Bone Marrow, Peripheral Blood Stem Cells or Umbilical Cord Blood transplantation?

E. Gluckman

WBMT meeting

Cape Town November 14-16, 2014

The ideal HSCs source

- Immediate availability
- Few **HLA restrictions** & adequate **cell dose**
- **Absence of risk for the donor**
- Applicable to all diseases and all ages
- Associated with:

  - rapid immuno-hematopoietic recovery
  - potent graft versus malignancy effect
  - little risk of acute and chronic GvHD
  - high disease free survival

Sources of HSCs

Bone Marrow (BM)

- ✓ *Aspirated from the posterior iliac crests under either local or general anesthesia*
- ✓ *Filtered and directly infused*

Peripheral Blood (PB)

- ✓ *Following mobilization (with growth factors)*
- ✓ *Collected by apheresis*

Umbilical Cord Blood (UCB)

- ✓ *Collected at birth*
- ✓ *Processed and cryopreserved in CB banks*

Type of donors

- **Autologous** → **Patient's own HSCs**
- **Allogeneic**
  - **Syngeneic donor** (identical twin) → **HLA-MATCHED (M)**
  - **Related donor** (sibling or other relative) → **HLA-M or HLA- MISMATCHED (MM) or HAPLOIDENTICAL**
  - **Unrelated donor** → **HLA-M or HLA-MM**

Allogeneic HSCT

To cure **malignant** and **non malignant** disorders

MA, NMA or RI conditioning chemotherapy (with or without TBI)

- **Eradicate the malignancy**
- **Create space to host donor's HSCs**
- **Immunosuppression to prevent graft rejection**

-**Create space to host donor's HSCs**
- **Immunosuppression to prevent graft rejection**

Infusion of donor's HSCs

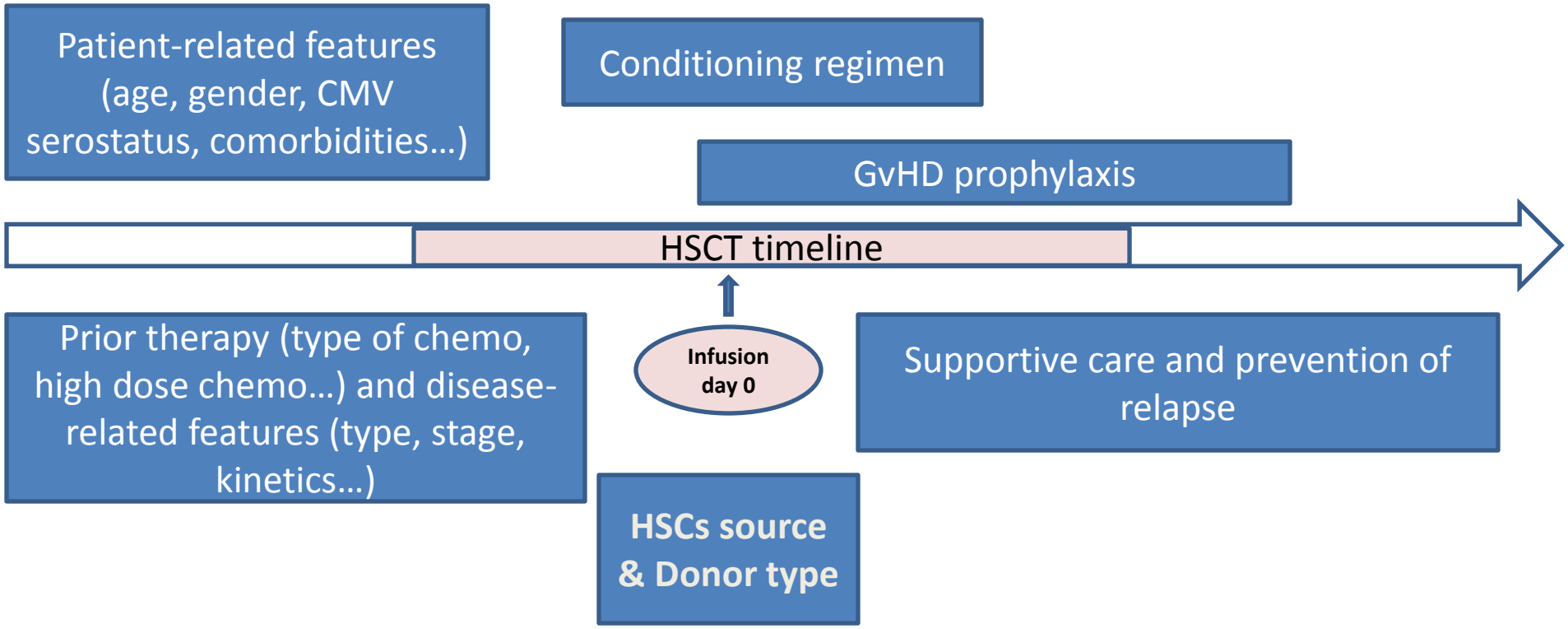
Graft versus tumor effect
(AML, ALL, MDS, MPN, HL, NHL, MM)

Recipient's hematopoiesis replacement
(Hbpathies, BMFS, Metabolic disorders, Immune deficiencies,)

Immunosuppressive prophylaxis to prevent GvHD

Allogeneic HSCT

Critical issues affecting outcomes*



*Survival, Engraftment, Morbidity (GvHD, immunological reconstitution, infections), Disease control (GvL effect)

Donor choice

HLA matched sibling (BM/PB) = first choice

25% pts

Alternatives

- **HLA-MM or Haploidentical related PB/BM**
- **HLA-M/MM adult unrelated (donor registries) PB/BM**
- **Related/unrelated HLA-M/MM UCB (CB banks)**

- ✓ **Relative merits of unrelated adult donors *vs* UCB *vs* haplo remains to be determined**
- ✓ **Most centres prefer the use of adult unrelated donors over the other alternative HSCs sources**

Cellular Characteristics

	BM	PB	UCB
Volume collected	700-1500 ml	150-400 ml	80-160 ml
Median CD34 content (x 10^6/kg*)	2-3	8-10	0.2
Median T cells content (x 10^6/kg*)	25	250	2.5
Target cell dose	> 2 x 10^8 (TNC /kg*)	5-10 x 10^6 (CD34+ /kg*)	> 0.3 x 10^8 (TNC /kg*)

* of recipient body weight

✓BM: high volume
✓PB: higher CD34 and T cells content
✓UCB: lower CD34 but *highly proliferative*, lower and *immature* T cells

Clinical Characteristics

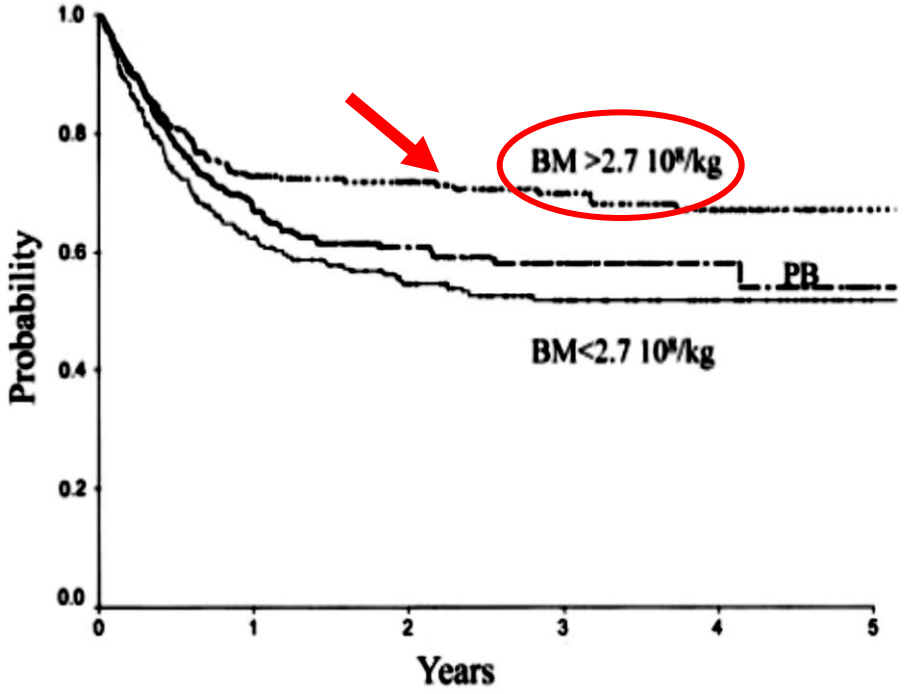
	BM	PB	UCB
HLA matching	Restrictive	Restrictive	Less restrictive (>tolerance)
Engraftment	Faster than CB but slower than PB	Fastest	Slowest
Acute GvHD	++	++/+++	+
Chronic GvHD	++	+++	+
Graft vs Tumor effect	++	++/+++	+++
Availability	Depends on donor type	Depends on donor type	Immediate access (CB banks)
Donor's Risk	Anesthesia Surgical Procedure	Use of GF Apheresis	None

Comparison Bone marrow vs PBSC

Marrow versus peripheral blood for geno-identical allogeneic stem cell transplantation in acute myelocytic leukemia: influence of dose and stem cell source shows better outcome with rich marrow

Norbert C. Gorin, Myriam Labopin, Vanderson Rocha, William Arcese, Meral Beksac, Eliane Gluckman, Olle Ringden, Tapani Ruutu, Josy Reiffers, Giuseppe Bandini, Michele Falda, Panagiotis Zikos, Roelf Willemze, and Francesco Frassoni, for the Acute Leukemia Working Party (ALWP) of the European Cooperative Group for Blood and Marrow Transplantation (EBMT)

LFS of patients receiving transplants with high-dose BM, low-dose BM, or PBSCs



➔ **In multivariate analyses, high-dose BM compared to PBSC was associated with lower TRM (RR 0.61; 95% CI, 0.39-0.98; *P* .04), better leukemia-free survival (RR 0.65; 95% CI, 0.46-0.91; *P* .013), and better overall survival (RR 0.64; 95% CI, 0.44-0.92; *P* .016).**

Blood 2003;102:3043-3051

Allogeneic Peripheral Blood Stem-Cell Compared With Bone Marrow Transplantation in the Management of Hematologic Malignancies: An Individual Patient Data Meta-Analysis of Nine Randomized Trials

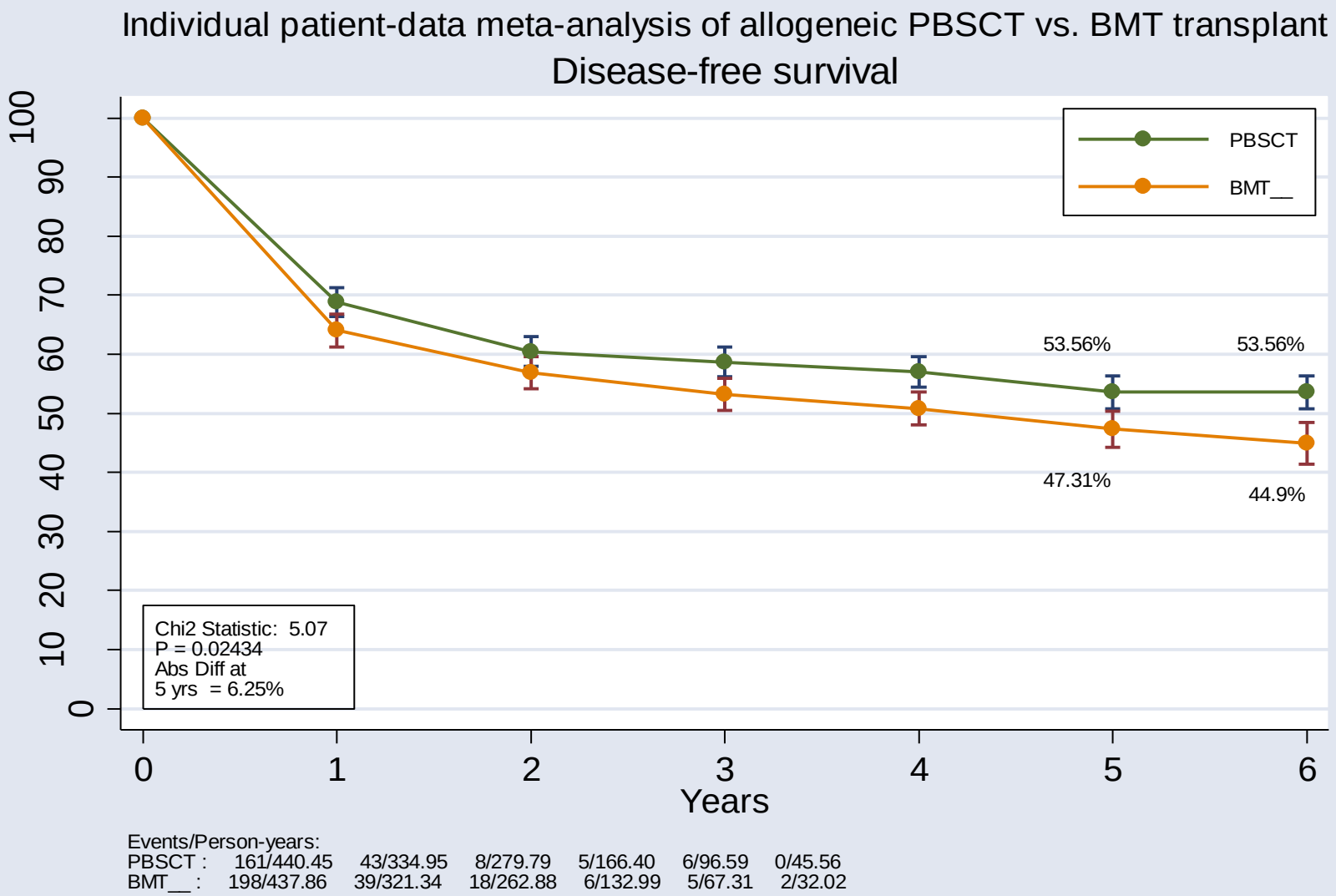
Stem Cell Trialists' Collaborative Group

VOLUME 23 · NUMBER 22 · AUGUST 1 2005

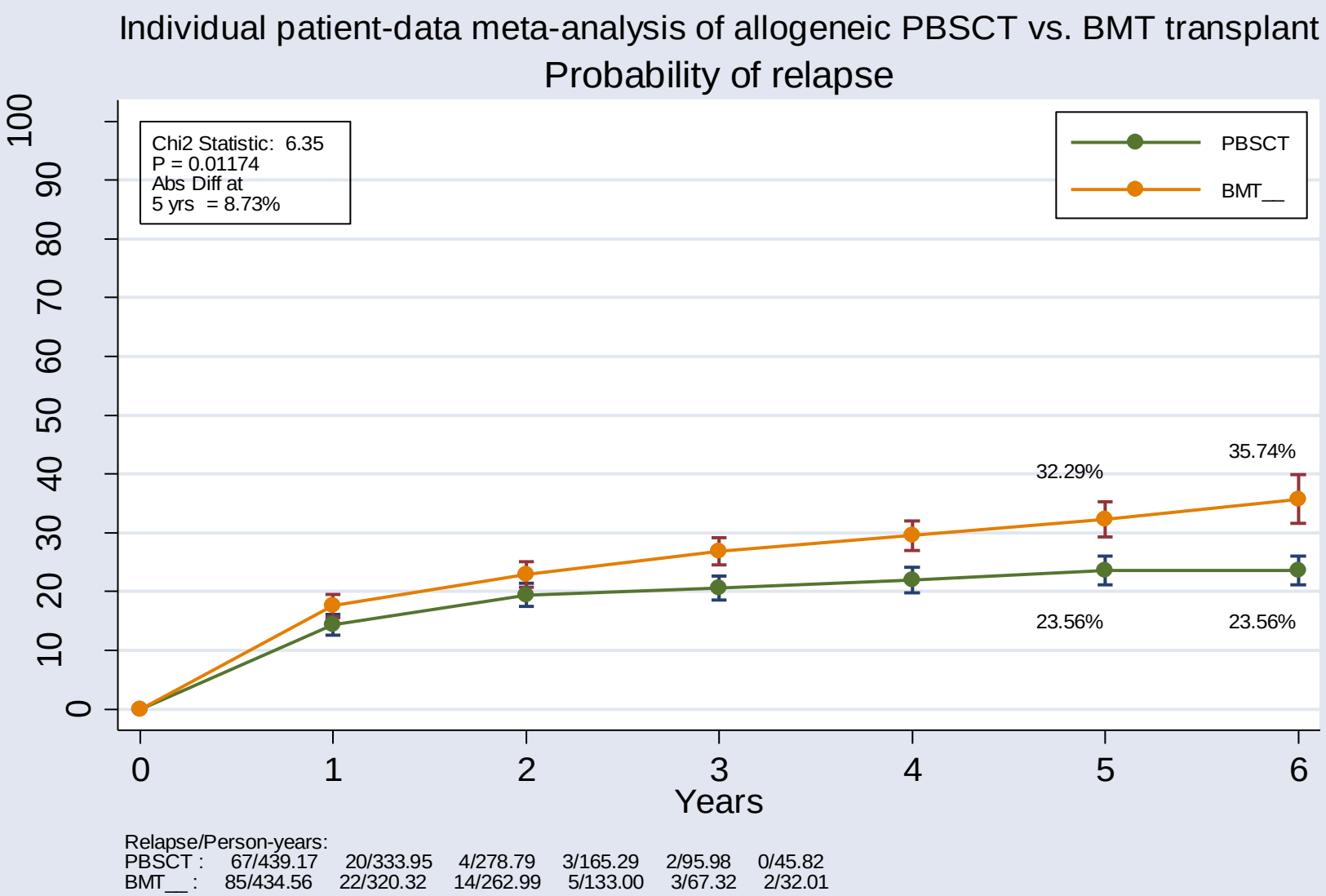
JOURNAL OF CLINICAL ONCOLOGY

- **12 randomized trials have been conducted**
  - **To answer the question which allo-SCT source is better**
- **No consistent results between trials were seen for any of the major outcomes**

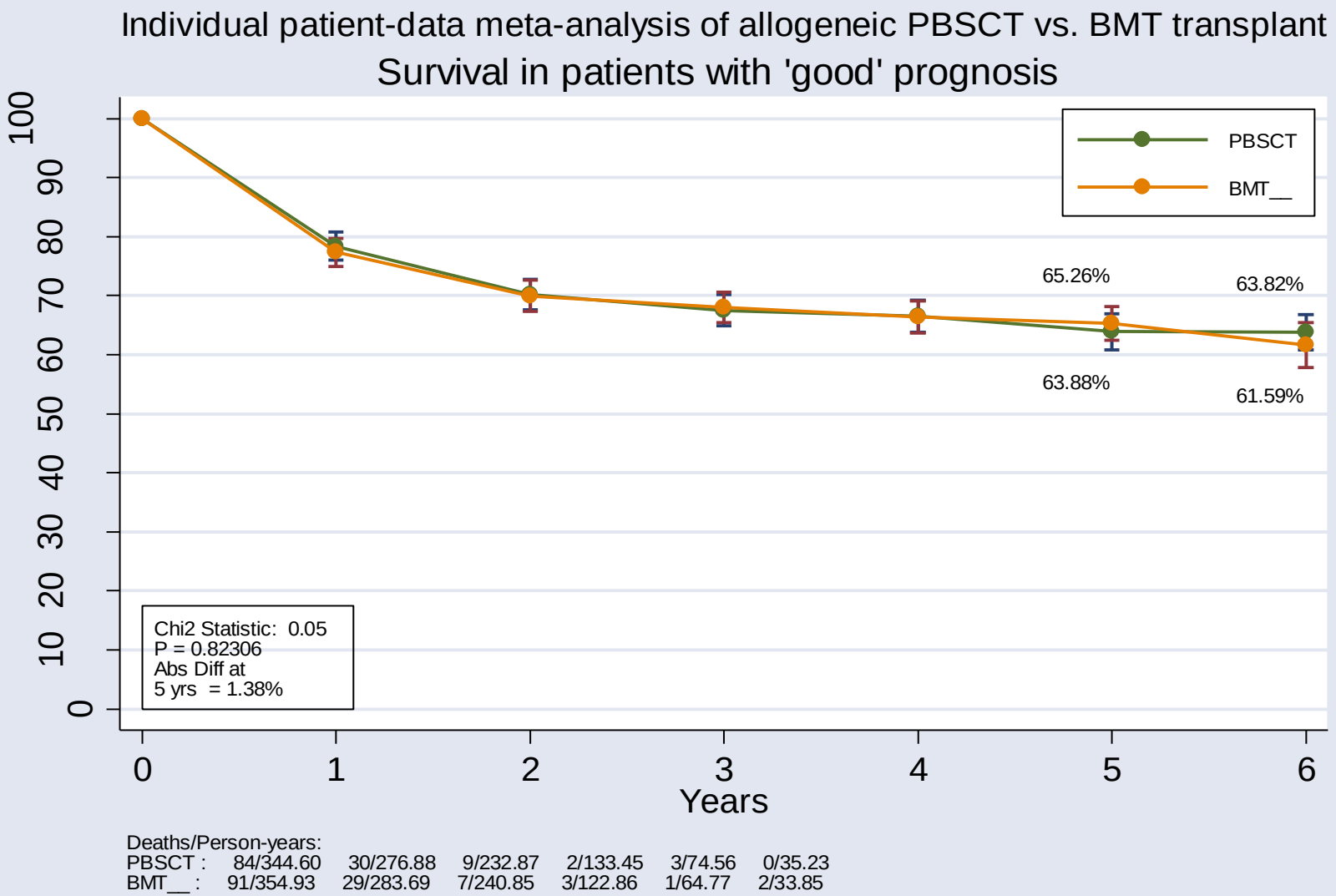
Effect on disease-free survival



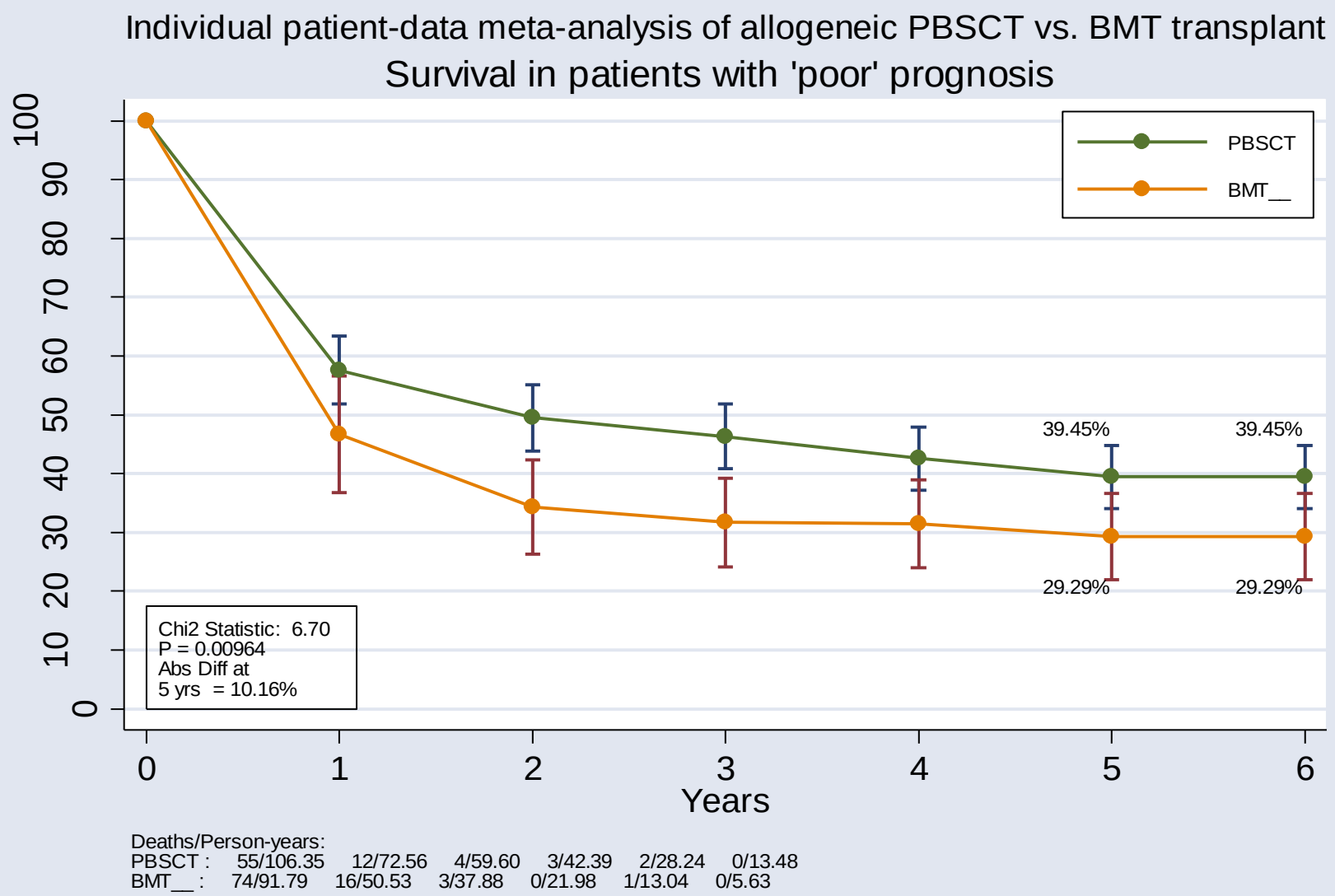
Effect on relapse



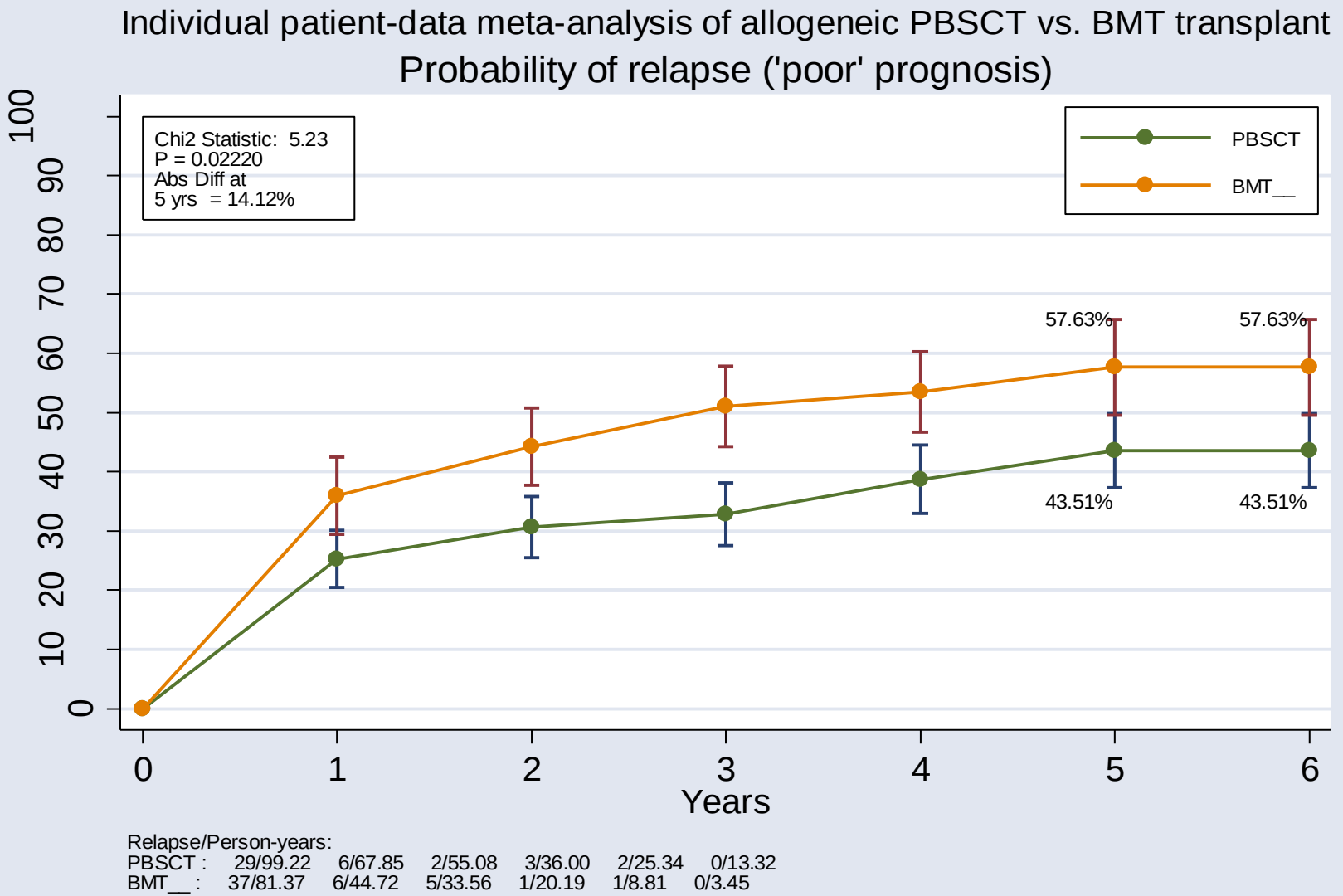
Survival in “favorable” prognostic category



Survival in “unfavorable” prognostic category

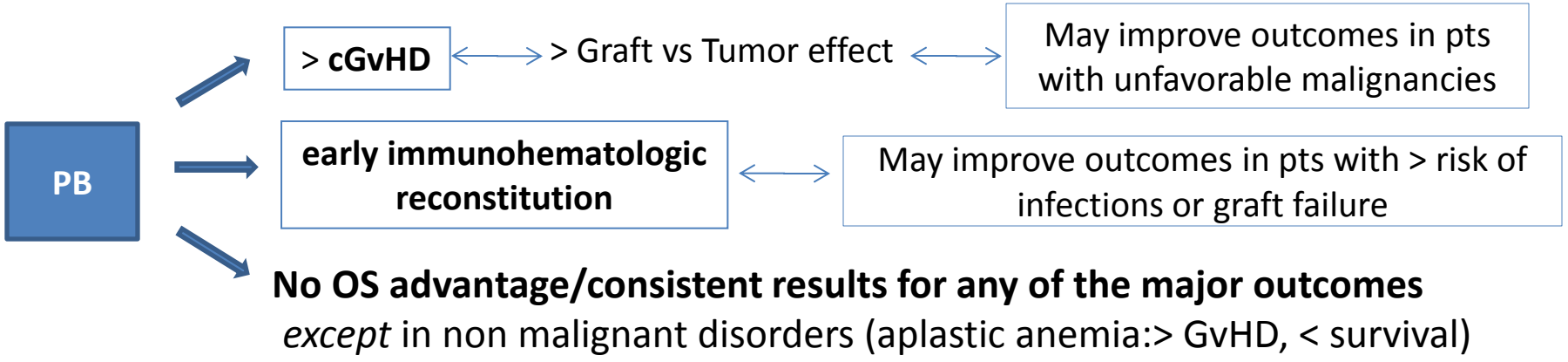


Relapse in “unfavorable” prognostic category



PB vs BM

Several studies have been conducted in the main HSCT settings:



No OS advantage/consistent results for any of the major outcomes
except in non malignant disorders (aplastic anemia:> GvHD, < survival)

- ✓ **The optimal product has yet to be determined, standardized indications are not available**
- ✓ **BM and PB are acceptable HSC sources**

Many factors involved in the choice → patient, disease and transplant-related, donor-related (personal choice, controindication to anesthesia), centre preference and logistics

PBSC vs BM
in the MUD setting

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

Claudio Anasetti, M.D., Brent R. Logan, Ph.D., Stephanie J. Lee, M.D., M.P.H., Edmund K. Waller, M.D., Ph.D., Daniel J. Weisdorf, M.D., John R. Wingard, M.D., Corey S. Cutler, M.D., M.P.H., Peter Westervelt, M.D., Ph.D., Ann Woolfrey, M.D., Stephen Couban, M.D., Gerhard Ehninger, M.D., Laura Johnston, M.D., Richard T. Maziarz, M.D., Michael A. Pulsipher, M.D., David L. Porter, M.D., Shin Mineishi, M.D., John M. McCarty, M.D., Shakila P. Khan, M.D., Paolo Anderlini, M.D., William I. Bensinger, M.D., Susan F. Leitman, M.D., Scott D. Rowley, M.D., Christopher Bredeson, M.D., Shelly L. Carter, Sc.D., Mary M. Horowitz, M.D., and Dennis L. Confer, M.D., for the Blood and Marrow Transplant Clinical Trials Network*

Outcomes at 2 years	PBSC	BM	p-value
Overall survival, intent-to-treat	51% (45%-57%)	46% (40%-52%)	0.25
Overall survival, transplanted	52% (46%-58%)	48% (42%-54%)	0.37
Disease-free survival, transplanted	47% (40%-53%)	44% (38%-50%)	0.60
Relapse	28% (22%-34%)	28% (23%-34%)	0.88
Non-relapse mortality	26% (20%-31%)	27% (22%-33%)	0.67
ANC > 500 by day 28	95% (80%-99%)	86% (78%-92%)	0.09
Acute GVHD II-IV by day 100	47% (40%-53%)	46% (39%-52%)	0.87
Acute GVHD III-IV by day 100	16% (12%-21%)	14% (10%-19%)	0.37
Any chronic GVHD	53% (45%-60%)	40% (33%-47%)	0.02

PBSC versus BM in the MUD setting: OS

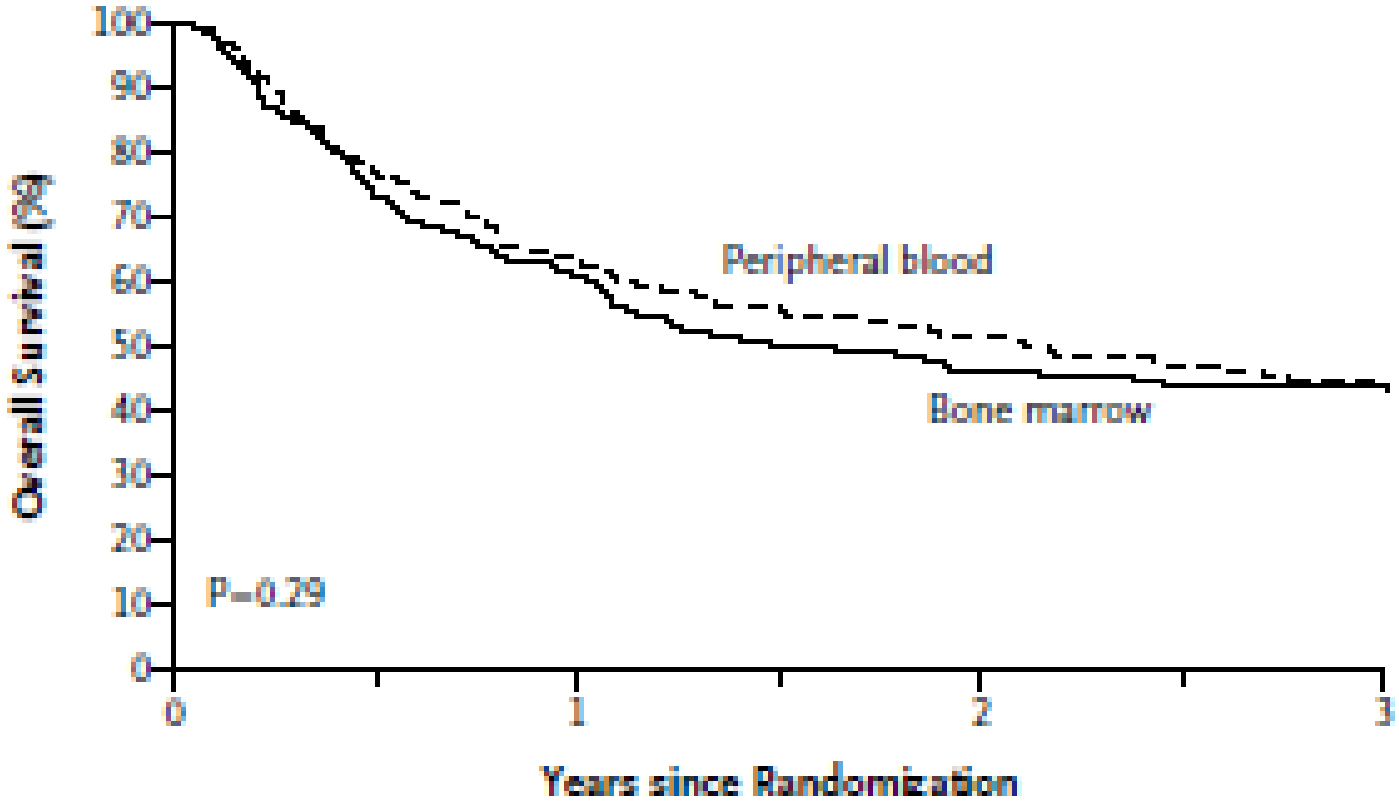
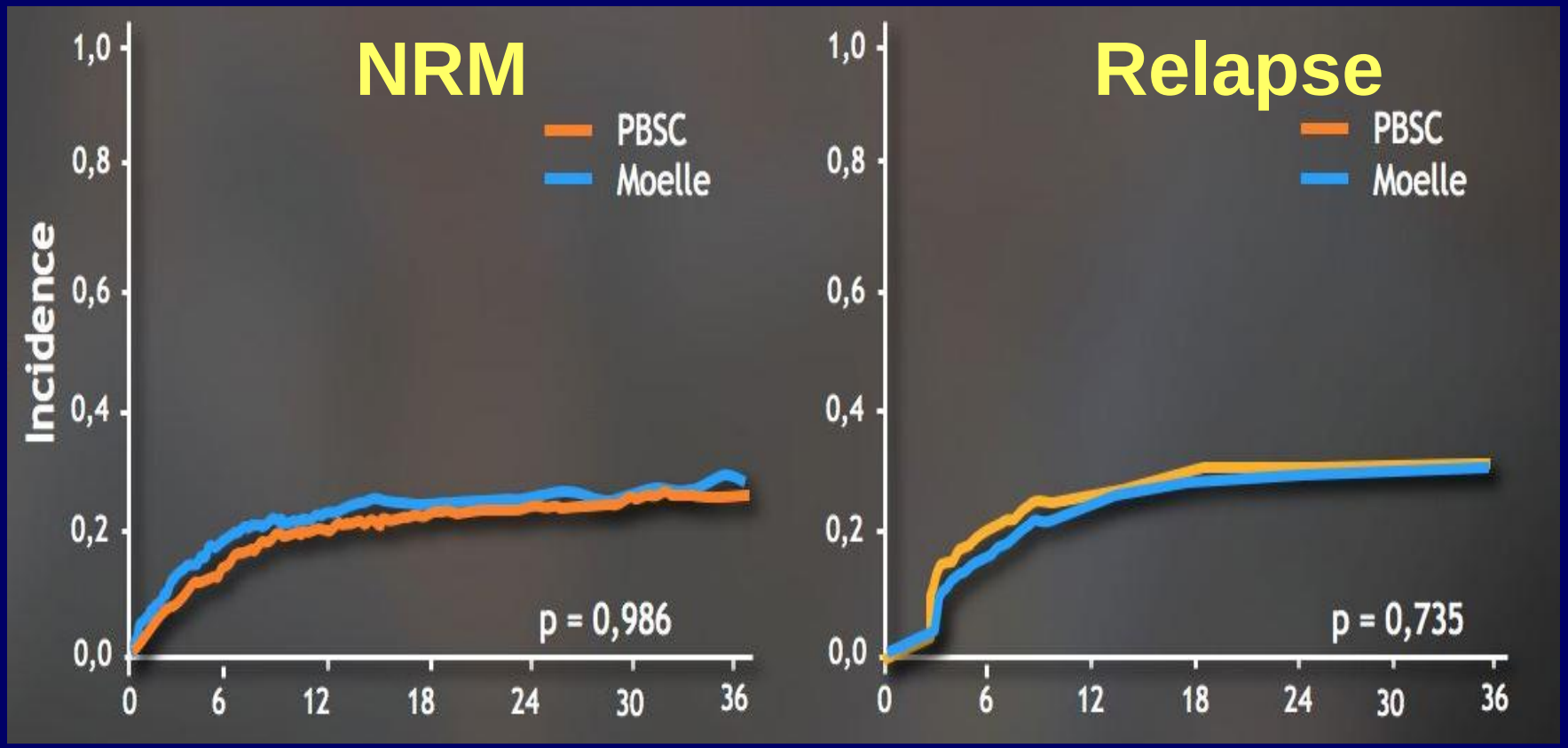


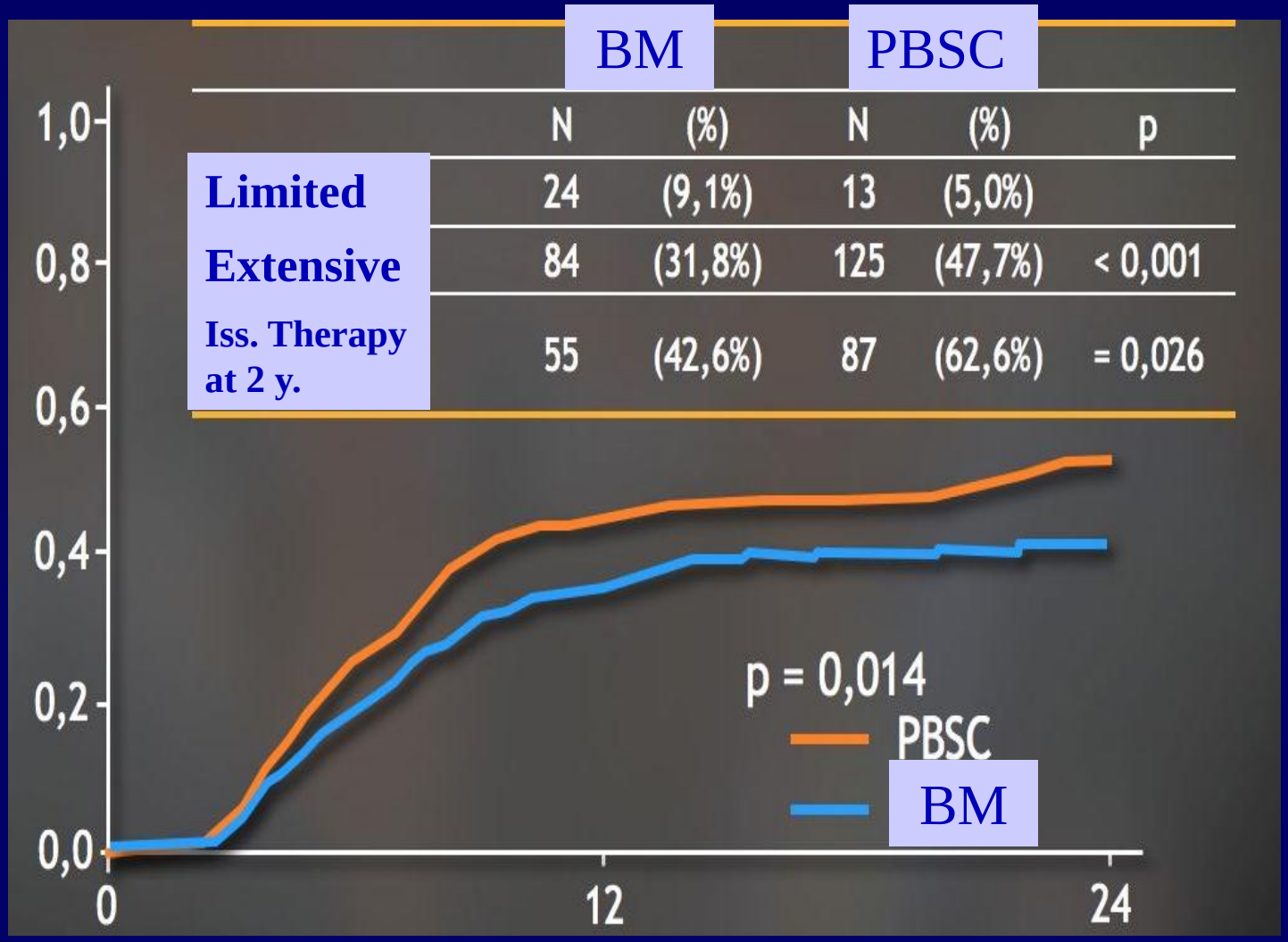
Figure 1. Survival after Randomization in the Intention-to-Treat Analysis.

The P value is from a stratified binomial comparison at the 2-year point. The P value from a stratified log-rank test was also not significant. A total of 75 patients in each group were still alive at 36 months.

PBSC versus BM in the MUD setting: NRM and Relapse



PBSC versus BM in the MUD setting: Chronic GVHD



Take home message

- PBSCs are used in >65% of allo-SCT cases
- PBSCs may improve outcome in patients with unfavorable prognostic features.
- However, it is also associated with significant risk of extensive chronic GVHD both in the sibling and MUD settings.
- This trade-off between benefits and harms should be taken into account in the choice of a stem cell source, but this is not always possible…

HLA Mismatched HSCT

- Unrelated HLA mismatched cord blood

- Haploidentical family donors

UCBT

Pros

- ✓ CB banks: ~600,000 units, immediate availability, no donor risk, advantage for ethnic minorities, low risk of transmissible infections
- ✓ Applicability for children and adults with malignant and non malignant disorders
- ✓ Survival outcomes comparable to other sources of HSCs
- ✓ HLA mismatch accepted; ↓ GvHD and relapse (> GvL)
- ✓ Use extended in older populations with RIC and double UCBT

Cons

- ✓ Delayed engraftment and immune reconstitution; high risk of graft failure (> TRM)
- ✓ Unavailability of the donor for additional donations (i.e DLI)
- ✓ Sustainability of CB banks (cost)

Critical issue in UCB unit selection:

CELL DOSE

- TNC dose ≥ 2.5×10^7/kg (≥ 4 in non malignant)
- 0-1 MM better than 2, avoid 3-4 MM
- higher cell dose allows > HLA mismatches

Haploidentical related donor

Only an haplotype is shared between the donor and the recipient

Critical issue = high risk of graft failure and GvHD

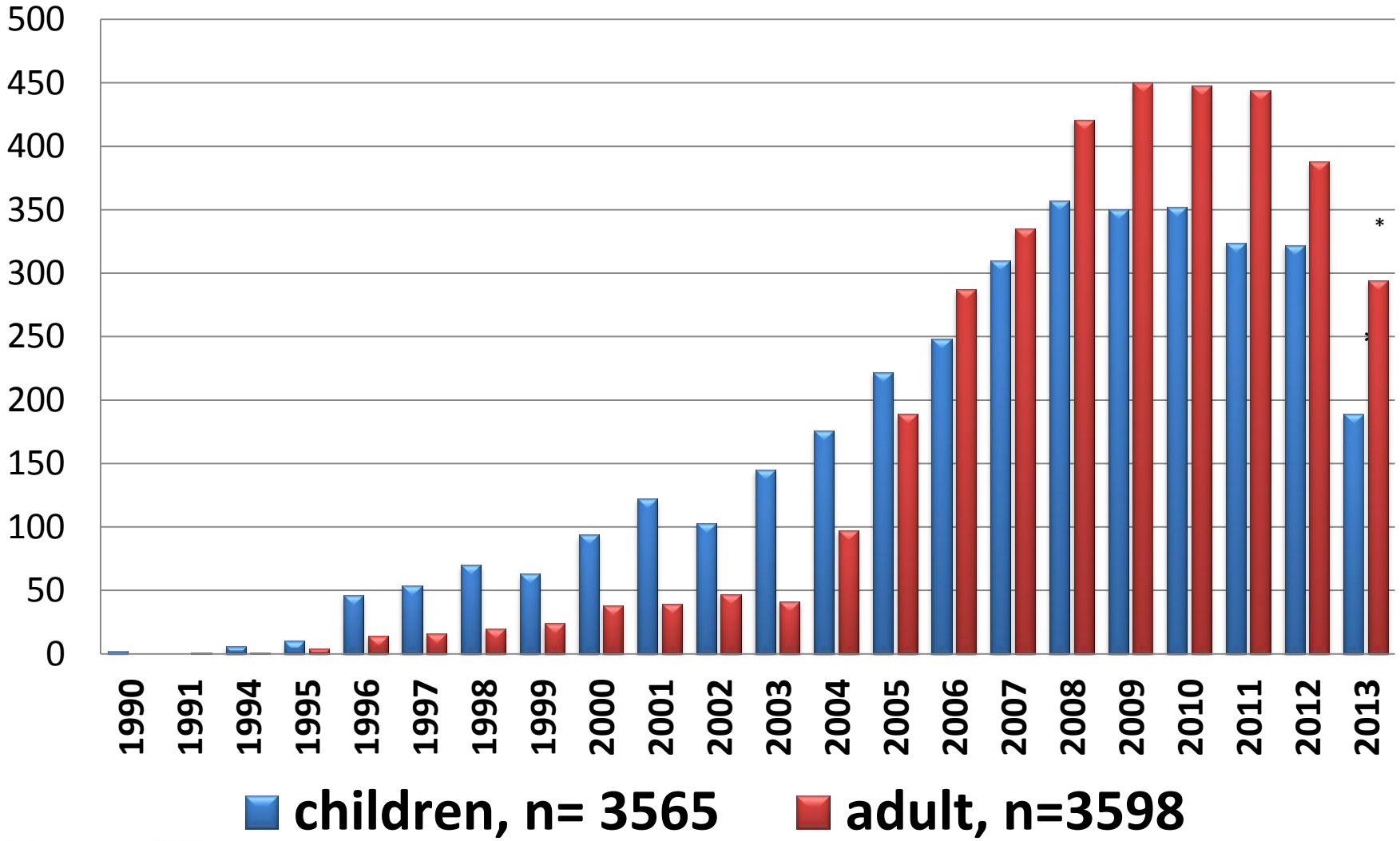
T cell depletion *or* enhanced GvHD prophylaxis

→ *delayed immune reconstitution*

(↑ risk of infections and relapse)

- ✓ Both BM (primed with GF or not) and PB used → potential risk for the donor
- ✓ Immediate availability; virtually everyone has at least an haploidentical donor
- ✓ Applicable to children and adults with malignant and non malignant disorders
- ✓ **Early results comparable to other HSCs sources**
- ✓ **Few publications on long term results**

UCBT by year and recipient age



* Still collecting 2013 data

“Haplo” is the fastest growing cell source but still is less than 2% of all transplants

	Stem Cell Transplants (%) 2008-2012					Stem Cell Transplants - YoY Growth			
	2008	2009	2010	2011	2012	2009	2010	2011	2012
BM & PBSC (Unrelated)	19.4%	19.6%	19.8%	19.8%	20.4%	9.5%	6.0%	8.3%	5.3%
CB (Unrelated)	5.2%	5.3%	5.0%	4.8%	4.3%	9.6%	-0.2%	4.1%	-7.6%
HLA-matched sibling	16.4%	15.2%	14.6%	14.0%	13.9%	0.4%	0.5%	4.1%	1.7%
Related Donor	2.1%	1.6%	0.9%	0.6%	0.6%	-18.4%	-42.9%	-29.2%	6.9%
Haplo-Identical	**0.6%**	**1.2%**	**1.5%**	**1.8%**	**1.9%**	110.1%	35.8%	25.2%	11.3%
HLA-mismatched relative	0.2%	0.3%	0.3%	0.3%	0.2%	84.6%	-2.1%	-4.3%	-4.4%
HLA-matched relative	0.3%	0.3%	0.4%	0.6%	0.6%	20.0%	43.8%	44.9%	5.0%
Identical Twin	0.4%	0.3%	0.2%	0.2%	0.2%	-26.6%	-12.8%	2.4%	-14.3%
Autologous	55.3%	56.2%	57.2%	58.0%	57.8%	10.2%	6.9%	9.8%	1.9%

CIBMTR Data

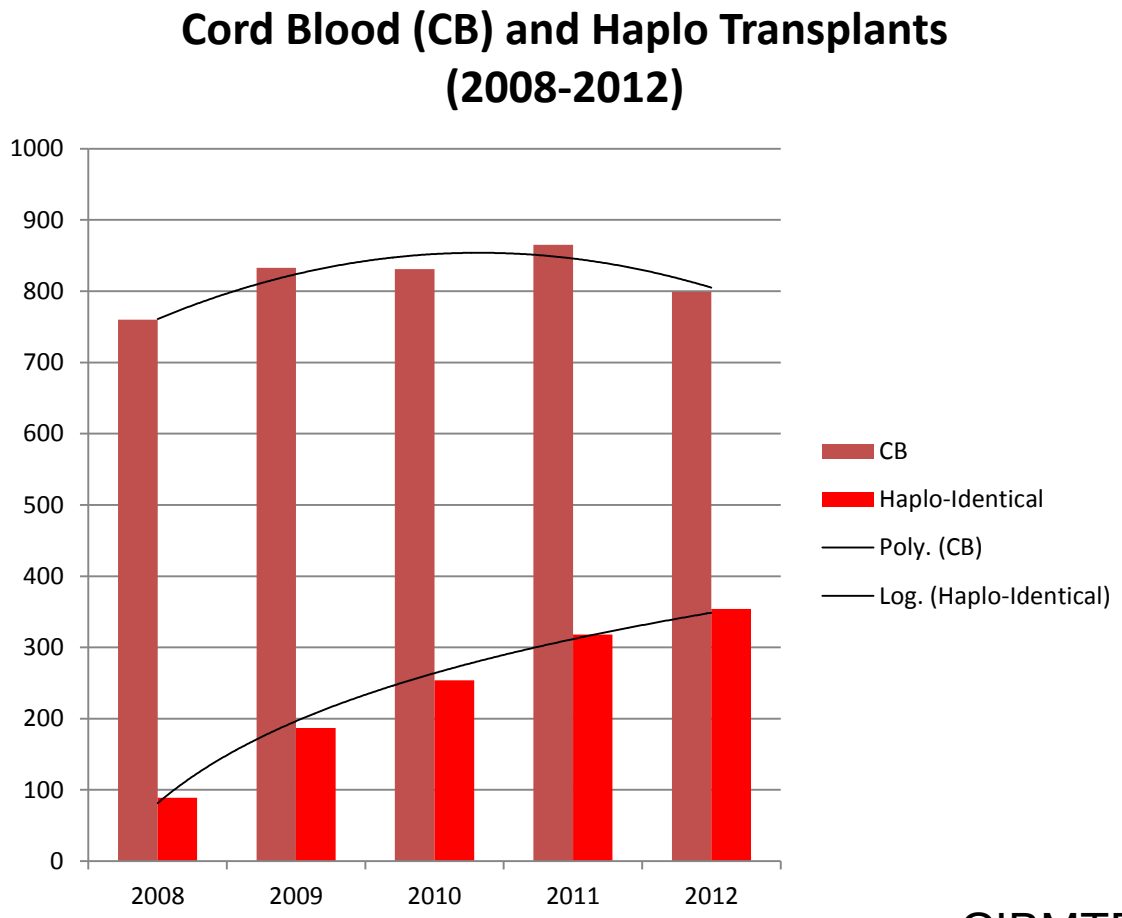
Haplo Transplants by Racial and Ethnic Groups

Haplo vs URD Transplants by Race/Ethnicity

	HAPLO		BM & PBSC		CB	
	Tx	%	Tx	%	Tx	%
CAUC	965	69%	16602	87%	2938	64%
BLACK_AA	327	23%	841	4%	659	14%
ASIAN	73	5%	393	2%	99	2%
Other	18	1%	65	0%	8	0%
AM_IND_AK_NTV	13	1%	37	0%	8	0%
NTV_HA_OTH_PI	8	1%	1096	6%	861	19%

CIBMTR Data

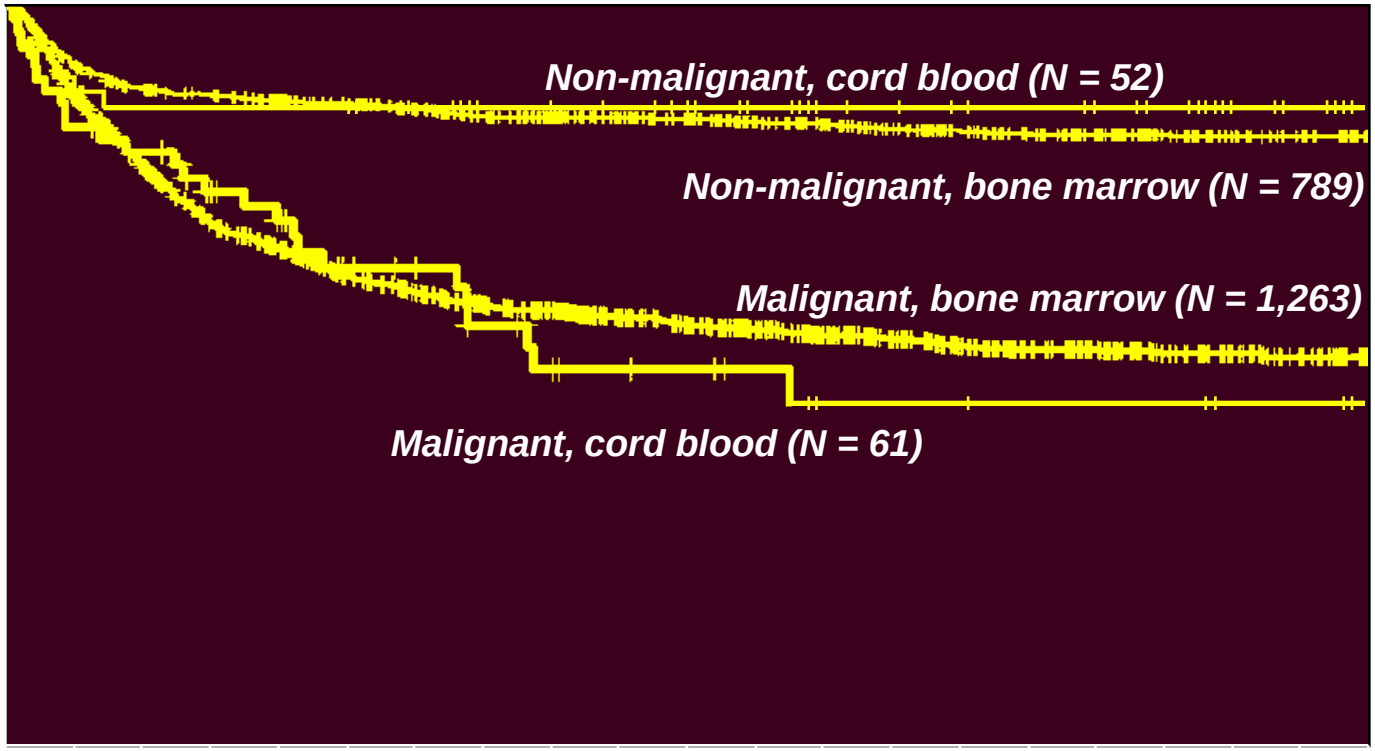
Haplo Transplants Compared to Cord Blood Transplants



CIBMTR Data

Comparative Studies of cord blood transplant with other stem cell sources

HLA-IDENTICAL SIBLING TRANSPLANTS (n=2052)
- by Disease and Graft Type -



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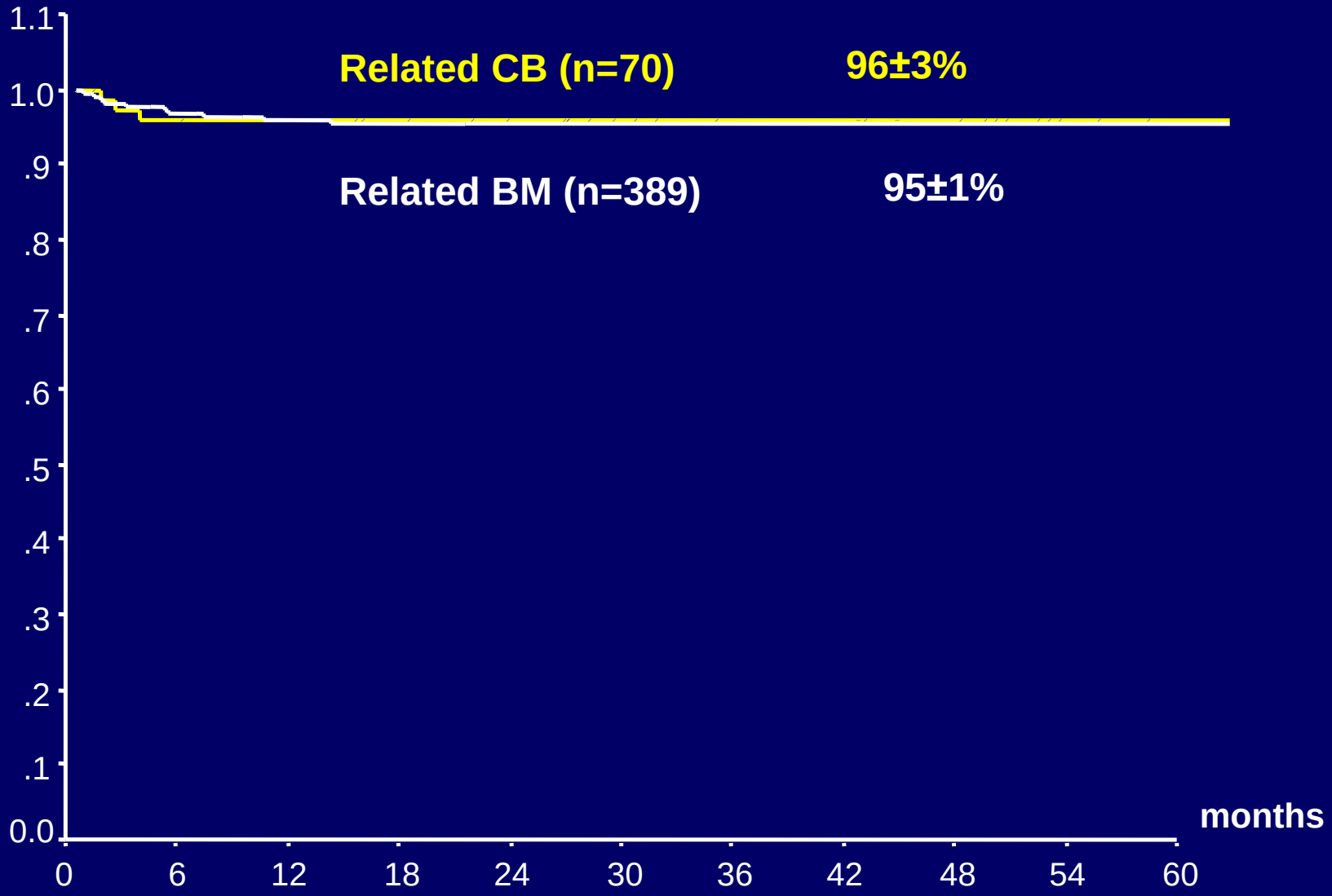
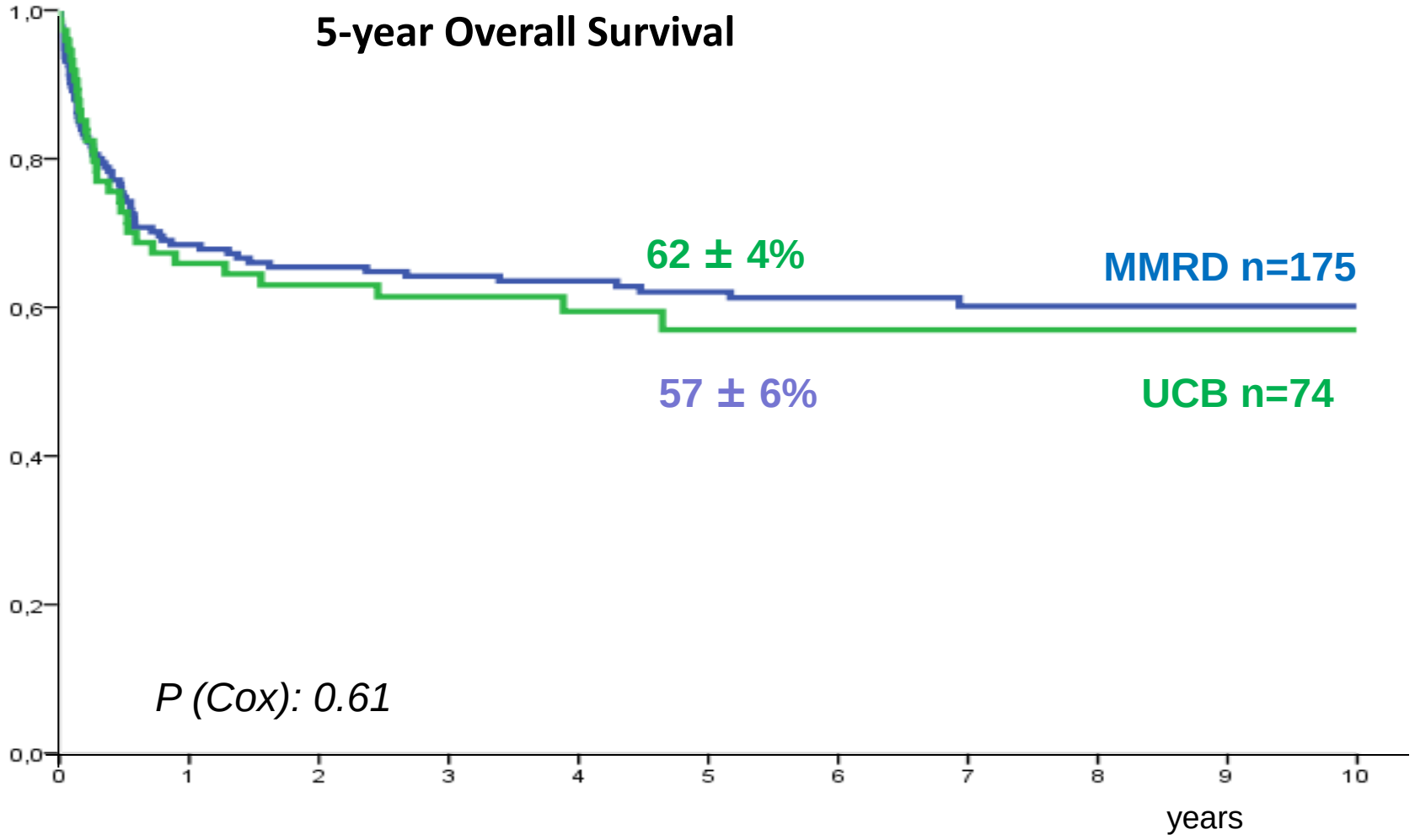
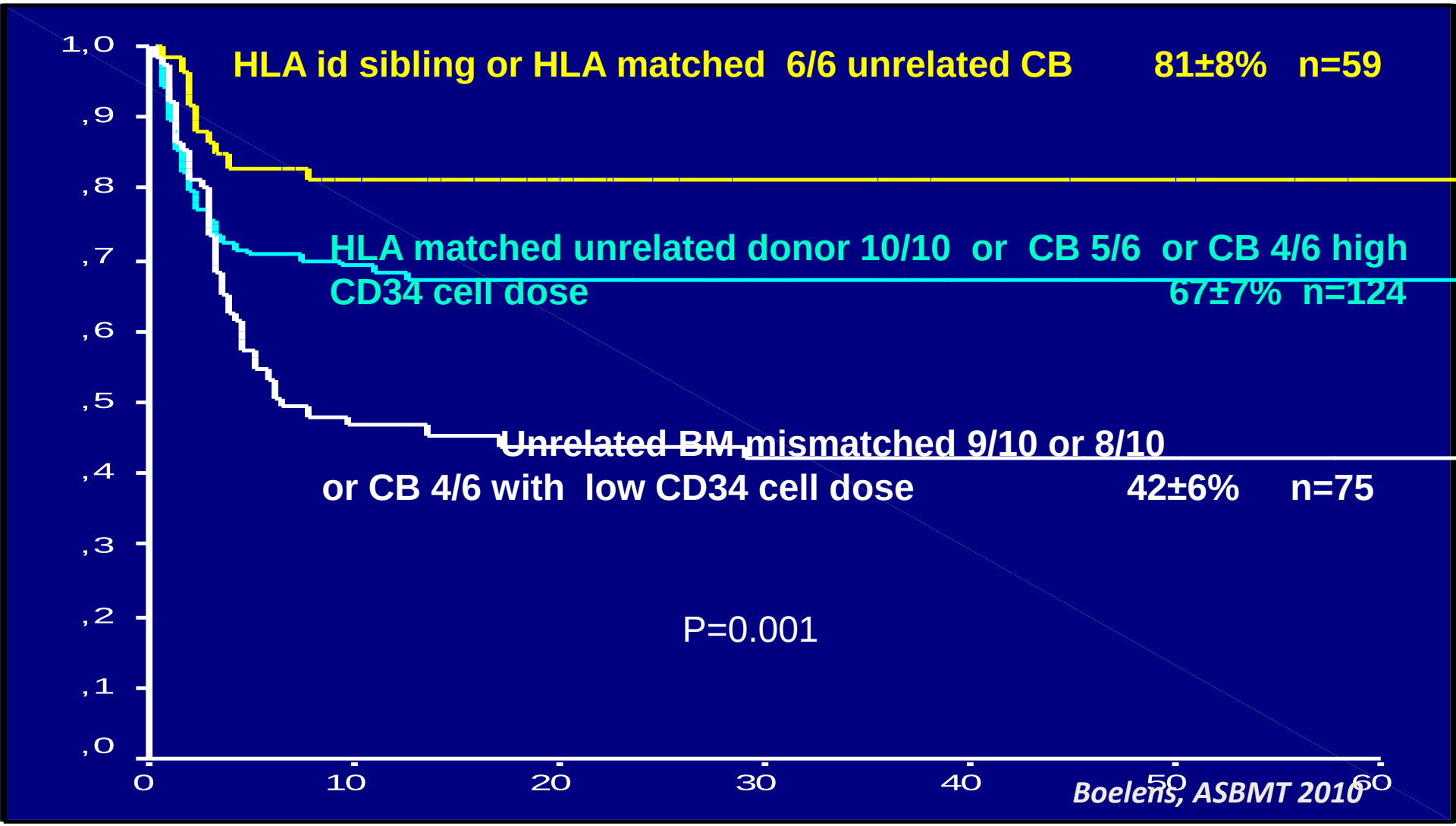
Overall Survival with HLA identical siblings for patie with Thalassemia and Sickle Cell Disease



Comparison of outcomes of mismatched related stem cell and unrelated cord blood transplants in children with severe T-cell deficiencies



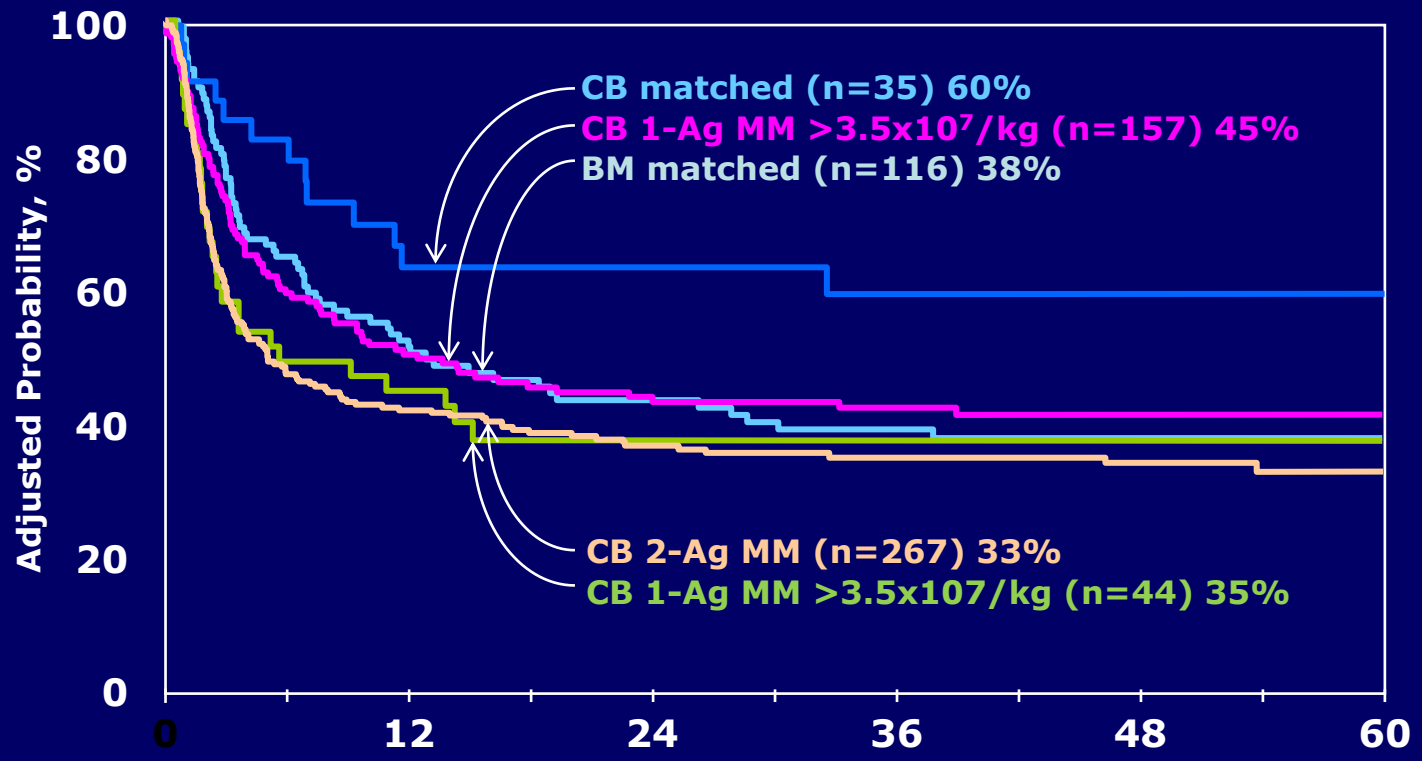
EFS by type of donor and HLA in children with Hurler disease



Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study

Mary Eapen, Pablo Rubinstein, Mei-Jie Zhang, Cladd Stevens, Joanne Kurtzberg, Andromachi Scaradavou, Fausto R Loberiza, Richard E Champlin, John P Klein, Mary M Horowitz, John E Wagner

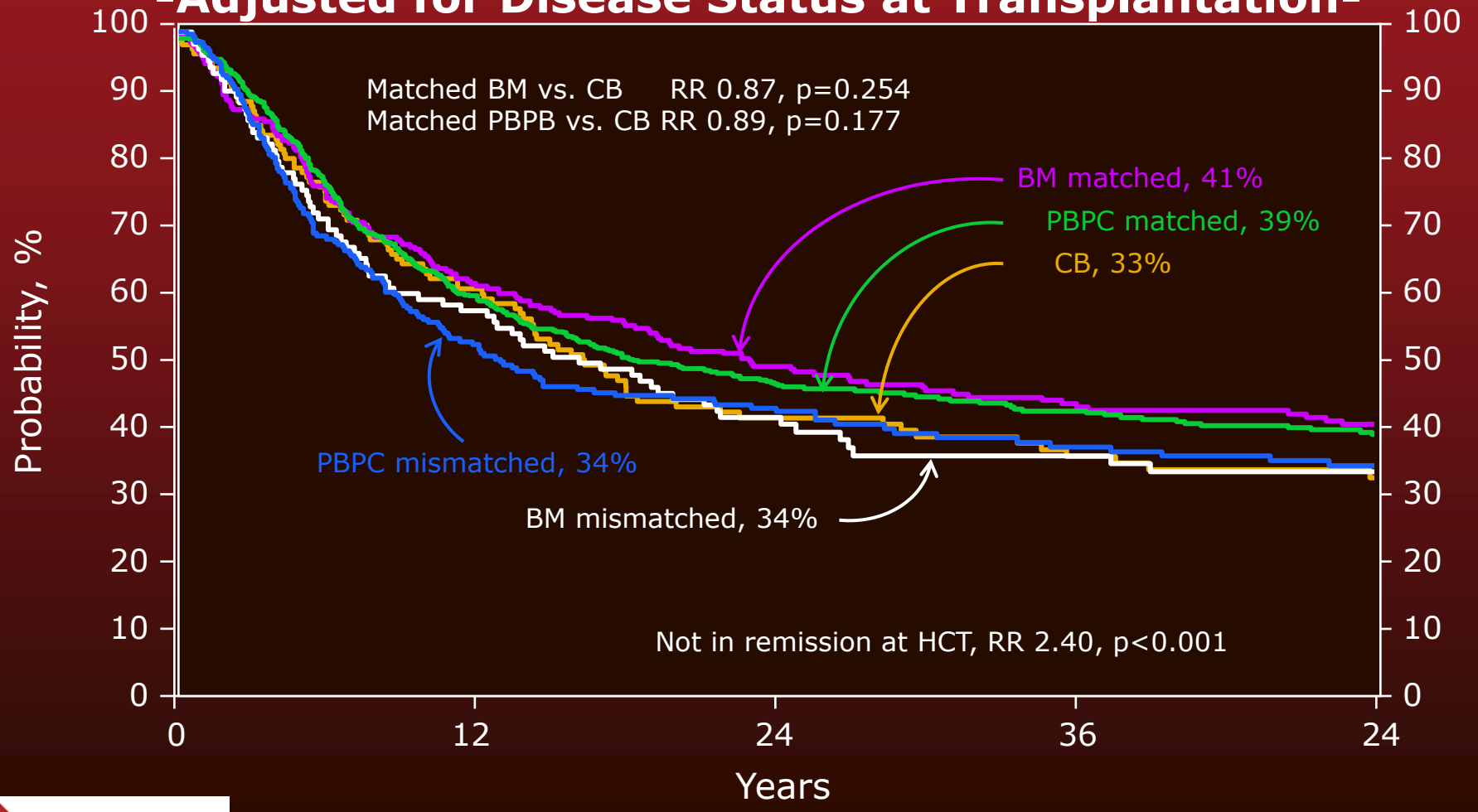
Survival and LFS are similar after UCBT compared to unrelated bone marrow in children with acute leukemias



Eapen M et al Lancet. 2007, 369:1947-54

Impact of Stem Cell Source in Adults with Acute Leukemia, n=1280

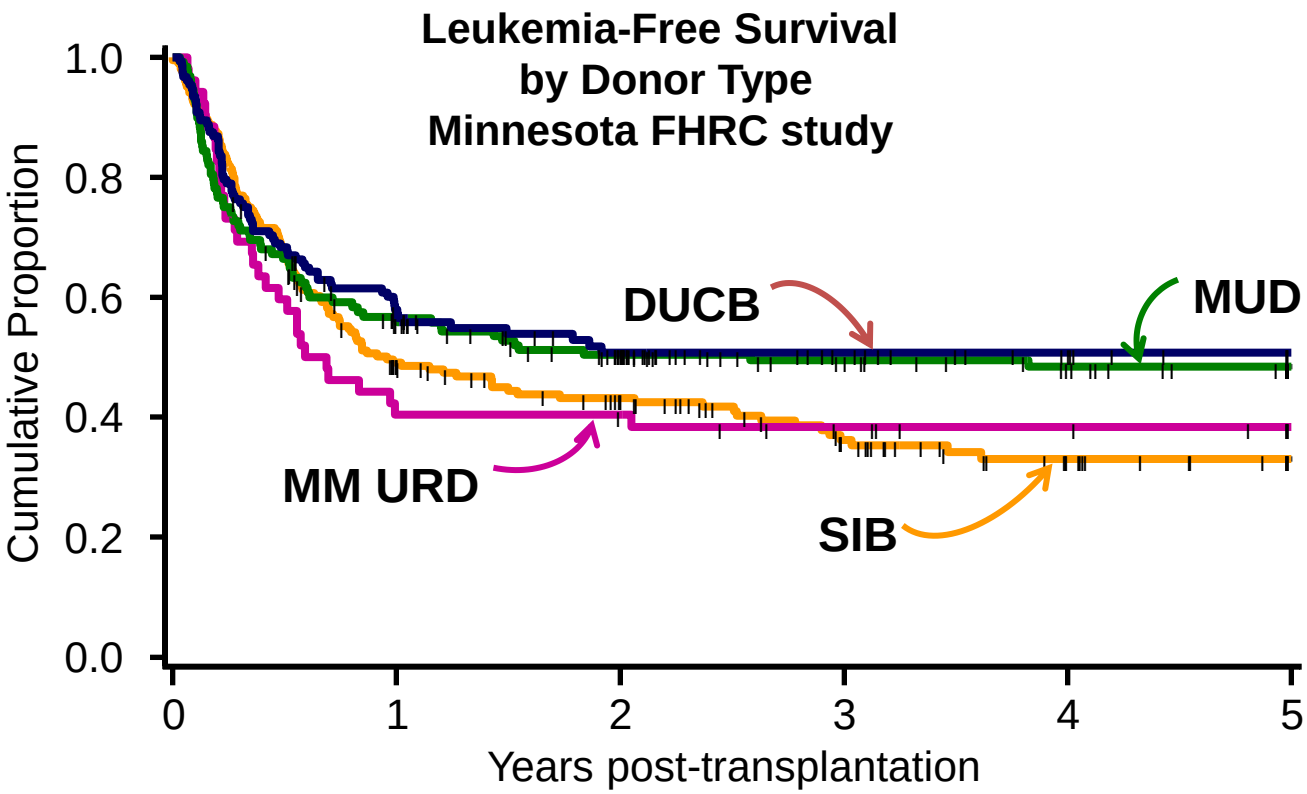
Leukemia-free Survival
-Adjusted for Disease Status at Transplantation-



Eapen M, Rocha V, Lancet Onc 2010

Allogeneic hematopoietic cell transplantation for hematologic malignancy: relative risks and benefits of double umbilical cord blood

Claudio G. Brunstein,[1] Jonathan A. Gutman,[2] Daniel J. Weisdorf,[1] Ann E. Woolfrey,[2] Todd E. DeFor,[1] Theodore A. Gooley,[2] Michael R. Verneris,[1] Frederick R. Appelbaum,[2] *John E. Wagner,[1] and *Colleen Delaney[2]



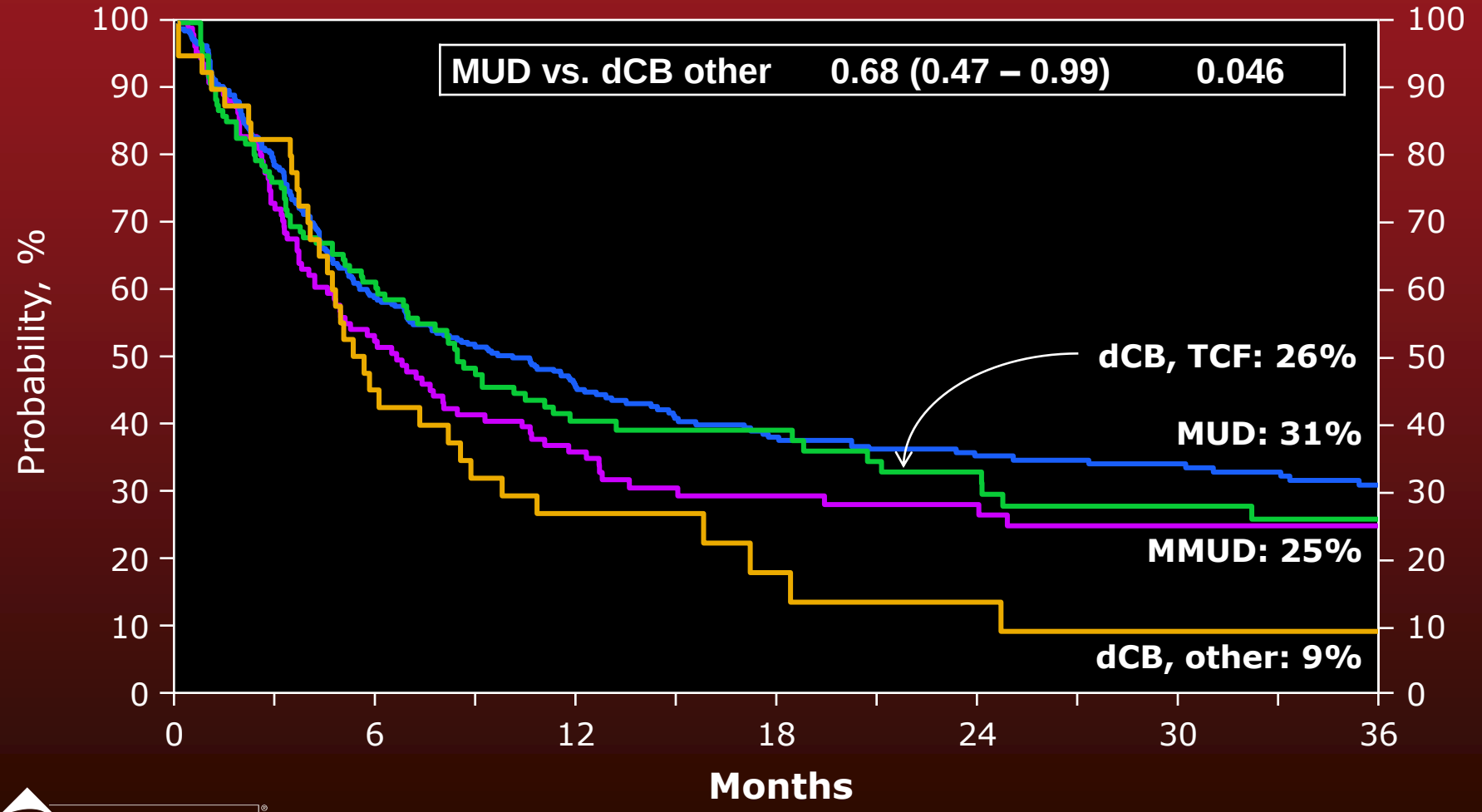
Matched Sibling*	**1.0**	
MUD	**0.83 (0.62-1.11)**	**P=.20**
MMUD	**1.04 (0.70-1.53)**	**P=.85**
DUCB	**1.00 (0.73-1.37)**	**P=.99**

Brunstein C, Blood 2010

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

Claudio G. Brunstein,[1] Mary Eapen,[2] Kwang Woo Ahn,[2,3] Frederick R. Appelbaum,[4] Karen K. Ballen,[5] Richard E. Champlin,[6] Corey Cutler,[7] Fangyu Kan,[2] Mary J. Laughlin,[8] Robert J. Soiffer,[7] Daniel J. Weisdorf,[1] Anne Woolfrey,[5] and John E. Wagner[1]

RIC Leukemia-Free Survival



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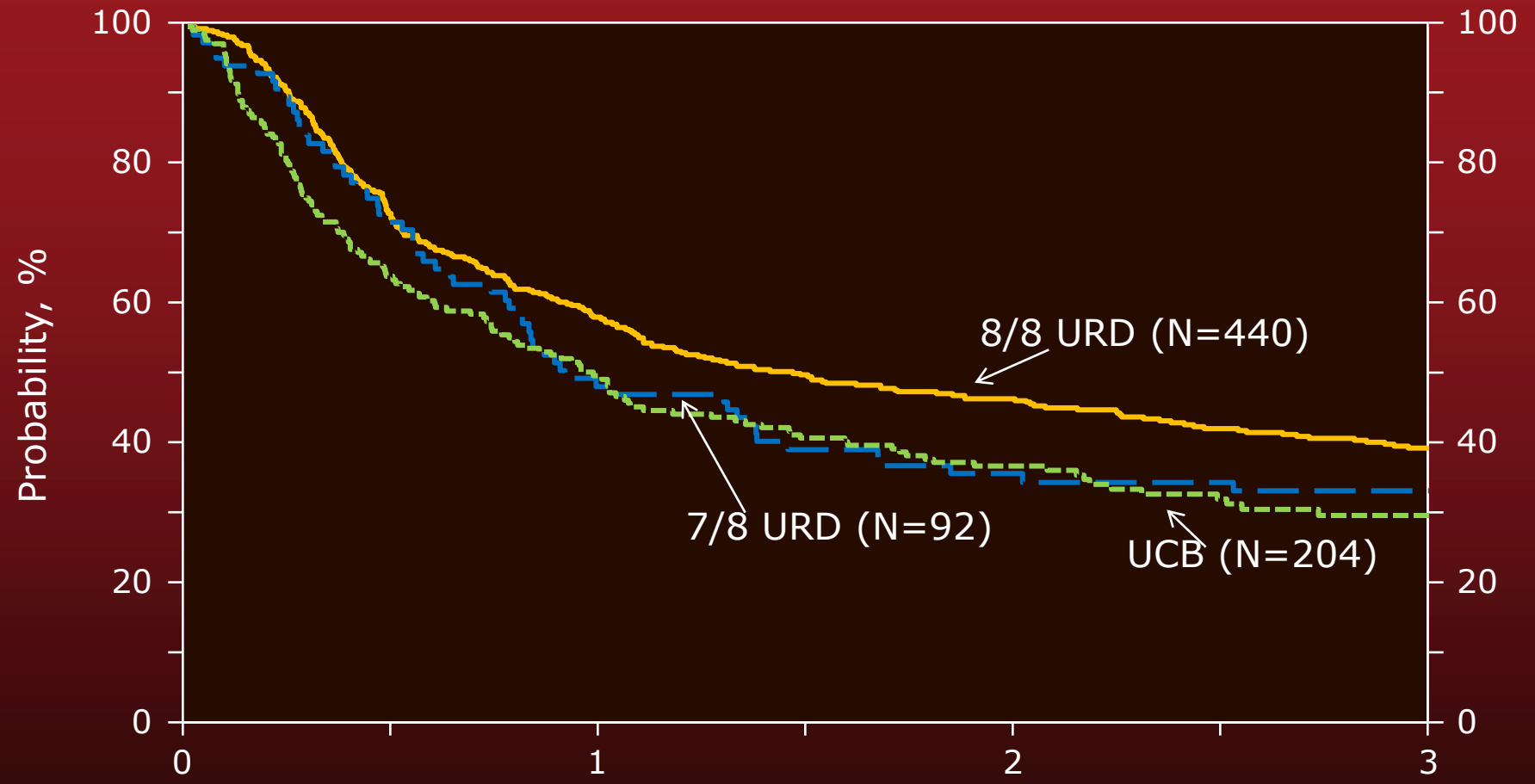
Brunstein C, Eapen M, Blood 2012

Leukemia-free Survival
Adults over 50 AML in CR1



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eurocord

Benefits of UCB: perhaps best for older patients

Less Chronic GVHD after UCB

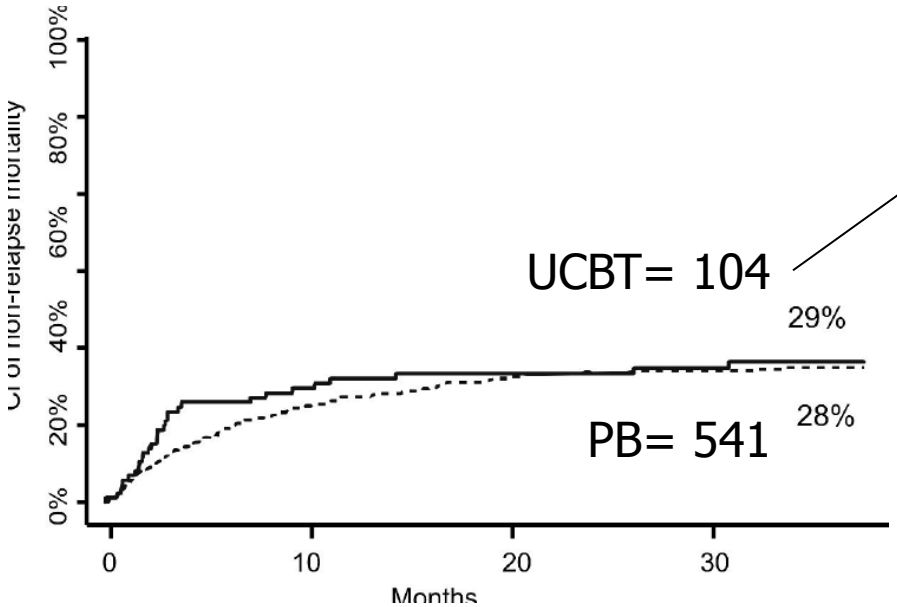
- Earlier discontinuation of immunosuppression
- Lesser medical interventions day 100 – 1 year
- Lesser late morbidity & cost

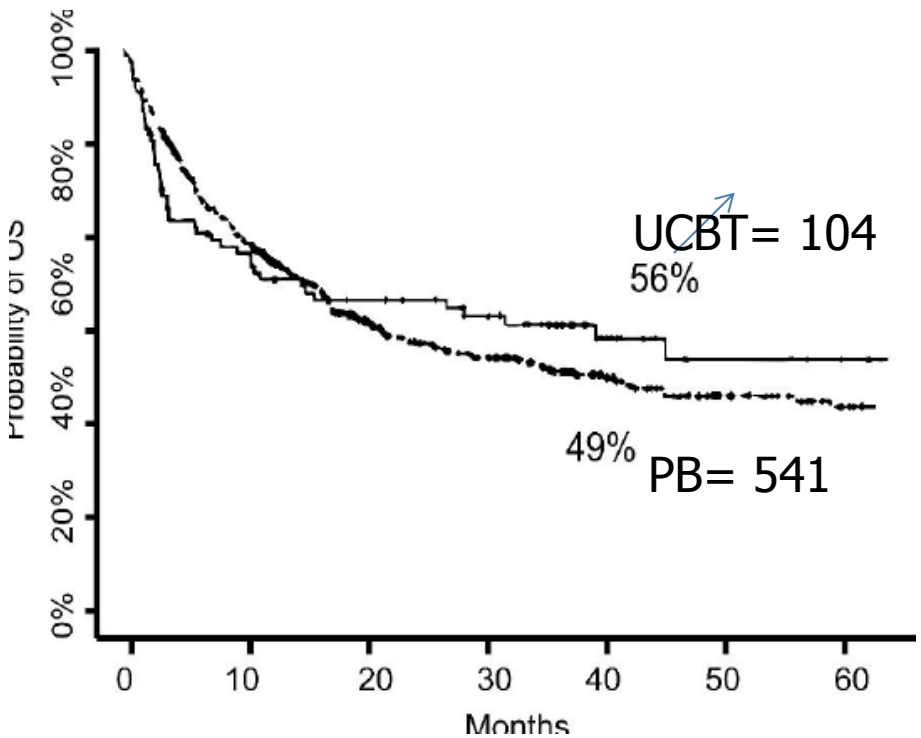
haematologica
the hematology journal

Early Release Paper

Alternative donor hematopoietic stem cell transplantation for mature lymphoid malignancies after reduced-intensity conditioning regimen: similar outcomes with umbilical cord blood and unrelated donor peripheral blood

by Celso Arrais Rodrigues, Vanderson Rocha, Peter Dreger, Claudio G. Brunstein, Henrik Sengeloev, Juergen Finke, Mohamad Mohty, Bernard Rio, Eefke Petersen, Francois Guilhot, Dietger Niederwieser, Jan J. Cornelissen, Pavel Jindra, Arnon Nagler, Nathalie Fegueux, Hélène Schoemans, Stephen Robinson, Annalisa Ruggeri, Eliane Gluckman, Carmen Canals, and Anna Sureda


Cumulative incidence of non-relapse mortality
0%
20%
40%
60%
80%
100%
0
10
20
30
Months
75% TCF
UCBT= 104
29%
28%
PB= 541


Probability of OS
0%
20%
40%
60%
80%
100%
0
10
20
30
40
50
60
Months
UCBT= 104
56%
49%
PB= 541

Comparison between cord blood and other sources of stem cells

- Same survival and leukemia free survival
- Engraftment is delayed
- Less acute and chronic GVHD

Alternative Donor Transplantation

Pros and cons

	Availability to pts	Timing	Cost for graft acquisition	Advantages	Concerns
Non TCD Haplo	>95%	<1 month	E10K	Low early TRM Immune reconstitution DLI possibility	GVHD and Relapse Heterogeneity of techniques Center experience
Cord	>90%	<1 month	E20K/Unit	Young HSCs No risk for donor Low GVH GVL effect 25 years experience	Cell content Immune reconstitution Early Mortality

Adapted from Richard Jones

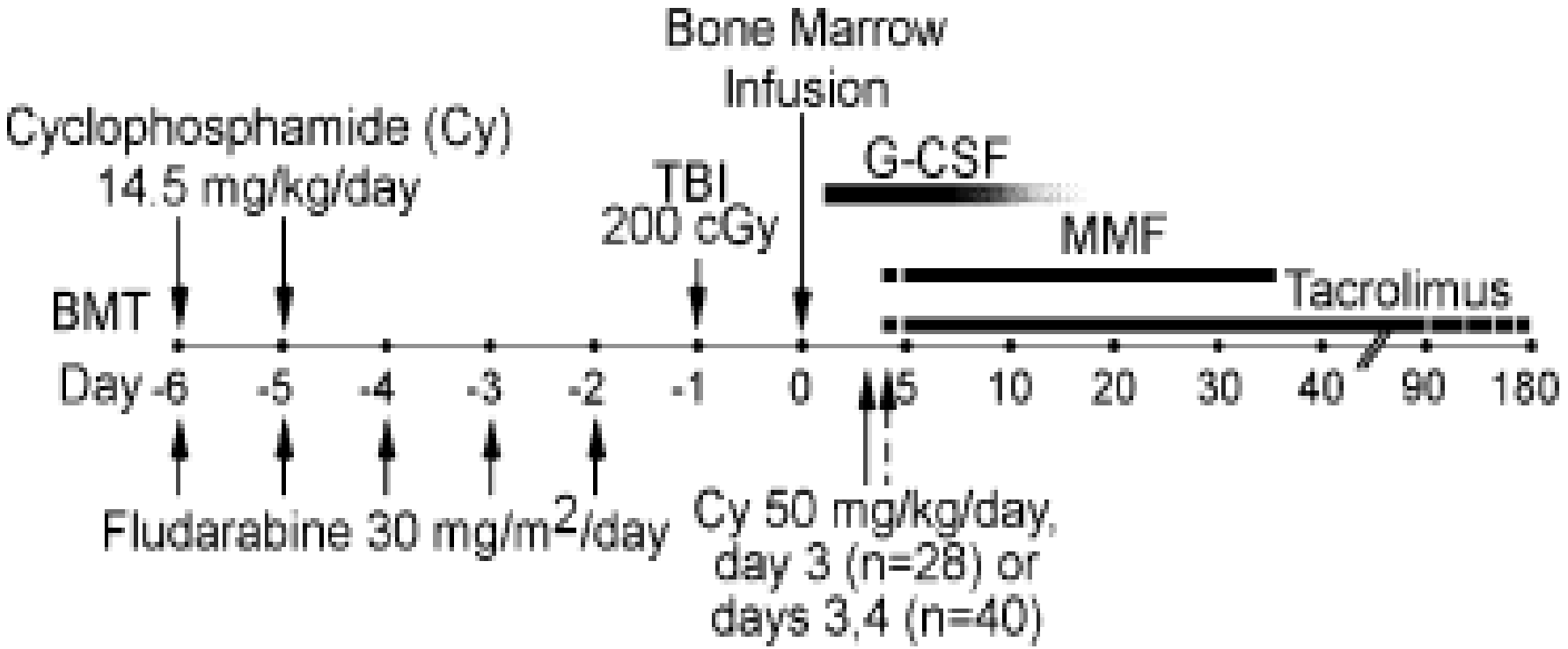
Haploidentical Transplants Platforms

- **T cell deplete** - selection of CD34+ cells (Perugia)
  with different immunossupression
  -depletion of T cells (Pavia-Rome)
- **T cell replete** - Chinese approach / Italian approach
  Mobilized bone marrow with high number of immunossupressive drugs
  - John Hopkins approach
  RIC M BM or PB with post CY
  - Genova approach
  MAC with post CY

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

BBMT 14:641-650, 2008

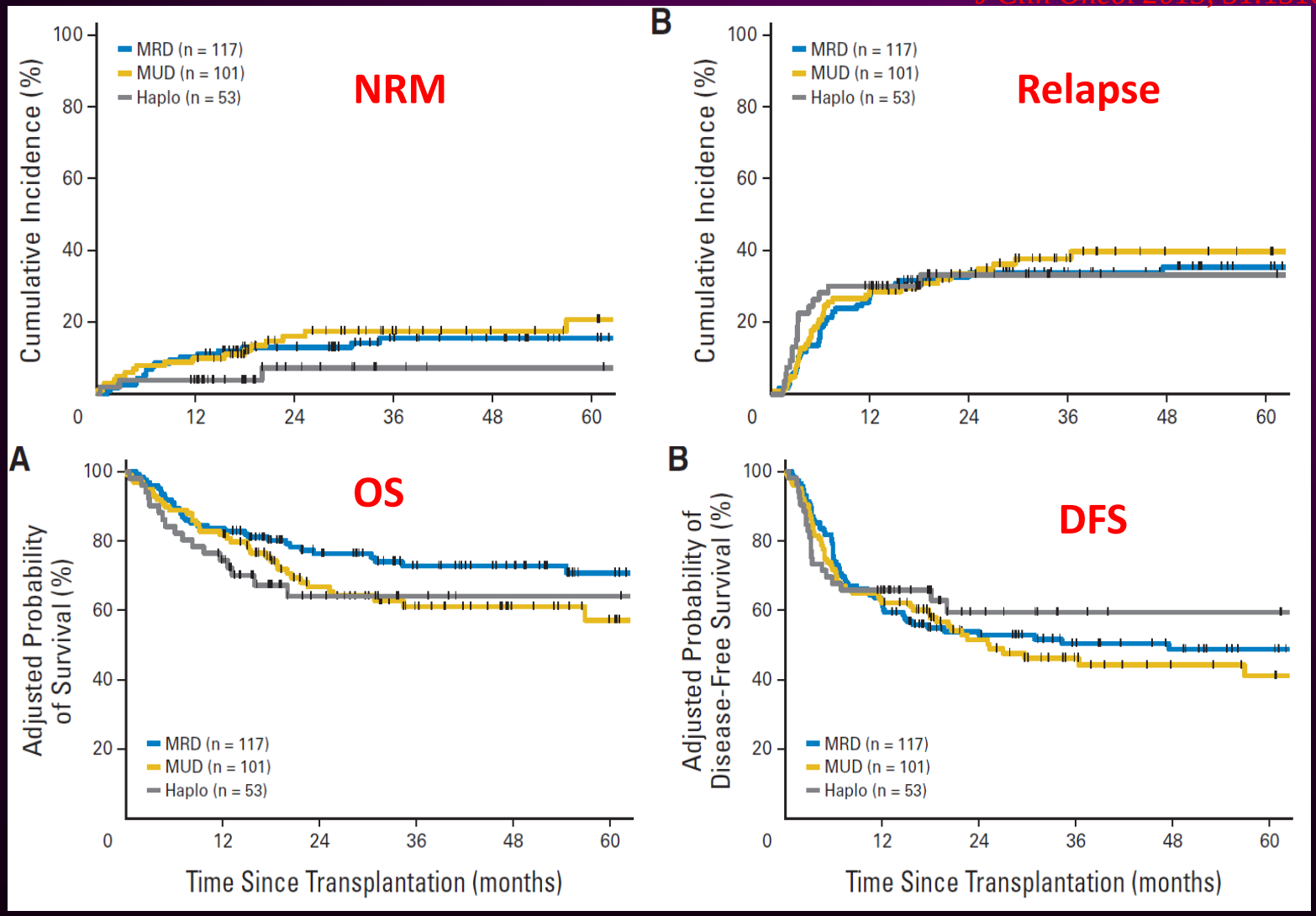
Leo Luznik,[1] Paul V. O'Donnell,[2,3]* Heather J. Symons,[1] Allen R. Chen,[1] M. Susan Leffell,[1] Marianna Zahurak,[1] Ted A. Gooley,[2,3] Steve Piantadosi,[1] Michele Kaup,[1] Richard F. Ambinder,[1] Carol Ann Huff,[1] William Matsui,[1] Javier Bolaños-Meade,[1] Ivan Borrello,[1] Jonathan D. Powell,[1] 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]*



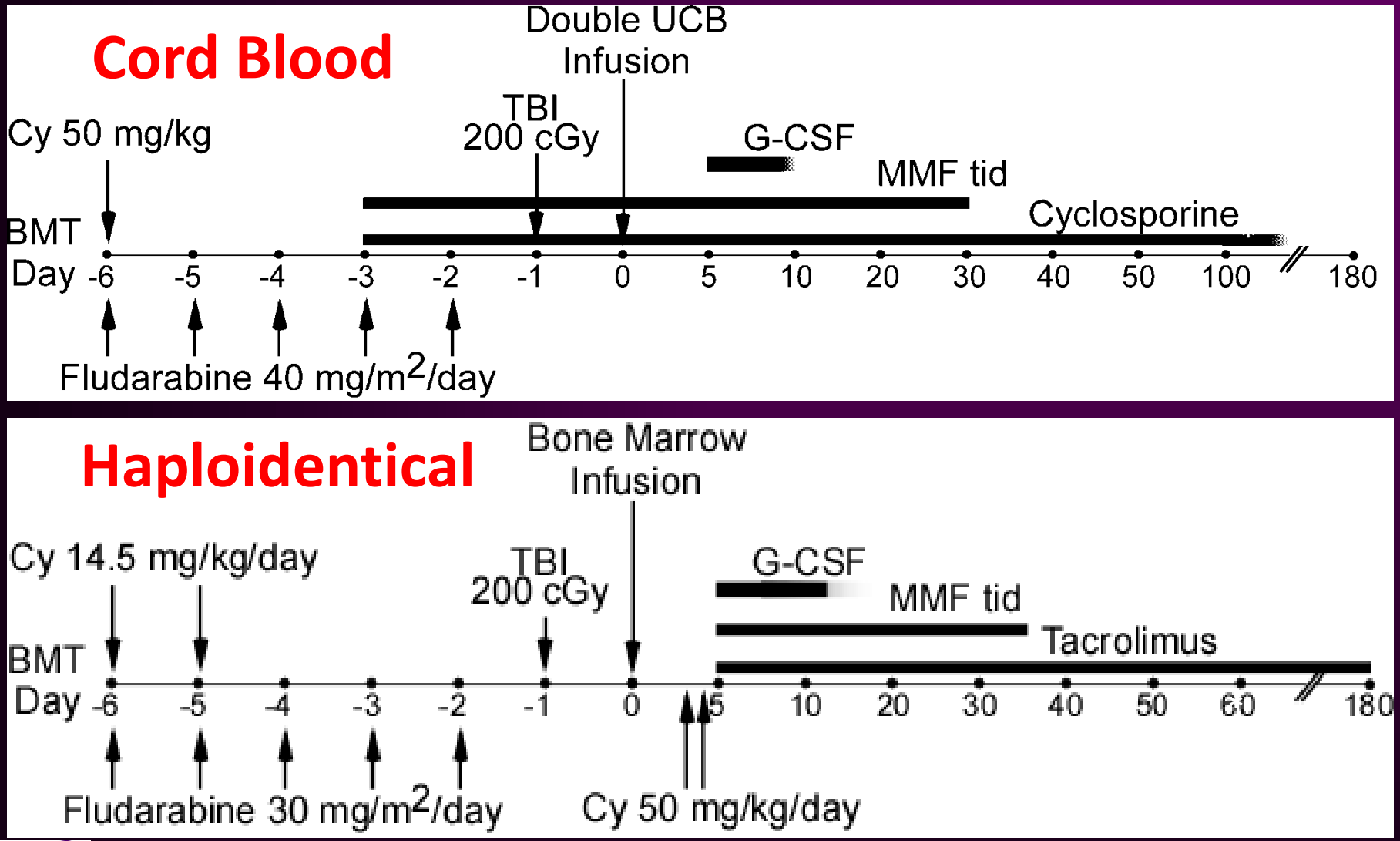
T-Cell–Replete HLA-Haploidentical Hematopoietic Transplantation for Hematologic Malignancies Using Post-Transplantation Cyclophosphamide Results in Outcomes Equivalent to Those of Contemporaneous HLA-Matched Related and Unrelated Donor Transplantation

Asad Bashey, Xu Zhang, Connie A. Sizemore, Karen Manion, Stacey Brown, H. Kent Holland, Lawrence E. Morris, and Scott R. Solomon

J Clin Oncol 2013, 31:1310-1316



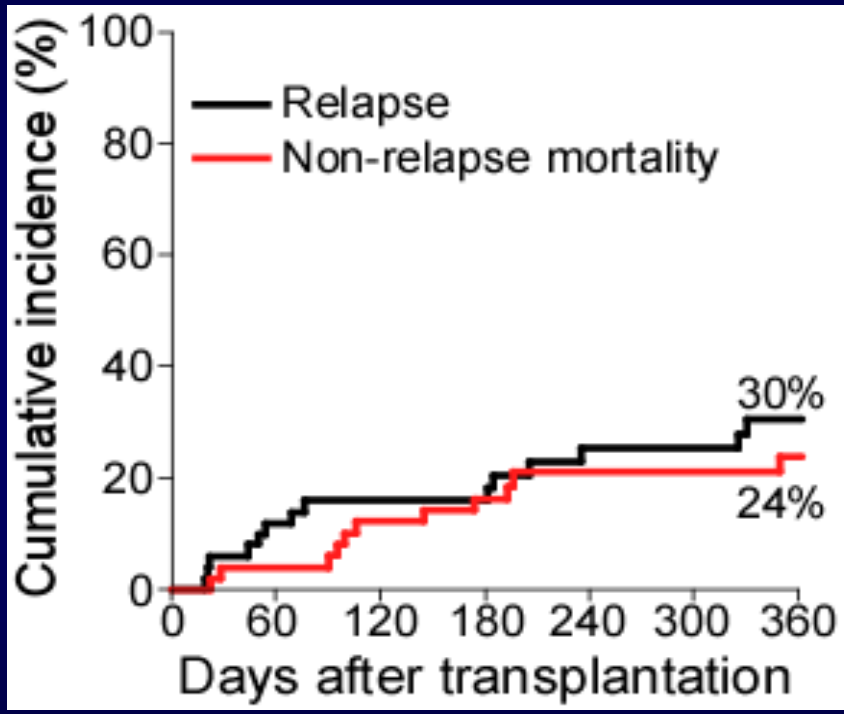
Treatment Schemas



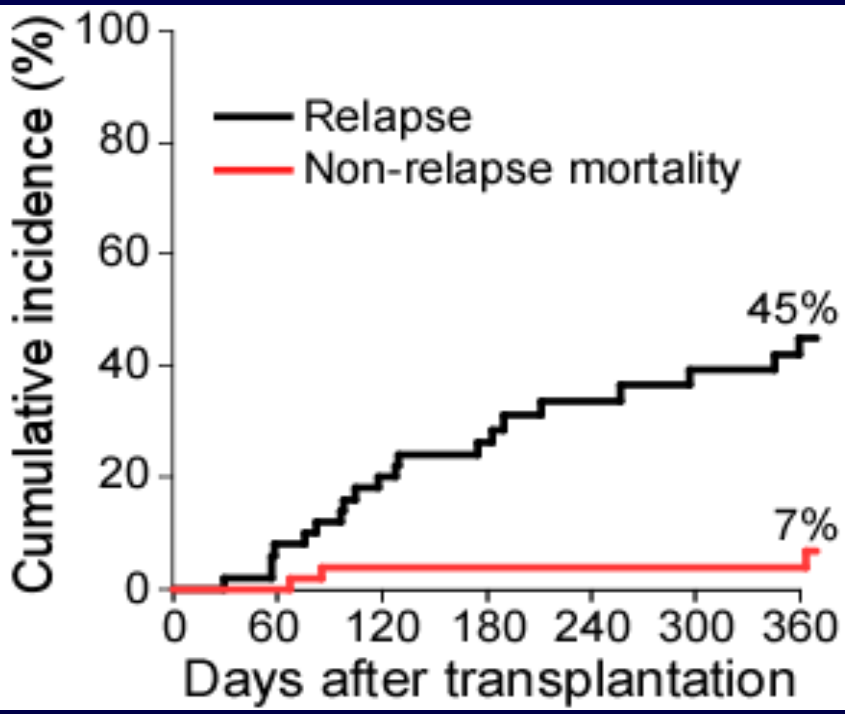
Courtesy of Mary Eapen

Relapse and Non-Relapse Mortality

Cord (0604)



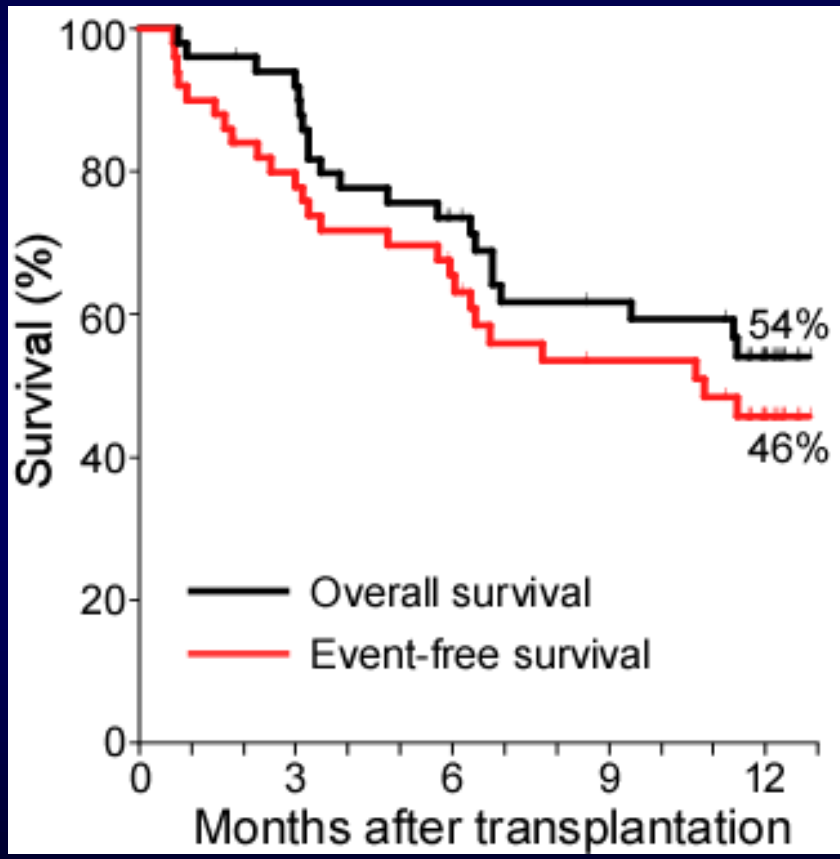
Haplo (0603)



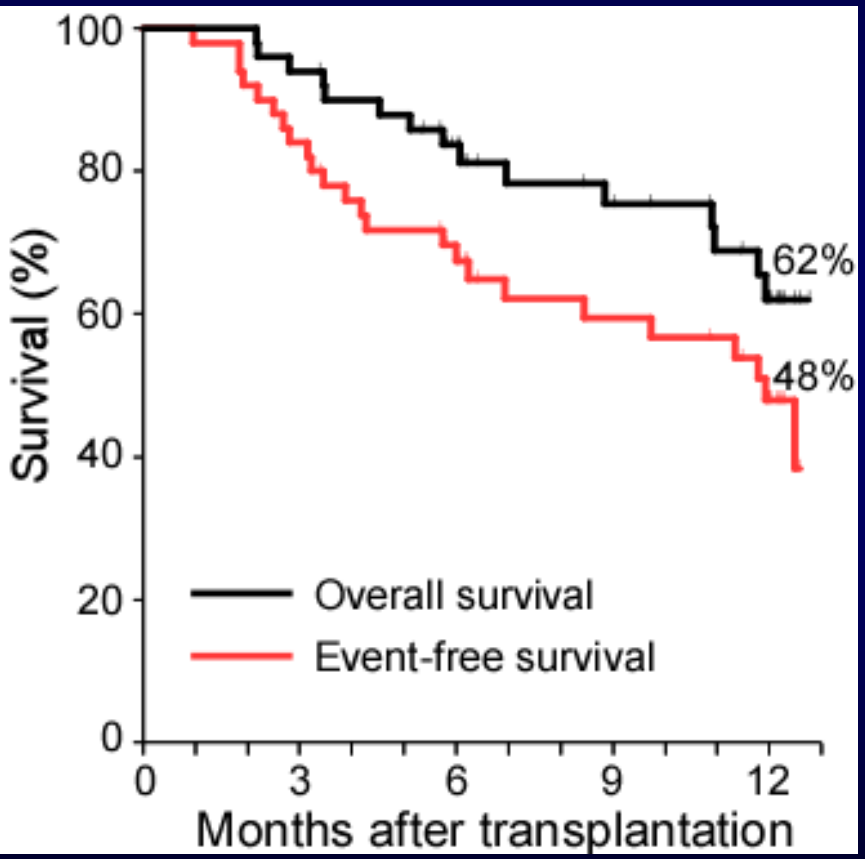
Courtesy of Mary Eapen

Overall and Disease-free Survival

Cord (0604)



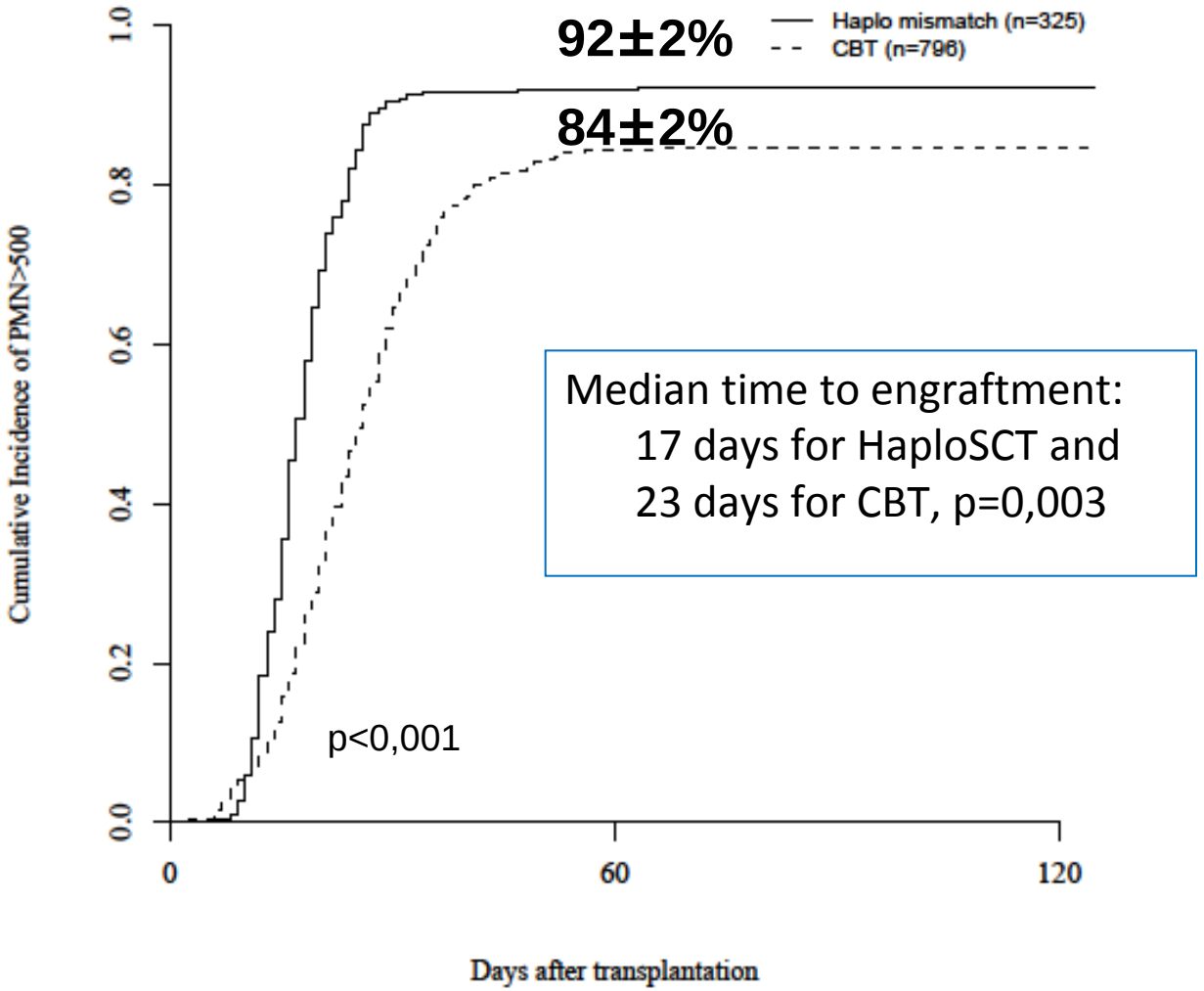
Haplo (0603)



Courtesy of Mary Eapen

Eurocord and ALWP-EBMT study for comparing outcomes after CBT and non TCD haploidentical Tx for adult patients with acute leukemia

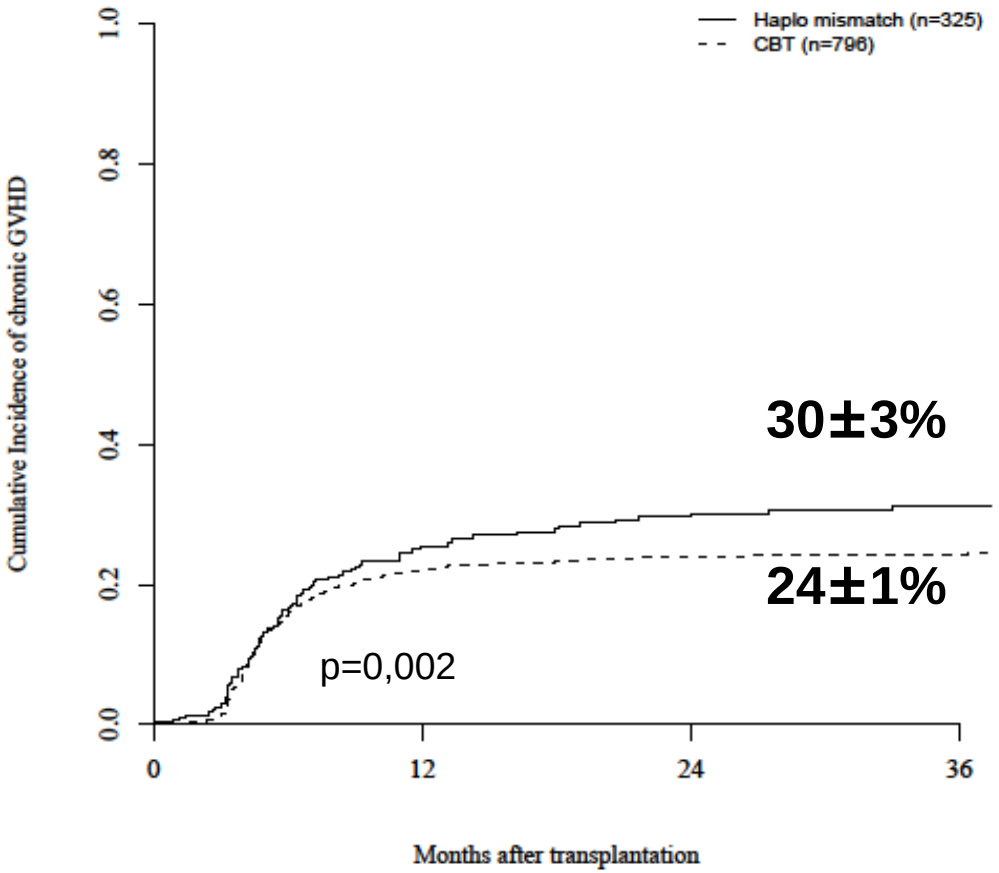
Result- CBT vs Haplo for adult with AL- Neutrophil Engraftment



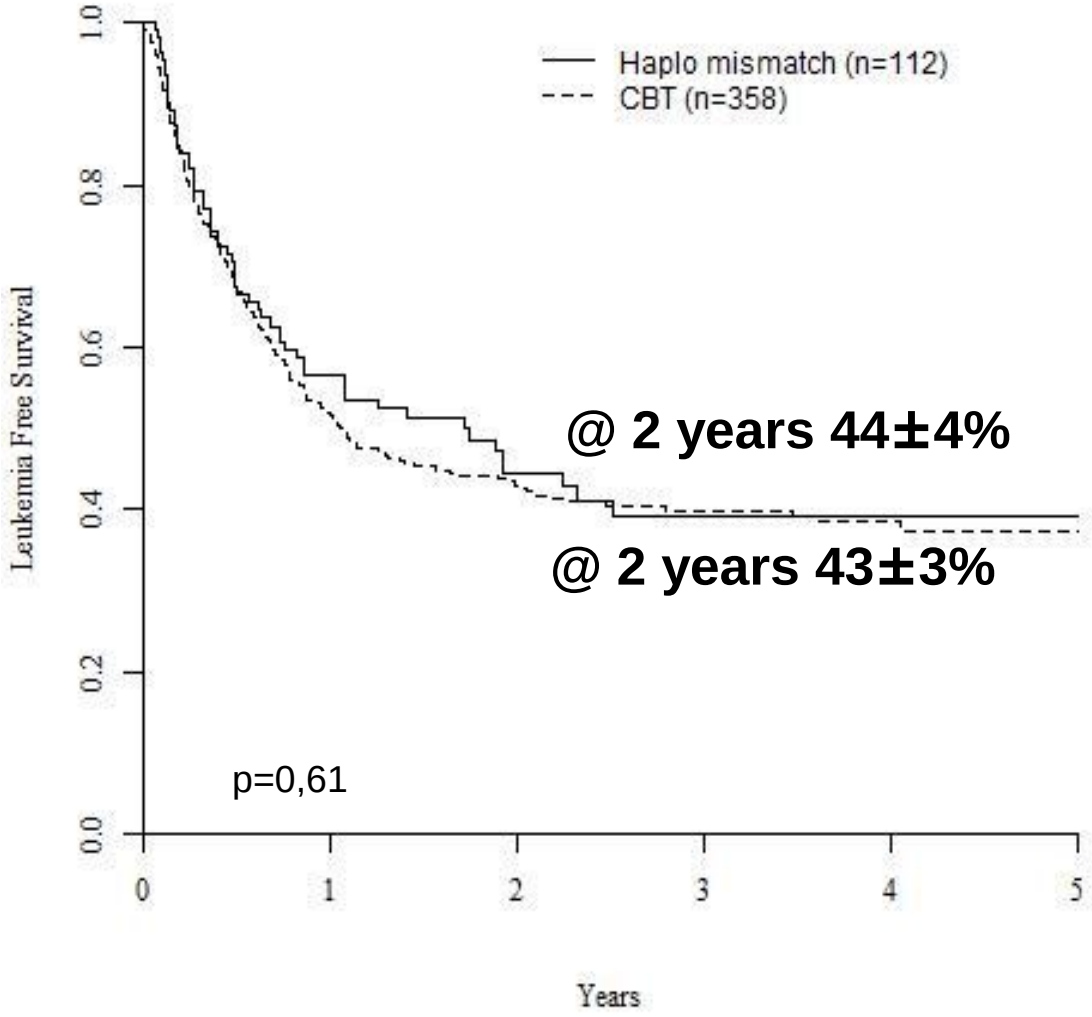
Median time to engraftment:
17 days for HaploSCT and
23 days for CBT, p=0,003

Result- CBT vs Haplo for adult with AL- GVHD

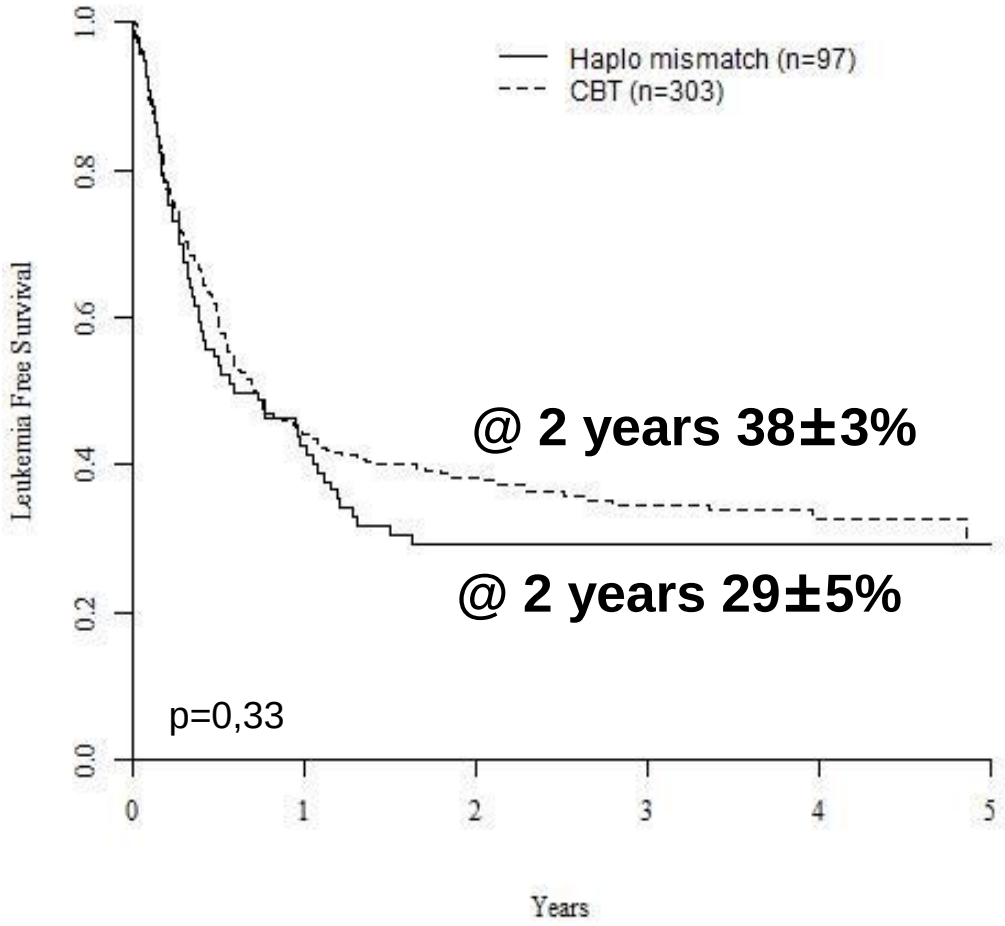
CI of acute GVHD was 27±3% and 31±3% after HaploSCT and CBT, p=0,14



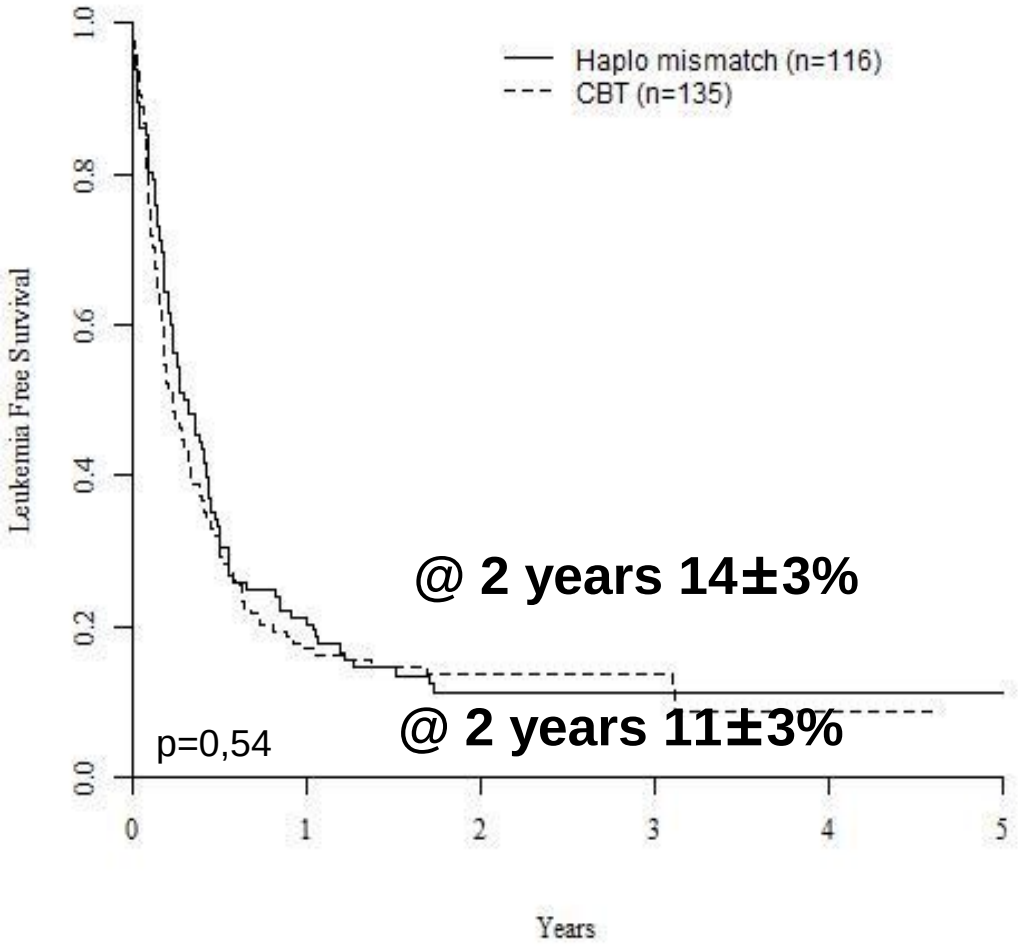
Result- CBT vs Haplo for adult with AL- CR1
LFS



Result- CBT vs Haplo for adult with AL- CR2 LFS



Result- CBT vs Haplo for adult with AL- Advanced disease status- LFS



Conclusion

- HLA mismatched transplants are feasible and there is no shortage of donors
- Preliminary results of our study show similar NRM, relapse and LFS for CBT and HaploSCT
- Heterogeneity of pts population and, for HaploSCT, of conditioning regimen and GVHD prophylaxys
- Disease status is the most important factor for Tx outcomes
- UCBT is associated with delayed engraftment and reduced chronic GVHD

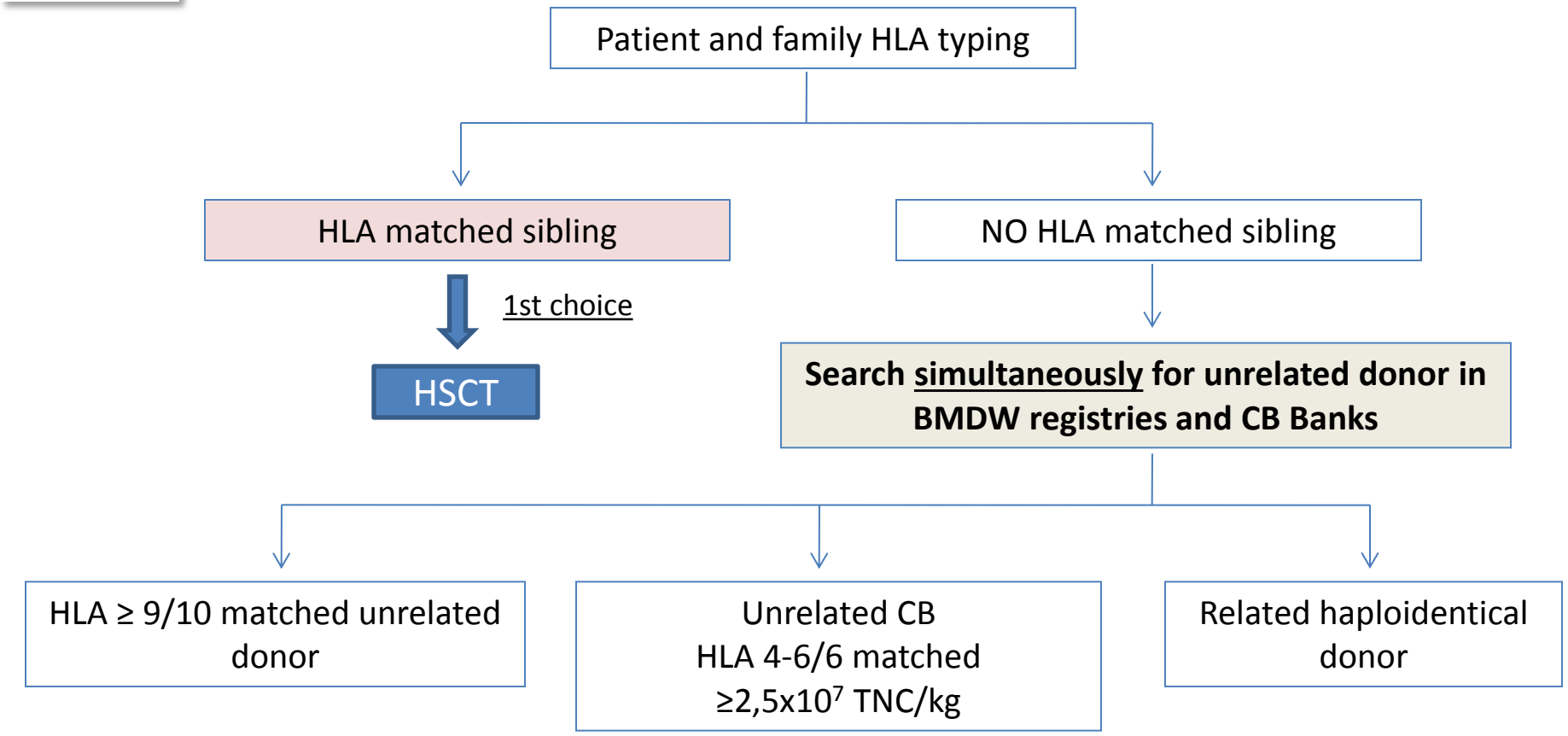
Donor selection algorithm in patients for whom alloHSCT is indicated

TO BE ANSWERED

- Does the patient have a sibling ?
- Does the patient have parents or children ?
- Does the patient have an unrelated donor (after registry search for URD and UCB) ?

Adapted from M.Eapen et al. BBMT 20 (2014):1485-1492

Algorithm of donor search

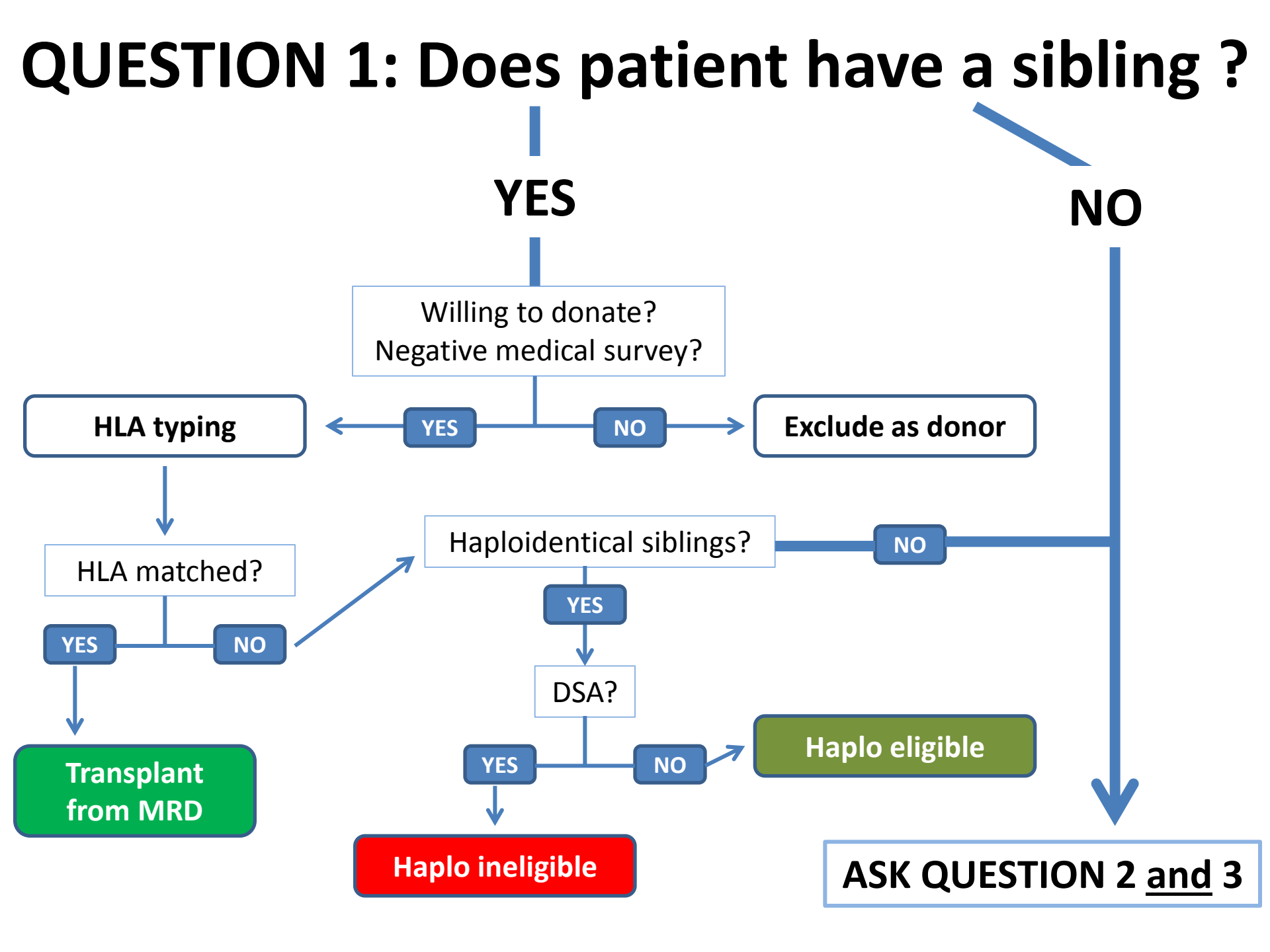


Consider: indication of the HSCT, pts and donor features (CMV, ABO, age, donor sex)

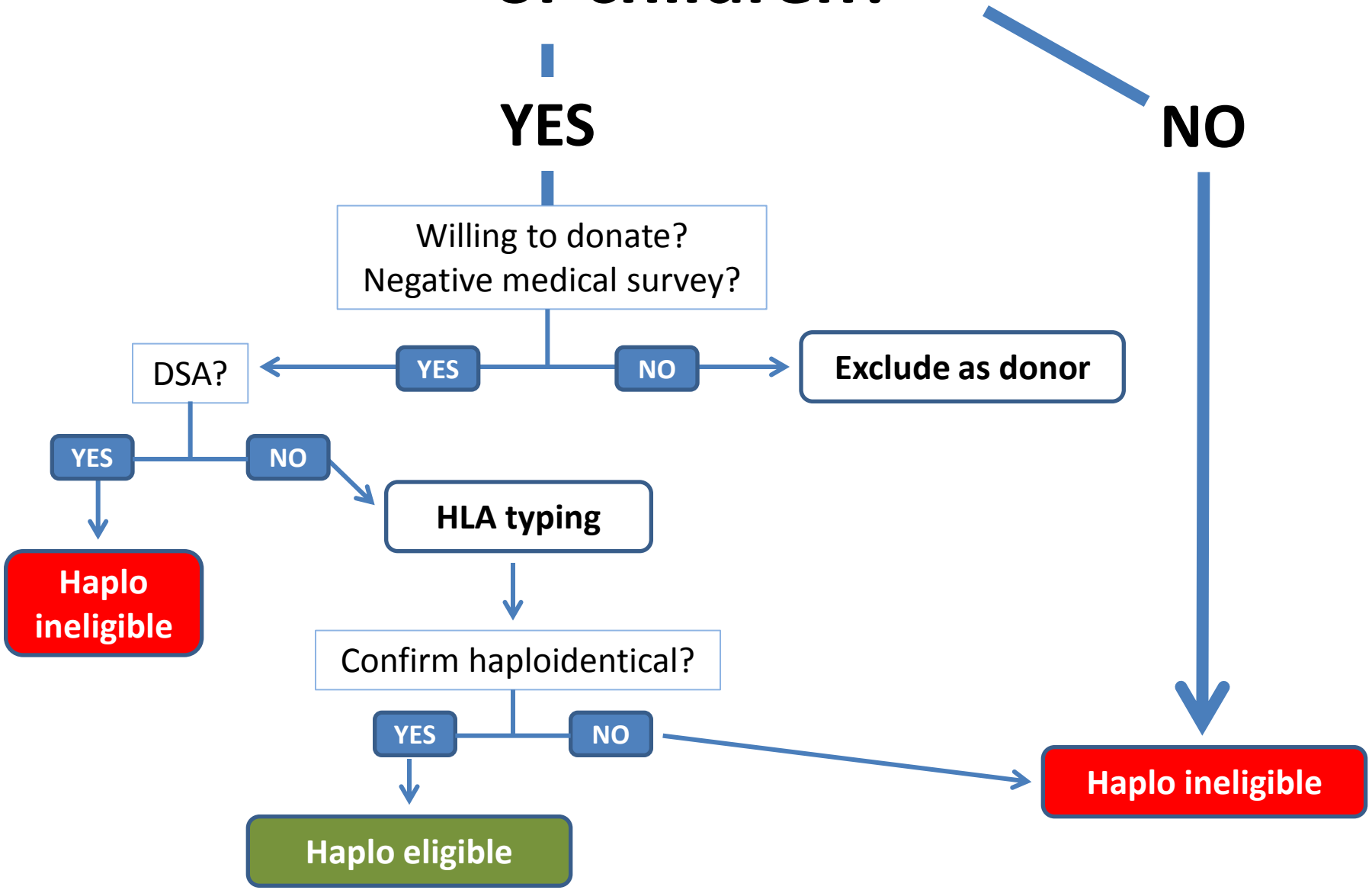
If urgent HSCT needed → prefer CB or related haploidentical donor

Expertise of the centre is very important

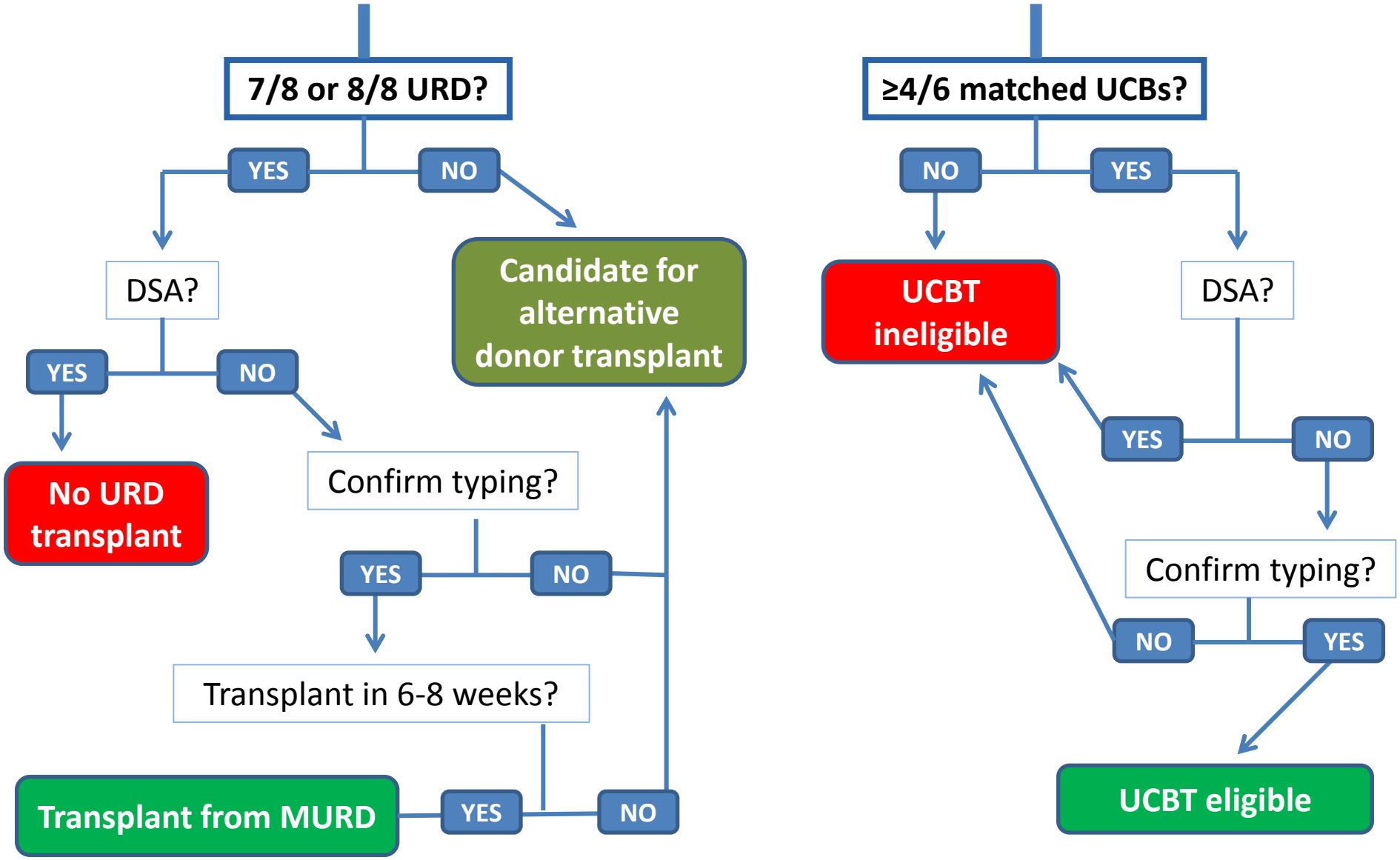
If low cell dose in a single unit UCB, consider a double UCBT


QUESTION 1: Does patient have a sibling ?
YES
NO
Willing to donate?
Negative medical survey?
YES
NO
HLA typing
Exclude as donor
HLA matched?
YES
NO
Haploidentical siblings?
NO
YES
DSA?
YES
NO
Haplo eligible
Transplant from MRD
Haplo ineligible
ASK QUESTION 2 and 3

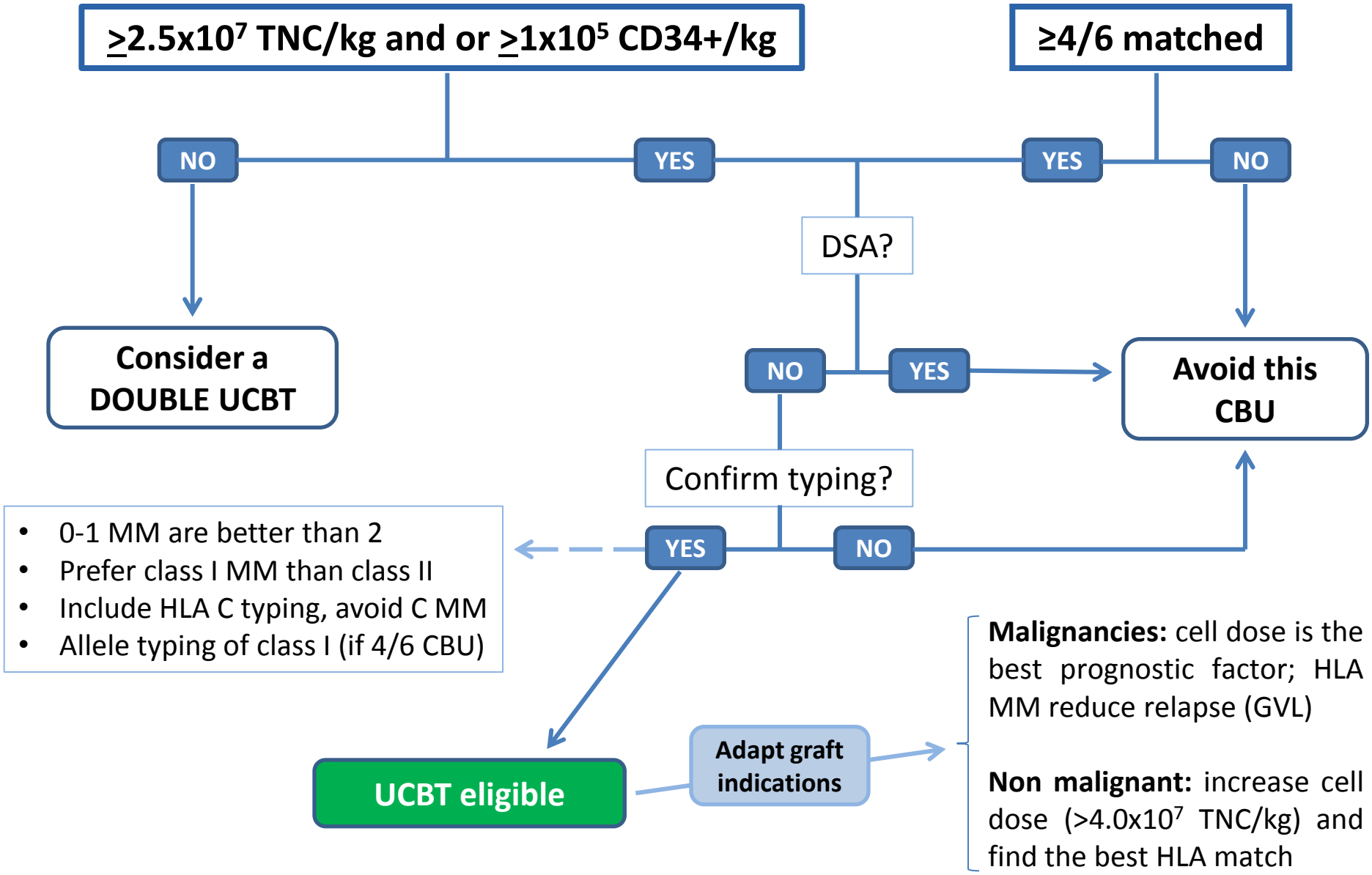
QUESTION 2: Does patient have parents or children?



QUESTION 3: Does patient have an unrelated donor (Registry search for URD and UCB) ?



Criteria of CBUs choice - EUROCORD



Conclusion and questions

- **HLA mismatched HSCT transplants are feasible, this means that there is no shortage of donors**
- **Is MUD=CB=Haplo?** All retrospective studies in children and adults with acute leukemia showed that alternative sources such as UBMT, UCBT or Haplo, can treat a number of patients with some different outcomes but similar LFS
- **Comparative registry-based studies are still necessary**
- **Collaborative Protocols should explore new methods to improve results**

The final choice of the SC source will depend on expertise and policy of each center

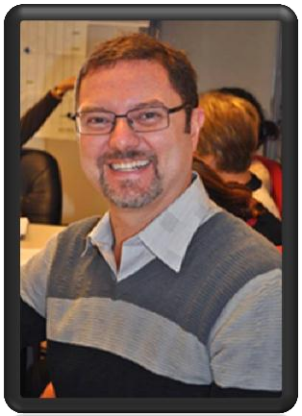
eurocord

Eurocord Meeting in Monaco

ESH /Eurocord
World Cord Blood Congress V and
Innovative cell Therapies
March 5-8, 2015 - Monaco,
Chair: Eliane Gluckman

Eurocord Monacord team 2014/2015

Annalisa Ruggeri, MD



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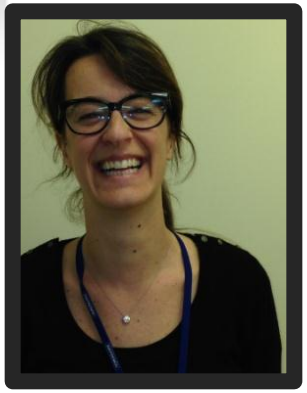

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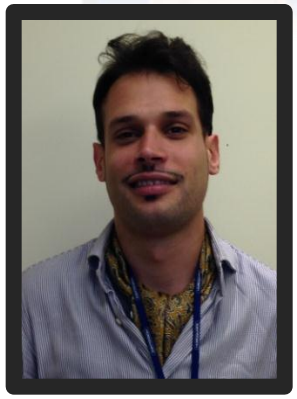

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