

Tools to Predict Outcomes in Allogeneic Hematopoietic Cell Transplantation

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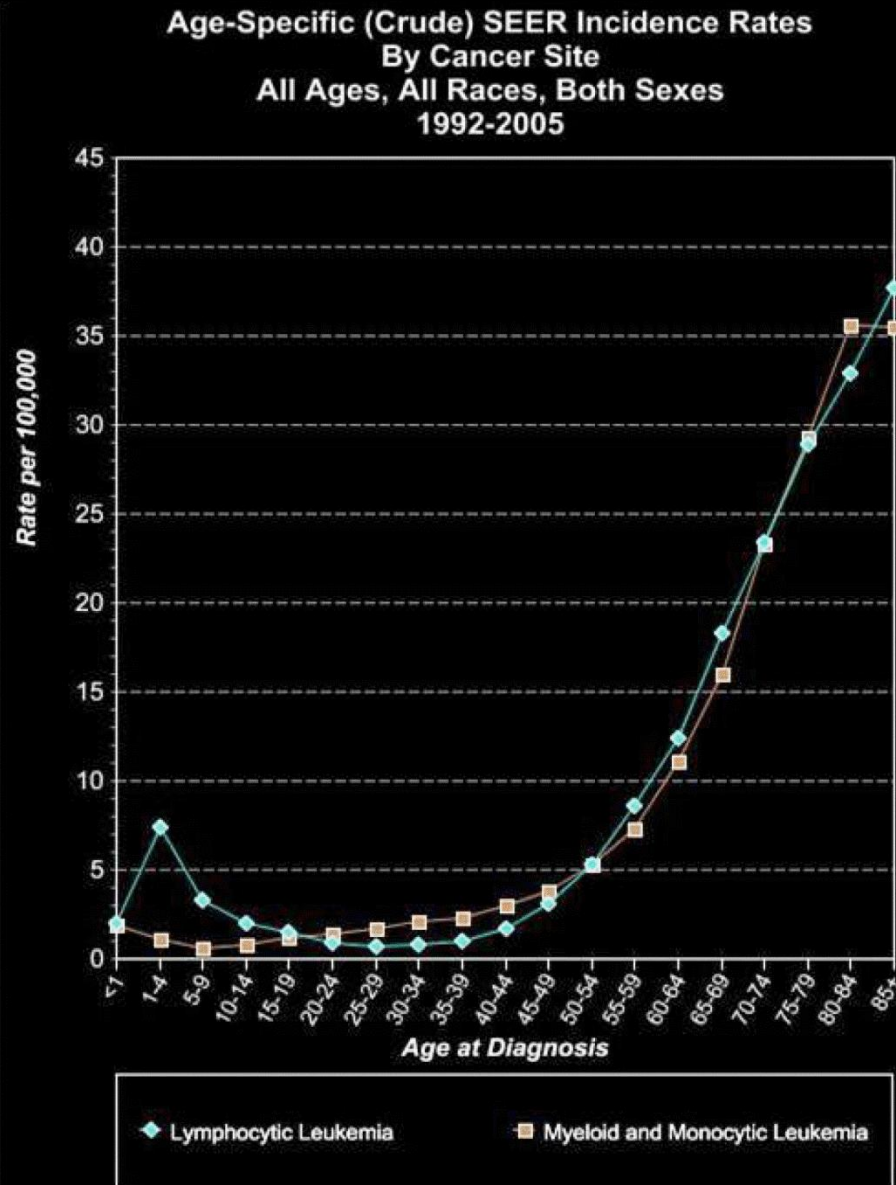
Patients

- Vulnerable
- Acute Myeloid Leukemia

Vulnerable patients

- Older
- Medical comorbidities
- Impaired physical performance
- Other health limitations

Acute Myeloid Leukemia (AML)



Disease of the Elderly

Median age: 66 years old

SEER Data

Cancer sites include invasive cases only unless otherwise noted.
Incidence source: SEER 13 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry and Rural Georgia).
Rates are per 100,000.

Effect of Cytogenetics and Performance Status

AML: n=968 patients >55 yrs old

Appelbaum F et al. Blood 2006;107:3481-3485

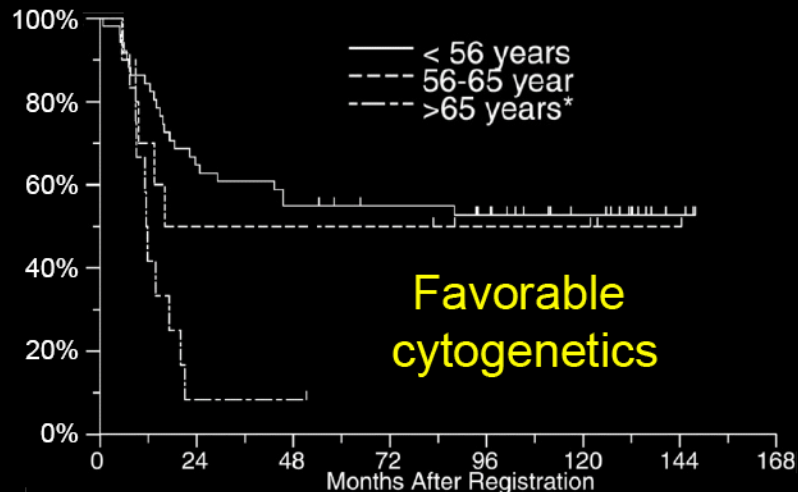
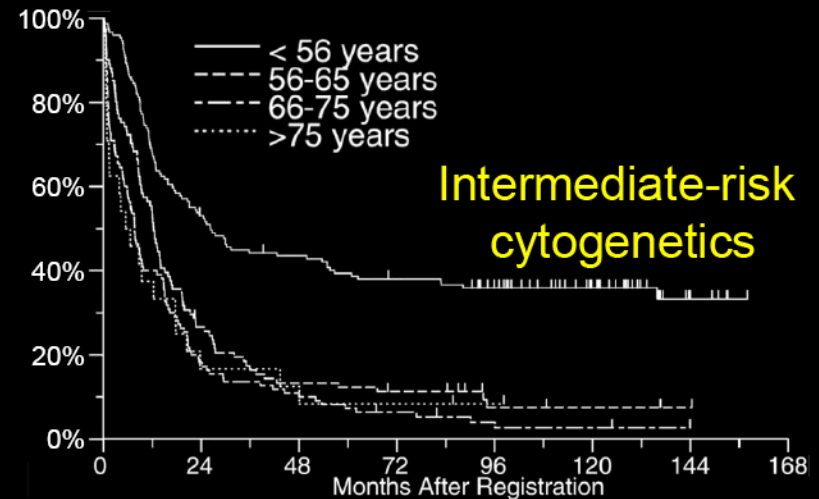
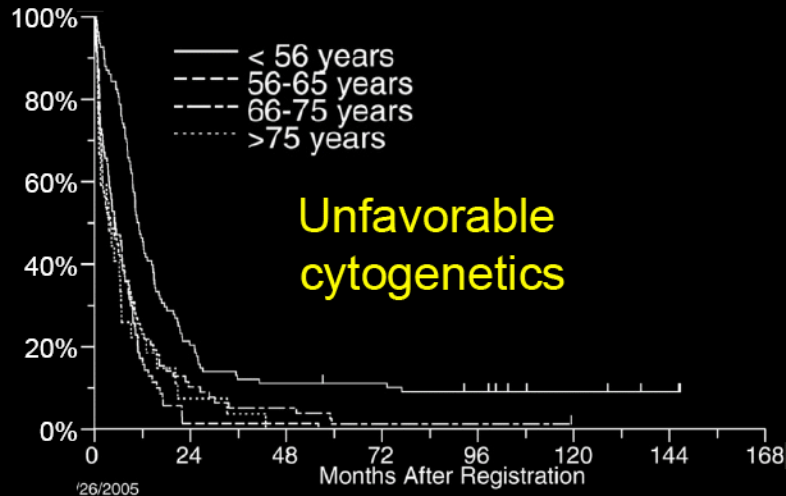
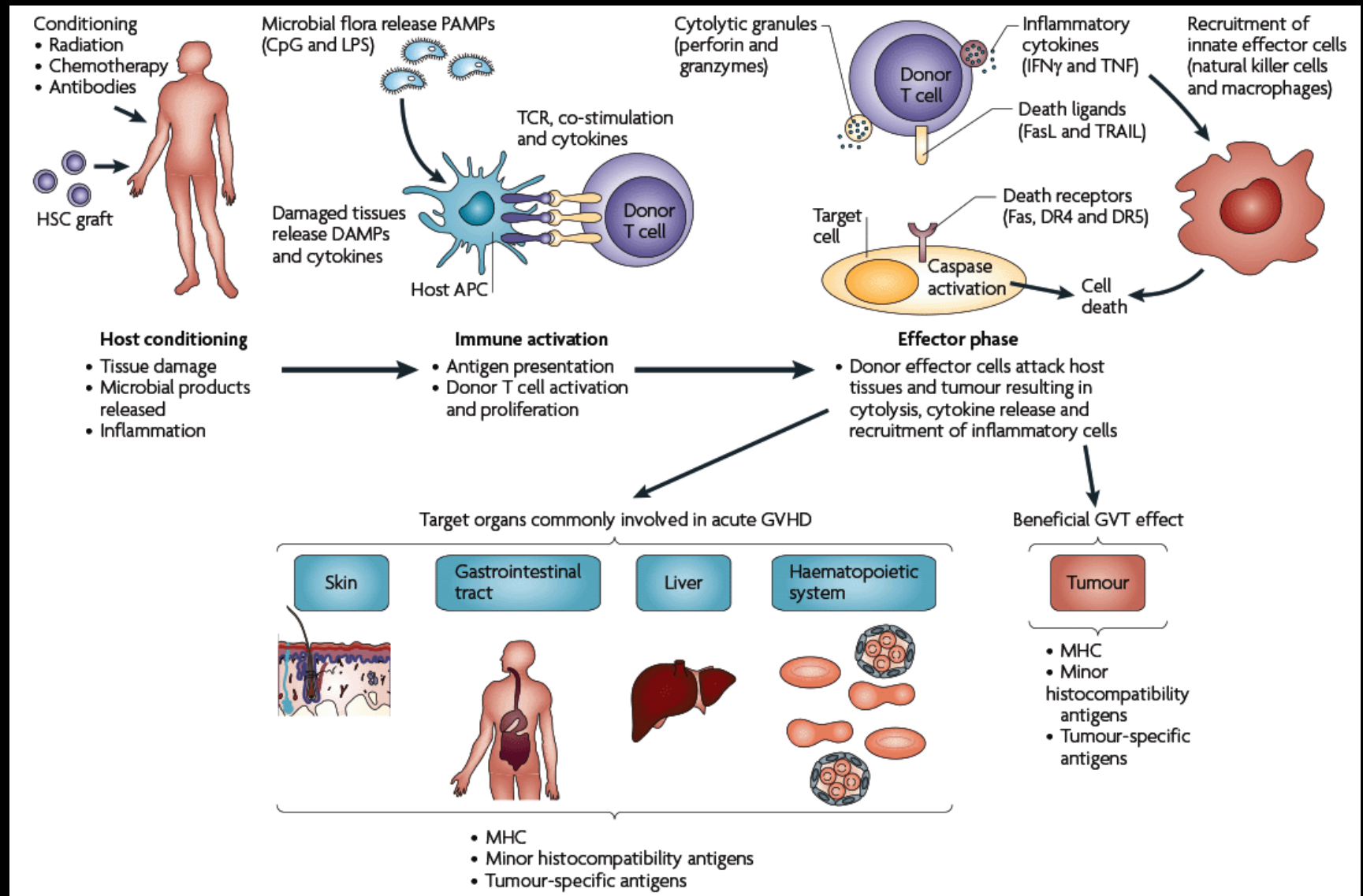


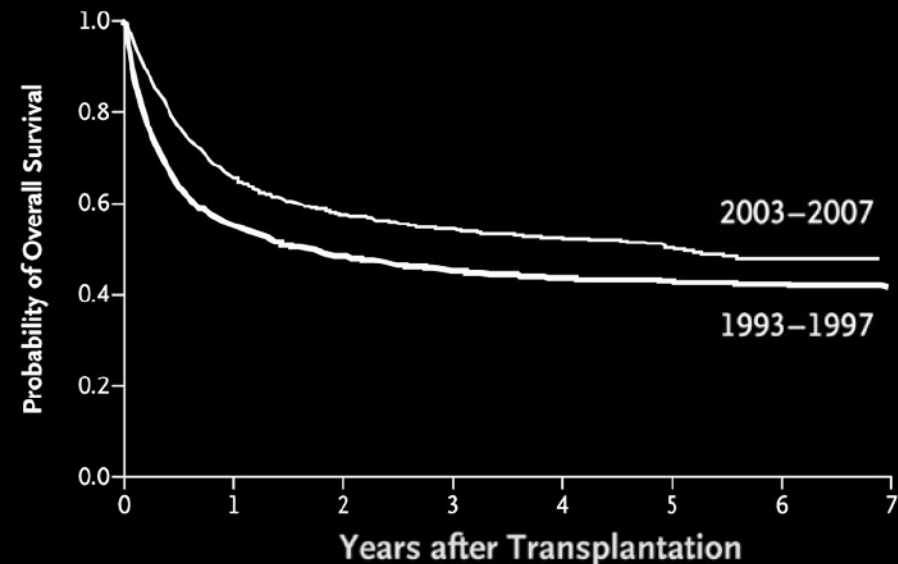
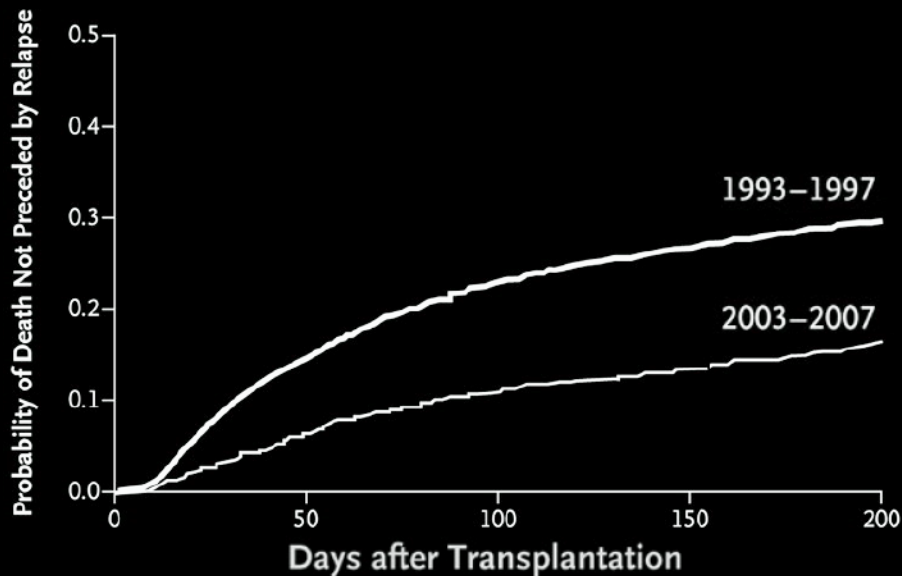
Table 5. Mortality within 30 days of initiation of induction

	Younger than 56 y	56-65 y	66-75 y	Older than 75 y
No. patients	364	242	270	79
Early deaths* by performance status, no./no. total patients (%)				
0	3/129 (2)	8/72 (11)	9/73 (12)	2/14 (14)
1	6/180 (3)	6/112 (5)	20/126 (16)	7/40 (18)
2	1/46 (2)	6/34 (18)	16/52 (31)	7/14 (50)
3	0/9 (0)	7/24 (29)	9/19 (47)	9/11 (82)

Allogeneic HCT = Potential Cure



Changes in Mortality Rates Following Allogeneic HCT Across Time



Decision-making:

- 79 years old male physician with AML in first complete remission (CR) asking for most appropriate post-remission therapy.

What tools to use for decision-making?

Allogeneic HCT

- The only potential curative therapy
- The most complicated procedure in Medicine

Transplant-related:

- Regimens
- Donor type
- HLA-matching
- Graft source
- Year



Patient-related:

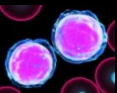
- Age
- Performance
- Comorbidities
- Genes



HCT
Success

Disease-related:

- Diagnosis
- Status
- Chromosomes
- Prior therapy



AML and HCT-Related Factors

Chromosomal Aberrations

Abnormalities	2-year relapse rates (from Dx)
• Inv (16) or t(8;21)	• 56% (70% in CLGB data)*
• Normal karyotype	• 78%
• Non-complex abnormalities	• 85%
• Complex karyotype	• 91%

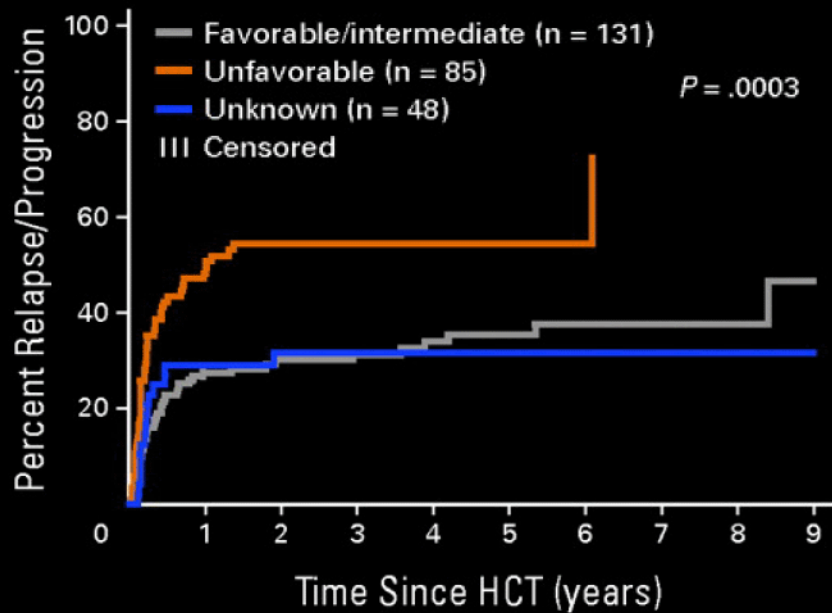
Grimwade D et al Blood 2001; 98(5): 1312-1320

Farag S et al Blood 2006; 108(1): 63-73

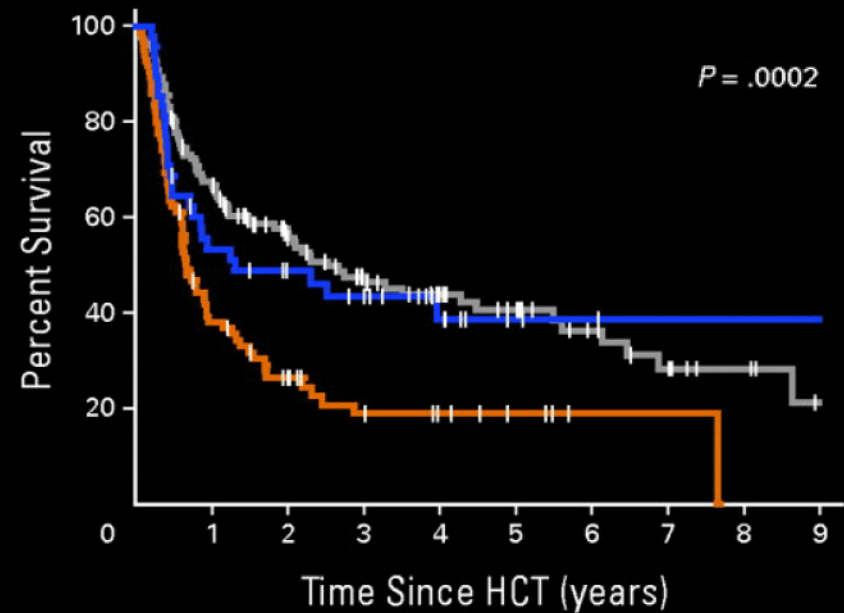
Cytogenetics

Patients = 274
Median age = 60 years

Relapse/progression



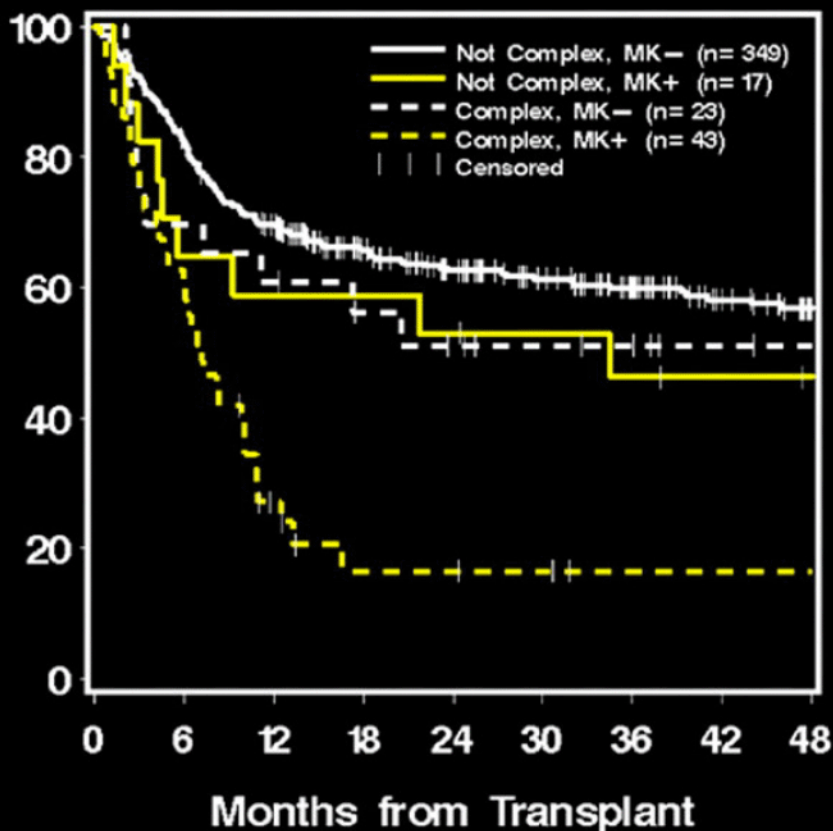
Overall survival



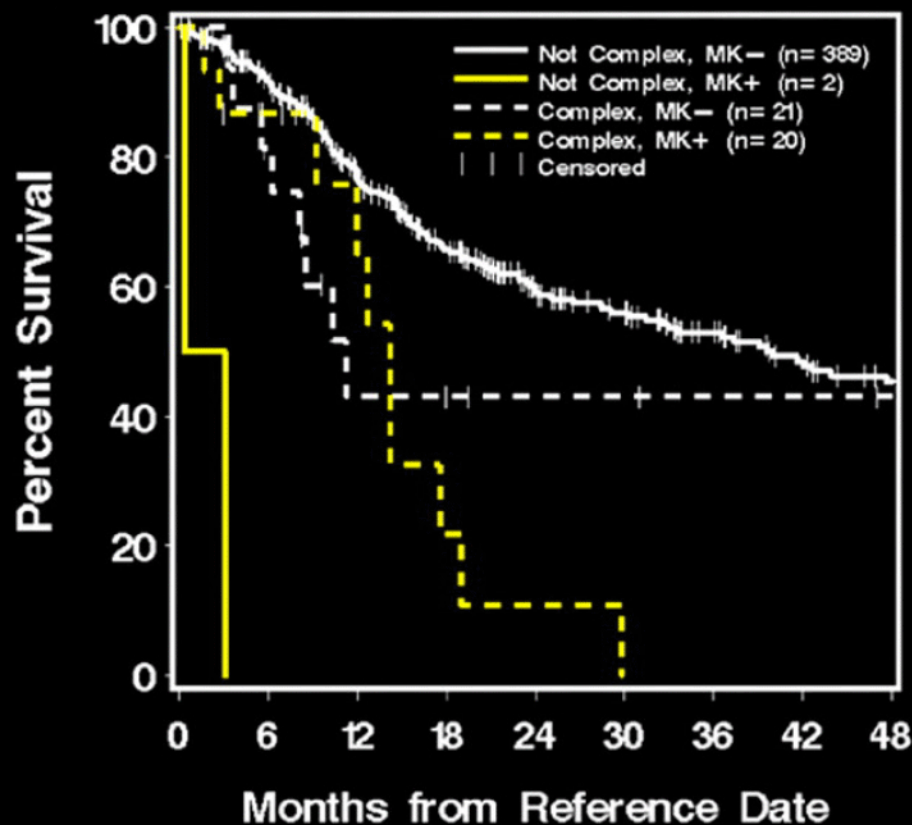
Gyurkocza B et al. JCO 2010;28:2859-2867

Monosomal Karyotype (MK) and complex karyotype.

HCT recipients



Non-HCT recipients



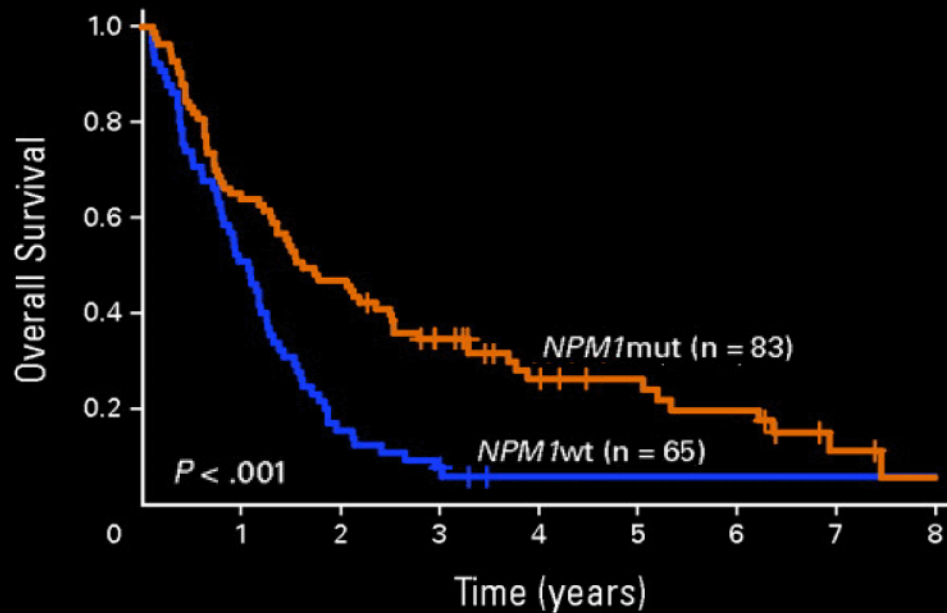
Among patients ≥ 60 years: 4-yr OS 44% for MK- vs 6% for MK+

Fang M et al. Blood 2011;118:1490-1494

Molecular markers

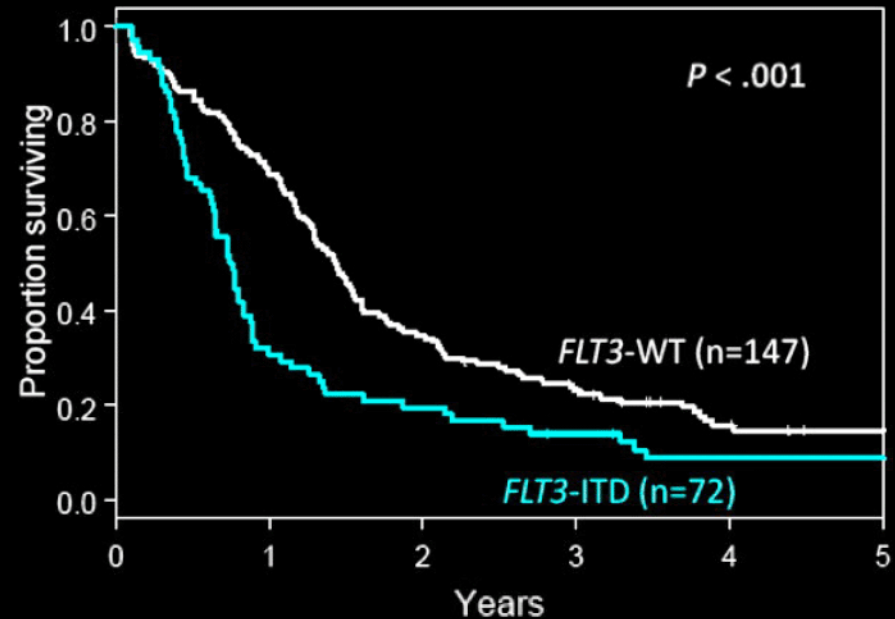
CLGB studies for older patients

Nucleophosmin gene
(NPM-1)



Becker H et al. JCO 2010;28:596-604

FMS-like tyrosine kinase gene
(FLT3 ITD)



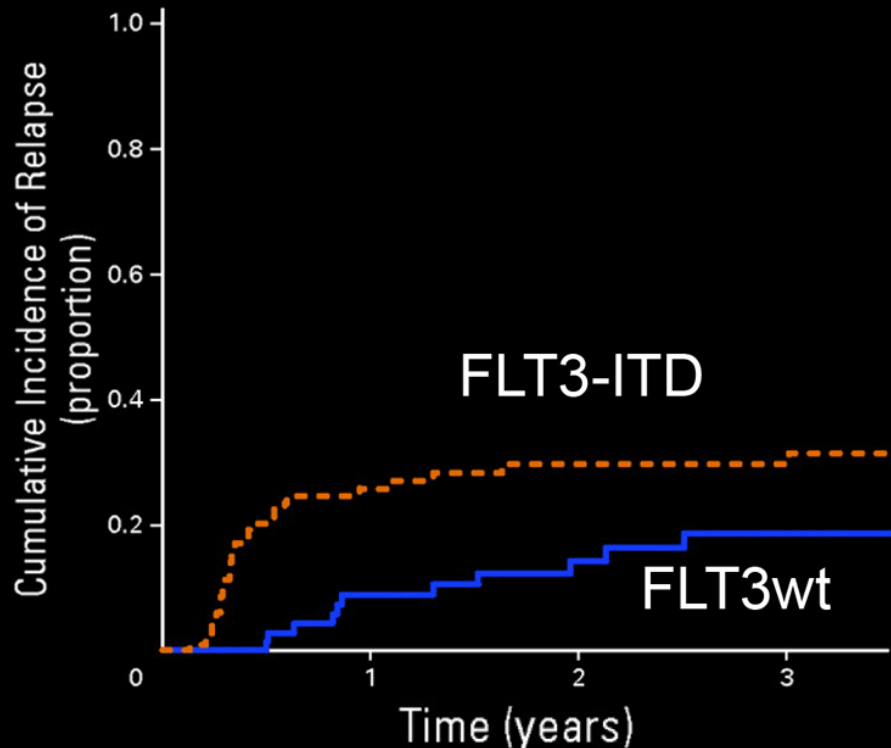
Whitman S P et al. Blood 2010;116:3622-26

Molecular Markers

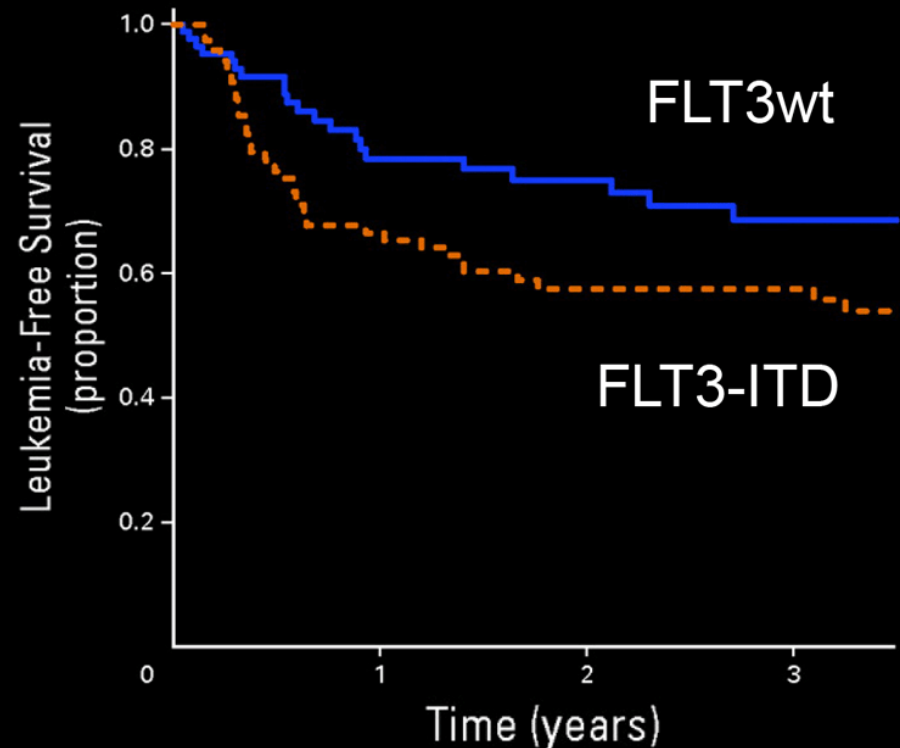
Allogeneic HCT in first CR and normal cytogenetics

Median age 41 (18-60) years

Relapse

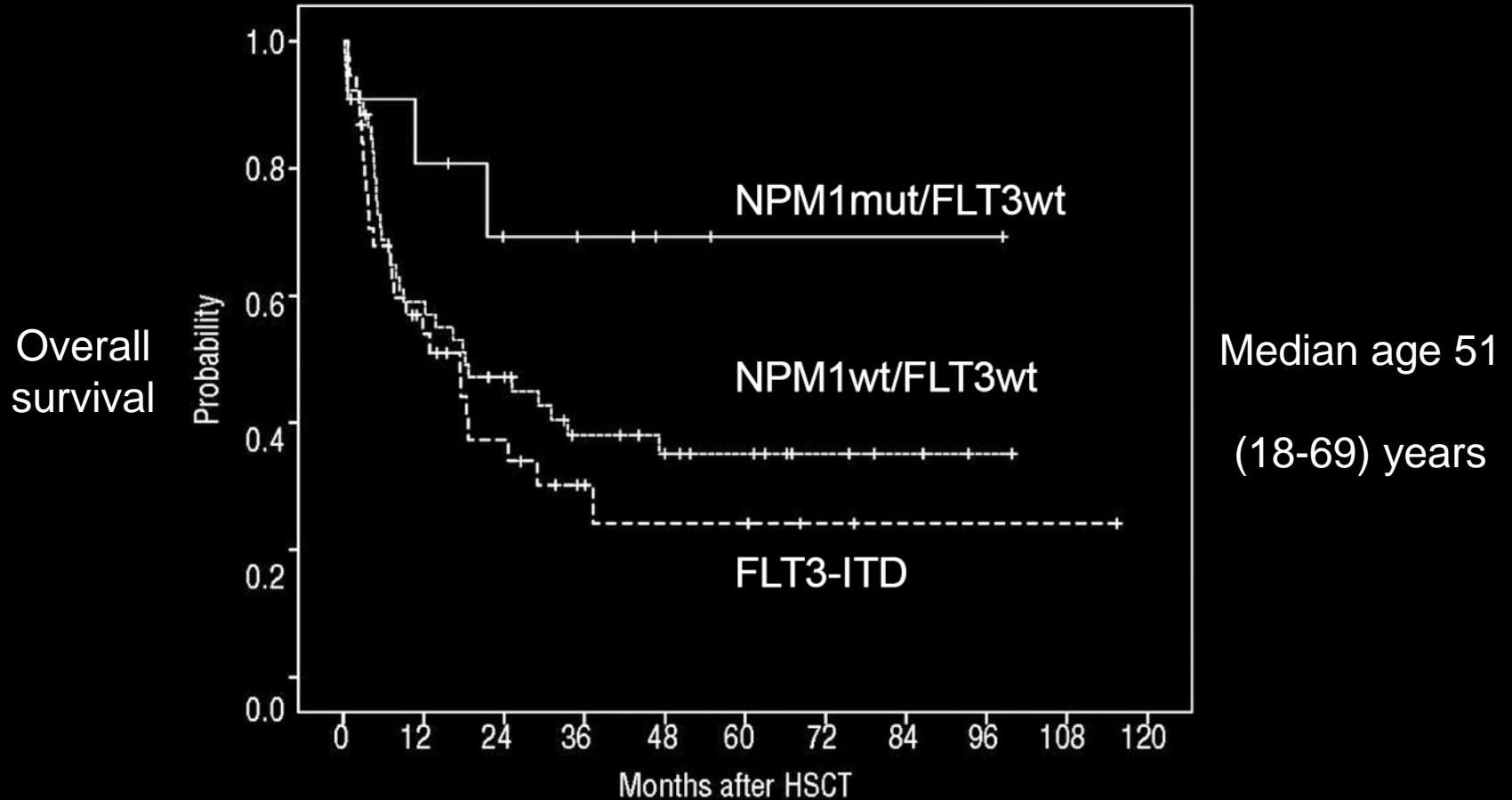


Leukemia-free survival



Brunet S et al (EBMT). JCO 2012;30:735-741

Allogeneic HCT beyond first CR and normal cytogenetics



Pfeiffer T et al. Haematologica 2013;98:518-525

Allogeneic HCT vs Chemotherapy in 60-70 yrs old Patients with Non-M3 AML - CR1: CIBMTR Study

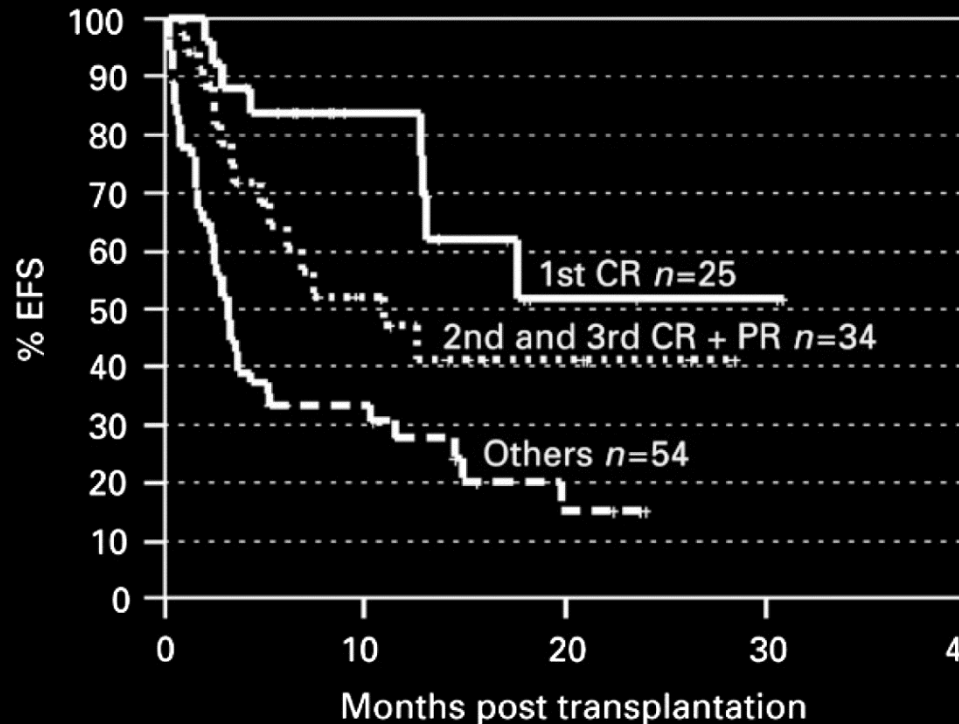
Table 2. Estimated 3-Year Incidence of Relapse, LFS, and OS by Cytogenetic Risk Group*

	HCT	Chemotherapy	P value
Cumulative incidence of relapse			<.001
Favorable karyotype	0	69 (38-93)	
Normal	33 (20-47)	79 (68-88)	
Intermediate-II	25 (6-51)	90 (76-98)	
Adverse karyotype	45 (23-68)	80 (60-94)	
LFS			.001
Favorable karyotype	100 (100-100)	19 (0-57)	
Normal	39 (24-55)	17 (8-28)	
Intermediate-II	30 (9-57)	10 (1-27)	
Adverse	22 (6-44)	13 (1-35)	
OS			.08
Favorable karyotype	100 (100-100)	50 (18-82)	
Normal	45 (30-61)	27 (16-39)	
Intermediate-II	32 (10-59)	23 (7-45)	
Adverse	23 (7-45)	13 (1-35)	

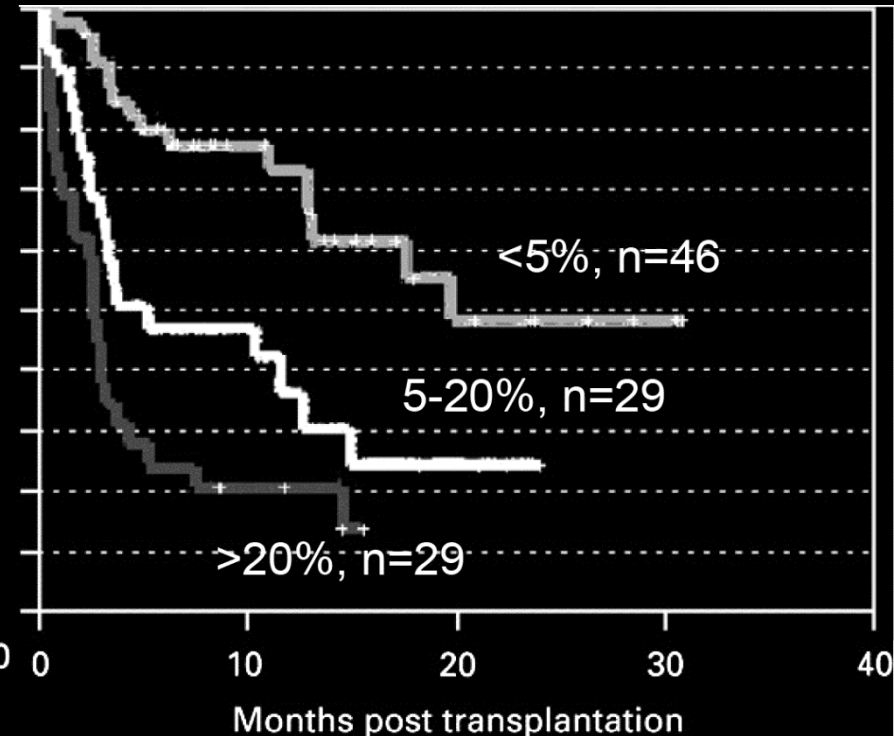
Pre-HCT Disease Status

Cooperative German Transplant Study Group
n=113 patients given mostly Bu/Flu

Disease status



Marrow blasts



Pre-HCT minimal residual disease (MRD)

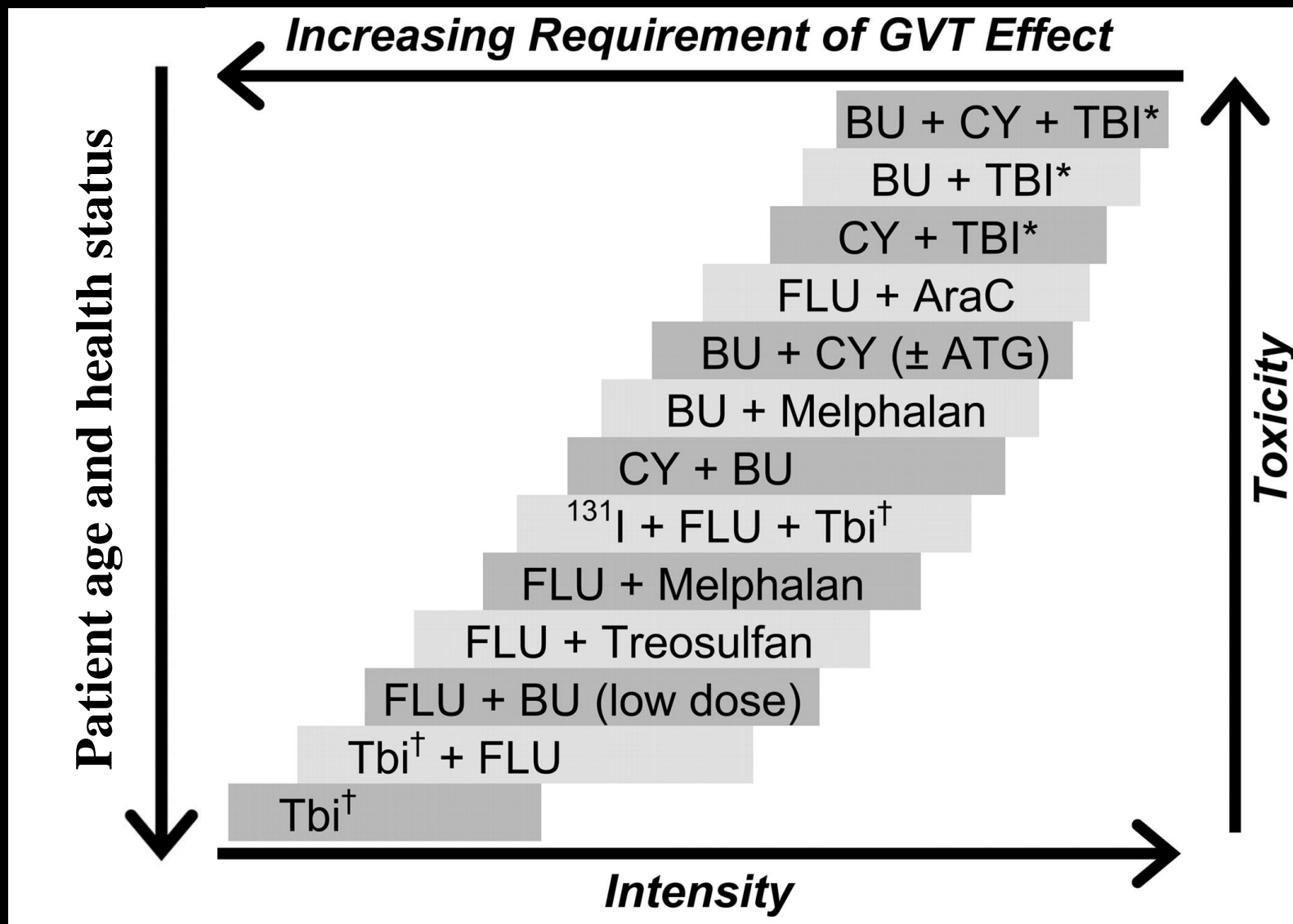
Table 2. Outcome probabilities stratified by MRD status and conditioning type

	<i>Nonmyeloablative HCT (n = 86)</i>	
	<i>MRD^{neg} (n = 65)</i>	<i>MRD^{pos} (n = 21)</i>
Overall survival at 3 years	48% (35–60%)	41% (20–61%)
Disease-free survival at 3 years	42% (30–54%)	33% (15–53%)
Cumulative incidence of relapse at 3 years	28% (18–39%)	57% (34–75%)
Cumulative incidence of non-relapse mortality at 3 years	30% (19–41%)	10% (2–26%)

Conditioning intensity

Myeloablative (MA) *
TBI ≥ 5 Gy single dose or ≥ 8 Gy fractionated
Bu > 8 mg/kg PO or IV equivalent
Nonmyeloablative (NMA) **
TBI ≤ 2 Gy \pm purine analog
Flu + Cy \pm ATG
Flu + AraC + Ida
Cladribine + AraC
Total Lymphoid Irradiation + ATG

Selected Conditioning Regimens of Different Dose Intensities

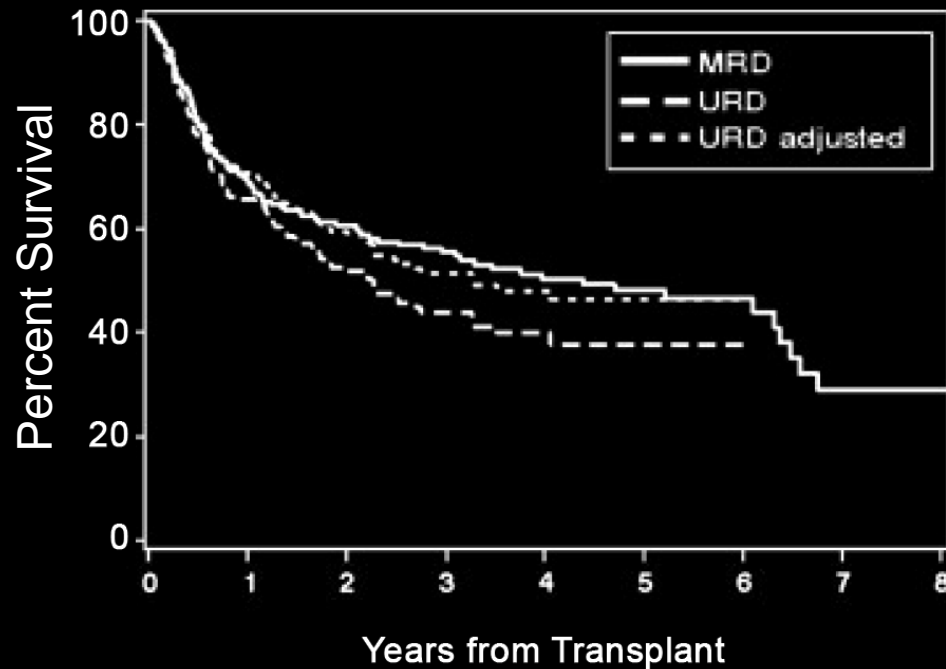


Donor type

HLA-matched related (MRD) vs unrelated (URD)

Low dose TBI \pm Flu

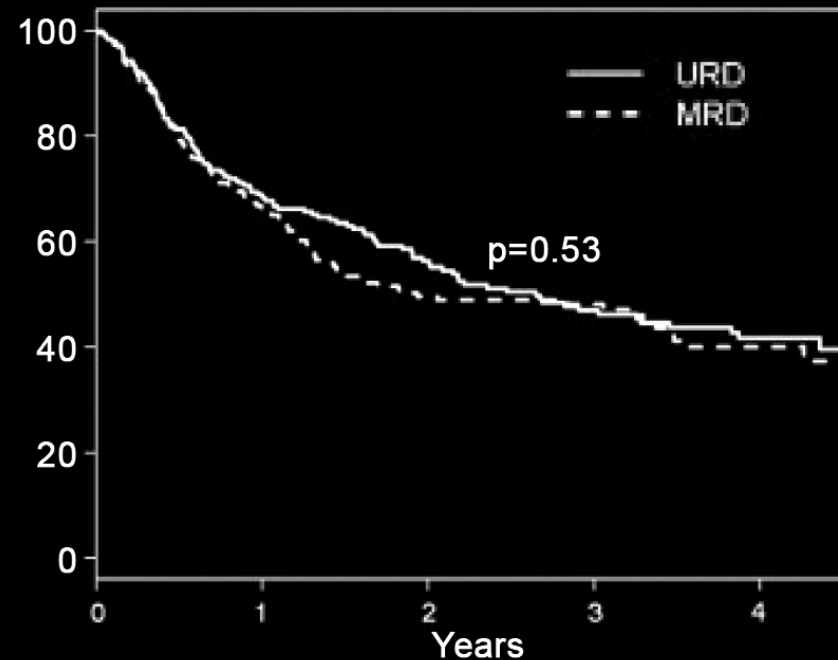
Median age ~55 years



Mielcarek et al. BBMT 2007; 13(12):1499-07

Low dose ivBu + Flu

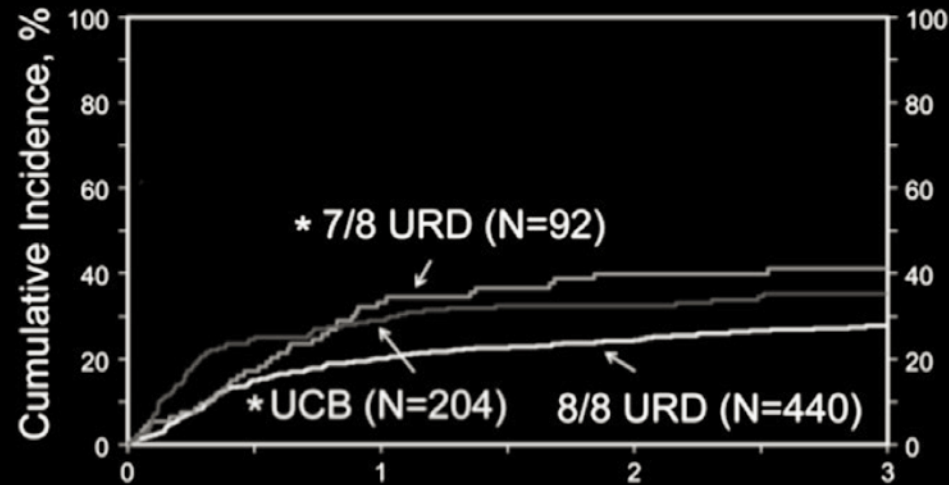
Median age ~56 years



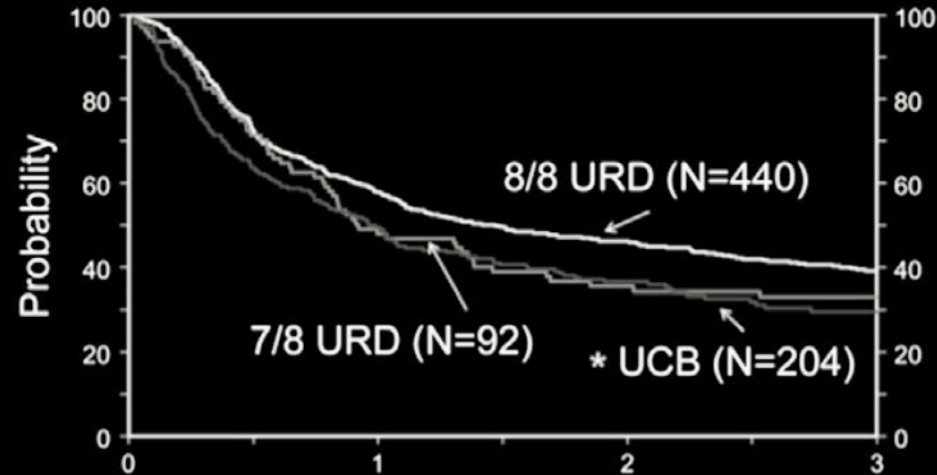
Ho VT et al. BBMT 2011; 17(8):1196-04

Alternative donors

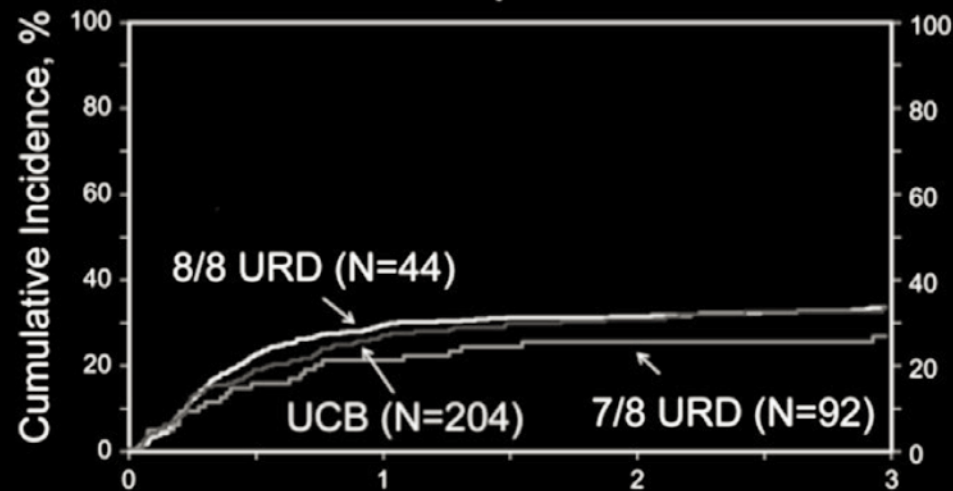
Treatment-Related Mortality



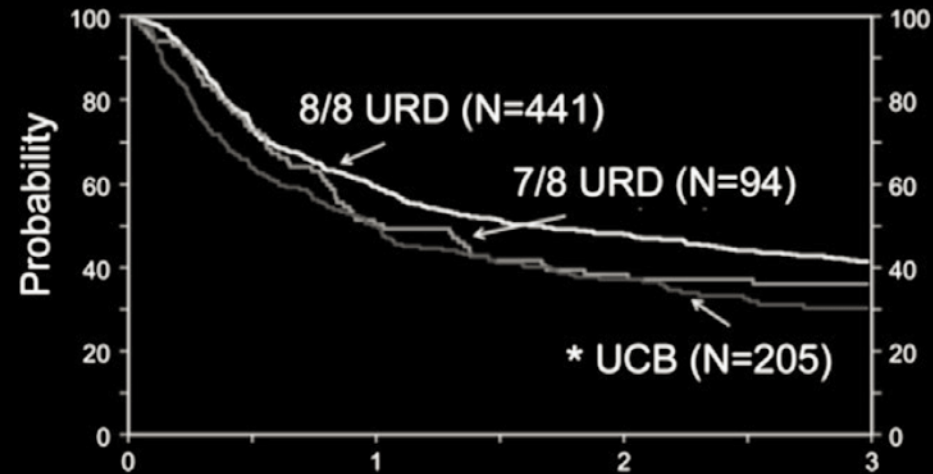
Leukemia-free Survival



Relapse

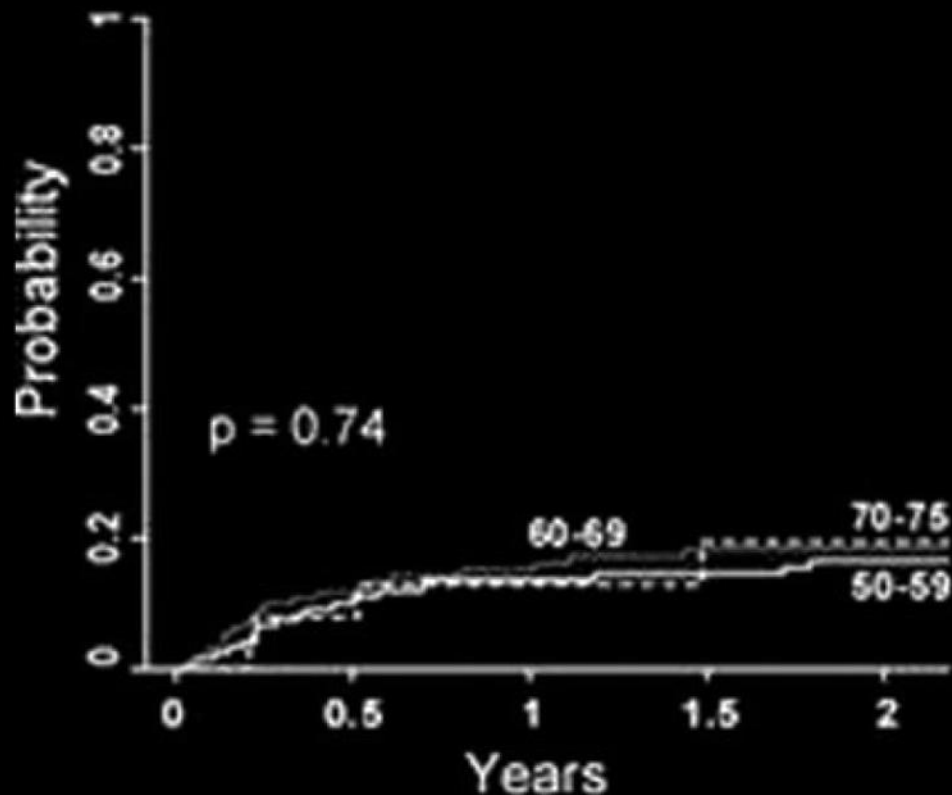


Overall Survival

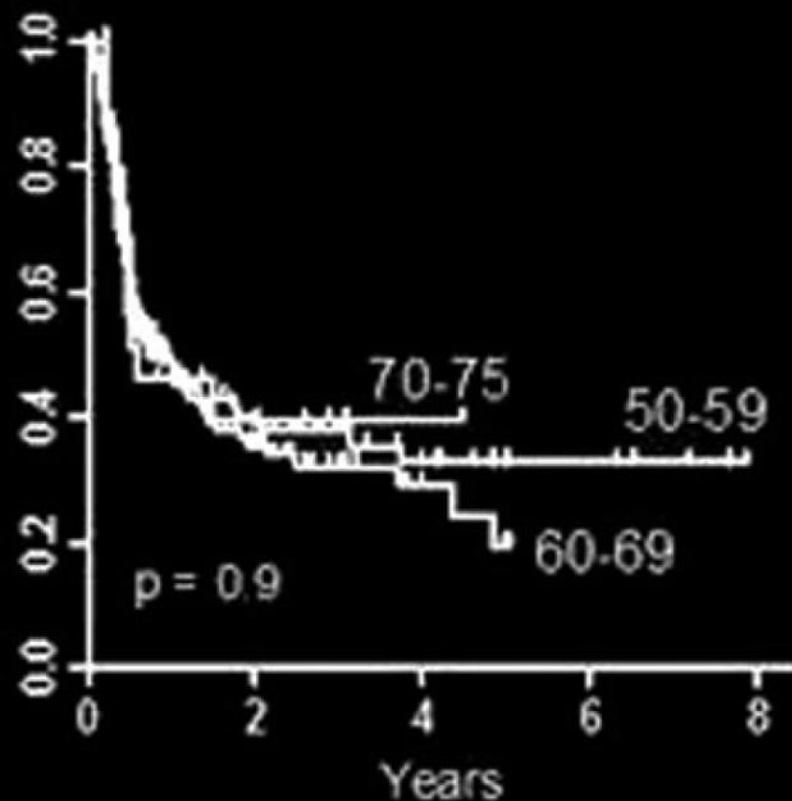


HLA-haploidentical Nonmyeloablative regimen + post-HCT Cy

A NRM by Age Group



B PFS by Age Group



Patient-Related Factors

The HCT-CI

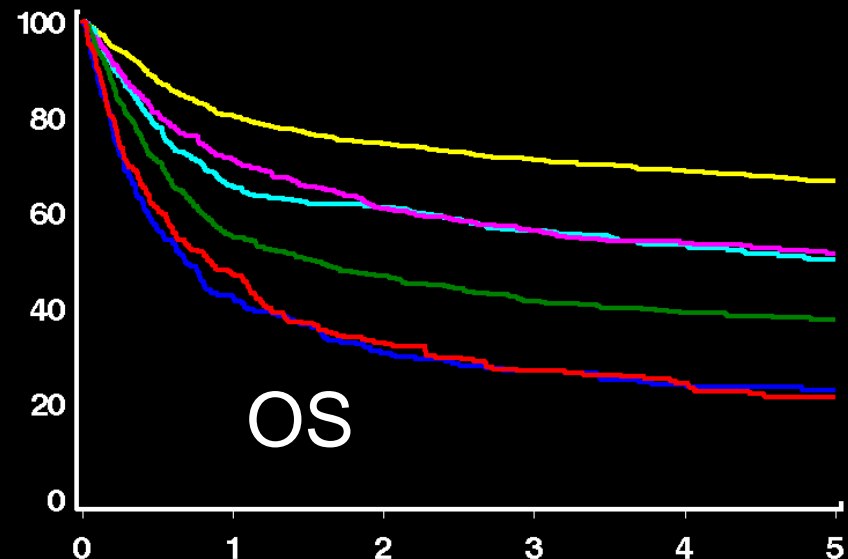
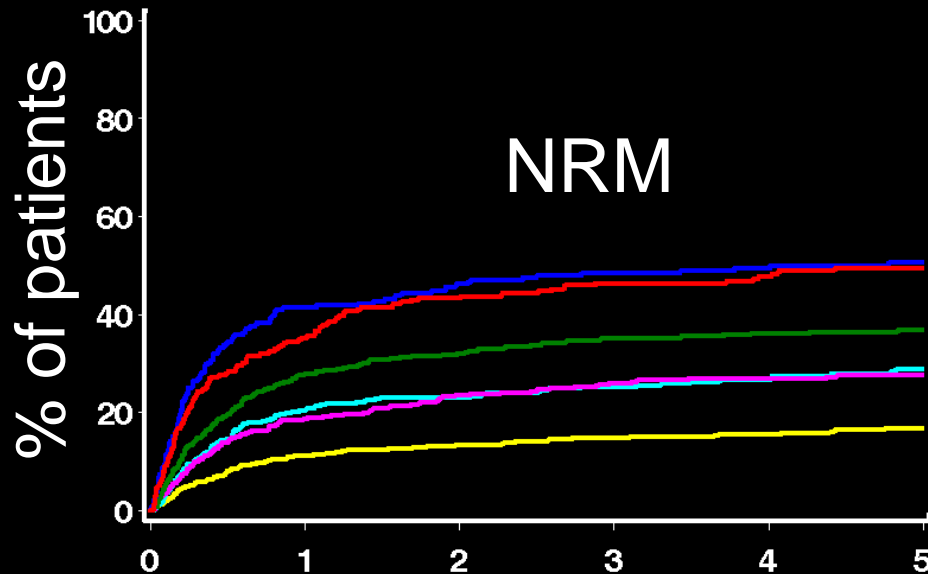
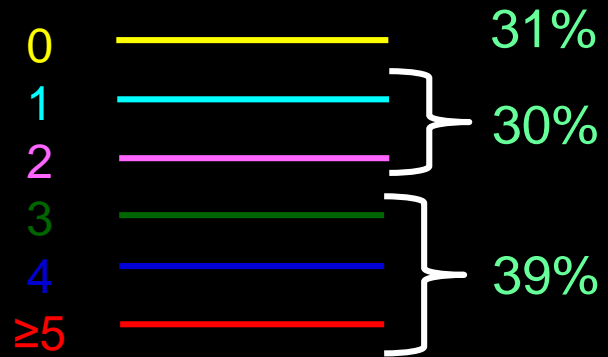
Comorbidity	HR*	Score	Prevalence (%)
Arrhythmia	1.3	1	5
Cardiac	1.3	1	5
Inflammatory bowel	1.3	1	1
Diabetes	1.6	1	3
Cerebro-vascular	1.6	1	1
Depression/anxiety	1.8	1	9
Hepatic-mild	1.9	1	16
Morbid obesity	1.9	1	2
Infection	1.9	1	4
Rheumatologic	2.3	2	4
Peptic ulcer	2.5	2	1
Renal-moderate/severe	2.6	2	2
Pulmonary-moderate	3.0	2	24
Prior Solid tumor	3.1	3	2
Heart Valve disease	3.3	3	2
Pulmonary-severe	3.7	3	9
Hepatic-moderate/severe	3.9	3	4

Multi-institutional validation of the HCT-CI

n=2523

$P < 0.0001$

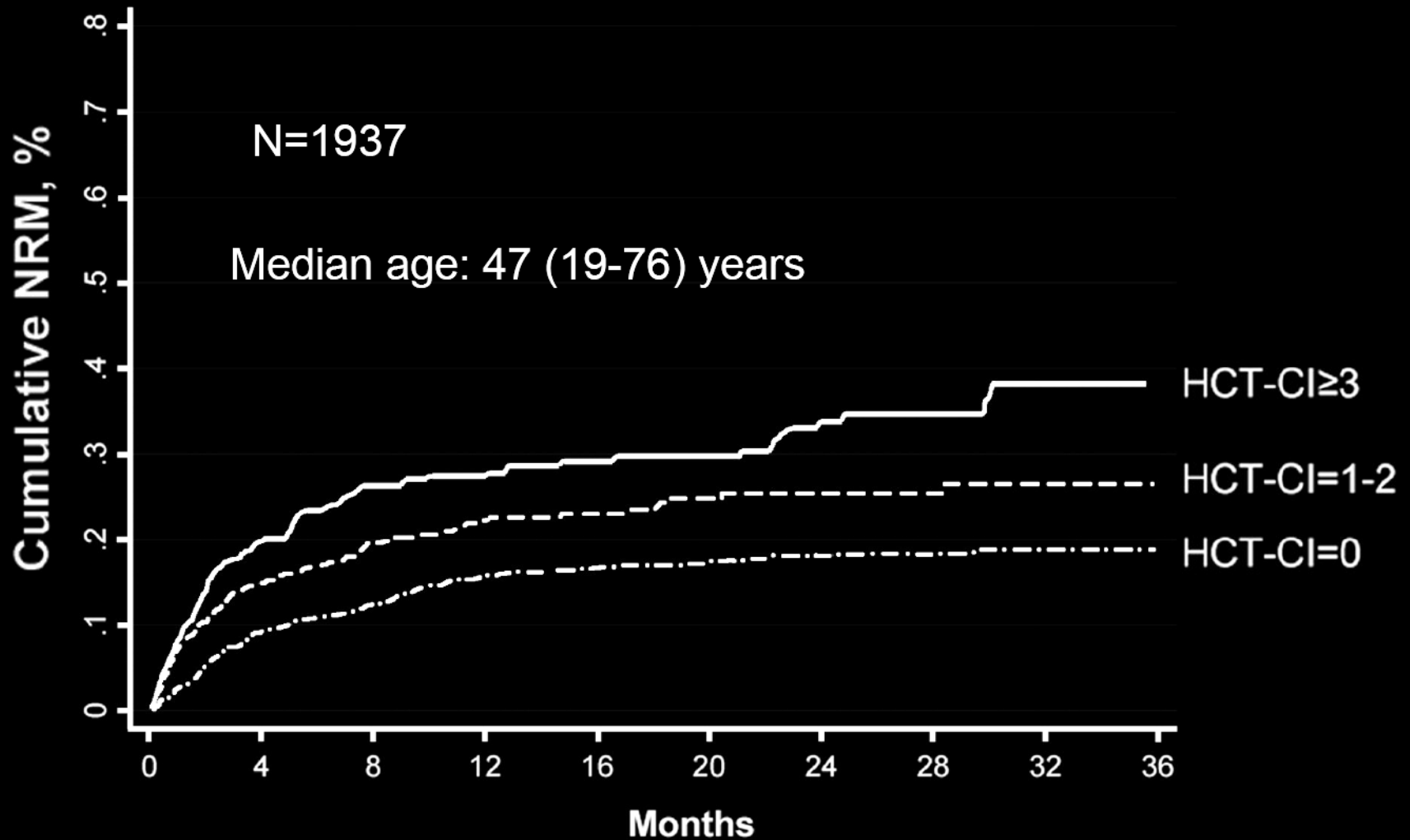
Scores



Years after HCT

Sorrer et al: ASH, 2011

Prospective Italian Experience (GITMO study)

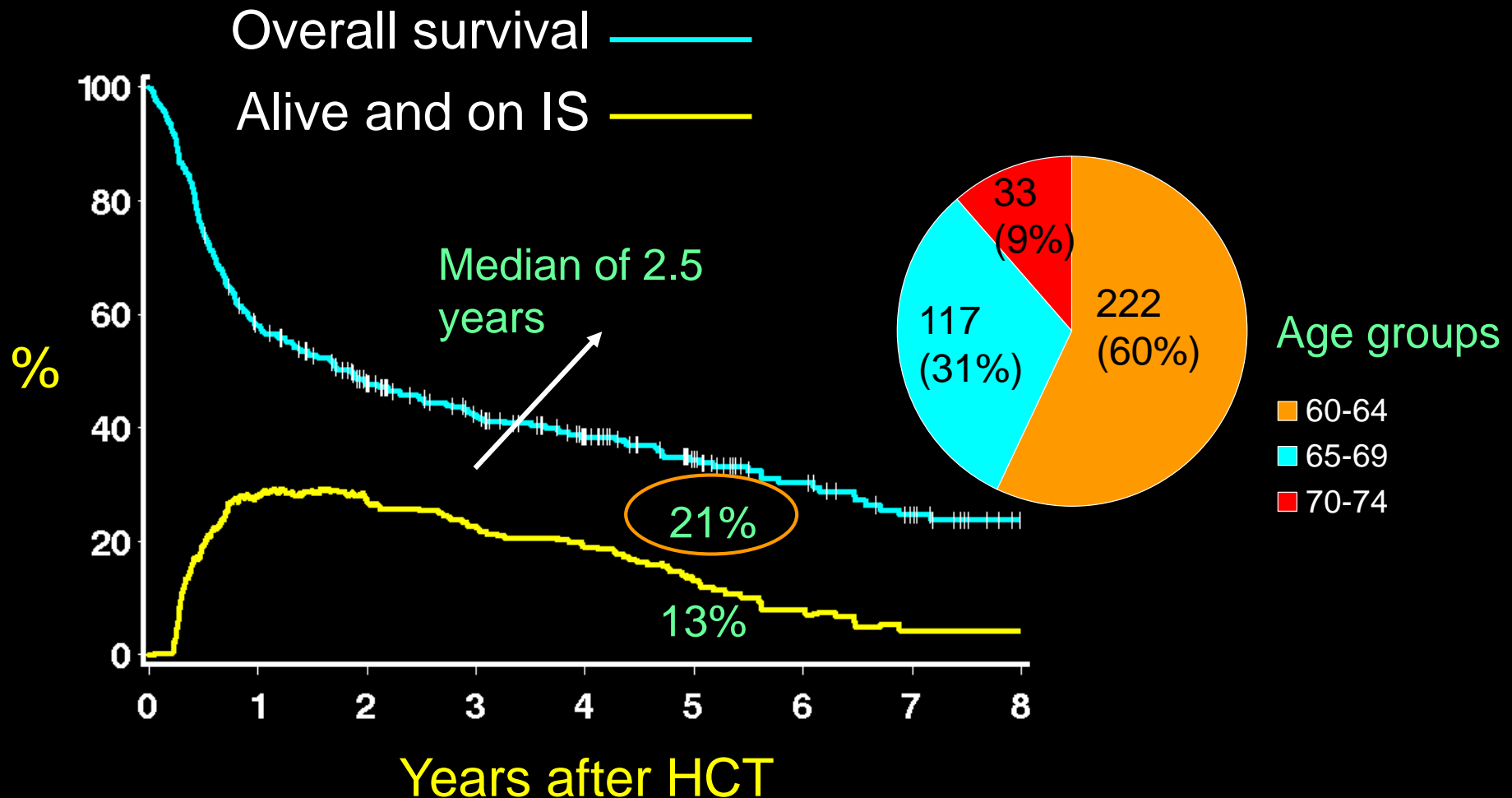


Raimondi R et al. Blood 2012;120:1327-1333



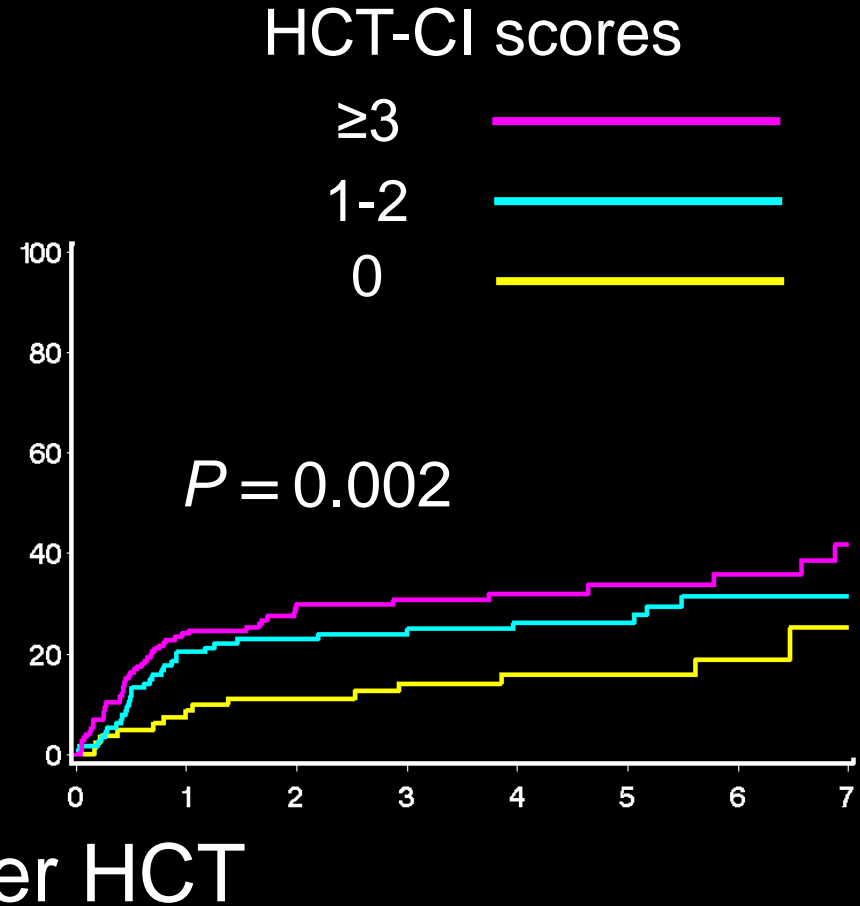
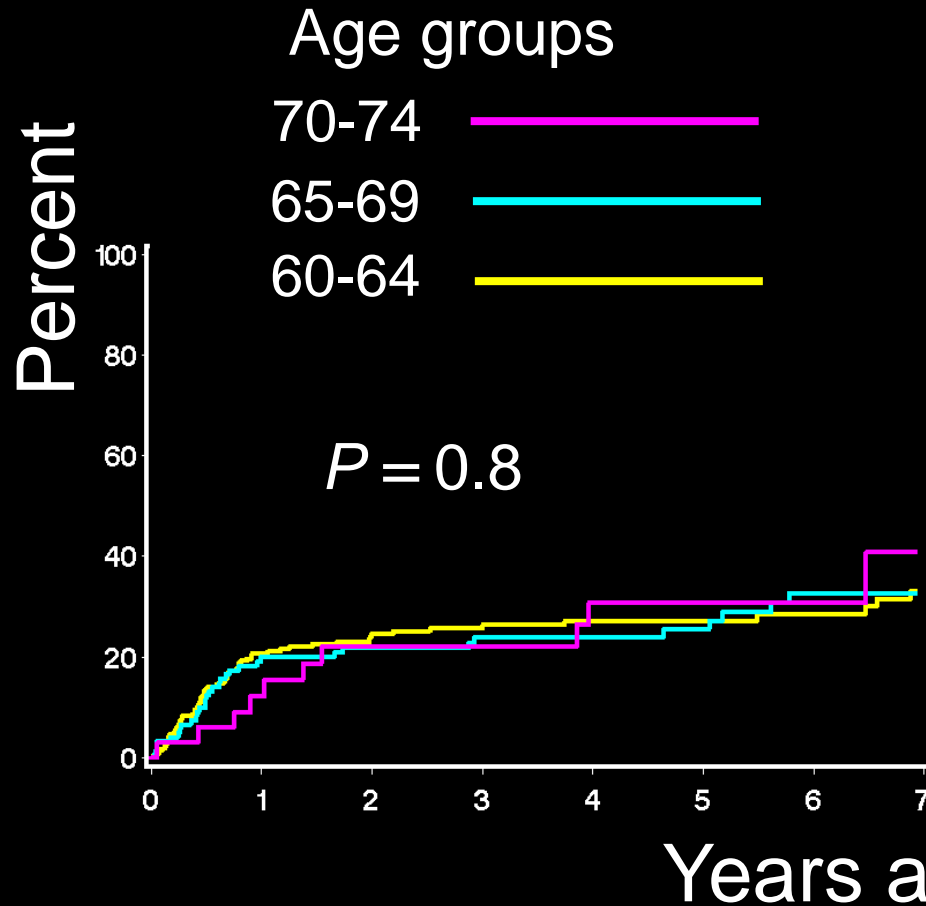
Recipient Age

Mini-Allogeneic HCT for Patients ≥ 60 years (n=372)



Mini-Allogeneic HCT for Patients ≥ 60 years (n=372)

Non Relapse Mortality (NRM)



Mini-Allogeneic HCT for Patients ≥ 60 years (n=372)

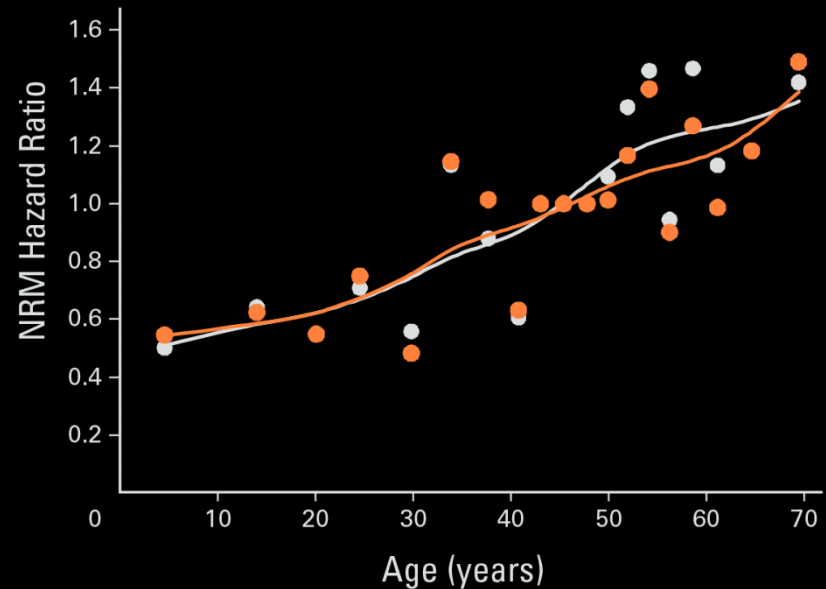
Survival at 5-years, %		HCT-CI scores		
		0	1-2	≥ 3
		%		
Relapse risks	Low	69	56	56
	Standard	45	44	23
	High	41	15	23

Could Age be Incorporated into the HCT-CI?

Training set, (n) = 1853

NRM

Age, yrs	HR	<i>p</i>
≤19	1.0	
20-39	1.21	0.29
40-49	1.48	0.04
50-59	1.75	0.004
≥60	1.84	0.005



Age >40 years = score of 1

Adjusted for HCT-CI scores, diagnoses, disease status, CMV sero-status, KPS, prior regimens, conditioning intensity, ATG, donor type, and stem cell source.

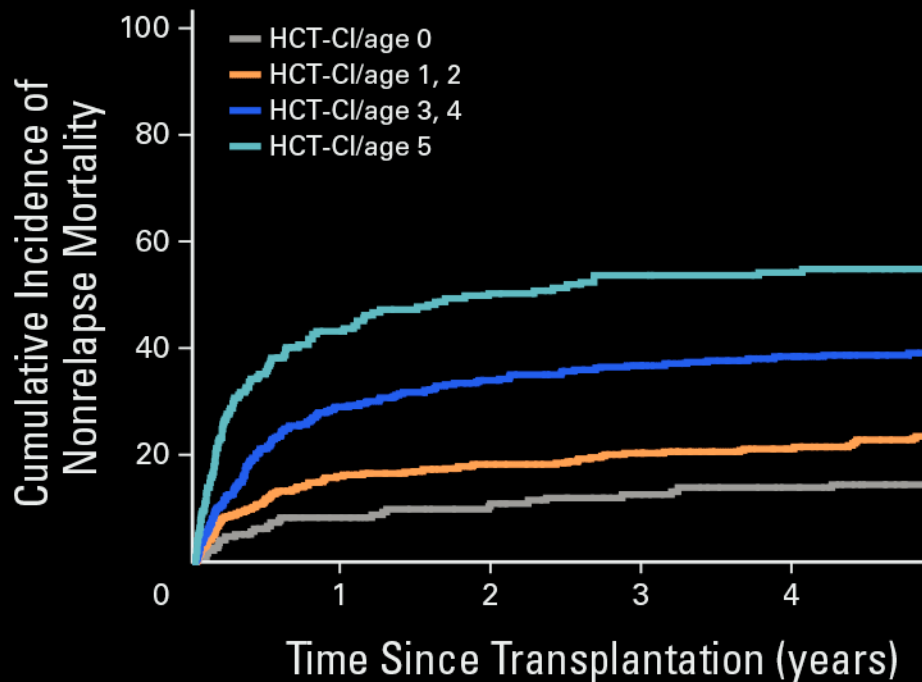
Sorrer et al. JCO, 2014; 32(29):3249-56

The HCT-CI/age Composite Index

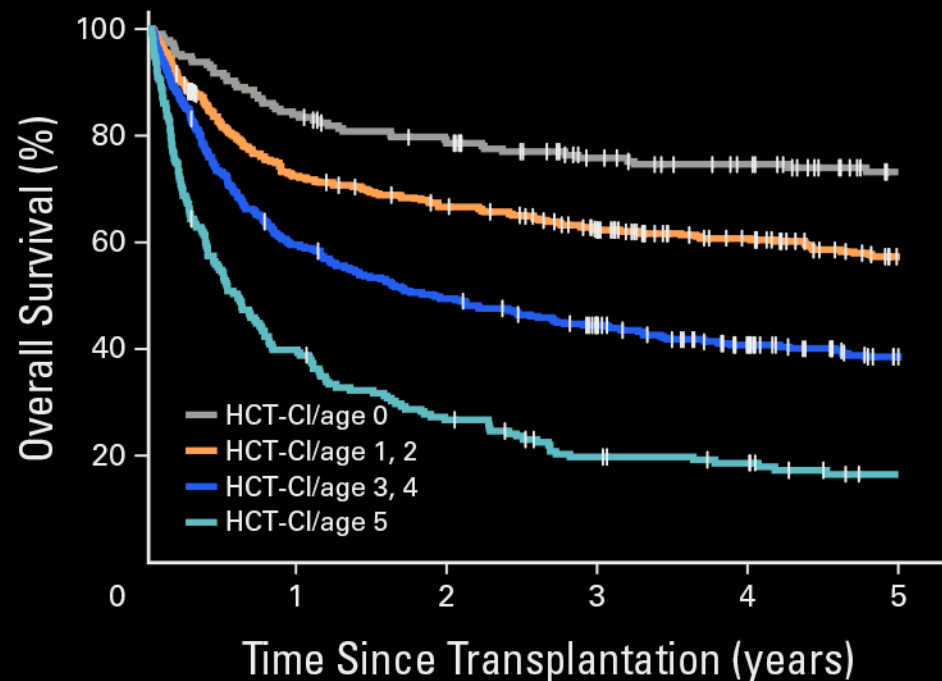
	Score
Age ≥ 40 years	1
Arrhythmia	1
Cardiac	1
Inflammatory bowel	1
Diabetes	1
Cerebro-vascular	1
Depression/anxiety	1
Hepatic-mild	1
Morbid obesity	1
Infection	1
Rheumatologic	2
Peptic ulcer	2
Renal-moderate/severe	2
Pulmonary-moderate	2
Prior Solid tumor	3
Heart Valve disease	3
Pulmonary-severe	3
Hepatic-moderate/severe	3

NRM and OS per the composite comorbidity/age index.

NRM



Overall Survival



SEATTLE CANCER CARE ALLIANCE OUTPATIENT REPORT
SCCA ARRIVAL HISTORY AND PHYSICAL EXAMINATION

IDENTIFICATION HCT-CI/age score of 8

is a 32-year-old woman who is here for an HLA-identical, related donor peripheral blood stem cell transplant for myelodysplasia evolving to AML.

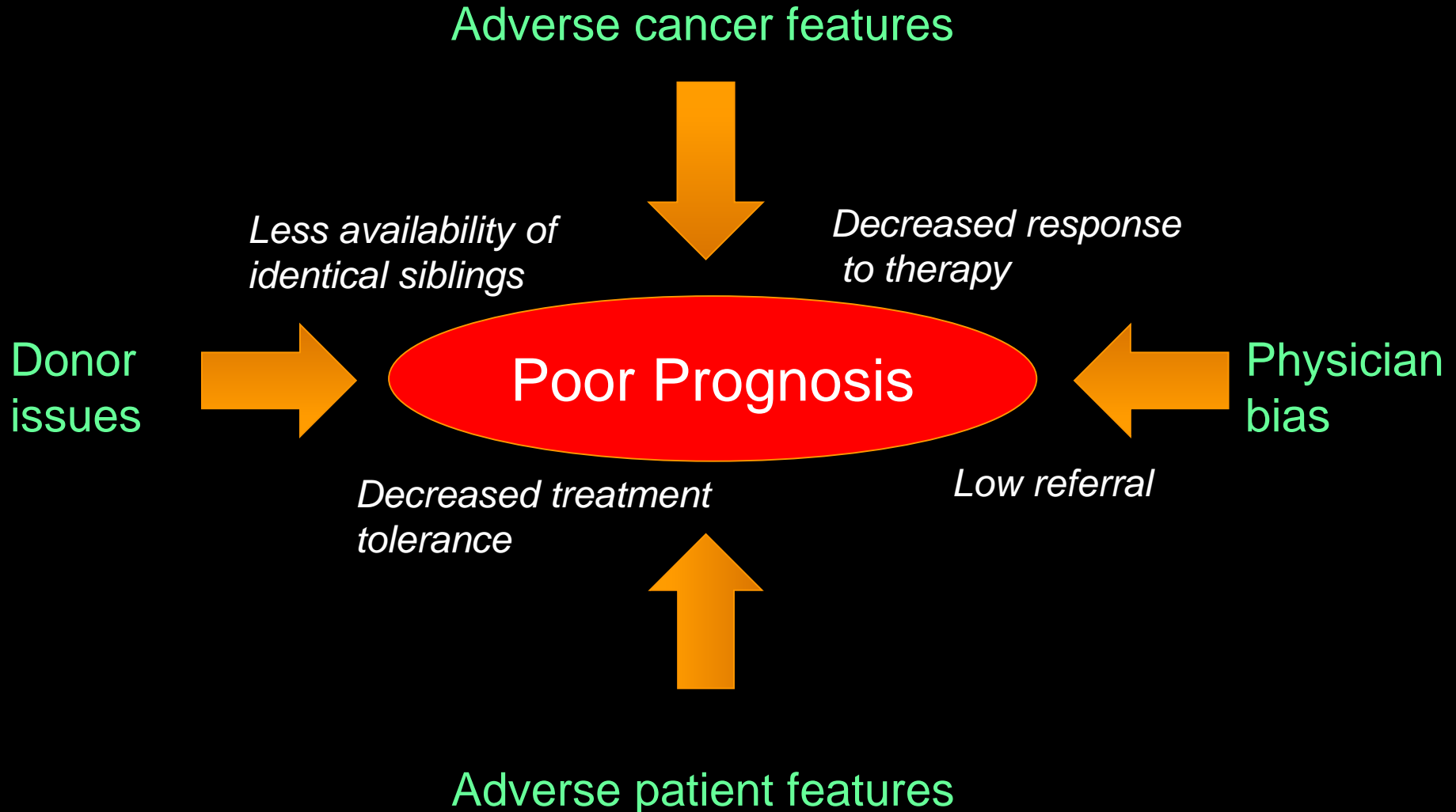
Bu/Cy

SEATTLE CANCER CARE ALLIANCE
HISTORY & PHYSICAL

PATIENT IDENTIFICATION HCT-CI/age score of 1

is a 62 year old man with a myeloproliferative disorder and myelofibrosis who presents for evaluation as a candidate for HLA-matched sibling hemopoietic cell transplantation.

Age is a Surrogate Measure



Decision-making

HCT-Adaptation scores

0-1

2-3

4

5

6

≥ 7

AML features

HCT-related risks
factors

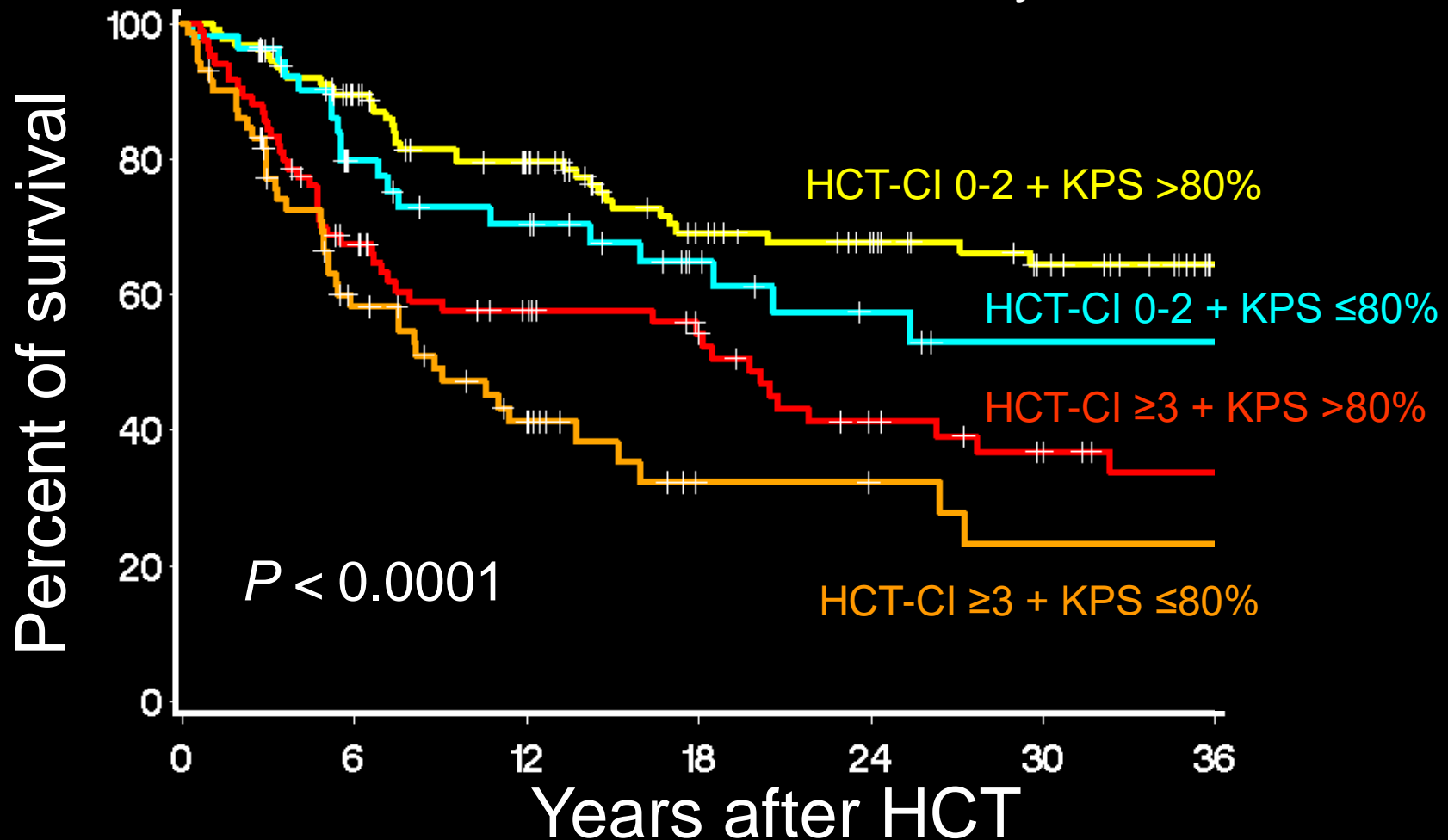
© Cartoonbank.com



*"You're fifty-seven years old. I'd
like to get that down a bit."*

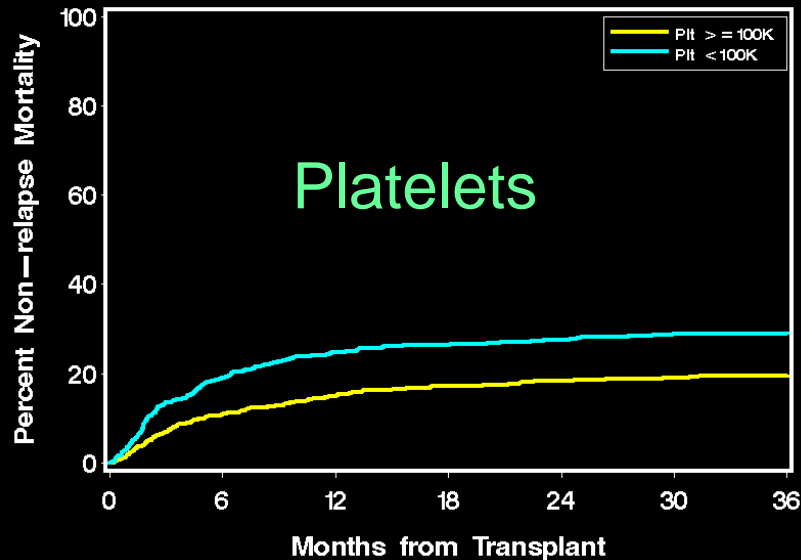
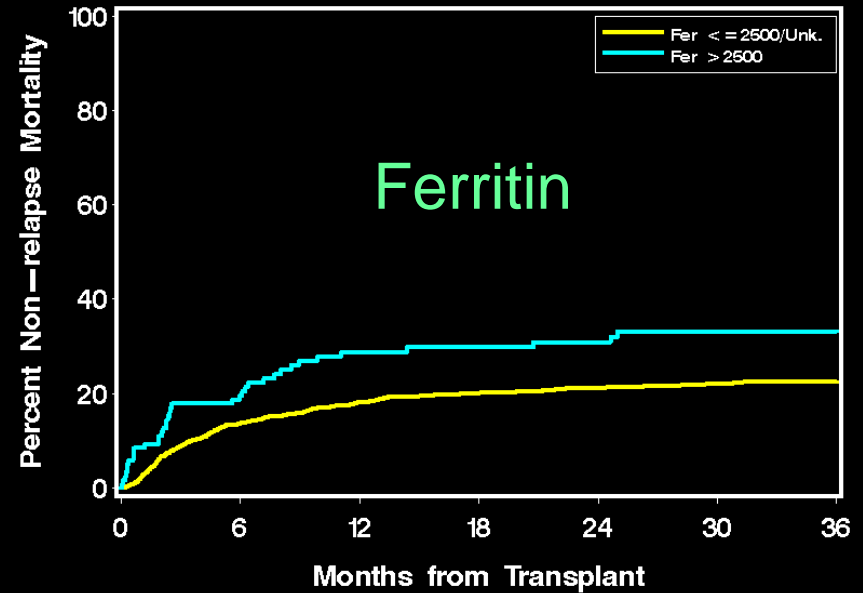
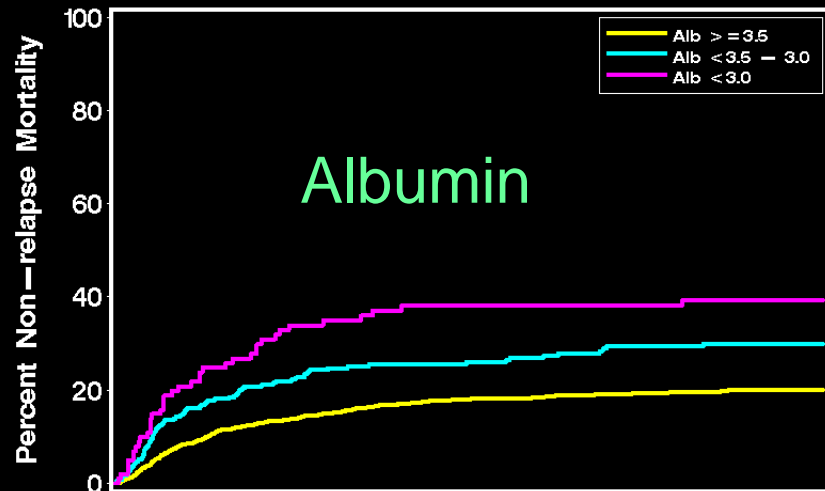
Performance Status (PS)

HCT-CI and Karnofsky PS



Biomarkers

Recipients of allogeneic HCT (N=1565)



Vaughn J et al Abstract #421

Artz A et al Abstract #422

Global Prognostic Models: EBMT Model

The HCT-CI + EBMT model

Risk group	% of patients	4-yr NRM, %	4-yr OS, %
HCTCI 0; EBMT 4	16	11	72
HCTCI 0; EBMT >4	13	19	61
HCTCI 1-2; EBMT 4	15	16	63
HCTCI 1-2; EBMT >4	19	28	48
HCTCI ≥3; EBMT 4	15	31	40
HCTCI ≥3; EBMT >4	22	41	30

Geriatric Assessment

- Different domains
 - Physical
 - Cognitive
 - Affective
 - Social
 - Functional
 - Financial

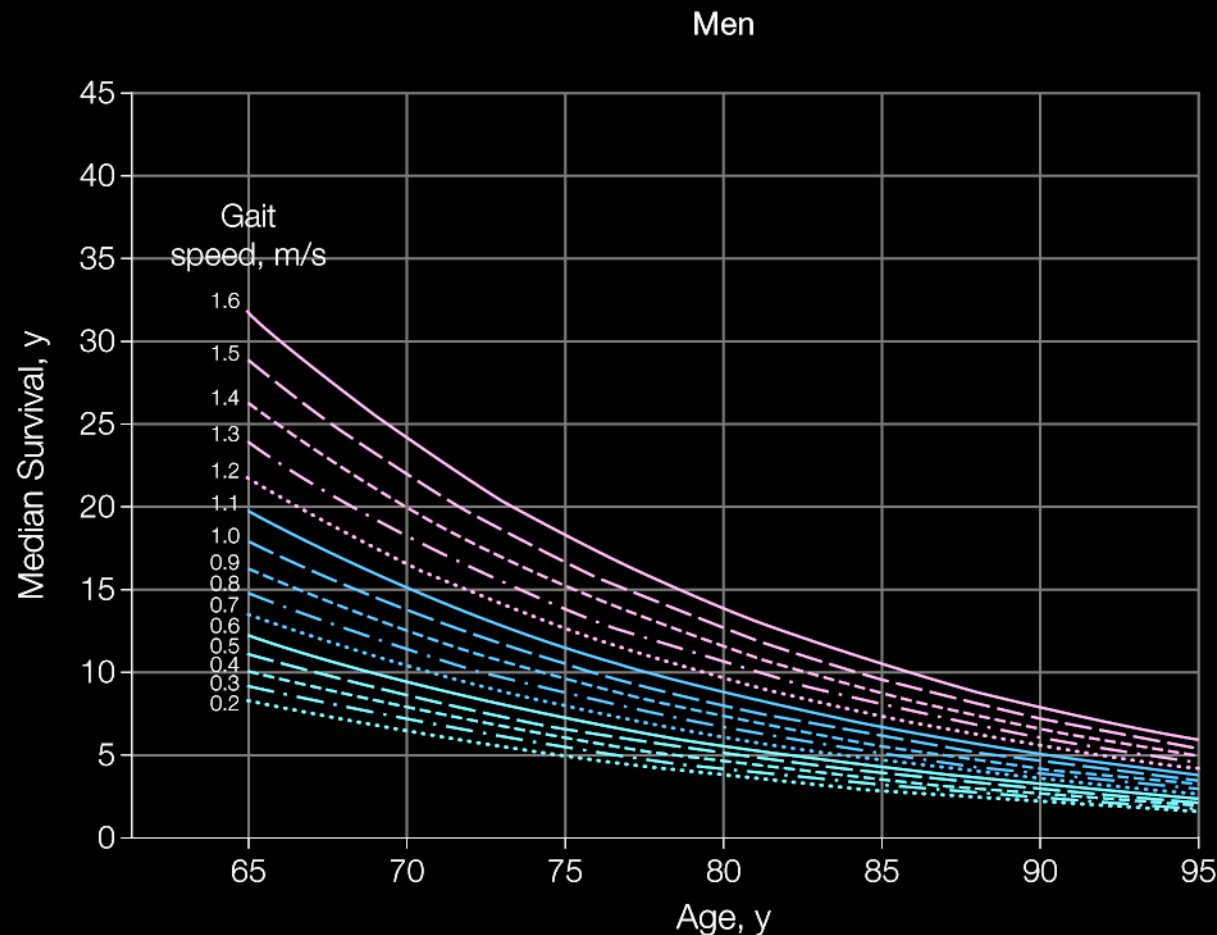
Gait Speed and Survival in Older Adults

Stephanie Studenski, MD, MPH

Subashan Perera, PhD

Kushang Patel, PhD

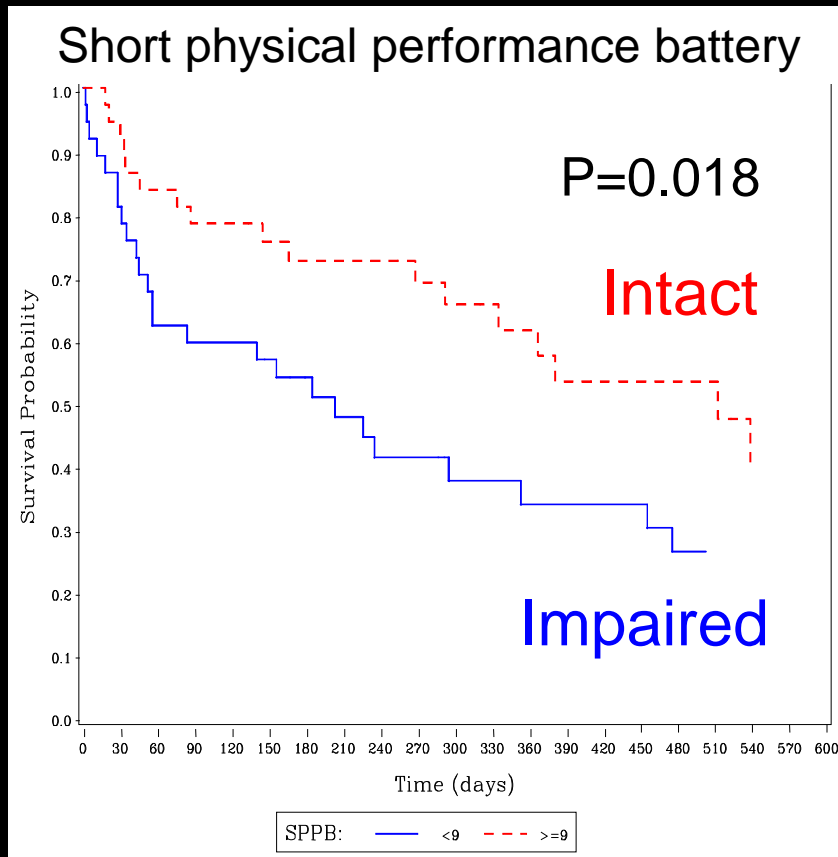
50 JAMA, January 5, 2011—Vol 305, No. 1 (Reprinted)



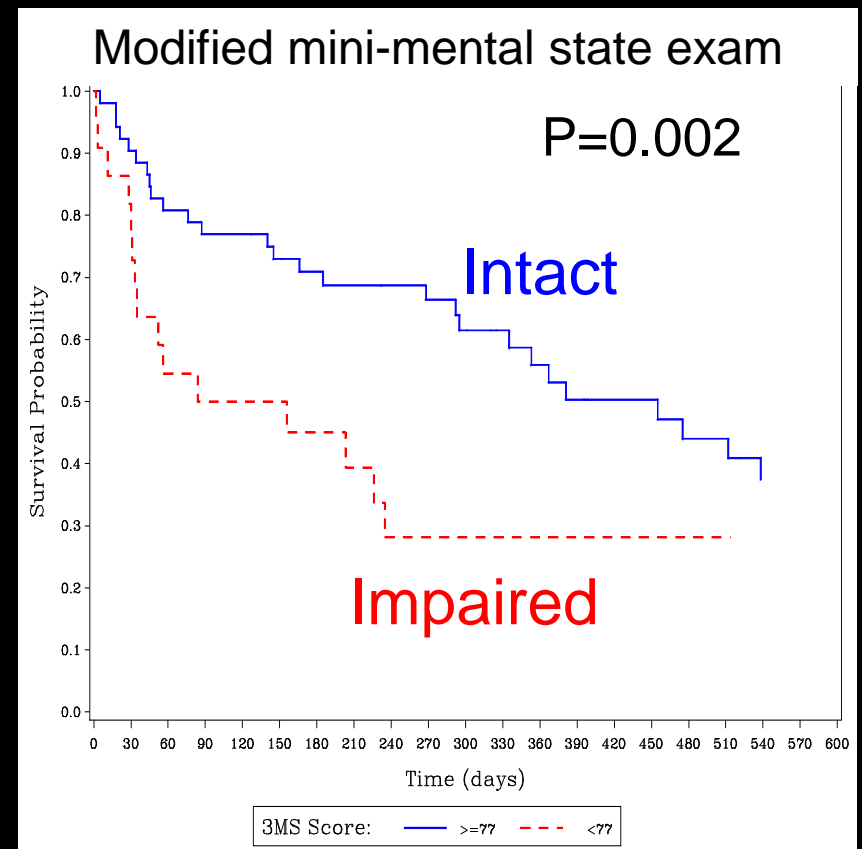
Frail =
gait speed <0.8 m/s

Physical and Cognitive Function & Survival in Older Adults with AML (N=74)

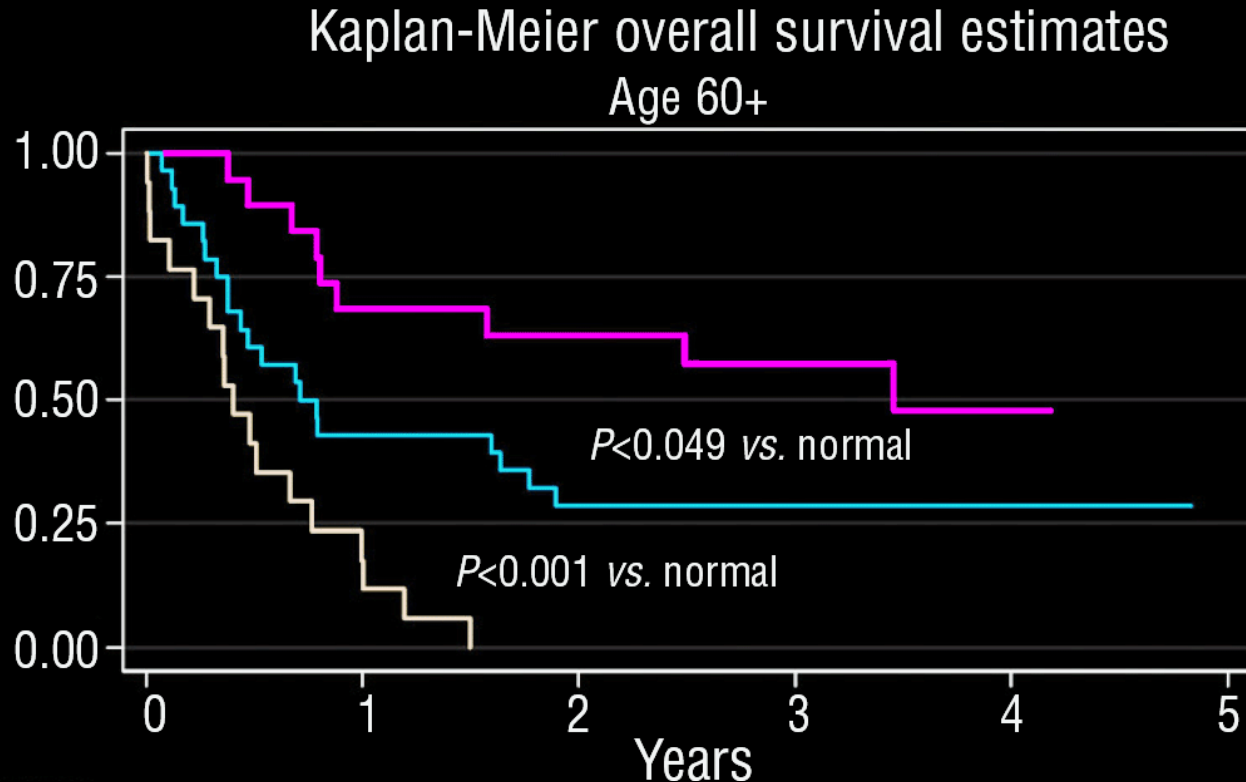
Objective physical function testing



Cognitive function testing



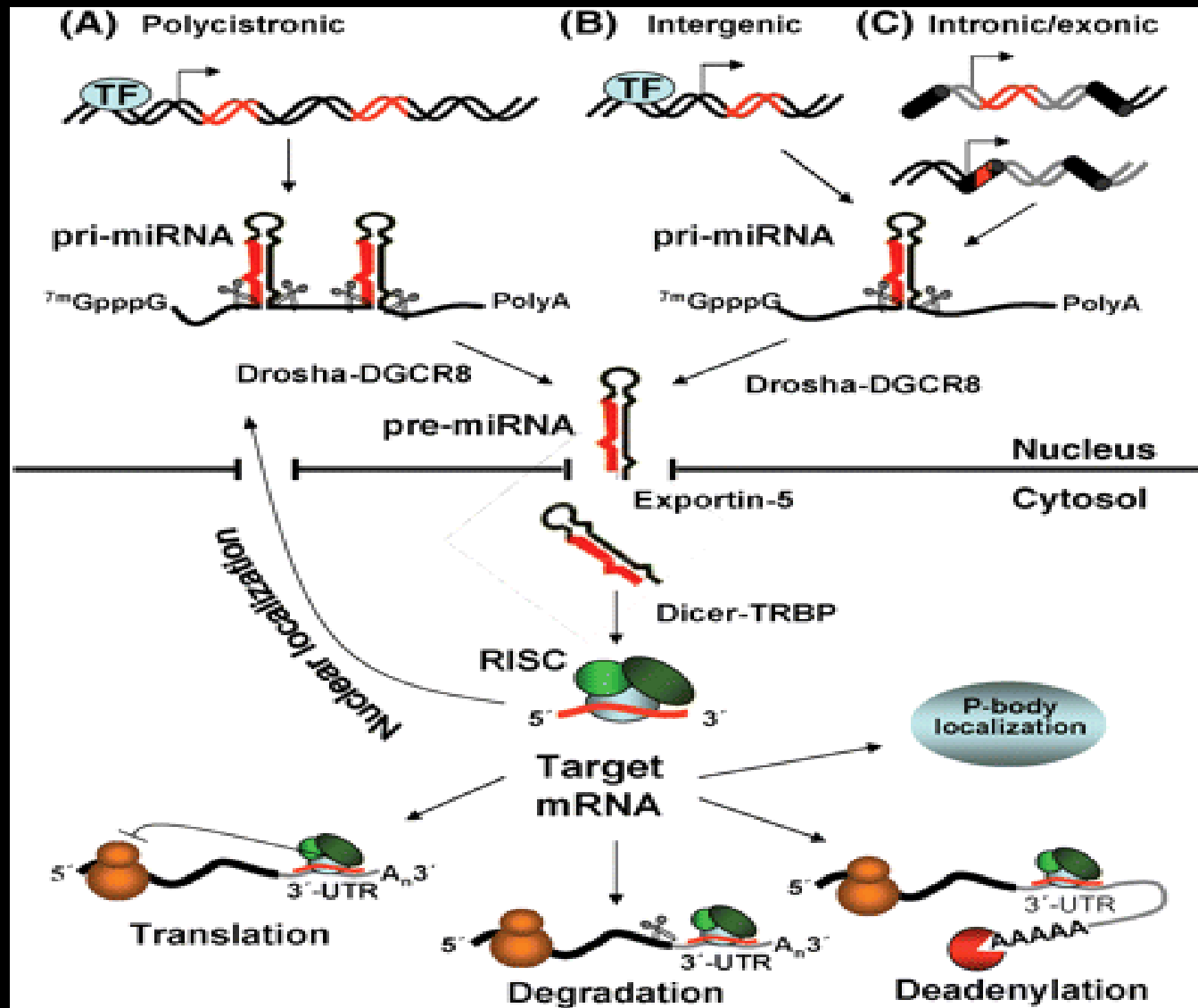
Comorbidities (HCT-CI) + Instrumental Activities of Daily Living (IADL) Older Recipients of Allogeneic HCT



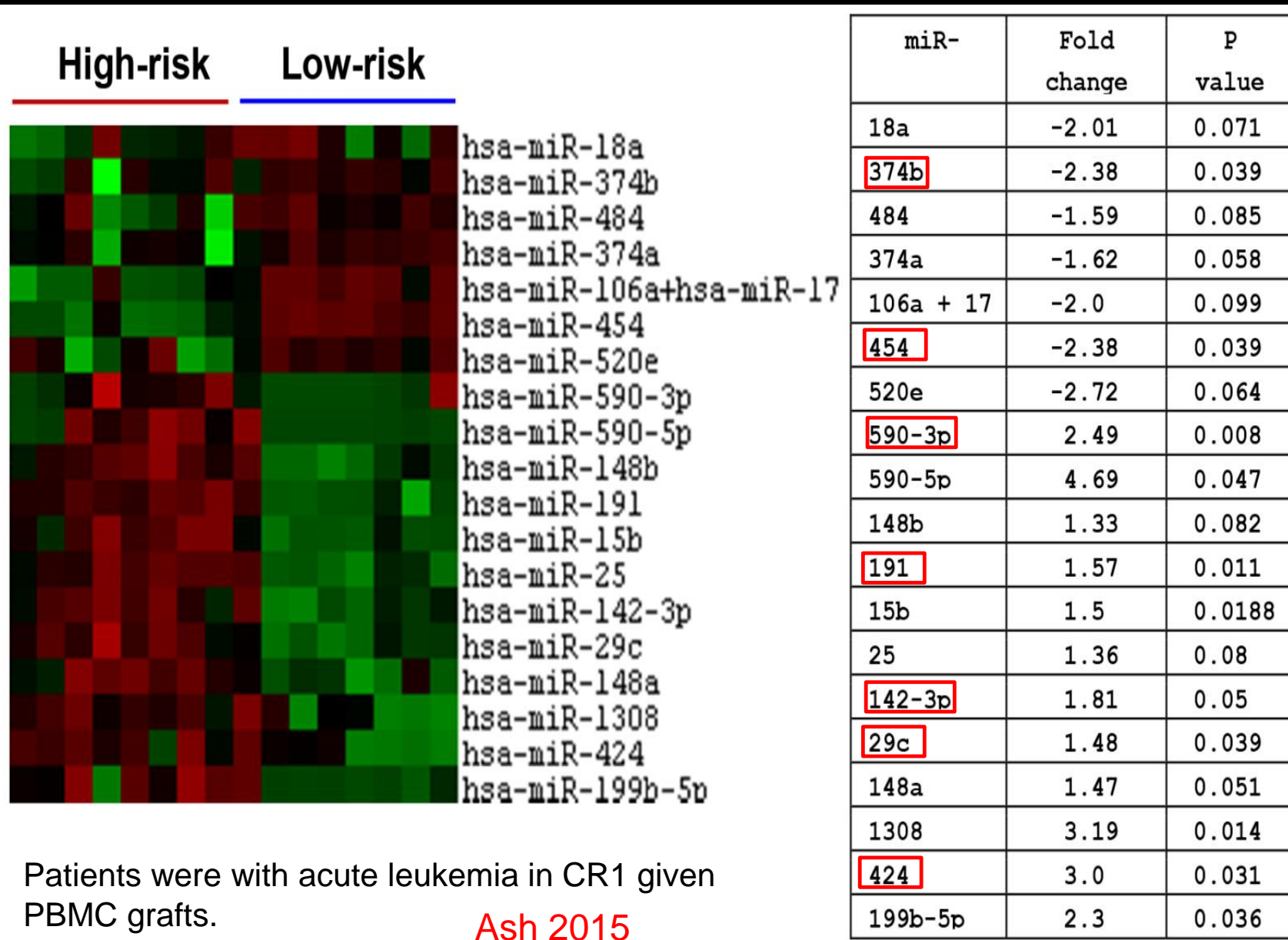
Muffy L S et al. Haematologica 2014;99:1373-1379

Ritchie EK et al (#3689): Comprehensive geriatric assessment did not predict survival in older patients with AML

Micro-RNAs



MiRs Per Comorbidity and Mortality Risks



BMT-CTN

State of the Science Symposium

Comorbidity-Regimen Related Toxicity Committee Improving prognostic assessment for older patients

Hypothesis:

- A composite health status risk model comprising HCT-CI, KPS, Geriatric Assessment (GA), and biomarkers will better predict morbidity and mortality following allogeneic HCT.

Outcomes

- NRM and Survival
- Post-HCT functional and quality of life (QoL) evaluation will be performed every 6 months for 2 years.

Decision-Making Factors

AML and HCT-related

- Important, strong evidence
 - Chromosomal abnormalities
 - Disease status
 - Donor & HLA-matching
- Important, no strong evidence
 - MRD (flow cytometry)
 - Molecular markers
- Additional info needed
 - Novel molecular biomarkers
 - miRNA expressions
 - Gene expression profiling

Patient-related

- Important, strong evidence
 - HCT-CI
 - PS
 - Composite models
- Important, no strong evidence
 - Geriatric & frailty assessment
 - Plasma biomarkers
- Additional info needed
 - SNPs
 - Socioeconomic factors
 - Biomarkers for GVHD

Proposed Risk-Schema for Older patients in CR1

Factors affecting relapse		Relapse rates, %		Factors affecting NRM		NRM, %
Cyto/molecular risks	Other factors*	Chemo or Auto-HCT	Allo-HCT	Max HCTCI	Other factors£	Allo-HCT
Favorable	Good-risk	40-50	10-20	1-2	Good-risk	0-5
Intermediate-I	Intermediate-risk	50-70	20-30	3-4	Good-risk	20-25
Intermediate-II	Poor-risk	70-80	30-40	5-7	Good-risk	30-35
Unfavorable	Poor-risk	90-100	40-50	≥8	Good-risk	40-45

*MRD at HCT, and duration between diagnosis-HCT

£EBMT score, KPS %, GA evaluation, inflammatory biomarkers, graft type.

Decision-making:

- 79 years old male physician with AML in first CR with intermediate-I cytogeneic/molecular risks. PMH: melanoma, resected in 1977. Fully active, takes care of activities of daily living. Married and accompanied by wife. He has an HLA-identical sibling. Preference: cure from AML.

What would you recommend as next step in therapy?:

- High-dose myeloablative allogeneic HCT
- Conventional chemotherapy with meticulous follow up
- Palliative care
- Reduced-intensity allogeneic HCT
- Hospice

Decision-making: 79Y M with AML 2nd CR

Risk factors	Patient-specific	
	Favorable	Unfavorable
Comorbidities		3
Gait speed	1.3 m/s	
VES-13	0	
Fried Frailty Index	0	
Taxonomy of Age	1	
QOL	Good	
Social support/activity	Good	
ADL / IADL	Excellent	
Geriatric syndromes	Absent	

Decision-making:

- 61 years old female with AML in first CR. Favorable cytogenetic/molecular risk. KPS 70%. FEV1 60%, ejection fraction 45%, depression, and chronic hepatitis. Limited daily activities. No available HLA-matched donor.

What would you recommend as next step in therapy?:

- High-dose myeloablative allogeneic HCT
- Conventional chemotherapy with meticulous follow up
- Palliative care
- Reduced-intensity allogeneic HCT
- Hospice

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