Pros and Cons of Stem Cell Sources and their availability in Africa

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Introduction

- The ability to perform a haematopoietic stem cell transplant depends on the availability of a suitable donor.
- Haematopoietic stem cells my be obtained by collection of **bone marrow** , mobilisation and collection of **peripheral blood stem cells** or collection of **umbilical cord blood**
- 32,000 patients in search of a donor for
- stem cell transplantation.
- 16,000 patients searching for an unrelated bone marrow donor, or alternative stem cell transplantation.
- Less than 30-40% of patients searching for a donor will find one

Stem Cell Sources

- HLA Identical Sibling
  - First Choice
  - Bone Marrow vs PBSC
- 1/3 chance

- Unrelated donor
  - 10/10 or 9/10
- 25 million donors worldwide

  SABMR 67000 , Nigerian Registry 300
- 600000 units

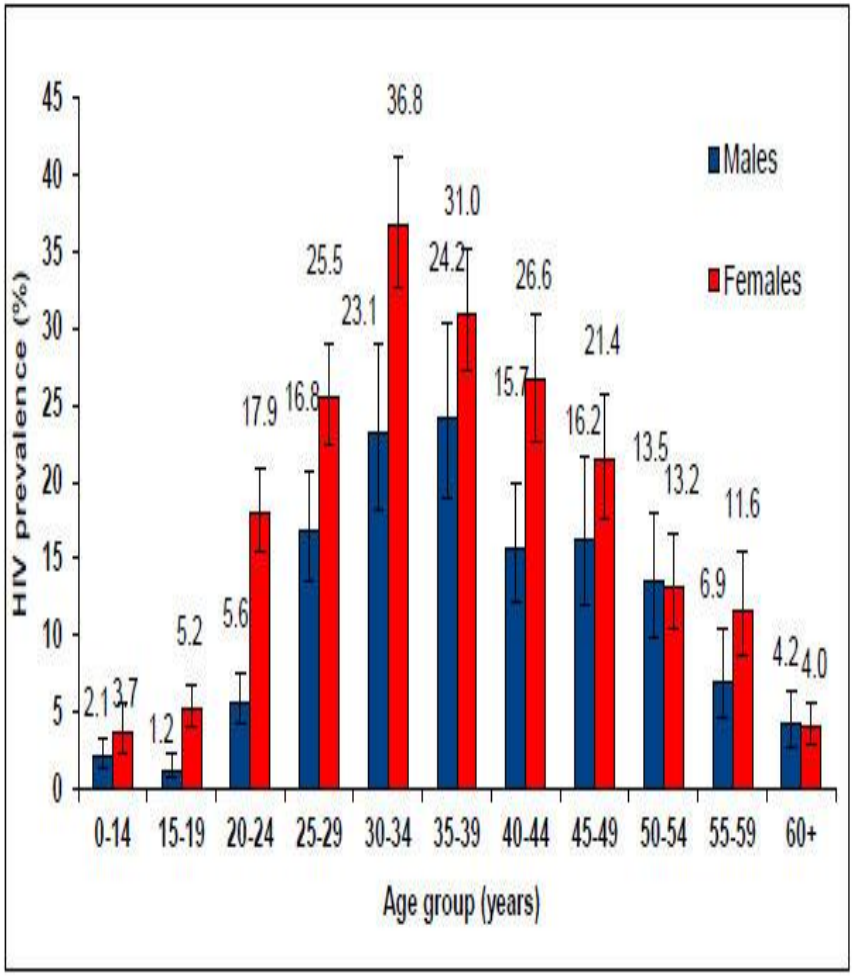
  No Public Cord Banks in Africa

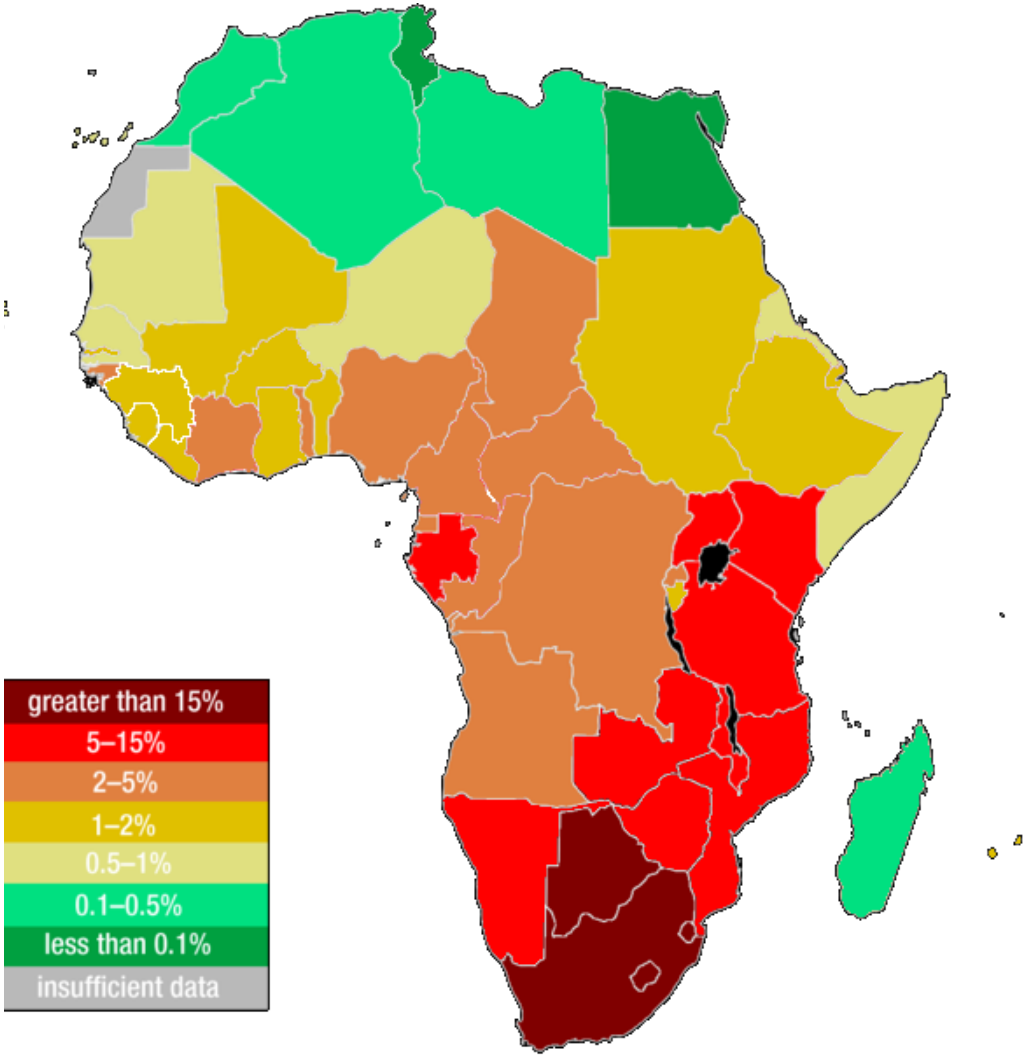
- Cord Blood

- Haploidentical
- Inevitable

SOUTHAFRICA
THE RAINBOW NATION

Figure 1: HIV prevalence by age and sex, South Africa, 2012



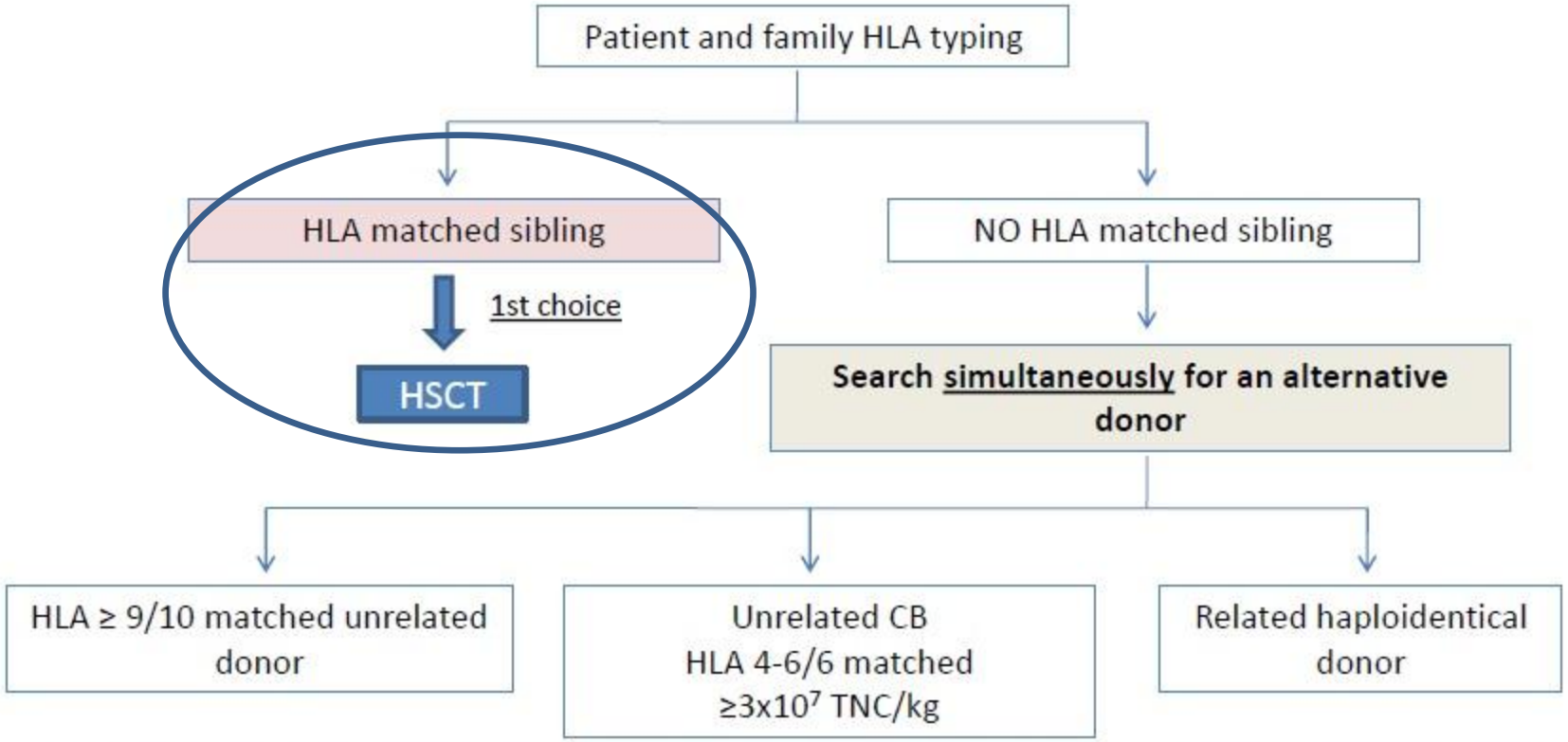


Obstacles in finding Donors in South Africa

- HIV
- Large families but not all same parents
- Fear
- Costs

- Ethnic and genetic diversity
- Largest population group – under represented on the Bone Marrow local registry

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

Peripheral Blood Stem Cells or Bone Marrow

Which is superior

Bone Marrow

ADVANTAGES

- Single collection
- No need for special catheter placement
- Use of cytokines not necessary

DISADVANTAGES

- Performed in theatre as it requires a general anaesthesia
- Slower neutrophil and platelet engraftment
- Higher rates of morbidity for the donor

Peripheral Blood

ADVANTAGES

- Does not require a general anaesthesia and can be performed in the outpatient setting
- Faster neutrophil and platelet engraftment
- Lower rates of morbidity
- Infusion of higher number of T cells with reduced capacity to produce IFN-g
- Enhanced early T cell reconstitution

DISADVANTAGES

- Collection may take several days
- Haemorrhage , embolism and infection are possible complications related to catheter placement
- Increased incidence of anti-HLA immunisation
- Increased early anti-A/B red cell antibody production
- Increased risk of extensive chronic GVHD
- Robust and reproducible CD34 counting should be available+apheresis machines

Bone Marrow versus PBSC

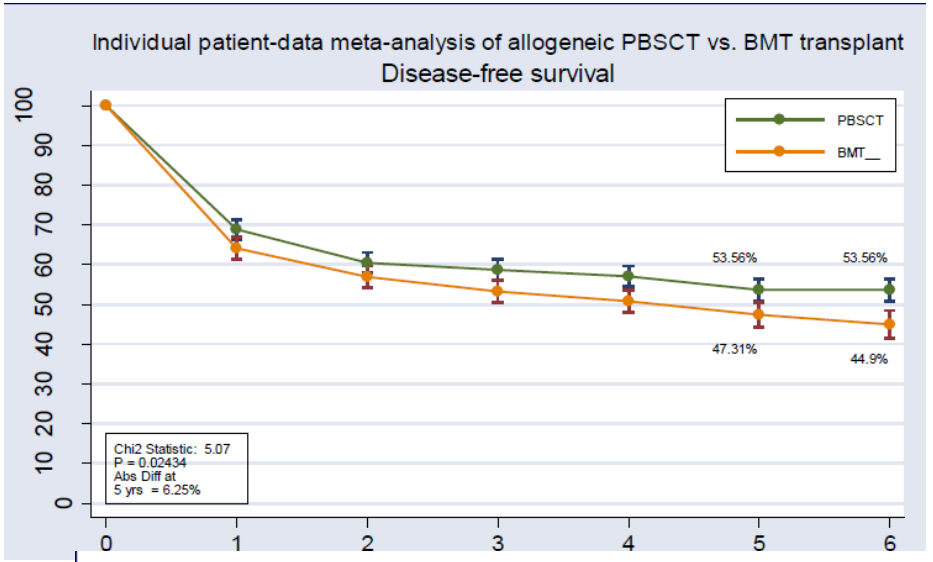
Allogeneic Peripheral Blood Stem-Cell Compared With Bone Marrow Transplantation in the Management of Hematologic Malignancies: An Individual Patient Data Meta-Analysis of Nine Randomized Trials

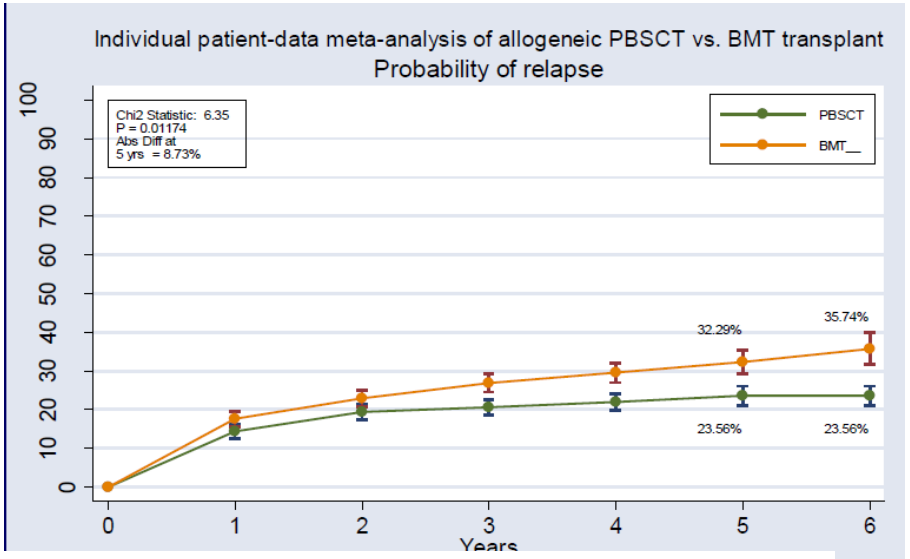
Stem Cell Trialists' Collaborative Group

VOLUME 23 · NUMBER 22 · AUGUST 1 2005

JOURNAL OF CLINICAL ONCOLOGY

- 12 randomised trials have been performed to answer the question – no consistent results between the trials seen for any of the major outcomes.
- PBSC transplants are associated with more aggressive cGVHD
- No overall survival benefit except in a subgroup of patients with unfavourable prognostic features.





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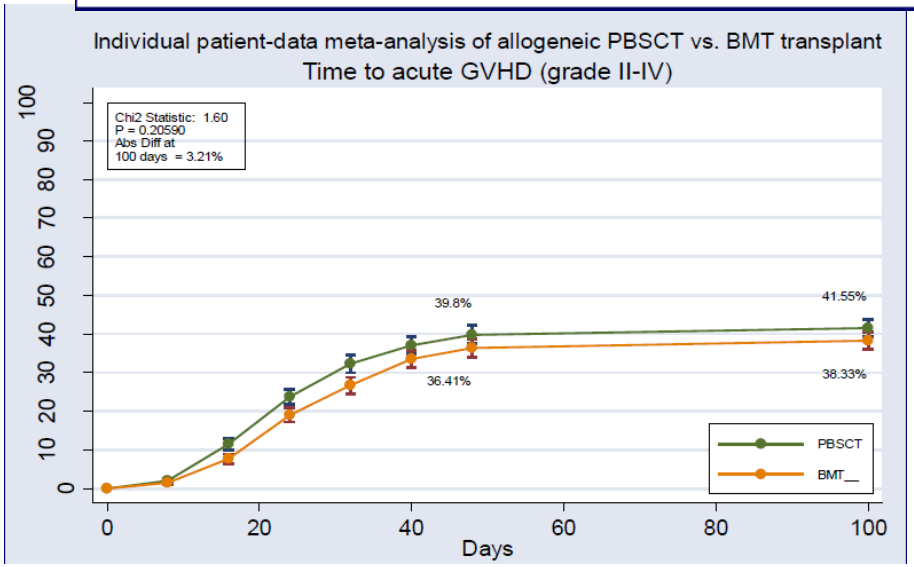

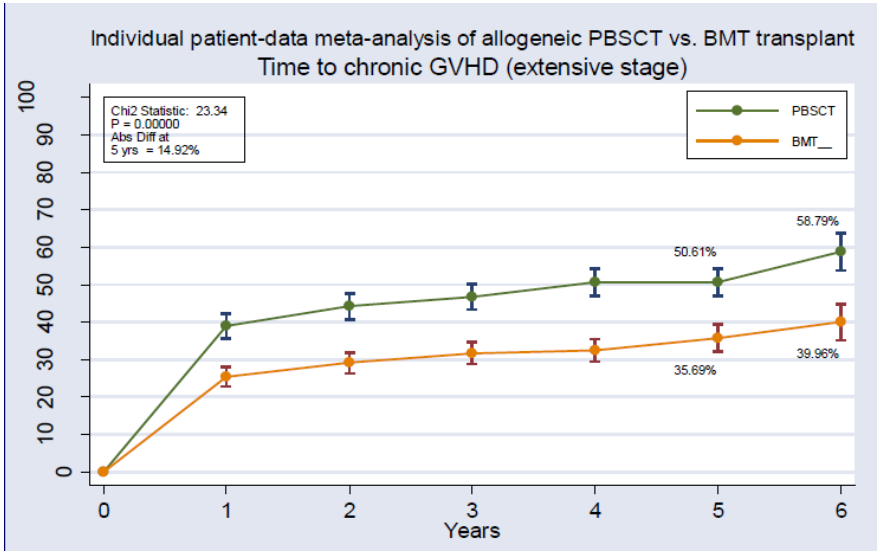

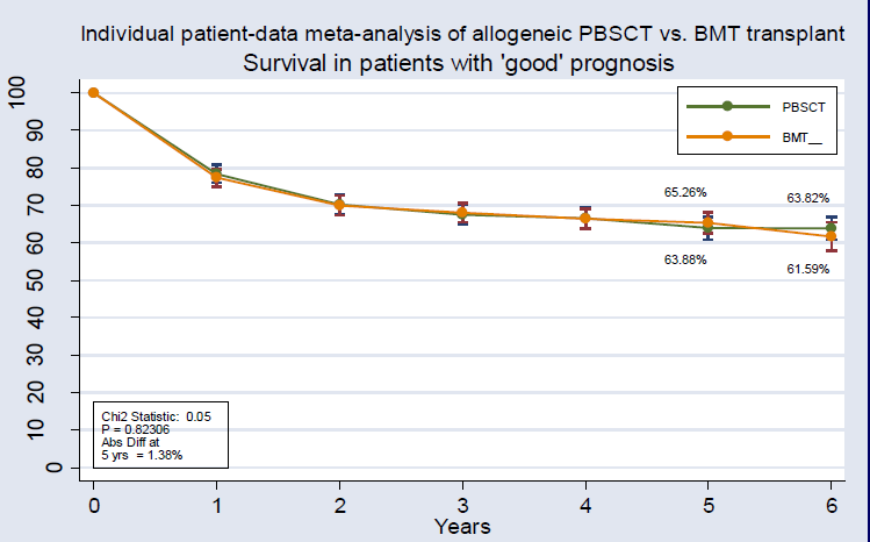

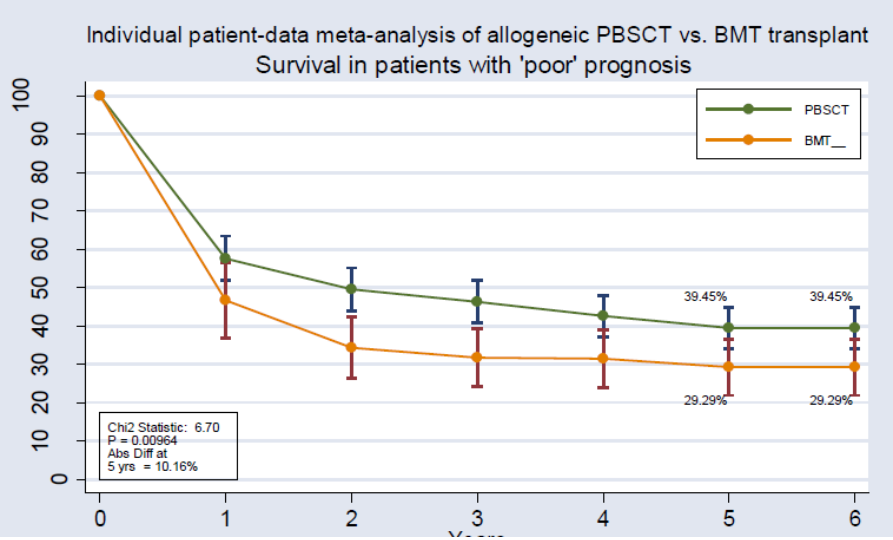

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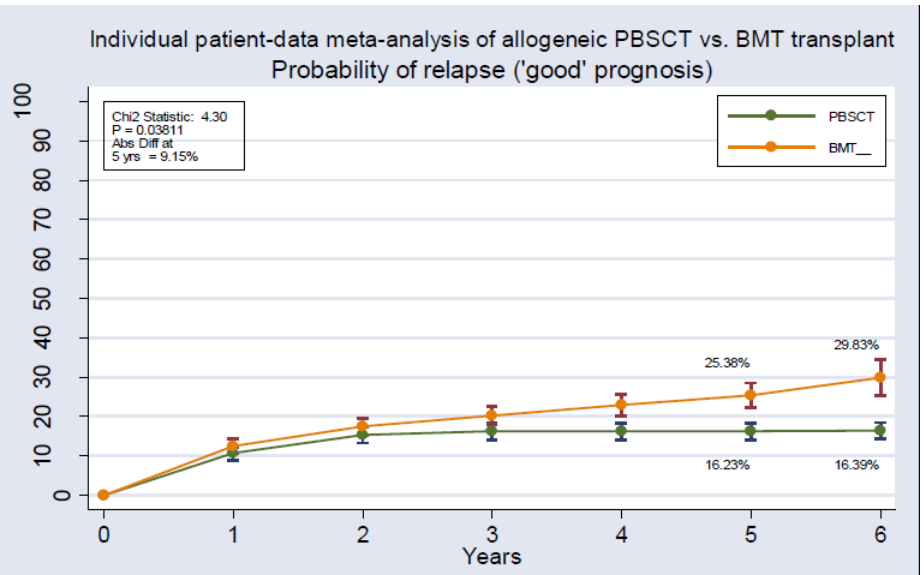
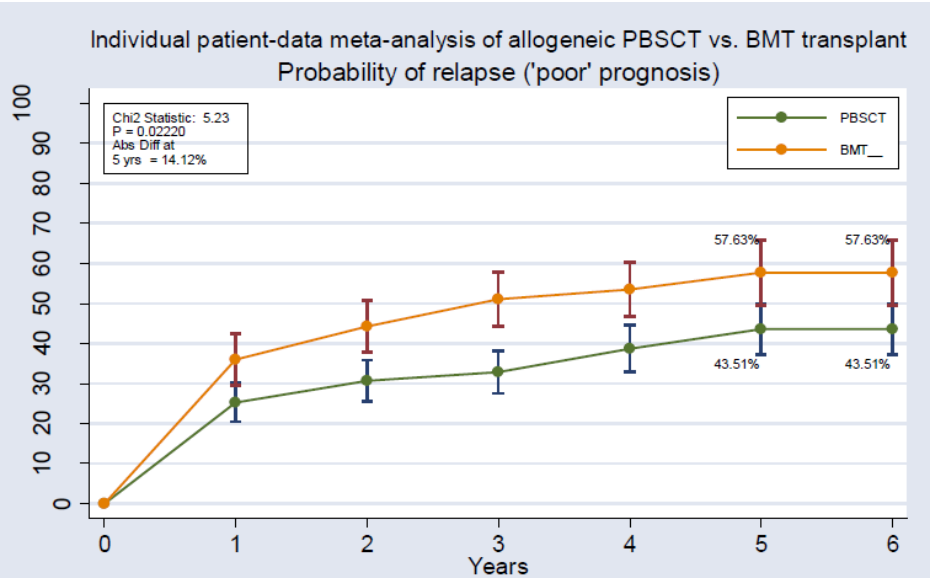
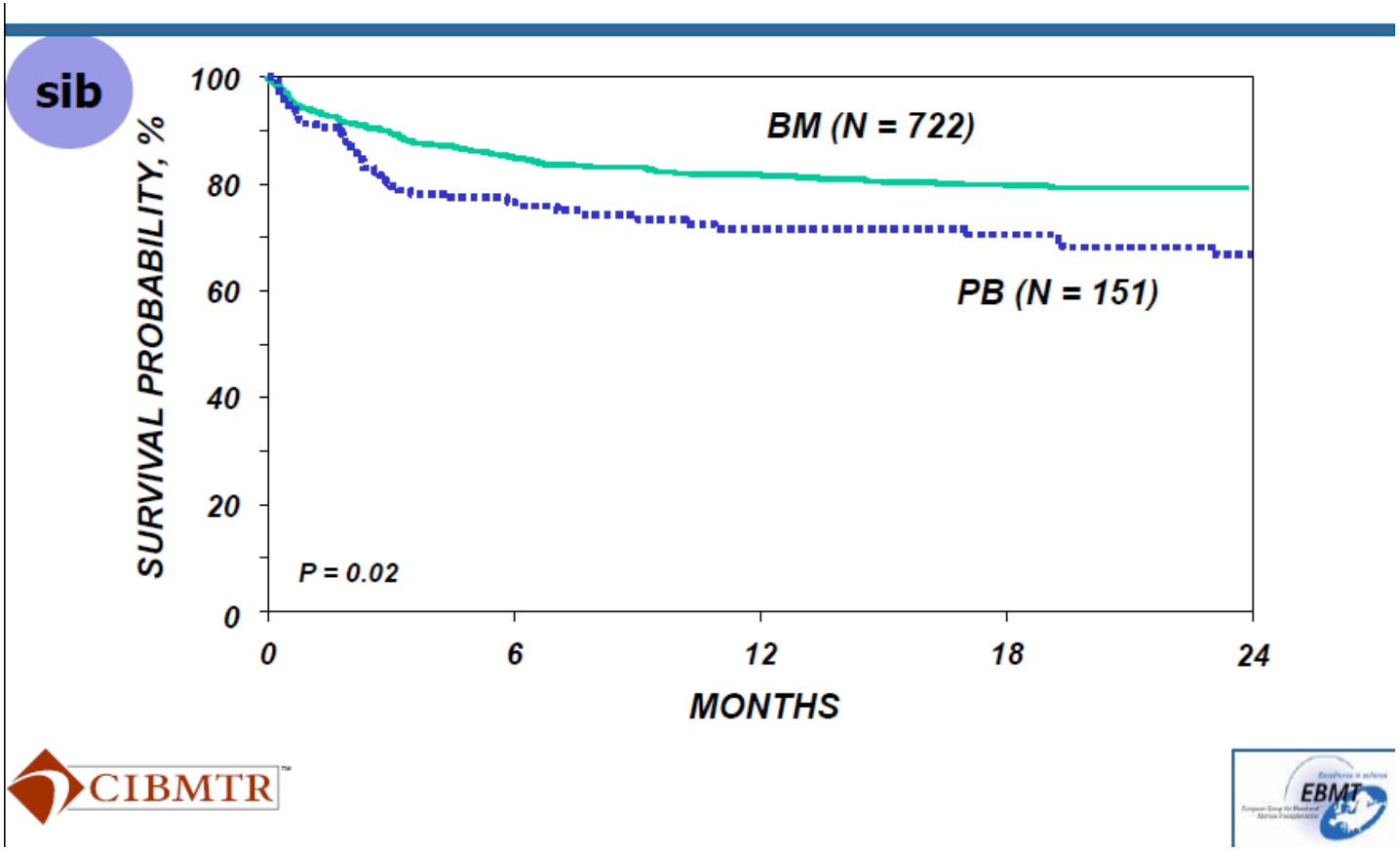




Bone Marrow versus PBSC Survival in Aplastic Anemia



The NEW ENGLAND JOURNAL of MEDICINE

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Peripheral-Blood Stem Cells versus Bone Marrow from Unrelated Donors

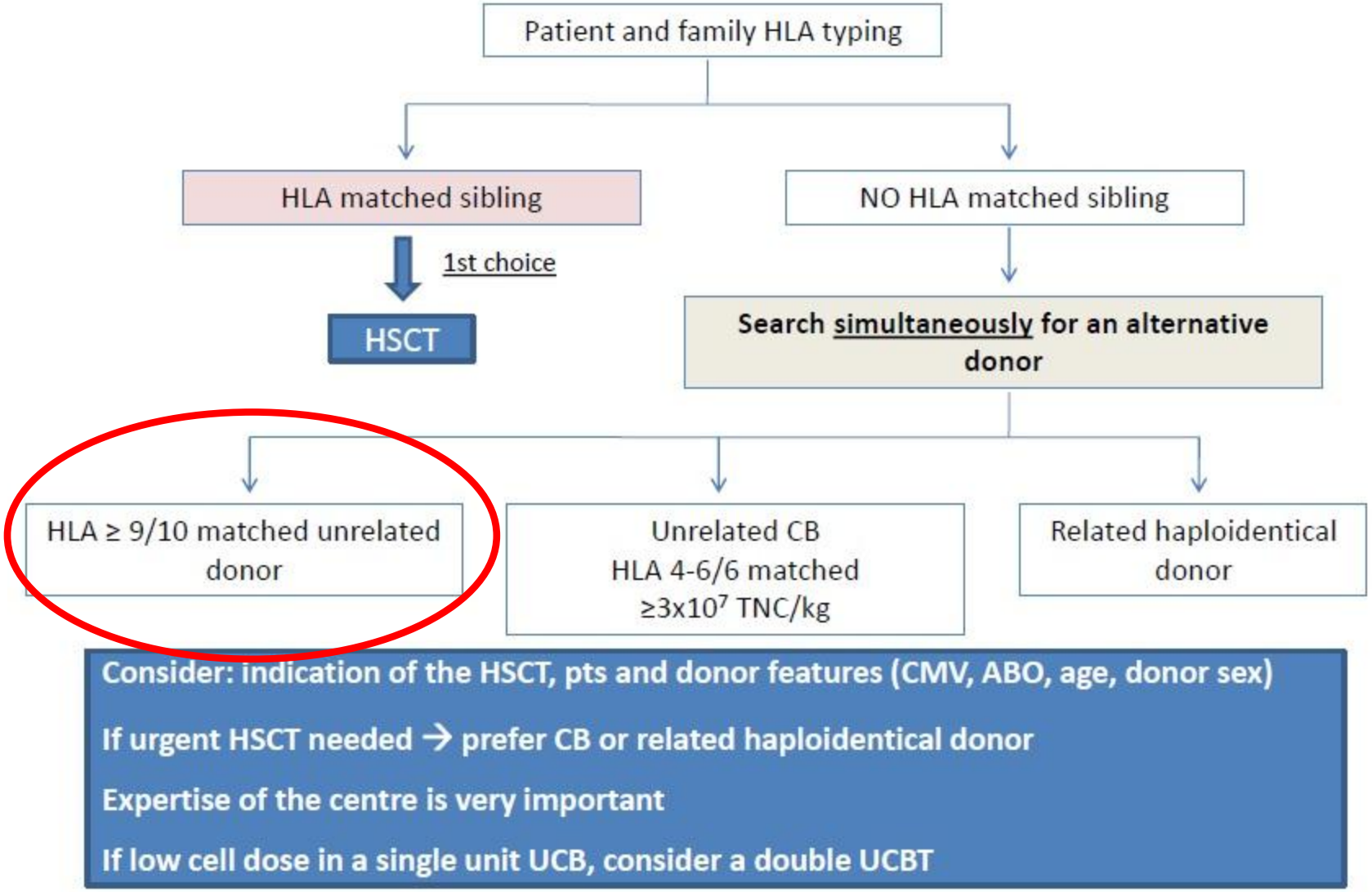
Claudio Anasetti, M.D., Brent R. Logan, Ph.D., Stephanie J. Lee, M.D., M.P.H., Edmund K. Waller, M.D., Ph.D., Daniel J. Weisdorf, M.D., John R. Wingard, M.D., Corey S. Cutler, M.D., M.P.H., Peter Westervelt, M.D., Ph.D., Ann Woolfrey, M.D., Stephen Couban, M.D., Gerhard Ehninger, M.D., Laura Johnston, 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

Bone Marrow versus PBSC

- PBSCs are used in >90% of allogeneic transplants in South Africa
- PBSCs may improve outcome in patients with unfavourable prognostic features.
- It is 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 stem cell source

Algorithm of donor search



Unrelated Donors

Bone Marrow Donors Worldwide
www.bmdw.org

- 25 million donors

-73 registries

-52 countries

- South Africa – 67000
- Nigeria – 300

- 600000 Cord Blood

- 47 Cord Banks

-33 Countries

- 0 in Africa

Matched Unrelated Donor Transplants

- Several factors should be considered in selection of the optimal URD in order to reduce transplant related mortality – the most important is the **degree of mismatch**
- Within the past decade , **high resolution typing** techniques have been developed to allow identification of the polymorphic alleles
- This combined with improved supportive care has resulted in the outcomes of matched unrelated donor transplants being almost similar to matched related donor transplants

Matched Unrelated Donor Transplants

- MUD transplants increase donor availability

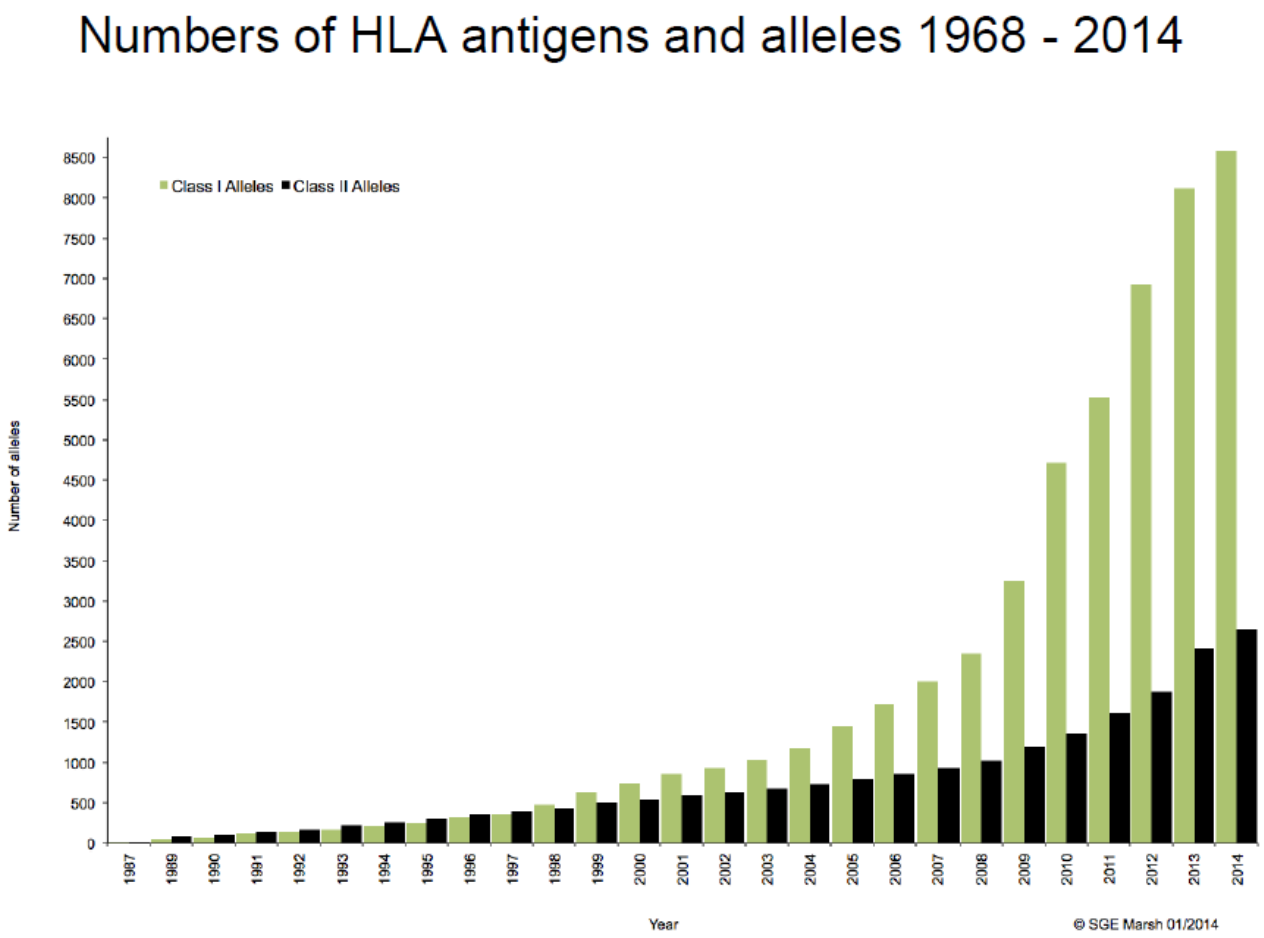
but

- 25 million donors – certain ethnic groups not well represented
- Costs +/- $40-50000
- Time to acquire graft – may not be appropriate in urgent transplants

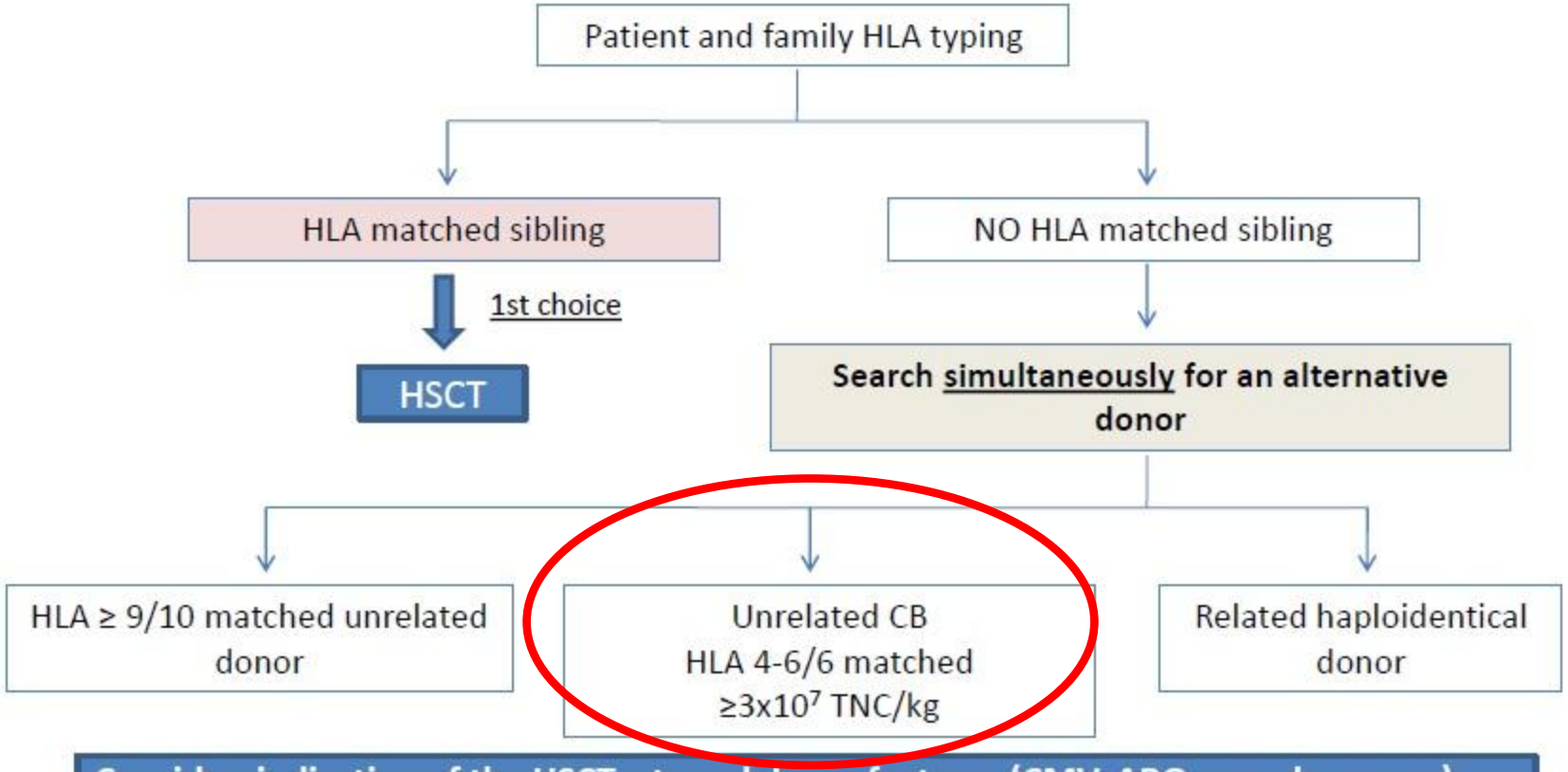
Matched Unrelated Donor Transplants

- Among world populations , Africans present the highest level of genetic diversity
- The complex genetic makeup of the HLA loci in Africans bears the marks of the history of each region which includes waves of migration , different levels of admixture with other populations , changes in the effective population size and strong selective pressure exerted by numerous pathogens in Africa.
- Africa is the most genetically diverse geographical region in the world and consequently it harbours diverse and novel HLA alleles.
- Africa can’t rely on established international registries to find unrelated donors for its population – need to establish own registries , larger number of donors

Matched Unrelated Donor Transplants



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

Cord Blood Transplantation

- Has been used since 1988 to successfully treat children and adults needing stem cell transplantation
- Cord blood is easily collected (non invasively) , and provides a rapidly available source of stem cells
- 600000 cord units available worldwide
- Currently no public cord blood bank in Africa

Cord Blood Transplantation Advantages

- More than 25 years experience
- Immediate availability
- Absence of donor risk , and few ethical problems
- Generally applicable for use in children and adults with malignant and non malignant disorders
- Cord Blood is immature so HLA mismatches are accepted
- Genetically diverse populations are more likely to benefit from cord blood
- Survival outcomes comparable to other alternate stem cell sources
- Use extended in older populations with reduced intensity conditioning and double cord transplant
- Low risk of transmissible infections

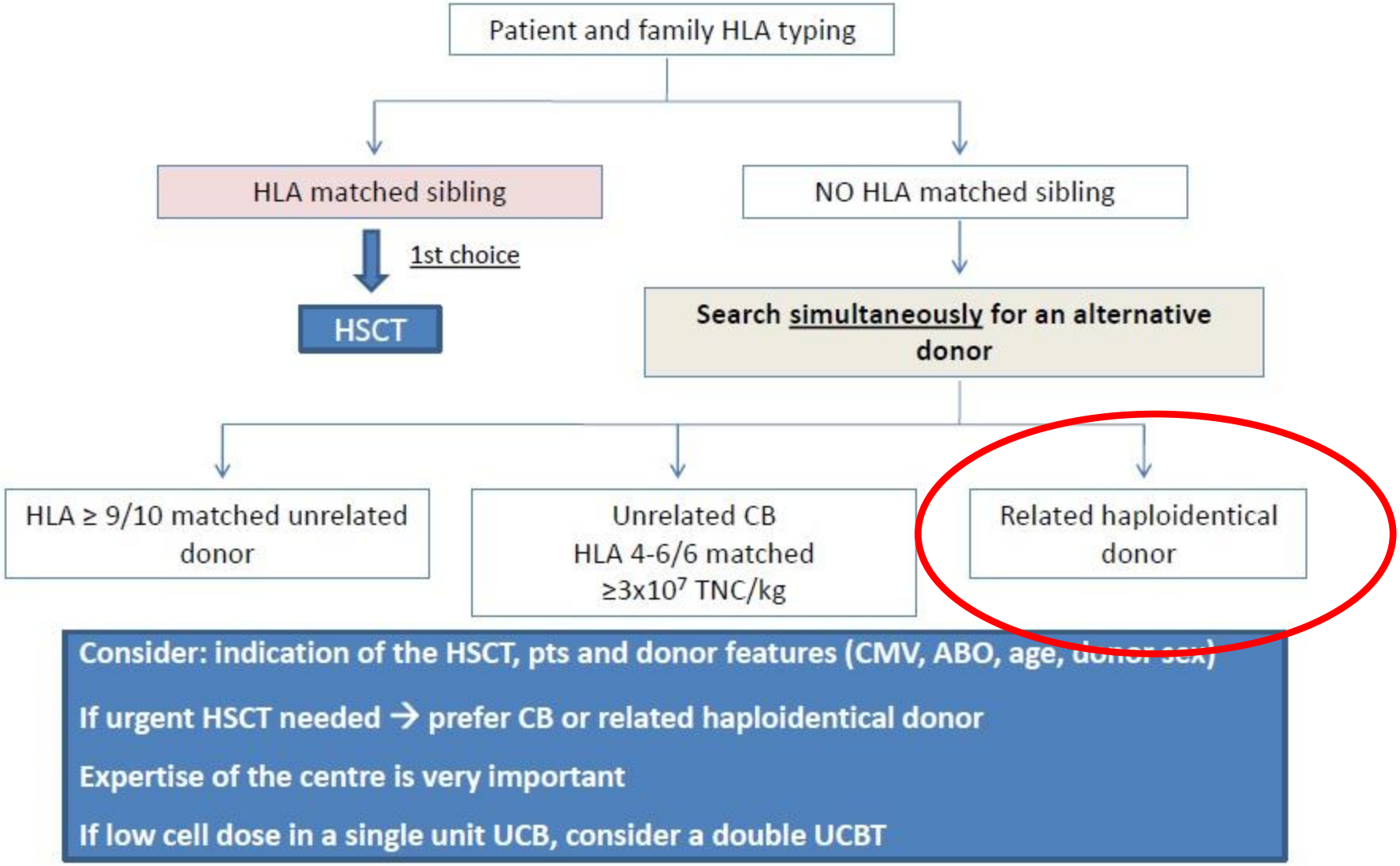
Cord Blood Transplantation Disadvantages

- Delayed haematopoietic recovery due to relatively low Total Nuclear Cell dose delivered and HLA mismatches
- Longer Length of hospital stay
- GVHD risks are much lower which may offer better quality of life but less graft versus tumour effect in aggressive malignancies.
- Cost
- No Public Cord Blood Banks in Africa

Double Cord Transplant

- Improves engraftment by increasing total cell dose
- Lowers risk of relapse
- Higher GVHD incidence
- Reduced TRM when compares to single unit historic controls
- Cost of acquisition of two cord blood units and cost effectiveness of the procedure.

Algorithm of donor search



Haploidentical Transplants

- Haplo-related transplants was pioneered in the 1970's – most results have been provided by single centres and few large series have been published
- Both BM (primed with G-CSF or not) and peripheral blood is used
- Selection of maternal overt paternal donors has been shown to result in better survival as the maternal immune system is tolerised to foetal antigens during pregnancy
- Use of haploidentical sibling with noninherited maternal antigens associated with lower TRM outcomes compared with haploidentical siling donors with noninherited paternal antigens

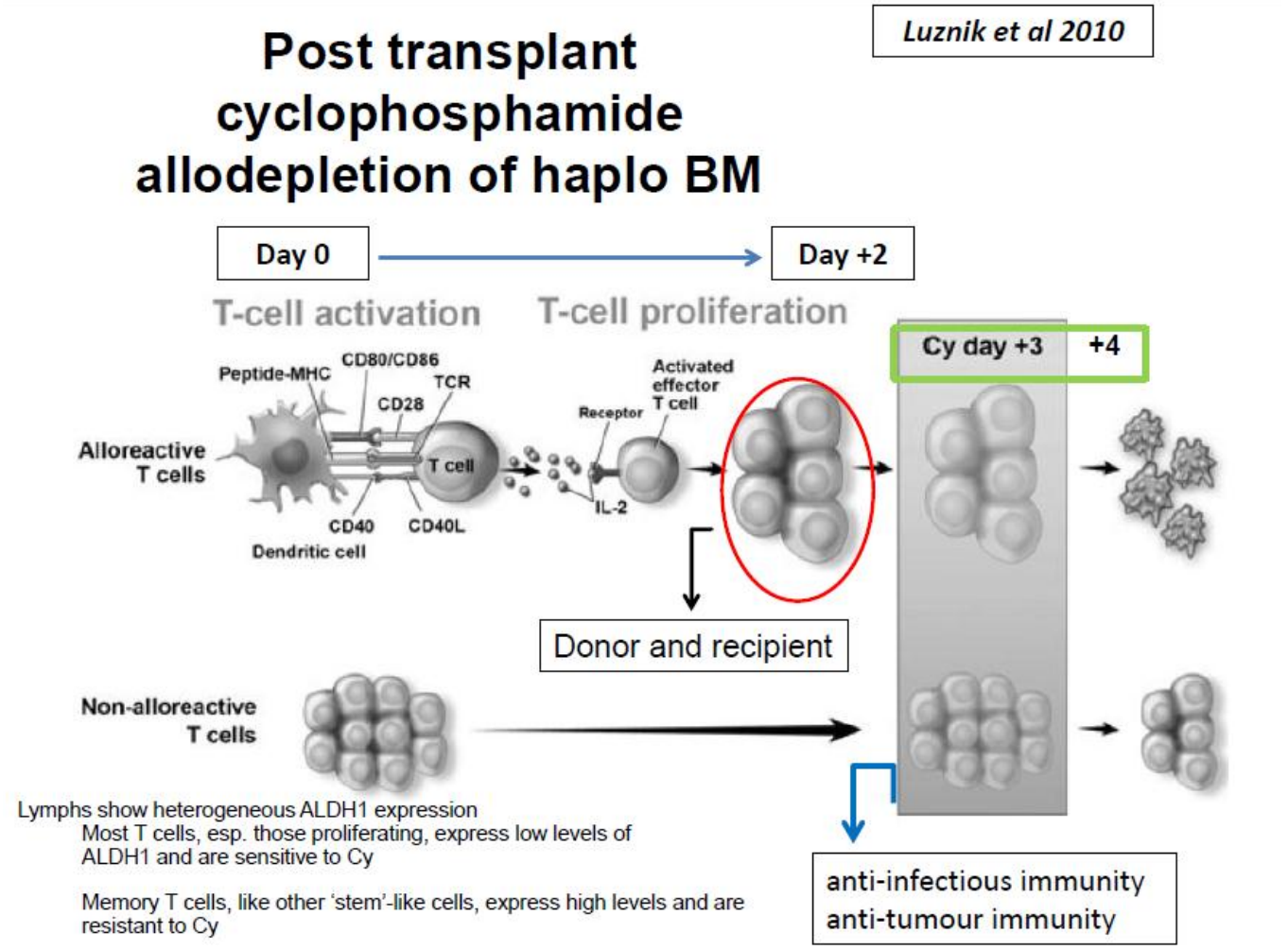
Haploidentical Transplants

- Only a haplotype (3/6 or 4/8 loci) is shared between the donor and the recipient.
- Virtually everyone has at least an haploidentical donor – immediately available
- Applicable to children and adult with malignant and no malignant disorders
- Cost of collection is less than cord blood or MUD
- Results comparable to other stem cell sources
- New technologies have been recently introduced with promising results (BALTIMORE)

Haploidentical Transplants Disadvantages

- High risk of graft failure and GvHD
- T cell depletion or enhanced GvHD prophylaxis is required resulting in delayed immune reconstitution (increased risk of infections and relapse)
- Few publications on long term results

The Baltimore Concept
Cylophosphamide Post Transplant



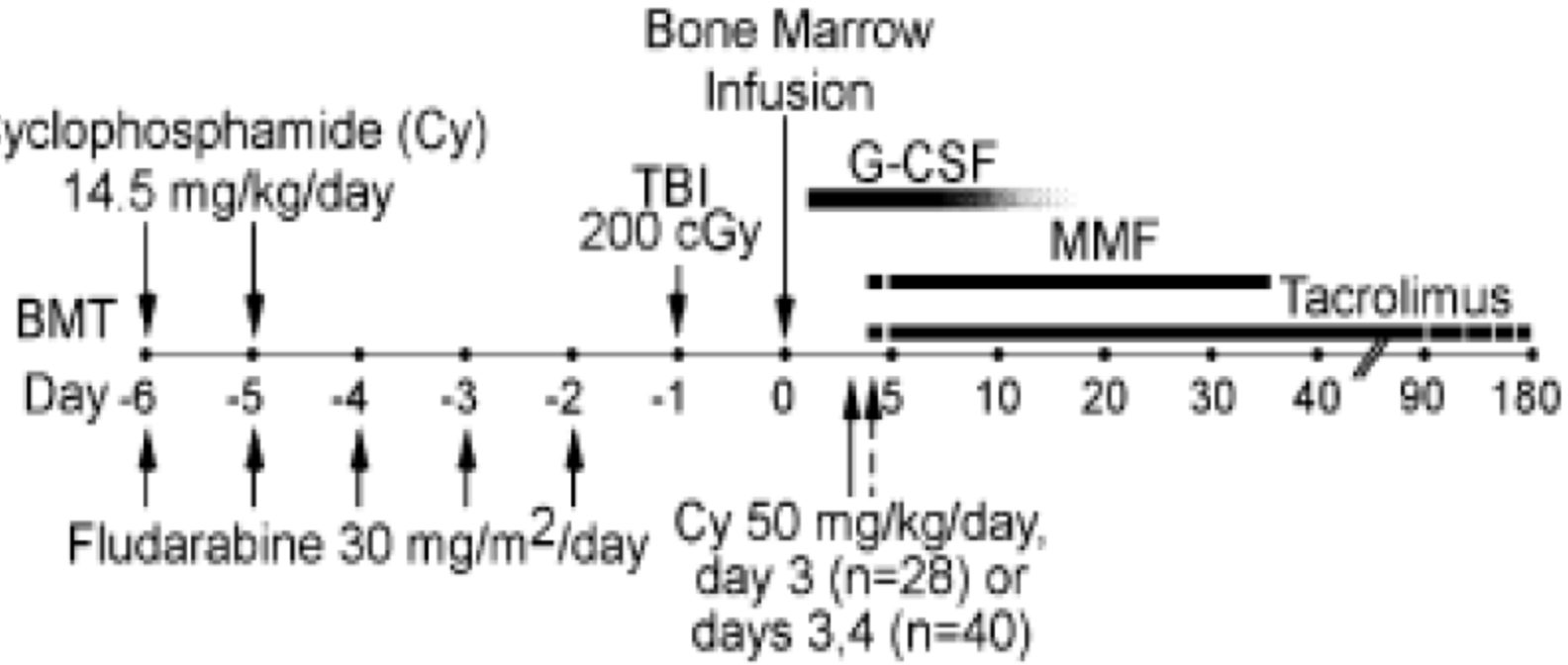
Lymphs show heterogeneous ALDH1 expression
Most T cells, esp. those proliferating, express low levels of ALDH1 and are sensitive to Cy

Memory T cells, like other 'stem'-like cells, express high levels and are resistant to Cy

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

BBMT 14:641-650, 2008

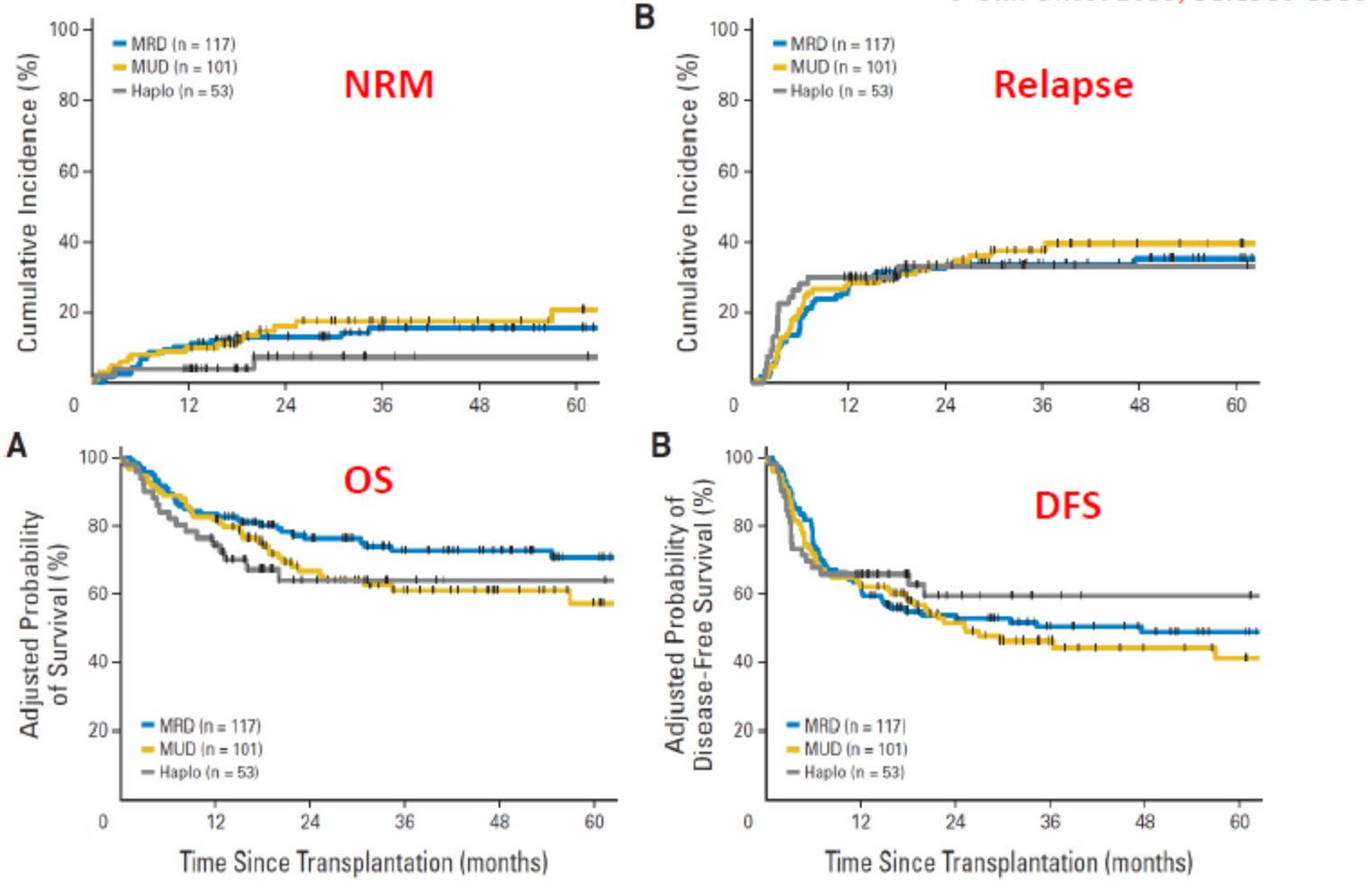
Leo Luznik,[1] Paul V. O'Donnell,[2,3]* Heather J. Symons,[1] Allen R. Chen,[1] M. Susan Leffell,[1] Marianna Zahurak,[1] Ted A. Gooley,[2,3] Steve Piantadosi,[1] Michele Kaup,[1] Richard F. Ambinder,[1] Carol Ann Huff,[1] William Matsui,[1] Javier Bolaños-Meade,[1] Ivan Borrello,[1] Jonathan D. Powell,[1]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



Haploidentical Transplants

- G-CSF primed , unmanipulated bone marrow transplantations from an haploidentical family donor followed by post transplant cyclophosphamide is feasible and very effective
- The procedure does not require expensive lab facilities or personnel specifically devoted to cell manipulation , provides an easier management of the transplant workup , does not involve costs related to unrelated graft acquistion .
- May extend the practice of haploidentical transplant to all centres involved in an allogeneic transplant program.

Multiple factors involved in the Donor and HSCs source choice

Donor's Safety & features

Patient's & Disease's features

Transplant setting

Centre Clinical Approach &Expertise

Cost

The wide choice of donor sources has extended the possibilities of offering HSCT to almost all patients who need this procedure However in Africa there are still many obstacles and challenges….