LETTER TO THE EDITOR

Neutrophil extracellular traps, endothelial injury and use of abatacept for graft-*versus*-host disease prophylaxis

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Supplemental table S1: Demographics and median day 14 dsDNA levels

	Allogeneic HSCT patients (N=262)	NETs (ng/mL, median)	p
Age at transplant (years, median)	8.57 (0-35)	160	
Gender			0.76
Female	110 (42%)	161.3	
Male	152 (58%)	158.9	
Race			0.14
Caucasian	237 (90%)	160.3	
African American	19 (7%)	188.4	
Asian	5 (2%)	150.6	
Hispanic	1 (1%)	410	
Diagnosis			0.0003
Malignancy, n (%)	74 (28%)	152	
Immune deficiency, n (%)	54 (21%)	174.4	
Marrow failure, n (%)	75 (29%)	187.7	
Hematologic disorder, n (%)	44 (18%)	135.1	
Metabolic disorder, n (%)	15 (6%)	125.7	
Donor type			0.34
Unrelated, n (%)	179 (68%)	162.3	
Related, n (%)	83 (32%)	154.3	
HLA type			0.62
Matched, n (%)	186 (71%)	160.8	
Mismatched, n (%)	76 (29%)	158.4	
Stem cell source			<0.0001
BM, n (%)	162 (62%)	155.1	
PBSC, n (%)	86 (33%)	181.4	
Cord, n (%)	14 (5%)	121.8	
Conditioning regimen type			0.0003
MAC, n (%)	177 (68%)	156.1	
RIC, n (%)	85 (32%)	162.7	
GVHD prophylaxis			<0.0001
CNI based	140 (53%)	164.8	
CNI based + abatacept	48 (18%)	125.4	
T cell depletion	74 (28%)	169.5	

*AA: African American; BM: Bone Marrow; PBSC: Peripheral Blood Stem Cell; MAC: Myeloablative conditioning; RIC: Reduced Intensity Conditioning

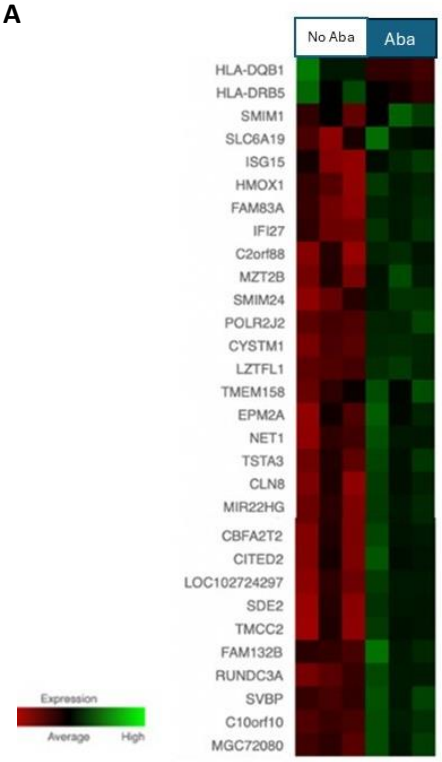
Supplemental Table S2. Bacterial blood stream infections within first 100 days, and viral reactivation within 1 year after HSCT according to GVHD prophylaxis

	CNI based (n=140)	CNI based with Abatacept (n=48)	T cell-depletion (n=74)	p
Viral reactivation within 1 year, n (%)				
EBV	63 (45%)	30 (63%)	25 (34%)	0.008
EBV viremia received treatment	25 (18%)	10 (21%)	16 (22%)	0.76
CMV	36 (26%)	20 (42%)	20 (27%)	0.11
ADV	28 (2%)	3 (6%)	8 (11%)	0.04
BKV	50 (36%)	11 (23%)	35 (47%)	0.02
BK Cystitis	23 (16.4%)	6 (12.5%)	20 (28%)	0.07
BSI in first 100 days, n (%)	36 (26%)	4 (8%)	14 (19%)	0.03

BSI: Bloodstream infection, any bacteriemia within 100 days. Positive viremia: Increased viral load more than two consecutive tests within 1 year from transplant (Ebstein-Barr Virus (EBV): >200 copies/mL, cytomegalovirus (CMV): >500 copies/mL, BK virus (BKV): >500 copies/mL, adenovirus (ADV): >500 copies/mL).

Supplemental Figure 1: Differential transcriptomics of day 14 neutrophils of patients who received abatacept and those who did not, with pathway analysis:

A



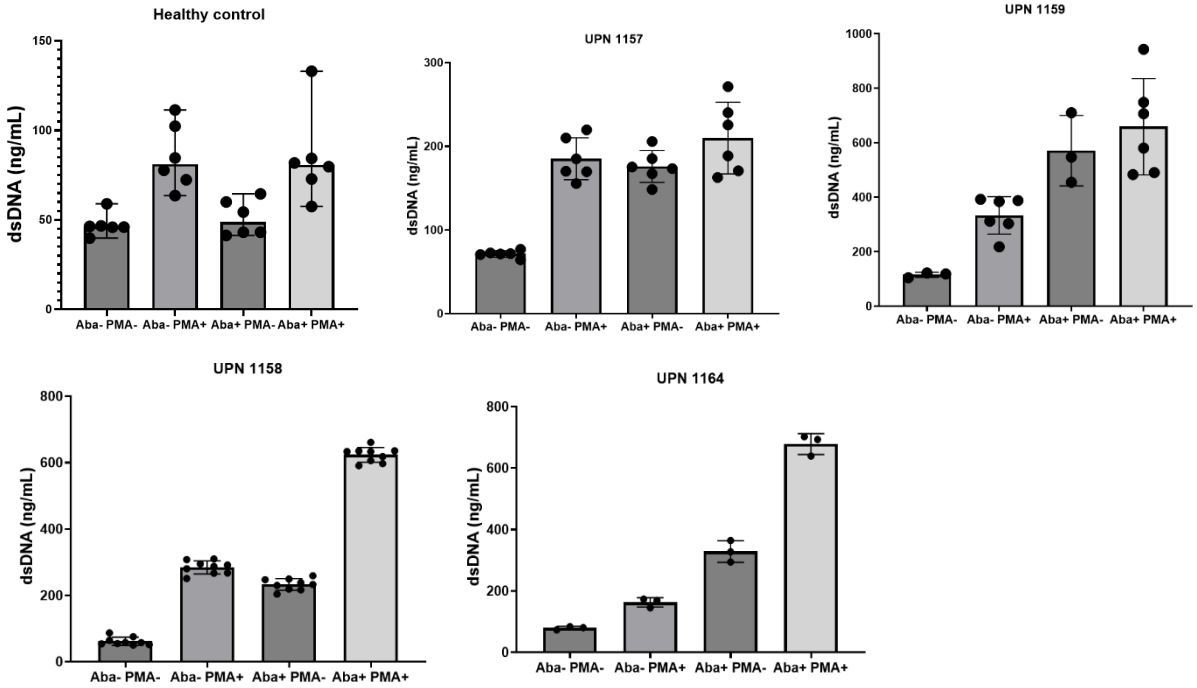
B

Pathways	p-value
Asthma	0.00098
Allograft rejection	0.00148
Graft-versus-host disease	0.0018
Type I diabetes mellitus	0.00189
Intestinal immune network for IgA production	0.00235
Autoimmune thyroid disease	0.00286
Epstein-Barr virus infection	0.00337
Mineral absorption	0.00365
Viral myocarditis	0.00365
Inflammatory bowel disease	0.00427
Leishmaniasis	0.00594
Antigen processing and presentation	0.00609
Th1 and Th2 cell differentiation	0.00837
Rheumatoid arthritis	0.00855
Staphylococcus aureus infection	0.00891
Hematopoietic cell lineage	0.00964
Th17 cell differentiation	0.01119
Toxoplasmosis	0.01221
Systemic lupus erythematosus	0.01739
Cell adhesion molecules	0.02066
Phagosome	0.02172
Influenza A	0.02732
Tuberculosis	0.02971
Human T-cell leukemia virus 1 infection	0.04247
RNA polymerase	0.0455
Ferroptosis	0.05975

C

#	Diagnosis	Age at HSCT (years)	Conditioning regimen	GVHD prophylaxis
1	Hemoglobin Hammersmith	20.25	Bu/Flu/TT	Abatacept/CNI/MMF
2	Beta-Thalassemia	2.08	Bu/Flu/TT	Abatacept/ CNI /MMF
3	SDS	2.43	Flu/Mel/Alemtuzumab	Abatacept/ CNI /MMF
4	Hurler syndrome	1.1	Bu/Cy/ATG	CNI /MMF
5	ALL	5.9	TBI/Cy	CNI /MMF
6	ALL	1.3	Carb/TT/Mel	CNI /MMF

D



Supplemental Figure 1: A. Heatmap of all the genes that are differentially expressed (NCBI accession number: 24929897): Red color is low expression, and green in high expression. First 3 patients (columns) (white heading) received CNI based regimen only without abatacept, and last 3 patients (columns) (blue heading) received abatacept as well. Expression of thirty genes were differentially regulated in the neutrophils of patients who received abatacept in addition to CNI based regimen. MHC class II molecules, HLA-DQB1 and HLA-DRB5 genes were upregulated in the neutrophils patients of who received CNI based regimen without abatacept compared with those receiving abatacept and a CNI-based regimen, suggesting decreased neutrophil activation in patients who received abatacept. **B.** Gene set enrichment pathway analysis using Enrichr (KEGG2021 pathway library) showing enrichment in pathways associated with inflammatory processes, including antigen presentation, T cell differentiation, and ferroptosis. **C.** Demographics of patients who had day +14 neutrophil isolation for RNA transcriptomics. **D.** dsDNA levels (ng/mL) in the supernatant of ex-vivo neutrophils stimulated with phorbol myristate acetate (PMA) with and without abatacept (Neutrophils were isolated (Mitenyi, 130-104-434) and incubated with and without 300 ug/mL abatacept for 1 hour at 37°C before stimulation with 50 nM PMA at 37°C for 4 hours