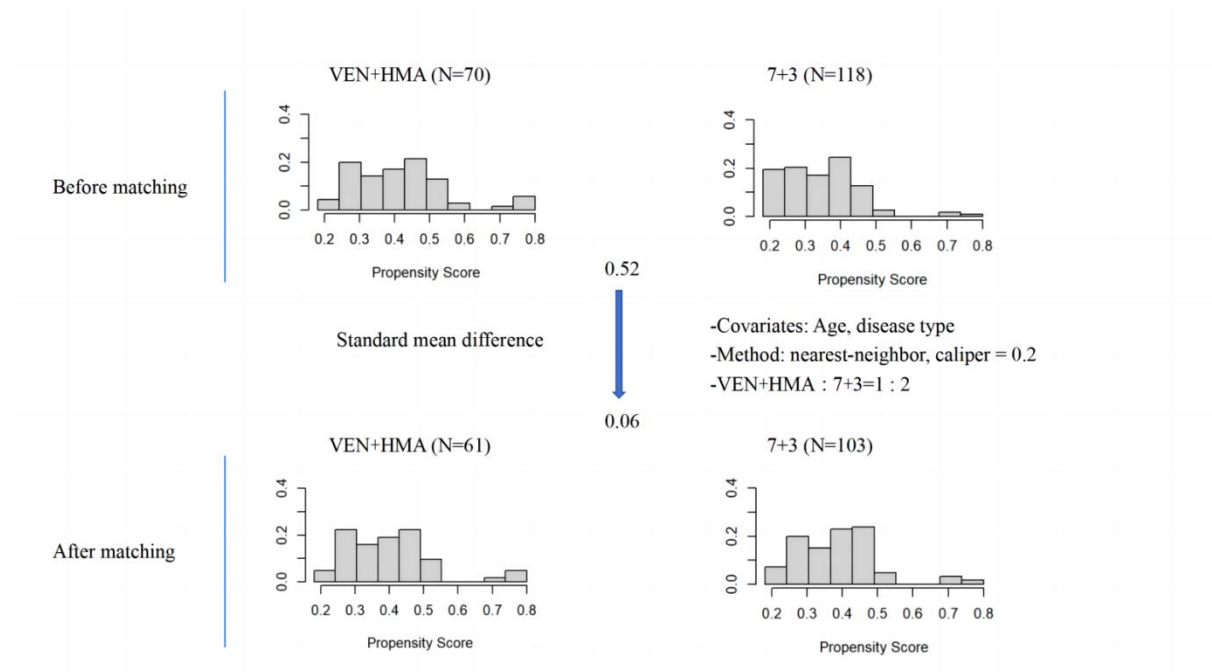
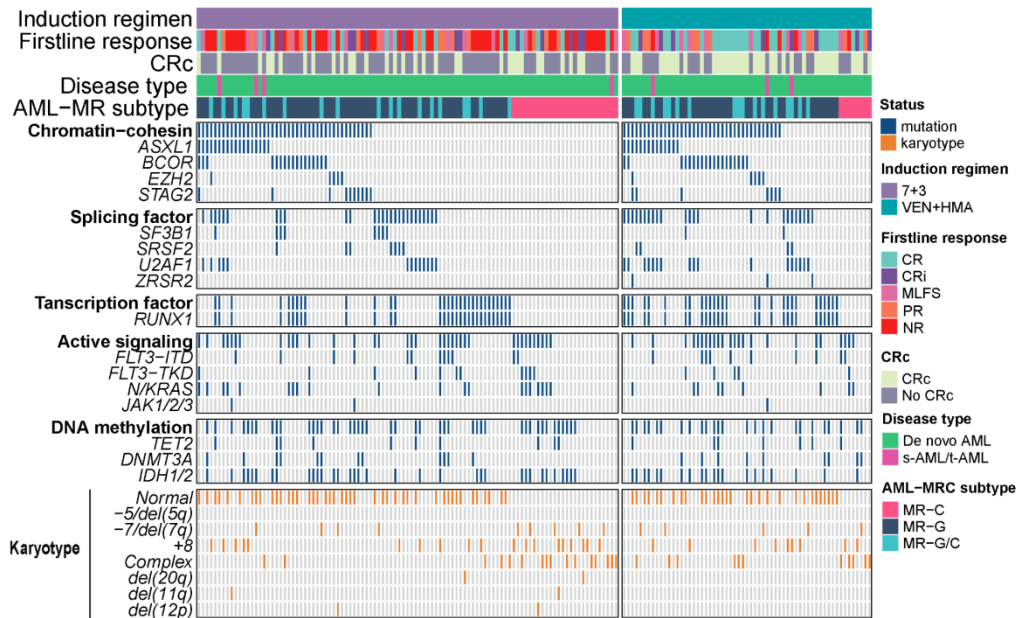


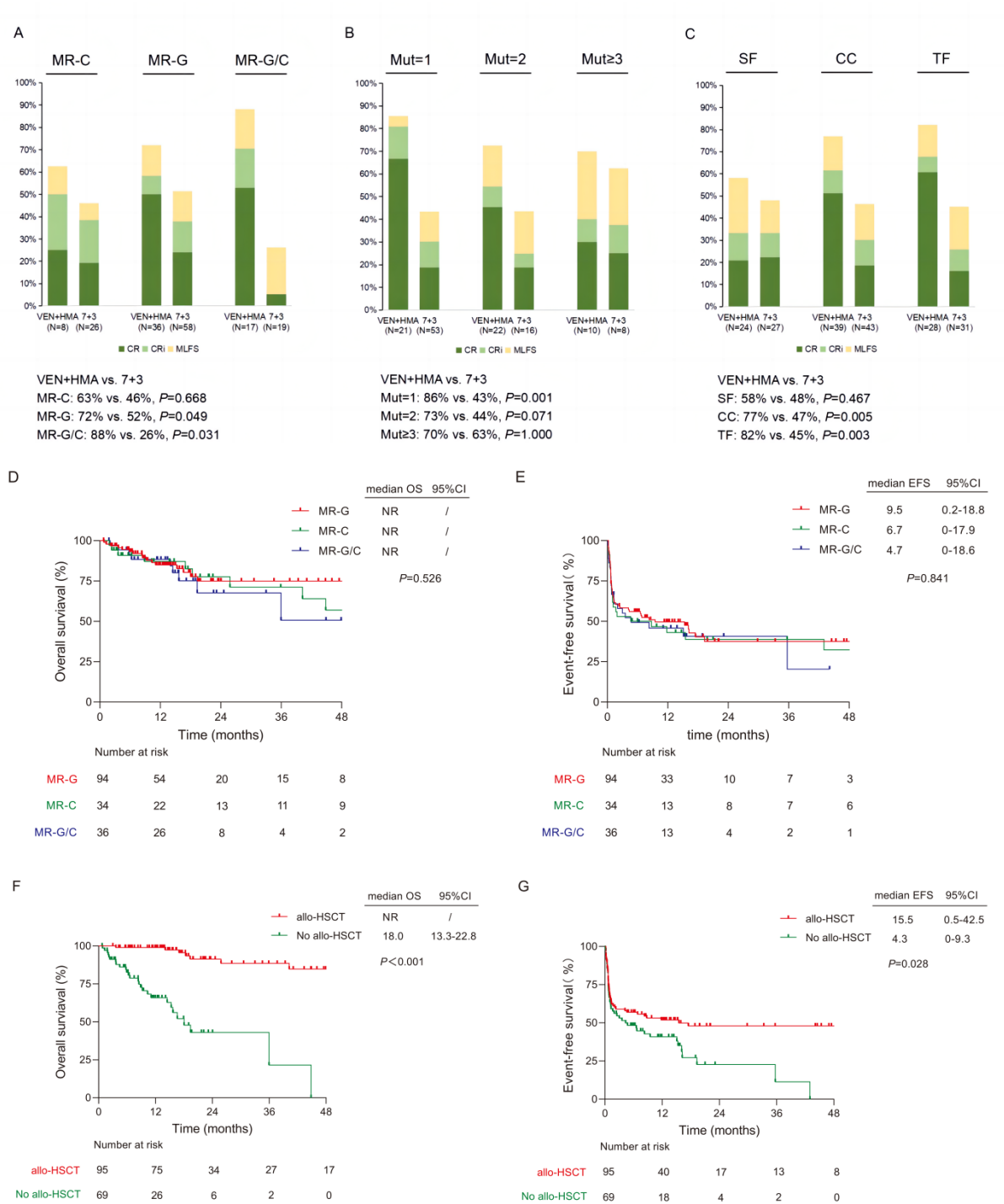
Supplementary Figure



Supplementary figure 1. Propensity score matching process. VEN+HMA, venetoclax plus hypomethylating agents; Disease type: de novo AML or secondary/therapy-related AML.



Supplementary figure 2. Clinical response and cytogenetic landscape of 103 AML-MR patients in 7+3 cohort and 61 AML-MR patients in VEN+HMA cohort. Abbreviations: CR, complete remission; CRi, CR with incomplete count recovery; CRc, composite complete remission; MLFS, morphologic leukemia-free state; PR, partial remission; NR, no remission; MR-C, myelodysplasia-related cytogenetic abnormalities; MR-G, myelodysplasia-related gene mutations; MR-G/C, both myelodysplasia-related gene mutations and cytogenetic abnormalities; s-AML, secondary AML; t-AML, therapy-related AML; VEN+HMA, venetoclax plus hypomethylating agents.



Supplementary figure 3. Responses and survival analysis. (A-C) Comparison of treatment overall response rate in subgroups. (D-E) OS and EFS comparison between patients with different myelodysplasia-related abnormalities. (F-G) OS and EFS comparison between AML-MR patients with or without allo-HSCT. Abbreviations: MR-C, myelodysplasia-related cytogenetic abnormalities; MR-G, myelodysplasia-related gene mutations; MR-G/C, both myelodysplasia-related gene mutations and cytogenetic abnormalities; mut=1, one myelodysplasia-related gene mutation; mut=2, two myelodysplasia-related genes mutation; mut≥3, three or more myelodysplasia-related genes mutation; SF, splicing factor; CC, chromatin-cohesin; TF, transcription factor; UVA, Univariable analysis; MVA, multivariable analysis; CI, confidence interval; allo-HSCT, allogeneic hematopoietic stem cell transplantation; NR, not reached; OS, overall survival; EFS, event-free survival; VEN+HMA, venetoclax plus hypomethylating agents.

Supplementary Table

Supplementary table 1. Breakdown of MDS related cytogenetic abnormalities in VEN+HMA and 7+3 cohorts.

Cytogenetic abnormalities	VEN+HMA	7+3
	n=61	n=103
Complex karyotype	11 (18%)	16 (16%)
del(5q)/t(5q)/add(5q)	0	0
-7/del(7q)	5 (8%)	9 (9%)
+8	9 (15%)	19 (18%)
del(12p)/t(12p)/add(12p)	0	2 (2%)
i(17q)	0	0
-17/add(17p)/del(17p)	0	0
idic(X)(q13)	0	0

Abbreviations: VEN+HMA, venetoclax plus hypomethylating agents.

Supplementary table 2. Distribution of different regimens in VEN+HMA and 7+3 cohorts.

VEN+HMA	
	n=61
VEN+Azacitidine	32
VEN+Decitabine	28
VEN+Azacitidine+Sorafenib	1
7+3	
	n=103
IA	80
IAC	14
IA+Sorafenib	1
DA	2
MA	3
HA	3

Abbreviations: VEN, Venetoclax; IA, Idarubicin and Cytarabine; IAC, Idarubicin, Cytarabine and Cladribine; DA, Daunorubicin and Cytarabine; MA, Mitoxantrone and Cytarabine; HA, Homoharringtonine and Cytarabine.

Supplementary table 3. Comparison of treatment responses to different induction regimens in the matched cohorts.

	VEN+HMA (n=61)	7+3 (n=103)	<i>P</i> -value
Response outcome after 1 cycle of induction			
ORR	46 (75%)	47 (46%)	<0.001
CR	29 (48%)	20 (19%)	
CRi	8 (13%)	13 (13%)	
MLFS	9 (15%)	14 (14%)	
PR	10 (16%)	14 (14%)	
NR	5 (8%)	42 (41%)	
CRc rate	37 (61%)	33 (32%)	<0.001
MFC MRD available	35	32	
CR with negative MFC MRD	28 (46%)	20 (19%)	<0.001
CR with positive MFC MRD	7 (11%)	12 (12%)	
Splicing factor mutation	24	27	
CRc rate	8 (33%)	9 (33%)	1.000
Chromatin-cohesin mutation	39	43	
CRc rate	24 (62%)	13 (30%)	0.004
Transcription factor mutation	28	31	
CRc rate	19 (68%)	8 (26%)	0.001
Response outcome after 1~2 cycles of induction			
ORR	52 (85%)	72 (70%)	0.027
CR	35 (57%)	37 (36%)	
CRi	7 (11%)	17 (17%)	
MLFS	10 (16%)	18 (17%)	
PR	2 (3%)	9 (9%)	
NR	7(11%)	22 (21%)	
CRc rate	42 (69%)	54 (52%)	0.039
MFC MRD available	39	48	
CR with MFC MRD negative	34 (56%)	37 (36%)	0.013
CR with MFC MRD positive	5 (8%)	11 (11%)	

Abbreviations: ORR, Overall response rate; CR, complete remission; CRi, CR with incomplete blood count recovery; MLFS, morphologic leukemia-free state; CRc, Composite complete remission; PR, partial remission; NR, no response; VEN+HMA, venetoclax plus hypomethylating agents; MFC, multi-parameter flow cytometry; MRD, measurable residual disease.

Supplementary table 4. Treatment response of matched patients categorized according to gene mutation.

Mutations	VEN+HMA (n=61)			7+3 (n=103)			P-value ¹	P-value ²
	All patients	Patients in CRc	Patients in ORR	All patients	Patients in CRc	Patients in ORR		
Splicing factor	24 (39%)	8 (33%)	14 (58%)	27 (26%)	9 (33%)	13 (48%)	1.000	0.467
<i>U2AF1</i>	17 (28%)	3 (18%)	9 (53%)	13 (13%)	4 (31%)	5 (38%)	0.666	0.484
<i>SF3B1</i>	2 (3%)	2 (100%)	2 (100%)	8 (8%)	2 (25%)	3 (38%)	0.133	0.444
<i>SRSF2</i>	4 (7%)	3 (75%)	4 (100%)	7 (7%)	3 (43%)	5 (71%)	0.545	0.491
<i>ZRSR2</i>	3 (5%)	1 (33%)	1 (33%)	0	-	-	-	-
Chromatin-cohesin	39 (64%)	24 (62%)	30 (77%)	43 (42%)	13 (30%)	20 (47%)	0.004	0.005
<i>ASXL1</i>	14 (23%)	8 (57%)	10 (71%)	18 (17%)	4 (22%)	8 (44%)	0.068	0.165
<i>BCOR</i>	19 (31%)	11 (58%)	15 (79%)	17 (17%)	5 (29%)	7 (41%)	0.106	0.039
<i>EZH2</i>	5 (8%)	4 (80%)	5 (100%)	5 (5%)	2 (40%)	3 (60%)	0.524	0.444
<i>STAG2</i>	7 (11%)	4 (57%)	5 (71%)	10 (10%)	5 (50%)	7 (70%)	1.000	1.000
Transcription factor	28 (46%)	19 (68%)	23 (82%)	31 (30%)	8 (26%)	14 (45%)	0.001	0.003
<i>RUNX1</i>	28 (46%)	19 (68%)	23 (82%)	31 (30%)	8 (26%)	14 (45%)	0.001	0.003

Abbreviations: CRc, Composite complete remission; ORR, Overall response rate; VEN+HMA, venetoclax plus hypomethylating agents.

P-value¹: CRc rate comparison between VEN+HAM and 7+3 cohorts.

P-value²: ORR comparison between VEN+HAM and 7+3 cohorts.