

Hematopoietic Cell Transplantation for Myelofibrosis and CMML

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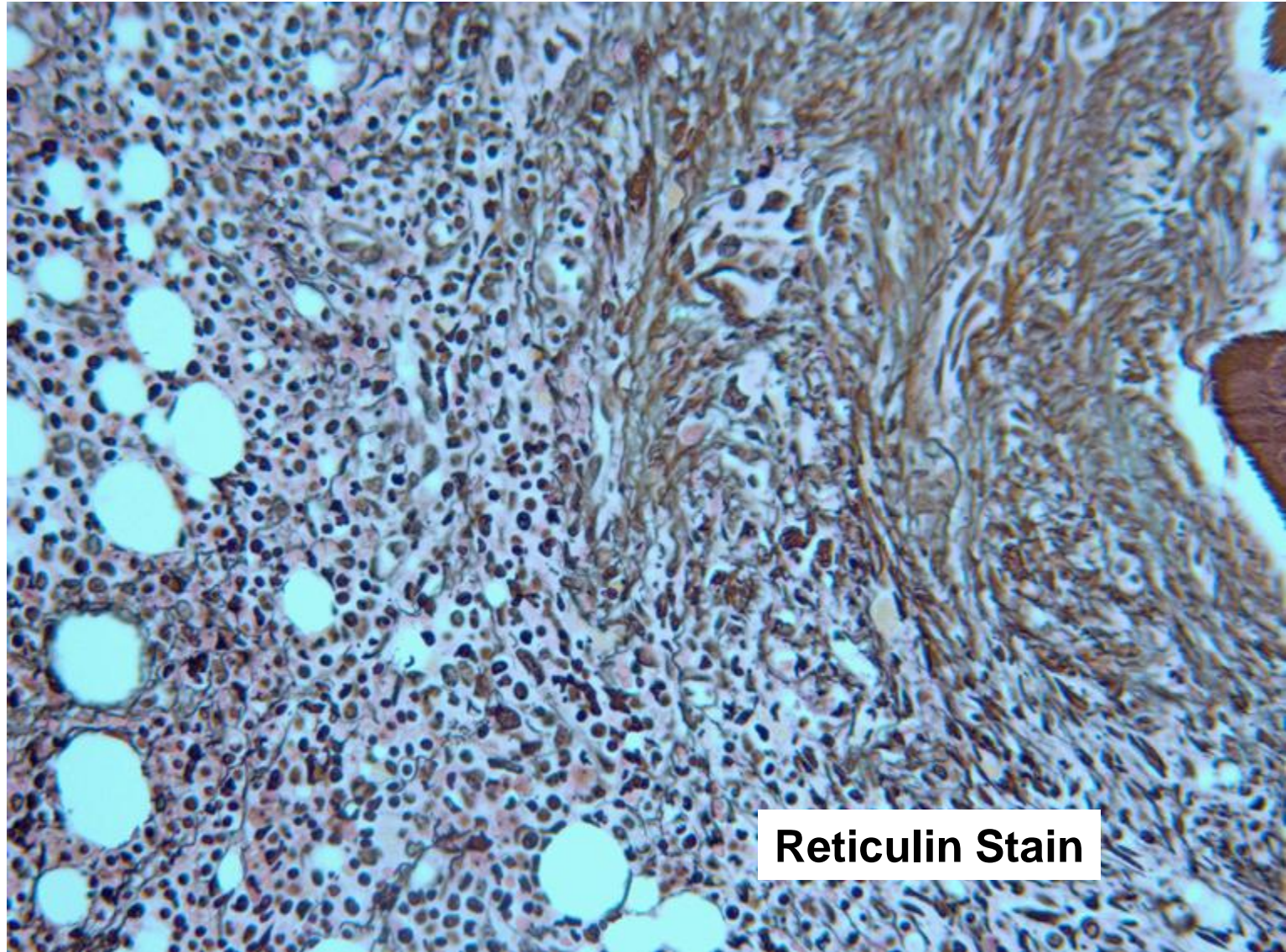
I will discuss:

- **Rationale for hematopoietic cell transplantation (HCT)**
- **Diagnoses to be considered**
- **Indications for Transplantation**
- **Transplant results in MF**
- **Transplant results in CMML**
- **Summary and conclusions**

**Myelofibrosis, PV and ET
are diseases of blood forming
stem cells:**

***Therefore, we should be able to cure
them by
replacing the patient's stem cells
with healthy stem cells.***

PMF *Pre* -Transplant



Risk Factors

(Defined in Non-Transplanted Patients)

- **Anemia (need of transfusions)**
- **Leukocytosis**
- **Circulating myeloblasts**
- **Age (> 65 years)**
- **Constitutional symptoms**

- **Cytogenetics**
- **Platelet count**

FHCRC Transplant Cohort: Patients and their Disease

- Number of patients 184
- *Age (ys), range (median)* 12 – 78 (51)
- Diagnoses
 - PMF 114
 - ET 46
 - PV 23
 - Other 1
- *Risk factors (by IWG)*
 - *Hgb <10* 119
 - *Circulating blasts >1%* 107
 - *Constitutional Symptoms* 83
 - *Leukocytosis > 25 k* 46
 - *Age >65* 9

IWG (Non-Transplant) Classification

applied to patients transplanted at FHCRC

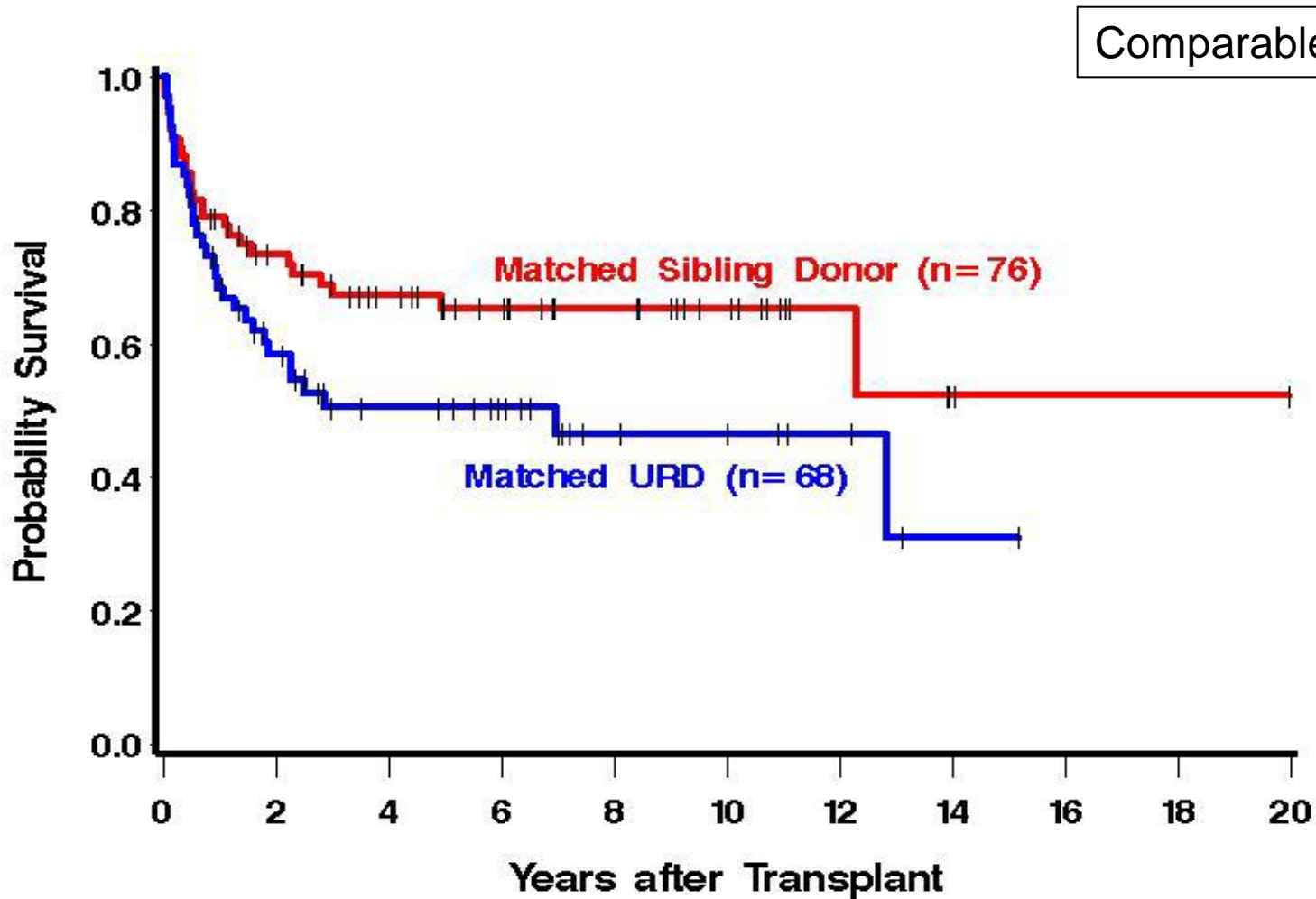
Donors

- Autologous (patient's own cells) 12
- Healthy donor 172
 - Related
 - HLA identical sibling 75
 - Syngeneic 3
 - HLA non-identical 8
 - Unrelated
 - HLA matched 68
 - HLA non-identical 18

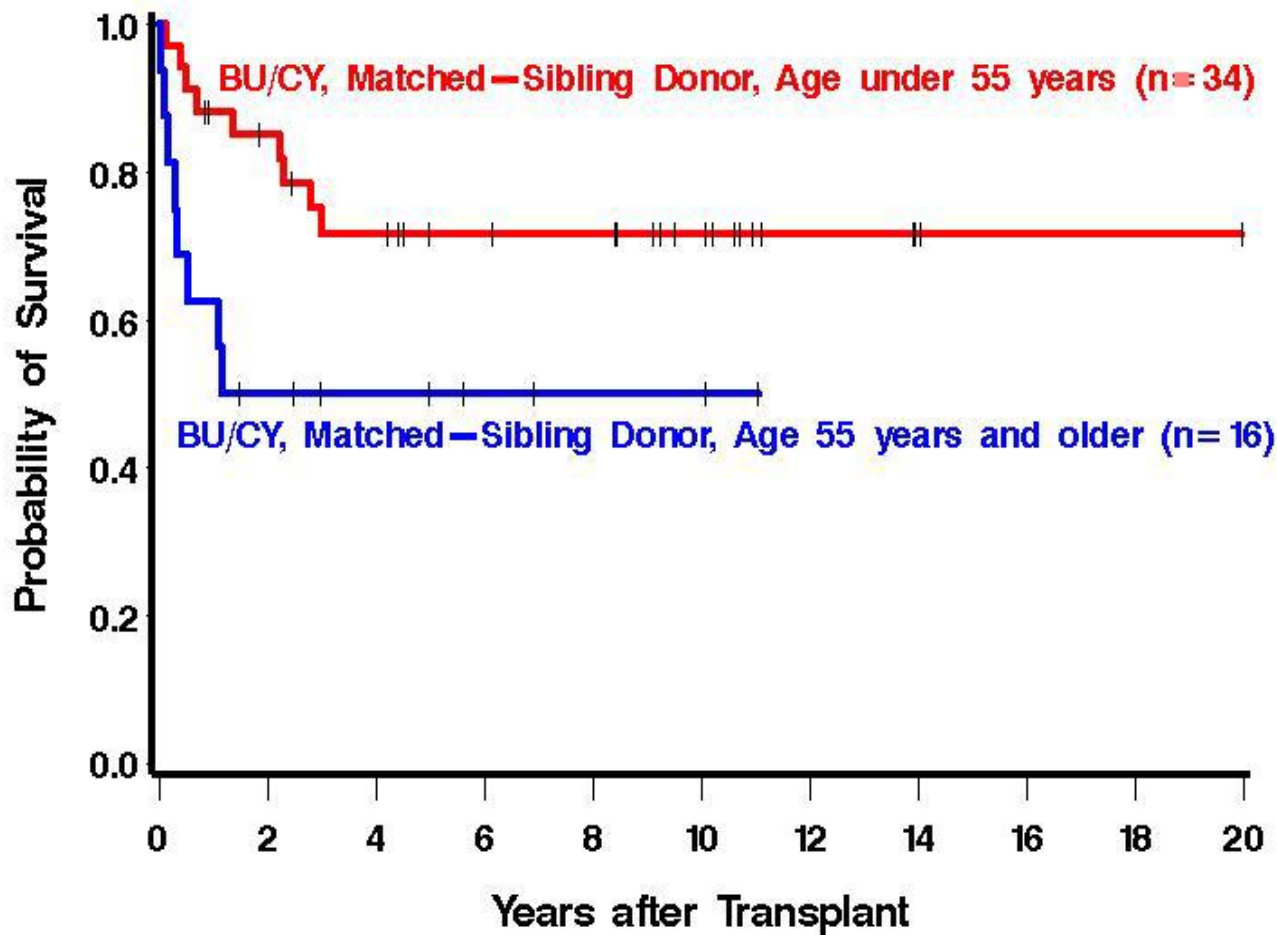
Transplant Procedure

| | | |
|---------------------------------------|-----|-----------------------|
| • Conditioning (excluding autologous) | | |
| – (t)BU + CY ± ATG | | } 108 No Radiation |
| – CY + (t)BU | 19 | |
| – Flu + BU ± ATG | 10 | } Radiation |
| – BU + (high dose)TBI | 10 | |
| – Flu + (low dose) TBI | 13 | |
| – Other | 12 | |
| • GVHD prophylaxis | | |
| – CSP + MTX | 102 | |
| – Tacrolimus + MTX | | 49 |
| – MMF ± Other | 18 | |
| – None | 3 | |
| • <i>Stem cells</i> | | |
| – <i>Marrow</i> | 46 | |
| – <i>PBPC</i> | 138 | |

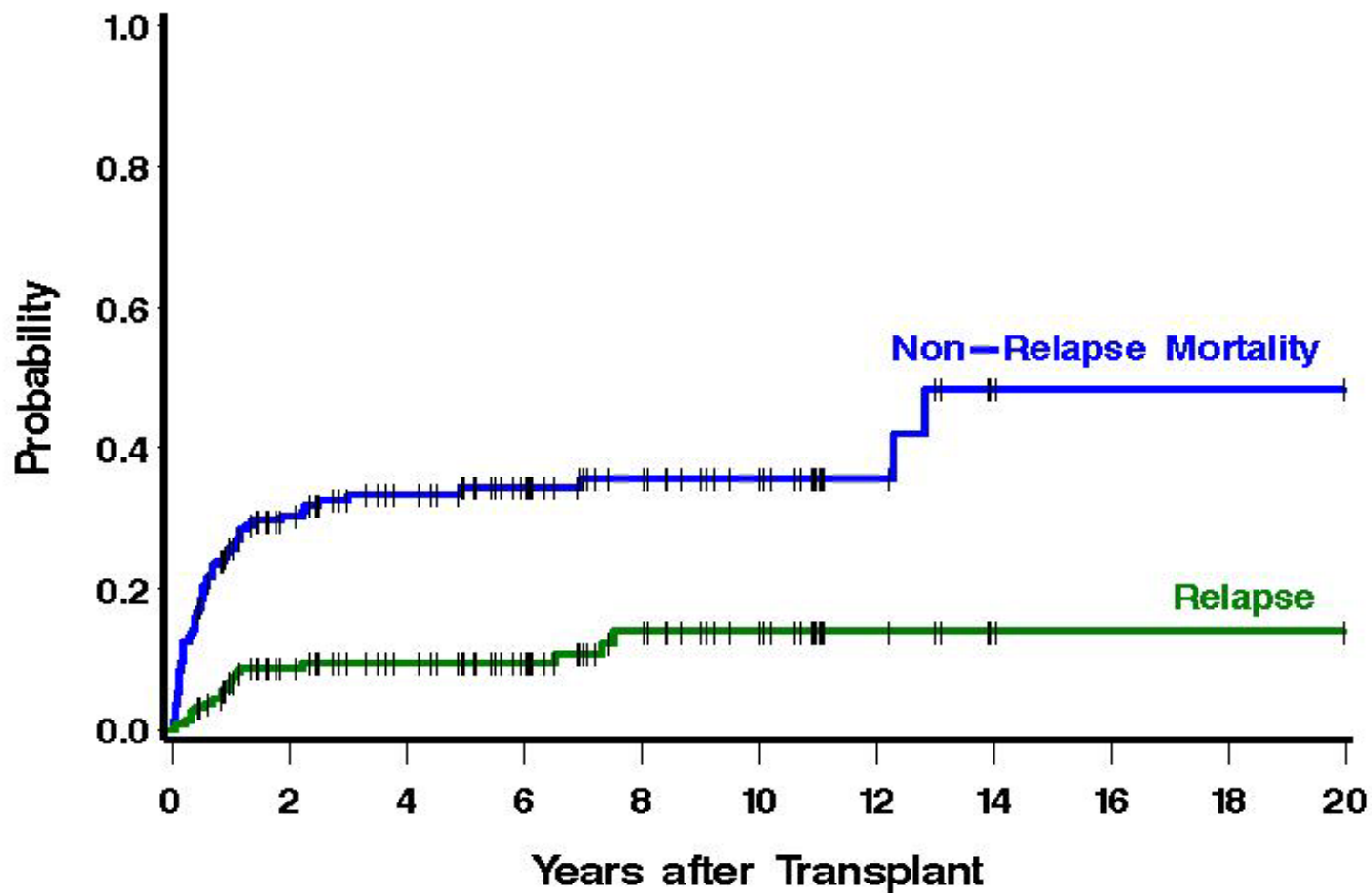
Relapse-Free Survival by *Donor Type*



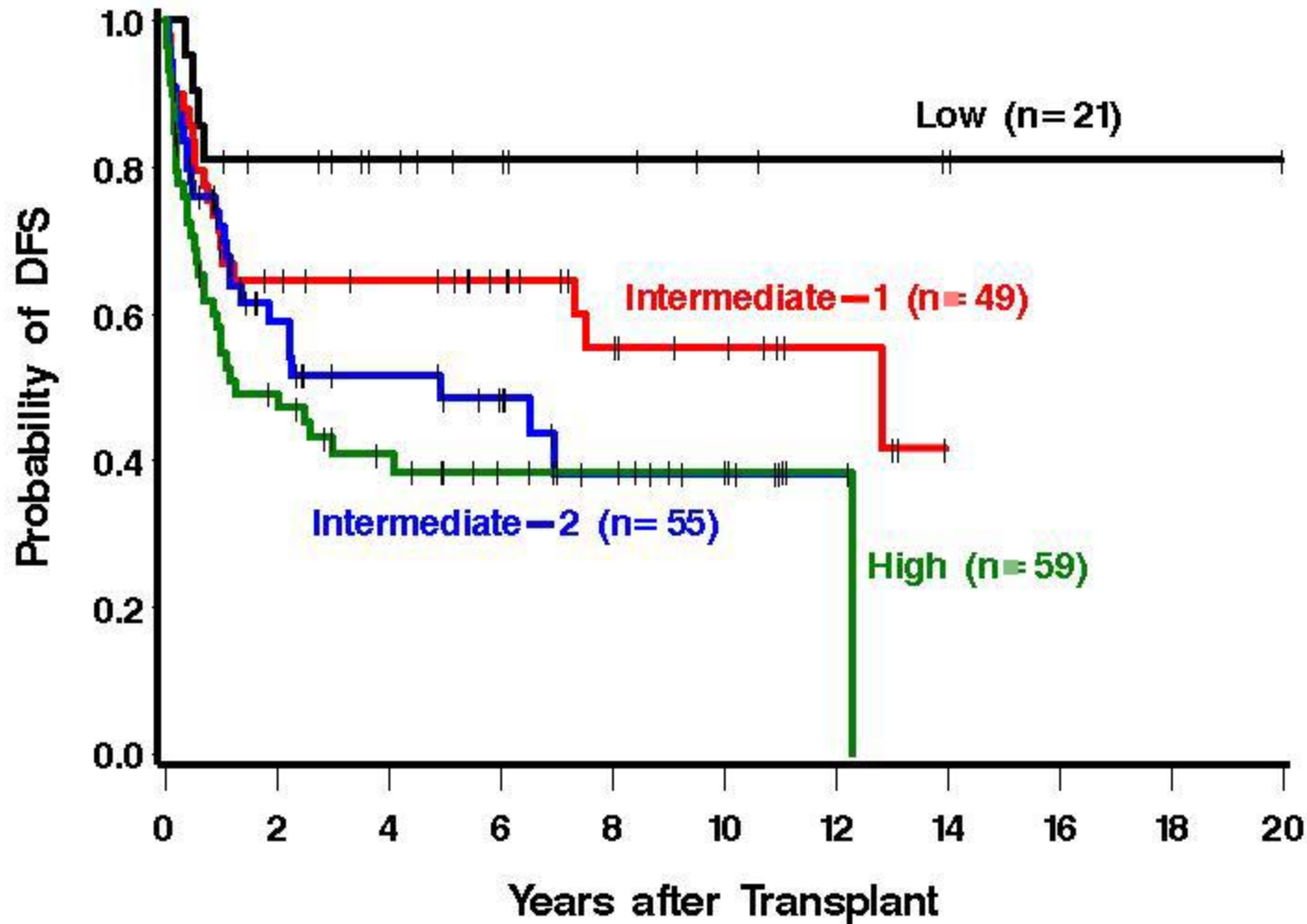
Relapse-Free Survival HLA Matched Siblings, *by Age*



Relapse and Non-Relapse Mortality



Relapse-Free Survival by IWG

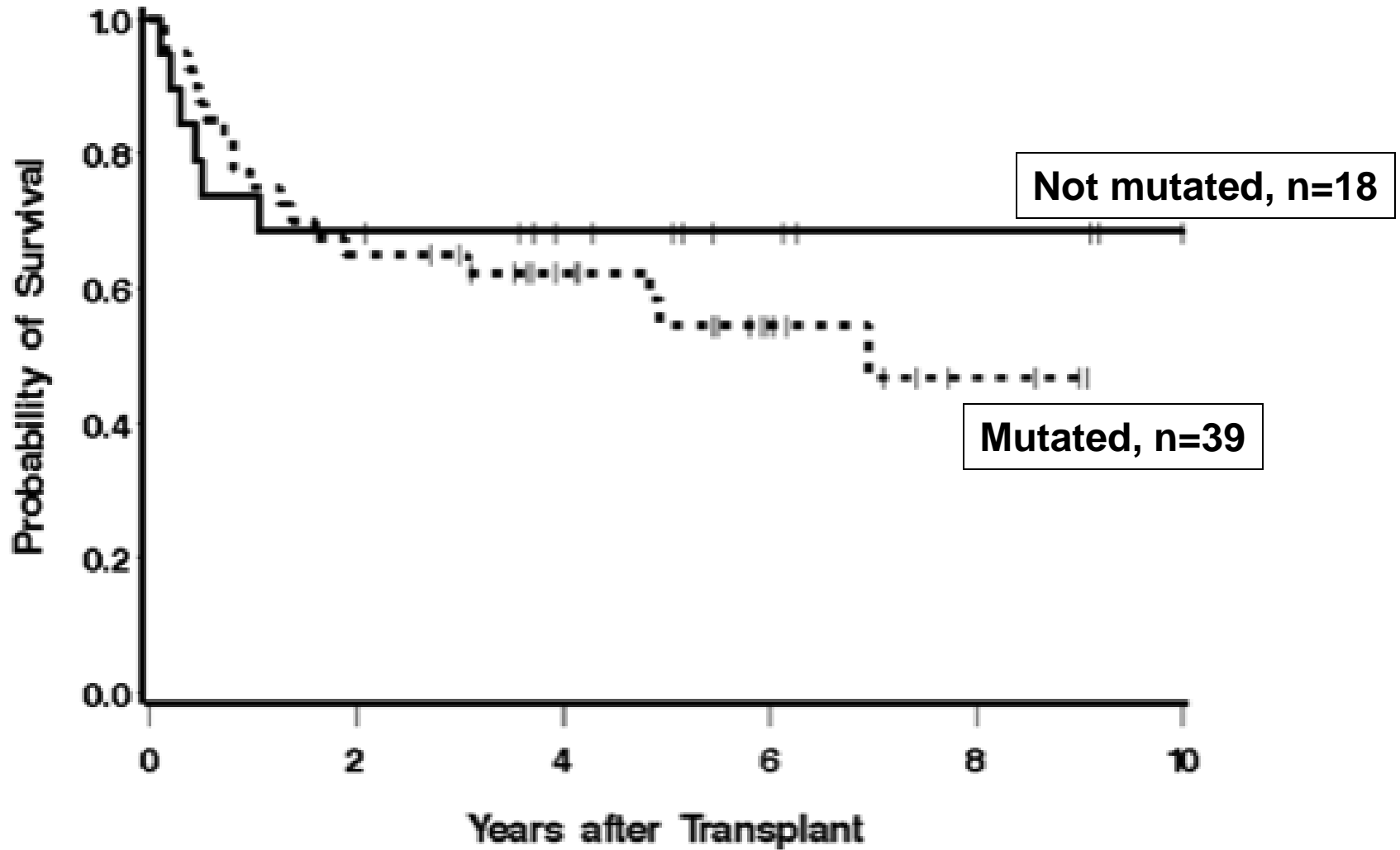


Multivariable Analysis

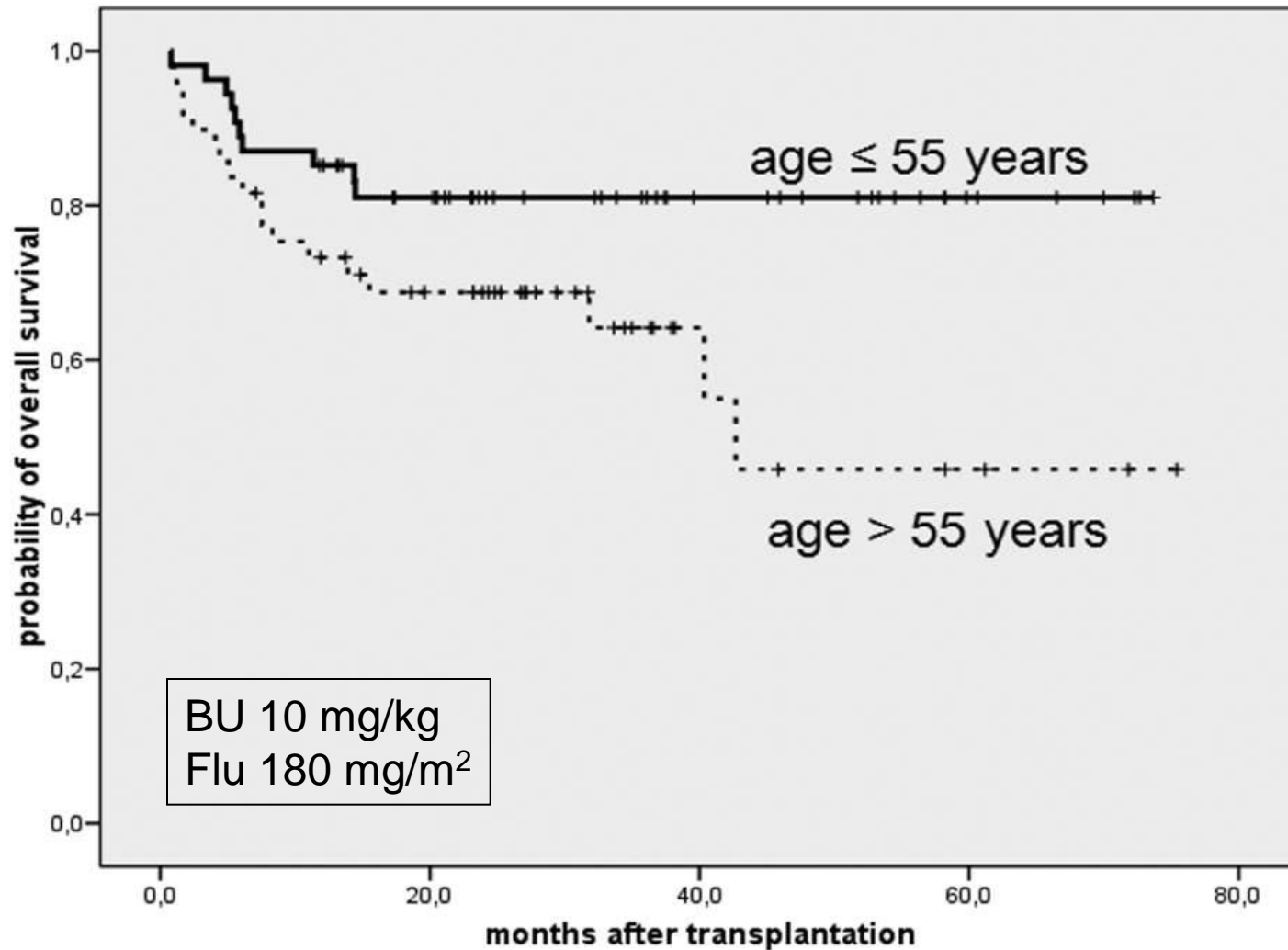
FHCRC Transplant Cohort

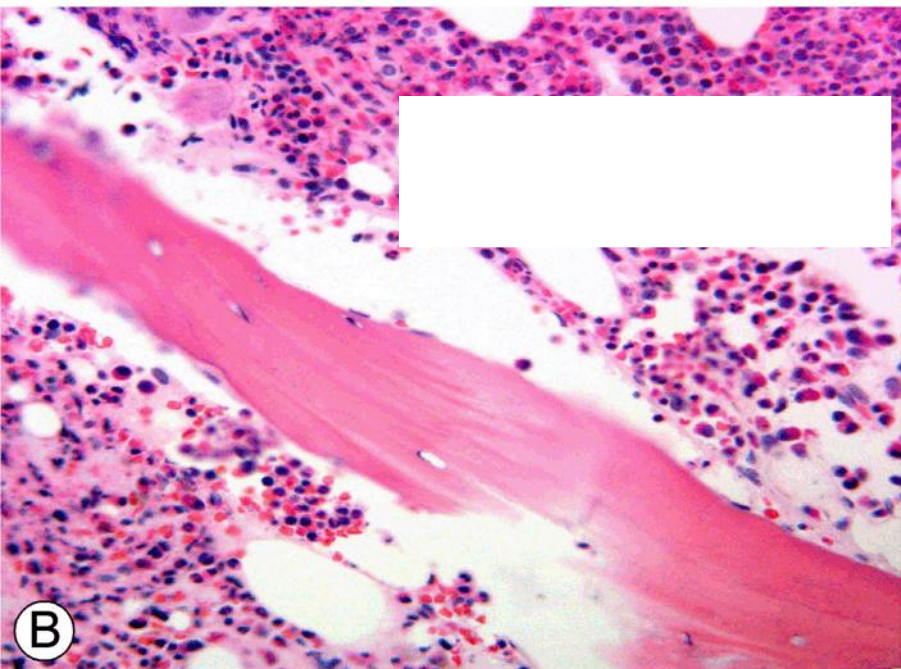
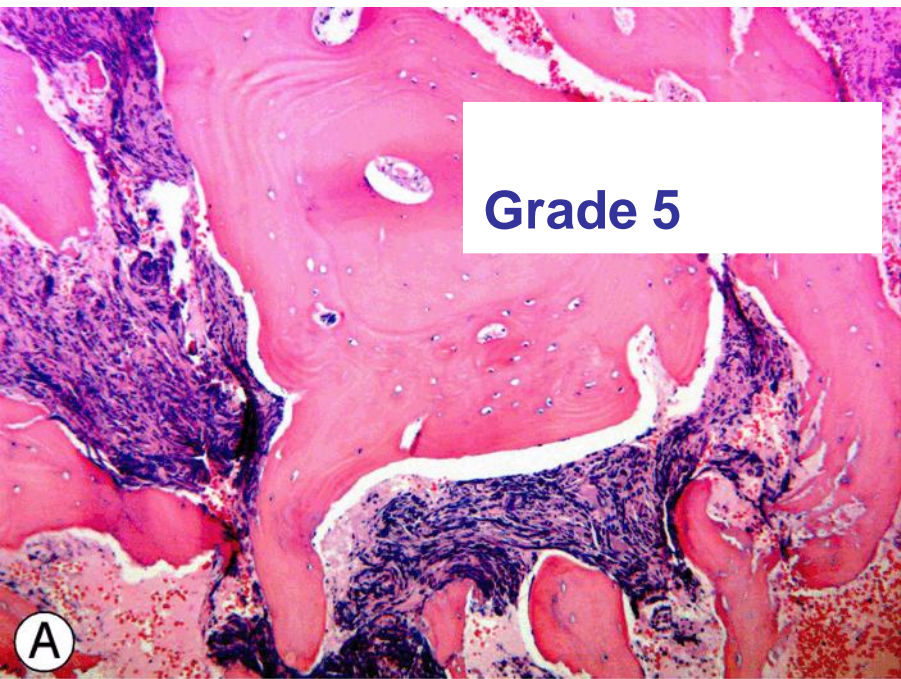
| Outcome by IWG | HR | CI | P value |
|------------------------------|-------------|-------------------|------------------|
| Overall Mortality | | | |
| Low | 1 | | |
| int-1 | 1.92 | 0.65-5.71 | 0.24 |
| Int-2 | 3.18 | 1.10-9.26 | 0.03 |
| High | 4.47 | 1.58-12.67 | <0.005 |
| Relapse | | | |
| Low | 0.00 | 0.00-0.00 | 0.99 |
| Int-1 | 1.04 | 0.40-2.70 | 0.94 |
| Int-2 | 0.60 | 0.20-1.89 | 0.38 |
| High | 1 | | |
| Non-Relapse Mortality | | | |
| Low | 1 | | |
| Int-1 | 1.41 | 0.45-4.42 | 0.56 |
| Int-2 | 3.11 | 1.05-9.52 | 0.04 |
| High | 3.80 | 1.30-11.08 | 0.01 |

Survival after HCT by JAK 2 mutation (V617F)



HCT for MF After Conditioning with BU + FLU





**Osteosclerosis:
Regression after
*high dose
conditioning* and
HCT
(H&E; x250)**

CMML

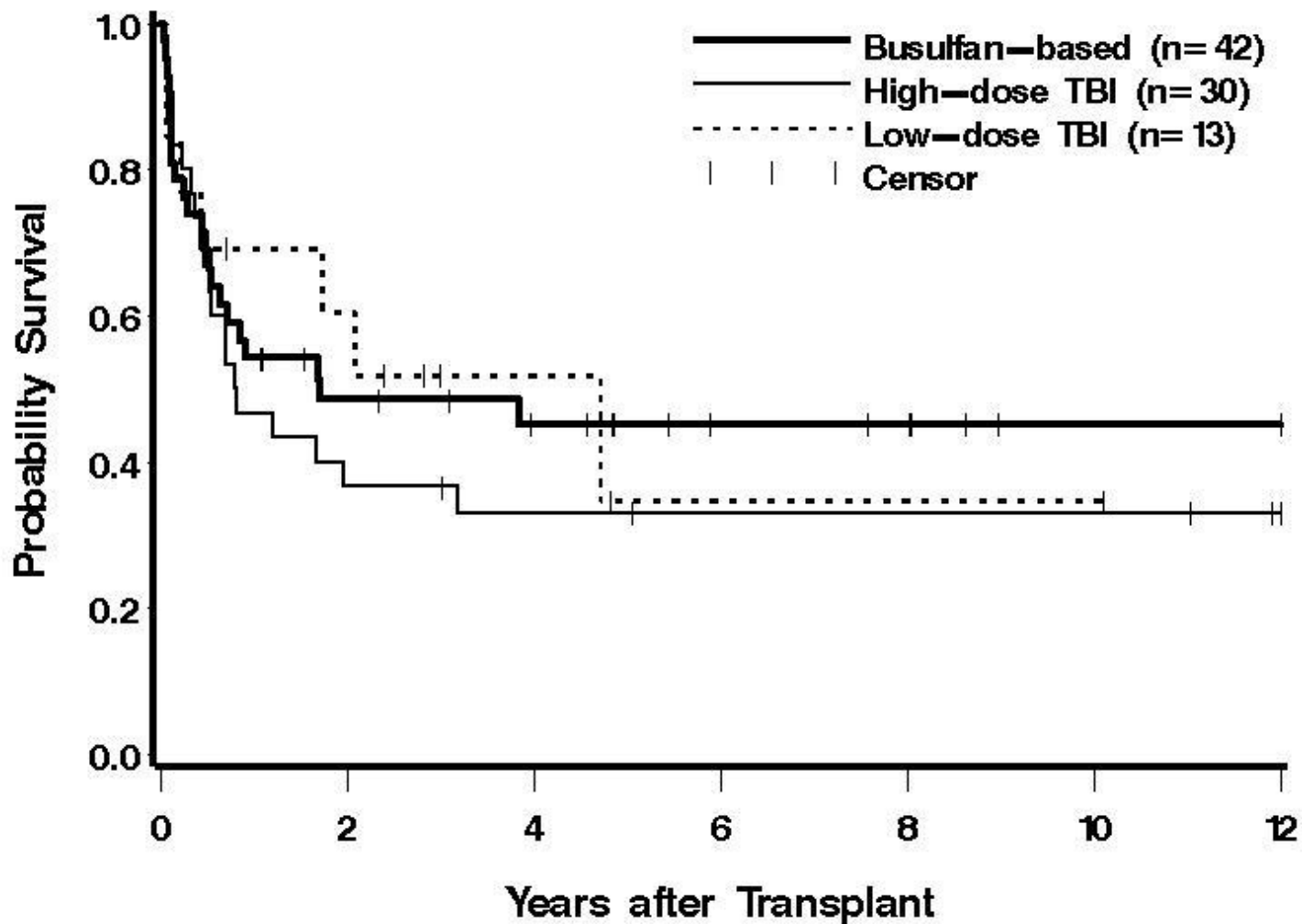
| Variable | | Number of Patients |
|--|----------------------|--------------------|
| Number of patients | | 85 |
| Age (years), range (median) | 1–69.1 (51.7) | |
| Sex (male/female) | | 52/33 |
| Diagnosis | | |
| WHO | | |
| CMML 1/2 | | 57/26 |
| MDAPS | | |
| Low | | 32 |
| Intermediate-1/2 | | 23/17 |
| High | | 8 |
| Hematology Parameters median (range) | | |
| WBC (x 10 ⁹ /L) | 7.38 (0.08–85.5) | |
| Lymphocytes (x 10 ⁹ /L) | 1.55 (0-12.83) | |
| Platelets (x 10 ⁹ /L) | 63 (7-882) | |
| Hemoglobin (gm/dL) | 10.5 (7.2-15.7) | |
| Cytogenetics risk (by IPSS) | | |
| Good/intermediate/poor | | 45/14/22 |
| Pre-transplantation therapy | | |
| None or Transfusion only | | 13 |
| Cytoreductive with or without HU | | 49 |
| Splenectomy with or without other treatment modalities | | 15 |
| Other modalities | | 19 |

CMML: Patients and their Disease

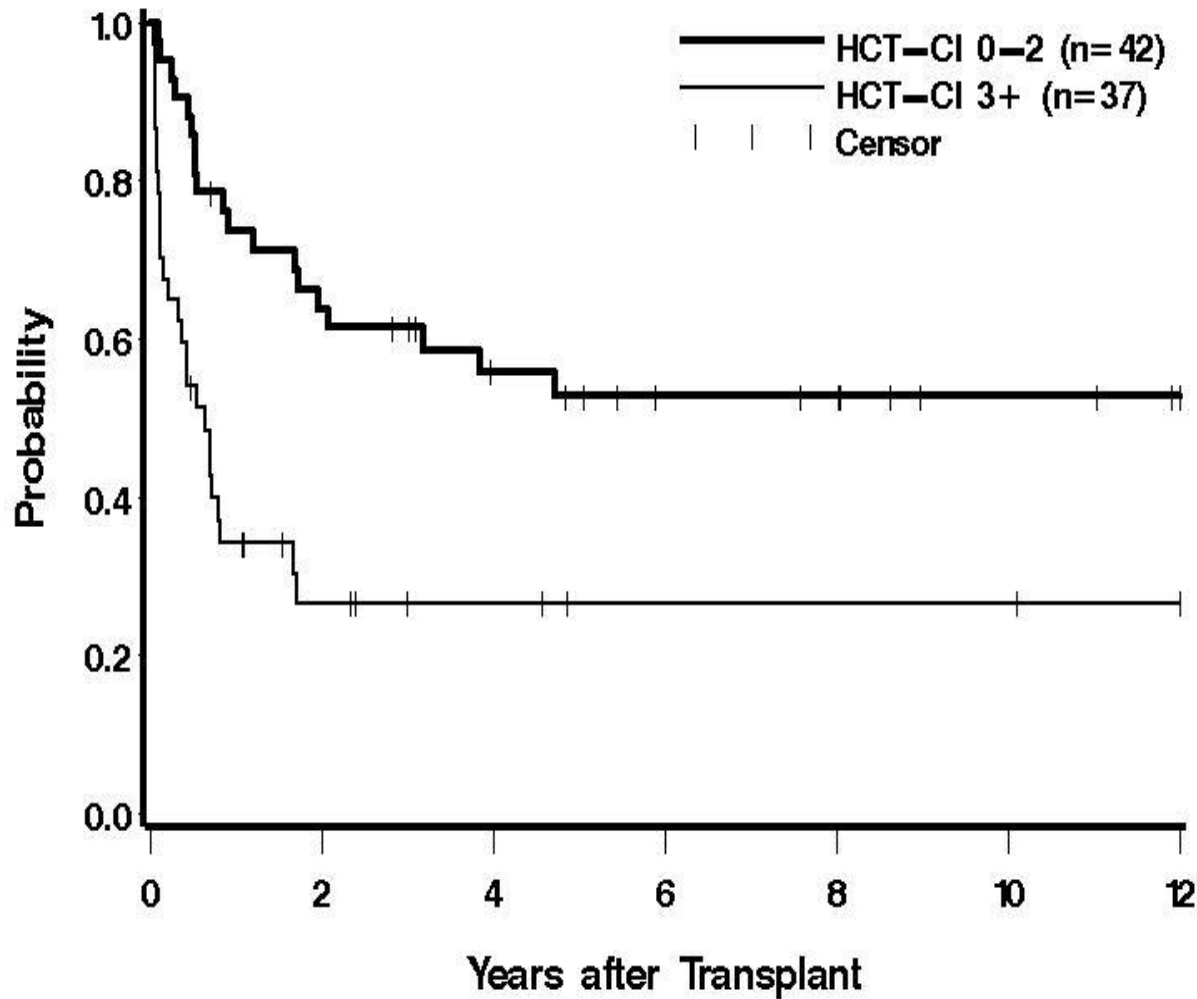
CMML: Donor and Transplant Characteristics

| Variable | Number of Patients |
|--|--------------------|
| Donor age (yrs), range(median) | 3.4–69.1 (40.1) |
| Donor patient relationship | |
| –Related | |
| HLA-identical sibling/other | 32/6 |
| –Unrelated | |
| HLA-matched/mismatched | 39/8 |
| Conditioning regimen | |
| BU (7 mg/kg)/CY (50 mg/kg)/TBI (12 Gy) | 10 |
| BU (7 mg/kg)/TBI (12 Gy) | 11 |
| BU (16 mg/kg)/CY (120 mg/kg)/THY (4.5 mg/kg) | 29 |
| CY (120 mg/kg)/TBI (14.4 or 13.2 Gy) | 8 |
| TBI (2-3 Gy) ± FLU (90 mg/m ²) | 6 |
| FLU (120 mg/m ²)/BU (16 mg/kg) | 12 |
| TBI (2 Gy)/iodine 131-anti-CD45 antibody | 6 |
| FLU (150 mg/m ²)/Treosulfan (3×14 g/m ²) | 3 |
| GVHD prophylaxis | |
| CSP+MTX/+MMF/+other | 44/12/6 |
| FK506+MTX/+MMF | 20/3 |
| Source of Stem Cells | |
| Marrow | 32 |
| PBPC | 53 |

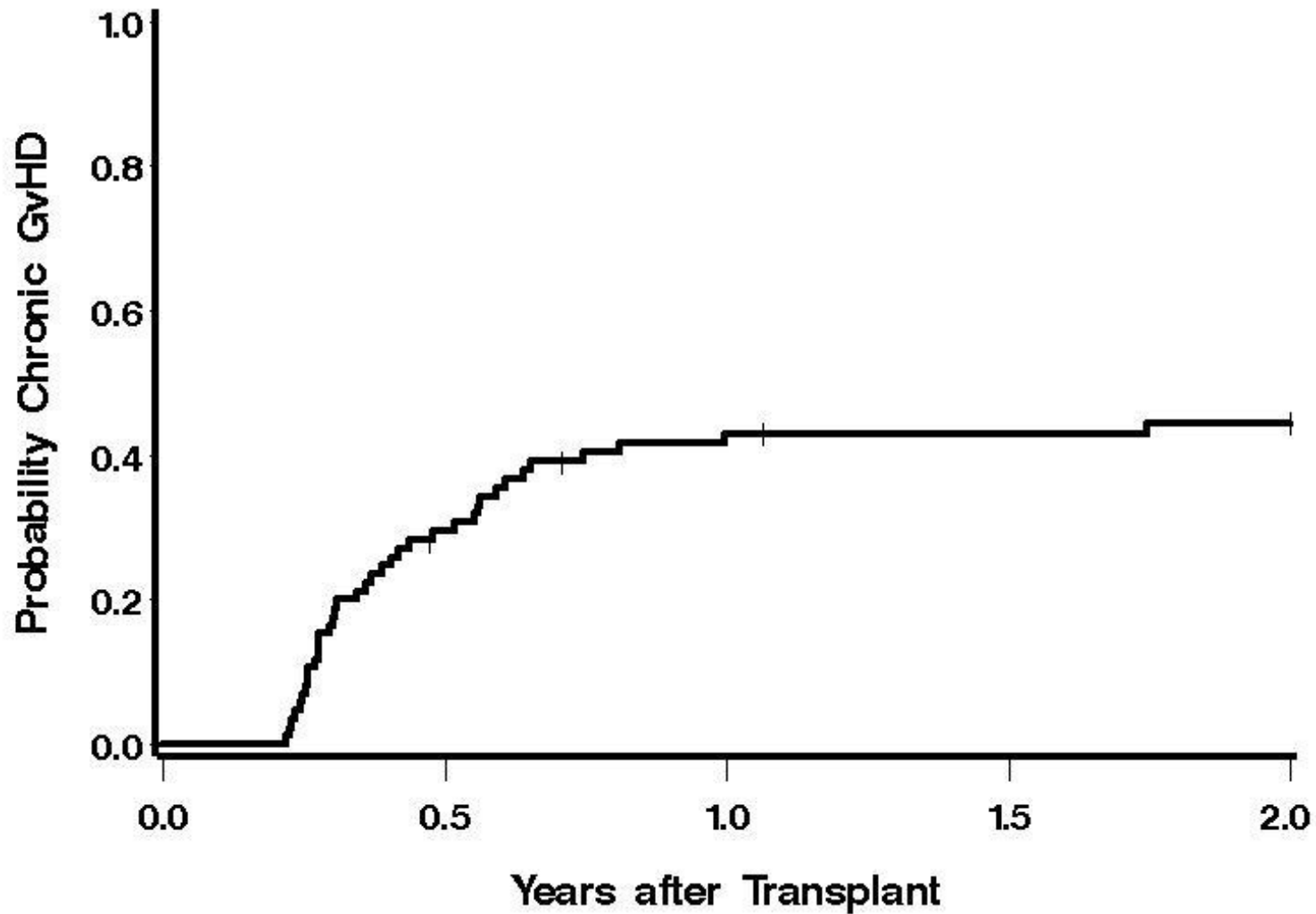
CMML: Survival by Conditioning Regimen



CMML: Other illnesses have a negative effect on transplant outcome



CMML: Incidence of Chronic GVHD

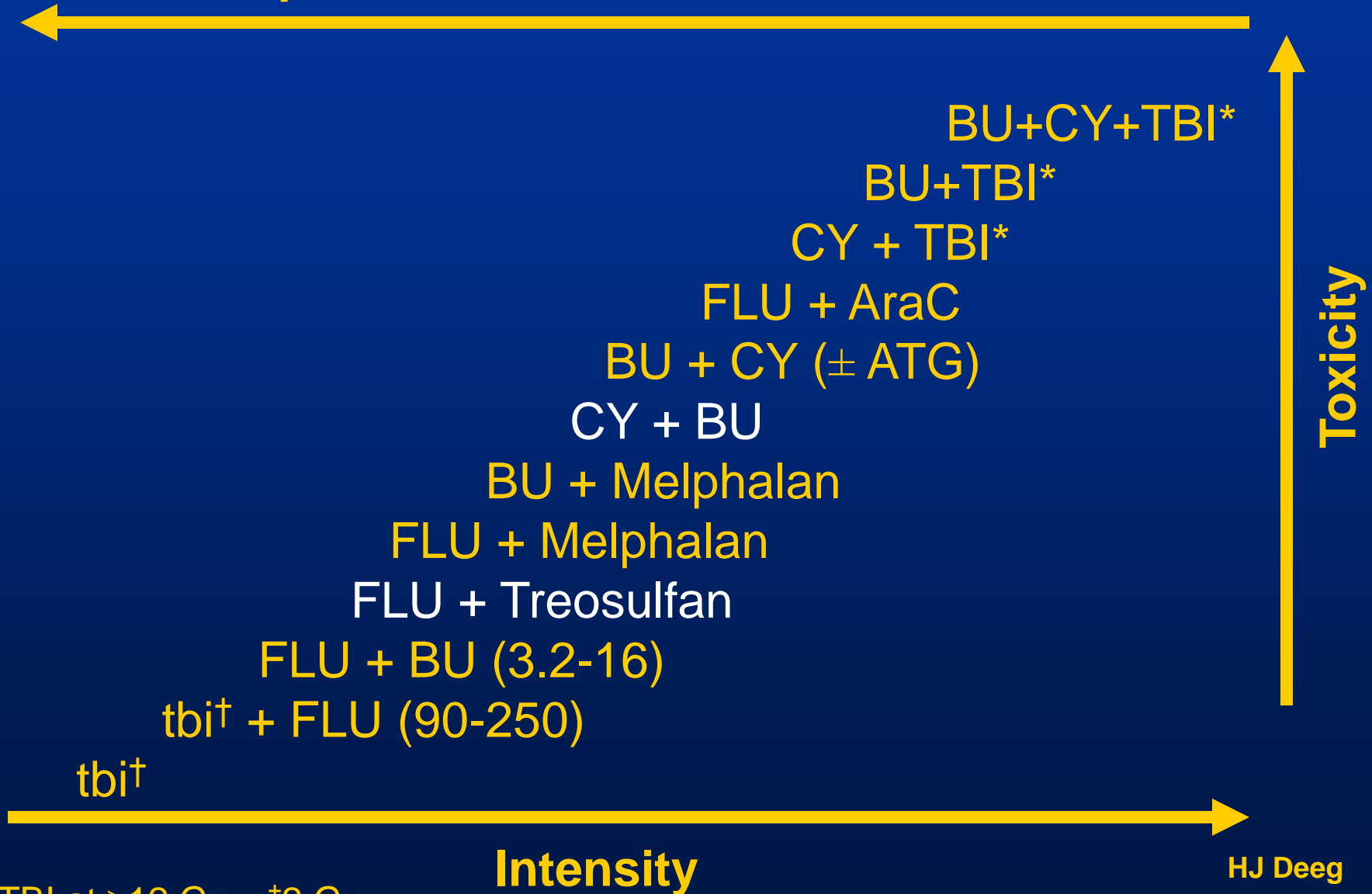


CMML: Multivariable Analysis of Outcomes

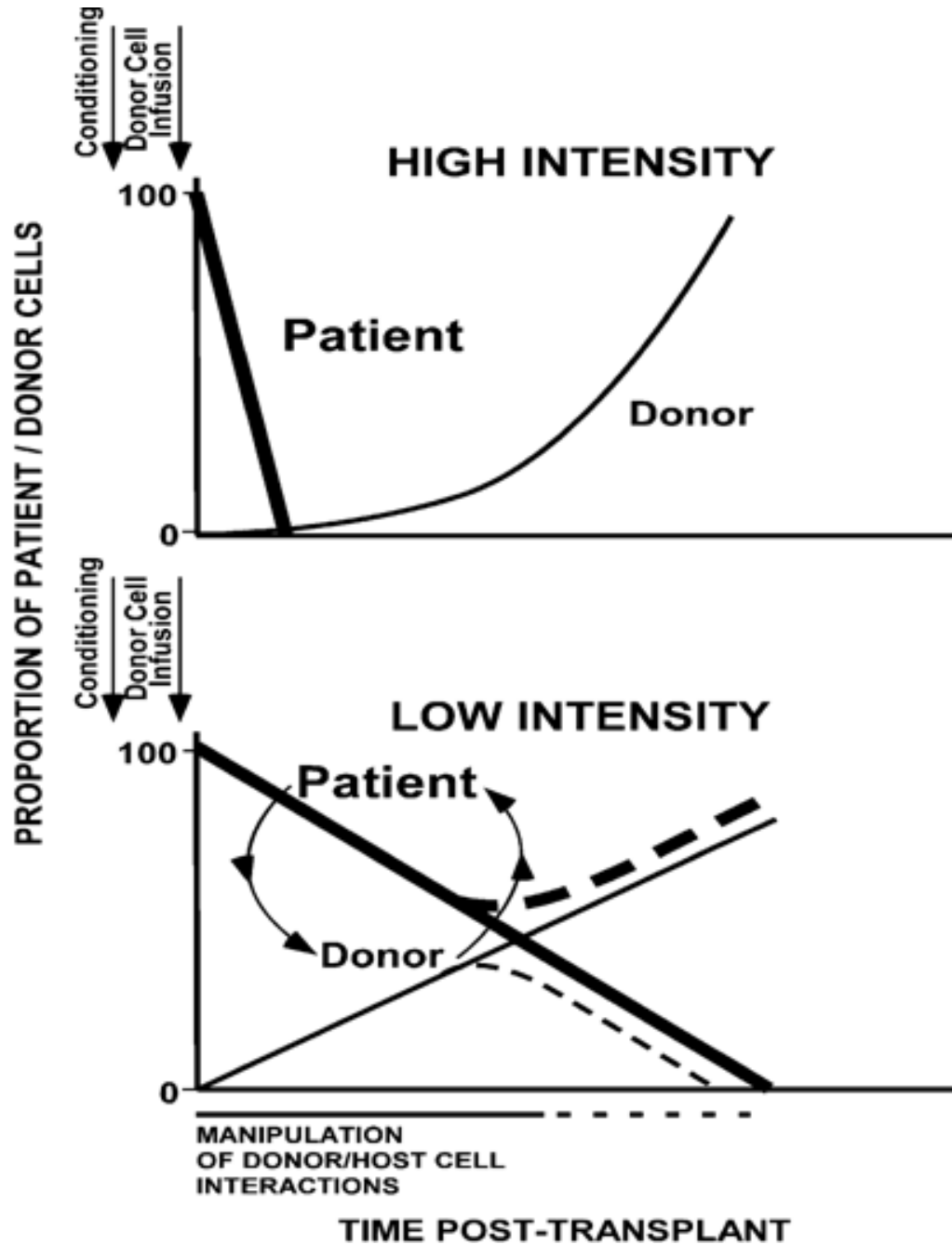
| | Relapse | NRM | Mortality or Relapse | Overall Mortality |
|----------------------------|-------------------------------|-----------------------------------|------------------------------------|-----------------------------------|
| MDAPS | 1.65 (p=.01) | | | |
| Hematocrit | | 0.92 (p=.06) | | 0.94 (p=.04) |
| HCT-CI | | | | |
| 0-2 | | 1 | 1 | 1 |
| >2 | | 3.97 (p=.004) | 2.46 (p=.004) | 2.62 (p=.004) |
| Cytogenetics (IPSS) | | | | |
| Good/Interm. | | 1 | 1 | 1 |
| Poor | | 3.09 (p=.02) | 3.35 (p=.0003) | 2.73 (p=.004) |
| Age | | 1.04 (p=.06) | 1.03 (p=.009) | 1.03 (p=.02) |

Conditioning Regimens

Required Contribution of GVT Effect



*TBI at ≥ 12 Gy; †2 Gy;



Donor/Host Interactions: High Intensity versus Low Intensity Conditioning

Summary and Conclusions

- **Transplantation is curative for a large proportion of patients with myeloproliferative diseases**
- **Non-transplant prognostic classification also impacts transplant results**
- **Pre-HCT comorbidities have a major impact on outcome**
- **With modifications of conditioning results have improved progressively**
- **Patients with early/low grade disease do best**
- **Select patients in the 7th or even 8th decade of life may be eligible for HCT**
- **Outcome with HLA matched unrelated donors is similar, but not identical to that with HLA identical siblings**

Thank you

- Bart Scott
- Ted Gooley
- Olga Sala-Torra
- Hesham Eissa
- Andrew Rezvani
- And of course all our patients