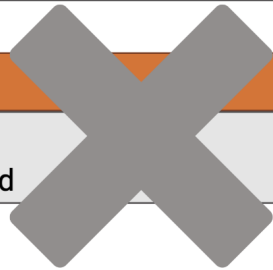
## IWG 2006 HR MDS

### CR

- BM:<5%
- Blood count parameters all met: ANC $\geq$ 1X10<sup>9</sup>/L; Hb $\geq$ 11g/dL; PLT $\geq$ 100X10<sup>9</sup>/L

### Marrow CR

- BM:<5%
- No blood count improvement required



## IWG 2023 HR MDS

### CR

- BM:<5%
- Blood count parameters all met: ANC $\geq$ 1X10<sup>9</sup>/L; Hb $\geq$ 10g/dL; PLT $\geq$ 100X10<sup>9</sup>/L

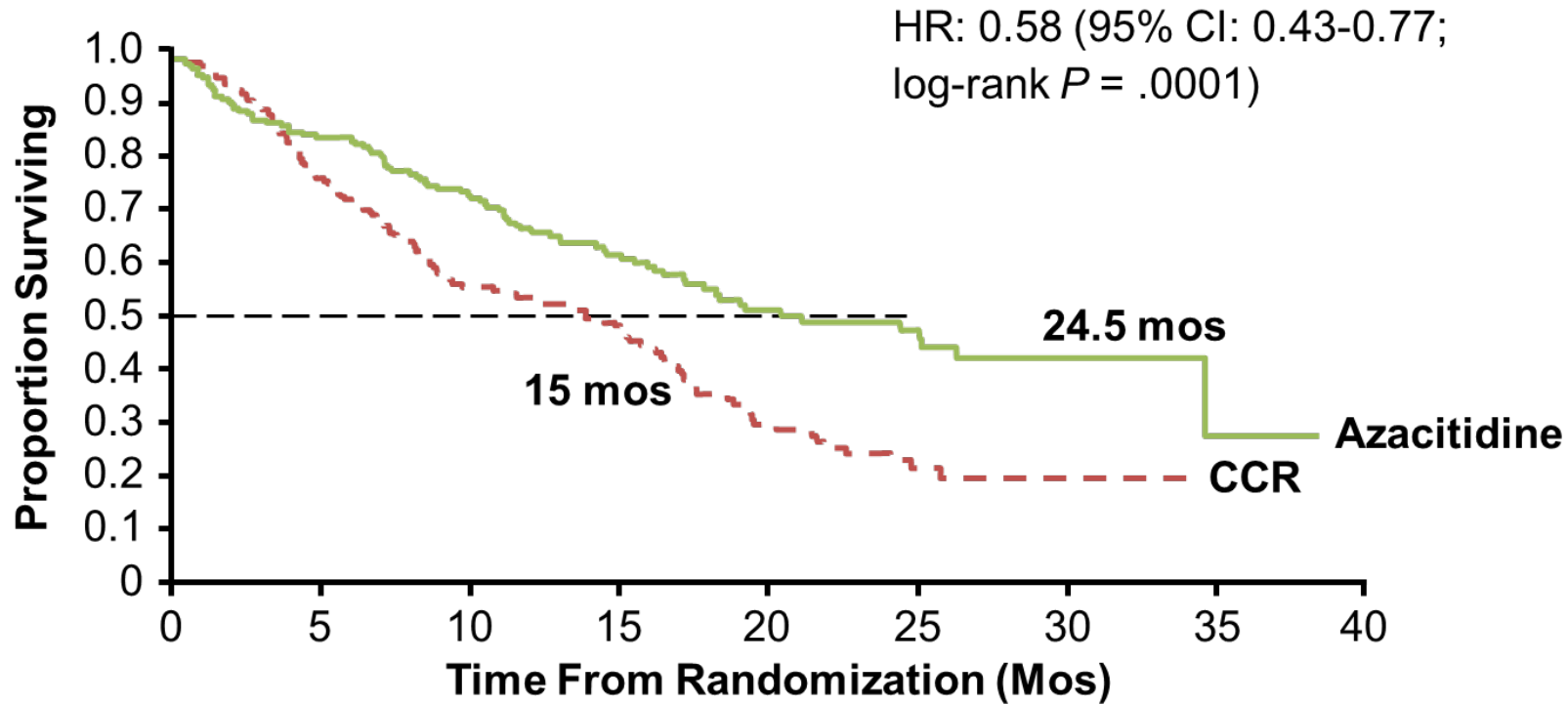
### CR<sub>L</sub> = CR<sub>uni</sub> + CR<sub>bi</sub>

- BM blasts<5%
- CR<sub>uni</sub>: only 1 PB parameter met or CR<sub>bi</sub>: 2 PB parameters met

### CRh

- BM blasts<5%
- No Hb threshold required, PLT $\geq$ 50X10<sup>9</sup>/L; ANC $\geq$ 0.5X10<sup>9</sup>/L

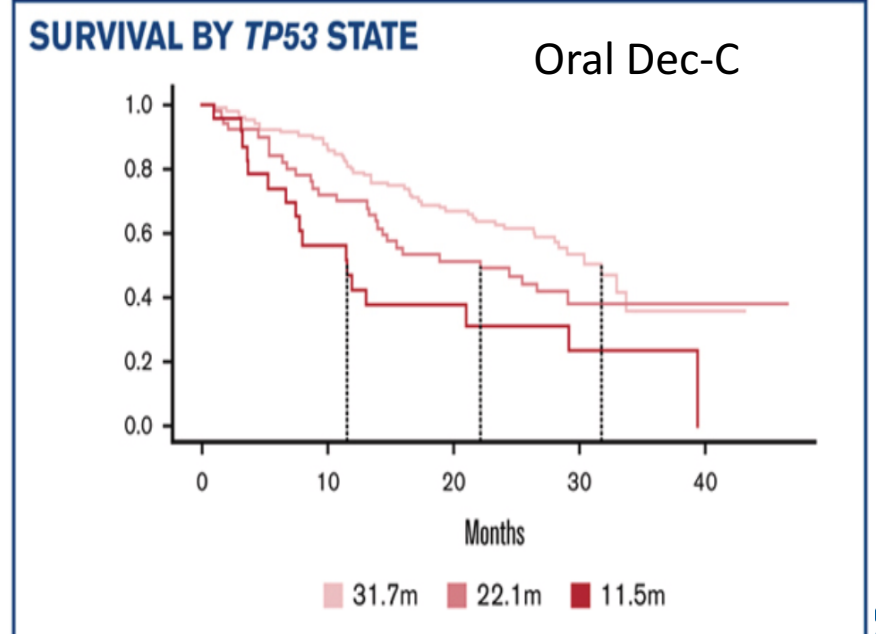
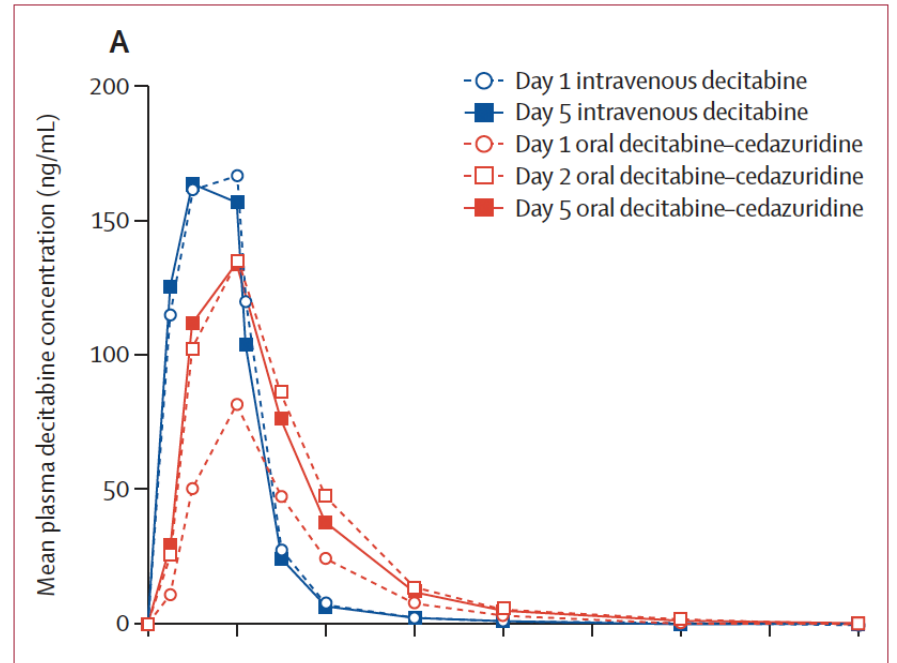
# AZA-001 and OS



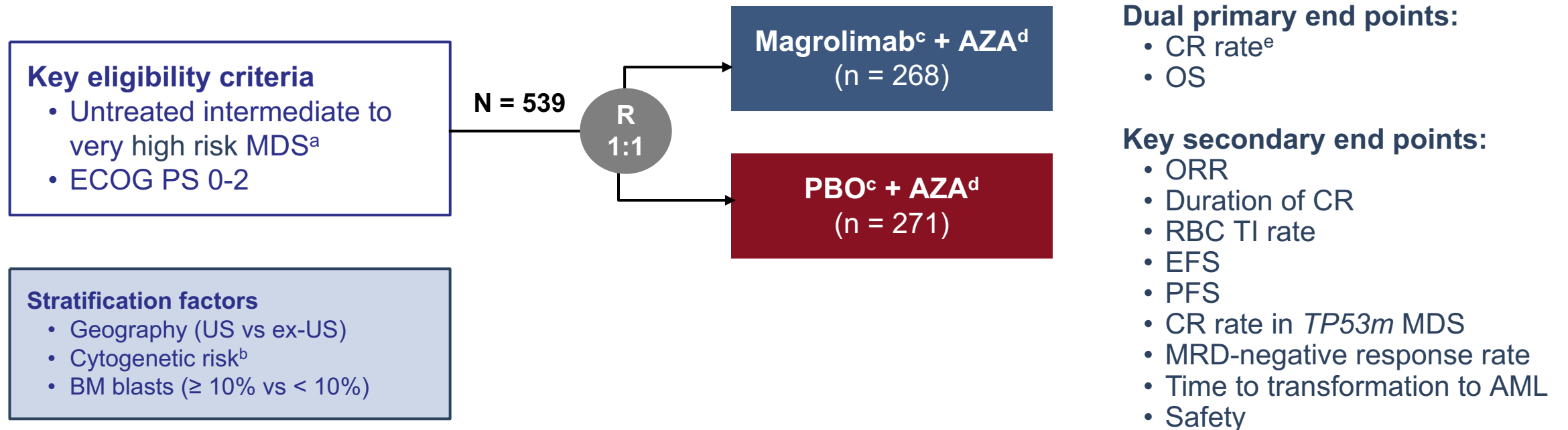
Real World OS was 14-18 months; 40-50% ORR; 15-20% CR  
Modern day studies 20-22 months with 20-30% CR

# Oral HMA Agents

- Oral Decitabine/cedazuridine has had long-term data with similar efficacy with some ? of increased myelosuppression
- ? Mild Improved OS in Multi-hit *TP53*
- Cost and Compliance Concerns
- Useful with Maintenance Considerations
- Challenges with Aza main comparator arm for HR MDS Studies
- ASTX-030 (oral aza equivalent with cedazuridine) showed similar safety/efficacy to parenteral aza with comparable PK although with significant impact by BSA
- P3 AZTOUND is ongoing (similar design to ASCERTAIN)



# ENHANCE: Randomized, Double-Blind, Phase 3 Study



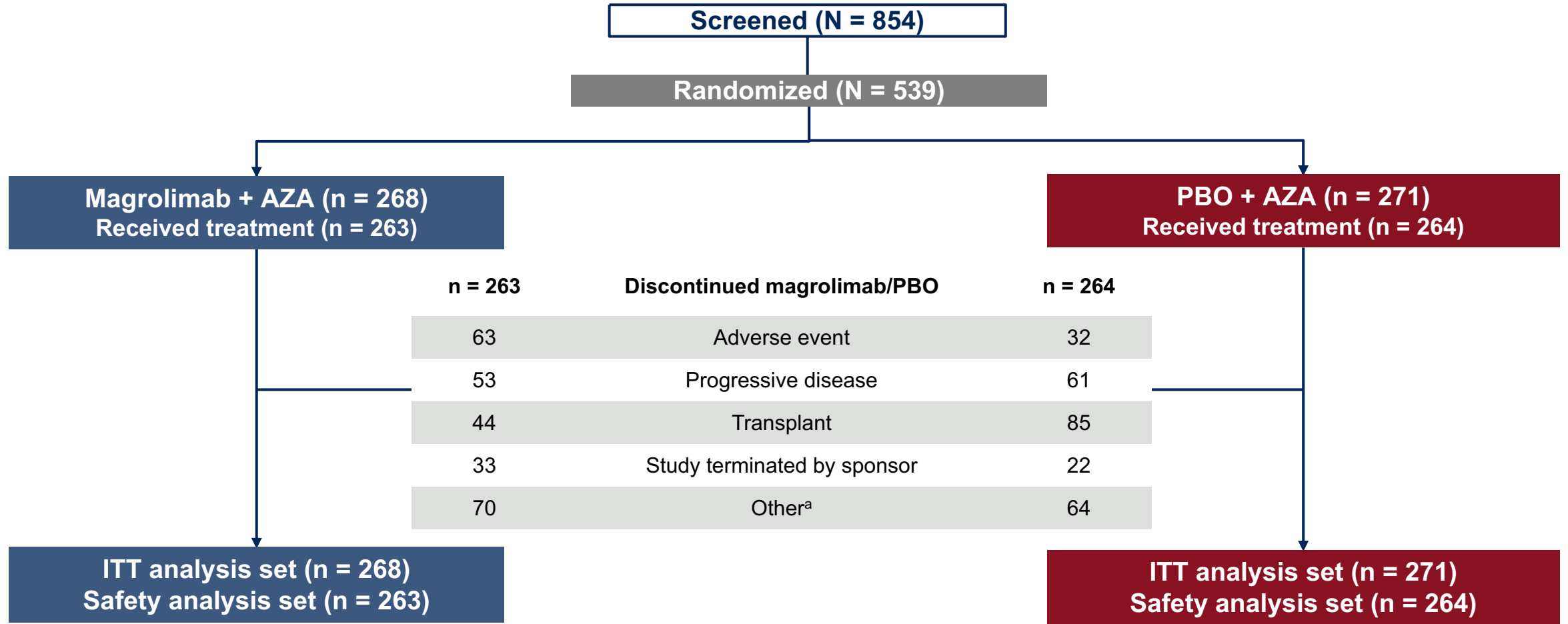
- Study stopped early at prespecified interim analysis due to futility

<sup>a</sup>Per IPSS-R<sup>1</sup>: intermediate, > 3-4.5; high, > 4.5-6; very high, > 6. <sup>b</sup>Per IPSS-R<sup>1</sup>: very good/good/intermediate vs poor/very poor vs unknown. <sup>c</sup>Magrolimab priming doses given at 1 mg/kg IV on days 1 and 4, 15 mg/kg on day 8, and 30 mg/kg on days 11 and 15, then weekly for 5 doses, and then maintenance doses of 30 mg/kg every 2 weeks beginning 1 week after the fifth weekly dose. PBO mirrored the magrolimab dosing schedule. <sup>d</sup>All patients received subcutaneous or IV AZA 75 mg/m<sup>2</sup> on Days 1-7 or Days 1-5, 8, and 9 every 28-day cycle (6-cycle minimum). One cycle was 28 days. <sup>e</sup>Primary analysis of CR rate was conducted 8 months after 348 participants had been randomized.

**AML**, acute myeloid leukemia; **AZA**, azacitidine; **BM**, bone marrow; **CR**, complete remission; **ECOG PS**, Eastern Cooperative Oncology Group performance score; **EFS**, event-free survival; **HR**, high risk; **IPSS-R**, Revised International Prognostic Scoring System; **IV**, intravenous; **MDS**, myelodysplastic syndrome; **MRD**, minimal residual disease; **ORR**, objective response rate; **OS**, overall survival; **PBO**, placebo; **PFS**, progression-free survival; **PR**, partial remission; **R**, randomization; **RBC**, red blood cell; **SCT**, stem cell transplant; **TI**, transfusion independence; **TP53m**, *TP53*-mutated; **US**, United States.

1. Greenberg PL, et al. *Blood*. 2012;120:2454-65.

# Patient Disposition



**33% to Transplant in Ctrl Arm vs 17% Exp**

Final analysis data cutoff: November 29, 2023.

<sup>a</sup>Physician decision (magrolimab + AZA vs PBO + AZA, n = 21 vs n = 24); patient decision but continued follow-up (n = 19 vs n = 12); lack of efficacy (n = 16 vs n = 17); withdrew consent (n = 8 vs n = 4); other (n = 3 vs n = 5); death (n = 1 vs n = 1); magrolimab could not be given alone (n = 2); noncompliance with study drug (PBO + AZA, n = 1).

AZA, azacitidine; ITT, intent-to-treat; PBO, placebo.

# Safety Outcomes

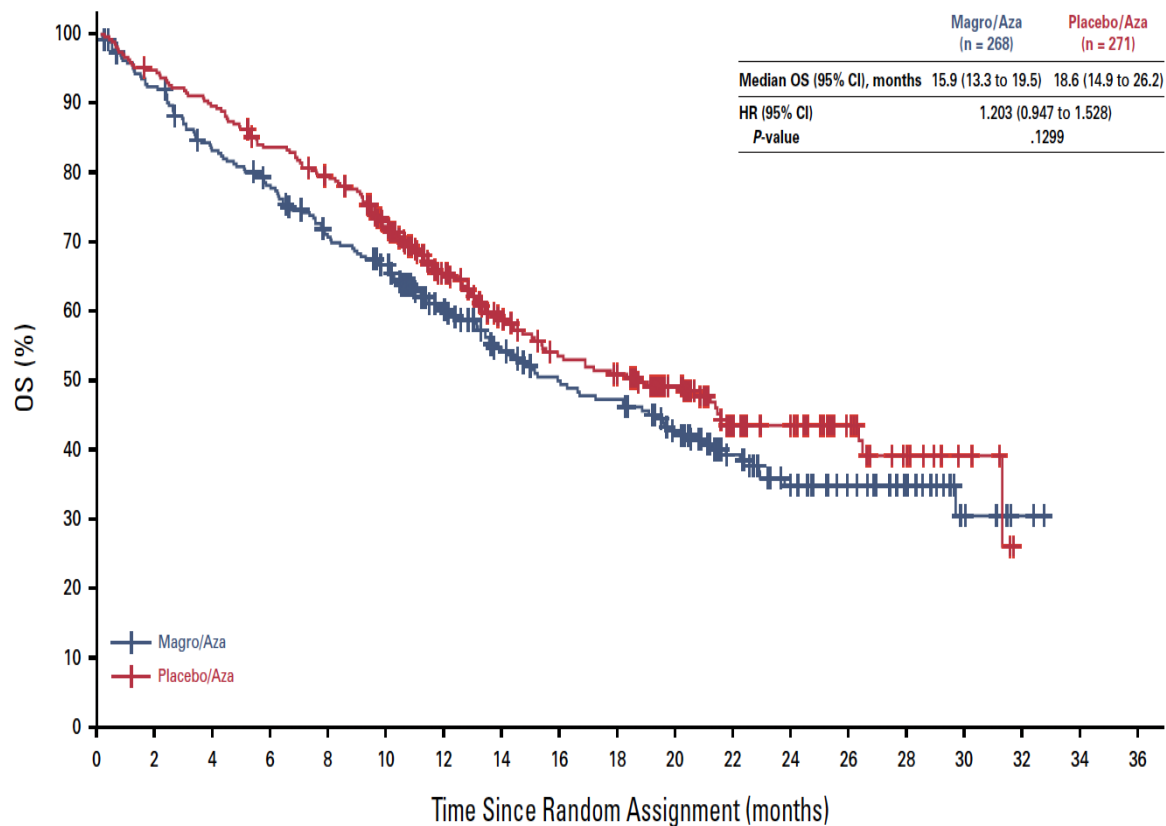
Safety outcome, n (%) <sup>a</sup>	Overall		Before Hb requirement		On/after Hb requirement	
	Magrolimab + AZA (n = 263)	PBO + AZA (n = 264)	Magrolimab + AZA (n = 190)	PBO + AZA (n = 187)	Magrolimab + AZA (n = 73)	PBO + AZA (n = 77)
Grade ≥ 3 TEAE	244 (92.8)	209 (79.2)	177 (93.2)	144 (77.0)	67 (91.8)	65 (84.4)
Related to any study drug	201 (76.4)	149 (56.4)	144 (75.8)	104 (55.6)	57 (78.1)	45 (58.4)
Serious TEAE	189 (71.9)	136 (51.5)	138 (72.6)	96 (51.3)	51 (69.9)	40 (51.9)
Related to any study drug	114 (43.3)	52 (19.7)	82 (43.2)	38 (20.3)	32 (43.8)	14 (18.2)
TEAE leading to discontinuation of any study drug	63 (24.0)	32 (12.1)	51 (26.8)	23 (12.3)	12 (16.4)	9 (11.7)
TEAE leading to delay or interruption of any study drug	199 (75.7)	147 (55.7)	144 (75.8)	105 (56.1)	55 (75.3)	42 (54.5)
TEAE leading to death <sup>a</sup>	40 (15.2)	26 (9.8)	30 (15.8)	21 (11.2)	10 (13.7)	5 (6.5)

- Magrolimab + AZA was associated with a higher incidence of fatal TEAEs, grade ≥ 3 and serious TEAEs, and TEAE-associated study drug discontinuations vs PBO + AZA
- After enrollment of 380 patients, a Hb requirement of ≥ 9 g/dL 24 hours before and Hb monitoring for 3–6 hours after the first 2 doses of magrolimab/PBO was implemented<sup>b</sup>; the requirement reduced discontinuations due to TEAEs in the magrolimab + AZA arm and led to a minor improvement in other safety parameters

<sup>a</sup>The most common TEAE with fatal outcome by system organ class was infections (21 deaths [8.0%] for magrolimab + AZA vs 12 deaths [4.5%] for PBO + AZA); all other system organ classes had ≤ 5 deaths per treatment. <sup>b</sup>The Hb requirement was implemented via an Urgent Safety Measure in April 2022. AZA, azacitidine; Hb, hemoglobin; PBO, placebo; TEAE, treatment-emergent adverse events.

# ENHANCE and OS across *TP53* mutant and Wildtype

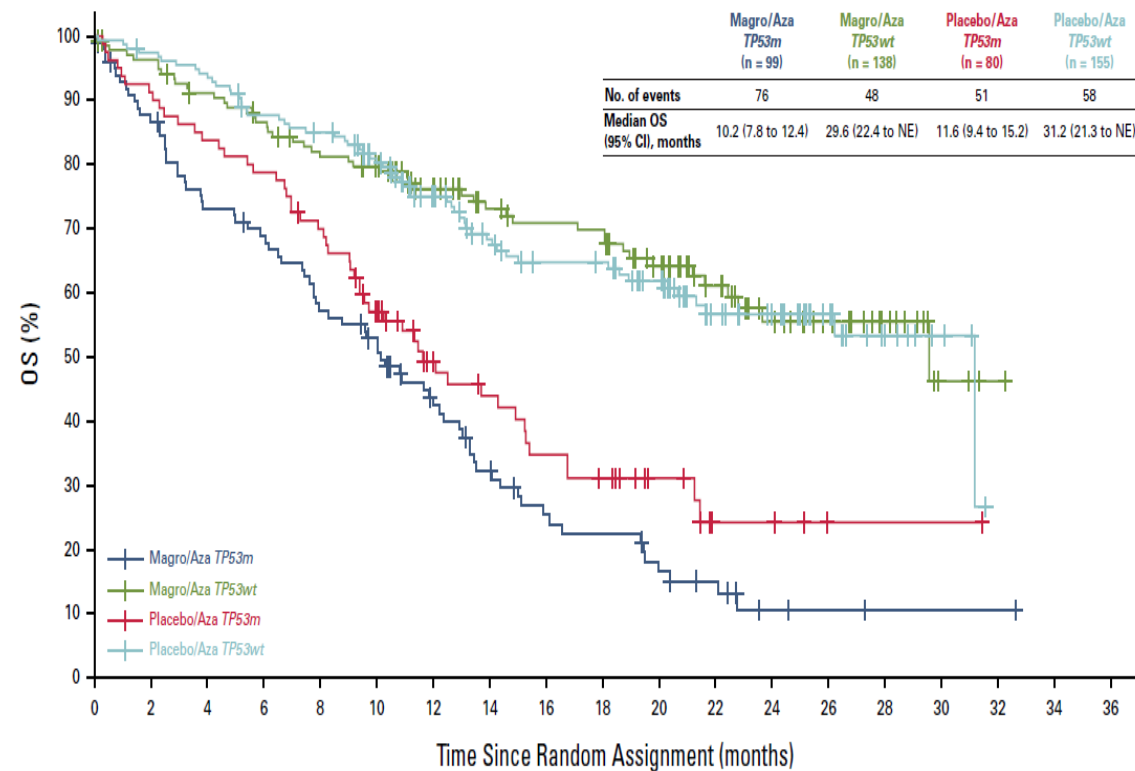
A



No. at risk (No. of events)

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	
Magro/Aza	268 (0)	242 (21)	216 (44)	200 (58)	176 (78)	163 (86)	126 (102)	105 (113)	92 (122)	88 (126)	70 (135)	50 (139)	32 (144)	24 (144)	15 (144)	5 (145)	2 (145)	0 (145)
Placebo/Aza	271 (0)	255 (15)	242 (28)	224 (44)	210 (56)	179 (76)	141 (90)	115 (104)	101 (115)	94 (119)	74 (122)	46 (129)	38 (129)	22 (129)	11 (131)	6 (131)	0 (132)	

C



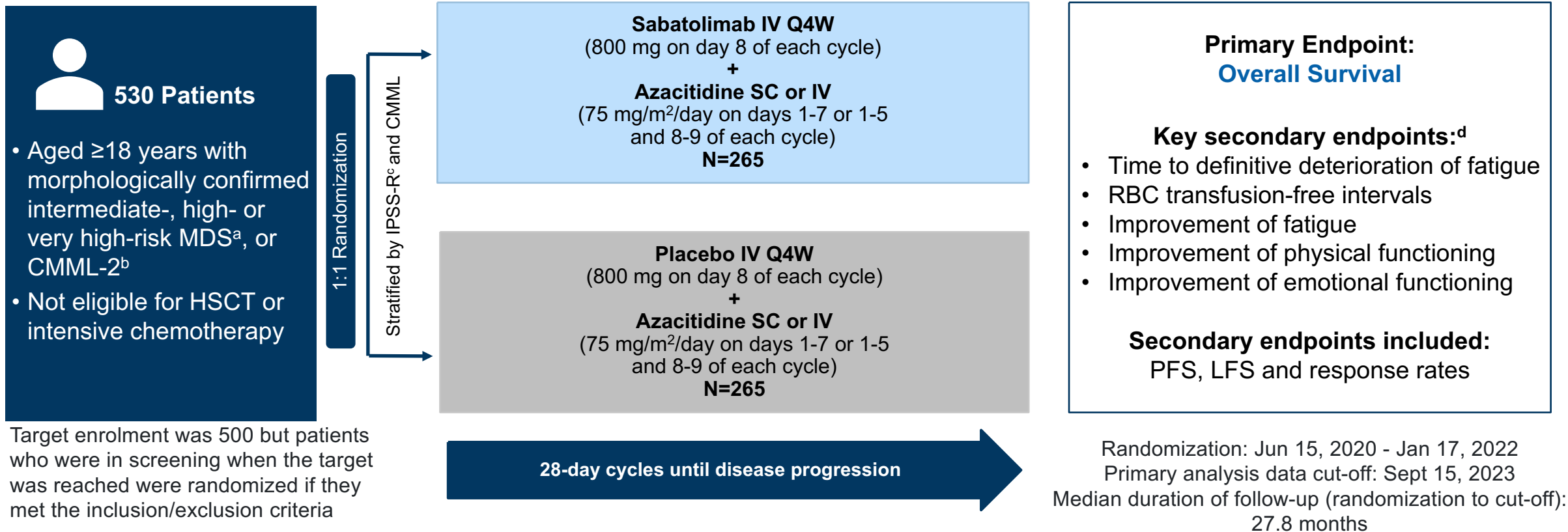
No. at risk (No. of events)

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	
Magro/Aza <i>TP53m</i>	99 (0)	84 (13)	70 (26)	65 (30)	54 (41)	48 (45)	34 (54)	25 (62)	18 (67)	16 (69)	11 (73)	8 (74)	3 (76)	2 (76)	1 (76)	1 (76)	1 (76)	0 (76)
Magro/Aza <i>TP53wt</i>	138 (0)	130 (5)	121 (12)	114 (18)	105 (25)	100 (27)	80 (31)	69 (34)	65 (36)	64 (37)	52 (42)	38 (44)	26 (47)	19 (47)	12 (47)	3 (48)	1 (48)	0 (48)
Placebo/Aza <i>TP53m</i>	80 (0)	73 (7)	67 (13)	63 (17)	55 (24)	42 (34)	28 (39)	24 (42)	19 (47)	16 (49)	10 (49)	4 (51)	4 (51)	1 (51)	1 (51)	1 (51)	0 (51)	
Placebo/Aza <i>TP53wt</i>	155 (0)	150 (4)	145 (9)	133 (19)	128 (23)	113 (30)	93 (37)	78 (45)	70 (49)	69 (49)	58 (52)	37 (56)	30 (56)	19 (56)	10 (57)	5 (57)	0 (58)	

38% *TP53* mutant in Trial; 41% *TP53* mutant Combo; 34% *TP53* mutant placebo

# STIMULUS-MDS2 design

## Randomized, double-blind, placebo-controlled, multi-centered Phase III study

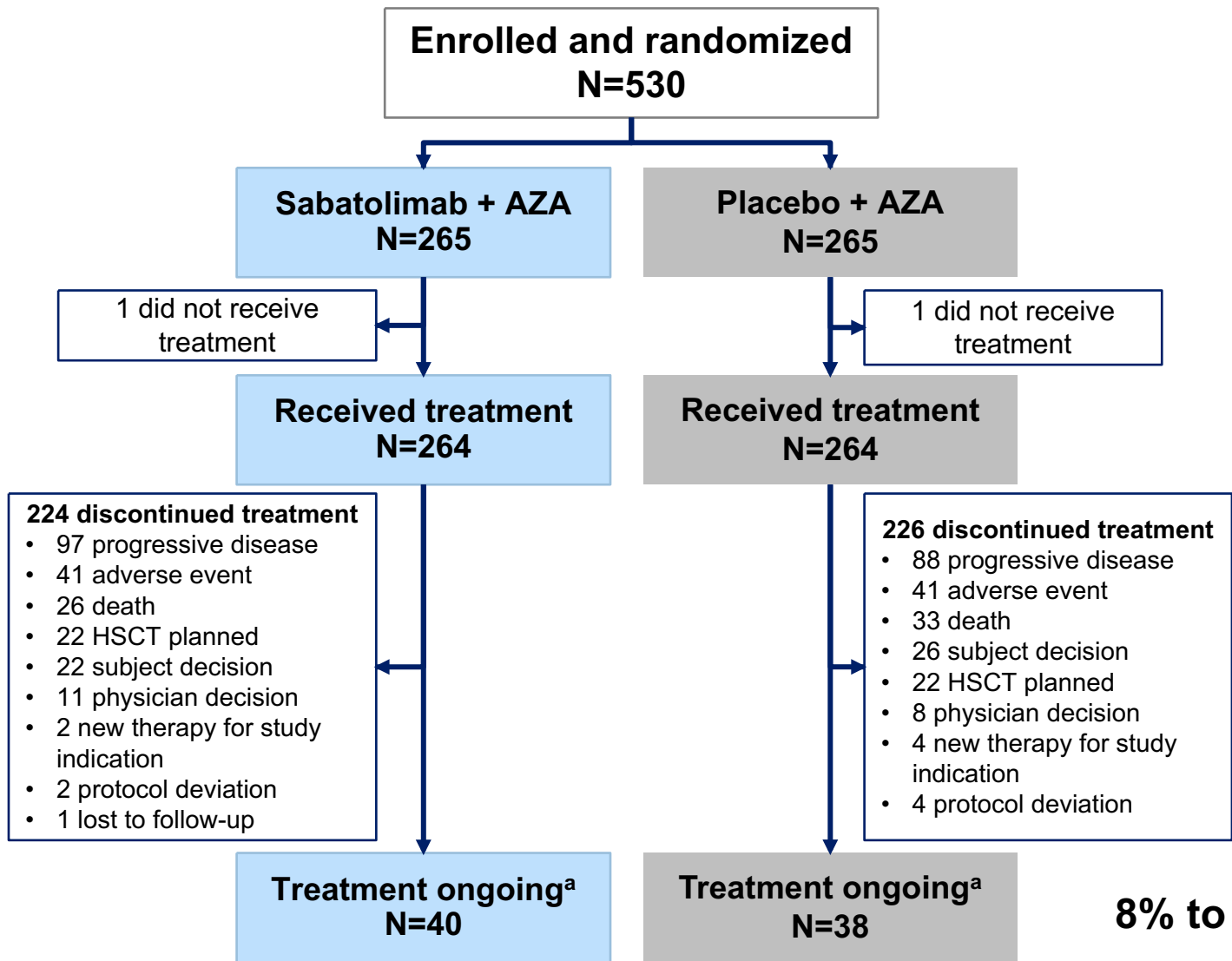


 36 countries  151 study centers

NCT04266301. CMML-2, chronic myelomonocytic leukemia 2; CR, complete response; HSCT, hematopoietic stem cell transplantation; IPSS-R, Revised International Prognostic Scoring System; IV, intravenous; LFS, leukemia-free survival; MDS, myelodysplastic syndromes; OS, overall survival; PFS, progression-free survival; Q4W, every 4 weeks; RBC, red blood cell; SC, subcutaneous; WBC, white blood cell.

<sup>a</sup>Defined according to the IPSS-R criteria: very high risk ( $>6$  points), high risk ( $>4.5$ – $\leq 6$  points), or intermediate risk ( $>3$ – $\leq 4.5$  points). <sup>b</sup>WBC  $<13 \times 10^9/L$  at time of initial diagnosis. <sup>c</sup>IPSS-R prognostic risk score (intermediate, high, very high). <sup>d</sup>If the primary endpoint was significant at the primary analysis, the first two key secondary endpoints were tested and if at least one of the first two key secondary endpoints was statistically significant, the remaining key secondary endpoints were tested in a sequence.

# Patient disposition



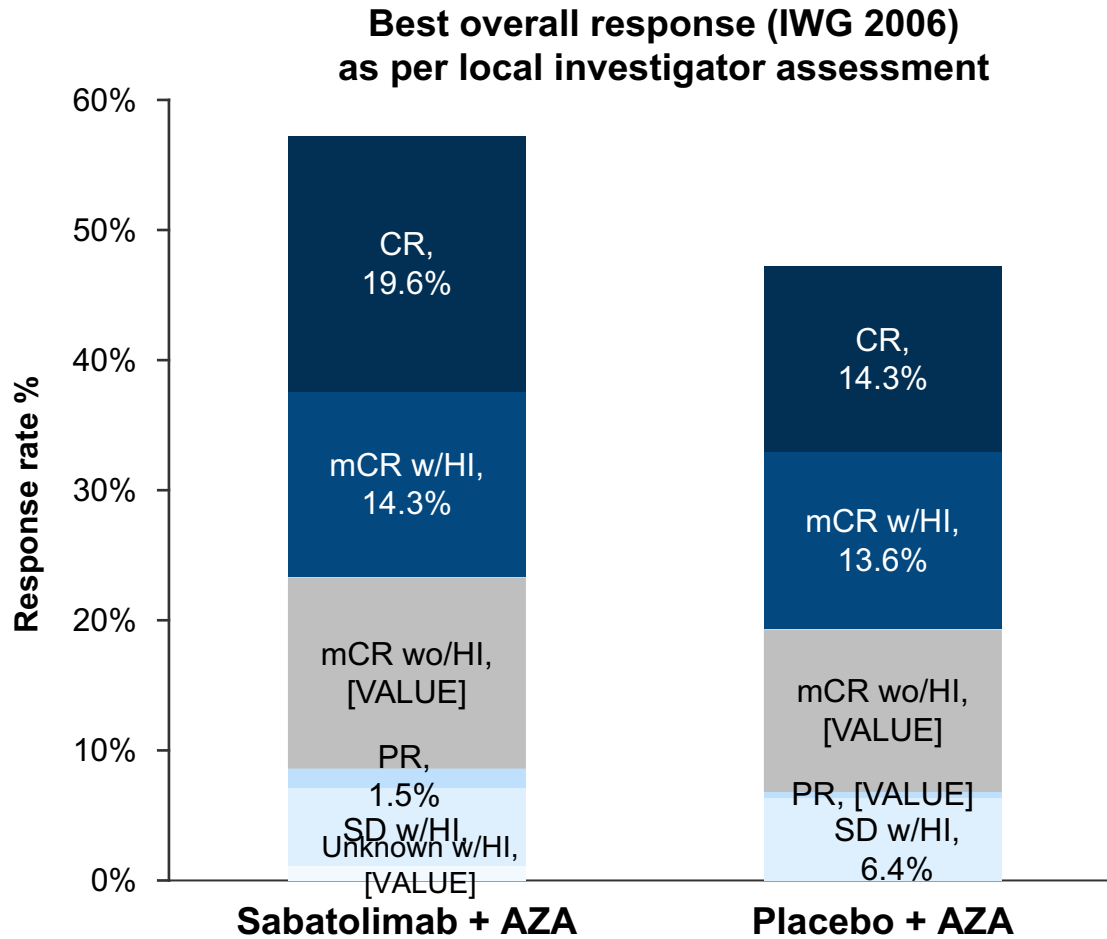
Treatment exposure		
	Sabatolimab + AZA	Placebo + AZA
<b>Median</b>	8.8 months	6.8 months
<b>Q1-Q3</b>	4.8-19.9 months	3.3-14.0 months
<b>Maximum</b>	35.9 months	37.7 months

As of September 15, 2023, 186 patients (91 patients receiving sabatolimab + AZA and 95 patients receiving placebo + AZA) were still ongoing in study for follow-up

**8% to Transplant in Ctrl Arm and Exp**

AZA, azacitidine; HSCT, hematopoietic stem cell transplantation. <sup>a</sup>As of the cutoff date (September 15, 2023).

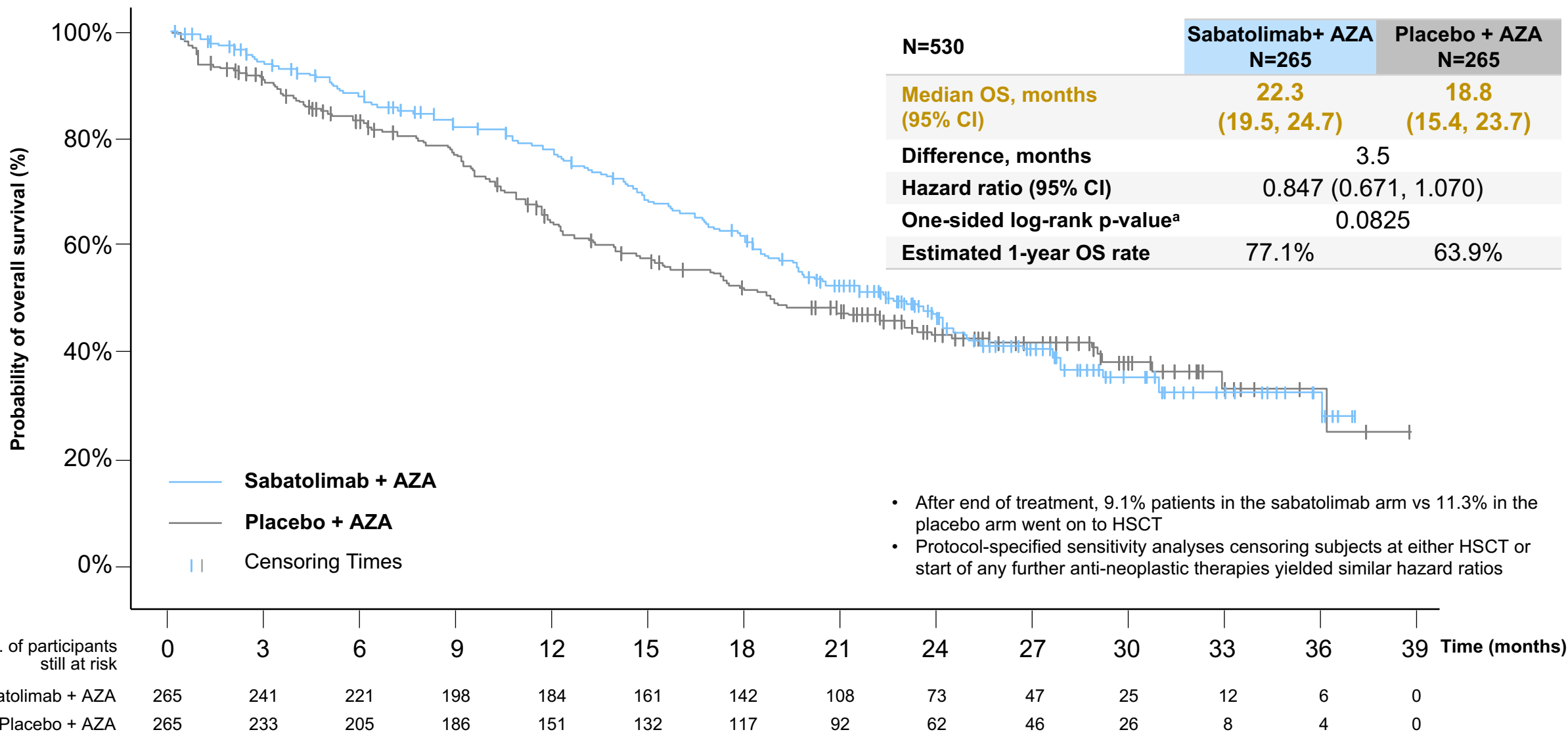
# Best overall response



	Sabatolimab + AZA N=265	Placebo + AZA N=265
<b>CR<sup>a</sup>, % (95% CI)</b>	<b>19.6</b> (15.0, 24.9)	<b>14.3</b> (10.4, 19.1)
<b>CR+PR+HI<sup>b</sup>, % (95% CI)</b>	<b>42.6</b> (36.6, 48.8)	<b>34.7</b> (29.0, 40.8)

AZA, azacitidine; CI, confidence interval; CR, complete remission; (w/wo) HI, (with/without) hematological improvement; IWG, International Working Group; mCR, marrow CR; PD, progressive disease; PR, partial remission; SD, stable disease; w/wo, with/without. Full analysis set. <sup>a</sup>CR bone marrow assessments were performed less frequently than in the STIMULUS-MDS1 study and therefore CRs are not directly comparable; first assessment performed after 6 cycles. <sup>b</sup>HI must be concurrent with best overall response.

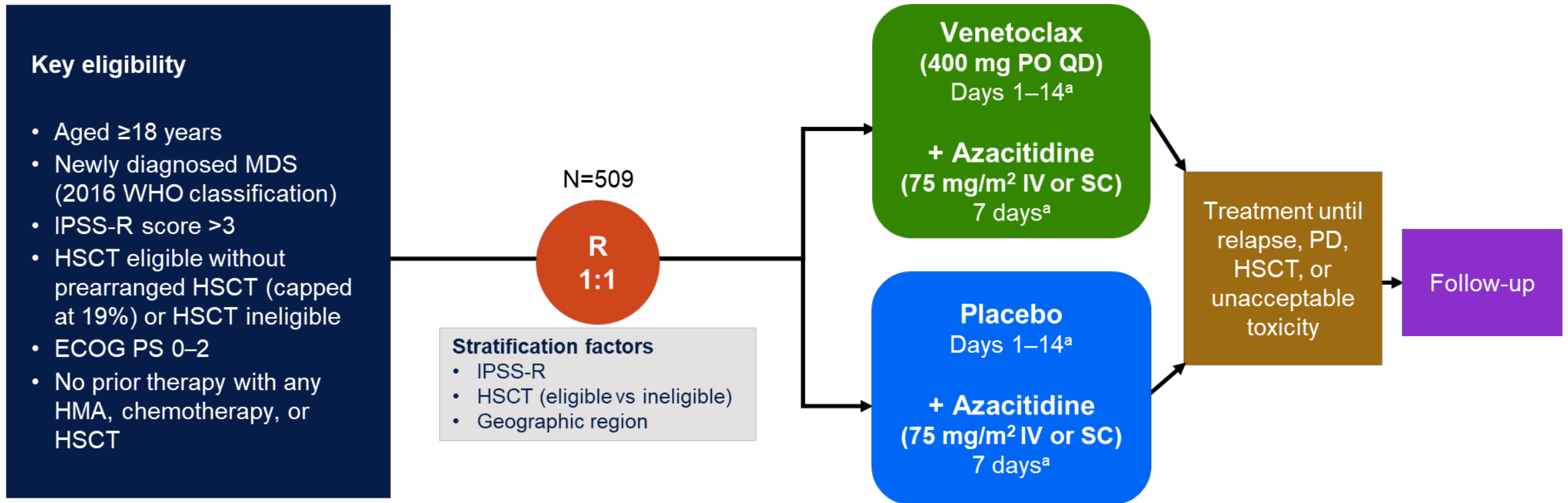
# Overall survival (primary endpoint) (N=530)



- After end of treatment, 9.1% patients in the sabatolimab arm vs 11.3% in the placebo arm went on to HSCT
- Protocol-specified sensitivity analyses censoring subjects at either HSCT or start of any further anti-neoplastic therapies yielded similar hazard ratios

AZA, azacitidine; CI, confidence interval; CMML-2, chronic myelomonocytic leukemia 2; HSCT, hematopoietic stem cell transplantation; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndromes; OS, overall survival. Full analysis set. Cox-model are stratified by randomization stratification factor (Intermediate-risk MDS, High-risk MDS, Very high-risk MDS, CMML-2) as per interactive response technology. <sup>a</sup>Log-rank test stratified by the randomization stratification factor (IPSS-R very high, IPSS-R high, IPSS-R intermediate, CMML-2) with critical alpha level 0.0246.

# Study design and endpoints of phase 3 VERONA study (NCT04401748)



- **Primary endpoint:** Overall survival
- **Key secondary endpoints:** mOR (CR + PR + mCR)<sup>b</sup>, overall hematologic improvement (platelet, neutrophil, or erythroid)<sup>b</sup>, CR<sup>b</sup>, red blood cell and platelet transfusion independence<sup>c</sup>, PROs, OR (CR + PR)<sup>b</sup>, and safety

<sup>a</sup>28-day cycles. <sup>b</sup>Investigator-assessed per IWG 2006 criteria. <sup>c</sup>For patients who were transfusion dependent on red blood cells and/or platelets at baseline. ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplantation; IV, intravenous; IWG, International Working Group; mOR, modified overall response; PD, progressive disease; PO, oral; PRO, patient-reported outcome; QD, once daily; R, randomization; SC, subcutaneous; WHO, World Health Organization.



# Demographic and baseline characteristics

Characteristic	Ven + Aza (n=256)	Pbo + Aza (n=253)
<b>Median age, years (range)</b>	72 (31–86)	72 (25–92)
18–64 years, n (%)	53 (20.7)	64 (25.3)
≥65 years, n (%)	203 (79.3)	189 (74.7)
≥75 years, n (%)	87 (34.0)	103 (40.7)
<b>Male, n (%)</b>	162 (63.3)	166 (65.6)
<b>Race, n (%)<sup>b</sup></b>		
White	186 (72.7)	182 (72.2)
Asian	64 (25.0)	66 (26.2)
Black or African American	5 (2.0)	4 (1.6)
Other	1 (0.4)	0
Missing	0	1 (0.4)
<b>Region, n (%)</b>		
Europe	112 (43.8)	111 (43.9)
North America	57 (22.3)	56 (22.1)
China	26 (10.2)	27 (10.7)
Japan	25 (9.8)	23 (9.1)
Rest of world	36 (14.1)	36 (14.2)
<b>ECOG PS</b>		
0	97 (37.9)	101 (39.9)
1	140 (54.7)	132 (52.2)
2	19 (7.4)	20 (7.9)

Characteristic	Ven + Aza (n=256)	Pbo + Aza (n=253)
<b>IPSS-R prognostic risk,<sup>a</sup> n (%)</b>		
Intermediate	70 (27.3)	71 (28.1)
High	96 (37.5)	99 (39.1)
Very high	90 (35.2)	83 (32.8)
<b>Baseline eligibility for HSCT, n (%)</b>		
Yes	50 (19.5)	47 (18.6)
No	206 (80.5)	206 (81.4)
<b>Bone marrow blast count, n (%)</b>		
<5%	48 (18.8)	48 (19.0)
≥5% to <10%	83 (32.4)	93 (36.8)
≥10% to <20%	125 (48.8)	108 (42.7)
≥20%	0	4 (1.6)
<b>Baseline mutations detected, n (%)<sup>c</sup></b>		
<i>ASXL1</i>	60 (30)	68 (33.5)
<i>TP53</i>	49 (24.5)	38 (18.7)
<i>RUNX1</i>	29 (14.5)	49 (24.1)
<i>EZH2</i>	5 (2.5)	13 (6.4)

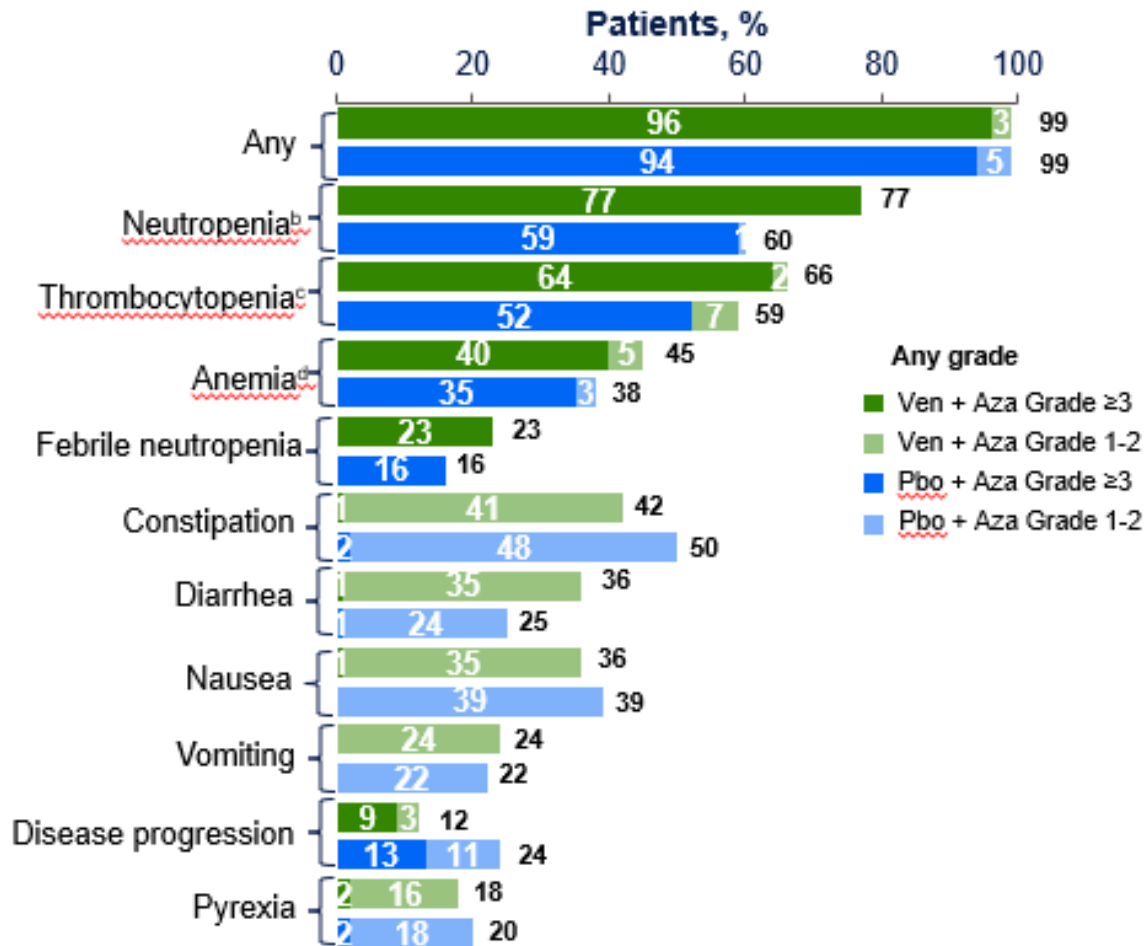
Data cutoff date: April 10, 2025

<sup>a</sup>In the Pbo + Aza arm, percentages were calculated omitting missing patients (n=252). <sup>b</sup>From IVRS/IWRS. <sup>c</sup>Based on samples available for testing. IVRS, Interactive Voice Response System; IWRS, Interactive Web Response.



# No new safety signals were observed

Most common TEAEs<sup>a</sup>



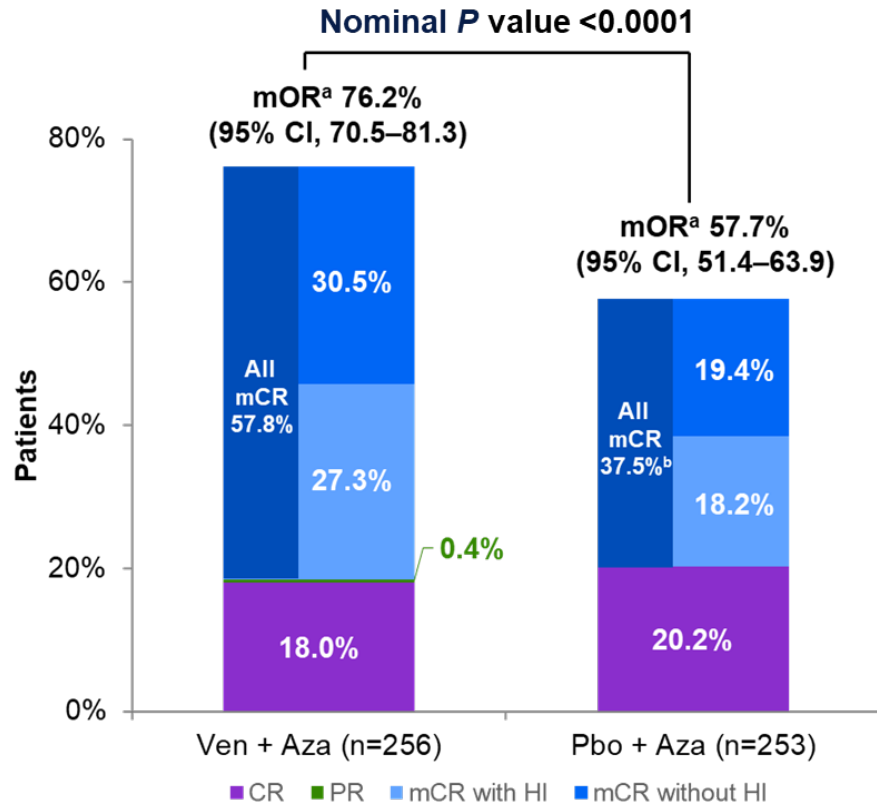
HMA was Dose Reduced First Leading to Decreased HMA Exposure in Combo Arm

AEs, n (%)	Ven + Aza (N=255)	Pbo + Aza (N=246)
<b>Serious AEs</b>	<b>167 (65.5)</b>	<b>135 (54.9)</b>
<b>AEs leading to death<sup>e</sup></b>	<b>18 (7.1)</b>	<b>20 (8.1)</b>
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)
<b>Deaths</b>	<b>167 (65.5)</b>	<b>169 (68.6)</b>
Most common cause <sup>f</sup>		
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)



# Improved ORR although No Improvement of CR with HMA ven

Median number of cycles: 6 (range, 1–53)



mOR	Ven + Aza (n=195)	Pbo + Aza (n=146)
Median duration, months (95% CI)	15.3 (12.3–20.7)	14.8 (12.4–16.7)

HI	Ven + Aza (n=256)	Pbo + Aza (n=253)
Overall HI, % (95% CI)	49.4 (43.0–55.8)	41.2 (35.0–47.6)
Nominal P value	0.0723	

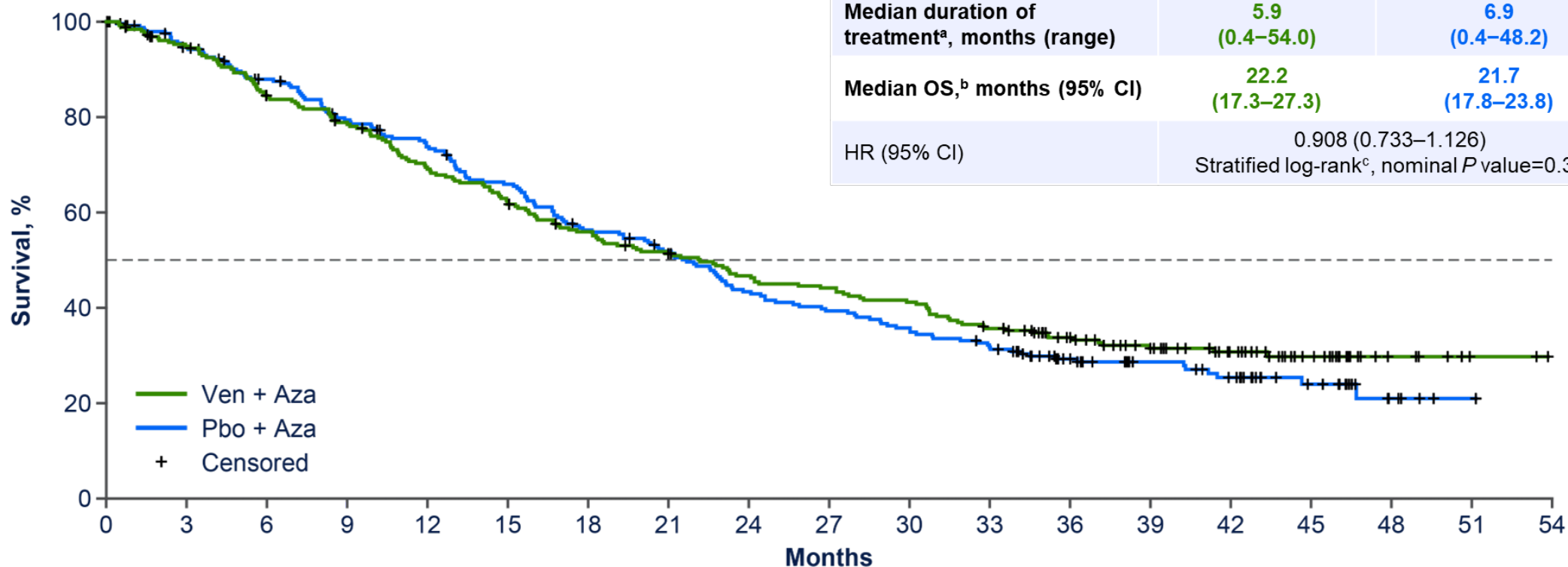
TI <sup>c</sup>	Ven + Aza (n=256)		Pbo + Aza (n=253)	
	Red blood cells	Platelets	Red blood cells	Platelets
Rate, n/N (%) [95% CI]	73/131 (55.7) [46.8–64.4]	24/35 (68.6) [50.7–83.1]	41/122 (33.6) [25.3–42.7]	14/38 (36.8) [21.8–54.0]
Median duration, months (range)	5.7 (1.8–45.9)	4.7 (1.9–43.1)	7.7 (1.8–42.6)	5.8 (1.9–22.5)

All P values are nominal. <sup>a</sup>CR+PR+mCR. <sup>b</sup>The percentage of patients achieving mCR with HI + those without HI is different from the percentage of all patients achieving mCR rate due to rounding. <sup>c</sup>Patients having red blood cell or platelet transfusion within 8 weeks prior to or up to first dose of study drug (red blood cell and/or platelet transfusion dependent at baseline). HI, hematological improvement; TI, transfusion independence.



# Primary Endpoint OS

Median follow-up: 41.2 months (range, 0.03–53.9)



	Ven + Aza (N=256)	Pbo + Aza (N=253)
Median duration of treatment <sup>a</sup> , months (range)	5.9 (0.4–54.0)	6.9 (0.4–48.2)
Median OS, <sup>b</sup> months (95% CI)	22.2 (17.3–27.3)	21.7 (17.8–23.8)
HR (95% CI)	0.908 (0.733–1.126) Stratified log-rank <sup>c</sup> , nominal P value=0.38	

### Patients at Risk

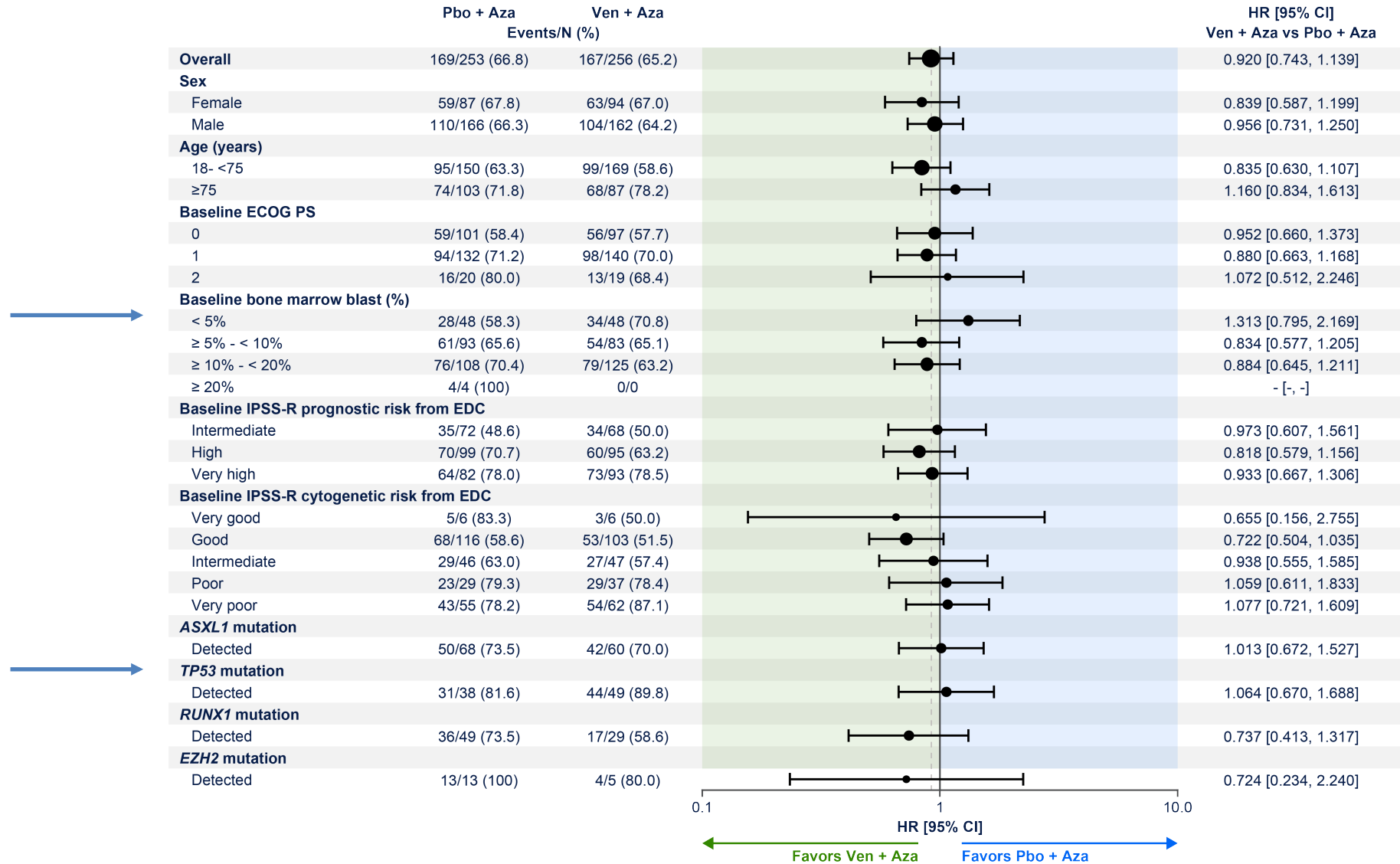
256	239	210	194	169	151	135	122	110	104	97	83	66	50	37	22	7	2	0
253	228	207	185	170	151	128	116	97	88	80	70	48	36	29	16	5	1	0

HMA Ven Trend for improved OS Very good-good IPSSR cyto risk (HR .66-.72) and worse OS in patients with BM Blasts < 5%; HR 1.3

<sup>a</sup>Duration of treatment is from (date of the first dose in the last cycle + 27 days, date of death, cutoff date) - date of the first dose in first cycle + 1. <sup>b</sup>Overall survival is defined as the time from the date of randomization to the date of death. The data were censored at the date when a patient was last known to be alive on or before the cutoff date. <sup>c</sup>Stratified by IPSS-R (intermediate, high, very high) and HSCT eligibility (eligible, ineligible) from IVRS/IWRS.



# OS in select subgroups by treatment arm



# HSCT

	Ven + Aza (n=256)	Pbo + Aza (n=253)
HSCT		
<b>Overall HSCT, n (%)<sup>a</sup></b>	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 (%) <sup>b</sup>	39 (15.2)	23 (9.1)
Additional post-study treatment prior to HSCT n (%) <sup>c</sup>	4 (9.3)	10 (30.3)
Venetoclax	0	5 (15.2)
<b>Best response on study treatment prior to HSCT, n (%)</b>		
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		
<b>All post-study therapy, n (%)</b>	<b>73 (28.5)</b>	<b>98 (38.7)</b>
Venetoclax	27 (10.5)	53 (20.9)

**No OS Subset Available for Transplant OS**

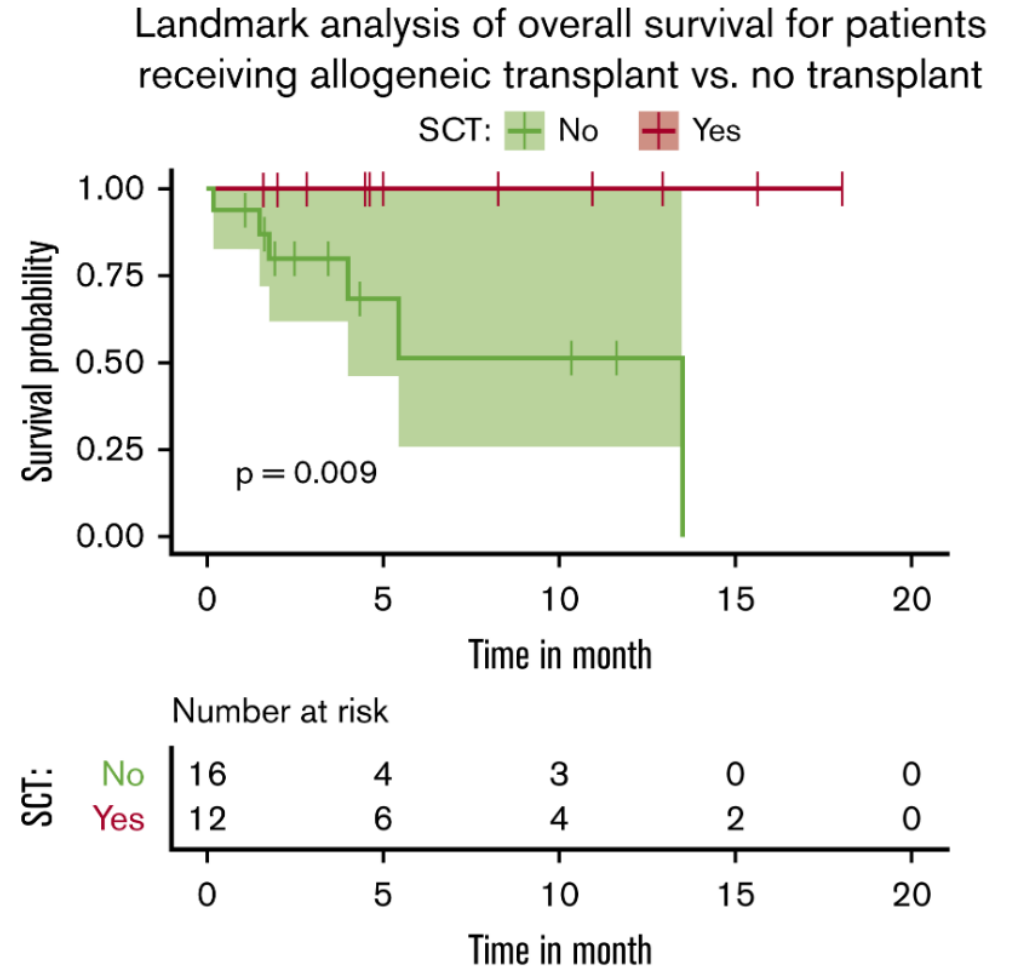


# Real-World Responses to Venetoclax + HMA in HR-MDS

	1L HMA VEN	1L HMA	
<b>All cohort</b>	n=35	n=1127	
ORR	77%	40%	<.005
CR	34%	13%	
mCR	37% (62% + HI)	11%	
PR	3%	1%	
HI	3%	15%	
<b>ASXL-1 MT</b>	n=16	n=106	
ORR	87%	32%	<.005
CR	44%	8%	
<b>TP53 MT</b>	n=12	n=137	
ORR	75%	44%	.038
CR	25%	17%	.47

## HMA Failure setting (n=31)

- CR 13%, mCR 48%
- 9/31 to allo-HSCT
- Median OS in R/R was 33 months and 21 months in 1L (independent of transplant status)

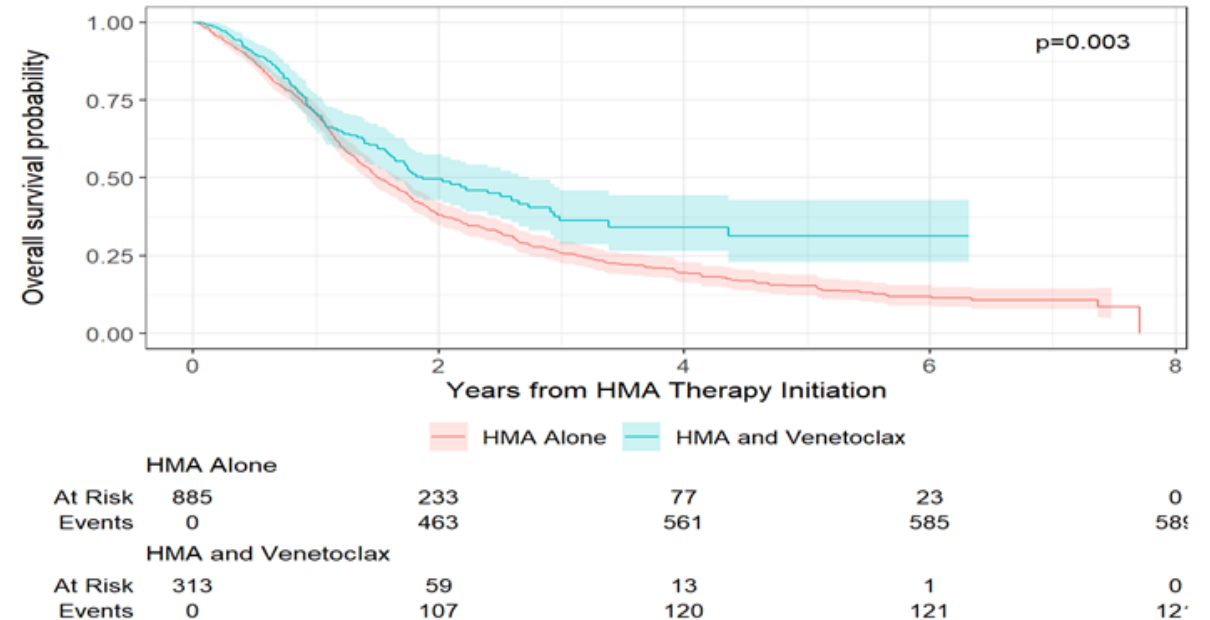


# Baseline Characteristics

Characteristic	Overall N = 1,198	HMA Alone N = 885	HMA- Venetoclax N = 313
<b>Age at Diagnosis</b>	70 (63-77)	71 (64-77)	<b>68 (61-73)</b>
<b>ECOG PS</b>			
<b>0</b>	201 (17%)	118 (13%)	<b>83 (27%)</b>
<b>1</b>	862 (73%)	675 (77%)	<b>187 (62%)</b>
<b>2</b>	108 (9.1%)	77 (8.8%)	<b>31 (10%)</b>
<b>3</b>	11 (0.9%)	9 (1.0%)	<b>2 (0.7%)</b>
<b>Unknown</b>	16	6	<b>10</b>
<b>MDS type</b>			
<b>De Novo</b>	875 (73%)	666 (75%)	<b>209 (67%)</b>
<b>Therapy-related</b>	323 (27%)	219 (25%)	<b>104 (33%)</b>
<b>IPSS-R</b>			
<b>Intermediate</b>	346 (29%)	291 (33%)	<b>55 (18%)</b>
<b>High</b>	362 (30%)	265 (30%)	<b>97 (31%)</b>
<b>Very High</b>	490 (41%)	329 (37%)	<b>161 (51%)</b>

Median BM Blasts: HMA-Ven=**10%** (7-15),  
HMA=**6.6%** (4-13); ORR and CR Imp

1198 patients overall, **313 with HMA-venetoclax**



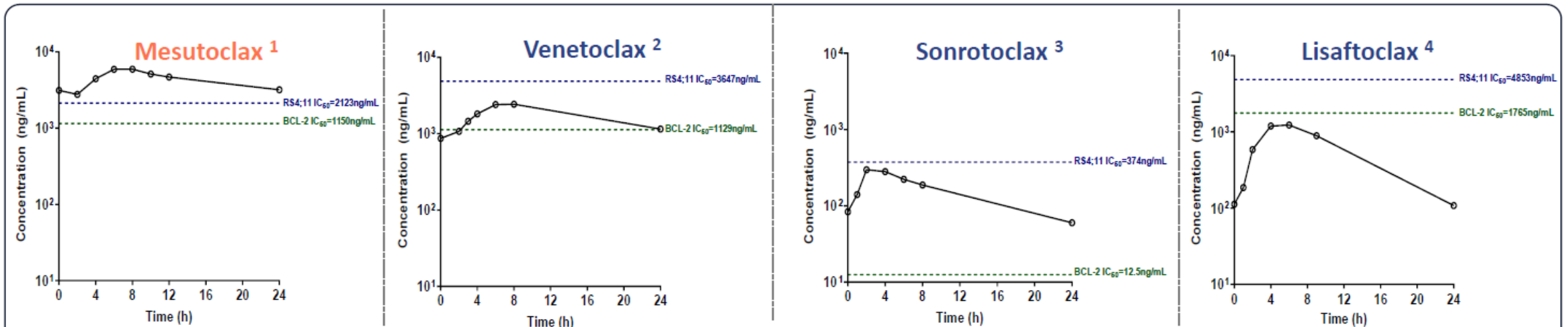
- Median OS **22 (20-33) months vs 18 (17-20) months**
- Therapy related MDS and TP53 mutation were predictors of worse OS
- Allogeneic HCT was associated with improved OS as an independent variable



# Novel BCL-2 Inhibitors in Clinical Development for MDS/AML

	Mesutoclax (ICP-248)	Venetoclax (ABT-199)	Lisaftoclax (APG-2575)	Sonrotoclax (BGB-11417)
$T_{1/2}$	21h	26h	4-6h	~5h
BCL-2 IC <sub>50</sub> (nM)	1.3 <sup>a</sup>	1.3 <sup>a</sup> /0.2 <sup>b</sup>	2.0 <sup>c</sup>	0.014 <sup>b</sup>
BCL-XL inhibition	None	None	YES	YES
Metabolite	None	M27	Not reported	Not reported

- a. IC<sub>50</sub> of Venetoclax and Mesutoclax were tested by FP assay in InnoCare.  
 b. IC<sub>50</sub> of Venetoclax and BGB-11417 were reported by BeiGene by TR-FRET assay in 2020 AACR.  
 c. WO2018027097A1



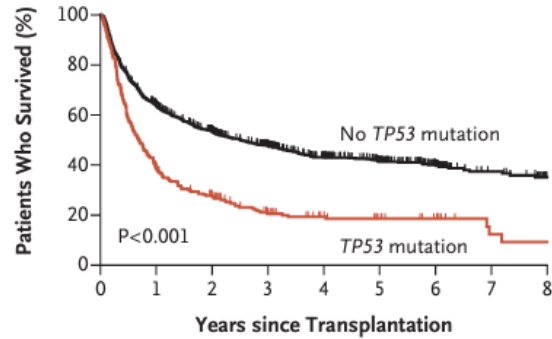
Note: Steady state concentration-time curve at clinical dose. IC<sub>50</sub> values are multiplied by 1000 to take account of PPB (PPBs are less than 0.01 for all four drugs).

1. ICP-CL-01201 study. Chinese CLL/SLL patients with 125mg Mesutoclax 2. Venetoclax at 400mg. VENCLEXTA Clinical Pharmacology Reviews. 3. Sonrotoclax at 640mg. 2022 ASH 4. Lisaftoclax at 600mg. 2022 ASCO



# Outcomes to Transplant in *TP53* mutant MDS/AML

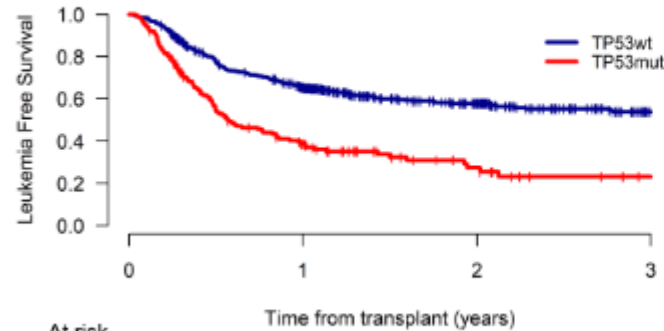
**B Overall Survival, According to *TP53* Mutation Status**



No. at Risk

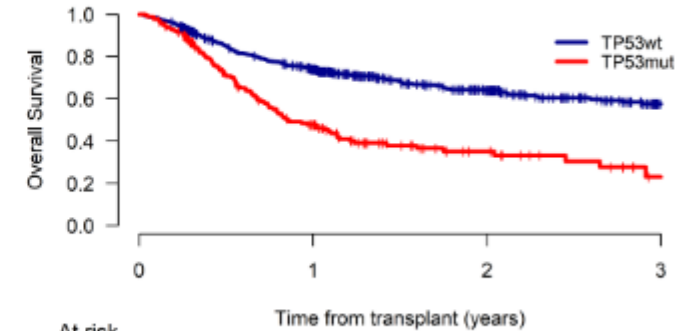
No <i>TP53</i> mutation	1224	757	529	370	261	183	109	53	32
<i>TP53</i> mutation	289	109	66	39	26	20	14	6	5

**LFS**



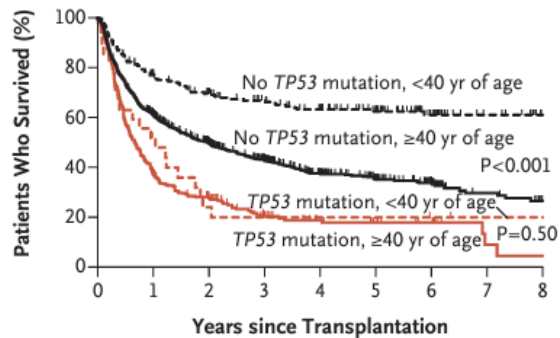
At risk	601	299	140	53
	179	48	15	3

**OS**



At risk	601	342	157	57
	179	63	20	4

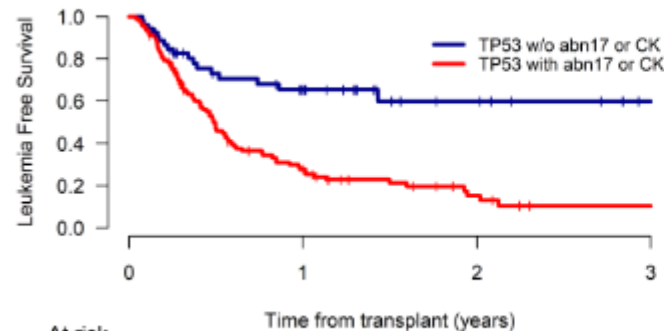
**C Overall Survival, According to *TP53* Mutation Status and Age**



No. at Risk

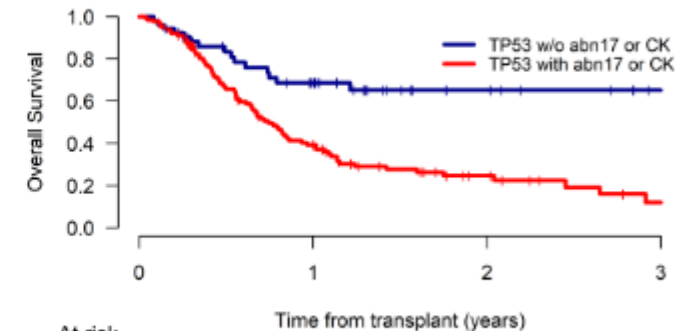
No <i>TP53</i> mutation									
<40 yr of age	214	159	133	115	100	78	42	23	13
≥40 yr of age	1010	598	396	255	161	105	67	30	19
<i>TP53</i> mutation									
<40 yr of age	27	14	7	5	5	5	4	4	3
≥40 yr of age	262	95	59	34	21	15	10	3	2

**LFS**



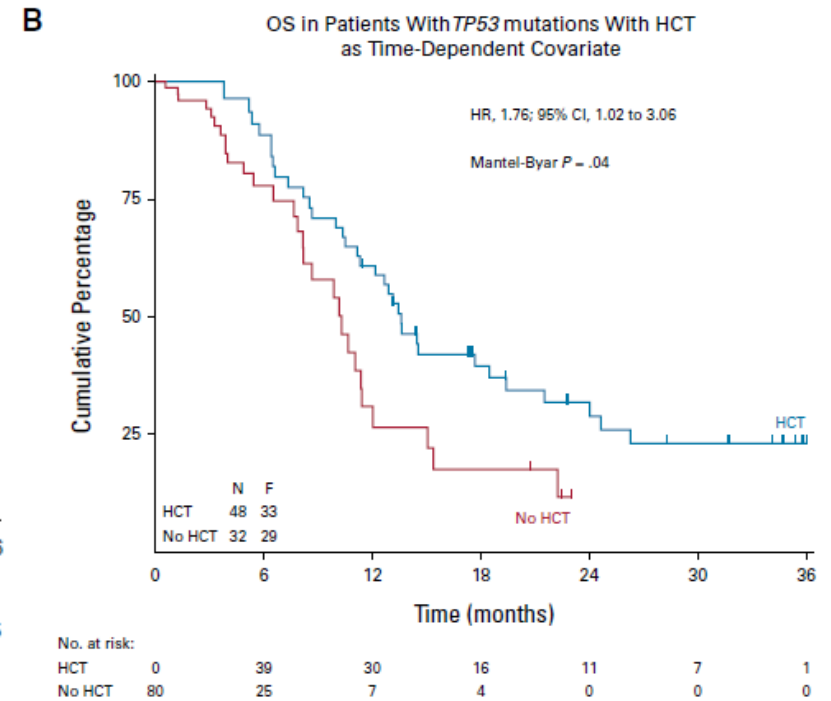
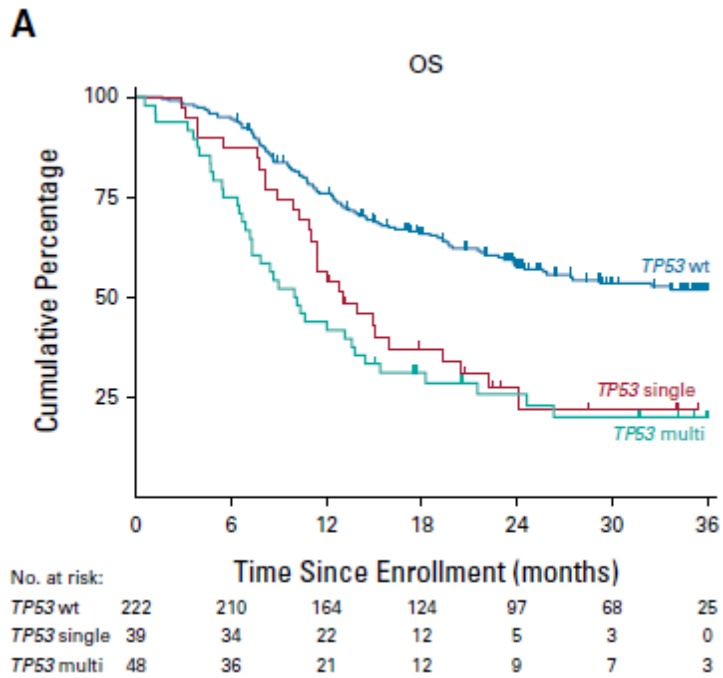
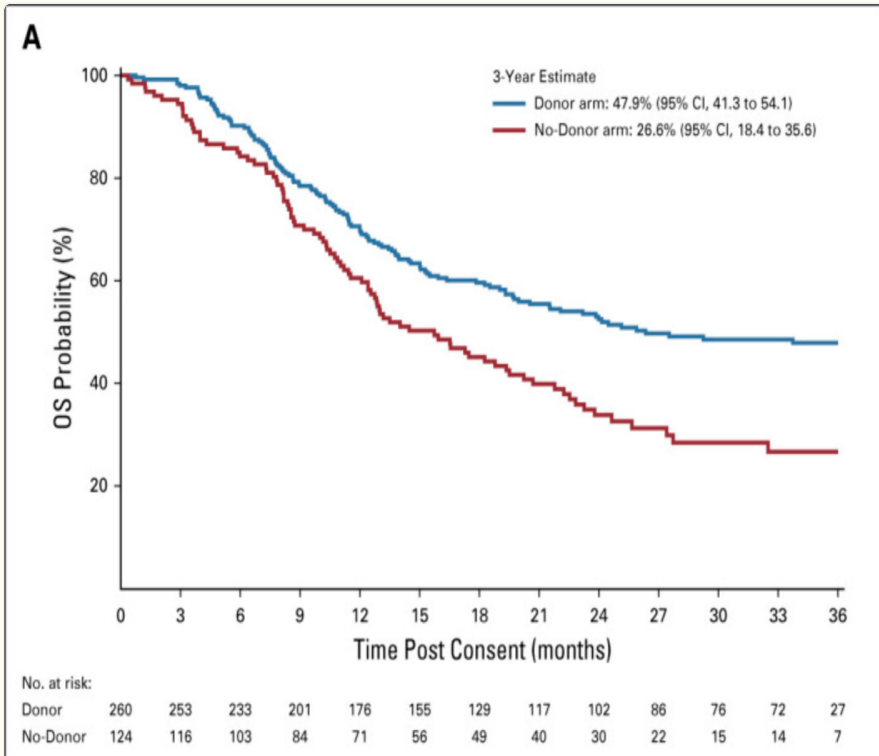
At risk	53	23	8	1
	126	25	7	2

**OS**

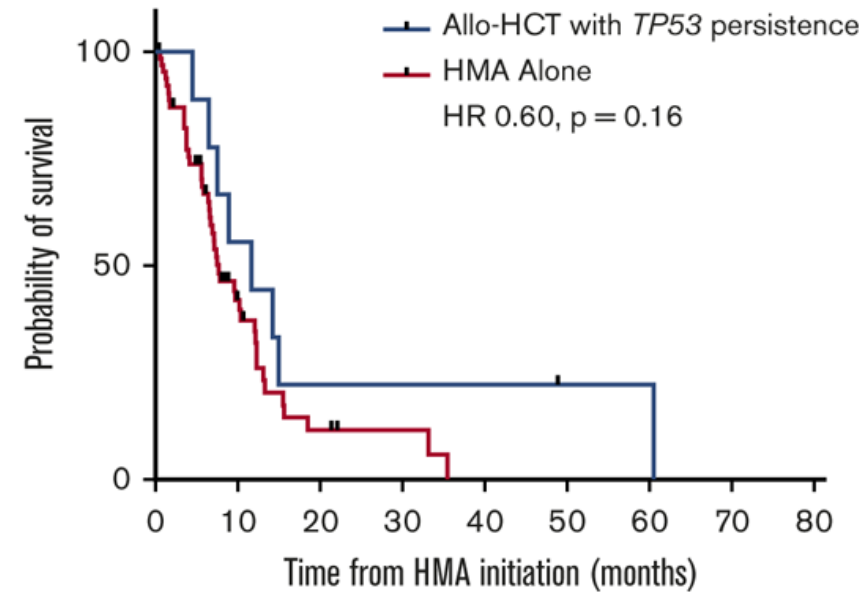
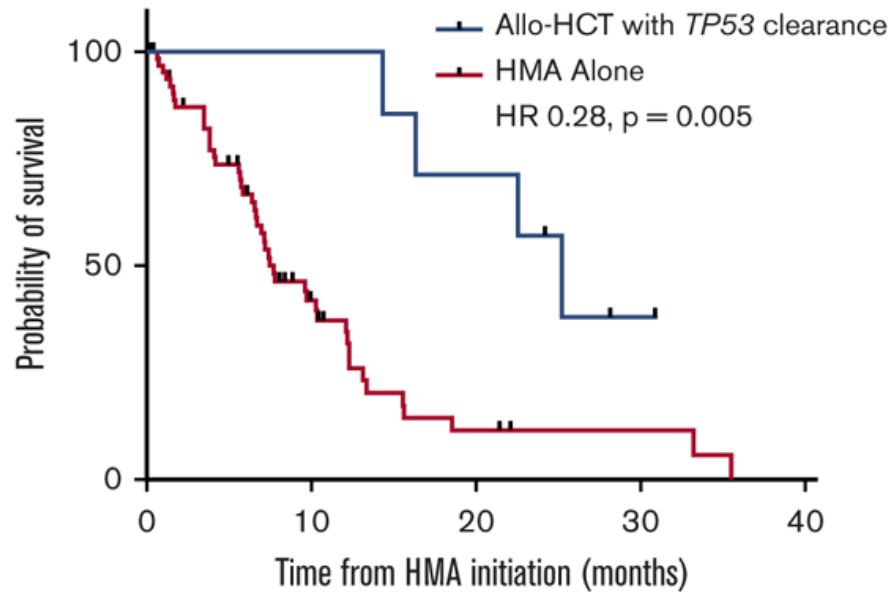


At risk	53	25	8	1
	126	38	12	3

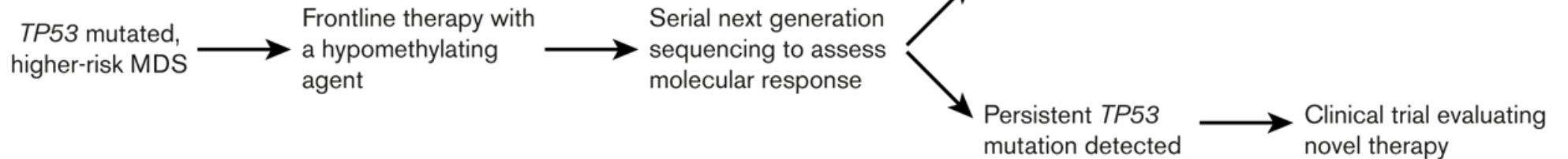
# Allo-HSCT Outcomes and *TP53*



# Allo-HSCT Outcomes and *TP53* Clearance

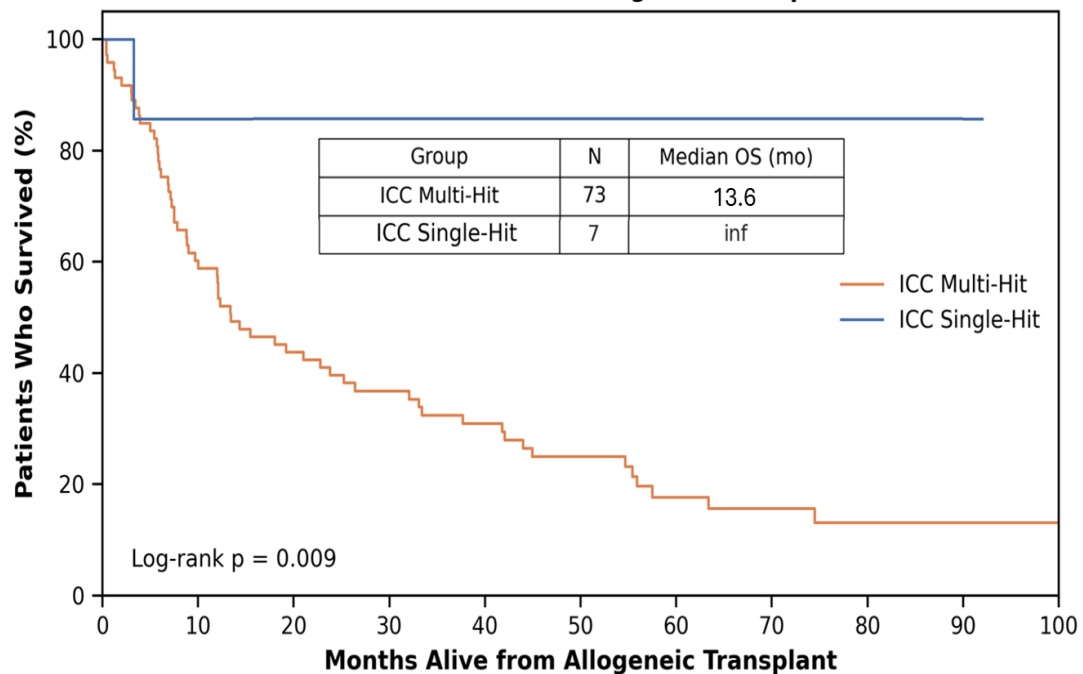


## Proposed treatment algorithm for *TP53* mutated MDS:



# Outcomes with Allo-SCT based on Hit Status and Donor Source

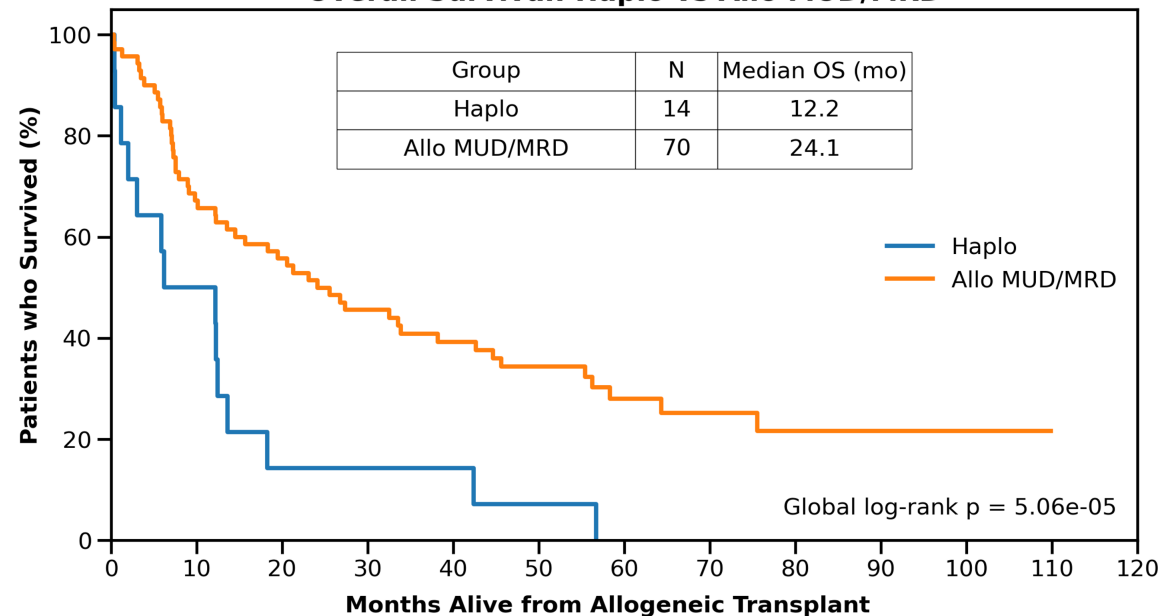
Overall Survival from Allogeneic Transplant



No. at Risk

	0	10	20	30	40	50	60	70	80	90	100
ICC Multi-Hit	73	44	33	26	22	17	10	7	6	4	2
ICC Single-Hit	7	7	7	6	5	5	2	2	2	2	1

Overall Survival: Haplo vs Allo MUD/MRD

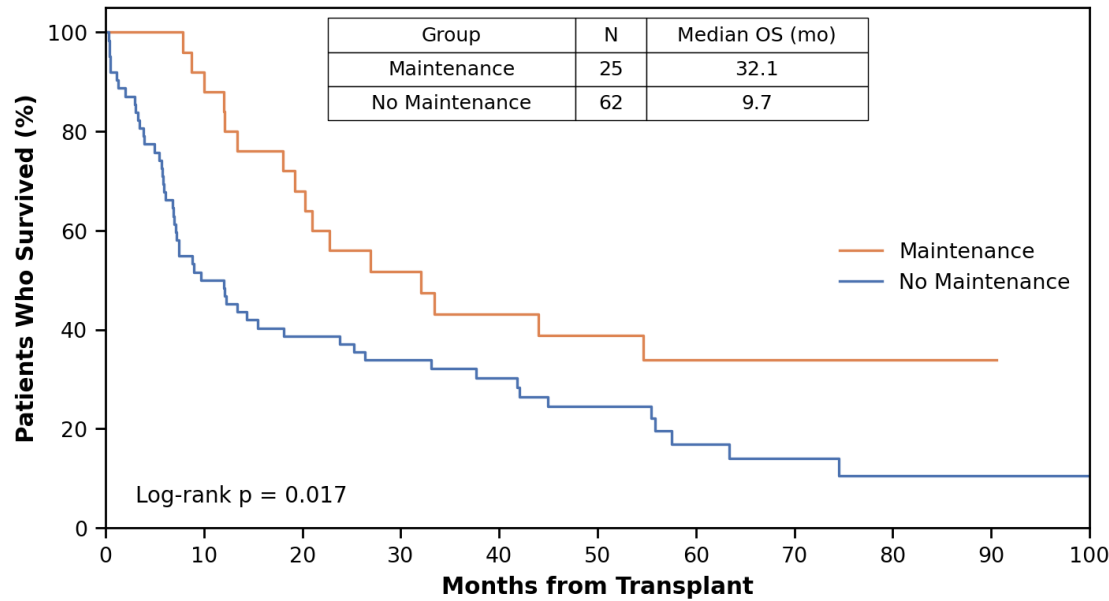


No. at Risk

	0	10	20	30	40	50	60	70	80	90	100	110	120
Haplo	14	8	3	3	3	2	1	1	1	1	1	1	1
Allo	70	48	40	30	25	21	11	9	7	5	2	1	1

# Impact of HMA Maintenance Post-HCT for TP53 MDS/AML

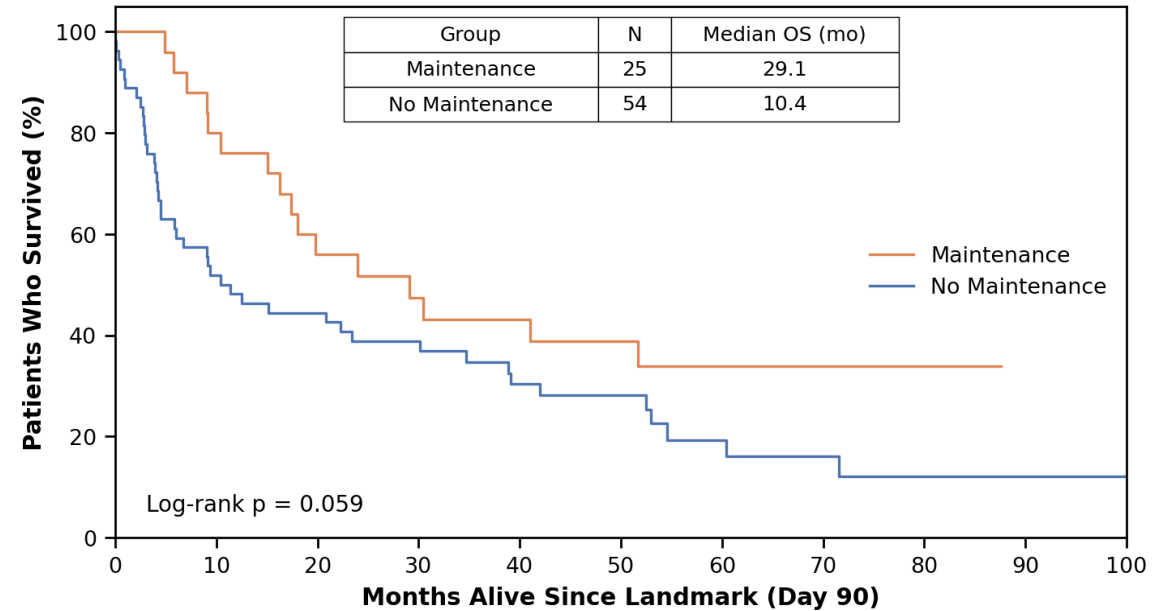
Overall Survival: Maintenance vs No Maintenance



No. at Risk

	0	10	20	30	40	50	60	70	80	90	100
Maint. 25	25	23	18	13	11	9	5	4	4	2	1
No Maint. 62	62	32	25	20	17	14	7	5	4	4	2

Overall Survival from 3-Month Landmark



No. at Risk

	0	10	20	30	40	50	60	70	80	90	100
Maint. 25	25	21	15	12	11	9	5	4	3	1	1
No Maint. 54	54	29	25	20	15	12	7	5	4	3	2

MV analysis confirmed Improved OS Independent of ICC Multi-HIT, TP53 VAF  $\geq 23\%$ , CK, MDS/AML or Donor Type  
 HR 0.36 (95% CI .17-.8; P=0.01)

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## Collaborators across VALIDATE

