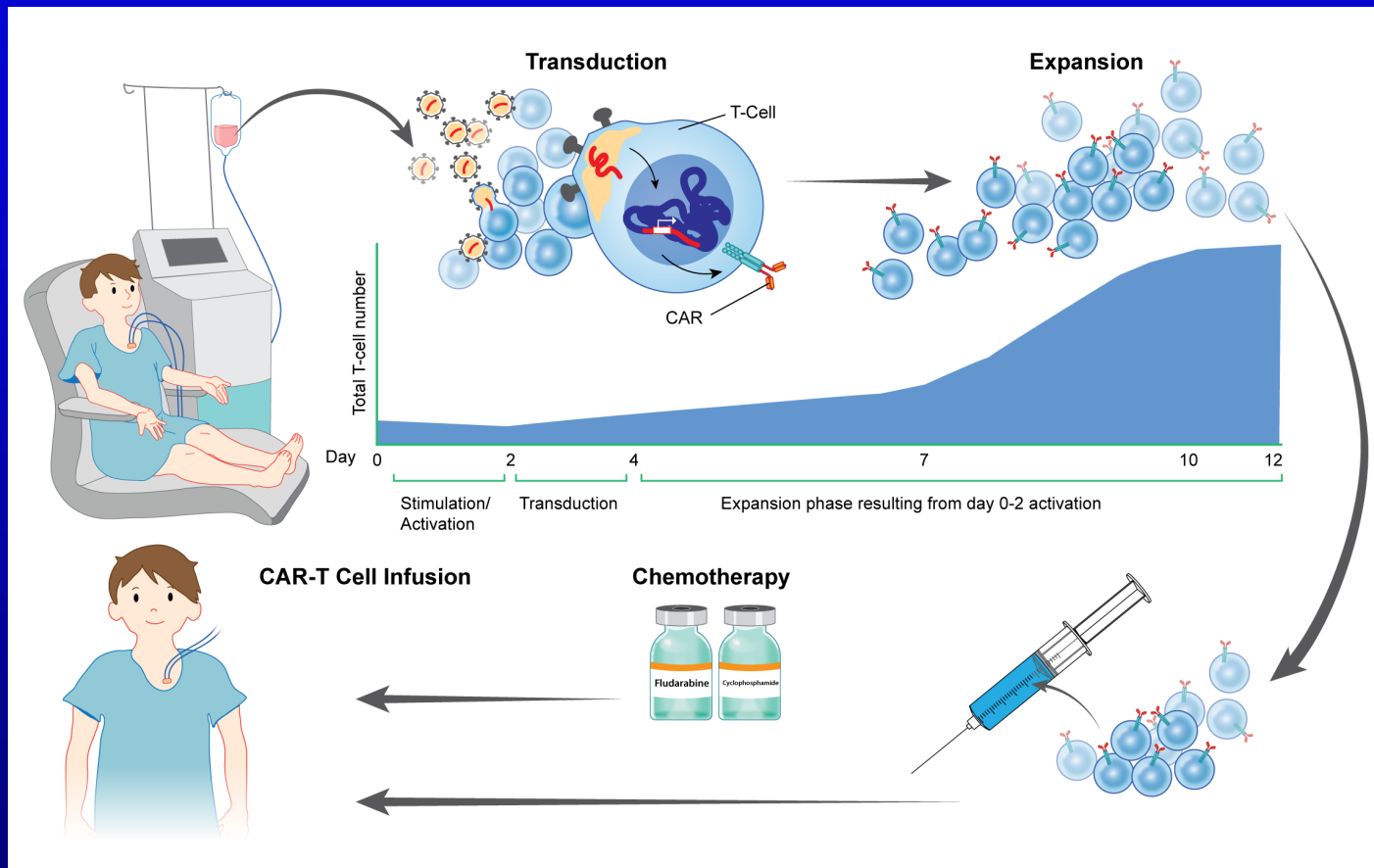


CAR-T Cell Therapy and Hematopoietic Stem Cell Transplantation Current Status and Future Directions

**RICHARD W. CHILDS M.D.
NIH, BETHESDA MD**

What are CAR-T-Cells and How Do You Make Them



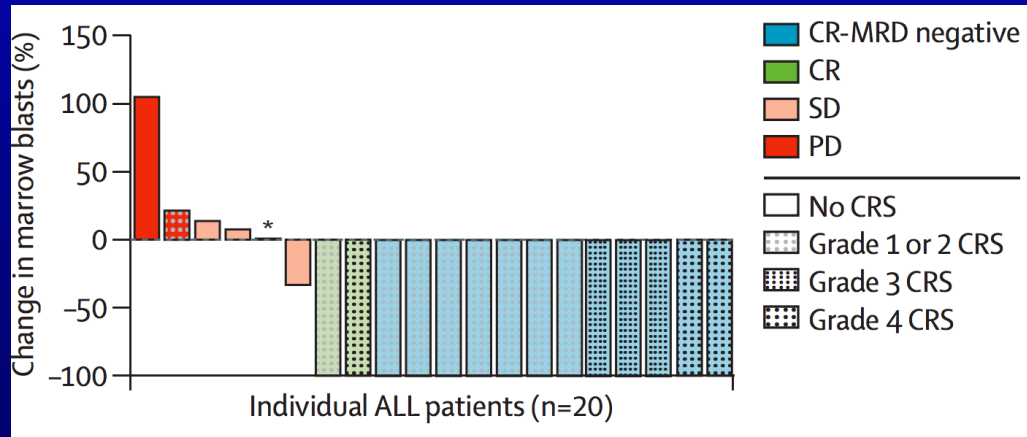
1. Apheresis
2. Stimulation and Transduction
3. Expansion
4. Lympho-depletion
5. Infusion

- Retains the functionality of a T-cell with the antigen recognition properties of antibody
- Recognize cell surface antigens independent of MHC, have co-stimulatory signals integrated

CD19 CAR Clinical Updates (NCI-POB)

T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial

Daniel W Lee, James N Kochenderfer, Maryalice Stetler-Stevenson, Yongzhi K Cui, Cindy Delbrook, Steven A Feldman, Terry J Fry, Rimas Orentas, Marianna Sabatino, Nirali N Shah, Seth M Steinberg, Dave Stroncek, Nick Tschernia, Constance Yuan, Hua Zhang, Ling Zhang, Steven A Rosenberg, Alan S Wayne, Crystal L Mackall



Lee et al. Lancet 2015
67% CR rate (intention to treat)
All responders with CRS

CD19 CAR Clinical Updates (Novartis)

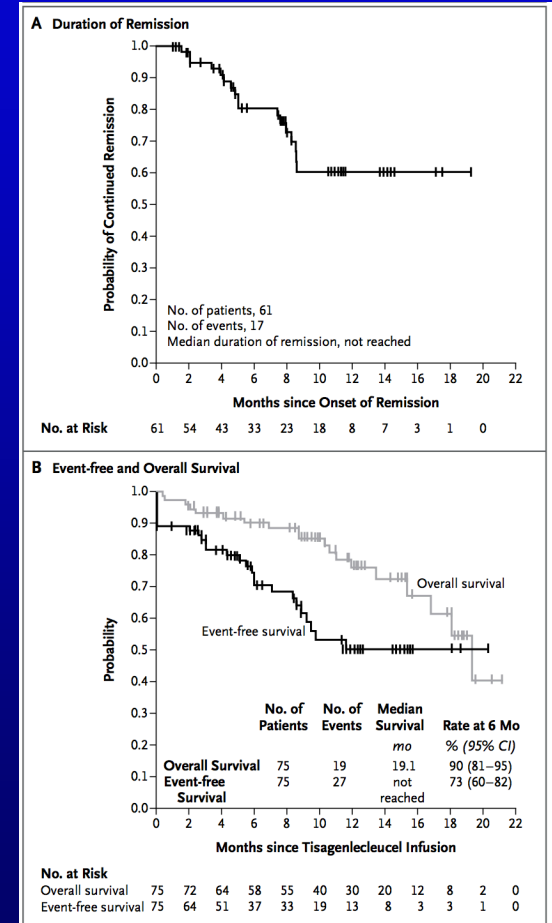
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

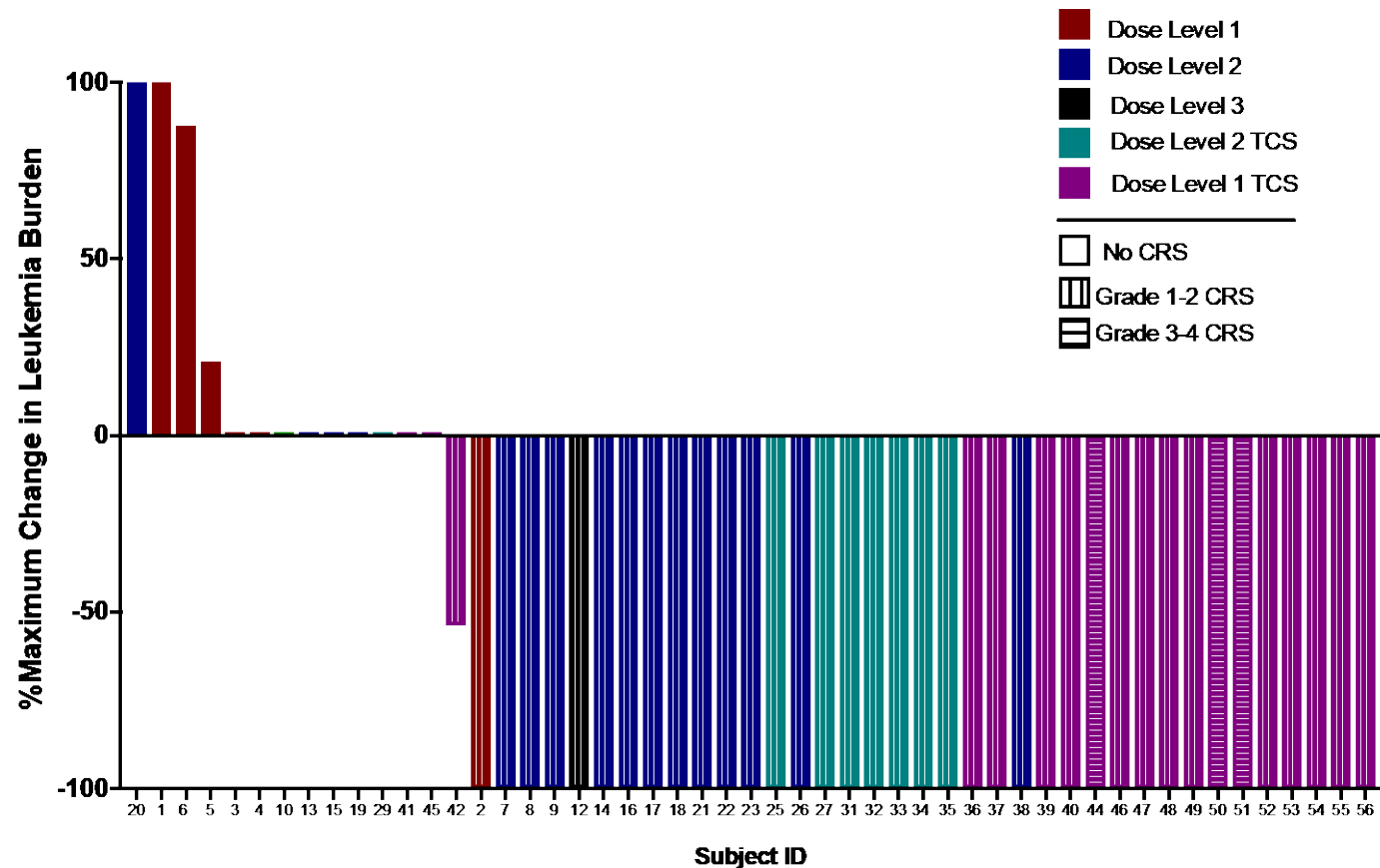
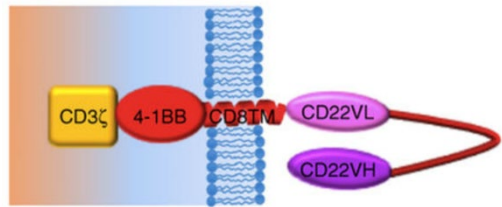
Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

S.L. Maude, T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt, P. Bader, M.R. Verneris, H.E. Stefanski, G.D. Myers, M. Qayed, B. De Moerloose, H. Hiramatsu, K. Schlis, K.L. Davis, P.L. Martin, E.R. Nemecek, G.A. Yanik, C. Peters, A. Baruchel, N. Boissel, F. Mechinaud, A. Balduzzi, J. Krueger, C.H. June, B.L. Levine, P. Wood, T. Taran, M. Leung, K.T. Mueller, Y. Zhang, K. Sen, D. Lebwohl, M.A. Pulsipher, and S.A. Grupp

81% Complete remission rate
(not intention to treat)

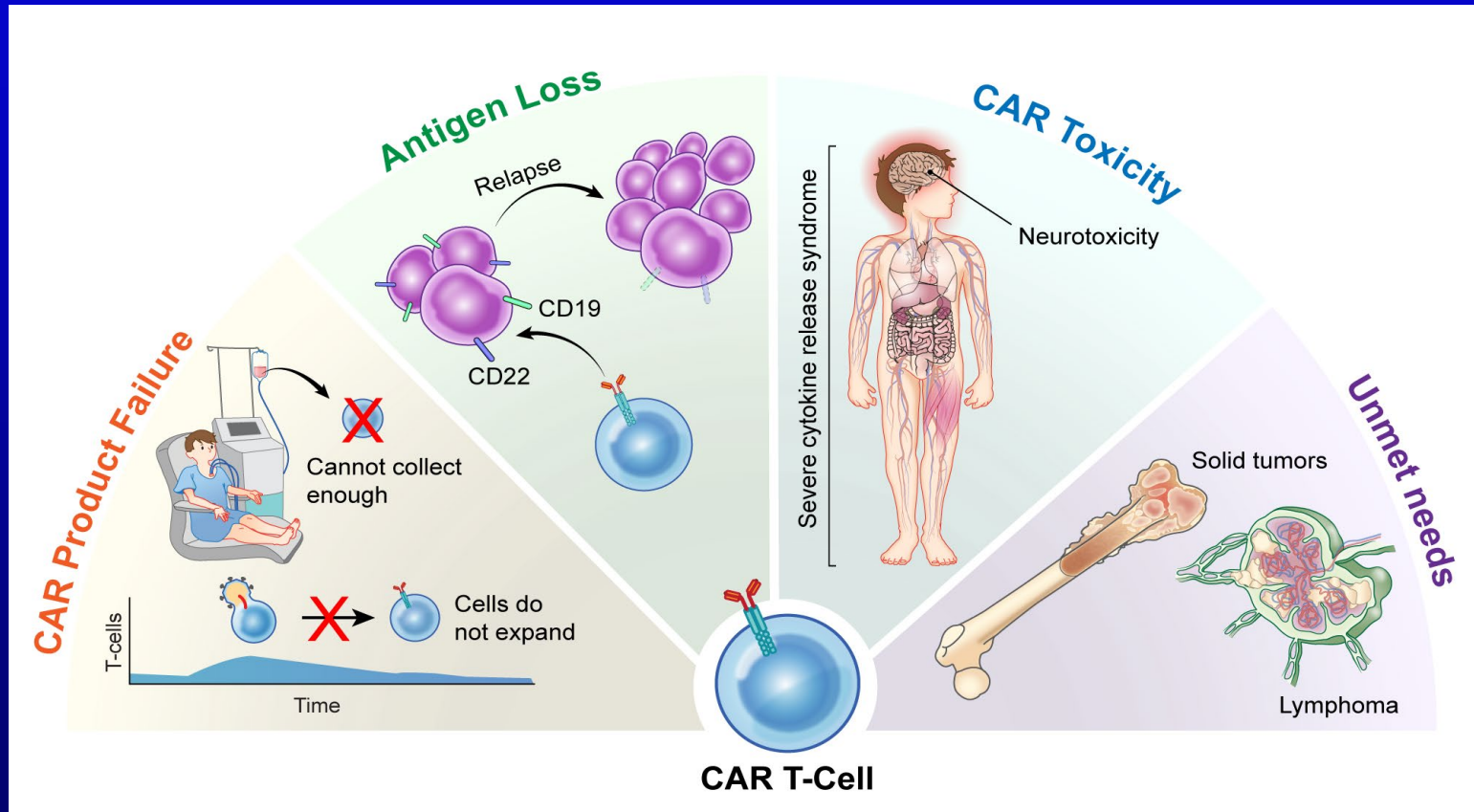


CD22 CAR Results (NCI POB)

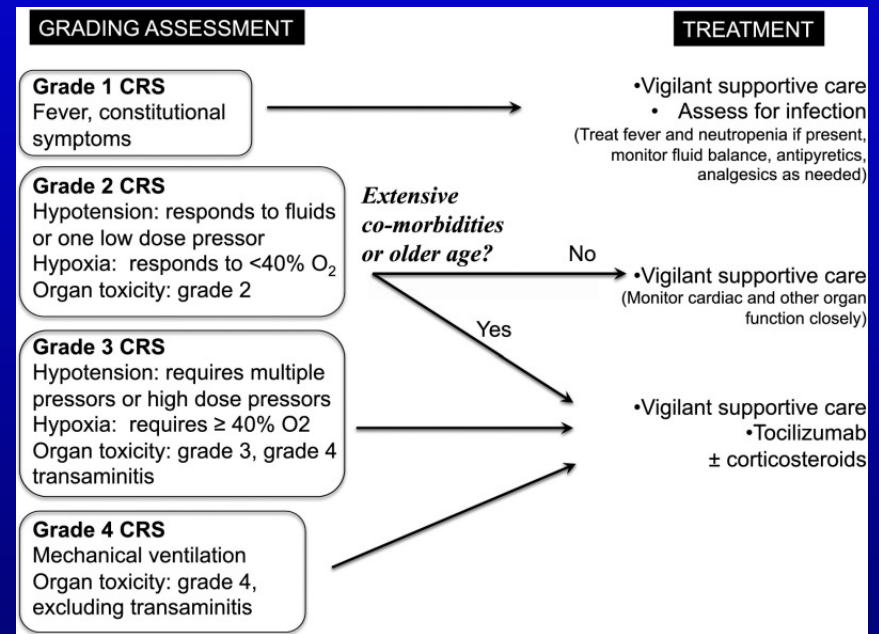
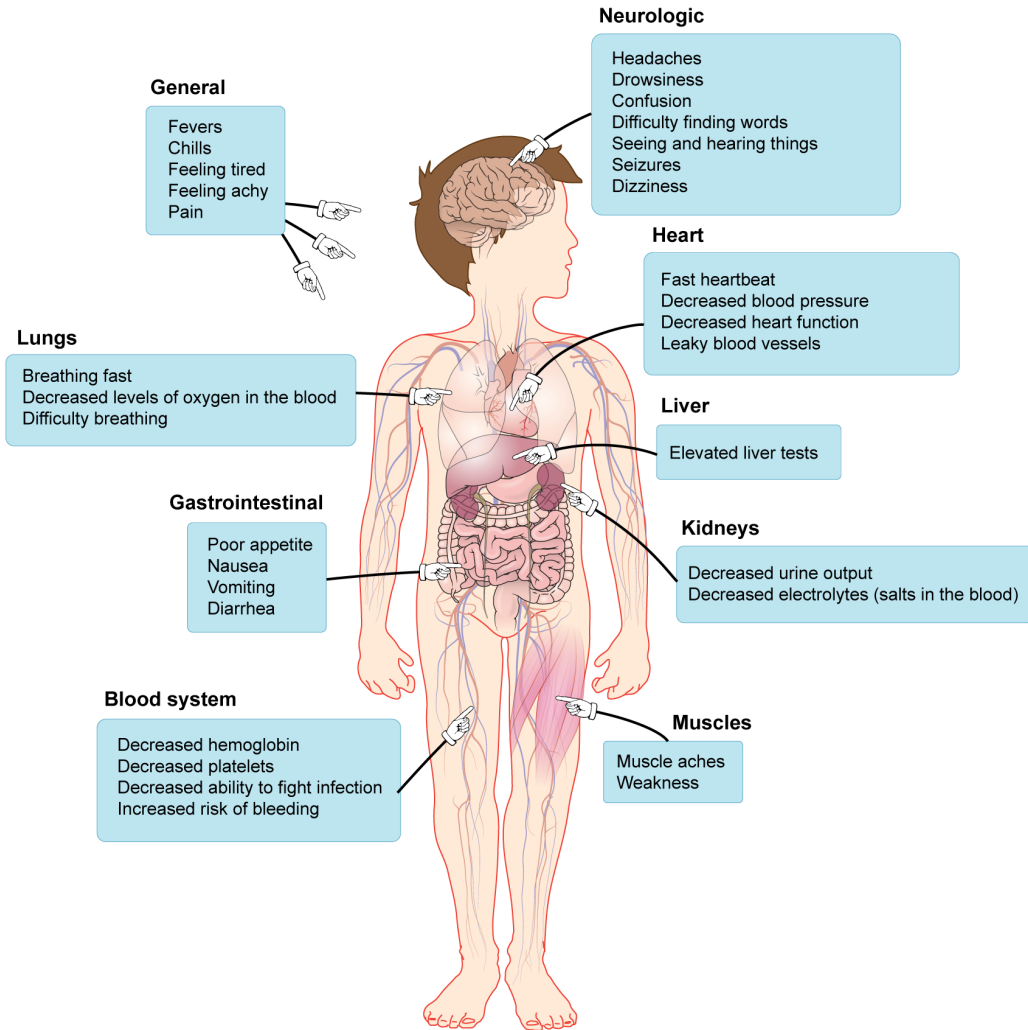


Salvage CAR for CD19 negative relapse

Limitations to Durable CAR-T cell Induced Remissions



Cytokine Release Syndrome

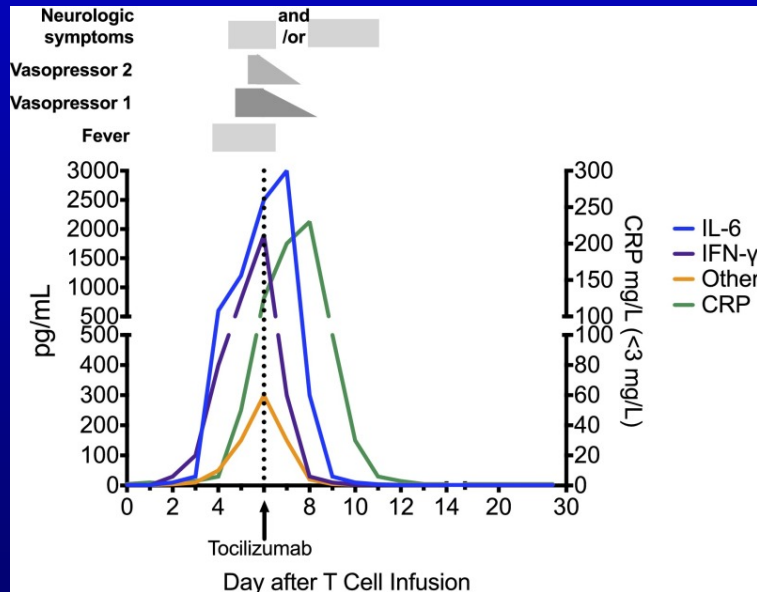


FDA Approvals

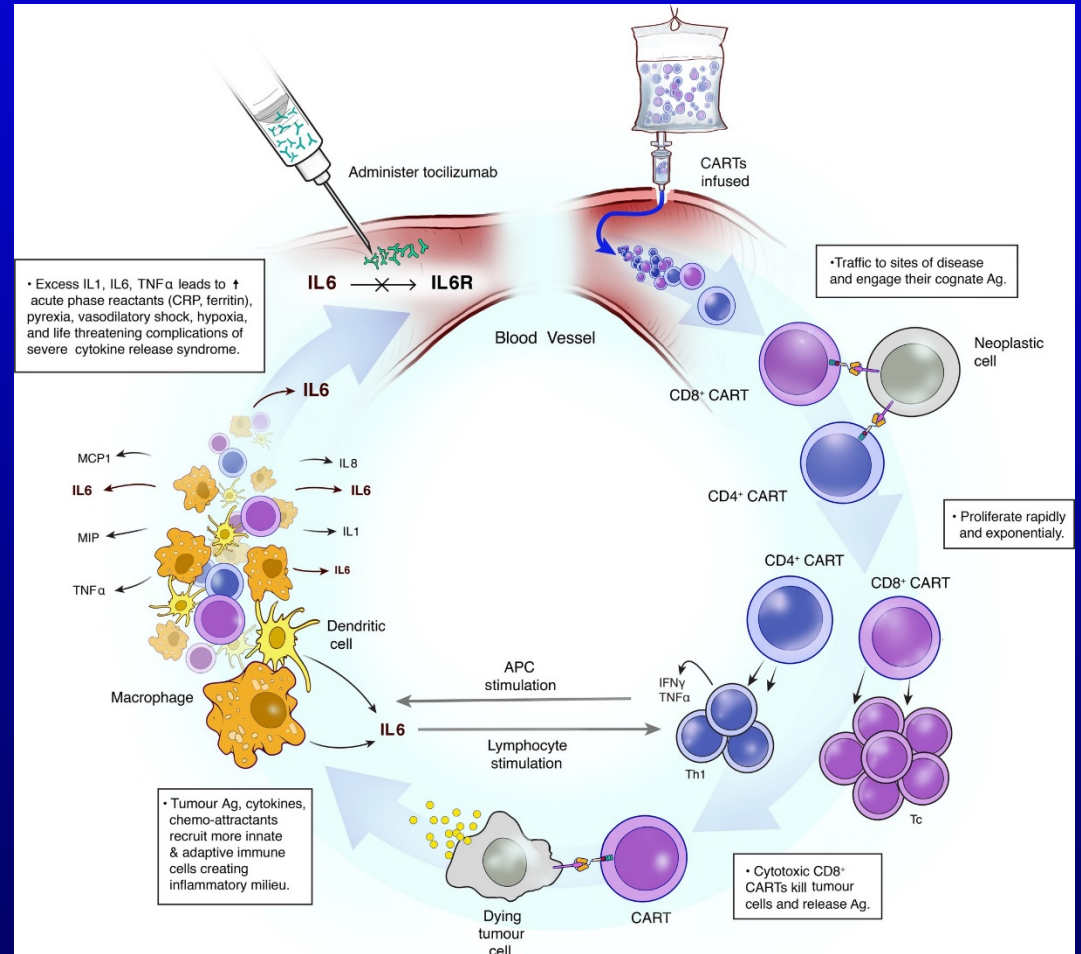
- Kymriah (Tisagenlecleucel, Novartis: For children up to age 25 with ALL (August 2017)
 - 81% complete remission rate
- Yescarta™ (axicabtagene ciloleucel, KITE): For adults with Diffuse Large B Cell Lymphoma (October 2017)
- Tocilizumab (anti-IL6 receptor blockade)
 - To treat CRS

Targeting IL6 has demonstrated clinical efficacy in the treatment/prevention of severe CRS

- Tocilizumab, FDA approved
 - IL6 receptor antibody

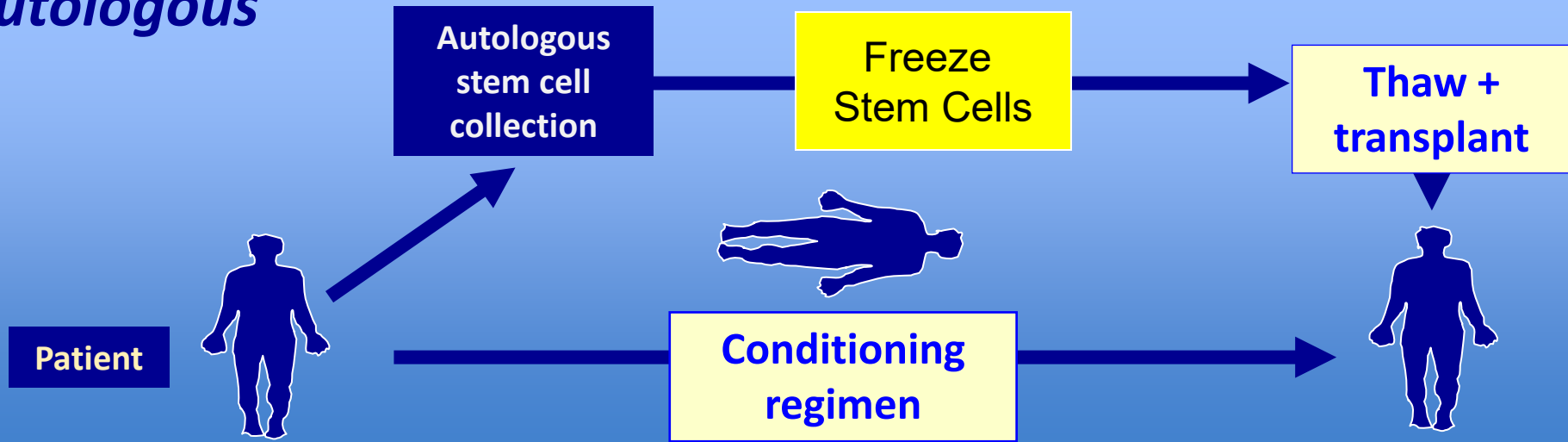


Lee et al. Blood 2014
Orlowski RJ, et al. BJH. 2016



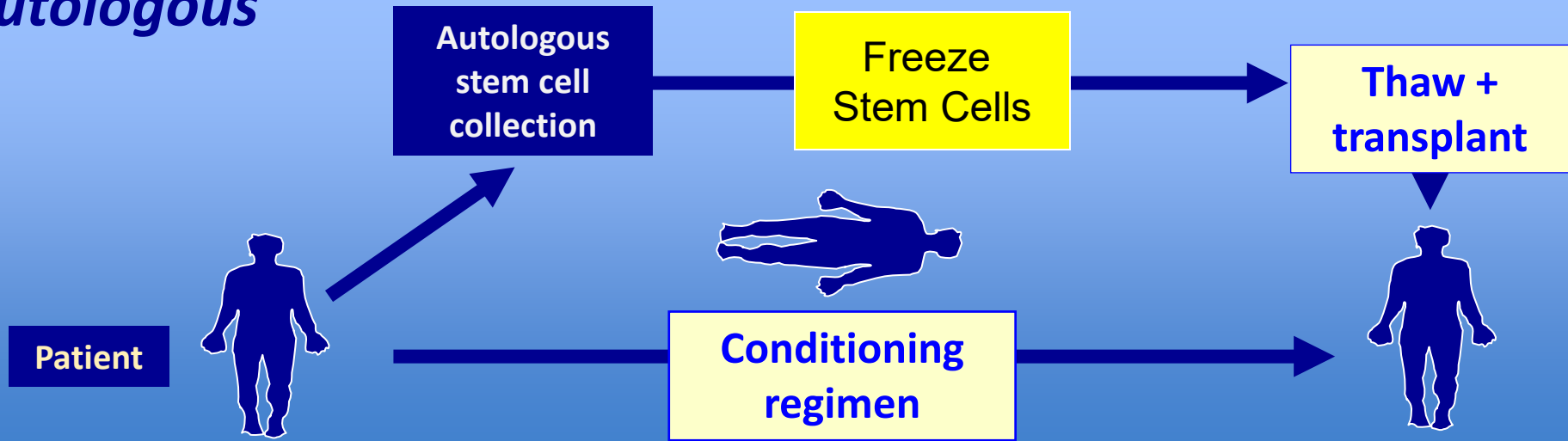
Stem cell transplantation

Autologous



Stem cell transplantation

Autologous



Allogeneic

Tissue or HLA matched

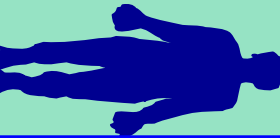
Stem cell donor



Allogeneic stem cell collection

transplant

Patient



Conditioning regimen

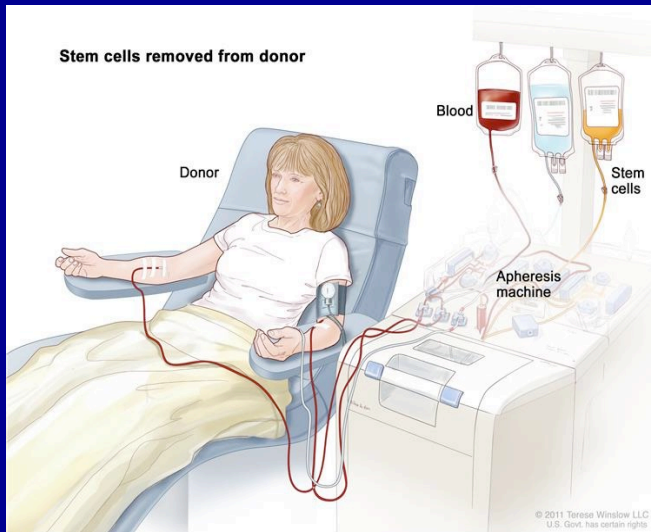


Stem Cells Source

Peripheral Blood



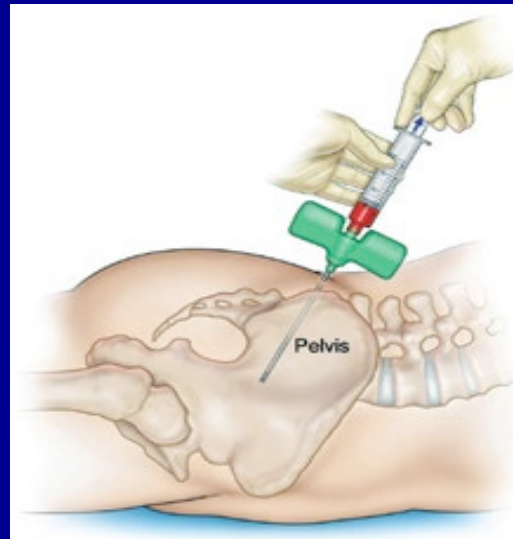
G-CSF subcutaneous injection for 5 days. Mononuclear cells collected by apheresis



Bone Marrow



Direct aspiration under general



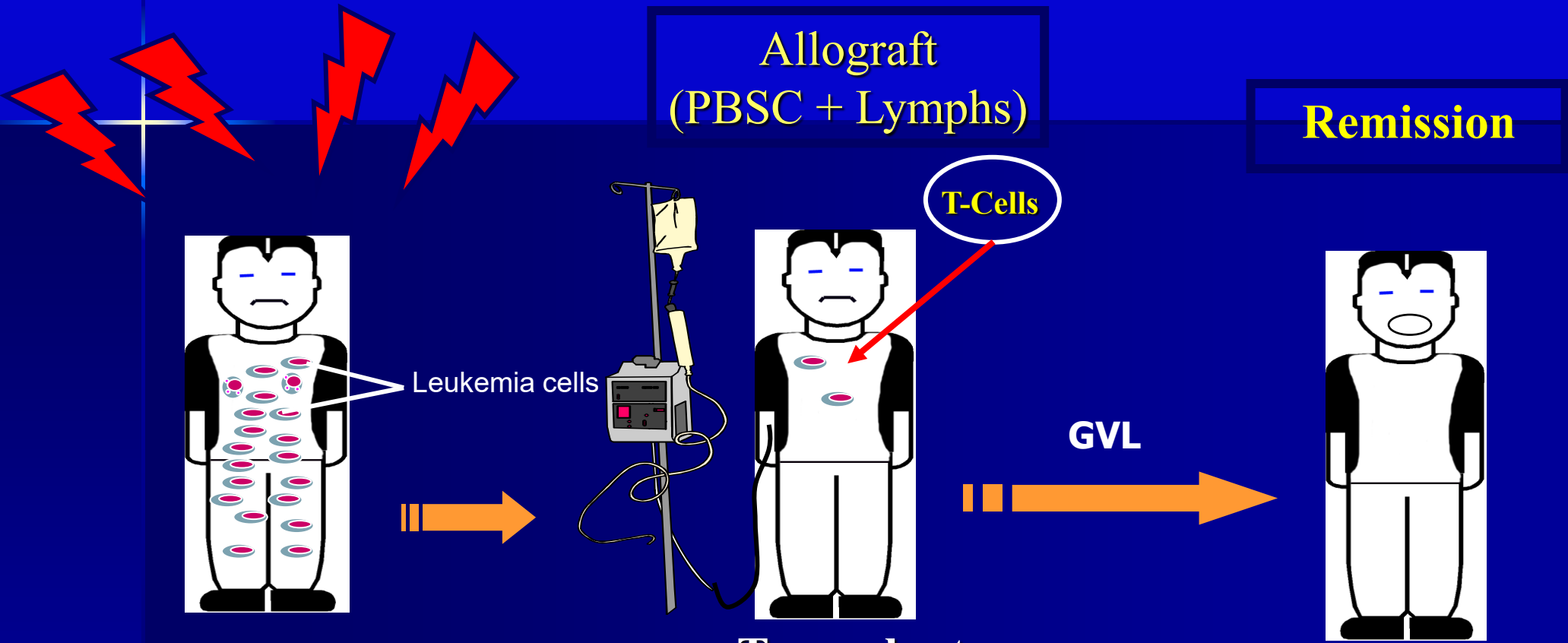
Umbilical Cord Blood



Placental blood directly drained into bag



How Does Myeloablative Allogeneic BMT Cure?



Pre-transplant intensive Therapy (kill the cancer)

Transplant

-Rescue the bone marrow
-Immunotherapy

1) Conditioning Regimen

2) Graft-vs-Tumor

**Allogeneic Hematopoietic Stem Cell Transplantation:
Can Cure Patients With Chemotherapy Refractory
Hematological Malignancies**

T-cell Mediated Graft-Vs-Leukemia Effects Can Cure Chemotherapy Resistant Malignancies



May 2006
1 month
After transplant

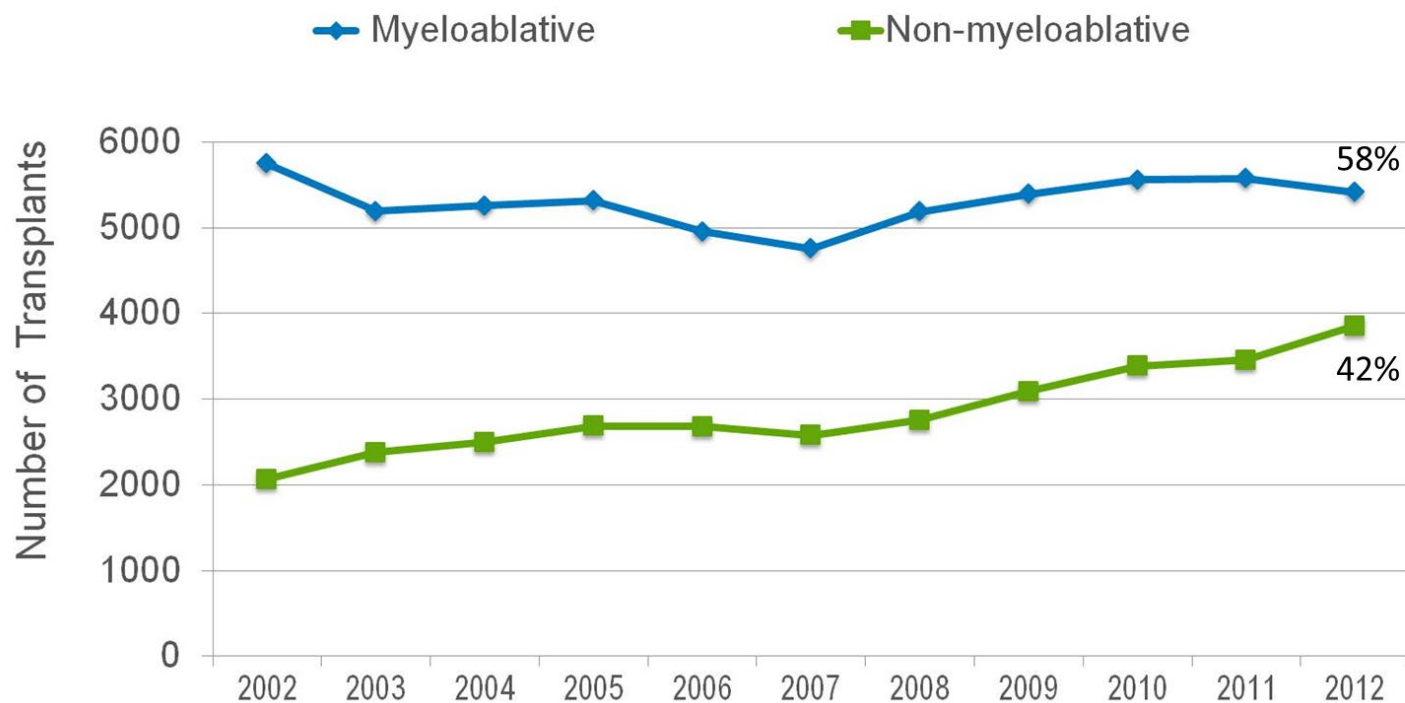
Types of Allogeneic Transplants

- *Conventional High Dose or Myeloablative Transplant*
 - Conditioning fully eradicates the hosts bone marrow

- *Reduced Intensity Conditioning (RIC)*
 - Low dose or non-myeloablative transplant
 - Immunologically eradicates host bone marrow

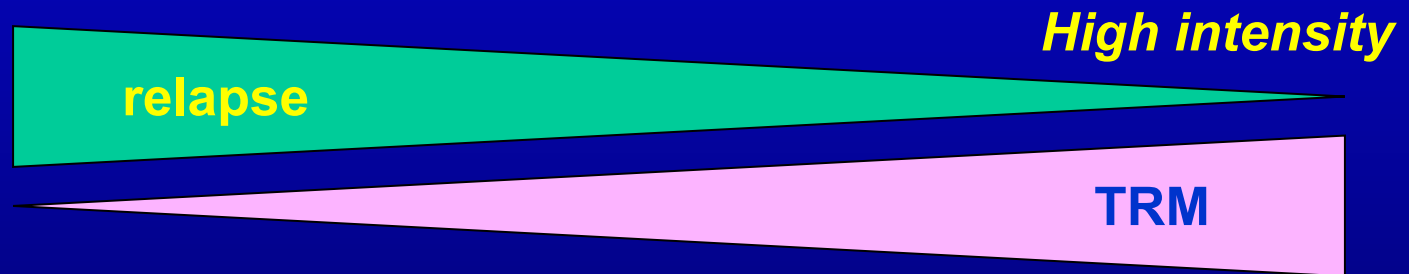
Use of Reduced Intensity Conditioning on the Rise

Allogeneic Transplants Registered with the CIBMTR



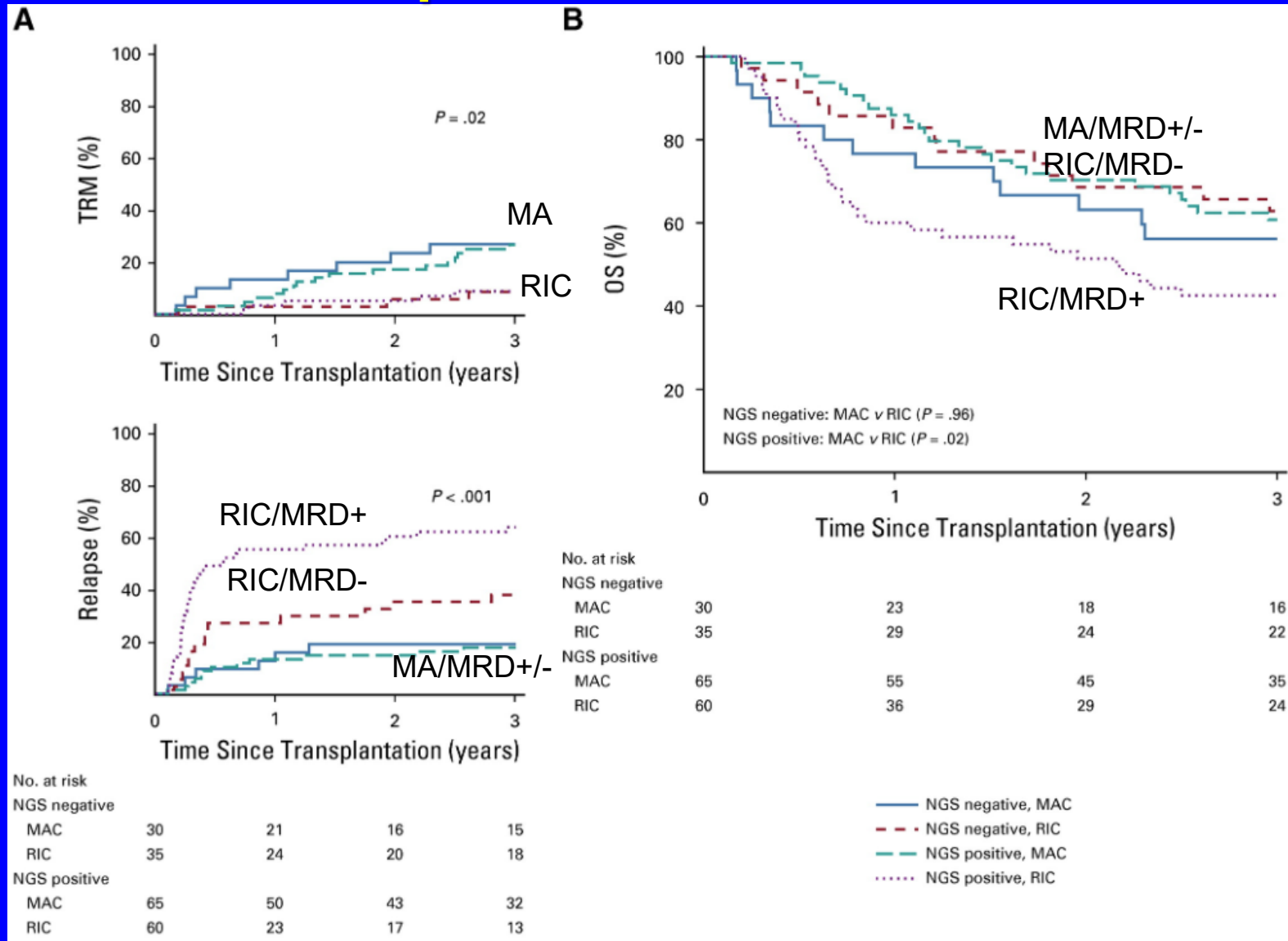
Reduced Intensity Conditioning (RIC): Decreases Risk Of TRM But May Increase Risk of Relapse For Some Malignancies

***Low intensity
Conditioning
(RIC)***



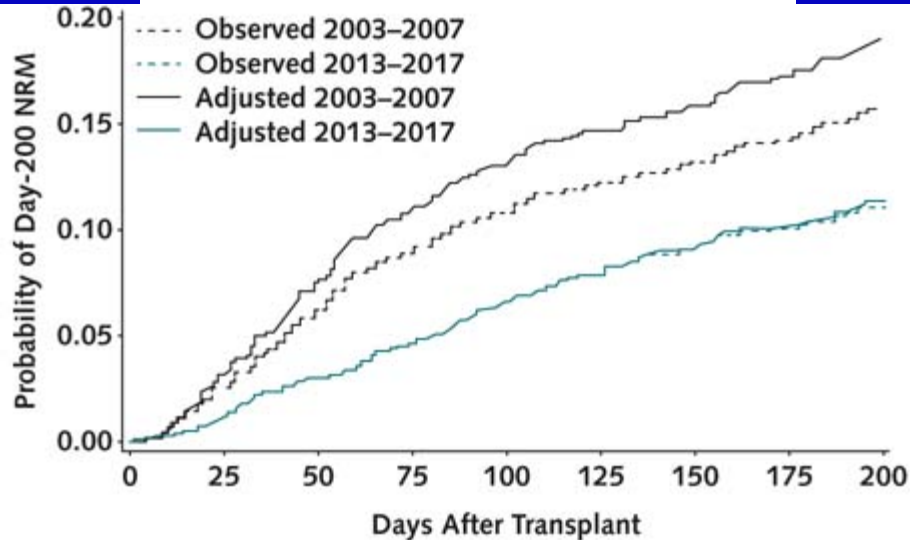
Possibility of increased risk of relapse (i.e. AML, MDS) with reduced intensity transplants

Trial: Myeloablative vs. Reduced Intensity Allogeneic Transplantation for AML/ MDS

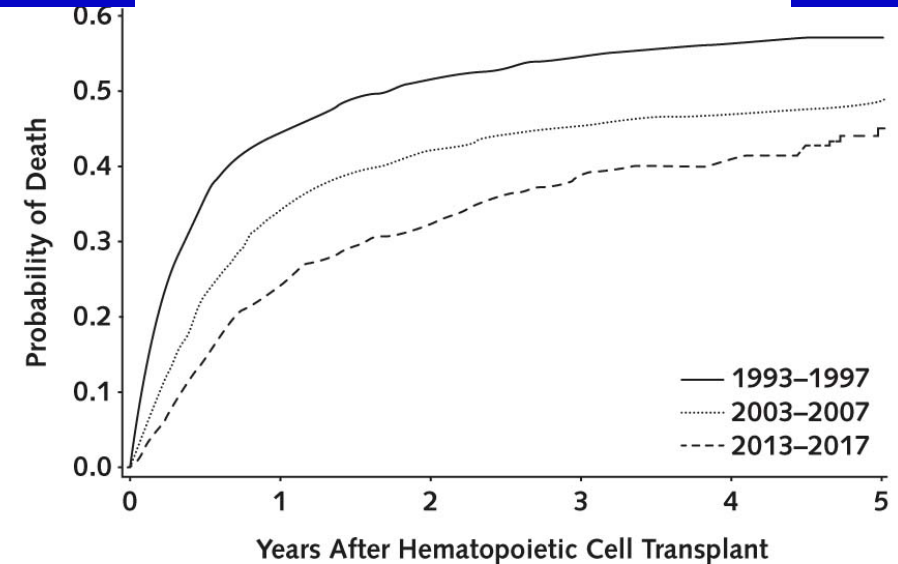


Major Improvements in Transplant Safety Over the Past 2 Decades

Day 200 NRM



Death After Transplant



At risk, *n*

1993–1997	1418	787	682	638	608	689
2003–2007	1148	755	662	618	594	565
2013–2017	1131	810	523	310	161	50

2003-2007-n=1148

2013-2017- n=1131

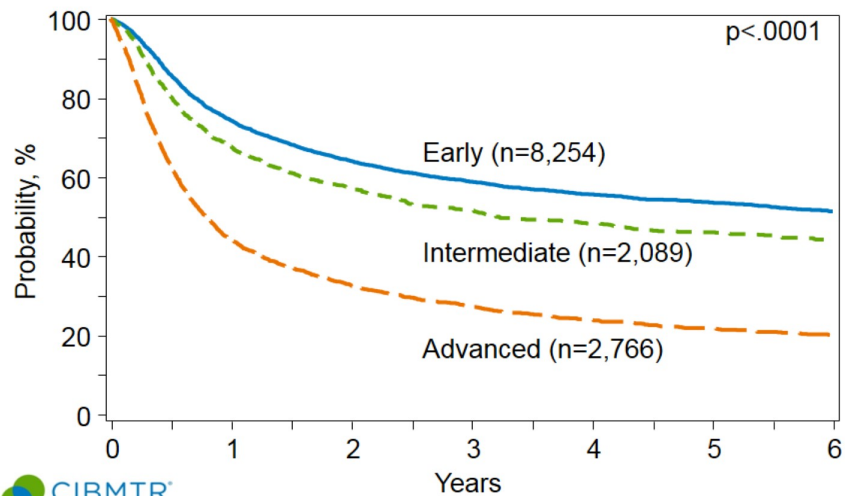
In the era of precision medicine, why do we still perform these dangerous allogeneic transplants?

- **Remains only curative modality for certain diseases associated with short survival with conventional therapy**
 - Relapsed AML
 - Relapsed ALL
 - High Risk MDS
- **Is the only curative modality for many non-malignant debilitating diseases**
 - Sickle cell Anemia
 - Aplastic Anemia- Relapsed refractory to IST

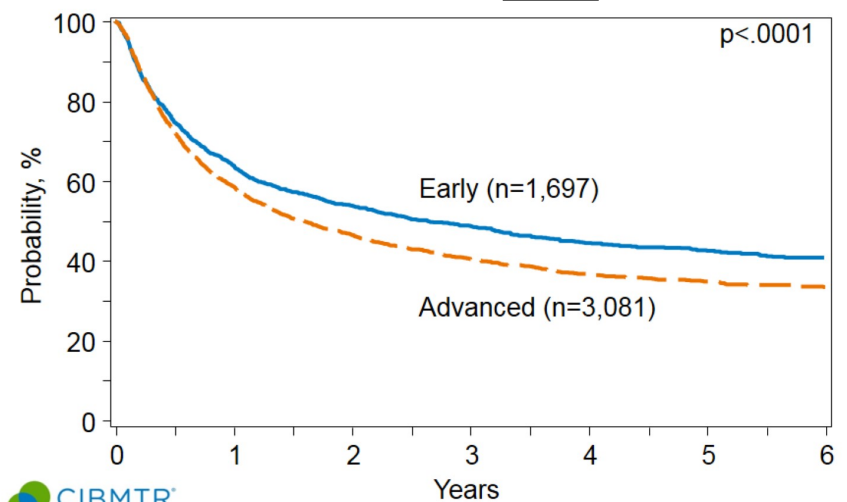


Allogeneic Transplant For Hematological Malignancies

Survival after HLA-Matched Sibling Donor HCT for AML, 2005-2015

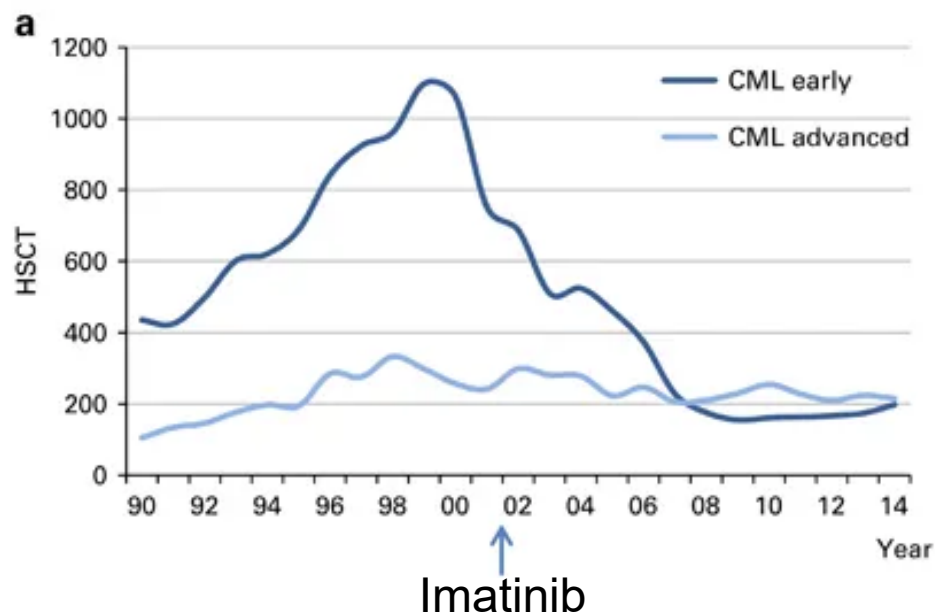


Survival after Unrelated Donor HCT for MDS, 2005-2015

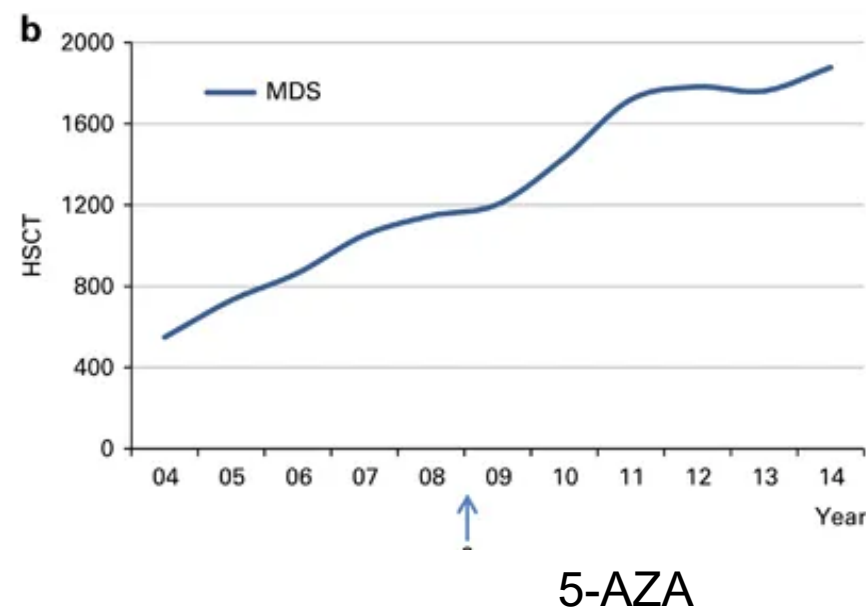


Impact of Drug Advances On Transplant Numbers

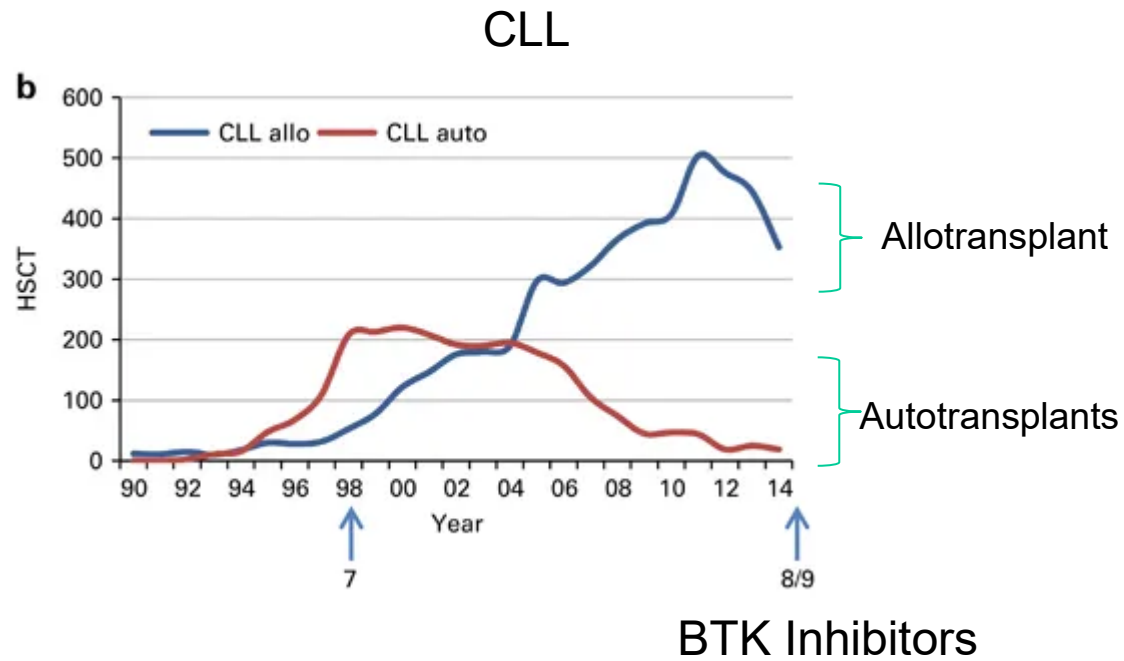
CML



MDS

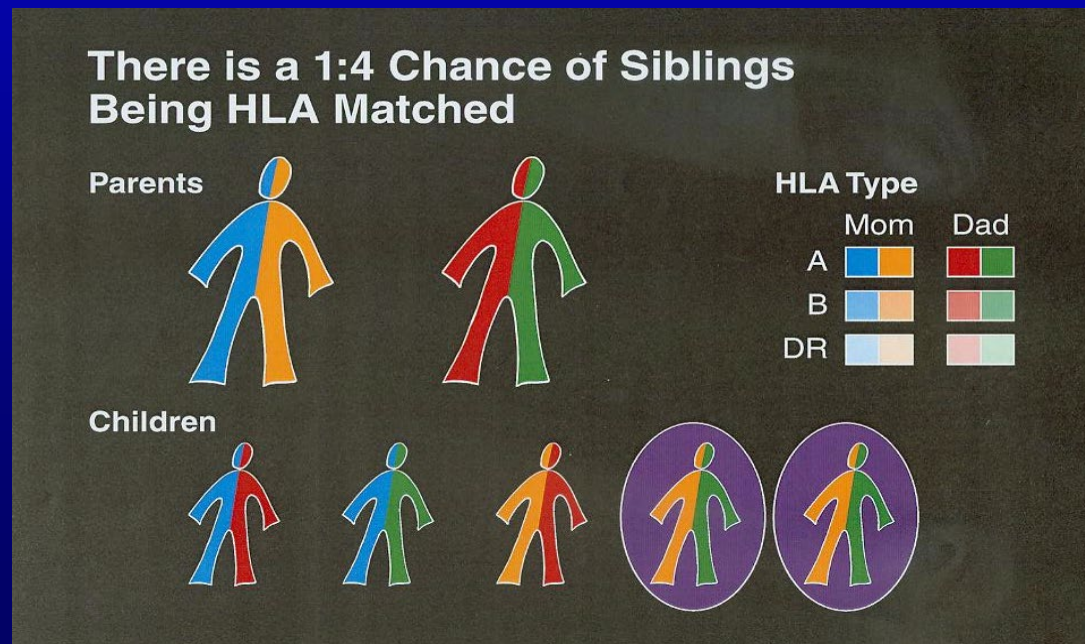


Impact of Drug Advances On Transplant Numbers



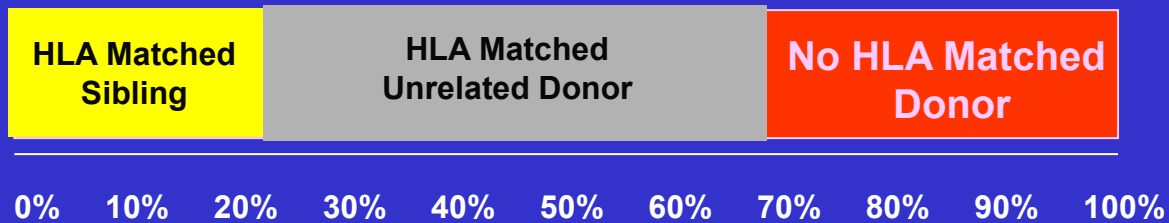
REQUIREMENTS FOR ALLOGENEIC TRANSPLANTATION

- An HLA compatible donor to donate stem cells
 - 25% each sibling will be HLA identical
 - In the U.S., there is approximately a 25% that a patients will have an HLA identical sibling



Availability of a Stem Cell Sources for Allogeneic Transplantation

Chances of Finding a Stem Cell Donor



Potential Candidates
For a Cord Blood Transplant or
A Haploidentical Transplant

Graft Donor Sources- who to choose?

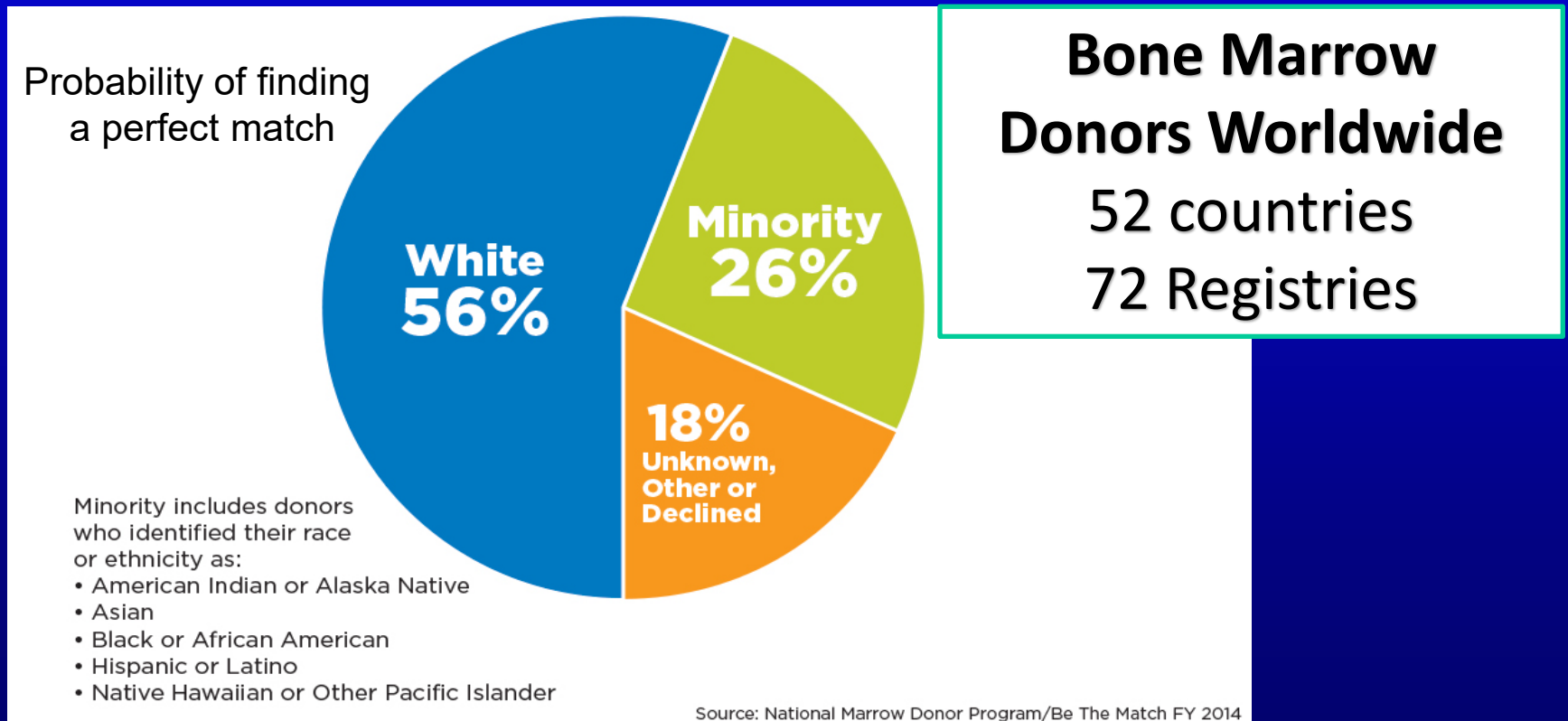
- 1) HLA Identical Sibling (SIB)- still best
- 2) 8/8 Allele Matched Unrelated Donor (MUD)- maybe still 2nd best
- 3) alternative donors:

HLA-Haploidentical related donor (Haplo)

Cord Blood transplant

7/8 Allele Matched Unrelated Donor (MMUD)

Unrelated Donor Transplants: Diversity of Adult Donors on the Be The Match Registry® 2014



Unrelated Cord Blood Transplantation (UCBT)

Unrelated Cord Blood (UCB) transplants are a transplant option for patients lacking an HLA identical donor:

- Cord blood is a rich source of Hematopoietic progenitor cells- more than human BM



60-80% of patients will have a cord unit in the public registry that could be used for a transplant



Placenta

Umbilical Cord

Cord Blood Unit

Advantages of Cord Blood

Lower Graft vs. Host Disease (GVHD)



HLA-mismatched Transplants Possible

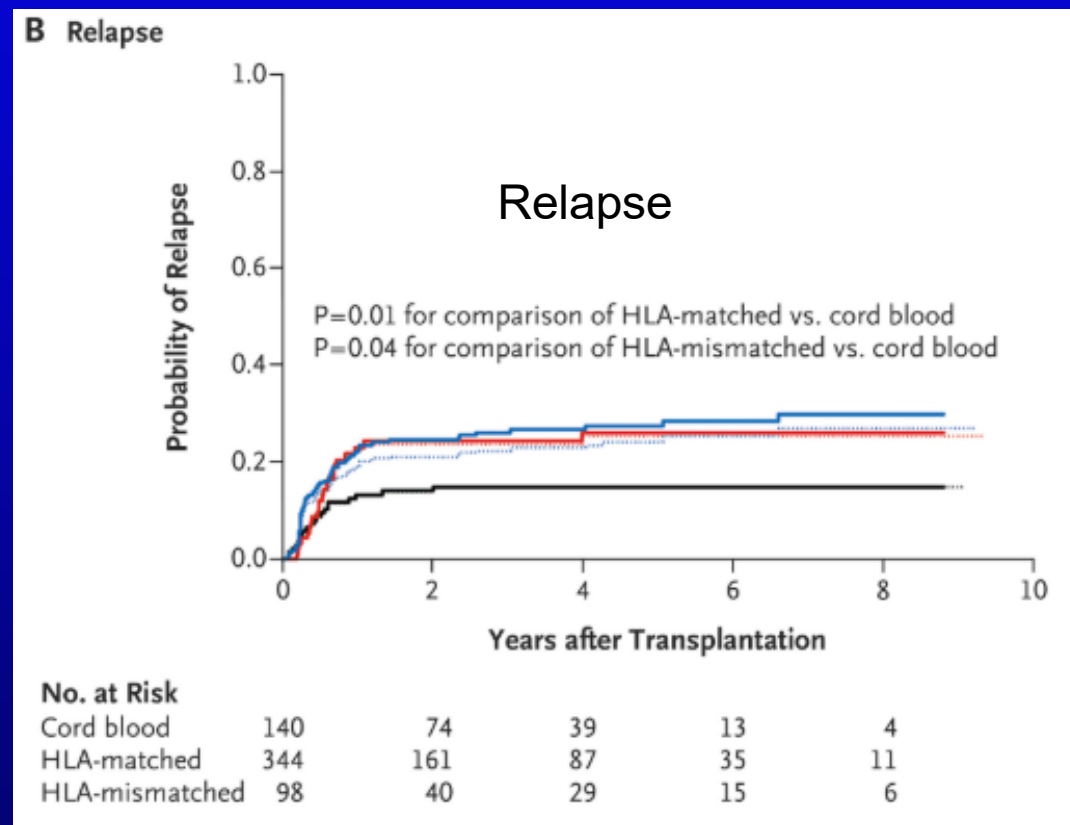
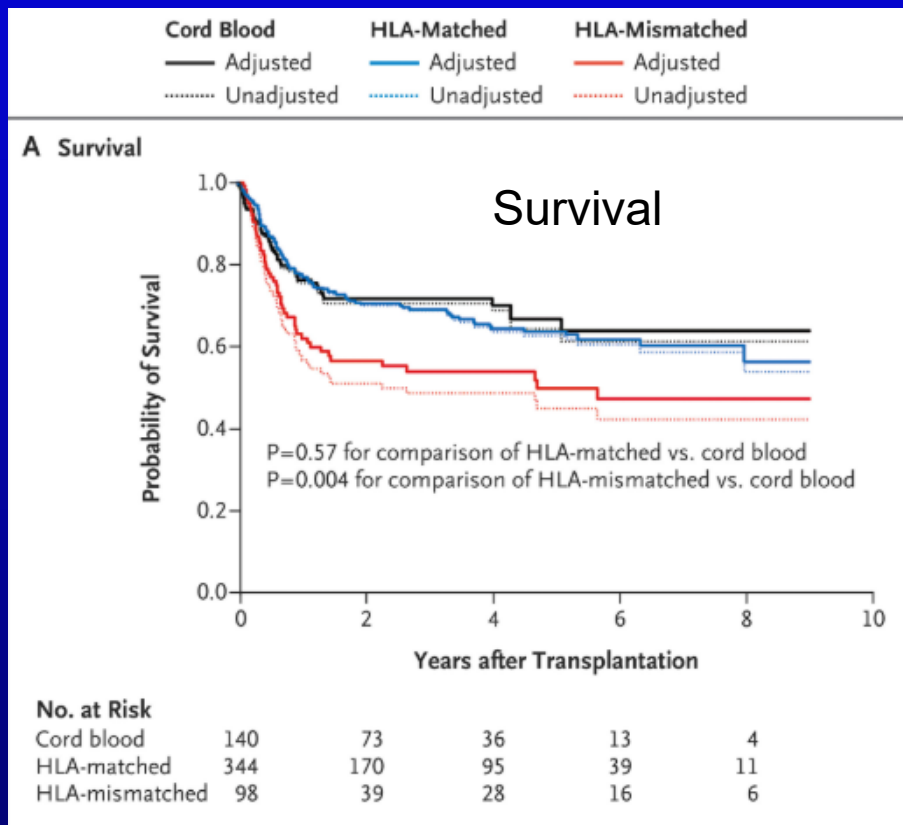


Off the shelf product quickly available



Cord Grafts available to Patients with Rare HLA Types And Ethnic Minorities

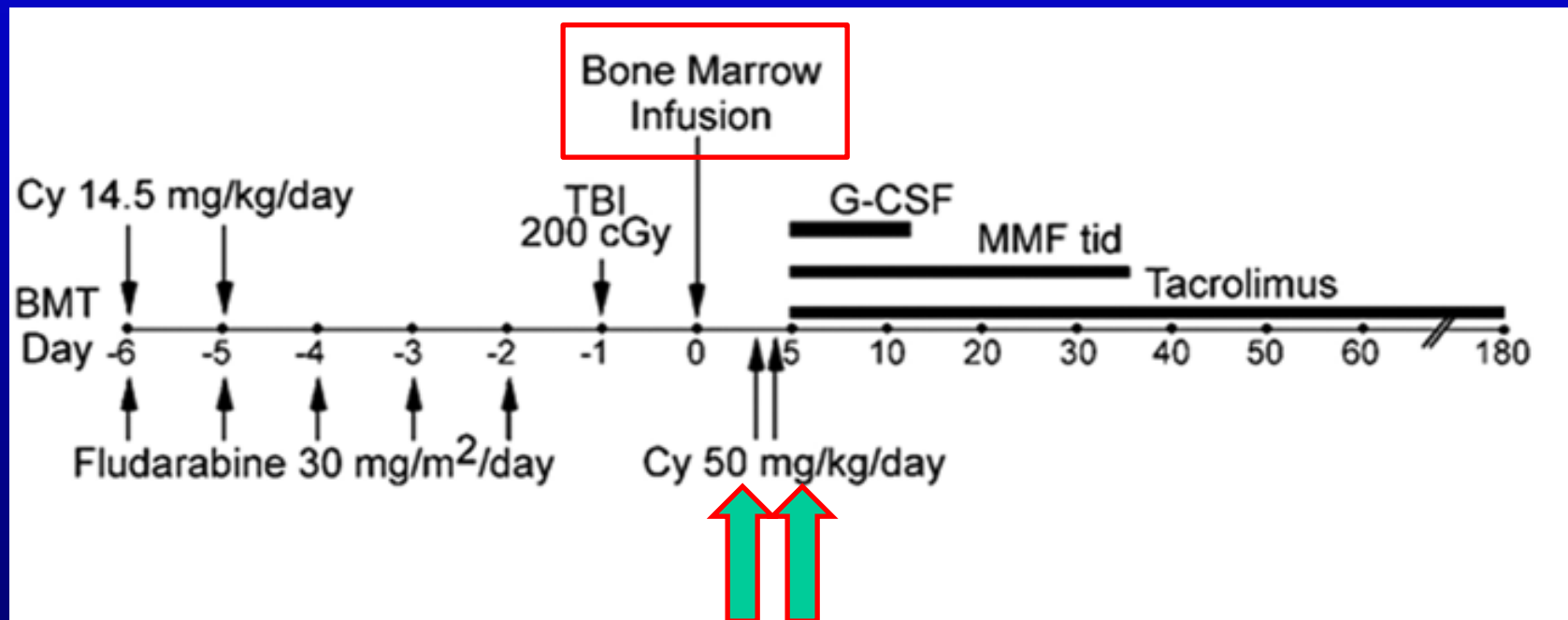
Cord Transplants Compares Favorably with Matched Unrelated Donor Transplants



Haploidentical BM Transplants

- Transplants that utilize stem cells collected from a relative who only matches for half of the HLA tissue antigens
 - **Advantages;**
 - Virtually every patient will have a haplo-identical relative to serve as a stem cell donor
 - **Disadvantages:**
 - Higher incidence of graft versus host disease
 - Obligates use of T-cell depletion

Post Transplant Cyclophosphamide Following T-cell Replete Haploidentical Transplantation of BM or PBSC



Chemotherapy to kill cells
That cause graft-vs-host disease

Haploidentical Transplant With Post-Transplant Cyclophosphamide has similar outcome to matched unrelated transplants

Survival

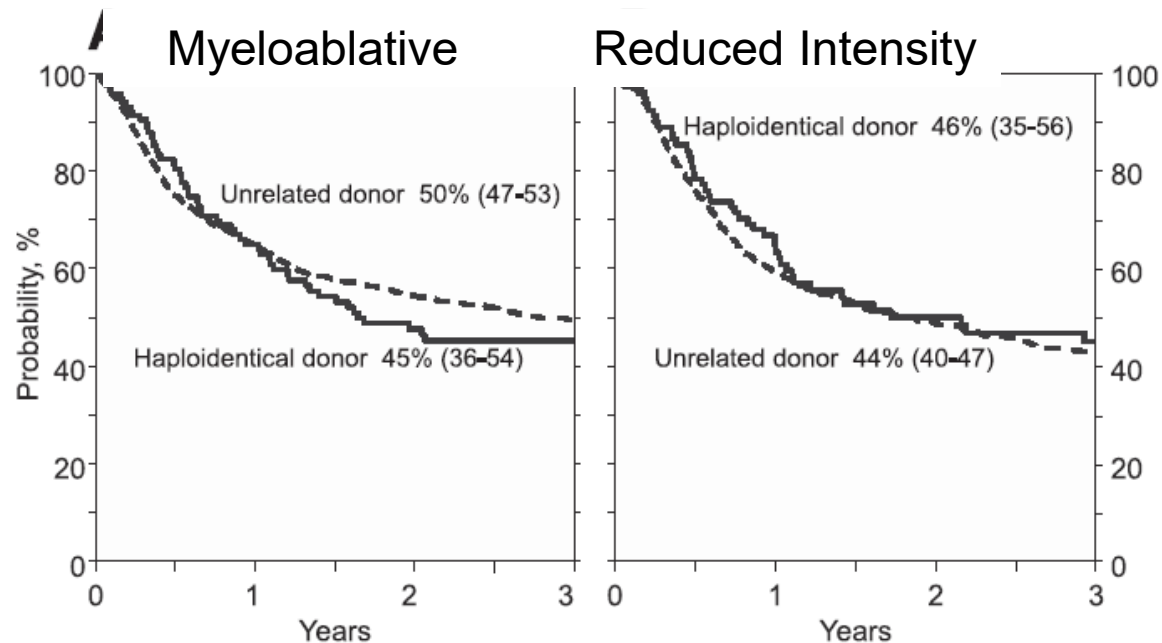
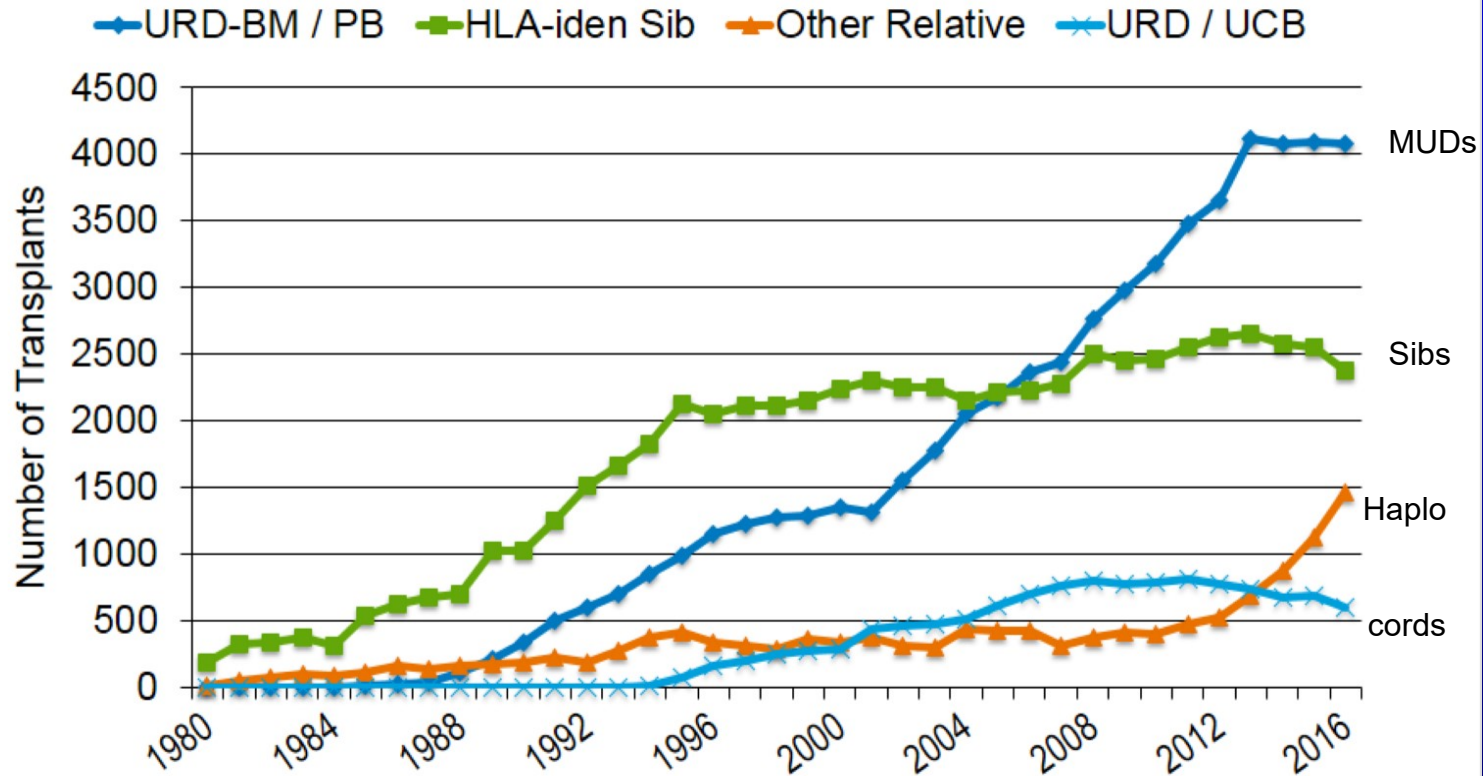


Figure 3. Overall survival. (A) The probability of OS by donor type after myeloablative conditioning regimen, adjusted for age and disease risk index. (B) The probability of OS by donor type after reduced intensity conditioning regimen, adjusted for disease risk index and secondary AML.

Allogeneic HCT Recipients in the US, by Donor Type



Questions To Be Answered

- **Does the potential benefit of a transplant justify the risk?**
(i.e. do I have a disease that chemotherapy can cure or make me live a long time or a disease where chemotherapy is unlikely to cure in contrast to a transplant that has a higher probability of cure)
- **Is my disease controlled sufficiently to where a transplant would help? Timing is everything!!**
i.e. Acute leukemias should be in remission before transplant
- **Do I Have a stem cell donor?**
 - HLA tissue matched sibling
 - Matched Unrelated donor
 - Cord blood or haplo-identical donor
- **What are the chances I could be harmed by a transplant?**
 - Am I Healthy enough to go through the procedure?
 - Am I young enough?
 - Have prior treatments put me at increased risk for complications