

F.D.A Workshop: Clinical Trial Endpoints for Patients with Acute GVHD

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Financial Conflicts of Interest

- None

"The future will be better tomorrow."

The goal of this review was to determine the prognostic value of response to systemic therapy for treatment of aGVHD at day +7, +14, +28.

QUESTIONS

- I. Is response simply a surrogate of favorable patient and/or acute GVHD characteristics?

- II. Is response an independent predictor of outcome?
 - NRM @ 6 months post therapy
 - Overall survival @ 2 years post therapy

STUDY POPULATION

83 patients were enrolled onto two Phase III randomized trials for patients with newly diagnosed acute GVHD at M.D. Anderson between 2000-2008.

Randomized Phase III Trial Infliximab (PI: Daniel R. Couriel)

- Single-Center, Phase III trial for pts with newly diagnosed Acute GVHD comparing MP (2mg/kg) vs. Infliximab + MP
- Primary Endpoint was response rate @ 1 month.
- 57 pts enrolled between 2000-2003.
- Closed early after analysis determined no difference between Infliximab arm and control.

BMT CTN Randomized Phase II (PI: Daniel Weisdorf)

- Multi-center, phase II trial for pts with newly diagnosed Acute GVHD.
- Four arms: MP (2mg/kg) +
 - Etanercept
 - Denileukin
 - Mycophenolate
 - Pentostatin
- Primary Outcome= Day 28 CR rate compared against historical rate of 35%.
- 26 pts enrolled at M.D. Anderson between 2005-2008.
- Mycophenolate found to have highest Day 28 CR rate of 60%.

Statistical Methods

- I. Correlation between patient, transplant, and aGVHD characteristics and response to systemic therapy was assessed by Chi square test.
- II. Predictors of overall survival and NRM since day of response were evaluated in a landmark analysis using Cox's proportional hazards model on univariate and multivariate analysis
- III. Cumulative Incidence of NRM was estimated considering death due to recurrence/persistence of malignancy as competing risk (results were comparable when disease recurrence was considered a competing risk).

Patient Characteristics-I Assigned Upfront Therapies

	N	%
Randomized Phase III Infliximab		
MP (2mg/kg)	28	49
Infliximab + MP	29	51
TOTAL	57	69
Randomized Phase II BMT CTN		
Etanercept + MP (2mg/ Kg)	5	19
Mycophenolate + MP	5	19
Denileukin + MP	6	23
Pentostatin + MP	10	38
TOTAL	26	31

Patient Characteristics-II

	N	%
Infliximab	57	69
BMT CTN	26	31
Age , median years (range)	49 (20-70)	
Male / Female	52/ 31	63/ 37
Donor / Recipient Gender		
Female / Male	19	23
Male / Female	17	20
Male/ Male or FM/ FM	46	57
Diagnosis		
Acute Leukemia	43	52
Others	40	48
Conditioning Regimen		
Myeloablative	43	52
Other	40	48

Patient Characteristics-III

	N	%
Disease Status at Transplantation		
Remission	26	31
Active Disease	57	69
Donor Type		
Matched Sibling	41	49
Matched Unrelated	33	40
Mismatched	9	11
Stem Cell Source		
Peripheral Blood Stem Cells	45	54
Bone Marrow	38	46
GVHD Prophylaxis		
Tacrolimus/ MTX	72	87
Tacrolimus/MTX/Pentostatin	9	11
Other	2	2

GVHD Characteristics

	N	%
Acute Grade		
I	4	5
II	52	63
III / IV	27	32
Organ Involvement		
Skin Only	33	40
Visceral Organ Involvement	50	60
Days to aGVHD onset		
Median	25	
Range	9-83	
Days from onset to systemic therapy		
Median	2	
Range	0-81	

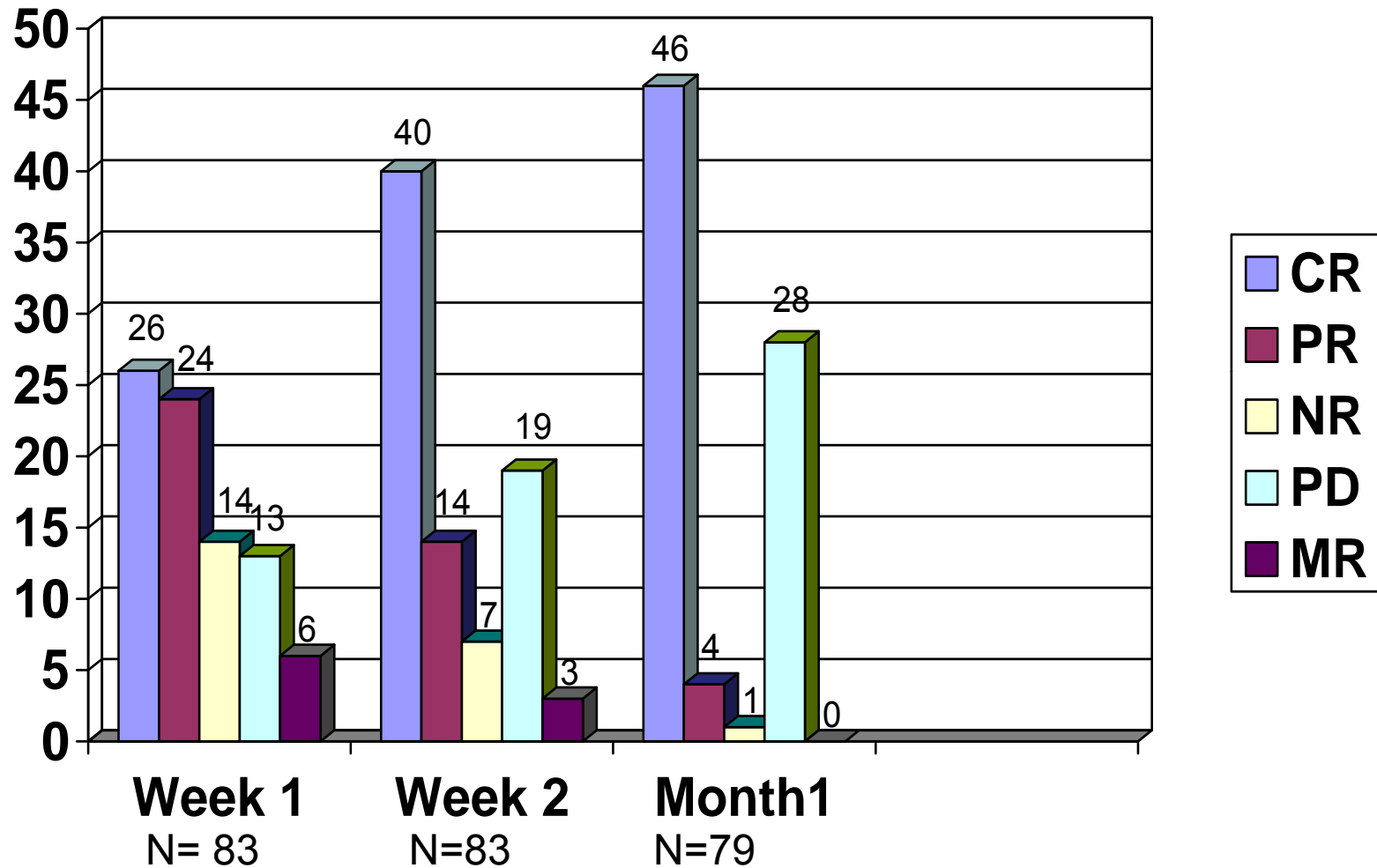
Definitions for Response

- Complete Response (CR)= complete resolution of all signs and symptoms of GVHD in all organs without intervening salvage therapies.
- Partial Response (PR)= improvement of one stage in one or more organs involved by GVHD without progression in others.
- Mixed Response (MR)= improvement in at least one involved organ with progression or newly developed GVHD in one or more organs.
- No Response (NR)= no improvement or deterioration in any organ within 14 days of therapy initiation.
- Progression (PD)= worsening in one or more organs by one or more stage without improvement in any involved organ.

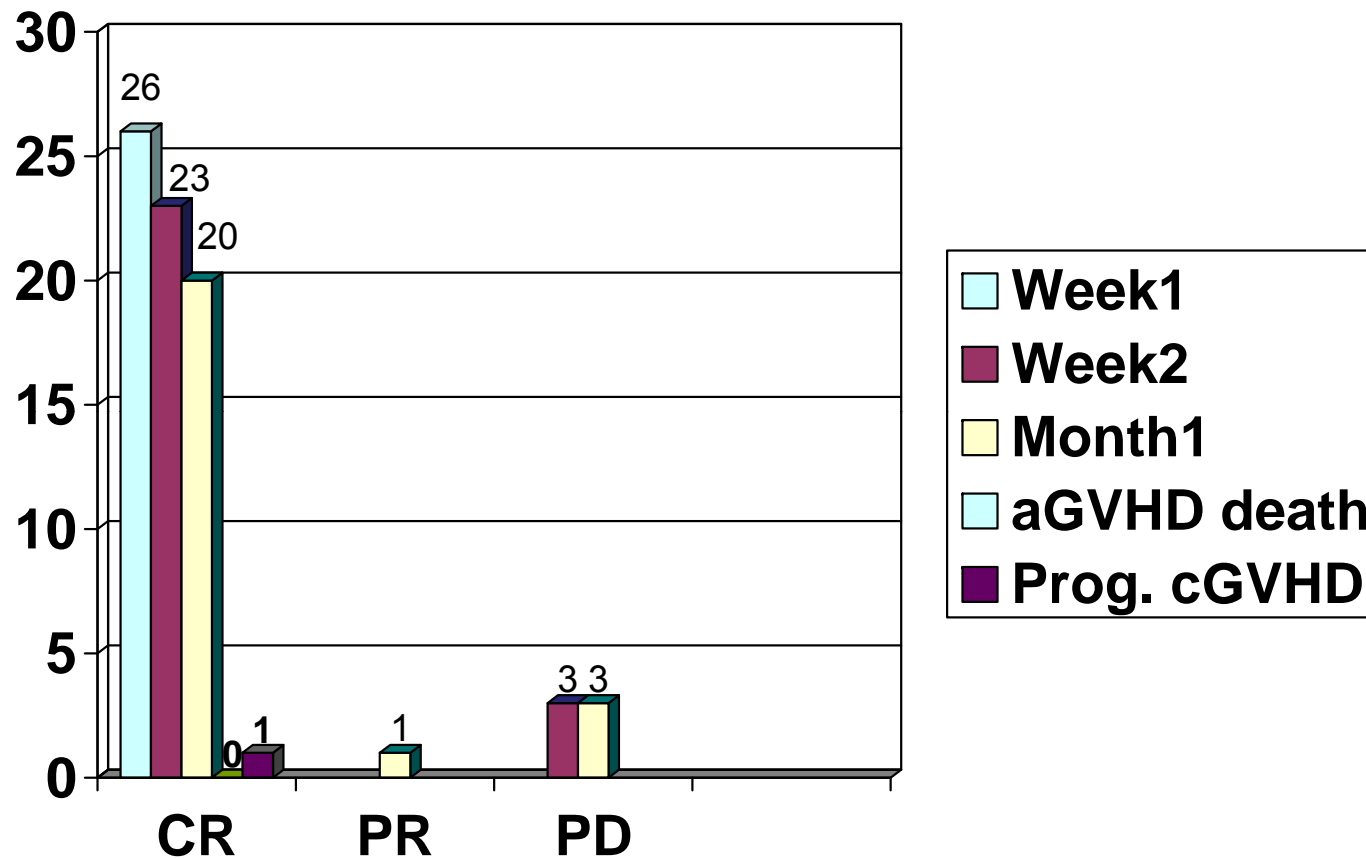
Distribution of Response Days 7, 14 & 28

	N / N	%
Day 7		
CR / PR	26 / 24	60
No Response	14	17
Progression	13	16
Day 14		
CR / PR	40 / 14	65
No Response	7	8
Progression	19	23
Day 28		
CR / PR	46 / 4	60
No Response	1	1
Progression	28	34
Missing/NE	4	4

Response Frequency at Weeks 1, 2 and 1 month

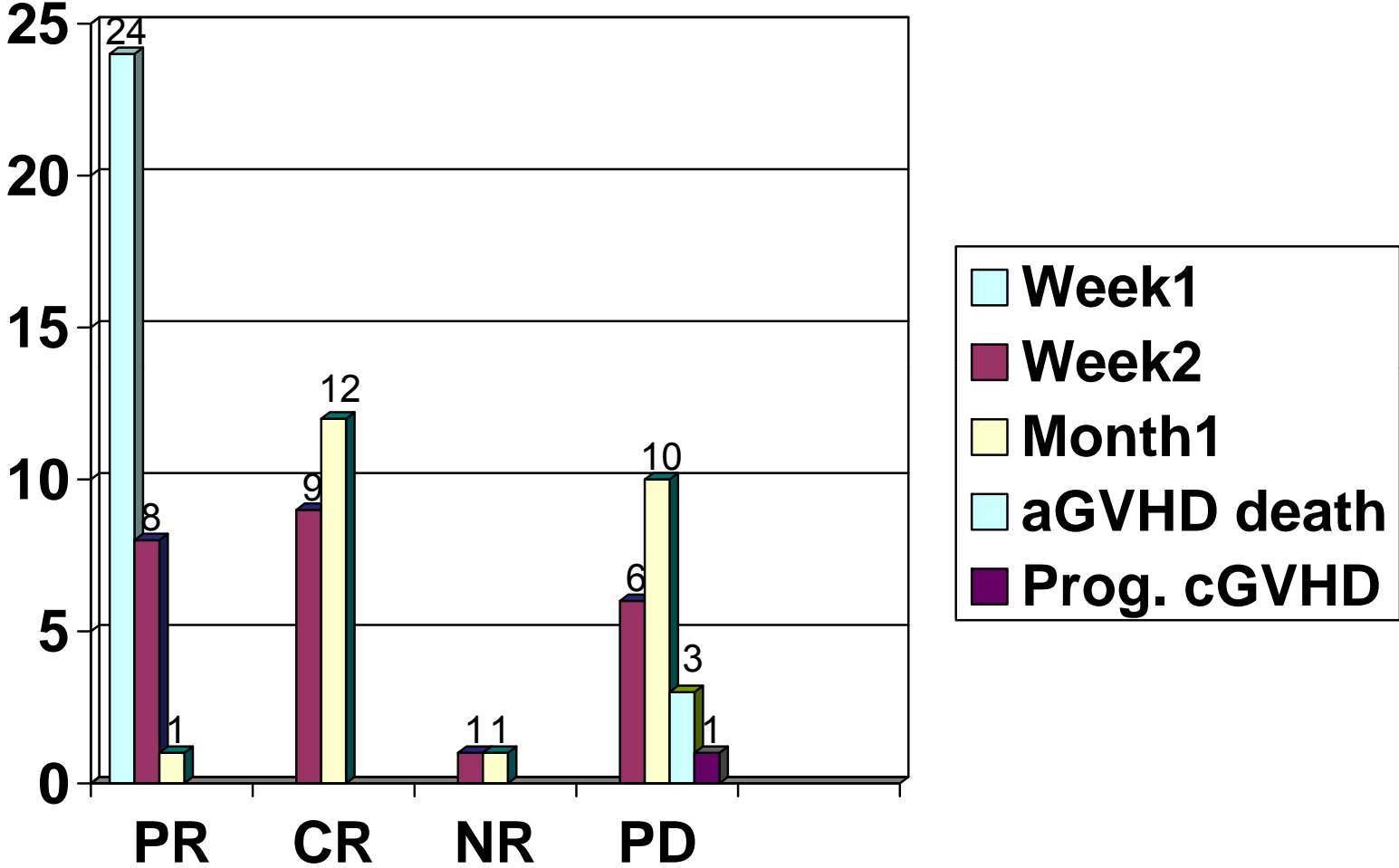


Response over time in 26 patients who were in CR Week 1



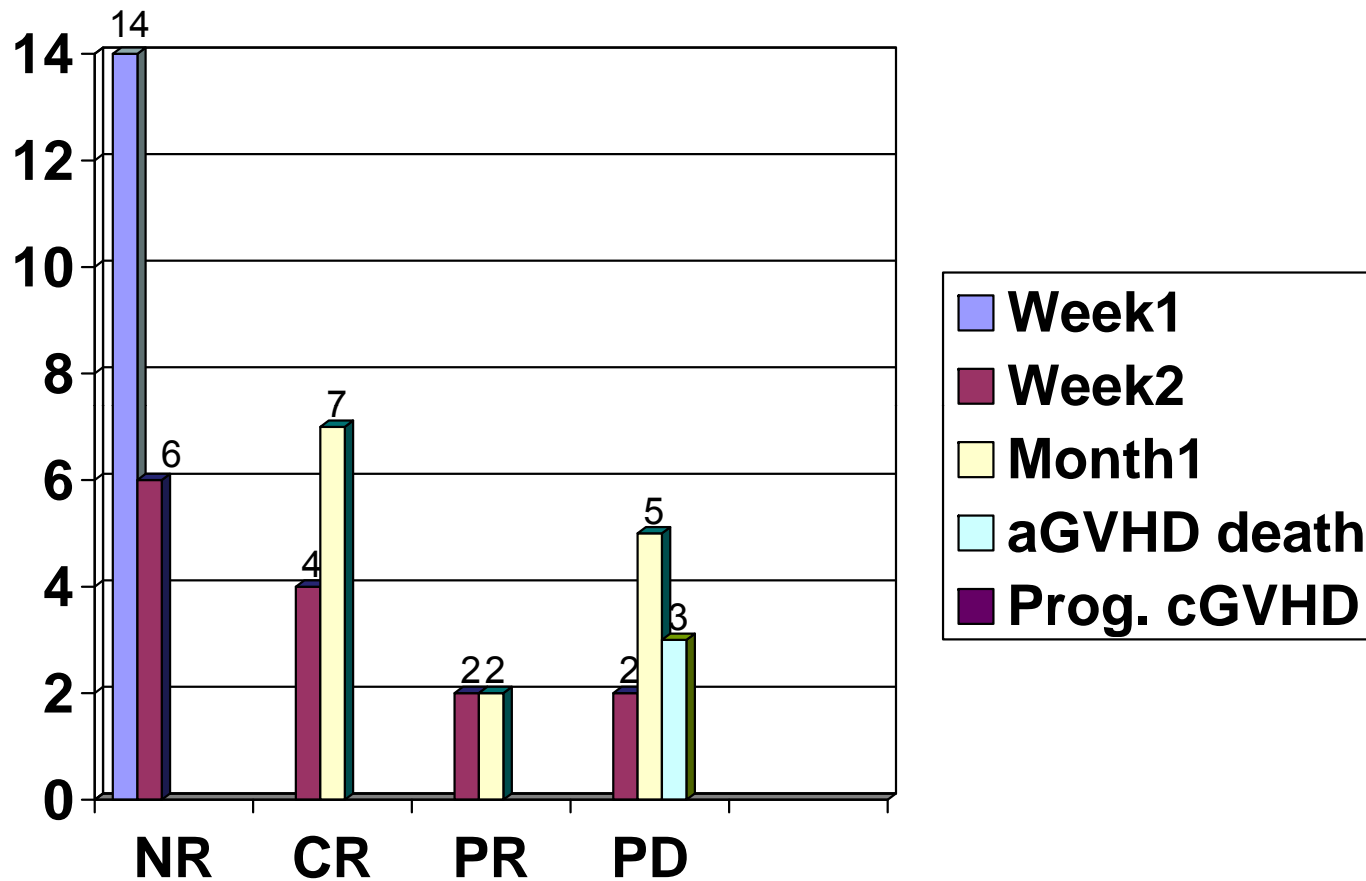
Status at 1 month: 20/26 still in CR, 3/26 PD; 2/26 unknown response

Response status over time for 24 patients in PR Week 1



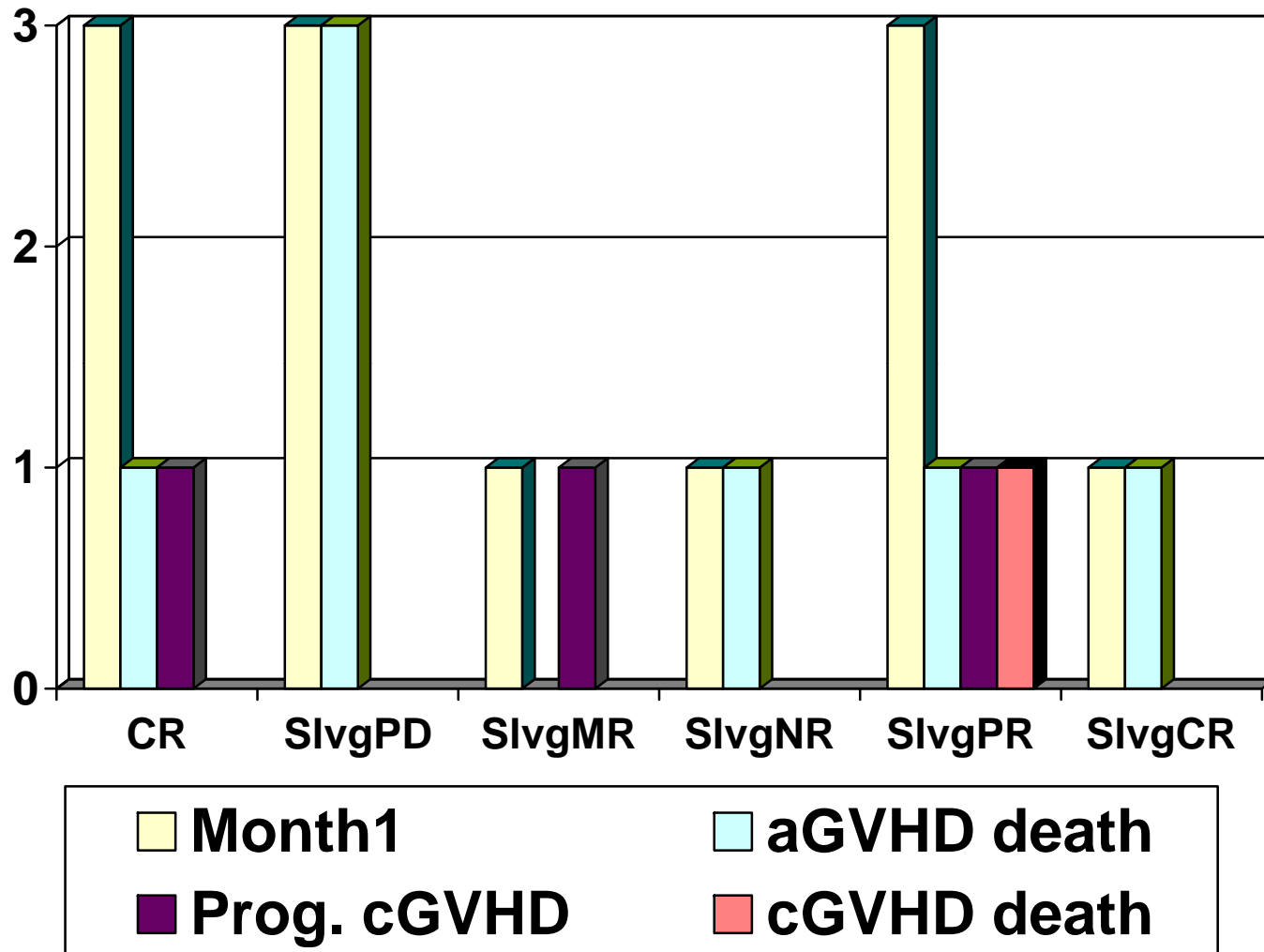
Status at 1 month: 12/24 convert to CR; 10/24 PD;
 low aGVHD death 3/24, low progressive cGVHD 1/24

Response over time in 14 patients who were NR Week 1



Status at 1 month: 7/14 convert to CR; 2/14 convert to PR; 5/14 PD

Status at 1 month of 12 patients with PD at Week 1
High aGVHD mortality irrespective of salvage therapy



Is Response Simply a Surrogate
of Favorable aGVHD and/or Patient
Characteristics?

Predictors for Day 28 Response GVHD Characteristics

	Responders (CR/PR) n/N (%)	Non- Responders n/N (%)	P-value
Acute GVHD Grade			
I-II	35 / 55 (64)	20 / 55 (36)	0.6
III-IV	15 / 26 (58)	11 / 26 (42)	
Organ Involvement			
Skin-only	21 / 32 (66)	11 / 32 (34)	0.6
Visceral Organ	29 / 49 (59)	20 / 49 (41)	

Predictors for Day 28 Response

Patient Characteristics

	Responders (CR/PR) n/N (%)	Non- Responders n/N (%)	P-value
Age, median (range)	49 yrs (20-67)	49 yrs (25-70)	0.6
BMT CTN Infliximab	16/24 (67) 34/57 (60)	8/24 (33) 23/57 (40)	0.5
Donor/ Recipient Gender Female / Male Others	10 /19 (53) 39/61 (64)	9/19 (47) 22 /61 (36)	0.4
Disease Status Remission Active Disease	12/ 26 (46) 38/ 55 (69)	14/ 26 (54) 17/ 55 (31)	0.05

Predictors for Day 28 Response

Transplant Characteristics

	Responders (CR/PR) n/N (%)	Non- Responders n/N (%)	P-value
Stem Cell Source			
Peripheral Blood Stem Cell	28/ 43 (65)	15/ 43 (35)	0.5
Bone Marrow	22/ 38 (58)	16/ 38 (42)	
Conditioning Regimen			
Ablative	27/ 43 (63)	16/ 43 (37)	0.8
Non-Ablative	23/ 38 (61)	15/ 38 (39)	
Donor Type			
Matched Sibling	26/ 39 (67)	13/ 39 (33)	0.4
Matched Unrelated	19/ 33 (58)	14/ 33 (42)	
Mismatched	5/ 9 (56)	4/ 9 (44)	

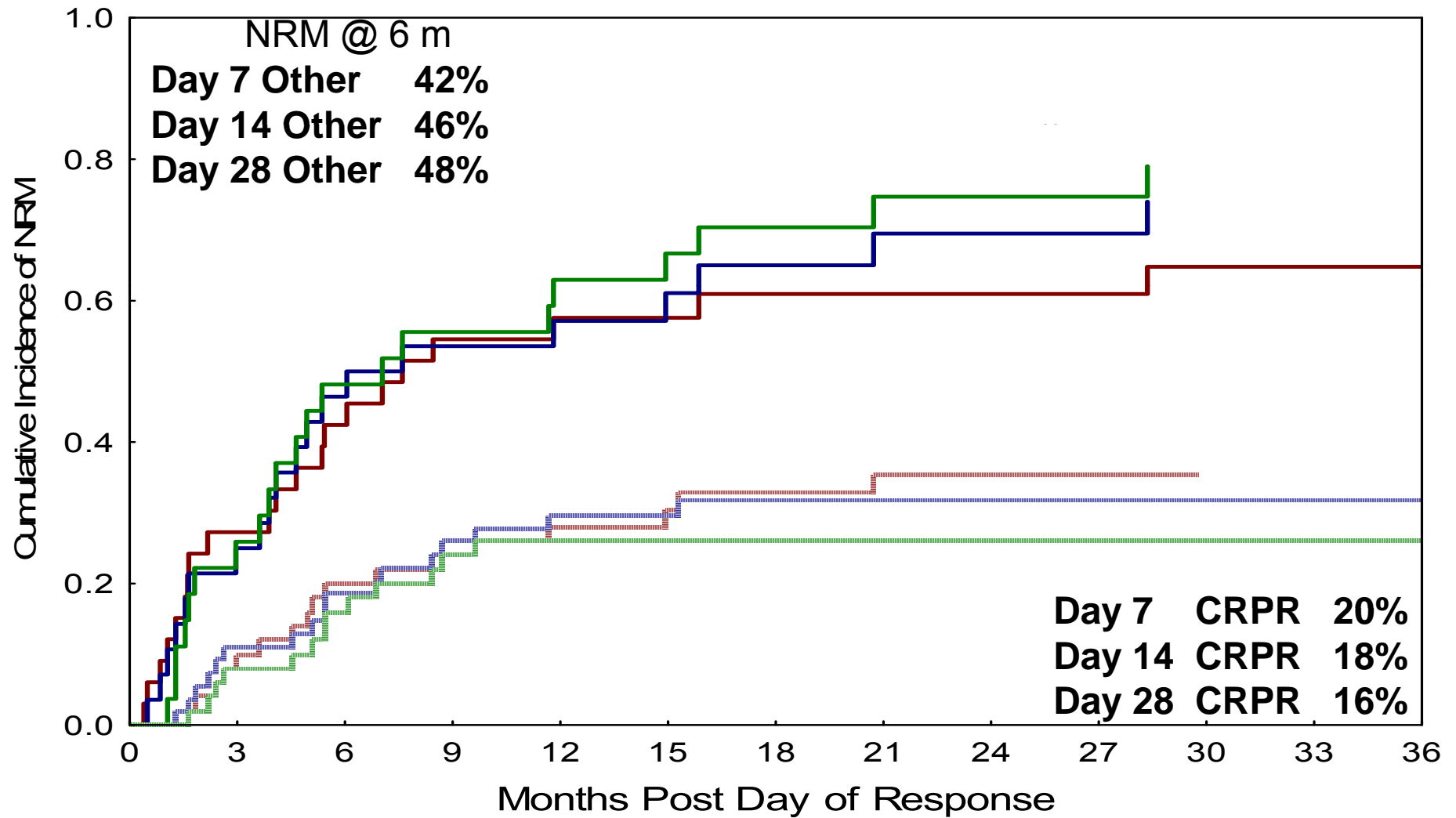
Is Response
an Independent Predictor
of Outcome?

SUMMARY OF OUTCOMES

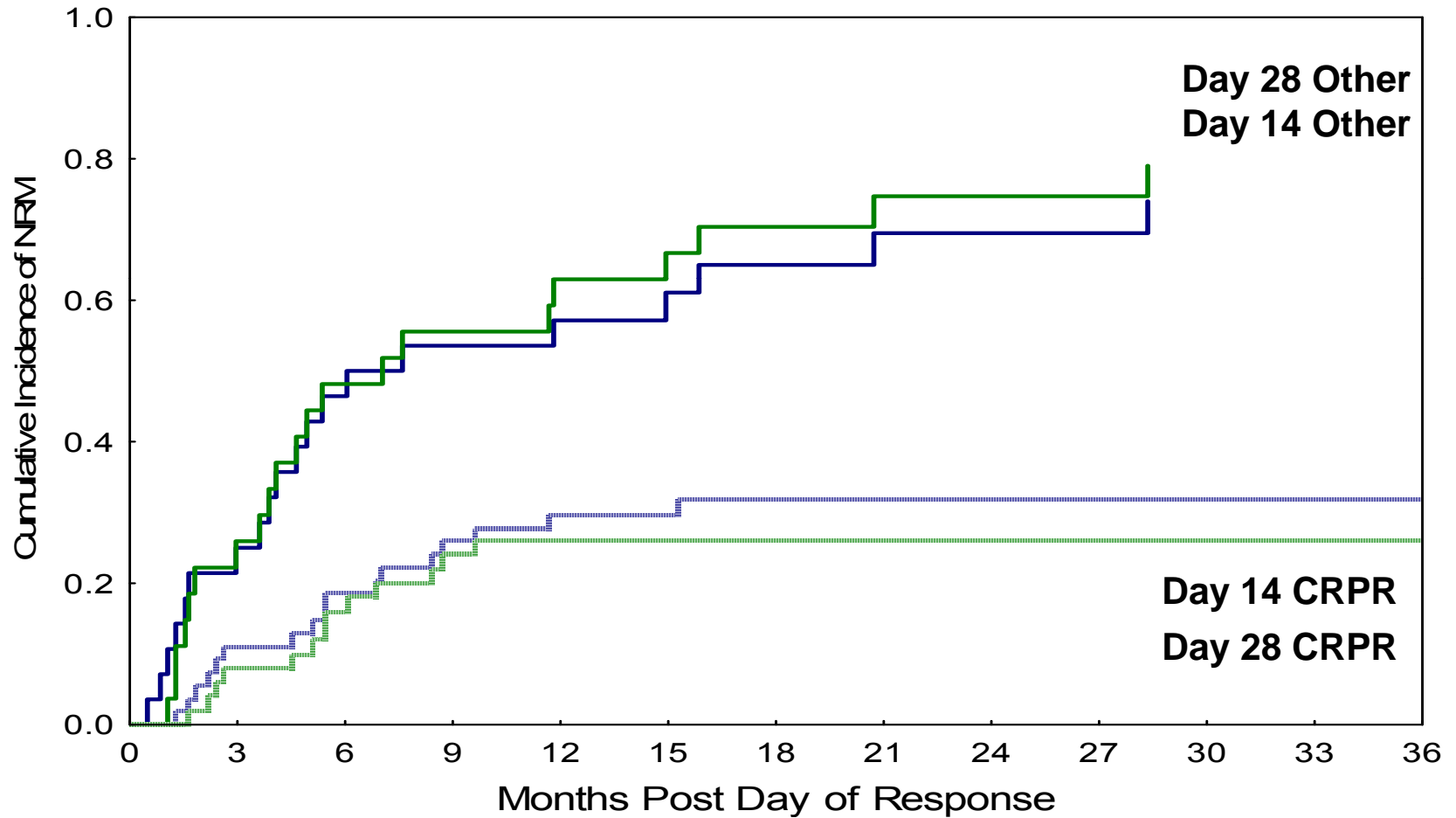
	Median Follow-up in surviving pts (mn)	%OS* @ 6m 37 deaths	%OS* @ 24m 58 deaths	%NRM* @6m 24 NRM	%NRM* @ 24m 37 NRM
DY14 CRPR	36 (12-79)	59%	29%	18%	32%
DY14 OTHER	66 (15-79)	46%	27%	46%	69%

* Estimates as of time of response

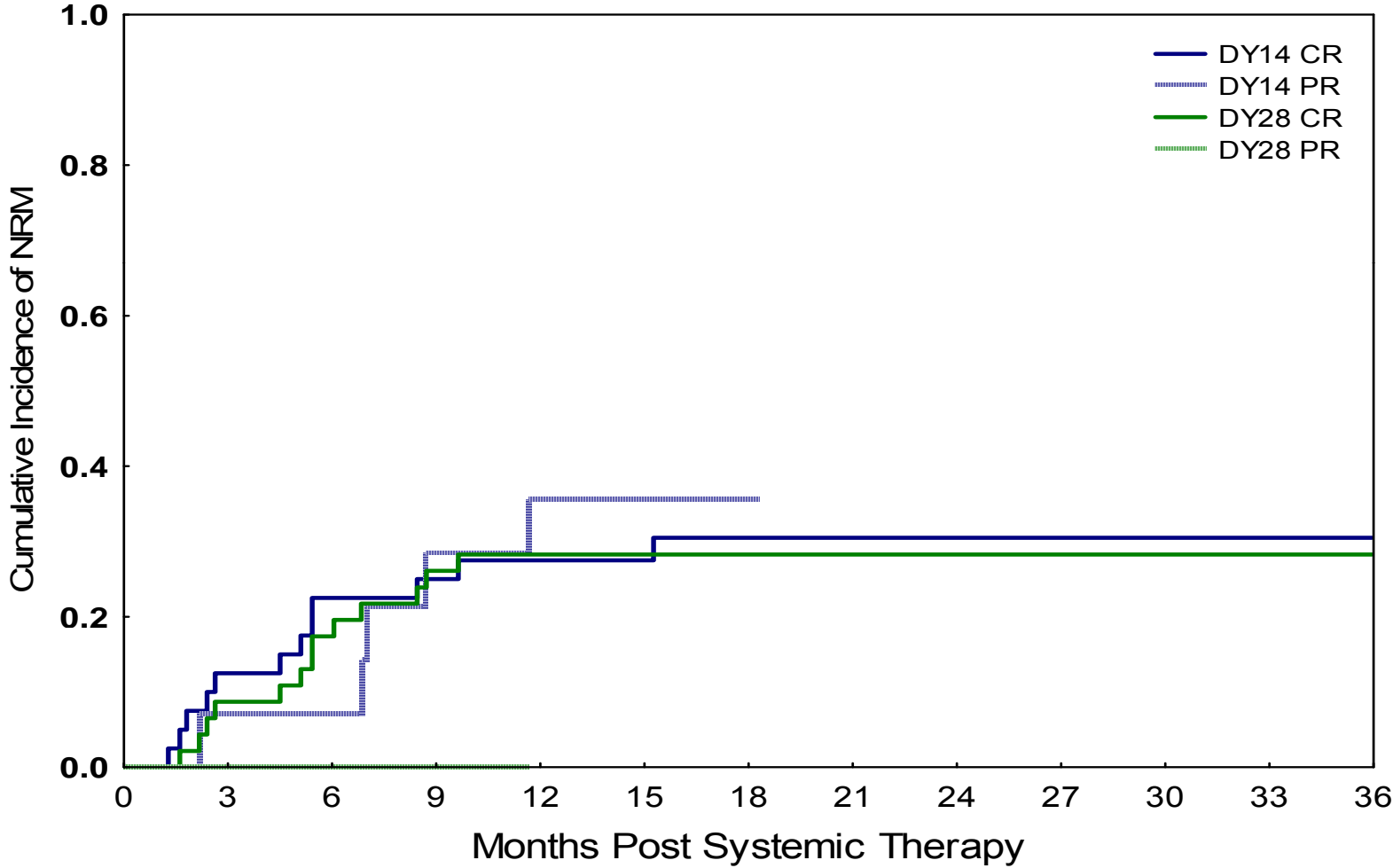
Non-Relapse Mortality based on Response on Days 7, Day 14 and Day 28



Non-Relapse Mortality based on Response on Days 14 and Day 28



Response Status PR vs. CR



Predictors for NRM at 6 months

Significant Factors on Univariate and Multivariate Analysis-I

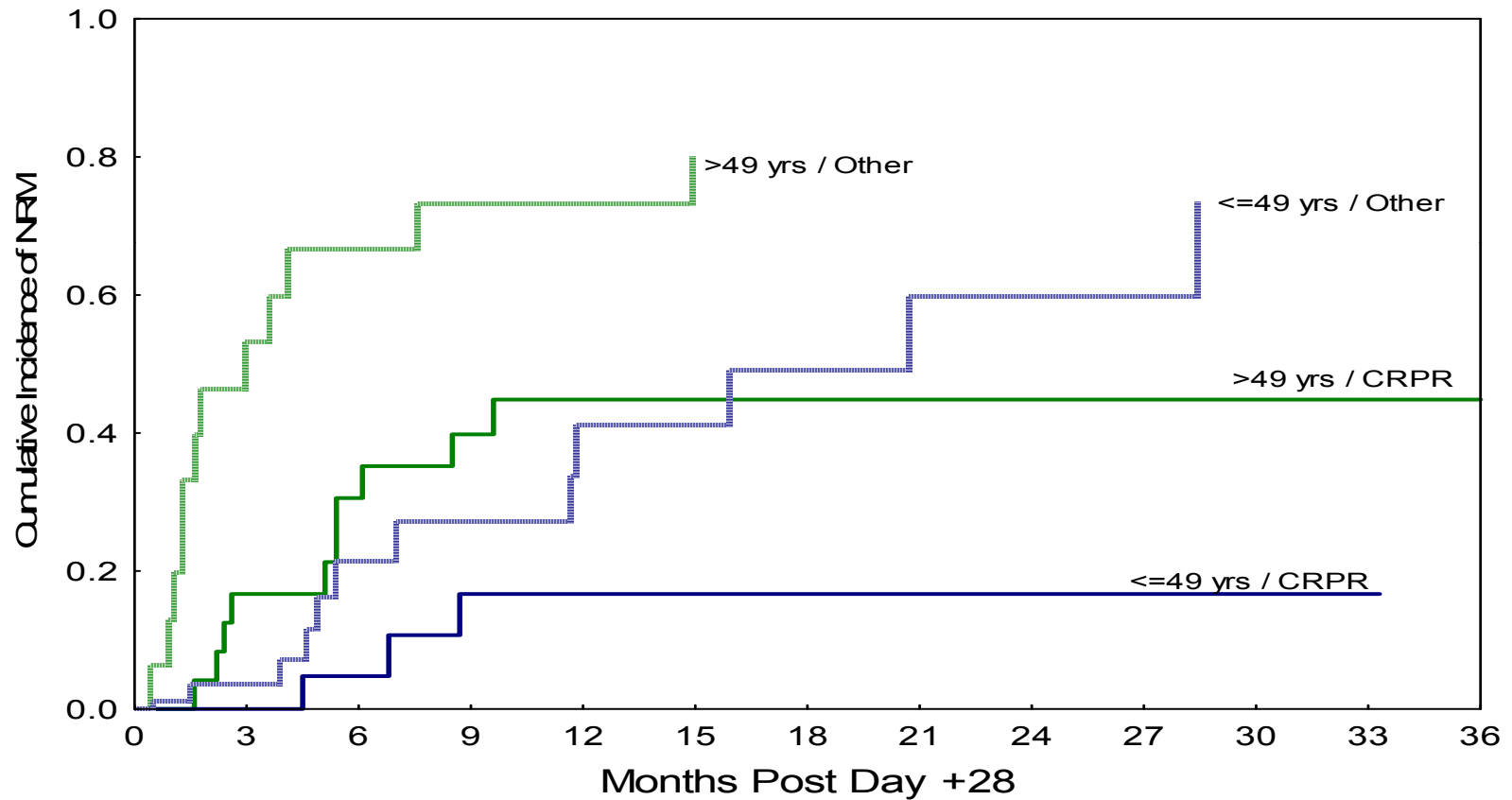
	HR Univar.	95% C.I.	P	HR Multivar.	95% C.I.	P
<u>D 14 Response</u>						
CR/PR	0.3	0.1- 0.8	0.01	0.3	0.1- 0.7	0.008
Other						
<u>Age</u>						
> 49 yrs	2.6	1.1- 6.4	0.03	2.9	1.2- 7.0	0.02
≤ 49 yrs						

Predictors for NRM at 6 months

Significant Factors on Univariate and Multivariate Analysis-II

	HR Univar.	95% C.I.	P	HR Multivar.	95% C.I.	P
<u>D 28 Response</u>						
CR/PR	0.3	0.1- 0.7	0.005	0.2	0.1- 0.6	0.002
Other						
Age						
> 49 yrs	2.9	1.1- 7.6	0.03	3.6	1.4- 9.3	0.009
≤ 49 yrs						

Age and Response Status on Day 28 Independently Predict for Non-relapse Mortality

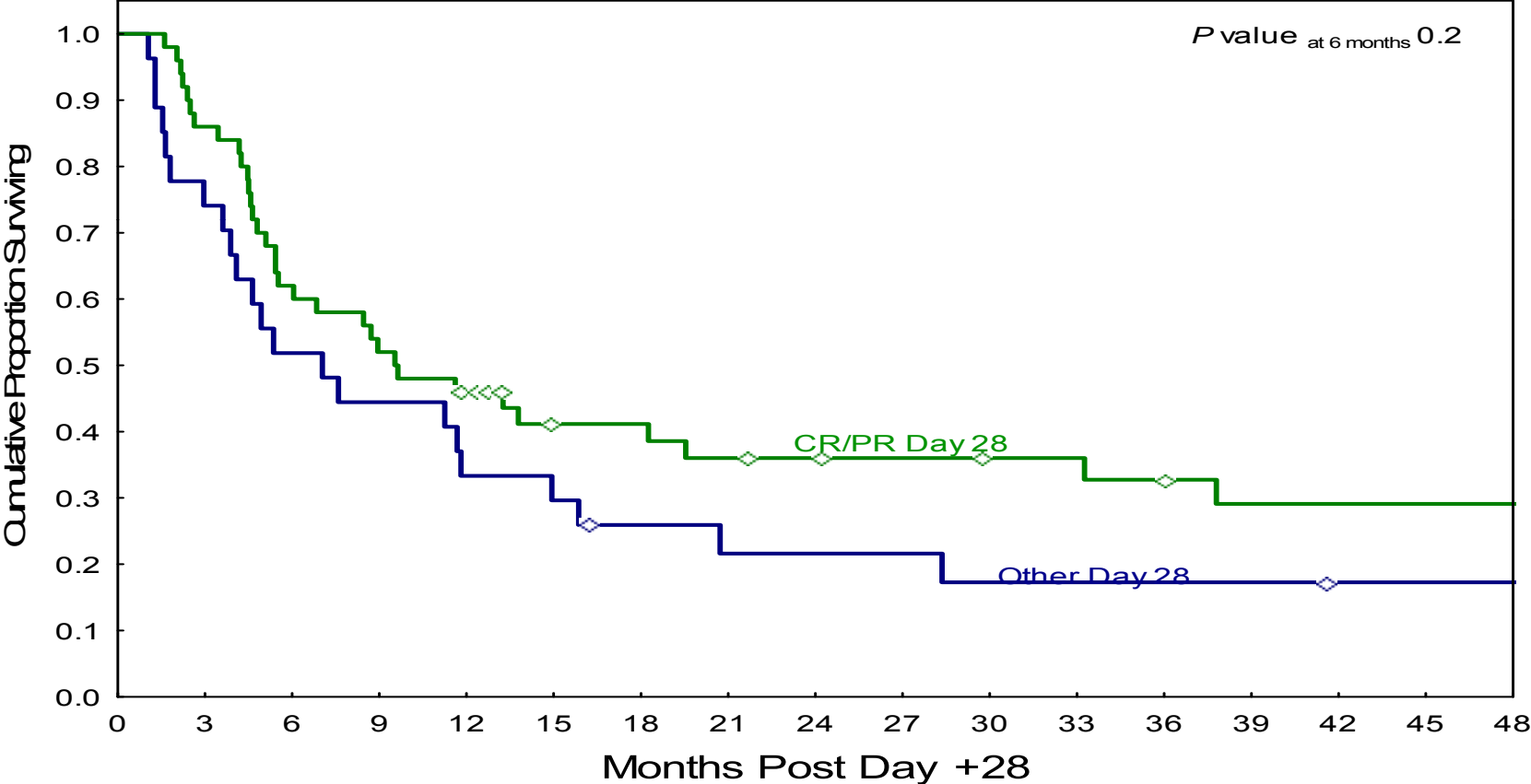


Predictors for NRM at 6 months

Non-Significant Factors

	HR DY14	95%C.I.	P	HR DY28	95%C. I.	P
BMT CTN vs. Infliximab	1.1	0.5-2.7	0.8	1.1	0.4-2.6	0.9
Skin-only AGVHD vs. Visceral Organ	0.9	0.4-2	0.8	1	0.4-2.4	0.9
AGVHD Grd I/ II vs. III/IV	0.6	0.3-1.4	0.2	0.6	0.3- 1.5	0.3
Donor/ Recipient Gender Female-> Male	1	0.4-2.6	0.2	1.2	0.5- 3	0.7
Matched Sibling donor	1.1	0.5-2.5	0.8	1.3	0.6- 3.2	0.5
Myeloablative Conditioning	0.7	0.3-1.6	0.4	0.5	0.2-1.3	0.2
Remission vs. active disease	0.7	0.3-1.6	0.4	0.9	0.3- 2.0	0.6
Acute Leukemia	1.0	0.4-2.5	0.9	1.0	0.4-2.4	0.9
PBSC vs. BM	2.1	0.85-5	0.1	2.3	0.9-6	0.1

Overall Survival post Day 28 CRPR vs. OTHER



Predictors for OS at 2 years post therapy

Univariate Analysis-I

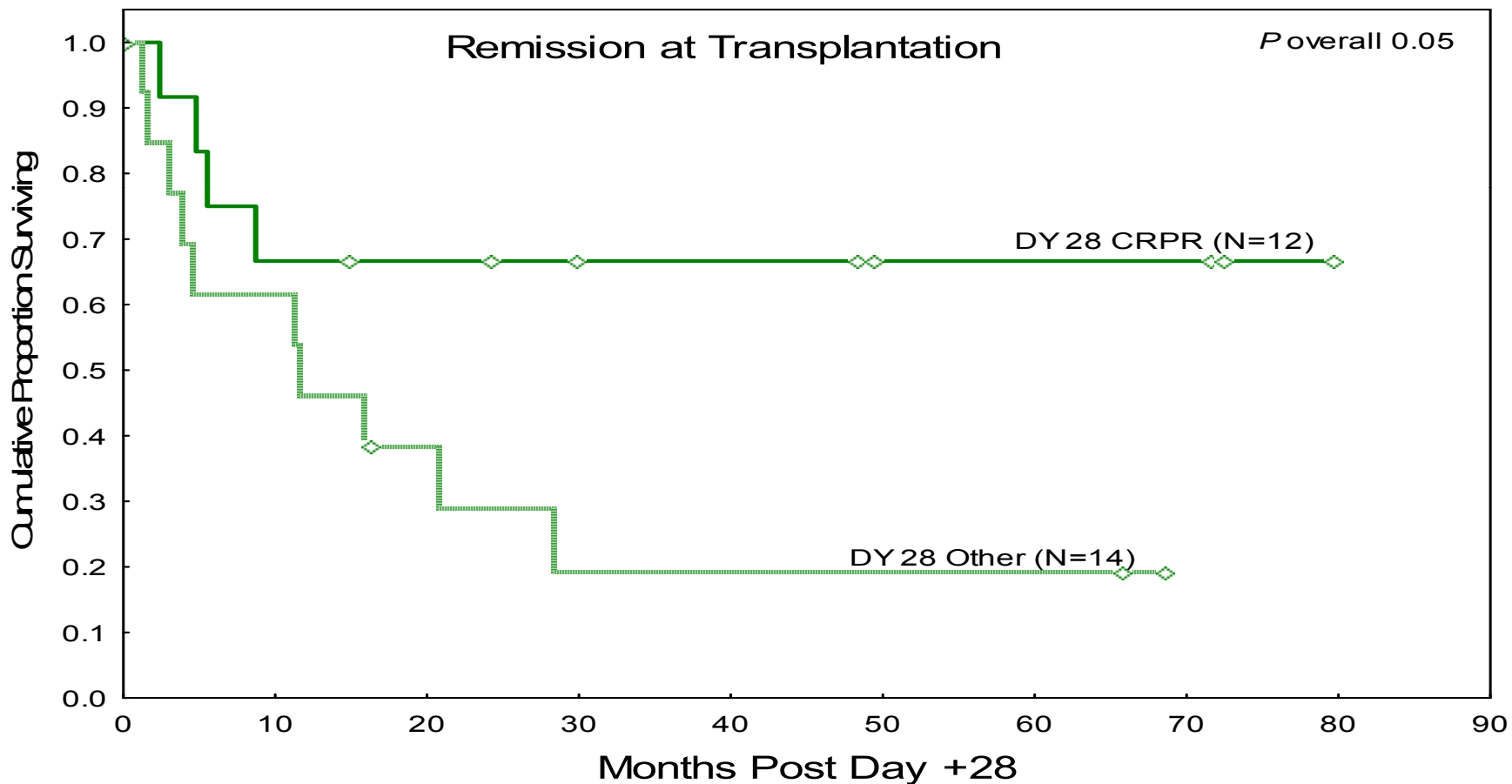
Factor	HR Univar.	95% C.I.	P
D 14 Response CR/PR	0.9	0.5-1.5	0.6
D 28 Response CR/PR	0.7	0.4-1.2	0.2
Disease Status Remission	0.5	0.3-0.96	0.04
Stem Cell Type PBSC	1.5	0.9-2.6	0.1
Age >49 yrs	1.3	0.8-2.3	0.3

Predictors for OS at 2 years post therapy

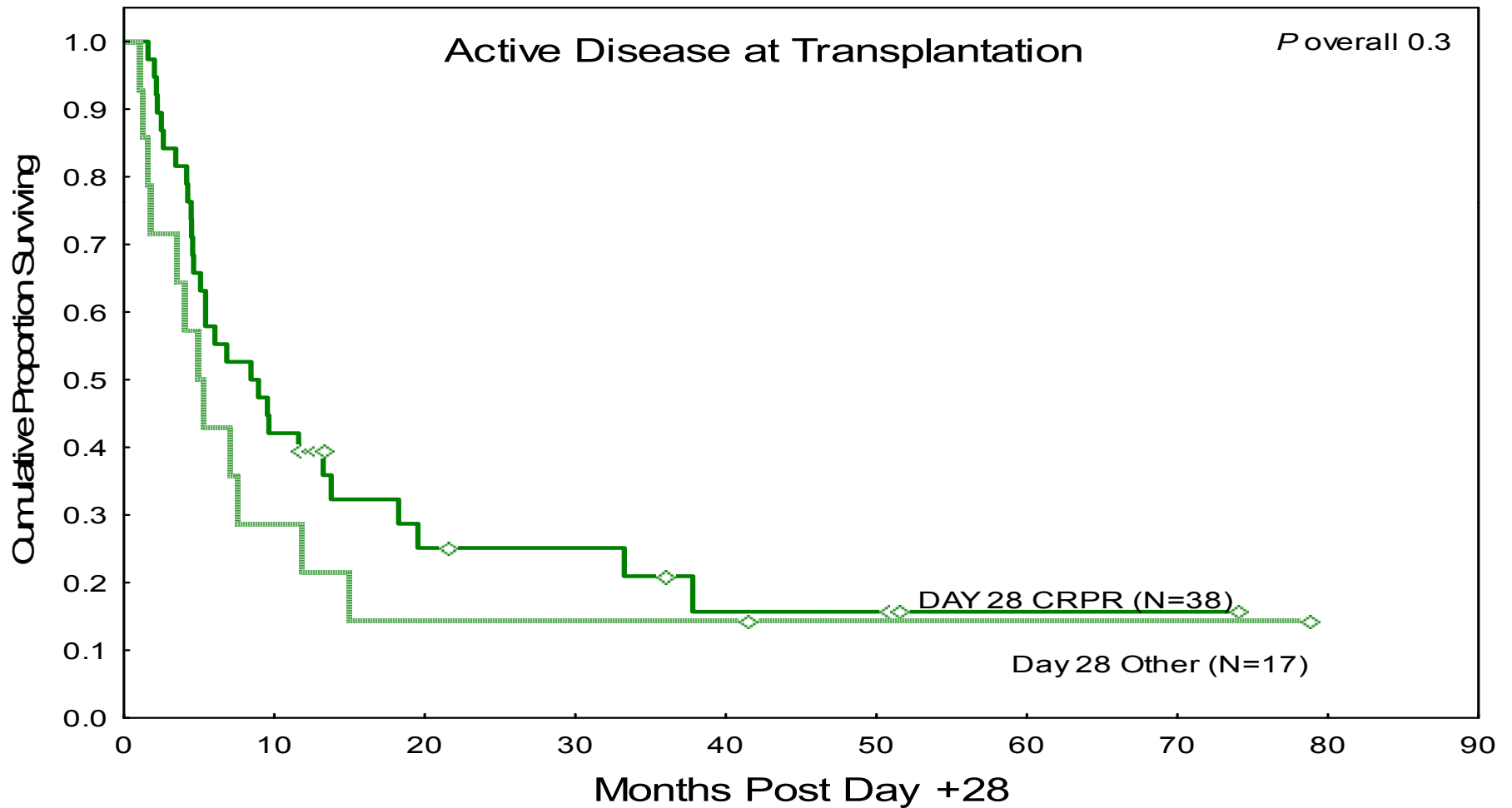
Univariate Analysis-II

	H.R Univar.	95% C.I.	P- value
BMT CTN Infliximab	0.9	0.5-1.6	0.6
Skin-only AGVHD Visceral Organ	1.4	0.8-2.5	0.2
AGVHD Gd I/ II AGVHD Gd III/ IV	0.8	0.4-1.3	0.3
Donor/ Recipient Gender Female-> Male Other	1	0.6-1.9	0.9
Matched Sib Others	1.1	0.7-1.9	0.7
Myeloablative Conditioning Other	0.9	0.5-1.5	0.7

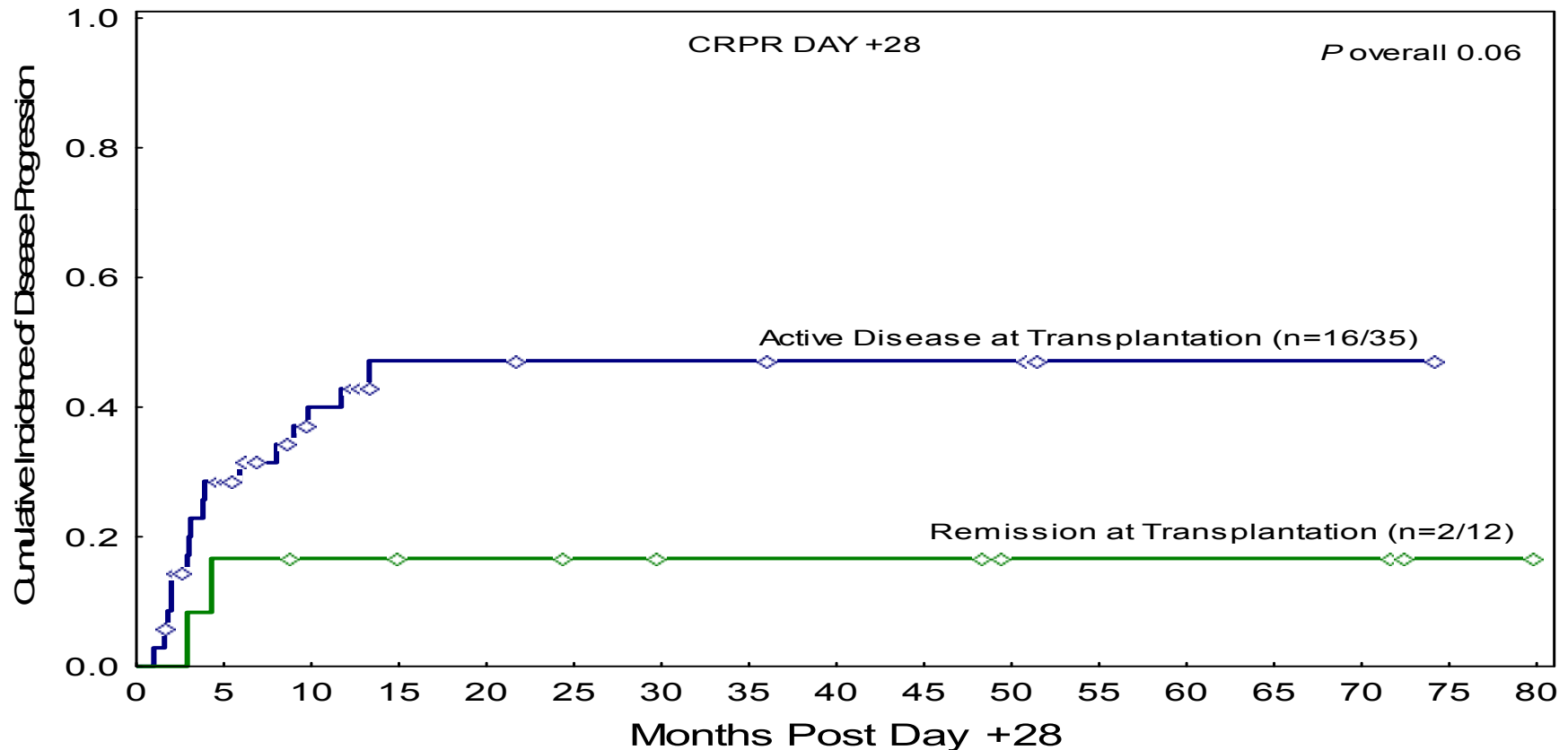
Overall Survival post Day 28 CRPR vs. OTHER Patients in Remission at Transplant



Overall Survival post Day 28 CRPR vs. OTHER Patients with Active Disease at Transplant



Disease Progression according to Disease Status at Transplant in CRPR Patients Day 28

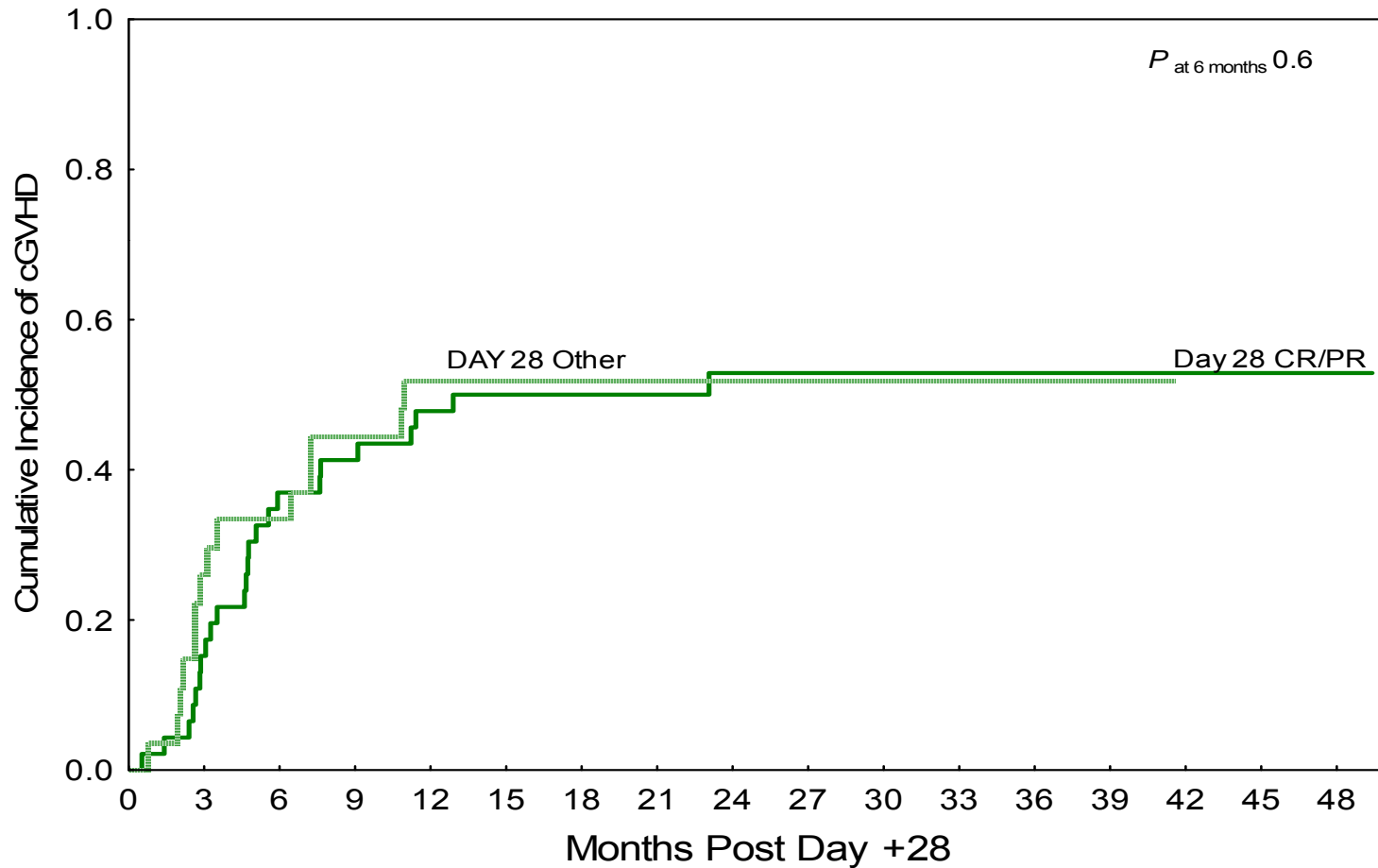


ONLY 2/12 patients in remission at transplant progressed

Causes of Death According to Response Day 28

	CR/PR N=33 (%)	Other N=26 (%)
Treatment Related	14 (42%)	24 (92%)
Disease Related	19 (58%)	2 (8%)

Cumulative Incidence of Chronic GVHD in Day 28 CRPR vs. OTHER



Steroid Dose According to Response

	DAY 28 CR/PR	DAY 28 OTHER	P value
Steroid Dose			
Median			
Range			
<u>Day 28</u>	0.5	0.96	
	0-1.4	0-1.9	0.001
<u>Day 56</u>	0.2	0.5	
	0-1.9	0-1.3	0.001

Conclusions

- Responses on Day 14 and Day 28 are valid markers of outcome for aGVHD treatment trials.
- Day 7 assessment may become more informative if coupled with biomarkers (proteomics, genomics).
- Age and disease status at transplantation are potential confounding factors that need to be considered in randomization of future trials.
- Outcomes in patients with complete or partial response seem comparable; however larger confirmatory studies are needed.
- What if therapy lowers the cumulative dose of steroids but does not necessarily improve response rates- this might be clinically important.

Limitations of This Review

- **Patients at M.D. Anderson might not be representative of general patients.**
 - No pediatric pts in this analysis.
 - Pts at High- risk for Relapse
 - Patients were on a clinical trial which likely represent a worst (or better?) pt group.
- **No information on Quality of Life End-points as a factor of Response.**
 - We are in the process of evaluating the influence of response to Acute GVHD therapy and steroid dose on symptom burden as assessed by the M.D. Anderson Symptom Inventory (MDASI).

Limitations of This Review

- **Day 14 and 28 response might not be a suitable surrogate for TRM/Survival for all studies.**
 - Extracorporeal Photopheresis + Steroids vs. Steroids alone: study endpoint includes an assessment of the ability to taper steroids in addition to response as it is believed this therapy might improve the later without necessarily impacting the former.
- **Previous clinical trials have taught us that trial designs must include interval assessments of Relapse Rates and Toxicities in addition to Response Rates.**
 - Cragg et al: ATG + Steroids vs. Steroids-alone
 - Found an increase in infections resulting in no improvement in OS.
 - Lee et al.: Dacluzimab + Steroids vs. Steroids-alone
 - Found an increase in Relapse resulting in no improvement in OS.

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