SCIENTIFIC SYMPOSIUM OF THE WBMT 2013

Salvador-Bahia, Brazil

HCT in lymphoma

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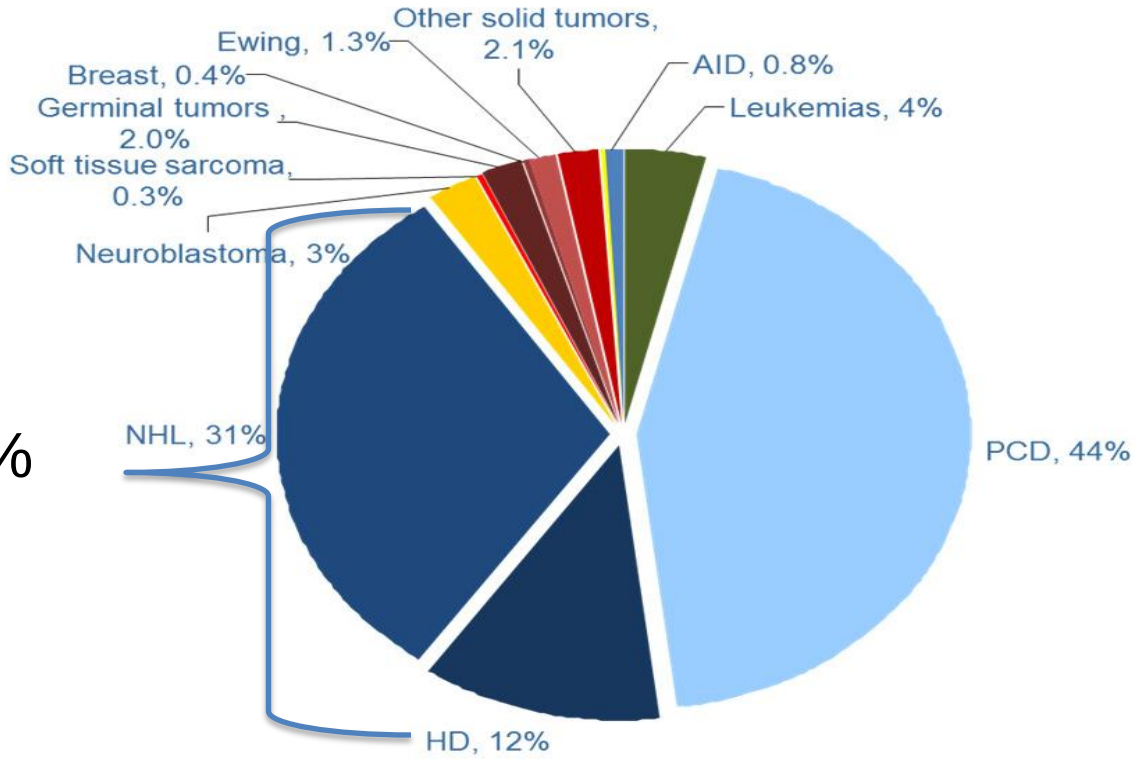
Outline

- Introduction and epidemiology
- Role of HSCT in:
  - Diffuse large B-cell lymphoma (DLBCL)
  - Folicular lymphoma (FL)
  - Mantle cell lymphoma (MCL)
- Conclusions

01 Non Hodgkin Lymphoma Epidemiology

- Incidence: 22.4 cases / 100.000
- 50 % pts. are under the age of 64 y.
- Initial treatments responses rates are high
- Treatment response after relapse/refractory disease ??
- HSCT has an important role in the management of relapsing and high risk patients

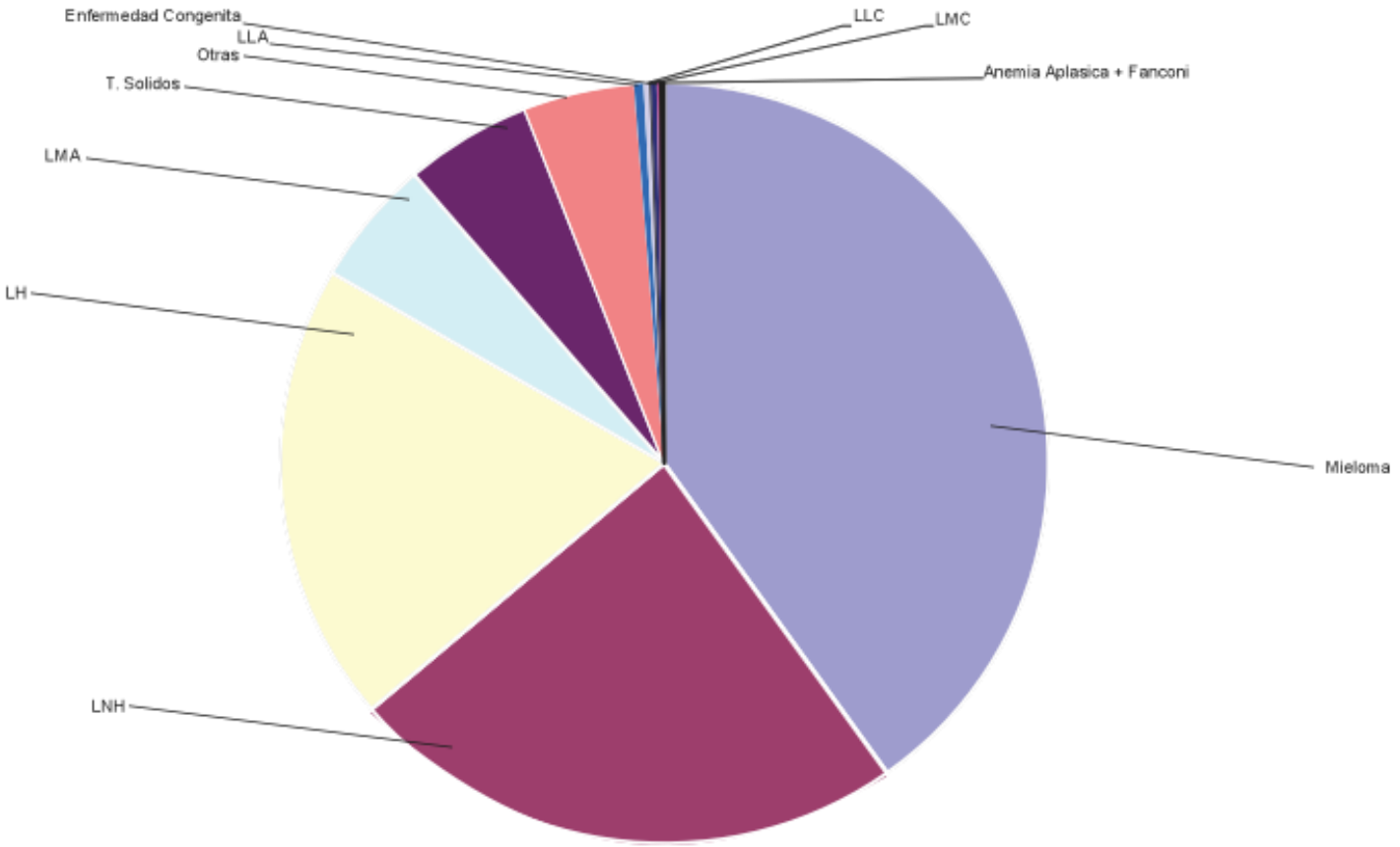
01 Indications for autologous HSCT in Europe in 2010



43%

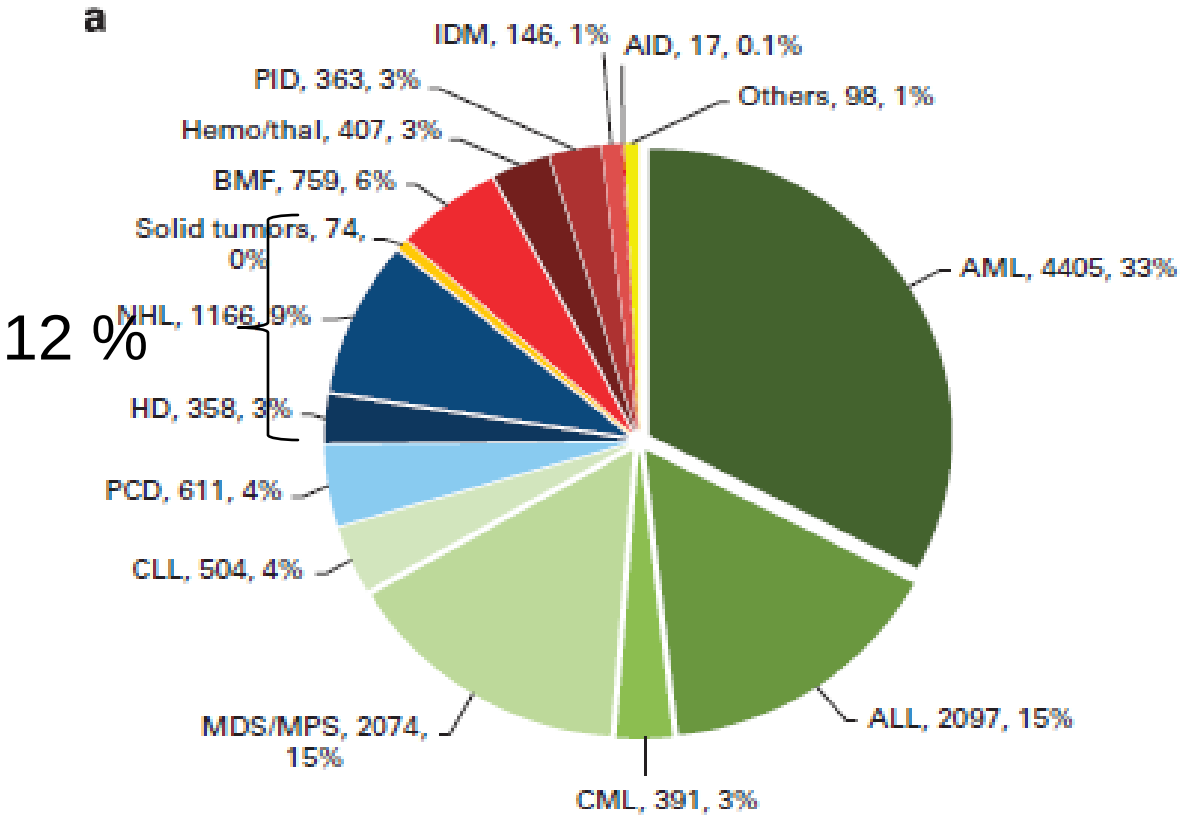
The EBMT activity survey: 1990–2010. Bone Marrow Transplant. 2012;47(7):906-23

01 Indications for autologous HSCT Argentina in 2010



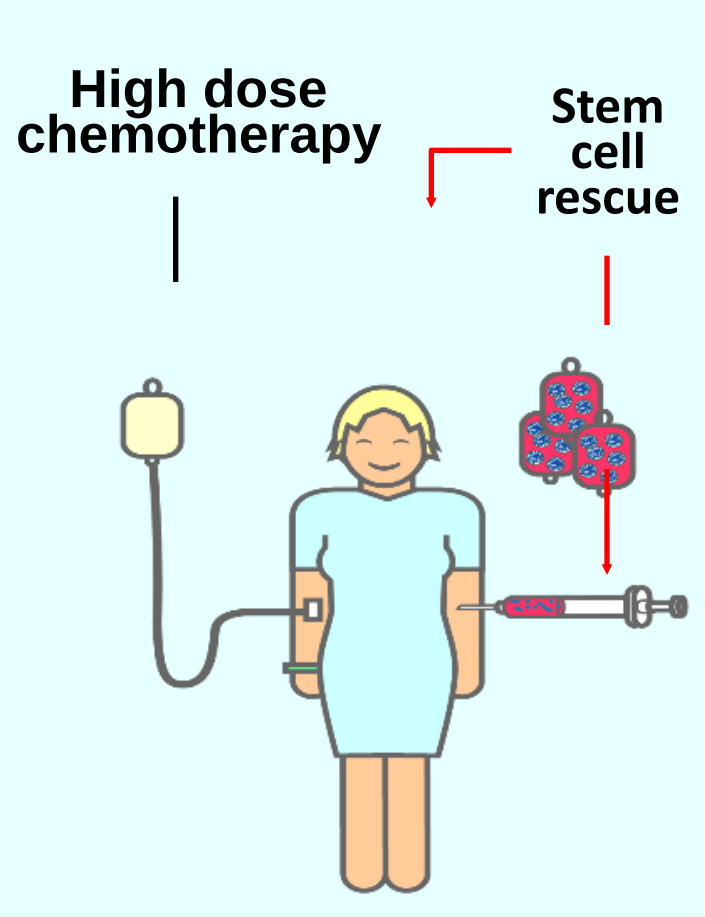
01 Indications for allogeneic HSCT in Europe in 2011

EBMT activity survey 2011
JR Passweg *et al*



12 %

01 Autologous SCT



Shortens time to hematological recovery

- ↓ infections
- ↓ hospitalization
- ↓ mortality

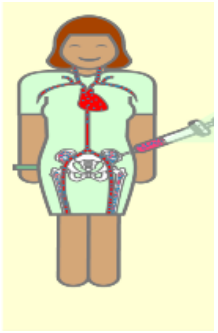
Enables administration of very intensive chemotherapy regimens

⇓

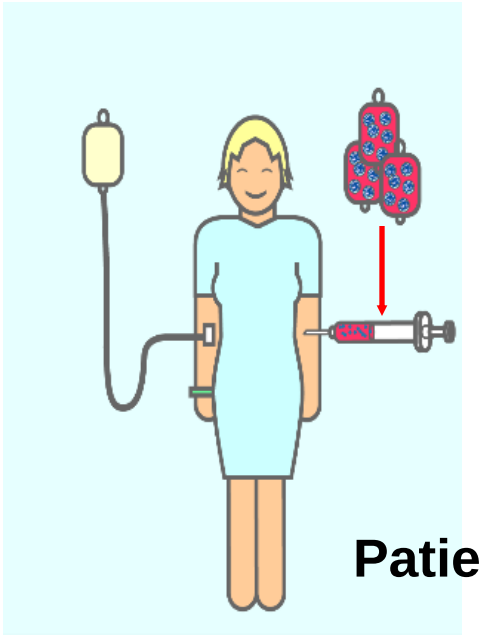
↑ efficacy if chemosensitive disease

01 Allogeneic SCT

Donor



High dose chemotherapy



Patient

1. High dosechemotherapy

- Anti-tumor effect
- Bonemarrowspace
- Avoidrejection
- Immunosupression

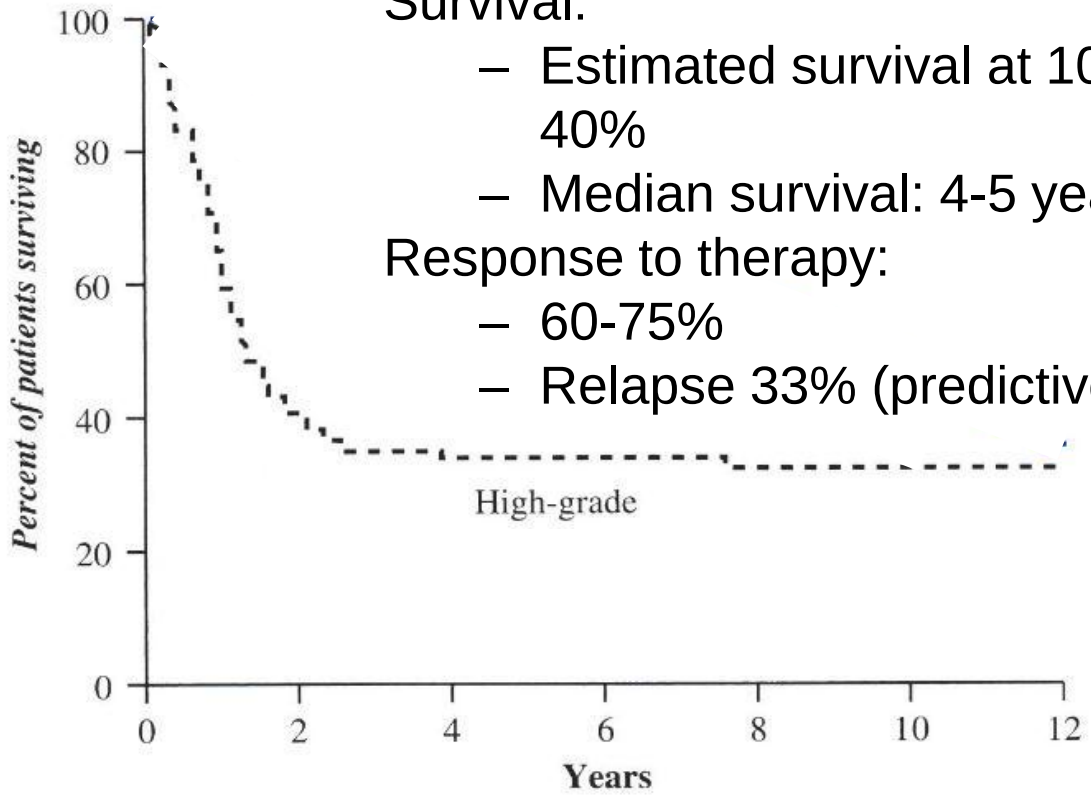
2. Infusion of stem cells

- Stem cell rescue
- Immune therapy
  - Graft-versus-host disease
  - Graft-versus-tumor effect

02

Role of SCT in DLBCL

Natural History



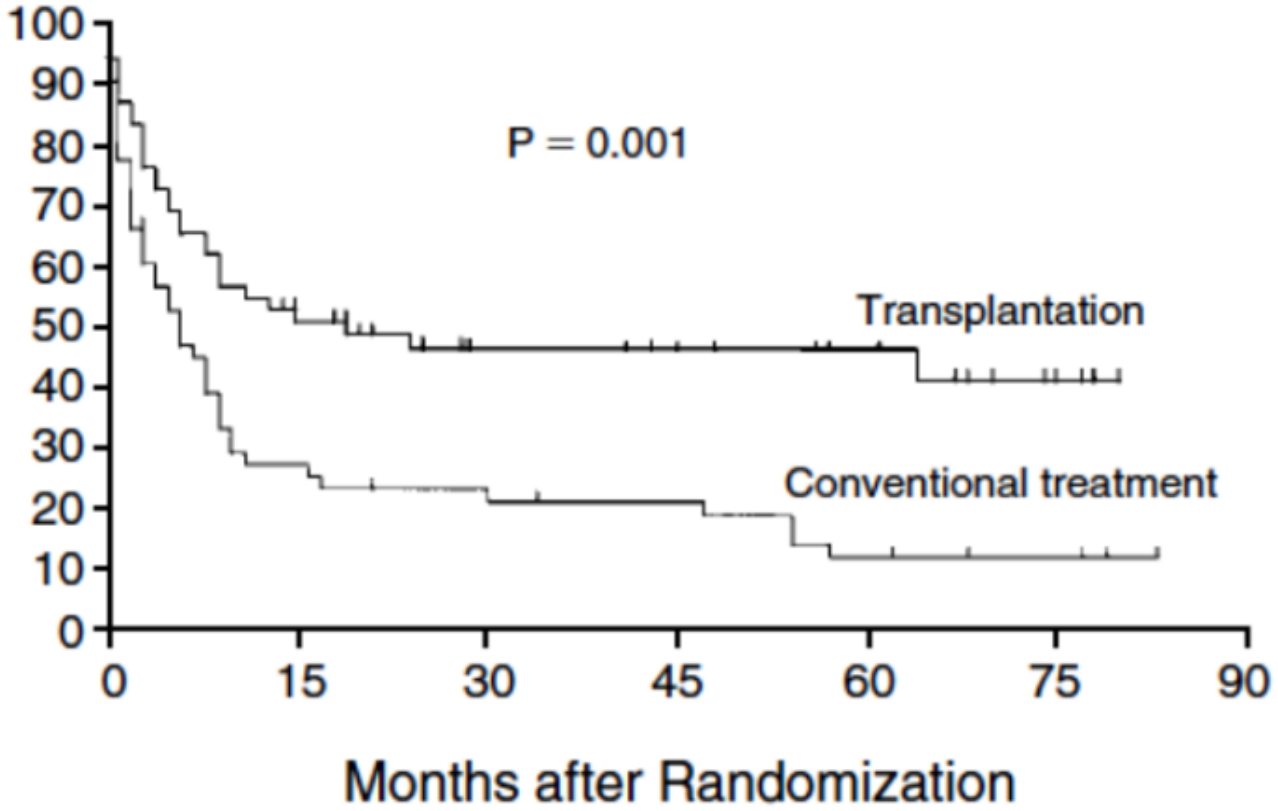
Survival:

- Estimated survival at 10 years: 30-40%
- Median survival: 4-5 years

Response to therapy:

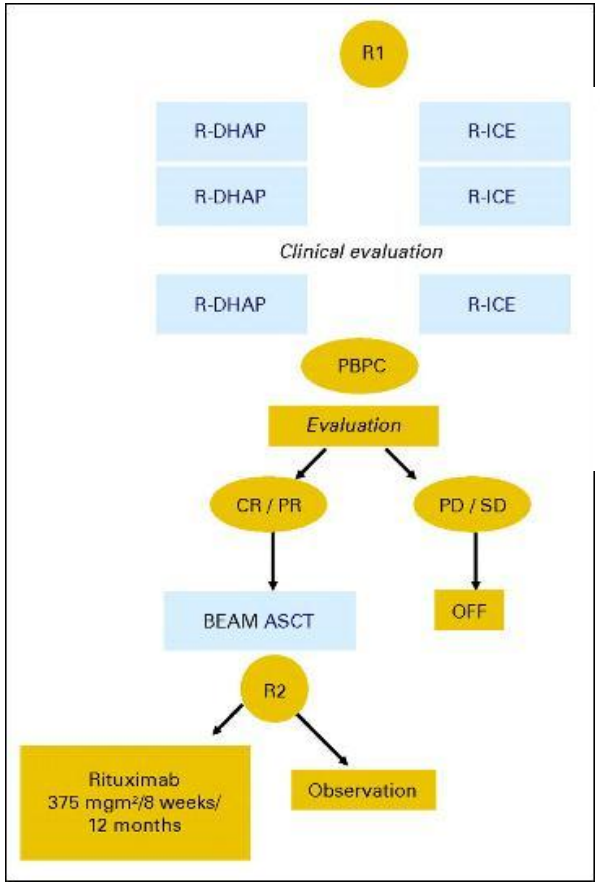
- 60-75%
- Relapse 33% (predictive with IPI)

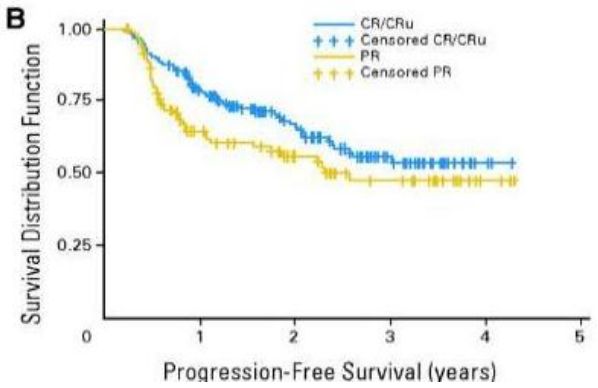
02 Role of SCT in DLBCL
Salvage therapy: CHT vs ASCT

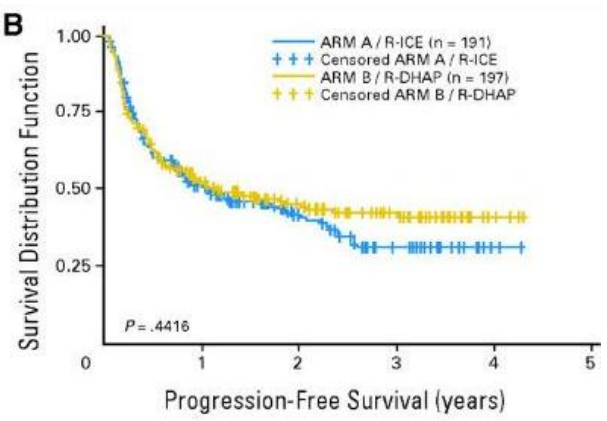


Philip T, et al. N Engl J Med. 1995; 333:1540-1545

02 Role of SCT in DLBCL
Salvage therapy: CHT + ASCT







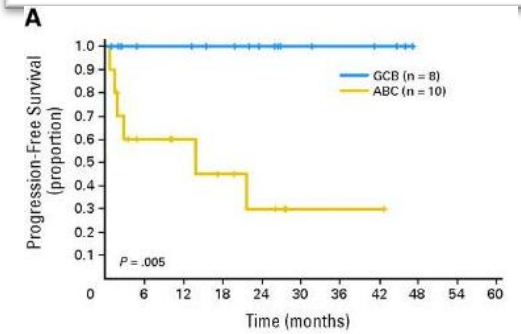
Gisselbrecht C et al. JCO 2010;28:4184-4190

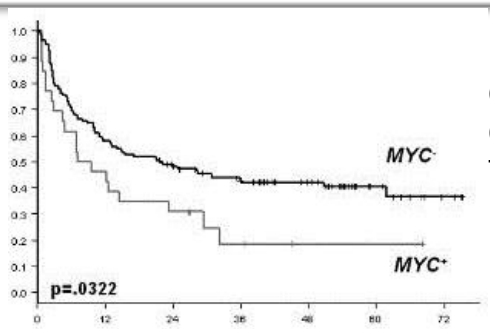
02 Risk factors in salvage CHT + ASCT

Table 3. Response Rate and Survival According to Prognostic Factors

Factor	Total No. of Patients	Response CR/CRu/PR			3-Year Event-Free Survival		3-Year Overall Survival	
		No. of Patients	%	*P*	%	*P*	%	*P*
All patients	398	246	63		31		50	
CR/CRu		148	38		51		70	
Prior rituximab								
No	147	122	83	< .001	47	< .001	66	< .01
Yes	244	124	51		21		40	
Relapse, > 12 months	160	140	88	< .001	45	< .001	64	
Refractory, < 12 months	228	106	46		20		39	< .001
saaIPI								
< 2	224	160	71	< .001	40		62	
> 1	146	76	52		18	< .001	32	< .001

Abbreviations: CR, complete response; CRu, unconfirmed complete response; PR, partial response; saaIPI, secondary age-adjusted International Prognostic Index.





Gisselbrecht C. J ClinOncol. 2010;28:4184-4190
Cuccuini W et al. Blood 2012;119:4619-4624
Thieblemont C et al. JCO 2011;29:4079-4087

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02 Role of SCT in DLBCL Novel conditioning regimens

BEAM-CBV is standard of care: <5% mortality + low morbidity

Alternatives

- TBI-containing regimens
- ^{131}I Tositumomab + BEAM
- ^{90}Y ibritumomab tiuxetan +BEAM

02 Role of SCT in DLBCL
Novel conditioning regimens

TBI-containing regimens

	Odds Ratio	95% CI	P-value
Cataracts			
Hodgkin's lymphoma	1.1	0.4-3.0	0.79
TBI	4.9	1.5-15.5	0.007
Female	1.1	0.6-2.3	0.72
Dry Mouth			
Hodgkin's lymphoma	0.5	0.2-1.4	0.17
TBI	3.4	1.1-10.4	0.03
Female	1.5	0.7-3.1	0.26

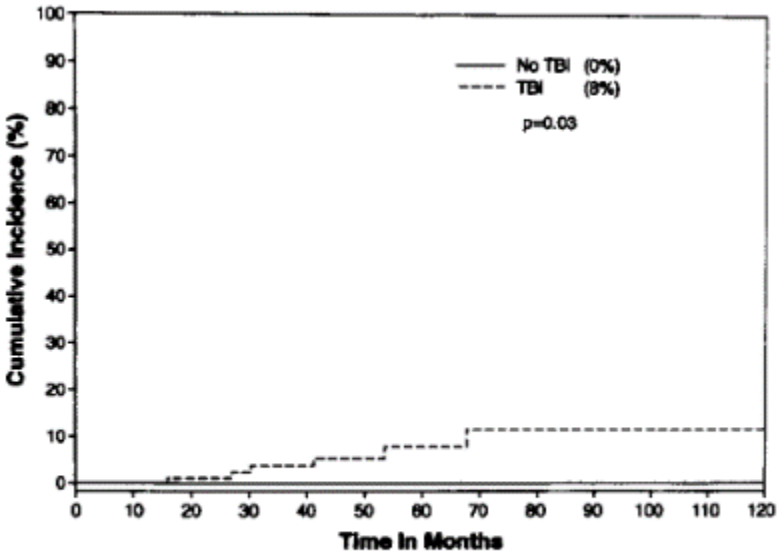


Fig 3. Cumulative incidence of MDS/AML posttransplant in NHL patients who received TBI and those who did not receive TBI.

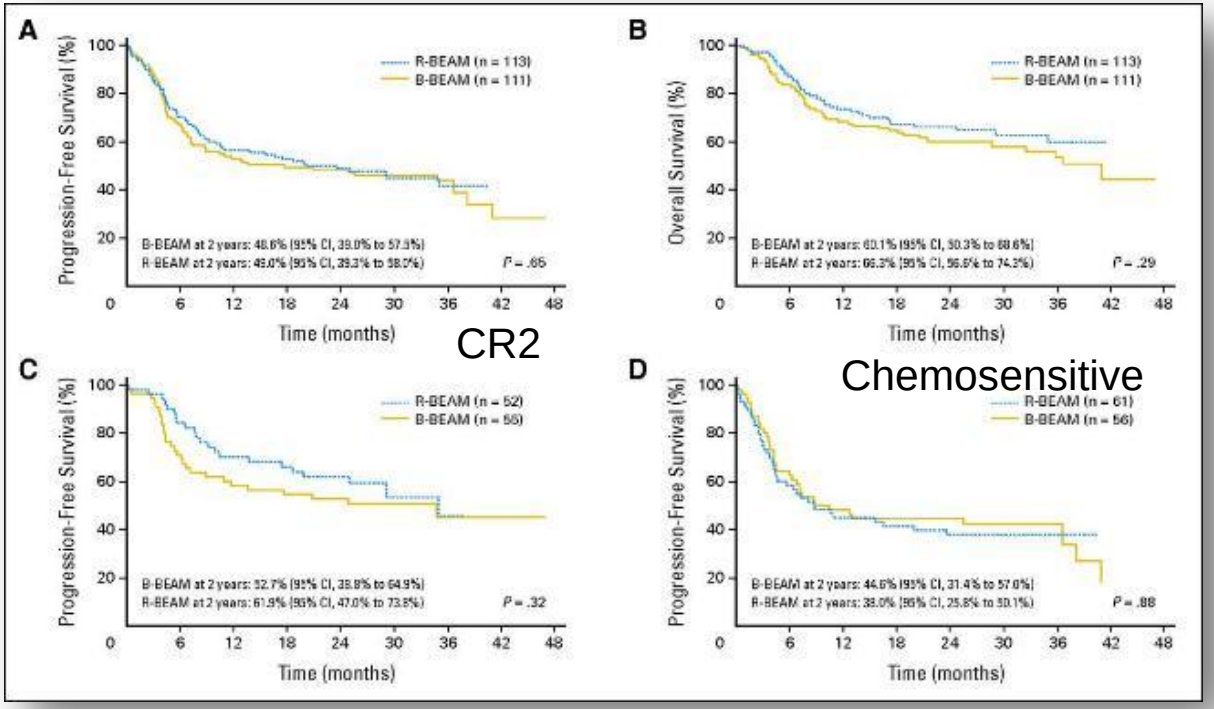
Increased early and late toxicities
No survival benefit

Majhail NS. BBMT. 2007;13: 1153

Darrington DL. J Clin Oncol 1994; 12:2527

02 Role of SCT in DLBCL Novel conditioning regimens for ASCT

^{131}I Tositumomab + BEAM

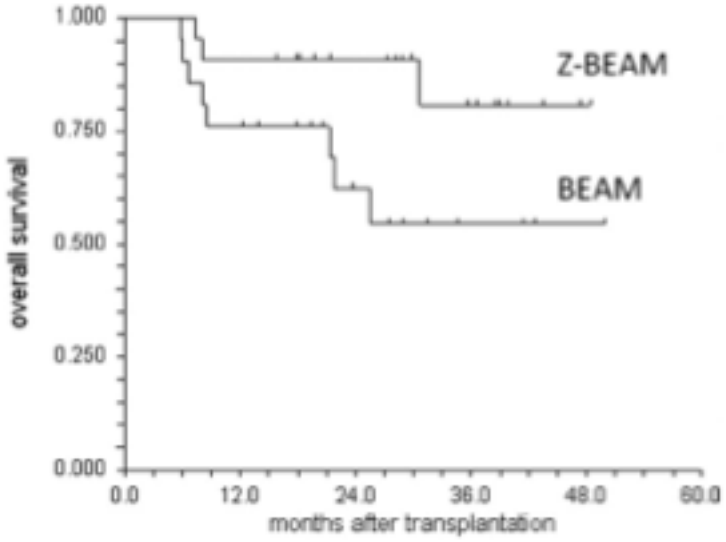


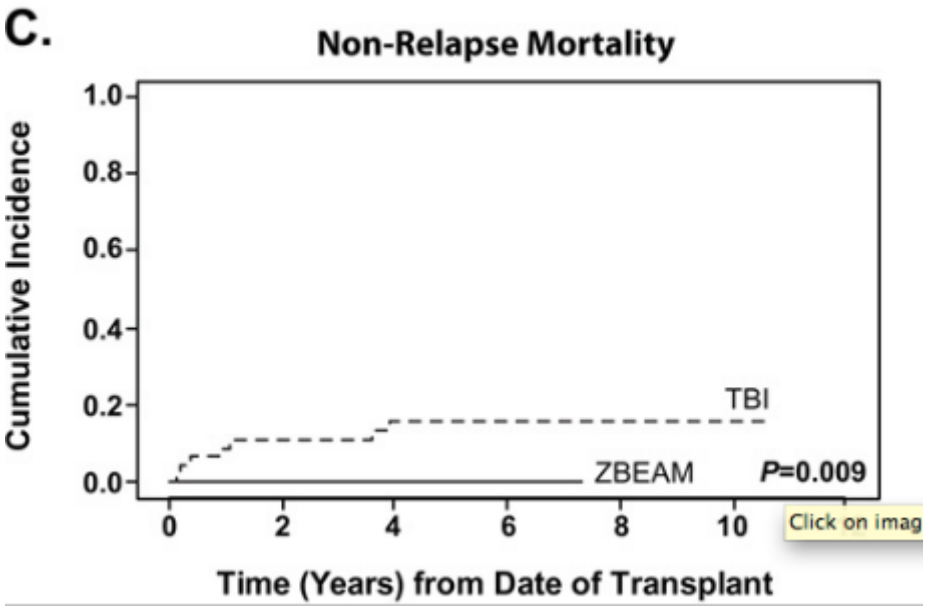
Large randomized negative study

Vose JM. JCO 2013; 31: 1662

02 Role of SCT in DLBCL Novel conditioning regimens for ASCT

^{90}Y ibritumomab tiuxetan +BEAM





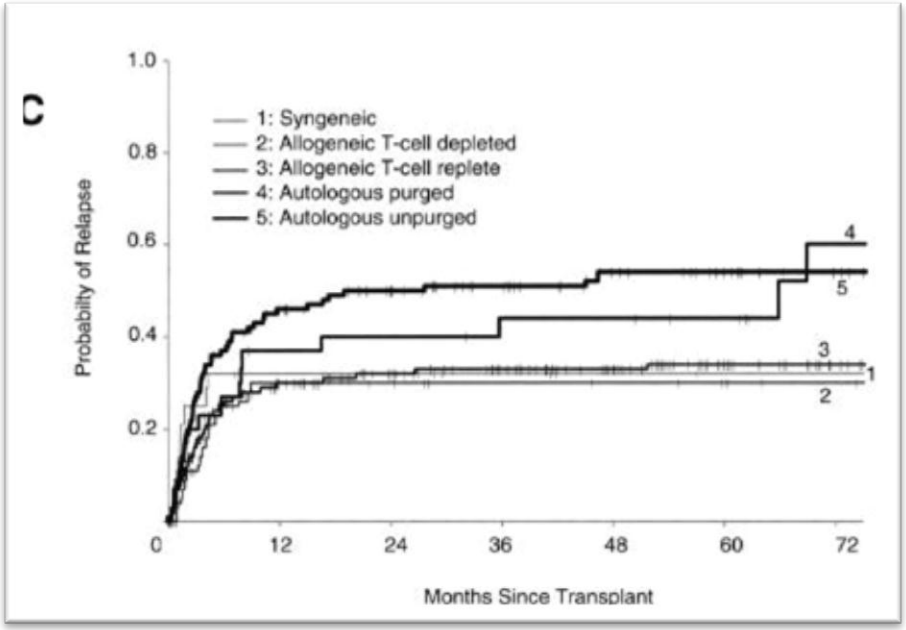
Phase II and a small positive randomized study

Shimoni A. Cancer 2012; 118: 4706

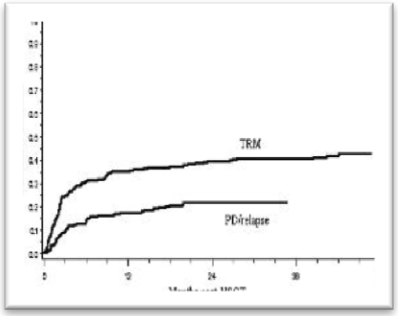
Krishnan A. BBMT 2012;18:441

02 Role of SCT in DLBCL Allogeneic stem cell transplantation

Relapse according to type of SCT



Toxicity with MAC



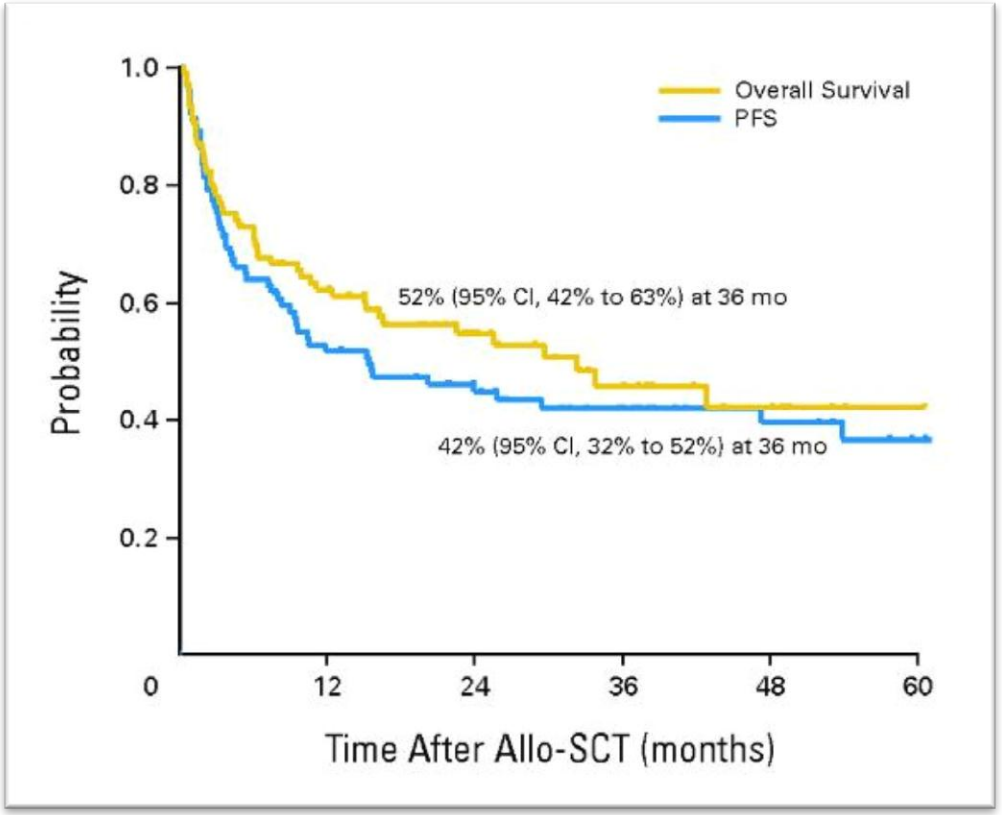
able 2. Causes of treatment-related mortality

Causes of TRM	Patients, no. (%)
VHD	11 (11)
fection	29 (30)
terstitial pneumonitis	16 (17)
enoocclusive disease	11 (11)
hrombotic microangiopathy	8 (8)
eart failure	7 (7)
emorrhage	4 (4)
enal failure	3 (3)
therst	9 (9)
otal	98 (100)

Bierman P J et al. JCO 2003;21:3744-3753
Kim S et al. Blood 2006;108:382-389

02 Role of SCT in DLBCL Allogeneic stem cell transplantation

N: 101
RIC: 64
MAC:37

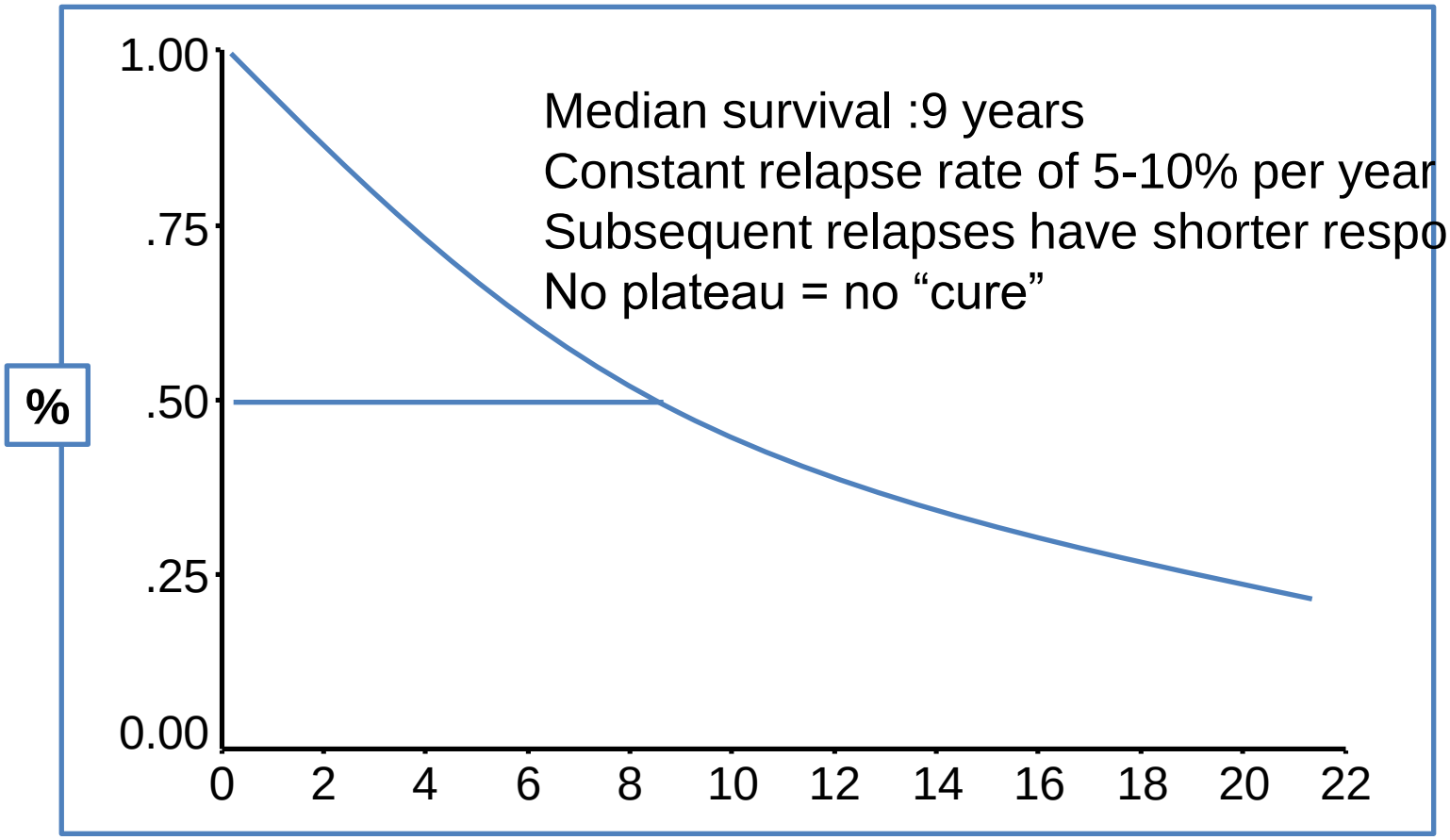


van Kampen R J et al. JCO 2011;29:1342-1348

02 Role of SCT in DLBCL EBMT recommendations

Disease status	Autologous	Allogeneic		
		HLA-matched		HLA-mismatched
		Sibling	Unrelated	
CR1 High-intermediate IPI	Optional	No		
Chemosensitive relapse; CR2	Standard	Optional		No
Refractory	No	Experimental		

03 Role of SCT in FL Natural History



Median survival :9 years
Constant relapse rate of 5-10% per year
Subsequent relapses have shorter responses
No plateau = no “cure”

03 Role of SCT in FL Autologous SCT in first remission

Table 1. Autologous stem cell transplant in FL as first line treatment

	PROTOCOLS		RESULTS	
Lenz et al. 2004 GLSG	Induction: CHOP or MCP ASCT vs Maintenance: IFN ASCT conditioning regimen: TBI+Cy		5 years PFS: ASCT 64.7% Not ASCT 33.3% *p<0.001*	No impact on OS
Deconick et al. 2005 Gyan et al. 2009 GOELAMS	Induction: VCAP/DHAP ASCT vs Maintenance: IFN ASCT conditioning regimen: TBI+Cy	ORR ASCT 81% Not ASCT 69%	Median PFS: Not reached 45 months *p<0.001*	No impact on OS
Sebban et al. 2006 GELA	Induction: CHOP ASCT vs Maintenance: IFN ASCT conditioning regimen: TBI+Cy+VP16	ORR ASCT 79% Not ASCT 78%	No impact on PFS	No impact on OS
Ladetto et al. 2008 GITMO	R-CHOP vs R-HDS + ASCT	CR R-CHOP 62% ASCT 85%	4 years PFS: ASCT 61% Not ASCT 28% *p<0.001*	No impact on OS

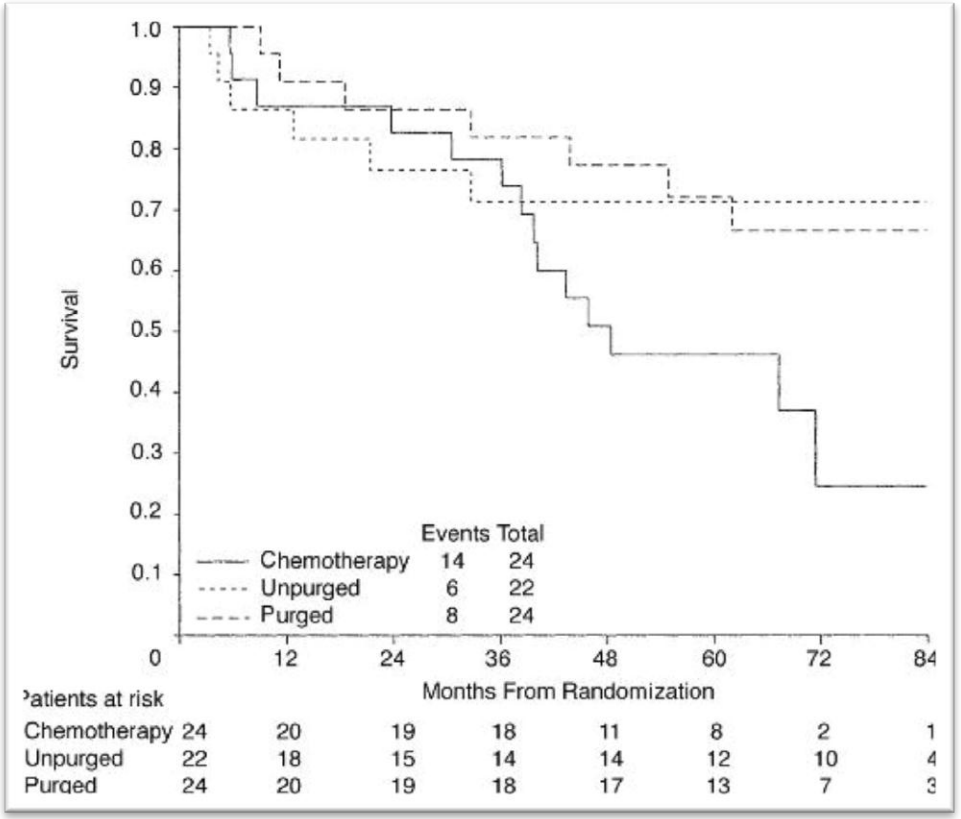
Mediterr J Hematol Infect Dis 2012; 4: Open Journal System

No benefit in overall survival

Not recommended

03 Role of SCT in FL Autologous SCT in relapsed disease

Overall survival for patients randomized to three arms.



Schouten HC, et al. JCO 2003

03 Role of SCT in FL Autologous SCT in relapsed disease

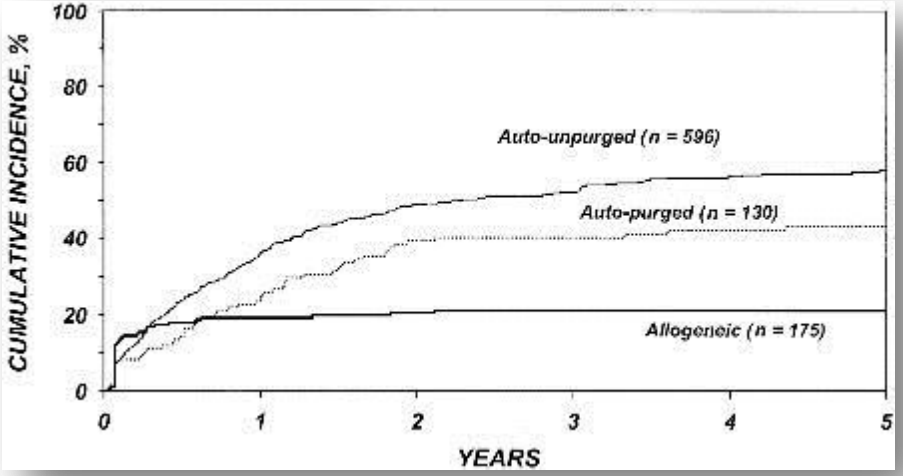
Candidates for ASCT

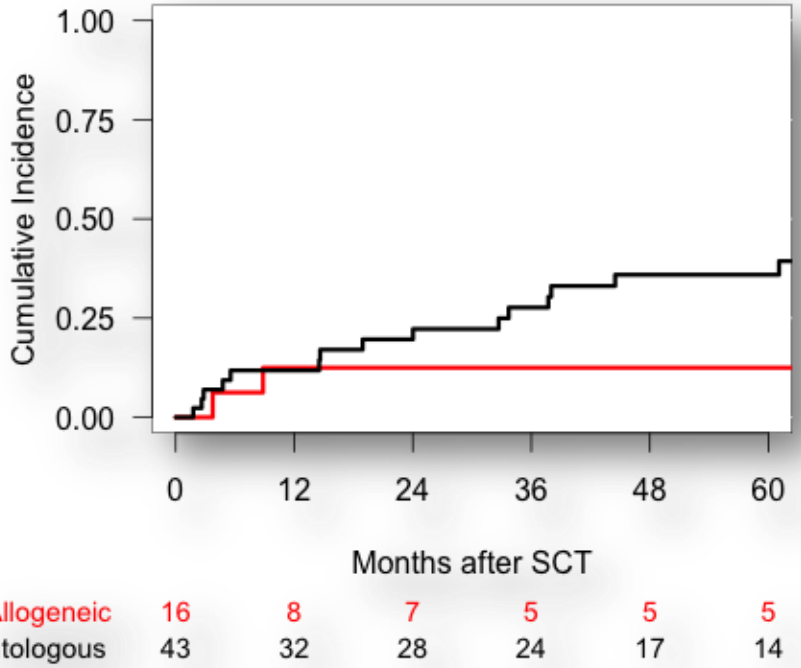
- >CR1
- Chemosensitive disease
- No marrow involvement
- Good performance status

Standard conditioning regimens: chemotherapy based

03 Role of SCT in FL Allogeneic stem cell transplantation

Relapse according to type of SCT





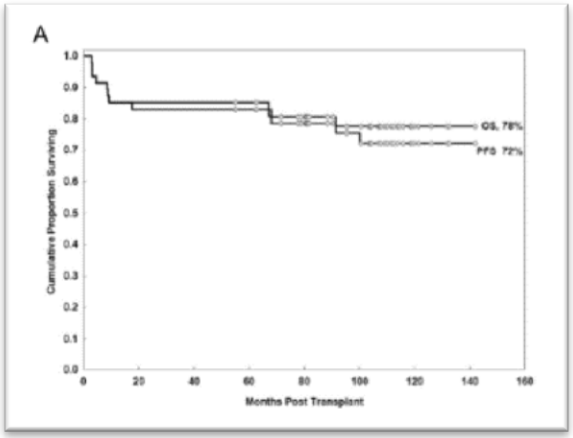
van Besien K et al. Blood 2003;102:3521-3529

H.U La Fe. Unpublished data

03 Role of SCT in FL
RIC allogeneic stem cell transplantation

Study	n	Median age, y (range)	Prior auto-HSCT	Prep regimen	Donor type	DFS/EFS	OS	TRM	Median follow-up
MD Anderson[54]	47	53 (33-68)	19%	Flu/Cy/RTX	MRD URD	72%	78%	21%	107 mo
	26	55 (26-66)	0%	Flu/Cy/Y^{90}	MRD URD	87% 80%	94% 80%	8%	33 mo
CALGB[71]	44 (16 with FL)	53 (39-68)	0%	Flu/Cy	MRD	75%	81%	9%	4.6 y
United Kingdom[72]	82	45 (26-65)	26%	Flu/Mel/Alem	MRD URD	76%	76%	15%	43 mo
GELTAMO[73]	37	50 (34-62)	46%	Flu/Mel	MRD	57%	54%	37%	52 mo
FHCRC[74]	62 (54 with FL)	54 (33-66)	32%	TBI ± Flu	MRD URD	43%	52%	42%	36 mo

CALGB indicates Cancer and Leukemia Group B; GELTAMO, Grupo Español de Linfomas/Trasplante Autólogo de Médula Ósea; FHCRC, Fred Hutchinson Cancer Research Center; flu: fludarabine; Cy: cyclophosphamide; alem, alemtuzumab; mel, melphalan; MRD, matched related donor; URD, unrelated donor; DFS, disease-free survival; Y^{90}, Y^{90}-ibritumomab tiuxetan.



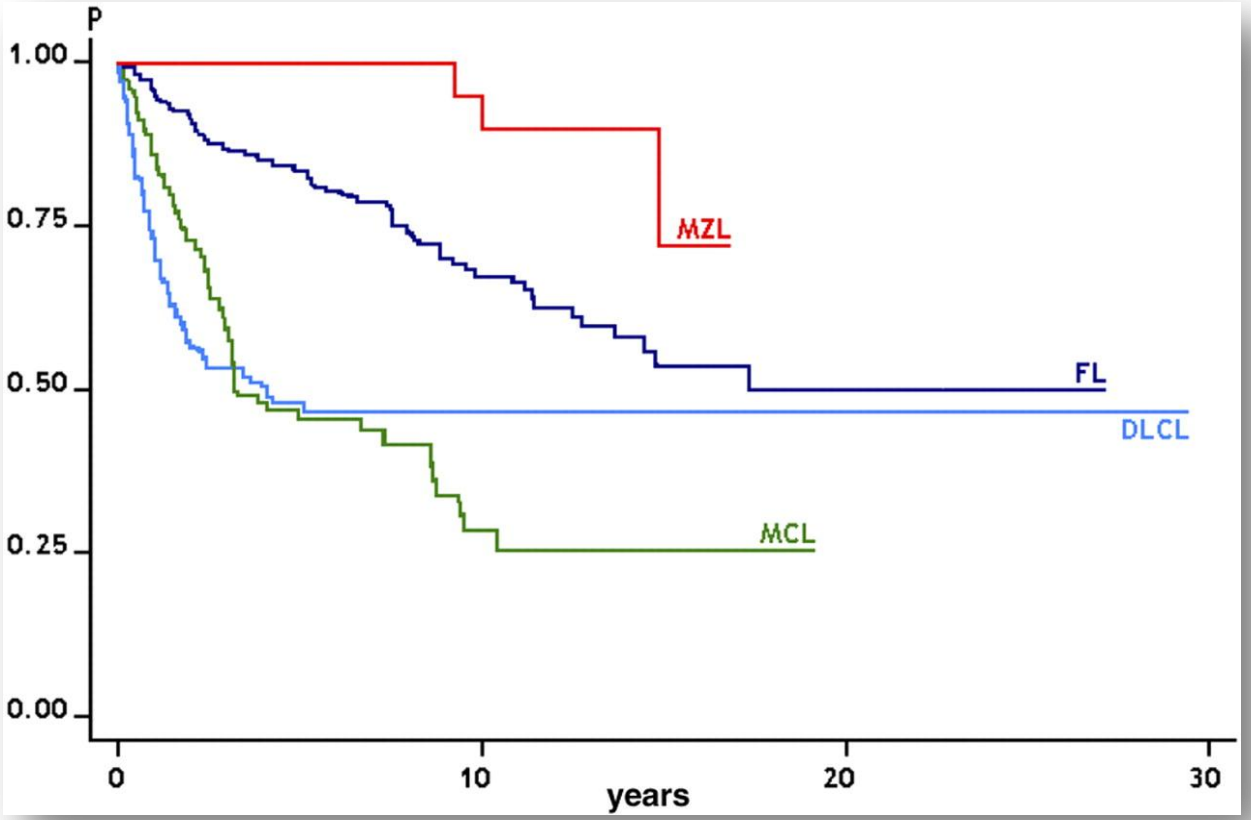
Phase 2 study in chemosensitive FL

Khouri IF, et al. *Blood*. 2012;119(26):6373-6378

03 Role of SCT in FL
Recomendaciones EBMT 2012

Disease status	Autologous	Allogeneic		
		HLA-matched		HLA-mismatched
		Sibling	Unrelated	
CR1 High-intermediate FLIPI	Optional	No		
Chemosensitive relapse; CR2	Standard	Optional		Experimental
Refractory	No	Optional		Experimental

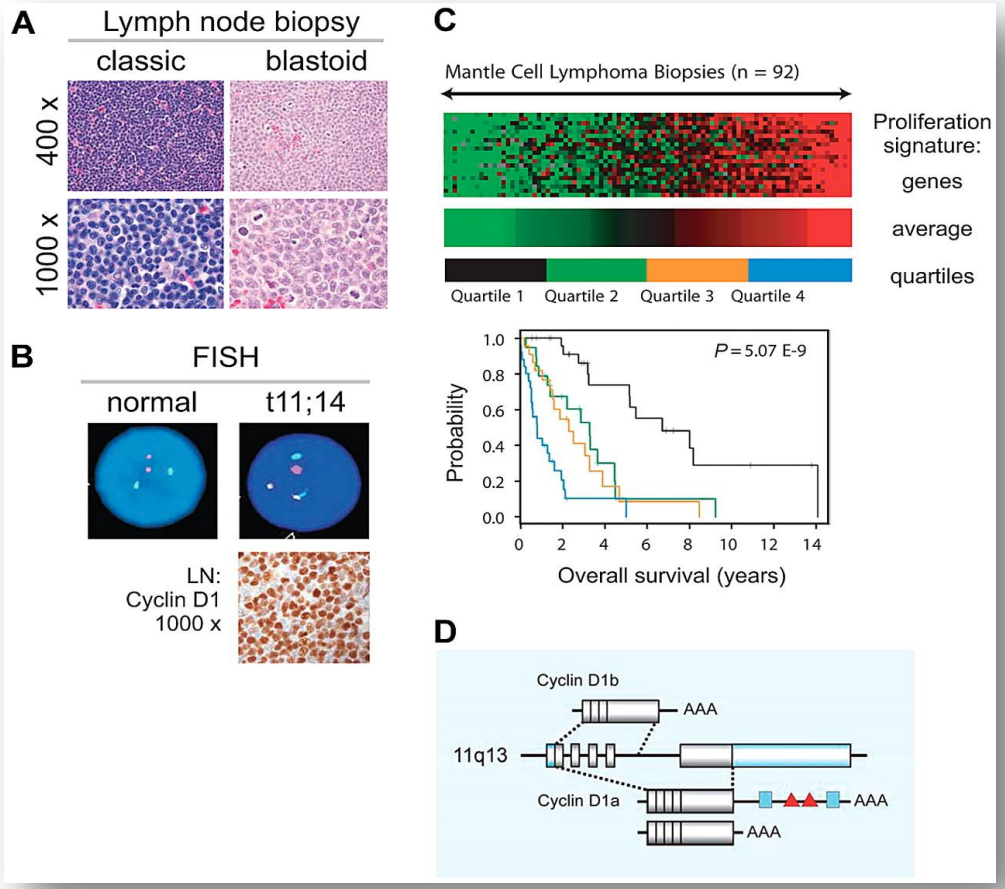
04 Role of SCT in MCL Cause specific survival in B cell lymphoma



Ghielmini M , and Zucca E Blood 2009;114:1469-1476

04 Clinical and biologic characteristics of MCL

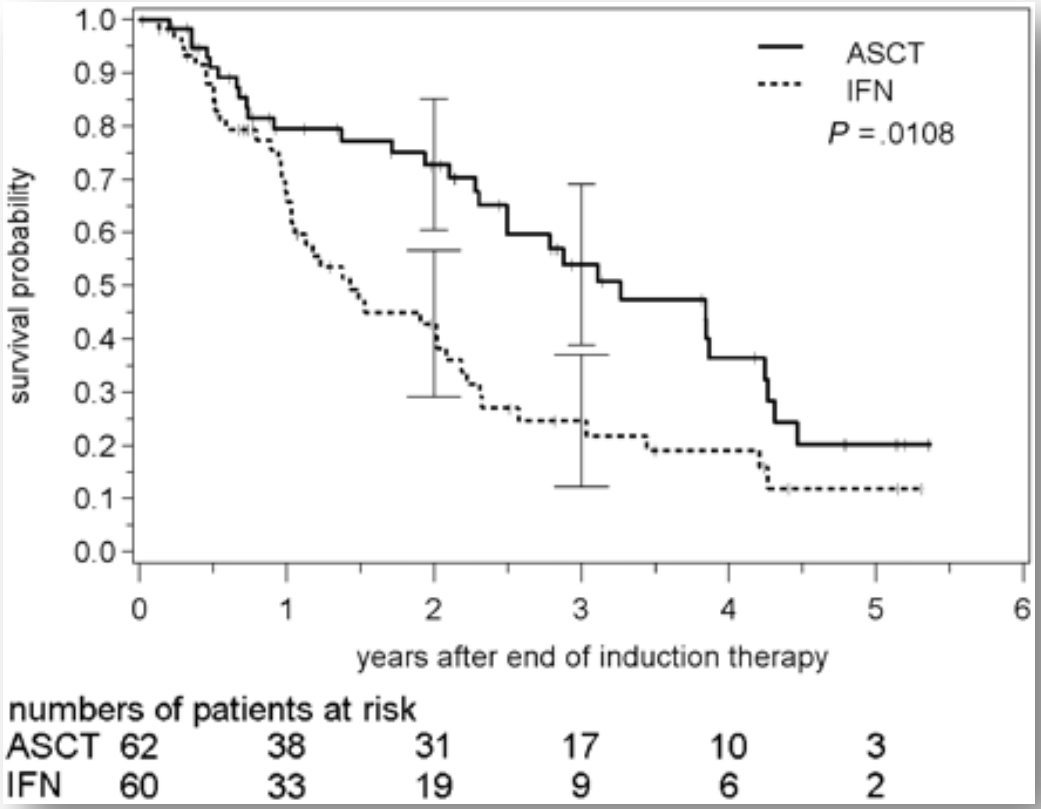
MCL diagnosis is based on morphology and immunophenotyping (CD20+, CD5+, CD23−, FMC7+).

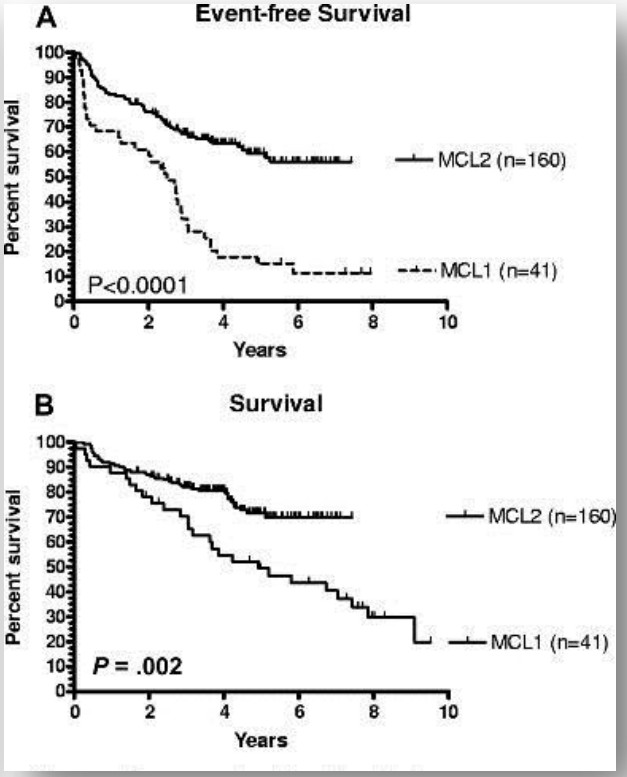


Pérez-Galán P et al. Blood 2011;117:26-38

04 Role of SCT in MCL
Autologous SCT in first remission

Dreyling et al. Blood 2005



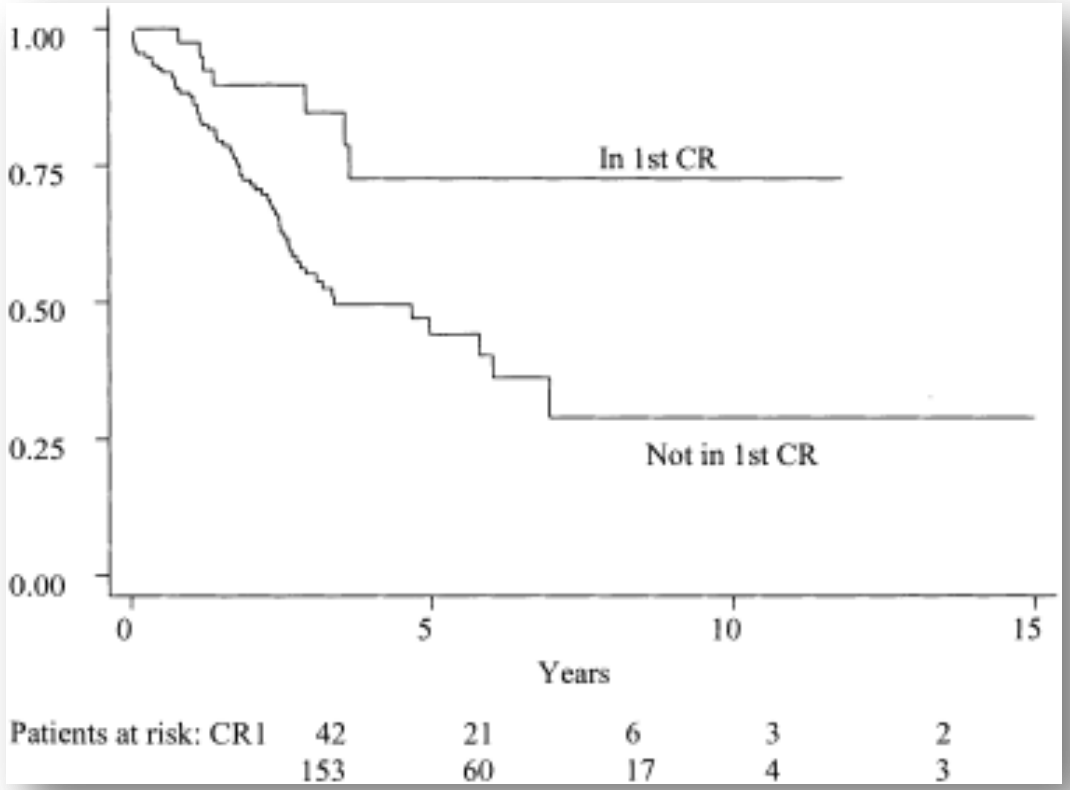


Geisler CH. Blood 2008; 112: 2687

04 Role of SCT in MCL

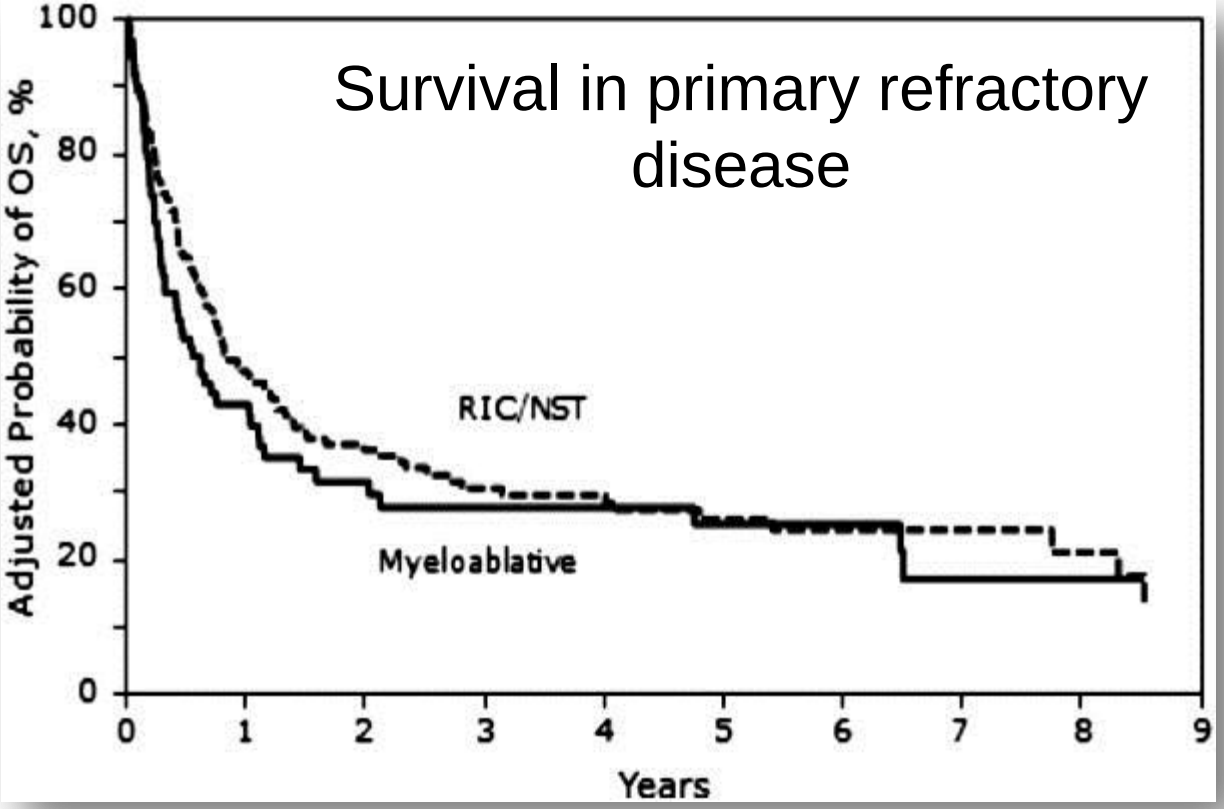
Autologous SCT in relapsed disease

Overall survival from time of transplantation by disease status

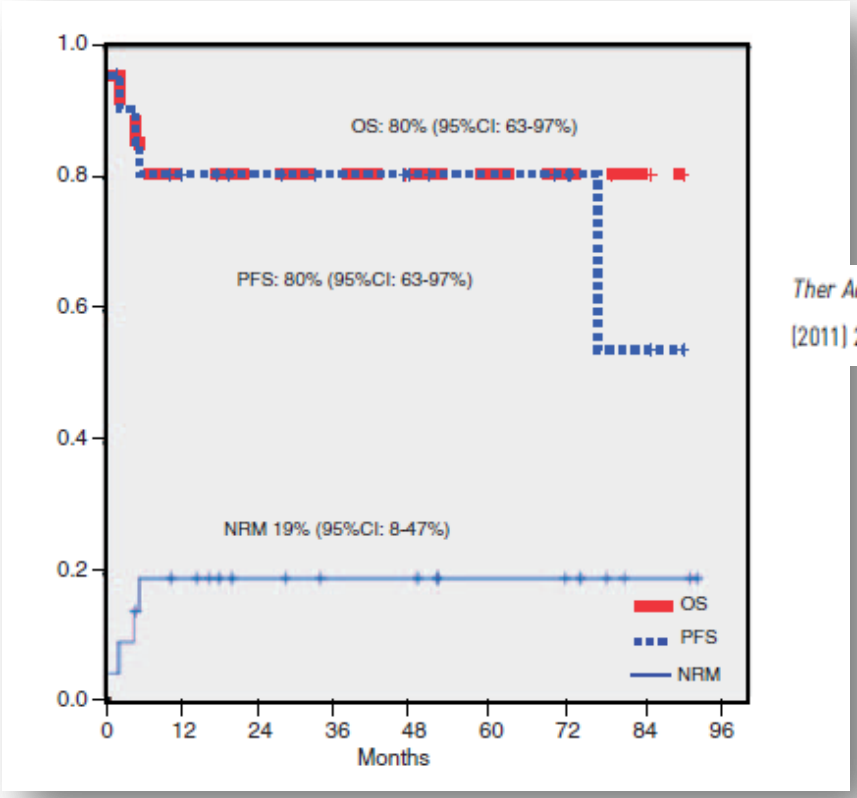


Vandenberghe E. Br J Haematol 2003; 120: 793

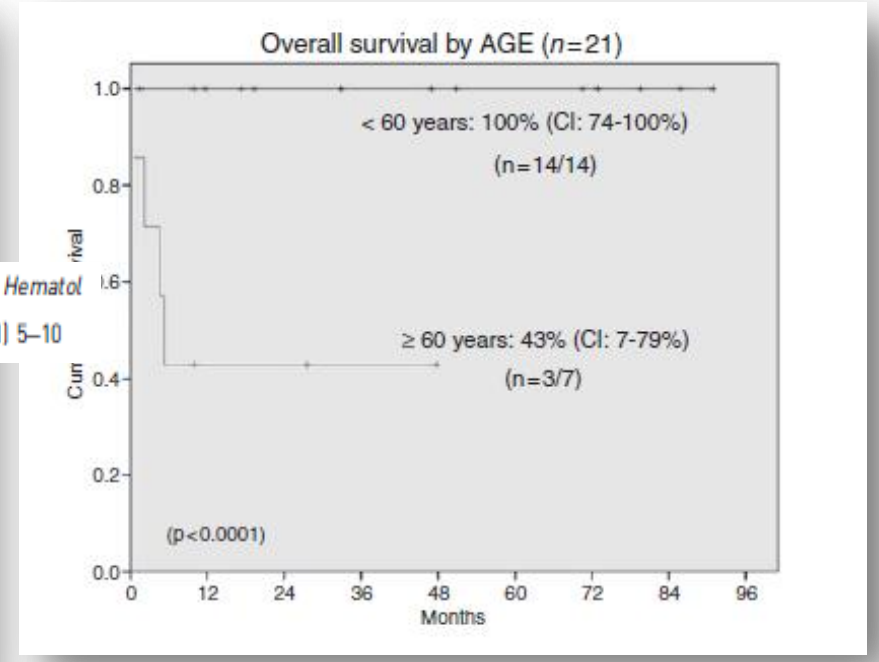
04 Role of SCT in MCL
Allogeneic SCT in first line



04 RIC allo in MCL



Ther Adv Hematol [2011] 2[1] 5–10



OS, PFS and NRM. Median followup 48 m.

04 Role of SCT in MCL
Recomendaciones EBMT 2012

Disease status	Autologous	Allogeneic		
		HLA-matched		HLA-mismatched
		Sibling	Unrelated	
CR1 High-intermediate FLIPI	Standard	Experimental		No
Chemosensitive relapse; CR2	Standard	Optional		
Refractory	No	Experimental		

HCT in lymphoma Conclusions

- Autologous and allogeneic HSCT for lymphoma continues to evolve.
- Timing and transplantation type are being refined.
- Early referral to a TC is warranted
- The low TRM of auto HSCT and for RIC allogeneic HSCT allows more patients receive these beneficial therapies.