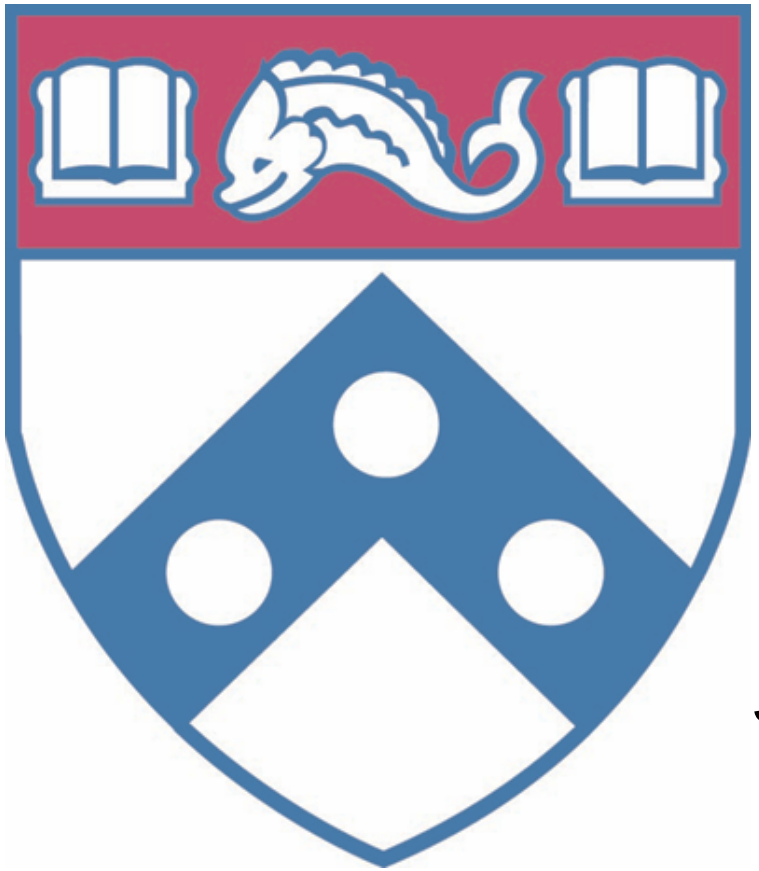
What's new in Blood and Marrow Transplant?



Saar Gill, MD PhD

Division of Hematology-Oncology

University of Pennsylvania Perelman School of Medicine

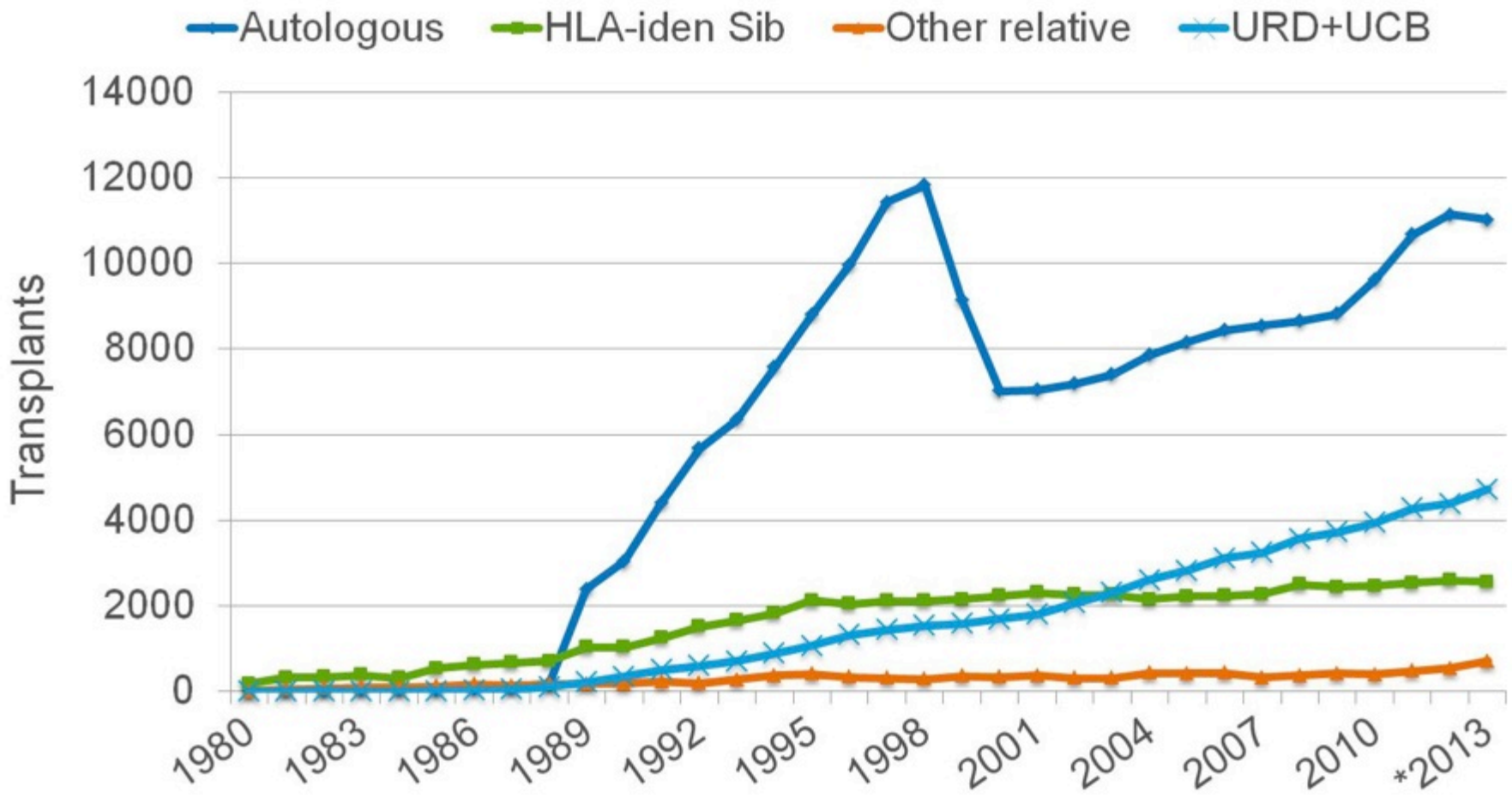
Jan 22, 2016

Who should be transplanted and how?

Updates on:

- **Donor selection**
- **Type of conditioning**
- **Source of graft**
- **GVHD prophylaxis**

Transplant Recipients in the US, by Transplant and Donor Type



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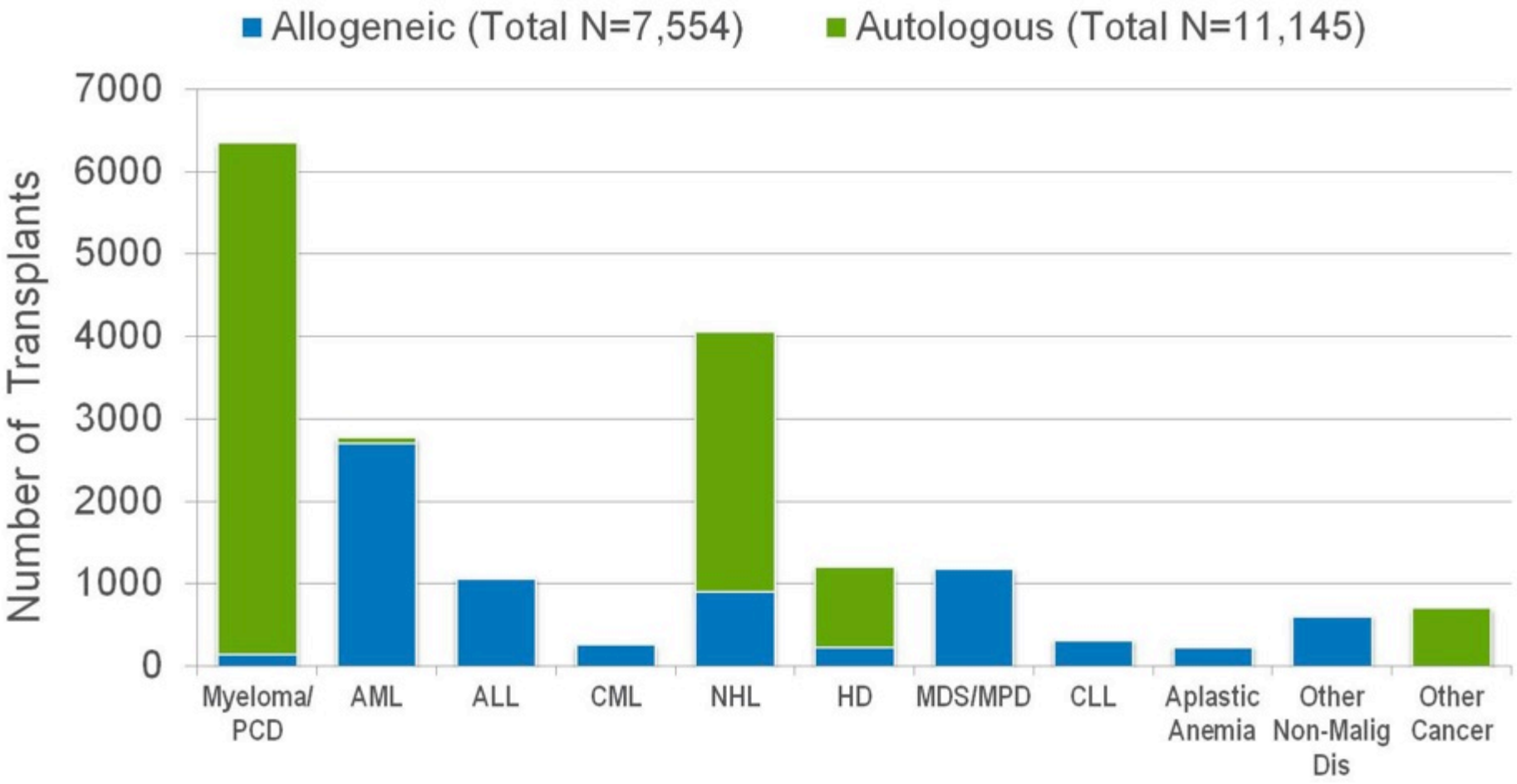
* 2013 Data incomplete

Indications for Hematopoietic Stem Cell Transplants in the US, 2012



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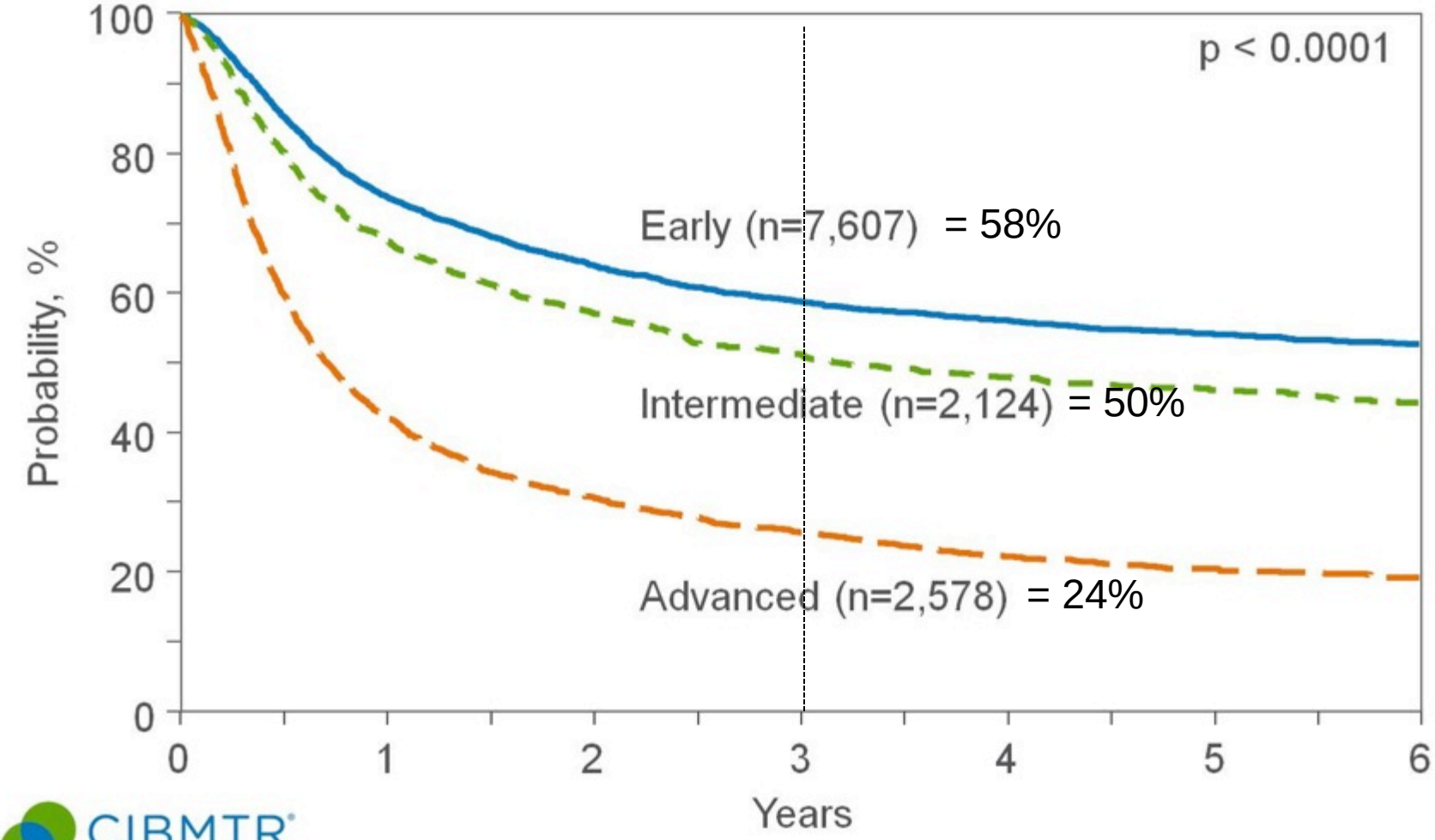
Survival after HLA Match Sibling Donor Transplants for AML, 2002-2012



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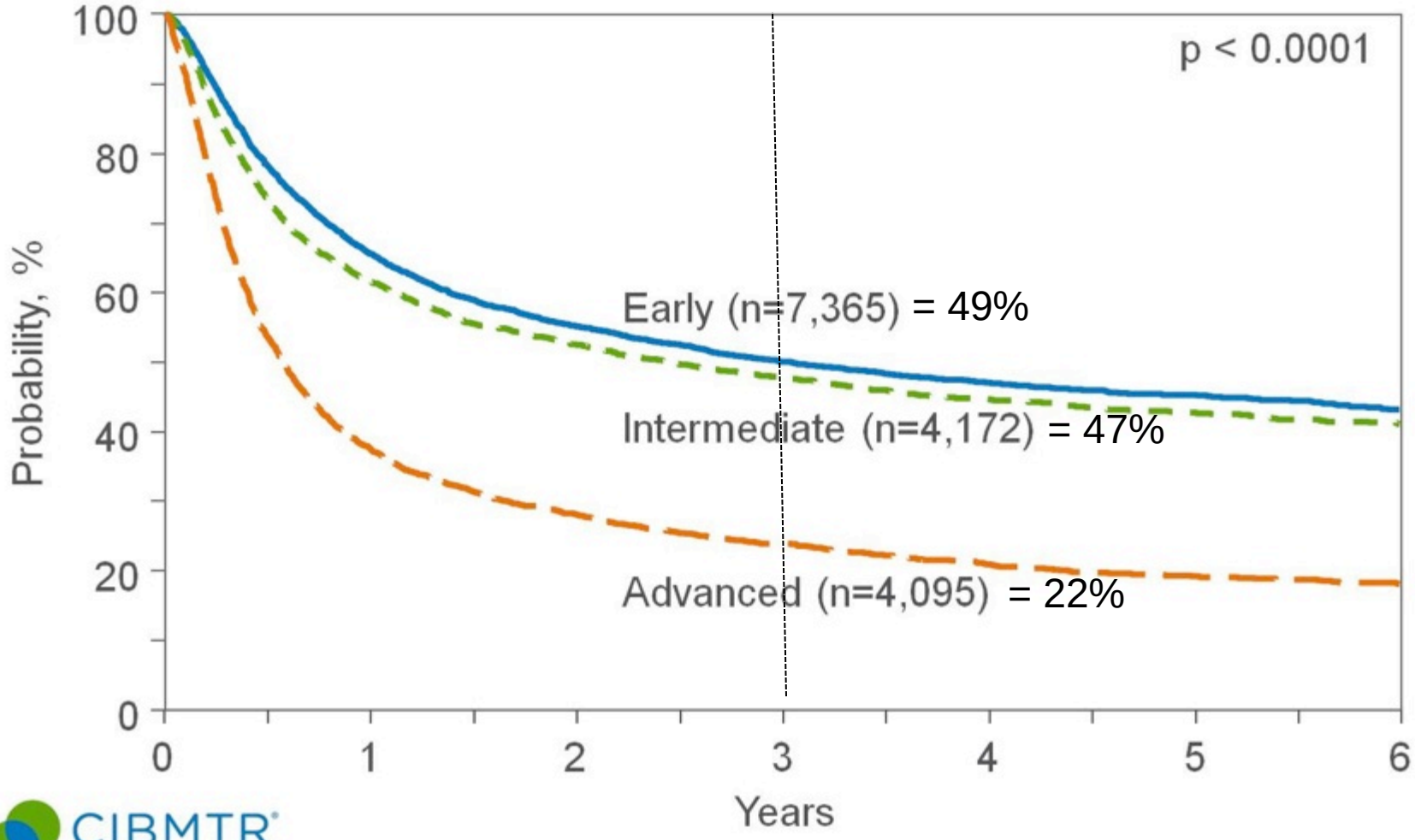
By Disease Status

Survival after Unrelated Donor Transplants for AML, 2002-2012



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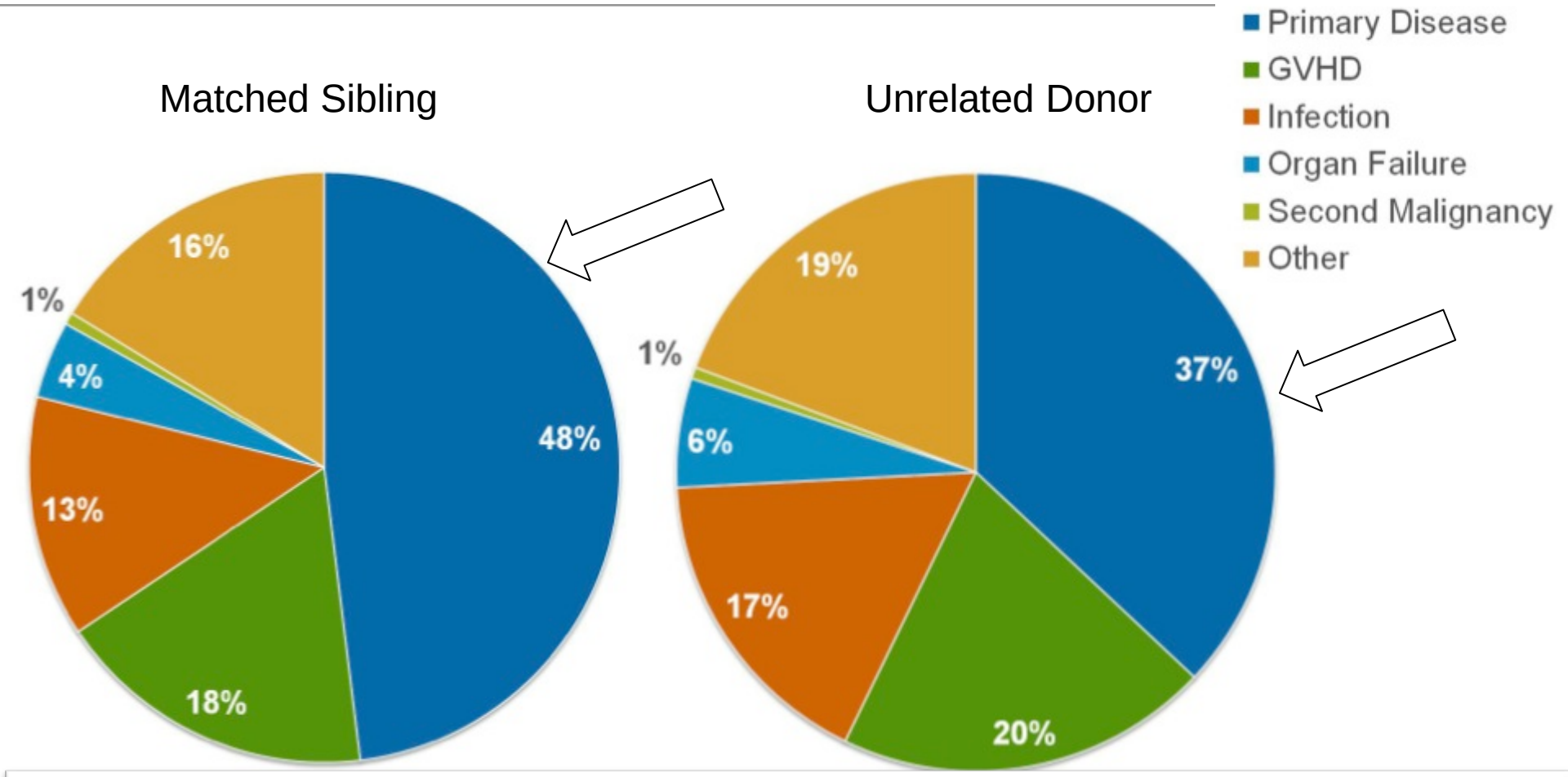
By Disease Status

Causes of death after alloHCT in 2011-2012 (CIBMTR data)

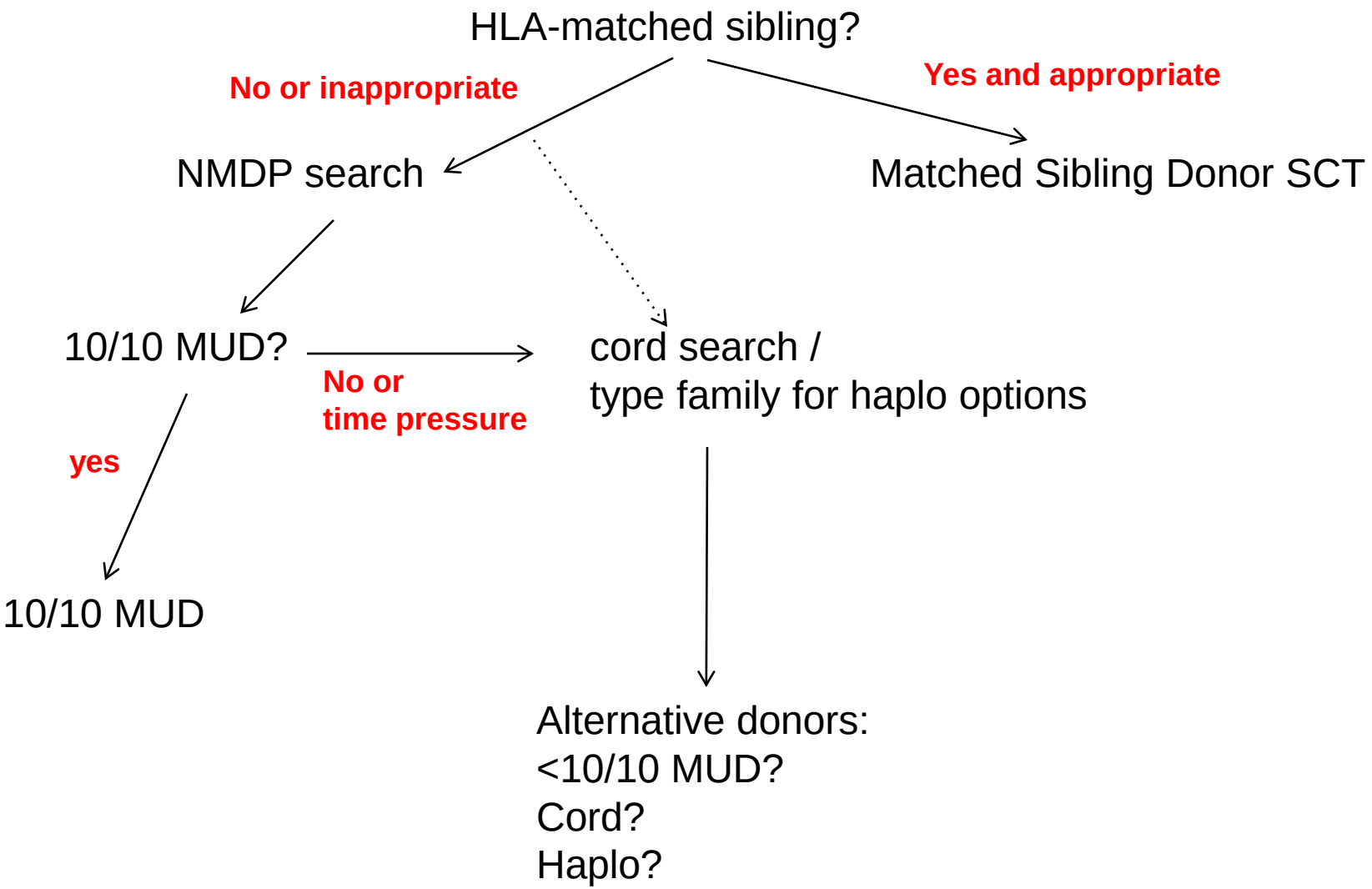


Who should be transplanted and how?

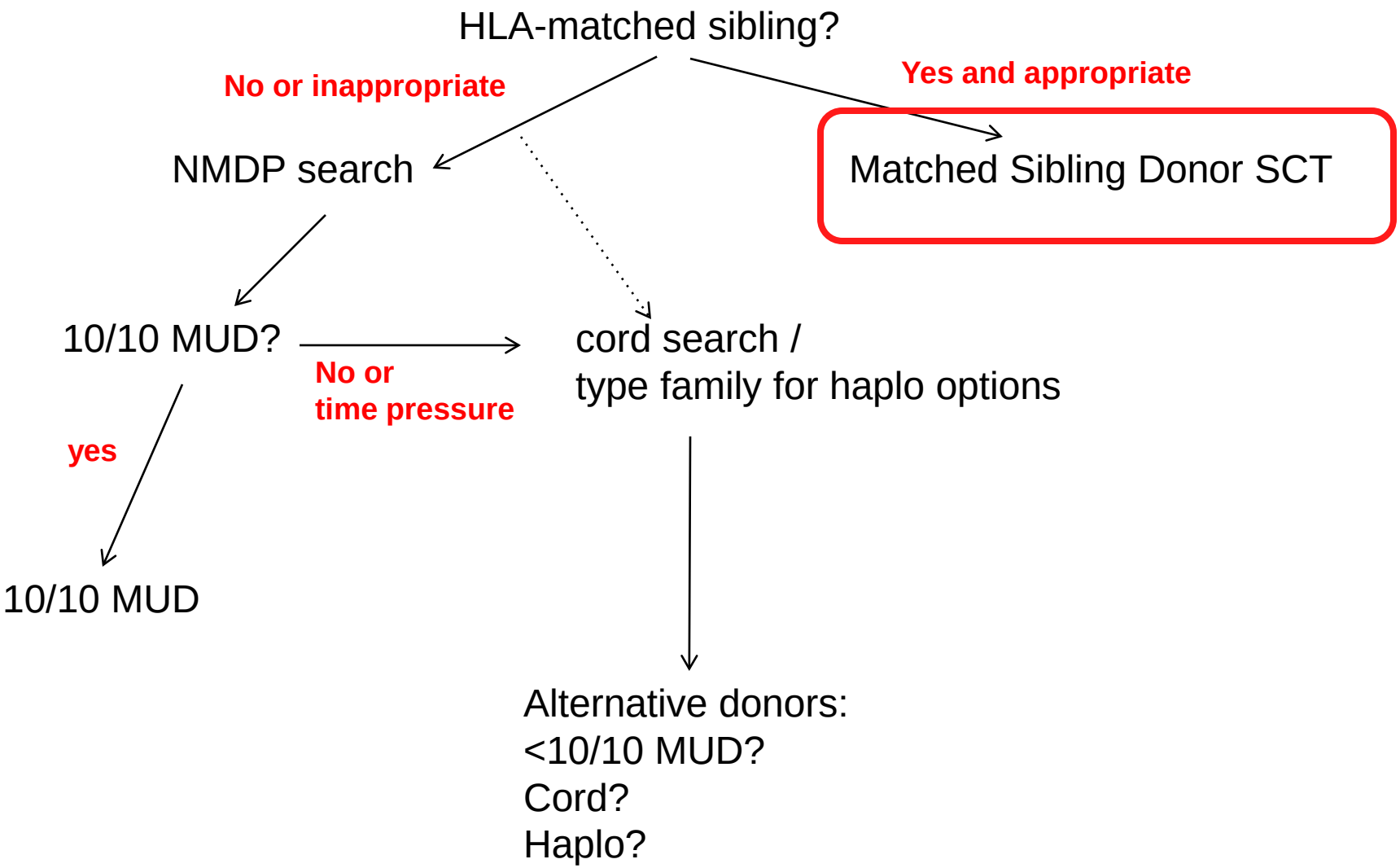
Updates on:

- **Donor selection**
- Type of conditioning
- Source of graft
- GVHD prophylaxis and management

Donor selection algorithm 2016



Donor selection algorithm 2016



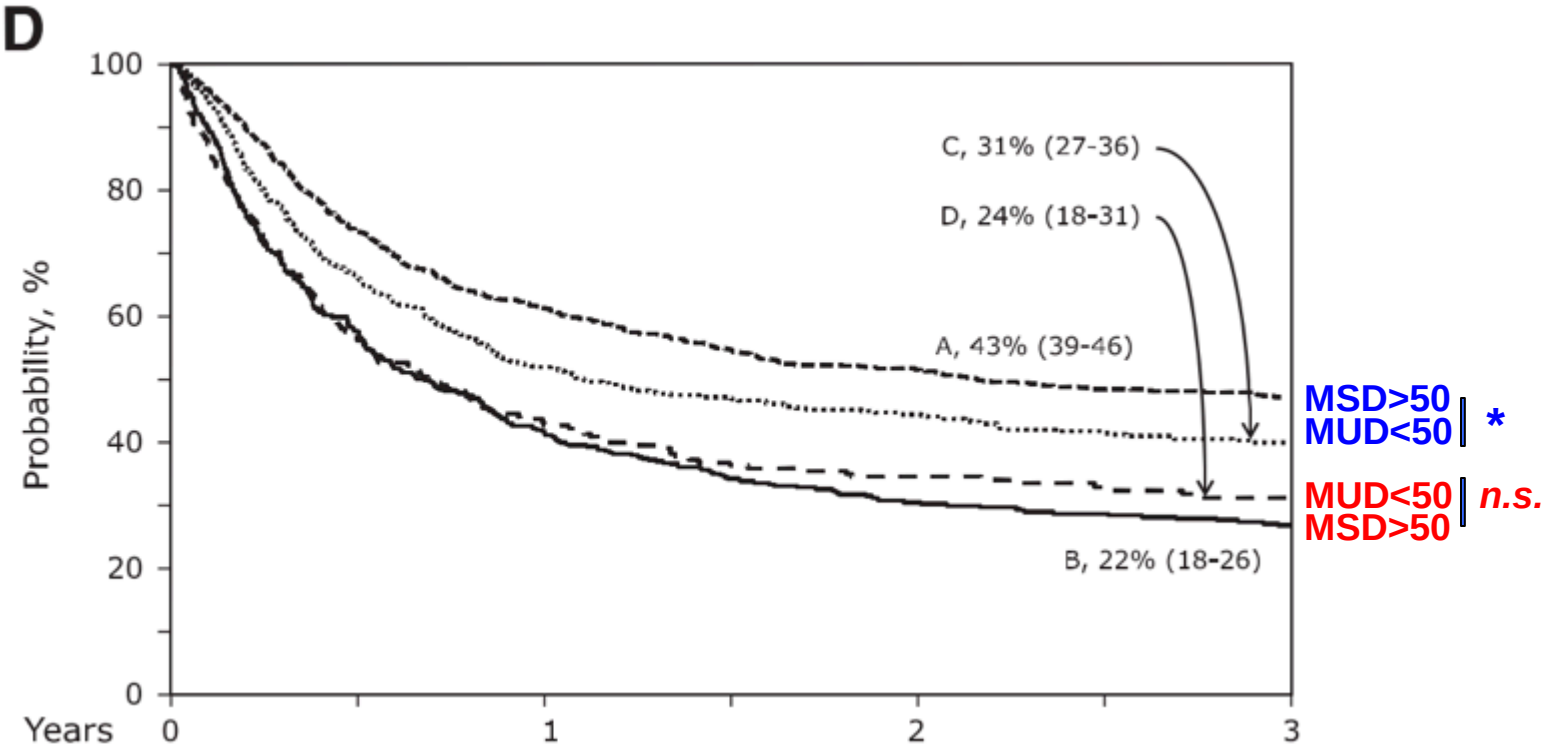
blood
2013 121: 2567-2573
doi:10.1182/blood-2012-08-453860 originally published online January 29, 2013

Who is the better donor for older hematopoietic transplant recipients: an older-aged sibling or a young, matched unrelated volunteer?

- **GVHD and TRM increase with recipient age (and possibly donor age)**
- **Registry study**
- **Recipients >50yo**
- **Transplant outcomes with MSD >50 vs. MUD <50**

blood
2013 121: 2567-2573
doi:10.1182/blood-2012-08-453860 originally published online January 29, 2013

Who is the better donor for older hematopoietic transplant recipients: an older-aged sibling or a young, matched unrelated volunteer?



- For patients with a good performance score, older MSD is better than younger MUD
- For patients with a lower performance score, outcomes are similar

VOLUME 33 · NUMBER 21 · JULY 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

High Graft CD8 Cell Dose Predicts Improved Survival and Enables Better Donor Selection in Allogeneic Stem-Cell Transplantation With Reduced-Intensity Conditioning

Ran Reshef, Austin P. Huffman, Amy Gao, Marlise R. Luskin, Noelle V. Frey, Saar I. Gill, Elizabeth O. Hexner, Taku Kambayashi, Alison W. Loren, Selina M. Luger, James K. Mangan, Sunita D. Nasta, Lee P. Richman, Mary Sell, Edward A. Stadtmauer, Robert H. Vonderheide, Rosemarie Mick, and David L. Porter

- **Are all older sibling donors the same?**
- **Are all younger unrelated donors the same?**
- **Single-center retrospective study**
- **RIC alloSCT**

VOLUME 33 · NUMBER 21 · JULY 20 2015
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

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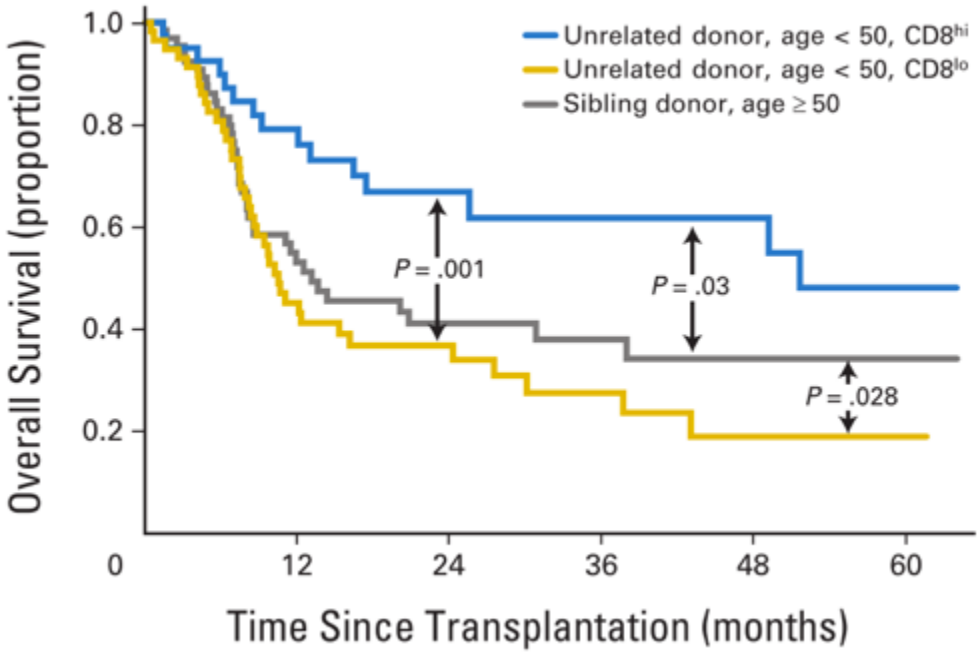
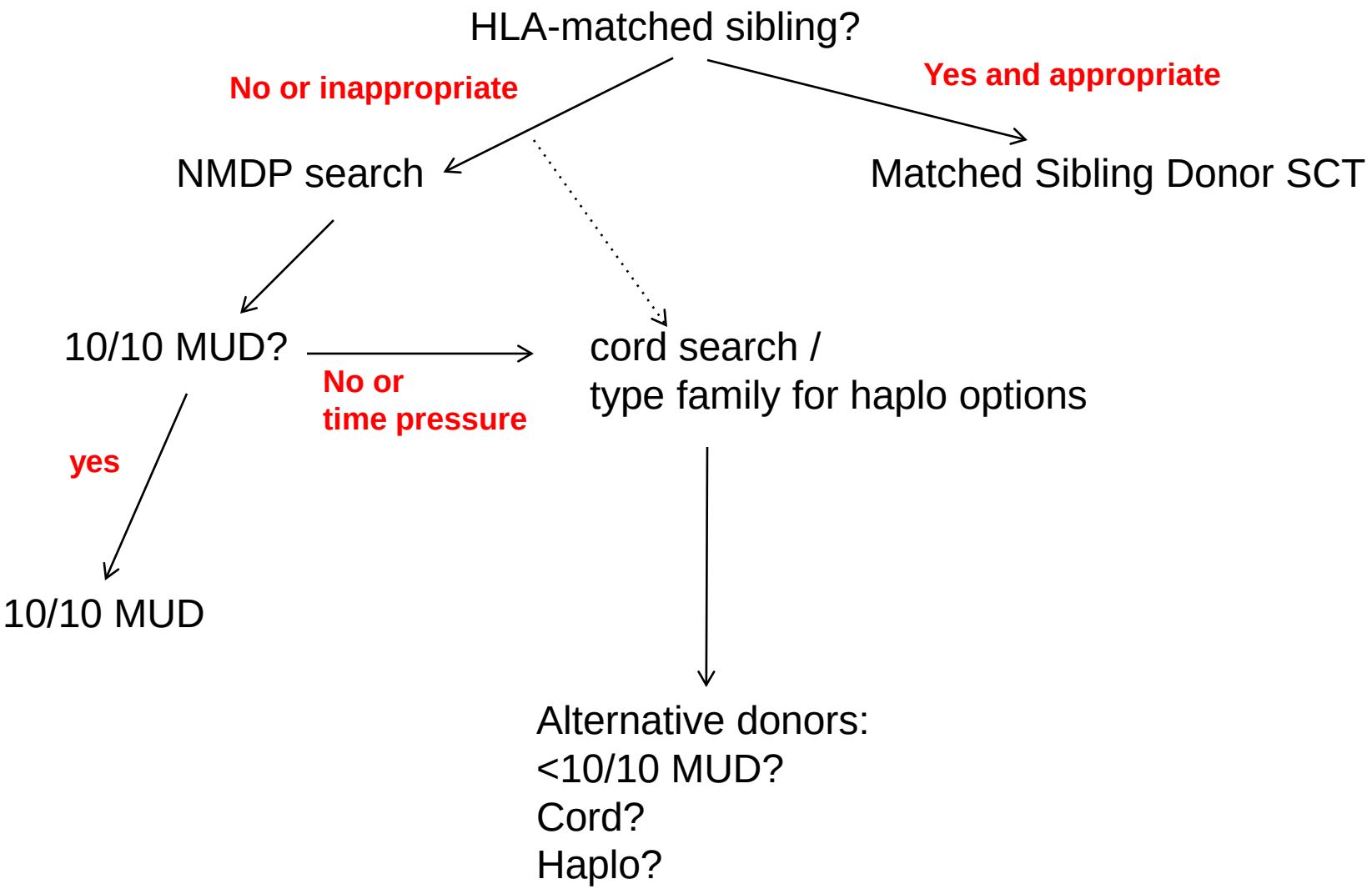
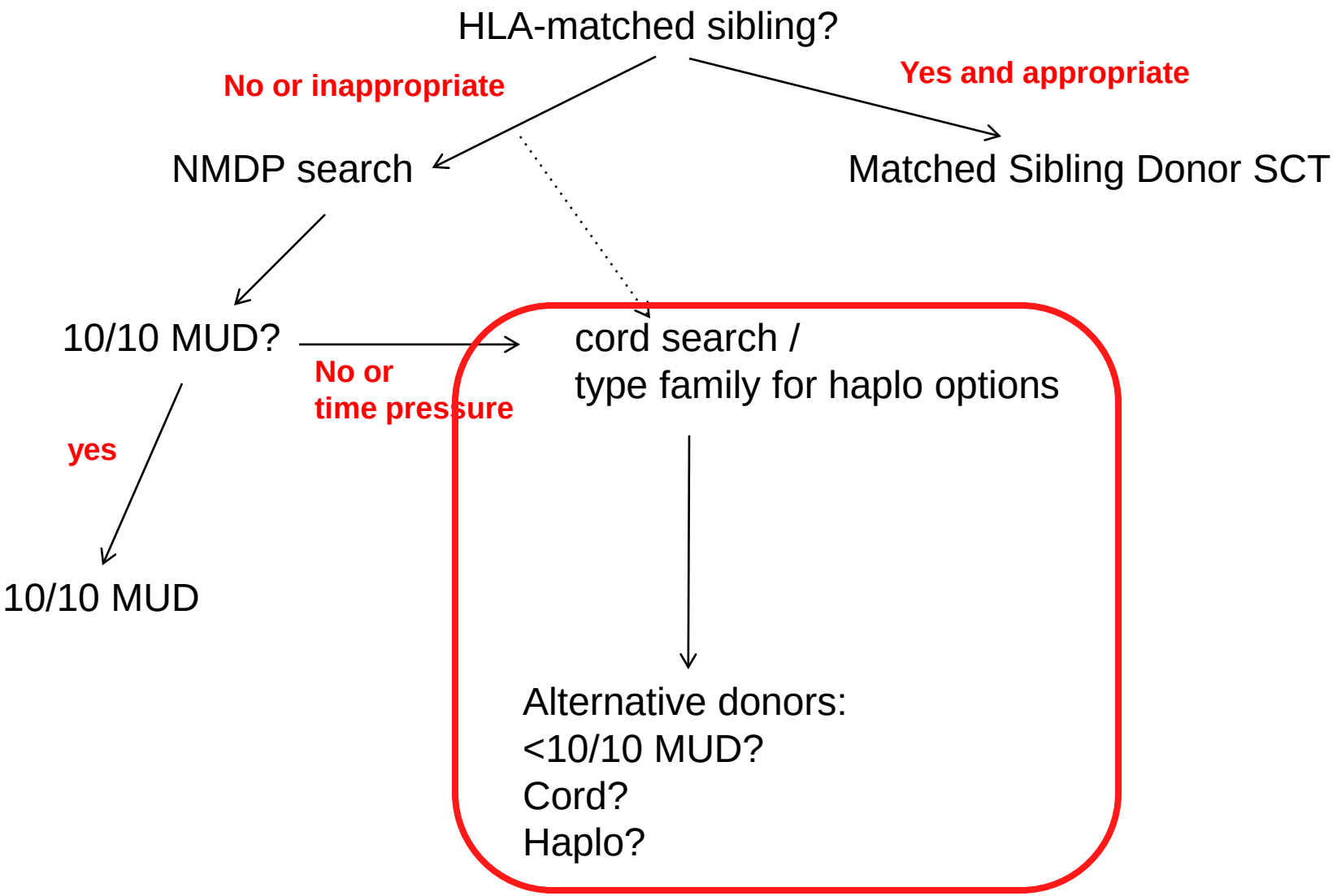


- **Higher graft CD8+ cell dose are associated with improved RFS & OS without increasing GVHD**
- **Donor age inversely correlates with CD8 dose**
- **Survival was better from MUD with a high CD8 dose**

Donor selection algorithm 2016



Donor selection algorithm 2016



No matched sibling: which donor?

blood

2012 119: 5591-5598
doi:10.1182/blood-2011-12-400630 originally published online April 10, 2012

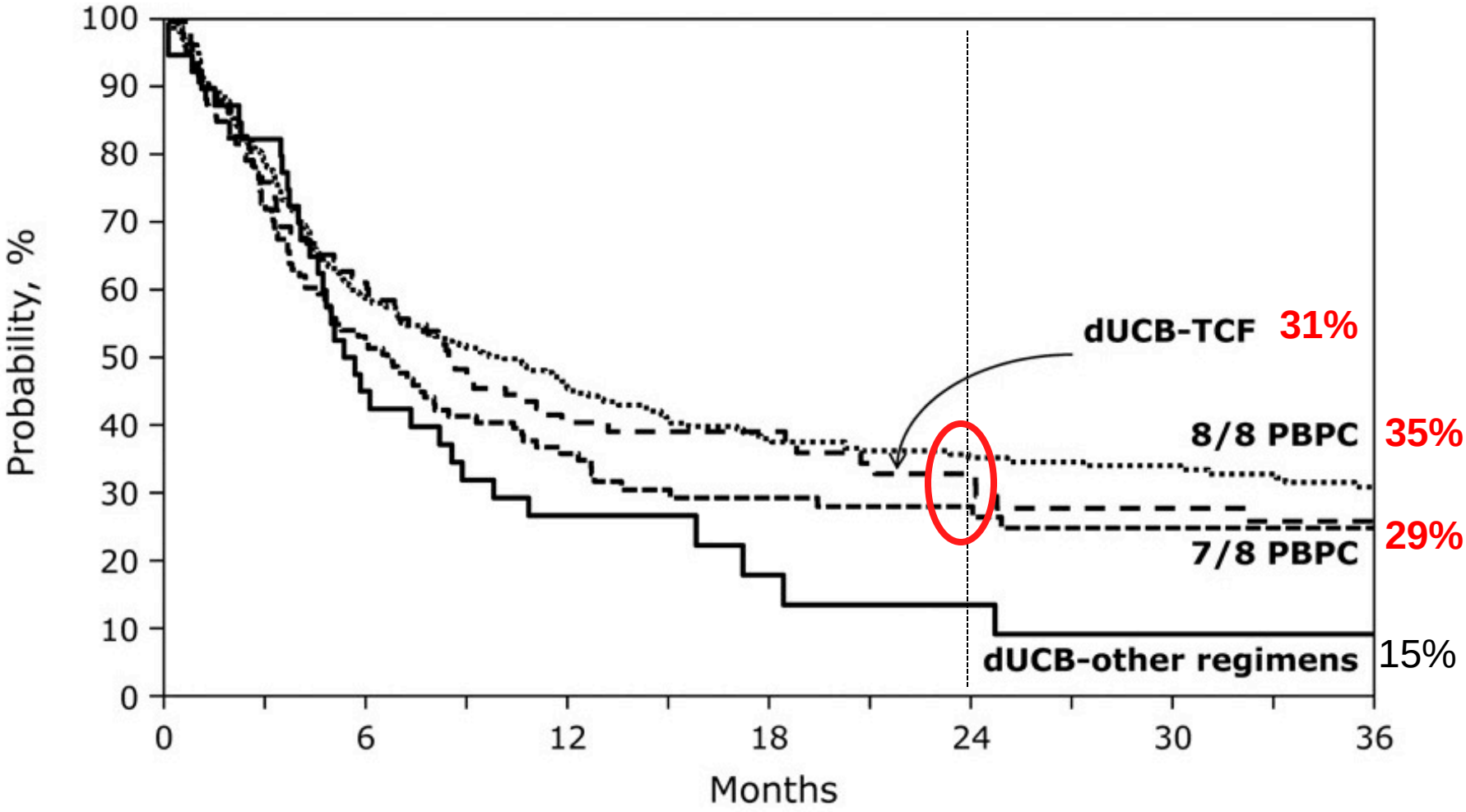
Reduced-intensity conditioning transplantation in acute leukemia: the effect of source of unrelated donor stem cells on outcomes

Claudio G. Brunstein, Mary Eapen, Kwang Woo Ahn, Frederick R. Appelbaum, Karen K. Ballen, Richard E. Champlin, Corey Cutler, Fangyu Kan, Mary J. Laughlin, Robert J. Soiffer, Daniel J. Weisdorf, Anne Woolfrey and John E. Wagner

- **Comparisons after MAC conditioning show similar LFS**
  - **?higher TRM ?lower GVHD**
- **Less data after RIC conditioning**
- **Retrospective, registry analysis (CIBMTR)**
- **Acute leukemia**

Eapen et al, Lancet Oncology 2010;

2 year leukemia-free survival: *no significant difference*



Claudio G. Brunstein et al. Blood 2012;119:5591-5598

VOLUME 33 · NUMBER 28 · OCTOBER 1 2015

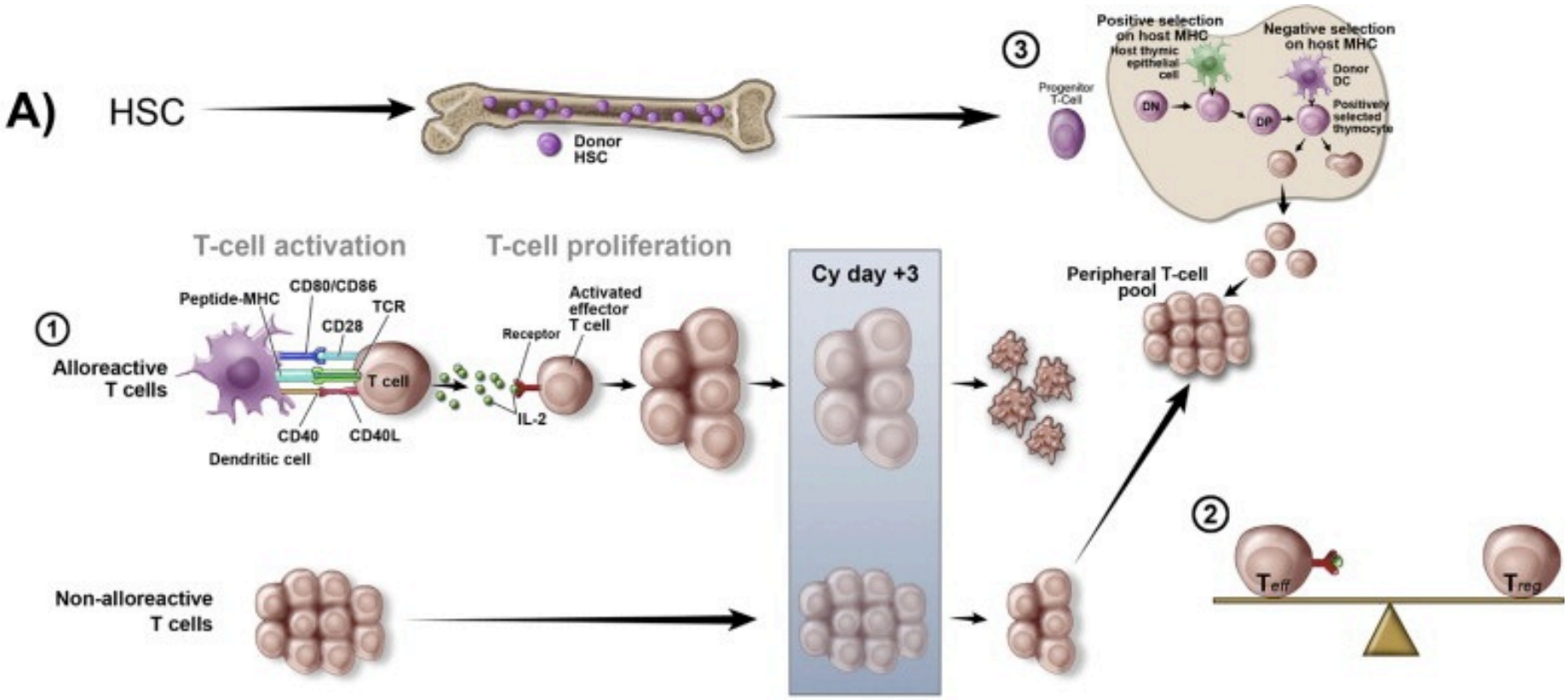
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

- **Reduced-intensity conditioning**
- **Mostly intermediate or high-risk disease status**
- **Single-center retrospective series**

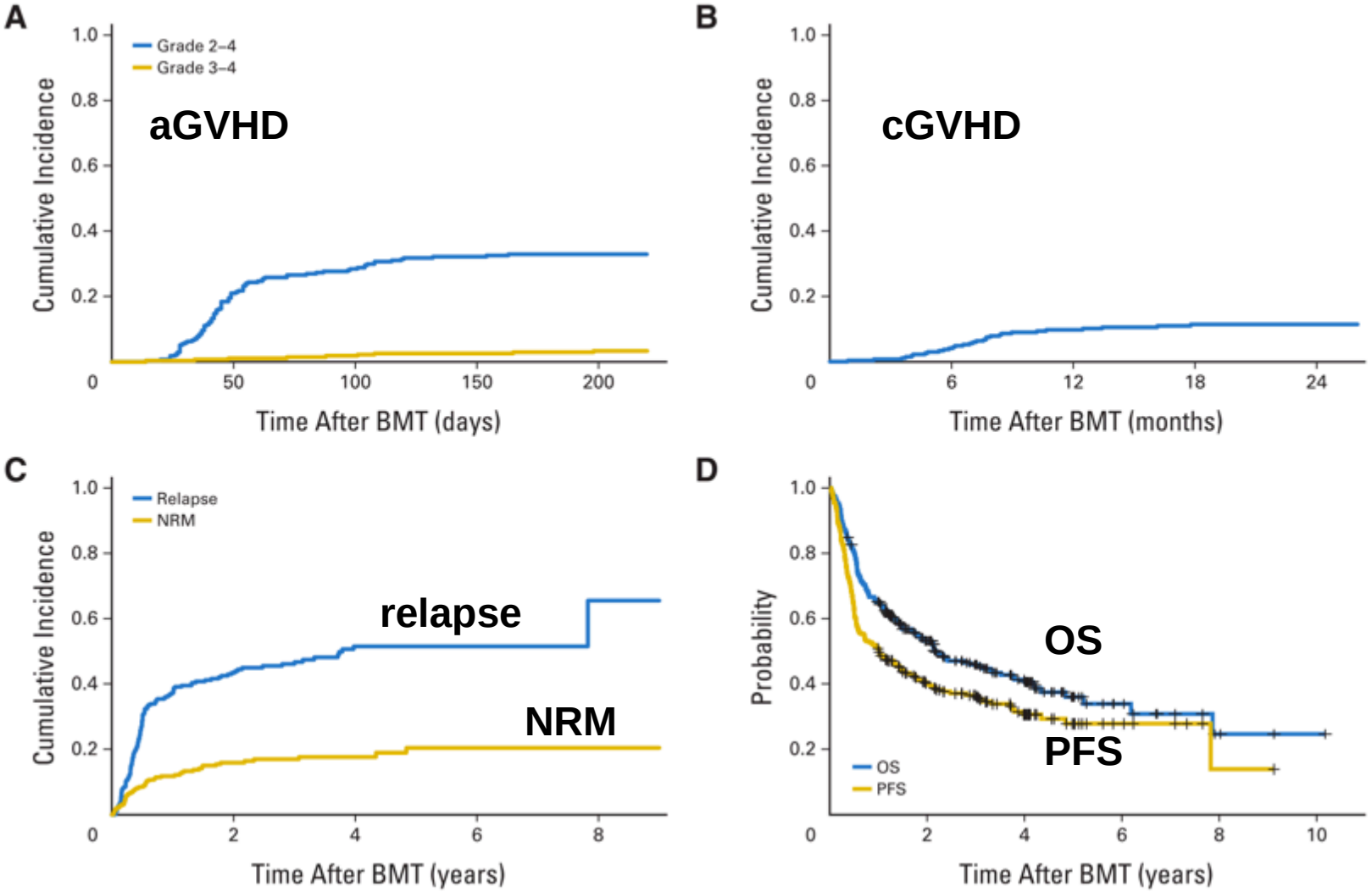
Post-Transplantation Cyclophosphamide for Tolerance Induction in HLA-Haploidentical BMT



Luznik et al, Seminars in Oncology, 2012

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

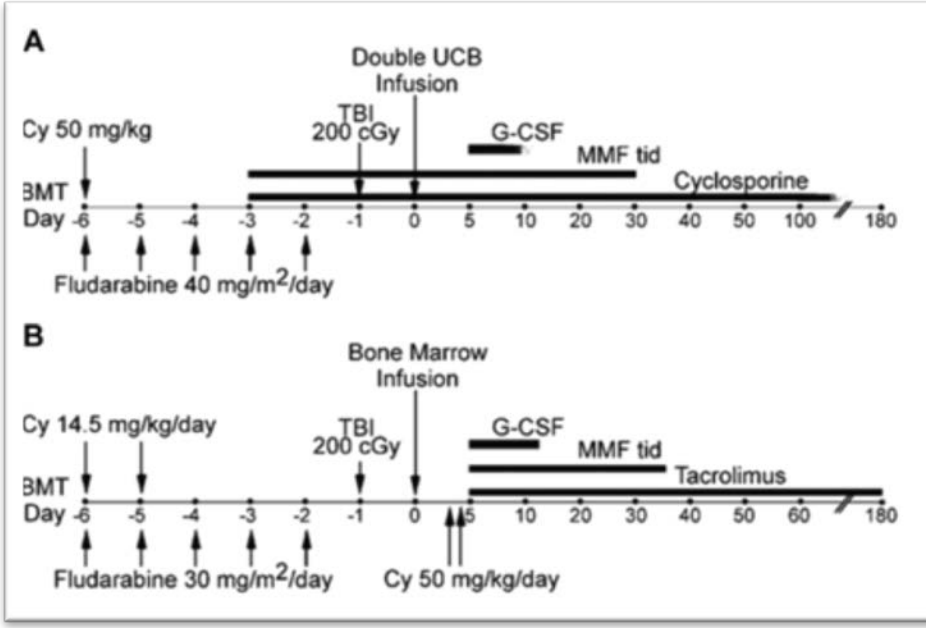


blood

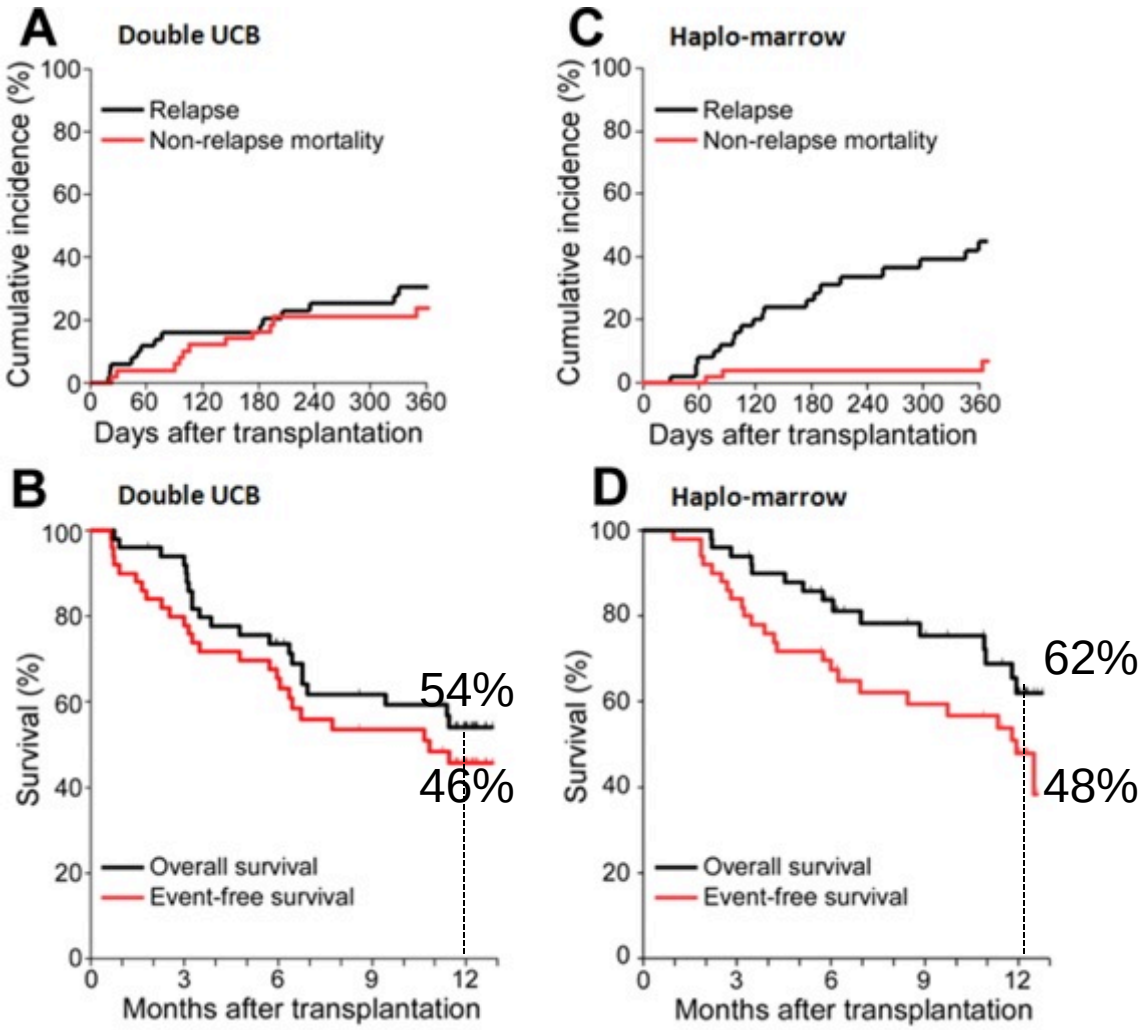
2011 118: 282-288
Prepublished online April 28, 2011;
doi:10.1182/blood-2011-03-344853

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

- **NOT randomized**
- **RIC dUCB or RIC haplo marrow**
- **To inform a subsequent randomized trial**



Long-term outcomes: cord or haplo



Claudio G. Brunstein et al. Blood 2011;118:282-288

Cord vs haplo

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Find Studies | About Clinical Studies | Submit Studies | Resources

Home > Find Studies > Study Record Detail

Double Cord Versus Haploidentical (BMT CTN 1101)

This study is currently recruiting participants. (see Contacts and Locations)

Verified August 2015 by Medical College of Wisconsin

Sponsor:

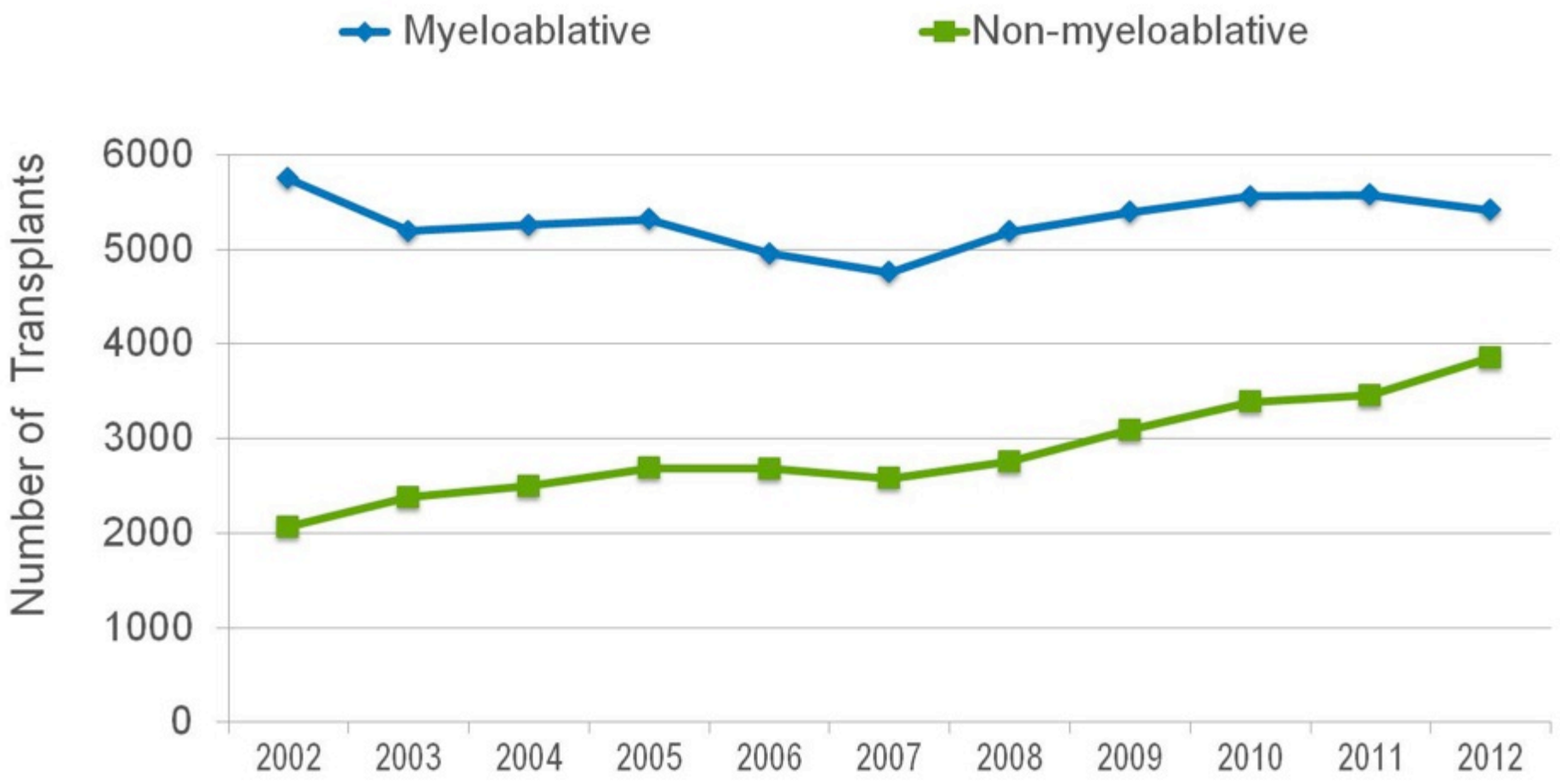
Medical College of Wisconsin

Who should be transplanted and how?

Updates on:

- Donor selection
- **Type of conditioning (“full vs mini”)**
- Source of graft
- GVHD prophylaxis and management

Allogeneic Transplants Registered with the CIBMTR



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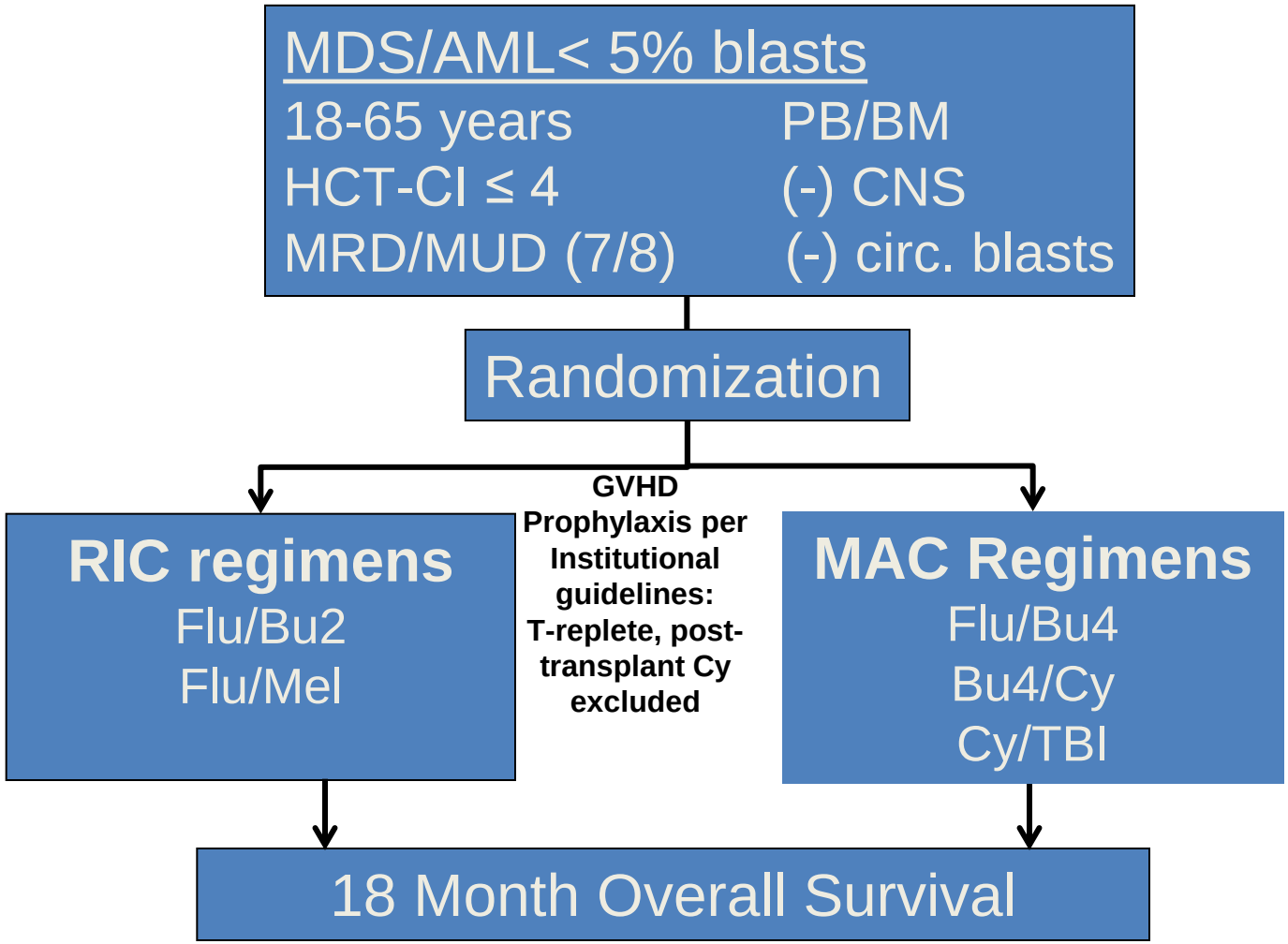
by Conditioning Regimen Intensity

BMT CTN PROTOCOL 0901

A Randomized, Multi-Center, Phase III Study of Allogeneic Stem Cell Transplantation Evaluating Regimen Intensity in Patients with Myelodysplastic Syndrome or Acute Myeloid Leukemia

BLOOD AND MARROW
TRANSPLANT
CLINICAL TRIALS NETWORK

BMT CTN 0901: Randomized Phase III design



Statistical Considerations

Primary Objective: Compare 18 month OS

Secondary Objectives: Compare RFS, TRM, relapse, hematologic recovery, graft failure, acute and chronic GvHD, QOL, toxicity

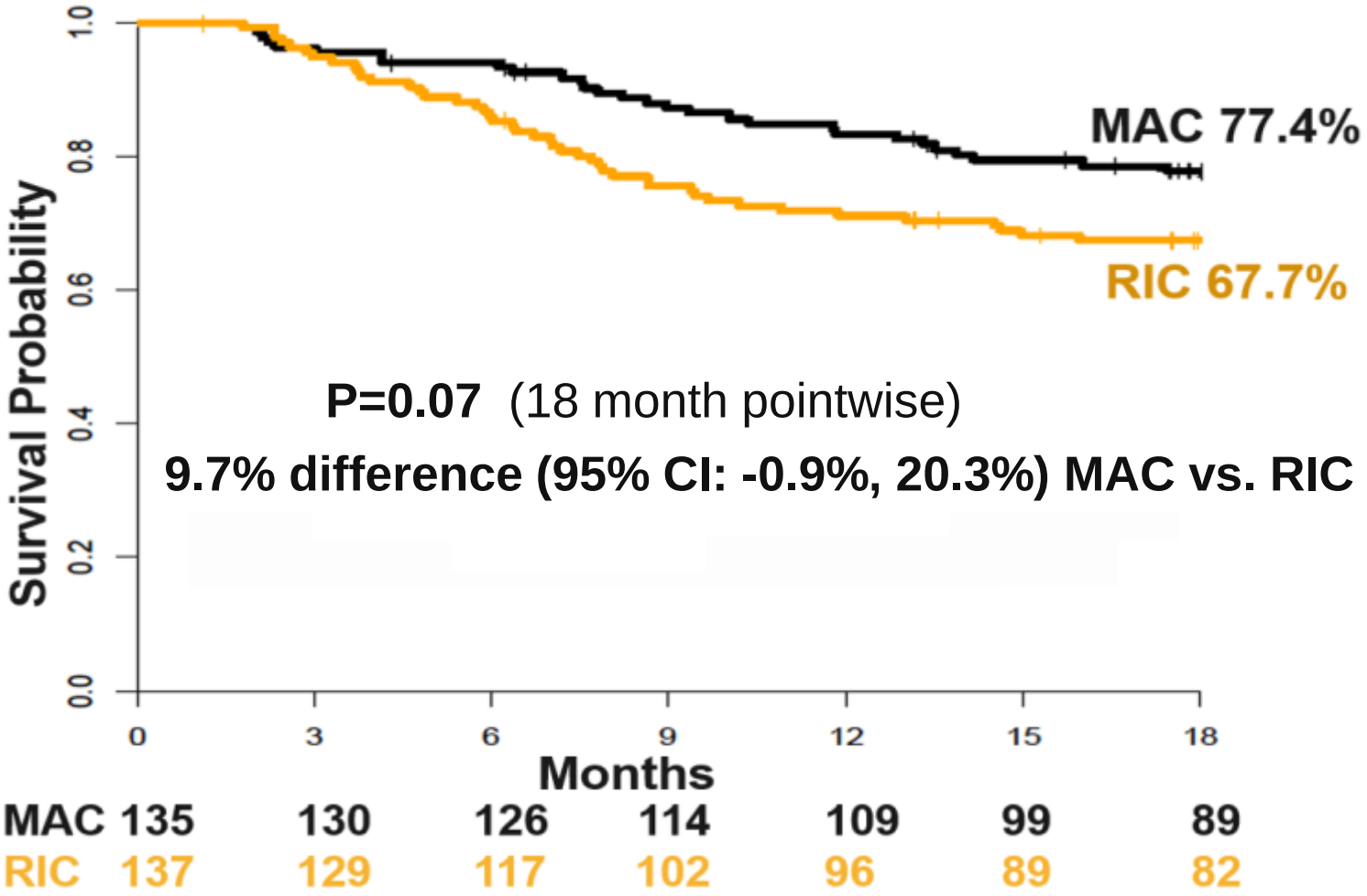
Hypothesis: Decreased TRM from RIC results in improved OS @ 18 months

Patient and Disease Characteristics

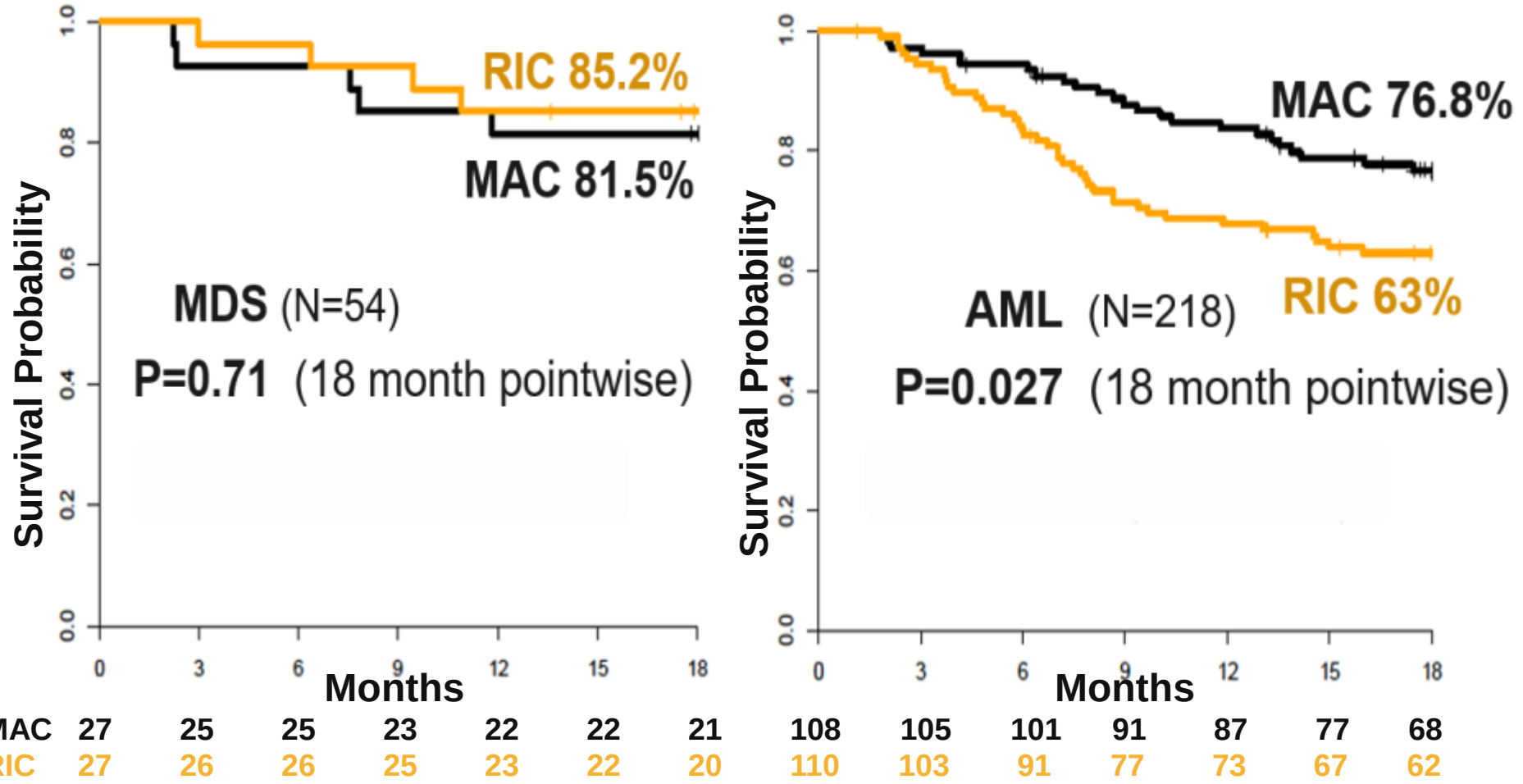
Characteristic, no of patients (%)	MAC N=135	RIC N=137
Total who underwent HCT	132 (98)	133 (97)
Age, median (range), y	54.8 (21.9-66)	54.8 (21.9-65.9)
Gender, M/F	76/59	67/70
Primary Diagnosis		
AML	108 (80)	110 (80)
MDS	27 (20)	27 (20)
Disease duration, range (median), mo	6 (2-87)	6 (2-13)

7 patients did not receive HCT due to relapse (n=5), withdrawing consent (n=1), and physician decision (n=1)

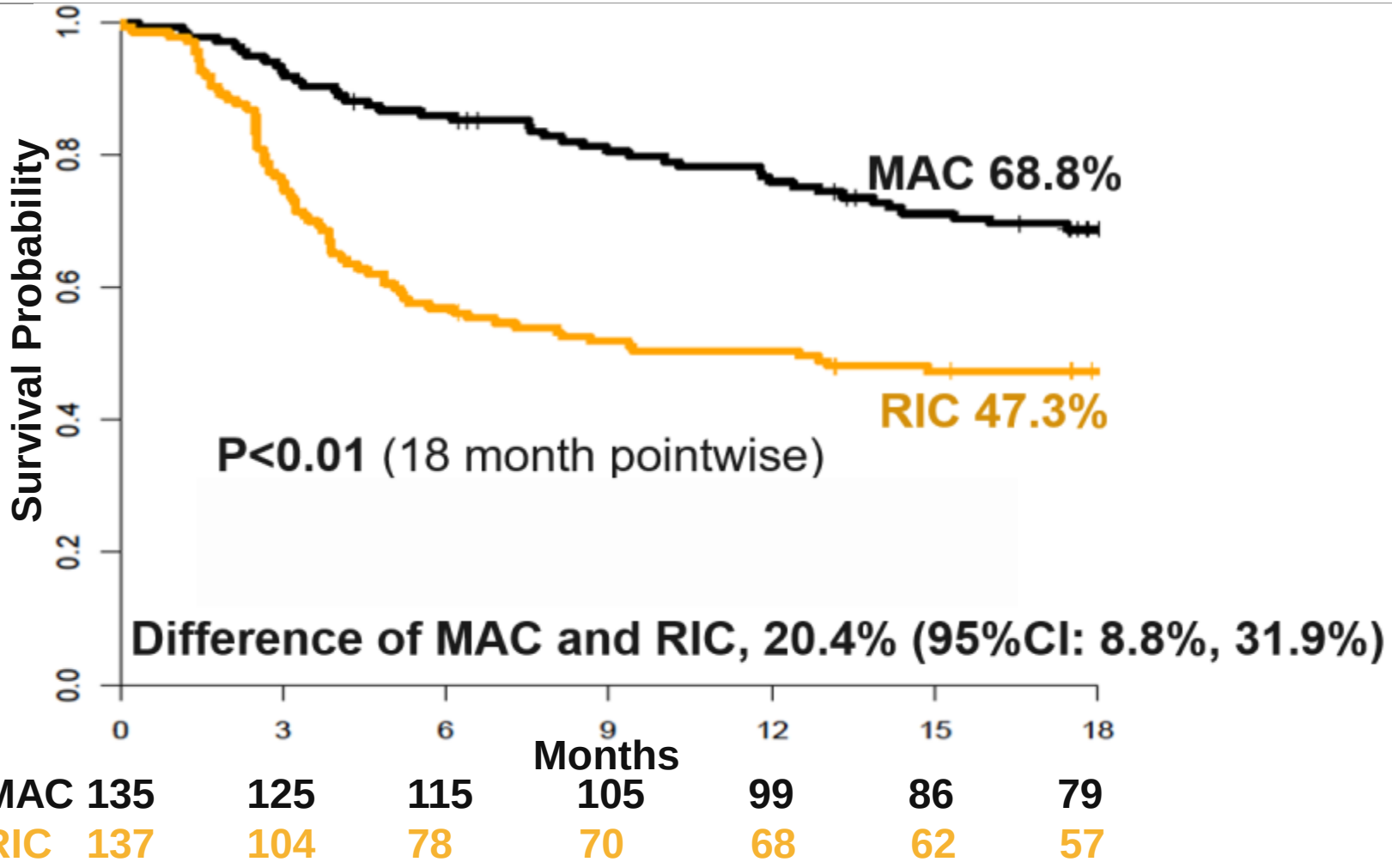
Overall Survival by Treatment Arm



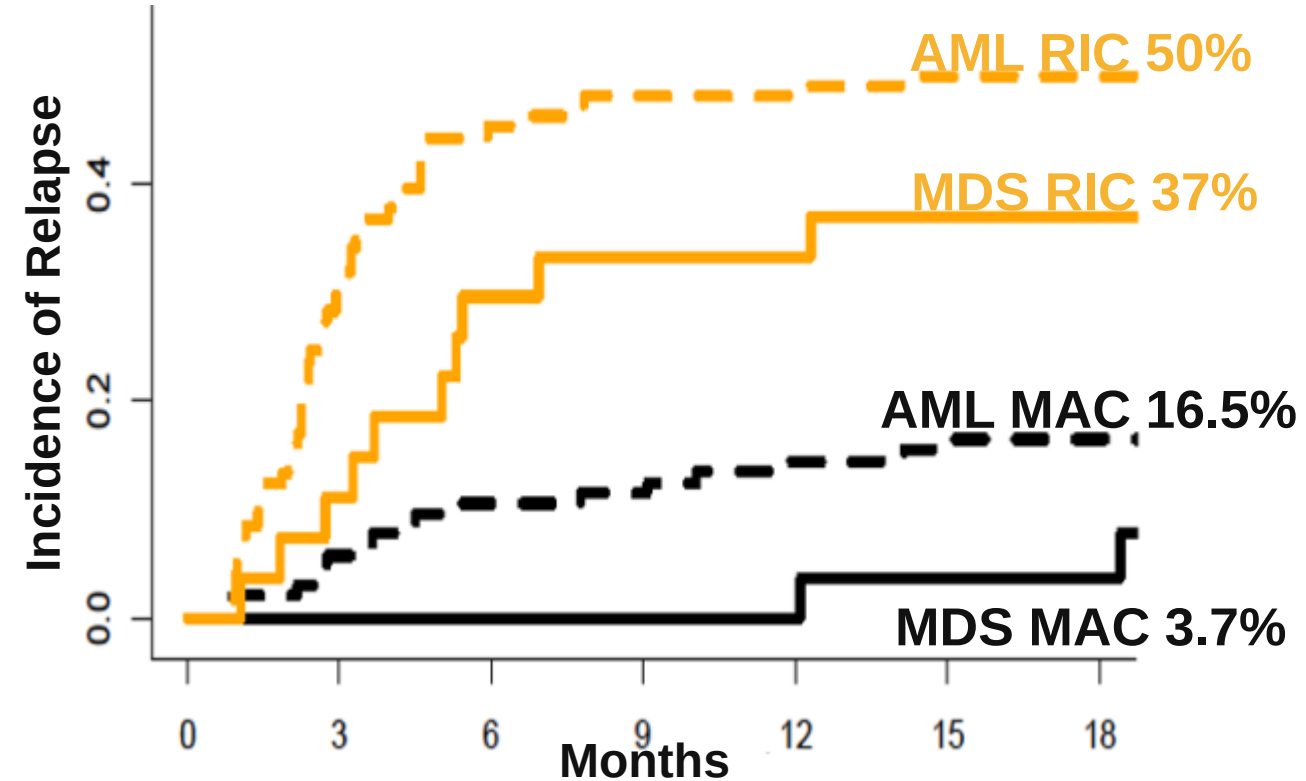
Overall Survival by Disease Group



Relapse-free survival by treatment arm

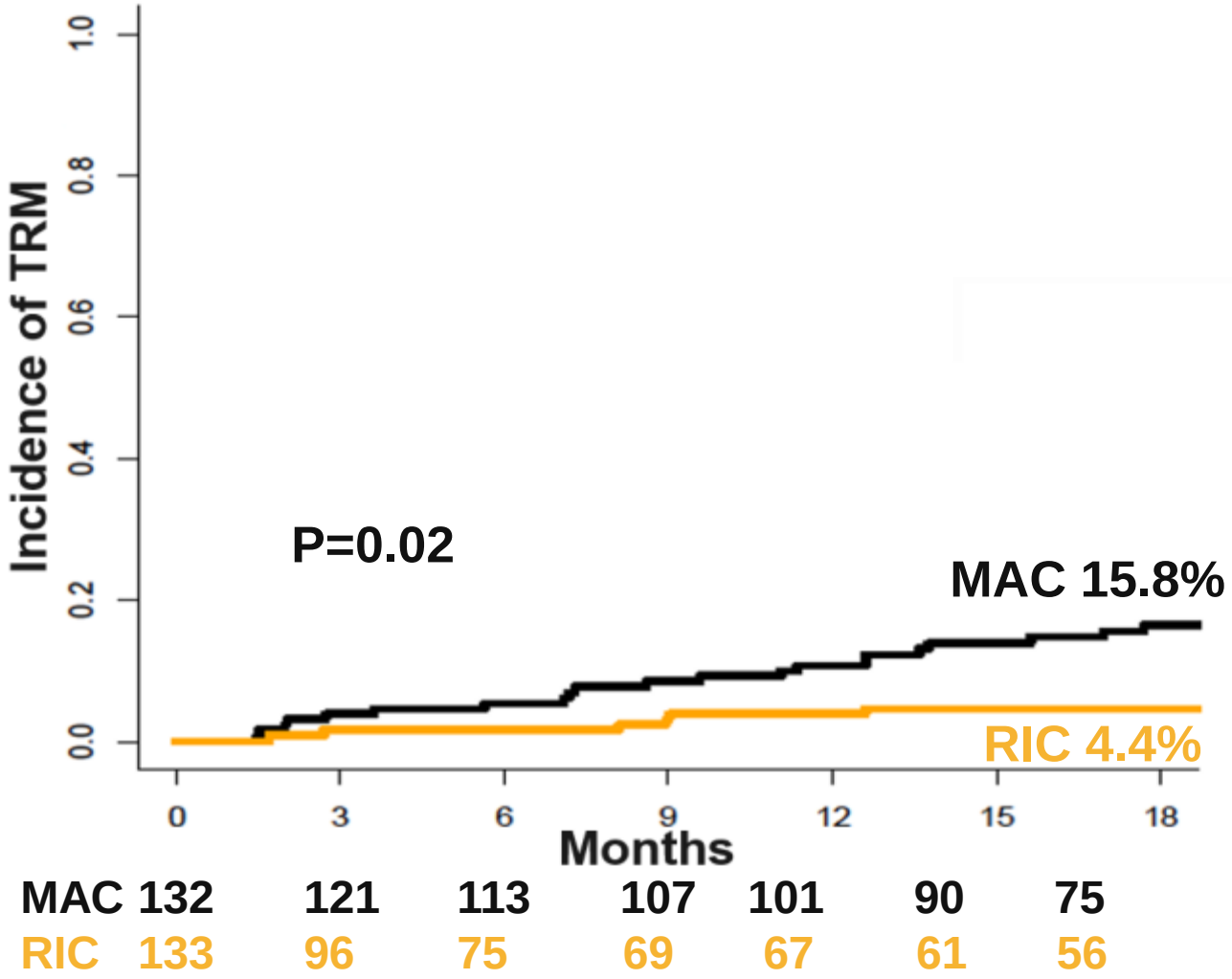


Relapse/Progression by Disease and Treatment Arm



MDS	27	25	25	23	22	21	19
MDS	27	23	18	17	16	15	13
AML	105	96	88	84	79	69	56
AML	106	73	57	52	51	46	43

Treatment-related Mortality



Summary: Choice of conditioning intensity

- Incidence of acute and chronic GVHD was higher following MAC
- No significant difference in OS (p=0.07)
- RIC results in significantly increased risk of relapse and inferior RFS (p<0.01)
- MAC remains the treatment of choice over RIC (if patient is appropriate candidate for MAC)
- Novel, less toxic MAC or effective post-transplant maintenance regimens are needed to improve disease control in those who require RIC

Who should be transplanted and how?

Updates on:

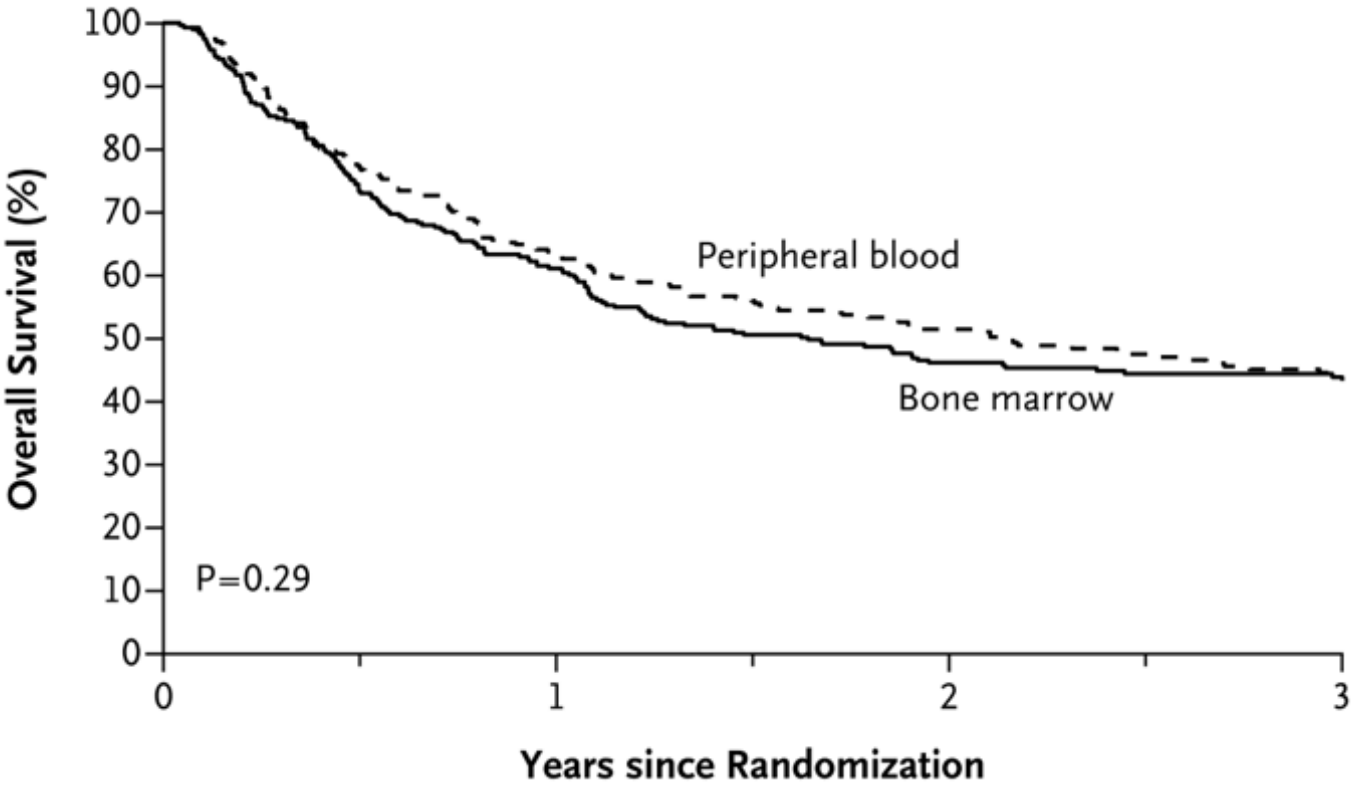
- Donor selection
- Type of conditioning
- **Source of graft**
- GVHD prophylaxis and management

- **After MSD, stem cells from G-CSF mobilized PB vs BM source:**
  - **accelerate engraftment, increase acute & chronic GVHD**
  - **Decrease relapse and may increase survival esp. in high risk**

- **Phase 3 RCT aiming to compare 2yr survival by ITT in URD**

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 18, 2012 VOL. 367 NO. 16

Peripheral-Blood Stem Cells versus Bone Marrow from Unrelated Donors



- **OS, aGVHD or relapse not significantly different**
- **Increased graft failure (9 vs 3%) in BM source**
- **Decreased cGVHD (41 vs 53%) in BM source**

Who should be transplanted and how?

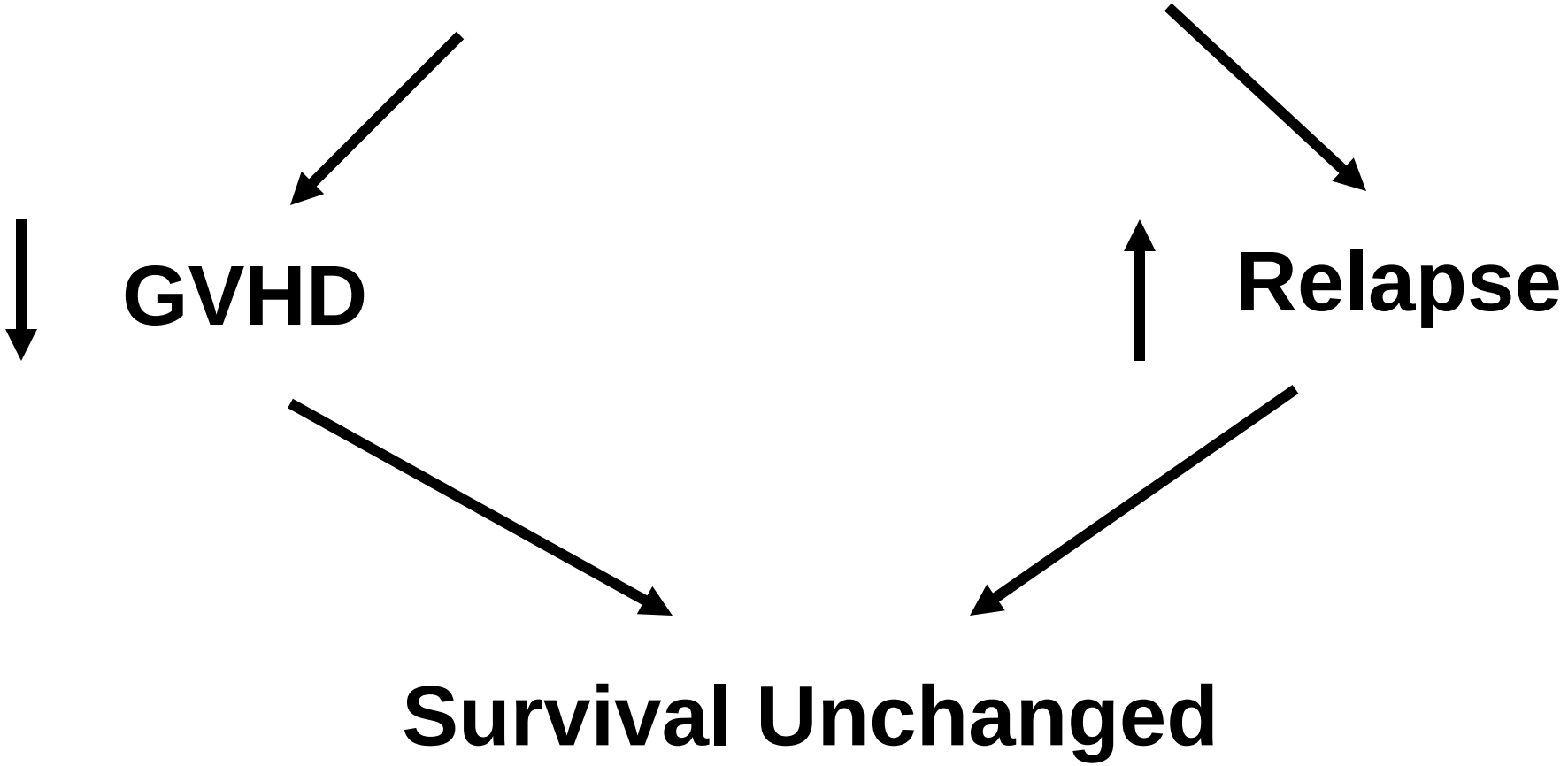
Updates on:

- Donor selection
- Type of conditioning
- Source of graft
- **GVHD prophylaxis**

GVHD Prophylaxis

Intervention	aGVHD frequency
No prophylaxis	70-100%
MTX or CSA	50%
CSA plus MTX	25-40%
T cell depletion	0-20%

T cell depletion of donor graft

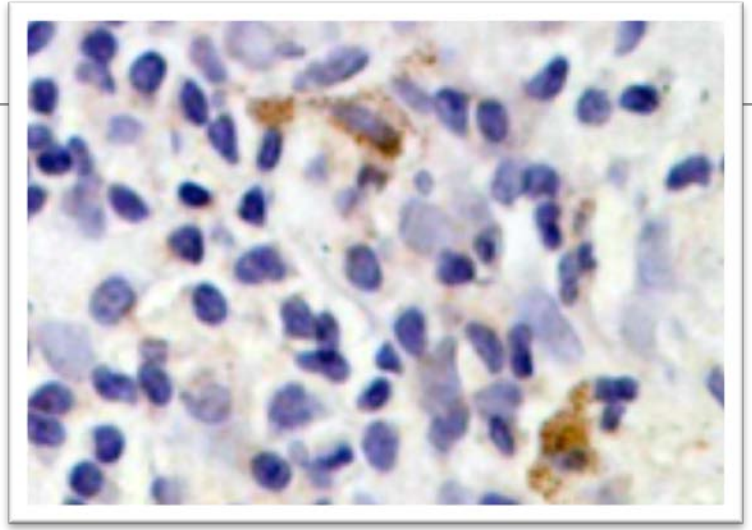


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

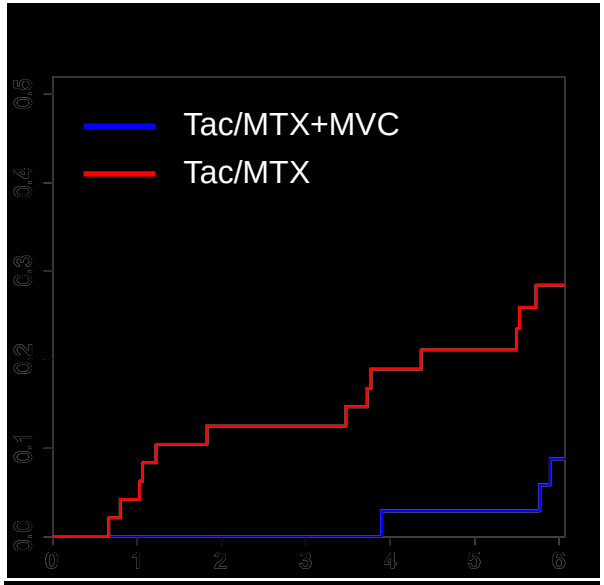
Ran Reshef, M.D., Selina M. Luger, M.D., Elizabeth O. Hexner, M.D., Alison W. Loren, M.D., Noelle V. Frey, M.D., Sunita D. Nasta, M.D., Steven C. Goldstein, M.D., Edward A. Stadtmauer, M.D., Jacqueline Smith, C.R.N.P., Sarah Bailey, B.A., Rosemarie Mick, M.S., Daniel F. Heitjan, Ph.D., Stephen G. Emerson, M.D., Ph.D., James A. Hoxie, M.D., Robert H. Vonderheide, M.D., D.Phil., and David L. Porter, M.D.

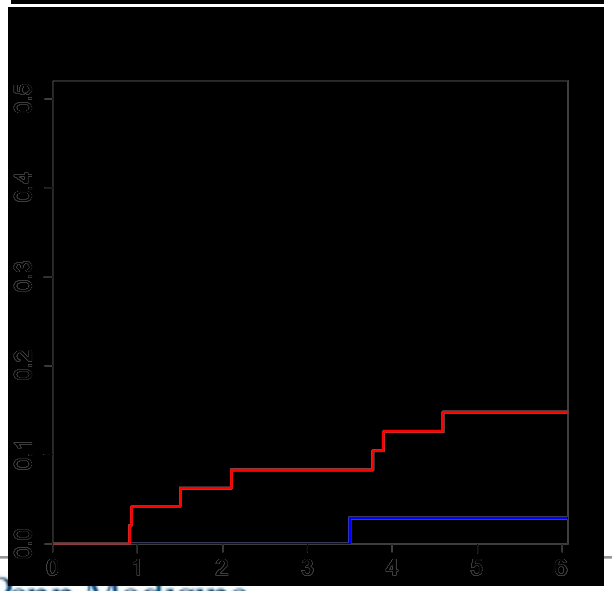


Rash bx D22 post SCT, CCR5 staining

- Blocking T cell trafficking to target organs should prevent GVHD
- CCR5 (HIV receptor on T cells) important for T cell trafficking through ligands CCL3, 4, 5.
- In mice, anti-CCR5 Ab blocks migration of T cells to liver and gut and prevents GVHD.
- In clinical transplant certain CCR5 polymorphisms are protective for GVHD and associated with improved survival.
- Homozygous Δ32-CCR5 associated with low rates of GVHD

Efficacy: Significant decrease in visceral GvHD





Gut

Rate ± SE (%)	100 days	180 days
Tac/MTX+MVC	0	8.8 ± 5.0
Tac/MTX	12.5 ± 4.8	18 ± 6.8
P-value	**0.009**	**0.02**

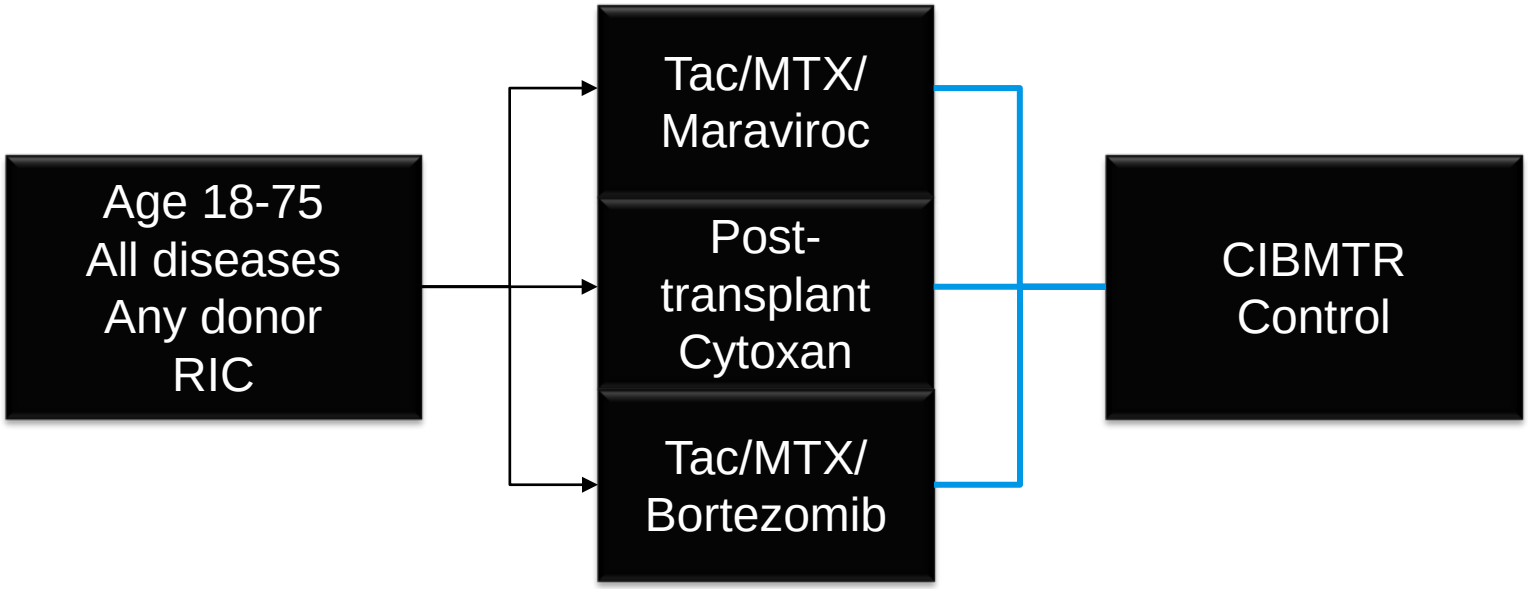
Liver

Rate ± SE (%)	100 days	180 days
Tac/MTX+MVC	0	2.9 ± 2.9
Tac/MTX	8.3 ± 4.0	14.8 ± 5.2
P-value	**0.04**	**0.05**

Randomized Phase II multi-center trial of novel GvHD prevention strategies (BMT-CTN 1203)

Primary objective:

- GVHD/Relapse-free survival at 1 year → baseline rate of 23%
- N= 90 per arm
- Comparison to 270 contemporary control patients from the CIBMTR registry



Summary: GVHD prophylaxis

- **Multiple different regimens**
- **T cell depletion is the most potent way to prevent GVHD (but leads to increased relapses)**
- **Separation of GVL from GVHD still remains the “holy grail”…**

CONCLUSIONS 2016

- **Donor selection:** HLA-matched sibling > MUD > cord/haplo
- **Type of conditioning:** myeloablative > reduced intensity
- **Source of graft:** marrow or mobilized PB
- **GVHD prophylaxis:** Depletion of alloreactive T cells, inhibition of T cell trafficking, other….

Thank you.