II SESSIONE:
Prevenzione e gestione delle complicanze immunologiche ed infettive del trapianto

La fotoaferesi extracorporea va utilizzata precocemente nel trattamento della GVHD acuta e cronica? Sì!

Maria Teresa Lupo-Stanghellini

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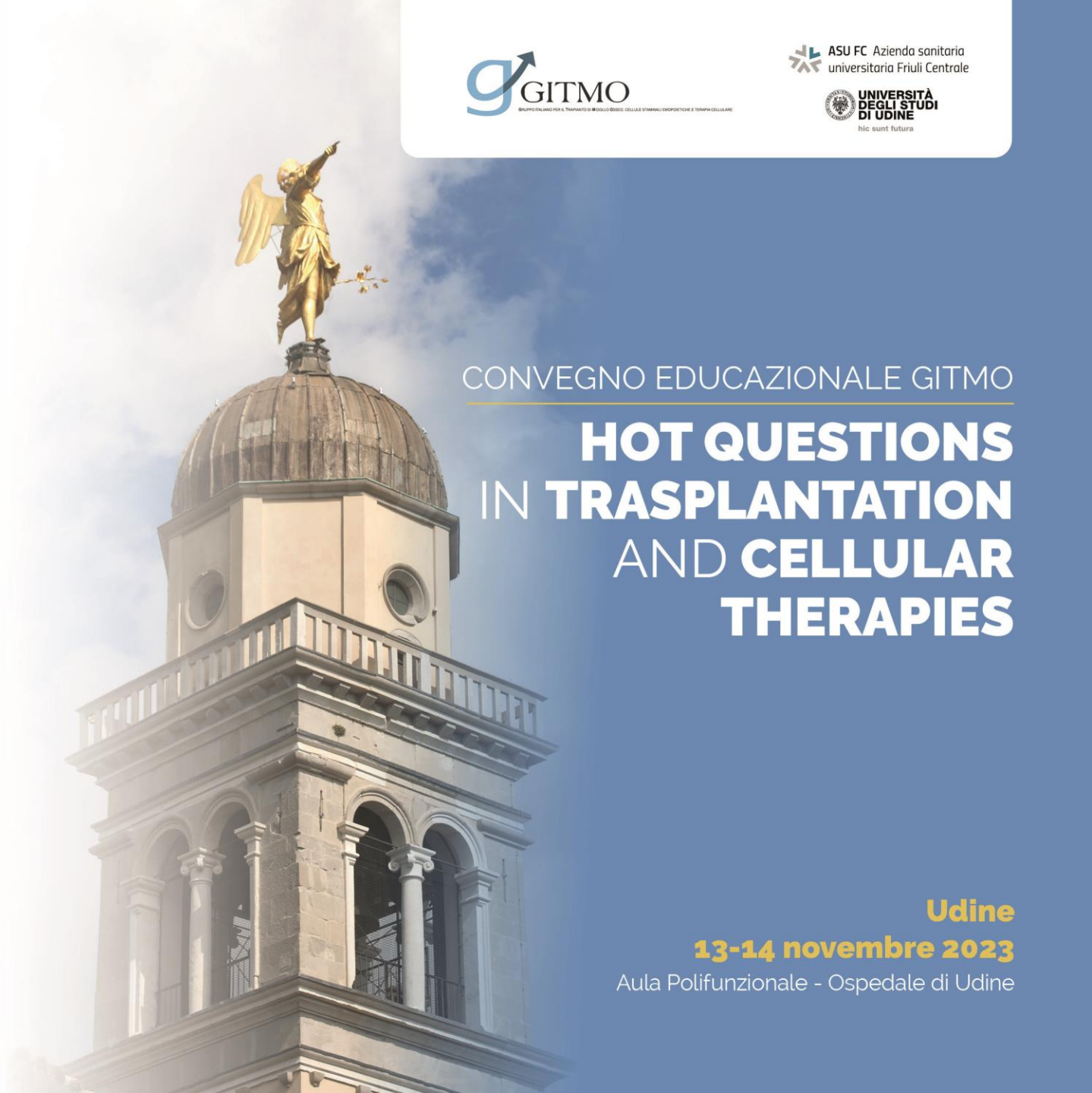


Disclosures of Maria Teresa Lupo-Stanghellini

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

Background

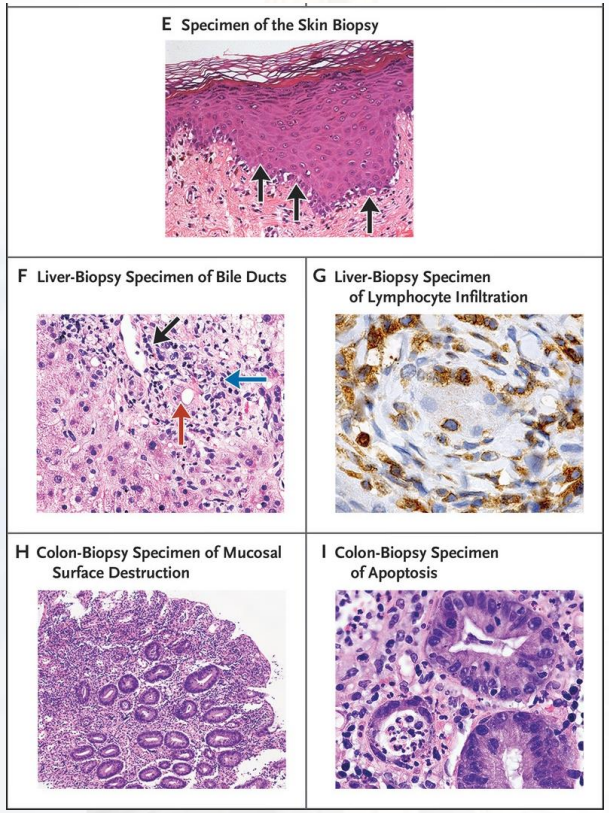
Standard treatment acute GvHD
Risk Factor acute GvHD
ECP in acute GvHD
Early use of ECP in acute GvHD

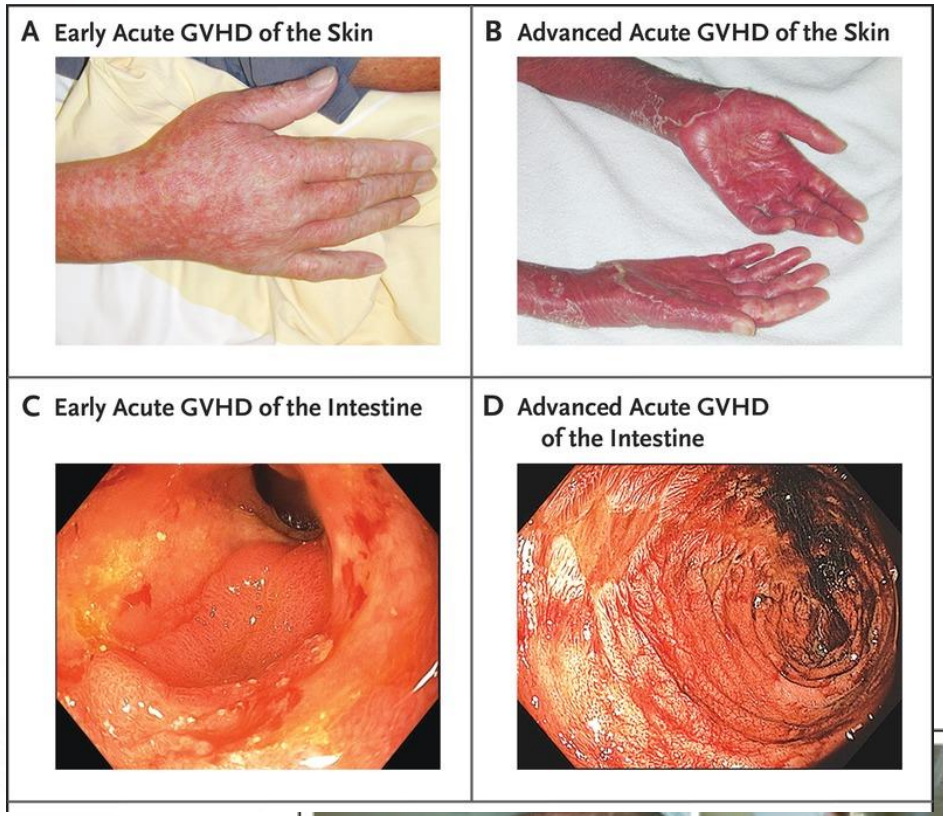
Standard treatment chronic GvHD
ECP in chronic GvHD
Early use of ECP in chronic GvHD

"ECP is expected to have:
limited side effects
no increased risk of infectious complications,
no metabolic or organic impairment
Potential preservation of the graft-versus-leukemia effect"

"**Early**"

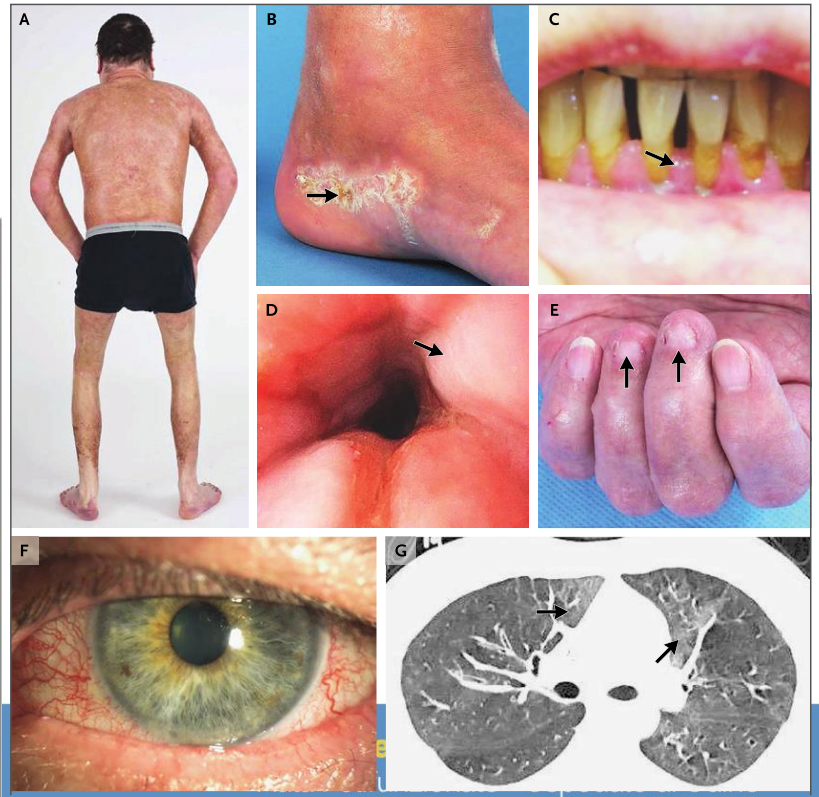
1^ Line – at GvHD onset
1^ Line – day 7 aGvHD / week 2 chGvHD
2^ Line – when Ruxolitinib is not available or feasible
2^ Line – with Ruxolitinib when response to Ruxo is not satisfactory
Before chronic damage
Before advanced stage / grade





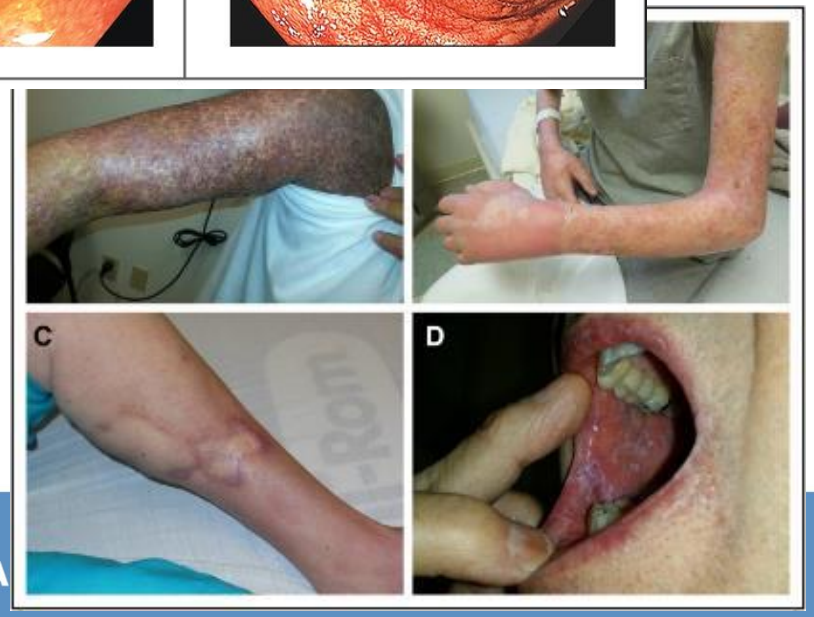
ChGvHD

1^ NRM among survivors >2y
↓ QoL e LT-outcome
↑Immune-disregulation
50-60% 1° line failure
30-50% of day-100 survivors
BUT ↓ up to 10-12% with PTCy???

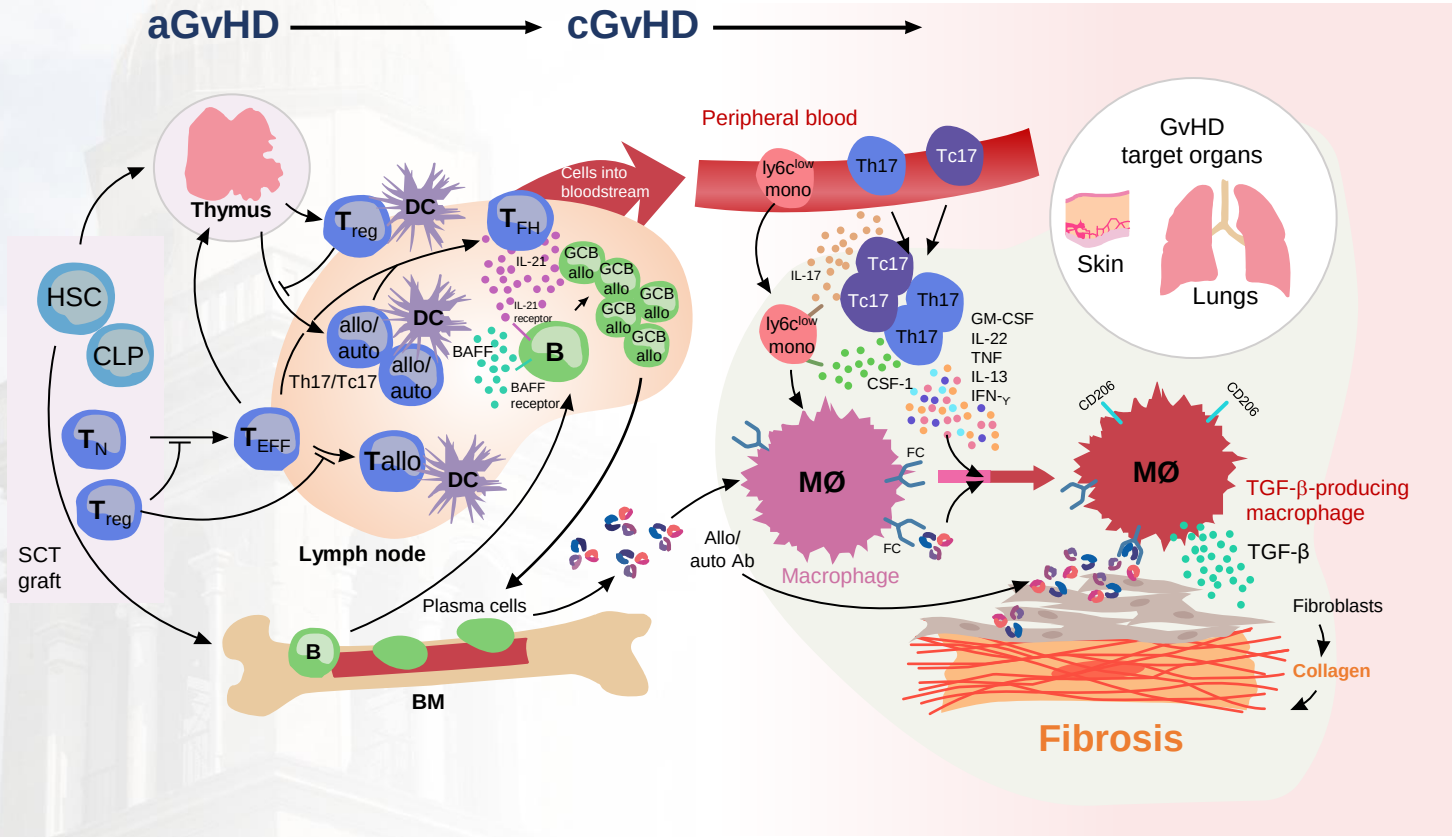


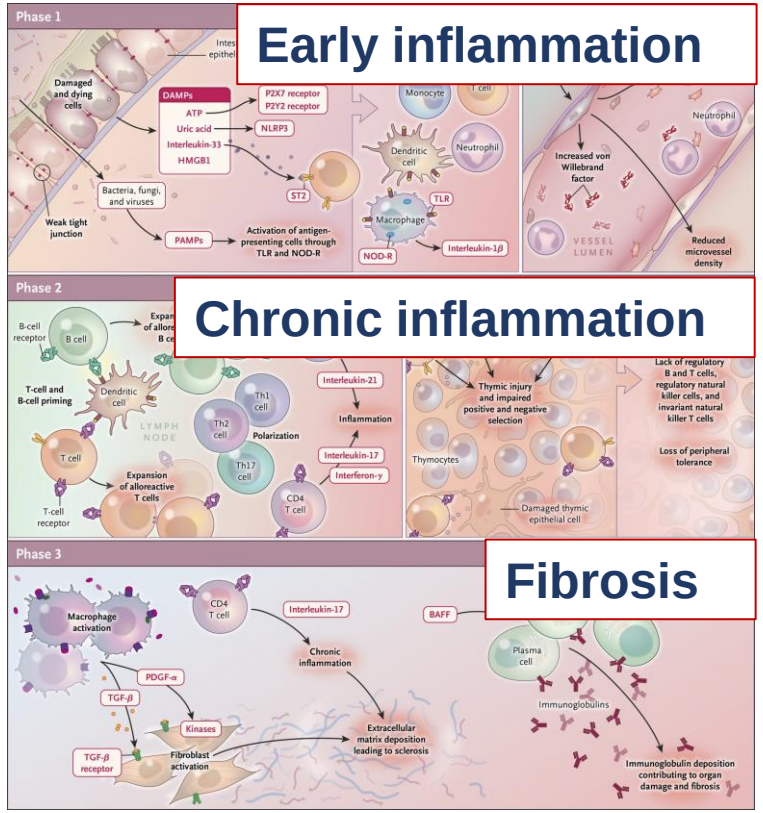
aGvHD

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



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

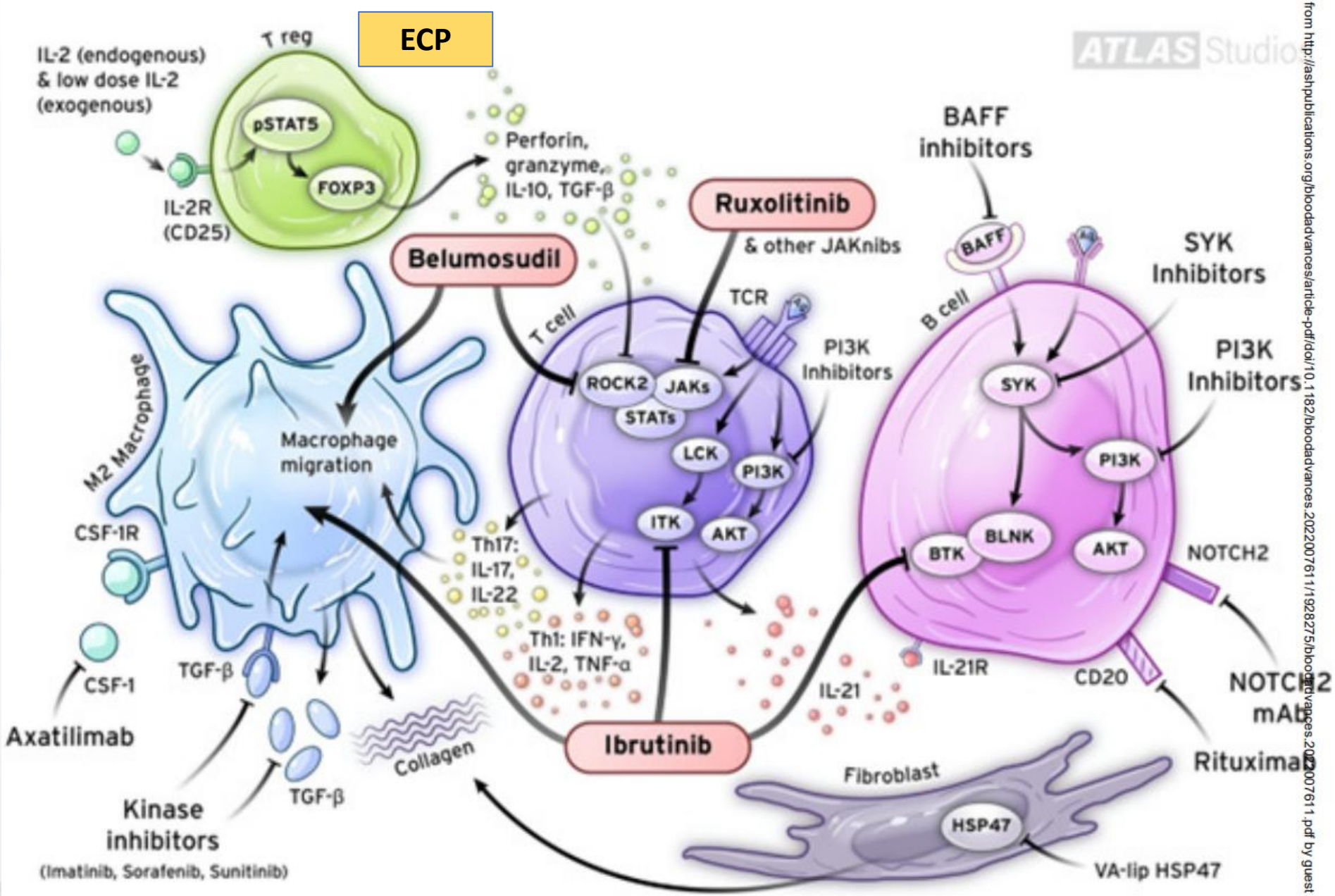




Zeiser R, Blazar BR. N Engl J Med ;377:2565-2579

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

ECP



Buxbaum et al, Blood Advances 2023

How we treat Acute GvHD

*EBMT recommendation **2023***

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 **Ruxolitinib**
Clinical trial

3^ Line ECP – Infliximab – MMF - FMT etc
Clinical Trial

Acute GvHD – 1st line: What?

MAGIC grade I

More infections and no advantage when grade I acute GvHD was treated in a randomised trial

Topical steroids

Optimize TDM of GvHD prophylaxis therapy

**** Clinical trial***

MAGIC grade II Skin or upper GI only

Systemic treatment

Methylprednisolone 1 mg/kg per day or equivalent prednisone 1 mg/kg per day

MAGIC grade II – IV

Systemic treatment

Methylprednisolone 2 mg/kg per day or equivalent prednisone 2.0–2.5 mg/kg per day

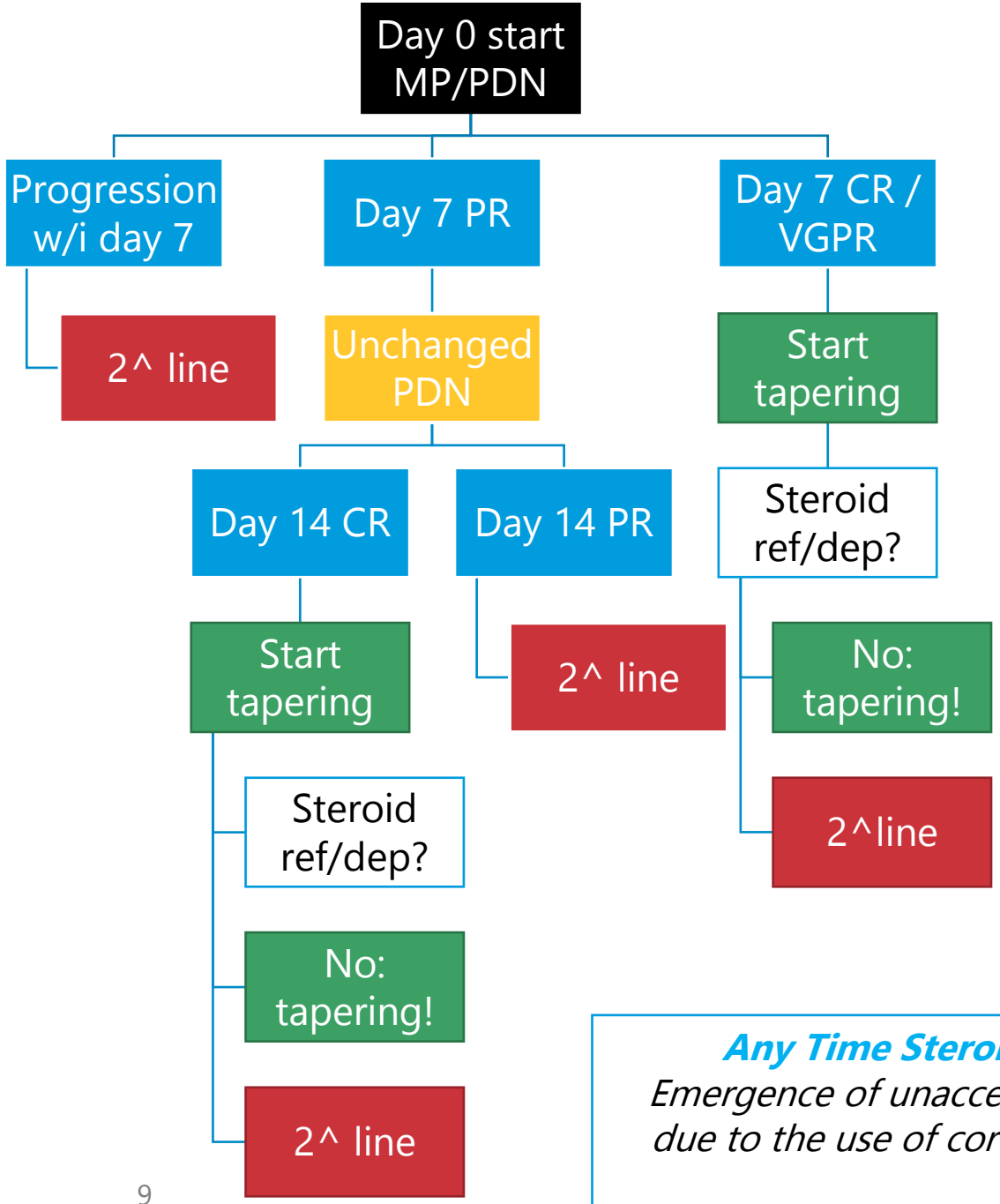
No evidence of better outcome from association of additional immunomodulating agents or higher dosage of steroids

+ Topical steroids

+ Non-absorbable oral steroids

****Clinical trial***

Response evaluation



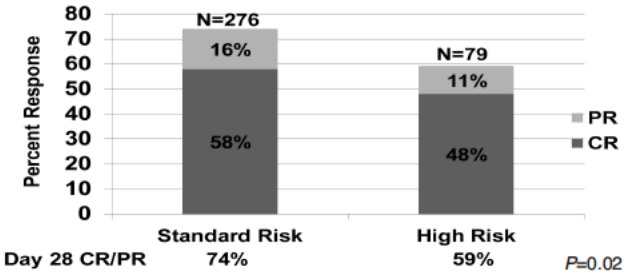
UniSR

Any Time Steroid intolerance

Emergence of unacceptable toxicity due to the use of corticosteroids → 2nd line

A Refined Risk Score for Acute Graft-versus-Host Disease that Predicts Response to Initial Therapy, Survival, and Transplant-Related Mortality

Margaret L. MacMillan [1,2,*], Marie Robin [3], Andrew C. Harris [4], Todd E. DeFor [1,5], Paul J. Martin [6], Amin Alousi [7,8], Vincent T. Ho [8,9], Javier Bolaños-Meade [8,10], James L.M. Ferrara [4,8], Richard Jones [8,10], Mukta Arora [1,11], Bruce R. Blazar [1,2], Shernan G. Holtan [1,11], David Jacobsohn [8,12], Marcelo Pasquini [8,13], Gerard Socie [3], Joseph H. Antin [8,9], John E. Levine [4,8], Daniel J. Weisdorf [1,8,11]



	Standard Risk	High Risk	P
Day 14 CR/PR	71%	56%	<0.01
Day 56 CR/PR	68%	49%	<0.01

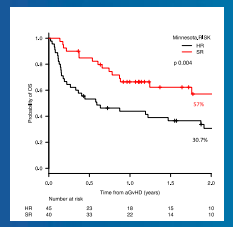
LETTERS TO THE EDITOR

Minnesota acute graft-*versus*-host disease risk score predicts survival at onset of graft-*versus*-host disease after post-transplant cyclophosphamide prophylaxis

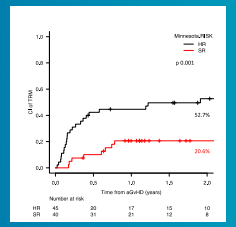
Ardizoia F, […] Lupo-Stanghellini MT, Haematologica 2022

Minnesota Risk Score and OS / TRM

2y OS



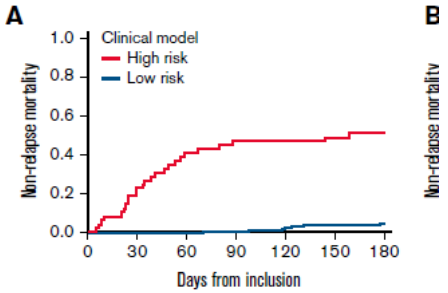
2y TRM



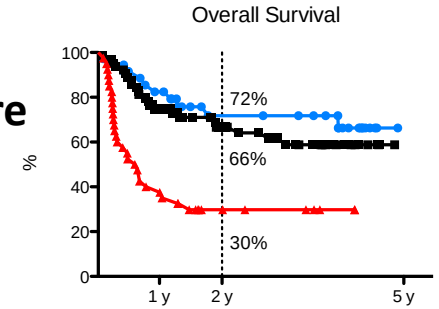
Prospective external validation of biomarkers to predict acute graft-versus-host disease severity

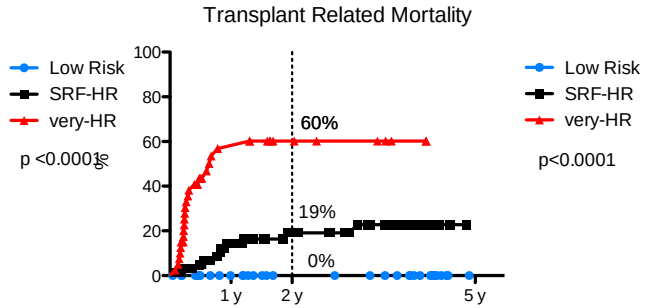
Clinical High Risk: initial liver GVHD, age >/=50 years, initial GVHD G 3

Robin M et al, Blood Adv 2023



OSR validation of Saint Louis risk - score

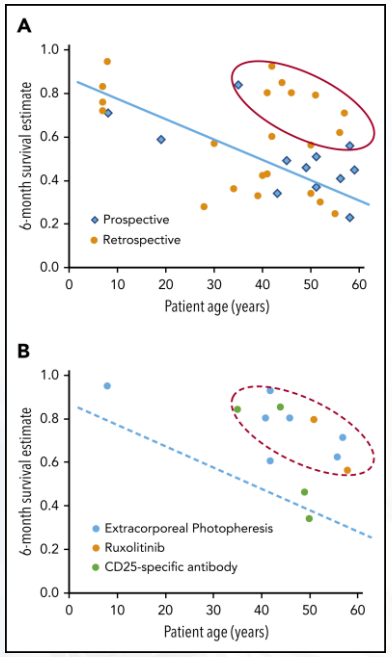




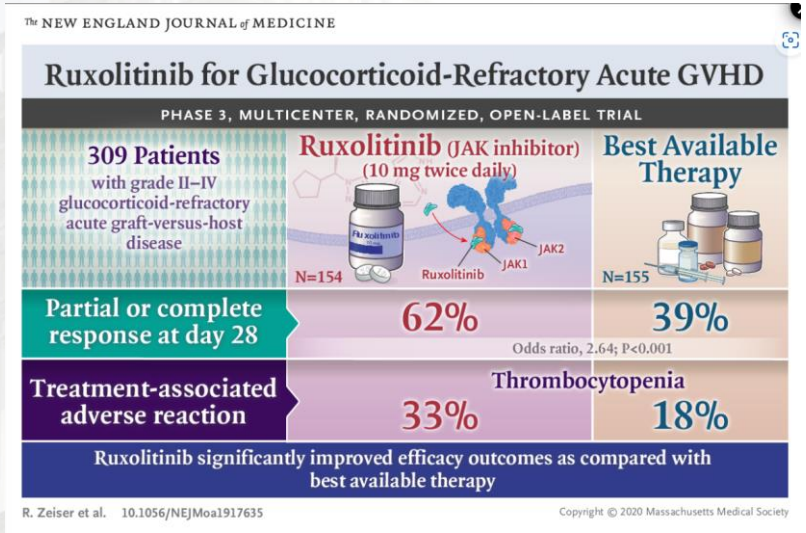
Criscimanna A, […] Lupo-Stanghellini MT, SIE 2023

GVHD Risk Score	One Organ	Two Organs		Three Organs
Standard Rsk	Stage 1-2 Skin (MAGIC 1)	Stage 1-2 skin + 1 UGI (MAGIC 2)	Stage 3 skin + 1 UGI (MAGIC 2)	
	Stage 3 Skin (MAGIC 2)	Stage 1-2 skin + 1 LGI (MAGIC 2)	Stage 3 skin + 1 LGI (MAGIC 2)	
	Stage 1 UGI (MAGIC 2)	Stage 1-2 skin + 1 liver (MAGIC 2)	Stage 3 skin + 1 Liver (MAGIC 2)	
	Stage 1 LGI (MAGIC 2)	Stage 1-3 skin + 2-3 liver (MAGIC 3)		
	Stage 2 LGI (MAGIC 3)	Stage 1-3 skin + 4 liver (MAGIC 4)		
High Risk	Stage 4 Skin (MAGIC 4)	Stage 1-3 skin + 2 GI (MAGIC 3)		Stage 1-3 skin + 1-2 GI + 1-3 liver (MAGIC 2-3)
	Stage 3 GI (MAGIC 3)	Stage 1-2 lower GI + 1-3 liver (MAGIC 2-3)		
	Stage 4 GI (MAGIC 4)			Stage 1-3 skin + 3-4 GI + 1-4 liver (MAGIC 3-4)
	Stage 1 Liver (MAGIC 2)	Stage 3-4 GI + 1-3 skin (MAGIC 3-4)		
	Stage 2 -3 Liver (MAGIC 3)	Stage 3-4 GI + 1-4 liver (MAGIC 3-4)		
	Stage 4 Liver (MAGIC 4)			

PJ Martin, Blood 2020



R Zeiser, NEJM 2020



Profilassi

- Nessuna evidenza

1^ Line

- Evidenze
- Standard steroid
- Steroid low dose

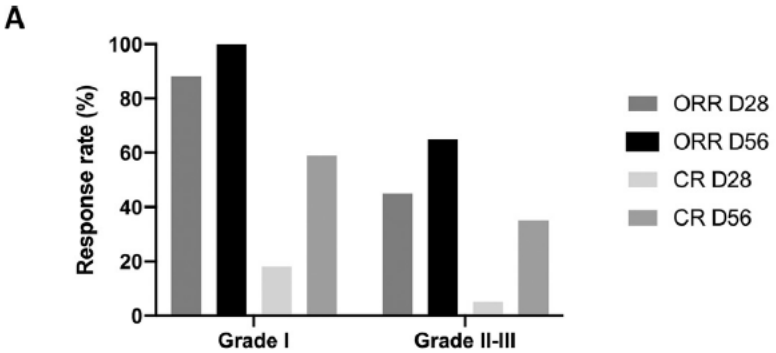
2^ Line

- Evidenze
- Alternativa a Ruxolitinib (disponibilità – diatesi infettiva)
- Steroid sparing

Stratificazione secondo fattori di rischio

Stem Cell Transplantation • Brief Report

The effect of intensified extracorporeal photochemotherapy on long-term survival in patients with severe acute graft-versus-host disease



Greinix et al, Haematologica 2006

Pilot + Phase II study
59 pts
2^ line ECP for grade II-IV SR-aGVHD
high response rate in **skin** (82%)
vs GUT (61%) and liver (61%)

Extracorporeal Photopheresis for Treatment of Acute and Chronic Graft Versus Host Disease: An Italian Multicentric Retrospective Analysis on 94 Patients on Behalf of the Gruppo Italiano Trapianto di Midollo Osseo

TABLE 3.
CR After ECP according to the severity of aGVHD and cGVHD

	CR After ECP		
aGVHD (grade) (n = 45)	Total	NR to steroids	PR to steroids
II (n = 36)	35/36 (97%)	13/14 (93%)	22/22 (100%)
III / IV (n = 9)	6/9 (67%)	6/8 (75%)	0/1 (0%)
cGVHD (n = 49)		CR after ECP	
Mild (n = 2)		0/2 (0%)	
Moderate (n = 26)		15/26 (58%)	
Severe (n = 21)		7/21 (33%)	

Malagola et al, Transplantation 2016

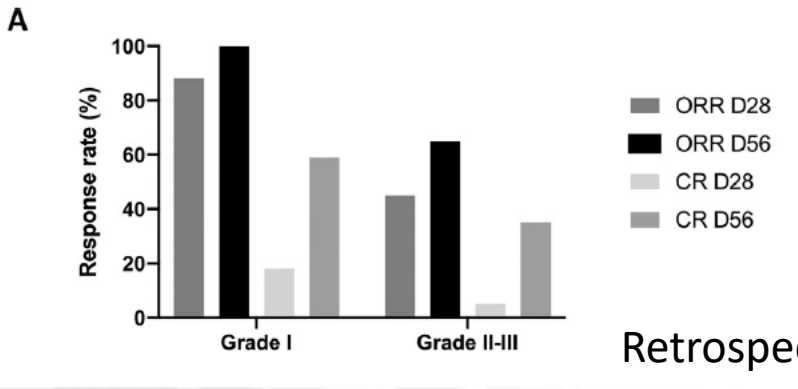
Retrospective
45 pts
2^ line ECP for grade II-IV SR-aGVHD
high response rate **grade II** vs III/IV
High response rate in **PR to steroid** vs refractory

Extracorporeal photopheresis as first-line strategy in the treatment of acute graft-versus-host disease after hematopoietic stem cell transplantation: A single-center experience

Sestili et al, Cytotherapy 2020

Table 2
Acute GVHD characteristics at baseline.

Revised Glucksberg criteria	Stage I	Stage II	Stage III	Stage IV
Skin, n (%)	3 (8%)	22 (59%)	12 (32%)	0
Gastrointestinal tract, n (%)	6 (16%)	0	0	0
Liver, n (%)	2 (5%)	2 (5%)	0	0
Overall grade	17 (46%)	18 (49%)	2 (5%)	0



Retrospective
37 pts
1^ line ECP
26 PDN 1 mg/Kg + ECP
11 topical steroids + ECP
Skin predominant aGvHD

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

Metha et al, BMT 2020

Single center - open label – adaptively randomized Bayesian design
New onset
Biopsy proven
1st line 2 mg/Kg alone vs **2 mg/Kg + ECP**

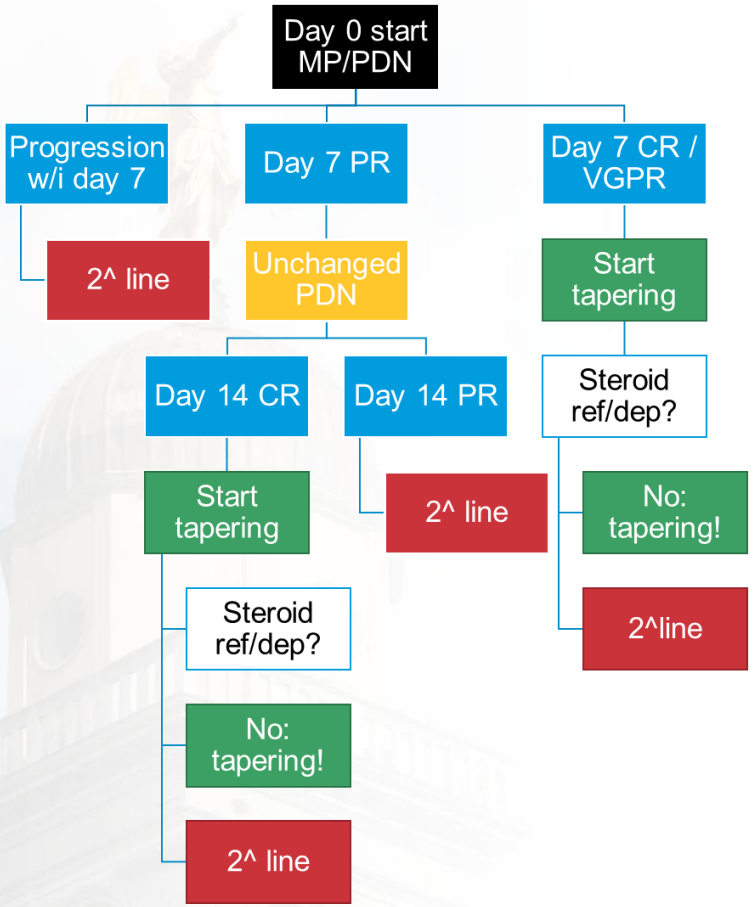
Table 2 Primary outcome: day 56 treatment success[a].

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

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

Potentially more beneficial than steroid alone in skin-only GvHD
than for visceral organ aGvHD
Patients with treatment success had a markedly lower risk for NRM when compared to those with treatment failure

Early use of ECP in acute GvHD – a proposal



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	Stage 2 LGI (MAGIC 3)	Stage 1-3 skin + 4 liver (MAGIC 4)	

Profilassi

- Nessuna evidenza

1^ Line

- **Trial clinico** – stratificazione rischio
- **Day 7 PR** – con stratificazione rischio
- **Steroido-intolleranti**
- **Skin predominance**

2^ Line

- **Alternativa a Ruxolitinib** (disponibilità – diatesi infettiva)
- Steroid sparing in grade II
- Steroid sparing in assenza di refrattarietà steroidea
- Skin-predominance

How we treat Chronic GvHD

EBMT recommendation ***2023***

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 **Ruxolitinib** – clinical trial
3^ Line **Ibrutinib - Belumosudil** «in adults with steroide refractory chGvHD B & I are potential therapeutic option»
ECP – Infliximab – MMF – TKi - etc
Clinical Trial

Chronic GvHD – 1st line: What?

NIH moderate / severe

The **1st line** treatment of newly diagnosed cGVHD is prednisone taken orally at a dose of 1 mg/kg

+ Ancillary therapy

+ Supportive Care

If *Lung GvHD* add FAM regimen

(inhaled fluticasone 440 µg twice a day, azithromycin 250 mg three times a week, and montelukast 10 mg once a day)

**** Clinical trial***

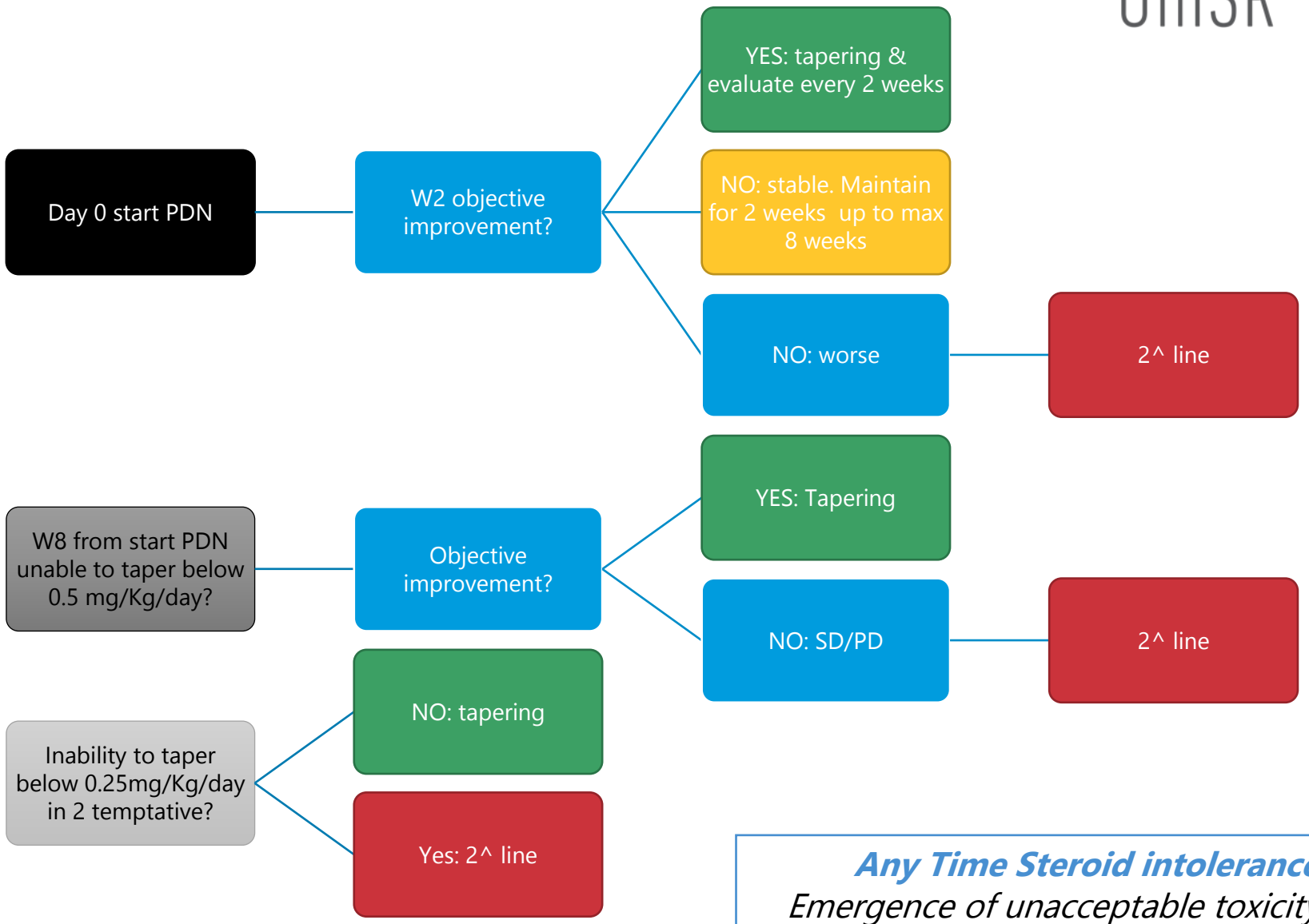
Tips & Tricks

If a patient is already receiving corticosteroid treatment, corticosteroid dose can be increased (if it is <1 mg/kg) and an alternative strategy is usually applied (eg. calcineurin inhibitor or **ECP**).

If the patient is already receiving full-dose corticosteroid and ciclosporin at the time of cGvHD onset, no standard treatment is available - these patients should be treated in clinical trials, if possible.

Response Evaluation

UniSR



Any Time Steroid intolerance

Emergence of unacceptable toxicity due to the use of corticosteroids → 2nd line

Ruxolitinib (2015&beyond)

Acute GvHD

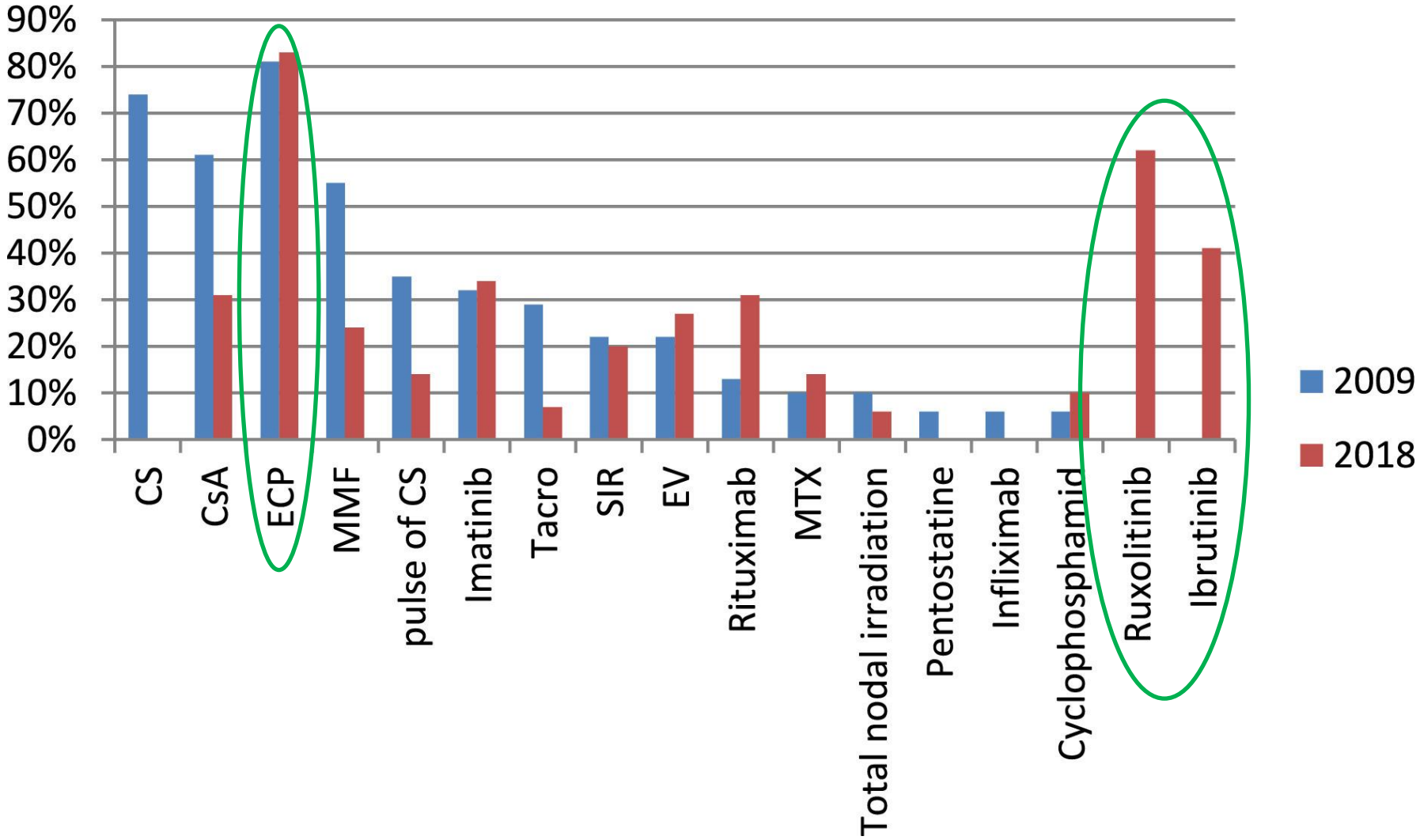
1Ph 2 & 1Ph 3	2 prospective trials	4 retrospective trials
225 pts	72 pts	126 pts
Day 28 ORR 62%	Worst outcome in liver	CMV reactivation

Chronic GvHD

1 Ph 3	1 prospective trial	9 retrospective trials
165 pts	43 pts	373 pts
Skin-Mouth-Upper/Lower GI ORR>40%	No change eyes, lung, joint, genitalia	Good mouth response, worst lung

Greinix HT, Ayuk F, Zeiser R. Leukemia. 2022.

Changing Paradigm



Wolff et al, BBMT 2019

Applied salvage treatment for cGVHD with cutaneous deep sclerosis.

Favorable impact of extracorporeal photopheresis in acute and chronic graft versus host disease: Prospective single-center study

Sakellari et al, J Clin Apher 2018

Prospective
88 pts

- 52 cutaneous sclerosis manifestations
- 53 mucocutaneous disease
- 31 liver
- 37 visceral
- 12 lung involvement

Response rate
Cutaneous 83% - visceral 53% - lung 27% (p 0.031)

Higher response rates in patients with severe chronic skin graft-versus-host disease treated with extracorporeal photopheresis

Afram Gi et al, Cent Eur J Immunol 2020

Extracorporeal Photopheresis for Treatment of Acute and Chronic Graft Versus Host Disease: An Italian Multicentric Retrospective Analysis on 94 Patients on Behalf of the Gruppo Italiano Trapianto di Midollo Osseo

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Severe (n = 21)		7/21 (33%)	

Malagola et al, Transplantation 2016

Retrospective
49 pts
2^ line ECP for SR-cGVHD
high response rate **moderate cGvHD**

Biomarker profile predicts clinical efficacy of extracorporeal photopheresis in steroid-resistant acute and chronic graft-vs-host disease after allogenic hematopoietic stem cell transplant

Amat et al, J Clin Apher 2021

	Total		
	Overall	Grade I and II	Grade III and IV
Total	37 (100.0%)	17 (100.0%)	20 (100.0%)
Response	27 (73.0%)	17 (100.0%)	10 (50.0%)
Complete	15 (40.5%)	10 (58.8%)	5 (25.0%)
Partial	12 (32.4%)	7 (41.2%)	5 (25.0%)
NR/progression	10 (27.0%)	0 (0.0%)	10 (50.0%)

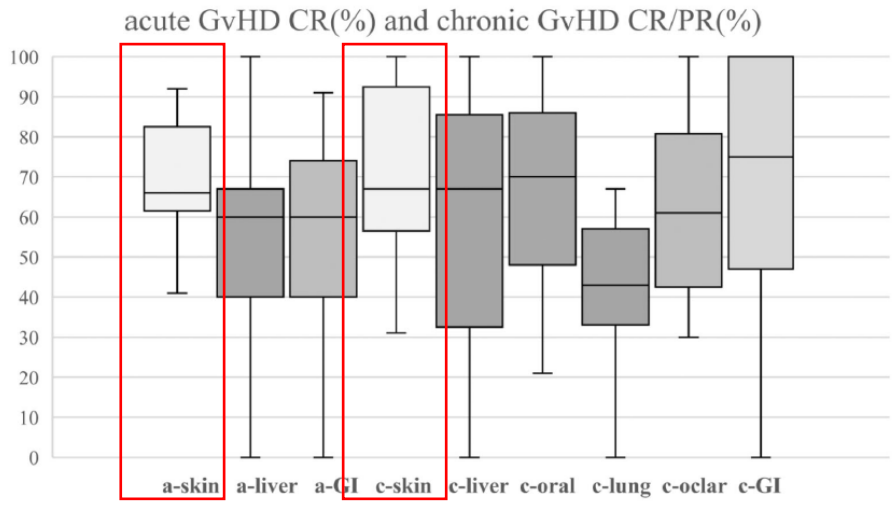
aSR-GvHD G I-II > G III-IV
ORR 73%
cSR-GvHD moderate > severe
ORR 88%

TABLE 4 Response to treatment by overall cGVHD grade and affected area

	Total	Response	Complete	Partial	Progression
Total	25 (100.0%)	22 (88%)	6 (24.0%)	16 (64%)	3 (12%)
Mild–Moderate	13 (100.0%)	13 (100%) ((100(100.0%)	3 (23.1%)	10 (76.9%)	0 (0.0%)
Severe	12 (100.0%)	9 (75%)	3 (25%)	6 (50%)	3 (25%)
Mucosal/cutaneous	24 (100.0%)	21 (87.5%)	5 (20.8%)	16 (66.7%)	3 (12.5%)
Scleroderma	10 (100.0%)	10 (100%) (100.0%)	1 (10%)	9 (90%)	0 (0.0%)
Genital	9 (100.0%)	6 (66.7%)	2 (22.2%)	4 (44.4%)	3 (33.3%)
Hepatic	4 (100.0%)	4 (100%)	1 (25%)	3 (75%)	0 (0.0%)
Fasciitis	3 (100.0%)	3 (100%)	0 (0.0%)	3 (100%)	0 (0.0%)
Pulmonary	2 (100.0%)	2 (100%)	1 (50%)	1 (50%)	0 (0.0%)
Intestinal	1 (100.0%)	1 (50%)	1 (50%)	0 (0.0%)	1 (50%)

What is photopheresis? Role of extracorporeal photopheresis in the treatment of GvHD and its practice in Sweden

Karllson YF and Berlin G, Ther Apjher Dial 2023



Propensity Score Matching Analysis Comparing the Efficacy and Steroid Tapering Benefit of Extracorporeal Photopheresis to Best Available Therapy in Third-Line or Beyond Treatment for Chronic GvHD

Novitzky-Basso et al, TCT 2023

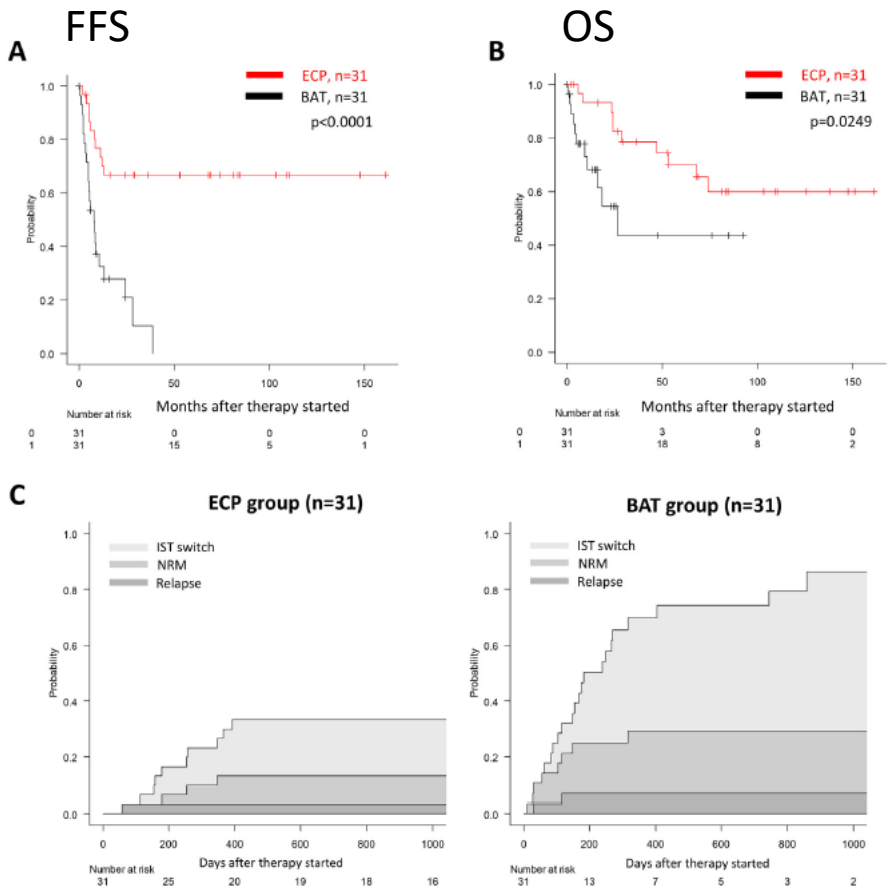
Propensity score matching analysis

- ECP patients (n=74; 31 extracted by PSM)
- historical cohort of cGvHD patients treated with BAT third-line therapy or beyond (n=132; 31 extracted by PSM).

Propensity scores, a binary logistic regression model was applied using 3 pre-treatment variables:

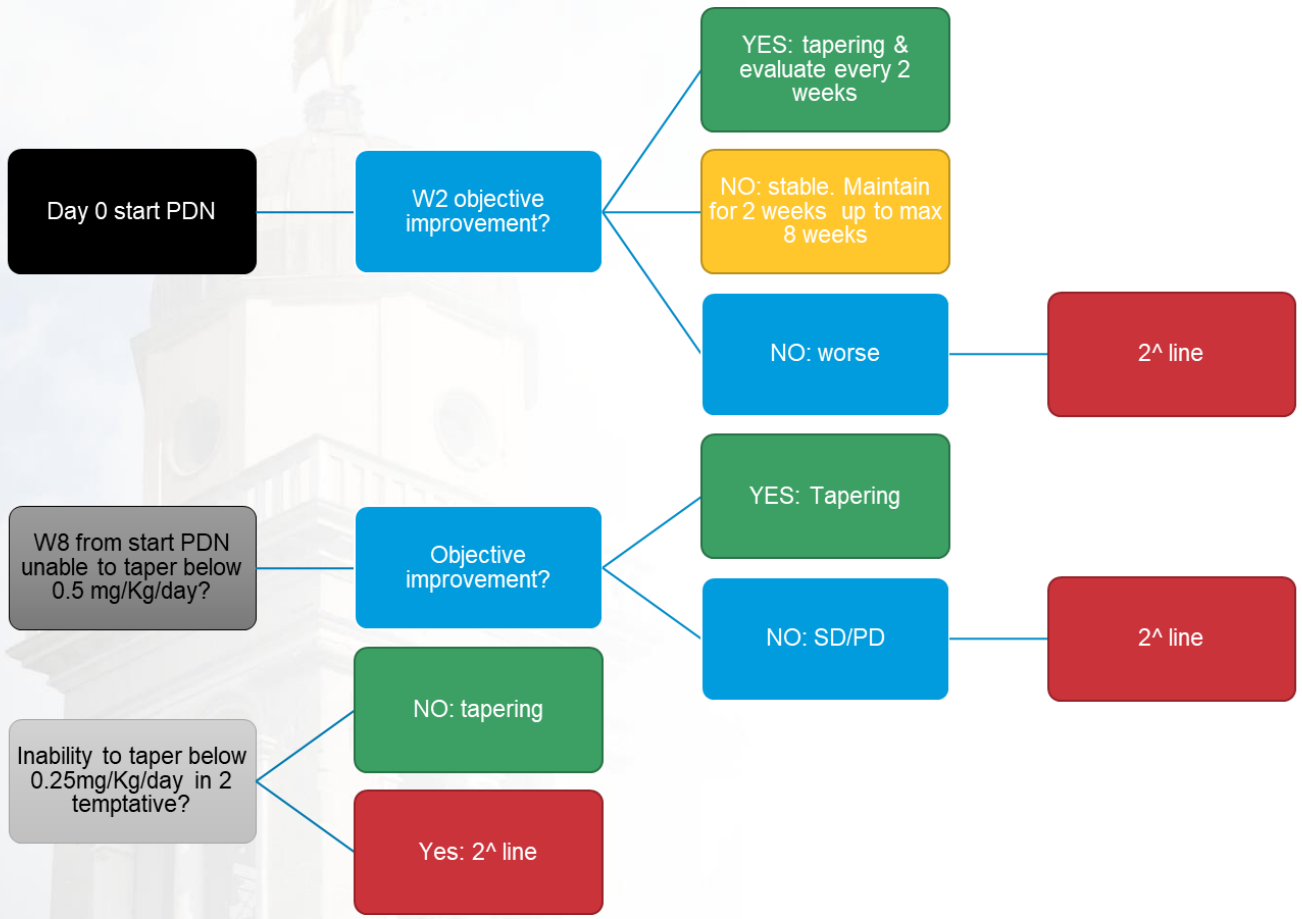
- GVHD severity (mild/moderate versus severe grade),
- aGVHD history (yes versus no),
- baseline daily steroid dose(<.5 versus >.5mg/kg/day).

Multivariate analysis confirmed ECP superior to BAT
OS
FFS
% prednisone discontinuation



Cumulative incidence of treatment failure with defined causes

Early use of ECP in chronic GvHD – a proposal



1^ Line

- **Ongoing PDN at declaration**
- **Trial clinico** – stratificazione rischio
- **Week 2 SD** – con prevalente interessamento cutaneo / mucosale
- **Steroido-intolleranti**
- Failure to taper w/o progression and with skin predominance

2^ Line

- **Alternativa a Ruxolitinib** (disponibilità – diatesi infettiva)
- **Alternativa a Ibrutinib** (disponibilità – tossicità)
- Skin-predominance

3^ Line

- **Alternativa a Belumosudil** (disponibilità)
- Among BAT better FFS / OS / steroid tapering
- COMBO ECP and Ruxo (few evidence)

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