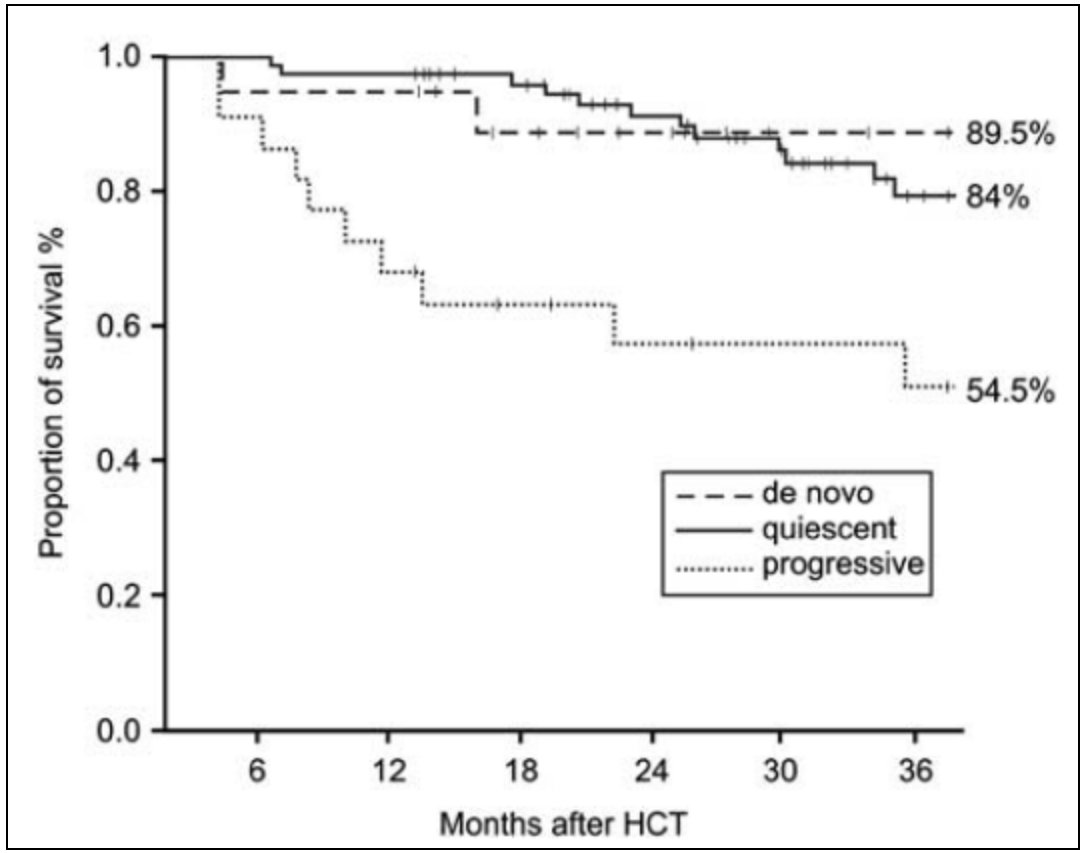
ECP in the Era of New Drugs for cGvHD: Which Role and which Schedule?

Prof. Hildegard T. Greinix
Division of Hematology
Medical University Graz
Austria

Disclosure

Company	Speakers Bureau	Advisory Board
Therakos	√	√
Roche	√	
Novartis	√	√
Gilead	√	√
BMS		√
Sanofi	√	√
Menarini Stemline	√	
Takeda	√	√

Current Situation in cGvHD



Kuzmina…. Greinix et al, Leukemia 26, 746-56, 2012.

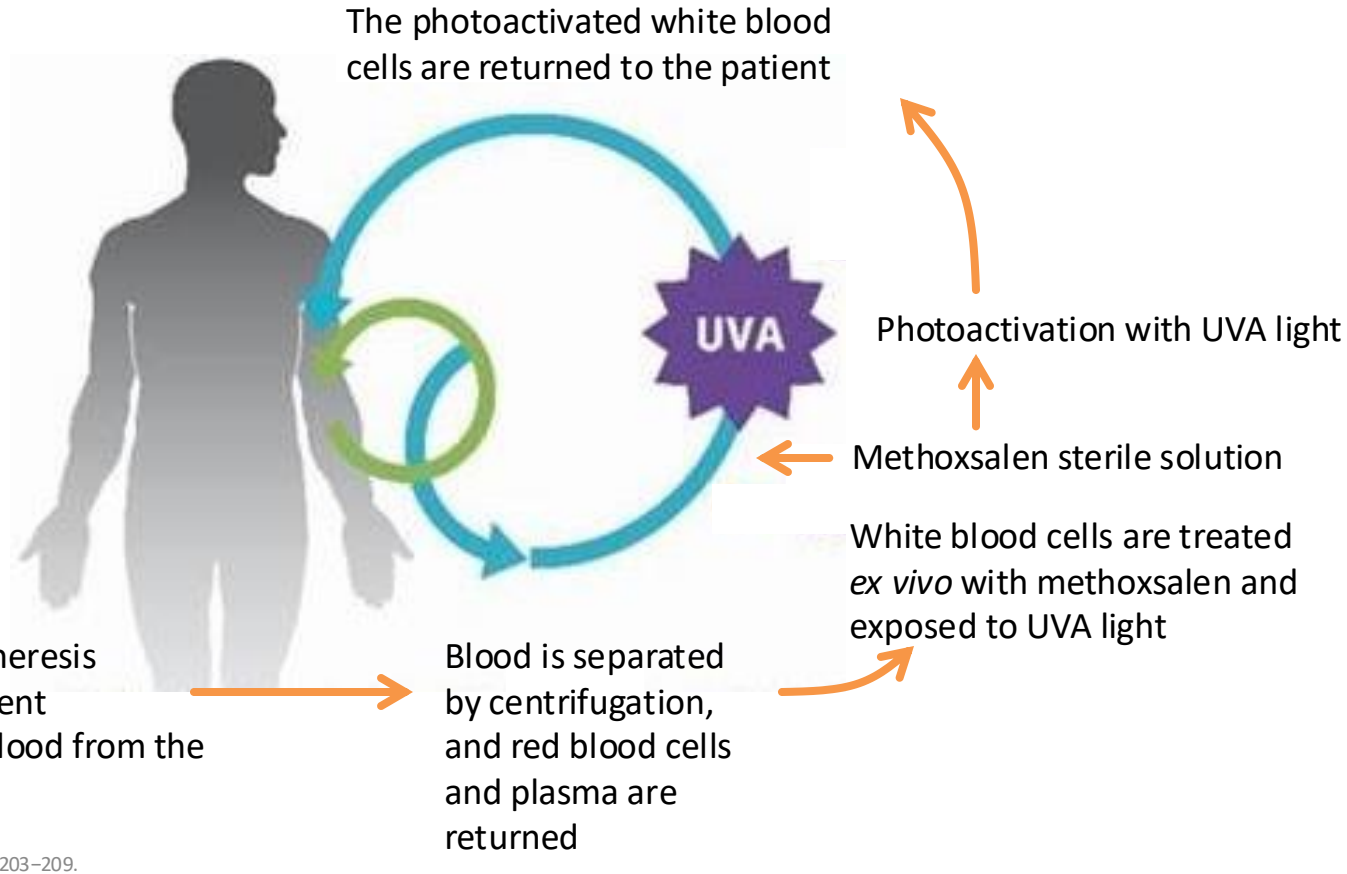
- Improved understanding of pathophysiology of cGvHD.
- Improved staging/severity scoring and response assessment due to NIH consensus.
- Dismal prognosis in high-risk cGvHD has remained.
- cGvHD is main reason for late NRM.
- Steroids are still standard first-line therapy of moderate/severe cGvHD.
- Ruxolitinib, Ibrutinib, Belumosudil and Axatilimab FDA/EMA approved for refractory cGvHD.

EBMT Consensus Recommendations on Salvage Therapy of cGvHD

A second-line treatment for cGvHD is recommended if corticosteroid resistance or dependence occurs.	Recommendation made from standard practice and expert opinion.
In adults with SR-cGvHD, we recommend ruxolitinib (NCCN classification 1).	Large beneficial effect on ORR and FFS in a randomised trial, a propensity-adjusted retrospective analysis and three meta-analyses. Fan S.2022;Hui L.2020;Zhang MY.2022;Zeiser R.2021;Novitzky-Baso I.2023.
In adults with SR-cGvHD, belumosudil is a potential therapeutic option (NCCN classification 2C).	Encouraging ORR in non-randomised trials showing a low drug induced toxicity profile. Cutler C.2021;Jagasia M.2021;Lee SJ.2022;DeFilipp Z.2022.
In adults with SR-cGvHD, ibrutinib is a potential therapeutic option (NCCN classification 2B).	Encouraging ORR in non-randomised trials in patients with moderate GvHD burden and an acceptable toxicity profile. Doki N.2021;Miklos D.2017;Waller EK.2019;Chin KK.2021;Kaloyannidis P.2021.

Penack O et al. Lancet Haematol 2024;11:de147

Outline of ECP Therapy Procedure



1. Goussetis E, *et al. Transfus Apher Sci*. 2012;46:203–209.

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.

How does ECP work?

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

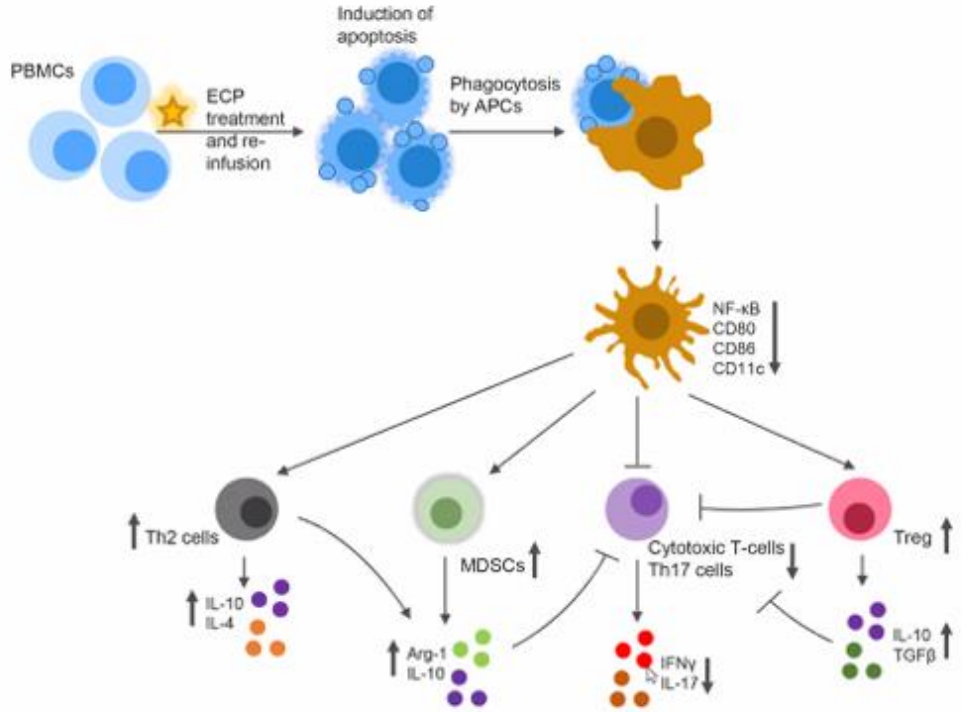
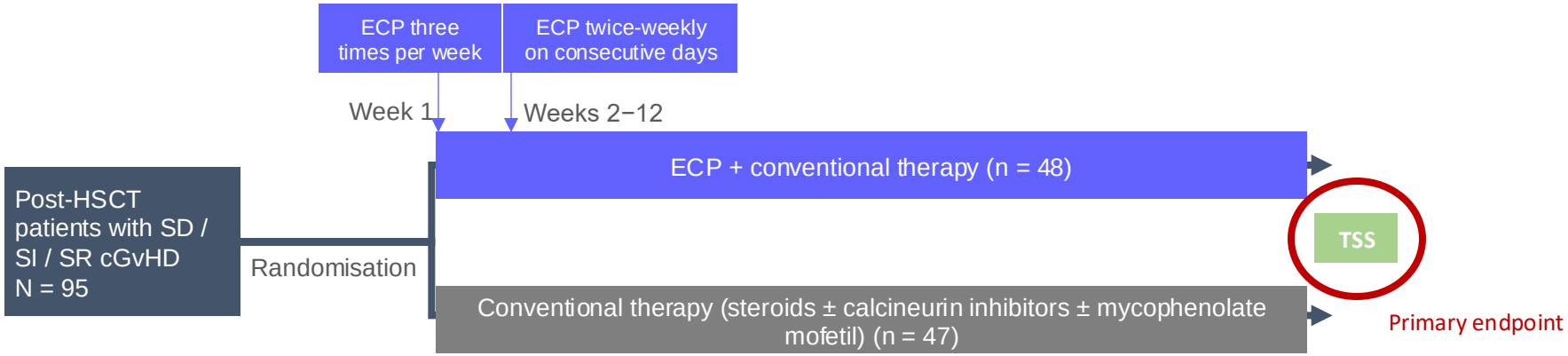


Figure provided by R Zeiser.

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.

Prospective Randomized Study for SR or SD cGvHD Patients: Role of ECP



Primary endpoint:
Median % change in TSS at week 12 compared with baseline

Flowers MED…..Greinix HT. Blood 2008;112:2667-74.

Prospective Randomized Study for SR or SD cGvHD Patients: Primary endpoint Total Skin Score

At week 12
N = 95
Blinded assessment

Corticosteroid response to ECP treatment

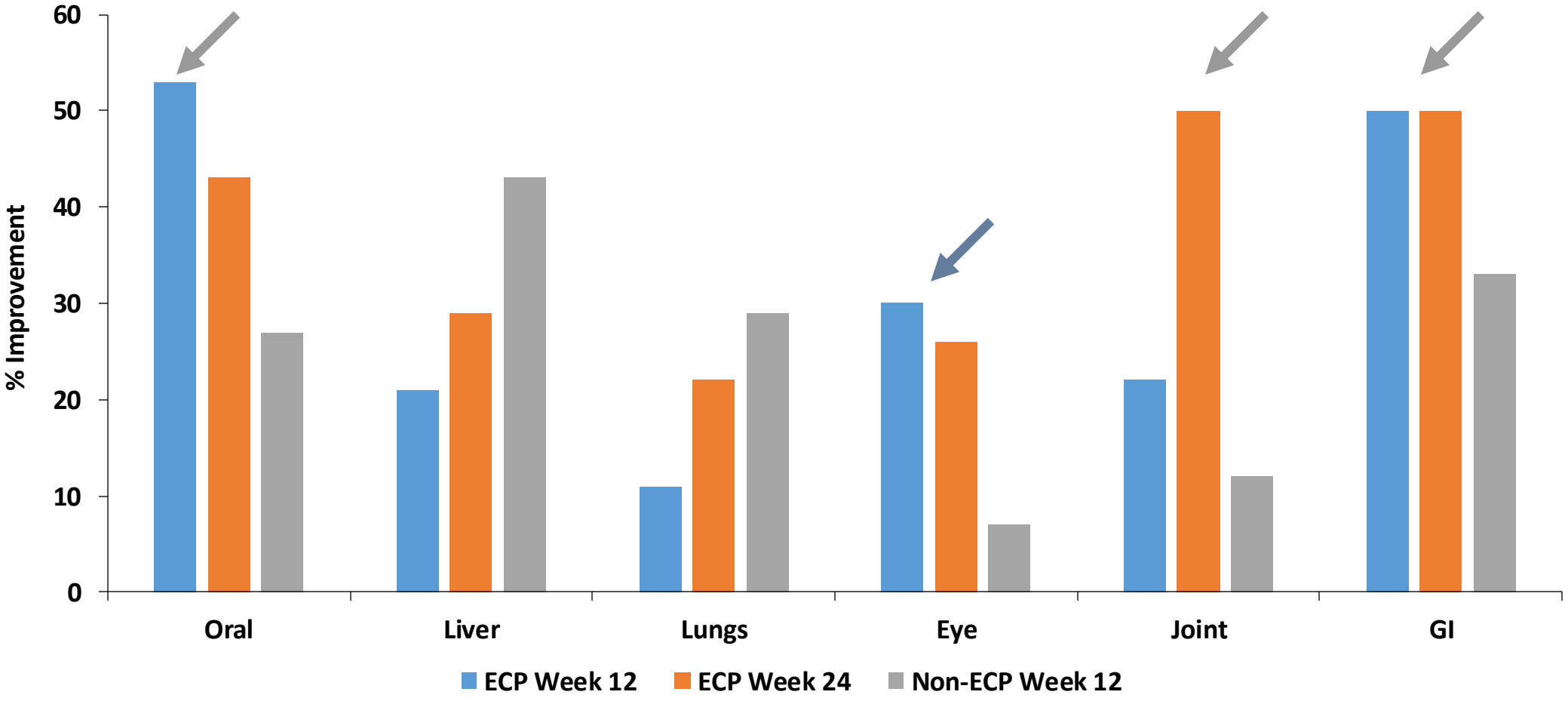
Parameter	Week 12 ECP (n = 48)	Week 12 Control (n = 47)	*p*
Median percent change from baseline in TSS	–14.5	–8.5	0.48
≥ 50% reduction in corticosteroid dose and ≥ 25% improvement in TSS, %	8.3	0	0.04
≥ 50% reduction in corticosteroid dose and final corticosteroid dose of <10 mg/day, %[†]	20.8	6.4	0.04

[*] The large number of patients who discontinued the study in the control arm precluded statistical comparison for week 24.
[†] In both groups, the last known dose of corticosteroids was used when the week 12 dose was missing.

Flowers MED.....Greinix HT. Blood 2008;112:2667-74.

Resolution/Improvement in Extracutaneous cGvHD at Week 12

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



Flowers MED…. Greinix HT, Blood 2008;112:2667-2674

ECP in Chronic GvHD: Steroid-Sparing Effects

Study	Steroid-sparing effects
Greinix HT, *et al*. 1998[1]	Steroid therapy could be discontinued after a median of 80 days
Apisarnthanarax N, *et al*. 2003[2]	64% of patients achieved a steroid-sparing response while on ECP
Foss FM, *et al*. 2005[3]	52% discontinued corticosteroids; 44% had discontinuation of ≥1 immunosuppressive medication
Couriel DR, *et al.* 2006[4]	22% discontinuation of steroids at one year; 10% discontinuation of all immunosuppressive therapy at one year
Greinix HT, *et al*. 2006[5]	Accelerated tapering of steroids, which had a favourable impact on survival
Flowers MED, *et al.* 2008[6]	20.8% and 35.4% of patients had ≥50% reduction in steroid dose and final steroid dose <10 mg/day after 12 and 24 weeks of ECP, respectively
Jagasia MH, *et al.* 2009[7]	ECP led to significant decrease in steroid dose in cGvHD patients (P = 0.009)
Greinix HT, *et al.* 2011[8]	17% and 25% of patients had ≥ 50% reduction in steroid dose and final steroid dose <10 mg / day after 12 and 24 weeks of ECP, respectively
Dignan F, *et al*. 2014[9]	20 out of the 25 (80%) patients that completed six months of ECP had reduction in immunosuppression and 17 of 19 (89%) of evaluable patients had a reduction of steroids during ECP treatment

1. Greinix HT, *et al. Blood* 1998;92:3098–3104; 2. Apisarnthanarax N, *et al. Bone Marrow Transplant.* 2003;31:459–465; 3. Foss FM, *et al. Bone Marrow Transplant*. 2005;35:1187–1193; 4. Couriel DR, *et al. Blood* 2006;107:3074–3080; 5. Greinix HT, *et al. Haematologica*. 2006;91:405–408; 6. Flowers MED, *et al. Blood*. 2008;112:2667–2674; 7. Jagasia MH, *et al. Biol Blood Marrow Transplant*. 2009;15:1288–1295; 8. Greinix HT, *et al. Biol Blood Marrow Transplant*. 2011;17:1775–1782; 9. Dignan F, *et al. Bone Marrow Transplant.* 2014;49:704–708.

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-Vinvent (2010)	6	Retrospective	0.83 (0.36–1.00)
Subtotal (I^2=57.05%, p = 0.00)			**0.68 (0.62–0.74)**

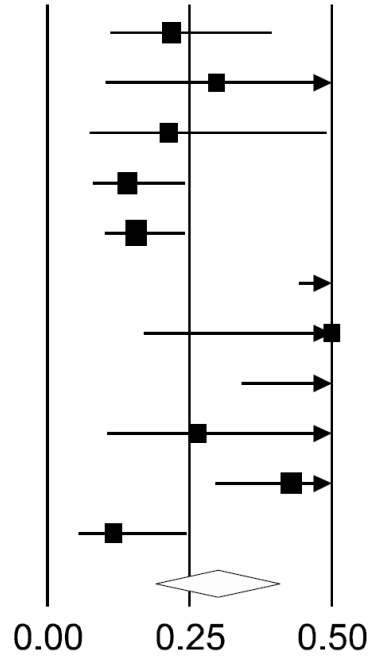
Olivieri J et al. Lancet Haematol 2015;2:e297-305

Meta-Analysis on ECP in cGvHD

Complete Response Rate

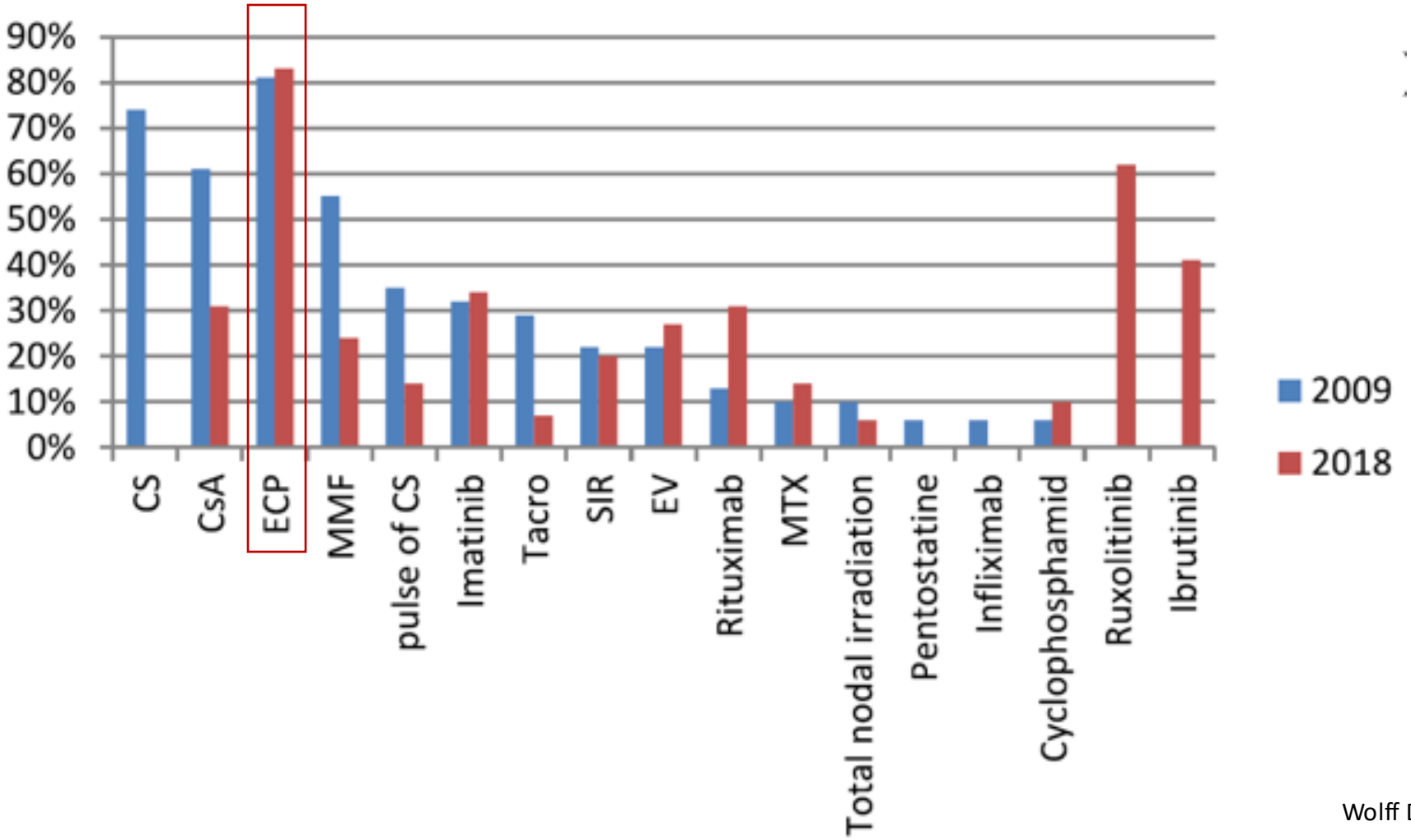
Meta-analysis: complete response rates (%)

	Event rate	Lower limit	Upper limit
Apisarnthanarax *et al*. (2003) [6]	0.22	0.11	0.39
Berger *et al*. (2007) [7]	0.30	0.10	0.62
Bisaccia *et al*. (2006) [8]	0.21	0.07	0.49
Couriel *et al*. (2006) [10]	0.14	0.08	0.24
Del Fante *et al*. (2012) [11]	0.16	0.10	0.24
Foss *et al*. (2005) [26]	0.64	0.44	0.80
Gonzalez Vicent *et al*. (2010) [27]	0.50	0.17	0.83
Greinix *et al*. (1998) [20]	0.52	0.34	0.69
Kanold *et al*. (2007) [25]	0.27	0.10	0.53
Messina *et al*. (2003) [29]	0.43	0.30	0.58
Jagasia *et al*. (2009) [30]	0.12	0.05	0.25
	0.29	0.19	0.42

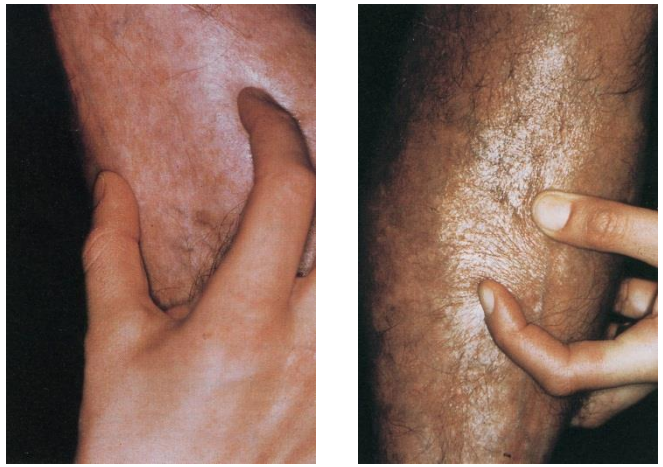


Malik MI et al. Blood Res 2014;49:100-6

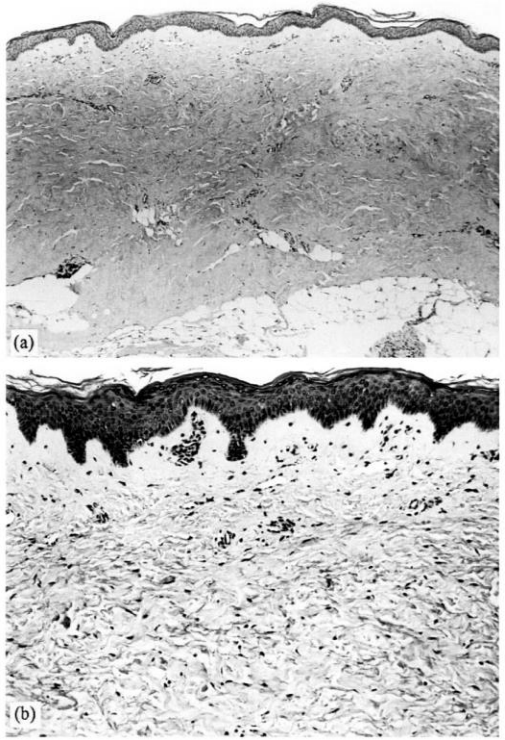
Why is ECP still so Popular as Second-Line Treatment of cGvHD?



Wolff D…. Greinix HT. BBMT 2019;25:1450



Sclerodermatous chronic GvHD before and after ECP

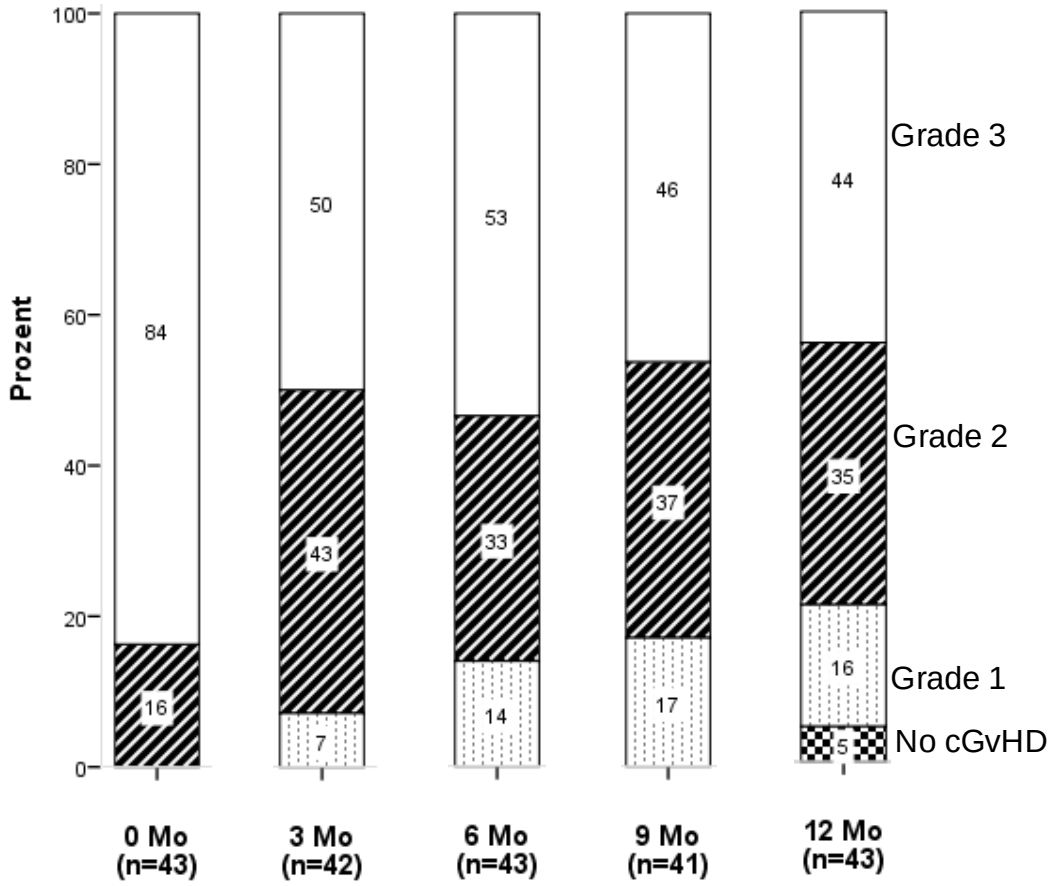


ECP in Steroid-Refractory Sclerodermatous cGvHD

ECP was the first and only treatment demonstrating clinically meaningful responses in sclerodermatous cGvHD.

Author	No pts	Response (% ORR)	Comment
Greinix 98	12	9 CR, 3 PR (100)	Med. duration of ECP 12 (4-31) mo. Same ORR as lichen.
Apisarnth-anarax 03	17	2 CR, 7 PR (53)	Same ORR as in lichenoid
Bisaccia 06	12	1 CR, 4 PR (42)	
Couriel 06	21	14 (67)	Higher ORR than in lichenoid

Long Duration ECP in cGvHD: Overall Response



43 pts (54% ECP as 2nd-line).

ECP start: median of 11.4 mo after onset of cGvHD.

36 pts (84%) with severe cGvHD.

84% skin, 51% liver, 49% oral mucosa, 47% eye, 16% lung involvement.

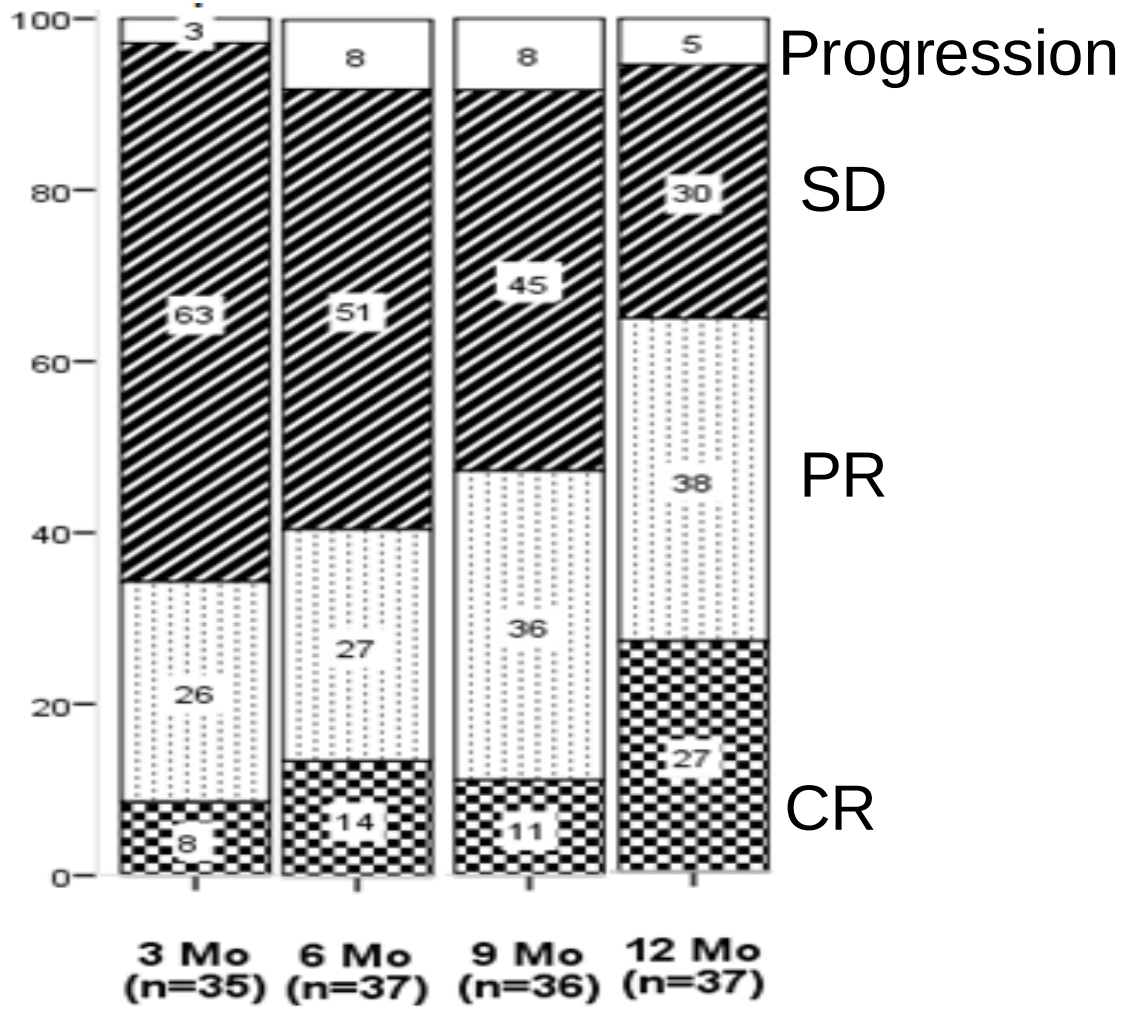
ECP duration: median of 19 (12-93) mo.

29 pts (67%) DC ECP after a median of 17 (12-38) mo.

Significant improvement after 3, 6, 9 and 12 months of ECP.

Worel N & Greinix HT unpublished

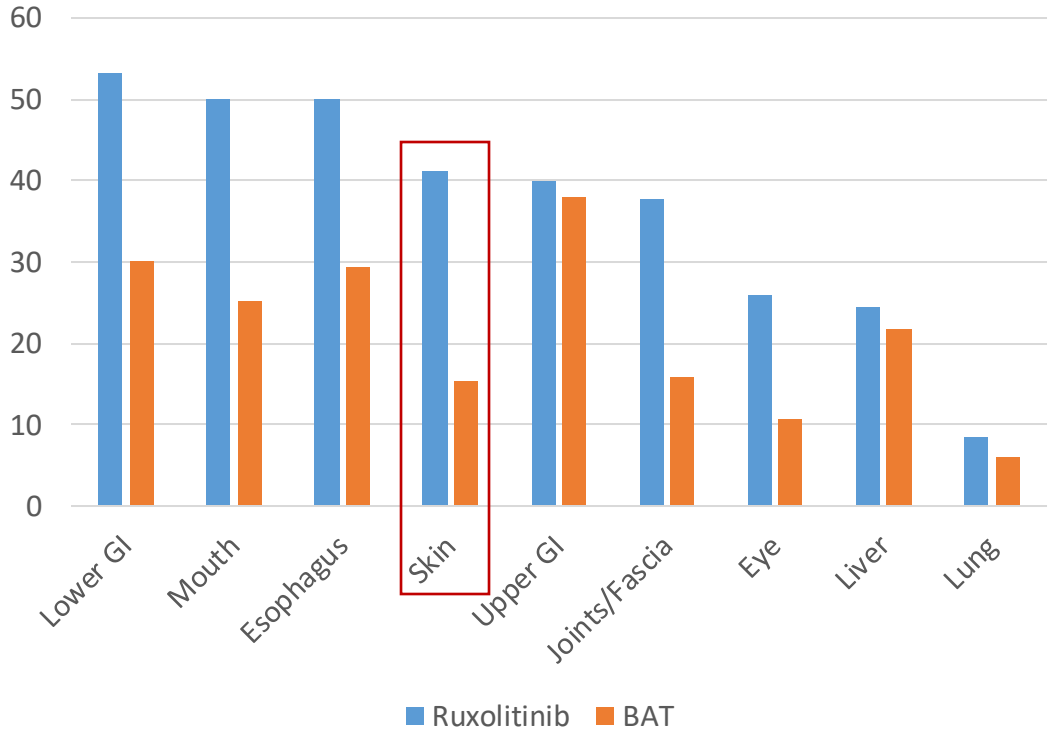
Long Duration ECP in cGvHD: Response of Skin



Worel N & Greinix HT unpublished

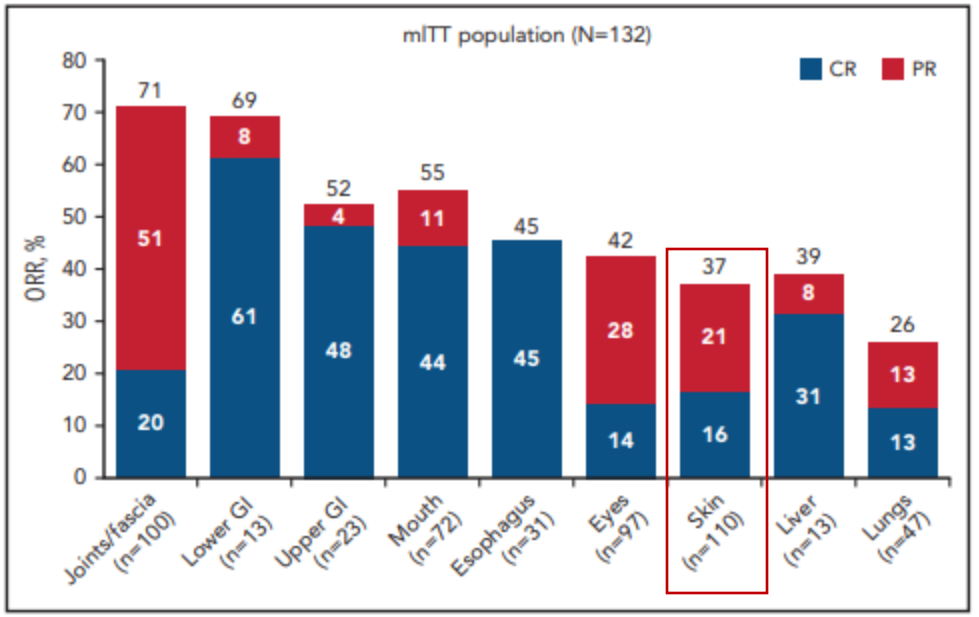
cGvHD Organ Responses: Skin

Ruxolitinib vs BAT at Week 24



Zeiser R et al. NEJM 2021;385:228

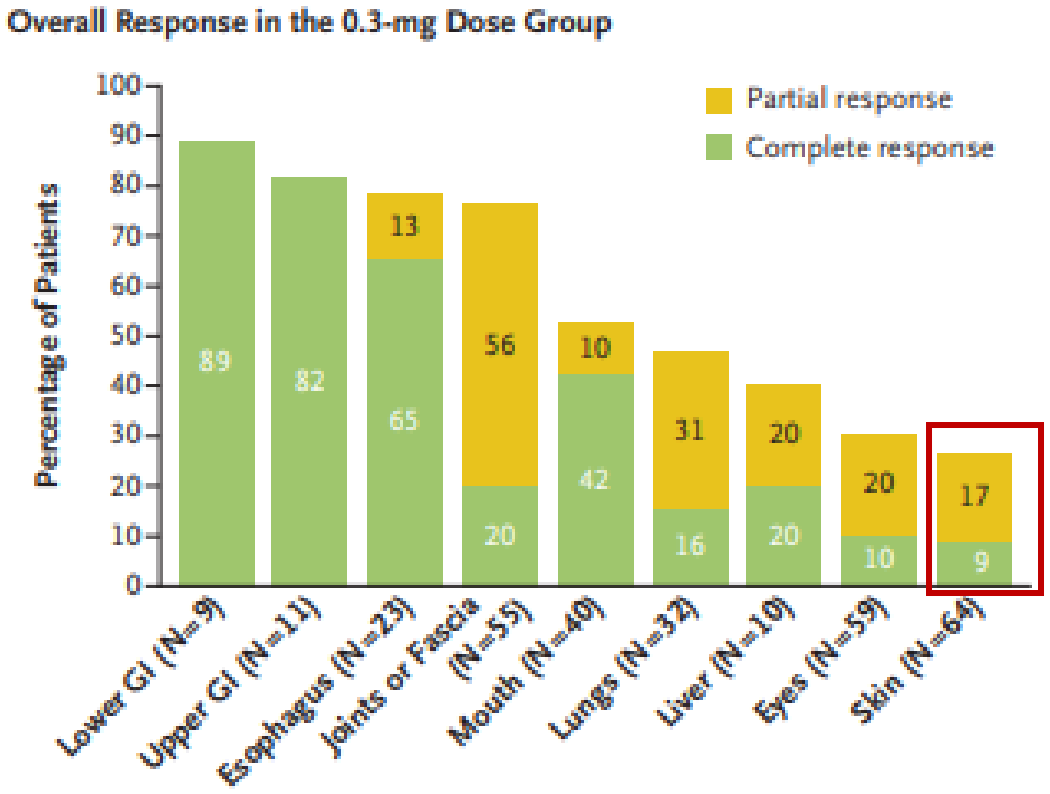
Belumosudil



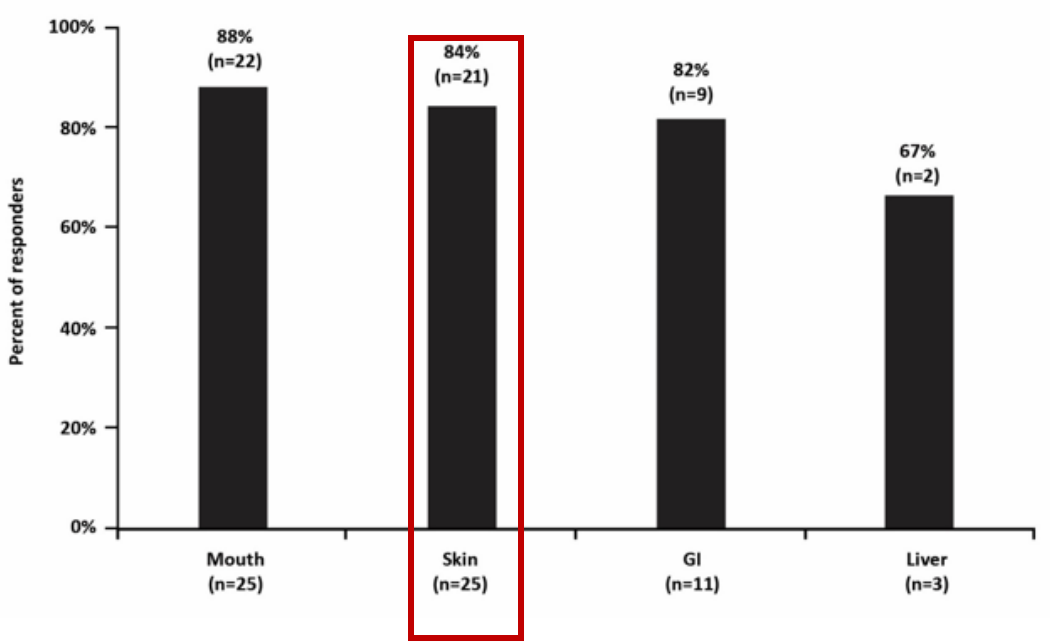
Cutler C et al. Blood 2021;138:2278

cGvHD Organ Responses: Skin

Axatilimab



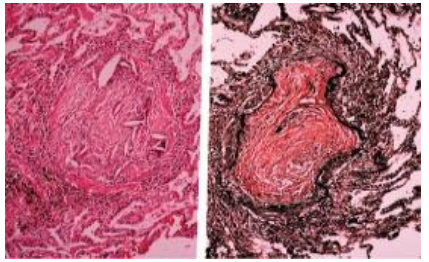
Ibrutinib



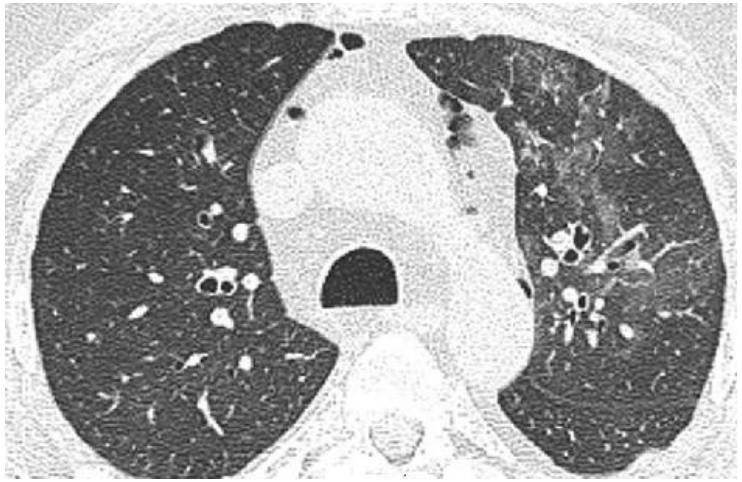
11/18 (61%) patients with sclerosis at baseline showed a decrease in sclerosis (50% decrease or CR)

Wolff D et al. NEJM 2024;391:1002-14

Waller EK et al. BBMT 2019;25:2002-7



ECP in Newly Diagnosed BOS after HCT



Prospective Study on BOS

Patient Characteristics

	All pts (%)	ECP first-line (%)	Other first-line (%)
Pts with BOS	**46**	**10 (22)**	**36 (78)**
Severity of BOS at onset			
Mild: FEV_1 60-79%	25 (54%)	8 (80%)	17 (47%)
Moderate: FEV_1 40-59%	16 (35%)	1 (10%)	15 (42%)
Severe: $FEV_1 \leq 39\%$	5 (11%)	1 (10%)	4 (11%)
HR-CT changes at onset			
Airtrapping	32 (70%)	5 (50%)	27 (75%)
Bronchiectasis	5 (11%)	0	5 (14%)
Small airway disease	22 (48%)	4 (40%)	18 (50%)
Fibrosis	21 (46%)	2 (20%)	19 (53%)
Median time from HCT to BOS in mo (range)	11.2 (3-41.8)	14 (3-41.8)	10.5 (3-26)

Kuzmina Z.... Greinix HT. Blood 2013;121:1886

Prospective Study on BOS

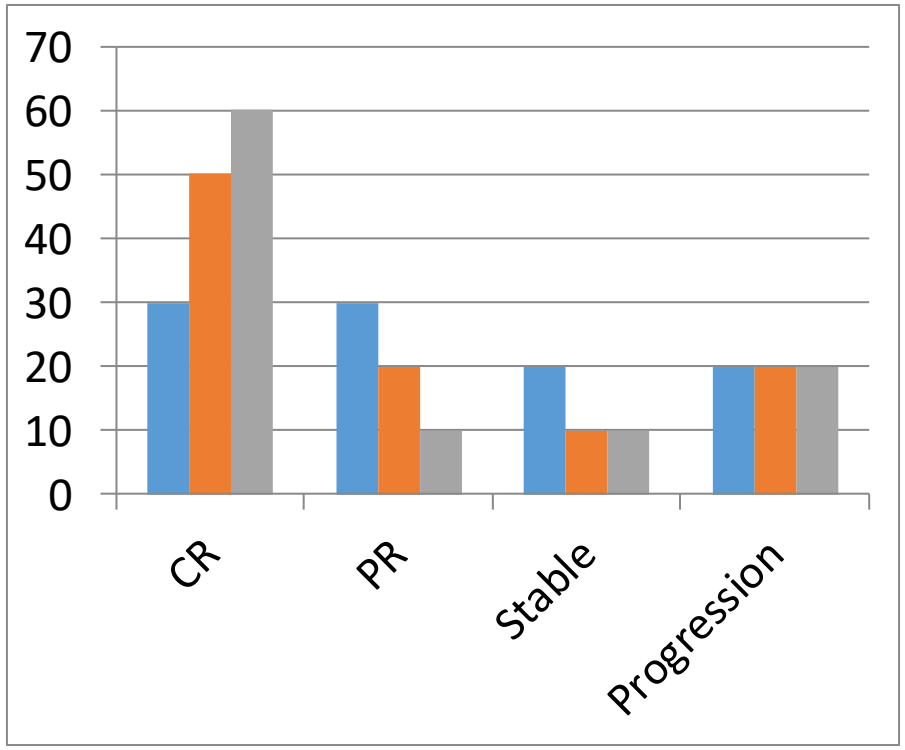
Characteristics of Therapy

Number of patients		N	%
		46	100
First-line	P+/- CNI + ECP	10	22
	P+/- CNI	28	61
	Others	8	17
Salvage (n=38)	P +/- CNI + ECP	6	16
	P + ECP +/- Others	11	29
	Others	21	55
Supportive care	Macrolides Inhalative steroids + bronchodilator	All patients	
ECP schedulle	2 times per week, every other week for 6 months		

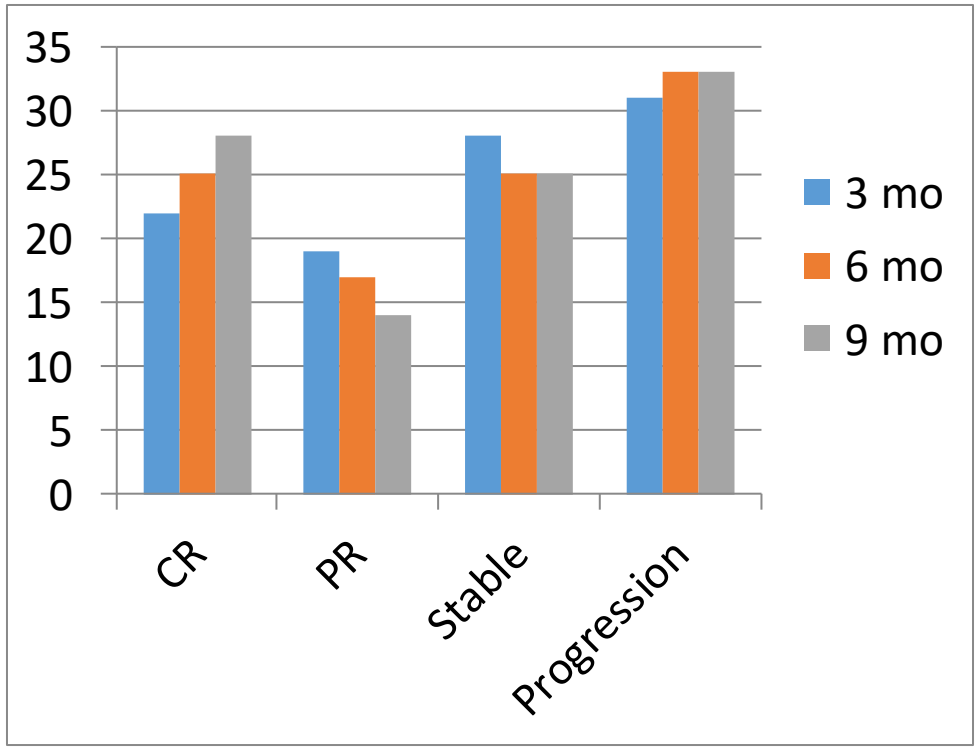
Kuzmina Z.... Greinix HT. Blood 2013;121:1886

Prospective Study on BOS

Response to First-Line ECP (n=10)



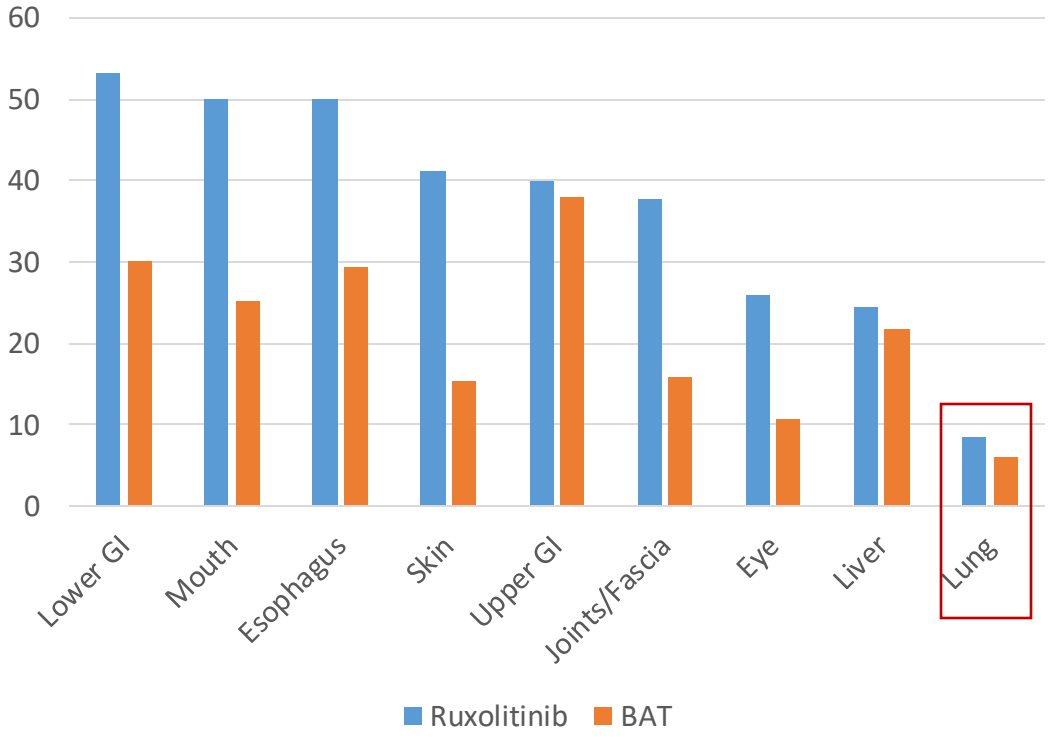
Response to Other First-Line IS (n=36)



Kuzmina Z.... Greinix HT. Blood 2013;121:1886

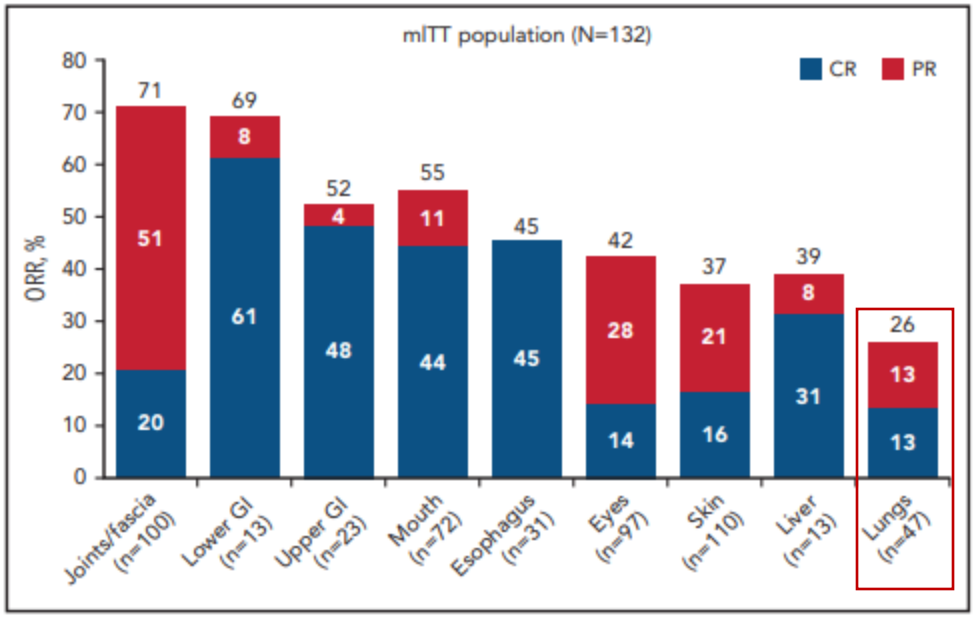
cGvHD Organ Responses: Lung

Ruxolitinib vs BAT at Week 24



Zeiser R et al. NEJM 2021;385:228

Belumosudil

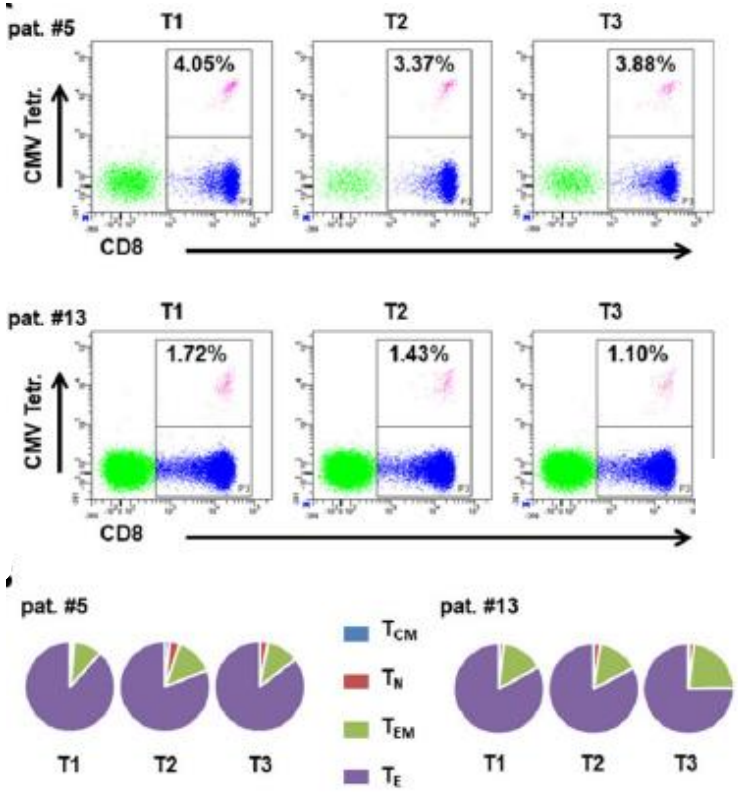


Cutler C et al. Blood 2021;138:2278

Impact of ECP on Antiviral Immune Response

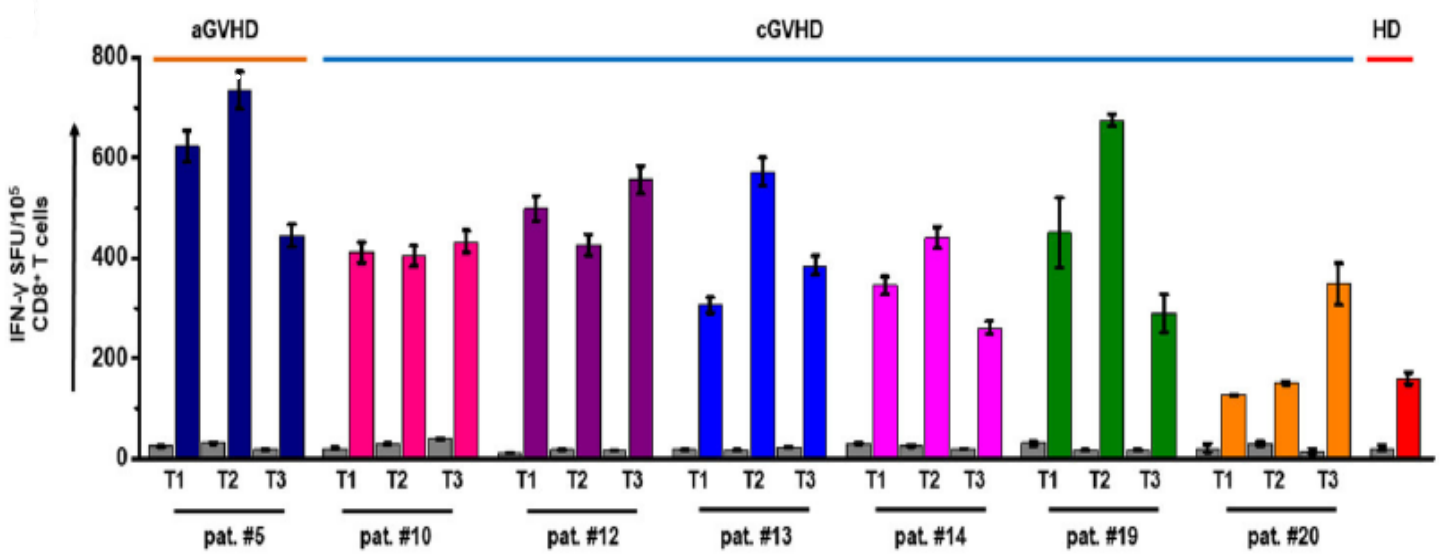
CMV-specific CD8⁺ T cells before and after ECP in acute and chronic GvHD are not different

Cell function measured by IFN-γ release remains stable



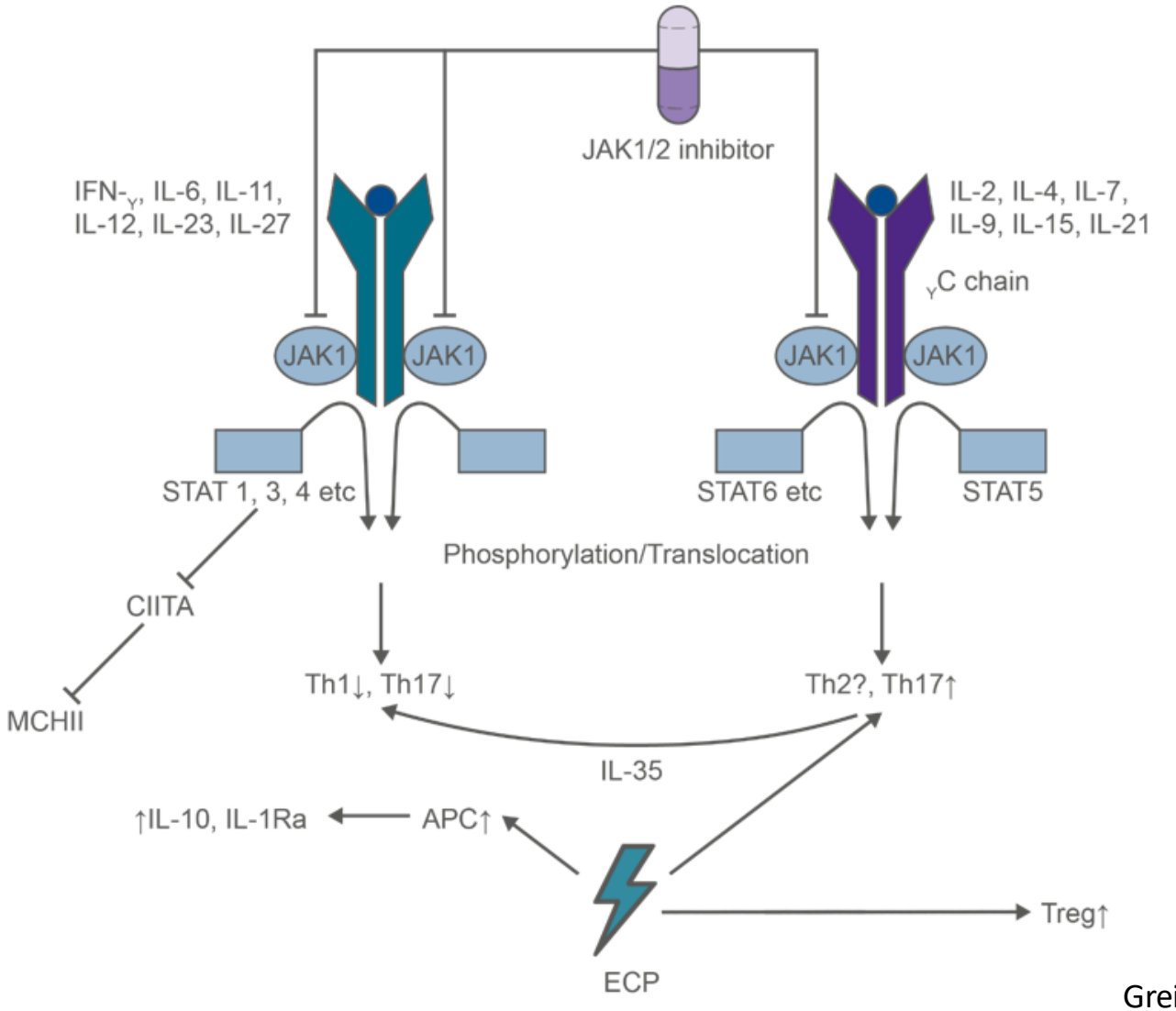
Wang L, et al. *Front Immunol.* 2018;9:2207.

ECP does not cause generalized immunosuppression



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

Complimentary Mechanisms of Action of ECP plus Ruxolitinib



Greinix HT et al. Leukemia 2022;36:2558

Ruxolitinib + ECP for Severe Refractory cGvHD

Retrospective survey in 23 patients

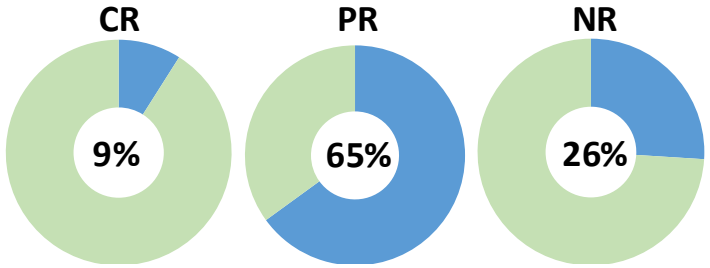
Patient characteristics	Patients, n (%)
>1 organ with GvHD features	20 (87)
Organ affection	
Skin	18 (78)
Liver	14 (61)
GI	13 (57)
Eye	10 (43)
Lung	8 (35)
cGvHD NIH Grade III	13 (57)
Beyond second-line treatment	21 (91)

Treatment

- Two treatments of ECP (on consecutive days) every 2–4 weeks
- Median time of RUX-ECP was 6 months (1–27 month)
- 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%
- Skin, 44%
- Liver, 21%
- Eye, 20%
- Lung, 13%

- 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)

Maas-Bauer K et al. BMT 2020;56:909.

Conclusions

- cGvHD has remained a serious complication of HCT.
- **ECP is an efficient, safe, well-tolerated, steroid-sparing treatment of cGvHD.**
- **ECP does not cause general immunosuppression.**
  - Anti-infectious and anti-leukemic immune responses are not negatively affected.
- Severe cGvHD patients may need ECP therapy for longer duration to achieve maximum benefit, shorter treatment duration with combination therapies?
- Better insight into mechanism of action of ECP could allow its improved use.
- **Prospective studies of ECP in combination with novel drugs are warranted.**
  - More rapid responses, faster reduction of steroids/other immunosuppressants
  - Improved organ responses
  - Longer duration of responses
  - ? Tolerance induction

Collaboration Group

Vienna

BMT Unit
- P. Kalhs
- W. Rabitsch
- Z. Kuzmina
- M. Mitterbauer
- R. Weigl

Dept. Immunology
- W.F. Pickl
- U. Körmöczy
- A. Rottal

Dept. Dermatology
- R. Knobler
- U. Just
- W. Bauer
- G. Stary

Dept. Transfusion Medicine
- N. Worel

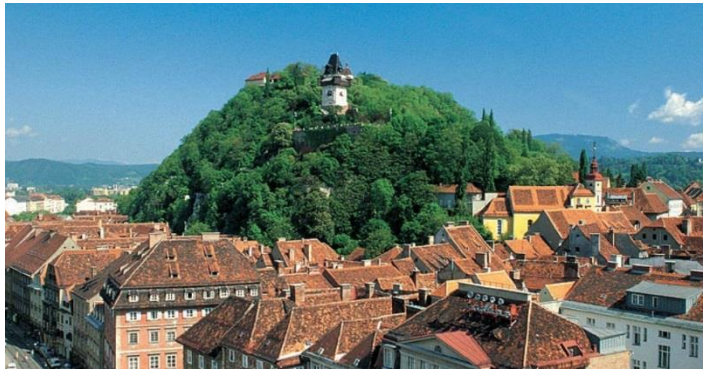
Dept. Pulmonology
- V. Petkov

Graz

BMT Unit
- P. Neumeister
- B. Huber-Kraßnitzer
- K. Prochazka
- L. Gaksch
- H. Sill

Dept. Dermatology
- P. Wolf
- I. Wolf

Dept. Transfusion Medicine
- P. Schlenke



NIH NATIONAL CANCER INSTITUTE

GvHD
Graft-versus-Host Disease
German-Austrian-Swiss Consortium

EBMT
European Society for Blood and Marrow Transplantation