Supplemental Methods

Treatment Regimens: The presence of a *CEBPA* mutation was not used for risk stratification on CCG2961, AAML03P1 or AAML0531. Patients treated on CCG2961 who achieved complete remission (CR, <5% blasts) following induction I, II and consolidation with an available matched family donor (MFD) were allocated to allogeneic hematopoietic stem cell transplant (HSCT) while those without an MFD continued with chemotherapy and received an IL-2 maintenance.[1] Patients treated on AAML03P1 and AAML0531 with <15% blasts at end induction I and in CR at end of induction II were allocated to receive allogeneic HSCT from an MFD if available or otherwise proceeded with a total of 5 cycles of chemotherapy. Patients with refractory disease (≥20% blasts) after induction I on AAML03P1 were removed from study, while those with refractory disease (≥15%) blasts after induction I on AAML0531 were non-randomly allocated to receive allogeneic HSCT. All patients treated on AAML03P1 received gemtuzumab ozogamicin (GO) with combination chemotherapy in induction I and intensification II, while patients AAML0531 were allocated to the primary randomization of receiving GO or no GO with chemotherapy as on 03P1.[2,3] Patients treated on AAML1031 with any *CEBPA* bZip mutation were allocated to standard risk therapy with 4 cycles of chemotherapy and did not receive allogeneic HSCT unless they had refractory disease. While patients treated on AAML1031, including *CEBPA*-mutant patients, were randomized to receive bortezomib or no bortezomib in combination with chemotherapy, there were no overall outcome differences in patients allocated to either treatment arm.[4]

Supplemental Figure Legends

Supplemental Figure 1. *CEBPA* mutations detected in pediatric and young adult AML. Mutations were detected in the bZip domain and TAD regions using PCR amplification of the entire coding region or by fragment length analysis of the bZip domain. In all cases with a bZip

mutation identified, subsequent Sanger sequencing and sequencing of N-terminal region were performed.

Supplemental Figure 2. Outcomes of *CEBPA*-bZip and *CEBPA*-dm patients over time across the different studies analyzed. (A) EFS on CCG2961 and AAML03P1. For purposes of analysis and smaller numbers, the 2 earlier studies of CCG2961 and AAML03P1 were combined. (B) EFS on AAML0531. (C) EFS on AAML1031.

Supplemental Figure 3. Outcomes of *CEBPA*-mutant patients according to *FLT3*-ITD mutational status (A) Event free survival (B) Overall survival. *FLT3*-ITD positive was defined as presence of a *FLT3*-ITD mutation with an allelic ratio of >0.1.

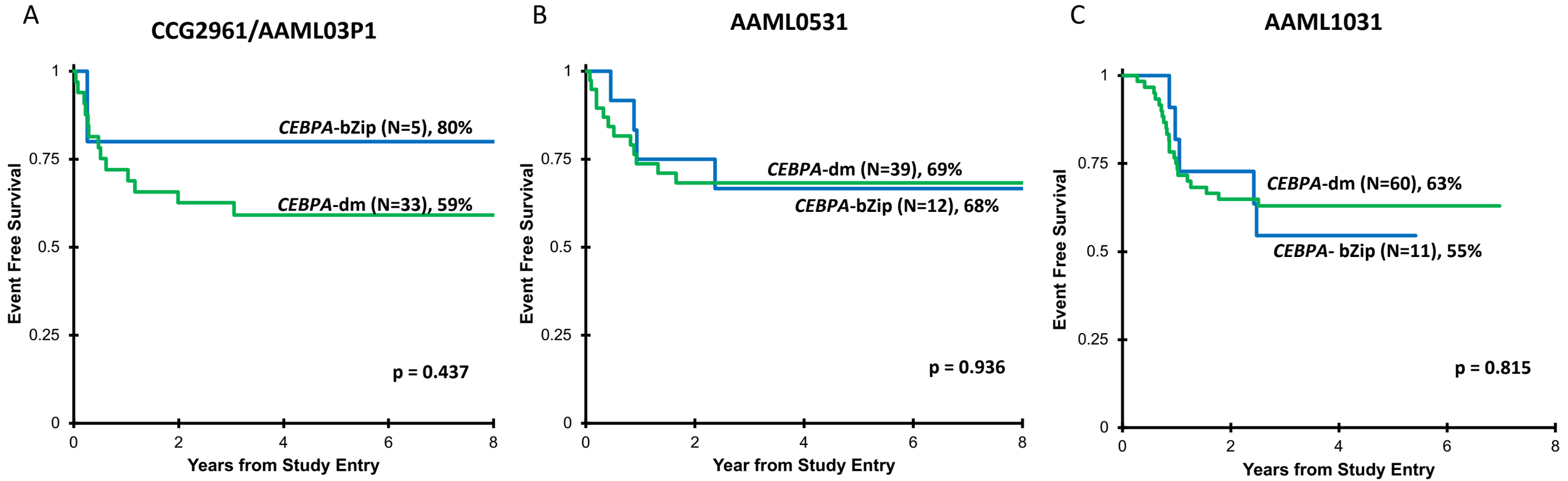
Supplemental Table 1. Utilization of hematopoietic stem cell transplant in the cohort overall for *CEBPA*-mutant and WT patients for all treatment studies.

Supplemental Table 2. Outcomes of *CEBPA*-bZip only and dm patients according to age.

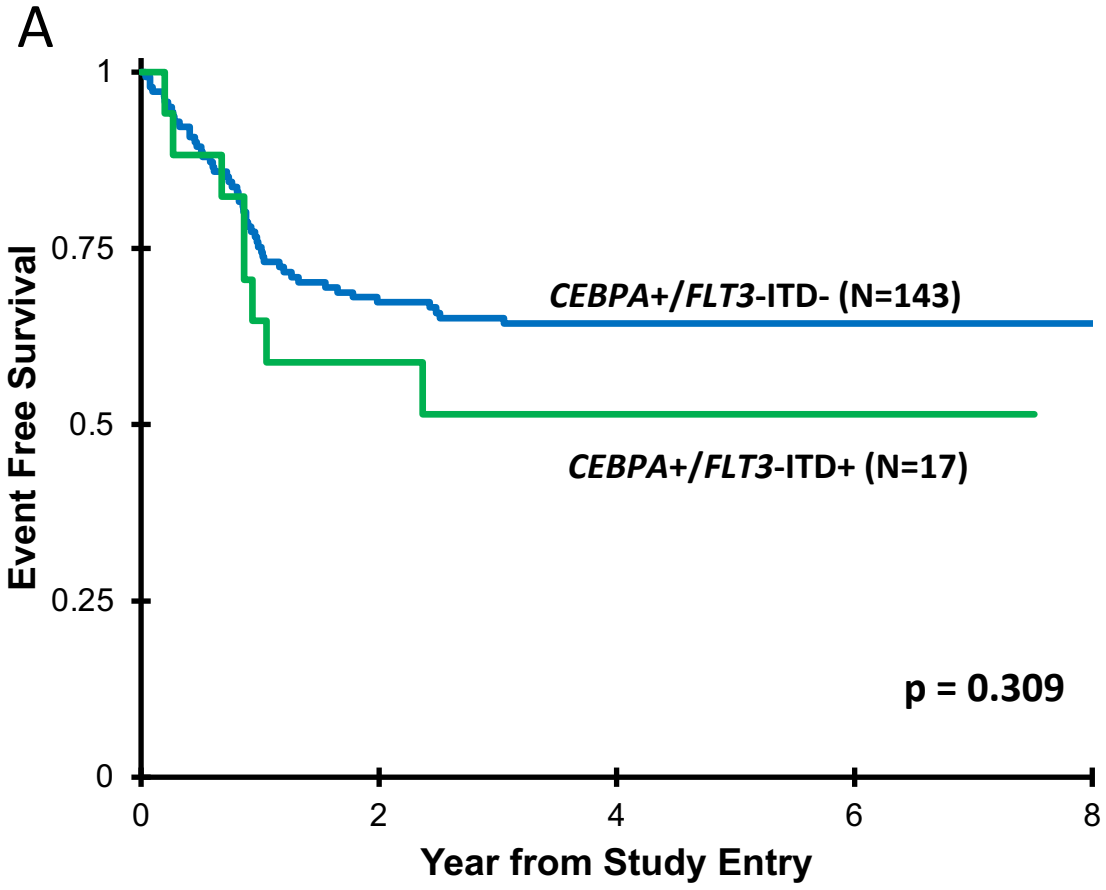
References:

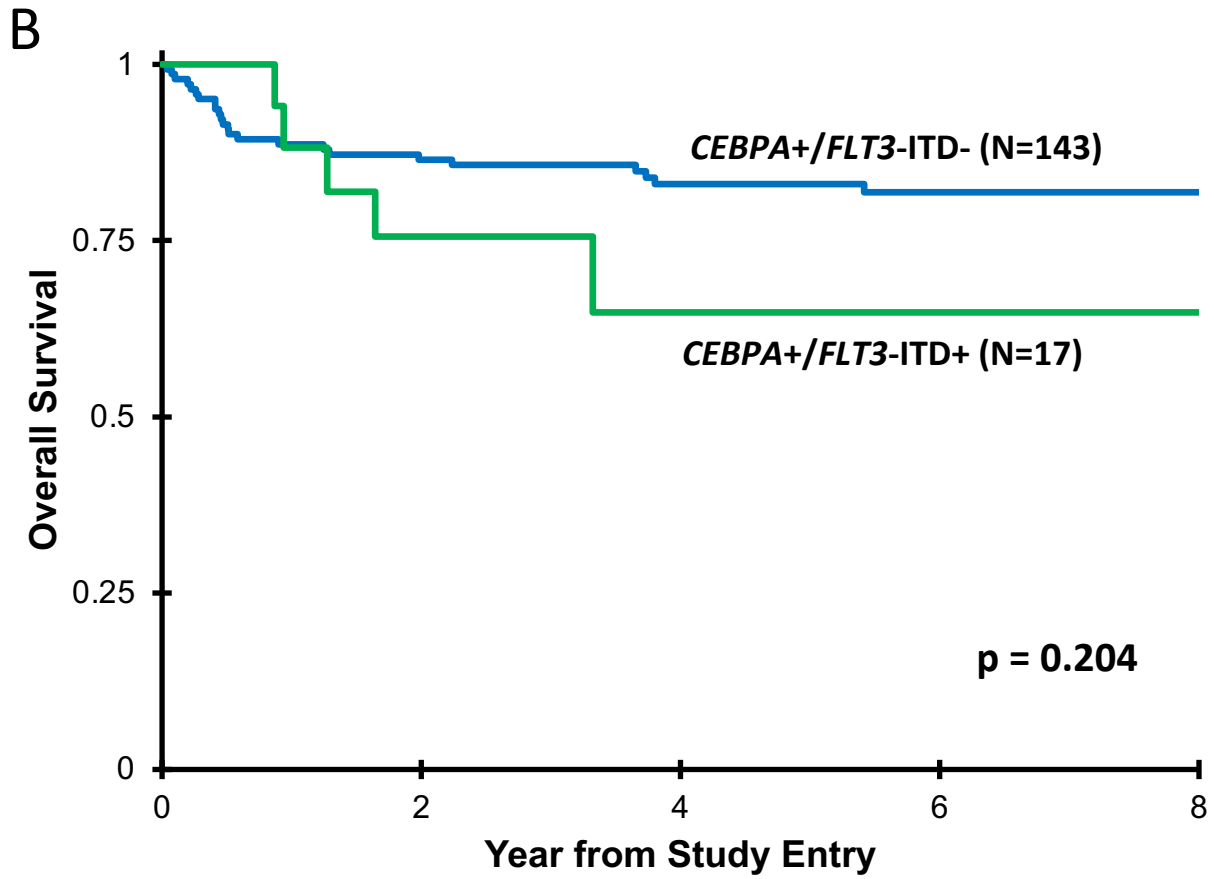
1. Lange BJ, Smith FO, Feusner J, et al. Outcomes in CCG-2961, a children's oncology group phase 3 trial for untreated pediatric acute myeloid leukemia: a report from the children's oncology group. *Blood*. 2008;111(3):1044-1053.
2. Cooper TM, Franklin J, Gerbing RB, et al. AAML03P1, a pilot study of the safety of gemtuzumab ozogamicin in combination with chemotherapy for newly diagnosed childhood acute myeloid leukemia: a report from the Children's Oncology Group. *Cancer*. 2012;118(3):761-769.
3. Gamis AS, Alonzo TA, Meshinchi S, et al. Gemtuzumab ozogamicin in children and adolescents with de novo acute myeloid leukemia improves event-free survival by reducing relapse risk: results from the randomized phase III Children's Oncology Group trial AAML0531. *J Clin Oncol*. 2014;32(27):3021-3032.
4. Aplenc R, Meshinchi S, Sung L, et al. Bortezomib with standard chemotherapy for children with acute myeloid leukemia does not improve treatment outcomes: a report from the Children's Oncology Group. *Haematologica*. 2020.

Supplemental Figure 2

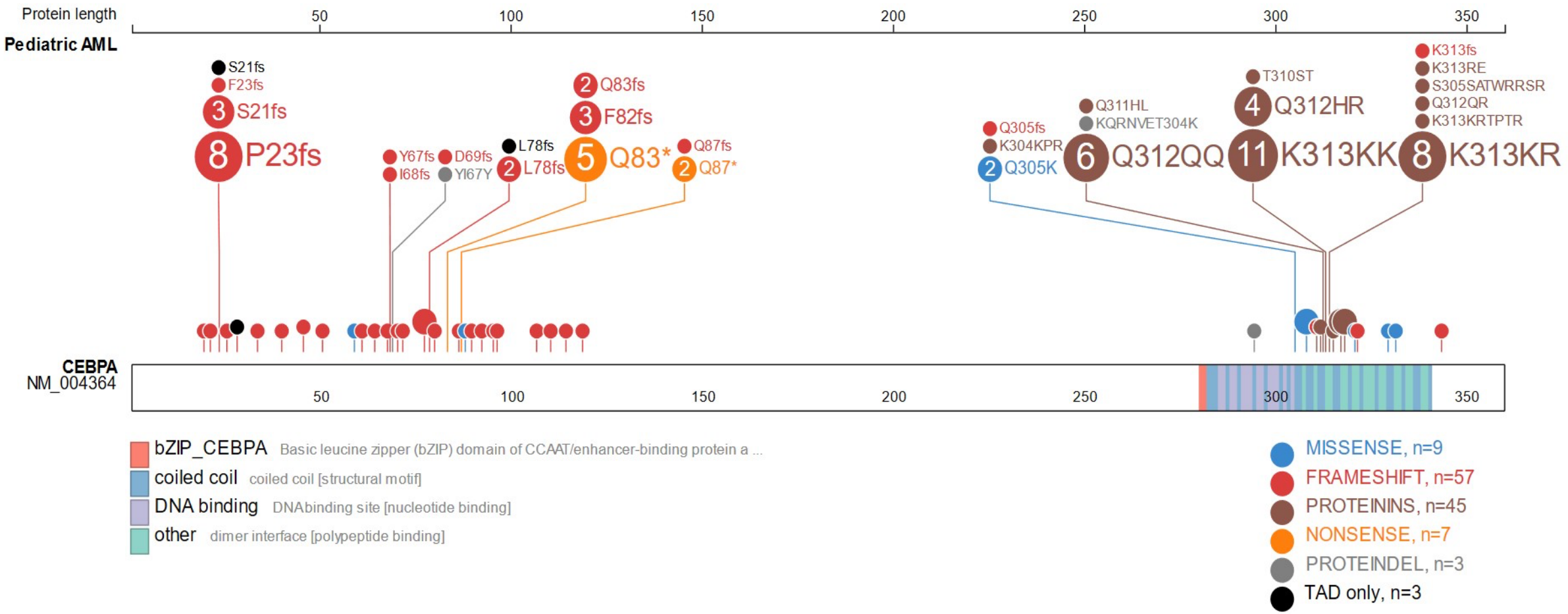


Supplemental Figure 3.





Supplemental Figure 1.



Supplemental Table 1

	CEBPA-WT N (%)	CEBPA-mut N (%)	CEBPA-bZip N (%)	CEBPA-dm N (%)	p-value CEBPA-WT vs. mutant	p-value CEBPA-bZip vs. dm
HSCT Overall						
No	2397 (85.8%)	142 (88.7%)	24 (85.7%)	118 (89.4%)	0.290	0.524
Yes	398 (14.2%)	18 (11.3%)	4 (14.3%)	14 (10.6)		
HSCT CCG2961						
No	449 (84.9%)	20 (87%)	2 (100%)	18 (85.7%)	1.000	1.000
Yes	80 (15.1%)	3 (13%)	0 (0%)	3 (14.3%)		
HSCT AAML03P1						
No	213 (84.9%)	13 (86.7%)	2 (66.7%)	11 (91.7%)	1.000	0.371
Yes	38 (15.1%)	2 (13.3%)	1 (33.3%)	1 (8.3%)		
HSCT AAML0531						
No	735 (85.2%)	43 (84.3%)	10 (83.3%)	33 (84.6%)	0.868	1.000
Yes	128 (14.8%)	8 (15.7%)	2 (16.7%)	6 (15.4%)		
HSCT AAML1031						
No	1000 (86.8%)	66 (93%)	10 (90.9%)	56 (93.3%)	0.133	0.581
Yes	152 (13.2%)	5 (7%)	1 (9.1%)	4 (6.7%)		

Supplemental Table 2

	CEBPA-bZip % ± 2SE, N	**CEBPA-dm % ± 2SE, N**	**CEBPA-WT % ± 2SE, N**	**p-value CEBPA-bZip vs dm.**
0-9 years				
5-year OS	100 ± 0%, N=10	89 ± 14%, N=21	62 ± 3%, N=1447	0.177
5-year EFS	80 ± 25%, N=10	75 ± 19%, N=21	46 ± 3%, N=1447	0.769
5-year RR	22 ± 30%, N=9	22 ± 20%, N=18	42 ± 3%, N=1052	0.997
10-15 years				
5-year OS	80 ± 25%, N=10	83 ± 10%, N=71	58 ± 3%, N=871	0.672
5-year EFS	50 ± 32%, N=10	66 ± 11%, N=71	46 ± 3%, N=871	0.273
5-year RR	25 ± 33%,N=9	22 ± 11%, N=60	42 ± 3%, N=639	0.816
16-29 years				
5-year OS	88 ± 23%, N=8	72 ± 14%, N=40	60 ± 5%, N=477	0.323
5-year EFS	63 ± 34%, N=8	54 ± 16%, N=40	47 ± 5%, N=477	0.445
5-year RR	40 ± 50%,N=6	26 ± 15%, N=36	34 ± 5%, N=373	0.651