GITMO

Emopatie non maligne e trapianto:

NAPOLI

CHRONIC GVHD: TREATMENT AND LONG-TERM IMPACT

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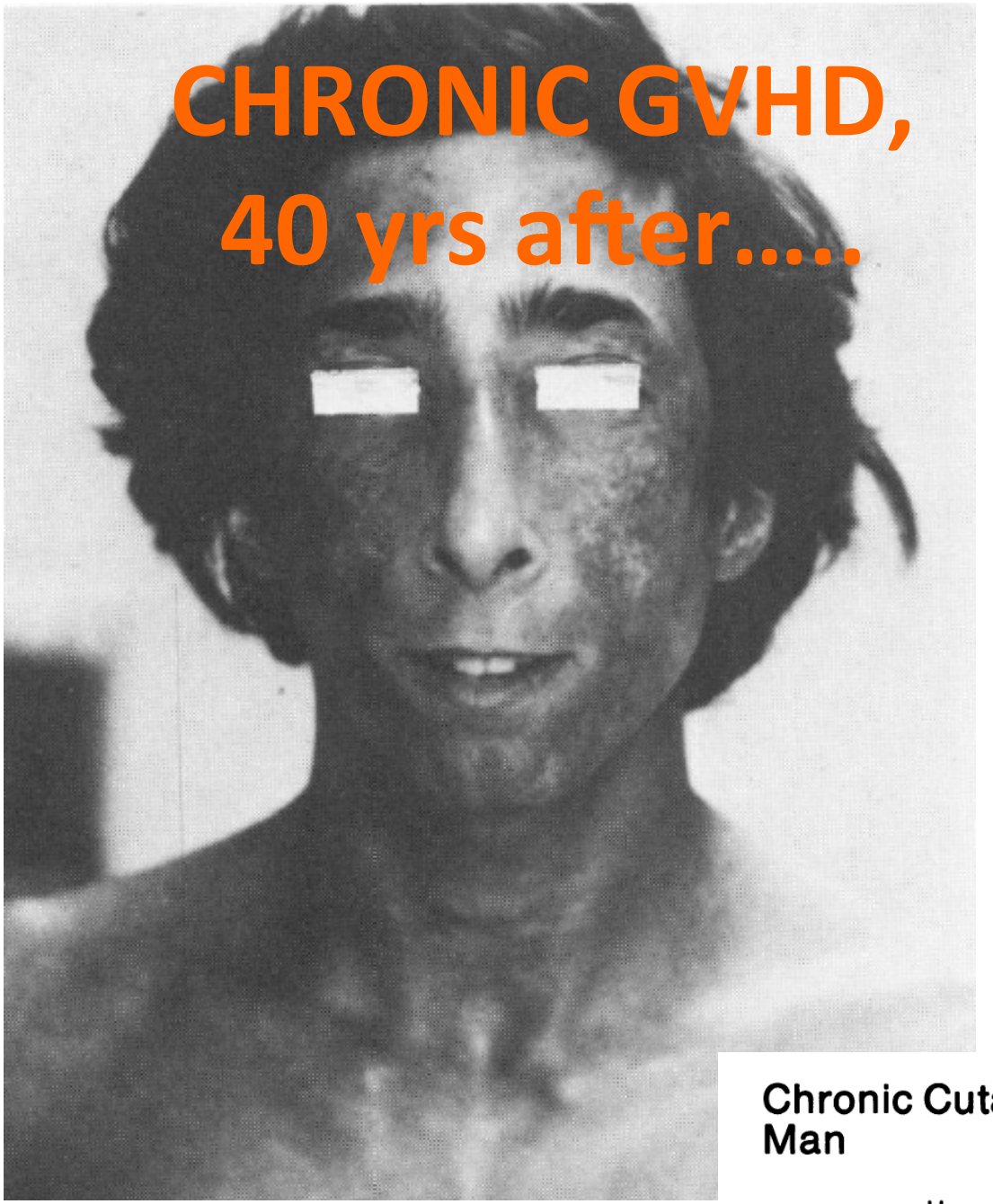
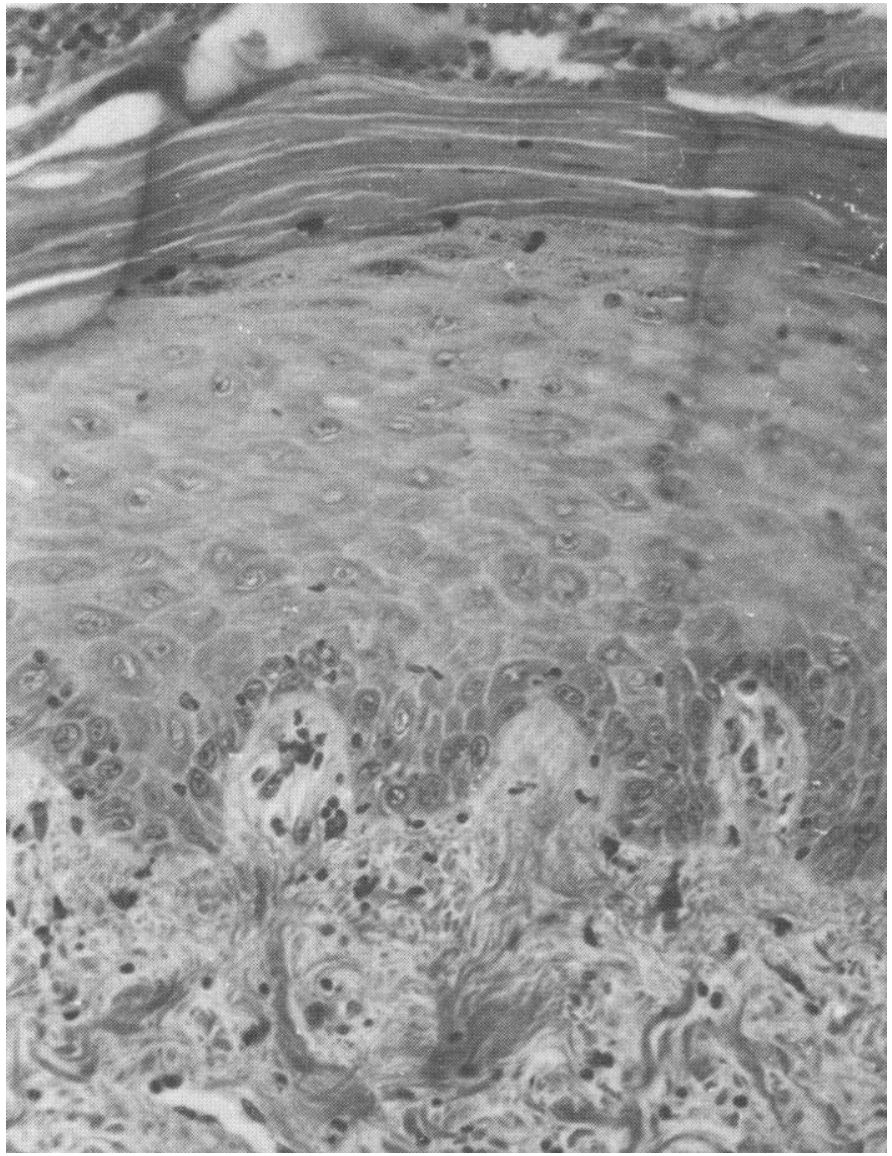
OSPEDALI RIUNITI

Università Politecnica delle Marche

CHRONIC GVHD, 40 yrs after…..





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

American Journal of Pathology

1978

GVH and transplant: relevance of the problem….

1978

nal disease. Sixty to 75% of these long-term survivors are leading normal lives and, in particular, have no evidence of graft-versus-host disease (GVHD). However, between 25% and 40% of long-term allogeneic survivors develop the polymorphous syndrome of chronic GVHD.[7,8] Manifestations of this collagen vascular-like disorder include debilitating skin disease, generalized sicca syndrome, severe oral and esophageal mucositis, malabsorption, pulmonary insufficiency, chronic liver disease, recurrent bacterial infections and generalized wasting.[7–14] Previous descriptions of chronic GVHD have shown little benefit of treatment.[10,11,14]

Categories of acute and chronic GVHD

Category	Time of symptoms after HCT or DLI	Presence of acute GVHD features	Presence of chronic GVHD features
Acute GVHD			
Classic acute	≤ 100 days	Yes	No
Persistent, recurrent or late-onset acute	> 100 days	Yes	No
Chronic GVHD			
Classic chronic	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

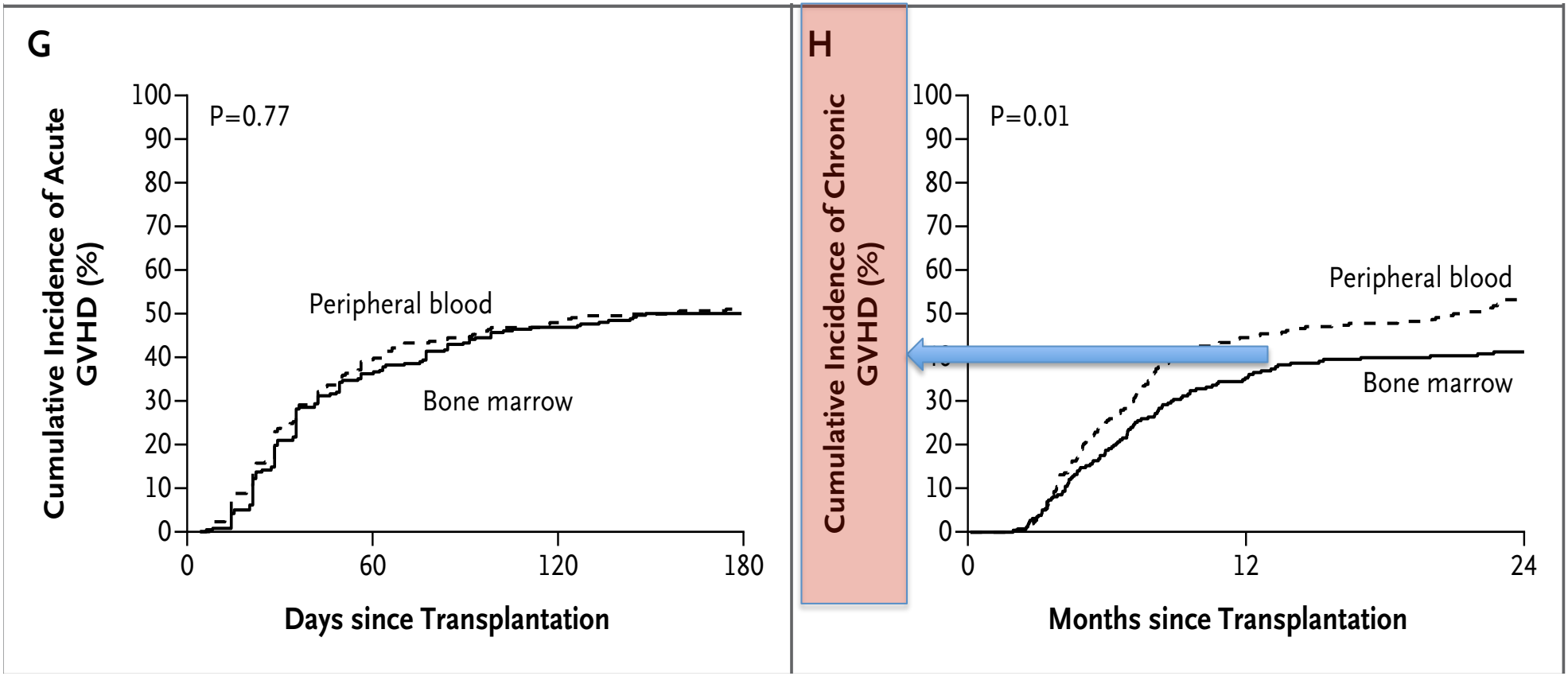
- *Currently, between 10% and 70% of patients develop chronic GVHD depending upon donor and transplant characteristics;*
- ***Multi-center and registry statistics show an aggregate cumulative incidence of 30% to 50%.***

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 18, 2012 VOL. 367 NO. 16

Peripheral-Blood Stem Cells versus Bone Marrow from Unrelated Donors

Claudio Anasetti, M.D., Brent R. Logan, Ph.D., Stephanie J. Lee, M.D., M.P.H., Edmund K. Waller, M.D., Ph.D.,



Typical biological findings in cGVHD

- ✓**Marked increase in collagen deposition in target organs**
- ✓**Lack of T lymphocyte infiltration**
- ✓**Increased B cell activity (BAFF)**
- ✓**Reduced number of T-reg***

*donor graft Treg inversely correlates with aGVHD, and cGVHD is associated with decreased numbers of circulating Tregs

Thymic and peripheral T-cell selection defects result in cGVHD

- In both preclinical(1) and clinical studies (2), *naive T-cell–depleted grafts have a significantly reduced cGVHD* incidence, while allowing transferred memory T cells to contribute to immune reconstitution and protective immunity.

1-Anderson BE et al. J Clin Invest. 2003

2-Teschner D et al Bone Marrow Transplant. 2014

Chronic GVHD and autoimmunity

- Animal models of cGVHD depend on the proliferation of self-reactive host B cells.
- Autoantibody production is commonly observed after transplantation (associated with incresed BAFF)
- Some of the clinical manifestations of cGVHD in humans are similar to those in scleroderma, lichen planus, and other autoimmune diseases

PATHOGENESIS of cGVHD (summary)

Hypothesis 1: cGVHD results from thymic damage, often caused by aGVHD, resulting in failure to delete auto/alloreactive T cells, recognizing antigens on donor or recipient cells.

Hypothesis 2: this hypothesis implicates a central role for fibrogenic cytokines, such as TGF-β and PDGF, especially in the pathogenesis of fibrotic damage in the course of cGVHD.

Hypothesis 3: this hypothesis implicates B cells (BAFF) and antibody-mediated mechanisms as pivotal actors.

Hypothesis 4: deficiency in the numbers or function of regulatory T cells (Treg) has been recently invoked.

These 4 hypotheses are not mutually exclusive.

How I treat

BLOOD, 1 MARCH 2001 • VOLUME 97, NUMBER 5

How I treat chronic graft-versus-host disease

Georgia B. Vogelsang

Primary TX of cGVHD

In newly diagnosed patients with extensive disease patients are treated with daily prednisone at 1 mg/kg per day and daily CsA at 10 mg/kg per day……

The addition of a CNI to steroids does not ⇧RR, but it allows for a reduction in steroid dosing.

The combination of other drugs with steroids was not beneficial in prospective randomized trials

How I Treat BLOOD, 22 JANUARY 2015 • VOLUME 125, NUMBER 4

How we treat chronic graft-versus-host disease

Mary E. D. Flowers and Paul J. Martin

Case summary

A 45-year-old man received growth factor–mobilized blood cells from an HLA-matched unrelated male donor after conditioning with 12 Gy total body irradiation and cyclophosphamide for treatment of acute myeloid leukemia with persistent disease. He received meth-

Treatment was started with prednisone at 1 mg/kg/day

No consensus has been reached regarding the optimal choice of agents for secondary treatment of cGVHD

The patient was enrolled in a randomized clinical trial comparing imatinib vs rituximab for SR GVHD

SR-cGVHD is an ORPHAN DISEASE

No FDA- or EMA-approved treatments

limited appeal for pharmaceutical industries

- CHRONIC disease
- UNPREDICTABLE course
- It affects FRAIL patients
- MULTISYSTEMIC disorder
- Management is highly SPECIALISTIC

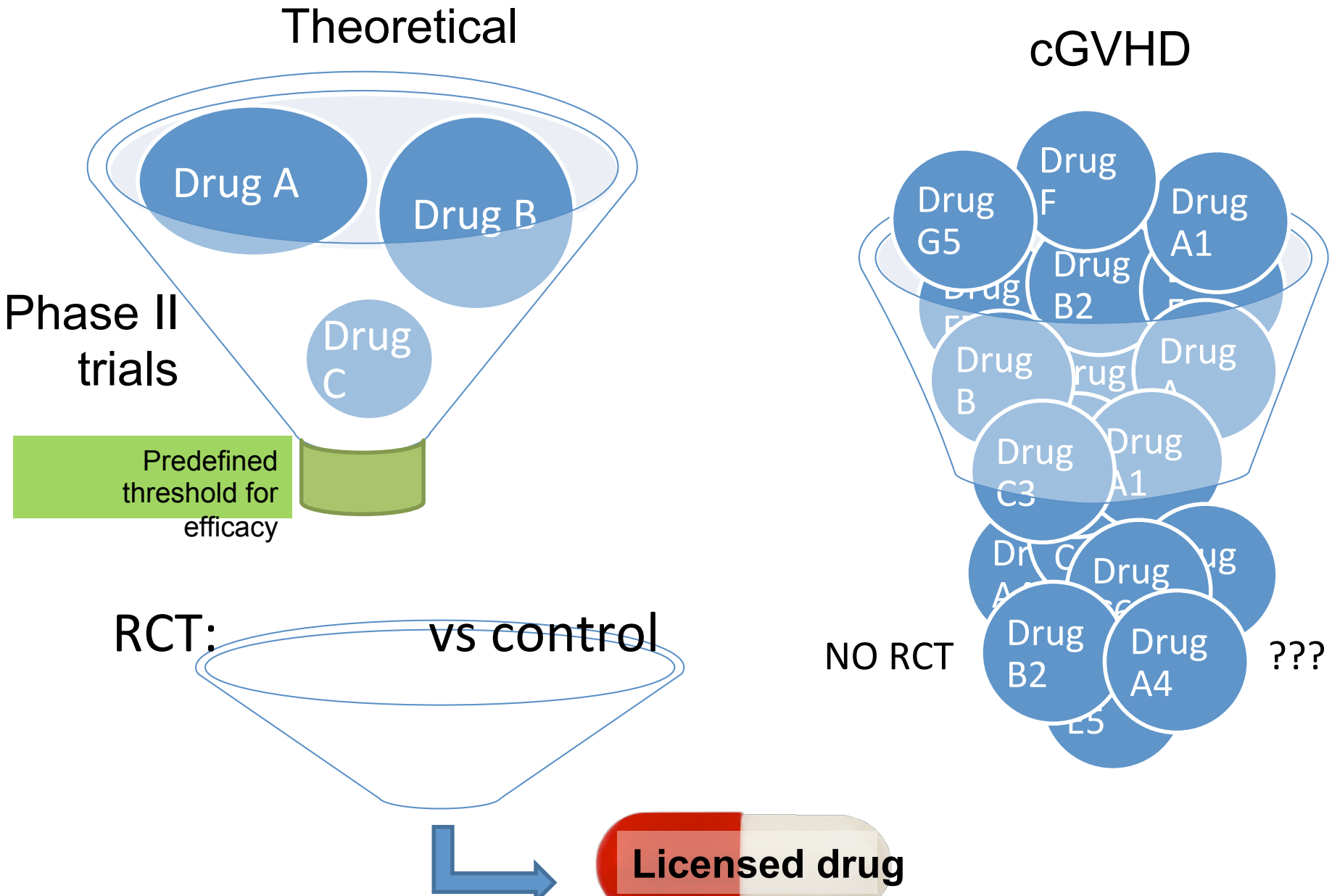
SR-cGVHD:
a neglected disease?

Not really:

- >50 interventions tested in the last 15 years in >150 studies
- Most of candidate drugs have shown promising efficacy in single-arm, open-label trials
- Only 1 RCT (phase II) with inconclusive results

  (Flowers, Blood 2008)
- 3 international groups issued guidelines in the last 5 years for management and TX of SR-cGVHD: **none of the interventions evaluated was discouraged as clearly ineffective**

Drug development process

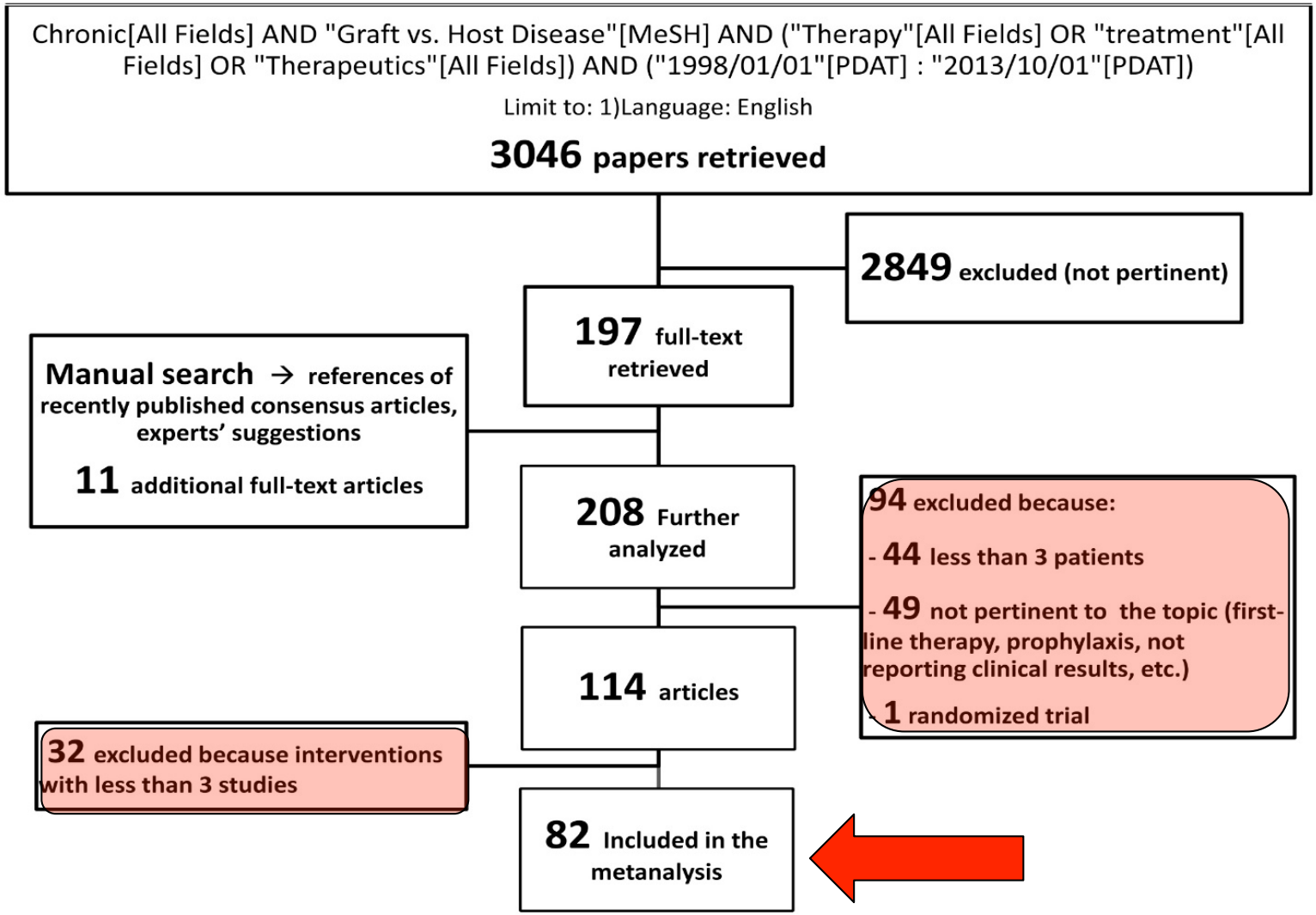


Consensus recommendations for improvement of unmet clinical needs—the example of chronic graft-versus-host disease: a systematic review and meta-analysis

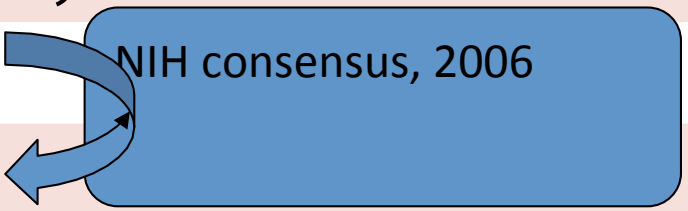
Lancet Haematol 2015

Published **Online**
June 17, 2015

Jacopo Olivieri, Lucia Manfredi, Laura Postacchini, Silvia Tedesco, Pietro Leoni, Armando Gabrielli, Alessandro Rambaldi, Andrea Bacigalupo, Attilio Olivieri, Giovanni Pomponio



	Data
Included in the meta-analysis	82 (100%)
Published before 2008	49 (60%)
Published after 2008	33 (40%)
Intervention	
Extracorporeal photopheresis	35 (45%); 24 (29%)
Rituximab	12 (15%); 5 (6%)
Mycophenolate mofetil	11 (13%); 8 (10%)
Imatinib	5 (6%); 0
Mesenchymal stem cells	4 (5%); 0
Methotrexate	4 (5%); 3 (4%)
Pentostatin	4 (5%); 2 (2%)
Sirolimus	3 (4%); 3 (4%)
Thalidomide	4 (5%); 4 (5%)



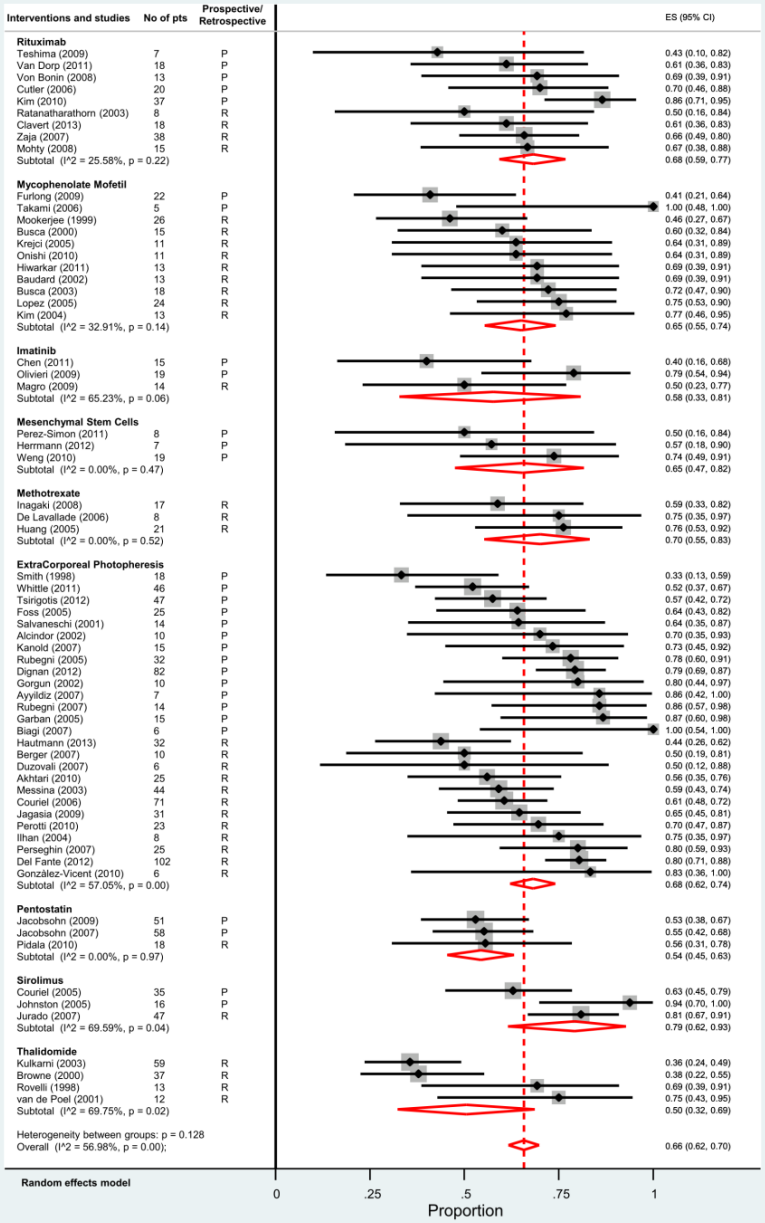
Meta-analysis for OVERALL RESPONSE

Lancet Haematol 2015

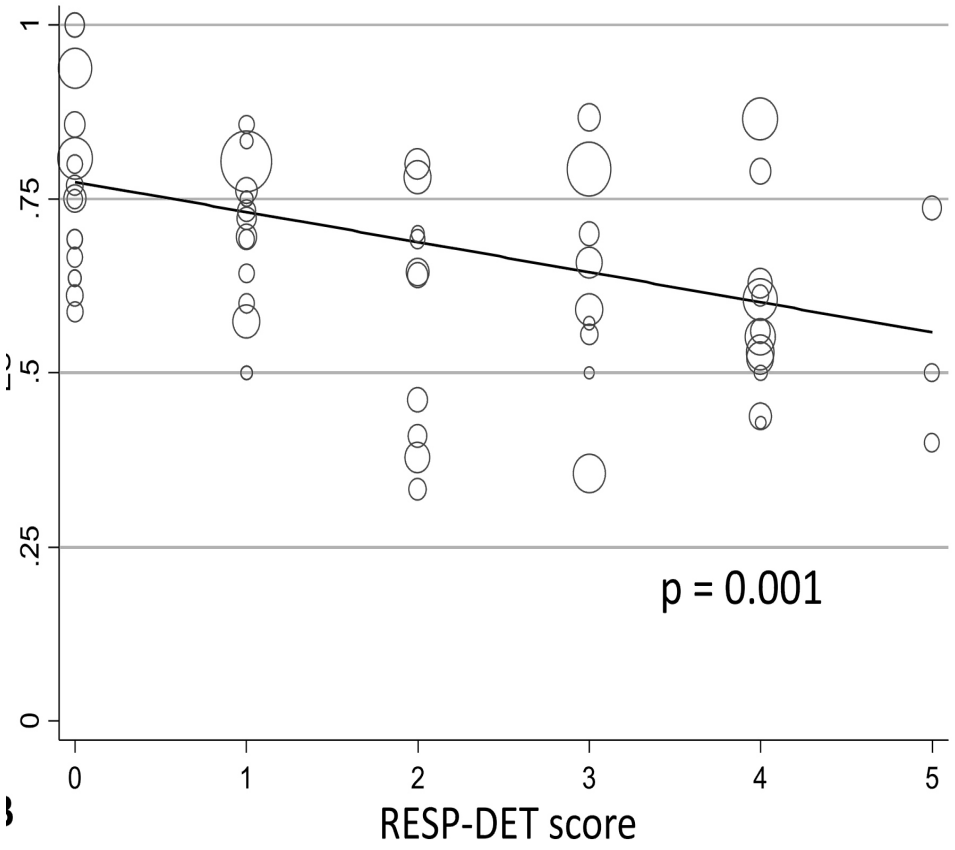
Published Online

June 17, 2015

- The pooled overall response rate was 0.66 (95%CI 0.62-0.70)
- For each of the interventions the pooled overall response was > 50%
- ***Not bad, isn't it?***
- ***Perhaps too good!***



Metaregression analyses correlated the 4 methodological scores* to Overall Response rate



1-SR-GVHD definition
2-Primary intervention
3-Concomitant TX
4-Response determination
** According to the NIH Cons 2006*

- **Better adherence to NIH recommendations in items defining correct response assessment was associated with a significantly lower ORR (p=0.001)**
- **Adherence to NIH recommendations in this subset was significantly higher after their publication.**

Lancet Haematology 2015

Real life efficacy of treatments for SR-cGVHD

- No change in cGVHD mortality since 1980 (FHRC data from Lee, Best Pract Res Hem 2010)

- The efficacy of second-line agents is limited, with response rates of 30% regardless of the agent that is chosen.

- Disagreement about identification of the truly ineffective drugs

- Survey of worldwide transplant centers (Duarte, BMT 2014): *the highest research priority* (for physicians) was the completion of clinical trials *to develop an effective treatment for SR-cGVHD*

A jammed drug development in SR-cGVHD??

ORR overestimation → ***Accumulation of promising interventions worthy to be further tested***

No standard Arm!!

↓

Difficulties of conducting RCTs

Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease

Daniel Wolff,[1] Michael Schleuning,[2] Stephanie von Harsdorf,[3] Ulrike Bacher,[4] Armin Gerbitz,[5] Michael Stadler,[6] Francis Ayuk,[4] Alexander Kiani,[7] Rainer Schwerdtfeger,[2] Georgia B. Vogelsang,[8] Guido Kobbe,[9] Martin Gramatzki,[10] Anita Lawitschka,[11] Mohamad Mohty,[12] Steven Z. Pavletic,[13] Hildegard Greinix,[14] Ernst Holler[1]

ASBMT American Society for Blood and Marrow Transplantation

Wolff et al
BBMT 2011

Therapy	Rec.	Evid.	Comment
Steroid	B	III-1	Serious side effects
Photopheresis	**C-1**	**II**	**Steroid-sparing, excellent safety profile**
mTOR – Inhib.	C-1	III-1	↑ TAM with CNI
Cyclosporin / FK506	C-1	III-1	Spare steroids
MMF	C-1	III-1	↑ viral infections, GI toxicity
Imatinib	C-2	III-1	Best in sclerodermoid GvHD and BO
Rituximab	C-2	II	Effective in autoAB mediated diseases
Total nodal Rx	C-2	III-2	Best in fasciitis and mucocutaneous cGvHD

Current treatments (2016) for SR-cGVHD in real life*

- ECP
- Rituximab
- Imatinib
- MMF, Rapamicin
- MTX, Pentostatin
- ***Ancillary TX***

"REAL-LIFE" REPORT ON THE MANAGEMENT OF CHRONIC GRAFT-VERSUS-HOST DISEASE IN ITALIAN TRANSPLANT CENTERS PART OF GRUPPO ITALIANO TRAPIANTO MIDOLLO OSSEO (GITMO)

***Giaccone L. et al on behalf of GITMO manuscript in preparation**

cGVHD: ancillary treatment

- Infection prophylaxis
- Symptom management
- Physical and occupational therapy
- Topic drugs (skin, eye, mouth, genitalia)

ECP in Refractory Chronic GvHD

blood 1998 92: 3098-3104

Successful Use of Extracorporeal Photochemotherapy in the Treatment of Severe Acute and Chronic Graft-Versus-Host Disease

Hildegard T. Greinix, Beatrix Volc-Platzer, Werner Rabitsch, Bernd Gmeinhart, Carlos Guevara-Pineda, Peter Kalhs, Jean Krutmann, Herbert Hönigsmann, Marina Ciovica and Robert M. Knobler

Extracorporeal photochemotherapy for the treatment of steroid-resistant chronic GVHD

Daniel R. Couriel, Chitra Hosing, Rima Saliba, Elizabeth J. Shpall, Paolo Anderlini, Beverly Rhodes, Veronica Smith, Issa Khouri, Sergio Giralt, Marcos de Lima, Yvonne Hsu, Shubhra Ghosh, Joyce Neumann, Borje Andersson, Muzzafar Qazilbash, Sharon Hymes, Stella Kim, Richard Champlin, and Michele Donato

BLOOD, 15 APRIL 2006 • VOLUME 107, NUMBER 8

Extracorporeal photochemotherapy for paediatric patients with graft-versus-host disease after haematopoietic stem cell transplantation

Chiara Messina,[1] Franco Locatelli,[2] Edoardo Lanino,[3] Cornelio Uderzo,[4] Graziella Zacchello,[5] Simone Cesaro,[1] Marta Pillon,[1] Cesare Perotti,[6] Claudia Del Fante,[6] Maura Faraci,[3] Lucia Rivabella,[7] Elisabetta Calore,[1] Pietro De Stefano,[2] Marco Zecca,[2] Giovanna Giorgiani,[2] Alessandra Brugiolo,[1] Adriana Balduzzi,[4] Giorgio Dini,[3] Luigi Zanesco[1] and Roberto Dall'Amico[5]* [1]*Paediatric Haematology and Oncology Unit, University of Padua,* [2]*Paediatric Haematology and Oncology Unit, IRCCS Policlinico San Matteo,* [3]*Paediatric Haematology and Oncology Unit, IRCCS G. Gaslini, Genova,* [4]*Department of Paediatrics, Nuovo Ospedale S. Gerardo, Monza,* [5]*Department of Paediatrics, Nephrology Unit, University of Padua, Thiene,* [6]*Immunohaematology and Transfusion Unit, IRCCS Policlinico San Matteo, Pavia, and* [7]*Immunohaematology and Transfusion Unit, IRCCS G. Gaslini, Genova, Italy*

British Journal of Haematology, 2003, **122**, 118–127

- **High response rates**
  - Skin 40-90%, liver 0-80%, mucosal 20-90%
- **Excellent safety profile**
- The most frequently applied **salvage therapy** in adults and children with steroid-refractory cGvHD
- **ECP can be associated** with other TX

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. Greinix[14]

BLOOD, 1 OCTOBER 2008 • VOLUME 112, NUMBER 7

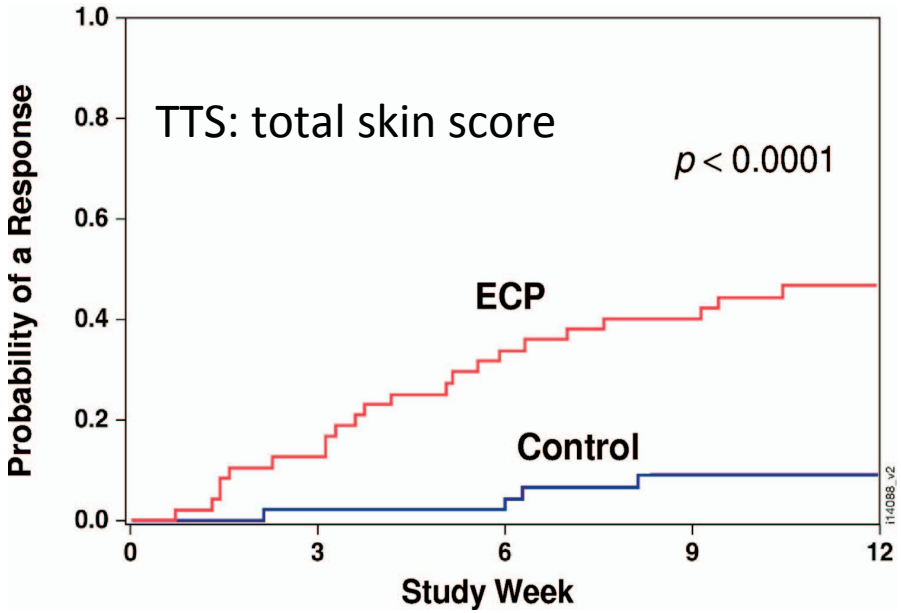


Figure 4. Cumulative incidence of complete or partial skin response.

Randomized Study

Median improvement

in TSS at week 12:

14.5% for the ECP arm VS 8.5% for the control arm.

Proportion of pts who had at least a 50% reduction in steroid dose and at least a 25% decrease from

baseline in TSS at week 12: 8.3% in ECP arm Vs 0% in the control arm.

95 patients randomized to ECP+ standard therapy or standard therapy alone

- **No benefit for OS/PFS**

The mechanism of action of ECP in the treatment of cGVHD is not fully understood

ECP exerts an immunomodulatory activity, by inducing 3 main events:

1- PUVA-related massive apoptosis of T lymphocytes and differentiation of monocytes into active dendritic APCs.

2- ECP inhibits pro-inflammatory cytokine production and increases anti-inflammatory cytokine production.

3-ECP effectively reduces the stimulation of effector T cells, and induces donor-derived Tregs,

Extracorporeal Photochemotherapy Is Accompanied by Increasing Levels of Circulating cD4+CD25+GITR+Foxp3+CD62L+ Functional Regulatory T-Cells in Patients With Graft-Versus-Host Disease

Ettore Biagi,[1,4] Iolanda Di Biaso,[1] Veronica Leoni,[1] Giuseppe Gaipa,[1] Vincenzo Rossi,[1] Cristina Bugarin,[1] Giuliano Renoldi,[1] Matteo Parma,[2] Adriana Balduzzi,[1] Paolo Perseghin,[3] and Andrea Biondi[1]

Targeting B cells

- ***prevention*** of aberrant B-cell development by administration of CD20 monoclonal antibody

  RTX is more effective when used as a preventative* but not as treatment strategy

- *One concern over the routine use of B-cell depletion in the post- HSCT setting is the persistent and profound hypogammaglobulinemia*

*Cutler C, Kim HT, Bindra B, et al. Rituximab prophylaxis prevents corticosteroid-requiring chronic GVHD after allogeneic peripheral blood stem cell transplantation: results of a phase 2 trial. Blood. 2013;122(8):1510-1517.

Table 2. Clinical Studies Evaluating the Efficacy of Rituximab in the Setting of Steroid-Refractory cGVHD

Author, Year	Study Design	Number of Patients Enrolled	Median Age, Years (Range)	ORR, %	TTR Days, Median	Morbidity, %	Mortality, % (n/N)	Dose (Median Number of Doses) (Cycles)
				By Organ (Responders/Total)				
Von Bonin et al., 2008 [18]	Retrospective	13	60 (40-67)	ORR, 69% Skin, 56% (5/9) Eyes, 0% (0/4) Liver, 0% (0/3) Gut, 0% (0/2) Lungs, 0% (0/2) Oral mucosa, 50% (4/8) Muscles, 75% (3/4)	NR	Infectious complications, 2	8% (1/13)	50 mg/m^2 (weekly intervals for 3 weeks) (3)*
Mohty et al., 2008 [21]	Retrospective	15	50 (20-67)	ORR, 66% Skin, 69% Eyes, NR Liver, 66% Gut, 20% Lungs, 0% (0/2) Oral mucosa, NA	NR	Negligible	33% (5/15)	375 mg/m^2 (weekly intervals for 4 weeks) (1)
Zaja et al., 2007 [24]	Retrospective	38	48 (22-61)	ORR, 65% Skin, 63% Eyes, 43% Liver, 25% Gut, 75% Lungs, 38% Oral mucosa, 30% Musculoskeletal, 80%	57 days 138 days 49 days NR 60 days 46 days 78 days	Infusion reaction, 11% Pneumonia, 8% Renal failure, 3% Central nervous system, 3% Sepsis, 3%	21% (8/38)	375 mg/m^2(weekly intervals for 4 weeks) (1)
Okamoto et al., 2006 [22]	Prospective (noncontrolled)	3	35 (33-42)	ORR, NE Skin, 100% Eyes, 0% (0/3) Liver, 0% (0/2) Gut, NR Lungs, 0% (0/1) Oral mucosa, 0% (0/2)	60-90 days	Pneumonia, 33% Sepsis, 33% Herpes zoster, 33%	33% (1/3)	375 mg/m^2 (weekly intervals for 4 weeks) (1)
Cutler et al., 2006 [20]	Prospective (noncontrolled)	28‡	42 (21-62)	ORR, 68% Skin, (§/17) Eyes, 0% (0/8) Liver, NR (NR/1) Gut, NA Lungs, NA Oral mucosa, 0% (0/7)	NR	Infant diarrhea, 14% Viral conjunctivitis, 5% Hepatitis B reactivation, 5% Septic arthritis, 5% GI hemorrhage, 5% Nephrolithiasis, 5% Infusion reaction, 5%	11% (3/28¶)	375 mg/m^2 (weekly intervals for 4 weeks) (1)

B-cell depletion with Rituximab is often followed by a cGVD relapse

- The Stanford group treated 35 subjects with cGVHD using RTX plus steroids, with an ORR of 77% at 6 months and a CRR of 34%.
- However, by 24 months, the majority of subjects required additional therapy or succumbed to chronic GVHD.
- Pidala used ofatumumab plus steroids, in 12 subjects. Treatment was well tolerated, but, only 4/12 patients had CR after 6 months of therapy.

The limited success of RTX may in part be due to the existence of memory-type plasma cells that survive depleting strategies

Platelet-derived growth factor (PDGF)

- PDGF is a mitogen for fibroblasts that serve in wound healing.
- PDGF overexpression has been linked to different types of fibrotic disorders.
- PDGF-R stimulation can induce fibroblast to exagerated collagen production
- *Stimulating anti-PDGF-R Abs have been found in pts with SS and may have pathogenetic role*

Blood 2007

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]

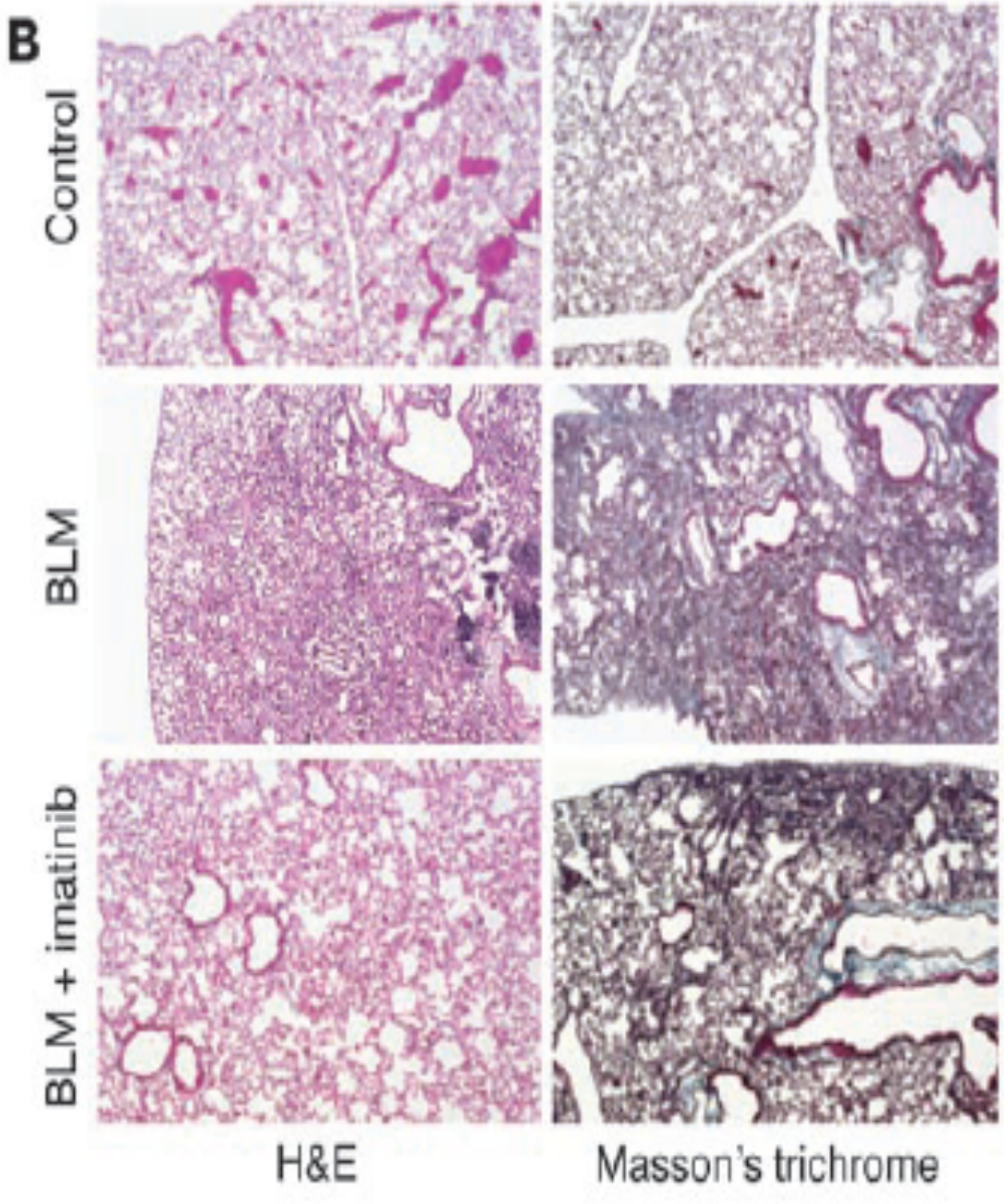
[1]Dipartimento di Scienze Mediche e Chirurgiche, Sezione di Clinica Medica, and [2]Sezione di Ematologia, Università Politecnica delle Marche, Ancona, Italy; [3]Divisione di Ematologia, Ospedale S. Martino, Genova, Italy; and [4]Dipartimento di Biologia e Patologia Molecolare e Cellulare, Centro di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

- like Scleroderma, patients with cGVHD have stimulatory antibodies against PDGF-R.
- These Abs were present in all (22) patients with cGVHD and never in transplanted patients (17) without cGVHD.
- These Abs induce type I collagen and ROS production, converting the normal fibroblasts phenotype to SS-like fibroblast.
- … these Abs and the PDGF-R pathway may have a role in the fibrotic damage of cGVHD….

Another profibrotic cytokine in SSc: TGF-b

TGF-b is up-regulated in the skin of SSc patients and strongly stimulates matrix synthesis by dermal fibroblasts.

Blockade of TGF-b signaling has been shown to reduce the development of fibrosis in experimental models.



mouse model of bleomycin-induced pulmonary fibrosis

Imatinib:
a dual inhibitor of TGF-b and PDGF-R pathways,
can prevent skin and lung fibrosis in experimental models

Regular Article

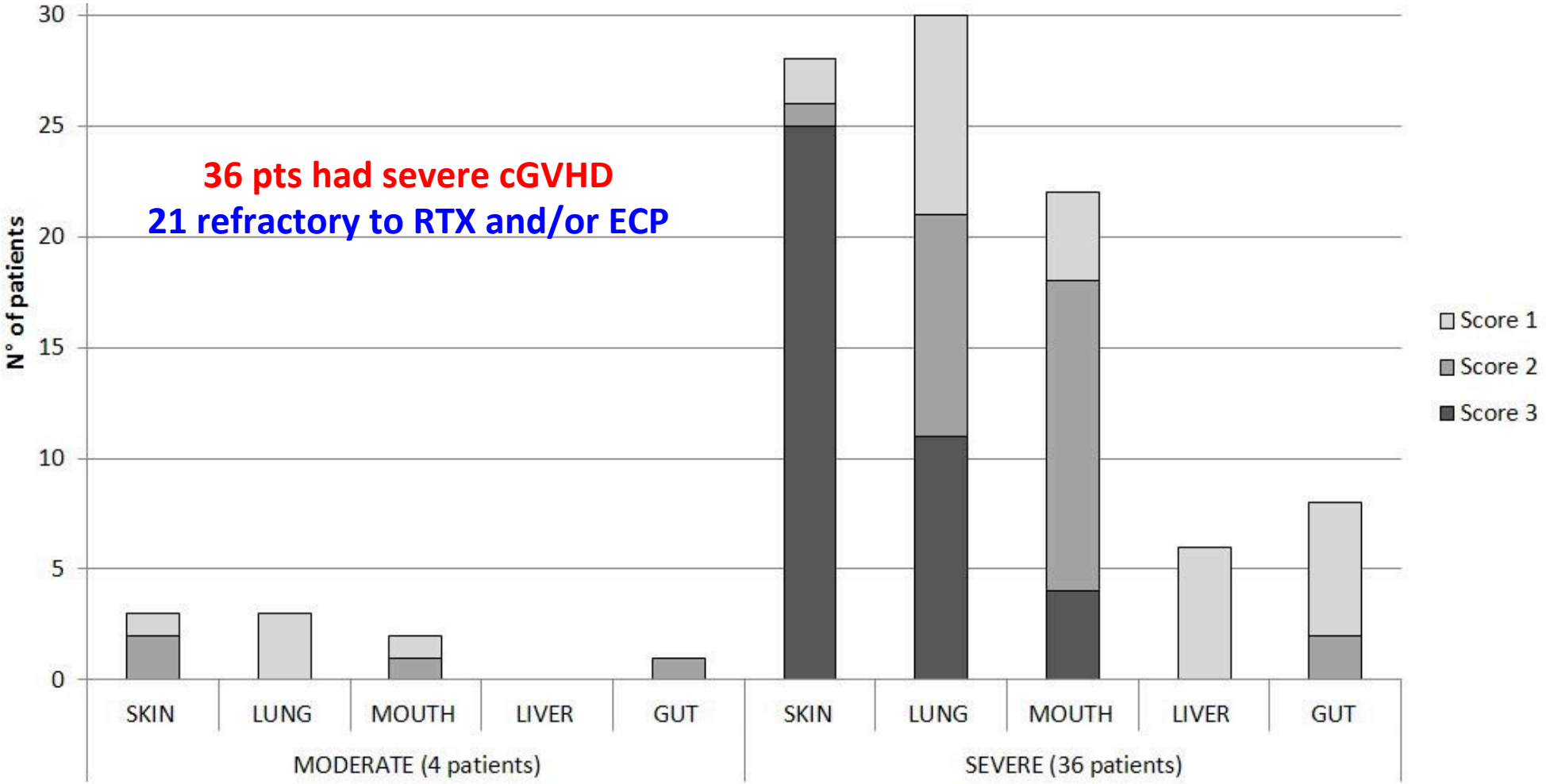
BLOOD, 12 DECEMBER 2013 • VOLUME 122, NUMBER 25

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]

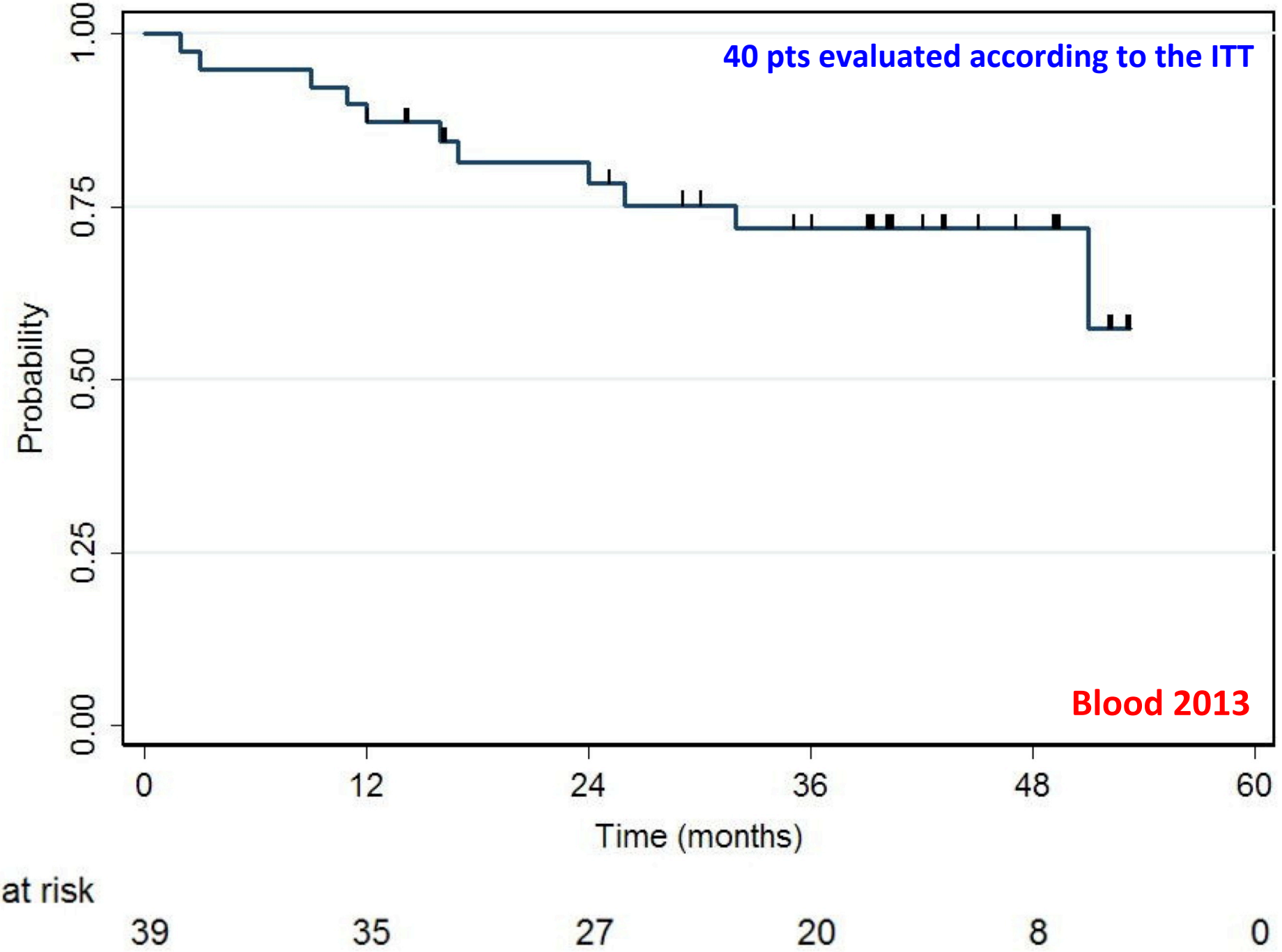
Fig.1



A

Overall Survival

Fig.2



TKI and immune system

•CML patients treated with imatinib develop hypogammaglobulinemia. Santachiara et al Haematologica 2008

•Patients with CML and concomitant autoimmune pathology improved their clinical autoimmune symptoms during Imatinib treatment. Miyachi K, Clin Rheumatol. 2003

- **TKs play a prominent role in TCR signal transduction** and thus it is conceivable that imatinib may interfere with this process.

Imatinib inhibits T-cell receptor–mediated T-cell proliferation and activation in a dose-dependent manner BLOOD, 15 MARCH 2005 VOLUME 105, NUMBER 6

Ruth Seggewiss, Karin Loré, Elisabeth Greiner, Magnus K. Magnusson, David A. Price, Daniel C. Douek, Cynthia E. Dunbar, and Adrian Wiestner

Why TKI for cGVHD patients?

- Oral feasible outpatient treatment (85%!)
- Low dose Imatinib is not so expensive!
- Good safety profile for long treatment duration
- Large experience in CML patients
- Absence of heavy immunesuppression
- Possibility to associate TKI with other drugs (CSA, RTX, ECP)

Alternative drugs for refractory cGVH today (2017)……..

- *FK 506 w/w MMF*
- *Etretinate/Acetretin*
- *Clofazimine*
- *Plaquenil: synergistic with CSA and tacrolimus in vitro*

- **Pentostatin**
- **Rapamycin**
- **MMF**

- **New drugs……..?????....YES!!!**

New strategies based on recent insights to cGVD pathophysiology

- Increasing T-reg: in vivo expansion or adoptive T-reg infusion (MSC infusion)
- Targeting B-cell pathway (BTK/SYK signal)
- Targeting the proteosome
- *Blocking the homing of effector cells (acute and cGVHD)*
- Targeting the Jak signaling (acute and cGVHD)

Adoptive Treg-cell therapy

- Zorn E. Combined CD4+ donor lymphocyte infusion and low-dose recombinant IL-2 expand FOXP3+ regulatory T cells following allogeneic HSCT, BBMT, 2009
- Theil A. Adoptive transfer of allogeneic regulatory T cells into patients with chronic GVHD, Cytotherapy 2015
- Yang J, Amelioration of acute GVHD by adoptive transfer of ex vivo expanded human cord blood CD4+CD25+ forkhead box protein 3+ regulatory T cells is associated with the polarization of Treg/Th17 balance in a mouse model, Transfusion. 2012
- Hoffmann P, Isolation of CD4+CD25+ regulatory T cells for clinical trials, BBMT 2015

MSC *in acute* and cGVHD

- *Le Blanc K, Lancet 2004; 363: 1439–41.*
- *Ringdén O, MSC for therapy-resistant GVHD,Transplantation 2006*
- *Le Blanc K, Mesenchymal stem cells for treatment of severe GVHD Blood 2006; 108: 753a.*

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],

Improvement of lung histology and PTF

- MSC As a Salvage Treatment for 53 pts with Refractory BOS after Allogenetic HSCT (ASH abstract, 2015)

- Mesenchymal Stem Cells Combined with Budesonide, Almeterol and Azithromycin for the Treatment of BOS (7 pts) after HSCT Cao XP, 2016

In vivo expanding Treg agents

- Rapamicin
- IL-2 low dose
- Ruxolitinib, hypomethylating agents*, and proteasome inhibitors.
- Bortezomib

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

OPEN ACCESS Freely available online

PLOS ONE

Inhibition of Calcineurin Abrogates While Inhibition of mTOR Promotes Regulatory T Cell Expansion and Graft-Versus-Host Disease Protection by IL-2 in Allogeneic Bone Marrow Transplantation

Atsushi Satake[1,2], Amanda M. Schmidt[1], Shosaku Nomura[2], Taku Kambayashi[1]*

Rapamycin enables expansion of Treg and combination with IL-2 is synergistic in vitro

- Retrospective analysis including 34 patients with sclerodermatous cGVHD treated with sirolimus or everolimus. Jedlickova Z, *Biol Blood Marrow Transplant.* 2011

- Addition of **sirolimus** to the GVHD prophylaxis in RIC HSCT for lymphoma reduced the incidence of severe aGVHD, but not NRM: a randomized trial. *Armand P JH.Br J Haematol. 2016*

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 1, 2011 VOL. 365 NO. 22

John Koreth, M.B.,

N Engl J Med 2011;365:2055-66.

Response

23 evaluable;
12/23 Major Clinical Response in 8 weeks;
0/23 progression or relapse;
Steroid dose tapered by a mean of 60% (25-100).

Immunologic response

CD4+ Tregs increased in all patients (x8 compared to baseline), without affecting Tcons.

Tolerance

28 evaluable;
Max Toler Dose $1x10^6/m^2$;
highest dose induced unacceptable constitutional symptoms;
Other adverse event possibly related to IL2:
- injection site induration (3/28),
- grade 2 renal dysfunction (1),
- grade 2 trombocytopenia (1).
- Thrombotic microangoipathy + renal failure (2 pts IL2+sirolimus +tacrolimus);
- Grade 3 infections (3 pts);

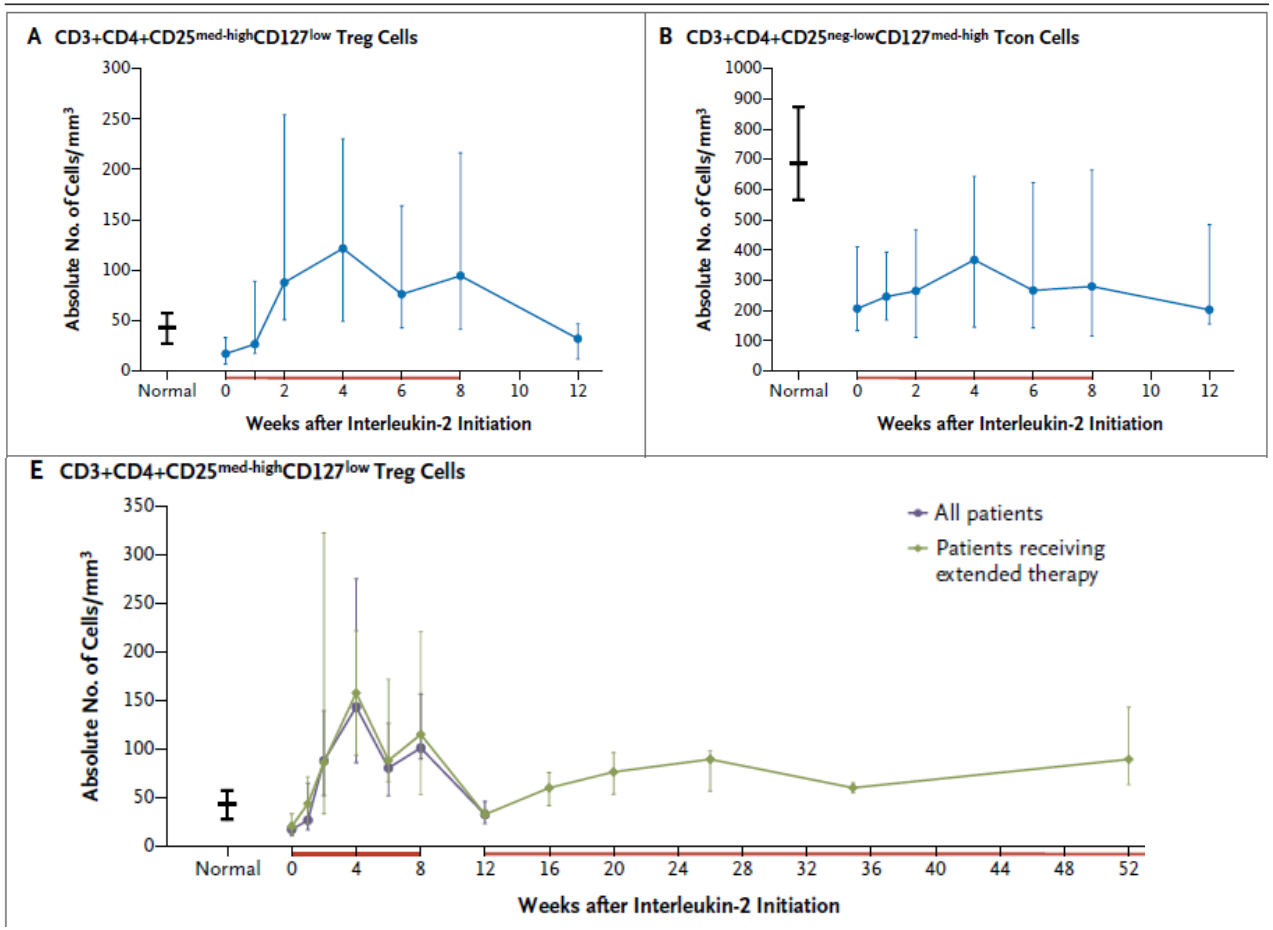
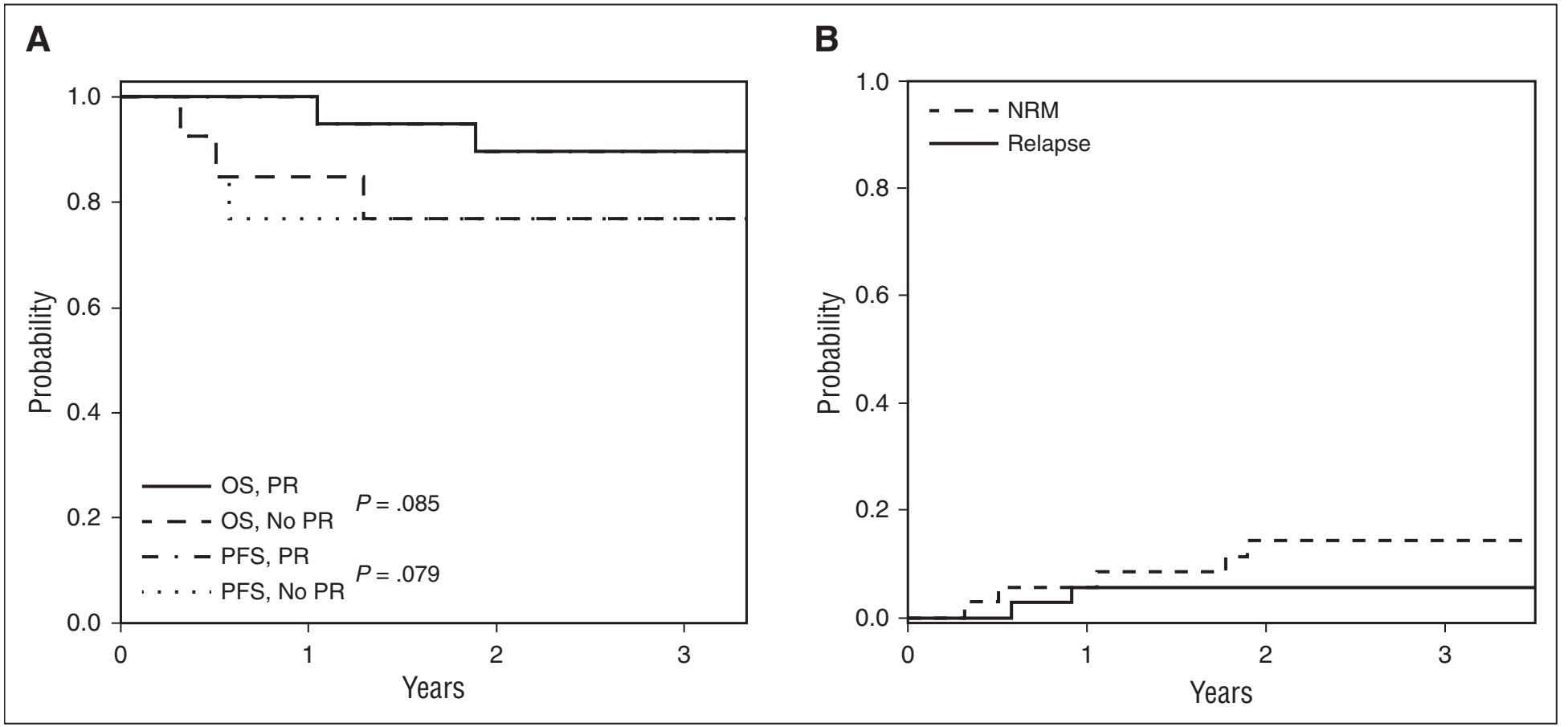


Figure 2. Immunologic Effects of 8 Weeks of Low-Dose Interleukin-2 Therapy and of Extended Therapy.

Panels A through D show the immunologic effects of 8 weeks of low-dose interleukin-2 (red line), followed by 4 weeks without interleukin-2. Medians and interquartile ranges are shown. Panel E shows the immunologic effects of extended treatment with interleukin-2 (red line) on regulatory T (Treg) cells. A sustained increase in CD4+CD25$^{med-high}$CD127^{low} Treg cells during 12-month treatment with interleukin-2 is shown. Medians and interquartile ranges are shown. NK denotes natural killer, and Tcon CD4+ conventional T.

Efficacy, durability, and response predictors of low-dose interleukin-2 therapy for chronic graft-versus-host disease

John Koreth,[1] Haesook T. Kim,[2] Kyle T. Jones,[1] Paulina B. Lange,[1] Carol G. Reynolds,[1] Marie J. Chammas,[1] Katherine Dusenbury,[1] Jennifer Whangbo,[1] Sarah Nikiforow,[1] Edwin P. Alyea III,[1] Philippe Armand,[1] Corey S. Cutler,[1] Vincent T. Ho,[1] Yi-Bin Chen,[3] David Avigan,[4] Bruce R. Blazar,[5] Joseph H. Antin,[1] Jerome Ritz,[1] and Robert J. Soiffer[1]



Blood 2016

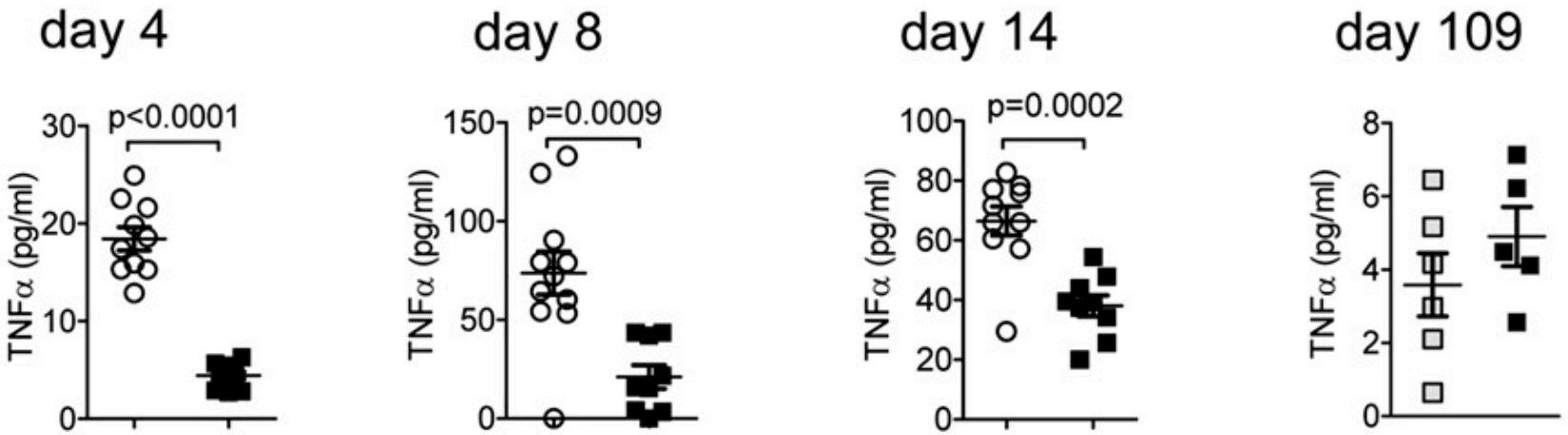
JAK1/2 PATHWAY

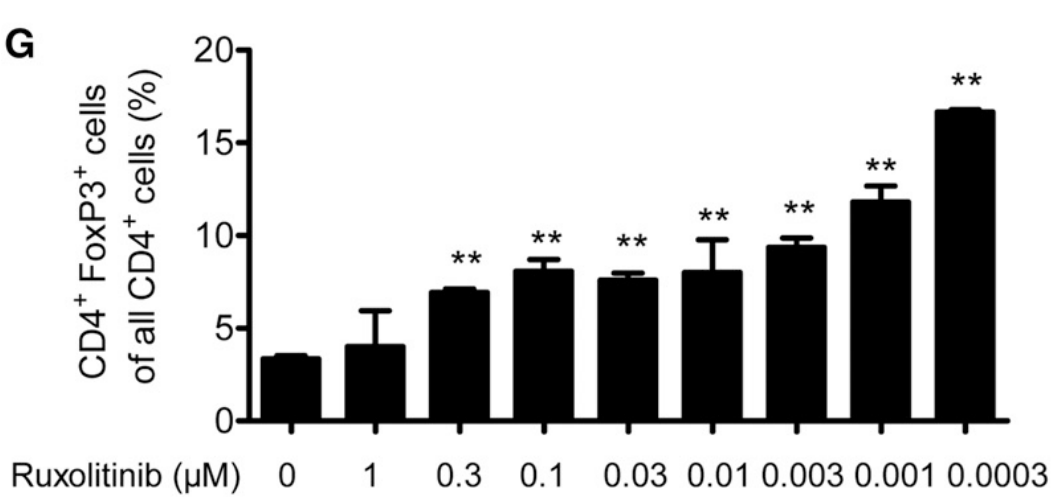
- JAK1/2 signaling is pivotal in multiple steps leading to inflammation and tissue damage in GVHD.
- A critical event involved in T-cell activation, lineage commitment and survival is signaling through the common gamma chain, a constituent of the receptor complexes for six different interleukins including IL-2/IL-6

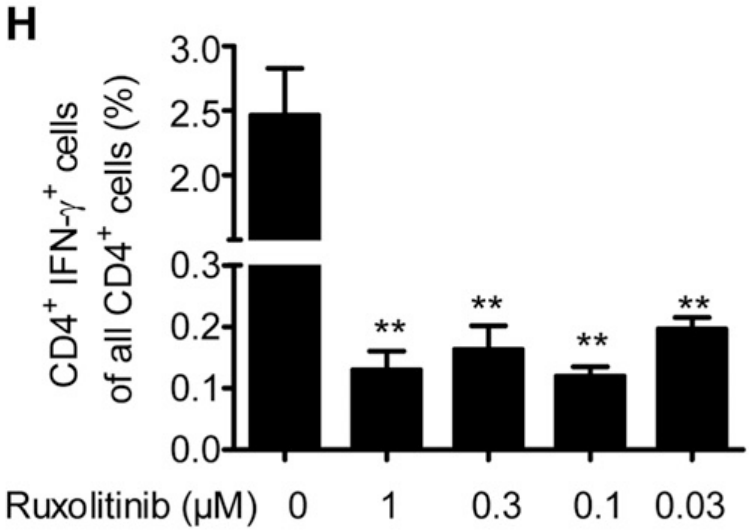
Activity of therapeutic JAK 1/2 blockade in graft-versus-host disease

Silvia Spoerl,[1] Nimitha R. Mathew,[2] Michael Bscheider,[1] Annette Schmitt-Graeff,[3] Sophia Chen,[2] Tony Mueller,[2] Mareike Verbeek,[1] Julius Fischer,[1] Vera Otten,[1] Martina Schmickl,[1] Kristina Maas-Bauer,[2] Jürgen Finke,[2] Christian Peschel,[1] Justus Duyster,[2] Hendrik Poeck,[1] Robert Zeiser,[2] and Nikolas von Bubnoff[2]

BLOOD, 12 JUNE 2014 • VOLUME 123, NUMBER 24







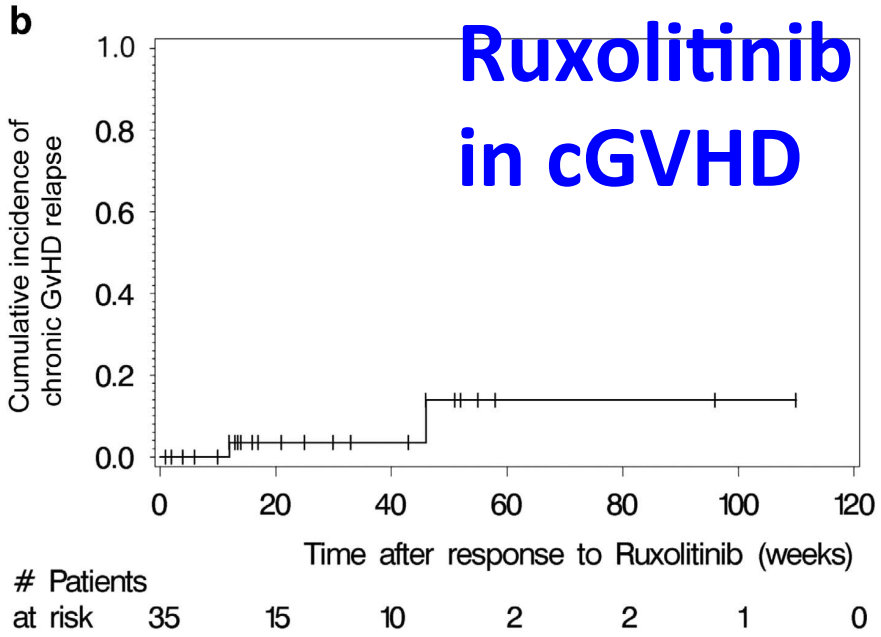
Leukemia (2015), 1–7

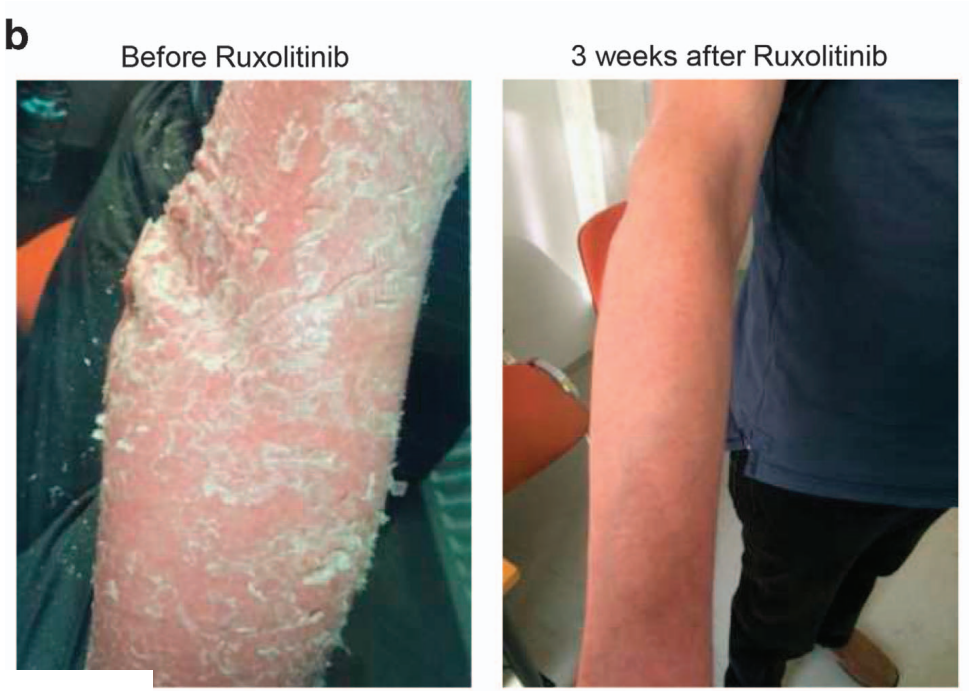
Variable	*aGVHD(n = 54)*	*cGVHD (n = 41)*
Patients age in years median (range)	51 (21–75)	55 (22–74)

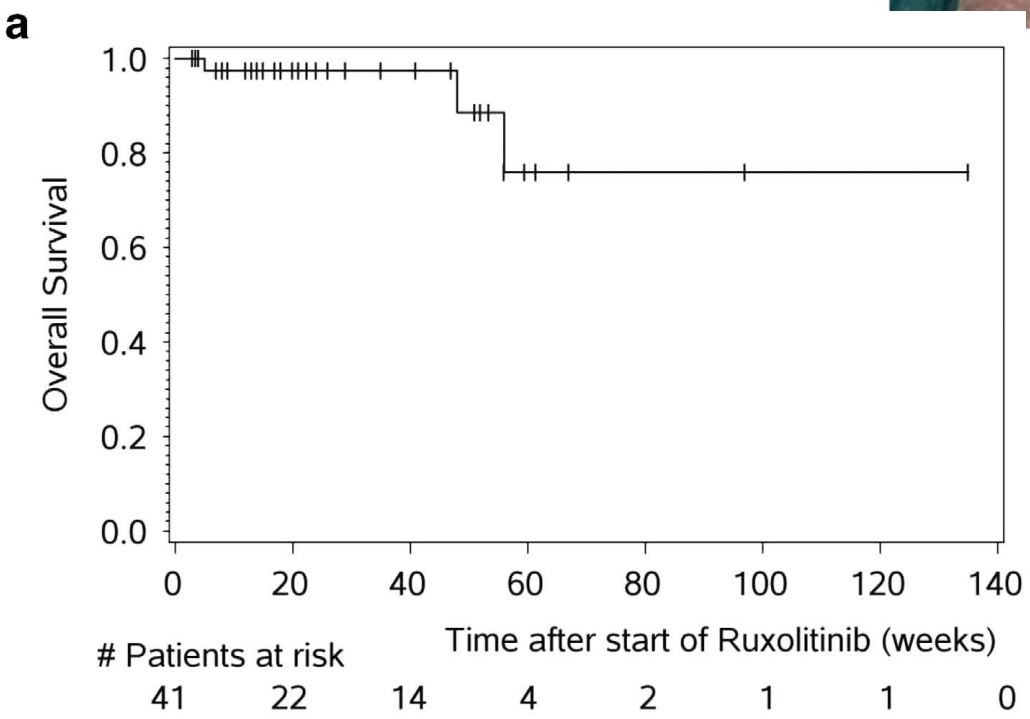
Table 2. Adverse events

Variable	*aGVHD(n = 54)*	*cGVHD(n = 41)*
	% (Absolute number)	*% (Absolute number)*
CMV reactivation	33.3(18)	14.6(6)
Severe cytopenia (grades 3 and 4)	33.3(18)	7.3(3)
Mild cytopenia (grades 1 and 2)	22.2(12)	9.7(4)
Cytopenia before ruxolitinib	51.8(28)	14.6(6)
Malignancy relapse	9.2(5)	2.4(1)

Ruxolitinib in cGVHD







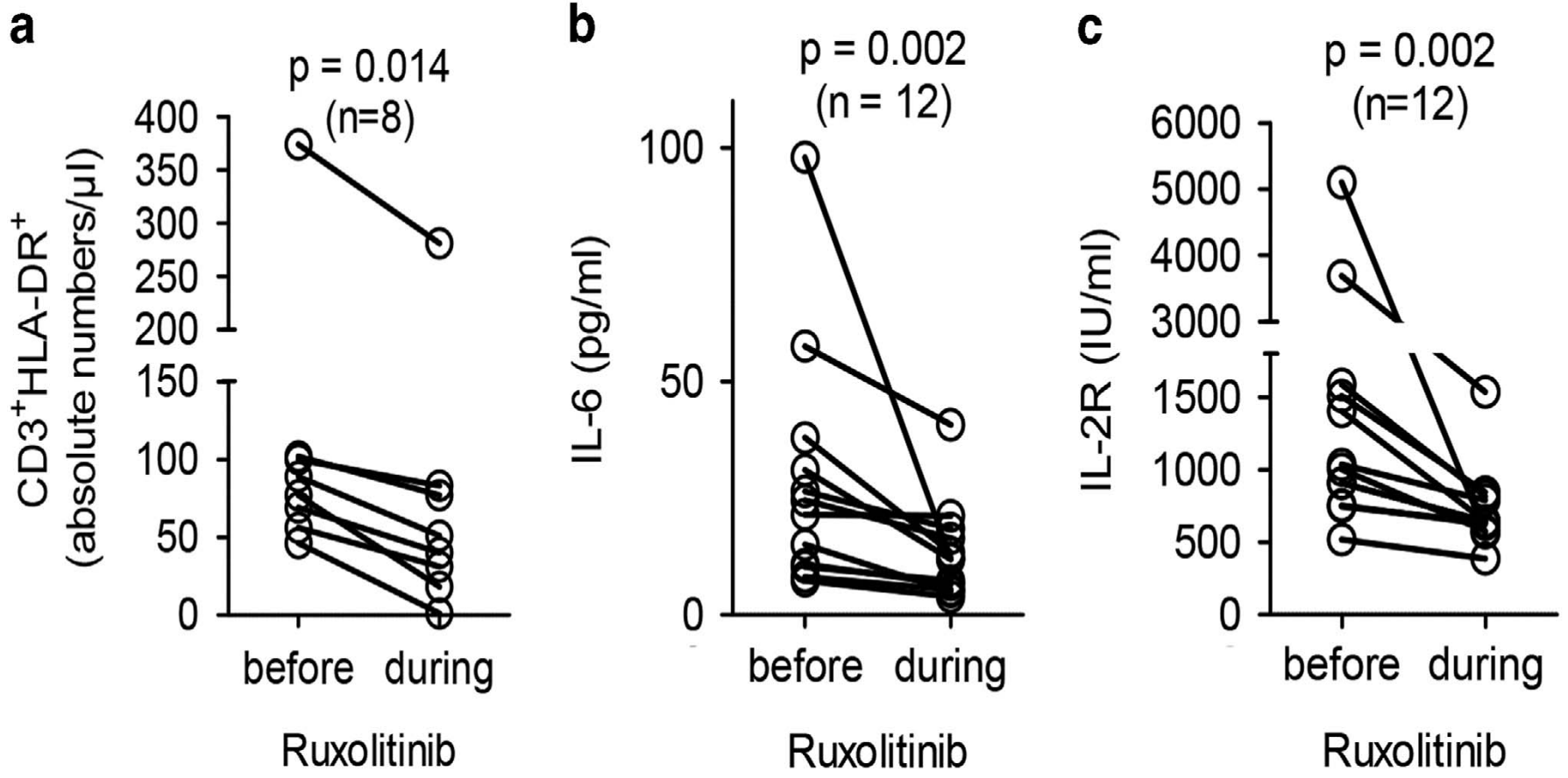
ORR: 85.4% (35/41), with 78% (32/41) PR and 7.3% (3/41) CR

Leukemia (2015), 1–7

Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey

Leukemia (2015), 1–7

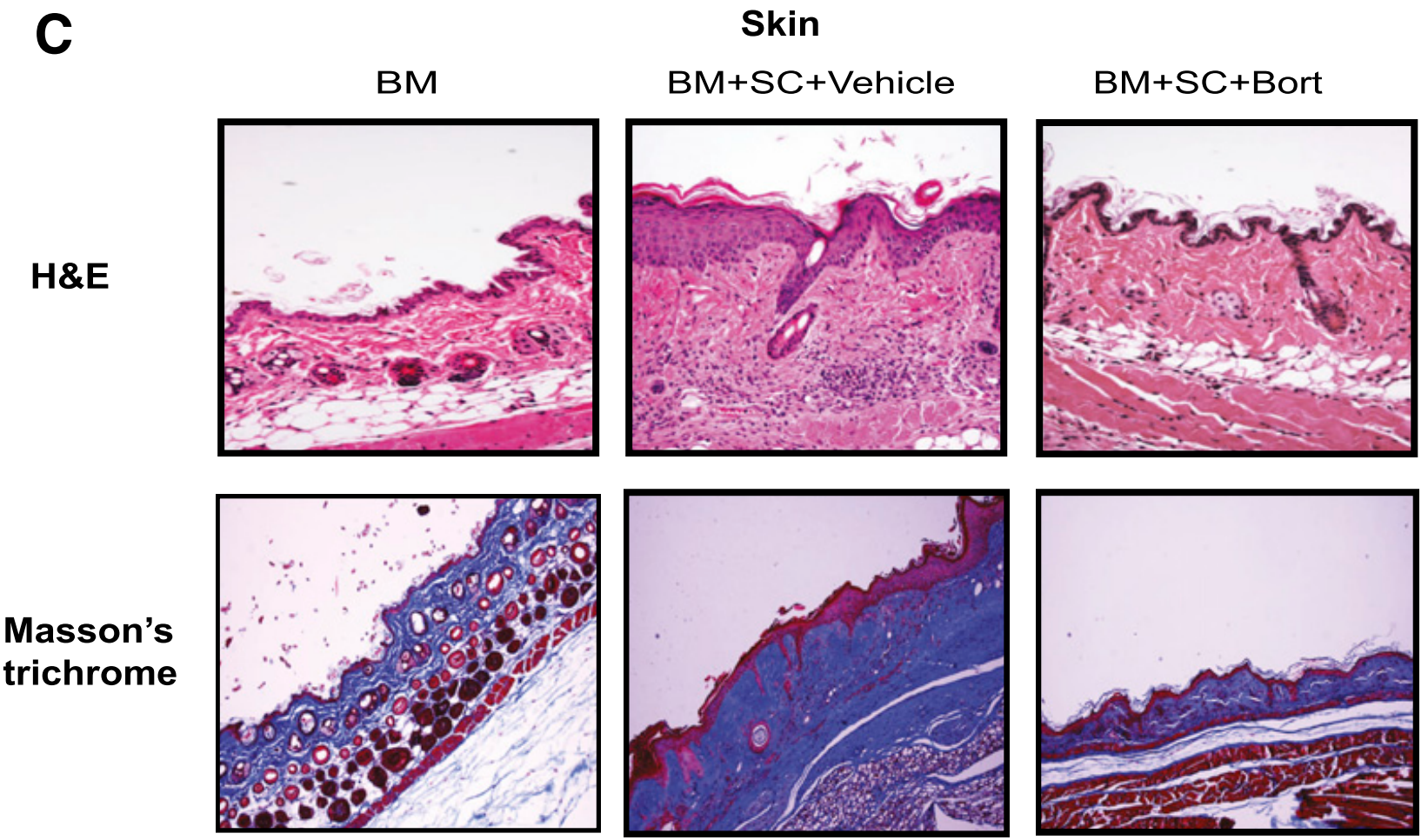
R Zeiser[1], A Burchert[2], C Lengerke[3], M Verbeek[4], K Maas-Bauer[1], SK Metzelder[2], S Spoerl[4], M Ditschkowski[5], M Ecsedi[3], K Sockel[6],



Treatment of chronic graft-versus-host disease with bortezomib

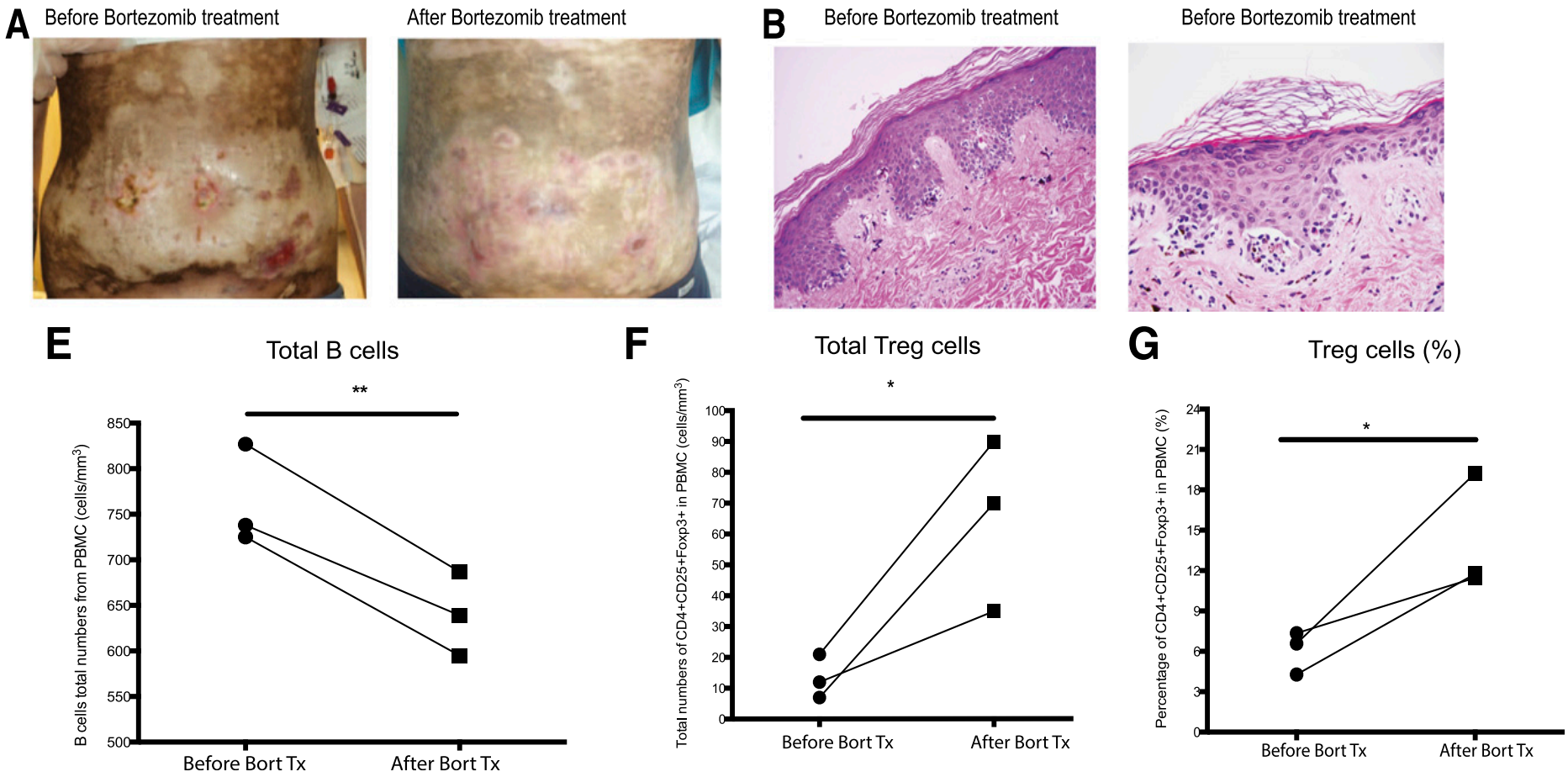
Chien-Chun Steven Pai,[1] Mingyi Chen,[2] Annie Mirsoian,[1] Steven K. Grossenbacher,[1] Joseph Tellez,[1] Erik Ames,[1] Kai Sun,[3] Jared Jagdeo,[1] Bruce R. Blazar,[4] William J. Murphy,[1,5] and Mehrdad Abedi[5]

Blood. 2014;124

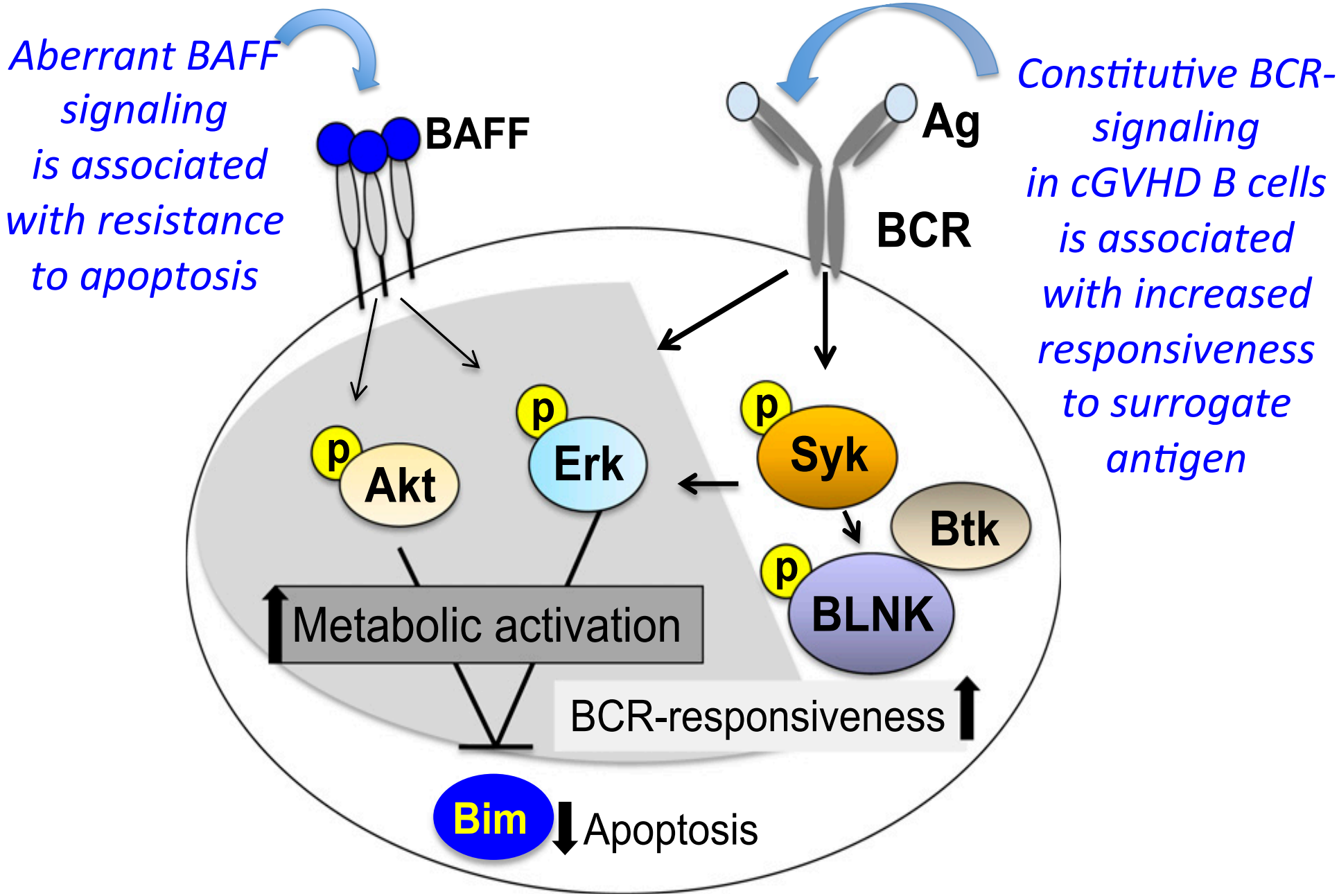


Bortezomib in patients with active steroid-refractory cGVHD

NCT01672229



Aberrant B-cell signaling in active cGVHD



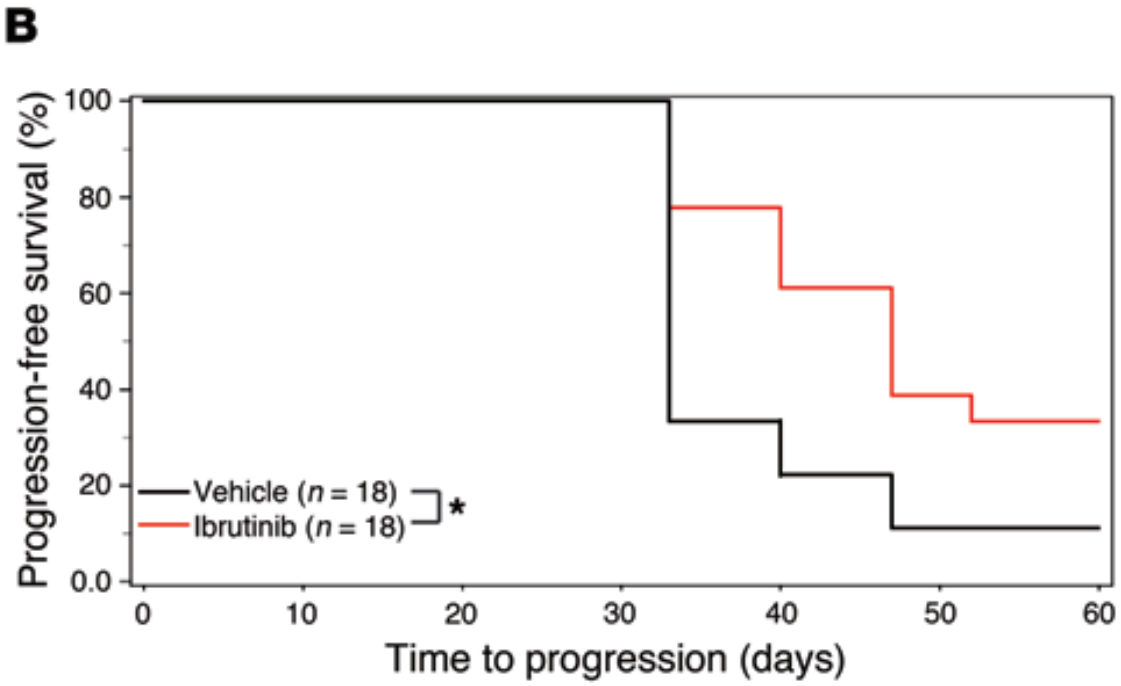
Targeting the B-cell receptor signaling pathway

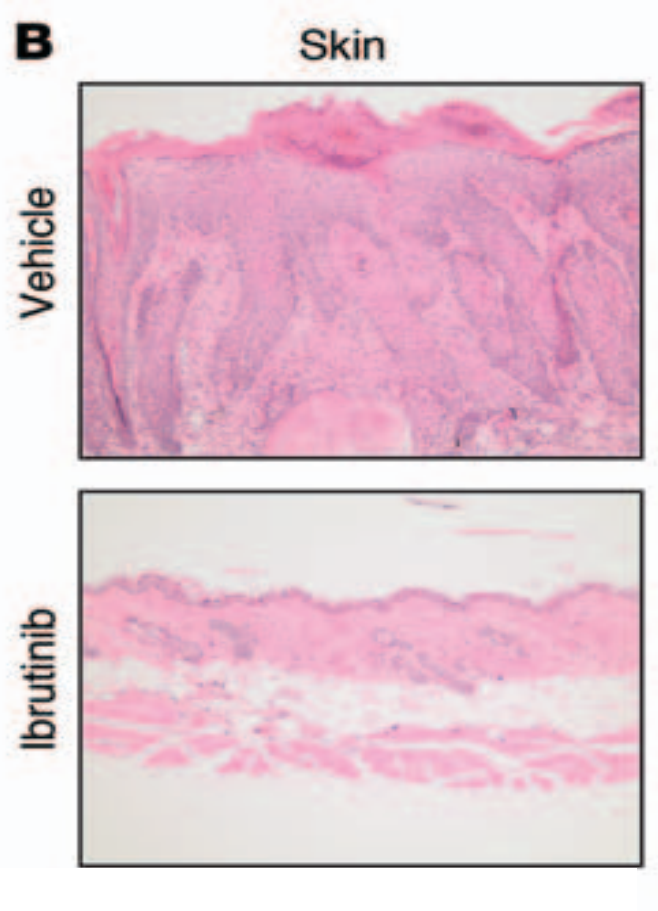
- Fostamatinib, SYK inhibitor: tested in rheumatologic diseases and currently in cGVHD (#NCT02611063).

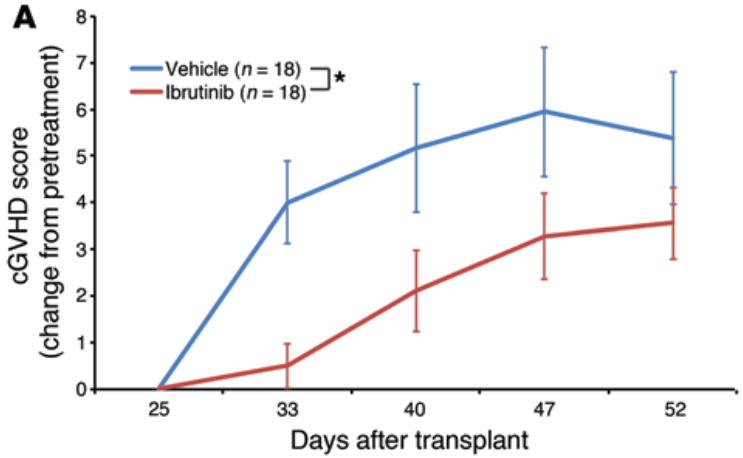
- BTK inhibitor ibrutinib in 28 subjects with steroid- refractory cGVHD: of 22 evaluable subjects, 11 had a PR and 1 had a CR, and the median corticosteroid dose reduction was 35%

Ibrutinib treatment ameliorates murine chronic graft-versus-host disease

Jason A. Dubovsky,[1] Ryan Flynn,[2] Jing Du,[2] Bonnie K. Harrington,[3] Yiming Zhong,[1] Benjamin Kaffenberger,[1] Carrie Yang,[1] William H. Towns,[1] Amy Lehman,[1] Amy J. Johnson,[1] Natarajan Muthusamy,[1] Steven M. Devine,[1] Samantha Jaglowski,[1] Jonathan S. Serody,[4] William J. Murphy,[5] David H. Munn,[6] Leo Luznik,[7] Geoffrey R. Hill,[8] Henry K. Wong,[1] Kelli K.P. MacDonald,[8] Ivan Maillard,[9] John Koreth,[10] Laurence Elias,[11] Corey Cutler,[10] Robert J. Soiffer,[10] Joseph H. Antin,[10] Jerome Ritz,[10] Angela Panoskaltsis-Mortari,[2] John C. Byrd,[1] and Bruce R. Blazar[2]





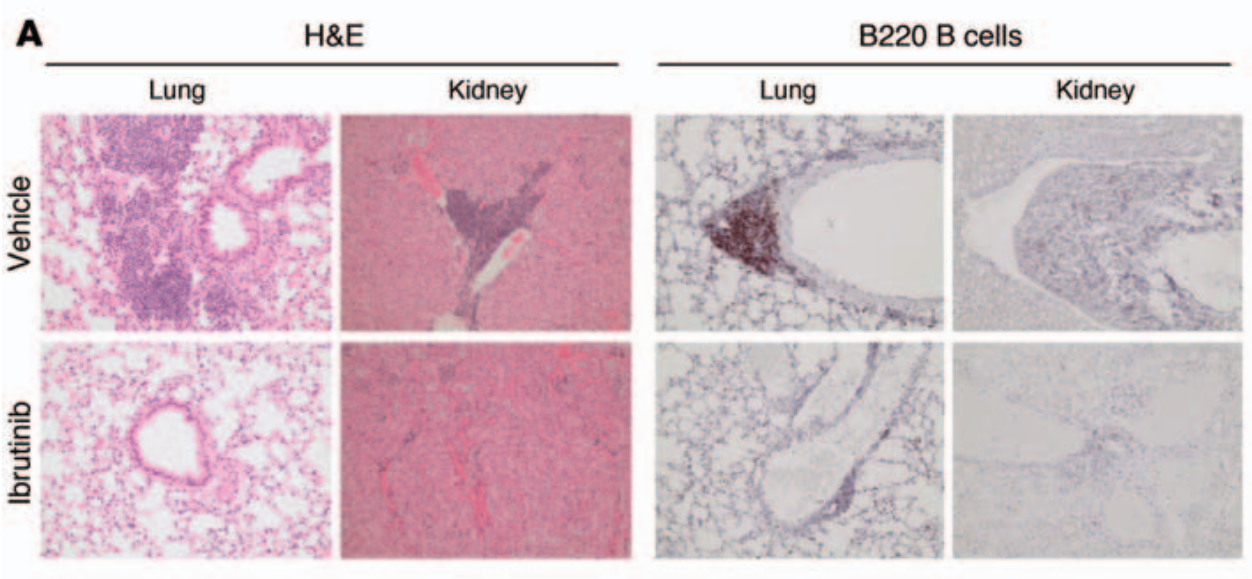


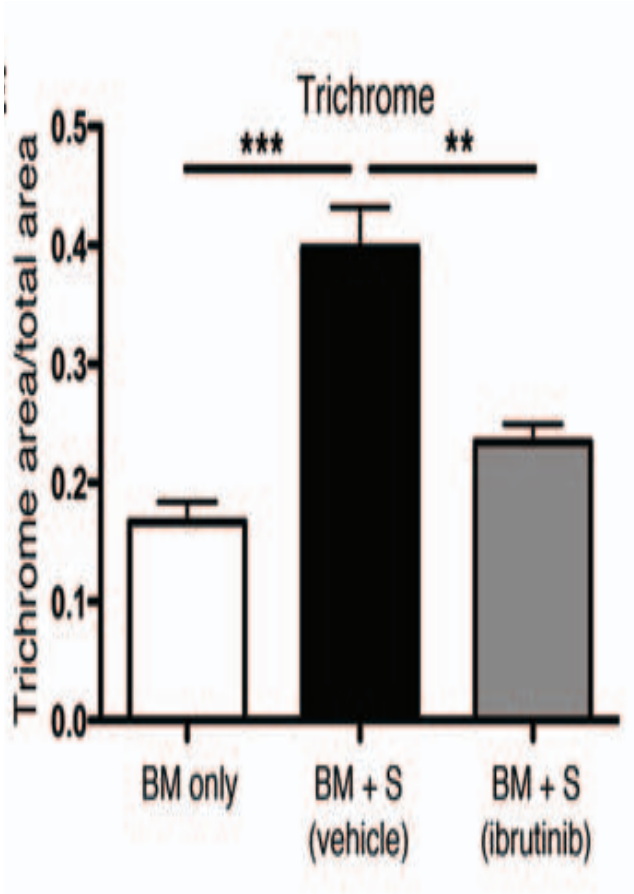
Ibrutinib therapy prevents autoimmune injury in a T cell–dependent model of cGVHD and reduces collagen production in lung

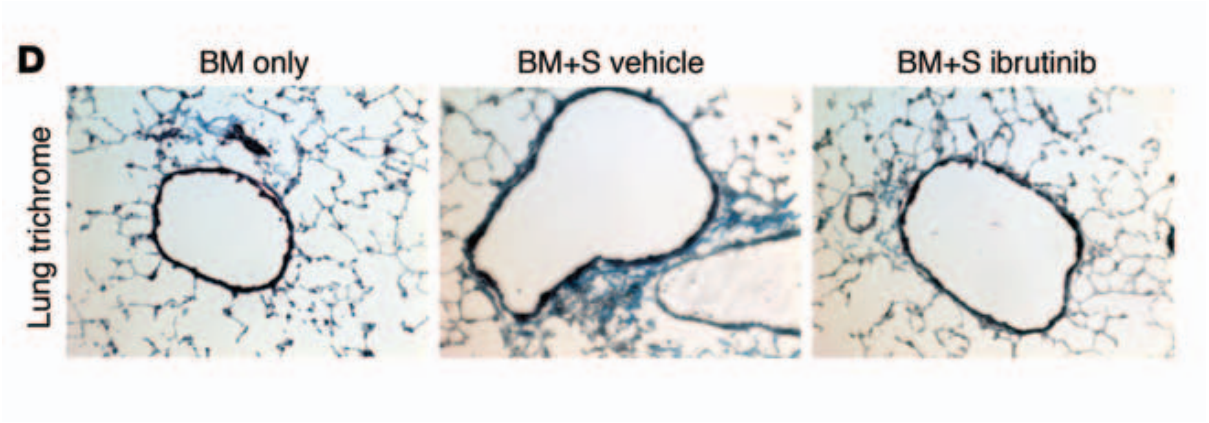
The Journal of Clinical Investigation RESEARCH ARTICLE

Ibrutinib treatment ameliorates murine chronic graft-versus-host disease

Jason A. Dubovsky,[1] Ryan Flynn,[2] Jing Du,[2] Bonnie K. Harrington,[3] Yiming Zhong,[1] Benjamin Kaffenberger,[1] Carrie Yang,[1] William H. Towns,[1] Amy Lehman,[1] Amy J. Johnson,[1] Natarajan Muthusamy,[1] Steven M. Devine,[1] Samantha Jaglowski,[1] Jonathan S. Serody,[4] William J. Murphy,[5] David H. Munn,[6] Leo Luznik,[7] Geoffrey R. Hill,[8] Henry K. Wong,[1] Kelli K.P. MacDonald,[8] Ivan Maillard,[9] John Koreth,[10] Laurence Elias,[11] Corey Cutler,[10] Robert J. Soiffer,[10] Joseph H. Antin,[10] Jerome Ritz,[10] Angela Panoskaltsis-Mortari,[2] John C. Byrd,[1] and Bruce R. Blazar[2]







brutinib ameliorates pulmonary fibrosis and the development of BO

Phase 3 international, randomized, double-blind study of ibrutinib plus PDN vs placebo plus PDN in new onset cGVHD

- 186 subjects* with newly diagnosed moderate/severe cGVHD, randomized in a 1:1 ratio to receive ibrutinib+prednisone (Arm A) Vs placebo+prednisone (Arm B).
- **Primary EP: ORR at 24 weeks**
- Sec EP corticosteroid dose reduction, withdrawal of all immunosuppressants and OS
- *Assuming a 30% RR at 24 weeks for Arm B, with 80% power *to detect a 20% difference btw the two arms.*

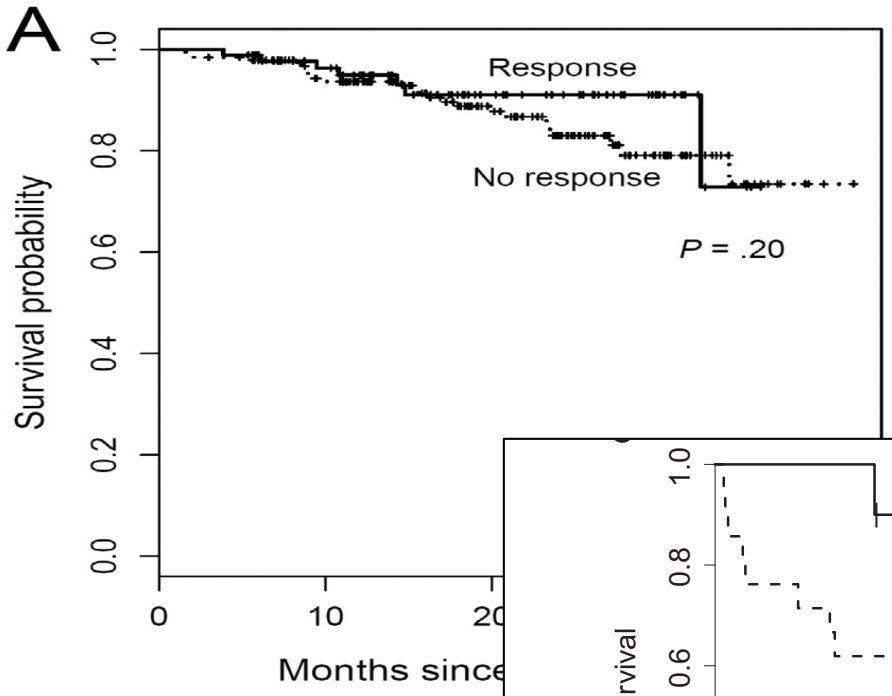
Can we estimate a realistic RR in cGVHD, according to the NIH criteria?

*Poor Agreement between Clinician Response Ratings and Calculated Response Measures in Patients with Chronic Graft- versus-host Disease**

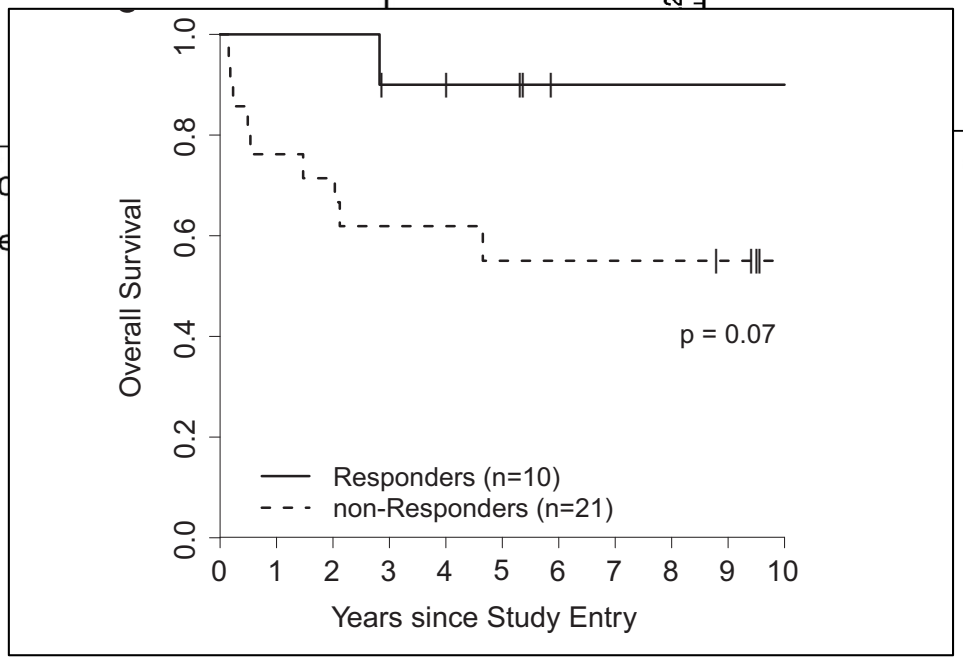
- Based on a set of objective measures, 37% of the patients (290) achieved CR or PR, whereas clinicians reported an overall (PR+CR) response rate of 71%.

*PALMER BBMT 2012

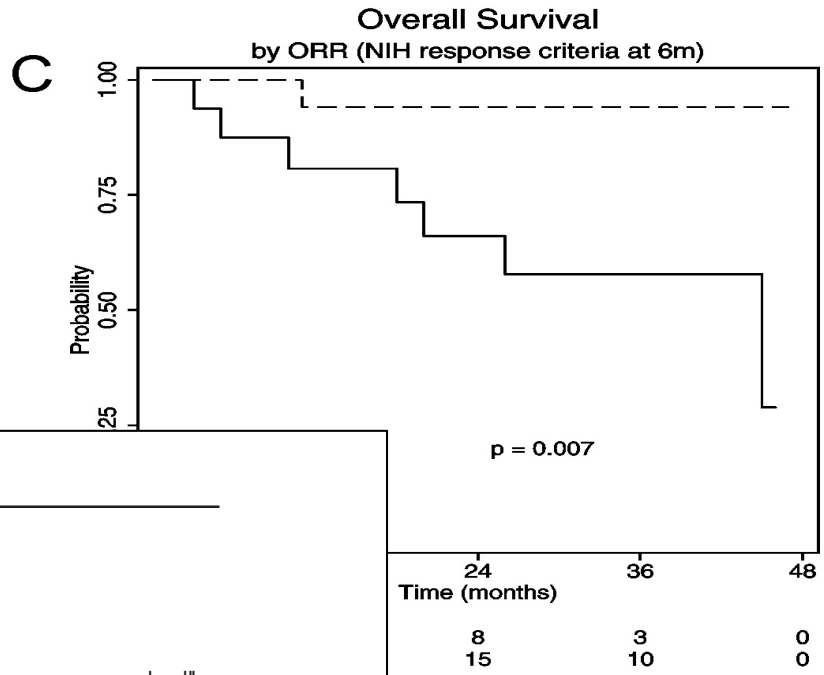
Changes in objective response measures, according to NIH criteria, can predict the hard outcomes (OS, PFS,QOL)?



Inamoto BBMT, 2012



Yanik, BBMT2012



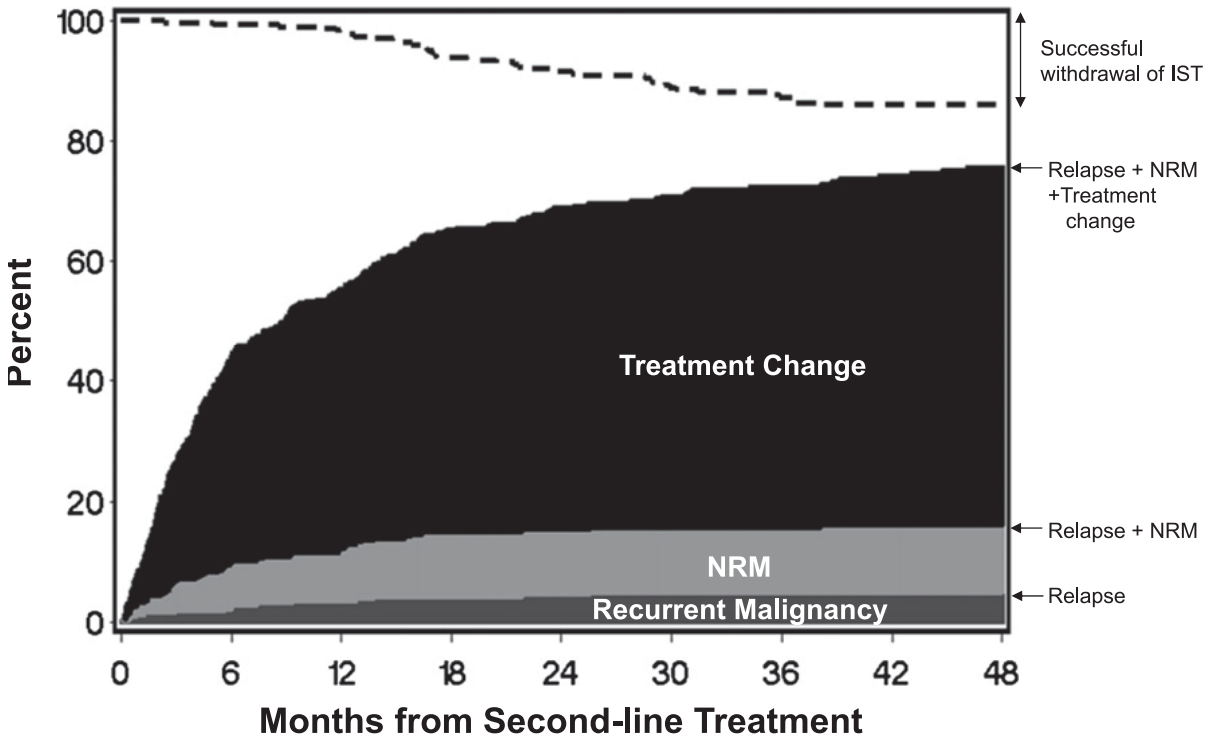
Olivieri Blood,2013

OS is not appropriate as primary EP in cGVHD trials

FFS is easy to document and change of therapy has been associated with a higher mortality rate

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]



EFS measured from

- Start of IMA until: death, 2nd neoplasia, *or treatment failure(TF)*.

TF defined as:

- cGVHD Prog or Death due to cGVHD; Leuk REL; addition (or increase) of immunosuppressive drug/procedure, excluding a transient steroid dose increase in the event of a GVHD flare;

or severe toxicity requiring Stop IMA

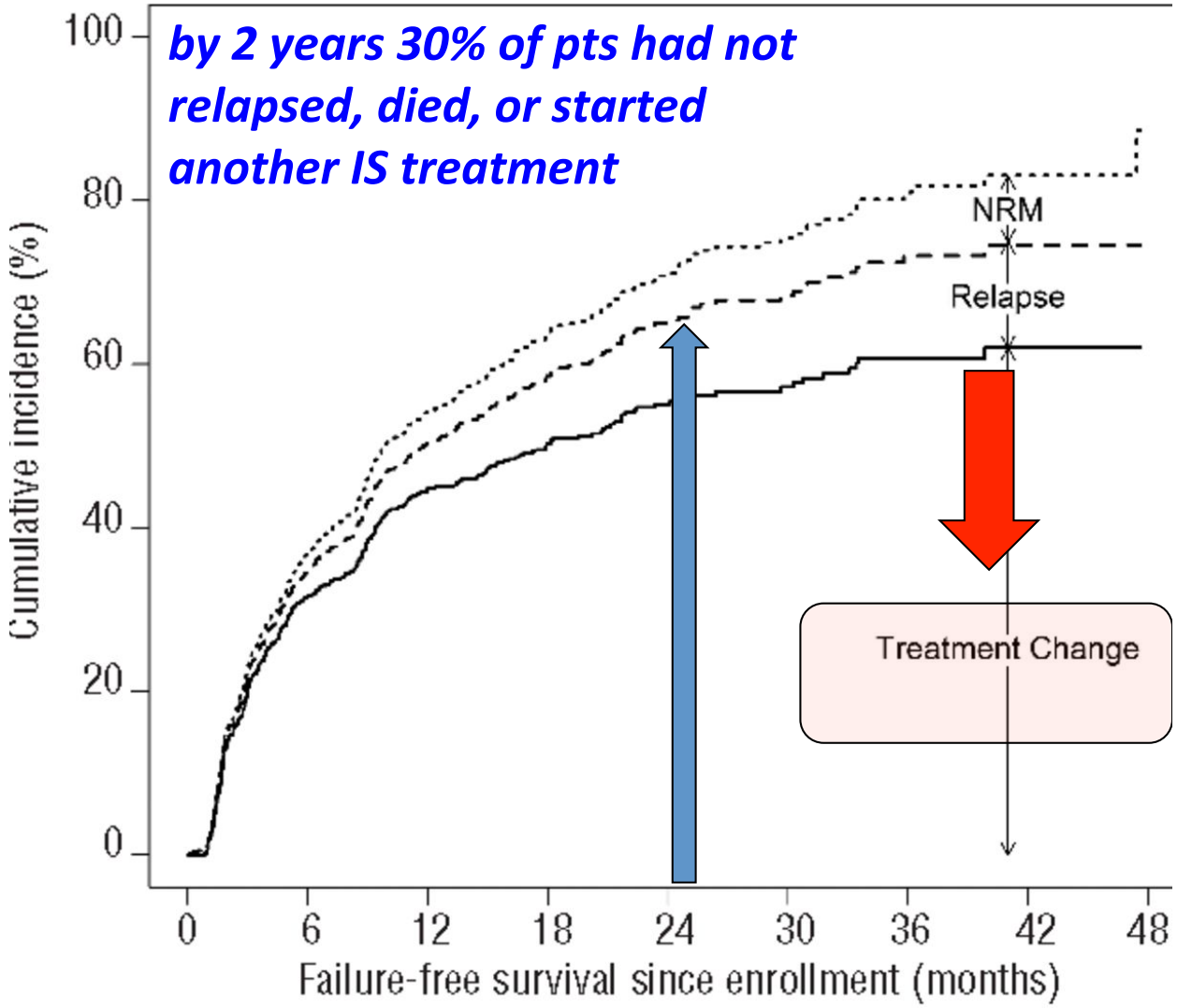
Failure-Free Survival in a Prospective Cohort Of Patients With Chronic Graft-*Versus*-Host Disease

Jeanne Palmer, Haematologica 2015

Prospective cohort of 575 pts with cGVHD

68% failures

median FFS: 9.8 months

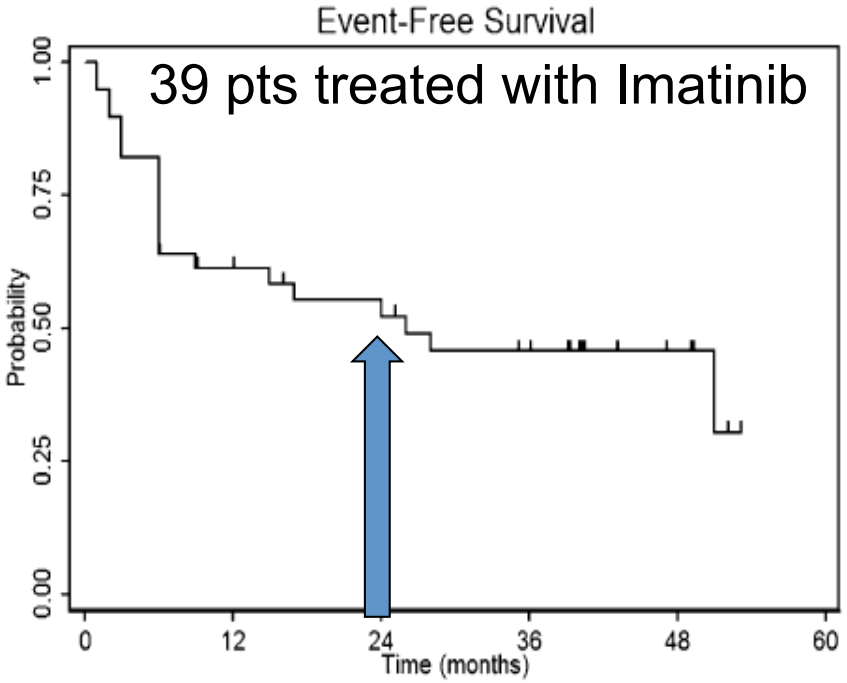


Absence of failure events should be recognized as minimal definition of success for an investigational trial

EBMT16-PH-2015

Nilotinib for steroid-refractory chronic graft versus host disease (cGVHD): a phase I-II GITMO study

Attilio Olivieri[*1], Michele Cimminiello[2], Paola Marenco[3], Nicola Mordini[4], Olivieri Jacopo[5], Elena Marinelli Busilacchi[5], Francesco Onida[6], Roberta Fedele[7], Paolo Corradini[8], Francesca Patriarca[9], Vincenzo Pavone[10], Roberta Nuccorini[11], Sara Pasquina Pascale[12], Francesco Saraceni[1], Giorgia Mancini[13], Angelo Michele Carella[14], Elisa Pirro[15], Arnon Nagler[16], Sonia Mammoliti[17], Francesca Bonifazi[18] and GITMO Gruppo Italiano Trapianto di Midollo Osseo



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

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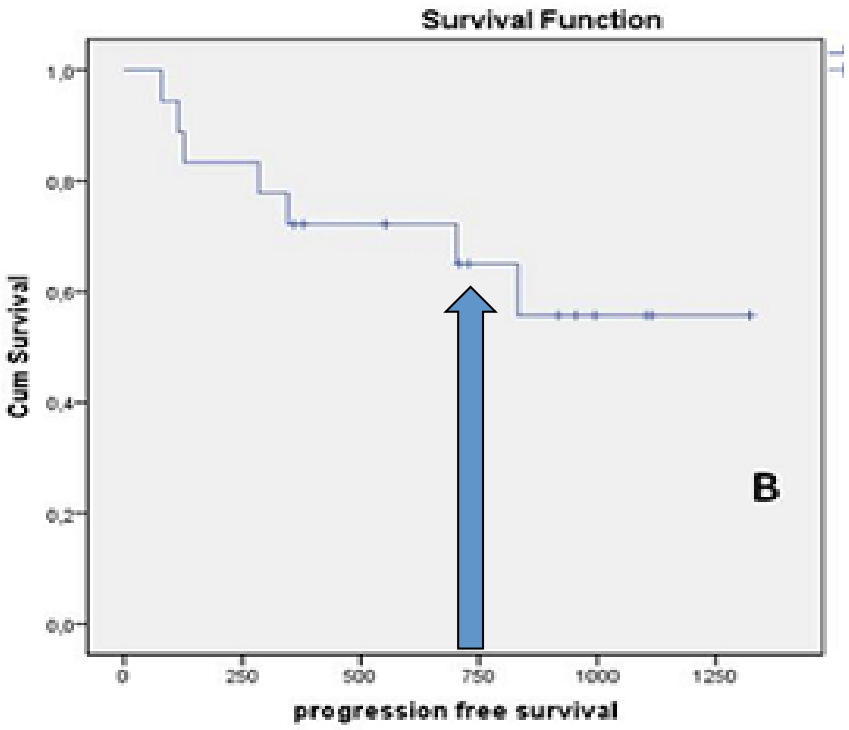


21 pts treated with Nilotinib

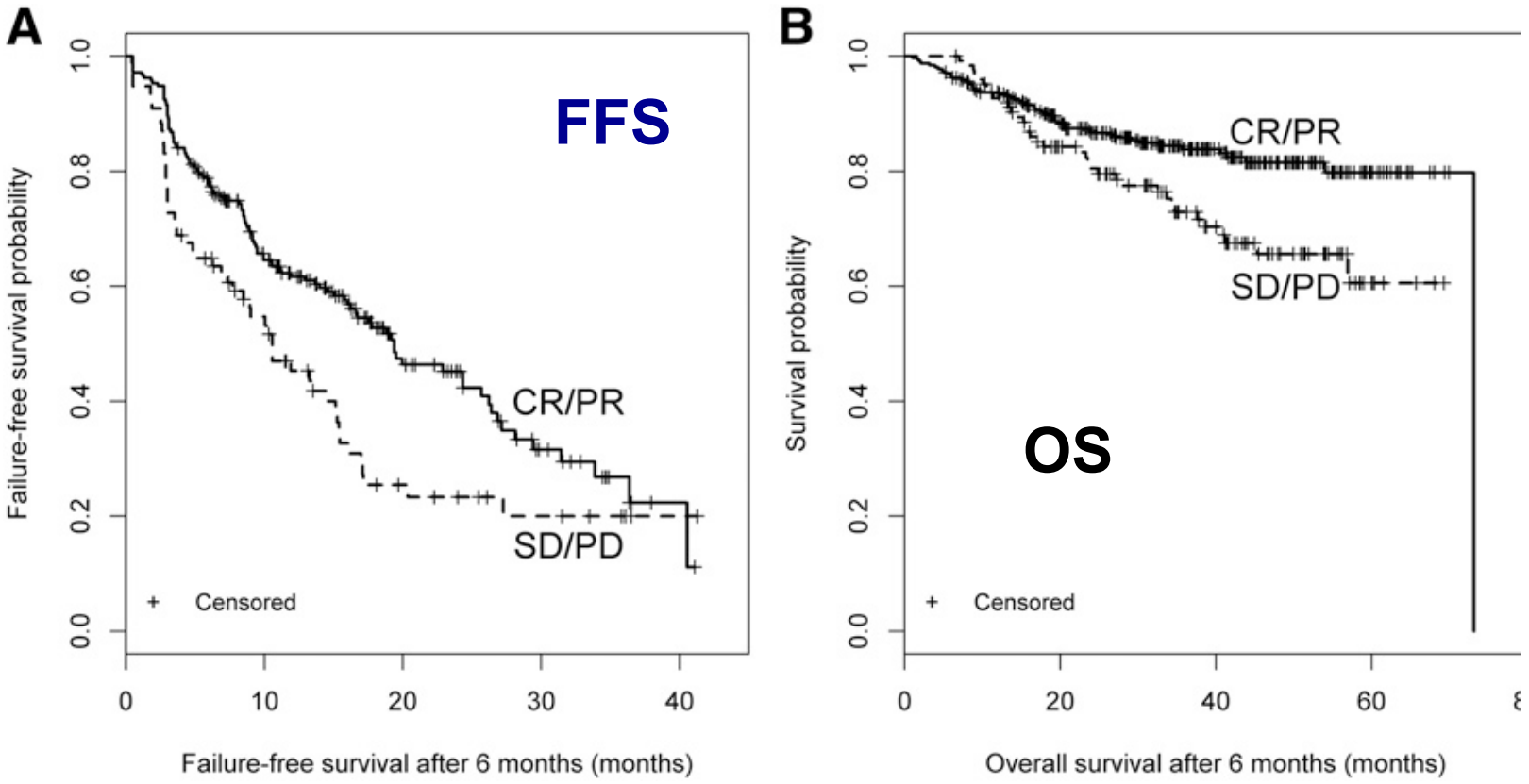
Key Points

- Survival of chronic GVHD patients was predicted by clinician-assessed response and changes in patient-reported outcomes.
- FFS was predicted by clinician-assessed response, changes in patient-reported outcomes, and the 2014 NIH response criteria.

Predictors of survival, nonrelapse mortality, and failure-free survival in patients treated for chronic graft-versus-host disease

Jeanne Palmer,[1] Xiaoyu Chai,[2] Joseph Pidala,[3] Yoshihiro Inamoto,[2,4] Paul J. Martin,[2] Barry Storer,[2] Iskra Pusic,[5] Mary E. D. Flowers,[2] Mukta Arora,[6] Steven Z. Pavletic,[7] and Stephanie J. Lee[2]

Outcome according to Clinician-reported response



Predictors of survival, nonrelapse mortality, and failure-free survival in patients treated for chronic graft-versus-host disease

Jeanne Palmer,[1] Xiaoyu Chai,[2] Joseph Pidala,[3] Yoshihiro Inamoto,[2,4] Paul J. Martin,[2] Barry Storer,[2] Iskra Pusic,[5] Mary E. D. Flowers,[2] Mukta Arora,[6] Steven Z. Pavletic,[7] and Stephanie J. Lee[2]

Multivariate landmark analyses at 6 mo for FFS, OS, and NRM

Outcome	Parameter*	*P*	HR (95% CI)
FFS	Change in 2005 NIH 0 to 3 skin score	.001	1.53 (1.19-1.96)
	Change in patient 0 to 10 skin itching	.002	1.15 (1.06-1.24)
OS	Change in Lee skin symptom score	.005	1.02 (1.01-1.04)
	FACT-BMT total score	.04	0.98 (0.97-0.99)
NRM	Change in Lee skin symptom score	.001	1.03 (1.01-1.04)

Patient-reported data!!!

GITMO observational study

Registration of all newly diagnosed cGVHD needing sistemic TX

Standard 1°-line TX according to the ongoing cGVHD survey

Response:
Continue same TX

Failure: each center must declare “apriori” its policy for failure TX

- GVCrOSy

A web-based software for cGVHD according to 2015 NIH consensus criteria

Primary Endpoint is FFS: percentage of patients alive without cGVHD progression or not needing new immunosuppressive treatment, or experiencing, NRM, relapse or severe toxicity

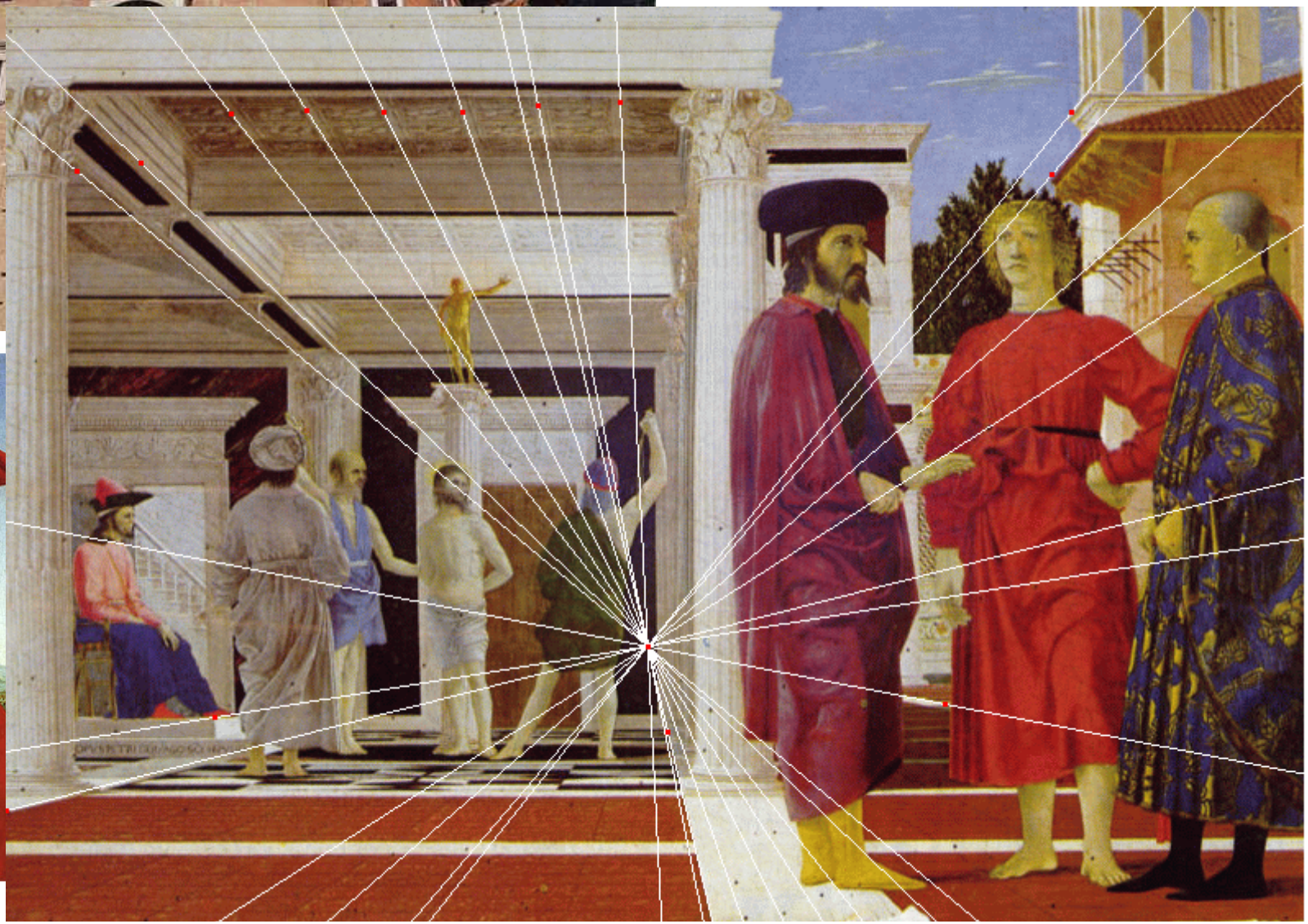
Objectives

- generating a reliable benchmark for future clinical studies
- evaluating the prognostic ability of NIH response criteria
- to evaluate safety of current treatments for cGVHD.

- *to evaluate the feasibility of an electronic tool both for data collection and for daily clinical practice*

g - GVCrOSy

Piero della Francesca
1444-1470
olio su tavola
Galleria Nazionale delle Marche, Urbino



Frederico da Montelfeltro, Della Francesca, 1465