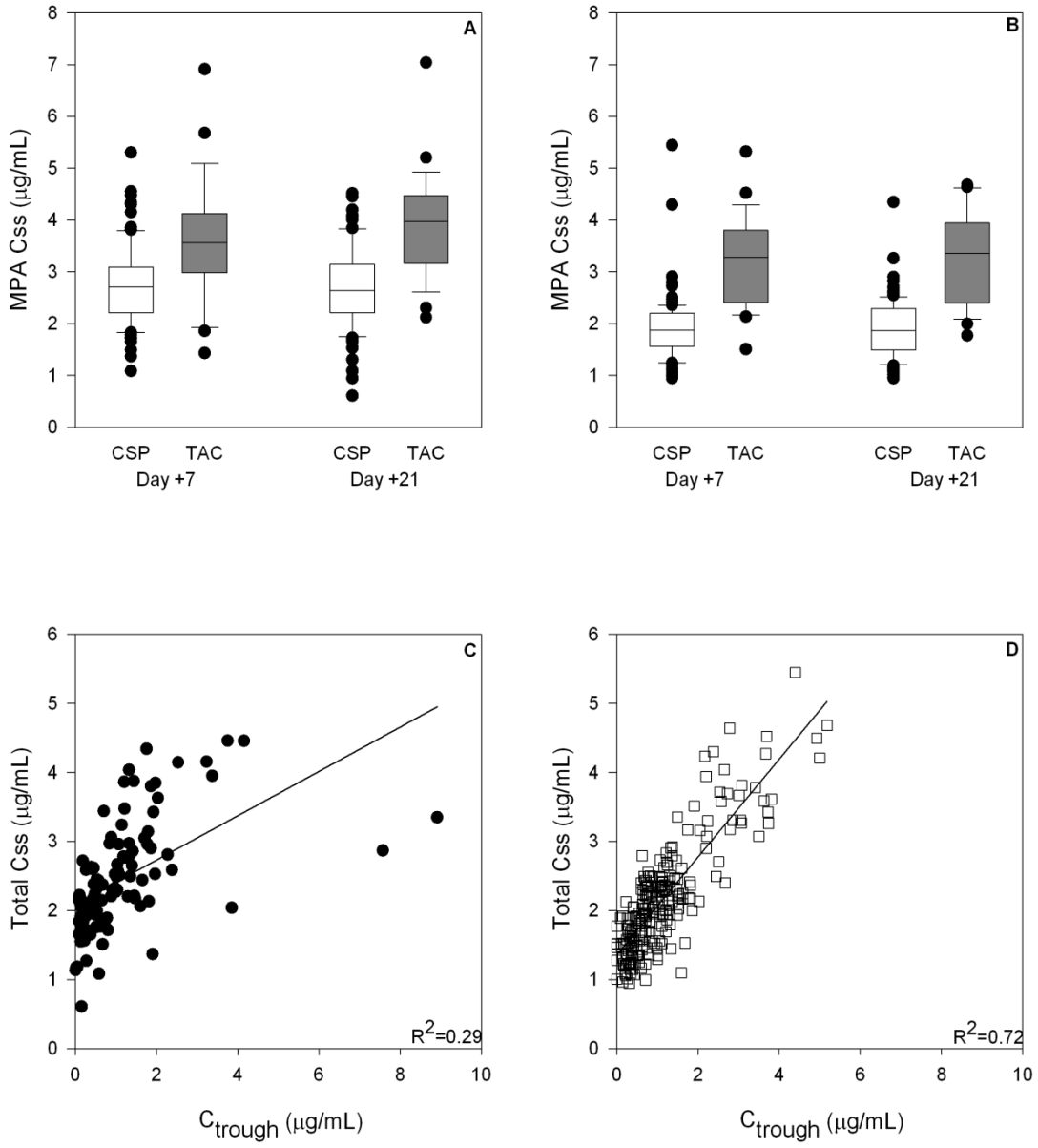
Supplemental Figure 1. Total MPA Css by day and CNI in patients receiving MMF Q8hr (A) or Q12hr (B) and total MPA Css versus C_{trough} in patients receiving MMF Q8hr (C) or Q12hr (D). In Panels A and B, the CNI are abbreviated cyclosporine (CSP) and tacrolimus (TAC). In Panels C and D, each point represents one C_{trough} - Css pair; one patient may have multiple data points.



Supplemental Table 1. Mycophenolic acid (MPA) pharmacodynamic studies in adult allogeneic HCT recipients receiving mycophenolate mofetil (MMF) as post grafting immunosuppression (IS)[a]

Citation	Study population	Postgrafting IS	MPA sampling times	Pharmacodynamic results
Jenke, 2001(12)	N=15 26-57 yr All MA (Various) 9 related (1 marrow, 8 PBSC); 6 URD (2 marrow, 4 PBSC)	Cyclosporine 2 mg/kg IV BID (trough 200-300 ng/mL) and MMF 12.5 to 17 mg/kg IV BID until day 21, then 1000 mg PO BID	-Daily trough concentrations drawn to day +21 -AUCs obtained on days 1, 7, 14, 21	-aGVHD: average MPA trough concentrations did not differ between patients experiencing grades 0-1 to grades 2-3 but, patients with grades 2-3 GVHD had trough < 200 ng/mL. -No other pharmacodynamic associations evaluated.
Jacobson, 2005(14)	N=87 19-69 yr All NMA (BU or CY + FLU/TBI) 33 related PBSC; 54 URD (4 marrow; 50 UCB)	Cyclosporine 2.5 mg/kg IV BID (trough 200-400 ng/mL) and MMF 1000 mg PO BID or 15 mg/kg IV BID (if could not tolerate PO)	-MPA samples drawn to estimate AUC after oral MMF administration before HCT and after either IV or oral MMF administration one week after HCT	-aGVHD: Unbound MPA $AUC_{0\text{-}6hr}$< 150 ng h/mL associated with higher cumulative incidence grades 2-4 aGVHD vs. greater AUC (68% vs. 40%, *P* = .02). -Unbound $AUC_{0\text{-}12hr}$ <300 ng h/mL associated with more frequent aGVHD (58% vs. 35%, P =.05). -No association between GVHD and trough concentrations (*P* ≤.62). No association between total or unbound trough concentrations and grades 2-4 or grades 3-4 aGVHD (*P* ≥0.17). -Engraftment: All engraftment failures occurred in UCB. Total MPA trough increasing by 1 μg/mL increases engraftment by 58% (P=0.05). Higher engraftment associated with total MPA trough concentrations > 1 μg/mL (*P* <.01).
Giaccone, 2005(7)	N=85 18-70 yr Flu/TBI All URD (6 marrow, 79 PBSC)	Cyclosporine 6.25 mg PO BID (trough 500 ng/mL) and MMF 15 mg/kg PO Q12hr or Q8HR	-MPA samples drawn to estimate $AUC_{0\text{-}8hr}$ or $AUC_{0\text{-}12hr}$ on days 7 and 21. -All AUC results divided by dosing interval to provide concentration at steady state (Css).	-aGVHD: No association with MPA exposure. -Engraftment and rejection worse with marrow compared to PBSC(3), so recipients of marrow graft excluded from pharmacodynamic analysis. -Rejection: 6 patients with MPA Css less than 2.5 μg/mL had graft rejection (*P*=0.34). -Donor T-cell chimerism: 16 patients with a total MPACss less than 3μg/mL had low (< 50%) donor T-cell chimerism (P=.03). -Relapse: no association with total or unbound MPA Css. -CMV reactivation: Elevated unbound MPA Css associated with CMV reactivation (P=.03).

[a]Excludes those studies where MMF was used as treatment of GVHD(39-42) or where only pharmacokinetic results were reported,(3, 4, 10, 43-

46), or where MMF doses were personalized to total MPA pharmacokinetics, specifically an $AUC_{0\text{-}12hr}$ 35-60 μg/mL/hr(10), a trough concentration < 3.5 μg/mL,(8) or a trough concentration of 1 - 3.5 μg/mL.(9) [b]Abbreviations: acute GVHD (aGVHD), area under the curve (AUC), cytomegalovirus (CMV), graft versus host disease (GVHD), myeloablative (MA), nonmyeloablative (NMA), reduced intensity conditioning (RIC), peripheral blood stem cells (PBSC), umbilical cord blood (UCB), unrelated donor (URD)

Supplemental Table 2. Effect of increasing mean unbound MPA Css as fixed covariate on clinical outcomes after day 25[a]

	Donor Type			
	Related (N=107)		Unrelated (N=132)	
	OR/HR (95% CI)	P-value	OR/HR (95% CI)	P-value
Day 28 T cell chimerism < 50%	0.90 (0.53-1.52)	0.70	1.29 (0.81-2.07)	0.29
Acute GVHD 2-4	0.97 (0.76-1.26)	0.84	1.09 (0.82-1.46)	0.56
Acute GVHD 3-4	0.91 (0.47-1.77)	0.78	0.88 (0.51-1.52)	0.65
Chronic GVHD	0.82 (0.59-1.13)	0.23	1.01 (0.81-1.25)	0.95
Relapse	1.06 (0.77-1.44)	0.73	1.14 (0.87-1.50)	0.34
Neutropenia	1.29 (0.85-1.96)	0.24	1.06 (0.80-1.41)	0.69
CMV reactivation	1.07 (0.79-1.46)	0.67	1.02 (0.75-1.40)	0.89
Non-relapse mortality	1.06 (0.70-1.60)	0.78	0.96 (0.70-1.31)	0.77
Overall mortality	1.18 (0.92-1.53)	0.20	1.05 (0.85-1.30)	0.63

[a]MPA Css fit as continuous variable (truncated at 97.5th percentile to avoid outliers); HR per unit of unbound MPA Css (ng/mL), adjusted for Kahl disease risk, antigen/2-allele mismatch, mean CNI concentration during week 2, year of transplant, female donor to male patient, tacrolimus prophylaxis, and fludarabine in conditioning (related donors only). Mean CNI week 2 fit as continuous variable, rescaled as standard deviation units to account for difference between cyclosporine and tacrolimus concentrations.

Supplemental Table 3. Effect of increasing average trough MPA as fixed covariate on clinical outcomes occurring after day 25[a]

	Donor Type			
	Related (N=108)		Unrelated (N=48)	
	OR/HR (95% CI)	P-value	OR/HR (95% CI)	P-value
Day 28 T cell chimerism < 50%	1.57 (0.61-4.00)	0.35	3.73 (0.44-31.7)	0.23
Acute GVHD 2-4	1.09 (0.72-1.66)	0.67	1.03 (0.60-1.78)	0.91
Acute GVHD 3-4	1.42 (0.64-3.12)	0.39	0.48 (0.07-3.12)	0.44
Chronic GVHD	0.77 (0.53-1.12)	0.18	1.41 (0.99-2.00)	0.06
Relapse	1.06 (0.76-1.48)	0.73	0.67 (0.34-1.31)	0.24
Neutropenia	1.61 (0.99-2.61)	0.05	0.94 (0.57-1.54)	0.79
CMV reactivation	0.82 (0.52-1.31)	0.41	1.23 (0.79-1.92)	0.37
Non-relapse mortality	0.73 (0.33-1.61)	0.43	0.94 (0.57-1.53)	0.79
Overall mortality	1.08 (0.79-1.47)	0.65	0.99 (0.69-1.42)	0.96

[a]MPA trough fit as continuous variable (truncated at 97.5th percentile to avoid outliers); HR per unit of MPA trough (μg/mL), adjusted for Kahl disease risk, antigen/2-allele mismatch, mean CNI concentration during week 2, year of transplant, female donor to male patient, tacrolimus prophylaxis, and fludarabine conditioning (related donors only). Mean CNI week 2 fit as continuous variable, rescaled as standard deviation units to account for difference between cyclosporine and tacrolimus concentrations.