MEDIZINISCHE UNIVERSITÄT WIEN

Univ. Klinik für
Innere Medizin I

Acute Graft-versus-host disease

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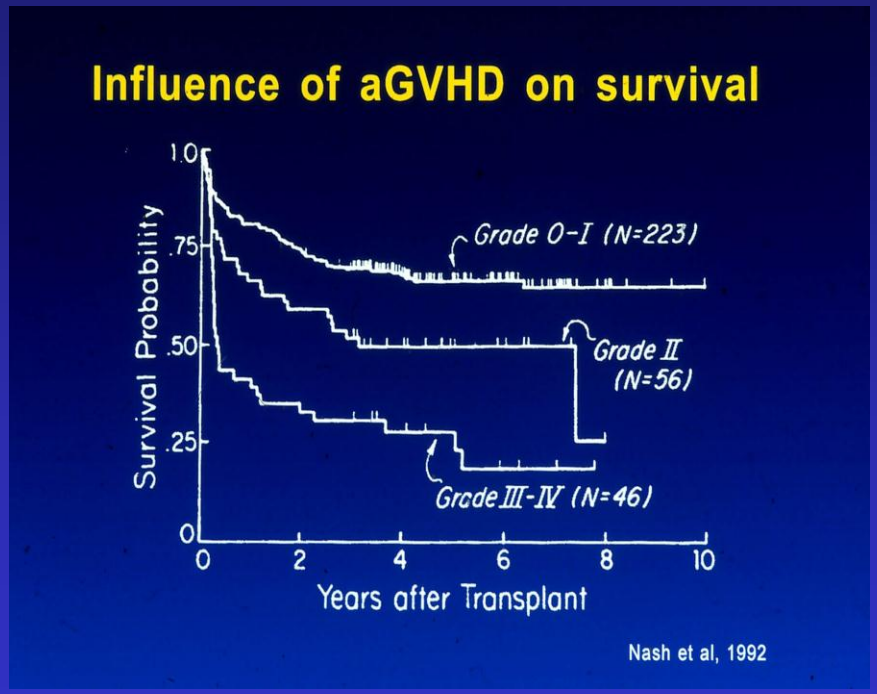
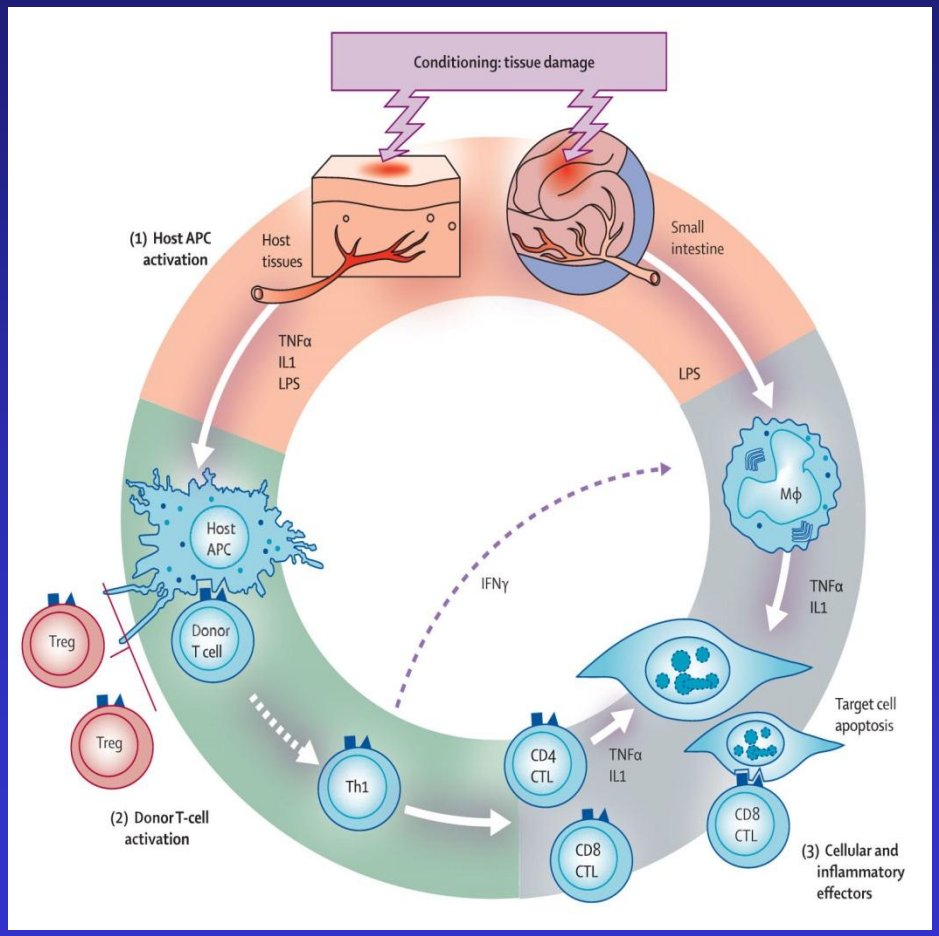
Austria

Acute GVHD is Serious Complication of Allo HCT



- **Challenge**: GVL effect vs. morbidity and mortality due to severe GVHD
- GVHD has significant negative impact on survival
- **Challenge**: Efficacy vs toxicity of IS

Pathophysiology of Acute GVHD



Requirements for GVHD: Billingham 1966

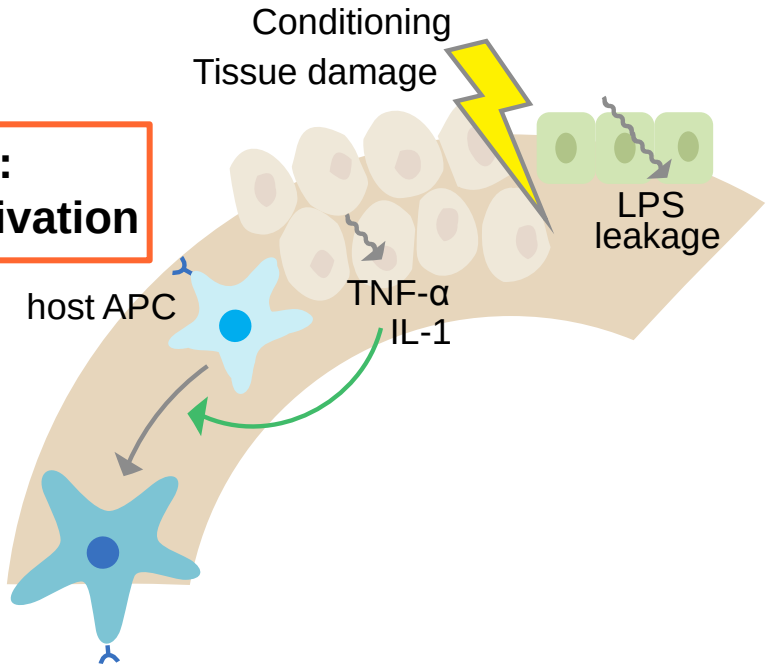
- Graft contains immunocompetent cells.
- Host expresses minor or major transplantation antigens lacking in the donor.
- Host is incapable of rejecting the graft.

Ferrara J, Hill G, Holler E et al.

Pathogenesis model: Acute GVHD

The „three-phase model“ *(adapted from Ferrara et al. 1994)*

Phase 1:
host APC activation



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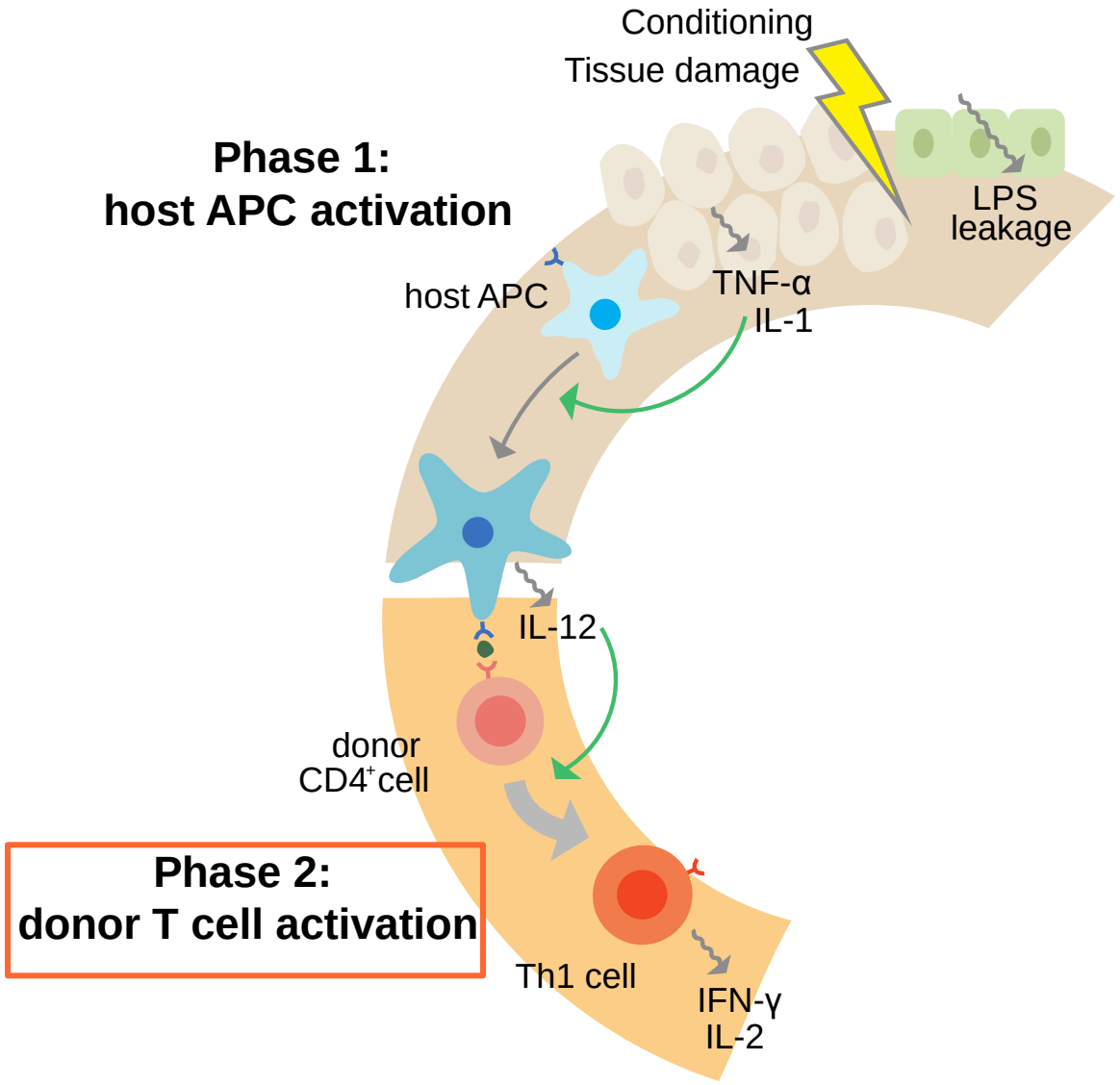

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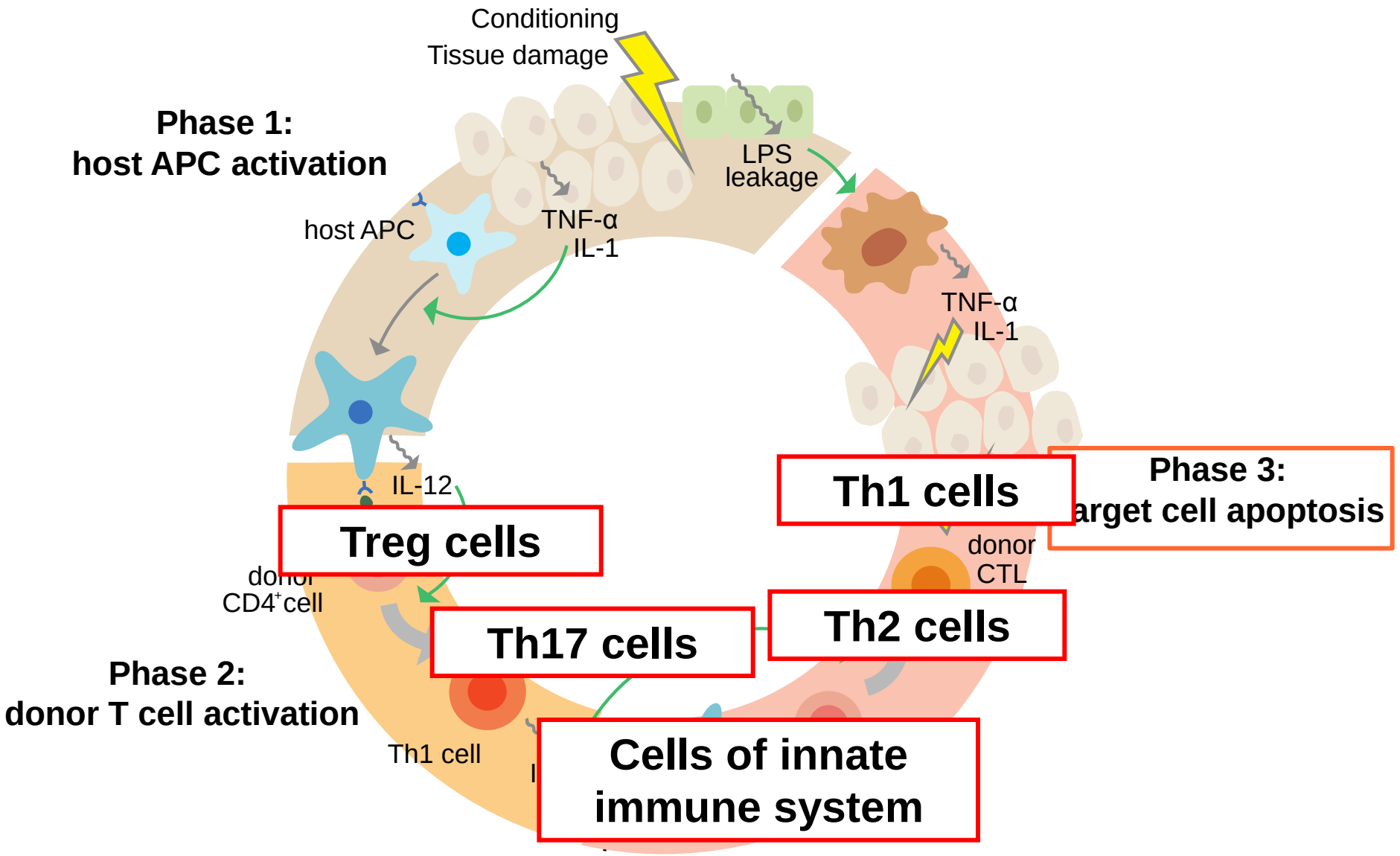
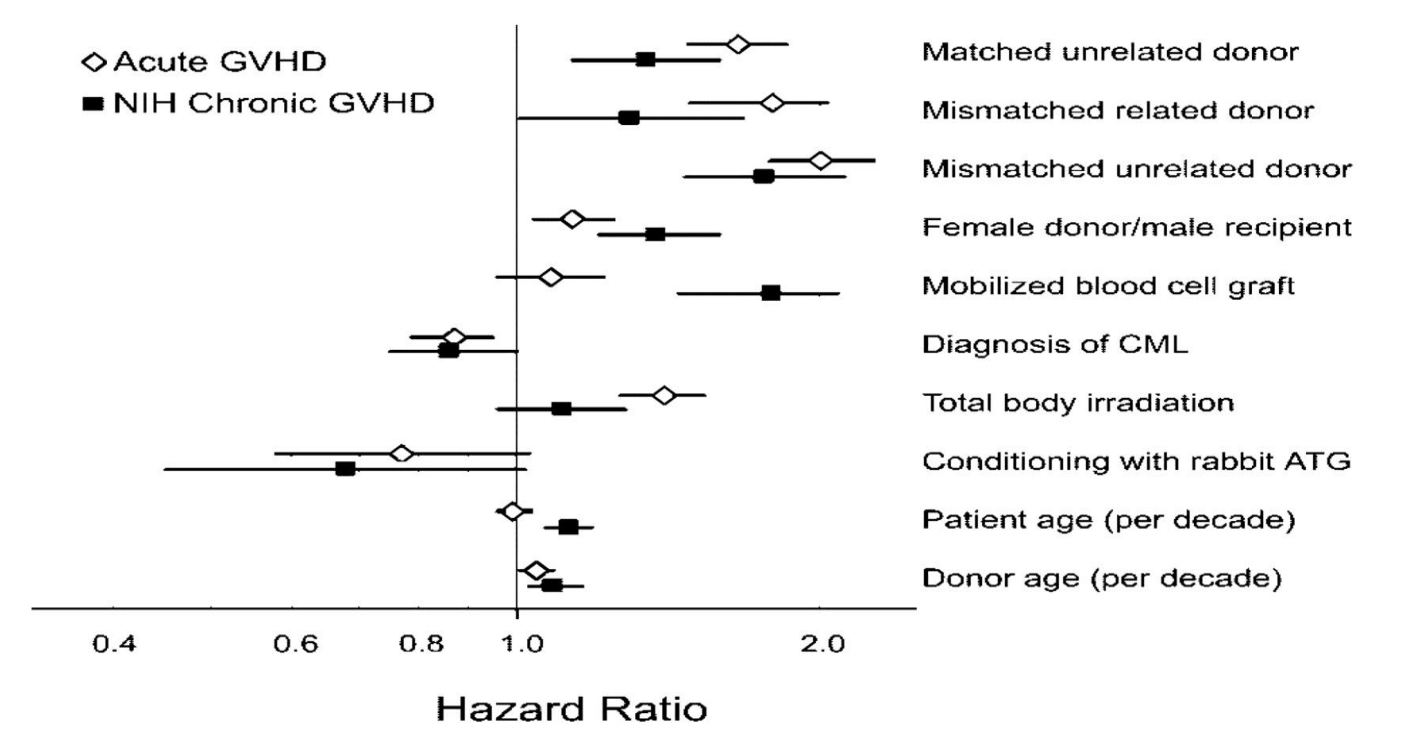
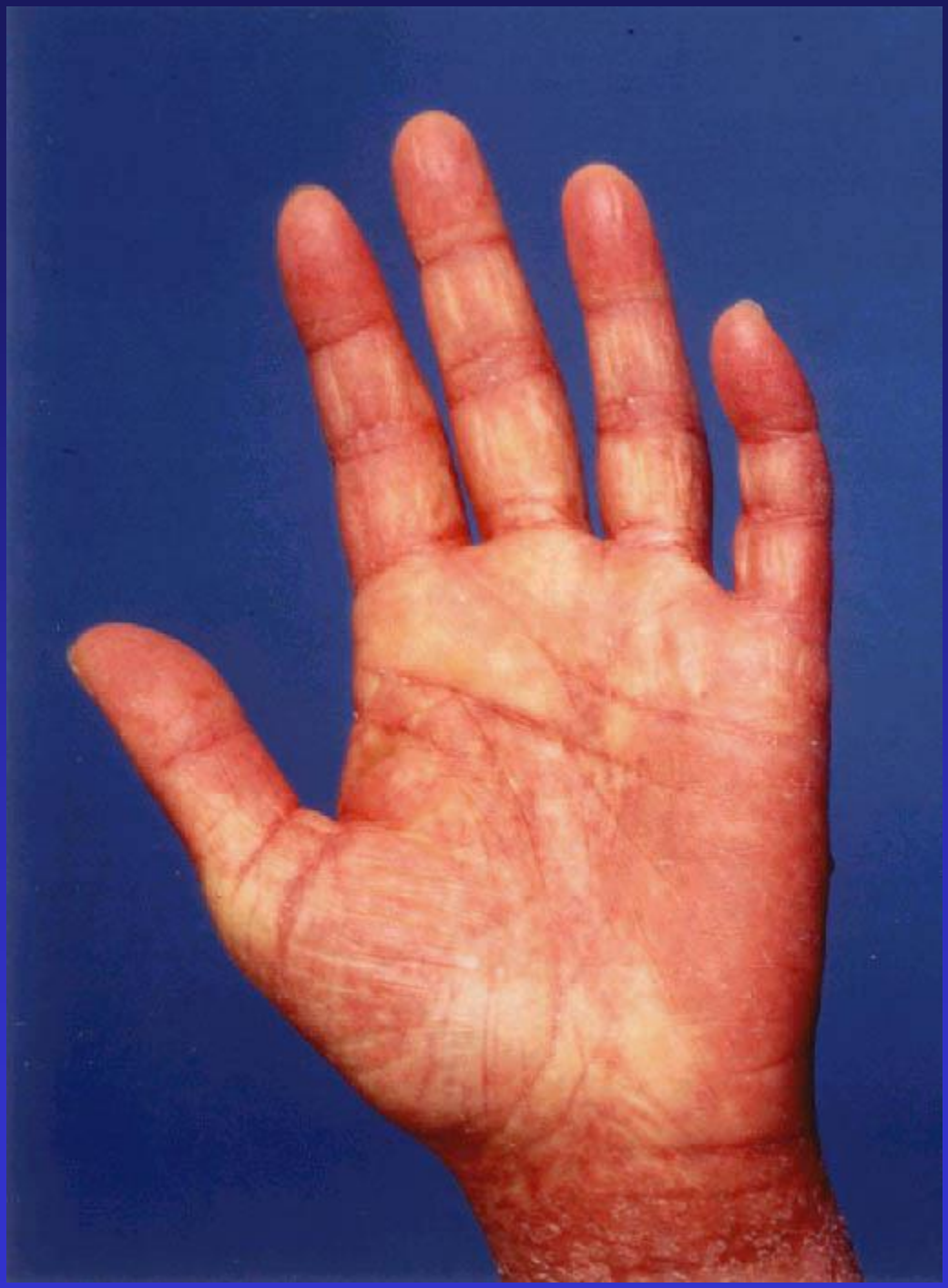


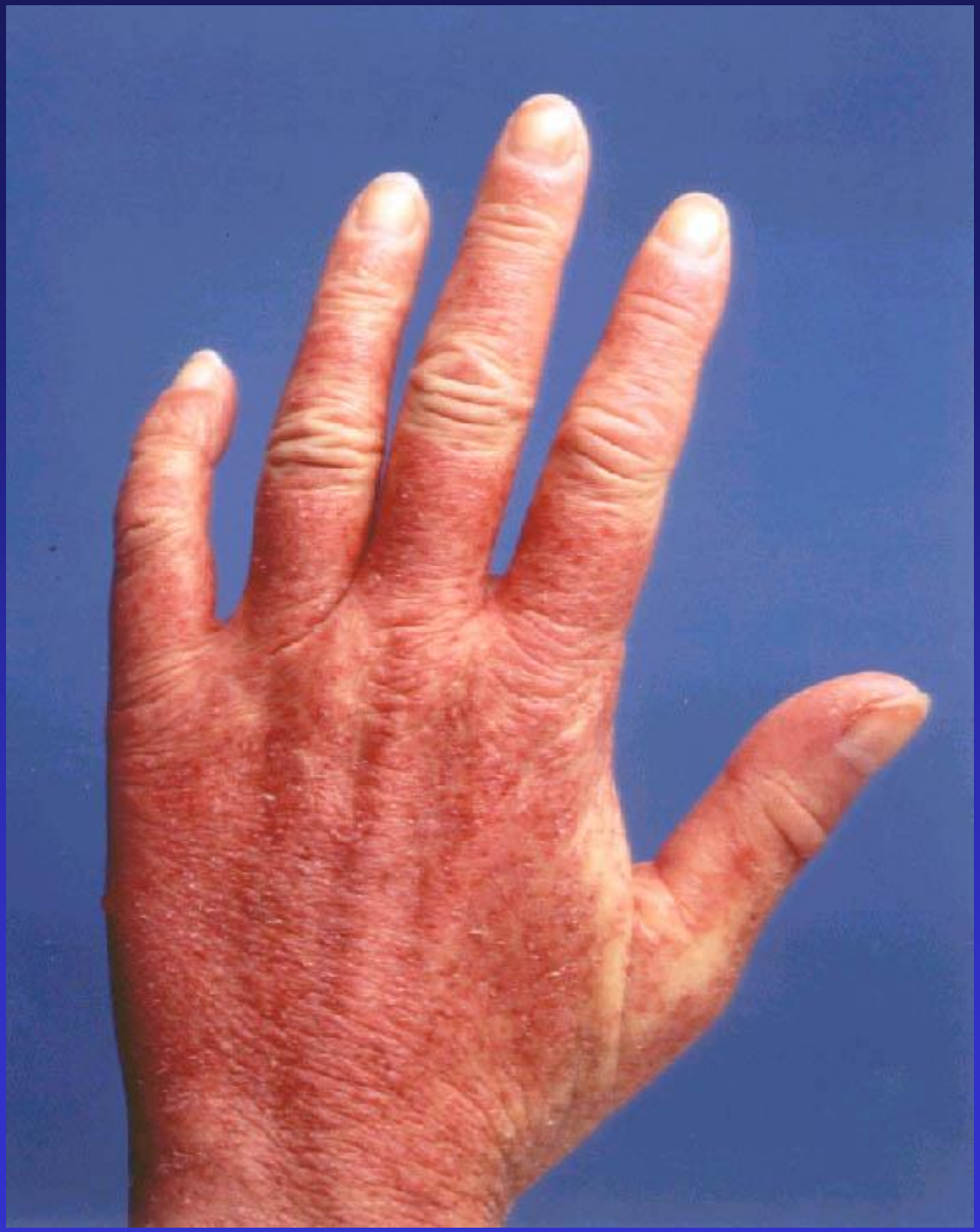
Risk Factors for Acute and Chronic GVHD According to NIH

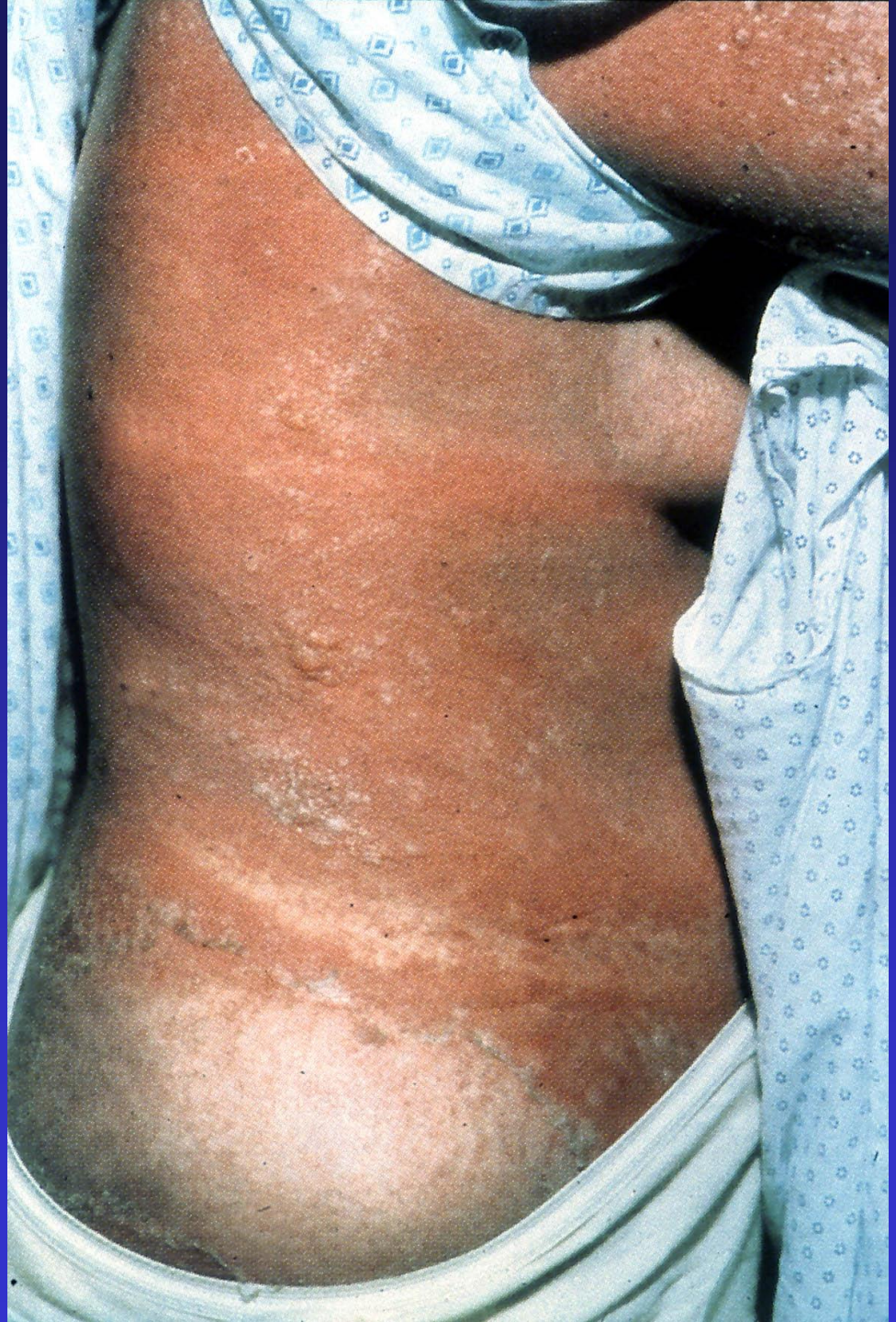


2941 adult and pediatric pts with first allo HCT

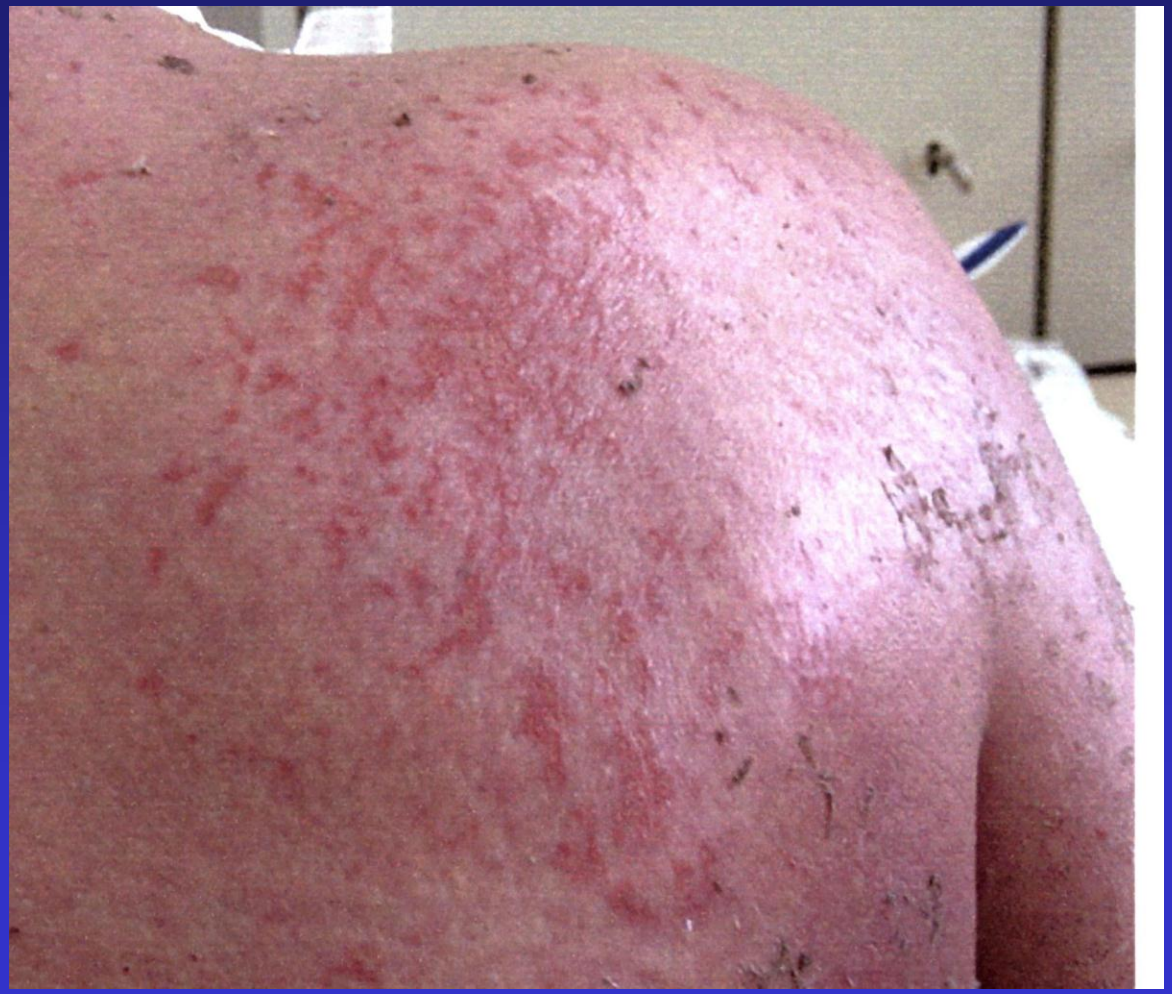
Flowers MED et al, Blood 17:3214-3219, 2011



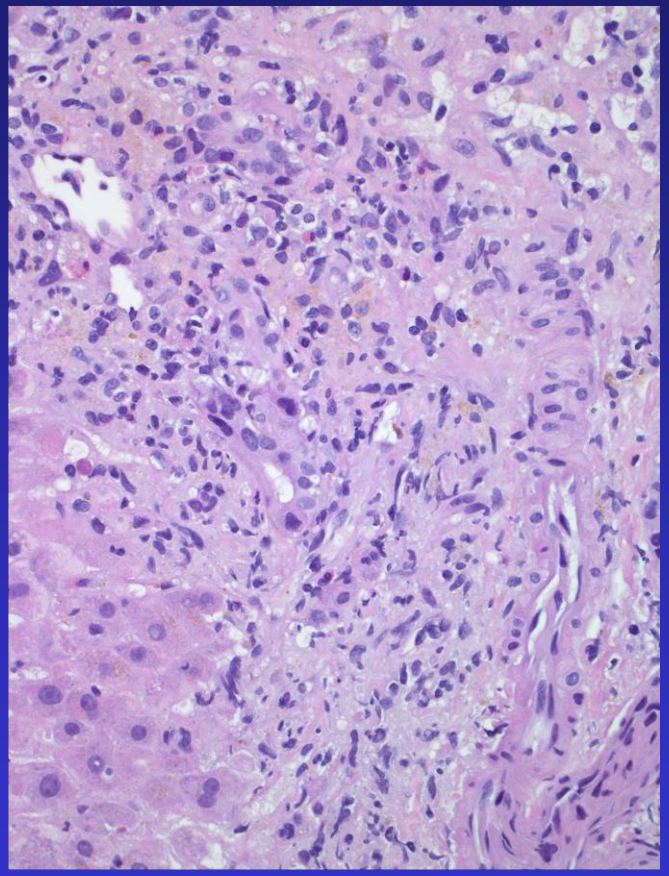


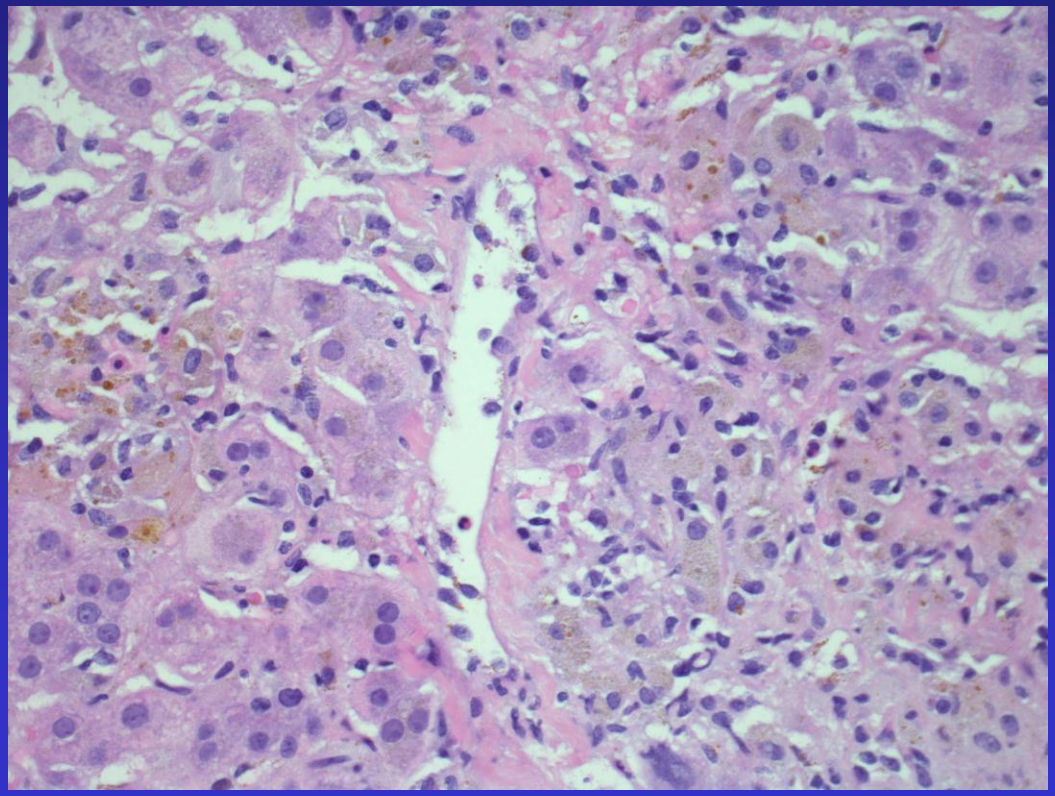


Akute GVHD of Skin Stage IV

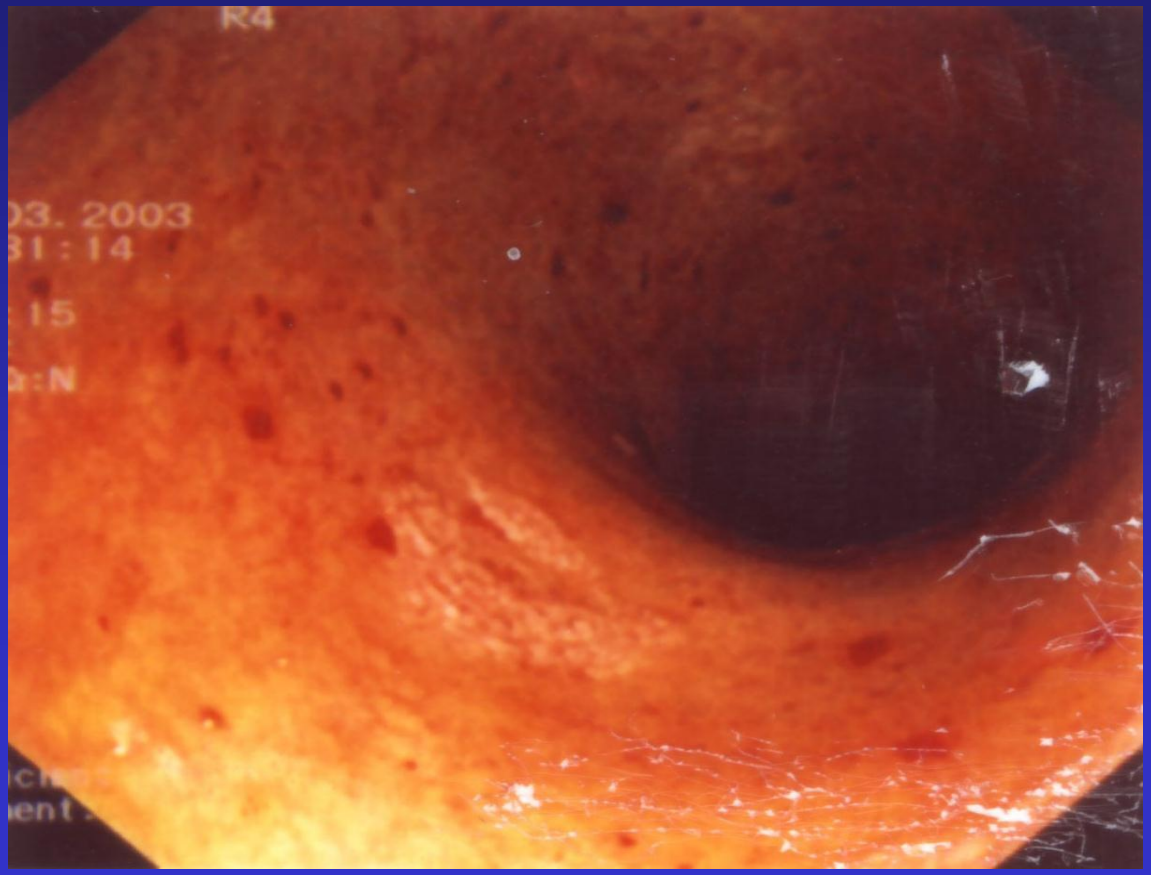


Acute GVHD of Liver





Acute GVHD of GI

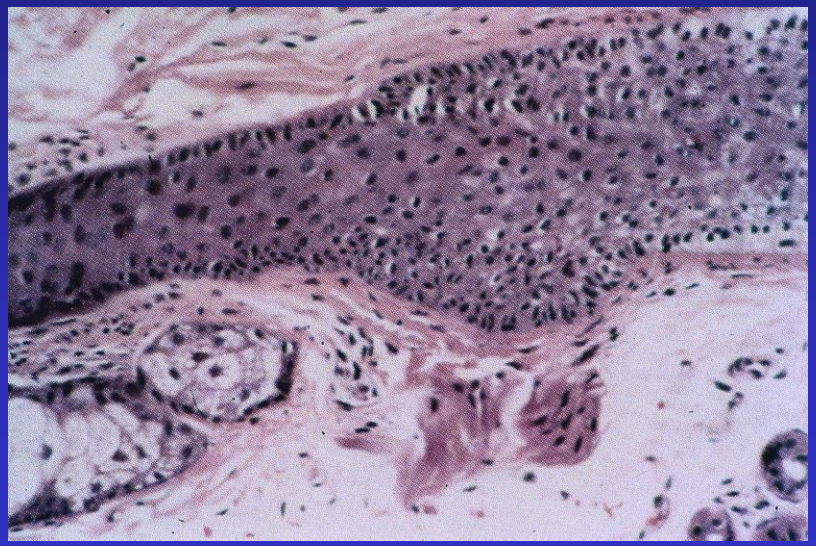


Consensus Conference on Acute GVHD Grading

Stage	Skin	Liver (Bilirubin mg/dl)	Gut (diarrhea ml/day)
1 2 2 4	<25% 25-50% >50% Erythroderma	2-3 3-6 6-15 >15	>500 or nausea >1000 >1500 Pain/ileus
Functional	Skin	Liver	Gut
I II III IV	Stage 1-2 Stage 3 or - Stage 4 or	None Stage 1 or Stage 2-3 or Stage 4	None Stage 1 Stage 2-4 -

Przepiorka 1995

Acute GVHD as Severe Complication of allogeneic HCT



30-80% of pts

Old definition:

Onset before day 100 after HCT

Categories of NIH-Defined GVHD

Category	Time of sy after HCT	Presence of acute GVHD features	Presence of chronic GVHD features
Acute GVHD			
Classic acute GVHD	≤ 100 d	yes	no
Persistent, recurrent or late onset acute GVHD	> 100 d	yes	no
Chronic GVHD			
Classic chronic GVHD	No time limit	no	yes
Overlap syndrome	No time limit	yes	yes

Filipovich et al. BBMT 2005;11:945-56

Acute GVHD is reduced after nonmyeloablative vs myeloablative conditioning HCT

Related

Unrelated

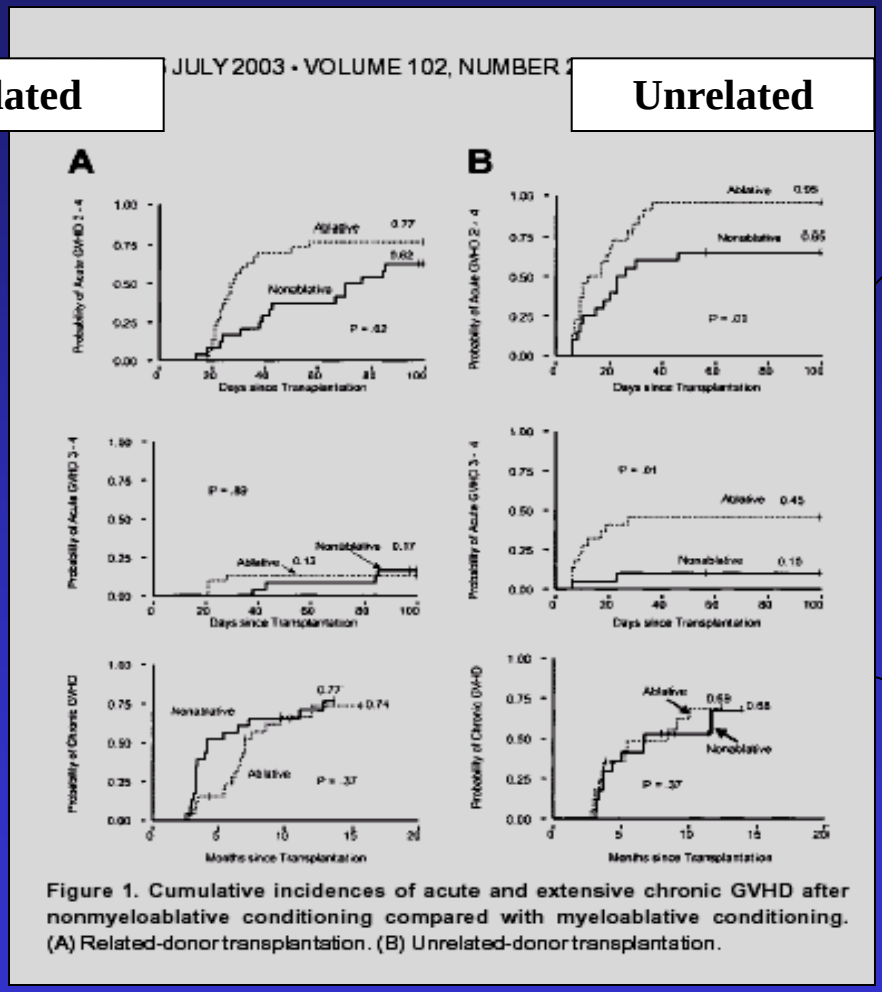
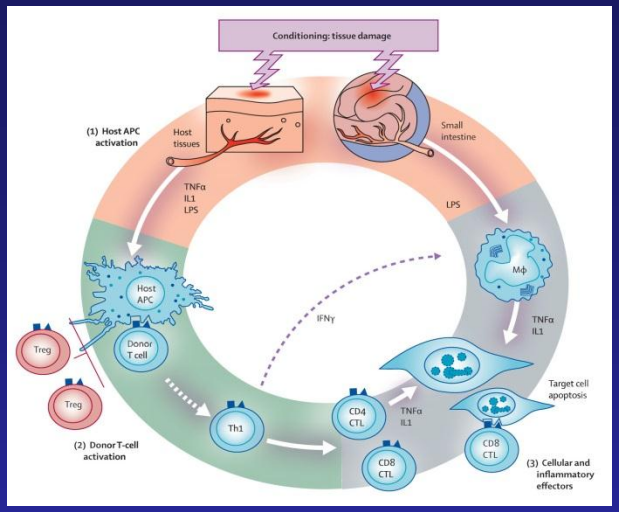


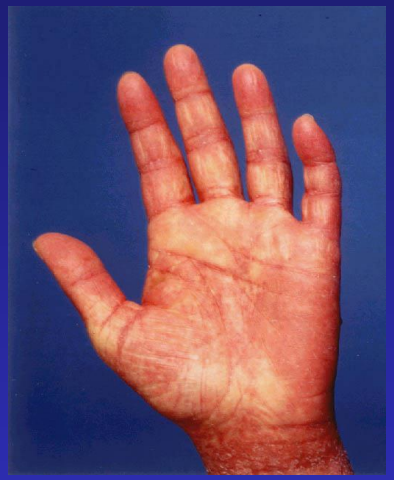
Figure 1. Cumulative incidences of acute and extensive chronic GVHD after nonmyeloablative conditioning compared with myeloablative conditioning. (A) Related-donor transplantation. (B) Unrelated-donor transplantation.

Acute GVHD: Delayed and reduced incidence

Chronic GVHD: No difference

Mielcarek et al, Blood 2003





Prophylaxis of GVHD

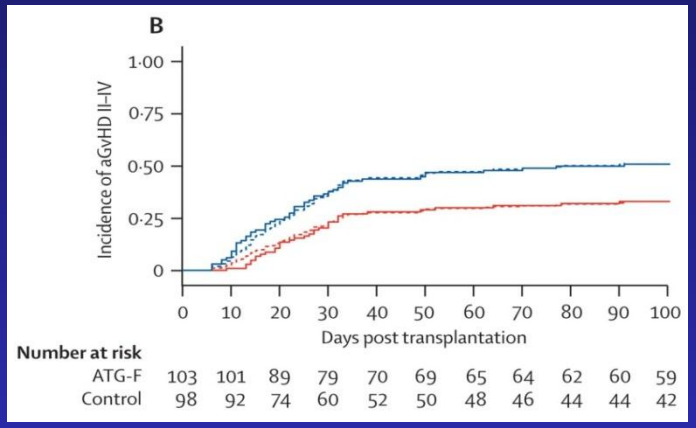
Standard Prophylaxis of GVHD: CNI (= Cyclosporine/Tacrolimus) + MTX

	regimen	Acute GvHD	Chronic GvHD	Overall survival
Storb (SAA)	MTX	53	36	58
1989	**MTX+CsA**	18	58	73
Storb (leuk)	CsA	54	24	54
1989	**MTX+CsA**	33	26	65
Chao (leuk)	MTX + CsA	20	54	51
2000	MTX+CsA+P	18	46	60
Ruutu (div)	MTX + CsA	56	48	72
2000	MTX+CsA+P	19	36	65
Ratanath.	MTX+CsA	44	49	57
1998	MTX+TACR	32	56	47
Nash (URD)	MTX+CsA	74	70	50
2000	MTX+TACR	56	76	54

Randomized Phase III Study in HCT with URD
Standard GVHD prophylaxis +/- ATG-F

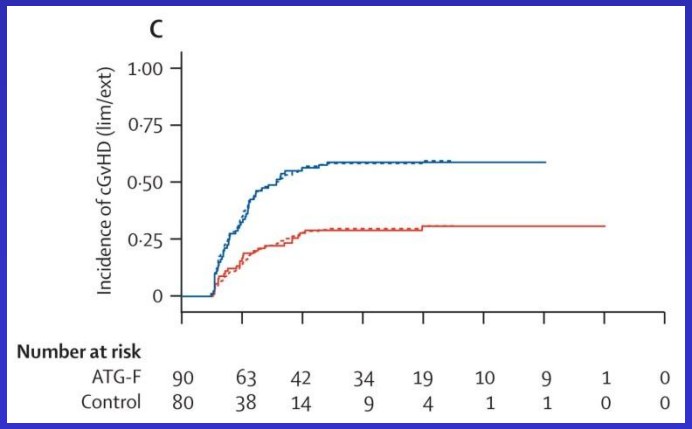
Acute GVHD II-IV

p=0.011



Chronic GVHD

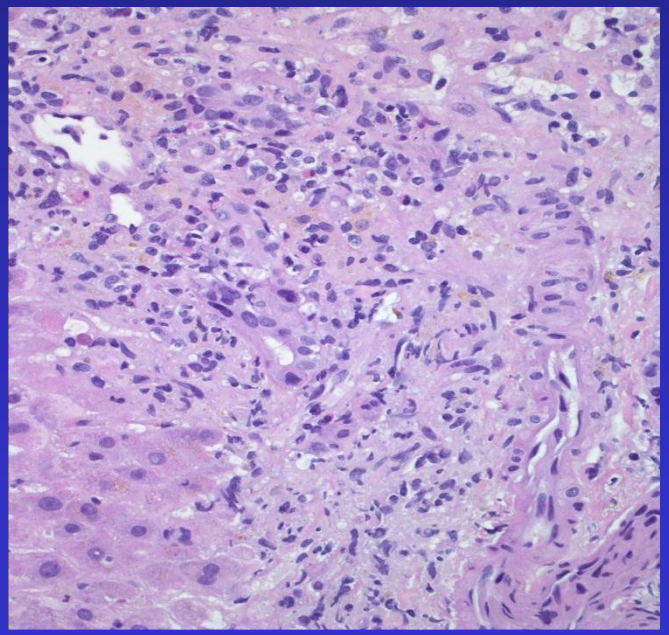
p<0.0001

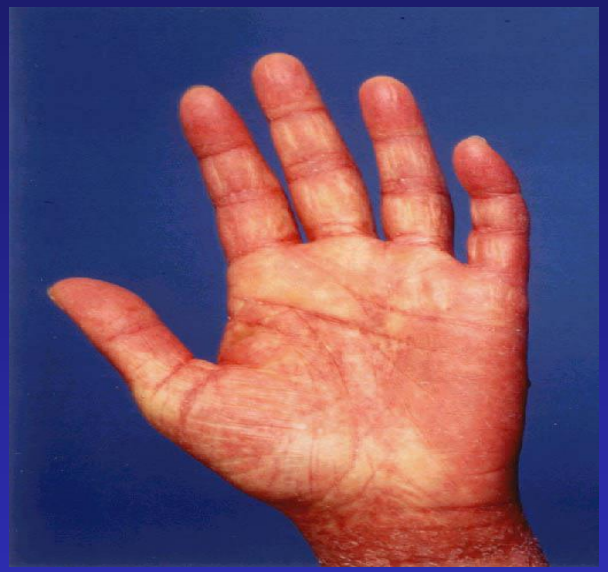


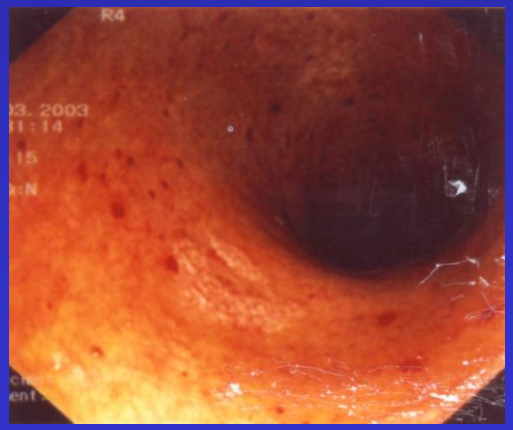
- 201 pts after MA-HCT
- **CSA/MTX+/- ATG-F** 20mg/kg days -3,-2,-1
- Significantly **lower acute GVHD II-IV** after ATG-F
- Significantly **lower chronic GVHD** after ATG-F
- No differences in relapse, NRM, OS, and mortality from infections

Finke et al, Lancet 2009
Socie et al, Blood 2011

Therapy of Acute GVHD





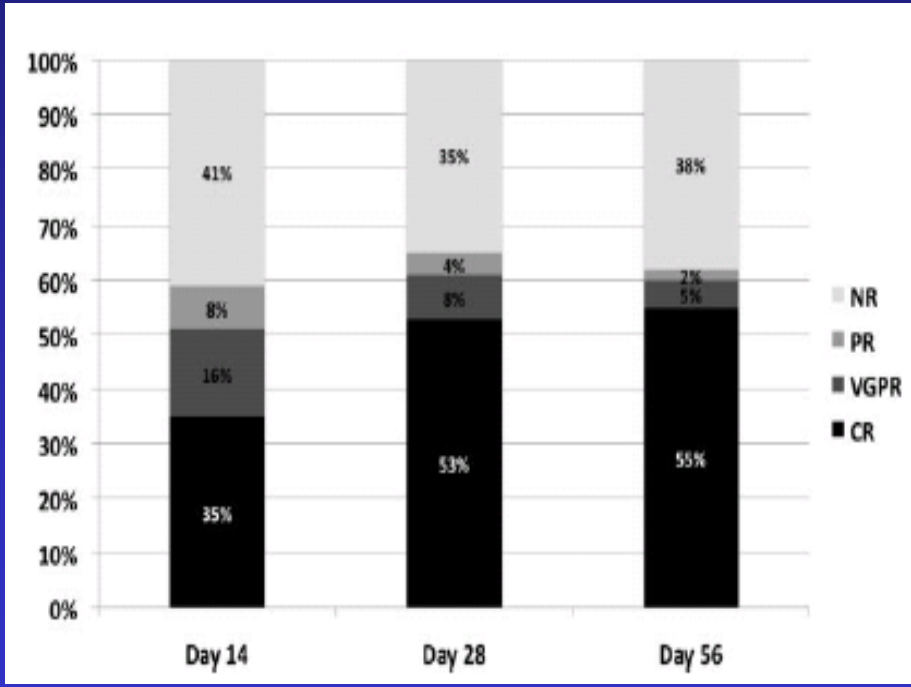


First-Line Therapy of Acute GVHD: Corticosteroids as Standard

Author	Number of patients	Design	Response	Comment
Martin 1990 [1]	197	MP	Up to 55% CR	Significantly higher CR rates in grade II and 1 organ involvement
Weisdorf 1990 [2]	160	MP	Up to 55%	Significantly higher CR rates in grade II and 1 organ involvement
Van Lint 1998 [5] *	47	MP 2 mg	68% RR	28% TRM, 63% 3-year OS
	48	MP 10 mg	71% RR	32% TRM, 62% 3-year OS
MacMillan 2002 [4]	443	MP	35% CR, 20% PR	
Cragg 2000 [6] *	46	MP	76% RR	2-year OS 50%
	50	ATG/MP	76% RR	2-year OS 40%, n.s.
Cahn 1995 [7]*	34	MP + P	54% CR	
	34	MP + anti-CD25	44% CR	OS n.s. different
Lee 2004 [8]*	49	MP + P	49% CR	1-year OS 60%
	53	MP + Daclizumab	43% CR	1-year OS 29%, p = 0.002

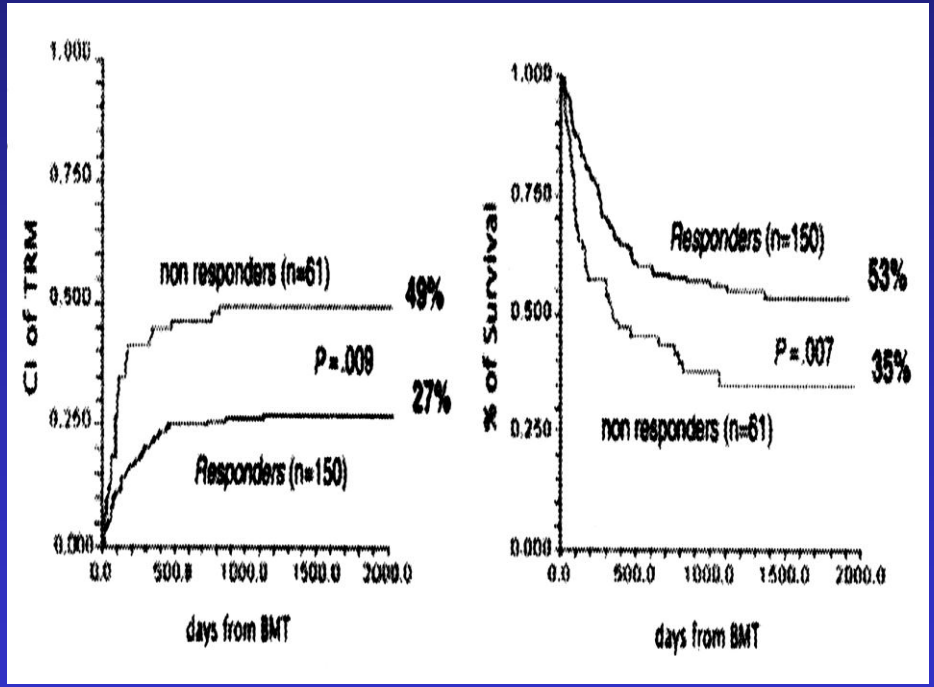
Steroids as Established First-Line Therapy of Acute GVHD

Response to Steroids



MacMillan et al, Blood 2010

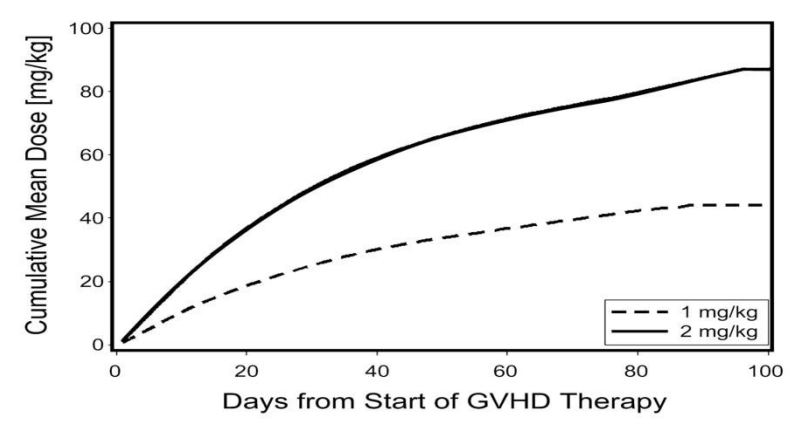
NRM and OS



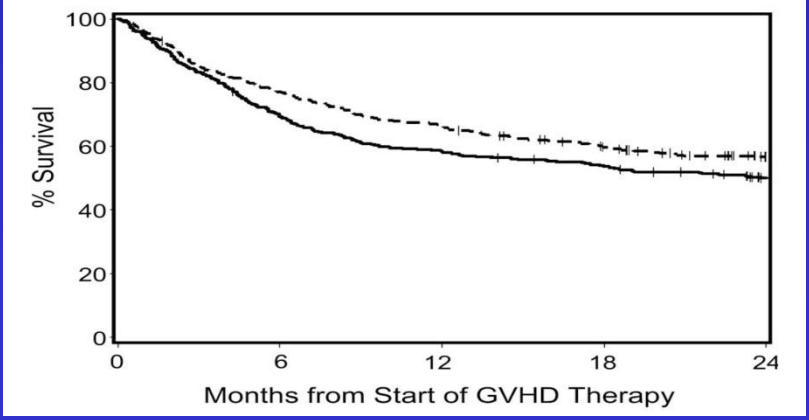
Van Lint et al, Blood 2006

Low Dose Prednisone in Acute GVHD

Cum. steroid dose



Survival



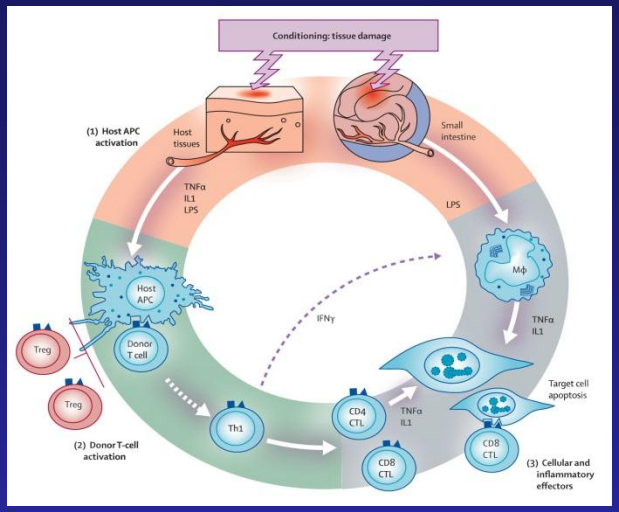
- 733 pts with mainly acute **GVHD I-II**
- Retrospective analysis
- **2 mg/kg vs 1 mg/kg** of steroids
- No difference in NRM, relapse and OS
- **Reduced fungal infections** in low-dose steroid group
- Reduced duration of hospitalization in low-dose steroid group.

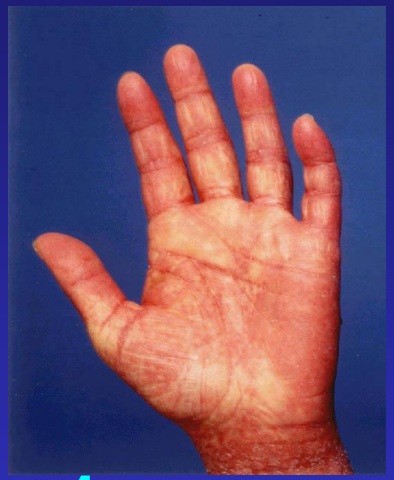
Mielcarek et al, Blood 2009;113:2888-94

ASBMT Recommendations First-line Therapy of Acute GVHD

- No advantage of steroid doses > 2.5 mg/kg/d.
- At least in grade II no disadvantage of 1mg/kg/d.
- Optimal rate for steroid taper not yet defined.
- Tapering of steroids should begin as soon as GVHD manifestations show major improvement.

Martin PJ et al, BBMT 2012;18:1150-63.





Salvage Therapy of Acute GVHD

ASBMT Recommendations
Second-line Therapy of Acute GVHD

- Second-line therapy indicated when:
  - After 3 days with **progression**
  - After 1 week with **persistent unimproving** grade III GVHD
  - After 2 weeks with **persistent unimproving** grade II GVHD

Martin PJ et al, BBMT 2012;18:1150-63.

ASBMT Recommendations: Second-line Therapy of Acute GVHD

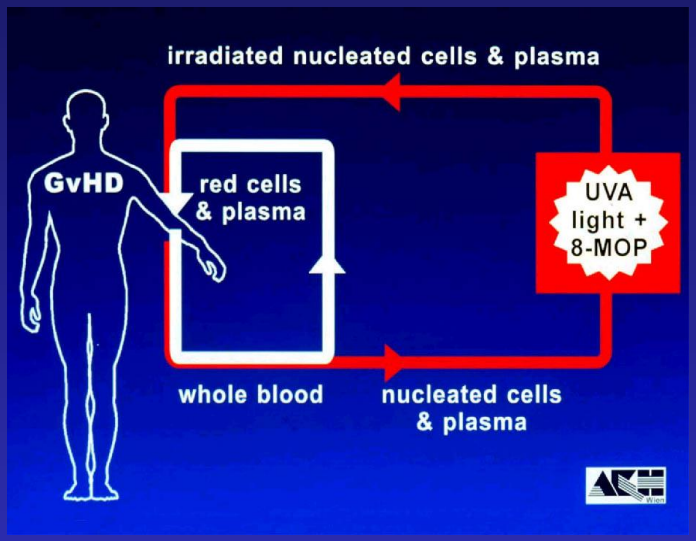
- **Evaluation of CR rates and 6-month survival** do not support the choice of any specific agent for secondary therapy of acute GVHD.
- No evidence that any specific agent should be avoided for secondary therapy of acute GVHD.

Martin PJ et al, BBMT 2012; 18:1150-63

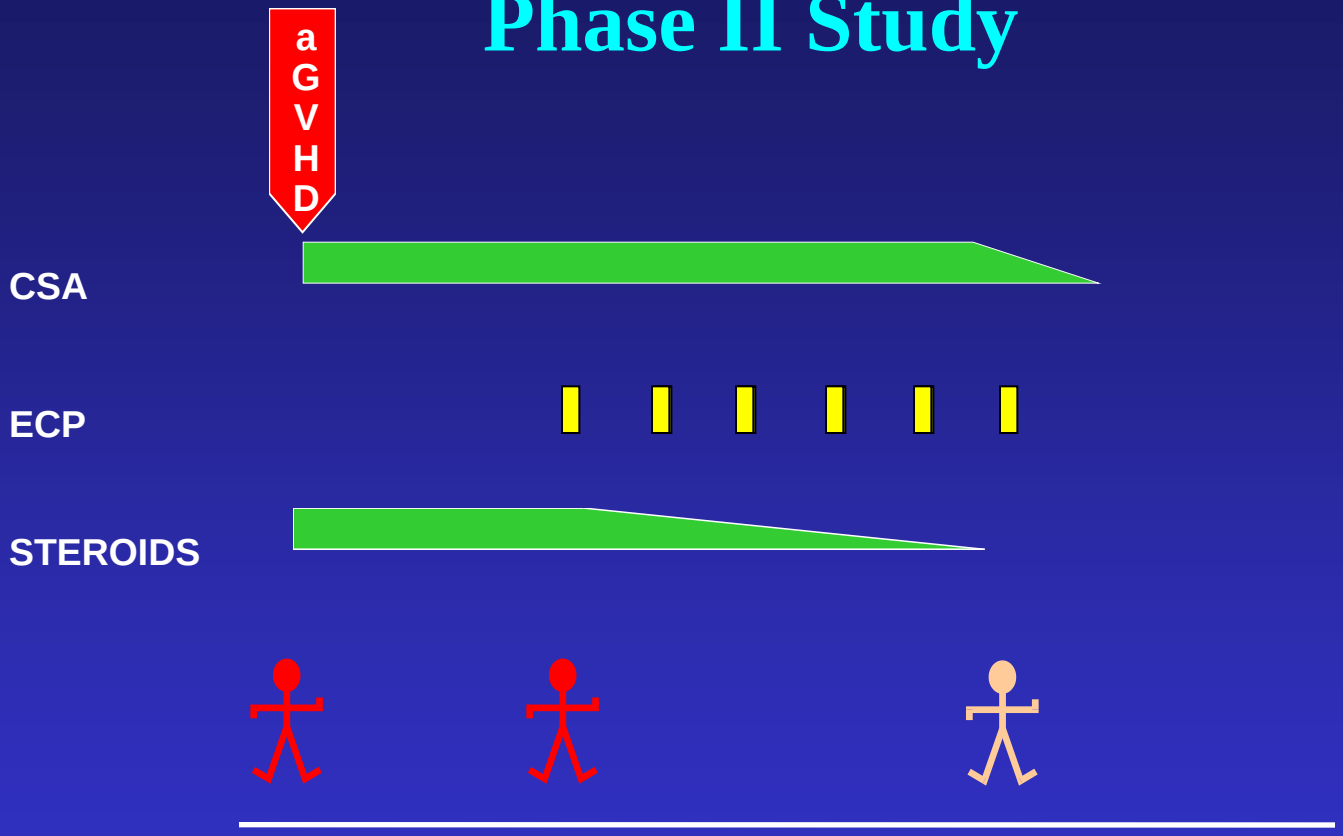
ASBMT Recommendations
Second-line Therapy of Acute GVHD

	Toxicity	Sig. interactions	Viral reactivation
ECP	**Limited**	**None**	**Not increased**
Steroids	High	None	High
MMF	Cytopenia, GI	Myelosuppress.	Moderately high
Denileukin Diftitox	↑ hepatic transam.	None	High
Sirolimus	Cytopenia, HUS/TAM	CYP3A or P-glyc.	Moderate
Infliximab	None	None	Very high
Etanercept	None	None	High
Pentostatin	Myelosuppress., liver, renal	None	Very high
Horse ATG	Anaphylaxis, cytopenia	None	Very high
Rabbit ATG	Cytopenia, infections	None	Very high
Alemtuzumab	Pancytopenia, infusion-AE	None	Very high

Extracorporeal Photopheresis



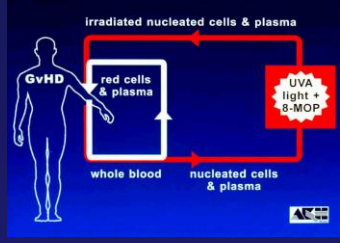
Intensified ECP in Acute Steroid - Refractory/Dependent GVHD Phase II Study

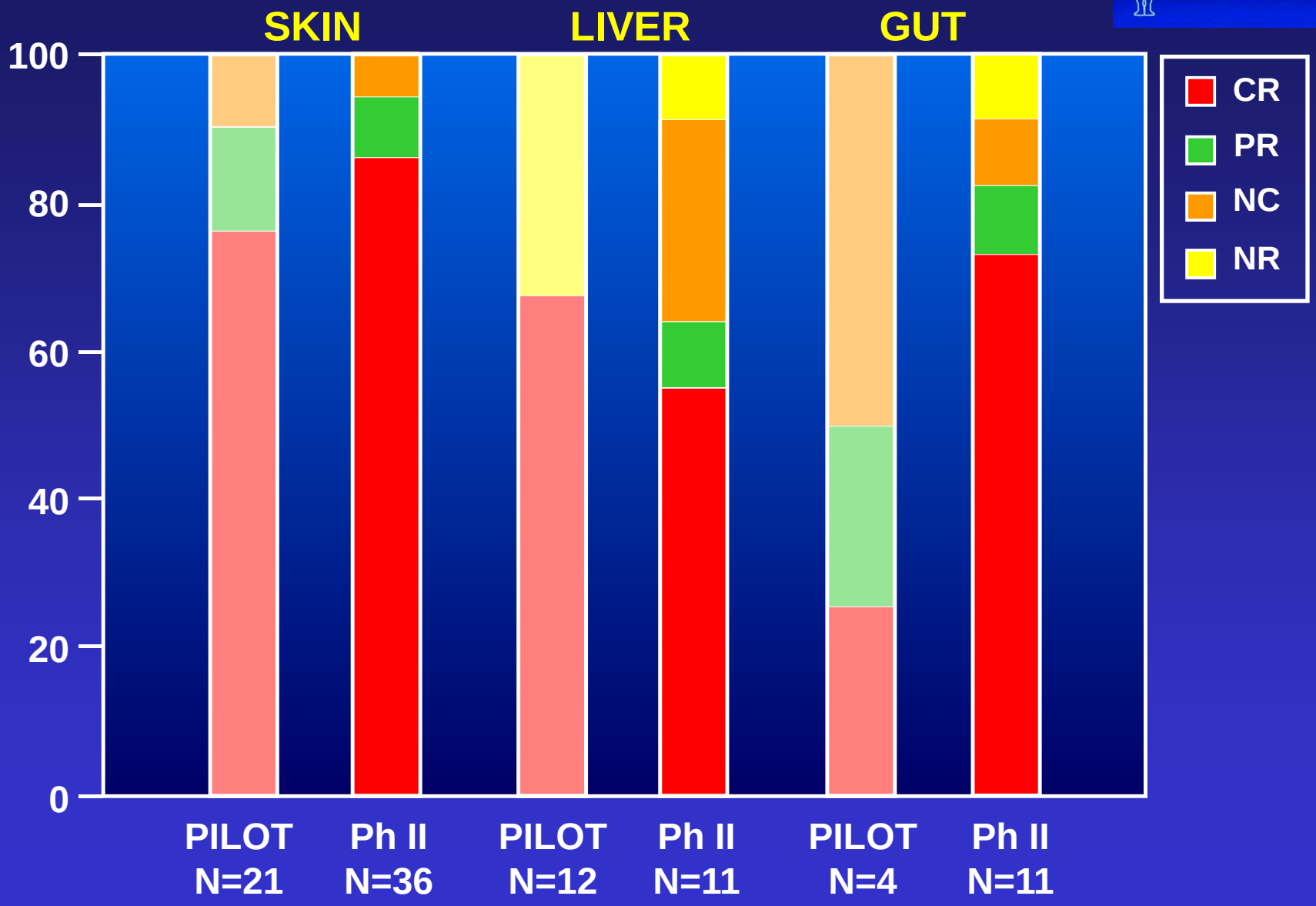


- **ECP started earlier** (steroids at 2mg/kg b.w. for at least 4 days or flare-up during steroid taper)
- Grades II to IV
- ECP on **2 consecutive days per week**
- No maintenance ECP

Greinix et al, Haematologica 2006

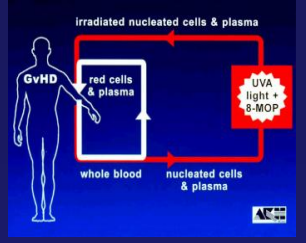
ECP as Second-line Therapy in Acute Steroid-Refractory and Steroid-Dependent GVHD



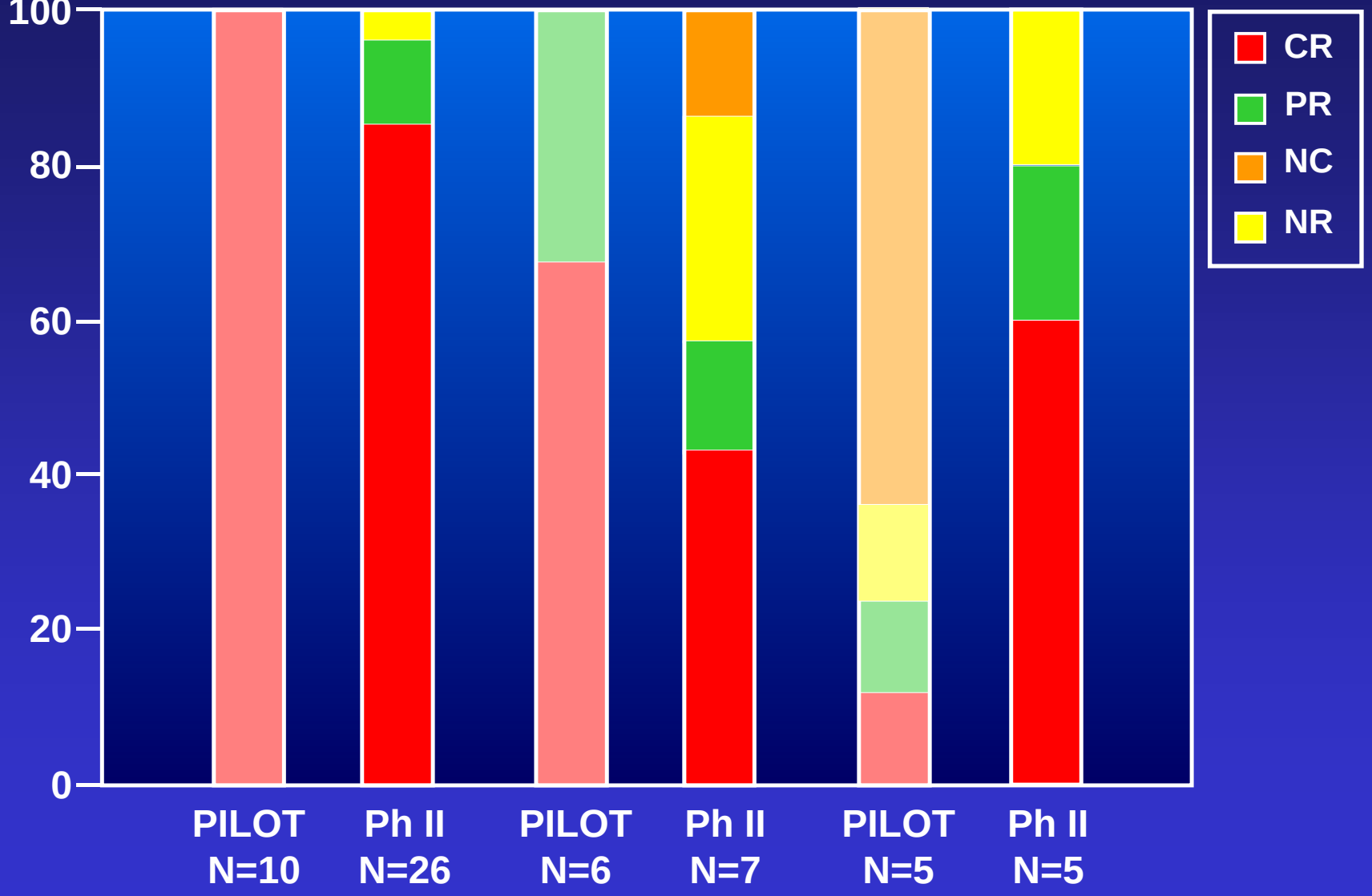


Greinix et al, Haematologica 2006

ECP as Second-line Therapy in Acute Steroid-Refractory and Steroid-Dependent GVHD



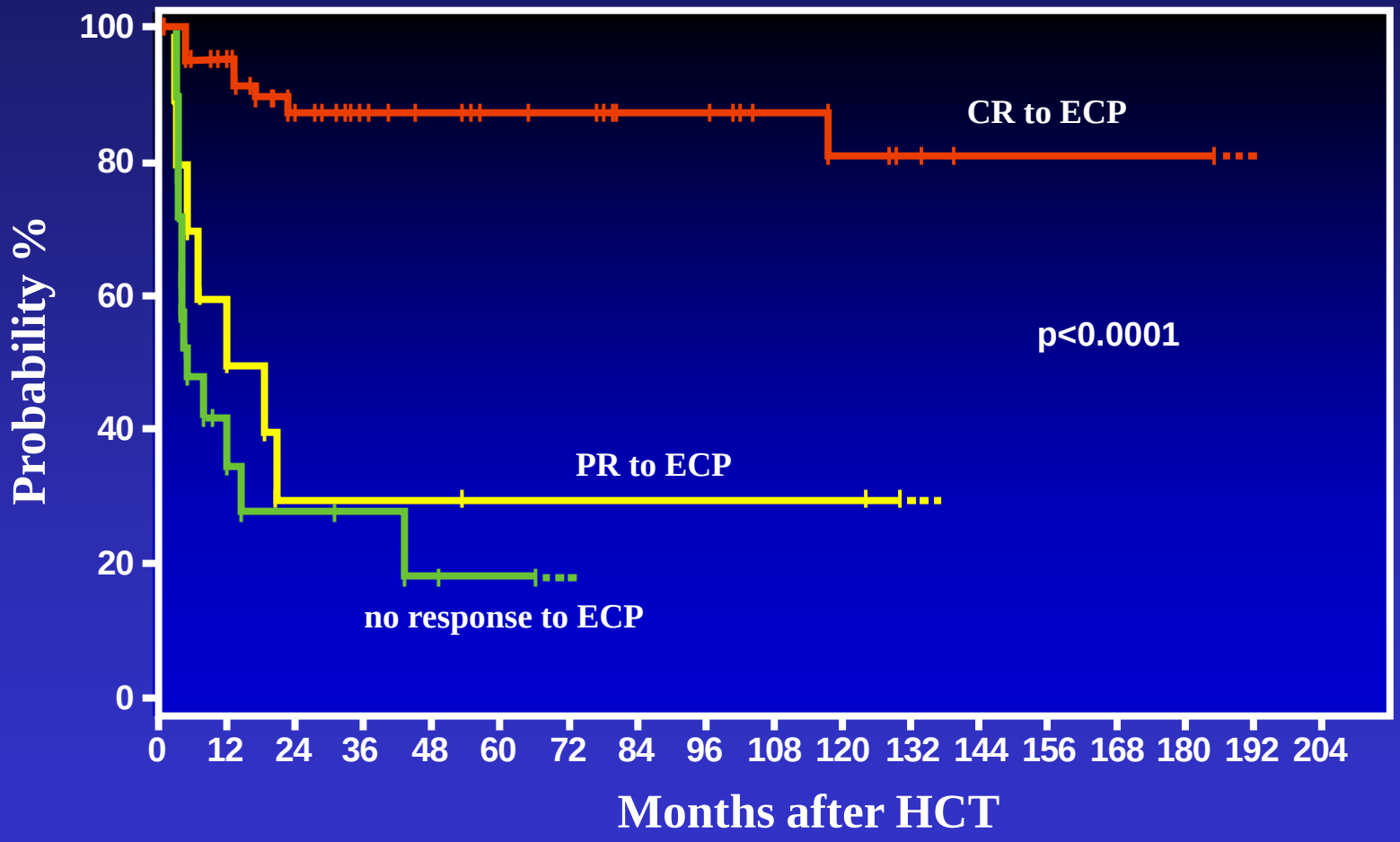
II III IV



Greinix et al, Haematologica 2006

ECP in Steroid-refractory Acute GVHD

Long-Term Survival according to Response (n=96)



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ASBMT Recommendations: Second-line Therapy of Acute GVHD

- **Choice of second-line regimen** should be guided by considerations of:
  - Effects of any previous treatment
  - Potential toxicity (infections)
  - Interactions with other agents
  - Familarity of physician with agent
  - Prior experience of physician with agent
  - Convenience
  - Expense
- **Steroids should be continued** after starting second-line agent for therapy of steroid-refractory acute GVHD.

Martin PJ et al, BBMT 2012; 18:1150-63

Conclusions

- Acute GVHD has significant impact on survival.
- No clear separation of beneficial vs harming cell populations in graft/post-transplant cell therapy available yet: **GVL vs GVHD**.
- Lack of well-defined prospective studies.
- **No progress** in first-line therapy of aGVHD.
- How to obtain **improved outcome**
  - Improved GVHD prophylaxis
  - Biomarkers for GVHD: prophylactic/preemptive therapy
  - ECP as immunomodulatory therapy

GVHD Study Group Vienna

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- –A. Tanew
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Dept. Transfusion Medicine
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- V. Petkov