

Treatment of Acute GVHD: Predictors of Survival

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Potential conflicts/disclosures

Research support

for BMT CTN trial

Roche, Eisai, Ligand, Merck, Amgen,
Supergen (6 supporters; 4 drugs)

for GVHD trials at Minnesota

Genzyme, Amgen

Analysis was conducted with no knowledge or input from
Industry supporters

Targets of GVHD

Lymphohematopoietic tissues

Complete transition to donor chimerism
GVL—for hematopoietic malignancy

Epithelial and other host alloantigens

Skin, Gut, Liver, ?lung tissues

Targets of GVHD

Lymphohematopoietic tissues

Complete transition to donor chimerism

GVL—for hematopoietic malignancy

This is necessary GVHD—should not be prevented or treated; needed for stable tolerance and immunocompetence

Epithelial and other host alloantigens

Skin, Gut, Liver, ?lung tissues

Toxic and unnecessary, “pathologic GVHD”

*Is prophylaxis just preemptive therapy for “toxic”
GVHD*

Initial vs. Max Grade

Endpoint of prophylaxis
Max GVHD Grade

But max grade is sum of;

Prophylaxis failure—time to II/IV or needing
therapy plus

Therapy failure—time to III/IV

(grade worse than starting grade)

*If early or more intense therapy is effective; it
makes the impact of prophylaxis more
apparent*

Recent habits: treat earlier (URD, older
patients)

possibly with differing therapy

Acute GVHD--Treatment

Standard GVHD treatment—Corticosteroids

Starting dose 2 → 1.5 → 1 mg/kg/d

Durable response 40% Sibling donors

25% Unrelated donors

60-75% need additional therapy

For steroid-refractory disease, no standard effective treatments are available

Treat the symptoms; Permit immunocompetence;

Permit tolerance and spare GVL

Steroid therapy of Acute GVHD

N = 443 PR/CR cGVHD
20/35% 42%

<u>Initial Grade (%)</u>		<u>cGVHD %</u>
I	28	39
II	60	44
III/IV	13	42

Factors predicting PR/CR to steroid therapy

Variable	Relative Likelihood of CR/PR (95% CI)	P
<u>Type of donor</u>		
Related	1.0	
Matched unrelated	0.8 (0.5 - 1.4)	0.52
Mismatched unrelated	0.5 (0.3 - 0.8)	<0.01
<u>GVHD prophylaxis</u>		
CSA	1.0	
Methotrexate	0.3 (0.1 - 0.6)	<0.01
T-cell depletion	0.9 (0.5 - 1.6)	0.77
Tacrolimus	1.2 (0.4 - 3.8)	0.63
<u>Initial grade of GVHD</u>		
I	1.0	
II	0.9 (0.6 - 1.5)	0.79
III	0.8 (0.4 - 1.7)	0.66
IV	0.2 (0.1 - 1.0)	0.22

MacMillan et al,
BBMT, 2002

Factors predicting 1 year mortality after steroid therapy of GVHD

Factor	Relative Risk of Death (95% CI)	P
<u>Type of donor</u>		
Related	1.0	
Matched unrelated	1.3 (0.9 - 1.9)	0.10
Mismatched unrelated	1.8 (1.3 - 2.6)	<0.01
<u>GVHD prophylaxis</u>		
Other	1.0	
T-cell depletion	1.4 (1.0 - 2.1)	0.04
<u>Age (in decades)</u>		
	1.2 (1.1 - 1.3)	<0.01
<u>Initial grade of GVHD</u>		
I-II	1.0	
III-IV	1.5 (1.0 - 2.2)	0.05

2009 Analysis

Total	N (%)	615	all 1 st transplants
Year of Transplant			
1990-1995		265 (43%)	
1996-2000		225 (37%)	
2001-2006		125 (20%)	
Age			
<18		238 (39%)	
≥18		377 (61%)	
	Median (range), (interquartile range)		28 (0.2-69), (10-41)
Donor Type			
Related Marrow		161 (26%)	
Related PBSC		39 (7%)	
URD Marrow		273 (44%)	
UCB		132 (23%)	[1 unit/2 units 75/67 (12/11%)]
Myeloablative		563 (92%)	
Non-Myeloablative		52 (8%)	

Initial Acute GvHD Grade at Treatment

I	194 (32%)
II	342 (56%)
III	71 (12%)
IV	8 (1%)

Initial Organ Involvement

Skin Only	374 (61%)
Multi-Organ Involvement	159 (26%)

Days to Onset of Acute GvHD

Median (range), (interquartile range) 28 (8-94), (21-38)

Days to Onset of Rx from Acute GvHD diagnosis

Median (range) 0 (-5-7)

Type of Acute GvHD Treatment

Prednisone 60 mg/m² or 2.4 mg/kg 100%

MacMillan, 2009

Initial Acute GvHD Grade at Treatment

I	194 (32%)	<u>2002</u> 28%
II	342 (56%)	60%
III	71 (12%)	11%
IV	8 (1%)	2%

Initial Organ Involvement

Skin Only 374 (61%)

Multi-Organ Involvement 159 (26%)

Days to Onset of Acute GvHD

Median (range), (interquartile range) 28 (8-94), (21-38)

Days to Onset of Rx from Acute GvHD diagnosis

Median (range) 0 (-5-7)

Type of Acute GvHD Treatment

Prednisone 60 mg/m² or 2.4 mg/kg 100%

MacMillan, 2009

Day 14 Response

Complete Response	216 (35%)
Partial Response 1	24 (20%)
No Response	275 (45%)

Day 28 Response

Complete Response	291 (47%)
Partial Response	66 (11%)
No Response	210 (34%)
Missing	48 (8%)

Day 56 Response

Complete Response	292 (47%)
Partial Response	41 (7%)
No Response	190 (31%)
Missing	92 (15%)

Response at day 14 versus day 28

Day 14 Response	Day 28 Response			Total	
	CR	PR	NR		
Complete Response		192	6	18	216
Partial Response	60	42	22	124	
No Response		65	18	192	275
Total	317	66	232	615	

Weighted Kappa: 0.55 (95% CI: 0.50-0.61)
good agreement

Response at day 14 versus day 56

Day 14 Response	Day 56 Response			Total	
	CR	PR	NR		
Complete Response		187	9	20	216
Partial Response	65	29	30	124	
No Response		82	19	174	275
Total	334	57	224	615	

Weighted Kappa: 0.47 (95% CI: 0.41-0.53)
good agreement

Response at day 14 versus day 56

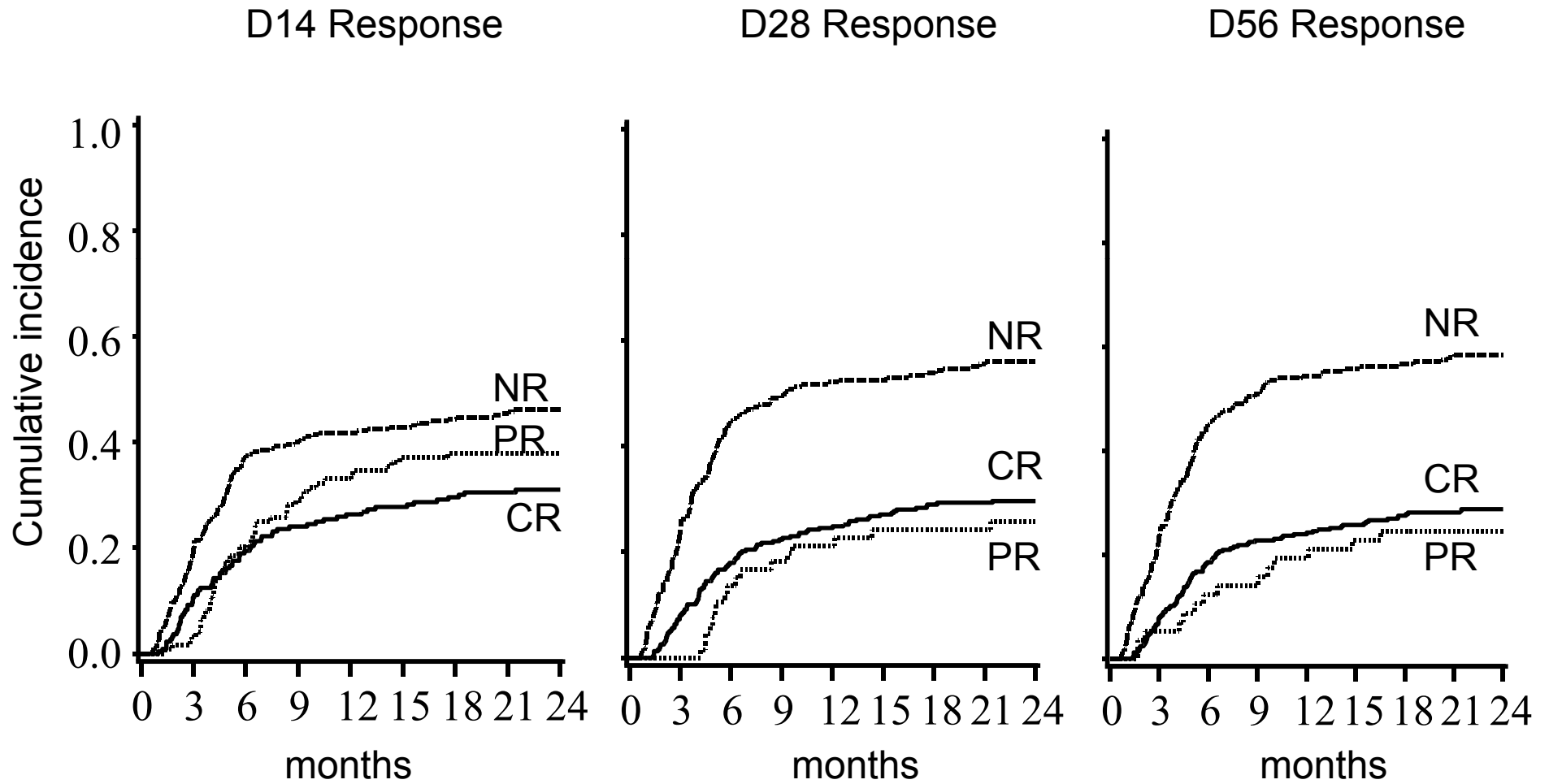
Day 14 Response	Day 56 Response			Total	
	CR	PR	NR		
Complete Response		271	22	24	317
Partial Response	29	23	14	66	
No Response		34	12	186	232
Total	334	57	224	615	

**Weighted Kappa: 0.67 (95% CI: 0.62-0.73)
good agreement**

Cumulative incidence of Non-Relapse Mortality (Initial Grades

	N	1 year # died	2 year TRM (95% CI)	2year TRM (95% CI)	competing risk (relapse)	P
All Patients	615	241	35% (31-39%)	39% (35-43%)	18%	
Day 14 post RX response						<0.001
Complete response	216	67	26% (20-32%)	31% (25-37%)	20%	
Partial Response	124	47	33% (25-41%)	38% (29-47%)	18%	
No Response	275	127	42% (36-48%)	46% (40-53%)	16%	
Day 28 post RX response						<0.001
Complete response	317	94	25% (21-29%)	30% (24-35%)	19%	
Partial Response	66	17	21% (11-31%)	26% (15-36%)	23%	
No Response	232	130	52% (45-59%)	56% (49-63%)	16%	
Day 56 post RX response						<0.001
Complete response	334	96	24% (20-28%)	29% (24-34%)	21%	
Partial Response	57	14	19% (9-29%)	25% (13-36%)	16%	
No Response	224	131	54% (47-61%)	58% (51-66%)	14%	

Non-Relapse Mortality by Response to Steroids All Patients



MacMillan, 2009

Predictors of 2 year NRM: Multivariate analysis

Factors	RR of TRM (95% CI)	P	Overall P	Adjusted Likelihood Ratio
Day 28 response			<0.001	92.66
Complete response*	1.0			
Partial Response	0.68 (0.41-1.13)	0.14		
No Response	2.37 (1.79-3.13)	<0.001		
Days to GVHD Treatment			0.08	
<28*	1.0			
≥28	0.80 (0.63-1.02)	0.08		
Grade of AGvHD at RX			0.02	
I*	1.0			
II	1.37 (0.98-1.91)	0.06		
III-IV	2.08 (1.20-3.60)	0.009		
Affected Organs			0.03	
Other*	1.0			
Skin Only	1.48 (1.04-2.11)	0.03		
Age			0.03	
<18*	1.0			
≥18	1.43 (1.03-1.97)	0.03		
Donor Type			0.05	
Matched sibling*	1.0			
MM sibling and URD	1.52 (1.07-2.14)	0.02		
UCB	1.08 (0.68-1.70)	0.75		

MacMillan, 2009

Predictors of 2 year NRM: Multivariate analysis

Factors	RR of TRM (95% CI)	P	Overall P
Conditioning			0.19
Myel./TBI	1.0		
Myel. No TBI	0.85 (0.52-1.38)	0.51	
Non-myeloablative	0.51 (0.26-1.00)	0.05	
GvHD Prophylaxis			0.53
Mtx+mtx/atg/pred*	1.0		
T-cell Depletion	0.98 (0.49-1.97)	0.96	
CsA containing	0.83 (0.44-1.57)	0.58	
Disease Risk			0.004
Standard*	1.0		
High	1.50 (1.14-1.98)	0.004	
CMV Serostatus			0.98
Recipient-, Donor-*	1.0		
Recipient-, Donor+	1.10 (0.73-1.66)	0.64	
Recipient+	1.04 (0.78-1.40)	0.77	

Predictors of 2 year NRM

	RR (95% C.I.)	P	Overall P
Day 14 post RX response			<0.001
Complete response*	1.0		
Partial Response	1.06 (0.72-1.56)	0.76	
No Response	1.70 (1.25-2.32)	<0.001	
Day 28 post RX response			<0.001
Complete response*	1.0		
Partial Response	0.68 (0.41-1.13)	0.14	
No Response	2.37 (1.79-3.13)	<0.001	
Day 56 post RX response			<0.001
Complete response*	1.0		
Partial Response	0.68 (0.39-1.20)	0.19	
No Response	2.51 (1.92-3.29)	<0.001	

MacMillan, 2009

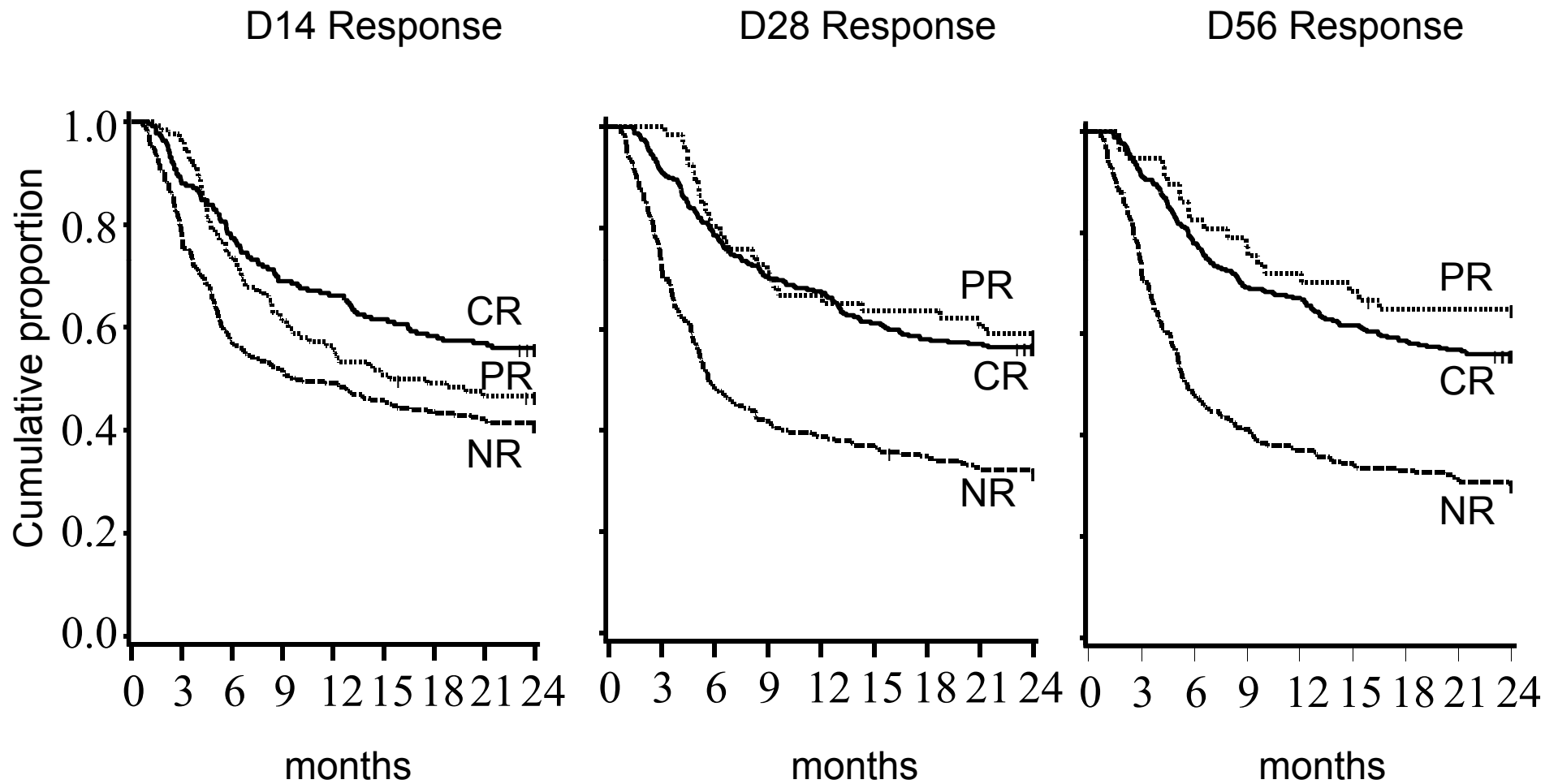
Multivariate Model: Predictors of 2 year NRM

	RR	Overall P	% change in RR from D14	Adjusted † Likelihood Ratio	C‡ (S.E.)	P	P	P
						14v.28	14v.56	28v.56
Day 14 response		<0.001		55.60	0.56 (0.02)	<0.001	<0.001	0.68
CR	1.0							
PR	1.06							
NR	1.70							
Day 28 response		<0.001		92.66	0.64 (0.03)			
CR	1.0							
PR	0.68		-56%					
NR	2.37		+39%					
Day 56 response		<0.001		96.02	0.65 (0.02)			
CR	1.0							
PR	0.68		-56%					
NR	2.51		+48%					

2 year survival

	N	# died	1 year OS (95% CI)	2 year OS (95% CI)	P
All Patients	615	323	57% (53-61%)	47% (43-51%)	
Day 14 post RX response					<0.001
Complete response	216	95	66% (60-72%)	56% (49-62%)	
Partial Response	124	66	56% (47-65%)	47% (38-55%)	
No Response	275	162	49% (43-55%)	41% (35-47%)	
Day 28 post RX response					<0.001
Complete response	317	138	68% (63-73%)	56% (51-62%)	
Partial Response	66	27	67% (56-78%)	59% (46-70%)	
No Response	232	158	39% (33-45%)	32% (26-38%)	
Day 56 post RX response					<0.001
Complete response	334	147	67% (62-72%)	56% (50-61%)	
Partial Response	57	20	72% (60-84%)	65% (51-76%)	
No Response	224	156	37% (31-43%)	30% (24-36%)	

Overall Survival by Response to Steroids All Patients



MacMillan, 2009

Predictors of 2 year Survival: Multivariate Analysis

	<u>RR of death (95% CI)</u>	<u>P</u>	<u>Overall P</u>
Day 28 response			<0.001
Complete response*	1.0		
Partial Response	0.76 (0.49-1.19)	0.22	
No Response	2.21 (1.73-2.82)	<0.001	
Days to Treatment		0.86	
<28*	1.0		
≥28	1.02 (0.80-1.31)	0.86	
Initial Grade			0.02
I*	1.0		
II	1.24 (0.93-1.66)	0.14	
III-IV	1.95 (1.21-3.14)	0.006	
Affected Organs			0.001
Other*	1.0		
Skin Only	1.68 (1.24-2.29)	0.001	
Age			0.008
<18*	1.0		
≥18	1.48 (1.11-1.98)	0.008	

Predictors of 2 year Survival: Multivariate analysis

Factor	RR (95% CI)	P	Overall P
CMV Serostatus			0.92
Recipient-, Donor-*	1.0		
Recipient-, Donor+	0.93 (0.65-1.33)	0.69	
Recipient+	0.99 (0.78-1.27)	0.96	
Donor Type			0.40
Matched sibling*	1.0		
MM related/URD	1.03 (0.76-1.40)	0.84	
UCB	0.81 (0.54-1.21)	0.30	
Conditioning			0.34
Myel. TBI	1.0		
Myel. No TBI	0.71 (0.45-1.12)	0.14	
Non-myeloablative	0.99 (0.62-1.56)	0.95	
GvHD Prophylaxis			0.42
Mtx+- ATG/pred	1.0		
T-cell Depletion	1.23 (0.65-2.36)	0.52	
CsA+ other	0.99 (0.56-1.76)	0.97	
Disease Risk			<0.001
Standard*	1.0		
High	1.62 (1.28-2.06)	<0.001	

MacMillan, 2009

Multivariate Model: Predictors of 2 year Survival

	RR	Overall P	% change in RR from D14	Adjusted † Likelihood Ratio	C‡ (S.E.)	P 14v.28	P 14v.56	P 28v.56
Day 14 response		<0.001		59.30	0.61 (0.02)	<0.001	<0.001	0.68
CR	1.0							
PR	1.13							
NR	1.71							
Day 28 response		<0.001		92.07	0.68 (0.02)			
CR	1.0							
PR	0.76		-49%					
NR	2.21		+29%					
Day 56 response		<0.001		96.72	0.68 (0.03)			
CR	1.0							
PR	0.68		-69%					
NR	2.51		+30%					

CTN 0302

GVHD
Responses

CR 33%
PR 26%
NR 40%

Baseline Characteristics	Overall	CR (N=60)	PR (N=46)	NR (N=72)	Chi-square p- value
Donor Source					0.536
Related	84	25	24	34	
Unrelated	94	35	22	36	
Conditioning Regimen					0.786
Myeloablative	116	39	28	47	
Non-ablative	62	21	18	23	
Graft source					0.073
Bone Marrow	44	19	11	12	
PBSC	109	31	26	52	
Cord Blood	25	10	9	6	
Age					0.694
<35	46	18	12	16	
35-54	72	21	21	29	
>=55	60	21	13	27	
Acute GVHD Grade					0.021
grade 0 or I	22	8	4	11	
grade II	101	40	30	30	
grade III or IV	55	12	12	31	

Day 14 Response	Day 28 Response						Total
	CR without later flare	CR with later flare	PR without later flare	PR with later flare	Death	Other Alive	
CR without later flare	19	0	0	0	0	0	19
CR with later flare	2	27	4	2	0	6	41
PR without later flare	7	0	5	0	1	3	16
PR with later flare	0	17	0	10	0	3	30
Death	0	0	0	0	2	0	2
Other Alive	3	6	4	5	9	45	72
Total	31	50	13	17	12	57	180

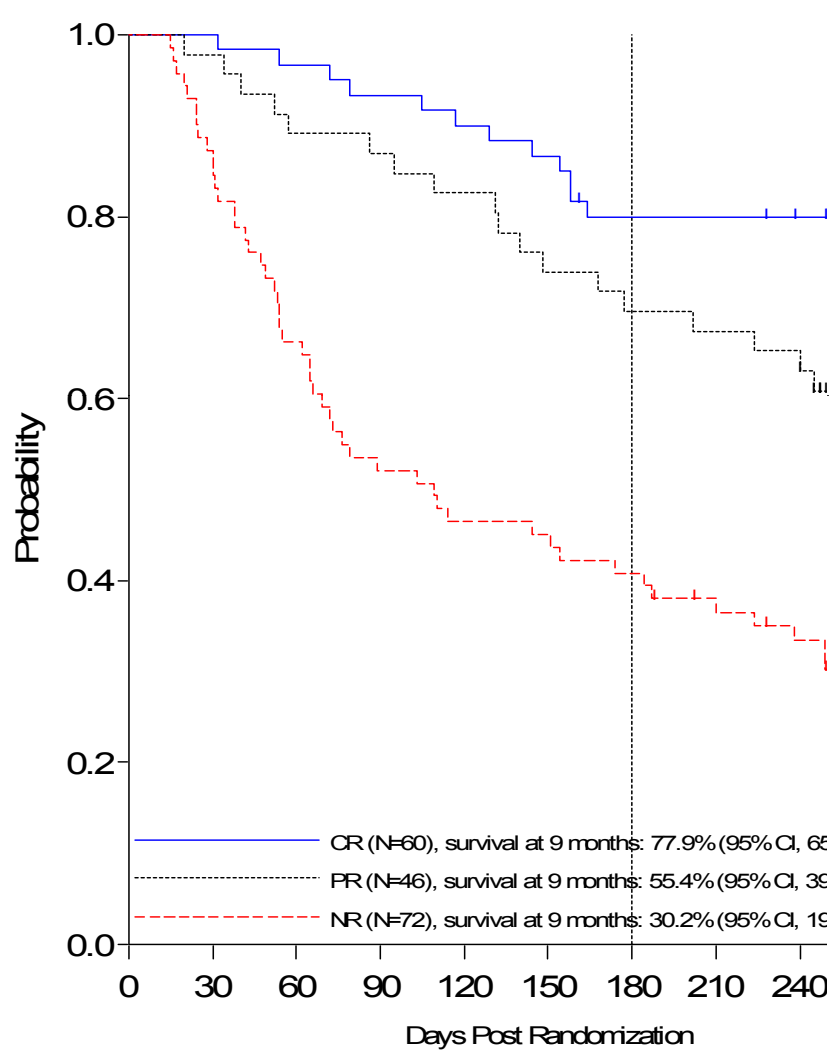
Day 14 Response	Day 56 Response						Total
	CR without later flare	CR with later flare	PR without later flare	PR with later flare	Death	Other Alive	
CR without later flare	18	0	0	0	1	0	19
CR with later flare	14	18	2	1	1	5	41
PR without later flare	7	0	4	0	3	2	16
PR with later flare	5	18	4	1	1	1	30
Death	0	0	0	0	2	0	2
Other Alive	8	17	6	0	24	17	72
Total	52	53	16	2	32	25	180

0302: Survival after initial treatment

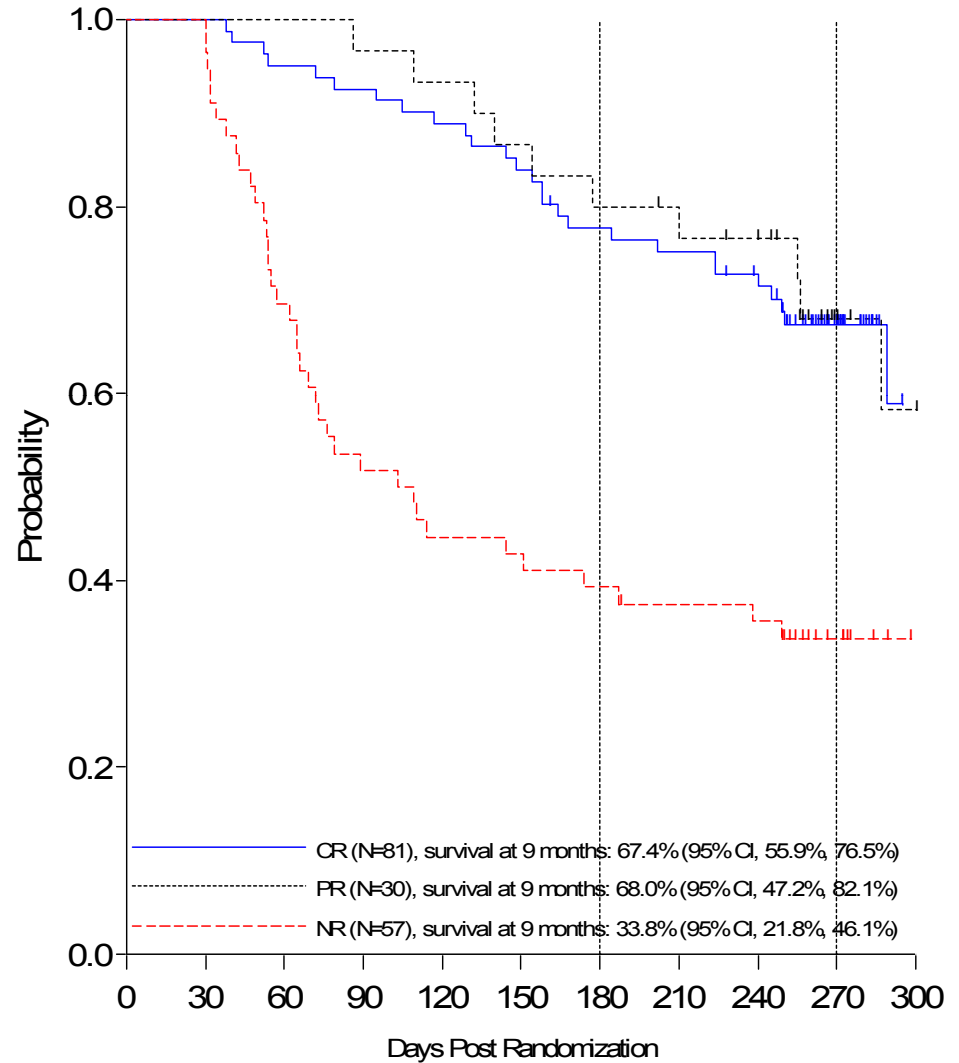
Time Points	Response Status	Estimate at 6 month (Day 180) (95% CI)	Estimate at 9 month (Day 270) (95% CI)	P-value
Day 14	CR	80.0% (67.4%, 88.1%)	77.9% (65.0%, 86.6%)	<0.0001
Day 14	PR	69.6% (54.1%, 80.7%)	55.4% (39.6%, 68.6%)	
Day 14	NR	40.8% (29.4%, 51.9%)	30.2% (19.9%, 41.2%)	
Day 28	CR	77.7% (67.0%, 85.3%)	67.4% (55.9%, 76.5%)	<0.0001
Day 28	PR	80.0% (60.8%, 90.5%)	68.0% (47.2%, 82.1%)	
Day 28	NR	39.3% (26.6%, 51.7%)	33.8% (21.8%, 46.1%)	
Day 56	CR	81.9% (73.1%, 88.0%)	71.2% (61.2%, 79.1%)	0.0001
Day 56	PR	66.7% (40.4%, 83.4%)	61.1% (35.3%, 79.2%)	
Day 56	NR	45.8% (25.6%, 64.0%)	33.3% (15.9%, 51.9%)	

Survival after GVHD therapy

Day 14 response



Day 28 response

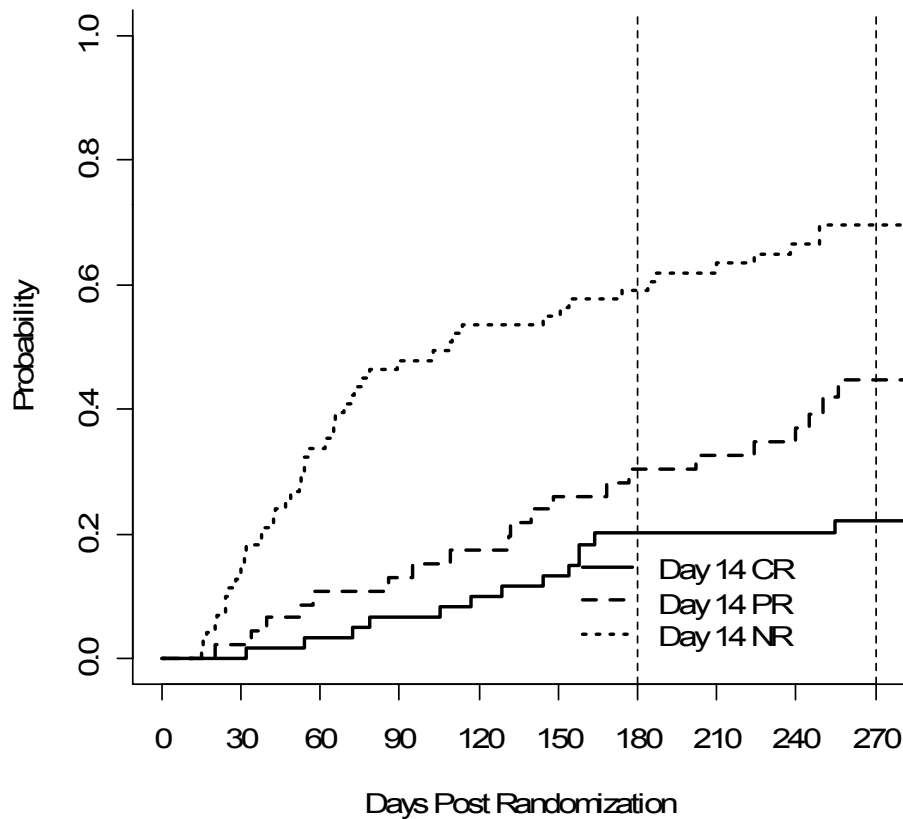


Non-relapse mortality after acute GVHD

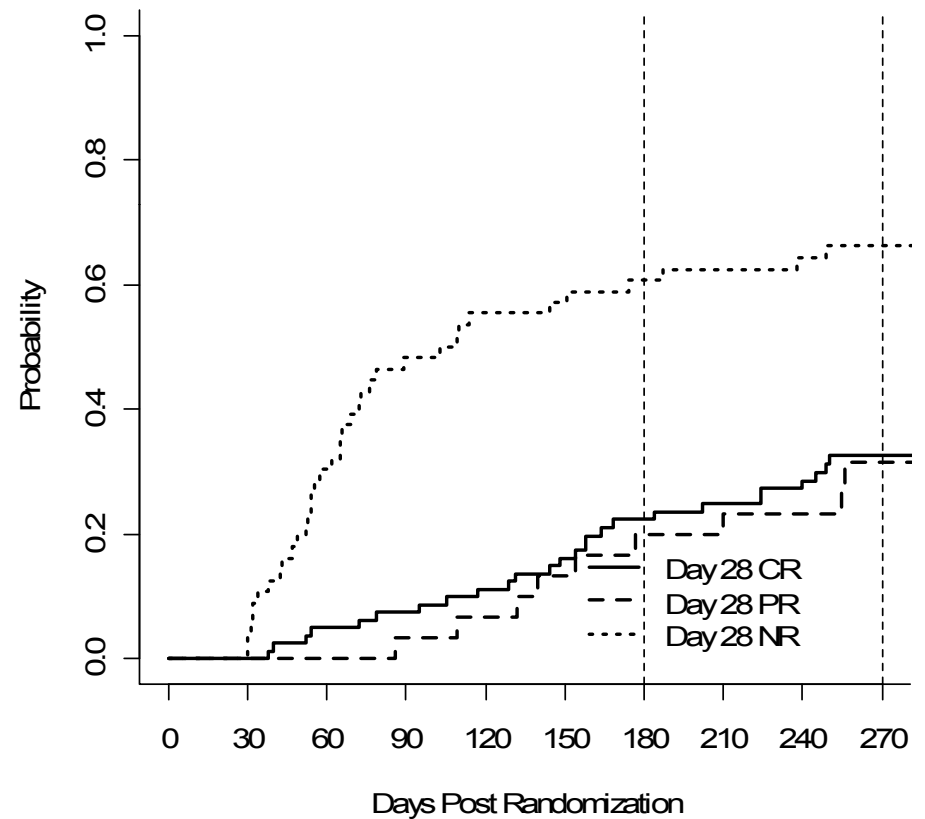
Day 14 response

Day 28 response

Cumulative Incidence of Non-Relapse Mortality



Cumulative Incidence of Non-Relapse Mortality



Censored by earlier relapse

Predictors of Survival: Multivariate model

Variable	Level	RR	Lower	Upper	p-value
Donor Type	Related	1.00			
	Unrelated	1.80	1.12	2.91	0.016
Graft Type	BM	1.00			0.020*
	PBSC	1.58	0.93	2.68	0.087
	CB	0.60	0.26	1.38	0.234
Grade at entry	0-1	1.00			0.024*
	2	1.04	0.54	2.03	0.897
	3-4	1.99	0.97	4.05	0.059

Adjusted predictors of Survival

Variable	Level	n	RR	Lower	Upper	p-value
Day 14	CR	60	1.00			
	PR	46	1.99	1.02	3.87	0.043
	NR	70	4.44	2.48	7.95	<0.001
Day 28	CR	81	1.00			
	PR	30	0.98	0.48	1.99	0.957
	NR	56	2.96	1.82	4.83	<0.001
Day 56	CR	105	1.00			
	PR	18	1.34	0.62	2.93	0.458
	NR	24	4.70	2.54	8.71	<0.001
Most recent	CR		1.00			
	PR		1.11	0.53	2.31	0.79
	NR		5.22	3.17	8.62	<0.001

Predictors of Survival: Impact of flares

Variable	Level	n	RR	Lower	Upper	p-value
Best prior response	NR	39	1.00			
	CR	121	0.12	0.06	0.22	<0.001
	PR	18	0.25	0.12	0.51	<0.001
Flare (prior CR only)	No	34	1.00			
	Yes	87	1.71	0.89	3.29	0.105

Predictive model for NRM

Time	Response	NRM	Alive or Relapse	Kappa
D14	Not CR	51	68	0.246
	CR	7	52	
D14	Not CR+PR	41	32	0.413
	CR+PR	17	88	
D28	Not CR	45	53	0.284
	CR	13	67	
D28	Not CR+PR	41	27	0.461
	CR+PR	17	93	
D56	Not CR	43	31	0.451
	CR	15	89	
D56	Not CR+PR	39	17	0.535
	CR+PR	19	103	

Predictive model for Mortality

Time	Response	Dead	Alive	Kappa
D14	Not CR	58	61	0.235
	CR	12	47	
D14	Not CR+PR	44	29	0.357
	CR+PR	26	79	
D28	Not CR	52	46	0.296
	CR	18	62	
D28	Not CR+PR	46	22	0.456
	CR+PR	24	86	
D56	Not CR	51	23	0.510
	CR	19	85	
D56	Not CR+PR	45	11	0.561
	CR+PR	25	97	

Conclusions

- Remarkable concordance of 2 data sets
- Day 14 CR somewhat but
Day 28 CR/PR best predicts NRM & survival
Day 56 CR/PR has similar predictive associations
- Modest effect of flare after CR

Though later (and other) endpoints need attention
[cGVHD, infections, toxicity, *steroid sparing*]

Day 28 CR+PR best predicts the
lowest 6-24 month mortality and NRM

**Day 28 (or later) CR/PR (Overall RR) should be
the primary endpoint for trials of aGVHD therapy**