

Treatment of Chronic Graft versus Host Disease

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October 2013

Transplant Events

d-8

0

1mo

3mo

6mo

Conditioning

Transplant

Engraftment

Mucositis
Organ toxicity
(VOD)

Acute GVHD

Chronic GVHD

Infections

Bacterial

Fungus

CMV

Varicella

Factors affecting chronic GVHD

Increased risk

Unrelated donor

Peripheral blood stem cell

Older age

Prior acute GVHD

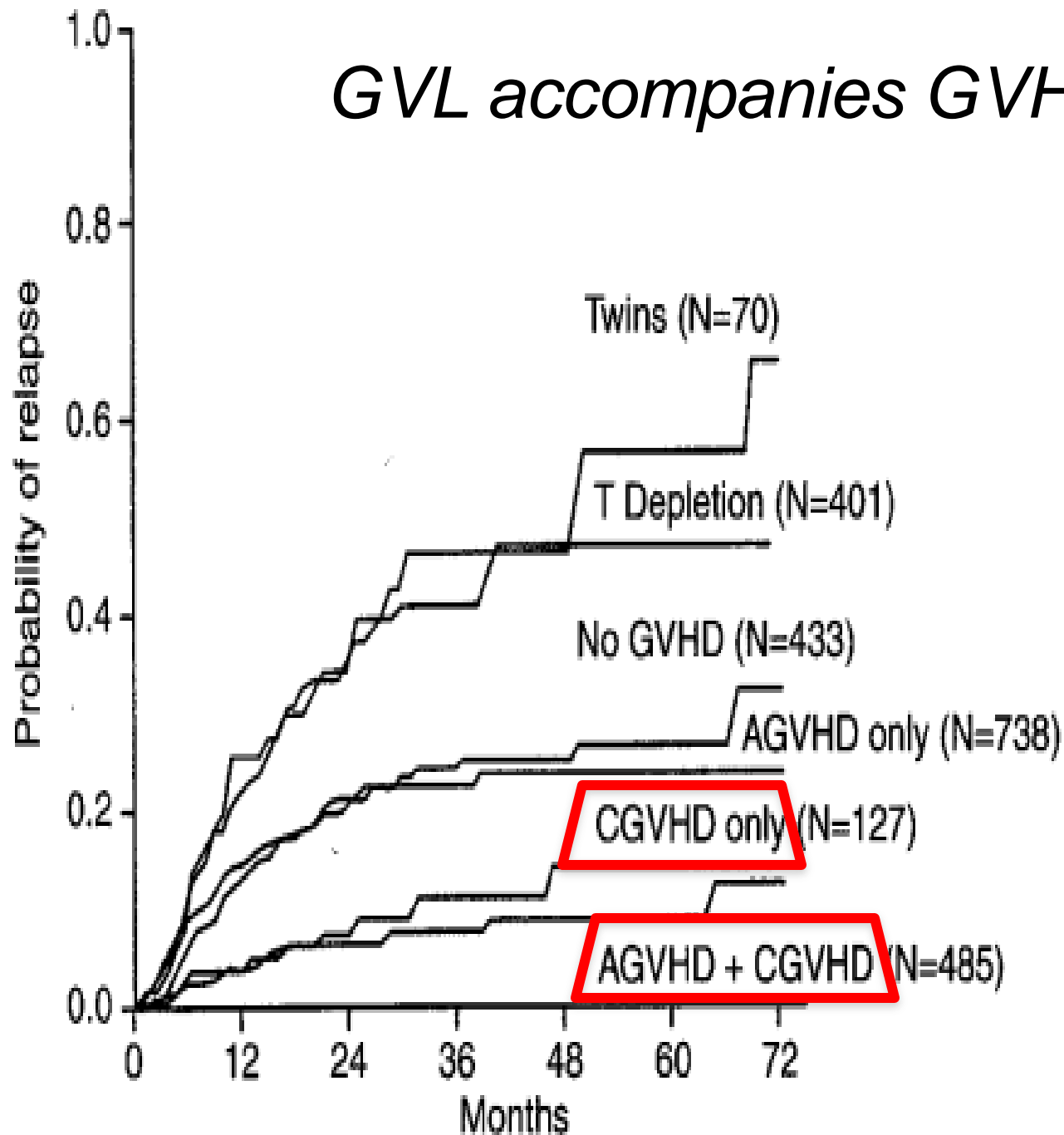
HLA mismatch

Transplant from alloimmune female donor

Decreased risk

Cord Blood

GVL accompanies GVHD



Clinical Presentation
Response to Treatment
Duration of Immunosuppression

Acute GVHD

Chronic GVHD

Dermatitis

±

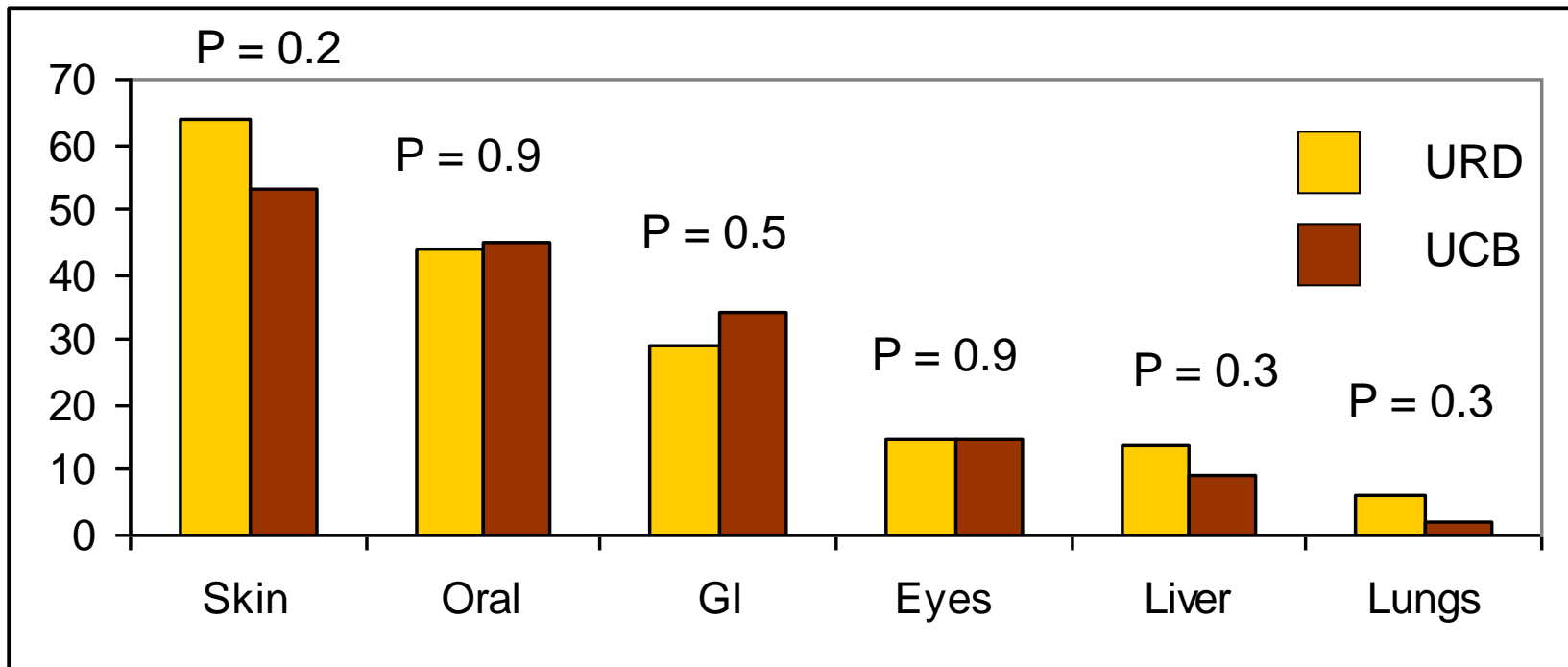
Hepatitis

±

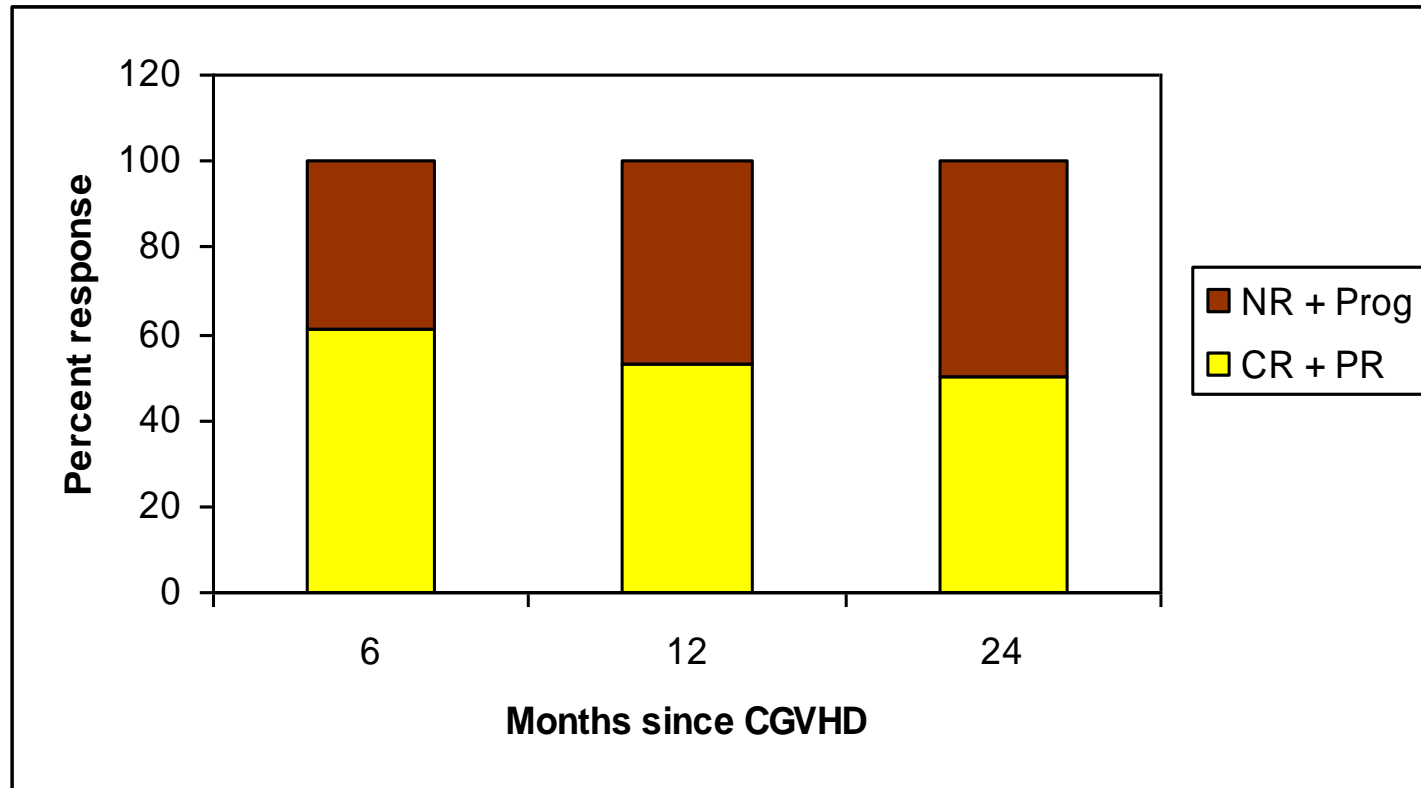
Enteritis

Skin: Lichen planus,
Hyper/ hypo pigmentation,
ichthyosis,
onychodystrophy, morphea,
scleroderma, hair changes.
Oral: sicca, atrophy, lichenoid,
Hyperkeratosis
GI: wasting, dysphagia,
odynophagia, strictures
Eye: keratoconjunctivitis sicca
Lungs: Bronchiolitis obliterans
Others: myofascial, genital

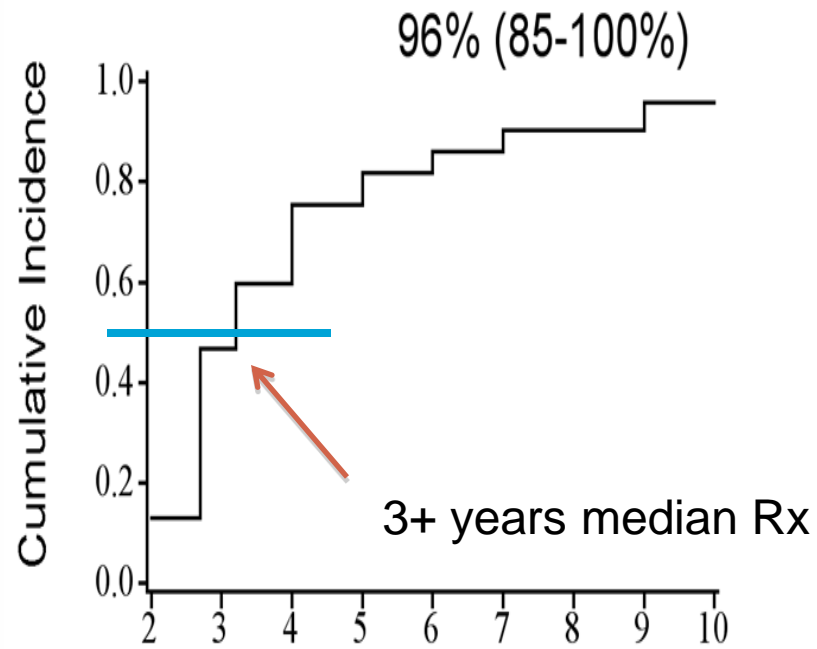
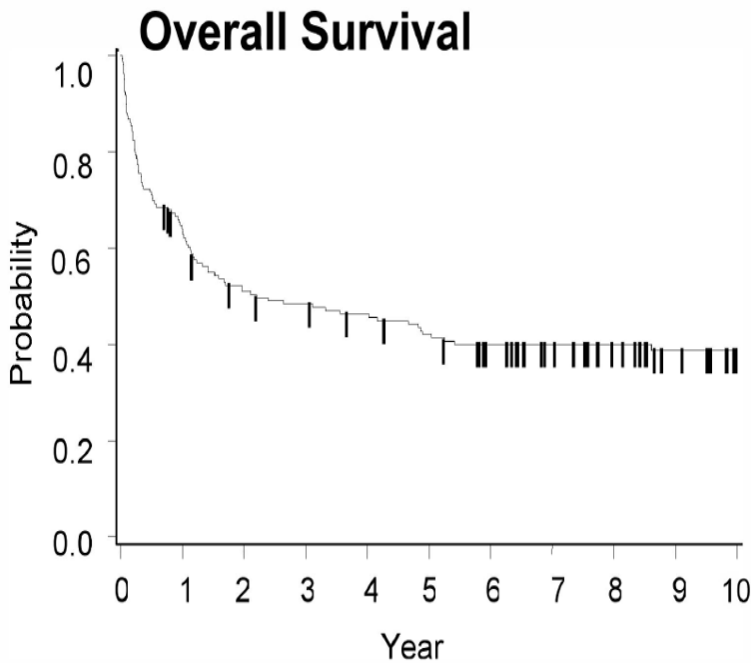
Organ Involvement with cGVHD



Treatment of CGVHD: Response to Immunosuppressive therapy



Overall Survival and Cumulative Incidence of Discontinuation of Immunosuppression



Factors predicting poor prognosis

- Progressive onset of disease
- Thrombocytopenia
- Extensive skin involvement
- Lichenoid histology
- Elevated bilirubin
- Lung disease
- Older age
- Poor KPS

TREATMENT of CGVHD

Standard Risk pts (Plt $>10^5$) **High Risk pts (Plt $<10^5$)**

┌ Prednisone+placebo
└ Prednisone+AZA

┌ Prednisone
└ CSP / Prednisone

Prednisone

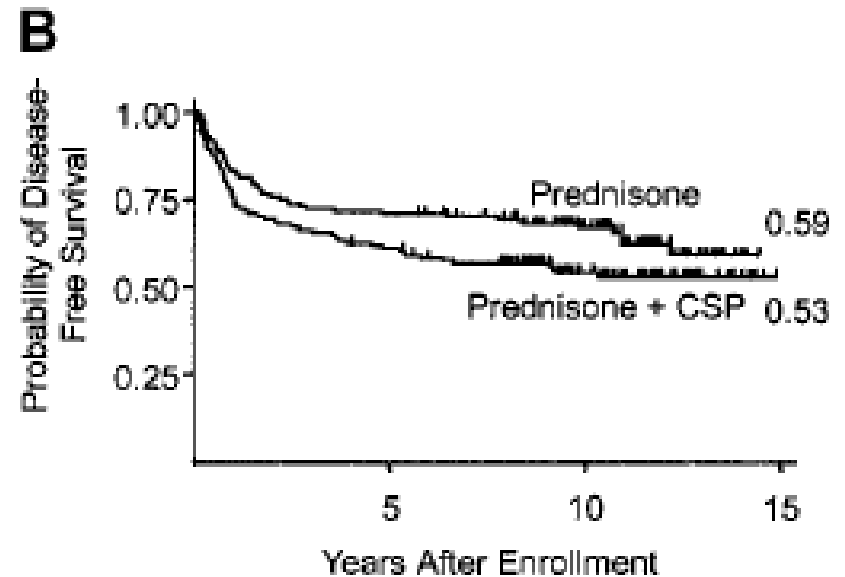
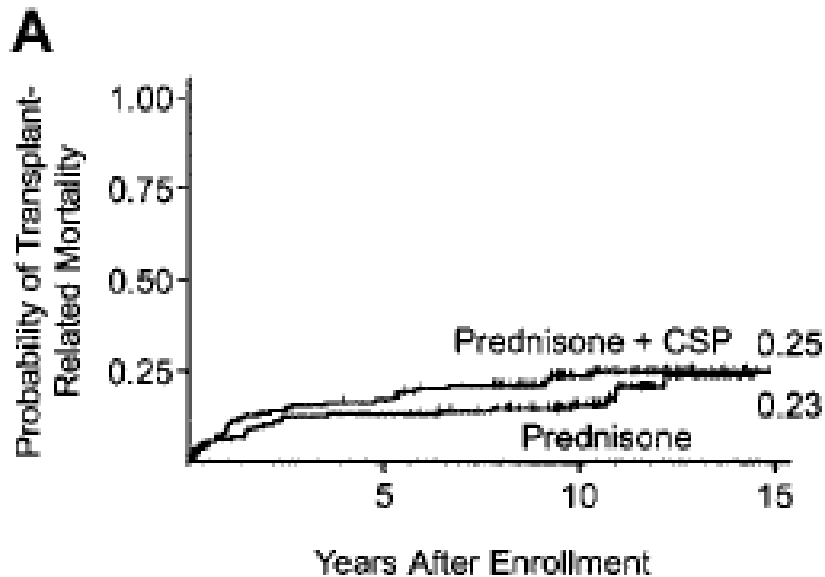
CSP / Prednisone

┌ CSP
└ CSP / Prednisone

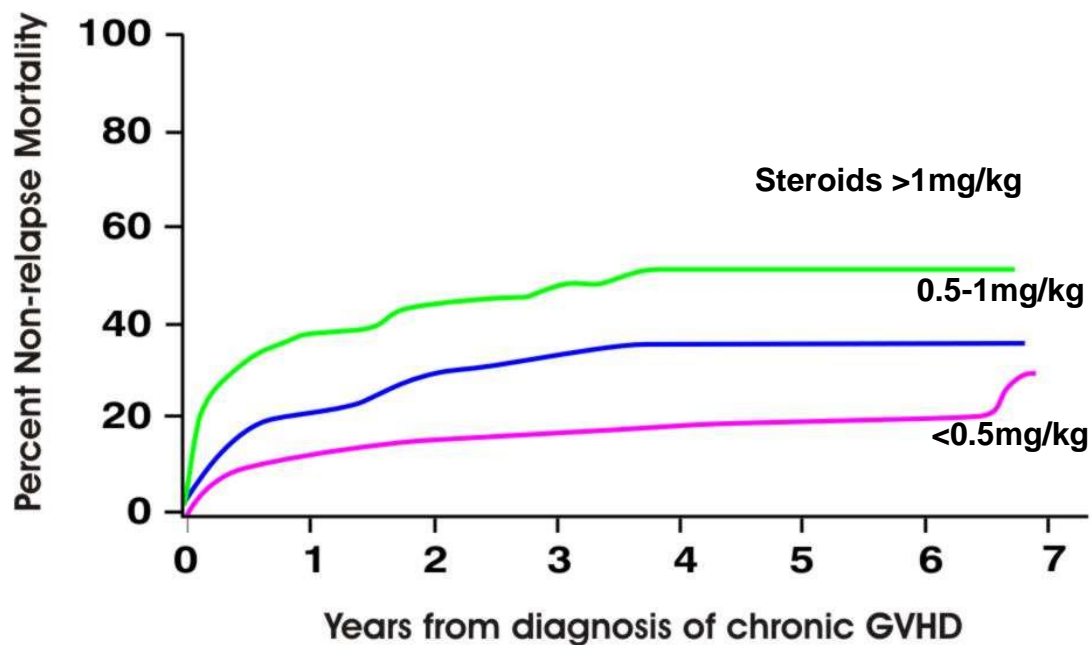
Randomized Trials: Initial therapy using steroids with or without additional agents: additional immunosuppression not beneficial

Trial	N	NRM	5 year survival
Prednisone ± Azathioprine	N= 126	21 % vs. 40%	61% vs. 47%
Prednisone ± cyclosporine	307	13% vs 17%	72% vs. 67%

	<i>Alternate – day treatment</i>	N	Survival	Non relapse mortality
R	Prednisone	145	72%	17%
	CSP / Prednisone	142	67%	13%

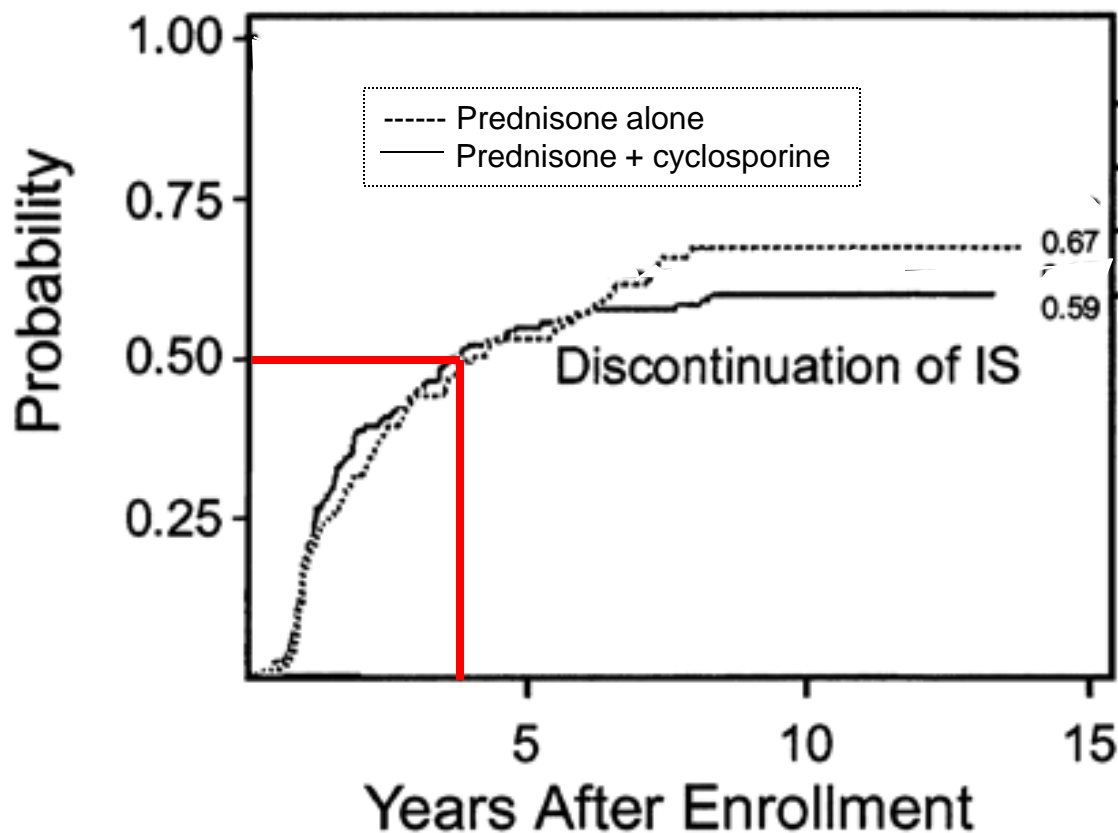


Toxicity of CGVHD treatment with Steroids



NRM according to steroid dose at cGvHD diagnosis

Similar incidence of discontinuation of immunosuppression in single & two drug arms



Thalidomide as Initial Therapy: Similar response and survival

¹ Prednisone and CNI ± Thalidomide	N= 52	OS 49% vs. 47% at 3 years Similar outcomes, drug not well tolerated
² Prednisone and CNI ± Thalidomide	N= 54	OS 66% vs 54% at 2 years Similar response and survival.

MMF as Initial therapy

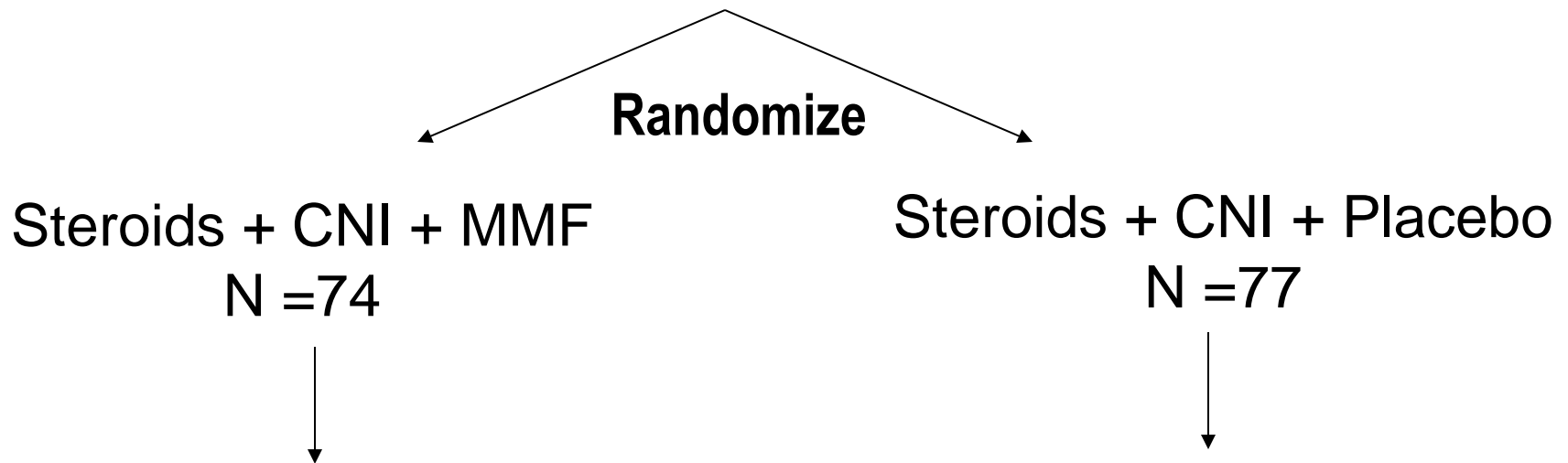
Randomized multicenter double blind
placebo controlled trial

Blood, 2009

Martin et al,

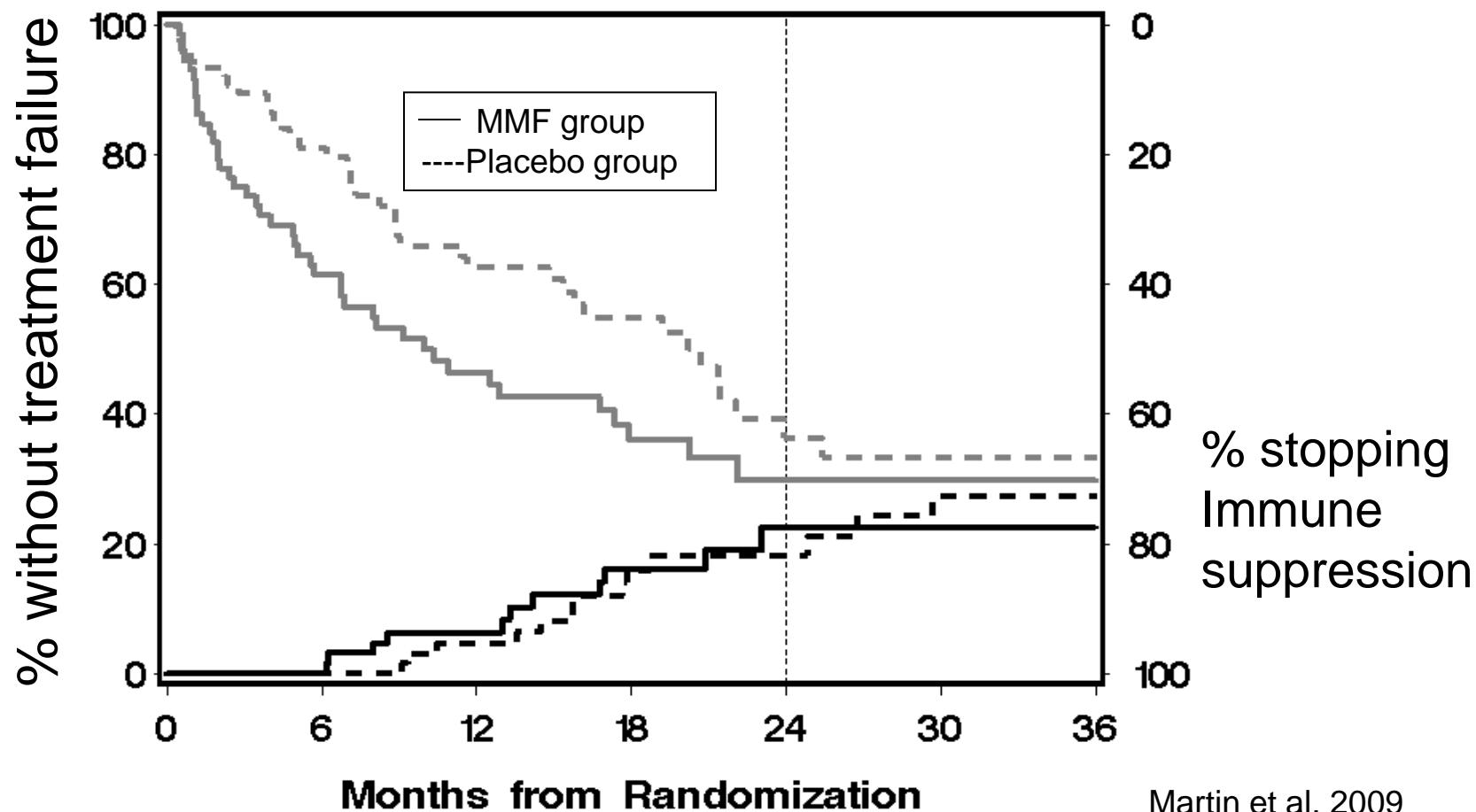
Study Schema

Eligible CGVHD Patients



Primary Endpoint: resolution of chronic GVHD & withdrawal of systemic treatment within 2 years without secondary treatment

Similar discontinuation of immunosuppression but more treatment failure with MMF



Secondary Therapy of cGVHD

- No standard second line therapy available
- Several agents tested
 - case series
 - phase II trials
- Not comparable
 - heterogenous patient population
 - different response criteria

Summarize

Therapy	N	Response	Survival
Sirolimus	98	63-93%	41-89%
Rituximab	35	50-83%	-
<i>ECP</i>	276	40-80%	19-93%
MMF	65	46-72%	83-92%
Thalidomide	161	20-59%	41-64%

Other Agents

Agent	N	Inclusion	Response
Pulsed steroids	61	Refractory	48% major, 27% minor response
Daclizumab	4	Steroid resistant	1 CR, 2 PR
Clofazimine	22	Persistent symptoms	55% PR
Etanercept	10	Steroid dependent	1CR, 5 PR
Low dose MTX	14	Refractory	71% required < 1mg/kg PSE
Etretinate	32	Refractory sclerodermatous	74% improvement

BMT CTN 0801

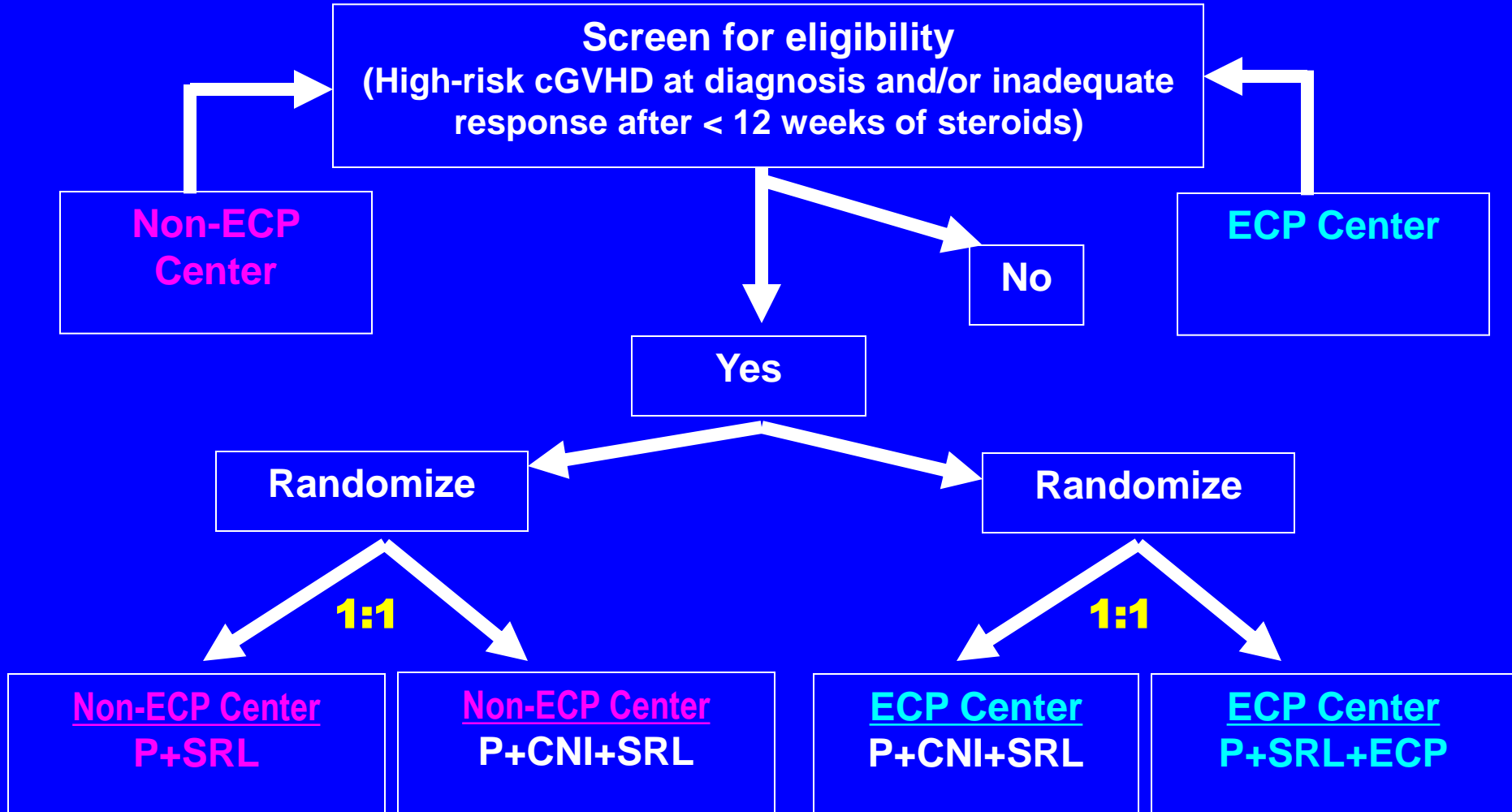
A Phase II/III Randomized Trial Comparing

- Sirolimus + Prednisone (test arm- ↑ T-regs)**
- Sirolimus + CNI + Prednisone (control arm)**
- Sirolimus + ECP + Prednisone (test arm- ↑ T-regs)**

Study Chairpersons:

Paul Carpenter MBBS. & Mukta Arora M.D.

BMT CTN 0801 Study Schema



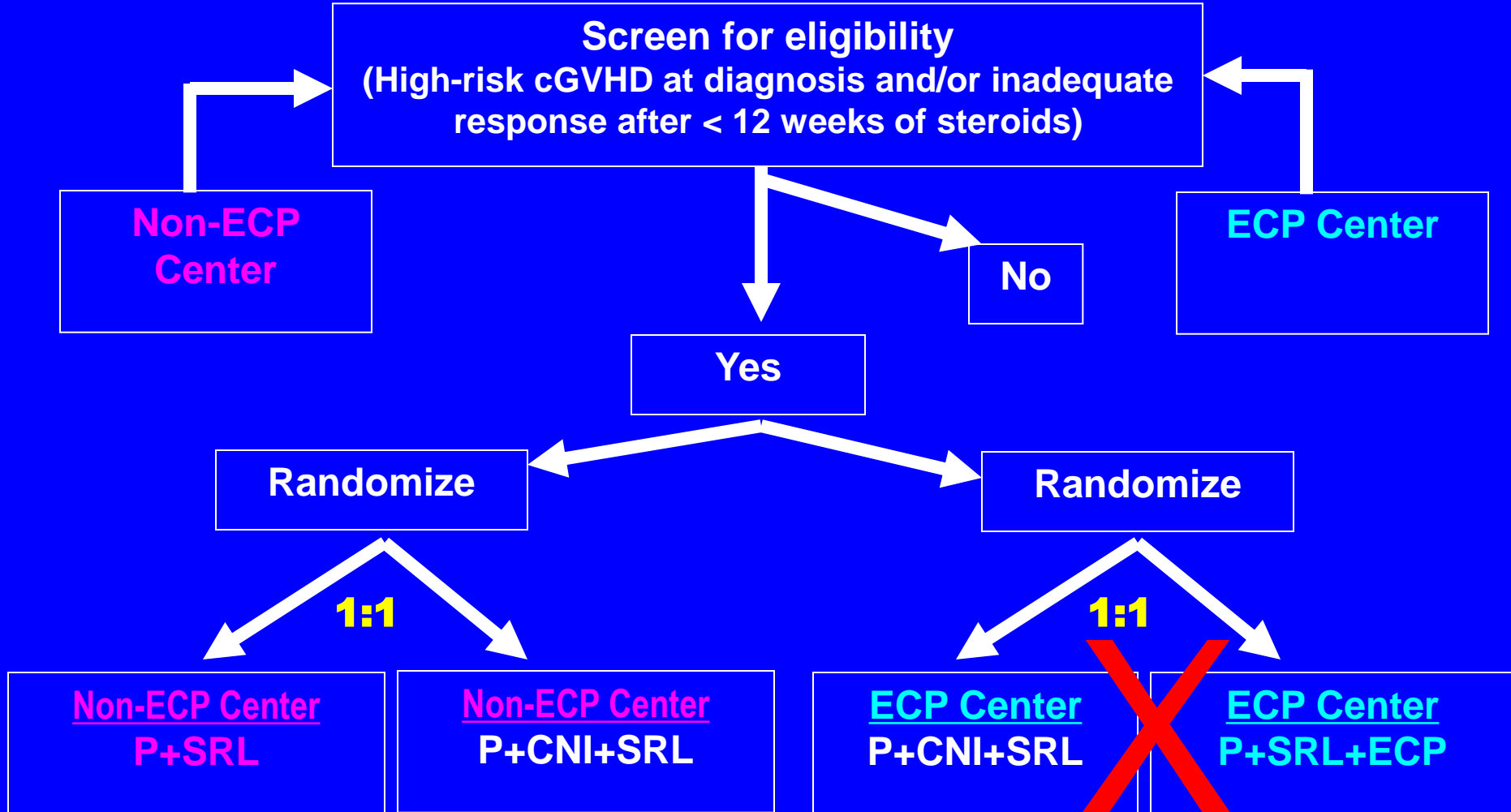
Evaluate comparator Arms from **Non-ECP** + **ECP Centers** for analysis



0801 Enrollment Challenges

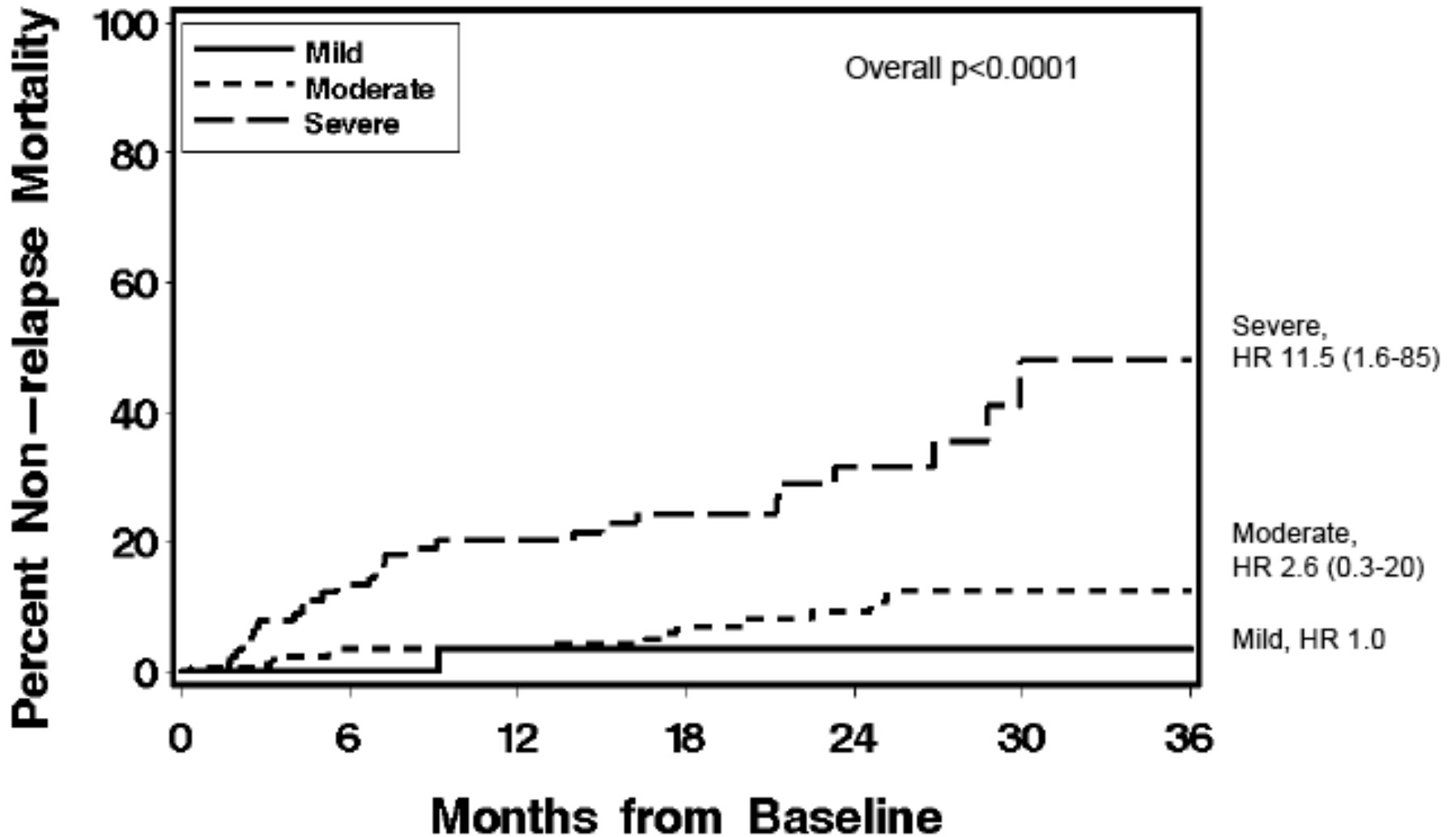
<u>2009-2010</u>	<u>allografts</u>	<u>~cGVHD(40%)</u>	<u>Enrollment</u>
Non ECP Centers	2077	831	25
ECP Centers	3085	1234	5

BMT CTN 0801 Study Schema

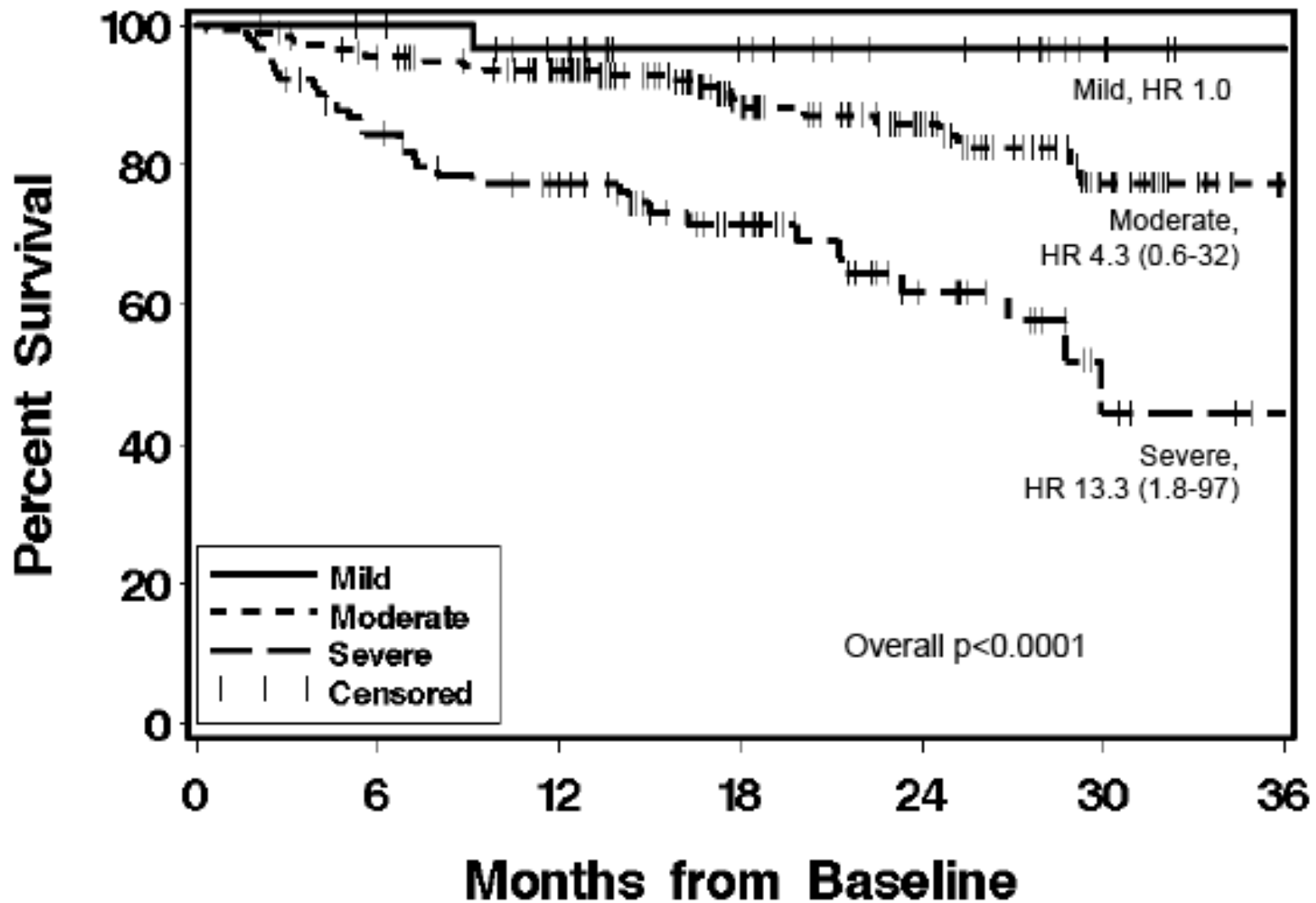


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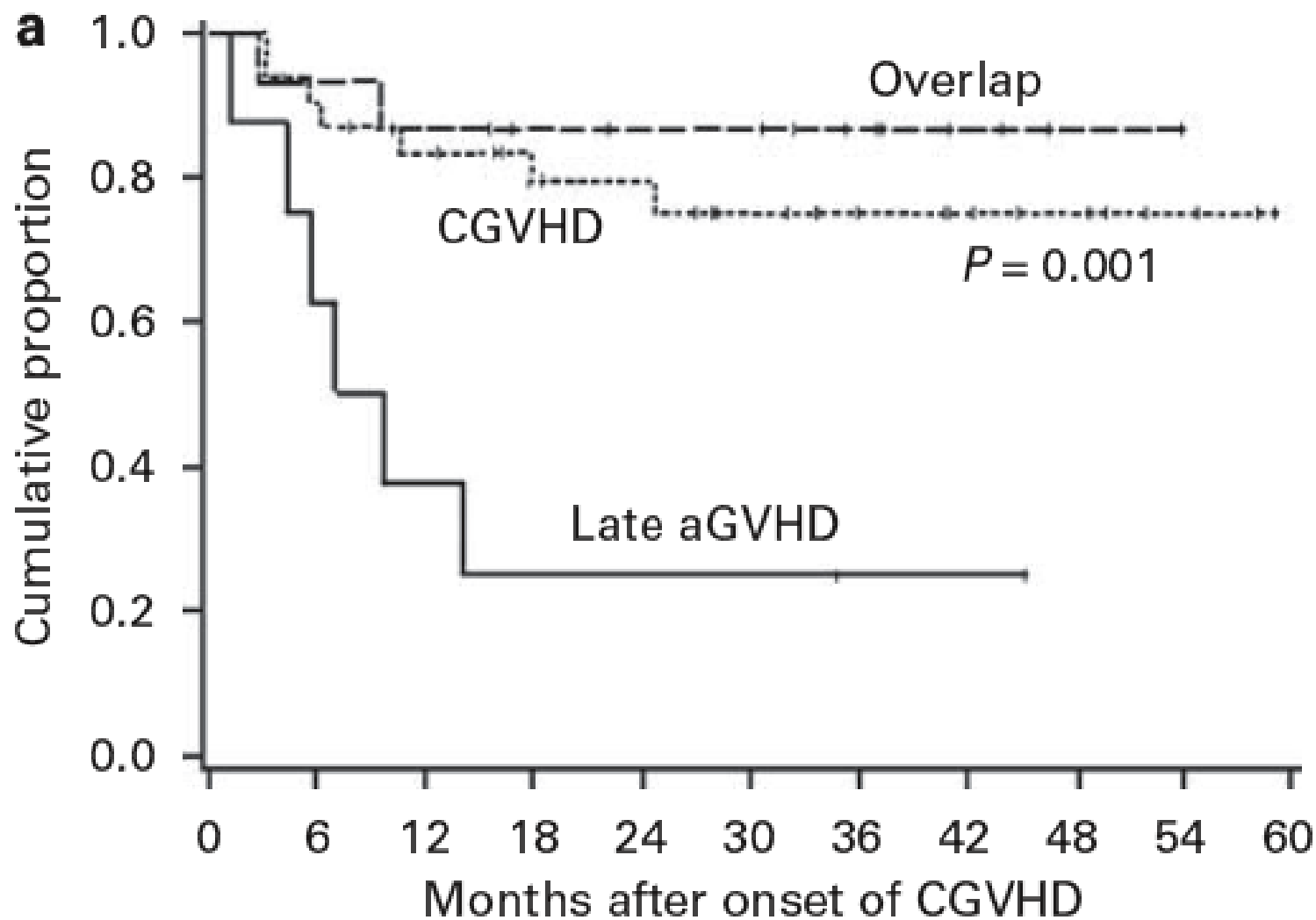
Non Relapse Mortality: CGVHD Severity Score



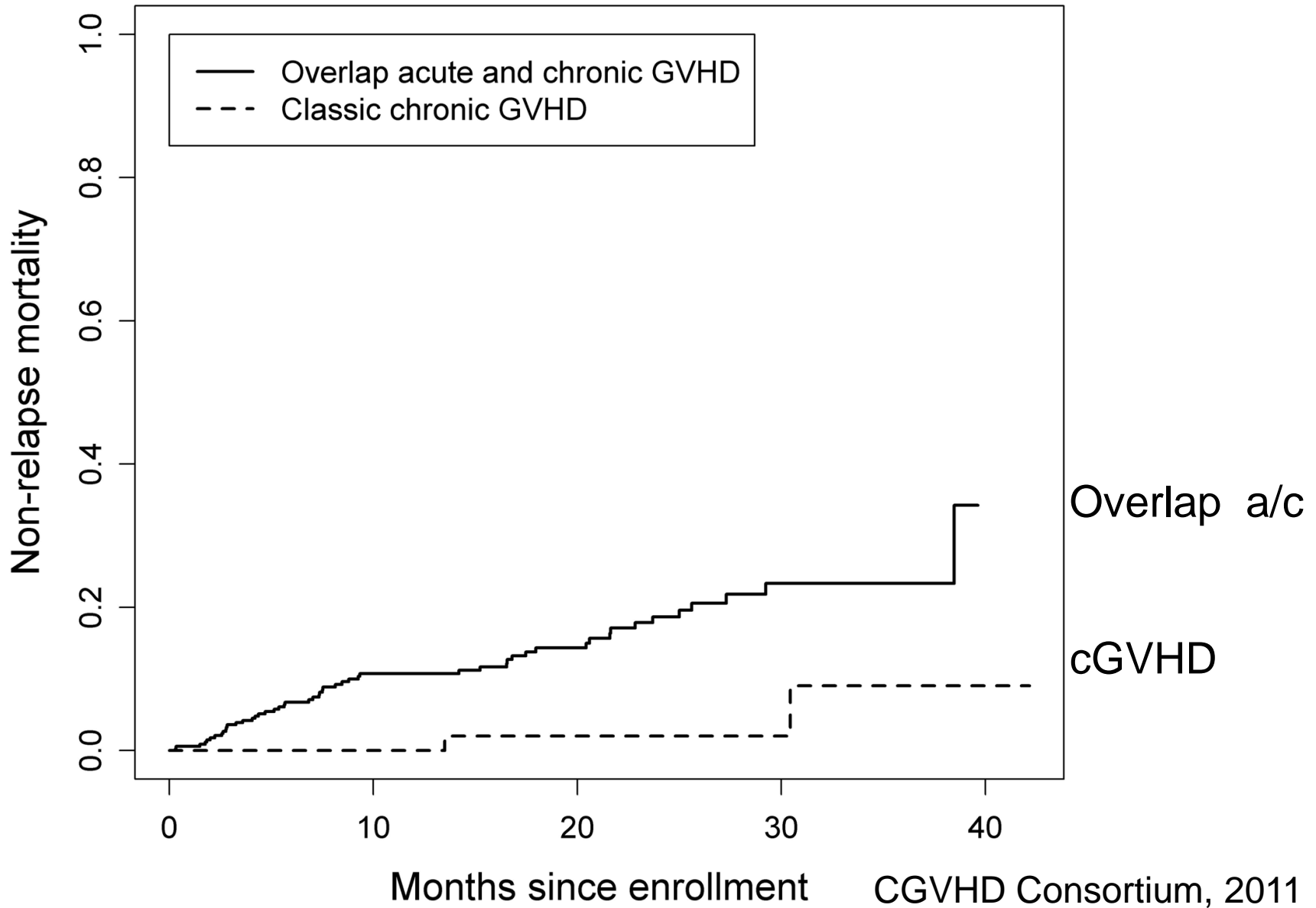
Survival: CGVHD Severity Score



Worse Survival with Late onset acute GVHD simulating CGVHD



CGVHD Overlap: Influence on non-relapse mortality



Key Points

cGVHD therapy remains frustrating

Incidence is increasing

Thrombocytopenia and progressive onset are markers of poor prognosis

Treatment requires prolonged immunosuppression

Infections are the commonest cause of death