SUPPLEMENTARY APPENDIX

Impact of luteinizing hormone suppression on hematopoietic recovery after intensive chemotherapy in patients with leukemia

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Supplementary Material

Impact of Luteinizing Hormone Suppression on Hematopoietic Recovery after Intensive Chemotherapy in Patients with Leukemia

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Table 1S: Mutational profile of matched AML cohorts.

	Leuprolide	**Control**	***P***
FLT3	16/62 (26%)	25/99 (25%)	1
NPM1	15/47 (32%)	13/73 (18%)	0.8
IDH1/2	6/38 (16%)	13/47 (28%)	0.3
RAS	13/65 (20%)	18/85 (21%)	1
PTPN11	2/30 (7%)	2/30 (7%)	1
TP53	0/31 (0%)	4/34 (12%)	0.1
JAK2	2/32 (6%)	5/161 (3%)	0.3
Mutated/tested (%)			

Table 2S: Leuprolide dosing characteristics for propensity matched cohorts.

	AML (N = 64)	**ALL (N =49)**
N (%) of patient with leuprolide given between day -7 and day 15 of chemotherapy	33 (52)	22 (45)
N (%) of patient with leuprolide given between day -7 and day 0 of chemotherapy	16 (25)	10 (20)
Median cumulative leuprolide dose (range), mg	22.5 (3 – 78.75)	22.5 (11.25 – 135)
N (%) of patient by single leuprolide dosing		
1 mg	1 (2)	0 (0)
3.75 mg	3 (5)	2 (4)
7.5 mg	1 (2)	0 (0)
11.25 mg	57 (89)	42 (86)
22.5 mg	8 (13)	11 (22)
30 mg	1 (2)	0 (0)

Leuprolide is given as leuprolide acetate 1 mg daily, or depot at 3.75 mg monthly, 7.5 mg monthly, 11.25 mg every 3 months, 22.5 mg every 3 months, 30 mg every 4 months. Some patient received different dosing each injection.

Table 3S: Univariate analysis for factors predicting count recovery with leuprolide.

	ANC		ALC		Platelets		Hemoglobin	
	10^6/L/year (95% CI)	*P*	10^6/L/year (95% CI)	*P*	10^6/L/year (95% CI)	*P*	10^3 g/dL/year (95% CI)	*P*
AML								
Age	0.3 (-1.4, 2.1)	0.7	-0.3 (-1.2 , 0.6)	0.5	6.8 (-86.7, 100.4)	0.8	0.3 (-0.7, 1.2)	0.6
PS ≤1	-53.7 (-118.6, 11.3)	0.1	61.6 (21.3, 101.8)	**0.003**	5028.9 (3903.2, 6154.6)	**<0.001**	31.2 (-26.5, 88.9)	0.2
Adverse Risk	22.9 (-57.5, 103.4)	0.5	-20.1 (-44.4, 4.2)	0.1	-4013.9 (-7289.2, -738.6)	**0.02**	-4.4 (-37.3, 28.5)	0.79
AMML/AMOL	31.5 (-0.7, 63.7)	0.06	-18.4 (-41.6, 4.8)	0.12	604.3 (-857.6, 2066.2)	0.42	13.2 (-4.4, 30.8)	0.14
BM blast %	0.3 (-0.6, 1.3)	0.51	0.4 (-0.3, 1)	0.27	10.6 (-32, 53.3)	0.63	0.5 (0.3, 0.7)	**<0.001**
Targeted therapy	-23.3 (-52.8, 6.3)	0.12	1.2 (-17.4, 19.9)	0.89	-2033.8 (-3101.4, -966.1)	**<0.001**	-16.3 (-37.7, 5.2)	0.27
Leuprolide (D -7 - D15)	-30.3 (-100.5, 39.8)	0.4	-0.3 (-19.1, 18.5)	0.98	-541 (-3338.5, 2256.4)	0.7	12.2 (-17.9, 42.4)	0.43
Cumulative leuprolide dose	0.5 (-1.2, 2.1)	0.58	0 (-0.9, 0.9)	0.96	-5 (-82.1, 72.2)	0.9	0.3 (-0.5, 1.1)	0.45
Relapse	14.7 (-34.6, 64)	0.56	-25.7 (-49.7, -1.7)	**0.04**	628.9 (-1734.3, 2992.2)	0.6	-25.6 (-45.8, -5.4)	**0.01**
Transplant	1.2 (-52.9, 55.3)	0.97	33.4 (-7.7, 74.5)	0.11	1887.8 (-1605.5, 5381.1)	0.29	21.6 (-0.5, 43.7)	0.05
Triplet therapy	-28.6 (-62.3, 5.2)	0.1	31.8 (10.8, 52.7)	**0.003**	-235.7 (-1962.3, 1489.9)	0.79	20.9 (2.8, 39.1)	**0.02**
ALL								
Age	-1.5 (-4.1, 1.2)	0.27	0.6 (-0.1, 1.4)	0.1	15.2 (-111.5, 141.8)	0.81	0.7 (-0.6, 1.9)	0.29
PS ≤1	-92.6 (-202.4, 17.2)	0.1	58.7 (15.7, 101.7)	**0.008**	2211.8 (-2187.9, 6611.5)	0.32	-20.5 (-155.1, 114.1)	0.77
Adverse Risk	-13.5 (-55.2, 28.1)	0.52	6.6 (-9.7, 22.9)	0.43	1485.4 (-130.5, 3101.3)	0.07	17.3 (1, 33.6)	**0.04**
B vs T ALL	26.5 (-19, 72)	0.25	-28.8 (-49, -8.7)	**0.005**	-224.4 (-1713, 1264.3)	0.77	14.7 (-5, 34.4)	0.14
BM blasts %	0.2 (-0.8, 1.3)	0.65	-0.4 (-1, 0.2)	0.16	-13.8 (-58.1, 30.5)	0.54	-0.2 (-0.7, 0.3)	0.51
Leuprolide (D -7 - D15)	-8.1 (-48.7, 32.4)	0.7	2.5 (-13.3, 18.3)	0.76	90.7 (-1784.2, 1965.5)	0.92	4.1 (-10.8, 19)	0.59
Cumulative leuprolide dose	-0.2 (-0.7, 0.3)	0.38	0 (-0.3, 0.2)	0.88	-11.5 (-46.4, 23.4)	0.52	-0.1 (-0.5, 0.2)	0.4
Relapse	70 (28.4, 111.7)	**0.001**	-10.9 (-30.1, 8.4)	0.27	340.4 (-1232, 1912.1)	0.67	-13 (-29.6, 3.6)	0.12
HyperCVAD	-48.5 (-83.8, -13.2)	**0.006**	14.5 (1.9, 27.1)	**0.02**	1179.2 (-755, 3113.5)	0.23	2.6 (-19.9, 25.2)	0.8
Transplant	44.4 (9.8, 78.9)	**0.01**	-0.4 (-15.6, 14.8)	0.96	-798.7 (-2657.5, 1060)	0.4	-3.9 (-20.5, 12.8)	0.65

Values shown represent effect of variable on change in count per year (95% confidence interval).
ANC: absolute neutrophil count; ALC: absolute lymphocyte count; PS: Eastern Cooperative Oncology Group performance status, assessed as PS ≤1 vs PS≥2; Adverse risk in AML according to the European LeukemiaNet risk stratification, adverse risk in ALL corresponds to complex karyotype (≥ 5 abnormalities) t(9;22), t(4;11), and low hypodiploidy/near-triploidy, assessed as adverse vs non-adverse; BM blasts: bone marrow blasts, assessed a continuous variable; Triplet chemotherapy: idarubicin and cytarabine plus a nucleoside analog (ie. cladribine, clofarabine, or fludarabine), compared to doublet chemotherapy. Transplant corresponds to an allogeneic hematopoietic stem cell transplant; HyperCVAD: hyperfractionated cyclophosphamide, vincristine, Adriamycin, dexamethasone, compared to all other treatments. Relapse and transplant were assessed as time-dependent variables.

Figure 1S: Time to platelet and neutrophil count recovery following induction chemotherapy with and without leuprolide. Time in days from the start of induction chemotherapy to platelet and neutrophil count recovery defined as achievement of platelet count above 100 x 10^9/L and absolute neutrophil count above 1 x 10^9/L in AML (A-C) and ALL (B-D).

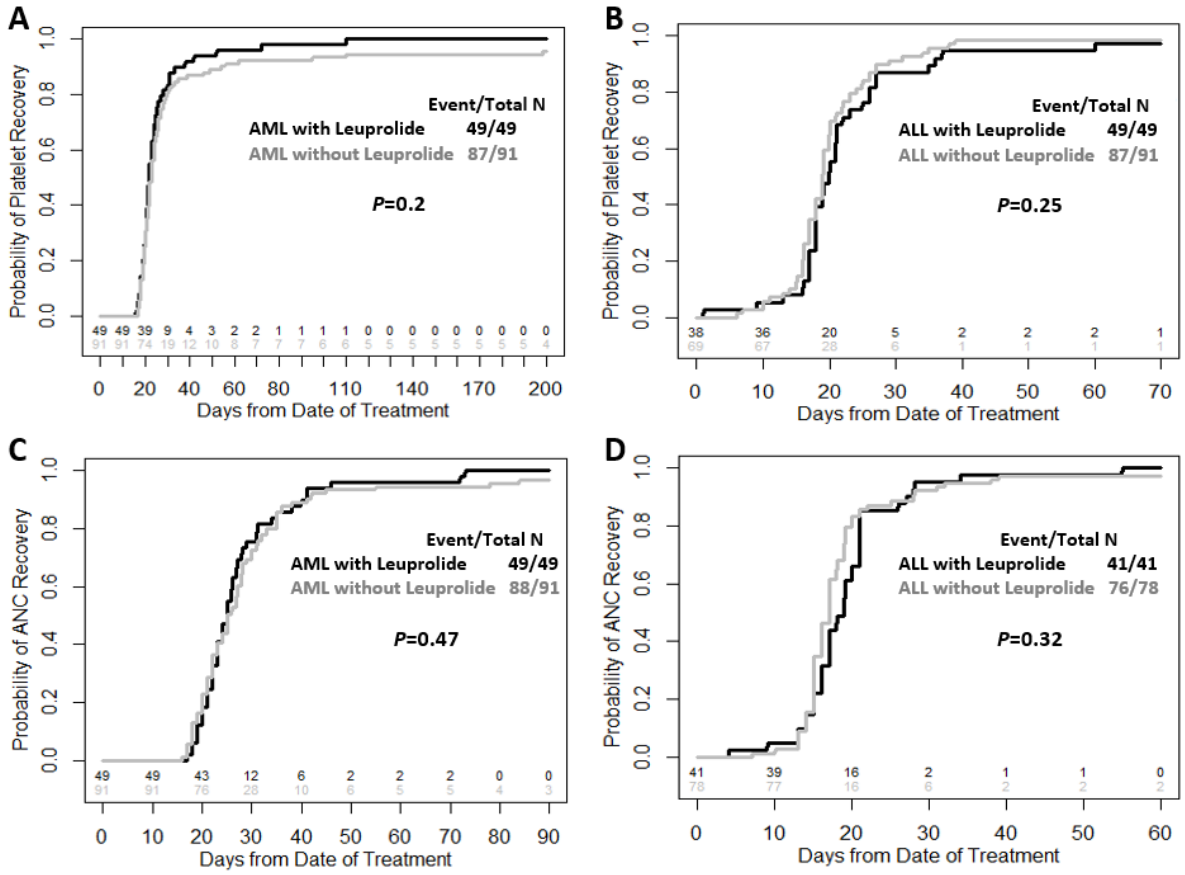

Figure 2S: Long-term changes in hematocrit and red blood cell levels with and without leuprolide. Scatterplots of all corresponding peripheral blood hematocrit (HCT) and red blooc cell (RBC) levels extracted from health records, collected between induction chemotherapy (Day 0) and last follow-up date where each dot represents a single value (blue for leuprolide, red for control). Lowess smooth curves were used for indicating longitudinal trajectories of counts and differences were assessed using the generalized estimation equation model.

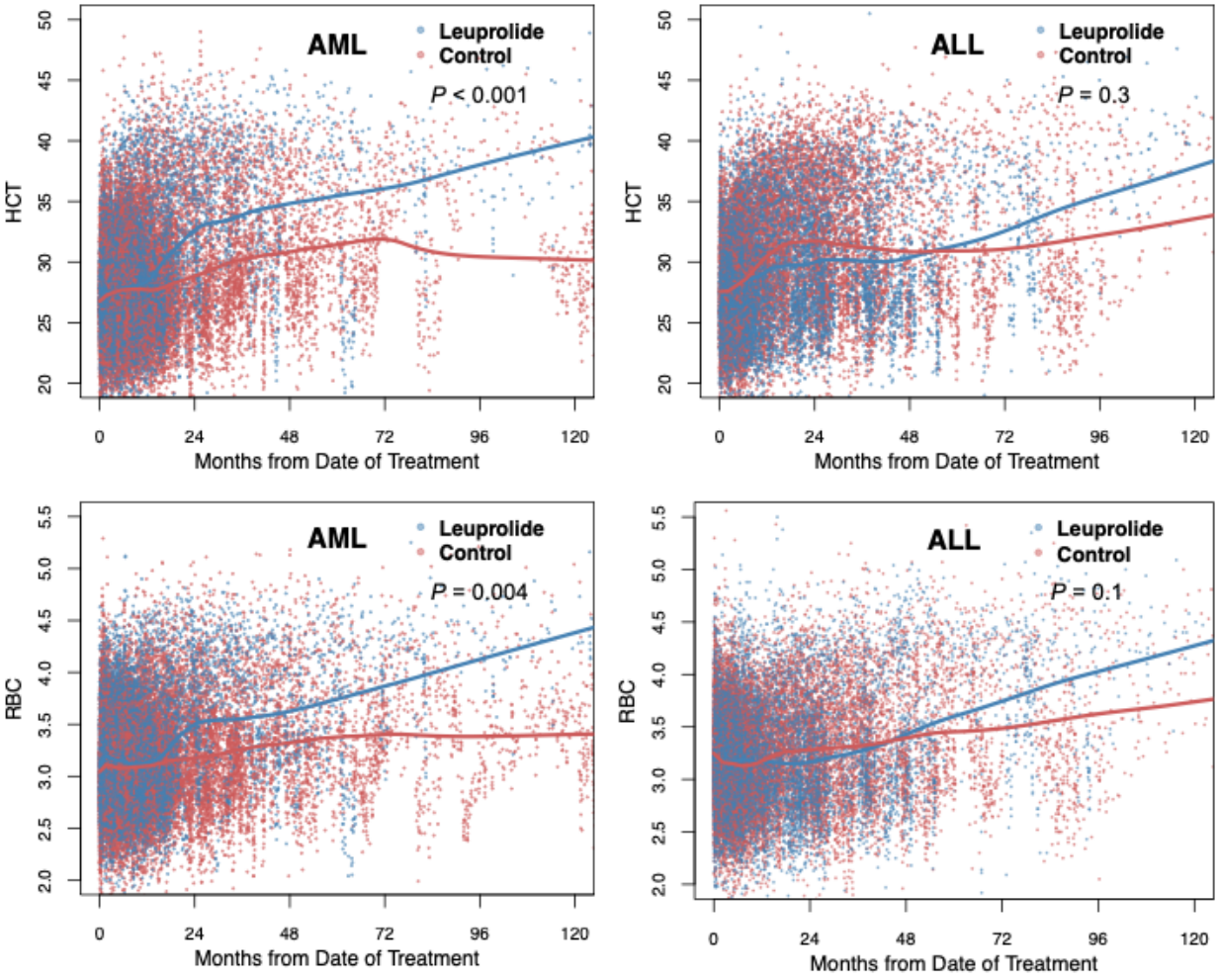

Figure 3S. Event-free survival in AML and ALL cohorts before and after propensity score matching.

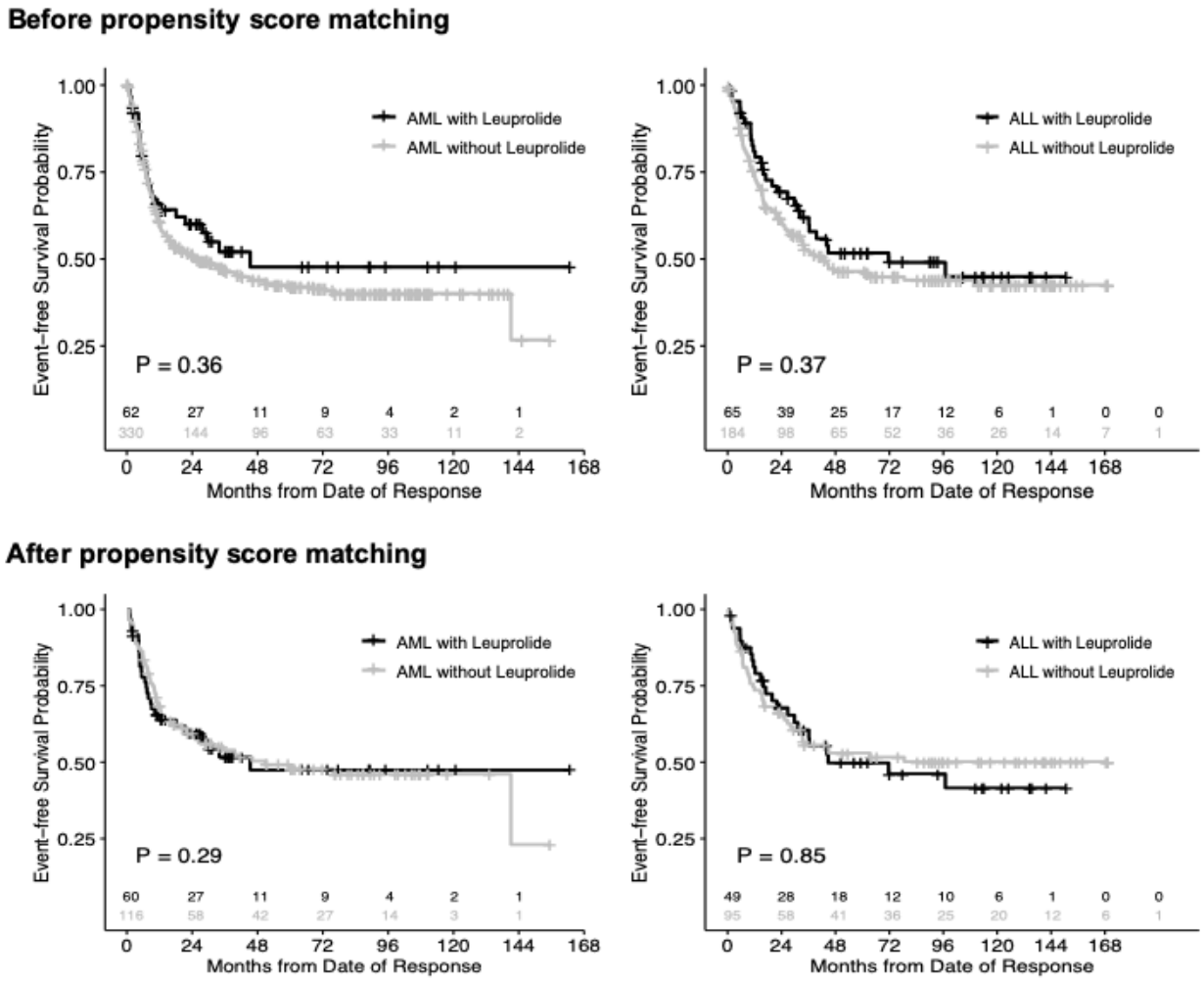

Figure 4S: Event-free survival and overall survival in AML and ALL cohorts after propensity score matching censored for allogeneic stem cell transplantation.