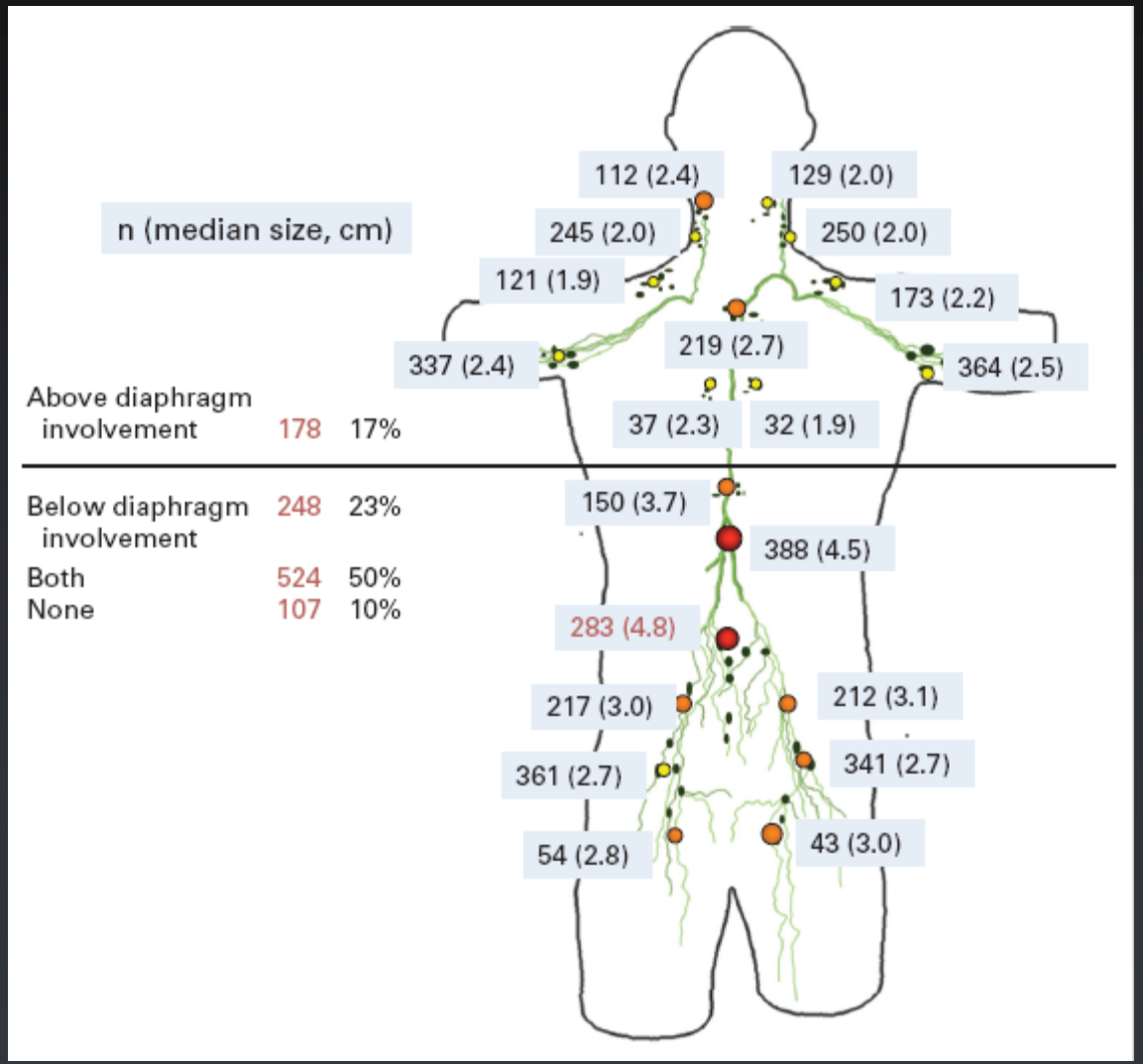
Tratamiento de los linfomas del manto y folicular en pacientes jóvenes

MD Caballero, Reñaca ,Chile 23 de octubre, 2009

Linfoma Folicular



Características

No. of patients	362
Age, y, median (range)	56 (24-90)
Age 60 years or older	137 (38)
Male sex	155 (43)
Stage IV	248 (70)
B-symptoms present	143 (40)
LDH > UNL	104 (29)
Hb < 12 g/dL	74 (21)
ECOG 2-4	22 (6)
No. involved nodal areas > 4	221 (64)
No. involved extranodal sites > 1	51 (15)
FLIPI risk group	
Low risk	49 (14)
Intermediate risk	138 (41)
High risk	151 (45)

Federico J Clin Oncol 2009,Buske, Blood 2006

FLIPI

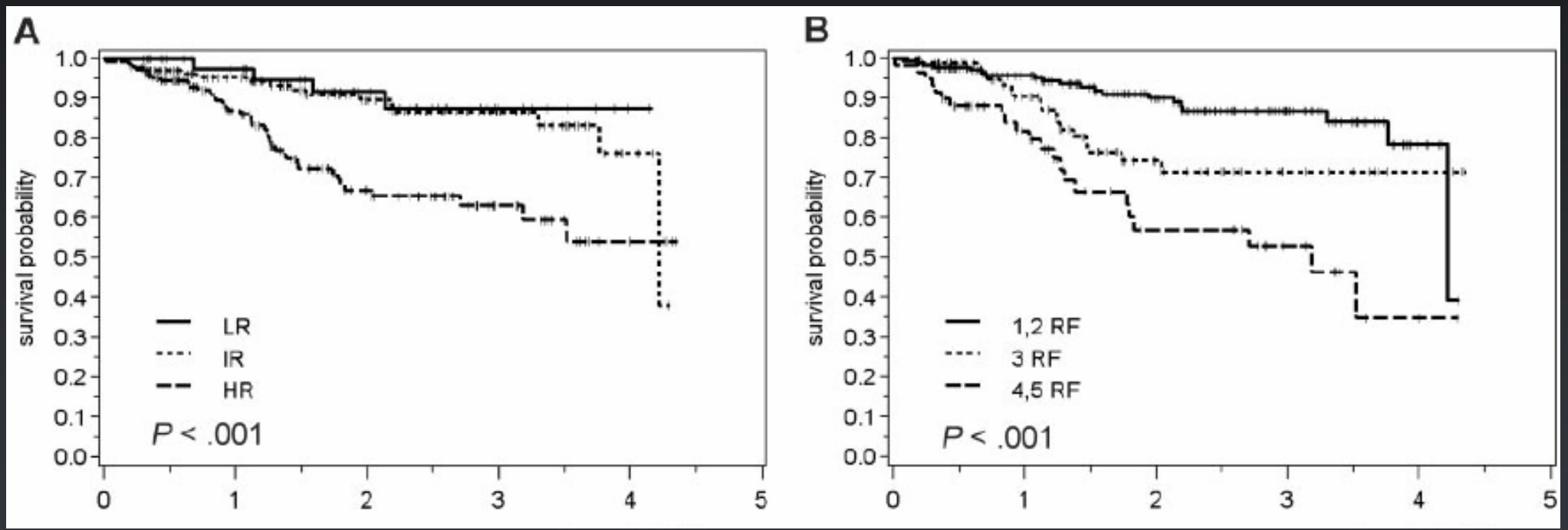
FL International Prognostic Index

Parameter	Adverse factor	RR	95% CI
Age	≥ 60 y	2.38	2.04 – 2.78
Ann Arbor stage	III – IV	2.00	1.56 – 2.58
Hemoglobin	< 12 g/dL	1.55	1.30 – 1.88
Serum LDH level	> ULN	1.50	1.27 – 1.77
Number of nodal sites	> 4	1.39	1.18 – 1.64

Pronóstico	*N° factores*	*% Ptes*	*Sup 5a*	*Sup 10a*
Bueno	**0-1**	**36**	**90,6%**	**70,7%**
Intermedio	**2**	**37**	**77,6%**	**50,9%**
Malo	**≥3**	**27**	**52,5%**	**35,5%**

Solal-Celigny *et al*, *Blood* 2004

FLIPI separates High and Intermediate/low risk in FL patients treated with R-CHOP

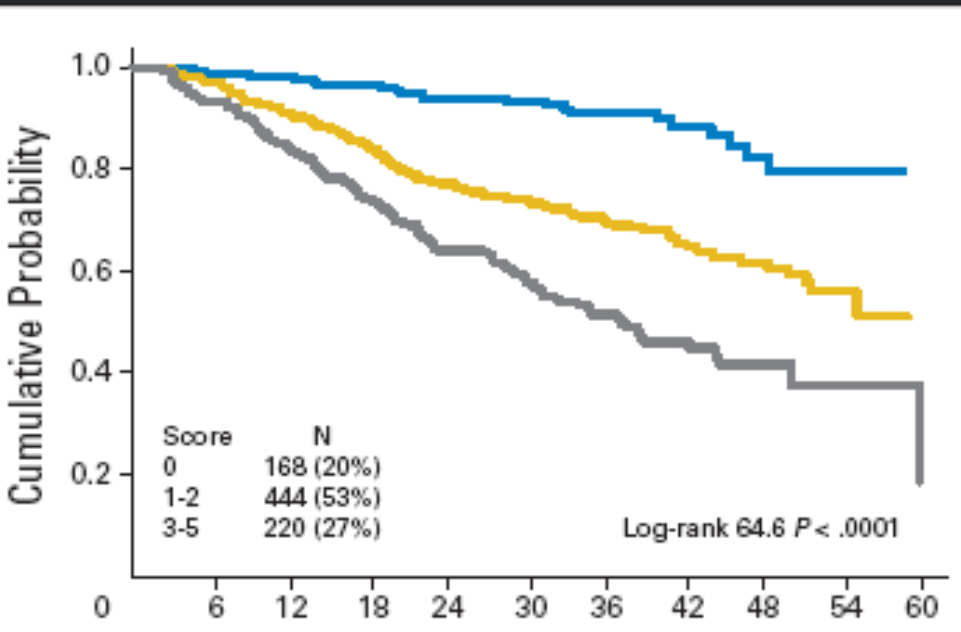


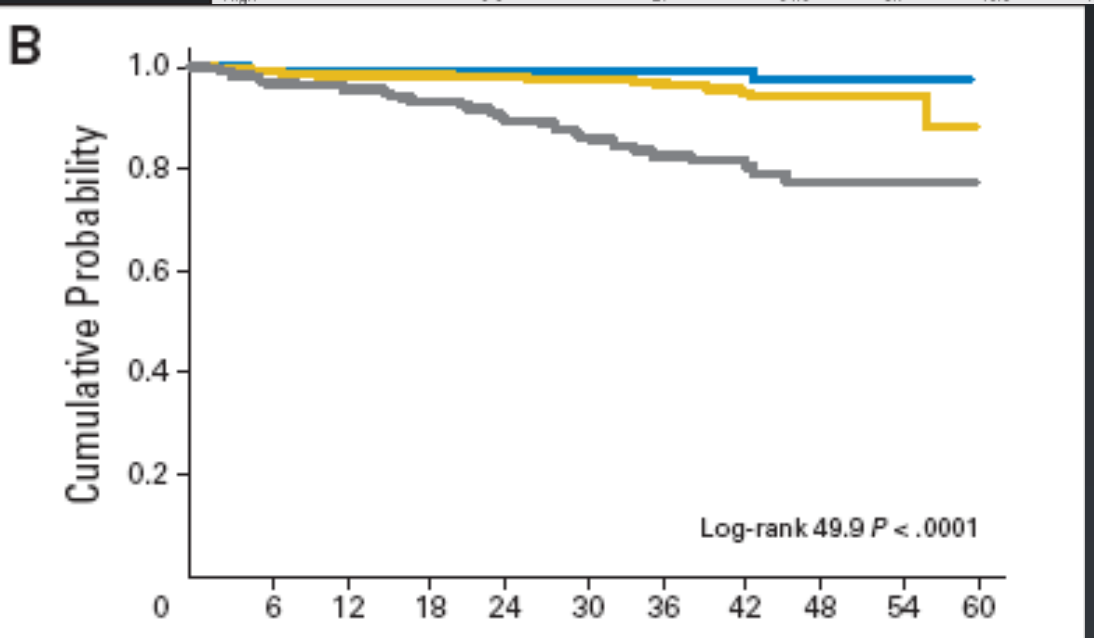
Buske, Blood 2006

SLP y SG according to FLIPI2

Variable	Adverse Factor	Patients (%)	PFS (%) 3-Year	PFS (%) 5-Year
B2M	> UNL	42	58	21
BMI	+	40	58	20
Hemoglobin, g/dL	< 12	18	52	42
LoDLIN, cm	> 6	25	54	24
Age, years	> 60	43	63	46

Risk Group	No. of Factors	Patients (%)	PFS 3-Year %	PFS 3-Year SE	PFS 5-Year %	PFS 5-Year SE
Low	0	20	90.9	2.4	79.5	5.0
Intermediate	1-2	53	69.3	2.4	51.2	5.7
High	3-5	27	51.3	3.7	18.8	13





Federico J Clin Oncol 2009

- Tratamiento de inducción
- Mantenimiento o consolidación
- Tratamiento a la recaída
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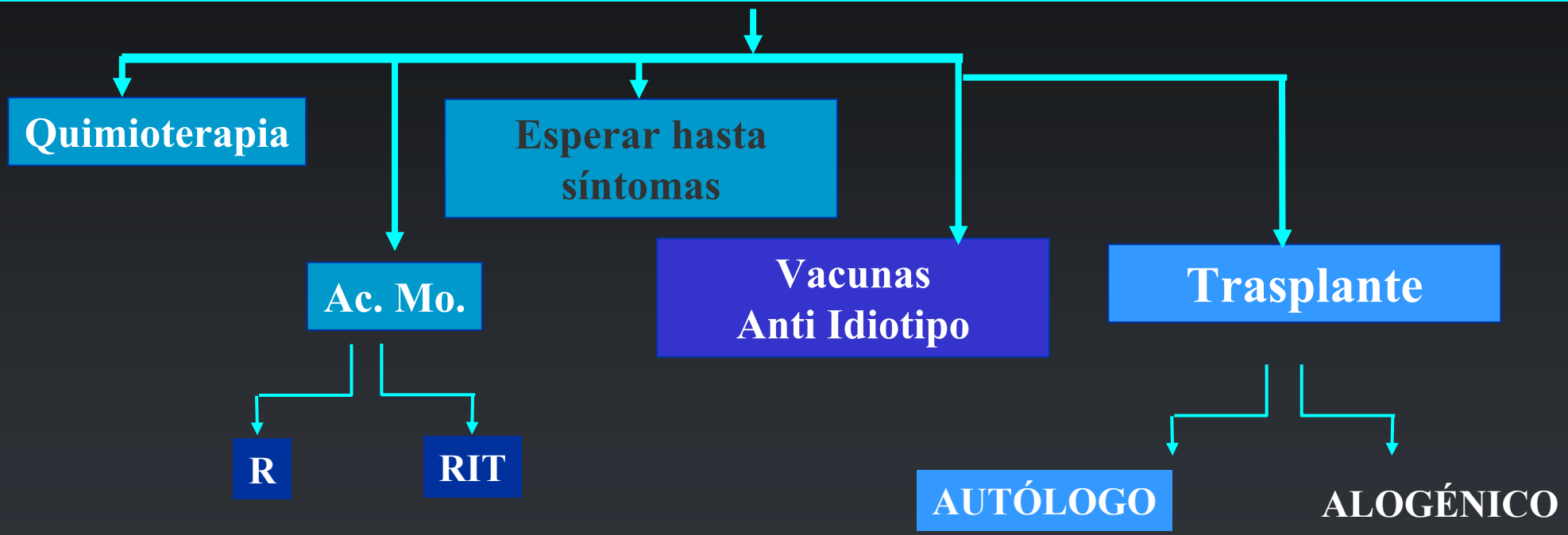
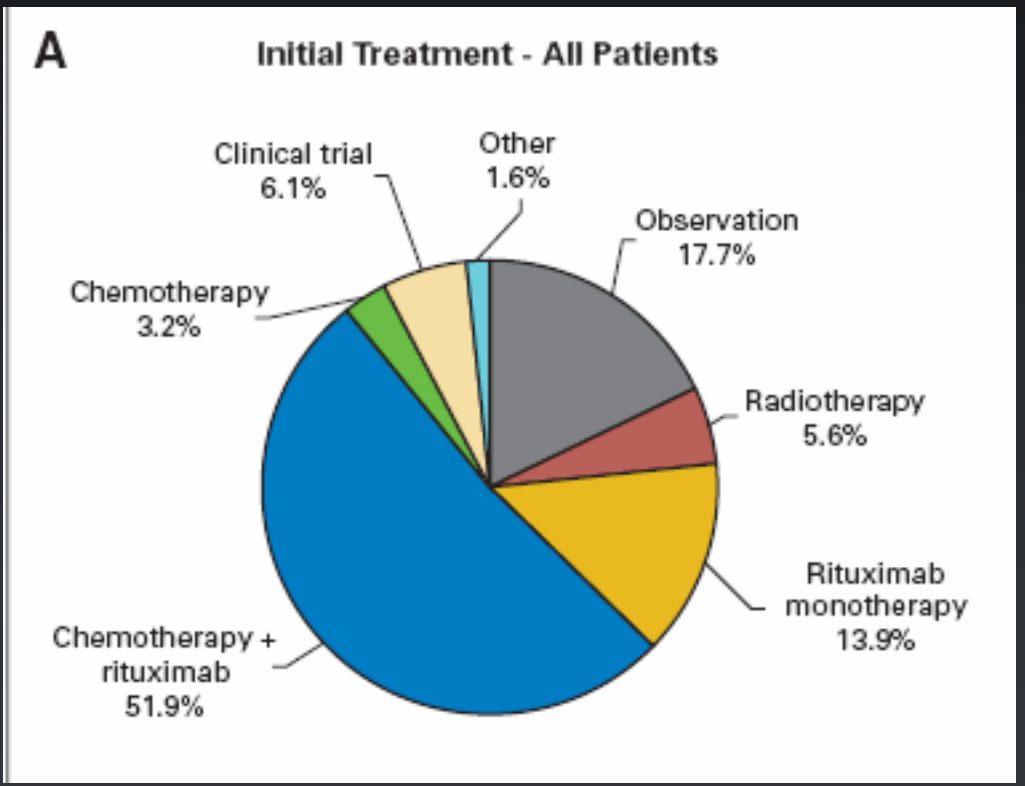
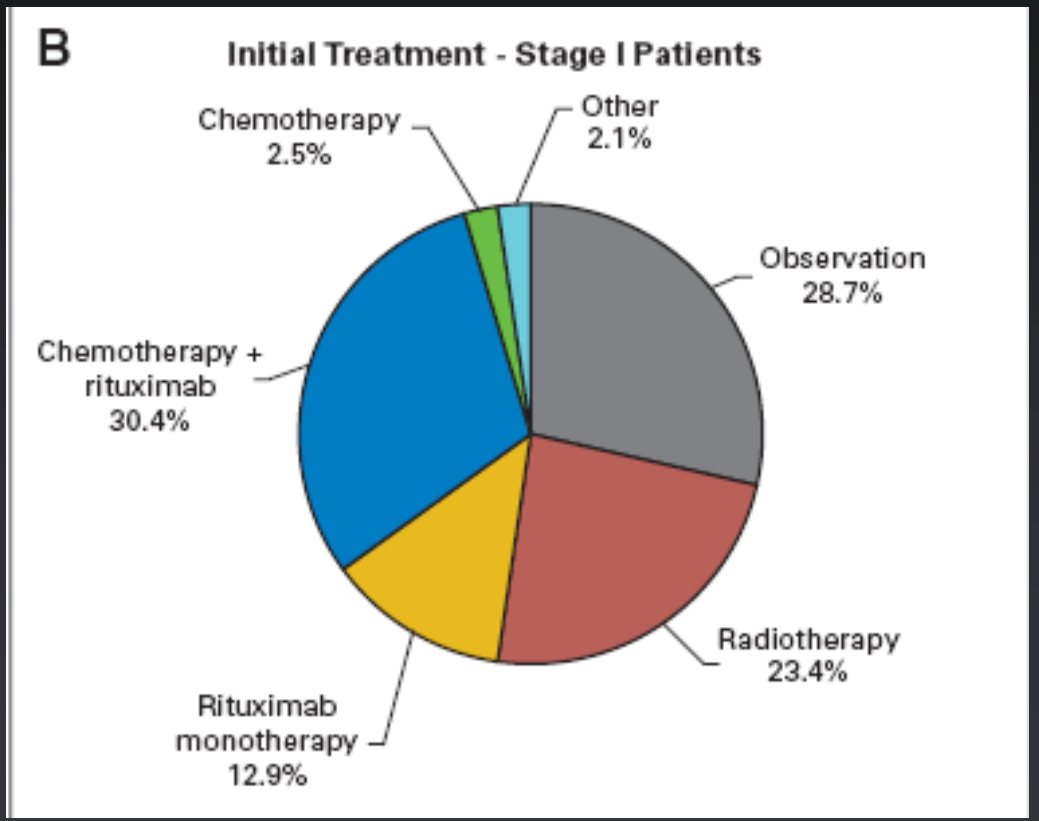
Opciones Terapeúticas en el LNH Folicular



Tratamiento inicial del Linfoma Folicular





Follicular Lymphoma in the United States: First Report of the National LymphoCare Study

Friedberg et al J CLIn Oncol 2009

First Line therapy in advanced stage Follicular Lymphoma. Randomised Trials

Author, year	Régimen	Resp	CR(u)	PFS/EFS	OS
Marcus, 2008	**CVP vs**	57%	10%	17 m	77%
n = 321 (LF)	**CVP + R**	81%	41%	37 m	83%
Hiddemann, 2005	**CHOP vs**	90%	17%	2,6 años	90%
n = 428 (LF)	**CHOP + R**	96%	20%	NA	95% (2 años)
Salles, 2008	**CHVP / IFN vs**	86%	44%	37%	79%
n = 358 (LF)	**CHVP / IFN + R**	94%	73%	53% (60 meses)	84%
Herold, 2007	**MCP vs**	75%	25%	40%	74%
n = 201 (LF)	**MCP + R**	92,4%	49,5%	71% (48 meses)	87% (30 meses)

CHOP ± rituximab versus FM ± rituximab

- CHOP x6 (n = 68) vs FM x6 (n = 72)
  - RC bcl-2/IgH neg ⇢ observación
  - RC bcl-2/IgH pos o RP ⇢ rituximab 375 mg/m^2/sem x4

	CHOP	FM	Valor p
RC, induccion	42%	68%	0,003
RC *bcl-2* neg	19%	39%	0,001
RC, rituximab	81%	90%	NS
RC *bcl-2* neg	41%	56%	NS
RC *bcl-2* negativo	51%	71%	0,01

Zinzani PL, et al. J Clin Oncol 2004;22:2654–61

¿ Cuál es el mejor esquema de R- quimioterapia?

Método:

- Modelo de decisión de Markov (1ª y 2ª líneas)
- Fuentes: Medline y abstracts Meeting
- Datos: RR, mortalidad relacionada, PFS, cardiotoxicidad, neutropenia

Resultados:

- Optima prímera línea R-CHOP seguido de R- Fludarabina
- R-CVP subóptimo tanto en primera como en segunda línea

#670 Olin RL(Choosing first-line therapy for follicular lymphoma (FL): A decision analysis).ASH 2008

- Tratamiento de inducción
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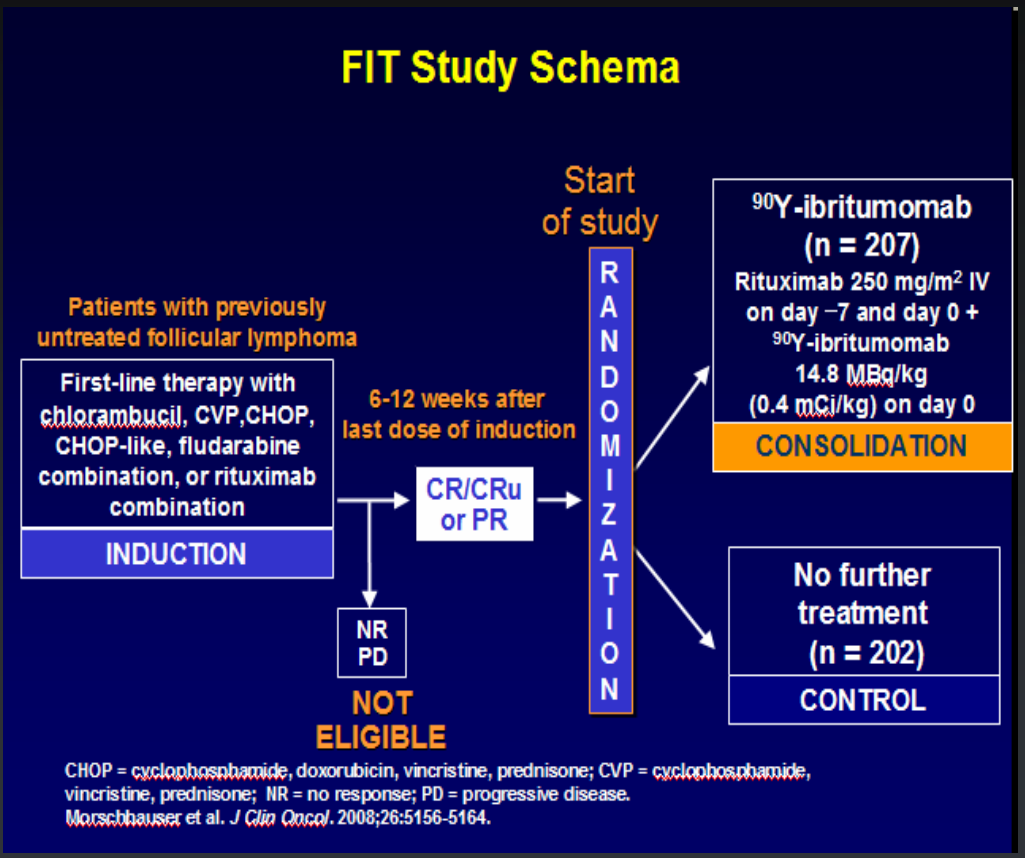
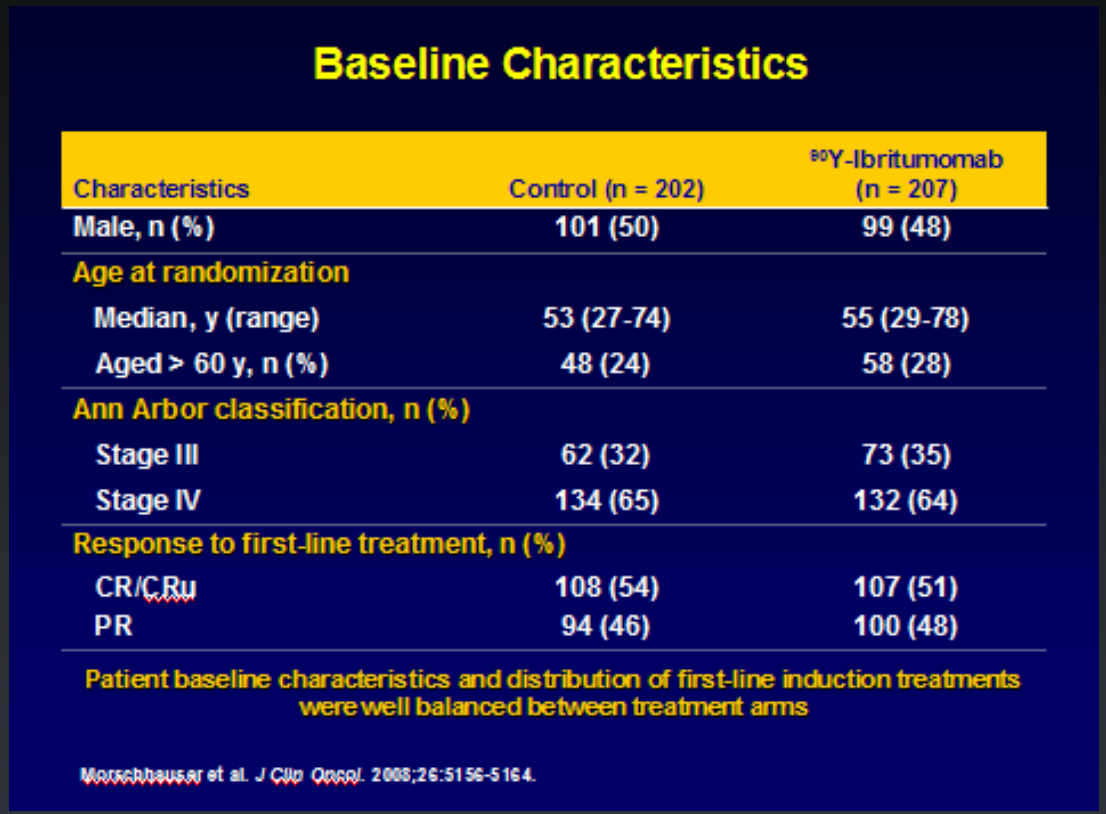
Radioinmunoterapia

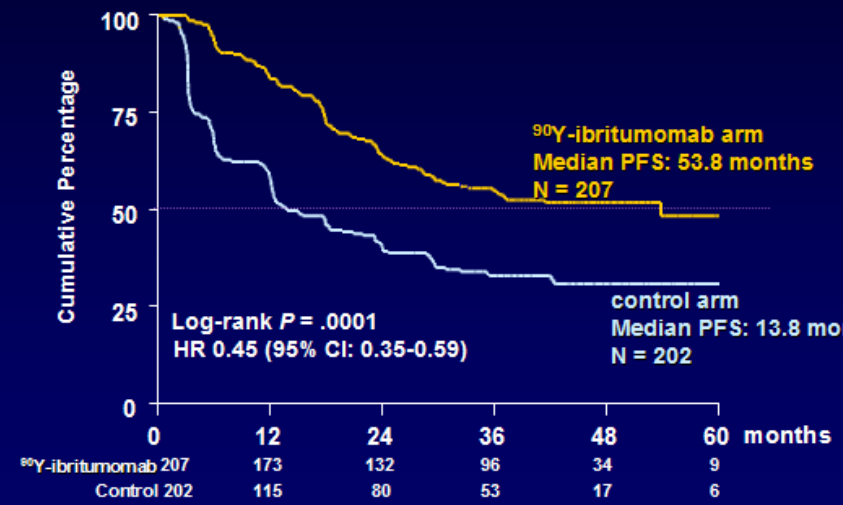
(#2002 Morschhauser F et al "Extended follow-up of the International phase 3 First-Line Trial shows durable benefit of 90Y-Ibritumomab Tiuxetan (Zevalin)Consolidation of first remision advenced stage follicular non-Hodgkins lymphoma)





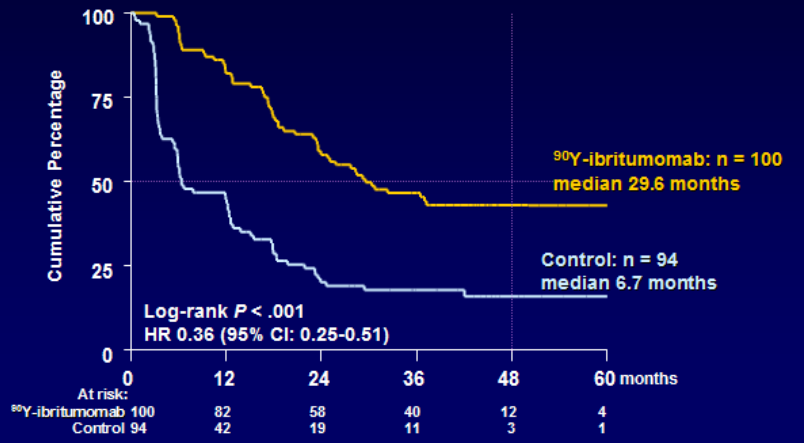
Overall PFS for Treatment Groups

The 4-year overall PFS is
52% in the ^{90}Y-ibritumomab arm compared with 31% in the control arm



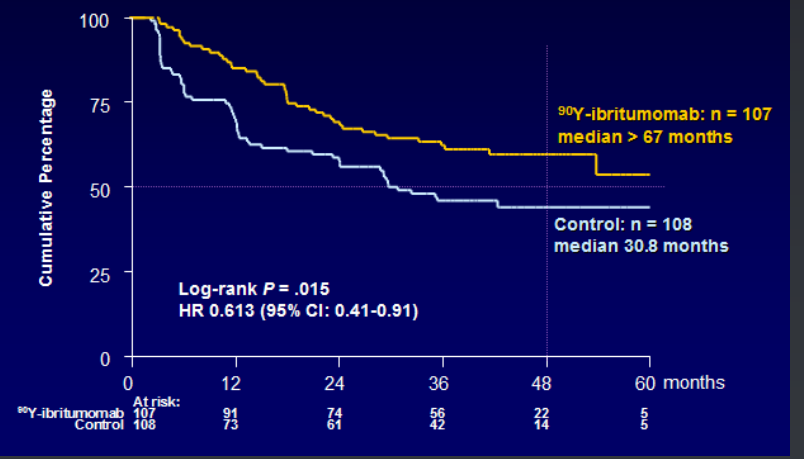
PFS for Patients in PR After Induction

The 4-year PFS among patients with a PR after induction
is 43% in the ^{90}Y-ibritumomab arm compared with 15% in the control arm



PFS for Patients in CR/CRu After Induction

The 4-year PFS among patients with a CR after induction
is 60% in the ^{90}Y-ibritumomab arm compared with 44% in the control arm



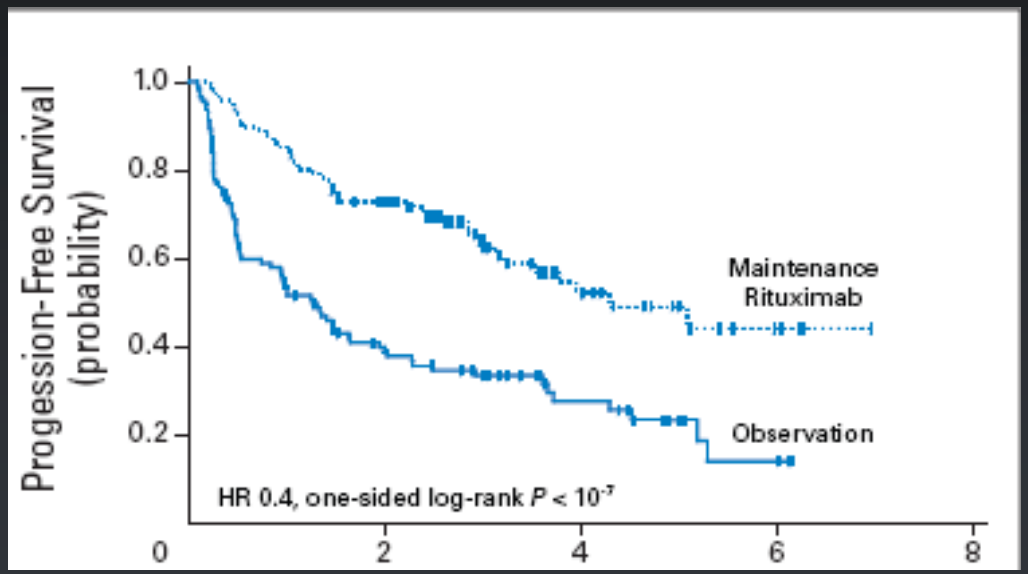
Rituximab as maintenance in FL

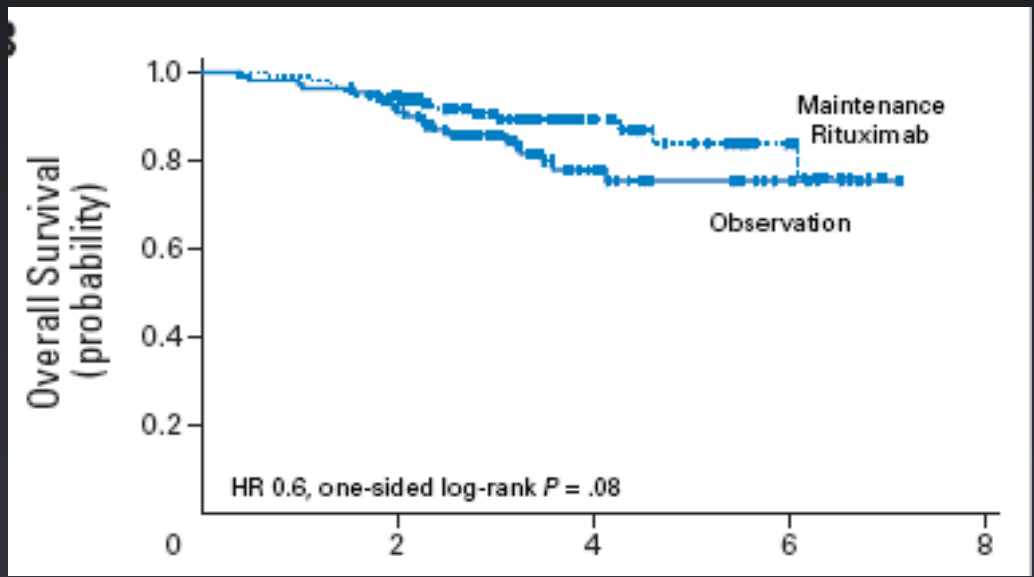
Study/group	Trial design	Setting	Study induction	Rituximab maintenance
Minnie Pearl[1]*	Ph. II	1st line	Rituximab	OR 74%,PFS 37mo
SAKK 35/98[2]	Ph. III	1st/2nd line	Rituximab	EFS 12 → 23 mo
Minnie Pearl[3]*†	Ph. II	2nd line	Rituximab	PFS 7 → 31 mo
ECOG 1496[4]	Ph. III	1st line	CVP	PFS 18 → 50 mo
EORTC 20981[5]	Ph. III	2nd line	CHOP ± R	PFS 15 → 51 mo
GLSG[6]‡	Ph. III	2nd line	FCM ± R	RD 19 → NR (3y)

1. Hainsworth JD, *et al. J Clin Oncol* 2002; 20:4461–4467.
2. Ghielmini M, *et al. Blood* 2004; 103:4416–4423.
3. Hainsworth JD, *et al. J Clin Oncol* 2005; 23:1088–1095.
4. Hochster HS, *et al. Proc Am Soc Clin Oncol* 2004; 22:Abstract 6502.
5. van Oers M, *et al. Blood* 2004; 104:Abstract 586.
6. Hiddemann W, *et al. Proc Am Soc Clin Oncol* 2005; 23:Abstract 6527.

* Included patients with small lymphocytic lymphoma
† Randomized – maintenance versus retreatment
‡ Included patients with MCL

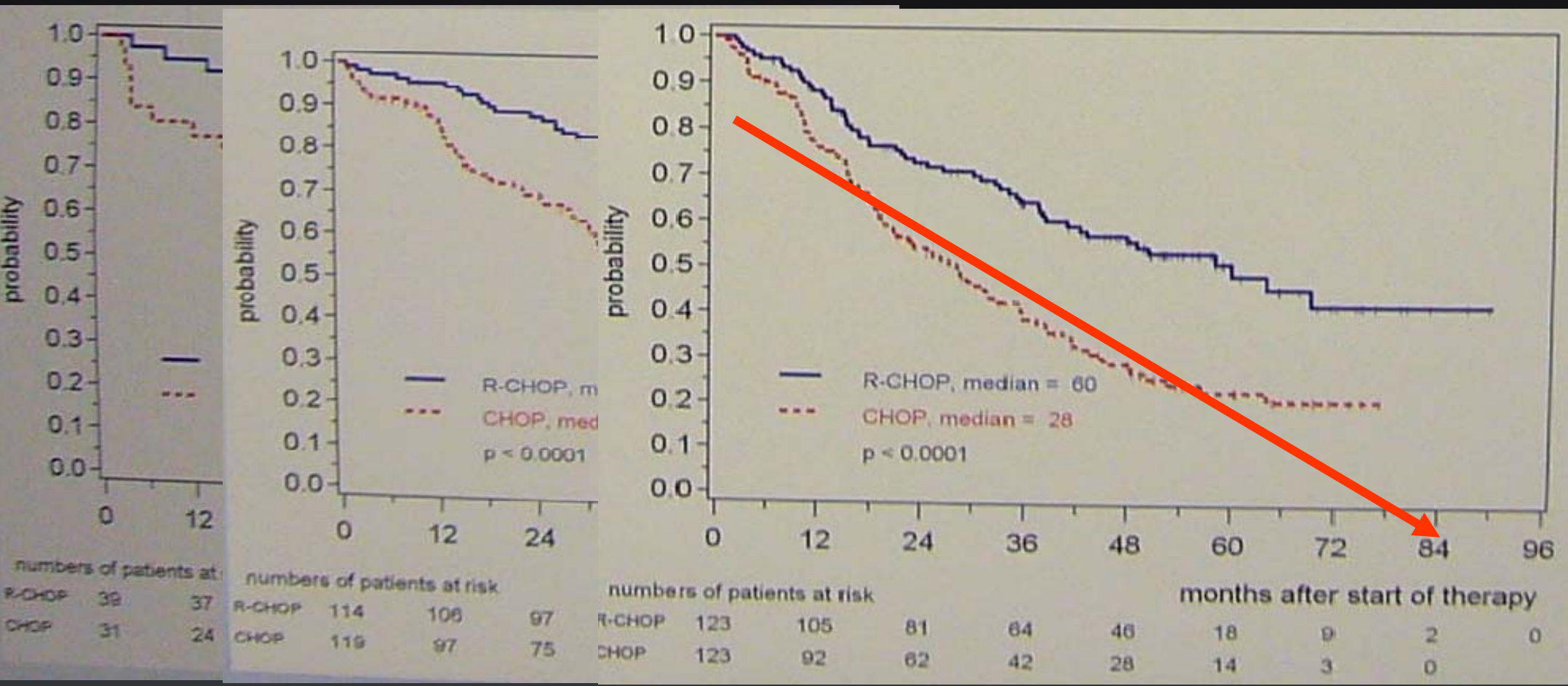
Maintenance Rituximab After Cyclophosphamide, Vincristine, and Prednisone Prolongs Progression-Free Survival in Advanced Indolent Lymphoma: Results of the Randomized Phase III ECOG1496 Study





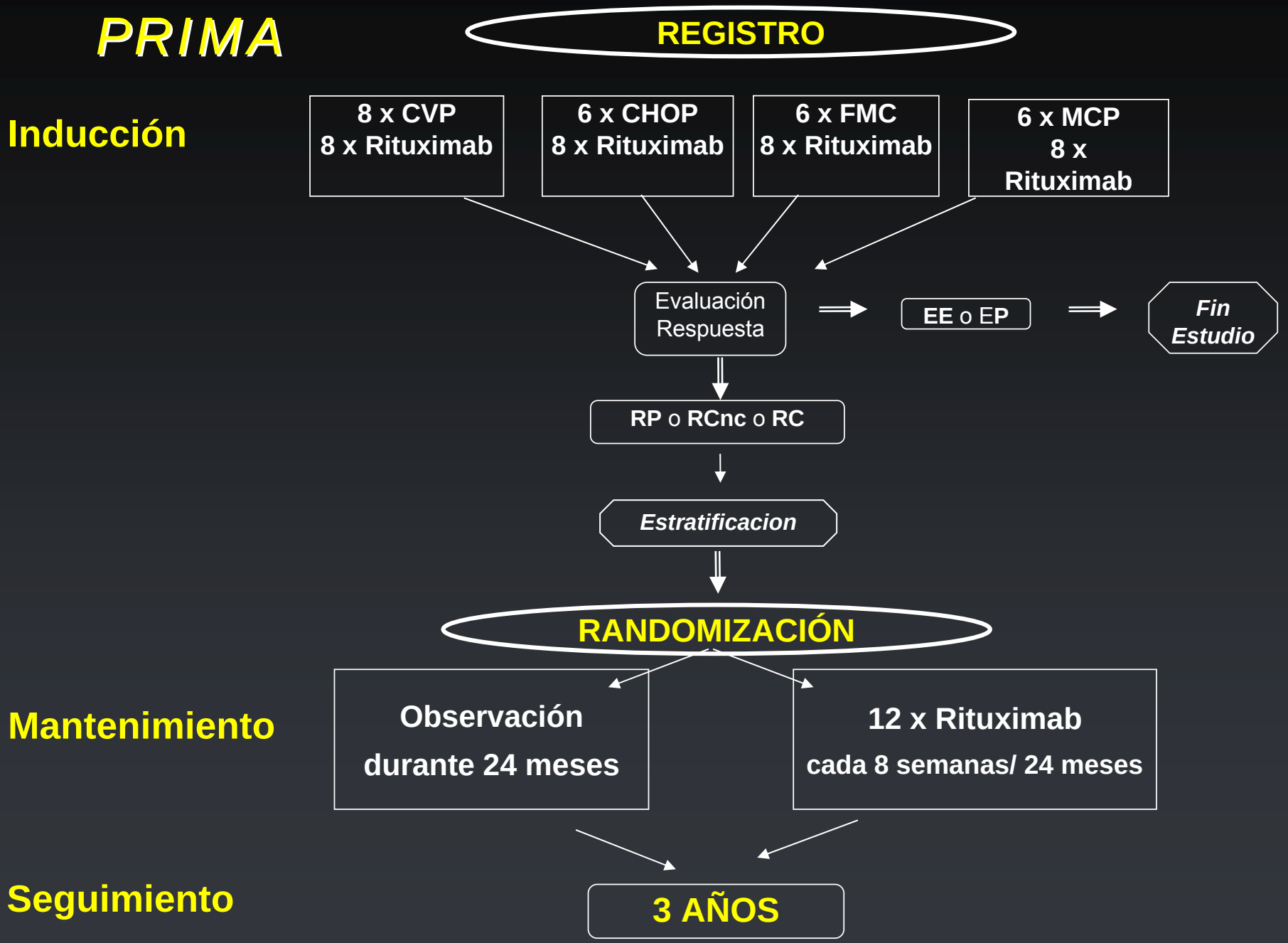
Hochster J Clin Oncol 2009

R- CHOP in Follicular Lymphoma: Treatment Outcome of 552 Patients Treated in a Randomized Trial of the German Low Grade Lymphoma Study Group (GLSG) after a Follow up of 58 Months

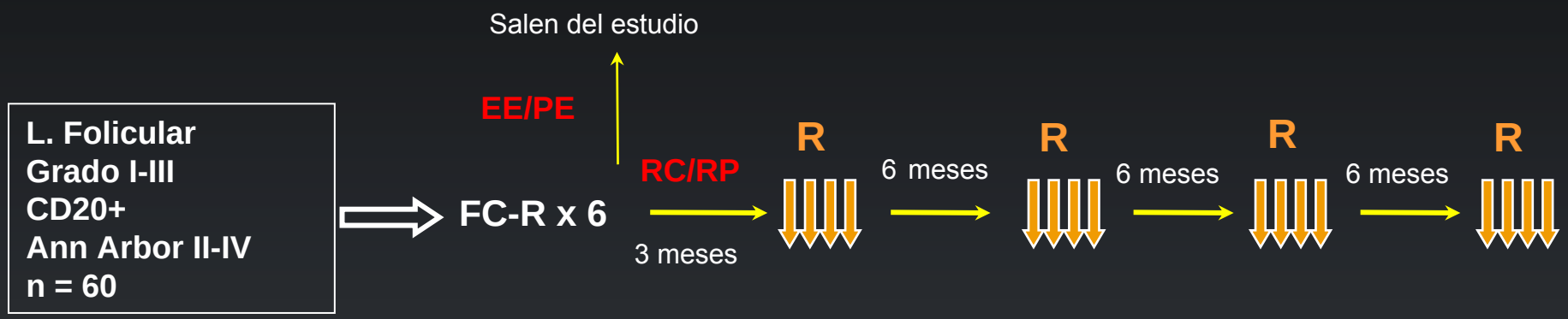


Buske, ASH 2009 ,abtr 2599

PRIMA


REGISTRO
Inducción
8 x CVP
8 x Rituximab
6 x CHOP
8 x Rituximab
6 x FMC
8 x Rituximab
6 x MCP
8 x
Rituximab
Evaluación
Respuesta
EE o EP
Fin
Estudio
RP o RCnc o RC
Estratificacion
RANDOMIZACIÓN
Mantenimiento
Observación
durante 24 meses
12 x Rituximab
cada 8 semanas/ 24 meses
Seguimiento
3 AÑOS

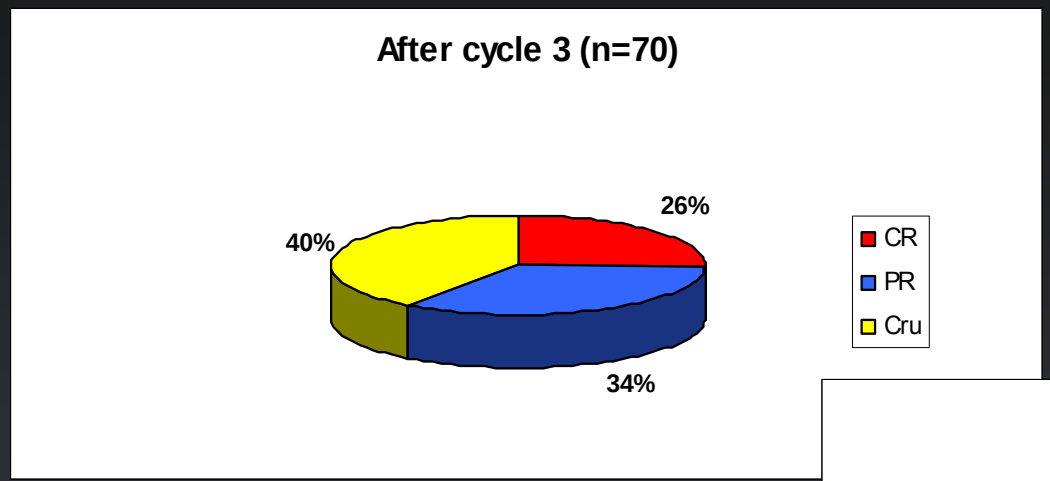
Protocolo FCR
Descripción del tratamiento y dosis

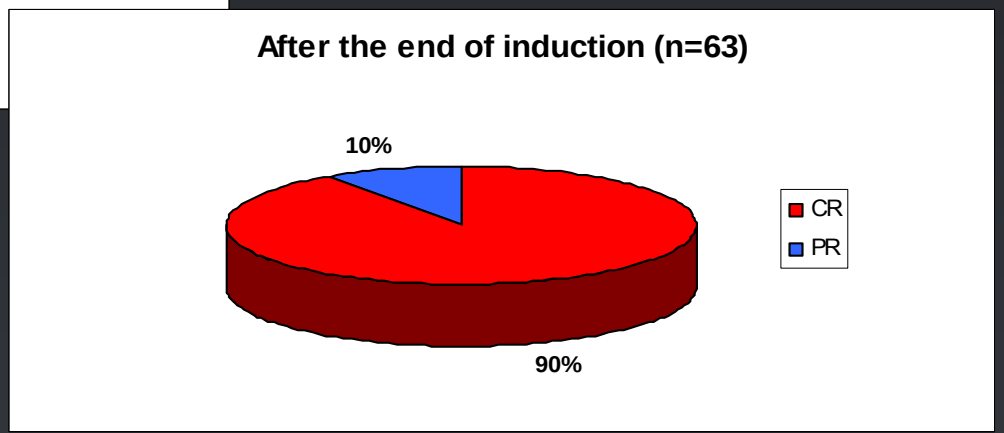


FCR (6 ciclos):

FLUDARABINA	**25 mg/m^2 iv**	**días 1-3 (dosis total 75 mg/m^2)**
CICLOFOSFAMIDA	**1000 mg/m^2 iv**	**día 1 (dosis total 1000 mg/m^2)**
RITUXIMAB	**375 mg/m^2 iv**	**día 3 (1º ciclo) día 1 (resto de ciclos) (dosis total 375 mg/m^2)**

Protocolo FCR
Respuesta al tratamiento





Cortesía del Dr. J.F. Tomás

Respuestas en linfoma folicular

Autor, año	n	Esquema	RR (RC) %
Marcus, 2005	151	R-CVP	81 (41)
Hiddemman, 2005	223	R-CHOP	96 (20)
Herold, 2005	105	R-MCP	92 (49)
Foussard, 2006	175	R-CHVP/IFN	94 (76)
McLaughlin, 2005	41	R-ATT	95 (85)
Czuczman, 2005	27	R-Flu	91 (81)
McLaughlin, 2005	82	R-FND	100 (88)
Tomás, 2006	75	R-FluCy	100 (90)

Protocolo FCR
Supervivencia global

9 Deaths (11%) have occurred to date since cycle 1

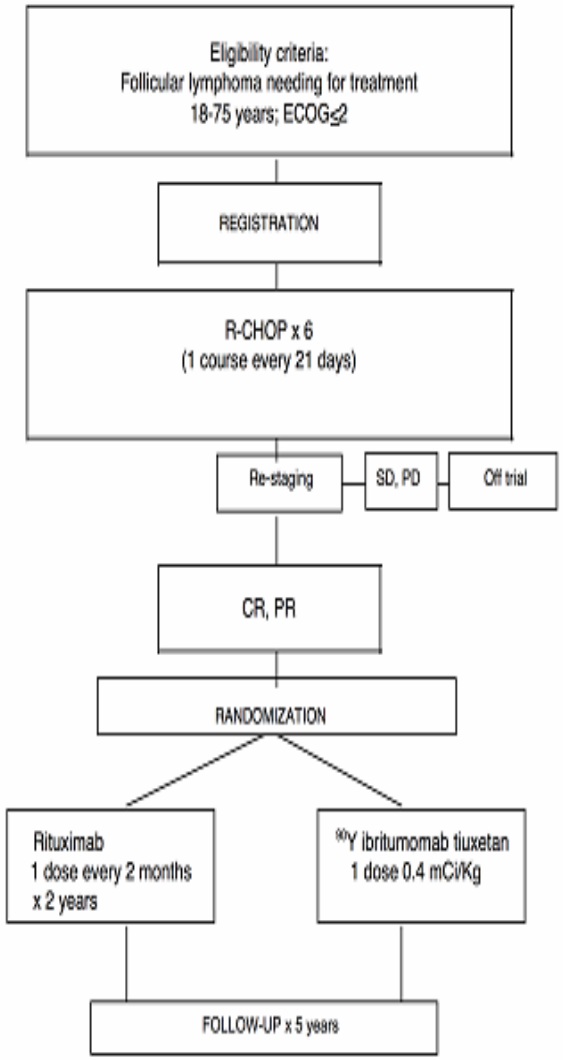
Surviving time	# patients	Cause of death
8 mo.	2	Obliterative bronchiolitis
		CMV/Aspergillus/Staph. infection
10 mo.	1	Fever + disease progression
11 mo.	3	Fever
		Bilateral lung infiltration
		Secondary AML (M6)
>12 mo.	3	Cranial nerves multineuritis syndrome
		Secondary AML (M1, del(7))
		Gastric Carcinoma

6/9 patients > 65 y

Cortesía del Dr. J.F. Tomás

Estudio ZAR

Diseño del estudio



Papel del trasplante Autologo en LNH folicular

- 4 estudios aleatorizados en primera. No recomendado fuera de ensayos clínicos

Trasplante en primera linea?’

#772 ASH 2008. Hiddemann W (Autologous stem cell transplantation after myeloablative therapy in first remission may be beneficial in patients with advanced stage follicular lymphoma after front-line therapy with R-CHOP. An analysis of the GLSG)

’96 CHOP vs MCIP (312)

’00 CHOP vs R-CHOP (268)

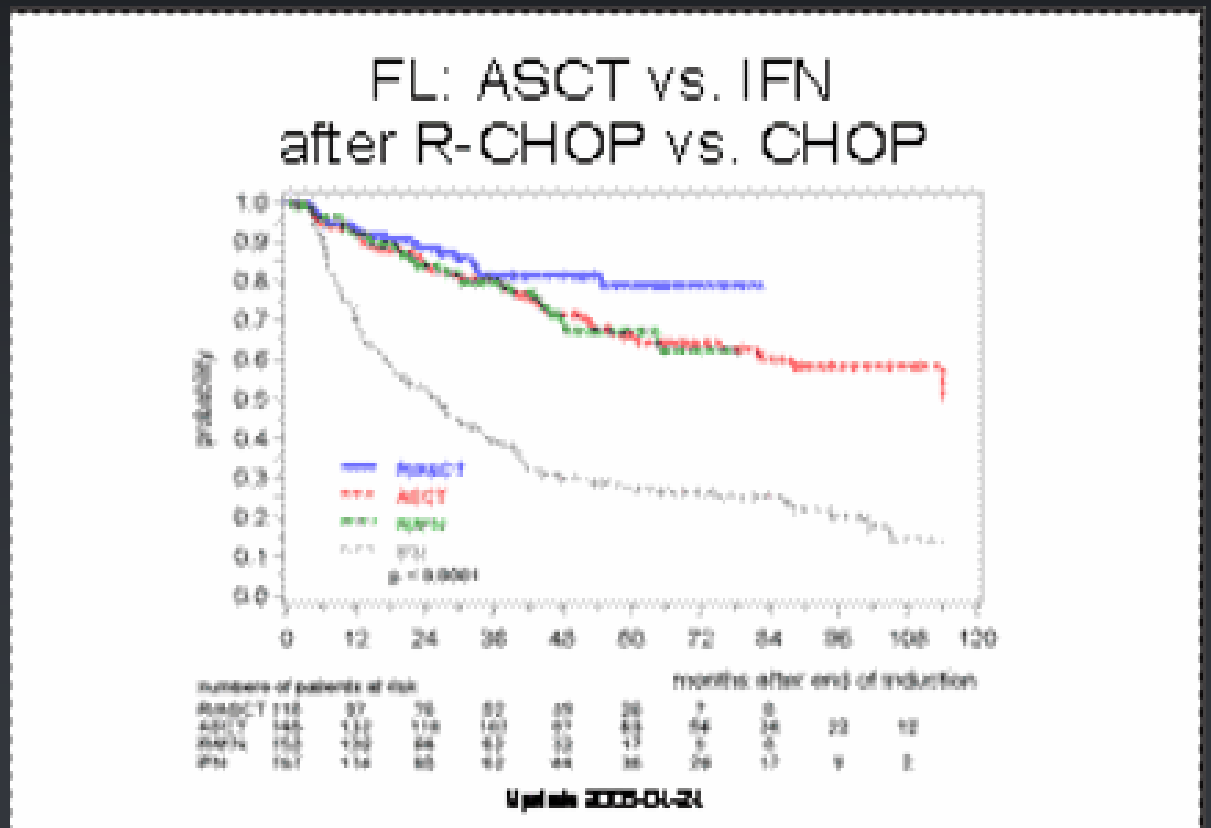
αIFN ← → TASPE

5 años PFS CHOP+INF: 27 %

CHOP+TASPE: 67%

R-CHOP+IFN: 67%

R-CHOP+TASPE: 79%



- Tratamiento de inducción
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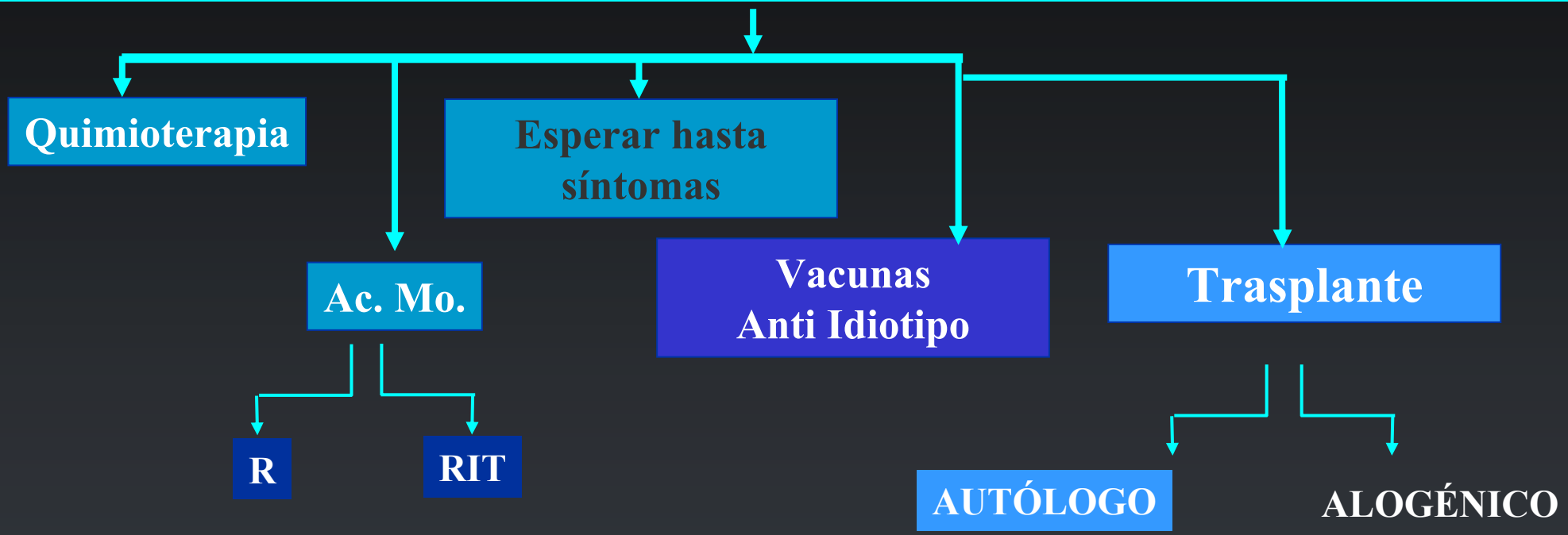
Opciones Terapeúticas en el LNH Folicular



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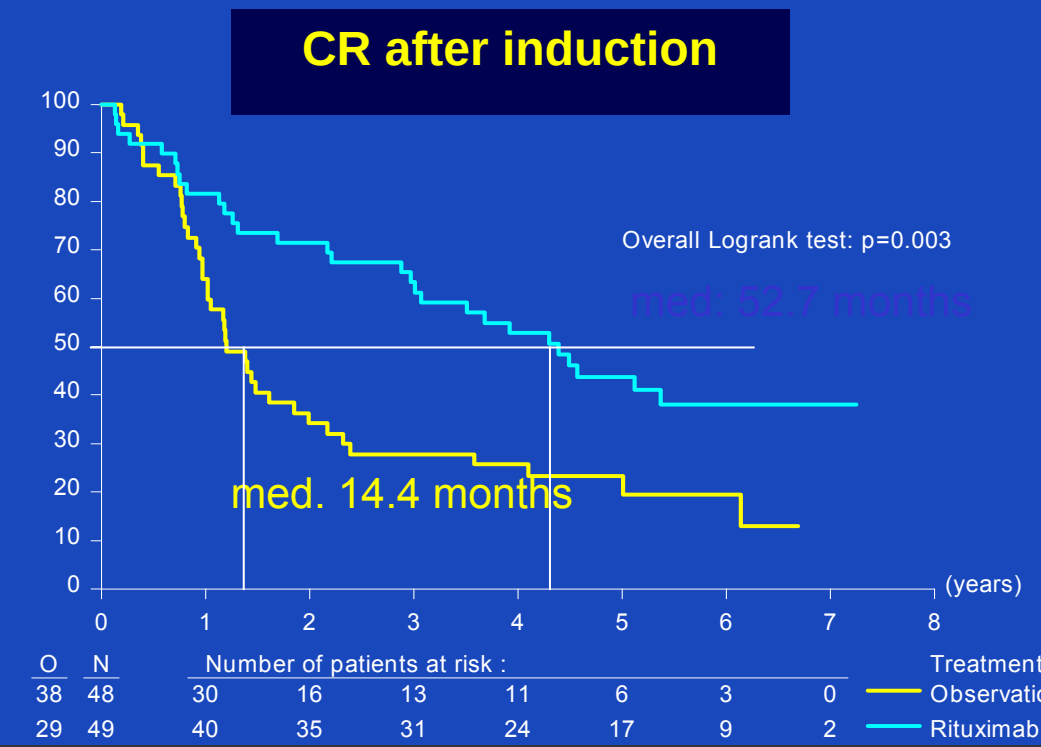
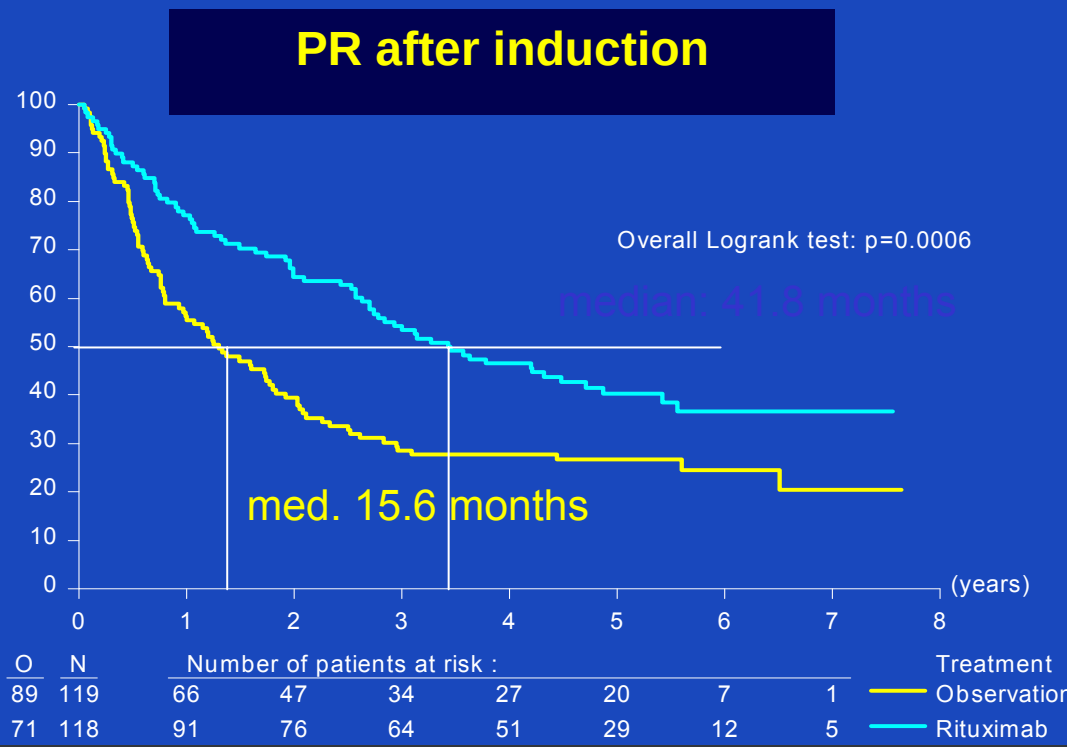
EORTC 20981 Intergroup phase III trial

PFS from 2nd randomization

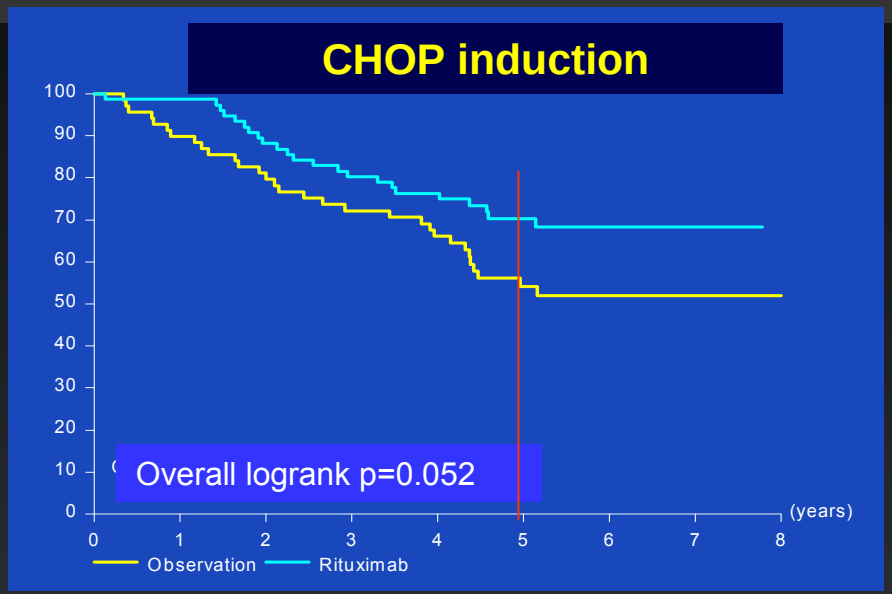
Subgroups according to response quality after induction

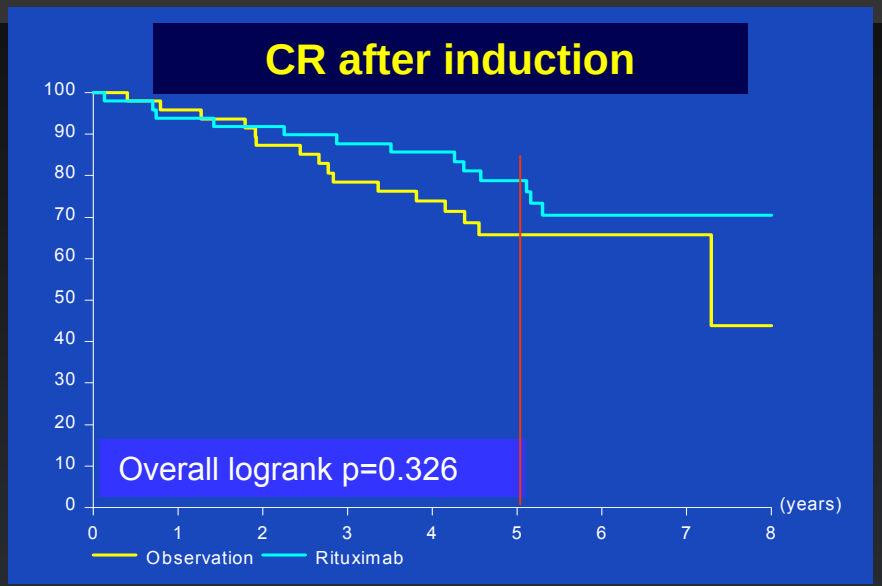


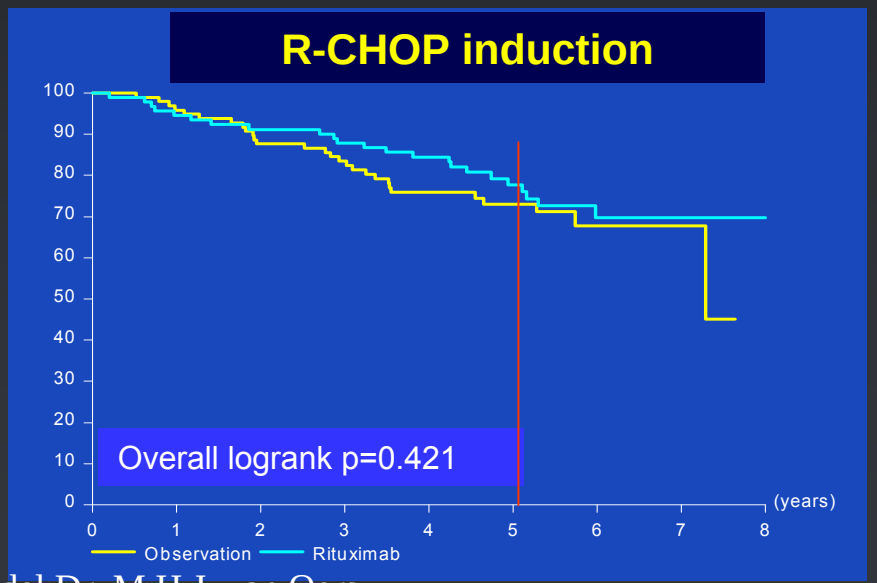


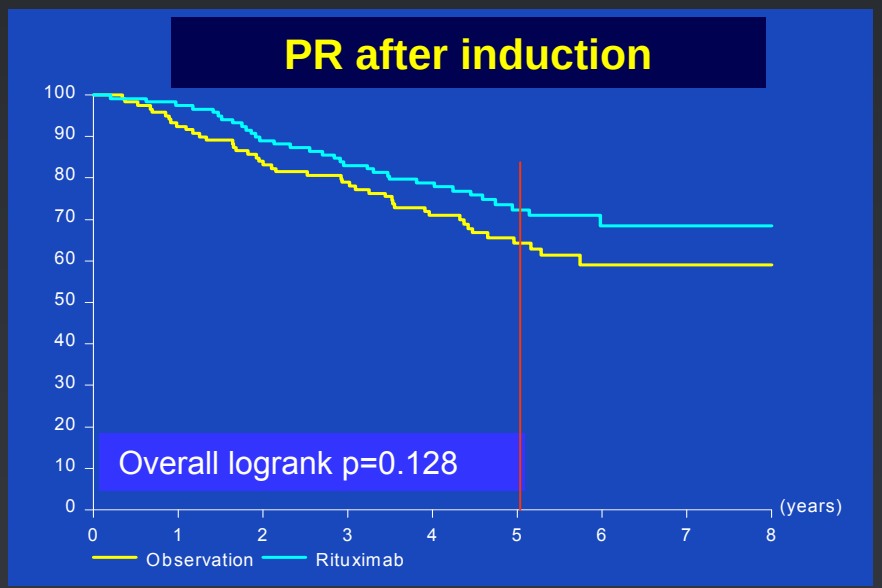
Cortesía del Dr. M.H.J. van Oers,ASH 2008

OS from 2nd randomization: subgroup analysis









Cortesía del Dr. M.H.J. van Oers

Bendamustina en LNH Indolentes

Study	Histology	No. of Patients	Regimen	Overall Response Rate	
				%	CR (%)
Rummel (phase II)[20]	Relapsed, refractory, indolent (16 MC)	63	B: 90 mg/m^2 days 1, 2; + R: 375 mg/m^2 day 1, every 28 days	90 75 (MC)	60 50
Robinson (phase II)[21]	Relapsed	66 (12 MC)	B: 90 mg/m^2 days 1, 2; + R: 375 mg/m^2 day 1, every 28 days	92 92 (MC)	55 (CR/CRu) 42 (MC)
Weide (phase II)[44]	Relapsed, refractory, indolent (18 MC)	57	B: 90 mg/m^2 days 1, 2; + Mitox: 10 mg/m^2 day 1; + R: 375 mg/m^2 day 8, every 28 days	89	35

Cheson J Clin Oncol 2009

Estudio Fase II abierto prospectivo no aleatorizado para valorar la combinación de rituximab, bendamustina, mitoxantrone, dexametasona (R-BMD) en pacientes con Linfoma Folicular refractarios o en recaída

BENDAMUSTINA:	90 mg/m^2/día, días 1 y 2 de cada ciclo, i.v.
MITOXANTRONE:	6 mg/m^2/día, día 1 de cada ciclo, i.v.
DEXAMETASONA:	20 mg/día, días 1 a 5 de cada ciclo, v.o.
RITUXIMAB:	375 mg/m^2/ día, días 1 de cada ciclo, i.v.

Metanalisis

- Preliminary meta-analysis
  - evidence for improved overall survival among indolent and mantle cell lymphoma patients treated with rituximab plus chemotherapy compared to chemotherapy alone
  - Coste eficaz (Lewis G,Blood ASH 2006)

Shultz et alJ Natl Cancer Inst 2007

Papel del trasplante en LNH folicular

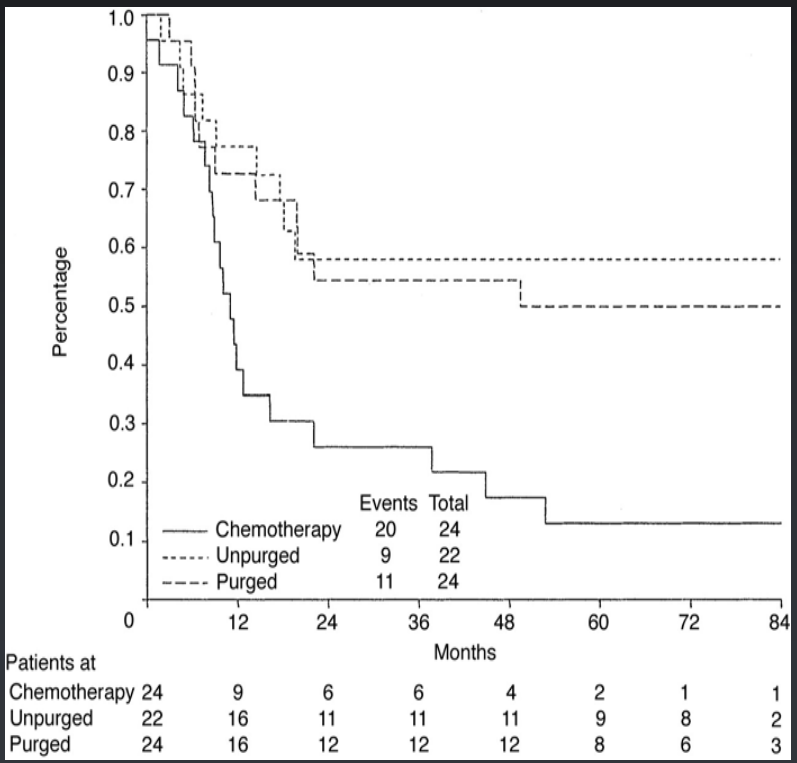
- 4 estudios aleatorizados en primera.No recomendado fuera de ensayos clínicos
- Si en 2ª respuesta (discutir con el paciente si auto o minialo o nuevos fármacos)

T Autólogo en LNH folicular en recaída. Estudio randomizado entre ADQ(+/- purging) vs TTO convencional (Estudio CUP.EBMT).SLP y SG

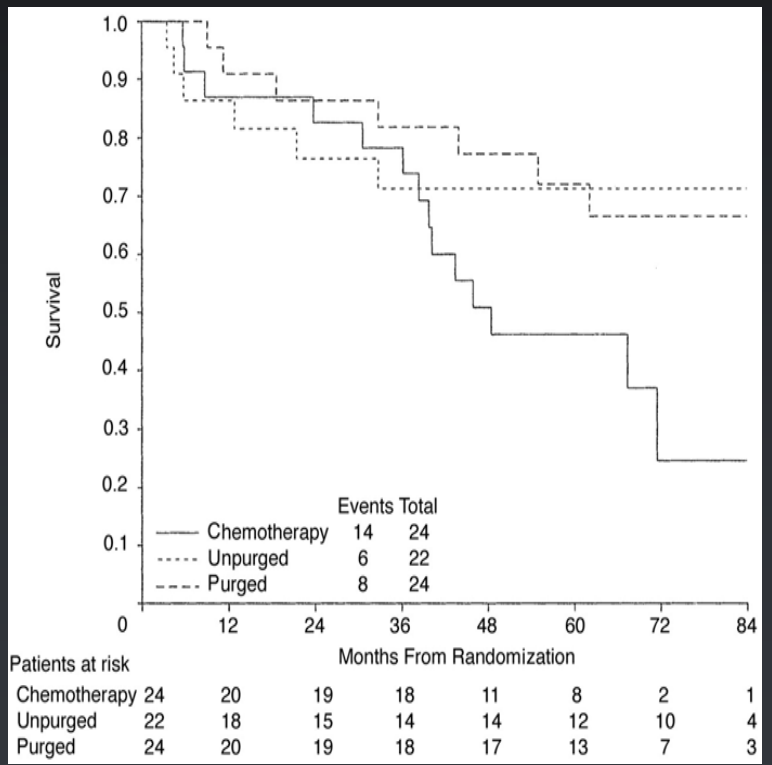
N=140 (7 años)

- **mediana seguim 69 meses**
- **SLP(2 a):55%vs 58%vs26% (p=0.0037)**
- **SG(4 a):77% vs 71 %vs 46% (p=0.026)**

SLP

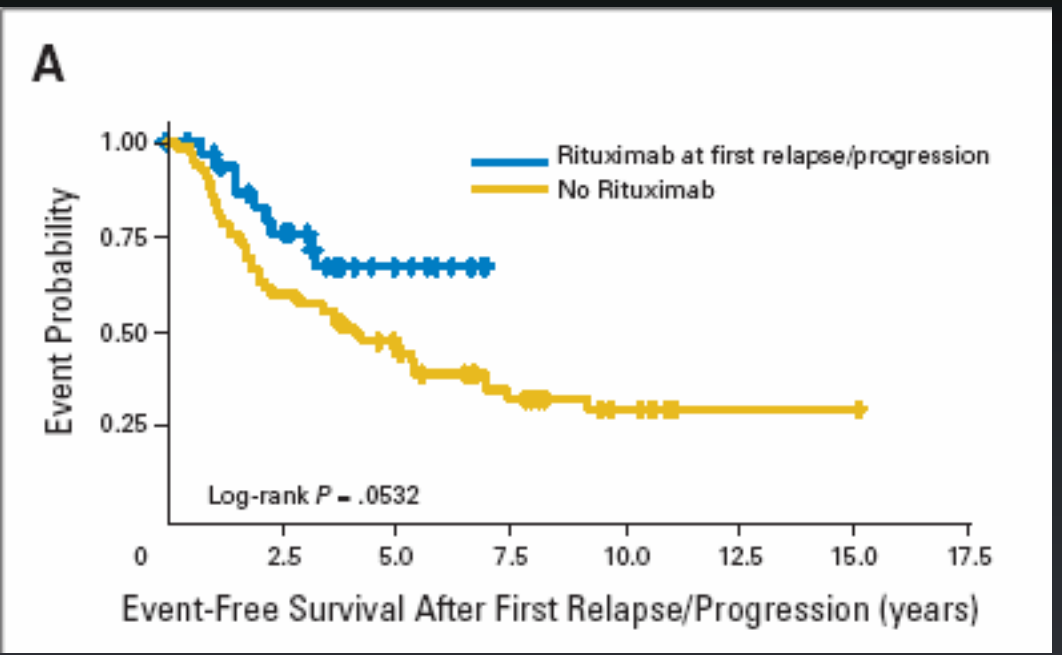


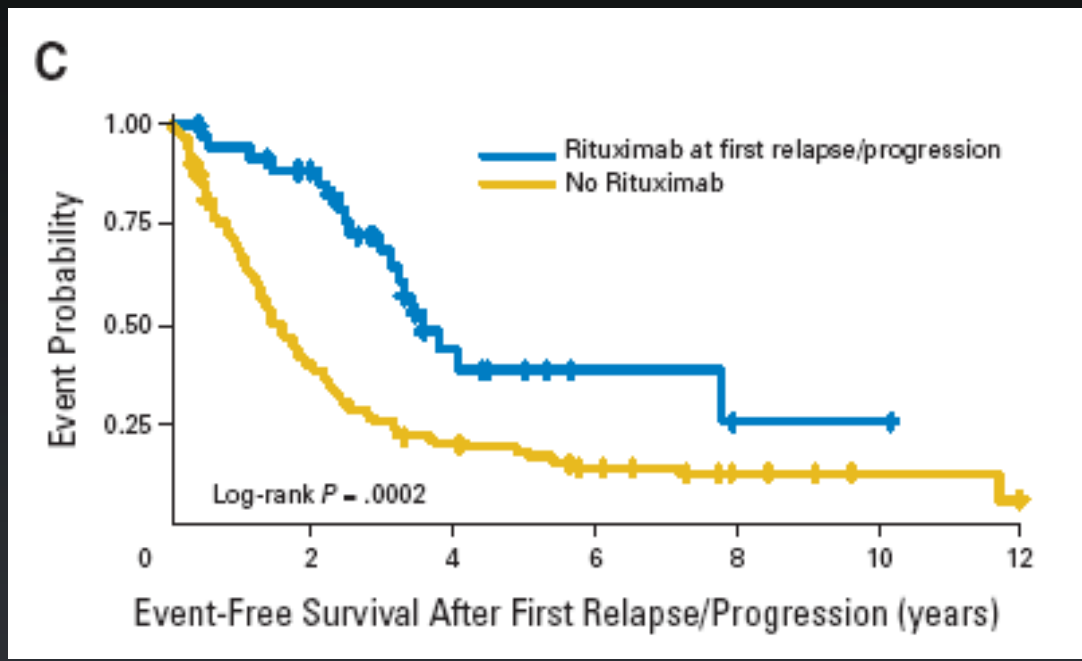
SG



Schouten JCO 2003

Impact of Rituximab and/or High-Dose Therapy With Autotransplant at Time of Relapse in Patients With Follicular Lymphoma: A GELA Study



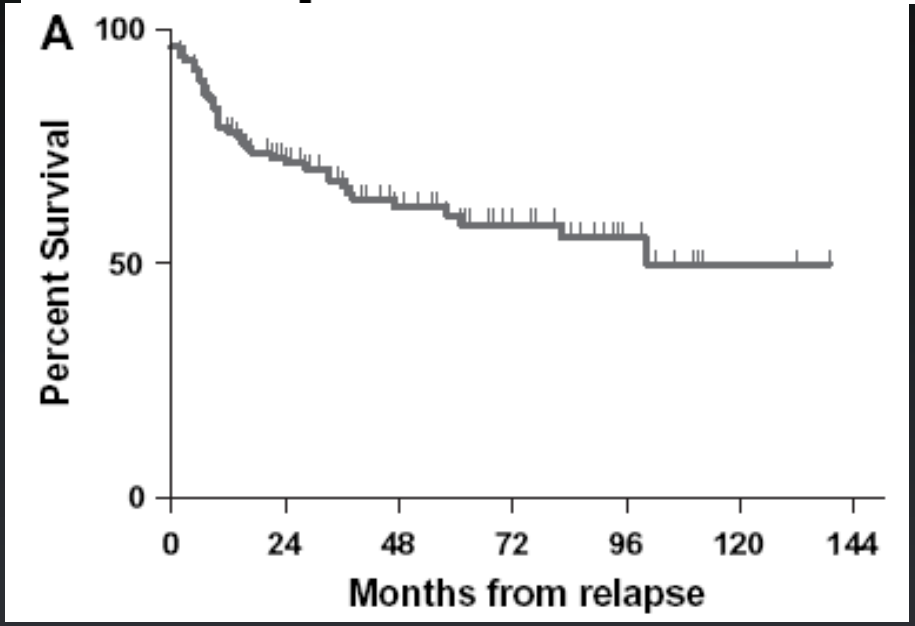


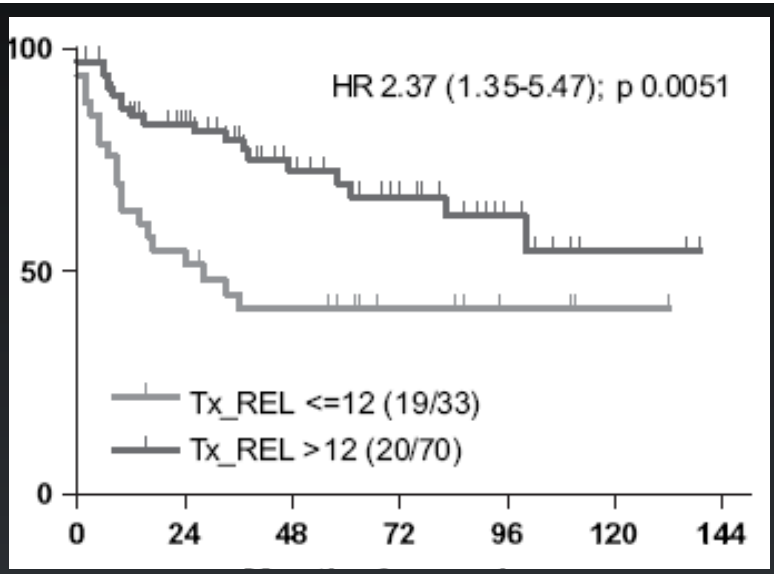
Con trasplante

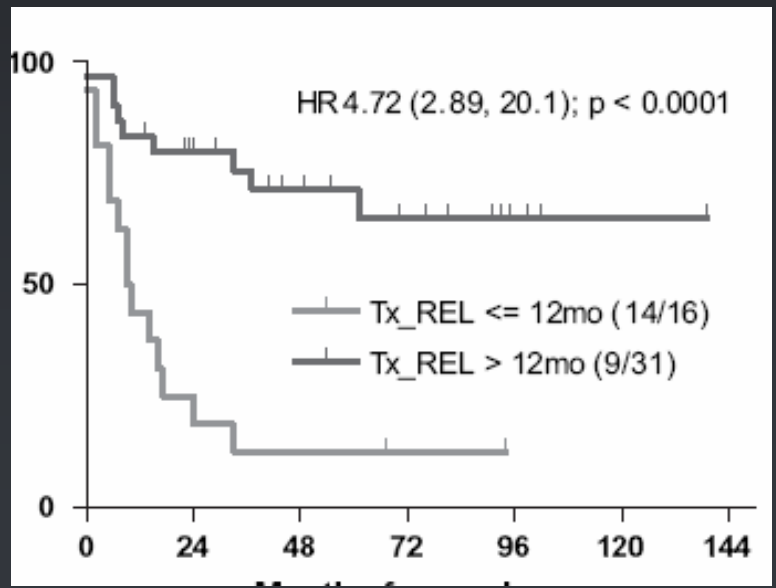
Sin trasplante

Sebban J Clin Oncol 2008

Characteristics of relapse after autologous stem-cell transplantation for follicular lymphoma: a long-term follow-up







- Mejor SG para pacientes trasplantados en primera linea
- Influencia desfavorable en la SG del momento de la recaída (arriba primera linea y abajo rescate)
- No influencia del FLIPI a la recaída
- Influencia favorable del rituximab en la recaída

Kornacker Ann Oncol 2009

Table 1. Unconjugated Monoclonal Antibodies for B-Cell Cancers.*

Antibody	Target	Status in the United States
Rituximab (Rituxan, Genentech or Biogen Idec)	CD20	Commercially available
Alemtuzumab (Campath, Bayer HealthCare Pharmaceuticals)	CD52	Commercially available
Human or humanized anti-CD20 antibodies	CD20	Phase 1–2 investigation
Lumiliximab (Biogen Idec)	CD23	Phase 3 investigation
Anti-TRAIL (Human Genome Sciences)	DRD	Phase 1–2 investigation
Bevacizumab (Avastin, Genentech)	VEGF	Phase 3 investigation
Galiximab (Biogen Idec)	CD80	Phase 2–3 investigation
Epratuzumab (Immunomedics)	CD22	Phase 2 investigation
SGN-40 (Seattle Genetics)	CD40	Phase 2–3 investigation
Anti-CD74 (milatuzumab, Immunomedics)	CD74	Phase 1 investigation

* DRD denotes death receptor domains, TRAIL tumor necrosis factor–related apoptosis-inducing ligand, and VEGF vascular endothelial growth factor.

- Tratamiento de inducción
- Mantenimiento o consolidación
- Tratamiento a la recaída
- Trasplante Autólogo
- Trasplante Alogénico

REDUCED INTENSITY CONDITIONING ALLOGENEIC TRANSPLANT IN INDOLENT LYMPHOMA

Patients (n)	Conditioning	Refractory %	Median follow-up	Relapse/ progression	Progression free survival	OS %	Non relapse mortality
62*(54FL)[1]	Fluda+TBI 200cGy	23	36.6(na)	38 transfus. 14 indolent	21 transfus. 54 indolent	18 transf 67 indolent	42
47 FL[2]	Fluda+Cy± R	0	60(19-94)	4	85	83	14
28[3]	BEAM+ Alemtuzumab	NA	17(1-67)	20	69	74	16
53[4]	Fluda+Cy+ Thiotepa	NA	31(6-70)	NA	73	66	18
73[5]	Fluda+ATG+BU	26	37(16-17)	9.6	51	56	40
41(FL29)[6]	Fluda +TBI Fluda+ Melf+alent.	24	36(18-60)	44	55	73	11

Authors: 1. Rezvani. 2. Khouri 3.Faulkner 4. Corradini 5. Vigoroux 6. Morris

[3-6] Follicular & other indolent lymphomas are included

* Also transformed lymphomas

FL: follicular lymphoma. TBI: total body irradiation; NA: not available

Eight-year experience with allogeneic stem cell transplantation for relapsed follicular lymphoma after nonmyeloablative conditioning with fludarabine, cyclophosphamide, and rituximab

No. of patients	47
Median age, y (range)	53 (33-68)
Sex, no. (%)	
Male	25 (53)
Female	22 (47)
Chemotherapies before transplantation (%)	
Rituximab-chemo combinations	35 (74)
3 regimens	7 (15)
4 regimens	12 (25.5)
>5 regimens	5 (10.5)
No. of patients with prior autologous transplantation (%)	9 (19)
Median time from diagnosis to transplantation, y (range)	3 (0.7-24)
Disease status at transplantation, no (%)	
Complete remission	18 (38)
Partial remission	29 (62)

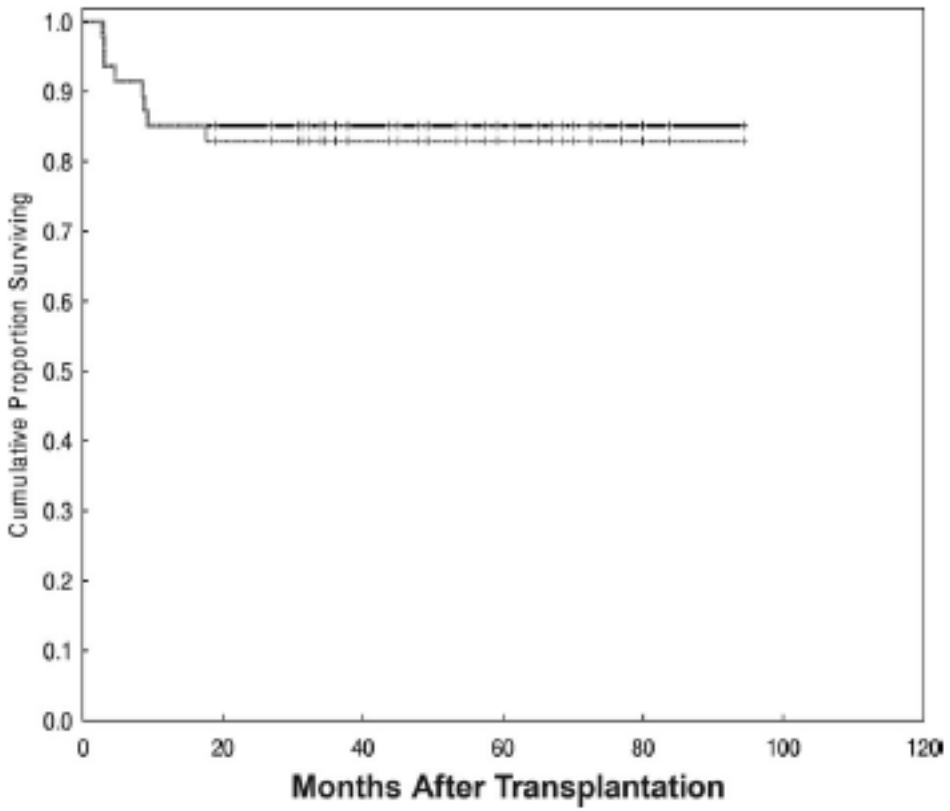


Figure 3. OS (solid line) and PFS were 85% and 83%, respectively, with a median follow-up of 60 months (range, 19-94 months).

Khouri Blood 2008

Conditioning regimen with RI conditioning
The GELTAMO experience

Days	-8	-7	-6	-5	-4	-3	-2	-1	0	+1+3+6+11
Fludarabine (30 mg/m²/d)	F	F	F	F	F					
Melphalan (70-140 mg/m²)						M	M			
MTX + Folinic acid (10 mg/m2)										M M M M
CSA i.v.	1 mg/kg								2 mg/kg	
Donor G-CSF (10-16 µg/kg)	→					G	G	G	G	→
PBSC Infusion (>4 ·10⁶/kg CD34+)									P	

GELTAMO

TRASPLANTE ALOGÉNICO CON AIR EN LNH Foliculares (n=37)

Caracteristicas de los pacientes

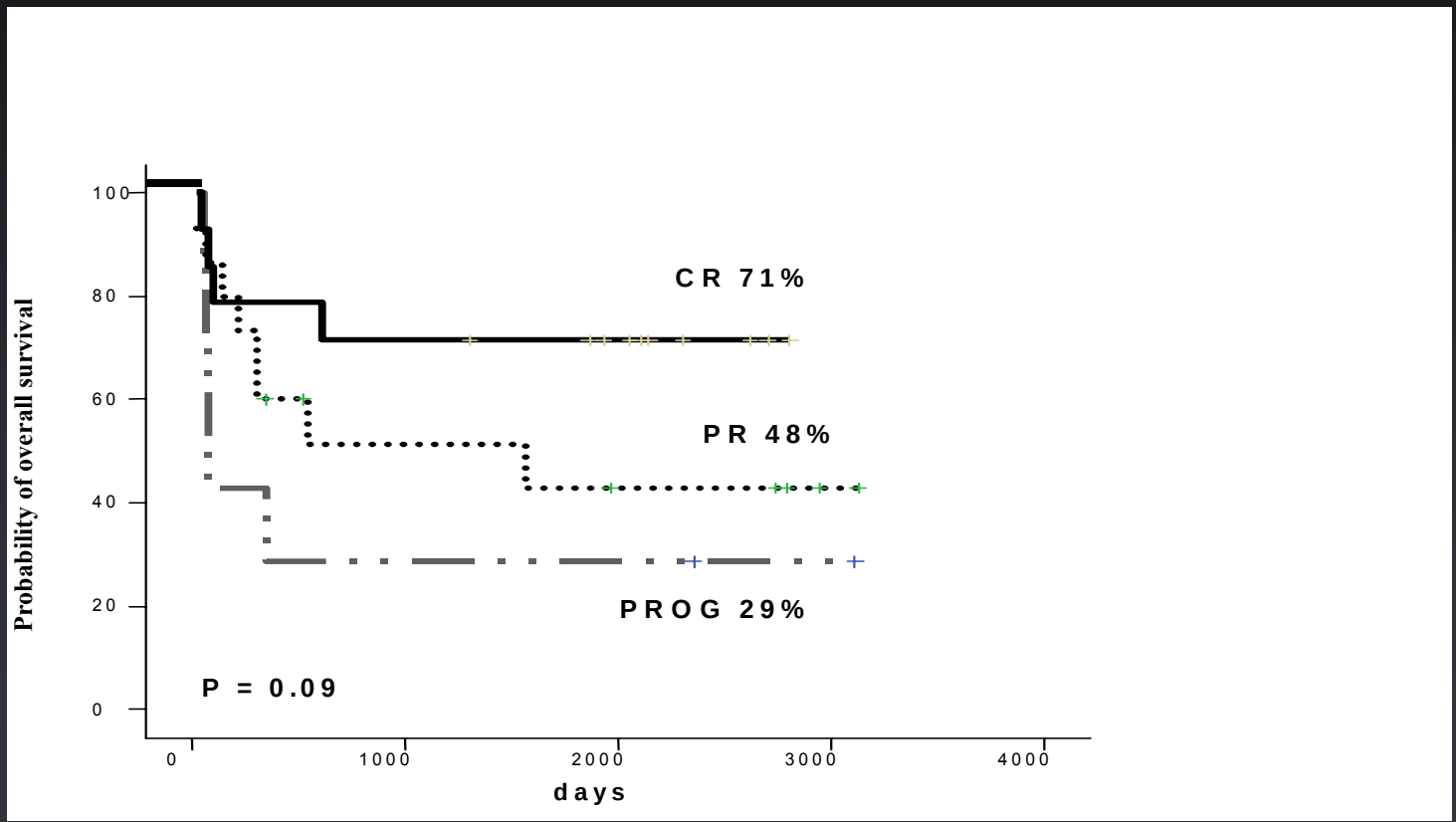
Edad :50(34-62) Sexo V/M(26/11)

+>2 lineas	59%
+Auto previo	46%
+Enf activa quimiosensible	43%
+ENF quimiorrefractaria	18%

GELTAMO

3 LF grado 3

TRASPLANTE ALOGÉNICO CON AIR EN LNH Foliculares . Supervivencia global



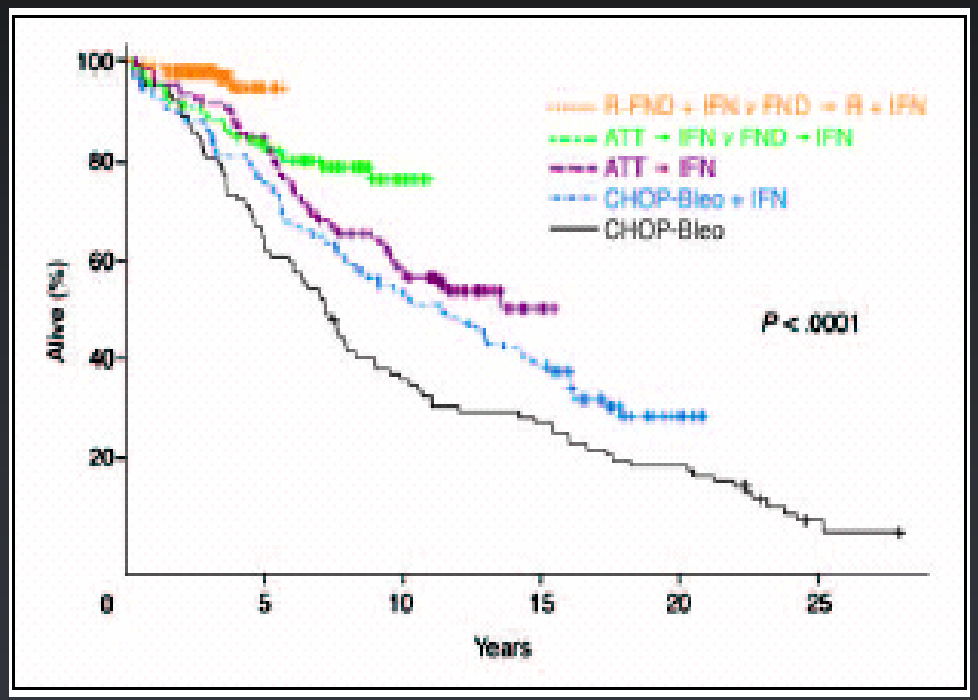
REDUCED INTENSITY IN ALLOGENEIC TRANSPLANT IN FOLLICULAR LYMPHOMA

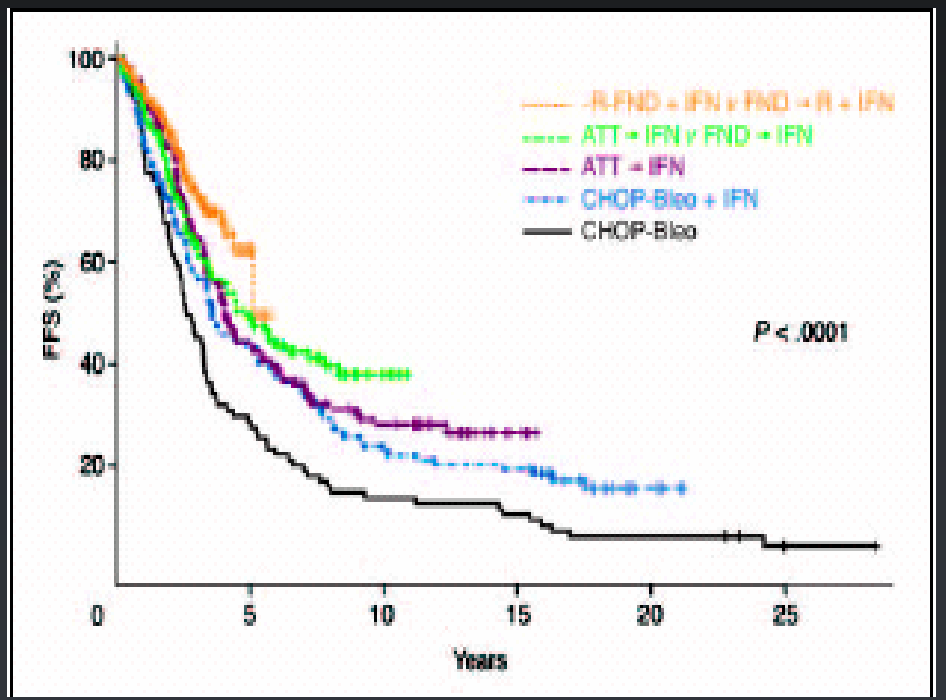
Disease Status	aGVHD n/n evaluable	Status +120	OS d +120	cGVHDn/n evaluable*	Outcome after +120	OS at 4 y.	Final outcome at last F-up
Prog (n=7)	6/7	2CR 1PR[2] 4NRM	43%	3/3	2CR 1NRM 10CR	29%	2CR 5NRM 10CR
PR (n=16)	6/15[1]	2NR[3] 2NRM 10CR	88%	11/14	2PROG[4] 2NRM 10CR	48%	2 deaths (lymph.) 4NRM 10CR
CR (n =14)	6/14	1PROG[4] 3NRM	78%	8/11	1NRM	71%	4NRM

GELTAMO

Improvement of Overall and Failure-Free Survival in Stage IV Follicular Lymphoma: 25 Years of Treatment Experience at The University of Texas M.D. Anderson Cancer Center

Qi Liu, Luis Fayad, Fernando Cabanillas, Fredrick B. Hagemeister, Gregory D. Ayers, Mark Hess, Jorge Romaguera, M. Alma Rodriguez, Apostolia M. Tsimberidou, Srdan Verstovsek, Anas Younes, Barbara Pro, Ming-Sheng Lee, Ana Ayala, and Peter McLaughlin





JCO 2006

Comentarios al LNH Folicular

- Los regimenes con R-Q han mejorado la respuesta, la SLP, el TST y la Supervivencia global
- La consolidación con zevalin mejora la SLP en pacientes que no habían recibido R en la inducción
- El mantenimiento en 1 ª linea tras CVPmejora la SLP El mantenimiento en segunda linea mejora la SLP pero la SG solo mejora en pacientes quie no habían recibido R en la inducción
- El TASPE no está indicado en 1ª RC; en 2ª RC mejora la SLP y quizas la SG
- En pacientes refractarios a R o con recaida precoz tras R-QT el trasplante alogénico puede ser una opción curativa

LINFOMAS FOLICULARES

estadio I ,0

en pacientes mayores e incluso en pacientes jóvenes PET negativo y no EMR en MO al DX:
1.Abstención terapéutica, ó
2.RT local, la RT local + RCHOP x3 ó la RT local + rituximab por 4 dosis.

Tratamiento de Estadios Precoces (I y II)

1. pacientes jóvenes candidatos a terapia curativa: RT local + Rituximab x 4
2. pacientes mayores: RT a no ser que No quede enfermedad visible tras la biopsia en cuyos casos, el Tratamiento será la abstención

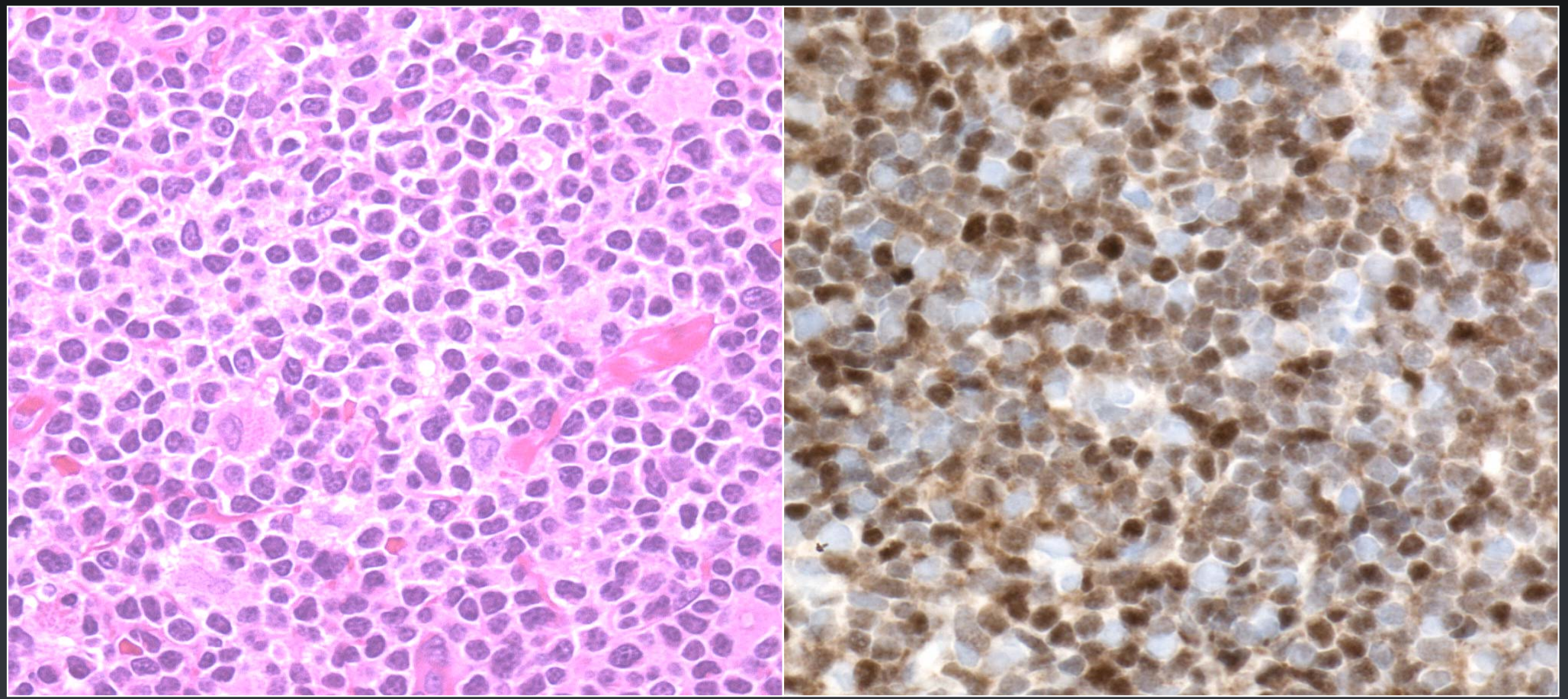
Estadios Avanzados

1. una opción, en pacientes asintomáticos es esperar y ver hasta la progresión
2. 2.-R-CHOP x 6 ciclos (en ausencia de ensayo clínico

criterios de inicio de tratamiento:

1) > 3 áreas nodales de al menos 3 cms, en distinta localización,
2) cualquier masa nodal o extranodal superior a 7 cms,
3) síntomas B
4) bazo voluminoso
5) síndrome compresivo
6) derrame pleural o ascitis
7) beta 2 micro o LDH elevada.

Mantle cell lymphoma



CyclinD1

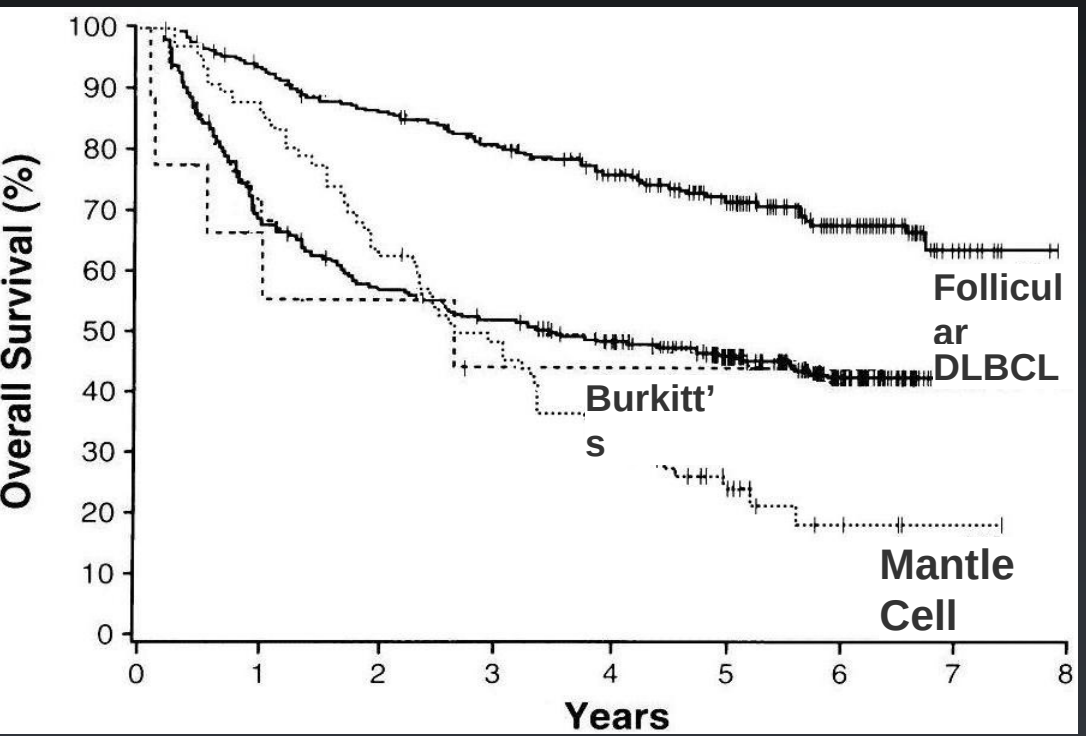
Mantle cell lymphoma

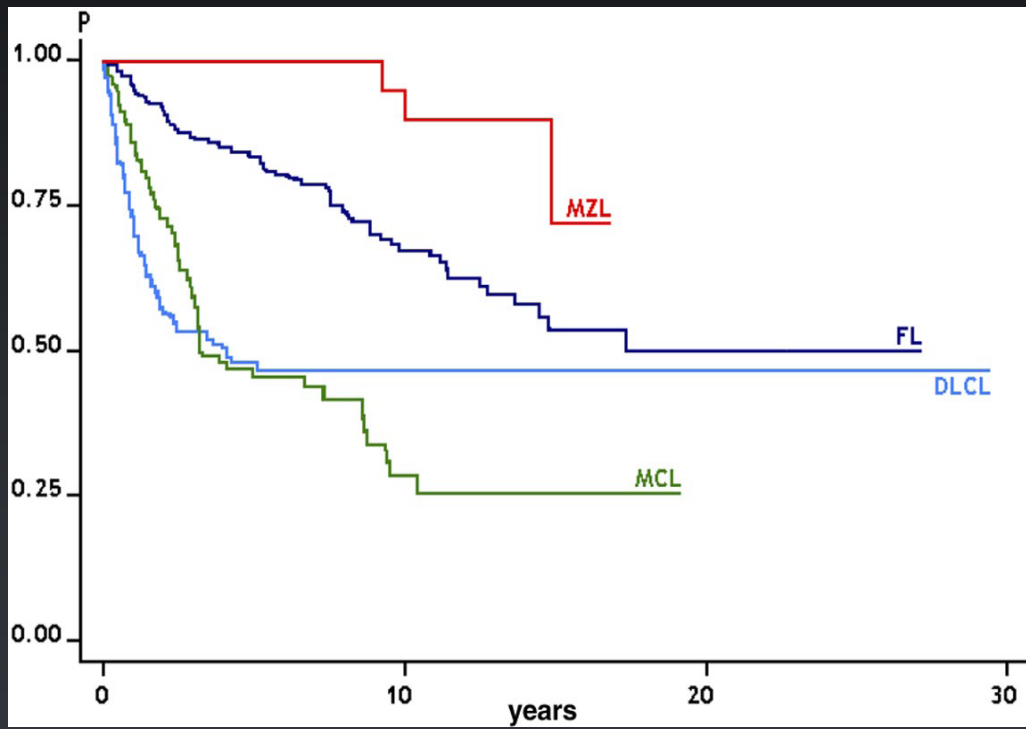
Frequency	6%
Median age	63
Age range	37-82
M	74 %
B symptoms	28 %
Extranodal site	81 %
Bone marrow	64 %

Immunophenotype	CD20+, CD5+, CD23-, cyclinD1+
Cytogenetics	t(11;14)(q13;q32)
Oncogenes	bcl-1 (cyclinD1)

Mantle cell lymphoma

The worst lymphoma to have?
Have improvements been made?





The International Lymphoma Study Group. Blood 1997

Ghielmini Blood 2009

Resultados con QT standard en LNH Manto

Regimen	N	ORR, %	CRR, %	PFS/EFS, months	2-Year OS, %
COP/CVP	37	84	22	10	65
	35	60	40	20	45
	46	83	18	—	—
CHOP	26	88	38	7	60
	60	75	7	19	76
	46	87	15	21	85
MCP	40	73	20	15	85
	46	63	15	13	—
R-MCP	44	71	32	18	—
R-CHOP	62	94	34	20	76
	40	96	48	17	—
VcR-CVAD	30	90	77	73% at 18 months	97% at 18 months

Ghielmini Blood 2009

Regímenes con altas dosis de ARA-C

	N	ORR, %	CRR, %
Hyper-CVAD/MTX-Ara-C	45 (20 untreated)	93	38
Hyper-CVAD/MTX-Ara-C	25 (age > 65 y)	92	68
R-Hyper-CVAD/R-MTX-Ara-C	97	97	87
R-Hyper-CVAD/R-MTX-Ara-C	49	88	58
R-Hyper-CVAD/R-MTX-Ara-C	32	53	50
R-DHAP	25	96	92
CHOP × 3 + DHAP × 3	28	92	84
R-CHOP × 3 + R-DHAP × 3	60	95	61
R-CHOP × 3 + HD-Ara-C × 1	87	72	29

Ghielmini Blood 2009

R-HyperCVAD como TTO de 1ª linea en LM (n=97)

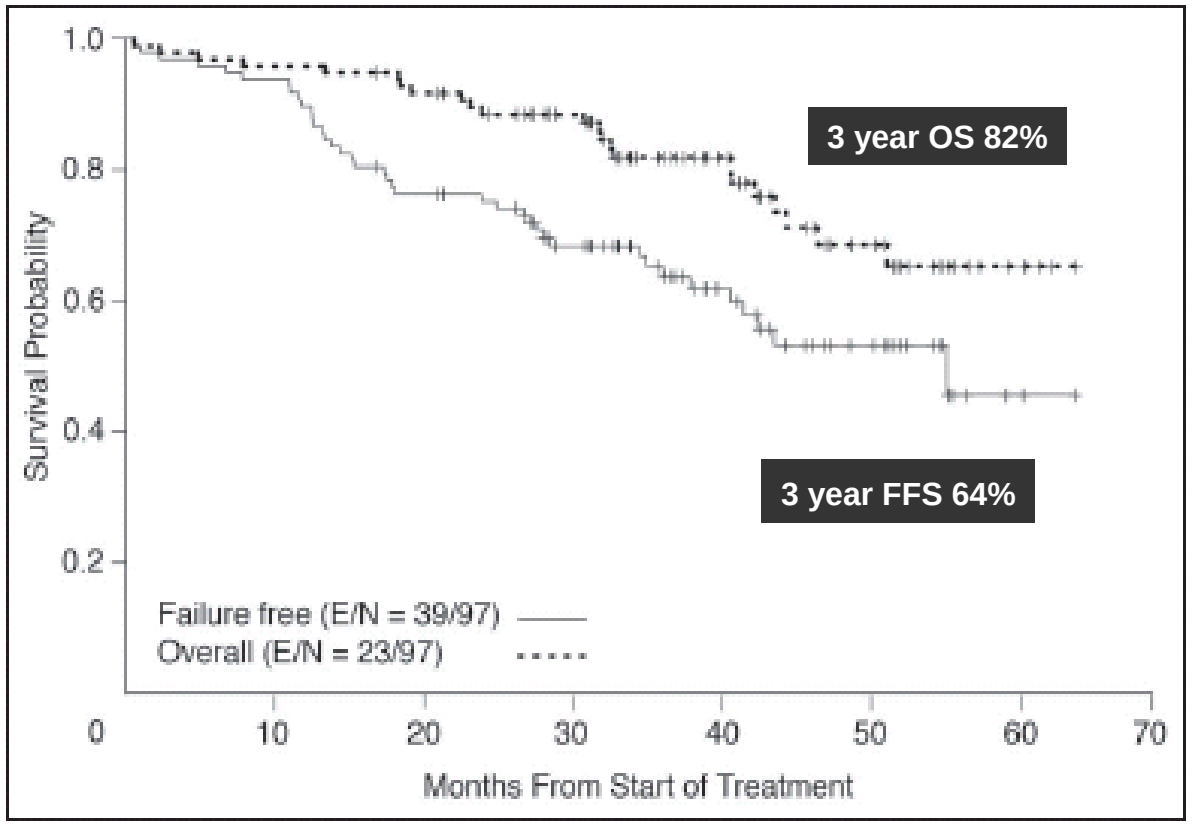
RR 97%

CR 87%

PR 10%

MFU 40 mo

Mortality:8%



Romaguera, JCO2005

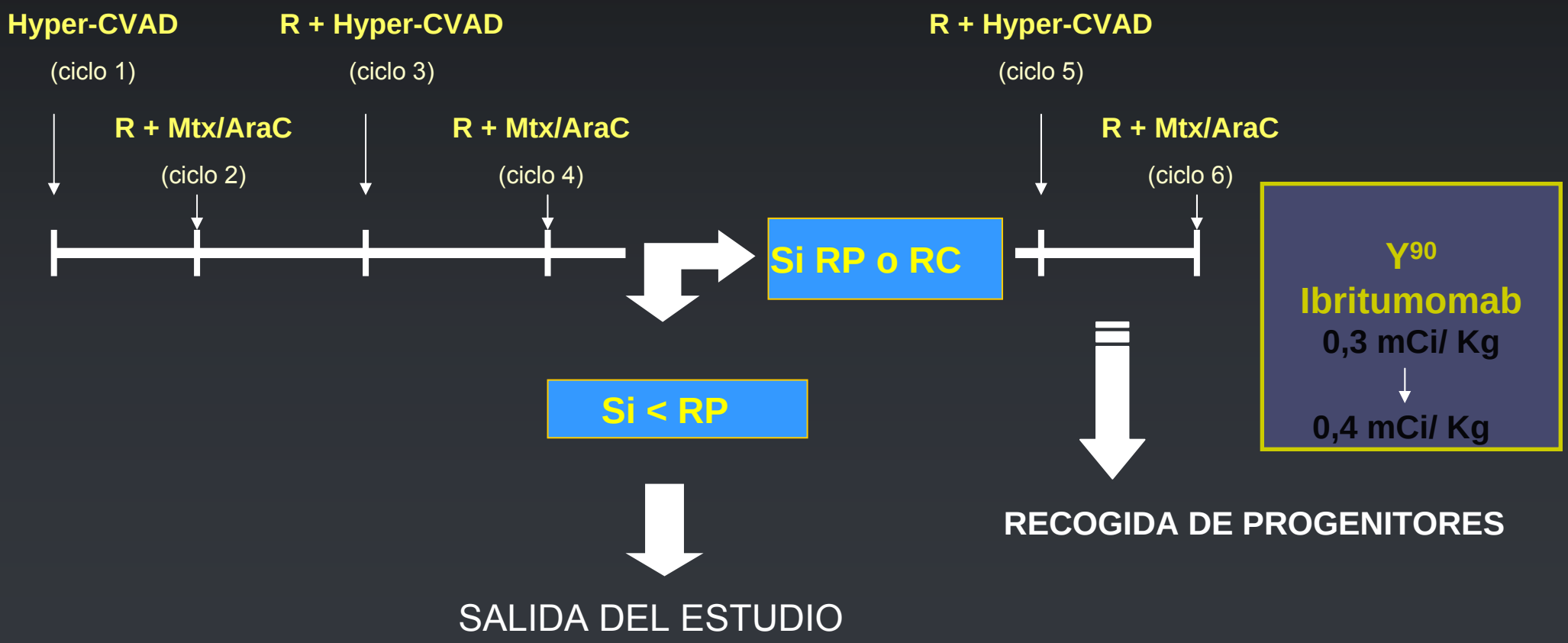
R + Hyper-CVAD y R+ METOTREXATO/CITARABINA
Y CONSOLIDACIÓN
CON Y90-IBRITUMOMAB TIUXETAN
EN PACIENTES CON LINFOMA DE CÉLULAS DEL MANTO

CÓDIGO : GEL/TAMO-LCM -04-02

Dra R.Arranz

ESQUEMA DEL TRATAMIENTO

INDUCCION | **CONSOLIDACION**



Características

28 pacientes monitorizados

Edad	60 (41-70)
Histología blástica	11 %
Varones	79 %
ECOG ≤1	93 %
Estadio IV	93 %
Infiltración medular	85 %
Infiltración tubo digestivo	59 %
LDH aumentada	27 %
β2 microglobulina alta	68%

Seguridad en la Inducción (sobre 156 ciclos)

Grados 3-4	HYPERCVAD	**MTX/ARA C**
Hemoglobina	21/81 (26%)	37/75 (50%)
Neutropenia	43/81 (53 %)	66/75 (89%)
Trombopenia	28/81 (35 %)	72/75 (96%)
Hemorragias	0/81 (0%)	1/75 (1.3 %)

SAES 56 (36%)

Neutropenia febril	29 (19%)	
Bacteriemia	6 (4%)	
Shock séptico	6 (4%)	(1 éxitus)
Trombosis venosas	2 (1%)	
Otros	11 (7%)	(sd cerebeloso, estomatitis…)
No relacionados	2 (1%)	(1 suicidio, neutropenia febril)

Eficacia en la Inducción

- **Tras 4 ciclos : sobre 27 evaluados**

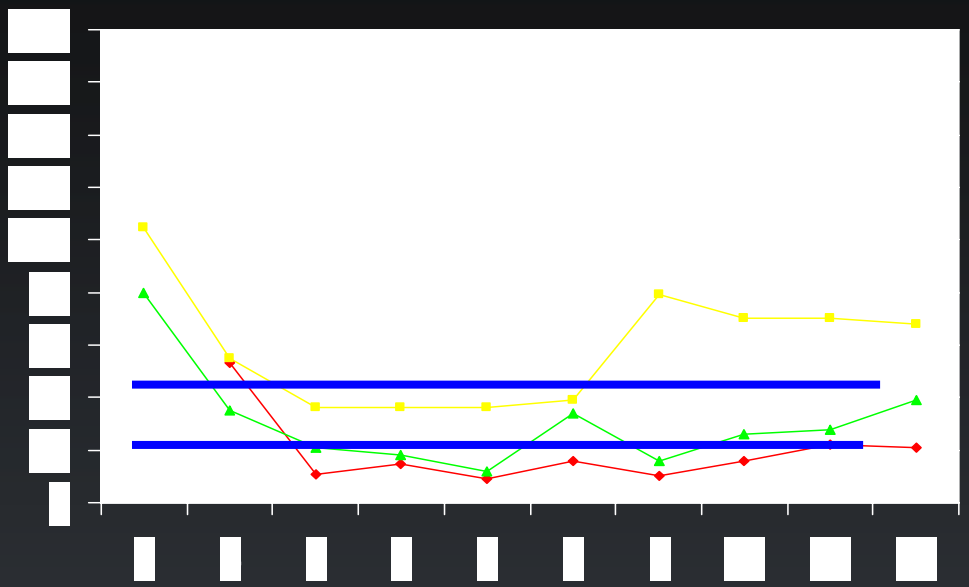
RC	14 (52%)
RCi	4 (15%)
RP	6 (22%)
No evaluables (Toxicidad)	3 (11%)

- **Fin de la inducción: 20 evaluados**

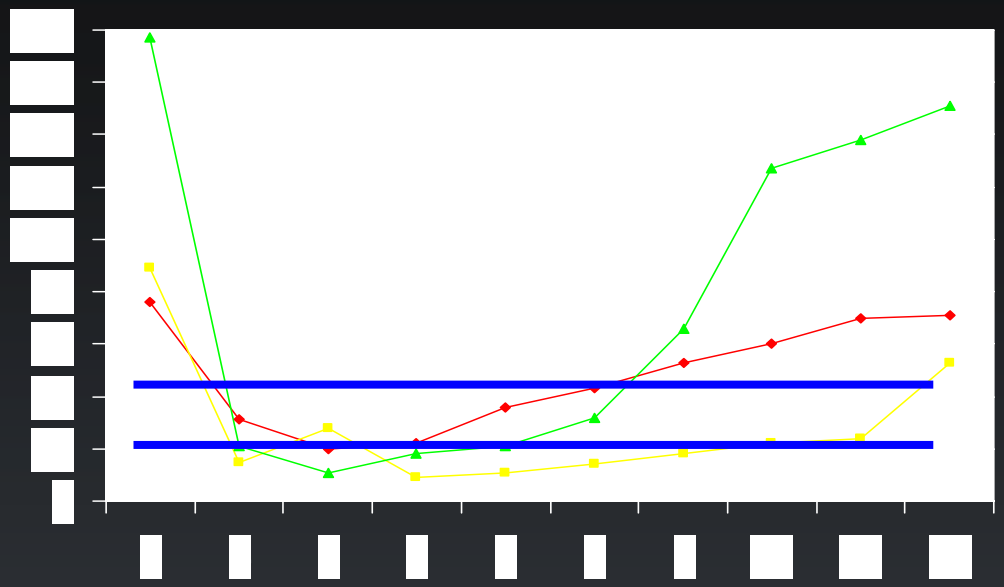
RC	16 (80%)
RCi	3 (15%)
Progresión	1 (5%)

Salidas por toxicidad (7) y abandono (1): 30%

Consolidación con Y^{90}Ibritumomab Tiuxetan 0,3 mCi/ Kg



2/3 trombopenia grado 4
Duración: 5 y 8 semanas



5/6 trombopenia grado 4
Duración: 5,5 semanas

POR TANTO…….

- Y^{90} Ibritumomab 0,3 mCi/ Kg
- Se dejan de recoger progenitores

Consolidación con Y^{90}Ibritumomab Tiuxetan

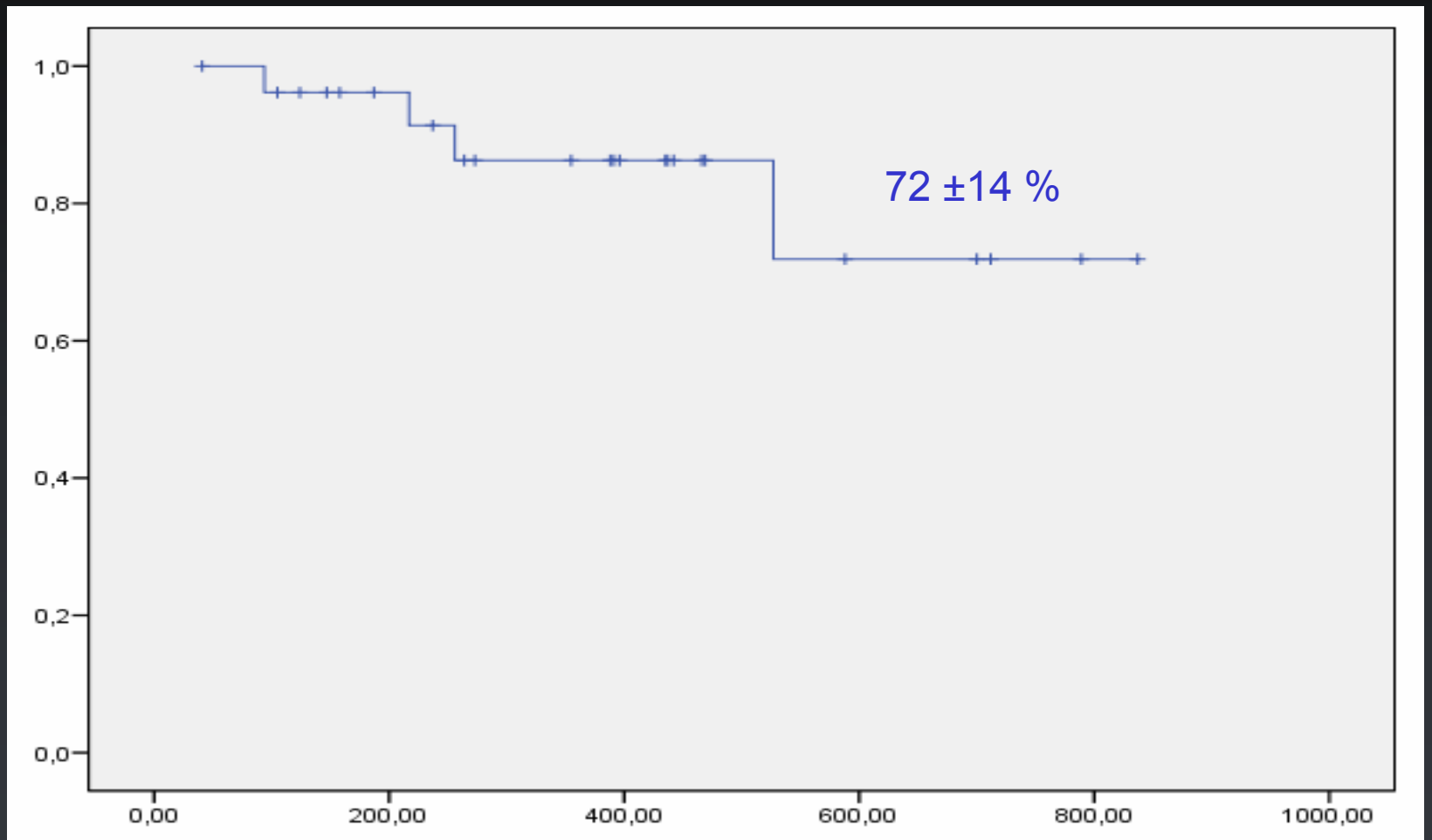
- 12 pacientes
- Toxicidad hematológica:

	Grado III (%)	Duración	Grado IV (%)	Duración
Neutropenia	6/12 (50%)	2 (1-4)	1/12 (8%)	3 (3-3)
Trombopenia	9/12 (75%)	3 (1-5)	9/12 (75%)	4 (1-8)
Anemia	1/12 (8%)	2 (1-1)	0	

SAES: 4

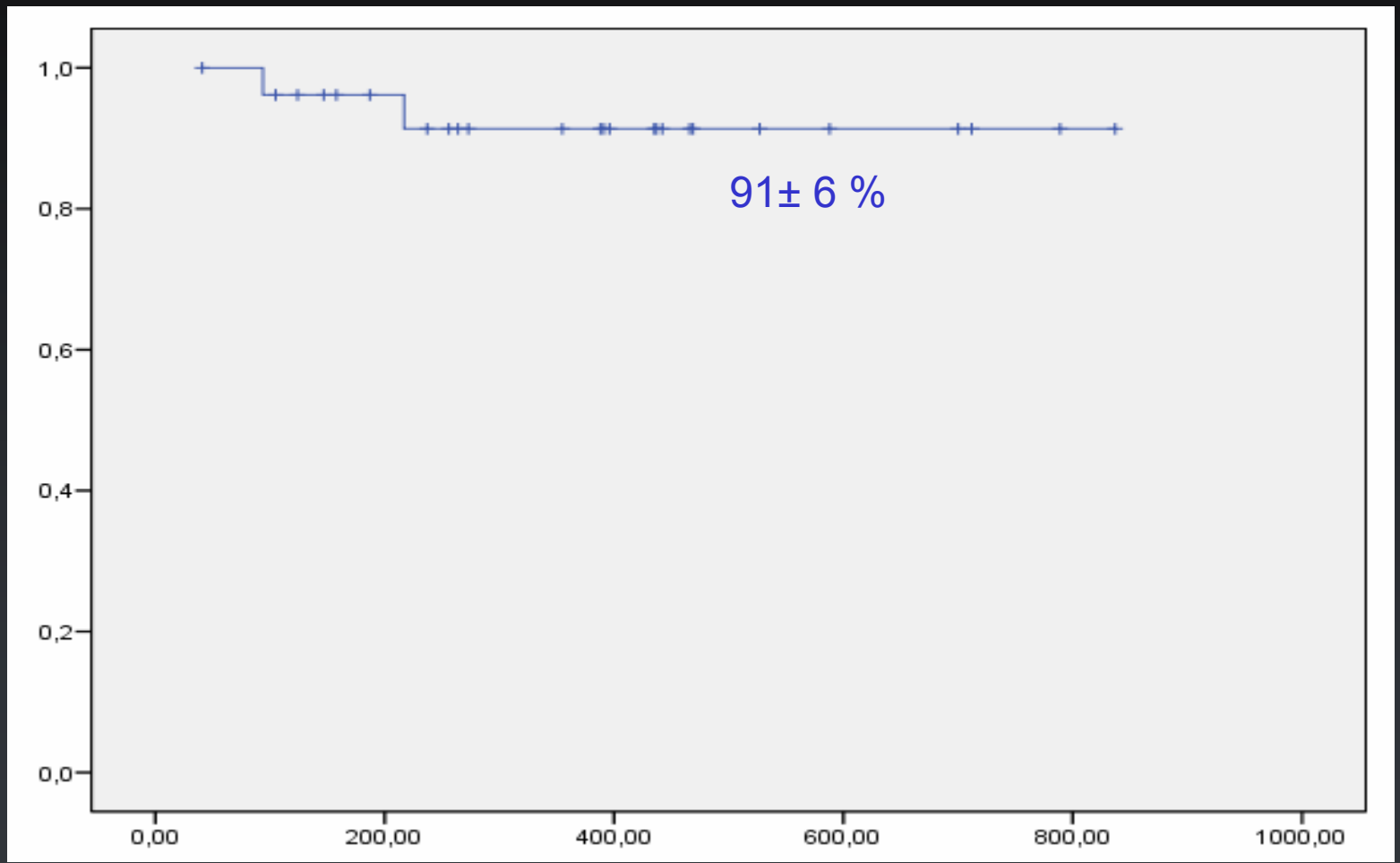
- neoplasia secundaria (LAM con inversión 16)
- herpes zoster
- neutropenia febril
- AIT

Supervivencia Libre De Progresión



Mediana seguimiento 13 meses (rango 1.3 – 27.4 meses)

Supervivencia Global



Mediana seguimiento 13 meses (rango 1.3 – 27.4 meses)

ASCT IN MANTLE CELL LYMPHOMA

Author	Patients Study design	Status at transplant (months)	Median follow-up	PFS% (yr)	OS% (yr)
Khouri	33 Prospective	PR/CR1	49	43 (5y)	77(5y)
Andersen	41(21 transplant.) Prospective	PR/CR	34	15(4y) by ITT	52(4y) by ITT
Mangel	20 Prospective	CR1(40%)	25	89	88
Dreger	34 upfront vs 34 historical control	PR/CR(100%) (after ARA-C)	30vs90	83vs47 (4 y)	87vs77 (4y)
Gianni	28 Retrospective	na	35 (4.5y)	79 (4.5y)	89
Vandenberghe	195 Retrospec.	CR(37%)	30	70(3y)	87(3y)
Vose	ASCT after CHOP+/-R (48) vs HyperCVAD+/-R(32) Retrospec.	na	38	55vs78(3y) (p=0.05)	68vs97(3y) (p=0.01)
Dreyling	62vs 60 Randomized (ASCT vs Quemothe.)	PR/CR1	25	39m vs17m (p<0.01)	87vs77(3y) ns
Geisler	86 Prospective	CR1(60%)	na	68(3y)	85(3y)

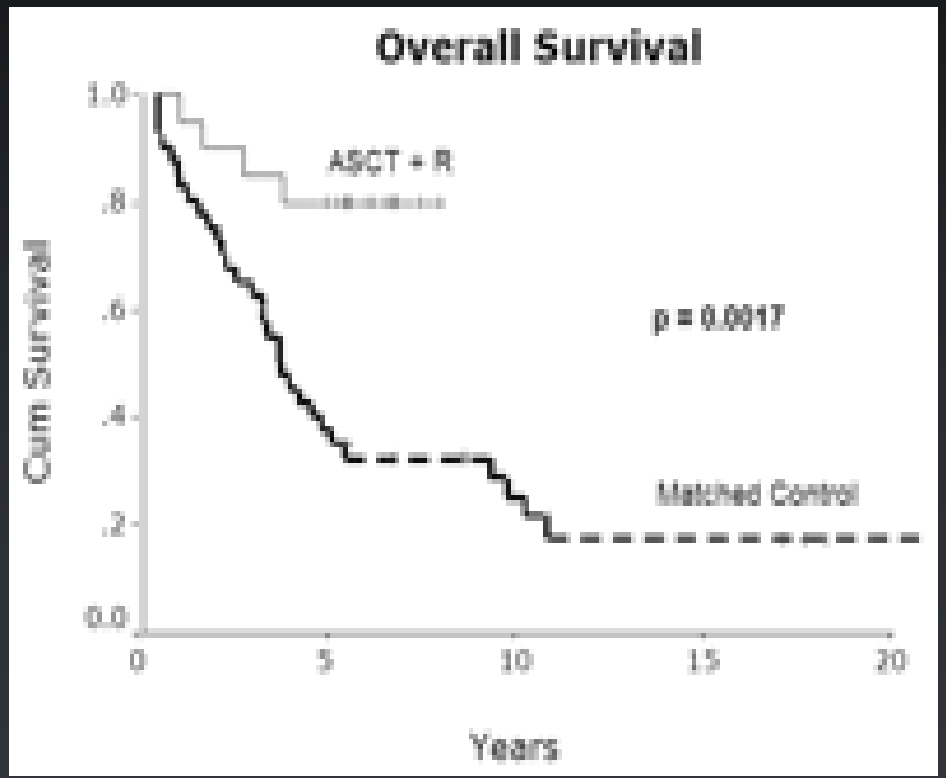
T. Autólogo en LNH Manto.1ª línea

Nº Abtr	*Tratamiento*	*Nº Pts*	*Mediana*	*SLP/SG*	*Comentario*
581 Delarue GELA	CHOPx3(Rx1) +R-DHAPx3 +TBI, ARA-C MEL o BEAM	60 TASPE 49	67 meses	SLE 83m SG media: No alcanzada. SG:75%(5años)	Mejores resultados que otro estudio previo sin R *(Lefrere et al. Hematologica 2007*
769 Dreyling Eur MCLNetwork	CHOP+AUTO vs IFN (randomizado)	232 75 TASPE 69 IFN	6,1 años	Respuesta 4,5 años vs1.6 a/ SG: 7,5 años vs 5,3 años (0.07)	Mayor duración de la respuesta y casi mejor SG
1904 Zulfiqar Nebraska	HYPERCVAD o CHOP +/-R,+/-TASPE	102		SLP:64%(3años si HIPERCVAD (+TASPE) 0% (sin TASPE)	Mejor SLP y SG en pacientes trasplantados

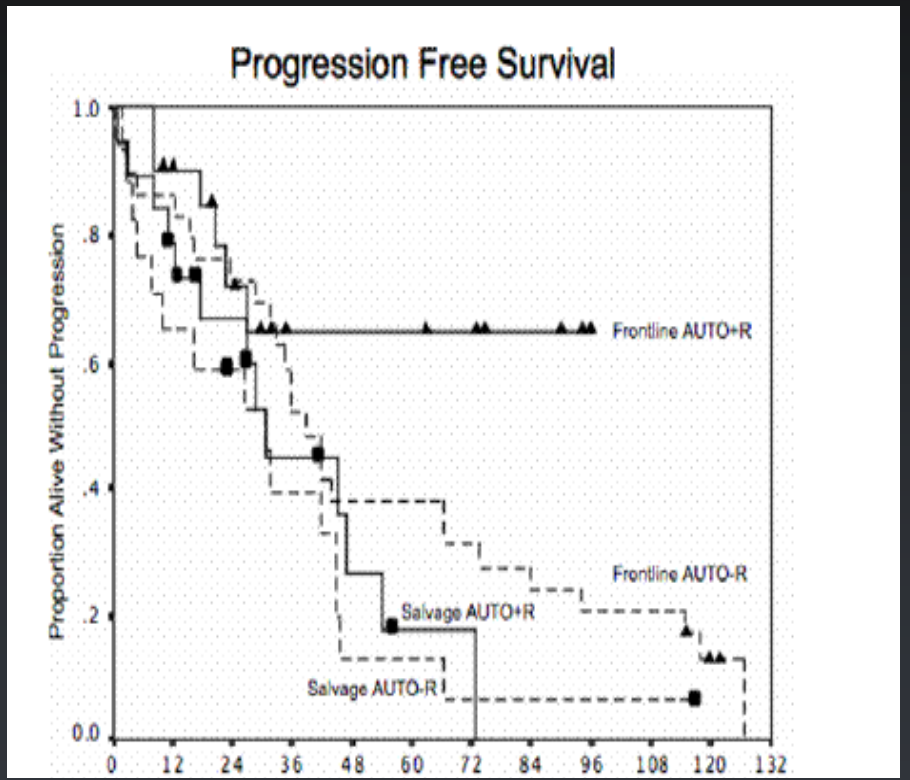
T. Autólogo en LNH Manto.

Nº Abtr	*Tratamiento*	*Nº Pts*	*Mediana*	*SLP/SG*	*Comentario*
2737 Damon CALGB **1ª línea**	R-MTX+MEGA CHOP+(Vp16, ARAC) mov+CBV	79	27 meses	SLP 56% / SG:82%(3 años)	
3051 Hicks Vancouver **1ª línea**	CHOP+R(mov)+TASPE+R mantenim(2 x4 a las 18 y 24s)	20 vs 40 controles históricos	5,3 años 10 años	72 vs 19 meses / 80 vs 38 meses	Mejor SLP y SG frente a controles históricos
1142 Tam MDA **1ª y 2ª línea**	HYPERCVAD o CHOP +/- R,+/-TASPE Con RT+CY o R-BEAM	86 50 de entrada 21 con R) 36 de 2ª línea			R-TASPE (sólo 9 pts) podria ser curativo en manto pero solo en RC1?

Trasplante autólogo en LNH manto.1ª Línea



3051.Hicks et al. *Autologous Stem-Cell Transplant with a Rituximab Purge and Maintenance vs. Standard Chemotherapy for Mantle Cell Lymphoma: Extended Follow-Up of a Matched Pair Analysis.*



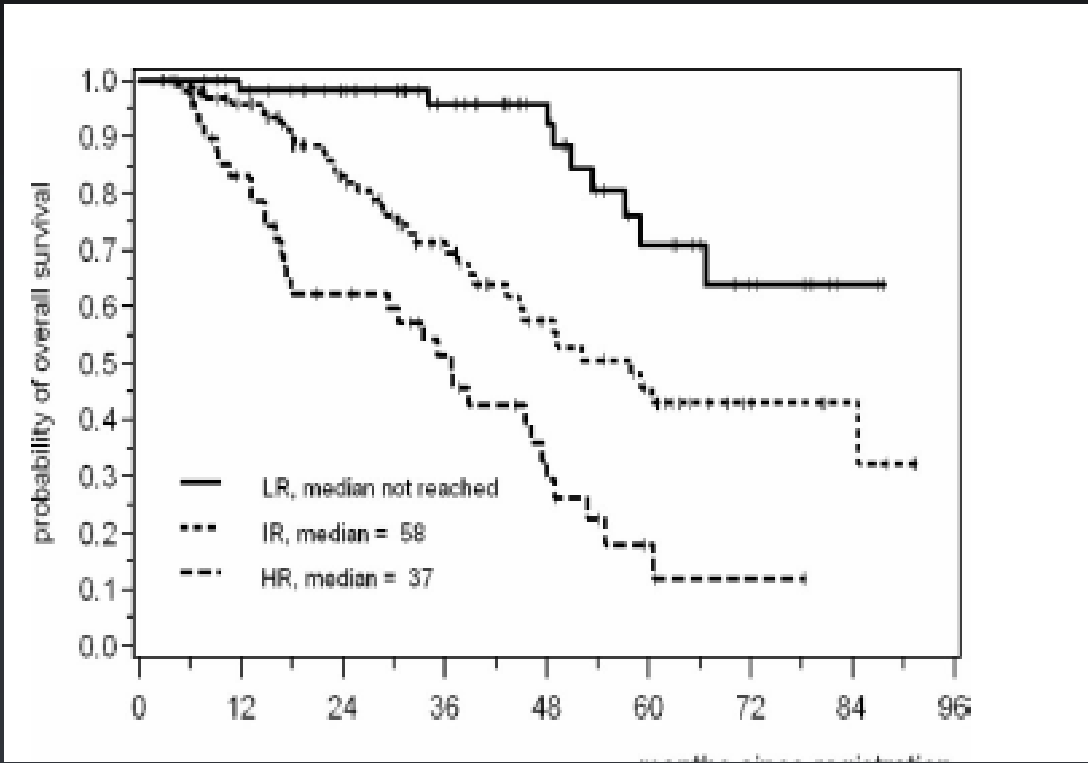
1142 Tam et al: *Rituximab Containing Autologous Stem Cell Transplantation May Be Curative in Mantle Cell Lymphoma for Patients in First Remission, but Not for Patients with Recurrent Disease*

Un indice pronóstico (MIPI) útil en Manto??

Table 7. Simplified prognostic index

Points	Age, y	ECOG	LDHULN	WBC, 10^9/L
0	<50	0-1	<0.67	< 6.700
1	50-59	—	0.67-0.99	6.700-9.999
2	60-69	2-4	1.000 -1.49	1.000-14.999
3	≥70	—	≥1.5000	≥15000

- 0-3 :bajo
- 4-5 :intermedio
- >5 :alto



Hoster Blood 2008

Esperar y ver en el LNH manto

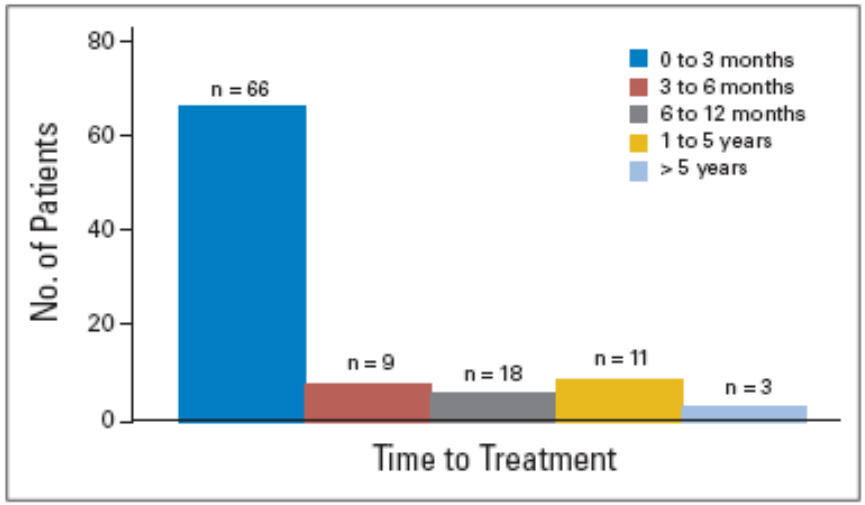


Fig 1. Time from diagnosis to first treatment in 97 patients with mantle-cell lymphoma.

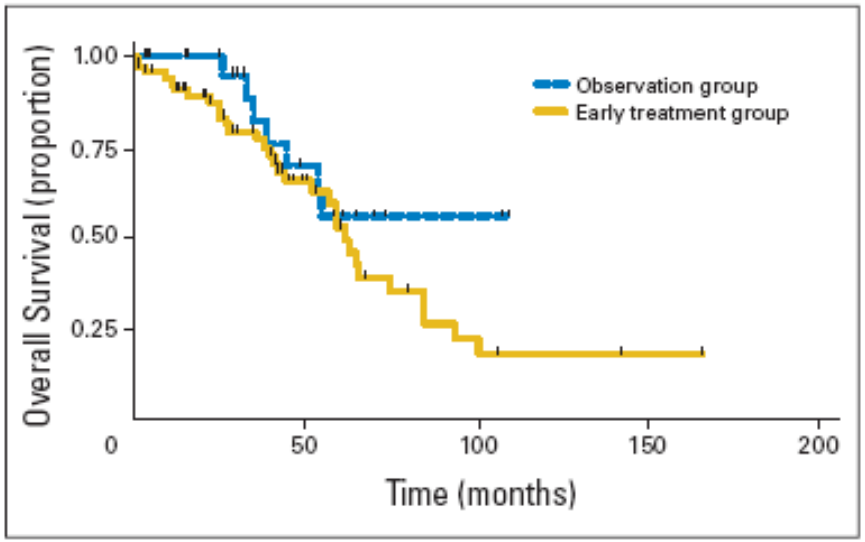


Fig 3. Overall survival of the observation versus early treatment groups from start of first systemic therapy.

Martin at all .Outcome of Deferred Initial Therapy in Mantle-Cell Lymphoma. *J Clin Oncol 27:1209-1213.*

Tratamiento de la recaída

Gemcitabine+Oxaliplatine in MCL

- 14 patients with refractory(9) or relasing (5)MCL
- 50% reslapsing after HyperCVAD
- Gemcitabine 1000mg/msq+Oxaliplatin 100mg/msq +R every two weeks

Rodriguez et al Leuk and lymphoma 2007

Gemcitabine+Oxaliplatine in MCL

- CR:64%(n=9) ;PR (21%) (n=3)
- Median follow-up for alive patients 11mo (4-36) mo
- OS 58% ; PFS 45% at 12 months
- Median survival 14.4 months.
- 7 patients (50%) alive and 6 patients (43%) free of progression
- 7 patients have died: 6 due to progression and 1 due to complications (graft versus host disease).

Treatment outcome for refractory/relapsed MCL patients treated with bortezomib

ORR	33%
CR/CRu	8%
PR	26%

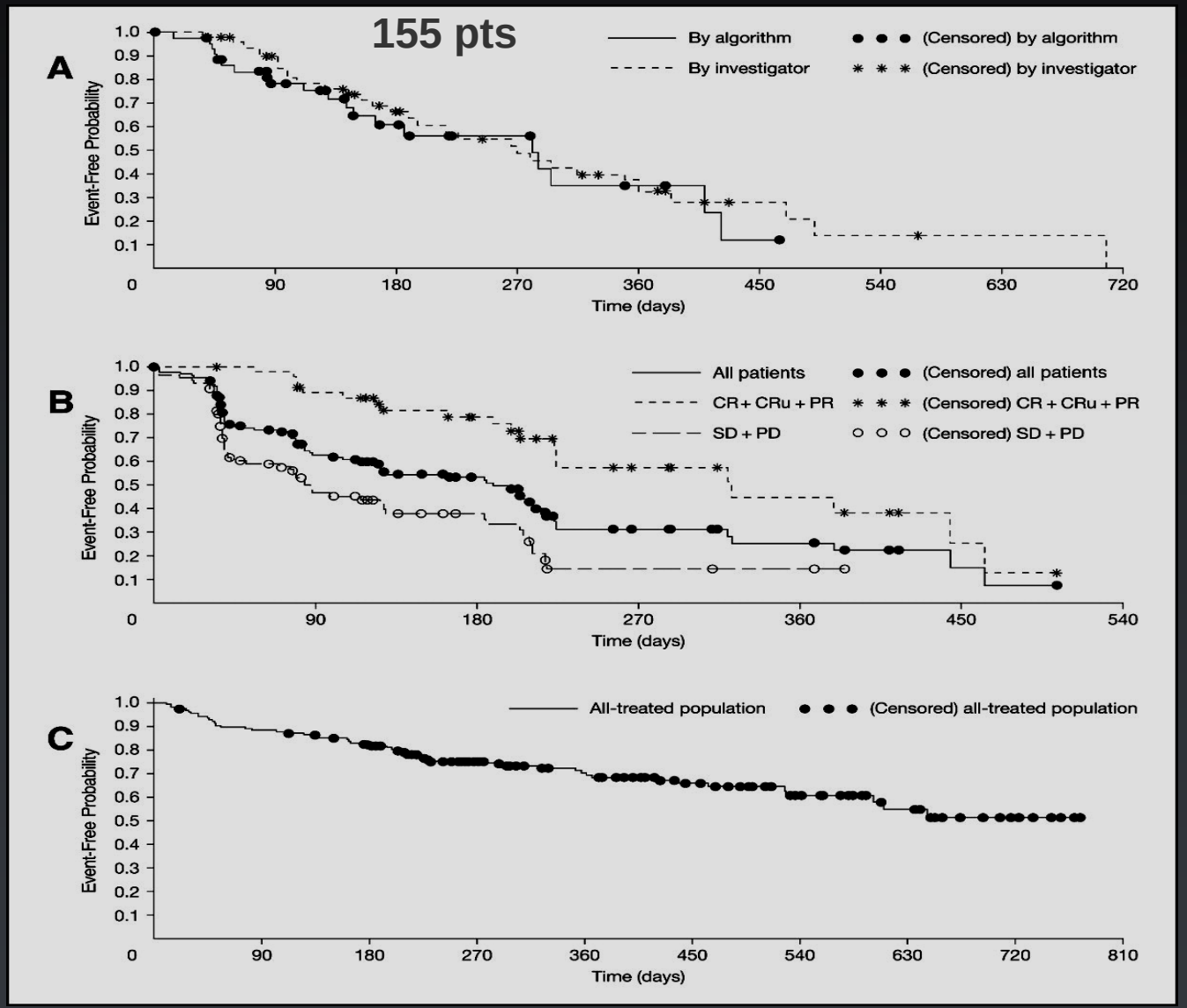
A: Duration of response

B: TTP for all pts (155)

C: OS for all pts (155)

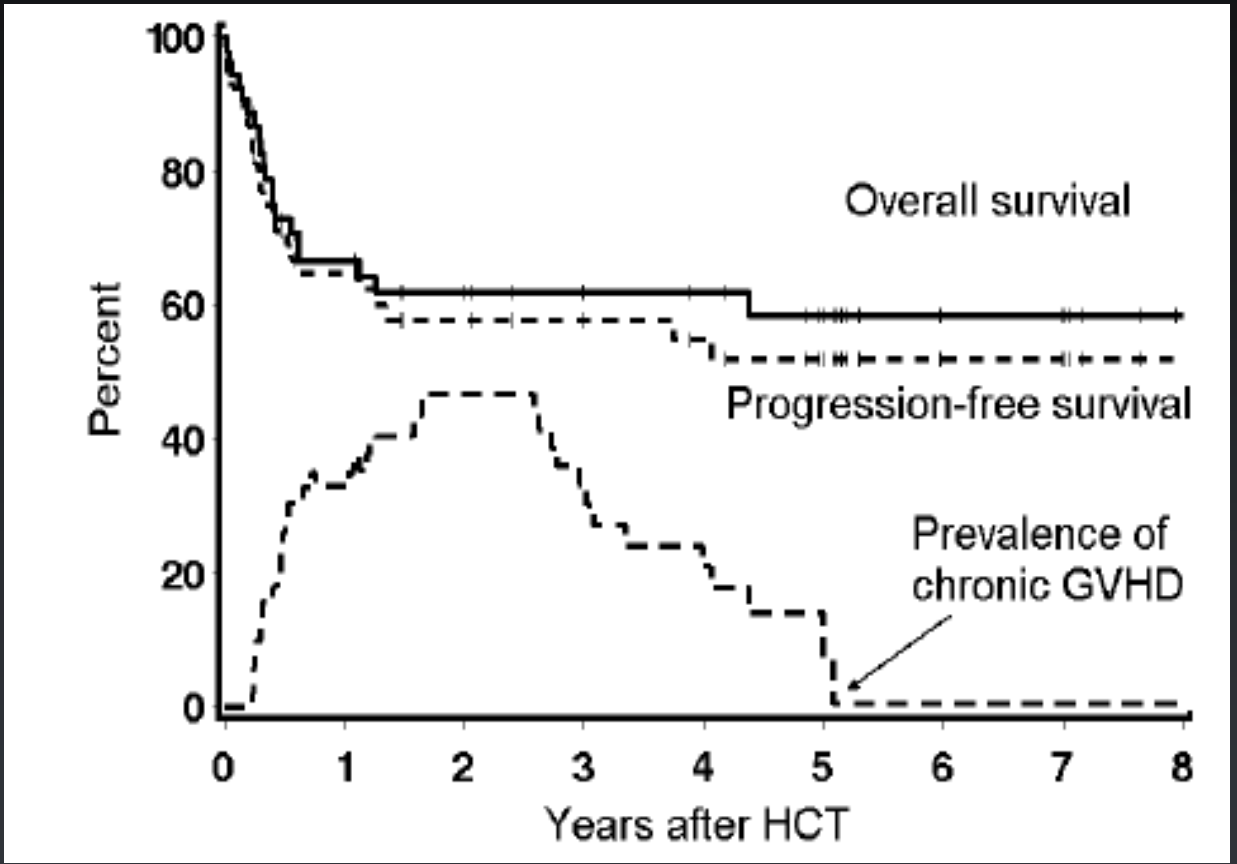
Toxicity ≥ grade 3:

Fatique	12%
Perif neuropathia	13%
Thrombocytop	11%



Fisher, R. I. et al. J Clin Oncol; 24:4867-4874 2006

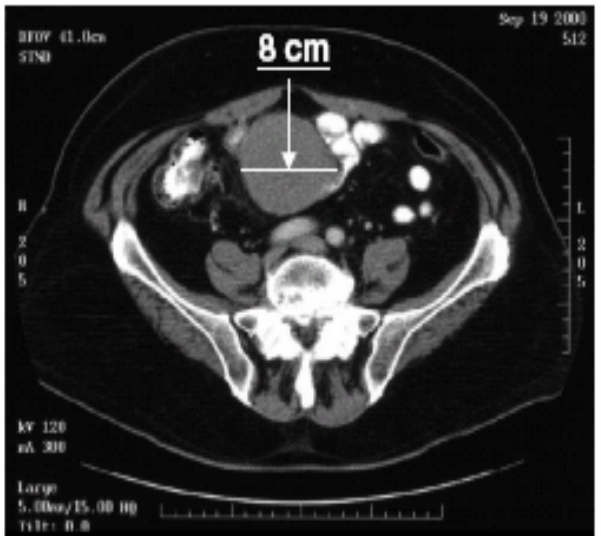
Trasplante Alogénico No Mieloablativo en Manto



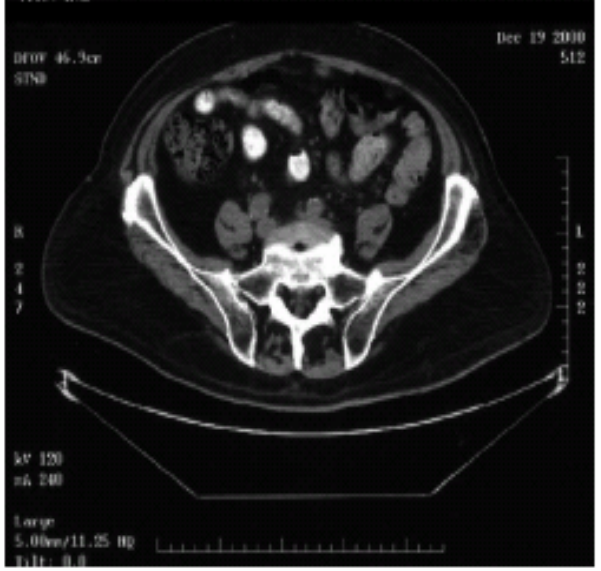
ASH 2008. 2147 Sorror et al: Sustained Graft-Versus-Lymphoma Effect among Patients (pts) with Mantle Cell Lymphoma (MCL) Given Nonmyeloablative Allogeneic Hematopoietic Cell Transplantation (HCT)

Allogeneic transplant in MCL

Pre-HCT



74 Days after HCT



Conditioning regimen in NM transplant. The GELTAMO experience (n=38)

Days	-8	-7	-6	-5	-4	-3	-2	-1	0	+1+3+6+11
Fludarabine (30 mg/m²/d)	F	F	F	F	F					
Melphalan (70-140 mg/m²)						M	M			
MTX + Folinic acid (10 mg/m2)										M M M M
CSA i.v.	1 mg/kg								2 mg/kg	
Donor G-CSF (10-16 µg/kg)						G	G	G	G	
PBSC Infusion (>4 ·10⁶/kg CD34+)									P	

25 patients received Rituximab 375 mg /msq on days –8, +1,+8 and +15

GELTAMO

TRASPLANTE ALOGÉNICO CON AIR EN LNH Manto (n=21)

Caracteristicas de los pacientes

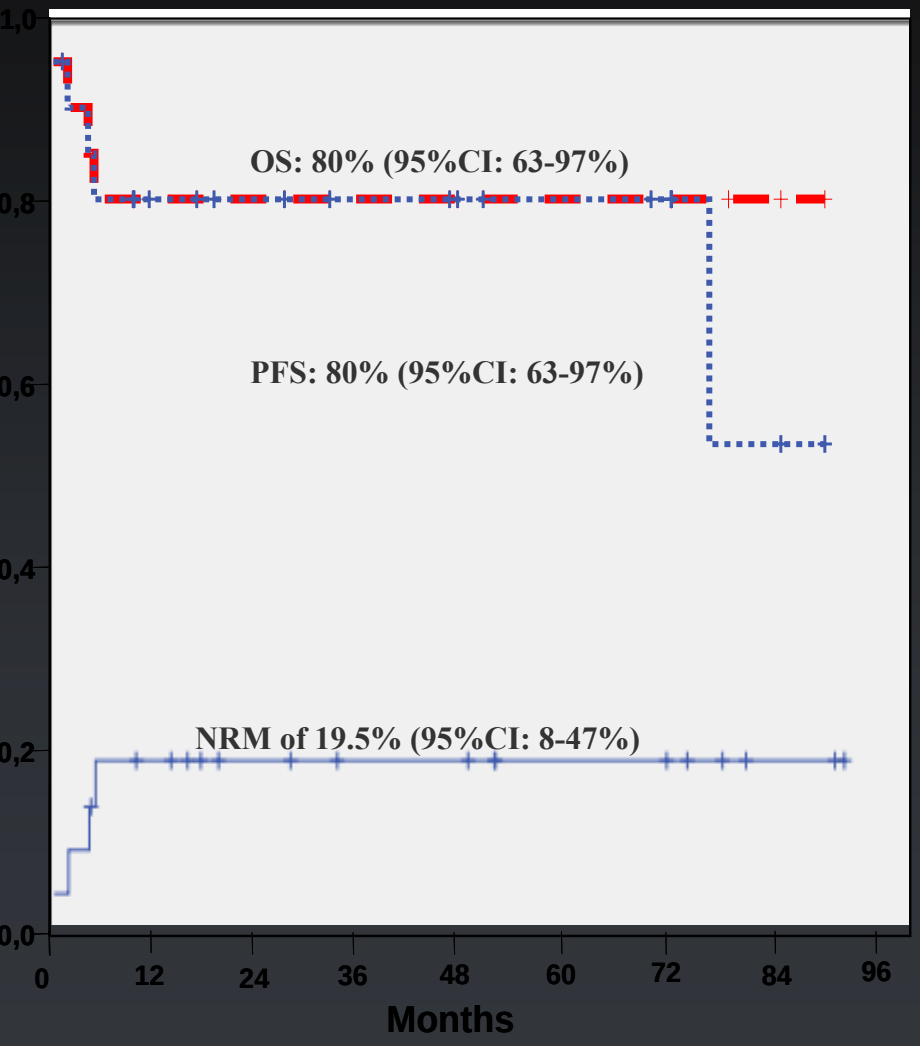
Edad :56(40-68) Sexo V/M(10/11)

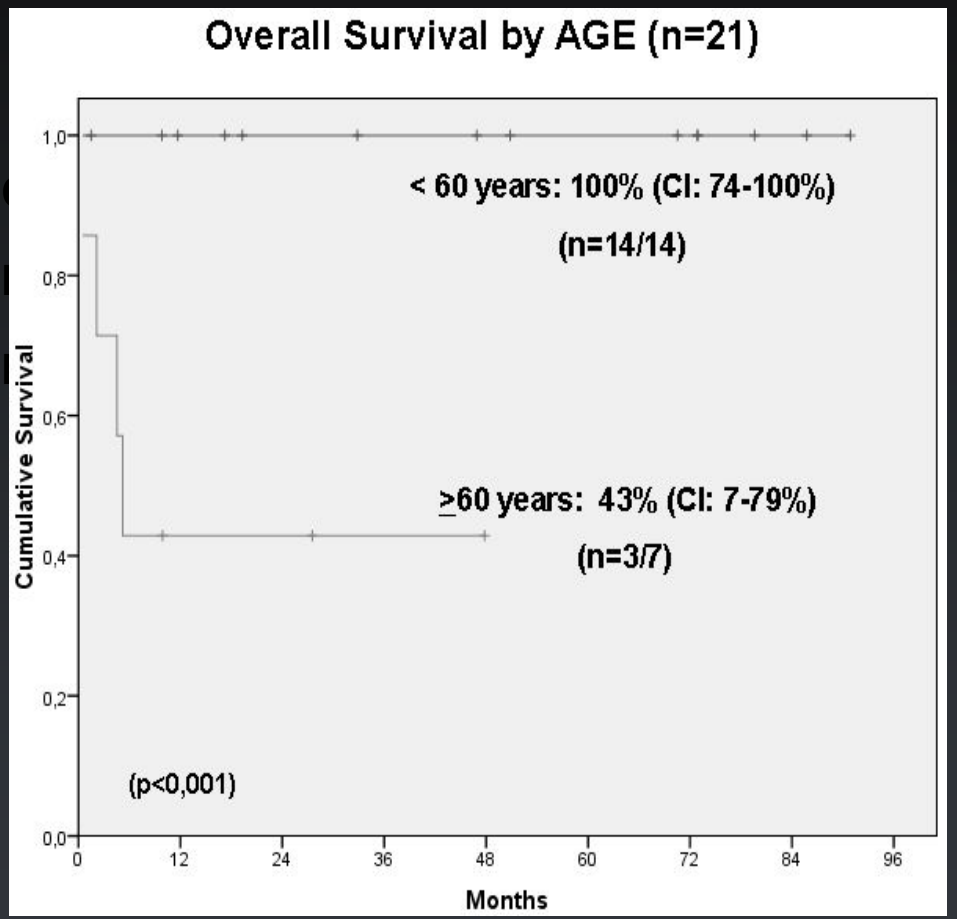
= >2 lineas	67%
+Auto previo	14%
+Enf activa quimiosensible	29%
+RC	71%

GELTAMO

Gayoso,EBMT 2009

T.alogénico con IR en L Manto .MFU 48 meses.





Comentarios al LNH Manto

- TASPE mejor que QT en SLP y probable SG *(Aleatorizado alemán)*
- R-QT agresiva +TASPE parece mejorar los resultados cuando se emplea en 1ª RC o RP
- En pacientes asintomáticos y mayores ,esperar y ver puede ser una opción
- El trasplante alogénico es curativo

LINFOMA DEL MANTO

HASTA 70 AÑOS

1. R-HIPERCVAD + ZEVALIN de consolidación (ensayo del GELTAMO).
2. Fuera del ensayo: recibirán el mismo tto, y si donante familiar, recibirán trasplante alogenico de intensidad reducida.

MAYOR O IGUAL A 70 AÑOS

R-CHOP por 6, seguido de zevalin o rituximab de mantenimiento por 2 años si RC.