MEDIZINISCHE UNIVERSITÄT WIEN

Photopheresis in Acute Graft-versus-Host Disease

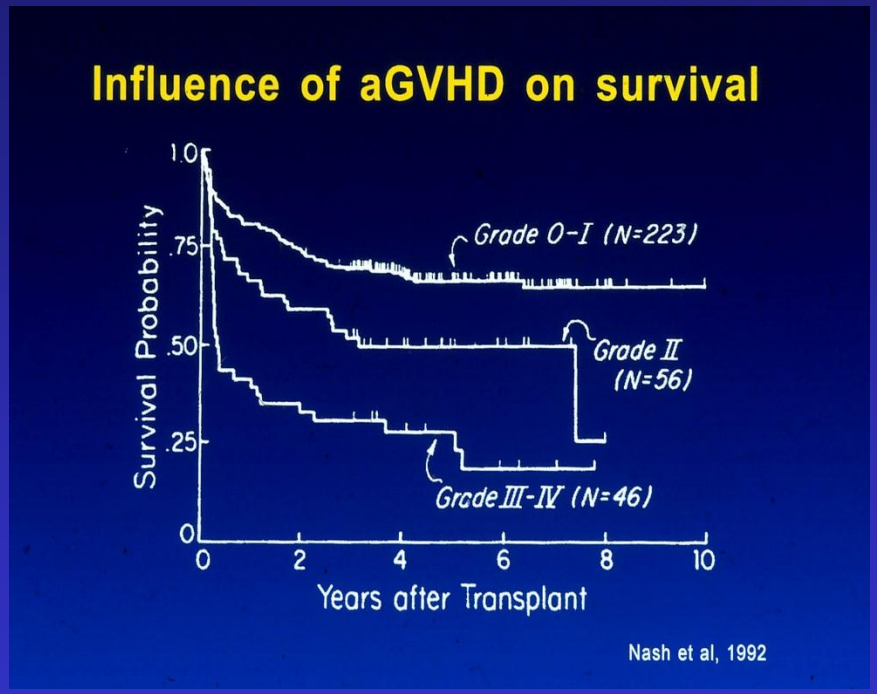
Hildegard T. Greinix

Medical University of Vienna

Austria

Univ. Klinik für
Innere Medizin I

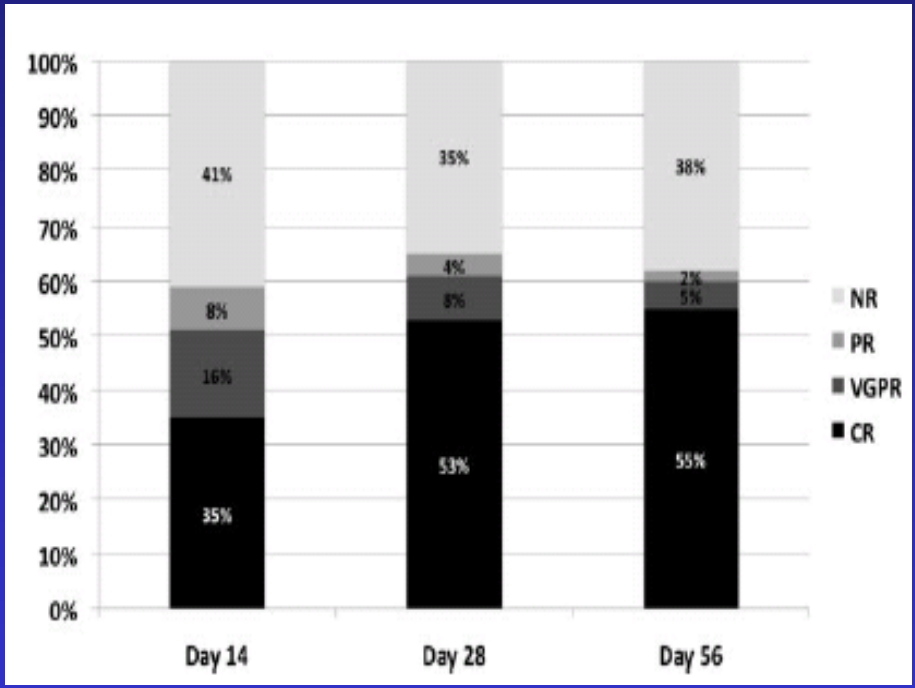
Acute GvHD is Serious Complication of Allo HCT



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

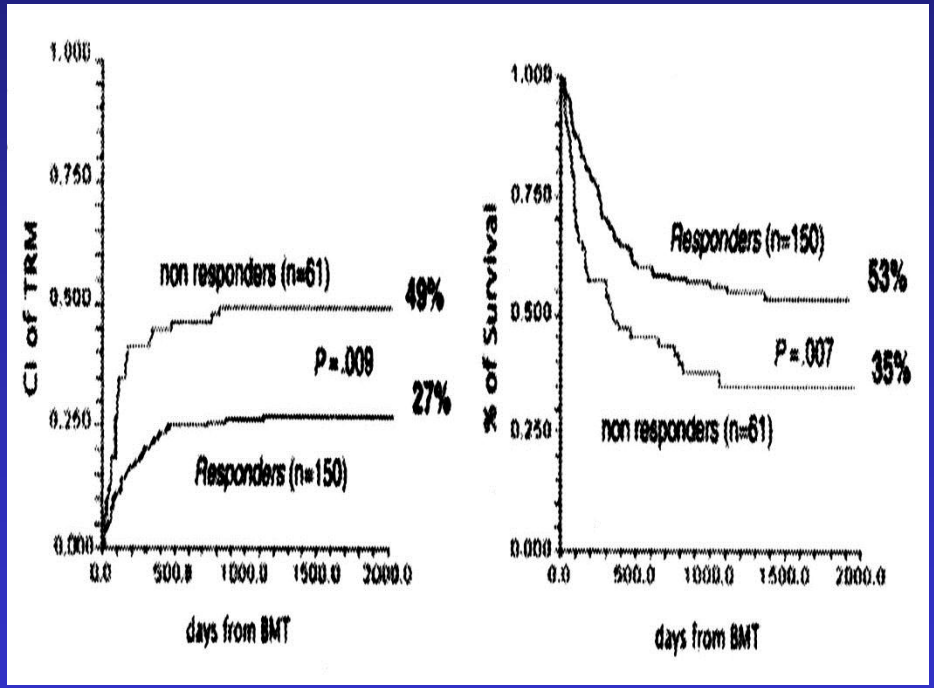
Steroids as Established First-Line Therapy of Acute GvHD

Response to Steroids



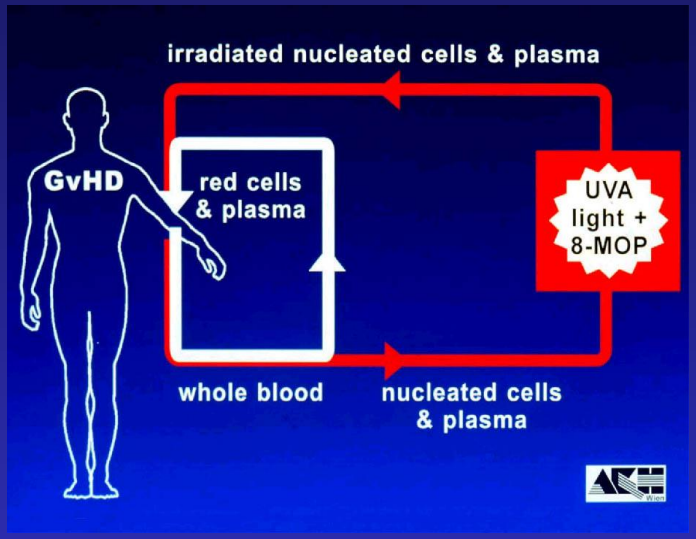
MacMillan et al, Blood 2010

NRM and OS

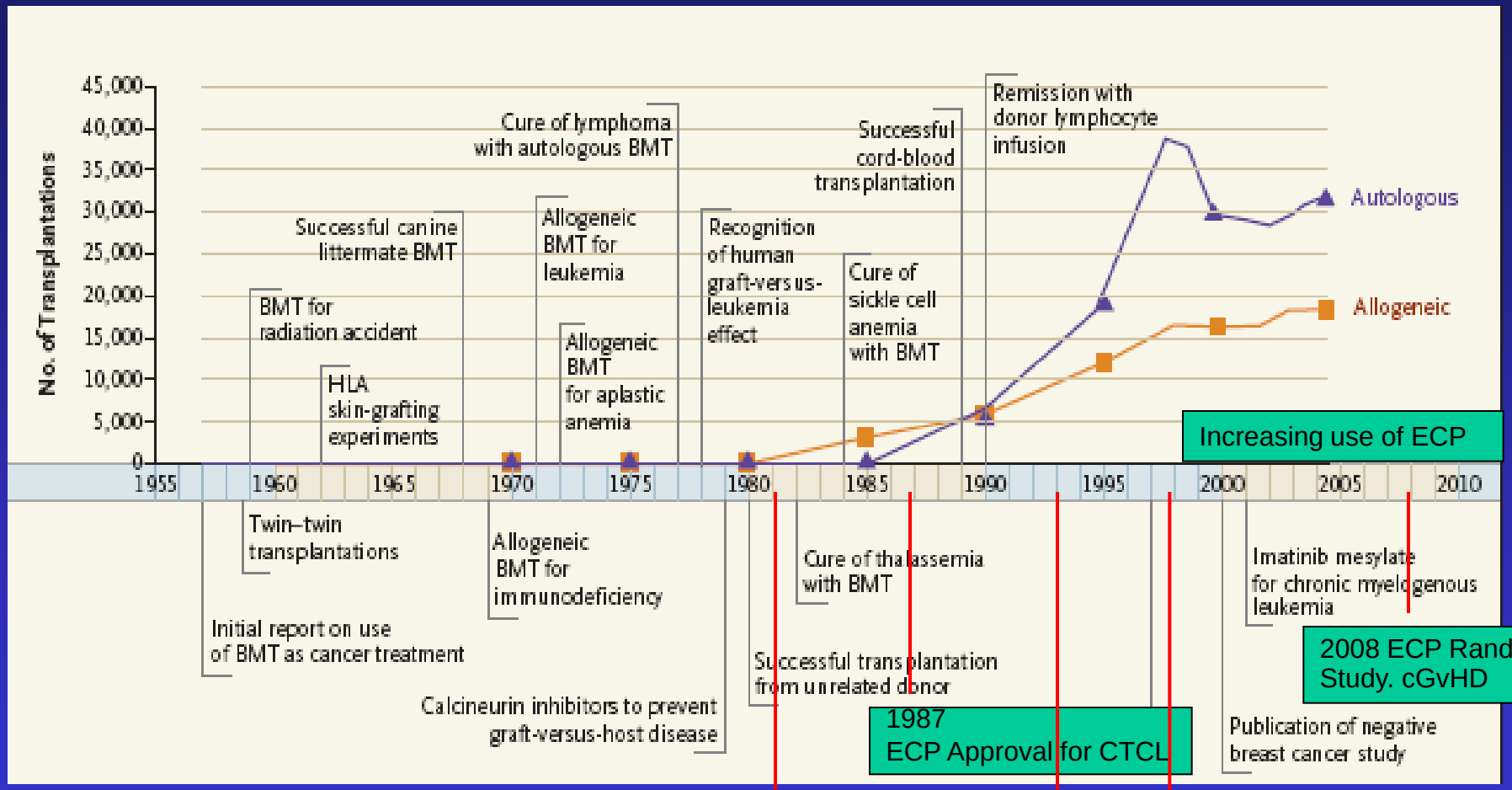


Van Lint et al, Blood 2006

ECP in Acute Steroid-Refractory GvHD



Development of ECP for Clinical Use



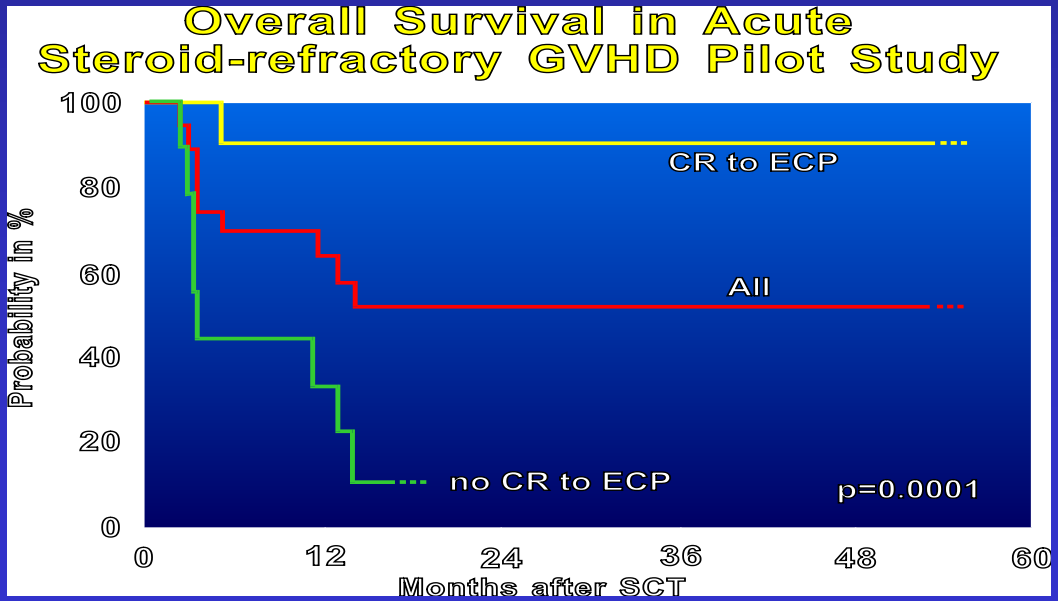
Pilot Study of ECP in Acute Steroid-Refractory GvHD

blood 2000 96: 2426-2431

Extracorporeal photochemotherapy in the treatment of severe steroid-refractory acute graft-versus-host disease: a pilot study

Hildegard T. Greinix, Beatrix Volc-Platzer, Peter Kalhs, Gottfried Fischer, Agatha Rosenmayr, Felix Keil, Hubert Hönigsmann and Robert M. Knobler

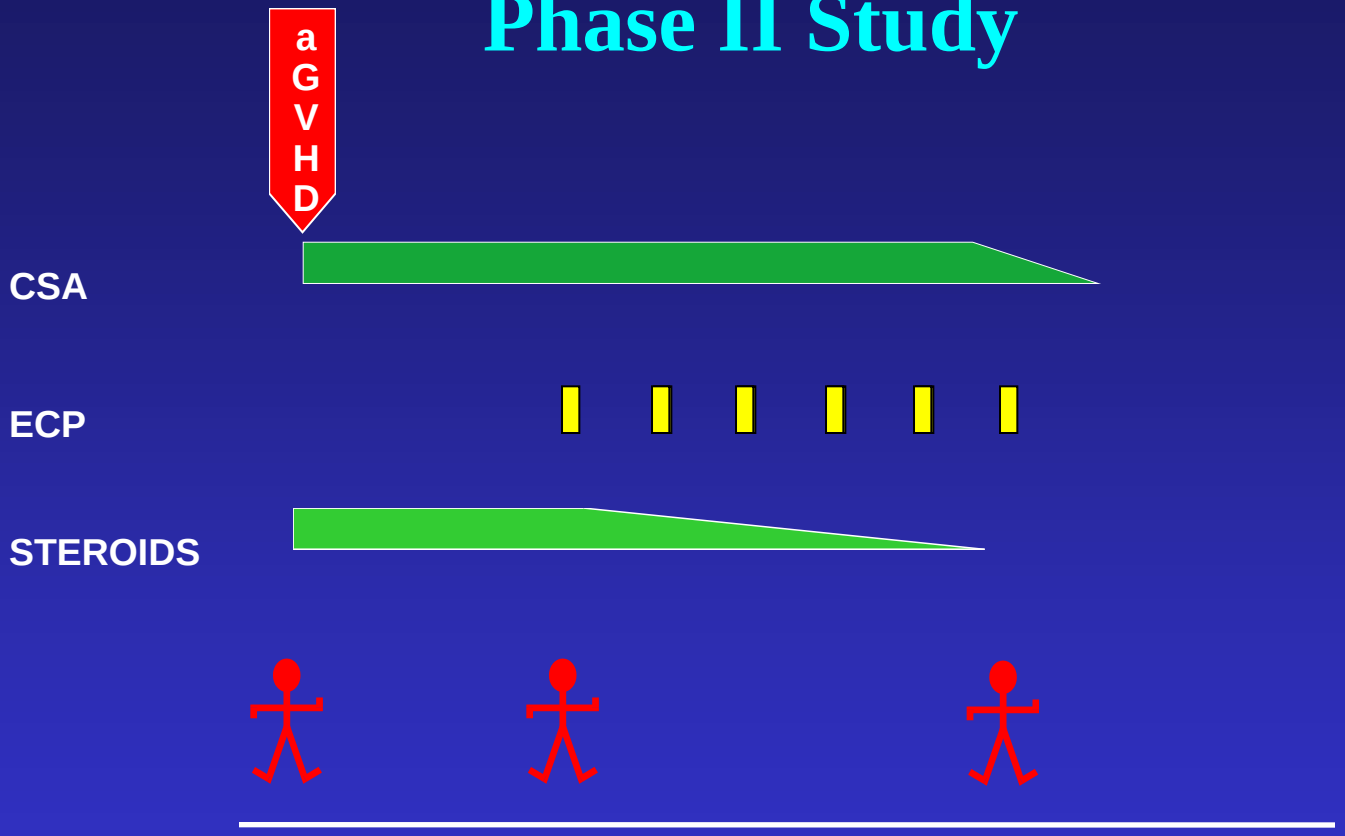
- To evaluate the **safety and efficacy of ECP**.
- In addition to CSA and steroids at 2 mg/kg ECP performed on 2 consecutive days at 1 to 2 week intervals until improvement, then every 2 to 4 weeks until maximal response.



ECP in acute GvHD

- **Inclusion criteria**
  - Grades II to IV
  - Steroid-refractory (steroids at 2mg/kg b.w. for at least 4 days)
  - Steroid-dependent (flare-up during taper)
  - Karnofsky $\geq$ 50%
  - Signed written informed consent
- **Exclusion criteria**
  - Uncontrolled infection
  - ANC < 1.0 X 10^9/l
  - Plts < 20 X 10^9/l
  - Hemodynamic instability
  - Hypersens. to 8-MOP
  - Poor compliance

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

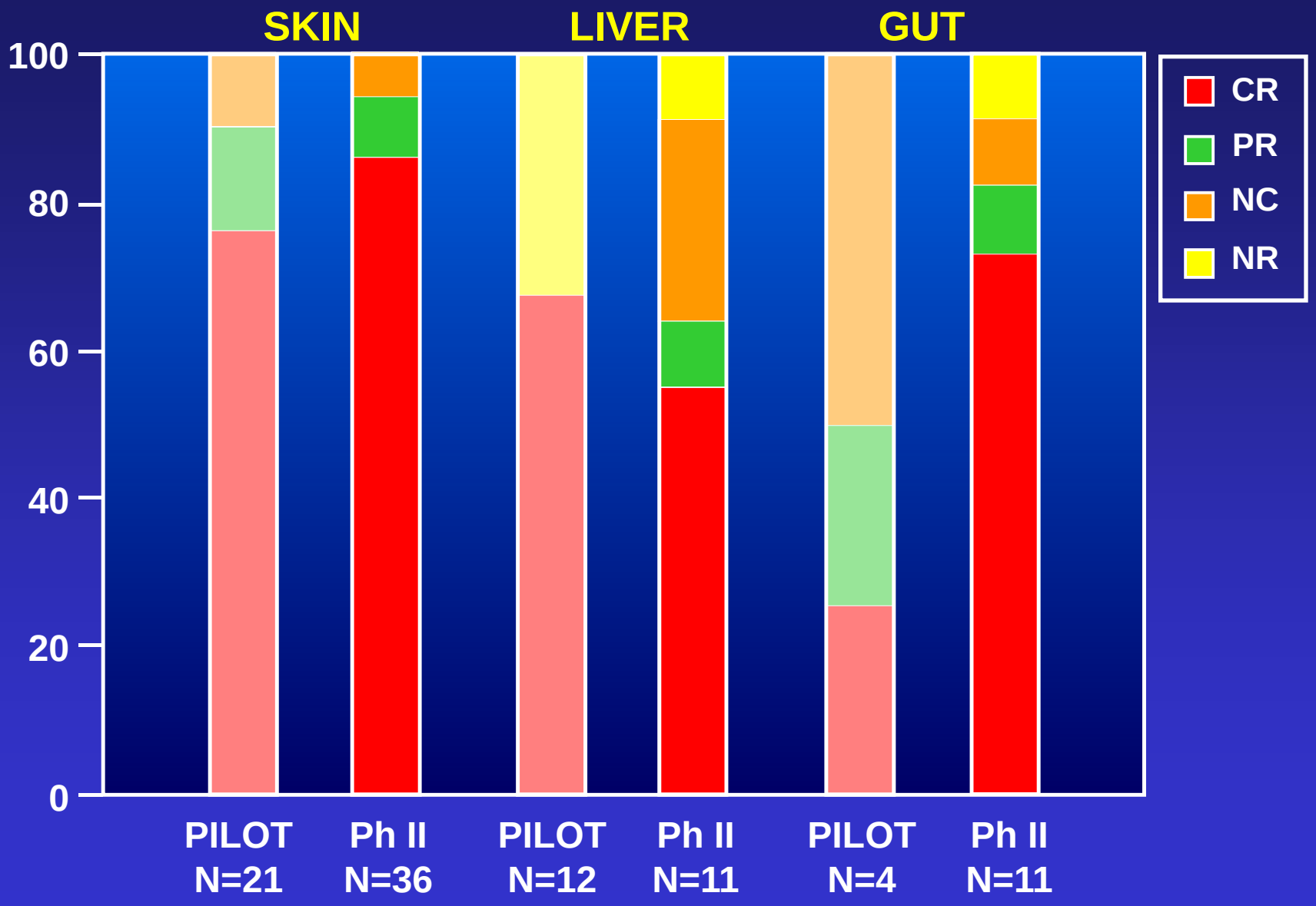
MEDIZINISCHE UNIVERSITÄT WIEN

Comparison Pilot Study and Phase II Study

	All N=59	**Pilot** N=21	**Phase II** N=38
II/III/IV at ECP	36/13/10	10/6/5	26/7/5
Skin alone Skin+liver Skin+liver+gut Others	31 13 8 7	8 9 3 1	23* 4 5 6
HCT-ECP d	37 (17-70)	41 (20-70)	36 (17-69)*
D steroids prior ECP	17 (4-49)	21 (9-49)	16 (4-43)*
Cum.steroid dose first-line mg/kg	2.8 (2-10.4)	3.9 (2-10.4)	2.1 (2-6.5)*
Med.steroids at start of ECP mg/kg	2.1 (0.7-10.4)	2.6 (1.1-10.4)	1.9 (0.7-2.3)*

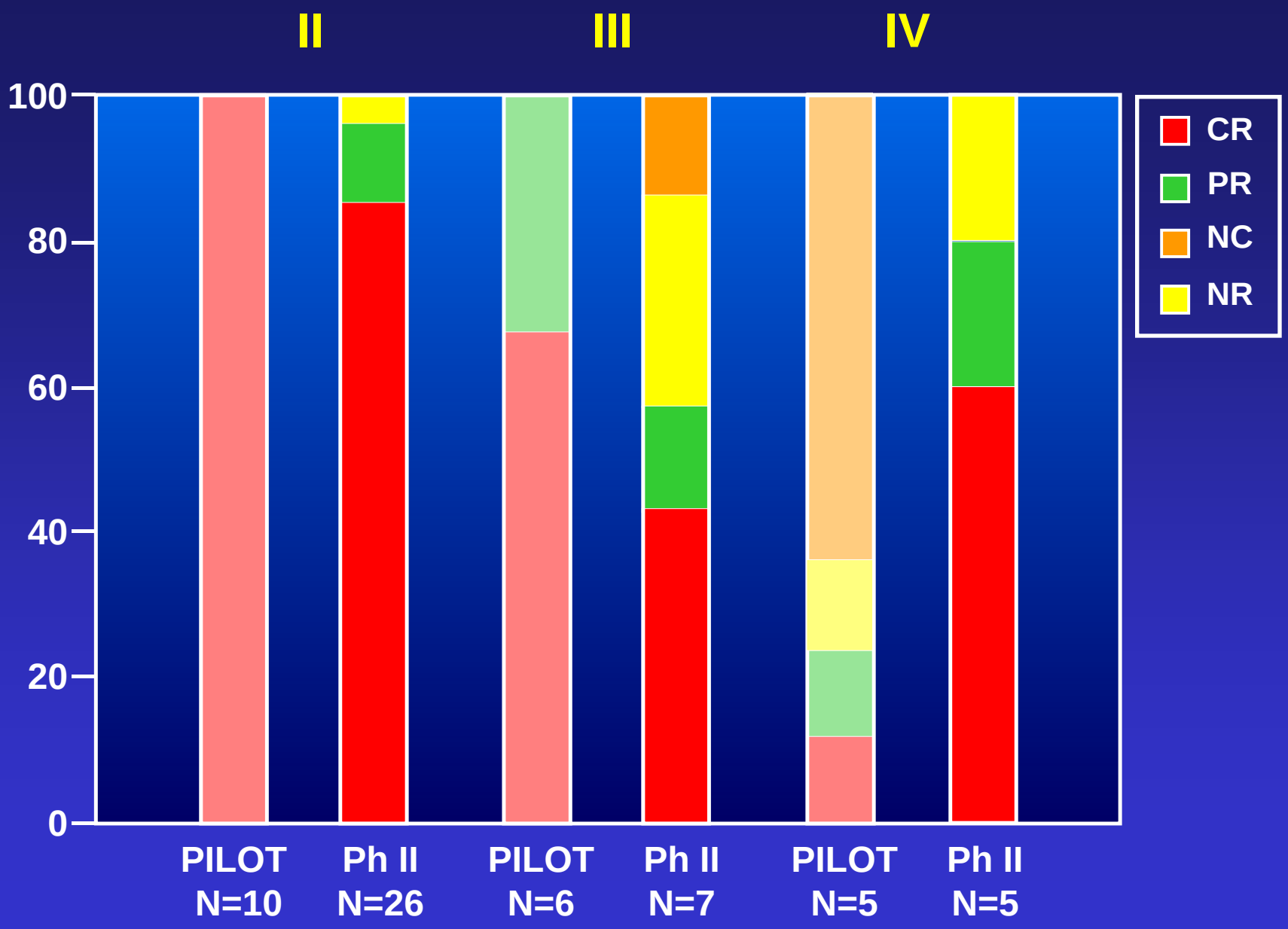
Greinix et al, Haematologica 2006

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



Greinix et al, Haematologica 2006

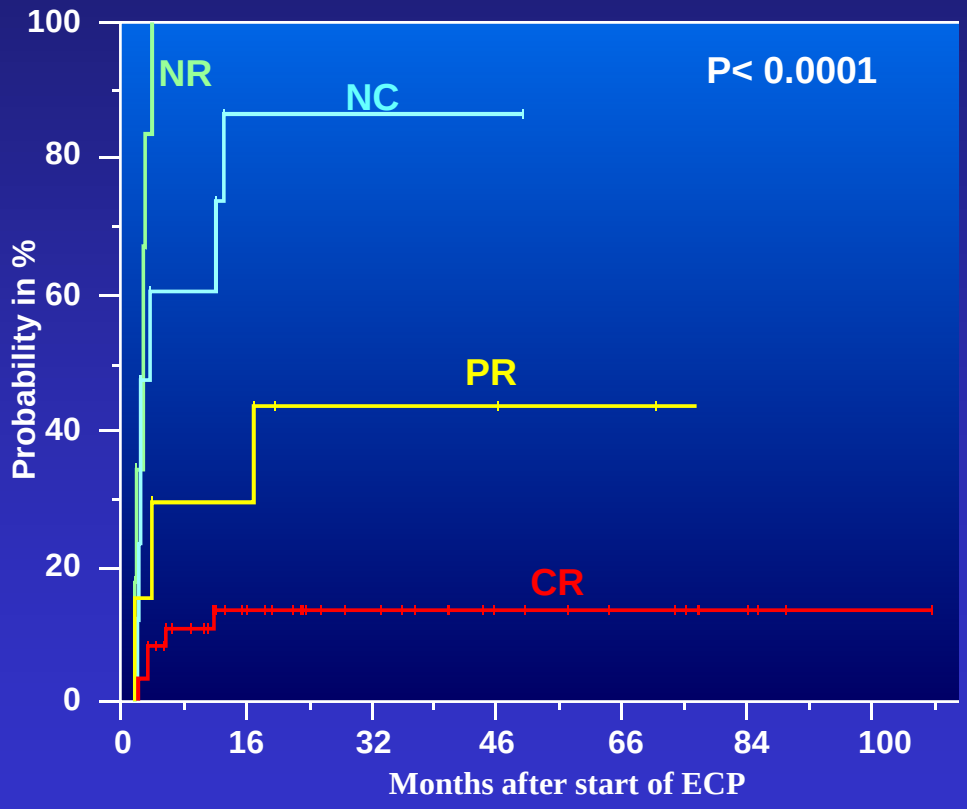
Acute Steroid-Refractory and Steroid-Dependent GvHD

Results of ECP

	All	Pilot	Phase II
No ECP cycles	7 (1-45)	11 (1-45)	5 (1-16)
Length ECP mo	3 (0.5-31)	5 (1-31)	1.5 (0.5-7)
Max. response after ECP cycle	**4 (1-13)**	**4 (1-13)**	**4 (1-8)**
Max. response after months	**1.3 (0.5-6)**	**2 (0.5-6)**	**1.2 (0.5-4.5)**
DC steroids d	55 (17-284)	53 (18-122)	56 (17-284)
Steroid dose 4 weeks after start	0.9 (0-5) mg/kg	1.1 (0-5) mg/kg	0.7 (0-2) mg/kg
Steroid dose 8 weeks after start	0.3 (0-1.5)mg/kg	0.3 (0-1.3)mg/kg	0.2 (0-1.5)mg/kg

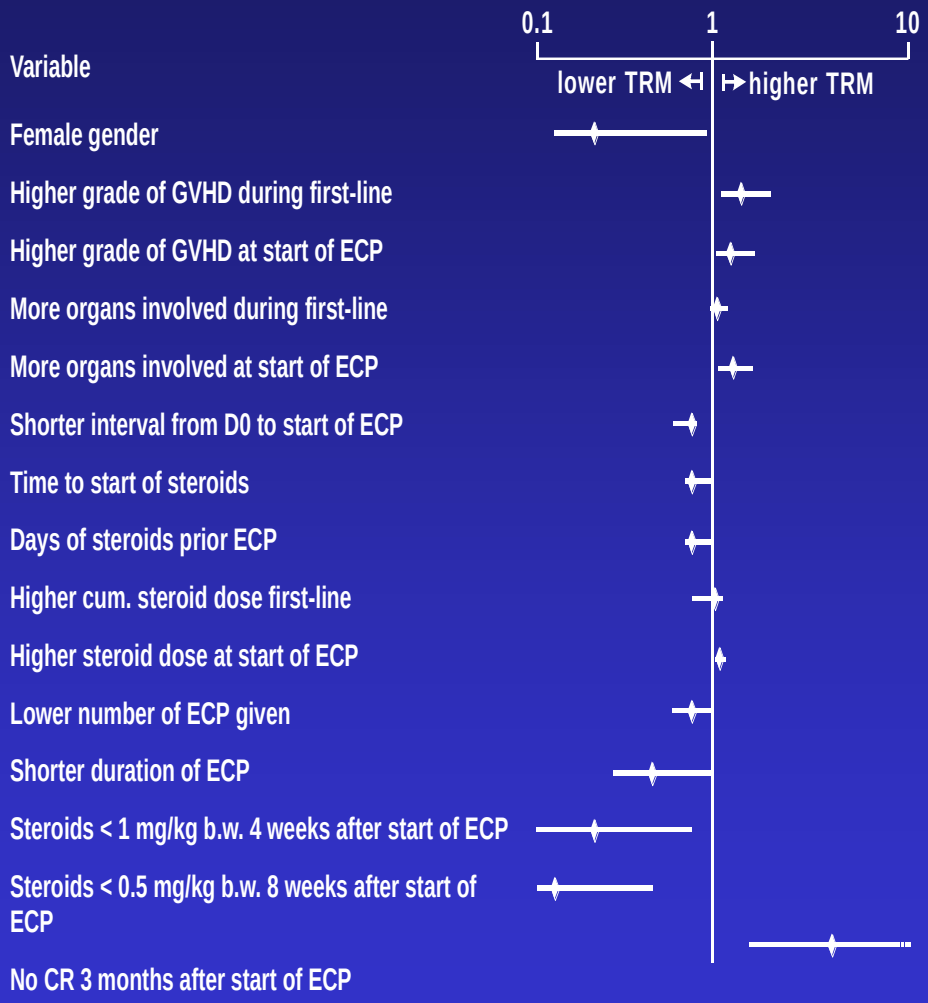
Greinix et al, Haematologica 2006

TRM of Patients with Steroid-Refractory Acute GvHD According to Response to Second-Line ECP

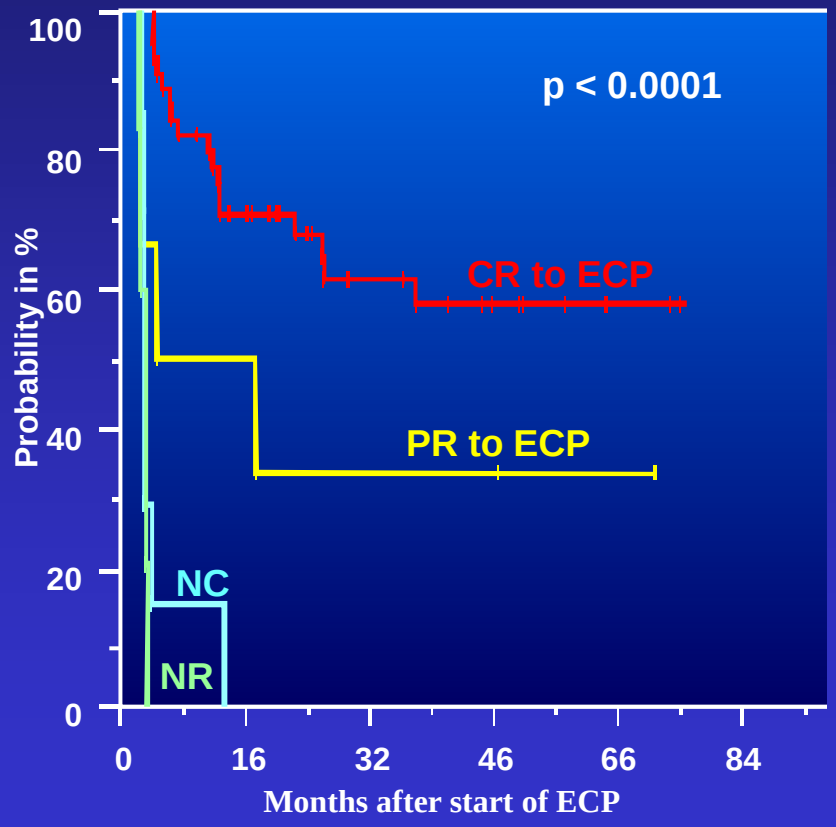


Greinix et al, Haematologica 2006

Hazard Ratios for TRM

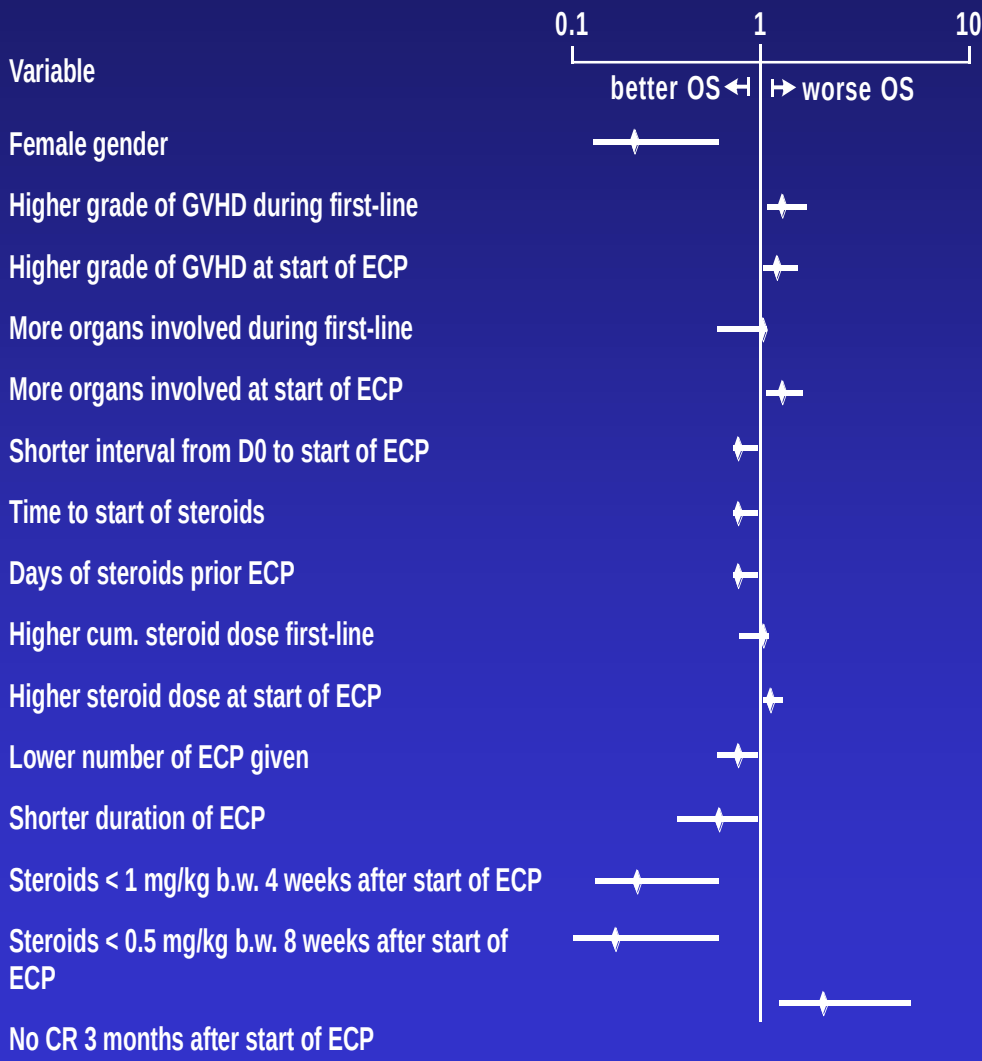


Overall Survival of Patients with Steroid-Refractory Acute GvHD According to Best Response to Second-Line ECP



Greinix et al, Haematologica 2006

Hazard Ratios for Overall Survival



MEDIZINISCHE UNIVERSITÄT WIEN

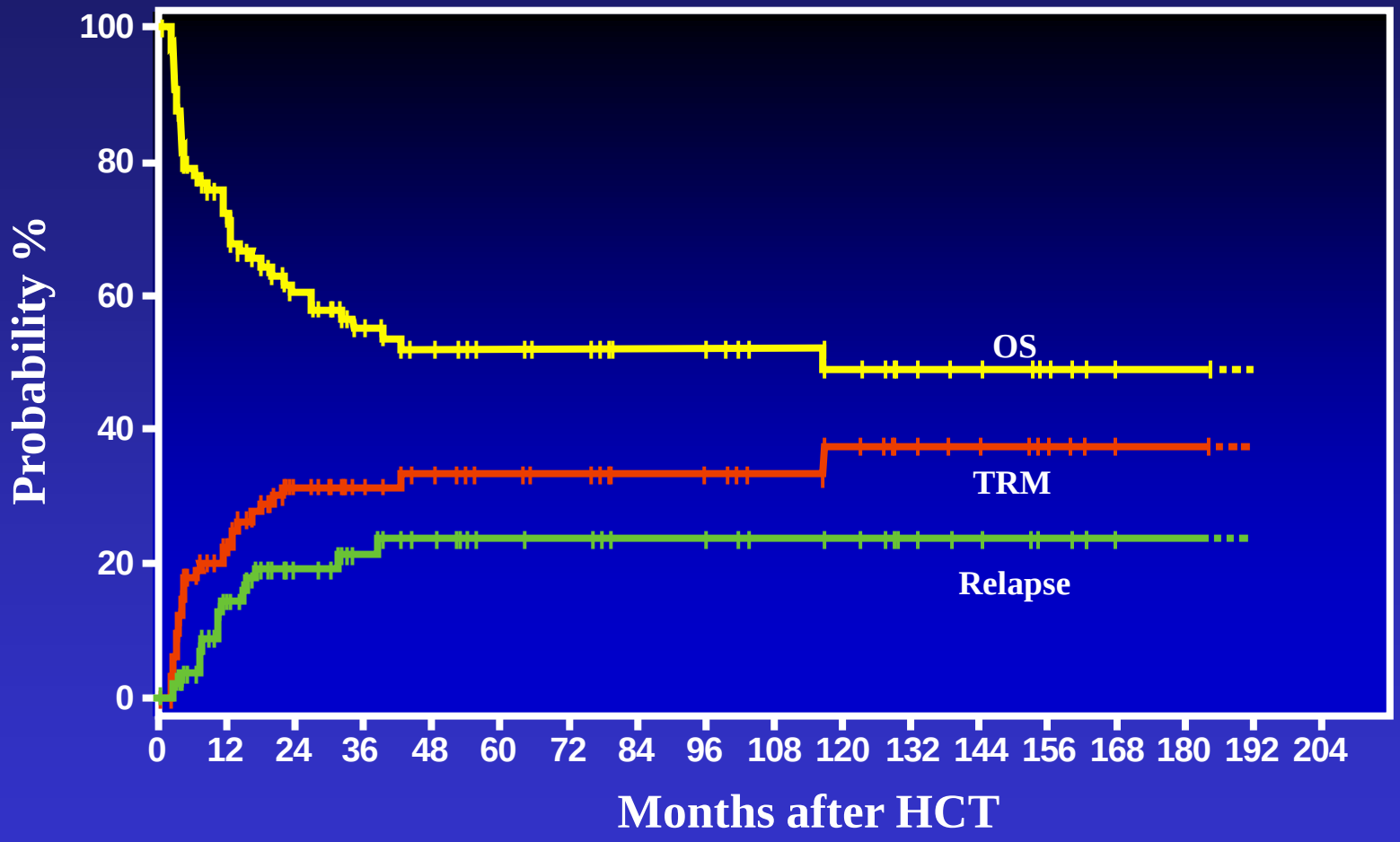
Acute Steroid-Refractory/Dependent GvHD

Outcome after ECP (n=96)

Outcome	No (%)
Alive	52 (54)
No chronic GVHD	36/52 (69)
Relapse	17 (18)
Med. FU yrs	6 (0.5-15)

ECP in Steroid-refractory Acute GvHD

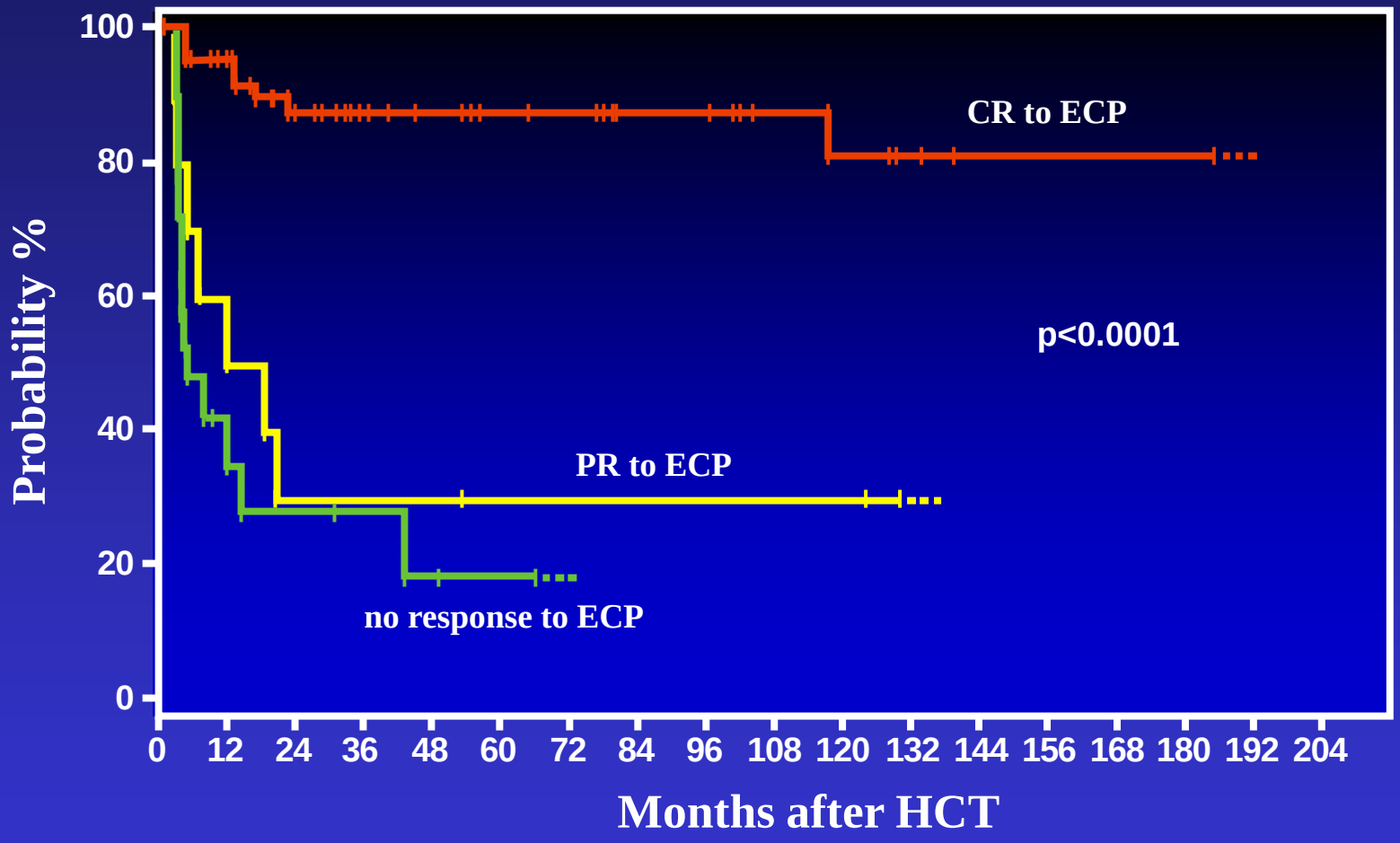
Long-Term Results (n=96)



MEDIZINISCHE UNIVERSITÄT WIEN

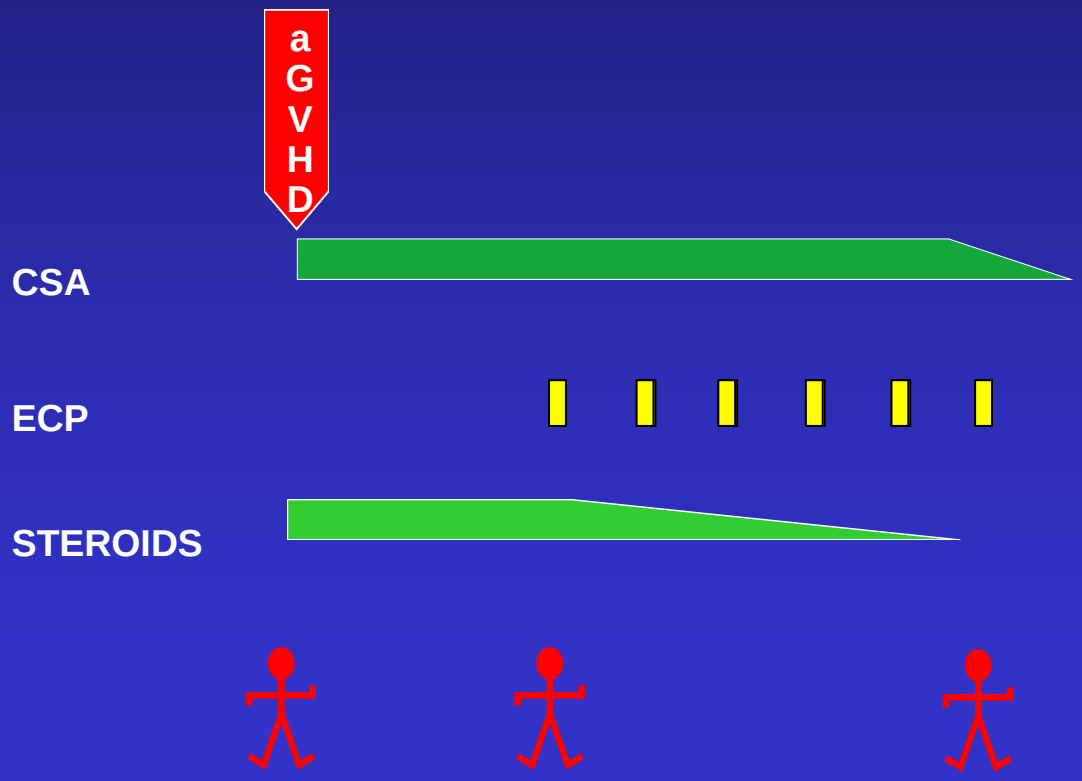
ECP in Steroid-refractory Acute GvHD

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



Second-Line ECP in Acute Steroid-Refractory GvHD

Intensified Second-Line ECP



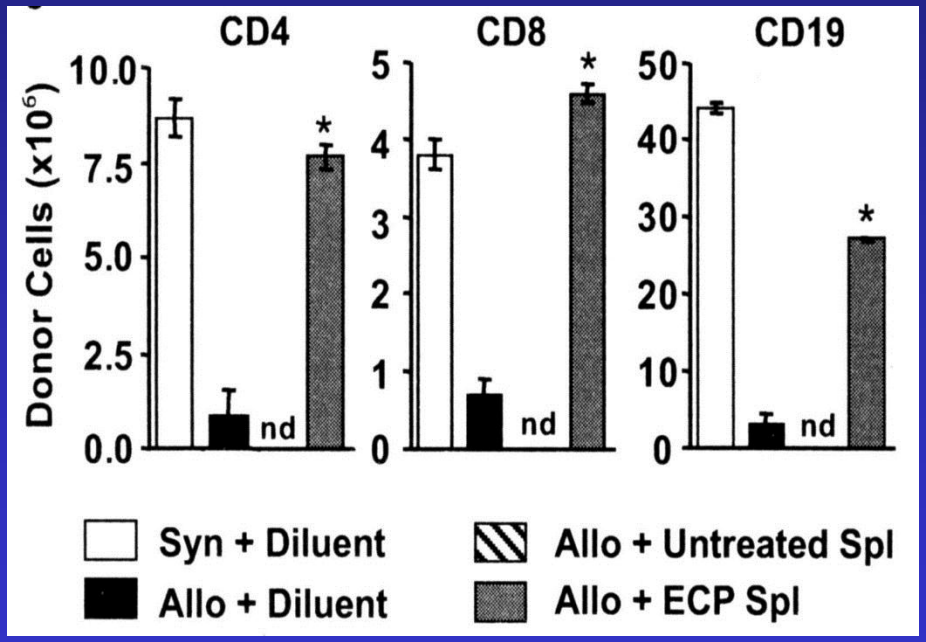
- ECP is effective and well-tolerated adjunct second-line therapy.
- **Start ECP early** for ↑ CR and ↓ TRM.
- **Apply ECP weekly** on 2-3 days.
- Short ECP treatment times, **no flare-ups**.
- **Rapid steroid taper**: ↓ TRM and ↑ OS.
- GvL not affected.

Efficacy of ECP is not a result of generalized immunosuppression

- No increase of opportunistic infections or relapse during ECP
- No suppression of T-or B-cell responses to novel or recall antigens after ECP

Suchin et al, J Am Acad Dermatol 1999

Improvement in immune reconstitution after ECP in experimental allo BMT

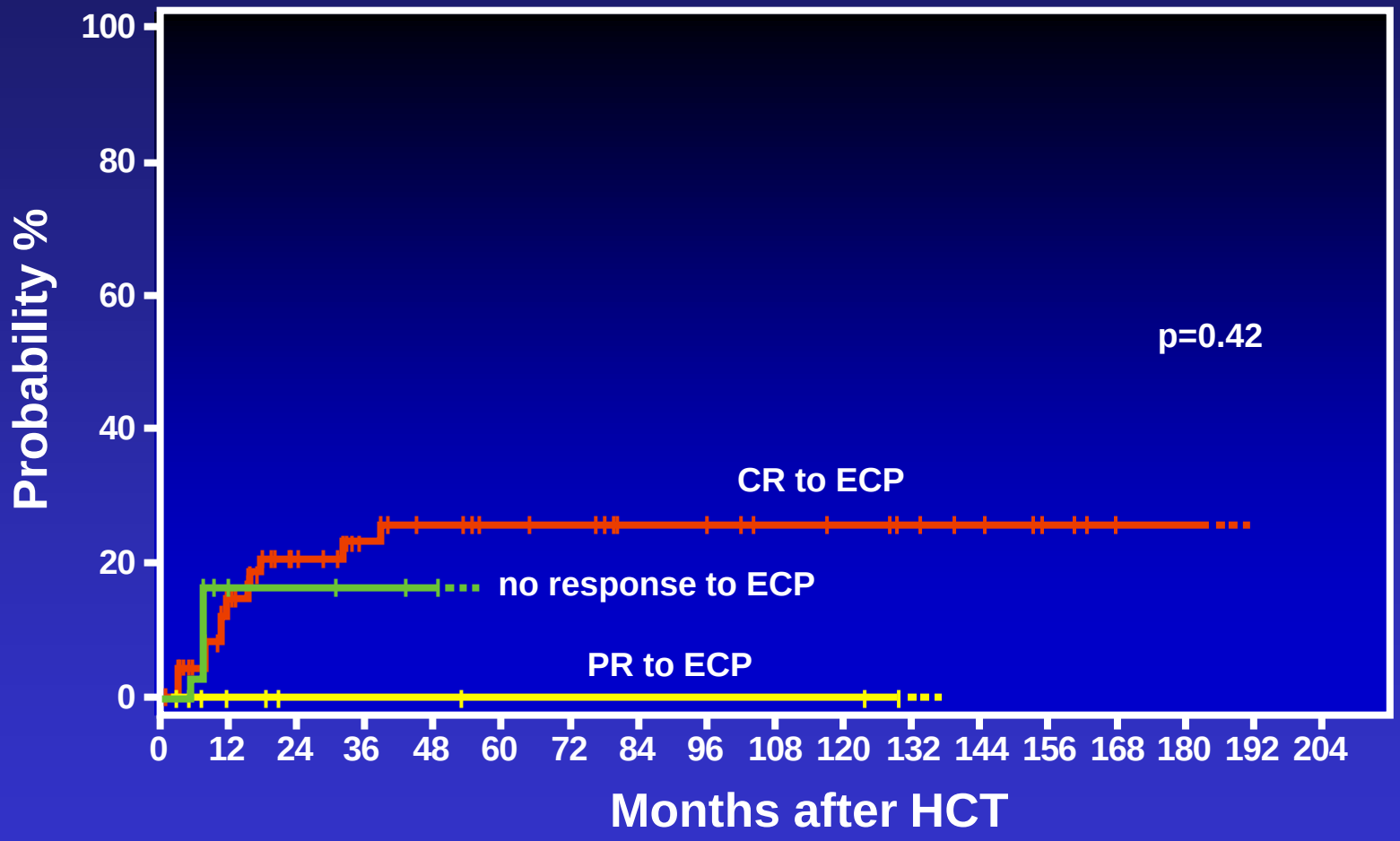


Gatza et al, Blood 2008

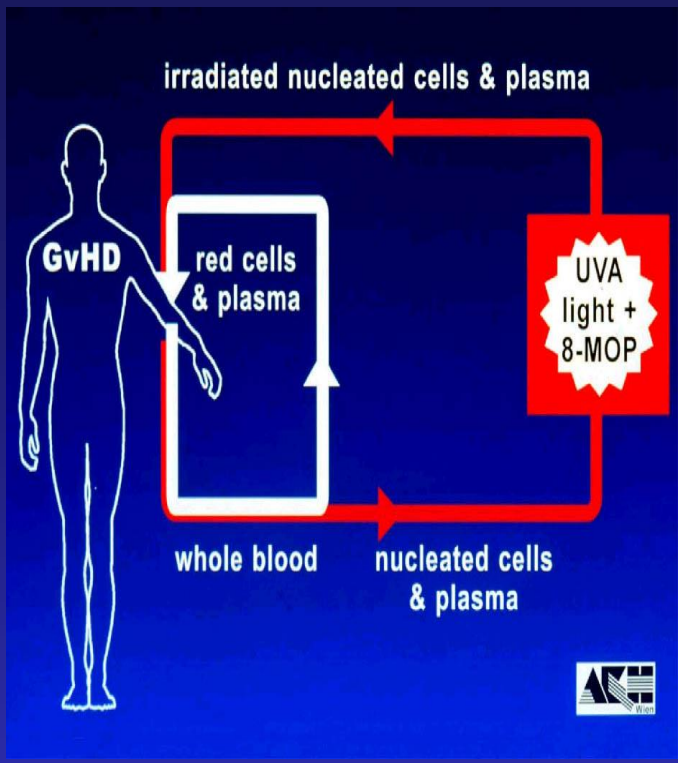
MEDIZINISCHE UNIVERSITÄT WIEN

ECP in Steroid-refractory Acute GvHD

Long-Term Results on Relapse (n=96)



Safety



- **Excellent safety profile**
- Reported adverse events
  - Hypotension in 2-4%
  - Dizziness in up to 4%
  - Chills in up to 5%
  - Anemia
- **Catheter-related side effects**
  - CVC-related infections
  - Venous thrombosis

ECP in Steroid-Refractory Acute GvHD

Author	Pts	CR/PR Skin %	CR/PR Liver %	CR/PR Gut %	OS %
Salvaneschi 01	9	89	20	60	67
Dall'Amico 02	14	79	57	70	57
Messina 03	33	82	60	75	69
Kanold 07	12	100	67	83	75
Greinix 06	59	93	65	74	47
Calore 08	15	92	100	71	85
Perfetti 08	23	66	27	40	48
Perotti 10	50	83	67	73	64

ECP in Steroid-Refractory Acute GvHD

297 pts reported in 24 publications.

CR/PR Skin	75%	(50-100%)
CR/PR Liver	47%	(0-100%)
CR/PR Gut	58%	(0-100%)
OS	60%	(37.5-85%)

ECP is effective and well-tolerated adjunct second-line therapy.

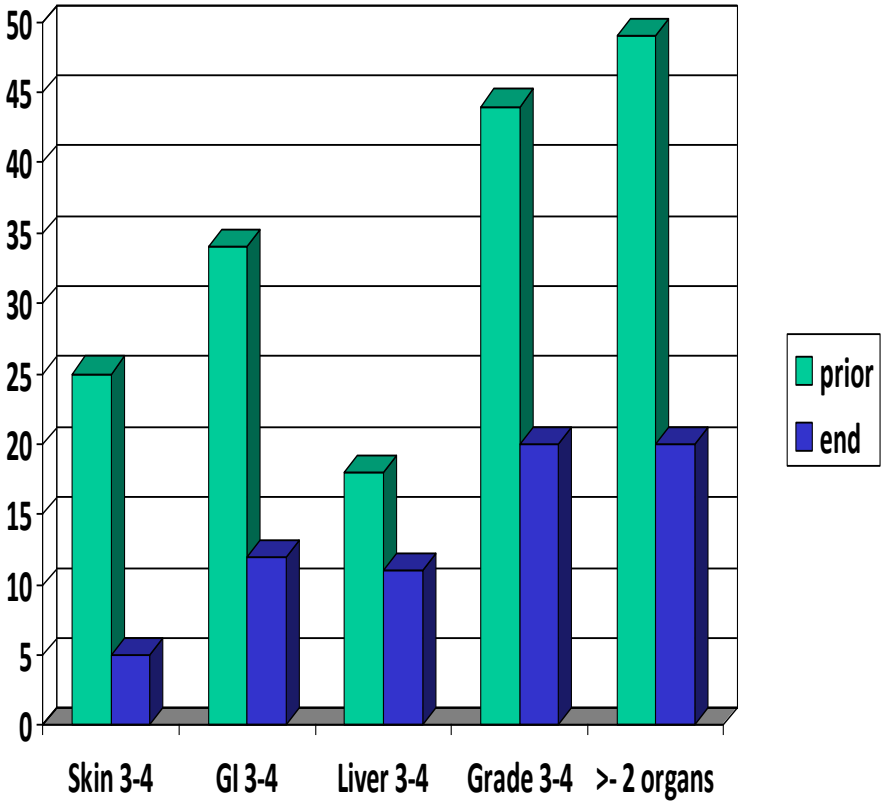
ECP vs Anticytokine Therapy

- **Retrospective comparison** of patients with aGvHD given second-line treatment
  - Steroid-Refractory: progression after 3 d or no response after 7 d
  - Steroid-Dependent: recurrence during taper
- **Patient selection criteria**
  - HCT after January 2005
  - ≥ grade 2
  - Steroids ≥ 1 mg/kg/day alone as first-line therapy
- Continuation of CNIs during second-line therapy
- **Comparison of extracorporeal photopheresis with anticytokines**
  - **Inolimomab** (anti-IL2R): 0.3 mg/kg/d x 8 d, 0.4 mg/kg x 3/w for 3 w
  - **Etanercept** (anti-TNR): 25 mg x 2/w for 4 w, 25 mg/w for 4 w
  - **ECP**: 2-3 d/week

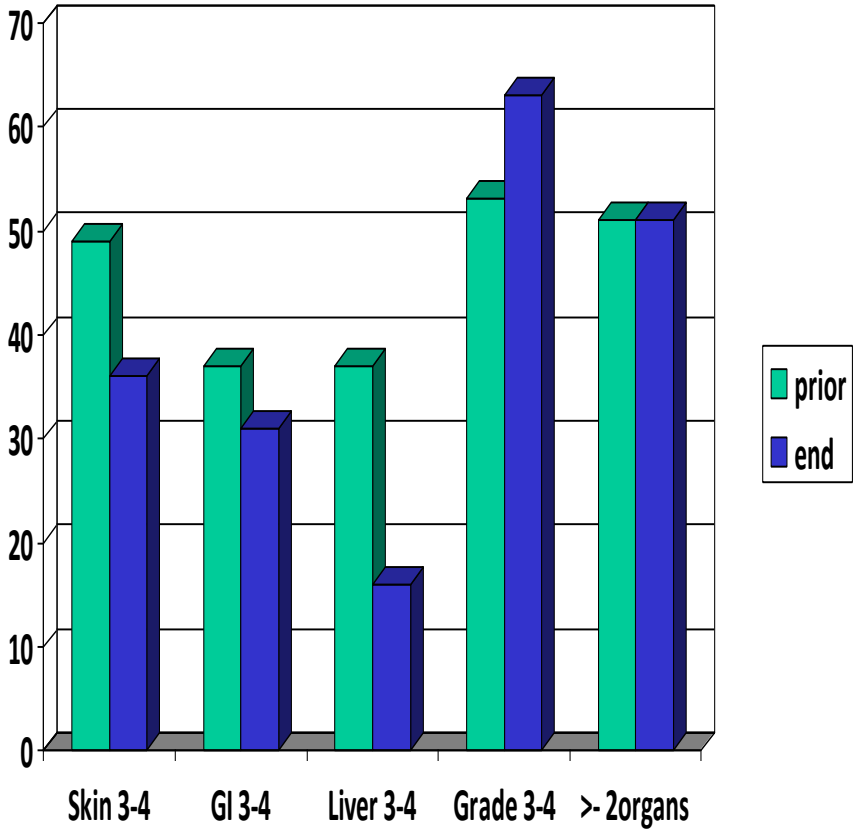
Jagasia et al, BBMT 2013;19:1124-35.

Patient Characteristics N (%) (n=127)		
Center	**ECP (n=86)**	**Non-ECP (n=41)**
Vanderbilt	29	-
Nottingham	22	-
Vienna	35	-
Paris	-	41
Gender		
Male	48 (56%)	25 (61%)
Female	38 (44%)	16 (39%)
Age (y) (median)	47 (range, 17-67)	44 (5-64)
Diagnosis		
Acute Leukemia	50 (58%)	21 (51%)
Lymphoma	18 (21%)	5 (12%)
Myeloid Disorders	16 (19%)	10 (24%)
Myeloma	2 (2%)	5 (12%)

Response to ECP (n=86)



Response to Anticytokine Therapy (n=41)



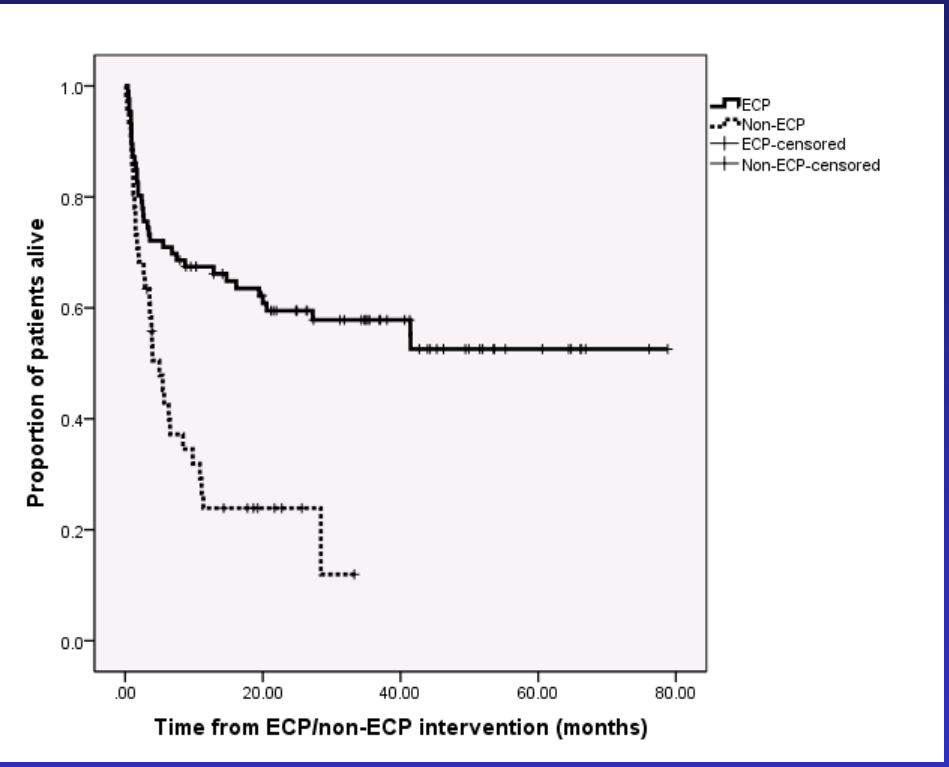
Overall Response to 2nd Line Therapy

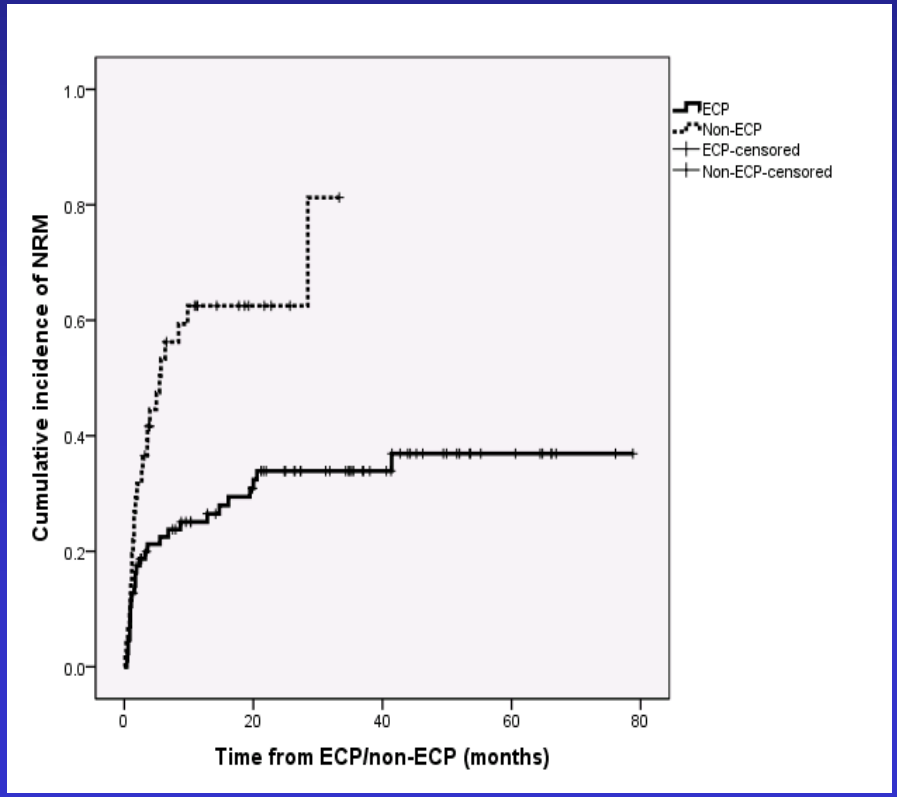
Variable	ECP N (%)	Non-ECP N (%)
Overall Response*	62 (73%)	13 (32%)
PR	9 (11%)	5 (12%)
CR**	53 (62%)	8 (20%)

Jagasia et al, BBMT 2013;19:1124-35.

* P<0.0001
** P<0.001

Survival and NRM: ECP vs. Non-ECP

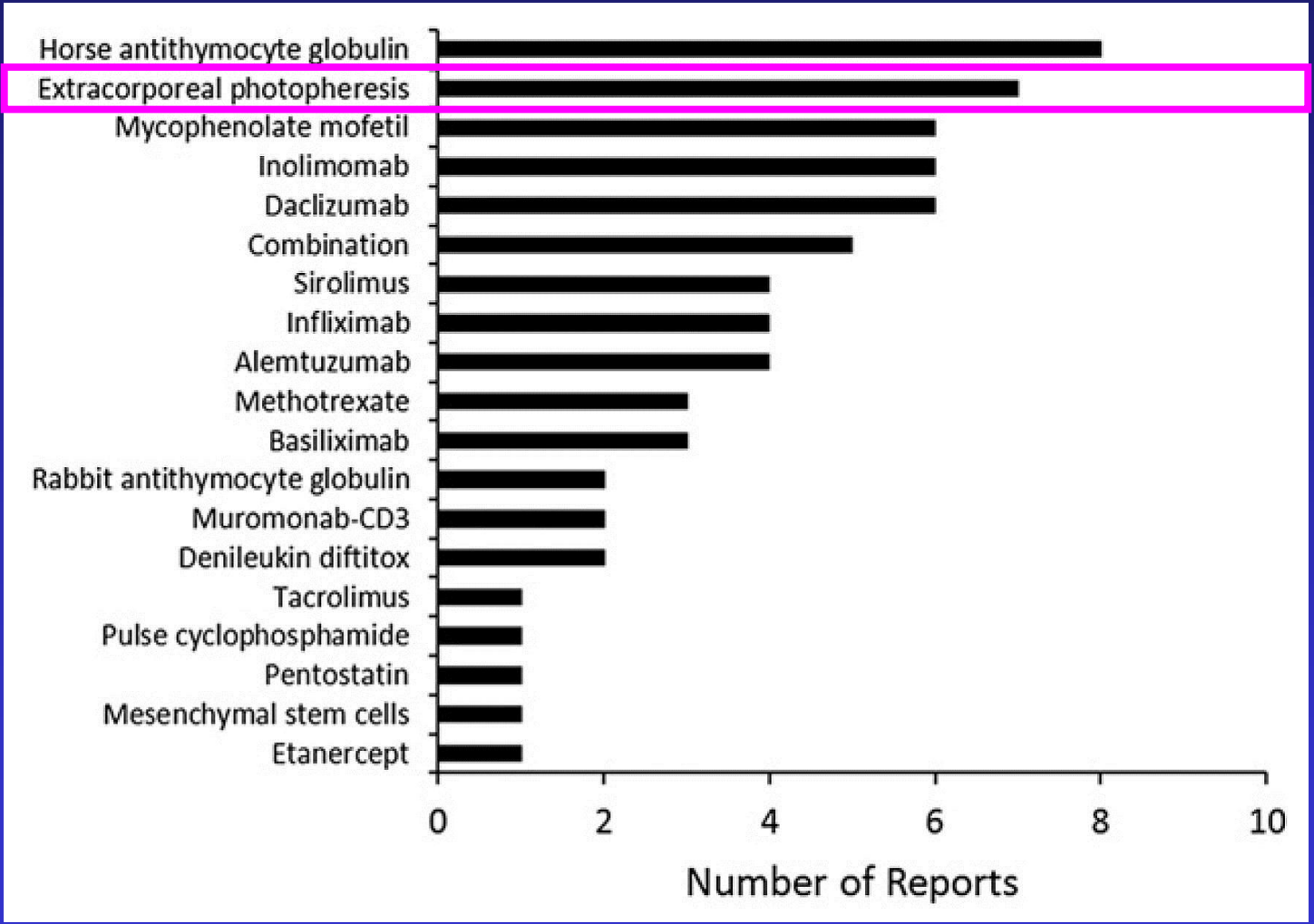




Jagasia et al, BBMT 2013;19:1124-35.

Inclusion of ECP in Acute GvHD Treatment Guidelines

Frequency of Treatments Evaluated in Literature Review of ASBMT



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

ASBMT Recommendations
ECP for Second-line Therapy

- **Toxicity concerns**

  Limited, blood loss from the extracorporeal circuit, hypocalcemia due to anticoagulant, mild cytopenia, catheter-associated bacteremia but on increased risk of overall infections
- **Significant interactions:** None
- **Viral reactivation concerns:** Not increased
- **Schedule**

  3 in week 1, 2 per week weeks 2-12 and 2 per 4 weeks thereafter.

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

ASBMT Recommendations
Second-line Therapy of aGvHD

	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

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

BCSH and BSBMT Recommendations on Second-Line Therapy of Acute GvHD

- The following agents are suggested:
  - **ECP**
  - Anti-TNFα antibodies
  - mTOR inhibitors
  - MMF
  - IL-2R antibodies
- Level of evidence: **2C** (suggest, current evidence from observational studies, case series)

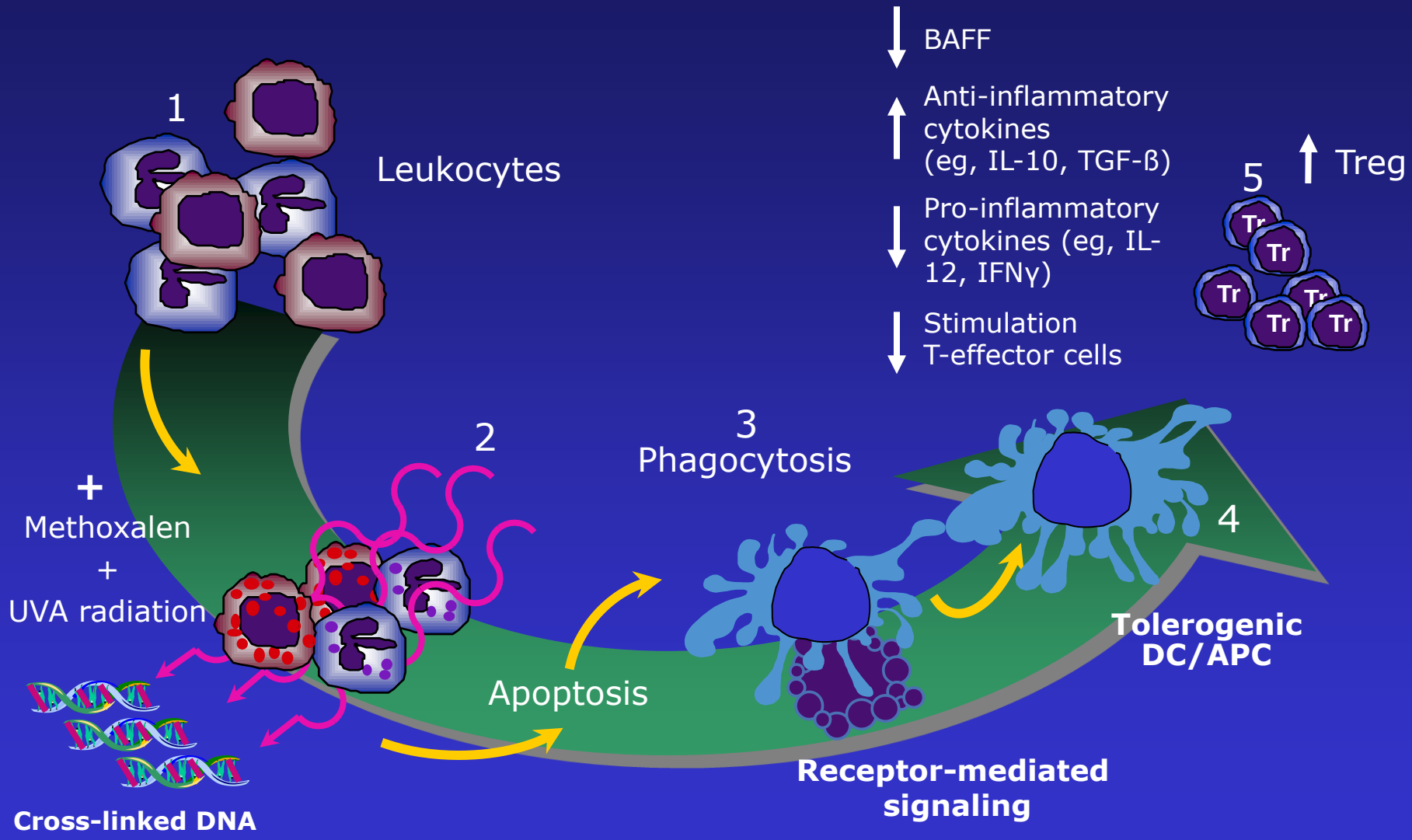
Dignan FI et al, BJH 2012;158:30-45

SIdEM and GITMO Recommendations on Use of ECP in Acute GvHD

- ECP is a **valuable option for acute GvHD not responding to steroids and CNI**.
- ECP may be used in adults and children.
- Early start of ECP is indicated particularly in children and recipients of haploidentical or unrelated donor HCT.

Pierelli L et al, Transfusion accepted Nov 2, 2012

ECP and Mechanisms of Action 2013



ECP for Treatment of GvHD

- **Chronic GvHD**
  - Established second-line therapy worldwide
  - High response rates in cutaneous and extracutaneous GvHD manifestations
  - Steroid-sparing effect, no main side effects
  - Improved quality of life and OS
  - No negative effect on GvL
  - Investigation of ECP upfront ongoing
- **Acute GvHD**
  - Accepted salvage therapy of steroid-refractory disease
  - Investigation of ECP upfront ongoing

GvHD Study Group Vienna

BMT Unit
- –P. Kalhs
- –W.Rabitsch
- –Z. Kuzmina
- –A. Schulenburg
- –C. Zielinski

Dept. Immunology
- –W.F. Pickl

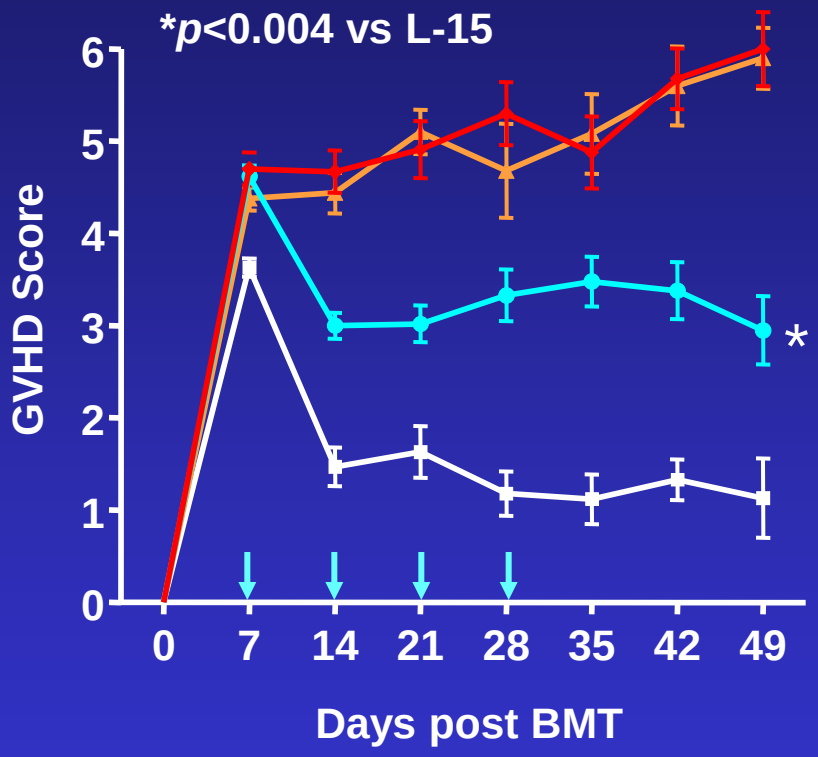
Dept. Dermatology
- –R. Knobler
- –U. Just
- –A. Tanew
- –G. Bauer

Dept. Transfusion Medicine
- –N.Worel
- –G. Leitner

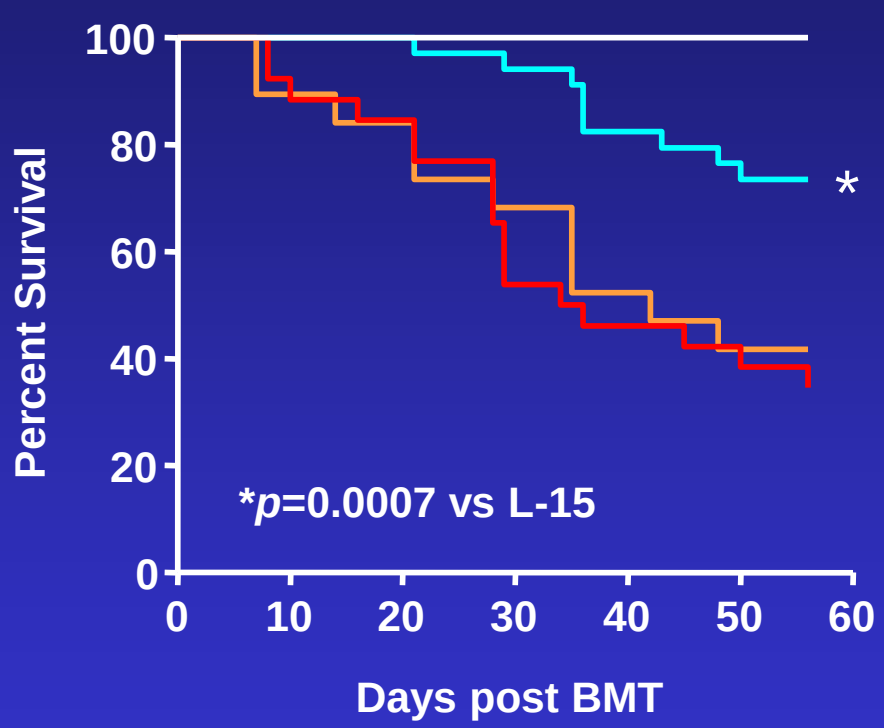
Dept. Gastroenterology
- - J. Hammer

Dept. Pulmonology
- - V. Petkov

ECP Reduces GvHD and Mortality in Minor-MM Mouse Model



Gatza et al, Blood 2008



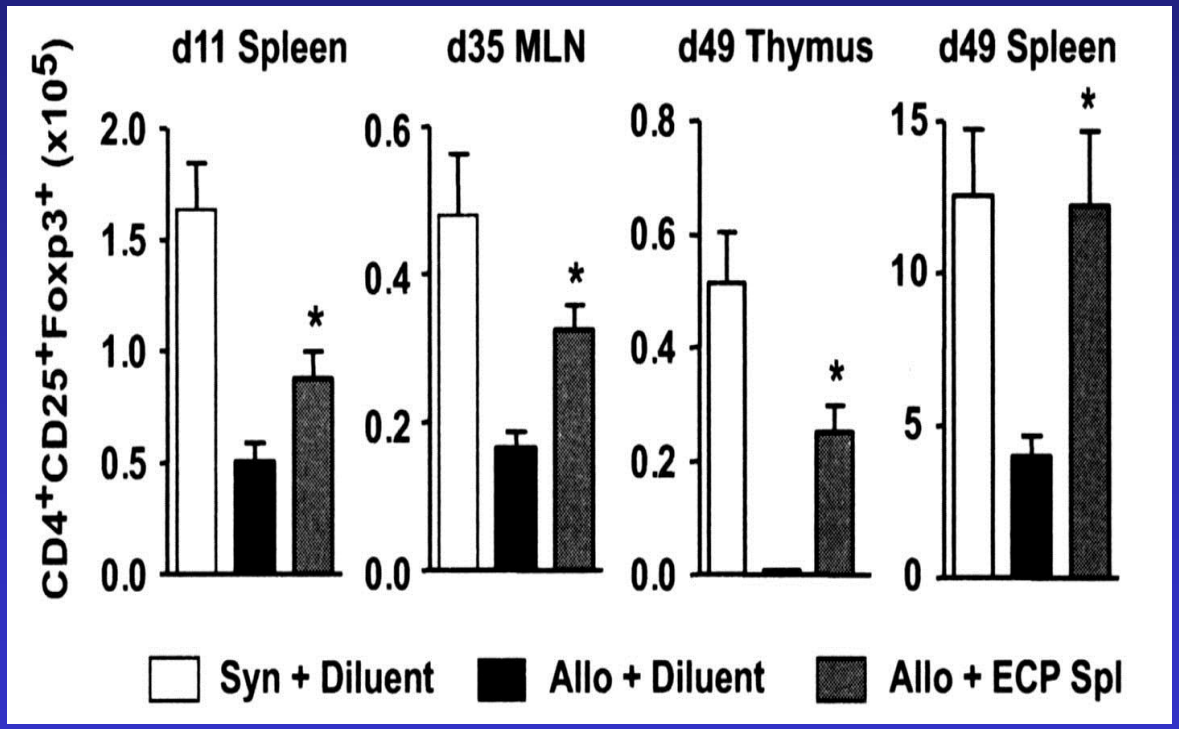
SYN +/- ECP (n=15)

ALLO + Spl + ECP (n=34)

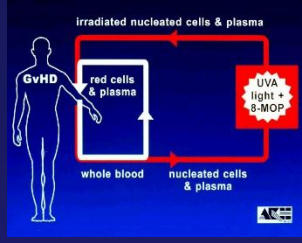
ALLO + Diluent (n=26)

ALLO + Spl w/o ECP (n=19)

Infusion of ECP-treated Splenocytes Increases Donor Treg after Allo BMT

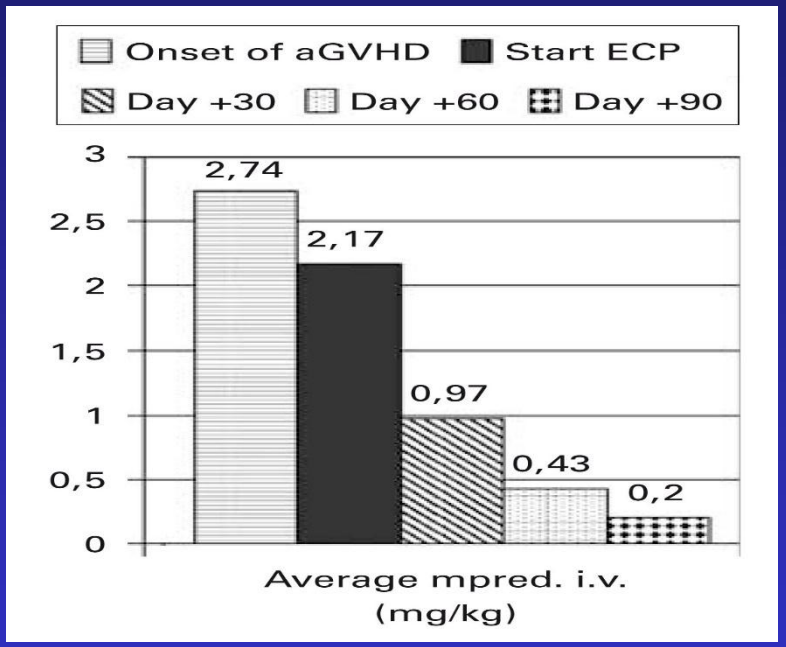


Gatza et al, Blood 2008

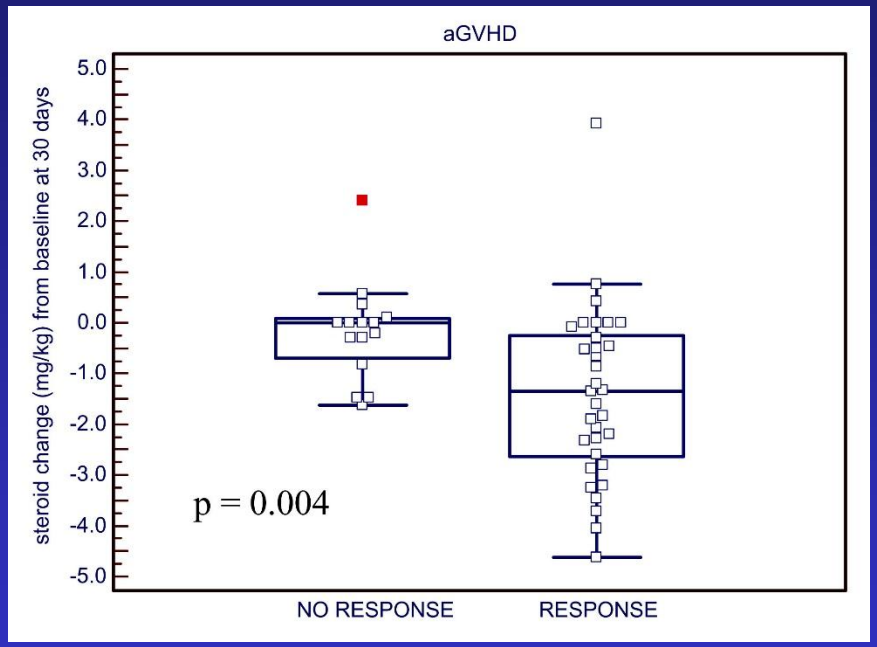


Salvage ECP in Acute Steroid-Refractory GvHD

Rapid Steroid Reduction during ECP



Perfetti et al, BMT 2008



Perotti et al, Transfusion 2010

Greinix 2000 and 2006, Salvaneschi 2001, Messina 2003, Garban 2005, Perfetti 2008

ECP in Steroid-Refractory Acute GvHD

Adverse Events*

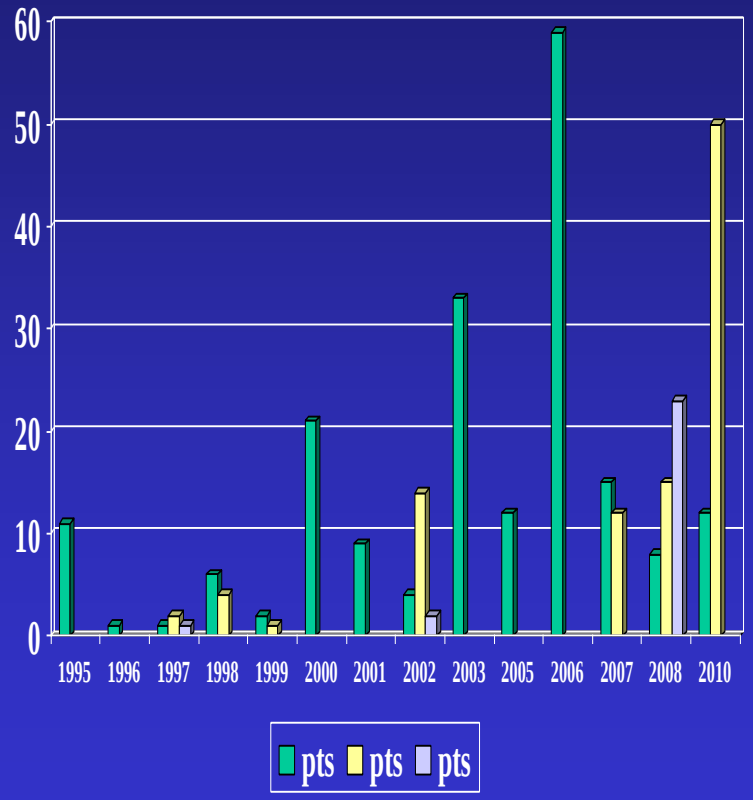
Event	No pts (%)	No episodes (%)
↓ Hb ≥1g/dL	19 (90)	74 (16)
Renewed RBC Tf	10 (48)	26 (6)
↓ ANC <1.5 x 10^9/L	17 (81)	40 (9)
↓ ANC <1 x 10^9/L	7 (33)	12 (3)
↓ ANC <0.5 x 10^9/L	5 (24)	5 (1)
↓ Plts ≥50%	15 (71)	75 (16)
↓ Plts <20 x 10^9/L	5 (24)	8 (2)
Renewed Plts Tf	7 (33)	20 (4)
Bleeding	3 (14)	3 (0.6)

*21 pts, 460 procedures

Blood 2000;96:2426-2431

ECP in Steroid-Refractory Acute GvHD

Publications (n=24)



Published Patients (n=297)