GIIMA
GRUPPO ITALIANO INTERDISCIPLINARE MANIPOLAZIONE E AFERESI PER TERAPIE CELLULARI

IX CONGRESSO NAZIONALE GIIMA

30 NOVEMBRE 2022
Aula San Raffaele
Ospedale San Raffaele - Milano

Maria Teresa Lupo-Stanghellini, MD
Ematologia e Trapianto di Midollo Osseo
Ospedale San Raffaele - IRCCS

UPDATE ECP

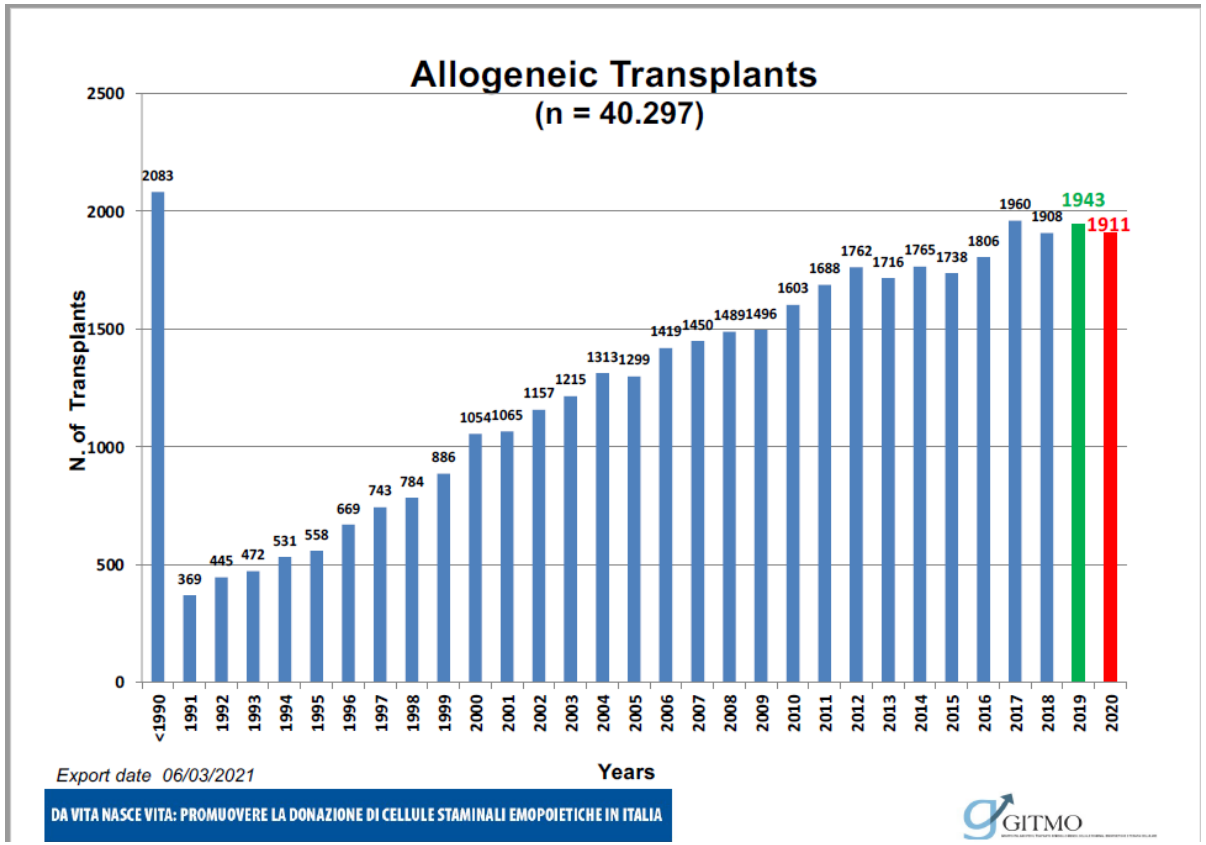
Disclosures of Maria Teresa Lupo-Stanghellini

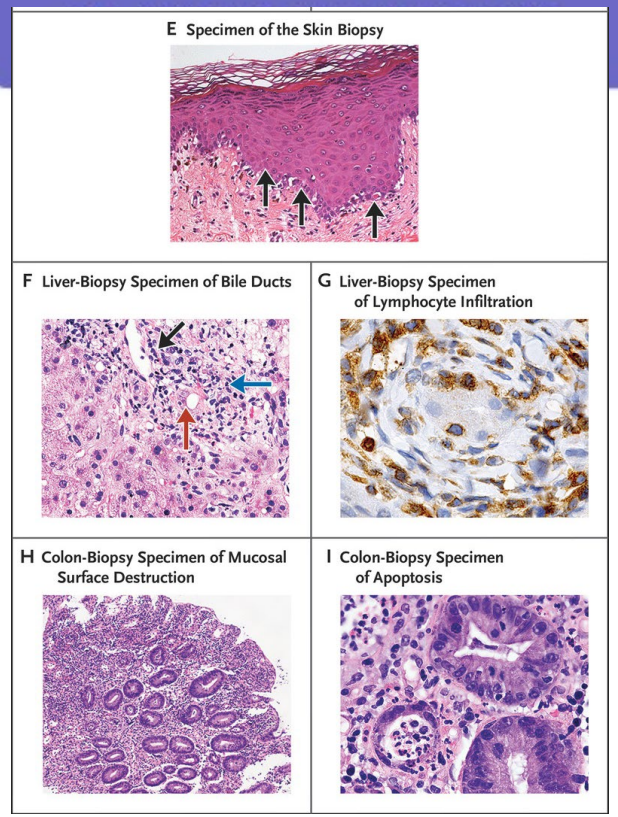
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis						x	
Mallinckrodt						x	
Incyte							x
Neovii							x

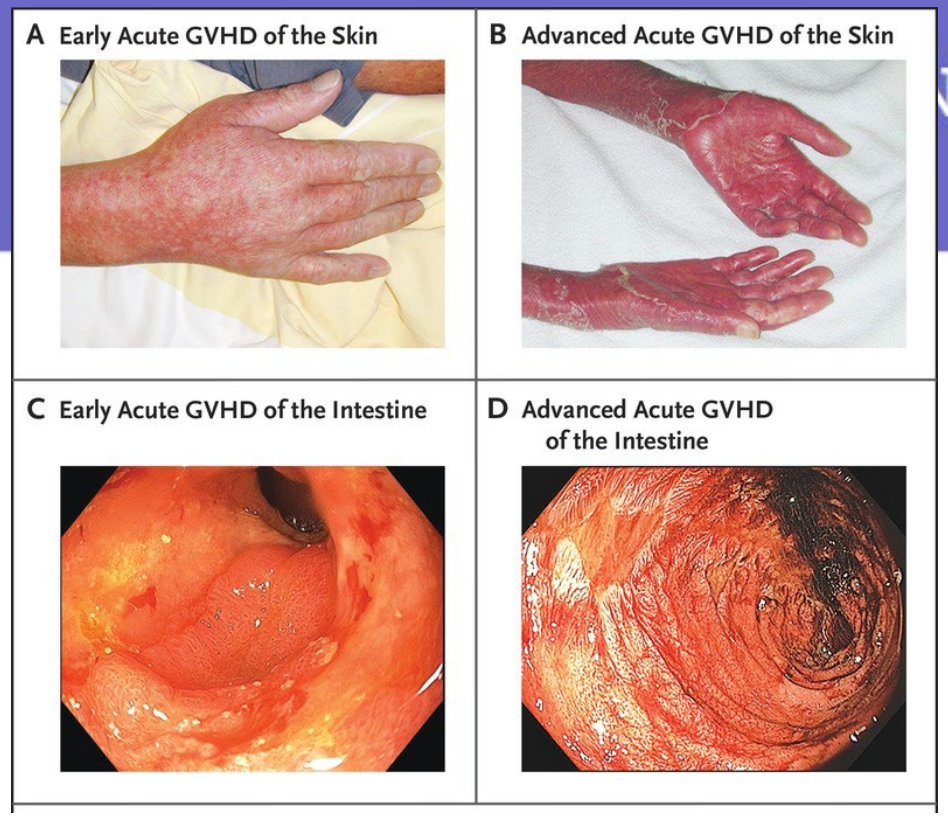
Agenda

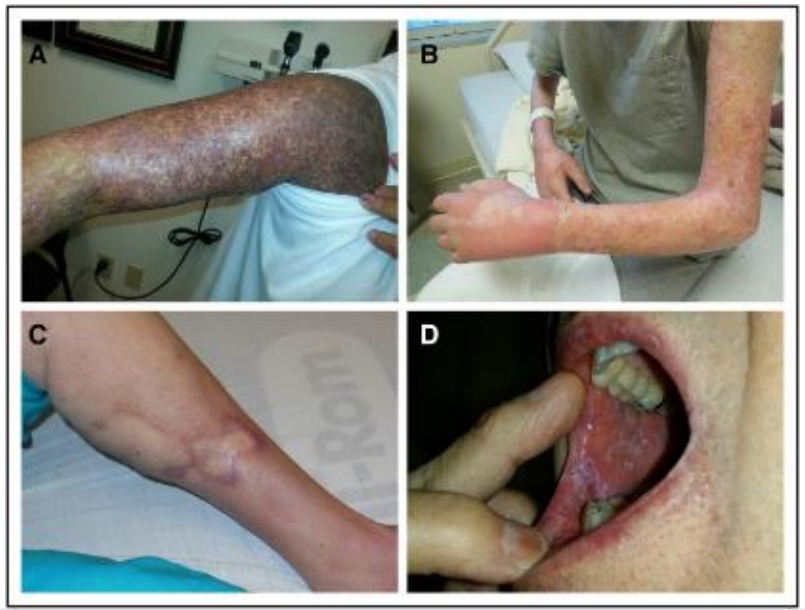
- ✓GvHD – dove siamo
- ✓ECP – al tempo dei nuovi farmaci
- ✓ECP – in profilassi e in I linea – i trial
- ✓ECP – in combinazione – cosa sappiamo
- ✓Revisione delle Linee Guida – dove andiamo

GITMO – Allo HSCT activity







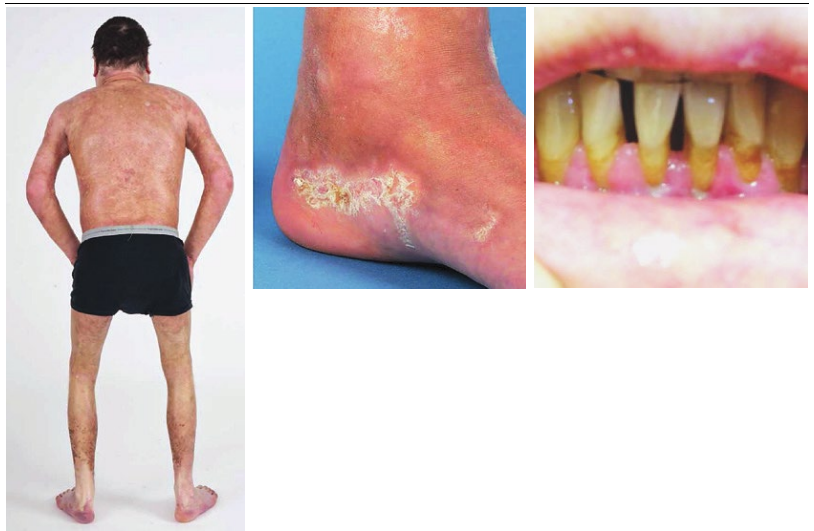


aGvHD

incidence 50%
G3-4 14%
mortality G3-4 36%
60% fail 1° line
5-30% LT-survival

ChGvHD

1^ NRM among survivors >2y
↓ QoL e LT-outcome
↑Immune-disregulation



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How we treat aGvHD

EBMT recommendation 2020

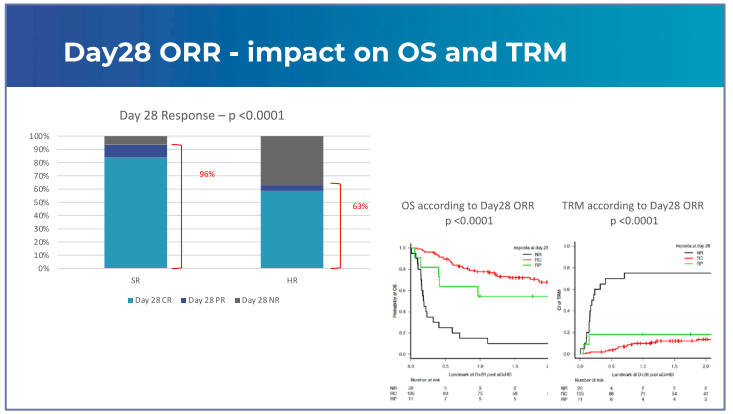
Clinical trial

Overall MAGIC	Topical Treatment	Systemic Treatment	When?
Grade I	**Yes**	**Not recommended**	The decision to initiate treatment for acute GVHD is based on clinical signs. Biopsies are recommended.
Grade II	**Yes**	**Yes***	
Grade III	**Yes**	**Yes***	
Grade IV	**Yes**	**Yes***	

*Systemic treatment - Methylprednisolone 2 mg/kg per day or equivalent prednisone
*Clinical trial

2^ Line and Beyond

no drugs in label in Europe (FDA 2019 Ruxolitinib)
ECP – Ruxolitinib – Infliximab – MMF etc
Clinical Trial



Ardizoia F, Lorentino F, […] Lupo-Stanghellini MT, Haematologica 2022

How we treat ChGvHD

EBMT recommendation 2020

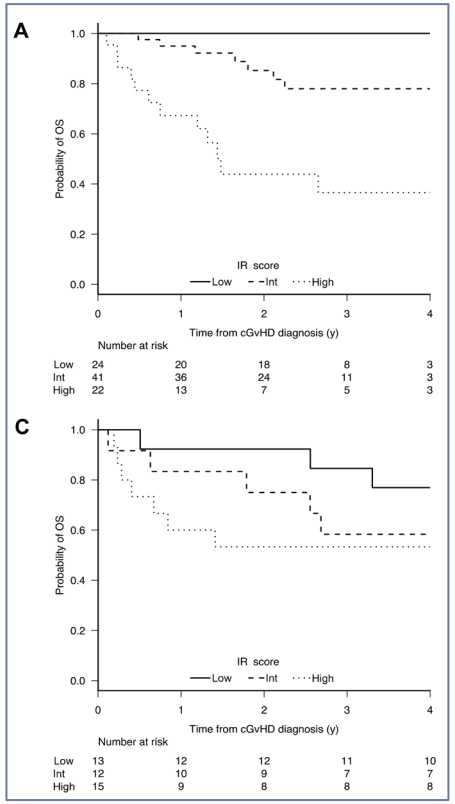
Clinical trials

Overall NIH	Topical Treatment	Systemic Treatment	When?
Mild	**Yes**	**Not recommended**	According to symptom type, severity (moderate / severe), dynamics of progression. Other relevant variables: disease risk, chimerism, minimal residual disease.
Moderate	**Yes**	**Yes***	
Severe	**Yes**	**Yes***	

*Systemic treatment - Prednisone 1 mg/kg per day
*Clinical trial

2^ Line and Beyond

no drugs in label in Europe
(FDA approved Ruxolitinib – Ibrutinib - Belumosudil)
ECP – Ruxolitinib – Infliximab – MMF – TKi – Ibrutinib - etc
Clinical Trial



Serpenti F – Lorentino F […] Lupo-Stanghellini MT, Frontiers in Oncology, 2021

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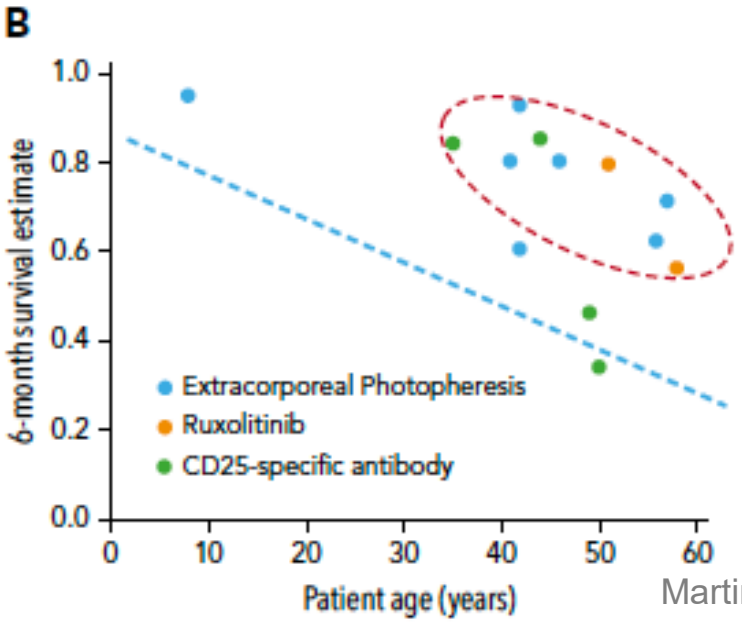
Ruxolitinib is approved by FDA and EMA for both a/c GvHD

Meta-analysis **Ruxo and ECP** are **superior to other 2^ line in SR-aGvHD**.

Preference for ECP in case of infection or severe cytopenia.

☹ Durable overall response in aGvHD 40%

☹ Unsatisfactory ORR in eyes – liver – lung ch GvHD



Martin P, Blood 2020

Changing Paradigm

GITMO / SIDEM BestPractice ECP 2022

GITMO GvHD guideline → ongoing

PTCy

ECP

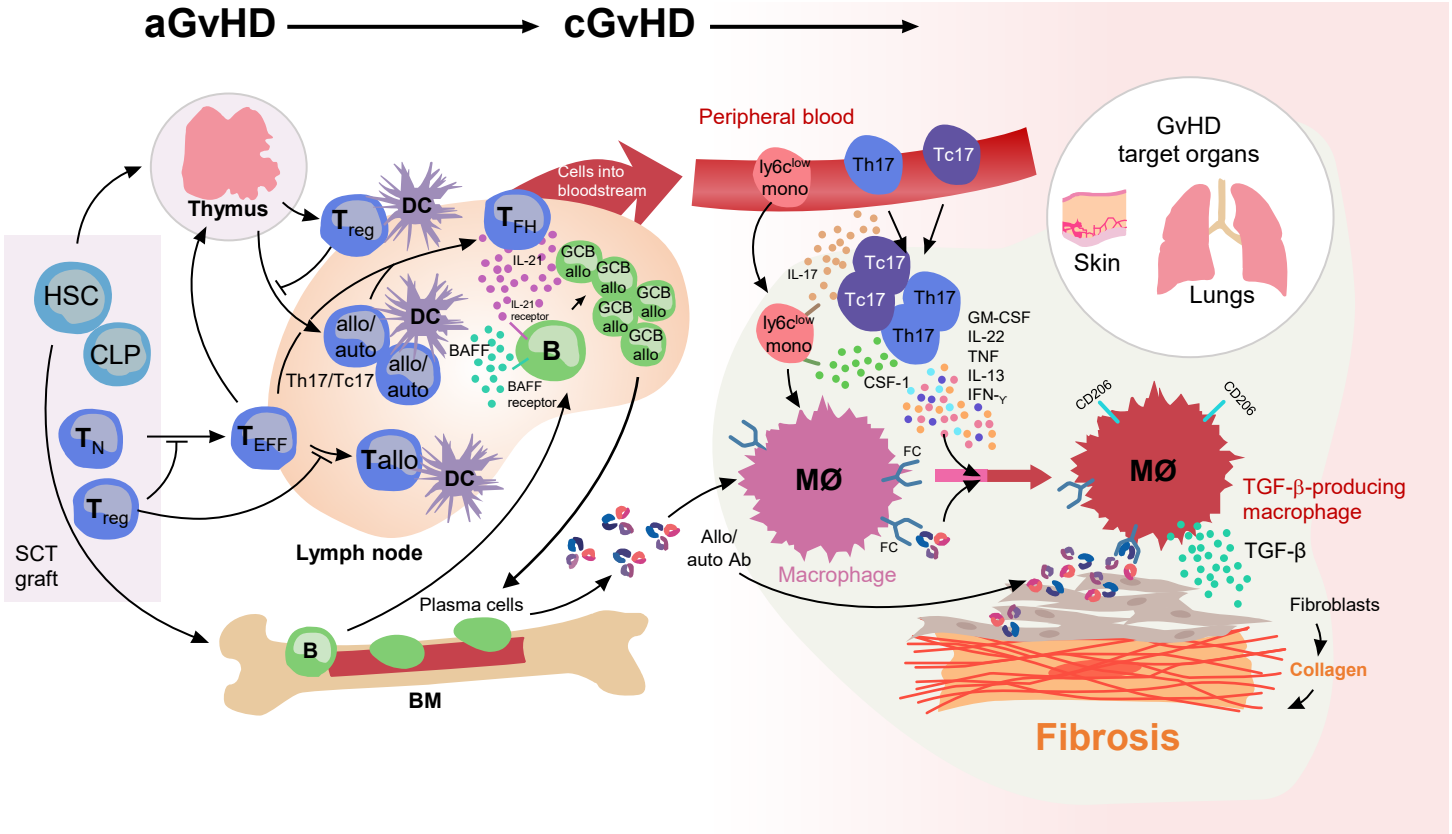
Ruxo

Anti-TNF

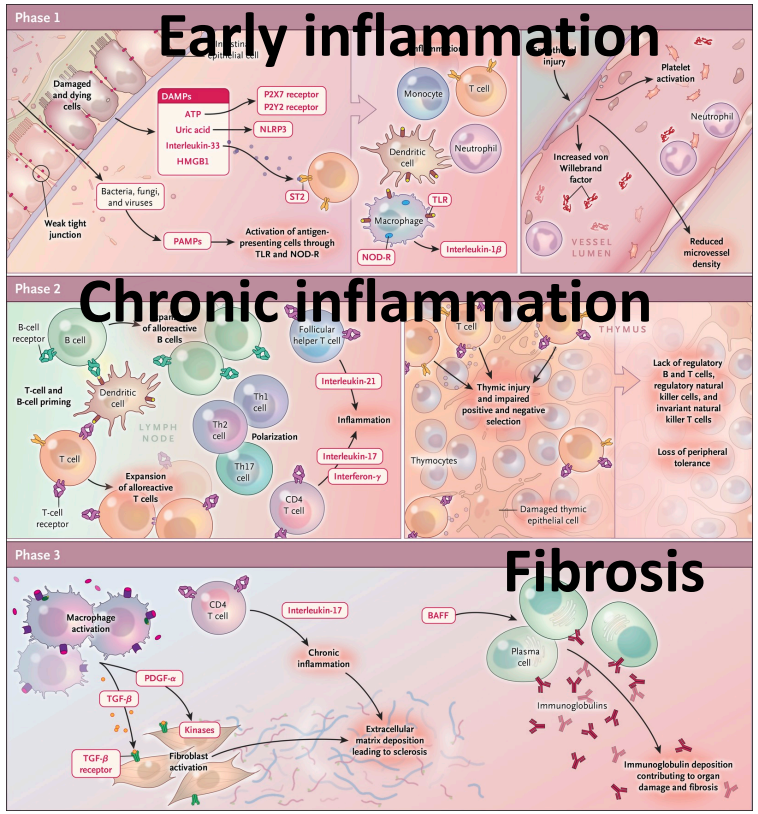
MMF

EBMT 2020 Recommendation → up-date

Cellular and molecular mediators contributing to the continuum of aGvHD and cGvHD pathology



Markey KA, et al. Blood. 2014;124:354-62.



Zeiser R, Blazar BR. N Engl J Med ;377:2565-2579

Second Line & Beyond - ECP

ECP recommended grade 1B evidence in 2° line chGvHD for pts (skin – mouth – eyes – liver)
Excellent safety profile
Minimal side effects
No long term complications
No increased risk of organ toxicities or opportunistic infections
No impact on relapse
Steroid sparing effect

Caveat logistic / central line access

aGvHD ECP independent predictor of response
lower NRM

New onset of chGvD had a higer response to ECP

ECP – mTOR inhib – MMF most frequently used 2° line tp

Greinix HT, Ayuk F and Zeiser R, Leukemia 2022

2nd line & beyond

- 875 pts in 15 studi prospettici
  - 10 single center
    5 multicenter
  - ORR aGvHD 55-84%
  - ORR chGvHD 29-88%
- 533 pts in 10 studi retrospettivi
  - 4 single center
    6 multicenter
  - ORR aGvHD 37-91%
  - ORR chGvHD 46-77%

chGvHD

- ✓ Retrospective studies
- ✓ Few studies used NIH criteria (standardization)
- ✓ ECP grade 1B evidence for 2nd line
  → primarily if skin mouth eyes or liver
- ✓ Agreement on safety profile
  minimal side effects a
  no long-term complication

Biology

A Prospective Trial of Extracorporeal Photopheresis for Chronic Graft-versus-Host Disease Reveals Significant Disease Response and No Association with Frequency of Regulatory T Cells

Jocelyn S. Gandelman[1,2], D. Joanne Song[2], Heidi Chen[3], Brian G. Engelhardt[2], Yi-Bin Chen[4], William B. Clark[5], Cynthia R. Giver[6], Edmund K. Waller[7], Dae Kwang Jung[2], Madan Jagasia[2,*]

[1] Vanderbilt University School of Medicine, Nashville, Tennessee

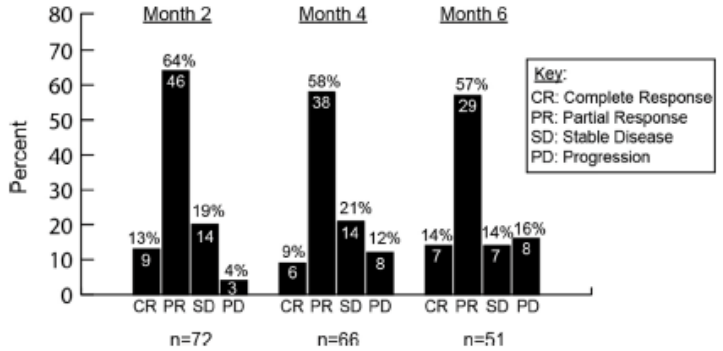
Prospective multicenter trial to study ECP in 3 domain – 2nd line and beyond:

- ✓ Patient response -> NIH 2005 consensus criteria
- ✓ Barriers to treatment
- ✓ Cellular mechanism
  → hypothesis
  → response to ECP & increase %Treg
  → skin response & skin-homing Treg cells

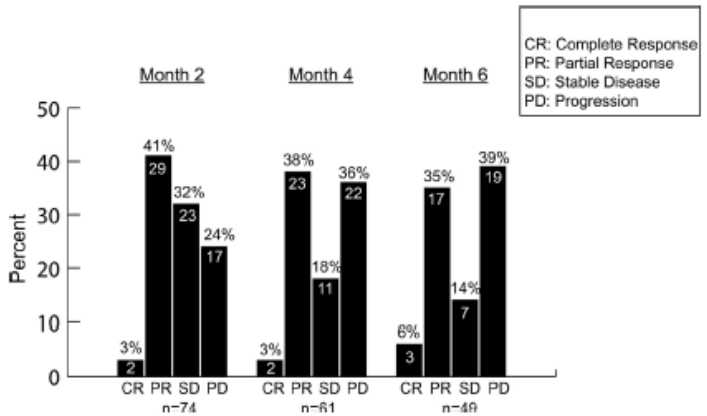
JS Gandelman et al, BBMT 2018

Baseline Characteristics at Transplant (N = 77)

	No. of Patients	Median [IQR] or n (%)
Demographics		
Median age at transplant	75	49 [35.5-58.5]
White	77	68 (88)
Female	77	29 (38)
Disease characteristics		
Disease histology	77	
Acute leukemia		21 (27)
Myeloid disorder		15 (19)
Lymphoid disorder*		26 (34)
Other		15 (20)
Disease status	74‡†	
Advanced		11 (15)
Intermediate		43 (58)
Early		20 (27)
Transplant characteristics		
Transplant source	75†	
Bone Marrow		5 (7)
Cord Blood		2 (3)
Peripheral Blood		68 (91)
Myeloablative transplant	73†	37 (51)
Donor match	76	
HLA-matched/identical relative		41 (53)
Unrelated donor		35 (46)
cGVHD characteristics at study entry		
Platelet count	77	187 [121-243]
Type of GVHD	77	
Classic chronic		63 (82)
Overlap chronic		14 (18)
Acute GVHD week before cGVHD	74†	20 (27)
Involvement by NIH criteria (score ≥ 0)		
Skin	76	65 (86)
Mouth	77	40 (52)
Gastrointestinal tract	77	23 (29)
Eye	77	48 (62)
Joint and Fascia	77	40 (51)
Genital tract	70	8 (11)
Lung	77	22 (28)
NIH severity	77	
Mild		0 (0)
Moderate		37 (48)
Severe		40 (52)

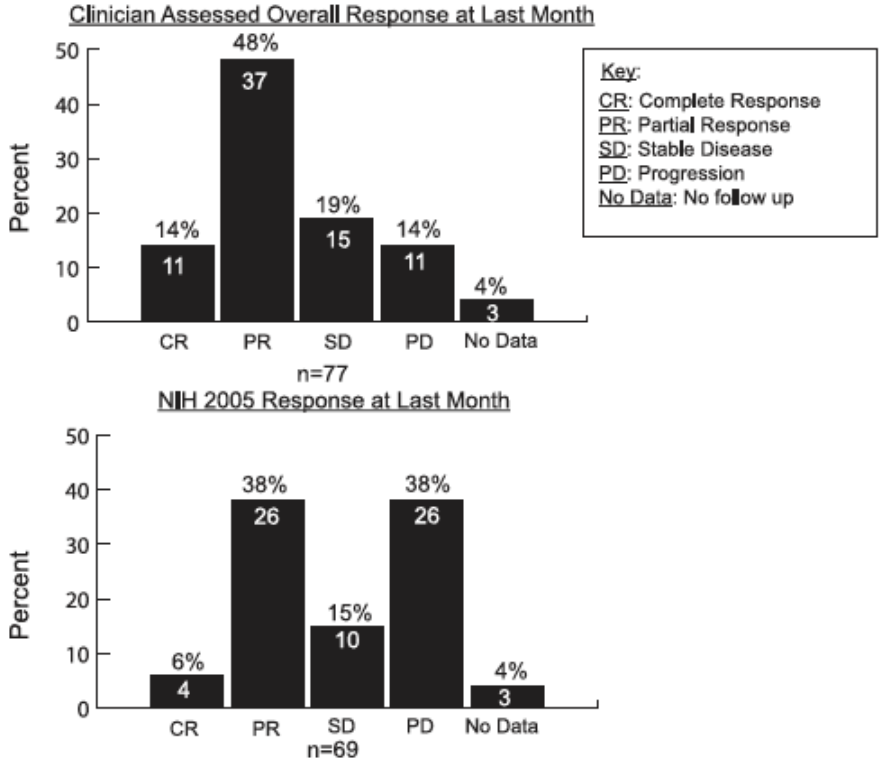


Patient response over time by provider-assessed response

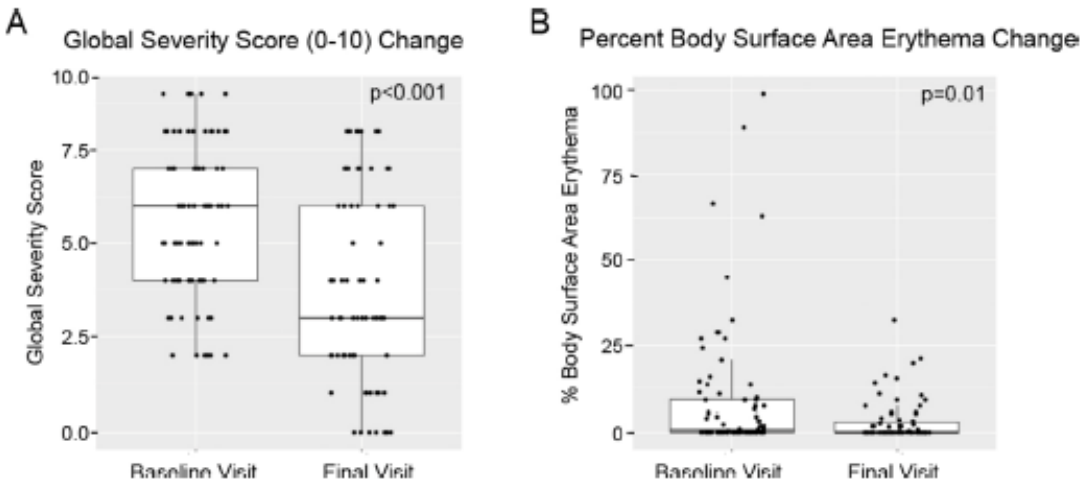


Patient response over time by NIH 2005

K statistic analysis 0.9



JS Gandelman et al, BBMT 2018



Immunologic response

Logistic regression model:
% of Treg at baseline - study completion and over change did not differ between ECP responder and non-responders by both overall provider assessment and NIH response.
This is true also in unadjusted analysis.
% of Treg skin homing did not differ between ECP responder and non-responders

JS Gandelman et al, BBMT 2018

ECP treatment response rate

Provider assessment 62%

consistent with previous studies

Number of patients	> 6pts – 102 pts*
ORR	36-100%*
Steroid-sparing	most studies
Start of treatment	median from cGVHD 2-24 months
Schedule	weekly->every 2-weeks->monthly
Duration	median 6 - 20 months and longer
First effect	slow

Nygaard M et al, Eur J Haematol 2020

NIH criteria response 43%

common language in the context of trials with new drugs

JS Gandelman et al, BBMT 2018

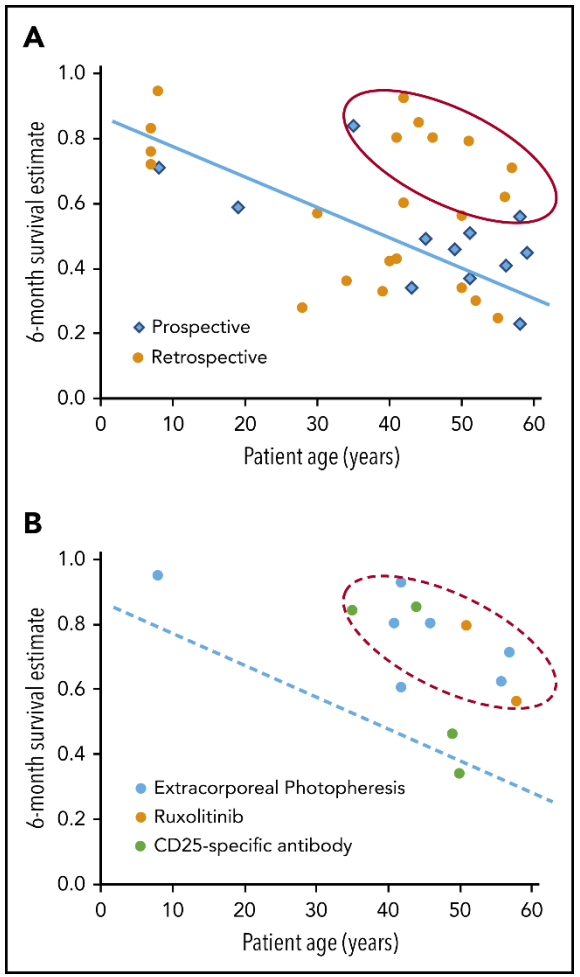
Second Line & Beyond

	aGvHD	ChGvHD
ECP	Skin Liver	Skin Mouth Eyes Liver
Ibrutinib	n.a.	Skin Mouth GI
Ruxolitinib	Skin Upper / Lower GI	Skin Mouth Upper GI
Belumosudil	n.a.	Skin Mouth Esophagus Eyes Lung Liver J&F Lower GI

Greinix HT, Ayuk F and Zeiser R, Leukemia 2022

ECP vs Ruxolitinib

	ECP pros	ECP cons	Ruxo pros	Ruxo cons
Citopenia		X		X
Infezioni	X			X
Assenza accessi venosi periferici		X	X	
Drug Drug Interactions	X			X
Disponibilità sul territorio		X*	X*	
Acute vs Chronic	X		X	



Paul J. Martin, How I treat SR aGvHD, Blood, 2020

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Profilassi

ref	studio	retrospettivo / prospettico	acute / chronic	adults /kids	schedule	type	assessment	n pts	association w drugs	response rate ORR
Kitko CL, et al Combination Therapy for Graft-versus-Host Disease Prophylaxis with Etanercept and Extracorporeal Photopheresis: Results of a Phase II Clinical Trial. Biol Blood Marrow Transplant. 2016 May;22(5):862-8.	phase 2	prospettico	profilassi	adults	12 treatment, weekly since day 28		weekly	48	etanercept	failure in prevent chGvHD
Michallet M, et al Extracorporeal photopheresis for GVHD prophylaxis after reduced intensity conditioning allogeneic hematopoietic stem cell transplantation: a prospective multicenter phase 2 study. Leuk Lymphoma. 2018 Feb;59(2):372-380.	phase 2 multicenter	prospettico	profilassi	adults	2/w x 2w, 1/w x 4	in-line	n.a.	20	n.a.	encouraging
Abdelhakim H, et al Peri-transplant extracorporeal photopheresis to mitigate GVHD- a pilot clinical trial. Bone Marrow Transplant. 2021 Apr;56(4):980-982.	studio pilota single center	prospettico	profilassi	adults	2 session pre TX, than 2 session/w	Cellex / UVAR	every week	17	PDN and CsA / MTX / ATG	no significant AE, not conclusive on GvHD
Foss FM, et al. Incorporation of extracorporeal photopheresis into a reduced intensity conditioning regimen in myelodysplastic syndrome and aggressive lymphoma: results from ECOG 1402 and 1902. Transfusion. 2020 Aug;60(8):1867-1872.	phase 2 cooperative	prospettico	profilassi	adults	2 session day -6/-7	na	na	23	n.a.	feasible
Crocchiolo R, et a. Tregs and GvHD prevention by extracorporeal photopheresis: observations from a clinical trial. Exp Hematol Oncol. 2021 Feb 16;10(1):14	single center	prospettico	profilassi	adults	1/w m6-7, 1/2w m 8-9, 1/m 10-18	unk	every visit	12	n.a.	n.a.

1st Line

ref	studio	retrospettivo / prospettico	acute / chronic	adults /kids	schedule	type	assessment	n pts	association w drugs	response rate ORR
Castagna L, et al. First-line extracorporeal photochemotherapy for acute GVHD after unmanipulated haploidentical BMT following nonmyeloablative conditioning and post transplantation CY. Bone Marrow Transplant. 2014 Feb;49(2):317-8.	single center	prospettico	acute	adults	2/w x 4 w, 2/eow x 6 w, 2/m	off-line	n.a.	7	n.a.	RC 6/7
Jagasia M, et al. Randomized controlled study of ECP with methoxsalen as first-line treatment of patients with moderate to severe cGVHD. Blood Adv. 2019 Jul 23;3(14):2218-2229.	Phase I, random controllato	prospettico	chronic		3/w1, 2/w2-10,2/we2w 11-18, 2/we4w 19-26	therakos	every 2-4 w	60		ORR w 28 in ITT 74 vs 60%
Sestili S, et al. Extracorporeal photopheresis as first-line strategy in the treatment of acute graft-versus-host disease after hematopoietic stem cell transplantation: A single-center experience. Cytotherapy. 2020 Aug;22(8):445-449.	single center	retrospettivo	acute	adults	1-2/w untill response than tapered	therakos	day 14 28 56	37	n.a.	ORR 81%
Mehta RS, et al. Randomized phase II trial of extracorporeal phototherapy and steroids vs. steroids alone for newly diagnosed acute GVHD. Bone Marrow Transplant. 2021 Jun;56(6):1316-1324.	randomized phase 2	prospettico	acute	adults	8-9 session till day 14, 6 session day 15-28, 2 session /w after	Cellex / UVAR	as per MAGIC	81	PDN and CsA	day 28 ORR 74 vs 56%

Bone Marrow Transplantation
https://doi.org/10.1038/s41409-020-01188-4

ARTICLE

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

Rohtesh S. Mehta[1] · Roland Bassett[2] · Gabriela Rondon[1] · Bethany J. Overman[1] · Uday R. Popat[1] · Chitra M. Hosing[1] · Katy Rezvani[1] · Muzaffar H. Qazilbash[1] · Paolo Anderlini[1] · Roy B. Jones[1] · Partow Kebriaei[1] · David Marin[1] · Issa F. Khouri[1] · Betul Oran[1] · Stefan O. Ciurea[1] · Kayo Kondo[1] · Daniel R. Couriel[3] · Elizabeth J. Shpall[1] · Richard E. Champlin[1] · Amin M. Alousi[1]

Single center - open label – adaptively randomized
Bayesian design

- *20 pts randomized fairly*
- *Subsequent assignment to be harmonized to an arm based on probability of success in each arm*

New onset
Biopsy proven
1st line

Treatment success on day 56 (primary endpoint):

- Be alive
- Be in remission from malignancy
- Achieved aGvHD response w/o need for additional therapy
- Be on < 1mg/Kg PDN on day 28 and <0,5 mg/Kg PDN on day 56

Table 2 Primary outcome: day 56 treatment success[a].

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

[a]Defined as being alive, in a remission, achieving a GVHD response (CR or PR) without additional therapy and on a prednisone (MP equivalent) dose of <1 mg/kg/day on day 28 and <0.5 mg/kg/day by day 56. The probability the ECP + steroids arm has a higher success rate compared to steroids alone for day 56 treatment success was 81.5%.

1st line

Caveat
study not powered for subgroup analyses

ECP arm higher probability of success (0.815) – response rate 65% vs 53%.

Potentially more beneficial than steroid alone in skin-only GvHD (response rate 72% vs 57%) than for visceral organ aGvHD (47% vs 43%).

Patients with treatment success (regardless of arm assignment) **had a markedly lower risk for NRM when compared to those with treatment failure** (HR 0.32 – p 0,003)

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30 NOVEMBRE 2022

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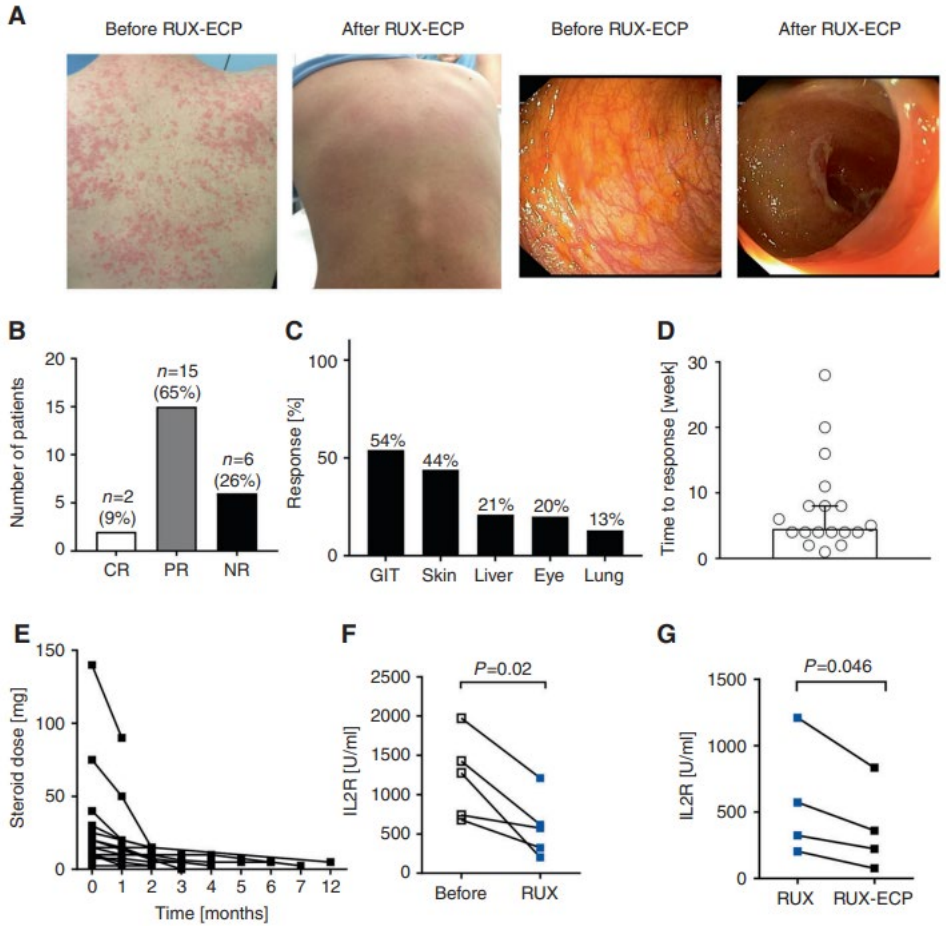
Ospedale San Raffaele - Milano

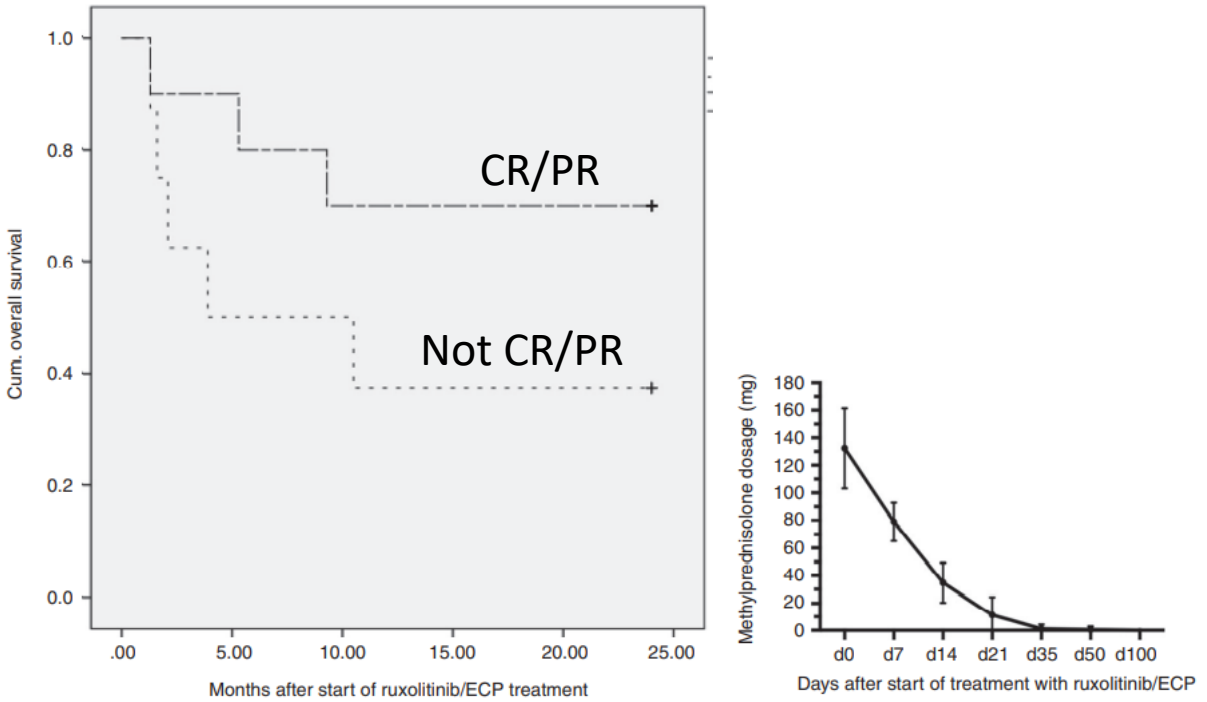
Ruxolitinib–ECP combination treatment for refractory severe chronic graft-versus-host disease

Kristina Maas-Bauer[1] · Chrissoula Kiote-Schmidt[1] · Hartmut Bertz[1] · Petya Apostolova[1] · Ralph Wäsch[1]
Gabriele Ihorst[2] · Jürgen Finke[1] · Robert Zeiser[1]



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

Franziska Modemann[1,2] · Francis Ayuk[1] · Christine Wolschke[1] · Maximilian Christopeit[1] · Dietlinde Janson[1] ·
Ute-Marie von Pein[1] · Nicolaus Kröger[1]



ECP + Ruxolitinib

aGvHD	increased cytopenias rate higher CMV reactivation vs REACH2 (67% vs 26%)
chGvHD	increased cytopenias rate higher CMV reactivation vs REACH3 (26% vs 5.5%)

ECP+MSC - NCT05333029

A Phase II Study of Combination Treatment With Extracorporeal **Photopheresis** and Mesenchymal Stem Cell Infusion for High-Risk and Steroid-Refractory Acute **GVHD**

University of Cleveland

ECP 2-3 times/week/4week + MSC day 1-8-15

High risk aGVHD:
- Skin stage 4
- Lower gastrointestinal (GI) stage ≥ 3
- Liver stage ≥ 3
- Skin stage 3 and lower GI or liver stage ≥ 2 GVHD
- Hyper-acute GVHD as defined by aGVHD within the first 14 days of transplant
- Overall grade 2-4 aGVHD with high-risk disease identified by the Viracor Eurofins Symptomatic Onset or Post-Treatment Algorithm

OR

Steroid refractory aGVHD (standard definition)

Itacitinib (INCB039110) and ECP for 1st-Line Treatment in ChGVHD (FLIGHT) NCT04446182

An open-label, Phase II trial designed to assess the recommended phase 2 dose (RP2D) of itacitinib in combination ECP and efficacy of the combination after 24 weeks of therapy.

University of Utah

Active, clinically diagnosed, moderate or severe chronic GVHD as defined by the NIH 2014.
No previous systemic treatment for chronic GVHD.
Topical or inhaled treatments for chronic GVHD are allowed.

Itacitinib every morning regardless of food.
ECP twice weekly on consecutive days for 8 weeks → start a standard ECP taper schedule and itacitinib unchanged
After six cycles of therapy, itacitinib may be tapered at the treating investigator's discretion as described below.

ECP and Low Dose Aldesleukin in Treating Patients With Steroid Refractory Chronic Graft-Versus-Host Disease NCT03007238

Phase II trial → efficacy of ECP and low dose aldesleukin (interleukin-2) in treating patients with chGVHD that does not respond to upfront treatment with steroids.

City of Hope Medical Center

Steroid refractory chronic GVHD as defined by the NIH 2014.

Patients receive aldesleukin SC daily for 12 weeks.
Patients also undergo ECP twice weekly on weeks 1-4 and then 2 ECP treatments every 2 weeks on weeks 5-12.

REGULAR ARTICLE
blood advances

Efficacy and immunologic effects of extracorporeal photopheresis plus interleukin-2 in chronic graft-versus-host disease

Roger Belizaire,[1] Haesook T. Kim,[2] Samuel J. Poryanda,[3] Nikola V. Mirkovic,[3] Evelyn Hipolito,[3] William J. Savage,[1] Carol G. Reynolds,[3] Marie J. Fields,[3] Jennifer Whangbo,[3] Tomohiro Kubo,[3] Sarah Nikiforow,[3] Edwin P. Alyea,[3] Philippe Armand,[3] Corey S. Cutler,[3] Vincent T. Ho,[3] Bruce R. Blazar,[4,5] Joseph H. Antin,[3] Jerome Ritz,[3] Robert J. Soiffer,[3] and John Koreth[3]

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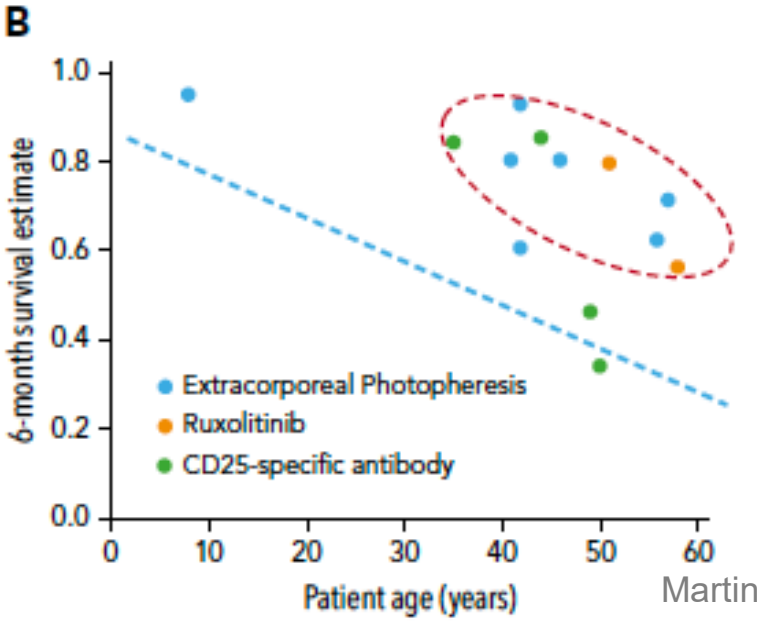
REVIEW ARTICLE OPEN

STEM CELL TRANSPLANTATION

Extracorporeal photopheresis in acute and chronic steroid-refractory graft-versus-host disease: an evolving treatment landscape

Hildegard T. Greinix[1✉], Francis Ayuk[2] and Robert Zeiser[3]



Martin P, Blood 2020

Agenda

- ✓GvHD – dove siamo
- ✓ECP – al tempo dei nuovi farmaci
- ✓ECP – in profilassi e in I linea – i trial
- ✓ECP – in combinazione – cosa sappiamo
- ✓Revisione delle Linee Guida – dove andiamo

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, and Alberto Bosi for Società Italiana di Emaferesi and Manipolazione Cellulare (SIdEM) and Gruppo Italiano Trapianto Midollo Osseo (GITMO)

Metodologia

Domande PICO

Il formato è sostanza

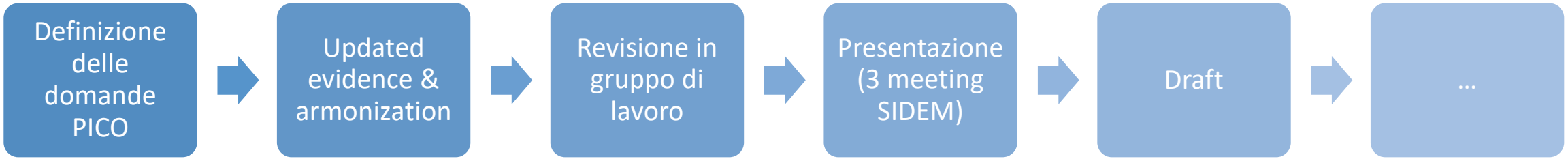
Il formato consente un passaggio esplicito alla raccomandazione

P	paziente /popolazione
I	intervento
C	azione di confront
O	esiti

SIDEM / GITMO Best Practice Task Force

Irene Bianco
Anna Colpo
Fabio Cruciani
Francesco Ipsevich
Maria Teresa Lupo-Stanghellini
Monia Marchetti
Mauro Montanari

Angelo Ostuni
Fabio Ciceri



Hematology - Transplantation & Cellular Therapy Unit
Stem Cell Programme

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