SUPPLEMENTAL FIGURES AND TABLES LEGENDS

Supplemental Figure 1: Treatment flow chart of "7+7" cohort.

Supplemental Figure 2: HMA and venetoclax dosing for the "std-HMA/VEN"cohort in cycles 1 through 3. **(A)** HMA type and duration and **(B)** venetoclax duration for cycle 1 (n=173). **(C)** HMA type and duration and **(D)** venetoclax duration for cycle 2 (n=133). **(E)** HMA type and duration and **(F)** venetoclax duration for cycle 3 (n=102).
Abbreviations: ASTX, ASTX727 (oral decitabine/cedazuridine); AZA, azacitidine; DAC, decitabine; HMA, hypomethylating agent; MDACC, MD Anderson Cancer Center.

Supplemental Figure 3: Overall survival and event-free survival censored for allogeneic SCT of "7+7" vs "std-HMA/VEN" cohorts.
(A) Overall survival censored for allogeneic SCT stratified by treatment cohort. (B) Event-free survival censored for allogeneic SCT stratified by treatment cohort. Abbreviations: EFS, event-free survival; HMA, hypomethylating agent; OS, overall survival; VEN, venetoclax.

Supplemental Figure 4: Overall survival and event-free survival with 10-day decitabine versus other regimens, including TP53-mutated subset. **(A)** Overall survival with the 7+7 regimen, 10-day decitabine regimen, and other HMA VEN doublets. **(B)** Event-free survival with the 7+7 regimen, 10-day decitabine regimen, and other HMA VEN doublets. **(C)** Overall survival in patients with *TP53*-mutated AML with the 7+7 regimen versus 10-day decitabine. **(D)** Event-free survival in patients with *TP53*-mutated AML with the 7+7 regimen versus 10-day decitabine. Abbreviations: DAC, decitabine; EFS, event-free survival; HMA, hypomethylating agent; OS, overall survival; VEN, venetoclax.

Supplemental Figure 5: OS stratified by treatment cohort and mPRS, censored for SCT. **(A)** Overall survival stratified by treatment cohort and molecular prognostic risk signature (mPRS) predicted benefit (high, intermediate, or low benefit). **(B)** Event-free survival stratified by treatment cohort and mPRS. Abbreviations: EFS, event-free survival; HMA, hypomethylating agent; mPRS, molecular prognostic risk signature; OS, overall survival; VEN, venetoclax.

Supplemental Figure 6: OS in mPRS high benefit, stratified by treatment cohort and presence or absence of *NPM1* (A) or *IDH1/2* mutations (B).
(A) Overall survival stratified by treatment cohort and *NPM1* mutation status in patients with a high-predicted benefit by molecular prognostic risk signature (mPRS). **(B)** Overall survival stratified by treatment cohort and *IDH1/2* mutation status in patients with a high-predicted benefit by molecular prognostic risk signature (mPRS).

Supplemental Figure 7: Univariate and multivariate analysis of OS in intermediate- and lower-benefit predicted by mPRS.
(A) Univariate and multivariate analysis of overall survival in patients with intermediate-benefit predicted by molecular prognostic risk signature (mPRS). **(B)** Univariate and multivariate analysis of overall survival in patients with lower-benefit predicted by molecular prognostic risk signature (mPRS). Abbreviations: AML-pCT, AML post-cytotoxic therapy; CG, cytogenetic; DAC, decitabine; HMA, hypomethylating agent; mPRS, molecular prognostic risk signature; OS, overall survival; PS, Performance Status; VEN, venetoclax.

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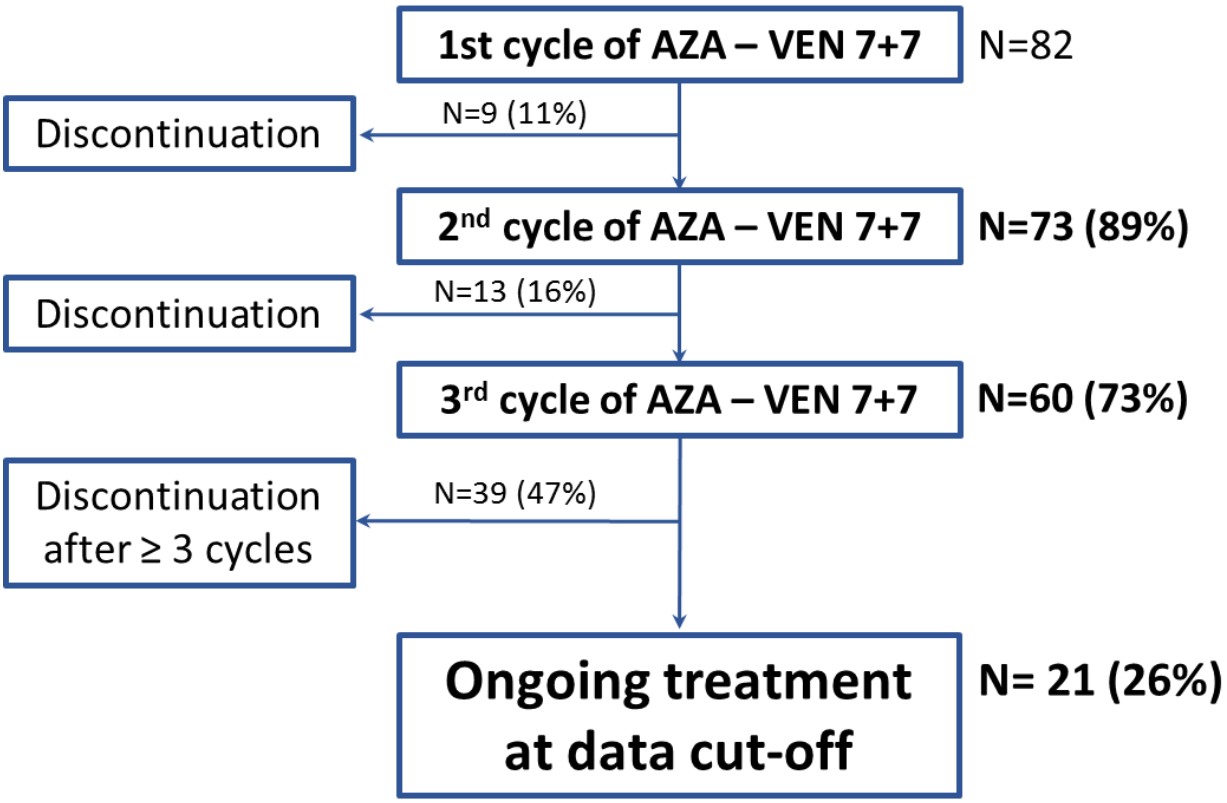

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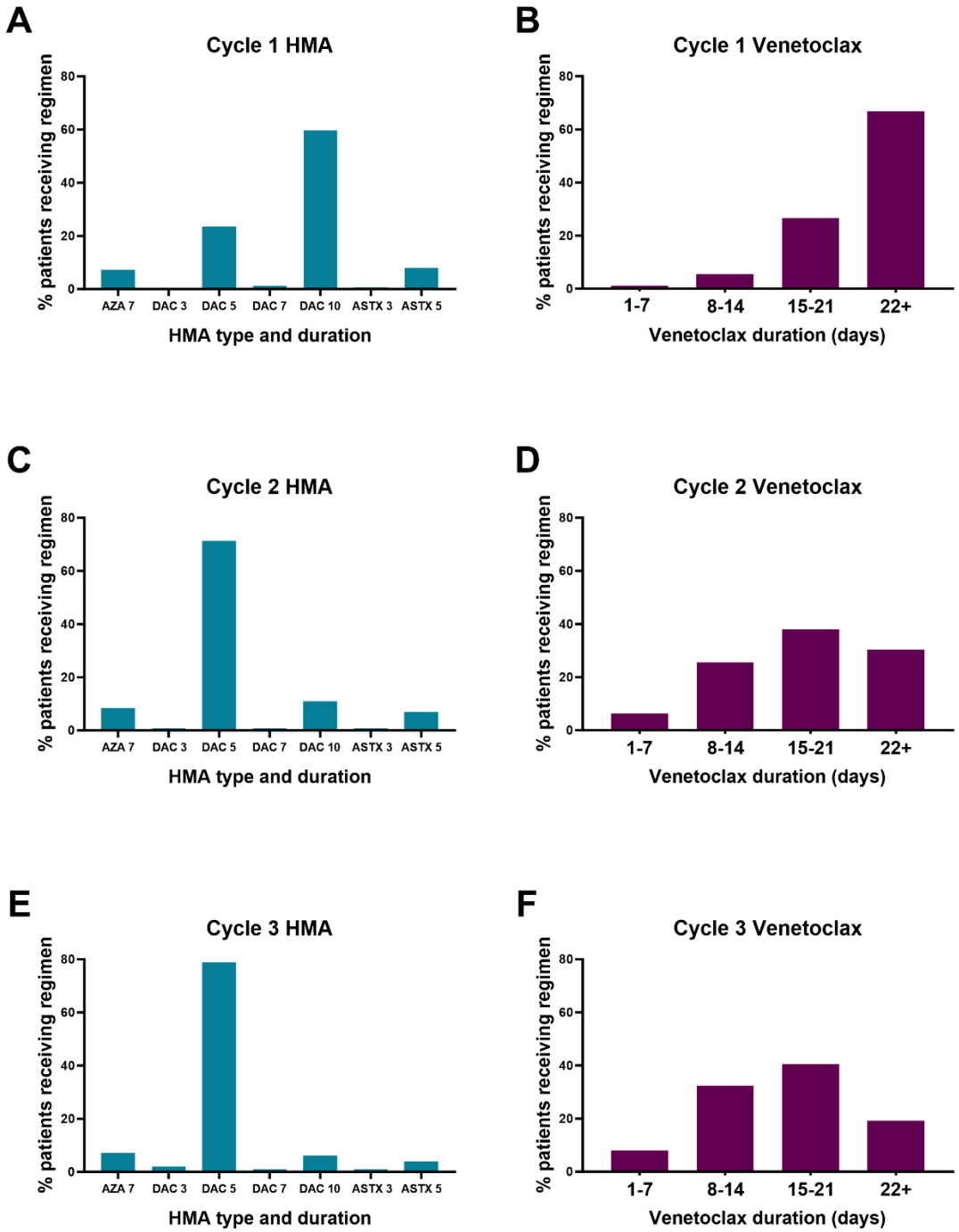

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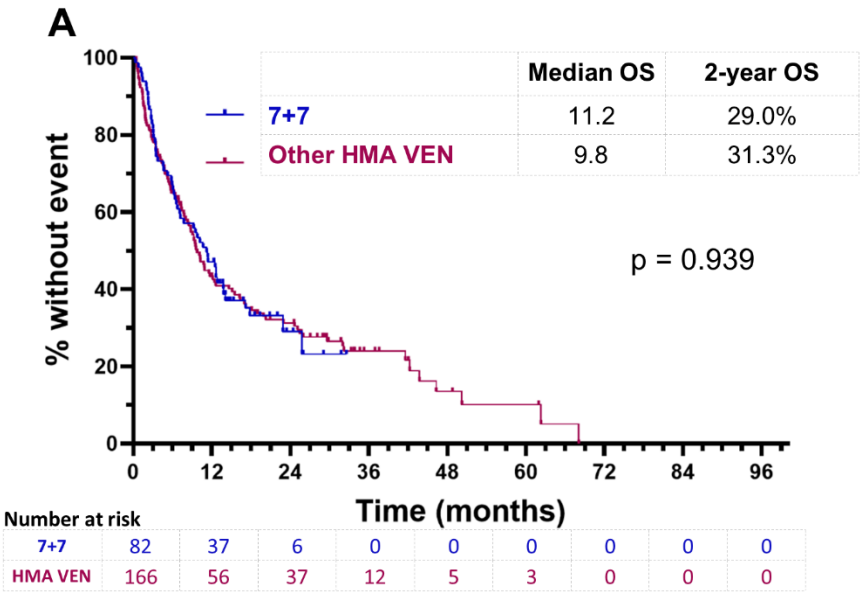

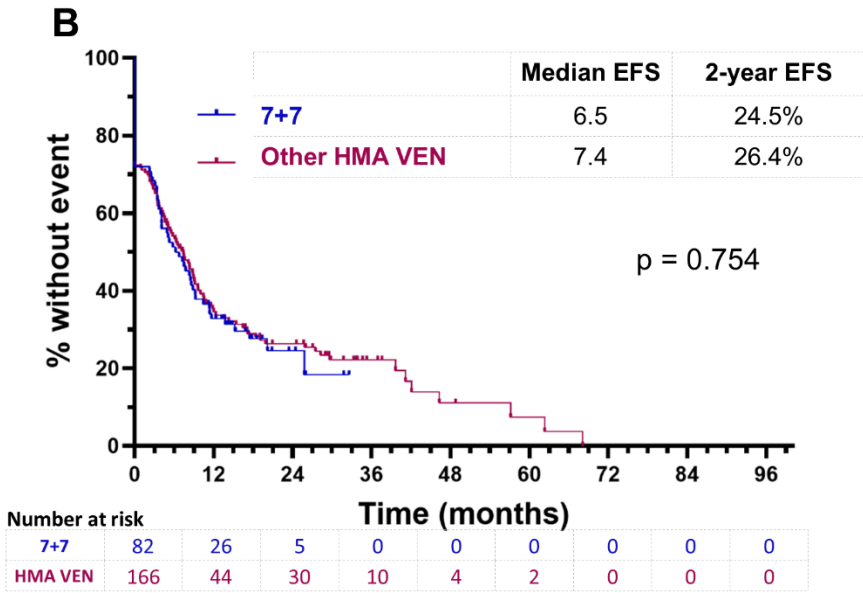

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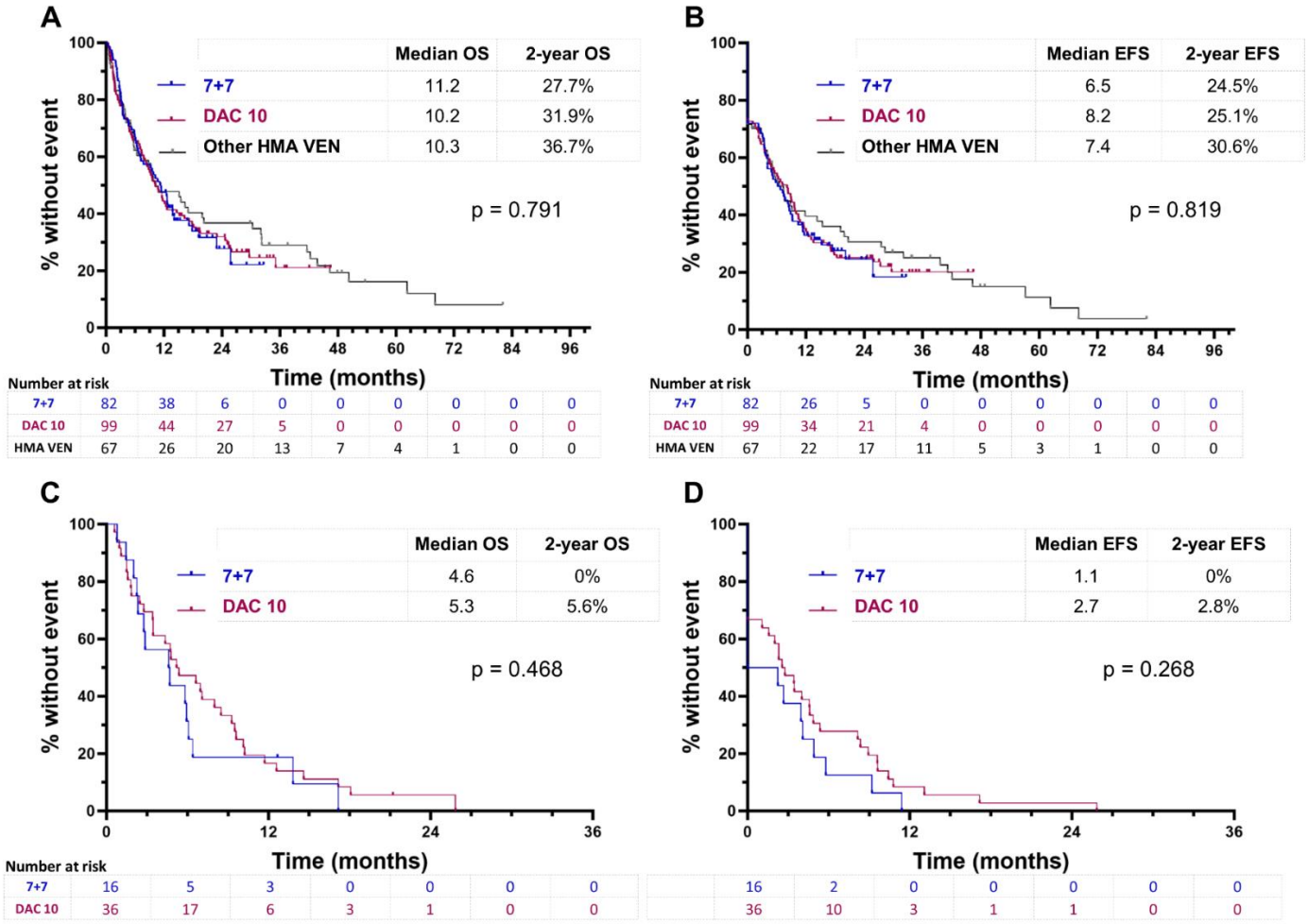

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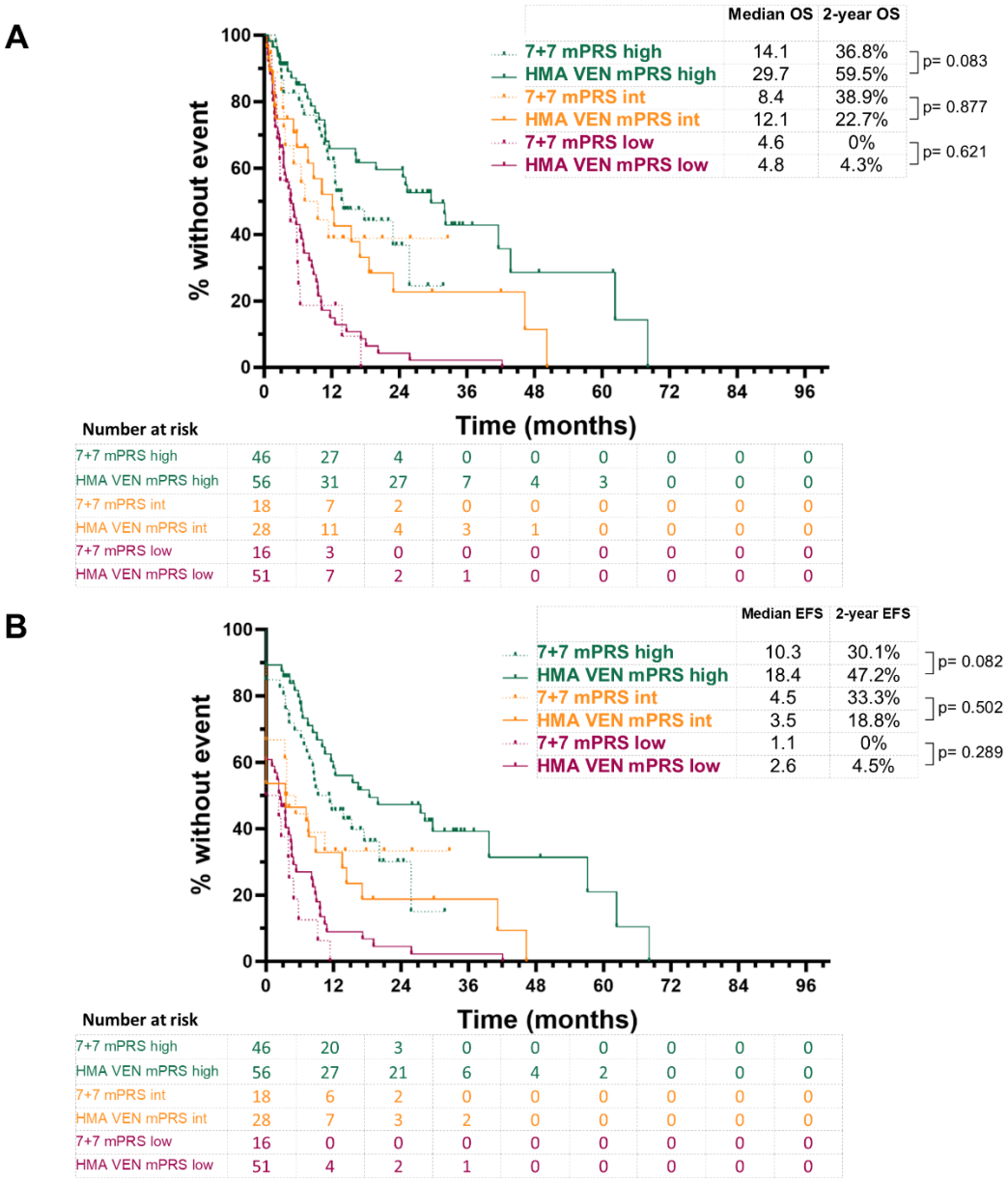

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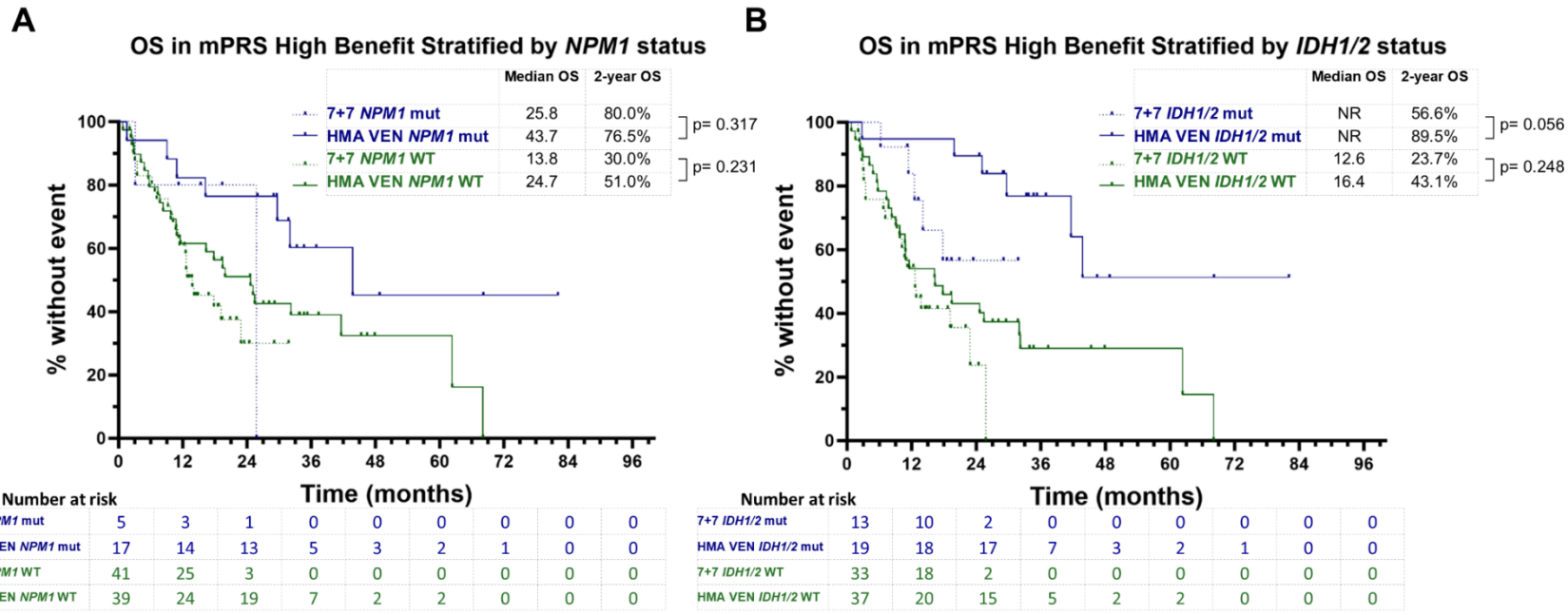

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A

Overall Survival (OS) for mPRS Intermediate benefit							
	Univariate analysis for OS				Multivariate analysis for OS			
Variable	N event/ N total	HR (95% CI)		P val	N event/N total	HR (95% CI)		P val
Treatment								
HMA+Ven	11/15	Ref		-	11/15	Ref		-
Dac10Ven	11/13	1.2 (0.49-2.89)		0.692	10/12	1.14 (0.41-3.2)		0.805
7+7	11/18	1.12 (0.46-2.73)		0.81	10/17	1.17 (0.39-3.52)		0.779
Age (≥ 75)	21/31	1.25 (0.59-2.64)		0.555	20/30	1.52 (0.58-3.94)		0.393
PS (≥ 2)	11/15	1.8 (0.84-3.85)		0.13	10/14	2.44 (0.94-6.33)		0.067
Complex CG	5/5	3.44 (1.25-9.51)		0.017	5/5	3.57 (0.99-12.82)		0.051
NPM1 mut	12/15	0.89 (0.44-1.82)		0.751	10/13	0.74 (0.28-1.91)		0.529
IDH1/2 mut	6/8	1.37 (0.56-3.38)		0.494	6/8	0.84 (0.28-2.51)		0.751
Prior MDS/MPN	7/9	2.23 (0.93-5.36)		0.072	7/9	1.68 (0.55-5.19)		0.364
AML-pCT	4/7	0.49 (0.17-1.42)		0.189	3/6	0.48 (0.13-1.84)		0.287

B

Overall Survival (OS) for mPRS Lower benefit							
	Univariate analysis for OS				Multivariate analysis for OS			
Variable	N event/ N total	HR (95% CI)		P val	N event/N total	HR (95% CI)		P val
Treatment								
HMA+Ven	14/15	Ref		-	14/15	Ref		-
Dac10Ven	35/36	1.16 (0.59-2.26)		0.668	31/32	1.13 (0.54-2.36)		0.751
7+7	15/16	1.4 (0.64-3.06)		0.401	14/15	1.44 (0.58-3.58)		0.430
Age (≥ 75)	27/28	1 (0.6-1.66)		0.988	24/25	1.09 (0.57-2.09)		0.787
PS (≥ 2)	23/25	1.34 (0.79-2.29)		0.277	22/24	1.48 (0.8-2.76)		0.213
Complex CG	57/60	0.64 (0.27-1.49)		0.298	54/57	0.51 (0.16-1.57)		0.241
NPM1 mut	1/1	1.7 (0.23-12.46)		0.604	1/1	1.21 (0.14-10.81)		0.864
IDH1/2 mut	3/3	1.26 (0.39-4.04)		0.698	3/3	1.29 (0.36-4.62)		0.692
Prior MDS/MPN	11/12	0.79 (0.41-1.52)		0.485	11/12	0.68 (0.34-1.39)		0.292
AML-pCT	27/28	1.06 (0.65-1.76)		0.806	25/26	0.91 (0.48-1.72)		0.762

Supplemental Table 1: Medical conditions captured by retrospective analysis explaining reduced VEN exposure in "7+7" cohort.

	Number (%)	Details
PATIENTS WITH AT LEAST ONE EXCLUSION CRITERIA TO VIALE-A PROTOCOL N=35/82 (44%)		
Previously non resected tumor or concomitant solid/lymphoid neoplasia (metastatic disease or requiring therapy)*	21/82	Multiple myeloma (N=4) ; Large B-cell lymphoma (N=1); Chronic lymphocytic leukemia (N=1); Metastatic or relapsing breast cancer (N=4); Progressive ovarian cancer (N=1); Metastatic breast and ovarian cancer (N=1); Metastatic thymic carcinoma (N=1); Liposarcoma (N=1); Progressive non-seminomatous germ cell cancer (N=1); Progressive squamous cell carcinoma of head and neck (N=2); Urothelial carcinoma (N=1) Prostate cancer (N=2); Spinal ependymoma (N=1)
Altered ECOG Performans status (≥3 if ≥75 years; ≥4 if <74 years)	7/82	
Chronic renal failure (creatinine clearance <30ml/min)	4/82	
Prior MPN	3/82	
AML with t(8;21)	1/82	
PATIENTS WITH MEDICAL CONDITIONS WITH POSSIBLE EXCLUSION CRITERIA'S TO CLINICAL TRIAL N=13/82 (16%)		
Liver transplant	1/82	
Denutrition (Body Mass Index <17)	3/82	
Significant cardiac or artery disease (i.e. with sequellae of ischemia or requiring artery bypass)	8/82	
Chronic renal failure (creatinine clearance <40ml/min)	2/82	

* Supplemental patients (N=6) had previous breast cancer treated with surgery and chemotherapy +/- radiotherapy but considered as treated with a curative intent and potentially included in the VIALE-A trial.

Supplemental Table 2: Baseline Characteristics in mPRS high benefit patients.

Parameter	Gustave Roussy Cohort "7+7" n=46	MDACC Cohort "std-HMA/VEN" n=56	p
Age	76 [59-89]	72 [61-89]	0.075
Male	23 (50)	33 (59)	0.367
ECOG PS			
0-1	33 (72)	36/47 (77)	0.593
2-4	13 (28)	11/47 (23)	
BM blast %	39 [16-98]	35 [4-90]	0.164
WBC (x 10^9/L)	3.5 [0.3-21.7]	2.5 [0.6-25.5]	0.079
Hemoglobin (g/dL)	9.5 [6.6-11.6]	9.3 [7.2-12.7]	0.880
Platelets (x 10^9/L)	71 [12-720]	54 [9-310]	0.099
Total bilirubin (mg/dL)	0.58 [0.41-4.62]	0.50 [0.20-2.70]	**0.018**
Creatinine (mg/dL)	0.83 [0.33-3.01]	0.90 [0.55-1.78]	0.127
Cytogenetics			
Diploid	20/43 (47)	29/55 (53)	0.541
Other intermediate	13/43 (30)	13/55 (24)	0.463
11q23 rearranged	1/43 (2)	3/55 (5)	0.629
inv(3)	2/43 (5)	1/55 (2)	0.580
-5/5q-	4/43 (9)	5/55 (9)	1.00
-7/7q-	6/43 (14)	4/55 (7)	0.327
-17/17p-	3/43 (7)	0/55 (0)	0.081
Complex	2/43 (5)	5/55 (9)	0.462
Mutations			
NPM1	5 (11)	17 (30)	**0.017**
IDH1/IDH2	13 (28)	19 (34)	0.539
Prior MDS or MPN	17 (37)	12 (21)	0.084
AML-pCT	11 (24)	10 (18)	0.452

Data displayed as n (%) or median [range].

Abbreviations: BM, bone marrow; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ELN, European LeukemiaNet; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; mPRS, molecular prognostic risk signature; WBC, white blood cell; AML-pCT : acute myeloid leukemia post cytotoxic therapy.

Supplemental Table 3: Azole antifungal use during cycle 1 by treatment regimen.

	Gustave Roussy Cohort "7+7" n=82	**MDACC Cohort "std-HMA/VEN" n=166**
Any azole antifungal	30 (37)	122 (73)
Posaconazole	29 (35)	77 (46)
Voriconazole	1 (1)	19 (11)
Isavuconazole	0	25 (15)
Fluconazole	0	1 (1)

Supplemental Table 4: CRc rates between regimens stratified by mutation status in *NPM1*, *IDH1/2*, and *TP53*.

	Gustave Roussy Cohort "7+7"	MDACC Cohort "std-HMA/VEN"	p-value
***NPM1*-mutated**	11/12 (92%)	26/29 (90%)	1.000
***IDH1/2*-mutated**	13/14 (93%)	26/31 (84%)	0.648
***TP53*-mutated**	8/16 (50%)	31/51 (61%)	0.445