LETTER TO THE EDITOR

KMT2A partner genes in infant acute lymphoblastic leukemia have prognostic significance and correlate with age, white blood cell count, sex, and central nervous system involvement: a Children's Oncology Group P9407 trial study

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SUPPLEMENTARY MATERIALS

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Supplementary Table 1. Alternate multivariable Cox regression models

	Only *KMT2A*-R Cases		**Continuous Age**		**Treatment Cohort Included**	
	Estimated HR (95% CI)	**P***	**Estimated HR (95% CI)**	**p**	**Estimated HR (95% CI)**	**p**
Sex						
Male	1.60 (1.04- 2.46)	0.032	1.53 (1.02- 2.28)	0.039	1.60 (1.07- 2.40)	0.022
Female	Reference		Reference		Reference	
Age at diagnosis (months)			0.84 (0.78- 0.91)	<0.001		
≤ 90 days	2.89 (1.75- 4.78)	<0.001			2.61 (1.62- 4.21)	<0.001
> 90 days	Reference				Reference	
WBC count						
< 50 × 10^9/L	Reference		Reference		Reference	
≥ 50 × 10^9/L	2.33 (1.11- 4.92)	0.026	2.43 (1.27- 4.66)	0.008	2.69 (1.41- 5.15)	0.003
***KMT2A* Status/Partner Gene**						
***KMT2A*-G**			Reference		Reference	
***KMT2A*-R**						
AFF1	Reference		2.15 (1.17- 3.96)	0.014	2.49 (1.35- 4.59)	0.004
MLLT1	1.34 (0.80- 2.26)	0.272	2.61 (1.32- 5.17)	0.006	3.31 (1.67- 6.59)	0.001
MLLT3	0.41 (0.12- 1.38)	0.152	0.98 (0.28- 3.45)	0.969	1.05 (0.30- 3.71)	0.944
Other Partner Gene	1.01 (0.52- 1.96)	0.983	2.15 (1.00- 4.63)	0.051	2.54 (1.17- 5.52)	0.019
Unknown Partner Gene	1.13 (0.44- 2.94)	0.795	2.66 (0.96-7.40)	0.060	2.76 (0.98- 7.72)	0.054
CNS Status		0.455		0.912		0.948
CNS1	Reference		Reference		Reference	
CNS2	1.36 (0.80- 2.31)	0.252	0.99 (0.60- 1.62)	0.96	1.07 (0.65- 1.76)	0.777
CNS3	1.03 (0.58- 1.84)	0.910	0.90 (0.53- 1.51)	0.69	1.00 (0.58- 1.70)	0.986
Treatment Cohort						
Cohorts 1 & 2					Reference	
Cohort 3					0.92 (0.59- 1.43)	0.71

* p-values correspond to Wald tests comparing to reference levels (or one unit increase) in joint models including all listed factors.

Supplementary Table 2. Correlations of *KMT2A*-G *vs.* *KMT2A*-R status and partner genes with demographic and clinical covariates

	***KMT2A*-R**	***AFF1***	***MLLT1***	***MLLT3***	***KMT2A*-R ‘Other’ Partner Gene**	***KMT2A*-R ‘Unknown’ Partner Gene**	***KMT2A*-G**	**Comparison**	**FET *P* value**
Variable	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)		
Age at diagnosis								≤ 90 d *vs.* >90 d	
≤ 90 d	40 (25.5%)	23(29.5%)	11 (33.3%)	3 (21.4%)	1 (5.0%)	2 (16.7%)	6 (11.5%)	*KMT2A*-G *vs.* all *KMT2A*-R	0.036
								‘Other’ *KMT2A*-R *vs. AFF1, MLLT1* or *MLLT3*	0.026
> 90 d	117 (74.5%)	55(70.5%)	22 (66.7%)	11 (78.6%)	19 (95.0%)	10 (83.3%)	46 (88.5%)	*AFF1 vs.* all non-*AFF1 KMT2A*-R*	0.35
								AFF1 vs. MLLT3	0.75
								AFF1 vs. ‘Other’ *KMT2A*-R	0.022
								MLLT1 vs. all non-*MLLT1 KMT2A*-R	0.37
								MLLT1 vs. MLLT3	0.50
								MLLT1 vs. ‘Other’ *KMT2A*-R	0.020
								MLLT3 vs. all non-*MLLT3 KMT2A*-R	1.00
WBC Count								$< 50\times10^{9}$/L *vs.* $\geq 50\times10^{9}$/L	
$< 50\times10^{9}$/L	32 (20.4%)	6 (7.7%)	6 (18.2%)	8 (57.1%)	7 (35.0%)	5 (41.7%)	25 (48.1%)	*KMT2A*-G *vs.* all *KMT2A*-R	0.0003
								AFF1 vs. all non-*AFF1 KMT2A*-R**	<0.0001
								MLLT1 vs. all non-*MLLT1 KMT2A*-R	1.00
$\geq 50\times10^{9}$/L	123(78.3%)	71(91.0%)	26 (78.8%)	6 (42.9%)	13 (65.0%)	7 (58.3%)	27 (51.9%)	*MLLT1 vs. AFF1*	0.18
								MLLT1 vs. MLLT3	0.015
Unknown	2 (1.3%)	1 (1.3%)	1 (3.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	*MLLT1 vs.* ‘Other’ *KMT2A*-R	0.21
								MLLT3 vs. AFF1, MLLT1, or ‘Other’ *KMT2A*-R	0.0008
								MLLT3 vs. AFF1	<0.0001
								MLLT3 vs. ‘Other’ *KMT2A*-R	0.30

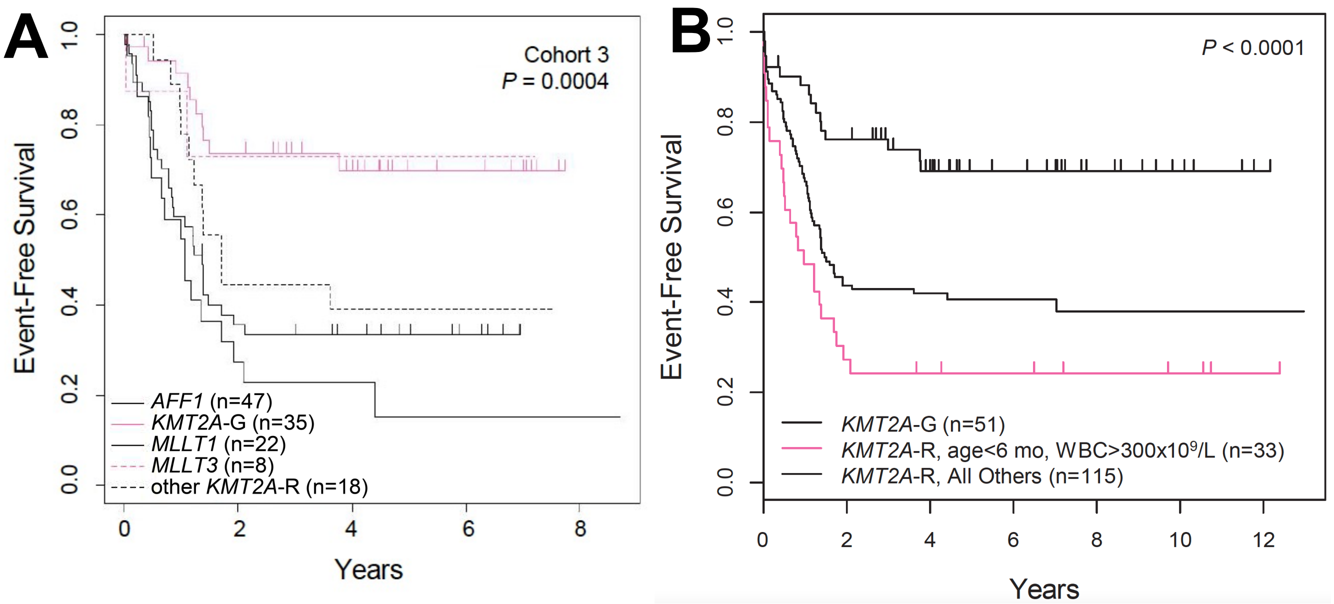
Supplementary Table 2 (cont'd). Correlations of *KMT2A*-G *vs*. *KMT2A*-R status and partner genes with demographic and clinical covariates

	***KMT2A*-R**	***AFF1***	***MLLT1***	***MLLT3***	***KMT2A*-R 'Other' Partner Gene**	***KMT2A*-R 'Unknown' Partner Gene**	***KMT2A*-G**	**Comparison**	**FET *P* value**
Variable	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)		
Sex								Male *vs*. Female	
Male	72 (45.9%)	36 (46.2%)	16 (48.5%)	7 (50.0%)	10 (50.0%)	3 (25.0%)	33 (63.5%)	all *KMT2A*-R *vs*. *KMT2A*-G	0.037
								AFF1 vs. *KMT2A*-G	0.073
								AFF1 vs. *MLLT1*	0.84
								AFF1 vs. *MLLT3*	1.00
Female	85 (54.1%)	42 (53.8%)	17 (51.5%)	7 (50.0%)	10 (50.0%)	9 (75.0%)	19 (36.5%)	*AFF1 vs*. 'Other' *KMT2A*-R	0.81
CNS Status									
CNS1	71 (45.2%)	32 (41%)	13 (39.4%)	8 (57.1%)	12 (60%)	6 (50%)	32 (61.5%)	CNS1; all *KMT2A*-R *vs*. *KMT2A*-G	0.056
								CNS1 or CNS2; all *KMT2A*-R *vs*. *KMT2A*-G	0.029
								CNS1; *AFF1 vs*. *KMT2A*-G	0.032
								CNS1 or CNS2; *AFF1 vs*. *KMT2A*-G	0.024
								CNS1; *MLLT1 vs*. *KMT2A*-G	0.074
								CNS1 or CNS2; *MLLT1 vs*. *KMT2A*-G	0.020
								CNS1; *AFF1 vs*. all non-*AFF1 KMT2A*-R	0.32
								CNS1 or CNS2; *AFF1 vs*. all non-*AFF1 KMT2A*-R	0.85
								CNS1; *AFF1 vs*. *MLLT1*	1.00
								CNS1 or CNS2; *AFF1 vs*. *MLLT1*	0.65
CNS2	46 (29.3%)	25 (32.1%)	10 (30.3%)	1 (7.1%)	5 (25%)	5 (41.7%)	15 (28.8%)	CNS1; *AFF1 vs*. *MLLT3*	0.23
								CNS1 or CNS2; *AFF1 vs*. *MLLT3*	0.74
								CNS1; *AFF1 vs*. 'Other' *KMT2A*-R	0.21
								CNS1 or CNS2; *AFF1 v*. 'Other' *KMT2A*-R	0.39
CNS3	38 (24.2%)	20 (25.6%)	10 (30.3%)	4 (28.6%)	3 (15%)	1 (8.3%)	5 (9.6%)		
Unknown	2 (1.3%)	1 (1.3%)	0 (%)	1 (7.1%)	0 (0%)	0 (%)	0 (0%)		

Fisher's exact tests (FET) compared the frequencies among the categories specified.

'Other' Partner Gene includes: *EPS15* (n=4); *MLLT10* (n=1); *ACTN4* (n=1); *ACER1* (n=1); and non-*AFF1*/non-*MLLT1*/non-*MLLT3* not further classified (n=13). 'Unknown' Partner Gene includes: non-*AFF1* not further classified (n=5); and *KMT2A*-R not further classified (n=7).

*1 of 5 *KMT2A*-R non-*AFF1* not further classified was ≤ 90 d. **2 of 5 *KMT2A*-R non-*AFF1* not further classified had WBC ≥ 50×10^9/L.



Supplementary Figure 1. Five-year EFS in COG P9407 infant ALL trial estimated by Kaplan-Meier method. (A) Five-year EFS in Cohort 3 after treatment modifications to reduce toxicities plotted as a function of *KMT2A*-G and *KMT2A* partner genes. Note similar EFS by genetic subtype in Cohort 3 compared to Cohorts 1, 2, and 3 combined (please see Figure 1A). (B) Kaplan-Meier estimates of EFS in COG P9407 trial plotted by Interfant-99 risk groups. Any *KMT2A*-R with age <6 months and WBC>300x10^9/L (high-risk); *KMT2A*-R without either of these features (intermediate-risk; IR); *KMT2A*-G (low-risk; LR). (A-B) Numbers of patients in each risk group are at bottom in the plots. *P* values (top right) were calculated by the log-rank test.