# Bone Marrow Transplantation and malignant haematology

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@marrow

# Tips for haematological malignancies

- Splenomegaly
  - Never see in myeloma
  - In AML confined to monocytic leukaemias
    - Don’t forget the gums (and potassium)
  - Common in MPNs
  - Thrombocytopenia may not be real
- Post splenectomy changes
  - Howell-Jolly bodies
  - Target cells

# More tips: genes

- CML
  - BCR-ABL Philadelphia chromosome: t(9;22)
- MPN
  - JAK2 and CALR
- AML
  - FLT3, NPM1
  - t(15;17): PML-RAR$\alpha$
    - Coagulopathy
    - Differentiation syndrome
  - inv(16), t(8;21): core-binding-factor mutations
- ALL
  - Philadelphia chromosome

# Some more random tips

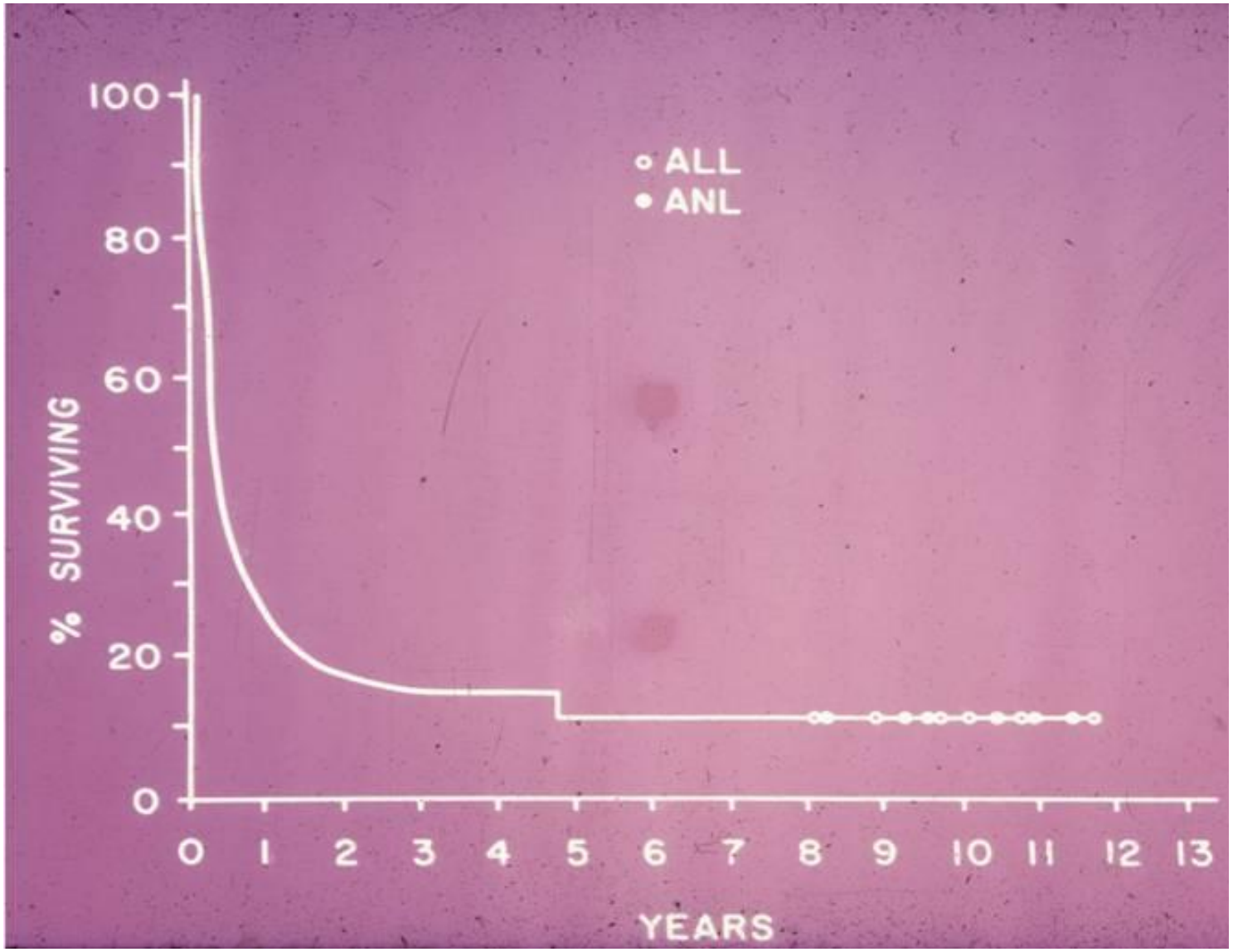
- Myeloid cells are stickier than lymphoid cells
  - Rarely will see hyperviscosity from intense lymphocytosis
- IgM > IgA >> IgG for hyperviscosity

- Hyperkalaemia in an asymptomatic patient with very high leukocyte count
  - Time on bench

# Transplant types

- Donor source
  - Allogeneic
    - HLA-identical sibling
    - HLA-matched unrelated volunteer donor
    - Haploidentical family member donor
    - Stem cell source:
      - Peripheral blood derived
      - Bone marrow
      - Umbilical cord blood
  - Autologous
    - Almost 100% peripheral blood

# It all started here

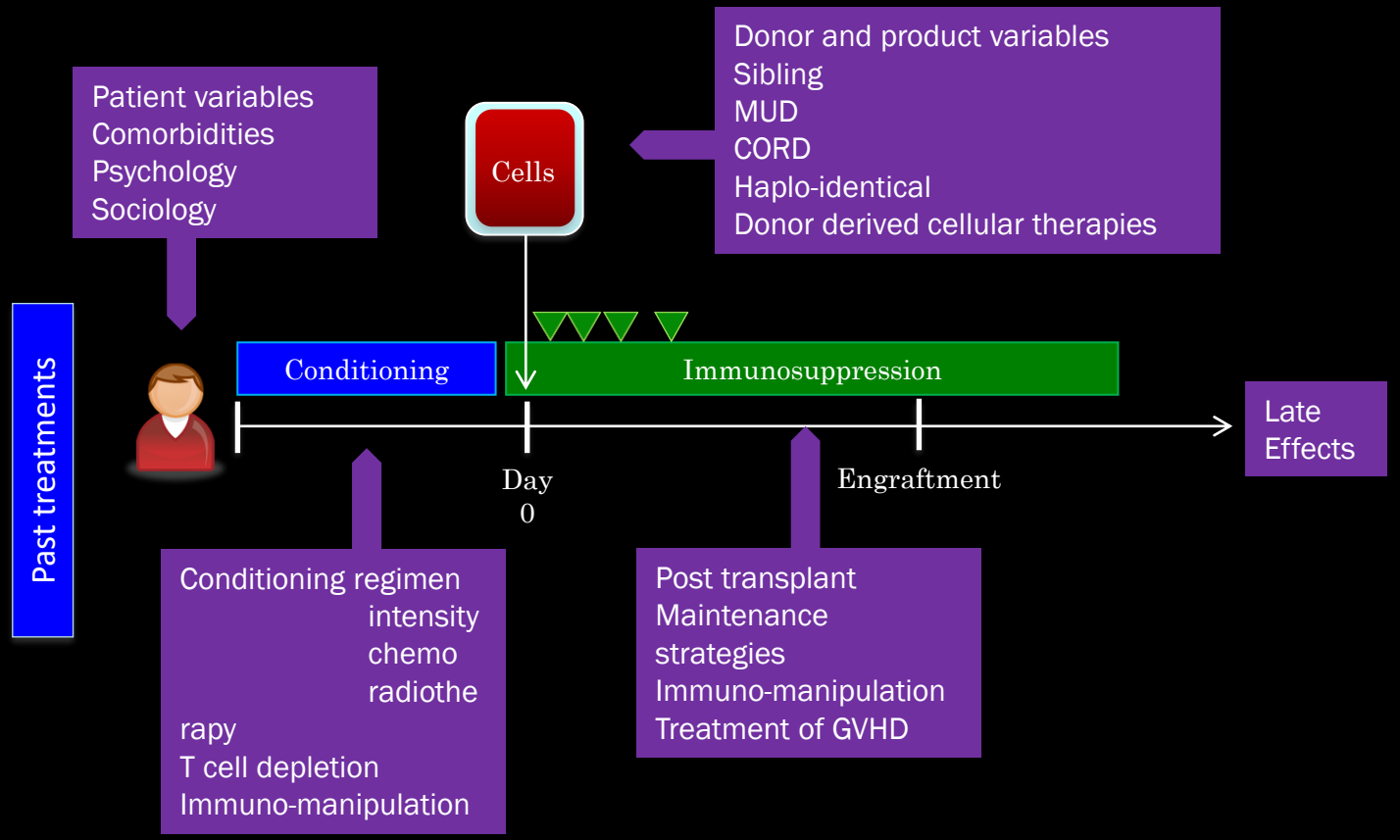


# Difference between allogeneic and autologous transplants

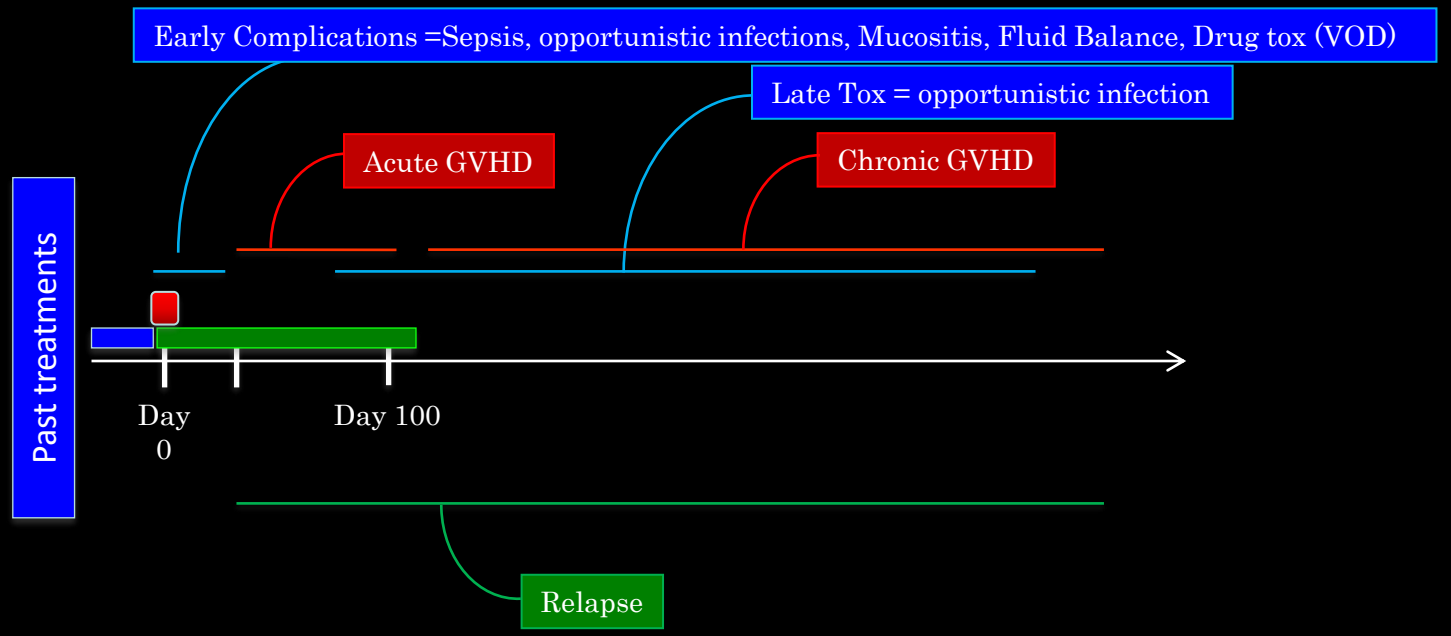
- Autologous transplants are simply a vehicle for delivering highly marrow-toxic therapy
  - Myeloma
  - NHL and HL
  - Rarely, specific solid tumours (germ cell, small round cell)
- Allogeneic transplants
  - High dose therapy
  - Also reduced-intensity
  - Graft-versus-host disease: T lymphocyte driven
    - Immunotherapy
      - CML>AML>ALL
      - FL=MCL=CLL>>DLBCL (except Primary Mediastinal)

# Timing and planning of allogeneic transplants

- Important to understand patient eligibility and timing
  - Stable disease
  - Appropriate time in disease process
- Pre-transplant involvement
  - Ensure treatments given do not preclude transplant
  - Allow patients to move quickly to transplant if needed, prior to disease progression or development of complications
  - Allow adequate time for donor search if needed.


Patient variables
Comorbidities
Psychology
Sociology
Cells
Donor and product variables
Sibling
MUD
CORD
Haplo-identical
Donor derived cellular therapies
Past treatments
Conditioning
Immunosuppression
Late Effects
Day 0
Engraftment
Conditioning regimen
intensity
chemo
radiotherapy
T cell depletion
Immuno-manipulation
Post transplant
Maintenance
strategies
Immuno-manipulation
Treatment of GVHD

# ANATOMY OF AN ALLOGRAFT



# Who gets what?

- Patients with active and especially refractory disease (except for MDS and MF) rarely are offered transplant
  - Exception: autologous transplant for myeloma
- Patients with bone marrow failure are not eligible for autologous transplants (obvious)
- Poorer risk leukaemias do worse after transplant as well
- The earlier in the course of treatment a transplant is done
  - Less toxicitiy
  - Greater chance of disease control
  - Most difficulty with risk/benefit

# Who gets what?

- Autologous transplants for myeloma
  - Early in disease course
  - Improve survival and QOL
  - Non curative
- Autologous transplants for lymphoma (inc Hodgkin)
  - After salvage therapy
  - Curative intent
- Allogeneic transplants
  - Always with curative intent

# Graft versus host disease

- Donor T cell driven
  - But not as simple as that
- Acute
  - In first 100 days traditionally
    - Skin liver and gut
    - Prophylaxis:
      - Tissue typing (blood groups largely irrelevant
      - Ciclosporin/MTX; ATG; Post-transplant cyclophosphamide (PTCy)
    - Treatment
      - Corticosteroids

# Graft versus host disease

- Chronic
  - Generally after day 100
  - The major impediment to Karnofsky score of 100
  - Risk factors:
    - Prior acute GVHD
    - Older donors
    - Peripheral blood derived stem cell source
  - Target organs
    - All (kidneys extremely rare)
    - Looks like many autoimmune diseases (but is alloimmune)
  - Treatment
    - Corticosteroids

# What might you see?

- Graft versus host disease
  - Skin: dry, itchy, dyspigmentation,. sclerodermatous
  - Oral: ulceration, lichenoid
  - Liver: usually tests only
  - Gut: chronic diarrhoea, malnutrition, pancreatic insufficiency
  - Ocular: dry eyes, cataracts
  - Lungs: Bronchiolitis Obliterans
  - Effects of ongoing immunosuppression: steroids ± …..

  - Remember infection risk and effective post-splenectomy state
    - Secondary immunoglobulin deficiency
    - Lymphopoenia

# AML Prognostic Risk Groups

## *Based on Cytogenetic Risk and Molecular Profile (NCCN Guidelines)*

| Risk Group | Cytogenetic Profile | Molecular Abnormalities |
|---|---|---|
| Favorable | Core binding factor (CBF):<br>t(8;21)* or inv(16)* or<br>t(16:16)<br>t(15;17) | Normal ctogenetics: Mutated *NPM1* without *FLT3*-ITD or isolated mutated biallelic *CEBPA* |
| Intermediate | Normal cytogenetics<br>trisomy 8 alone<br>t(9;11)<br>Other non-defined | |
| Poor | Complex (≥ 3 clonal chromosomal abnormalities)<br>Monosomal karyotype<br>del 5, 5q, del 7, 7q<br>11q23 – non t(9;11)<br>inv(3), t(3;3)<br>t(6;9), t(9;22) | Cytogenetically normal (CN) with *FLT3*-ITD<br>TP53 mutation |

*Emerging data indicate that the presence of c-KIT mutations in patients with t(8:21), and to a lesser extent inv(16), confers a higher risk of relapse. These patients are considered intermediate risk and should be considered for clinical trials, if available.

# Timing for HCT Consultation

*Adult Leukemias and Myelodysplasia*

## Acute Myelogenous Leukemia (AML) - Adult

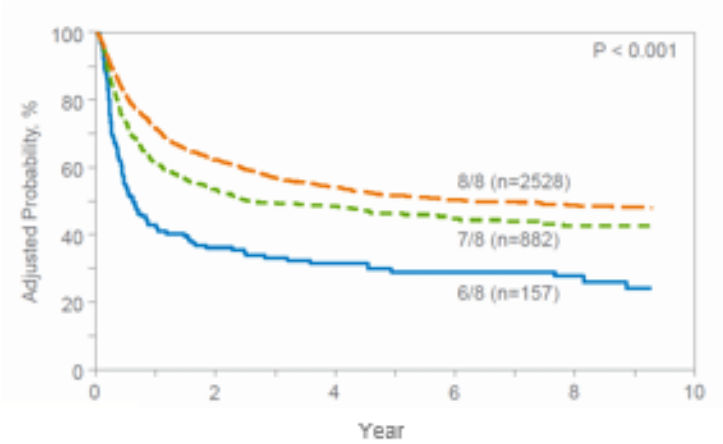
*High-resolution HLA typing is recommended at diagnosis for all patients*

Early after initial diagnosis, all AML patients including:

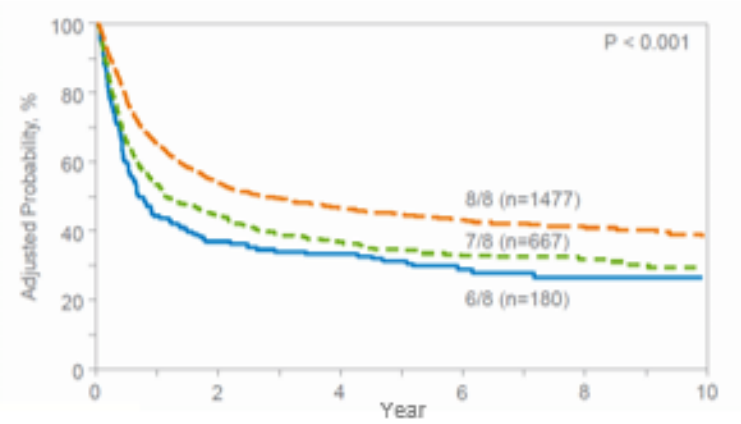
- CR1 — except favorable risk AML [defined as: t(16;16), inv 16, or t(8;21) without c-KIT mutation; t(15;17); normal cytogenetics with NPM1 or isolated biallelic CEBPA mutation and without FLT3-ITD]
- Antecedent hematological disease (e.g., myelodysplastic syndrome (MDS))
- Treatment-related leukemia
- Primary induction failure or relapse
- Presence of minimal residual disease after initial or subsequent therapy
- CR2 and beyond, if not previously evaluated

# Transplantation Timing Matters

## Early Stage

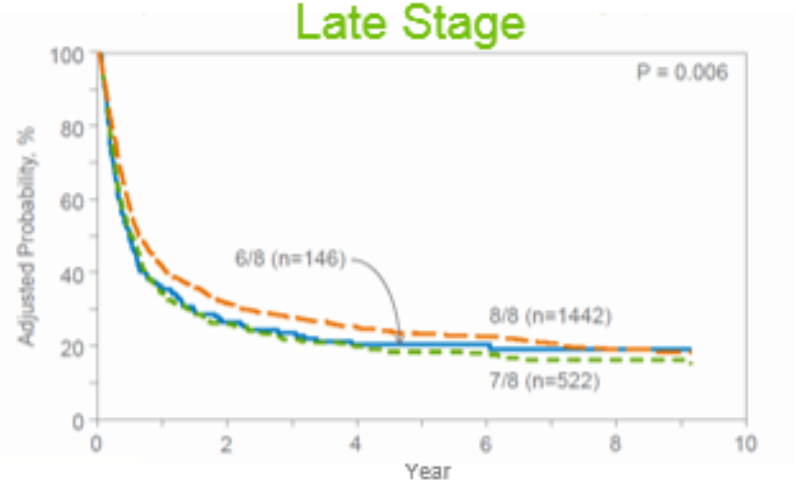



## Intermediate Stage




Patients transplanted earlier in their disease have better outcomes than patients with advanced disease, regardless of the degree of match.

## Late Stage

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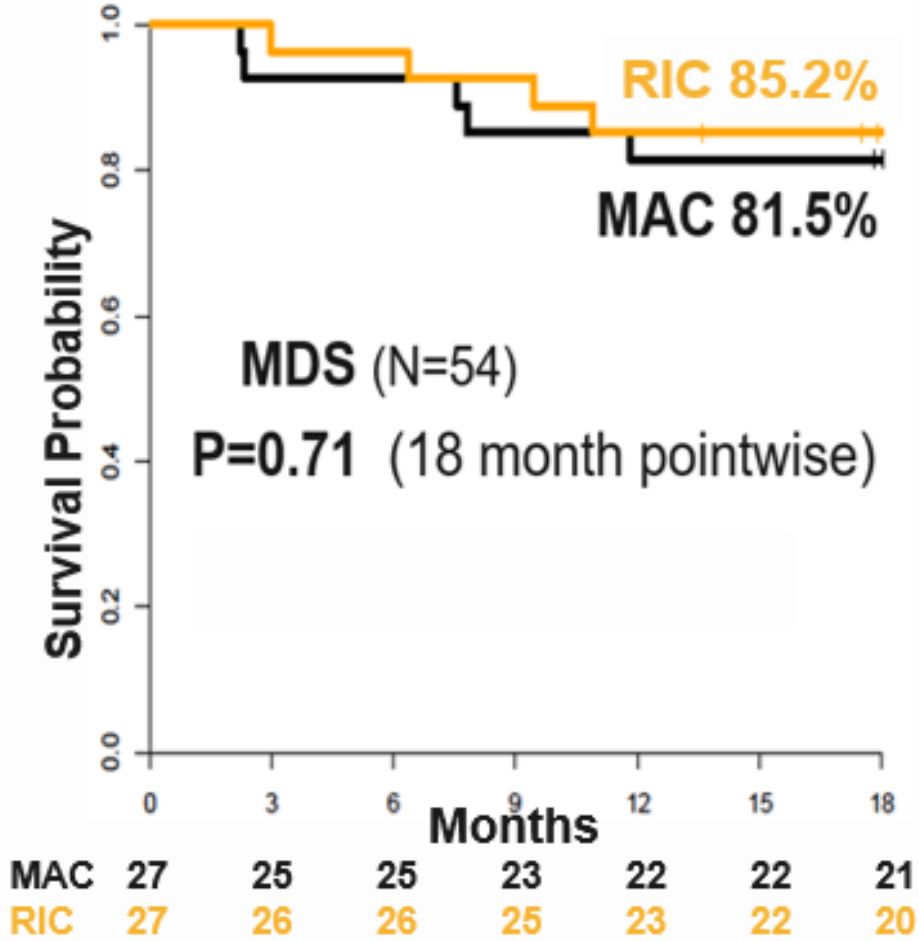
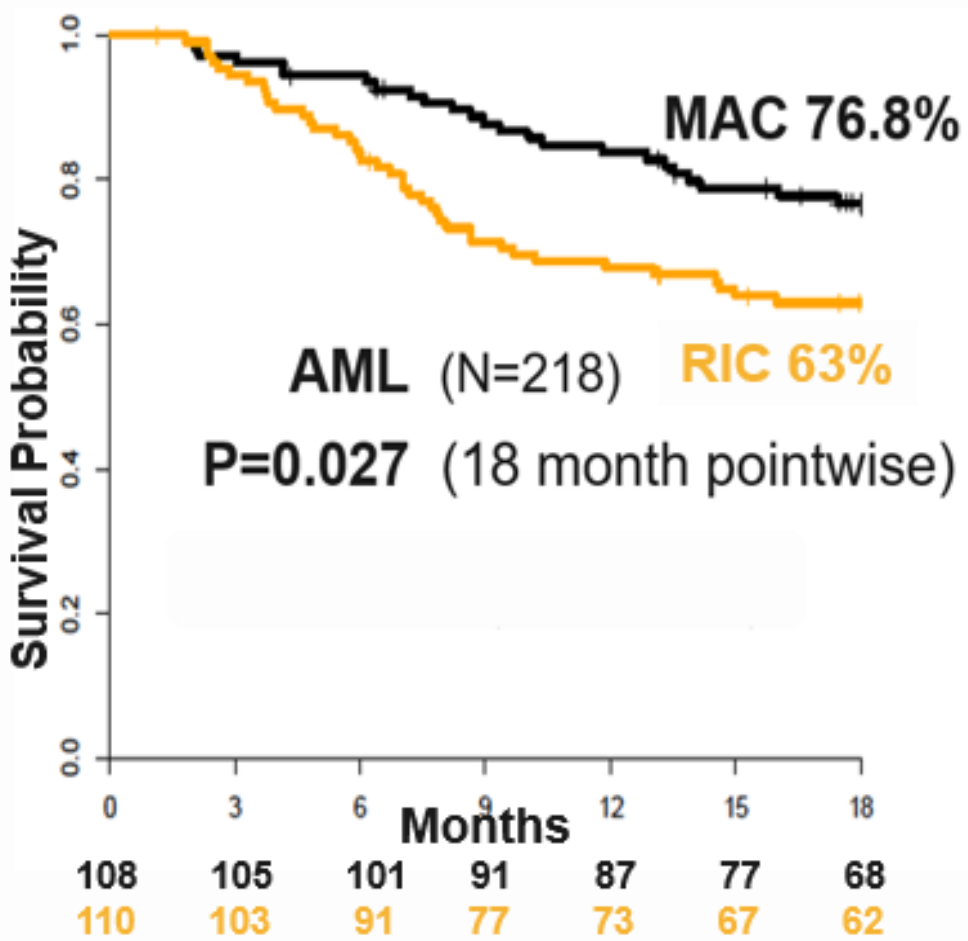
Pidala J. et al. Blood. 2014;124(16):2596-2606.

# Overall Survival by Disease Group



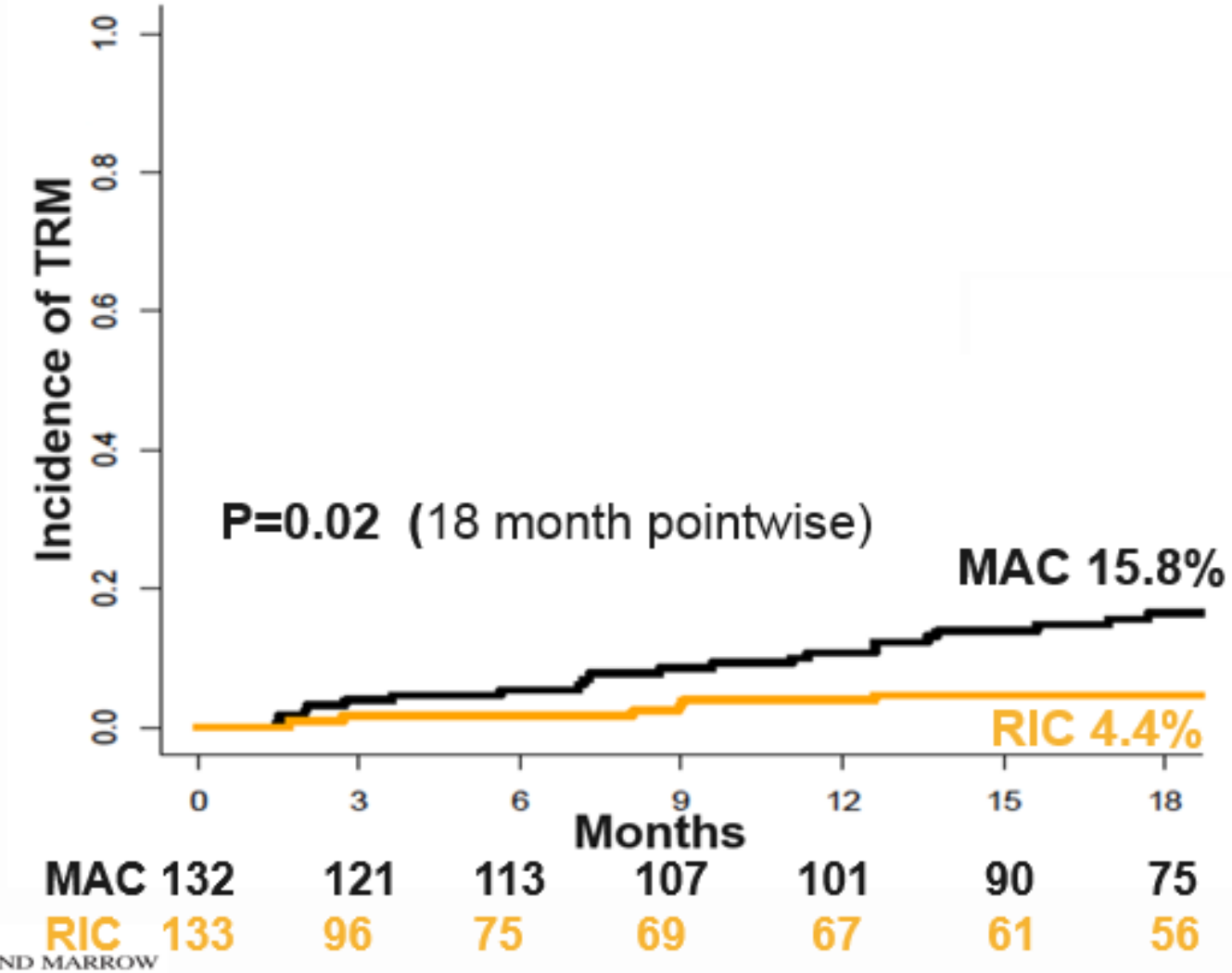




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| MAC | 27 | 25 | 25 | 23 | 22 | 22 | 21 |
| RIC | 27 | 26 | 26 | 25 | 23 | 22 | 20 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| MAC | 108 | 105 | 101 | 91 | 87 | 77 | 68 |
| RIC | 110 | 103 | 91 | 77 | 73 | 67 | 62 |

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

# Treatment-related Mortality




BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Scott BL, et al. Blood. 2015:126:LBA-8

# Timing for HCT Consultation

## *Adult Leukemias and Myelodysplasia*

### Acute lymphoblastic leukemia (ALL) – Adult

*High-resolution HLA typing is recommended at diagnosis for all patients*

Early after initial diagnosis, all ALL patients including:

- CR1
- Primary induction failure or relapse
- Presence of minimal residual disease after initial or subsequent therapy
- CR2 and beyond, if not previously evaluated

# HCT for Myeloproliferative *Neoplasm*

- Most of the outcome data are from retrospective studies and relate to HCT for primary myelofibrosis or myelo-fibrosis (MF) evolved from other myeloproliferative neoplasms.
- DIPSS has as been validated as predictor for post-HCT outcomes.
- DIPSS independent factors - karyotype (DIPSS plus) and gene mutation profile (JAK2/MPL/CALR or ASXL-1) may also be valuable for decision making
- No prospective HCT versus non-HCT comparative studies



Gangat N, et al. JCO 2011;29(4):392-397
Scott BL,et al. Blood 2012;119(11):2657-2664

# HCT for Myeloproliferative *Neoplasm*

- In the largest study (n=438) outcomes with allo-HCT versus non-HCT approach were compared in primary MF patients grouped by DIPSS status
- DIPSS intermediate-2 or high risk patients clearly benefited from HCT. Low risk did better with non-HCT approach. Intermediate-1 had similar survival with the two approaches
- Caveats:
  - Only patients with primary MF were included
  - Ruxolitinib was not used
  - All patients were < 65 years old

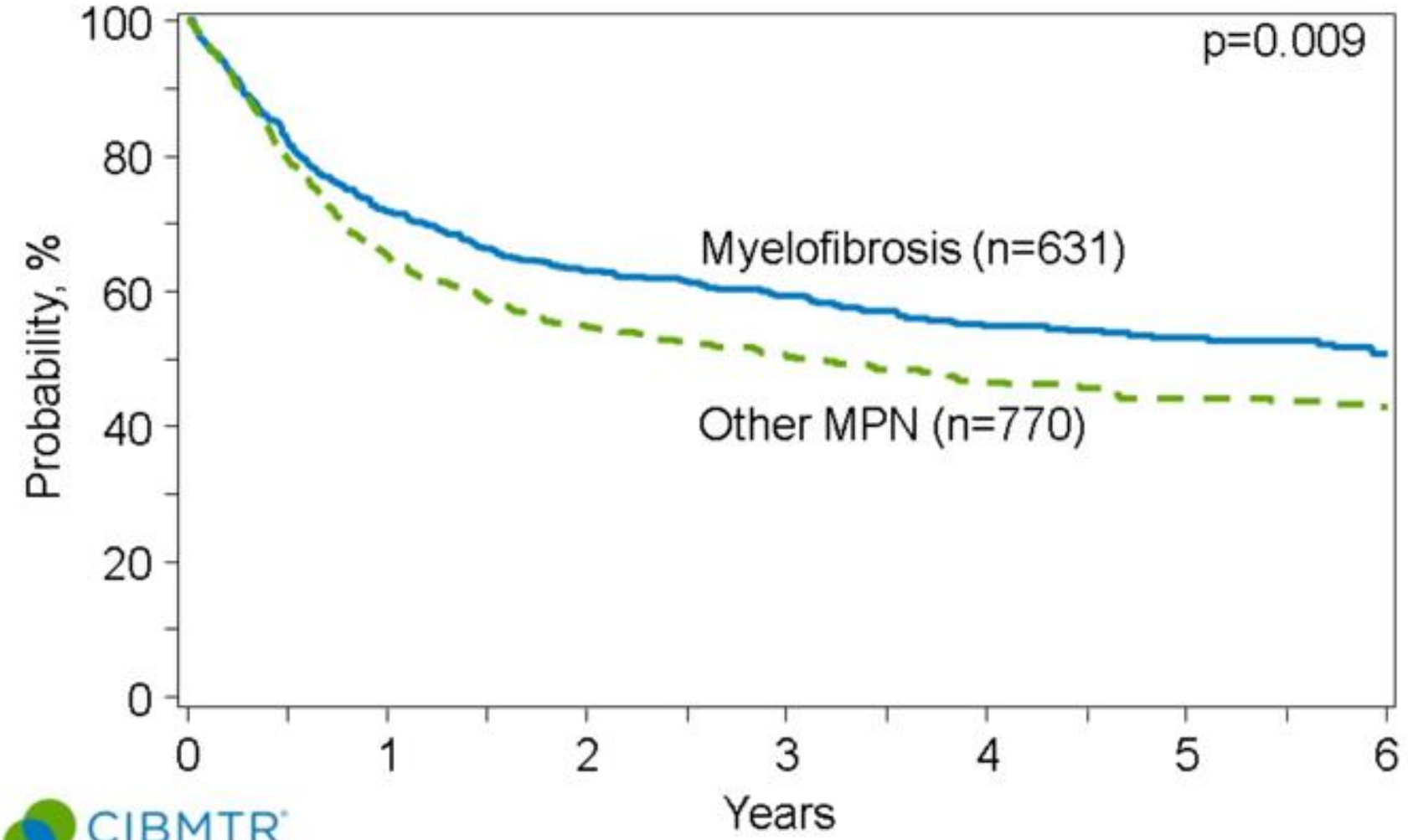


Kroger N, et al. Blood 2015; 25(21):3347-50

# HCT for Myeloproliferative *Neoplasm*

- Generally accepted indications:
  - Primary Myelofibrosis DIPSS Int-2 or High Risk
  - High Risk karyotype and gene profile (even with low risk DIPSS)
  - AML after MF
  - Secondary MF after ET or PV
  - ELN: < 5 years expected survival
- The balance of risk versus benefit has to be assessed for each patient individually.
- Early referral is strongly advocated to allow optimal patient selection and timing to ensure the highest likelihood of benefiting from HCT

# Survival after HLA-Matched Sibling Donor HCT for MPNs, 2004-2014

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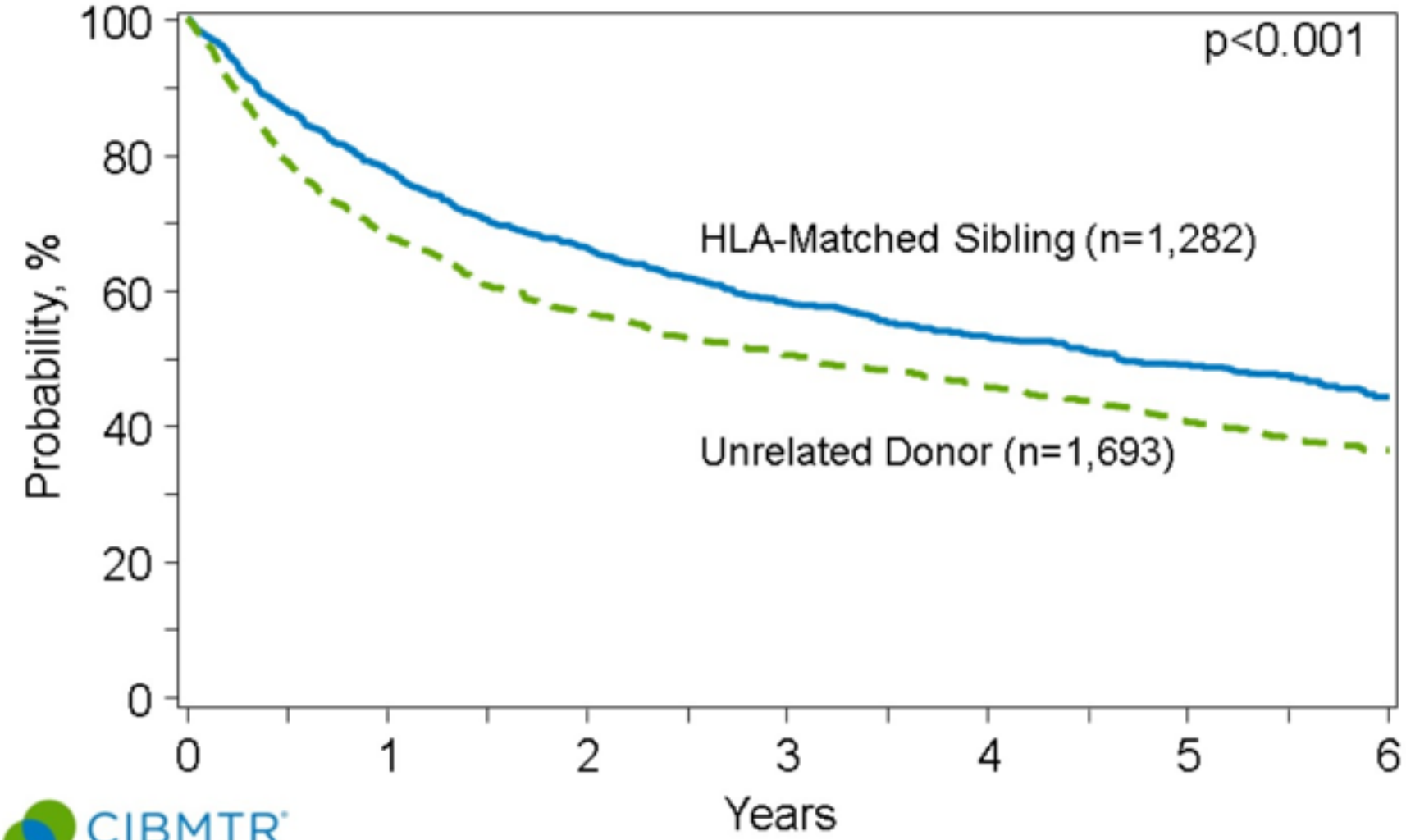
D'Souza A, Zhu X. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides, 2016. Available at: http://www.cibmtr.org

# Survival after Allogeneic HCT for Chronic Lymphocytic Leukemia (CLL), 2004-2014

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# ASBMT Recommendations for HCT in Non-Hodgkin Lymphoma

| Recommendation | Grade of Recommendation |
|---|---|
| ➢ ASCT is not recommended as first-line therapy except for high IPI group. | A |
| ➢ ASCT is not recommended for pts who achieve PR to abbreviated (3 cycles) induction regimen. | A |
| ➢ ASCT is recommended as part of salvage therapy for pts with chemosensitive relapsed DLBCL. | A |
| ➢ Older age (>60 years) is not a contraindication for ASCT. | B |
| ➢ OS outcomes are equivalent for ASCT and Allo-HCT; they have competing risks with regard to relapse and TRM; neither option is recommended over the other. | N/A |

ASBMT
American Society for Blood and Marrow Transplantation

*Oliansky DM, et al. Biol Blood Marrow Transplant. 2011;17:20-47;*
Stiff PJ e.t al. N Engl J Med 2013;369:1681-1690
*Gisselbrecht C, et al. J Clin Oncol. 2012;30:4462-4469*

# ASBMT Recommendations for HCT in Non-Hodgkin Lymphoma

| Recommendation | Grade of Recommendation |
|---|---|
| ➢ PBSC is the standard for stem cell source for ASCT. | A |
| ➢ Rituximab maintenance is not recommended post ASCT. | A |
| ➢ There are insufficient data to make a treatment recommendation regarding number of cycles of induction therapy prior to first-line autologous SCT. | N/A |
| ➢ Planned tandem ASCT is not recommended. | B |
| ➢ RIC appears to be an acceptable alternative approach for pts who cannot tolerate a myeloablative regimen. | N/A |

ASBMT American Society for Blood and Marrow Transplantation

*Oliansky DM, et al. Biol Blood Marrow Transplant. 2011;17:20-47;*
Stiff PJ e,t al. N Engl J Med 2013;369:1681-1690
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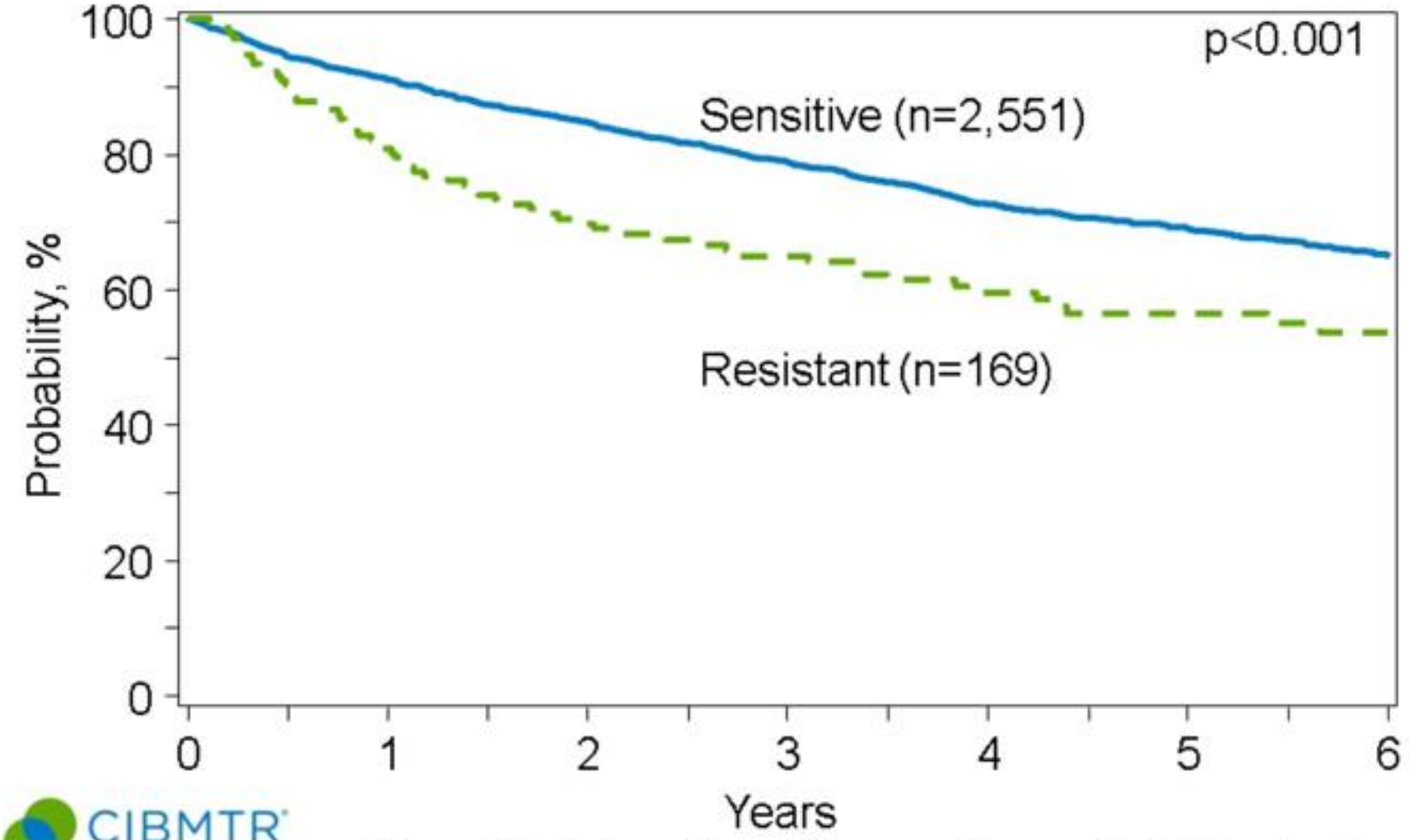
# Survival after Autologous HCT for Follicular Lymphoma, 2004-2014

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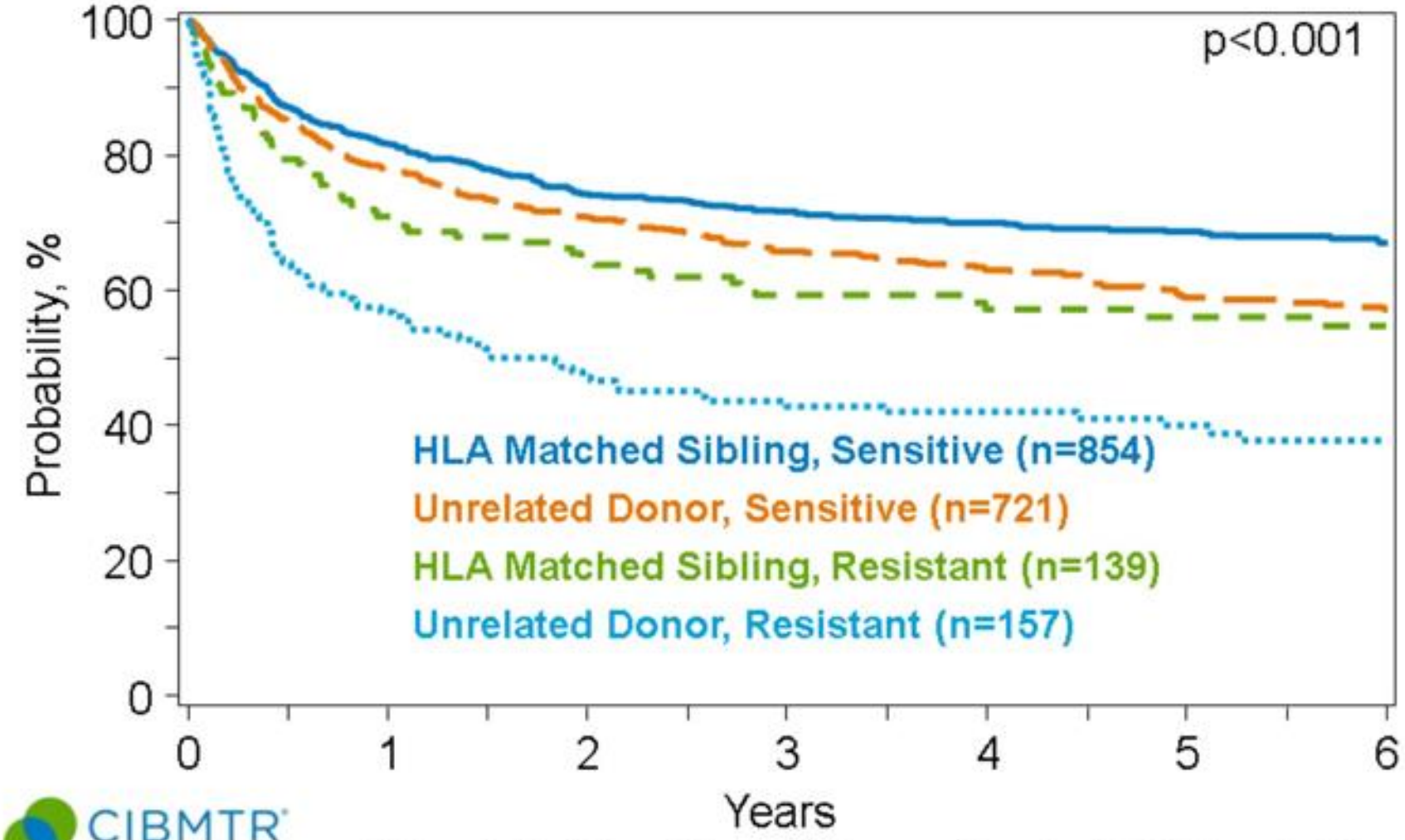
# Survival after Allogeneic HCT for Follicular Lymphoma, 2004-2014

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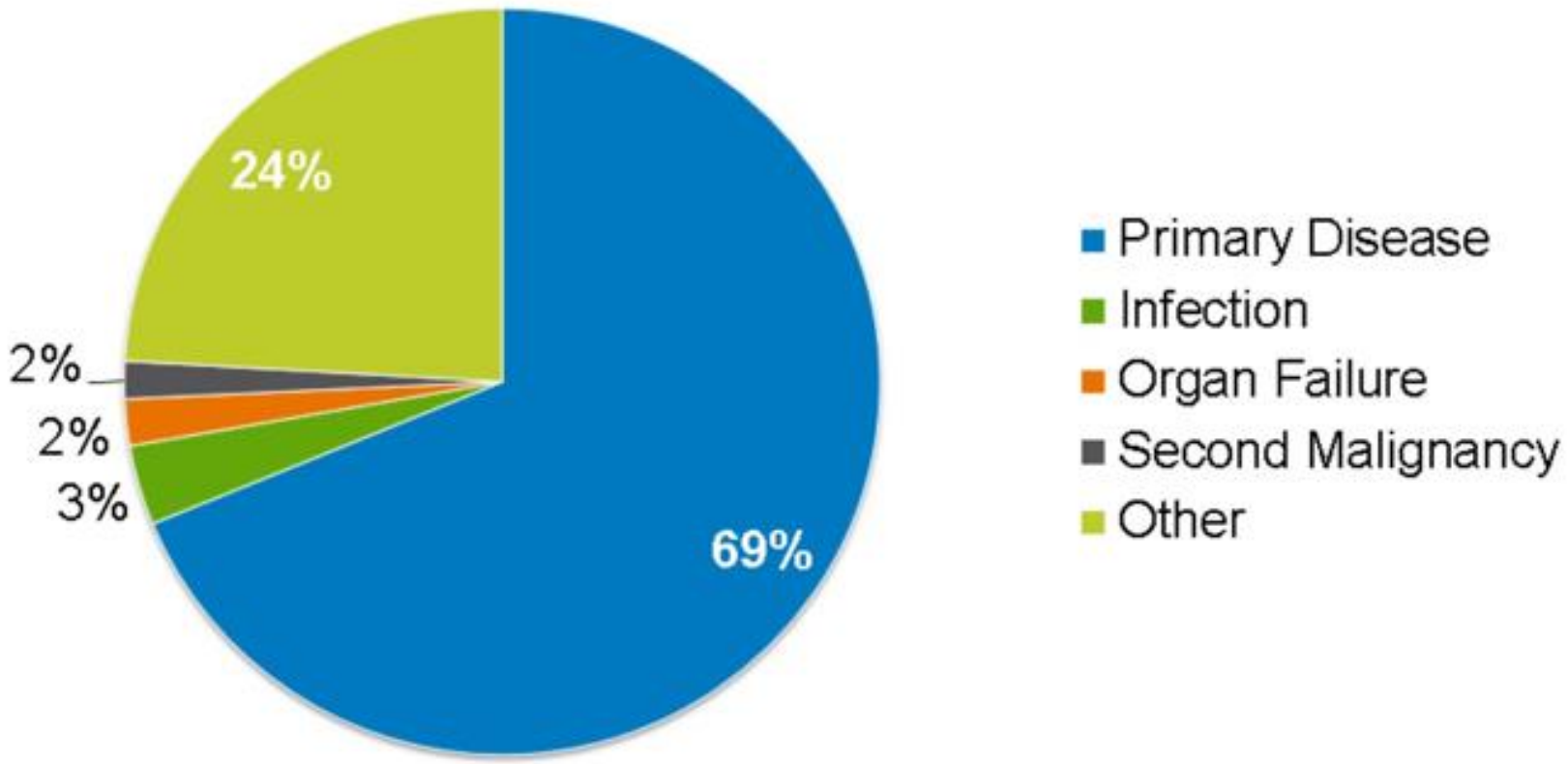
# Causes of Death after Autologous HCT done in 2013-2014

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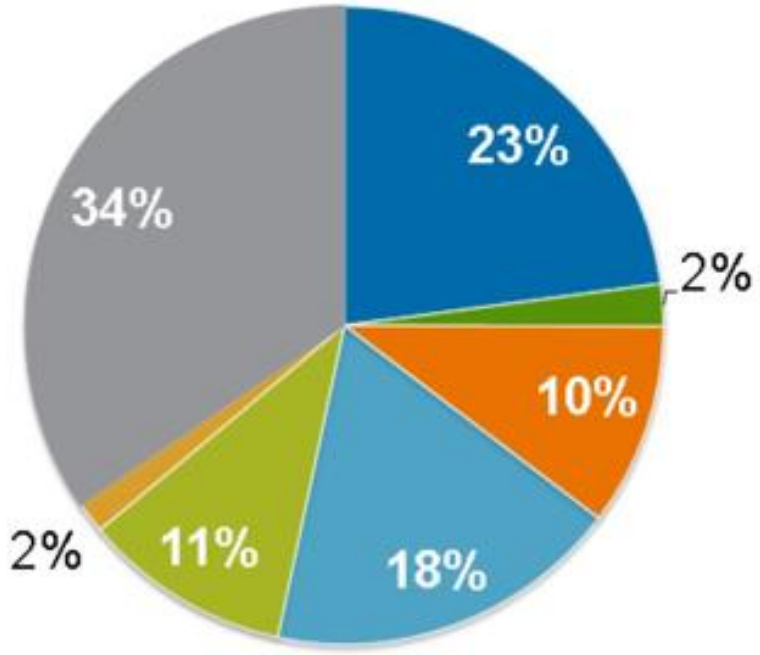
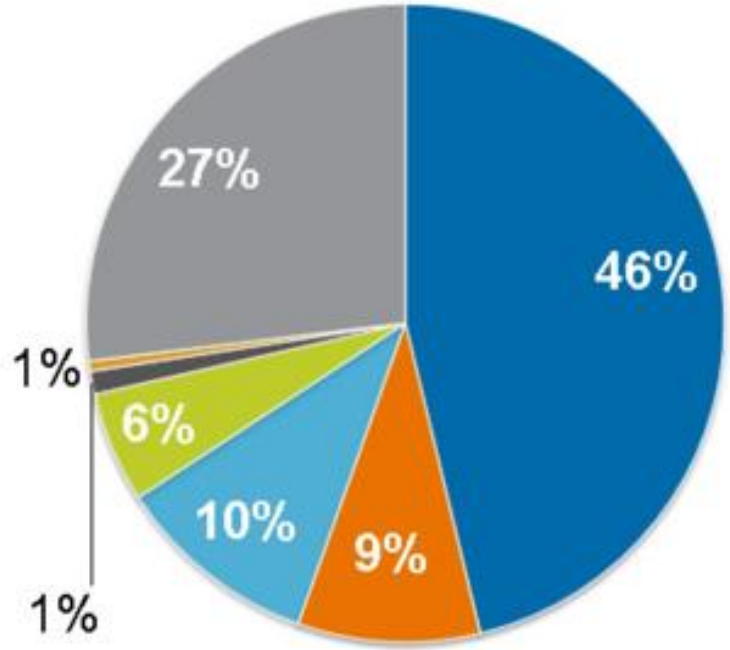
# Causes of Death after Unrelated Donor HCT done in 2013-2014

Died within 100 days post-transplant




- Primary Disease
- Graft Rejection
- GVHD
- Infection
- Organ Failure
- Hemorrhage
- Other

Died at or beyond 100 days post-transplant




- Primary Disease
- GVHD
- Infection
- Organ Failure
- Secondary Malignancy
- Hemorrhage
- Other

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# Conclusions

- In the current era, almost all patients will have a suitable donor
- Optimal timing of HCT is critical to good outcomes
- Early referral to the transplant center ensures that the RIGHT patient gets transplanted at the RIGHT time with the BEST graft source
- Post transplant survivors are at risk for early and late complications months to years following HCT and need ongoing screening, preventive care and follow up