SUPPLEMENTARY APPENDIX:

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SUPPLEMENTAL METHODS:

The 300 patient multicenter BMT CTN validation set was formed from 107 patients who participated in BMT CTN 0302 (Initial systemic treatment of acute GVHD: A phase II randomized trial evaluating etanercept, mycophenolate mofetil (MMF), denileukin diftitox (ONTAK) and pentostatin in addition to corticosteroids) and 193 patients who participated in BMT CTN 0802 (A multi-center, randomized, double blind, phase III trial evaluating corticosteroids with mycophenolate mofetil vs. corticosteroids with placebo as initial systemic treatment of acute GVHD) and whose serum samples from GVHD onset were available for analysis.

The eligibility criteria for both protocols were similar. For BMT CTN 0302, patients 6 years and older who had undergone an allogeneic hematopoietic stem cell transplant and who had developed new onset acute GVHD requiring systemic therapy were eligible. Patients were required to enroll within 48 hours of initiation of corticosteroid therapy (≥ 1 mg/kg/day methylprednisolone). Patients with severe neutropenia (absolute neutrophil count <500/μL), renal failure (estimated creatinine clearance <30 mL/minute), uncontrolled infections, or chronic GVHD were excluded. For BMT CTN 0802, the same criteria were employed except the lower age limit was removed, patients were permitted to receive up to 72 hours of corticosteroid therapy prior to enrollment, and patients with severe hepatic sinusoidal obstruction syndrome were excluded.

The treatment plan for BMT CTN 0302 has been previously published.[1] Briefly, patients were randomized to treatment with methylprednisolone 2 mg/kg/day intravenously (IV) (or prednisone 2.5 mg/kg/day orally) and either etanercept, MMF, denileukin diftitox or pentostatin. Etanercept was dosed at 25 mg subcutaneously twice weekly for up to 4 weeks. Dosing for patients less than 17 years of age or with body surface area (BSA) < 0.6 m^2 received 0.4 mg/kg subcutaneously twice weekly up to a maximum of 25 mg per dose. MMF was administered for 8 weeks and dosed according to body surface area (BSA). Patients with a BSA > 1.5 m^2 received 20 mg/kg (actual body weight) PO or IV twice daily (maximum 1 g per dose). Patients with a BSA from 1.25 to 1.5 m^2 received 750 mg IV or orally twice daily. Denileukin diftitox was administered on six occasions at 9 micrograms/kg (actual body weight) IV on study days 1, 3, 5, 15, 17, and 19. Pentostatin was administered on six occasions at 1.5 mg/m^2 daily (BSA calculated using actual body weight) on study days 1-3 and 15-17. Steroid tapers could begin after day 7 but the minimum permitted steroid dose on day 28 was methylprednisolone 0.6 mg/kg/day intravenously (or prednisone 0.75 mg/kg/day).

The treatment plan for BMT CTN 0802 has been previously published.[2] Briefly, patients were randomized to treatment with methylprednisolone 1.6 mg/kg/day IV (or prednisone 2 mg/kg/day orally) and either placebo or MMF. MMF was administered for 8 weeks and dosed according to body weight as follows: Patients >60 kg received MMF 1 gm orally or IV every 8 hours, between 40-60 kg received 750 mg orally or IV every 8 hours, and <40 kg received 20 mg/kg orally or IV (up to 750 mg/kg) every 8 hours. Steroid tapers could begin after day 3 but the minimum permitted steroid dose on day 28 was methylprednisolone 0.2 mg/kg/day intravenously (or prednisone 0.25 mg/kg/day).

Patients were enrolled from the following institutions: Avera Hematology & Transplant Center (Sioux Falls, SD), Baylor University Medical Center (Dallas, TX), Blood & Marrow Transplant Program at Northside Hospital (Atlanta, GA), City of Hope National Medical Center (Duarte, CA), Colorado Blood Cancer Institute (Denver, CO), Dana Farber Cancer Institute/Brigham & Women's/Massachusetts General Hospital (Boston, MA), Duke University Medical Center (Durham, NC), Fred Hutchinson Cancer Research Center (Seattle, WA), Hackensack University Medical Center (Hackensack, NJ), Indiana Blood and Marrow Transplant (Indianapolis, IN), Johns Hopkins University (Baltimore, MD), Levine Children's Hospital/Carolinas Medical Center (Charlotte, NC), Mayo Clinic (Rochester, MN), Medical College of Wisconsin (Milwaukee, WI), Medical University of South Carolina (Charleston, SC), Memorial Sloan-Kettering Cancer Center (New York, NY), Ohio State University (Columbus, OH), Oregon Health & Science University (Portland, OR), Rush University Medical Center (Chicago, IL), Stanford Hospital and Clinics (Palo Alto, CA), Texas Transplant Institute (San Antonio, TX), Tufts Medical Center (Boston, MA), University California San Diego Medical Center (San Diego, CA), University Hospitals Case Medical Center (Cleveland, OH) , University of Florida (Gainesville, FL), University of Iowa (Iowa City, IA), University of Maryland (Baltimore, MD), University of Minnesota (Minneapolis, MN), University of North Carolina (Chapel Hill, NC), University of Pennsylvania (Philadelphia, PA), University of Texas/MD Anderson Cancer Center (Houston, TX), Medical College of Virginia (Richmond, VA), Washington University/Barnes Jewish Hospital (St. Louis, MO), Weill Cornell Medical College/ The New York Presbyterian Hospital (New York, NY).

MODIFIED GLUCKSBERG GRADING SYSTEM

GVHD was graded according to modified Glucksberg criteria, as shown below:

Stage	Skin (% body surface area)	Liver (bilirubin)	GI tract (stool output/day)*
0	No GVHD rash	<2 mg/dL	Adult: <500 mL/day Child: <10 mL/kg/day
1	Maculopapular rash <25%	2-3 mg/dL	Adult: 500-999 mL/day Child: 10-19.9 mL/kg/day OR persistent nausea, vomiting, or anorexia with a positive upper GI biopsy
2	Maculopapular rash 25-50%	3.1-6 mg/dL	Adult: 1000-1500 mL/day Child: 20-30 mL/kg/day
3	Maculopapular rash >50%	6.1-15 mg/dL	Adult: >1500 mL/day Child: >30 mL/kg/day
4	Generalized erythroderma plus bullous formation and desquamation >5% BSA	>15 mg/dL	Severe abdominal pain with or without ileus, or grossly bloody stool (regardless of volume).

*For GI staging: The "adult" stool output values are used for patients > 50kg in weight

Overall Clinical Grade

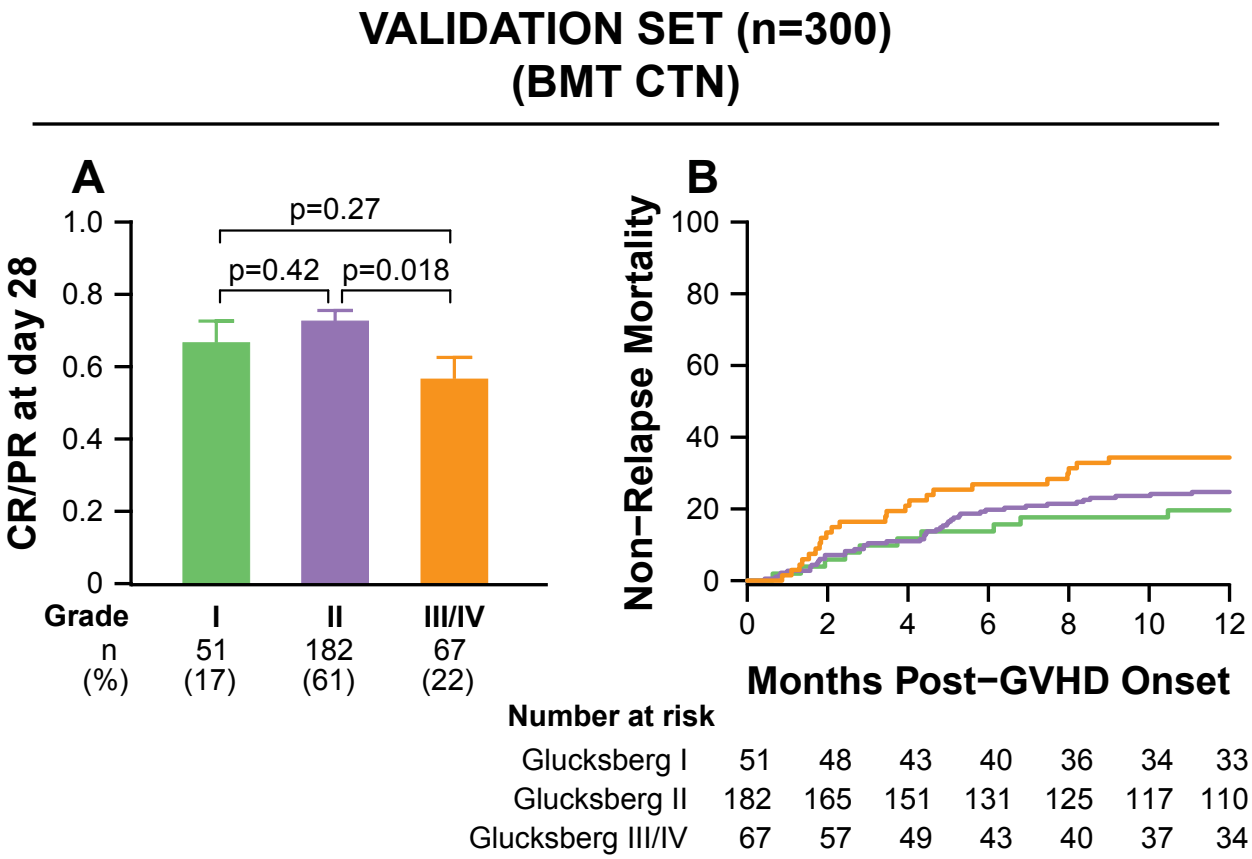
Grade 0: No stage 1-4 of any organ
Grade I: Stage 1-2 rash and no liver or GI involvement
Grade II: Stage 3 rash and/or Stage 1 liver and/or GI involvement
Grade III: Stage 0-3 rash with Stage 2-3 liver or GI involvement
Grade IV: Stage 4 skin, liver, or GI involvement

IBMTR ACUTE GVHD SEVERITY INDEX

Grade	Skin rash (% body surface area)	Liver (bilirubin)	GI tract (stool output/day)
A	<25%	<2 mg/dL	<500 mL/day
B	25-50%	2-6 mg/dL	550-1500 mL/day
C	>50%	6.1-15 mg/dL	>1500 mL/day
D	Bullae	>15 mg/dL	Severe abdominal pain and ileus

Grade is assigned by maximum involvement in an individual organ system

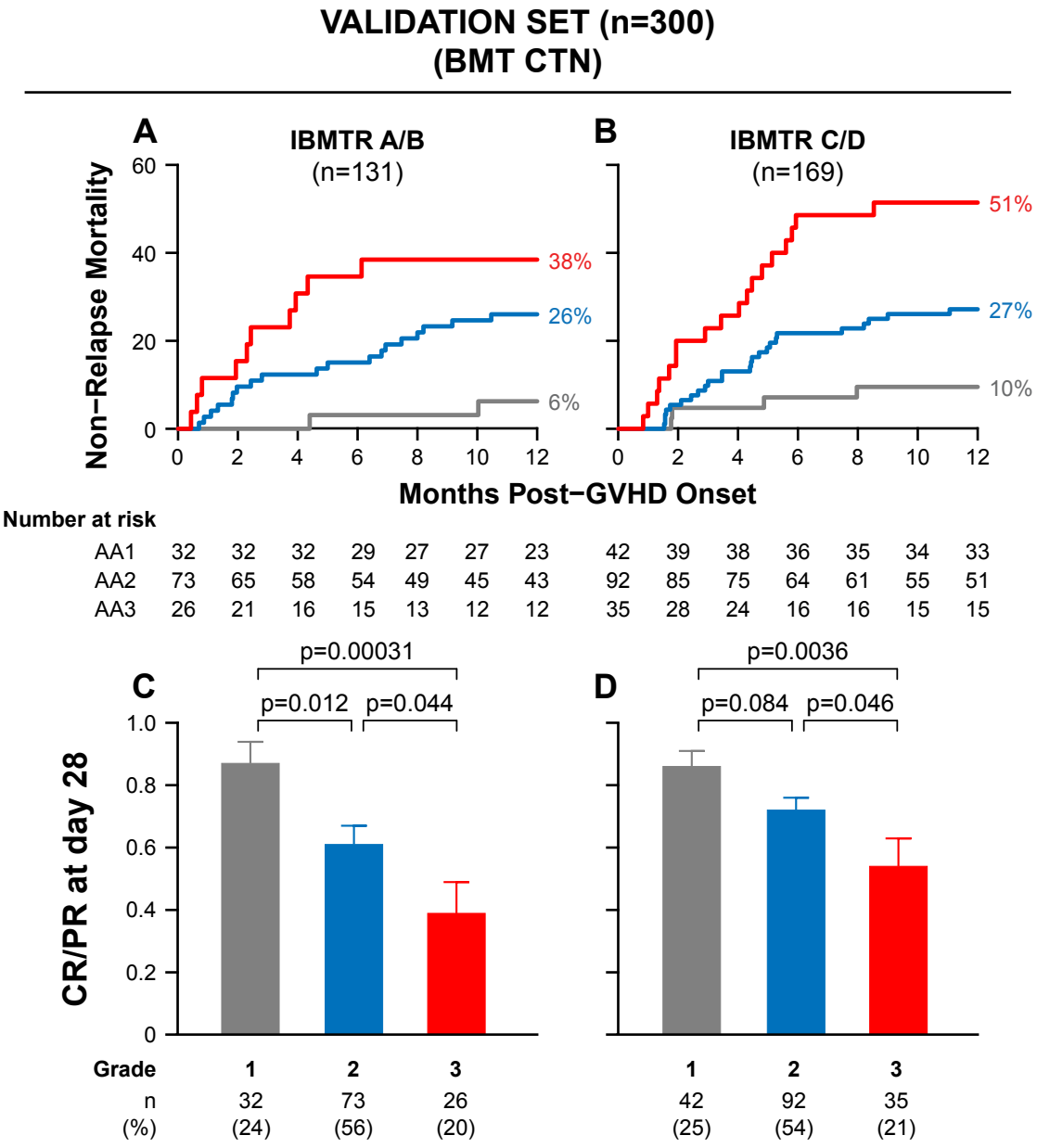
FIGURE S1: OUTCOMES BY GLUCKSBERG GRADE AT GVHD ONSET.



LEGEND:

Panel A shows the proportion of patients with complete or partial response in the multicenter BMT CTN validation set with Glucksberg grade I (green), II (purple), or III/IV (orange) at GVHD onset. The numbers in parentheses are the proportion of patients with each Glucksberg grade. Panel B shows the cumulative incidence of non-relapse mortality by Glucksberg grade (p=NS).

FIGURE S2: OUTCOMES BY ANN ARBOR SCORES STRATIFIED BY IBMTR GRADE.



LEGEND:

Outcomes for the multicenter validation set for IBMTR grade by Ann Arbor score (1, grey; 2, blue; 3, red). Cumulative incidence of non-relapse mortality is shown for (A) IBMTR grade A/B, p=0.0090 and (B) IBMTR grade C/D, p=0.00012. P-values relate to any pairwise comparison of curves. The 11 patients with IBMTR grade A GVHD were combined with the 120 patients with IBMTR grade B. The corresponding proportion of patients with complete or partial response are shown in Panels C and D. The numbers in parentheses are the proportion of patients assigned to each Ann Arbor score within each subset.

TABLE S1: REPRESENTATIVE THRESHOLDS THAT DEFINE ANN ARBOR SCORES

Patients were rank ordered according to the predicted probability of NRM, *p*, in the training and validation sets. Multiple values of *p* met the predefined criteria for Ann Arbor 1 GVHD (NRM ≤10%) and for Ann Arbor 3 GVHD (NRM >40%); three representative values each are shown in the table. The threshold $p = 0.4$ was selected to define Ann Arbor 1 GVHD and $p = 0.66$ was selected to define Ann Arbor 3 GVHD.

		Training set (N=328)				Test set (N=164)		
Thresholds	**Ann Arbor score**	**N**	**6 month NRM**	**p-value vs. AA2**		**N**	**6 month NRM**	**p-value vs. AA2**
0.35/0.63	1	99	10%	0.0021		54	9%	0.025
	2	143	24%			57	25%	
	3	86	44%	0.0018		53	42%	0.025
0.4/0.63	1	131	9%	<0.0001		64	9%	0.020
	2	111	29%			47	28%	
	3	86	44%	0.038		53	42%	0.15
0.41/0.63	1	137	9%	<0.0001		68	10%	0.022
	2	105	30%			43	28%	
	3	86	44%	0.056		53	42%	0.080
0.35/0.66	1	99	10%	0.0025		54	9%	0.026
	2	151	23%			68	24%	
	3	78	47%	0.00031		44	45%	0.0060
0.4/0.66	**1**	**131**	**9%**	**<0.0001**		64	9%	0.0069
	2	**119**	**28%**			56	27%	
	3	**78**	**47%**	**0.0080**		44	45%	0.024
0.41/0.66	1	137	9%	<0.0001		68	10%	0.024
	2	113	28%			52	27%	
	3	78	47%	0.012		44	45%	0.022
0.35/0.68	1	99	10%	0.0033		54	9%	0.024
	2	154	23%			69	25%	
	3	75	49%	<0.0001		41	46%	0.0041
0.4/0.68	1	131	9%	<0.0001		64	9%	0.0069
	2	122	27%			59	27%	
	3	75	49%	0.0019		41	46%	0.016
0.41/0.68	1	137	9%	<0.0001		68	10%	0.022
	2	116	28%			55	27%	
	3	75	49%	0.0033		41	46%	0.015

TABLE S2: PATIENT CHARACTERISTICS

Characteristic		Training set (N=328)	Test set (N=164)	Validation set (N=300)	p-value[a]	p-value[b]
Median age, years (range)		50 (0-70)	48 (0-69)	52 (9-76)	0.0090	0.0012
Indication for HCT					0.022	0.33
	Acute leukemia	162 (49%)	83 (51%)	154 (51%)		
	MDS/MPD	46 (14%)	15 (9%)	47 (16%)		
	Lymphoma	60 (18%)	38 (23%)	43 (14%)		
	Other Malignant	53 (16%)	26 (16%)	43 (14%)		
	Non-Malignant	7 (2%)	2 (1%)	13 (4%)		
Disease Status at HCT[c]					<0.0001	<0.0001
	Other/Low/Intermediate	190 (58%)	94 (57%)	203 (68%)		
	High	138 (42%)	70 (43%)	59 (20%)		
	Unknown	-	-	38 (13%)		
Donor type					0.11	0.0073
	Related	107 (33%)	68 (41%)	129 (43%)		
	Unrelated	221 (67%)	96 (59%)	171 (57%)		
HLA-match					0.17	0.021
	Matched[d]	234 (71%)	121 (74%)	238 (79%)		
	Mismatched	94 (29%)	43 (26%)	62 (21%)		
Stem cell source					0.016	0.32
	Marrow	54 (16%)	18 (11%)	63 (21%)		
	Peripheral blood	257 (78%)	139 (85%)	220 (73%)		
	Cord blood	17 (5%)	7 (4%)	17 (6%)		
Conditioning Regimen Intensity					0.75	0.19
	Full	192 (59%)	102 (62%)	191 (64%)		
	Reduced	136 (41%)	62 (38%)	109 (36%)		
GVHD prophylaxis					<0.0001	<0.0001
	CNI/MTX ± other	222 (67%)	114 (70%)	172 (57%)		
	CNI/MMF ± other	99 (30%)	43 (26%)	50 (17%)		
	CNI/sirolimus	0 (0%)	1 (<1%)	15 (5%)		
	Post-HCT cyclophosphamide	0 (0%)	0 (0%)	14 (5%)		
	Other	7 (2%)	6 (4%)	49 (16%)		
GVHD onset day, Median (range)		26 (5-213)	27 (7-168)	34 (11-237)	0.0042	<0.0001
GVHD grade at onset					<0.0001	<0.0001
I		130 (40%)	60 (37%)	51 (17%)		
II		144 (44%)	73 (45%)	182 (61%)		
	Isolated stage 3 skin	69 (21%)	27 (16%)	103 (34%)		
	Stage 1 GI ± skin and/or liver	70 (21%)	43 (26%)	77 (26%)		
	Stage 1 liver ±skin GVHD	5 (2%)	3 (2%)	2 (1%)		
III		42 (13%)	27 (16%)	59 (20%)		
IV		12 (4%)	4 (2%)	8 (3%)		

a – p-value for comparison of test to validation set
b – p-value for comparison of training set to validation set
c – Disease risk according to 2014 ASBMT RFI classifications (http://c.ymcdn.com/sites/asbmt.site-ym.com/resource/resmgr/Docs/ASBMT_RFI_2014_Translation_t.pdf)
d – Donor-patient pairs were considered matched if all 8 HLA-A, -B, -C and –DRB1 alleles matched for related and unrelated marrow or peripheral blood transplants and if 5 or 6/6 HLA-A, -B and –DRB1 alleles matched for cord blood transplants
abbreviations: MDS/MPD, myelodysplastic syndrome/myeloproliferative disorder; CNI, calcineurin inhibitor; MTX, methotrexate; MMF, mycophenolic acid

TABLE S3: PRIMARY GVHD THERAPY

Primary GVHD Therapy		**Training set (N=328)**	**Test set (N=164)**	**Validation set (N=300)**
No Systemic Steroids, N (%)		86 (26%)	39 (24%)	0 (0%)
Systemic Steroids alone, N (%)		188 (57%)	104 (63%)	96 (32%)
Systemic Steroids with additional agent(s), N (%)		54 (16%)	21 (13%)	204 (68%)
	Mycophenolate Mofetil	7 (2%)	1 (1%)	126 (42%)
	Denileukin Diftitox	0 (0%)	0 (0%)	25 (8%)
	Etanercept	40 (12%)	15 (9%)	28 (9%)
	Pentostatin	2 (1%)	1 (1%)	25 (8%)
	Other	5 (2%)	4 (2%)	0 (0%)

TABLE S4: COMPARISON OF ANN ARBOR SCORES AND GLUCKSBERG GRADES TO PREDICT NRM RISK (MULTICENTER VALIDATION SET)

				95% Confidence Interval		
Model	**Grading**	**Comparison (vs 2/II)**	**Hazard Ratio**	**Lower Bound**	**Upper Bound**	**p-value**
Univariate	Ann Arbor	1	0.27	0.12	0.63	0.0023
		3	2.07	1.30	3.29	0.0021
	Glucksberg	I	0.75	0.38	1.48	0.41
		III/IV	1.47	0.90	2.38	0.12
Multivariate	Ann Arbor	1	0.27	0.11	0.62	0.0020
		3	1.98	1.23	3.18	0.0048
	Glucksberg	I	0.76	0.39	1.50	0.43
		III/IV	1.37	0.83	2.27	0.22

TABLE S5: NON-RELAPSE MORTALITY FOR ANN ARBOR SCORES STRATIFIED BY PATIENT CHARACTERISTICS

	Ann Arbor Score	Sample Size	HR (95 % Confidence Interval)
HLA-matched	**1**	**61**	**0.26 (0.11-0.66)**
	2	135	1.00
	3	42	1.73 (0.97-3.08)
HLA-mismatched	1	13	0.29 (0.03-2.38)
	2	30	1.00
	3	**19**	**2.75 (1.11-6.82)**
Related Donor	**1**	**35**	**0.16 (0.04-0.67)**
	2	69	1.00
	3	25	1.40 (0.69-2.84)
Unrelated Donor	1	39	0.41 (0.14-1.17)
	2	96	1.00
	3	**36**	**2.88 (1.56-5.29)**
Age ≤54 years	**1**	**43**	**0.20 (0.05-0.83)**
	2	99	1.00
	3	31	1.65 (0.78-3.48)
Age >55	**1**	**31**	**0.32 (0.11-0.92)**
	2	66	1.00
	3	**30**	**2.32 (1.26-4.27)**
Reduced Intensity	**1**	**41**	**0.28 (0.09-0.93)**
	2	112	1.00
	3	**38**	**2.01 (1.08-3.73)**
Full Intensity	**1**	**33**	**0.23 (0.07-0.76)**
	2	53	1.00
	3	23	1.99 (0.99-4.02)

Bolded rows indicate the Ann Arbor scores where NRM is significantly different from Ann Arbor 2 GVHD in the subset analysis.

TABLE S6: PATIENT CHARACTERISTICS FOR TRAINING SET BY ANN ARBOR SCORE

Characteristic		Ann Arbor 1 (N=131)	Ann Arbor 2 (N=119)	Ann Arbor 3 (N=78)	p-value[a]
Median age, years (range)		47 (1-69)	50 (0-70)	52 (6-68)	0.20
Indication for HCT					0.33
	Acute leukemia	67 (51%)	65 (55%)	30 (38%)	
	MDS/MPD	15 (12%)	19 (16%)	12 (15%)	
	Lymphoma	26 (20%)	19 (16%)	15 (19%)	
	Other Malignant	20 (15%)	14 (12%)	19 (24%)	
	Non-Malignant	3(2%)	2 (2%)	2 (3%)	
Disease Status at HCT[b]					0.63
	Other/Low/Intermediate	74 (56%)	73 (61%)	43 (55%)	
	High	57(44%)	46 (39%)	35 (45%)	
	Unknown	0	0	0	
Donor type					0.0050
	Related	55 (42%)	27 (23%)	25 (32%)	
	Unrelated	76 (58%)	92 (77%)	53 (68%)	
HLA-match[c]					0.0023
	Matched	105 (80%)	84 (71%)	45 (58%)	
	Mismatched	26 (20%)	35 (29%)	33 (42%)	
Stem cell source					0.27
	Marrow	21 (16%)	24 (20%)	9 (12%)	
	Peripheral blood	105 (80%)	86 (72%)	66 (85%)	
	Cord blood	5 (4%)	9 (8%)	3 (4%)	
Conditioning Regimen Intensity					0.95
	Full	78 (60%)	69 (58%)	45 (58%)	
	Reduced	53 (40%)	50 (42%)	33 (42%)	
GVHD prophylaxis					0.0094
	CNI/MTX ± other	98 (75%)	80 (67%)	45 (58%)	
	CNI/MMF ± other	33 (25%)	37 (31%)	28 (36%)	
	CNI/sirolimus	0	0	0	
	Post-HCT cyclophosphamide	0	0	0	
	Other	0	2 (2%)	5 (6%)	
GVHD onset day, Median (range)		26 (7-174)	27 (5-162)	22 (9-213)	0.050
GVHD grade at onset					0.017
I		65 (50%)	43 (36%)	22 (28%)	
II		53 (40%)	54 (45%)	37 (47%)	
	Isolated stage 3 skin	26 (20%)	25 (21%)	18 (23%)	
	Stage 1 GI ± skin and/or liver	25 (19%)	27 (23%)	18 (23%)	
	Stage 1 liver ±skin GVHD	2 (2%)	2 (2%)	1 (1%)	
III		11 (8%)	18 (15%)	13 (17%)	
IV		2 (2%)	4 (3%)	6 (8%)	

a – p-value for comparison of Ann Arbor scores
b – Disease risk according to 2014 ASBMT RFI classifications (http://c.ymcdn.com/sites/asbmt.site-ym.com/resource/resmgr/Docs/ASBMT_RFI_2014_Translation_t.pdf)
c – Donor-patient pairs were considered matched if all 8 HLA-A, -B, -C and –DRB1 alleles matched for related and unrelated marrow or peripheral blood transplants and if 5 or 6/6 HLA-A, -B and –DRB1 alleles matched for cord blood transplants
abbreviations: MDS/MPD, myelodysplastic syndrome/myeloproliferative disorder; CNI, calcineurin inhibitor; MTX, methotrexate; MMF, mycophenolic acid

TABLE S7: PATIENT CHARACTERISTICS FOR TEST SET BY ANN ARBOR SCORE

Characteristic		Ann Arbor 1 (N=64)	Ann Arbor 2 (N=56)	Ann Arbor 3 (N=44)	p-value[a]
Median age, years (range)		48 (0-68)	48 (16-69)	46 (9-68)	0.82
Indication for HCT					0.46
	Acute leukemia	35 (55%)	28 (50%)	20 (45%)	
	MDS/MPD	7 (11%)	2 (4%)	6 (14%)	
	Lymphoma	10 (16%)	17 (30%)	11 (25%)	
	Other Malignant	11 (17%)	9 (14%)	6 (14%)	
	Non-Malignant	1 (2%)	0	1 (2%)	
Disease Status at HCT[b]					0.056
	Other/Low/Intermediate	44 (69%)	29 (52%)	21 (48%)	
	High	20 (31%)	27 (48%)	23 (52%)	
	Unknown	0	0	0	
Donor type					0.053
	Related	34 (53%)	19 (34%)	15 (34%)	
	Unrelated	30 (47%)	37 (66%)	29 (66%)	
HLA-match[c]					0.0046
	Matched	56 (88%)	38 (68%)	27 (61%)	
	Mismatched	8 (13%)	18 (32%)	17 (39%)	
Stem cell source					0.83
	Marrow	7 (11%)	8 (14%)	3 (7%)	
	Peripheral blood	54 (84%)	46 (82%)	39 (89%)	
	Cord blood	3 (5%)	2 (4%)	2 (5%)	
Conditioning Regimen Intensity					0.42
	Full	38 (59%)	33 (59%)	31 (70%)	
	Reduced	26 (41%)	23 (39%)	13 (30%)	
GVHD prophylaxis					0.99
	CNI/MTX ± other	45 (70%)	38 (68%)	31 (70%)	
	CNI/MMF ± other	17 (27%)	15 (27%)	11 (25%)	
	CNI/sirolimus	0	1 (2%)	0	
	Post-HCT cyclophosphamide	0	0	0	
	Other	2 (3%)	2 (4%)	2 (5%)	
GVHD onset day, Median (range)		28 (7-121)	27 (8-168)	23 (9-100)	0.21
GVHD grade at onset					0.18
I		24 (38%)	24 (43%)	12 (27%)	
II		33 (52%)	21 (38%)	19 (43%)	
	Isolated stage 3 skin	14 (22%)	7 (13%)	6 (14%)	
	Stage 1 GI ± skin and/or liver	17 (27%)	13 (23%)	13 (30%)	
	Stage 1 liver ±skin GVHD	2 (3%)	1 (2%)	0	
III		7 (11%)	9 (16%)	11 (25%)	
IV		0	2 (4%)	2 (5%)	

a – p-value for comparison of Ann Arbor scores
b – Disease risk according to 2014 ASBMT RFI classifications (http://c.ymcdn.com/sites/asbmt.site-ym.com/resource/resmgr/Docs/ASBMT_RFI_2014_Translation_t.pdf)
c – Donor-patient pairs were considered matched if all 8 HLA-A, -B, -C and –DRB1 alleles matched for related and unrelated marrow or peripheral blood transplants and if 5 or 6/6 HLA-A, -B and –DRB1 alleles matched for cord blood transplants
abbreviations: MDS/MPD, myelodysplastic syndrome/myeloproliferative disorder; CNI, calcineurin inhibitor; MTX, methotrexate; MMF, mycophenolic acid

TABLE S8: PATIENT CHARACTERISTICS FOR VALIDATION SET BY ANN ARBOR SCORE

Characteristic		Ann Arbor 1 (N=74)	Ann Arbor 2 (N=165)	Ann Arbor 3 (N=61)	p-value[a]
Median age, years (range)		52 (11-70)	52 (9-71)	54 (16-76)	0.59
Indication for HCT					0.11
	Acute leukemia	40 (54%)	87 (53%)	27 (44%)	
	MDS/MPD	13 (18%)	19 (12%)	15 (25%)	
	Lymphoma	8 (11%)	23 (14%)	12 (20%)	
	Other Malignant	12 (16%)	27 (16%)	4 (7%)	
	Non-Malignant	1 (1%)	9 (5%)	3 (5%)	
Disease Status at HCT[b]					0.88
	Other/Low/Intermediate	53 (72%)	111 (67%)	39 (64%)	
	High	12 (16%)	34 (21%)	13 (21%)	
	Unknown	9 (12%)	20 (12%)	9 (15%)	
Donor type					0.69
	Related	35 (47%)	69 (42%)	25 (41%)	
	Unrelated	39 (53%)	96 (58%)	36 (59%)	
HLA-match[c]					0.089
	Matched	61 (82%)	135 (82%)	42 (69%)	
	Mismatched	13 (18%)	30 (18%)	19 (31%)	
Stem cell source					0.40
	Marrow	14 (19%)	39 (24%)	10 (16%)	
	Peripheral blood	54 (73%)	120 (73%)	46 (75%)	
	Cord blood	6 (8%)	6 (4%)	5 (8%)	
Conditioning Regimen Intensity					0.17
	Full	41 (55%)	112 (68%)	38 (62%)	
	Reduced	33 (45%)	53 (32%)	23 (38%)	
GVHD prophylaxis					0.24
	CNI/MTX ± other	42 (57%)	95 (58%)	35 (57%)	
	CNI/MMF ± other	15 (20%)	24 (15%)	11 (18%)	
	CNI/sirolimus	7 (9%)	7 (4%)	1 (2%)	
	Post-HCT cyclophosphamide	2 (3%)	7 (4%)	5 (8%)	
	Other	8 (11%)	32 (19%)	9 (15%)	
GVHD onset day, Median (range)		38 (12-237)	32 (11-216)	28 (11-178)	0.021
GVHD grade at onset					0.12
I		12 (16%)	30 (18%)	9 (15%)	
II		46 (62%)	101 (61%)	35 (57%)	
	Isolated stage 3 skin	29 (39%)	59 (36%)	15 (25%)	
	Stage 1 GI ± skin and/or liver	17 (23%)	40 (24%)	20 (33%)	
	Stage 1 liver ±skin GVHD	0	2 (1%)	0	
III		11 (15%)	31 (19%)	17 (28%)	
IV		5 (7%)	3 (2%)	0	

a – p-value for comparison of Ann Arbor scores
b – Disease risk according to 2014 ASBMT RFI classifications (http://c.ymcdn.com/sites/asbmt.site-ym.com/resource/resmgr/Docs/ASBMT_RFI_2014_Translation_t.pdf)
c – Donor-patient pairs were considered matched if all 8 HLA-A, -B, -C and –DRB1 alleles matched for related and unrelated marrow or peripheral blood transplants and if 5 or 6/6 HLA-A, -B and –DRB1 alleles matched for cord blood transplants
abbreviations: MDS/MPD, myelodysplastic syndrome/myeloproliferative disorder; CNI, calcineurin inhibitor; MTX, methotrexate; MMF, mycophenolic acid

TABLE S9: ORGAN SPECIFIC GLUCKSBERG GRADE PREDICTS DURABILITY OF RESPONSE

Glucksberg Grade	Sample Size	Durable Response	Percentage	*p*-value for difference
Skin only at onset (stage 1-3) (n=286)				
I	190	89	47%	0·0070
II	96	29	30%	
Lower GI GVHD present at onset (± other organ involvement) (n=151)				
II	75	33	44%	0·0014
III/IV	76	15	20%	

REFERENCES

1. Alousi AM, Weisdorf DJ, Logan BR, et al. Etanercept, mycophenolate, denileukin or pentostatin plus corticosteroids for acute graft vs. host disease: a randomized phase II trial from the BMT CTN. Blood 2009;114:511-7.
2. Bolaños-Meade J, Logan BR, Alousi AM, Phase III clinical trial of steroids/mycophenolate mofetil vs steroids/placebo as therapy for acute graft-versus-host disease: BMT CTN 0802. Blood, 2014; doi: 10.1182/blood-2014-06-577023.