

Supplementary Materials

Supplementary Table 1: Multivariate Analysis of Event-Free Survival, Cumulative Incidence of Relapse, and Overall Survival in whole cohort

Multivariable analysis	OS			EFS			CIR		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
KMT2A-r Yes/No	0.95	0.7-1.28	0.724	0.95	0.72-1.26	0.734	1.67	1.09-2.54	0.017
CNS status CNS +VE CNS -VE	1.52	0.96-2.4	0.072	1.47	0.95-2.26	0.084	1.09	0.52-2.27	0.8
TLC WBCs < 100 WBCs ≥100	0.98	0.7-1.37	0.896	0.94	0.68-1.29	0.696	1.05	0.64-1.72	0.9
Complex karyotype Yes/No	11.34	0.86-2.08	0.196	1.3	0.85-1.98	0.230	0.8	0.38-1.67	0.6
MRD EO11 <0.1 ≥ 0.1	0.71	0.53-0.94	0.018	0.7	0.54-0.91	0.008	1.06	0.71-1.57	0.8

HR=Hazard Ratio,CI=Confidence interval,EFS: Event Free Survival, OS: Overall Survival, CIR: Cumulative incidence of relapse

Supplementary Table 2: Outcomes of 121 children with KMT2A-r AML and stratified by fusion-based partners

	t (10;11)	t (11;19)	t (9;11)	KMT2A-r other group
MLL partners	n=10	n=15	n=49	n=47
5-year OS*	50%	27%	54%	44%
5-year CIR**	38%	75%	45%	41%
5-year EFS***	50%	17%	47%	37%

* OS: Overall Survival.

** CIR: Cumulative incidence of relapse

***EFS: Event Free Survival

Supplementary Table 3: Distribution of additional cytogenetic abnormalities and complex karyotype among different KMT2A-r partners

KMT2A-r partners (N= 121)	With ACA (N= 39)	With complex karyotype (N= 19)
t(9;11) 9p22 (KMT2A::MLLT3) (n=49)	18 (46%)	7 (36.8%)
t(11; 19)19p13.3 (KMT2A::MLLT1) (n=15)	4 (10%)	2 (10.5%)
t(10 ;11) (n=10)	2 (5%)	1 (5%)
t(11;17) 17q12 (n=7)	0	0
t(6 ;11) 6q27 (KMT2A::AFDN) (n=5)	1 (2.5%)	1 (5%)
t(x ;11) Xq24 (KMT2A::SEPT6) (n=3)	0	0
t(1 ;11) 1p32 (KMT2A::EPS15) (n=2)	1 (2.5%)	1 (5%)
Other partners (n=30)	13 (33.3%)	7 (36.8%)

*Abbreviations, ACA (Additional cytogenetic abnormalities)

Supplementary Table 4 : Clinical Characteristics of 90 patients excluded from survival analysis

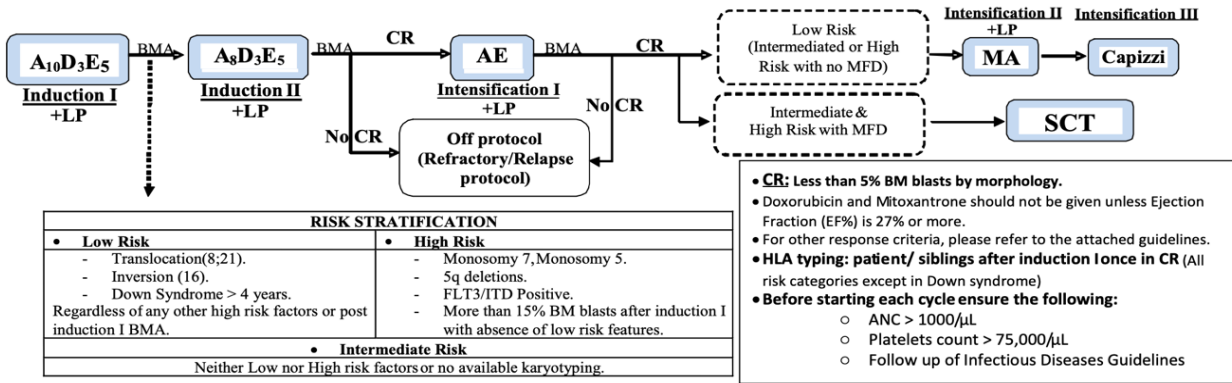
Variant	Total Cohort n= 90 (%)
Initial WBCs (x109)/L)	
<100	70
≥ 100	20
CNS involvement	
Positive	12
Negative	64
Not available	14
KMT2A-r status	
KMT2A +VE	29
KMT2A -VE	61
Started treatment	
Yes	84
No	6
Causes of death	
Due to disease	35
Covid pandemic	6
Sepsis	32

*Abbreviations, WBCs (white blood cell counts), CNS (central nervous system), EOI 1(End of induction 1)

ROADMAP OF AML PROTOCOL

Children's Cancer Hospital Egypt (57357)

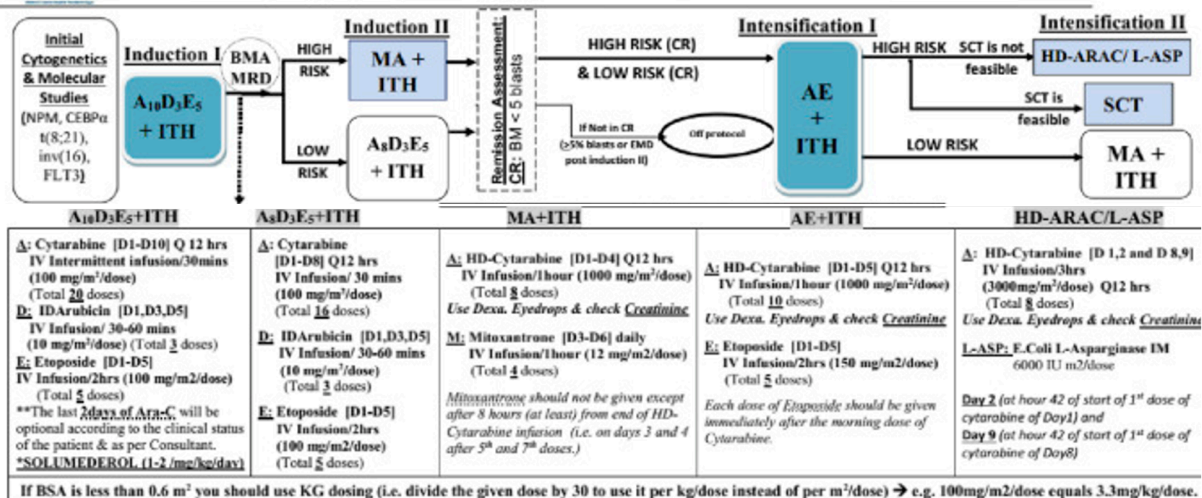
CCHE_AML#2-1-2008
Roadmap v1.2: Release date: 07/06/2011
Please discard any previous versions(prior to 07/06/2011)



A ₁₀ D ₃ E ₅	A ₈ D ₃ E ₅	AE	MA	Capizzi
<p>A: Cytarabine IV push 100 mg/m²/dose (3.3 mg/kg/dose if BSA < 0.6 m²) every 12 hours (total of 20 doses), D1-D10.</p> <p>D: Doxorubicin 50 mg/m²/dose (1.67 mg/kg/dose if BSA < 0.6 m²) over 4 hours every other day (total of 3 doses) D1, 3, 5.</p> <p>E: Etoposide 100 mg/m²/dose (3.3 mg/kg/dose if BSA < 0.6 m²) daily over 2 hours (total of 5 doses), D1-D5.</p>	<p>A: Cytarabine IV push 100 mg/m²/dose (3.3 mg/kg/dose if BSA < 0.6 m²) every 12 hours (total of 16 doses), D1-D8.</p> <p>D: Doxorubicin 50 mg/m²/dose (1.67 mg/kg/dose if BSA < 0.6 m²) over 4 hours every other day (total of 3 doses) D1, 3, 5.</p> <p>E: Etoposide 100 mg/m²/dose (3.3 mg/kg/dose if BSA < 0.6 m²) daily over 2 hours (total of 5 doses), D1-D5.</p>	<p>A: HDCytarabine 1000 mg/m²/dose (33 mg/kg/dose if BSA < 0.6 m²) over 1 hour every 12 hours (total of 10 doses), D1-D5.</p> <p><i>Use eye drops & check serum Cr.</i></p> <p>E: Etoposide 150 mg/m²/dose (5 mg/kg/dose if BSA < 0.6 m²) daily over 1 hour (total of 5 doses), D1-D5.</p> <p><i>Each dose of etoposide should immediately follow the AM dose of cytarabine.</i></p>	<p>A: HDCytarabine 1000 mg/m²/dose (33 mg/kg/dose if BSA < 0.6 m²) over 1 hour every 12 hours (total of 8 doses), D1-D4.</p> <p>M: Mitoxantrone 12 g/m²/dose (0.4 mg/kg/dose if BSA < 0.6 m²) over 1 hour daily (total of 4 doses), D3-D6.</p> <p><i>On days both HD AraC & Mitox given, Mitoxantrone should be given 8 h after infusion of HD AraC is complete.</i></p>	<p>A: HDCytarabine 3000 mg/m²/dose (100 mg/kg/dose if BSA < 0.6 m²) every 12 hours over 3 hours (total of 8 doses), D1, 2, 8, 9.</p> <p><i>Use eye drops & check serum Cr.</i></p> <p>E: Coif L-Asparaginase: IM 6000 International Units/m²/dose (200 International Units/kg/dose if BSA < 0.6 m²) (total of 2 doses).</p> <p>Day 2 (at hour 42 of start of 1st dose of cytarabine on Day 1) and Day 9 (at hour 42 of start of 1st dose of cytarabine on Day 8)</p>

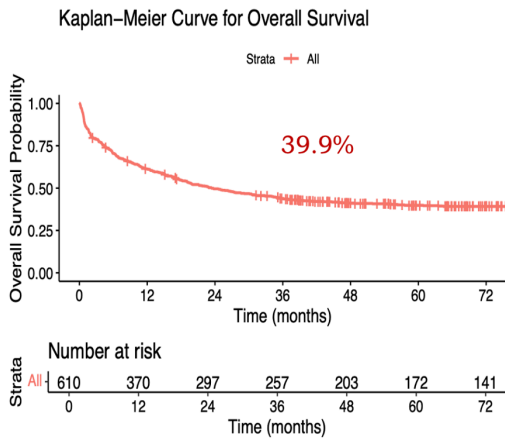
Triple ITH is to be given at day 1 (Except in CAPIZZI)				<p>For CNS positive patients:</p> <p>If CNS disease is present at diagnosis, patients should receive two courses of "triple" ITH each week until CNS is clear plus further 2 courses. A minimum of 6 courses should be given in a period of 3 weeks from diagnosis.</p> <p>This intensive phase is followed by monthly courses of the same "triple" therapy until after the final course of systemic chemotherapy has been completed (Except in CAPIZZI)</p>
Age (years)	Methotrexate	Cytarabine	Hydrocortisone	
<1	5 mg	15 mg	5 mg	
1	7.5 mg	20 mg	7.5 mg	
2	10 mg	25 mg	10 mg	
3+	12.5 mg	30 mg	12.5 mg	

Supplementary Figure 1: Treatment Protocol Roadmap adopted from modified COG AAML 0531

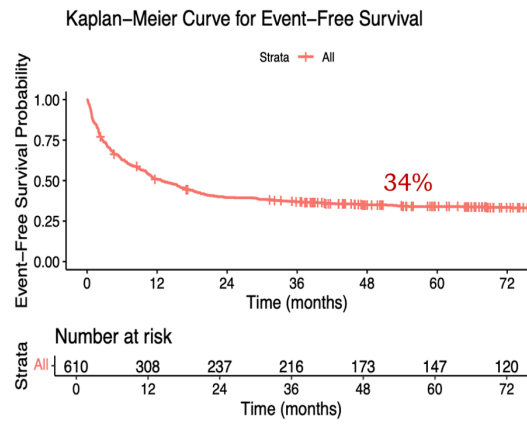


Supplementary Figure 2: Treatment Protocol Roadmap adopted from modified COG AAML 1031

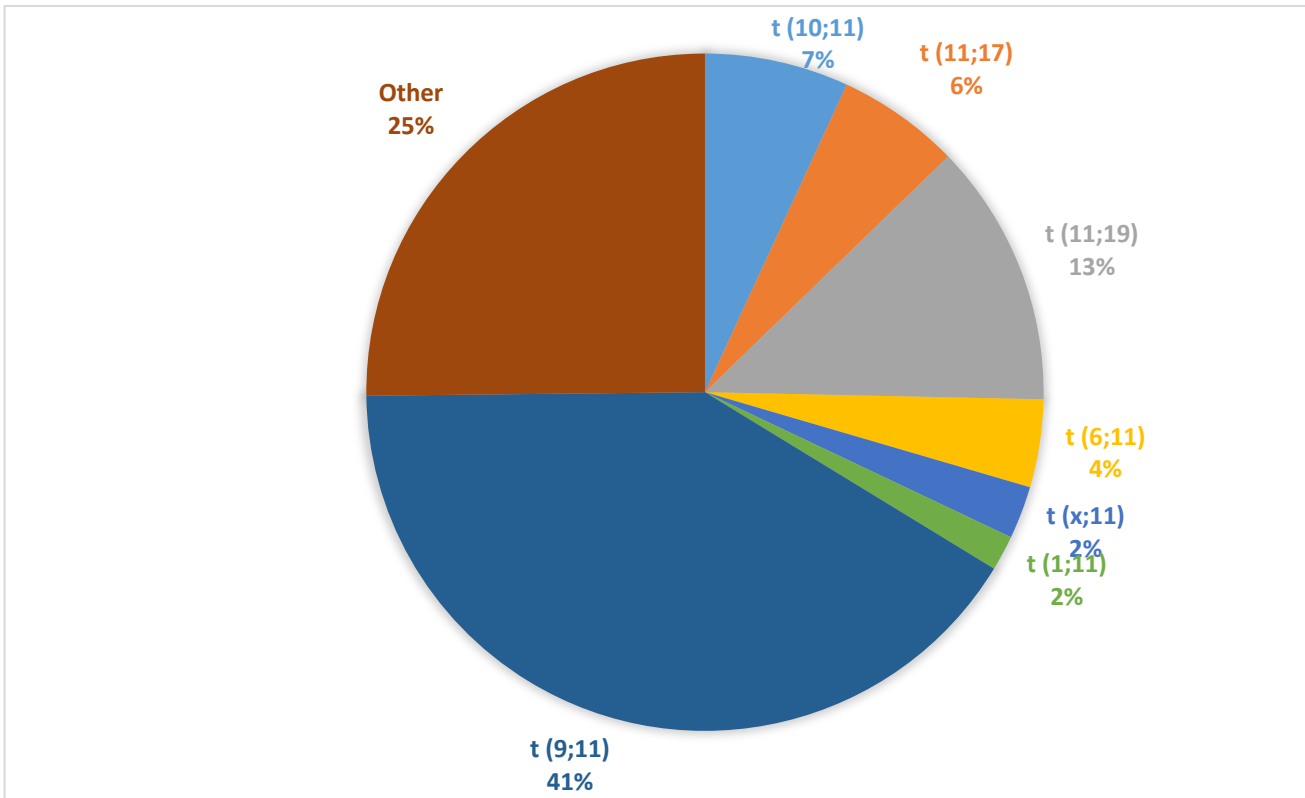
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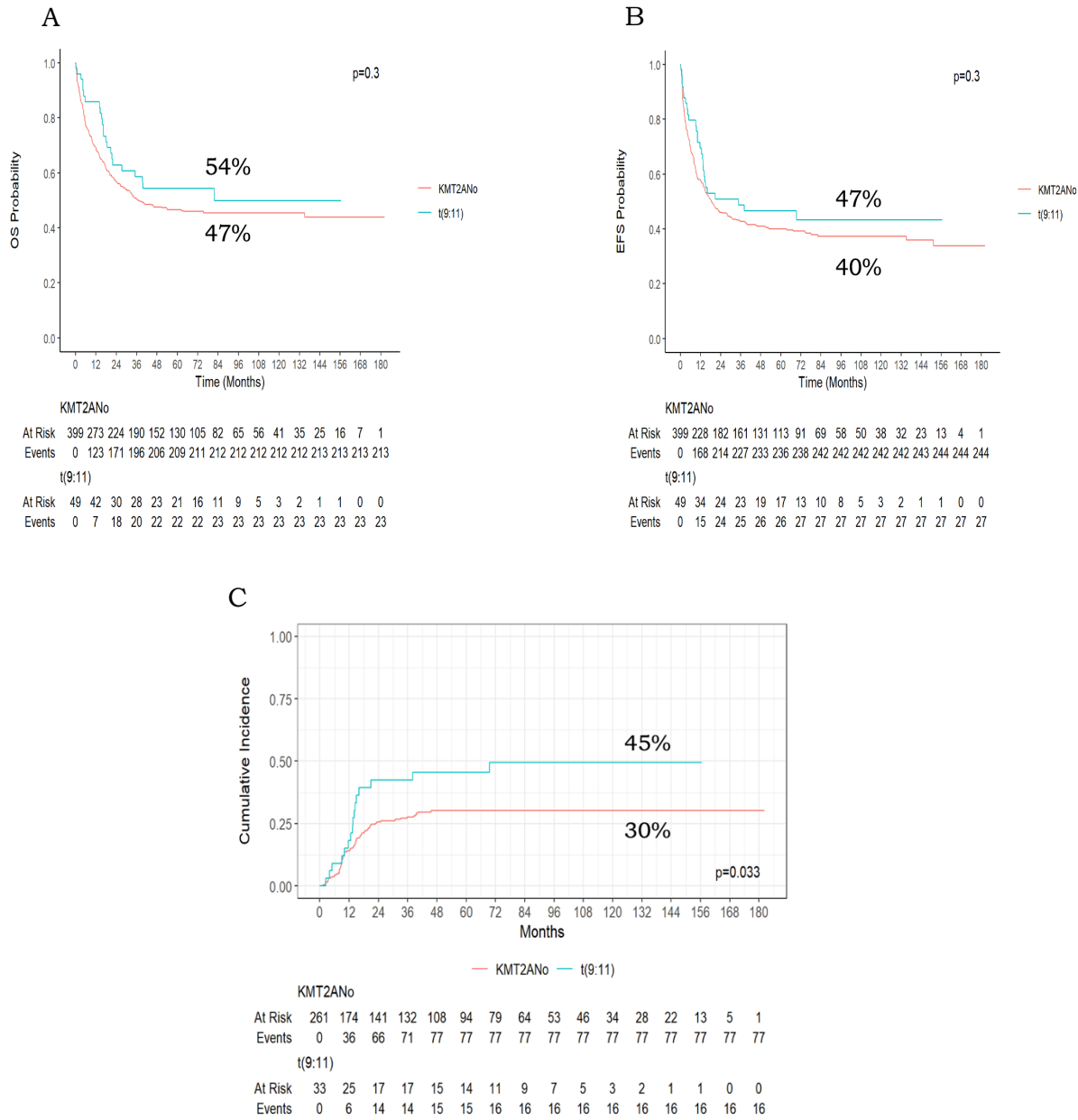
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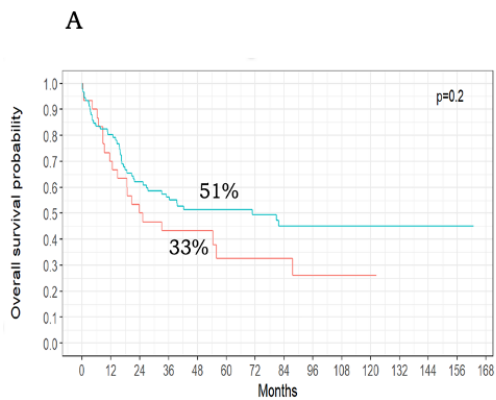
Supplementary Figure 3: Outcomes of whole cohort including 90 patients with induction deaths. (A) OS (Overall survival), (B) EFS (Event free survival).



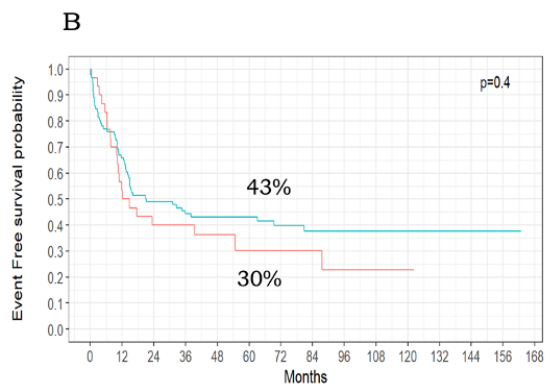
Supplementary Figure 4: Distribution of the fusion based KMT2A-r partners in our cohort of childhood KMT2A-r IR-AML. t(9;11)(p22;q23) (9p22/KMT2A::MLLT3) (n=49) , t(11;19) 19p13.3 (KMT2A::MLLT1) (n=15), t(10;11) (n=10), t(11;17) 17q12 (n=7), t(6;11) 6q27 (KMT2A::AFDN) (n=5), t(X;11) Xq24 (KMT2A::SEPT6) (n= 3) & t(1;11) 1q21/ KMT2A::MLLT11(n= 2). There were 30 were included in other groups including structural abnormalities in KMT2A gene, triple translocations & other patients with unknown partners.



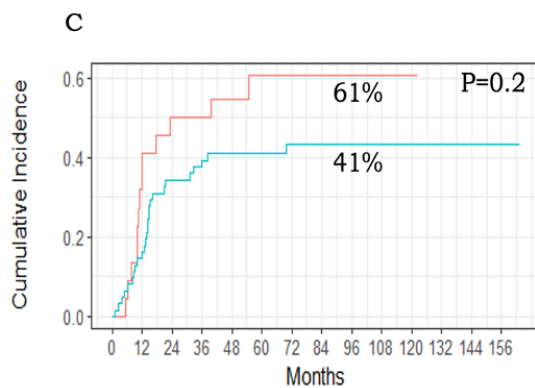
Supplementary Figure 5: Outcomes of t(9;11) in comparison to other IR-AML patients with KMT2A-no. (A) OS (Overall survival), (B) EFS (Event free survival), (C) CIR (Cumulative incidence of relapse).



		KMT2A_r_risk																													
		High risk								Non High risk																					
At Risk		30	21	15	13	9	6	6	5	4	2	1	0	0	0	0	91	72	54	48	40	35	26	20	16	11	5	3	2	2	0
Events		0	9	15	17	17	19	19	19	20	20	20	20	20	20	20	0	18	34	39	43	43	44	46	46	46	46	46	46	46	46



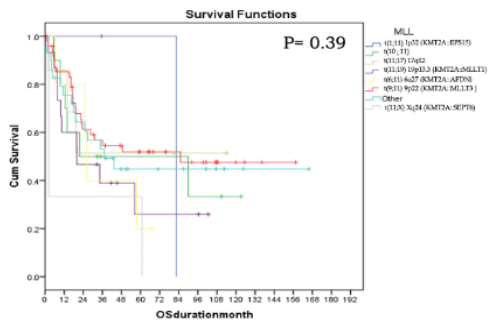
		KMT2A_r_risk																													
		High risk								Non High risk																					
At Risk		30	16	12	12	7	5	5	4	3	2	1	0	0	0	0	91	59	42	38	34	29	21	17	14	10	5	3	2	2	0
Events		0	14	18	18	19	20	20	20	21	21	21	21	21	21	21	0	31	46	50	51	51	53	54	54	54	54	54	54	54	54



		KMT2A_r_risk																											
		HIGH RISK								Non HIGH RISK																			
At Risk		22	12	9	9	6	5	5	4	3	2	1	0	0	0	62	43	31	28	26	23	19	16	13	10	4	3	2	2
Events		0	8	11	11	12	13	13	13	13	13	13	13	13	13	0	10	21	24	25	25	26	26	26	26	26	26	26	26

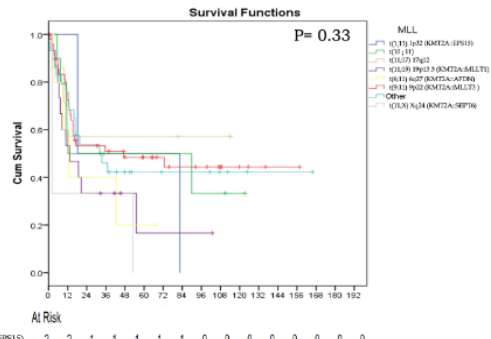
Supplementary Figure 6: Outcomes of KMT2A-r AML Stratified by Fusion-Based Groups into High Risk and Non-High-Risk Groups. (A) OS (Overall survival), (B) EFS (Event free survival), (C) CIR (Cumulative incidence of relapse)

A



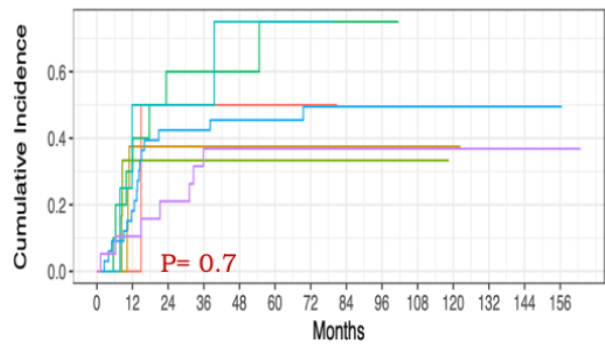
At Risk	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180	192
t(1;11) 1p32 (KMT2A::EP315)	2	2	2	1	1	1	1	0	0	0	0	0	0	0	0	0	0
t(10;11)	0	7	5	3	3	3	3	2	2	1	0	0	0	0	0	0	0
t(11;17) 17q12	7	5	3	3	3	3	3	2	2	0	0	0	0	0	0	0	0
t(11;19) 19p13.3 (KMT2A::MLLT1)	15	10	7	6	4	2	2	2	2	0	0	0	0	0	0	0	0
t(6;11) 6q27 (KMT2A::AFDN)	5	4	3	2	2	1	1	0	0	0	0	0	0	0	0	0	0
t(9;11) 9p22 (KMT2A::MLLT3)	49	42	30	28	23	21	16	11	9	5	3	2	1	1	0	0	0
Other partners	30	22	18	15	12	9	6	6	5	4	2	1	1	1	0	0	0
t(11;X) Xq24 (KMT2A::SEPT6)	3	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0

B



t(1;11) 1p32 (KMT2A::EP315)	2	2	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0
t(10;11)	10	5	5	3	3	3	3	2	2	1	0	0	0	0	0	0	0
t(11;17) 17q12	7	4	3	3	3	3	3	2	2	0	0	0	0	0	0	0	0
t(11;19) 19p13.3 (KMT2A::MLLT1)	15	9	5	5	3	1	1	1	1	0	0	0	0	0	0	0	0
t(6;11) 6q27 (KMT2A::AFDN)	5	2	2	2	1	1	1	0	0	0	0	0	0	0	0	0	0
t(9;11) 9p22 (KMT2A::MLLT3)	49	34	24	23	19	17	13	10	8	5	3	2	1	1	0	0	0
Other partners	30	18	13	10	10	7	4	4	4	3	2	1	1	1	0	0	0
t(11;X) Xq24 (KMT2A::SEPT6)	3	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0

C



At Risk	0	12	24	36	48	60	72	84	96	108	120	132	144	156
t(1;11) 1p32 (KMT2A::EP315)	2	2	1	1	1	1	1	0	0	0	0	0	0	0
t(10;11)	8	4	4	4	3	3	3	2	2	1	0	0	0	0
t(11;17) 17q12	6	3	3	3	3	3	3	2	2	0	0	0	0	0
t(11;19) 19p13.3 (KMT2A::MLLT1)	10	6	3	3	2	1	1	1	1	0	0	0	0	0
t(6;11) 6q27 (KMT2A::AFDN)	4	2	2	2	1	1	1	0	0	0	0	0	0	0
t(9;11) 9p22 (KMT2A::MLLT3)	33	25	17	17	15	14	11	9	7	5	3	2	1	1
Other	19	13	10	7	7	5	4	4	4	3	1	1	1	1
t(11;X) Xq24 (KMT2A::SEPT6)	2	0	0	0	0	0	0	0	0	0	0	0	0	0

Supplementary Figure 7: Outcomes of KMT2A-r AML fusion partners. (A) OS (Overall survival), (B) EFS (Event free survival), (C) CIR (Cumulative incidence of relapse)