Stem Cell Transplantation in Leukemia

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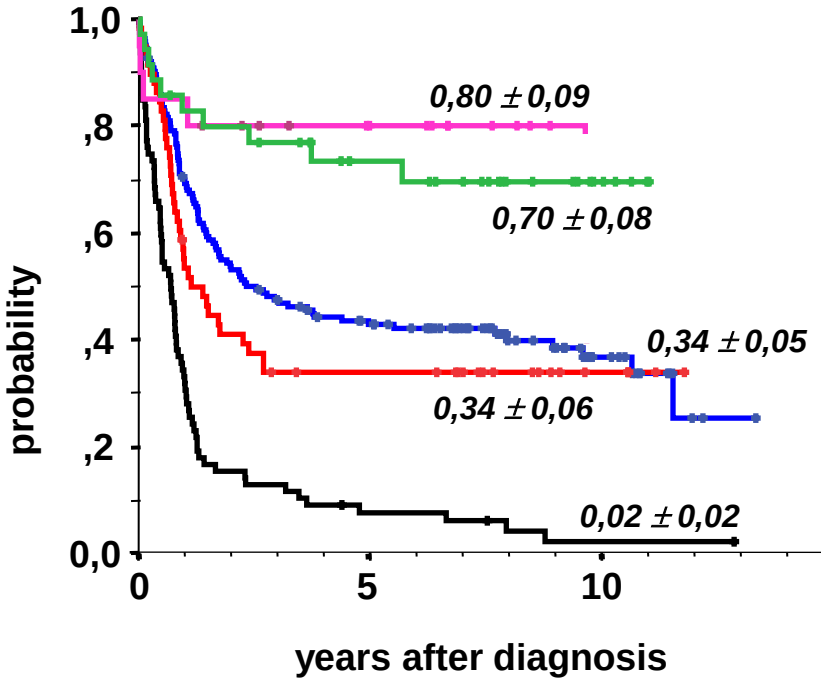
Stem Cell Transplantation in Acute Myeloid Leukemia

Outcome according to cytogenetics

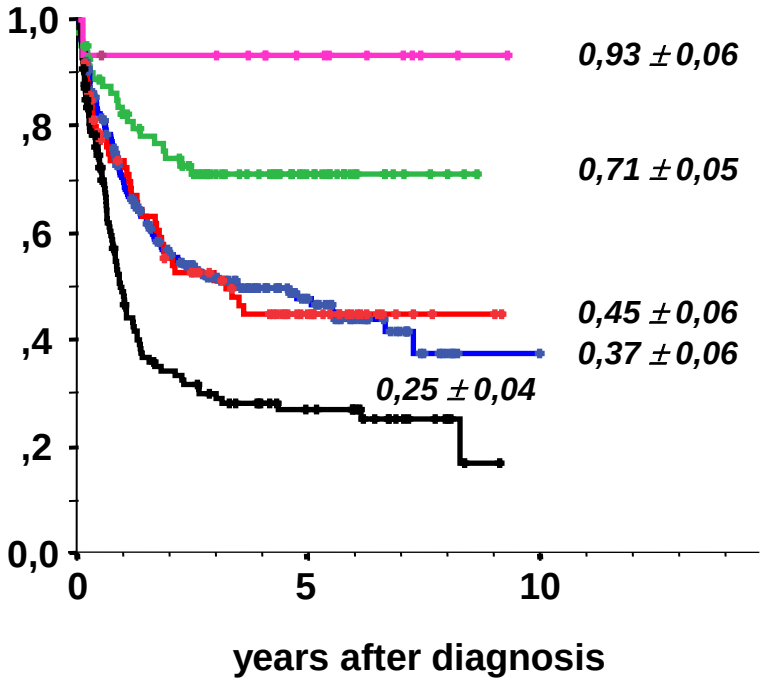
AML ´96 n = 35, 163, 58, 79, 20

p < 0,0005



AML ´02 n = 82, 242, 86, 141, 15

p < 0,0005



- *t(8;21), inv(16)*
- *normal*
- *APL: t(15;17)*
- *others: z.B. +8, 20q-, ...*
- *abn(3q26), t(6;9), -5/5q-, -7/7q-, abn(11q23), complex*

{incl. HCT; 04/2012}

Stem Cell Transplantation in Acute Myeloid Leukemia

family donor vs. no donor according to cytogenetics

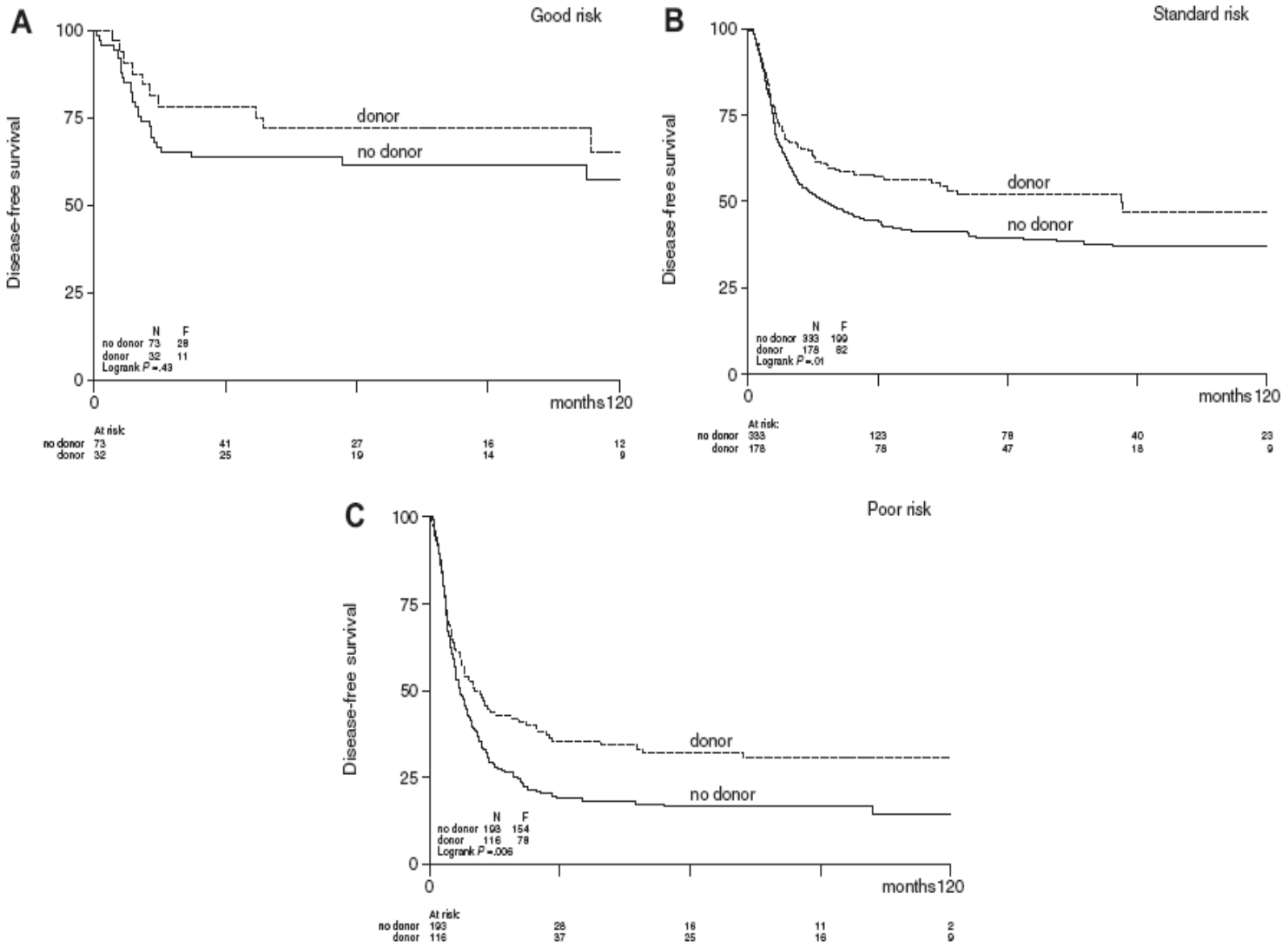


Figure 2. Actuarial disease-free survival of patients with acute myeloid leukemia in first complete remission according to risk category and donor availability.
(A) Good risk ($P = .43$), (B) intermediate risk ($P = .01$), (C) poor risk ($P = .006$).

Cornelissen et al., Blood.2007;109:3658-3666

Stem Cell Transplantation in Acute Myeloid Leukemia

Efficacy of allo HSCT in the treatment of AML CR1

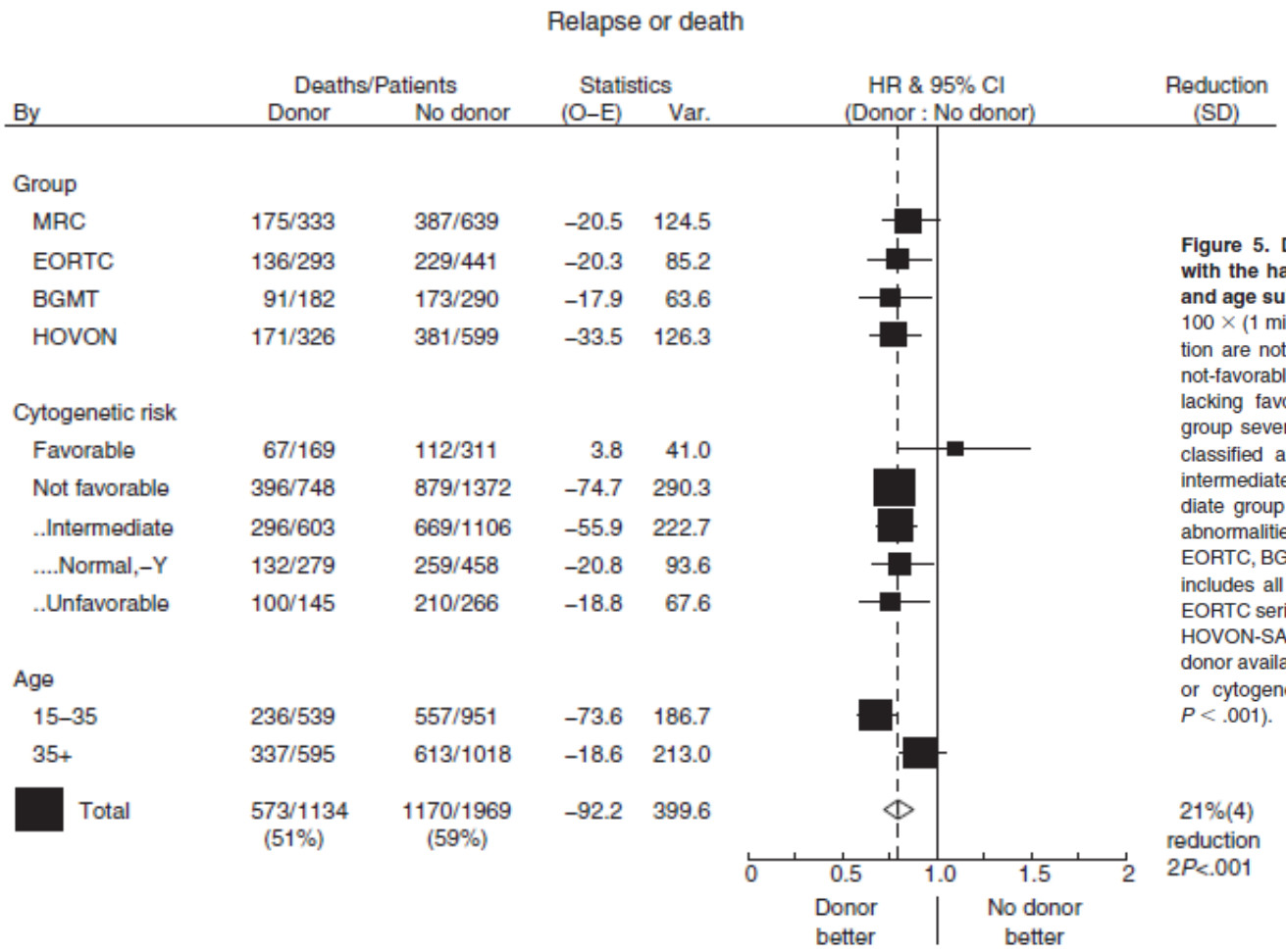
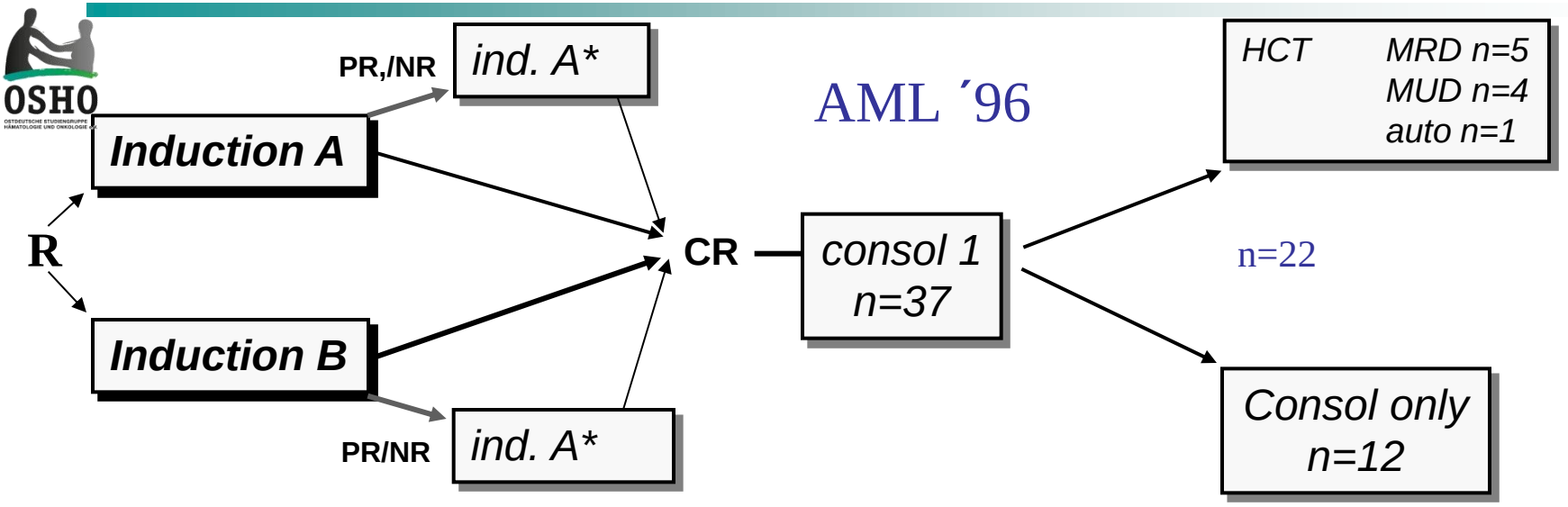


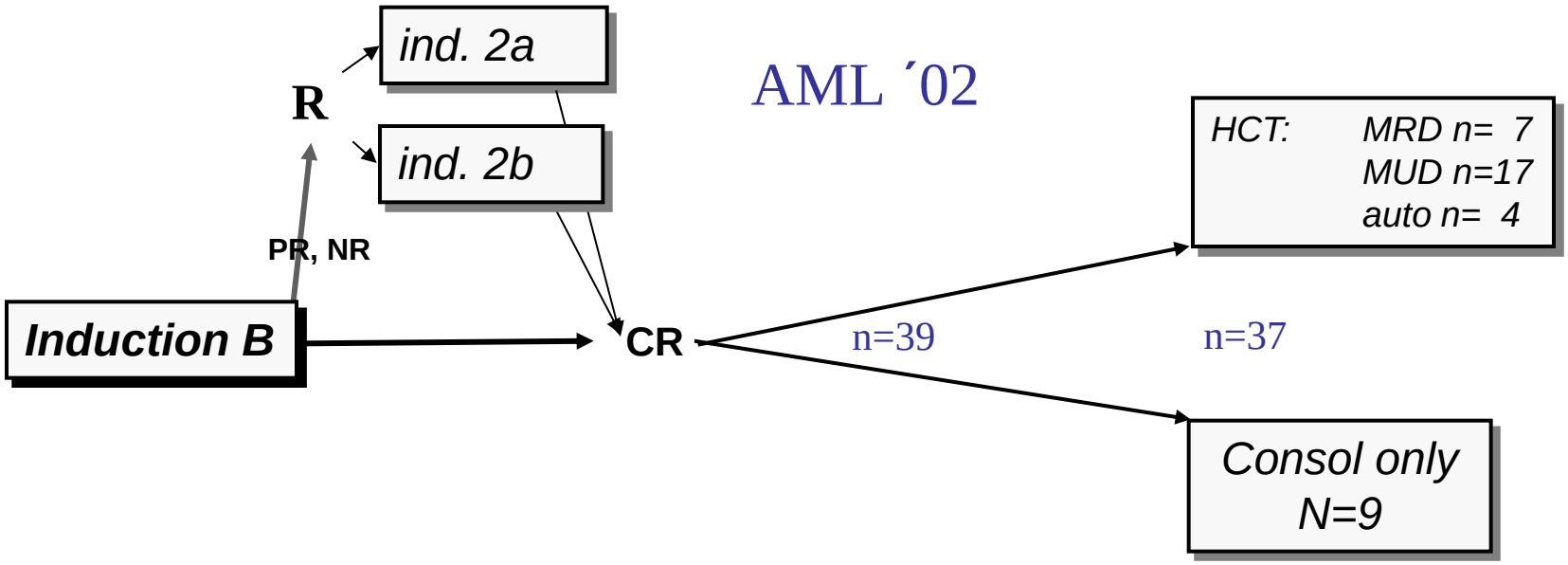
Figure 5. Disease-free survival by donor availability with the hazard ratio (HR) plots for study group, risk, and age subgroups. The percentage reduction is equal to 100 × (1 minus] HR). Patients without cytogenetic information are not included in a cytogenetic risk subgroup. The not-favorable cytogenetic group consists of all patients lacking favorable cytogenetic abnormalities. Within that group several subgroups are considered. All patients not classified as favorable or unfavorable were considered intermediate risk. Normal, −Y is a subgroup of the intermediate group and contains all patients without cytogenetic abnormalities or with only −Y, as was derived from the EORTC, BGMT, and HOVON series. The unfavorable group includes all patients classified as bad or very bad in the EORTC series or as unfavorable in the other studies (MRC, HOVON-SAKK, BGMT). The pooled estimate of the HR of donor availability for DFS for all patients irrespective of age or cytogenetic subgroup is 0.79 (95% CI, 0.72-0.88; $P < .001$).

Cornelissen et al., Blood 2007

Stem Cell Transplantation in Acute Myeloid Leukemia

High risk cytogenetics

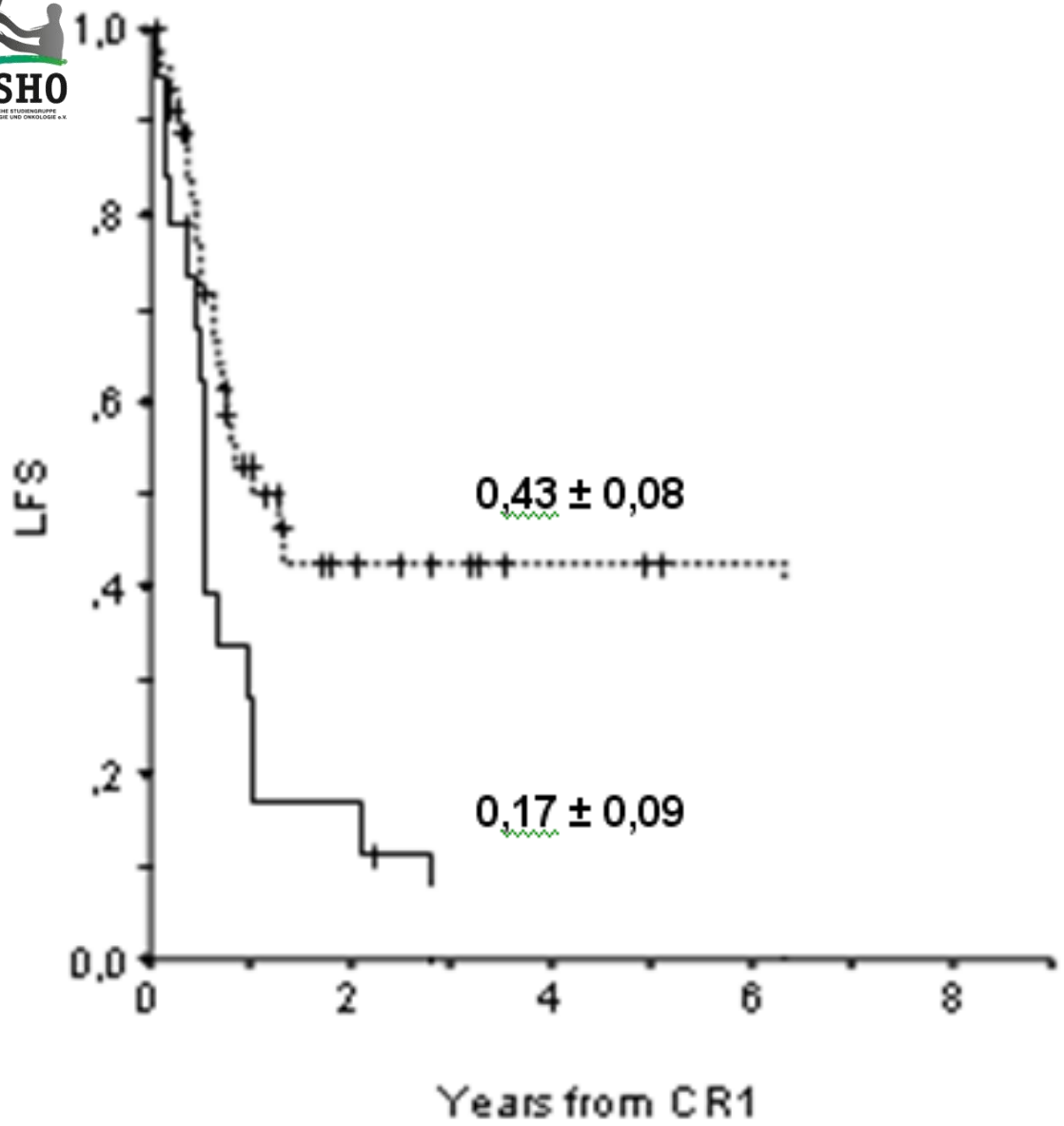




Basara et al, Leukemia, 2009

Stem Cell Transplantation in Acute Myeloid Leukemia

High risk cytogenetics: outcome HCT vs. CT



allogeneic HCT, n=47;
p=0.005 vs. CT

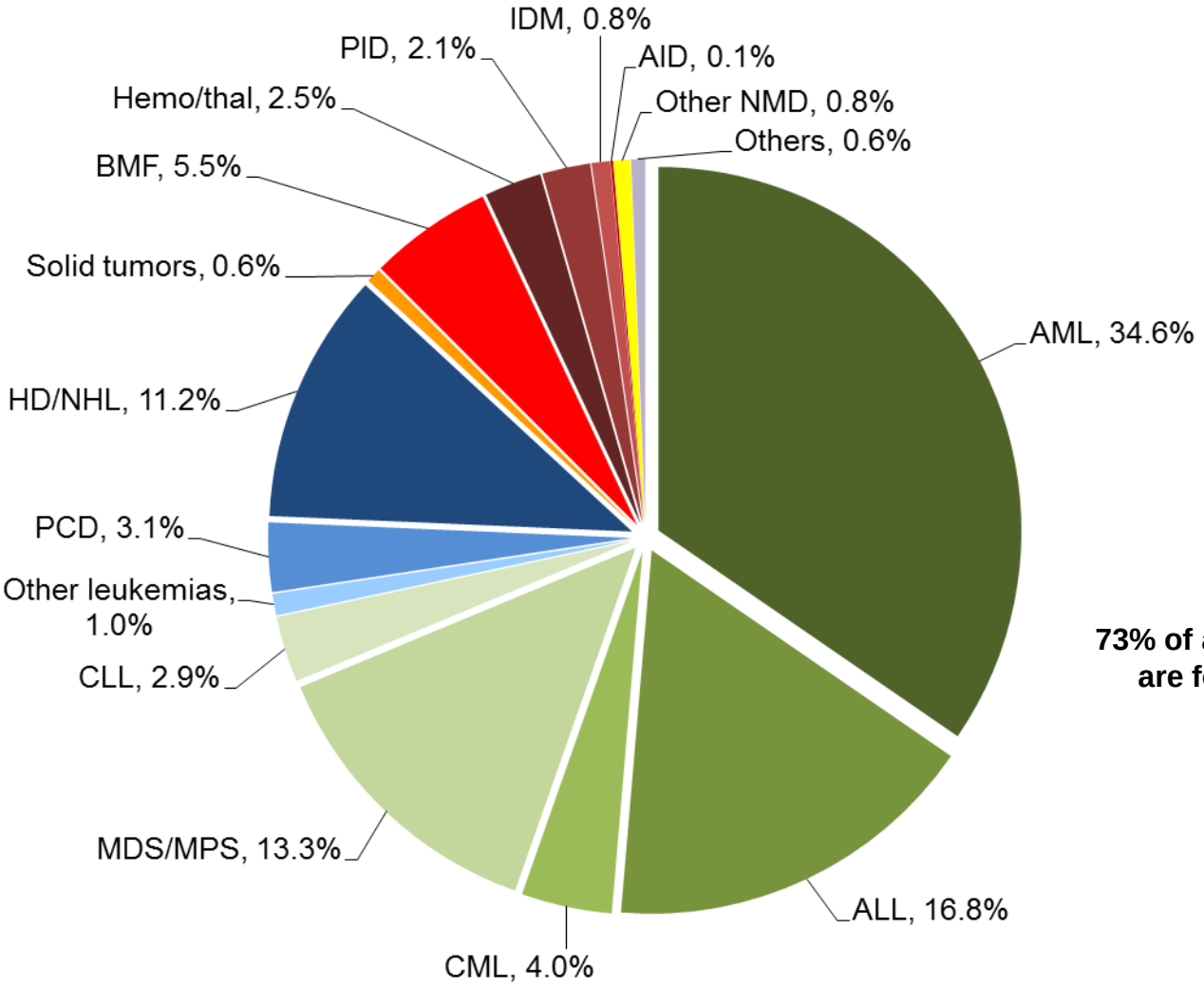
CT, n=21

Basara et al, Leukemia, 2009

Stem Cell Transplantation in Acute Myeloid Leukemia

role of Allo-SCT in AML

Allogeneic HSCT in 2010 (n=26241)



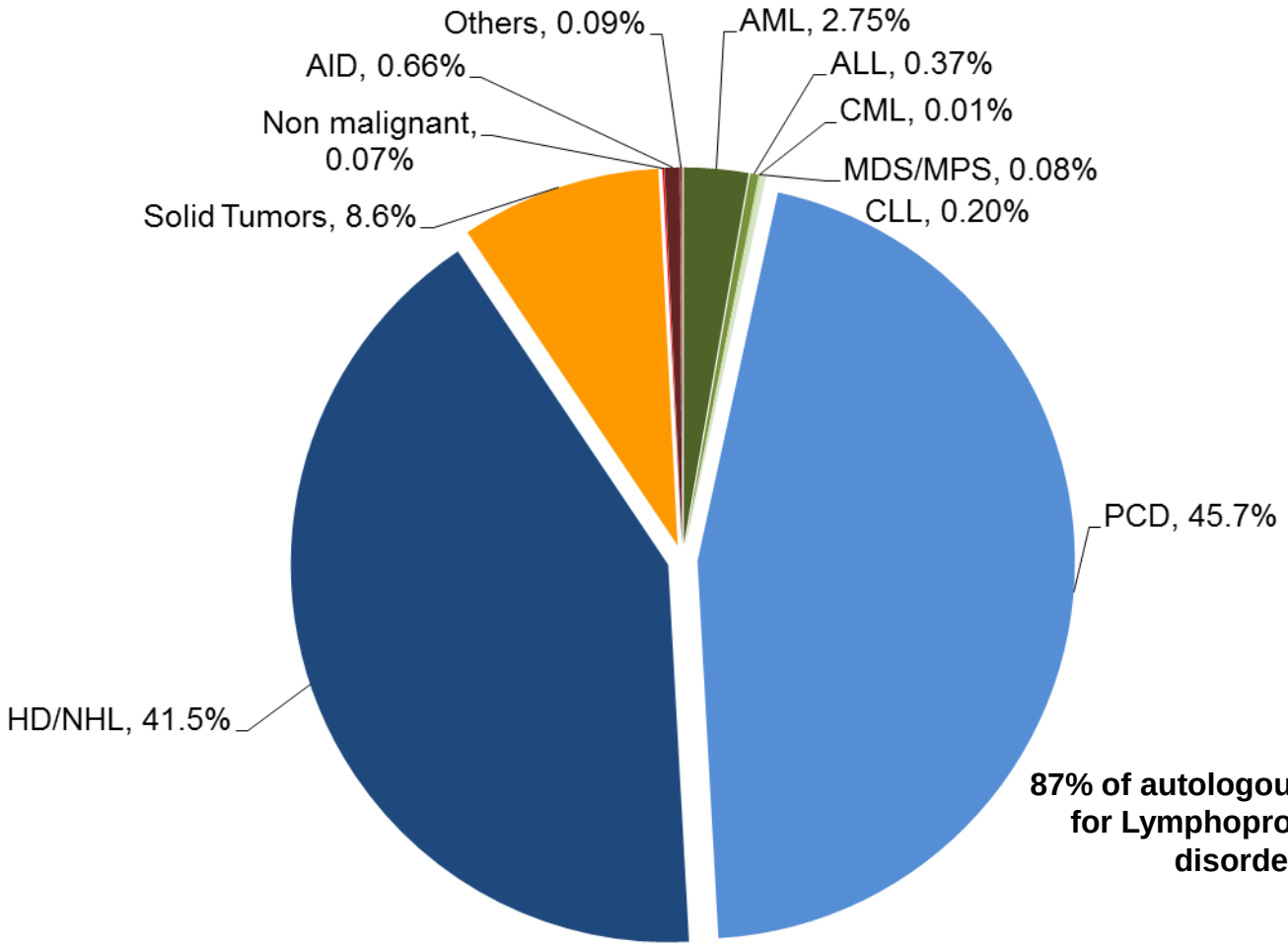
73% of allogeneic HSCT are for Leukemias

09/10 preliminary data

Stem Cell Transplantation in Acute Myeloid Leukemia

role of Allo-SCT in AML

Autologous HSCT in 2010 (n=30498)



87% of autologous HSCT are for Lymphoproliferative disorders

09/10 preliminary data

Stem Cell Transplantation in Acute Myeloid Leukemia

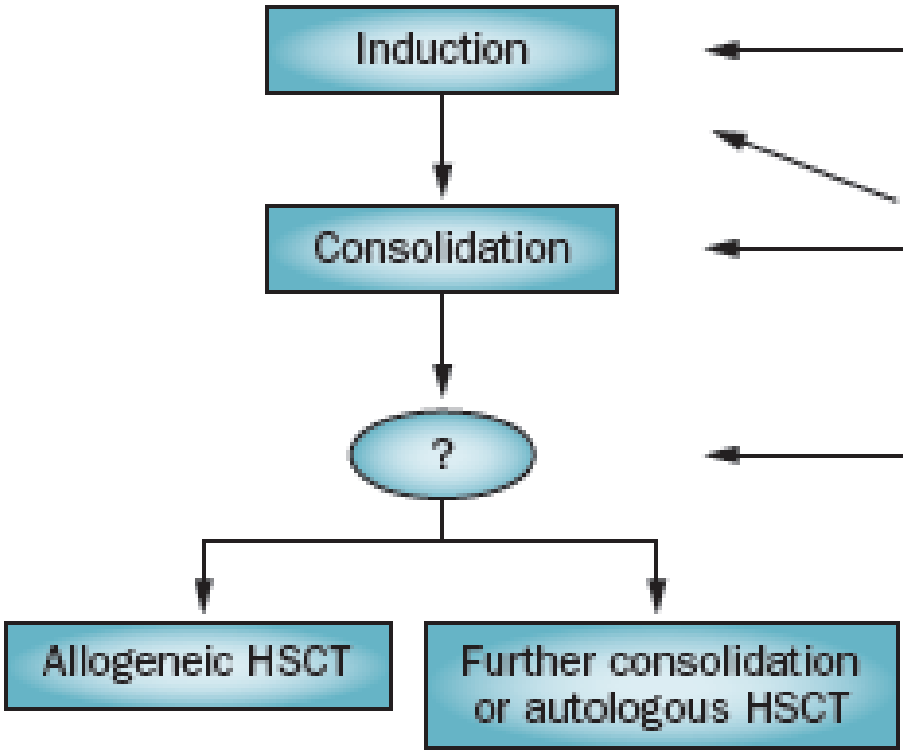
Global activity survey 2006-2010

Allogeneic	**2006**	**2009**	**2010**		
Acute Leuk/MDS/MPS	12 502	16 070	17 227	↑	38%
Chronic Leuk	1 890	1 693	1 828	-	
Lymphoproliferative disorders	3 219	3 742	3 739	↑	16%
Solid Tumors	150	152	168	-	
Non Malignant disorders	2 360	3 973	3 116	↑	32%
BMF	*1 292*	*1 413*	*1 442*	↑	12%
Others	212	102	163	↓	
Total	20 333	24 732	26 241	↑	29%
Autologous					
Leukemias	1 726	1 169	1 043	↓	40%
PCD	10 675	12 732	13 937	↑	31%
Lymphomas	10 980	12 349	12 648	↑	15%
Solid Tumors	2 560	2 495	2 620	-	
Non Malignant disorders	193	229	222	-	
Others	96	28	28	↓	
Total	26 230	29 001	30 498	↑	16%
Total	**46 563**	**53 734**	**56 739**	↑	22%

preliminary data

Stem Cell Transplantation in Acute Myeloid Leukemia

Update on SCT approaches – treatment



I. AML risk group classification at diagnosis; HLA-typing; donor availability

II. Quality of remission: haematological, cytogenetic, immunophenotype and molecular profile (MRD)

III. Risk of TRM according to patient parameters (HCT–CI) and patient–donor parameters (Gratwohl score)

IV. Prospects after relapse

Cornelissen et al., Nat. Rev. Clin. Oncol. 2012

Stem Cell Transplantation in Acute Myeloid Leukemia

Update on SCT approaches – AML-related prognostic markers

Table 1 | AML-related prognostic parameters

Cytogenetic markers	Molecular markers	Clinical factors
Favourable prognostic factors		
t(8;21)	Mutated *CEBPA* (double)	MRD-negative
inv(16)/t(16;16)	Mutated *NPM1* (without	
t(15;17)	*FLT3*–ITD mutation)	
Adverse prognostic factors		
inv(3)/t(3;3)	Enhanced *Evi-1* expression	Increased age
t(9;22)	*MLL* rearrangements	Elevated WBC count
t(9;11)	*FLT3*–ITD mutation	Extramedullary disease
t(6;9)	*DNMT3A* mutation	No early complete remission
–5 or del(5q)	*BAALC* expression	Persistent MRD
–7	*ERG* expression	$CD34^+$ blasts
abn(17p)	*MN1* expression	Treatment-related AML
Complex karyotype	*WT1* polymorphism	
Monosomal karyotype	*BCR–ABL*-positive	

Abbreviations: AML, acute myeloid leukaemia; *BAALC*, gene encoding brain and acute leukaemia cytoplasmic protein; *CEBPA*, gene encoding CCAAT/enhancer binding protein; *DNMT3A*, gene encoding DNA (cytosine-5)-methyltransferase 3A; *ERG*, gene encoding transcriptional regulator ERG; Evi-1, MDS1 and EVI1 complex locus protein EVI1 (also known as ecotropic viral integration site 1); *FLT3* fms-like tyrosine kinase receptor-3; ITD, internal tandem duplication; *MLL*, gene encoding histone-lysine *N*-methyltransferase MLL; MRD, minimal residual disease; *MN1*, gene encoding probable tumour suppressor protein MN1; *NPM1*, gene encoding nucleophosmin; WBC, white blood cell; *WT1*, gene encoding Wilms tumour protein.

Cornelissen et al., Nat. Rev. Clin. Oncol. 2012

Stem Cell Transplantation in Acute Myeloid Leukemia

Update on SCT approaches – SCT-prognostic markers

Table 2 | Prognostic factors for allogeneic-HSCT-related nonrelapse mortality

Pretransplantation	Peritransplantation	Post-transplantation
Favourable prognostic factors		
Sibling donor (HLA-matched) Shorter time from diagnosis to transplant* White ethnicity	Nonmyeloablative conditioning Stem-cell source (bone marrow or peripheral blood) T-cell depletion of the graft	Early immune recovery
Adverse prognostic factors		
Increased recipient age* Recipient and donor sex* Comorbidities (assessed using HCT–CI) Cytomegalovirus serostatus Cytokine polymorphism Unrelated donor HLA-mismatched Performance score Refractory leukaemia Therapy-related AML	Myeloablative conditioning regimen Alternative stem-cell source (umbilical cord blood)	Severe acute grade III–IV GVHD Persistent chronic extensive GVHD

*Incorporated into the EBMT risk score. Abbreviations: AML, acute myeloid leukaemia; EBMT, European Group for Blood and Marrow Transplantation; GVHD, graft-versus-host disease; HCT–CI, haematopoietic cell transplantation comorbidity index; HLA, human leukocyte antigen; HSCT, haematopoietic stem cell transplantation.

Cornelissen et al., Nat. Rev. Clin. Oncol. 2012

Stem Cell Transplantation in Acute Myeloid Leukemia

Update on SCT approaches – comorbidity score

Table 3 | Nonrelapse mortality (%) at 2 years after allogeneic HSCT*

Study	HCT–CI score			
	0	1–2	≥3	>5
Sorror *et al.*[69] Training set: *n* = 708	9	14–27	41–43	Not reported
Sorror *et al.*[69] Validation set: *n* = 346	14	19–22	40–41	Not reported
Sorror *et al.*[70] *n* = 244‡	7	19–21	27–37	Not reported
Barba *et al.*[78] *n* = 194	15	9–36	24–39	28–56

*The studies included recipients of both matched sibling or matched unrelated donor grafts following either myeloablative or nonmyeloablative conditioning. ‡177 patients from The Fred Hutchinson Cancer Research Center, Seattle, WA, USA and 67 patients from MD Anderson Cancer Center, Houston, TX, USA. Abbreviations: HCT–CI, haematopoietic cell transplantation comorbidity index; HSCT, haematopoietic stem cell transplantation.

Cornelissen et al., Nat. Rev. Clin. Oncol. 2012

Stem Cell Transplantation in Acute Myeloid Leukemia

Update on SCT approaches – recommendations

Table 4 | Recommendations for allogeneic HSCT in patients with AML in their first complete remission based on integrated-risk profiles*

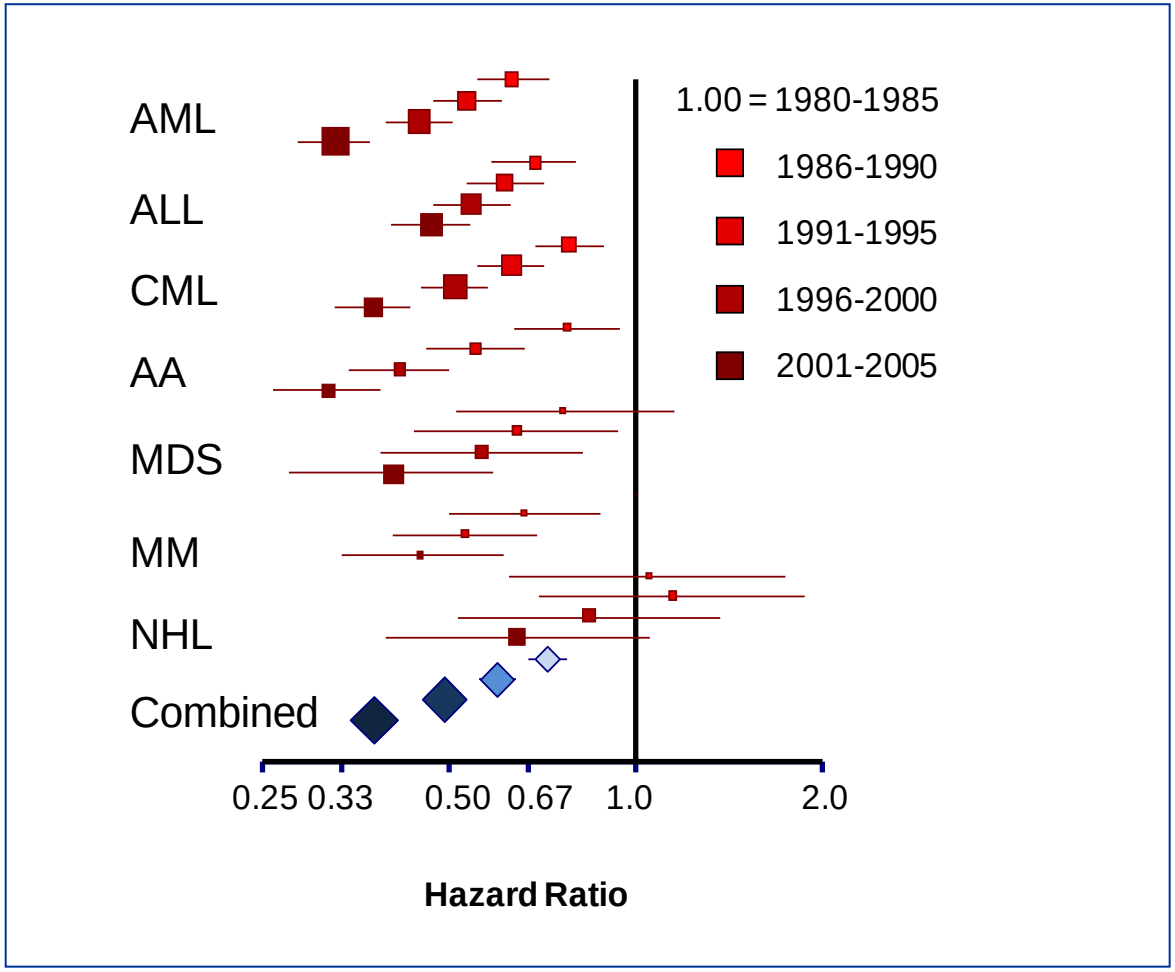
AML risk group‡	AML risk assessment§	Risk of relapse following consolidation approach		Prognostic scores for nonrelapse mortality that would indicate allogeneic HSCT as preferred consolidation		
		Chemotherapy or autologous HSCT (%)	Allogeneic HSCT (%)	EBMT score	HCT–CI score	Nonrelapse mortality risk (%)
Good	t(8;21) with WBC ≤20 Inv(16)/t(16;16) Mutated *CEBPA* (double allelic) Mutated NPM1 (No *FLT3*–ITD mutation) Early first complete remission and no MRD	35–40	15–20	NA (≤1)	NA (<1)	10–15
Intermediate	T(8;21) with WBC >20 Cytogenetically normal (or with loss of X and Y chromosomes), WBC count ≤100 and early first complete remission (after first cycle of chemotherapy)	50–55	20–25	≤2	≤2	<20–25
Poor	Otherwise good or intermediate, but no complete remission after first cycle of chemotherapy Cytogenetically normal and WBC >100 Cytogenetically abnormal	70–80	30–40	≤3–4	≤3–4	<30
Very poor	Monosomal karyotype Abn3q26 Enhanced Evi-1 expression	>90	40–50	≤5	≤5	<40

*The proposed patient-specific application of allogeneic HSCT in patients with AML in their first complete remission integrates the individual risks for relapse and nonrelapse mortality and aims for a DFS benefit of at least 10% for the individual patient compared with consolidation by a nonallogeneic HSCT approach. ‡The categorization of AML is based on cytogenetic, molecular and clinical parameters (including WBC) into good, intermediate and (very) poor subcategories and is subject to continuing study and debate. Here, categories are arbitrarily presented according to the latest policy of the Dutch–Belgian Cooperative Trial Group for Hematology Oncology and Swiss Group for Clinical Cancer Research (HOVON–SAKK) consortium.[144] Relapse percentages were derived from published reports.[5,15,20,38,40,50] §Includes response to first induction. Categorization requires one of the parameters indicated. Abbreviations: AML, acute myeloid leukaemia; EBMT, European Group For Blood and Marrow Transplantation; DFS, disease-free survival; Evi-1, Ecotropic viral integration site 1, HCT–CI, haematopoietic cell transplantation comorbidity index; HSCT, haematopoietic stem cell transplantation; *CEBPA*, gene encoding CCAAT enhancer-binding protein α; *FLT3*, gene encoding fms-like tyrosine kinase receptor-3; ITD, internal tandem duplication; NA, not advocated; *NMP1*, gene encoding nuclear matrix protein; MRD, minimal residual disease; WBC, white blood cell count.

Cornelissen et al., Nat. Rev. Clin. Oncol. 2012

Stem Cell Transplantation in Acute Myeloid Leukemia

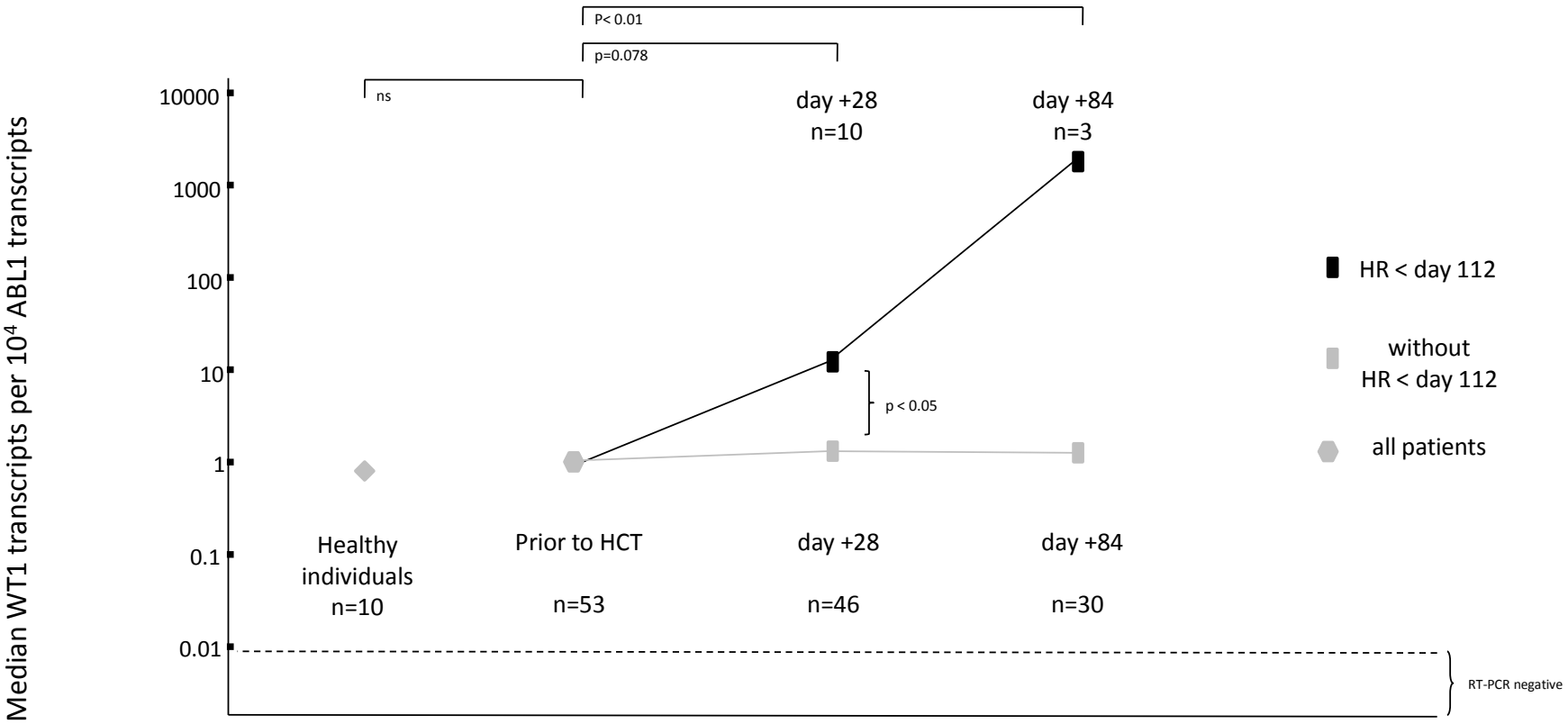
Update on SCT approaches – improving over time



Gratwohl et al, Cancer, 2009

Stem Cell Transplantation in Acute Myeloid Leukemia

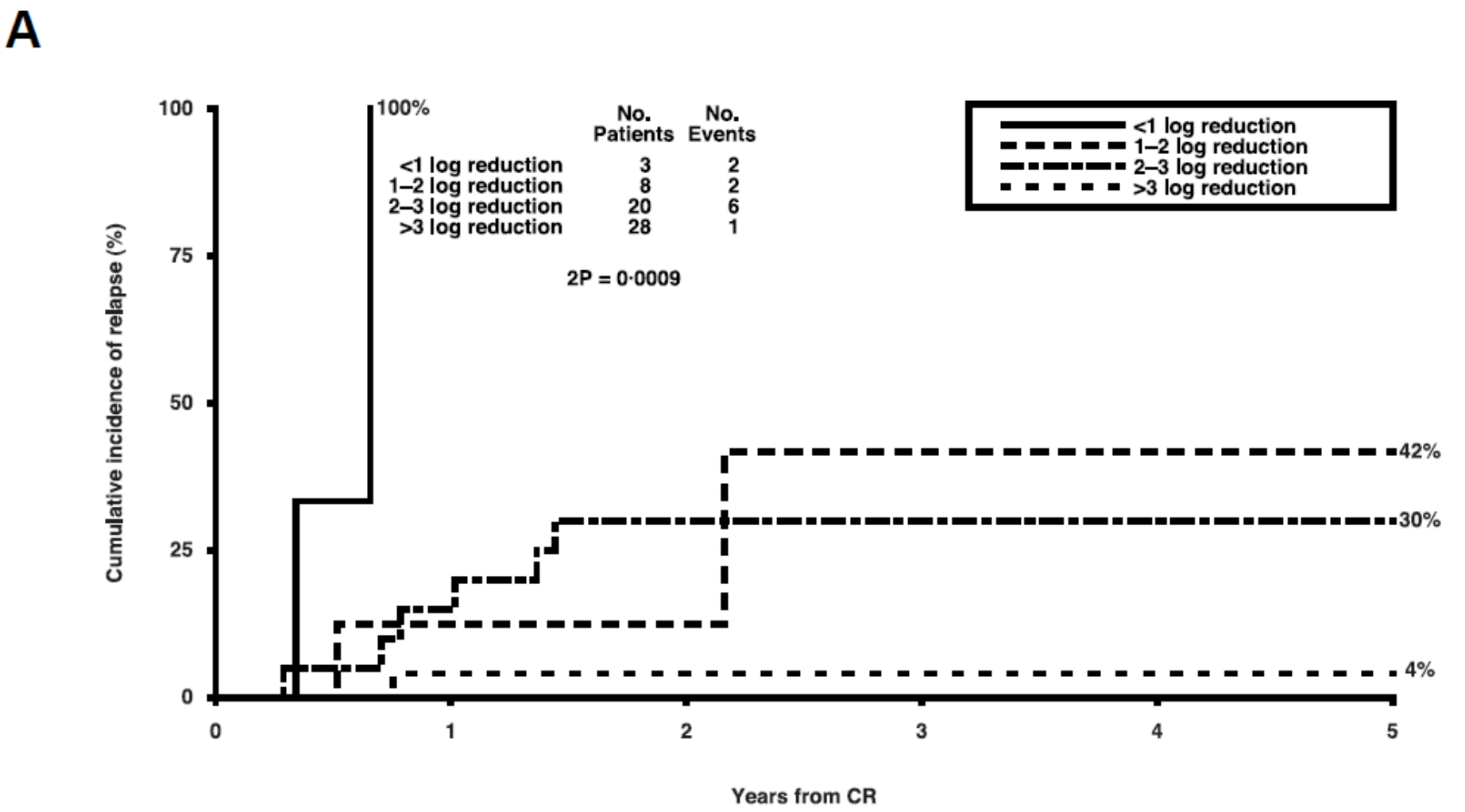
WT1 transcript level to predict relapse



Lange et al, Leukemia 2011

Stem Cell Transplantation in Acute Myeloid Leukemia

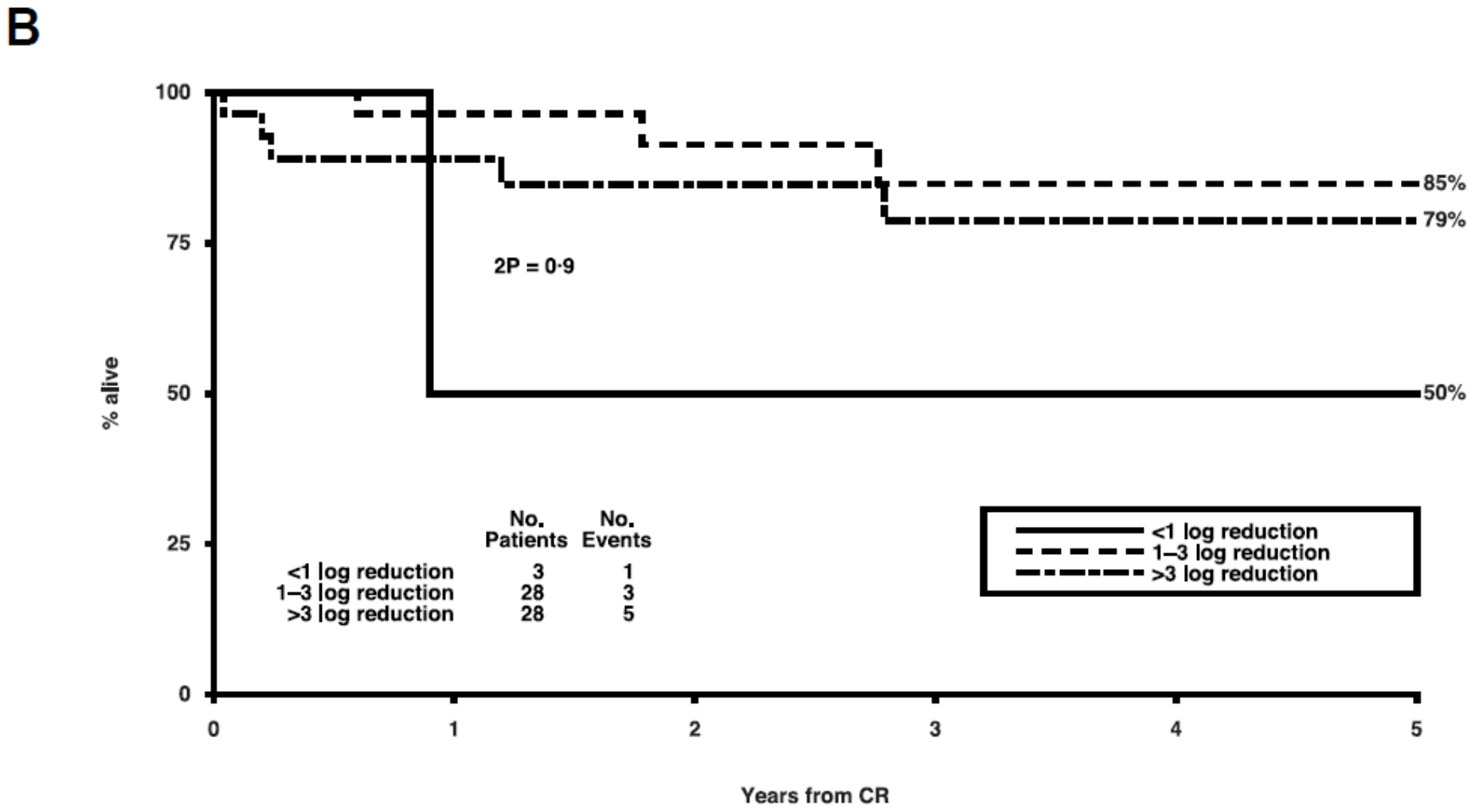
Molecular monitoring t(8;21) and relapse



Liu Yin, Blood 2012

Stem Cell Transplantation in Acute Myeloid Leukemia

Molecular monitoring t(8;21) and survival



Liu Yin, Blood 2012

Stem Cell Transplantation in Acute Myeloid Leukemia

Update on SCT approaches – non-relapse mortality

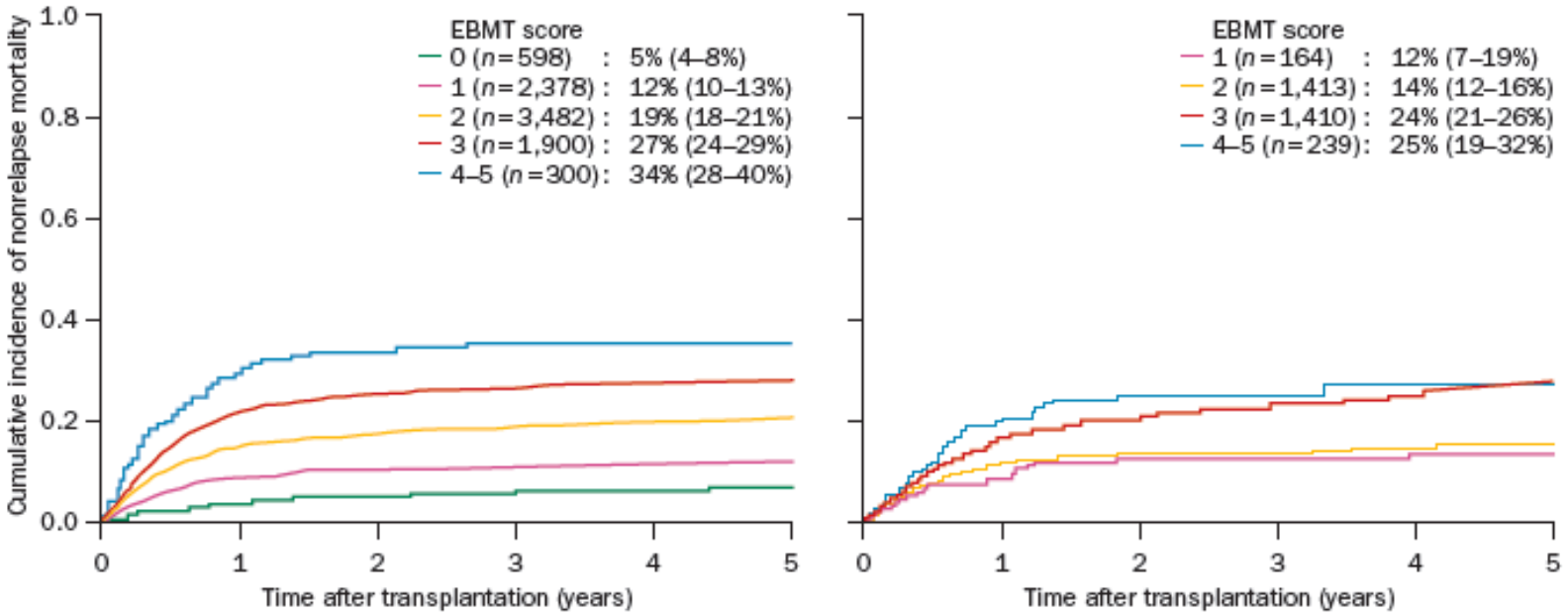


Figure 2 | Cumulative incidence of nonrelapse mortality, with relapse as a competing risk, in patients with AML in their first complete remission. Data for patients in Europe (2000–2010) were generated by the EBMT Acute Leukemia Working Party using the EBMT risk score, which includes the following parameters: patient age, donor type, time interval from diagnosis to transplantation and donor–recipient gender combination.[45] **a** | Patients who received myeloablative conditioning prior to allogenic HSCT. **b** | Patients who received RIC prior to allogeneic HSCT. Patients receiving RIC allogeneic HSCT were significantly older than patients receiving myeloablative allogeneic HSCT (median age 38 years [range 35–77] versus 56 years [range 54–77]; $P<0.0001$). Abbreviations: AML, acute myeloid leukaemia; EBMT, European Group for Blood and Marrow Transplantation; HSCT, haematopoietic stem cell transplantation; RIC, reduced-intensity conditioning.

Cornelissen et al., Nat. Rev. Clin. Oncol. 2012

Stem Cell Transplantation in Acute Myeloid Leukemia

do we need two consolidations?

1 consolidation prior to HCT

n = 77

2 consolidation prior to HCT

n = 78

Stem Cell Transplantation in Acute Myeloid Leukemia

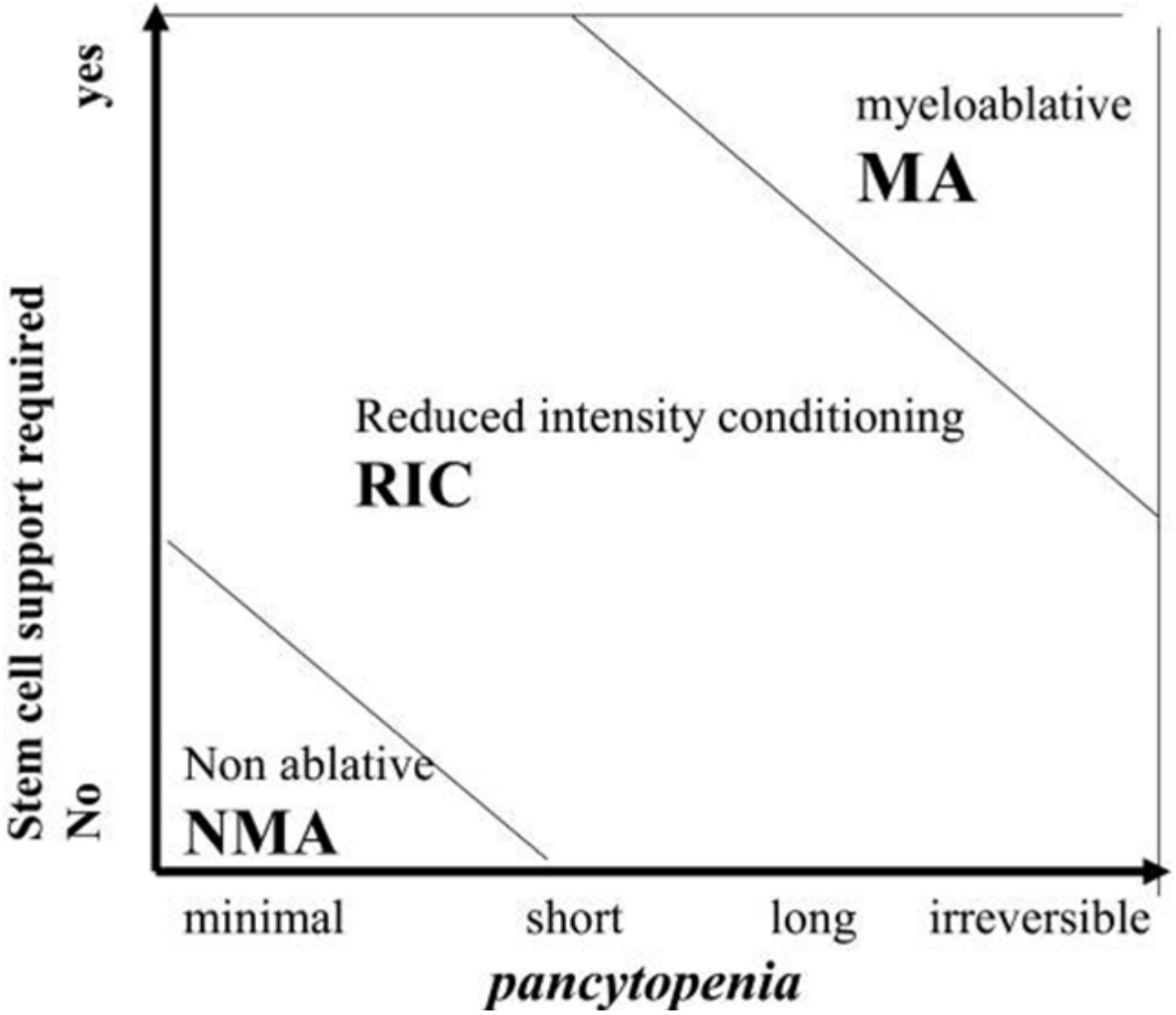
definition of conditioning

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

Bacigalupo et al, BBMT 2009

Stem Cell Transplantation in Acute Myeloid Leukemia

definition of conditioning

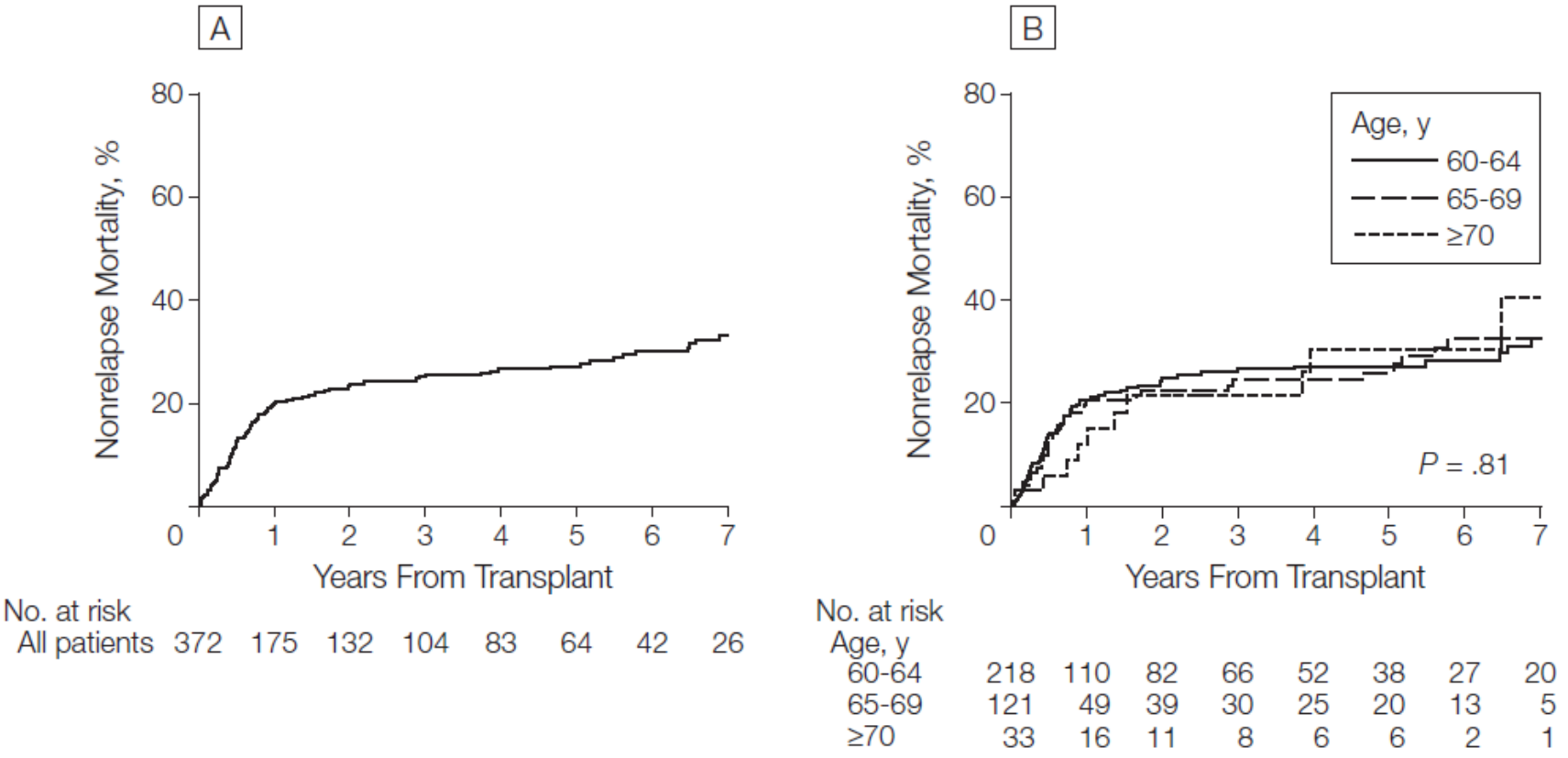


Bacigalupo et al, BBMT 2009

Stem Cell Transplantation in Acute Myeloid Leukemia

Update on SCT approaches – role of age

Figure 1. Nonrelapse Mortality in All Patients and in Those 60 Through 64 Years, 65 Through 69 Years, and 70 Years or Older



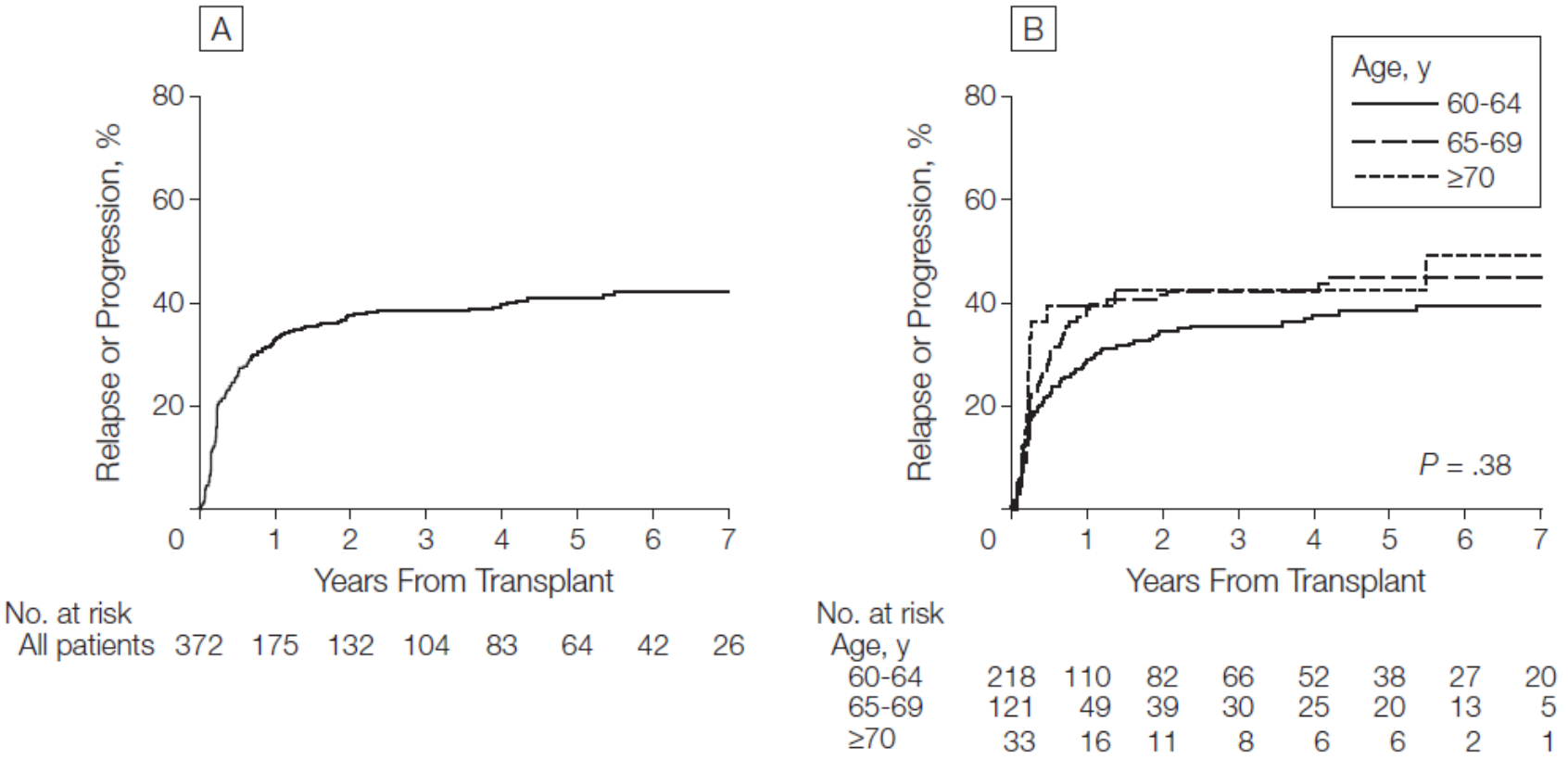
A, Cumulative incidence of nonrelapse mortality of 27% at 5 years among 372 patients 60 years or older treated with nonmyeloablative conditioning and hematopoietic cell transplantation. B, No statistically significant difference ($P=.81$, likelihood ratio statistics from Cox regression model) detected in cumulative incidences of nonrelapse mortality among patients 60 through 64, 65 through 69, and 70 years or older.

Sorror et al. *JAMA. 2011*

Stem Cell Transplantation in Acute Myeloid Leukemia

Update on SCT approaches – role of age

Figure 2. Disease Progression or Relapse in All Patients and in Those 60 Through 64 Years, 65 Through 69 Years, and 70 Years or Older

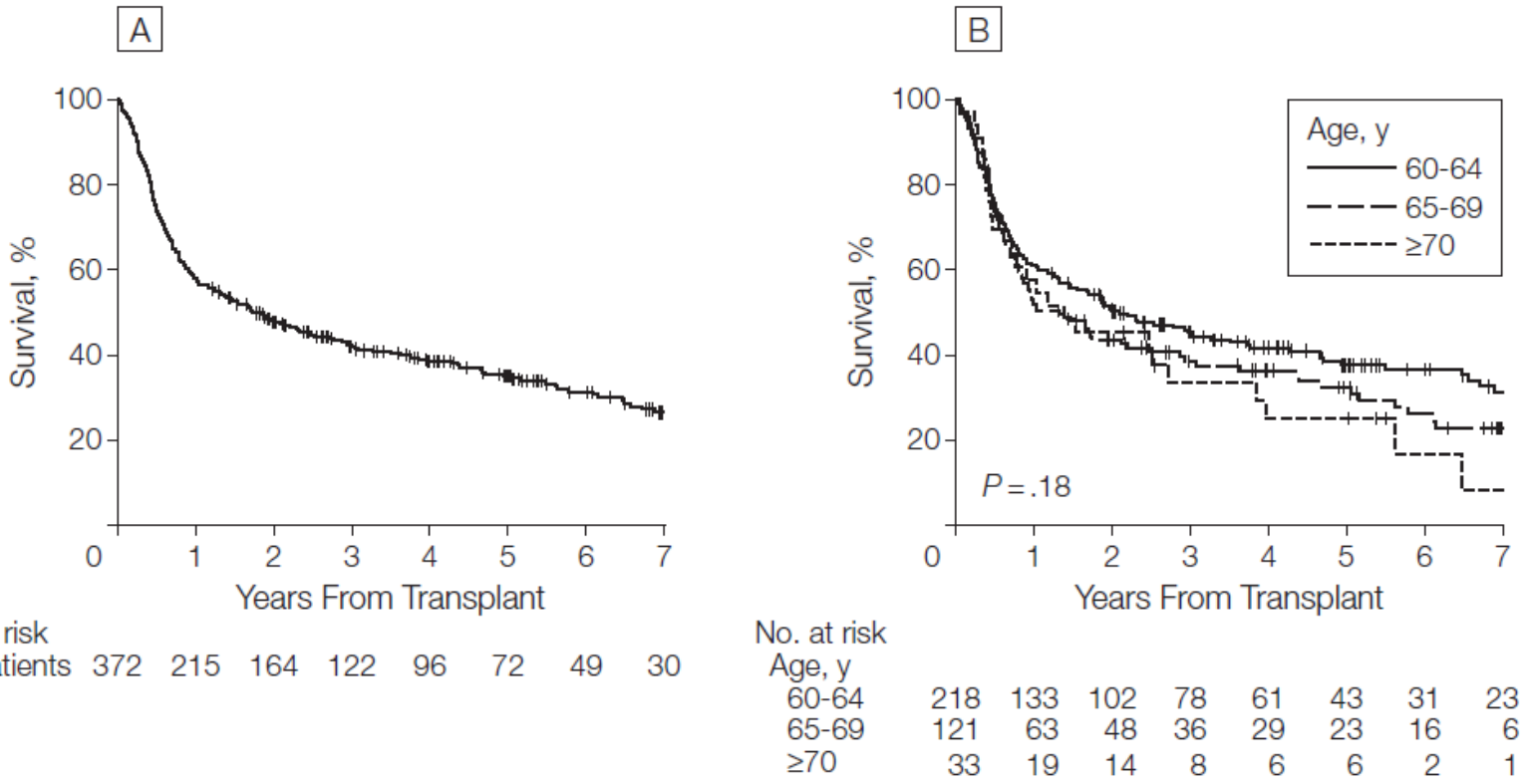


A, Rate of disease progression or relapse of 41% at 5 years among 372 patients aged 60 years or older, who were treated with nonmyeloablative conditioning and hematopoietic cell transplantation. B, No statistically significant difference ($P = .38$, likelihood ratio statistics from Cox regression model) detected in rates of disease progression or relapse among patients 60 through 64, 65 through 69, and 70 years or older. Sorror et al. *JAMA. 2011*

Stem Cell Transplantation in Acute Myeloid Leukemia

Update on SCT approaches – role of age

Figure 3. Overall Survival in All Patients and in Those 60 Through 64 Years, 65 Through 69 Years, and 70 Years or Older

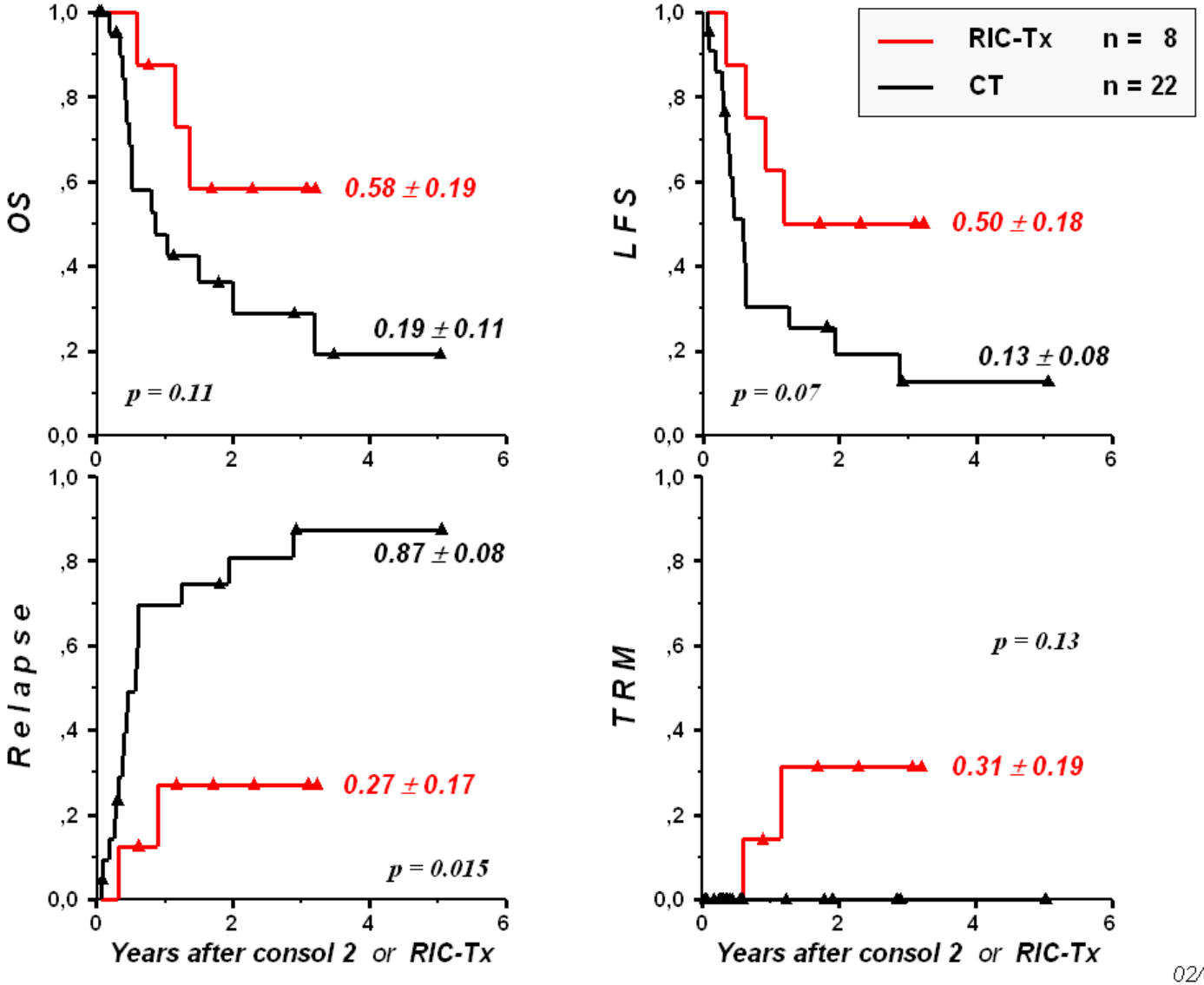


Vertical lines indicate censored events. A, Kaplan-Meier estimate of overall survival of 35% at 5 years among 372 patients aged 60 years or older, who were treated with nonmyeloablative conditioning and hematopoietic cell transplantation. B, No statistically significant difference ($P = .18$, likelihood ratio statistics from Cox regression model) detected in rates of overall survival among patients 60 through 64, 65 through 69, and 70 years or older.

Sorror et al. *JAMA. 2011*

RIC: influence on patient treatment and clinical outcome

OSHO – HOVON study / high risk cytogenetics



02/06

Stem Cell Transplantation in Acute Myeloid Leukemia

Update on SCT approaches – role of age

Z K R D - Zentrales Knochenmarkspender-Register Deutschland
Helmholtzstrasse 10, POB 4244, D-89032 Ulm, Germany
Telefon: (49)731-1507-200, Telefax: (49)731-1507-500

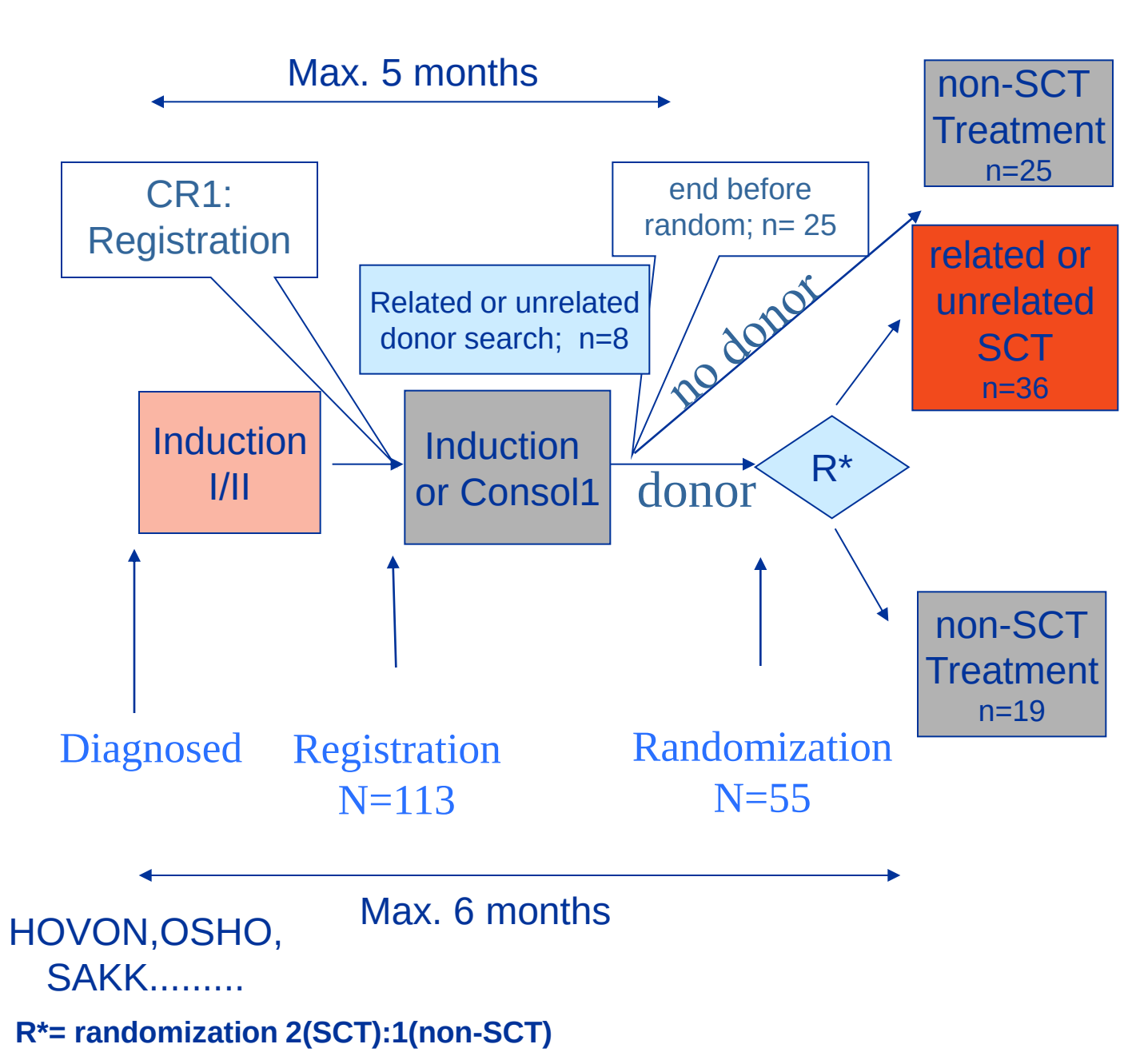
Anzahl der deutschen Blutstammzellspender pro Spenderdatei

Datei	gesamt	nur AB-typ.	AB/DR-typ.	AB/HR-typ.
AKB	245139	90973	154166	65976
BBB	38314	23839	14475	1292
COL	16415	4580	11835	747
DKM	2859122	392802	2466320	1792107
DUS	159555	37426	122129	53532
FFM	102543	2849	99694	54559
FRB	62845	31031	31814	11542
GIS	5352	358	4994	506
GOE	26740	14052	12688	1675
GRW	7940	2310	5630	473
HAN	246338	94470	151868	53685
HHU	26298	11213	15085	13392
HLL	3555	1547	2008	129
Gesamt	4798954	965353	3833601	2439032

Stand 2013-01-01

Sorror et al. *JAMA. 2011*

EBMT study in AML > 60 yrs



If relapse

Induction

Related or unrelated SCT.

RIC: influence on patient treatment and clinical outcome

Age distribution ALL

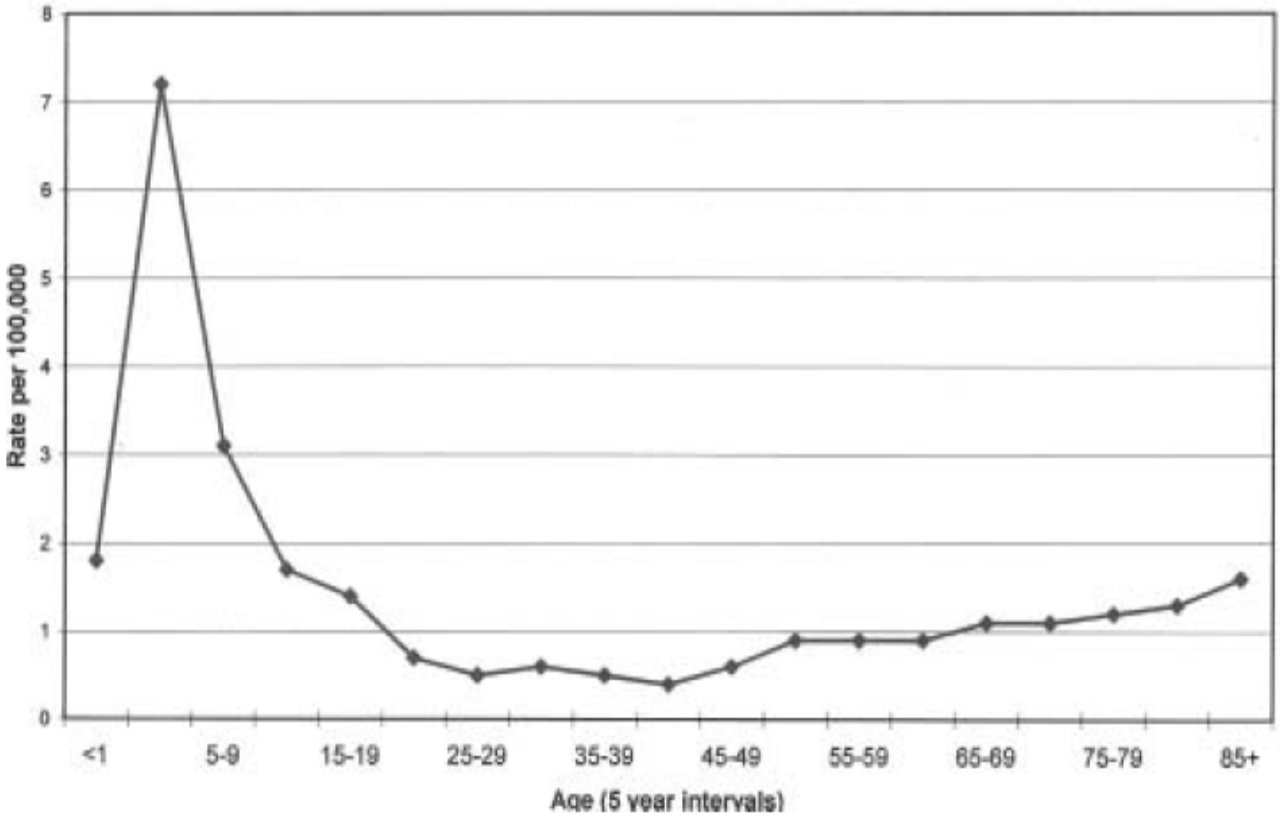
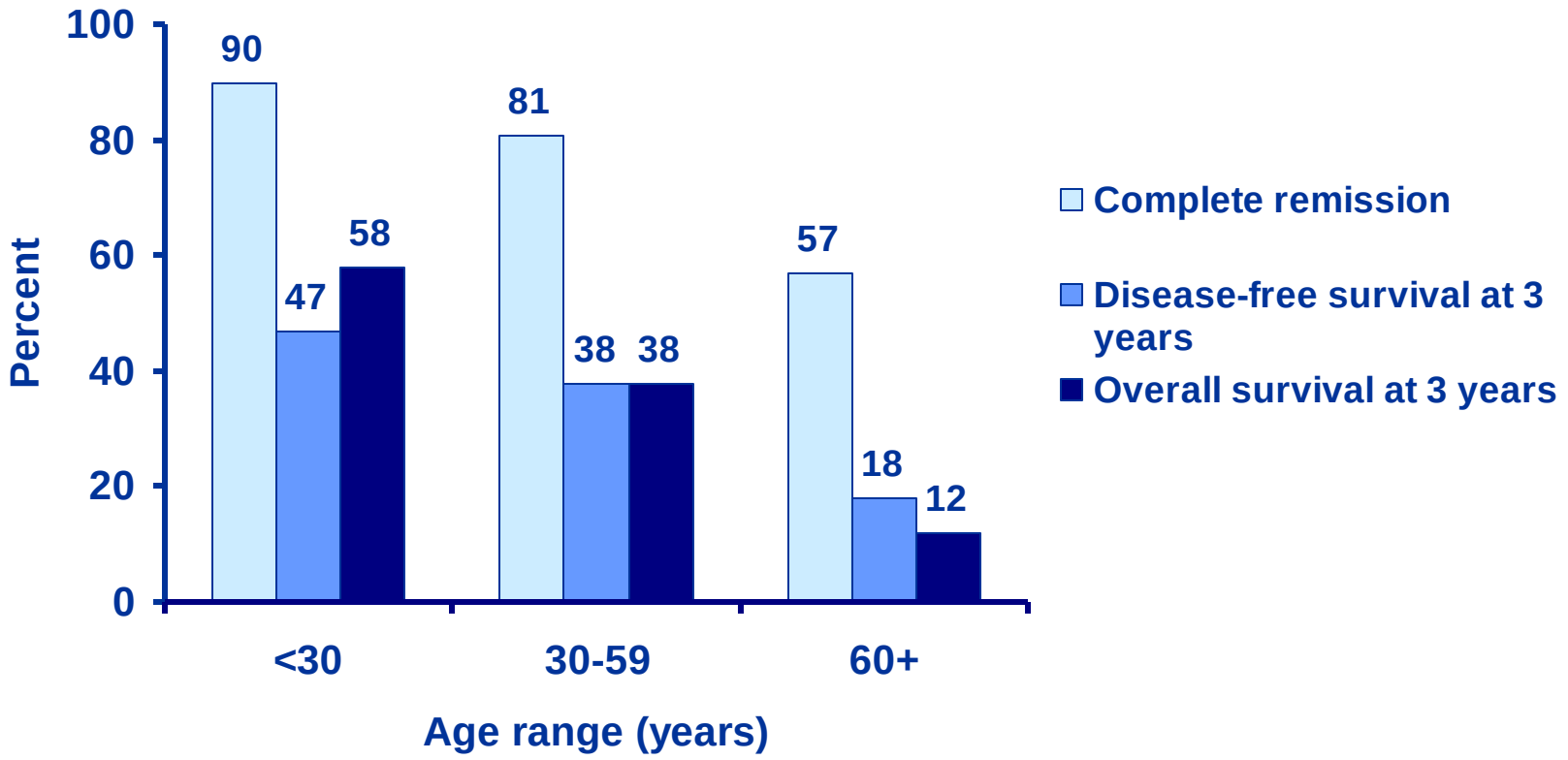


Figure 1. Age-specific annual incidence of acute lymphoblastic leukemia (US-SEER data, 1998–2002).

RIC: influence on patient treatment and clinical outcome

Outcome after chemotherapy (CALGB)



Treatment outcome by age cohort (CALGB studies with 759 ALL patients, 1988–2002)

Larson RA. Hematology Am Soc Hematol Educ Program 2005:131–6.

RIC: influence on patient treatment and clinical outcome

Seattle consortium

Non-myeloablative conditioning with allogeneic hematopoietic cell transplantation for the treatment of high-risk acute lymphoblastic leukemia

Ron Ram,[1] Rainer Storb,[1,2] Brenda M. Sandmaier,[1,2] David G. Maloney,[1,2] Ann Woolfrey,[1,2] Mary E. D. Flowers,[1,2] Michael B. Maris,[3] Ginna G. Laport,[4] Thomas R. Chauncey,[2,5] Thoralf Lange,[6] Amelia A. Langston,[7] Barry Storer,[1,2] and George E. Georges[1,2]

[1]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [2]University of Washington School of Medicine, Seattle, WA, USA; [3]Rocky Mountain Cancer Center, Denver, CO, USA; [4]Stanford University, Stanford, CA, USA; [5]Veterans Affairs Puget Sound Health Care System, Seattle, WA, USA; [6]University of Leipzig, Leipzig, Germany, and [7]Emory University, Atlanta, GA, USA

Haematologica 2011;96(8):1113-1120.

RIC: influence on patient treatment and clinical outcome

Ram et al, Haematologica, 2011

Table 1. Characteristics of ALL patients, disease and transplantation.

Characteristics	Ph⁻ ALL (*n*=26)	Ph⁺ ALL (*n*=25)
Median age: years (range)	56 (8-65)	57 (38-69)
Disease status at time of HCT: *n*, (%)		
CR1 without MRD	12 (46%)	13 (52%)
CR1 with MRD	1 (4%)	6 (24%)
>CR1 (CR2/CR3)	13 (50%)	5 (20%)
Persistent disease	0	1 (4%)
Months from diagnosis to HCT: median, (range)		
CR1	7.7 (4-10.7)	7.6 (4.4-10.9)
Beyond CR1	30.6 (10.7-90.7)	38.7 (8.9-126.1)
History of myeloablative HCT (%)	4 (15%)	2 (8%)
HCT-CI[1] (%)		
0-1	9/17 (53%)	14/18 (78%)
≥2	8/17 (47%)	4/18 (22%)
Recipient gender (male/female)	11/15	16/9
Female donor to male recipient: (%)	5 (19%)	6 (24%)
Donor type: (%)		
HLA-identical sibling	4 (15%)	5 (20%)
Unrelated HLA matched	14 (54%)	17 (68%)
1 HLA allele mismatched	3 (12%)	3 (12%)
1 HLA antigen mismatched	5 (19%)	0
Cell dose × 10^6 CD34⁺ cells/kg: median, (range)	8.8 (2-20.2)	8.2 (0.9-24.4)
Cell source (marrow/PBSC)	0/26	1/25

ALL: acute lymphoblastic leukemia, CR1: first complete remission, HCT-CI: hematopoietic cell transplantation comorbidity index, MRD: minimal residual disease, PBSC: peripheral blood stem cells, Ph: Philadelphia chromosome. [1]Data were available for 17 Ph– ALL patients and for 18 Ph⁺ ALL patients.

RIC: influence on patient treatment and clinical outcome

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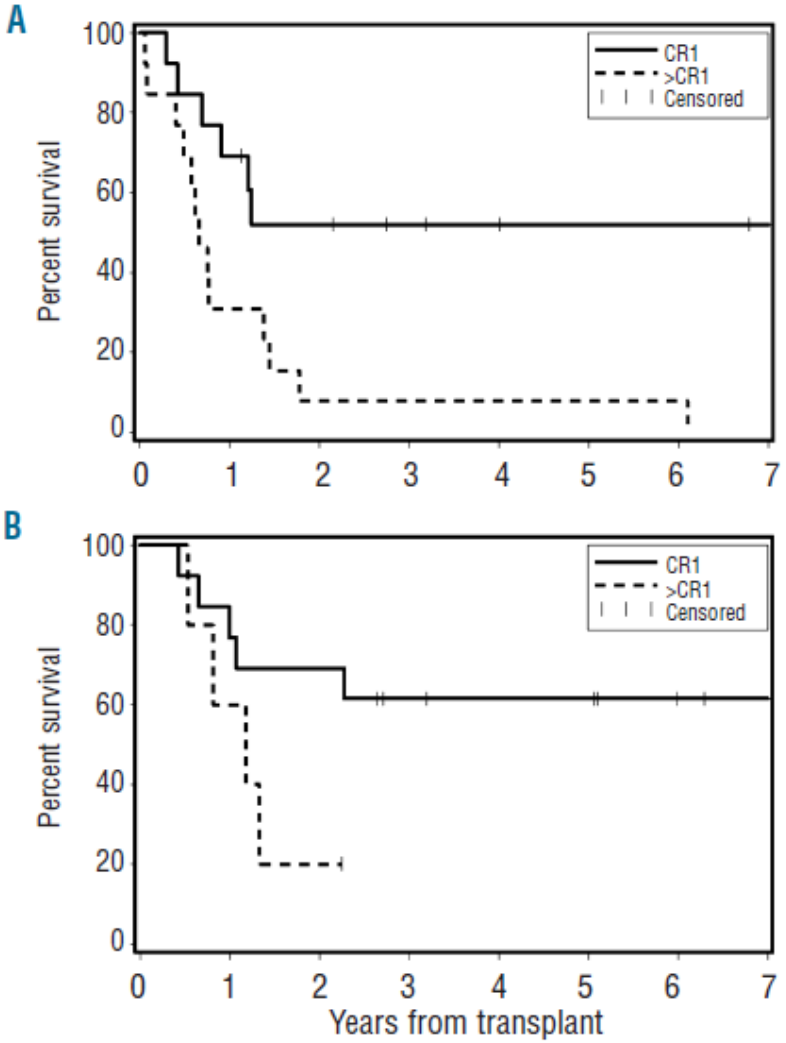

Figure 3. Overall survival for (A) Ph⁻ ALL, in first complete remission (CR1) (n=13) *versus* beyond CR1 (n=13) and (B) Ph⁺ ALL patients receiving imatinib after hematopoietic cell transplantation, CR1 (n=13) *versus* beyond CR1 (n=5).

RIC: influence on patient treatment and clinical outcome

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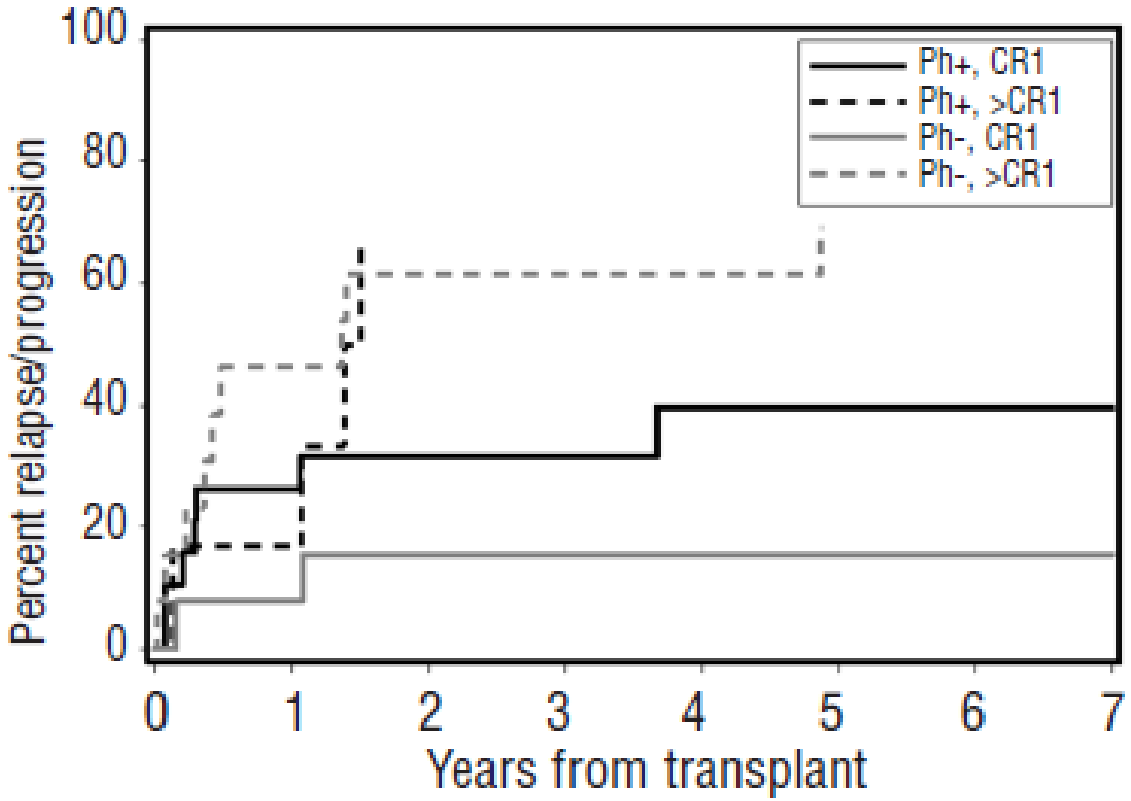

Figure 2. Cumulative relapse rate for Ph– ALL, in first complete remission (CR1) (n=13) *versus* beyond CR1 (n=13) and Ph⁺ ALL CR1 (n=19) *versus* beyond CR1 (n=6). Molecular disease relapse (PCR or flow cytometry positive) without morphological evidence of disease was included as relapse.

RIC: influence on patient treatment and clinical outcome

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Table 3. Prognostic factors for relapse and mortality using univariate analysis.

	Relapse HR (95% CI)	*P*	Mortality HR (95% CI)	*P*
Entire cohort (n=51)				
Beyond CR1	3.9 (1.6-9.5)	0.002	2.7 (1.4-5.3)	0.005
Matched URD (vs. sibling)	1.1 (0.3-3.9)	0.86	0.6 (0.2-1.3)	0.16
Acute GVHD[1]	0.5 (0.2-1.2)	0.11	0.9 (0.4-1.7)	0.69
Chronic GVHD[1]	0.7 (0.2-2.3)	0.53	1.0 (0.5-2.2)	0.98
Ph+ ALL (n=26)				
Beyond CR1	2.4 (0.7-8.6)	0.20	1.8 (0.6-5.4)	0.32
Additional cytogenetic abnormalities	3.4 (0.9-13)	0.06	2.0 (0.7-5.5)	0.19
Treatment with imatinib	0.4 (0.1-1.5)	0.20	0.3 (0.1-0.9)	0.03

ALL: acute lymphoblastic leukemia, CI: confidence interval, Beyond CR1: disease stage greater than first complete remission, GVHD: graft-versus-host disease, HR: hazard ratio, Ph: Philadelphia chromosome, URD: unrelated donor. [1]Analyzed as a time-dependent covariate.

Stem Cell Transplantation in Acute Myeloid Leukemia

Conclusions

leukemia most frequent indication for allogeneic SCT worldwide

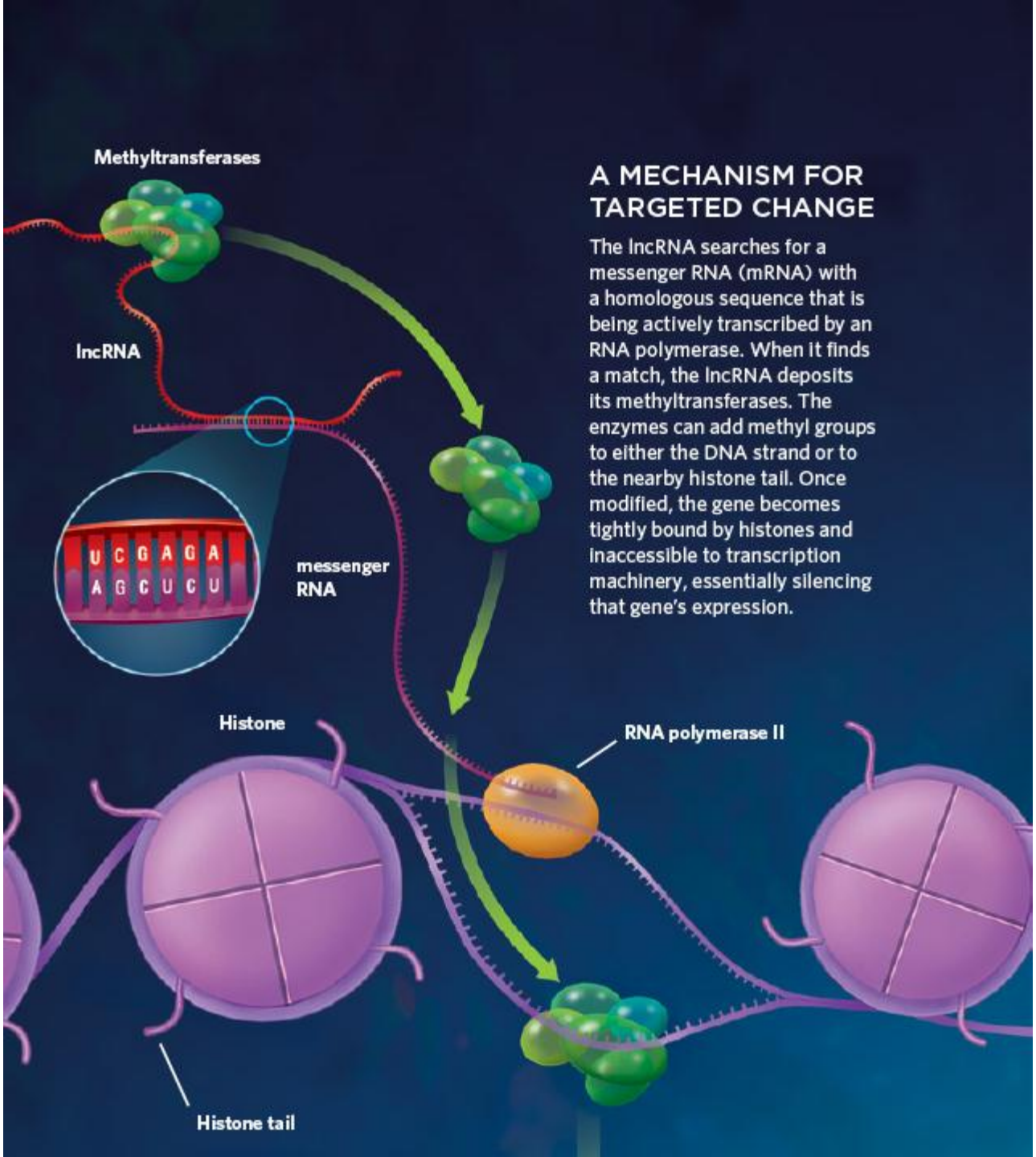
decreasing incidence of autologous SCT

no other option for patients with high risk cytogenetics

molecular marker increasingly important not only for prediction and monitoring but also for treatment indication

patient´s age is not a limiting factor any more

clinical studies needed to further improve outcome



A MECHANISM FOR TARGETED CHANGE

The lncRNA searches for a messenger RNA (mRNA) with a homologous sequence that is being actively transcribed by an RNA polymerase. When it finds a match, the lncRNA deposits its methyltransferases. The enzymes can add methyl groups to either the DNA strand or to the nearby histone tail. Once modified, the gene becomes tightly bound by histones and inaccessible to transcription machinery, essentially silencing that gene's expression.