Hematopoietic Cell Transplantation (HCT) for MDS

H.Joachim Deeg

Fred Hutchinson Cancer Research Center,

University of Washington, Seattle

jdeeg@fredhutch.org

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The only treatment with curative potential for MDS.
Considerable progress,
but problems remain.

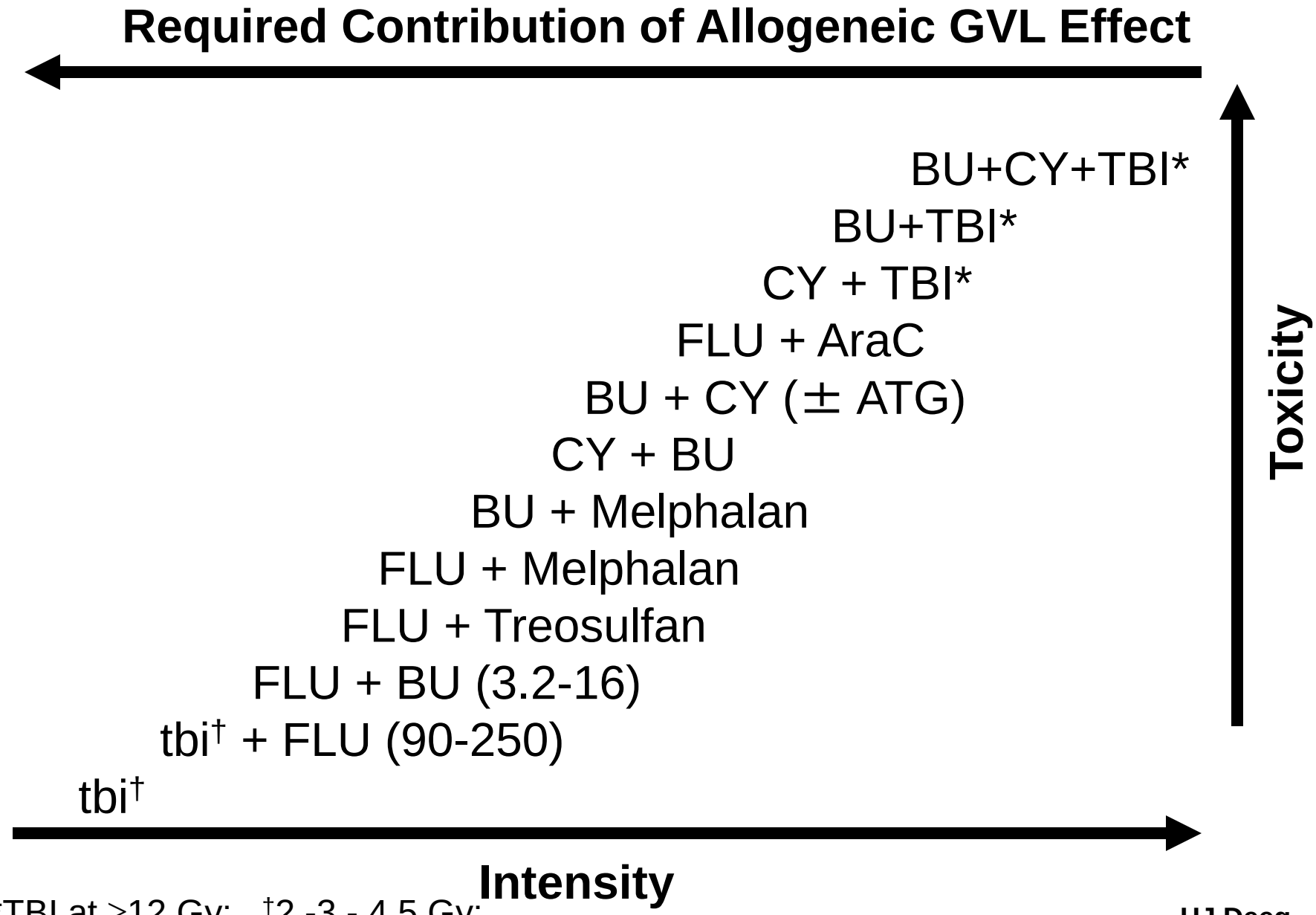
Basics of HCT

- **Objective**: Cure the disease
- **Method:**
  - Condition the patient
  - Infuse healthy donor cells
- **Problems:**
  - Donor cells react against the patient's body (GVHD)
  - Long-term complications

Conditioning

- **Why?**
  - Suppress the immune system
  - Kill disease cells
- **Potential problems**
  - “Systemic” effects and toxicity
- **Important**
  - Coordinate conditioning with other therapy given before transplantation

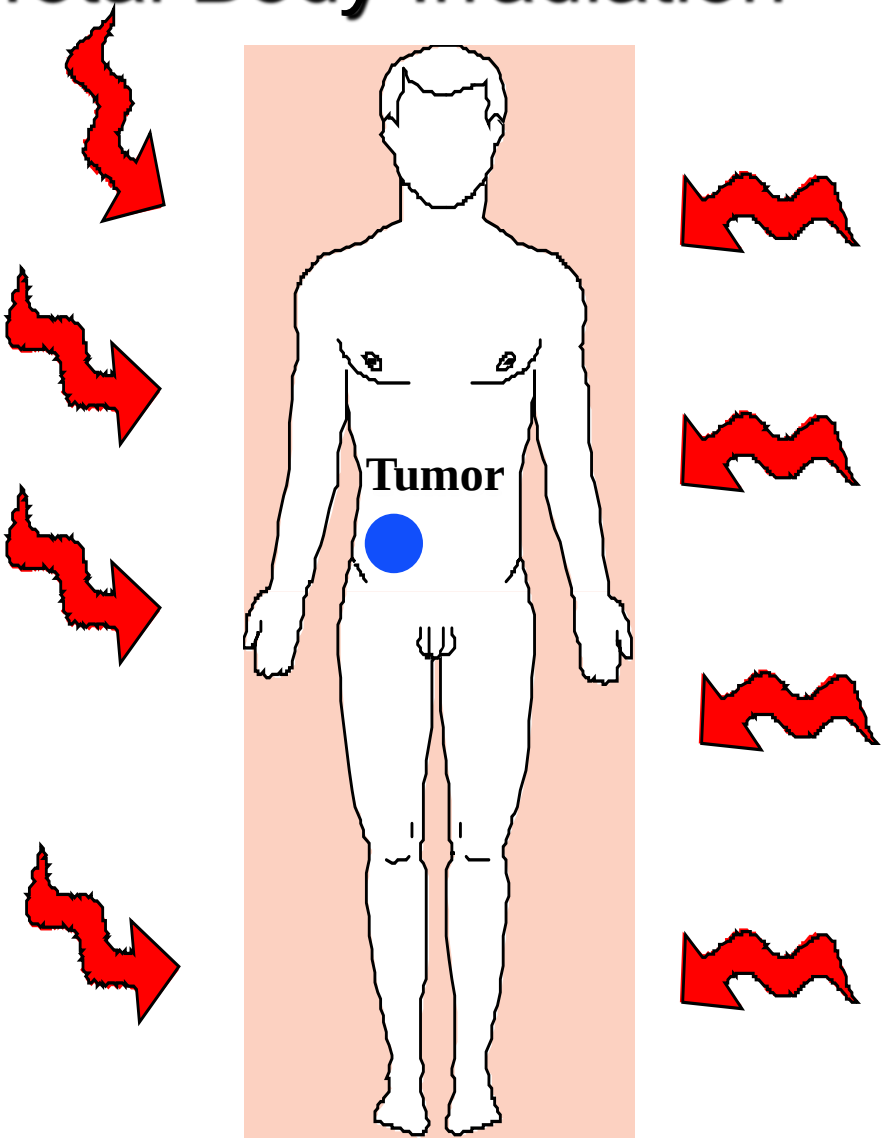
Condtioning Intensity, Toxicity and GVL Effect



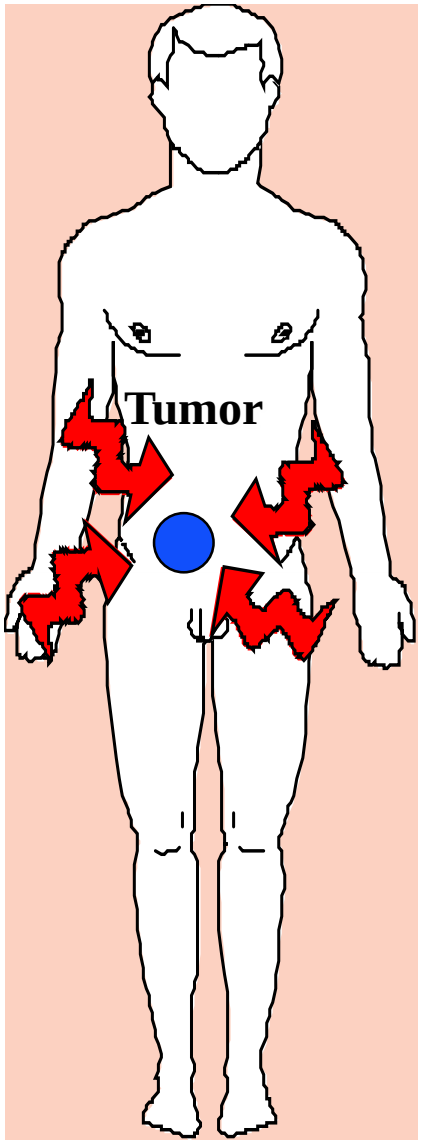
*TBI at ≥12 Gy; †2 -3 - 4.5 Gy;

HJ Deeg

Total Body Irradiation

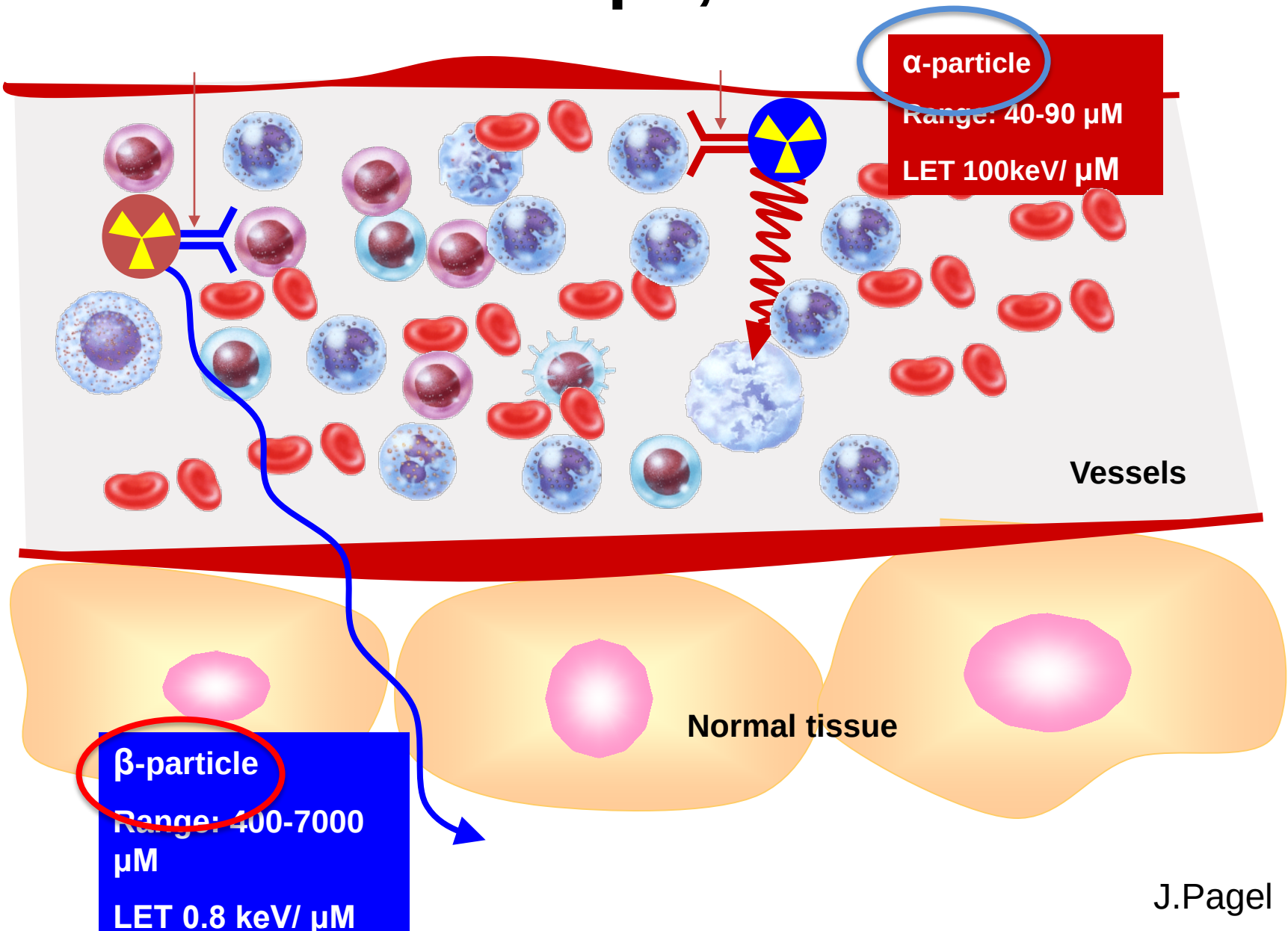


Radioimmunotherapy



J.Pagel

Characteristics of β -, α - emitters



J.Pagel

Cell Donors

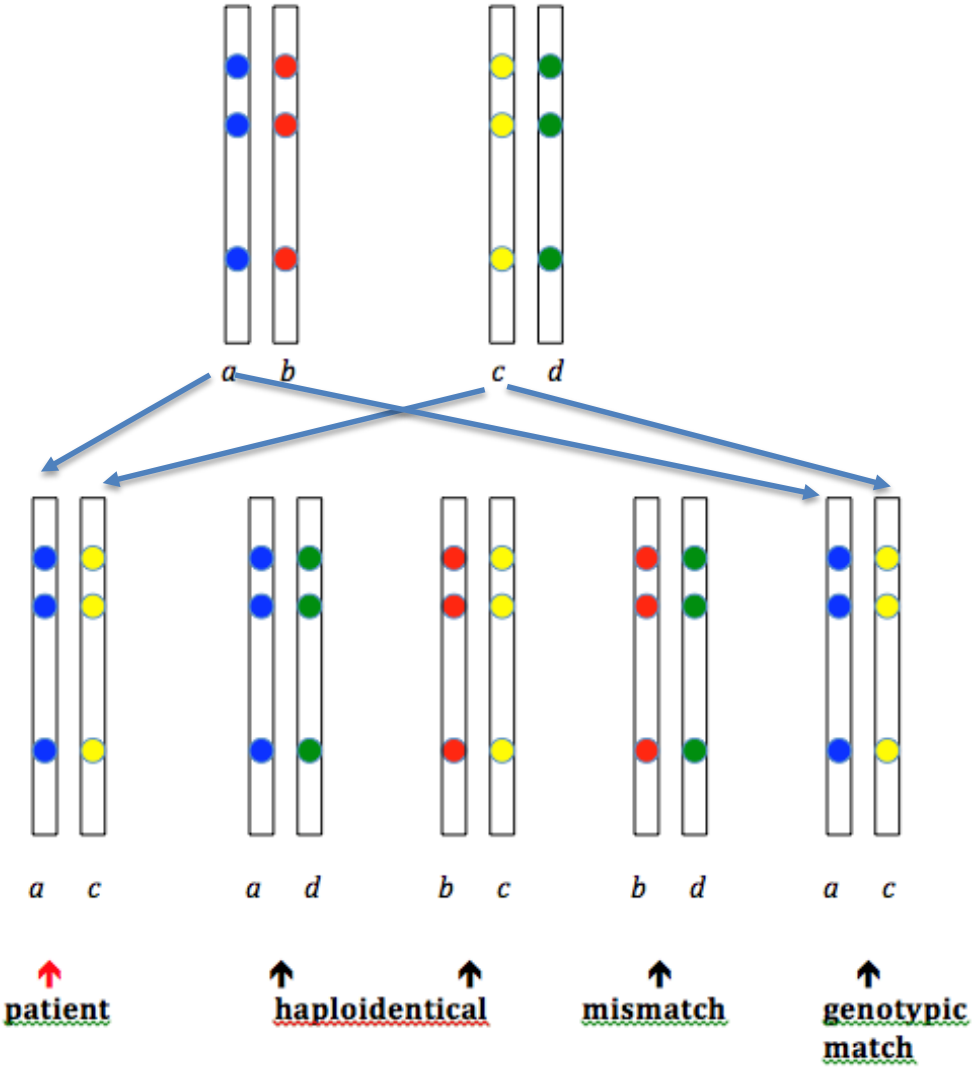
- **HLA* matched**
  - **Full siblings**
  - **Unrelated volunteers (NMDP etc)**
- **HLA *mis*matched**
  - **HLA *haplo*identical family members**
  - **Unrelated volunteers**
- **Umbilical Cord blood (unrelated or related)**

* HLA = Human Leukocyte Antigen

Family HLA Study

Parents

Children



Sources of stem cells

- Bone marrow
- Blood, after “mobilization” of cells from the marrow (with G-CSF)
- Cord blood cells

Engraftment

- Definition:
  - *Donor cells* have established themselves and produce new cells *in the patient*
- How do you know?
  - *Rise in neutrophil (poly/ ANC) count*
  - Rise in platelets
  - Rise in red blood cells (later)

Graft Failure

- *Infrequent*
- Donor cells fail to get established in the marrow
  - *Primary* – neutrophils never rise appropriately
  - *Secondary* - Cells initially rise, but then decline again

GVHD

- Donor cells contain/produce *immune cells,* which recognize the *new environment* (the patient) and *“get turned on”*.
- These cells then can attack and damage the patient ‘s body → GVHD
- GVHD can be acute, chronic or both

GVHD often associated with Infections

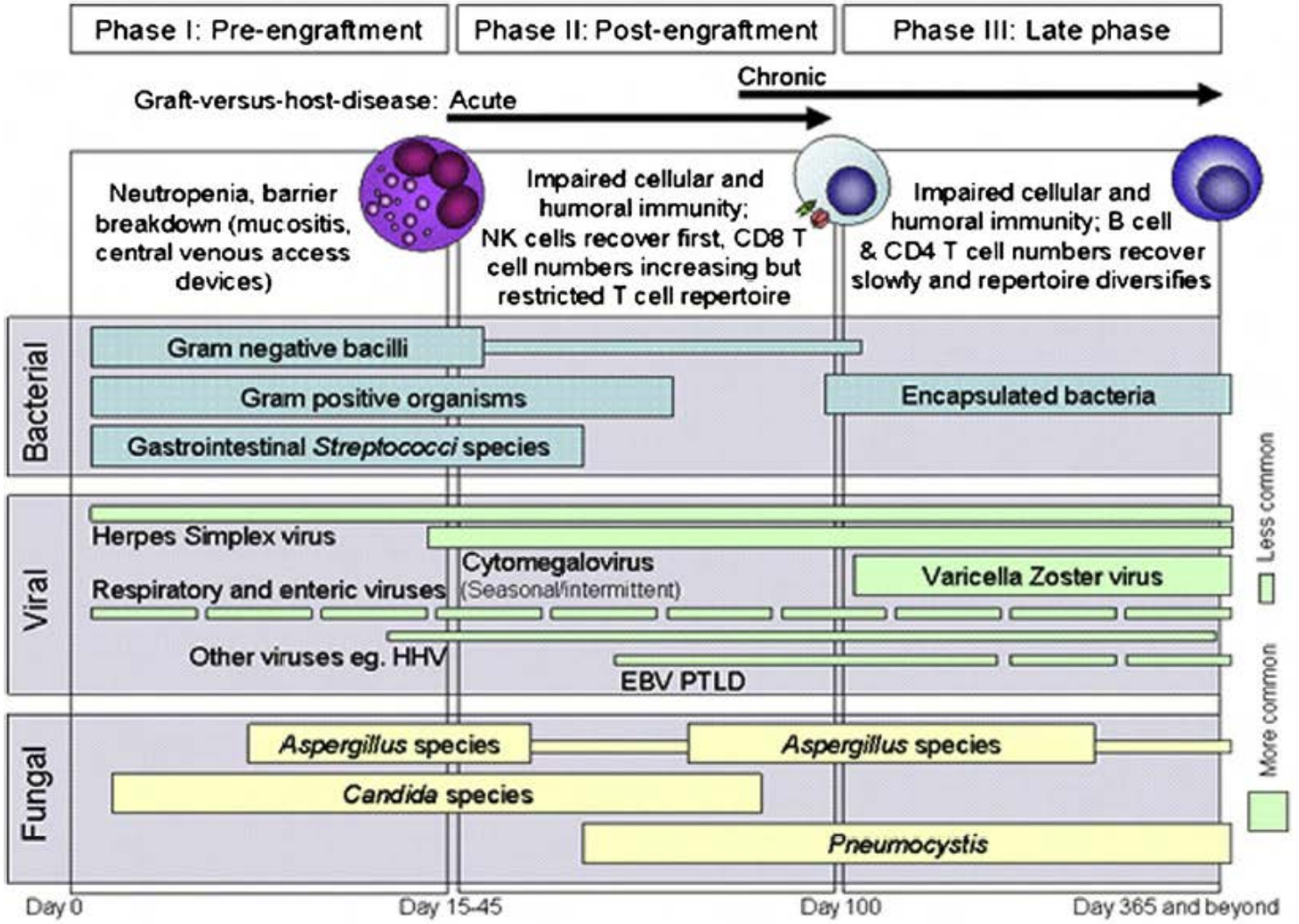


Figure 2. Phases of opportunistic infections among allogeneic HCT recipients Abbreviations: EBV, Epstein-Barr virus; HHV6, human herpesvirus 6; PTLD, posttransplant lymphoproliferative disease.

Tomblyn M et al. BBMT 2009

GVHD Prevention

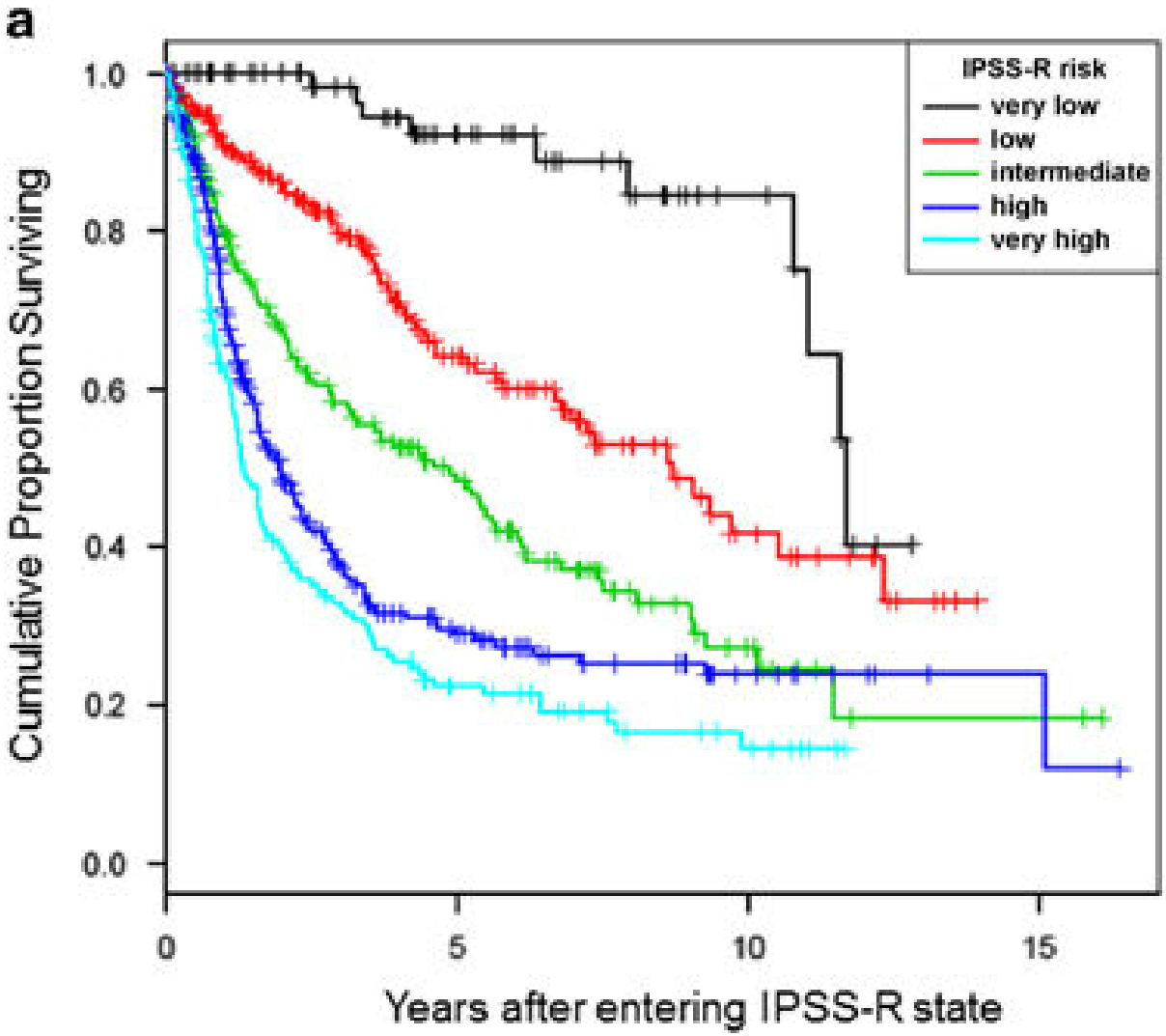
- Eliminate donor T cells before infusion, *in vitro (*in the laboratory)
- Eliminate donor T cells/T cell effects after infusion, *in vivo,* by treating the patient
    - CSP, Tacrolimus, MTX, Sirolimus, ATG
    - Cyclophosphamide
- Change the patient's microbiome (Bacteria in the gut)

Risk Factors and Results

Risk Parameters (in MDS)

- IPSS-R
- Co-morbidities
  - HCT-CI
  - Age
- Mutations

Survival by IPSS-R risk*:



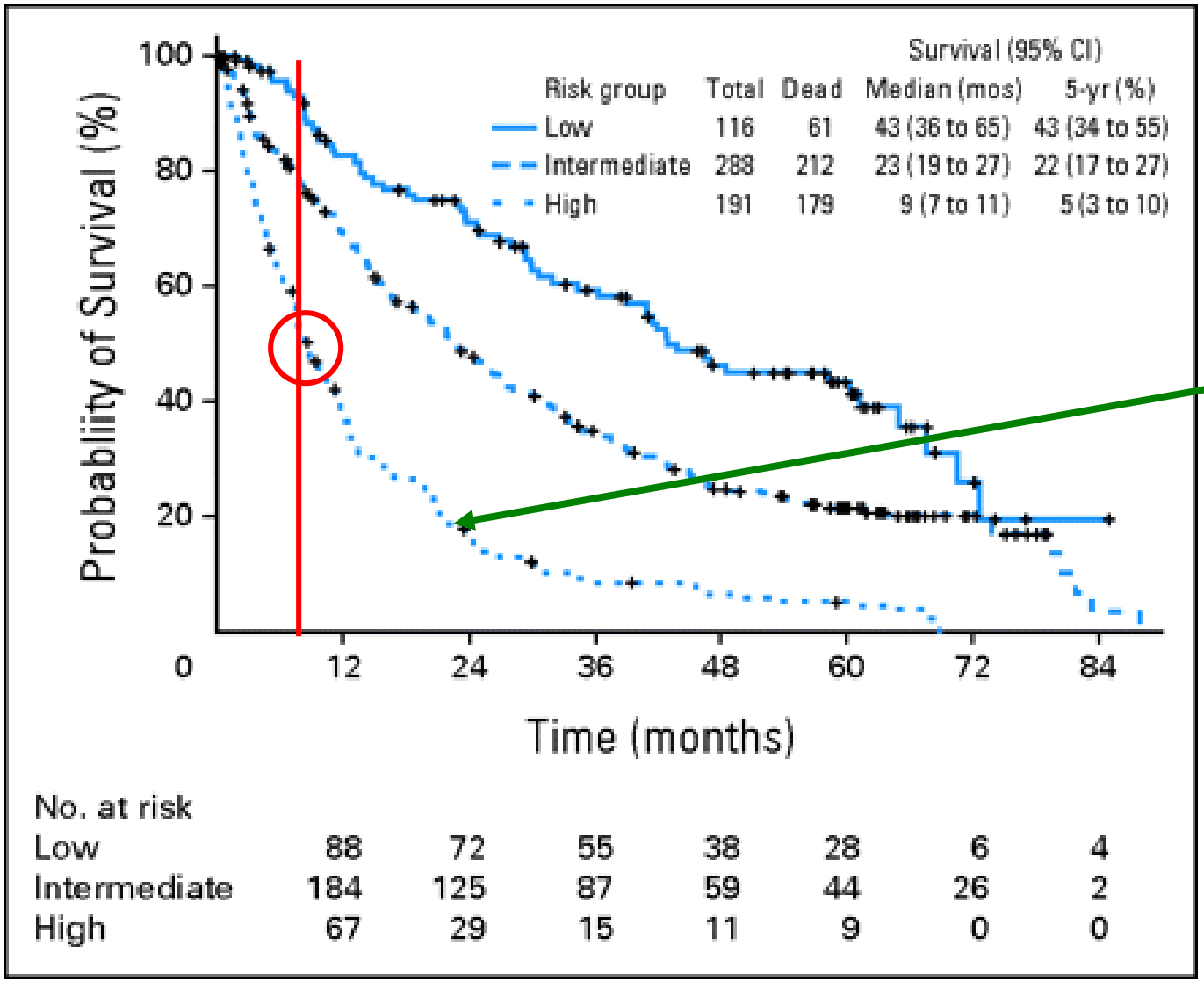
*Since meeting risk criteria

The HCT-CI

Comorbidity	Score
Arrhythmia	1
Cardiac	1
Inflammatory bowel	1
Diabetes	1
Cerebro-vascular	1
Depression/anxiety	1
Hepatic-mild	1
Morbid obesity	1
Infection	1
Rheumatologic	2
Peptic ulcer	2
Renal-moderate/severe	2
Pulmonary-moderate	2
Prior Solid tumor	3
Heart Valve disease	3
Pulmonary-severe	3
Hepatic-moderate/severe	3

M. Sorror et al

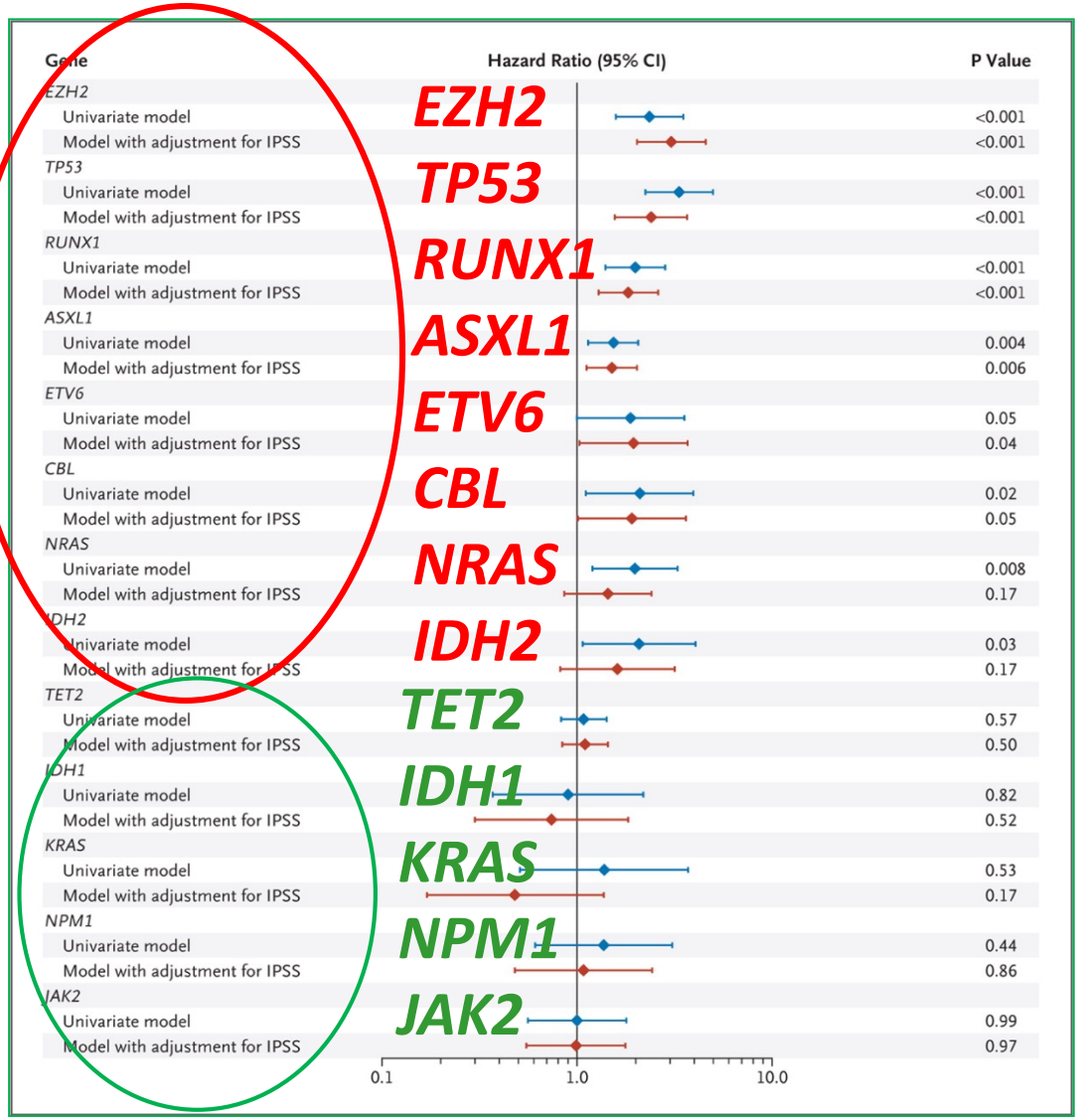
Risk and Survival in *non-transplanted* patients:



↑ IPSS
Age ≥ 65
↑ Comorbidity

K. Naqvi et al. JCO 2011

Mutations and Survival in MDS (N=439)



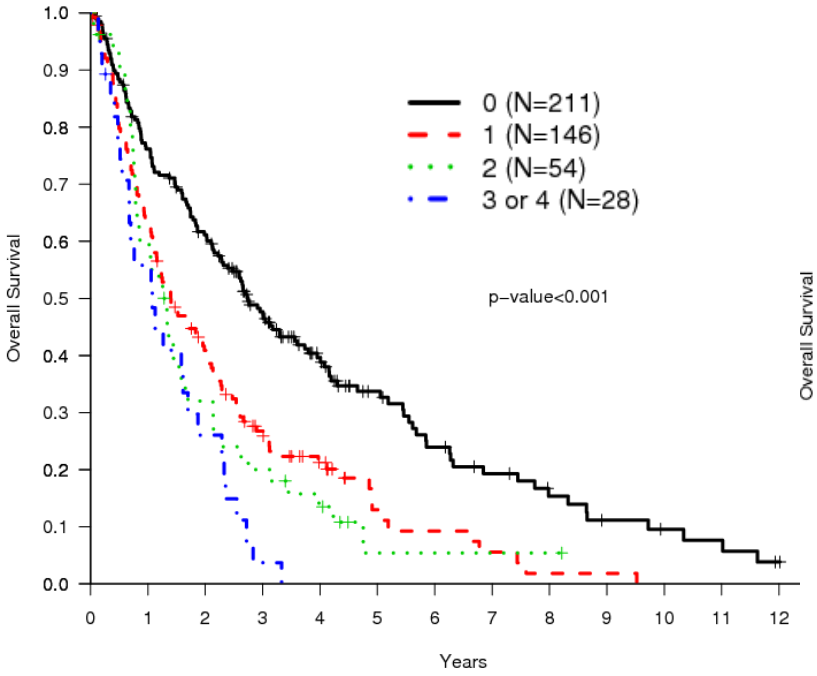
Bejar R et al. *N Engl J Med* 2011;364:2496

Mutations, karyotype and survival (no transplants)

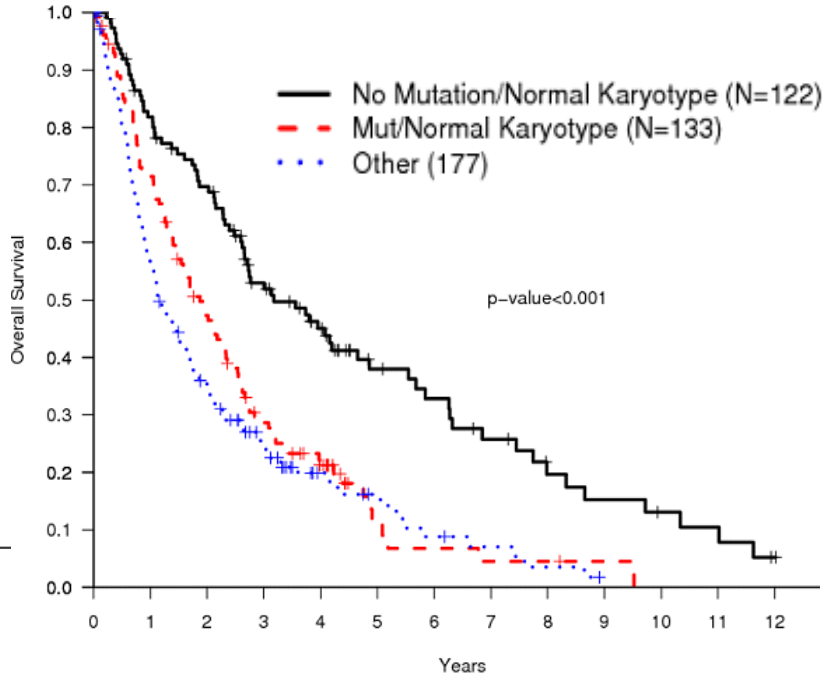
Candidate Genes

TET2
ASXL1
RUNX1
TP53
EZH2
NRAS
JAK2
ETV6
CBL
IDH2
NPM1
IDH1
KRAS
GNAS
PTPN11
BRAF
PTEN
CDKN2A

Mutations



Mutations and Cytogenetics



R. Bejar et al, NEJM, 2011

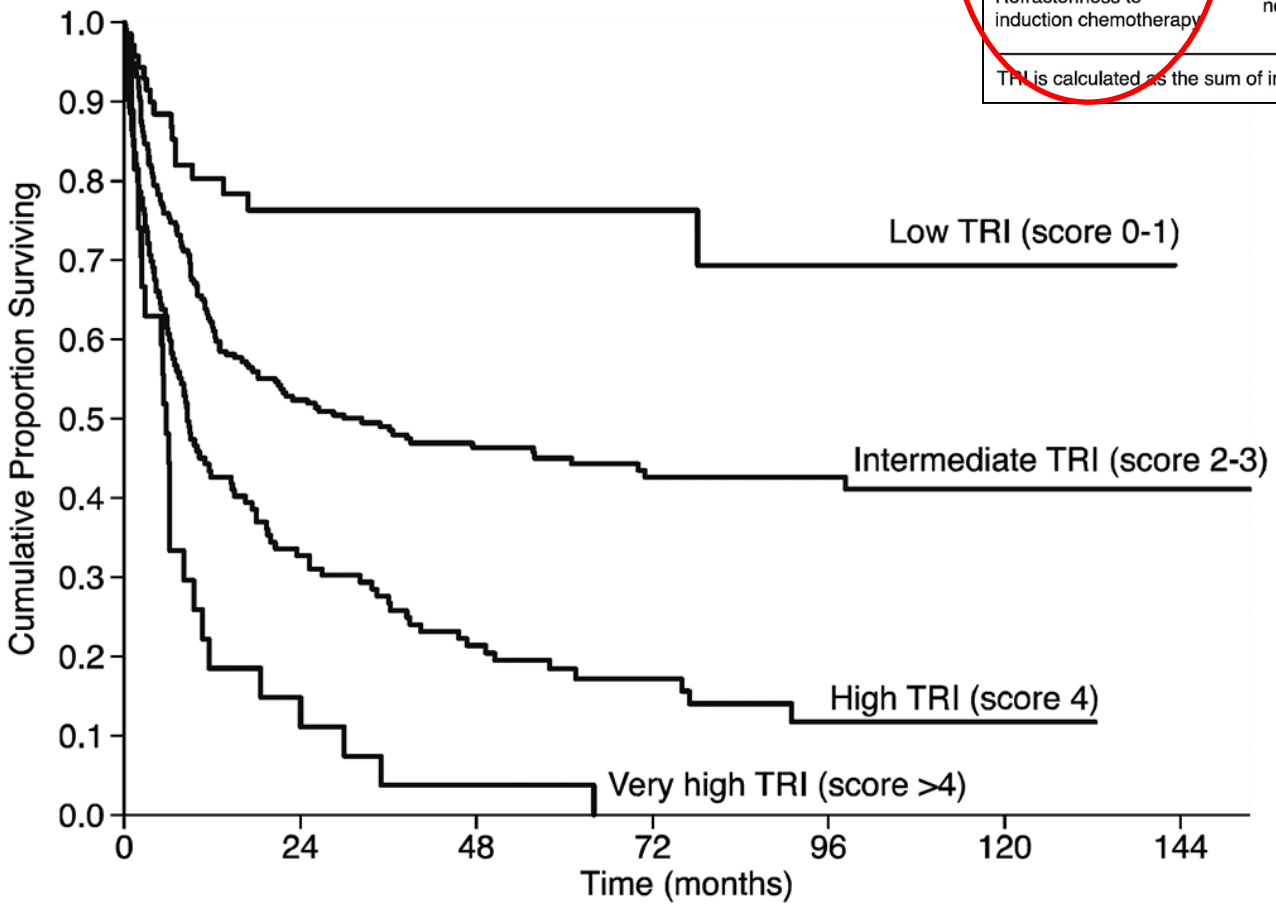
How does all this impact Transplant Outcome?

Transplant outcome by Transplant Risk

MDS transplantation risk index (TRI) calculation

Prognostic variable	Score values			
	0	1	2	3
Age, yr	<50	≥50	-	-
IPSS-R	low	intermediate	high	very high
Monosomal karyotype	no	yes	-	-
HCT-CI	low/intermediate	high	-	-
Refractoriness to induction chemotherapy	no	yes	-	-

TRI is calculated as the sum of individual score values



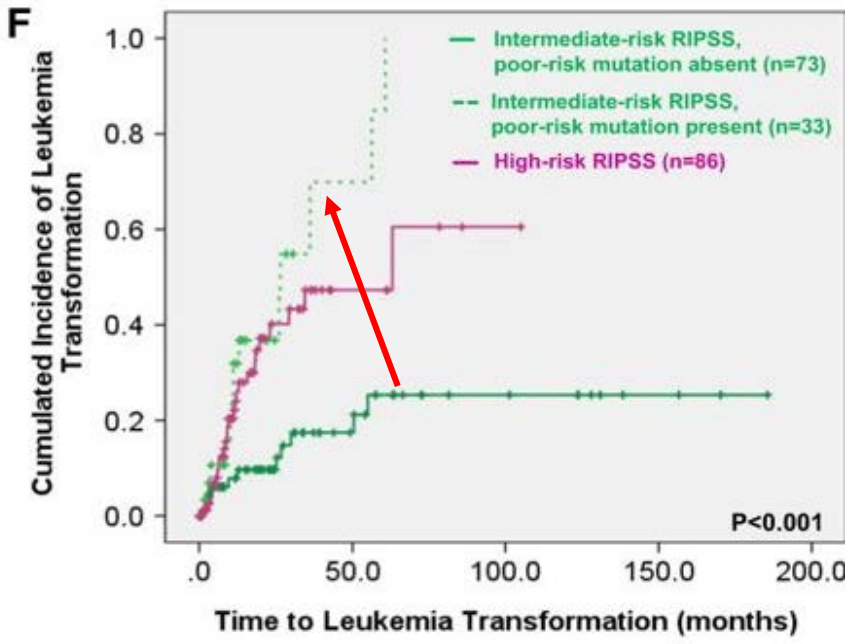
Della Porta et al., *Blood*, 2014

IPSS-R plus Mutations

neg

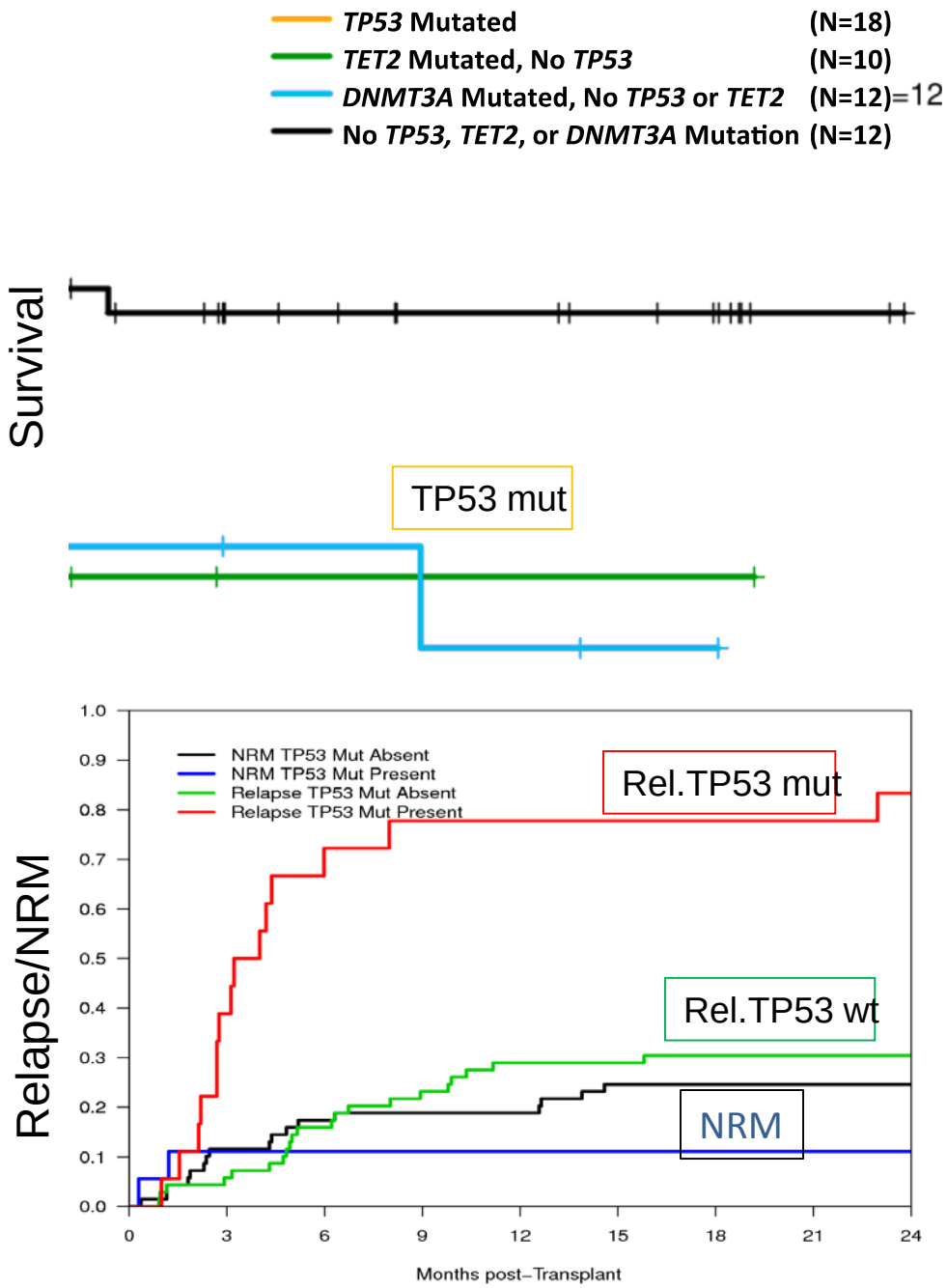
pos

High risk mutations:
IDH1,ASXL1,
DNMT3A, CBL, TP53



H.A. Hou et al ,Blood Cancer Journal, 8:39, 2018

Mutations and Outcome after Transplantation for MDS

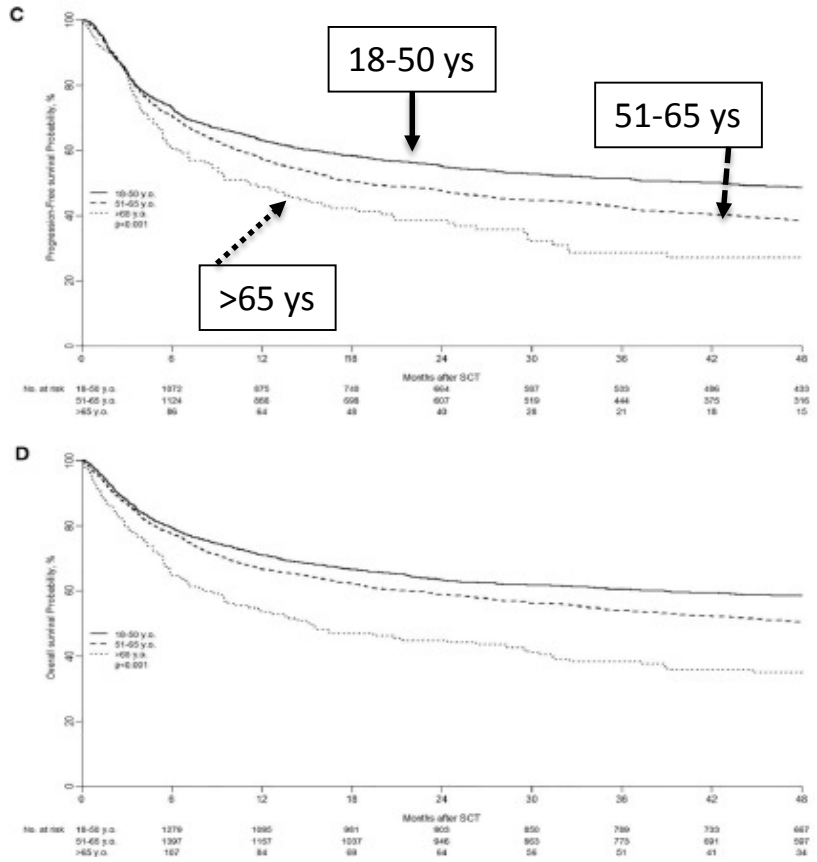


Adjusted for blast %, conditioning regimen, HLA match and complex karyotype

Bejar *et al*, J Clin Onc 2014

Age and Transplant Outcome

(various diagnoses andregimens, related or unrelated donors, N=3,910)

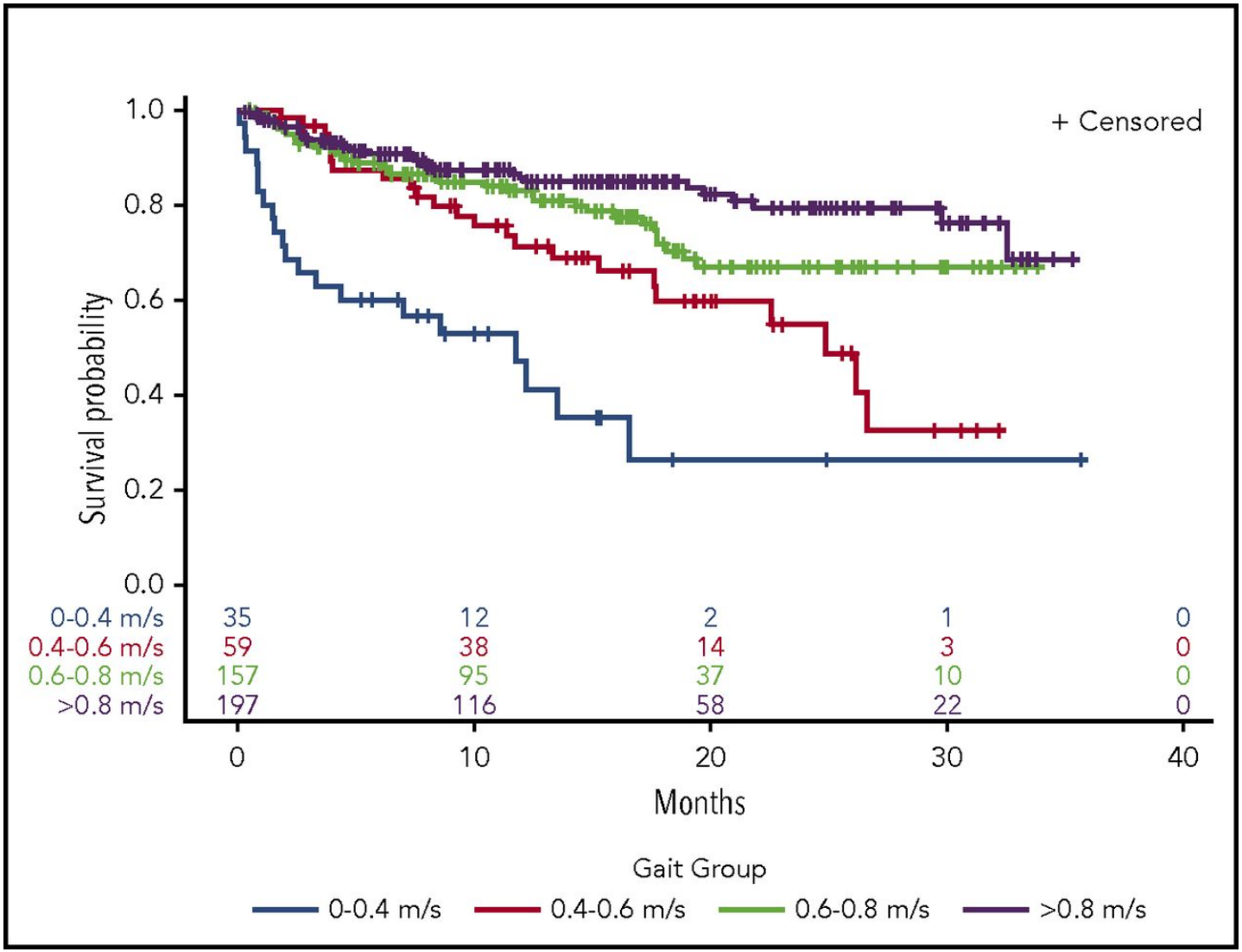


Progression-free Survival

Overall Survival

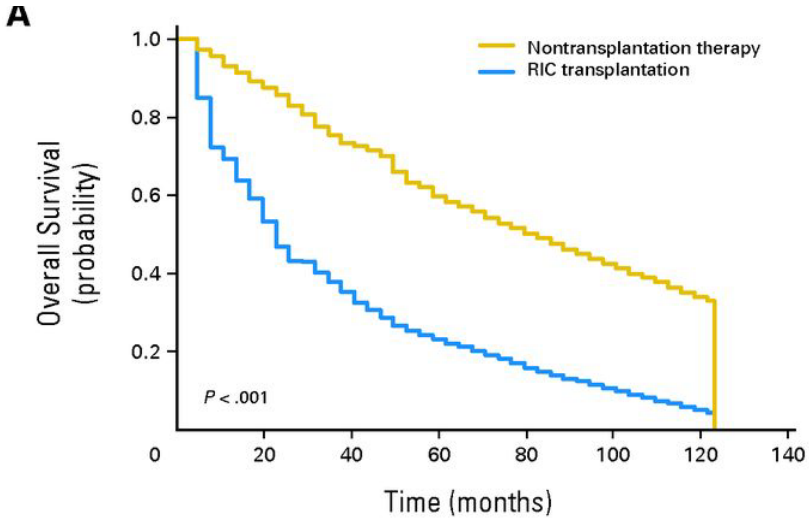
Ch. Kyriakou et al, BBMT 24:86, 2019

Survival by gait speed

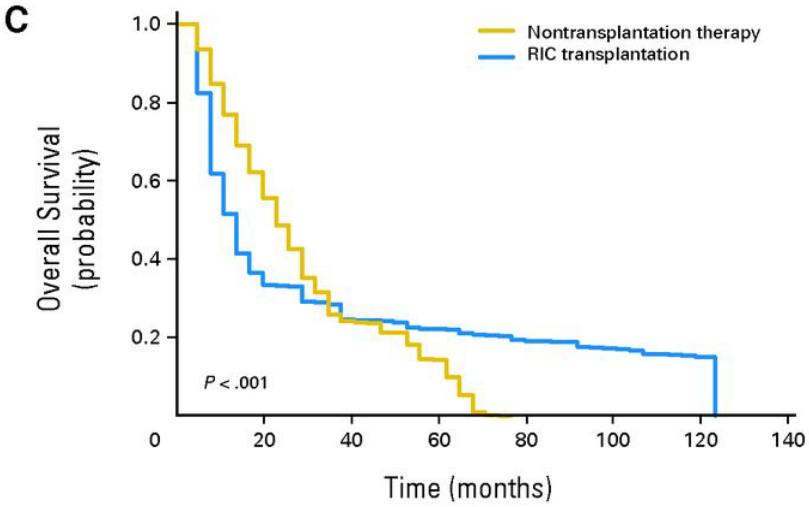


Michael A. Liu et al. Blood 2019;134:374-382

RIC in patients 60 – 70 ys of age
(by IPSS risk)



IPSS Low/Int-1

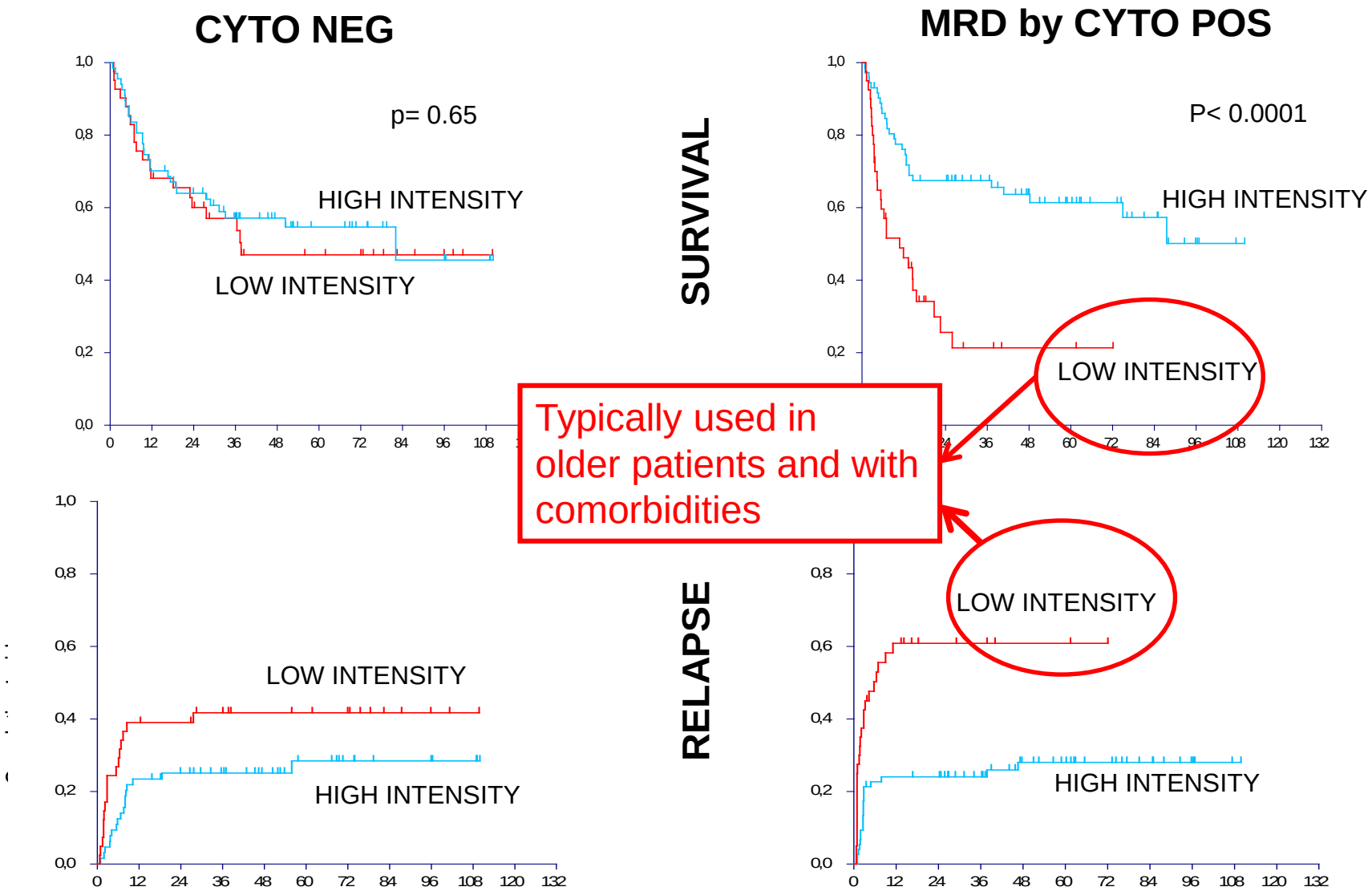


IPSS Int-2/High

Koreth J et al *JCO* 2013; 31: 2662

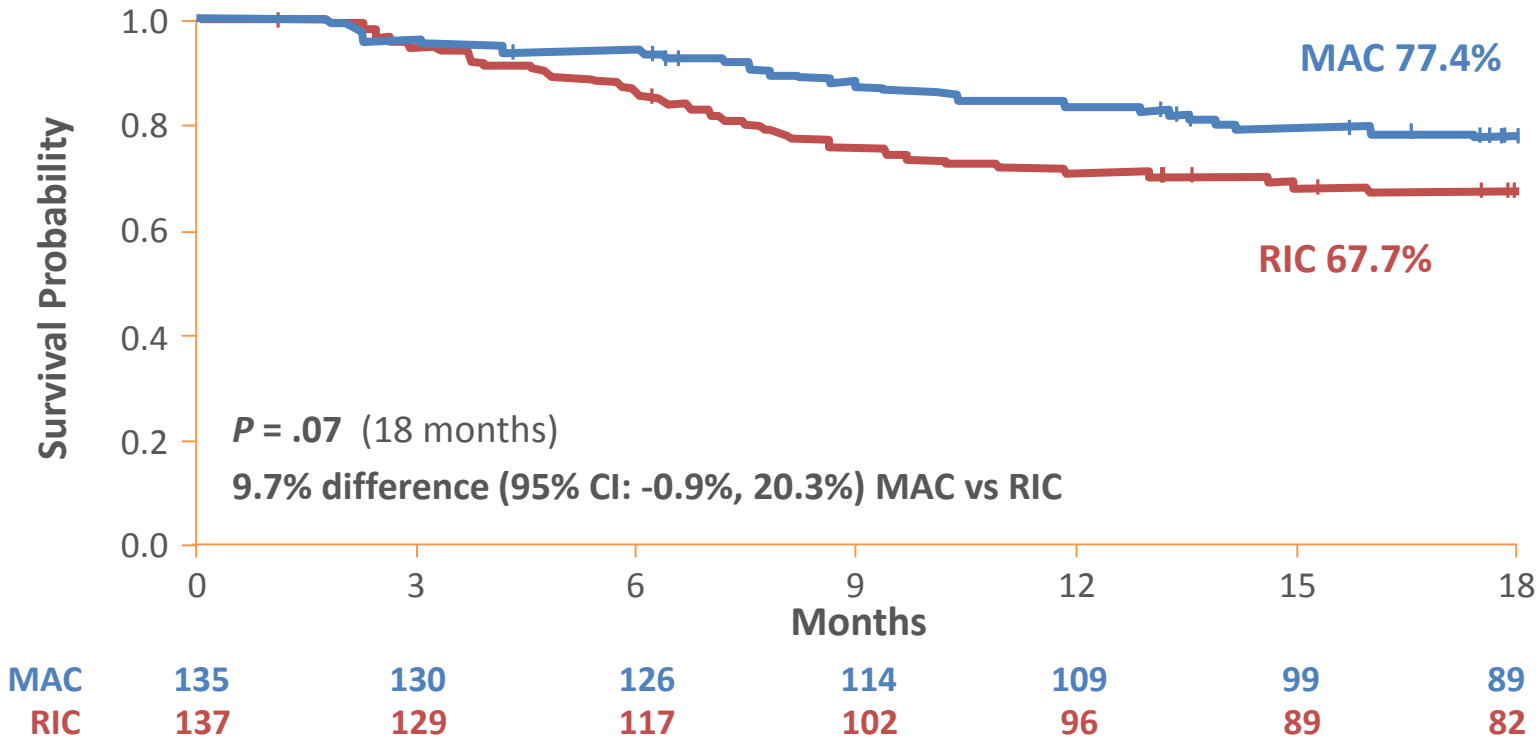
MRD and CONDITIONING Intensity

(Patients in *morphologic remission*)



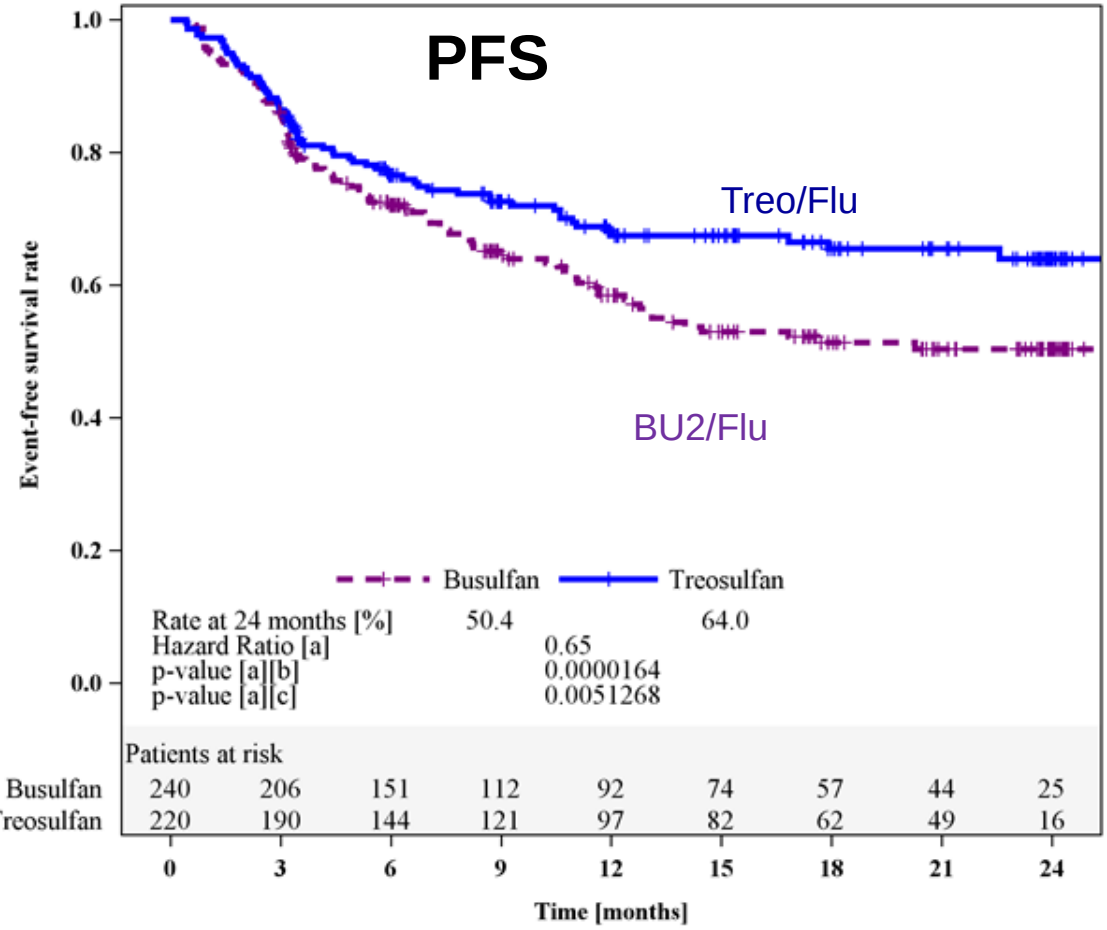
M. Festuccia et al, BBMT 2016

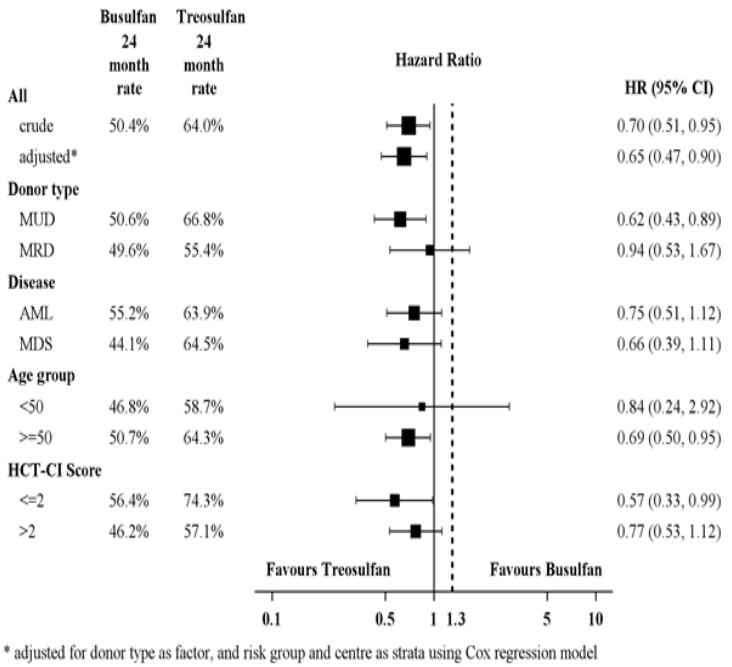
Conditioning Intensity and Survival



Scott B. et al. *J Clin Oncol.* 2017;35:1154-1161

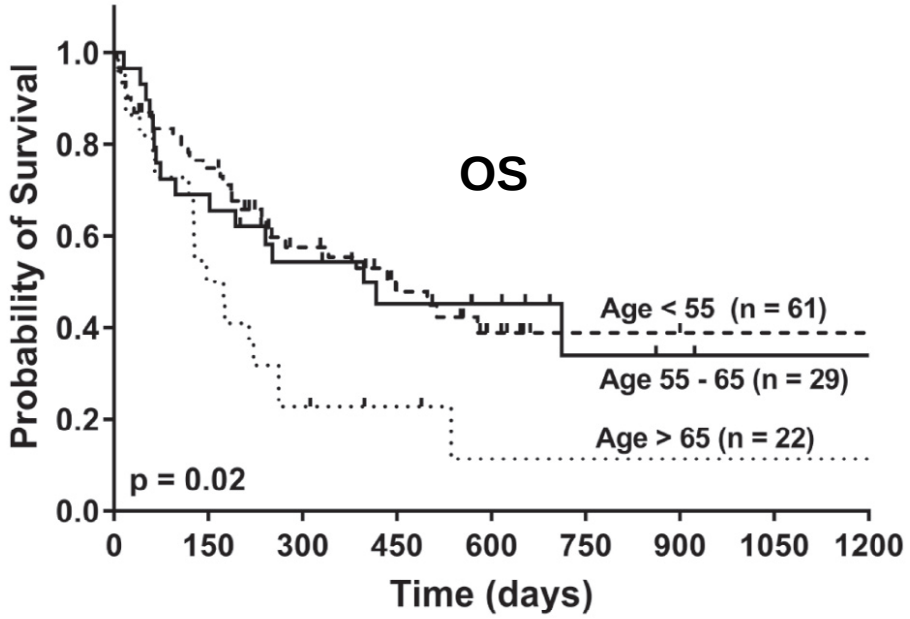
BU2/Flu vs Treosulfan/Flu

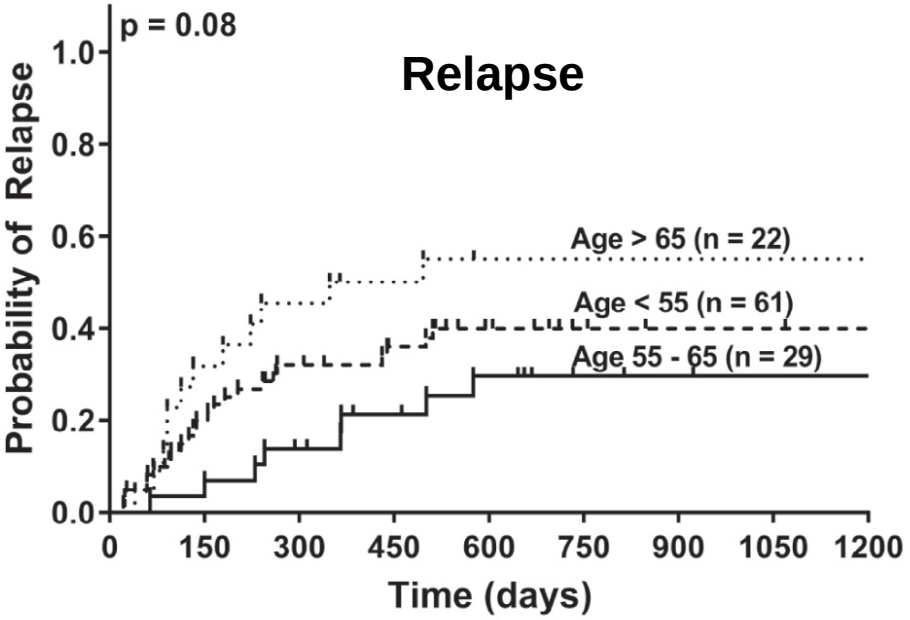




* adjusted for donor type as factor, and risk group and centre as strata using Cox regression model

D. Beelen et al, EBMT 2018





HLA *haplo*identical HCT for MDS and AML with post-HCT CY

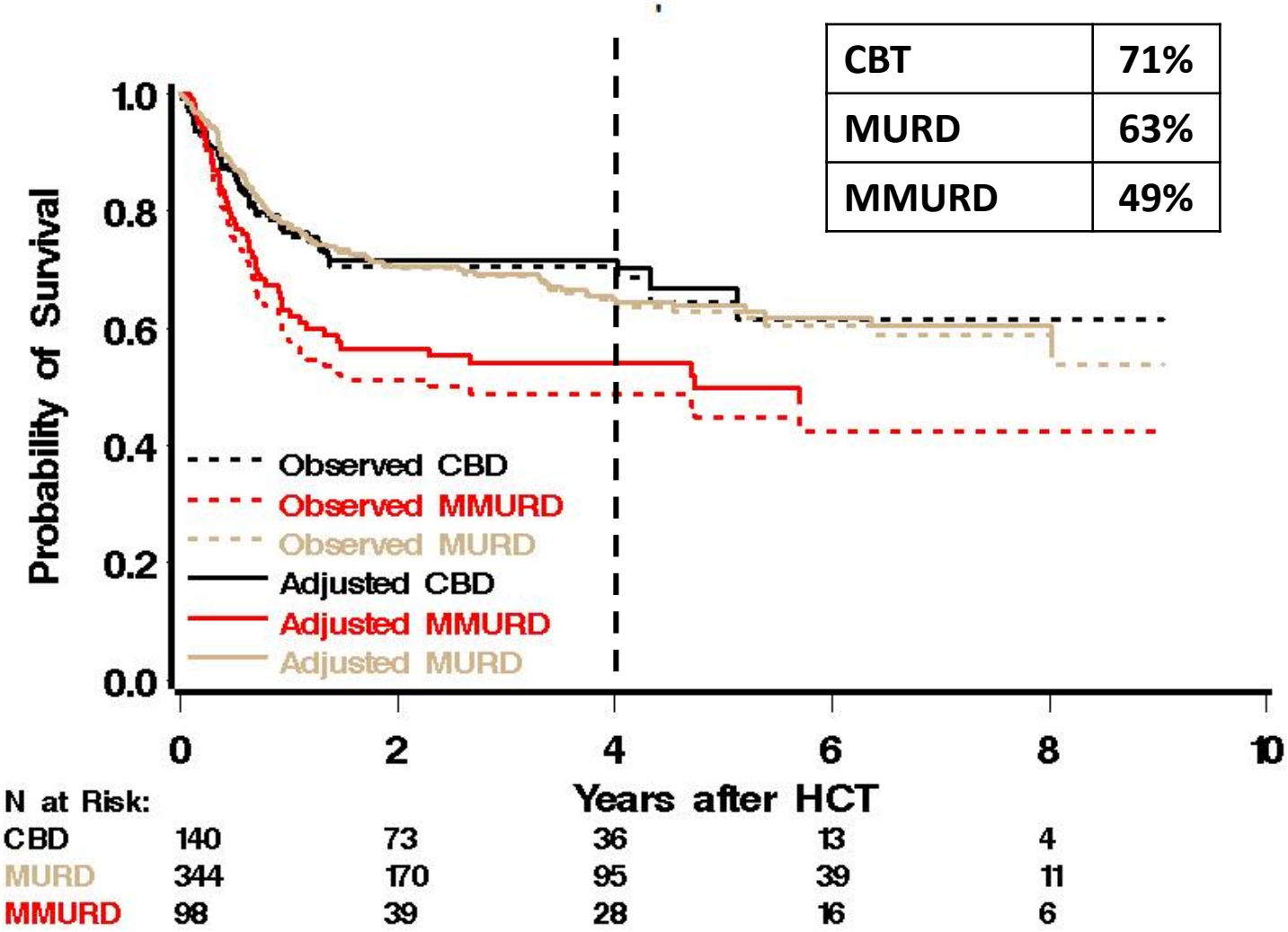
M. Slade et al, BBMT 23:1736, 2017

Umbilical Cord Blood

Cord Blood HCT

(High intensity conditioning)

CBT	71%
MURD	63%
MMURD	49%

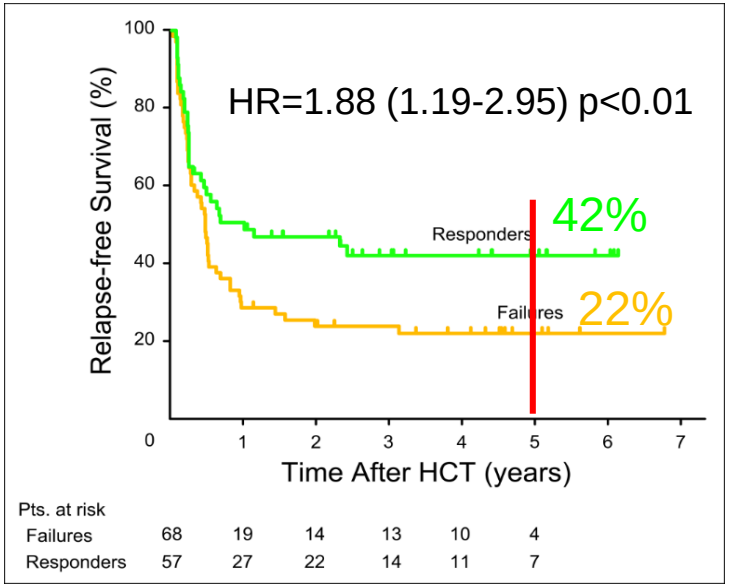


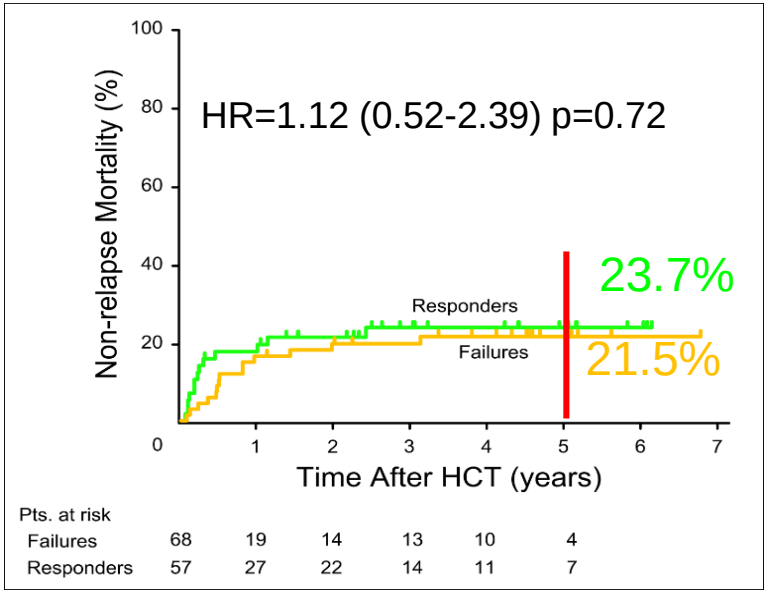
N at Risk:					
CBD	140	73	36	13	4
MURD	344	170	95	39	11
MMURD	98	39	28	16	6

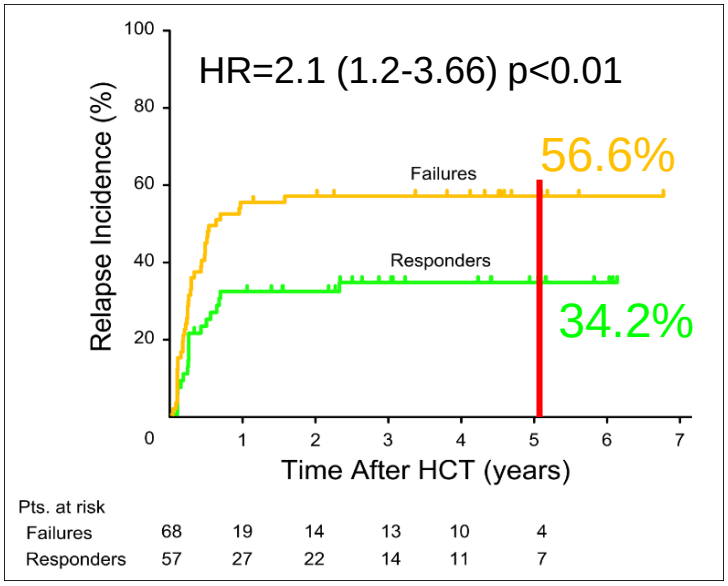
F.Milano et al NEJM 375: 944, 2016

“Bridging” Treatment pre-Transplant?

Post-HCT Outcomes after HMA Failure



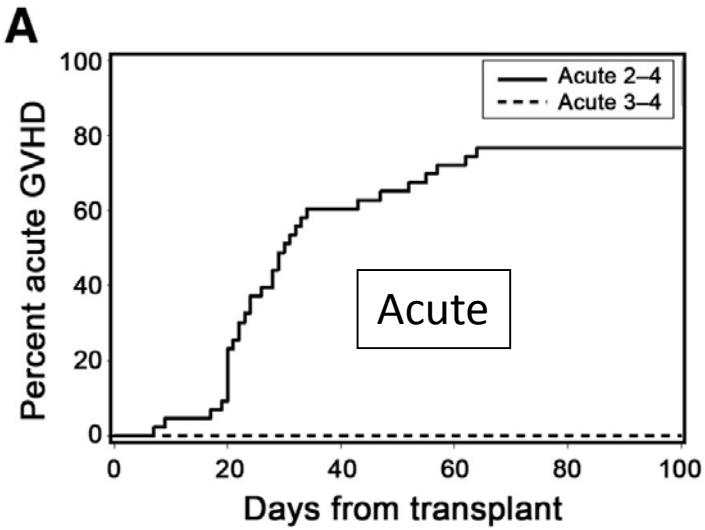


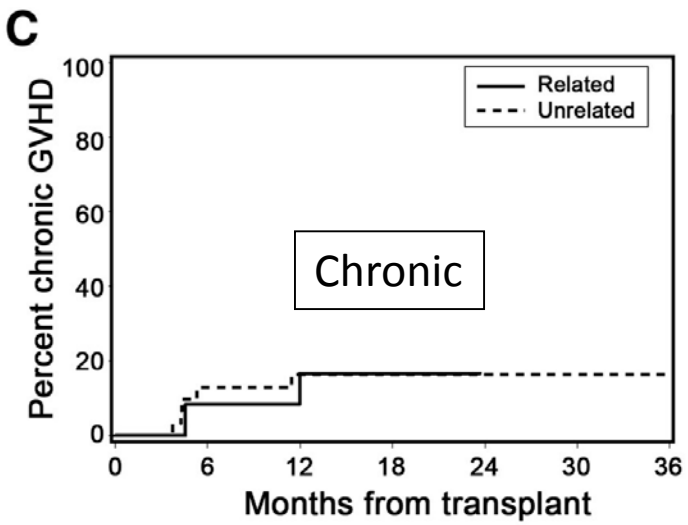


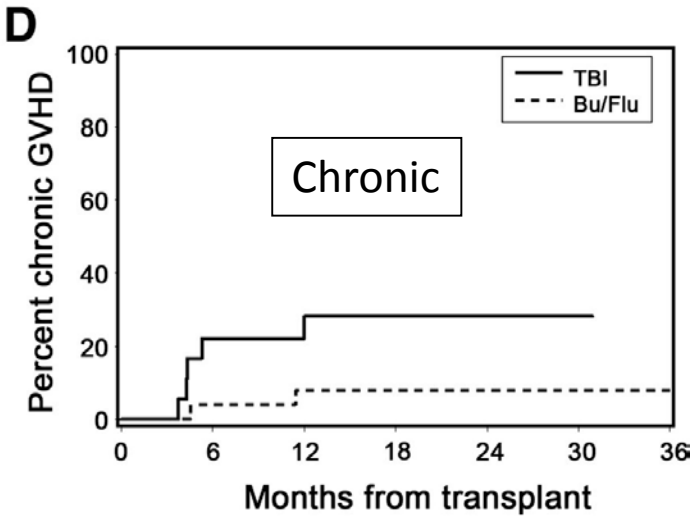
M. Festuccia et al, BBMT 2017

GVHD

Acute and chronic GVHD with post-transplant CY





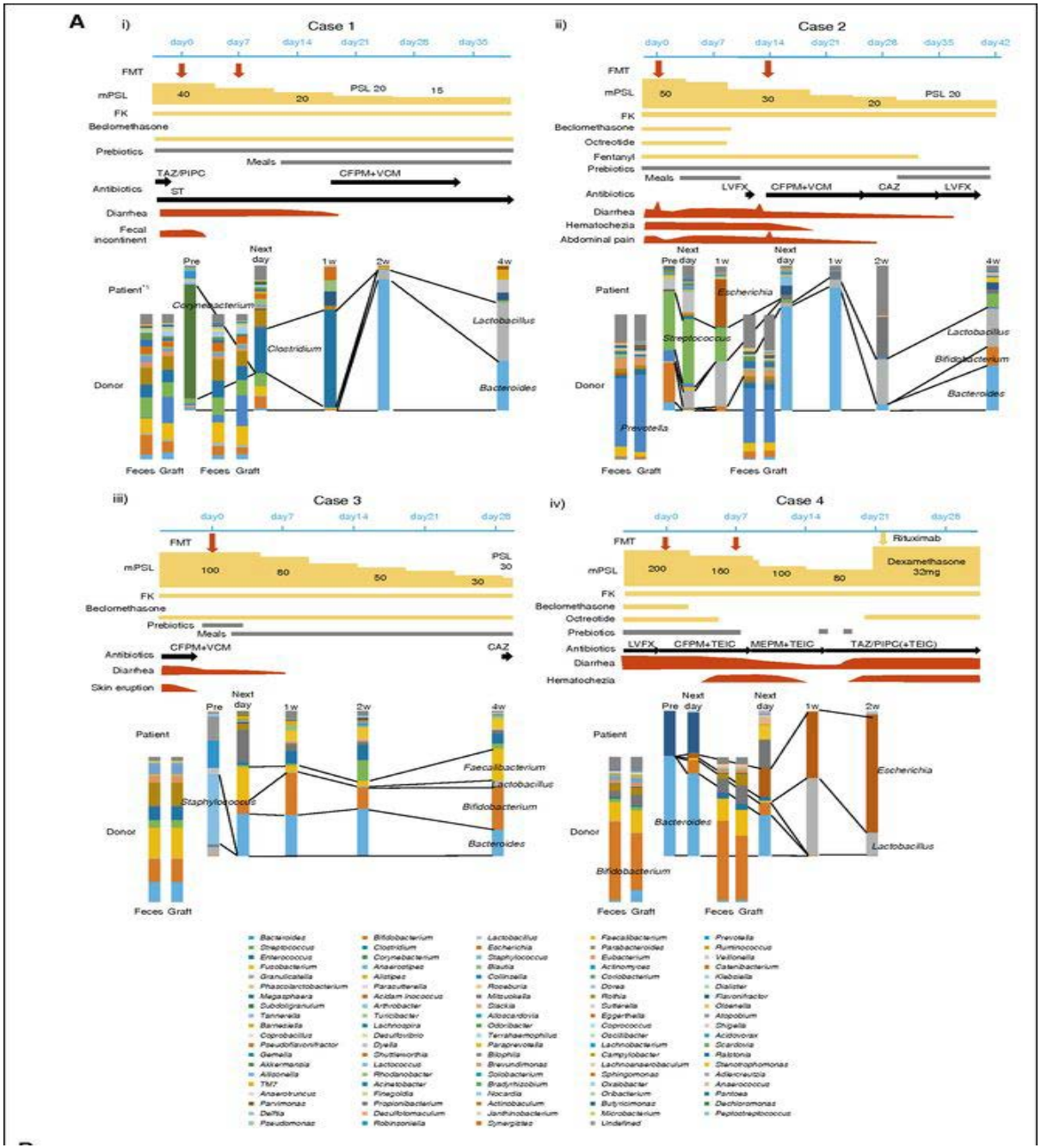


M. Mielcarek et al. Blood 27:1502, 2016

New Developments

Intestinal Bacteria (microbiome) and GVHD

Changing intestinal microbiota by *fecal transplants* in patients



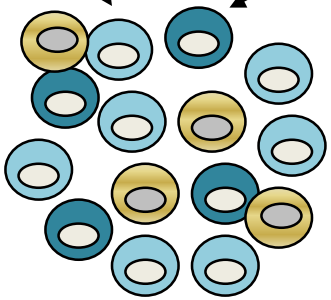
Kazuhiko Kakihana et al. Blood 2016;128:2083-2088

Naïve T cell Depletion

Selective T_N depletion for GVHD reduction

GVHD (T_N)

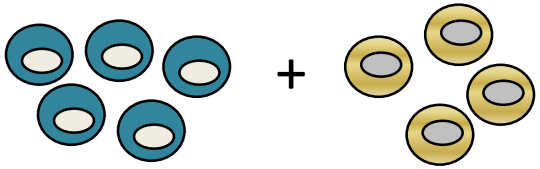
Pathogen-specific T cells (T_M)



No T cell depletion

GVHD

Immune reconstitution



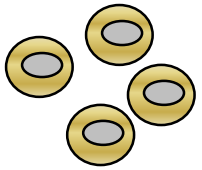
Selective T_N *de*pletion

Goal:

GVHD

Immune reconstitution

CD34$^+$ stem cells



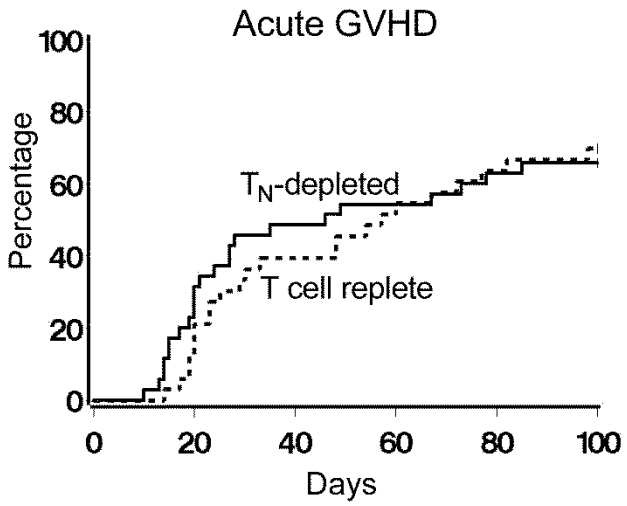
Complete T cell *de*pletion

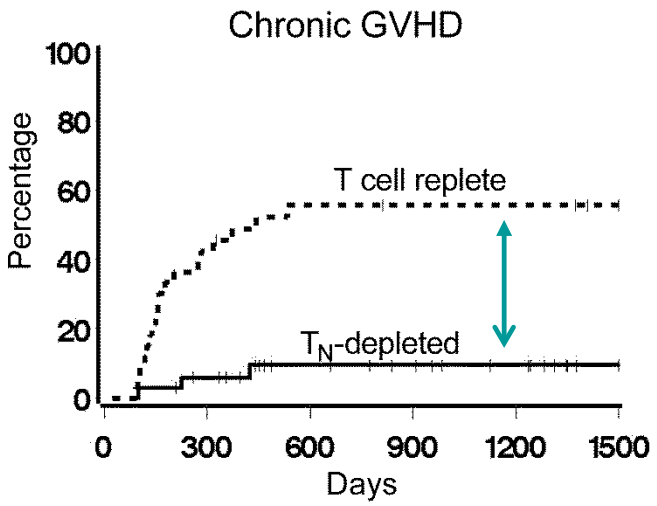
GVHD

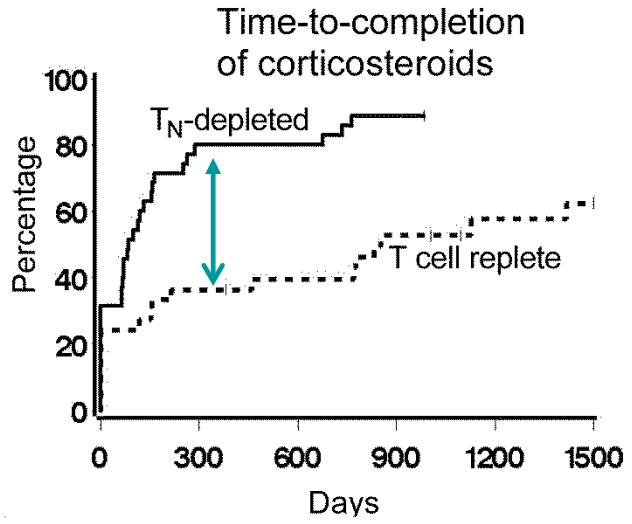
Immune reconstitution

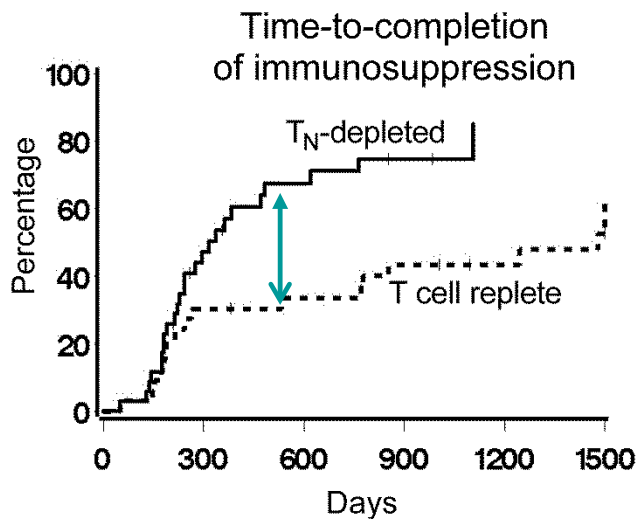
M. Bleakley et. al JCI 2015

T_N-depleted HCT: Less/shorter treatment needed for GVHD









(Compared to T cell replete HCT, HLA = sibs conditioned with TBI-Cy, given Tacrolimus, MTX)

M. Bleakley et. al JCI 2015

Anti-CD117 antibody

Summary

- **Indications for Transplantation**
  - Intermediate or higher risk MDS
  - Life threatening cytopenias
  - High risk mutations
- **Relative contraindications**
  - Comorbidities
  - Older age
- **Choice of Conditioning Regimen**
  - Based on underlying disease risk, stage and health of patient

Thanks to many colleagues
– and our patients!