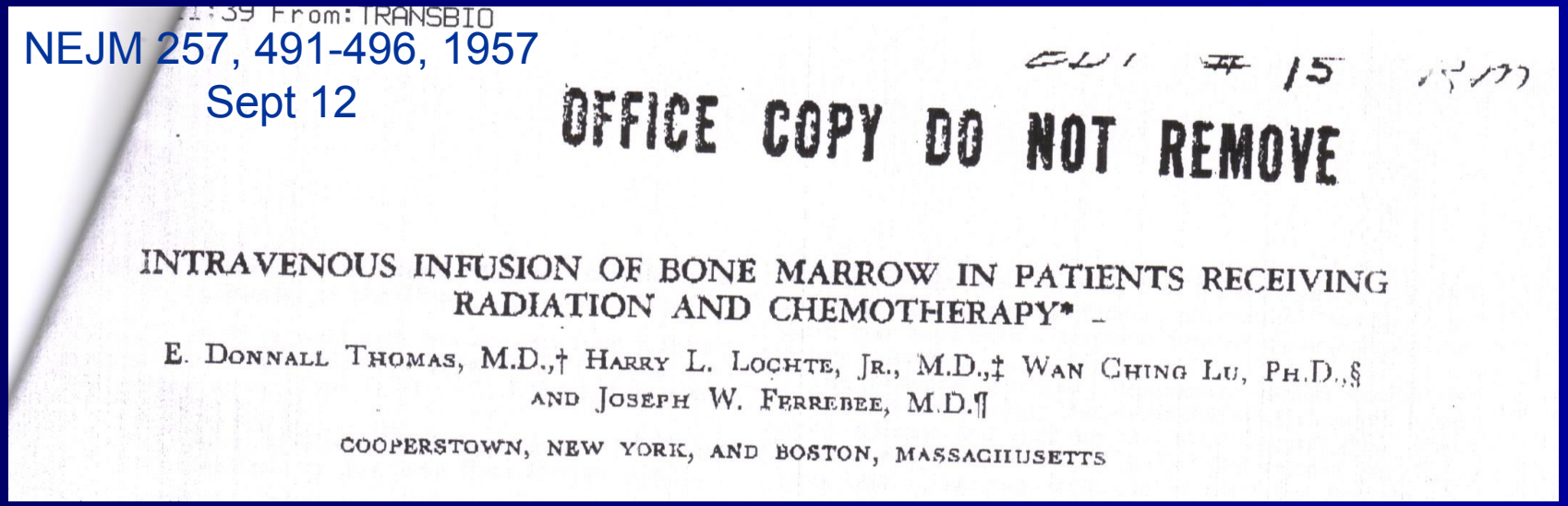
Stem Cell Transplantation: Past, Present and Future

Dietger Niederwieser
Leipzig, Germany

1957 - First stem cell transplants



1:39 From:TRANSBIO

NEJM 257, 491-496, 1957
Sept 12

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INTRAVENOUS INFUSION OF BONE MARROW IN PATIENTS RECEIVING RADIATION AND CHEMOTHERAPY*

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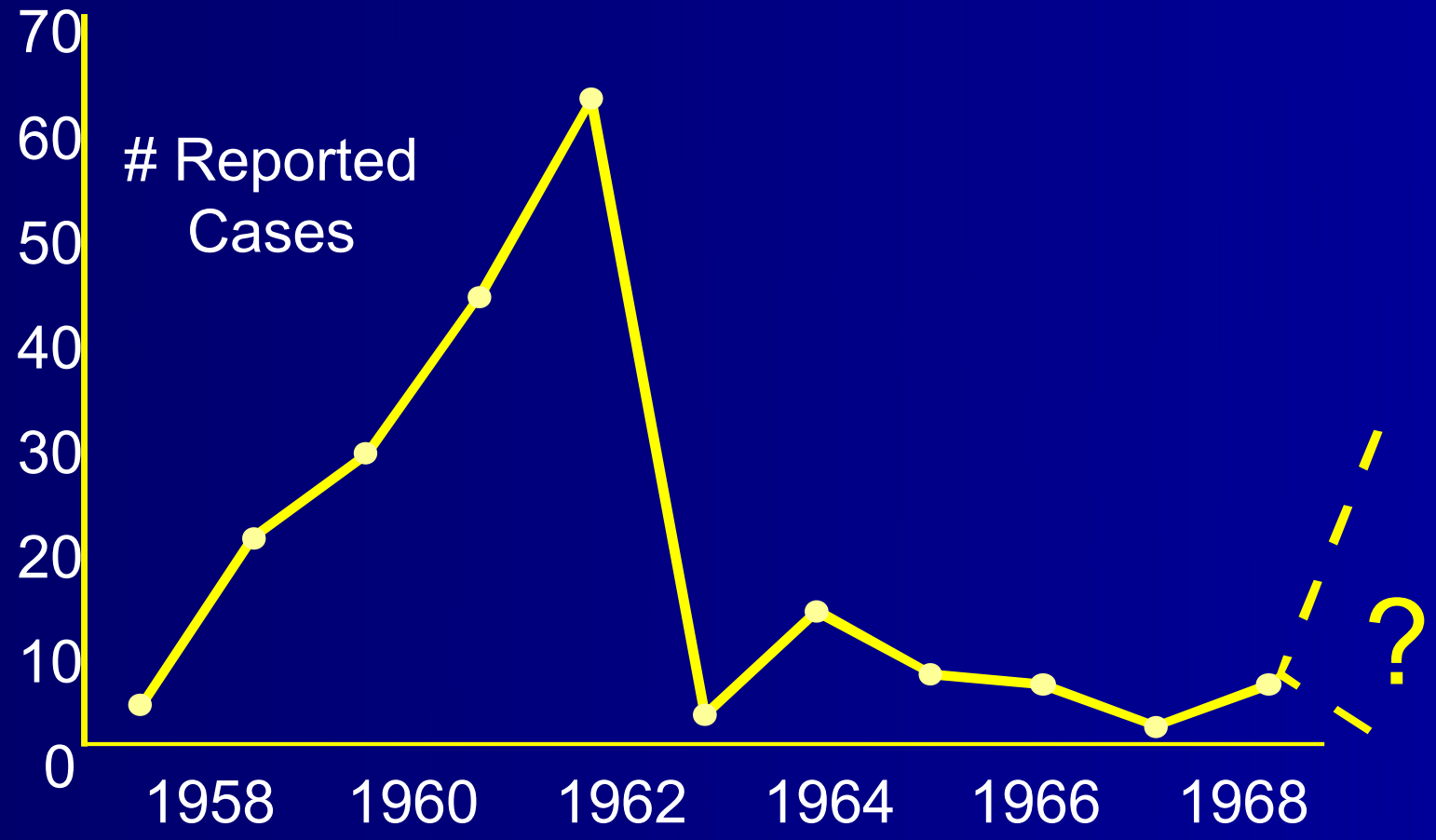
COOPERSTOWN, NEW YORK, AND BOSTON, MASSACHUSETTS

Human Marrow Grafts 1958-68

Diseases	# Patients			
	Total	Graft Failure	GVHD	Alive
Aplastic anemia	73	66	5	0
Hematologic malignancies	115	56	33	0
Immunodeficiencies	15	3	9	3
Total	203	125	47	3

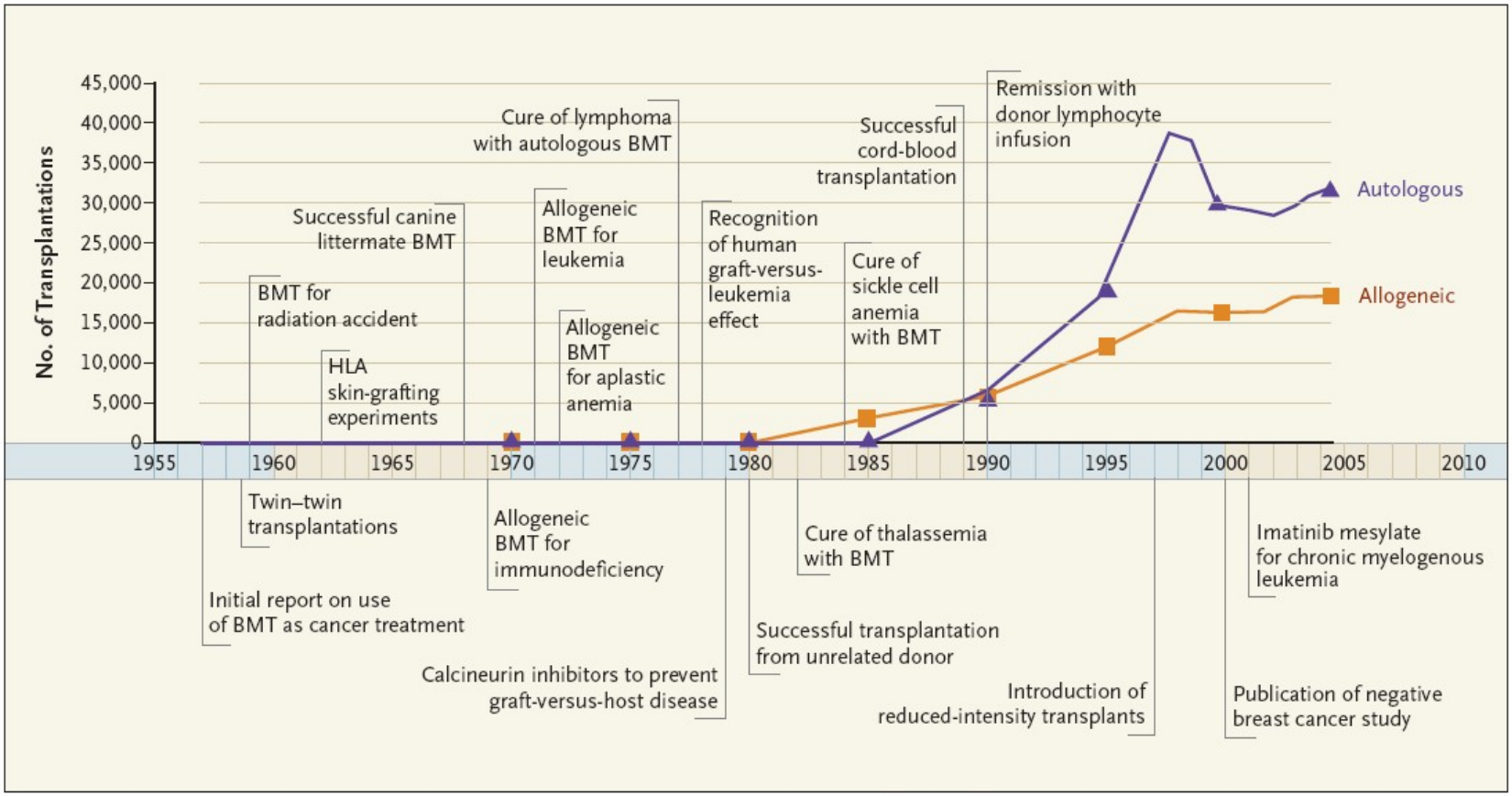
Bortin, *Transpl* 9: 571, 1970

Human Bone Marrow Transplants from 1958 to 1968 (n=203)



Bortin, *Transpl* 9: 571, 1970

History of hematopoietic cell transplantation



Timeline Showing Numbers of Bone Marrow Transplantations and Advances in the Field, 1957–2006.

Appelbaum et al. NEJM

Importance of organizations to support stem cell transplantation

- basic and clinical research
- education
- standardisation
- quality control
- accreditation of transplant procedures

Importance of registries

- **Survey (** 2007 survey **29,000** transplants**)**
- Registry
- Retrospective studies

EBMT Activity survey on HSCT in 2007: patient and transplant numbers

Indication	Allogeneic HSCT	Autologous HSCT	Total
1st transplants	10072	15491	25563
Retransplants	810	852	1662
Additional transplants	71	1873	1944
TOTAL	10953	18216	29169

Teams: 613

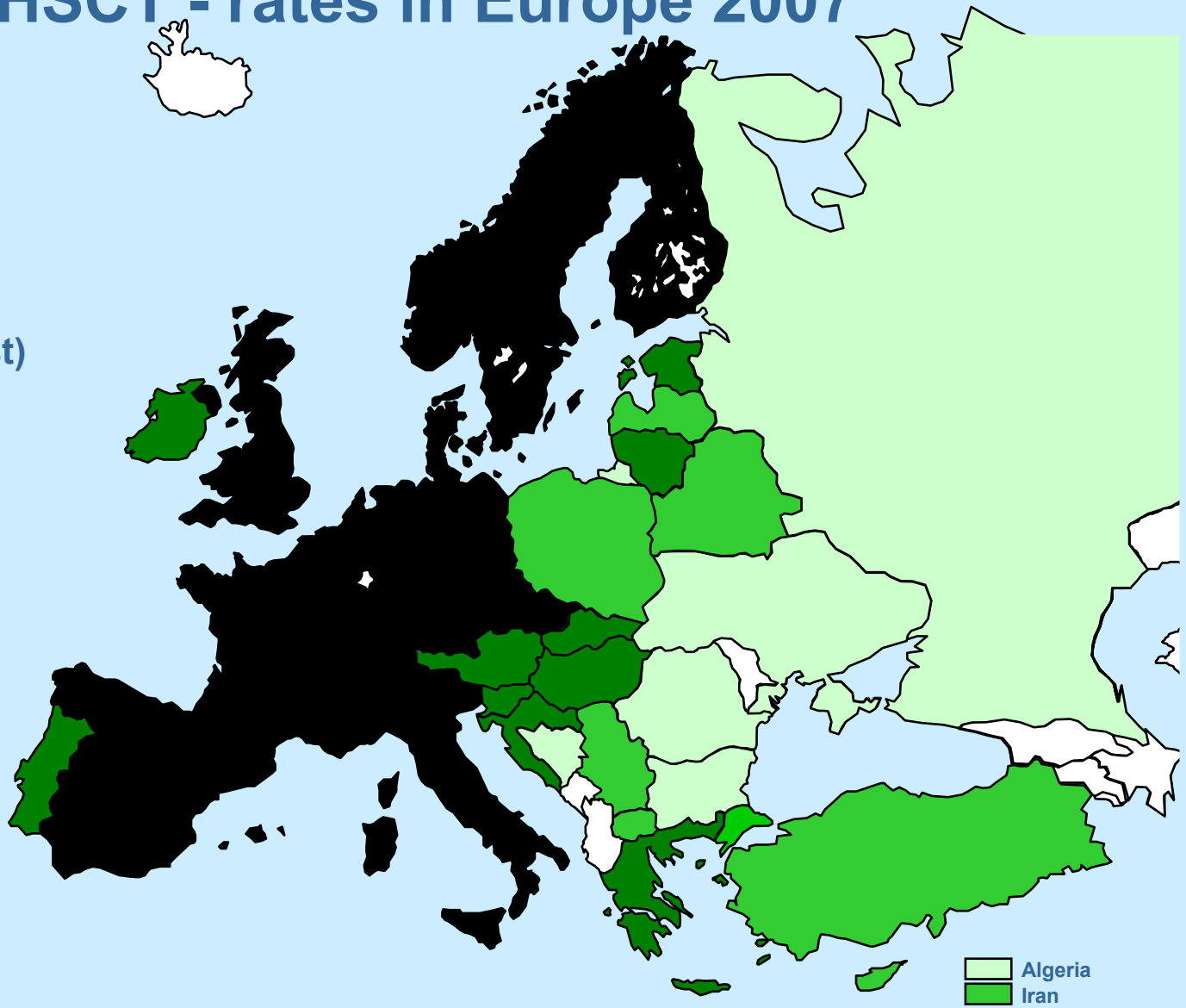
Final data

EBMT Activity survey on HSCT in 2007: donor type and source

	Source			
Donor	BM	PBSC	Cord	Total
Allogeneic total	2350	7137	585	10072
HLA-id	1231	3442	43	4716
HLA-nid	137	409	6	552
Twin	14	38	0	52
Unrelated	968	3248	536	4752
Autologous	256	15234	1	15491

Final data

HSCT - rates in Europe 2007

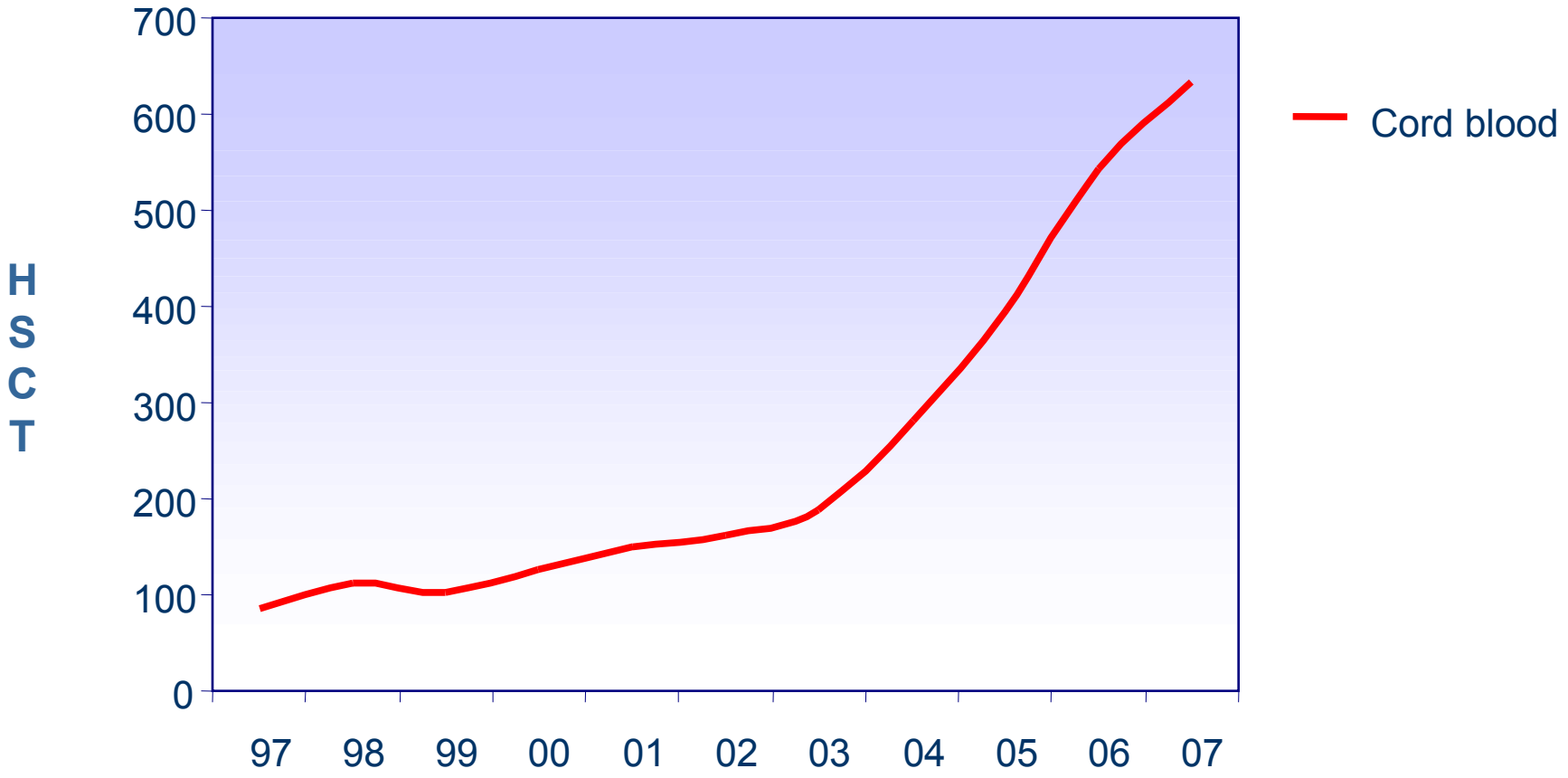


Excellence in science
EBMT
European Group for Blood and Marrow Transplantation

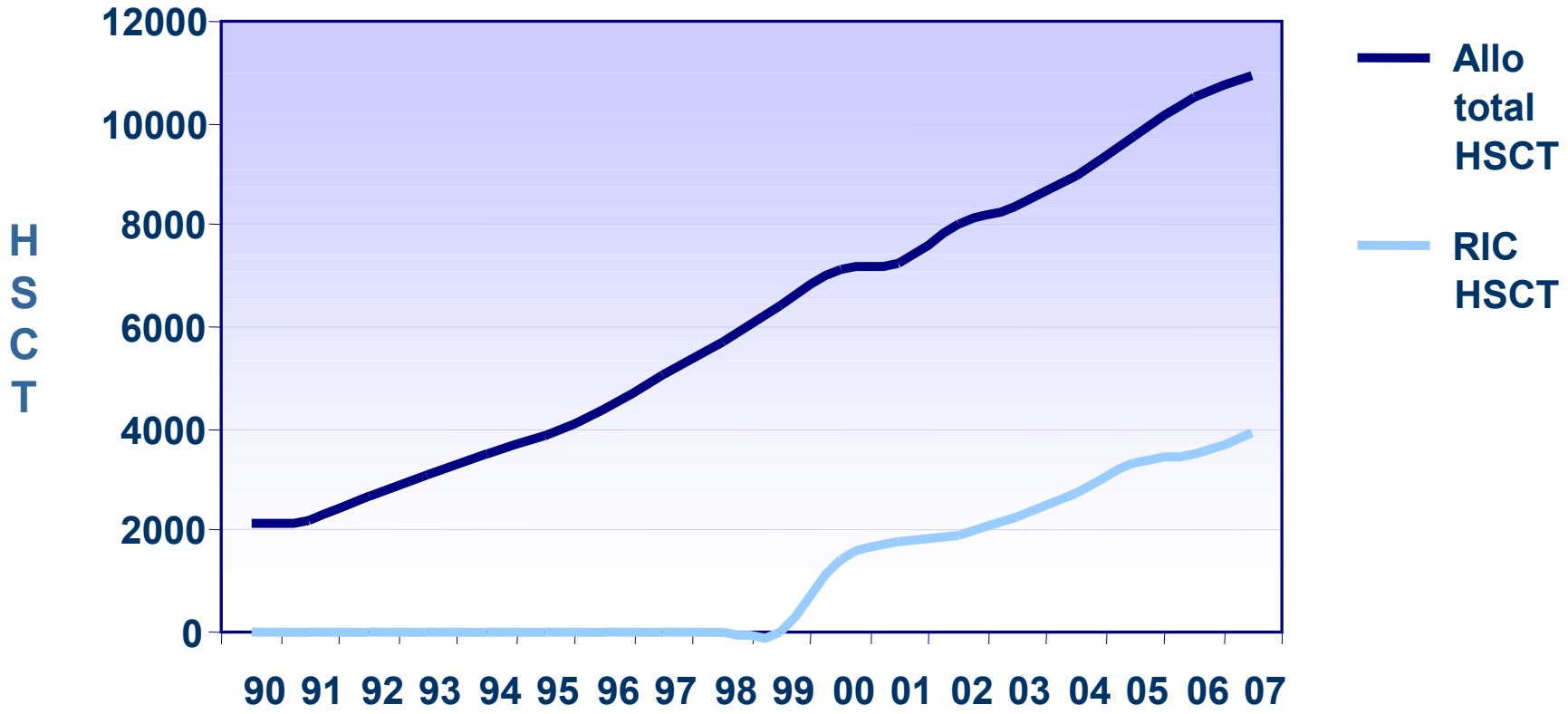
Final data

EBMT Activity Survey on HSCT 1990–2007

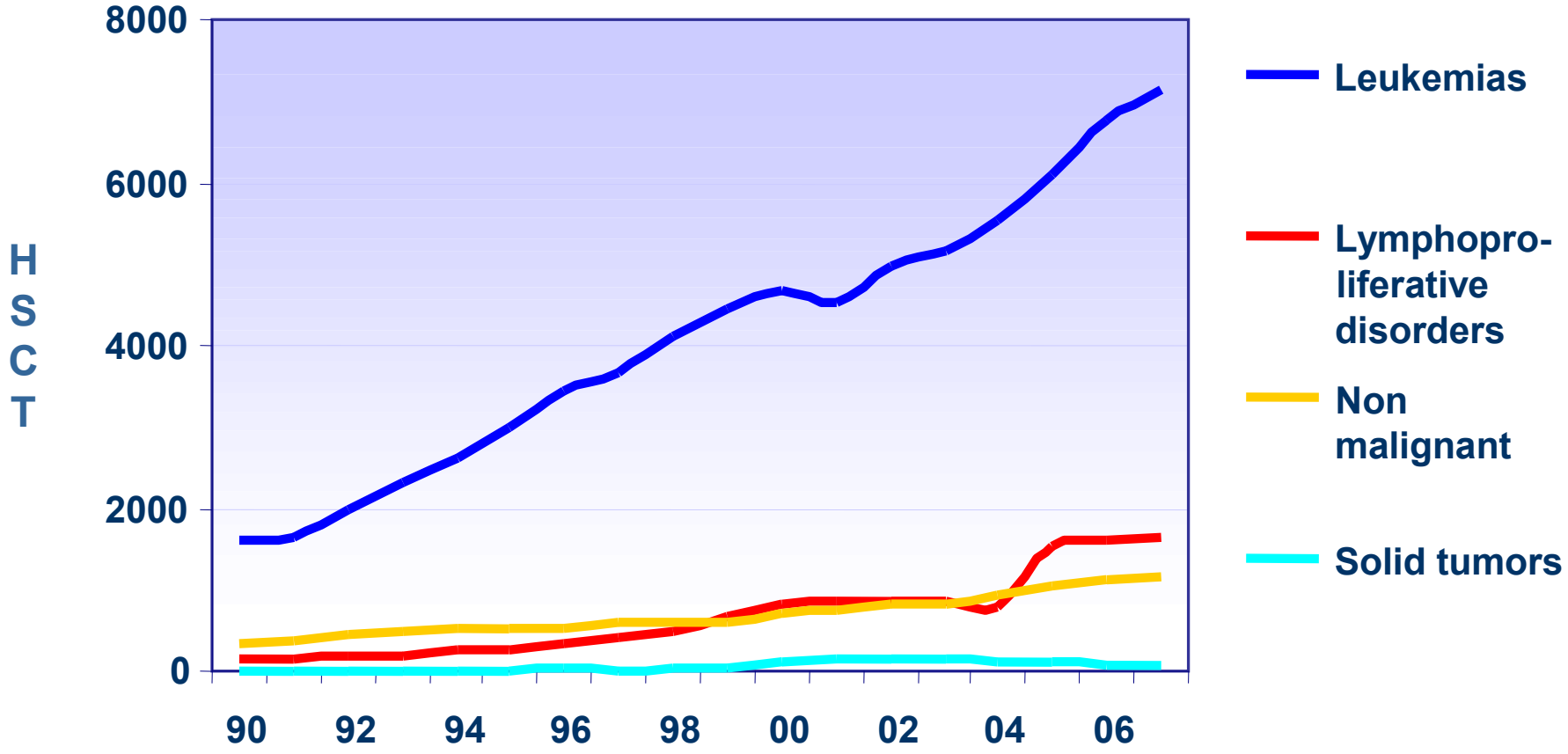
Cord blood HSCT



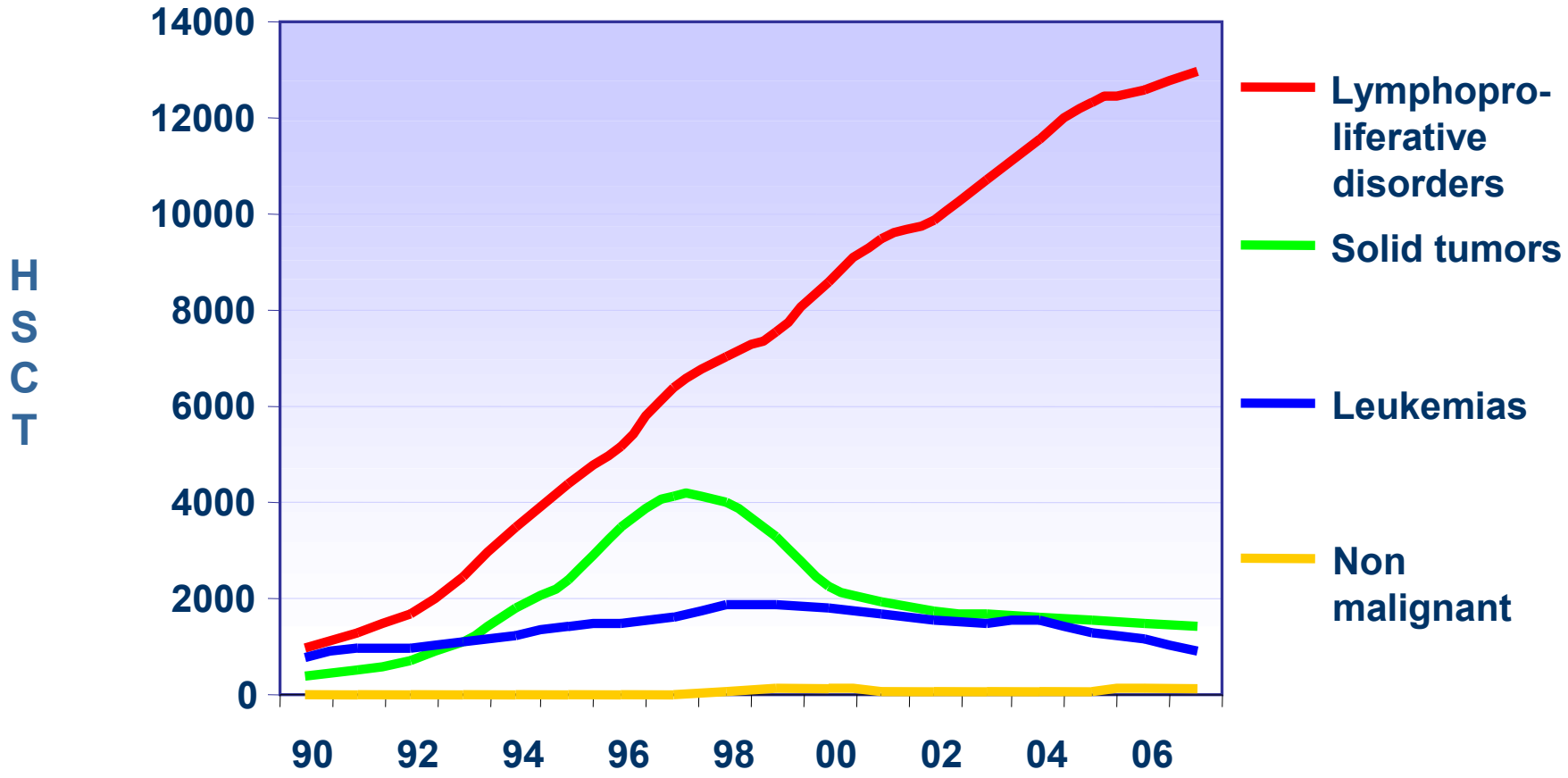
Evolution of RIC allogeneic HSCT in Europe 1990-2007



EBMT Activity Survey on HSCT 1990-2007 allogeneic



EBMT Activity Survey on HSCT 1990-2007 autologous



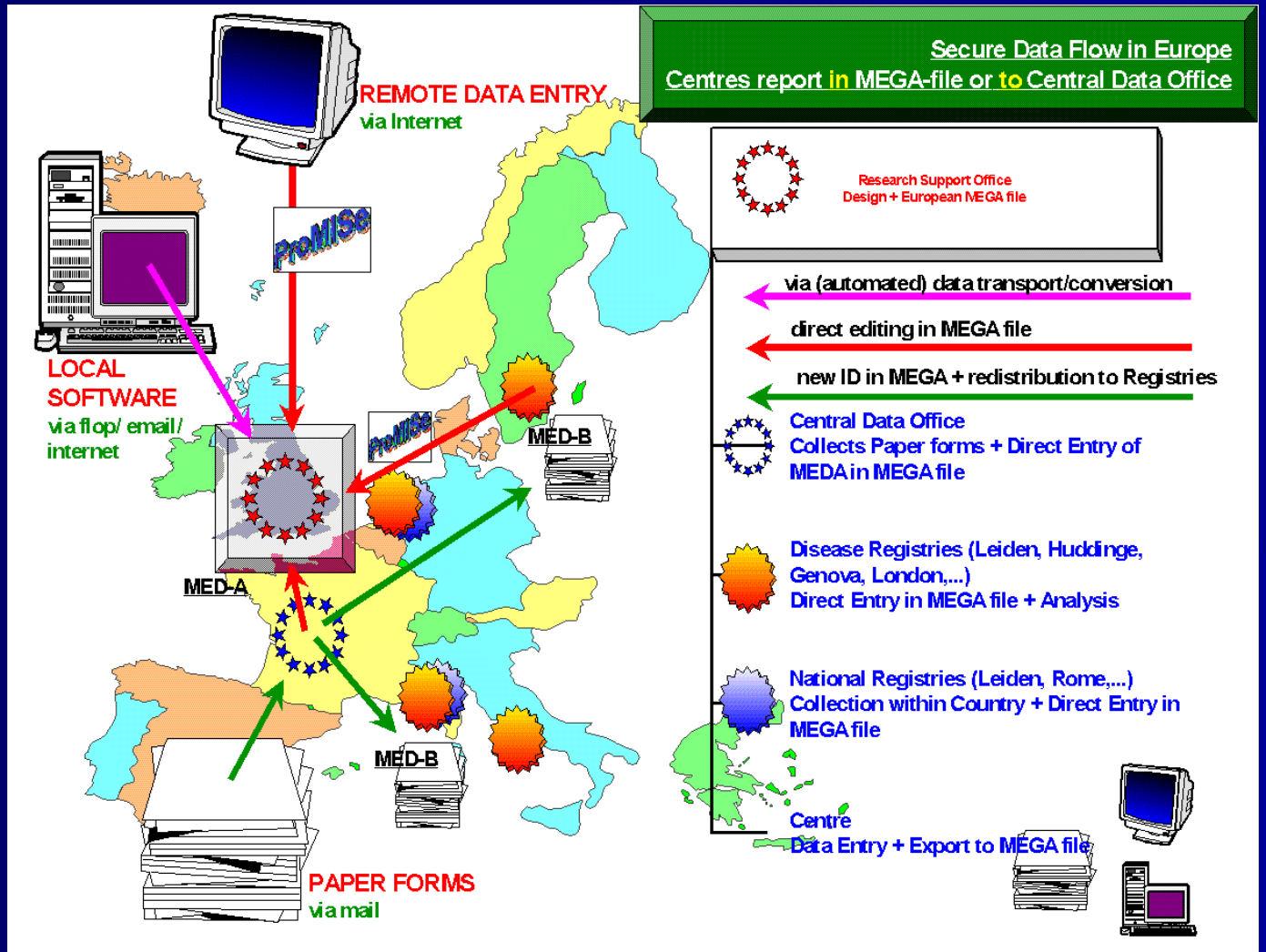
Importance of registries

- **Survey (** 2007 survey **29,000** transplants**)**
- **Registry**
- Retrospective studies

Tools for data collection

- Med-A: sufficient info to produce OS, DFS, TRM and RI
- Med-B: disease and transplant specific information
- Med-C: additional info for retrospective and prospective clinical studies

Changes with time

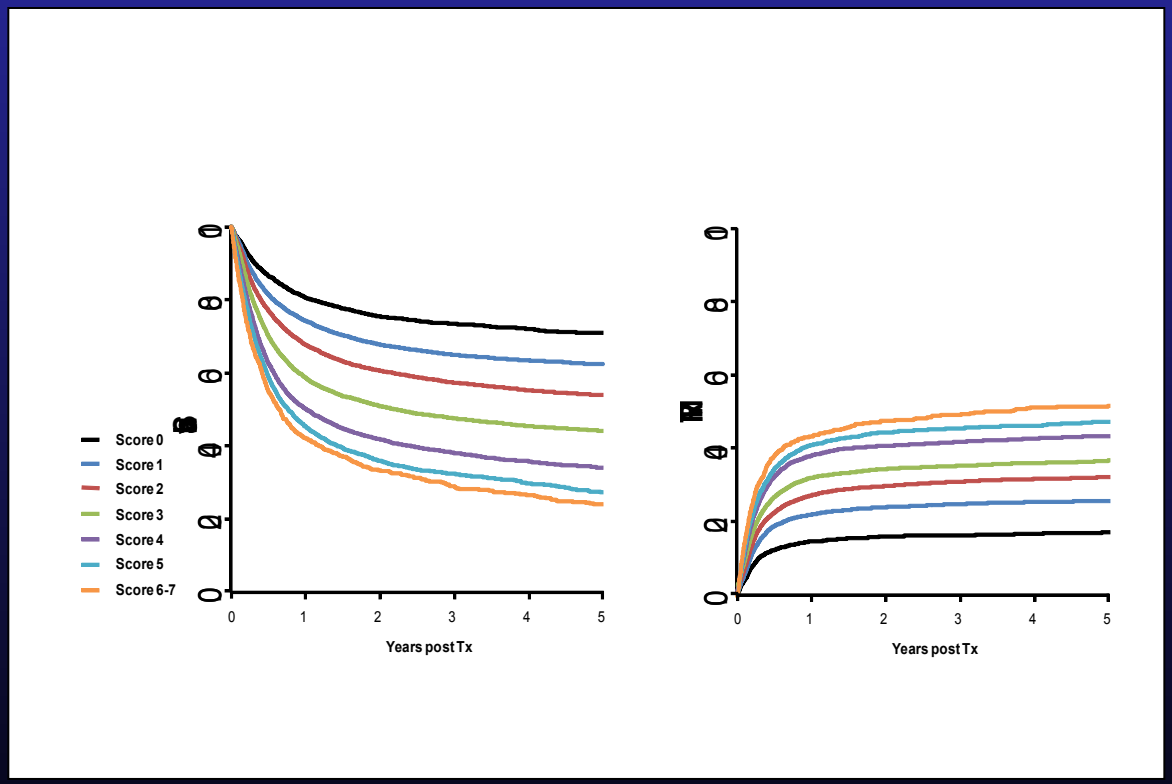


Importance of registries

- **Survey (** 2007 survey **29,000** transplants**)**
- **Registry**
- **Retrospective studies**

Hematopoietic cell transplantation

risk score for hematological malignancies

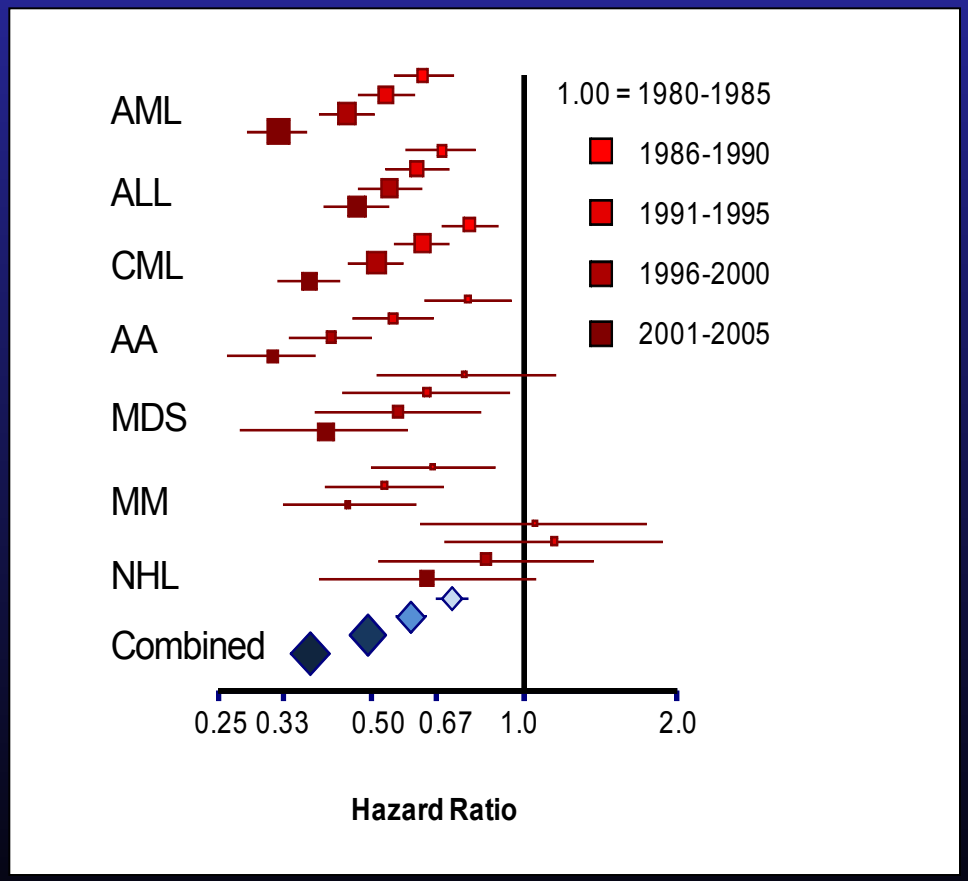


age of the patient,
disease stage,
time from Dg to HCT,
Matching,
gender combination

Gratwohl et al, submitted

Hematopoietic cell transplantation

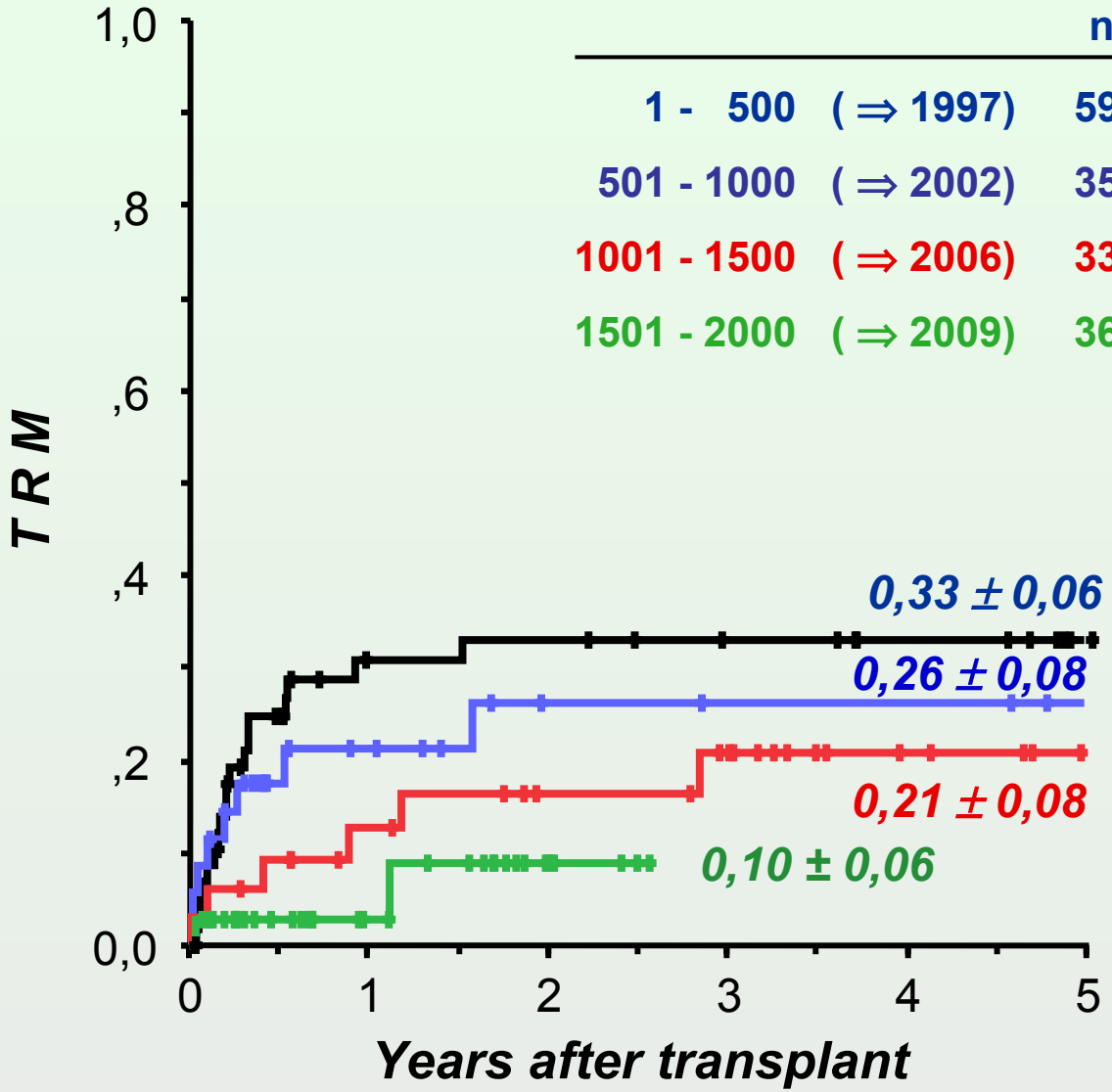
risk score for hematological malignancies



Gratwohl et al, submitted

Allogeneic conventional SCT:
AML in CR1 / CR2 / PR1 (1st Tx)

	n	age	RD / URD
1 - 500 (⇒ 1997)	59	*32* (17-55)	57 / 2
501 - 1000 (⇒ 2002)	35	*38* (17-53)	24 / 11
1001 - 1500 (⇒ 2006)	33	*37* (13-54)	16 / 17
1501 - 2000 (⇒ 2009)	36	*42* (19-55)	17 / 19



Hematology/Oncology
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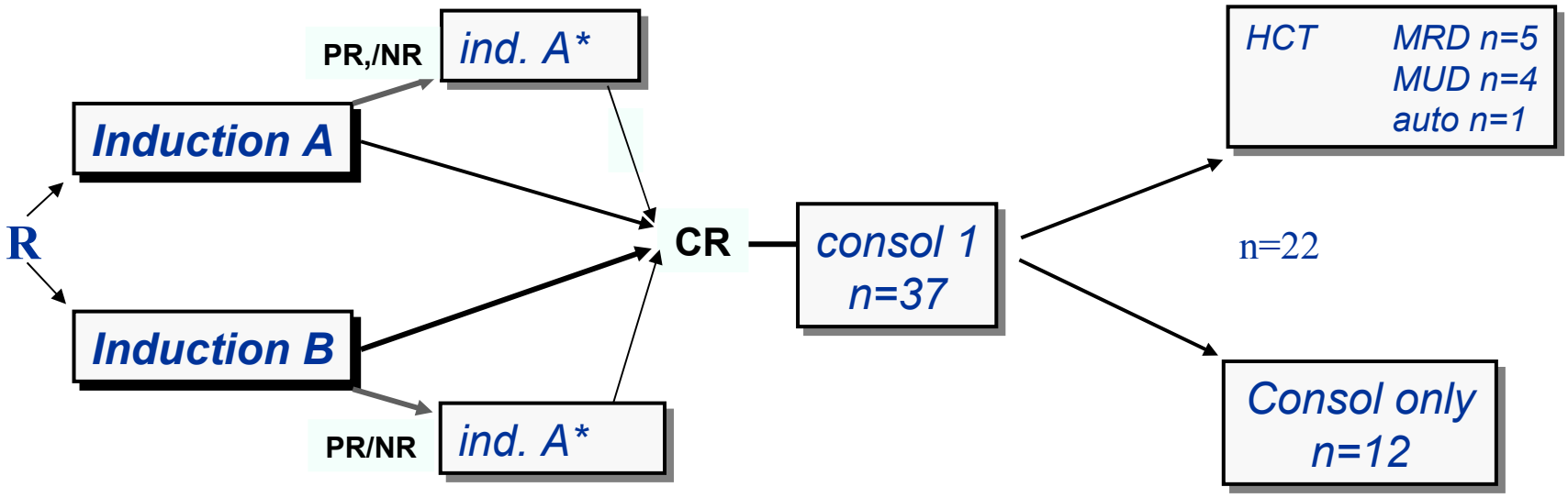
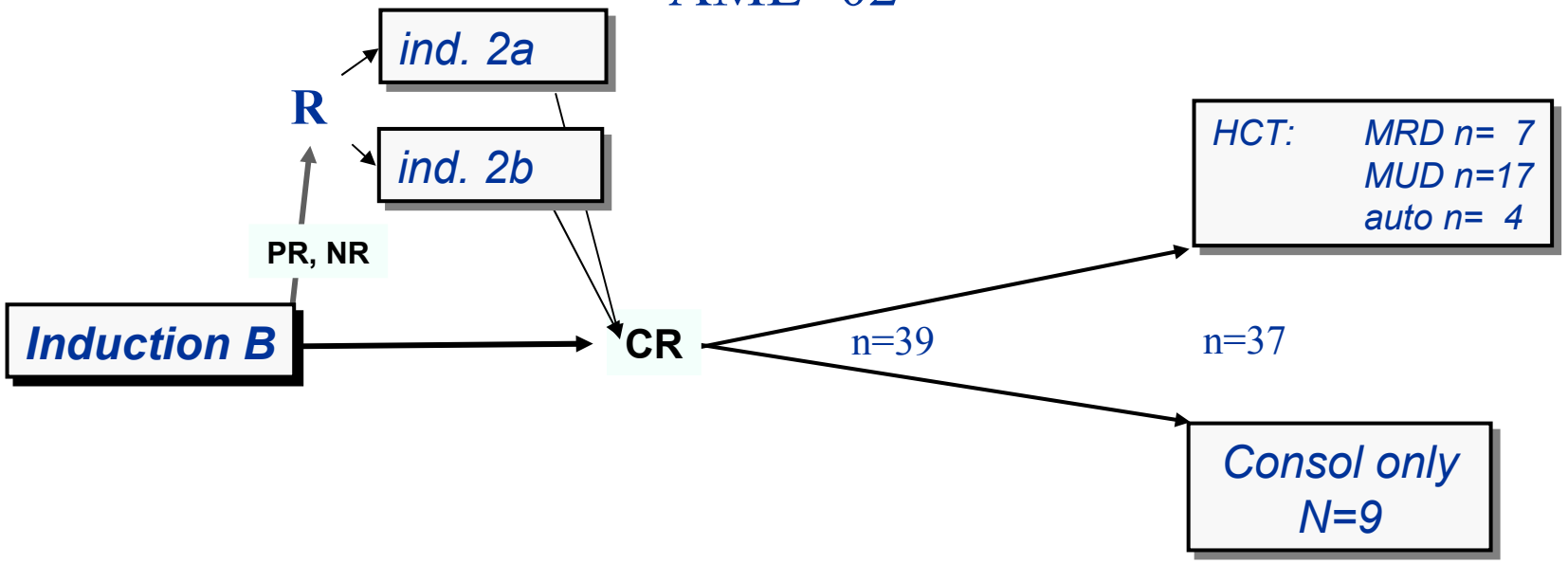
Leipzig

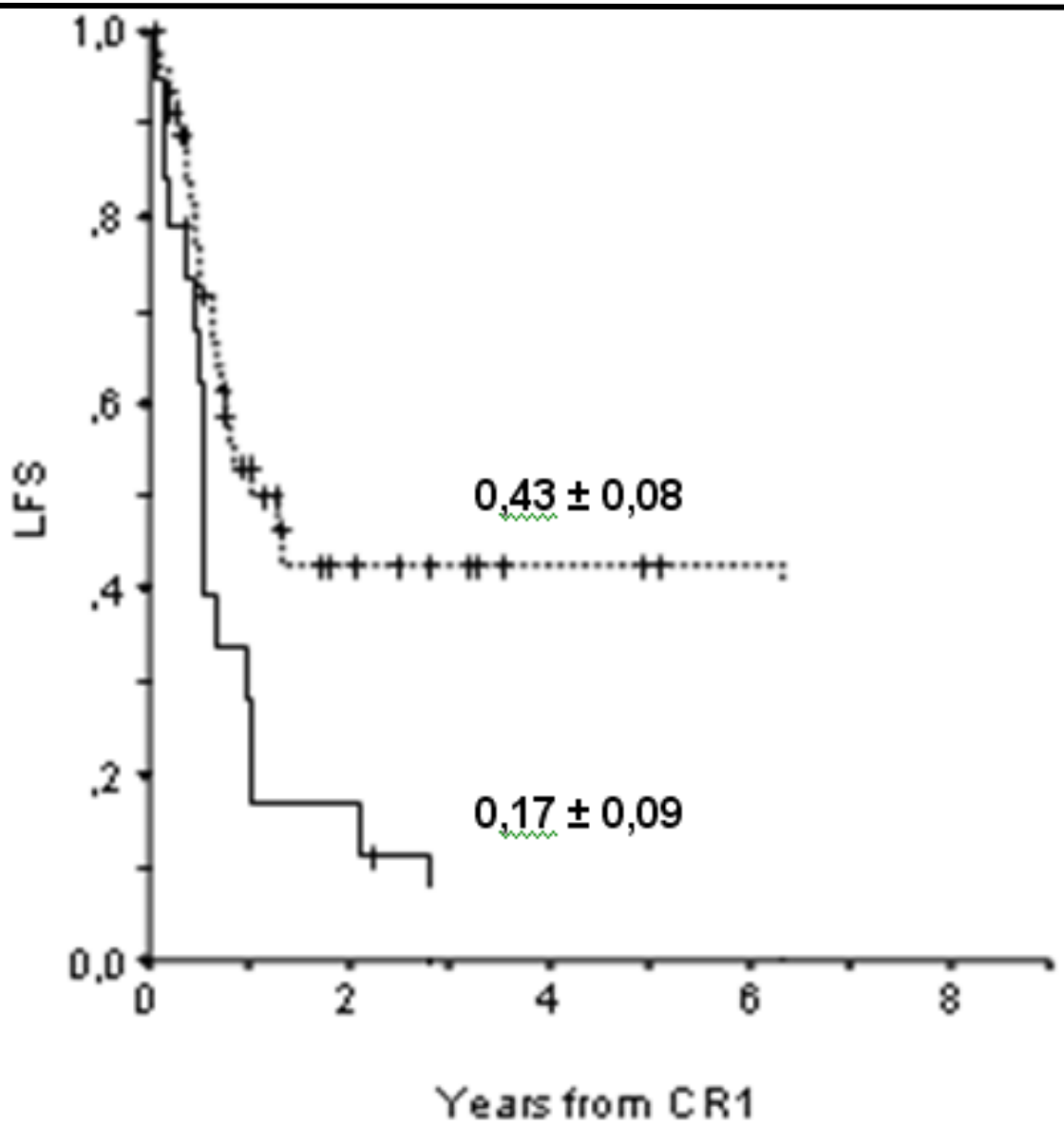
AML ´96 High Risk Cytogenetic AML



AML ´02



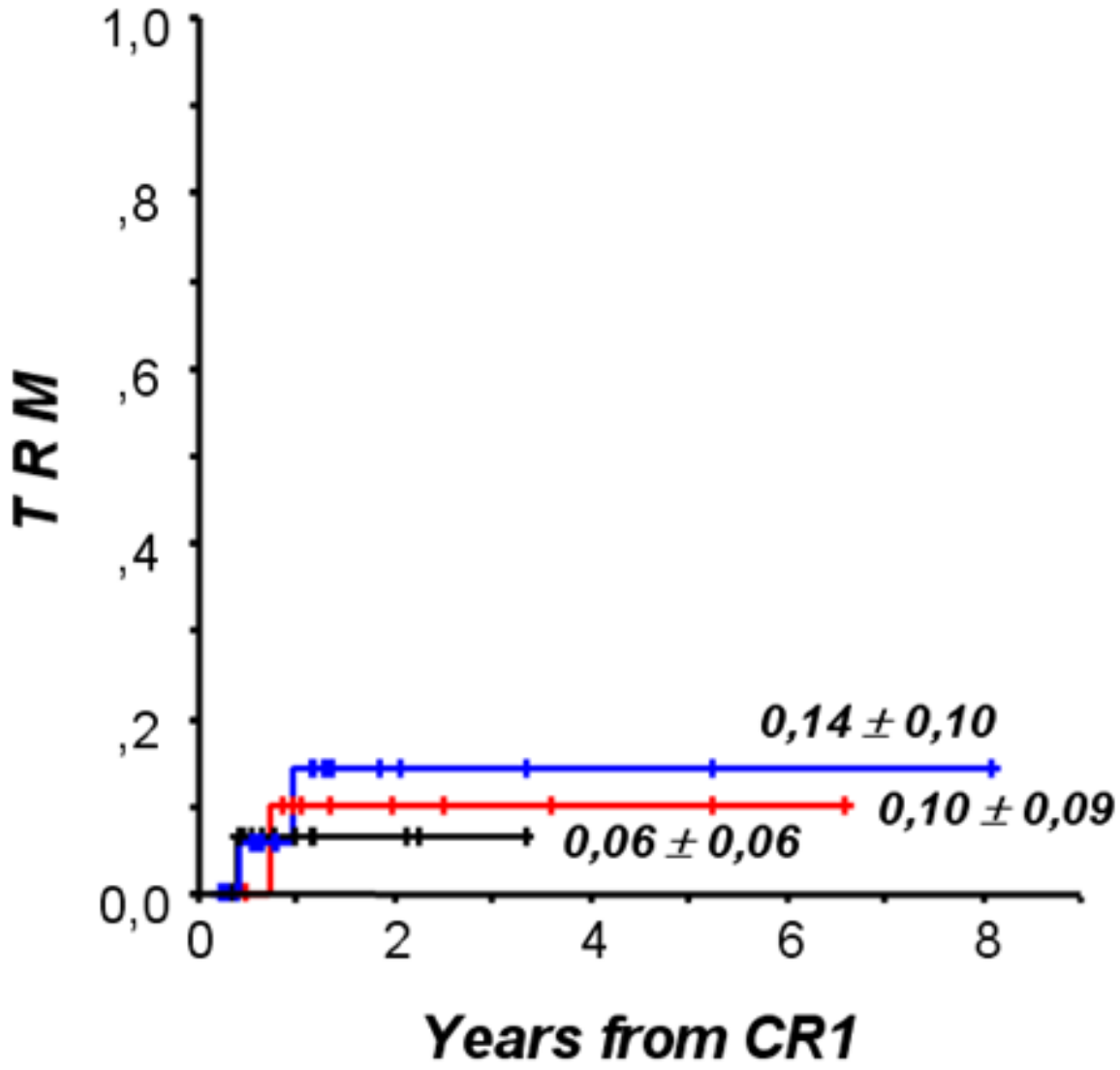
High-risk cytogenetics: chemotherapy vs. related vs. unrelated HCT



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

CT, n=21

High-risk cytogenetics: chemotherapy vs. related vs. unrelated HCT

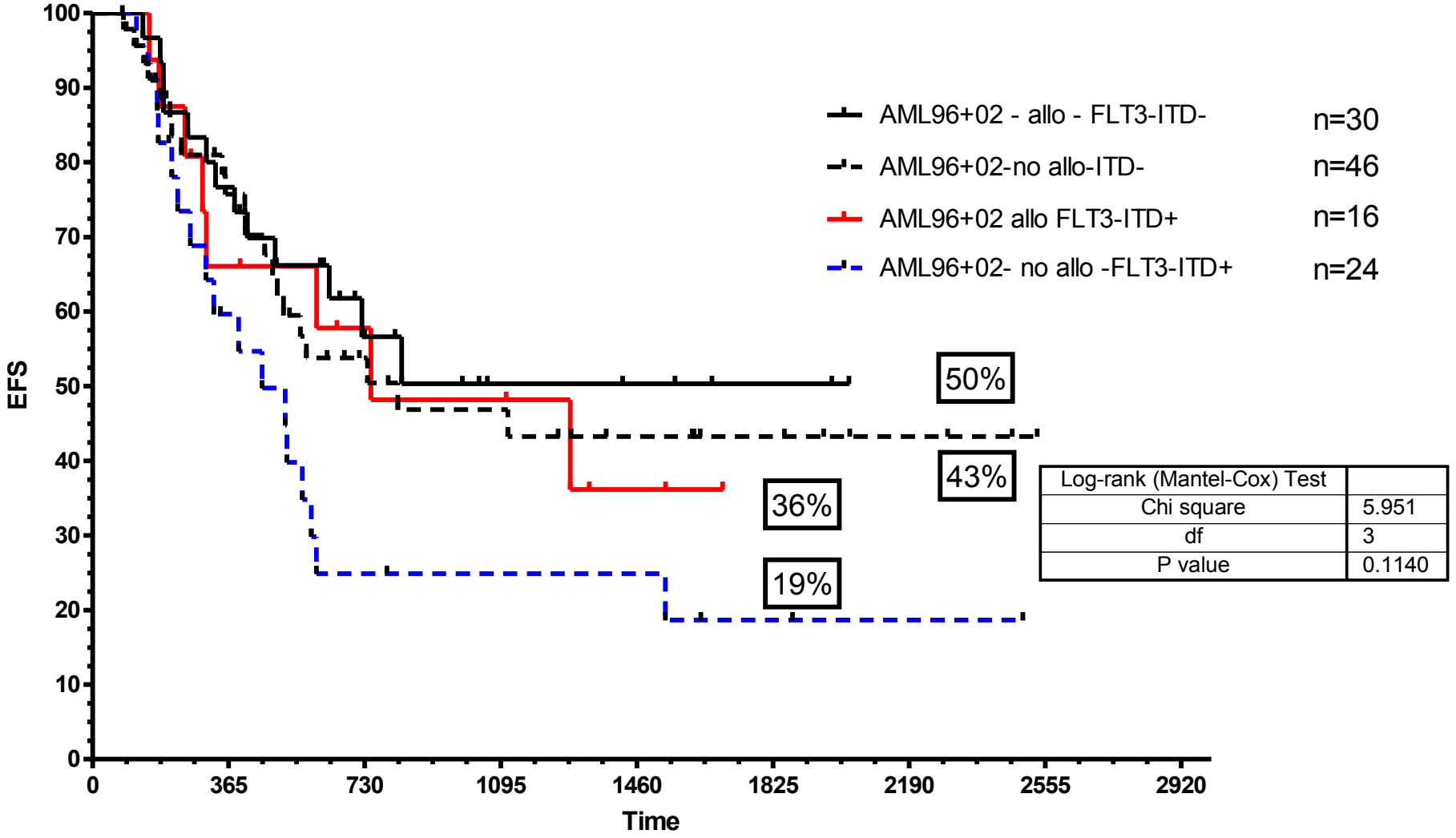


unrelated HCT, n=21; p=.98

related HCT, n=12; p=.74

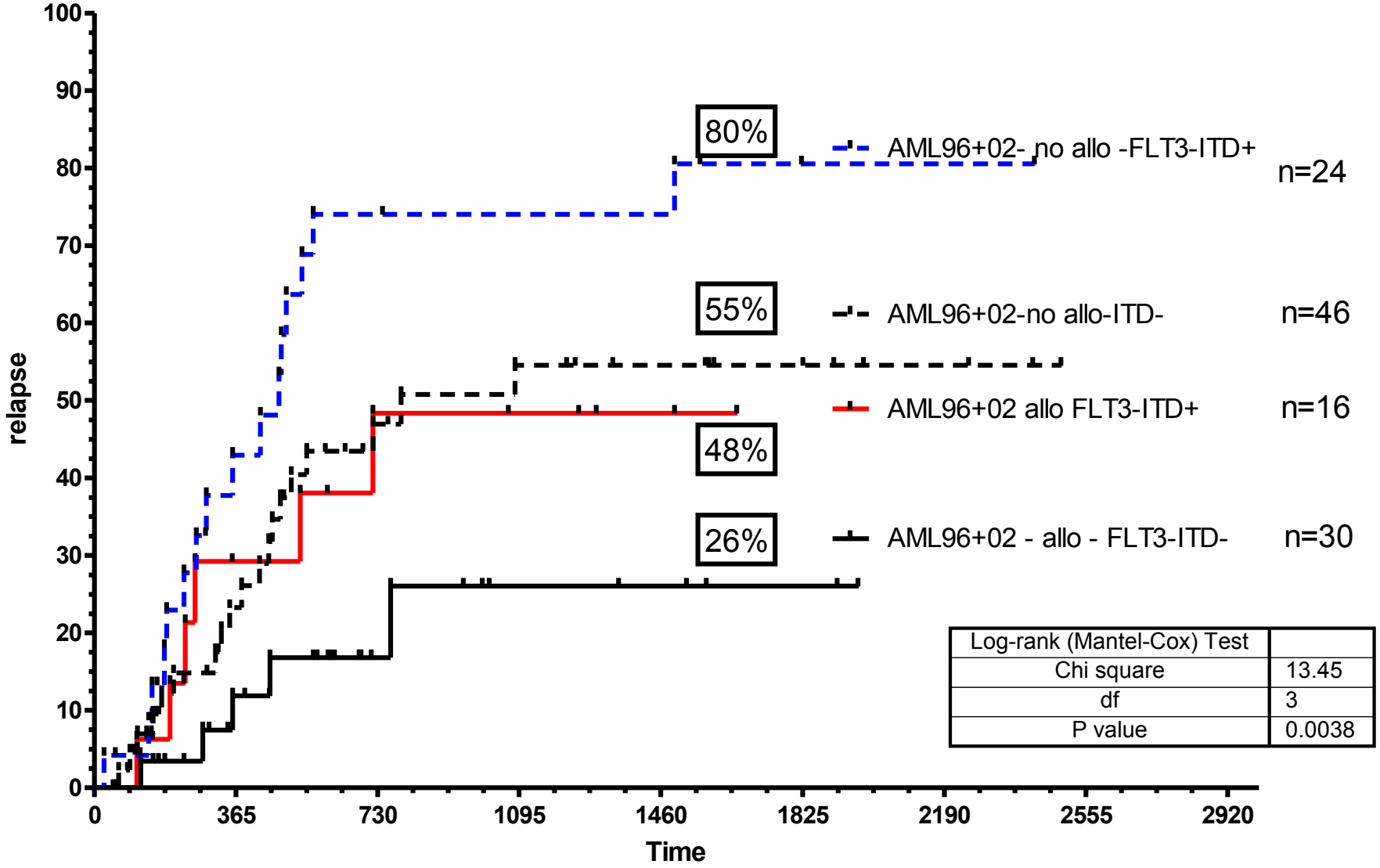
chemotheraphy n=21

EFS AML96+2002 - normal karyotype - postremission therapy: Allo Tx vs no Allo Tx n=116

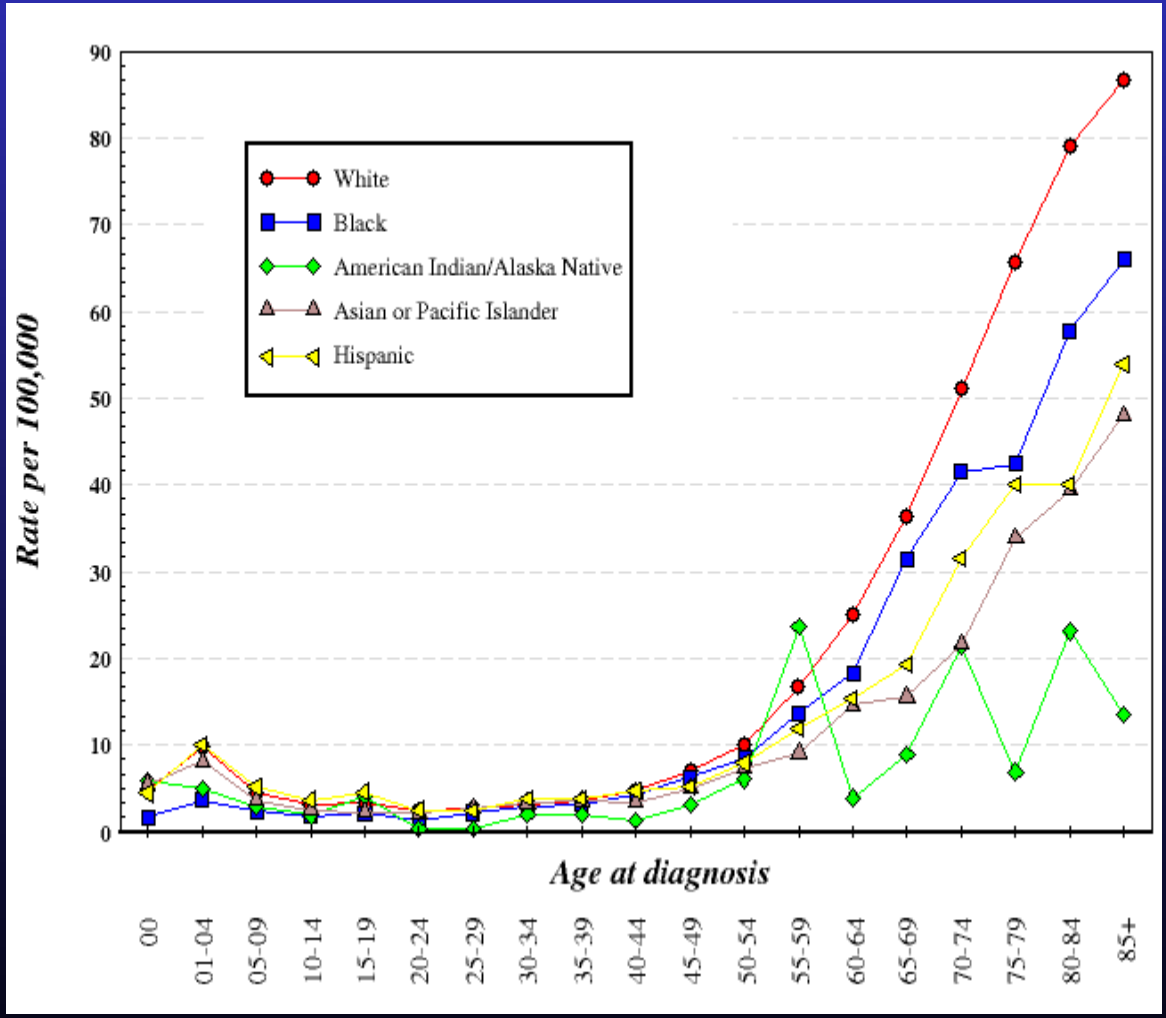


Log-rank (Mantel-Cox) Test	
Chi square	5.951
df	3
P value	0.1140

Relapse probability: AML96+2002 - normal karyotype - postremission therapy: Allo Tx vs no Allo Tx n=116

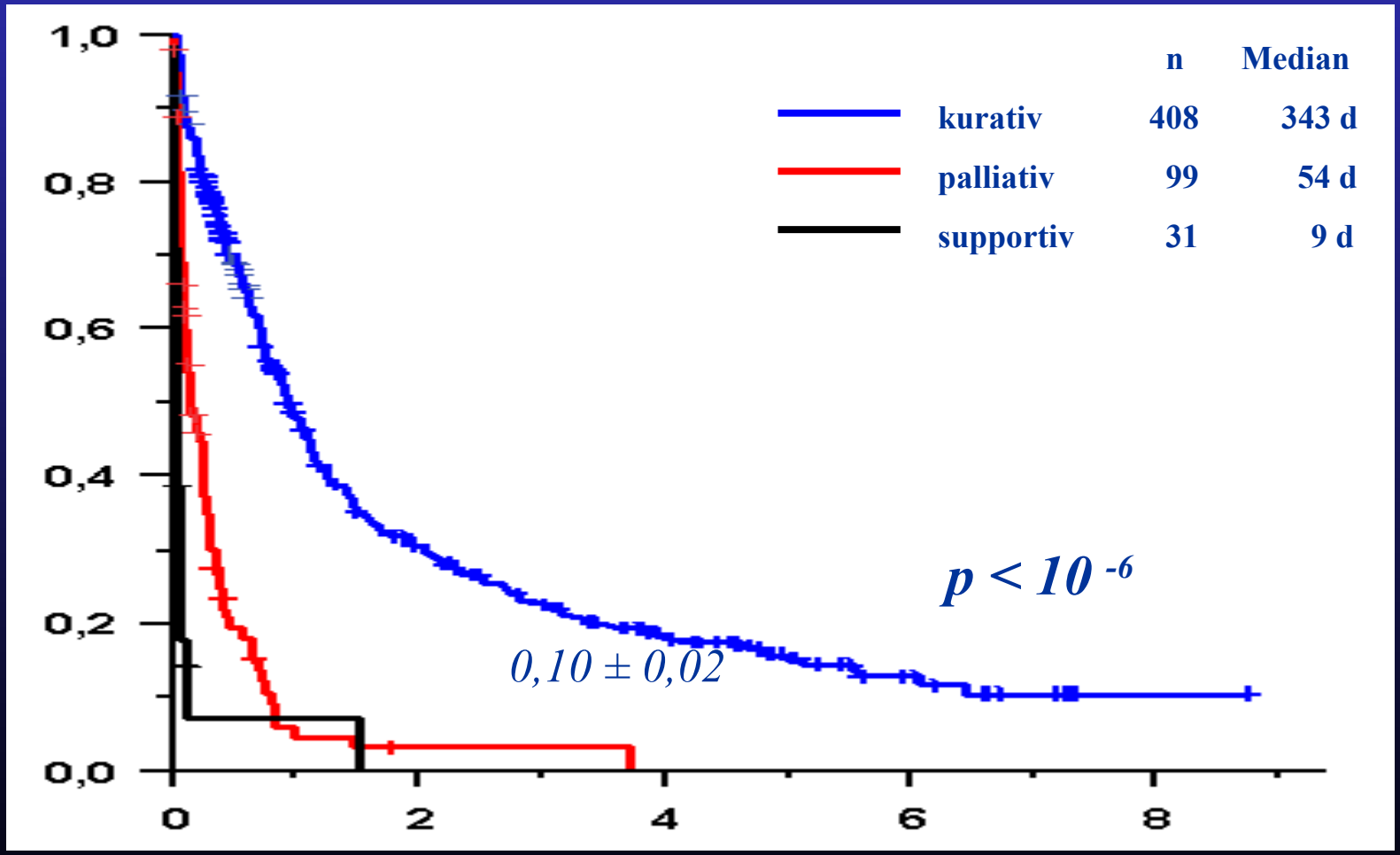


Incidence of acute myeloid leukemias

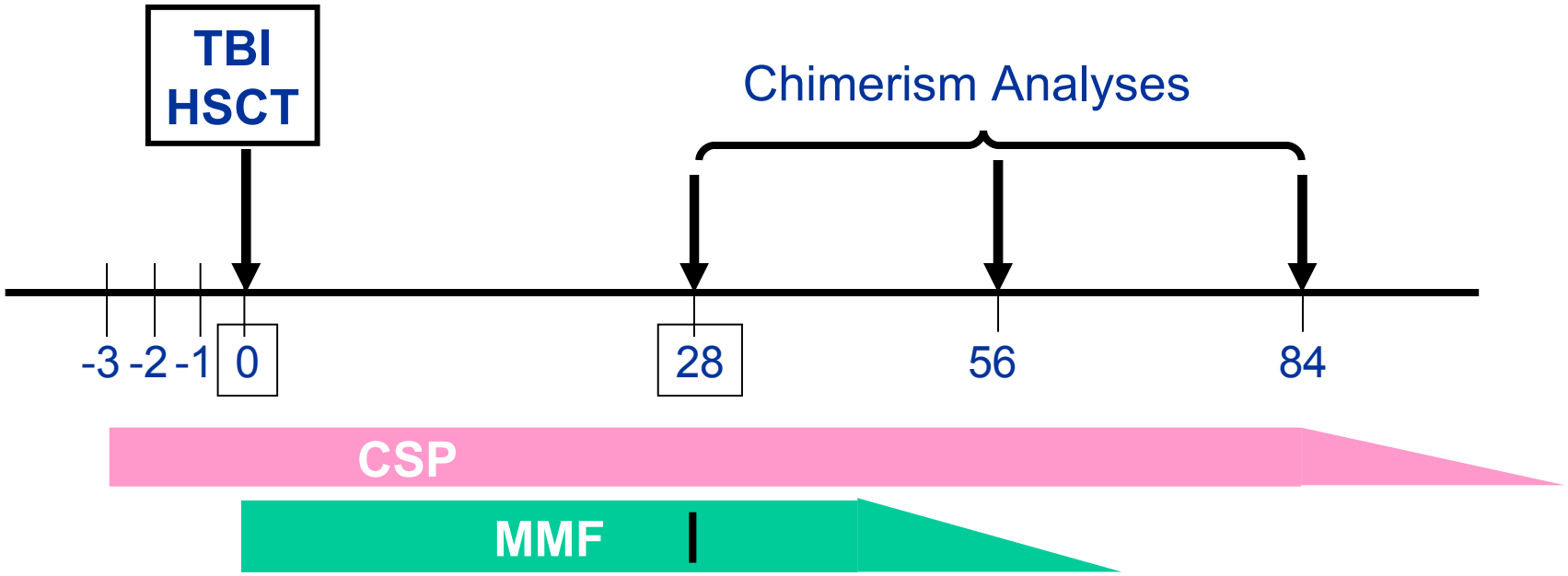


SEER Crude Incidence Rates Leukemia
SEER 13 Registries for 1998-2002

AML '97 : Überleben



Treatment Protocol



TBI: 200 cGy (7 cGy/min), single fraction

CSP: 6.25 mg/kg p.o. b.i.d. days -3 to +84 then taper

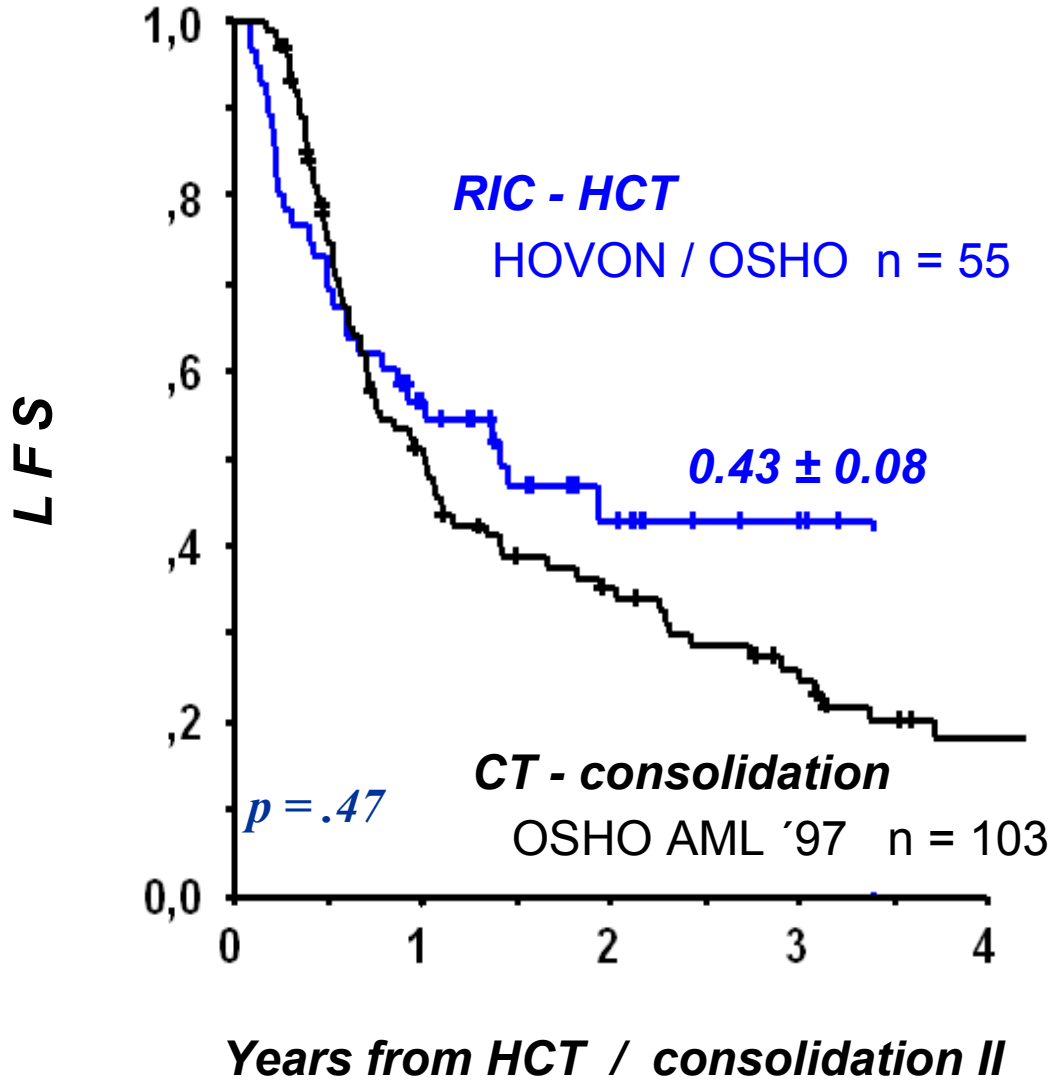
MMF: 15 mg/kg p.o. b.i.d. day 0 to +27

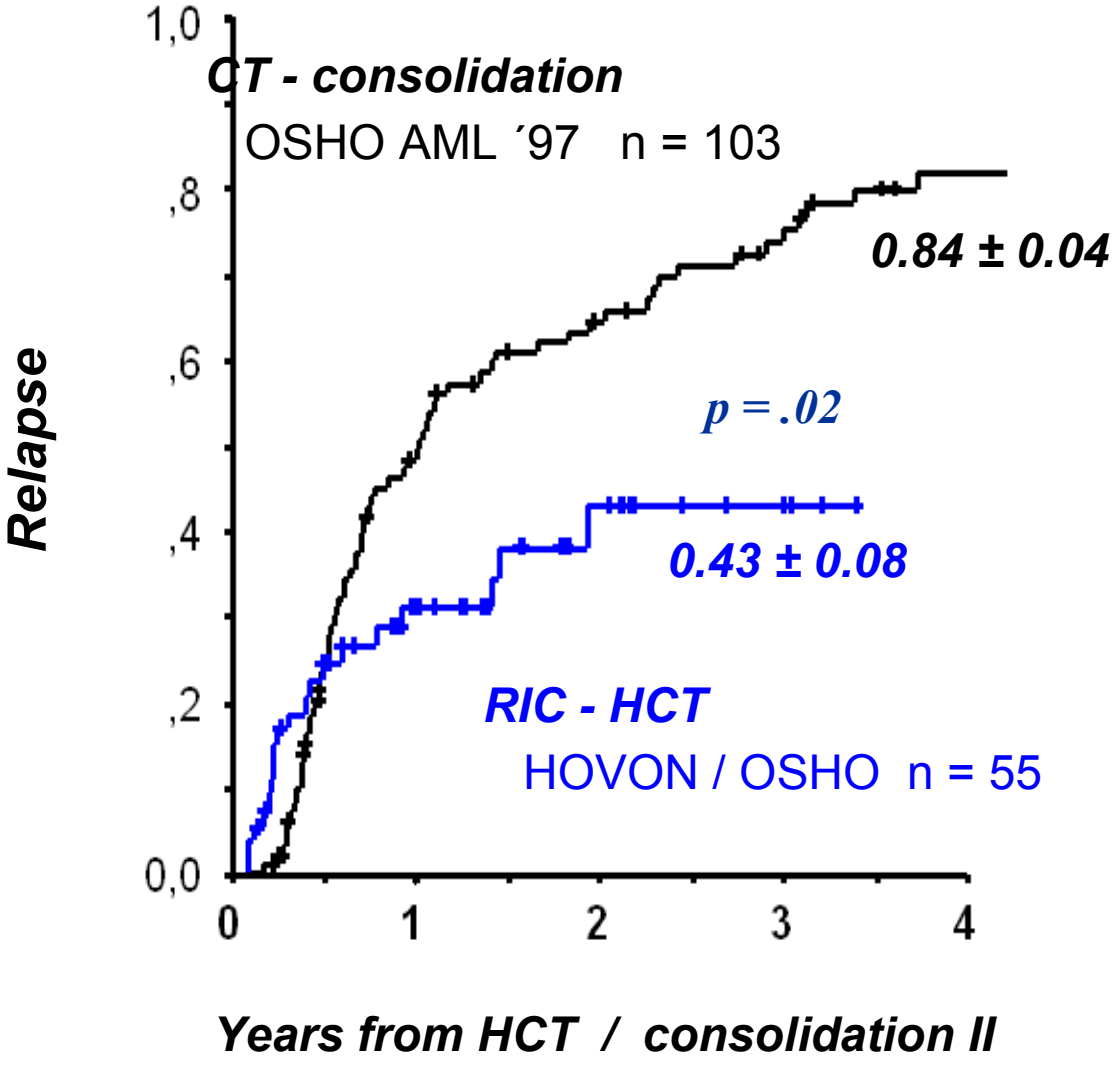
(**Fludarabine:** 30 mg/m^2 day -4 to -1)

Patient characteristics : RIC-HCT vs. CT

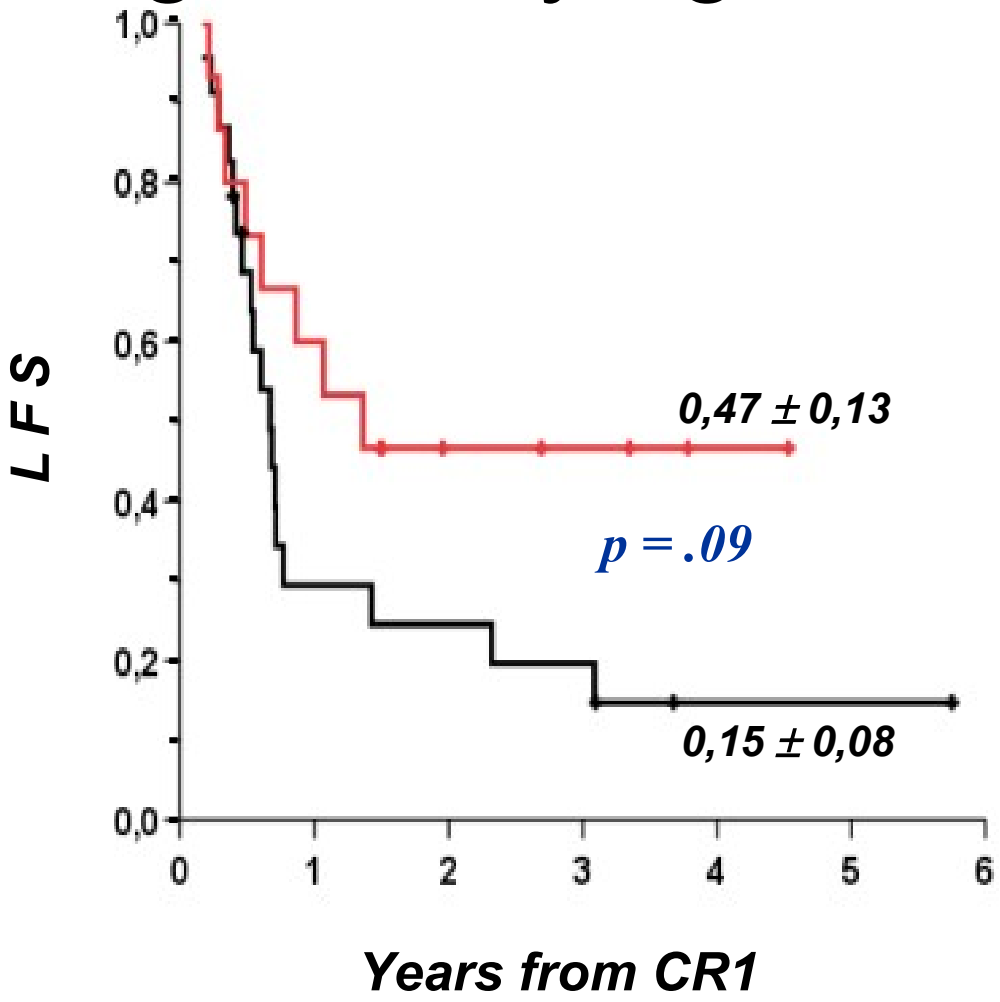
(CT - only patients in continuous CR1 before consolidation II; landmark analysis)

	RIC - HCT ***n = 55***	**AML ´97** *OSHO* ***n = 103***	***p***
Age (median, range) a	**65** (60-74)	**65** (60-78)	.27
AML (de novo / secondary)	**40 / 15**	**78 / 25**	.82
Cytogenetic risks			
low { t(8;21), inv(16) }	-	-	
intermediate (normal, other)	**15**	**81**	.66
high (-5/5q-, -7/7q-, ..., complex)	**6**	**22**	
CR1 - HCT or consolidation II (median, range) d	**77** (5-258)	**58** (24-147)	***.004***


1,0
,8
,6
,4
,2
0,0
0
1
2
3
4
LFS
RIC - HCT
HOVON / OSHO n = 55
0.43 ± 0.08
CT - consolidation
OSHO AML ´97 n = 103
p = .47
Years from HCT / consolidation II


1,0
,8
,6
,4
,2
0,0
Relapse
CT - consolidation
OSHO AML ´97 n = 103
0.84 ± 0.04
p = .02
0.43 ± 0.08
RIC - HCT
HOVON / OSHO n = 55
0
1
2
3
4
Years from HCT / consolidation II

LFS of patients with AML CR1 >60 a and high risk cytogenetics: HCT vs. CT



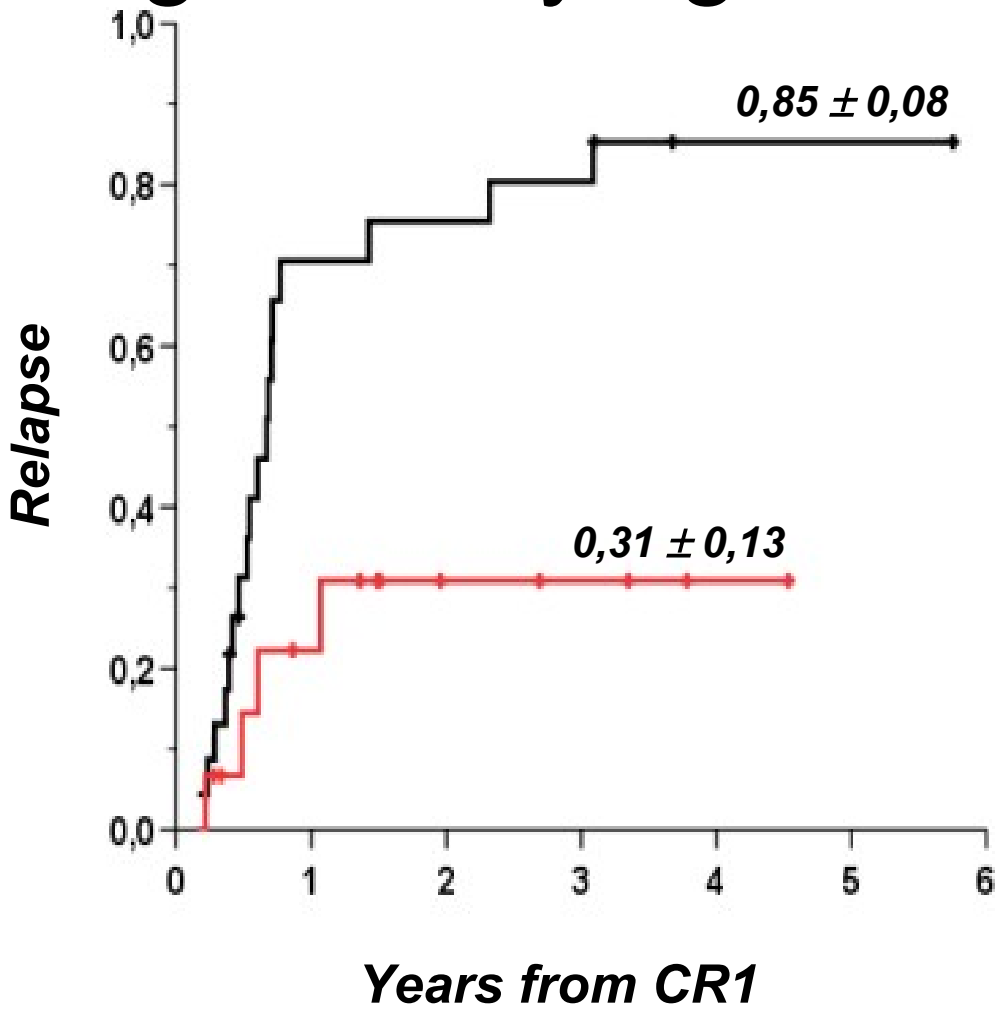
RIC – HCT n = 15

follow up median 2.7 (1.5 – 4.5) a

CT n = 23

follow up median 3.1 (0.4 – 5.8) a

RI of patients with AML CR1 >60 a and high risk cytogenetics: HCT vs. CT



RIC - HCT
n = 15

chemotherapy
n = 23

p = .008

RIC-HCT: risk factors for relapse

48/141 patients had hematological relapse

Risk factors: Absence of acute GvHD
Absence of chronic GvHD
CD34 chimerism day 28 ≤90%

RIC-HCT: response to relapse

50% CR, but survival is 3,6±0,03%.
None of the patients relapsing <100 days after HCT survived.

Independent prognostic factors (multiv. A.):
Reduction of IS and/or DLI (p=0.04)
Amount of donor chimerism at diagnosis (p=0.01)
Time from Tx to Rel (<100 vs >100 days; p=0.02)
Presence of GvHD (p=0.05)

RIC-HCT: response to relapse

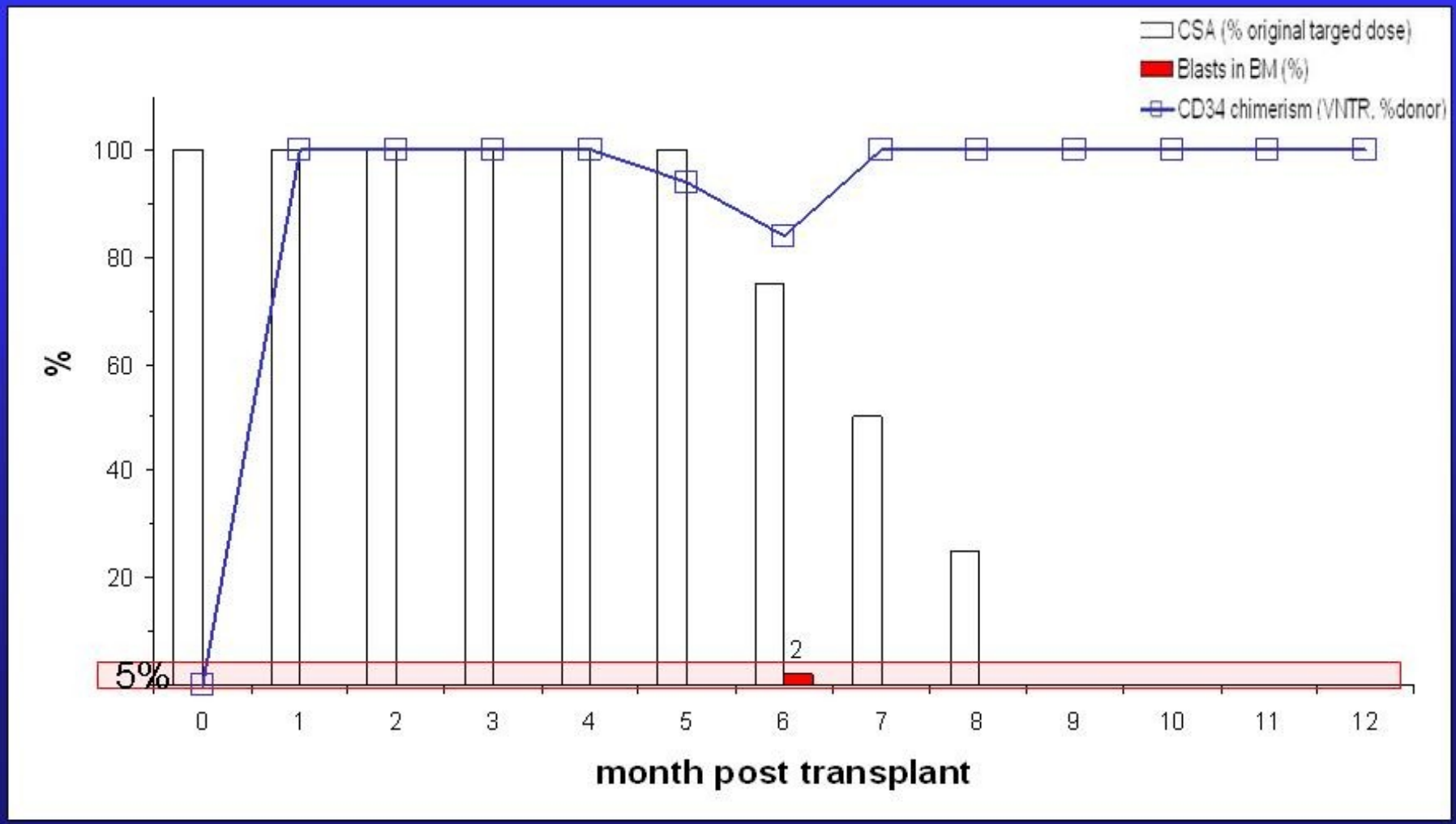
12 patients (8,7%) had CD34 decrease after HCT

Decrease of immunosuppression restored CD34 chimerism to 100%.

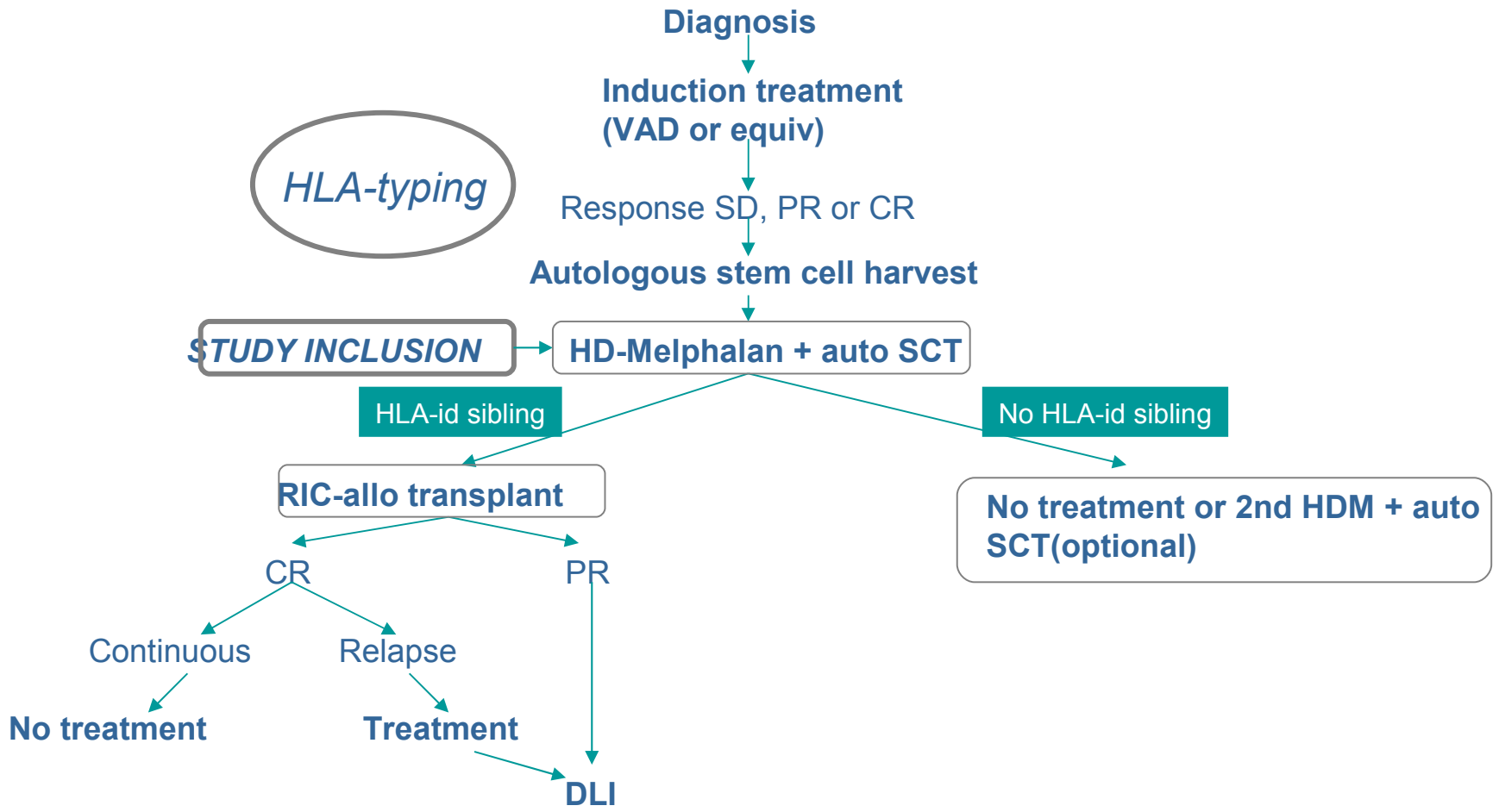
Survival of these patients is 90±9% at 4 years.

Conversion of CD34 chimerism without relapse with fast immunosuppression taper

69y/o female; AML 1. CR, MUD



Auto/RIC-allo versus Auto in Myeloma
Study design



Present of HCT

Treatment of first choice for many hemtological and non-hematological malignancies

Only curative treatment for many diseases

Almost no age limit

Risk factors defined

Alternatives for patients without a donor (Haplo, CB)

Understanding graft-versus-tumor mechanism

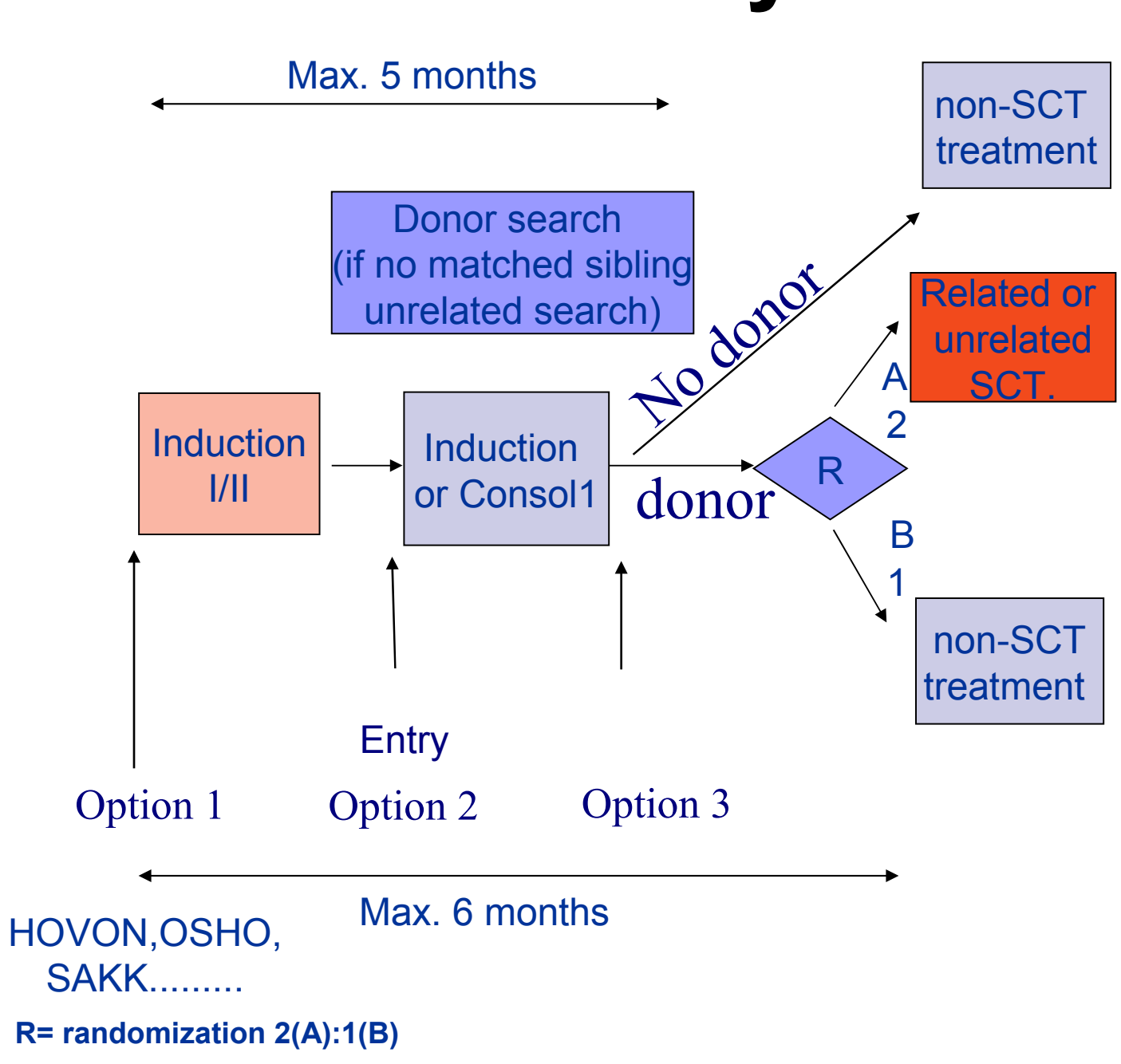
Future of HCT

Is there something to improve?

Future of HCT

- Reduce transplant related mortality
- Reduce relapse incidence
- Define optimal treatment for diseases on a regular basis
- Prospective Clinical Studies
- Networking
- Standardisation
- Education / Outreach
- Quality control (accreditation)

EBMT study in AML > 60 yrs



If relapse

Induction

Related or unrelated SCT.

Strategy Meeting of the EBMT

- More prospective clinical studies
- Promotion of basic science
- Cellular therapy outside haematological field
- Connect disease study groups and EBMT
- Consultor for EU, patients and families
- Education (MD, nurses, technical or DM)

CIBMTR® CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

EBMT

APBMTG
Asian Pacific Blood and Marrow Transplantation Group

TOPICS:

a. Global survey of transplant activity
b. Development of universal patient, donor and center ID numbers
c. Maintaining consensus on common data set for donors and recipients
d. Facilitating the development of national registries

Thanks to all

physicians, Ph. D., nurses, data manager, statisticians, emplojes, patients, families, politicians, national authorities