Hematopoietic Stem Cell Transplantation

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STEM CELLS

Have the capacity to :

- Self renew (make more stem cells by cell division)

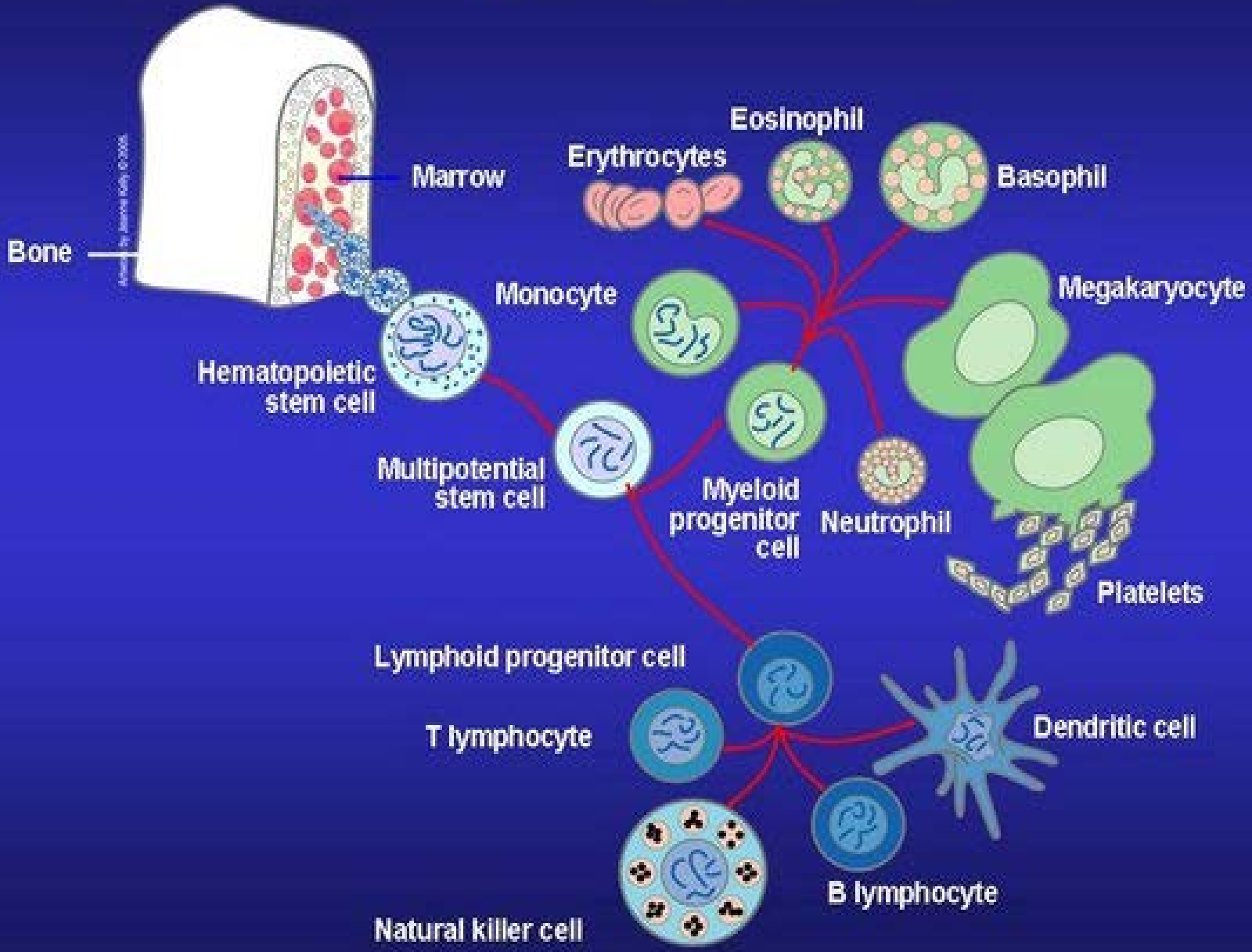
&

- Differentiate into mature, specialized cell

Types of Stem Cells

- **Embryonic SC** found in:
  - Embryos
- **Adult SC** found in:
  - Bone marrow & peripheral blood
  - Muscle, brain, skin & liver
  - Placental cord
  - Baby teeth

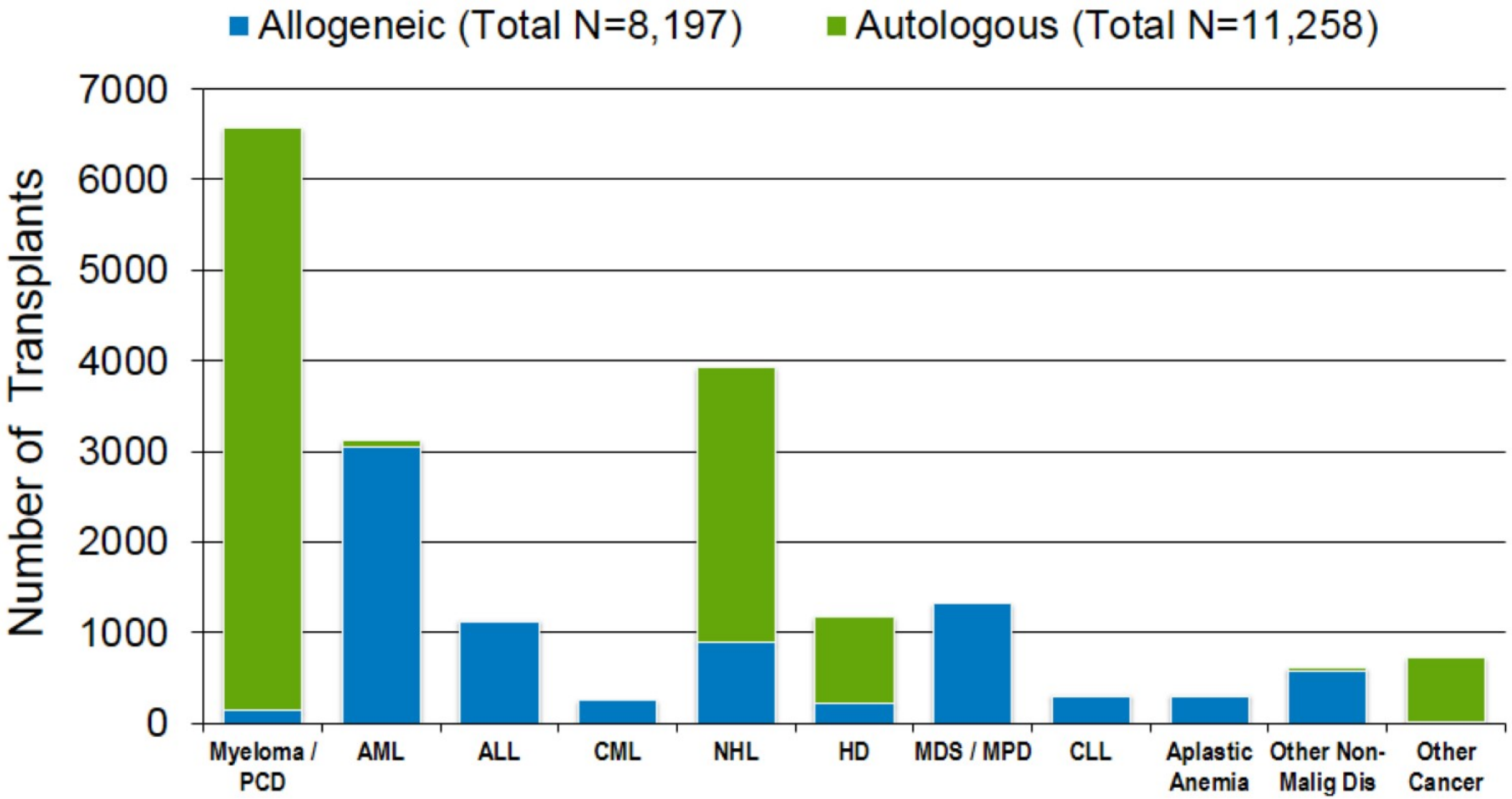
Hematopoietic Stem Cells



Hematopoietic Stem Cells

- Harvested from bone marrow, blood & umbilical cord
- They are CD 34 (+)
- A minimum of 2.5-3.0 million CD34 (+) cells/kg of recipient's body weight are needed to induce engraftment and bone marrow recovery

Indications for Hematopoietic Stem Cell Transplants in the US, 2013



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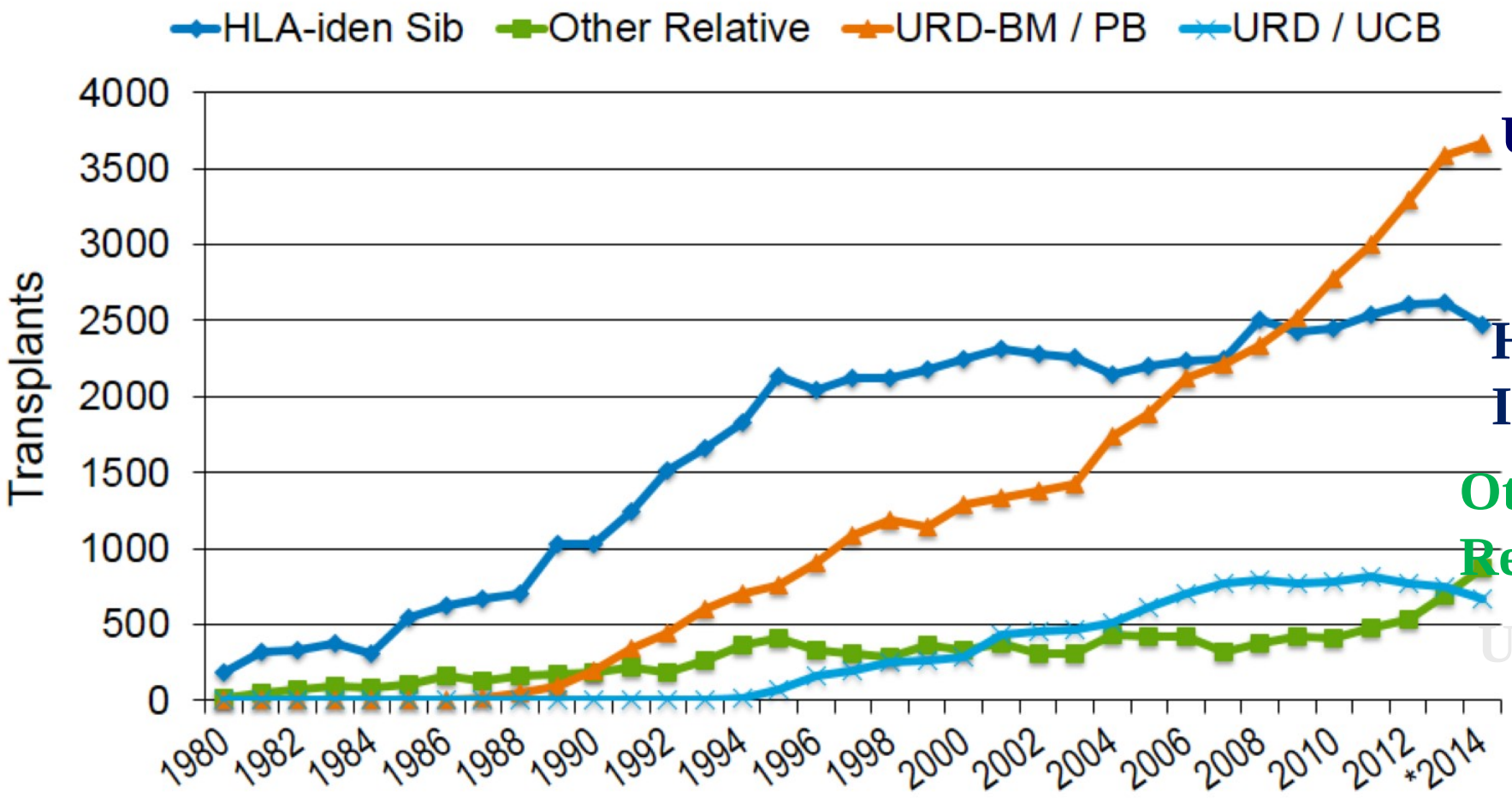
Pasquini MC, Zhu X. Current uses and outcomes of hematopoietic stem cell transplantation: CIBMTR Summary Slides, 2015. Available at: http://www.cibmtr.org

Allogeneic Transplant Recipients in the US, by Donor Type



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*2014 Data incomplete

Conditioning Regimens

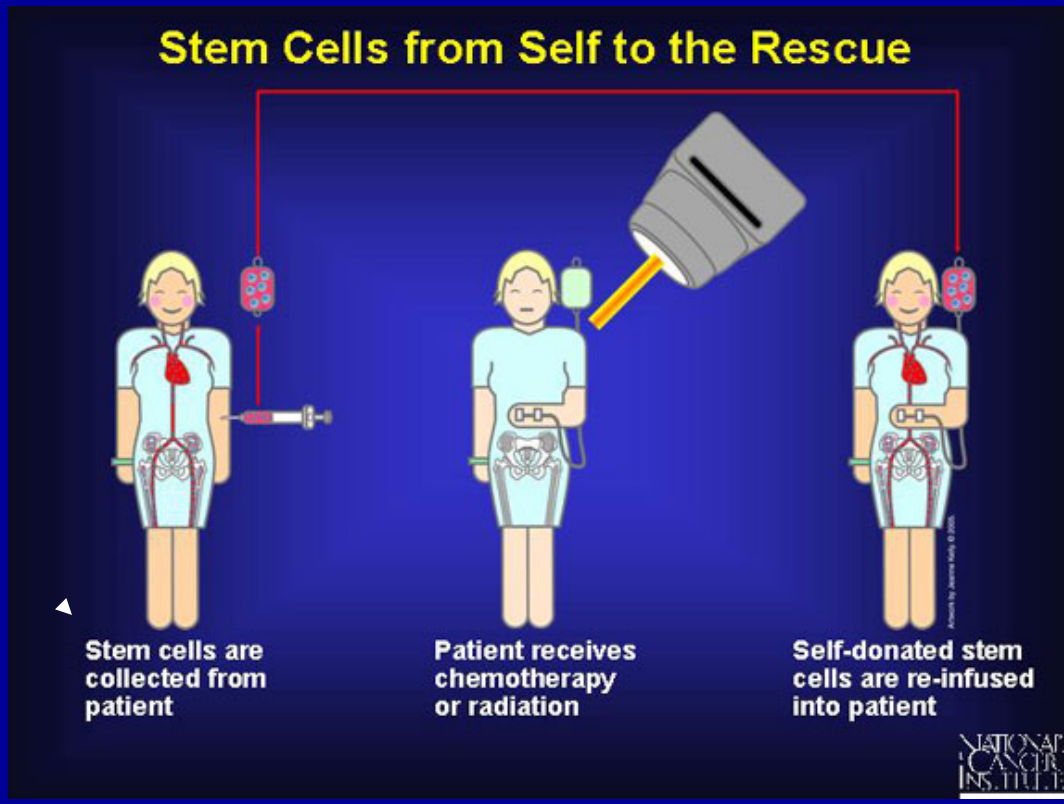
Myeloablative Regimens	Most Common Diseases
Cyclophosphamide/TBI “Cy/TBI” (fractionated, 1200 cGy)	Leukemia, lymphoma, MDS/MPD
Busulfan/Cyclophosphamide “Bu/Cy”	Leukemia, MDS/MPD
BCNU/Etoposide/Ara-C/Melphalan “BEAM”	Lymphoma (mainly Auto)
Cyclophosphamide/TBI/Etoposide	Lymphoma (Auto)
Cyclophosphamide/ATG	Aplastic Anemia
Melphalan	Myeloma (Auto)
Fludarabine/Busulfan “Flu/Bu”	MDS
Reduced Intensity Regimens	
Fludarabine/TBI (200-400 cGy)	
Intermediate dose melphalan, others	

Major Drugs Used in Conditioning

Drug	Major Toxicities	Considerations
High Dose Cyclophosphamide	Myelosuppression; SIADH, nasal stuffiness, rare cardiac necrosis, pericarditis, hemorrhagic cystitis (so need give with mesna and/or urinary irrigation)	Most frequent drug contributing to SOS; Given alone, not myeloablative; stem cell sparing.
High Dose Busulfan	Myelosuppression; Seizures (prophylaxis required); lung toxicity	Targeted dosing based on plasma levels; IV or p.o.
High Dose Melphalan	Mucositis, diarrhea; myelosuppression	
Fludarabine	Immunosuppression; autoimmune syndromes	Reduced intensity

Autologous Transplantation

- More than 30,000 annually
- 2/3 for MM and NHL
- High Dose Myeloablative Therapy
- “Stem cell rescue”



Autologous Transplantation

- Treat underlying disease with ablative therapy
- Risk for tumor contamination.
- CD34 selection did not change relapse rates and increased infection risks especially for CMV
- 100 day Non-relapse mortality: less than 5%
- Does not have GVHD issue
- Risk for secondary MDS/AML

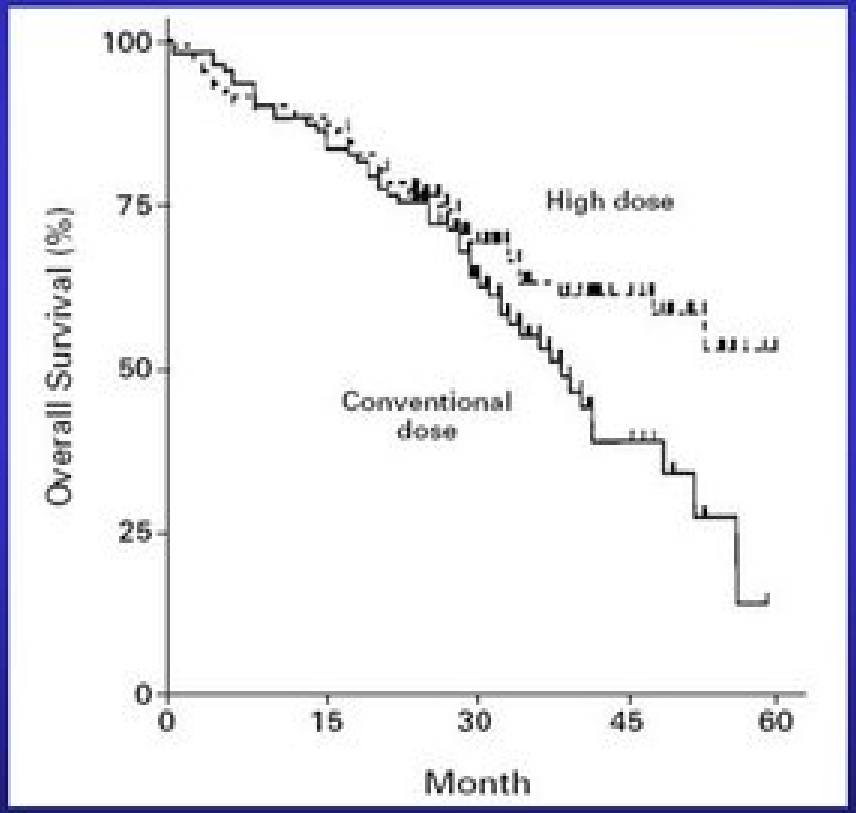
Autologous Peripheral Blood Stem Cells (PBSC)

PBSC have replaced BM as source of hematopoietic stem cells

- Superior in speed of engraftment post-transplant
- Decreased TRM to less than 5% and decreased morbidity
- No anesthesia and hospitalization for BM harvest
- Better able to collect stem cells from patients who previously received pelvic irradiation
- Decreased tumor contamination

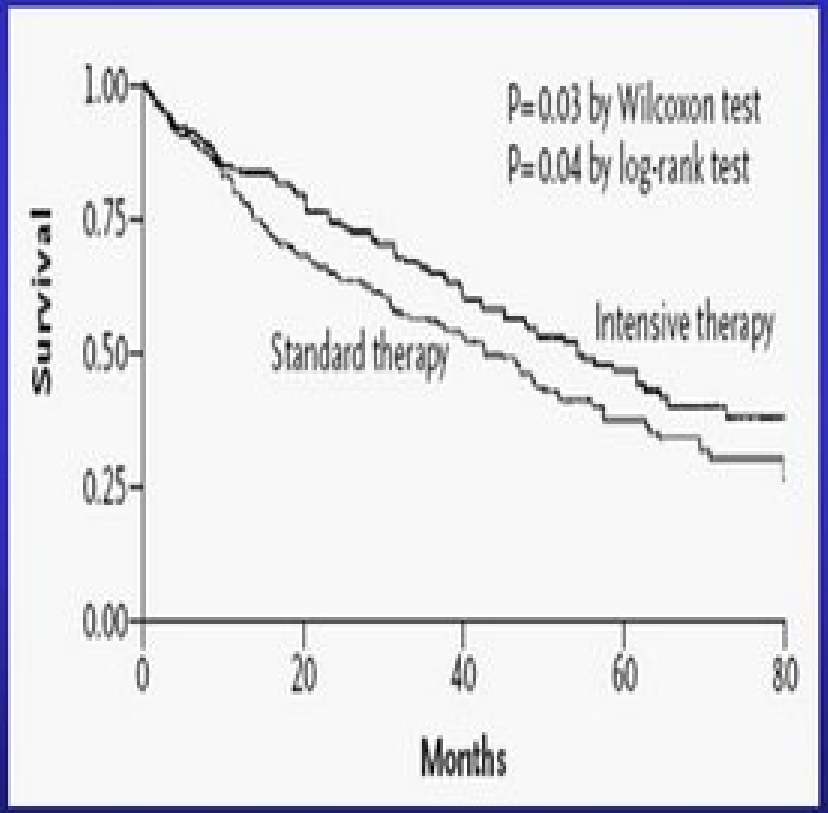
Autologous HSCT For Multiple Myeloma

Intergroupe Francais du Myelome



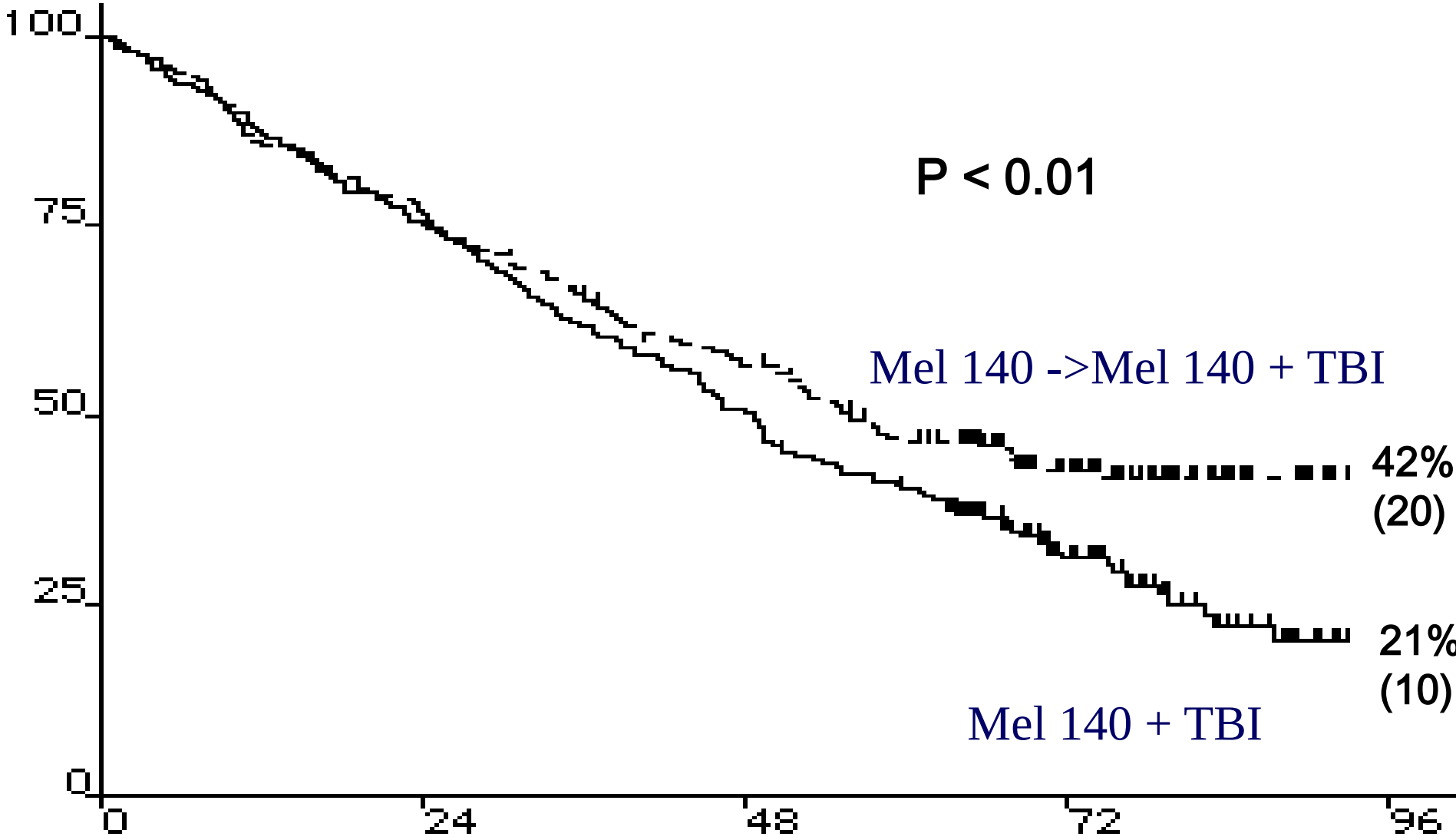
Attal et al. N Engl J Med 335:91, 1996

Medical Research Council



Child et al. N Engl J Med 348:1875, 2003

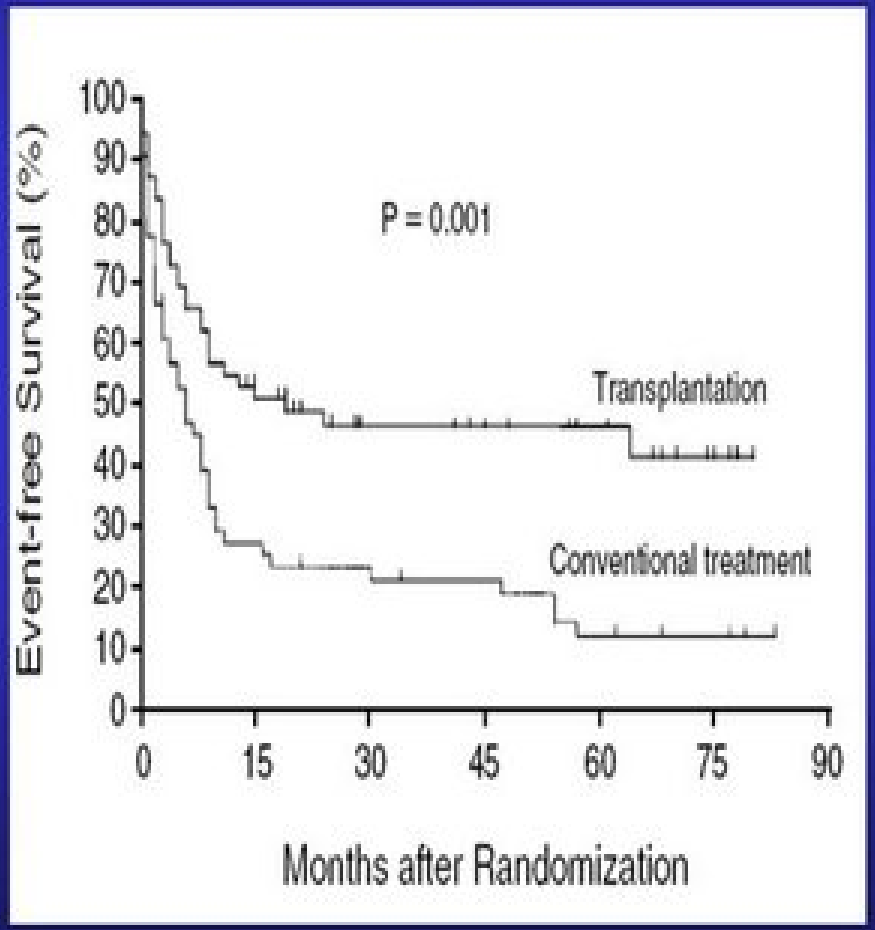
Tandem Autologous Transplants: IFM 94 : Overall Survival



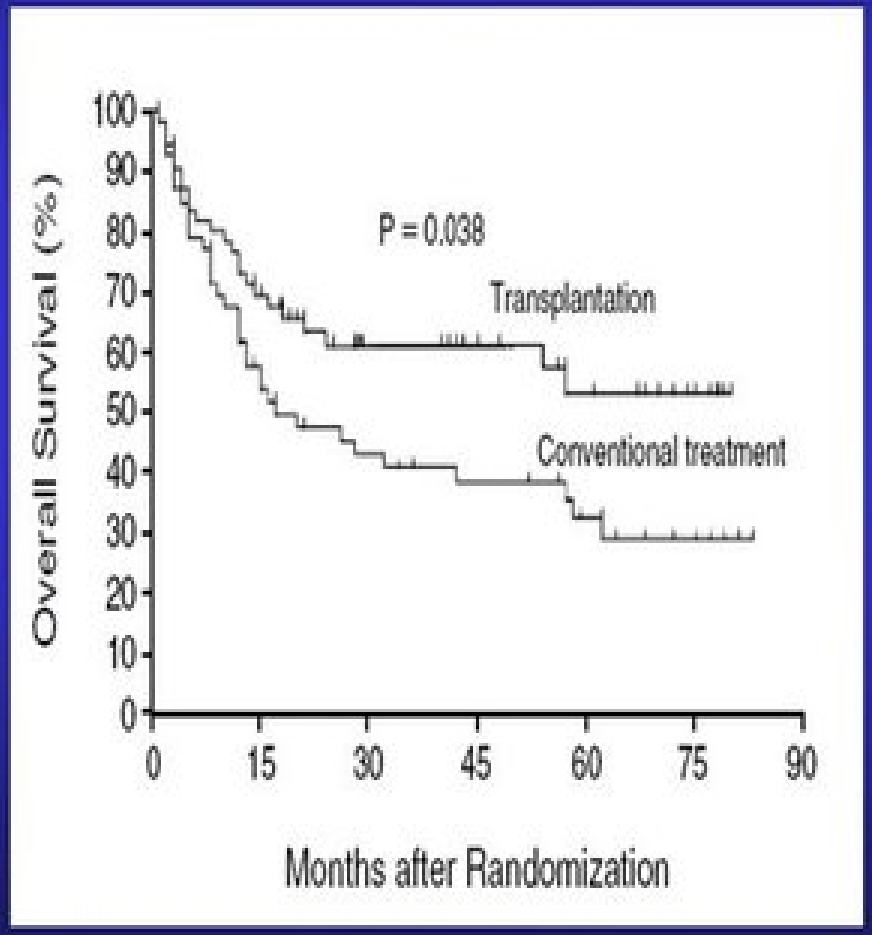
Attal, NEJM, 2003

Autologous Bone Marrow Transplantation vs. Salvage Chemotherapy In Relapses Of Chemotherapy-sensitive Aggressive NHL

Event-free Survival



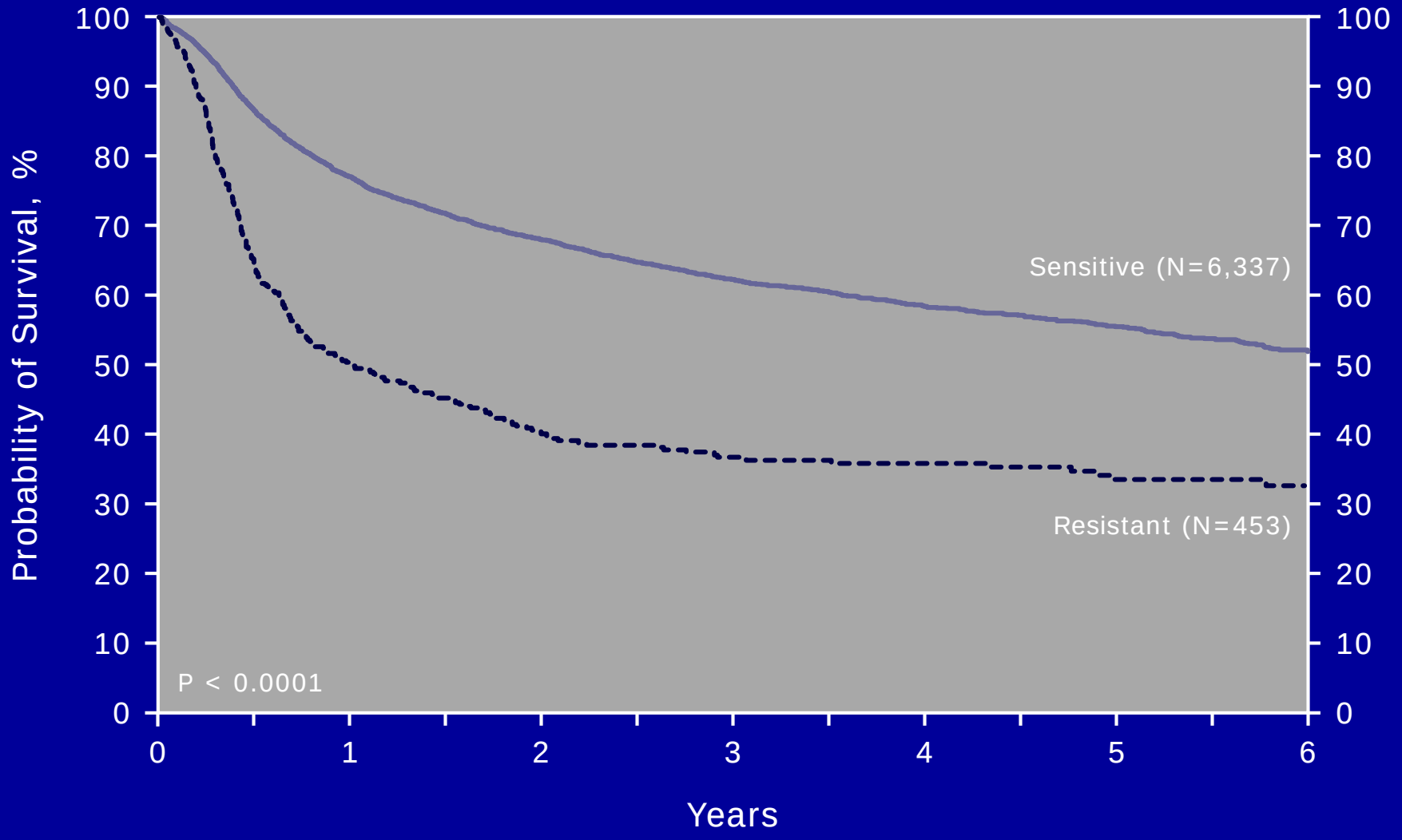
Overall Survival



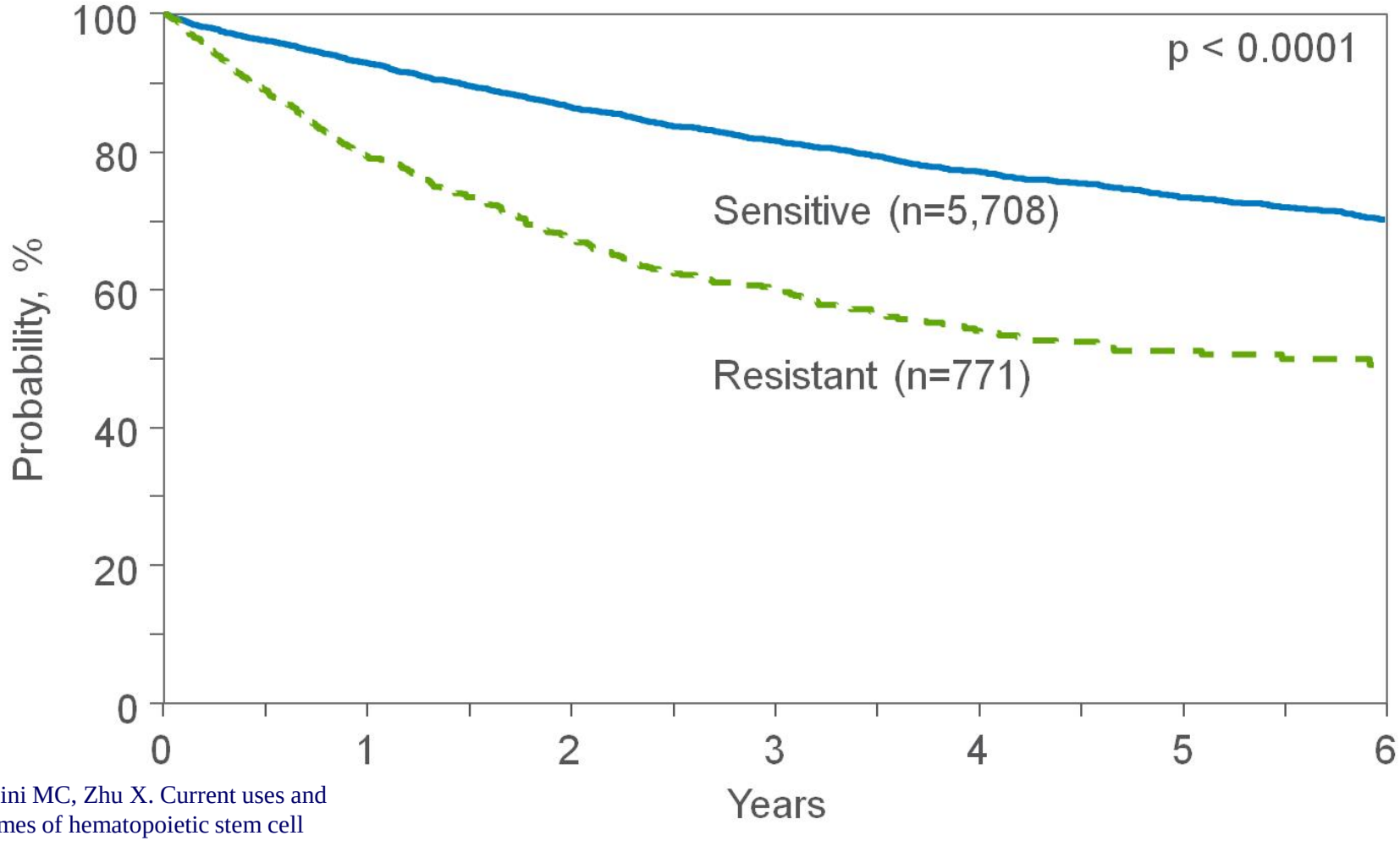
Philip et al. N Engl J Med 333:1540, 1995

Probability of Survival after Autologous Transplants for Diffuse Large B-Cell Lymphoma, 2000-2009

- By Disease Status -



Survival after Autologous Transplants for Hodgkin Lymphoma, 2002-2012



By Disease Status

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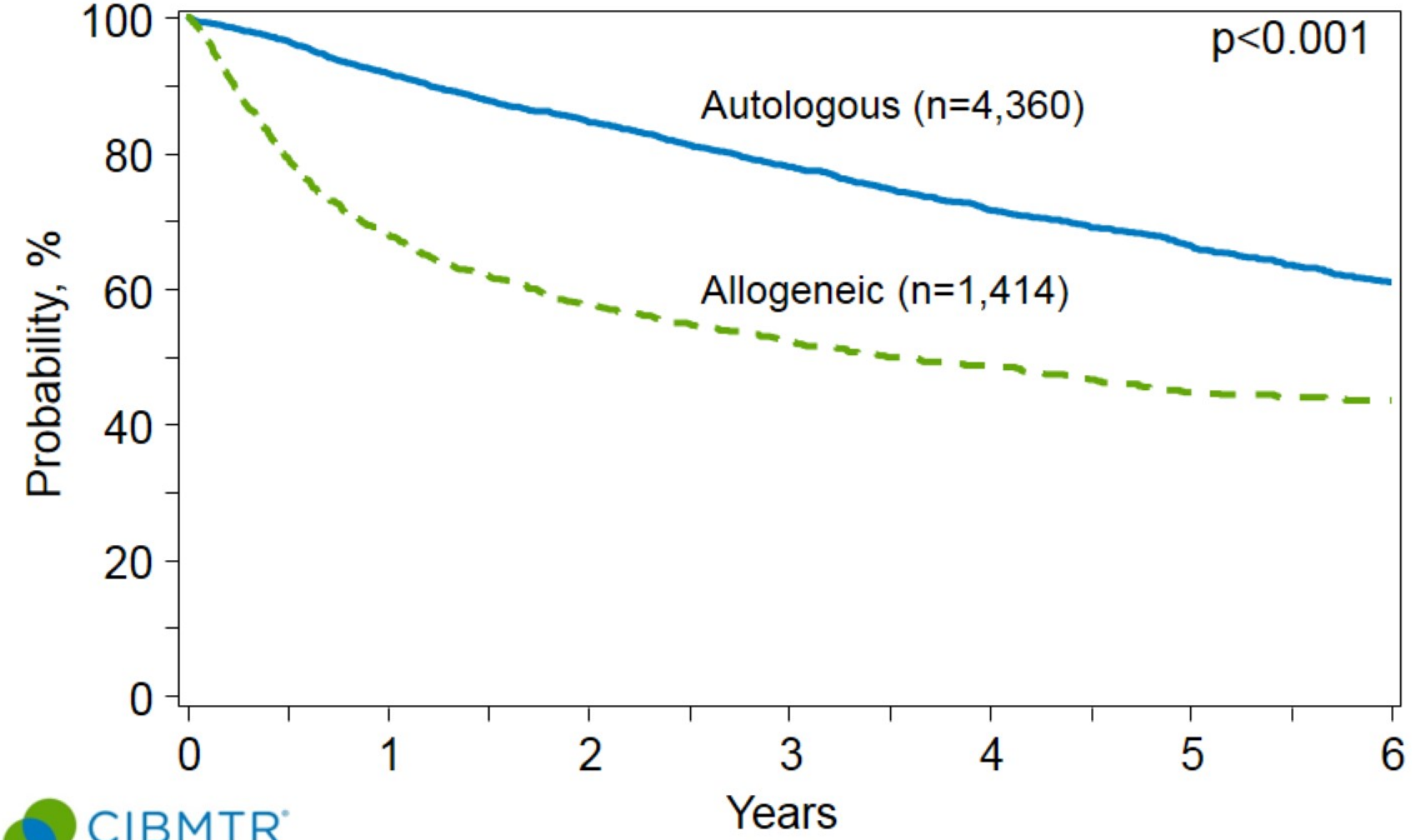
Survival after Transplants for Mantle Cell Lymphoma, 2003-2013



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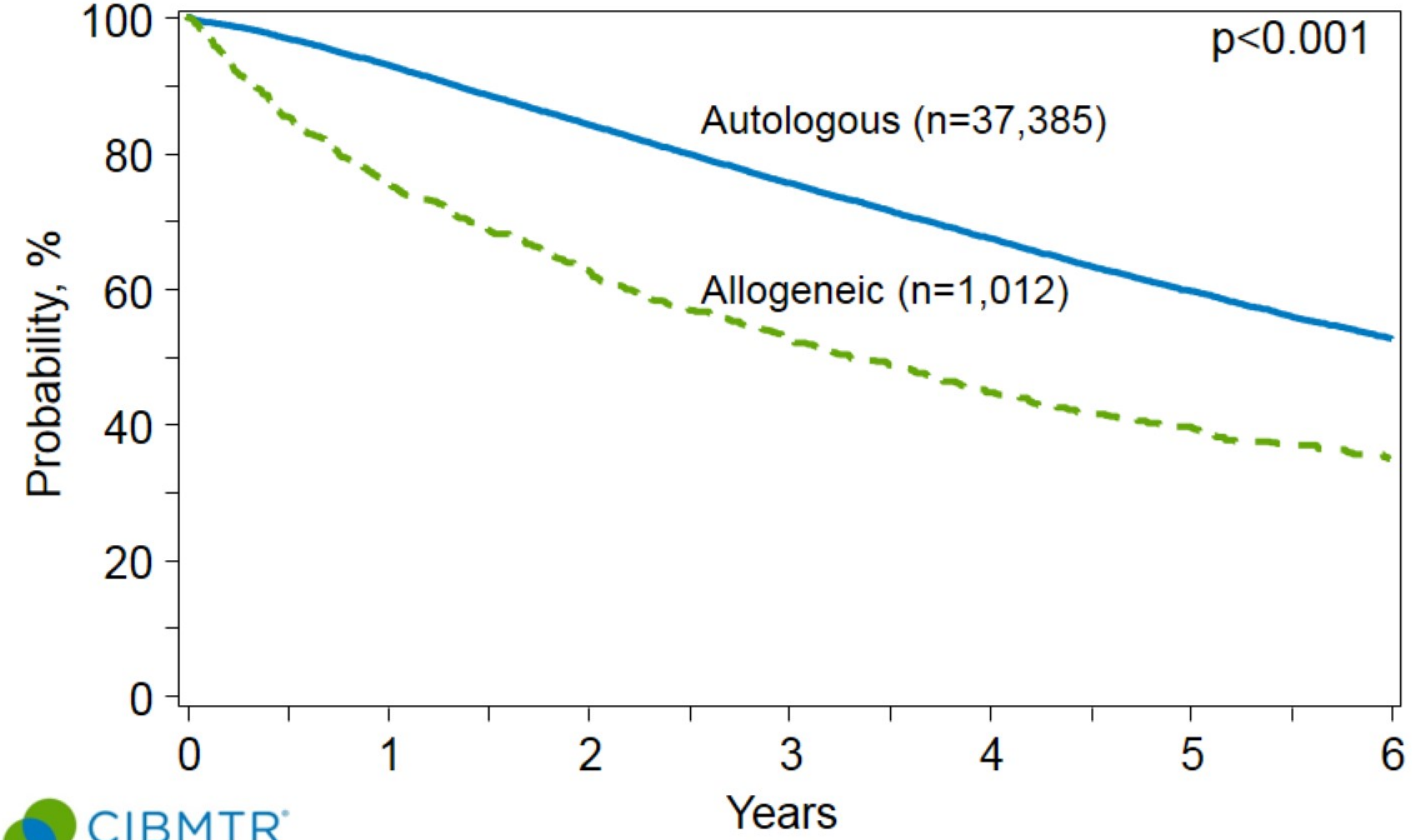
By Donor Type

Survival after Transplants for Multiple Myeloma, 2003-2013



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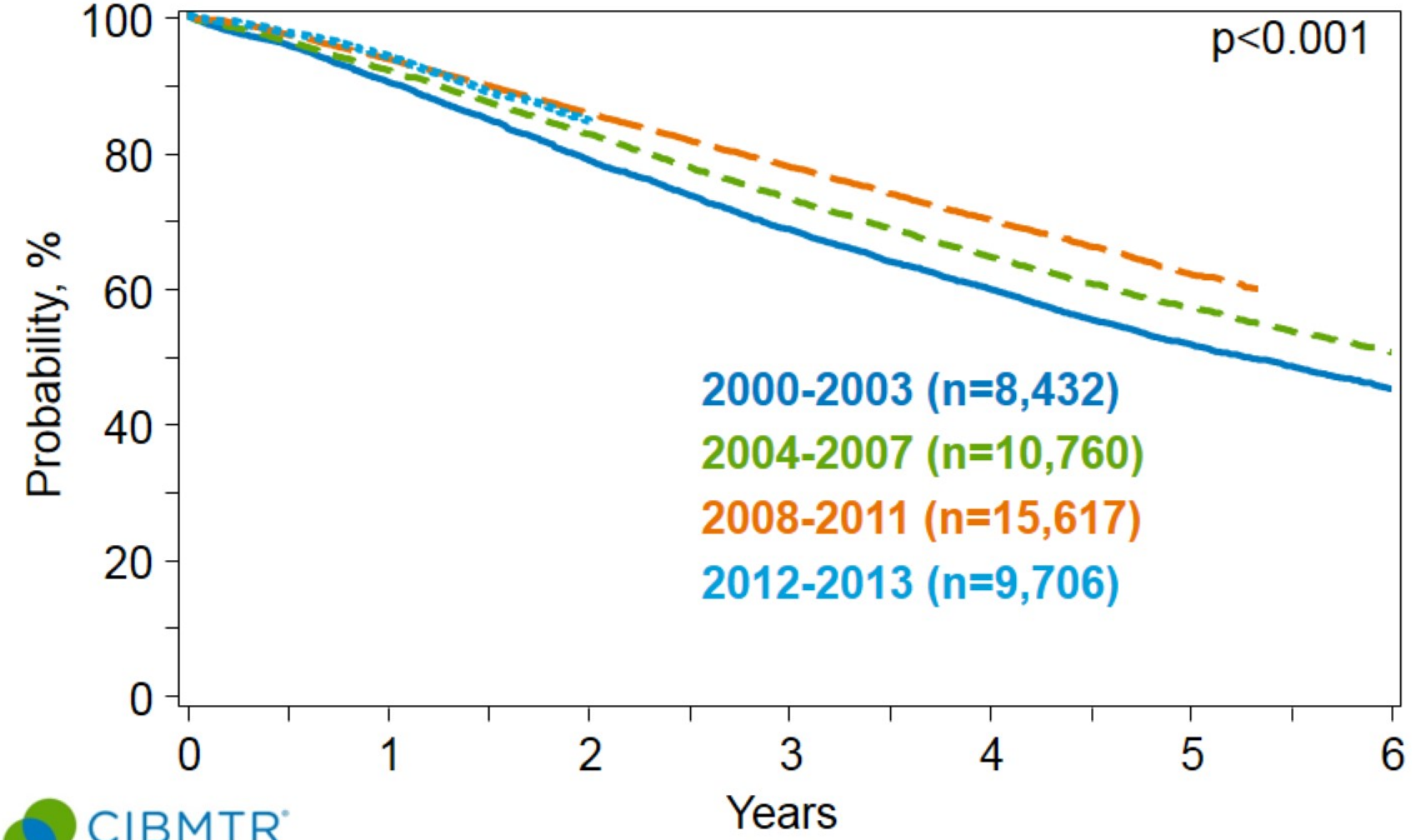
By Donor Type

Survival after Autologous Transplants for Multiple Myeloma, 2000-2013



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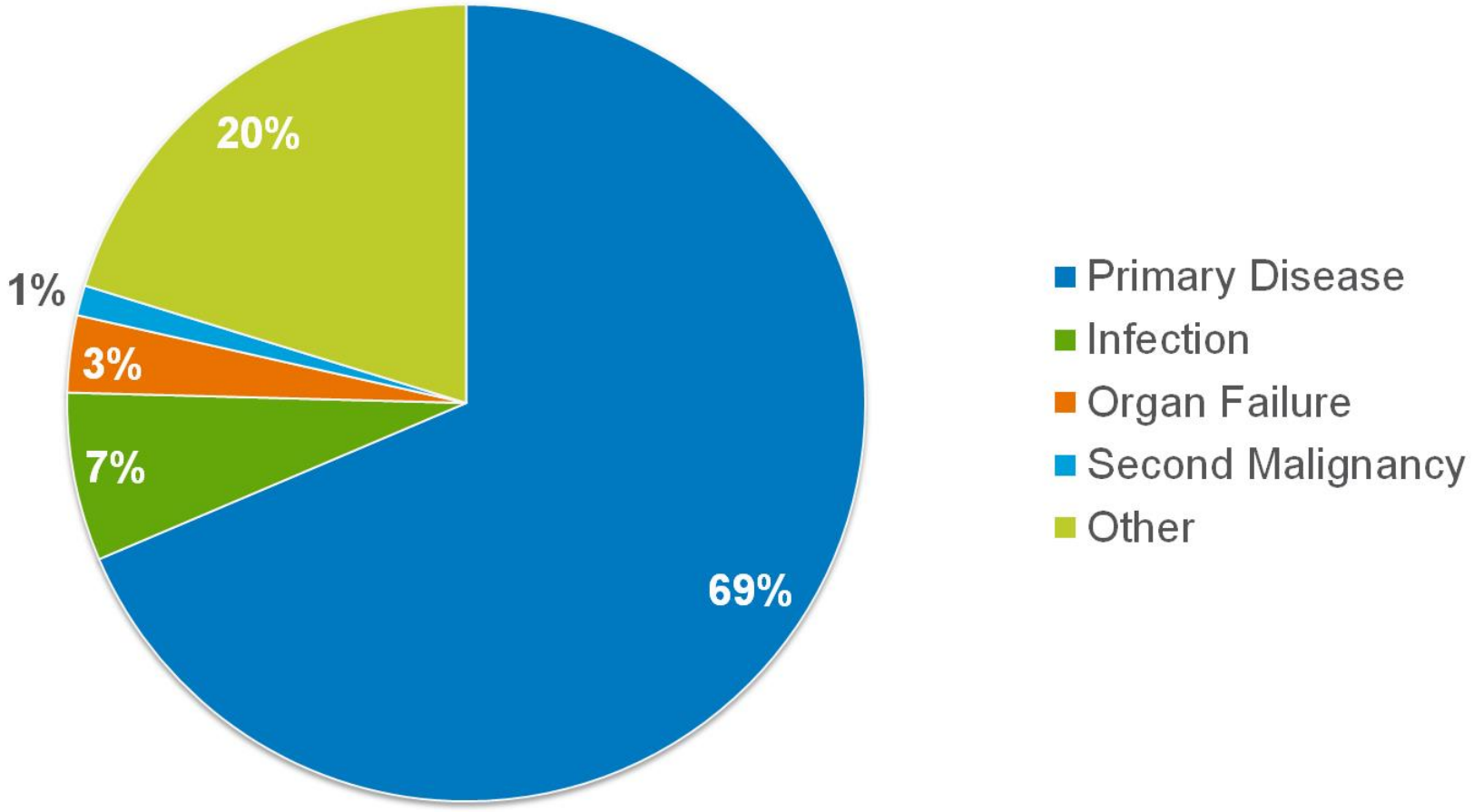
By Year of Transplant

Causes of Death after Autologous Transplants done in 2011-2012



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ALLOGENEIC STEM CELL TRANSPLANTATION

Allogeneic Donor Selection

- 25% likelihood of HLA matching with a sibling
- 1% chance of HLA matching with another relative.
- First option by conventional practice:
  - HLA matched family member
  - Then HLA matched Unrelated donor:
    - 60-70% chance of finding an 8 of 8 allele level, HLA-A, B, C, or DRB1 matched unrelated donor for Caucasian patients
    - 10% to 30% for U.S. ethnic minorities

Anasetti C, Biol Blood Marrow Transplant 18:S161-S165, 2012

Likelihood of a Sibling Match

Match likelihood	$1 - \text{no match}$	
"n" siblings	$1 - (0.75)^n$	
1 sibling	$1 - (0.75)^1$	$= 0.25$
2 siblings	$1 - (0.75)^2$	$= 0.44$
4 siblings	$1 - (0.75)^4$	$= 0.68$
7 siblings	$1 - (0.75)^7$	$= 0.87$

DONOR ASSESSMENT

Initial Evaluations

Donors

Evaluation:

- H and P, (hx of medical issues including malignancy plus hx of recreational drug use, transfusions, pregnancy, abortion, travel, vaccinations); determine caregiver support and reliability.
- Routine labs plus urine analysis, CMV PCR/Ab, hep A, hep BcAb, hep BsAg/Ab, HTLV I/II, HIV I/II, EBV, VZV, toxo, RPR, ß-HCG (females < age 55) West Nile (allo), Chagas Disease (allo). Chest X-ray (hx of pulmonary disease and SAT< 90%), and EKG (DM, Cardiovascular disease, Pulmonary disease, smoke >20 pack years, age: > 40 yr male and > 50 yr female)

- Ethical issues: 1 physician serves 2 persons whose medical care is interdependent

Patients

Evaluation:

- H and P (same)
- Routine Labs plus (same)

•Restaging studies

•BM

•Dental Evaluation

•RT consult if TBI or other RT

•? Fertility preservation

•ECG/Cardiac ejection fraction

•PFTs (DLCO > 50)

•PPD as clinically indicated

•CXR

•Sinus CT if clinically indicated

•Other tests/regulatory standards as indicated

O'Donnell P: Blood. 2010 Jun 17;115(24):5097-101

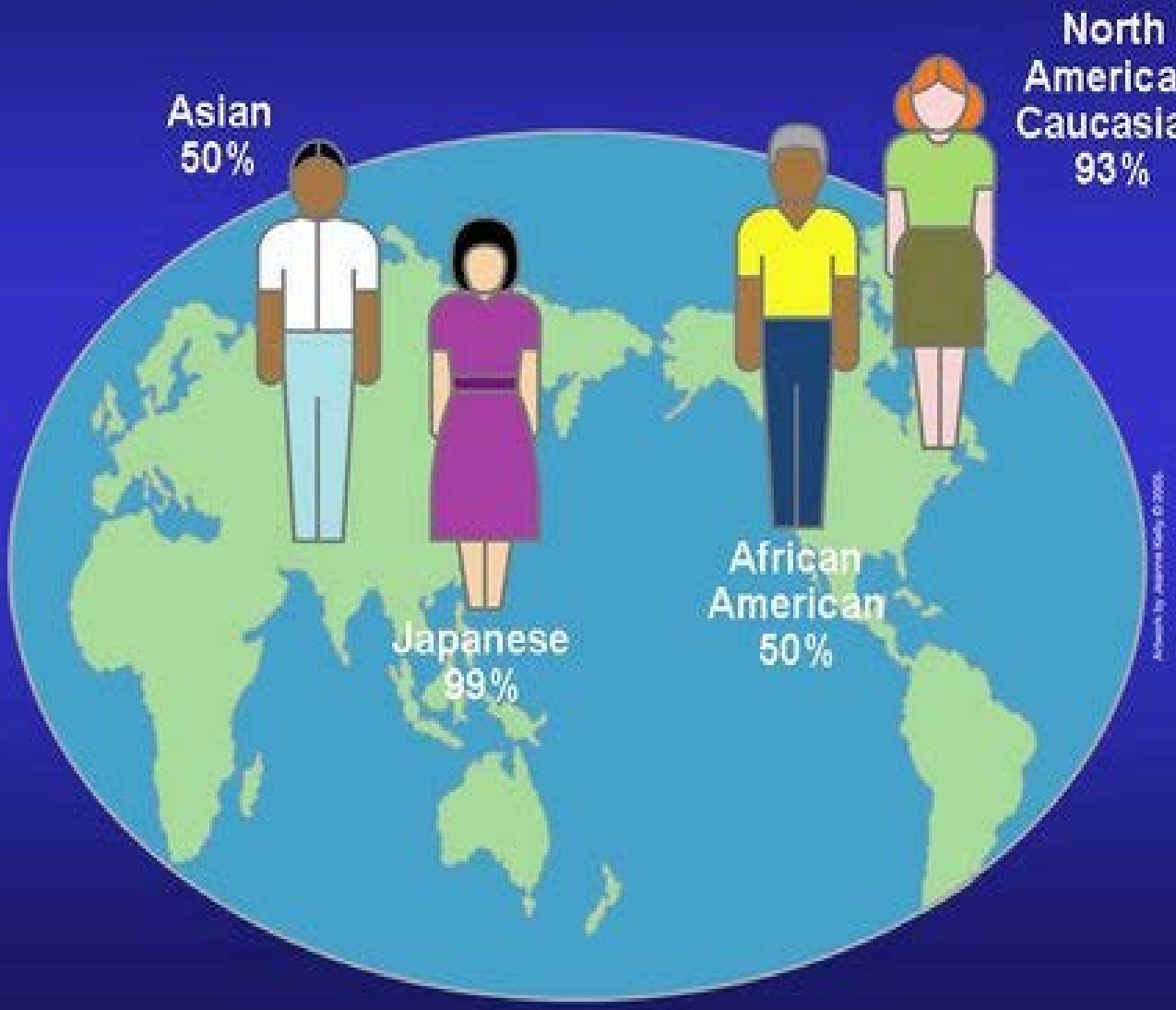
Other Considerations for Allogeneic Donor Selection

- CMV status of recipient and donor
- Age of donor (relevant if multiple donors are available)
- History of intermarriage in families rarely produce HLA ID cousins or combination of rare haplotype and common HLA haplotype.
- Mismatch HLA A, B and C increases risk of Graft rejection. Mismatch of HLA DR increase risk for GVHD (can occur the alternate way for Class I and II).
  - Single Ag mismatched related transplants
    - In the graft versus host direction have higher GVHD but same survival
    - In the host versus graft direction have higher graft failure and lower survival
    - Unknown whether to prefer single Ag mismatched related donor versus MUD

Other Considerations for Allogeneic Donor Selection

- For haploidentical related donors
  - Mother may be best choice (? Tolerance of fetal Ags during pregnancy)
  - Sibling donors – no difference in gender of donor related to outcome.
- ABO match – usually not an issue; but prefer match

Success in HLA-Matched Unrelated Matching Varies With Population



ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

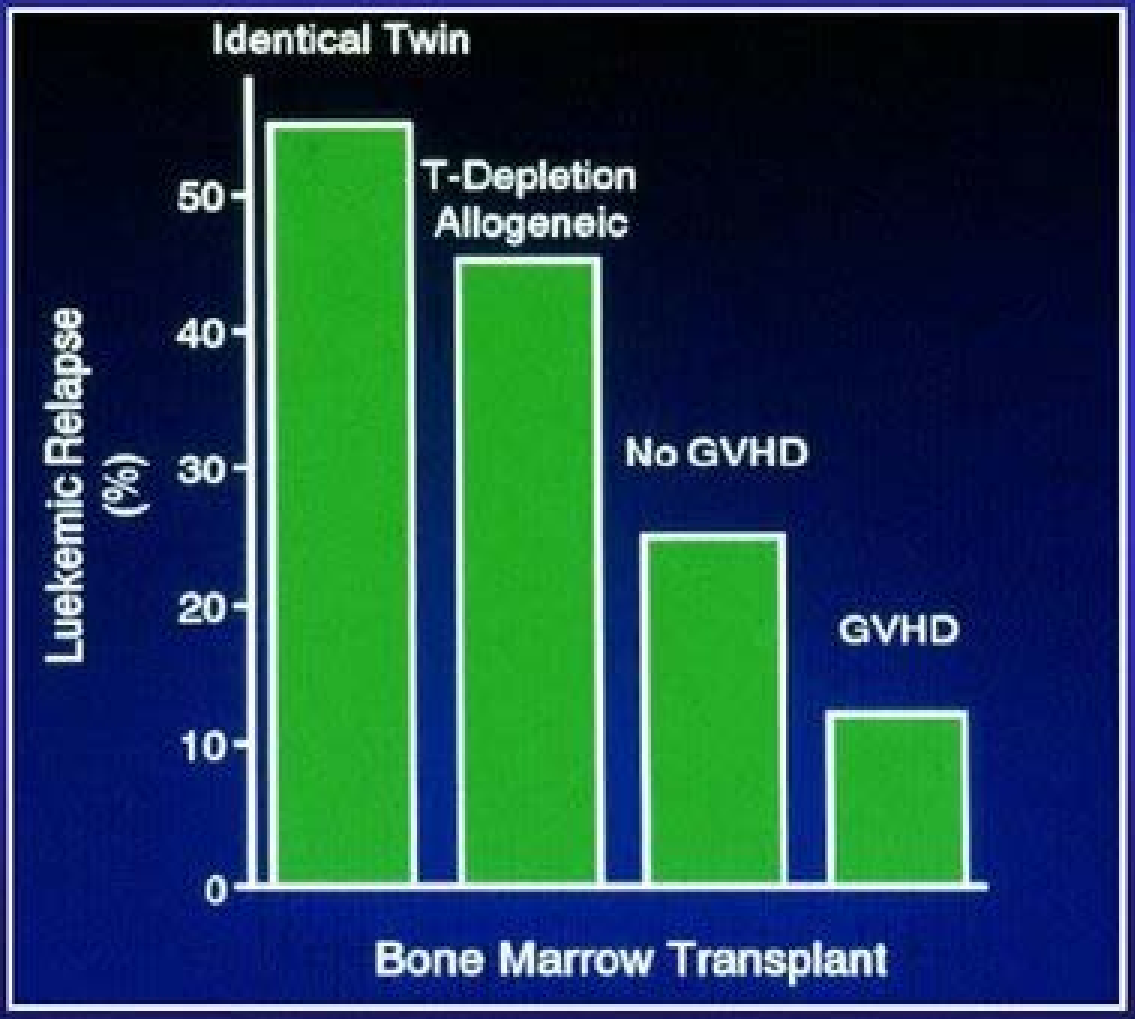
Old Paradigm

The allograft is a rescue product to replace the defective stem cells following ablation with cytotoxic therapy.

New Paradigm

A major therapeutic component of an allogeneic stem cell transplant is the "graft *vs.* leukemia" effect mediated by T-cells in the allograft.

Graft-versus-Leukemia Effect



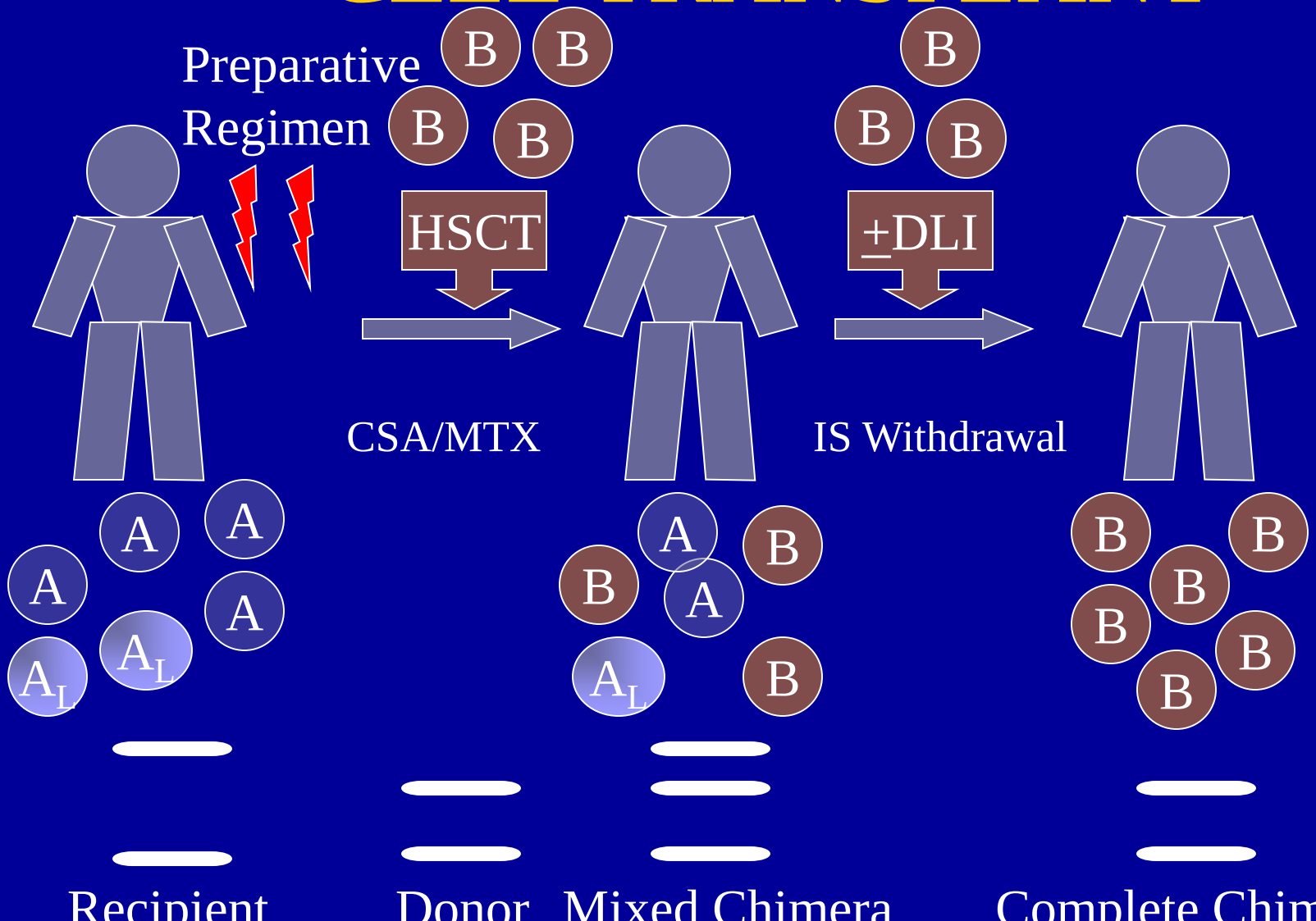
Most patients after allogeneic transplant are cured by immunotherapy not by chemotherapy?

- Higher relapse after T-cell depleted or syngeneic transplants
- Higher relapse in patients without GVHD
- Remission of underlying malignancy may occur after stopping immunosuppression
- Remission can be induced by donor lymphocyte infusion (DLI)

Non-Myeloablative Allogeneic HSCT

- Requires the suppression of the patient's immune system to prevent graft rejection
- Depends on the donor immune system to induce graft-vs-tumor effect
- Effective only in patients with complete or near complete remission of their malignant disease, at the time of transplant

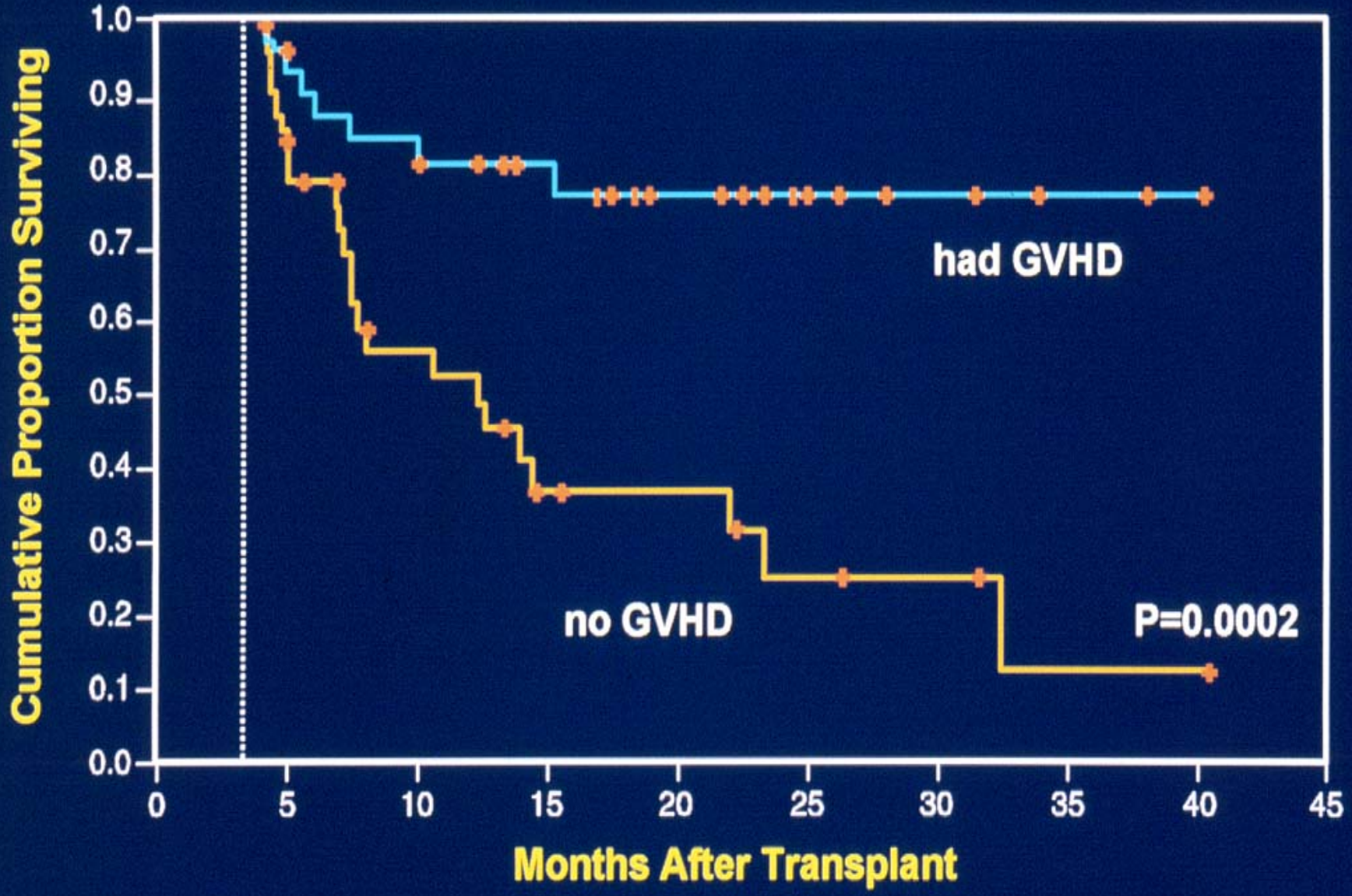
NON-ABLATIVE HEMATOPOIETIC CELL TRANSPLANT



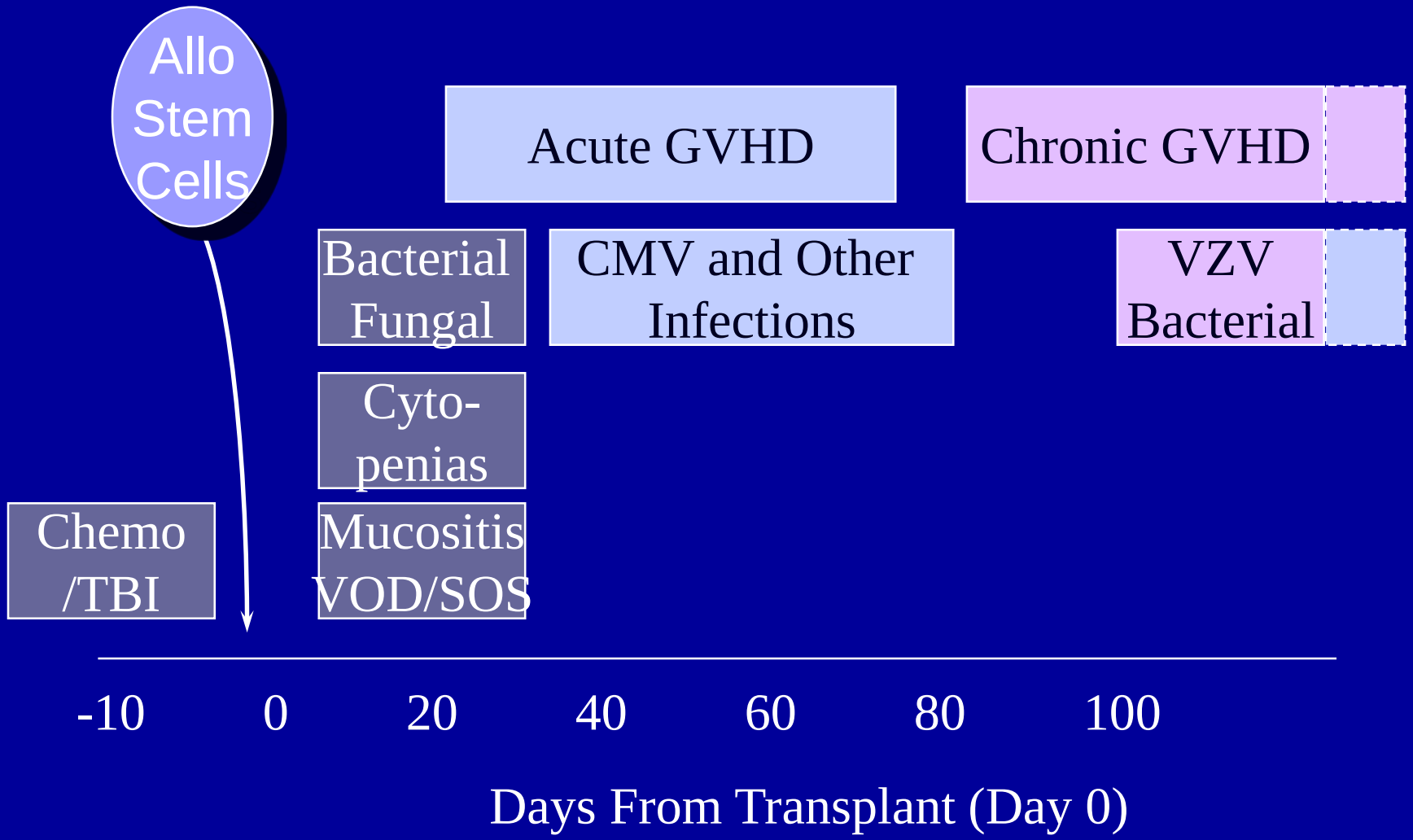
Donor Lymphocyte Infusion (DLI)

- Effective in inducing remission in patients with persistent or recurrent disease, after transplant, without additional cytotoxic therapy
- Increases risk for GVHD (40-60%)
- Direct correlation of GVHD & response

Nonablative BMT for AML



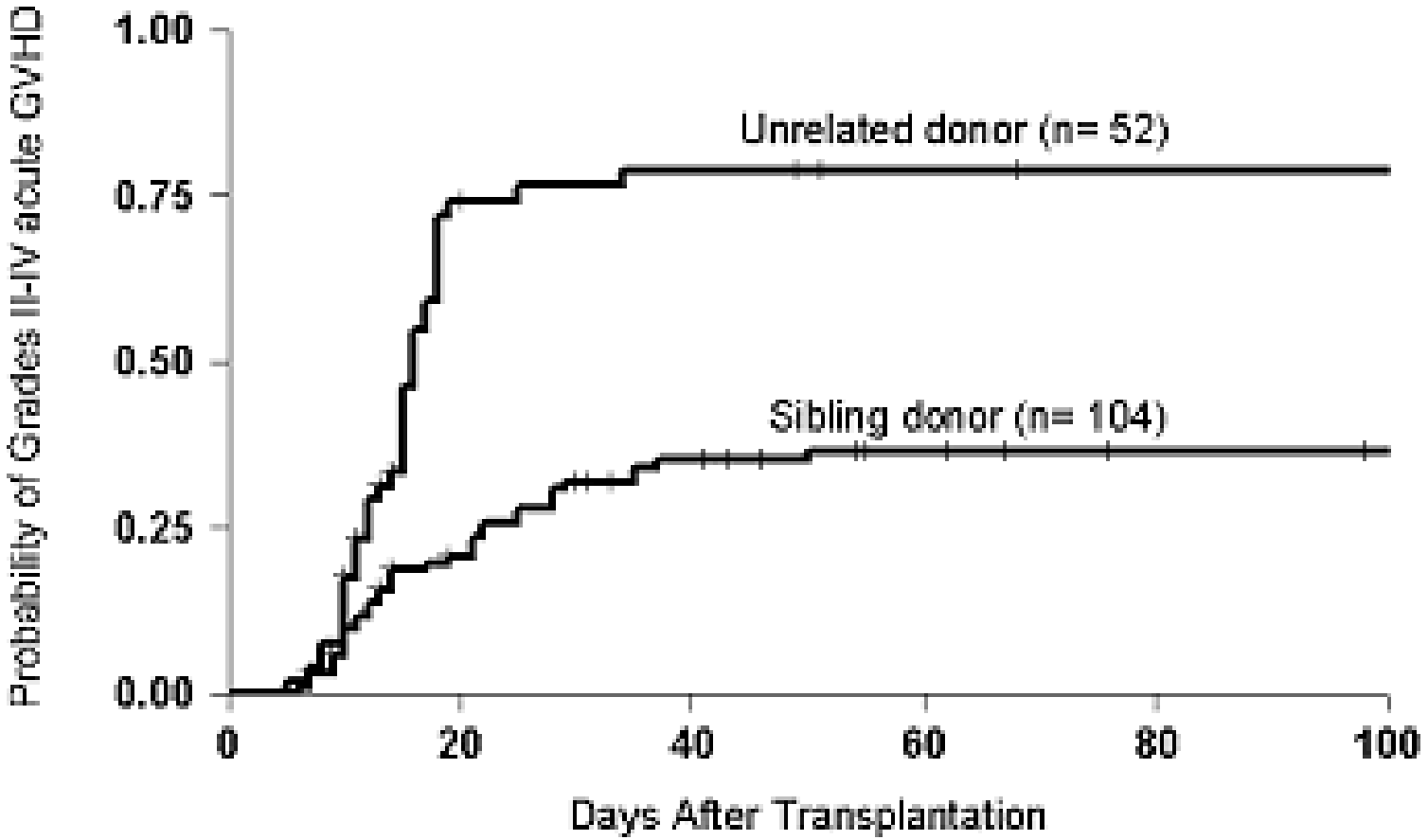
Complications Following Allogeneic Transplantation



Sinusoidal Obstructive Syndrome (Veno-occlusive Disease)

- Incidence: 10-60% of patients
- Occurs 7-10 days after conditioning regimen
- Tender hepatomegaly, jaundice, fluid retention
- Reversal of flow in portal system by doppler
- Risk Factors: Prior liver disease, previous chemotherapy (gemtuzumab), Busulfan or TBI in the conditioning regimen, C282Y allele of the HFE gene
- Mortality increases with severity of hyperbilirubinemia
- Treatment: supportive care, thrombolytic rx (tPA), defibrotide

Graft-versus-Host Disease

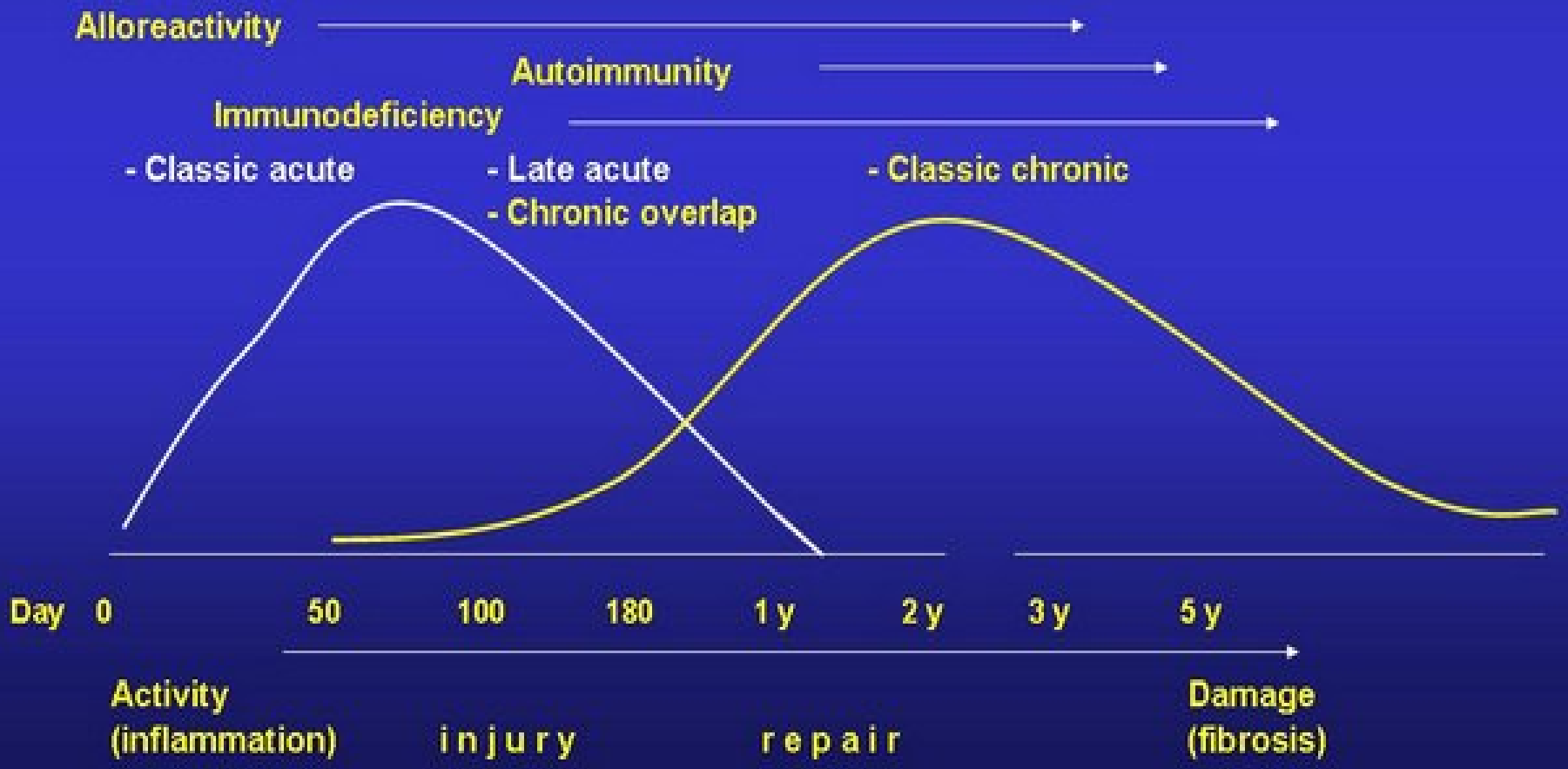


Beatty PG, et al. Transplantation 1991;51:443-447.

GVHD Syndrome After AlloHCT

Acute GVHD: rash, GI, liver

Chronic GVHD: skin, eyes, mouth, GI
liver, musculoskeletal, lungs, GU



Acute Graft-vs-Host Disease

- Occurs within 100 days post transplant
- Multi-organ involvement: Skin, GI tract, liver
- **Risk Factors**: Older age (patient/donor), HLA mismatch, unrelated donor, parous female donor
- **Prophylaxis**:
  - **T cell depletion**: effective but increased graft rejection and relapse of malignancy
  - **Immunosuppressive agents** : Cyclosporin, tacrolimus (FK506),Mycophenolate Mofetil, Sirolimus, methotrexate, steroids
- **Treatment**: Steroids

Ursodiol

- A large multi-center trial of prophylaxis after myeloablative allogeneic
  - beneficial effect on the incidence of clinical jaundice, severe acute GVHD and survival.
- Decrease in the number of patients with jaundice and elevated serum alanine aminotransferase (ALT).
- Lower incidence of grade 3-4 acute GVHD
- Lower incidence of stage 2-4 liver GVHD

Ruufu T et al: Blood. 2002 Sep 15;100(6):1977-83
Gooley TA et al N Engl J Med 2010; 25: 363_

Chronic GVHD

- Chronic multi-system disorder
- Occurs >100 days after allogeneic transplant
- **Incidence** : 30-80%
- **Characterized by** :
  - Chronic immunosuppression
  - Immune aberration
  - Organ dysfunction
  - Decreased survival

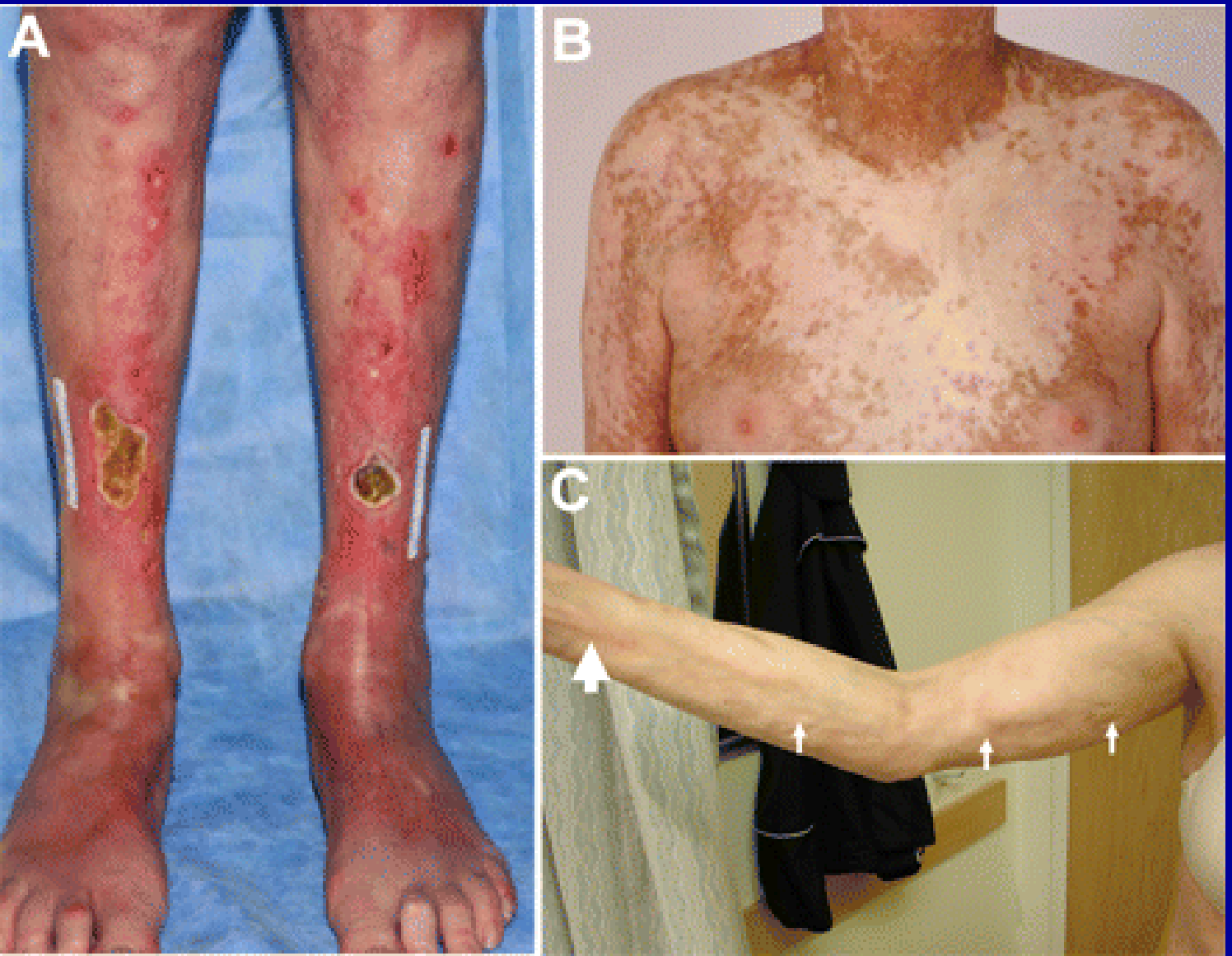
Diagnosis of Chronic GVHD

- NIH consensus Working Group standardized criteria :
  - No time limit
  - requires the presence of at least one diagnostic clinical sign of chronic GVHD (scleroderma or esophageal thickening) or the presence of at least one distinctive manifestation (keratoconjunctivitis sicca) confirmed by pertinent biopsy or other relevant tests (e.g. Schirmer's)
  - Exclusion of other possible diagnoses to explain clinical findings e.g. infection.
- Global assessment of chronic GVHD severity has been developed to replace the historical "extensive/limited" classification.

Chronic GVHD

- **Risk Factors:**
  - Prior acute GVHD
  - Unrelated donors
  - Older patient/donor pairs
  - Blood stem cells
  - Donor lymphocyte infusion
- **Treatment**: Steroids

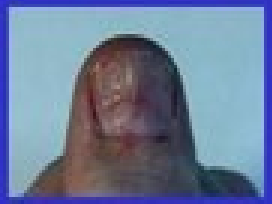
Chronic GVHD



Carpenter P. Blood ; 2011 vol. 118 no. 10 2679-2687

Dry eyes

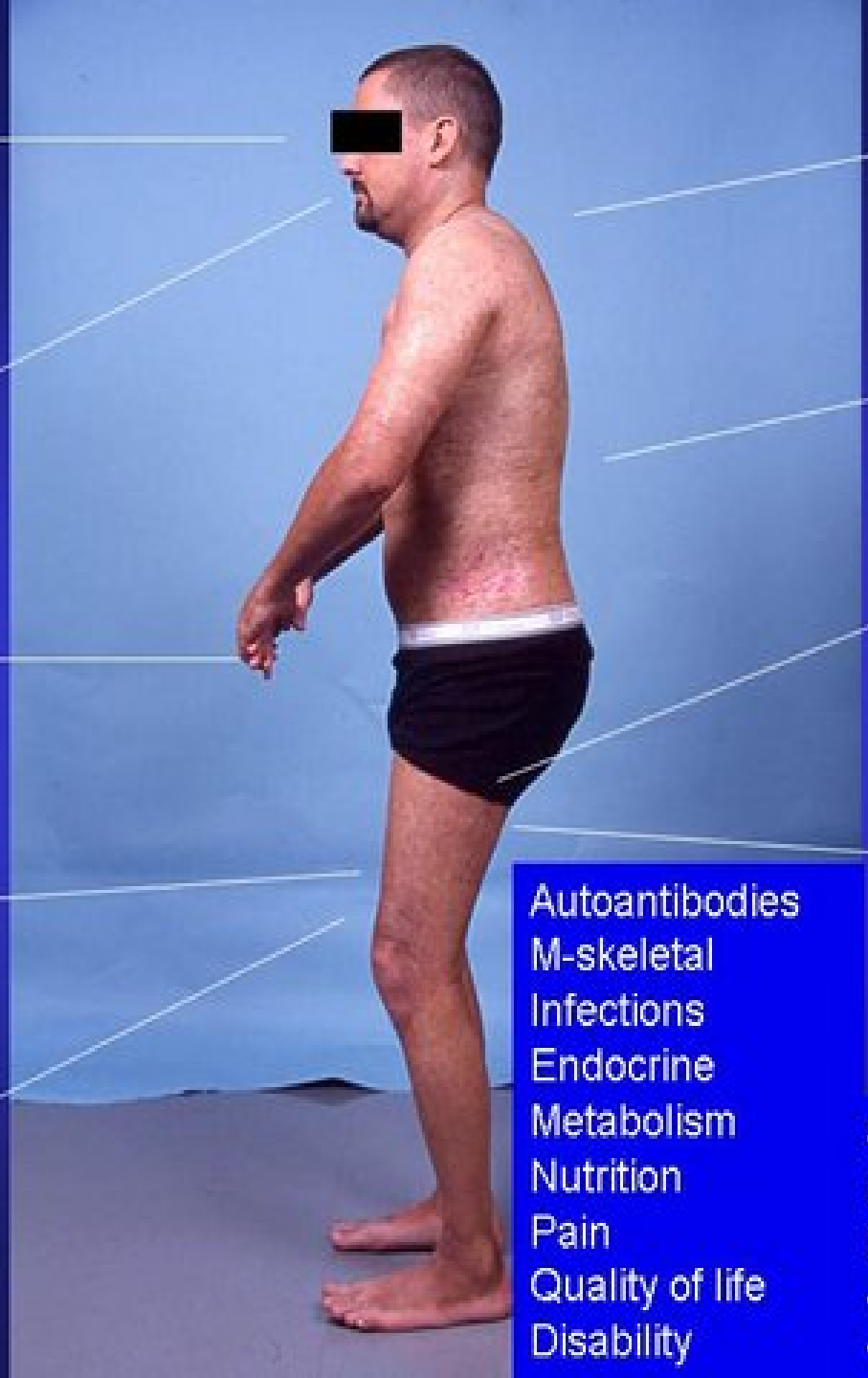
Oral lesions



Nail dystrophy

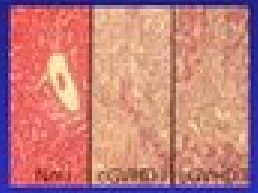
Skin sclerosis

Deep sclerosis

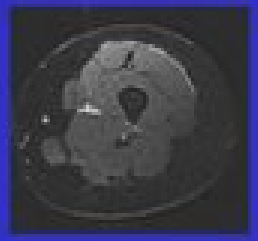


Autoantibodies
M-skeletal
Infections
Endocrine
Metabolism
Nutrition
Pain
Quality of life
Disability

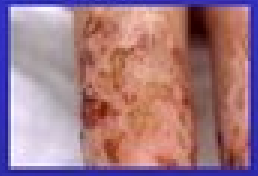
Bronchiolitis obliterans



Loss of bile ducts



Fasciitis

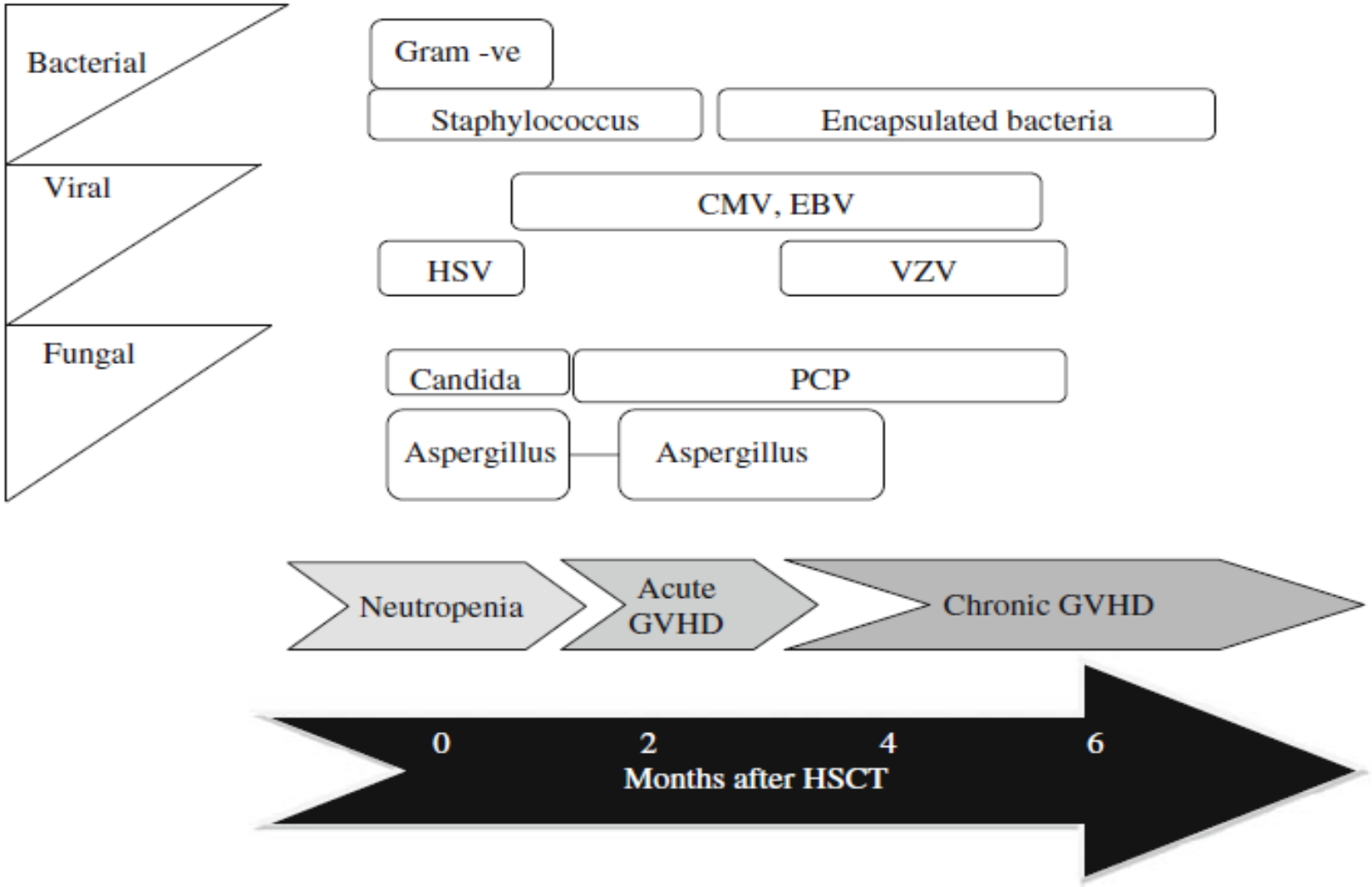


Skin ulcers

Spectrum of manifestations In cGVHD

- 50% Incidence

- 15% Life Threatening


Bacterial
Gram -ve
Staphylococcus
Encapsulated bacteria
Viral
CMV, EBV
HSV
VZV
Fungal
Candida
PCP
Aspergillus
Aspergillus
Neutropenia
Acute GVHD
Chronic GVHD
0
2
4
6
Months after HSCT

Infectious Complications

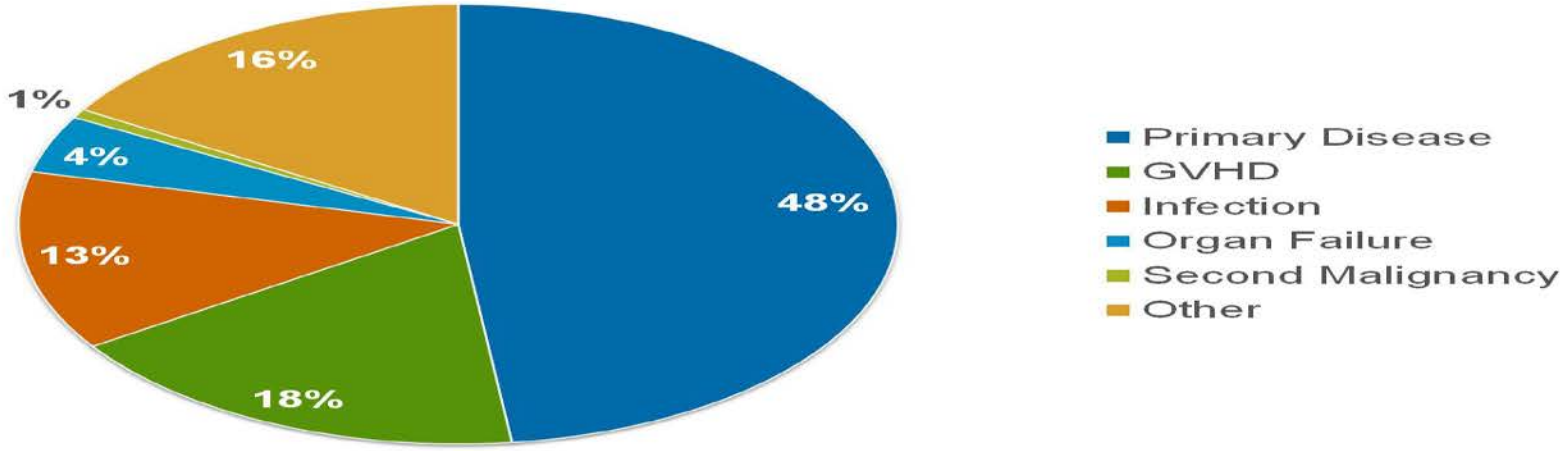
- **Bacterial, Fungal**
  - In the peri-transplant period
  - Increased risk for fungal infections in patients with prolonged neutropenia and/or chronic high dose steroid treatment
- **Viral**
  - **HSV**: rare due to prophylactic Acyclovir
  - **CMV**:
    - High mortality
    - Prevention: CMV negative blood products, leukocyte-depleted blood products, antigenemia monitoring

Infectious Complications

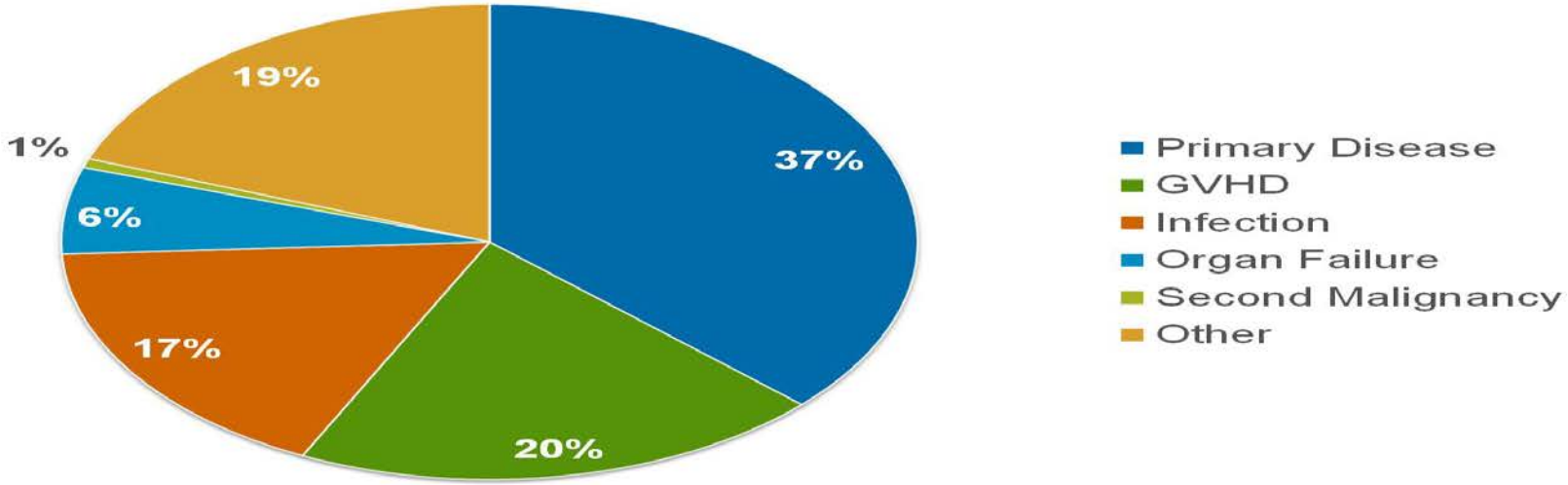
- **Viral**
  - **Varicella : delayed >3months post transplant**
- Pneumocystis
  - Very rare with prophylactic therapy (TMP-SMX, Pentamidine)

LONG-TERM COMPLICATIONS (ADULTS)

Causes of Death after HLA Match Sibling Transplants done in 2011-2012

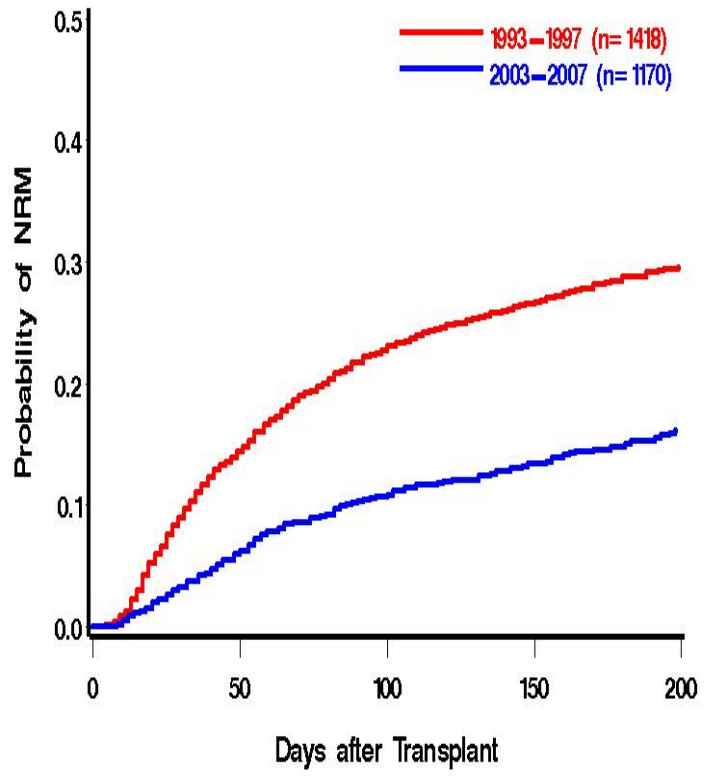


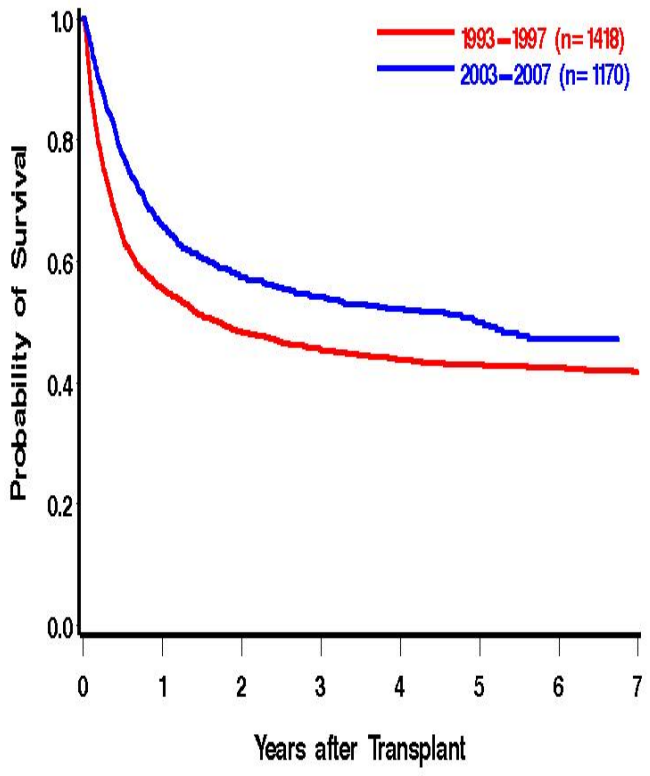
Causes of Death after Unrelated Donor Transplants done in 2011-2012



Pasquini MC, Zhu X. Current uses and outcomes of hematopoietic stem cell transplantation: 2014 CIBMTR Summary Slides. Available at: http://www.cibmtr.org

Reduced Mortality after Allogeneic BMT





Decreased risk of severe GVHD; viral, bacterial, and fungal infections; and damage to the liver, kidneys, and lungs.

N Engl J Med. 2010 Nov 25;363(22):2091.

Reasons for Improvement in Allogeneic BMT Over Time

- Better HLA matching
- Better supportive care including anti-fungal and anti-viral therapy
- Less aggressive conditioning regimens i.e. targeted busulfan

Long Term Complications After BMT

- Relapse
- Sequela of GVHD
  - Immunity and infections issues
  - Ocular, skin and oral ie. Cataracts, Oral cGVHD (mucosal changes, poor dentition, xerostomia)
  - Esophageal (webs, rings, submucosal fibrosis & strictures, aperistalsis, Pill esophagitis etc.)
  - Muscle, connective tissue and skeletal ie. Osteoporosis
  - Respiratory
  - Liver

- Chronic renal insuf.
- CHF
- Iron overload
- Endocrine (hypothyroidism adrenal insufficiency /gonadal dysfunction
- Psychiatric /integration into normal life, sexual dysfunction.
- CNS
- Secondary cancers

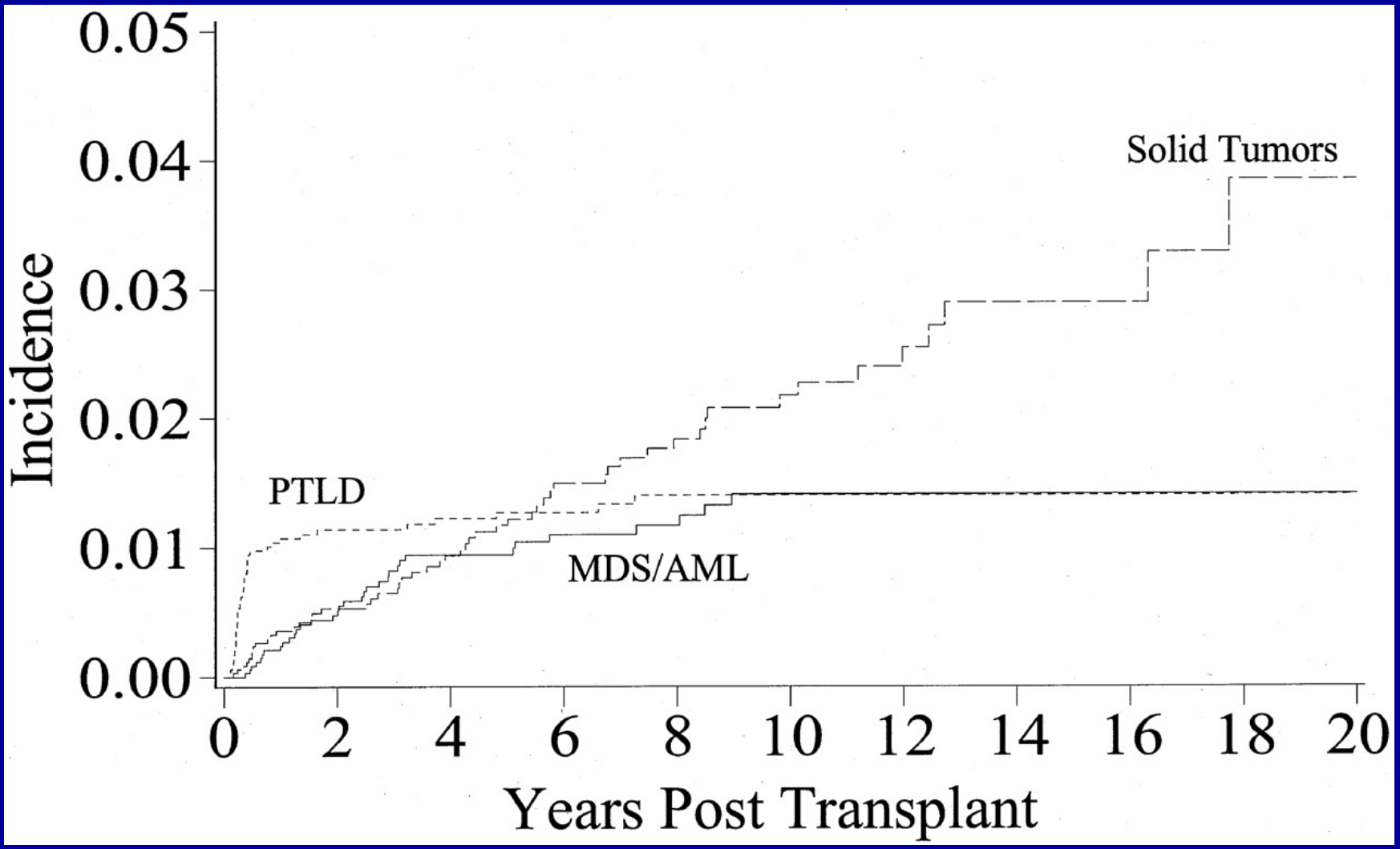
Bone Loss in Long-term Survivors

- Occurs predominantly within the first 6–12 months after autologous and allogeneic HCT.
- Recovery first occurs in the lumbar spine and is followed by a slower recovery in the femoral neck.
- Recovery slowed by steroids.
- DXA scan to determine use of anti-resorptive agents.

Late Mortality From Therapy Related Secondary Cancers After Autologous and Allogeneic Transplant

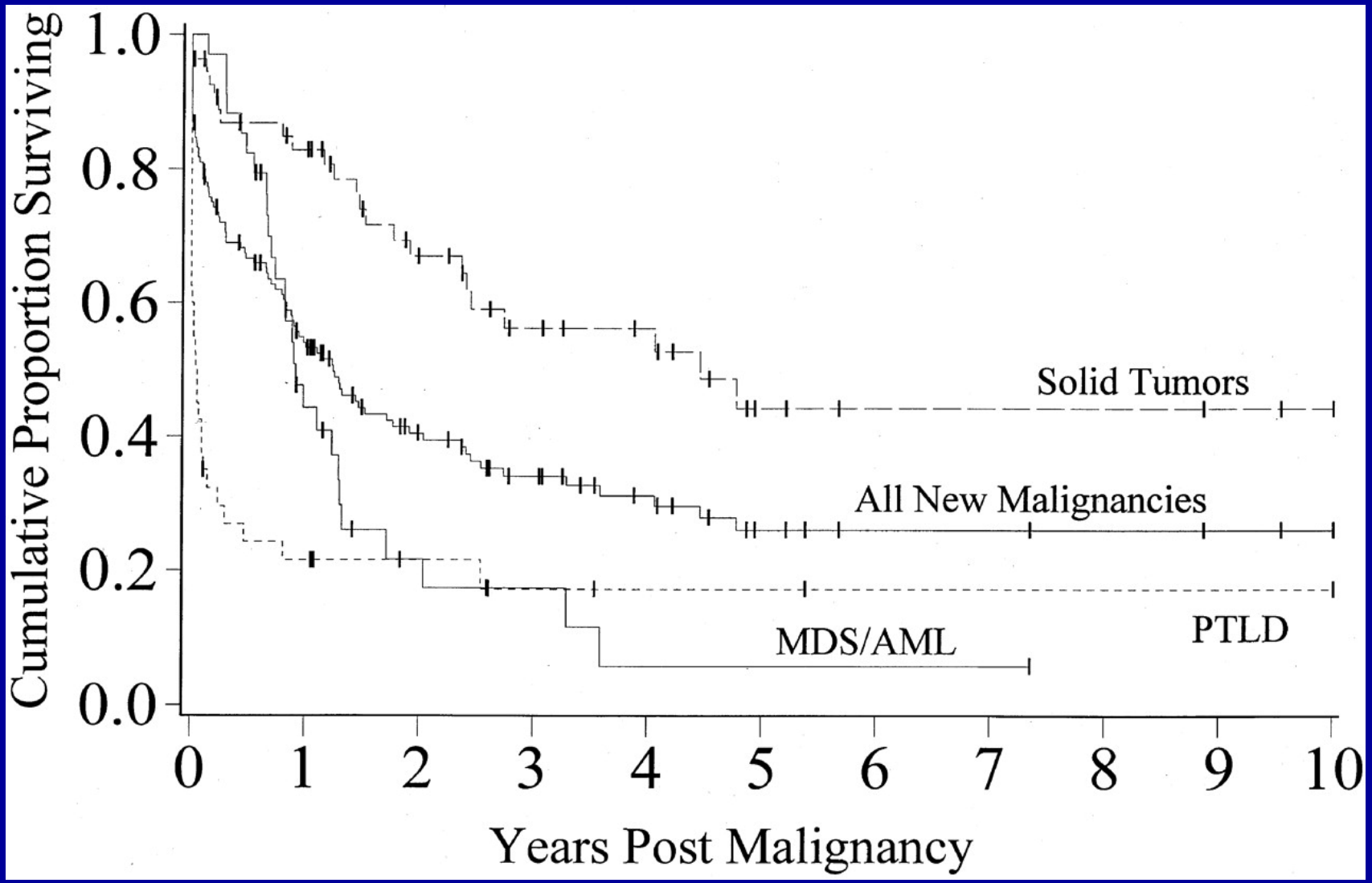
- After autotransplant:
  - 12 X more likely to die of new malignancy than general population
    - Hematological cancers (68%)
    - Solid tumors (32%)
- After allotranplant:
  - 3.6 X more likely to die of new malignancy than general population
    - Solid tumors (82%)

Bhatia S et al Blood 2007:110, 3784-3792 and
Bhatia S et al Blood 2005:105, 4215-4222



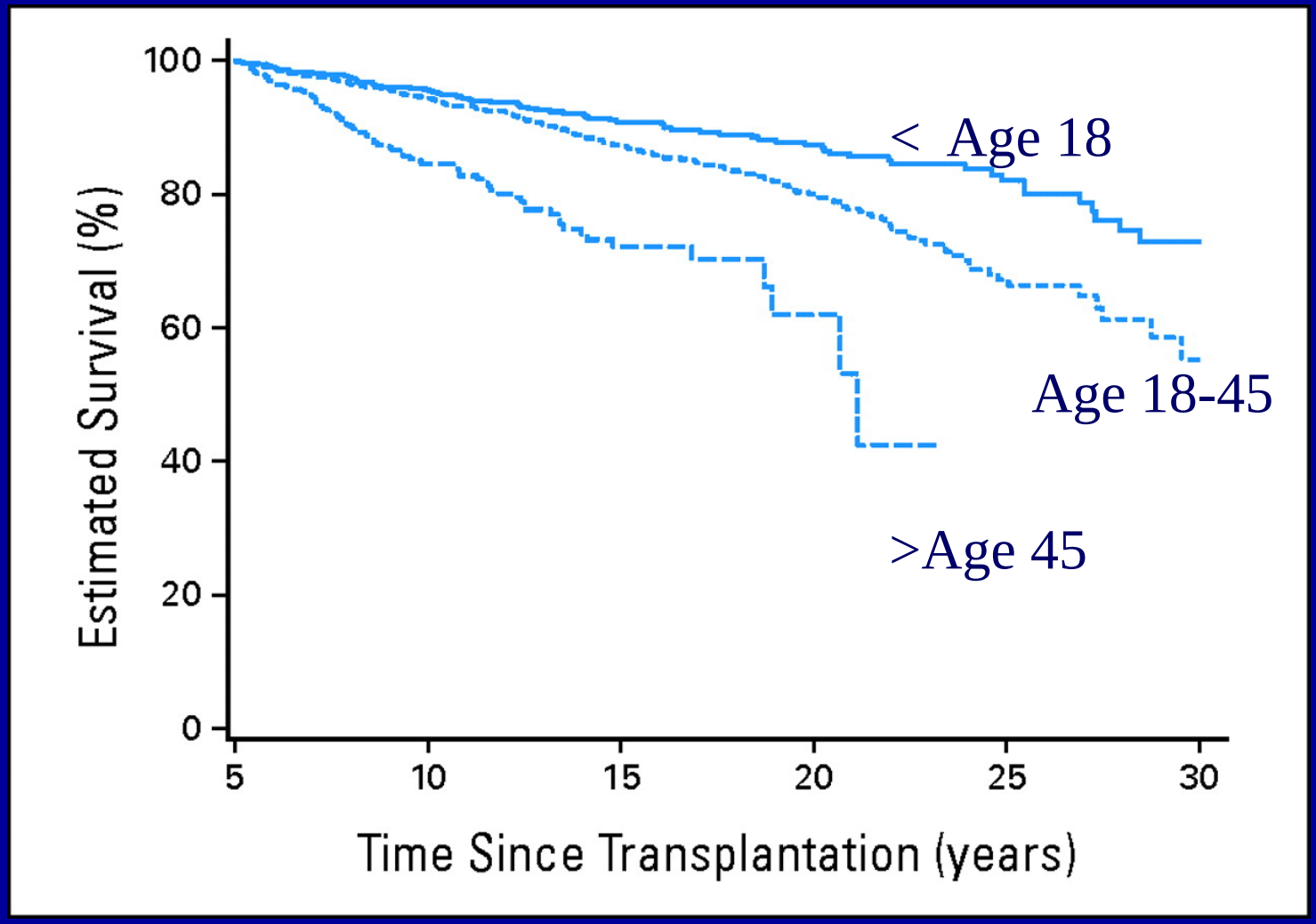
Baker K S et al. JCO 2003;21:1352-1358
n=3372/35% auto TX

JOURNAL OF CLINICAL ONCOLOGY



Baker K S et al. JCO 2003;21:1352-1358

Survival and mortality rates for patients younger than age 18 years (solid line), 18 to 45 years (short-dashed line), and older than age 45 years (long-dashed line) at the time of transplantation.



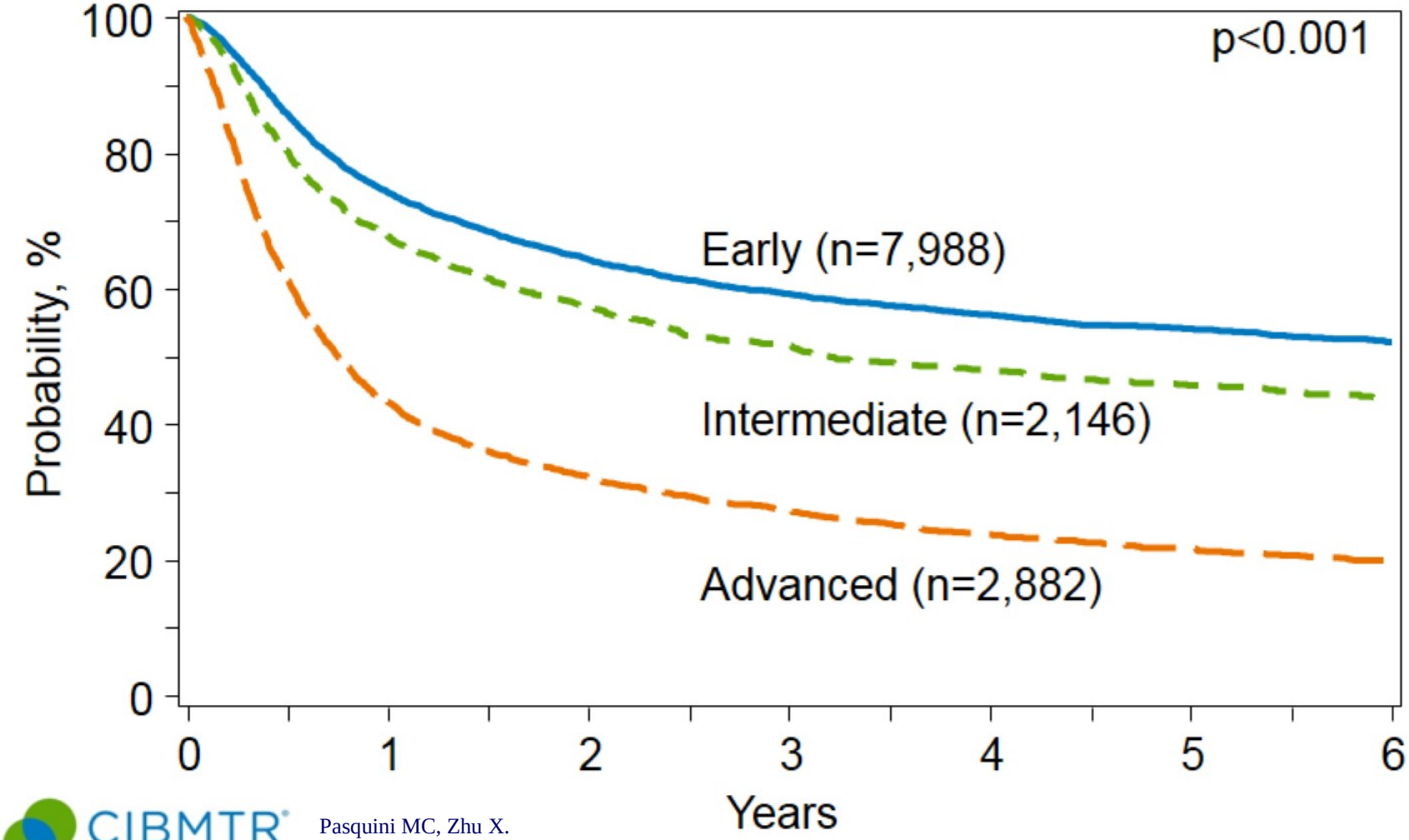
Martin P J et al. JCO 2010;28:1011-1016

Long Term Outcome of Patients Who Survived Initially At Least Five Years After Transplant

- Mortality rates remained four- to nine-fold higher than the expected population rate for at least 30 years after transplantation
- Yield an estimated 30% lower life expectancy compared with that in the general population, regardless of current age.
- In rank order, the leading causes of excess deaths were second malignancies and recurrent disease, followed by infections, chronic graft-versus-host disease, respiratory diseases, and cardiovascular diseases.

Martin P J et al. JCO 2010;28:1011-1016

Survival after HLA Match Sibling Donor Transplants for AML, 2003-2013



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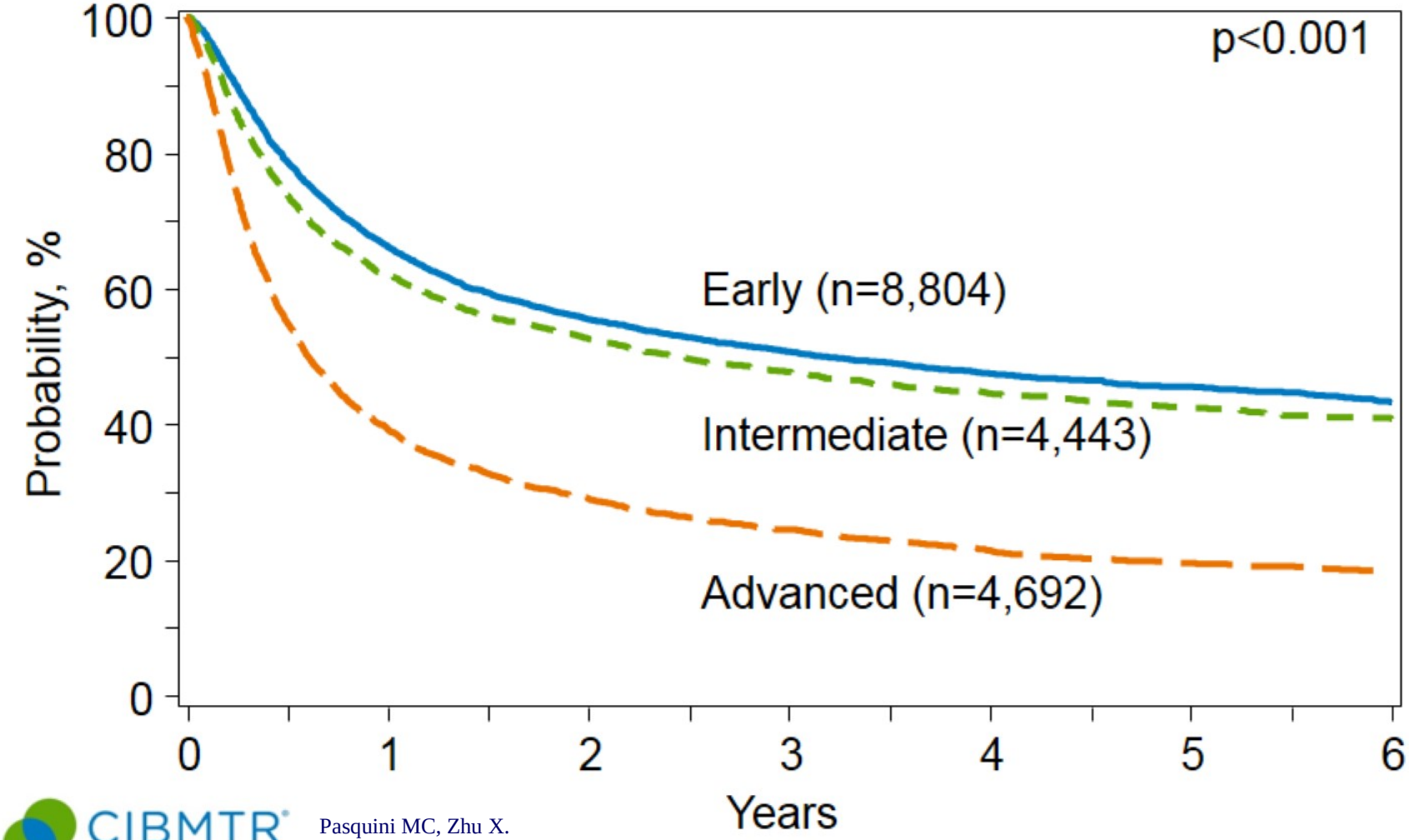
Pasquini MC, Zhu X. CIBMTR Summary Slides, 2015. Available at: http://www.cibmtr.org

By Disease Status

Survival after Unrelated Donor Transplants for AML, 2003-2013



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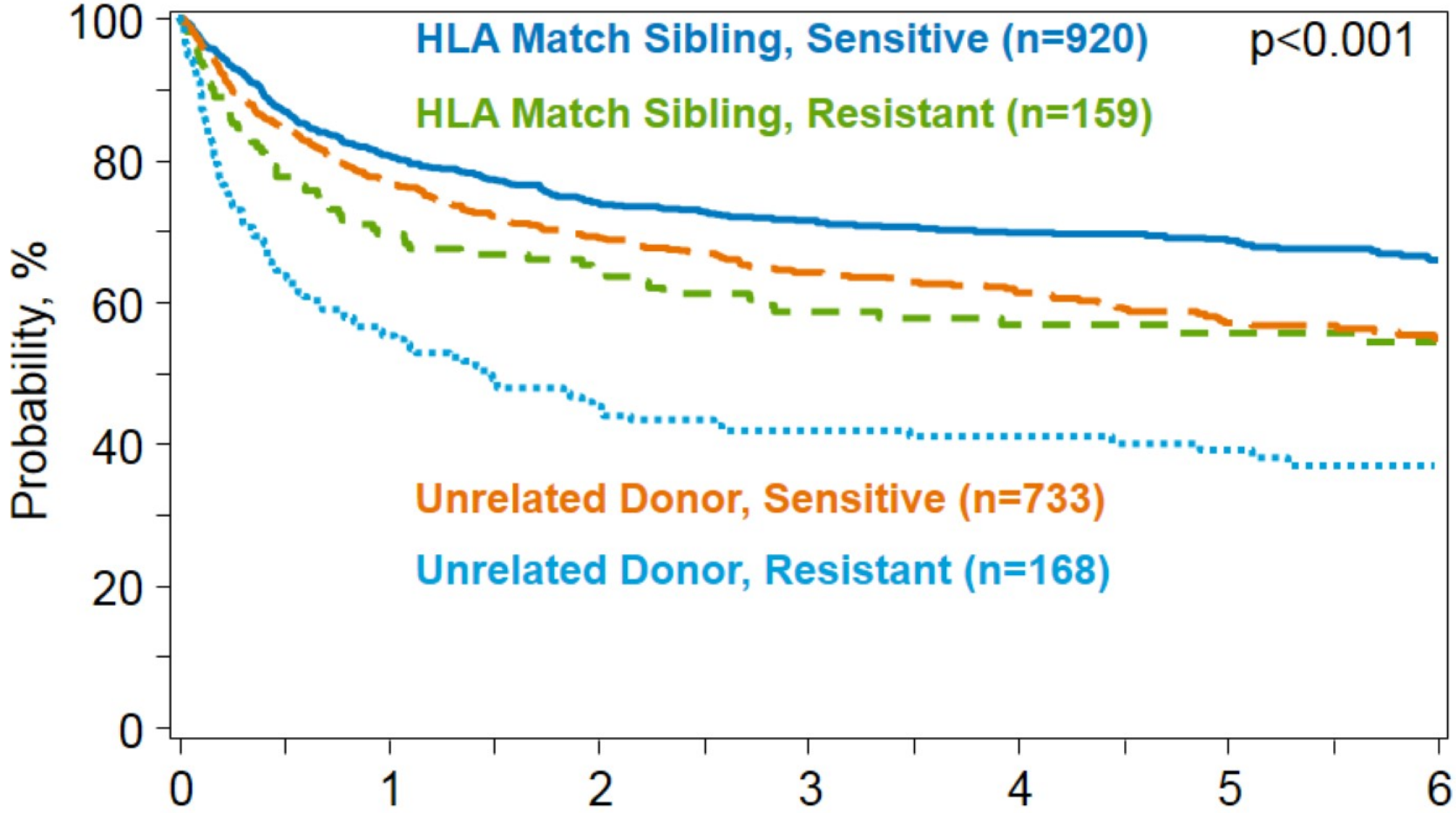
Pasquini MC, Zhu X. CIBMTR Summary Slides, 2015. Available at: http://www.cibmtr.org

By Disease Status

Survival after Allogeneic Transplants for Follicular Lymphoma, 2003-2013



By Disease Type and Donor Type

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Pasquini MC, Zhu X. Current uses and outcomes of hematopoietic stem cell transplantation: CIBMTR Summary Slides, 2015.

AUTOLOGOUS T-CELL THERAPY

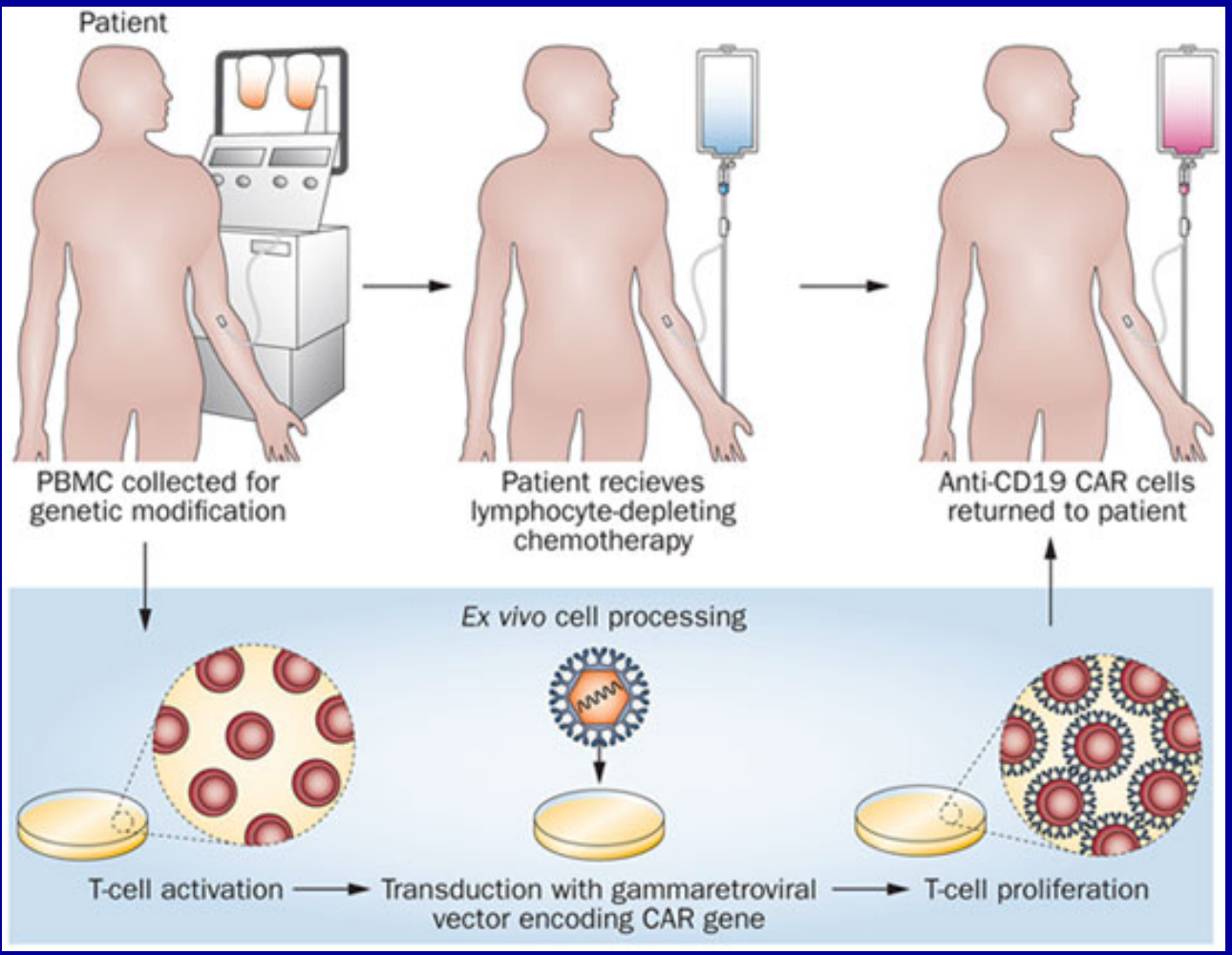
CD19 CAR-T Cells Induce Durable Responses in Relapsed/Refractory CD19-Positive Lymphomas

CTL019 in B-Cell Lymphomas: Background

- CTL019: engineered T-cells target CD19; provide activating and costimulatory signals (CD3ζ, 4-1BB)
- CD19-targeted CAR-modified T-cell therapy has shown efficacy in relapsed/refractory ALL, CLL[1-3]
- Current study evaluated feasibility, efficacy, safety of CTL019 CAR T-cell therapy in pts with advanced CD19-positive B-cell NHLs[4]

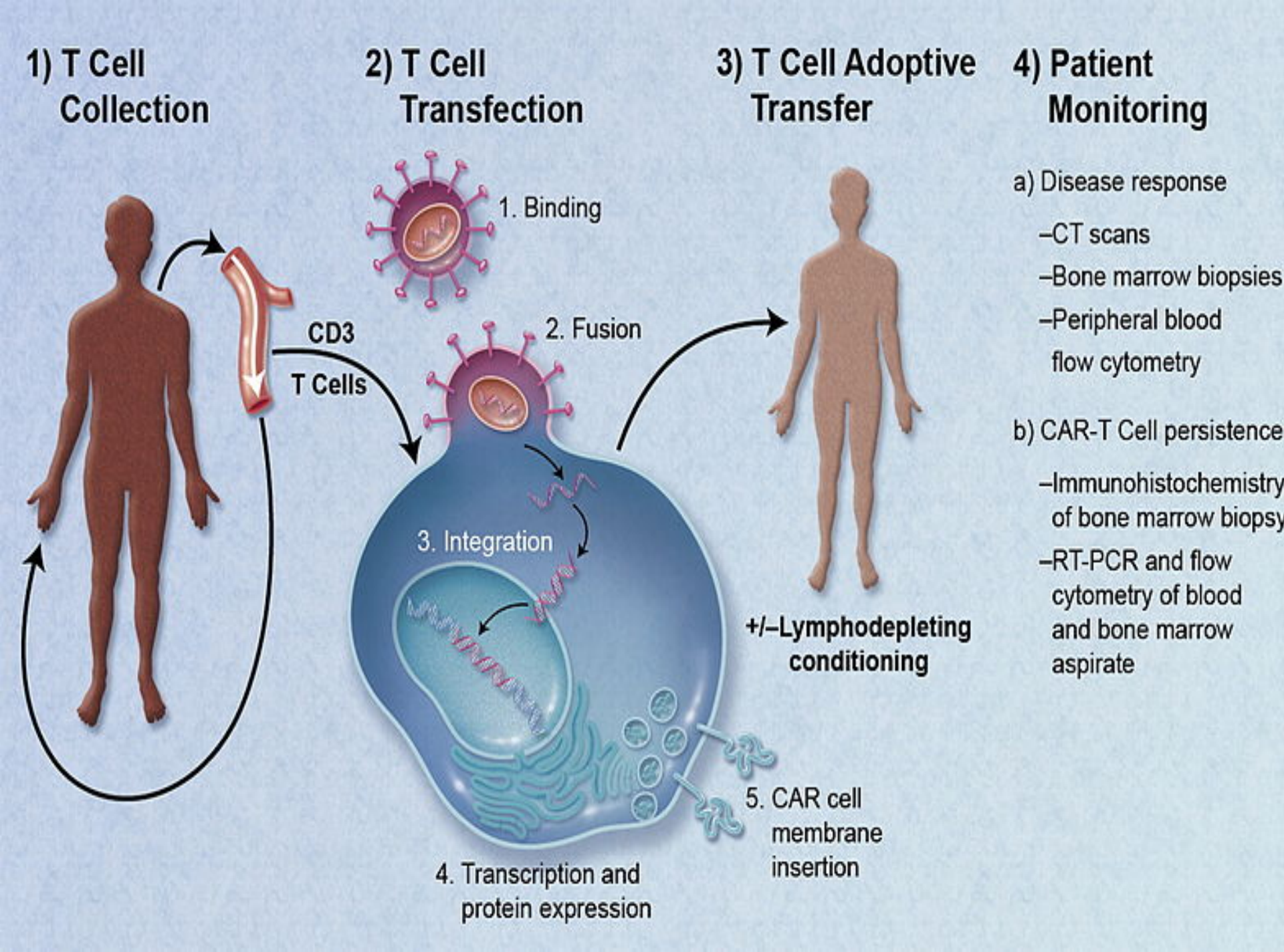
1. Maude et al. N Engl J Med. 2014;371:1507-1517. 2. Grupp, et al. N Engl J Med. 2013;368:1509-1518. 3. Porter, et al. N Engl J Med. 365:725-733. 4. Schuster S, et al. ASCO 2015. Abstract 8516.

CD-19 targeted chimeric antigen receptor (CAR) therapy



- Pt's T cells are harvested
- CAR directed against CD19 is introduced into these T cells
- These T cells are expanded ex vivo (for 2 wks),and then infused

www.nature.com


1) T Cell Collection
2) T Cell Transfection
3) T Cell Adoptive Transfer
4) Patient Monitoring
1. Binding
2. Fusion
3. Integration
4. Transcription and protein expression
5. CAR cell membrane insertion
CD3
T Cells
+/–Lymphodepleting conditioning
a) Disease response
–CT scans
–Bone marrow biopsies
–Peripheral blood flow cytometry
b) CAR-T Cell persistence
–Immunohistochemistry of bone marrow biopsy
–RT-PCR and flow cytometry of blood and bone marrow aspirate

CD19 CAR Therapy

- CD19 is almost exclusively expressed in malignant and normal B-cells, hence is a good target for CAR therapy in B-cell malignancies.
- CAR-modified T cells proliferate/persist in vivo (3+ years).
- In 14 R/R-CLL pts, ORR 57% (4 CRs)
- AEs: delayed cytokine release (CRS) syndrome, B-cell aplasia, hypogammaglobulinemia, neurologic complications
- CRS treatment: tocilizumab (IL-6 inhibitor), steroids

Kalos et al. *Blood*. 2013.

T-Cell Therapy: Cytokine Release Syndrome

Fever

Hypotension

CNS changes: mental status, seizures, obtundation.

Fractionated Dosing Optimizes CAR T-Cell Therapy in Adult R/R ALL

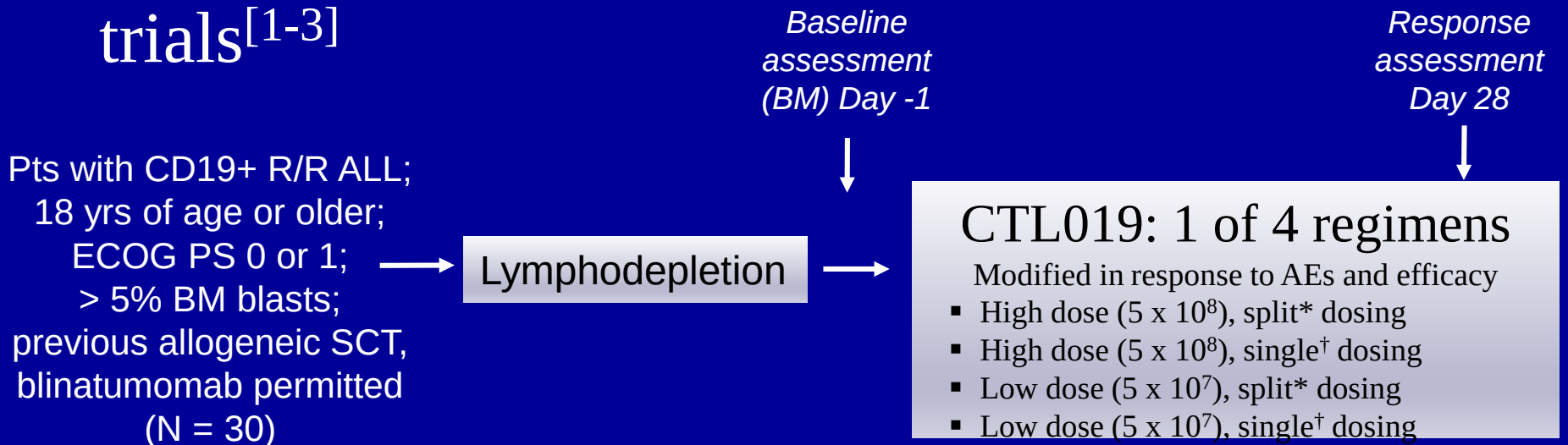
CTL019 in Adults With R/R ALL

- Prognosis poor for adults with relapsed/refractory ALL
- Anti-CD19 CAR T-cell therapy has demonstrated high response rates in children and adults with ALL[1-4]
- CRS occurs frequently with CAR T-cell therapy, may result in death[1-5]
  - Correlates with anti-CD19 CAR T-cell activation and expansion, marked cytokine elevations, disease burden
  - Clinical syndrome: high fever, myalgias, fatigue, anorexia, capillary leak, hypoxia, hypotension
  - Management includes supportive care, anti–IL-6 tx (tocilizumab)
- Updated data on safety and efficacy of 2 dosing approaches with CTL019, anti-CD19 CAR T-cell therapy, in 30 adults with R/R CD19+ ALL[6]

1. Maude SL, et al. N Engl J Med. 2014;371:1507-1517. 2. Davila ML, et al. Sci Transl Med. 2014;6:224ra25. 3. Lee DW, et al. Lancet. 2015;385:517-528. 4. Turtle CJ, et al. J Clin Invest. 2016;126:2123-2138. 5. Frey NV, et al. ASH 2014. Abstract 2296. 6. Frey NV, et al. ASCO 2016. Abstract 7002.

CTL019 in Adult R/R ALL

- CTL019 administered to 30 adults on 2 clinical trials[1-3]



*Split dosing: Day 1, 10%; Day 2, 30%; Day 3, 60% (doses held for early signs of CRS).
†Single dosing: Day 1, 100%.

1. Frey NV, et al. ASCO 2016. Abstract 7002.
2. ClinicalTrials.gov: NCT02030847.
3. ClinicalTrials.gov: NCT01029366.

CTL019 in Adult ALL: Pt Population

Characteristic	Pts (N = 30)
Median age, yrs (range)	44 (21-72)
Previous allogeneic SCT, n (%)	10 (33)
Previous blinatumomab therapy, n (%)	10 (33)
Philadelphia chromosome positive, n (%)	3 (10)
Baseline ALL burden, n (%)	
▪ > 5% blasts	27 (90)
▪ 0.01% to 5% blasts	3 (10)
▪ < 0.01% blasts	0

Frey NV, et al. ASCO 2016. Abstract 7002.

CTL019 in Adult ALL: CRS Correlated With Efficacy (Response)

Cohort	Dose	Schedule	N	CRS ≥ Gr 3, %	Response, %
1	High dose (5 x 10^8)	Split	15	66	86 (0 TRM)
2	High dose (5 x 10^8)	Single	6	100	100 (3 TRM)
3	Low dose (5 x 10^7)	Split	6	66	33
4	Low dose (5 x 10^7)	Single	3		
Overall	---	---	30	75	72 (3 TRM)

- 3 CRS-related deaths, all in single high-dose (5 x 10^8) cohort; concurrent infection/sepsis* noted, other factors similar to entire cohort
- Dose and neurotoxicity relationship unclear: 12 events reported (encephalopathy/delirium and seizures)
  - All self-limited and returned to baseline by Day 28

*Included influenza B, pseudomonas, and stenotrophomonas (n = 1 each).

Frey NV, et al. ASCO 2016. Abstract 7002.

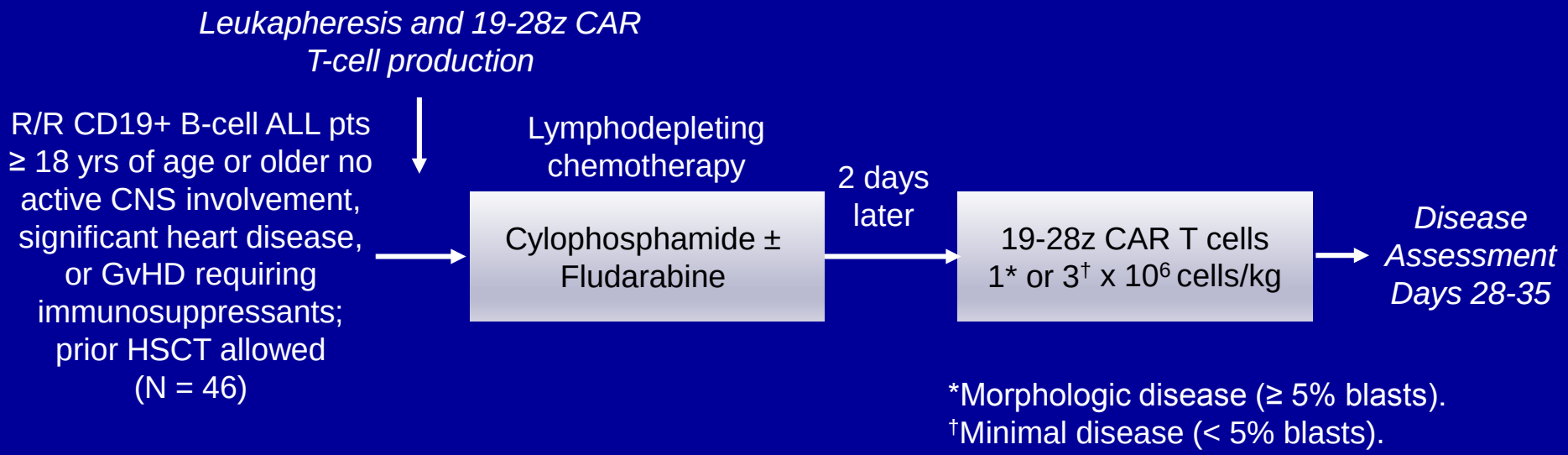
CTL019 in Adult ALL: Conclusions

- CTL019 dose and schedule correlate with response but also toxicity
- Fractionated (split) dosing allows for treatment modification to address CRS-related toxicity and maintain response
- CRS with concurrent sepsis portends poor prognosis
- Future studies needed to evaluate other dosing regimens and best timing for prophylactic and anticytokine therapy to minimize toxicity and optimize response

Frey NV, et al. ASCO 2016. Abstract 7002.

19-28z CAR T Cells in R/R B-Cell ALL: Study Design

- Phase I single-arm study with ongoing enrollment



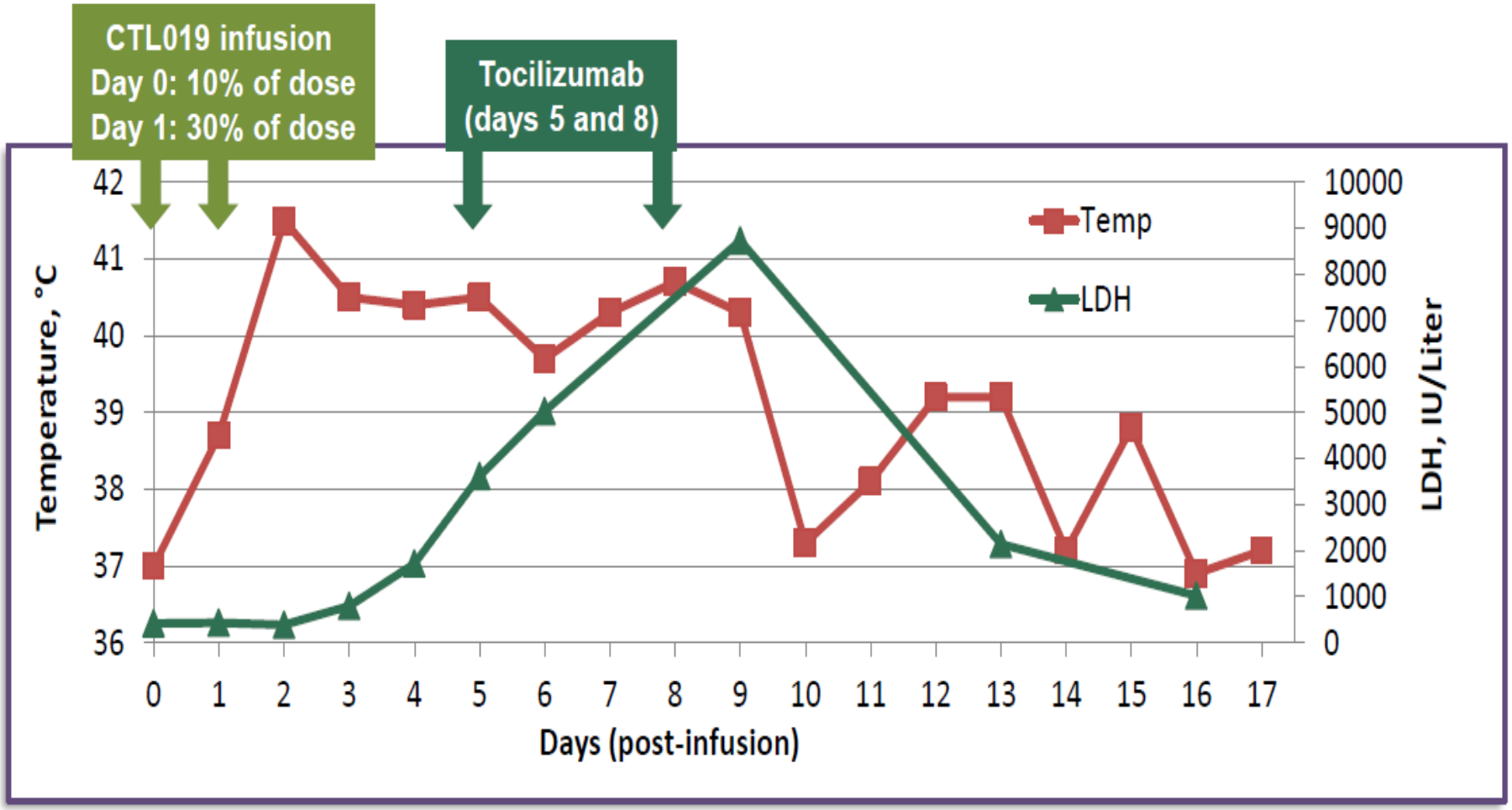
- Median follow-up: 6 mos
- 46 pts evaluable for toxicity, 45 pts evaluable for disease response
- Primary objective: evaluate safety/antitumor activity

Park JH, et al. ASH 2015. Abstract 682.

19-28z CAR T Cells in R/R B-Cell ALL: Conclusions

- High CR rate (82%) achieved in R/R B-cell ALL adults, often with MRD negativity
  - Independent of disease risk factors or burden
  - No subsequent allo-SCT required in subset of pts
- Achieving MRD-negative status after 19-28z CAR T infusion associated with superior OS vs MRD+
- Efficacy/safety of modified T-cell infusion similar in pts with/without prior allo-SCT
- Enrollment ongoing in phase II trial of 19-28z CAR T cells in adults with relapsed B-cell ALL

Park JH, et al. ASH 2015. Abstract 682.



Confusion (day 2-11)

Rasburicase (Day 9)

High dose steroids (days 7-11)

Respiratory support (days 3-10)

High-dose vasopressors (days 2-9)

Transfusion support (days 2-15)

Cryoprecipitate (days 10-15)

Maude, Shannon
Philadelphia Children's Hospital 2014

Umbilical Cord Blood Transplantation

Advantages

- Ease of procurement post-transplant and no donor risk.
- Availability for immediate use
- Low risk of GVHD despite HLA mismatch.
- Reduced risk of transmissible infections.
- Lower incidence of graft versus host disease (offset by mismatching).
- Extends transplant to minority populations (a unit can be found for many patients (4-6 of 6 HLA matched)

Limitations

- Limited cell dose in each unit and defects in bone marrow homing:
  - Delayed blood count recovery and engraftment
  - Higher rates of graft failure post-transplant (5-15%)
  - Delayed immune reconstitution and increased infections
  - Limit for large recipients
- Expense (2 cords, extended hospital stay)

Double Cord Blood Transplants

- In adults more frequent than single cords since 2005.
- Engraftment rate is comparable although higher Grade II acute GVHD in double cords versus single cord; chronic GVHD is equal.
- At day 21 post transplant single unit dominance can be detected in 80% (facilitator versus unit with ‘engrafting potential’ OR graft versus graft effects).
- Patients with mixed chimerism at 1 year more prone to GVHD.

Wagner: N Engl J Med 2014 Oct 30;371(18):1685-94

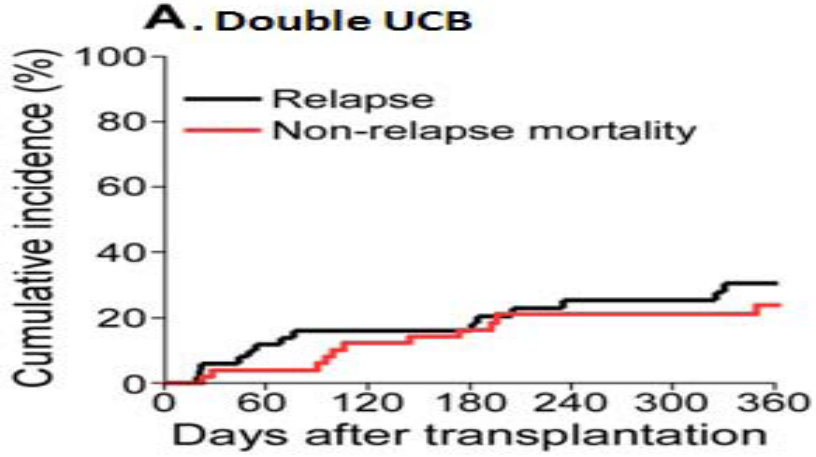
Haematologica 2011;96(8):1213-1220. doi:10.3324/haematol.2010.038836

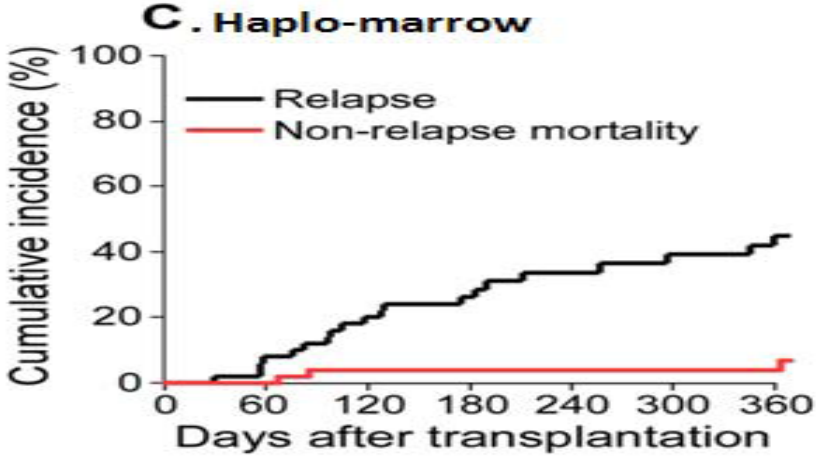
Haploidentical Related Donor Transplants

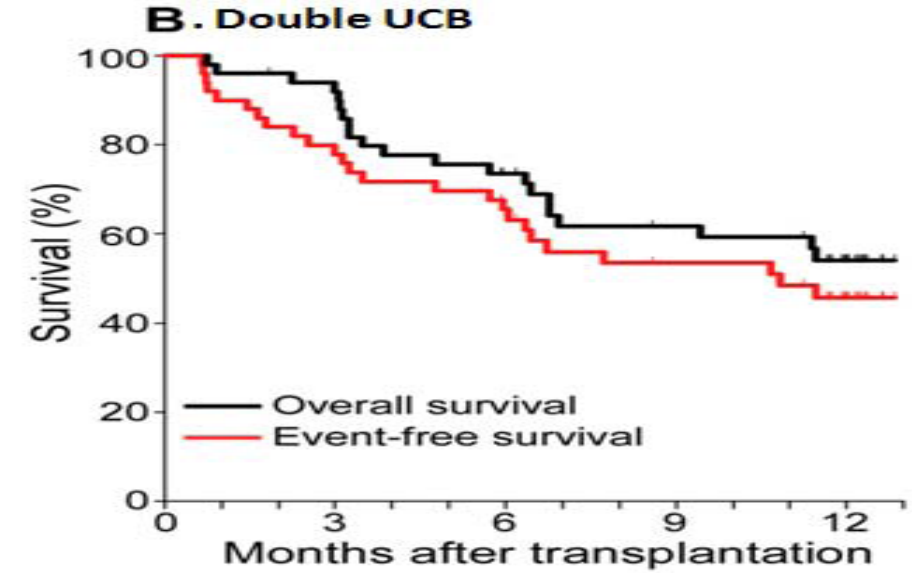
- Strategies for GVHD prophylaxis paved the way to test this possible approach.
  - Administering cyclophosphamide after transplantation to limit mutual donor/recipient allograft reactivity
- Advantages:
  - Likely available parent, child or sibling as a potential donor
  - Additional progenitor and immune cells available for cellular therapies
- Disadvantages:
  - With T-cell depletion:
    - Delayed immune reconstitution
    - Increase the risk of opportunistic infections and relapse
    - With post-transplant cytoxan – less risk of above

Anasetti C, Biol Blood Marrow Transplant 18:S161-S165, 2012

HLA mismatched haploidentical vs unrelated CB grafts comparison of parallel CTN phase 2 studies







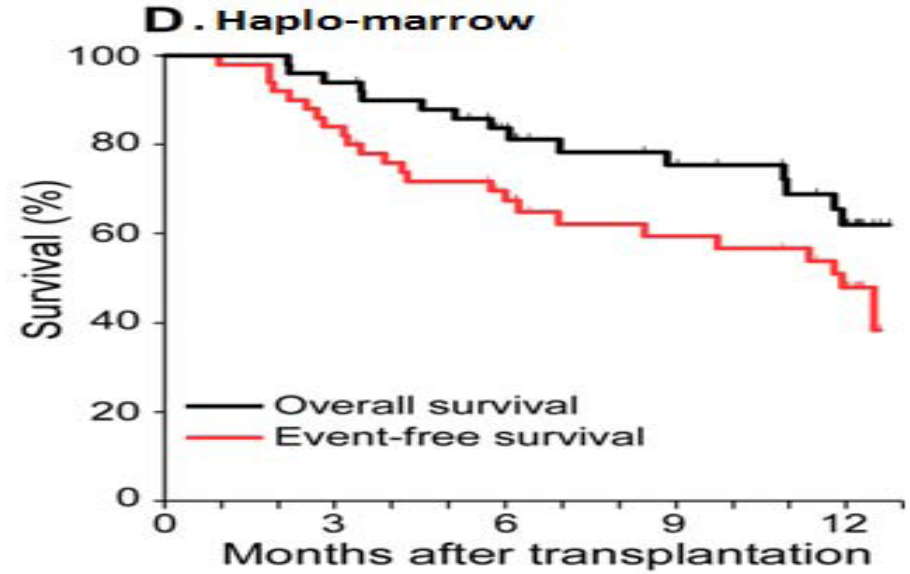


Figure 4

Brunstein et al Blood 2011

HLA mismatched haploidentical vs unrelated CB grafts comparison of parallel CTN phase II studies

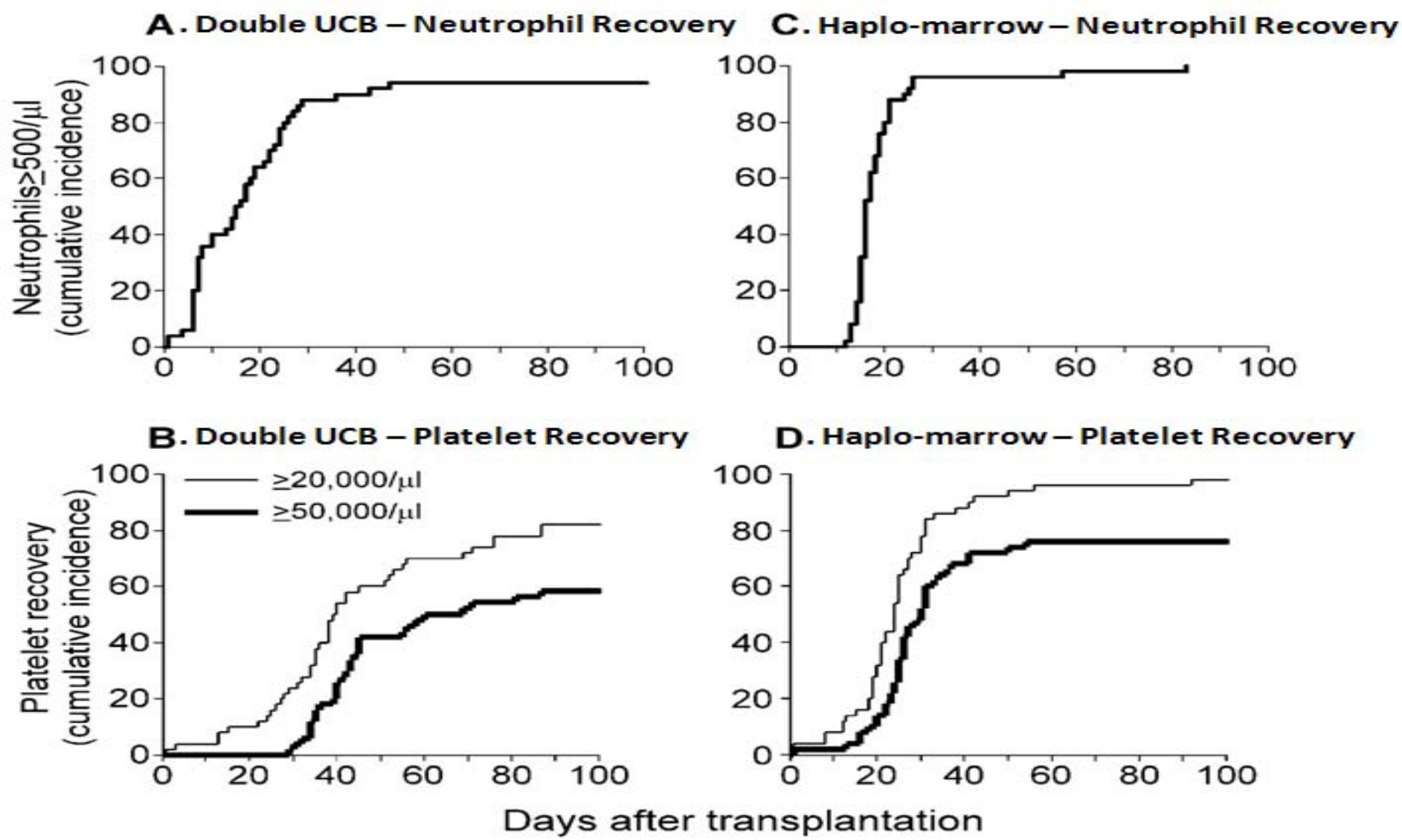


Figure 2

Brunstein et al Blood 201

HLA mismatched haploidentical vs unrelated CB grafts comparison of parallel CTN phase II studies

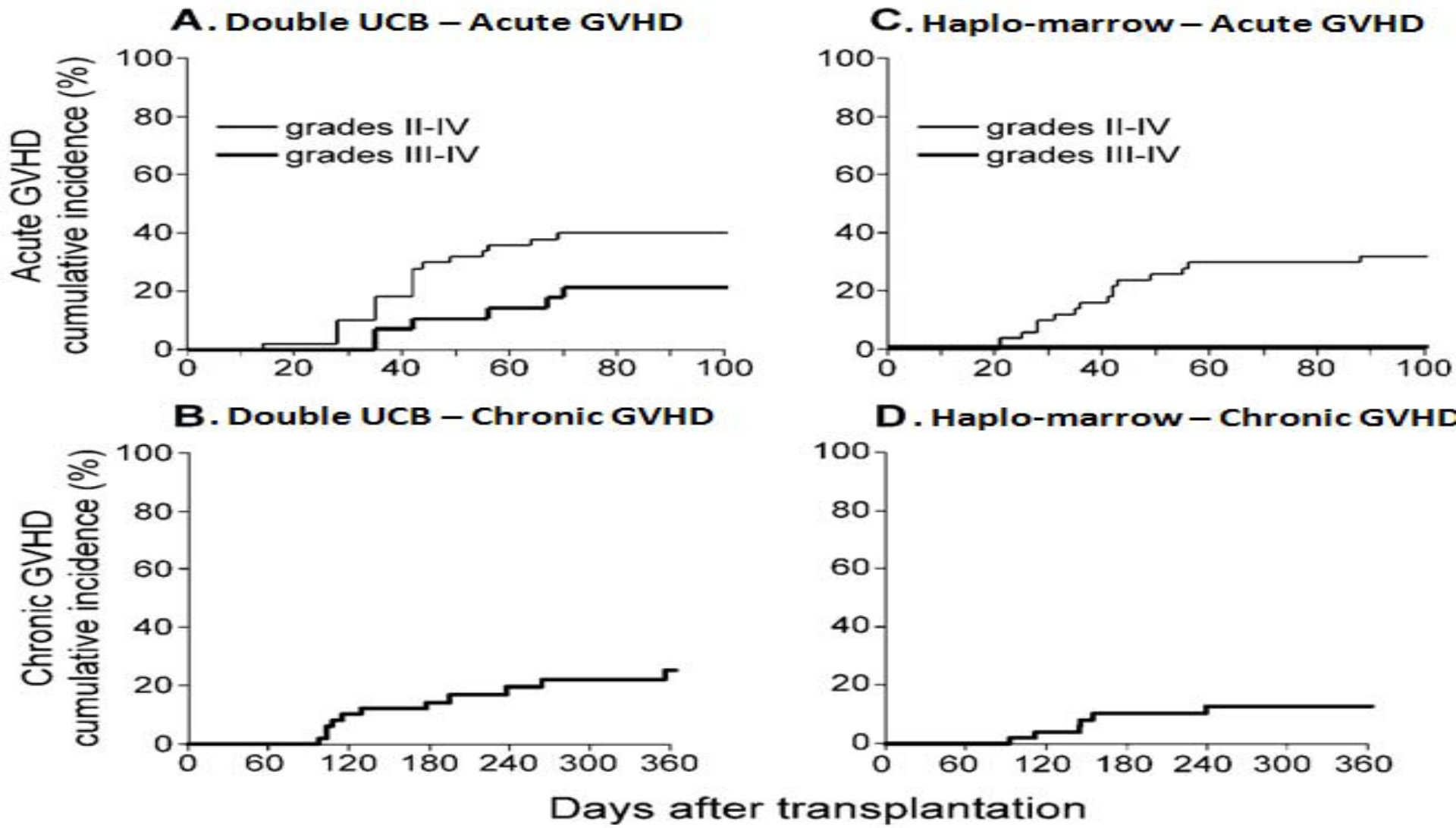


Figure 3