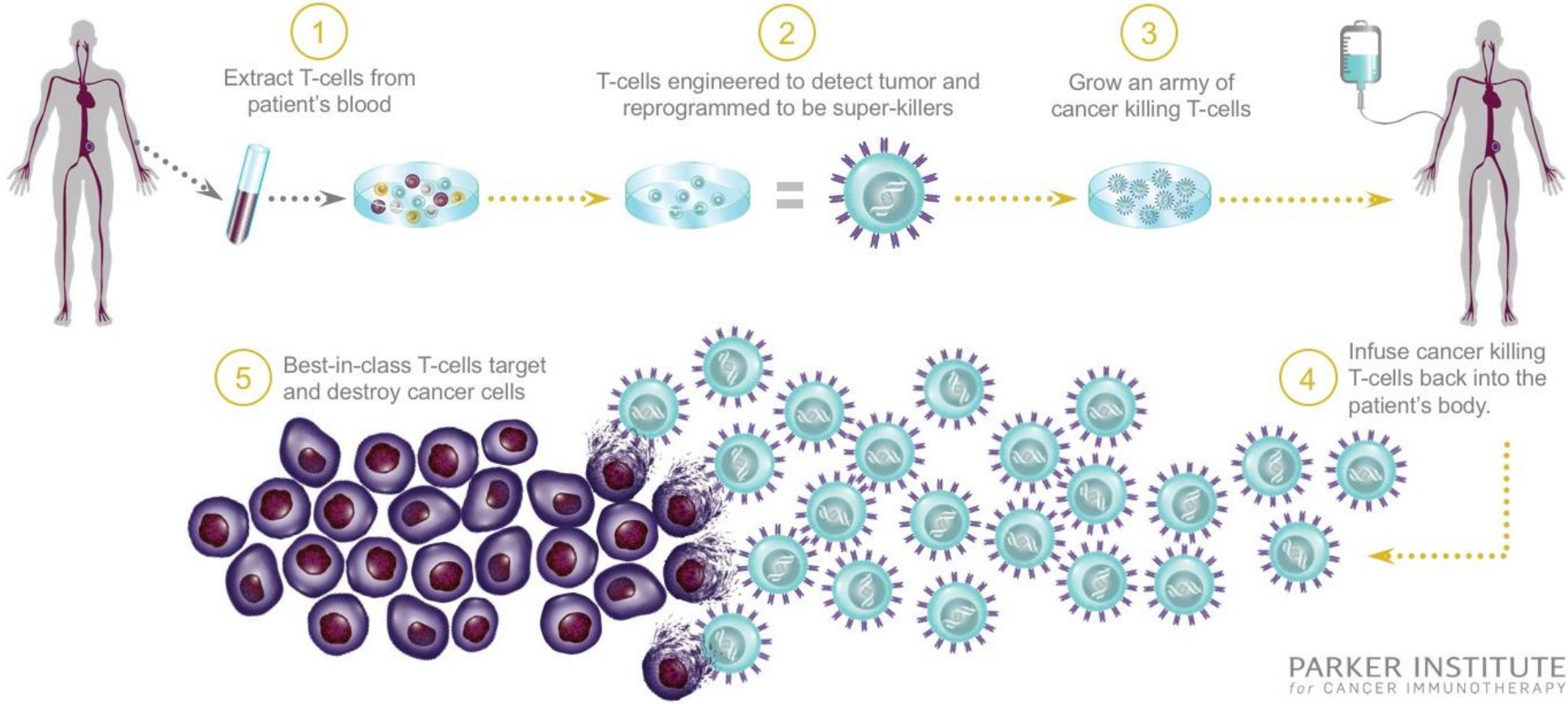
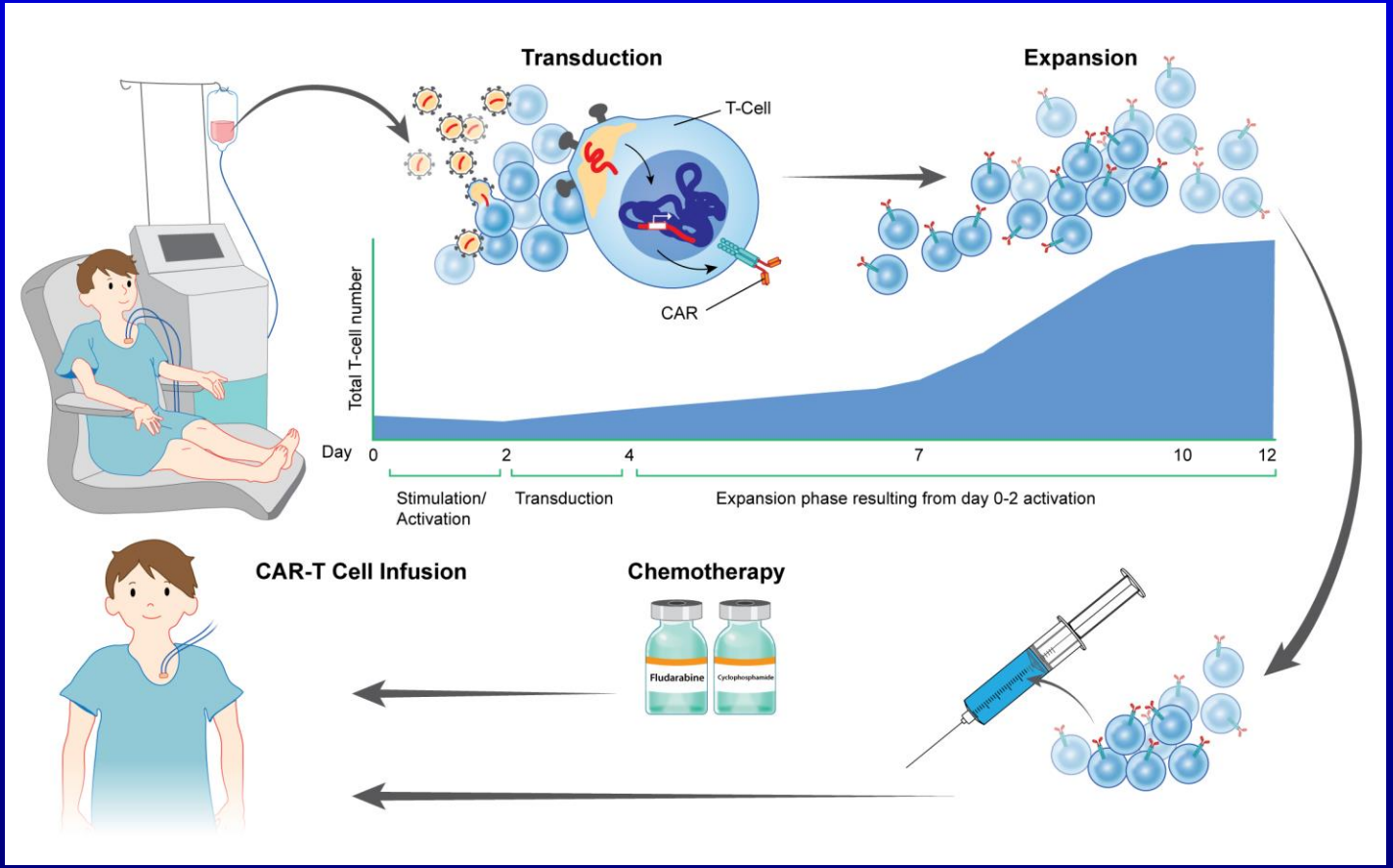
CAR-T Cell Therapy and Hematopoietic Stem Cell Transplantation: Current Status and Future Directions

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

CAR T-Cells: How it Works



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



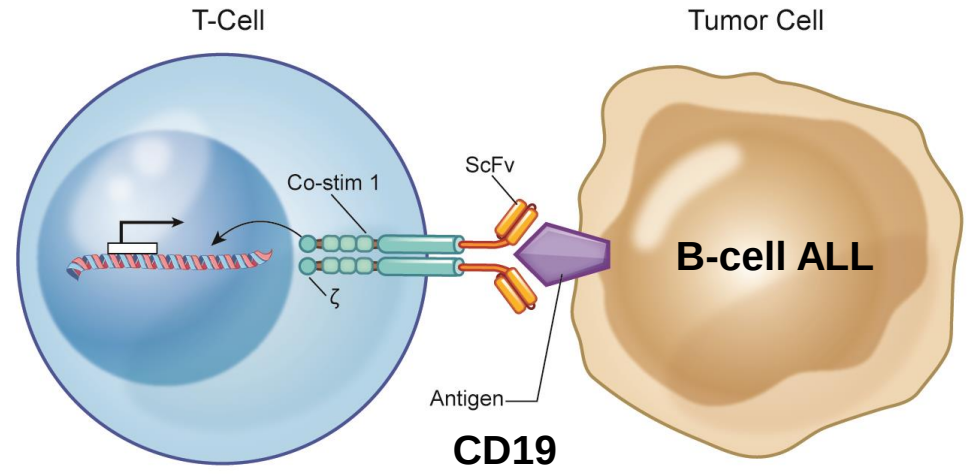
1. Apheresis
2. Stimulation and Transduction
3. Expansion
4. Lympho-depletion
5. Infusion

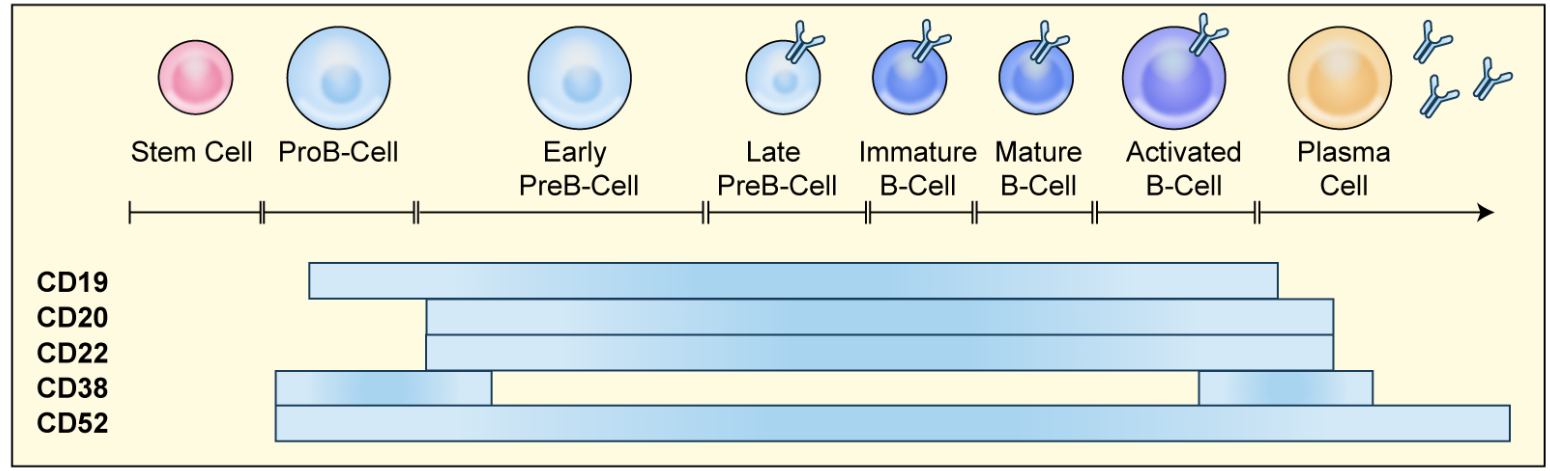
- Retains the functionality of a T-cell with the antigen recognition properties of antibody

Image, Courtesy of NIH Medical Arts

Targeting CD19

- CD19 ubiquitously found on B-cells





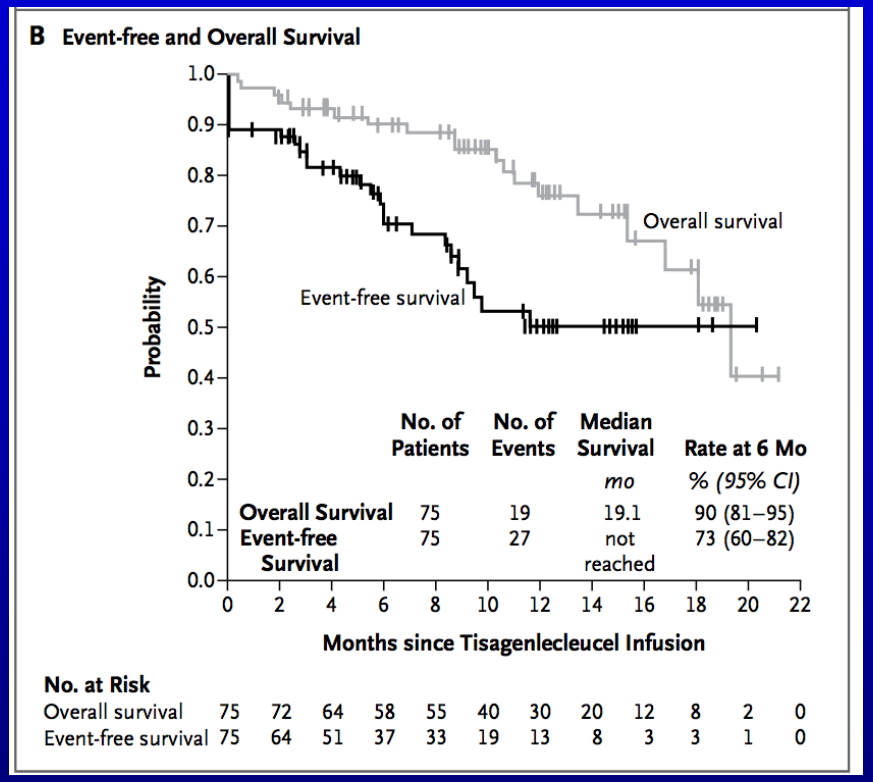
CD19 CAR Clinical Updates

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

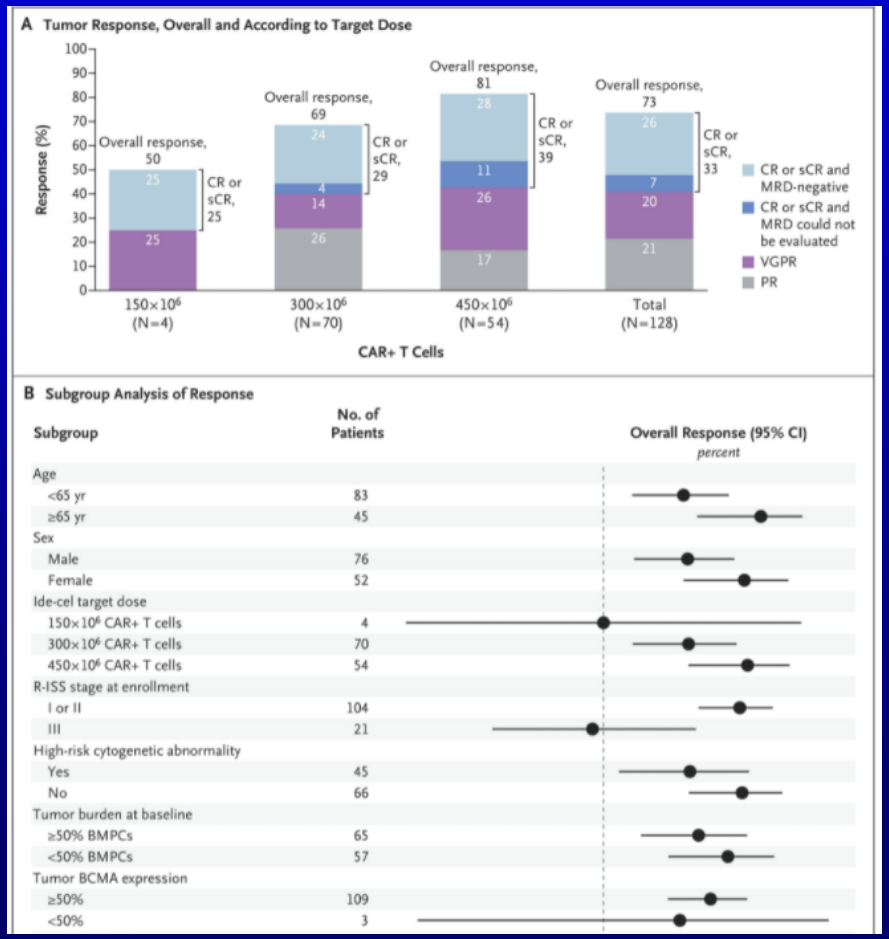
Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

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

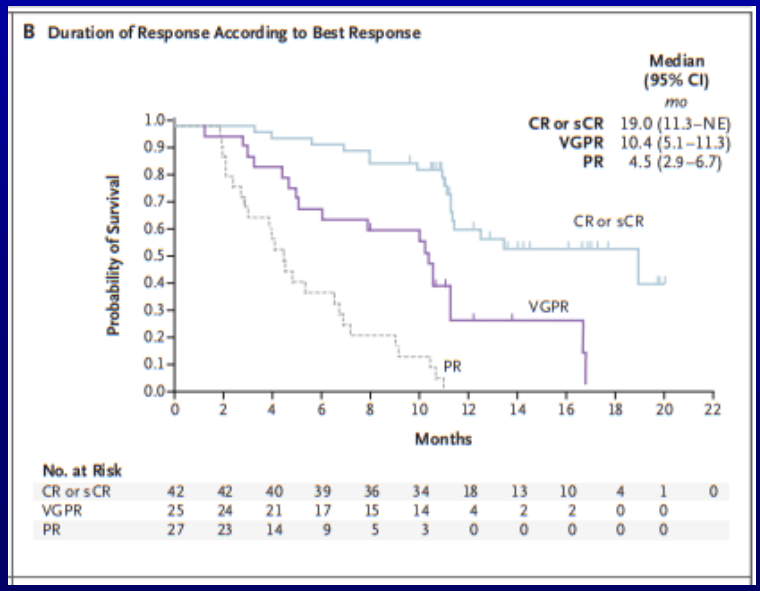


- ALL Leukemia
- Complete Remission Rate = 81%
- Event Free Survival Rate
  - 6 months: 73%
  - 12 months: 50%

Idecabtagene Vicleucel (ide-cel) CAR T cells For Myeloma: KarMMa Study



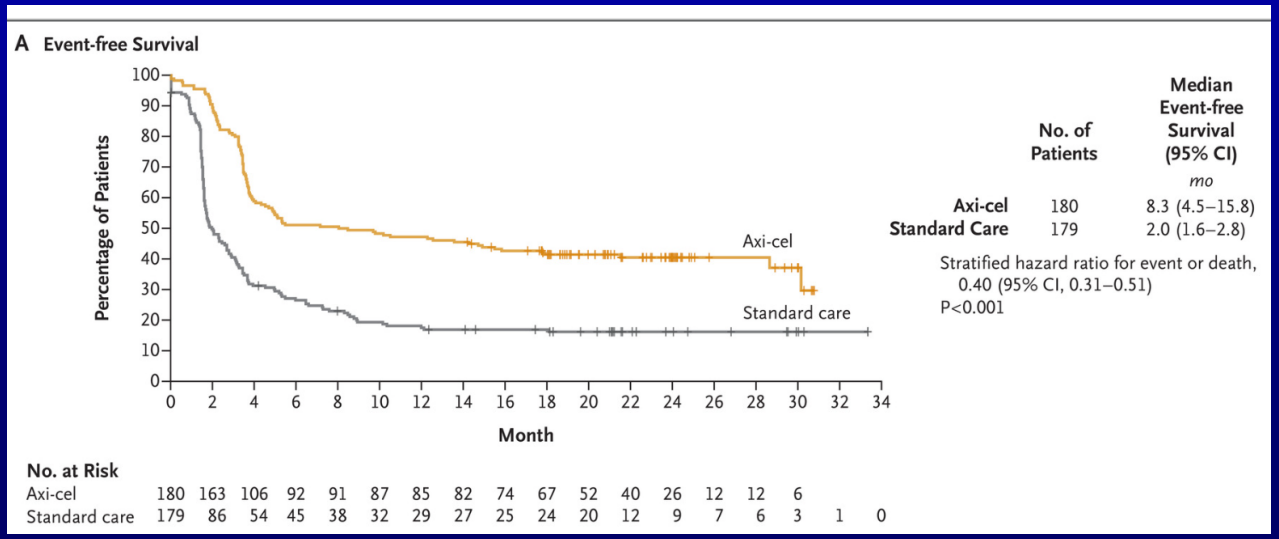
- CAR-T Cells Targeting BCMA
- Pts received a median 6 prior lines of therapy
- Almost all tumors expressed BCMA
  - 73% response rate (including 33% CR)
  - 26% of pts became MRD negative
  - 84% CRS (5% >=Gr 3)



Nikhil C. Munshi et al NEJM 2021

Axicabtagene Ciloleucel as Second Line Therapy for Relapsed or Refractory Large B-cell Lymphoma

- CAR-T Cells Targeting CD19
- Pts with large B-cell lymphoma relapsed withing 12 months or refractory to primary chemotherapy
- Patients randomized 1:1 to CAR-T cells (n=180) followed by Auto-HSCT vs chemo (n=179) and Auto- HCT
  - Median PFS superior in CAR-T cell group (8.3 months vs 2 months p<0.001)
  - PFS at 24 months superior in Car-T cell group (41% vs 16% P<0.001)
  - No CAR-T cell therapy toxicity deaths: 6% CRS >= grade 3 and 21% grade >= 3 neurologic events

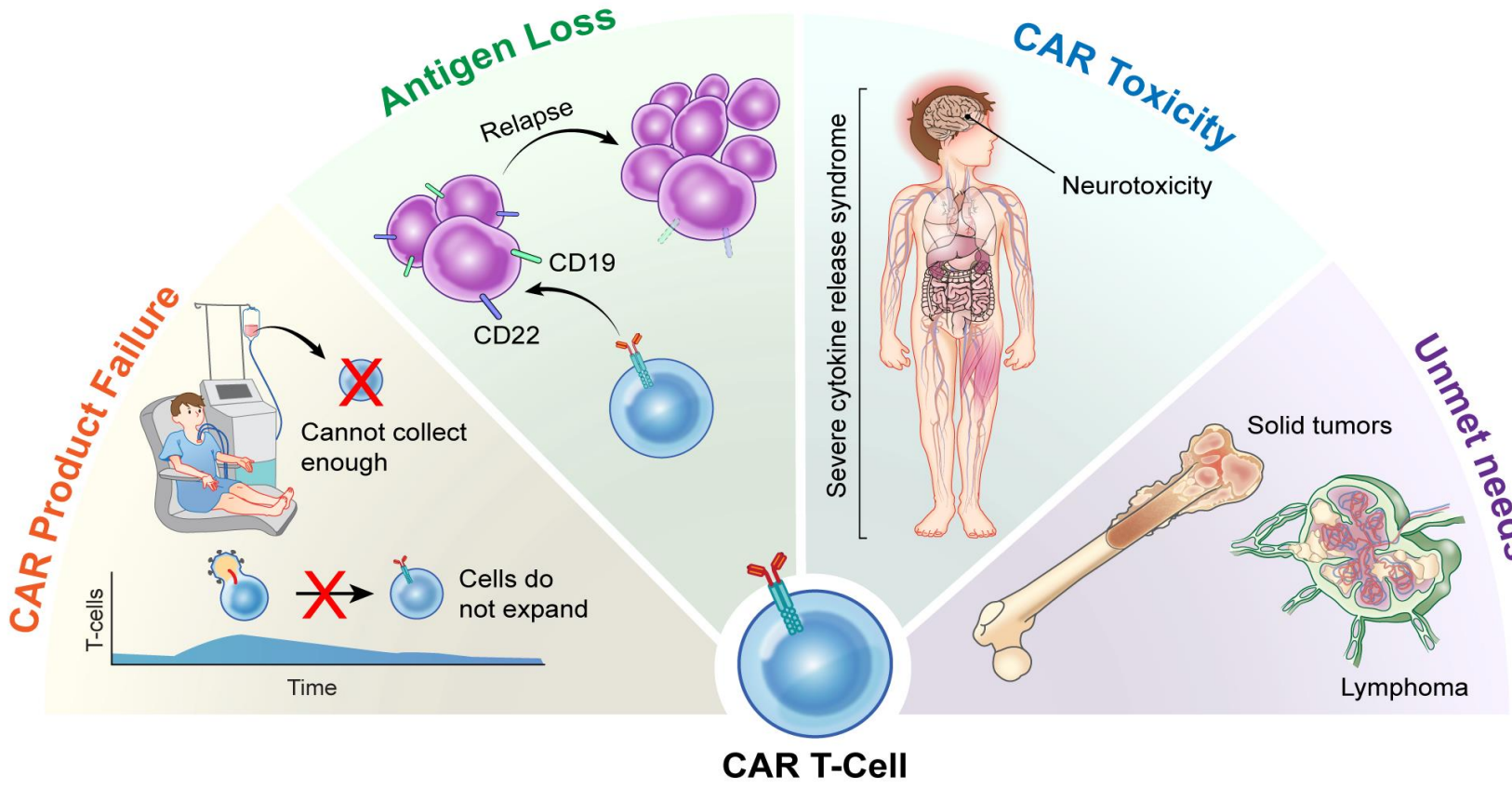


Locke FL et al NEJM 2022

Will CD19 CAR T-cells be the CURE?

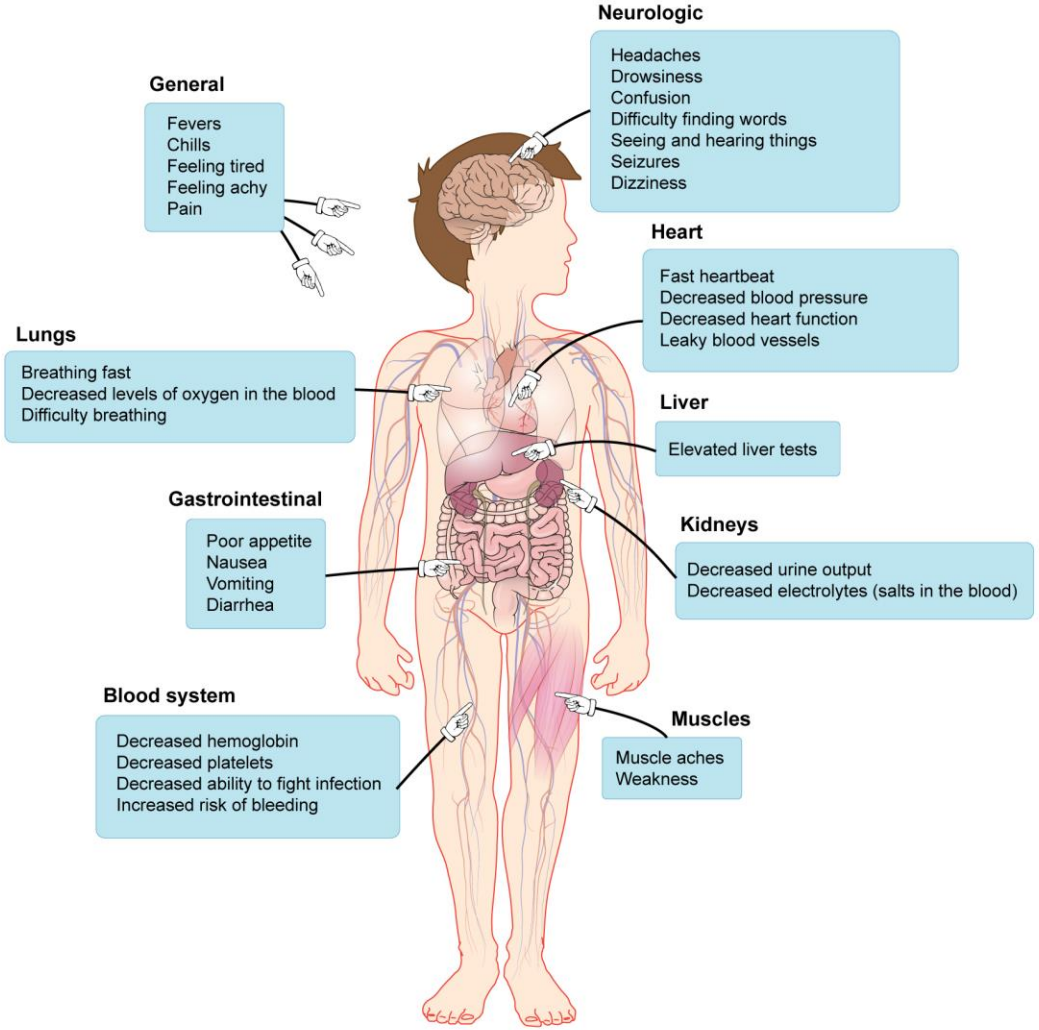
https://emilywhiteheadfoundation.or

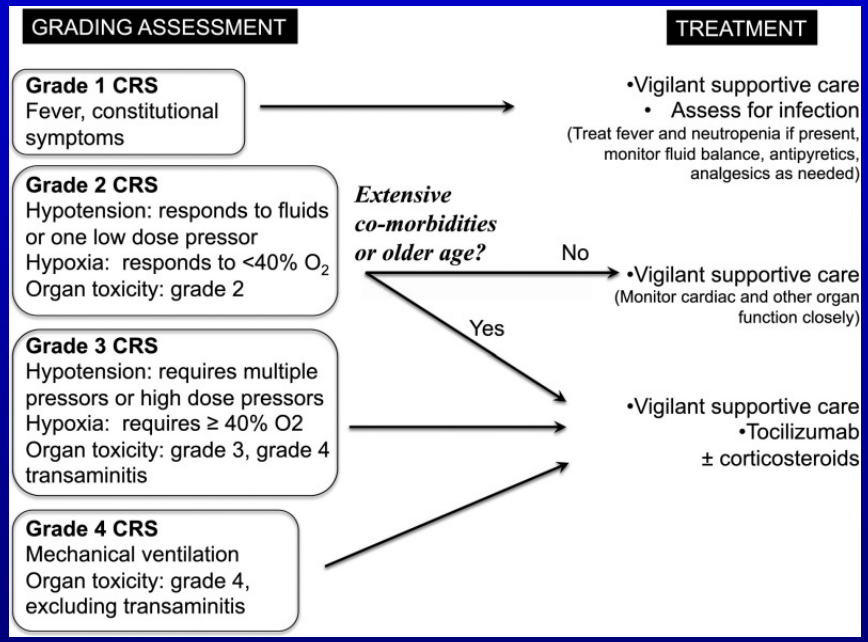
Current Challenges



Shah NN, Nat Rev Clin Oncol

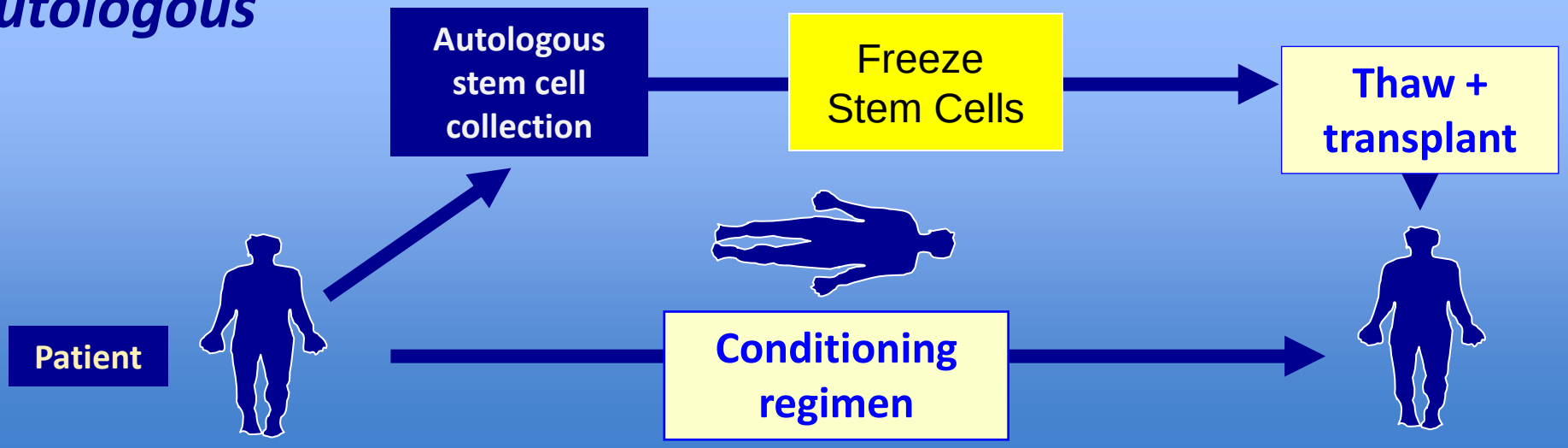
Cytokine Release Syndrome



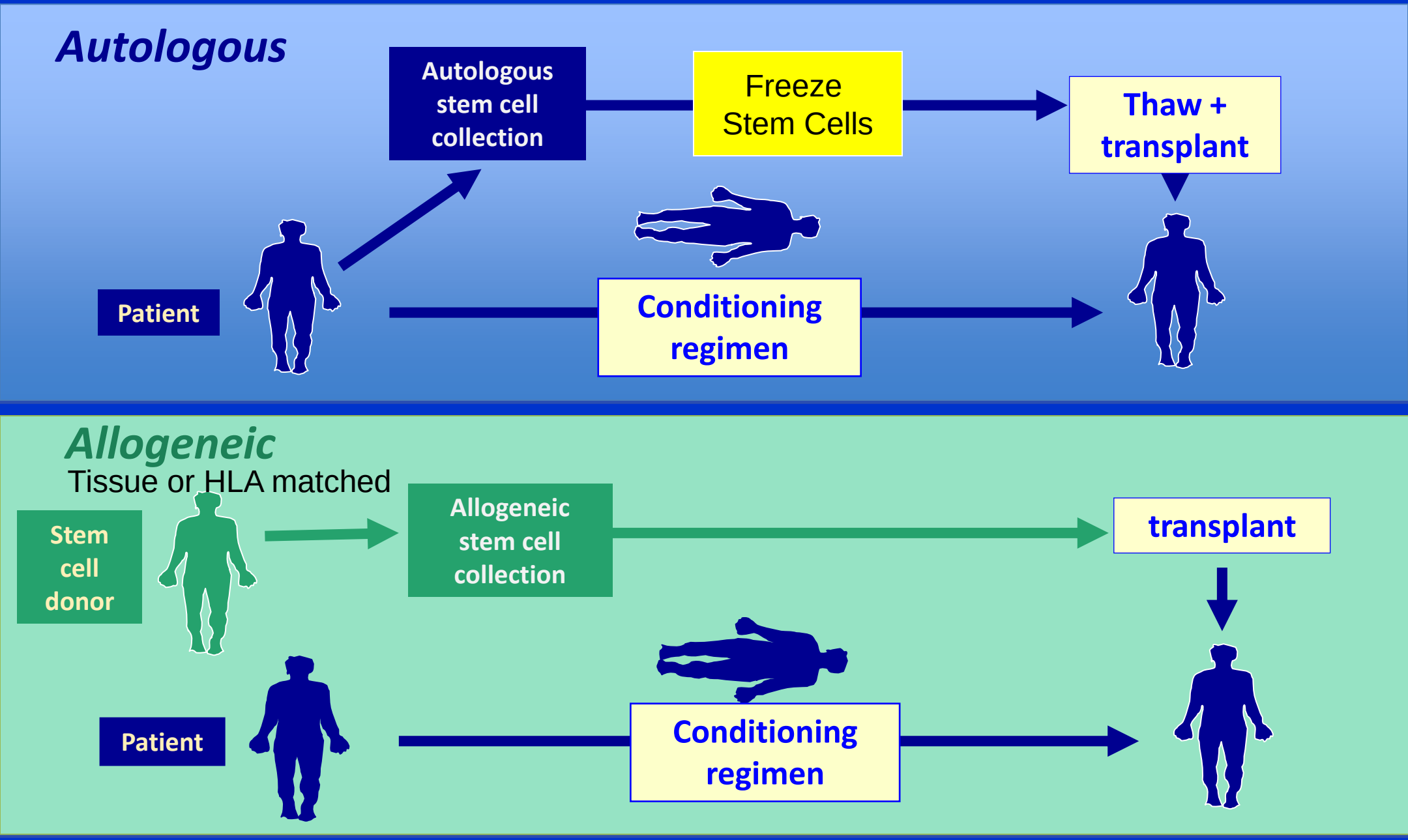


Stem cell transplantation

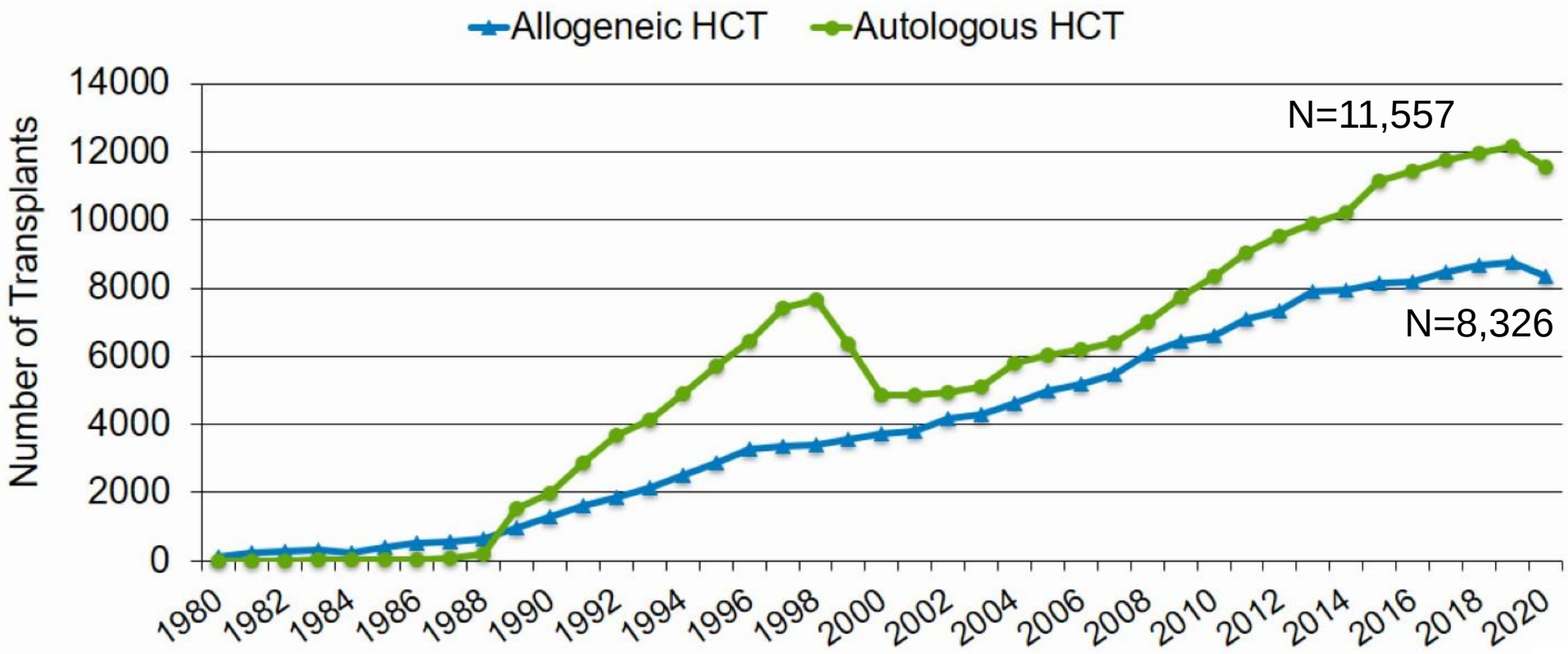
Autologous



Stem cell transplantation



Number of HCTs in the US Reported to CIBMTR by Transplant Type



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Data from the CIBMTR 2022

Stem Cells Source

Peripheral Blood

↓

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

Bone Marrow

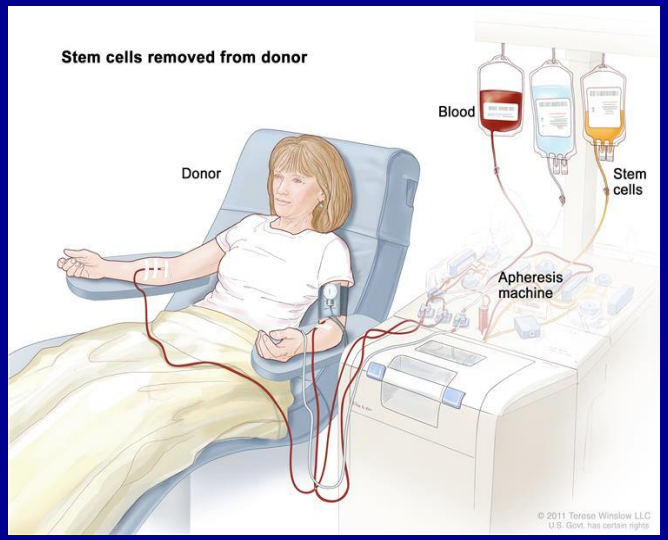
↓

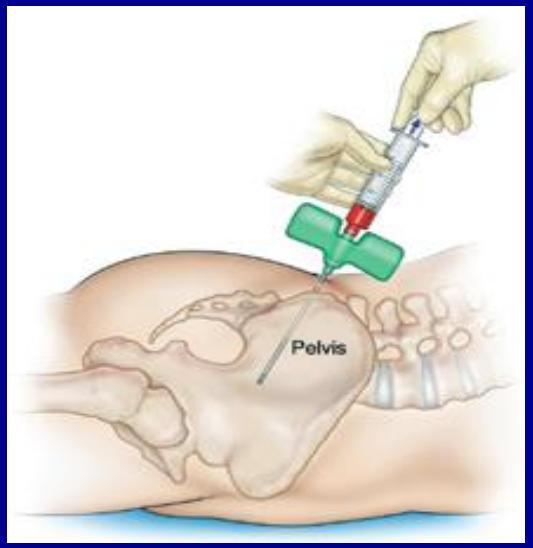
Direct aspiration under general

Umbilical Cord Blood

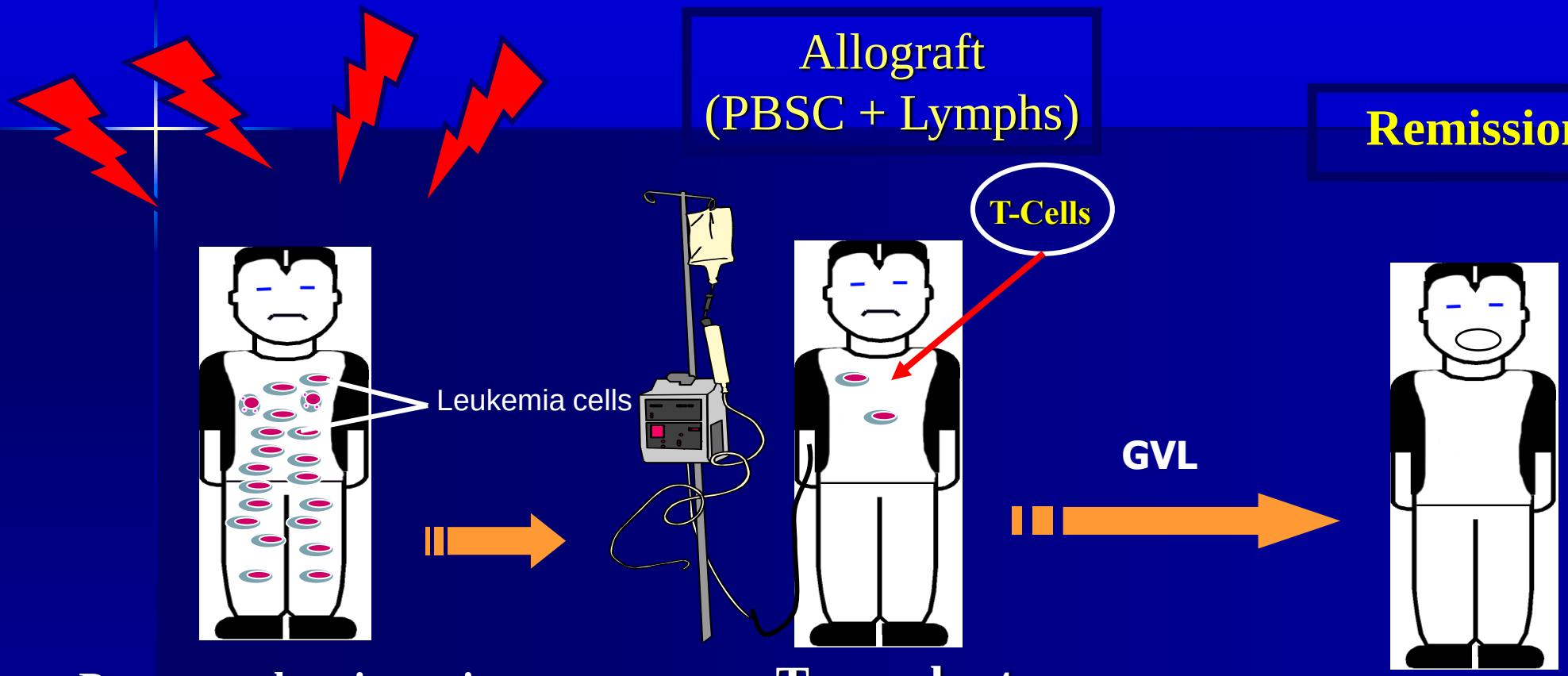
↓

Placental blood directly drained into bag





How Does Myeloablative Allogeneic BMT Cure?



Pre-transplant intensive Therapy (kill the cancer)

1) Conditioning Regimen

Transplant

-Rescue the bone marrow
-Immunotherapy

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

NHLBI Hematology Branch Transplant Protocol 02-H-0250

17 Years Post Transplant

2006

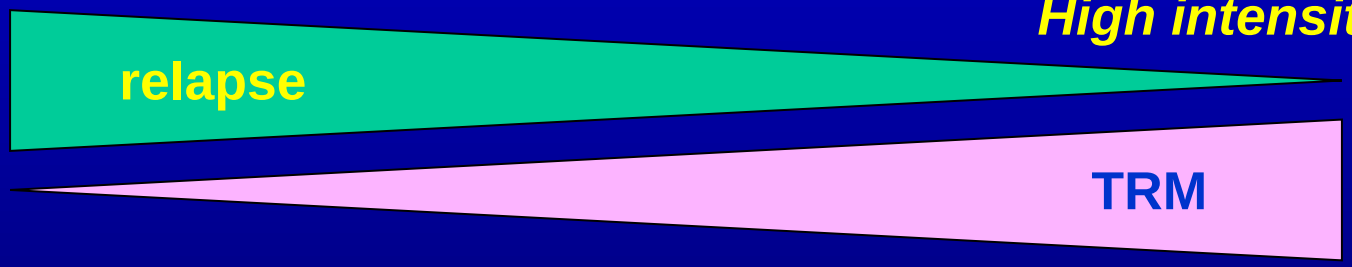
2022

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**

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

Low intensity Conditioning (RIC)

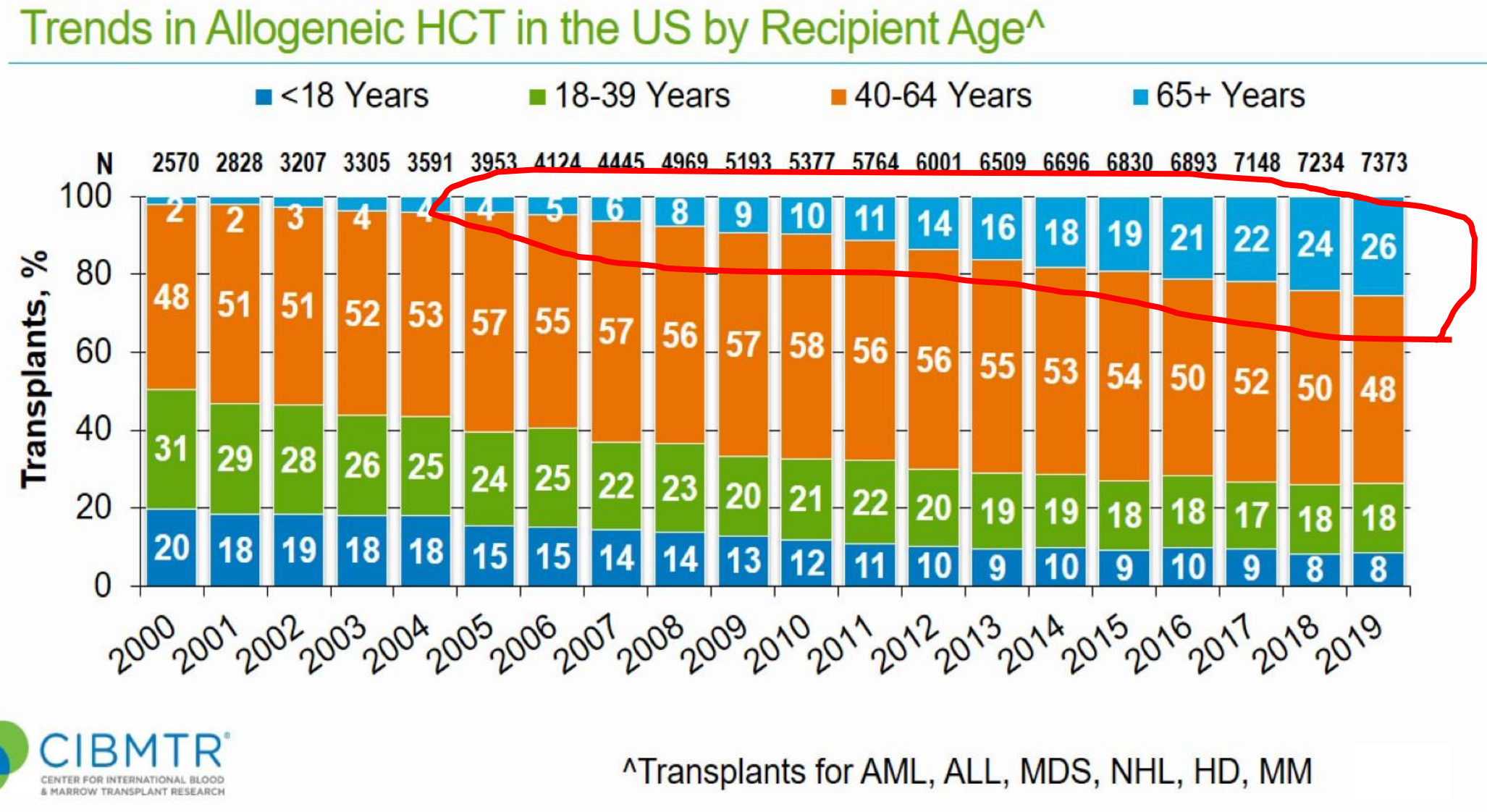


High intensity

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

TRM= Transplant Related Mortality

More Utilization of Allotransplants amongst Older Patients



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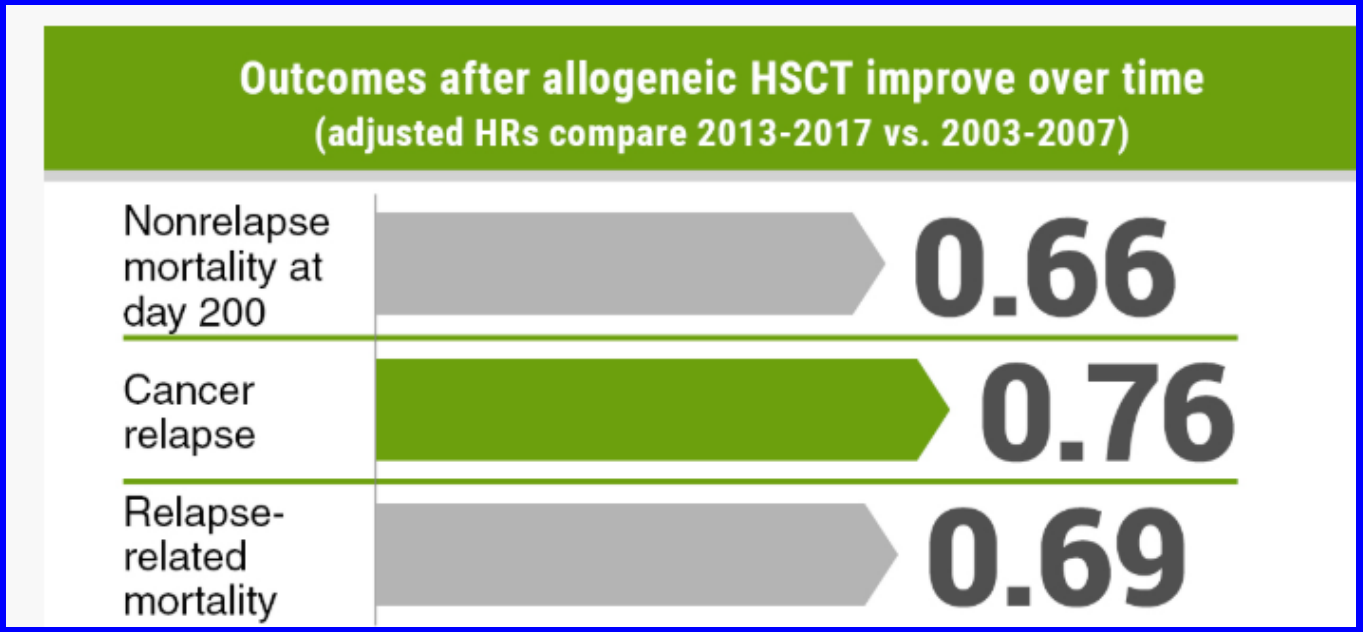
^Transplants for AML, ALL, MDS, NHL, HD, MM

Data from the CIBMTR 2022

Major Improvements in Transplant Safety Over the Past 2 Decades



2003-2007-n=1148
2013-2017- n=1131

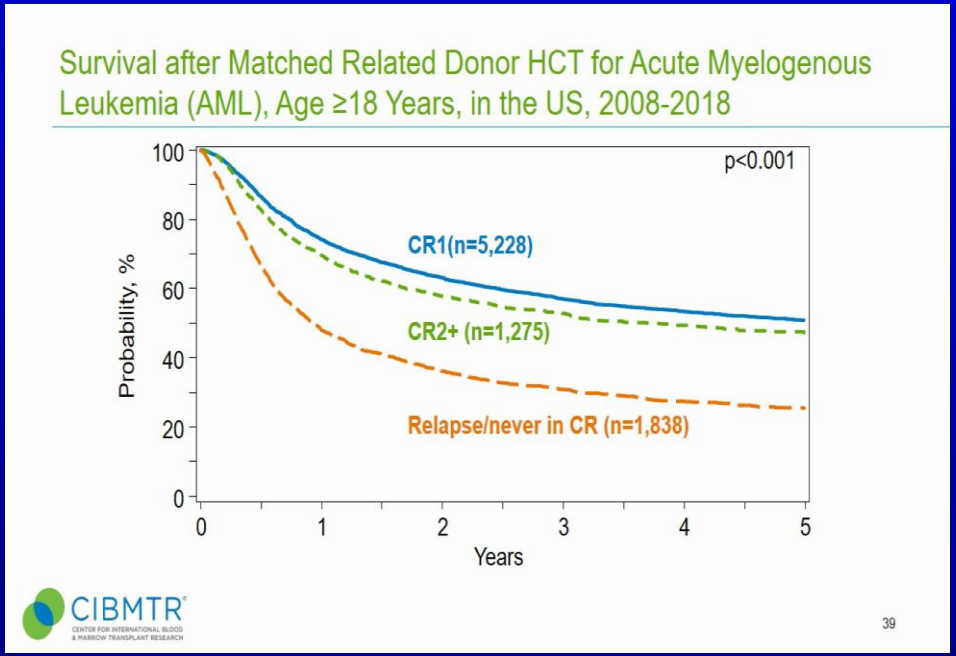
McDonald G.B. et al Annals Int Med 2020:Ann Intern Med. 2020;172:229-239.

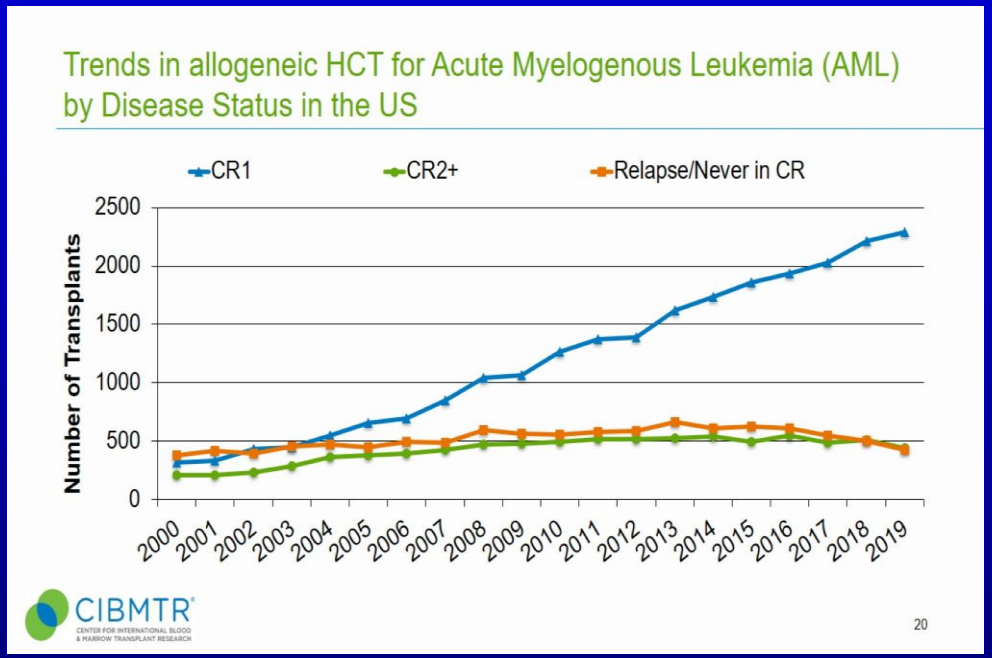
In the era of precision medicine, why do we still perform these dangerous allogeneic transplants?

- **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: The Earlier the Better !!



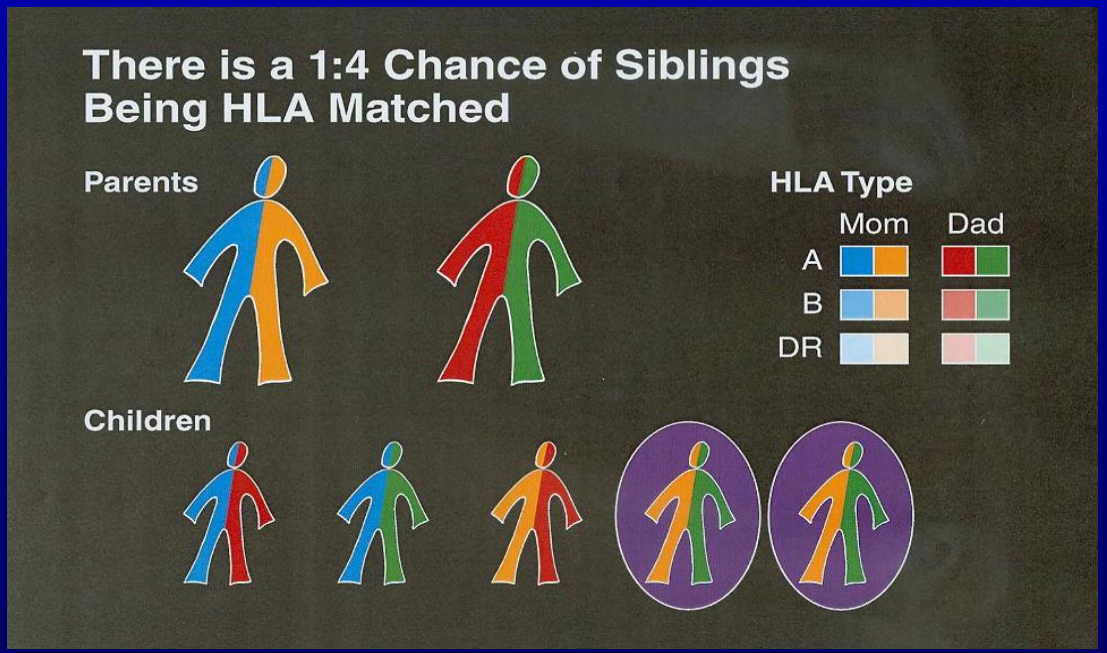


Reduced transplant-related mortality and lower relapse with the earlier use of transplants has led to an increasing use of allogeneic transplants upfront for AML in CR-1

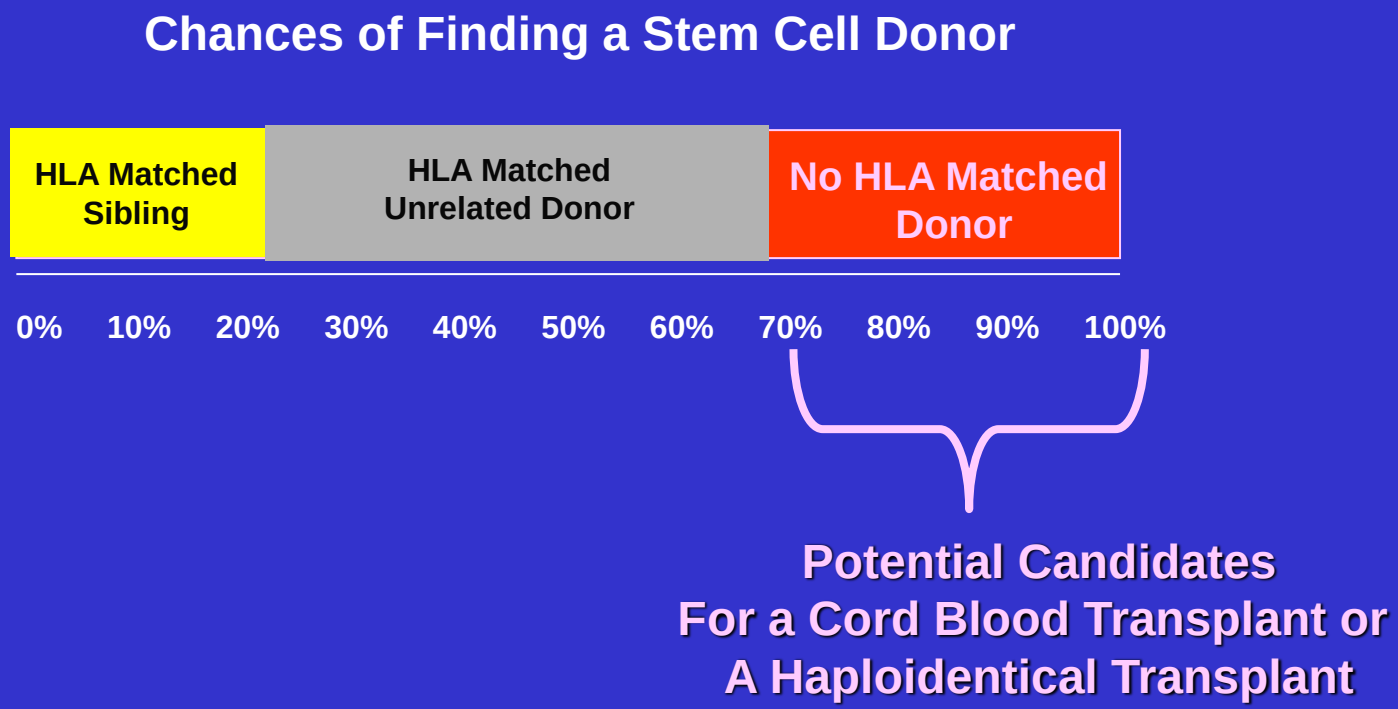
CIBMTR Data 2020

REQUIRMENTS 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

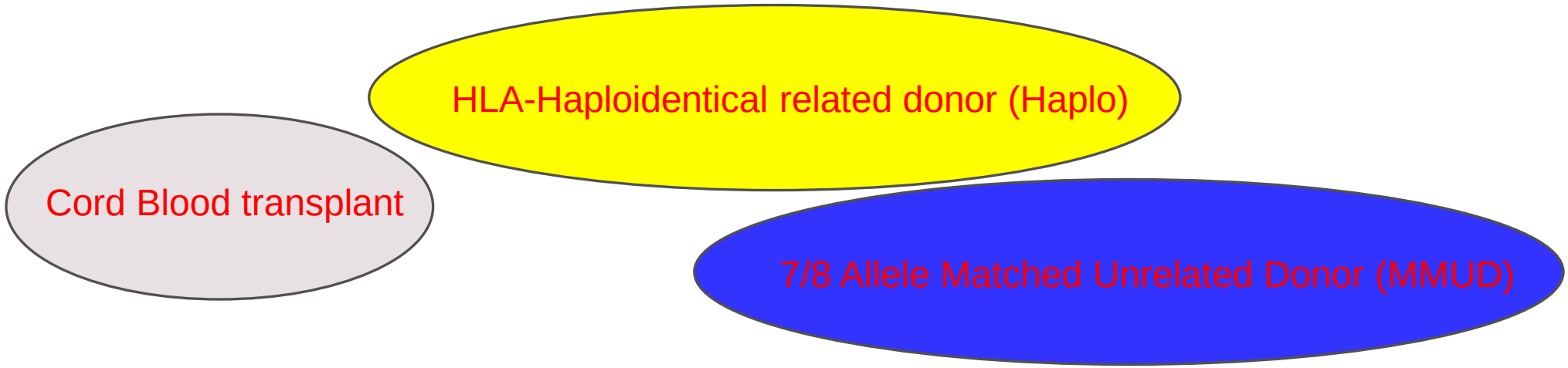


Graft Donor Sources- who to choose?

1) HLA Identical Sibling (SIB)- still best

2) 8/8 Allele Matched Unrelated Donor (MUD)- maybe still 2nd best

3) alternative donors:



Haploidentical BM Transplants

- Transplants that utilize stem cells collected from a relative who only matches for half of the HLA tissue antigens

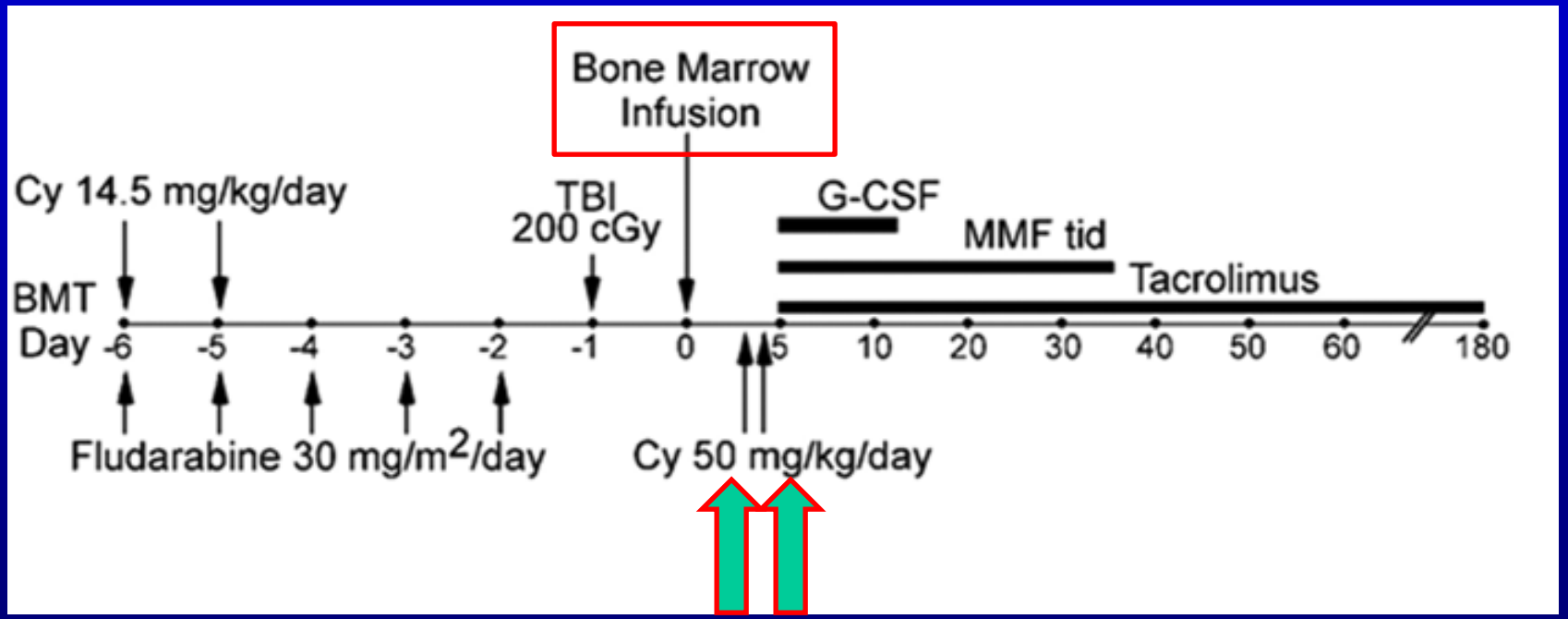
  - **Advantages;**

    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

Fuchs E. et al JHU

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

Survival

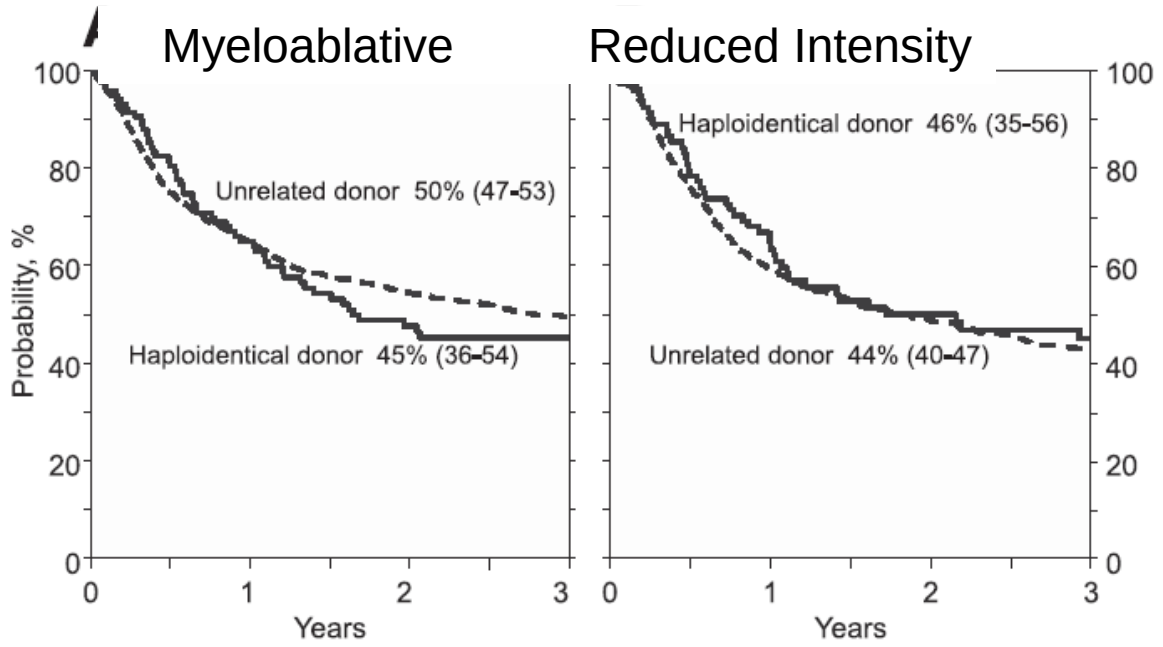


Figure 3. Overall survival. (A) The probability of OS by donor type after myeloablative conditioning regimen, adjusted for age and disease risk index. (B) The probability of OS by donor type after reduced intensity conditioning regimen, adjusted for disease risk index and secondary AML.

Ciurea S. et al Blood 2015 126:8:1033-40

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

Advantages of Cord Blood

Lower Graft vs. Host Disease (GVHD)

↓

HLA-mismatched Transplants Possible

↓

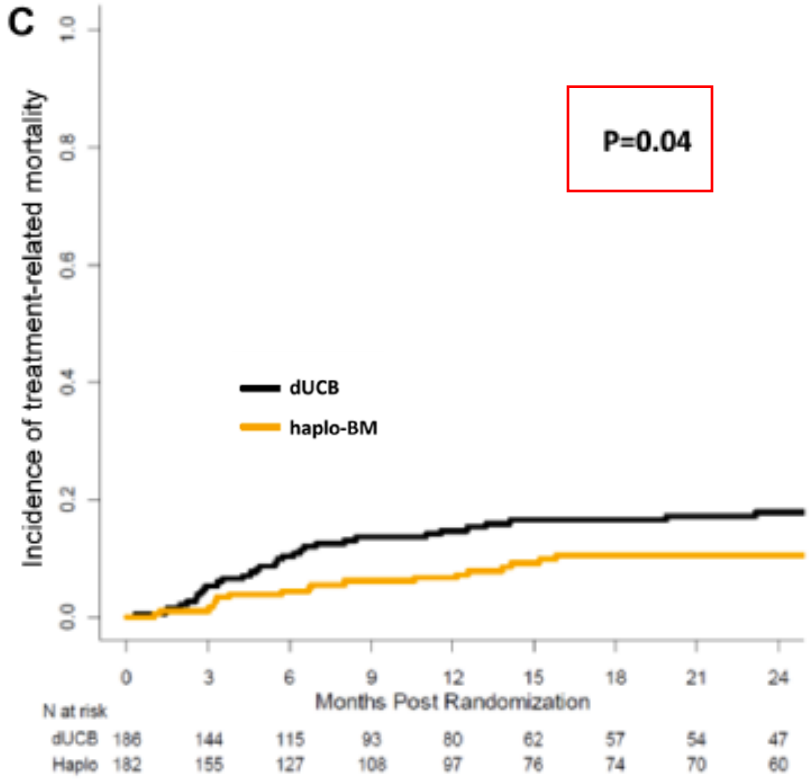
Off the shelf product quickly available

↓

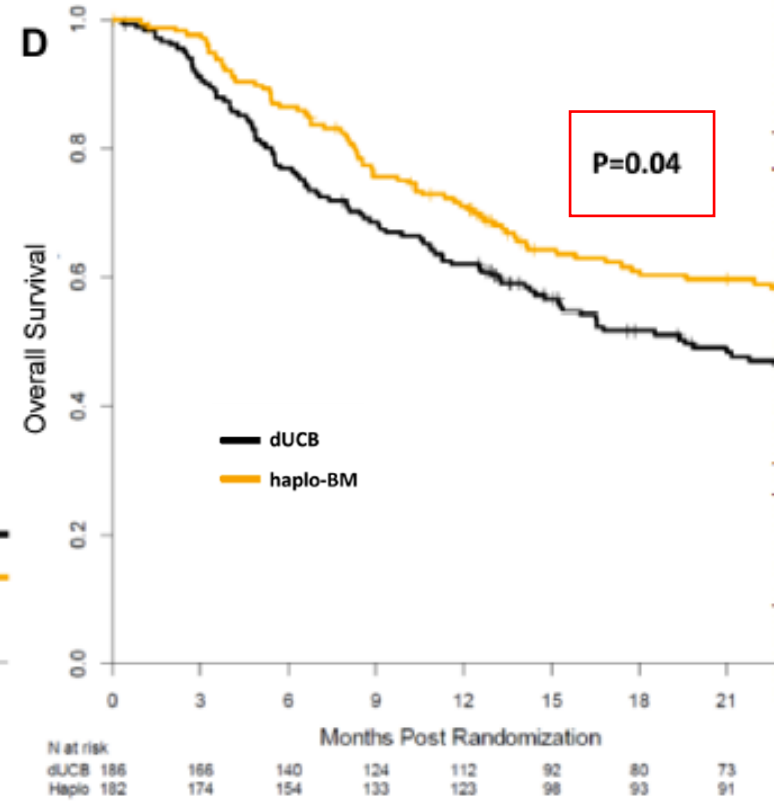
Cord Grafts available to Patients with Rare HLA Types And Ethnic Minorities

Which is Better: A Cord or a Haplo Transplant? CTN 1101: Cord vs. Haplo

Transplant related Mortality

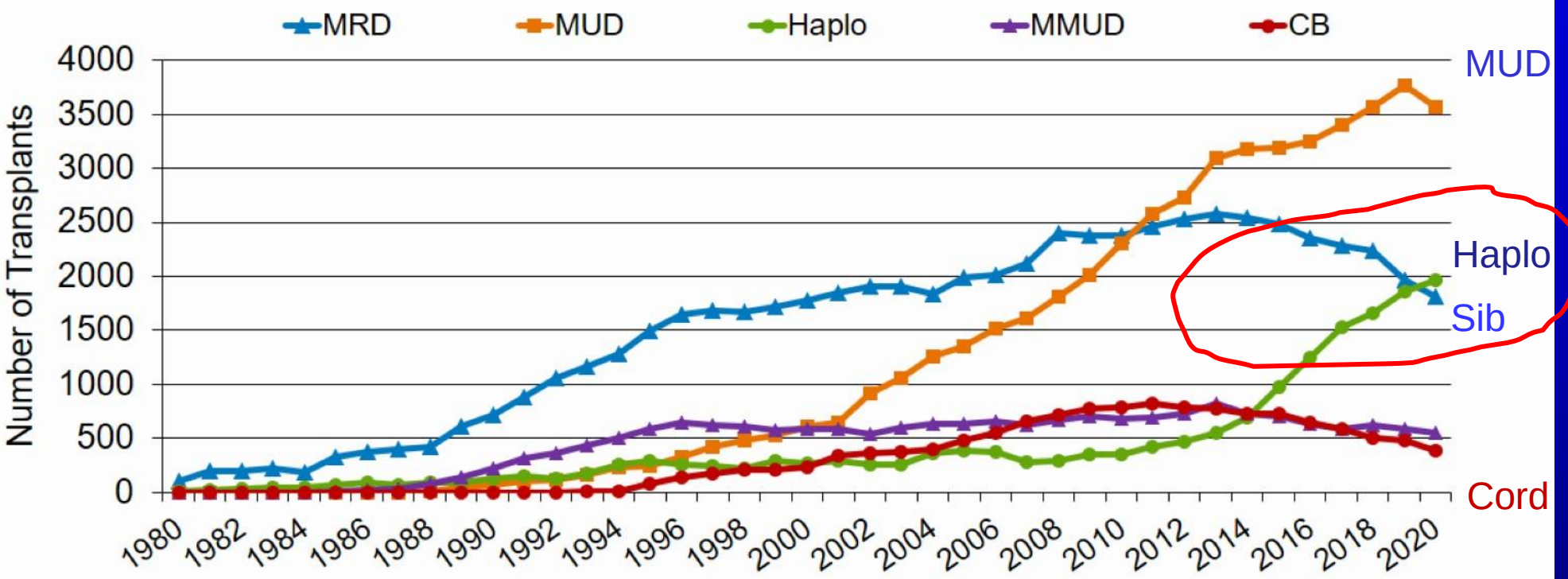


Overall Survival



Fuchs E. et al Blood 2021: 137:420428

Number of Allogeneic HCTs in the US by Donor Type



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Abbreviations - MRD: Matched related donor; MUD: Matched unrelated donor;
Haplo: Haploidentical donor (includes all mismatched related donors); MMUD: Mismatched unrelated donor; CB: Cord blood

Data from the CIBMTR 2022

Should I Get a Transplant Questions To Be Answered

- Does the potential benefit of a transplant justify the risk?
- Is my disease controlled sufficiently to where a transplant would help? Timing is everything!!
- Do I Have a stem cell 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?