

Supplementary Table 1. Sociodemographic and disease characteristics of patients in MEMS cohort, overall and by BMI category

Variable	All (n=435)	<85%ile (n=191)	85-98%ile (n=189)	≥99%ile (n=55)	P
Age at diagnosis in years					
Median (range)	4 (1-18)	5 (1-17)	4 (1-18)	4 (1-18)	0.07
Mean (±standard deviation)	5.9 (4.2)	6.4 (4.5)	5.5 (3.8)	5.8 (3.8)	
Age at study enrollment in years					
Median (range)	6 (2-19)	7 (2-19)	6 (2-19)	6 (2-19)	0.05
Mean (±standard deviation)	7.5 (4.2)	8.0 (4.6)	7.0 (3.8)	7.4 (4.1)	
Length of follow-up in years					
Median (range)	7.9 (0.2-10.6)	7.9 (0.2-10.0)	8.1 (0.5-10.6)	7.7 (0.2-9.5)	0.2
Sex, n (%)					
Male	293 (67.4)	130 (68.1)	123 (65.1)	40 (72.7)	0.5
Race/ethnicity, n (%)					
Non-Hispanic White	147 (33.8)	76 (39.8)	59 (31.2)	12 (21.8)	0.0003
Hispanic	156 (35.9)	54 (28.3)	69 (36.5)	33 (60.0)	
African-American or Black	66 (15.2)	24 (12.6)	37 (19.6)	5 (9.1)	
Asian	66 (15.2)	37 (19.4)	24 (12.7)	5 (9.1)	
Parental education, n (%)					
≤High school	144 (33.7)	60 (31.9)	59 (31.7)	25 (47.2)	0.09
Yearly Household Income, n (%)					
<\$50,000	249 (60.1)	104 (58.1)	103 (56.6)	42 (79.3)	0.009
Socioeconomic Strata, n (%)					
Low SES	125 (30.3)	52 (29.2)	49 (26.9)	24 (45.3)	0.07
ALL¹ sub-type, n (%)					
B-lymphoblastic leukemia	386 (88.7)	167 (87.4)	522 (90)	50 (90.9)	0.7
T-lymphoblastic leukemia	45 (10.3)	22 (11.5)	67 (10)	5 (9.1)	
NCI² Risk Group, n (%)					
High Risk	172 (39.7)	87 (45.8)	65 (34.6)	20 (36.4)	0.07
Cytogenetics, n (%)					
Favorable	183 (42.1)	76 (40.8)	82 (43.4)	25 (45.5)	0.5
Neutral	231 (53.1)	105 (55.0)	100 (52.9)	26 (47.3)	
Unfavorable [@]	21 (4.8)	10 (5.2)	7 (3.7)	4 (8.0)	
BMI%ile³					
Median (range)	88.4 (0-100)	64.3 (1.1-84.9)	94.4 (85.2-99)	99.5 (99-100)	<0.0001
6MP dose intensity⁵					
Median (range)	0.87 (0.2-3.0)	0.8 (0.2-3.0)	0.87 (0.2-1.67)	0.9 (0.4-1.5)	0.4
6MP Adherence					
Mean (SD)	90.9 (14.4)	91.6 (15.4)	91.7 (13.3)	89.8 (15.2)	0.4
Erythrocyte TGN⁶, pmol/8 × 10⁸ erythrocytes					

Variable	All (n=435)	<85%ile (n=191)	85-98%ile (n=189)	≥99%ile (n=55)	P
Median (range)	139.5 (0.3-453.7)	137.9 (0.3-453.7)	147.2 (0.7-432.9)	138.2 (63.2-306.2)	0.8
CV %, median (range)	28.8 (1.4-207.3)	28.8 (1.4-207.3)	28.4 (1.7-166.0)	30.2 (6.3- 89.9)	0.5
Methotrexate dose intensity					
Median (range)	0.87 (0.2-2.73)	0.85 (0.2-2.73)	0.89 (0.2-1.5)	0.89 (0.3-1.5)	0.7
Days oral chemotherapy held for toxicity or illness					
Median (range)	0 (0-56)	0 (0-56)	0 (0-48)	0 (0-48)	0.7

¹ALL denotes acute lymphoblastic leukemia; ²NCI denotes National Cancer Institute; ³BMI denotes body-mass index; ⁴CV denotes coefficient of variation, ⁵6MP denotes 6-mercaptopurine; ⁶TGN denotes thioguanine. Favorable cytogenetics included t(12;21); hyperdiploidy; trisomy 4 and 10; or trisomy 4, 10, and 17. Unfavorable cytogenetics included t(9;22), t(4;11), hypodiploidy, or extreme hypodiploidy. Neutral cytogenetics implied absence of favorable or unfavorable cytogenetics

Supplementary Table 2. Comparison of MEMS cohort and non-MEMS cohort

Variable	MEMS Cohort	Non-MEMS Cohort	P
Age at diagnosis in years			
Median (range)	4 (1-18)	5 (1-17)	0.04
Age at study enrollment in years			
Median (range)	6 (2-19)	6 (2-19)	0.06
Length of follow-up in years			
Median (range)	7.9 (0.2-10.6)	7.5 (0.1-13.0)	0.8
Sex, n (%)			
Male	293 (67.4)	171 (71.0)	0.3
Race/ethnicity, n (%)			
Non-Hispanic White	147 (33.8)	78 (32.8)	0.06
Hispanic White	156 (35.9)	69 (28.6)	
African-American or Black	66 (15.2)	54 (22.4)	
Asian	66 (15.2)	40 (16.6)	
Parental education, n (%)			
≤High school	144 (33.7)	83 (36.2)	0.5
>High school	283 (66.3)	146 (63.8)	
Yearly Household Income, n (%)			
<\$50,000	249 (60.1)	123 (57.8)	0.6
≥\$50,000	165 (39.9)	90 (42.2)	
ALL¹ sub-type, n (%)			
B-lymphoblastic leukemia	386 (88.9)	208 (87.0)	0.6
T-lymphoblastic leukemia	45 (10.4)	30 (13.0)	
NCI² Risk Group, n (%)			
Standard Risk	261 (60.3)	128 (53.8)	0.1
High Risk	172 (39.7)	110 (46.2)	
Cytogenetics, n (%)			
Favorable	183 (44.9)	86 (38.2)	0.2
Neutral	204 (50.0)	122 (54.2)	
Unfavorable	21 (5.1)	17 (7.6)	
BMI³ile³			
Median (range)	88.4 (1.1-100)	88.6 (0-100)	0.9
6MP⁵ dose intensity			
Median (range)	0.87 (0.2-2.97)	0.88 (0.0-2.1)	0.1
CV (range)	13.5 (0-73.5)	13.1 (0-102.9)	0.3
Erythrocyte TGN⁶, pmol/8 × 10⁸ erythrocytes			
Median (range)	139.5 (0.3-453.7)	141.8 (0.0-473.9)	0.3
CV%, median (range)	28.8 (1.4-207.3)	30.5 (0-241.2)	0.06
Methotrexate dose intensity			
Median (range)	0.87 (0.2-2.73)	0.88 (0.1-2.03)	0.1

¹ALL denotes acute lymphoblastic leukemia; ²NCI denotes National Cancer Institute; ³BMI denotes body-mass index; ⁴CV denotes coefficient of variation, ⁵6MP denotes 6-mercaptopurine; ⁶TGN denotes thioguanine. Favorable cytogenetics included t(12;21); hyperdiploidy; trisomy 4 and 10; or trisomy 4, 10, and 17. Unfavorable cytogenetics included t(9;22), t(4;11), hypodiploidy, or extreme hypodiploidy. Neutral cytogenetics implied absence of favorable or unfavorable cytogenetics.

Supplementary Table 3. Factors associated with extreme obesity during maintenance therapy for ALL

Variable	OR* (95% CI)	P
Age at diagnosis (per year increase)	1.1 (0.9-1.1)	0.9
Female sex (vs male)	1.1 (0.7-1.9)	0.7
Race/ethnicity (vs non-Hispanic white)		
Hispanic	2.0 (1.03-3.9)	0.02
African-American or Black	0.9 (0.4-1.9)	0.8
Asian	0.9 (0.4-2.2)	0.6
Low socioeconomic strata (vs high)	1.6 (0.9-2.8)	0.2

*Multivariable logistic regression analysis

Supplementary Table 4. Hazard of relapse by BMI%ile category among participants in MEMS sub-cohort

	BMI ≥99%ile vs <85%ile		BMI 85-98%ile vs <85%ile	
	HR (95%CI)	<i>P</i>	HR (95%CI)	<i>P</i>
Model 1	3.0 (1.3-6.5)	0.007	1.1 (0.5-2.2)	0.9
Model 2	4.0 (1.7-9.4)	0.002	1.2 (0.6-2.7)	0.6
Model 3	3.8 (1.6-8.8)	0.002	1.2 (0.5-2.5)	0.7
Model 4	3.1 (1.3-7.4)	0.009	1.0 (0.4-2.1)	0.9
Model 5	3.5 (1.5-8.6)	0.005	0.9 (0.3-2.2)	0.7
Model 6	3.5 (1.5-8.5)	0.005	0.8 (0.3-2.2)	0.7
Model 7	3.3 (1.4-8.2)	0.006	0.8 (0.3-2.1)	0.7
Model 8	3.6 (1.5-8.5)	0.004	0.8 (0.3-2.0)	0.7

HR denotes hazard ratio, 95%CI denotes 95% confidence interval

Model 1 shows unadjusted HR for relapse risk by BMI category

Model 2 shows adjusted HR for relapse risk by BMI category, adjusting for age at study entry, sex, NCI risk, cytogenetics, median 6MP dose intensity, median methotrexate dose intensity, number of days chemotherapy held due to toxicity/illness and time from start of maintenance to study entry

Model 3 adds to socioeconomic strata to covariates included in model 2

Model 4 adds race/ethnicity to covariates included in model 3

Model 5 adds mean adherence to model 4

Model 6 adds median TGN levels to covariates included in model 5

Model 7 removes median TGN and adds TGN CV% to covariates included in model 6

Model 8 substitutes NCI risk with disease phenotype (B-cell vs T-cell [reference]) in Model 6

Supplementary Table 5. Hazard of relapse by BMI%ile category among participants defining extreme obesity as BMI \geq 120% of 95%ile vs <85%ile

	Entire cohort		MEMS cohort	
	HR (95%CI)	<i>P</i>	HR (95%CI)	<i>P</i>
Model 1	3.2 (1.6-6.3)	0.008	3.6 (1.7-7.9)	0.001
Model 2	3.4 (1.8-6.4)	0.002	4.0 (1.9-8.3)	0.0003
Model 3	3.3 (1.8-6.3)	0.002	3.8 (1.8-7.8)	0.0004
Model 4	2.9 (1.5-5.7)	0.002	3.1 (1.4-6.6)	0.004
Model 5	-	-	3.7 (1.6-8.6)	0.002
Model 6	2.9 (1.5-5.7)	0.002	3.8 (1.6-8.6)	0.002
Model 7	3.2 (1.6-6.4)	0.001	3.5 (1.5-8.0)	0.003

HR denotes hazard ratio, 95%CI denotes 95% confidence interval

Model 1 shows unadjusted HR for relapse risk by BMI category

Model 2 shows adjusted HR for relapse risk by BMI category, adjusting for age at study entry, sex, NCI risk, cytogenetics, median 6MP dose intensity, median methotrexate dose intensity, number of days chemotherapy held due to toxicity/illness and time from start of maintenance to study entry

Model 3 adds socioeconomic strata to covariates included in model 2

Model 4 adds race/ethnicity to covariates included in model 3

Model 5 adds mean adherence to model 4 for MEMS cohort

Model 6 adds median TGN levels to covariates included in model 4 (4A for MEMS cohort)

Model 7 removes median TGN and adds TGN CV% to covariates included in model 5

Supplementary Table 6. Hazard of relapse by BMI%ile category among all participants with full model effects

Characteristic	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
BMI ≥99%ile vs. <85%ile	2.4 (1.2-4.7)	0.01	2.7 (1.3-5.7)	0.007	2.8 (1.3-5.7)	0.006	2.4 (1.1-5.1)	0.02	2.4 (1.1-5.1)	0.02	2.5 (1.2-5.5)	0.02
BMI 85-98%ile vs. <85%ile	0.9 (0.5-1.6)	0.7	1.0 (0.5-1.8)	0.9	0.9 (0.5-1.7)	0.8	0.8 (0.4-1.6)	0.6	0.8 (0.4-1.6)	0.6	0.9 (0.4-1.7)	0.7
Age at study entry (per year increase)	-	-	1.0 (1.0-1.1)	0.3	1.0 (1.0-1.1)	0.2	1.0 (1.0-1.1)	0.2	1.0 (1.0-1.1)	0.2	1.0 (1.0-1.1)	0.3
Sex (female vs male)	-	-	0.9 (0.5-1.7)	0.8	0.9 (0.5-1.7)	0.8	0.9 (0.5-1.6)	0.7	0.9 (0.5-1.6)	0.7	0.9 (0.5-1.7)	0.7
NCl risk group (high vs low)	-	-	0.9 (0.4-1.9)	0.9	1.0 (0.5-2.0)	0.9	1.0 (0.5-2.0)	0.9	0.9 (0.4-2.0)	0.9	1.0 (0.5-2.1)	0.9
Favorable cytogenetics vs unfavorable	-	-	0.9 (0.3-2.6)	0.8	0.9 (0.3-2.6)	0.8	0.9 (0.3-2.6)	0.8	0.9 (0.3-2.6)	0.8	0.9 (0.3-2.7)	0.9
Neutral cytogenetics vs unfavorable	-	-	0.5 (0.3-1.0)	0.1	0.6 (0.3-1.0)	0.1	0.5 (0.3-1.0)	0.1	0.5 (0.3-1.0)	0.1	0.5 (0.3-1.0)	0.1
Median 6MP dose intensity	-	-	3.7 (0.6-23.7)	0.2	3.5 (0.5-22.9)	0.2	2.9 (0.5-18.3)	0.3	2.9 (0.5-18.7)	0.3	3.3 (0.5-20.9)	0.2
Median methotrexate dose intensity	-	-	0.3 (0.0-2.2)	0.2	0.3 (0.0-2.2)	0.2	0.3 (0.0-2.2)	0.3	0.3 (0.0-2.3)	0.3	0.3 (0.0-2.3)	0.3
Number of days chemotherapy held due to toxicity/ illness (per day increase)	-	-	1.0 (1.0-1.0)	0.4	1.0 (1.0-1.0)	0.4	1.0 (1.0-1.0)	0.6	1.0 (1.0-1.0)	0.6	1.0 (1.0-1.0)	0.6
Time from start of maintenance	-	-	0.4 (0.2-0.8)	0.01	0.4 (0.2-0.8)	0.01	0.4 (0.2-0.8)	0.01	0.4 (0.2-0.8)	0.01	0.4 (0.2-0.8)	0.01
Low SES vs others	-	-	-	-	1.0 (1.0-1.0)	0.2	1.0 (1.0-1.0)	0.2	1.0 (1.0-1.0)	0.1	1.0 (1.0-1.0)	0.1
Asian race vs Non-Hispanic Whites	-	-	-	-	-	-	1.6 (0.6-4.0)	0.3	1.6 (0.6-4.1)	0.3	1.5 (0.6-3.9)	0.4
Black vs Non-Hispanic Whites	-	-	-	-	-	-	1.4 (0.6-3.7)	0.4	1.4 (0.6-3.7)	0.4	1.5 (0.6-3.7)	0.4
Hispanic vs Non-Hispanic Whites	-	-	-	-	-	-	2.3 (1.2-4.6)	0.02	2.3 (1.2-4.7)	0.02	2.1 (1.0-4.3)	0.02
Median TGN (per pmol/8x10 ⁸ erythrocytes increase)	-	-	-	-	-	-	-	-	1.0 (0.9-1.0)	0.7	-	-
TGN CV% (per % variation increase)	-	-	-	-	-	-	-	-	-	-	1.0 (0.9-1.0)	0.3

HR denotes hazard ratio, 95%CI denotes 95% confidence interval

Supplementary Figure 1. Study Schema for AALL03N1

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	← 6 months →						
	Day 1	Day 29	Day 57	Day 85/1	Day 113/29	Day 141/57	Day 169/85
Assent / consent	X						
Demographic questionnaire		X					
Self-report of 6MP intake		X	X		X	X	
MEMS monitoring of 6MP	→						
MEMS data download							X
TPMT genotype	X						
Red cell TGN levels		X	X	X	X	X	X

Abbreviations: 6MP, 6-mercaptopurine; MEMS, Medication Event Monitoring System; TPMT, thiopurine methyltransferase; TGN, erythrocyte thioguanine nucleotide concentrations

Supplementary Figure 2. Fitted means of erythrocyte thioguanine in patients with available adherence data (n=435)

Models adjusted for age at study enrollment, race/ethnicity, sex, 6MP dose intensity, adherence and study month

