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Extracorporeal photopheresis in graft versus host disease

Olivier Hequet

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HEMO[®] 2024

23 a 26 de Outubro

Congresso Brasileiro de Hematologia,
Hemoterapia e Terapia Celular

Extracorporeal photopheresis (ECP) in graft versus host disease

HEMO[®]
2024
23 a 26 de Outubro
Congresso Brasileiro de Hematologia,
Hemoterapia e Terapia Celular

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Apheresis Unit

French Blood Agency/ Center Hospitalier Lyon Sud
President of French Society of Hemapheresis
France



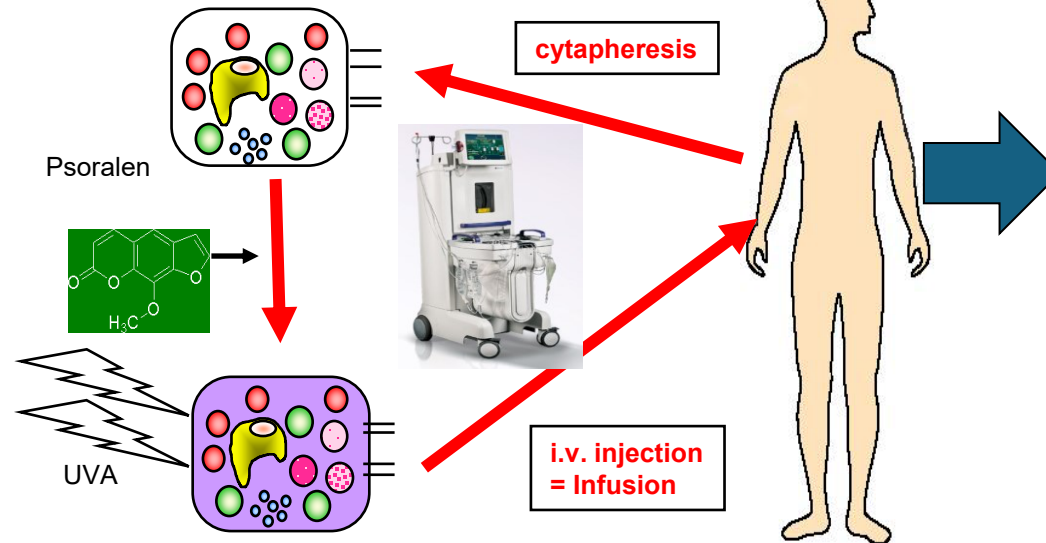
Conflict of Interest Disclosure

No conflict of interest for more than 5 years in ECP

Principle and clinical efficacy of ECP

Extracorporeal photochemotherapy = ECP

Blood mononuclear cells :
lymphocytes + monocytes + Dendritic Cells (DC)



Clinical efficacy:

-Cutaneous T cell lymphoma (CTCL)
Zic JA, Curr Opin Oncol 2012
Improvement : 63%

- Transplantation (Stem cells) Graft versus host disease
Courriel D, Blood 2006
Improvement : 60%
Complete response : 25%

- Transplantation (solid organs) graft rejection
Barr ML, N Eng J Med 1998
Improvement 50%

- Crohn disease
Abreu MT, Inflamm Boew Dis 2009
Improvement 50 %

- Lichen Planus
Guyot F, Br J Dermatol 2007
Improvement: 60%

- Severe psoriasis
Valhquist A, Arthritis Rheum 1996
Improvement 50 %

Aim of ECP:

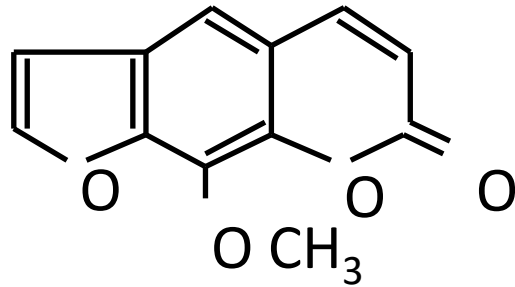
Antitumoral immune response

Restore immune tolerance

However mechanisms of action of ECP are still poorly known

First events after ECP-Treatment

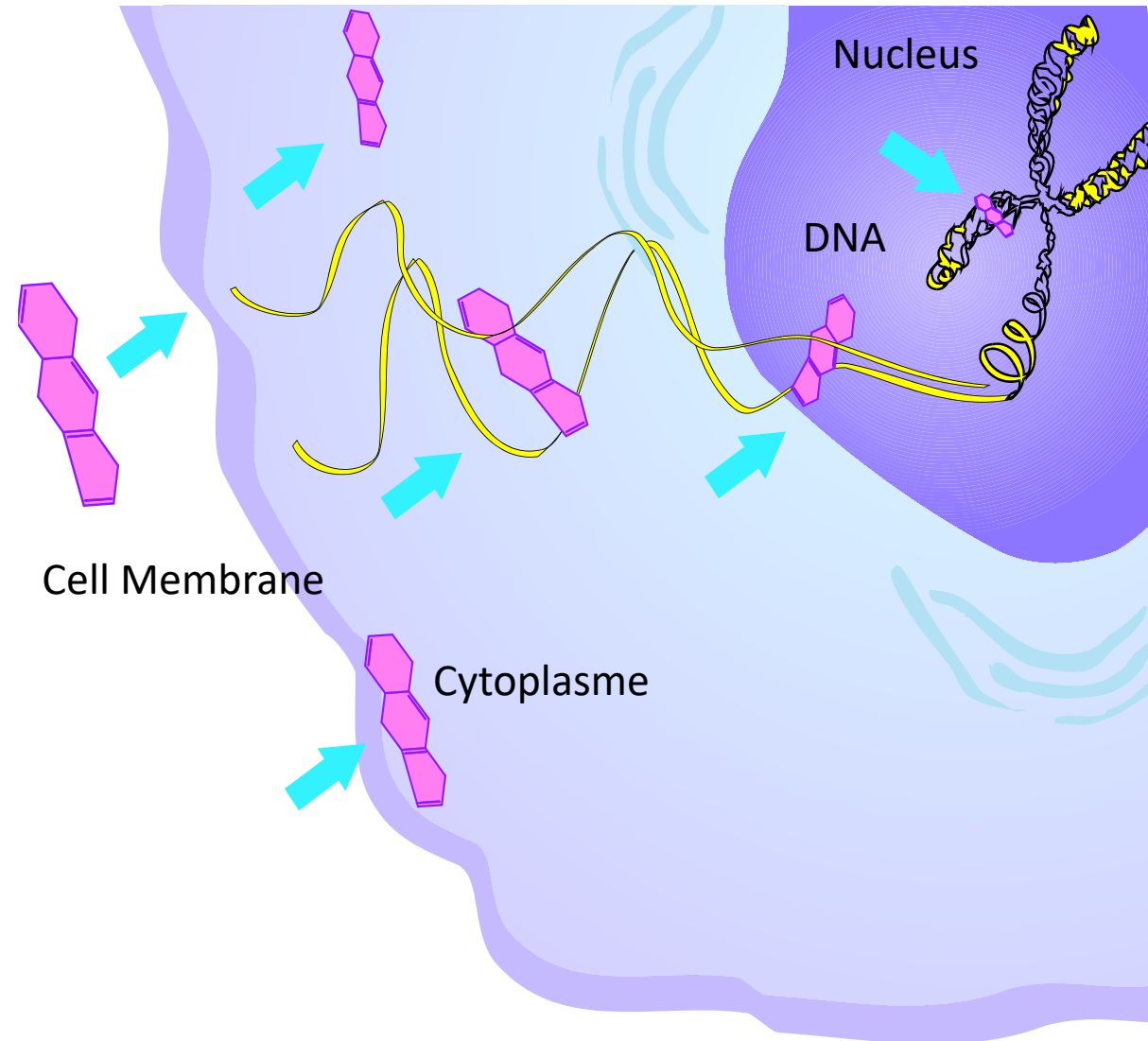
8-Methoxypsoralen (8-MOP)



8-MOP belongs to the furocoumarines,
(natural molecules in fruits and vegetables)

8-MOP fits between 2
DNA strands

UVA induce DNA breaks and cell apoptosis

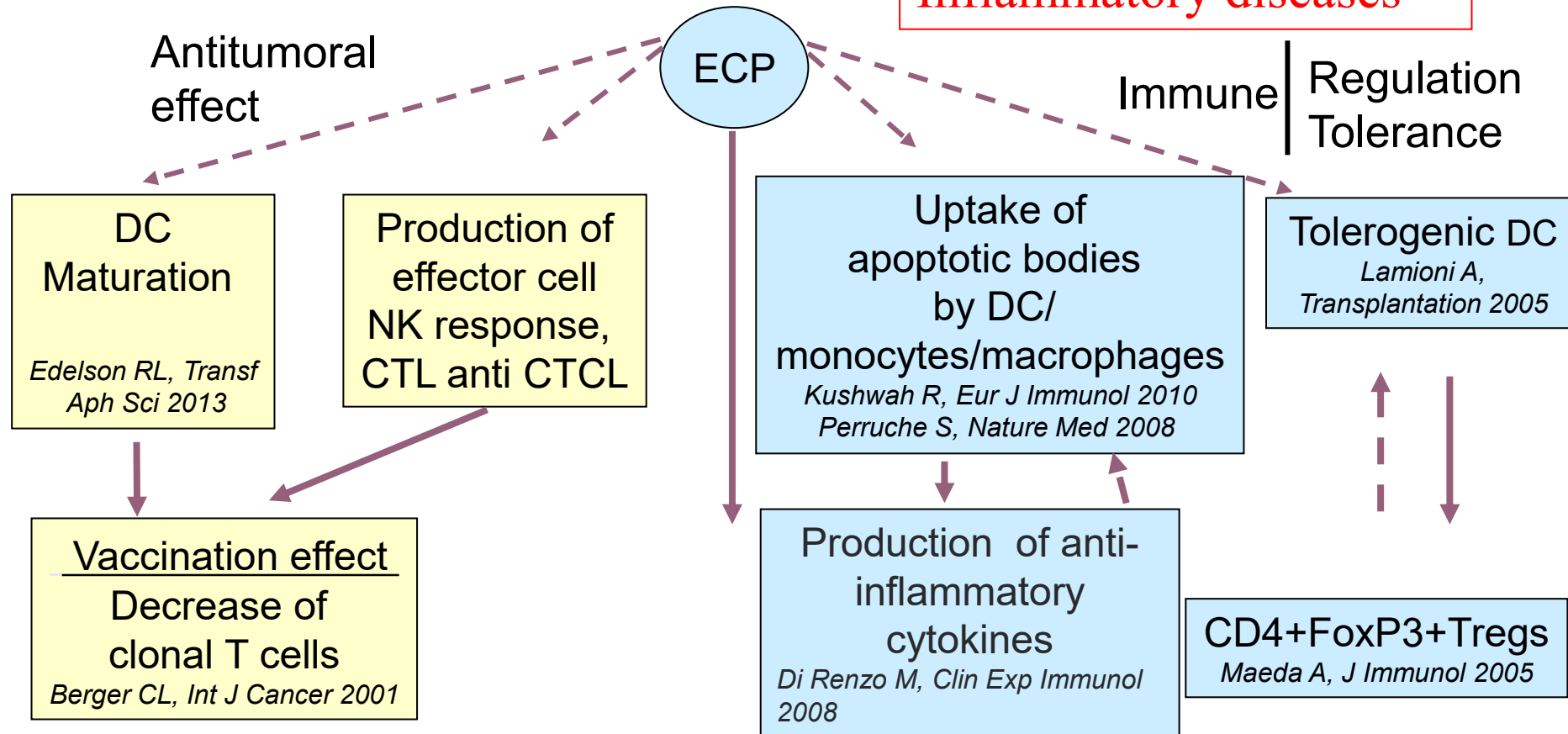


(Adapted from Gasparro FP *et al*, *Recent Results Cancer Res* 1997)

Summary of mechanisms of action

CTCL

Allogenic, autoimmune,
Inflammatory diseases



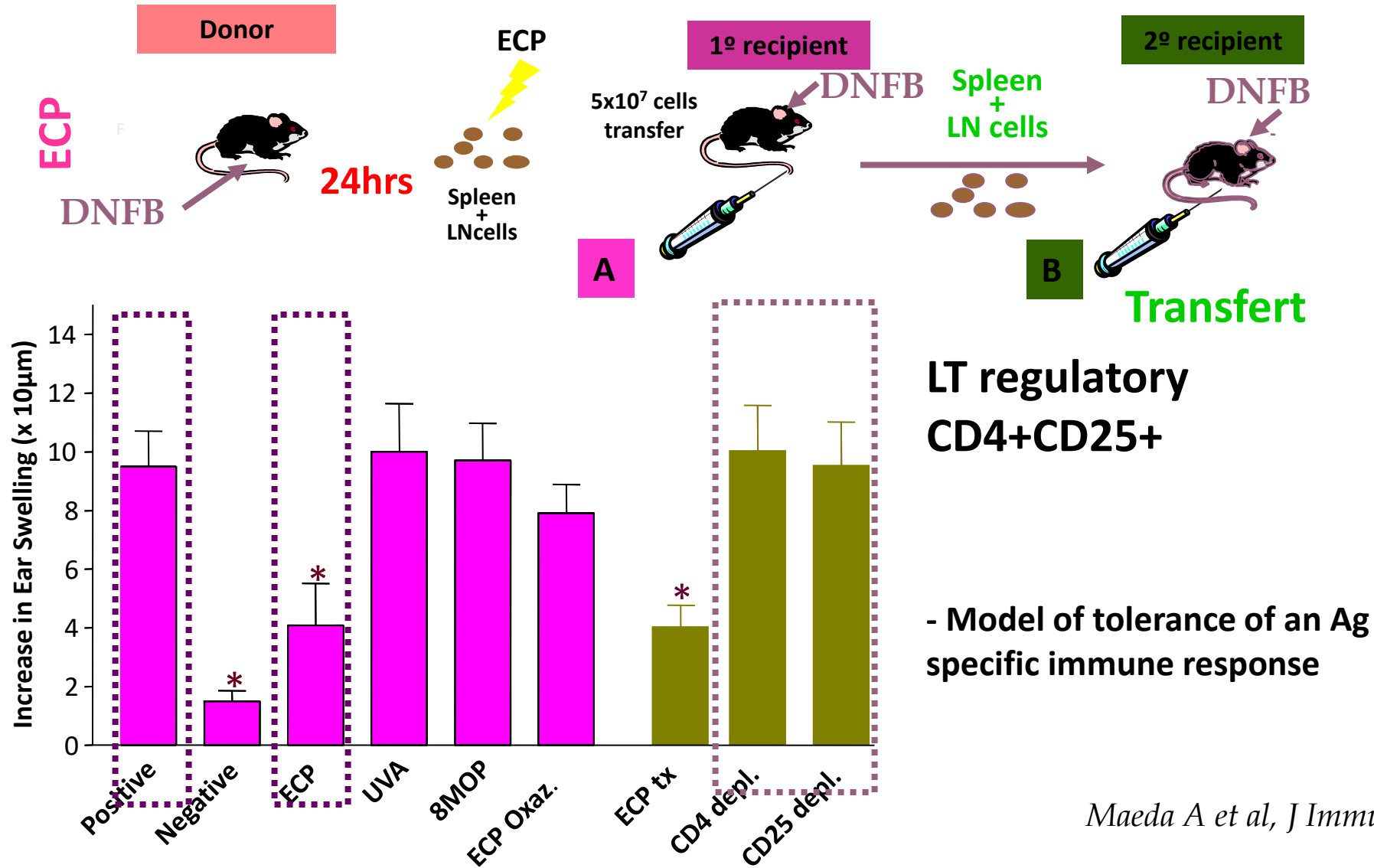
Vaccination effect
Decrease of clonal T cells
Berger CL, Int J Cancer 2001



Required : Apoptosis of T-lymphocytes bearing an antigen specificity



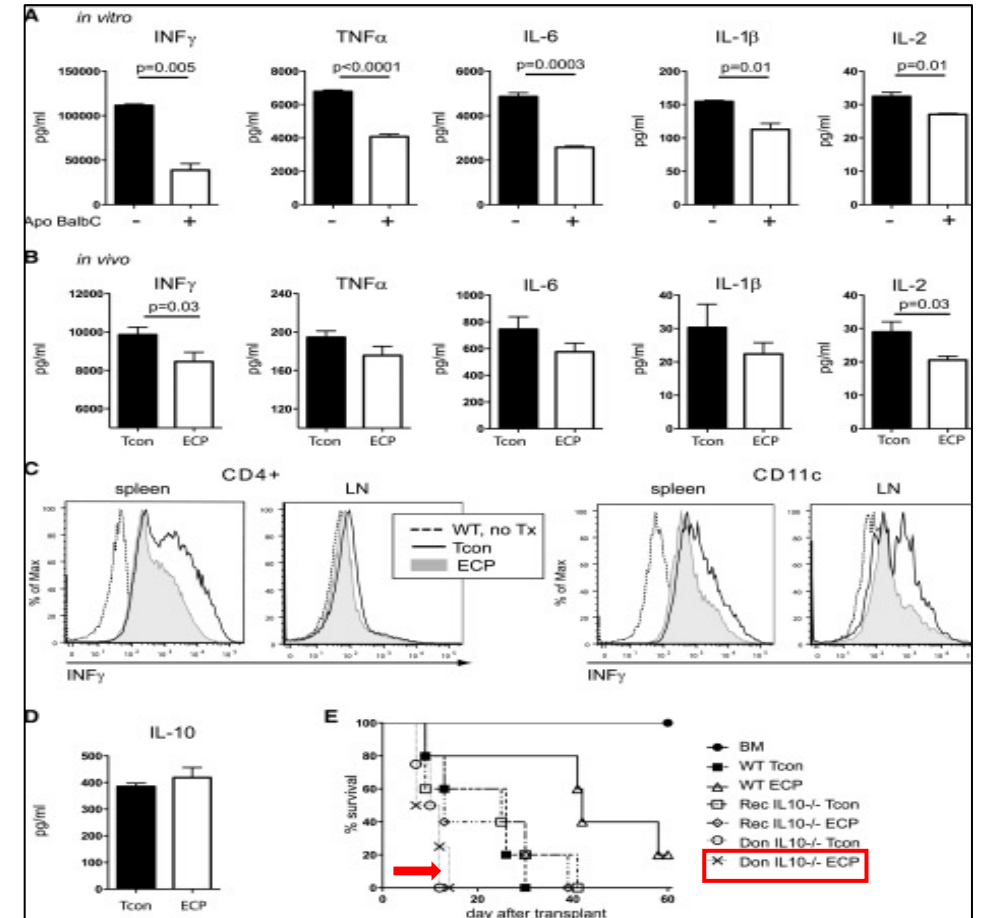
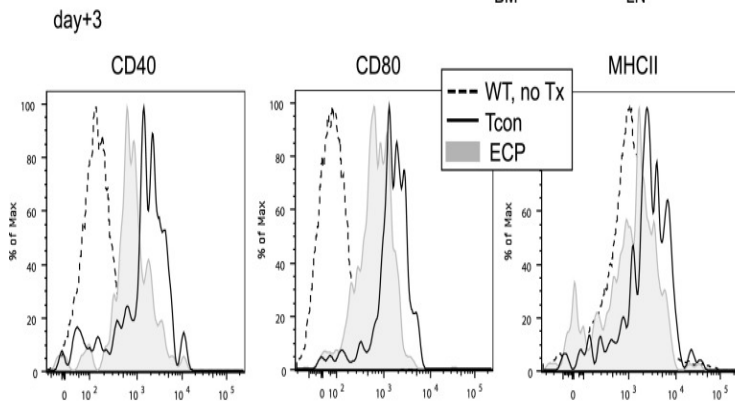
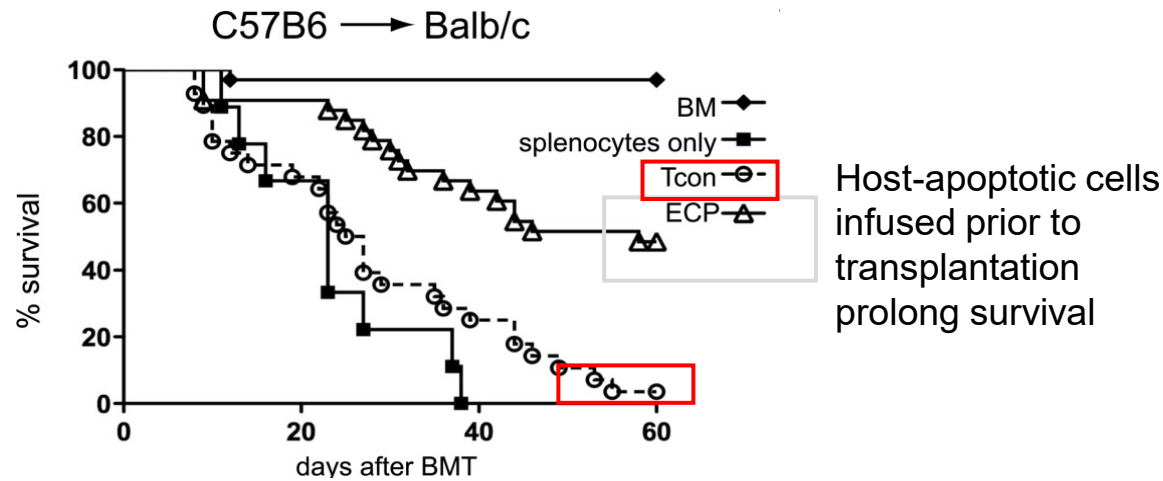
ECP could induce the production of LT Reg (CD4+CD25+?) *In Vivo*



Mechanisms of action in GVHD

Animal model

Florek M et al, Blood 2014

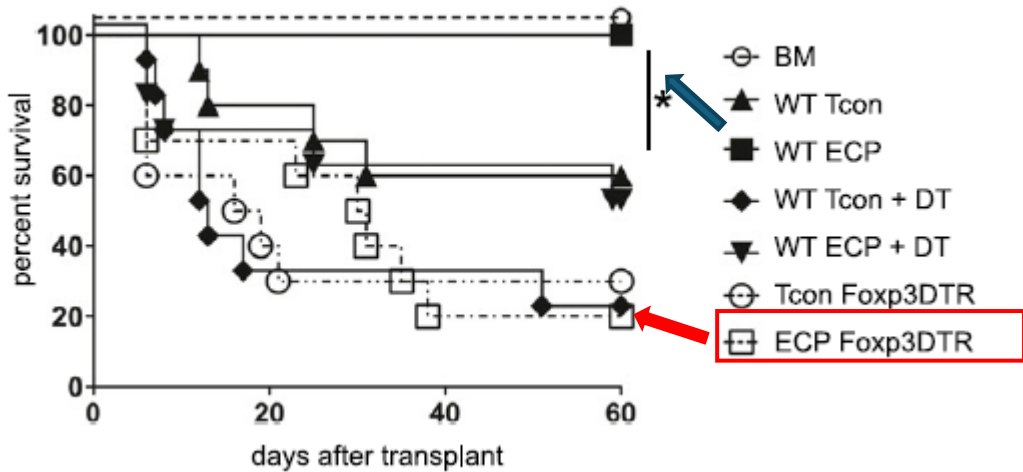
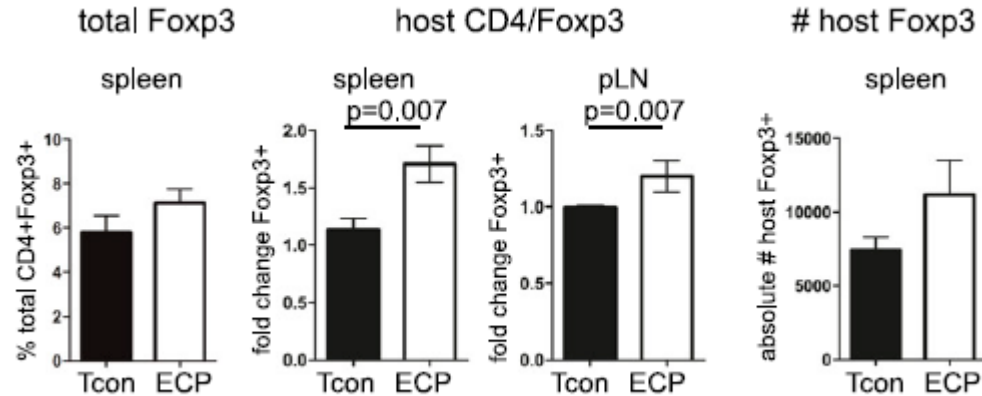


ECP reduces proinflammatory cytokine secretion and requires IL-10 secretion

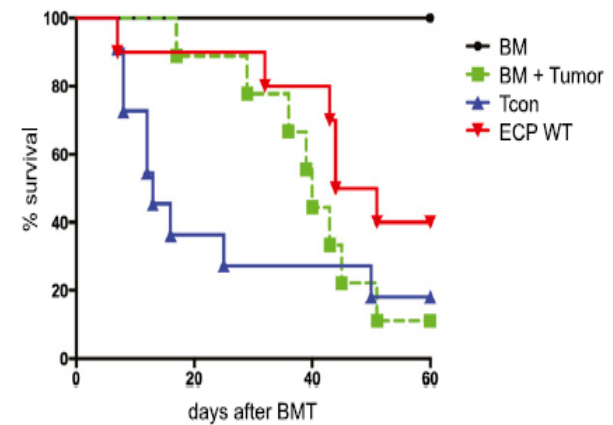
Mechanisms of action in GVHD

Animal model

Florek M et al, Blood 2014



ECP-Tregs contribute but are not solely responsible for improved outcome



ECP did not seem to hamper GVL effect

ECP and GVHD: an evolving treatment

No difference in efficacy between the techniques

On line=1 step	Uvar –Therakos (1985- 1999)	Uvar XTS (1999–2007)	Uvar 3ème génération (2007)	Cellex (Therakos) 2009
Off line = 2 steps		ViIber – Lourmat (1990)	Macogenic 1 Macopharma (2001)	Macogenic G2
Off line = 2 steps			UVA-PIT technology (2005-)	UVA -PIT

Techniques

2 consecutive days / month	2 consecutive days / 15 days	2 days /week 1 month <u>evaluation</u> and tapering	2 à 4/week/other week/tapering when RP or at 3 months (cGVHD)
Dippel 1999	Child 1999 Seaton 2003	Messina C 2003 Garban F 2005	Couriel D 2006 Amat P2021

Schedules

Assessment

aGVHD	Overall, PR and CR at day 28
Working group on cGVHD staging : National Institutes of health Consensus	2005 Revised in 2015

1994 - 1997	1997 - 2003	2003-2006	2006-2024
1 patient skin	1-5 patients Skin + joint	5-30 patients skin + lung + liver + eye + mouth	30-100 patients skin + lung + liver + eye + mouth

Size

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Ninth Special Issue

Connelly-Smith L et al, J Clin Apher 2023

GRAFT-VERSUS-HOST DISEASE

Incidence: after allogeneic HSCT, grade II to IV aGVHD in up to 60%; cGVHD in up to 70%

Indication	Procedure		Category	Grade
Acute/Chronic	ECP		II	IB
# reported patients: >300	RCT	CT	CS	CR
Acute	1 (81)	6 (296)	NA	NA
Chronic	2 (148)	8 (228)	NA	NA

Key messages

- Partial responses = 65% in aGVHD and cGVHD
- Maximal response in cGVHD requires at least 6 months of treatment
- ECP does not increase the risk of infections or disease relapse
- ECP may allow the weaning of immunosuppressive treatment (corticosteroids)
- ECP = second line for steroid resistant aGVHD and cGVHD (to be nuanced with anti JAK1/2)

Table 1. continued

Study	Trial design	Treatment	ORR %/CR%
b			
Acute GvHD			
Greinix et al. [34] (n = 59)	Prospective, single-arm, phase II	ECP + CS in second-line	70/60
Amat et al. [35] (n = 37)	Prospective, multicenter	ECP + CS in second-line	73/40.5
Jagsla et al. [36] (n = 108)	Retrospective, multicentre	ECP + CS vs Inolimomab/ Etanercept + CS in second-line	66/54 vs 32/20 (p = 0.001)
DasGupta et al. [37] (n = 128)	Retrospective, multicentre	ECP + CS in second-line	77/67
Worel et al. [38] (n = 99)	Retrospective, single center	ECP + CS in second-line	75/53
Calore et al. [39] (n = 72, children)	Retrospective	ECP + CS ± other IS	83/64
		ECP + CS in second-and third line	62/48
		ECP + CS	68/32
		ECP + CS in second-line	Na/91
		ECP + CS ± other IS	75/54
		ECP + CS ± other IS vs CS ± other IS	40 vs 10 at w12 in skin (p = 0.002)
		ECP + CS ± other IS	31% at w24 in skin
		ECP + CS	73/40
		ECP + CS ± other IS	62/14
		ECP + CS ± other IS	79/na
		ECP + CS ± other IS	61/20
		ECP + CS ± other IS	83/na

ECP and aGVHD

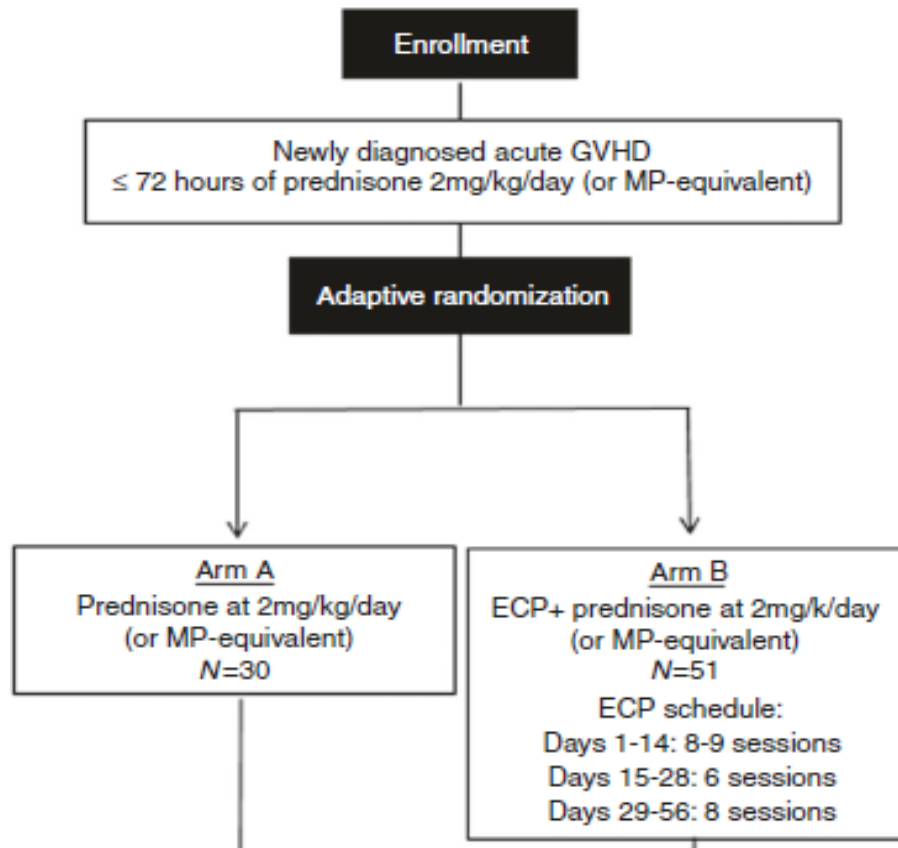
30 retrospective or prospective series
N= 30- 108 patients

Overall response rate (CR+PR) in :

- Skin: 80%
- Liver: 60%
- Gut: 60%
- Overall survival superior in ECP responders

Randomized phase II trial of extracorporeal phototherapy and steroids vs. steroids alone for newly diagnosed acute GVHD

Mehta RS et al BMT 2021



Treatment Arm	Risk group	Success	Failure	Total
Steroids alone	All patients	16 (53%)	14 (47%)	30
	Visceral	3 (43%)	4 (57%)	7
	Skin only	13 (57%)	10 (43%)	23
ECP + steroids	All patients	33 (65%)	18 (35%)	51
	Visceral	7 (47%)	8 (53%)	15
	Skin only	26 (72%)	10 (28%)	36

Response at d56

- Better global response when ECP plus steroids
- Better response in skin
- Low number of patients included

Authors	N	Method	CR/PR skin %	CR/PR liver %	CR/PR oral %	CR/PR lung %	CR/PR ocular %	CR/PR GI %	ORR %	Steroid sparing	OS n (%)
Rossetti et al ²⁴	8 ^b	In-line	-	-	-	-	-	-	50	Yes	100% alive at follow-up
Smith et al ²⁵	18 ^b	In-line	-	-	-	-	-	-	33	-	7/18 alive (39)
Greinix et al ⁶	15	In-line	100	90	100	-	80	-	93	Yes	14/15 (93)
Child et al ⁷	11	In-line	100	17	50	40	50	-	-	Yes	9/11 (82)
Salvaneschi et al ⁴⁸	14 ^a	Off-line	93	67	67	-	-	-	64	Yes	11/14 (79)
Halle et al ²⁶	8 ^a	Off-line	88	100	100	-	-	100	100	Yes	100% alive at follow-up
Seaton et al ²⁷	28	In-line	48	32	21	-	-	-	-	-	-
Apisarnthanasax et al ²⁸	32 ^b	In-line	56	-	-	-	-	-	-	-	-
Messina et al ²⁹	44 ^a	In-line	57	60	-	-	-	-	-	-	-
Ilhan et al ²⁸	8	In-line	100	80	100	-	-	-	-	-	-
Foss et al ²¹	25	In-line	64	0	46	-	-	-	-	-	-
Rubegni et al ²⁹	32	In-line	81	77	92	-	-	-	-	-	-
Garban et al ⁵⁰	15	Off-line	100	33	-	-	-	-	-	-	-
Bisaccia et al ⁷⁰	14	In-line	50	60	43	-	-	-	-	-	-
Couriel et al ⁷¹	71 ^b	In-line	57	71	78	-	-	-	-	-	-
Kanold et al ⁵²	15 ^a	Off-line	75	82	86	-	-	-	-	-	-
Motolese et al ⁷²	24	In-line	78	-	-	-	-	-	-	-	-
Duzovali et al ⁷³	7 ^a	In-line	100	40	0	-	-	-	-	-	-
Berger et al ²¹	10 ^a	Both in- and off-line	90	50	33	-	-	-	-	-	-
Perseghin et al ⁷⁴	25 ^b	Off-line	84	67	78	-	-	-	-	-	-
Flowers et al ²⁶	48	In-line	40	29	53	-	-	-	-	-	-
Jagasia et al ⁷⁵	43	???	-	-	-	-	-	-	-	-	-
Perotti et al ⁵³	23	Off-line	96	100	80	-	-	-	-	-	-
Dignan et al ⁷⁶	82	In-line	92	-	91	-	-	-	-	-	-
Greinix et al ²⁹	29	In-line	31	50	70	-	-	-	-	-	-
Del Fante et al ⁷⁷	102	Off-line	-	-	-	-	-	-	-	-	-
Ussowicz et al ⁵⁶	13 ^b	In-line	67	89	86	-	-	-	-	-	-
Hautmann et al ²⁷	32 ^b	Off-line	59	100	60	-	-	-	-	-	-
Dignan et al ⁷⁸	38	In-line	65	-	29	-	-	-	-	-	-
Berger et al ²³	37 ^b	Both in- and off-line	-	-	-	-	-	-	-	-	-
Brownback et al ⁷⁹	8	In-line	-	-	-	Reduced IS + slow decline in PFT	-	-	0	Yes	63% alive at follow-up

ECP and cGVHD

70 retrospective or prospective series

N= 50-100 patients

Optimal duration time for response = 6 months

Overall response rate :

- Skin: 80%
- Oral: 70%
- Liver: 50%
- Lung: 40-50%
- Overall survival superior in ECP responders

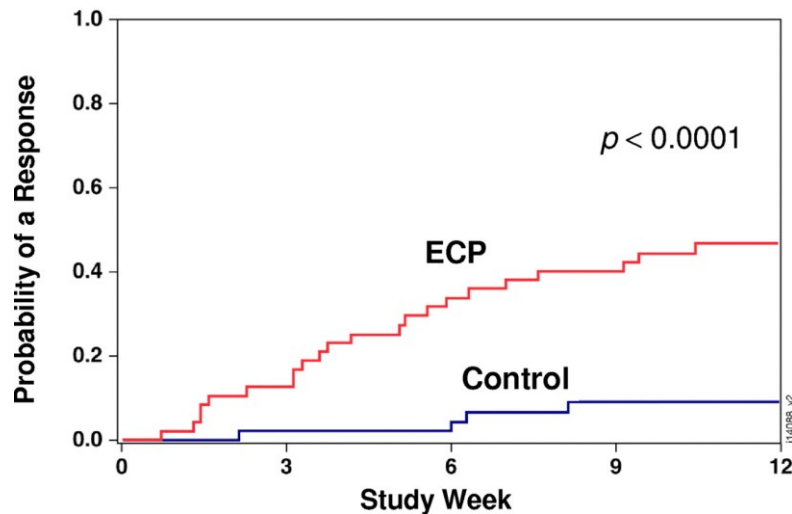
ECP and cGVHD

A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease

*Mary E. D. Flowers,¹ Jane F. Apperley,² Koen van Besien,³ Ahmet Elmaagacli,⁴ Andrew Grigg,⁵ Vijay Reddy,⁶ Andrea Bacigalupo,⁷ Hans-Jochem Kolb,⁸ Luis Bouzas,⁹ Mauricette Michallet,¹⁰ H. Miles Prince,¹¹ Robert Knobler,¹² Dennis Parenti,¹³ Jose Gallo,¹³ and *Hildegard T. Greinix¹⁴

Table 3. Total Skin Score (TSS) and corticosteroid response to ECP treatment

Parameter	Week 12		P	Week 24	
	ECP, n = 48	Control, n = 47		ECP, n = 48	Control, n = 47*
Median percent change from baseline in TSS	-14.5	-8.5	.48	-31.4	N/A
> 50% reduction in corticosteroid dose, n (%)†	12 (25)	6 (12.8)	.13	19 (39.6)	N/A
> 50% reduction in corticosteroid dose and > 25% improvement in TSS, n (%)	4 (8.3)	0 (0.0)	.04	11 (22.9)	N/A
> 50% reduction in corticosteroid dose and final corticosteroid dose of < 10 mg/day, n (%)†	10 (20.8)	3 (6.4)	.04	17 (35.4)	N/A



Cumulative incidence of complete or partial skin response.

ECP

- **Better response**
- **Increased reduction in corticosteroids**
- **Evaluation too early**

Progressive Improvement in Cutaneous and Extracutaneous Chronic Graft-versus-Host Disease after a 24-Week Course of Extracorporeal Photopheresis—Results of a Crossover Randomized Study

Hildegard T. Greinix,..... Mary E. D. Flowers,

Biol Blood Marrow Transplant 17: 1775-1782 (2011)

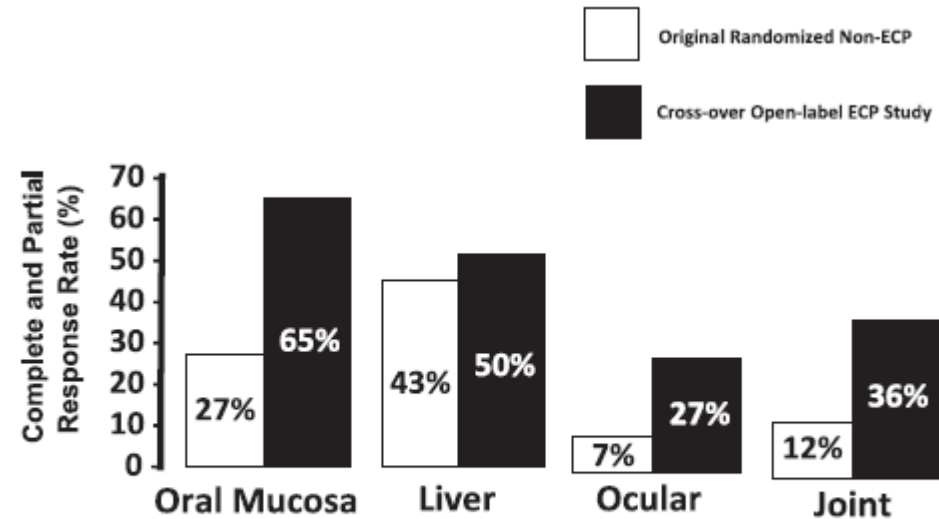
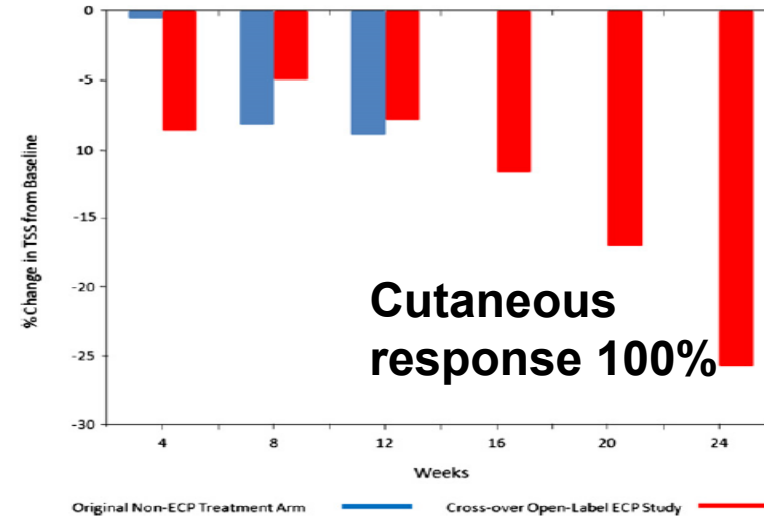
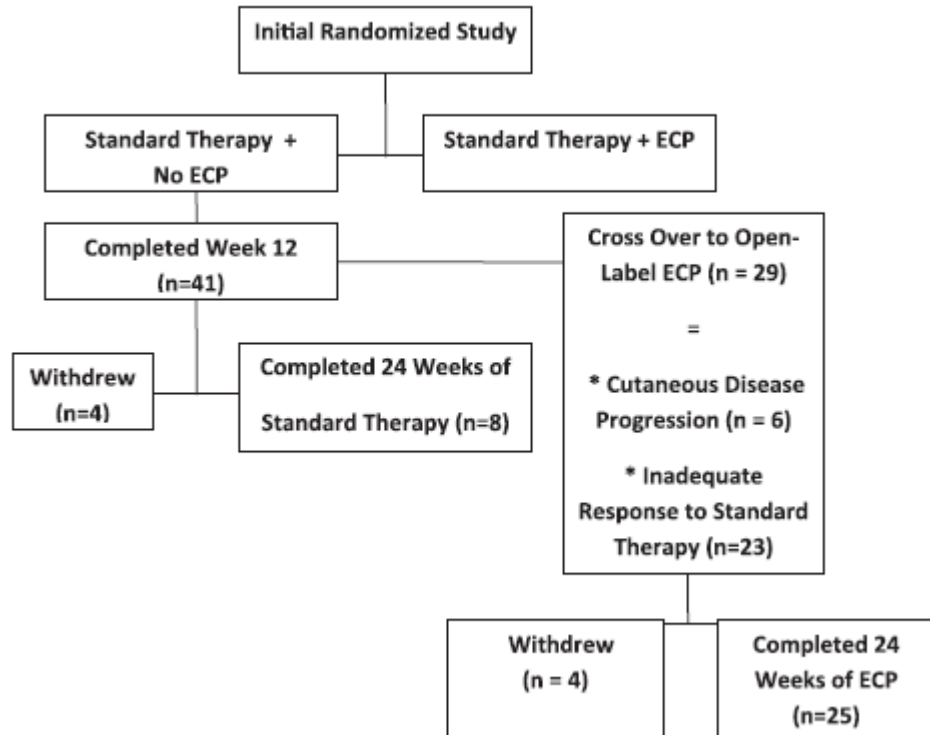
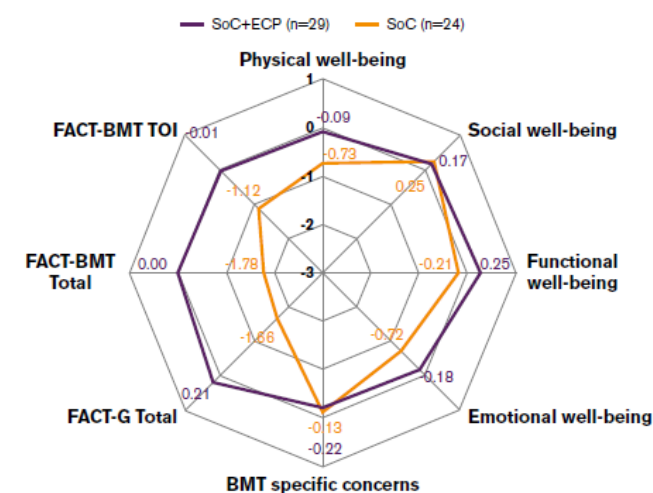
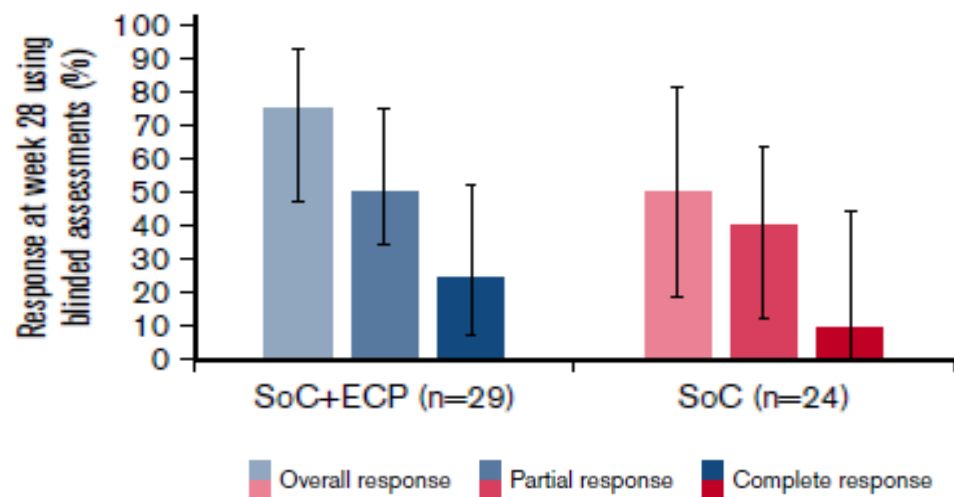
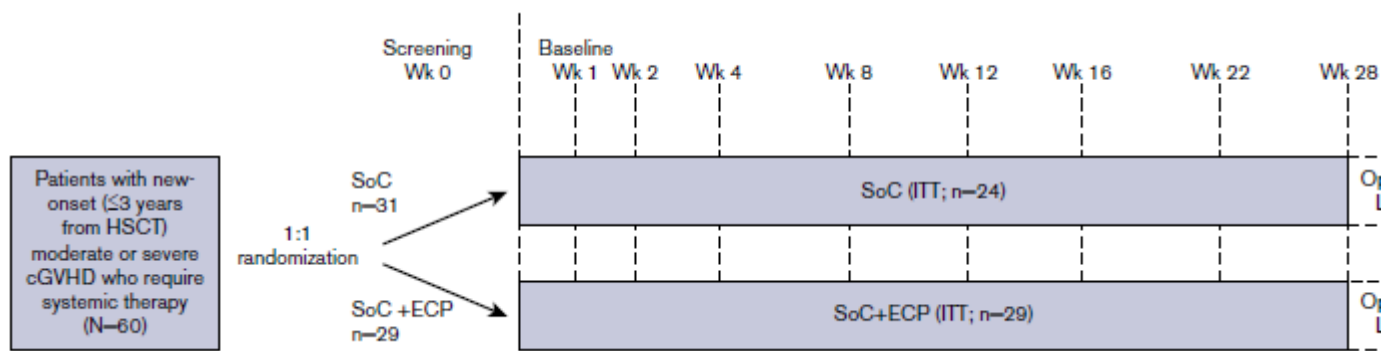


Figure 3. Complete and partial response of extracutaneous manifestations during standard non-ECP therapy and after crossover to adjunct ECP: comparison of results after 12 weeks.

Randomized controlled study of ECP with methoxsalen as first-line treatment of patients with moderate to severe cGVHD

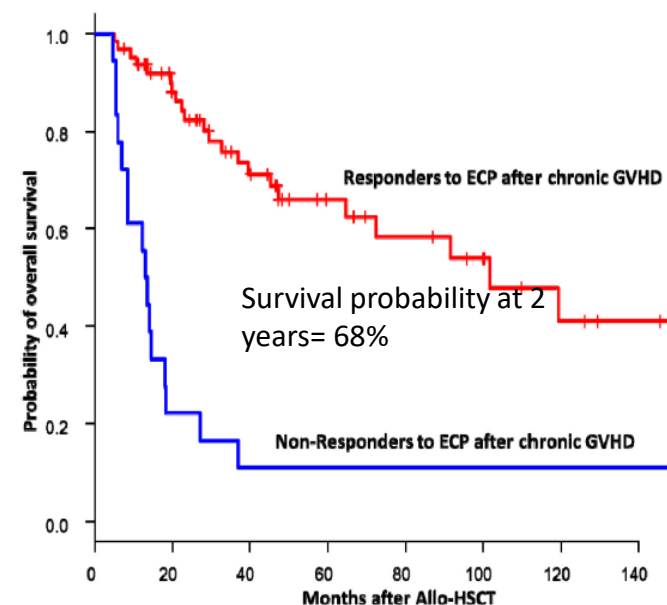
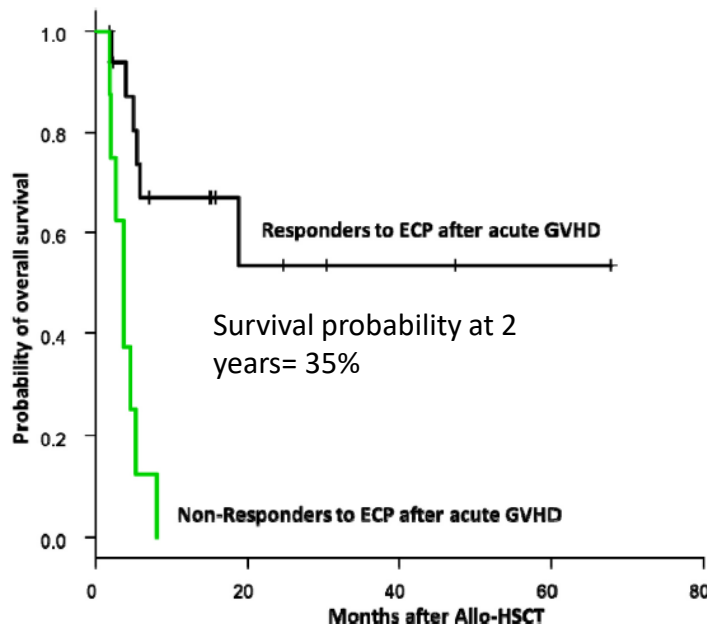
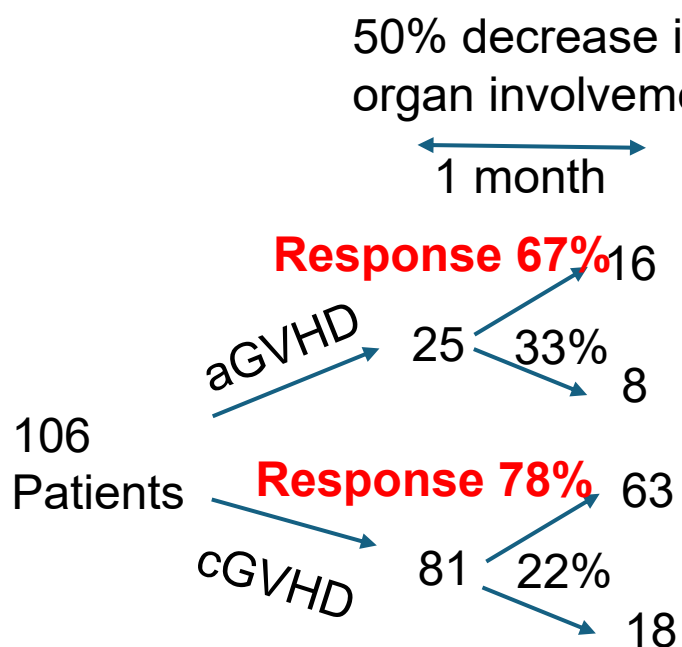
Jagasia M... Greinix HT. Blood Advances 2019



- Patients treated with SoC experienced a decline in Quality of life over the 28-week study
- QoL remained unchanged in SoC+ECP patients.

Second line extracorporeal photopheresis for cortico-resistant acute and chronic GVHD after allogeneic hematopoietic cell transplantation for hematological malignancies: Long-term results from a real-life study

Michallet M Hequet O; Transf Aph Sci 2024

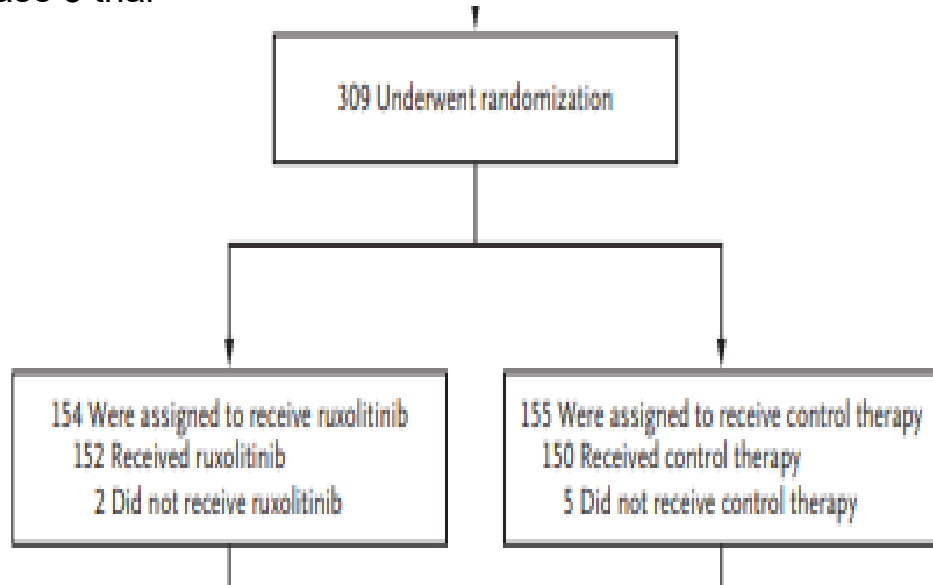


- High response rate in aGVHD and CGVHD

- Significant difference in terms of survival for patients responding to ECP compared to non-responders in both forms.

Ruxolitinib for Glucocorticoid-Refractory Acute Graft-versus-Host Disease

REACH2 multicenter,
randomized, openlabel,
phase 3 trial



antithymocyte globulin (16%)
extracorporeal photopheresis, (31%)
mesenchymal stromal cells (13%)
methotrexate,mycophenolate mofetil (22%),
(mTOR) inhibitor (everolimus or sirolimus) (13%)
etanercept, (21%)
infliximab. (13%)

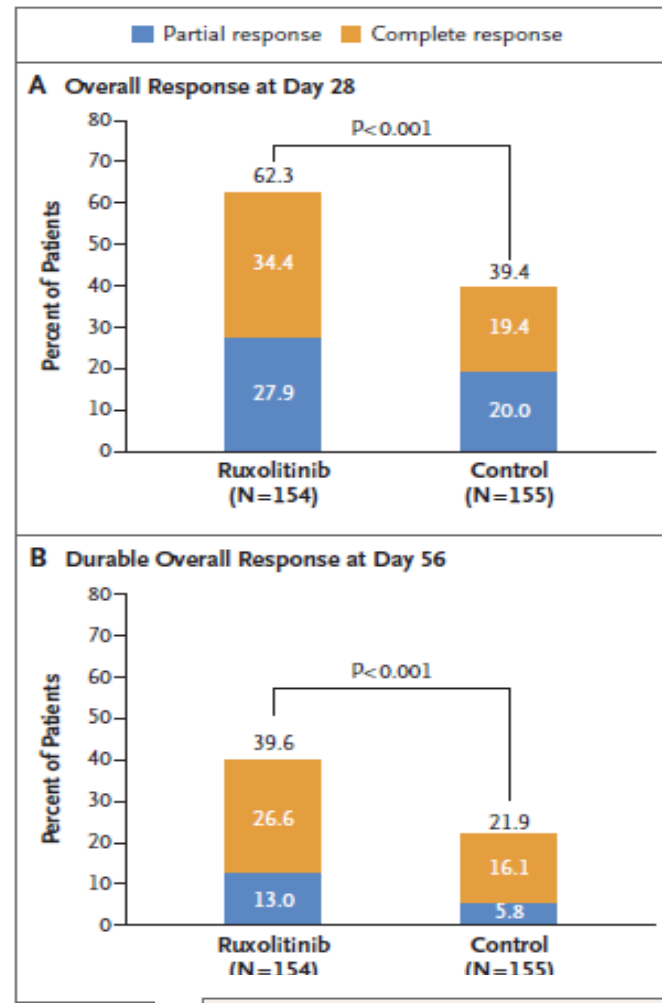


Table 2. Most Frequent Adverse Events up to Day 28 (Safety Population).*

Event	Ruxolitinib (N=152)		Control (N=150)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	<i>number of patients (percent)</i>			
Any adverse event	145 (95)	118 (78)	140 (93)	117 (78)
Thrombocytopenia	50 (33)	41 (27)	27 (18)	23 (15)
Anemia	46 (30)	33 (22)	42 (28)	28 (19)
Cytomegalovirus infection†	39 (26)	11 (7)	31 (21)	12 (8)

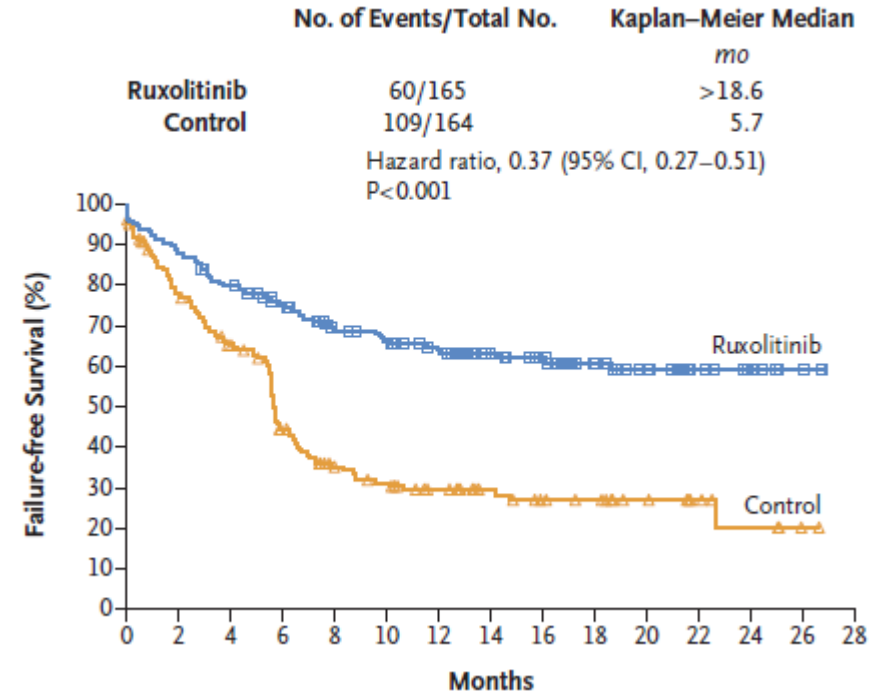
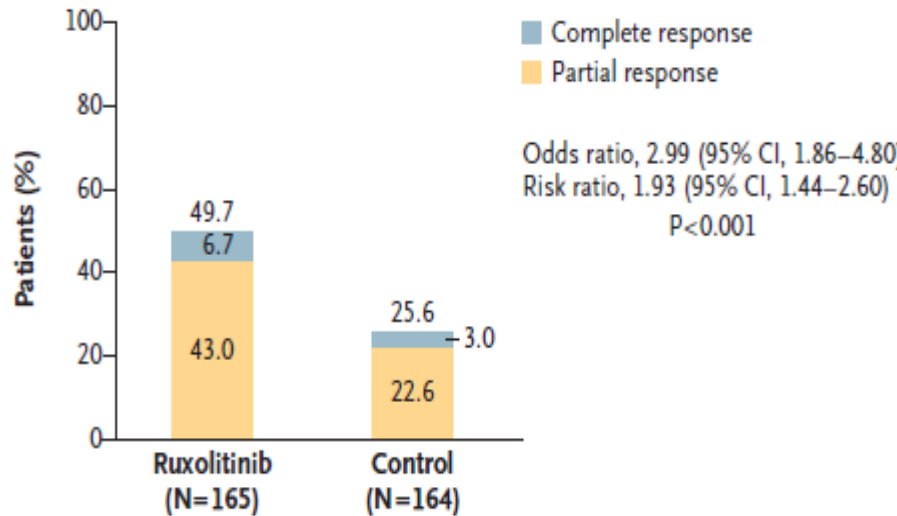
REACH3 multicenter, randomized, openlabel, phase 3 trial

R Zeiser et al. New Eng J Med 2021

Ruxolitinib for Glucocorticoid-Refractory Chronic Graft-versus-Host Disease

B Failure-free Survival

A Overall Response at Week 24



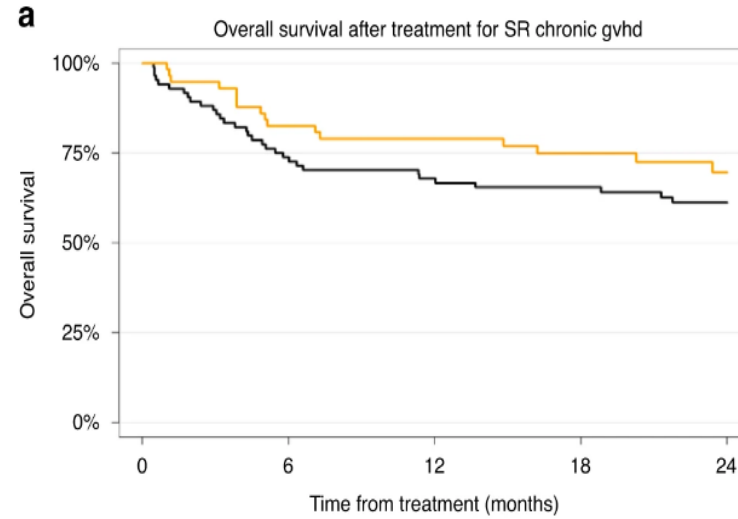
Adverse Event	Ruxolitinib (N=165)		Control (N=158)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any	161 (97.6)	94 (57.0)	145 (91.8)	91 (57.6)
Hematologic event				
Anemia	48 (29.1)	21 (12.7)	20 (12.7)	12 (7.6)
Thrombocytopenia†	35 (21.2)	25 (15.2)	23 (14.6)	16 (10.1)

number of patients with event (percent)

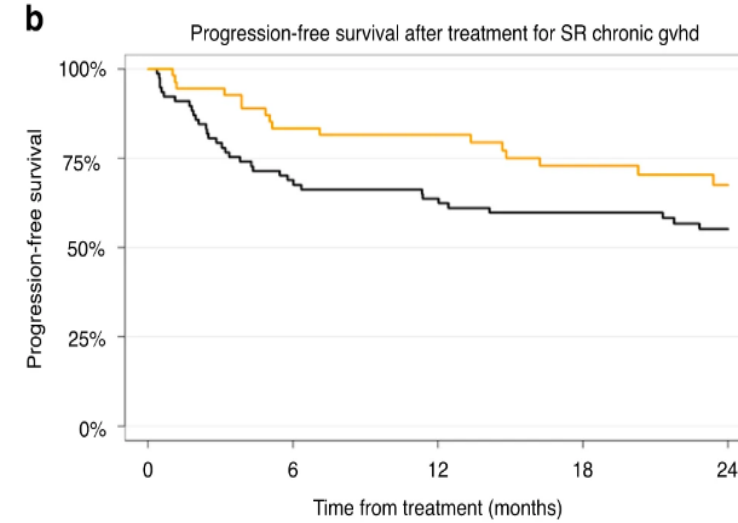
ECP versus ruxolitinib in steroid-refractory chronic GVHD – a retrospective study by the EBMT transplant complications working party

Penack O et al, BMT 2024

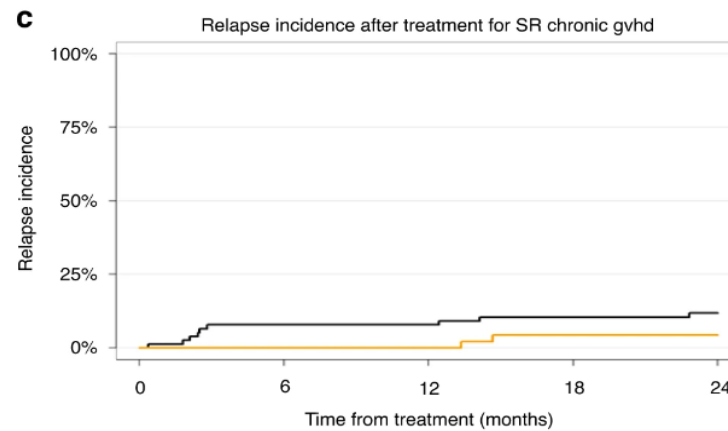
No difference between ECP and Ruxolutinib



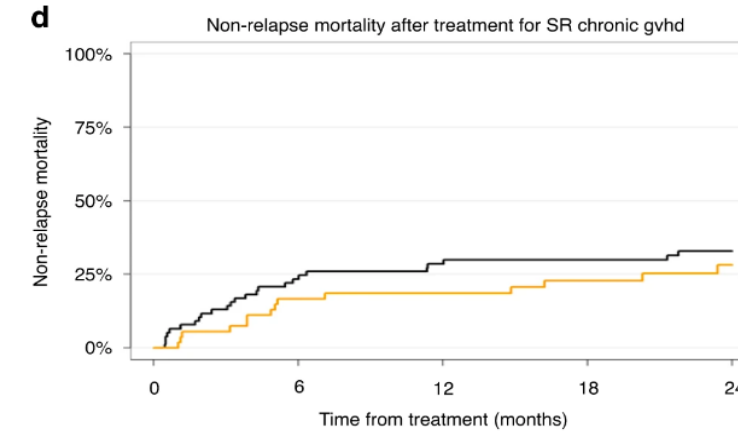
ECP only:	84	62	56	48	41
Ruxo only:	57	47	43	33	21



ECP only:	77	53	49	40	35
Ruxo only:	54	45	42	31	20



ECP only:	77	53	49	40	35
Ruxo only:	54	45	42	31	20

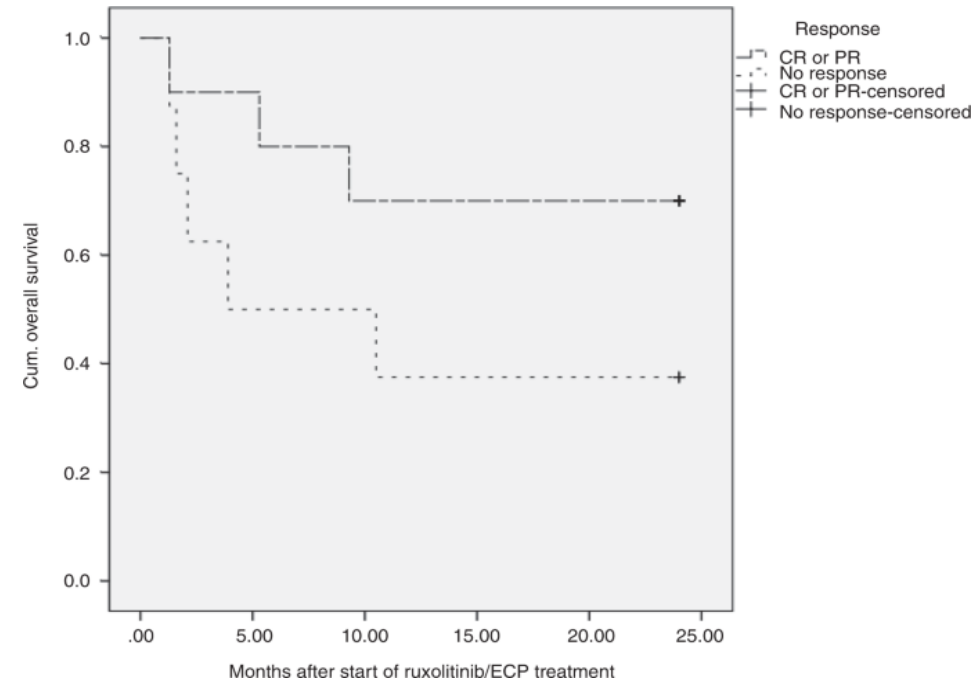
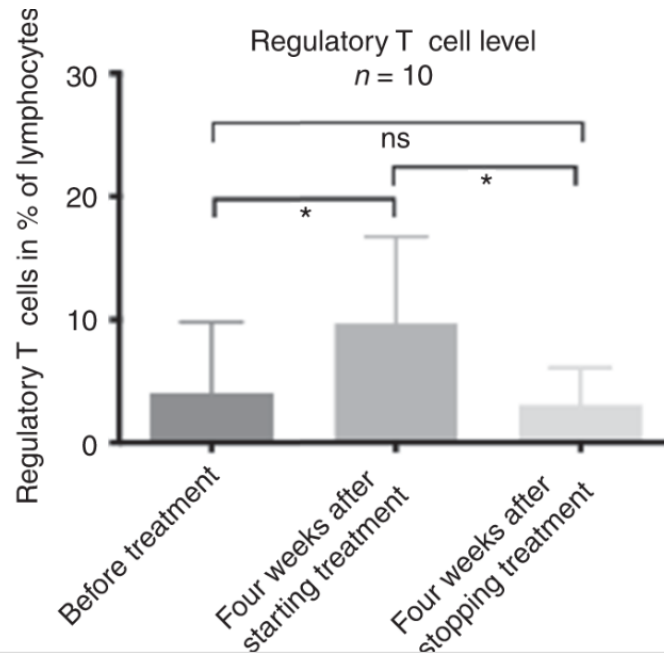
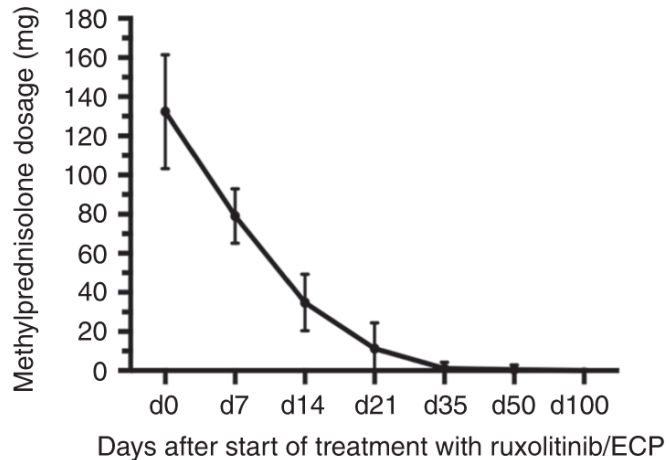


ECP only:	77	53	49	40	35
Ruxo only:	54	45	42	31	20

Ruxolitinib plus extracorporeal photopheresis (ECP) for steroid refractory acute graft-versus-host disease of lower GI-tract after allogeneic stem cell transplantation leads to increased regulatory T cell level

Modemann F, et al . BMT 2020

18 patients lower GI +/- skin CR 44% PR 11%

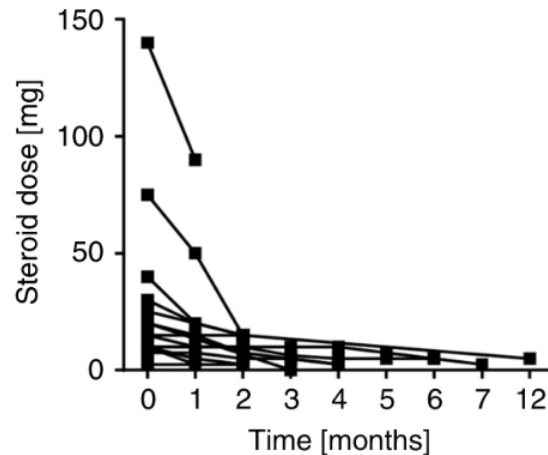
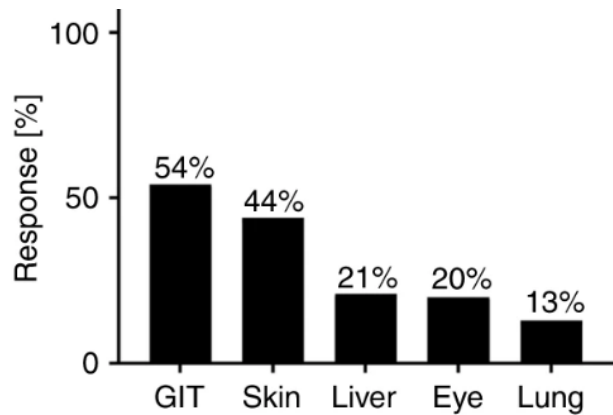


2 years overall survival = 56%

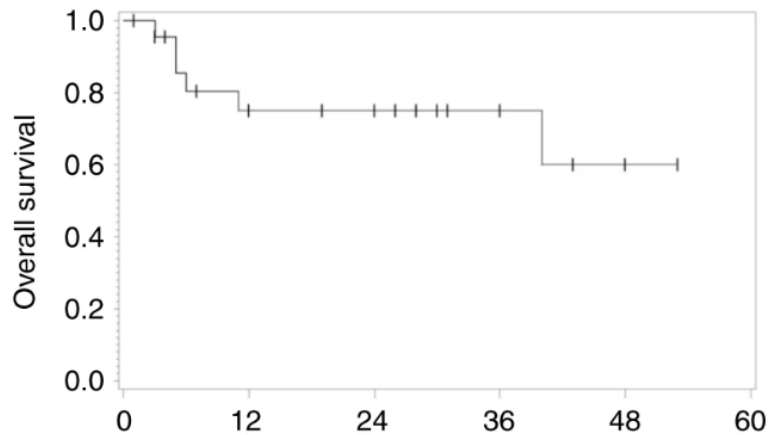
Ruxolitinib–ECP combination treatment for refractory severe chronic graft-versus-host disease

Maas-Bauer K... Zeiser R, BMT 2021

Duration allo SCT – begining Ruxo+ECP = 10 months
 20/23 patients = multiple organ involvement –
 Failure to multiple treatments to cGVHD



The best overall response rate (ORR) at anytime was 74% (17/23)



OS in patients treated with ruxolitinib and ECP at 24 months was 75%

Table 2 Adverse events during treatment.

AEs	
CMV reactivation	<i>Absolute number (%)</i> 6 (26)
Cytopenia	<i>Absolute number (%)</i>
Mild cytopenia (grade 1 and 2)	3 (13)
Severe cytopenia (grade 3 and 4)	8 (35)
Cytopenia <i>before</i> ruxolitinib	6 (26)
Relapse of Malignancy	<i>Absolute number (%)</i> 0 (0)

Contraindications to ECP

Nygaard M et al, Eur J Hematol 2020. Nordic ECP quality Group
Colpo A et al, Transfaph Sci 2024. Italian best practices ECP/GHVD (Sidem)

Definitive

- pregnancy
- unstable circulatory or respiratory condition
- known sensitivity to psoralen compounds
- known photosensitivity
- aphakia (absence of lens in the eye – risk of retinal damage by 8MOP)

Relative :

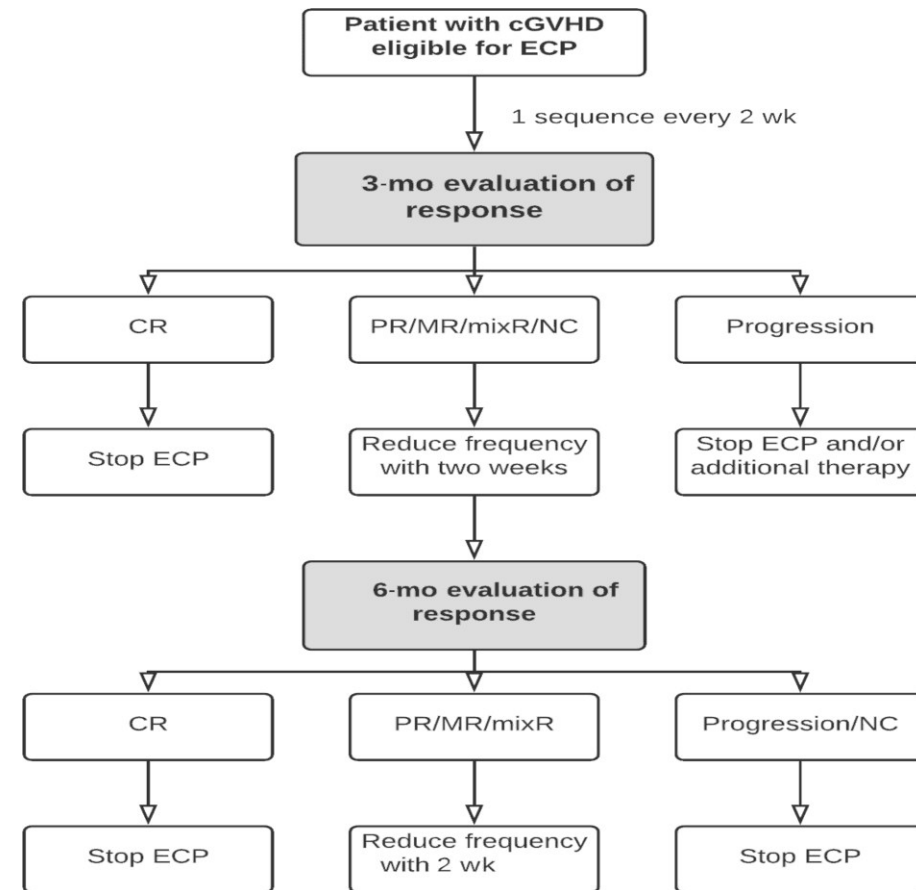
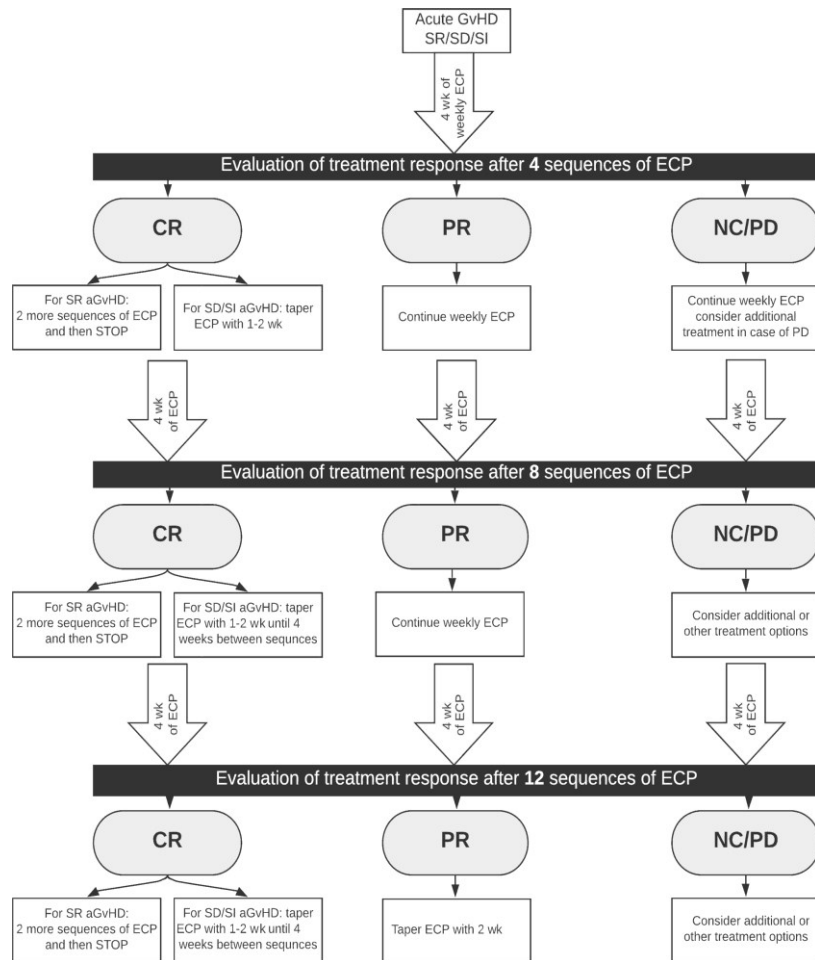
- low white blood cell count ($<1 \times 10^9/L$)

Precautions should be taken in patients with:

- low haematocrit
- low platelet count
- active bleeding or risk of bleeding
- active infection
- low body weight

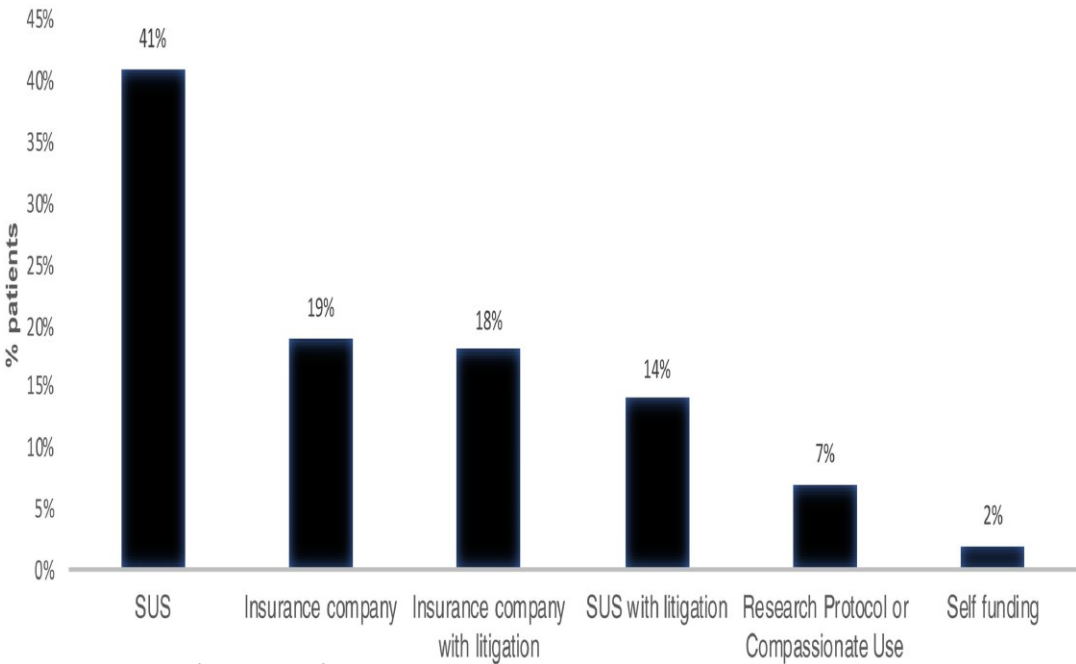
Schedules

Nygaard M *et al*, Eur J Hematol 2020. Nordic ECP quality Group



GVHD treatment with extracorporeal photopheresis in Brazil: a national survey

Giancarlo Fatobene¹, Ana Cordeiro², Livia Mariano³, Marcia Silva⁴, Luis Bouzas⁴, Nelson Hamerschlak⁵, Maria Cristina Macedo⁶, Alessandra Petta⁷, Vaneuza Funke⁸, Yana Novis⁹, Mary E Flowers¹⁰, Vanderson Rocha¹¹;
Chronic Graft-versus-Host Disease Brazil-Seattle Consortium Study Group*¹¹



Extracorporeal photopheresis in chronic graft-versus-host disease: clinical description and economic study

Dora Fraga Vargas^{b a}, Mariana Pinto Pereira^{b a}, Tatiana Schnorr Silva^{a,*}, Caroline Nespolo de David^{b a}, Alessandra Aparecida Paz^b, Claudia Caceres Astigarraga^a

Hematol Transf Cell Ther 2023

Hematol Transf Cell Ther 2022

Conclusion

- **ECP:**
 - Advantages : efficient – low levels of side-effects
 - No optimal schedule is defined, but sessions must be regular
 - Apheresis team – expertise in vascular access (1 or 2 venous access)
- Combination of Jak Inhibitors and ECP is encouraging
- Ruxolitinib is currently used. Potentialisation of ECP with other Jak Inhibitors ?
- The **immune mechanisms** of action of the combination ECP+Jak inhibitors must be studied to optimise this treatment

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2024

23 a 26 de Outubro
Congresso Brasileiro de Hematologia,
Hemoterapia e Terapia Celular

Obrigado(a)

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