Controversie nel Trapianto di Cellule Staminali Emopoietiche

GITMO

BARI 6-7 Giugno **2017**

Progressi nella GvHD acuta di III-IV grado?

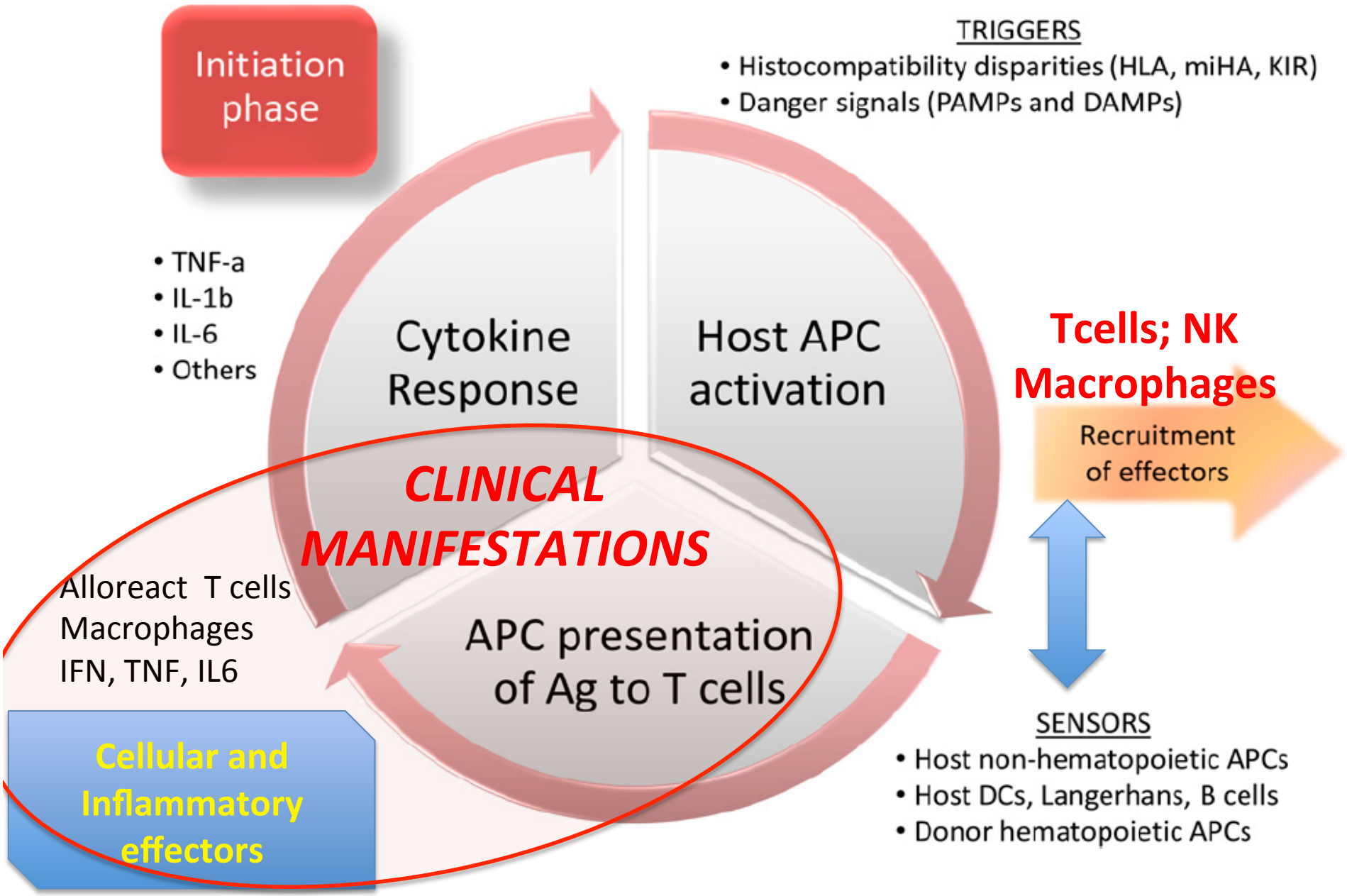
Attilio Olivieri

Head of SCT Unit

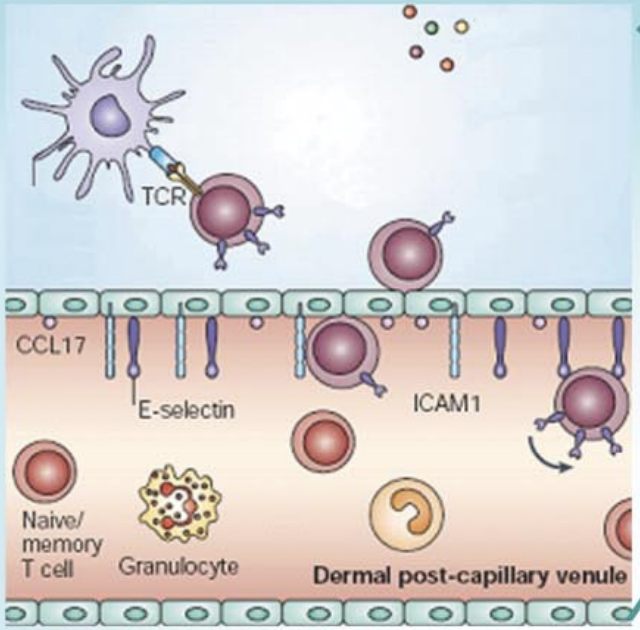
Clinica di Ematologia-Ancona

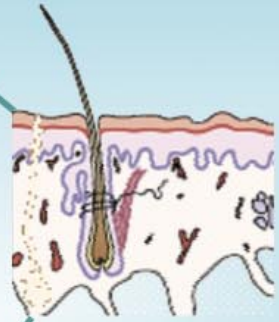
Università Politecnica delle Marche

Pathophysiology of acute GVHD



Step 4: T-cell trafficking





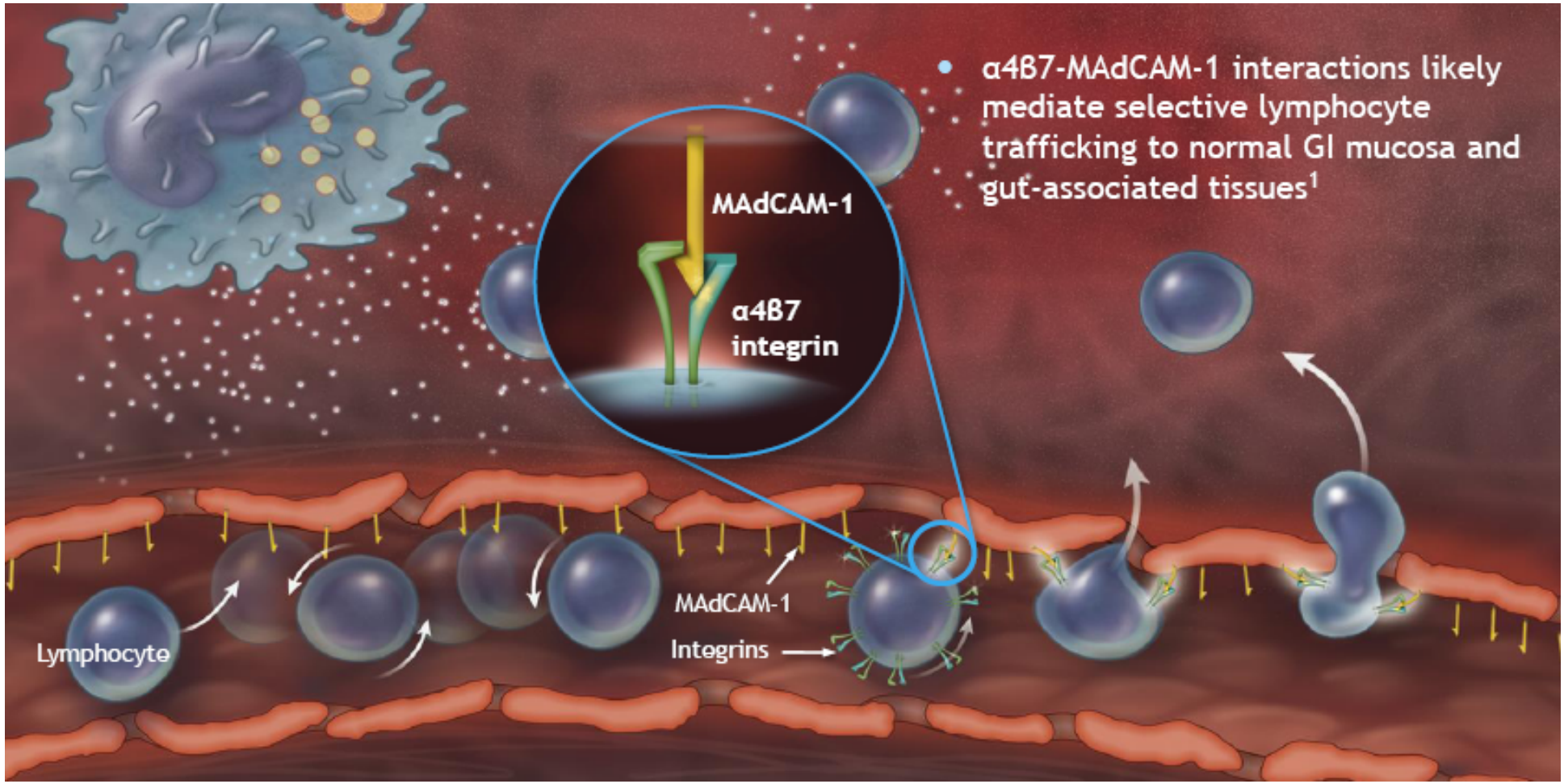
-Secondary lymphoid organs facilitate GVHD initiation.
-Parenchymal organs amplify GVHD
- Homing mechanisms (chemokine, selectin and adhesion molecules) well established

<u>Issue</u>
Chemokine/receptor redundancy hinder clinical applications

-GVHD initiation and amplification sites not well established
- Homing mechanisms (chemokines, selectin, adhesion molecules) not well established

Lymphocyte trafficking

The interaction between integrin α4β7 and MadCAM-1



Briskin, et al. Am J Pathol. 1997;151(1):97-110

Acute GVHD: clinical presentation

- skin rash, cutaneous blisters
- crampy abdominal pain with or without diarrhea,
- persistent nausea and vomiting
- *elevation of bilirubin and/or liver enzymes.*

Typically, these symptoms occur after engraftment and before day 100 after the HSCT (or later).

Hyperacute GVHD occurrs within
the first 14 days after SCT
(DD with Engraftment Sindrome)

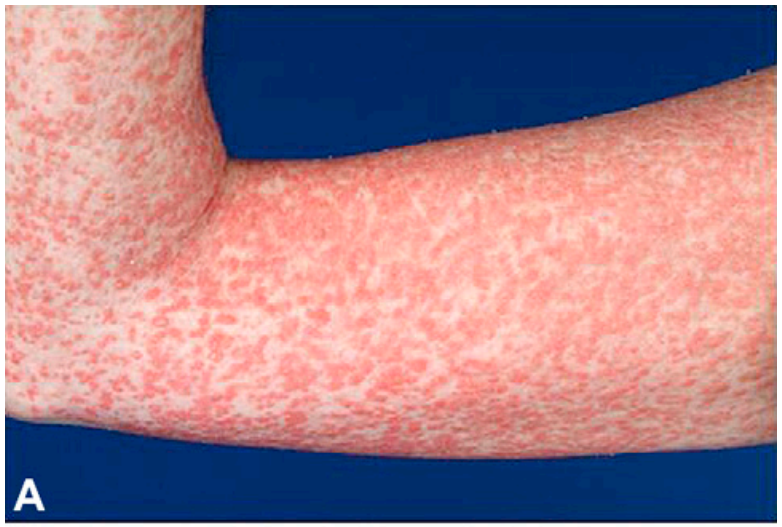
Dermatologic involvement

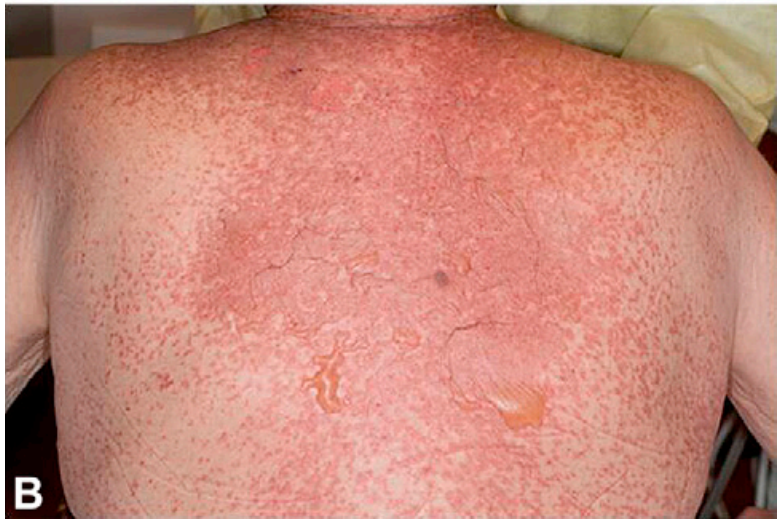
characteristic maculopapular rash can spread over the rest of the body. In severe cases, the skin may blister and ulcerate

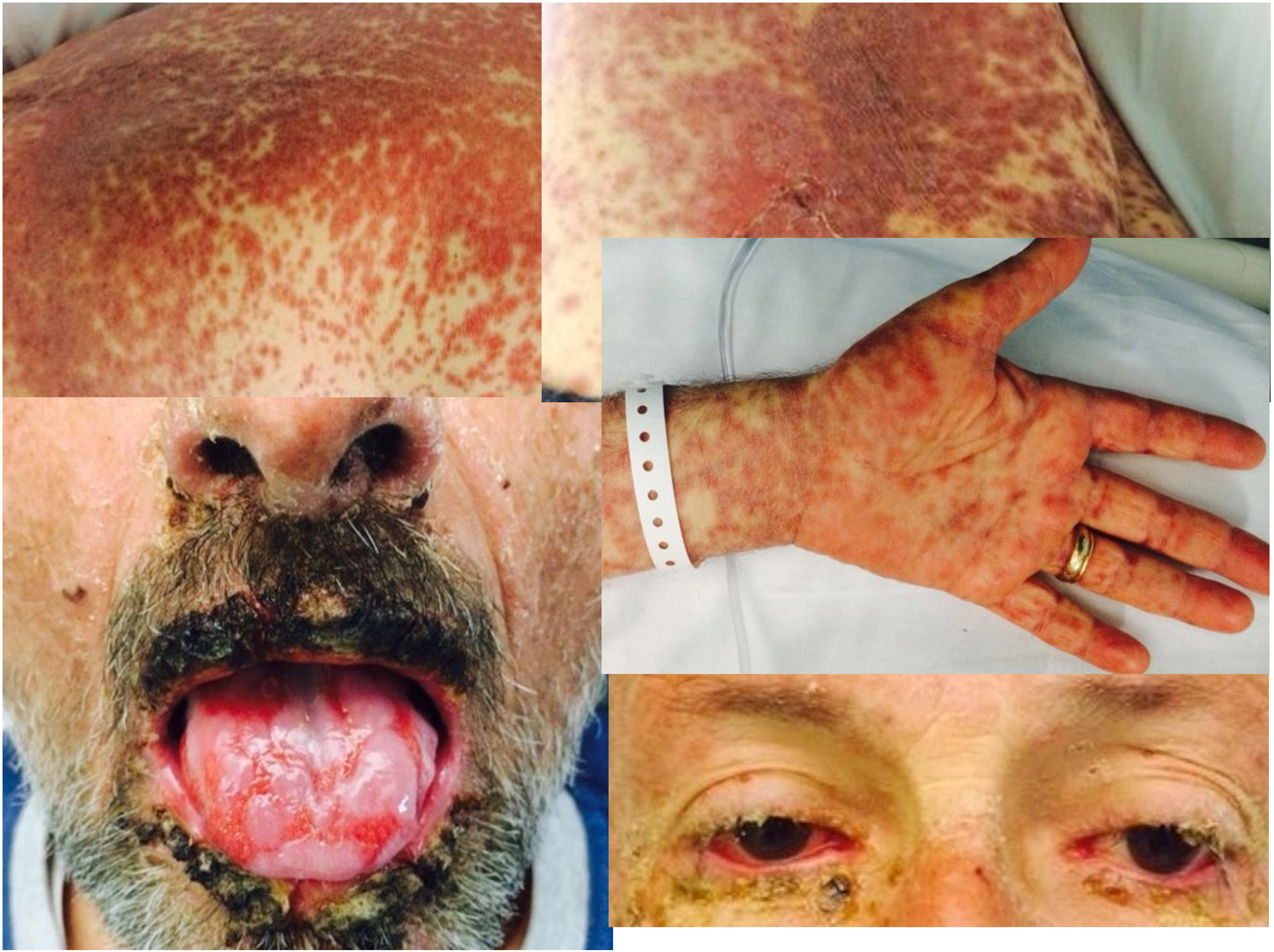
Table III. Histopathologic staging of acute graft-versus-host disease

Grade	Histopathologic features
0	Normal epidermis
1	Focal or diffuse vacuolar alteration of the basal cell layer
2	Grade 1 plus dyskeratotic squamous cells in the epidermis and/or hair follicle
3	Grade 2 plus subepidermal vesicle formation
4	Complete separation of the epidermis from dermis

Apoptosis at the base of dermal crypts is characteristic dermal perivascular lymphocytic infiltration

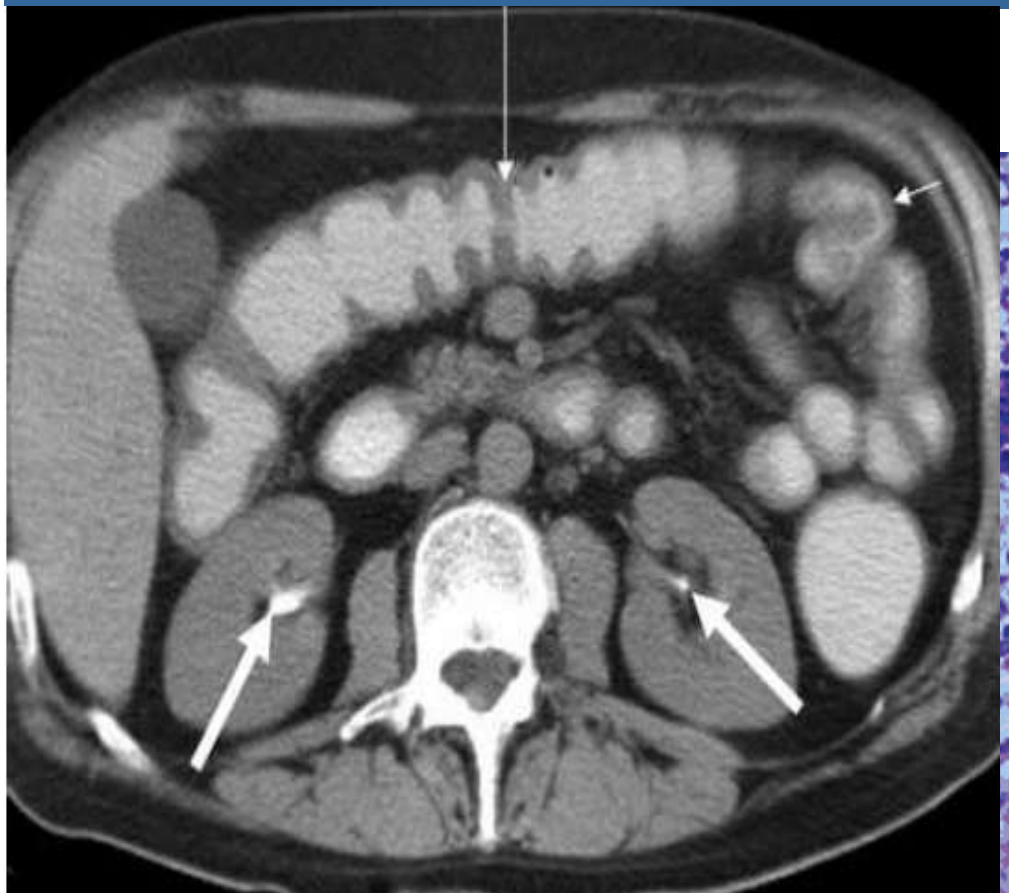






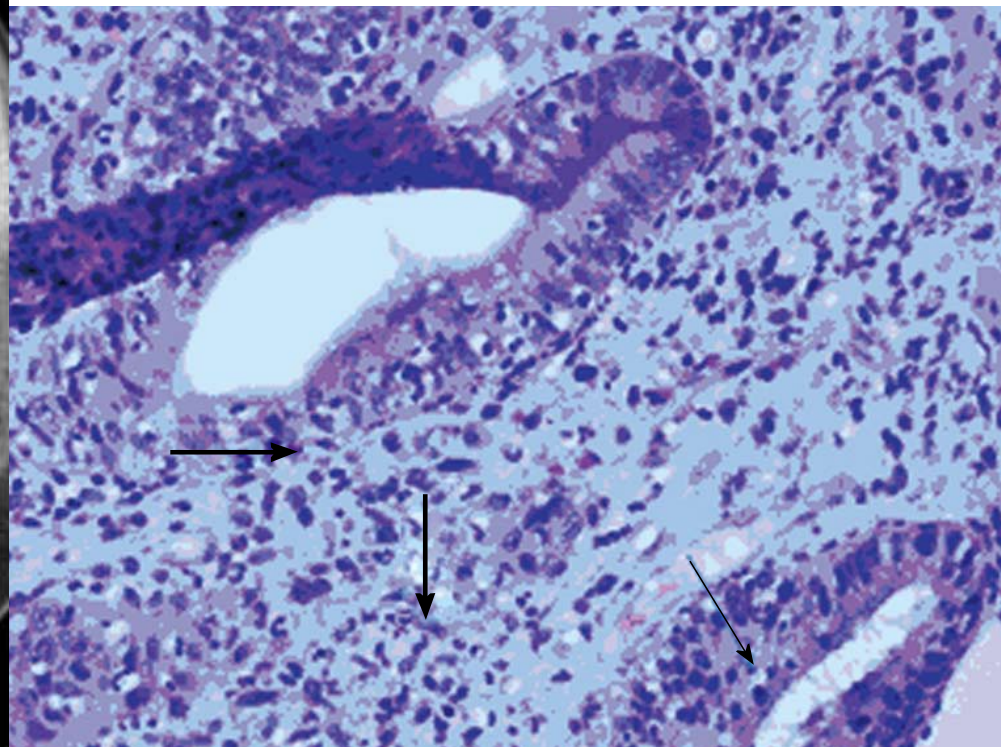
GUT GVHD

- Approximately 50% of cases
- Nausea, vomiting and anorexia
- Watery diarrhoea (typically green) and abdo cramps progressing to ileus and bloody diarrhoea
- Endoscopy: patchy ulceration
- CT scan: luminal dilatation with thickening of small bowel wall (ribbon sign), may have fluid levels



Pathology

apoptotic bodies in base of crypts, crypt abscesses, loss of surface epithelium

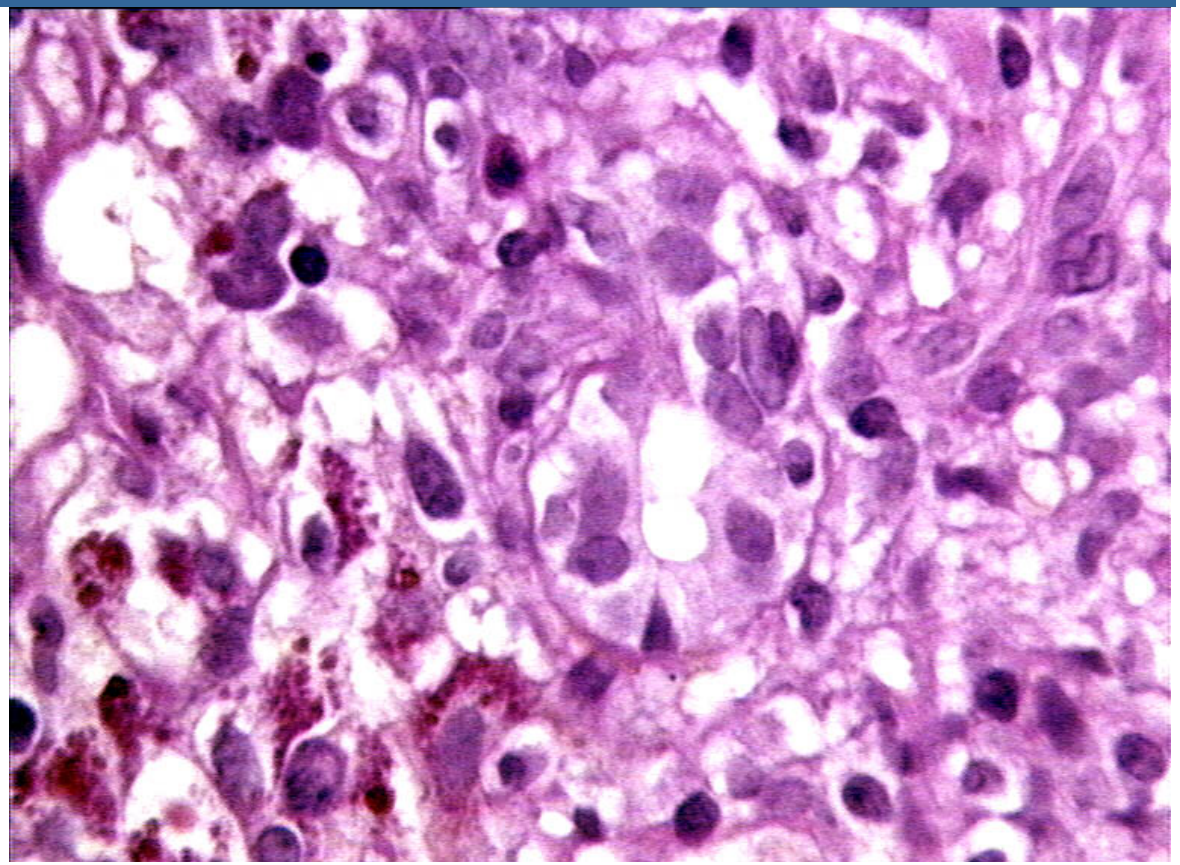


Liver involv. in GVHD

- Approximately 50% of cases
- Cholestatic hyperbilirubinaemia
- Difficult to distinguish from other causes of hepatic toxicity i.e. veno-occlusive disease, drugs, viral infections, sepsis, iron overload
- Pathology: endothelialitis, lymphocytic infiltrate of portal areas, pericholangitis, bile duct destruction

Biopsy often not performed because of concurrent thrombocytopenia

6% of cases of aGVHD present with exclusive Liver involvement



Meeting report

Consensus conference on acute GVHD grading

Bone Marrow Transplantation, (1995) 15, 825–828

D Przepiorka[1], D Weisdorf[2], P Martin[3], H-G Klingemann[4], P Beatty[5], J Hows[6] and ED Thomas[3]

Acute GvHD: Staging

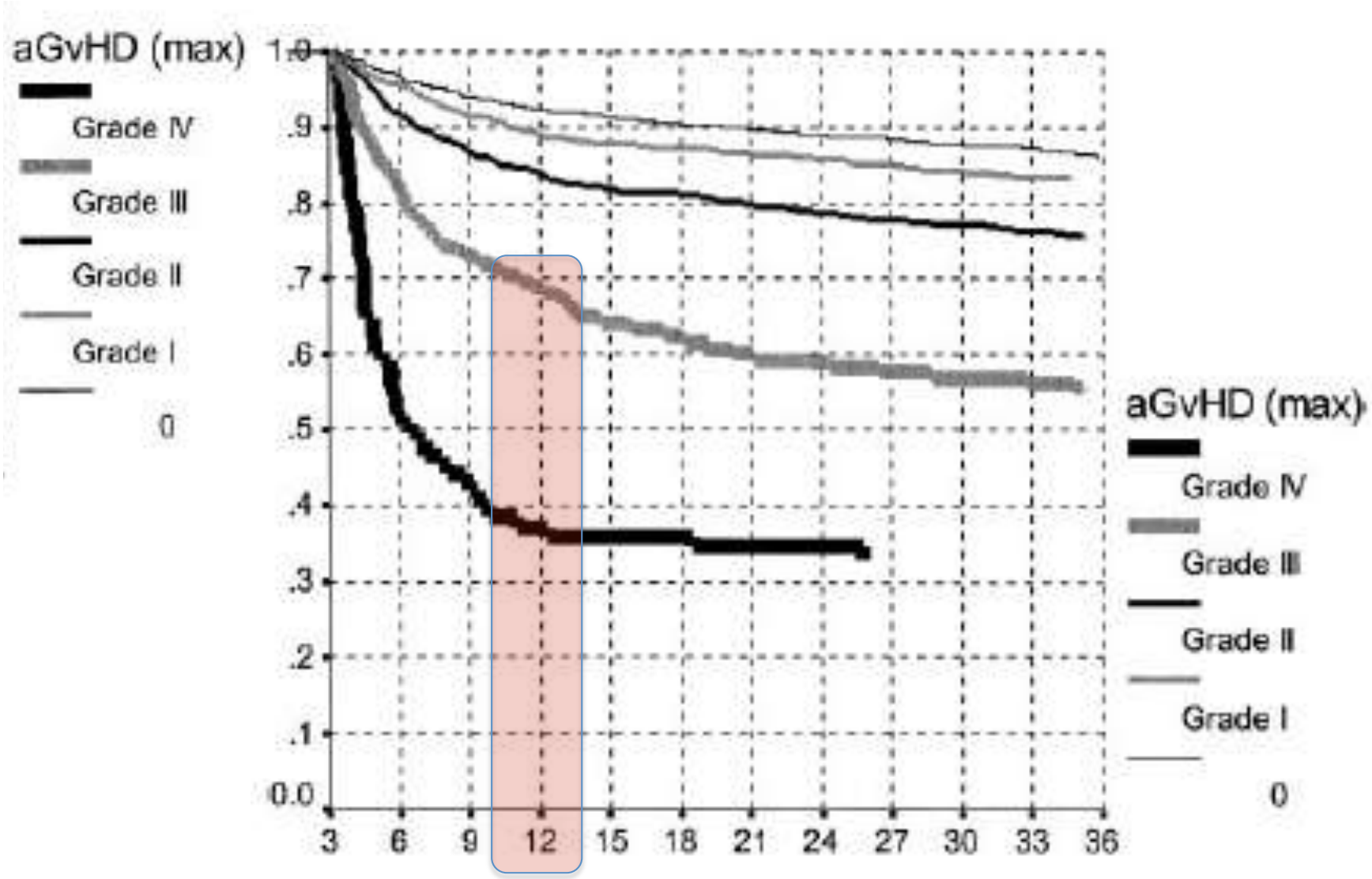
**In pediatric pts*
To be determined
according to the Vol/kg

stage	skin	Liver (bil:µmol/l)	*Gut diarrhoea
1	<25%	34-50 2-3 mg/dl	>500 ml
2	25-50%	51-102 3-6 mg/dl	>1000
3	>50%	103-255 6-15 mg/dl	>1500
4	Bullous disease	>255 >15 mg/dl	pain++

Overall Clinical Grade

- Grade 0: *No stage 1–4 of any organ*
- Grade 1: *Stage 1–2 skin rash and no liver or GI involvement*
- Grade 2: *Stage 3 skin rash, or Stage 1 liver involvement, or Stage 1 GI involvement*
- Grade 3: *Stage 0–3 skin rash, with Stage 2-3 liver involvement, and/or Stage 2–3 GI involvement*
- **Grade 4: *Stage 4 skin rash, liver, and/or GI involvement***

Impact of aGVHD on survival



Acute GvHD: Prevention-1

- Methotrexate
- Inhibition of cytoplasmic calcineurine: Cyclosporine/Tacrolimus (FK506)
- *Mycophenylate mofetil: Inhibits inosine monophosphate dehydrogenase*
- *Sirolimus (m-TOR inhib)*
- Antithymocyte globulin
- ***Cyclophosphamide (PTCy in Haplo setting)***

Acute GvHD: Prevention-2

- **Monoclonal antibodies:**

  -CD20: rituximab

  -CD52: alemtuzumab

  -CD3: OKT3, visilizumab-CD147: ABX-CBL-

  -***alpha/beta-*** **Tcell depletion**

  -anti-TNF: infliximab, etanercept, adalimumab,

  -amti-IL6 (Tocilizumab)

  -anti-IL2/IL2R (CD25): daclizumab, inolimomab, basiliximab, denileukin diftitox

- *Mesenchymal stem cells*
- *T-regulatory cells*
- *Suicide gene therapy of donor T-cells*

Prior Rituximab Correlates with Less Acute Graft-versus-Host Disease and Better Survival in B-Cell Lymphoma Patients Who Received Allogeneic Peripheral Blood Stem Cell Transplantation

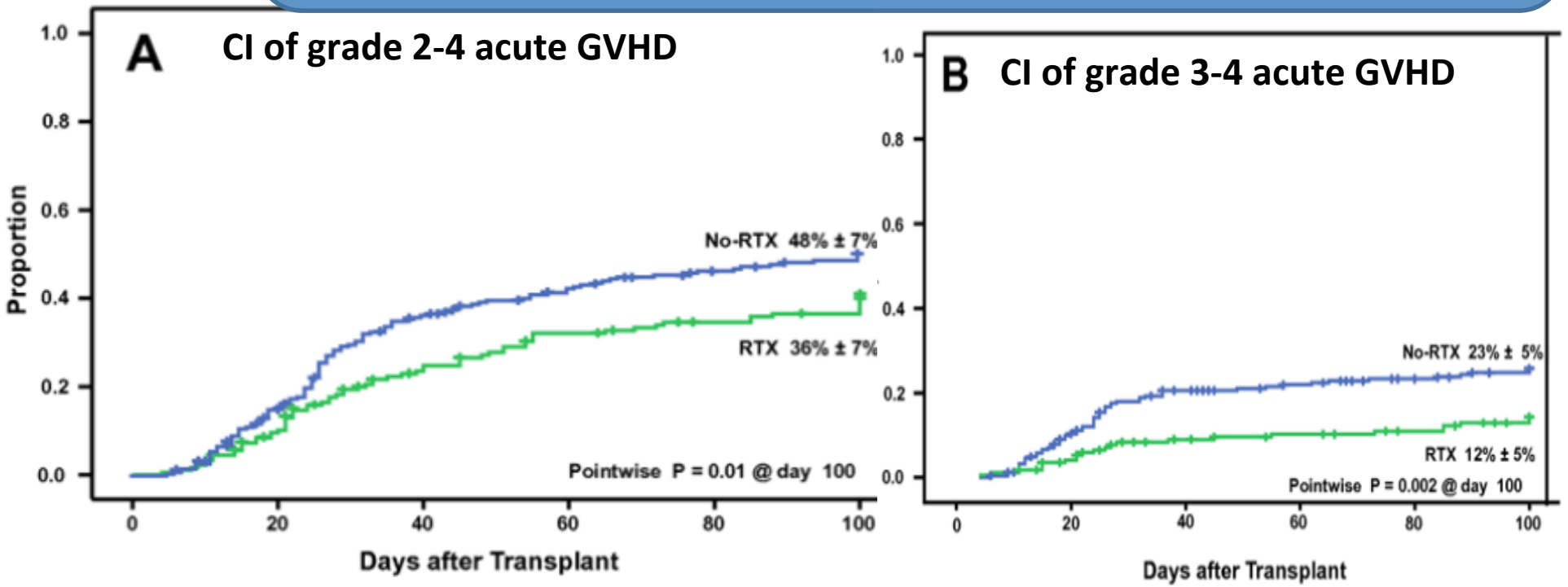
Br J Haematol. 2009 June ; 145

Characteristics	No Rituximab N (%)	Rituximab N (%)	P-value[d]
Number of patients	256	179	

late post-TX rituximab does not reduce GVHD

timing is critical: early B-cell depletion is crucial!

Ratanatharathorn et al.



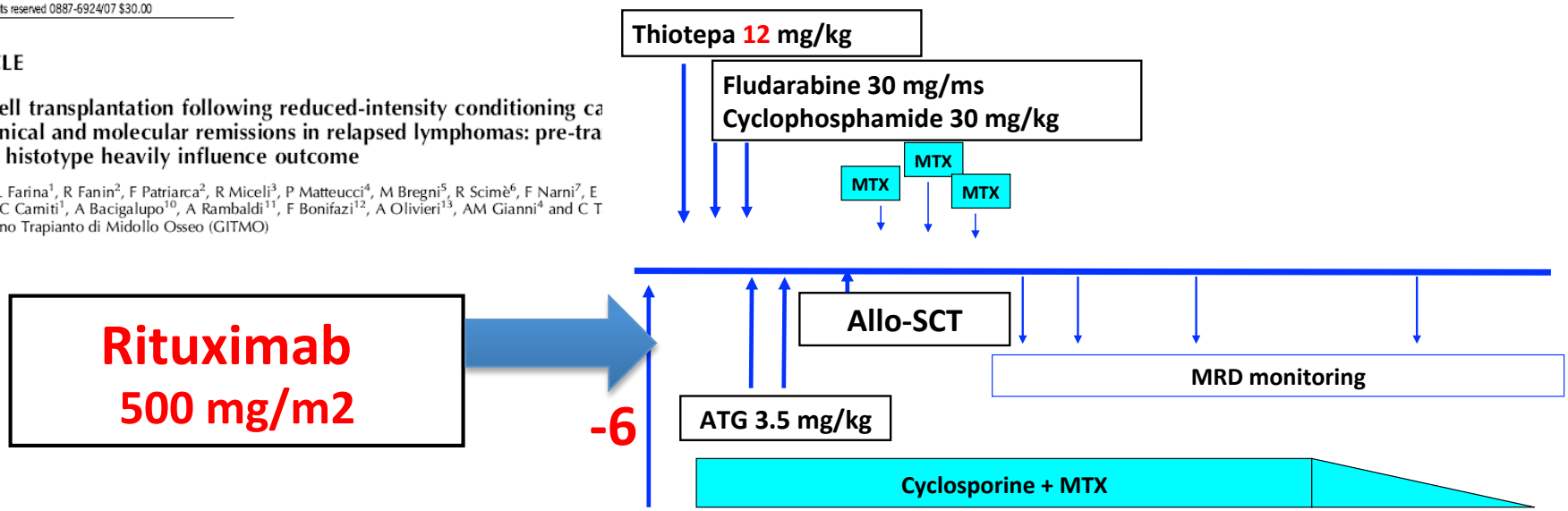
Leukemia (2007) 21, 2316–2323

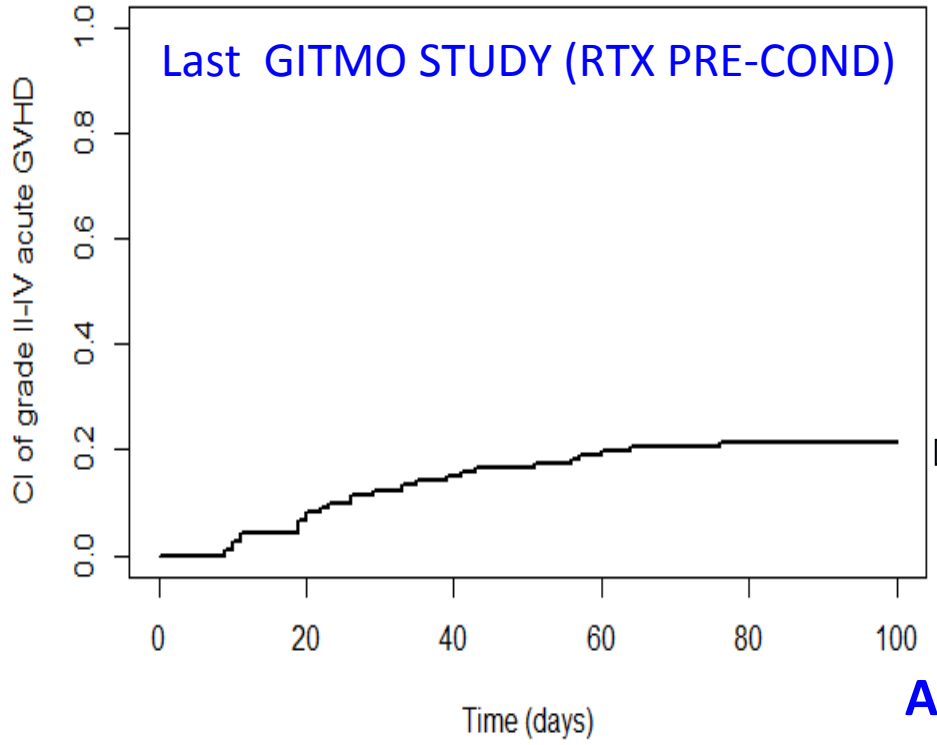
www.nature.com/leu

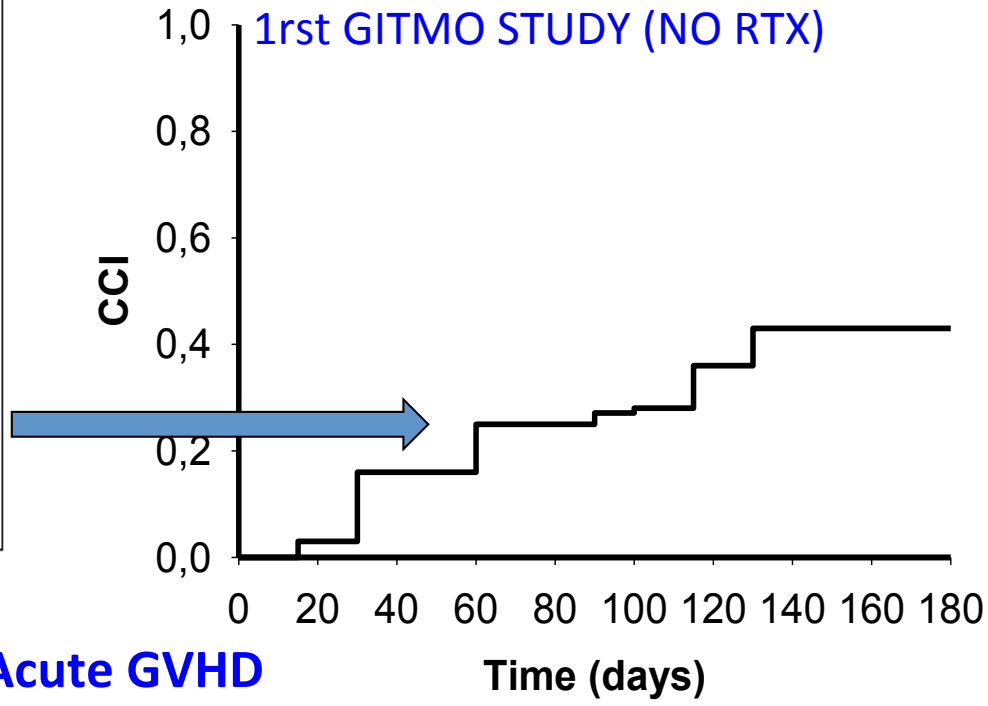
ORIGINAL ARTICLE

Allogeneic stem cell transplantation following reduced-intensity conditioning ca induce durable clinical and molecular remissions in relapsed lymphomas: pre-tra disease status and histotype heavily influence outcome

P Corradini[1], A Dodero[1], L Farina[1], R Fanin[2], F Patriarca[2], R Miceli[3], P Matteucci[4], M Bregni[5], R Scimè[6], F Narni[7], E A Locasciulli[9], R Milani[1], C Camiti[1], A Bacigalupo[10], A Rambaldi[11], F Bonifazi[12], A Olivieri[13], AM Gianni[4] and C T on behalf of Gruppo Italiano Trapianto di Midollo Osseo (GITMO)

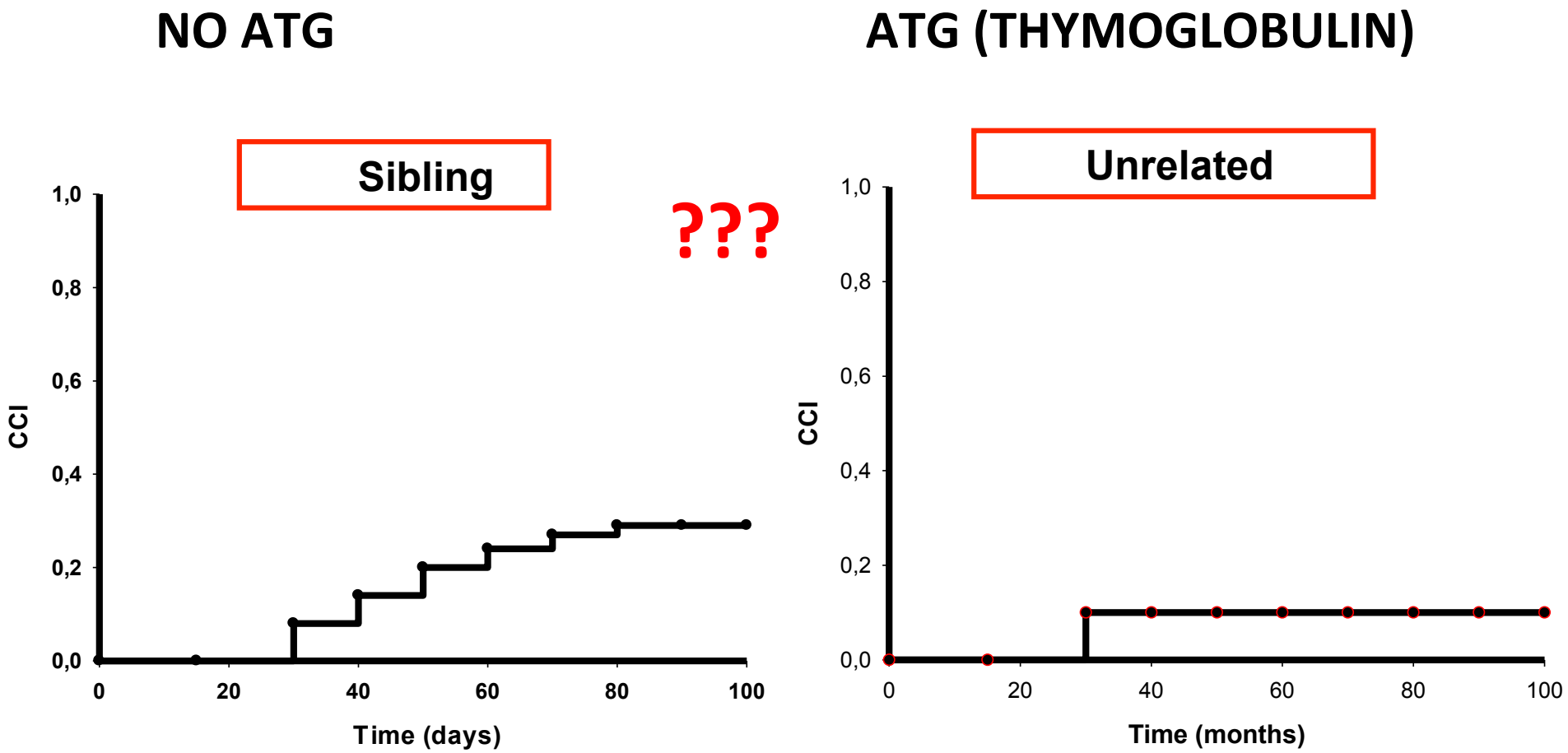






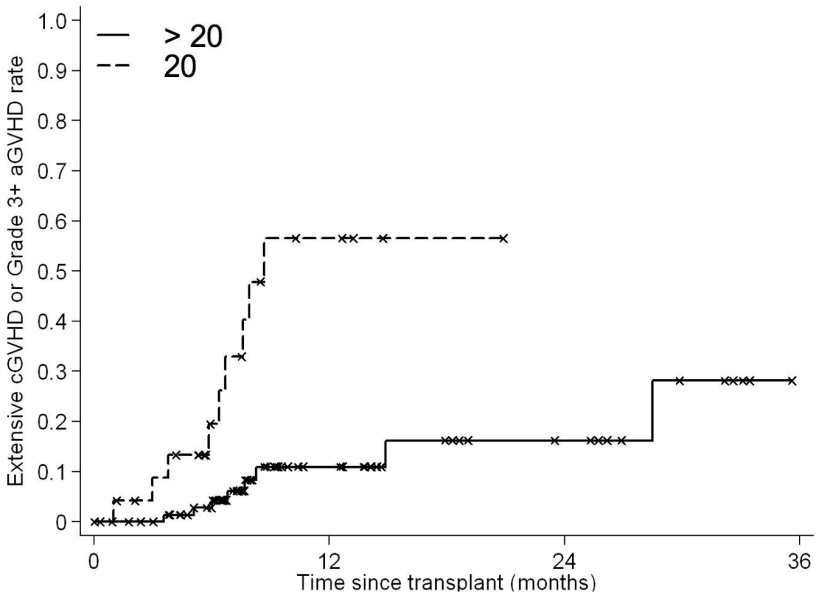
Acute GVHD

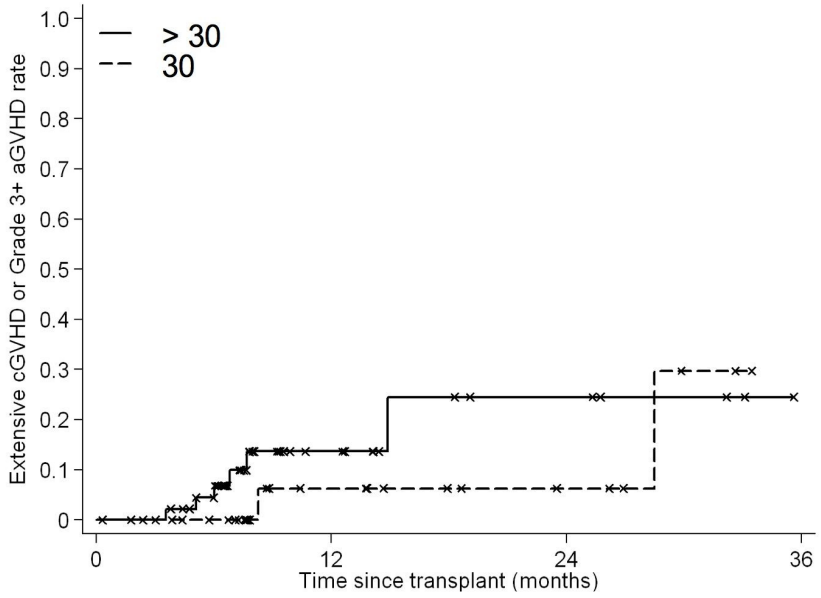
Acute GVHD by donor



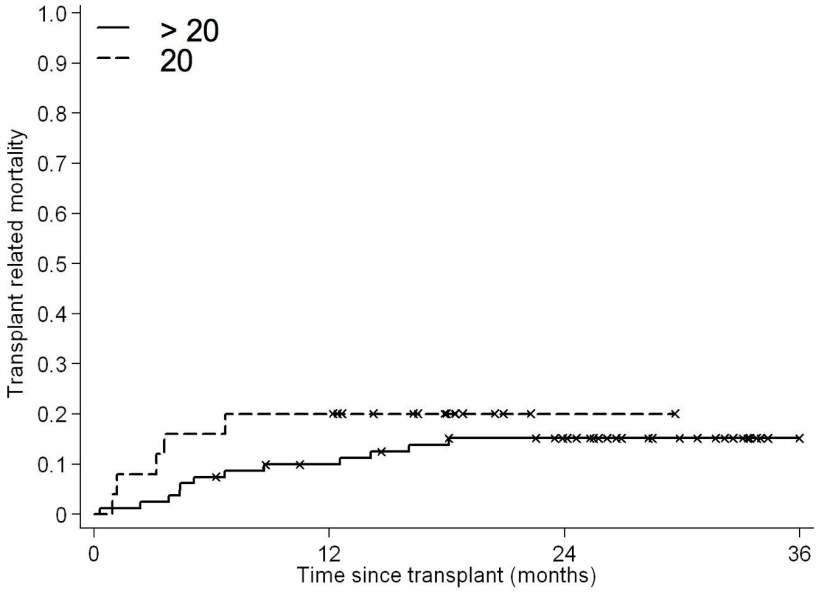
Alemtzumab dose de-escalation in HLA-identical sibling transplantations

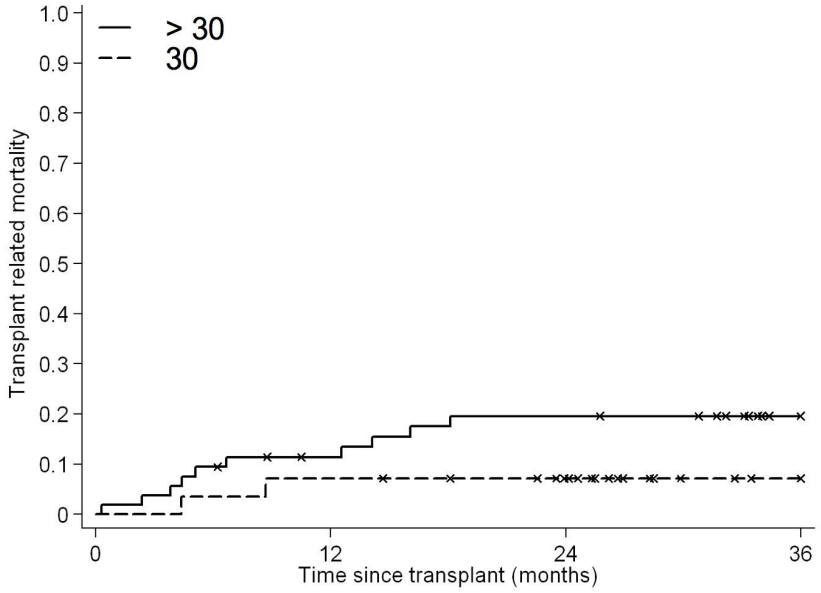
Severe GVHD





TRM





Depletion of Naive T cells CD45RA+

- Central and memory T-cells do not appear to induce GVHD although they mediate GVT responses.
- CD45RA-depleted graft is associated with lower GVHD incidence.

1-Alloreactive and leukemia-reactive T cells are preferentially derived from naive precursors in healthy donors: implications for immunotherapy with memory T cells. Distler E, Haematologica. 2011

2-Memory CD4+ T cells do not induce GVHD . Anderson BE et al. J Clin Invest. 2003

3-Depletion of naive T cells using clinical grade magnetic CD45RA beads: a new approach for GVHD prophylaxis. Teschner D et al Bone Marrow Transplant. 2014

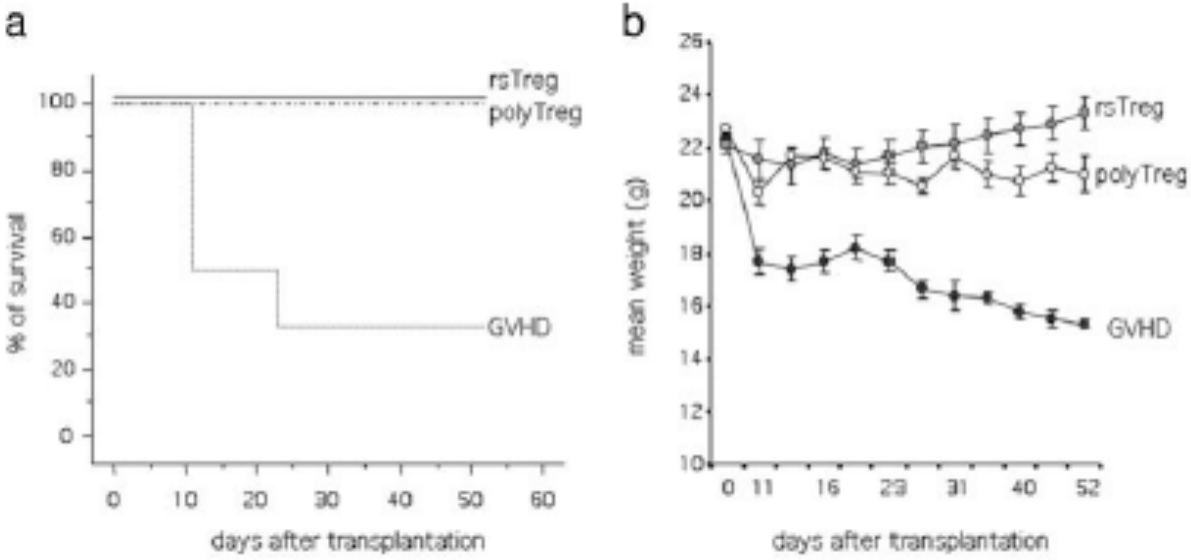
The Journal of Immunology

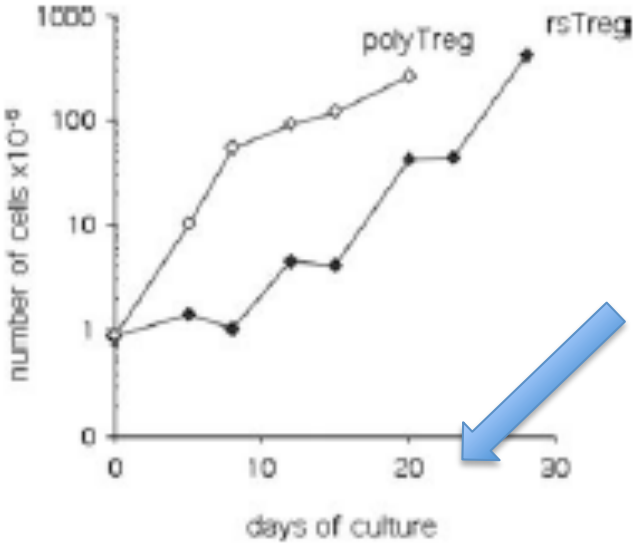
This information is current as of September 16, 2015.

Ex Vivo-Expanded CD4$^+$CD25$^+$ Immunoregulatory T Cells Prevent Graft-versus-Host-Disease by Inhibiting Activation/Differentiation of Pathogenic T Cells

Aurélie Trenado, Muriel Sudres, Qizhi Tang, Sébastien

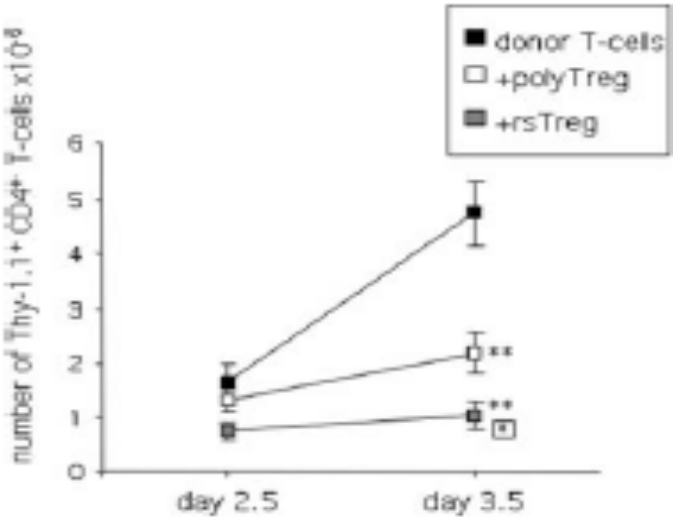
Expanded Tregs prevent GVHD





IL-2 is needed for Treg expansion

Expanded Tregs strongly inhibited the division and expansion of donor T cells.



Initial therapy of aGVHD

- The standard treatment of patients requiring systemic therapy is corticosteroids at a daily dose of 2 mg/kg.
- The optimal duration of steroid therapy is unknown.
- The preferred rate to taper steroids for aGVHD has been rarely studied, but tapering limits have been included in some prospective trials.

The aggregated results of standard treatment with prednisone showed 48% CR rate, 64% ORR and 66% OS at a 6 months

Steroid dosage for GVHD > grade I: gold standard 2mg/kg methylprednisolone

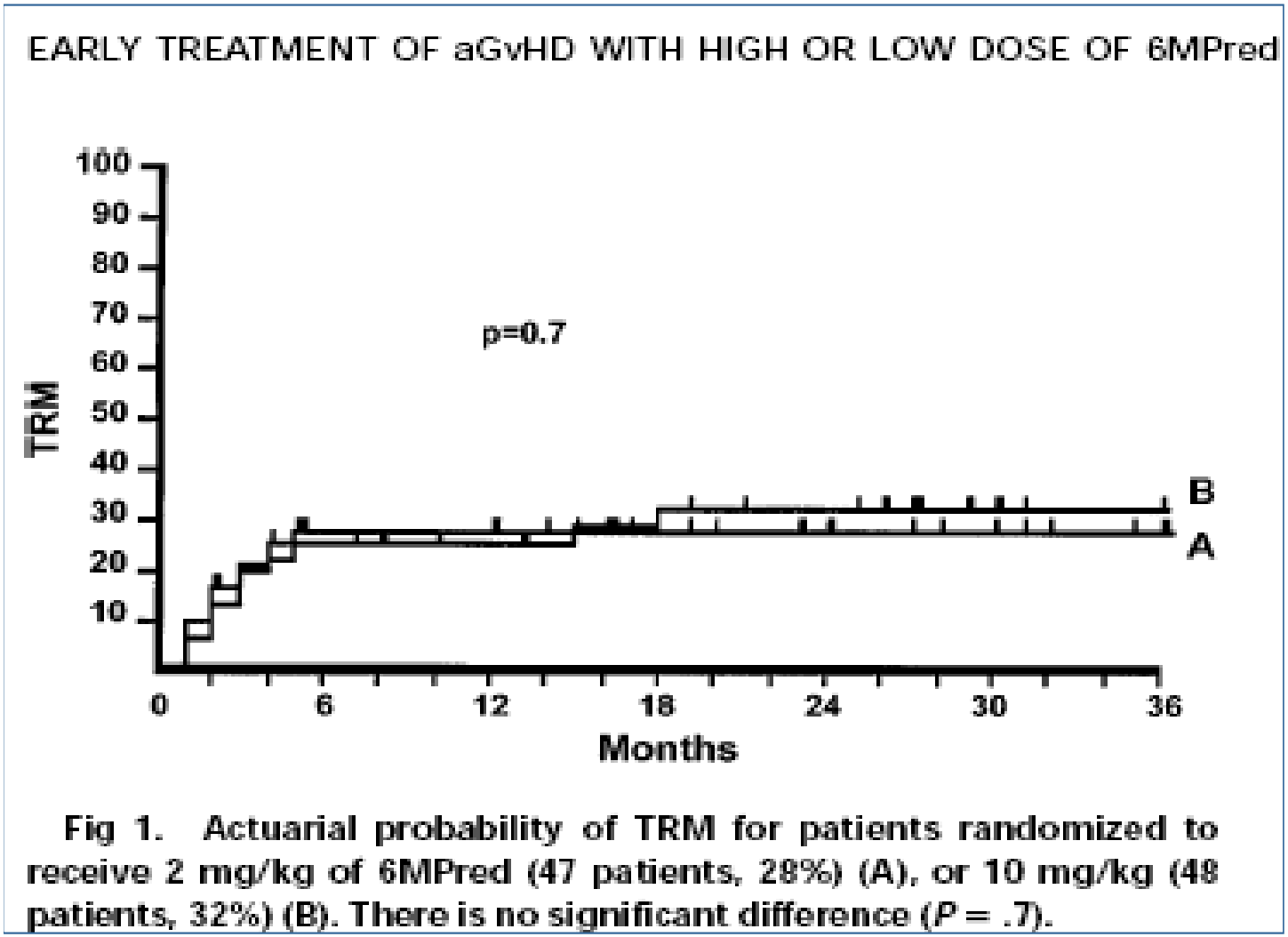


Fig 1. Actuarial probability of TRM for patients randomized to receive 2 mg/kg of 6MPred (47 patients, 28%) (A), or 10 mg/kg (48 patients, 32%) (B). There is no significant difference ($P = .7$).

Van Lint et al (GITMO) Blood 1998: 95 pts with > grade I aGvHD

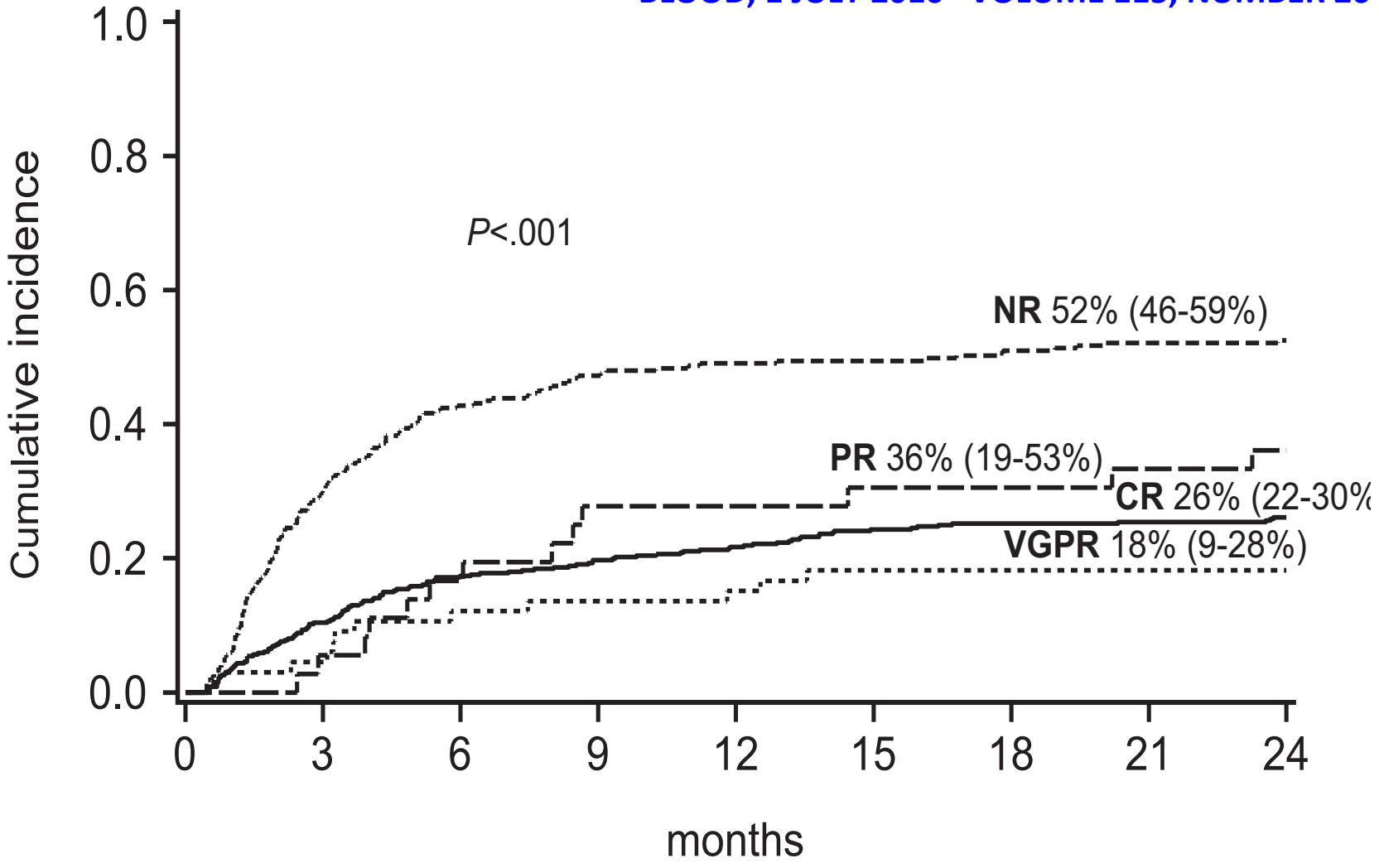
Response Definitions in acute GVHD

Term	Definition
Complete response (CR)	Resolution of aGVHD in all involved organs
Partial response (PR)	Organ improvement of at least 1 stage without worsening in any other organ system
Overall response (OR)	CR or PR
Mixed response (MR)	Improvement by at least 1 organ stage in at least 1 evaluable organ with worsening by at least 1 organ stage in at least 1 other organ
Stable disease	The absence of any clinically significant differences (improvement or worsening) sufficient to meet minimal criteria for improvement or deterioration in any evaluable organ
Worsening disease	Deterioration in at least 1 evaluable organ by 1 stage or more
No response	MR or stable disease or worsening disease

MacMillan ML, DeFor TE, Weisdorf DJ. The best endpoint for acute GVHD treatment trials. Blood. 2010;115:5412-5417.

Cumulative incidence of TRM at 2 years by response at day 28 after initiation of steroid therapy for acute GVHD

BLOOD, 1 JULY 2010 VOLUME 115, NUMBER 26



Biol Blood Marrow Transplant 15:777-784, 2009

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American Society for Blood and Marrow Transplantation

PERSPECTIVE

Endpoints for Clinical Trials Testing Treatment of Acute Graft-versus-Host Disease: A Joint Statement

Paul J. Martin,[1] Carlos R. Bachier,[2] Hans-Georg Klingemann,[3] Philip L. McCarthy,[4] Paul Szabolcs,[5] Joseph P. Uberti,[6] Michael W. Schuster,[7] Daniel Weisdorf,[8] Nelson J. Chao,[5] Partow Kebriaei,[9] Elizabeth J. Shpall,[9] Margaret L. MacM

For trial purposes the main clinical end points include:

- day 28 response;
- day 56 aGVHD-free survival;
- 6-month freedom from treatment failure;
- rates of cGVHD, NRM and OS

The determination of steroid-refractory disease should be made quickly, 7 to 10 days and progression even sooner if the patient is clearly worsening, e.g. 3 to 4 days after the start of high-dose steroids.

Refractory aGVHD

Minimal or absent response to first-line steroids
Inability to tapering corticosteroid therapy

- Approximately half of patients will not achieve a sustained CR after first-line therapy with steroids *and <50% of CR are maintained.*

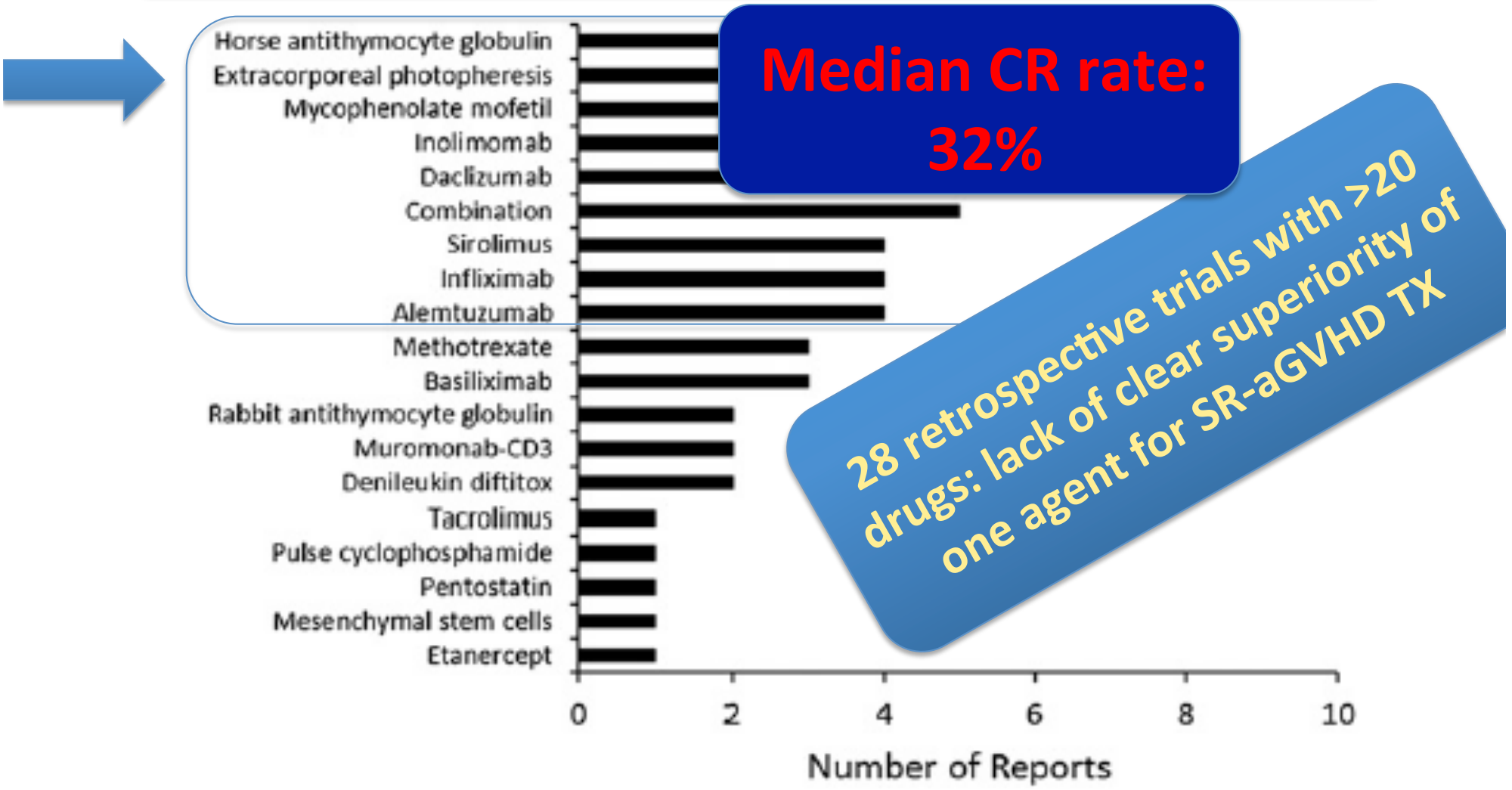
- OS in steroid-resistant (SR) aGVHD: 15% at 2 years (median 6 months).

REVIEW

American Society for Blood and Marrow Transplantation

Secondary Treatment of Acute Graft-versus-Host Disease: A Critical Review

Paul J. Martin,[1,2] Yoshihiro Inamoto,[1,2] Mary E. D. Flowers,[1,2] Paul A. Carpenter[1,3]

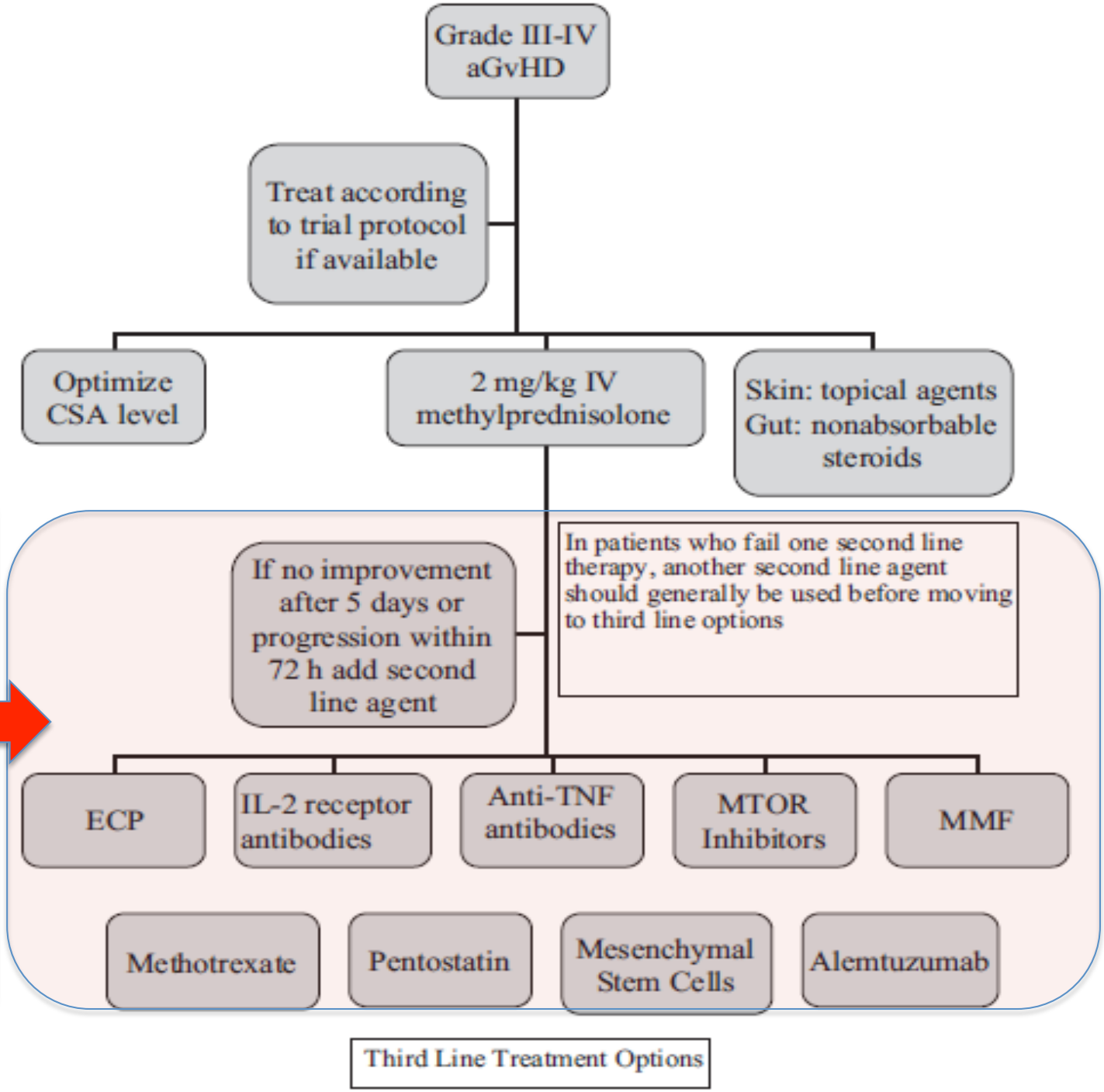


bjh guideline

Diagnosis and

Fiona L. Dignan,[1,2] Andrew
Julia J. Scarisbrick,[8] Peter C
Haemato-oncology Task For
and Marrow Transplantatio

2nd Line Options



New Tx currently evaluated in clinical Trials for aGVHD

- *MSC…….*
- Begedina (anti-CD26)
- Vedolizumab
- Cannabidiol
- Targeting intracellular pathways:

  Jak-inhibitors → Ruxolitinib;
- *others….Tocilizumab; HIDAC; Prot.-inhib.*

MSC *in acute……*

……. and cGVHD

SEMINAL STUDIES

- *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.*

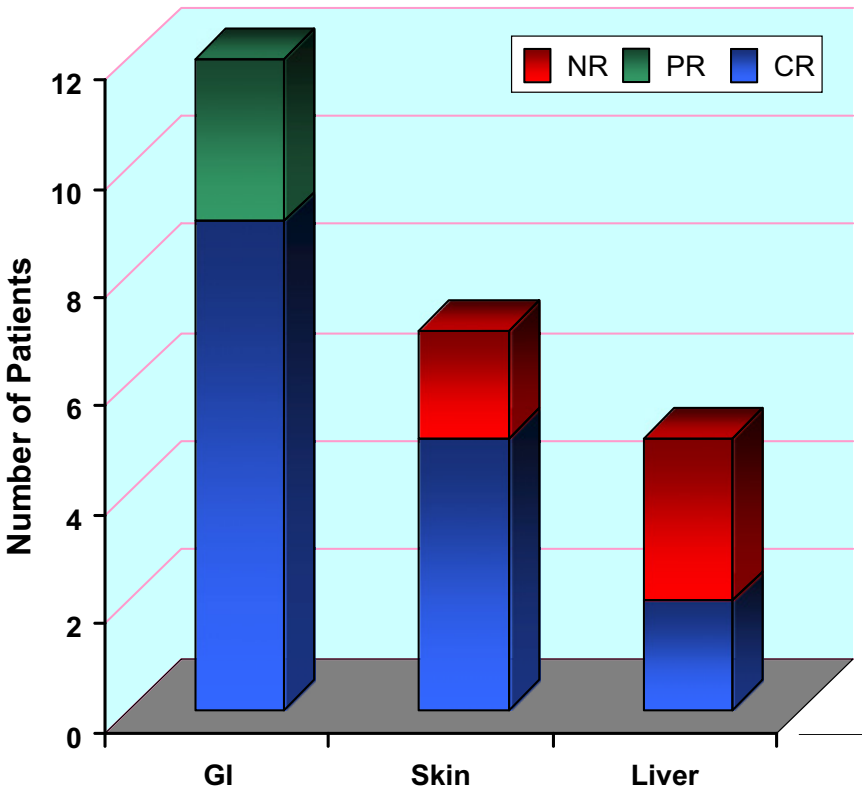
Efficacy of Mesenchymal Stem Cell Therapy for Steroid-Refractory Acute Graft-Versus-Host Disease following Allogeneic Hematopoietic Stem Cell Transplantation: A Systematic Review and Meta-Analysis

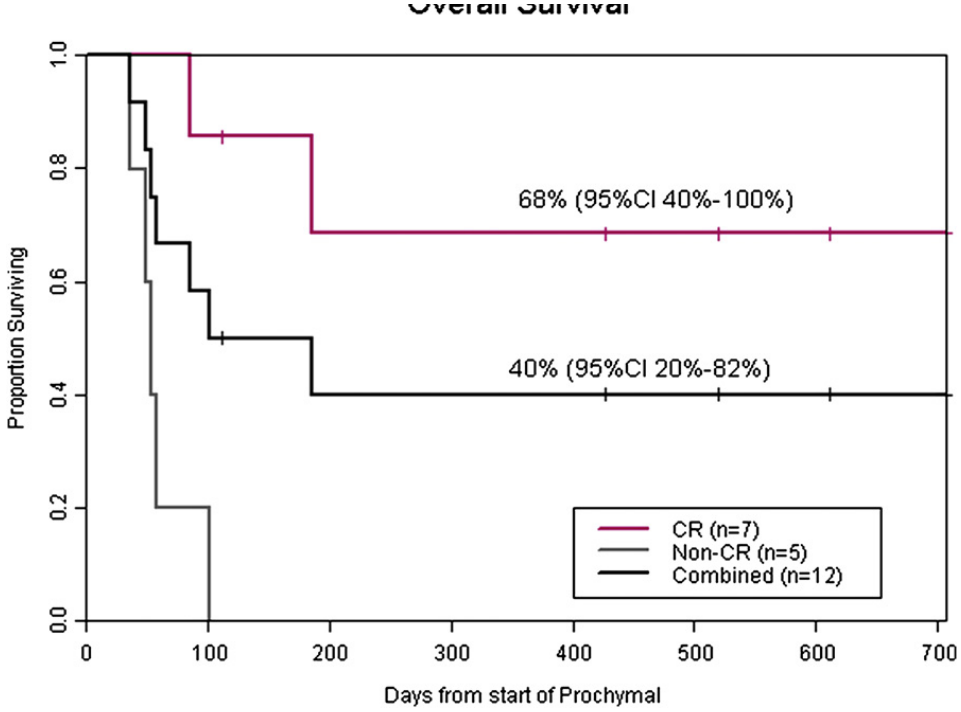
Xiaomei Chen, Chunyan Wang, Jin Yin, Jinhuan Xu, Jia Wei*, Yicheng Zhang*

PLOS ONE

August 31, 2015

Biol Blood Marrow Transplant 17:534-541, 2011





premanufactured, universal donor formulation of hMSCs (Prochymal) in children

Efficacy and Safety of Ex Vivo Cultured Adult Human Mesenchymal Stem Cells (Prochymal™) in Pediatric Patients with Severe Refractory Acute Graft-Versus-Host Disease in a Compassionate Use Study

Vinod K. Prasad,[1] Kenneth G. Lucas,[2] Gary I. Kleiner,[3] Julie An M. Talano,[4] David Jacobsohn,[5] Gloria Broadwater,[6] Rod Monroy,[7] Joanne Kurtzberg[1]

Pt. No.	Day of Onset of aGVHD	Days of aGVHD prior to hMSC	aGVHD Grade at start of hMSC	GI/Skin/Liver Stages at Start of hMSC
1	70	20	IV	4/1/3
2	81	45	III	3/3/0
3	22	46	IV	4/2/0
4	98	119	III	3/0/0
5	56	181	IV	4/0/2
6	72	30	IV	4/0/0
7	27	18	IV	4/1/3
8	22	76	IV	4/1/0
9	84	19	III	3/0/0
10	33	38	III	3/0/0
11	93	125	III	3/0/0
12	80	157	IV	4/0/1

Outcomes after MSCs therapy

- 40 patients (adults/children 25/15)
- Evaluation of response: at day +28 after the last MSC infusion

- Treatment response:

Adults	***CR 16%***	***CR+PR 68%***
Children	***CR 47%***	***CR+PR 67%***

- Median follow up from last MSC infusion: 250 (30-1066) days
- Deaths = 17

  Relapse = 3

  NRM = 14

M. Introna et al. / Biol Blood Marrow Transplant 20 (2014) 375-381

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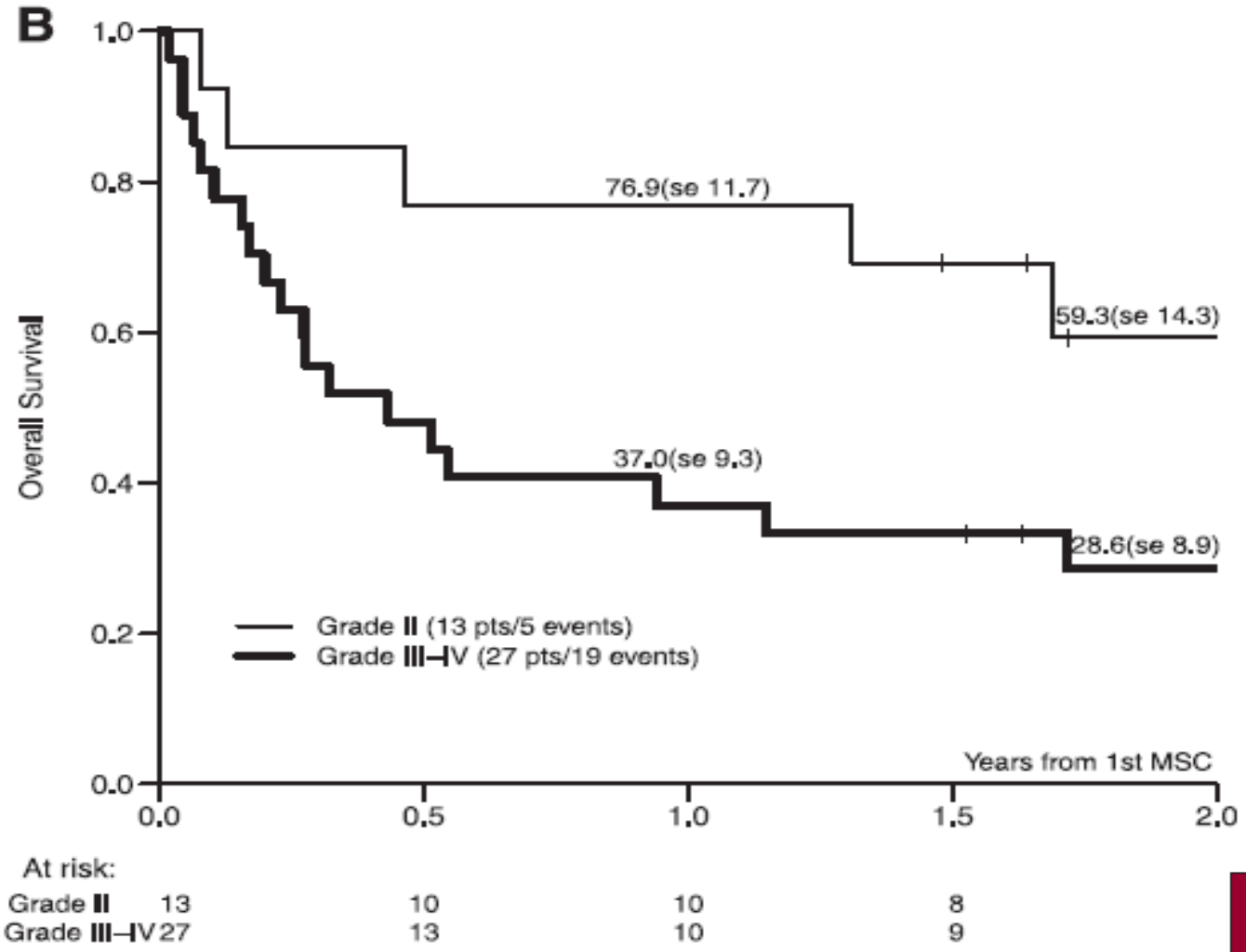
Survival according to GVHD grade



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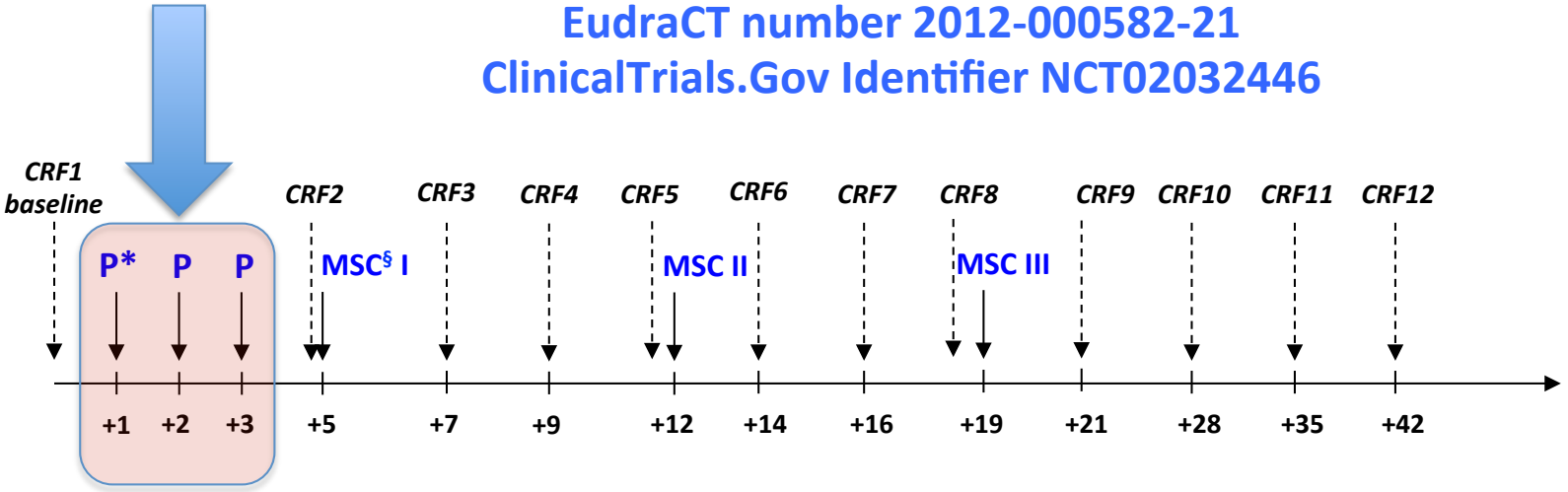
M. Introna et al. / Biol Blood Marrow Transplant 20 (2014) 375-381

The umbilical cord wall as an alternative source of MSCs

UMBILICAL CORD DERIVED MESENCHYMAL STROMAL CELLS (UC-MSC) FOR THE TREATMENT OF SEVERE (GRADE III-IV) STEROID-RESISTANT GRAFT VERSUS HOST DISEASE: A PHASE I/II TRIAL

EudraCT number 2012-000582-21
ClinicalTrials.Gov Identifier NCT02032446



*** P = pentostatin, dose 1 mg/m^2**

§ MSC doses:

a) 3 patients → 3 infusions of 1x10^6 cells /kg
b) 3 patients → 3 infusions of 2x10^6 cells /kg
c) 3 patients → 3 infusions of 3x10^6 cells /kg

Courtesy of

M. Introna and A. Rambaldi

UMBILICAL CORD DERIVED MESENCHYMAL STROMAL CELLS FOR SEVERE (GRADE III-IV) STEROID-RESISTANT GRAFT VERSUS HOST DISEASE: A PHASE I/II TRIAL

EudraCT number 2012-000582-21
ClinicalTrials.Gov Identifier NCT02032446

Inclusion Criteria

- SR grade III-IV classic acute GvHD occurring within 100 days
- SR GvHD is defined according to Pidala and Anasetti as follows: a) progression of at least 1 overall grade within 3 days of optimal steroid treatment; b) failure to demonstrate any overall grade improvement over 5 to 7 days; c) incomplete response by 14 days of 2 mg/kg/day of steroid therapy
- Persistent, recurrent, or late acute GvHD (occurring beyond 100 days)
- Overlap syndrome in which diagnostic or distinctive features of cGvHD and acute GvHD appear together

- **Exclusion criteria:** Inability to obtain written informed consent.

Innovations in ECP

- Photodepletion (PD) with a dibromorhodamine (TH9402) photosensitizer in lieu of 8- methoxypsoralen
- PD with TH9402 resulted in selective eradication of endogenous proliferating Tcon with concomitant sparing and expansion of Treg.
- This resulted in a higher level of circulating Tregs in patients receiving TH9402-based phototherapy*.

*Bastien JP. Photodepletion differentially affects CD41 Tregs versus CD41 effector T cells from patients with chronic graft-versus-host disease. Blood. 2010; 116(23): 4859-4869.

MAIN TRIALS WITH ECP IN GVHD

- A Randomized Study of ECP Therapy With UVADEX for Pts With Moderate/ Severe cGVHD. NCT01380535

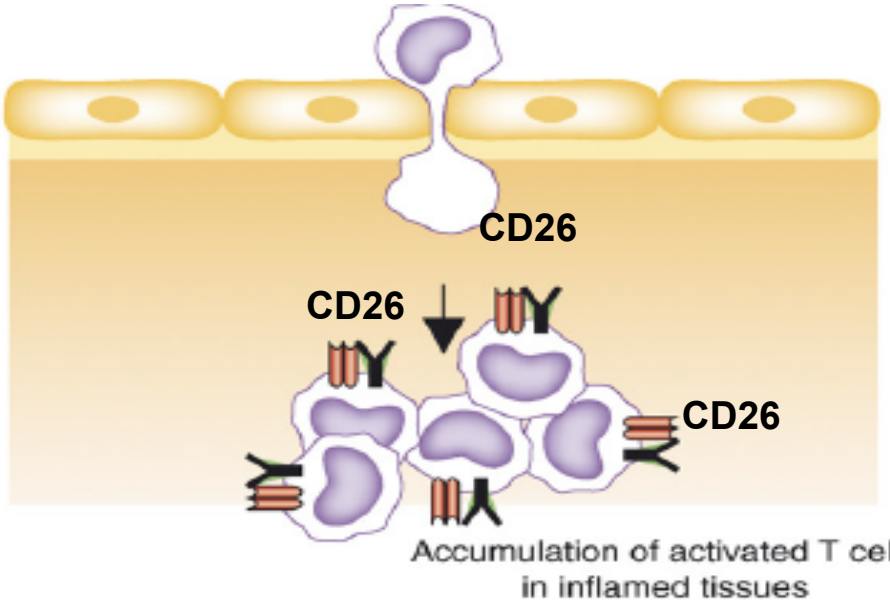
- *ECP for Progressive Bronchiolitis Obliterans Syndrome in Medicare-Eligible Recipients of Lung Allografts. NCT02181257-Prospective observational**

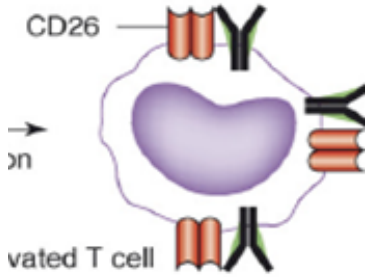
- Addition of Etanercept and ECP to Standard *GVHD Prophylaxis* in Stem Cell Transplant NCT00639717*

- A Randomized Phase II Study for the Evaluation of ECP plus Corticosteroids for Initial Treatment of aGVHD. NCT00609609

- A Phase II Trial of Low-Dose IL-2 Added to ECP for SR-cGVHD. NCT02340676

CD26 and T cell migration





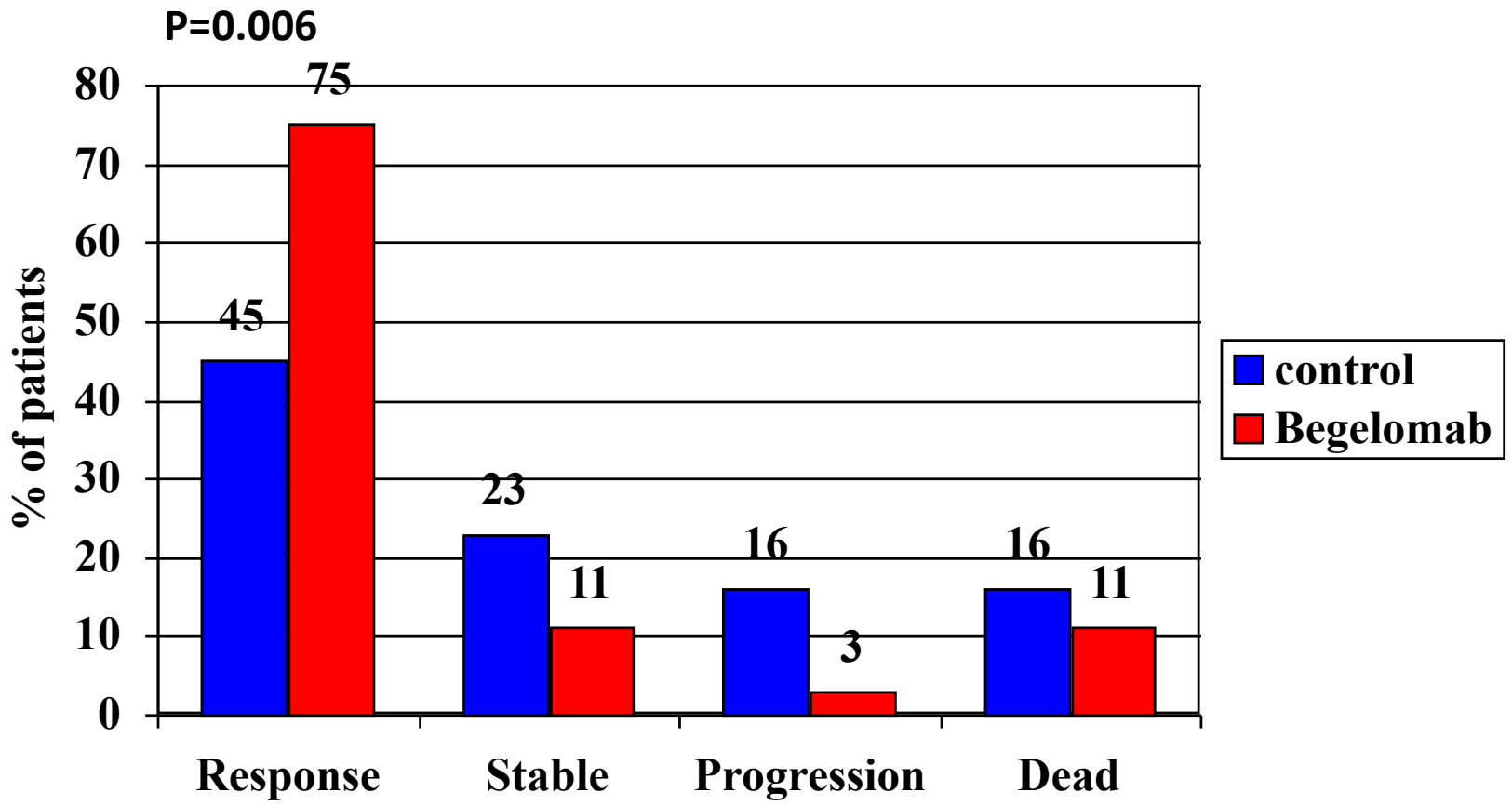
CD26 is highly expressed on T cells migrating through endothelial cell monolayers in vitro

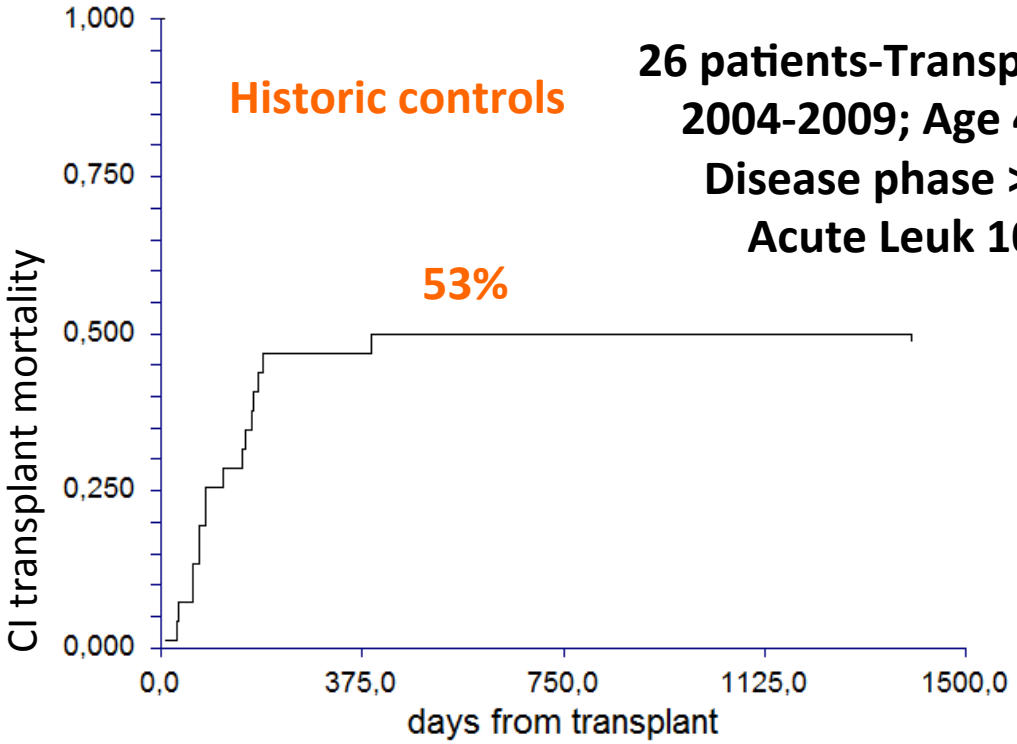
(J Immunol, 1992; 148: 1367)

- **Inhibition of CD26 impairs T cells migration across the endothelial barrier** *(Trends in Immunology 2008; 29:295)*

- **Inhibition of CD26 preserves pancreatic islet transplants in mice**. *Diabetes 2010; 59(7):1739-50*

Response and outcome on day +28

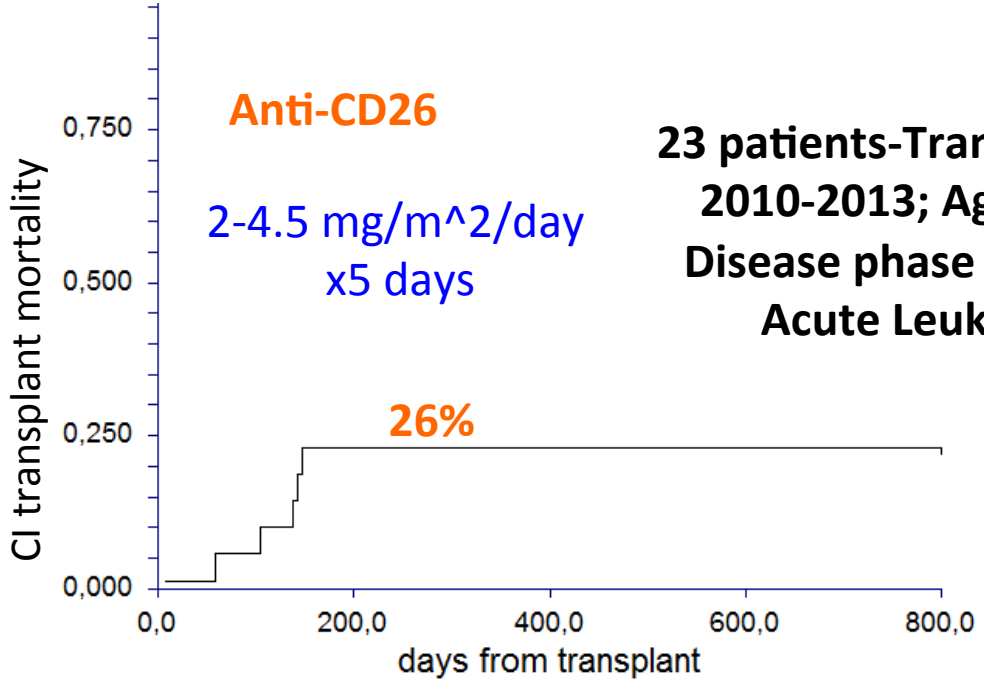




Historic controls

26 patients-Transplant period :
2004-2009; Age 44 (18-64)
Disease phase >CR1 70%
Acute Leuk 10 (38%)

53%



Anti-CD26

2-4.5 mg/m^2/day
x5 days

23 patients-Transplant period :
2010-2013; Age 43 (21-63)
Disease phase >CR1 73%
Acute Leuk 13 (46%)

26%

Courtesy of A. Bacigalupo
Unpublished data

DOSE FINDING

2, 3, 4.5 mg/m^2 /day

1 2 3 4 5

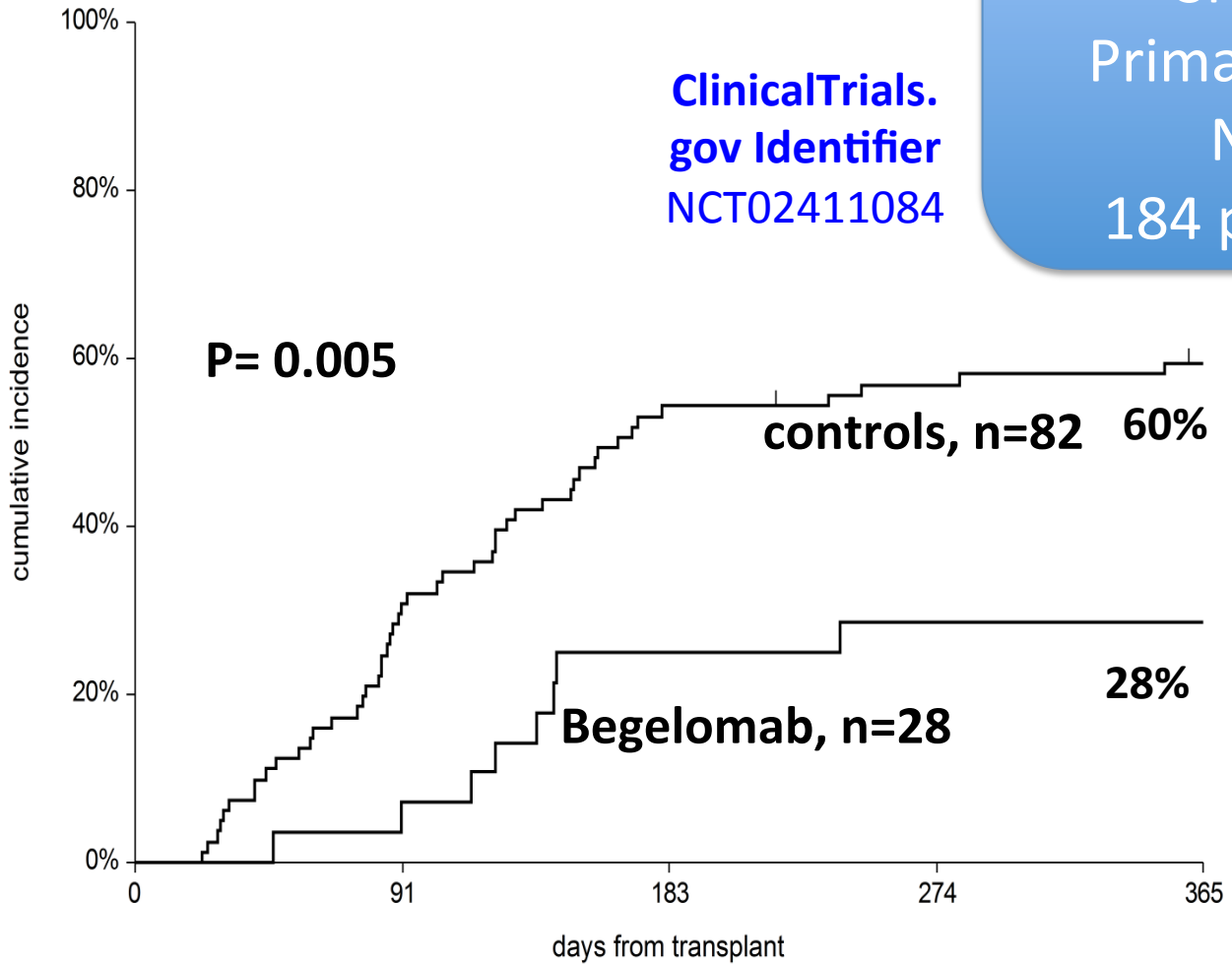
Study2, (EUDRACT 2012-001353-19)

BEGEDINA in aGVHD

Randomized Clinical Study to Compare BEGEDINA Vs BAT for SR-aGVHD in adults;
Primary EP: ORR at day 28;
NRM at 6 months
184 pts to be randomized

1 year TRM in SR aGvHD grade

ClinicalTrials.gov Identifier
NCT02411084



Recently stopped after evaluating the first 40 pts

Courtesy of A. Bacigalupo ASH 2016

Targeting Integrin α4β7 in Steroid-Refractory Intestinal Graft-versus-Host Disease

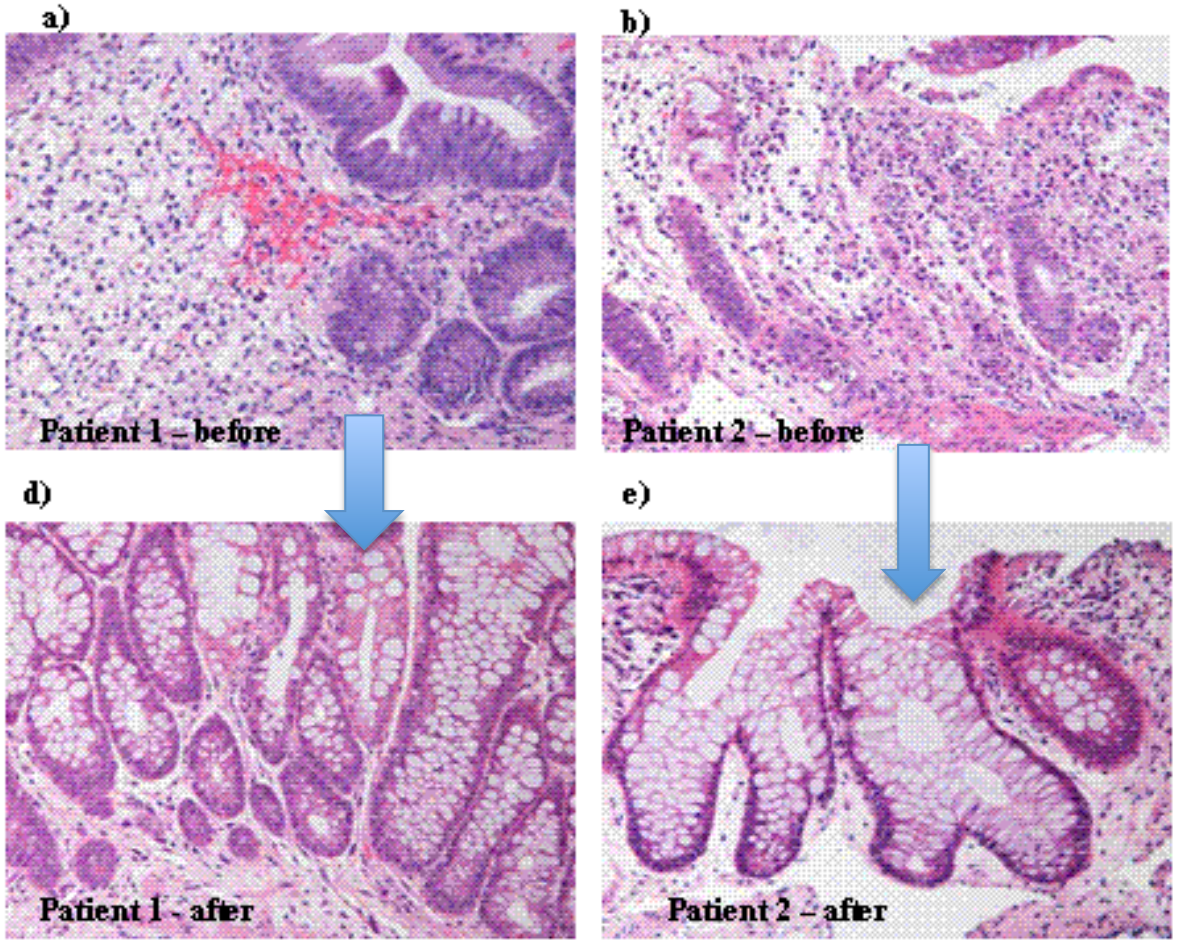
Yngvar Fløisand [1,*], Knut E.A. Lundin [1,2,3,4], Vladimir Lazarevic [5], Jørn Dehli Kristiansen [1], Liv T.N. Osnes [6], Geir E. Tjønnfjord [1,3], Henrik Mikael Reims [7], Tobias Gedde-Dahl [1]

Biol Blood Marrow Transplant 23 (2017) 172–175

- Dose-Finding Study of Vedolizumab IV Plus Standard of Care for **GvHD Prophylaxis** in Patients Undergoing HSCT NCT02728895

- Dose-Finding Study for **Steroid-Refractory Acute Intestinal GvHD** in Patients Undergo Allo HSCT
- *Vedolizumab 300-600 mg, IV once on Days 1, 15, 43, 71 and 99*
  NCT02993783

6/6 patients exhibited clinical responses within 7 – 10 days after start of TX

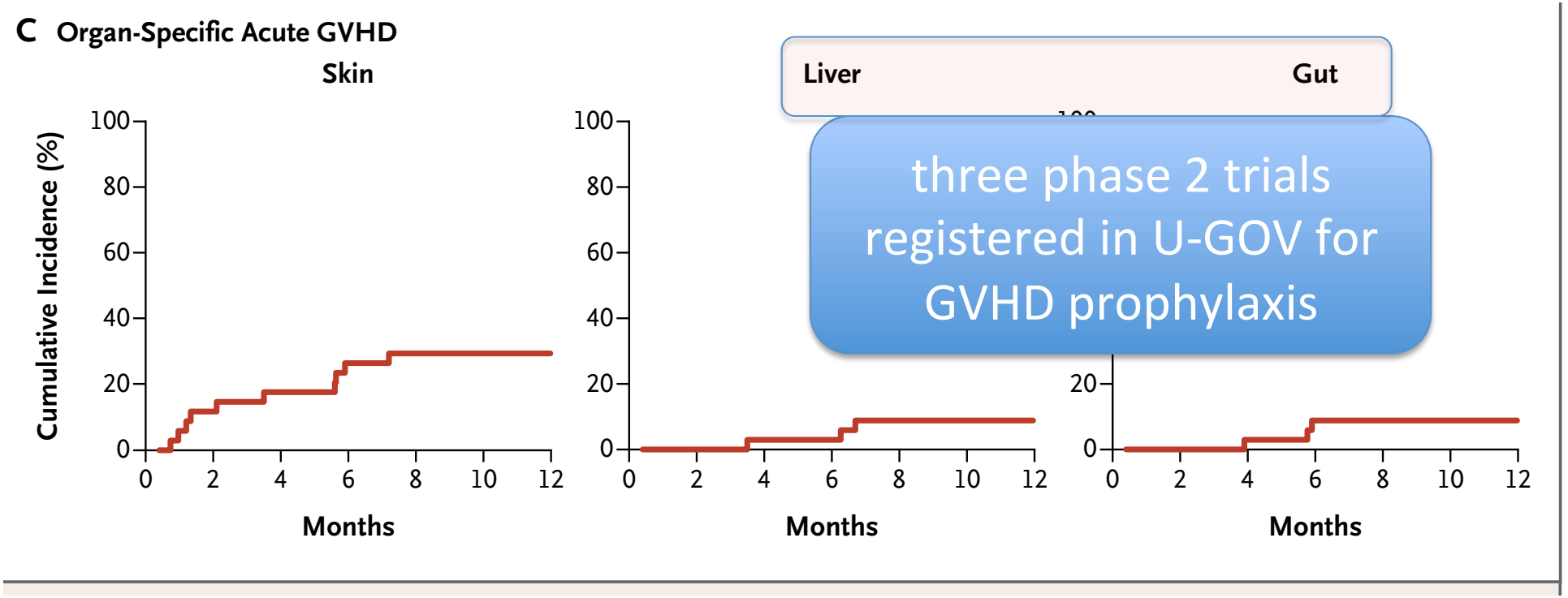


Blockade of Lymphocyte Chemotaxis in Visceral Graft-versus-Host Disease

Ran Reshef, M.D., Selina M. Luger, M.D., Elizabeth O. Hexner, M.D., Alison W. Loren. M.D.. Noelle V. Frev. M.D.. Sunita D. Nasta. M.D..

NEJM 2012

in murine models, migration of CCR5+CD8+ cells into the liver and gut is markedly reduced by anti- CCR5antibody,



Maraviroc orally twice daily starting 2 days before transplantation until day 30

The addition of maraviroc to standard GVHD prophylaxis resulted in a low incidence of GVHD in high-risk patients

Cannabidiol (CBD) in aGVHD

- Cannabis use in healthy subjects has been associated with a decrease lymphocyte proliferative response to mitogens and an increase in IL-10 and TGF-beta.
- Cannabis smoking induced clinical response in pts with refr. Crohn's disease
- *Pandey R et al. Targeting cannabinoid receptors as a novel approach in the treatment of GVHD: evidence from **an experimental murine model**. J Pharmacol Exp Ther. 2011;338.*
- In GVHD mice THC significantly decreased levels of IL-2 and INF-g; THC treatment reduced the expansion of donor effector T cells and increased Foxp3þT reg.
- **CBD does not produce psychoactive effects of THC. Similar to THC, CBD possesses potent anti-inflammatory and immunosuppressive properties.**
- **CBD reduces dendritic cells migration to secondary lymphoid organs**

Cannabidiol for the Prevention of Graft-versus-Host-Disease after Allogeneic Hematopoietic Cell Transplantation: Results of a Phase II Study

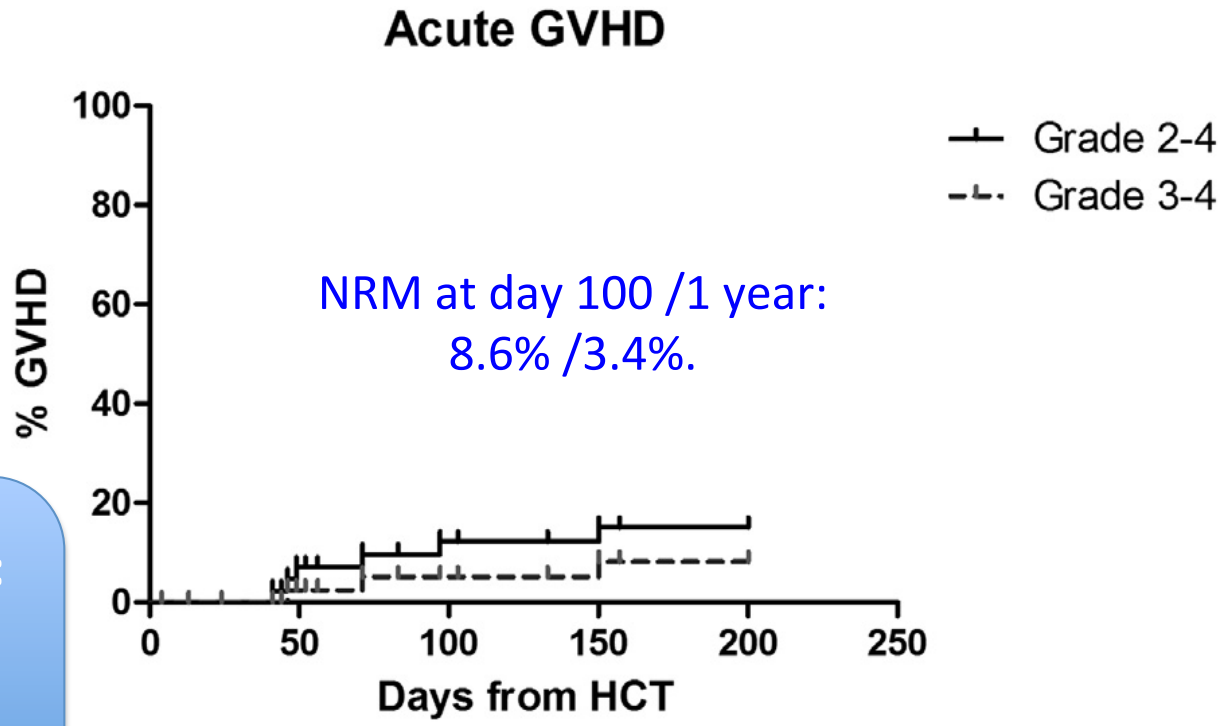
Moshe Yeshurun [1,2,*], Ofer Shpilberg [1,2], Corina Herscovici [1,2], Liat Shargian [1,2], Juliet Dreyer [1], Anat Peck [1], Moshe Israeli [3], Maly Levy-Assaraf [2,4], Tsipora Gruenewald [5], Raphael Mechoulam [6], Pia Raanani [1,2], Ron Ram [1,2]

CBD 300 mg/day orally starting 7 days before HSCT until day 30.

48 consecutive adult patients were enrolled

Prim End Point:
% of pts in CR
at 90 days

ClinicalTrials.gov Identifier:
NCT02392780;
Cannabidiol for the Treatment of Severe (Grades III/IV) aGVHD



NRM at day 100 /1 year:
8.6% /3.4%.

Figure 1. Cumulative incidence of acute GVHD.

Biol Blood Marrow Transplant 21 (2015) 1770–1775

Targeting intracellular pathways

- ***JAK-inhibitors***

- *Proteasome-inhibitors (Bortezomib)*
- *Hypomethylating agents (5-AZA)*
- *Histone deacetylase (HDAC) inhibitors*
- *Statins*

JAK1/2 signaling is pivotal in multiple steps leading to inflammation

- JAK1 and JAK2 mediate *proinflammatory cytokines* dowstream (IFN-g and IL-6)
- inhibition of this pathway suppress both *activation of DC and alloreactive T* cells.
- *T-reg cell* have down-regulated Jak pathway and *are spared by JAK-inhibitors*

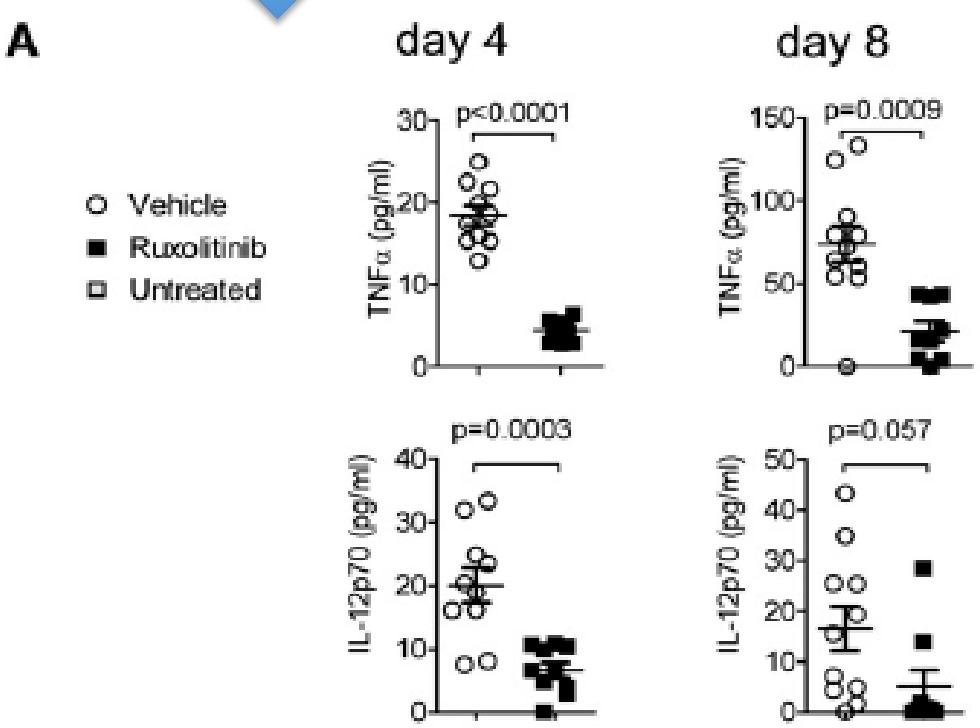
Activity of therapeutic JAK 1/2 blockade in graft-versus-host disease

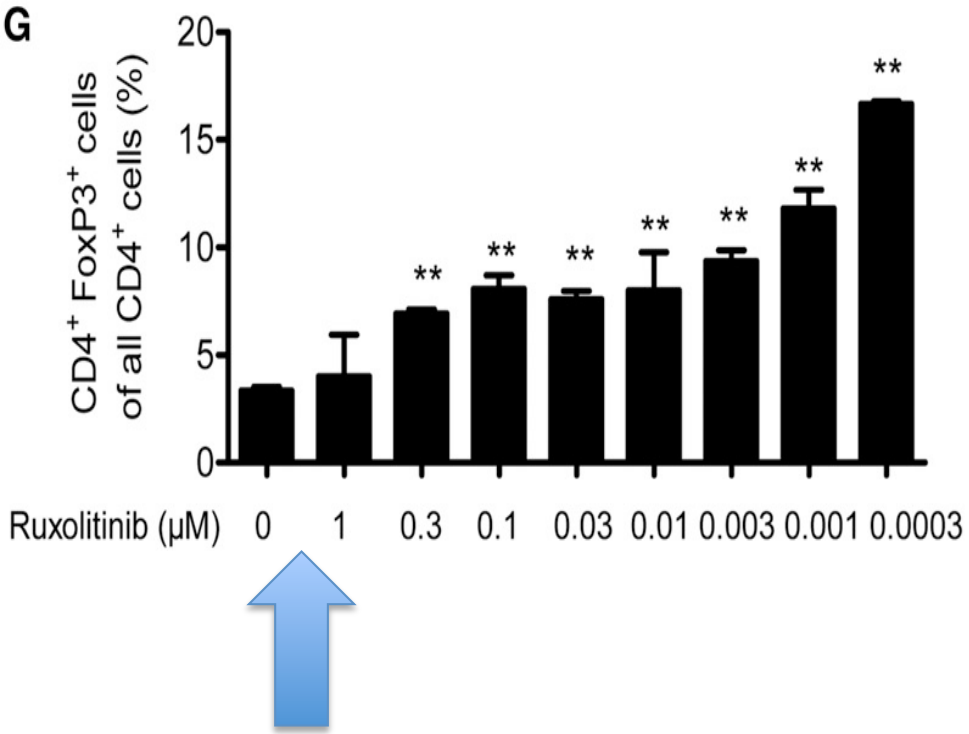
Silvia Spoerl,[1] Nimitha R. Mathew,[2] Michael Bscheider,[1] Annette Schmitt-Graeff,[3] Sophia Chen,[2] Tony Mueller,[2] Mareike Verbeek,[1] Julius Fischer,[1] Vera Otten,[1] Martina Schmickl,[1] Kristina Maas-Bauer,[2] Jürgen Finke,[2] Christian Peschel,[1] Justus Duyster,[2] Hendrik Poeck,[1] Robert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

BLOOD, 12 JUNE 2014 • VOLUME 123, NUMBER 24

Proinflammtory cytokine production is blocked by ruxolitinib treatment

SPOERL et al





Treg and T-cell phenotype changes during ruxolitinib treatment

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

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],

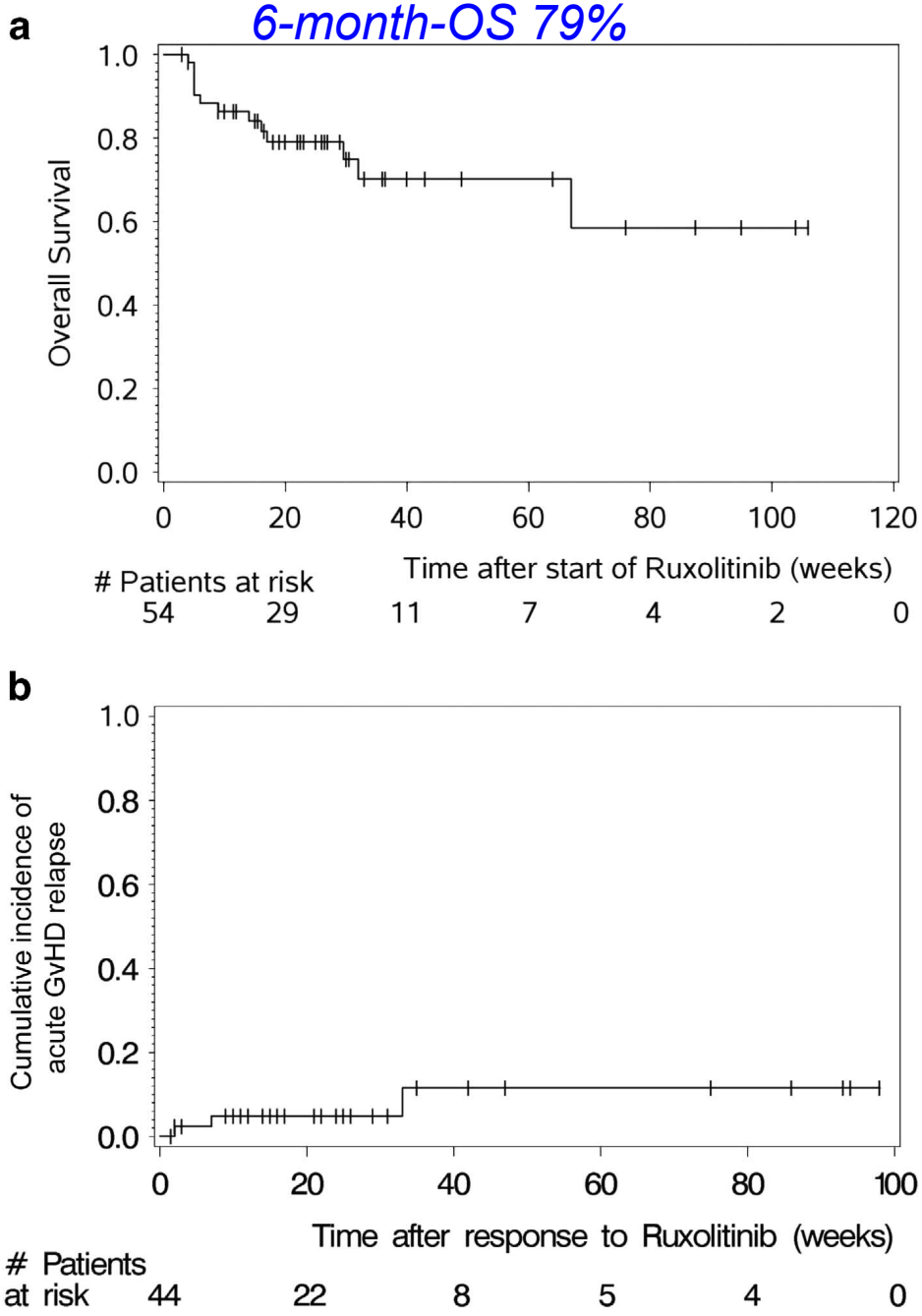
- Patients with SR-aGVHD (n = 54, all grades III or IV)
- *or SR-cGVHD (n = 41, all moderate or severe)*.

Cytopenia and CMV-reactivation

in SR-aGVHD 55.6% and 33.3%;

in SR-cGVHD 17.1% and 14.6%.

Leukemia (2015), 1–7



54 pts with SR-aGVHD (grades III/ IV)

ORR: 81.5% (44/54)

including 25 CR (46.3%)

Leukemia (2015), 1–7

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)

Trials with JAK-1/2 inhib. in aGVHD

Phase 2 Study of Ruxolitinib in Combination With Corticosteroids for the Treatment of **SR-aGVHD (REACH1)**	NCT02953678
Randomized phase 3.: Ruxolitinib Versus Best Available Therapy in Patients With **SR-aGVHD (REACH2**)	NCT02913261
PTCy and Ruxolitinib **GVHD Prophylaxis** in Myelofibrosis	NCT02806375
Ruxolitinib plus CHT Given **Before and After Reduced Intensity HSCT** in Myelofibrosis	NCT02917096
Randomized Phase 3 Study of *Itacitinib (JAK-1 inhib)* Vs Placebo plus steroids in **1st-Line Acute GvHD**	INCB 39110-301

Selective ROCK-2 inhibition

- Down-regulate the ability of T cells to secrete IL-2/17
- Diminished STAT3 phosphorilation and binding to IL-17 and IL-21 promoters
- Promotes the suppressive function of T reg through up-regulation of STAT5 phosphorilation and positive regulation Foxp3

- **KD025 has a strong activity in blocking the ROCK-2 PATH**

- **Targeting Rock2 with KD025 may restore disrupted immune homeostasis**

Flynn R., Blood 2016

Did we make progression in treatment of a SR-GVHD? Summary…

- **Several Abs** are effective when administered during the conditioning or before the GVHD clinical onset (Rituximab, anti-IL2R).
- Alemtuzumab: safe and effective both in preventing and treating aGVHD (in pediatrics and in GUT: few data).
- Anti-CD26, Vedolizumab, Brentuximab and Tocilizumab: safe profile and promising activity, but still preliminary results.

..besides antibodies…

- **Old drugs:** MMF, Pentostatin, Rapamycin…: no clear evidence of long term benefit.
- **New drugs:** Maraviroc; Ruxolitinib, Bortezomib, Vorinostat: promising activity
- **Cell therapy (GMP facilities required!):**

  Tolerogenic DC: promising, but too early

  Expanded T-reg: expensive; *maybe better expansion with anti-DR3.*

  Expanded MSC: safe; efficacy to be confirmed

  - ***ECP:*** *safe and effective as steroid-sparing strategy; no clear evidence of benefit outside the skin*.

aGVHD involvement is not limited to skin, GUT and liver……

the list of potential targets includes BM, lungs, CNS and thymus……

The central nervous system is a target of acute graft versus host disease in mice

Steffen Hartrampf,[1,4] Jarrod A. Dudakov,[1,5] Linda K. Johnson,[2] Odette M. Smith,[1] Jennifer Tsai,[1] Natalie V. Singer,[1] Mallory L. West,[1] Alan M. Hanash,[1] Michael H. Albert,[4] Bingfang Liu,[3] Miklos Toth,[3] and Marcel R.M. van den Brink[1,6]

The importance of bone marrow involvement in GVHD

Caroline A. Lindemans and Alan M. Hanash MEMORIAL SLOAN KETTERING CANCER CENT

TRANSPLANTATION

TRANSPLANTATION

Bone marrow graft-versus-host disease: early destruction of hematopoietic niche after MHC-mismatched hematopoietic stem cell transplantation

Yusuke Shono,[1,2] Satoshi Ueha,[1] Yong Wang,[1] Jun Abe,[1] Makoto Kurachi,[1] Yoshihiro Matsuno,[3] Tatsuki Sugiyama,[4] Takashi Nagasawa,[4] Masahiro Imamura,[2] and Kouji Matsushima[1]

[1]Department of Molecular Preventive Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo; [2]Department of Hematology and Oncology, Hokkaido University Graduate School of Medicine, Sapporo; [3]Department of Surgical Pathology, Hokkaido University Hospital, Sapporo; and [4]Department of Immunobiology and Hematology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto, Japan

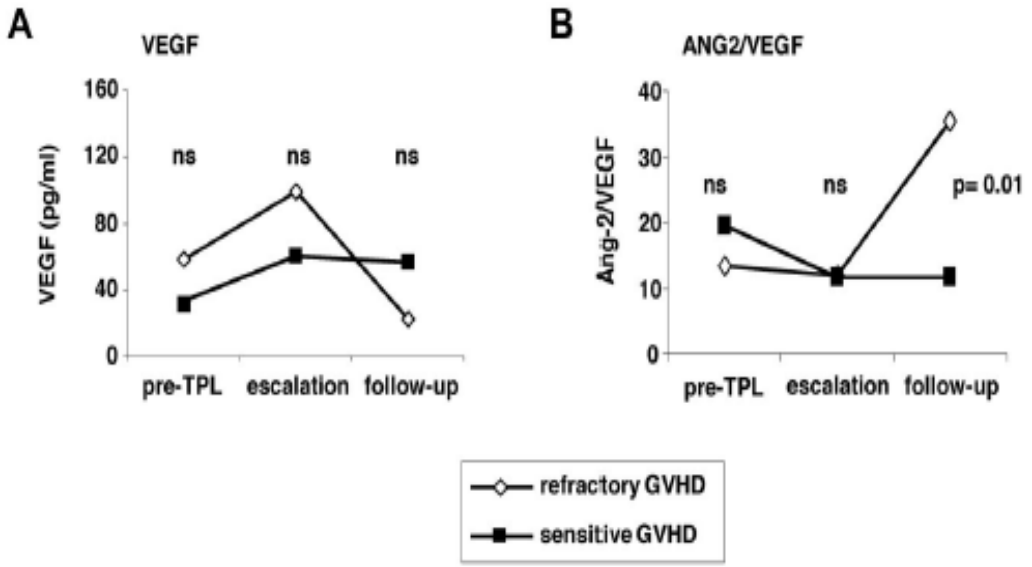
Thymic atrophy in murine acute graft-versus-host disease is effected by impaired cell cycle progression of host pro-T and pre-T cells

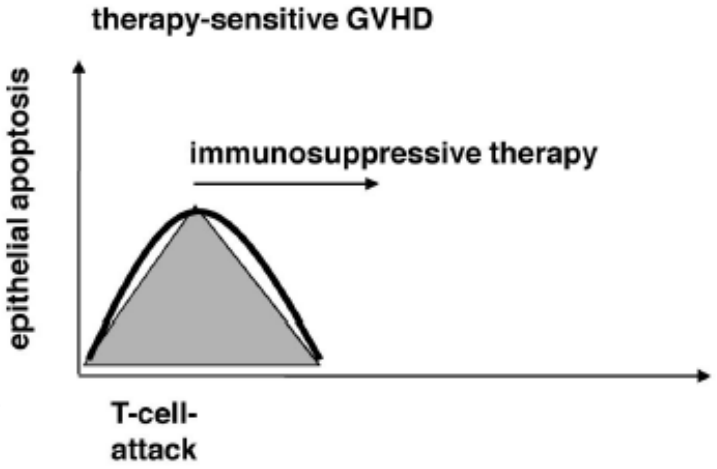
Werner Krenger, Simona Rossi, Luca Piali, and Georg A. Holländer

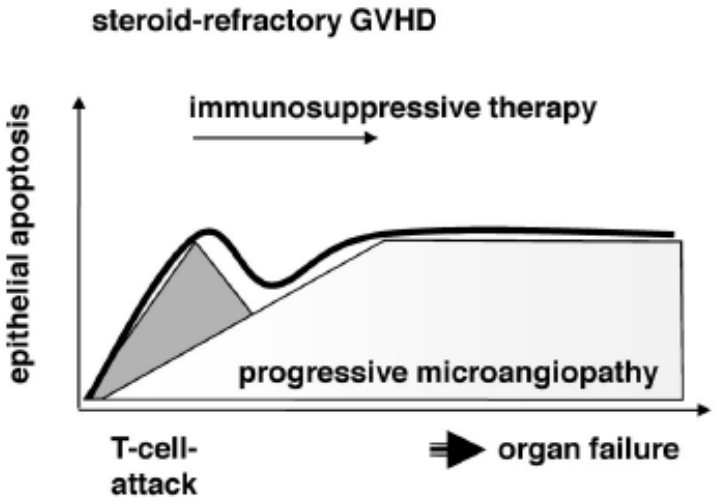
These results suggest that endothelial cell vulnerability and dysfunction, rather than refractory T-cell activity, drives treatment refractoriness of GVHD

Comparing kinetics of T-cell activation markers and markers of endothelial dysfunction in 23 pts with sensitive and 25 with refractory GVHD

- In contrast to sensitive GVHD, refractory GVHD was associated with rising thrombomodulin levels and high ANG2/ vascular endothelial derived growth factor ratios.
- Pts with refractory GVHD had significantly increased ANG2 levels already before SCT.







CORSO EDUCAZIONALE GITMO

VASCULAR ENDOTHELIAL SYNDROMES AFTER HEMOPOIETIC STEM CELL TRANSPLANTATION

ANCONA
6 *ottobre* 2017

Responsabile Scientifico

Prof. A Olivieri (Direttore programma trapianti,

Programma Scientifico

8.00 Registrazio

8.30 Salut

I SESSION

9.00 Le trapianto?"

A.

Mode

9.30 Danno . Ciceri (Milano)

10.00 VOD: fisi

10.30 VOD: criteri dia

Moderatori: B. Br

Thanks

Coffee Break

11.30 TAM: fisiopatologia e manifestazioni cliniche- S. Sica (Roma)

12.00 TAM: terapia- A. M. Risitano (Napoli)

12.30 Colite ischemica: E. Benedetti (Pisa)