Supplementary Table 1. Next-generation sequencing gene panel (A) Genes in the NGS Gene Panel (B) Exon coverage for hotspot genes

(A)

Complete coding region coverage (13/41)	**Hotspot coverage (28/41)**
BCOR	*ASXL1*
BCORL1	*BRAF*
CEBPA	*CALR*
CUX1	*CBL*
DNMT3A	*CSF3R*
ETV6	*FBXW7*
EZH2	*FLT3*
IKZF1	*GATA2*
PHF6	*GNAS*
RAD21	*IDH1*
RUNX1	*IDH2*
STAG2	*JAK2*
ZRSR2	*KIT*
	KMT2A
	KRAS
	MPL
	MYD88
	NOTCH1
	NPM1
	NRAS
	PTPN11
	SETBP1
	SF3B1
	SRSF2
	TET2
	TP53
	U2AF1
	WT1

(B)

Gene	Exon Coverage
ASXL1	12
BRAF	15
CALR	9
CBL	8, 9
CSF3R	14-17
FBXW7	9-11
FLT3	14, 15, 20
GATA2	2-6
GNAS	8, 9
IDH1	4
IDH2	4
JAK2	12, 14
KIT	2, 8-11, 13, 17
KMT2A	5-8
KRAS	2,3
MPL	10
MYD88	3-5
NOTCH1	26-28, 34
NPM1	12
NRAS	2, 3
PTPN11	3, 13
SETBP1	4
SF3B1	13-16
SRSF2	1
TET2	3-11
TP53	2-11
U2AF1	2, 6
WT1	7, 9

Supplementary Table 2. Summary descriptives table of study cohort by WHO-HAEM5

	AEL	AML-DIFF	AML-MR	AML-pCT	p-value
	N=3	***N=47***	***N=354***	***N=28***	
Sex:					0.030
Female	1 (33%)	22 (47%)	120 (34%)	16 (57%)	
Male	2 (67%)	25 (53%)	234 (66%)	12 (43%)	
Age at Diagnosis (yr)	71.3 (59.0, 80.0)	66.0 (18.0, 94.0)	72.0 (19.0, 95.0)	68.0 (22.0, 80.0)	0.031
Blast (%)	70.0 (40.0, 82.0)	42.5 (12.0, 95.0)	38.0 (12.0, 96.0)	51.5 (20.0, 97.0)	0.215
WBC (x10^9/L)	6.8 (6.0, 9.2)	4.0 (0.5, 188.4)	3.7 (0.1, 328.7)	3.9 (0.3, 209.4)	0.770
Hemoglobin (g/L)	85.0 (81.0, 89.0)	90.0 (40.0, 197.0)	86.0 (11.0, 169.0)	77.0 (37.0, 113.0)	0.274
Platelet (x10^9/L)	38.0 (23.0, 46.0)	71.0 (10.0, 419.0)	56.5 (6.0, 2,726.0)	40.0 (5.0, 247.0)	0.127
LDH (U/L)	952.0 (371.0, 2,438.0)	318.0 (148.0, 891.0)	309.0 (90.0, 9,473.0)	243.0 (154.0, 4,596.0)	0.241
CEBPA Mutation†	0 (0%)	1 (2.1%)	25 (7.1%)	1 (3.6%)	0.576
DNMT3A Mutation	1 (33%)	10 (21%)	66 (19%)	6 (21%)	0.703
IDH1 Mutation	0 (0%)	5 (11%)	37 (10%)	3 (11%)	>0.999
IDH2 Mutation	0 (0%)	7 (15%)	55 (16%)	2 (7.1%)	0.747
KRAS Mutation	0 (0%)	4 (8.5%)	17 (4.8%)	1 (3.6%)	0.529
NRAS Mutation	0 (0%)	4 (8.5%)	28 (7.9%)	5 (18%)	0.295
TP53 Mutation	3 (100%)	1 (2.1%)	100 (28%)	11 (39%)	<0.001
Karyotype Group:					<0.001
Abnormal karyotype	3 (100%)	21 (45%)	264 (75%)	20 (71%)	
Normal Karyotype	0 (0%)	26 (55%)	90 (25%)	8 (29%)	
Trisomy 8	0 (0%)	7 (15%)	63 (18%)	3 (11%)	0.798
Monosomy 17	1 (33%)	0 (0%)	53 (15%)	9 (32%)	<0.001
Type of Induction Treatment:					-

	AEL	AML-DIFF	AML-MR	AML-pCT	p-value
	N=3	*N=47*	*N=354*	*N=28*	
Best supportive care	2 (67%)	8 (17%)	62 (18%)	9 (32%)	
HMA/VEN	0 (0%)	2 (4.3%)	40 (11%)	1 (3.6%)	
Intensive chemotherapy	1 (33%)	31 (66%)	169 (48%)	14 (50%)	
Less intensive	0 (0%)	6 (13%)	83 (23%)	4 (14%)	
Response:					0.270
CR	1 (33%)	28 (62%)	140 (47%)	9 (47%)	
No CR	2 (67%)	17 (38%)	156 (53%)	10 (53%)	
Any Relapse	0 (0%)	15 (56%)	86 (65%)	9 (82%)	0.324
HCT	0 (0%)	19 (40.4%)	88 (24.9%)	8 (29%)	0.111
ELN 2022 Risk:					<0.001
Adverse	3 (100%)	8 (17.0%)	345 (97.5%)	21 (75%)	
Intermediate	0 (0%)	39 (83.0%)	8 (2.26%)	7 (25%)	
Mutation count	3 (1, 5)	2 (0, 6)	3 (0, 9)	2 (0, 9)	0.002

AEL, acute erythroid leukemia; AML-DIFF, AML by differentiation; AML-MR, AML with myelodysplasia-related; AML-pCT, AML post cytotoxic therapy; BM, bone marrow, WBC, white blood cell count; LDH, lactate dehydrogenase; ITD, internal tandem duplication; HMA/VEN, hypomethylating agents/venetoclax; CR, complete remission; HCT, hematopoietic stem cell transplant; ELN, European LeukemiaNet.

Continuous variables are expressed as median (range) and compared with Fisher's exact test. Categorical variables are expressed as frequency (percentage) and compared with Kruskal-Wallis rank sum test.

† *CEBPA* mutations other than those which meet the criteria from either WHO or ICC for defining AML with mutated *CEBPA*.

Supplementary Table 3. Patient Characteristics by *TP53* mutation status

	Negative ***N = 317***	**Positive** ***N = 115***	**p-value**
Sex			<0.001
Female	101 (32%)	58 (50%)	
Male	216 (68%)	57 (50%)	
Age at diagnosis (yr)	71.0 (18.0, 95.0)	73.0 (38.0, 94.0)	0.113
Blast (%)	40.0 (12.0, 97.0)	37.0 (20.0, 91.0)	0.219
WBC (x10^9/L)	4.0 (0.1, 328.7)	2.9 (0.1, 76.9)	0.005
Hemoglobin (g/L)	86.0 (11.0, 197.0)	84.0 (57.0, 123.0)	0.083
Platelet (x10^9/L)	63.5 (5.0, 2,726.0)	42.0 (6.0, 355.0)	0.001
LDH (U/L)	276.0 (90.0, 9,473.0)	323.0 (141.0, 3,569.0)	0.031
Prior myeloid neoplasms	45 (14%)	3 (2.6%)	<0.001
Prior cytotoxic therapy	17 (5.4%)	11 (9.6%)	0.117
Type of Karyotype:			<0.001
Abnormal karyotype	195 (62%)	113 (98%)	
Normal Karyotype	122 (38%)	2 (1.7%)	
Complex Karyotype	68 (21%)	108 (94%)	<0.001
Trisomy 8	53 (17%)	20 (18%)	0.851
Monosomy 17	7 (2.2%)	56 (49%)	<0.001
Mutation count	3.0 (0.0, 9.0)	2.0 (1.0, 6.0)	<0.001
FLT3-ITD	29 (25%)	0 (0%)	0.003
DNMT3A Mutation	63 (20%)	20 (17%)	0.563
IDH1 Mutation	36 (11%)	9 (7.8%)	0.288
IDH2 Mutation	61 (19%)	3 (2.6%)	<0.001
NRAS Mutation	33 (10%)	4 (3.5%)	0.023
KRAS Mutation	20 (6.3%)	2 (1.7%)	0.056
CEBPA Mutation[†]	26 (8.2%)	1 (0.9%)	0.005
ELN 2022 Risk:			<0.001

	Negative *N = 317*	Positive *N = 115*	p-value
Adverse	263 (83%)	114 (99%)	
Intermediate	53 (17%)	1 (0.9%)[§]	
Type of Induction chemotherapy:			<0.001
Best supportive care	46 (15%)	35 (30%)	
HMA/VEN	36 (11%)	7 (6.1%)	
Intensive chemotherapy	170 (54%)	45 (39%)	
Less intensive	65 (21%)	28 (24%)	
HCT	101 (32%)	14 (12%)	<0.001
Response:			<0.001
CR	154 (55%)	24 (29%)	
No CR	126 (45%)	59 (71%)	
Relapse	91 (61%)	19 (86%)	0.023

BM, bone marrow, WBC, white blood cell count; LDH, lactate dehydrogenase; ITD, internal tandem duplication; HMA/VEN, hypomethylating agents/venetoclax; CR, complete remission; HCT, hematopoietic stem cell transplant; ELN, European LeukemiaNet.

Continuous variables are expressed as median (range) and compared with Fisher's exact test. Categorical variables are expressed as frequency (percentage) and compared with Kruskal-Wallis rank sum test.

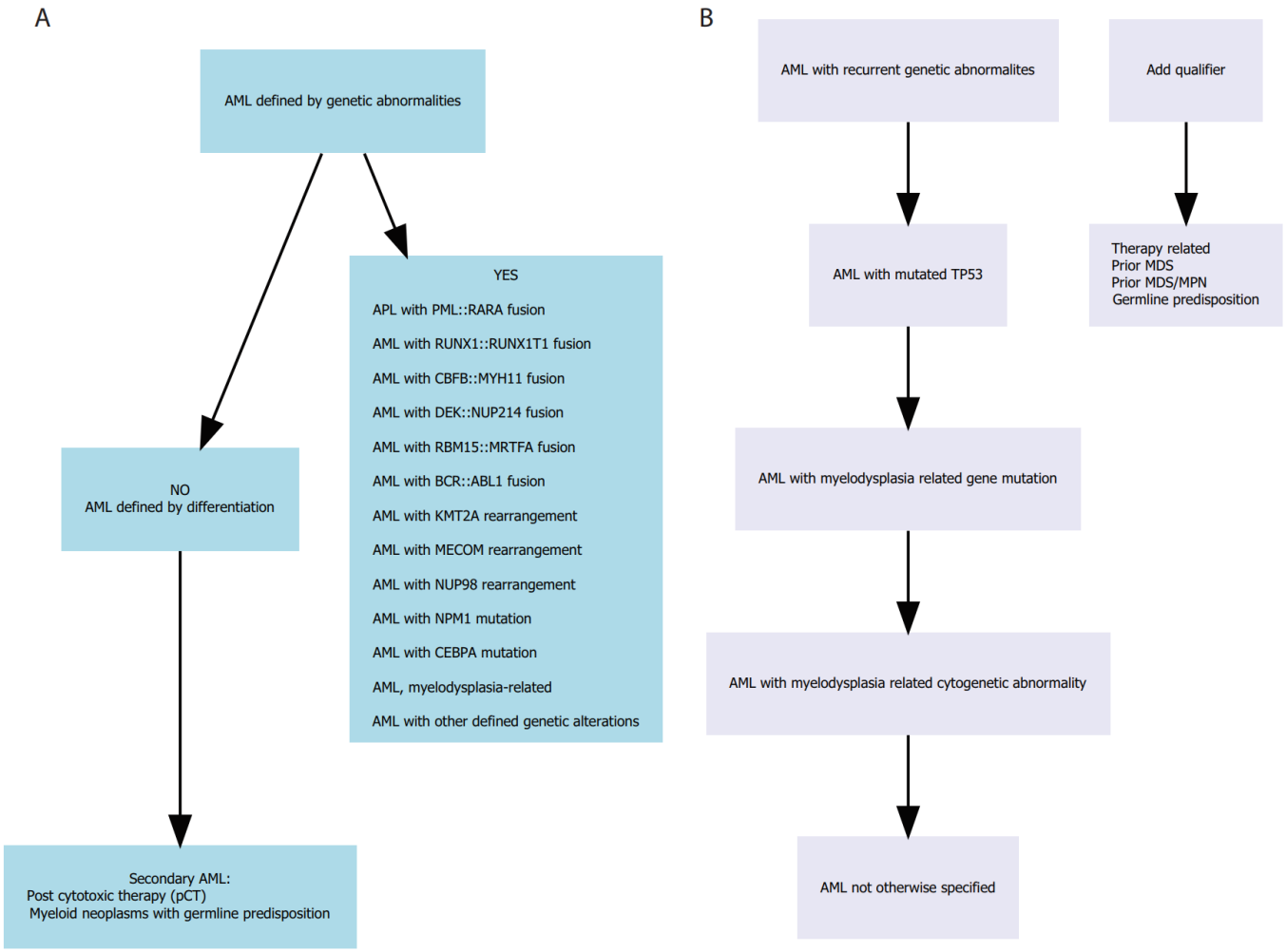
§ The *TP53* mutation allelic frequency is <10%; thus by ELN 2022 definition, this patient falls into intermediate risk category.

† *CEBPA* mutations other than those which meet the criteria from either WHO or ICC for defining AML with mutated *CEBPA*.

Supplementary Figure 1. The two simplified algorithms derived from newly published AML classifications.

A. WHO-HAEM5 classification of Acute Myeloid Leukemias

B. ICC classification of Acute Myeloid Leukemias



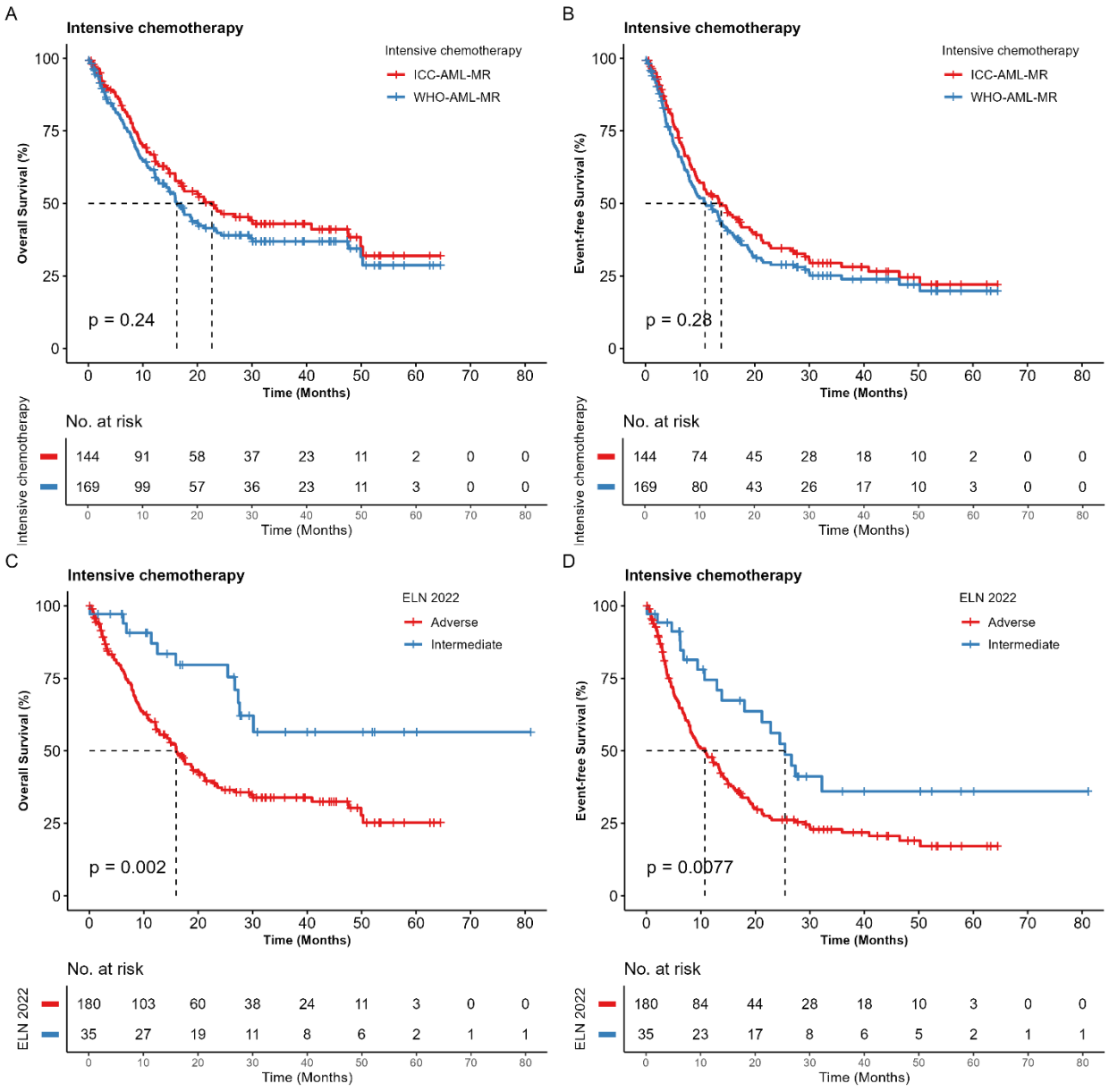
* Acute Erythroid Leukemia takes precedence over AML, myelodysplasia-related in WHO-HAEM5

Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic neoplasms; MDS/MPN, myelodysplastic neoplasm/myeloproliferative neoplasm.

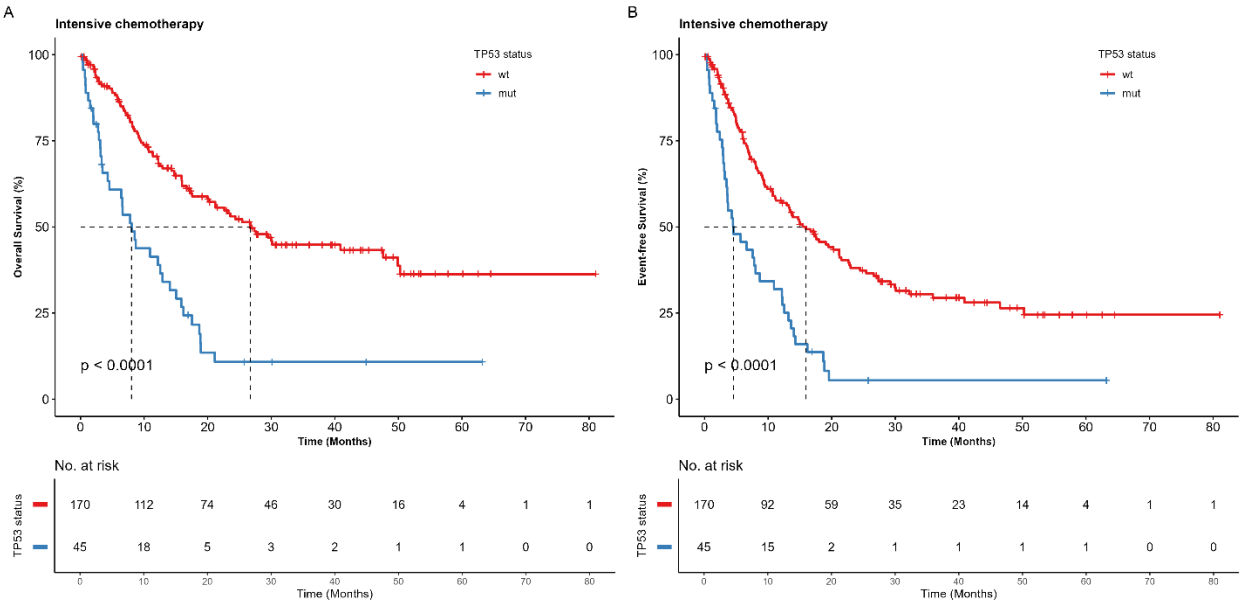
WHO defined myelodysplasia-related cytogenetic abnormalities: Complex karyotype (⩾3 abnormalities),5q deletion or loss of 5q due to unbalanced translocation, Monosomy 7, 7q deletion, or loss of 7q due to unbalanced translocation, 11q deletion, 12p deletion or loss of 12p due to unbalanced translocation,

Monosomy 13 or 13q deletion 17p deletion or loss of 17p due to unbalanced translocation Isochromosome 17q, idic(X)(q13)
ICC defined myelodysplasia-related cytogenetic abnormalities: complex karyotype (3 unrelated clonal chromosomal abnormalities in the absence of other class defining recurring genetic abnormalities), del(5q)/t(5q)/add(5q), 27/del(7q), 18, del(12p)/t(12p)/add(12p), i(17q), 217/add(17p) or del(17p), del(20q), and/or idic(X)(q13) clonal abnormalities

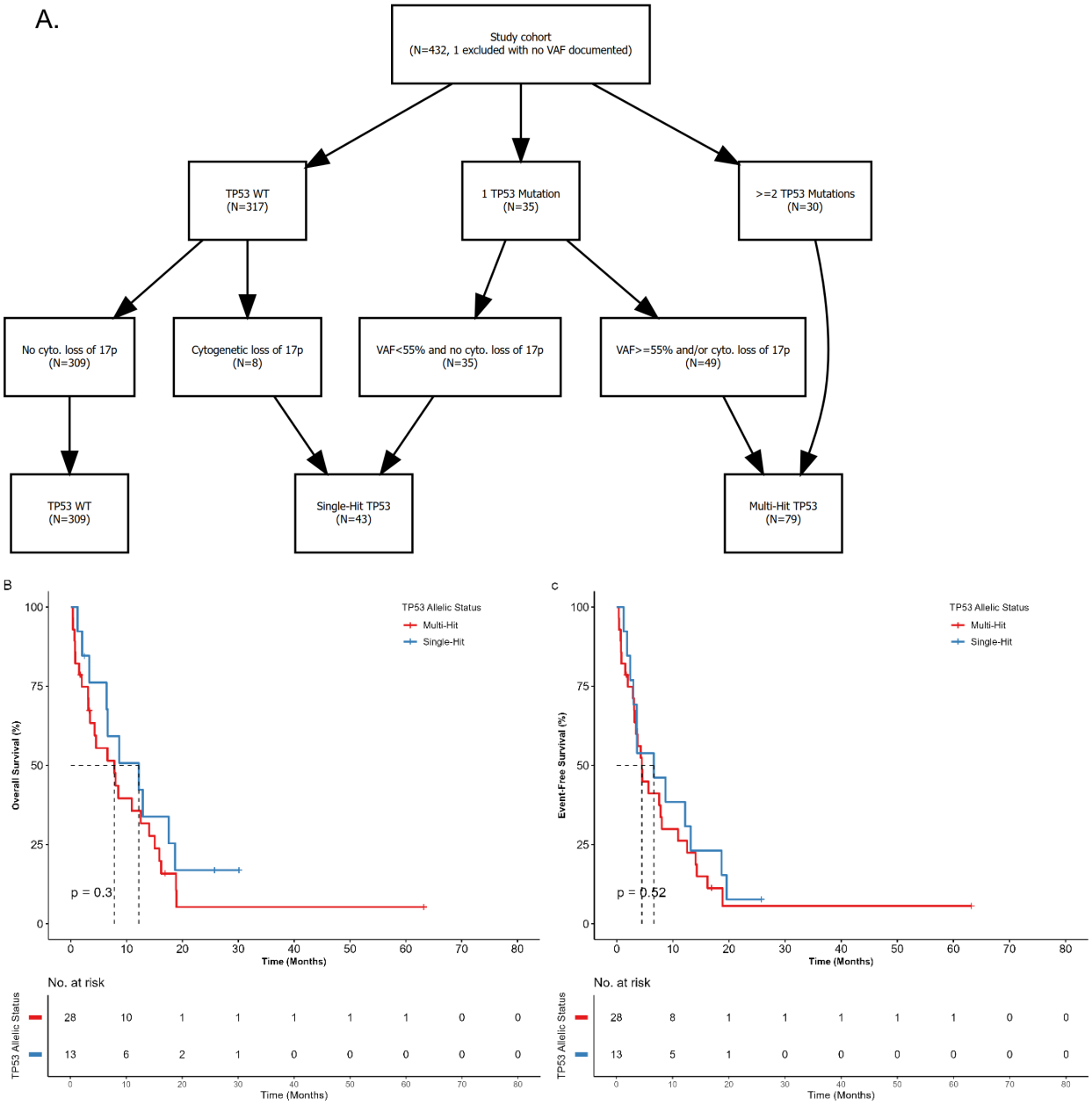
Supplementary figure 2. A. B. Kaplan-Meier curves comparing OS and EFS between ICC-AML-MR and WHO-AML-MR in patients who received intensive chemotherapies. **C. D.** Kaplan-Meier curves comparing OS and EFS between intermediate and adverse risk groups in ELN 2022 risk stratification.



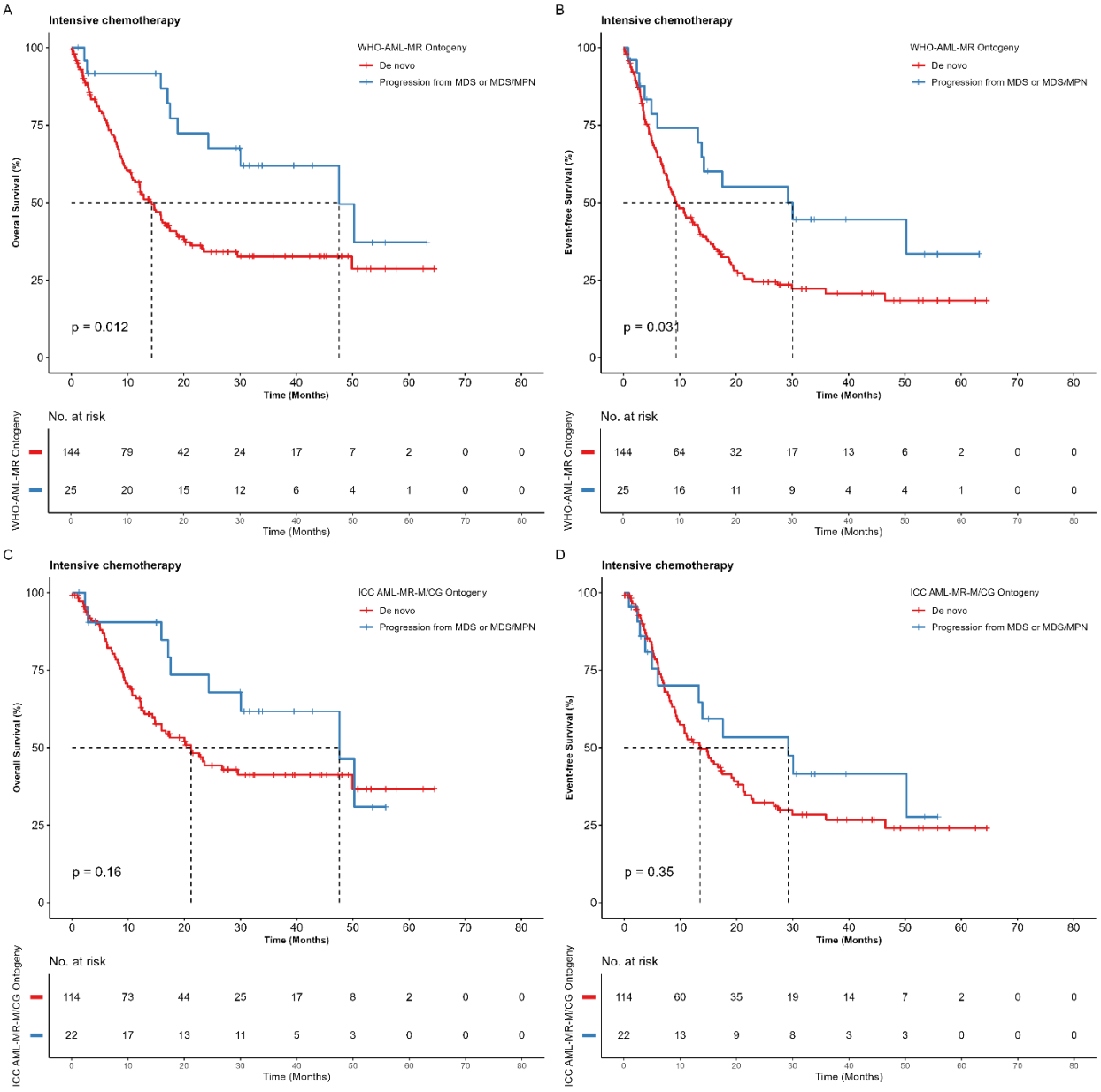
Supplementary figure 3. A. B. Kaplan-Meier curves of OS and EFS comparing *TP53* mutated and *TP53* wild-type in patients with intensive chemotherapy.



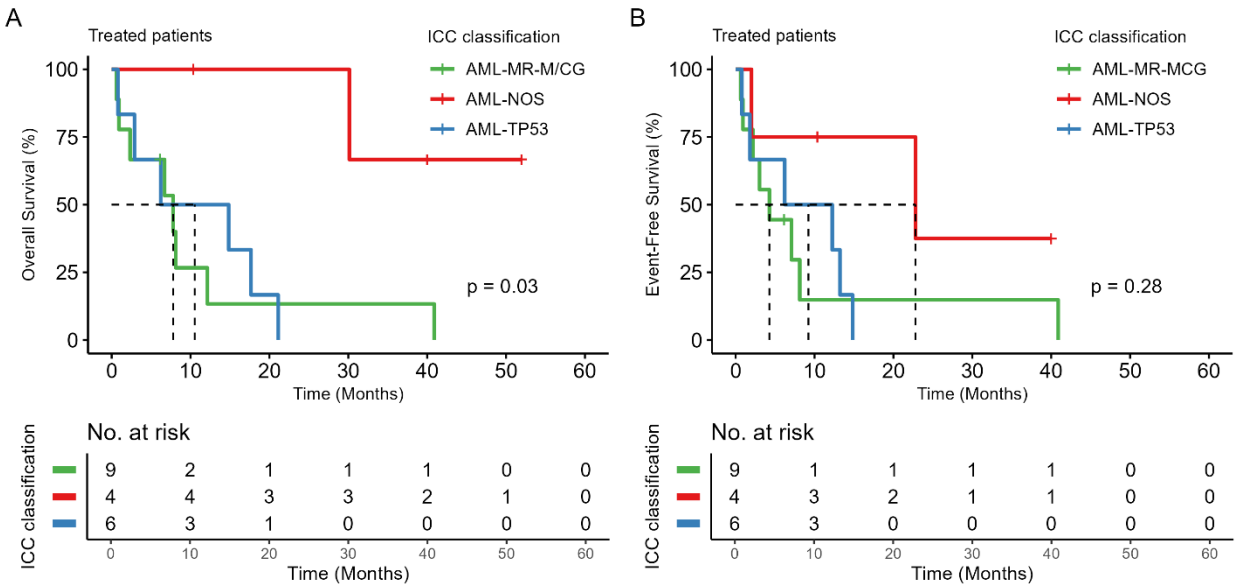
Supplementary figure 4. A. Schematic of clinical workflow to determine TP53 allelic state based on TP53 mutations and cytogenetic loss of chromosome 17p by karyotype assessment. **B.** and **C.** Kaplan-Meier survival curves comparing intensively treated AML-MR patients according to the TP53 allelic state.



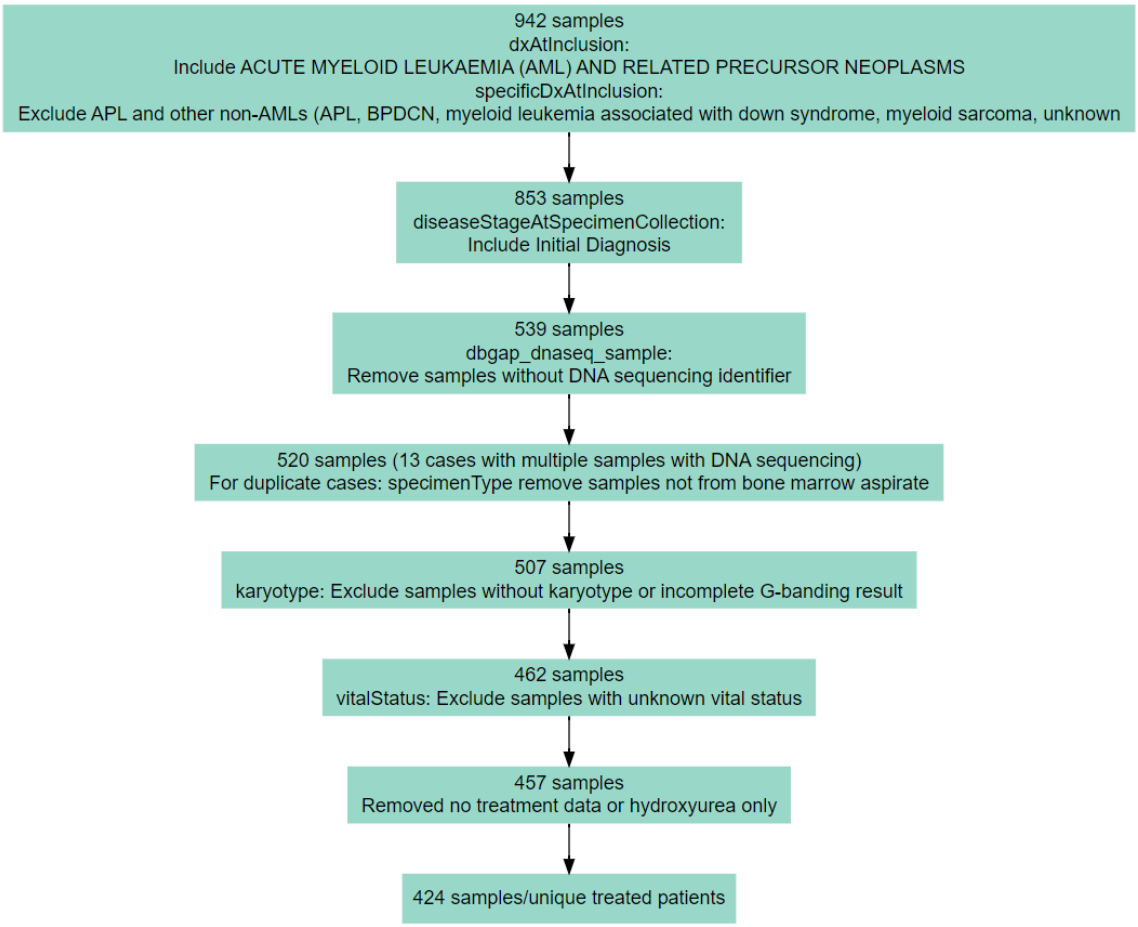
Supplementary Figure 5. Kaplan-Meier survival curves comparing ontogeny in WHO-AML-MR (A) and ICC-AML-MR-M/CG (B).



Supplementary Figure 6. Kaplan-Meier survival curves comparing patients with prior cytotoxic therapy according to ICC classification.

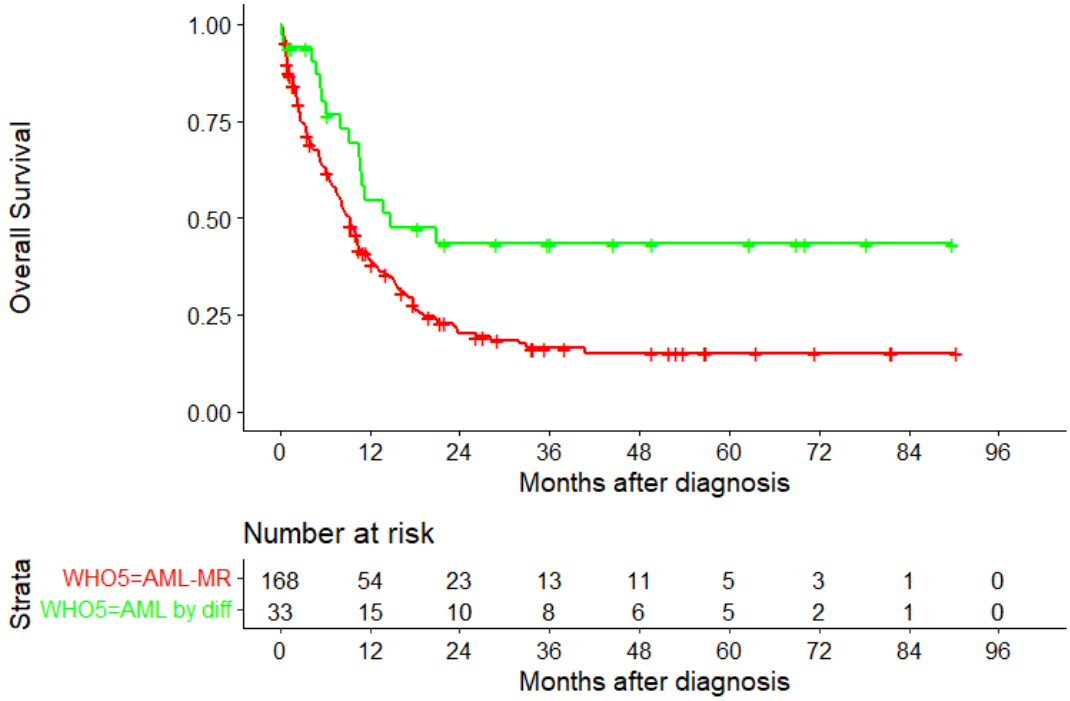


Supplementary Figure 7. BEAT AML 2.0 workflow

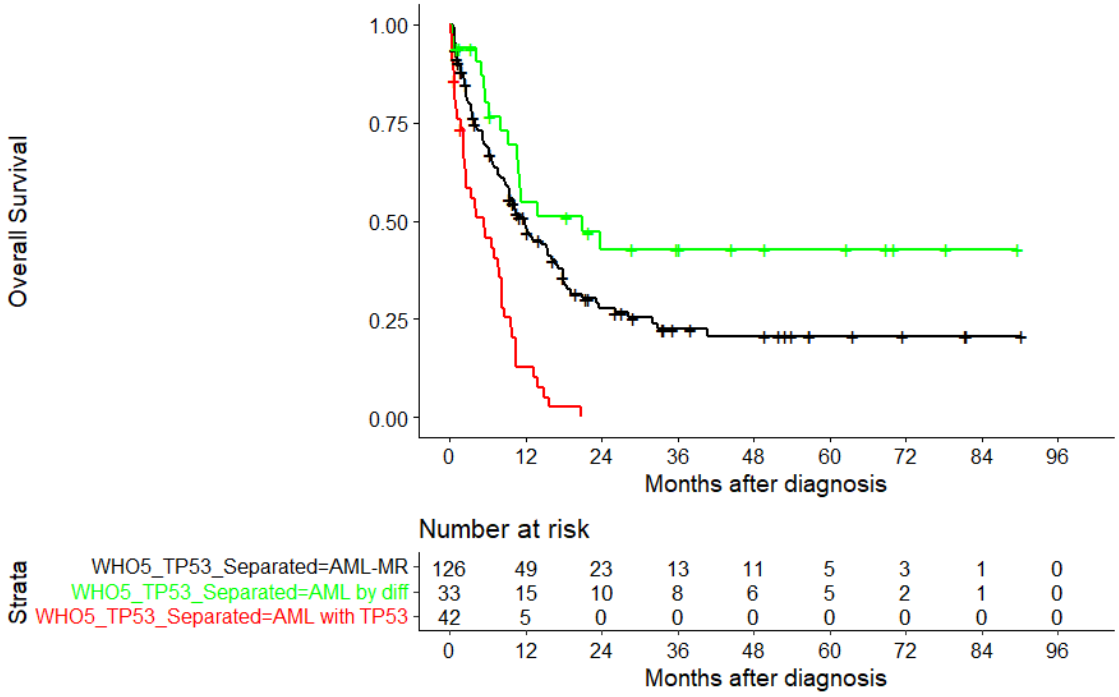


Supplementary Figure 8. BEAT-AML 2.0 cohort survival plots

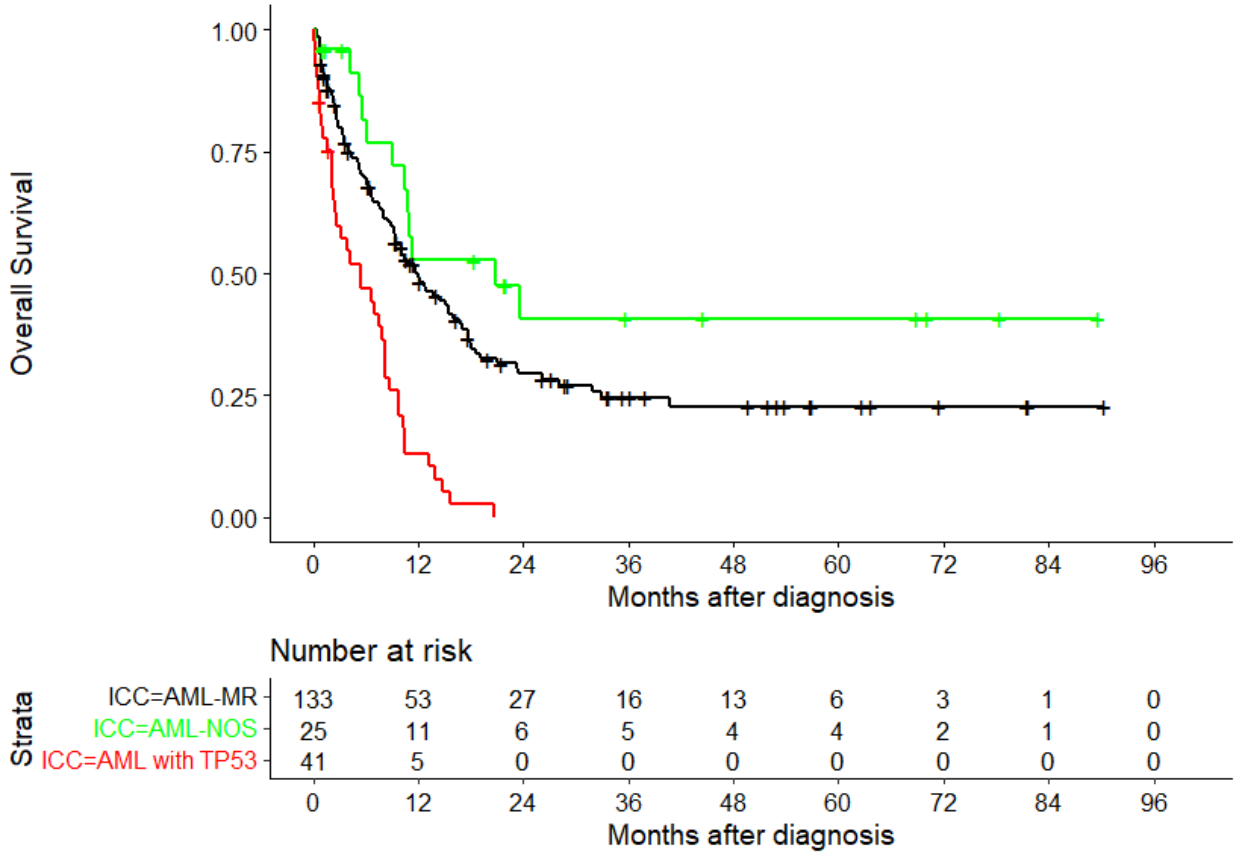
A. Classifying the cohort based on WHO-HAEM5, comparing AML-MR and AML by diff



B. Separating TP53-mutated cases into a separate entity, comparing AML-MR, AML by diff and AML with TP53



C. Classifying cohort based on ICC



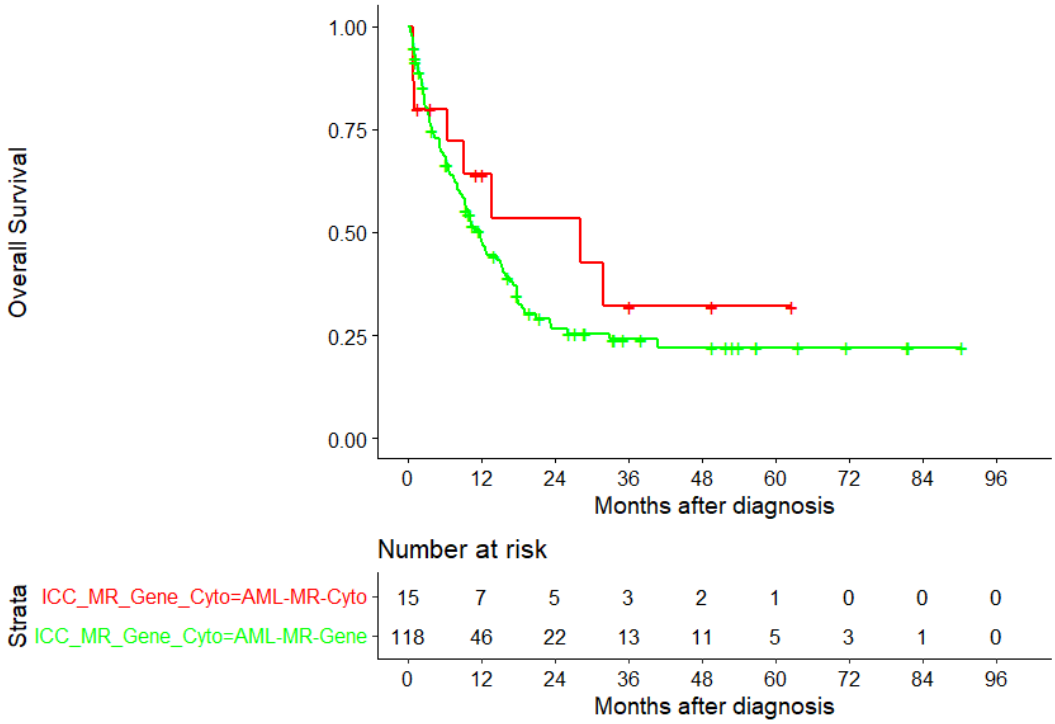
Number at risk

Strata	0	12	24	36	48	60	72	84	96
ICC=AML-MR	133	53	27	16	13	6	3	1	0
ICC=AML-NOS	25	11	6	5	4	4	2	1	0
ICC=AML with TP53	41	5	0	0	0	0	0	0	0

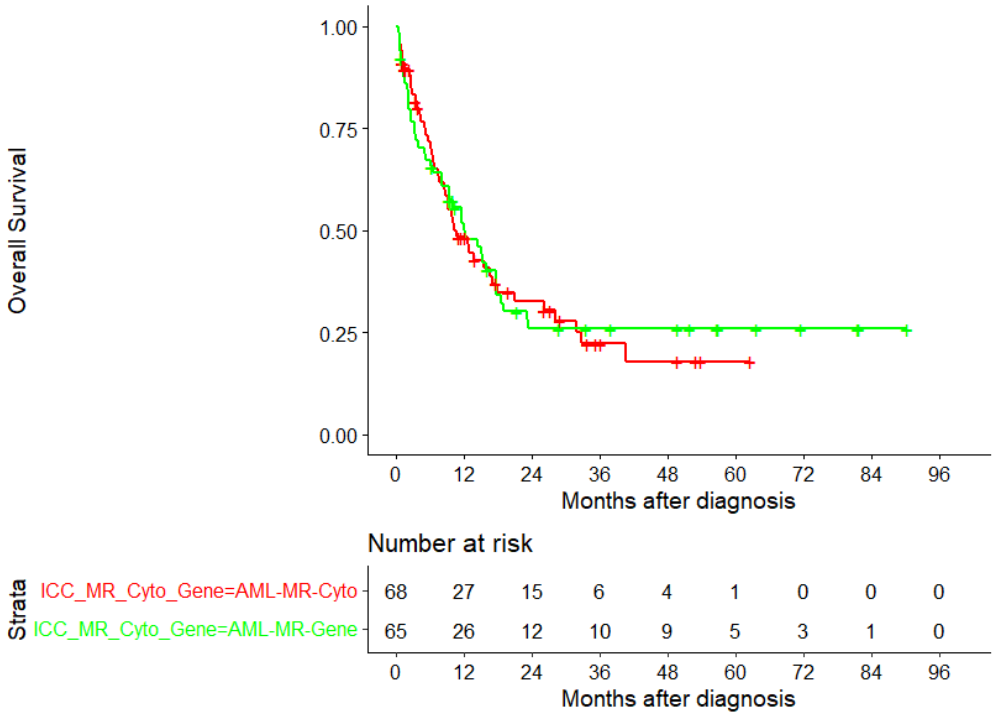
Months after diagnosis

D. Changing the order of assignments in AML-MR defined by ICC criteria

AML-MR by gene mutations > AML-MR by cytogenetics



AML-MR by cytogenetics > AML-MR by gene mutations



Supplementary Figure 9. A. B. Kaplan-Meier curves comparing OS and EFS between ICC and/or WHO defining AML-MR cytogenetic abnormalities.