Conditioning Regimens and Stem Cell Sources for Allogeneic Hematopoietic Cell Transplantation in MDS

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DISCLOSURE

I have the following financial relationships:

Consultant for: Medac Pharma, Inc.

Contracted Research for: Celgene Corporation

Transplantation comes as a package:

- Assessment of patient and disease characteristics
- Non-transplant/Pre-transplant therapy
- Stem cell source/Donor selection
- Transplant (HCT) conditioning
- Post-transplant care
  - GVHD prophylaxis
  - Relapse prevention

Background

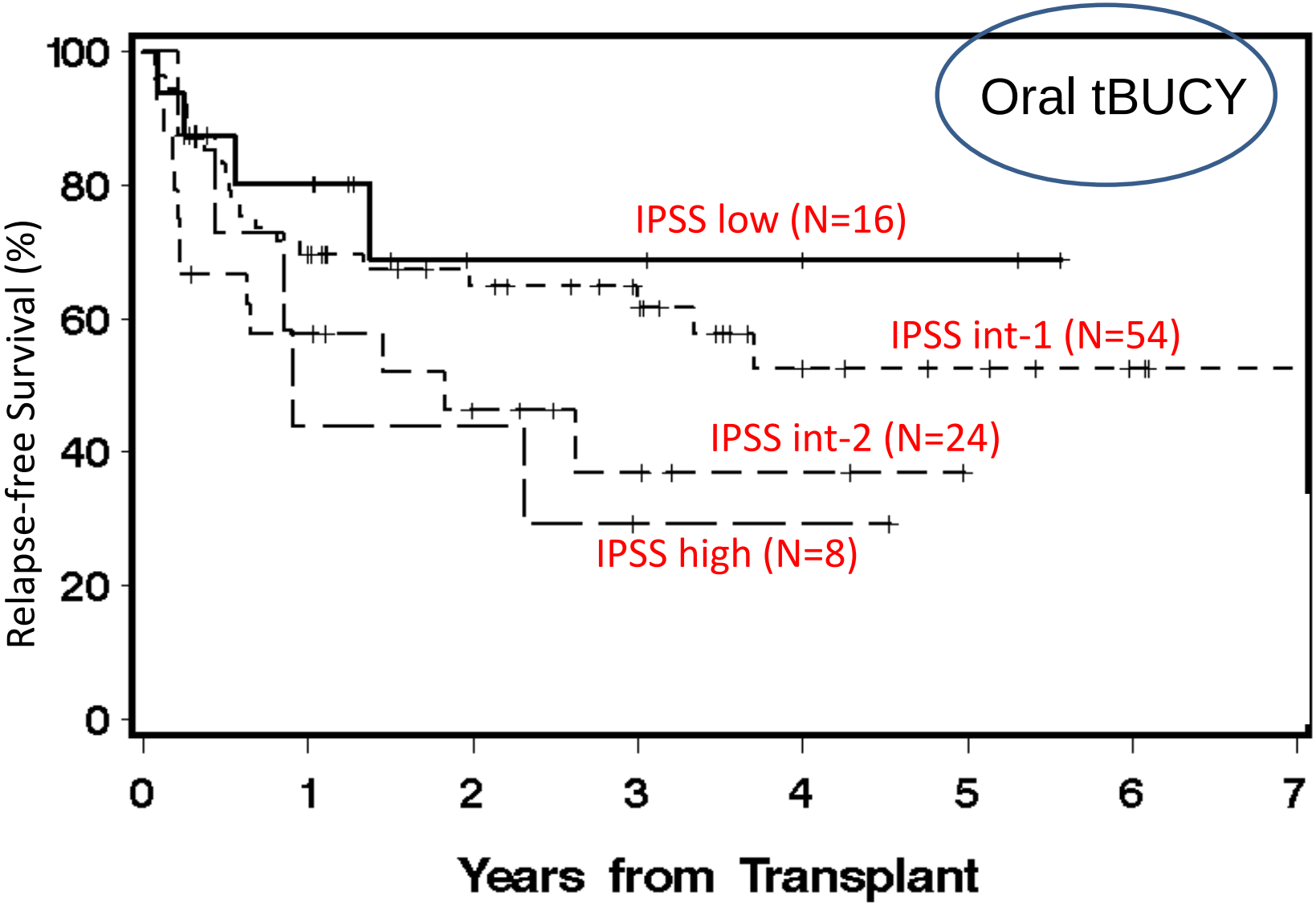
30 years ago……

- 10 patients, transplants from HLA matched siblings
  - 3 conditioned with CY (considered to have aplastic anemia) – persistent/recurrent disease
  - 7 conditioned with CY + TBI – 6 surviving in remission
- ***6 of 10 (60%) surviving***

F. Appelbaum et al, Ann Int Med 1984

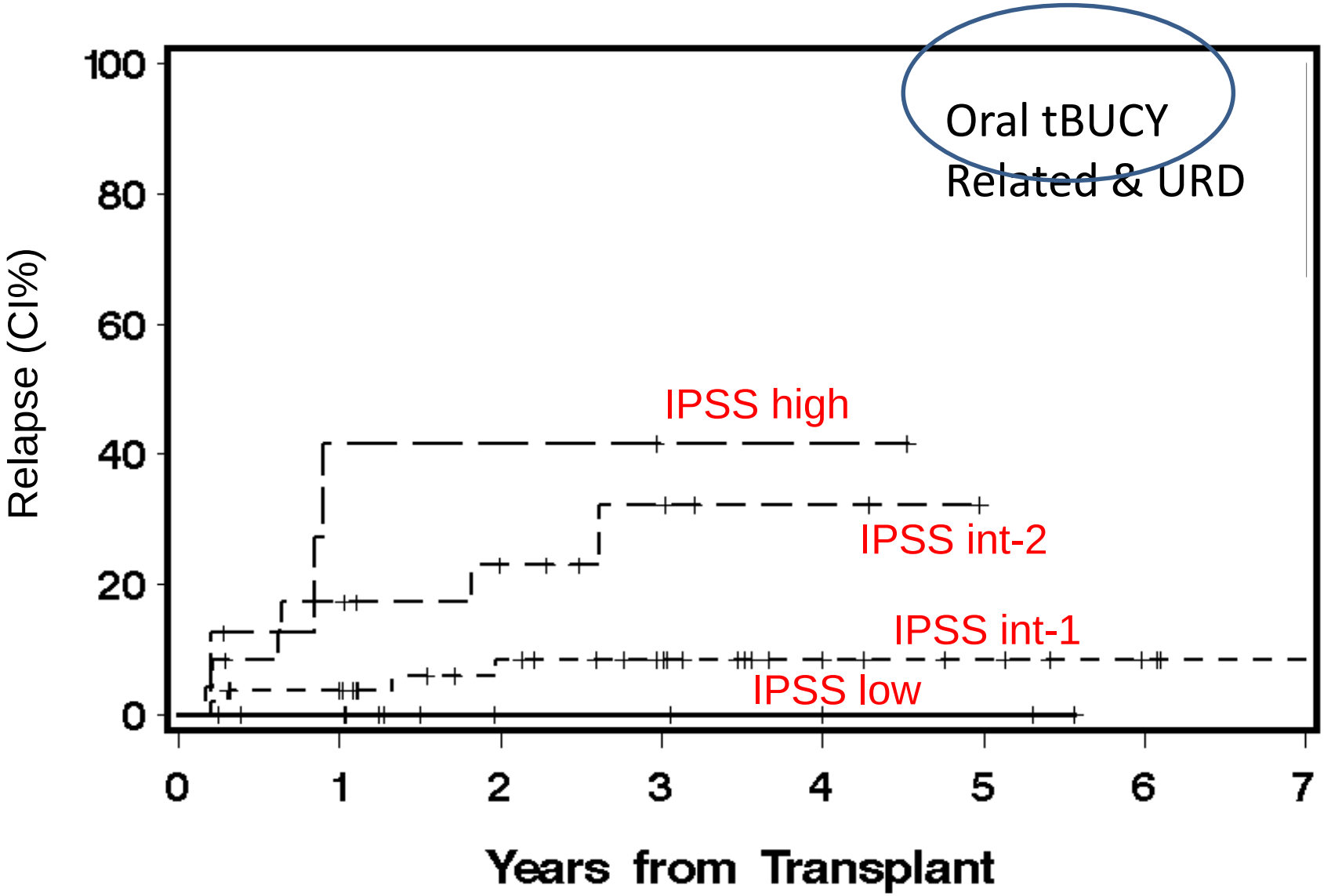
Relapse-free Survival (N=102)

Patients 6-66 years old, related or unrelated donors



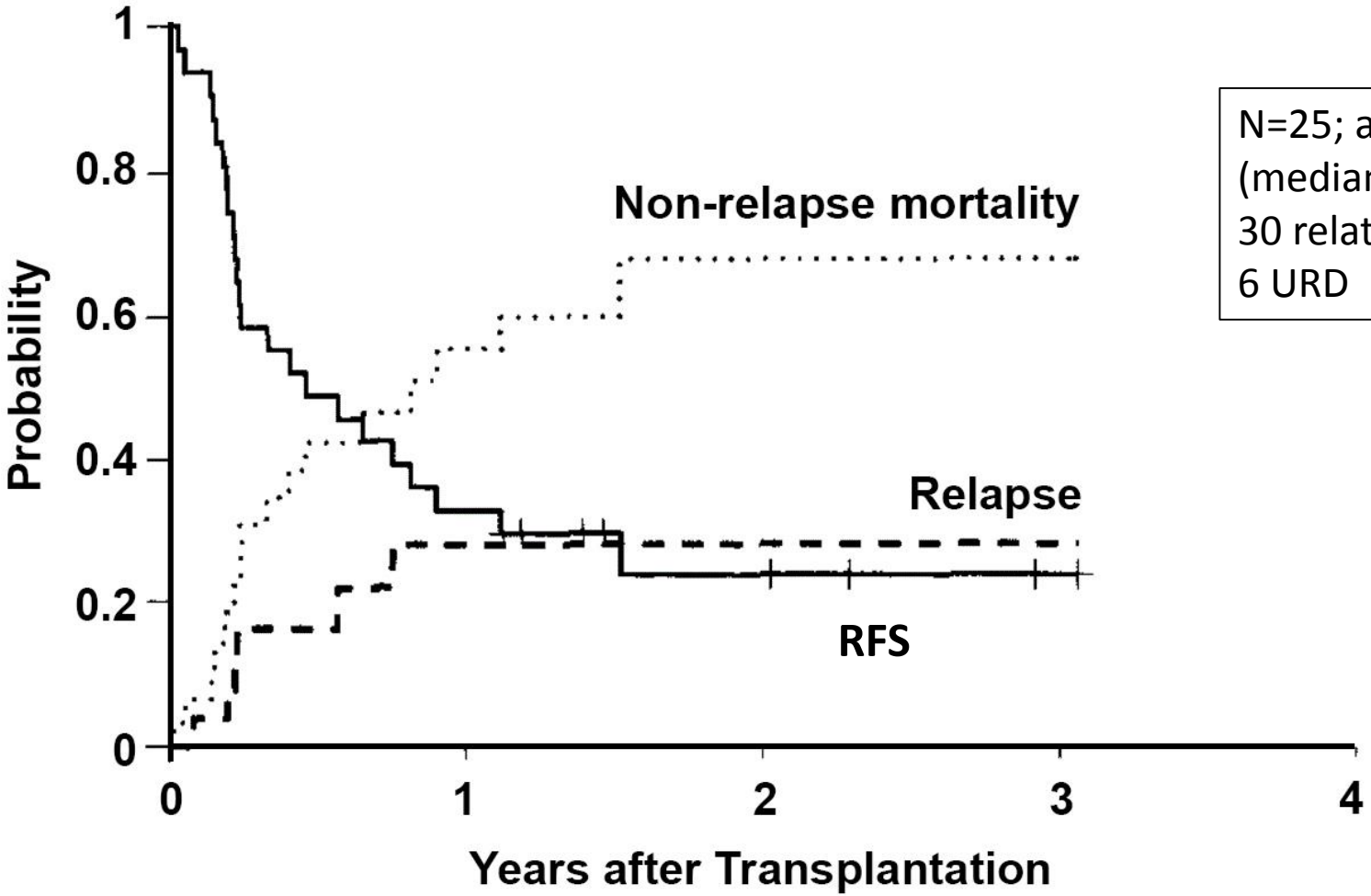
Deeg et al., Blood 2002

Relapse



Deeg et al., Blood 2002

Conditioning with BU/CY/TBI for HCT in MDS



N=25; ages 16-54 (median 41) ys
30 related = or ≠
6 URD

J E Anderson et al., *JCO 14: 220, 1996*

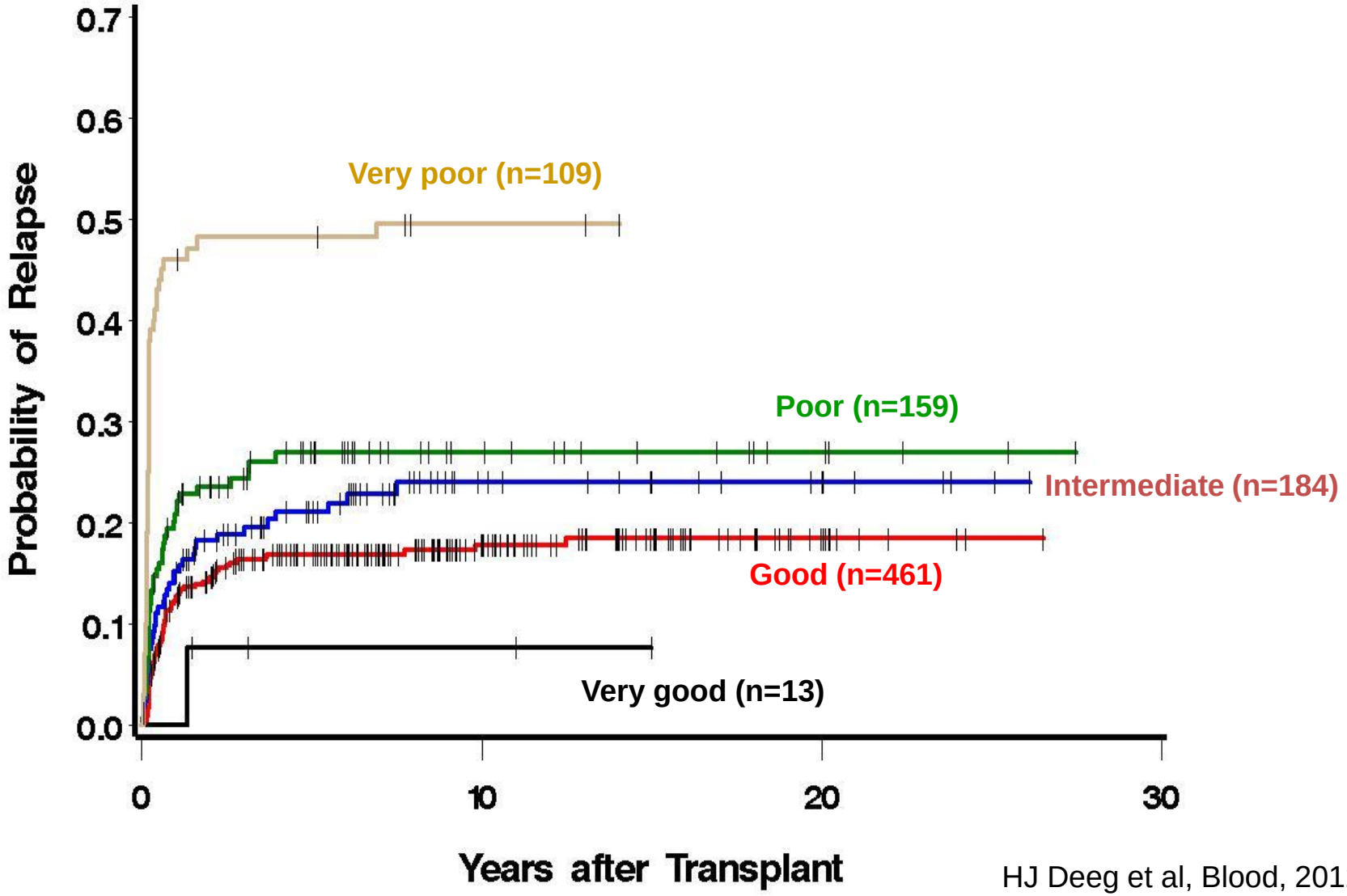
Recent Developments

5-Group Cytogenetic Classification

Prognosis	Cytogenetic Abnormality			Survival (ms) Median (CI)
	Single	Double	Complex	
Very good	del(11q) -Y	---	---	60.8 (50.3 –NR)
Good	normal del(5q) del(12p) del(20q)	incl.del(5q)	----	48.6 (44.6-54.3)
Intermediate	del(7q), +8, i(17q), +19, any other	any other	----	26.0 (22.1-31.0)
Poor	der(3)(q21;q26), -7	incl. -7, del(7q)	3 abnl.	15.8 (12.0-18.0)
Very poor	---	---	≥4 abnl.	5.9 (4.9-6.9)

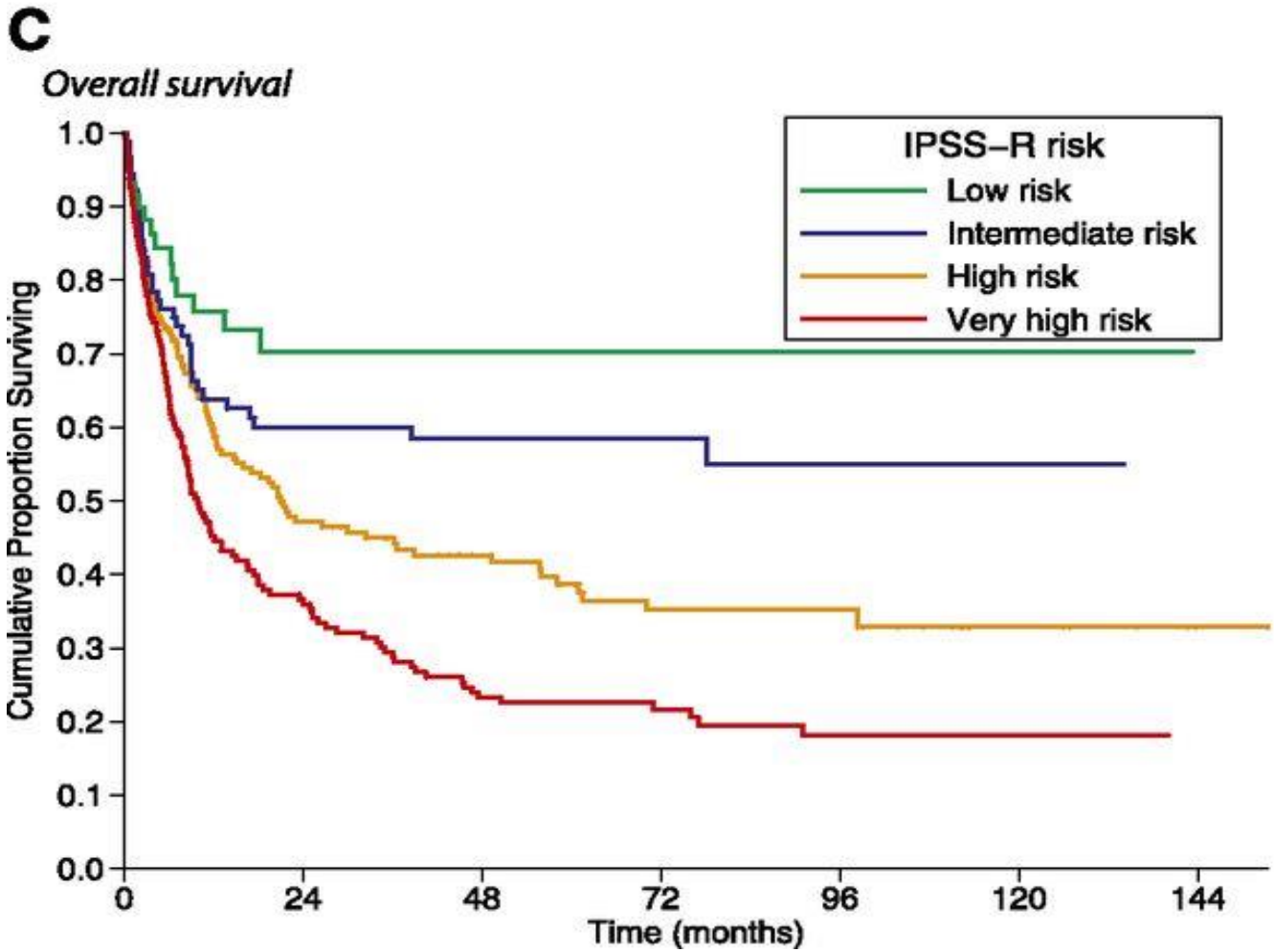
J. Schanz et al, JCO, 2011

Relapse by 5-Group Karyotype



HJ Deeg et al, Blood, 2012

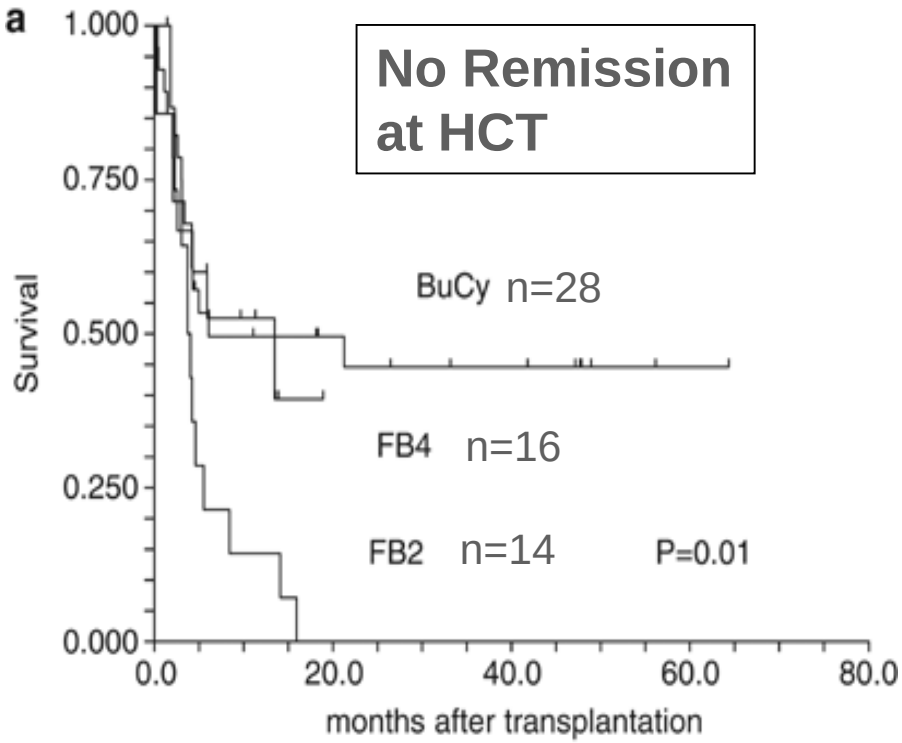
Survival and relapse by IPSS-R risk.

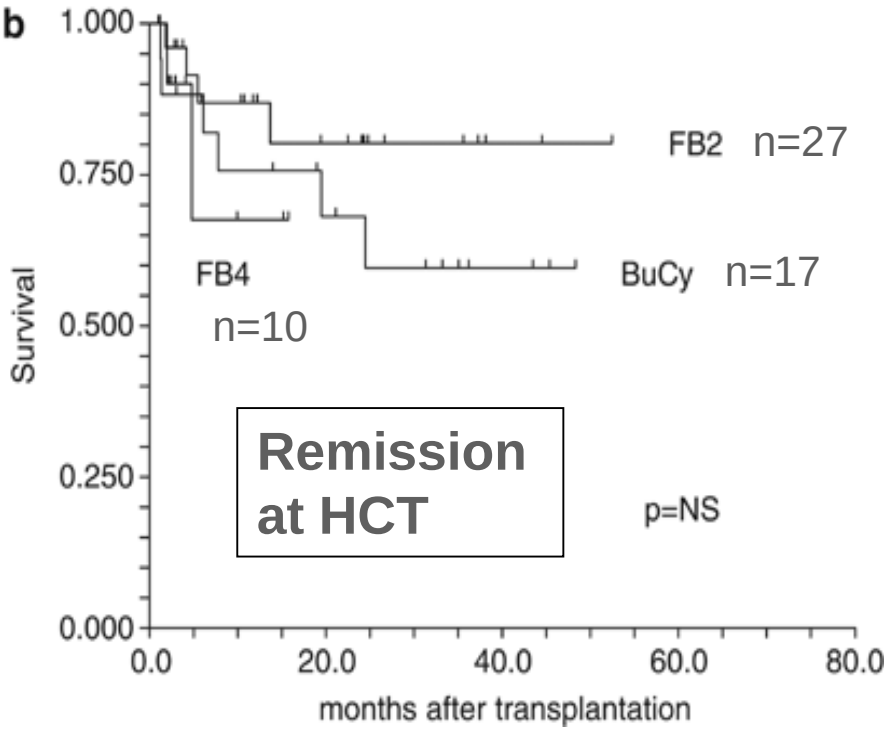


Della Porta M G et al. Blood 2014;123:2333-2342

Is Pre-HCT “pre-conditioning” effective in reducing post-HCT relapse?

Bu Dose Intensity in AML/MDS: Importance of *Disease Status*

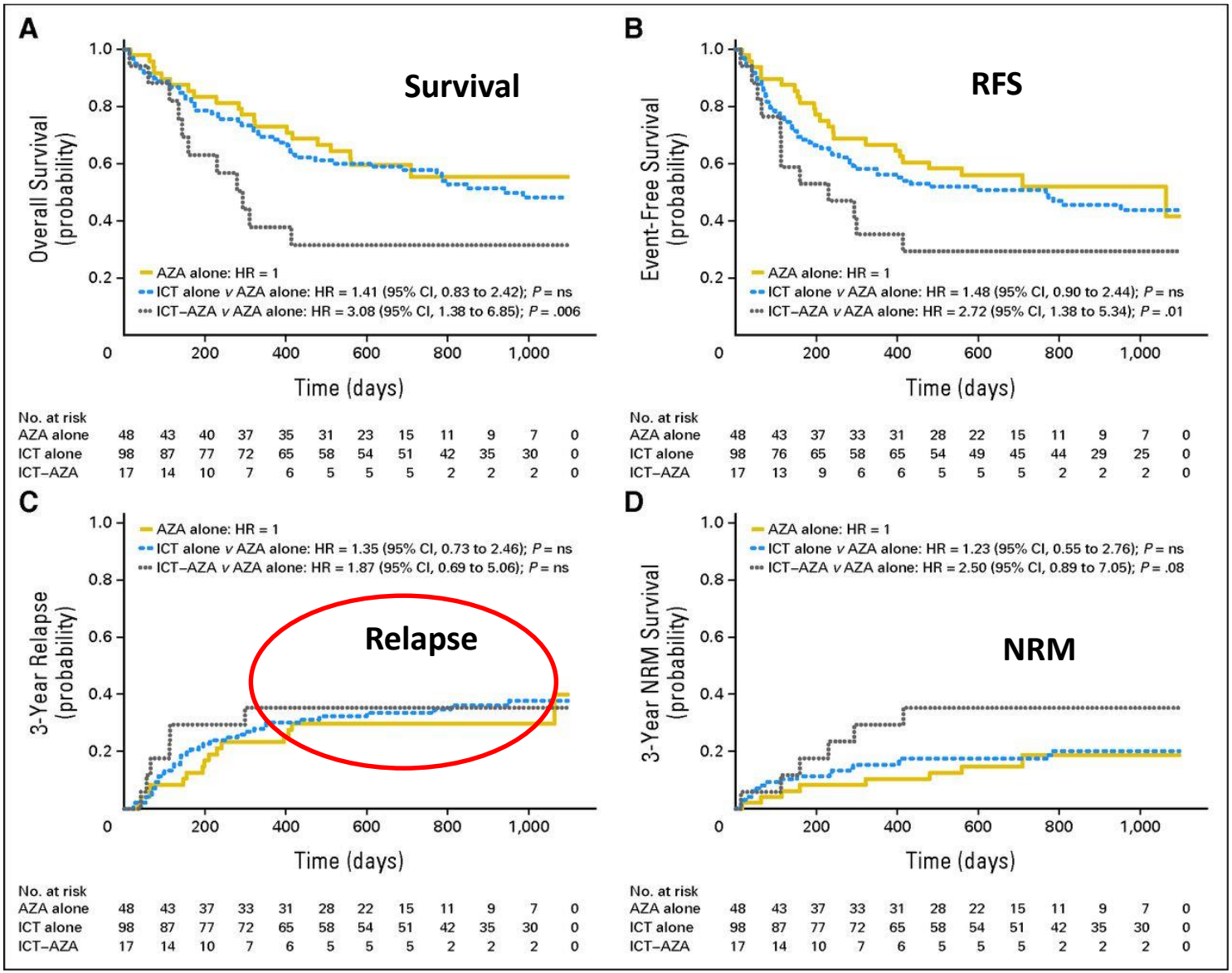




BuCy=12.8 mg/kg iv Bu + 120 mg/kg Cy
FB4=150-160 mg/m^2 Flu + 12.8 mg/kg Bu
FB2=150-160 mg/m^2 Flu + 6.4 mg/kg Bu

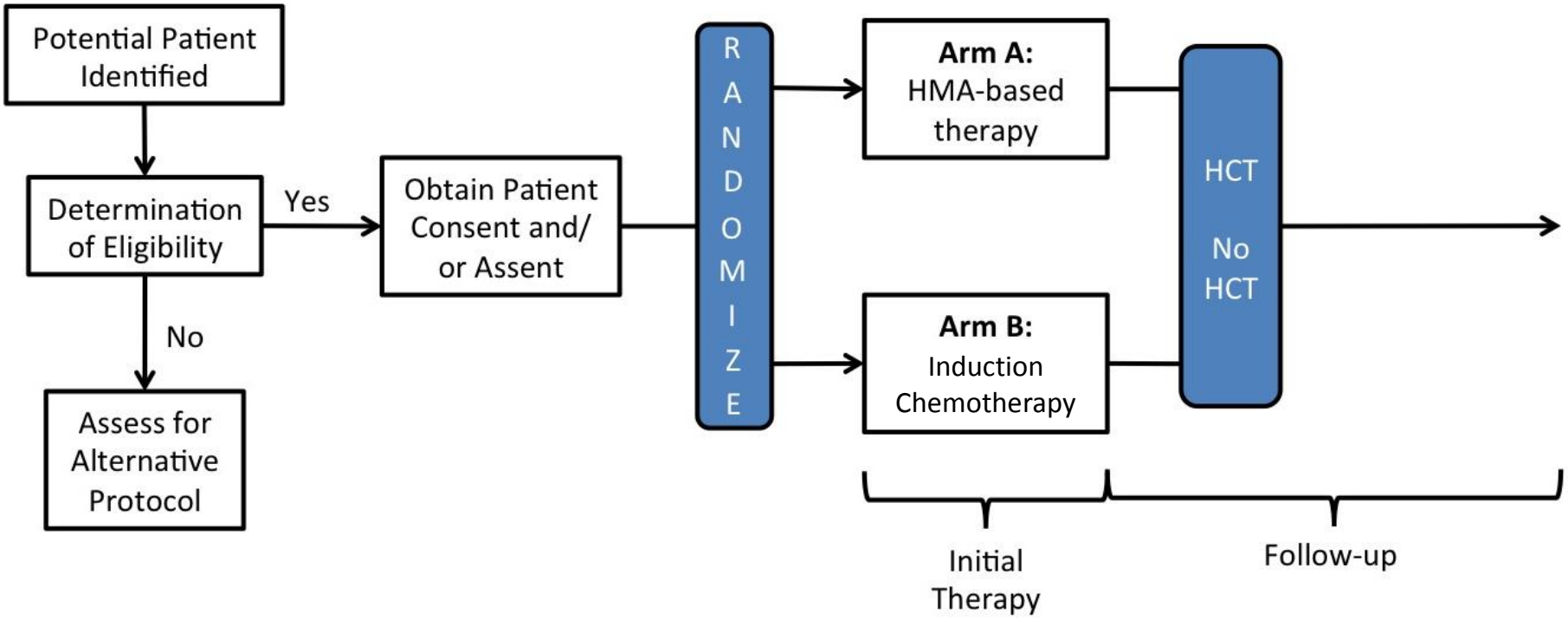
Shimoni et al. *Leukemia* 2006;20:322-328

Outcome according to pre-HCT treatment (N=163)



Damaj G et al. JCO 2012;30:4533-4540

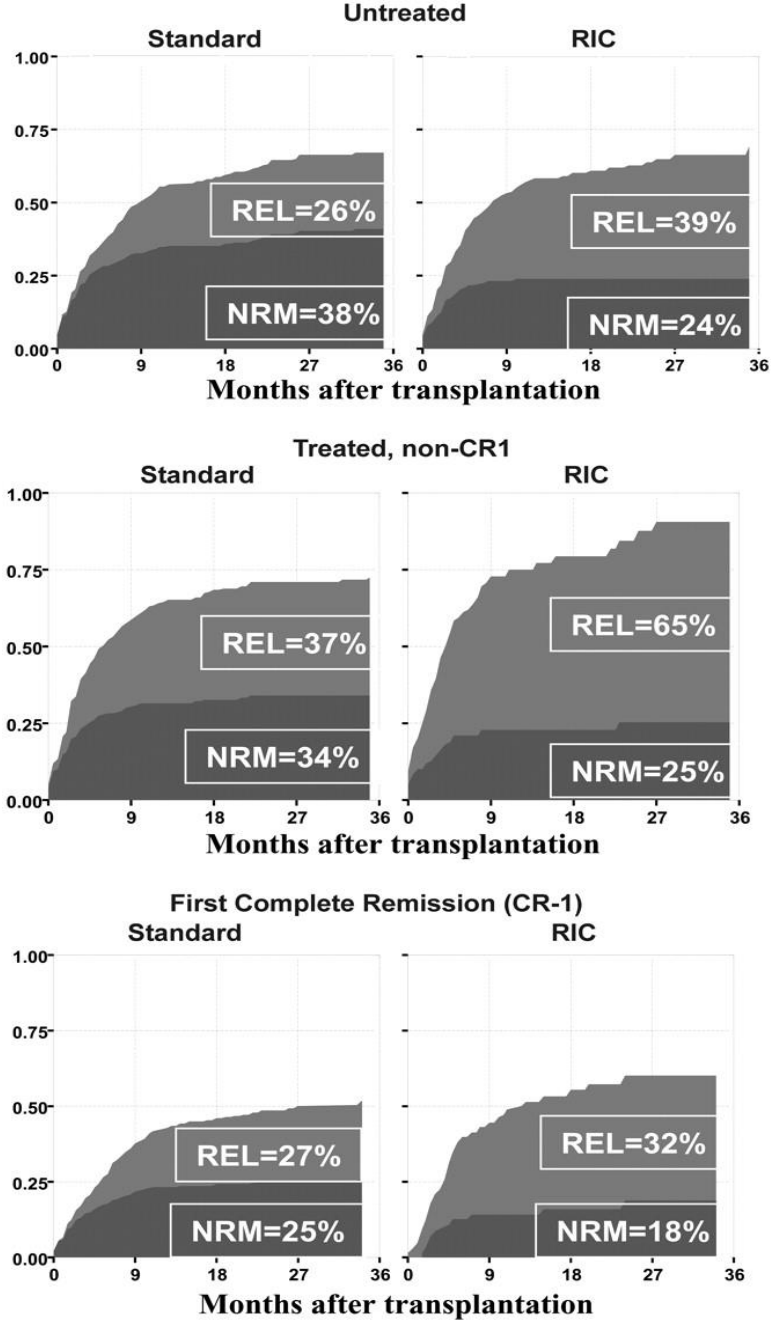
Study Schema (FHCRC # 2661)



A.Gerds, B.Scott, H.J.Deeg

Which Conditioning Regimen?

Relapse and Non-Relapse Mortality



Untreated

Treated no CR1

Treated CR1

Pre-Transplant

Martino, R. et al. Blood 2006;108:836-846

CTN Trial 0901 (*now closed*)

MDS/AML
< 5% blasts
Age 18-65 ys

Enrollment / Randomization

RIC Regimens

Flu/Bu

Flu/Mel

High Intensity Regimens

Bu/Flu

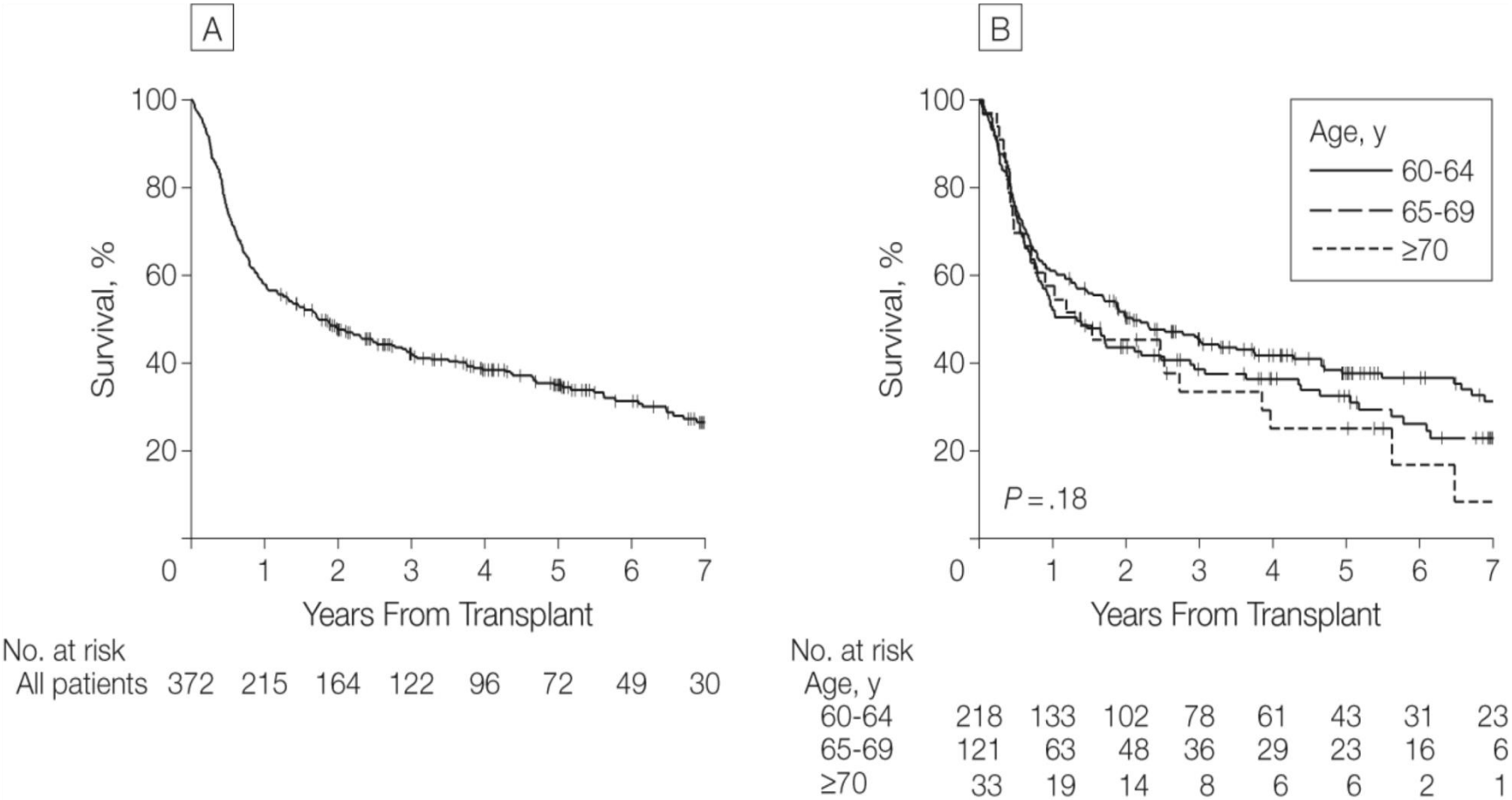
Bu/Cy

Cy/TBI

Primary Endpoint: 18-months Overall Survival

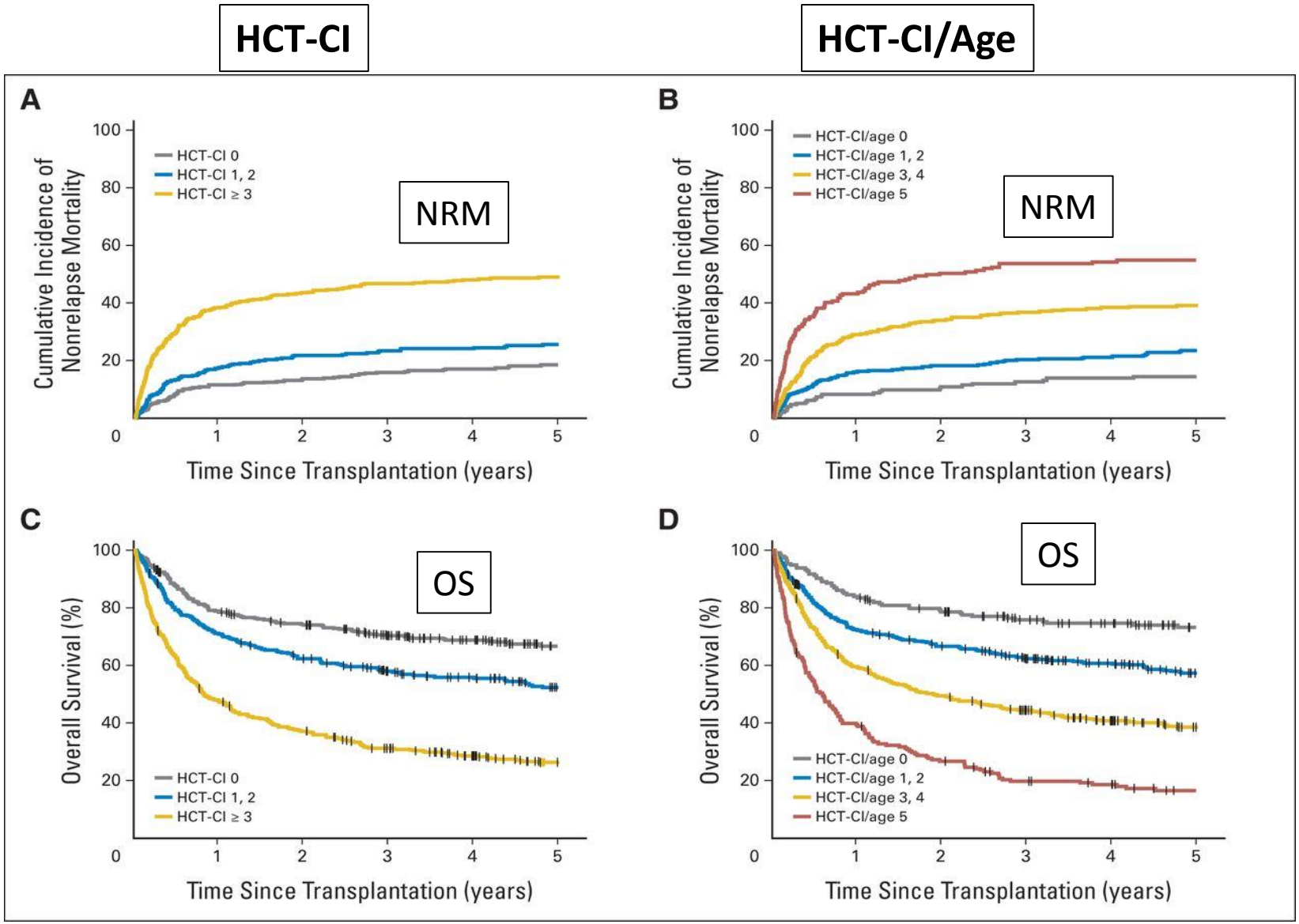
Age and Co-Morbidities

Survival by Age after NMA Conditioning and HCT for Advanced Hematologic Malignancies



JAMA. 2011;306(17):1874-1883. doi:10.1001/jama.2011.1558

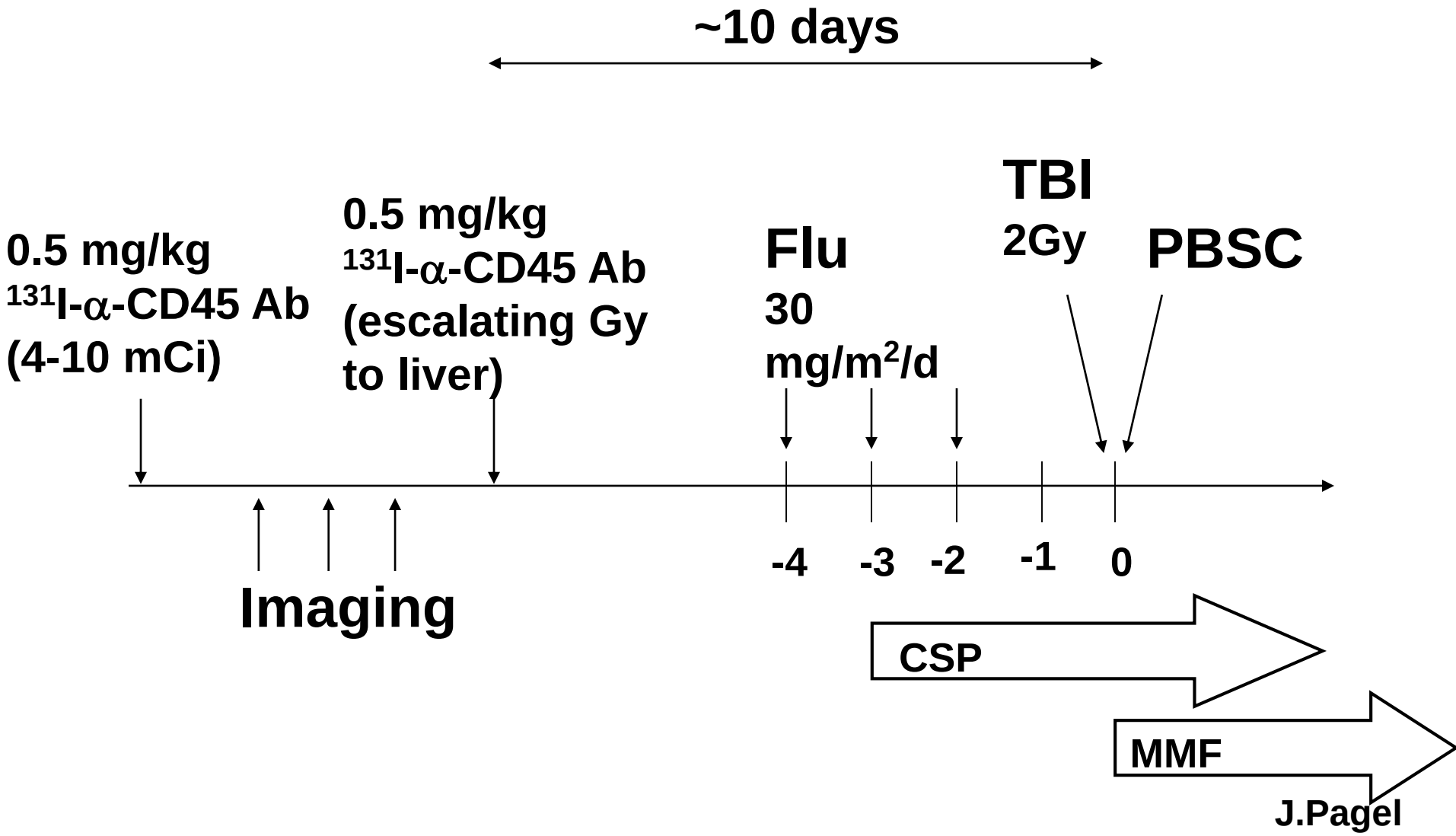
Impact of HCT-CI and the comorbidity/age index (HCT-CI/age)



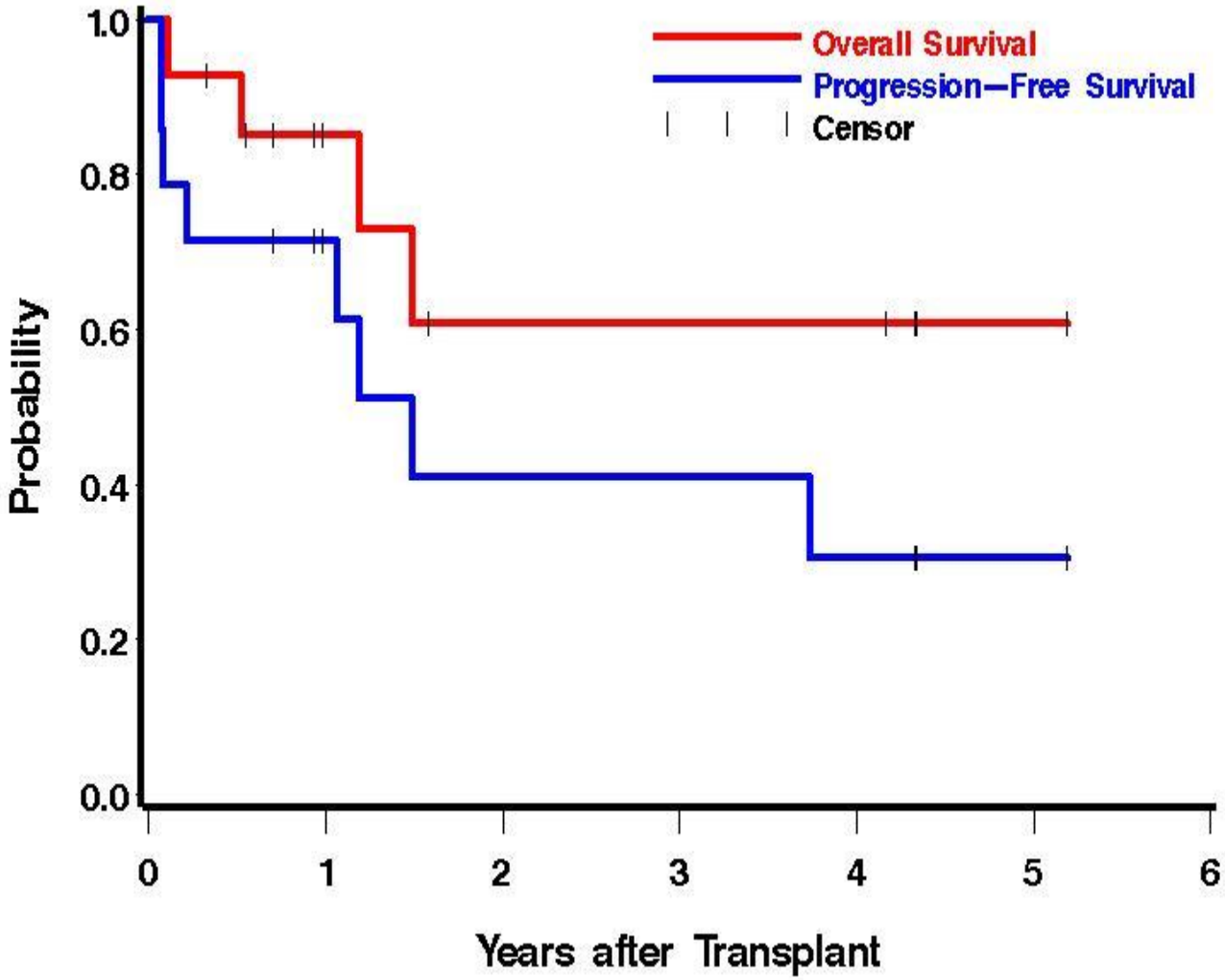
Sorror M L et al. JCO 2014;32:3249-3256

Other Conditioning Strategies

Radio-Immuno Therapy

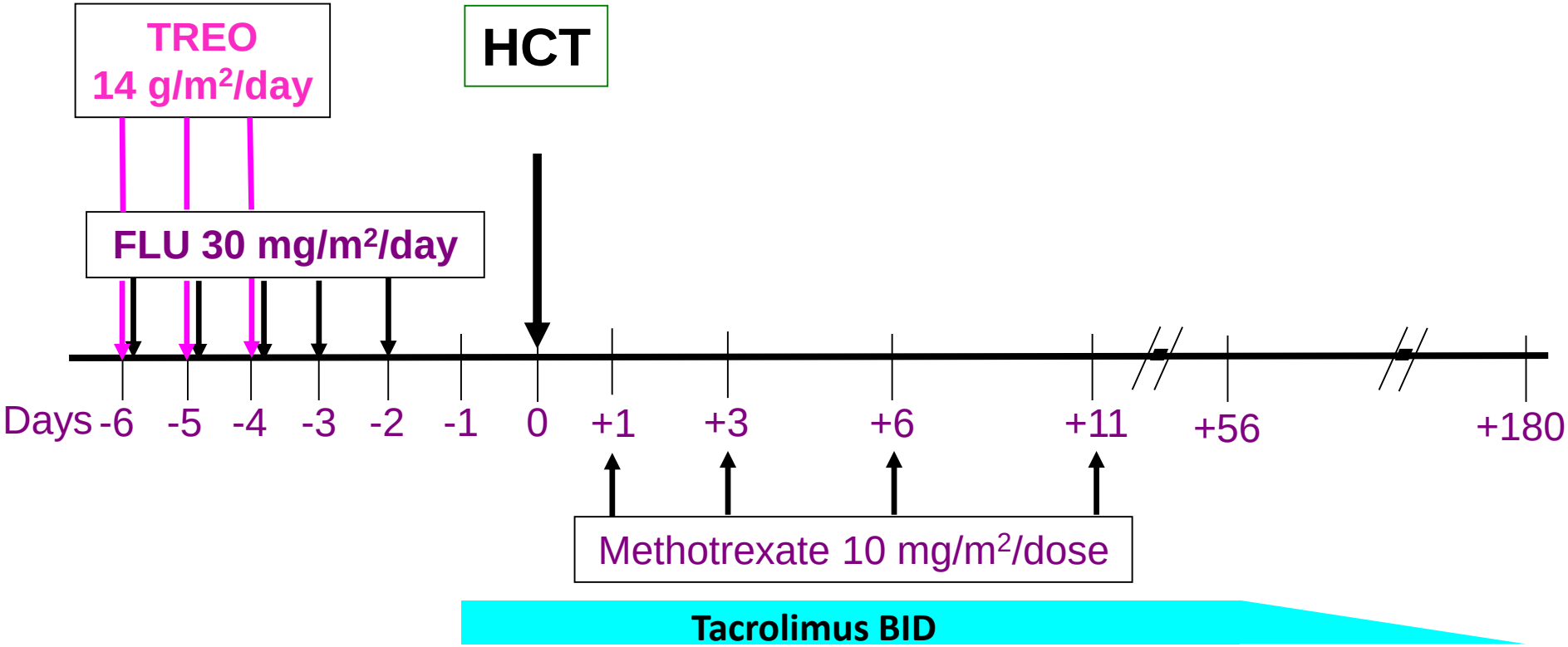


OS and PFS – Age < 50 ys, Advanced AML



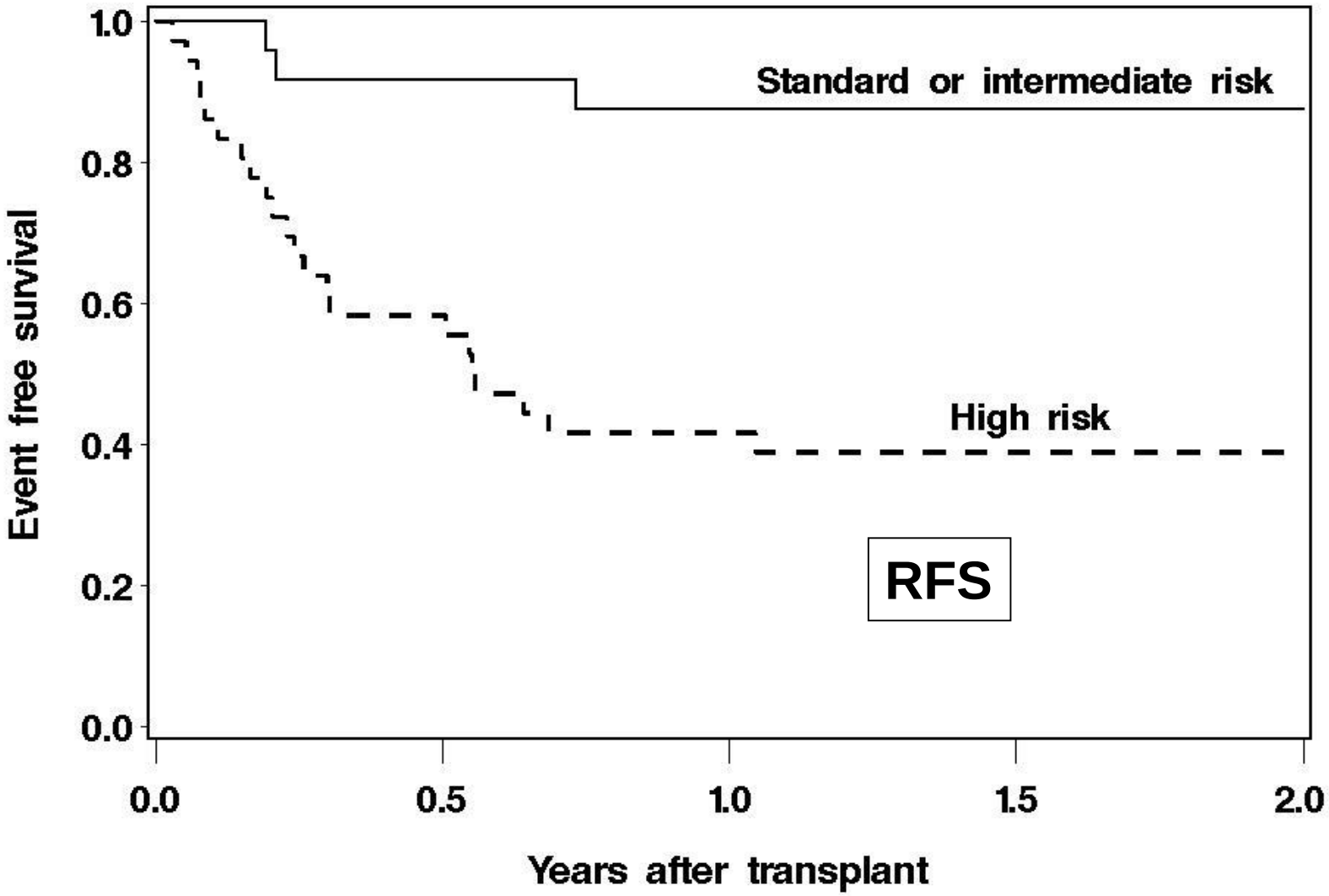
J.Pagel

Flu/Treo Conditioning



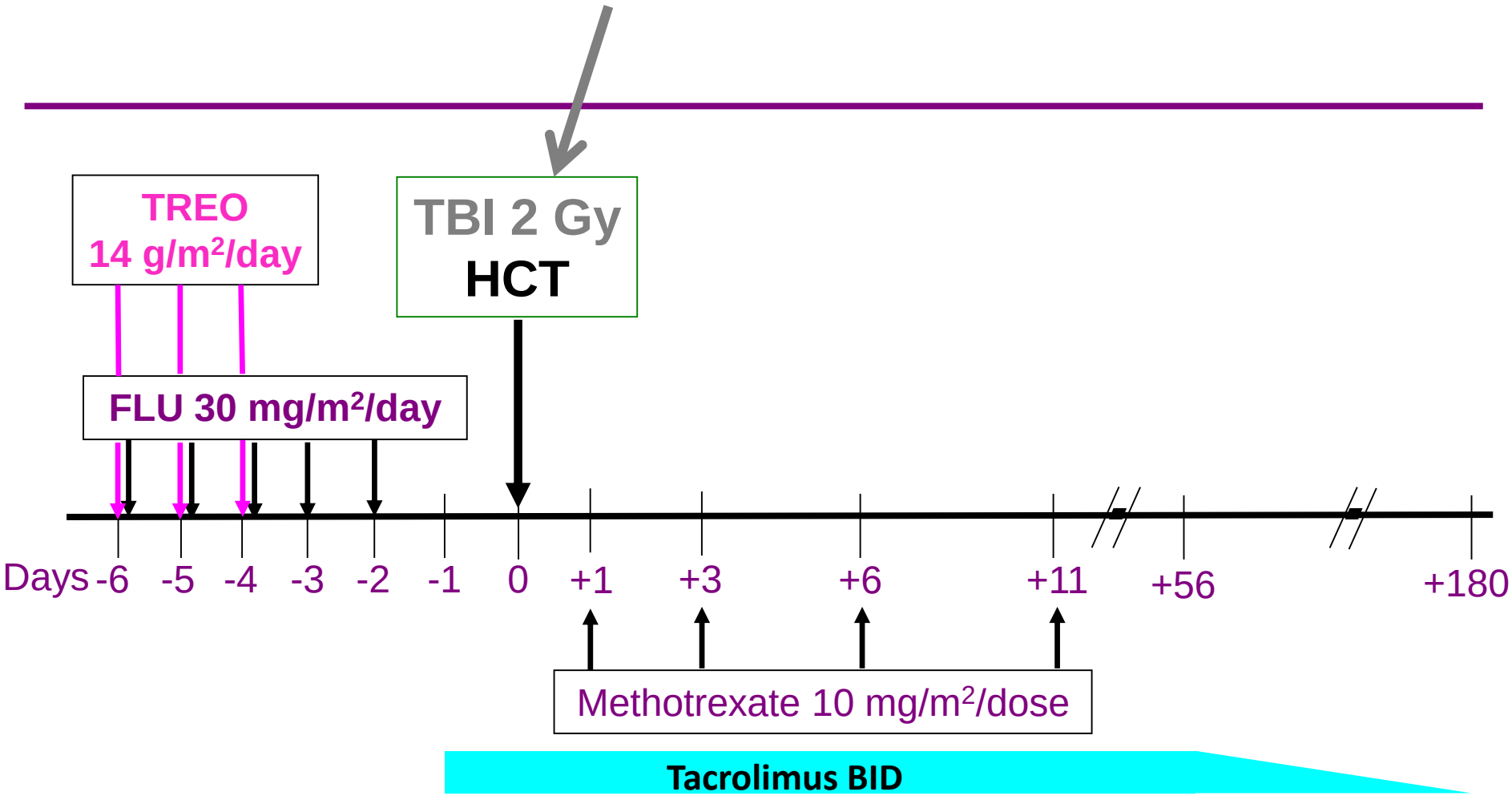
E. Nemecek et al, BBMT, 2011

Flu + Treo Conditioning: Impact of Karyotype



E.Nemecek et al, BBMT, 2011

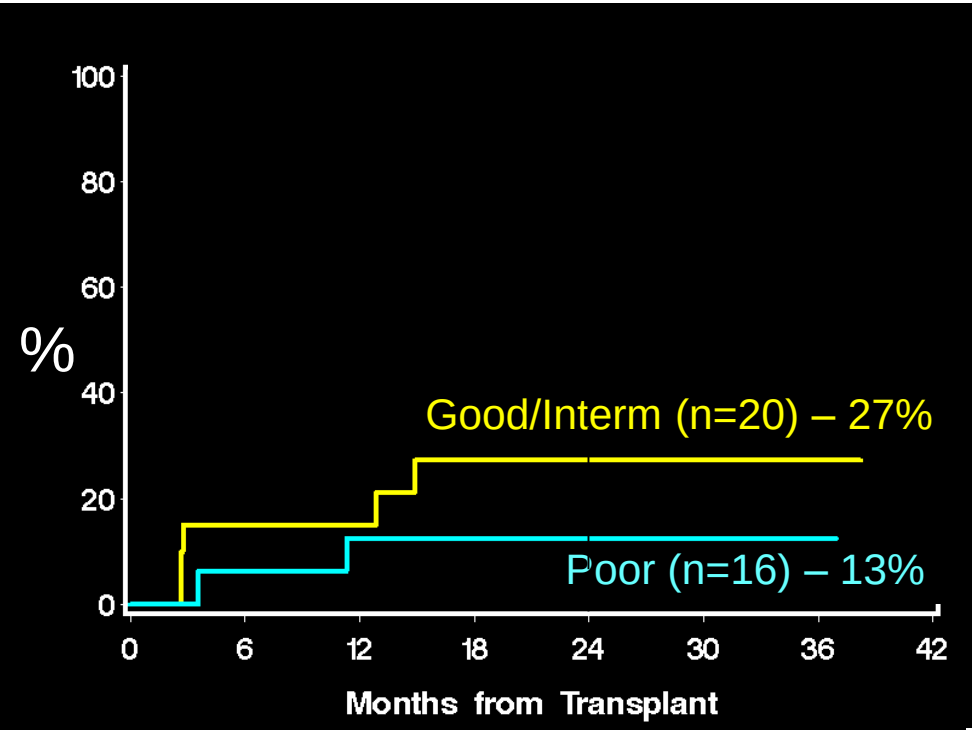
Flu/Treo/TBI Conditioning



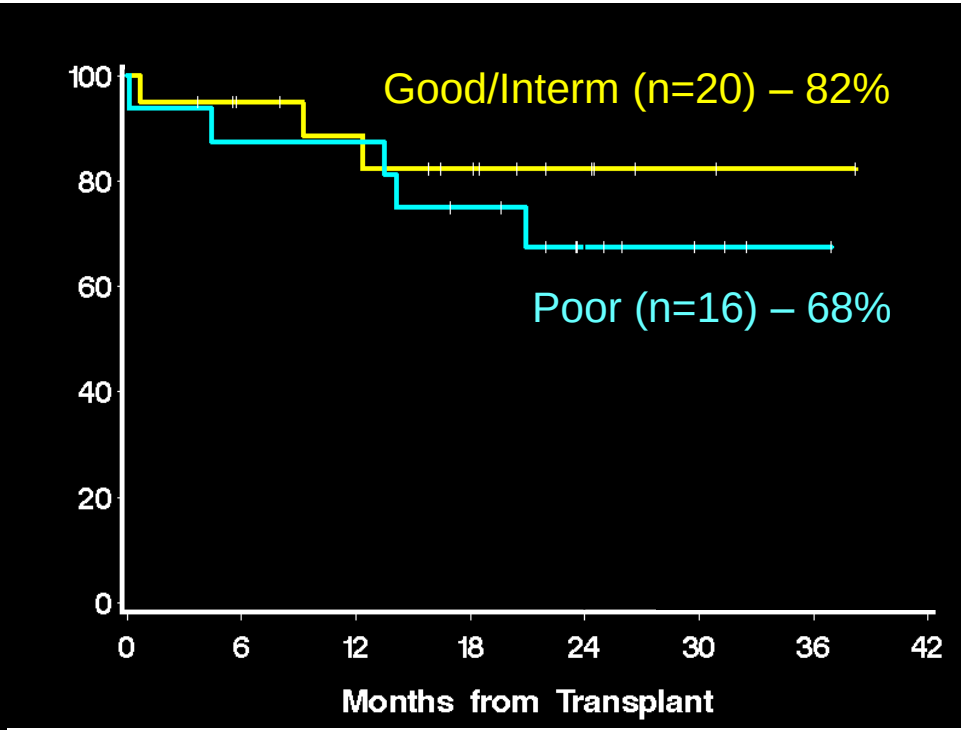
B.Gyurkocza et al, BBMT, 2014

Impact of Cytogenetics in Flu/Treo/TBI conditioned MDS patients (n=36)

Relapse

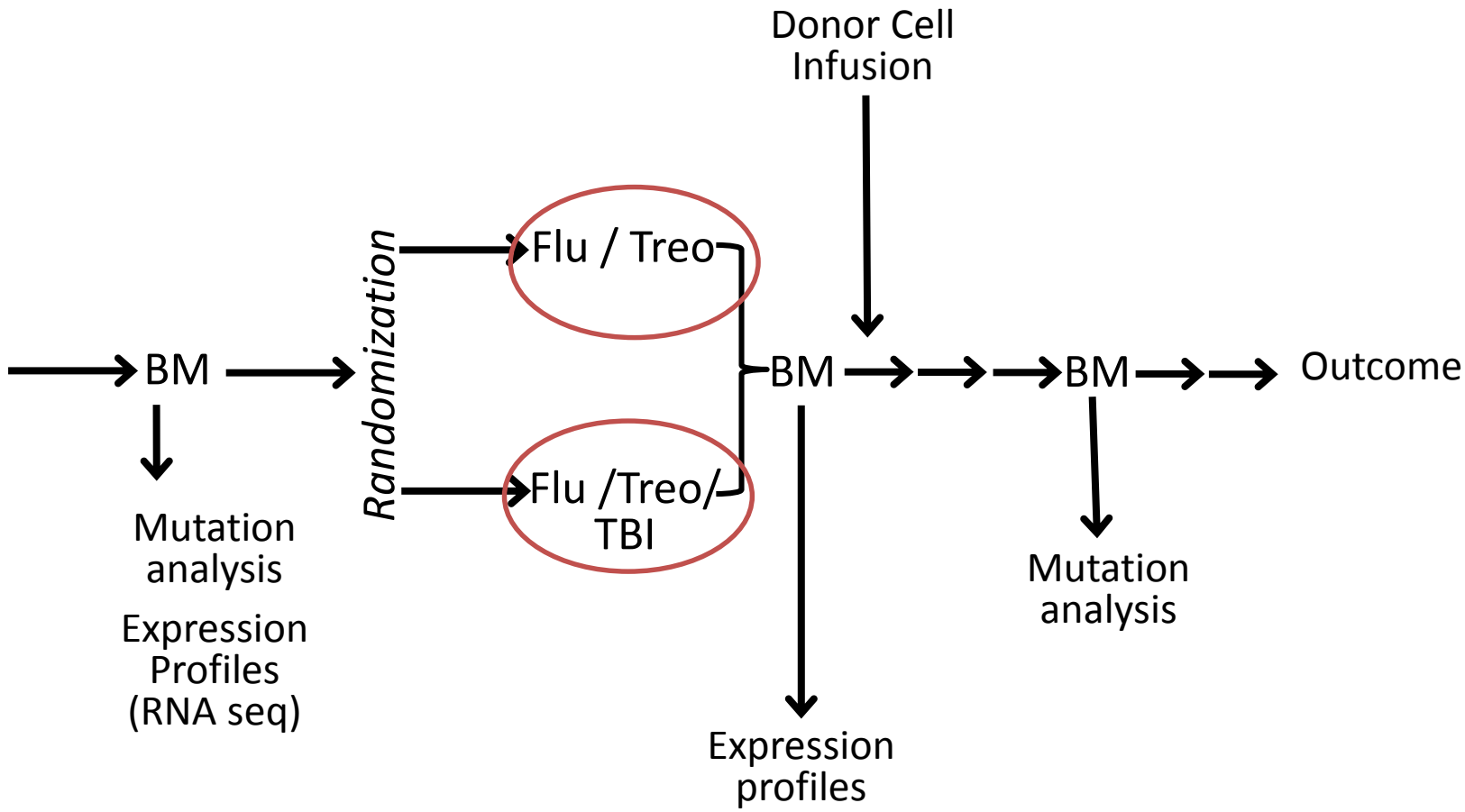


Survival



Months from HCT

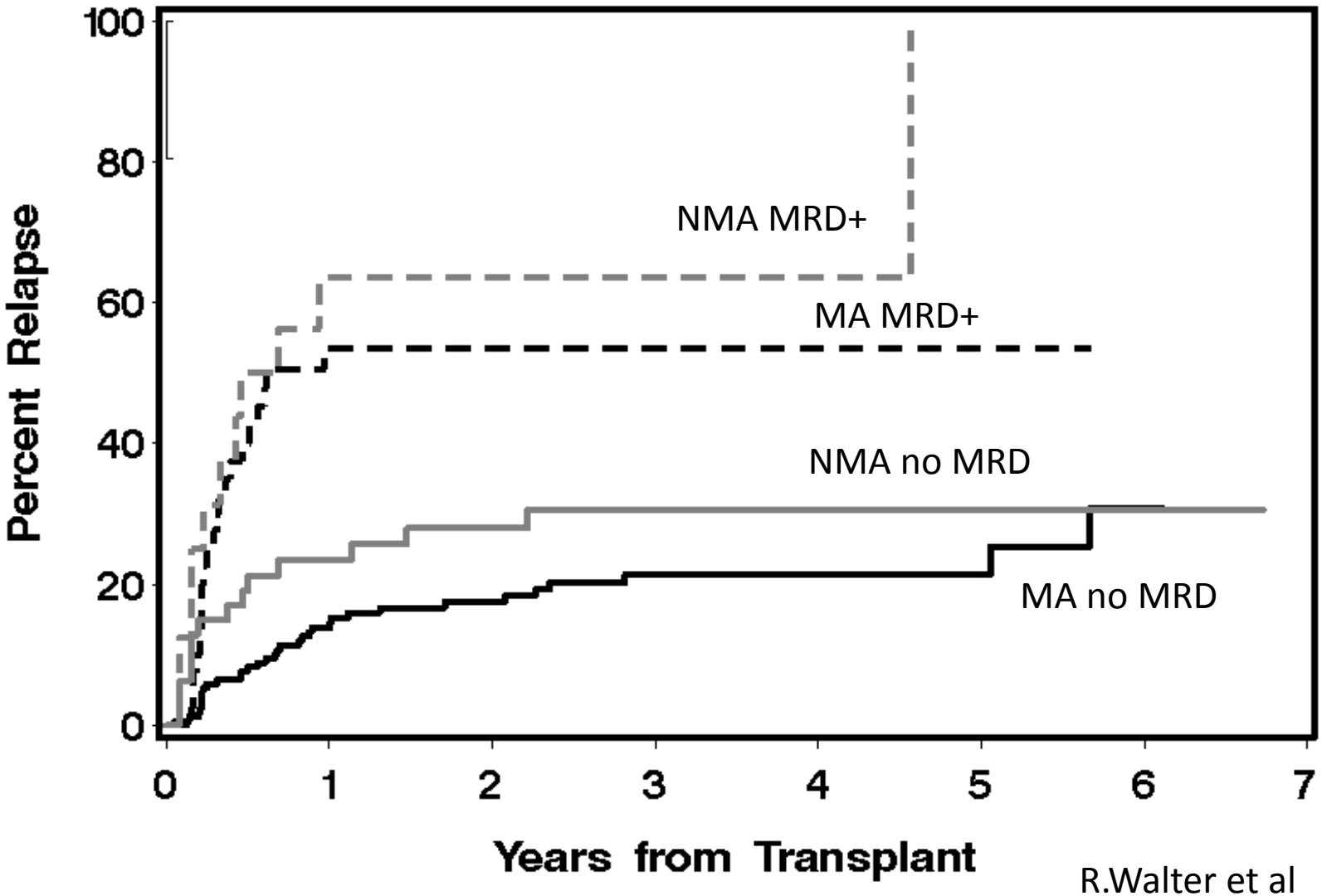
B.Gyurkocza et al, BBMT, 2014



Mutations, Conditioning and Gene expression

Conditioning Intensity and minimal residual disease

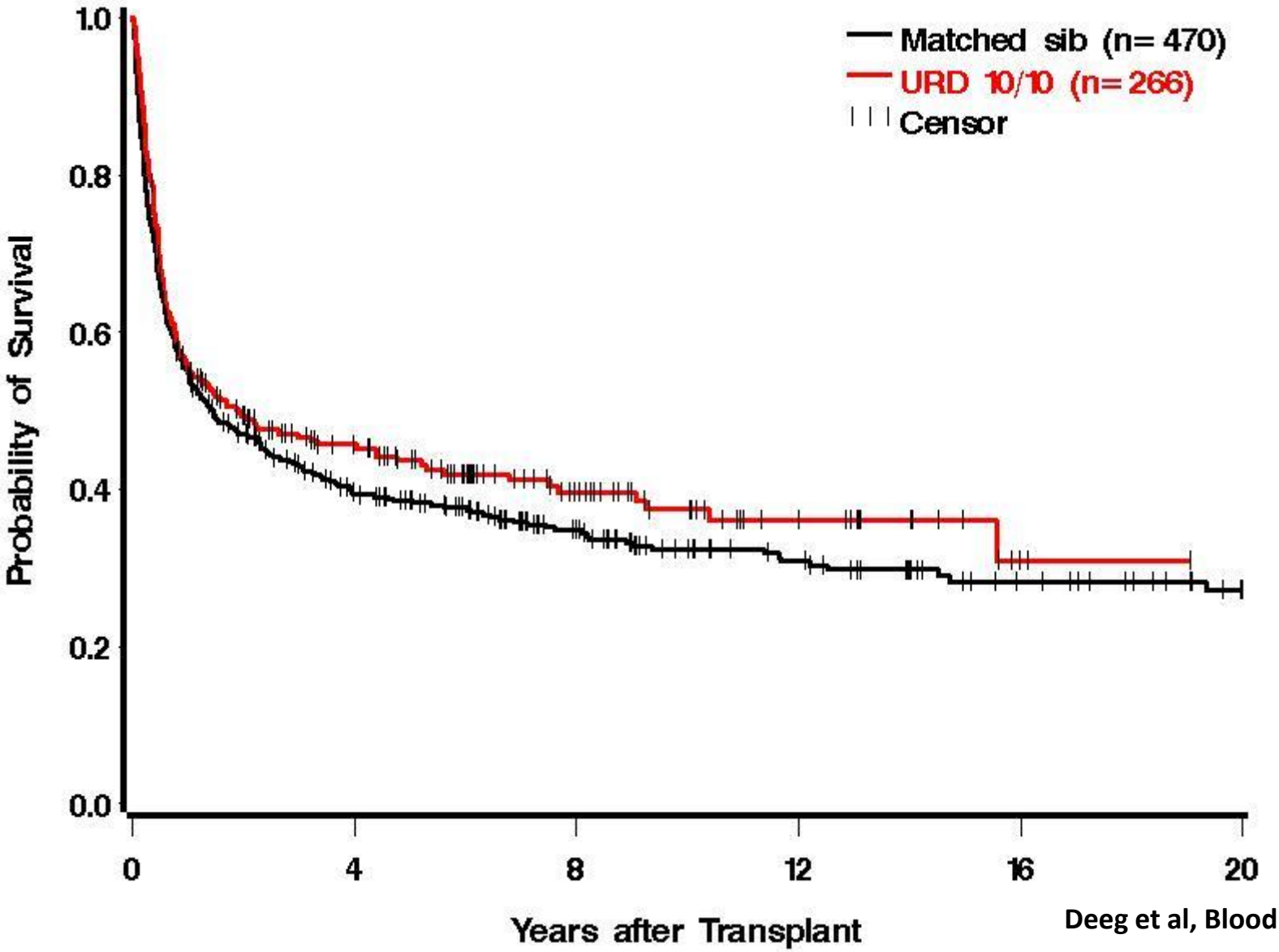
AML/high risk MDS



R.Walter et al

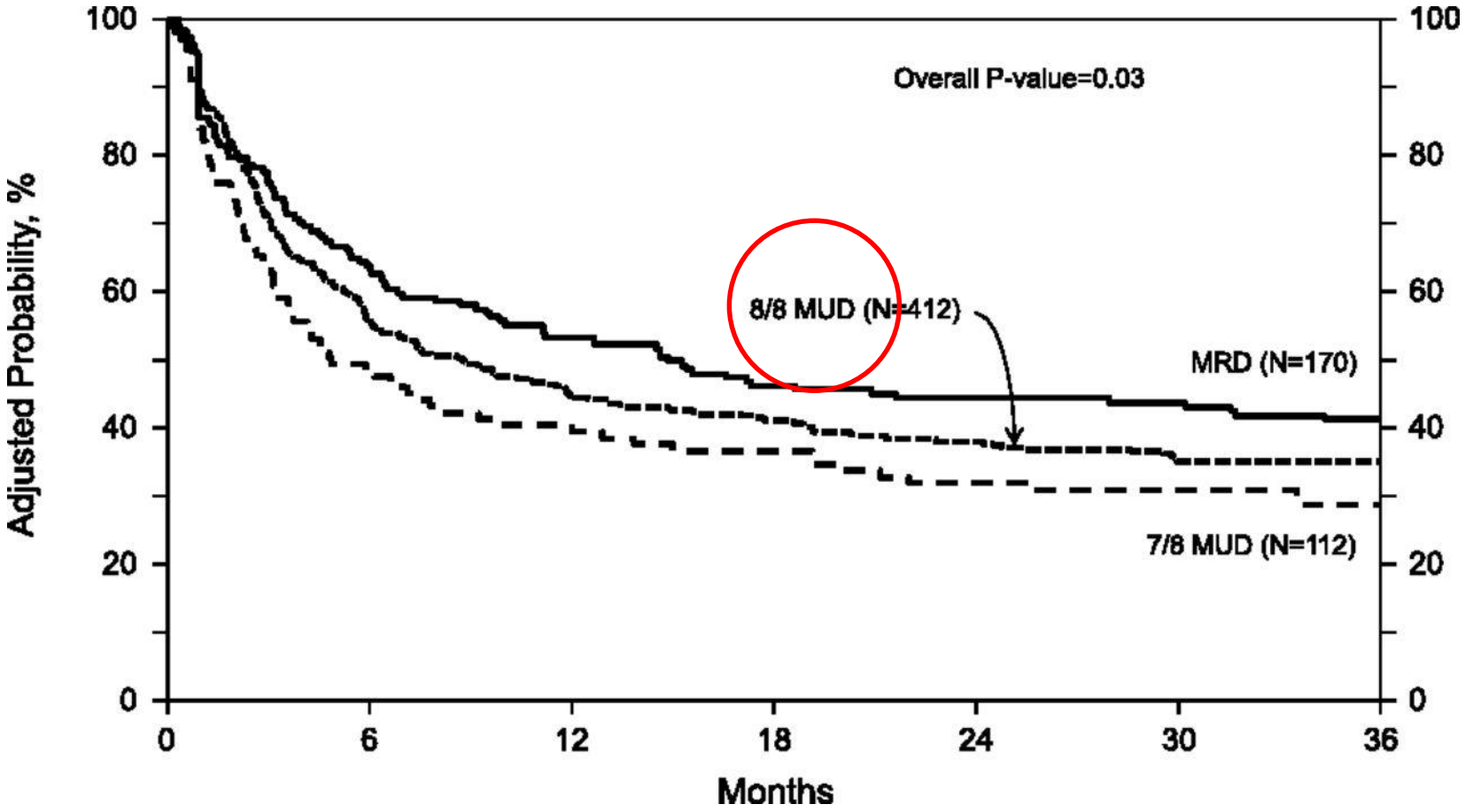
Source of stem cells

Survival by donor type



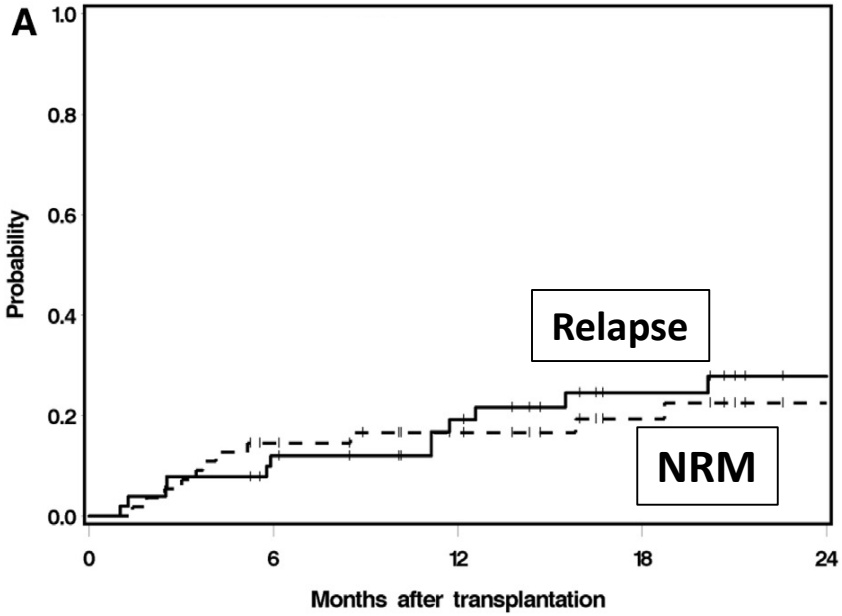
Deeg et al, Blood 2012

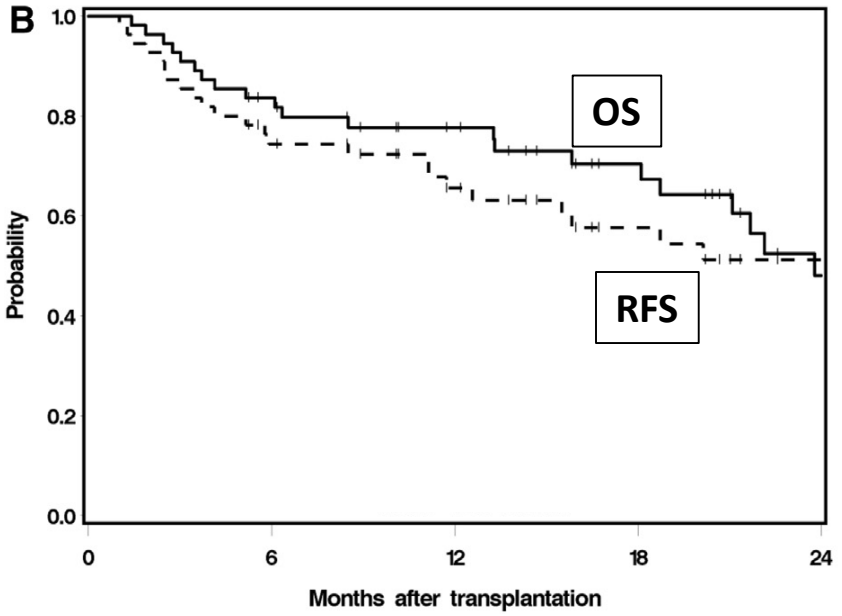
Relapse-free survival
(694 adult MDS patients)



Saber W et al. Blood 2013;122:1974-1982

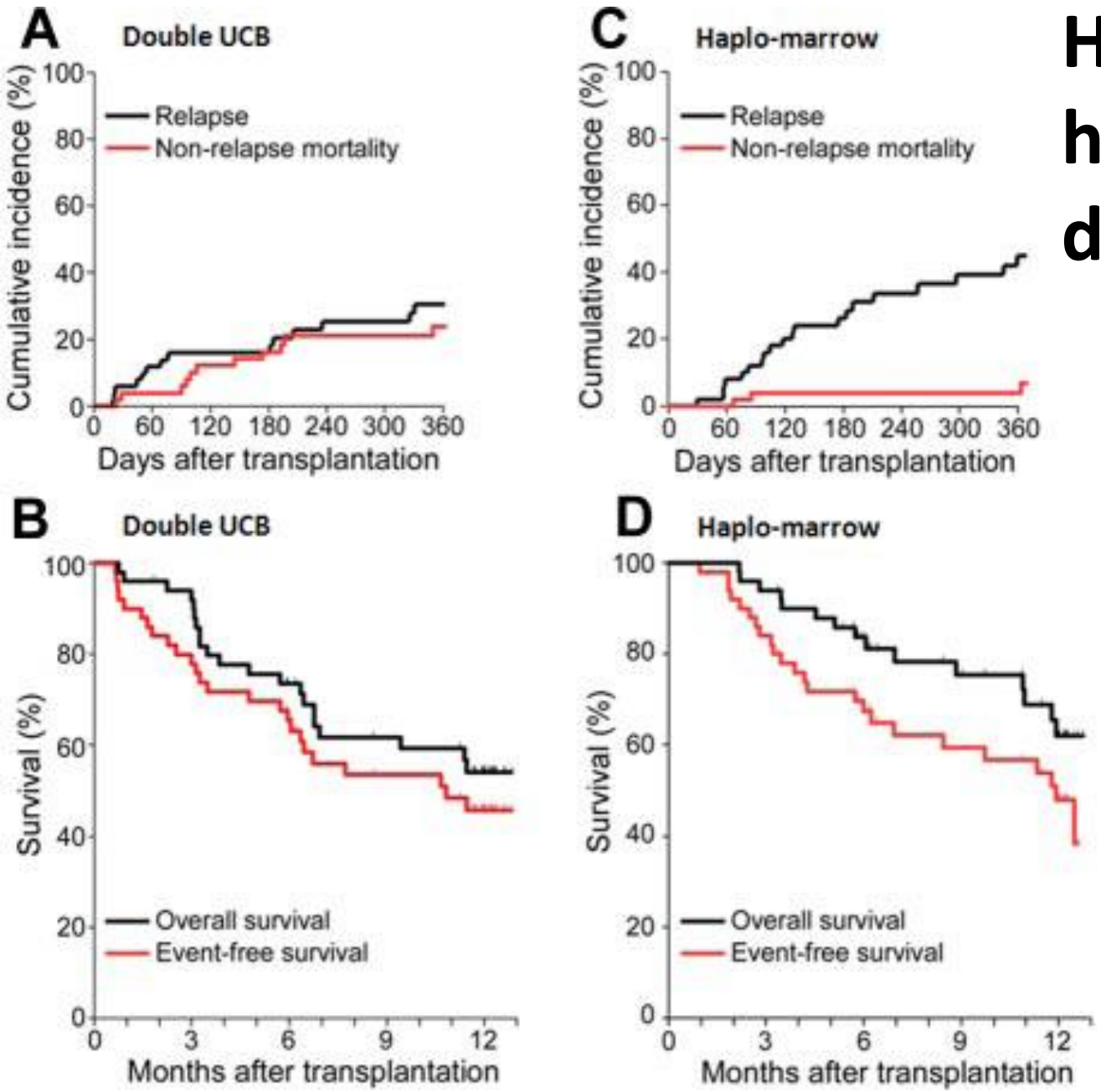
HLA haploidentical related donors





K. Raj et al, BBMT 20: 890, 2014

Cord blood vs HLA-haploidentical donors



C.G.Brunstein et al, Blood 2011

Summary and Conclusions

- Conditioning strategies continue to evolve
  - *Optimum regimen yet to be determined*
- Relapse is still an issue in high risk patients
- Donors are available for most patients
- Comorbidities impact outcome
- *Results with all stem cell sources have improved in recent years*
- GVHD (not discussed) may occur with *any* stem cell source

Summary and Conclusions

- Pre-transplant “debulking” may select for sensitive vs resistant disease
- Earlier HCT should improve results – less relapse and less NRM
- A place for pre-emptive targeted post-HCT therapy?

Thank you !