Patogenesi della GVHD e nuove frontiere terapeutiche

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Acute and Chronic Graft-Versus-Host Disease in Dogs Given Hemopoietic Grafts From DLA-Nonidentical Littermates

(Am J Pathol 1982, 108:196–205)

Two Distinct Syndromes

however this paradigm has been challenged in recent mouse and human studies and is not absolute

…aGVHD developed a median of 13 days after SCT….characterized by skin erythema, jaundice, diarrhea, and G- infections;

…….cGVHD developed a median of 124 days after SCT …..characterized by skin ulcerations, massive ascites, and G+ infections;

……cGVHD could be distinguished from aGVHD by epidermal atrophy, dermal fibrosis and by bile duct proliferation,

….and…

Thymus

Endothelium

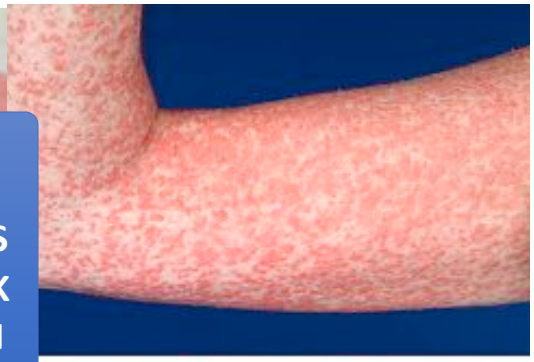
Bone Marrow

CNS

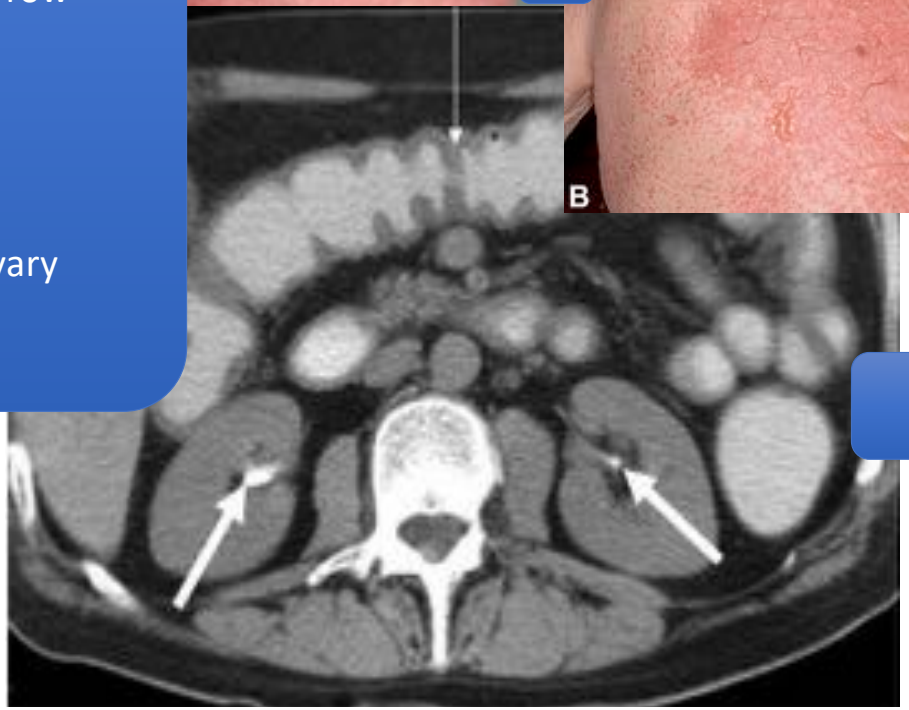
Lung

Pancreas

Other…ovary

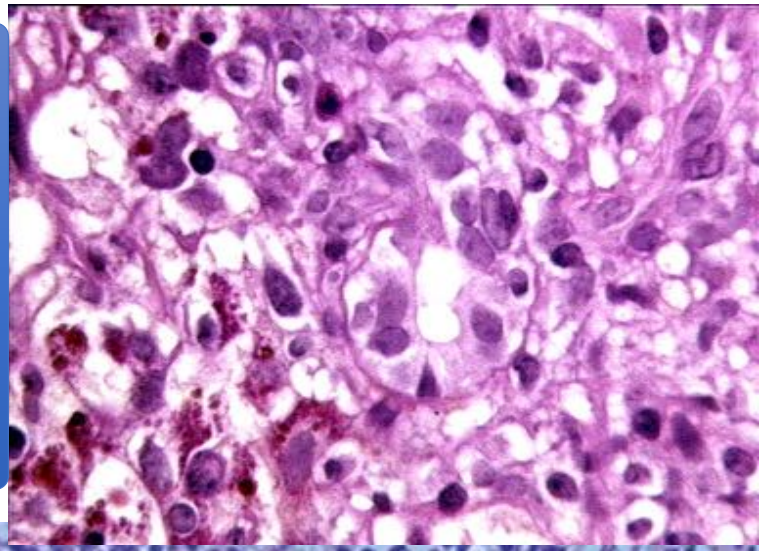


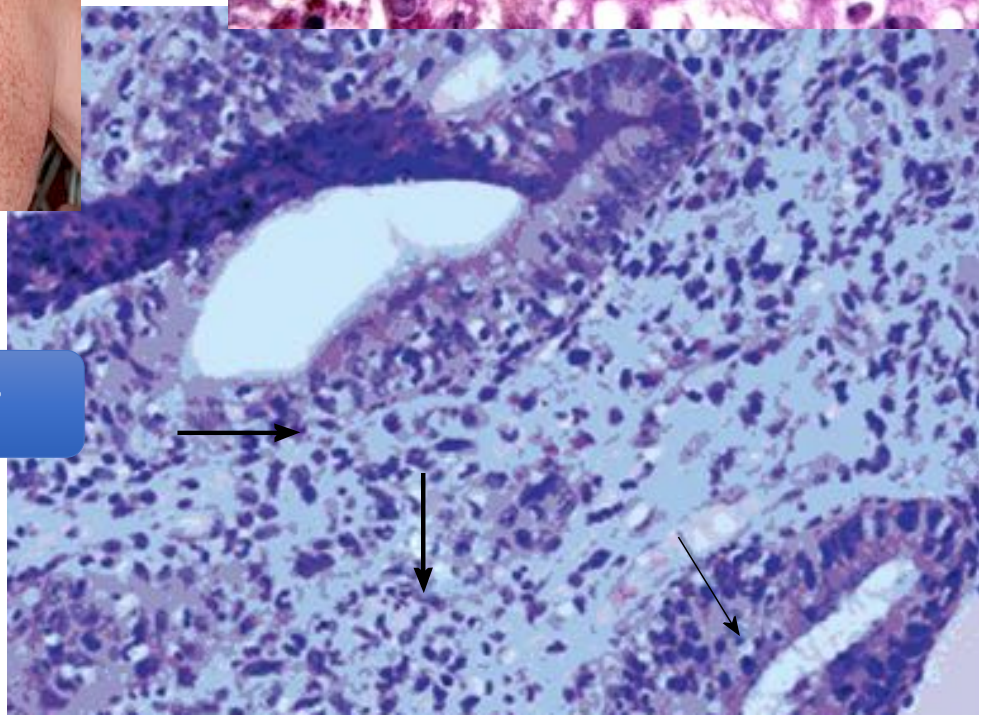
SKIN



GUT

LIVER

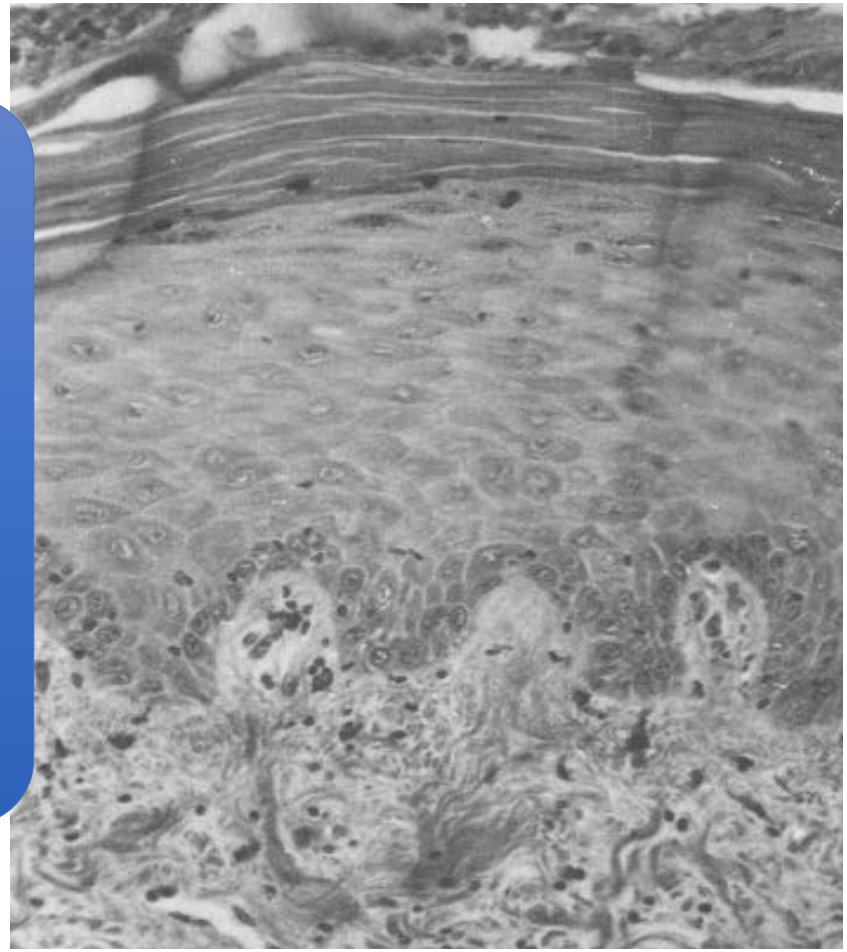




American Journal
of Pathology

1978

Skin
Lung
Joints
Eye
Oral
GUT
Liver
Genital
Kidney
CNS/PNS



Chronic Cutaneous Graft-Versus-Host Disease in Man

Howard M. Shulman, MD, George E. Sale, MD,
Kenneth G. Lerner, MD, Edward A. Barker, MD, Paul L. Welden, MD,
Keith Sullivan, MD, Betty Gallucci, RN, PhD, E. Donnall Thomas, MD,
and Rainer Storb, MD

Day+280

Day+28

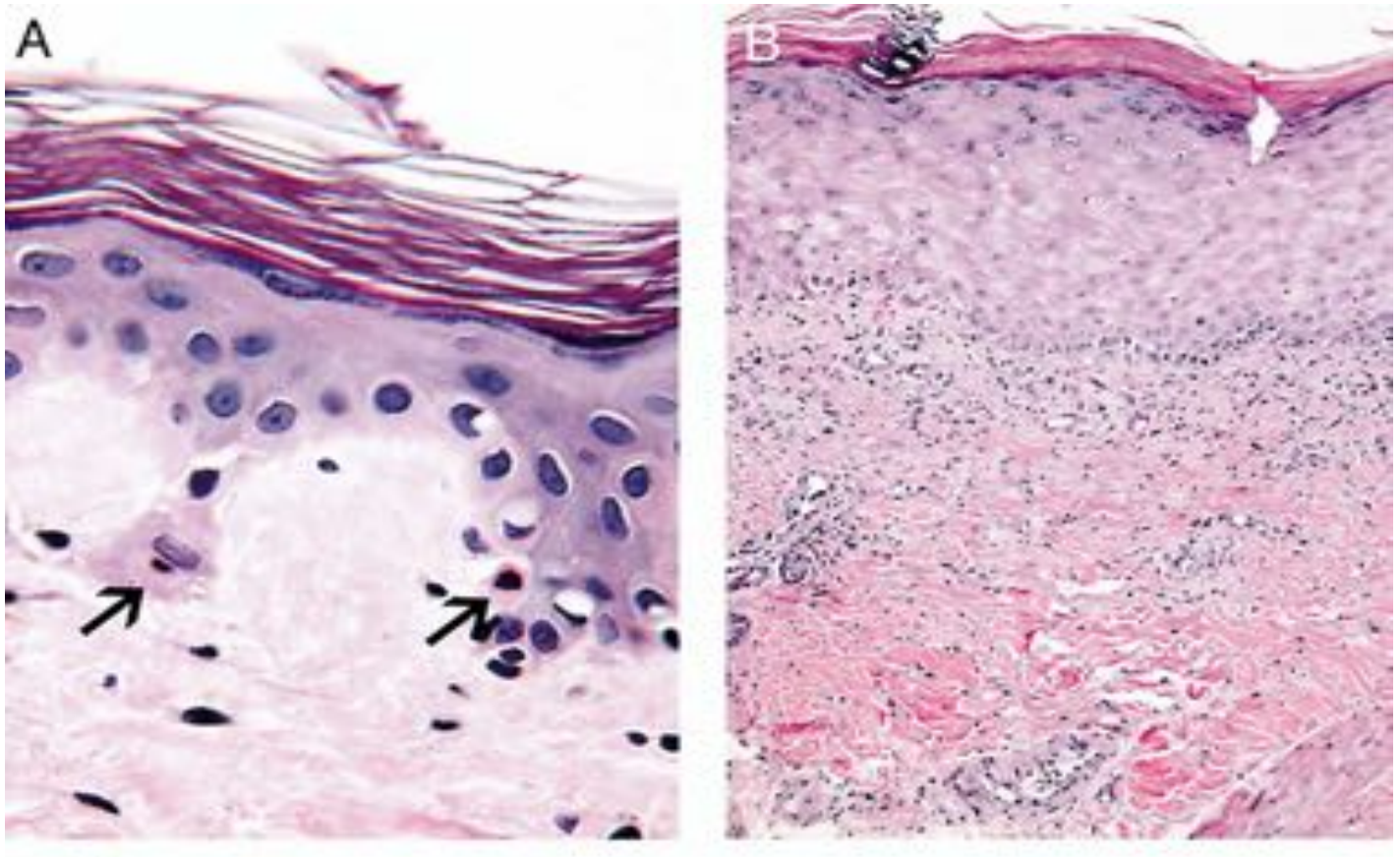
Late onset acute GVHD
Progressive cGVHD

Overlap syndrome At day +325

Progression of histologic changes from acute to chronic cutaneous GVHD

Day 98 → day 426

LICHEN



apoptotic body

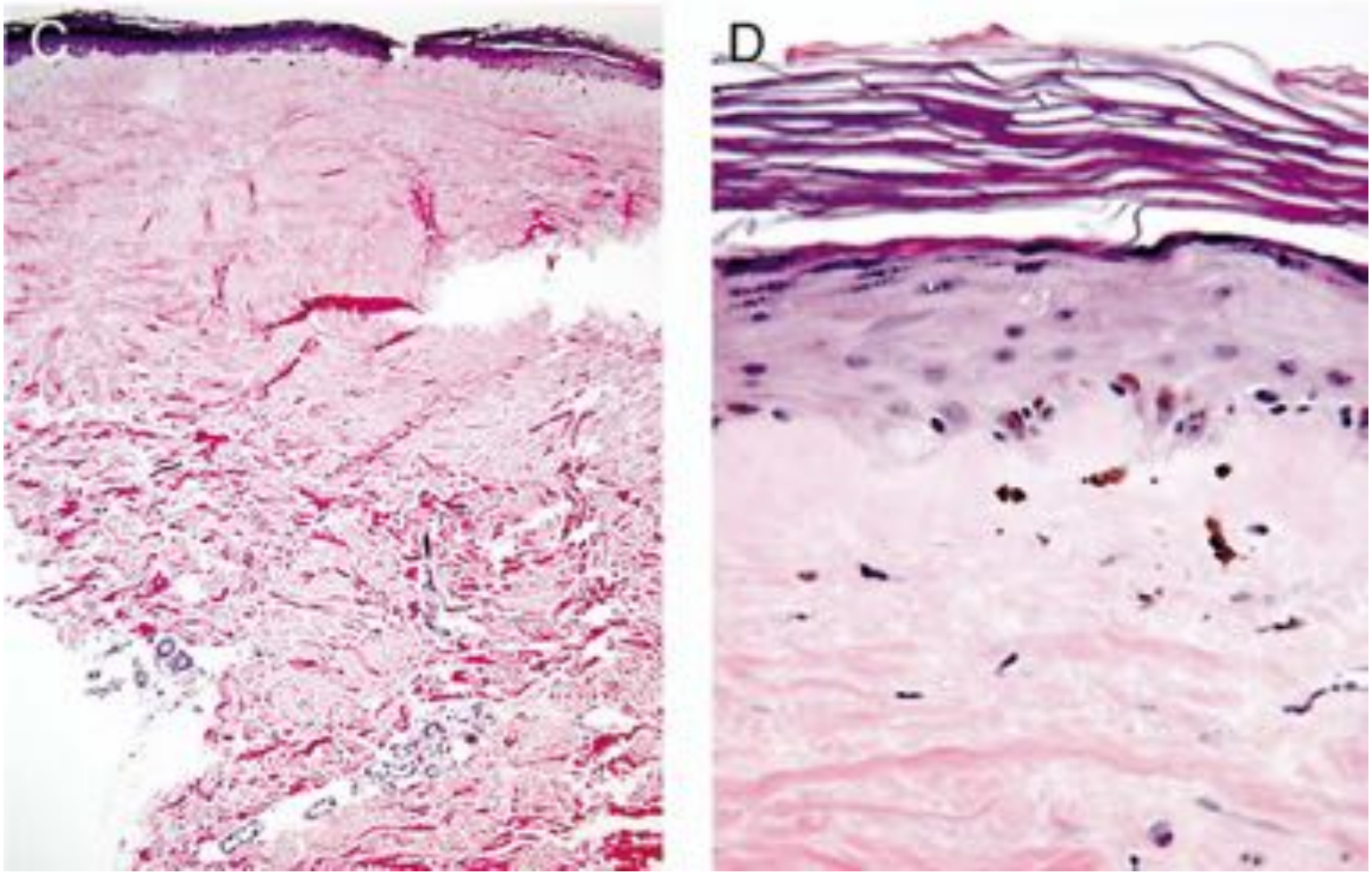
orthokeratosis, hypergranulosis and acanthosis.

Lymphocytic infiltration

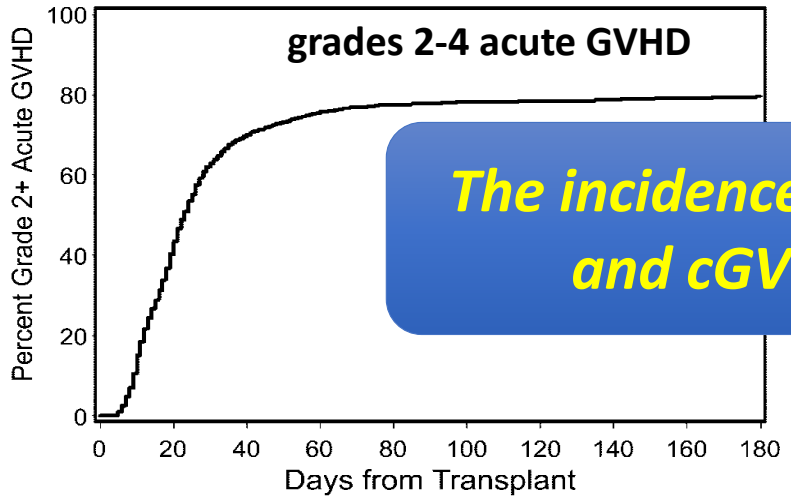
Progression into a sclerotic stage

Lichen

SS-like features



2941 patients



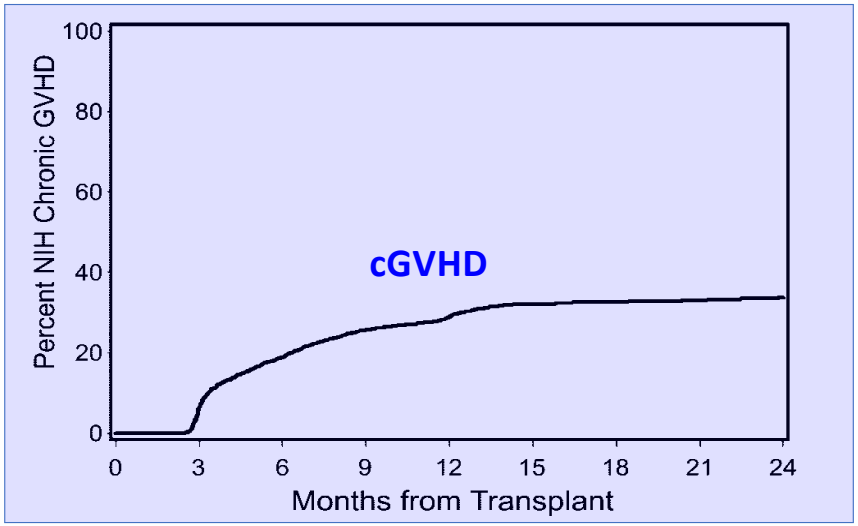
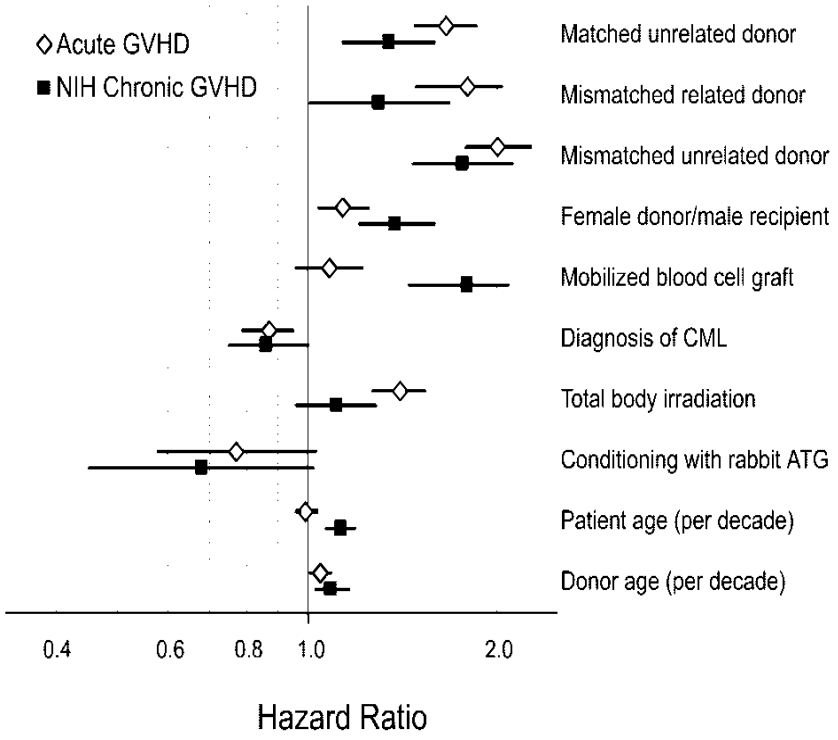


Figure 1. Cumulative incidence of grades 2-4 acute GVHD (top panel) and NI

Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria

Mary E. D. Flowers,[1,2] Yoshihiro Inamoto,[1] Paul A. Carpenter,[1,3] Stephanie J. Lee,[1,2] Hans-Peter Kiem,[1,2] Effie W. Petersdorf,[1,2] Shalini E. Pereira,[1] Richard A. Nash,[1,2] Marco Mielcarek,[1,2] Matthew L. Fero,[1,2] Edus H. Warren,[1,2] Jean E. Sanders,[1,3] Rainer F. Storb,[1,2] Frederick R. Appelbaum,[1,2] Barry E. Storer,[1,4] and Paul J. Martin[1,2]

The incidence and risk factors for acute and cGVHD are not the same!



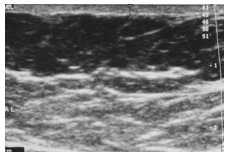
A 3-phase model of cGVHD in humans

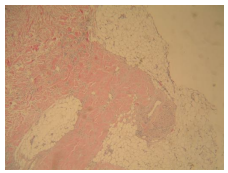
- *Phase I – acute inflammation and tissue injury*
- *Phase II – chronic inflammation and dysregulated immunity*
- *Phase III - aberrant tissue repair and fibrosis*


Ocular sicca


Oral ulcers

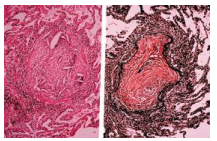

Nail dystrophy

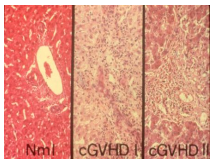

Skin sclerosis


Deep sclerosis

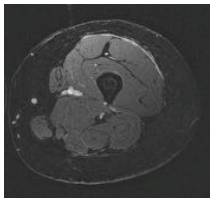
Third phase:

fibrotic damage and tissue remodelling


Bronchiolitis obliterans



Loss of bile ducts


Fasciitis


Skin ulcers

Although a number of animal models for cGVHD exist, none captures all of the manifestations

Specific biological findings in cGVHD

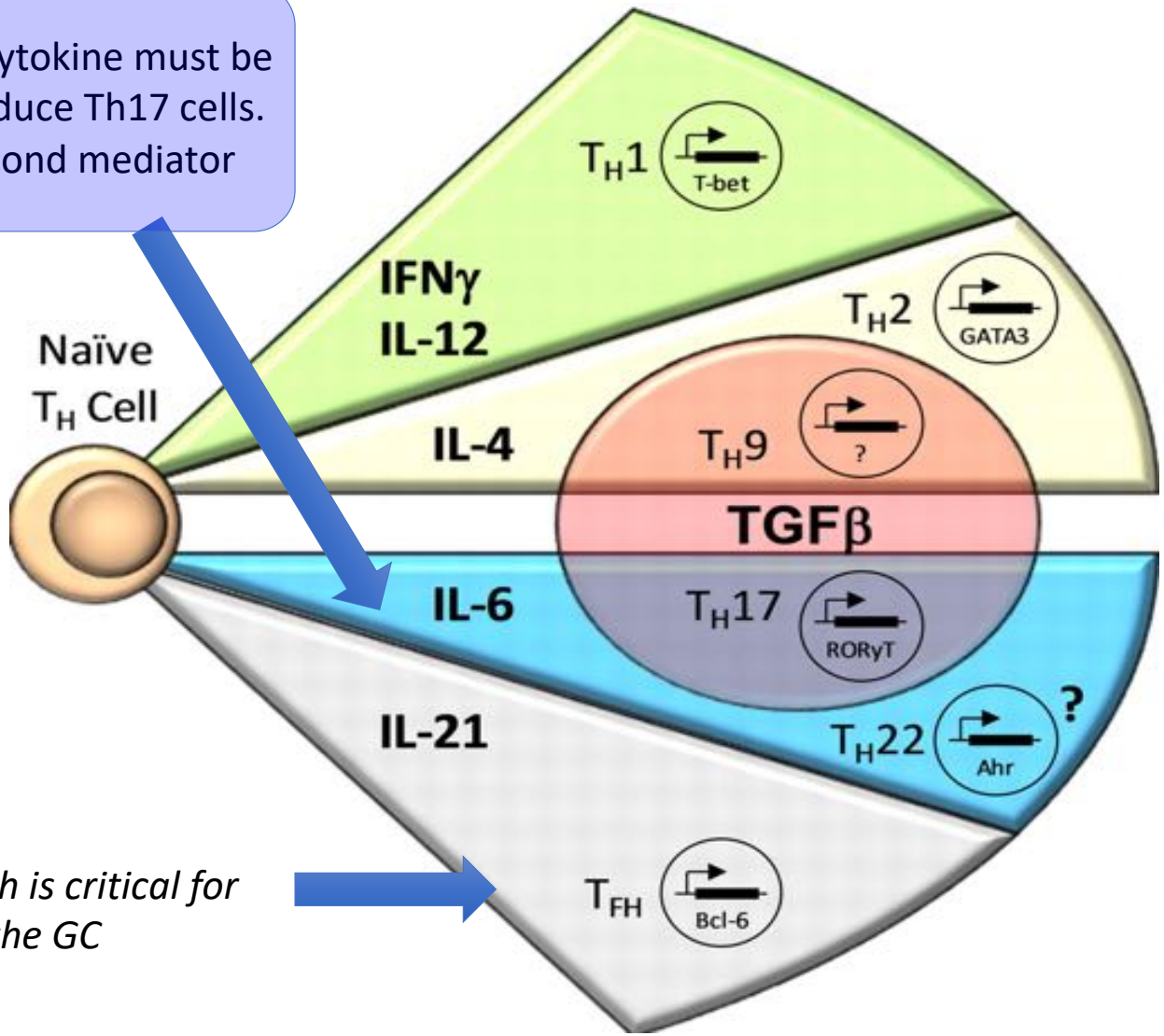
- ✓*Aberrant B cell activity* ➔*Auto/allo-antibodies*
- ✓**Increased TGF-beta concentration**
- ✓**.....macrophage polarization .....**
- ✓**Collagen deposition in target organs (tissue remodelling)**
- ✓*T-reg unbalance*

cGVHD requires both T and B cells:

experimental findings…

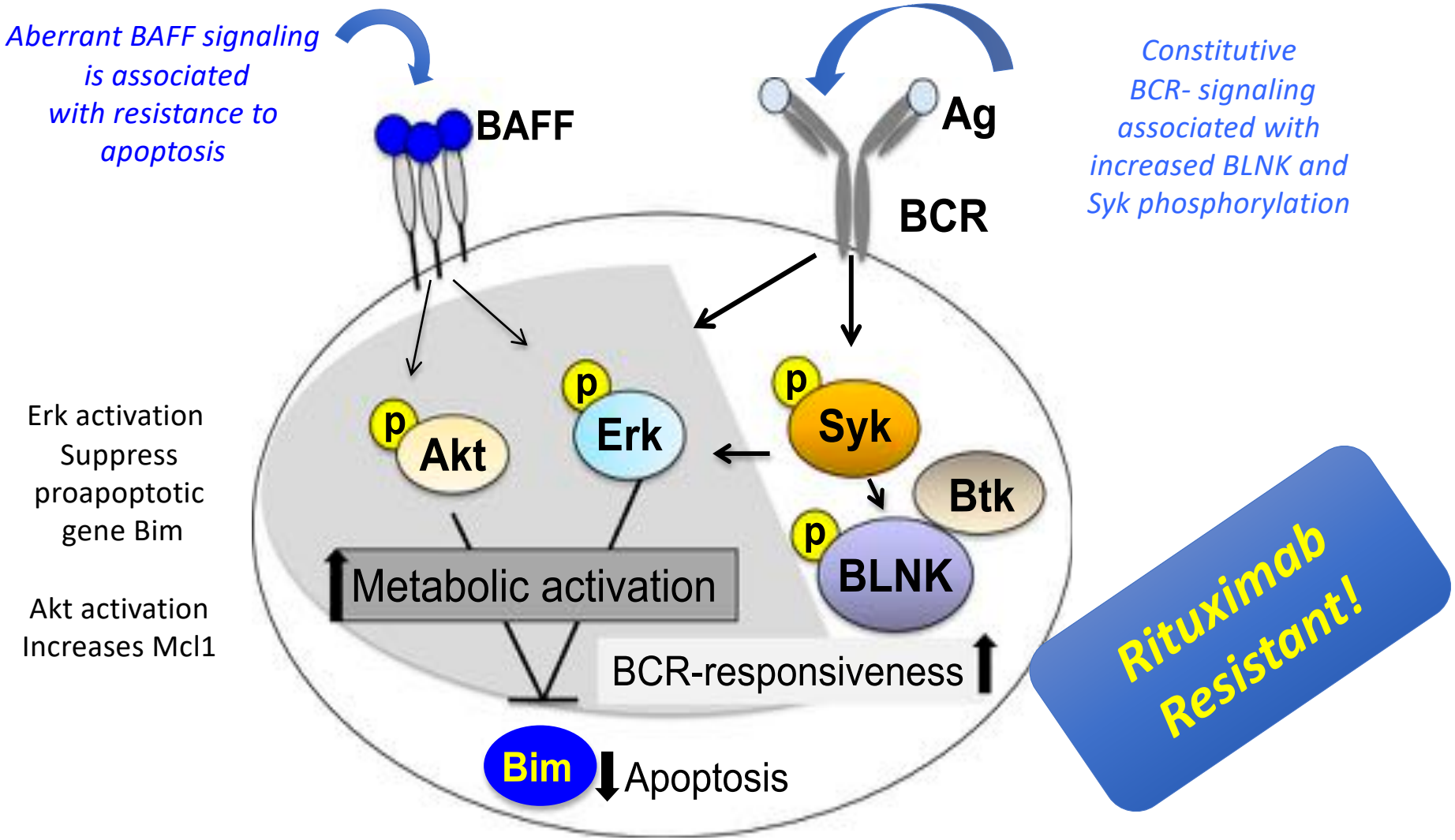
- thymectomy can prevent cGVHD pathology
- mice incapable of producing B cells do not develop cGVHD
- …Th17 cells and IL17 are the main actors of the tissue damage both in autoimmune diseases and in cGVHD….

At least one proinflammatory cytokine must be combined with TGF-beta to induce Th17 cells. In mice, IL-6 is the critical second mediator



Tfh cells express CXCR5, which is critical for their migration into the GC

Aberrant B-cell signaling in active cGVHD



Ibrutinib for chronic graft-versus-host disease after failure of prior therapy

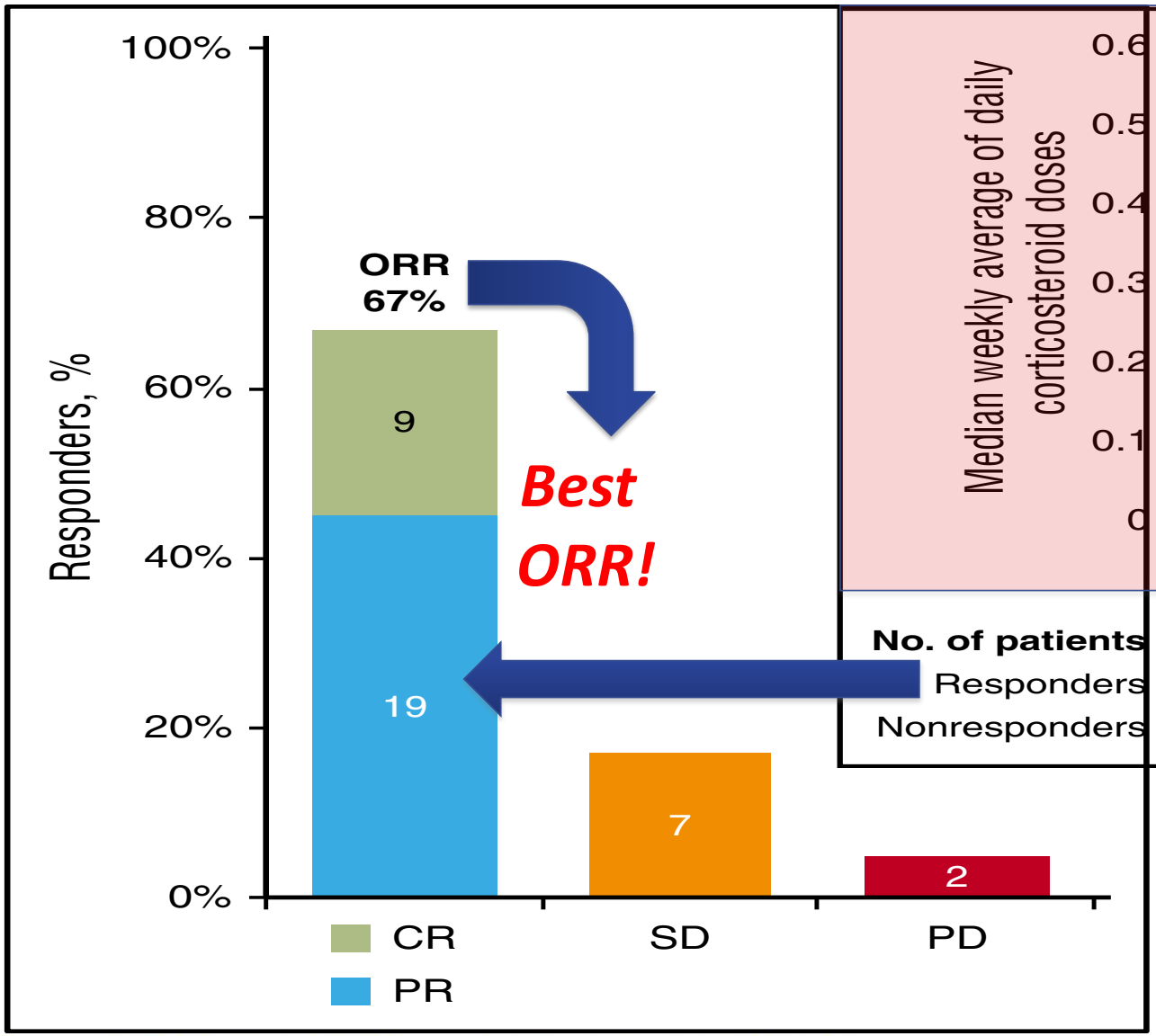
David Miklos,[1] Corey S. Cutler,[2] Mukta Arora,[3] Edmund K. Waller,[4] Madan Jagasia,[5] Iskra Pusic,[6] Mary E. Flowers,[7] Aaron C. Logan,[8] Ryotaro Nakamura,[9] Bruce R. Blazar,[3] Yunfeng Li,[10] Stephen Chang,[10] Indu Lal,[10] Jason Dubovsky,[10] Danelle F. James,[10] Lori Styles,[10] and Samantha Jaglowski[11]

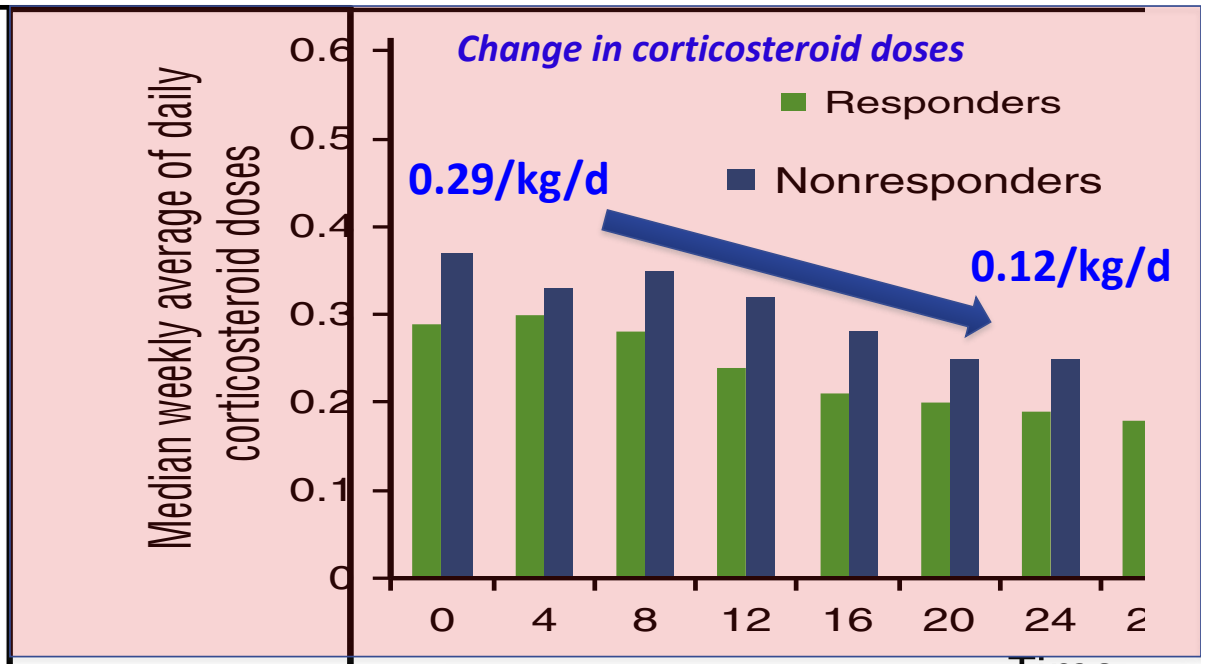
Primary endpoint: best ORR *(no time points!)*

Secondary EP: *sustained response at 20 wks; steroid sparing; PRO;* ***NO FFS***

- Response criteria based on the 2006 NIH cGVHD Consensus
- *Two changes based on the 2014 NIH update: a change in organ score from 0 to 1 not considered progression, and organ non evaluable for response when the organ response was confounded by a non-cGVHD–related factor.*
- response assessments conducted every 12 weeks.

Blood 2017

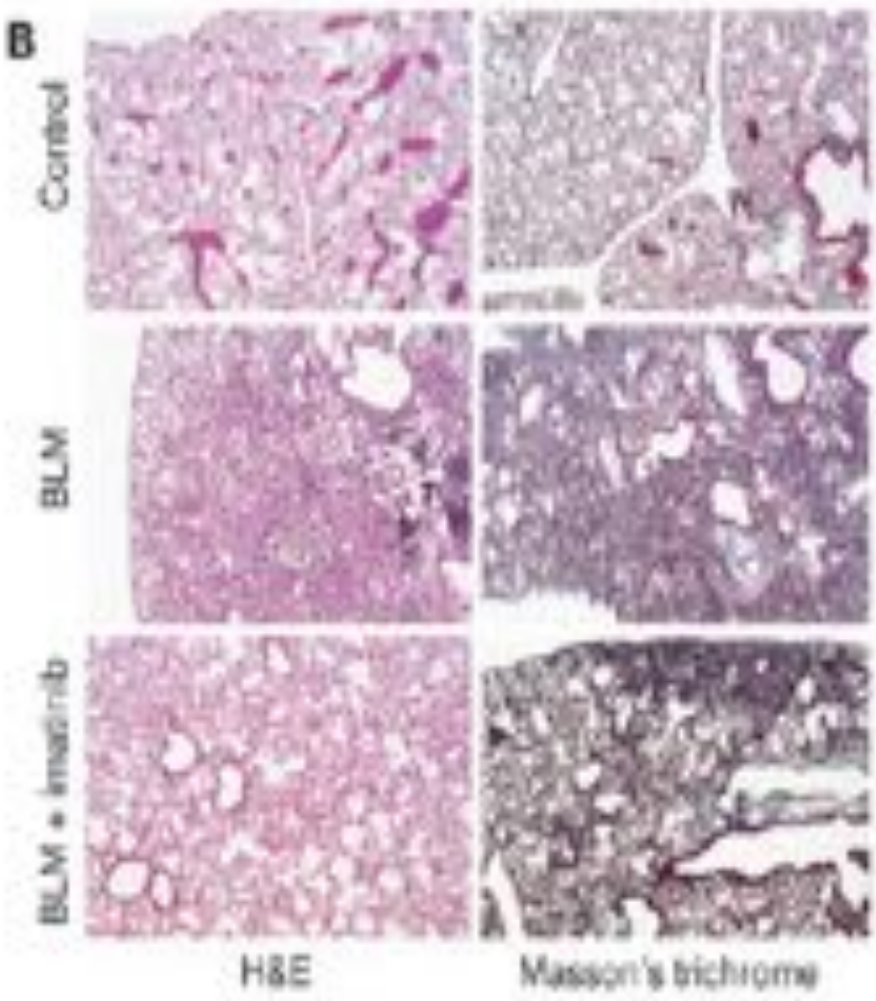




AEs led to treatment discontinuation in 14 patients (33%),

Among 71% of responders, 67% showed a sustained response for ǂ20 weeks

BLOOD, 23 NOVEMBER 2017 • VOLUME 130, NUMBER 21



Stimulatory autoantibodies to PDGF receptor in patients with extensive chronic graft-versus-host disease

Silvia Svegliati,[1] Attilio Olivieri,[2] Nadia Campelli,[1] Michele Luchetti,[1] Antonella Poloni,[2] Silvia Trappolini,[2] Gianluca Moroncini,[1] Andrea Bacigalupo,[3] Pietro Leoni,[2] Enrico V. Avvedimento,[4] and Armando Gabrielli[1]

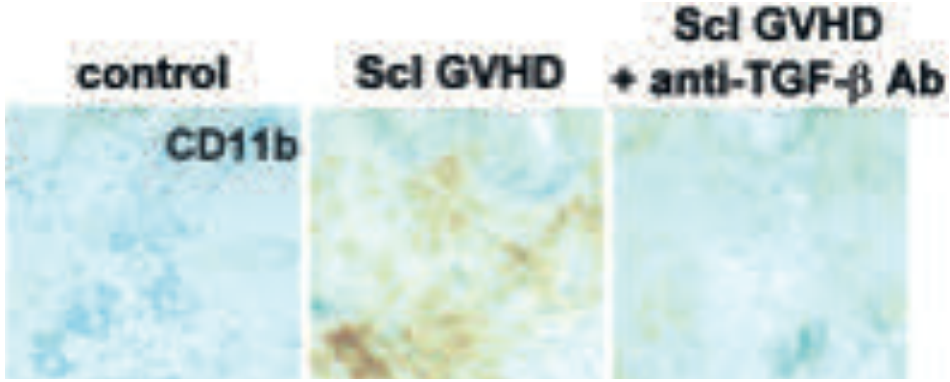
[1]Dipartimento di Scienze Mediche e Chirurgiche, Sezione di Clinica Medica, and [2]Sezione di Ematologia, Università Politecnica delle Marche, Ancona, Italy; [3]Divisione di Ematologia, Ospedale S. Martino, Genova, Italy; and [4]Dipartimento di Biologia e Patologia Molecolare e Cellulare, Centro di Endocrinologia ed Oncologia Sperimentale del CNR, Università Federico II, Naples, Italy

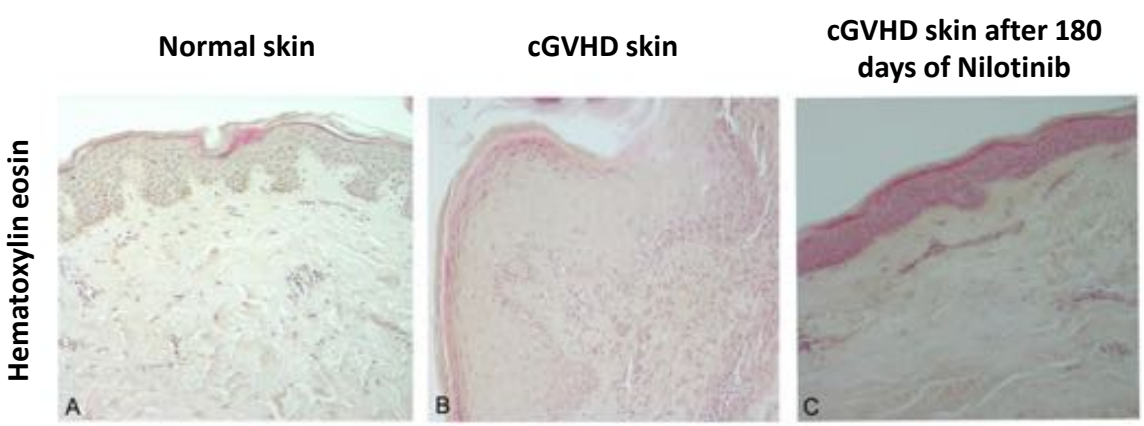
Regular Article

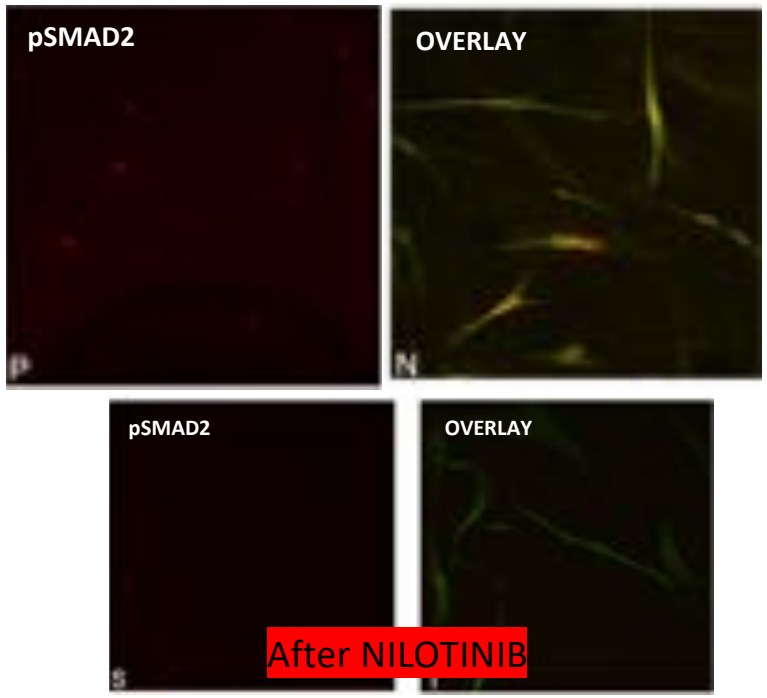
TRANSPLANTATION

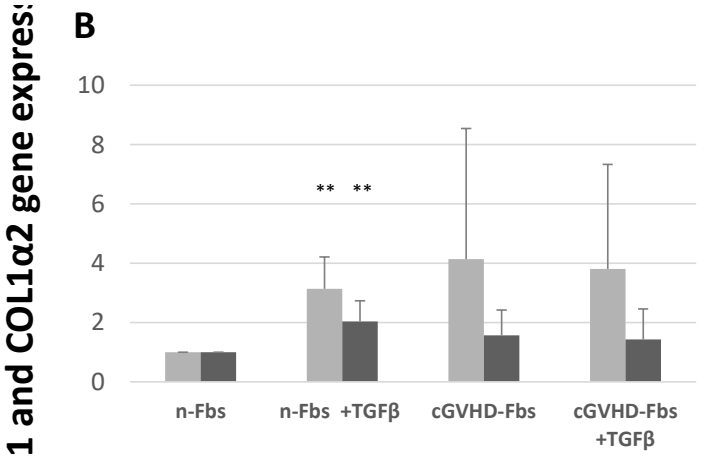
Long-term outcome and prospective validation of NIH response criteria in 39 patients receiving imatinib for steroid-refractory chronic GVHD

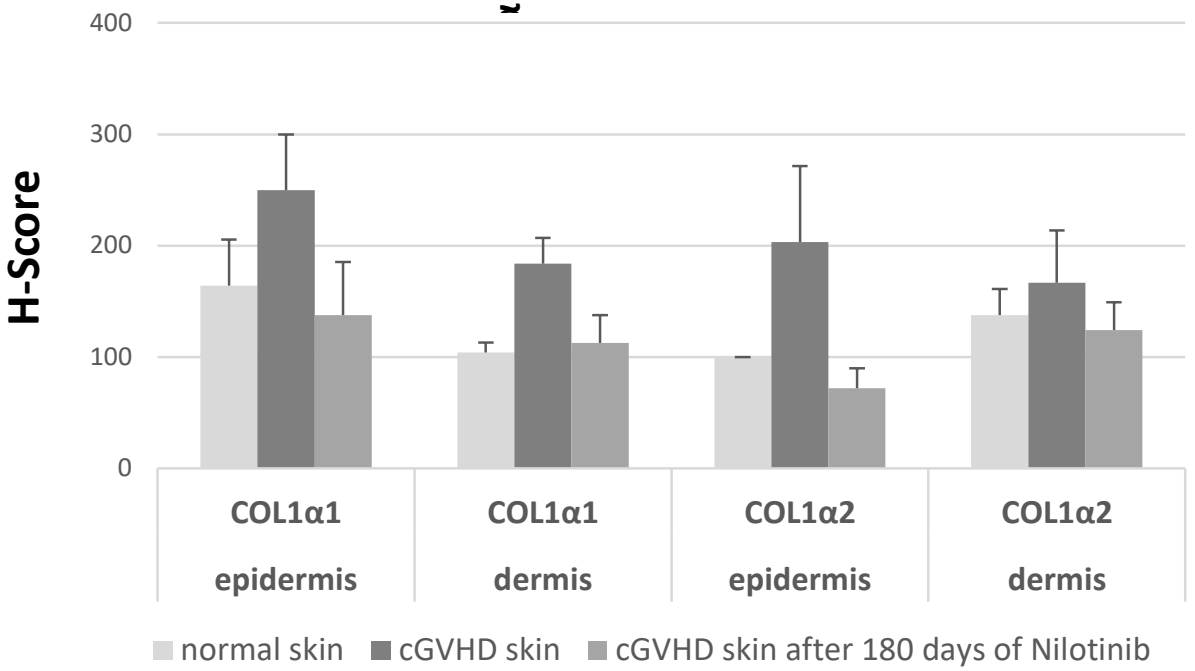
Attilio Olivieri,[1] Michele Cimminiello,[2] Paolo Corradini,[3] Nicola Mordini,[4] Roberta Fedele,[5] Carmine Selleri,[6] Francesco Onida,[7] Francesca Patriarca,[8] Enzo Pavone,[9] Silvia Svegliati,[10] Armando Gabrielli,[10] Paola Bresciani,[11] Roberta Nuccorini,[2] Sara Pascale,[2] Sabrina Coluzzi,[2] Fabrizio Pane,[12] Antonella Poloni,[1] Jacopo Olivieri,[13] Pietro Leoni,[1] and Andrea Bacigalupo[14]




Normal skin
cGVHD skin
cGVHD skin after 180 days of Nilotinib
Hematoxylin eosin
A
B
C


pSMAD2
OVERLAY
pSMAD2
OVERLAY
After NILOTINIB


B
10
8
6
4
2
0
** **
n-Fbs
n-Fbs +TGFβ
cGVHD-Fbs
cGVHD-Fbs +TGFβ


H-Score
400
300
200
100
0
COL1α1 epidermis
COL1α1 dermis
COL1α2 epidermis
COL1α2 dermis
normal skin
cGVHD skin
cGVHD skin after 180 days of Nilotinib

Rationale for targeting JAK signaling in cGVHD

- Inactivating APC (decreasing DC expression of major histocompatibility complex class II)
- Reducing alloreactive T-cell proliferation
- Expanding T-reg
- Decreasing inflammatory cytokine production
- *Inhibition of B cell activity in GC*

Heine A, Held SA, Daecke SN et al. The JAK-inhibitor ruxolitinib impairs dendritic cell function in vitro and in vivo. Blood 122(7), 1192–1202 (2013)

Stickel N, Hanke K, Marschner D et al. MicroRNA-146a reduces MHC-II expression via targeting JAK/STAT signaling in dendritic cells after stem cell transplantation. Leukemia 31(12), 2732–2741 (2017).

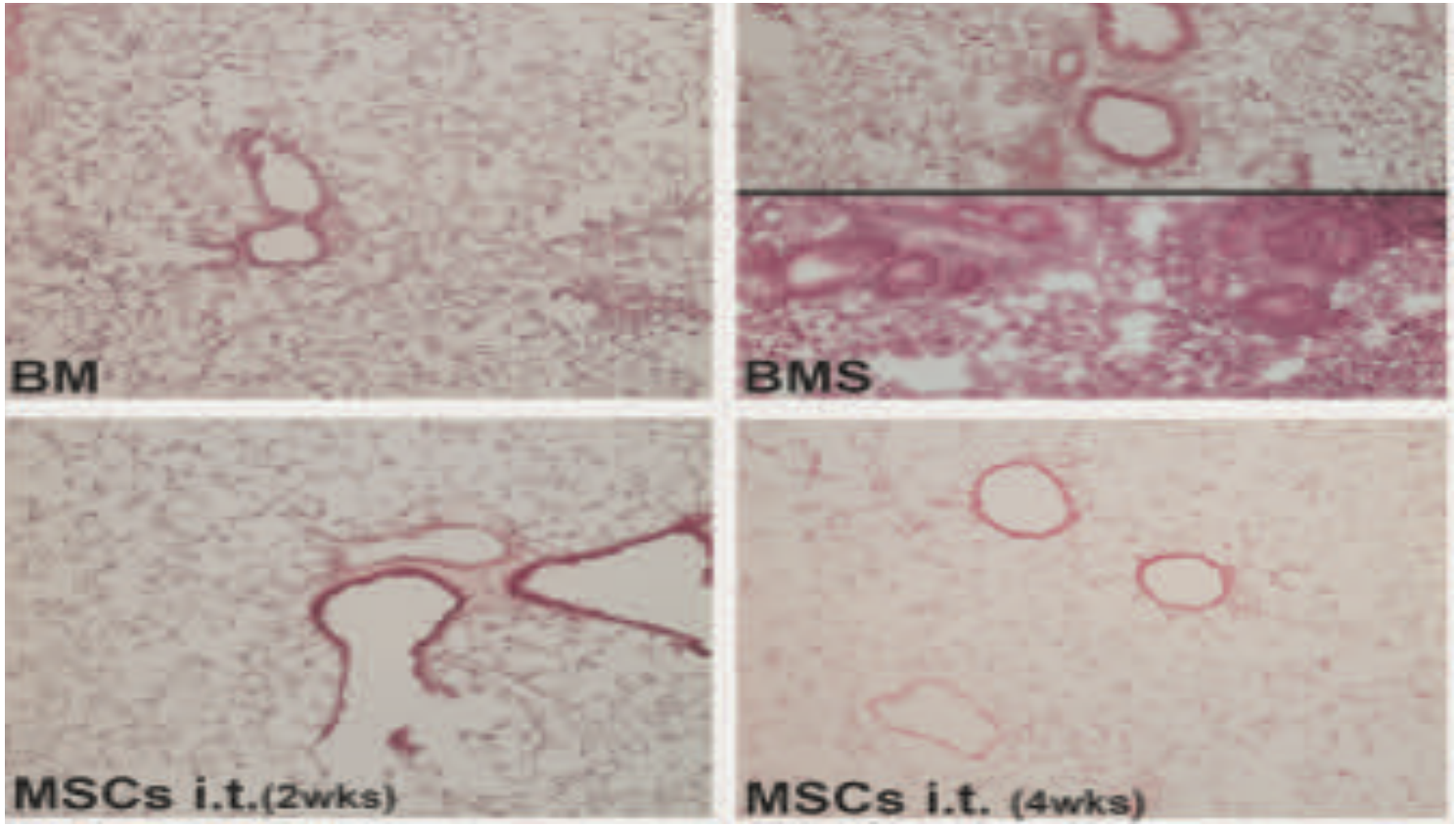
Spoerl S, Mathew NR, Bscheider M et al. Activity of therapeutic JAK 1/2 blockade in graft-versus-host disease. Blood 123(24), 3832–3842 (2014).

OPEN ACCESS Freely available online

PLOS ONE

MSC Therapy Attenuates Obliterative Bronchiolitis after Murine Bone Marrow Transplant

Kashif Raza[1¤a], Trevor Larsen[2☯], Nath Samaratunga[2☯], Andrew P. Price[3], Carolyn Meyer[3], Amy Matson[3¤b], Michael J. Ehrhardt[3], Samuel Fogas[3], Jakub Tolar[3], Marshall I. Hertz[1], Angela Panoskaltsis-Mortari[1,3*]



Mice were lethally conditioned and received allogeneic bone marrow without (BM)

or with

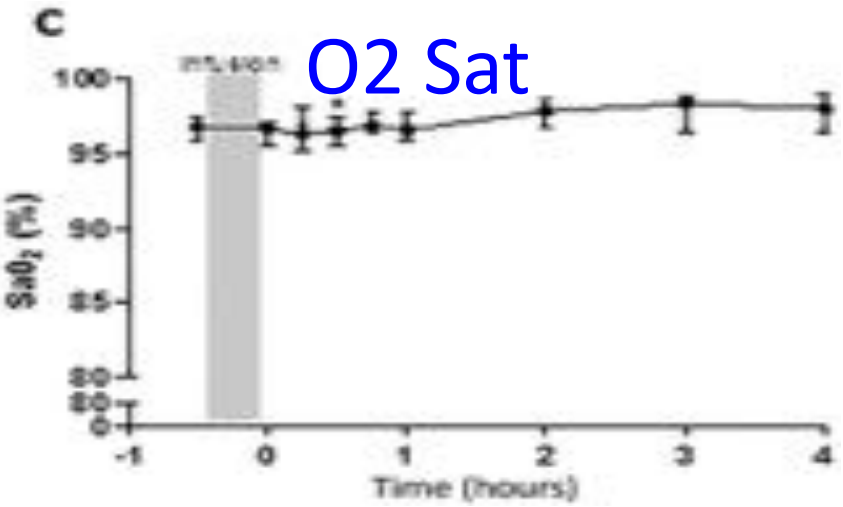
spleen cells (BMS), as a source of BO causing T-cells

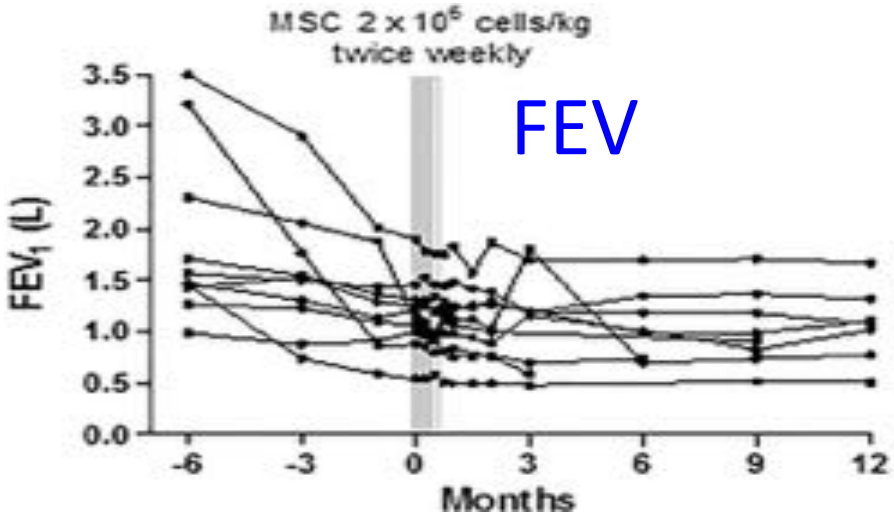
Mesenchymal Stromal Cell Therapy for Chronic Lung Allograft Dysfunction: Results of a First-in-Man Study

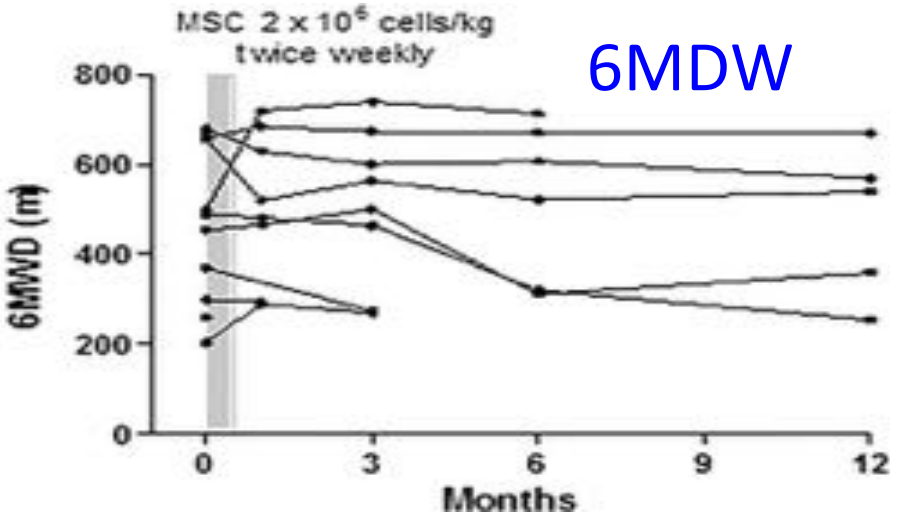
Daniel C. Chambers,[a,b] Debra Enever,[b] Sharon Lawrence,[c] Marian J. Sturm,[d,e] Richard Herrmann,[d,e] Stephanie Yerkovich,[a,b] Michael Musk,[c] Peter M.A. Hopkins[a,b]

Stem Cells Translational Medicine 2017;00:00–00

Effect of mesenchymal stromal cell on lung function in 10 pts

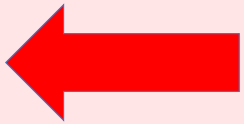






In vivo expanding Treg agents

- ***IL-2 low dose***
- ***Ruxolitinib***
- ***Bortezomib***
  - *hypomethylating agents**
  - *Rapamicin*
- *Cell therapy: MSC/Treg infusion*



Sparing Treg drugs

**Goodyear OC et al. Azacitidine augments expansion of regulatory T cells after allogeneic SCT in patients with AML. Blood. 2012*

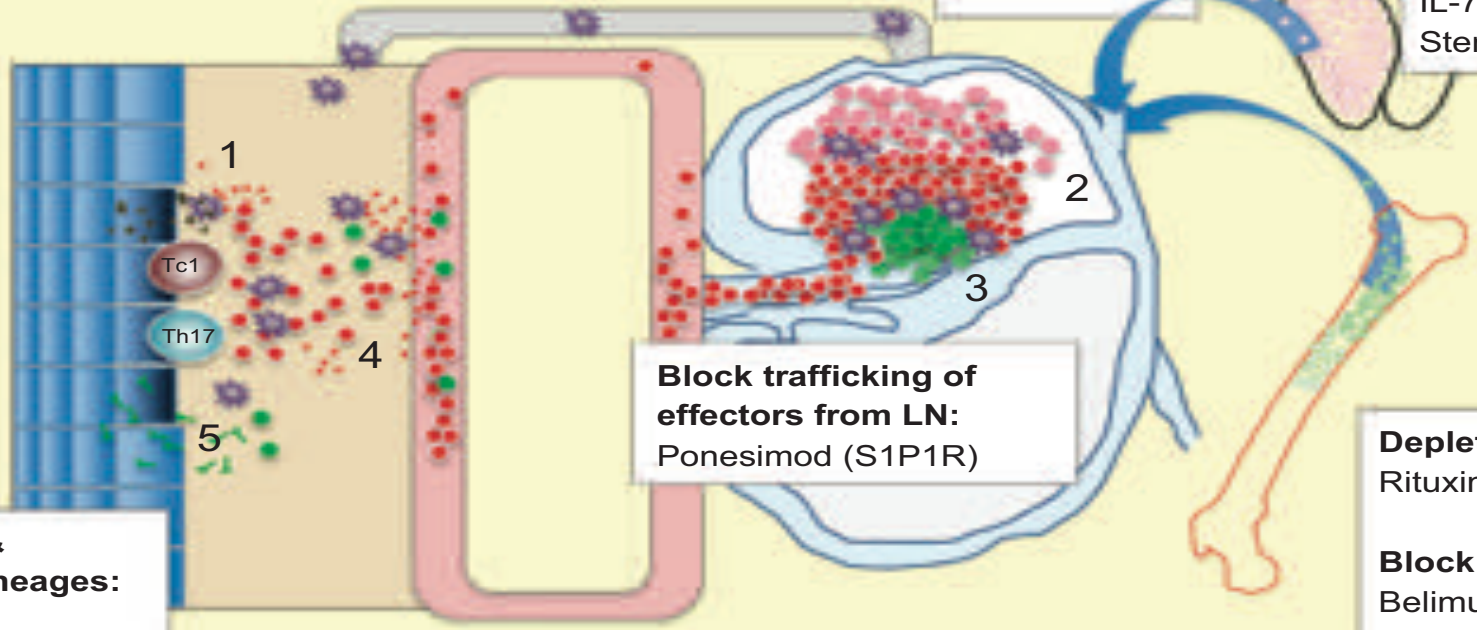
New targets in cGVHD

Non-lymphocyte targets:
Hedgehog inhibitors
Neutrophil elastase inhibitors

Expand Tregs:
IL-2

Expand thymopoiesis:
KGF
IGF
IL-7
Steroid blockade

➔*anti-TGF-β; PDGF agents (TKI, Pirfenidone, Nintenatinib)*



Block trafficking of effectors from LN:
Ponesimod (S1P1R)

Block T activation & cytokine-induced lineages:
JAK inhibitors
(Ruxolitinib, Baricitinib)
Proteasome inhibitors
CTLA4-Ig fusion protein

Deplete B cells:
Rituximab

Block B activation:
Belimumab (BAFF)
Fostamatinib (Syk)
Cerdulatinib (Syk)
Ibrutinib (BTK)

1. APC activated, move to LN
2. APC activate Th1, Th17, Tfh T cells
3. Tfh support Ab-producing B cells
4. T-& B-cells infiltrate tissue
5. Ab deposition and cytotoxic attack

How to evaluate the efficacy of a new TX in cGVHD?

End Point

- **Response according to NIH** *(physician reported measures/symptoms; patient reported symptoms; dynamic&global scales; functional activities);*

Pitfalls/advantages

- Confounding factors (topic TX; comorbidities/toxicities)
- Timing&duration of response
- Mixed responses&trivial worsening
- Ceiling effect

- ***FFS/PFS/OS*** → FFS: need of longer F-U; need to standardize failure criteria
  OS/PFS: lack of informations about toxicities or changes in IS TX

- ***Success of TX……*** → Need validation; absence of informations about death/toxicity


Thanks....