Related Haploidentical BMT (Repurposing Cyclophosphamide: Back to the Future)

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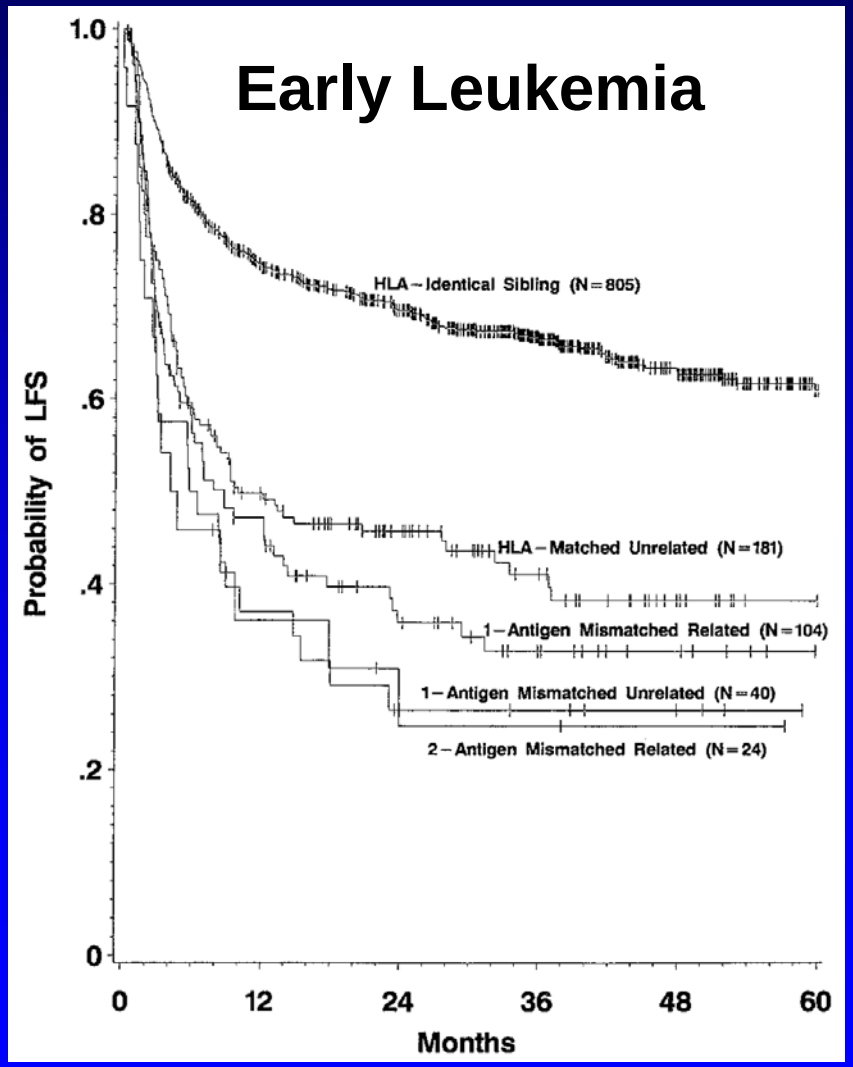
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Mismatched allogeneic BMT

Historically prohibitively toxic



Disease State/Type of Donor†	No.	TRM (%)	P*
Early			
HLA-identical sibling	805	21 ± 2	—
1-Antigen mismatched related	104	53 ± 5	< .001
2-Antigen mismatched related	24	55 ± 11	< .001
Matched unrelated	181	53 ± 4	< .001
1-Antigen mismatched unrelated	40	69 ± 8	< .001

IBMTR

Szydlo et al *JCO* 1997

Development of High-Dose Cy
Santos & Owens (1960s-70s)

- Explored alternative to TBI for BMT
  - Evaluated immunosuppressive properties of all known anti-cancer agents
  - High-dose Cy most immunosuppressive → allo-engraftment of mice
- First 36 BMTs at Hopkins (1968-75), high Cy alone
  - Still conditioning regimen for aplastic anemia
  - High relapse rate in leukemia, busulfan added

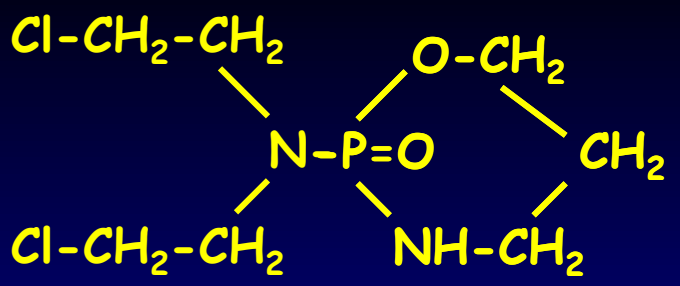
Cy for GVHD Prophylaxis

Back to the future

- Cy post alloBMT prevented GVHD in mice (Santos/Owens – 1960s)
  - Only high doses (150-300 mg/kg) effective
  - Lower doses - limited activity
- Standard Hopkins prophylaxis (1975-1984)
  - Low dose - 7.5 mg/kg/d x 4 (MTX schedule) because of hematologic toxicity fears
- Randomized trial - less effective than CsA (Santos *et al Clin Transplant* 1986)

Cyclophosphamide

History

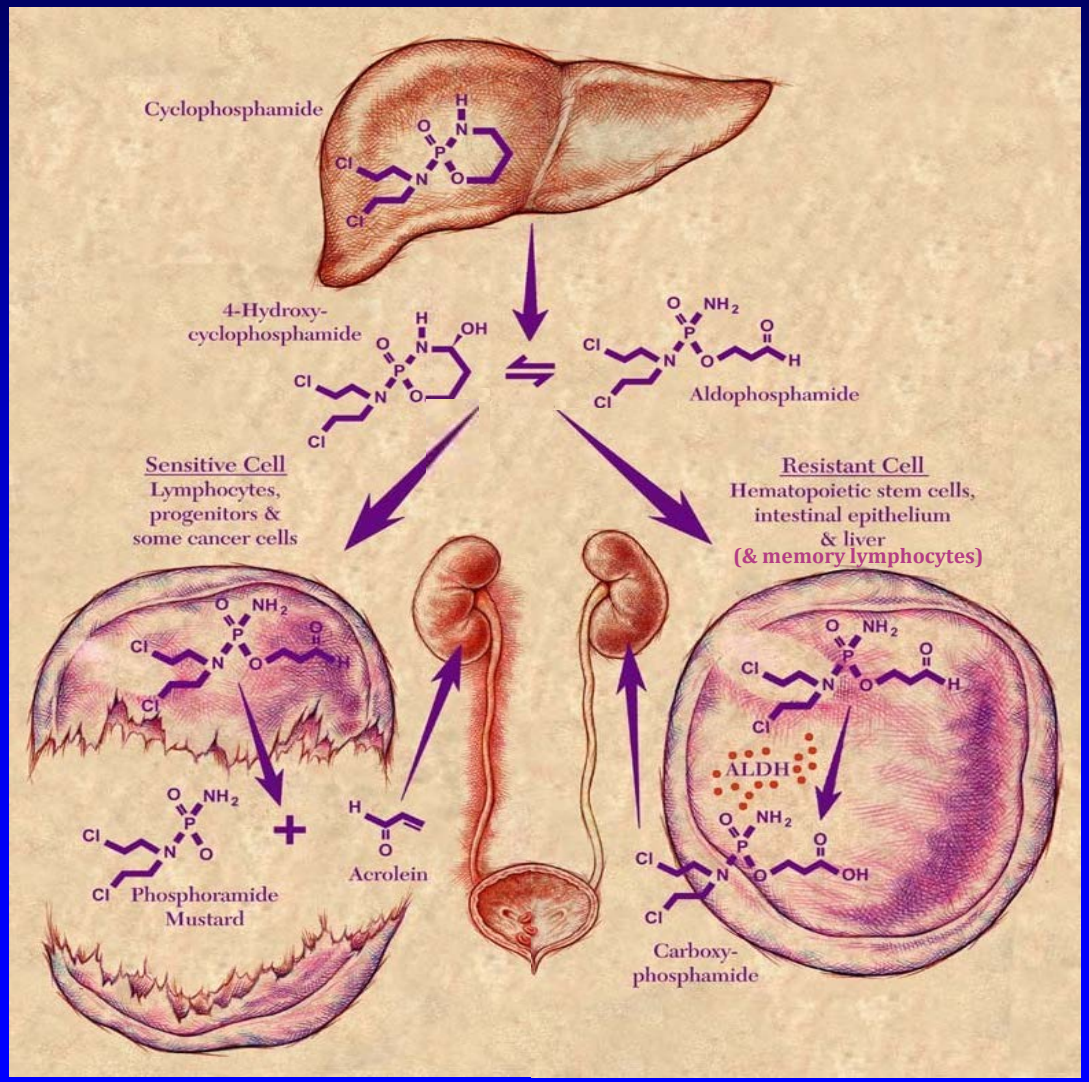


- Synthesized by Brock, Arnold, & Bourseaux – 1958
  - 8th anticancer agent FDA-approved - 1959
- Rationally designed to target cancer cells
  - Cancers over-express phosphamidase which can cleave P-N bond, releasing nitrogen mustard
  - Prodrug - but activation not via phosphamidase
  - Metabolic pathway of Cy unclear until 1984 (Hilton and Colvin)

Cyclophosphamide and cancer: golden anniversary

Nat Rev Clin Oncol 6:638-647, 2009

Ashkan Emadi, Richard J. Jones and Robert A. Brodsky

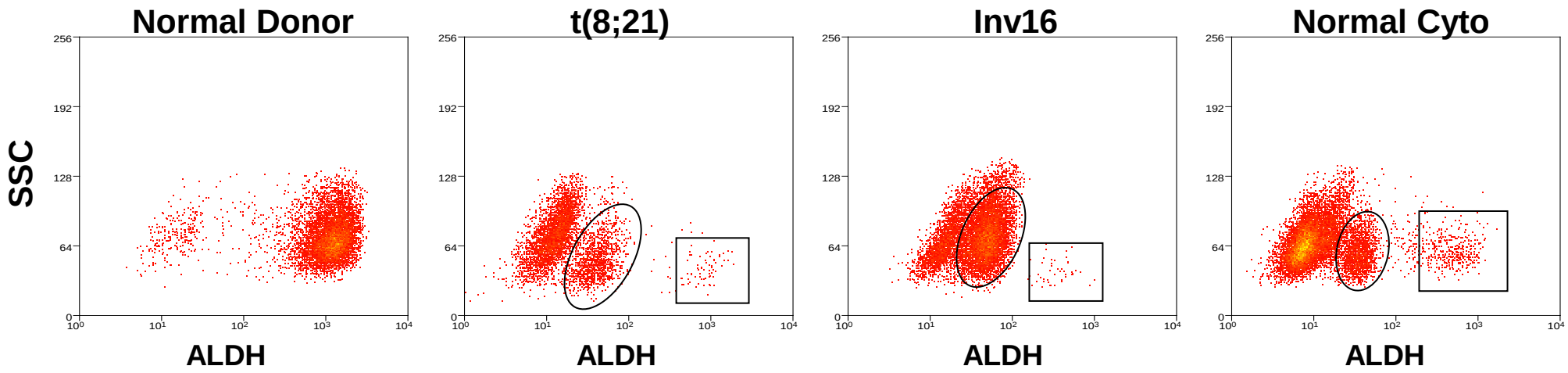


Aldehyde Dehydrogenase

Of stem cells, vitamin A, & cyclophosphamide

- Group of 18 isoenzymes
- ALDH1 family is rate limiting step in generating retinoic acid (RA) from vitamin A
  - ALDH1 also know as retinaldehyde dehydrogenase
  - HSCs and other stem cells require RA and highly express ALDH1 to generate RA
- Cells expressing high ALDH1 resistant to Cy
  - By serendipity, the Cy metabolic intermediate aldophosphamide is a substrate for ALDH1

ALDH distinguishes normal and leukemic $CD34^{+}CD38^{-}$ cells



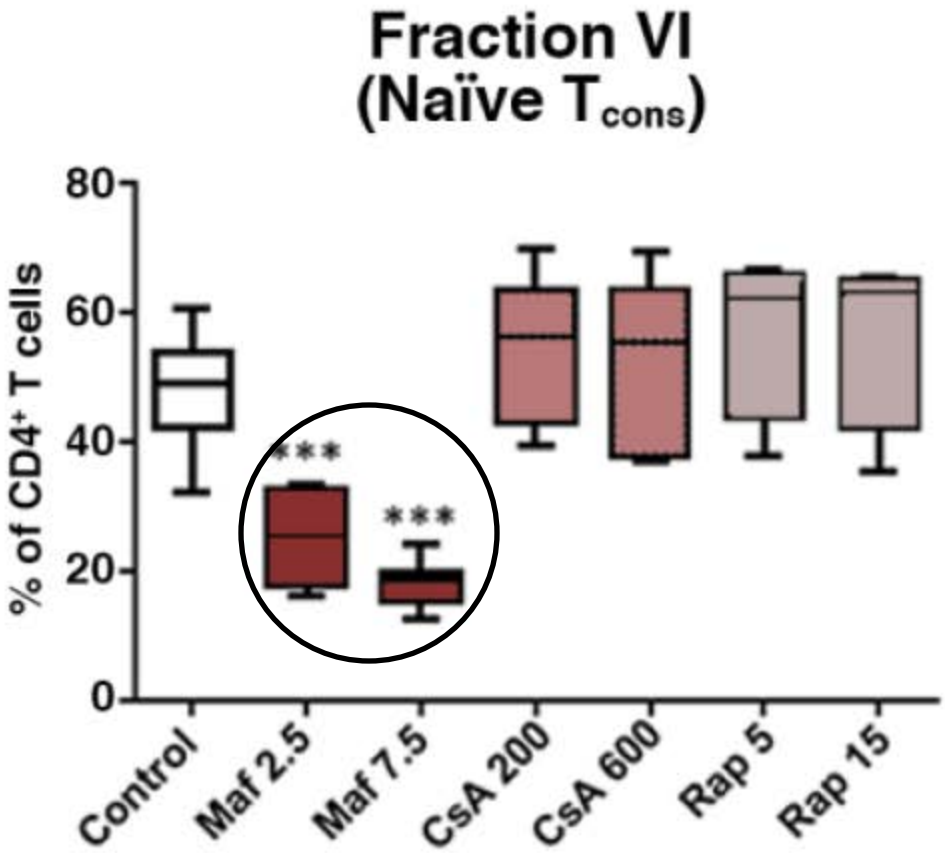
○ $CD34^{+}CD38^{-}$ $ALDH^{int}$ = 96% AML by FISH

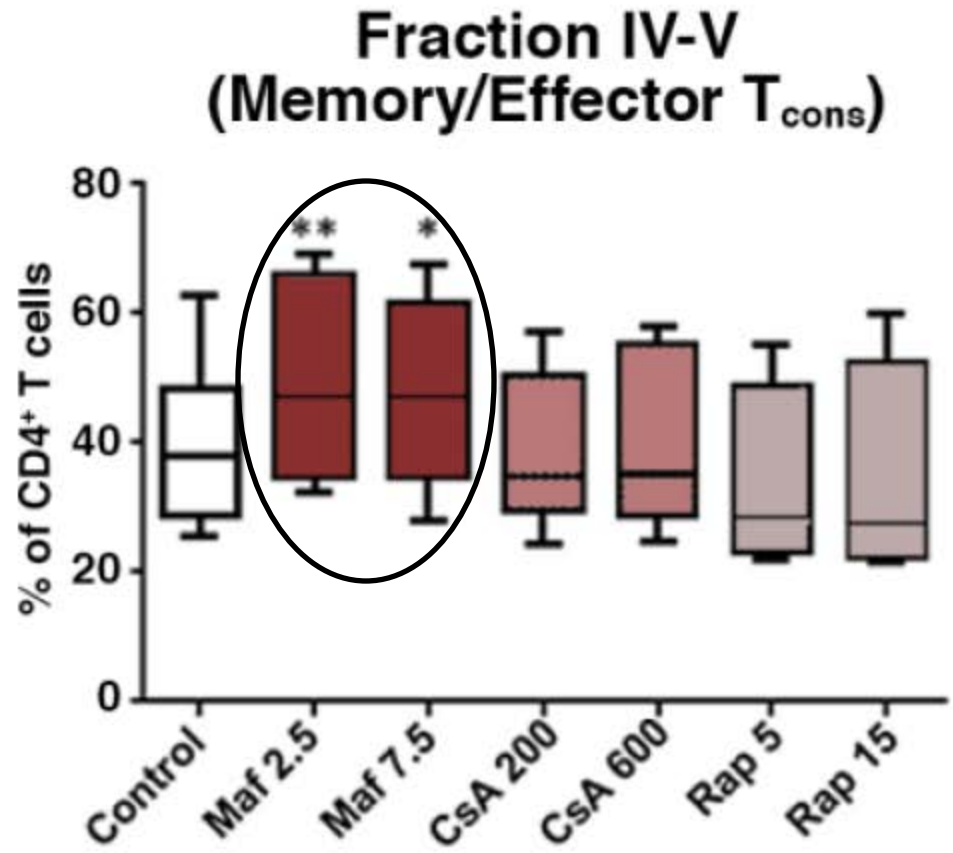
□ $CD34^{+}CD38^{-}$ $ALDH^{high}$ = 1.2% AML by FISH

Gerber *et al Blood 2012*

Cy Spares Memory T cells

Via their expression of ALDH1





Kanakry *et al Sci Transl Med* 2013

Cy for GVHD Prophylaxis
Hopkins (new millenium)

- Santos/Owens experiments from 1960s reconsidered
  - High dose Cy (200 mg/kg) prevented GVHD after haploBMT in mice (Luznik/Fuchs 2001)
  - 3 decades later, we now knew from both lab and clinical data that HSCs and memory lymphs are resistant to high-dose Cy
- Launched clinical trial that frightened George Santos

High-Dose Cyclophosphamide Without Stem Cell Rescue in 207 Patients With Aplastic Anemia and Other Autoimmune Diseases

Medicine 90:89-98, 2011

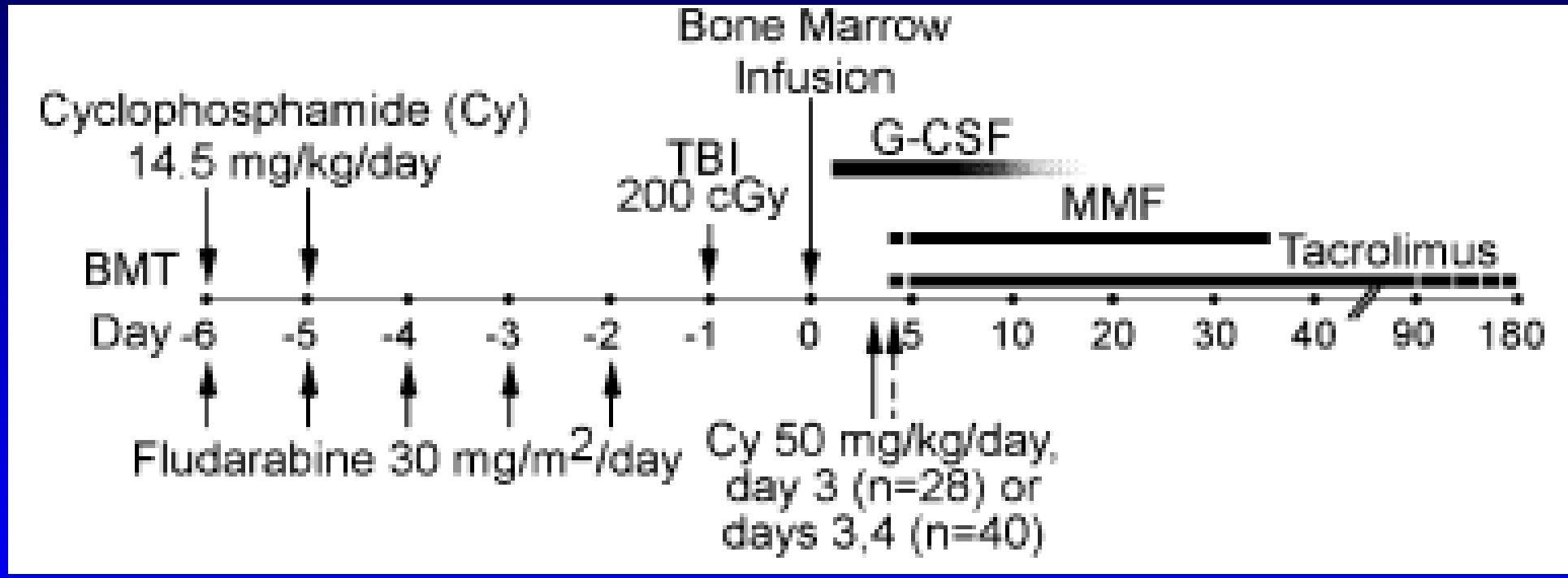
Amy E. DeZern, MD, Michelle Petri, MD, MPH, Daniel B. Drachman, MD, Doug Kerr, MD, PhD, Edward R. Hammond, MD, MPH, Jeanne Kowalski, PhD, Hua-Ling Tsai, ScM, David M. Loeb, MD, PhD, Grant Anhalt, MD, Fredrick Wigley, MD, Richard J. Jones, MD, and Robert A. Brodsky, MD

- High-dose Cy is immunoablative but allows rapid hematopoietic and immunologic recovery in autoimmunity
  - ANC >500 – median 13 (8-22) days
  - Last platelet transfusion – 12 (0-24) days
  - No opportunistic infections
- 5 year actuarial survival 91% and EFS 21% in 140 pts with refractory autoimmunity

HLA-Haploidentical Bone Marrow Transplantation for Hematologic Malignancies Using Nonmyeloablative Conditioning and High-Dose, Posttransplantation Cyclophosphamide

Biol Blood Marrow Transplant 14:641-650, 2008)

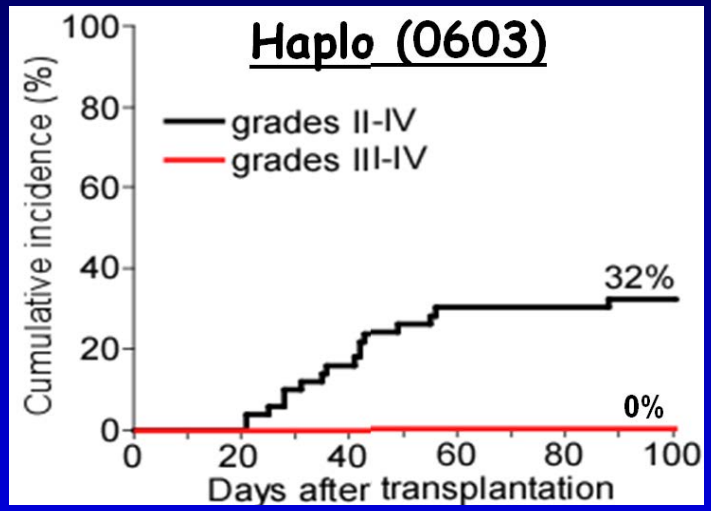
Leo Luznik,[1] Paul V. O'Donnell,[2,3]* Heather J. Symons,[1] Allen R. Chen,[1] M. Susan Leffell,[1] Marianna Zahurak,[1] Ted A. Gooley,[2,3] Steve Piantadosi,[1] Michele Kaup,[1] Richard F. Ambinder,[1] Carol Ann Huff,[1] William Matsui,[1] Javier Bolaños-Meade,[1] Ivan Borrello,[1] Jonathan D. Powell,[1] Elizabeth Harrington,[2] Sandy Warnock,[2] Mary Flowers,[2,3] Robert A. Brodsky,[1] Brenda M. Sandmaier,[2,3] Rainer F. Storb,[2,3] Richard J. Jones,[1] Ephraim J. Fuchs[1]*

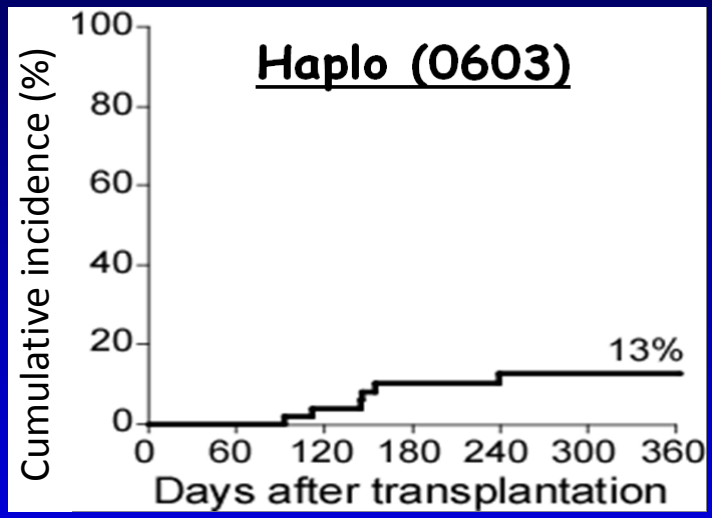


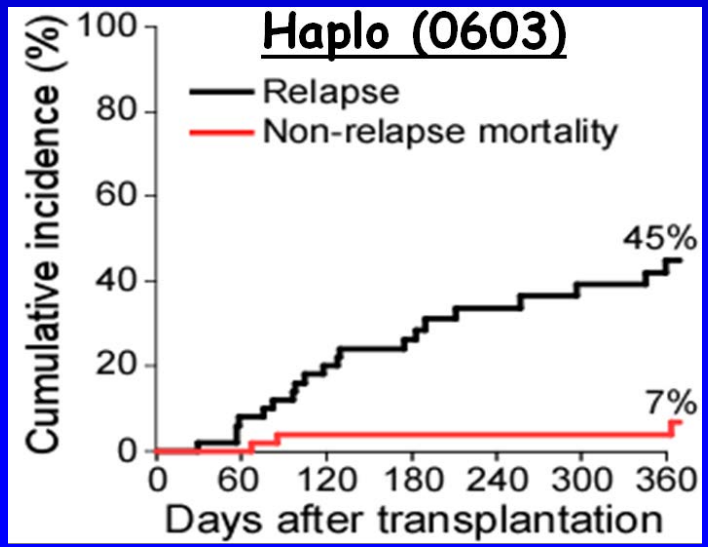
- Most lymphocytes express low levels of ALDH 1 and are sensitive to Cy
  - Memory lymphs and HSCs express high levels and are resistant to high dose Cy

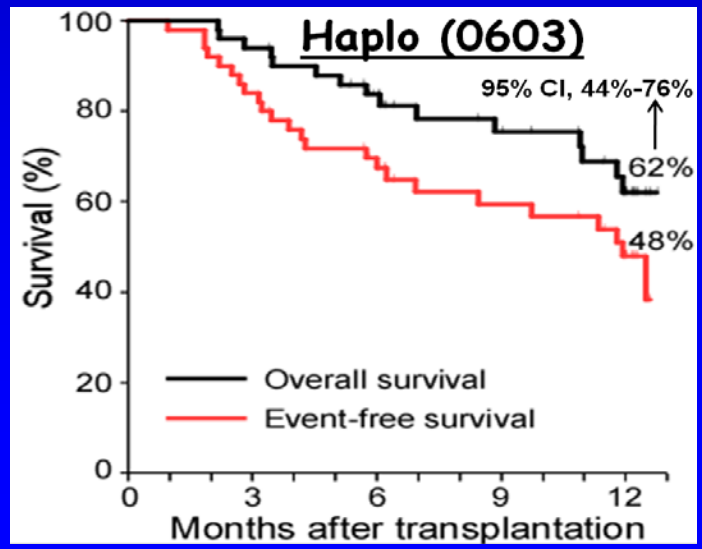
Alternative donor transplantation after reduced intensity conditioning: results of parallel phase 2 trials using partially HLA-mismatched related bone marrow or unrelated double umbilical cord blood grafts *Blood* 118(2):282-288, 2011

*Claudio G. Brunstein,[1] *Ephraim J. Fuchs,[2] Shelly L. Carter,[3] Chatchada Karanes,[4] Luciano J. Costa,[5] Juan Wu,[3] Steven M. Devine,[6] John R. Wingard,[7] Omar S. Aljitawi,[8] Corey S. Cutler,[9] Madan H. Jagasia,[10] Karen K. Ballen,[11] †Mary Eapen,[12] and †Paul V. O'Donnell,[13] on behalf of the Blood and Marrow Transplant Clinical Trials Network



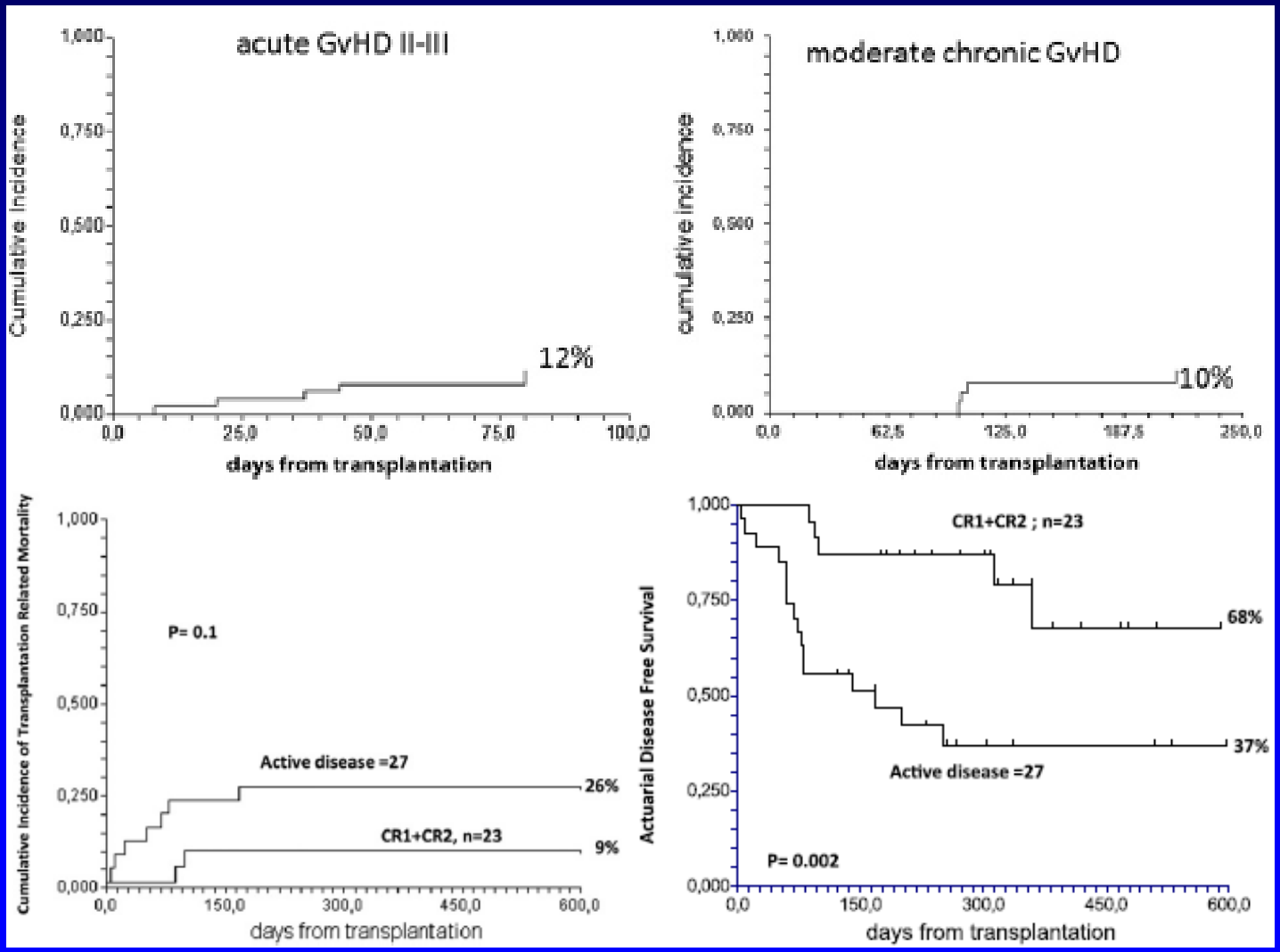






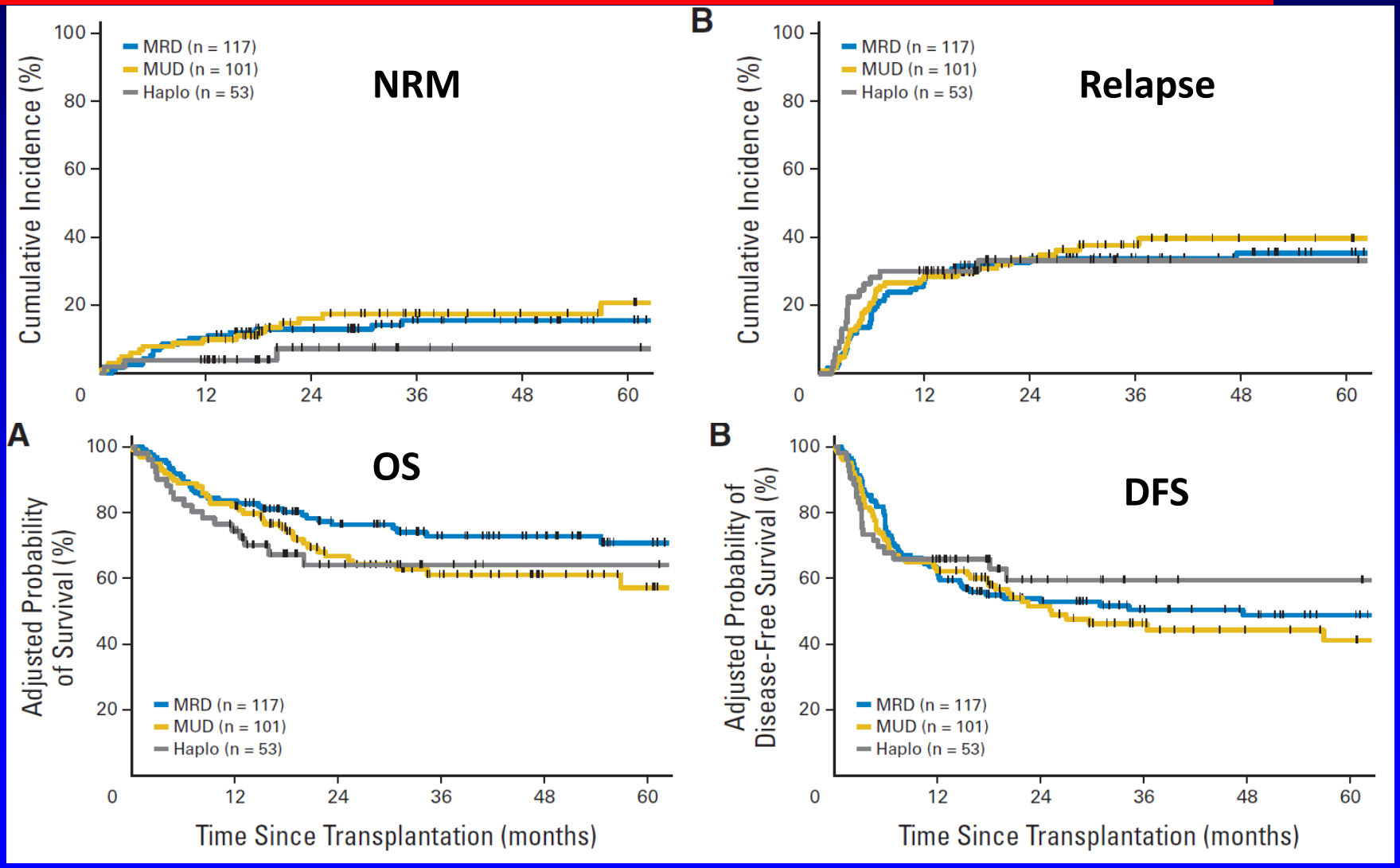
Unmanipulated Haploidentical Bone Marrow Transplantation and Posttransplantation Cyclophosphamide for Hematologic Malignancies after Myeloablative Conditioning *BBMT* 19: 117-22, 2013

Anna Maria Raiola, Alida Dominietto, Anna Ghiso, Carmen Di Grazia, Teresa Lamparelli, Francesca Gualandi, Stefania Bregante, Maria Teresa Van Lint, Simona Geroldi, Silvia Luchetti, Filippo Ballerini, Maurizio Miglino, Riccardo Varaldo, Andrea Bacigalupo*



T-Cell–Replete HLA-Haploidentical Hematopoietic Transplantation for Hematologic Malignancies Using Post-Transplantation Cyclophosphamide Results in Outcomes Equivalent to Those of Contemporaneous HLA-Matched Related and Unrelated Donor Transplantation

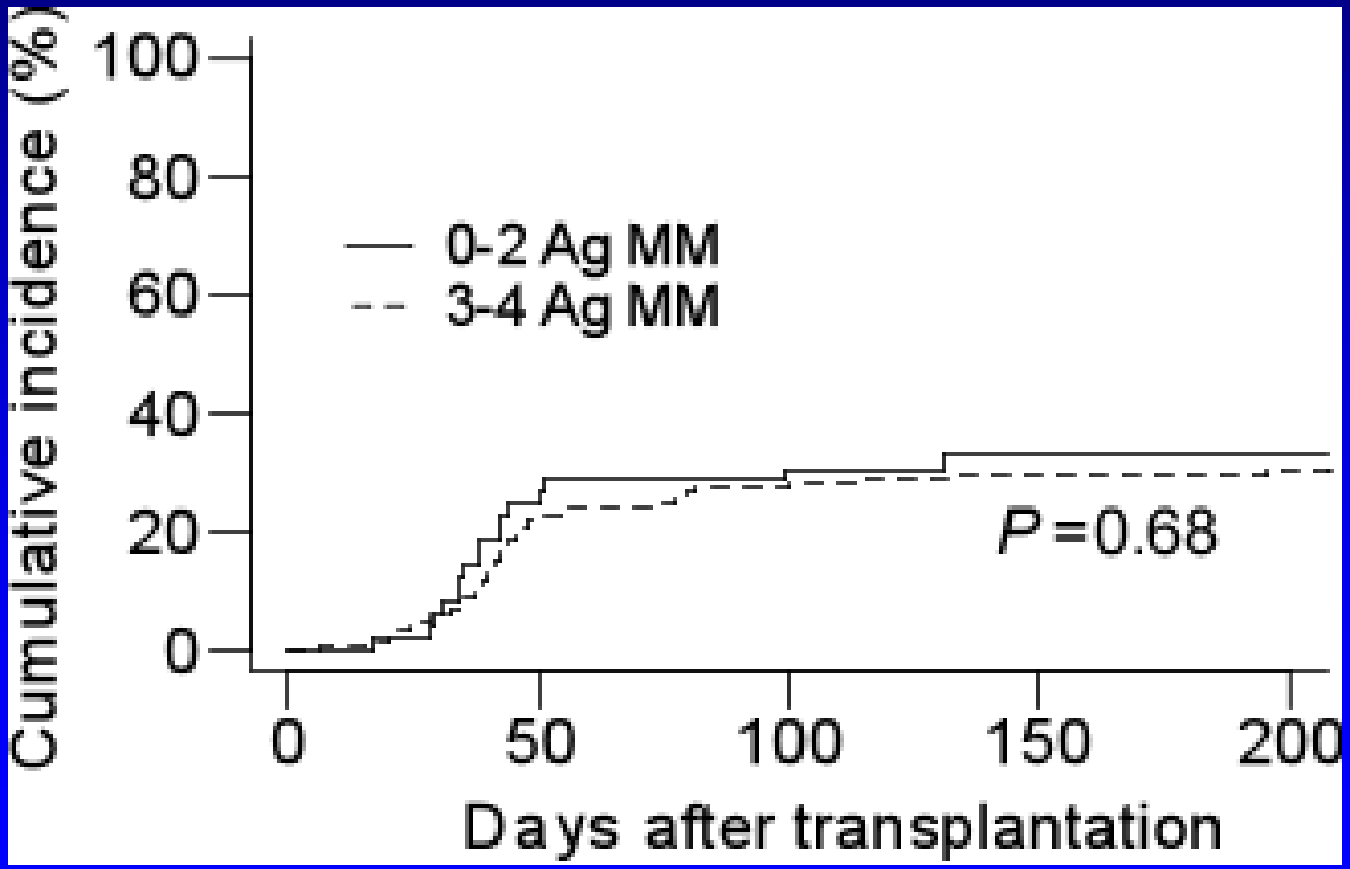
Asad Bashey, Xu Zhang, Connie A. Sizemore, Karen Manion, Stacey Brown, H. Kent Holland, Lawrence E. Morris, and Scott R. Solomon *J Clin Oncol* 31:1310-1316



HaploBMT with PTCy

↑'ing mismatch does not worsen outcome

Grade II-IV acute GVHD



Kasamon *et al BBMT* 2010

Post-transplant Cy (PTCy)

Immune recovery is excellent

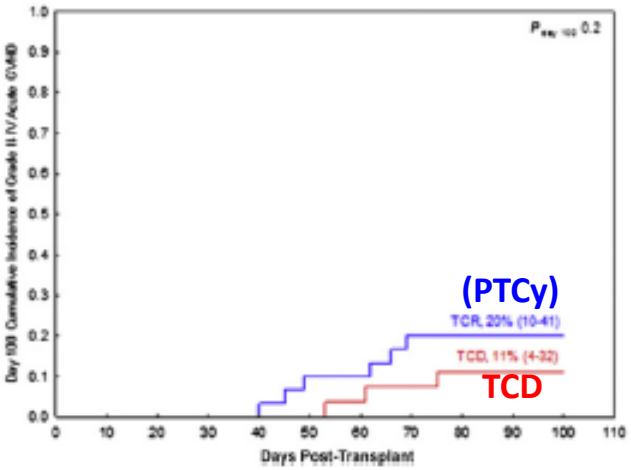
- PTCy selectively targets alloreactive T cells, which are maximally proliferative early after BMT
  - T cells specific for infectious agents are quiescent and thus less sensitive to Cy
  - Memory T cells, like other stem-like cells, highly express ALDH1 and are thus resistant to Cy
- All haplotransplants are not created equal

Improved Early Outcomes Using a T Cell Replete Graft Compared with T Cell Depleted Haploidentical Hematopoietic Stem Cell Transplantation

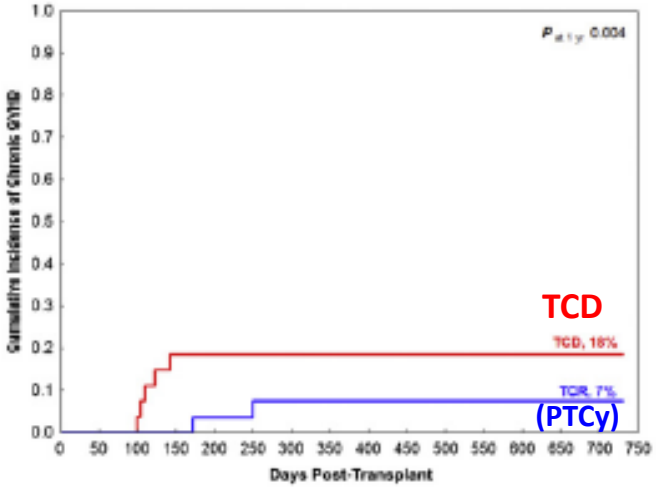
BBMT 18: 1835-1844, 2012

Stefan O. Ciurea,[1] Victor Mulanovich,[2] Rima M. Saliba,[1] Ulas D. Bayraktar,[1] Ying Jiang,[2] Roland Bassett,[3] Sa A. Wang,[4] Marina Konopleva,[5] Marcelo Fernandez-Vina,[6] Nivia Montes,[1] Doyle Bosque,[1] Julianne Chen,[1] Gabriela Rondon,[1] Gheath Alatrash,[1] Amin Alousi,[1] Qaiser Bashir,[1] Martin Korbling,[1] Muzaffar Qazilbash,[1] Simrit Parmar,[1] Elizabeth Shpall,[1] Yago Nieto,[1] Chitra Hosing,[1] Partow Kebriaei,[1] Issa Khouri,[1] Uday Popat,[1] Marcos de Lima,[1] Richard E. Champlin[1]

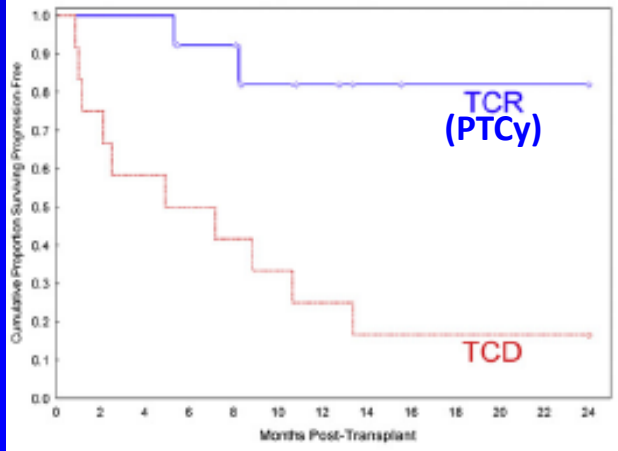
Cumulative incidence of gr II-IV aGVHD.



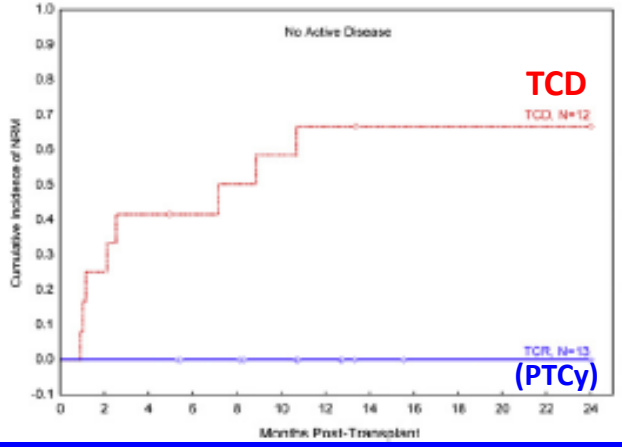
Cumulative incidence of cGVHD.



Progression-free survival for patients in remission at transplant.



Non-relapse mortality for patients in remission at transplant.



Thymic T-cell development in allogeneic stem cell transplantation

Werner Krenger,[1] *Bruce R. Blazar,[2] and *Georg A. Holländer[1,3] ***Blood*** **117(25):6768-6776, 2011**

T cell regeneration after allogeneic BMT:

- Thymic-dependent
  - Impaired by thymic damage from conditioning
  - Impaired by GVHD
  - Impaired by age-related involution
- Thymic-independent expansion of peripheral memory T cells
  - Major mechanism in older adults with thymic involution

TCD Haplos and Cord Blood
Immune recovery is impaired

- TCD shows no selectivity toward alloreactive T cells
  - Also eliminates T cells reactive against infectious agents and memory T cells
  - Older adults (with thymic involution) rely on the peripheral expansion of memory T cells
- Immune reconstitution and infections have also been concerns in older adults transplanted with umbilical cord blood
  - Cord blood also deficient in memory T cells

Excellent Immune Recovery with PTCy

Few opportunistic infections are seen

Table 3. *CMV Reactivation and Invasive Mold Infection*
(First 68 related haploidentical transplants)

No. of patients at high-risk for CMV reactivation	45
No. of high-risk patients with CMV reactivation (%)	17 (38%)
No. of high-risk patients with CMV disease	0
Median days to onset (range)	34 (17-80)
No. of patients with invasive mold infection (%)	5 (7%)

Luznik *et al Biol Blood Marrow Transplant* 14:641-650, 2008

Absence of Post-Transplantation Lymphoproliferative Disorder after Allogeneic Blood or Marrow Transplantation Using Post-Transplantation Cyclophosphamide as Graft-versus-Host Disease Prophylaxis

Biol Blood Marrow Transplant 19(10):1514-7, 2013

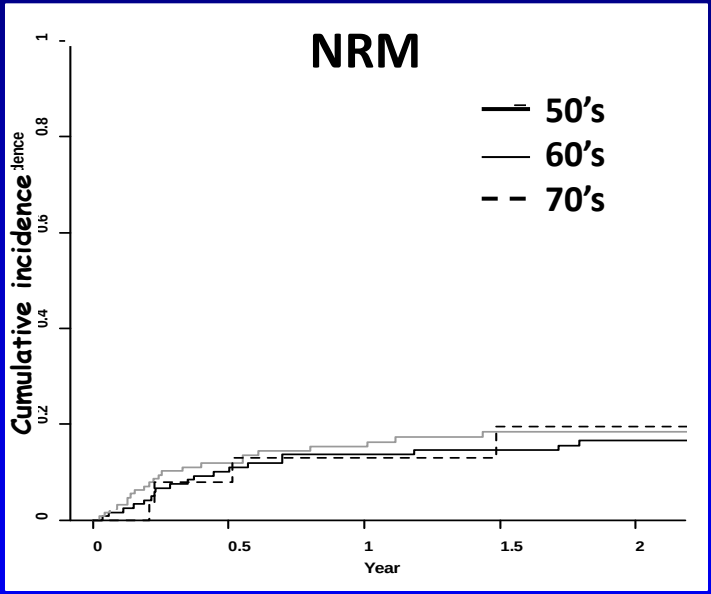
Jennifer A. Kanakry[1], Yvette L. Kasamon[2], Javier Bolaños-Meade[2], Ivan M. Borrello[2], Robert A. Brodsky[1], Ephraim J. Fuchs[2], Nilanjan Ghosh[2], Douglas E. Gladstone[2], Christopher D. Gocke[3], Carol Ann Huff[2], Christopher G. Kanakry[2], Leo Luznik[2], William Matsui[2], Huzefa J. Mogri[4], Lode J. Swinnen[2], Heather J. Symons[5], Richard J. Jones[2], Richard F. Ambinder[2,*]

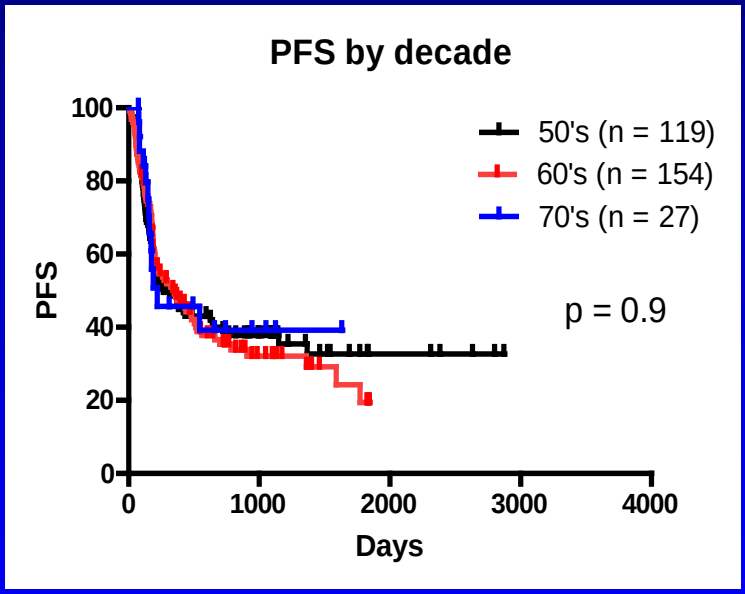
Outcomes of Nonmyeloablative HLA-Haploidentical Blood or Marrow Transplantation With High-Dose Post-Transplantation Cyclophosphamide in Older Adults

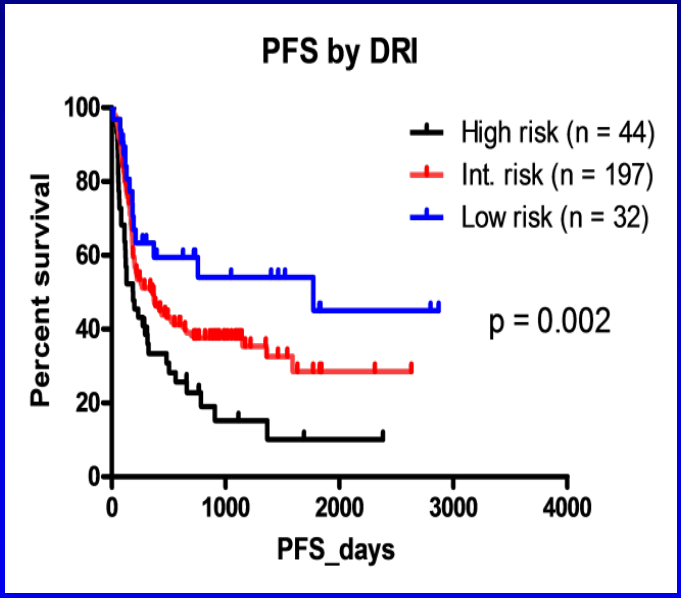
Yvette L. Kasamon, Javier Bolaños-Meade, Gabrielle T. Prince, Hua-Ling Tsai, Shannon R. McCurdy, Jennifer A. Kanakry, Gary L. Rosner, Robert A. Brodsky, Karlo Perica, B. Douglas Smith, Douglas E. Gladstone, Lode J. Swinnen, Margaret M. Showel, William H. Matsui, Carol Ann Huff, Ivan Borrello, Keith W. Pratz, Michael A. McDevitt, Ivana Gojo, Amy E. Dezern, Satish Shanbhag, Mark J. Levis, Leo Luznik, Richard F. Ambinder, Ephraim J. Fuchs, and Richard J. Jones

JCO in press, 2015

273 consecutive patients aged 50-75







50's - 119 patients
60's - 127 patients
70's - 27 patients

Risk-stratified outcomes of nonmyeloablative, HLA-haploidentical BMT with high-dose posttransplantation cyclophosphamide

Shannon R. McCurdy, Jennifer A. Kanakry, Margaret M. Showel, Hua-Ling Tsai, Javier Bolaños-Meade, Gary L. Rosner, Christopher G. Kanakry, Karlo Perica, Heather J. Symons, Robert A. Brodsky, Douglas E. Gladstone, Carol Ann Huff, Keith W. Pratz, Gabrielle T. Prince, Amy E. Dezern, Ivana Gojo, William H. Matsui, Ivan Borrello, Michael A. McDevitt, Lode J. Swinnen, B. Douglas Smith, Mark J. Levis, Richard F. Ambinder, Leo Luznik, Richard J. Jones, Ephraim J. Fuchs, and Yvette L. Kasamon

Blood 125(19):3024-31, 2015

Survival Estimates by DRI

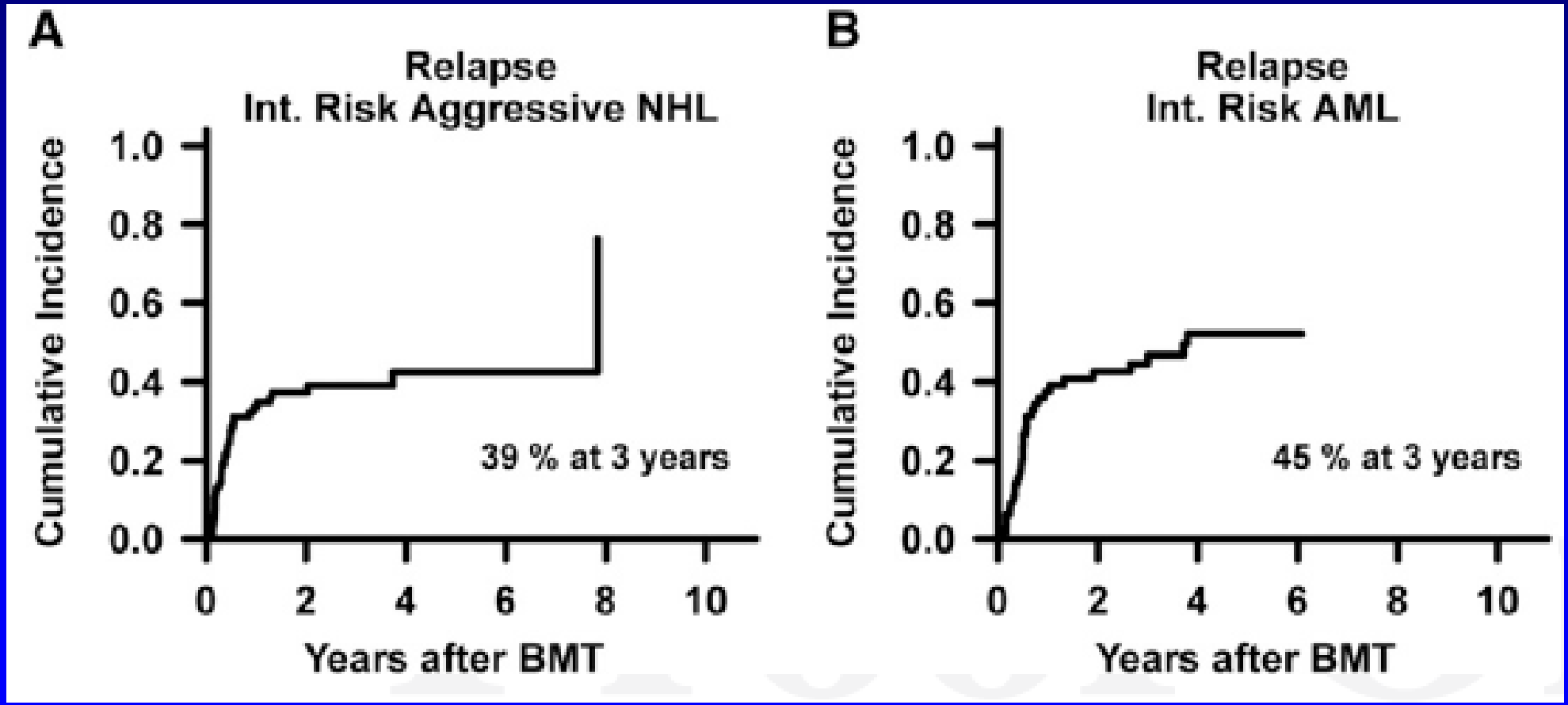
	3-year PFS (%)		3-year OS (%)	
DRI	Matched	Haplo	Matched	Haplo
Low	66	62	70	72
Intermediate	31	39	47	49
High / v high	15	25	25	37

DRI – disease-risk index (Armand et al Blood 120: 905-913)

Risk-stratified outcomes of nonmyeloablative, HLA-haploidentical BMT with high-dose posttransplantation cyclophosphamide

Shannon R. McCurdy, Jennifer A. Kanakry, Margaret M. Showel, Hua-Ling Tsai, Javier Bolaños-Meade, Gary L. Rosner, Christopher G. Kanakry, Karlo Perica, Heather J. Symons, Robert A. Brodsky, Douglas E. Gladstone, Carol Ann Huff, Keith W. Pratz, Gabrielle T. Prince, Amy E. Dezern, Ivana Gojo, William H. Matsui, Ivan Borrello, Michael A. McDevitt, Lode J. Swinnen, B. Douglas Smith, Mark J. Levis, Richard F. Ambinder, Leo Luznik, Richard J. Jones, Ephraim J. Fuchs, and Yvette L. Kasamon

Blood 125(19):3024-31, 2015



Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia

Stefan O. Ciurea,[1] Mei-Jie Zhang,[2,3] Andrea A. Bacigalupo,[4] Asad Bashey,[5] Frederick R. Appelbaum,[6] Omar S. Aljitawi,[7] Philippe Armand,[8] Joseph H. Antin,[8] Junfang Chen,[2] Steven M. Devine,[9] Daniel H. Fowler,[10] Leo Luznik,[11] Ryotaro Nakamura,[12] Paul V. O'Donnell,[6] Miguel-Angel Perales,[13] Sai Ravi Pingali,[1] David L. Porter,[14] Marcie R. Riches,[15] Olle T. H. Ringdén,[16] Vanderson Rocha,[17] Ravi Vij,[18] Daniel J. Weisdorf,[19] Richard E. Champlin,[1] Mary M. Horowitz,[2] Ephraim J. Fuchs,[11] and Mary Eapen[2] *Blood*. 2015;126(8):1033-1040

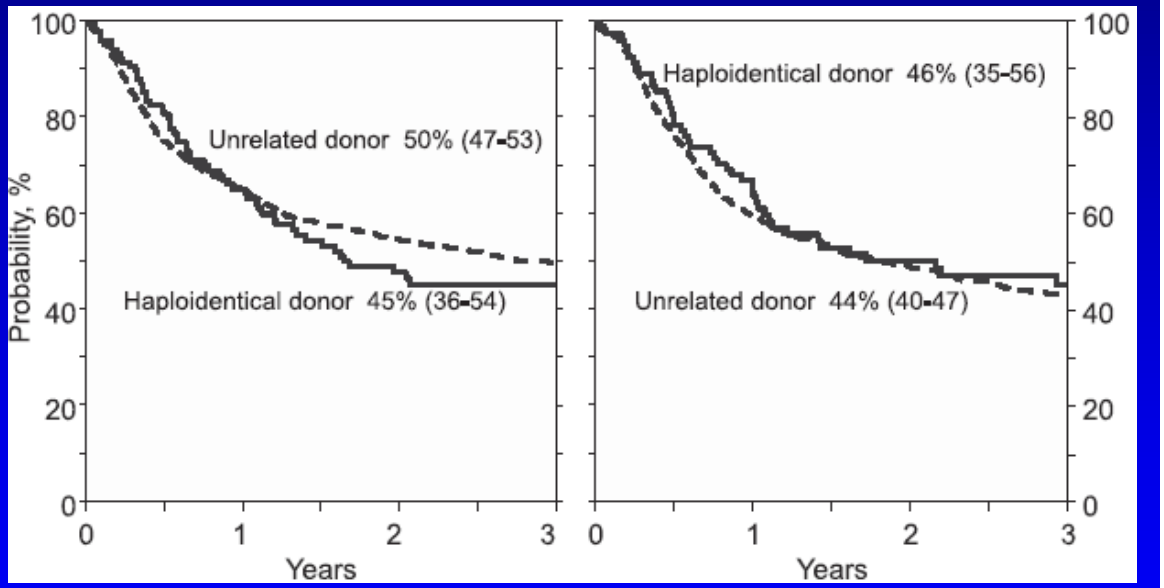


Table 5. Multivariate analysis (subset): risks of acute and chronic GVHD, nonrelapse mortality, relapse, and OS by donor type

Outcome	Transplant conditioning regimen intensity	
	Myeloablative* Hazard ratio (95% CI)	Reduced intensity† Hazard ratio (95% CI)
Grade 2-4 acute GVHD		
Matched unrelated donor	1.00	1.00
Haploidentical donor	0.37 (0.23-0.61) $P = .0001$	0.71 (0.44-1.15) $P = .16$
Grade 3-4 acute GVHD		
Matched unrelated donor	1.00	1.00
Haploidentical donor	0.33 (0.14-0.81) $P = .02$	0.21 (0.05-0.86) $P = .03$
Chronic GVHD		
Matched unrelated donor	1.00	1.00
Haploidentical donor	0.44 (0.29-0.66) $P = .0001$	0.45 (0.28-0.71) $P = .0006$

Allogeneic BMT 2015

Should an 8/8 match still be the gold standard?

- No patient in need should be denied BMT
  - Alternative donor results similar to matched, and may even be preferable (probably don't want sib donor over age 55 – 60)
  - Alternative donors allow minorities equal access - haplo vs cord (CTN 1101) has 30% minority accrual (16% AA, 14% Hispanic)
- Unnecessary delays should not occur - many pts can't wait 3-4 months for MUD

Allogeneic BMT 2015

It's time to get off the GVH/GVT vicious cycle

- There is no rheostat for GVHD/GVT – pick your poison
  - ↑GVHD – less relapses/higher TRM
  - ↓GVHD – lower TRM/more relapses
- Combining non-tolerant allo immune system with novel anticancer agents may provide GVT w/o toxicity of GVHD
  - AlloBMT followed by FLT3 TKIs for FLT3 AML
  - Should everyone get some form of postBMT maintenance?

Alternative Donor Transplantation

Pros and cons

	Availability to patient	Timing	Acquisition cost	Concerns	Potential Advantages
MUD	60%	3-4 mos	$35K	1. Relapse during search 2. Availability to all ethnic groups …s)	Long track record
Cord	>90%			…l cell #s …ory T …producing …immune …ution	1. No donor concerns 2. Young HSCs
Haplo (PTCy)	>95%	<4 wks	$10K (Total cost=$170K)	1. Historical GVHD/mortality rates 2. Relapse – low GVHD rates	1. Excellent immune reconstitution 2. Low TRM: allows post-BMT anti-cancer strategies

Haplo with PTCy is really easy for both patients and medical staff

Acknowledgments