Treatment of therapy-related acute myeloid leukemia and acute myeloid leukemia with myelodysplasia-related changes: a comparative analysis of higher-dose intensive 7+3 induction chemotherapy *versus* liposomal cytarabine and daunorubicin

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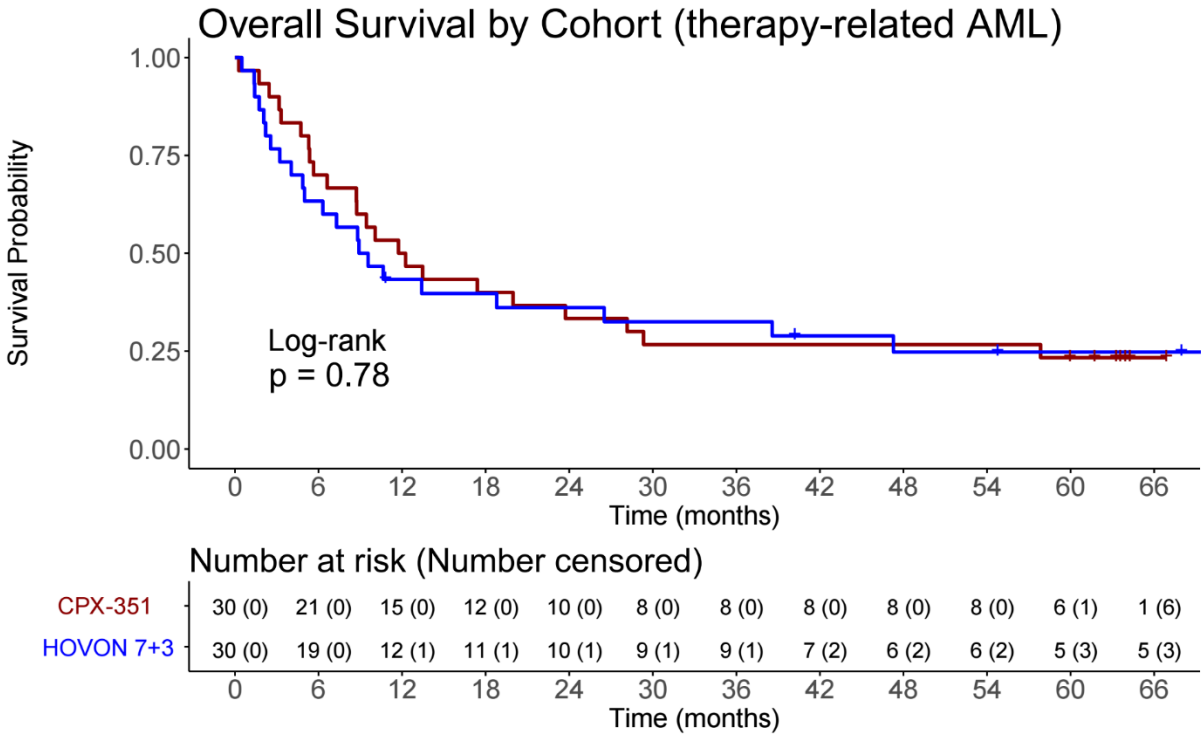
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SUPPLEMENTARY APPENDIX

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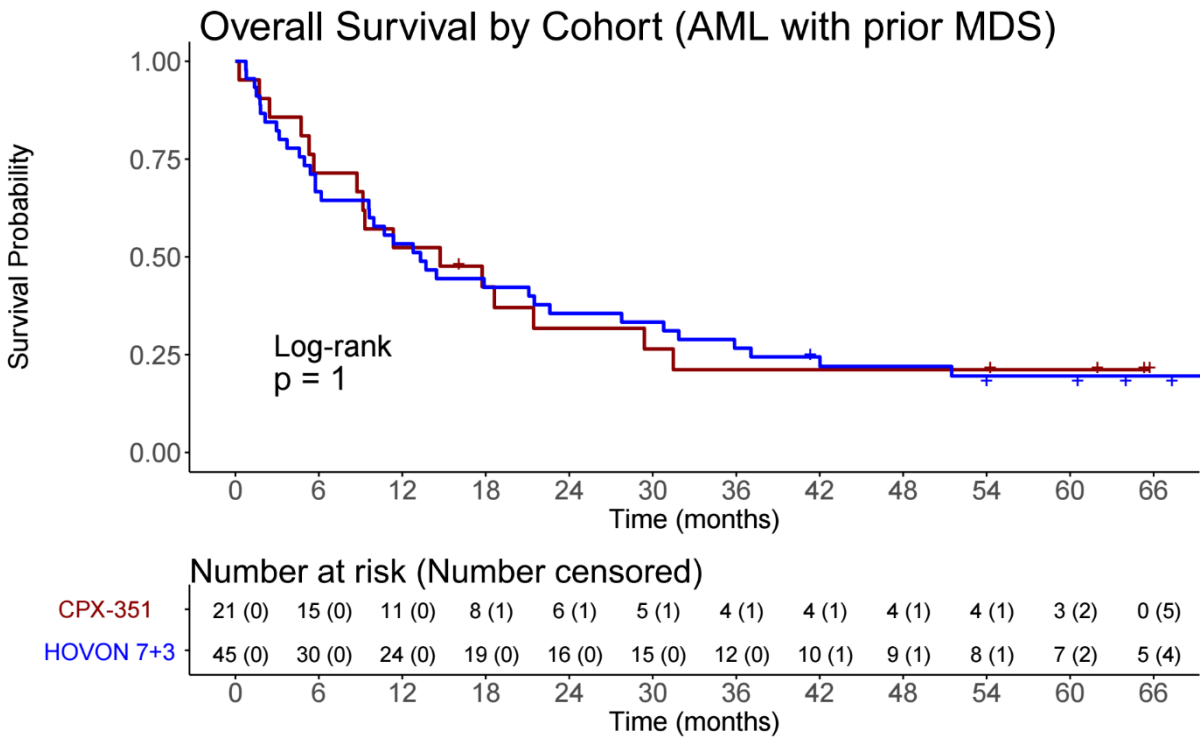
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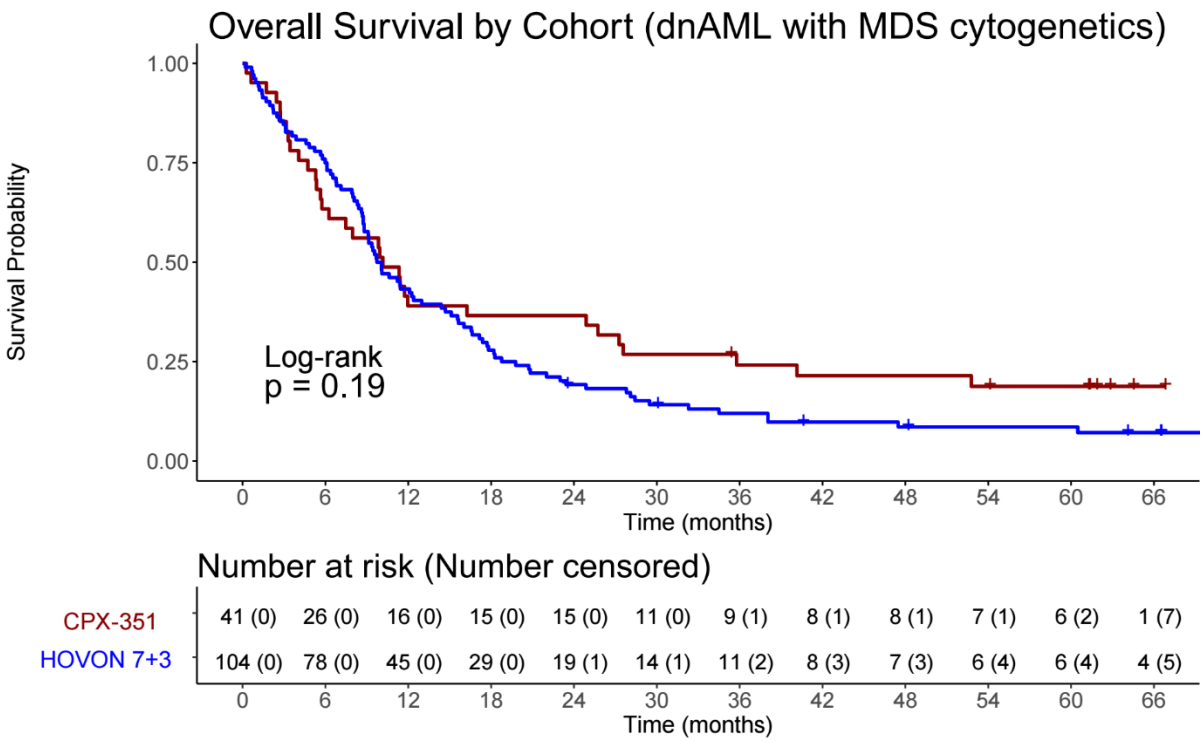
Supplementary Figure 1. Overall survival of the therapy-related AML subgroup of the CPX-351 arm of the phase III clinical trial versus the therapy-related AML subgroup of the HOVON 7+3 cohort.

Abbreviations: 7+3, 7 days of cytarabine and 3 days of an anthracycline; AML, acute myeloid leukemia; CPX-351, liposomal formulation of cytarabine and daunorubicin.



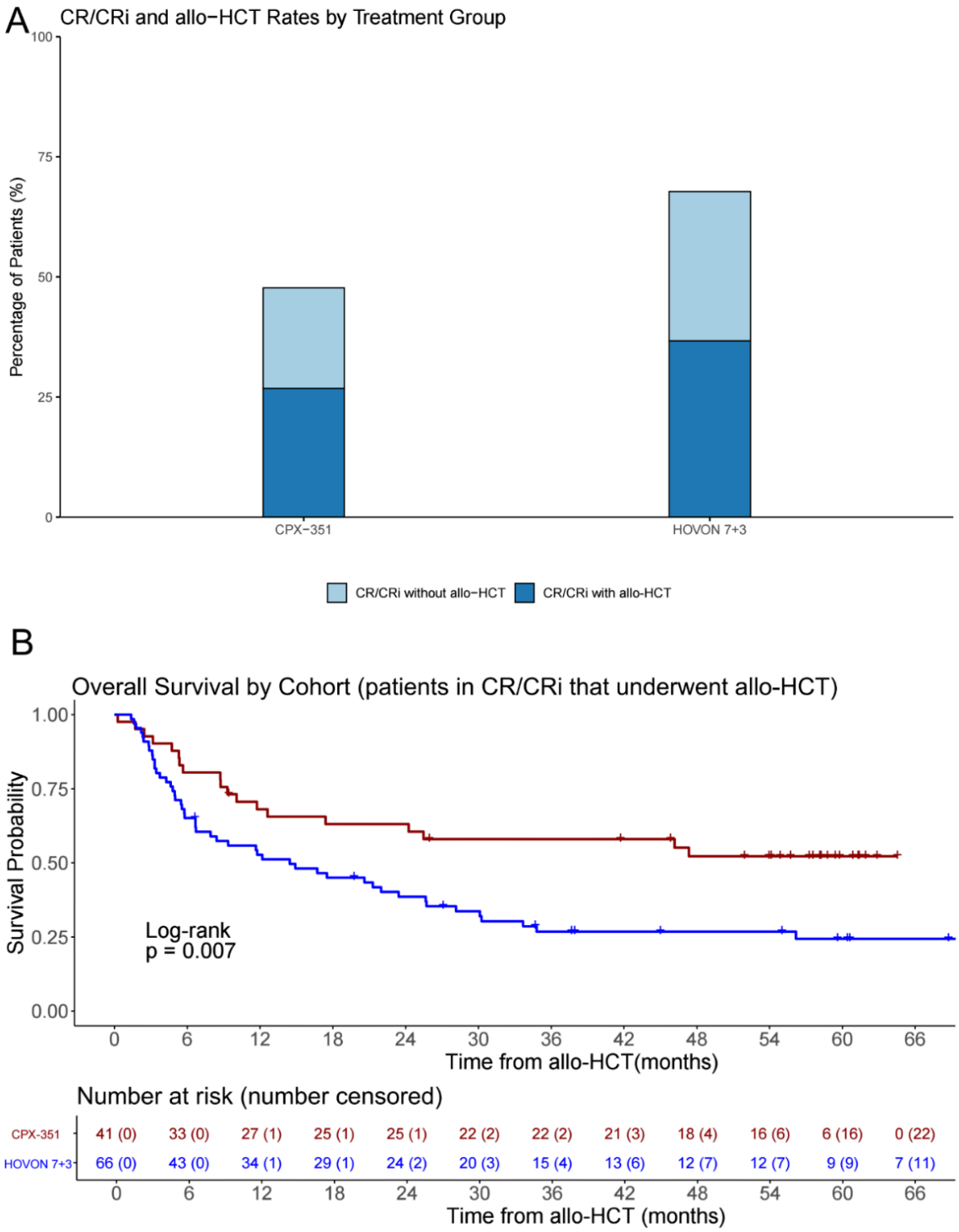
Supplementary Figure 2. Overall survival of the secondary AML with prior MDS subgroup of the CPX-351 arm of the phase III clinical trial versus the secondary AML with prior MDS subgroup of the HOVON 7+3 cohort.

Abbreviations: 7+3, 7 days of cytarabine and 3 days of an anthracycline; AML, acute myeloid leukemia; CPX-351, liposomal formulation of cytarabine and daunorubicin; MDS, myelodysplastic syndrome.



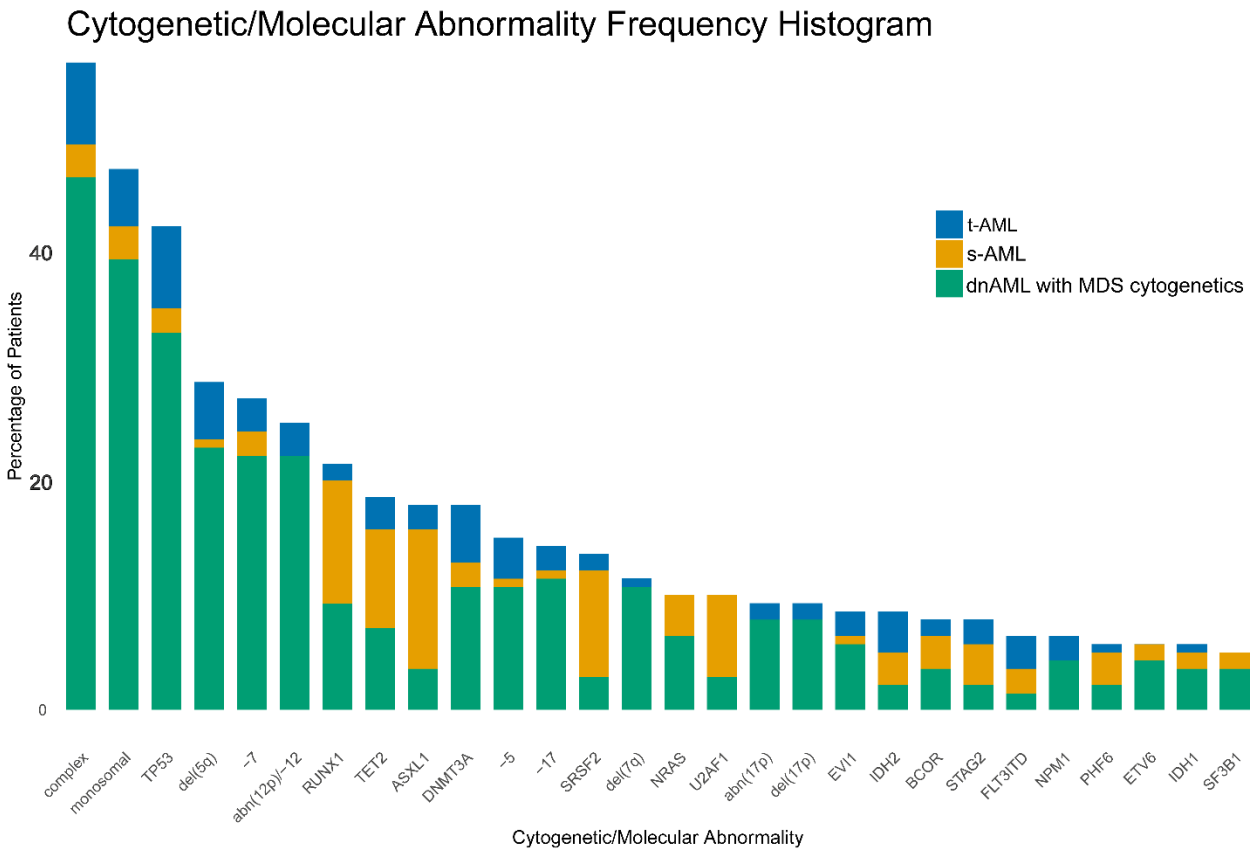
Supplementary Figure 3. Overall survival of the de novo AML with MDS cytogenetics subgroup of the CPX-351 arm of the phase III clinical trial versus the de novo AML with MDS cytogenetics subgroup of the HOVON 7+3 cohort.

Abbreviations: 7+3, 7 days of cytarabine and 3 days of an anthracycline; dnAML, de novo acute myeloid leukemia; MDS, myelodysplastic syndrome; CPX-351, liposomal formulation of cytarabine and daunorubicin.



Supplementary Figure 4. Allo-HCT rates and overall survival after allo-HCT in patients achieving CR/CRi. **(A)** Each bar represents the percentage of patients that proceeded to allo-HCT (dark blue) out of all patients in CR/CRi **(B)** Overall survival of the patients in CR/CRi that proceeded to allo-HCT of the CPX-351 arm of the phase III clinical trial versus the selected HOVON 7+3 cohort.

Abbreviations: 7+3, 7 days of cytarabine and 3 days of an anthracycline; allo-HCT, allogeneic hematopoietic cell transplantation; CPX-351, liposomal formulation of cytarabine and daunorubicin; CR, complete remission; CRi, complete remission with incomplete hematologic recovery.



Supplementary Figure 5. Driver events found in 140 out of 180 HOVON 7+3 patients with newly diagnosed AML. Each bar represents a driver lesion, including gene mutations and chromosomal abnormalities.

Abbreviations: 7+3, 7 days of cytarabine and 3 days of an anthracycline; dnAML, de novo acute myeloid leukemia; MDS, myelodysplastic syndrome; s-AML, secondary acute myeloid leukemia; t-AML, therapy-related acute myeloid leukemia.

Supplementary Table 1. Demographic and baseline characteristics of the entire t-AML/AML-MRC cohort and characteristics stratified by AML subtype.

Variable	Overall	t-AML	s-AML	dnAML with MDS cytogenetics	p-value
	N (%)	N (%)	N (%)	N (%)	
No. of patients	**428**	**60**	**136**	**232**	
Age (years)					
Median (IQR)	66 (63-70)	67 (64-70)	67 (64-71)	66 (63-70)	0.33
Age group	**428**	**60**	**136**	**232**	0.33
60-69	301 (70.3)	41 (68.3)	90 (66.2)	170 (73.3)	
≥70	127 (29.7)	19 (31.7)	46 (33.8)	62 (26.7)	
Sex	**428**	**60**	**136**	**232**	<0.001
Female	156 (36.4)	35 (58.3)	49 (36.0)	72 (31.0)	
Male	272 (63.6)	25 (41.7)	87 (64.0)	160 (69.0)	
WHO PS	**418**	**58**	**133**	**227**	0.83
0	209 (50.0)	29 (50.0)	72 (54.1)	108 (47.6)	
1	182 (43.5)	25 (43.1)	53 (39.8)	104 (45.8)	
2	27 (6.5)	4 (6.9)	8 (6.0)	15 (6.6)	
WBC count	**426**	**60**	**135**	**231**	0.07
<20 × 10^9/L	368 (86.4)	54 (90.0)	109 (80.7)	205 (88.7)	
≥20 × 10^9/L	58 (13.6)	6 (10.0)	26 (19.3)	26 (11.3)	
NCCN Risk Group	**420**	**59**	**129**	**232**	<0.001
Favorable/Intermediate	150 (35.7)	25 (42.4)	89 (69.0)	36 (15.5)	
Adverse	270 (64.3)	34 (57.6)	40 (31.0)	196 (84.5)	
ELN 2022 Risk Group	**327**	**51**	**95**	**181**	<0.001
Favorable	17 (5.2)	6 (11.8)	4 (4.2)	7 (3.9)	
Intermediate	23 (7.0)	11 (21.6)	6 (6.3)	6 (3.3)	
Adverse	287 (87.8)	34 (66.6)	85 (89.5)	168 (92.8)	
Best Response Rates	**428**	**60**	**136**	**232**	
CR/CRi	276 (64.5)	44 (73.3)	83 (61.0)	149 (64.2)	0.25
CR	237 (55.4)	42 (70.0)	66 (48.5)	129 (55.6)	0.02
Allo-HCT in CR/CRi	**276**	**44**	**83**	**149**	
Yes	125 (45.3)	18 (40.9)	38 (45.8)	69 (46.3)	0.81

Abbreviations: allo-HCT, allogeneic hematopoietic cell transplantation; AML; acute myeloid leukemia; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; dnAML, de novo acute myeloid leukemia; ELN, European LeukemiaNet; IQR, interquartile range; MDS, myelodysplastic syndrome; NCCN, national comprehensive cancer network; s-AML, secondary acute myeloid leukemia; t-AML, therapy-related acute myeloid leukemia; WBC count, white blood cell count; WHO PS, World Health Organization performance status.

Supplementary Table 2. Univariable analysis for OS in the t-AML/AML-MRC cohort.

Variable	Levels	n/(N=428) (%)	Hazard Ratio* (95% CI)	p-value
Age (years)	(continuous)		1.02 (0.98-1.05)	0.42
Age group (years)	60-69	301 (70.3)	(reference)	
	≥70	127 (29.7)	1.29 (0.99-1.69)	0.06
Sex	Female	156 (36.4)	(reference)	
	Male	272 (63.6)	0.95 (0.77-1.18)	0.65
WHO PS	0	209 (48.8)	(reference)	
	1	182 (42.5)	1.11 (0.89-1.37)	0.35
	2	27 (6.3)	2.07 (1.37-3.15)	<0.001
AML subtype	dnAML with MDS cytogenetics	232 (54.2)	(reference)	
	s-AML	136 (31.8)	0.76 (0.61-0.96)	0.02
	t-AML	60 (14.0)	0.55 (0.39-0.77)	<0.001
WBC count	< 20 × 10^9/L	368 (86.0)	(reference)	
	≥ 20 × 10^9/L	58 (13.6)	1.27 (0.94-1.70)	0.11
Platelets	≤ 50 × 10^9/L	187 (43.7)	(reference)	
	> 50 × 10^9/L	239 (55.8)	0.83 (0.68-1.02)	0.08
BM blast (%)	0-20	128 (29.9)	(reference)	
	20-40	117 (27.3)	0.74 (0.57-0.98)	0.03
	40-60	56 (13.1)	1.01 (0.73-1.39)	0.97
	≥60	84 (19.6)	0.89 (0.66-1.20)	0.43
Hemoglobin (g/dL)	≤9	341 (79.7)	(reference)	
	>9	3 (0.7)	0.48 (0.12-1.95)	0.31
Cytogenetic risk category (per NCCN)	Non-adverse	150 (35.0)	(reference)	
	Adverse	270 (63.1)	1.81 (1.45-2.27)	<0.001
MDS-related gene mutations	Absent	180 (42.1)	(reference)	
	Present	147 (34.3)	0.80 (0.63-1.02)	0.07
TP53 mutation	Absent	199 (46.5)	(reference)	
	Present	128 (29.9)	2.51 (1.95-3.21)	<0.001
RUNX1 mutation	Absent	255 (59.6)	(reference)	
	Present	72 (16.8)	0.91 (0.69-1.22)	0.54
DNMT3A mutation	Absent	262 (61.2)	(reference)	
	Present	65 (15.2)	0.66 (0.48-0.90)	0.008
ASXL1 mutation	Absent	264 (61.7)	(reference)	
	Present	63 (14.7)	1.09 (0.81-1.46)	0.59
TET2 mutation	Absent	269 (62.9)	(reference)	
	Present	58 (13.6)	1.06 (0.78-1.45)	0.56
SRSF2 mutation	Absent	272 (63.6)	(reference)	
	Present	55 (12.9)	0.89 (0.65-1.24)	0.49
IDH2 mutation	Absent	285 (66.6)	(reference)	
	Present	42 (9.8)	0.79 (0.55-1.12)	0.19
IDH1 mutation	Absent	306 (71.5)	(reference)	
	Present	21 (4.9)	0.62 (0.37-1.04)	0.07
EVI1 mutation	Absent	175 (40.9)	(reference)	
	Present	33 (7.7)	1.48 (1.01-2.19)	0.048
NRAS mutation	Absent	298 (69.6)	(reference)	

	Present	29 (6.8)	0.89 (0.58-1.36)	0.58
U2AF1 mutation	Absent	300 (70.1)	(reference)	
	Present	27 (6.3)	1.11 (0.73-1.69)	0.63
NPM1 mutation	Absent	304 (71.0)	(reference)	
	Present	23 (5.4)	0.63 (0.38-1.02)	0.06
STAG2 mutation	Absent	304 (71.0)	(reference)	
	Present	23 (5.4)	0.81 (0.50-1.32)	0.42
FLT3ITD mutation	Absent	307 (71.7)	(reference)	
	Present	20 (4.7)	0.98 (0.60-1.62)	0.95
BCOR mutation	Absent	308 (72.0)	(reference)	
	Present	19 (4.4)	0.81 (0.48-1.34)	0.43
PHF6 mutation	Absent	310 (72.4)	(reference)	
	Present	17 (4.0)	0.65 (0.37-1.14)	0.13
PTPN11 mutation	Absent	310 (72.4)	(reference)	
	Present	17 (4.0)	0.92 (0.55-1.55)	0.76
EZH2 mutation	Absent	312 (72.9)	(reference)	
	Present	15 (3.5)	1.11 (0.64-1.90)	0.72
ETV6 mutation	Absent	314 (73.4)	(reference)	
	Present	13 (3.0)	0.66 (0.34-1.28)	0.22
JAK2 mutation	Absent	314 (73.4)	(reference)	
	Present	13 (3.0)	1.33 (0.74-2.39)	0.34
KRAS mutation	Absent	314 (73.4)	(reference)	
	Present	13 (3.0)	1.50 (0.81-2.75)	0.22
SF3B1 mutation	Absent	315 (73.6)	(reference)	
	Present	12 (2.8)	0.60 (0.30-1.22)	0.16
SETBP1 mutation	Absent	315 (73.6)	(reference)	
	Present	12 (2.8)	1.77 (0.96-3.26)	0.07

*****Cox model stratified by treatment arm and trial number.

Abbreviations: AML, acute myeloid leukemia; BM, bone marrow; CI, confidence interval; dnAML, de novo acute myeloid leukemia; MDS, myelodysplastic syndrome; MDS-related gene mutations, myelodysplasia-related gene mutations; NCCN, national comprehensive cancer network; s-AML, secondary acute myeloid leukemia; t-AML, therapy-related acute myeloid leukemia; WBC count, white blood cell count; WHO PS, World Health Organization performance status.

Supplementary Table 3. Multivariable analysis for OS in the t-AML/AML-MRC cohort.

Variable	Levels	n/(N=428) (%)	Hazard Ratio* (95% CI)	p-value
Age group (years)	60-69	301 (70.3)	(reference)	
	≥70	127 (29.7)	1.13 (0.86-1.49)	0.38
WHO PS	0	209 (48.8)	(reference)	
	1	182 (42.5)	1.14 (0.91-1.42)	0.24
	2	27 (6.3)	2.08 (1.32-3.26)	0.002
AML subtype	dnAML with MDS cytogenetics	232 (54.2)	(reference)	
	s-AML	136 (31.8)	1.06 (0.81-1.39)	0.66
	t-AML	60 (14.0)	0.64 (0.45-0.91)	0.01
WBC count	<20 × 10^9/L	368 (86.0)	(reference)	
	≥20 × 10^9/L	58 (13.6)	1.52 (1.11-2.07)	0.008
Cytogenetic risk category (per NCCN)	Non-adverse	150 (35.0)	(reference)	
	Adverse	270 (63.1)	1.47 (1.12-1.95)	0.006
TP53 mutation	Absent	199 (46.5)	(reference)	
	Present	128 (29.9)	2.17 (1.62-2.91)	<0.001
DNMT3A mutation	Absent	262 (61.2)	(reference)	
	Present	65 (15.2)	0.68 (0.49-0.93)	0.02
SETBP1 mutation	Absent	315 (73.6)	(reference)	
	Present	12 (2.8)	2.63 (1.39-4.99)	0.003

*Cox model stratified by treatment arm and trial number.

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; dnAML, de novo acute myeloid leukemia; MDS, myelodysplastic syndrome; NCCN, national comprehensive cancer network; s-AML, secondary acute myeloid leukemia; t-AML, therapy-related acute myeloid leukemia; WBC count, white blood cell count; WHO PS, World Health Organization performance status.

Supplementary Table 4. Multivariable analysis for OS in the t-AML/AML-MRC cohort with allo-HCT as a time-dependent variable.

Variable	Levels	n/(N=276) (%)	Hazard Ratio* (95% CI)	p-value
Age group (years)	60-69	203 (73.6)	(reference)	
	≥70	73 (26.4)	1.04 (0.71-1.52)	0.85
WHO PS	0	148 (53.6)	(reference)	
	1	112 (40.6)	0.94 (0.70-1.25)	0.65
	2	10 (3.6)	0.78 (0.38-1.62)	0.51
AML subtype	dnAML with MDS cytogenetics	149 (54.0)	(reference)	
	s-AML	83 (30.1)	1.03 (0.72-1.47)	0.88
	t-AML	44 (15.9)	0.66 (0.42-1.02)	0.06
WBC count	<20 × 10^9/L	252 (91.3)	(reference)	
	≥20 × 10^9/L	24 (8.7)	1.52 (0.92-2.50)	0.10
Cytogenetic risk category (per NCCN)	Non-adverse	110 (39.9)	(reference)	
	Adverse	162 (58.7)	1.48 (1.03-2.13)	0.03
TP53 mutation	Absent	141 (51.1)	(reference)	
	Present	79 (28.6)	2.54 (1.76-3.66)	<0.001
DNMT3A mutation	Absent	174 (63.0)	(reference)	
	Present	46 (16.7)	0.70 (0.46-1.04)	0.08
SETBP1 mutation	Absent	216 (78.3)	(reference)	
	Present	4 (1.4)	1.21 (0.37-4.00)	0.75
Allo-HCT	No	151 (54.7)	(reference)	
	Yes	125 (45.3)	0.64 (0.46-0.89)	0.008

* Cox model stratified by treatment arm and trial number.

Abbreviations: allo-HCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; CI, confidence interval; dnAML, de novo AML; MDS, myelodysplastic syndrome; NCCN, national comprehensive cancer network; s-AML, secondary acute myeloid leukemia; t-AML, therapy-related acute myeloid leukemia; WBC count, white blood cell count; WHO PS, World Health Organization performance status.