ESH-EHA 12th Tutorial
Diagnostic Work-Up of Hematological Malignancies
Focus on Lymphoid Malignancies
Type III Tutorial

New modalities for Hodgkin Disease

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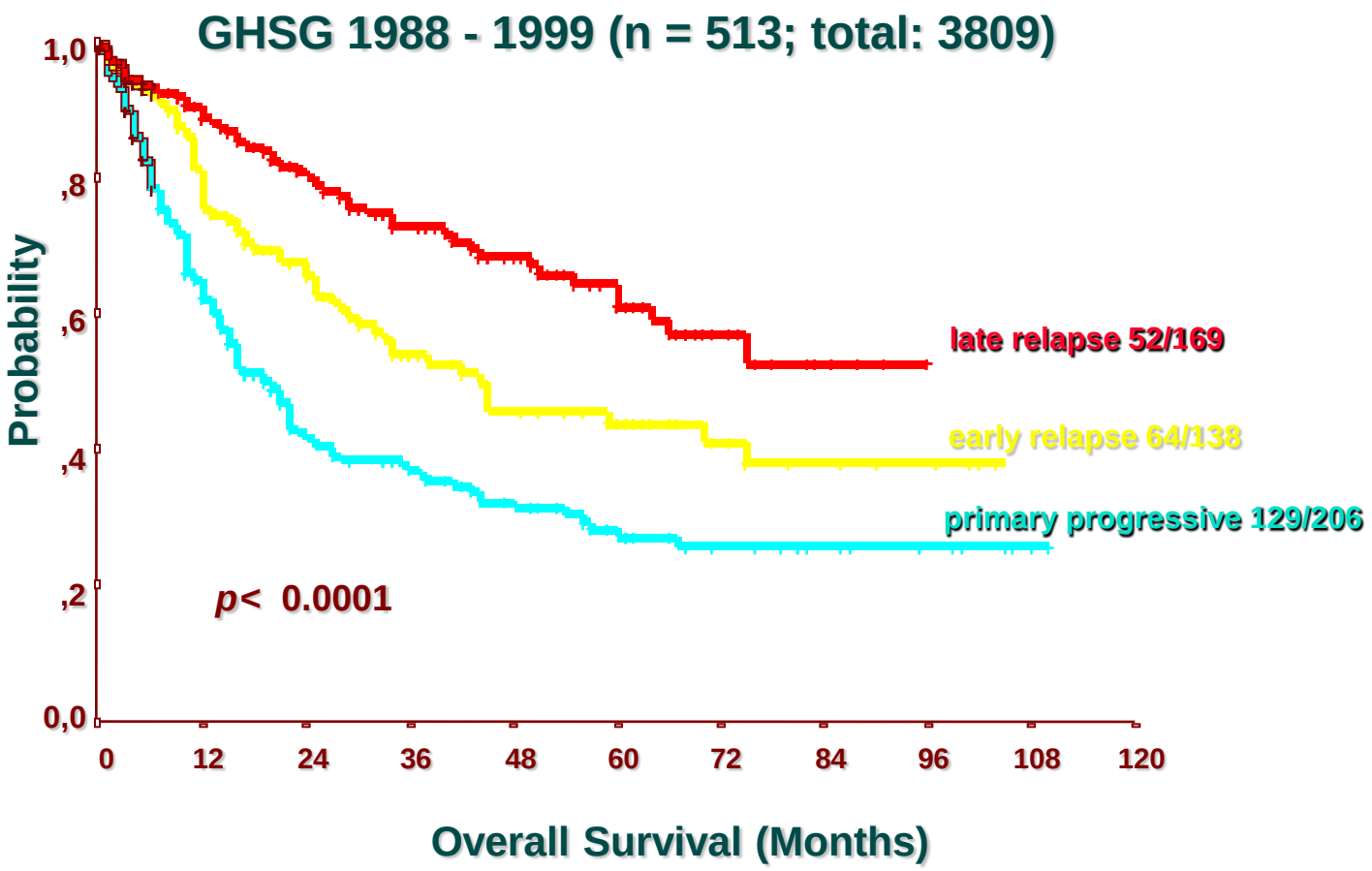
Kayseri, Turkey

September 25-27, 2009

Progressive and relapsed HD after first-line polychemotherapy



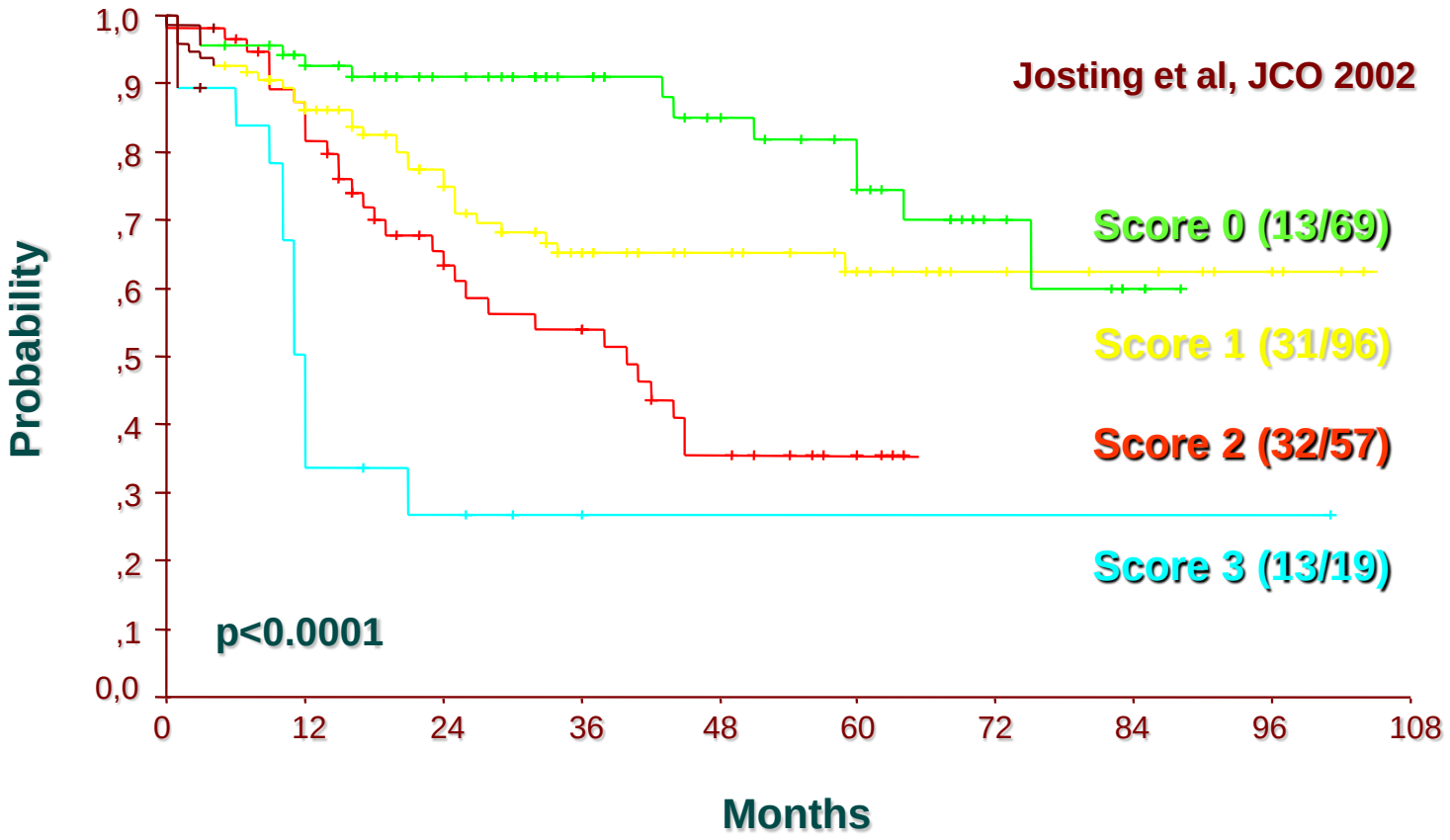
A prognostic score in relapsed Hodgkin`s disease (n = 422)

Factor		Groups with 4-year OS
Duration of 1. remission	Early relapse	47%
	vs.	
	Late relapse	73%
Stage at relapse	Stage III/IV	46%
	vs.	
	Stage I/II	77%
Hemoglobin	F < 10.5g/dl; M < 12.0g/dl	40%
	vs.	
	F > 10.5g/dl; M > 12.0g/dl	72%

Josting et al, JCO 2002

OS: Relapse after chemotherapy

Prognostic score: early relapse, stage III/IV, anemia



Treatment of relapse after primary chemotherapy

- Salvageradiotherapy
- Conventional chemotherapy
- HDCT und ASCT
- Allo SCT

Salvage Radiotherapy Alone For Relapse After Chemotherapy

Author	n	5y FFP (%)	5y OS (%)	Prognostic factors for FFP
Josting, 2003	100	29	51	B symptoms stage at relapse
Wirth, 1997	53	26	57	B symptoms extranodal sites histology
Leigh, 1993	44	38	48	extranodal sites
Petzner, 1994	28	40	63	n.e.
Brada, 1992	10	38	60	n.e.

Conventional salvage chemotherapy

Regimen	n	RR (%) Overall	RR (%) Relapse	RR (%) Progress	TRM (%)
DHAP	102	88	92	65	0
ASHAP	57	70	85	51	2
ESHAP	22	73	73	0	5
ICE	65	88	n.e.	n.e.	2
Dexa-BEAM	55	60	70	52	4
Mini-BEAM	44	74	85	52	0
CEVD	32	58	100	53	0
MINE	100	73	93	49	3

BNLI-trial

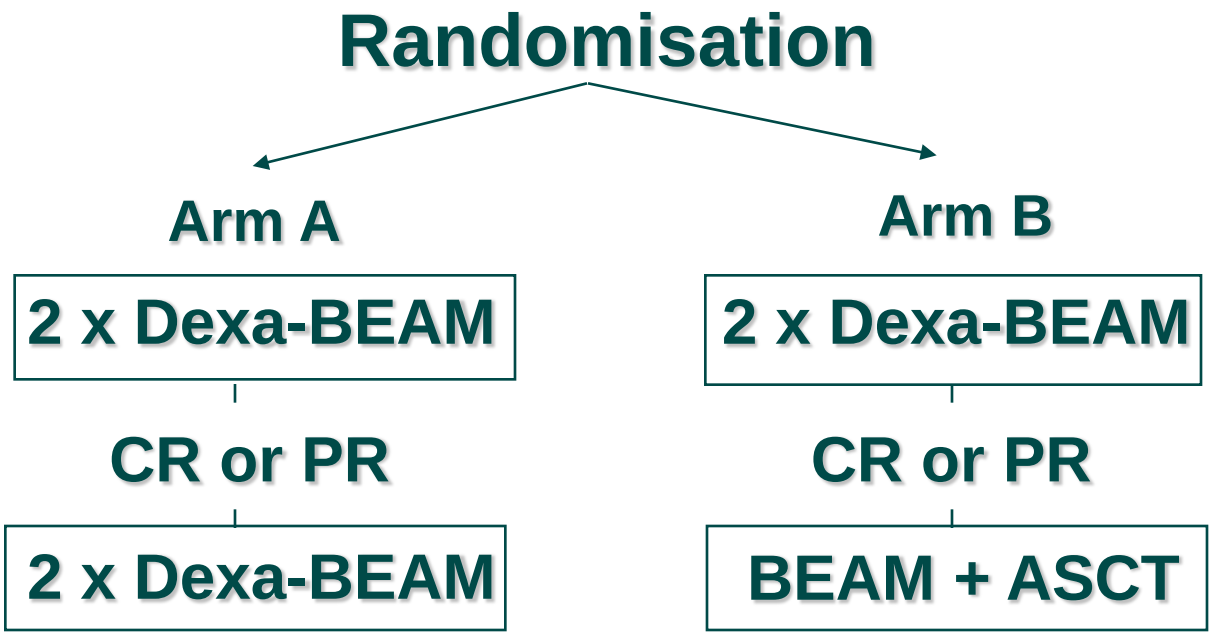
BEAM + ABMT *vs.* mini-BEAM

	n	TRM	EFS (3y)	*p*
BEAM+ABMT	20	5	53%	0.025
mini-BEAM	20	9	10%	

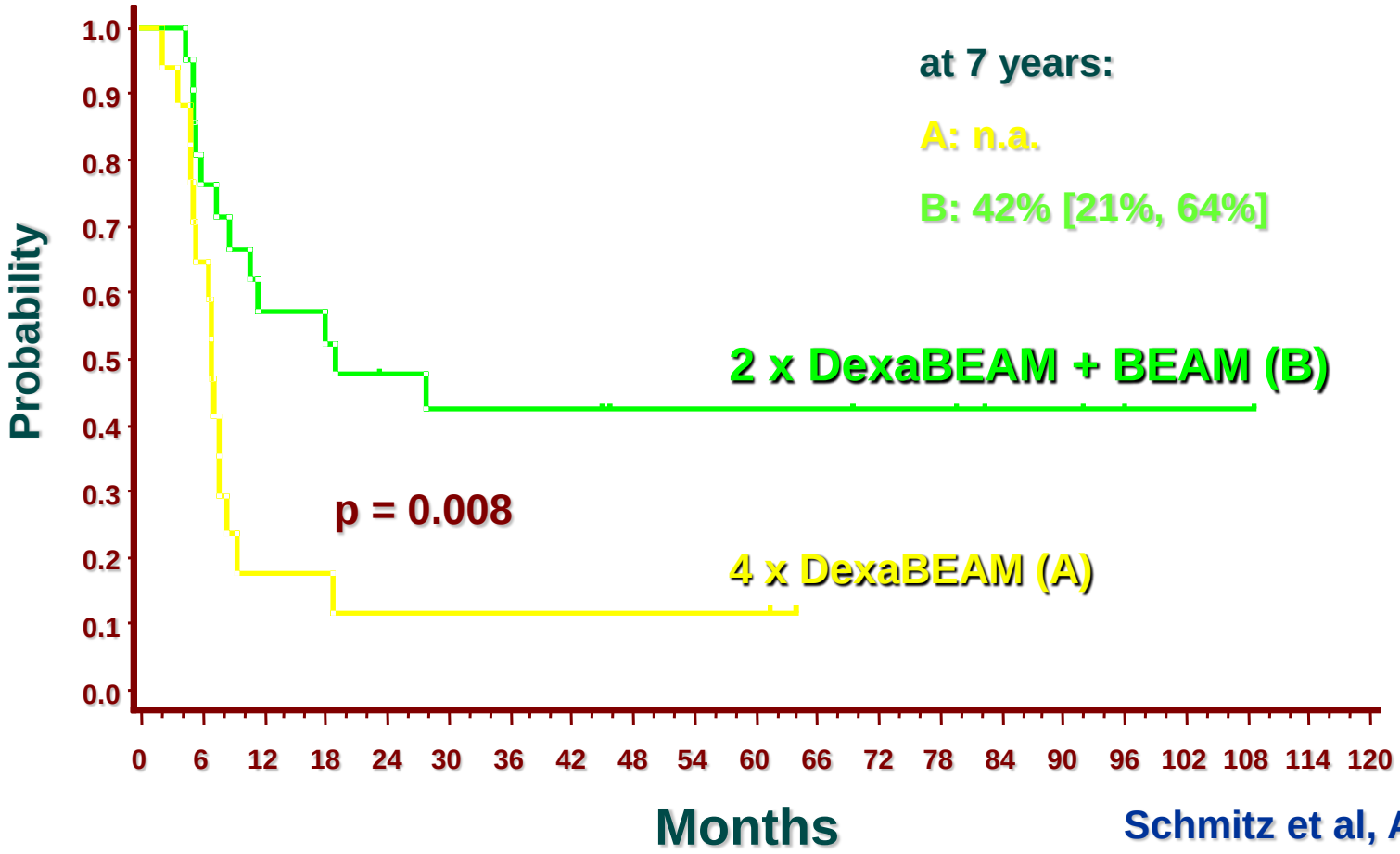
Linch, Lancet ’93

GHSG/EBMT: HD-R1-trial

Study design



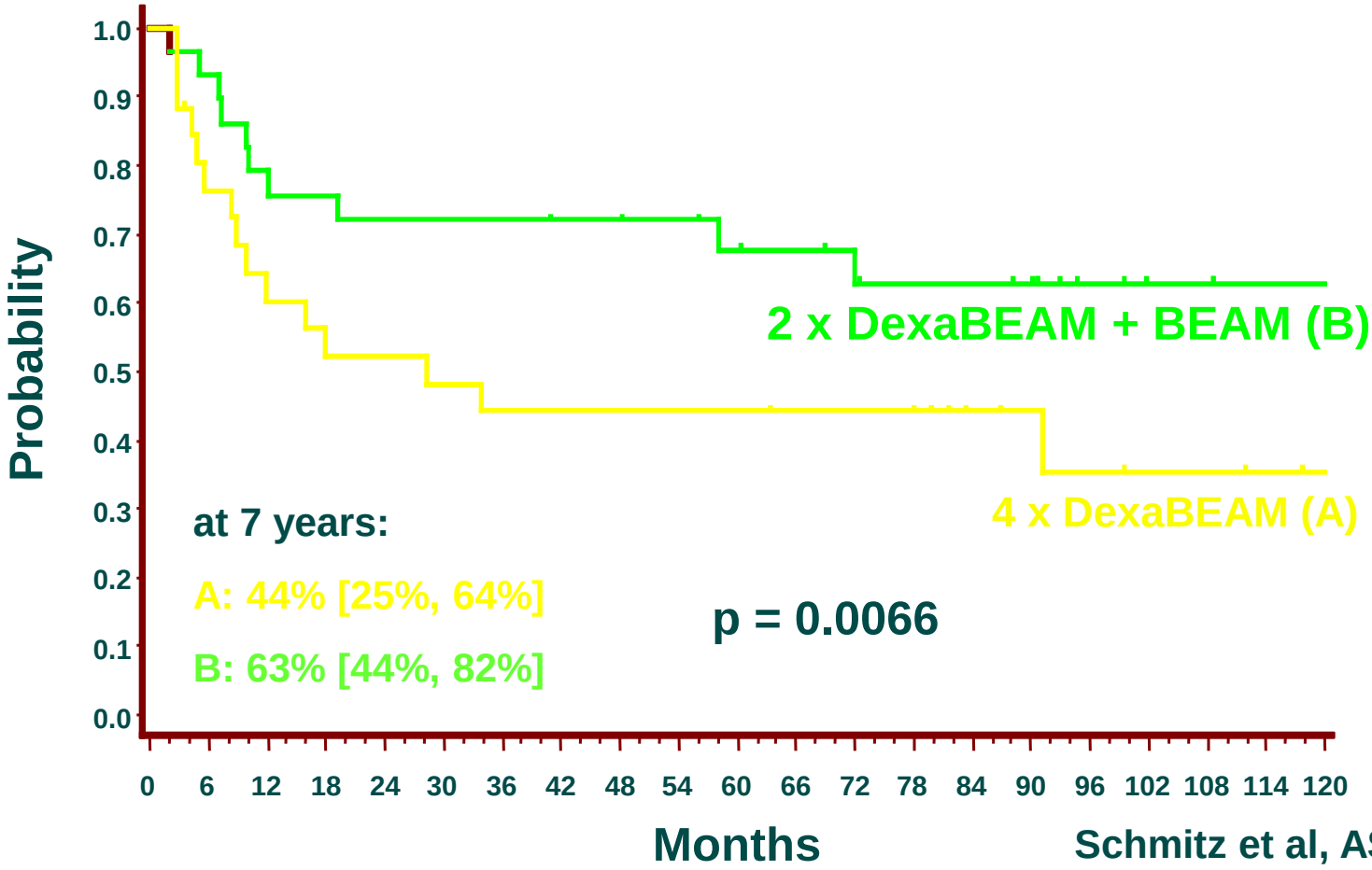
Freedom from Treatment Failure
chemosensitive patients after early relapse



Schmitz et al, ASCO 2005

Freedom from Treatment Failure

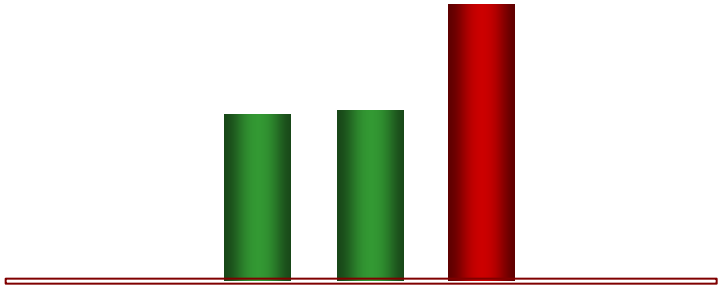
chemosensitive patients after late relapse



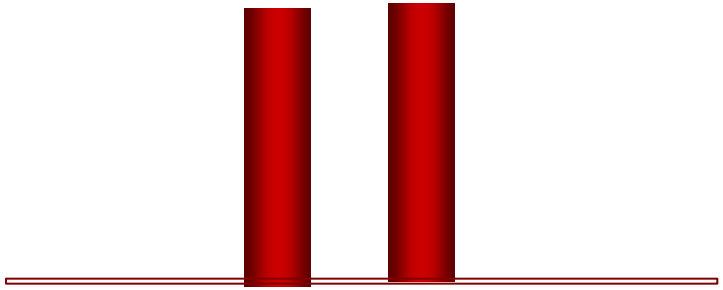
Schmitz et al, ASCO 2005

Dose-intensification strategies in relapsed lymphoma

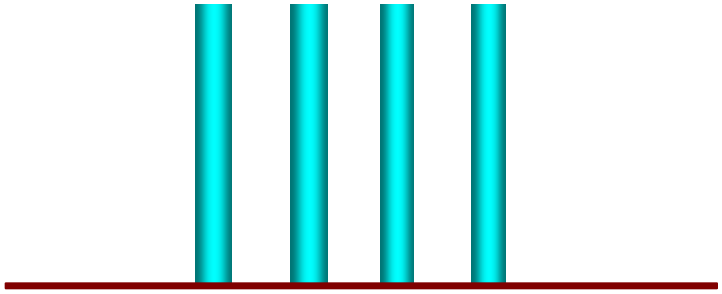
Late intensification



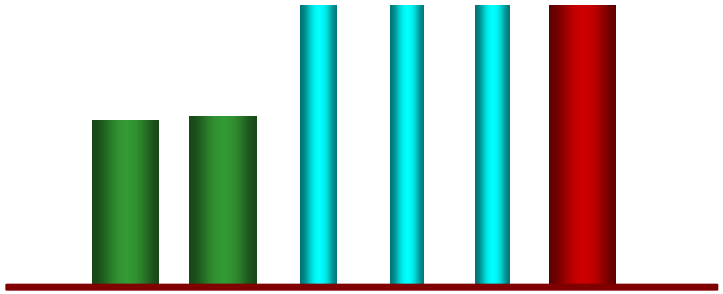
Upfront HD-CT



Sequential HD-CT



Cologne high-dose sequential



Cologne high-dose sequential (HDSC)

Study design

I. Induction: Two cycles DHAP + G-CSF

PR or CR ⟹ HDSC

II. HDSC: High-dose cyclophosphamide + G-CSF

PBSC – apheresis

High-dose methotrexate + vincristine

High-dose etoposide + G-CSF

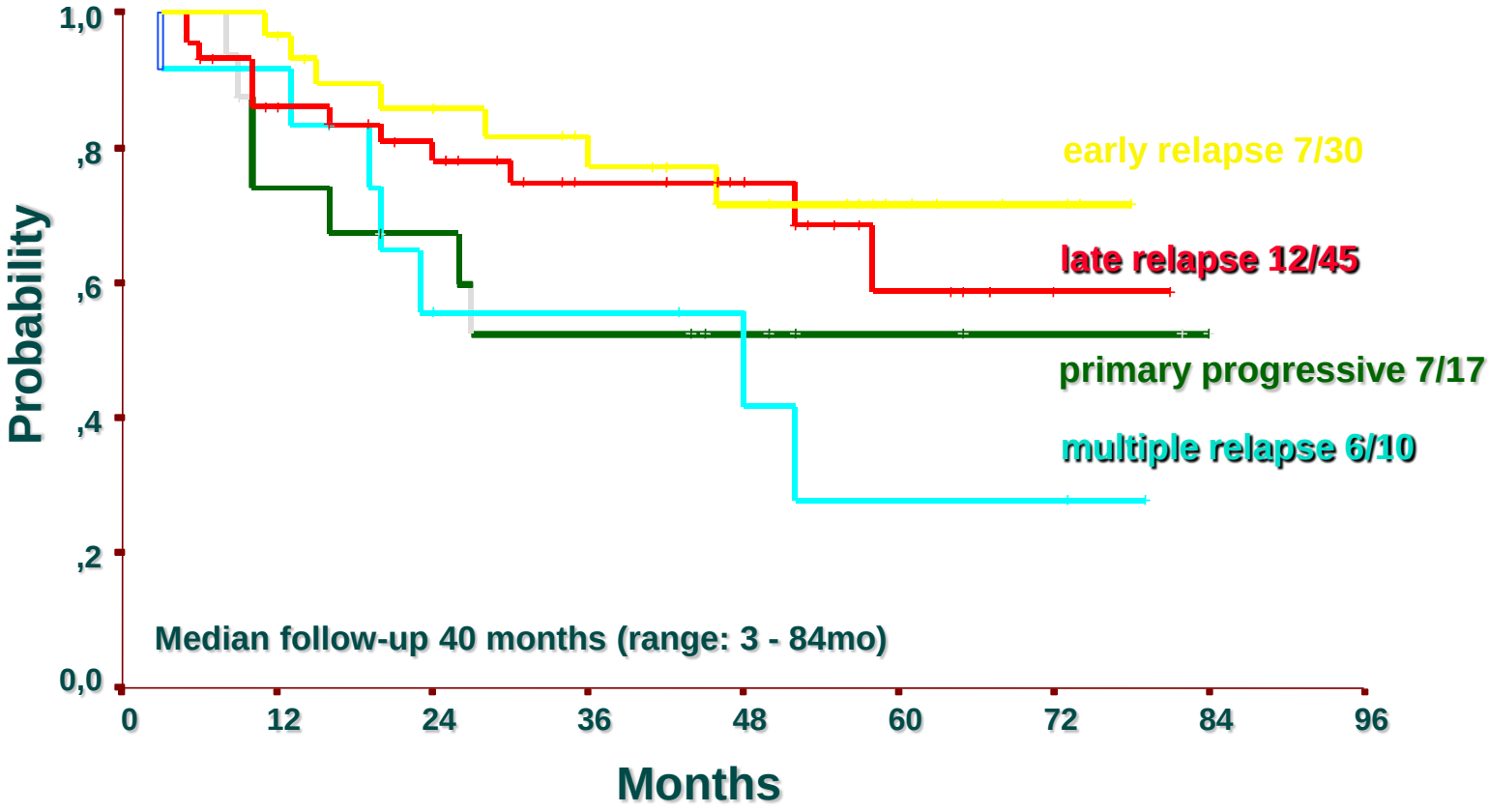
BEAM + PBSCT + G-CSF

Cologne high-dose sequential
Dose

Drug	Dose (mg/m²)
Cyclophosphamide	4000
Methotrexate +	8000
Vincristine	1.4
Etoposide	2000
BCNU	300
Etoposide	1200
Ara-C	1600
Melphalan	140

Cologne high-dose sequential

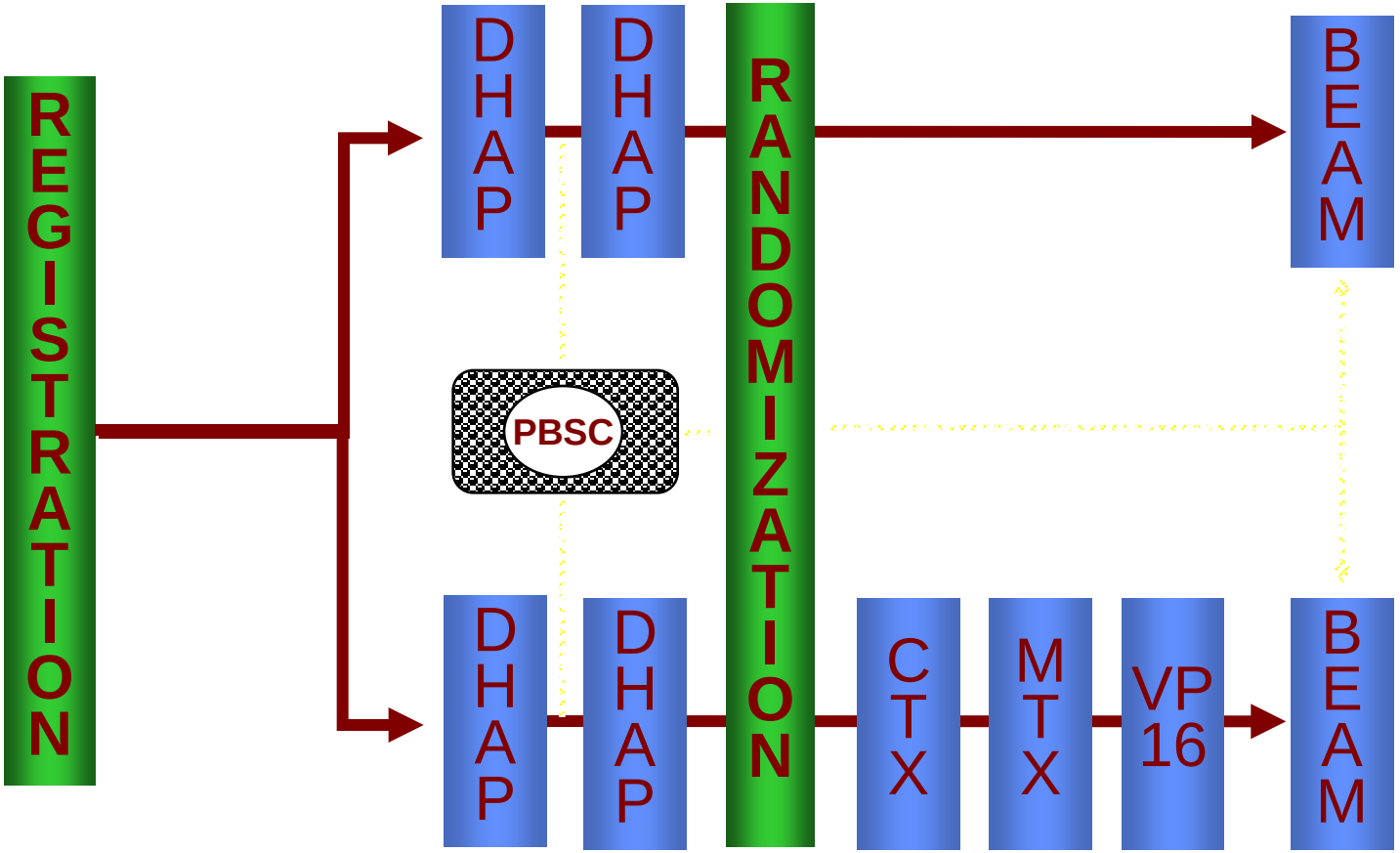
OS: Hodgkin lymphoma (n = 102)



Josting et al, Ann Oncol 2005

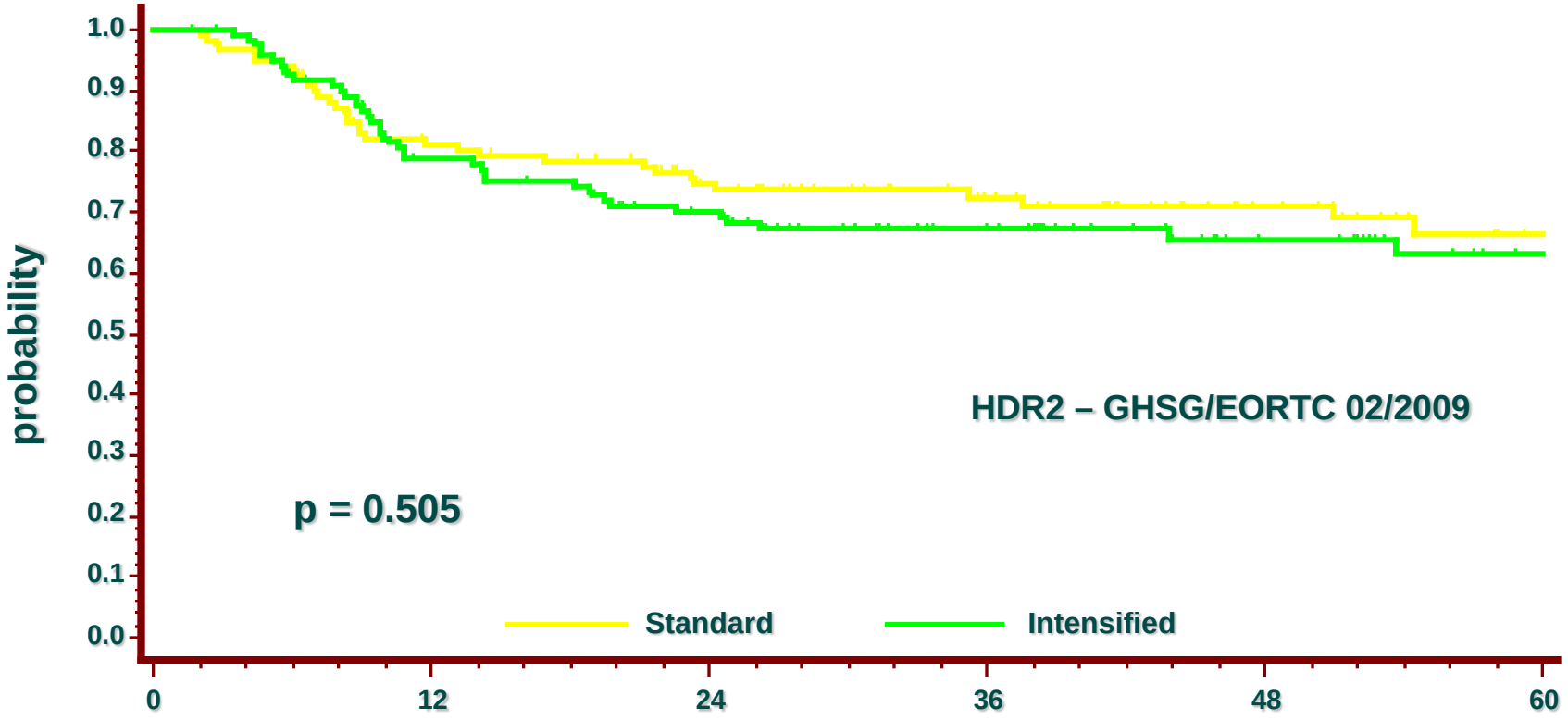
HDR-2: Study design

GHSG, EORTC, EBMT, GEL/TAMO



HDR2 study for patients with relapsed HL

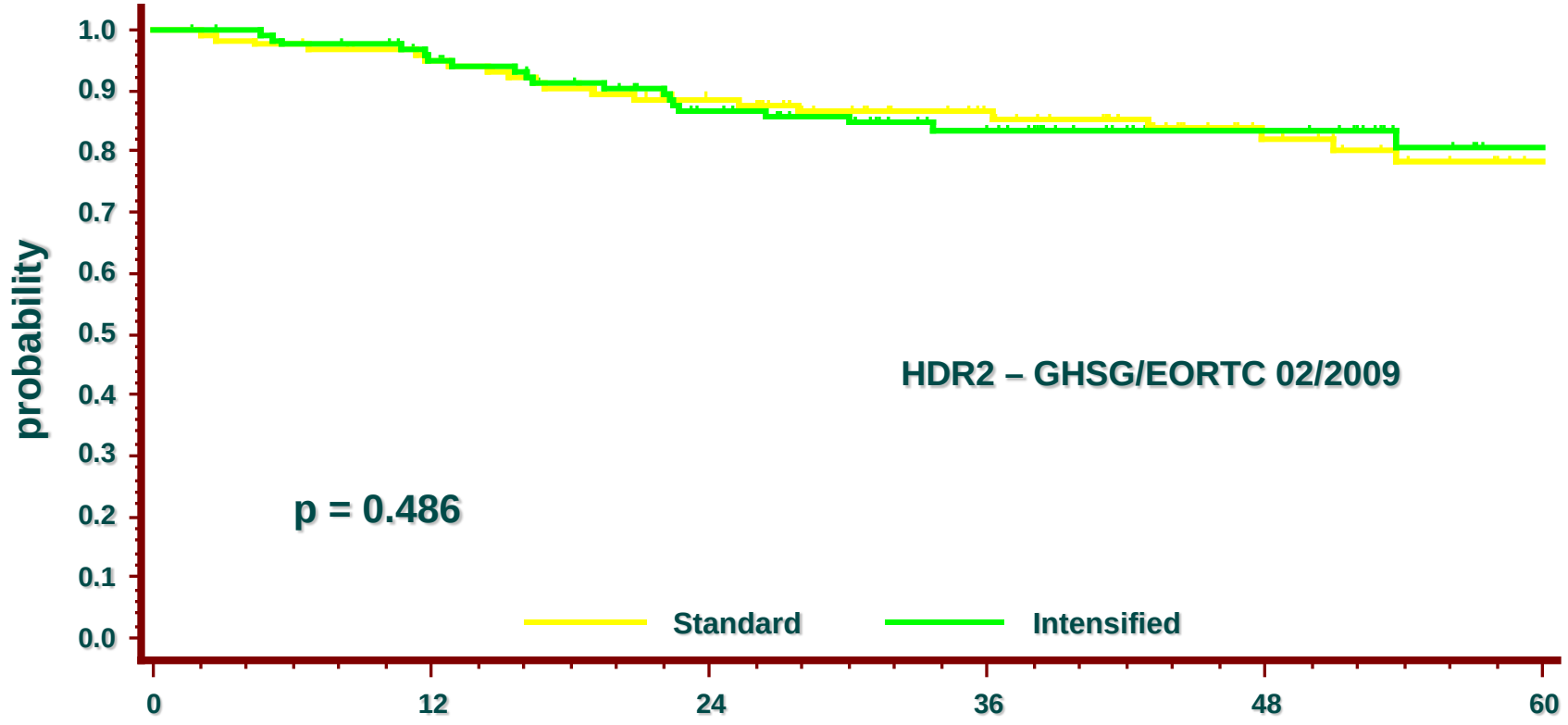
PFS (final analysis 2-09)



Pts. at Risk						
Standard	119	92	75	55	35	22
Intensified	122	90	75	53	34	22

HDR2 study for patients with relapsed HL

OS (final analysis 2-09)



Pts. at Risk						
Standard	119	109	92	69	46	31
Intensified	122	110	91	63	41	26

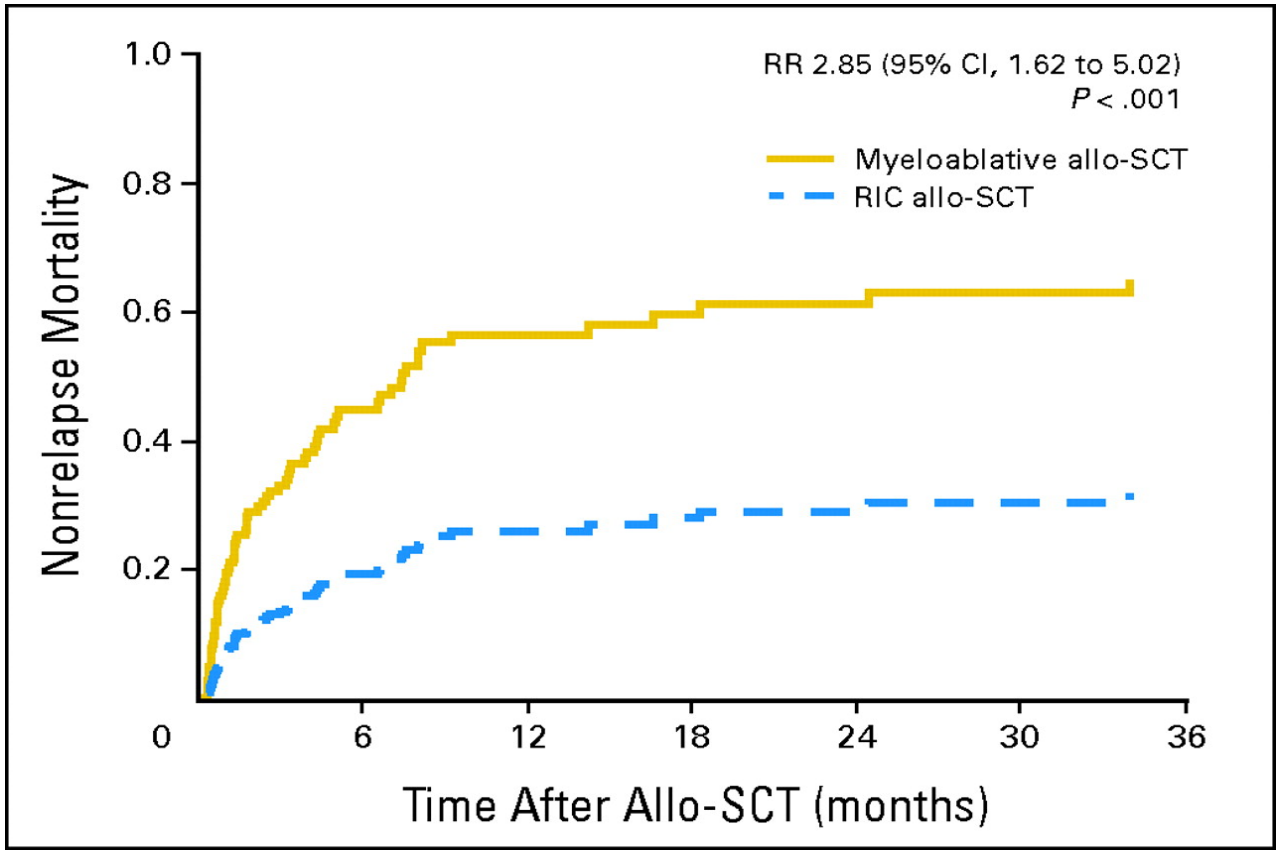
New reagents in early clinical trials
in Hodgkin Lymphoma

- Anti-CD30 (MDX060)
- ^{90}Yttrium-Daclizumab (anti-CD25)
- HCD122 (anti-CD40, Novartis)
- SGN35 (Immunotoxin, Seattle Genetics)
- Bevacicumab (plus Gemcar, Roche)
- Lenalidomide (IMID, Celgene)
- LBH589 (H-Dac Inhibitor, Novartis)
- MGCD103 (H-Dac Inhibitor, Methylgene)

Results with allo SCT

Reference	n	TRM	Outcome
Gajewsky `96	100	56%	15% DFS (2y)
Milpied `96	45	48%	15% PFS (4y)
Anderson `93	53	53%	26% EFS (5y)
Jones `90	21	52%	12% EFS (5y)

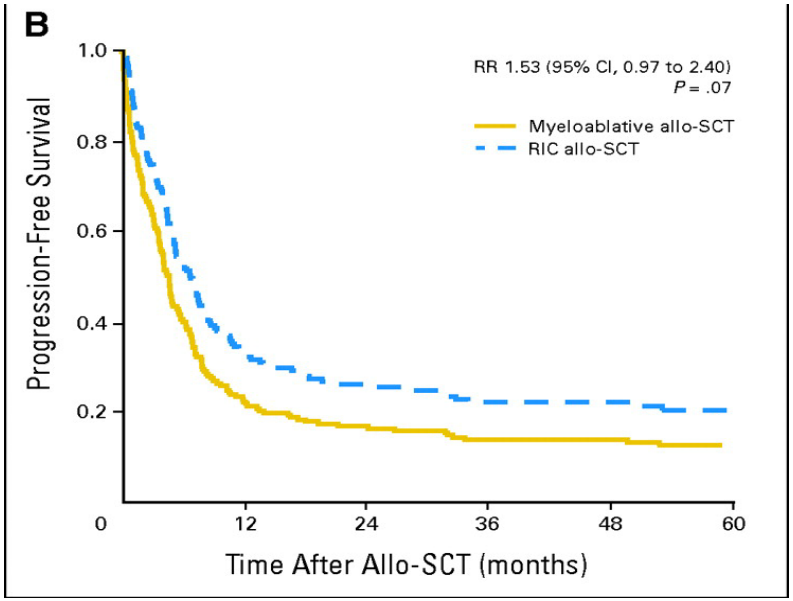
Conventional *vs* RIC allo-SCT
Transplant related mortality

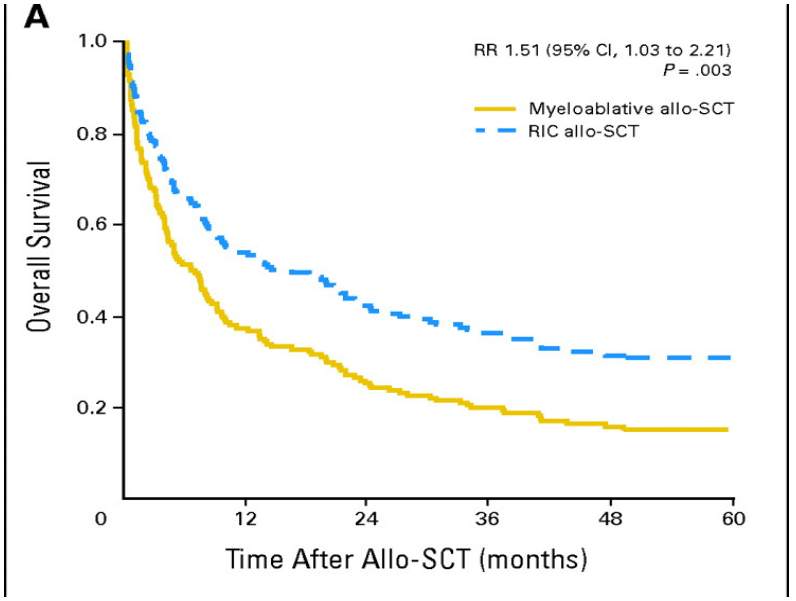


Sureda, JCO, 2008

Conventional *vs* RIC allo-SCT

PFS and OS





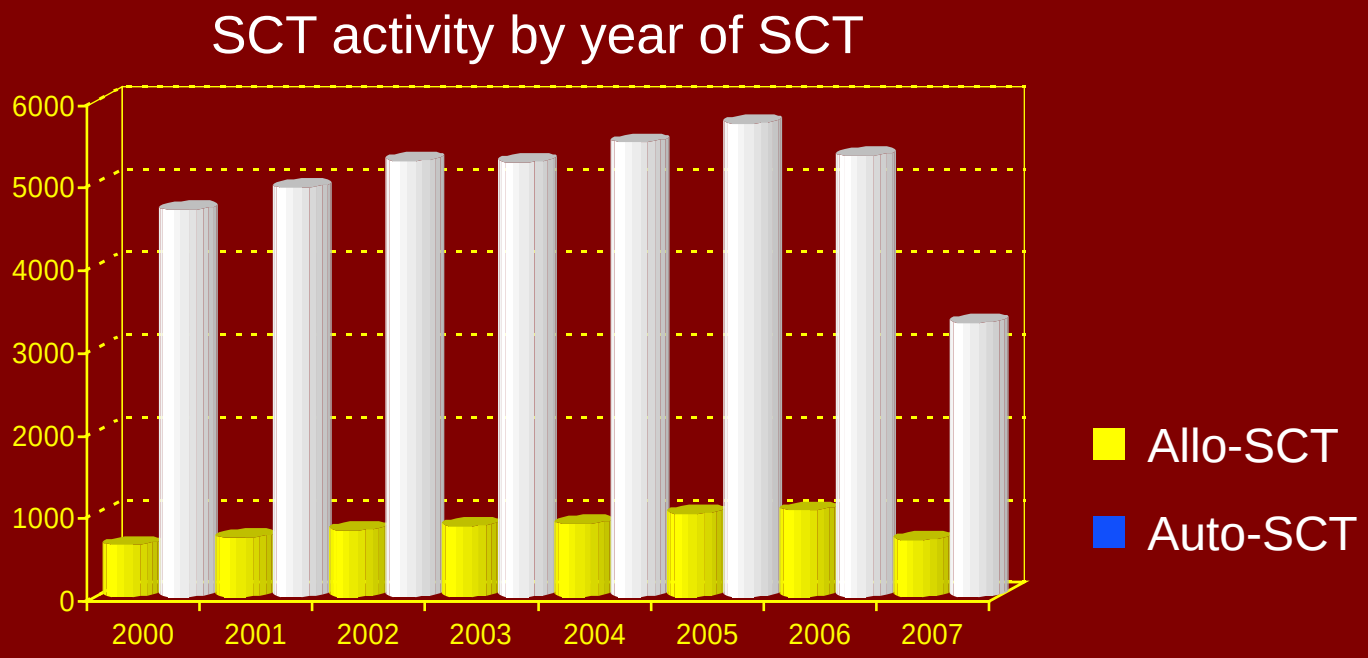
Sureda, JCO, 2008

Conclusions

- 8 x BEACOPP*esc* in advanced stages
- PET good NPV in pts after chemo (HD15)
- HDCT and ASCT for pts with relapse
- Development of new drugs ongoing
- Need better definition of individual risk profiles and reduction of long-term toxicity

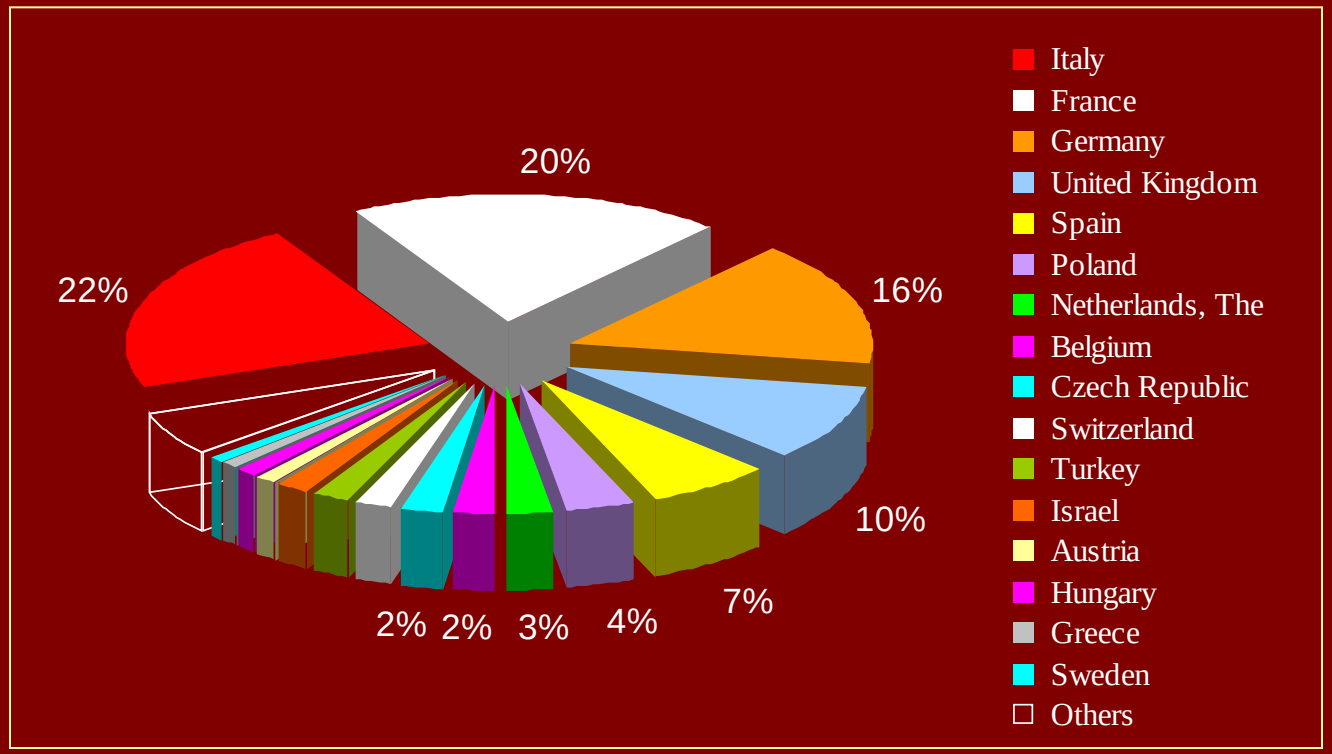
Lymphoma Registry: SCT activity 2000-2007

- Allo-SCT n= 6587 HL n=1407 / NHL n= 5180
- Auto-SCT n= 40008 HL n=9664 / NHL n= 30344

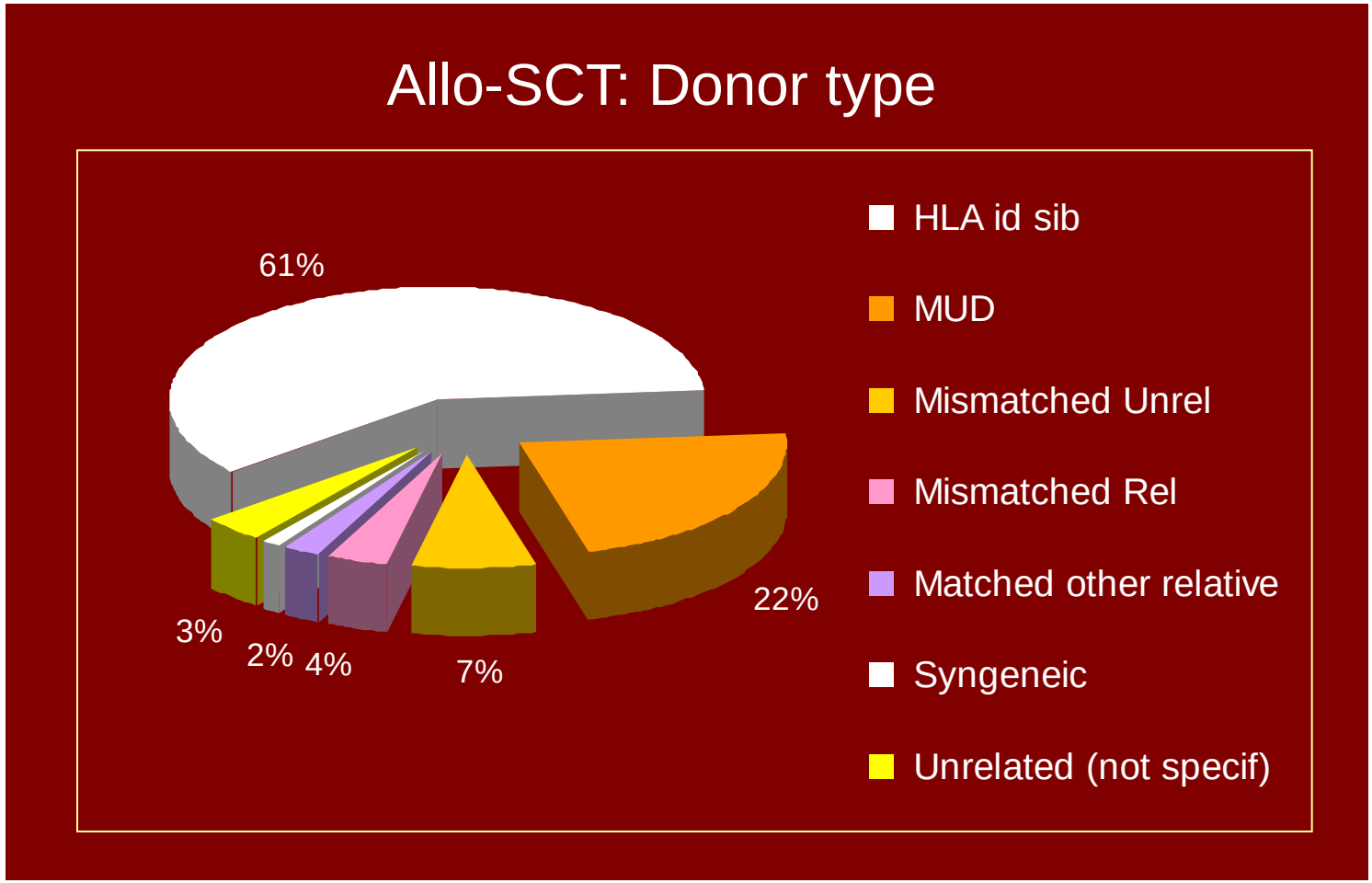


Lymphoma Registry: SCT activity 2000-2007

Activity by country



Lymphoma Registry: SCT activity 2000-2007



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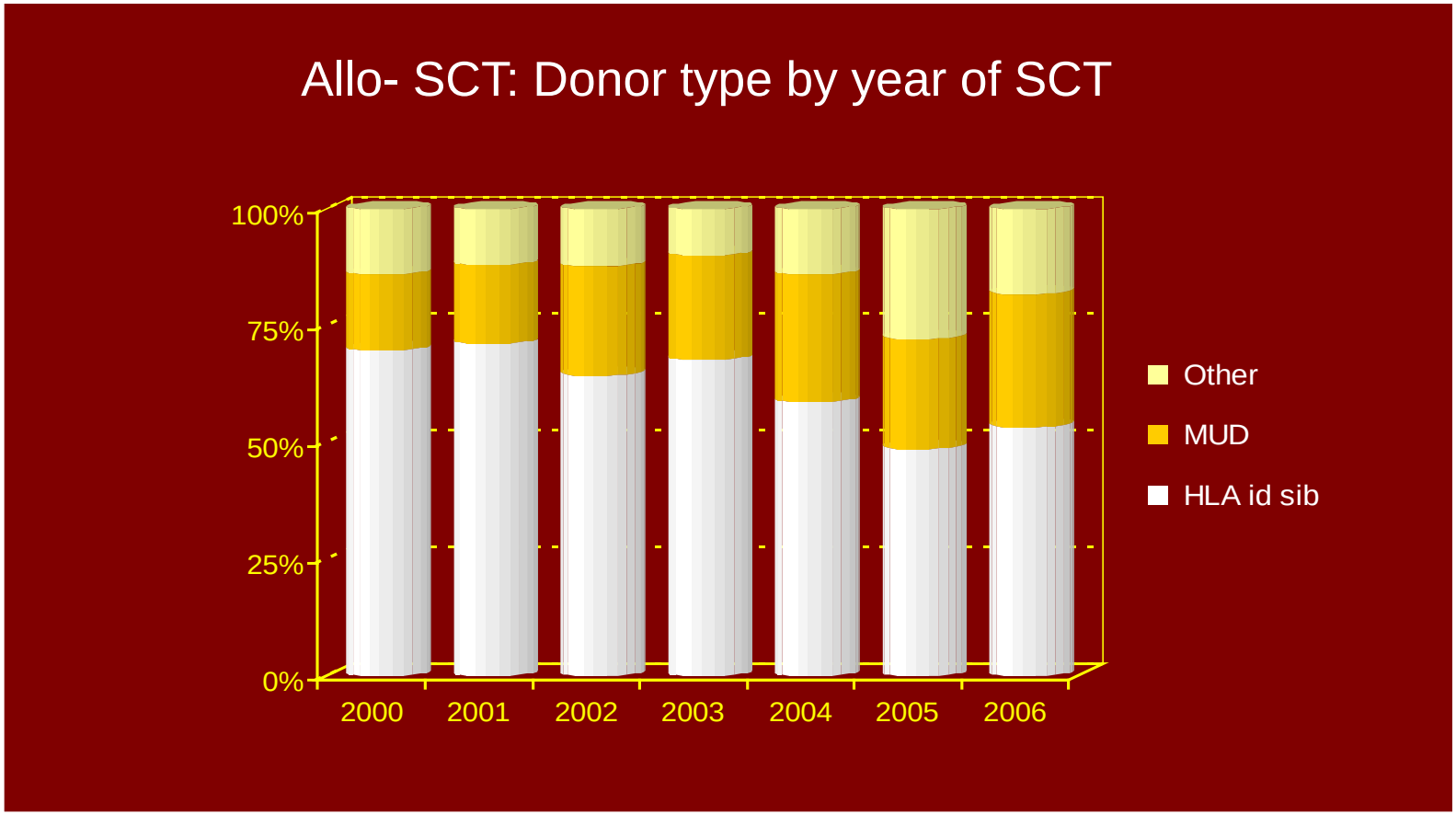
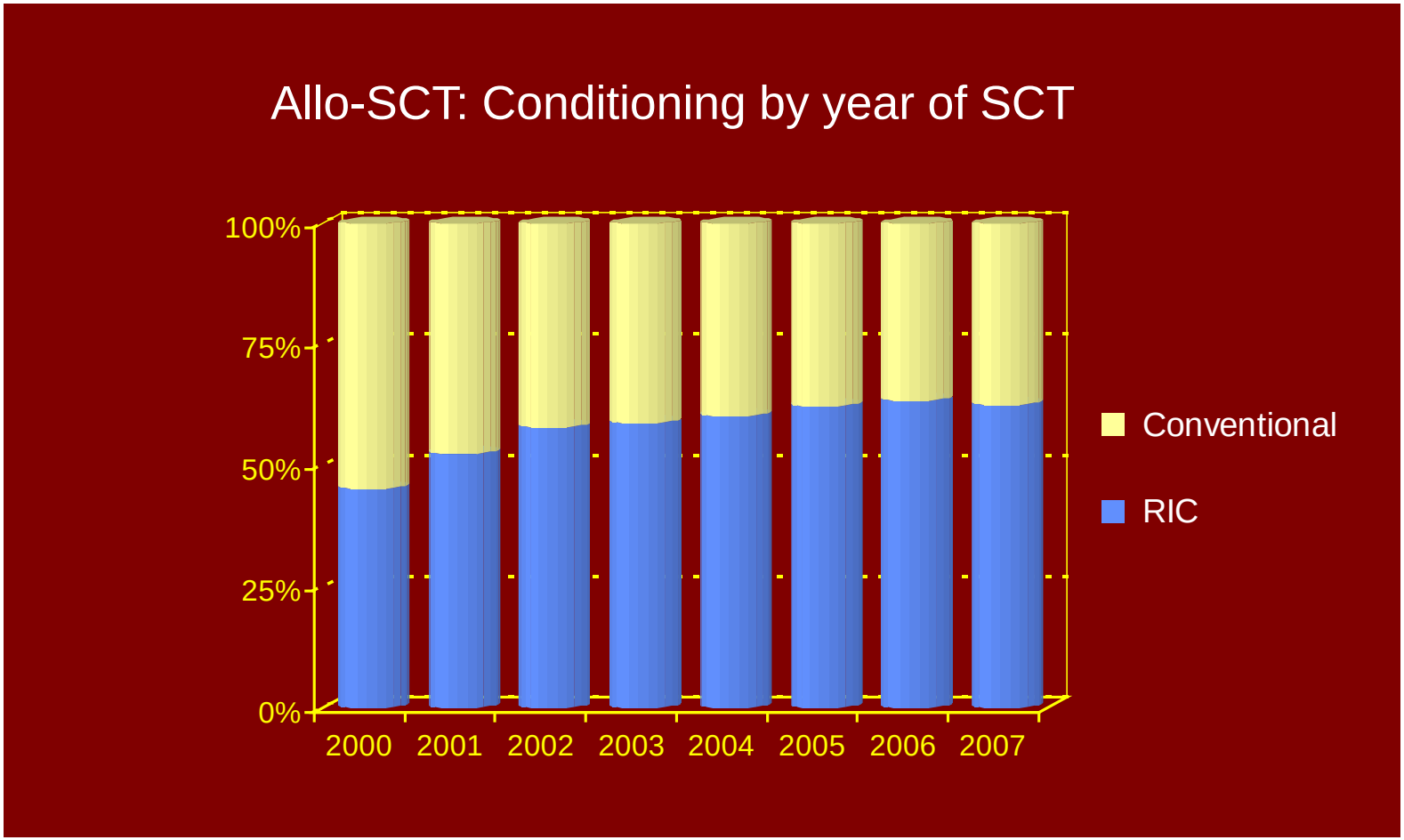


Lymphoma Registry: SCT activity 2000-2007



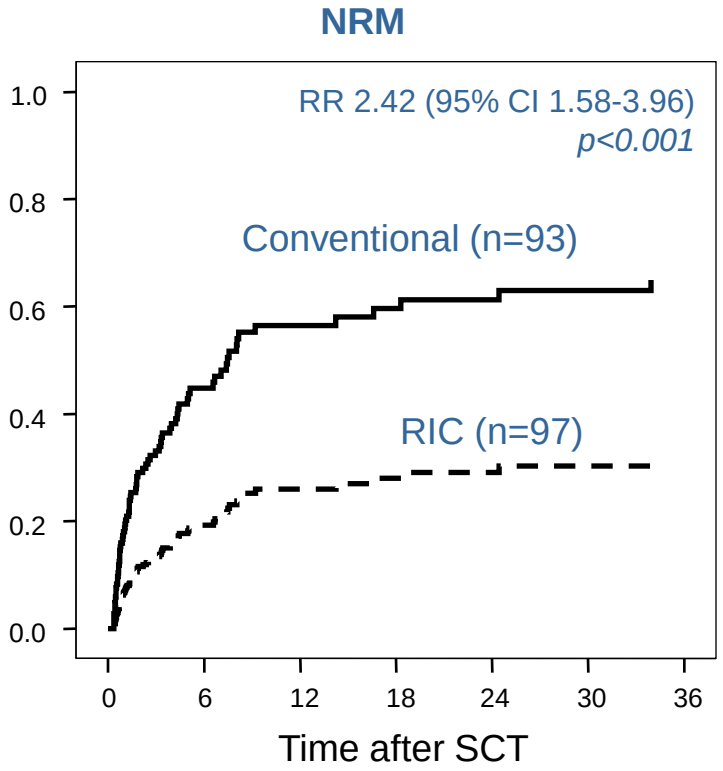
RIC compared with conventional allogeneic SCT in relapsed or refractory Hodgkin's lymphoma

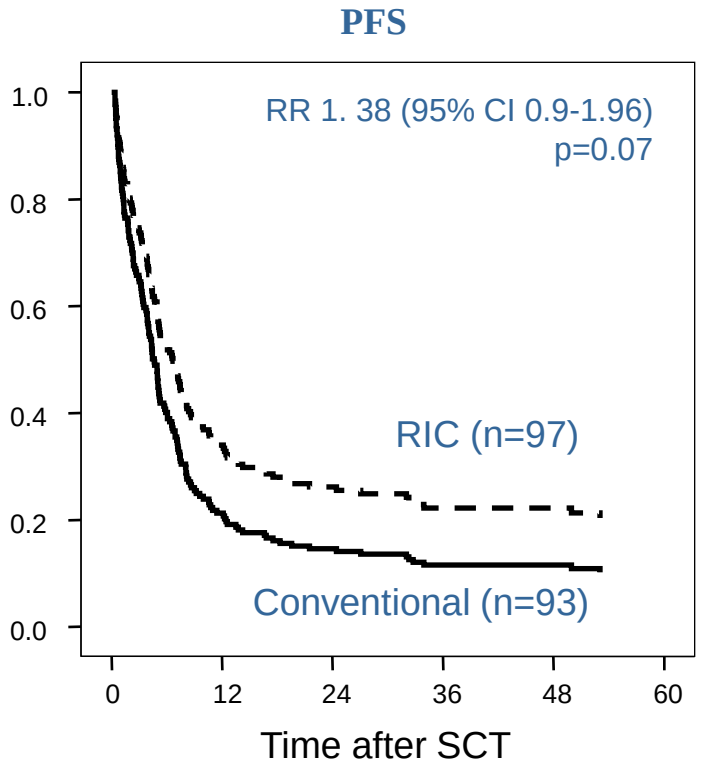
- n=190 1st allo-SCT 1997-2001 / Previous failed ASCT46%
- Male sex 51%; median age 30 y (9-64)

	Conventional 93 (49%)	*RIC* 97 (51%)	*p value*
Period of SCT: 1997-1998 / 1999-2001	*42% / 58%*	*16% / 84%*	*< 0.001*
Previous ASCT	*44%*	*61%*	*0.03*
Diagnosis – Allo-SCT (months)	*31 (7 – 181)*	*40 (4 – 242)*	*0.01*
Donor: HLA matched sib./MUD/Others	*76% / 10% / 14%*	*78% / 12 % / 9%*	*n.s.*
Stem cell source: BM /PB	*40% / 60%*	*15% / 85%*	*<0.001*
Chemorefractory disease at SCT	*54%*	*56%*	*n.s.*
Median Follow–up (months)	*50 (12 - 94)*	*54 (17 – 109)*	*n.s.*

Sureda et al. J Clin Oncol. 2008; 26:455-62

RIC compared with conventional allogeneic SCT in relapsed or refractory Hodgkin's lymphoma





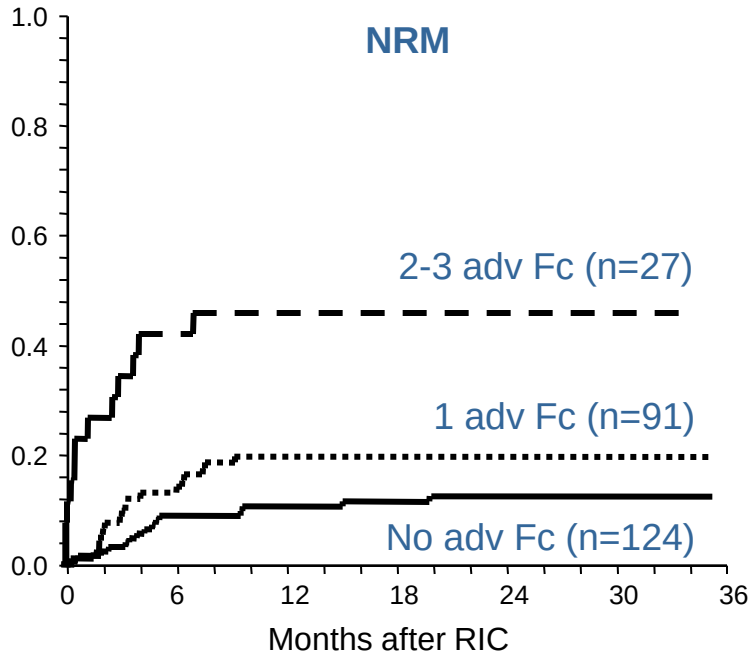
Estimate of the NRM and PFS based on a COX model, adjusted by all covariates with impact on the outcomes. RR and p values from multivariate Cox model.

Sureda et al. J Clin Oncol. 2008; 26:455-62

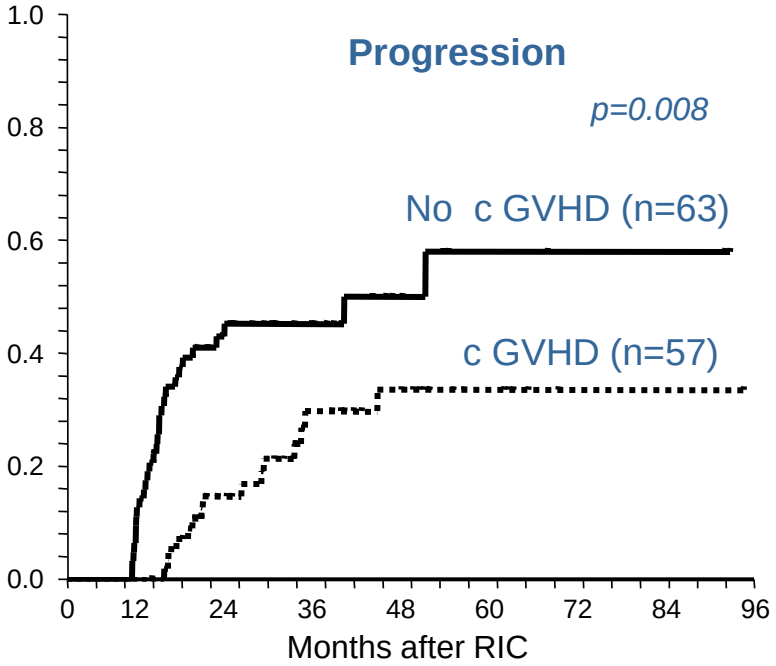
RIC Allo-SCT for Hodgkin's disease: Identification of prognostic factors predicting outcome

Adverse Fc for NRM:

- age ≥ 45 years
- poor performance
- chemorefract disease

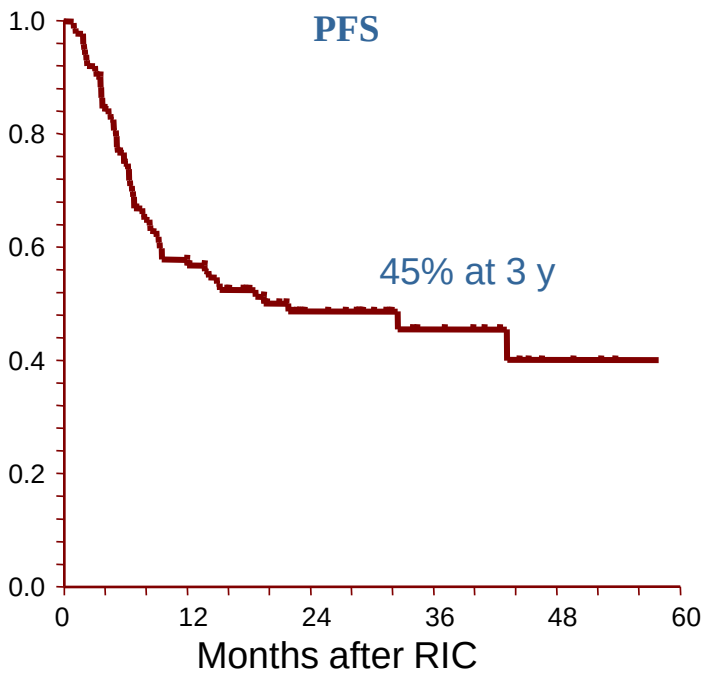


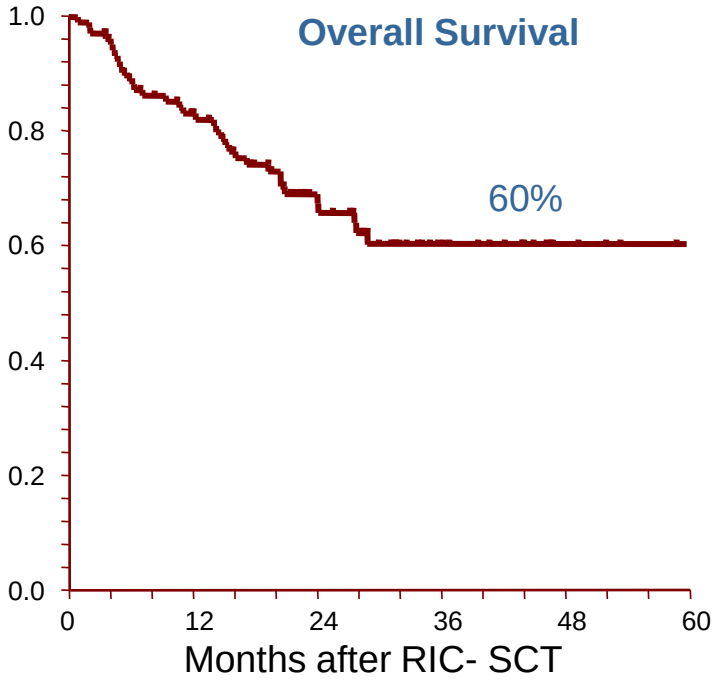
Risk of disease progression after 9 months of RIC according to the development of cGVHD (Landmark analysis)



Robinson et al. J Clin Oncol (submitted)

RIC Allo-SCT for Hodgkin's disease: Identification of prognostic factors predicting outcome

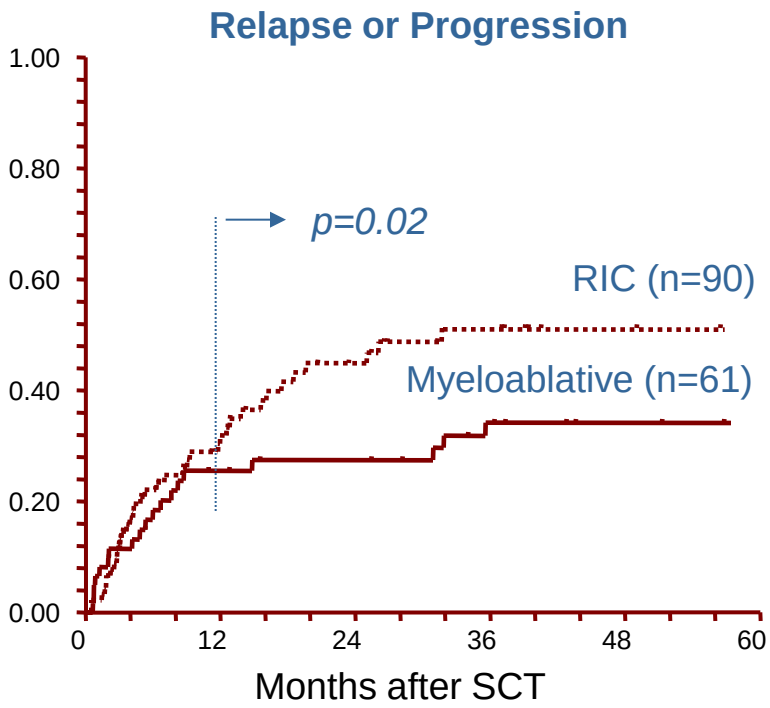


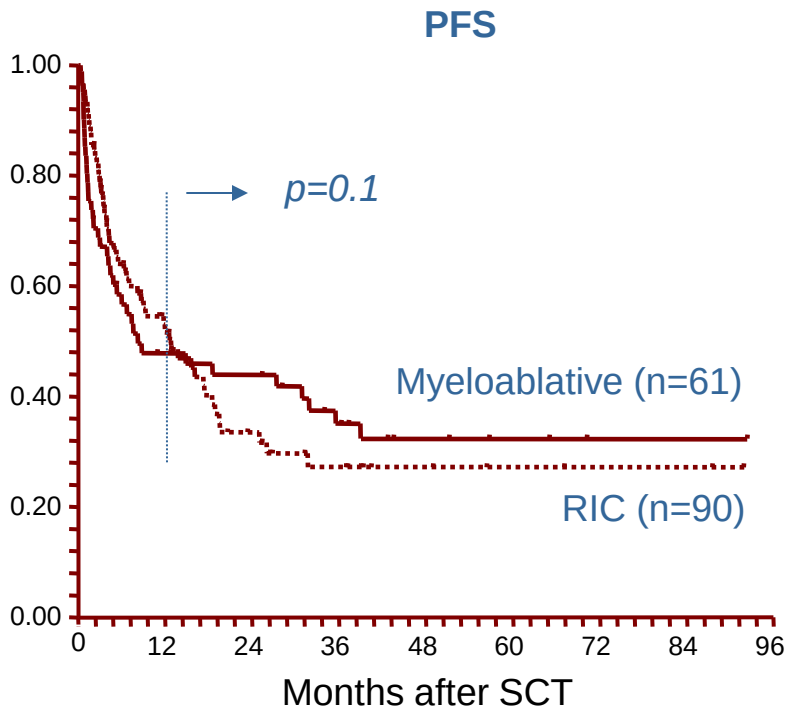


PFS and OS for patients with chemosensitive disease and good performance status at SCT treated with a RIC SCT in the period 2002-2005 (n=104).

Robinson et al. J Clin Oncol (submitted)

Allogeneic Hematopoietic SCT in Children and Adolescents With Recurrent Hodgkin's Lymphoma





RIC regimens are associated with a lower NRM the first period after Allo-SCT (p=0.1), but are followed subsequently by an increased risk of progression, with a trend to a lower PFS.

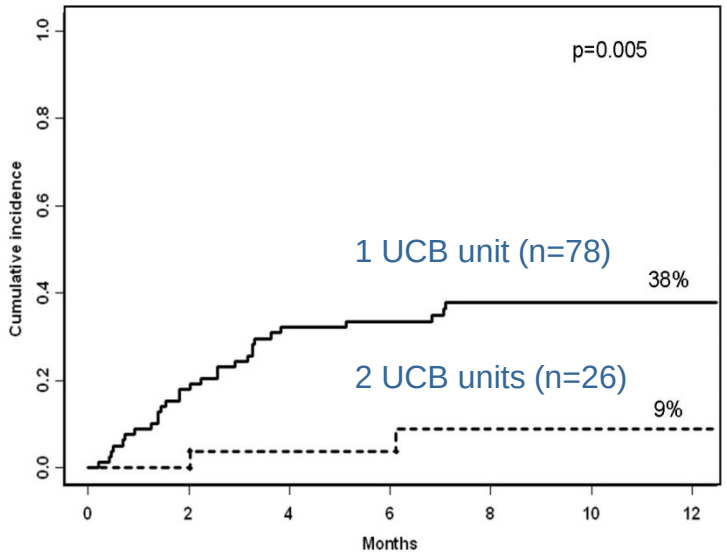
Claviez et al. J (in preparation)

Analysis of risk factors for outcomes after UCB transplantation in adults with lymphoid malignancies

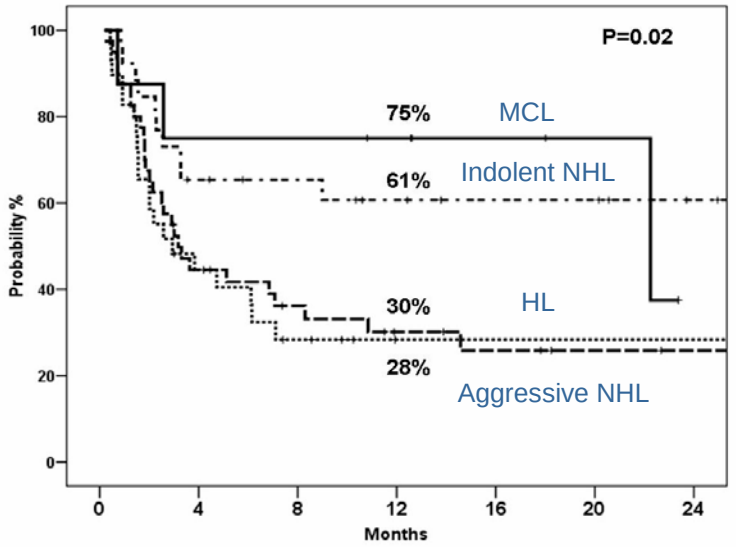
- n=104 Unrelated CBT 1996-June 2007
- NHL n=62 / HL n=29 / CLL n=13
- Neutrophil engraftment at day 60: 85%
- a GVHD at day 100: 24%

- NRM at 1 year: 28%
- Relapse or prog at 1 y: 31%
- PFS at 1 y: 41%
- Overall survival at 1 y: 47%

Relapse or progression



PFS



Arrais et al. (Submitted)