

# The role of ECP in the management of GvHD

November 29, 2022

Chair: Mohamad Mohty

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Professor Hildegard Greinix:  
What is ECP?

# Disclosures

Hildegard Greinix

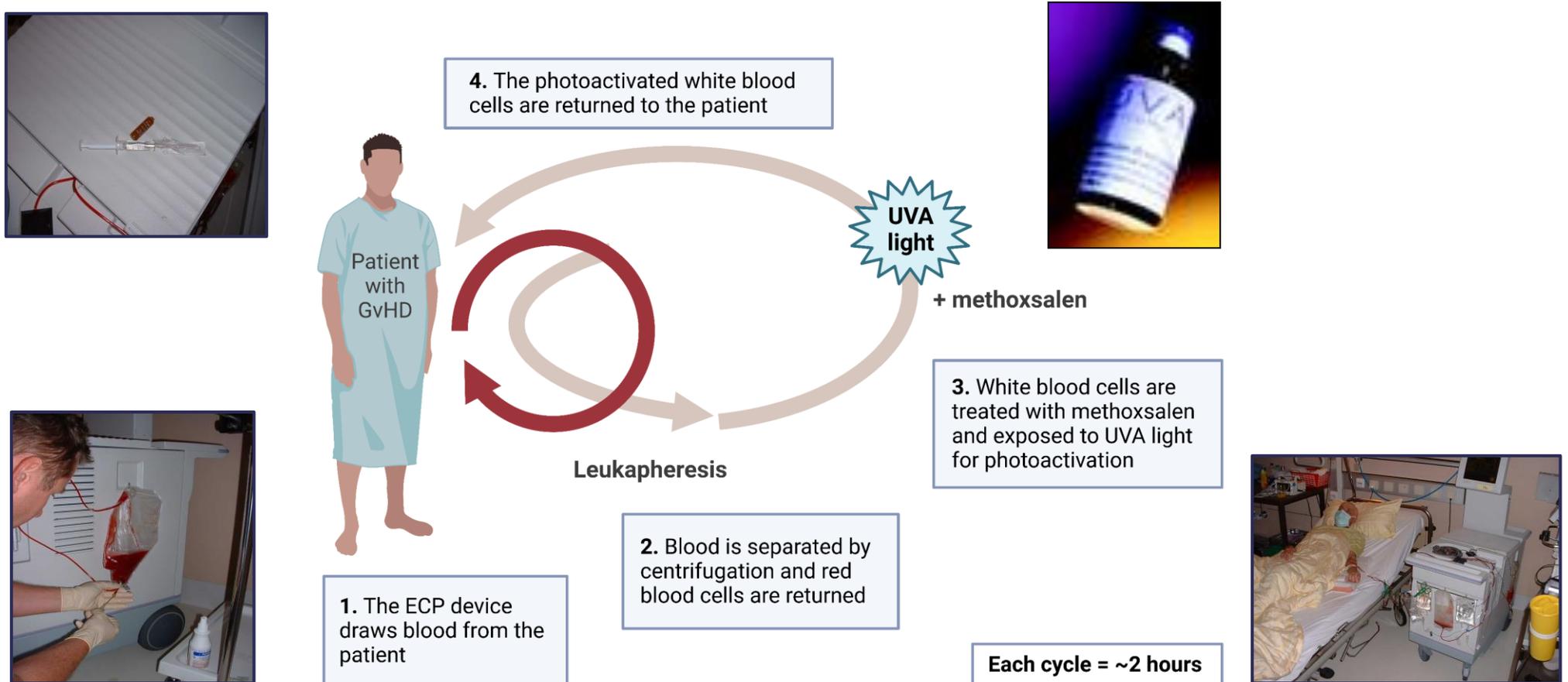
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- Research grant(s)/in kind support: None
- Participation in accredited CME/CPD: DGHO, EBMT, EHA, Gilead, Mallinckrodt
- Consultant/strategic advisor: Gilead, Mallinckrodt, Novartis, Sanofi
- Patents/shares or stocks related or unrelated to this presentation: None
- Non-financial interests: None



# Introduction

# What is extracorporeal photopheresis?



Adapted from Knobler R, et al. *J Am Acad Dermatol.* 2009;61(4):652-65.  
Created with BioRender.com.

# How does ECP work?<sup>1-6</sup>

## Direct effects

- Depletion of alloreactive donor T cells that can cause GvHD
- Depletion of proinflammatory myeloid cells
- Induction of Tregs

## Indirect effects

- Apoptotic cells can directly release soluble anti-inflammatory factors
- Uptake of apoptotic cells may affect the secretion of cytokines and pro-resolving factors by tissue-residing macrophages
- Apoptotic cells and their interactions may lead to increased tolerogenic DCs

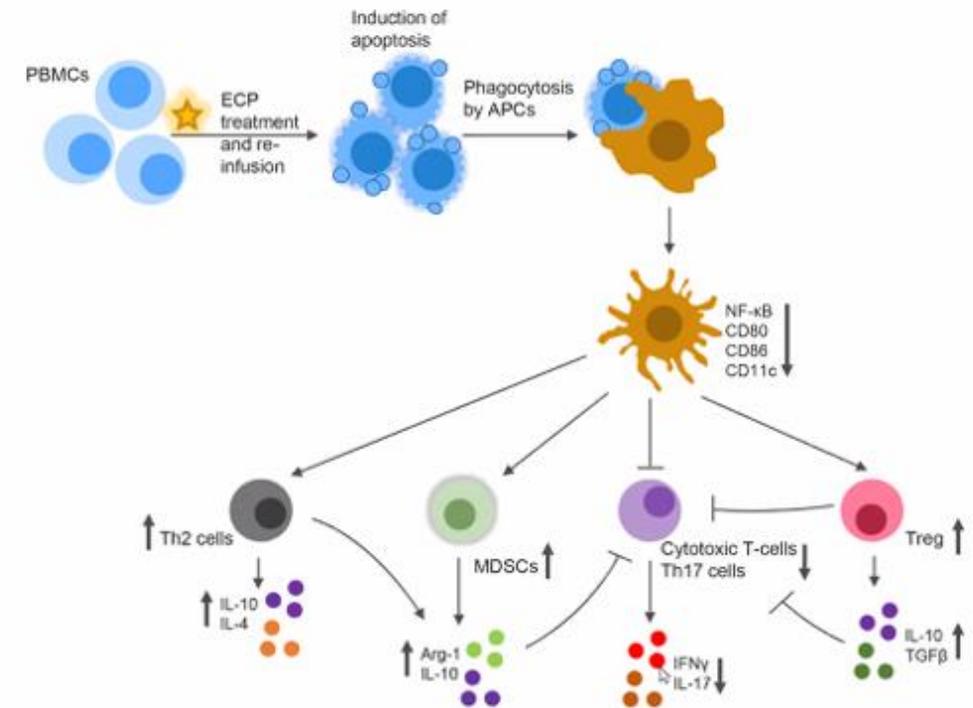


Figure provided by R Zeiser.

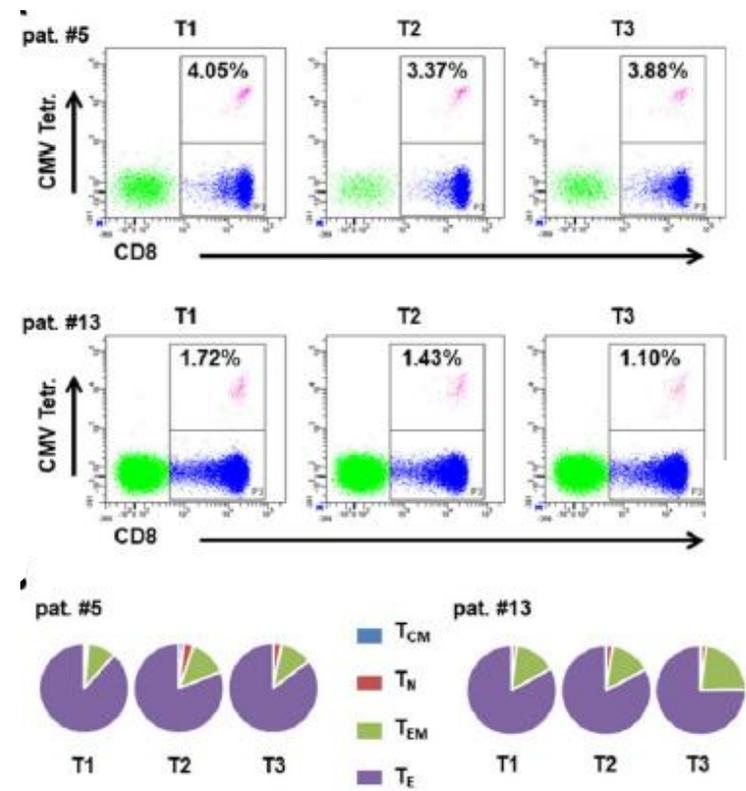
APCs, antigen presenting cells; CD, cluster of differentiation; DC, dendritic cell; ECP, extracorporeal photopheresis; IFN, interferon; IL, interleukin; MDSC, myeloid-derived suppressor cell; NF, nuclear factor; PBMC, peripheral blood mononuclear cell; TGF, transforming growth factor; Th, T helper cell; Treg, regulatory T cell.

1. Craciun LI, et al. *Transplantation*. 2002;74(7):995-1000. 2. Bladon J, Taylor PC. *Br J Haematol*. 1999;107(4):707-711. 3. Franklin C, et al. *PLoS One*. 2015;10(8):e0134518. 4. Gorgun G, et al. *Blood*. 2002;100(3):941-947. 5. Gerner M, et al. *Transplantation*. 2009;87(8):1134-1139. 6. Di Biaso I, et al. *Transplantation*. 2009;87(9):1422-1425. 7. Wang L, et al. *Front Immunol*. 2018;9:2207.

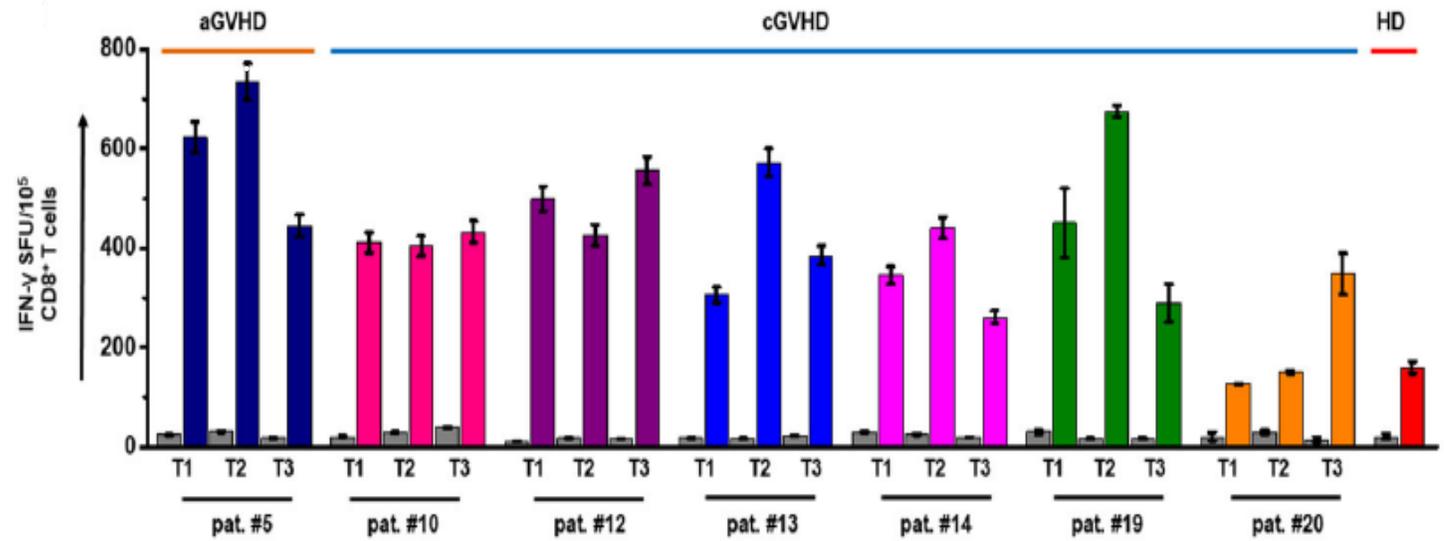
# Impact of ECP on antiviral immune response

CMV-specific CD8<sup>+</sup> T cells before and after ECP in acute and chronic GvHD are not different

Cell function measured by IFN- $\gamma$  release remains stable



**ECP does not cause generalized immunosuppression**



Wang L, et al. *Front Immunol.* 2018;9:2207.

Wang L, et al. *Front Immunol.* 2018;9:2207.

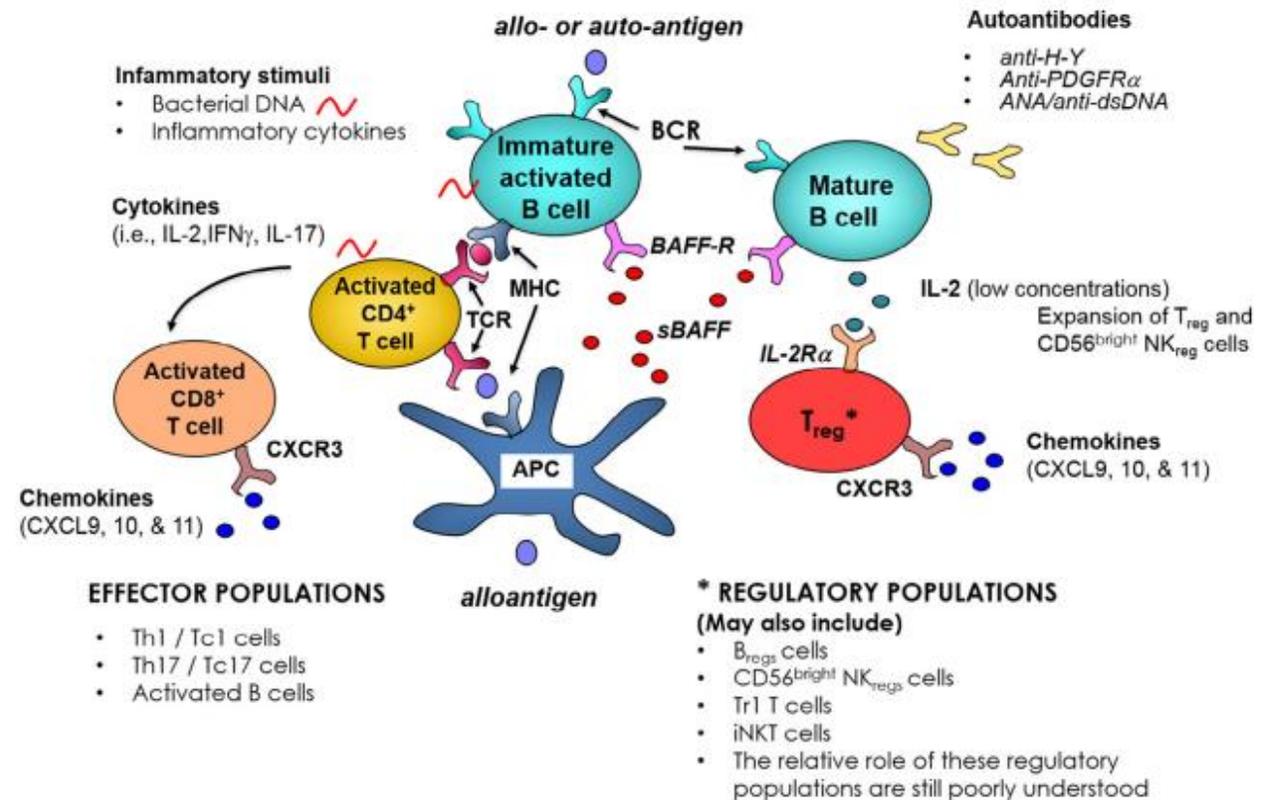
aGvHD, acute graft-versus-host disease; CD, cluster of differentiation; cGvHD, chronic graft-versus-host disease; CMV, cytomegalovirus; ECP, extracorporeal photopheresis; HD, healthy donor; IFN, interferon.

Wang L, et al. *Front Immunol.* 2018;9:2207.

# Impact of ECP on chronic inflammation and dysregulated immunity in cGvHD

## Potential impact of ECP

- Shift from Th1 to Th2 cytokine profile
- Shift to Th2 phenotype
- ↓ proinflammatory cytokines
- ↑ anti-inflammatory cytokines
- Tolerogenic DCs
- Neutrophilic MDSCs
- Impact on activated B cells



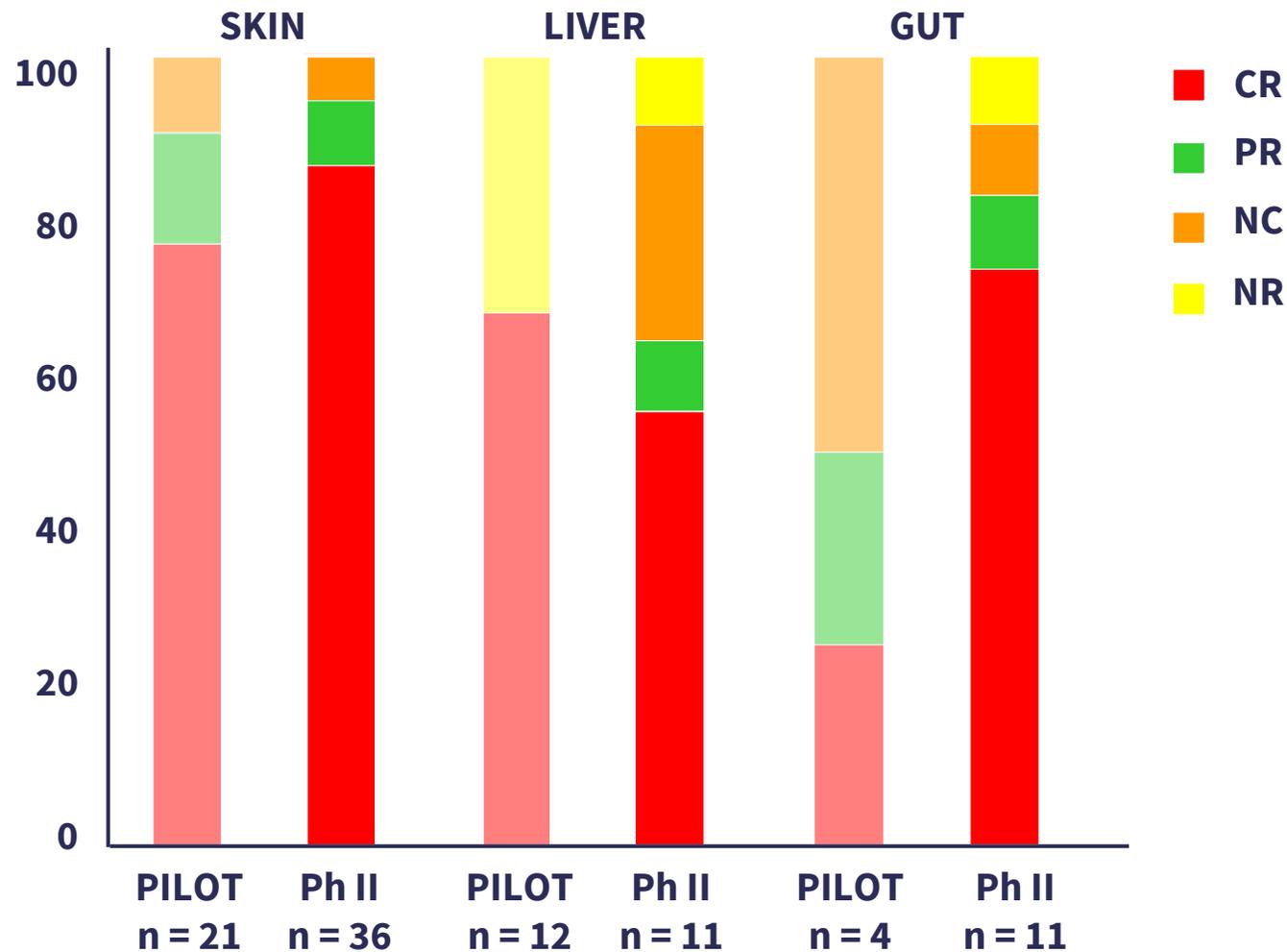
Cooke KR, et al. *Biol Blood Marrow Transplant.* 2017;23(2):211-234.

ANA, antinuclear antibody; APC, antigen presenting cell; BCR, B-cell receptor; CD, cluster of differentiation; cGvHD, chronic graft-versus-host disease; CXCL, chemokine ligand; DC, dendritic cell; ds, double stranded; ECP, extracorporeal photopheresis; IFN, interferon; IL, interleukin; iNKT, inducible natural killer T; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; NKreg, regulatory natural killer; PDGFR, platelet derived growth factor receptor; sBAFF, soluble B-cell activating factor; TCR, T-cell receptor; Th, T helper; Treg, regulatory T cell.



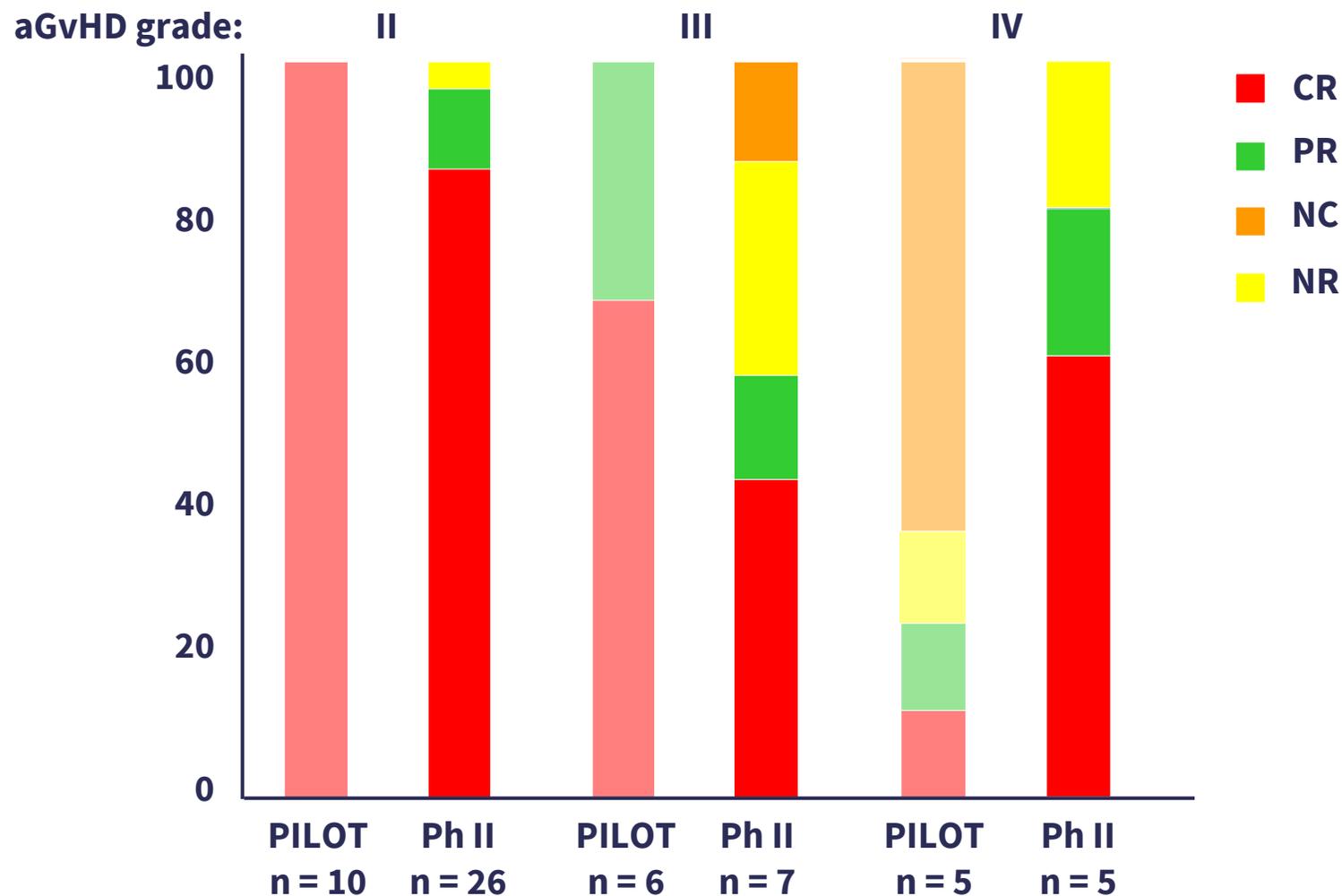
ECP in acute GvHD

# ECP as second-line therapy in acute steroid-refractory GvHD



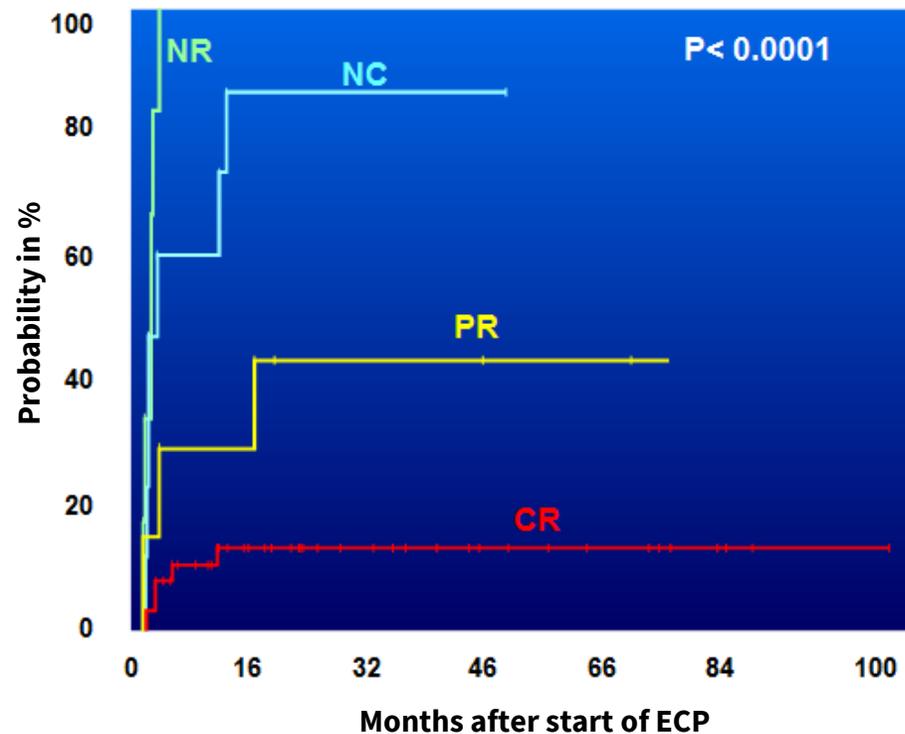
Adapted from Greinix HT, et al. *Haematologica*. 2006;91:405-408

# ECP as second-line therapy in acute steroid-refractory GvHD



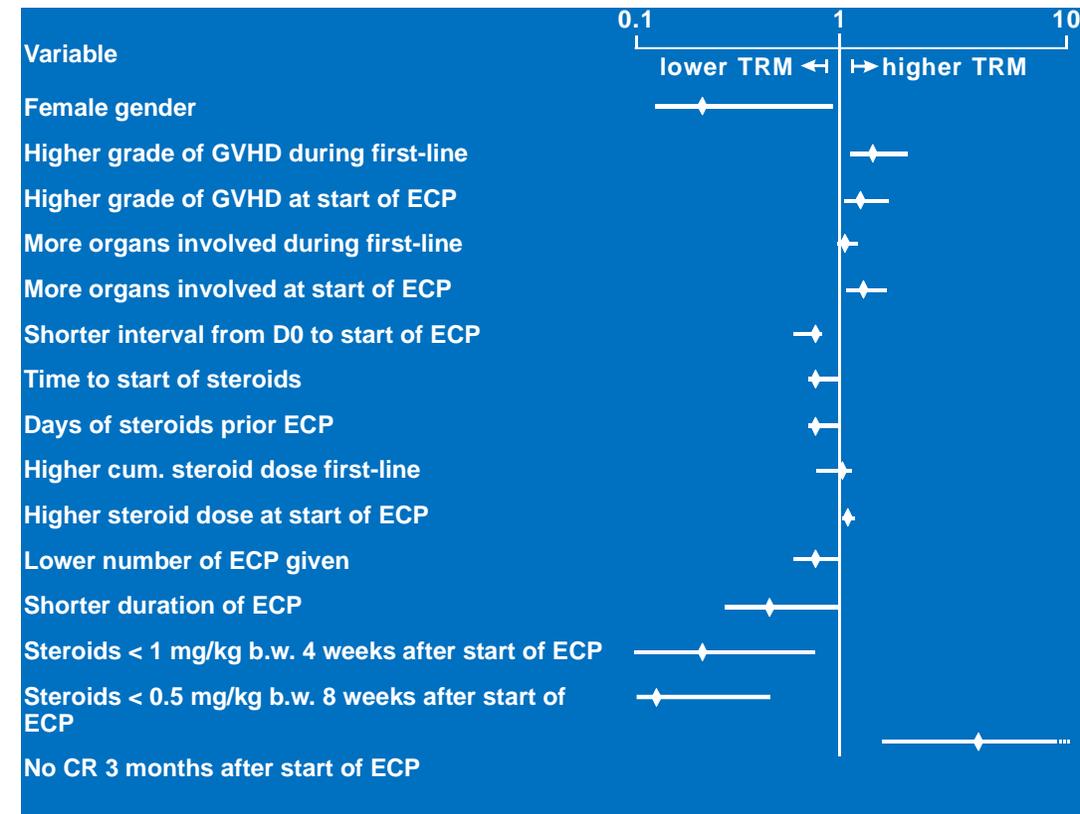
Adapted from Greinix HT, et al. *Haematologica*. 2006;91:405-408

# TRM of patients with steroid-refractory acute GvHD according to response to second-line ECP



Data from Greinix HT, et al. *Haematologica*. 2006;91(3):405-408.

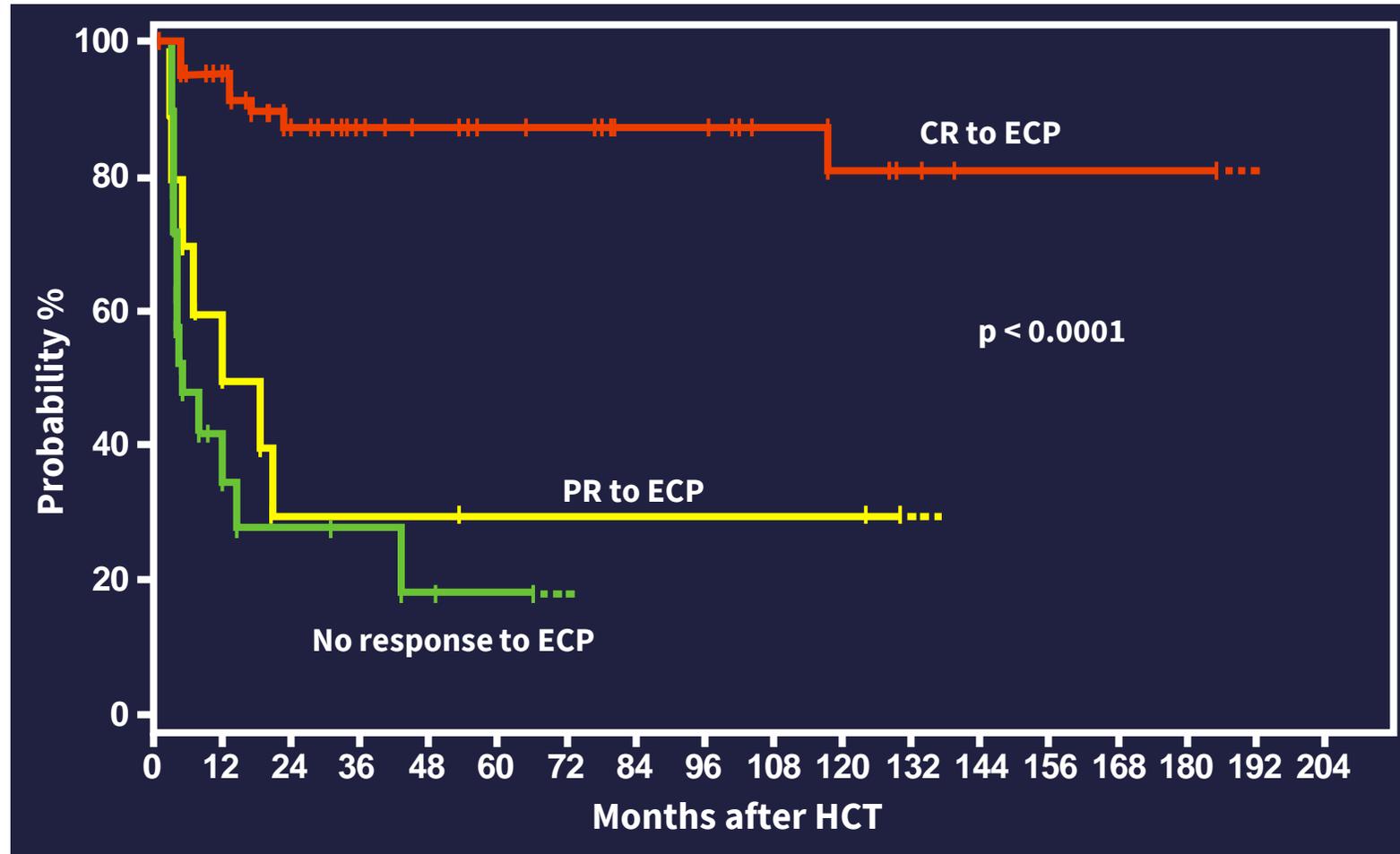
## Hazard ratios for TRM



Data from Greinix HT, et al. *Haematologica*. 2006;91(3):405-408.

# ECP in steroid-refractory acute GvHD

Long-term survival according to response (n = 96)



Adapted from Greinix HT, et al. *Haematologica*. 2006;91(3):405-408. PR-ECP line from personal data.

# ECP vs anticytokine therapy

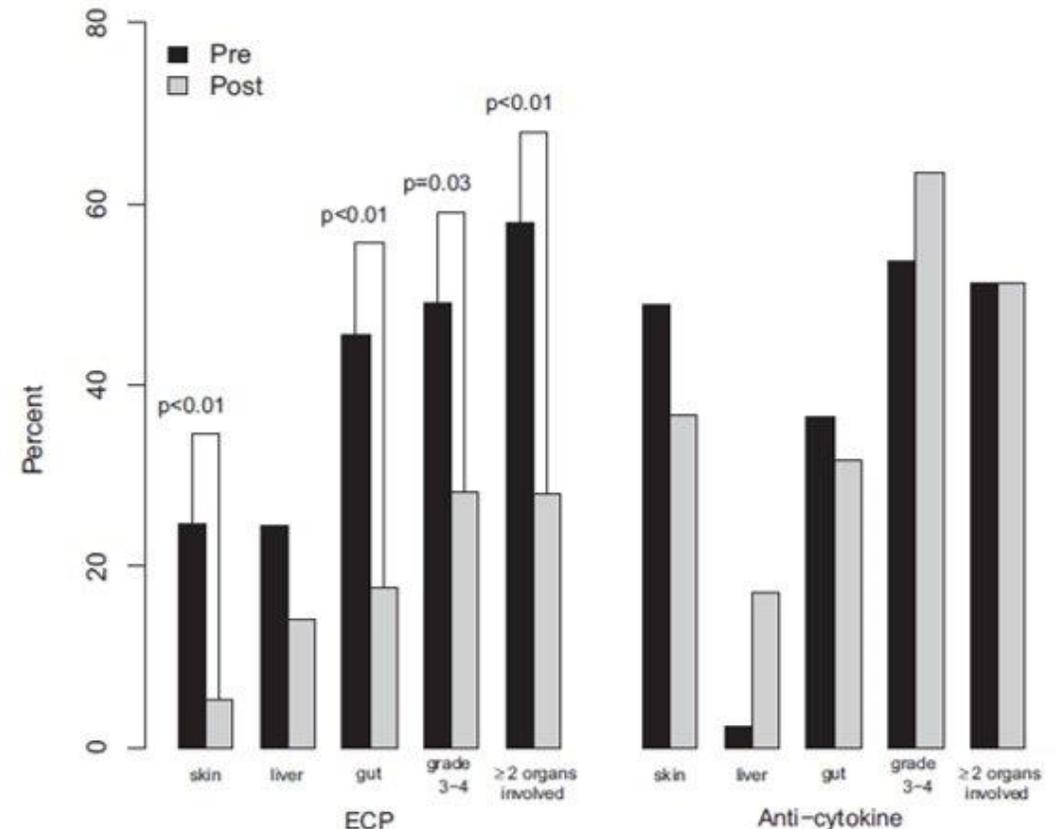
**Retrospective** comparison of patients with aGvHD given second-line treatment for SR/SD aGvHD

## Patient selection criteria

- Allo-SCT after January 2005
- >Grade II
- Steroids >1 mg/kg/d alone as first-line therapy and continuation of CNIs during second-line therapy

## Comparison of ECP with anticytokines

- Inolimomab (anti-IL2R):  
0.3 mg/kg/day × 8 days, 0.4 mg/kg × 3/week for 3 weeks
- Etanercept (anti-TNF):  
25 mg × 2/week for 4 weeks, 25 mg/week for 4 weeks
- ECP: 2–3/week



Jagasia M, et al. *Biol Blood Marrow Transplant.* 2013;19(7):1129-1133.

aGvHD, acute graft-versus-host disease; allo-SCT, allogeneic stem cell transplant; CNI, calcineurin inhibitor; d, day; ECP, extracorporeal photopheresis; IL-2R, interleukin-2R; SD, steroid-dependent; SR, steroid-refractory; TNF, tumor necrosis factor; w, week.

Jagasia M, et al. *Biol Blood Marrow Transplant.* 2013;19(7):1129-1133.

# ECP vs anticytokine therapy

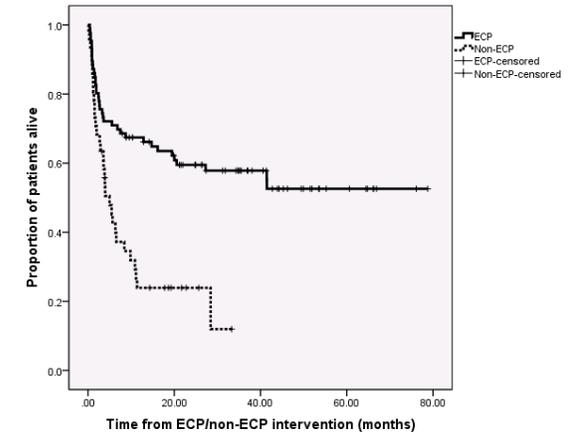
- **ECP was an independent predictor of response** (OR, 3.42;  $p = 0.007$ )
- **ECP was an independent predictor of survival** (HR, 2.12;  $p = 0.018$ )
- **ECP was associated with superior survival** (HR, 4.6;  $p = 0.016$ ) in SR Grade II aGvHD
- **ECP was associated with lower NRM** (HR, 0.45;  $p = 0.018$ )

Variable	ECP, n (%)	Non-ECP, n (%)
Overall response*	38 (66)	13 (32)
PR	7 (12)	5 (12)
CR*	31 (54)	8 (20)

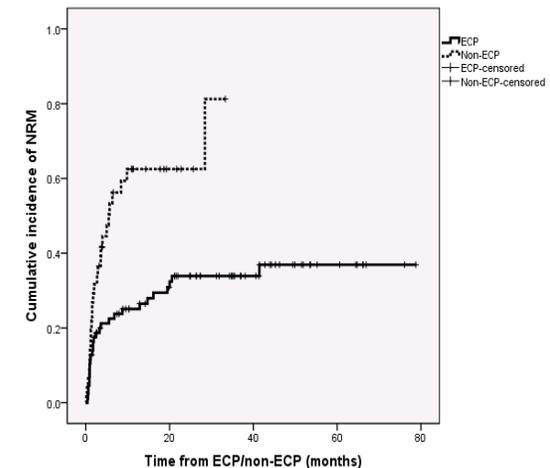
\* $p=0.001$

Jagasia M, et al. *Biol Blood Marrow Transplant.* 2013;19(7):1129-1133.

## Survival



## NRM



Jagasia M, et al. *Biol Blood Marrow Transplant.* 2013;19(7):1129-1133; Personal data.

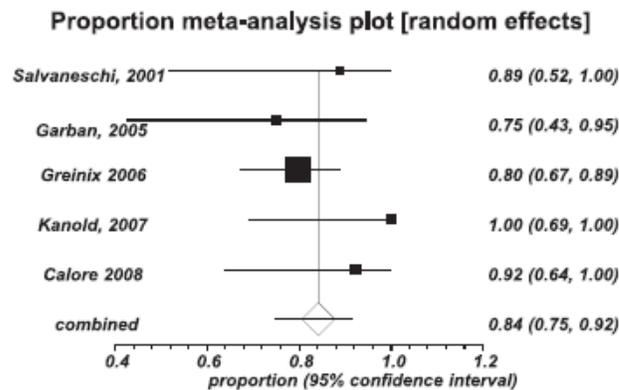
# ECP in steroid-refractory acute GvHD

## Systematic review of prospective studies

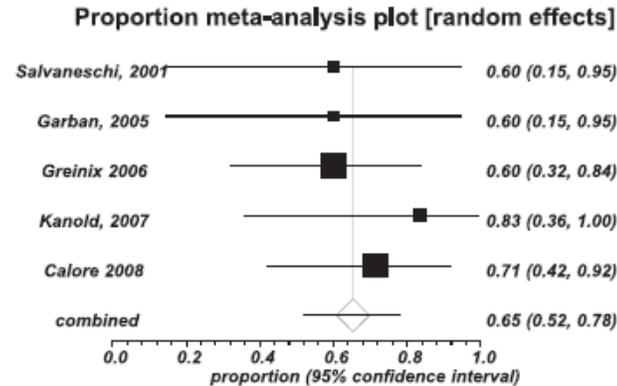
### Six studies with 103 patients

- ORR: 69%
- ORR in skin: 84%
- ORR in GI: 65%
- ORR in liver: 55%

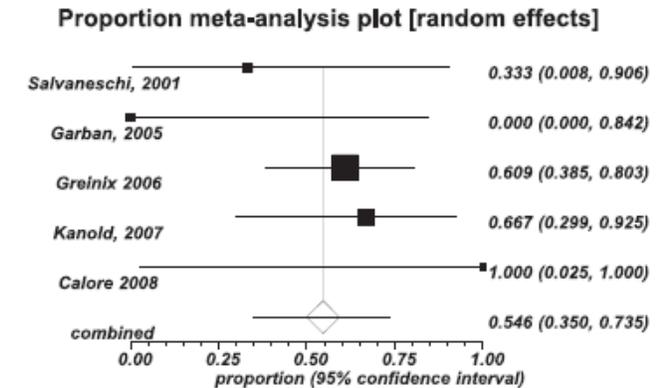
#### Response in skin



#### Response in GI



#### Response in liver



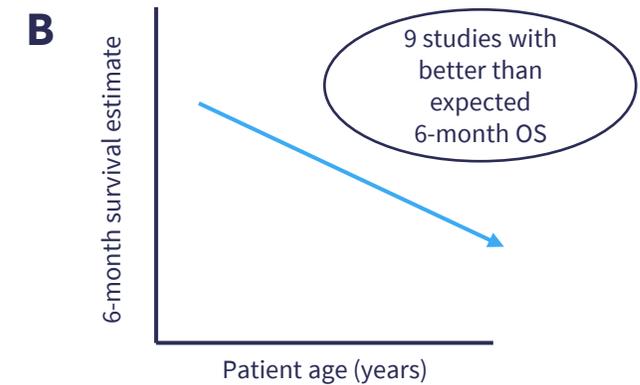
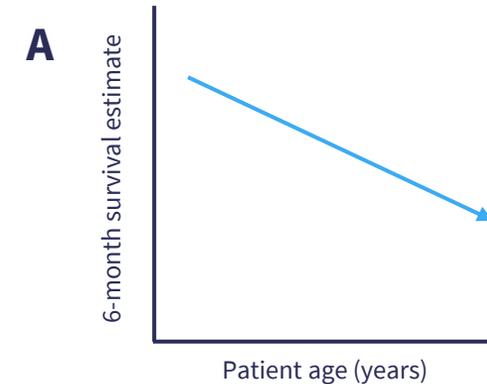
Abu-Dalle I, et al. *Biol Blood Marrow Transplant.* 2014;20(11):1677-1686.

# How I treat steroid-refractory aGvHD

**A:** Older age = lower 6-month OS across prospective and retrospective studies

**B:** Group of 9 studies with better than expected 6-month OS

- Ruxolitinib: n = 2  
(Jagasia 2020, Zeiser 2015)
- ECP: n = 5  
(Jagasia 2013, Das-Gupta 2014, Malagola 2016, Worel 2018, Nygaard 2019)
- CD25-specific Abs: n = 2  
(Girerd 2013, Tao 2015)
- “... patterns suggesting consistently favorable results with ruxolitinib and ECP would prompt me to use either of these agents preferentially in treating SR-aGvHD. For patients with active infection or severe neutropenia or thrombocytopenia, I would use ECP rather than ruxolitinib.”

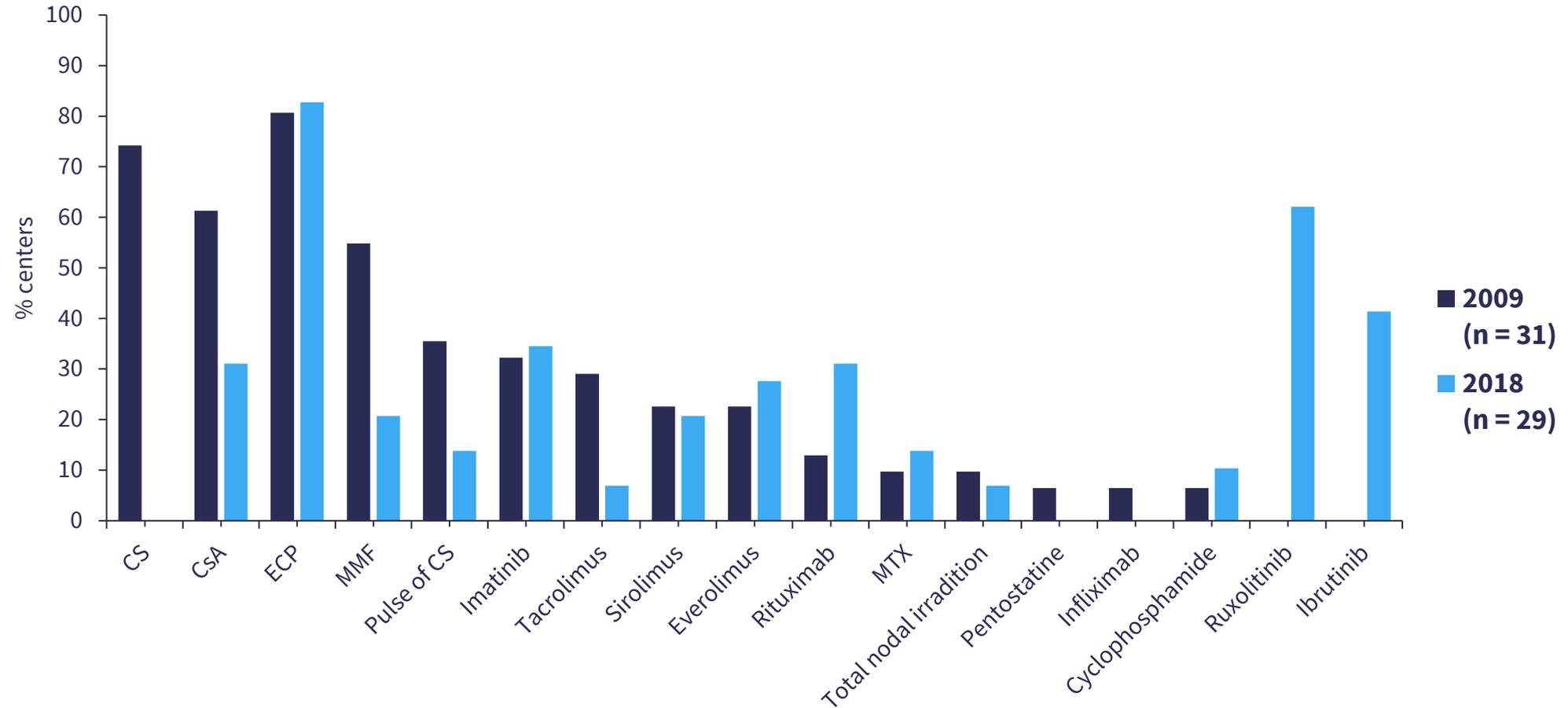




ECP in chronic GvHD

# Most frequently used cGvHD treatments

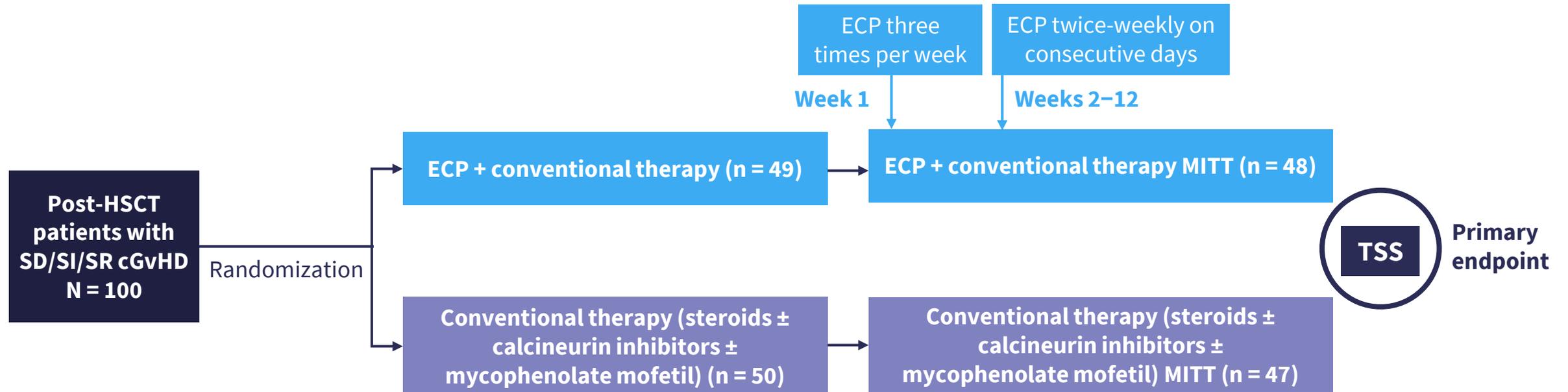
2009 vs 2018



Data from Wolff D, et al. *Biol Blood Marrow Transplant.* 2019;25(7):1450-1455.

# Prospective randomized study for patients with SR or SD cGvHD

## Role of ECP

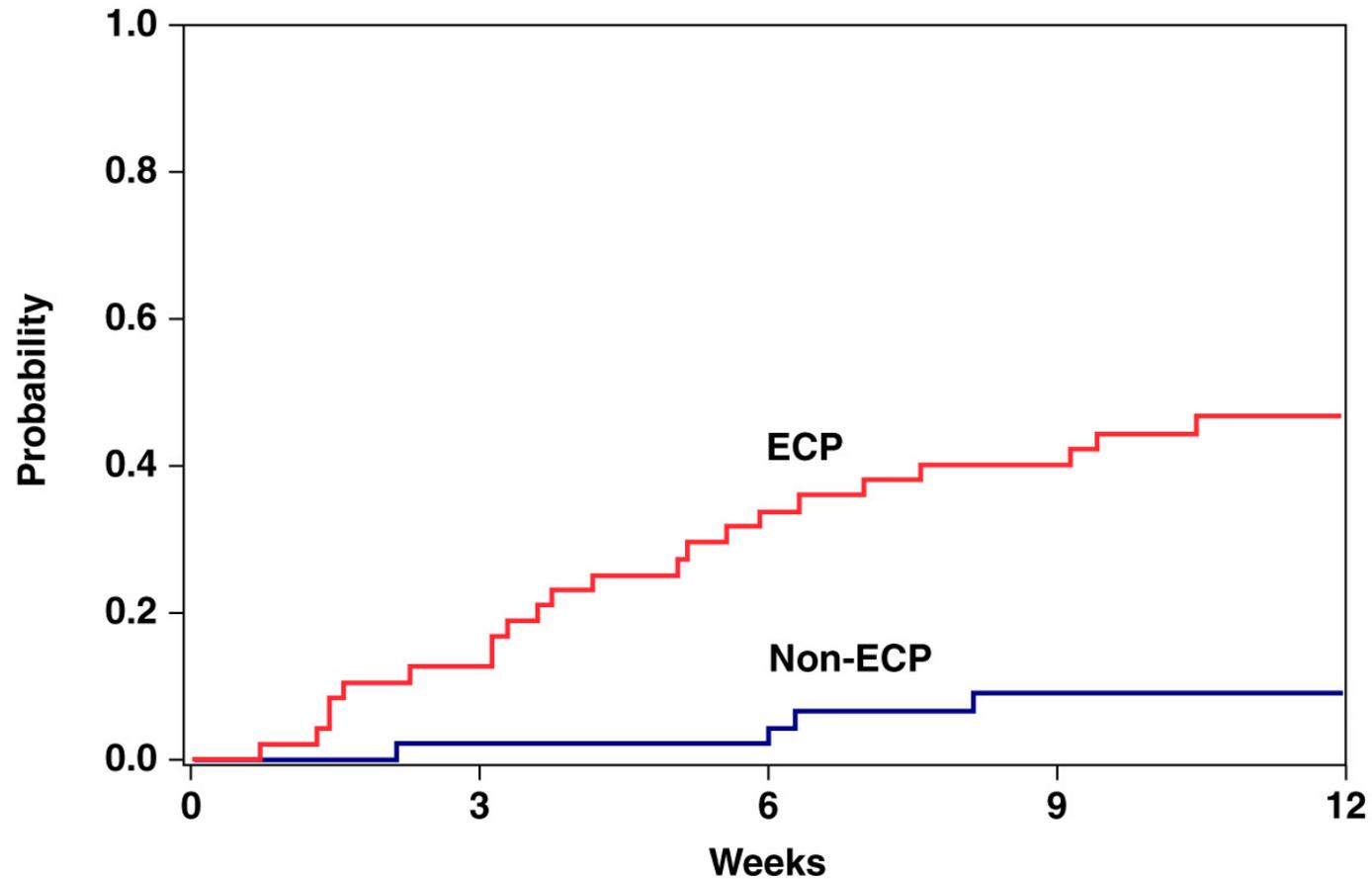


### Primary endpoint:

Median % change in TSS at Week 12 compared with baseline

# Cumulative incidence of CR/PR in skin

Phase II study of ECP in steroid-refractory/dependent cGvHD: Investigator assessment



Copyright © 2022 by Elsevier. Reproduced with permission. Flowers MED, et al. A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. *Blood*. 2008;112(7):2667-2674. DOI: [10.1182/blood-2008-03-141481](https://doi.org/10.1182/blood-2008-03-141481)

# Prospective randomized study for patients with SR or SD cGvHD

Primary endpoint: Total skin score

- At Week 12
- N = 95
- Blinded assessment

Corticosteroid response to ECP treatment*			
Parameter	Week 12 <sup>†</sup>		p
	ECP (n = 48)	Control (n = 47)	
Median percent change from baseline in TSS	-14.5	-8.5	0.48
≥50% reduction in corticosteroid dose and ≥25% improvement in TSS, %	8.3	0	0.04
≥50% reduction in corticosteroid dose and final corticosteroid dose of <10 mg/day, %	20.8	6.4	0.04

Data from Flowers MED, et al. *Blood*. 2008;112(7):2667-2674.

cGvHD, chronic graft-versus-host disease; CR, complete response; ECP, extracorporeal photopheresis; PR, partial response; SD, steroid-dependent; SR, steroid-refractory; TSS, total skin score.

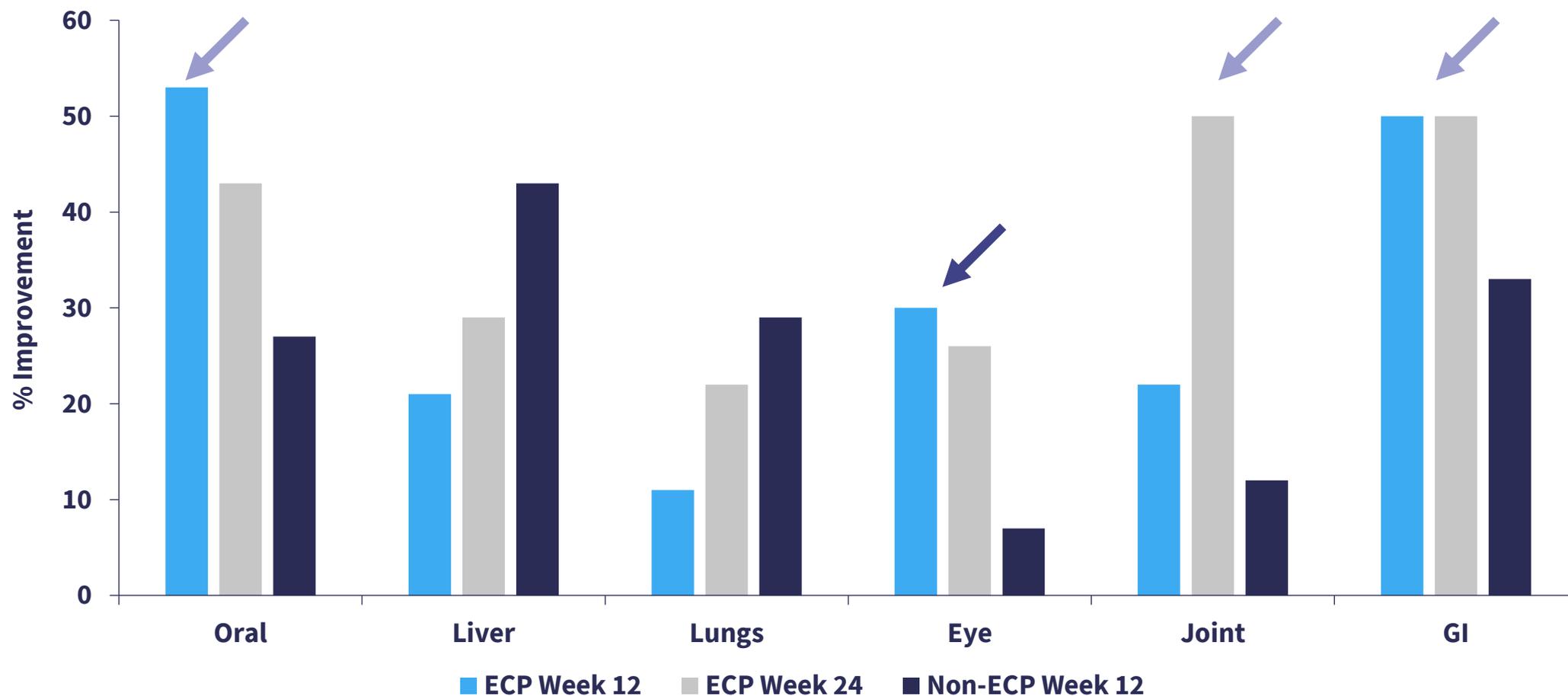
\*The large number of patients who discontinued the study in the control arm precluded statistical comparison for Week 24.

<sup>†</sup>In both groups, the last known dose of corticosteroids was used when the Week 12 dose was missing.

Flowers MED, et al. *Blood*. 2008;112(7):2667-2274.

# Resolution/improvement in extracutaneous cGvHD at Week 12

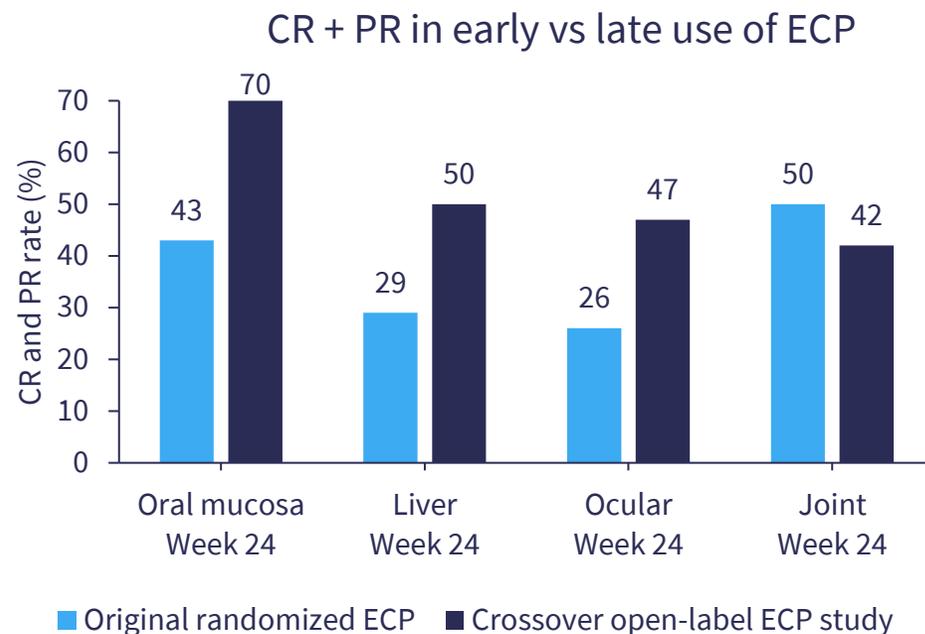
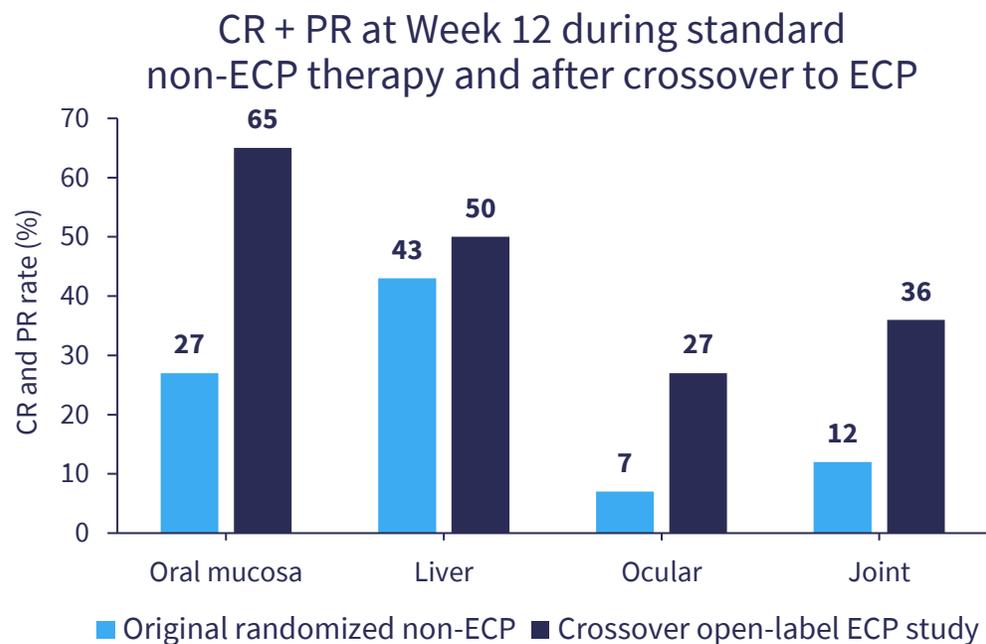
Phase II study of ECP in steroid-refractory/dependent/intolerant cGvHD



Data from Flowers MED, et al. *Blood*. 2008;112(7):2667-2274.

# Phase II study of ECP in SR/SD/SI cGvHD

- CR + PR of skin by investigator assessment in nine (31%) patients at Week 24
- 8/24 (33.3%) patients achieved  $\geq 50\%$  reduction in steroid dose at Week 24
- Similar response rates in skin and extracutaneous cGvHD compared with original ECP cohort despite longer duration of cGvHD



cGvHD, chronic graft-versus-host disease; CR, complete response; ECP, extracorporeal photopheresis; PR, partial response; SI, steroid-intolerant; SD, steroid-dependent; SR, steroid-refractory. Greinix H, et al. *Biol Blood Marrow Transplant.* 2011;17(12):1775-1782.

# Meta-analysis on ECP in cGvHD

## Overall response rate

**Effect size: 0.68**  
**(0.62–0.74)**

Study (ECP)	No. patients	Study type	Effect size (95% CI)
Smith (1998)	18	Prospective	0.33 (0.13–0.59)
Whittle (2011)	46	Prospective	0.52 (0.37–0.67)
Tsirigotis (2012)	47	Prospective	0.57 (0.42–0.72)
Foss (2005)	25	Prospective	0.64 (0.43–0.82)
Salvaneschi (2001)	14	Prospective	0.64 (0.35–0.97)
Alcindor (2002)	10	Prospective	0.70 (0.35–0.93)
Kanold (2007)	15	Prospective	0.73 (0.45–0.92)
Rubegni (2005)	32	Prospective	0.78 (0.60–0.91)
Dignan (2012)	82	Prospective	0.79 (0.69–0.87)
Gorgun (2002)	10	Prospective	0.80 (0.44–0.07)
Ayyildiz (2007)	7	Prospective	0.86 (0.42–1.00)
Rubegni (2007)	14	Prospective	0.86 (0.57–0.98)
Garban (2005)	15	Prospective	0.87 (0.60–0.98)
Biagi (2007)	6	Prospective	1.00 (0.54–1.00)
Hautmann (2013)	32	Retrospective	0.44 (0.26–0.62)
Berger (2007)	10	Retrospective	0.50 (0.19–0.81)
Duzovali (2007)	6	Retrospective	0.50 (0.12–0.88)
Akhtari (2010)	25	Retrospective	0.56 (0.35–0.76)
Messina (2003)	44	Retrospective	0.59 (0.43–0.74)
Couriel (2006)	71	Retrospective	0.61 (0.48–0.72)
Jagasia (2009)	31	Retrospective	0.65 (0.45–0.81)
Perotti (2010)	23	Retrospective	0.70 (0.47–0.87)
Ilhan (2004)	8	Retrospective	0.75 (0.35–0.97)
Perseghin (2007)	25	Retrospective	0.80 (0.59–0.93)
Del Fante (2012)	102	Retrospective	0.80 (0.71–1.00)
Gonzalez-Vincent (2010)	6	Retrospective	0.83 (0.36–1.00)
<b>Subtotal (I<sup>2</sup>=57.05%, p = 0.00)</b>			<b>0.68 (0.62–0.74)</b>

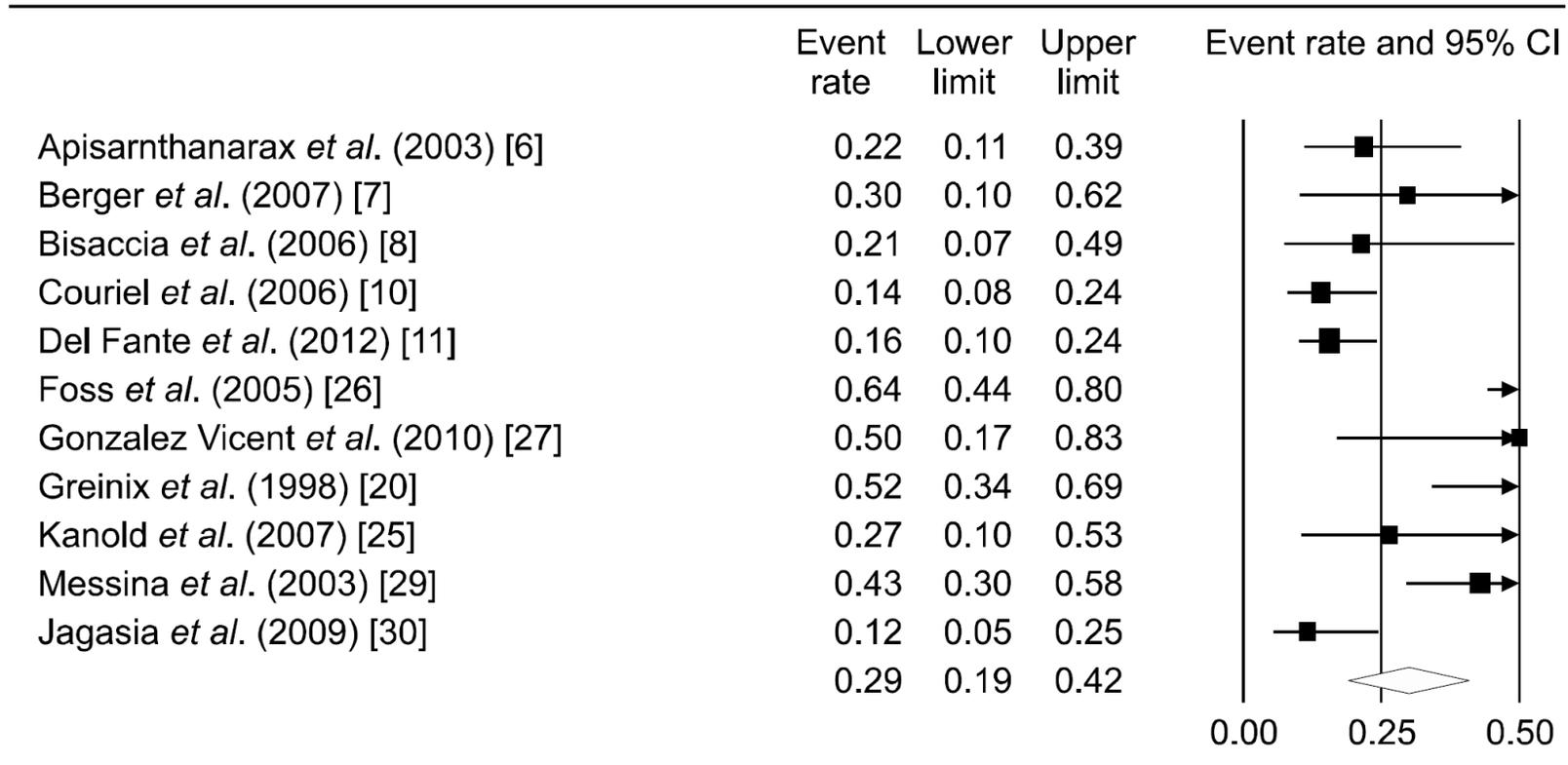
cGvHD, chronic graft-versus-host disease; CI, confidence interval; ECP, extracorporeal photopheresis.

Olivieri J, et al. *Lancet Haematol.* 2015;2:e297-305.

# Meta-analysis on ECP in cGvHD

## Complete response rate

Meta-analysis: complete response rates (%)



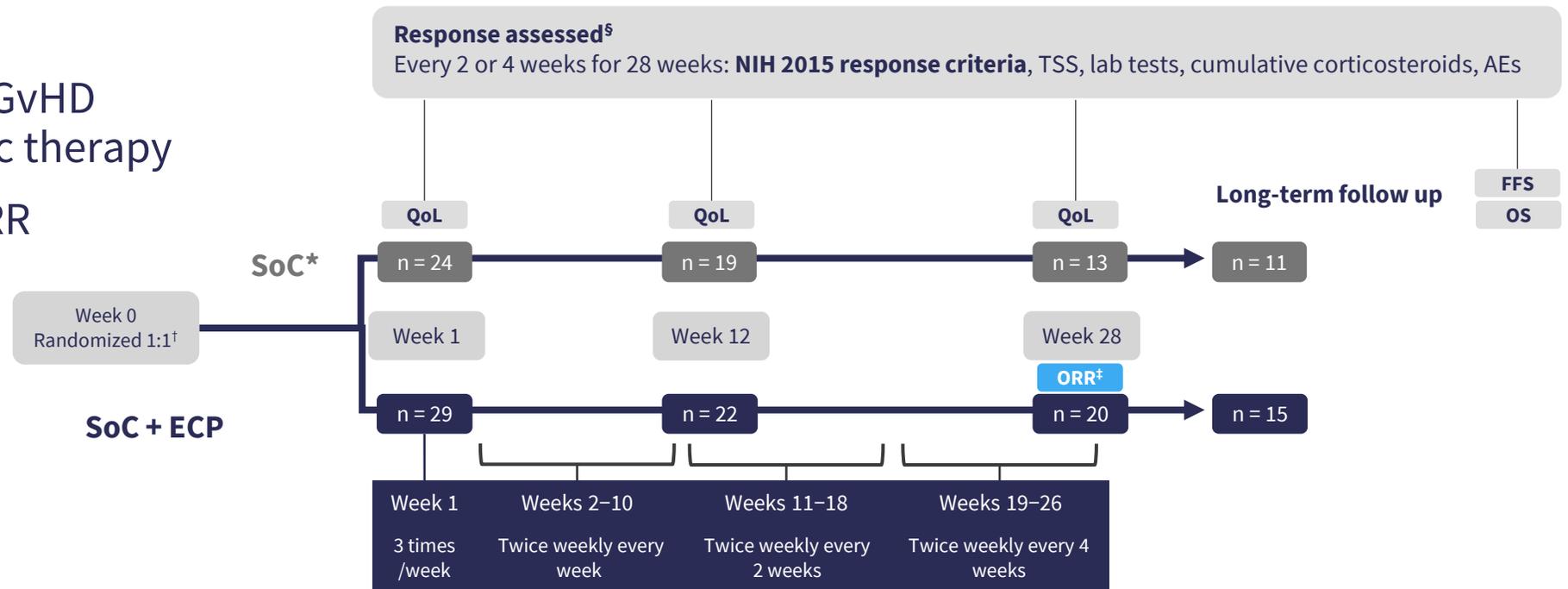
Malik MI, et al. *Blood Res.*2014;49(2):100-106.

# TKS-005: First prospective study in the first-line setting

Randomized, multicenter, active comparator-controlled, parallel group, pilot study



- New onset ( $\leq 3$  years from HSCT)
- Moderate or severe cGvHD that requires systemic therapy
- Primary endpoint: ORR
- N = 60



AE, adverse event; cGvHD, chronic graft-versus-host disease; ECP, extracorporeal photopheresis; FFS, failure-free survival; HSCT, hematopoietic stem cell transplant; NIH, National Institutes of Health; ORR, overall response rate; OS, overall survival; QoL, quality of life; SoC, standard of care.

\*Corticosteroids  $\pm$  cyclosporin A  $\pm$  tacrolimus.

<sup>†</sup>Corticosteroids were tapered down from 1 mg/kg/day at Week 1 to 0.5 mg/kg/day at Week 8 ( $\pm 1$ ), 0.25 mg/kg/day at Week 16 ( $\pm 1$ ), and 0.125 mg/kg/day at Week 24 ( $\pm 1$ ).

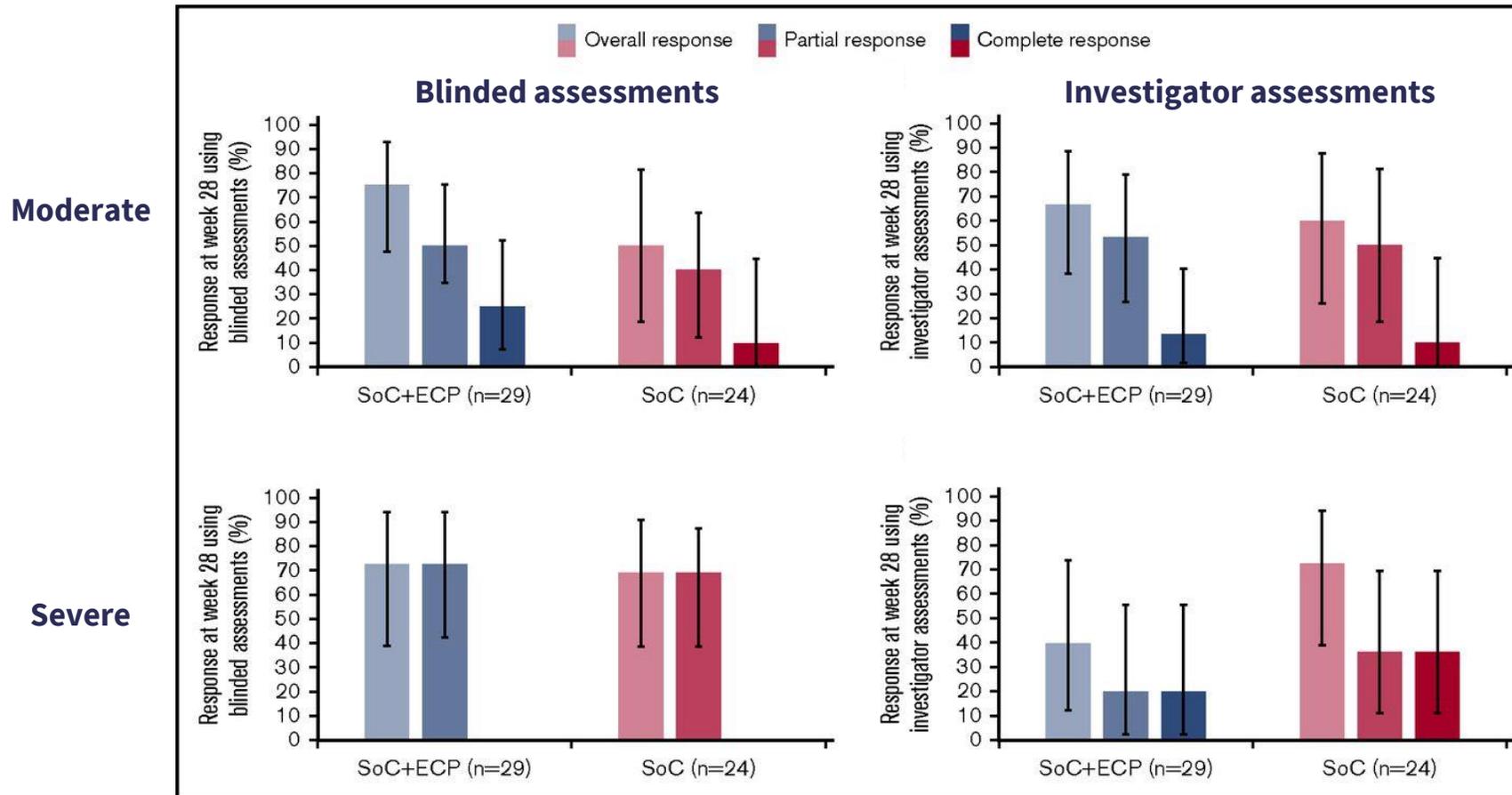
<sup>‡</sup>ORR is defined as clinically assessed complete response and partial response; partial response requires 50% improvement of the scale used to measure activity, according to NIH 2015 at Week 28.

<sup>§</sup>Response was assessed by a trained, blinded, third-party assessor for skin and mouth domains, as well as the primary physician.

Jagasia M, et al. *Blood Adv.* 2019;3(14):2218-2229.

# Overall response rate at Week 28 by severity

According to NIH cGvHD 2015 response criteria



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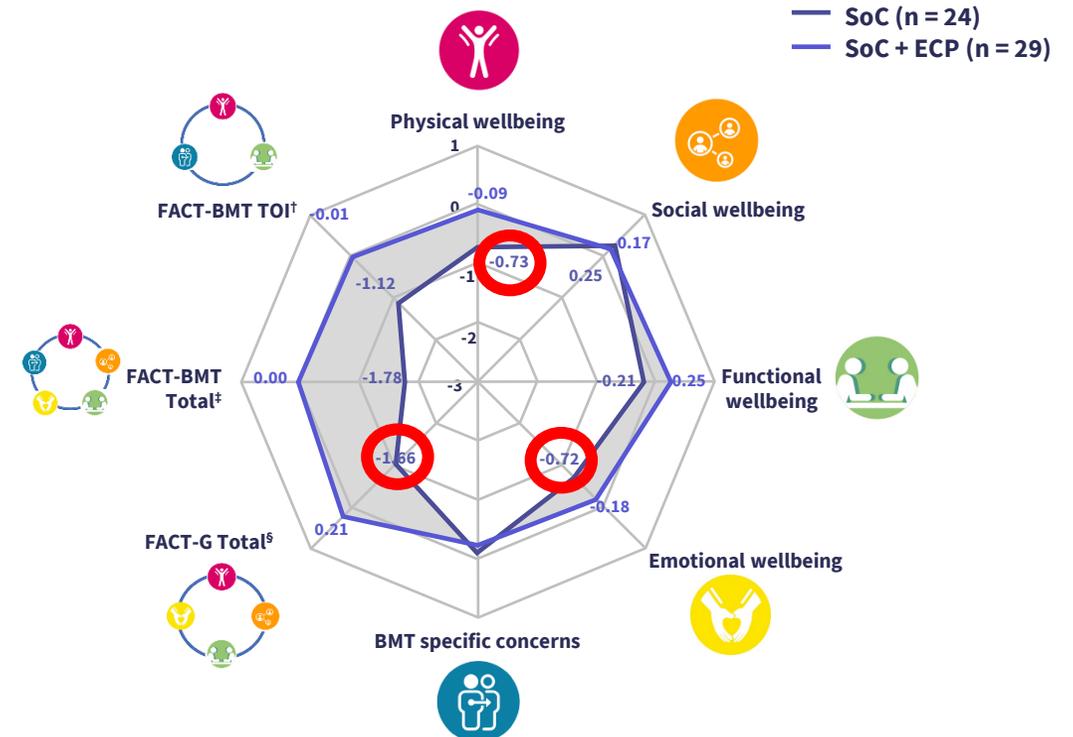
# Quality of life during treatment

## FACT-BMT

- At baseline, Week 12, and Week 28
- ITT population
- Post hoc analysis

## SoC: Significant worsened changes in scores\*

- Physical wellbeing ( $-0.7326$ ;  $p = 0.032$ )
- Emotional wellbeing ( $-0.7151$ ;  $p = 0.006$ )
- FACT-G ( $-1.6618$ ;  $p = 0.018$ )



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BMT, bone marrow transplantation; ECP, extracorporeal photopheresis; FACT, Functional Assessment of Cancer Therapy; ITT, intention to treat; SoC, standard of care; TOI, trial outcome index.

\*Physical wellbeing, social/family well-being, and functional wellbeing were scored from 0 to 28, emotion wellbeing was scored from 0 to 24, and BMT specific concerns were scored from 0 to 40.

<sup>†</sup>Physical wellbeing + functional wellbeing + BMT specific concerns; score: 0–96.

<sup>‡</sup>Physical wellbeing + social wellbeing + functional wellbeing + emotional wellbeing + BMT specific concerns; score: 0–148.

<sup>§</sup>Physical wellbeing + social wellbeing + functional wellbeing + emotional wellbeing; score: 0–108.

Jagasia M, et al. *Blood Adv.* 2019;3(14):2218-2229.

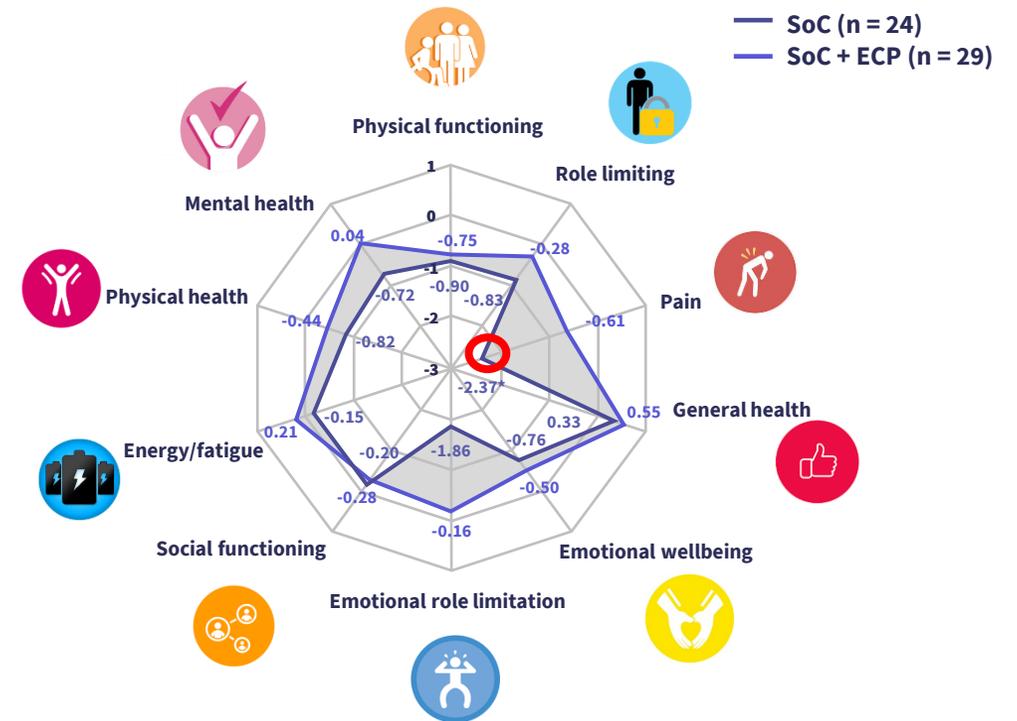
# Quality of life during treatment

## SF-36\*

- At baseline, Week 12, and Week 28
- ITT population
- Post hoc analysis

## SoC: Significant worsened changes in scores

- Pain ( $-2.3728$ ;  $p = 0.009$ )

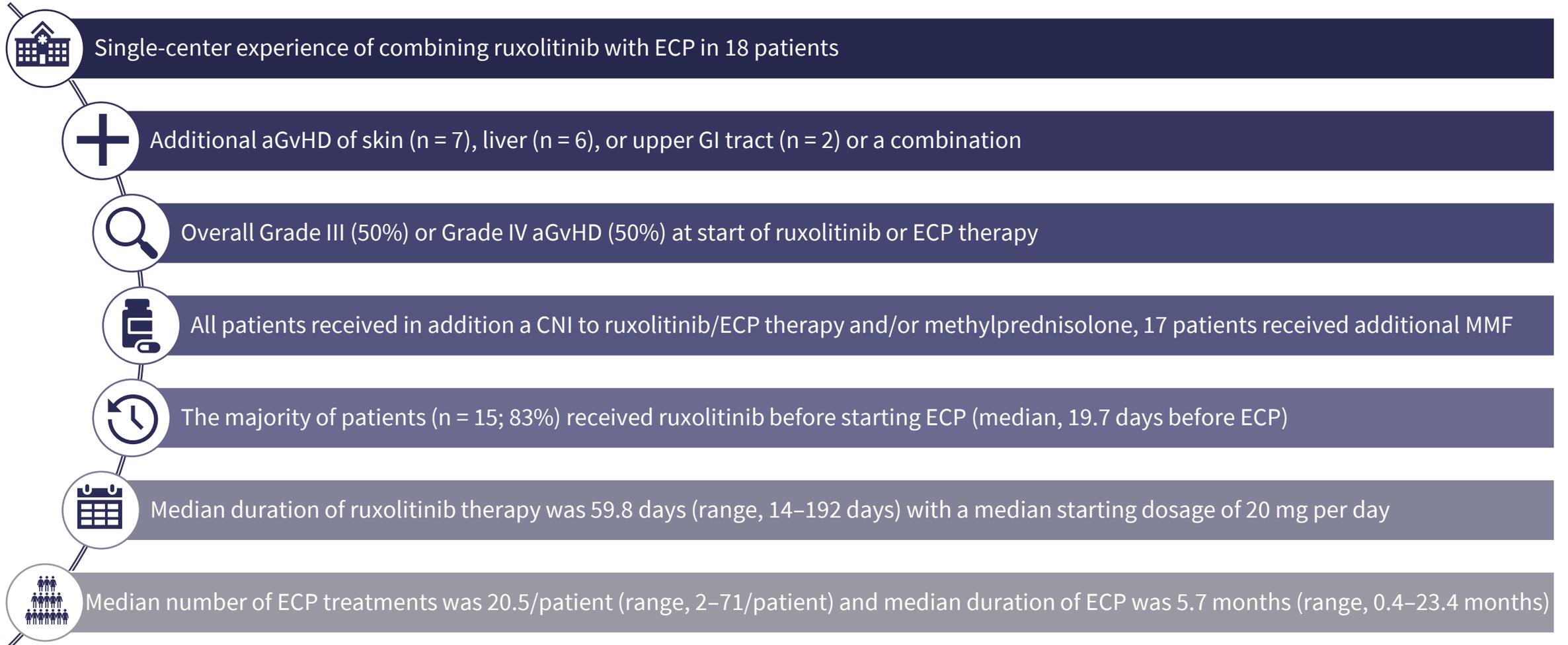


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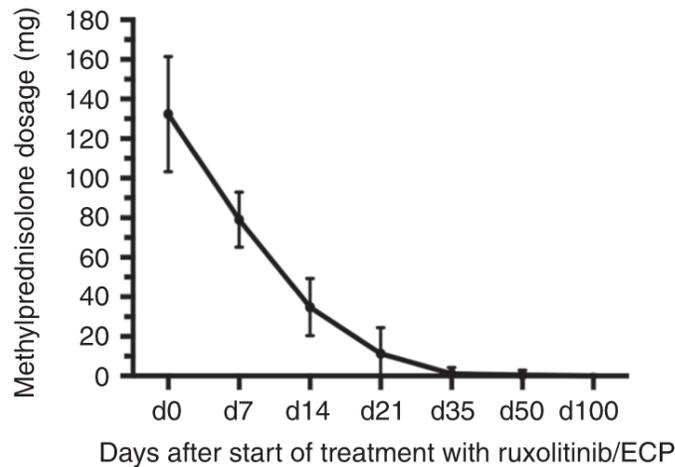


ECP in combination treatment

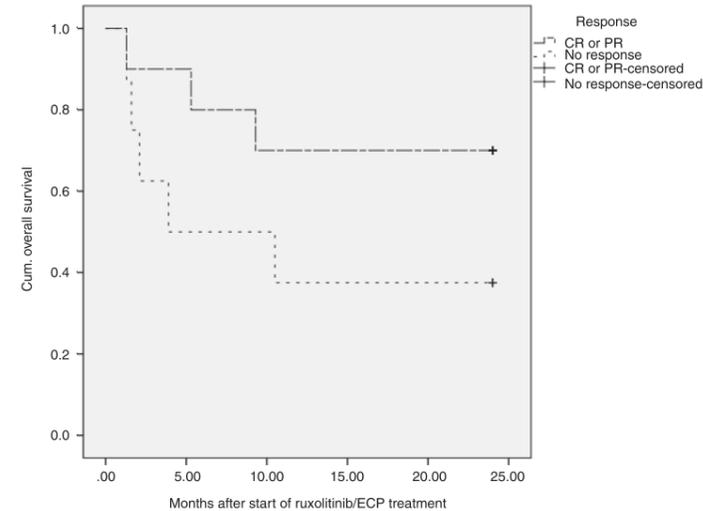
# Ruxolitinib plus ECP for SR aGvHD of lower GI tract



# Ruxolitinib plus ECP for SR aGvHD of lower GI tract



Modemann F, et al. *Bone Marrow Transplant.* 2020;55(12):2286-2293.



Modemann F, et al. *Bone Marrow Transplant.* 2020;55(12):2286-2293.

- Treatment was well tolerated
  - No severe (Grade IV) cytopenia, Grade III cytopenia in 3 patients
  - CR, 44%; PR, 11%
- Rapid steroid taper: median time for halving of dosage, 2 days
- In patients achieving CR/PR: 70% 2-year OS (median, 18.4 months)
- In patients with NR: 38% 2-year OS (median, 11.4 months)

# Ruxolitinib + ECP for refractory severe cGvHD

## Retrospective survey in 23 patients

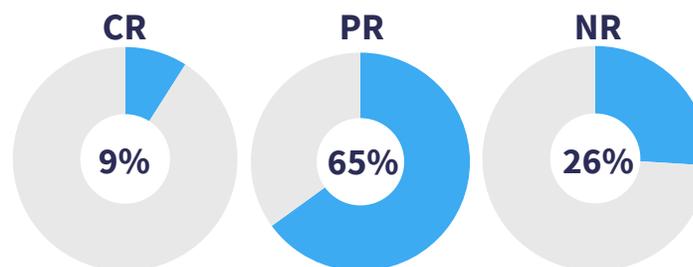
Patient characteristics	Patients, n (%)
>1 organ with GvHD features	20 (87)
Organ affection	
Skin	18 (78)
Liver	14 (61)
GI	13 (57)
Eye	10 (43)
Lung	8 (35)
cGvHD NIH Grade III	13 (57)
Beyond second-line treatment	21 (91)

## Treatment

- Two treatments of ECP (on consecutive days) every 2–4 weeks
- Median time of RUX-ECP was 6 months (1–27 months)
- 35% (8/23) started ruxolitinib first, median 15 months (range, 1–29 months) of ruxolitinib prior to combination therapy

## Results

Response rate after >1 week of combined therapy



- Best response (CR or PR) at any time point, 74% (17/23)
- 2-year OS, 75% (CI, 56.0–94.1)

Responses per cGVHD affected organ:

- GIT, 54%
- Liver, 21%
- Lung, 13%
- Skin, 44%
- Eye, 20%

- Steroid dose was reduced in 76% (13/17) of patients that responded to the RUX-ECP combination
- Serum levels of sIL-2R correlated with response
  - IL-2R levels declined once patients started RUX monotherapy (p=0.02)
  - IL-2R levels further declined after RUX-ECP combination therapy (p=0.046)



# ECP and IL-2 in steroid-refractory cGvHD

## Treatment

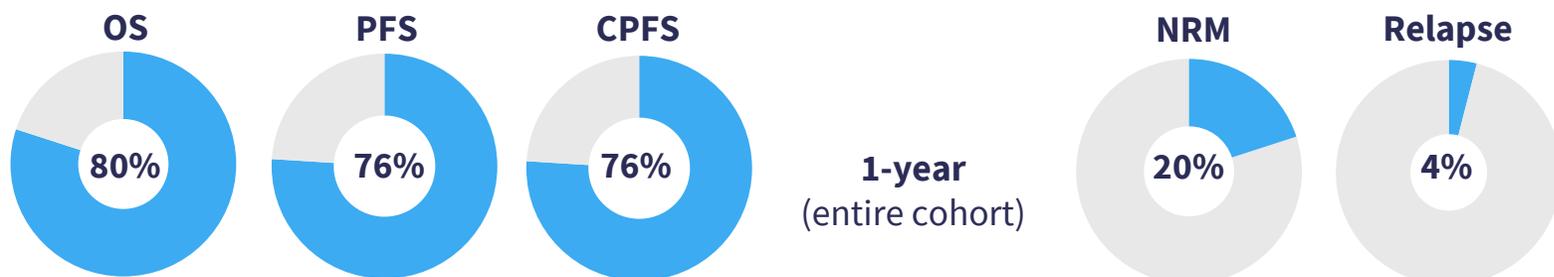


Response sites with ECP alone
Skin (n = 2)
GI tract (n = 2)
Joint/fascia (n = 4)
Lung (n = 1)
Liver (n = 1)

Additional response sites with ECP + IL-2
Skin (n = 7)
GI tract (n = 1)
Joint/fascia (n = 4)
Lung (n = 1)

## Results

- PR of 29% and 62% at 8 and 16 weeks of therapy, respectively; 1 ECP-related anemia and 2 infectious deaths
- After ECP: decline in CD4<sup>+</sup> T<sub>con</sub> and CD8<sup>+</sup> T cells
- After ECP + IL-2: increase in T<sub>reg</sub>, T<sub>reg</sub>:T<sub>con</sub> ratio, and NK cells





Approved and recommended use of ECP

# Approved and recommended use of ECP<sup>1-4</sup>

## Approved

- Treatment of advanced cutaneous T-cell lymphoma

## Recommended

- As second-line treatment for steroid-refractory acute and chronic GvHD



U.K. consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease

J.J. Scarisbrick, P. Taylor, U. Holtick, Y. Makar, K. Douglas, G. Berlin, E. Juvonen, S. Marshall, on behalf of the Photopheresis Expert Group

First published: 30 January 2008 | <https://doi.org/10.1111/j.1365-2133.2007.08415.x> | Citations: 127

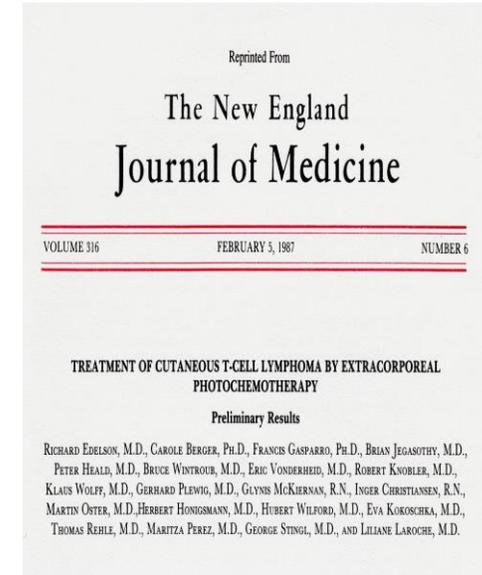


COMMITTEE REPORT

Extracorporeal photopheresis for the treatment of acute and chronic graft-versus-host disease in adults and children: best practice recommendations from an Italian Society of Hemapheresis and Cell Manipulation (SIdEM) and Italian Group for Bone Marrow Transplantation (GITMO) consensus process

Luca Pierelli, Paolo Perseghin ✉, Monia Marchetti, Chiara Messina, Cesare Perotti, Alessandro Mazzoni, Andrea Bacigalupo, Franco Locatelli, Paolo Carlier, Alberto Bosifor ... [See all authors](#) ▾

First published: 10 January 2013 | <https://doi.org/10.1111/trf.12059> | Citations: 38



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European dermatology forum – updated guidelines on the use of extracorporeal photopheresis 2020 – part 1

R. Knobler ✉, P. Arenberger, A. Arun, C. Assaf, M. Bagot, G. Berlin, A. Bohbot, P. Calzavara-Pinton, F. Child, A. Cho, L.E. French, A.R. Gennery, R. Gniadecki, H.P.M. Gollnick, E. Guenova ... [See all authors](#) ▾

First published: 06 October 2020 | <https://doi.org/10.1111/jdv.16890> | Citations: 23

GvHD, graft-versus-host disease; ECP, extracorporeal photopheresis.

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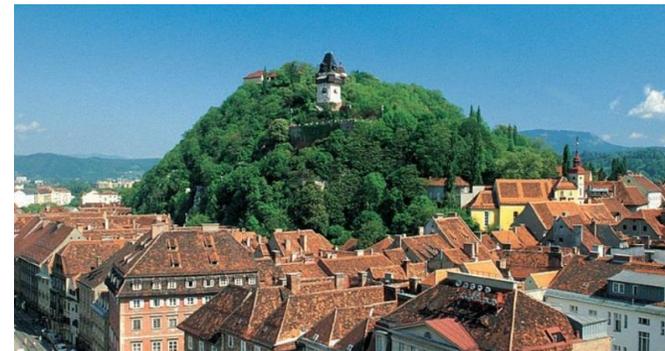
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Thank you