Hematopoietic Cell Transplantation for Myelofibrosis

H.Joachim Deeg MD
Fred Hutchinson Cancer Research Center &
University of Washington, Seattle WA

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The following diagnoses will be included in our discussion:

- **Primary Myelofibrosis (PMF)**
- **Polycythemia vera (PV)**
- **Essential Thrombocythemia (ET)**

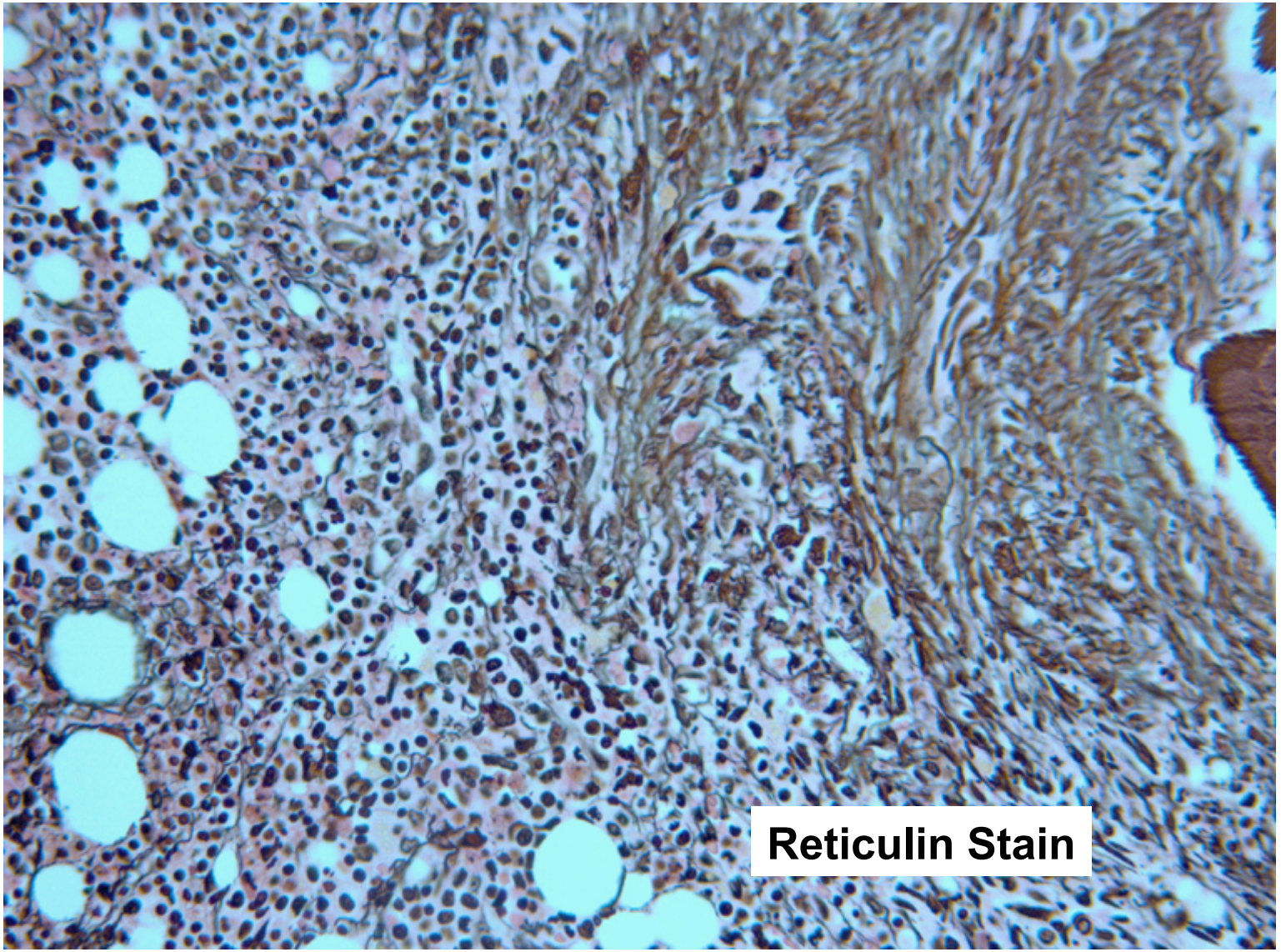
Outline

- **Why transplant patients with myelofibrosis?**
- **How safe is transplantation?**
- **How effective is transplantation?**
- **Who should be transplanted and when?**
- **Summary and conclusions**

Myeloproliferative neoplasms (MPN) – which cause myelofibrosis – are diseases of blood forming stem cells:

Therefore, it should be possible to cure them by replacing the patient's stem cells with healthy stem cells.

PMF *Pre* -Transplant



Risk Factors (DIPSS)

-Developed for non-transplanted patients-

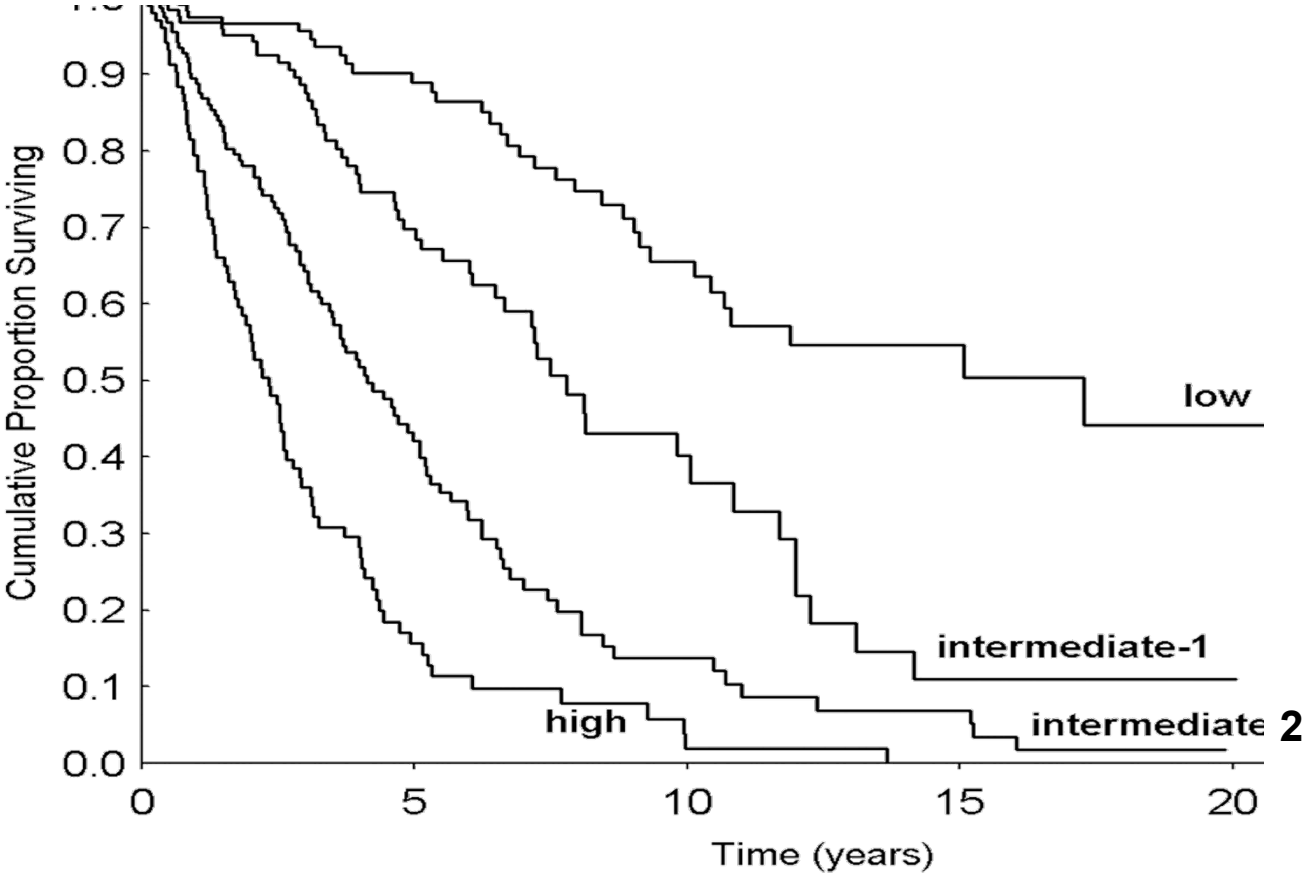
- Anemia
- WBC > 25,000
- Myeloblasts in blood
- Age (> 65 years)
- Symptoms

DIPPS

- Abnormal chromosomes
- Low platelet count
- Needing transfusions

DIPPS plus

Survival by DIPSS Category
(no transplant)



Passamonti F, et al. *Blood*. 2010;115:1703

Not included in current classifications:

- Severity of marrow fibrosis (and fibrosis in other organs)
- Spleen size (portal hypertemsion)
- Duration of the disease
- Mutations

Could those factors be important for transplantation?

- Severity of marrow fibrosis (and fibrosis in other organs) ►Non-relapse mortality
- Spleen size ►Delayed engraftment; difficult transfusion support
- Duration of the disease ►More comorbidities
- Mutations ► ?

Patient and Disease Characteristics

	Value
No. of patients	170
Age range y (median)	12.1–78.9 (51.5)
Sex, male/female, no (%) of patients	93 (55) / 77 (45)
Months from diagnosis to HCT (ms), range (median)	2-314 (15)
Type of myelofibrosis, no. (%)	
Primary	101 (59)
Secondary	69 (41)
Essential thrombocythemia	46 (67)
Polycythemia vera	22 (32)
Hairy cell leukemia	1 (1)
Cytogenetics no. (%)	
Favorable	17 (10)
Normal	88 (52)
Unfavorable	25 (15)
Other/unknown	40 (23)
JAK2 mutational status, no. (%)	
JAK2 wild-type	51 (30)
JAK2-V617F mutant	43 (25)
Not done	76 (45)

Scott *et al.*, *Blood* 119: 2657-2664, 2012

Patient and Disease Characteristics

	Value
Grade of bone marrow fibrosis, # (%)	
1	13 (8)
2	37 (22)
3	41 (24)
4	79 (46)
DIPSS components, # (%)	
Age > 65 years	9 (5)
Symptoms	79 (47)
Anemia (Hgb < 10 g/d)	120 (71)
WBC > 25 × 10^9/L	50 (29)
Blasts in blood ≥ 1%	95 (56)
Splenectomy, # (%)	
No	136 (80)
Yes	31 (18)
Unknown*	3 (2)
DIPSS Score # (%)	
Low	21 (12)
Intermediate-1	48 (28)
Intermediate-2	50 (30)
High	51 (30)

Scott *et al.*, *Blood* 119: 2657-2664, 2012

Transplant Characteristics

	N (%)
Conditioning for Allogeneic HCT, no. (%)	**167**
Bu* 16mg/kg oral + Cy 120 mg/kg	91 (54)
Bu* 16mg/kg oral + Cy 120 mg/kg + ATG	15 (9)
Cy 120 mg/kg + Bu* 16 mg/kg IV	**18 (11)**
Flu 120 mg/m^2 + Bu* 16 mg/kg oral	3 (2)
Flu 250 mg/m^2 + Bu* 16 mg/kg IV +ATG	4 (2)
Flu 120 mg/m^2 + Bu* 12.8 mg/kg IV +ATG	3 (2)
Bu* 16mg/kg oral + TBI 2 Gy	1
Bu 7 mg/kg oral + TBI 12 Gy	8 (5)
Cy 120mg/kg + TBI 12-14 Gy	5 (3)
Flu 150 mg/m^2 + Melphalan 140 mg/kg	3 (2)
Treosulfan 42 gm/m^2 + Flu 150 mg/m^2	1
Flu 90 mg/m^2 + TBI 2-3 Gy	**13 (8)**
I-131 + Flu 90 mg/m^2 + TBI 2 Gy	1
Cy 29 mg/kg + Flu 120 mg/m^2 + TBI 2 Gy + Cy 50 mg/kg†	1

*Busulfan was targeted to obtain plasma steady-state concentrations of 800 to 1000 ng/mL
†Haploidentical donor

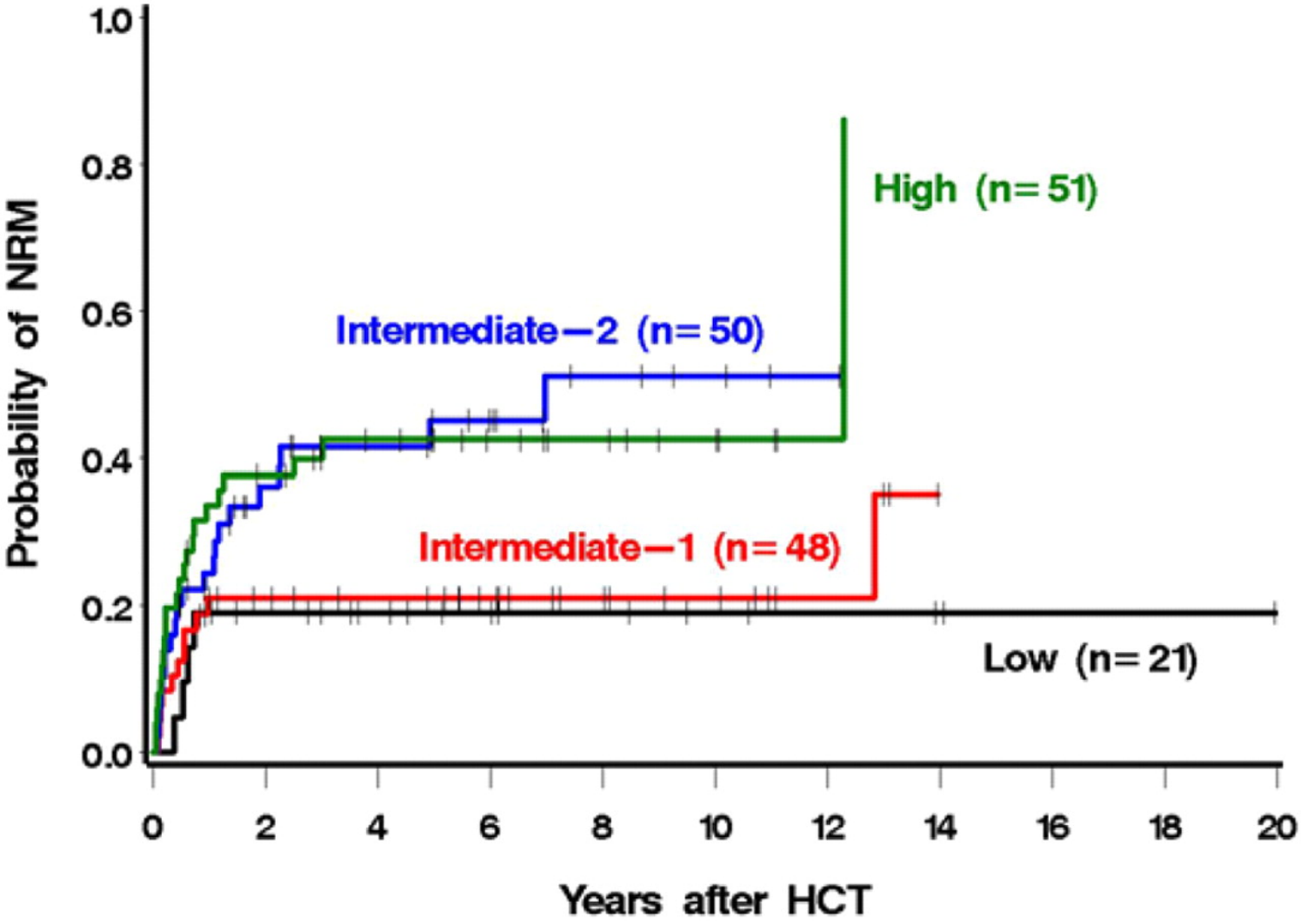
Scott *et al., Blood* 119: 2657-2664, 2012

Transplant Characteristics

	N (%)
Donor Type, # (%)	170
Syngeneic	3 (2)
Allogeneic	167 (92)
Related Donor	**83 (50)**
HLA-matched	79 (95)
HLA-Mismatched	4 (5)
Unrelated Donor	**84 (50)**
HLA-Matched	66 (79)
HLA-Mismatched	18 (21)
Source of Stem Cells # (%)	**170**
Bone Marrow	45 (26)
Peripheral Blood	125 (74)
GVHD Prophylaxis for Allogeneic HCT, #(%)	**167**
Cyclosporine + Methotrexate	100 (60)
Cyclosporine + Mycophenolate	14 (9)
Tacrolimus + Methotrexate	49 (29)
Tacrolimus + Mycophenolate	4 (2)

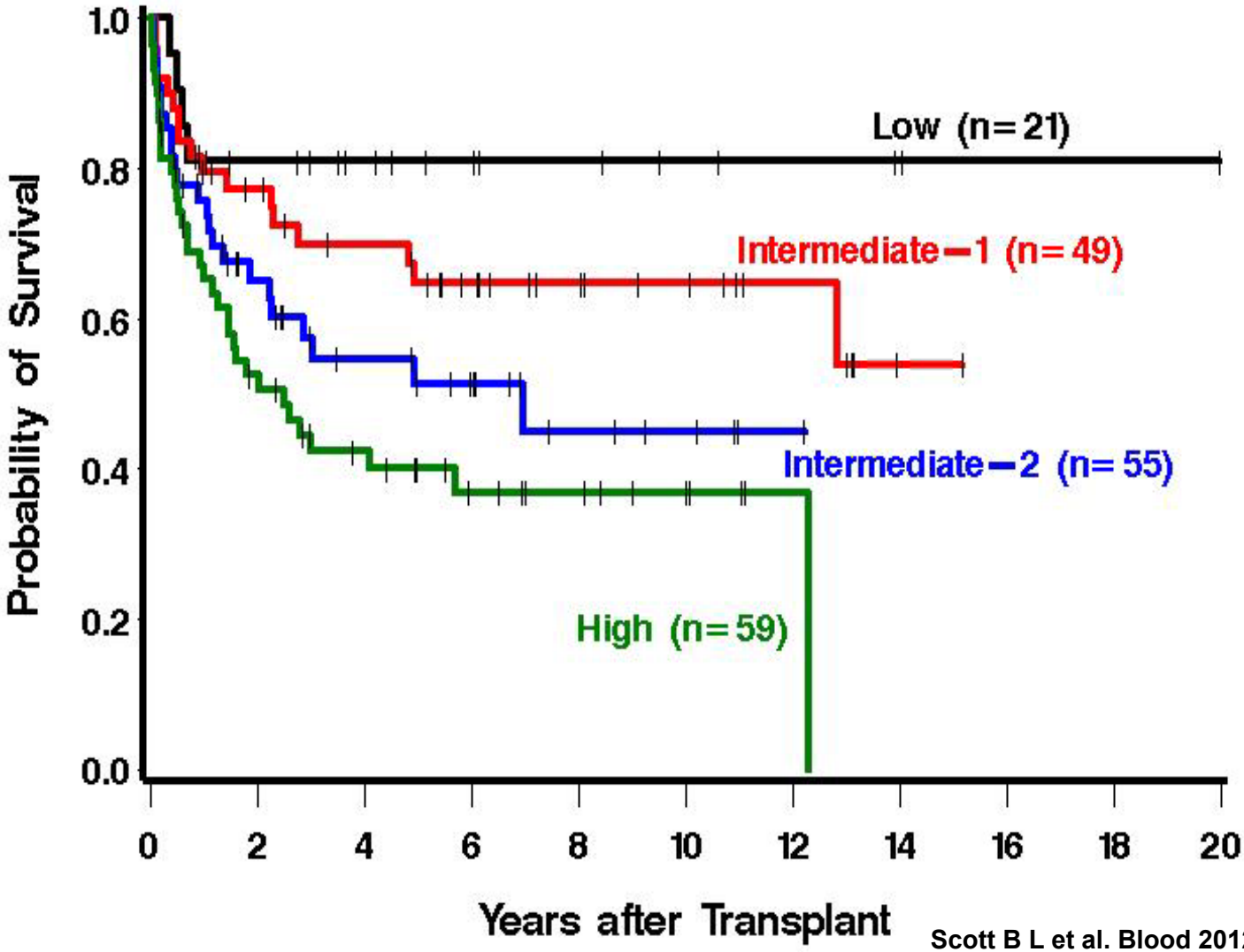
Scott *et al., Blood* 119: 2657-2664, 2012

Non-Relapse Mortality by DIPSS



Scott B L et al. Blood 2012;119:2657-2664

Survival after Transplantation



Scott B L et al. Blood 2012;119:2657-2664

Causes of Death

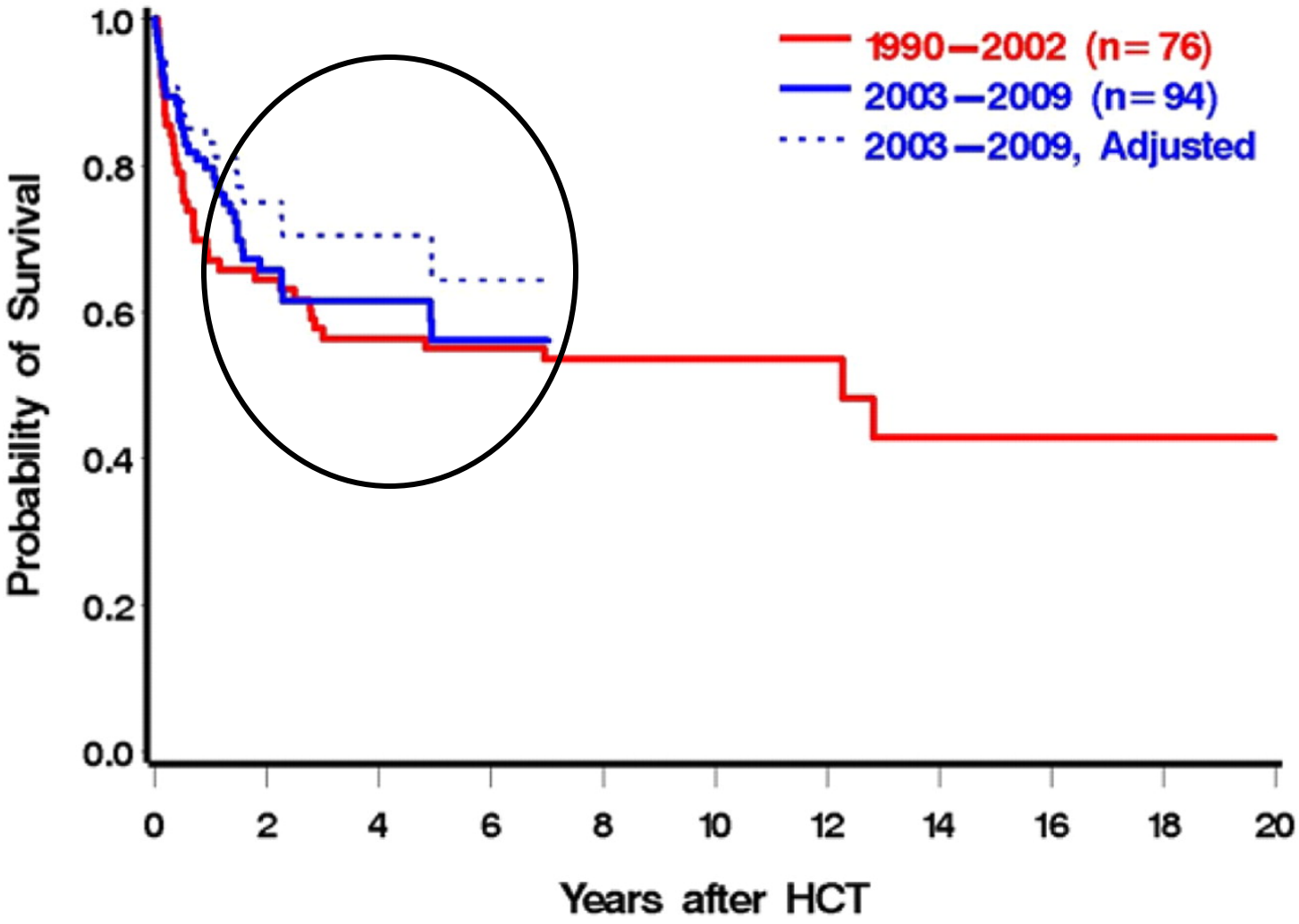
Cause	# (%)
Relapse	13 (18)*
GVHD	18 (25)
Infection	17 (24)
Multiorgan failure	13 (18)
Graft Failure/Rejection	8 † (11)
Secondary Cancer	2 (3)
Intracranial Hemorrhage	1 (1)

*6 patients who relapsed are alive.

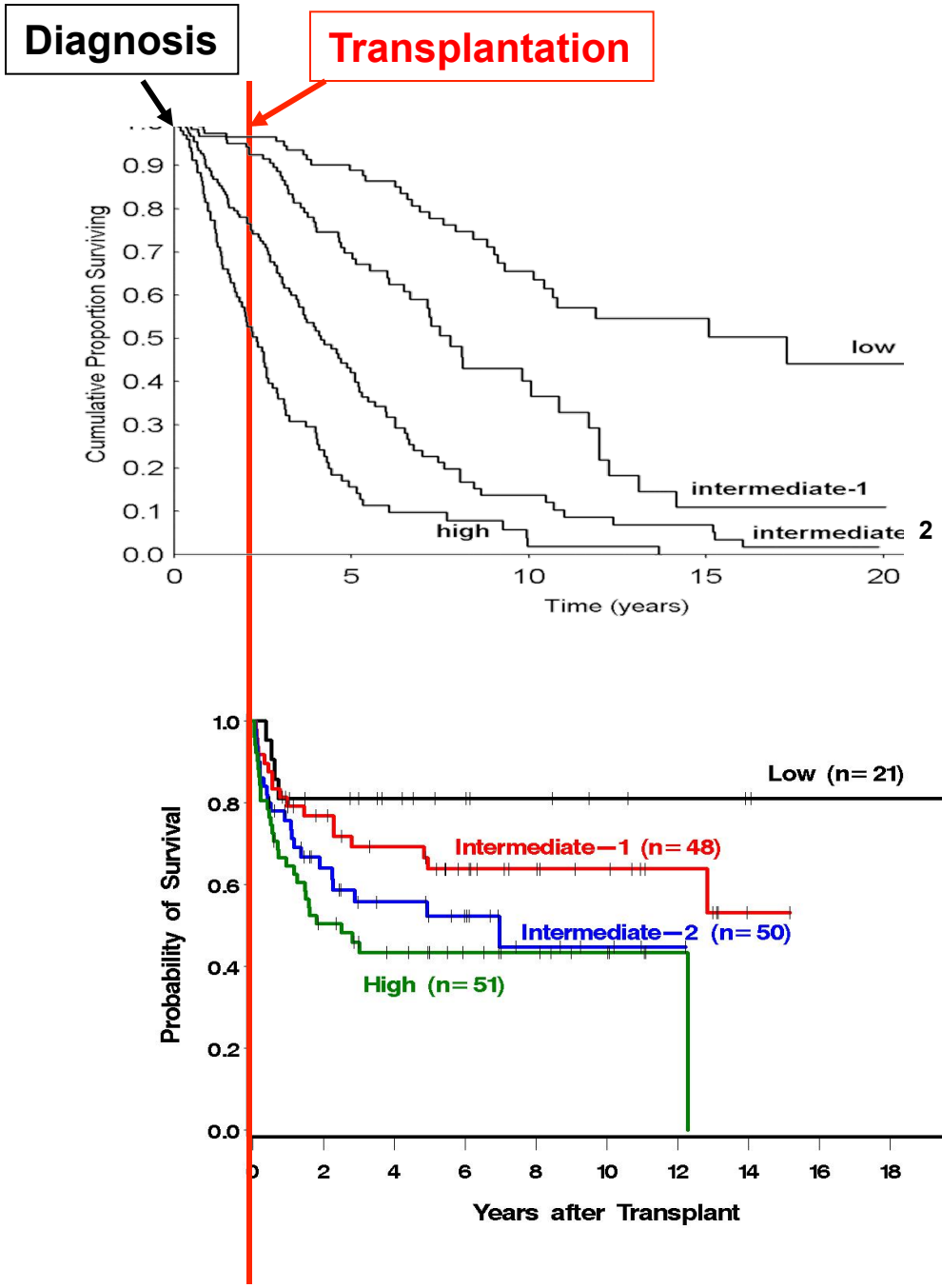
†Two patients with graft failure had autologous recovery and are alive.

Scott *et al., Blood* 119: 2657-2664, 2012

Overall Survival by year of HCT



Scott B L et al. Blood 2012;119:2657-2664



No Transplant

Passamonti F, et al. *Blood*. 2010;115:1703

Transplant

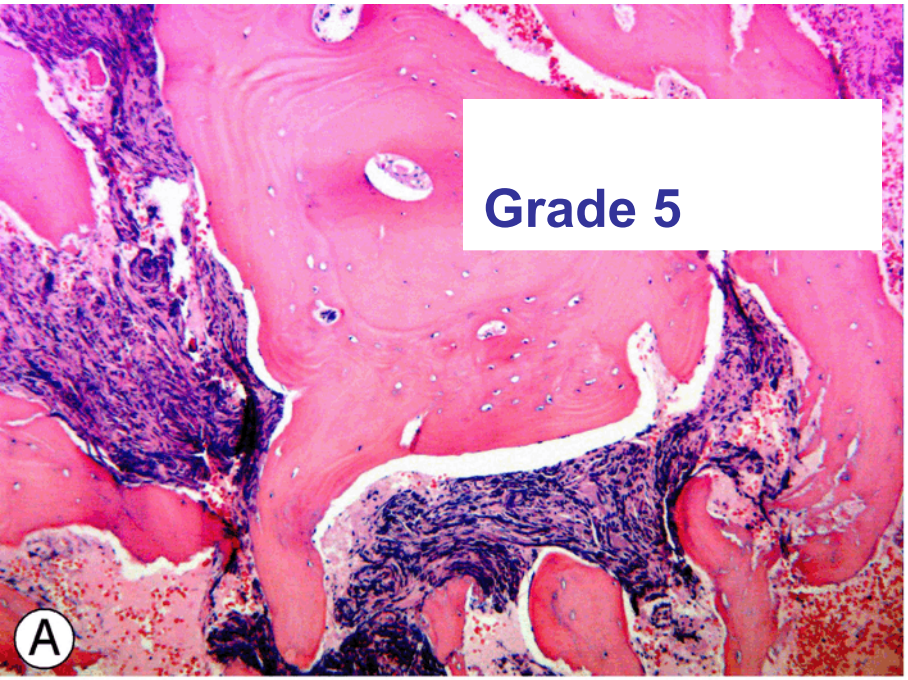
Scott et al. *Blood*. 2012; 119:2657

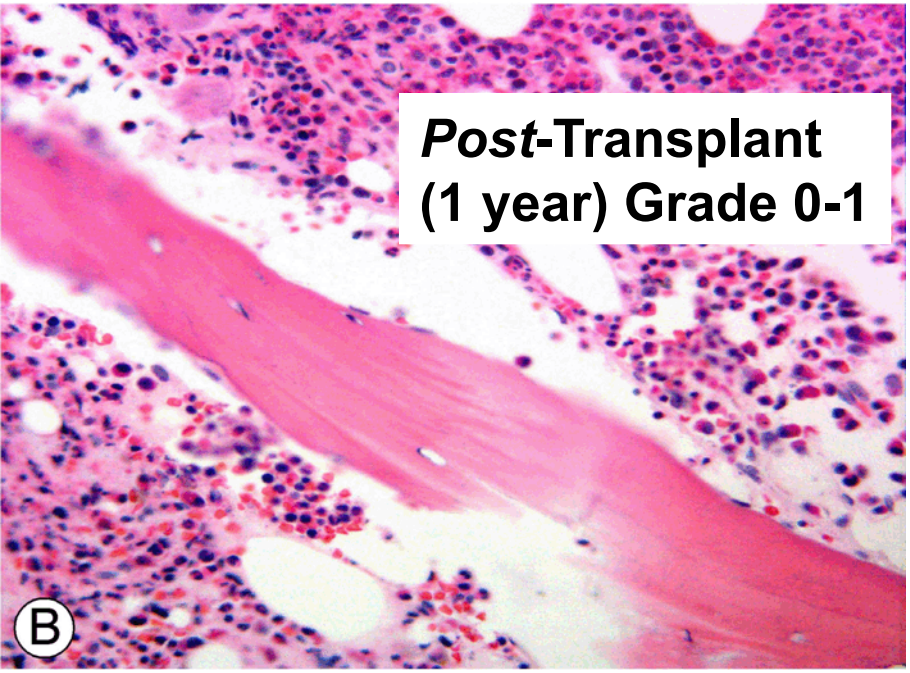
H.J. Deeg

Survival without and with Transplantation (by DIPSS)

DIPPS Risk	Survival (median; years)	
	No Transplant (at reporting)	Transplant (med F/U 5.9)
Low	Not reached	Not reached
Intermediate 1	14.2	Not reached
Intermediate 2	4	7
High	1.5	2.5

B.Scott, HJ Deeg et al, Blood, 2012



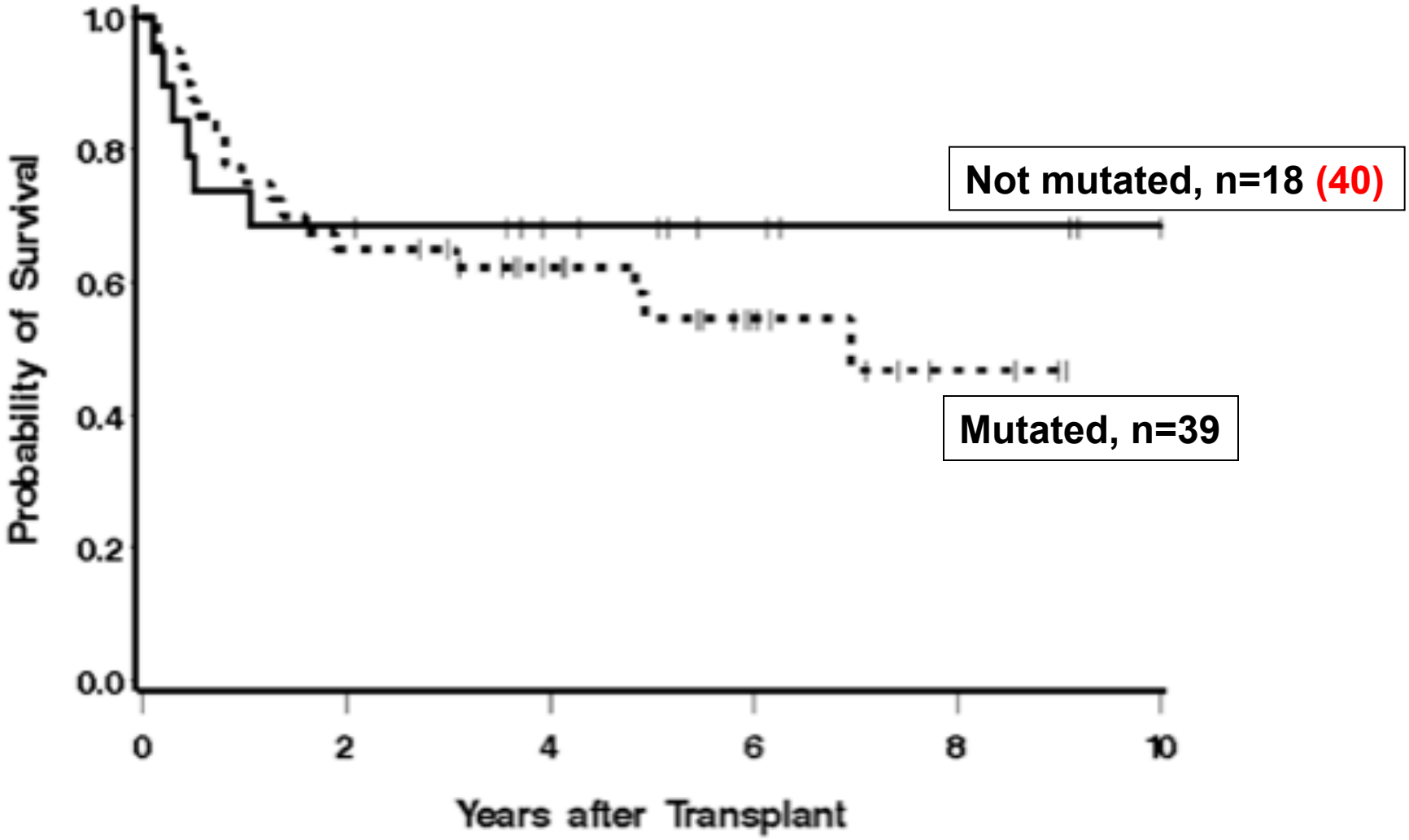


Osteosclerosis: Regression after *high dose conditioning* and HCT

(H&E; x250)

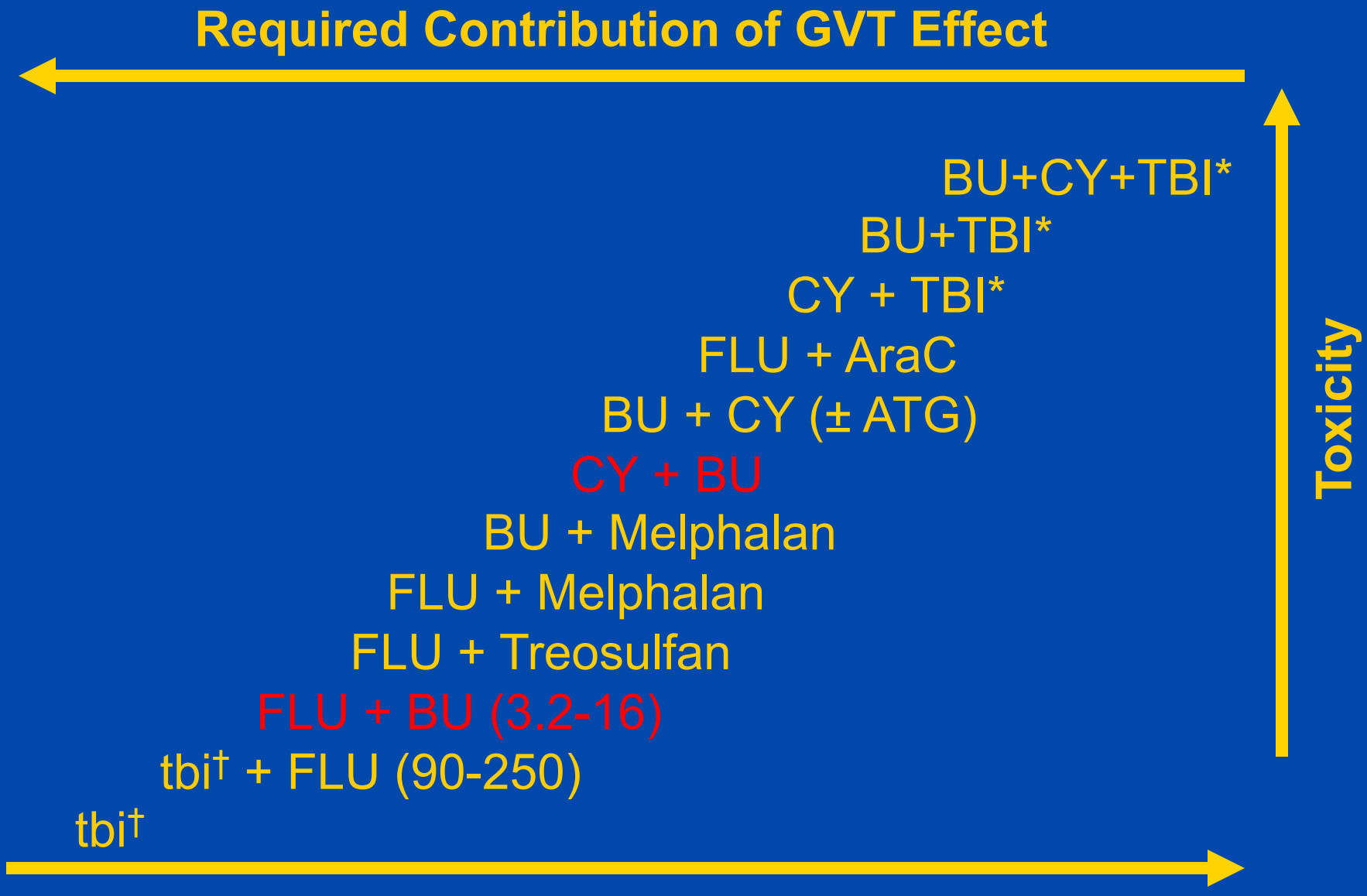
G. Sale

Survival after HCT by JAK 2 mutation (V617F)



Sala-Torra et al.

Conditioning Regimens



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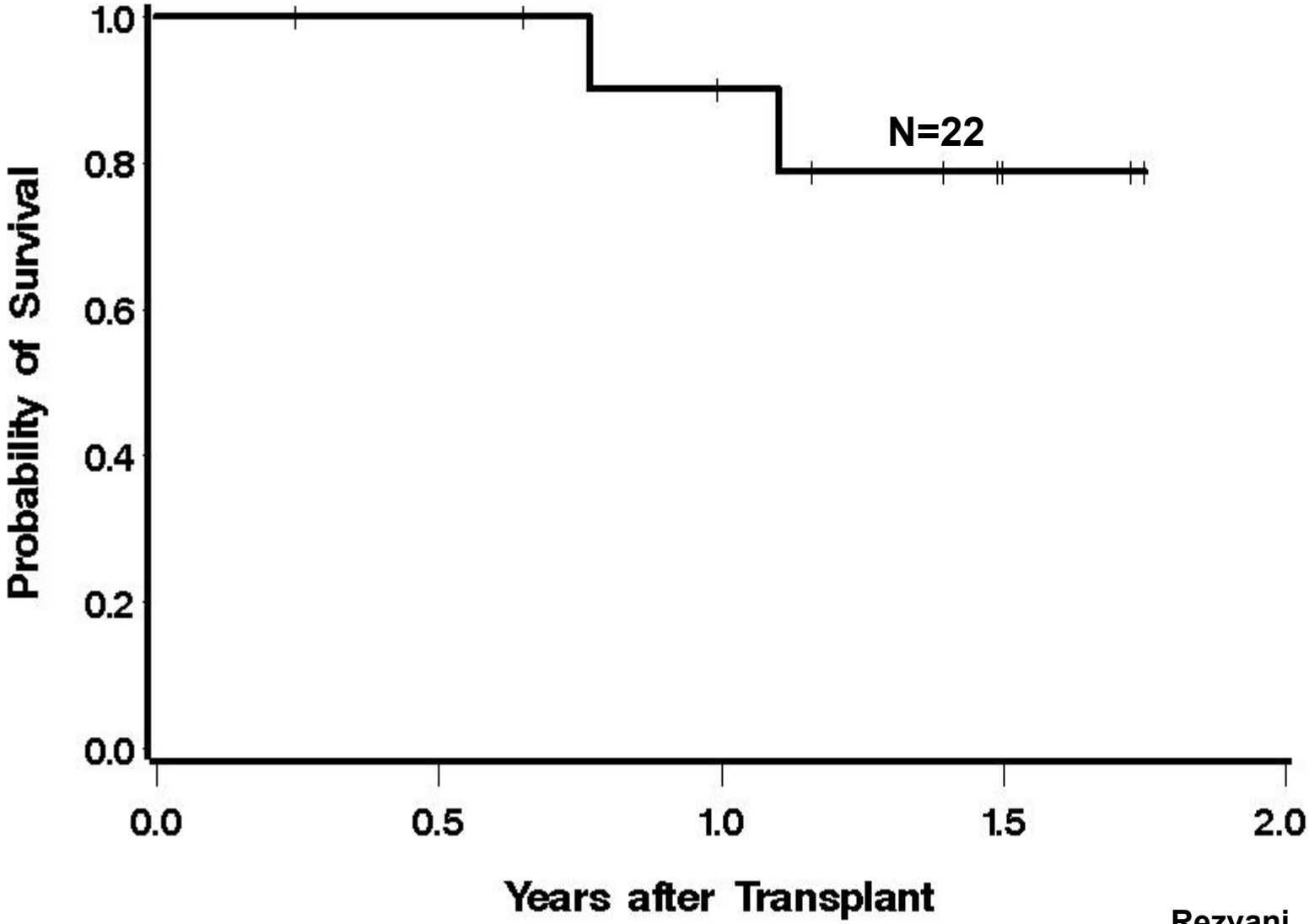
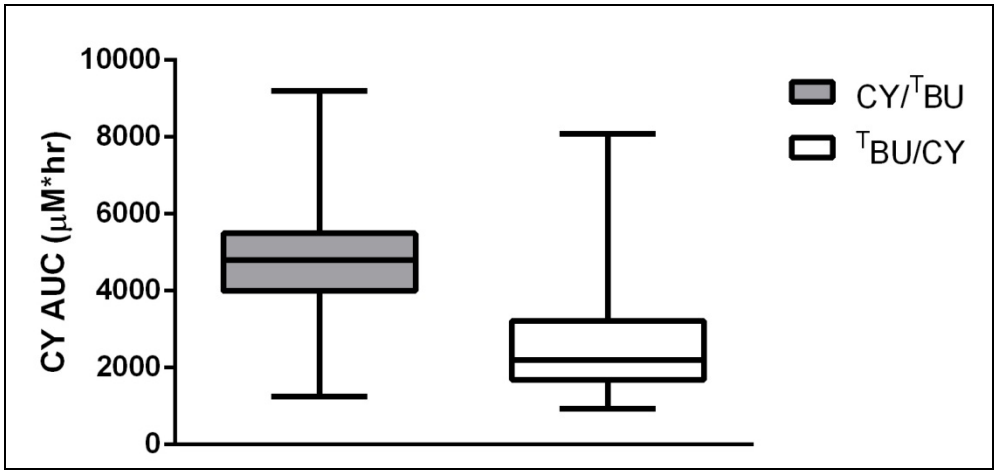
*TBI at ≥12 Gy; †2 Gy;

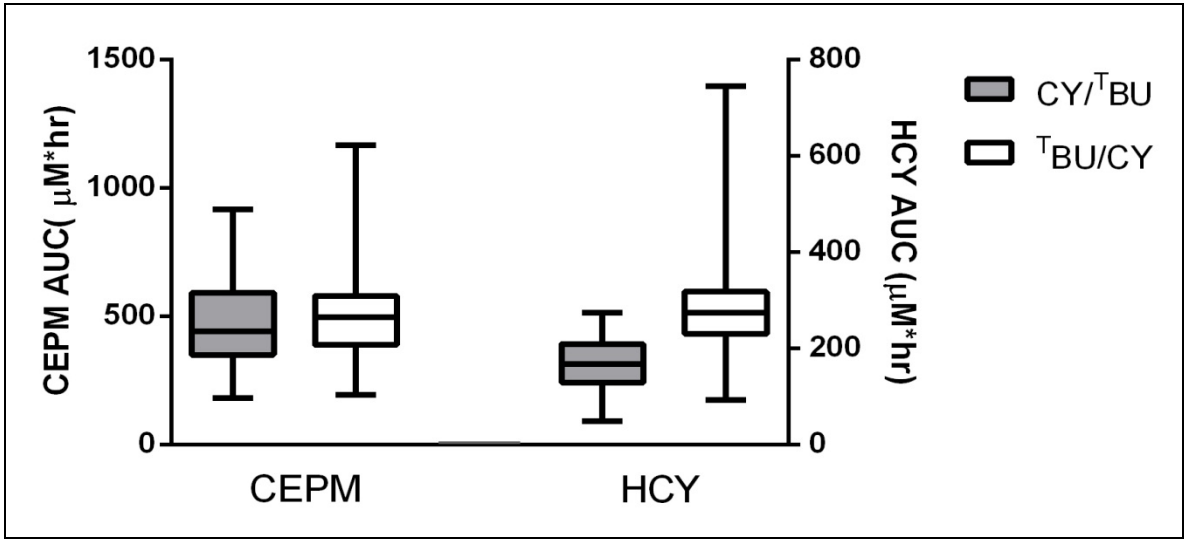
Myelofibrosis: CY → BU Conditioning



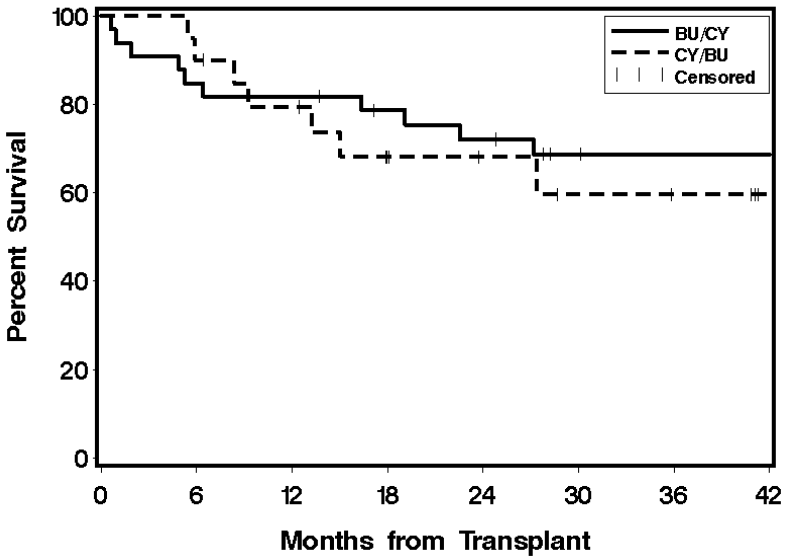
Rezvani, Deeg et al
unpublished

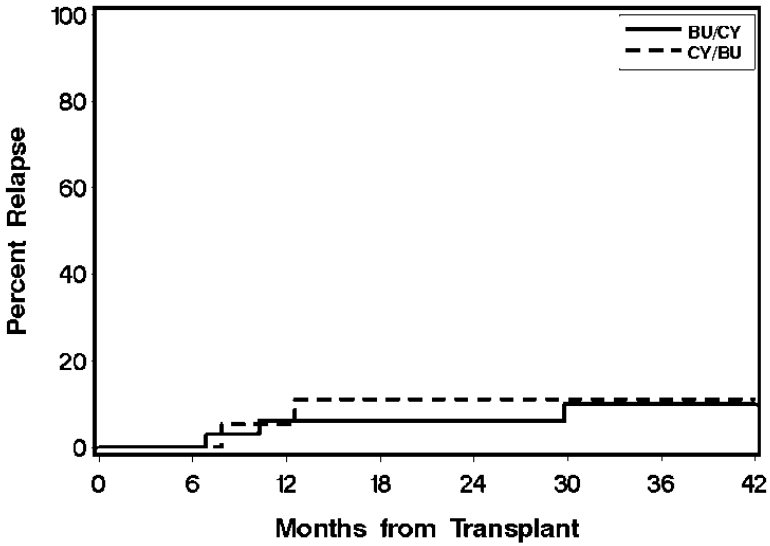
Cytoxan Pharmacogenetics

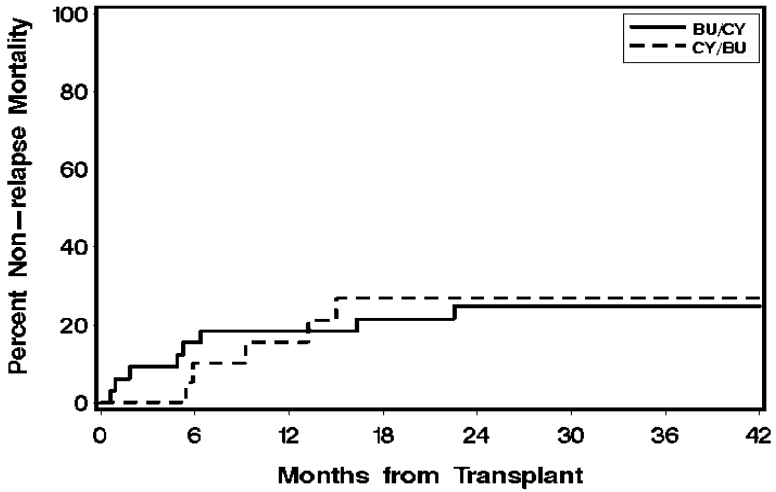




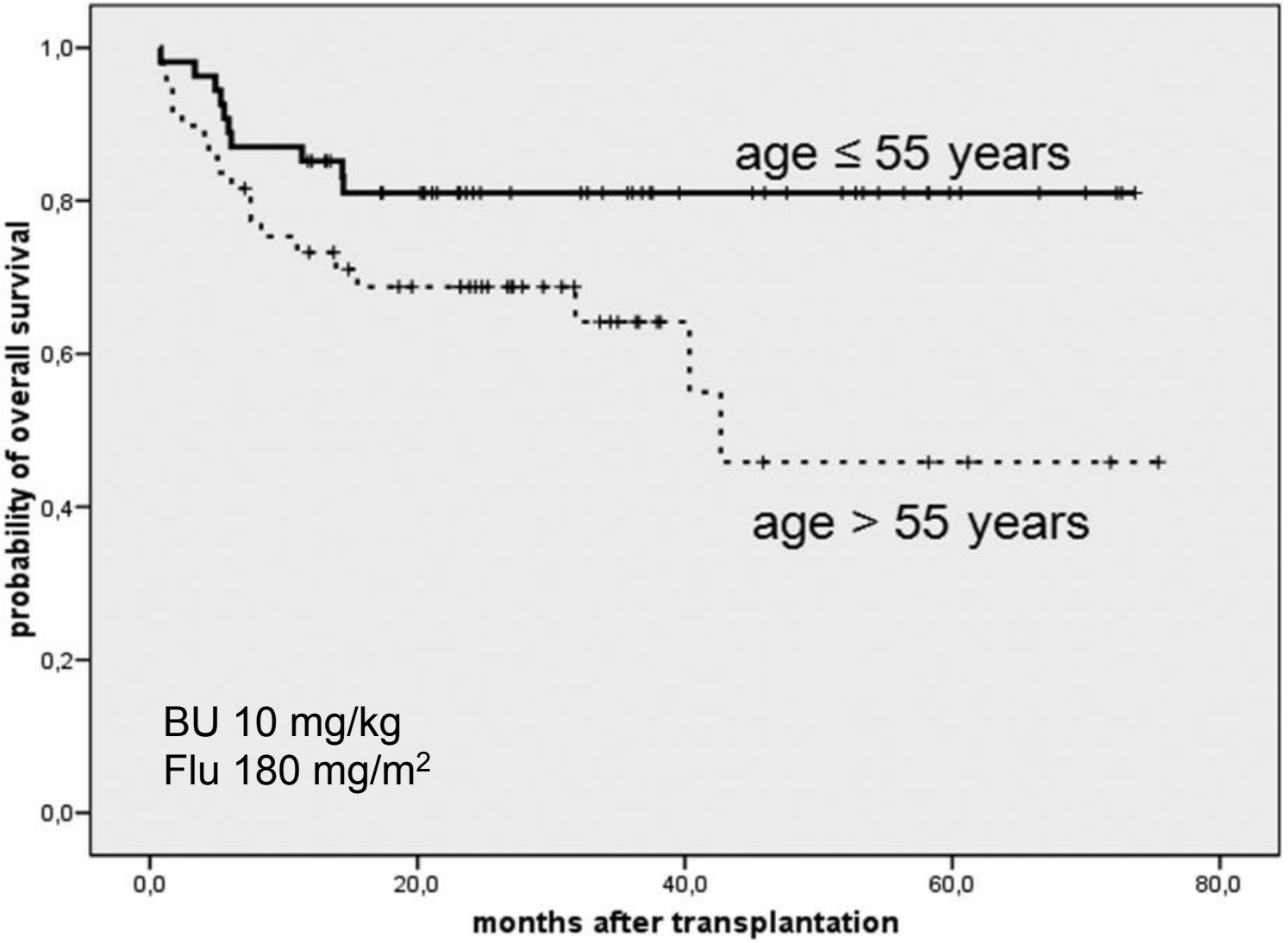
Results with CY → BU







Overall Survival by Age

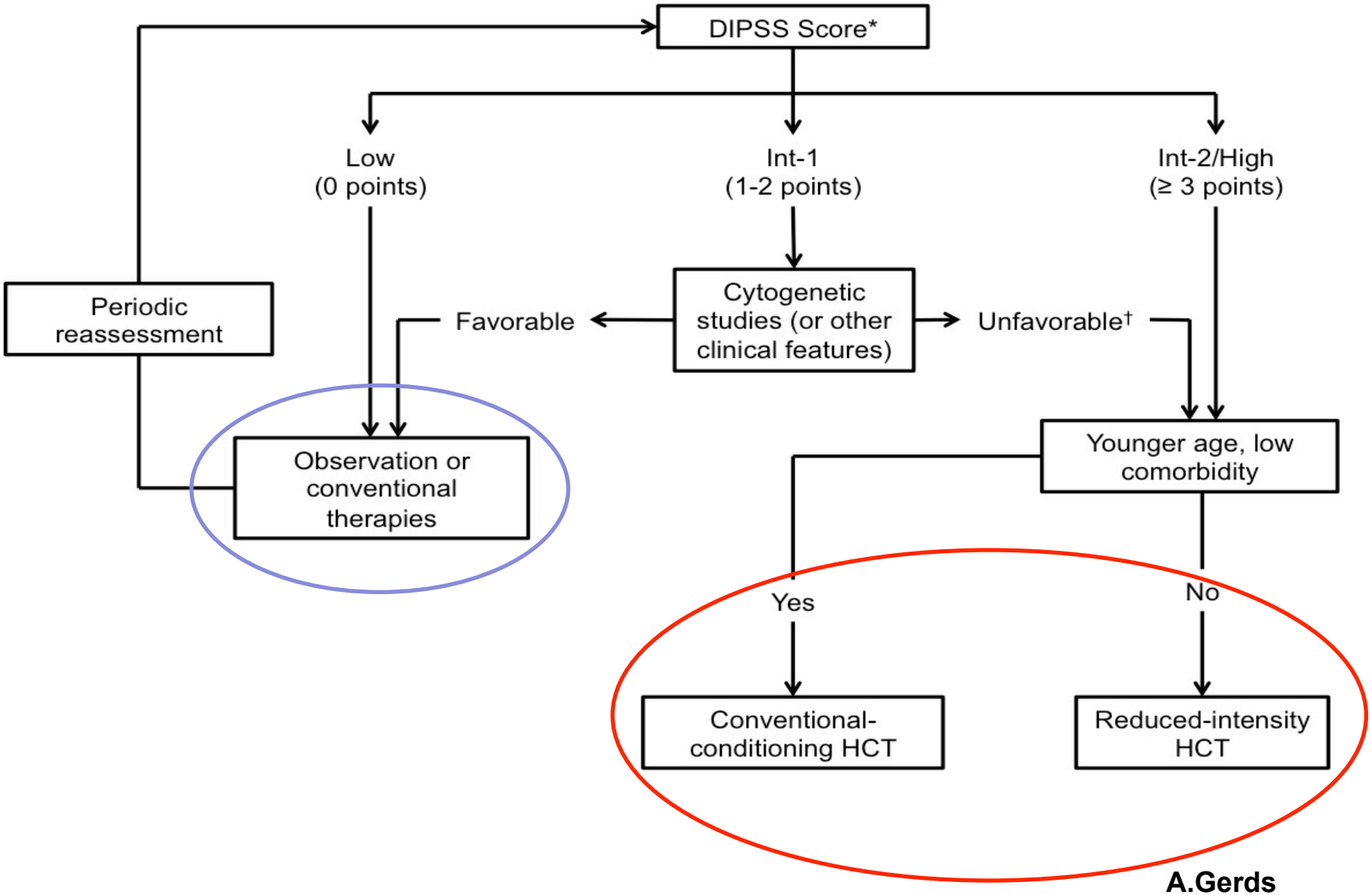


Kröger et al, Blood, 114:5264, 2009

Problems

- GVHD
- Organ toxicity
- Relapse

Decision Tree



A.Gerds

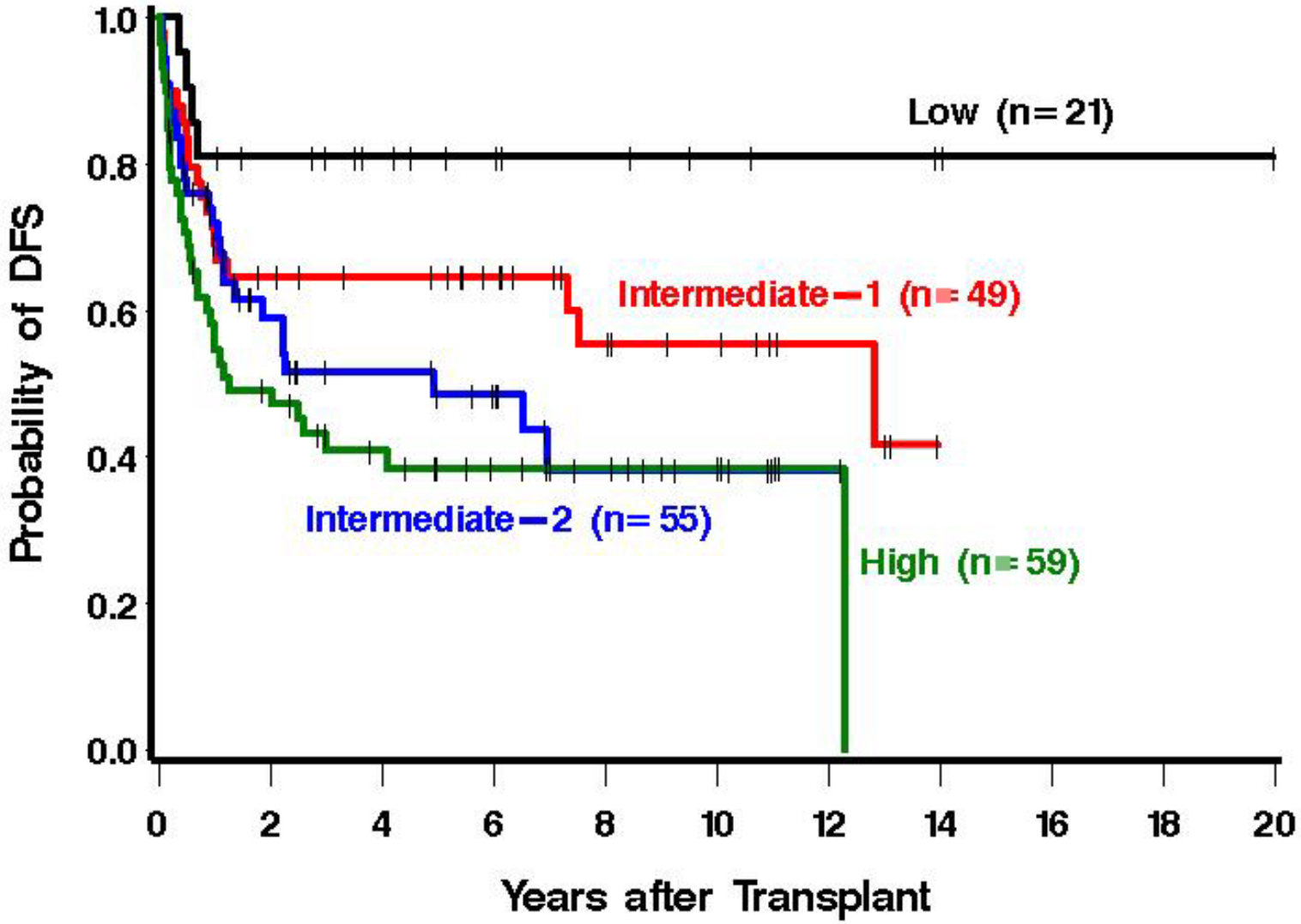
Summary

- **HCT offers effective, curative therapy for patients with MF**
  - Follow-up extending to 20 years
  - Few relapses
- **Safety has improved**
  - Decreasing NRM
- **HCT for MF is appropriate for most patients with advanced MF and for select patients with early stage disease**

Thank you

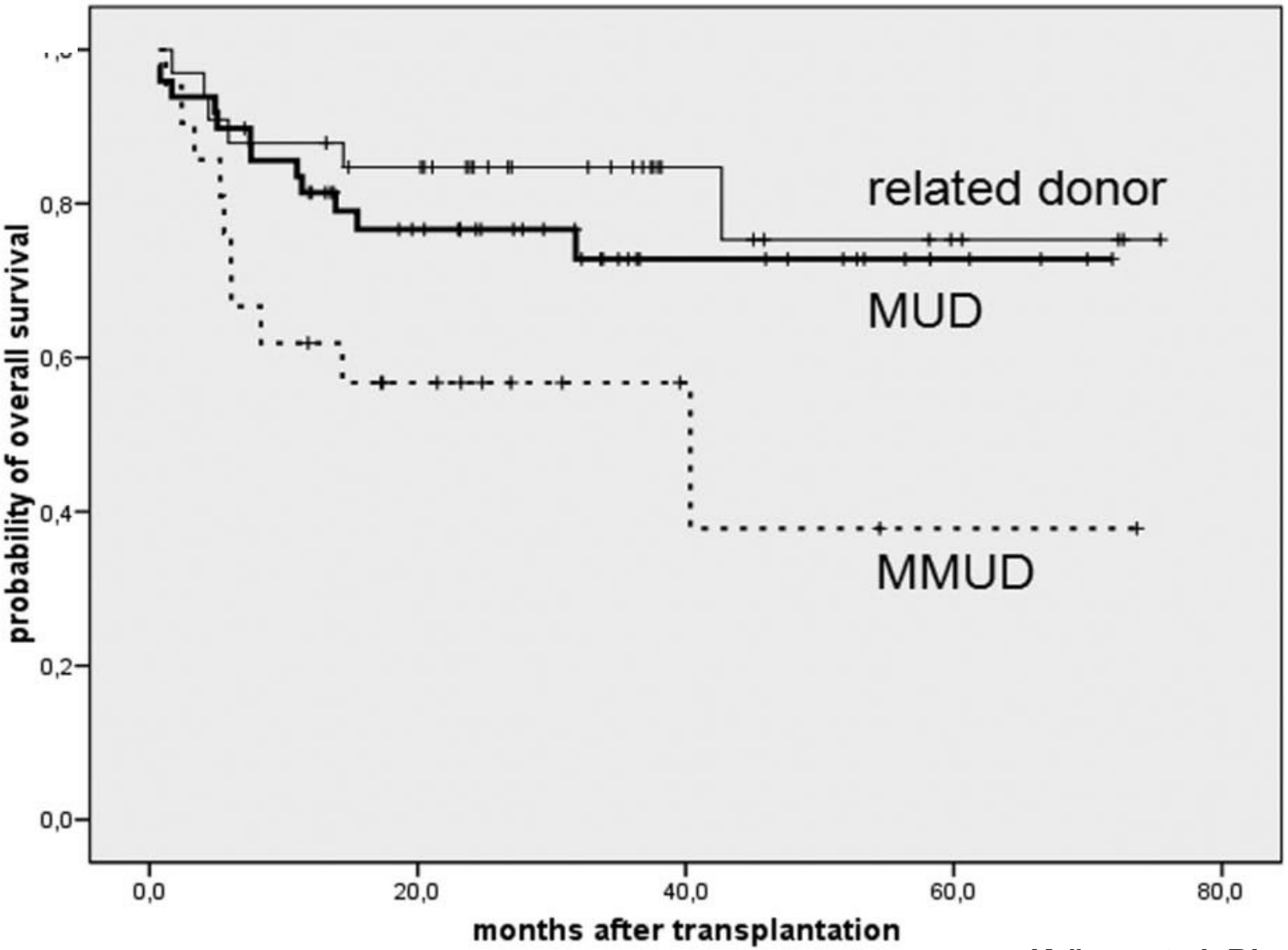
- Ted Gooley
- Bart Scott
- Olga Sala-Torra
- And, of course, all our patients

Relapse-Free Survival



Scott B L et al. Blood 2012;119:2657-2664

Overall Survival by Donor Type



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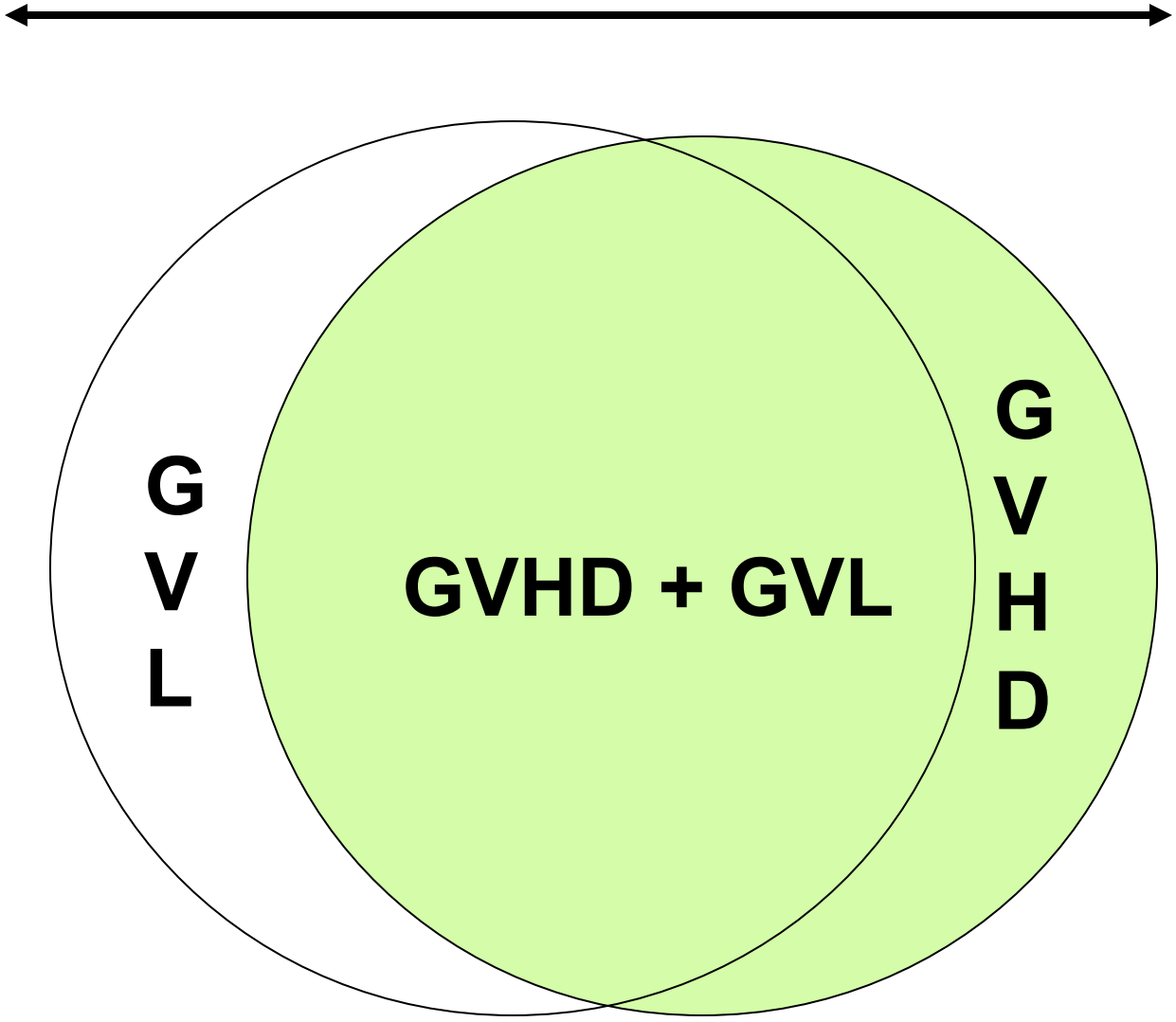
GVH Reaction



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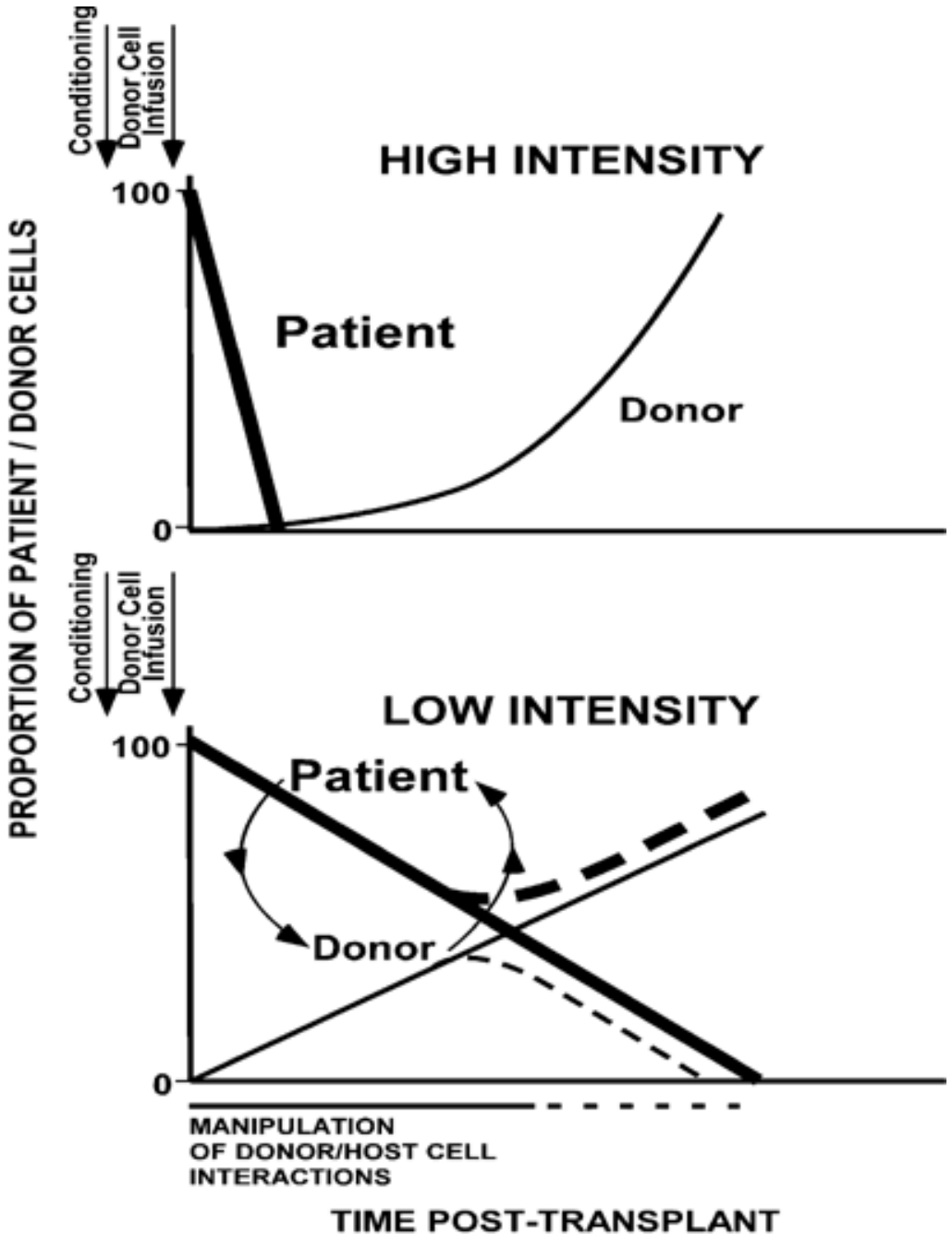

Donor/Host Interactions: High Intensity versus Low Intensity Conditioning

Deeg et al, Leukemia, 2006