Hematopoietic stem cell transplant (HSCT)

Dr Fatemeh Nejatifar

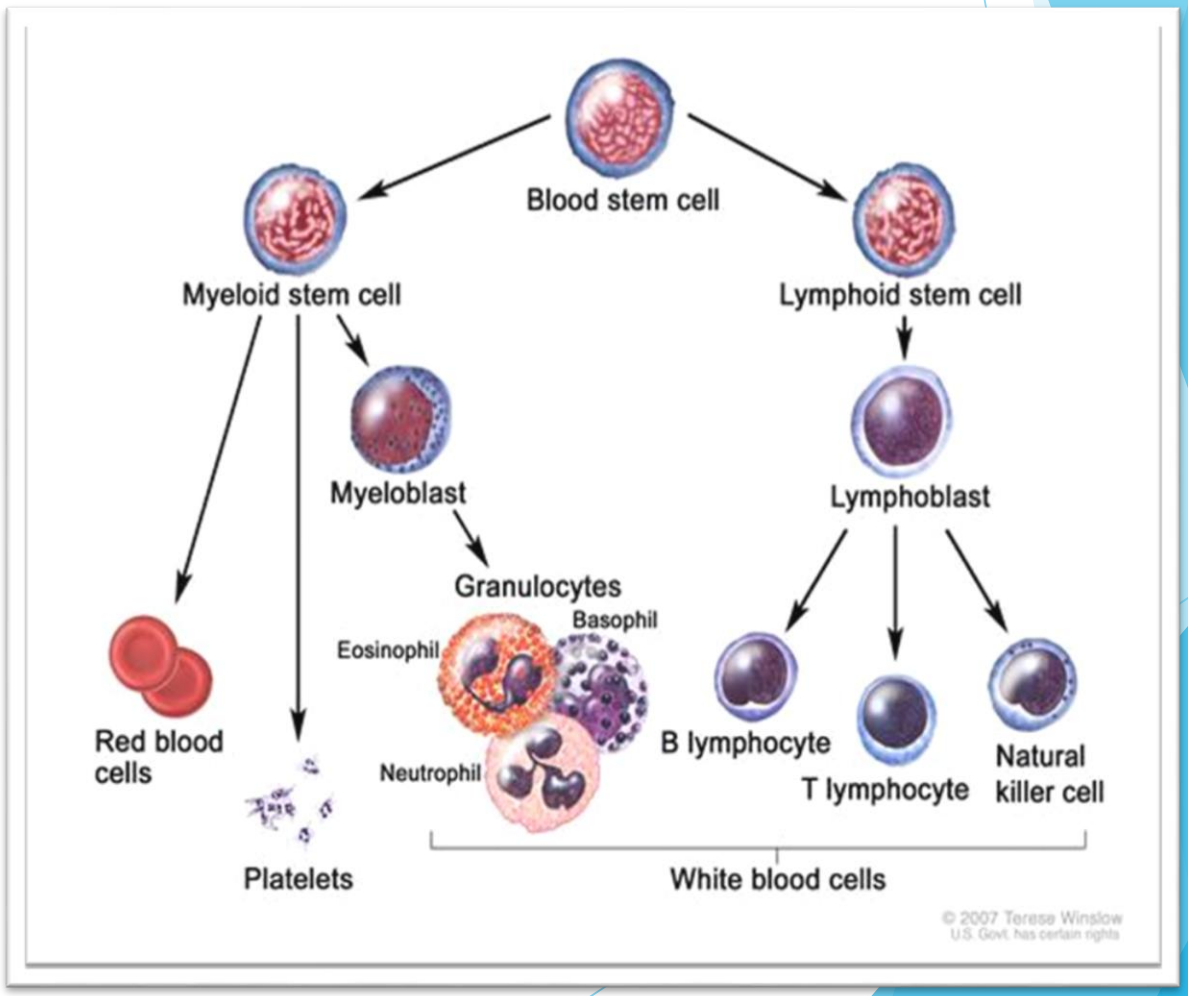
Hematologist & Medical Oncologist

Guilan University of Medical Sciences

Hematopoietic cell transplantation (HCT) is an important and potentially curative treatment option for a wide variety of malignant and nonmalignant diseases.

Hematopoietic stem cell

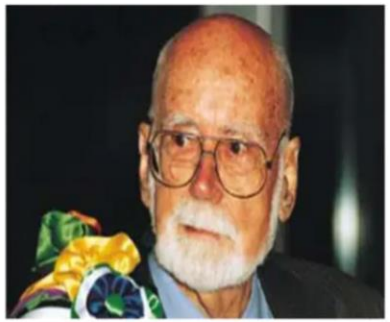
- HSCs formation start during embryonic development.
- Found in bone marrow and umbilical cord blood.
  - Hemati= Greek prefix "blood'
  - Poiesis/Poietic= Greek suffix 'formation"
- Express CD34.



History of BMT

- **1956 – The First** successful **Transplantation Between Identical Twins with** total body irradiation.

- E. Donnall Thomas
  first succsessful HSCT in treatment of acute leukemias with complete remission.



E. Donnall Thomas

The Nobel Prize, 1990

History of BMT

- **1958 – an Important Discovery**
  Allogeneic BMT was not performed on large scale until Jean Dausset, a French medical researcher, made a critical discovery about the human immune system : Human histocompatibility antigens "HLA"

- **1968 –** First Bone Marrow Transplant Between HLA matched Siblings.

- **Noble prize in 1980.**

Jean Dausset

Indications for Transplantation

- Hematologic Malignancies (leukemia, lymphoma, myeloma)
- Aplastic Anemia
- Myelodysplasia
- Myelofibrosis
- Hemoglobinopathies
- Immunodeficiencies
- HLH
- Enzyme deficiencies

Types of Transplant

- **Autologous** (your own cells)

- **Allogeneic**
- cells from another person
- Sibling
- Unrelated Donor
- Parent or relative
- or source: Umbilical cord

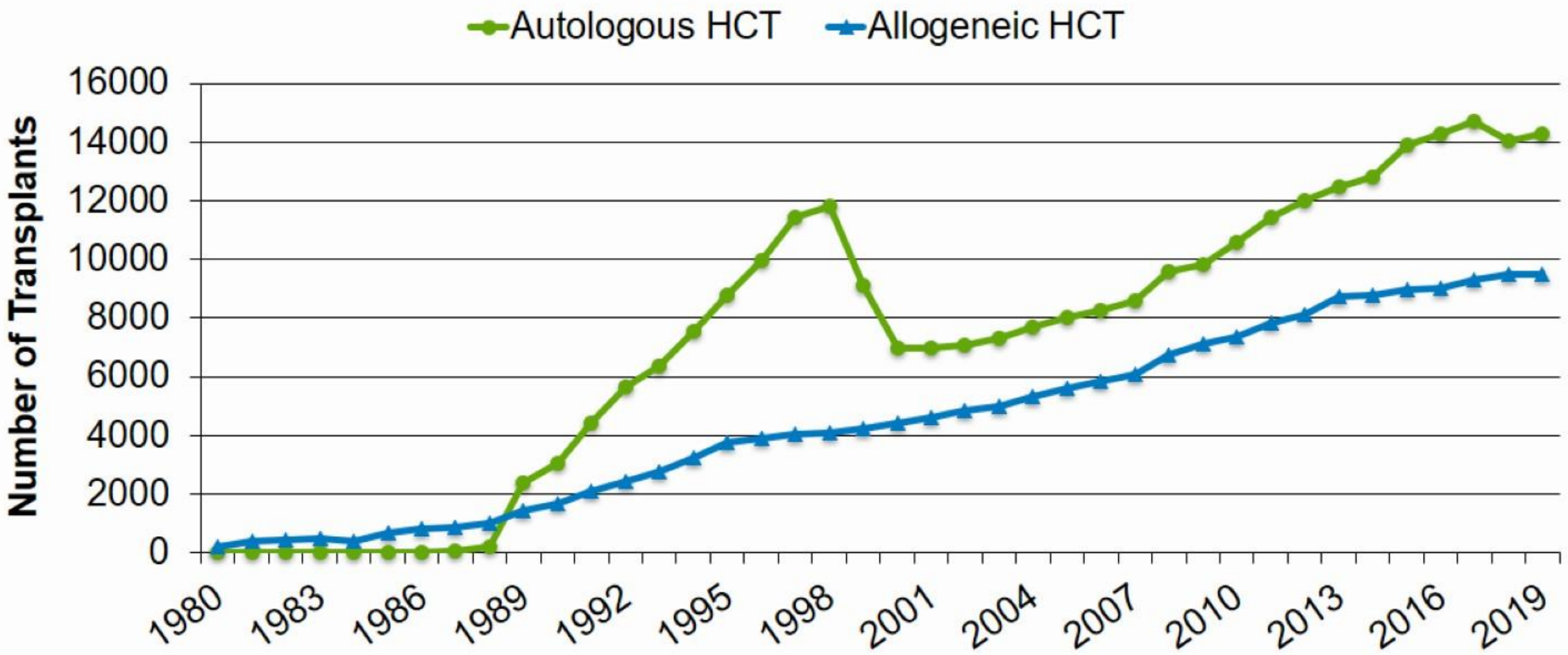
Hematopoietic Progenitor Cell Sources

- Bone Marrow
- PBSC (peripheral blood stem cells)
- Umbilical Cord

Sources of Stem Cells for Transplantation

Autologous	Allogeneic
• Donor available	Undamaged stem cells ?
• No GVHD	No tumor contamination
• No immunosuppression	Graft-vs-tumor effect
Less toxicity	*More toxicity*
Higher relapse rates	*Lower relapse rates*

Estimated Annual Number of HCT Recipients in the US by Transplant Type



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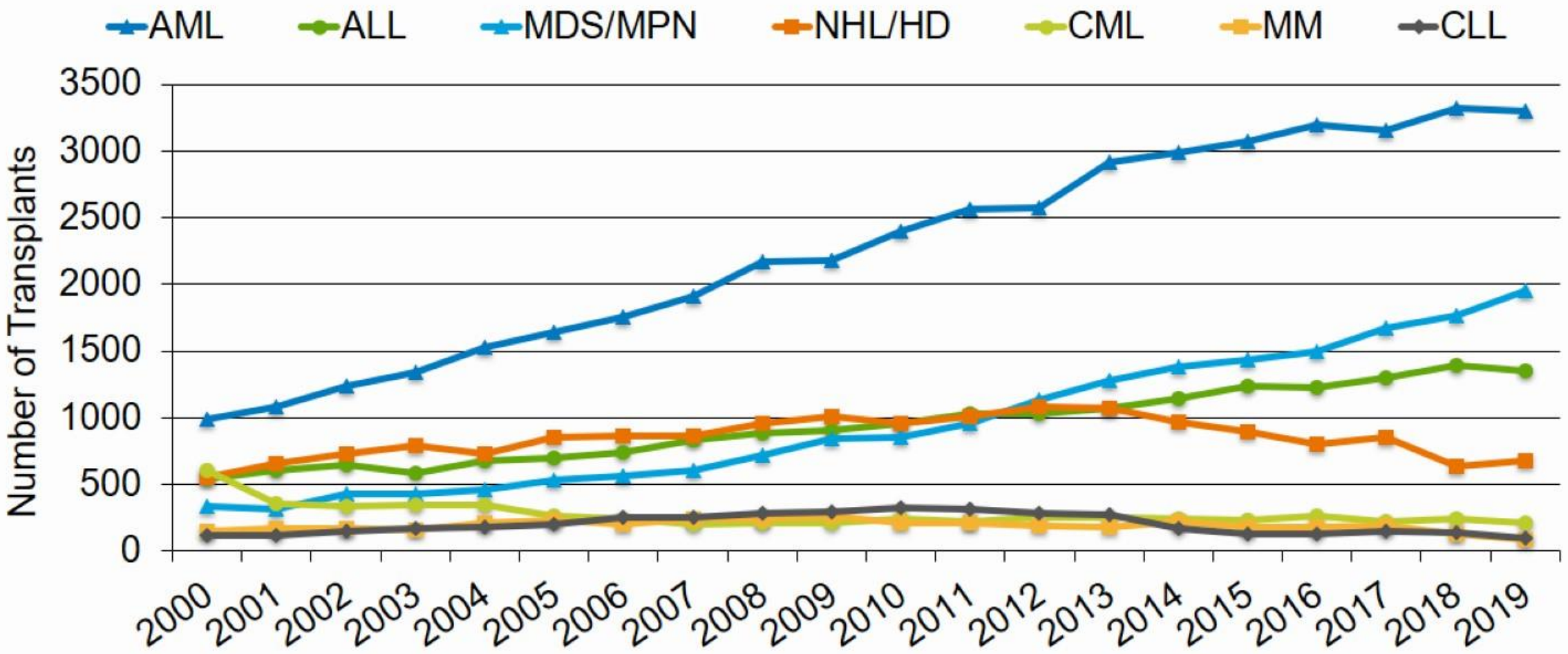
Selected Disease Trends for Allogeneic HCT in the US



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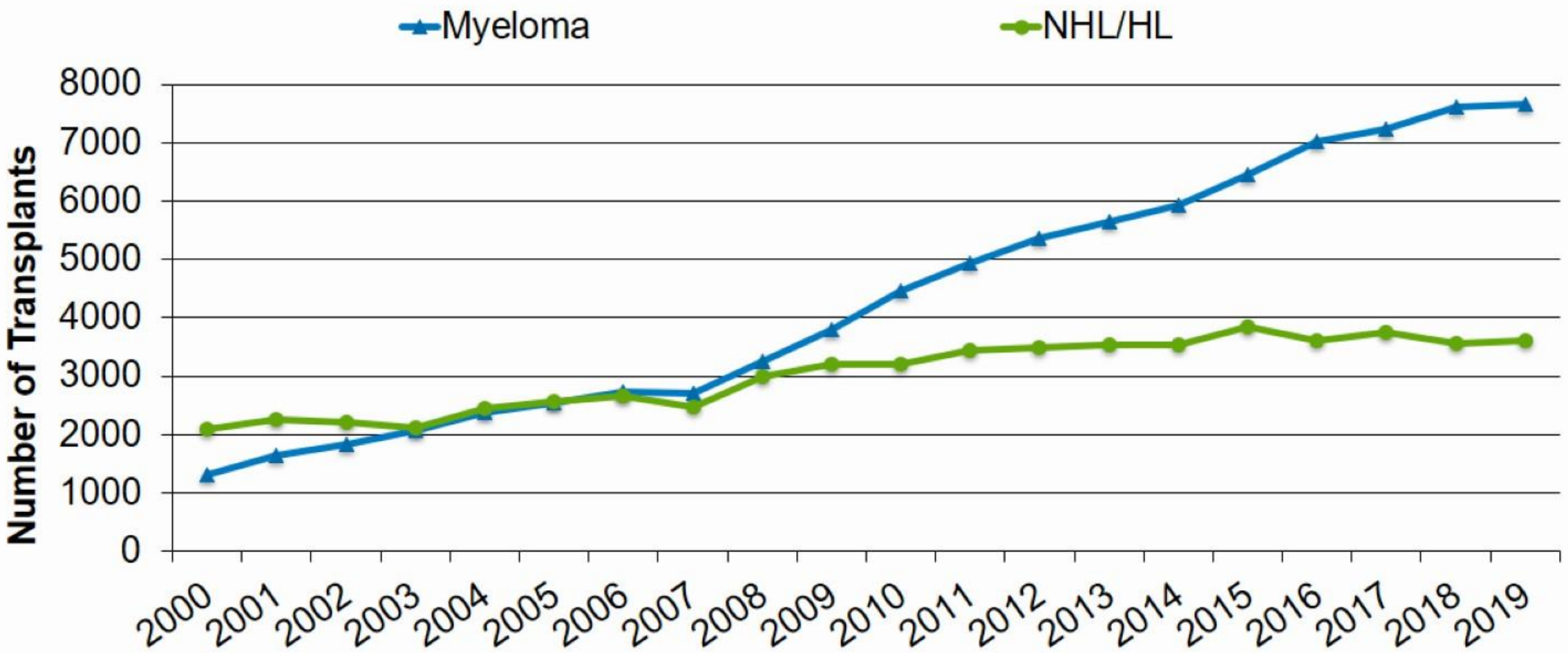
Selected Disease Trends for Autologous HCT in the US



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Challenges *and Advances* in Transplantation

- Donor Availability and Sources
- GVHD
- Immunologic Recovery
- Relapse

Obstacles to Success

- Finding a compatible donor
- Limiting transplant related complications
- Preventing disease relapse

Donor Availability...

Best Allogeneic Blood/Bone Marrow Donor is a brother or sister

- Only 25% of patients are that lucky!
- There is a 1 in 4 chance that any child will match another child of the same parents
- Major obstacle in the treatment of patients who would benefit from an allogeneic transplant.
- In 1986, the National Marrow Donor Program (NMDP) was established
- At present, there are over 25 million donors registered worldwide

Crossing HLA barriers - Options

- Mismatched unrelated donors
- Umbilical Cord Blood
- Haploidentical donors

Umbilical Cord Blood Transplantation

- Stem cells present in cord blood
- Number of mature T cells low
- UCB transplantation can be performed between 2-3 antigen mismatched donor/patient pairs with low GVHD
- Engraftment and immune reconstitution delayed compared with BM or PBSC

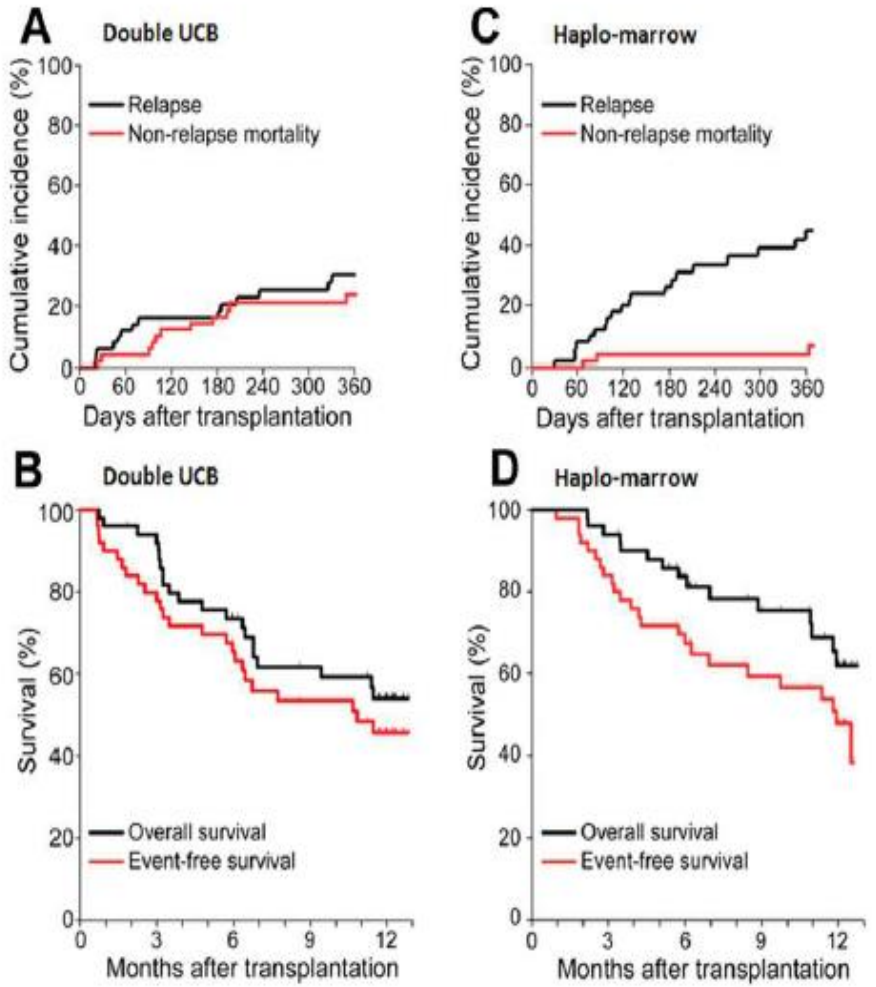
Haploidentical Transplantation

- **Traditionally associated with poor engraftment and prohibitively high GVHD incidence.**
- **Two promising approaches have emerged**

Megadose PBSC infusion after CD34 selection (Perugia)

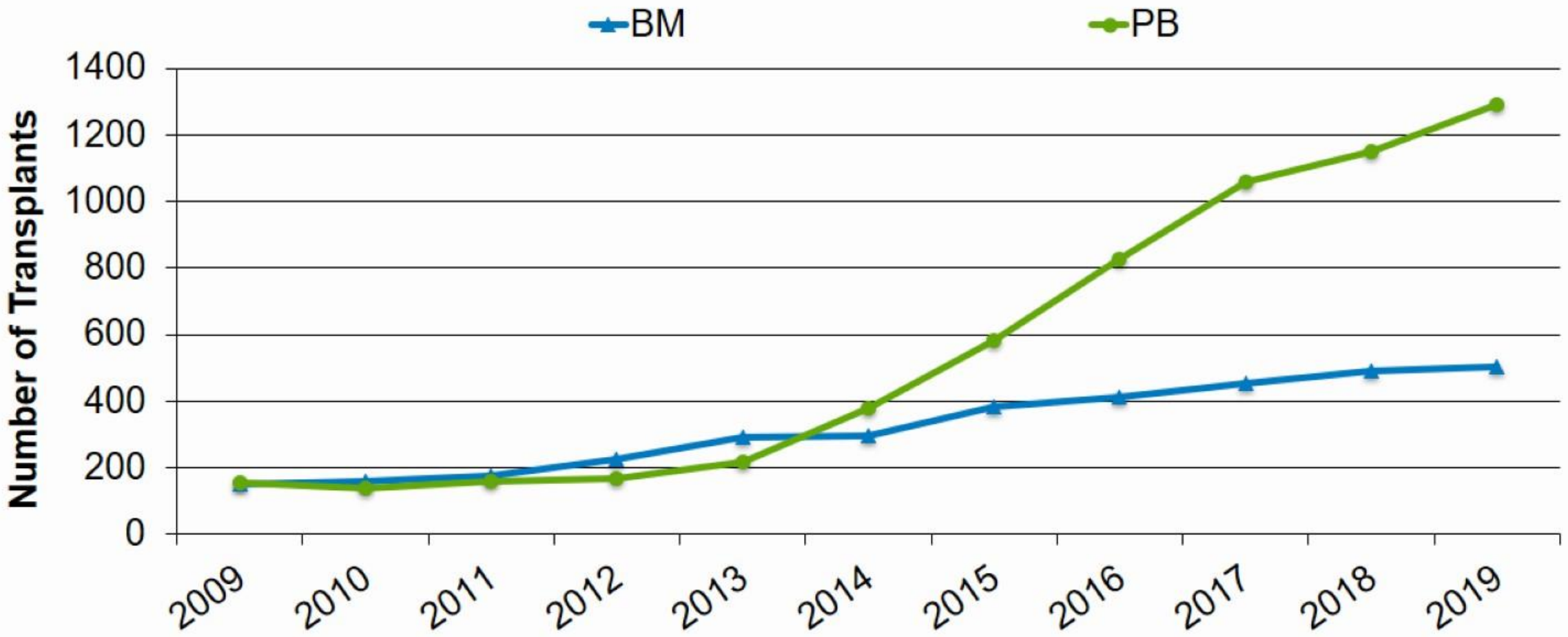
Post-BMT high dose cyclophosphamide (JHU)

Outcomes of double cord and haploidentical transplant (BMT CTN concurrent trials, randomized trial just opened)



Brunstein C G et al. Blood 2011;118:282-288

Haploidentical HCT in the US by Graft Type



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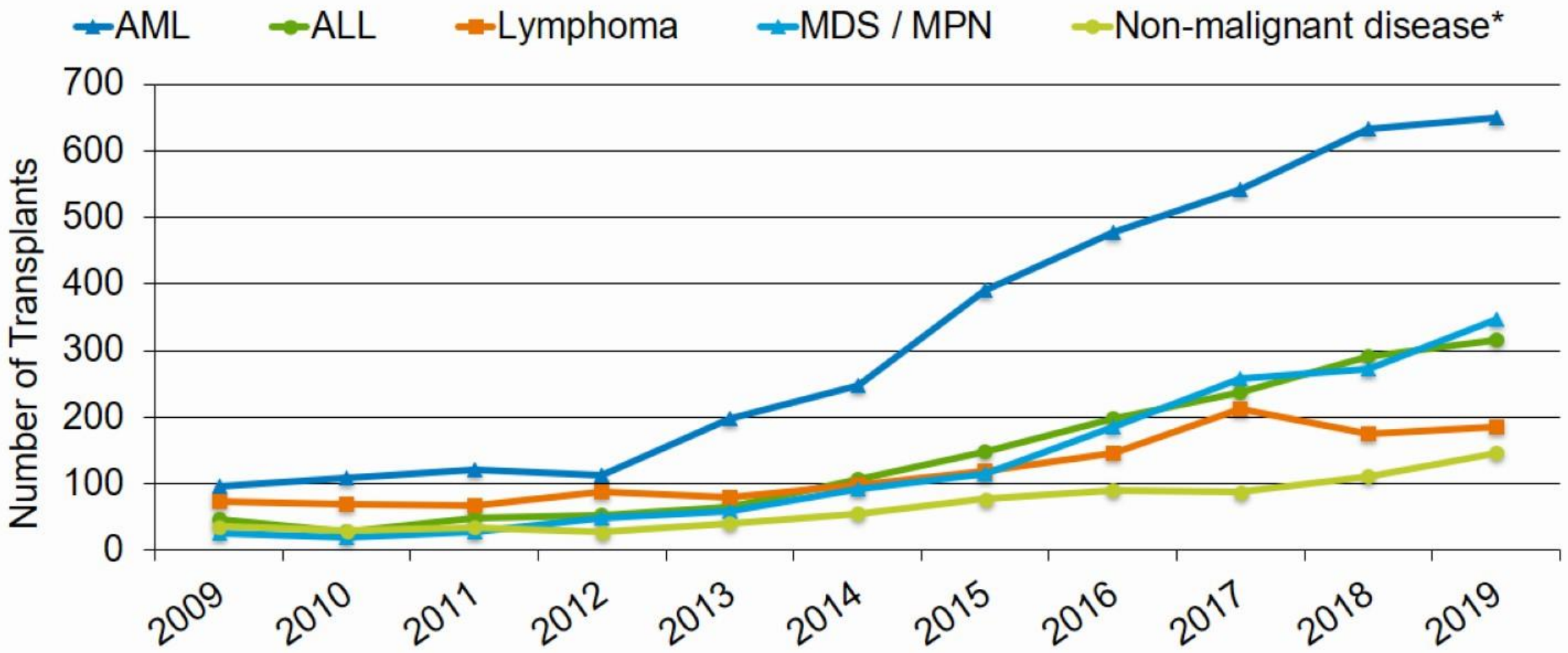
Haploidentical HCT in the US by Disease



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*Not including aplastic anemia

- An HLA-identical sibling is considered a donor of first choice
- For patients with hematological malignancies ,transplantation from fully HLA-MUD (8/8 or 10/10) is not inferior to transplantation from HLA-identical siblings in terms of EFS.
- The choice of alternative donors (haploidentical related donors, cord blood, mismatched unrelated donors) depends on center experience, urgency of transplant procedure, and detection of donor-specific anti-HLA antibodies.
- For pediatric patients and patients with nonmalignant disorders, BM is the preferred stem cell source.
- For adult patients with hematological malignancies, survival outcome after HSCT with PBSC and BM is comparable.
- In URD transplantation, donor age is probably the most relevant non-HLA donor factor.

Transplant Process (5 steps)

(1) Conditioning

(2) Stem cell infusion

(3) Neutropenic phase

(4) Engraftment phase

(5) Post-engraftment period

Optimal Conditioning….

conditioning

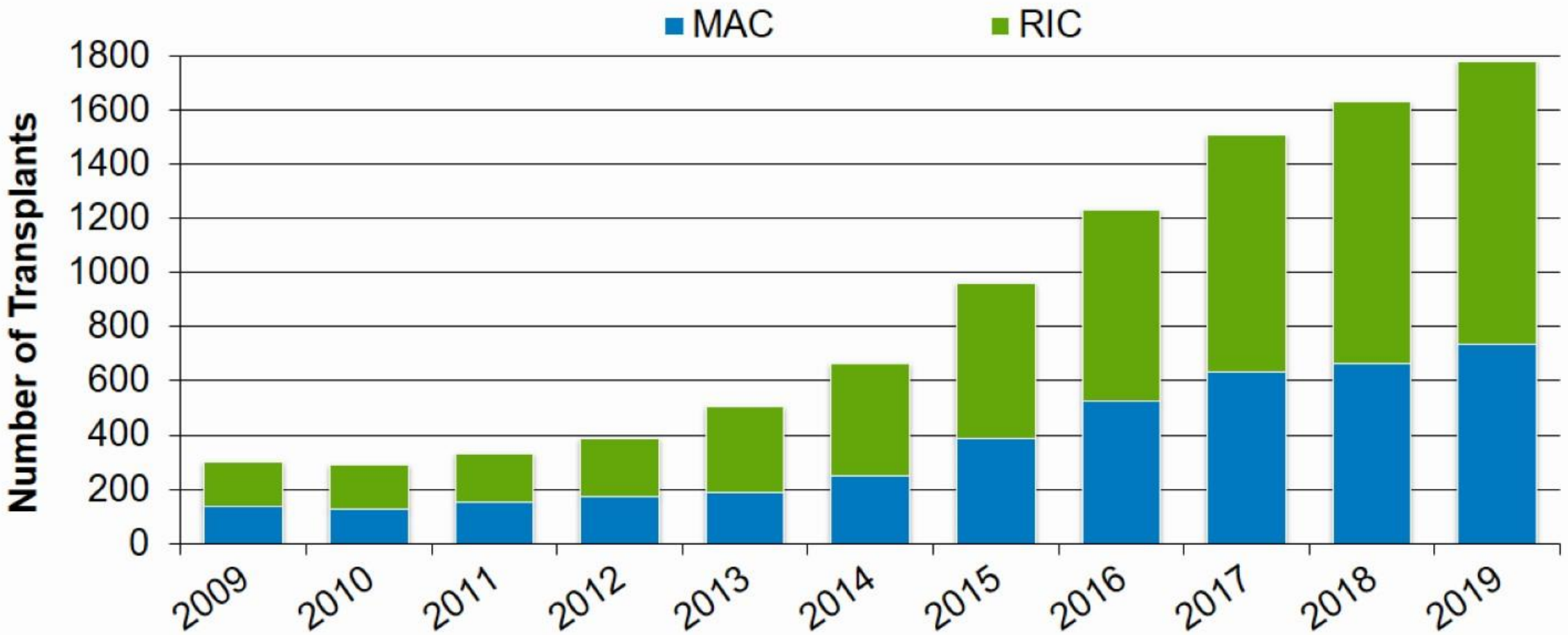
The purpose of the preparative regimen is:

- To provide adequate immunosuppression to prevent rejection of the transplanted graft

- To eradicate the disease for which the transplant is being performed

- Myeloablative
- Nonmyeloablative
- Reduced intensity

Haploidentical HCT in the US by Conditioning Intensity



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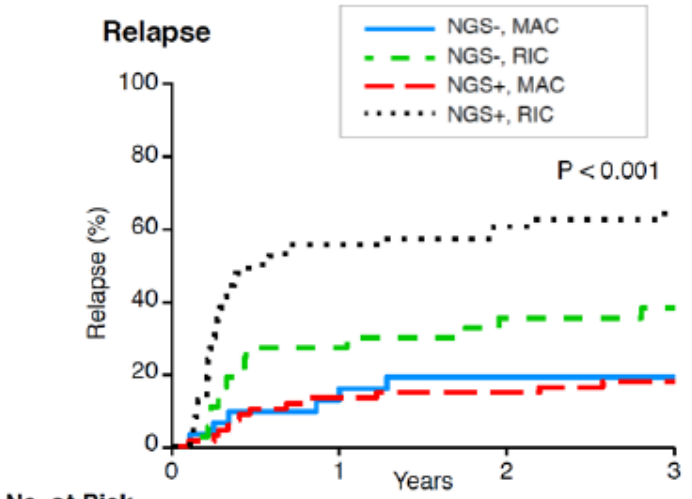
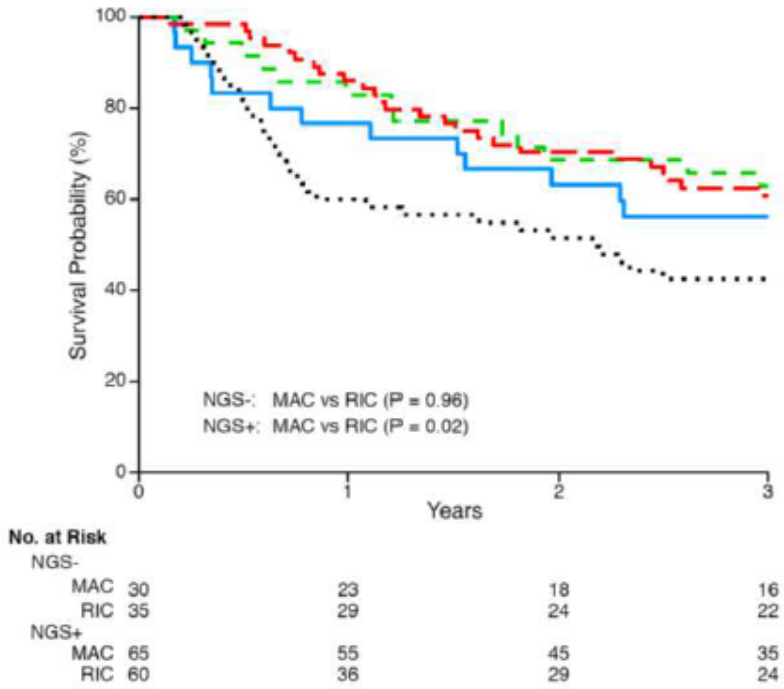
MAC: myeloablative conditioning, RIC: reduced intensity conditioning

NGS Analysis of MRD Shows Effect Modification





Hourigan et al. EHA 2019

Why Does GVHD Occur?

- Donor immune cells contained in the allograft mount an attack against the recipient antigens
- Cells in the graft see recipient tissue as foreign
- Immunocompetent cells begin to attack host cells both normal and those damaged by illness or by the preconditioning

Causes and Risk Factors

- Incompatible HLA match
- Older age of recipient and/or donor
- Multiparous female donor to male recipient
- Stem cells from peripheral blood rather than bone marrow or UCB
- Ineffective GVHD prophylaxis
- Intense preconditioning
- CMV serostatus

Nassereddine. Anticancer Res. 2017;37:1547. Zeiser. NEJM. 2017;377:2167. Copelan. Blood Rev. 2019;34:34

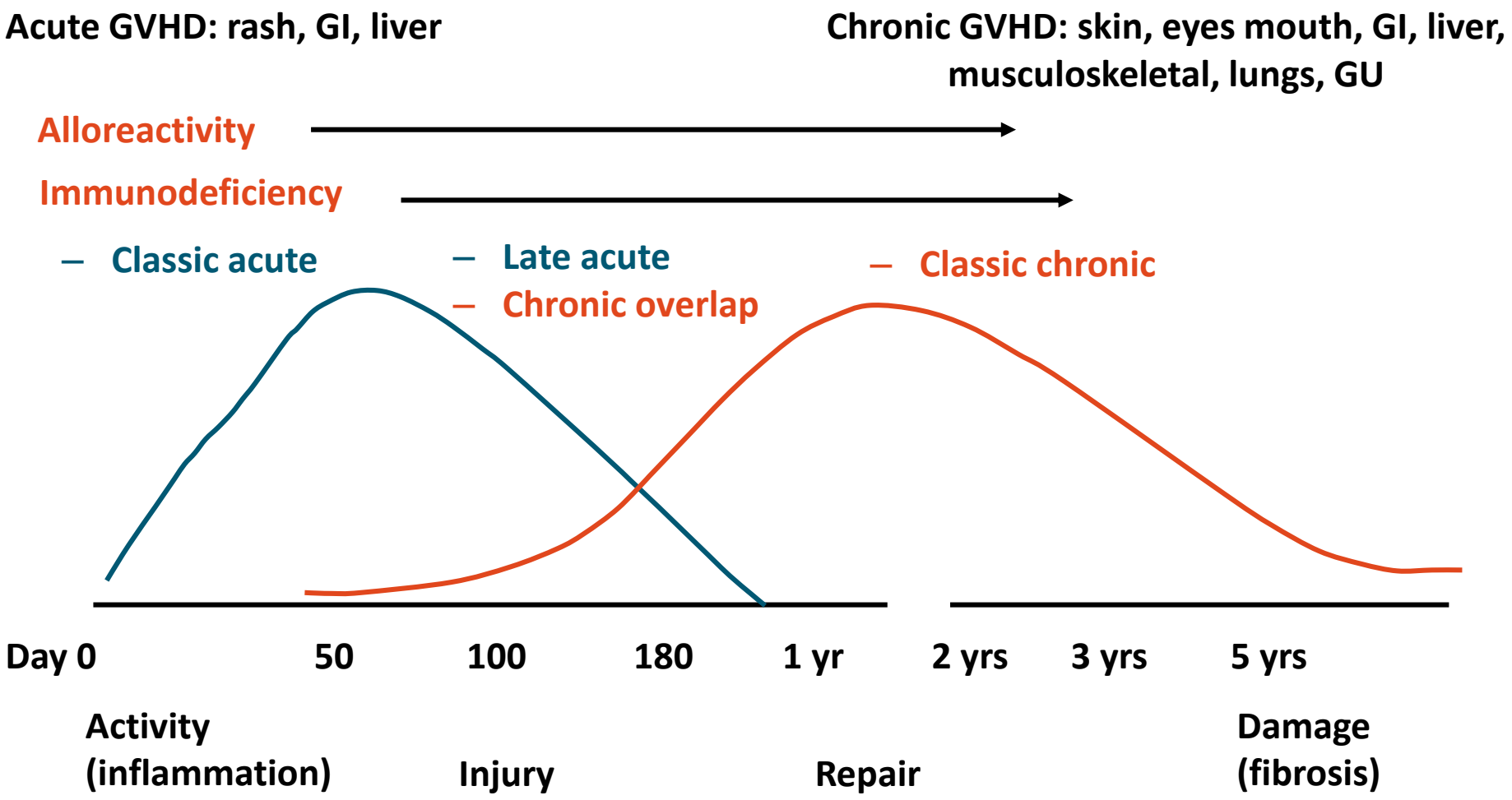
GVHD
Effect on Outcome

- Moderate-to-severe GVHD increases morbidity of transplantation. However randomized trials which have led to reductions in acute or chronic GVHD have not improved survival

- Development of GVHD may prevent disease relapse post-BMT. (CML>>AML, ALL).

- Effect of GVHD on relapse termed the graft-vs-leukemia (GVL) effect

Clinical Onset of GVHD Syndrome After AlloHCT



NCI cGVHD Consortium.

Slide credit: clinicaloptions.com

Strategies to Prevent GVHD

- Interfere with T cell activation/function
  - cyclosporine
  - tacrolimus
  - rapamycin (sirolimus)
- Interfere with T cell proliferation
  - methotrexate
  - Mycophenolate
- Reduce T cell number
  - T cell depletion
  - post-transplant cyclophosphamide ?

Treatment of Acute GVHD

- Corticosteroids - standard of care - 2 v 1 mg/kg
- ATG - negative Phase 3 randomized trial
- MMF - negative Phase 3 randomized trial
- Etanercept -negative Phase 2 randomized trial

Treatment of Chronic GVHD

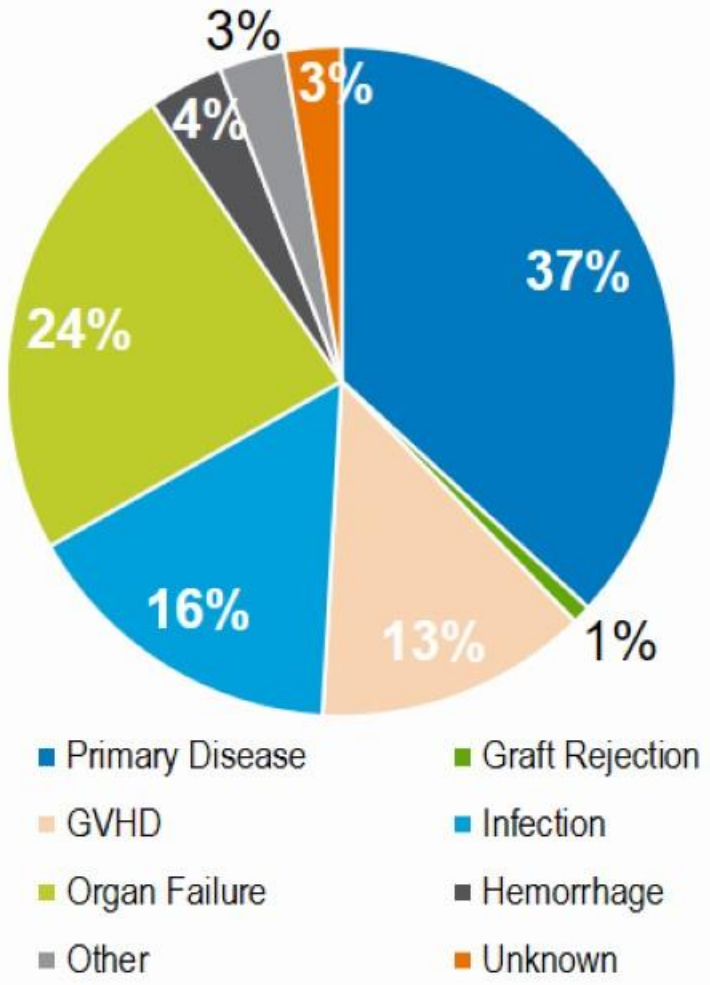
- Corticosteroids - standard of care
- Cyclosporine - negative Phase 3 randomized trial
- MMF - negative Phase 3 randomized trial
- Sirolimus - negative Phase 2 randomized trial
- Rituxan
- Extra Corporeal Photopheresis
- Low dose IL-2
- Ibrutinib – Now FDA approved on basis of 42 patient trial
- JAK2 inhibition (Jakafi)
- Imatinib
  - All of the above reported to induce responses but none have been proven effective in a randomized trial

Immune Competence

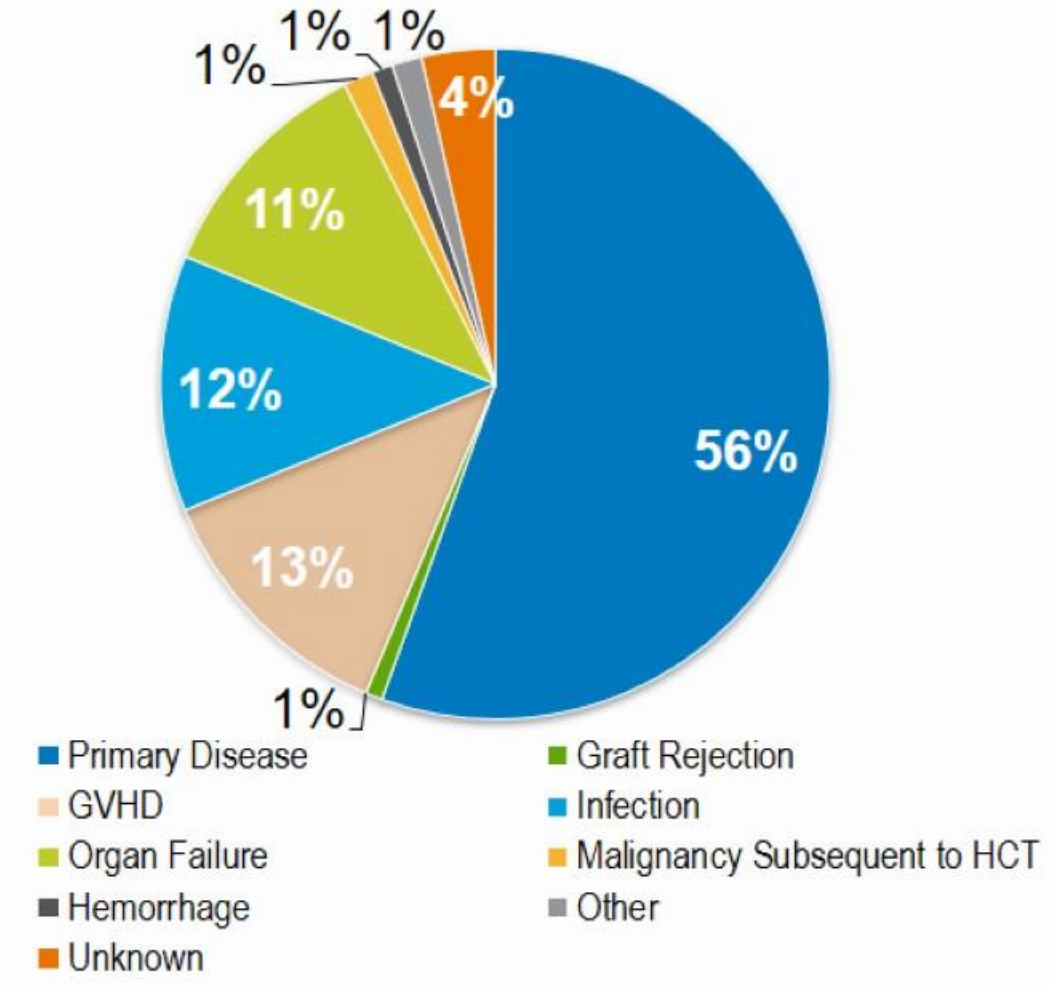
- Immunologic recovery is delayed up to 3 months after autologous HCT and up to a year after allo-HCT
- Factor such as T cell depletion, alternative donor transplantation, and need for ongoing immune suppression delay recovery
- Vigilance against infection including proper precautions, vaccinations, and prophylactic medications are mandatory

Causes of Death after Adult (age ≥18) Matched Related HCT in the US, 2017-2018

Died within 100 days post-transplant



Died at or beyond 100 days post-transplant*



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*Data reflects 3-year mortality

Relapse….

Potential Agents to Prevent or Treat Relapse

High Dose Chemotherapy

Tyrosine kinase inhibitors (bcr-abl, FLT3-ITD)

Hypomethylating agents

Imids

HDAC inhibitors

Checkpoint Blockade

Donor lymphocyte Infusions

CAR T Cells


Thank you