Updated 2012 guidelines for selecting unrelated donors and CBUs for HCT

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Chief Medical Officer, NMDP
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• Dennis L. Confer, MD	Presenter
• Darlene Haven	Planning Committee
• Ellyce Hayes, RD	Planning Committee
• Mary Horowitz, MD	Planning Committee
• Craig Malmberg, CHS	Planning Committee
• Michelle Setterholm, CHS	Planning Committee
• Stephen Spellman, PhD	Planning Committee

Learning objectives

- Identify pre/post-transplant factors that contribute to improved HCT survival
- Apply updated matching criteria for selecting marrow, PBSC, and cord blood cell sources for transplant recipients
- Identify strategies for selection between mismatched loci with consideration for decision-making based on strength of supporting research

Recent Update to Matching Guidelines

blood

2012 120: 259-265
Prepublished online May 17, 2012;
doi:10.1182/blood-2012-03-379032

A perspective on the selection of unrelated donors and cord blood units for transplantation

Stephen R. Spellman, Mary Eapen, Brent R. Logan, Carlheinz Mueller, Pablo Rubinstein, Michelle I. Setterholm, Ann E. Woolfrey, Mary M. Horowitz, Dennis L. Confer and Carolyn K. Hurley

Spellman SR, et al. Blood (2012) 120:259-265

Factors that Affect Transplant Outcomes

Pre-transplant

- HLA matching
- Patient CMV seropositivity
- Performance score
- Disease
- Disease status
- Graft cell dose

Post-transplant

- Infections
- aGVHD and cGVHD
- Organ toxicity
- Recurrent/2nd malignant neoplasms

Questions to Answer

- Which loci should be evaluated for HLA matching?
- How do antigen mismatches compare to allele mismatches?
- Are some loci more important than others?
- Is bone marrow the same as PBSC?
- What about HLA-DP?
- What about anti-HLA antibodies?
- What about cord blood unit transplants?
- Anything about KIR?

High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation

BLOOD (2007) 110: 4576-83

Stephanie J. Lee, John Klein, Michael Haagenson, Lee Ann Baxter-Lowe, Dennis L. Confer, Mary Eapen, Marcelo Fernandez-Vina, Neal Flomenberg, Mary Horowitz, Carolyn K. Hurley, Harriet Noreen, Machteld Oudshoorn, Effie Petersdorf, Michelle Setterholm, Stephen Spellman, Daniel Weisdorf, Thomas M. Williams and Claudio Anasetti

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Study Population

- N = 3,860 US transplants, 1988-2003
- AML, ALL, CML, MDS
- Myeloablative conditioning
- Calcineurin inhibitor-based GVHD prophylaxis, T replete grafts (79%)
- Bone marrow (94%)
- Median follow-up 6 years

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Any Single Locus Mismatch

9/10 associated with worse survival, DFS, TRM, acute GVHD

	n	RR (95% CI)	P-value
Survival	952	1.17 (1.06-1.329)	0.002
DFS	945	1.16 (1.05-1.28)	0.003
TRM	945	1.31 (1.16-1.47)	<0.0001
Relapse	945	0.90 (0.81-1.00)	0.04
Engraftment	956	OR 0.90 (0.80-1.01)	0.06
Acute GVHD	957	1.35 (1.19-1.56)	<0.0001
Chronic GVHD	910	0.96 (0.91-1.03)	0.25

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Single Antigen vs. Allele MM

	Antigen	Allele	P-value
Survival	1.16	1.19	0.69
DFS	1.16	1.17	0.92
TRM	1.34	1.32	0.86
Relapse	0.80	0.93	0.31
Engraftment	0.74	1.08	0.07
Acute GVHD	1.52	1.24	0.06
Chronic GVHD	0.95	0.97	0.84

No statistical difference if mismatched at antigen or allele level, except for C – Antigen worse than Allele

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HLA DQ Lacked Impact: As a Single Mismatch

	Survival		TRM		Acute GVHD	
	RR	p	RR	p	RR	p
10/10	1.00		1.00		1.00	
DQ MM	0.97	0.77	1.08	0.50	1.03	0.86

As a Second Mismatch

	8/10	9/10	RR (95% CI)	P-value
DQ MM	191	797	1.14 (0.94-1.38)	0.17

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Specific Single Locus Mismatches

Considering 8/8 as "fully matched"

	Survival		TRM		Acute GVHD	
	RR	p	RR	p	RR	p
8/8	1.00		1.00		1.00	
A MM	1.36	<0.0001	1.47	<0.0001	1.57	<0.0001
B MM	1.16	0.20	1.32	0.03	1.63	0.001
C MM	1.19	0.006	1.32	0.0002	1.43	<0.0001
DR MM	1.48	0.0005	1.56	0.0007	1.27	0.16

Survival: Mismatch at A or DRB1 vs. B or C, RR 1.18 (1.10-1.38), p=0.04

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Survival

9-10% lower overall survival with each additional mismatch

Match	n	Survival (CI)	RR (CI)	P-value
8/8	1840	52 (50-54)	1.00	
7/8	988	43 (40-46)	1.25 (1.13-1.37)	<0.0001
6/8	633	33 (30-37)	1.65 (1.48-1.84)	<0.0001

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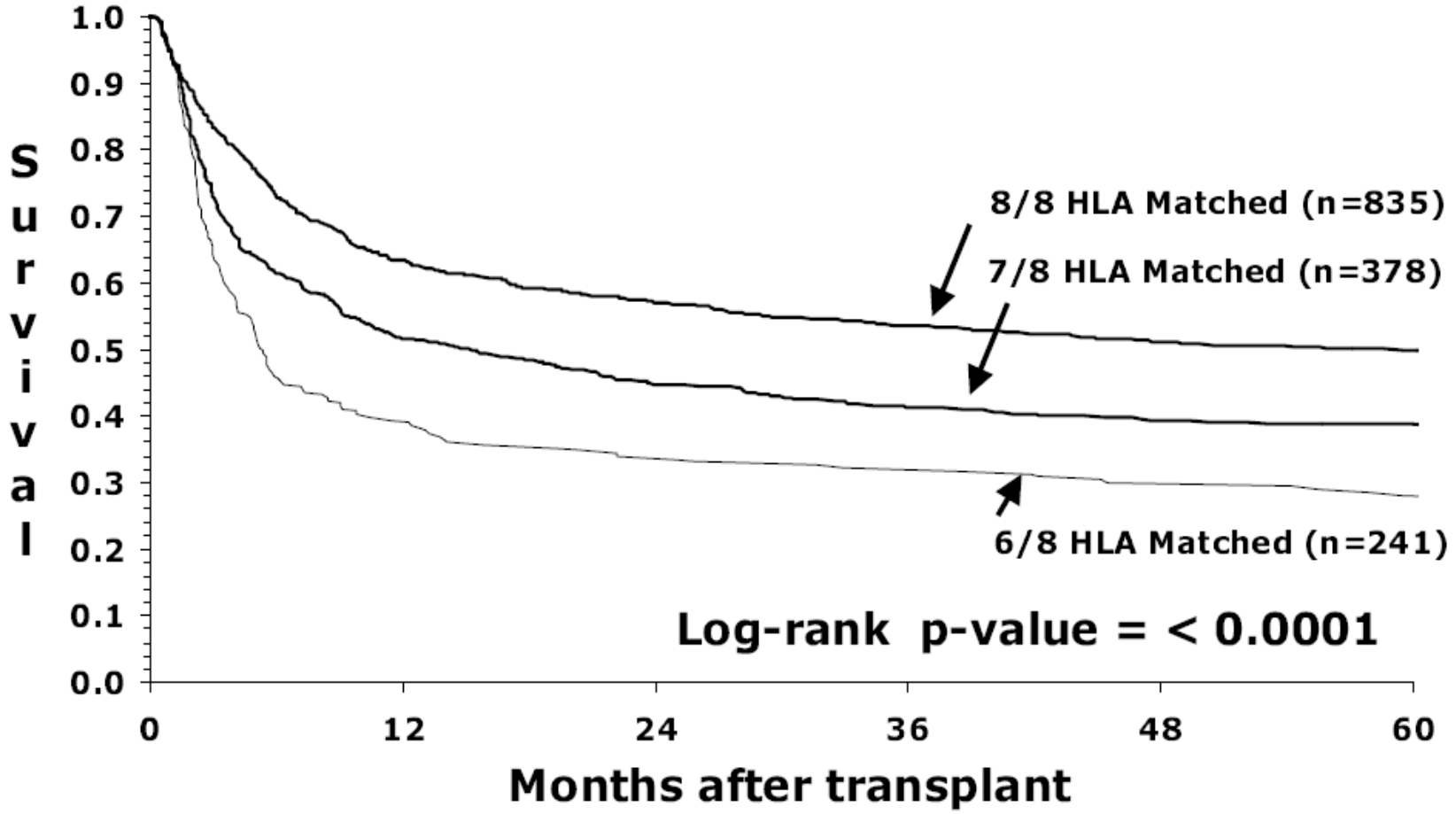
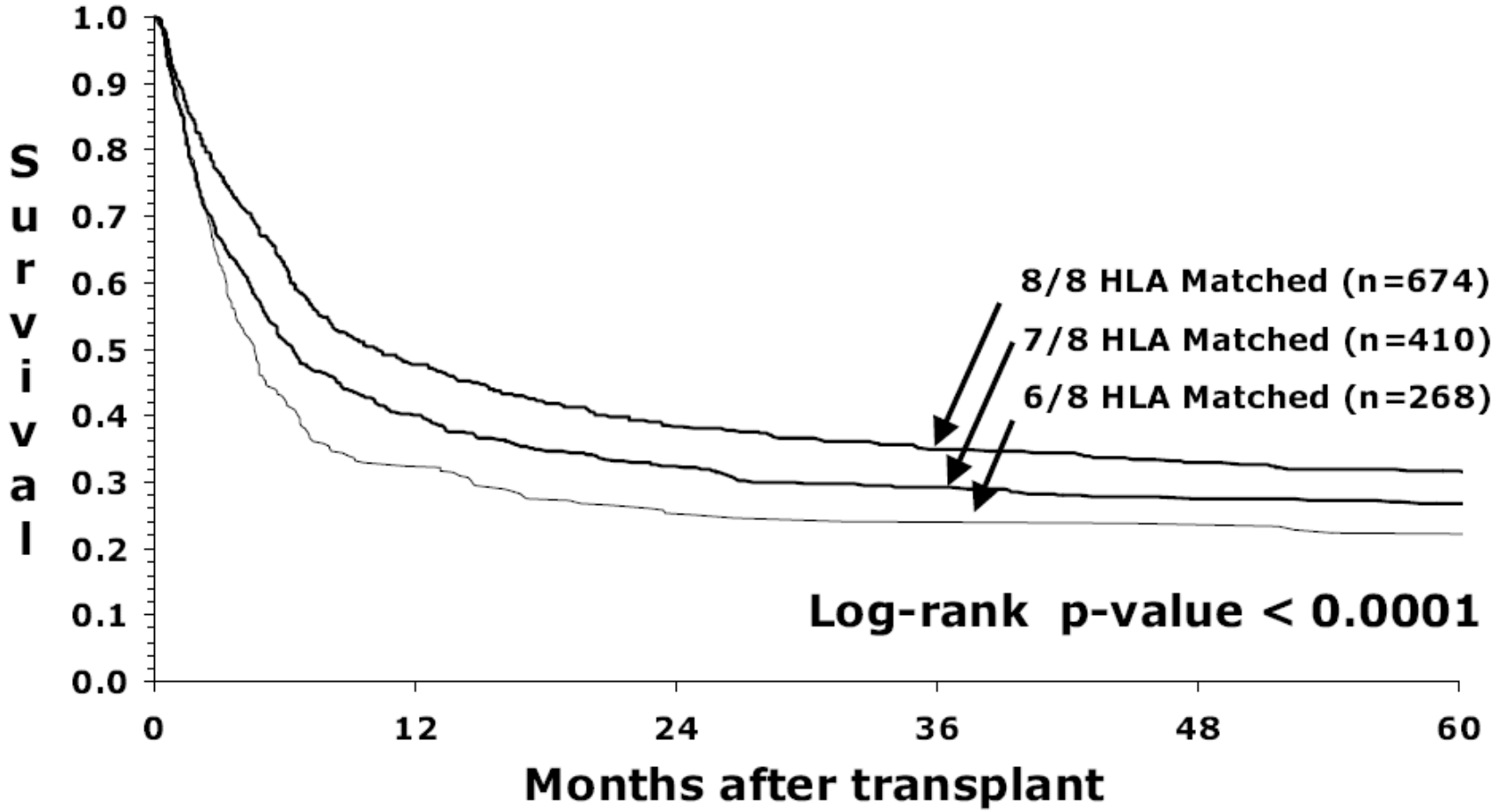
Early stage disease



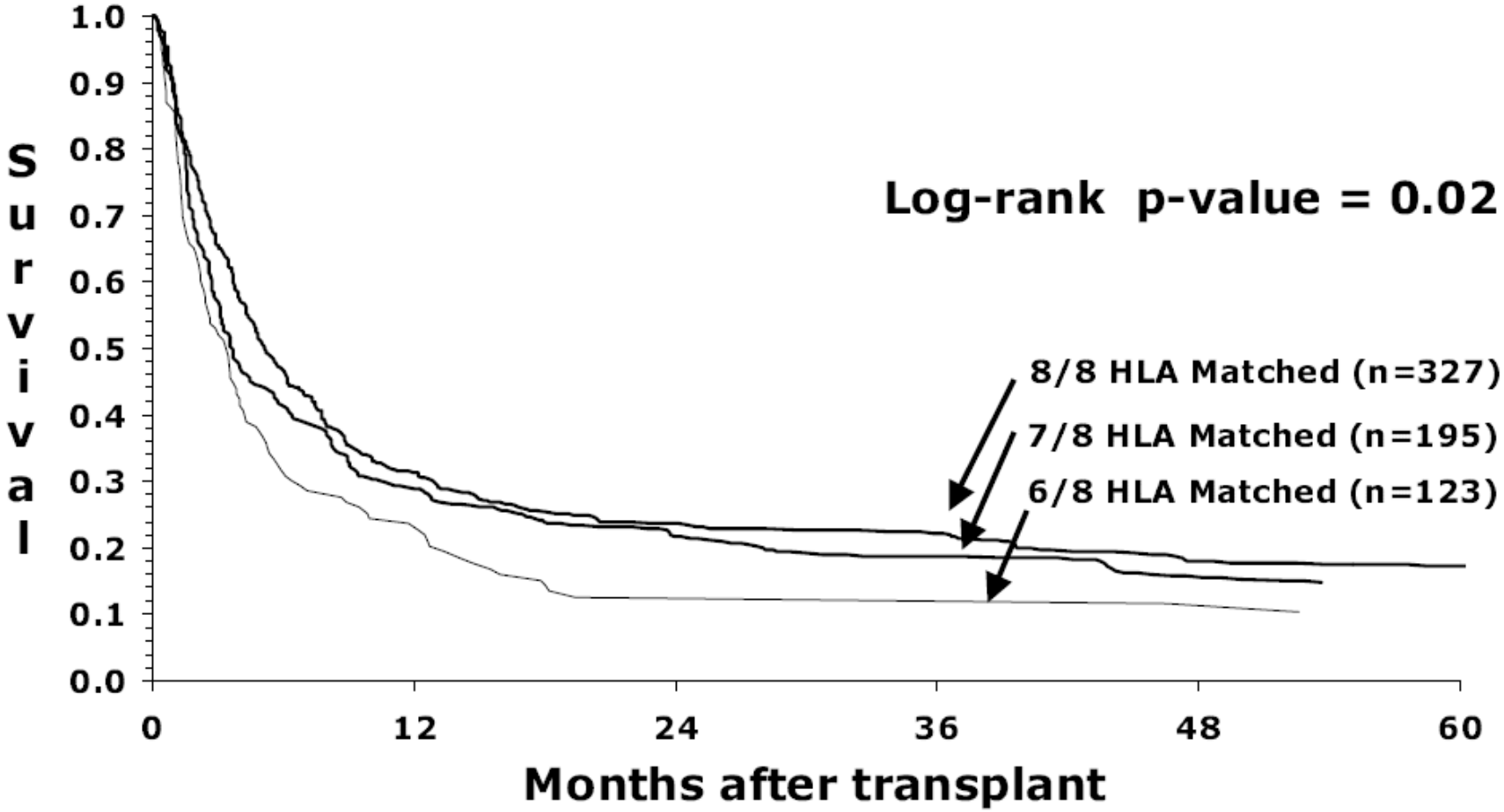
Lee SJ, et al. *B lood.*2007;110(13):4576-4583.10.

Intermediate stage disease



Lee SJ, et al. *Blood.*2007;110(13):4576-4583.10

Advanced stage disease



Lee SJ, et al. *Blood.*2007;110(13):4576-4583.10

Lee Study Conclusions

- High resolution matching of HLA-A, -B, -C, and DRB1 alleles is associated with the best survival
- The adverse effects of allele and antigen mismatches appear equivalent (except at C)
- HLA-DQ matching is not important for survival, TRM or acute GvHD

Lee Study Conclusions, cont.

- Single mismatches HLA-A or DRB1 may be more poorly tolerated than at HLA-B and HLA-C
- Each mismatch is associated with a 9-10% decrease in survival, and the absolute decrement in survival is most pronounced in the early stage patients

Questions to Answer

- Which loci should be evaluated for HLA matching?
- How do antigen mismatches compare to allele mismatches?
- Are some loci more important than others?
- Is bone marrow the same as PBSC?
- What about HLA-DP?
- What about anti-HLA antibodies?
- What about cord blood unit transplants?
- Anything about KIR?

Evaluation of HLA Matching Requirements for Unrelated PBSC Transplantation

Ann Woolfrey, John Klein, Michael Haagenson, Stephen Spellman, Effie Petersdorf, Machteld Oudshoorn, James Gajewski, Gregory Hale, John Horan, Minoo Battiwalla, Susana Marino, Michelle Setterholm, Craig Kollman, Stephanie Lee

On behalf of the
CIBMTR Immunobiology Working Committee

Woolfrey A, et al. *Biol Blood Marrow Transplant 2011;17:885-892.*

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Patient Characteristics (N=1933)

Variable	N (%)
Age, yrs Median (range)	46 (<1-74)
Male	1078 (56)
KPS ≥ 90	1163 (66)
Disease	
AML	946 (49)
ALL	359 (19)
CML	218 (11)
MDS	410 (21)

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Does DQ Matter?

8/8 Match with	N	RR	95% CI	p value
DQB1 match	1125	1.00		
DQB1 allele MM	68	0.97	0.71-1.34	0.87
DQB1 antigen MM	46	1.36	0.95-1.96	0.10

No Significant Effect of DQ Mismatch

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Mortality

	N	RR	95% CI	p value
8/8 match	1243	1.00		
1 allele MM	208	1.11	0.91-1.35	0.30
1 antigen MM	293	1.32	*1.12-1.55*	*0.0007*
2 allele MM	29	1.21	0.77-1.90	0.42
2 antigen MM	31	2.27	*1.55-3.34*	*<0.0001*
2 mixed MM	68	2.32	*1.78-3.02*	*<0.0001*

Mismatch for 1 antigen or >1 allele/antigen increases risk of mortality

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Locus-Specific Analysis — Mortality

	N	RR	95% CI	p value
8/8 match	1243	1.00		
A allele MM	51	1.16	0.80-1.67	0.43
A antigen MM	85	1.17	0.88-1.55	0.29
B allele MM	57	1.29	0.92-1.28	0.14
B antigen MM	16	1.01	0.50-2.04	0.97
C allele MM	61	0.82	0.57-1.19	0.30
C antigen MM	***187***	***1.41***	***1.16-1.70***	***0.0005***
DRB1 MM	39	1.30	0.87-1.94	0.20
C allele vs. antigen		***0.58***	***0.39-0.88***	***0.009***

C antigen mismatch increases risk for mortality, DFS, TRM & GVHD III-IV

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Unrelated Donor PBSC Transplantation Conclusions

- C antigen mismatch confers the greatest risk for poor outcome
- C antigen mismatch is important in both ablative & non-myeloablative HCT
- A larger sample size may reveal additional associations

Lee data (marrow) vs. Woolfrey (PBSC)

- Similar findings
  - One antigen level mismatch at A, B, C, or DRB1 caused worse OS
  - Survival not affected by isolated DQ or DP mismatches
- Woolfrey differs
  - Allele mismatches, no significant effect on survival
    - Far fewer patients to evaluate for comparisons than Lee

Can’t avoid C antigen mismatch?

- Further Lee and Woolfrey data analysis
- *No* significant advantage to using marrow over PBSC as graft source with isolated C antigen mismatch

Questions to Answer

- Which loci should be evaluated for HLA matching?
- How do antigen mismatches compare to allele mismatches?
- Are some loci more important than others?
- Is bone marrow the same as PBSC?
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- What about anti-HLA antibodies?
- What about cord blood unit transplants?
- Anything about KIR?

DPB1 Matching

Studies have suggested that a DPB1 matching does not impact overall survival

- DPB1 match increases relapse risk
- DPB1 mismatch increases acute GVHD and TRM

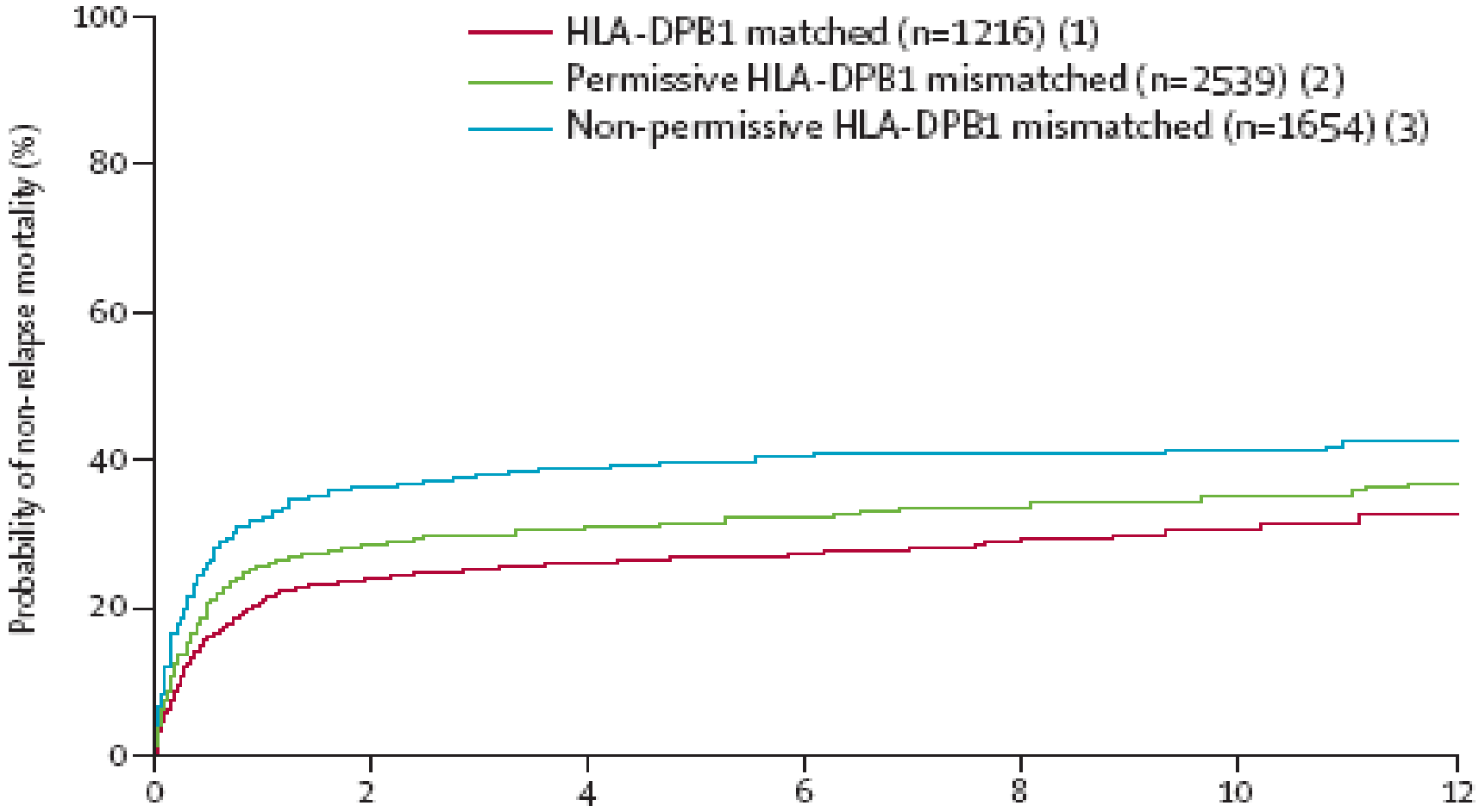
Lack of tight DPB1 linkage with other loci decreases the ease of finding a DPB1 match

- Only ~20% of 10 of 10 matched transplants will be matched for DPB1

DPB1 Permissive Mismatching

- Zino, et al, Blood (2004) 103:1417-1424
  - Grouped DPB1 alleles into groups based on cross-reactive T-cell epitopes
- Created the concept of **permissive** and **non-permissive** mismatches
- DPB1 matches and permissive mismatches are present in ~70% of 10 of 10 matched transplants

DPB1 and 10/10 donors, NRM



Fleischhauer K, et al. *Lancet Oncol.* 2012; 13(4):366-374.

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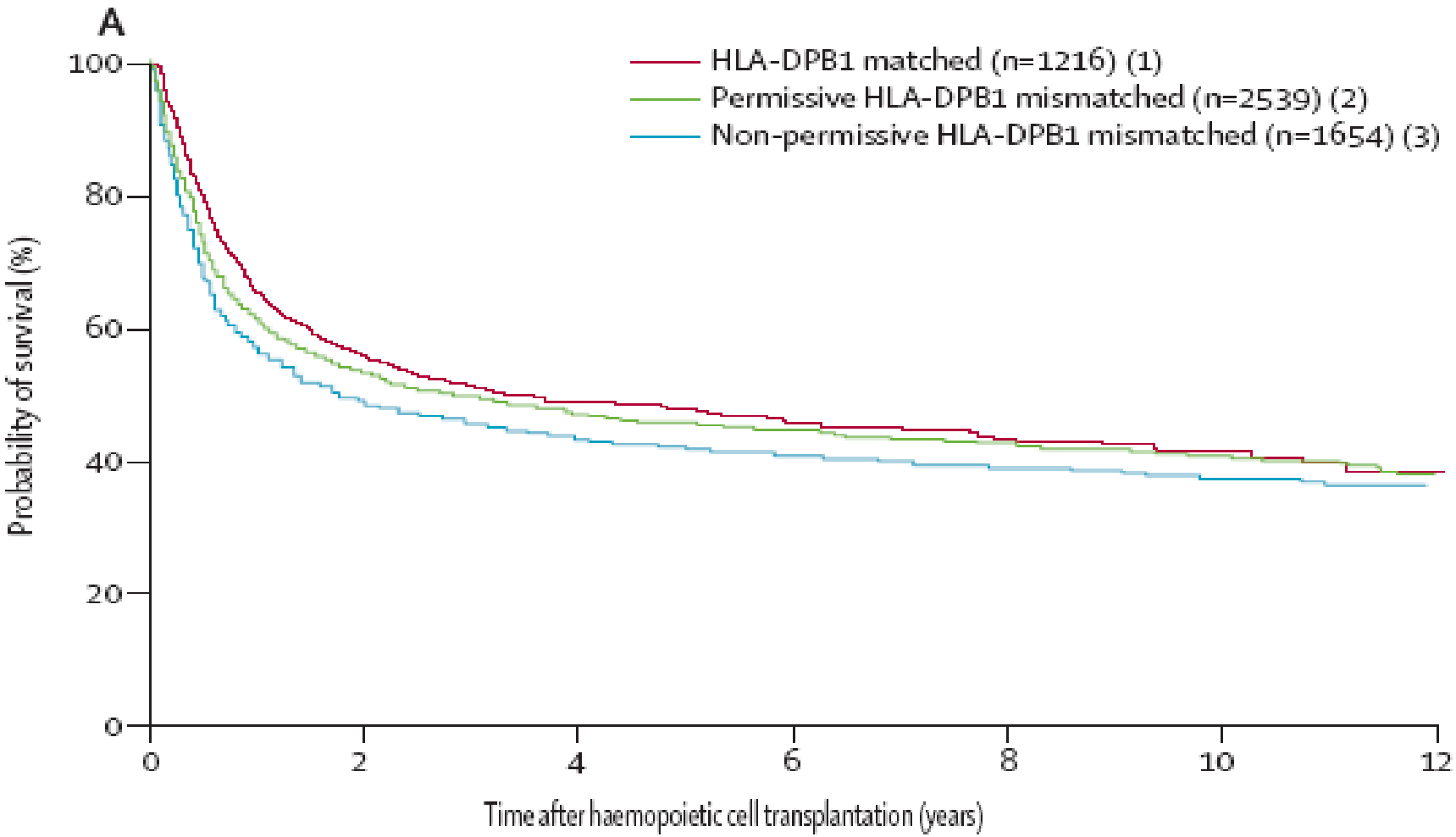
10 of 10 HLA-matched with DPB1 Assessment



Fleischhauer K, et al. *Lancet Oncol.* 2012; 13(4):366-374

DPB1 Permissive Mismatches May Benefit 9 of 10 Matched Transplant

	HLA 10/10 match, non-permissive DPB1 mismatch (n=1654)	HLA 9/10 match, permissive DPB1 mismatch (n=1595)		HLA 9/10 match, DPB1 match (n=500)	
		HR or OR	p value	HR or OR	p value
Overall mortality	1 (ref)	1·04 (0·94–1·14)	0·39	1·02 (0·89–1·18)	0·70
Non-relapse mortality	1 (ref)	1·01 (0·90–1·13)	0·81	1·00 (0·84–1·19)	0·98
Relapse*	1 (ref)	1·12 (0·96–1·31)	0·14	1·16 (0·92–1·45)	0·19
Grade 3–4 aGvHD	1 (ref)	1·00 (0·84–1·19)	0·97	0·93 (0·72–1·21)	0·62

Fleischhauer K, et al. *Lancet Oncol.* 2012; 13(4):366-374

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DPB1 Permissive Mismatches May Benefit 9 of 10 Matched Transplant

	HLA 10/10 match, non-permissive DPB1 mismatch (n=1654)	HLA 9/10 match, non-permissive DPB1 mismatch (n=1001)	
		HR or OR	p value
Overall mortality	1 (ref)	1·13 (1·02–1·26)	0·01
Non-relapse mortality	1 (ref)	1·19 (1·05–1·35)	0·006
Relapse*	1 (ref)	1·04 (0·87–1·24)	0·64
Grade 3–4 aGvHD	1 (ref)	1·36 (1·13–1·65)	0·001

Fleischhauer K, et al. *Lancet Oncol.* 2012; 13(4):366-374

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Questions to Answer

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- What about cord blood unit transplants?
- Anything about KIR?

THE DETECTION OF DONOR-DIRECTED, HLA-SPECIFIC ALLOANTIBODIES IN RECIPIENTS OF UNRELATED HEMATOPOIETIC CELL TRANSPLANTATION IS PREDICTIVE OF GRAFT FAILURE

Stephen Spellman, Robert Bray, Sandra Rosen-Bronson, Michael Haagenson, John Klein, Susan Flesch, Cynthia Vierra-Green, and Claudio Anasetti

Spellman S, et al. *Blood. 2010;115:2704-2708.*

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Background

- Alloantibodies directed against mismatched HLA antigens are well established as a significant risk factor in solid organ transplantation (renal, cardiac and pancreas)

- Previous studies in humans and recent animal studies have indicated a role for donor-specific HLA antibodies (DSA) as a risk factor for rejection of hematopoietic stem cell transplants

Study Design

- Retrospective, case-controlled study of recipients who received an unrelated stem cell transplant (SCTx) facilitated through the NMDP
- The study group was selected based on:
  - Preferred mismatched HCT (antigen or allele)
  - Survival past day 28
  - No sustained engraftment
  - Serum samples available in repository
- A total of 37 patients and 78 case-matched controls (2-3 to 1) were tested

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Study Design

- Controls were matched for disease, disease status, graft type, age, sex and year of transplant (1990-2002)
- Diseases included AML, CML, ALL, and MDS
- 98% Myeloablative Conditioning
  97% Bone Marrow Stem cells
  97% Calcineurin-Based GvHD Prophylaxis
  100% T-Replete Grafts

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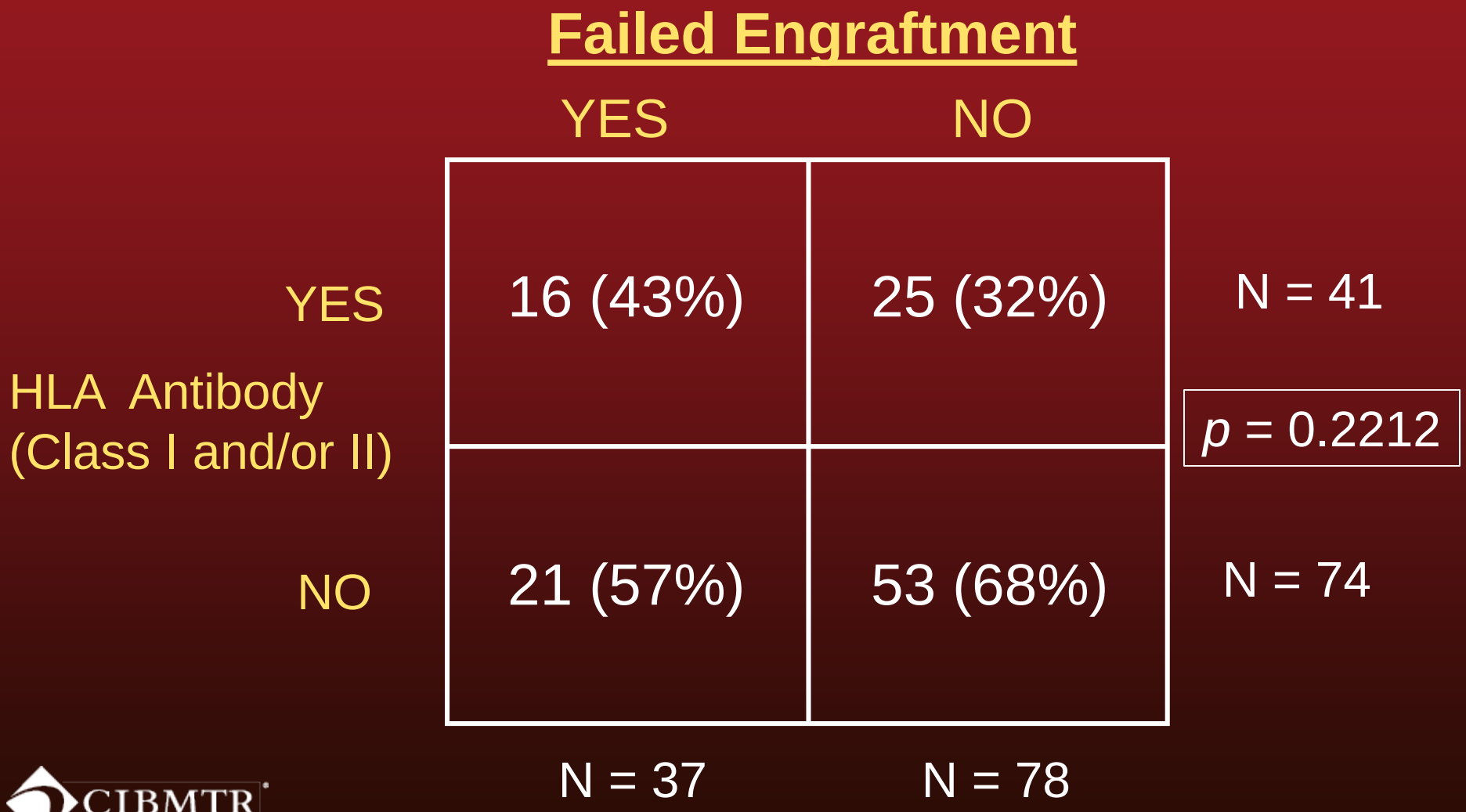
Lack of Association Between the Presence of HLA Antibody and Graft Failure



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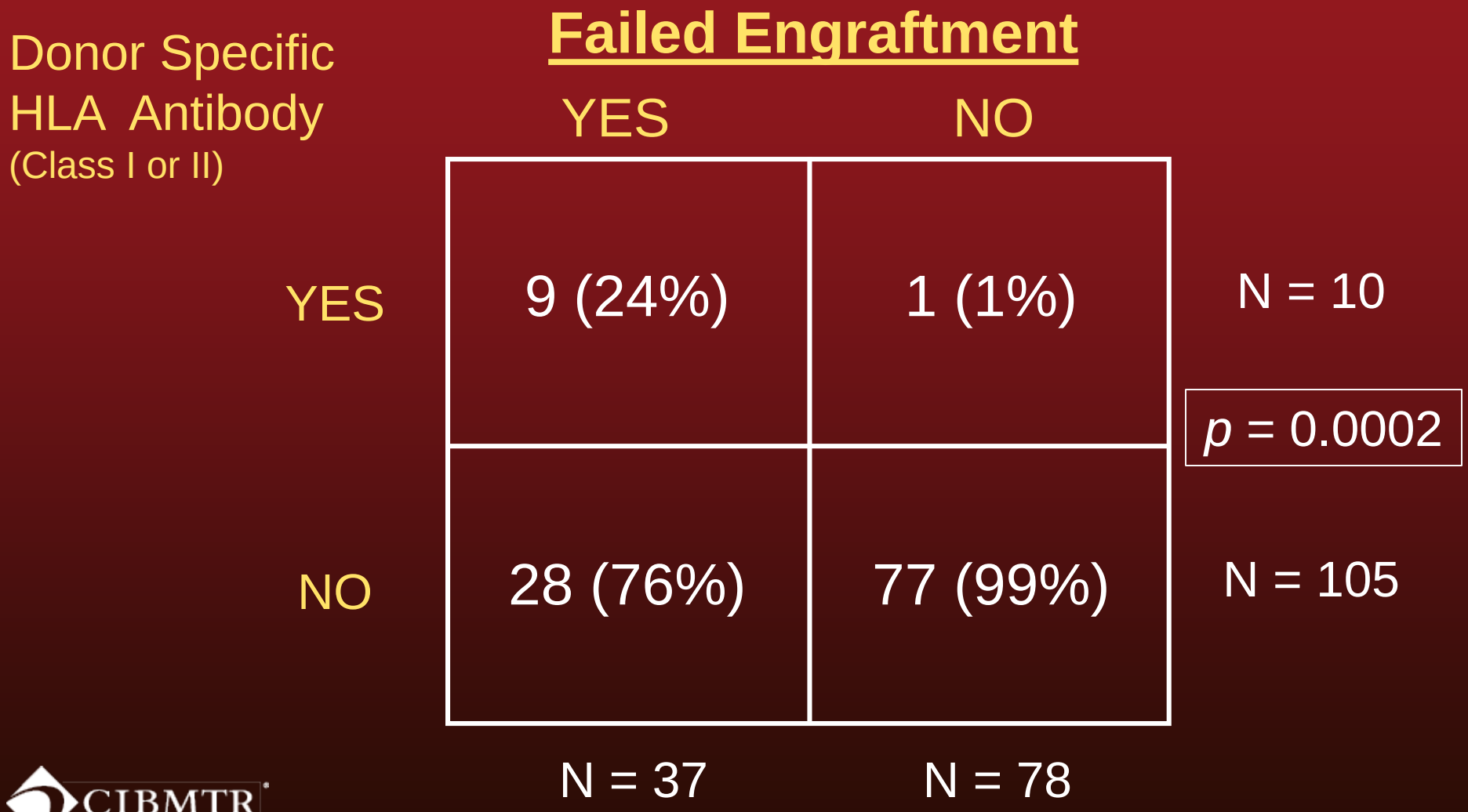
Positive Association Between the Presence of DSA and Graft Failure



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Study Conclusions

- Approximately 35% of patients receiving unrelated stem cell transplants possess HLA antibodies
- The presence of donor-specific HLA antibodies against HLA-A, B and/or DP as determined by solid-phase testing, associates with graft failure
- HLA antibody evaluations should be a part of the routine workup for unrelated stem cell transplantation

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Questions to Answer

- Which loci should be evaluated for HLA matching?
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- Are some loci more important than others?
- Is bone marrow the same as PBSC?
- What about HLA-DP?
- What about anti-HLA antibodies?
- What about cord blood unit transplants?
- Anything about KIR?

Fewer cord data available

- Better HLA matching + higher cell dose are significant in UCB outcomes
  - > 1,000 recipients

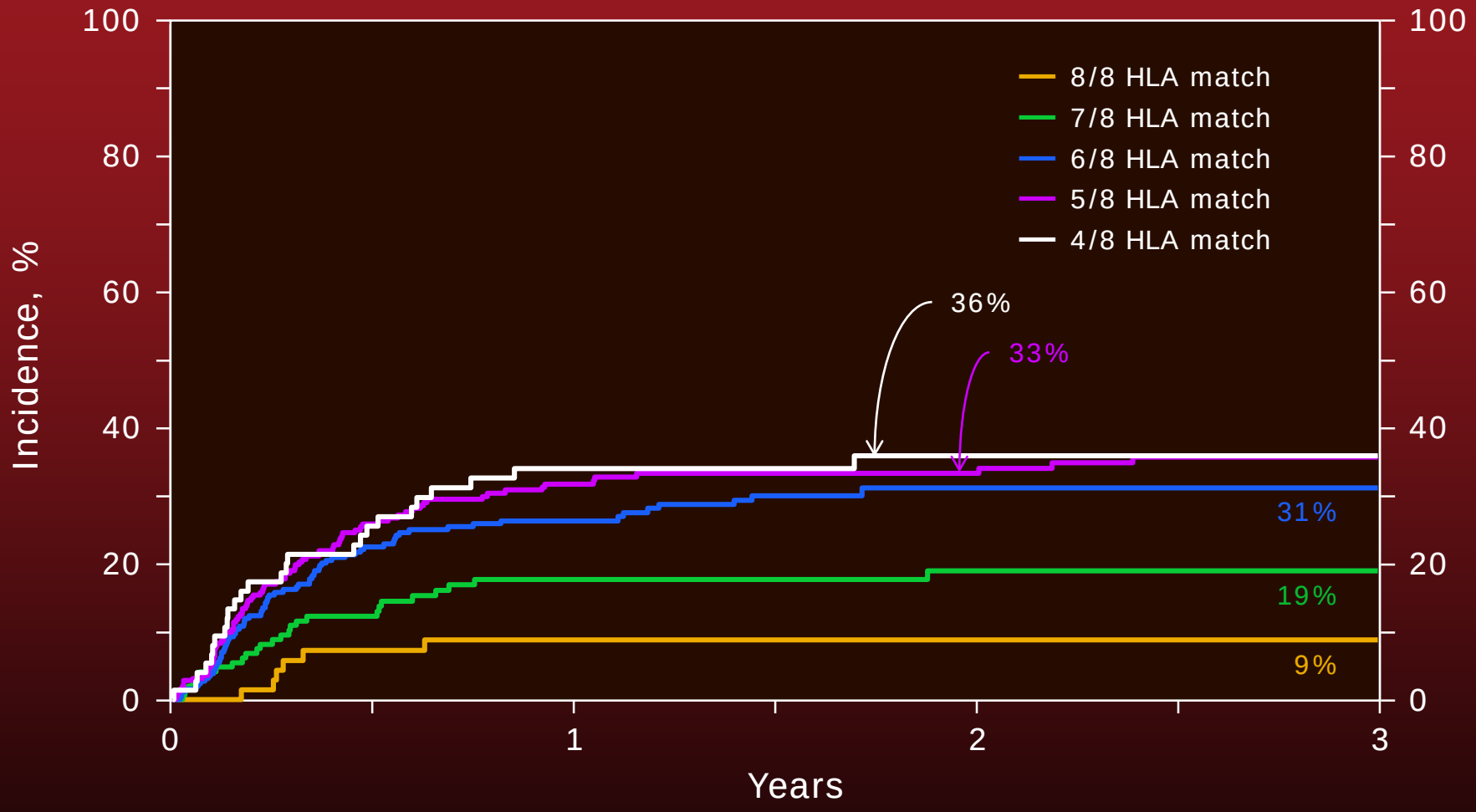
Barker JN, et al. *Blood. 2010;115(9):1843-1849.*

UCB and mismatch location data

- **C antigen** mismatch associated with higher mortality
- If 2 locus mismatches among the 4 major HLA loci, **C/DRB1** combo had highest mortality

Eapen M, et al. *Lancet Oncol. 2011;12(13):1214*-1221.

Transplant-related Mortality



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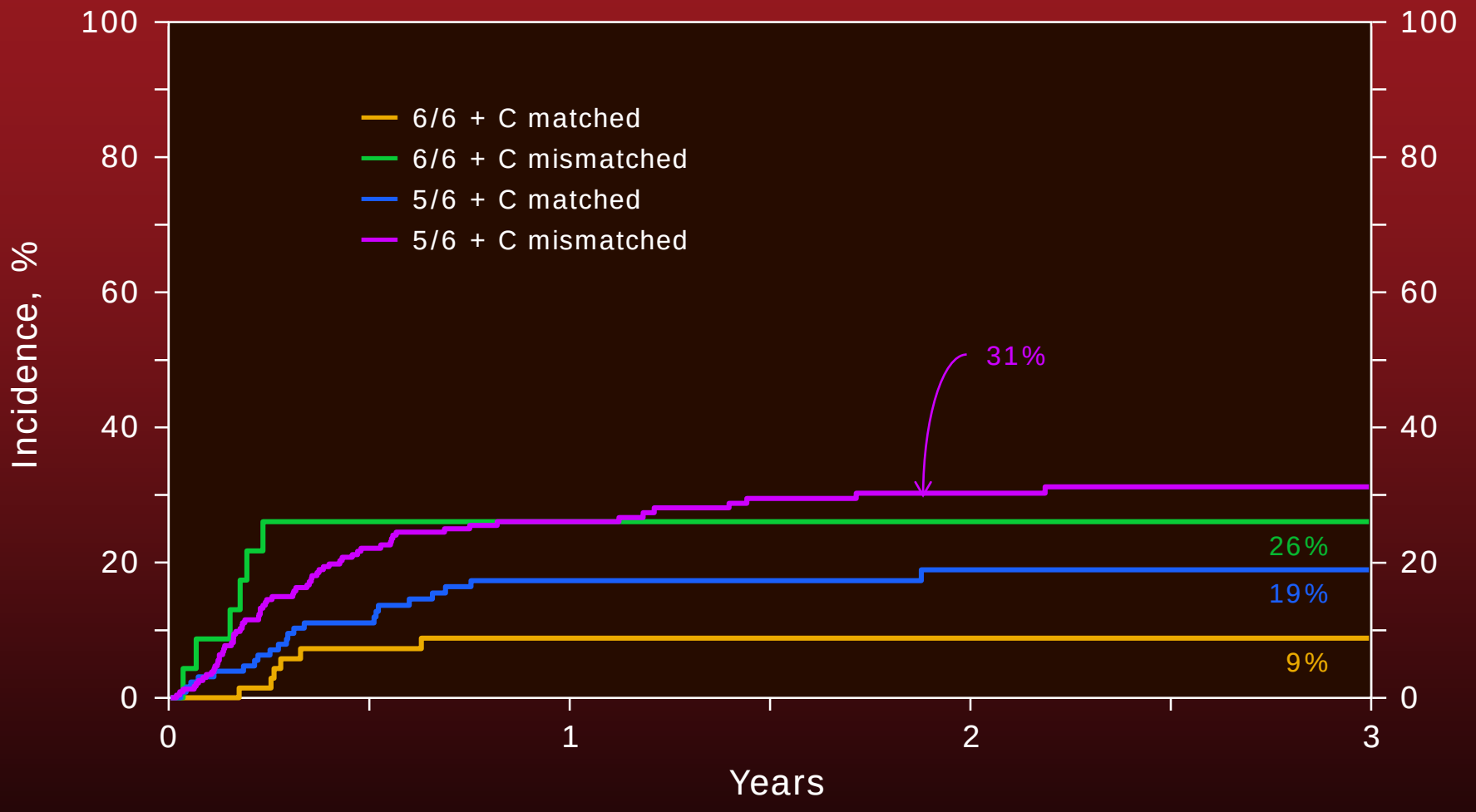
Eapen et al. Lancet Oncol 2011;12(13):1214-1221.

Treatment-related Mortality



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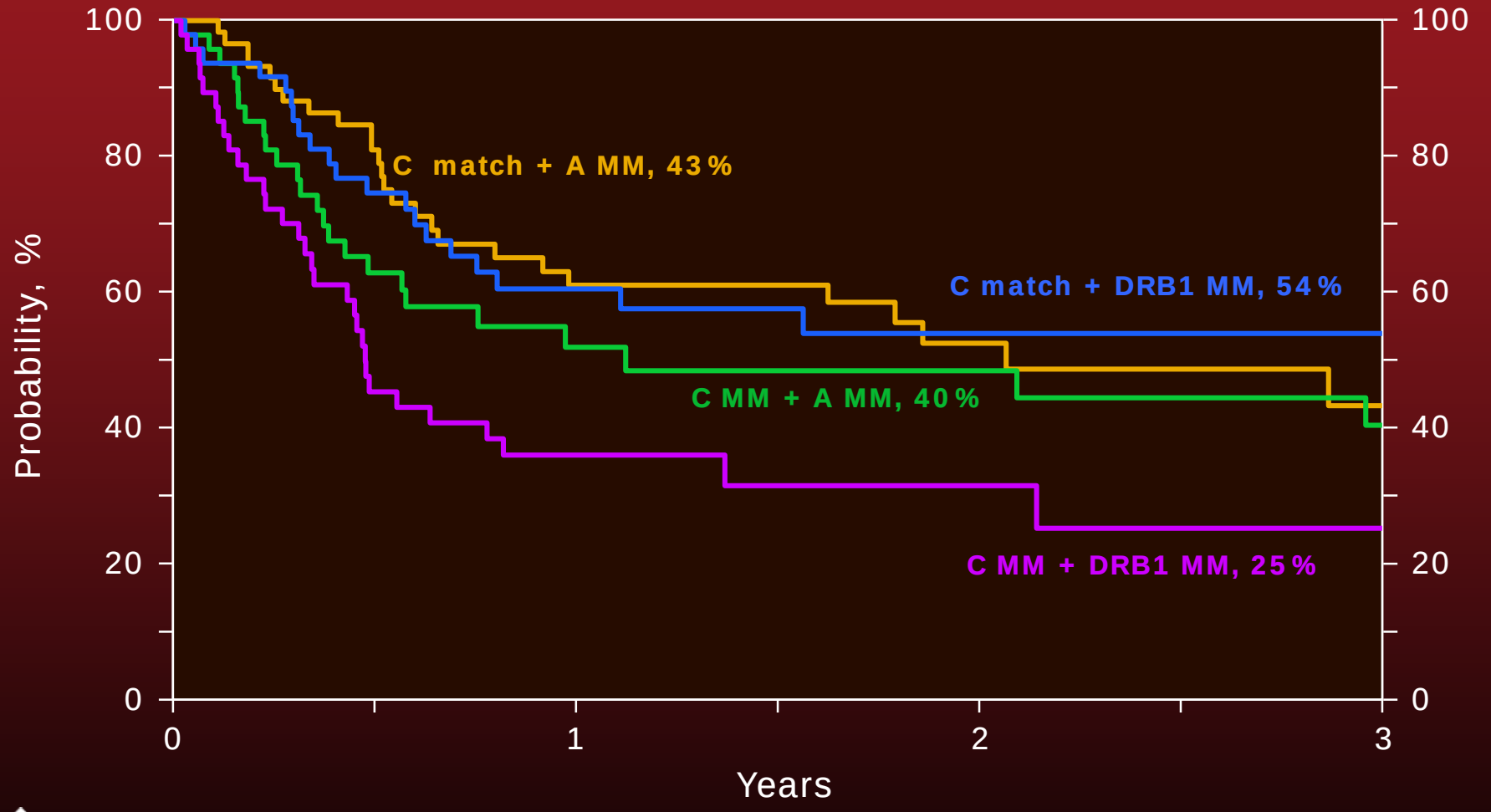
Eapen et al. Lancet Oncol 2011;12(13):1214-1221.

Overall Survival

- Mismatch at HLA-C + HLA A or DRB1 -



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Eapen et al. Lancet Oncol 2011;12(13):1214-1221.

Double Cord Blood Unit Transplant

- Some centers use two unit to increase cell dose
- No studies evaluate cord to cord matching
  - Currently, no standard practice
    - Some protocols match ≥ 3/6 cord to cord
    - Others require ≥ 4/6

Non-Inherited Maternal Antigens (NIMA)

	HLA-A	HLA-B	HLA-DRB1
NIMA matched *			
UCB unit/donor	A*02, 32	B*18, 35	DRB1*01:01, 11:04
UCB donor mother	A*24, 32	B*07, 35	DRB1*01:01, 13:01
Recipient	A*02, 24	B*18, 35	DRB1*01:01, 11:04

* HLA-A*24 is not carried by UCB donor. HLA-A*24 is carried by the UCB donor's mother and the recipient; thus, this is an NIMA-matched UCBT

van Rood JJ, et al. Proc Natl Acad Sci U S A 2009;106:19952-19957.

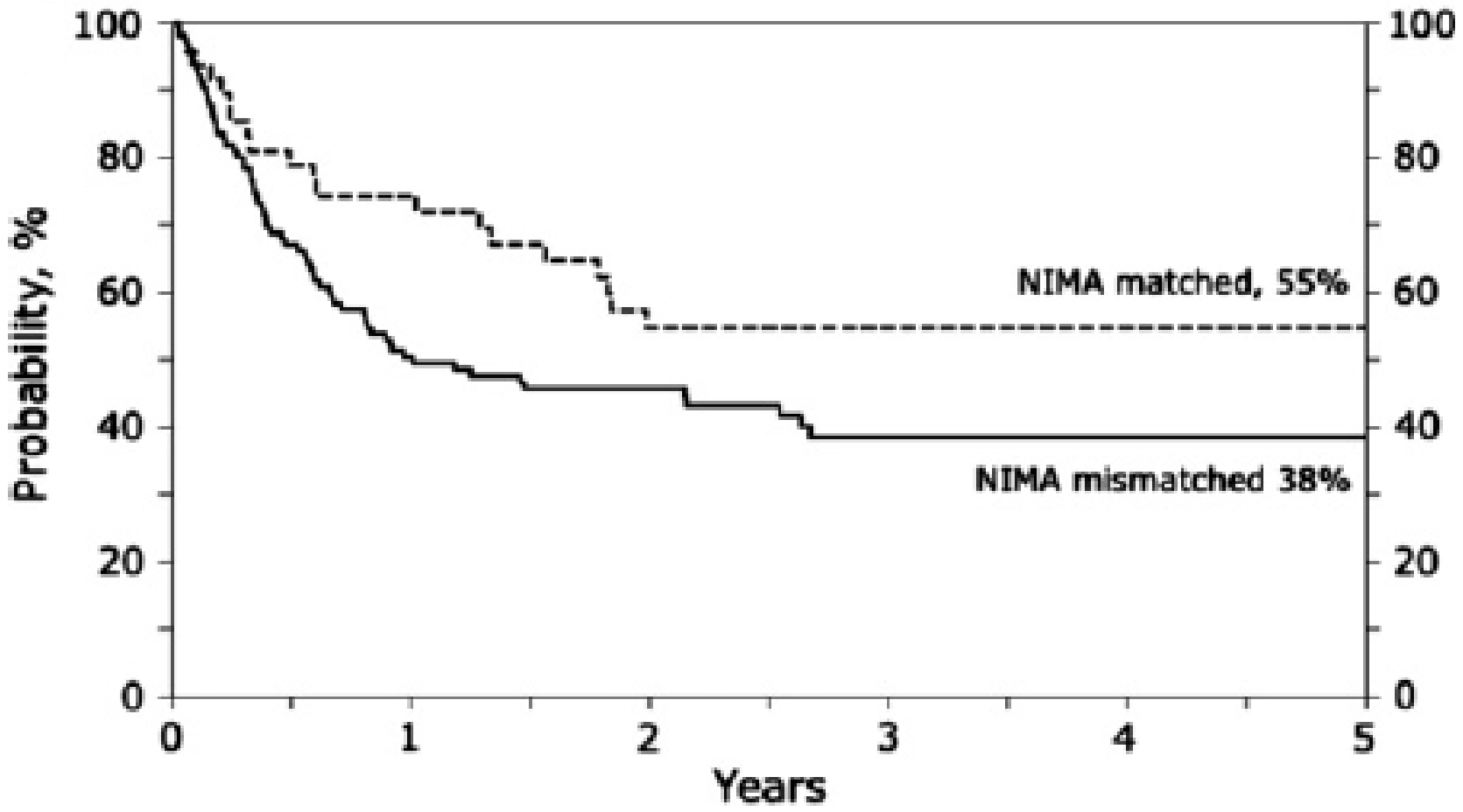
Rocha V, et al. *Biol Blood Marrow Transplant, 2012 July 17 Epub*

NIMA mismatch

	HLA-A	HLA-B	HLA-DRB1
NIMA matched *			
UCB unit/donor	A*02, 32	B*18, 35	DRB1*01:01, 11:04
UCB donor mother	A*24, 32	B*07, 35	DRB1*01:01, 13:01
Recipient	A*01, 02	B*18, 35	DRB1*01:01, 11:04

* HLA-A*01 is not carried by UCB donor or the UCB donor's mother; thus, this is an NIMA-mismatched UCBT

NIMA Matching Survival Data



Rocha V, et al. *Biol Blood Marrow Transplant, 2012 July 17 Epub*

Why not insist on UCB NIMA matching?

- NIMA matches relatively rare
- In the Rocha and van Rood studies, only 7-10% of transplants were NIMA matched
- Relative frequency of the mismatched antigen(s) will strongly influence the ability to find a NIMA match
- Searching for NIMA match may delay transplant

Questions to Answer

- Which loci should be evaluated for HLA matching?
- How do antigen mismatches compare to allele mismatches?
- Are some loci more important than others?
- Is bone marrow the same as PBSC?
- What about HLA-DP?
- What about anti-HLA antibodies?
- What about cord blood unit transplants?
- Anything about KIR?

KIR – Insufficient Data

- KIR (natural killer cell immunoglobulin-like receptors) and KIR Ligands
  - Early studies showed survival advantage for AML
  - Subsequent studies, varied conclusions
- No current data to unequivocally indicate that class I mismatching in unrelated donor HCT should be preferred in any clinical circumstance
  - Donor selection based on KIR should only be considered within the context of a clinical trial

Recent Update to Matching Guidelines

blood

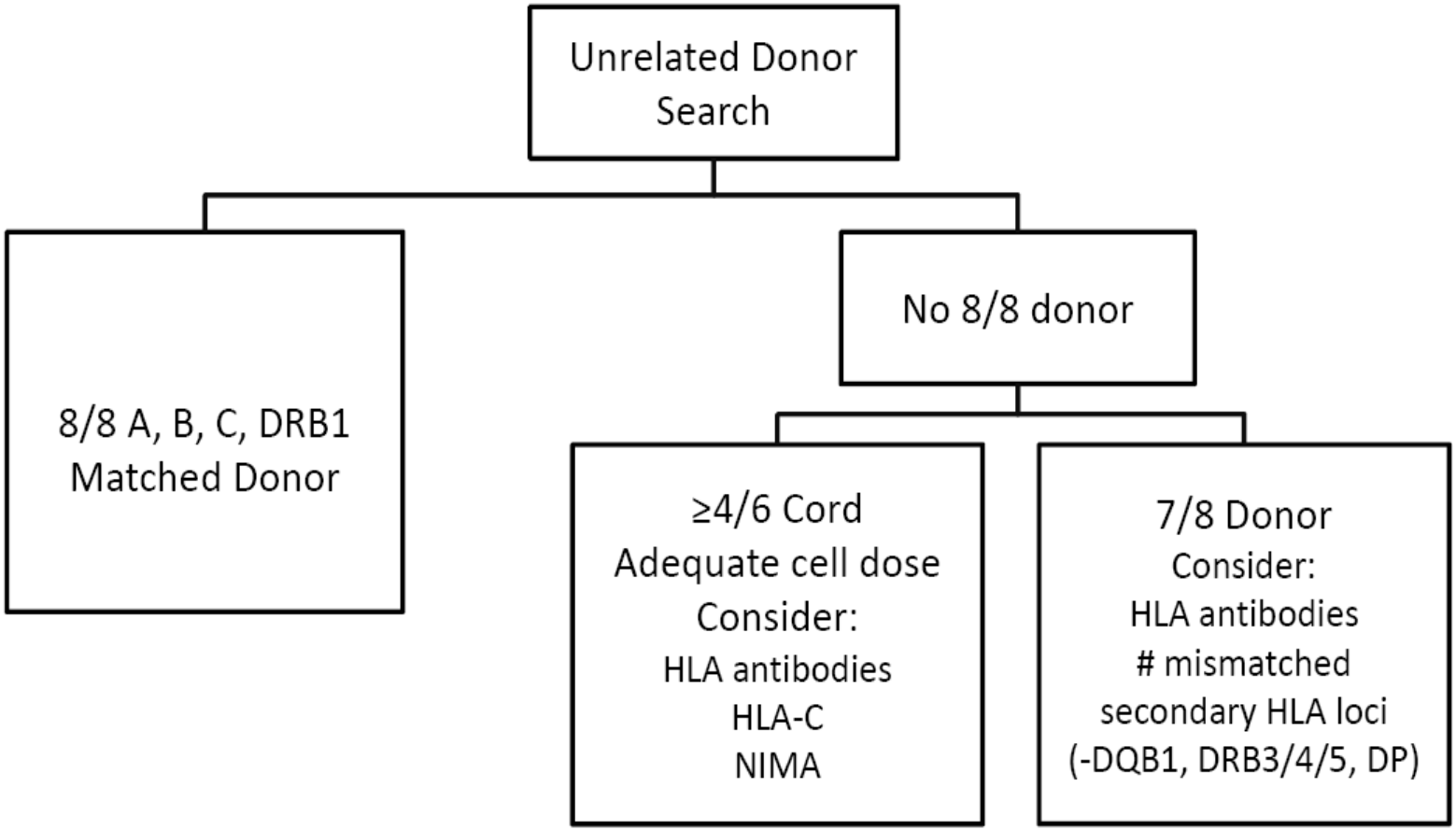
2012 120: 259-265
Prepublished online May 17, 2012;
doi:10.1182/blood-2012-03-379032

A perspective on the selection of unrelated donors and cord blood units for transplantation

Stephen R. Spellman, Mary Eapen, Brent R. Logan, Carlheinz Mueller, Pablo Rubinstein, Michelle I. Setterholm, Ann E. Woolfrey, Mary M. Horowitz, Dennis L. Confer and Carolyn K. Hurley

Spellman SR, et al. Blood (2012) 120:259-265

Recap: Graft source selection chart



Recap: Optimal donor matching, 8/8

- High likelihood of an 8/8 donor
  - Consider DQ, DP, and DRB3/4/5
  - Consider nature of DPB1 mismatches
    - Favor DPB1 match or permissive mismatch

Recap: Optimal donor matching, 7/8

- Marrow
  - B or C mismatches *may* be less detrimental than A or DRB1
  - Favor donors with the lowest cumulative number of DP, DQ, and DRB3/4/5 mismatches when other matching criteria equal
- PBSC
  - Avoid C antigen mismatch when possible
  - Allele mismatch *may* be better tolerated than antigen mismatch

Recap: Optimal cord selection

- Favor extended HLA matching and higher cell dose
- C antigen mismatch associated with higher TRM
- C/DRB1, likely most detrimental pair of mismatches
- Can increase cell dose with double cords
- May consider NIMA matching as a tiebreaker among similarly mismatched units if no transplant delay

HLA expert advice

- Local or NMDP HLA expert
- search-strategies@nmdp.org
  - HLA search strategy team provides commentary and donor/cord recommendations for NMDP searches
  - Focus on donors/cords most likely to match
  - Guide you to optimal CT selections with efficient typing strategies

Acknowledgments

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Thank you for participating

- You may continue to listen to this recording to hear the question and answer session from our live event.

Q & A

- Thanks for your attention
- Questions?