Linee innovative di trattamento della GVHD

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University of Illinois at Chicago

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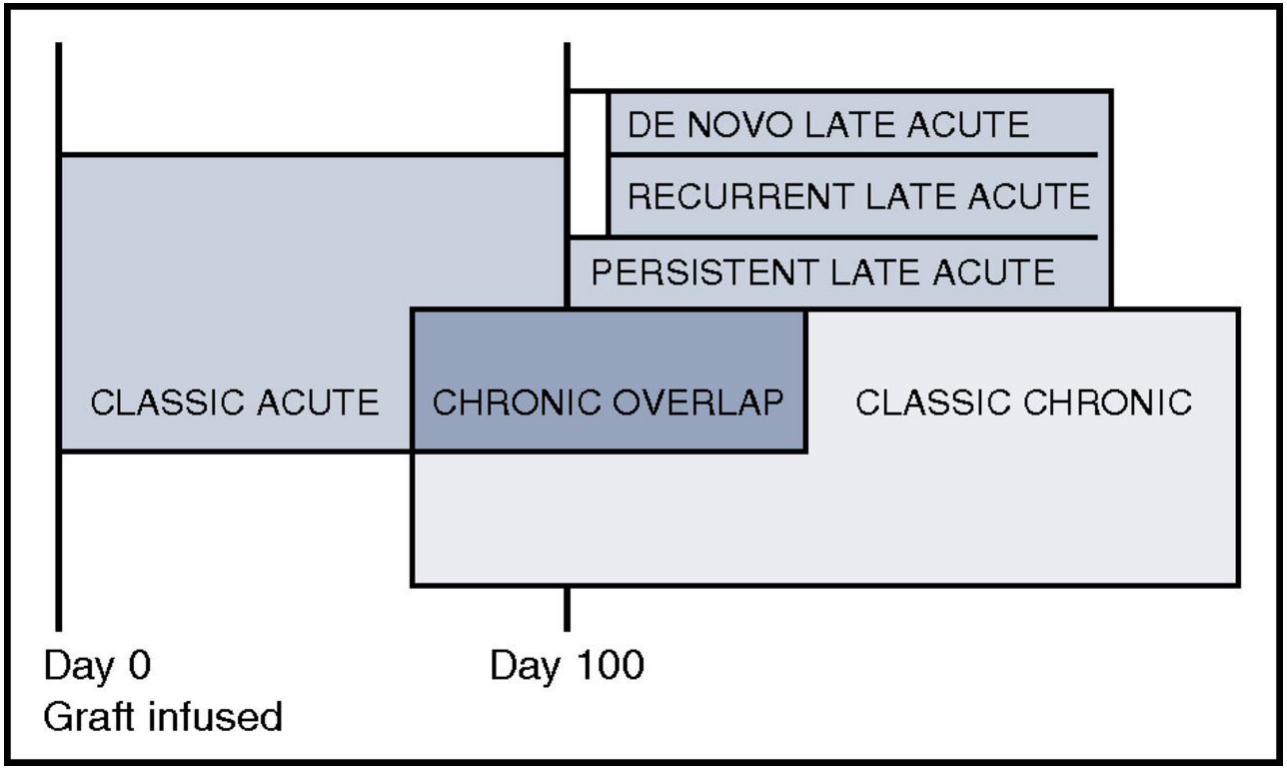
HIGHLIGHTS IN EMATOLOGIA
TREVISO, 1-2 DICEMBRE 2023

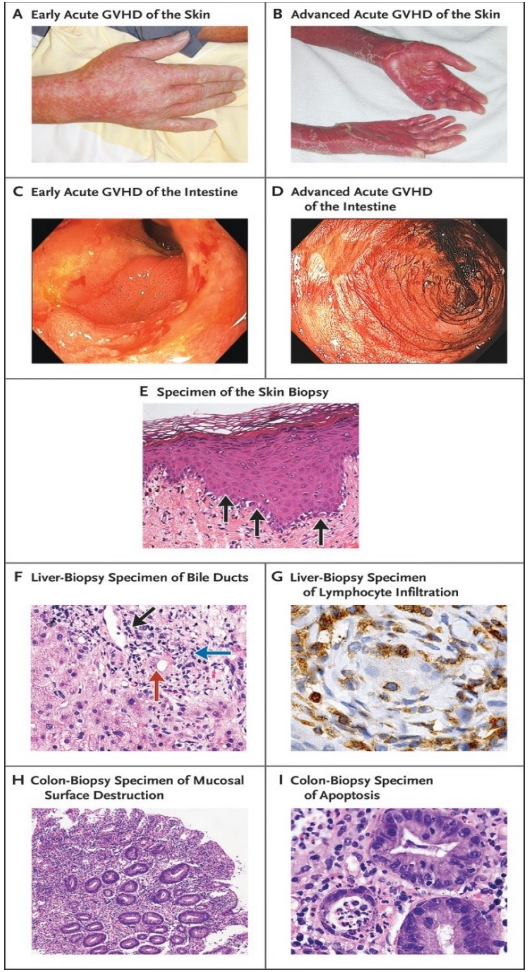
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Vertex			CTX001 Steering Committee				

GVHD



Lee SJ, Blood 2017: 129, 1: 30-37

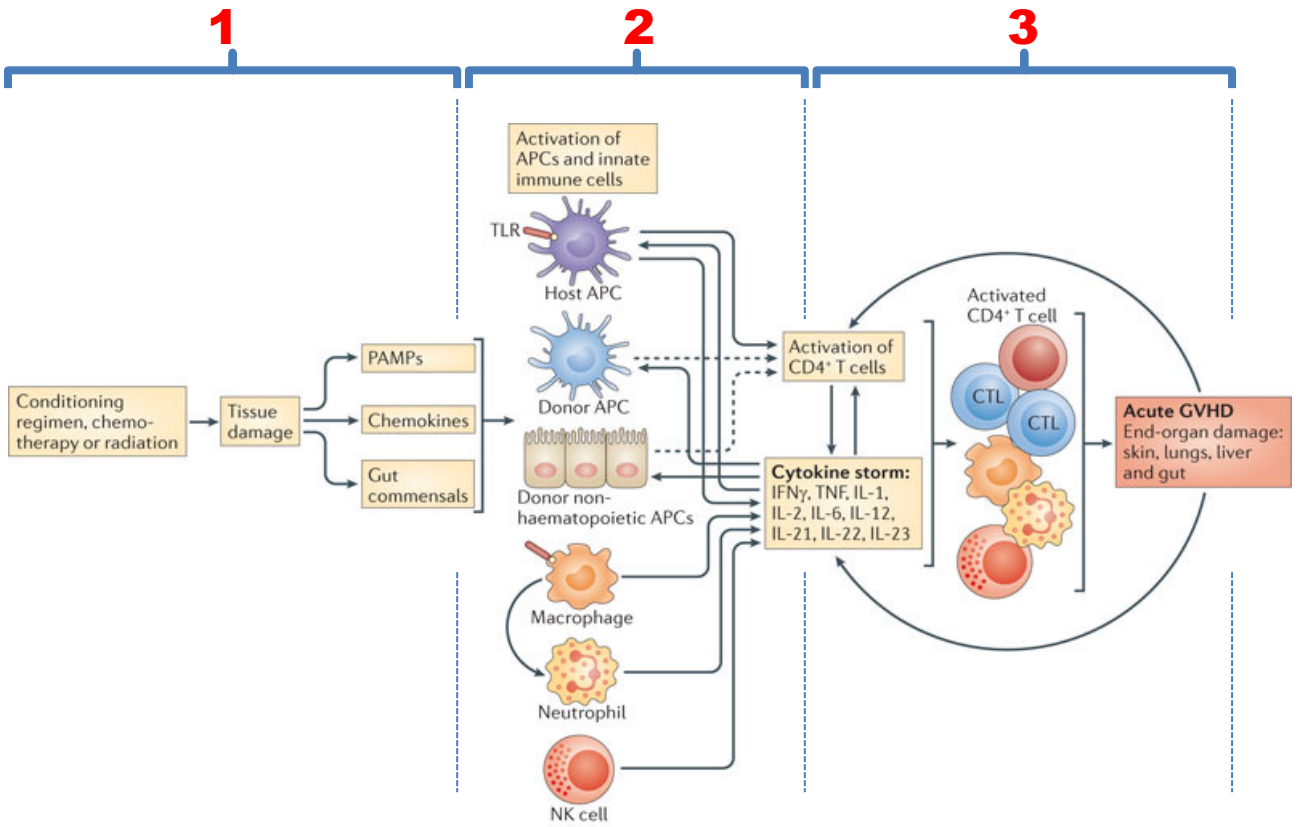


← Skin

← Liver

← Colon

Zeiser R, Blazar B. N Engl J Med 2017; 377:2167-2179

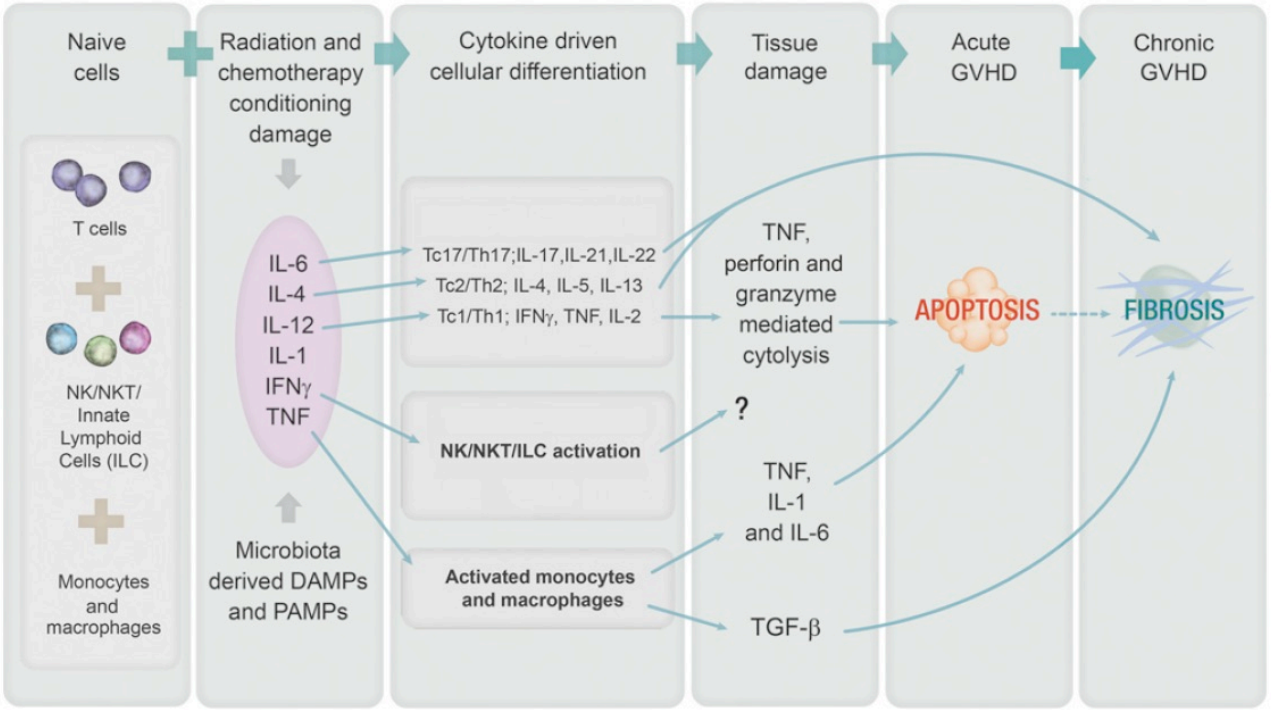


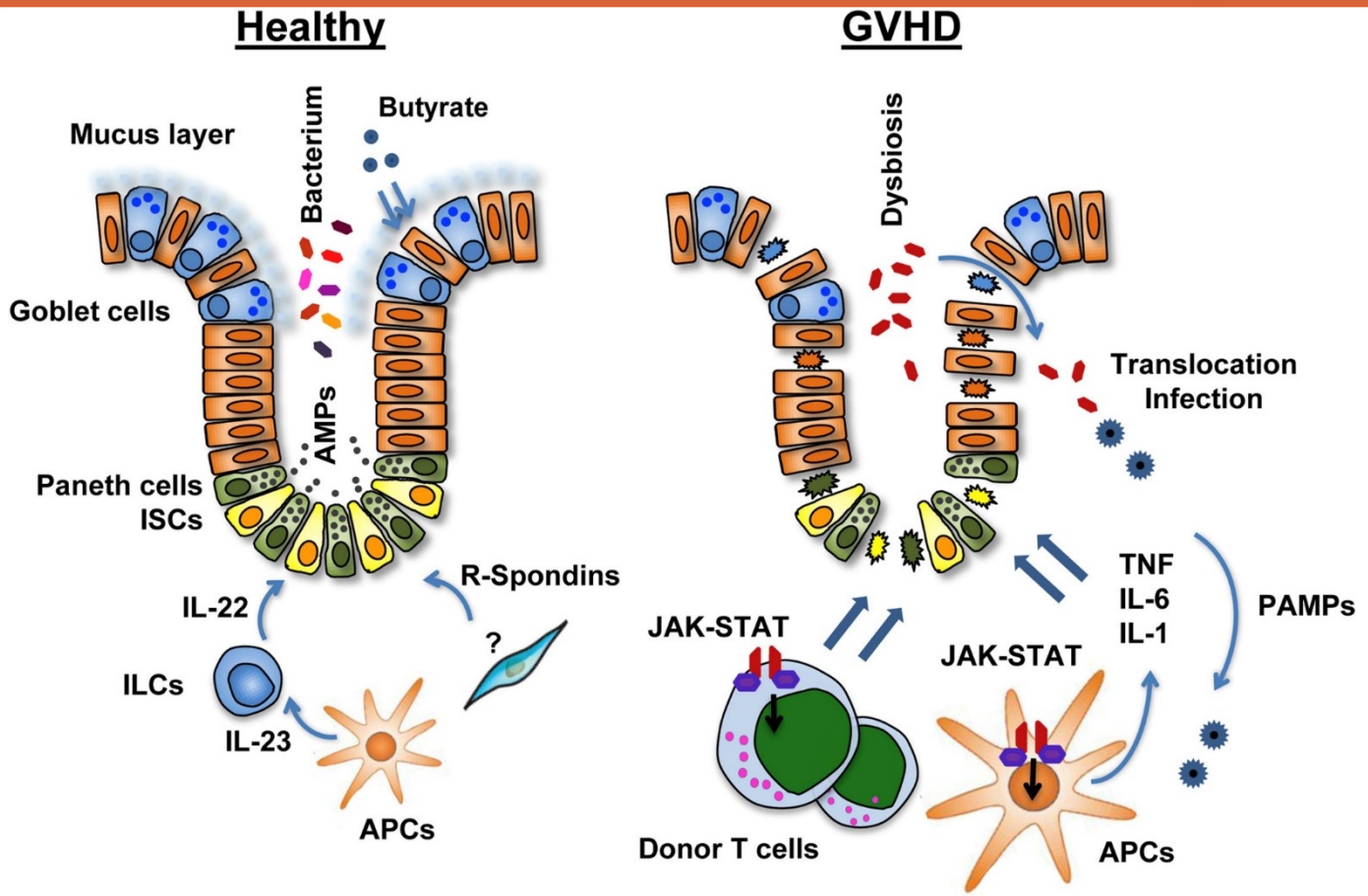
Blazar B, Nature Reviews Immunology 2012; 12, 443-458

Cytokines in Graft-versus-Host Disease

Andrea S. Henden and Geoffrey R. Hill

The Journal of Immunology, 2015





Teshima T, Reddy P, Zeiser R. TCT 2016

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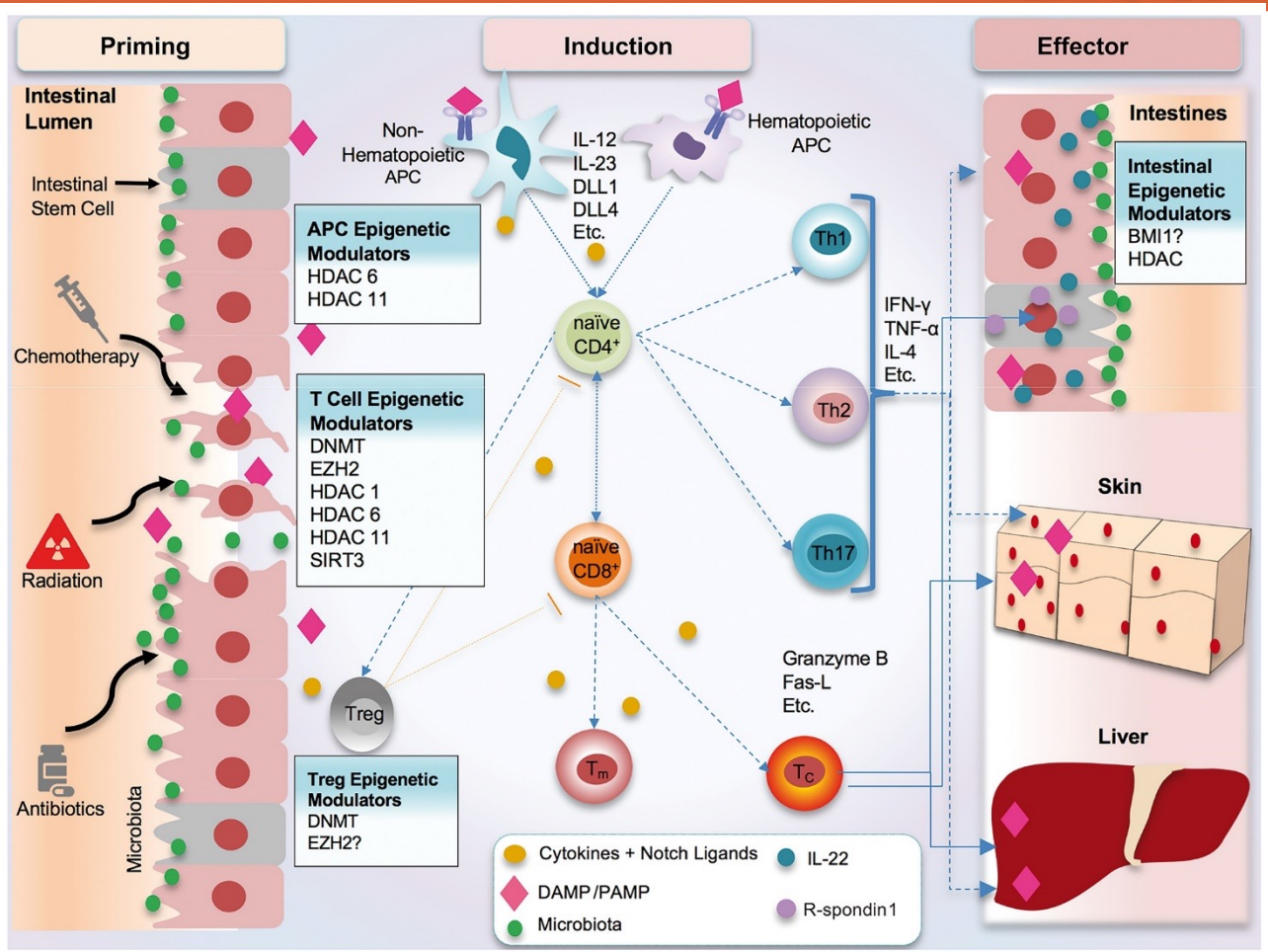

Li A, Haematologica Vol. 105 No. 11 (2020)

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Risk factors for GVHD

Donor

- HLA disparity (related/unrelated)
- Sex mismatch (F – M)
- Age >35 yrs
- Alloimmunisation (pregnancy, transfusions)
- SC source (PBSC>BM>CB)
- NK-cell alloreactivity

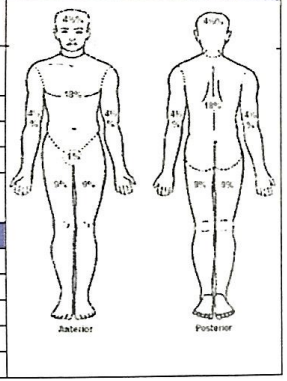
Host

- Age >35 yrs
- Intensity of conditioning
- Prevention of GVHD
- CMV, infections
- Genetic predisposition
- Rapid establishment of donor T-cell chimerism

STAGING & GRADING OF ACUTE GVHD

Acute GVHD:
Clinical Staging & Grading

CLINICAL STAGING			
Stage	SKIN	LIVER (bilirubin)	GUT (output)
0	No rash	<2 mg/dL	<50ml/day or nausea or vomiting
I	Maculopapular rash, <25% BSA	2-3 mg/dL	500-999ml/day
II	Maculopapular rash, 25-50% BSA	3.1-6 mg/dL	1000-1500ml/day
III	Maculopapular rash, >50% BSA	6.1-15 mg/dL	>1500ml/day
IV	General erythema and bullous formation	>15 mg/dL	severe cramping +/- ileus
CLINICAL GRADING			
Grade	SKIN	LIVER	GUT
1	Stage I-II		
2	Stage III or	Stage I or	Stage I
3		Stage II-III or	Stage II-IV
4	Stage IV or	Stage IV	



Nonclassical manifestations of acute GVHD

Zeiser R and Teshima T. Blood 2021, 138:22:2165-2172

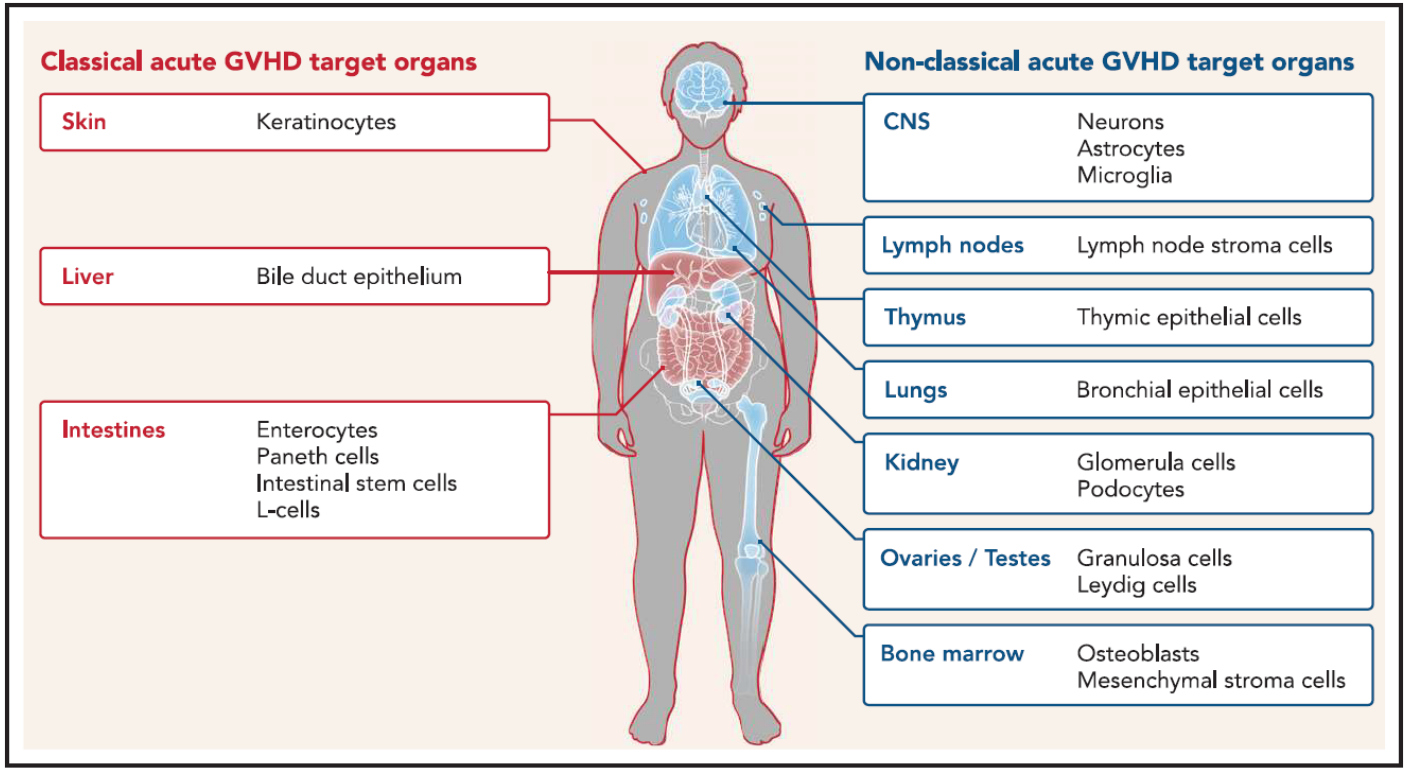


Figure 1. Classical (red) and nonclassical (blue) acute GVHD manifestations are shown. The typical GVHD target cell types that are primarily damaged by the alloreactive immune response are indicated. Additional cell types may be targets of aGVHD but further experimental evidence for their involvement is needed.

Table 1. Evidence for acute and chronic CNS GVHD

CNS GVHD (n, patient number reported)	Histology proven, n	MRI signs, n	Main finding of the report	Reference
7	2 (autopsy)	7	CNS-related GVHD is a cause of CNS disorders after allo-HSCT and is associated with a poor prognosis.	28
1	1 (biopsy)	1	Although rare, CNS GVHD should be included in the differential diagnosis of CNS lesions in patients after organ transplantation.	82
1	1 (biopsy)	1	Neurologic symptoms improved with methylprednisolone pulse	83
1	0	1	After intrathecal infusion of methylprednisolone, the clinical symptoms as well as the radiological abnormalities disappeared.	84
2	1 (biopsy) 1 (autopsy)	2	Histology showed profound perivascular lymphocytic infiltrates composed predominantly of T-lymphocytes that were of donor origin.	85
1	1 (biopsy)	1	Histology showed granulomas around small vessels, containing lymphocytes, histiocytes and giant cells.	86
1	1 (autopsy)	1	Angiitis-like syndrome of the CNS neurological manifestation of GVHD.	87
1	0	1	Steroid treatment caused an immediate improvement in headaches and functional status.	27
1	1 (biopsy)	1	Histologic confirmation of CNS granulomatous angiitis in a patient with GVHD.	88
10	10 (autopsy)	2	Histology showed $Iba1^{+}TNF^{+}$ cells in the CNS	25

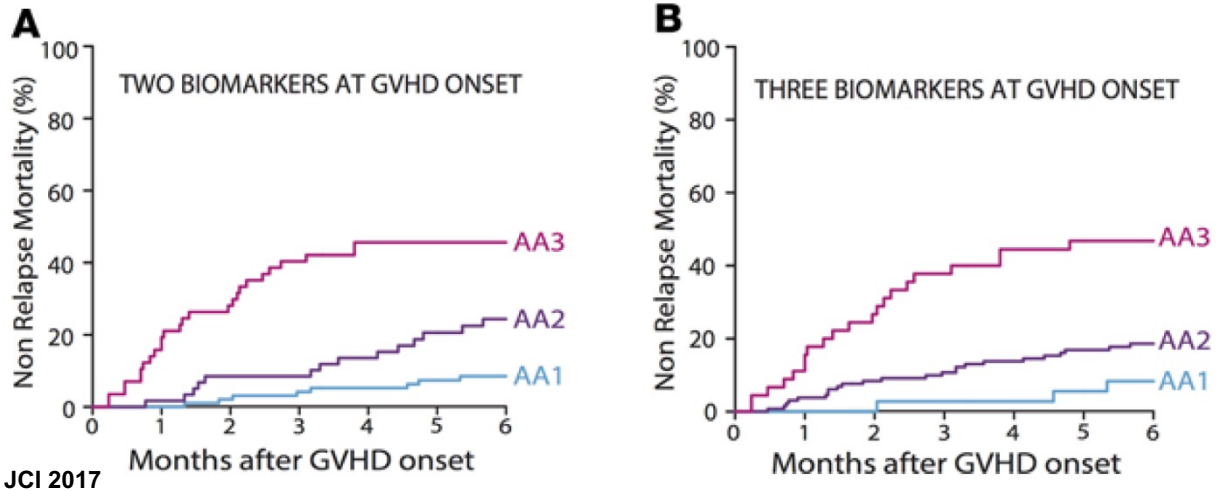
Zeiser R and Teshima T. Blood 2021, 138:22:2165-2172

JCI insight CLINICAL MEDICINE

An early-biomarker algorithm predicts lethal graft-versus-host disease and survival

Day 7 algorithm

ST2: a decoy receptor for IL-33, is shed from activated T cells in GVHD
REG3α: is released in the blood by damaged GI mucosa in GVHD
TNFR1: TNF receptor 1



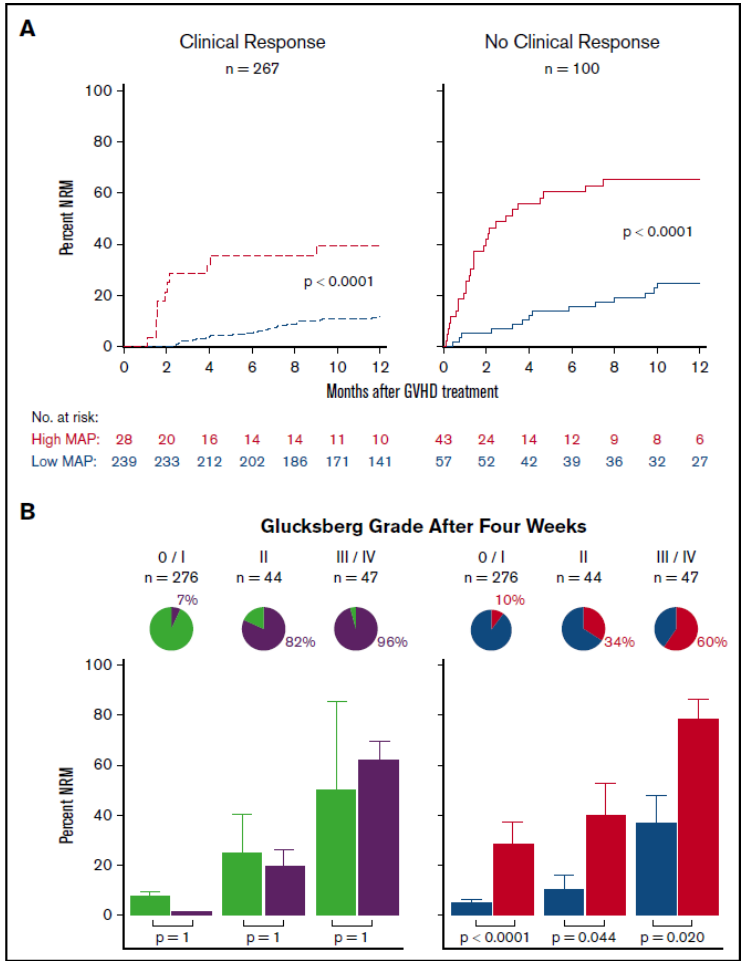
Hartwell MJ, …Ferrara JLM. JCI 2017

REGULAR ARTICLE
blood advances

The MAGIC algorithm probability is a validated response biomarker of treatment of acute graft-versus-host disease

Key Points

- The MAGIC algorithm probability, computed from 2 serum biomarkers, predicts mortality in all GVHD grades after 4 weeks of treatment.
- Dynamic changes in the MAGIC algorithm probability occur within all biomarker risk groups and can guide therapy.



Srinagesh HK, …Ferrara JLM, Blood Adv 2019, 23,3:4034-4042

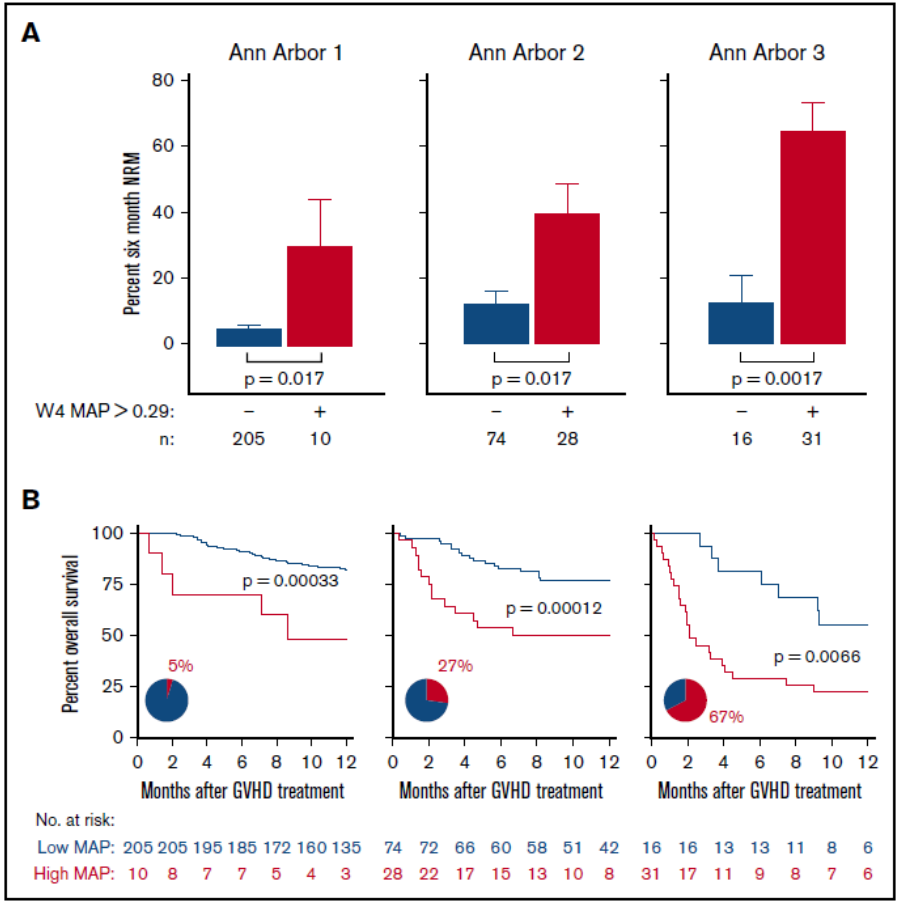
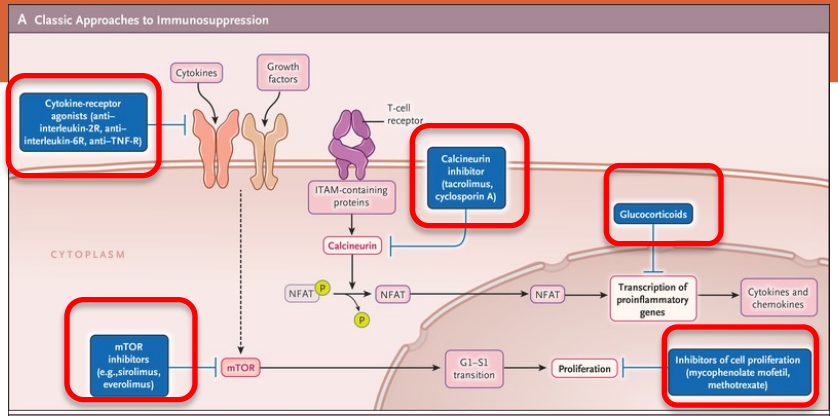


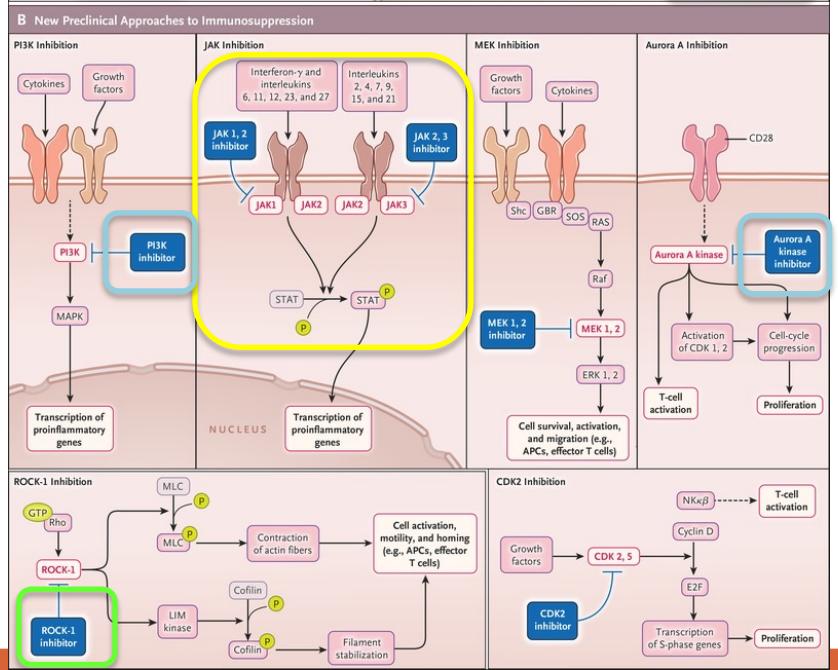
Figure 4. Long-term mortality by MAP threshold (0.290) after 4 weeks of treatment. (A) Crude proportions of 6-month nonrelapse mortality (± standard error) and (B) Kaplan-Meier estimates of overall survival according to Ann Arbor score for patients whose MAP after 4 weeks of treatment rose/remained above (red line) or fell/remained below (blue line) the threshold of 0.290. Ann Arbor scores were determined as in Figure 3.

Srinagesh HK, …Ferrara JLM, Blood Adv 2019, 23,3:4034-4042

ANTI-T CELL DRUGS

• CSA/FK-506	blocks NFAT and IL2 transcript. in activated limphocytes.
• mycophenolate	blocks the sinthesis of nucleotides in activated lymphoc.
• rapamicin	binds to FKBP and inhibits cell cycling from G1 to S phase
• anti-CD25 (IL2R)	blocks IL2-mediated T cell activation.
• [alemtuzumab	anti-CD52 ab]
• [etanercept	anti-TNF-R]





Standard IS

JAK inhib

ROCK-1 inhib

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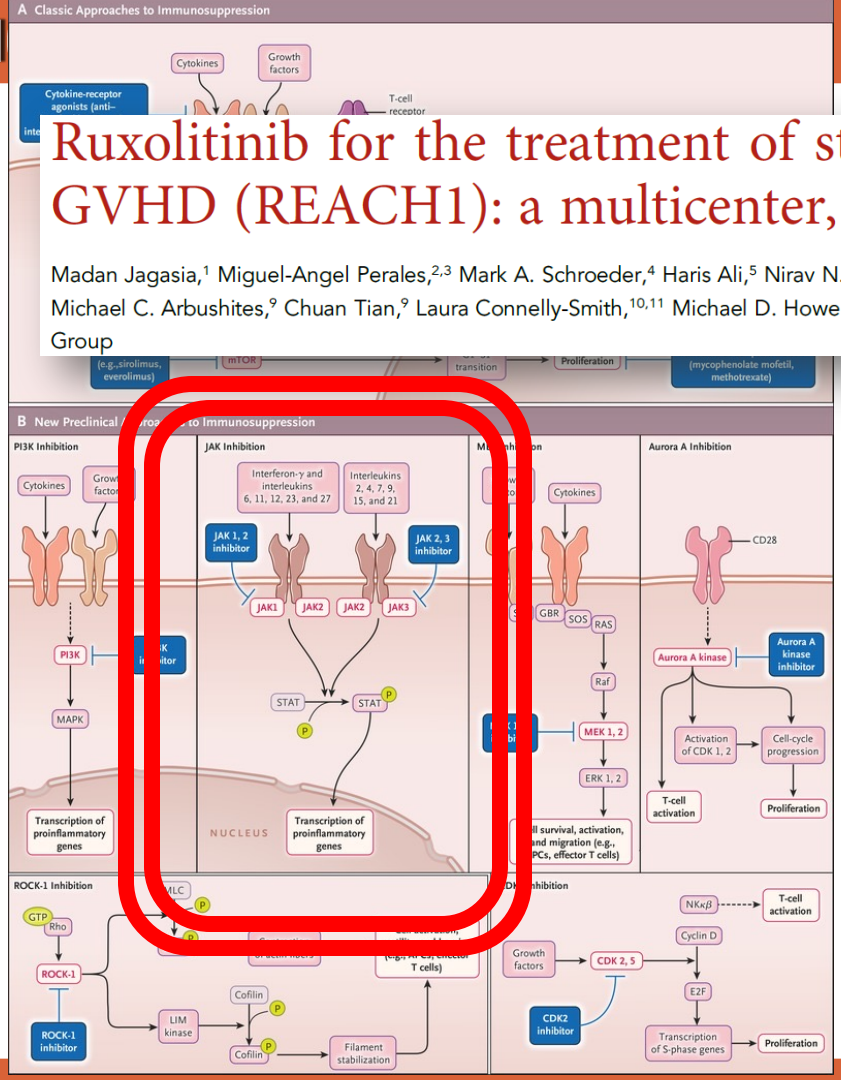
Zeiser R, Blazar B. N Engl J Med 2017; 377:2167-2179

Blood. 2020;135(20):1739-1749

Ruxolitinib for the treatment of steroid-refractory acute GVHD (REACH1): a multicenter, open-label phase 2 trial

Madan Jagasia,[1] Miguel-Angel Perales,[2,3] Mark A. Schroeder,[4] Haris Ali,[5] Nirav N. Shah,[6] Yi-Bin Chen,[7] Salman Fazal,[8] Fitzroy W. Dawkins,[9] Michael C. Arbushites,[9] Chuan Tian,[9] Laura Connelly-Smith,[10,11] Michael D. Howell,[9] and H. Jean Khoury,[12] on behalf of the REACH1 Study Group



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Blood. 2020;135(20):1739-1749

Steroid refractory aGVHD

Table 1. Patient demographics and baseline disease characteristics

Variable	Ruxolitinib (N = 71)
Median (range) age, y	58 (18-73)
Age group, n (%)	
<65 y	58 (81.7)
≥65 y	13 (18.3)
Female, n (%)	36 (50.7)
Race, n (%)	
White	66 (93.0)
Black	3 (4.2)
Asian	2 (2.8)
MAGIC aGVHD grade, n (%)	
II	23 (32.4)
III	34 (47.9)
IV	14 (19.7)
Steroid-refractory criteria, n (%)	
Progressive GVHD after 3 d of primary treatment	19 (26.8)
GVHD not improved after 7 d of primary treatment	30 (42.3)
Previously began CS therapy at a lower dose, but developed new GVHD in another organ system	8 (11.3)
Unable to tolerate CS taper	14 (19.7)
Median (range) prior exposure to corticosteroids, d	15 (3-285)

Table 4. ORR at day 28 by baseline steroid-refractory status

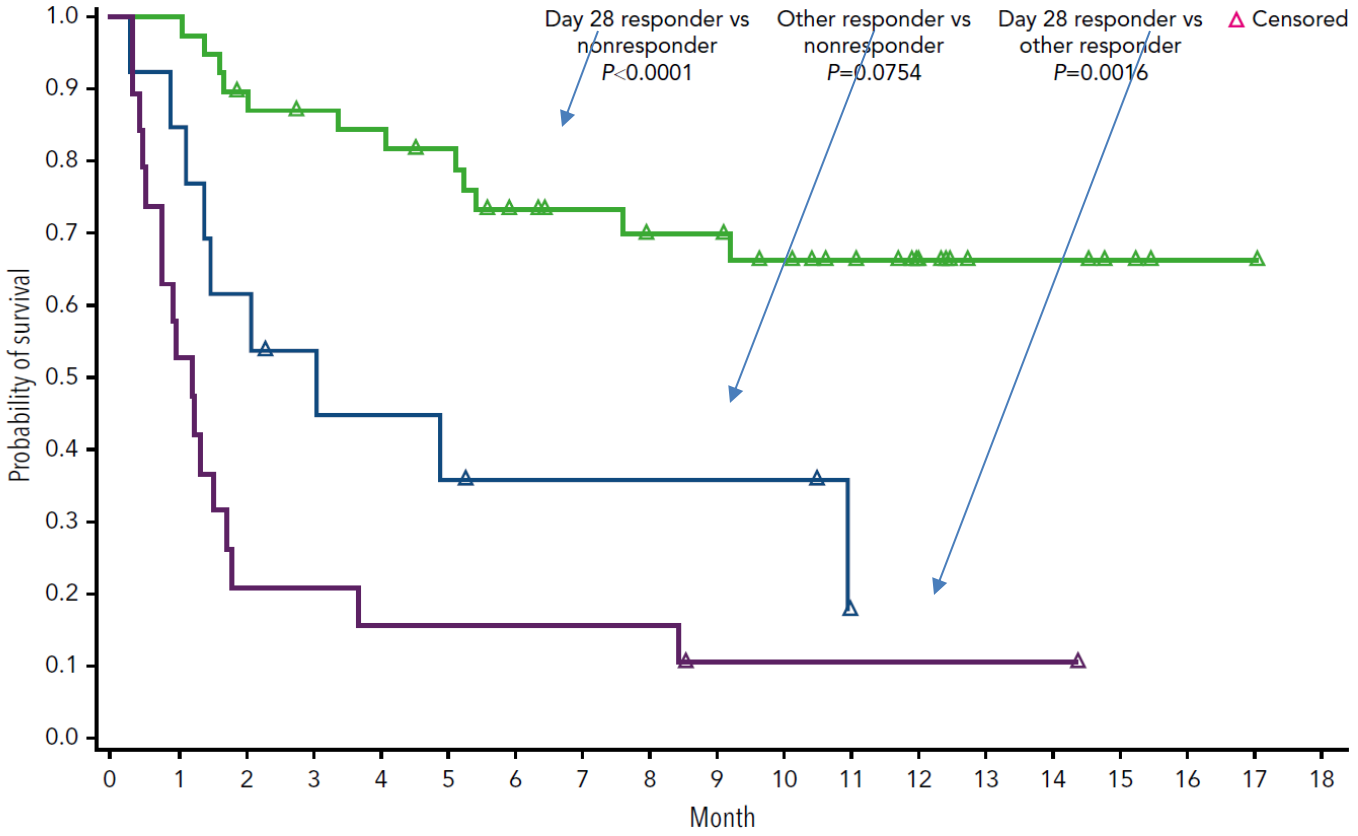
Response	GVHD progression after 3 d* (n = 19)	No improvement in GVHD after 7 d* (n = 30)	New GVHD† (n = 8)	Taper intolerant (n = 14)
CR	7 (36.8)	6 (20.0)	1 (12.5)	5 (35.7)
VGPR	4 (21.1)	1 (3.3)	1 (12.5)	1 (7.1)
PR	1 (5.3)	7 (23.3)	2 (25.5)	3 (21.4)
Overall response 95% CI	12 (63.2) 38.4-83.7	14 (46.7) 28.3-65.7	4 (50.0) 15.7-84.3	9 (64.3) 35.1-87.2

Table 5. ORR at day 28 by baseline organ involvement

Response	Skin (n = 36)	Liver (n = 15)	Upper GI (n = 22)	Lower GI (n = 50)
CR	9 (25.0)	2 (13.3)	5 (22.7)	12 (24.0)
VGPR	6 (16.7)	0	0	3 (6.0)
PR	7 (19.4)	2 (13.3)	5 (22.7)	8 (16.0)
Overall response 95% CI	22 (61.1) 43.5-76.9	4 (26.7) 7.8-55.1	10 (45.5) 24.4-67.8	23 (46.0) 31.8-60.7

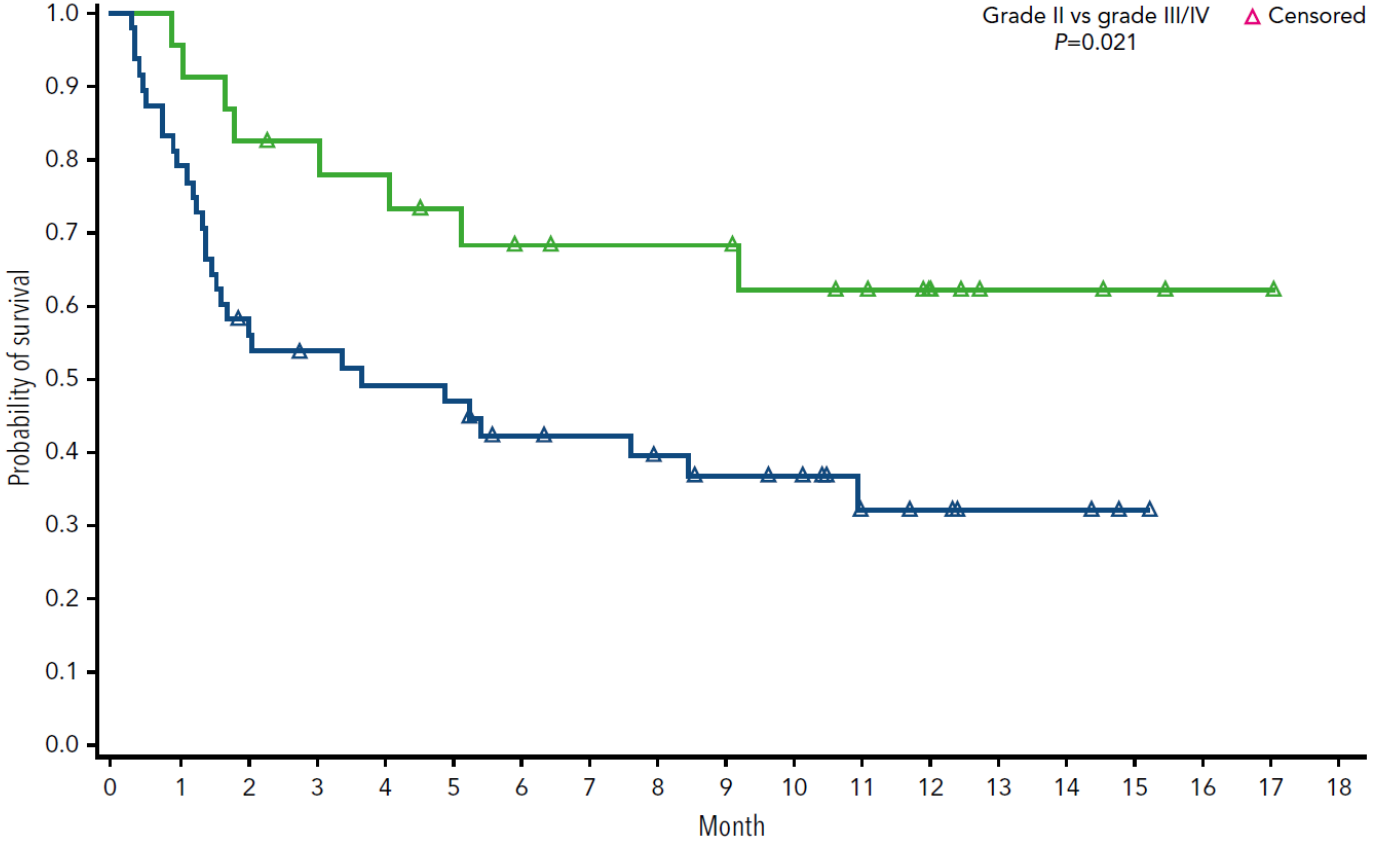
Blood. 2020;135(20):1739-1749

OVERALL SURVIVAL



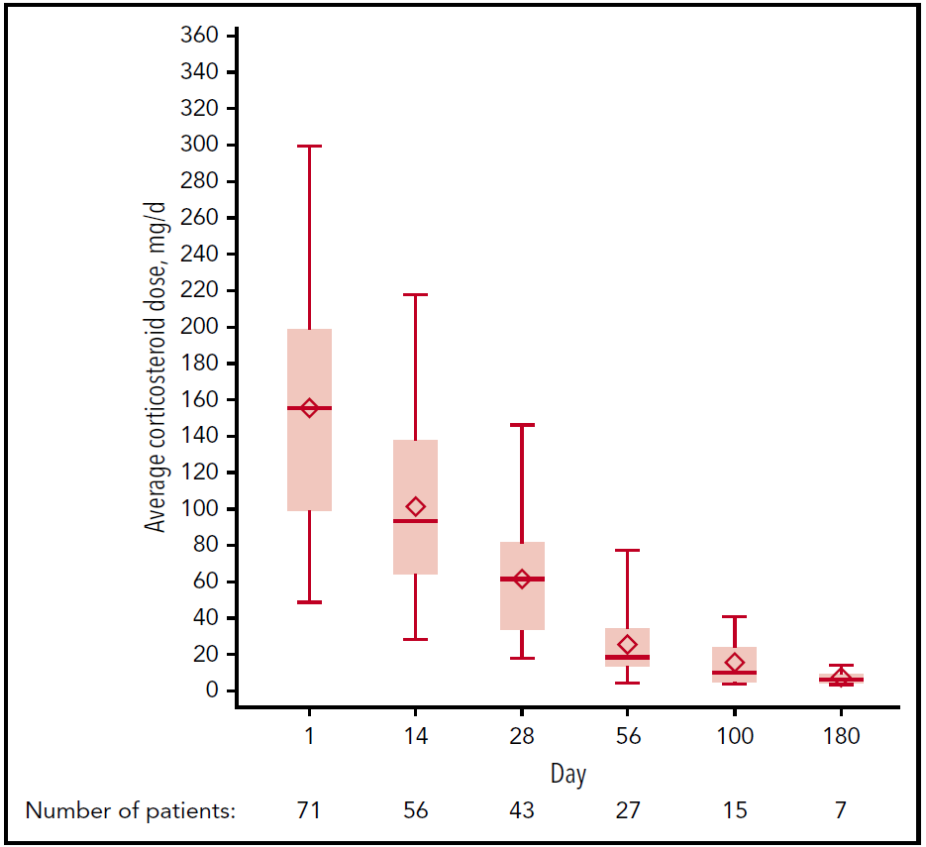
Blood. 2020;135(20):1739-1749

OVERALL SURVIVAL: Grade II vs Grade III/IV



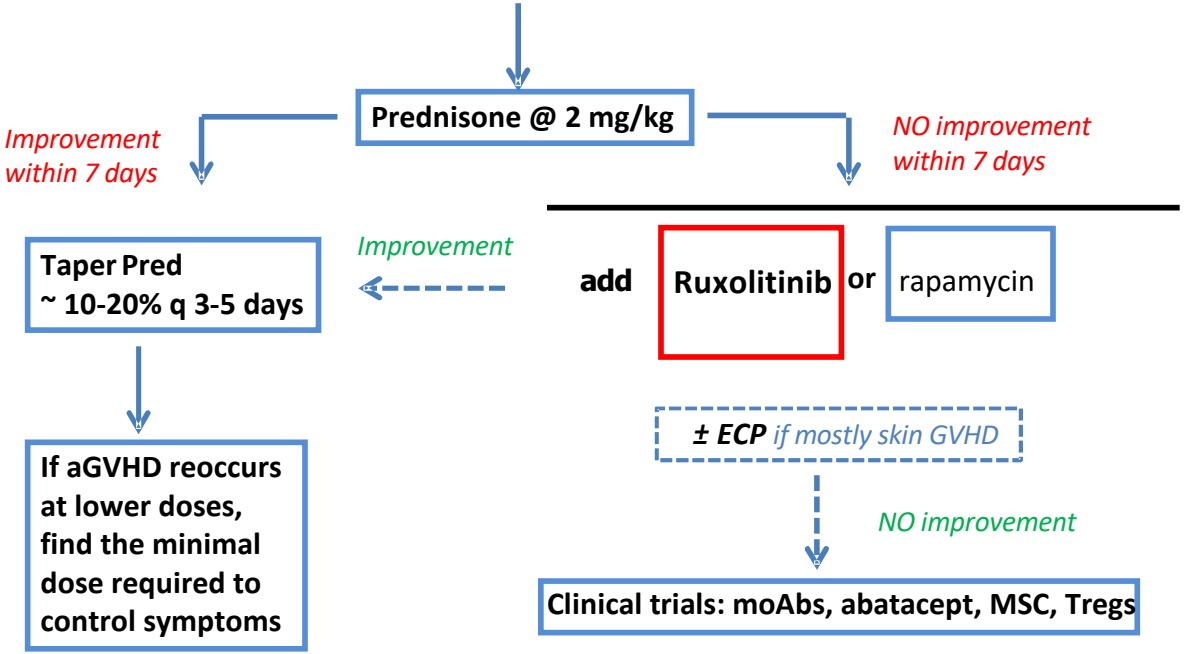
Blood. 2020;135(20):1739-1749

Figure 3. Average corticosteroid dose over time. The average corticosteroid dose in milligrams per day at days 1, 14, 28, 56, 100, and 180 is displayed for patients who continued receiving ruxolitinib treatment. Data shown indicate median (horizontal line), mean (diamond), 75th and 25th quartiles (upper and lower boundaries, respectively), and minimum (lower error bar)/maximum (upper error bar).

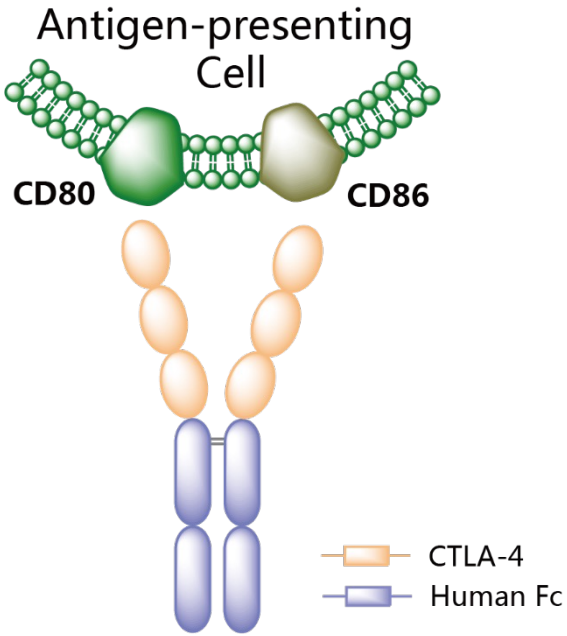


Blood. 2020;135(20):1739-1749

How I treat pts with acute GVHD grade II-IV on CNI



When achieved best response, continue until resolution or select best chronic treatment, possibly steroid-free



Abatacept

(recombinant human fusion protein CTLA4-Ig)

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J Clin Oncol 39:1865-1877. © 2021 by American Society of Clinical Oncology

original reports

Phase II Trial of Costimulation Blockade With Abatacept for Prevention of Acute GVHD

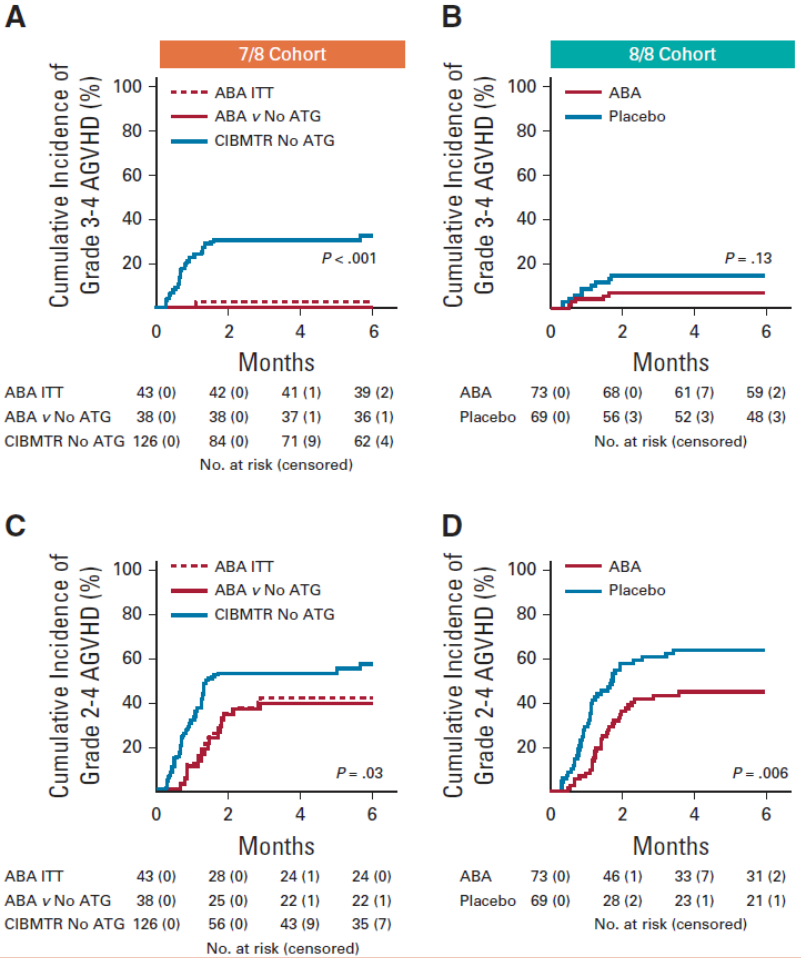
Benjamin Watkins, MD[1]; Muna Qayed, MD[1]; Courtney McCracken, PhD[2]; Brandi Bratrude, BA[3]; Kayla Betz, BS[3]; Yvonne Suessmuth, PhD[1]; Alison Yu, PhD[3]; Shauna Sinclair[4]; Scott Furlan, MD[5]; Steven Bosinger, PhD[6]; Victor Tkachev, PhD[3]; James Rhodes, PharmD[7]; Audrey Grizzle Tumlin, BS[7]; Alexandria Narayan, BA[5]; Kayla Cribbin, BS[4]; Scott Gillespie, MS[2]; Ted A. Gooley, PhD[5]; Marcelo C. Pasquini, MD[8]; Kyle Hebert, MS[8]; Urvi Kapoor, MD[9]; Andre Rogatko, PhD[10]; Mourad Tighiouart, PhD[10]; Sungjin Kim, MS[10]; Catherine Bresee, MS[10]; Sung W. Choi, MD[11]; Jeffrey Davis, MD[12]; Christine Duncan, MD[3]; Roger Giller, MD[13]; Michael Grimley, MD[14]; Andrew C. Harris, MD[15]; David Jacobsohn, MD[16]; Nahal Lalefar, MD[17]; Maxim Norkin, MD[18]; Nosha Farhadfar, MD[19]; Michael A. Pulsipher, MD[20]; Shalini Shenoy, MD[21]; Aleksandra Petrovic, MD[4]; Kirk R. Schultz, MD[12]; Gregory A. Yanik, MD[11]; Edmund K. Waller, MD[22]; John E. Levine, MD[9]; James L. Ferrara, MD[9]; Bruce R. Blazar, MD[23]; Amelia Langston, MD[22]; John T. Horan, MD[3]; and Leslie S. Kean, MD, PhD[3]

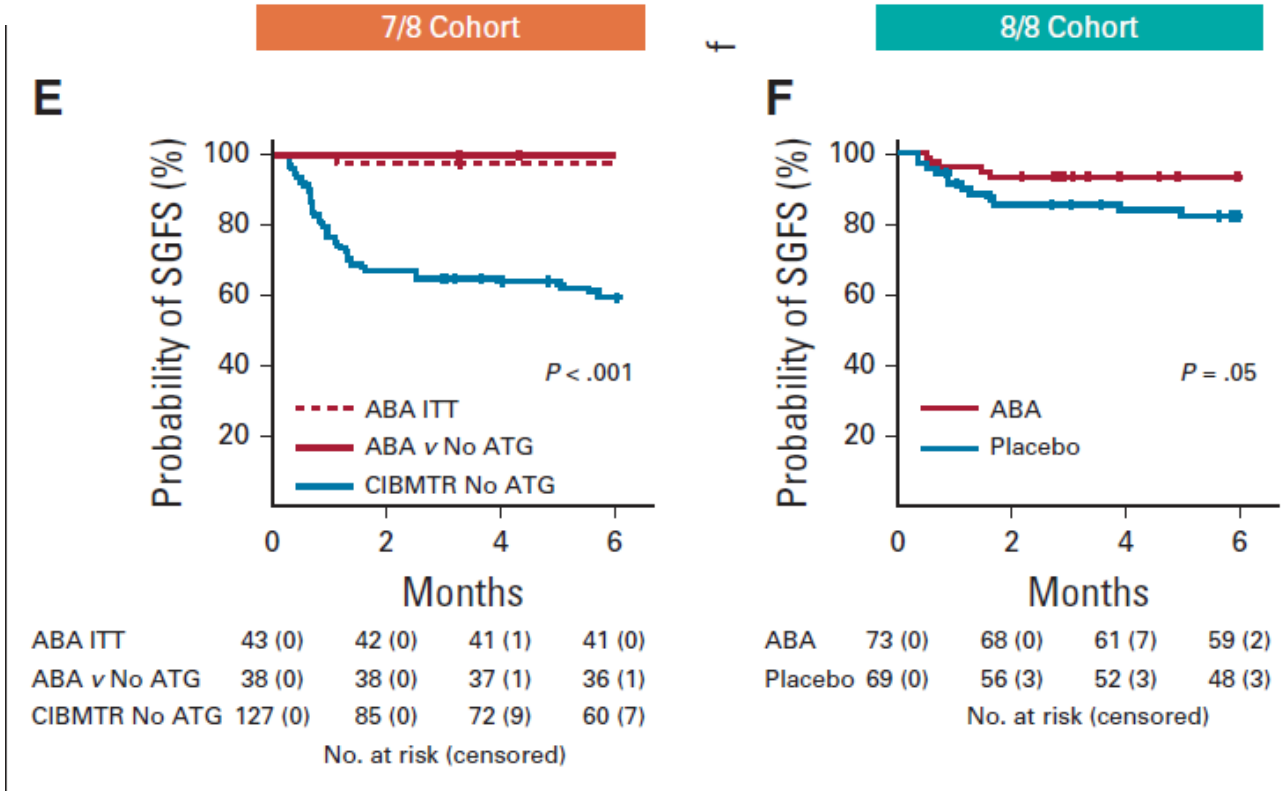
GVHD prophylaxis:

CsA or Tacro + MTX (d1,3,6,11 –full dose) x 100 d, then taper to d180

+/- Abatacept @ 10mg/kg/dose on d -1, +5, +14, +28

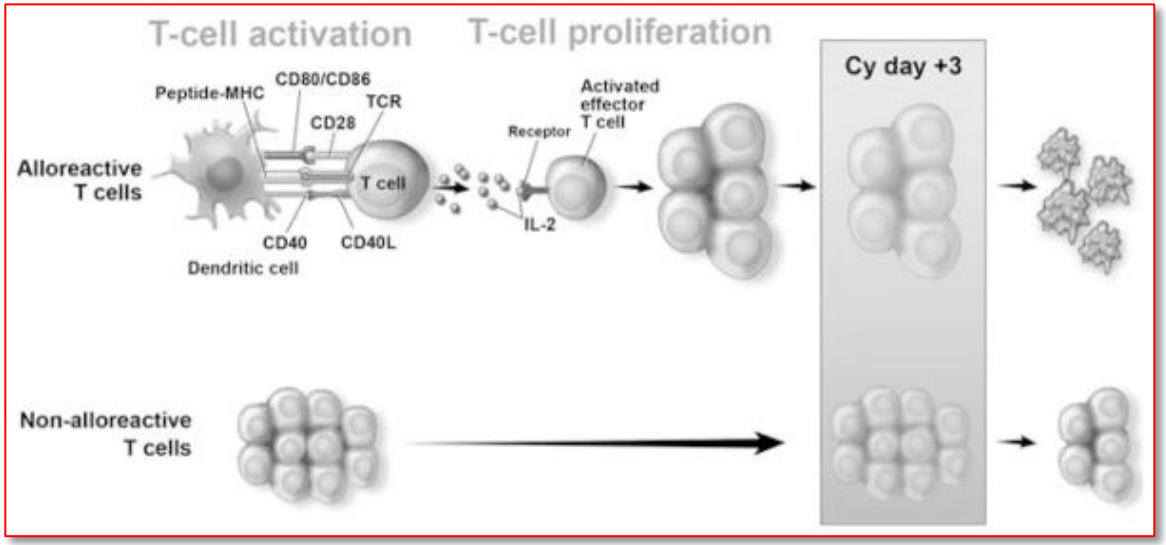
FDA Approves Abatacept-Based Combination for Prophylaxis of Acute Graft-vs-Host Disease - January 2022


A
7/8 Cohort
ABA ITT
ABA v No ATG
CIBMTR No ATG
Cumulative Incidence of Grade 3-4 AGVHD (%)
100
80
60
40
20
P < .001
0
2
4
6
Months
ABA ITT 43 (0) 42 (0) 41 (1) 39 (2)
ABA v No ATG 38 (0) 38 (0) 37 (1) 36 (1)
CIBMTR No ATG 126 (0) 84 (0) 71 (9) 62 (4)
No. at risk (censored)
B
8/8 Cohort
ABA
Placebo
Cumulative Incidence of Grade 3-4 AGVHD (%)
P = .13
Months
ABA 73 (0) 68 (0) 61 (7) 59 (2)
Placebo 69 (0) 56 (3) 52 (3) 48 (3)
No. at risk (censored)
C
ABA ITT
ABA v No ATG
CIBMTR No ATG
Cumulative Incidence of Grade 2-4 AGVHD (%)
P = .03
Months
ABA ITT 43 (0) 28 (0) 24 (1) 24 (0)
ABA v No ATG 38 (0) 25 (0) 22 (1) 22 (1)
CIBMTR No ATG 126 (0) 56 (0) 43 (9) 35 (7)
No. at risk (censored)
D
ABA
Placebo
Cumulative Incidence of Grade 2-4 AGVHD (%)
P = .006
Months
ABA 73 (0) 46 (1) 33 (7) 31 (2)
Placebo 69 (0) 28 (2) 23 (1) 21 (1)
No. at risk (censored)



J Clin Oncol 39:1865-1877. © 2021 by American Society of Clinical Oncology

The PTCY Strategy for GVHD prophylaxis in haploidentical transplant



1)Depletion of alloreactive T cells
2)Preservation of stem cells due to chemo-resistance
3)Expansion of Tregs

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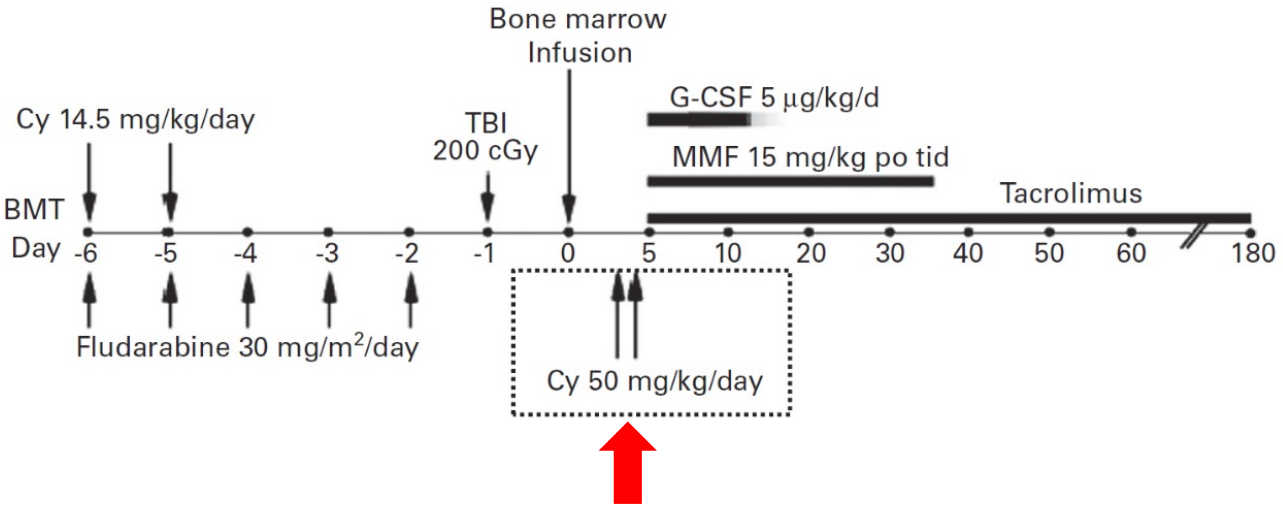
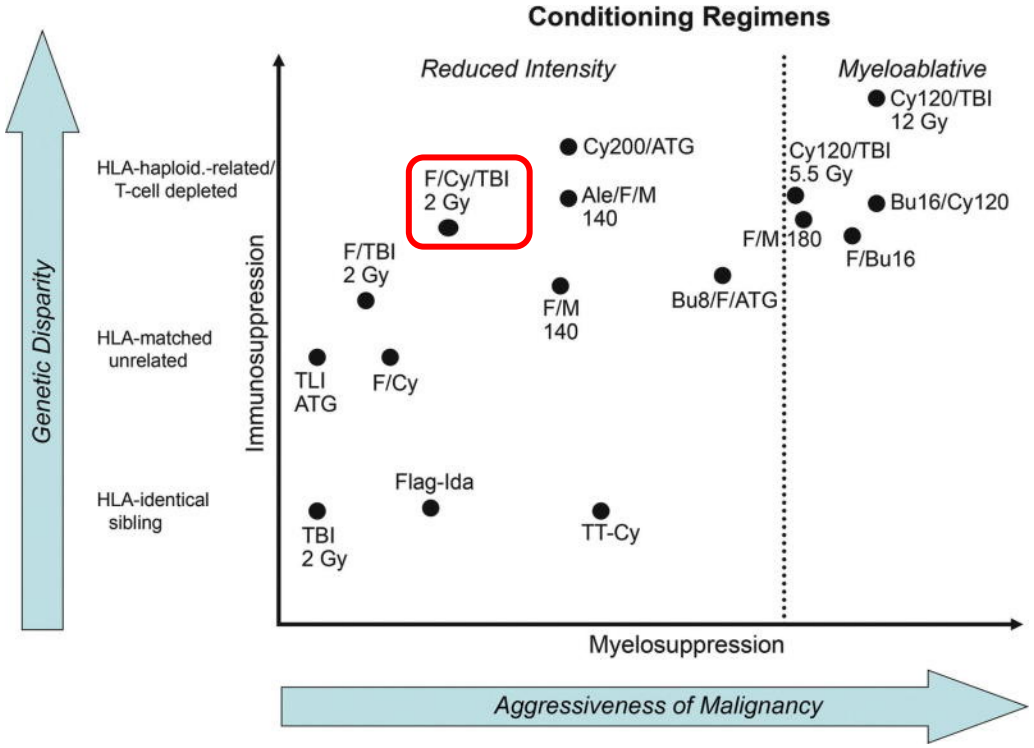
Luznik L, O'Donnell P, Symons H, et al. Biol Blood Marrow Transplant. 2008 Jun;14(6):641-50.

The Johns Hopkins' University Haploidentical BMT Protocol



Cy on days 3 and 4 to block proliferation of alloreactive T cells

Luznik L, O'Donnell P, Symons H, et al. Biol Blood Marrow Transplant. 2008 Jun;14(6):641-50.
Kasamon YL, Bolaños-Meade J, Prince GT, et al. J Clin Oncol. 2015 Oct 1;33(28):3152-61.



The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies [Internet]. 7th edition.

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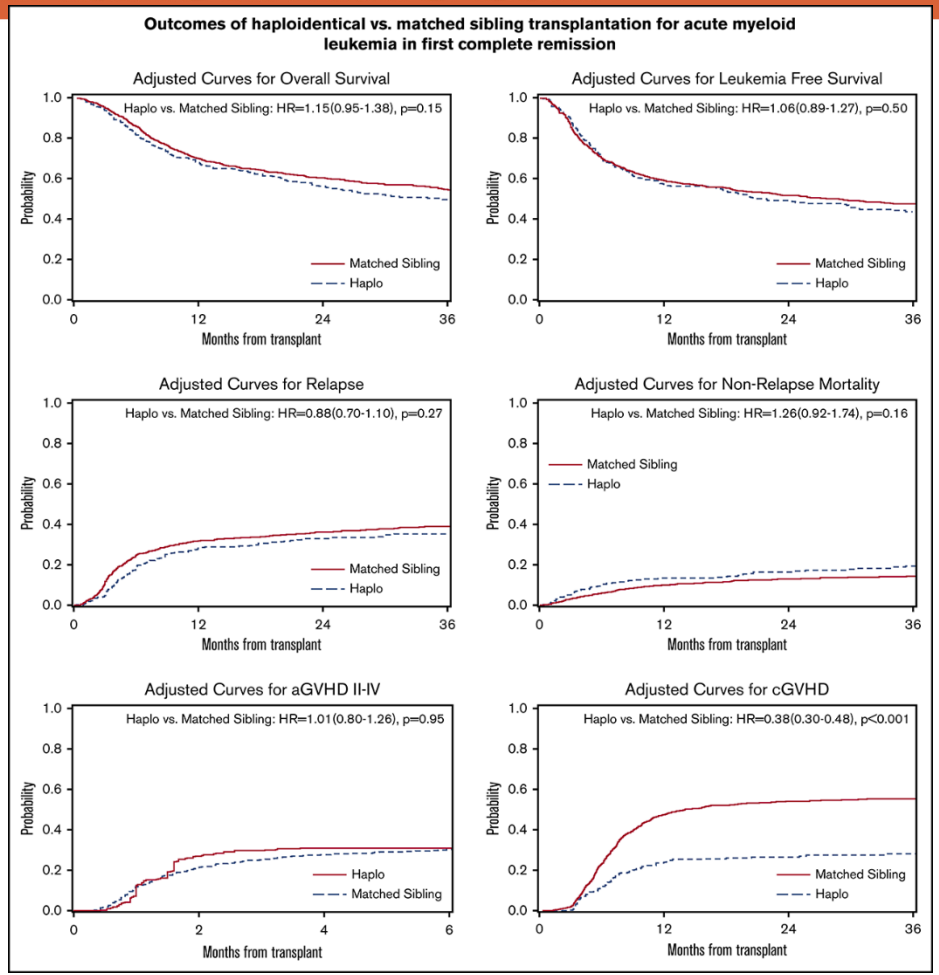
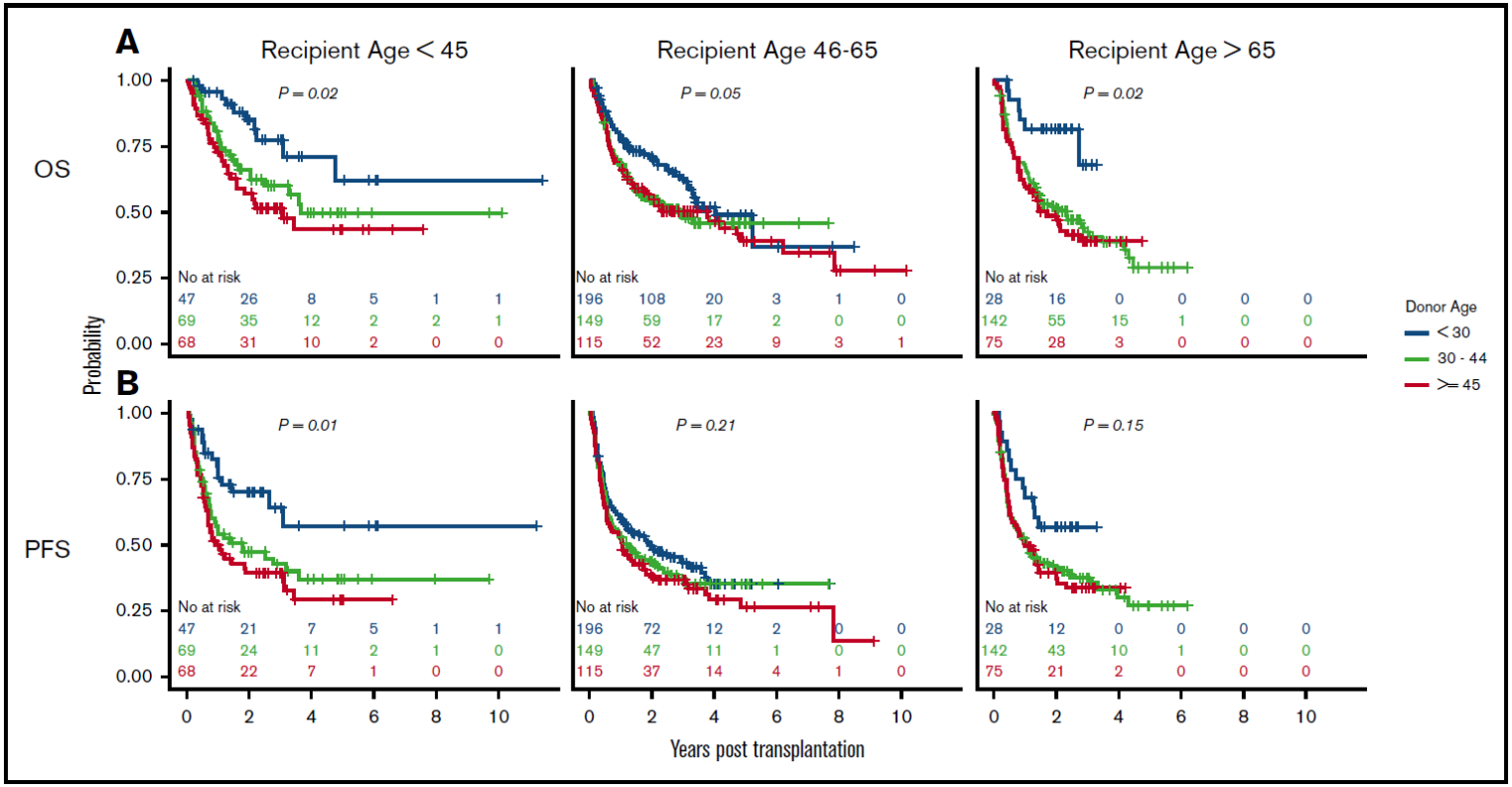


haploidentical vs MRD for AML in first CR

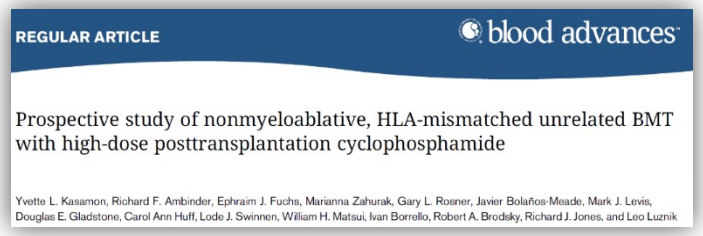
[CIBMTR 2008-2015]

Rashidi A, Blood Adv (2019) 3 (12): 1826–1836

Donor age and outcome in haplotransplant with PTCy



DeZern AE et al. Blood Adv 2021; 5 (5): 1360-1368


REGULAR ARTICLE

blood advances

Prospective study of nonmyeloablative, HLA-mismatched unrelated BMT with high-dose posttransplantation cyclophosphamide

Yvette L. Kasamon, Richard F. Ambinder, Ephraim J. Fuchs, Marianna Zahurak, Gary L. Rosner, Javier Bolaños-Meade, Mark J. Levis, Douglas E. Gladstone, Carol Ann Huff, Lode J. Swinnen, William H. Matsui, Ivan Borrello, Robert A. Brodsky, Richard J. Jones, and Leo Luznik

10 JANUARY 2017 • VOLUME 1, NUMBER 4

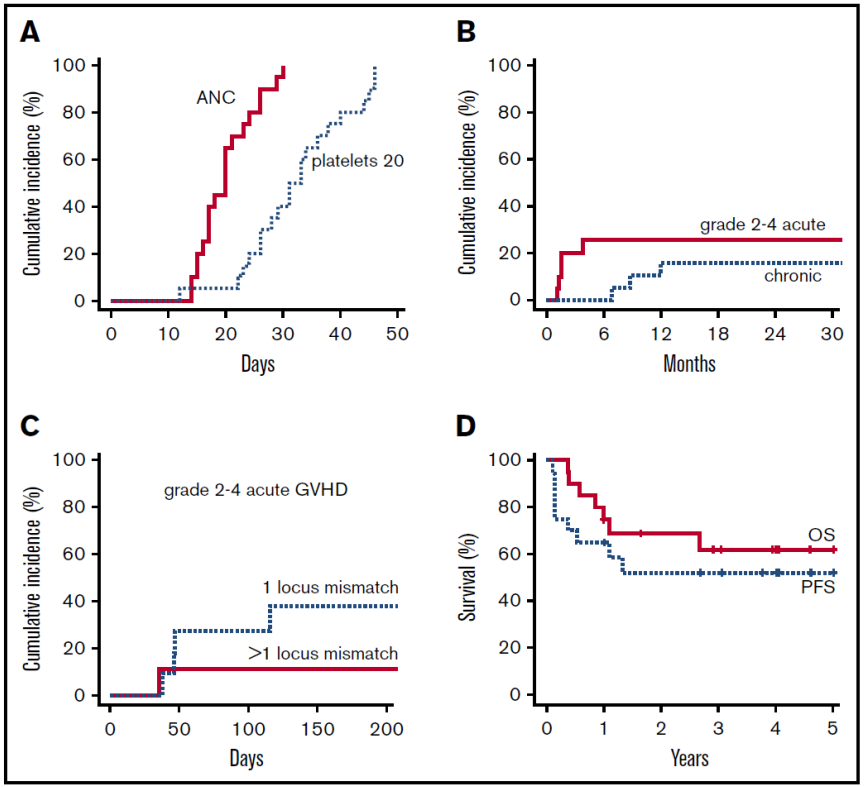
Multiple HLA Ag Mismatched UNRELATED

N. 20 MUD BMT with PT-CY (11 AML, 3 MDS, 2 CML, 4 NHL)

Unrelated grafts		
HLA matches§		
5/10 (1 locus mismatch at A, B, Cw, DRB1, DQB1)	1	(5%)
6/10 (1 A, 1 Cw, both B loci mismatched)	1	(5%)
7/10 (1 locus mismatch at class I, DRB1, DQB1)	3	(15%)
8/10	4‖	(20%)
9/10	11¶	(55%)

Table 2. (continued)

Variable	From N of 20	
Female donor/male recipient	6	(30%)
Cell dose infused, median (IQR)		
Total nucleated cells × 10^8/kg††	3.2	(2.7-4.4)
$CD34^+$ cells × 10^6/kg	2.8	(2.0-4.9)
$CD3^+$ cells × 10^7/kg	3.4	(2.7-5.0)



Kasamon YL, Blood Advances 2017; 1 (4):288-292

Can the dose of PTCy be reduced in haplo-transplants?

EBMT
www.nature.com/bmt

ARTICLE

Check for updates

Reduced post-transplant cyclophosphamide dose with antithymocyte globulin in peripheral blood stem cell haploidentical transplantation

Rémy Dulery[1,2], Florent Malard[1,2], Eolia Brissot[1,2], Anne Banet[1], Simona Sestili[1], Ramdane Belhocine[1], Martina Calabro[1], Zoé Van de Wyngaert[1], Agnès Bonnin[1], Tounes Ledraa[1], Ollivier Legrand[1,2], Myriam Labopin[1,3], Elodie Capderou[4], Ariel Cohen[4], Stéphane Ederhy[4] and Mohamad Mohty[1,2]

-Thiotepa-based (thiotepa - busulfan - fludarabine) in 25 (43%) patients
-Flamsa-like sequential (thiotepa - etoposide - cyclophosphamide, followed by fludarabine - busulfan) in 33 (57%).
GVHD prophylaxis included cyclosporin, mycophenolate mofetil, and ATG in all patients.

Thirty-three patients received PT-Cy at 70 mg/kg and 25 at 100 mg/kg.

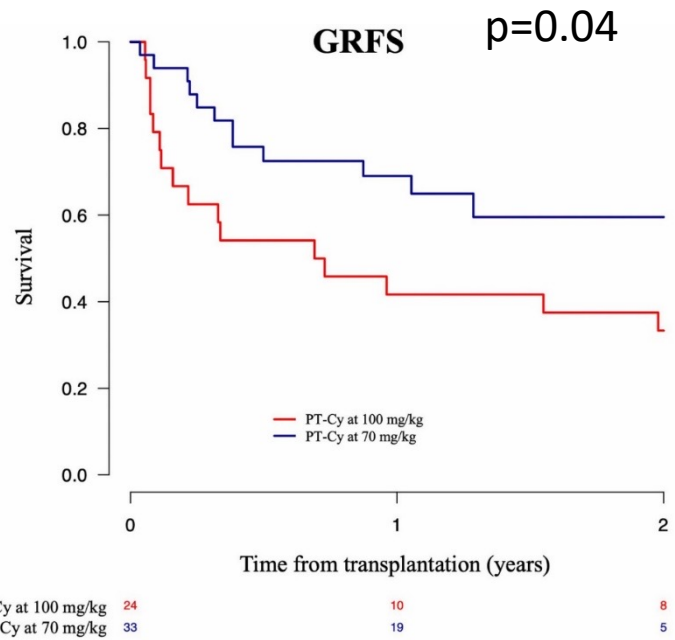


Figure 1. Kaplan-Meier estimates of graft-versus-host disease-free, relapse-free survival (GRFS) according to the dose of post-transplant cyclophosphamide (PT-Cy).

Dulery R, BMT 2023

Should we use PTCy also in HLA matched transplants?

ARTICLE

Triple post transplant cyclophosphamide (PTCY) based GVHD prophylaxis: HLA matched versus HLA haploidentical transplants

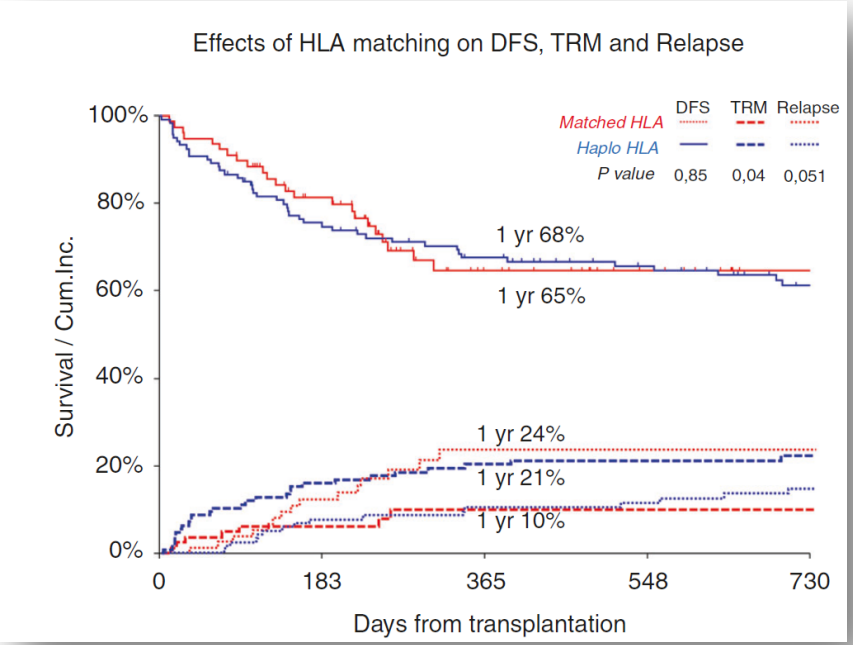
Check for updates

Bone Marrow Transplantation (2022) 57:532–537;

Eugenio Galli[1,2✉], Elisabetta Metafuni[2], Sabrina Giammarco[2], Maria Assunta Limongiello[2], Idanna Innocenti[2], Francesco Autore[2], Luca Laurenti[1,2], Federica Sorà[1,2], Patrizia Chiusolo[1,2], Luciana Teofili[1], Andrea Bacigalupo[1,2] and Simona Sica[1,2]

Table 1. Characteristics of population included in the study, overall and by HLA matching.

	Overall population	Matched HLA *n* (%)	Haplo HLA *n* (%)	*p* value
Total				
	198	78	120	
Patient age				
Median (95% CI)	55	49 (46–56)	56.5 (51–59)	0.05
Up to 60 yrs	127	55 (71)	72 (60)	0.13
Over 60 yrs	71	23 (29)	48 (40)	
Year of HSCT				
Median		2020	2018	
Recipient gender				
Males	106	42 (54)	64 (53)	0.94
Females	92	36 (46)	56 (47)	
Disease				
AML	81 (41)	26 (33)	55 (46)	0.06
ALL	32 (16)	15 (19)	17 (14)	
MPN	41 (21)	20 (26)	21 (17)	
MDS	17 (8.5)	4 (5)	10 (11)	
Lymphoma	24 (12)	10 (13)	14 (12)	
MM	3 (1.5)	3 (4)	0 (0)	



Transplantation and Cellular Therapy
journal homepage: www.tctjournal.org
ASTCT American Society for Transplantation and Cellular Therapy

Report

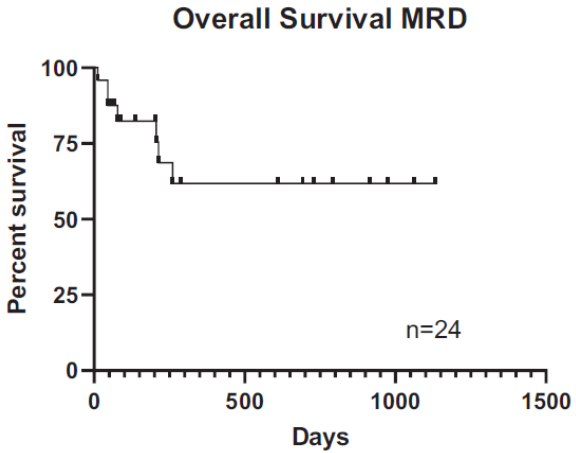
Hematopoietic Stem Cell Transplantation in Nepal: International Partnership, Implementation Steps, and Clinical Outcomes

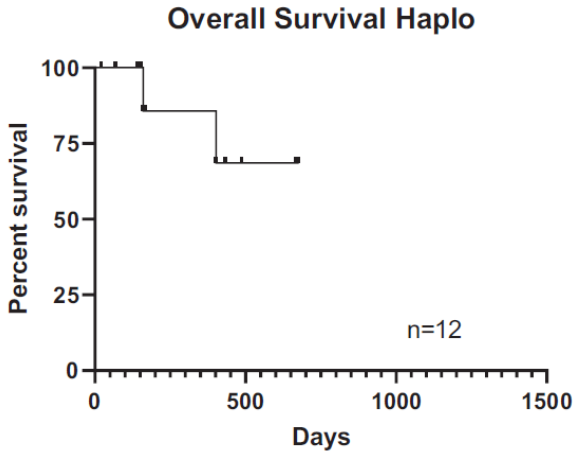
Bishesh Sharma Poudyal[1,*], Sampurna Tuladhar[1], Samir Neupane[1], Simit Sapkota[1,2], Subhas Pandit[1,2], Prem Raj Shrestha[1], Bishal Poudel[1], Malika Bajaracharya[1], Karen Sweiss[3], Pritesh Patel[3], Nadim Mahmud[3], Damiano Rondelli[3,4,**]

Matched Related Donor:
FLU/ivBU4 + PTCy [MMF+Tacro]
FLU/MEL + PTCy [MMF+Tacro]
FLU/CY + PTCy (in SAA)

Haplotransplant:
FLU/CY/TBI200 + PTCy [MMF+Tacro]

D





Poudyal B, Transplant Cell Ther. 2022 May;28(5):268-275

REGULAR ARTICLE

blood advances

Check for updates

HLA-matching with PTCy: a reanalysis of a CIBMTR dataset with propensity score matching and donor age

Alexander Ambinder,[1,*] Tania Jain,[1,*] Hua-Ling Tsai,[2] Mary M. Horowitz,[3] Richard J. Jones,[1,†] and Ravi Varadhan[2,†]

Herein, we present a reanalysis of the same CIBMTR dataset used to determine the impact of HLA matching on transplant outcomes on PTCy-based GVHD prophylaxis, considering the separate effect of donor age and using propensity score matching and weighting methods to correct for the imbalances between cohorts.

26 JULY 2022 • VOLUME 6, NUMBER 14

Table 1. Patient and BMT characteristics by haploidentical and MUD BMT in the propensity-matched cohort

Variables	Propensity score matching cohort in (RIC + MA)			*P* value
	Matched (n = 837)	MUD (n = 200)	Haplo (n = 637)	
Age at BMT				
Median (range)	58 (18-80)	60 (18-80)	58 (19-78)	.07
Race, n (%)				.41
Caucasian	742 (89)	181 (91)	561 (88)	
Other	95 (11)	19 (9)	76 (12)	
Gender, n (%)				.86
Female	467 (56)	110 (55)	357 (56)	
Male	370 (44)	90 (45)	280 (44)	
BMT Year, n (%)				.86
2011-2014	93 (11)	21 (11)	72 (11)	
2015-2018	744 (89)	[illegible]	[illegible]	
Dx to BMT (month)	10.15 (13.34)	10.55 (16.22)	10.02 (12.31)	.67
Median (range)	5.9 (1.45 165.16)	5.92 (1.45 165.16)	5.95 (1.61, 112.89)	.85
Disease, n (%)				.71
ALL	201 (24)	45 (22)	156 (25)	
AML	455 (54)	108 (54)	347 (54)	
MDS	181 (22)	47 (24)	134 (21)	
Condition, n (%)				.44
RIC	455 (54)	114 (57)	341 (54)	
MAC	382 (46)	86 (43)	296 (46)	

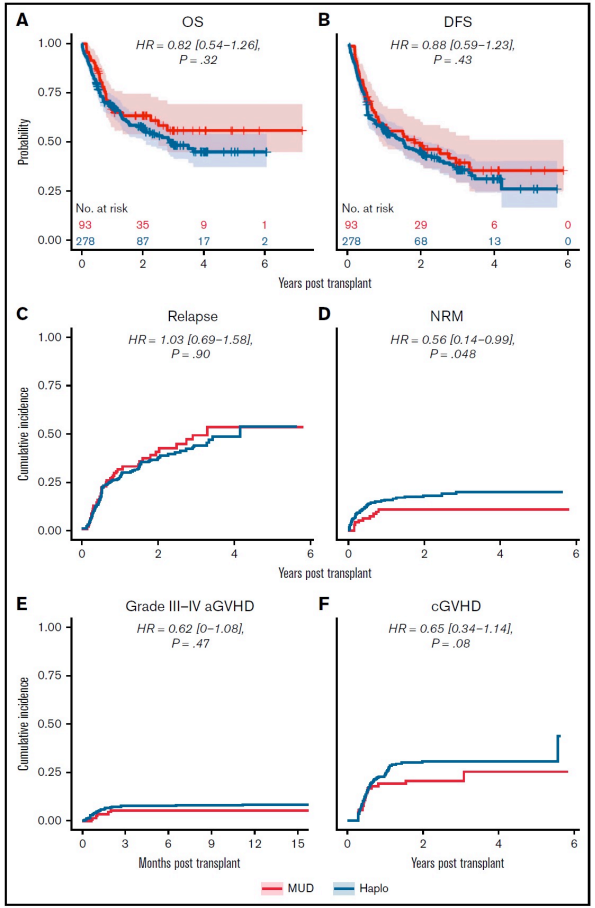
Ambinder A, Blood Adv 2022; 6 (14):4335-4346

Transplant source, n (%)				.84
KPS, n (%)				.73
<90	504 (60)	123 (62)	381 (60)	
90-100	333 (40)	77 (38)	256 (40)	
DRI, n (%)				.54
Low/intermediate	692 (83)	162 (81)	530 (83)	
High/very high	145 (17)	38 (19)	107 (17)	
Recip. CMV, n (%)				.32
Negative	300 (36)	78 (39)	222 (35)	
Positive	537 (64)	122 (61)	415 (65)	
Donor age				
Median (range)	30 (13-71)	29 (19-60)	30 (13-71)	.84

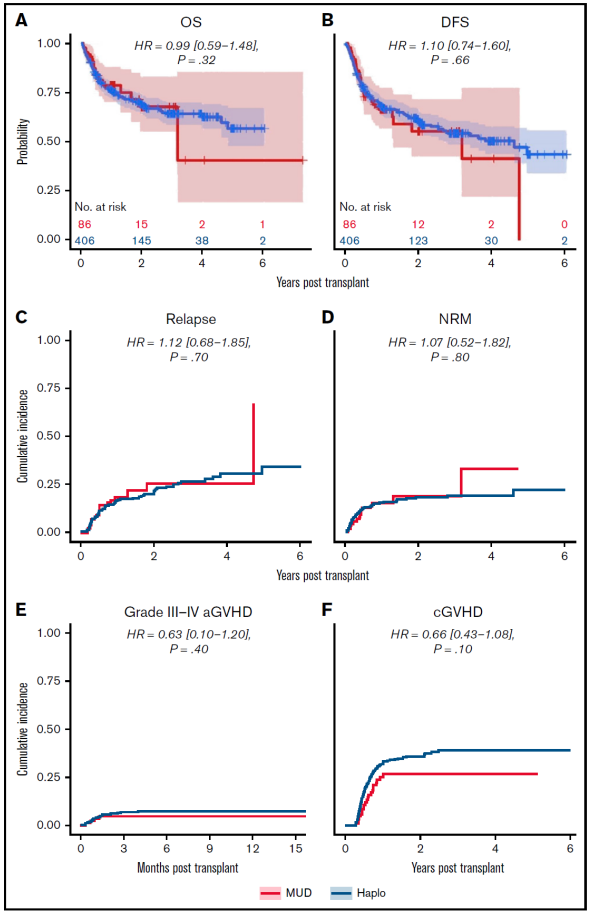
Ambinder A, Blood Adv 2022; 6 (14):4335-4346

Ambinder A, Blood Adv 2022; 6 (14):4335-4346

RIC



MAC



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Post-Transplantation Cyclophosphamide-Based Graft-versus-Host Disease Prophylaxis

J. Bolaños-Meade, M. Hamadani, J. Wu, M.M. Al Malki, M.J. Martens, L. Runaas, H. Elmariah, A.R. Rezvani, M. Gooptu, K.T. Larkin, B.C. Shaffer, N. El Jurdi, A.W. Loren, M. Solh, A.C. Hall, A.M. Alousi, O.H. Jamy, M.-A. Perales, J.M. Yao, K. Applegate, A.S. Bhatt, L.S. Kean, Y.A. Efebera, R. Reshef, W. Clark, N.L. DiFronzo, E. Leifer, M.M. Horowitz, R.J. Jones, and S.G. Holtan, for the BMT CTN 1703 Investigators*

RIC HSCT

FluBu2, FluMel, FluCyTBI200

Randomized study:

PTCy/MMFd5-35/tacro

vs

MTX d1,3,6,11/Tacro

N ENGL J MED 388;25 NEJM.ORG JUNE 22, 2023

Table 1. Baseline Characteristics of the Patients in the Intention-to-Treat Population.*

Characteristic	Experimental-Prophylaxis Group (N=214)	Standard-Prophylaxis Group (N=217)	All Patients (N=431)
Male sex — no. (%)	134 (62.6)	126 (58.1)	260 (60.3)
Race or ethnic group — no. (%)†			
Hispanic or Latinx ethnic group			
Hispanic or Latinx	9 (4.2)	22 (10.1)	31 (7.2)
Not Hispanic or Latinx	203 (94.9)	191 (88.0)	394 (91.4)
Not reported or unknown	2 (0.9)	4 (1.8)	6 (1.4)
American Indian or Alaska Native	0	1 (0.5)	1 (0.2)
Asian	10 (4.7)	4 (1.8)	14 (3.2)
Black	8 (3.7)	5 (2.3)	13 (3.0)
Native Hawaiian or Pacific Islander	0	0	0
White	186 (86.9)	193 (88.9)	379 (87.9)
Multiple	0	1 (0.5)	1 (0.2)
Unknown	10 (4.7)	13 (6.0)	23 (5.3)
Age			
Mean — yr	64.2±8.5	64.5±8.9	64.3±8.7
≥65 yr — no. (%)	120 (56.1)	125 (57.6)	245 (56.8)
Karnofsky performance-status score ≥90 — no. (%)‡	106 (49.5)	108 (49.8)	214 (49.7)
Primary disease — no. (%)			
Acute lymphoblastic leukemia	12 (5.6)	27 (12.4)	39 (9.0)
Acute myeloid leukemia	107 (50.0)	100 (46.1)	207 (48.0)
Myelodysplastic syndrome	63 (29.4)	65 (30.0)	128 (29.7)
Other§	32 (15.0)	25 (11.5)	57 (13.2)
Donor type and HLA matching — no. (%)			
Related donor 6/6	60 (28.0)	68 (31.3)	128 (29.7)
Unrelated donor 7/8	7 (3.3)	8 (3.7)	15 (3.5)
Unrelated donor 8/8	147 (68.7)	141 (65.0)	288 (66.8)

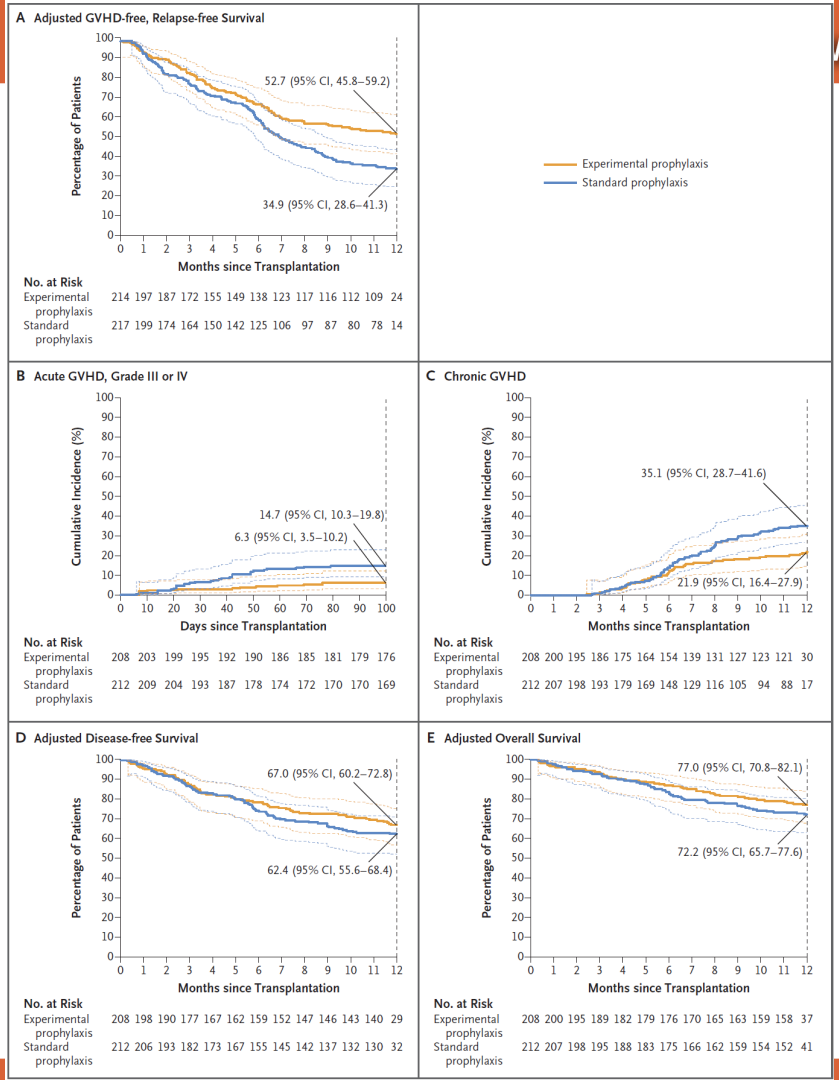
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Post-Transplantation Cyclophosphamide-Based Graft-versus-Host Disease Prophylaxis

J. Bolaños-Meade, M. Hamadani, J. Wu, M.M. Al Malki, M.J. Martens, L. Runaas, H. Elmariah, A.R. Rezvani, M. Gooptu, K.T. Larkin, B.C. Shaffer, N. El Jurdi, A.W. Loren, M. Solh, A.C. Hall, A.M. Alousi, O.H. Jamy, M.-A. Perales, J.M. Yao, K. Applegate, A.S. Bhatt, L.S. Kean, Y.A. Efebera, R. Reshef, W. Clark, N.L. DiFronzo, E. Leifer, M.M. Horowitz, R.J. Jones, and S.G. Holtan, for the BMT CTN 1703 Investigators*

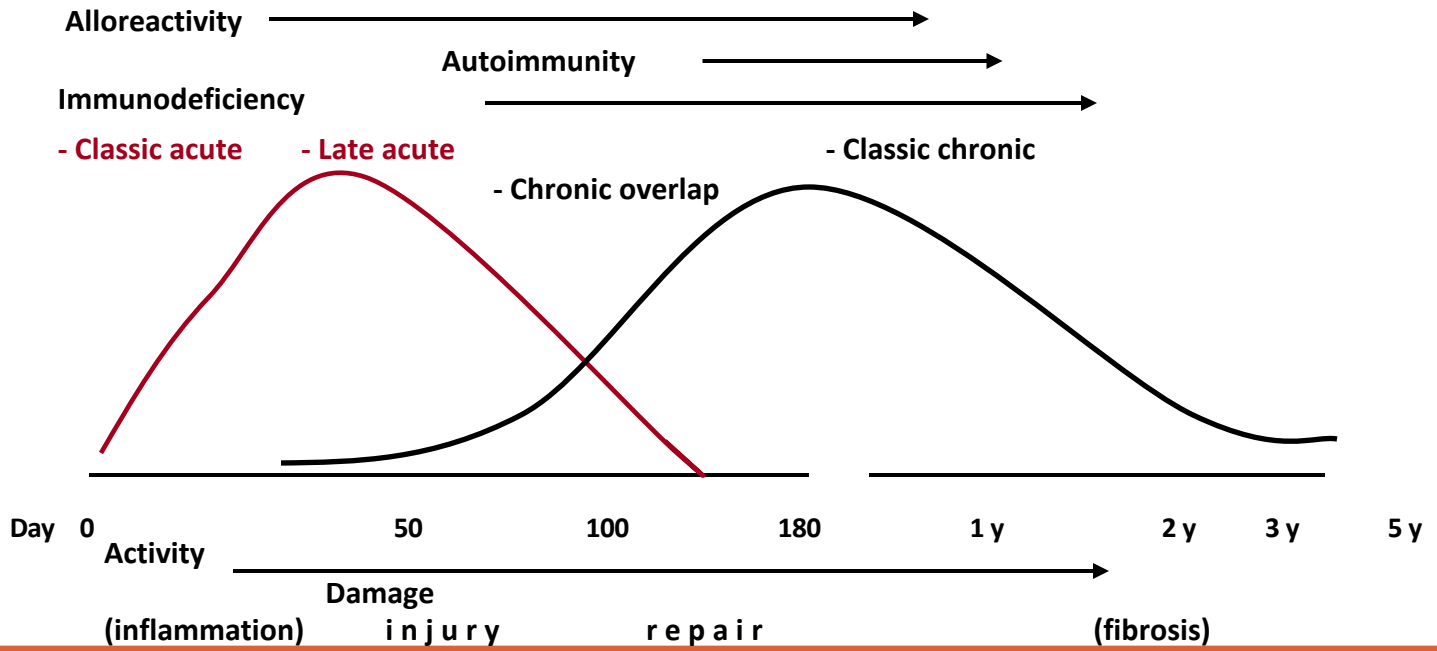
N ENGL J MED 388;25 NEJM.ORG JUNE 22, 2023



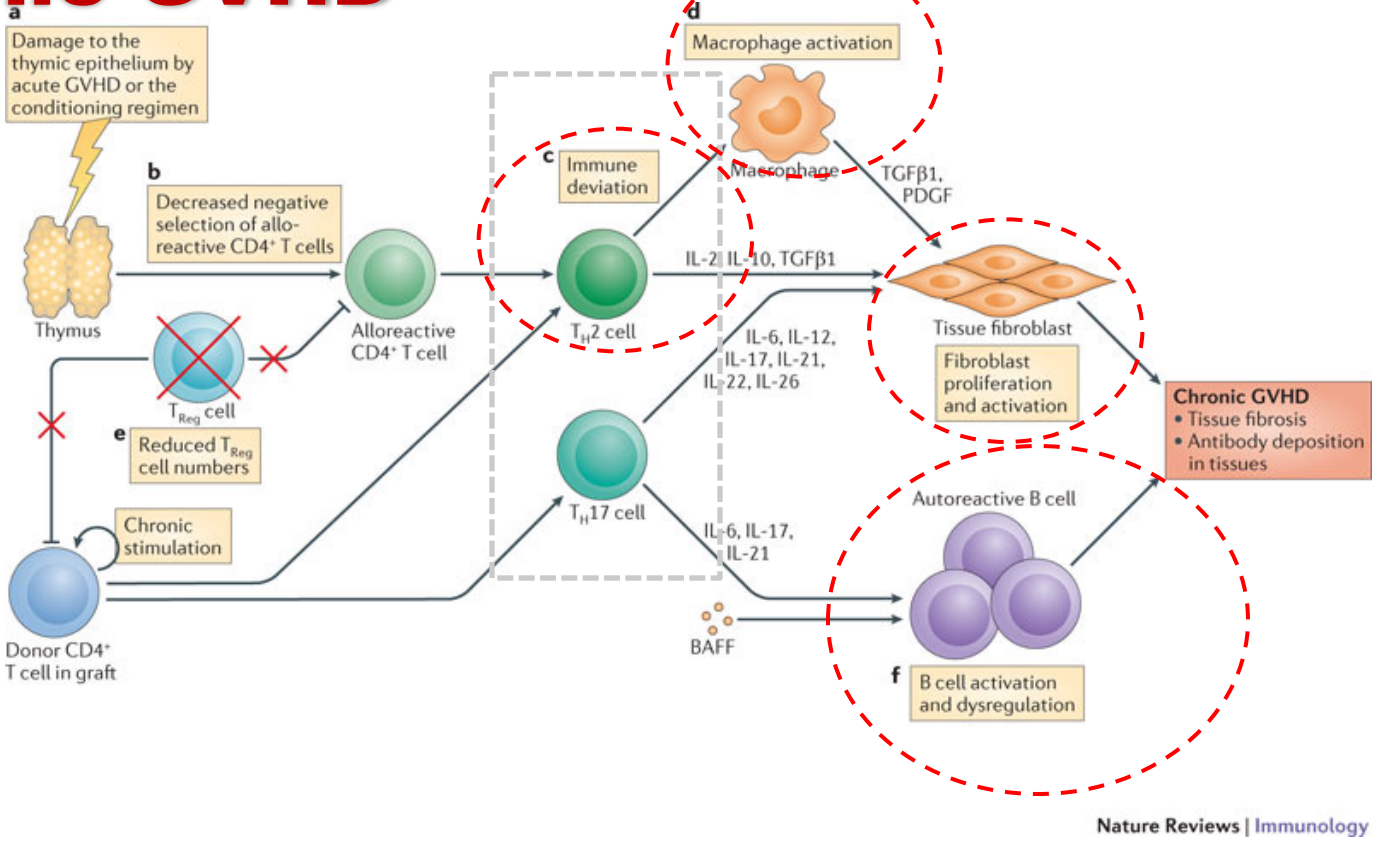
Changing Concepts: GVHD Syndrome After AlloHCT

Acute GVHD: rash, GI, liver

Chronic GVHD: skin, eyes, mouth, GI
liver, musculoskeletal, lungs, GU

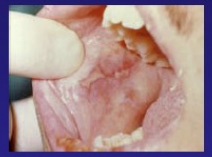


Chronic GVHD

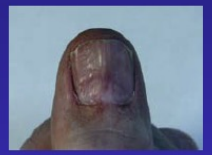


Blazar B, Nature Reviews Immunology 2012; 12, 443-458

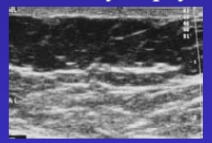
Dry eyes



Oral lesions

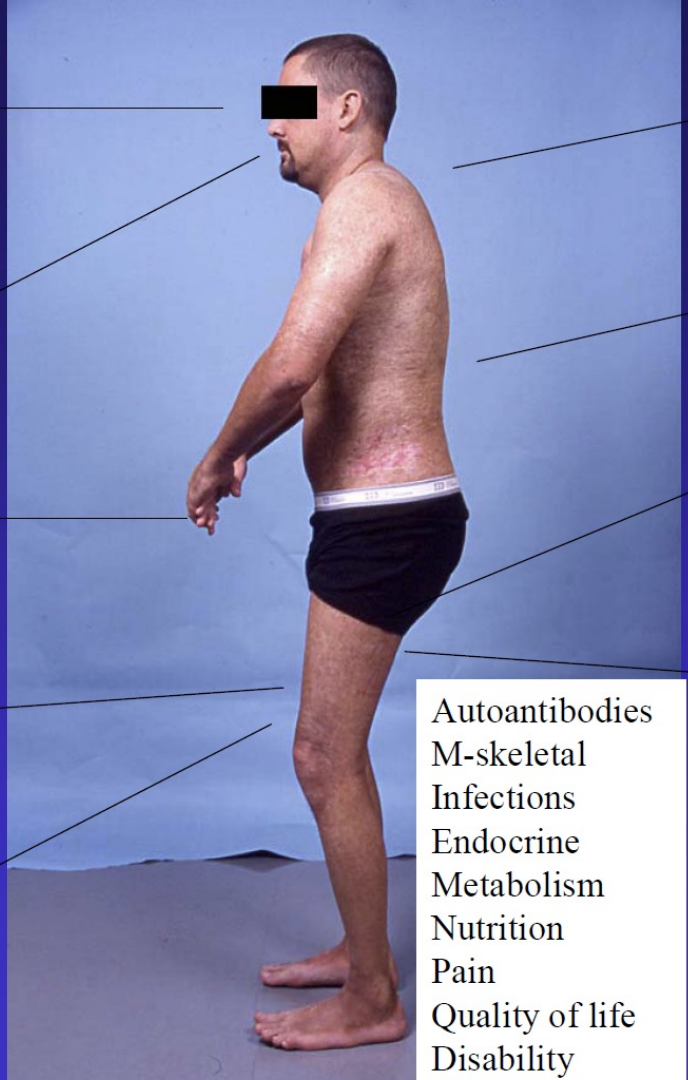


Nail dystrophy

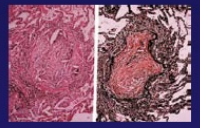


Skin sclerosis

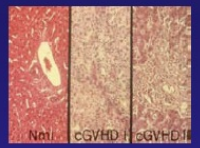
Deep sclerosis



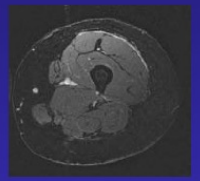
Autoantibodies
M-skeletal
Infections
Endocrine
Metabolism
Nutrition
Pain
Quality of life
Disability



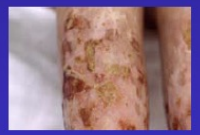
Bronchiolitis obliterans



Loss of bile ducts



Fasciitis



Skin ulcers

Increasing incidence:
Higher patient and donor age
More PBSC, DLI, HLA-MM

SCORING OF CHRONIC GVHD

Chronic GVHD: Clinical Scoring

SITE SCORING				
	0	1	2	3
PS (KPS)	100%	80-90%	60-70%	<60%
Skin (BSA)	No sxs	<18% and no sclerotic features	19-50% or sclerotic	>50% or hidebound sclerotic or impaired mobility
Mouth	No sxs	No limitations	Partial limits on PO intake	Major limitation of PO intake
Eyes	No sxs	Not affecting ADL	Partially affecting ADL	Majorly affecting ADL
GI	No sxs	<5% wt loss	5-15% wt loss	>15% wt loss, or requiring esophageal dilation
Liver	Normal LFT (bili, AP, AST, ALT)	< 2x ULN	2-5x ULN	>5x ULN
Lungs	No sxs and FEV1 > 80%	FEV1 60-79%	FEV1 40-59%	FEV1 <39%
Joints & Fascia	No sxs	Mild tightness not affecting ADL	Tightness or contractures + mild/mod limitation of ADL	Contractures + decrease in ROM + limitation of ADL
Genital tract	No sxs	No effect on coitus or exam	Moderate signs on exam and mild dyspareunia	Advanced signs on exam and severe pain with coitus

OVERALL SCORE		
	Involved Sites	Max score
MILD	1-2	1
MODERATE	≥ 3	1
	1	2
	Lung	1
SEVERE	≥ 1	3
	Lung	≥ 2

Mild	• 1 or 2 organs or sites (except lung) with score 1
	  • Mild oral symptoms, no decrease in oral intake
	  • Mild dry eyes, lubricant eyedrops ≤ 3x/day

Moderate	• 3 or more organs with score 1
	• At least 1 organ or site with score 2
	  • 19-50% body surface area involved or superficial sclerosis
	  • Moderate dry eyes, eyedrops > 3x/day or punctal plugs
	• Lung score 1 (FEV1 60-79% or dyspnea with stairs)

Severe	• At least 1 organ or site with score 3
	  • > 50% body surface area involved
	  • Deep sclerosis, impaired mobility or ulceration
	  • Severe oral symptoms with major limitation in oral intake
	  • Severe dry eyes affecting ADL
	• Lung score 2 (FEV1 40-59% or dyspnea walking on flat ground)

Lee SJ, Blood 2017: 129, 1: 30-37

Biol Blood Marrow Transplant 26 (2020) 562–567

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Survivorship

Reliability and Validity of the Modified 7-Day Lee Chronic Graft-versus-Host Disease Symptom Scale

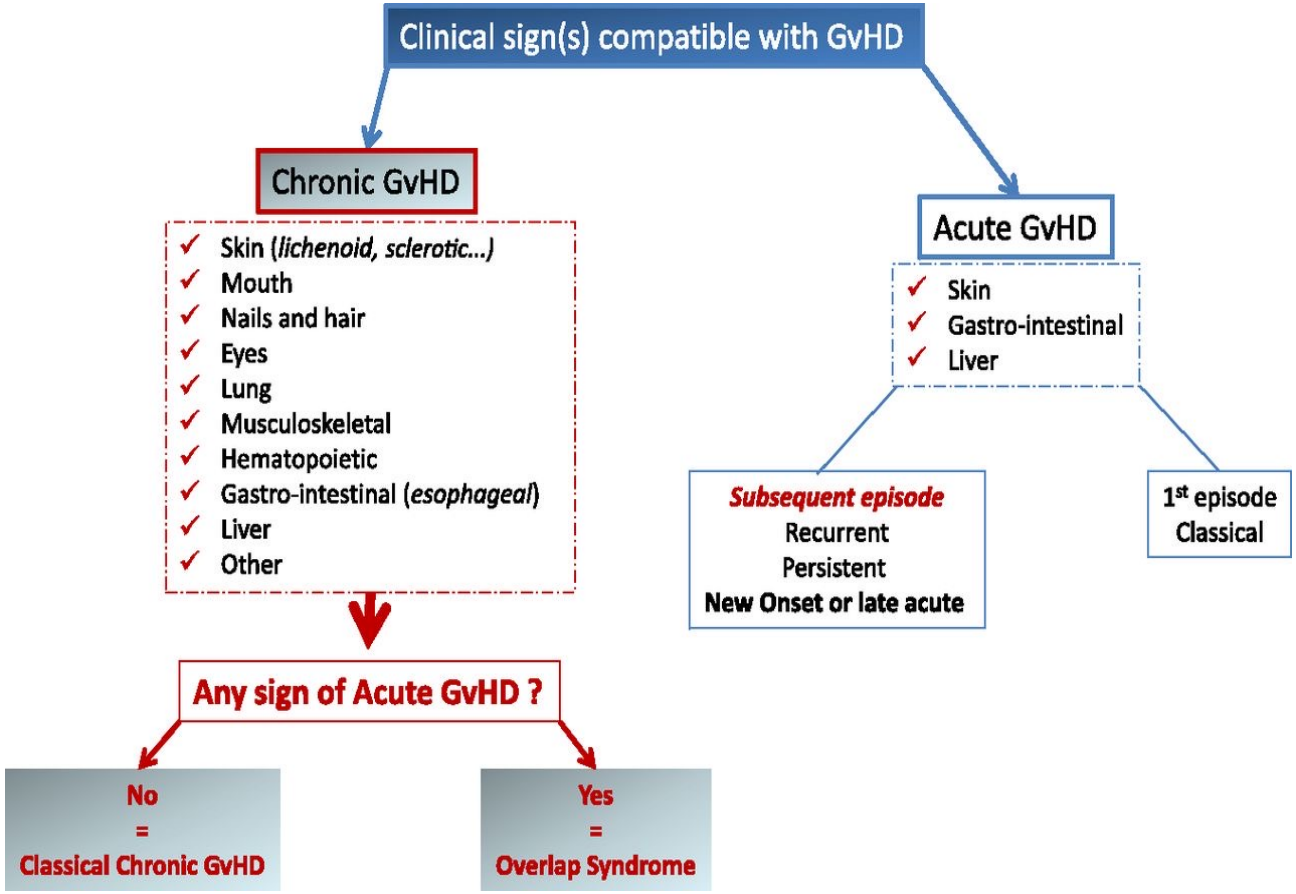
Christopher Teh, Lynn Onstad, Stephanie J. Lee*

Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington

Results show the modified 7-dayscale is reliable and valid in the modern era and may be used to assess the symptom burden of cGVHD in clinical trials. Using the distribution method, a 5- to 6-point difference (half a standard deviation) is considered clinically meaningful.

Scoring Algorithm for the mLSS

Subscale Name	Number of Items	Items
Skin	5	a. Abnormal skin color b. Rashes c. Thickened skin d. Sores on skin e. Itchy skin
Eye	3	f. Dry eyes g. Need to use eye drops frequently h. Difficulty seeing clearly
Mouth	2	i. Need to avoid certain foods due to mouth pain j. Ulcers in mouth
Lung	4	l. Frequent cough m. Colored sputum o. Shortness of breath at rest ~~p. Need to use oxygen~~ **aa. Fevers**
Nutrition	4	~~**k. Receiving nutrition from an intravenous line or feeding tube**~~ q. Difficulty swallowing solid foods r. Difficulty swallowing liquids s. Vomiting t. Weight loss
Energy	7	**n. Shortness of breath with exercise** **u. Joint and muscle aches** **v. Limited joint movement** **w. Muscle cramps** **x. Weak muscles** y. Loss of energy z. Need to sleep more/take naps
Psych	3	bb. Depression cc. Anxiety dd. Difficulty sleeping


Clinical sign(s) compatible with GvHD
Chronic GvHD
✓ Skin (lichenoid, sclerotic...)
✓ Mouth
✓ Nails and hair
✓ Eyes
✓ Lung
✓ Musculoskeletal
✓ Hematopoietic
✓ Gastro-intestinal (esophageal)
✓ Liver
✓ Other
Acute GvHD
✓ Skin
✓ Gastro-intestinal
✓ Liver
Subsequent episode
Recurrent
Persistent
New Onset or late acute
1st episode
Classical
Any sign of Acute GvHD ?
No
=
Classical Chronic GvHD
Yes
=
Overlap Syndrome

Pulmonary GVHD

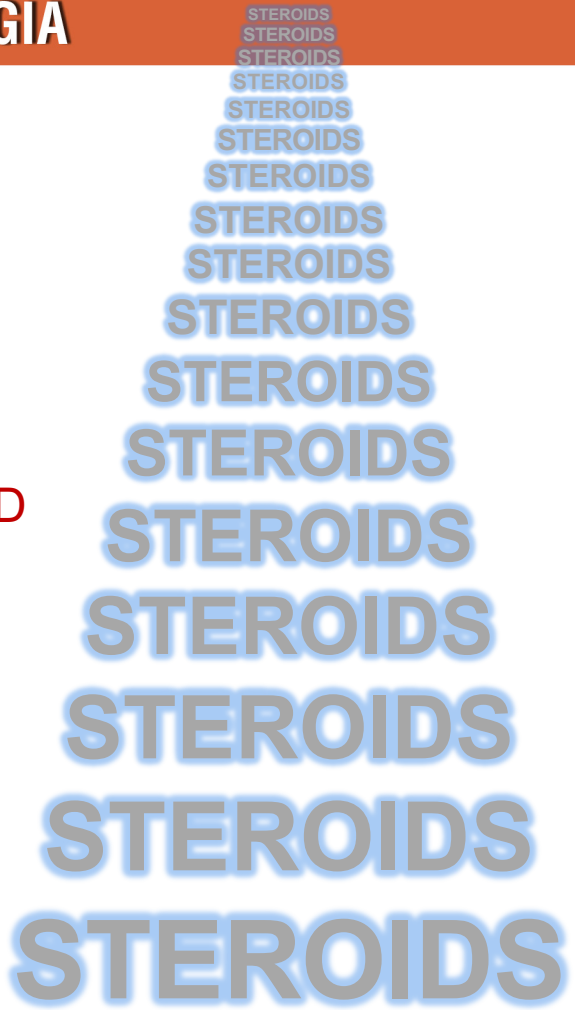
-Bronchodilator-resistant obstructive lung disease

histology: obliterative brochiolitis
Risk factors: long treatment with MTX, low IgG

Lung tx has been successful in patients resistant to immunosuppression

Treatment of chronic GVHD

Treatment of chronic GVHD



the recent past:

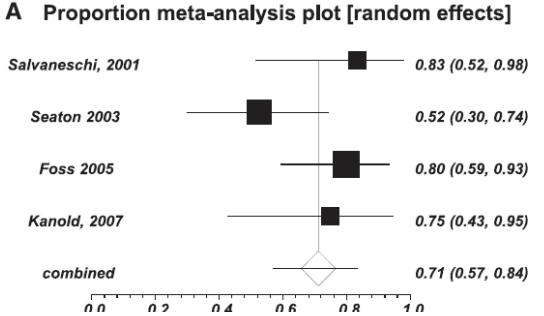
MMF, ECP, Rituxan, imatinib

Extracorporeal photopheresis (ECP)

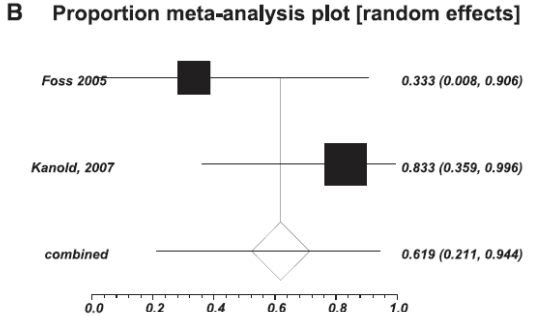
meta-analysis of prospective studies

I. Abu-Dalle et al. / Biol Blood Marrow Transplant 20 (2014) 1677–1686

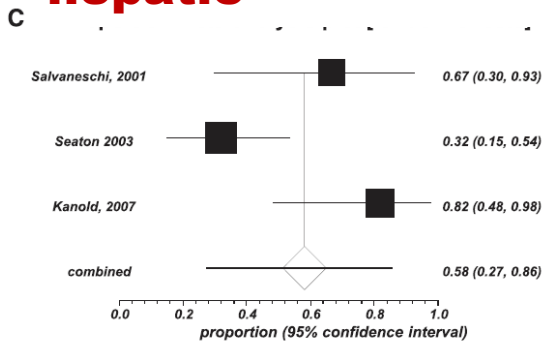
cutaneous



gastrointestinal



hepatic



oral mucosa

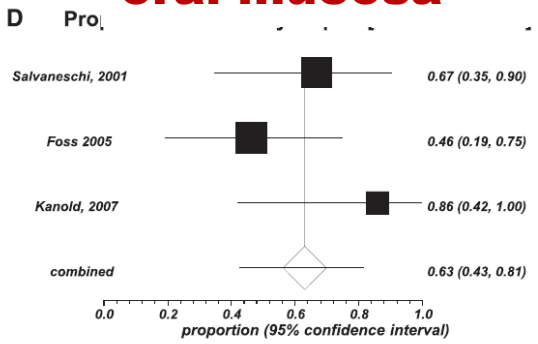


Figure 4. Chronic GVHD organ-specific response: cutaneous (A), gastrointestinal (B), hepatic (C), and oral mucosa (D).

Anti-CD20 mAb (Rituxan) in cGVHD

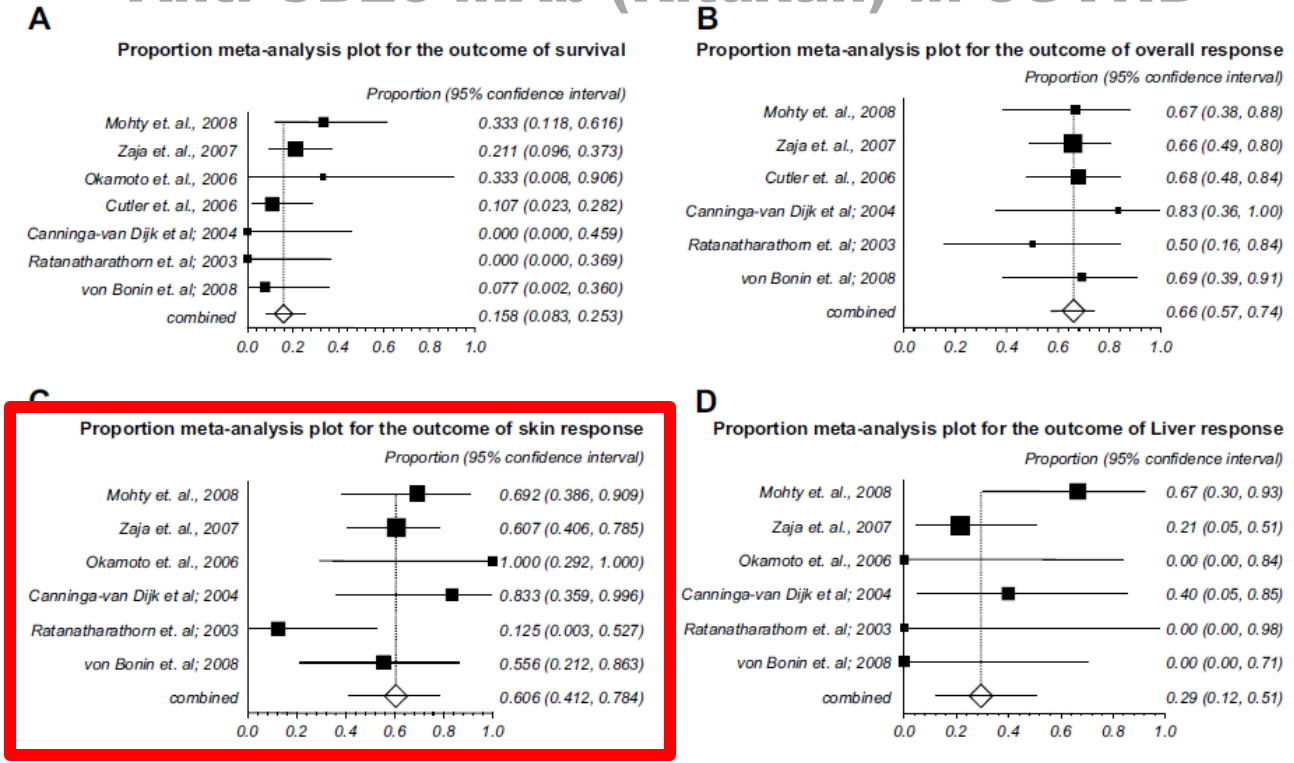


Figure 2. Forest plot for the outcomes of survival, overall response and organ specific response (skin and liver). The summary effect estimate (proportion) for individual studies are indicated by black rectangles (the size of the rectangle is proportional to the study weight), with the lines representing 95% confidence intervals (CIs). The overall summary effect estimate (proportion) and 95% CI are indicated by the diamond.

Imatinib in cGVHD with fibrotic features

TRANSPLANTATION

Imatinib for refractory chronic graft-versus-host disease with fibrotic features

Attilio Olivieri,[1] *Franco Locatelli,[2] Marco Zecca,[2] Adele Sanna,[3] Michele Cimminiello,[1] Roberto Raimondi,[4] Guido Gini,[5] Nicola Mordini,[6] Adriana Balduzzi,[7] Pietro Leoni,[5] Armando Gabrielli,[8] and *Andrea Bacigalupo[9]

Blood 2009; 114:709-718

CLINICAL TRIALS AND OBSERVATIONS

A phase 1 study of imatinib for corticosteroid-dependent/refractory chronic graft-versus-host disease: response does not correlate with anti-PDGFRA antibodies

George L. Chen,[1,2] Sally Arai,[1] Mary E. D. Flowers,[3,4] Joanne M. Otani,[1] Jingxin Qiu,[5] Ethan C. Cheng,[1] Alex McMillan,[6] Laura J. Johnston,[1] Judith A. Shizuru,[1] and David B. Miklos[1]

Blood 2011; 118:4070-4078

Imatinib in cGVHD

Regular Article

TRANSPLANTATION

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

Table 3. Global and organ-specific response according to center evaluation (response based on Couriel criteria), NIH response criteria, and changes in NIH severity score (NIH SS)

Center (Couriel)		NIH criteria							Changes in NIH SS						
Response	Overall	Response	Skin	Lungs	Mouth	Liver	Gut	Overall	Response	Skin	Lungs	Mouth	Liver	Gut	Overall
ORR corr*	46%	ORR corr*						51.3%	ORR corr*						56.4%
ORR	36%	ORR	32%	35%	16%	25%	50%	51.3%	ORR	22%	25%	38%	25%	50%	51.3%
CR	0	CR	3	2	4	2	5	0	CR	3	2	4	2	5	0
PR	14	PR	7	9	0	0	1	20	PR	4	6	5	0	0	20
MR/SD	12	SD	15	13	18	4	4	7	SD	20	17	13	5	3	9
NR/PD	5	PD	2	1	0	0	2	5	PD	0	1	0	0	2	3
NE	8	NE	4	7	3	2	0	7	NE	4	6	2	1	0	7
TOT.	39	TOT	31	32	25	8	12	39	TOT	31	32	24	8	10	39
EVAL	31	EVAL	27	25	22	6	12	32	EVAL	27	26	22	7	10	32

Olivieri A, Blood. 2013;122(25):4111-8

A randomized phase II crossover study of imatinib or rituximab for cutaneous sclerosis after hematopoietic cell transplantation.

Randomized two-arm phase II crossover trial

- imatinib (200 mg daily)
- or rituximab (375 mg/m2 intravenously weekly x 4 doses, repeatable after 3 months)

for treatment of CS diagnosed within 18 months

Clinical Significant Response at 6 mo:

Imatinib: 17%

Rituximab: 14%

Arai S, Clin Cancer Res. 2015 Sep 16. [Epub ahead of print]

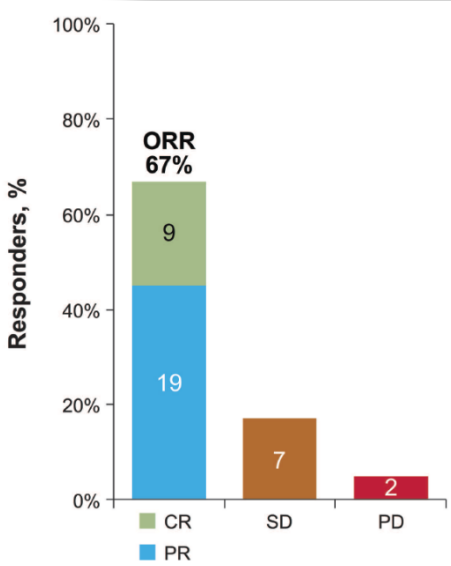
the new kids on the block:

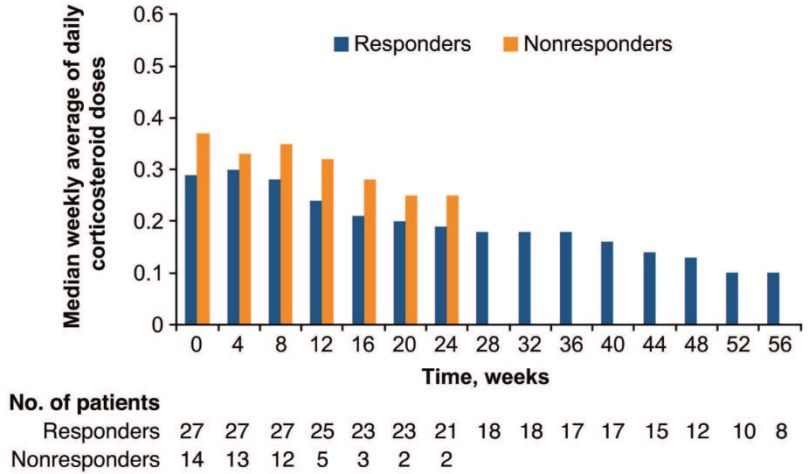
ibrutinib, ruxolitinib, belumosudil, axitalimab

blood®
Prepublished online September 18, 2017;
doi:10.1182/blood-2017-07-793786

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

David Miklos, Corey S. Cutler, Mukta Arora, Edmund K. Waller, Madan Jagasia, Iskra Pusic, Mary E. Flowers, Aaron C. Logan, Ryotaro Nakamura, Bruce R. Blazar, Yunfeng Li, Stephen Chang, Indu Lal, Jason Dubovsky, Danelle F. James, Lori Styles and Samantha Jaglowski





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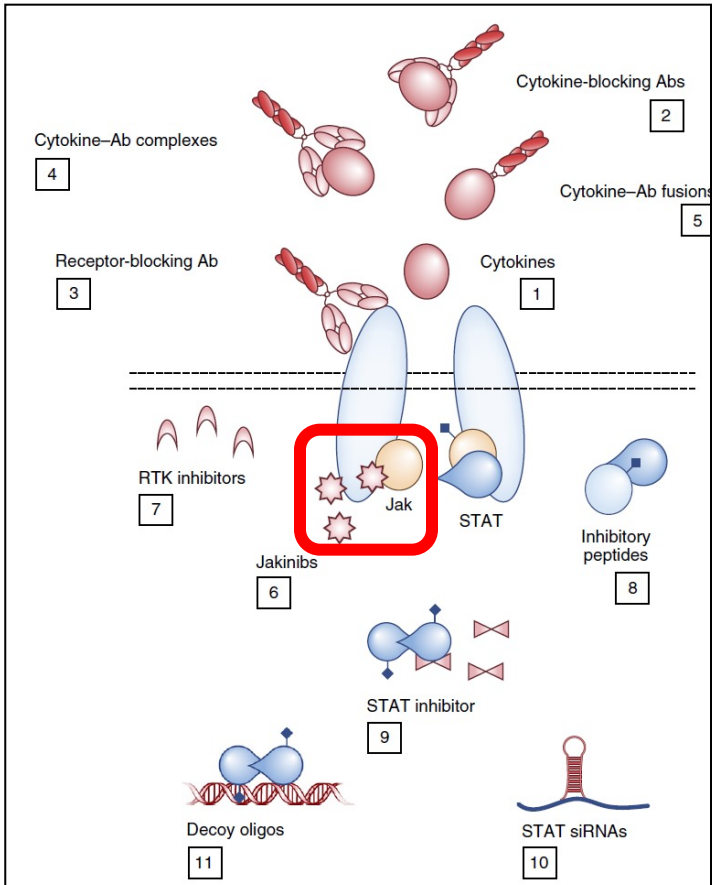


Figure 4 Therapeutic targeting of the Jak–STAT pathway. Numerous

Villarino AV, Nat Immunol 2017; 18 (4): 374-384

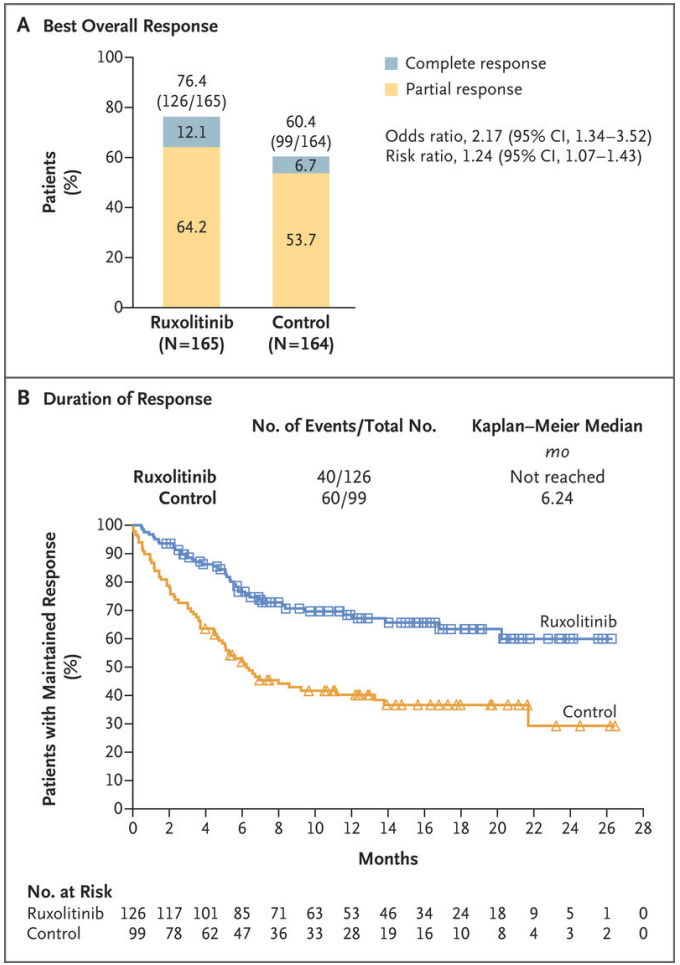
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ruxolitinib for Glucocorticoid-Refractory Chronic Graft-versus-Host Disease

Robert Zeiser, M.D., Nicola Polverelli, M.D., Ph.D., Ron Ram, M.D., Shahrukh K. Hashmi, M.D., M.P.H., Ronjon Chakraverty, M.D., Ph.D., Jan Moritz Middeke, M.D., Maurizio Musso, M.D., Sebastian Giebel, M.D., Ph.D., Ant Uzay, M.D., Peter Langmuir, M.D., Norbert Hollaender, Ph.D., Maanasa Gowda, Pharm.D., Tommaso Stefanelli, M.D., Stephanie J. Lee, M.D., M.P.H., Takanori Teshima, M.D., Ph.D., and Franco Locatelli, M.D., Ph.D., for the REACH3 Investigators*

N Engl J Med 2021;385:228-38.



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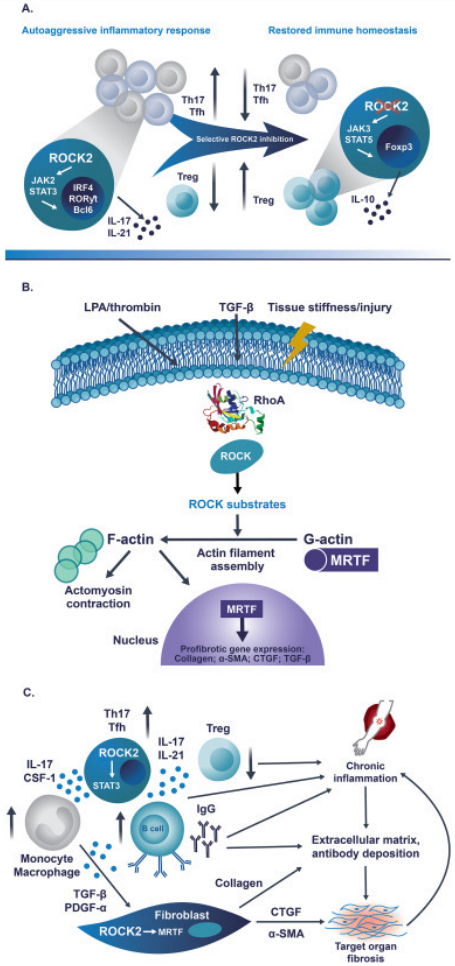


Belumosudil (Rho-associated coiled-coil-containing protein kinase 2, ROCK2 inhibitor)

- targets inflammation in cGVHD by reducing type 17 and follicular T helper cells via downregulation of STAT3 and enhances T Reg via upregulation of STAT5

- significantly reduces lung and skin fibrosis in animal models of bronchiolitis obliterans syndrome and sclerodermatous cGVHD, respectively, consistent with the central role of ROCK in facilitating multiple fibrotic pathways

TRANSPLANTATION

Belumosudil for chronic graft-versus-host disease after 2 or more prior lines of therapy: the ROCKstar Study

Corey Cutler,[1] Stephanie J. Lee,[2] Sally Arai,[3] Marcello Rotta,[4] Behyar Zoghi,[5] Aleksandr Lazaryan,[6] Aravind Ramakrishnan,[7]

2278 blood® 2 DECEMBER 2021 | VOLUME 138, NUMBER 22

KEY POINTS

- **Belumosudil, a selective ROCK2 inhibitor, was well tolerated in heavily pretreated subjects, with 44% continuing treatment beyond 1 year.**
- **Belumosudil demonstrated efficacy in patients with SR cGVHD, with responses in all organs and after failure of ibrutinib/ ruxolitinib.**

Belumosudil @ 200 mg daily or 200 mg bid until progression. After 2 weeks, CS could be tapered

FDA Approves Belumosudil to Treat Chronic Graft-Versus-Host Disease – August 2021

Characteristic	Belumosudil, 200 mg daily (n = 66)	Belumosudil, 200 mg twice daily (n = 66)	Total (N = 132)
Age, median (range), y	53 (21-77)	57 (21-77)	56 (21-77)
Males	42 (64)	33 (50)	75 (57)
Conditioning intensity			
Myeloablative	41 (62)	42 (64)	83 (63)
Nonmyeloablative	22 (33)	22 (33)	44 (33)
Unknown	3 (5)	2 (3)	5 (4)
HLA matching of donor/recipient			
Matched	57 (86)	62 (94)	119 (90)
Partially matched	8 (12)	3 (5)	11 (8)
Unknown	0	1 (2)	1 (1)
Missing	1 (2)	0	1 (1)
NIH cGVHD severity*			
Severe	46 (70)	43 (65)	89 (67)
Moderate	18 (27)	23 (35)	41 (31)
Mild	2 (3)	0	2 (2)

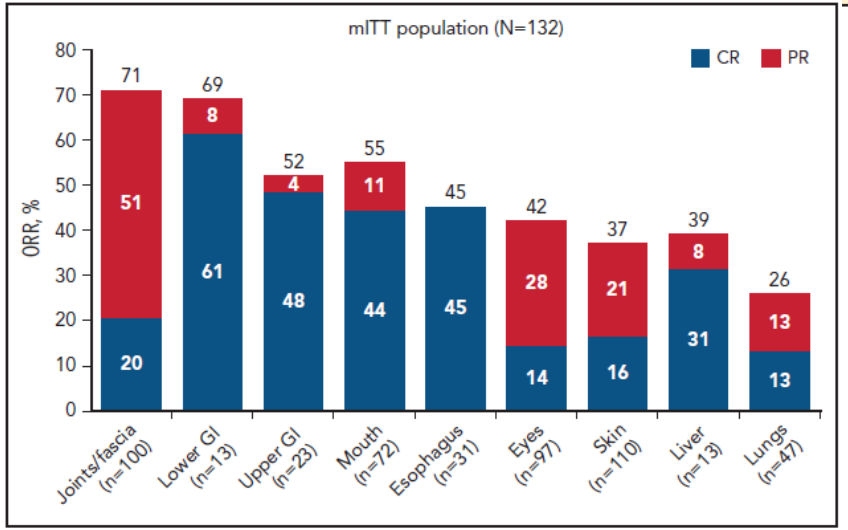
Cutler C, et al Blood 2021, 138, 22: 2278

Cutler C, et al Blood 2021, 138, 22: 2278

Characteristic	Belumosudil, 200 mg daily (n = 66)	Belumosudil, 200 mg twice daily (n = 66)	Total (N = 132)
Organ involvement			
No. of organs involved, median (range)	4 (0-7)	4 (2-7)	4 (0-7)
≥4 organs involved	33 (50)	35 (53)	68 (52)
Skin	55 (83)	55 (83)	110 (83)
Joints/fascia	51 (77)	49 (74)	100 (76)
Eyes	48 (73)	49 (74)	97 (74)
Mouth	30 (46)	42 (64)	72 (55)
Lungs	24 (36)	23 (35)	47 (36)
Esophagus	19 (29)	12 (18)	31 (24)
Upper GI	13 (20)	10 (15)	23 (17)
Lower GI	6 (9)	7 (11)	13 (10)
Liver	9 (14)	4 (6)	13 (10)
Prior systemic cGVHD therapy type			
CS (prednisone)	65 (99)	65 (99)	130 (99)
Tacrolimus	40 (61)	42 (64)	82 (62)
ECP	31 (47)	32 (49)	63 (48)
Sirolimus	29 (44)	33 (50)	62 (47)
Ibrutinib	22 (33)	23 (35)	45 (34)
Ruxolitinib	20 (30)	18 (27)	38 (29)
MMF	18 (27)	15 (23)	33 (25)
Rituximab	15 (23)	13 (20)	28 (21)
MTX	3 (5)	3 (5)	6 (5)
Cyclosporine	4 (6)	1 (2)	5 (4)
Imatinib	3 (5)	1 (2)	4 (3)
Ixazomib	0	1 (2)	1 (1)
Ofatumumab	0	1 (2)	1 (1)

Table 2. Efficacy end points in both arms within mITT population

Efficacy end point	Belumosudil, 200 mg daily (n = 66)	Belumosudil, 200 mg twice daily (n = 66)	Total (N = 132)
ORR	49 (74)	51 (77)	100 (76)
95% CI	62-84	65-87	68-83
ORR for responses occurring within 6 mo of treatment	47 (71)	48 (73)	95 (72)
95% CI	59-82	60-83	64-80
CR	2 (3)	1 (2)	3 (2)
PR	45 (68)	47 (71)	92 (70)
ORR for responses occurring within 12 mo of treatment	49 (74)	50 (76)	99 (75)
95% CI	62-84	64-86	67-82
CR	4 (6)	2 (3)	6 (5)
PR	45 (68)	48 (73)	93 (71)



blood

722.ALLOGENEIC TRANSPLANTATION: ACUTE AND CHRONIC GVHD, IMMUNE RECONSTITUTION | NOVEMBER 5, 2021

Safety, Tolerability, and Efficacy of Axatilimab, a CSF-1R Humanized Antibody, for Chronic Graft-Versus-Host Disease after 2 or More Lines of Systemic Treatment

Stephanie J. Lee, Mukta Arora, Zachariah Defilipp, Mohammad Issam Abu Zaid, Antonio Di Stasi, Vedran Radojcic, Michael L. Meyers, Hope Qam[illegible], Amandeep Salhotra,

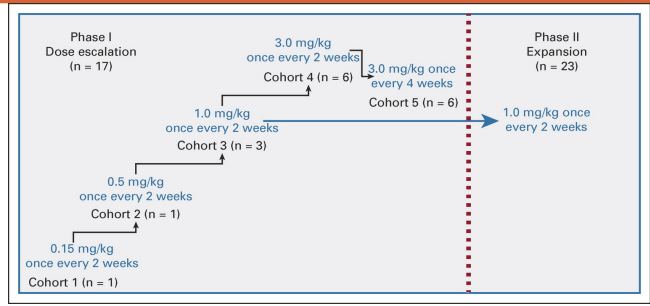
Blood (2021) 138 (Supplement 1): 263.

https://doi.org/10.1182/blood-2021-146050

Axatilimab (Axa) is a MoAb binding to CSF-R1. It blocks CSF1 and IL-34 binding and activation of CSF-R1 signaling, a key pathway involved in the expansion and infiltration of donor-derived macrophages that mediate chronic GVHD.

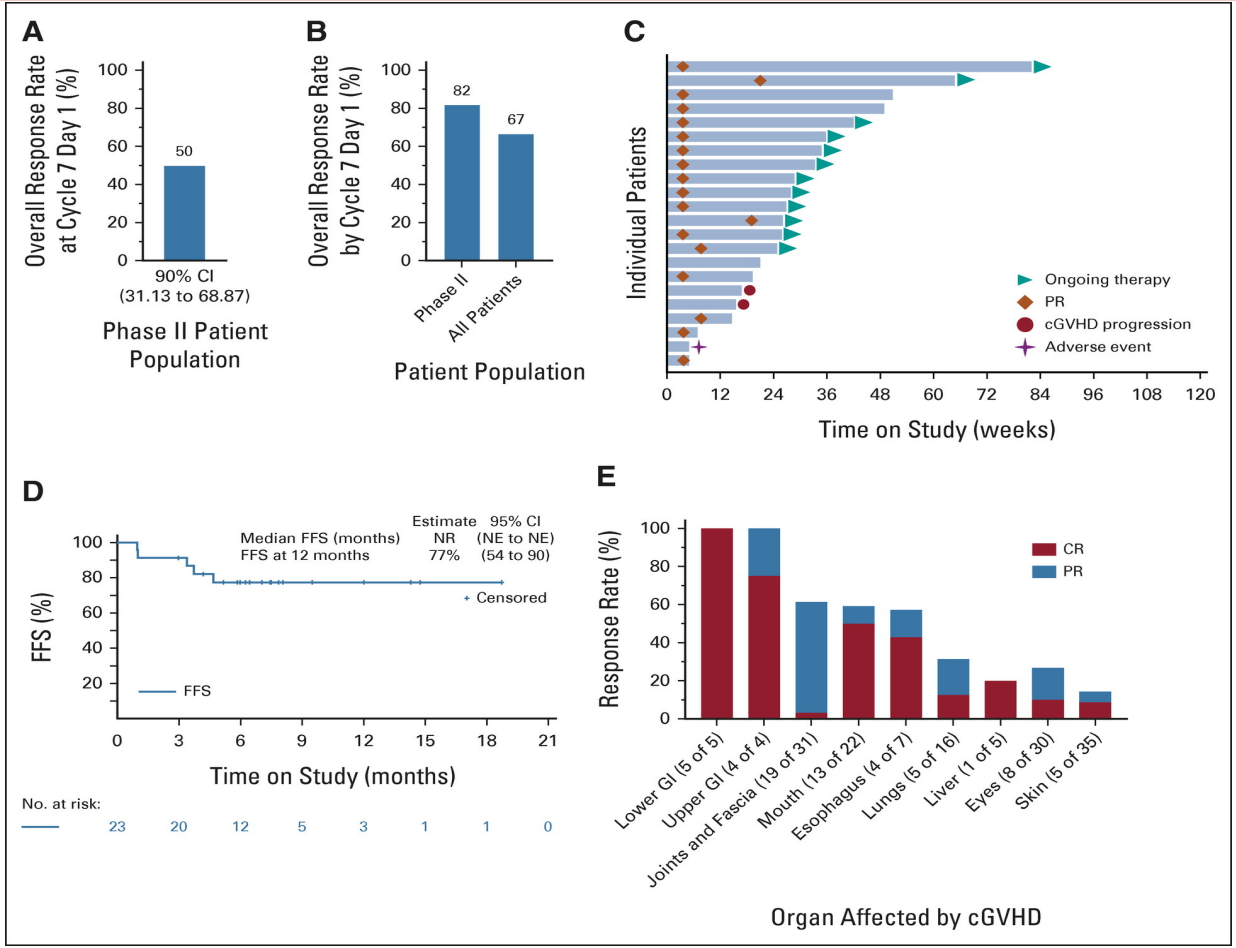
Axatilimab for Chronic Graft-Versus-Host Disease After Failure of at Least Two Prior Systemic Therapies: Results of a Phase I/II Study

Carrie L. Kitko, MD[1]; Mukta Arora, MD, MS[2]; Zachariah DeFilipp, MD[3]; Mohammad Abu Zaid, MD[4]; Antonio Di Stasi, MD[5]; Vedran Radojcic, MD[6,7]; Courtney B. Betts, PhD[8]; Lisa M. Coussens, PhD[8]; Michael L. Meyers, MD, PhD[7]; Hope Qamoos, MSN-NP[7,9]; Peter Ordentlich, PhD[7]; Vinit Kumar, PhD[7,10]; Christine Quaranto, BS[7,11]; Aaron Schmitt, BA[7]; Yu Gu, PhD[7]; Bruce R. Blazar, MD[12]; Trent P. Wang, DO[13]; Amandeep Salhotra, MD[14]; Iskra Pusic, MD[15]; Madan Jagasia, MD[16]; and Stephanie J. Lee, MD, MPH[17]



Characteristic	Phase I (n = 17)	Phase II (n = 23)	Total (N = 40)
Prior systemic therapy, No. (%)			
Corticosteroids	17 (100.0)	23 (100.0)	40 (100.0)
Ibrutinib	13 (76.5)	13 (56.5)	26 (65.0)
Ruxolitinib	10 (58.8)	11 (47.8)	21 (52.5)
Extracorporeal photopheresis	10 (58.8)	9 (39.1)	19 (47.5)
Sirolimus	6 (35.3)	11 (47.8)	17 (42.5)
Rituximab	7 (41.2)	6 (26.1)	13 (32.5)
Tacrolimus	3 (17.6)	9 (39.1)	12 (30.0)
Mycophenolate mofetil	3 (17.6)	6 (26.1)	9 (22.5)
Belumosudil	6 (35.3)	2 (8.7)	8 (20.0)
Total nodal irradiation	1 (5.9)	1 (4.3)	2 (5.0)
Methotrexate	1 (5.9)	1 (4.3)	2 (5.0)
Imatinib	1 (5.9)	1 (4.3)	2 (5.0)

Kitko CL, JCO 2023; 41:1864-1875



Kitko CL, JCO 2023; 41:1864-1875

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