

## **Supplementary Appendix**

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Tiong IS, Reynolds J, Bradstock KF, Seymour JF, and Wei AH, on behalf of the Australasian Leukaemia & Lymphoma Group. Dissecting causes for improved survival among patients with acute myeloid leukemia in two different eras receiving identical regimens in sequential randomized studies.

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**Table S1.** Univariate and multivariate analysis of predictor of 30-day mortality by logistic regression in the AMLM7 and AMLM12 study cohorts.

Factors	Univariate Analysis		Multivariate Analysis*	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Cohort: AMLM7	2.85 (1.56–5.34)	.002	3.46 (1.83–6.69)	< .001
Age	1.07 (1.03–1.11)	< .001	1.08 (1.04–1.12)	< .001
Gender: Male	0.73 (0.40–1.32)	.3	-	
ECOG PS > 0	2.20 (1.18–4.31)	.017	1.76 (0.91–3.55)	.1
Adverse cytogenetics	1.38 (0.63–2.77)	.4	-	
WCC, every 10x10 <sup>9</sup> /L	1.07 (1.02–1.11)	.003	1.06 (1.01–1.10)	.019
Febrile	1.39 (0.73–2.56)	.3	-	
Bleeding	1.62 (0.82–2.99)	.1	-	
DIC	2.69 (0.76–7.47)	.081	2.44 (0.63–7.74)	.2
G-CSF	0.58 (0.26–1.47)	.2	-	

\* Factors were included in the multivariate analysis if  $p < 0.10$  by univariate analysis.

*Abbreviations:* CI, confidence interval; DIC, disseminated intravascular coagulation; ECOG, Eastern Cooperative Oncology Group; G-CSF, granulocyte colony stimulating factor; PS, performance status; WCC, white cell counts.

**Table S2.** Supportive care in the AMLM7 and AMLM12 study cohorts.

	<b>AML7</b>	<b>AML12</b>	<b>P-value</b>
Prophylactic antifungal*, n (%)	75 (86.2)	397 (95.9)	.001
Fluconazole / Itraconazole	75 (100)	283 (71.3)	
Posaconazole / Voriconazole	-	149 (37.5)	
Amphotericin	3 (4.0)	33 (8.3)	
Infection, n (%)			.7
None	8 (8.3)	51 (12.0)	
Probable	21 (21.9)	84 (19.8)	
Clinical	11 (11.5)	43 (10.1)	
Microbiological	56 (58.3)	246 (58.0)	
Days febrile, median (IQR)	10.5 (5–17)	10 (6–15)	.7
G-CSF (%)	80.1	96.7	< .001
Palifermin, n (%)	-	74 (17.5)	
RBC (units), median (IQR)	10 (8–14)	12 (8–15)	.089
PLT (units), median (IQR)	9 (7–15)	10 (8–14)	.185

\*Many patients received >1 antifungal agent at different time points.

*Abbreviations:* G-CSF, granulocyte colony stimulating factor; IQR, interquartile range; PLT, platelets; RBC, red blood cells.

**Table S3.** Characteristics of patients who received standard IcE consolidation from the AMLM7 and AMLM12 (original and matched) study cohorts.

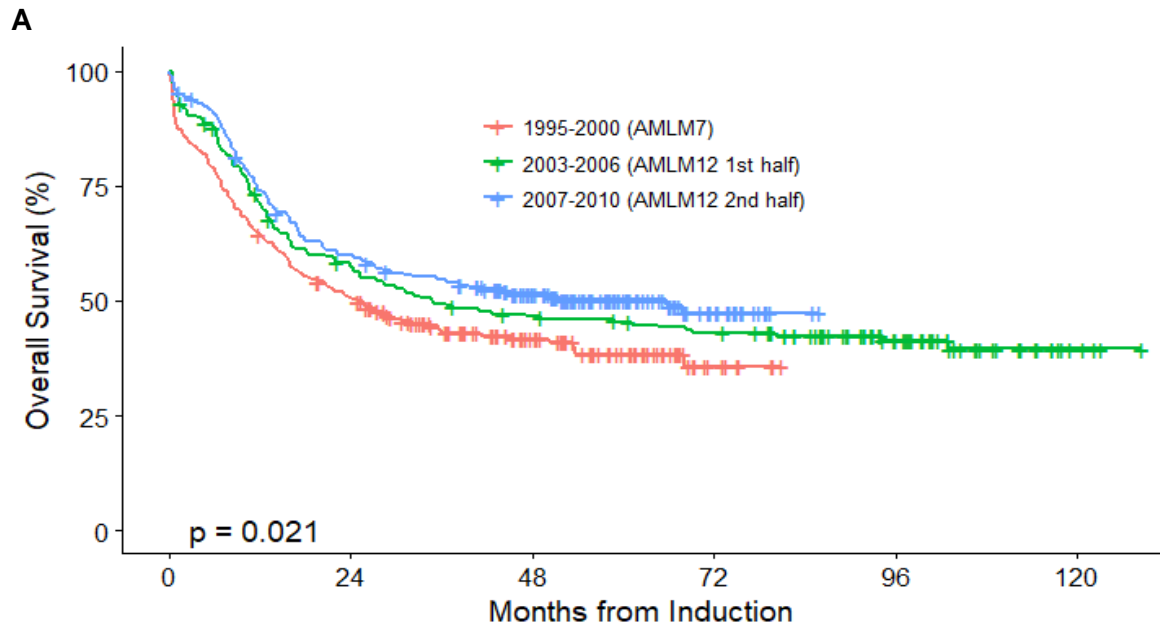
	<b>AML7 (n=87)</b>	<b>M12_original (n=146)</b>	<b>P- value<sup>a</sup></b>	<b>M12_matched<sup>b</sup> (n=87)</b>	<b>P- value<sup>a</sup></b>
Age, median years (IQR)	41.8 (33.3–50.6)	48.0 (38.8–55.3)	.001	41.8 (33.2–52.7)	.6
Male gender (%)	52.9	53.4	1	51.7	1
ECOG PS > 0 (%)	44.8	59.4	.041	46.0	1
Cytogenetics, n (%)			.6		1
Intermediate	69 (79.3)	122 (83.6)		69 (79.3)	
Adverse	13 (14.9)	19 (13.0)		13 (14.9)	
Unknown	5 (5.8)	5 (3.4)		5 (5.8)	
WCC (x 10 <sup>9</sup> /L), median (IQR)	10.1 (3.9–31.0)	11.6 (3.9–37.5)	.6	11.3 (4.9–37.0)	.5
> 40 x 10 <sup>9</sup> /L (%)	16.1	24.0	.2	23.0	.3
> 100 x 10 <sup>9</sup> /L (%)	4.6	6.2	.8	3.5	1
>1 induction cycle, n (%)	3 (3.5)	9 (6.2)	.5	5 (5.7)	.7
Allo-SCT, n (%)	30 (34.5)	85 (58.2)	<.001	53 (60.9)	<.001
Transplant in first CR	9 (10.3)	39 (26.7)	.003	24 (27.6)	.006
Transplant other status	21 (24.1)	46 (31.5)	.3	29 (33.3)	.2
Auto-SCT, n (%)	12 (13.8)	4 (2.7)	.002	1 (1.2)	.002

<sup>a</sup> Fisher's exact test for categorical variables; Mann-Whitney *U* tests for continuous variables.

<sup>b</sup> Propensity score matching by regression including age, gender, WBC and cytogenetic risk group. Matching was done using the nearest neighbor method with 1:1 ratio without replacement.

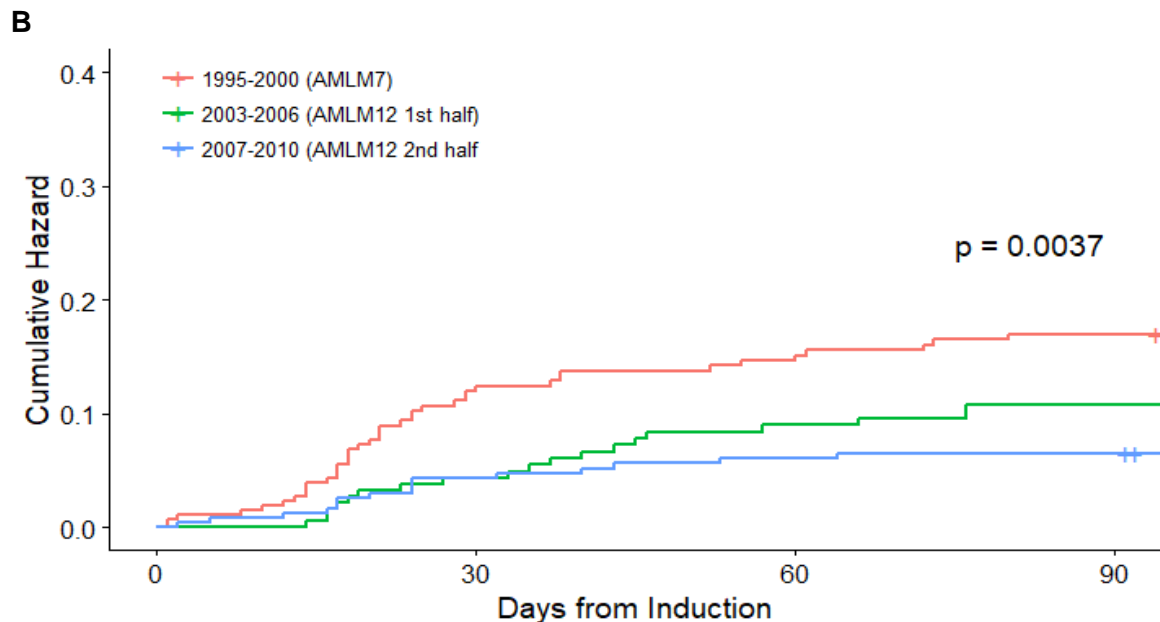
*Abbreviations:* CR, complete remission; DIC, disseminated intravascular coagulation; ECOG PS, Eastern Cooperative Oncology Group performance status; G-CSF, granulocyte colony stimulating factor; IQR, interquartile range; SCT, stem cell transplantation; WCC, white cell counts.

**Figure S1. (A)** Overall survival and **(B)** cumulative hazard of early deaths in the entire AMLM7 and AMLM12 cohorts, stratified by period of study recruitment. **(C)** Percentage of patients (%) receiving GCSF (line and dots) and prophylactic posaconazole/voriconazole (bar chart) over time (AML7: 1995-2000; AMLM12: 2003-2010).



No. at Risk

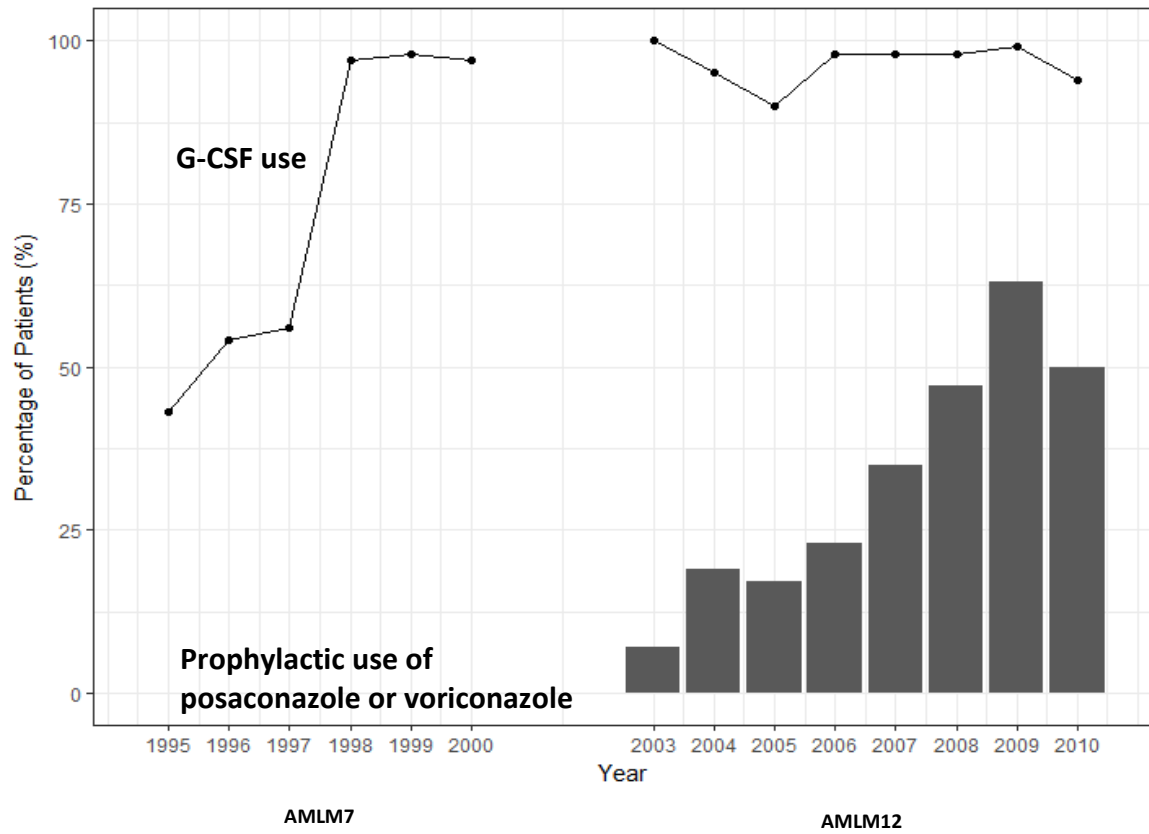
	0	24	48	72	96	120
1995-2000 (AML7)	256	127	57	8	0	0
2003-2006 (AML12 1st half)	186	103	81	72	38	4
2007-2010 (AML12 2nd half)	236	138	92	23	0	0



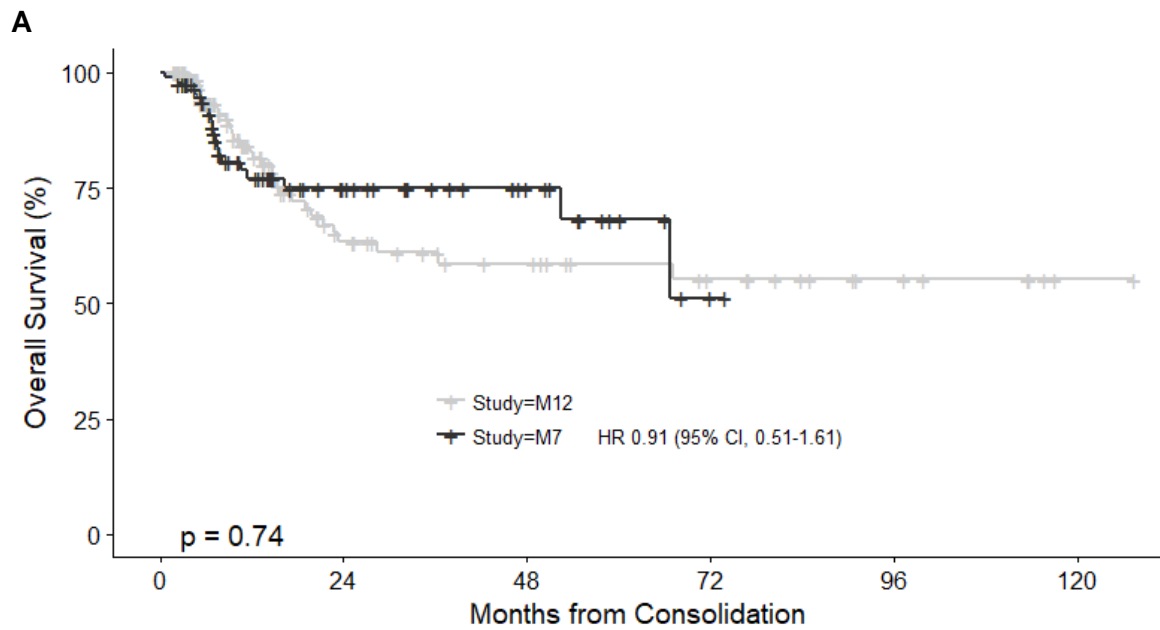
Cumulative No. of Events

	0	30	60	90
1995-2000 (AML7)	0	30	36	40
2003-2006 (AML12 1st half)	0	8	16	19
2007-2010 (AML12 2nd half)	0	10	14	15

C

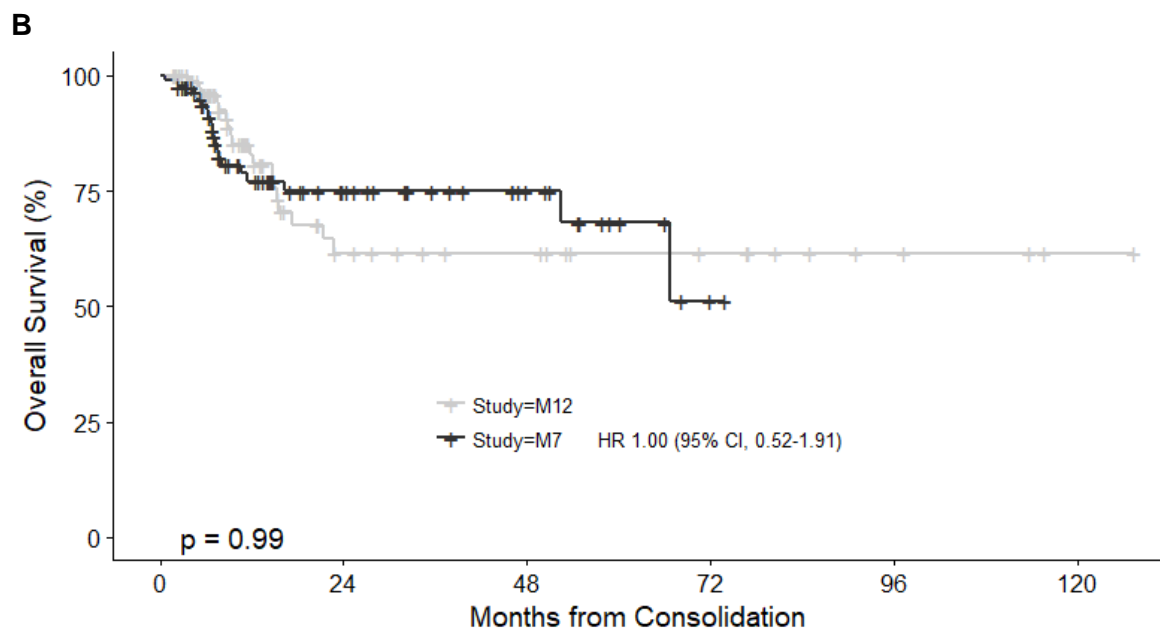


**Figure S2.** Overall survival censoring for SCT (both autologous and allogeneic) in patients receiving standard IcE consolidation in the AMLM7 and AMLM12 study cohorts. **(A)** Unmatched comparison between study cohorts. **(B)** Propensity score matching for age, gender, ECOG, WCC and cytogenetic risk.



No. at Risk

—	146	33	22	14	7	1
—	87	28	13	1	0	0

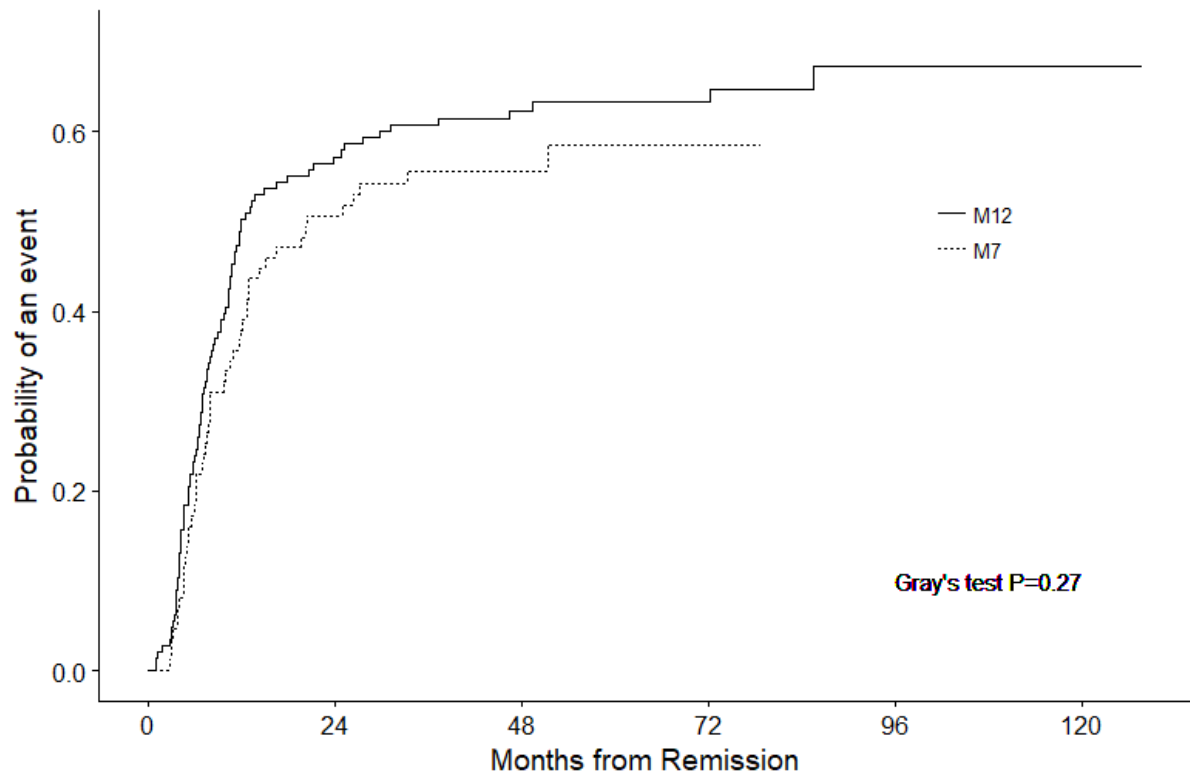


No. at Risk

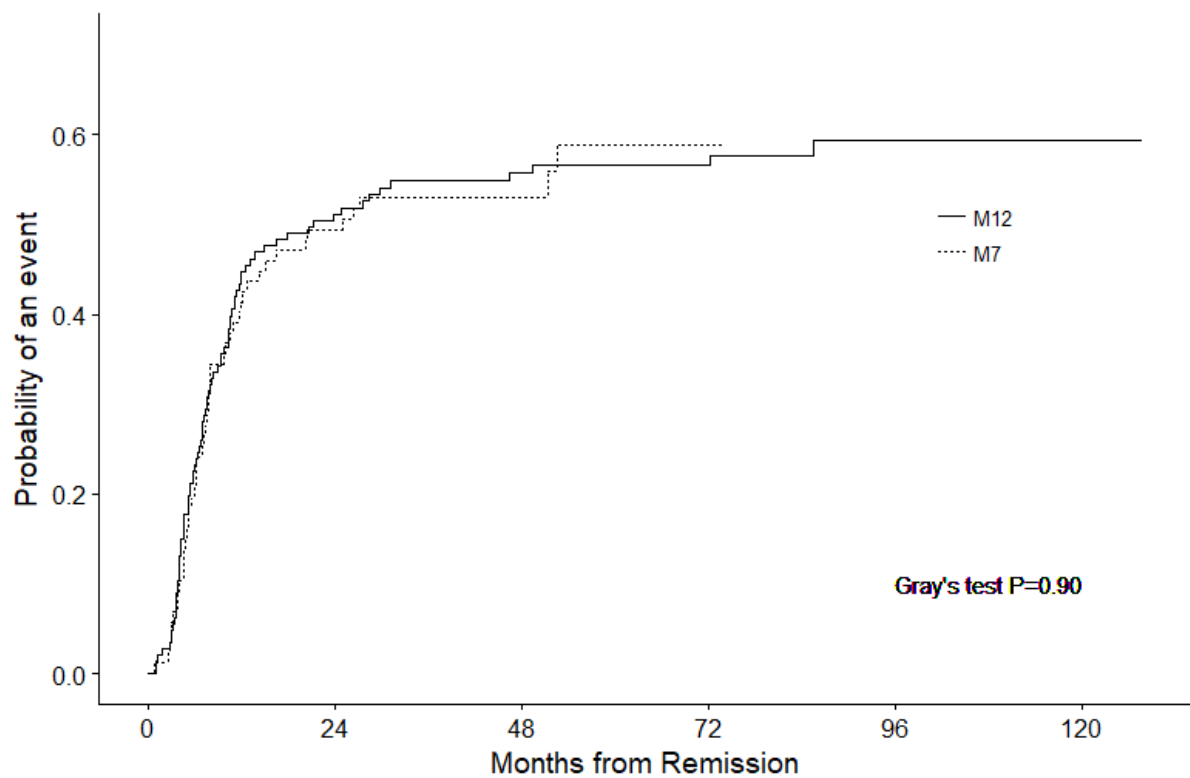
—	87	19	14	9	4	1
—	87	28	13	1	0	0

**Figure S3.** Cumulative incidence of relapse in patients receiving standard IcE consolidation in the AMLM7 and AMLM12 study cohorts, **(A)** ignoring SCT status (both autologous and allogeneic) and **(B)** treating SCT as competing risk.

**A**

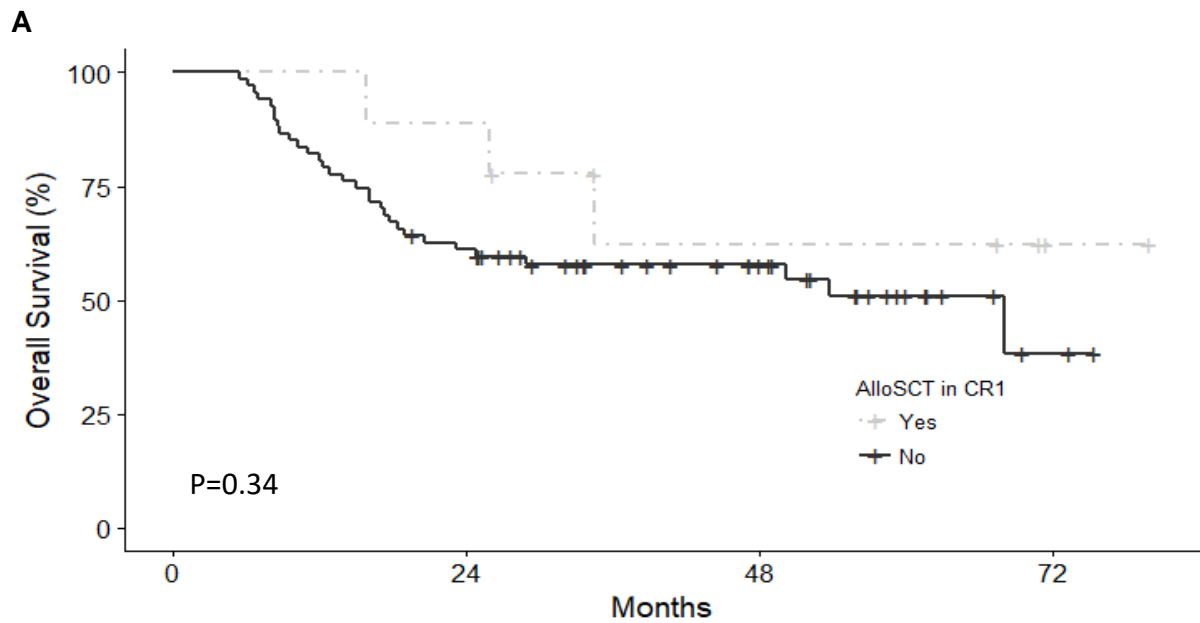


**B**



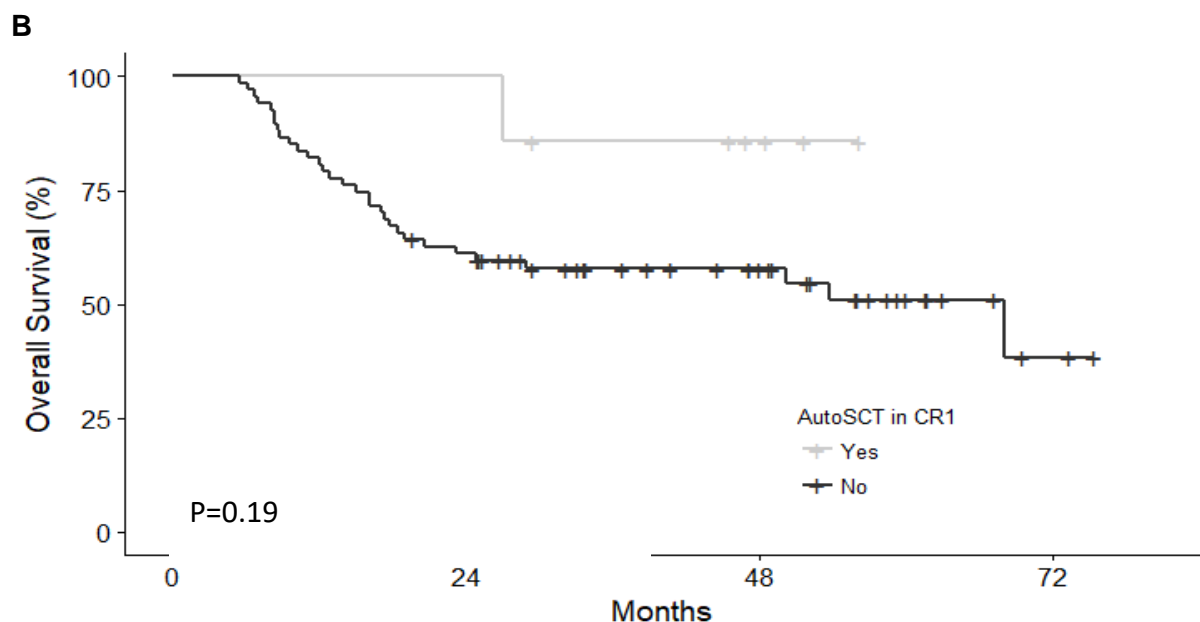


**Figure S4.** Overall survival in the AMLM7 study cohort receiving standard IcE consolidation chemotherapy, restricted to patients with >90 days of remission duration, stratified by **(A)** allogeneic SCT and **(B)** autologous SCT in first remission. Pairwise comparisons using log-rank test, with p-values adjusted by Benamini & Hochberg (BH) method.



No. at Risk

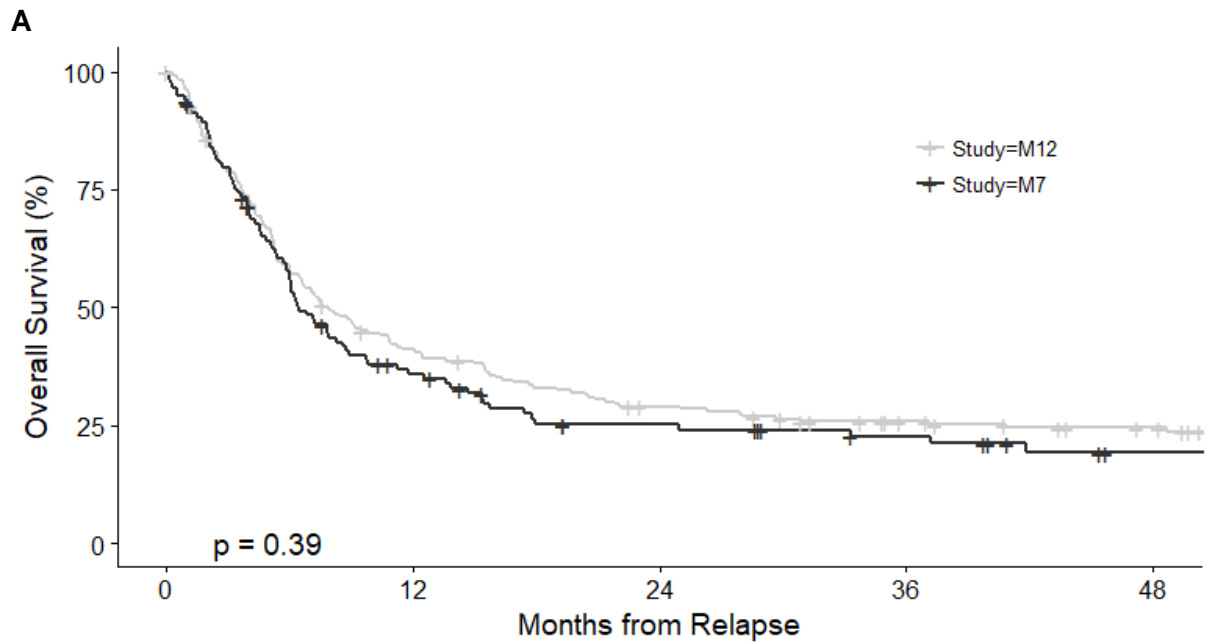
—	9	8	4	1
—	67	40	20	2



No. at Risk

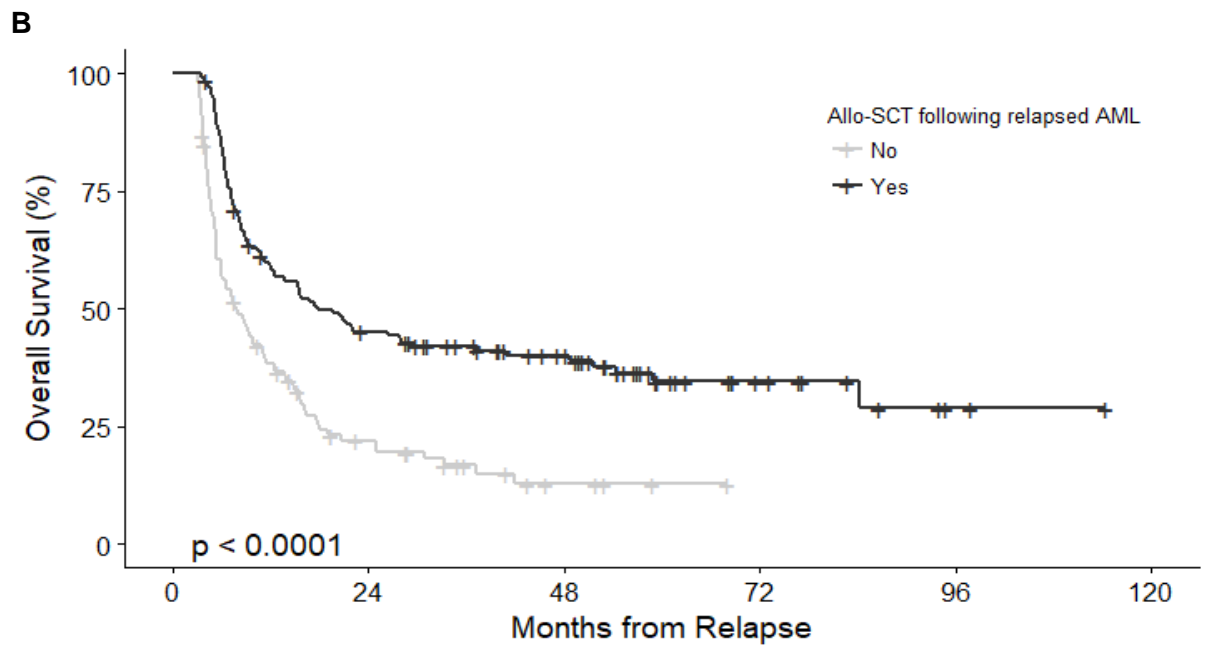
—	7	7	3	0
—	67	40	20	2

**Figure S5.** Overall survival after initial relapse of acute myeloid leukaemia, **(A)** in the entire AMLM7 and AMLM12 study cohorts and **(B)** following subsequent allogeneic stem cell transplantation in patients surviving >90 days from relapse.



No. at Risk

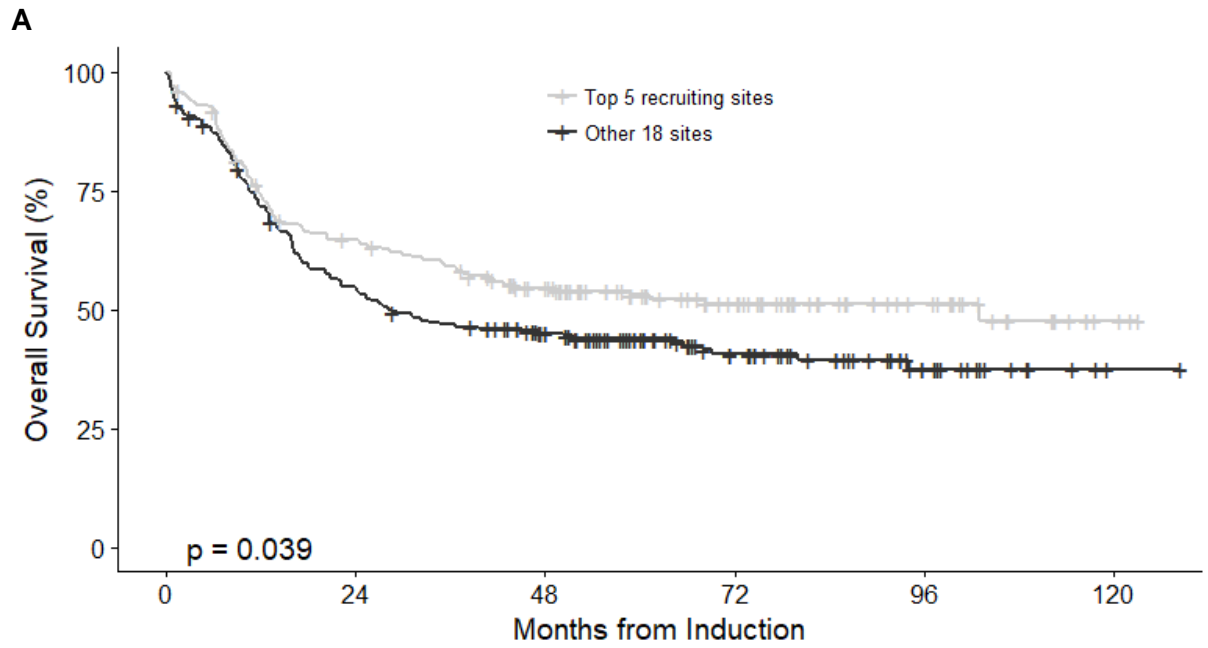
—	207	82	55	41	33
—	114	36	21	15	8



No. at Risk

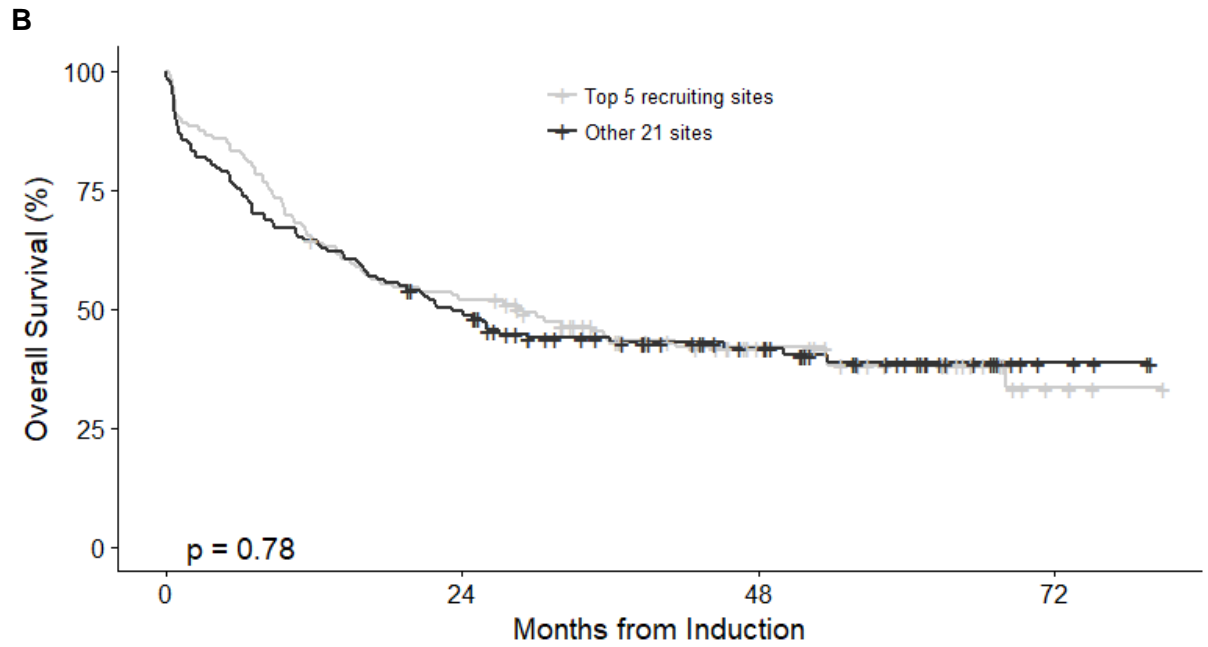
—	113	18	4	0	0	0
—	136	58	37	10	2	0

**Figure S6.** Overall survival according to recruiting volume in the **(A)** AMLM12 and **(B)** AMLM7 study cohorts.



No. at Risk

—	188	117	85	50	22	3
—	234	124	88	45	16	1



No. at Risk

—	119	61	25	4
—	137	66	32	4