SUPPLEMENT

METHODS

HHV-6B testing

We tested weekly plasma samples through 6 weeks post-HCT for HHV-6 with quantitative PCR at Viracor Eurofins Laboratory (Lee's Summit, MO). The lower the lower limit of quantification of this assay is 188 copies/mL, and it does not distinguish between species A and B. Among patients with HHV-6 detected using the Viracor assay, we performed additional PCR testing using the highest positive sample per patient to identify the HHV-6 species (A versus B) at the University of Washington Clinical Virology Laboratory (Seattle, WA) as previously described.[1]

RESULTS

HHV-6B plasma detection and timing among patients with any acute graft-versus-host disease (GVHD) and with rash during the study period

During the study period, acute GVHD grades 2-4 was reported in 37 (40%) patients receiving brincidofovir (median onset, 28 days) and 6 (10%) patients receiving placebo (median onset, 35 days). Of the 37 patients who developed grade ≥2 GVHD in the brincidofovir arm, first detection of HHV-6B viremia occurred prior to and after the diagnosis of GVHD in 5 (14%) patients and 2 (5%) patients, respectively. Of the 6 patients who developed grade ≥2 GVHD in the placebo arm, first detection of HHV-6B viremia occurred prior to and after the diagnosis of GVHD in 2 (33%) and 0 (0%) patients, respectively.

Treatment-emergent rash was reported less frequently among patients receiving brincidofovir (n=8, 9%) compared to placebo (n=16, 26%; p=0.006). Of the 8 patients who developed rash in the brincidofovir arm, 1 patient (12.5%) had HHV-6B viremia prior to the rash. Of the 16 patients who developed rash in the placebo arm, 3 patients (19%) had HHV-6B viremia prior to (n=2) or within 4 days after (n=1) the rash.

References

1. Hill JA, Mayer BT, Xie H, et al. Kinetics of Double-Stranded DNA Viremia after Allogeneic Hematopoietic Cell Transplantation. *Clin. Infect. Dis.* 2018;66(3):.

Table S1. Maximum grade of acute graft-versus host disease (GVHD) reported during the first 6-weeks after hematopoietic cell transplantation.

GVHD severity	Brincidofovir (N = 92)	Placebo (N = 61)
Grade 1	7 (7.6)	5 (8.2)
Grade 2	15 (16.3)	5 (8.2)
Grade 3	15 (16.3)	1 (1.6)
Grade 4	2 (2.2)	0
Grade 5	5 (5.4)	0

Data are presented as number (%) unless otherwise indicated.

Table S2. Variables associated with HHV-6B detection in plasma using Cox proportional hazards modeling.

	Univariate model		Multivariate model	
Variable	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Treatment arm		0.02		0.014
Placebo	Reference		Reference	
Brincidofovir	0.5 (0.2 – 0.9)		0.4 (0.2 – 0.8)	
Sex		0.89		
Female	Reference		nc	
Male	1.0 (0.5 – 1.9)			
Age, years		0.04		0.09
18-40	Reference		Reference	
41-60	0.5 (0.2 – 0.8)		0.4 (0.1 – 0.9)	
>60	0.3 (0.1 – 0.8)		0.5 (0.2 – 1.3)	
Race		0.49		
White	Reference		nc	
African American	2.1 (0.8 – 5.6)			
Asian	1.0 (0.2 – 4.1)			
Other	nc			
Conditioning regimen		0.19		0.16
Non-myeloablative	Reference		Reference	
Myeloablative	1.6 (0.8 – 3.2)		1.8 (0.8 – 4.1)	
Alemtuzumab				
No	Reference	0.51	Reference	
Yes	1.4 (0.5 – 4.1)			
Antithymocyte globulin		0.13		0.02
No	Reference		Reference	
Yes	0.5 (0.2 – 1.2)		0.3 (0.1 – 0.8)	
Ex-vivo T-cell depletion		0.26		0.49
No	Reference		Reference	
Yes	1.7 (0.7 – 4.1)		1.5 (0.5 – 4.3)	
Risk category		0.88		

Low-risk	Reference		nc	
High-risk	0.9 (0.4-2.0)			
HCT type		0.10		0.09
Matched related	Reference		Reference	
Cord blood	2.9 (0.9-9.1)		5.8 (1.4 – 24.1)	
Haploidentical	2.7 (0.8-8.4)		2.7 (0.8 – 9.1)	
Matched unrelated	0.8 (0.4-1.9)		1.2 (0.5 – 3.0)	
Mismatched	0.9 (0.2-3.3)		1.5 (0.4 – 5.9)	
Time from HCT to first dose		0.60		
≤1 week	Reference		nc	
>1 week - ≤2 weeks	1.2 (0.6 – 2.5)			
Acute GVHD[a]		0.38		
Grades 0-1	Reference		nc	
Grades 2-4	1.9 (0.4 – 8.3)			

HR indicates hazard ratio; CI, confidence interval; GVHD, graft-versus-host disease; nc, not calculated.
[a]Modeled as a time-dependent covariate.

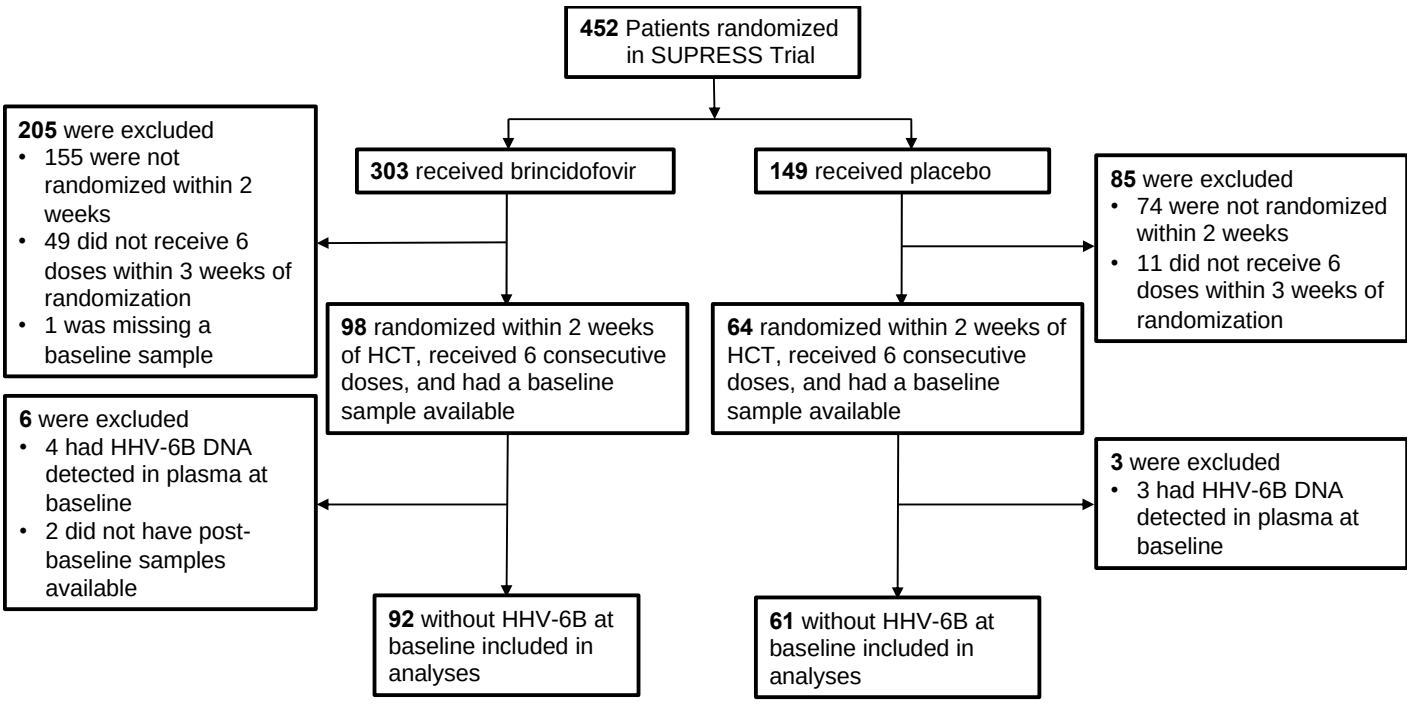

Figure S1. Consort diagram.