

# AVANCES TERAPÉUTICOS EN EL MANEJO DE PACIENTES CON LINFOMAS B

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Barcelona, 1 Juny 2012*



# *El LDCG-B, curable*

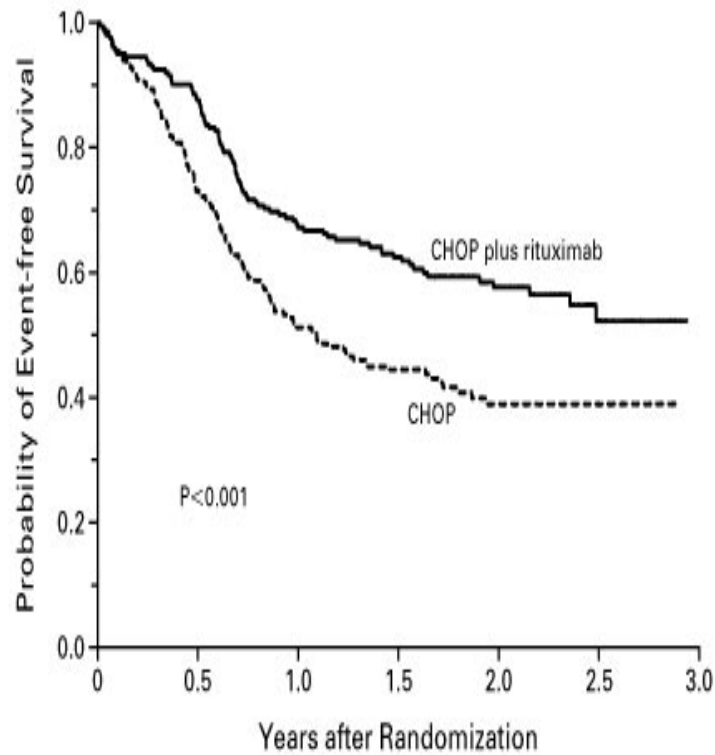
## **ADVANCED DIFFUSE HISTIOCYTIC LYMPHOMA, A POTENTIALLY CURABLE DISEASE**

### **RESULTS WITH COMBINATION CHEMOTHERAPY**

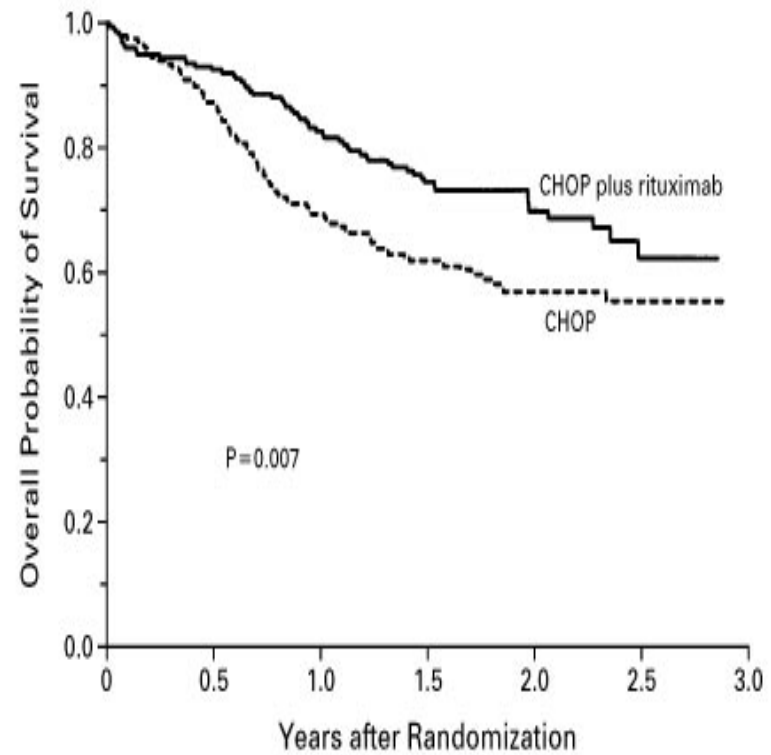
VINCENT T. DeVITA, JR.      GEORGE P. CANELLOS  
BRUCE CHABNER              PHILIP SCHEIN \*  
SUSAN P. HUBBARD          ROBERT C. YOUNG

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National Institutes of Health, Bethesda,  
Maryland 20014, U.S.A.*

# LDCG-B con R-CHOP

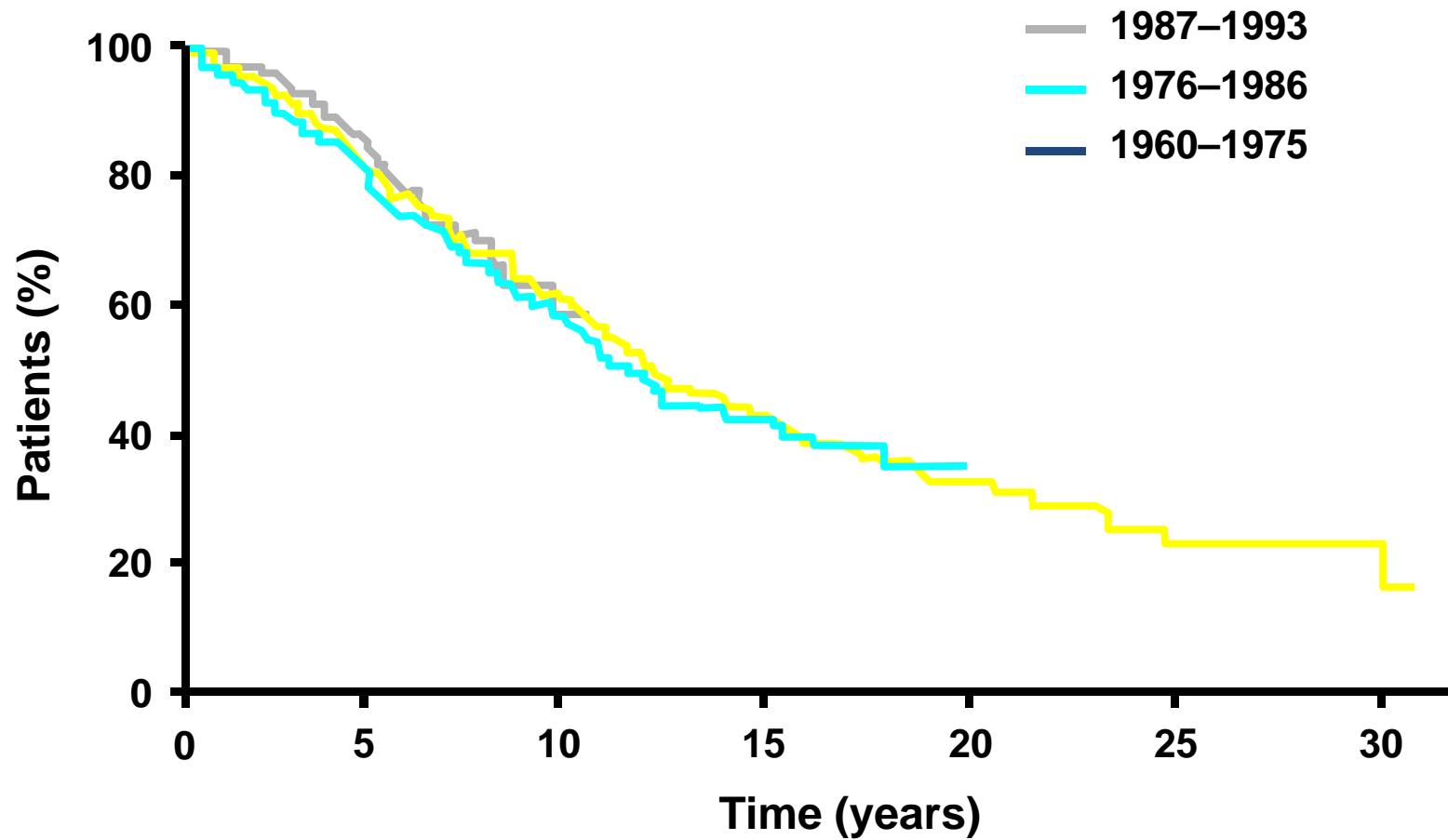


No. AT RISK	0	0.5	1.0	1.5	2.0	2.5	3.0
CHOP plus rituximab	202	177	137	108	63	19	
CHOP	197	144	101	72	42	17	



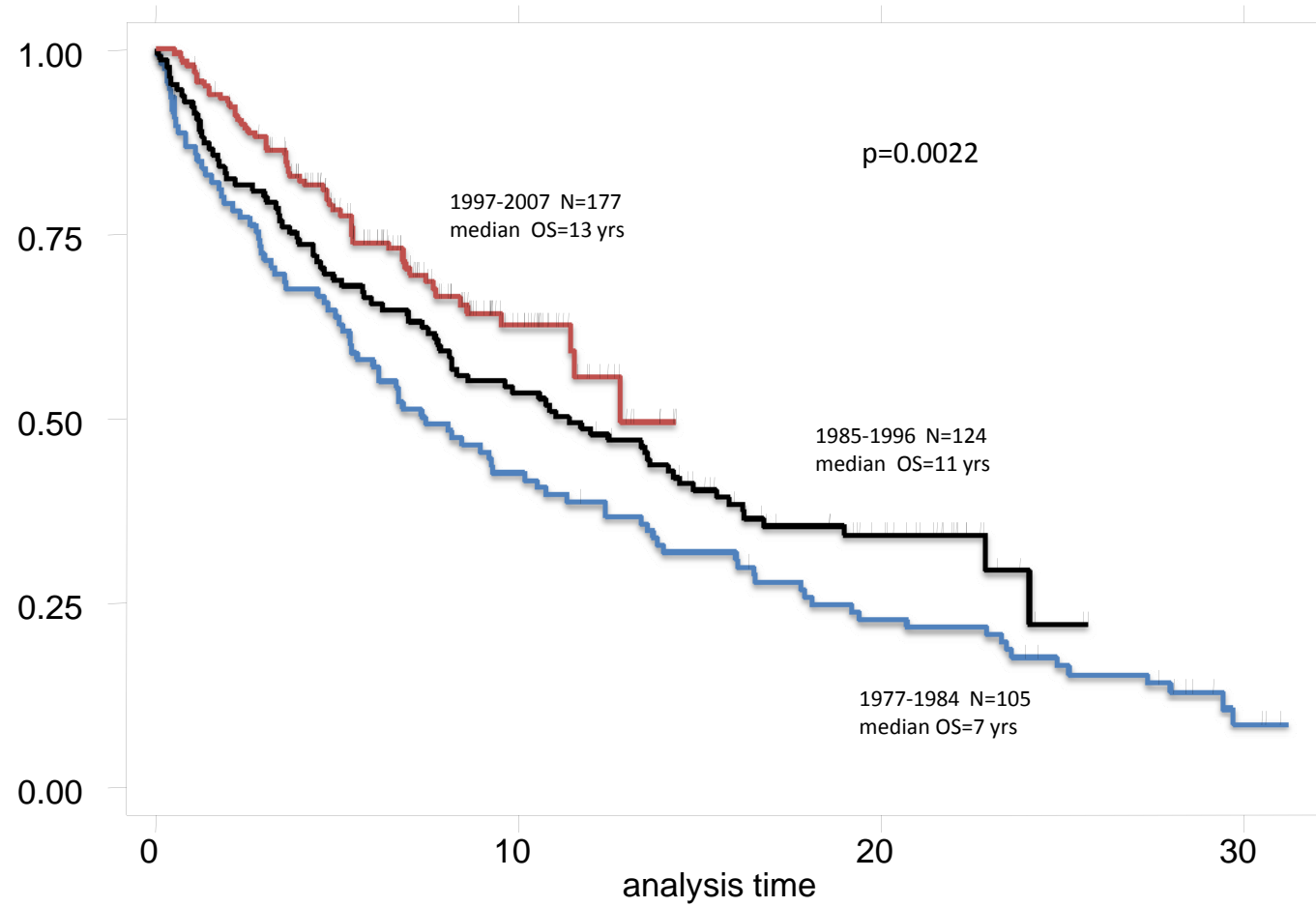
No. AT RISK	0	0.5	1.0	1.5	2.0	2.5	3.0
CHOP plus rituximab	202	187	167	118	64	21	
CHOP	197	171	136	96	58	16	

# *El LF en Stanford*



*Adapted from Horning S, Semin Oncol, 1993*

# *El LF en Barts*



# ¿Culpable?

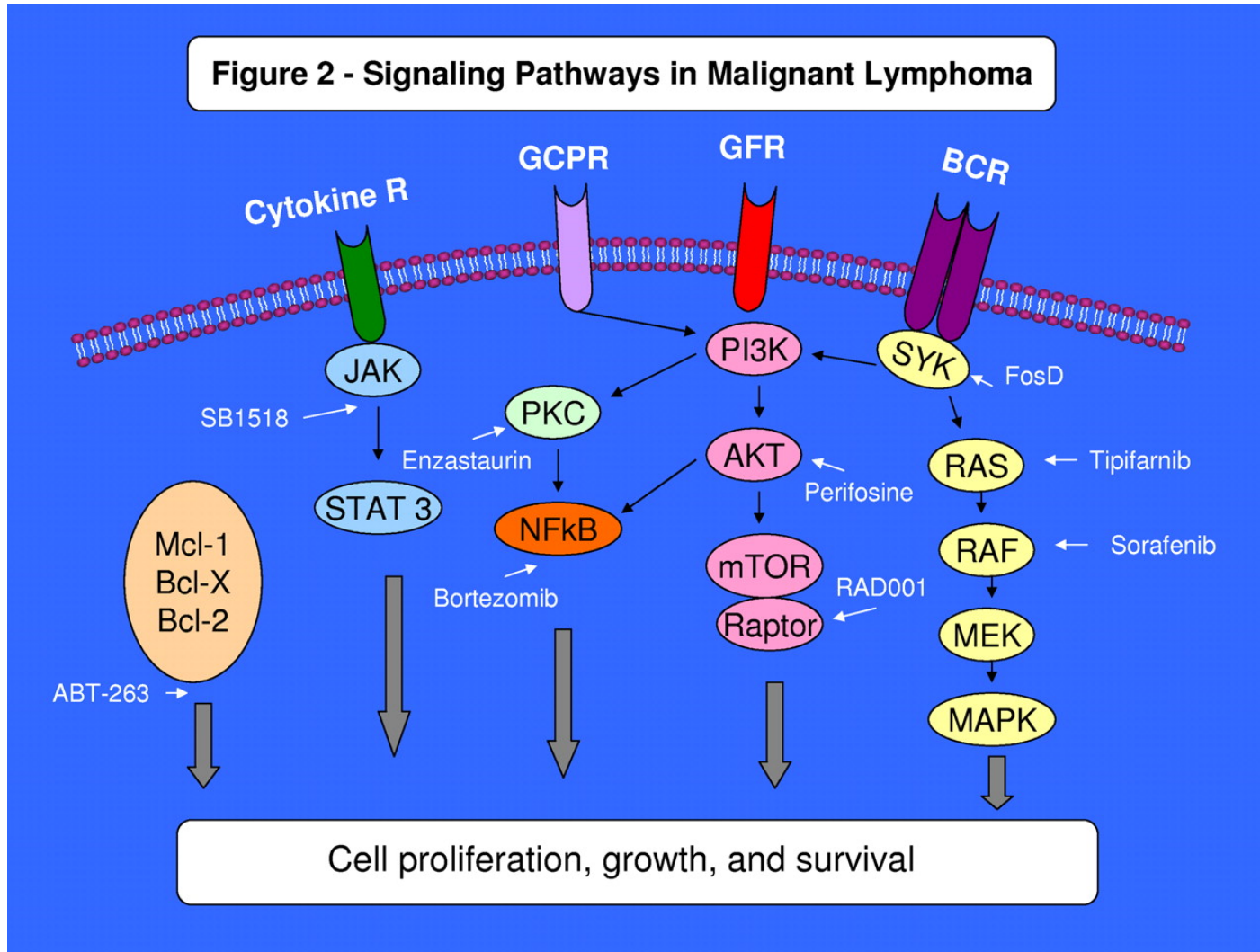


# *¿Y ahora qué?*

- Nuevos fármacos
- Mejores anti-CD20

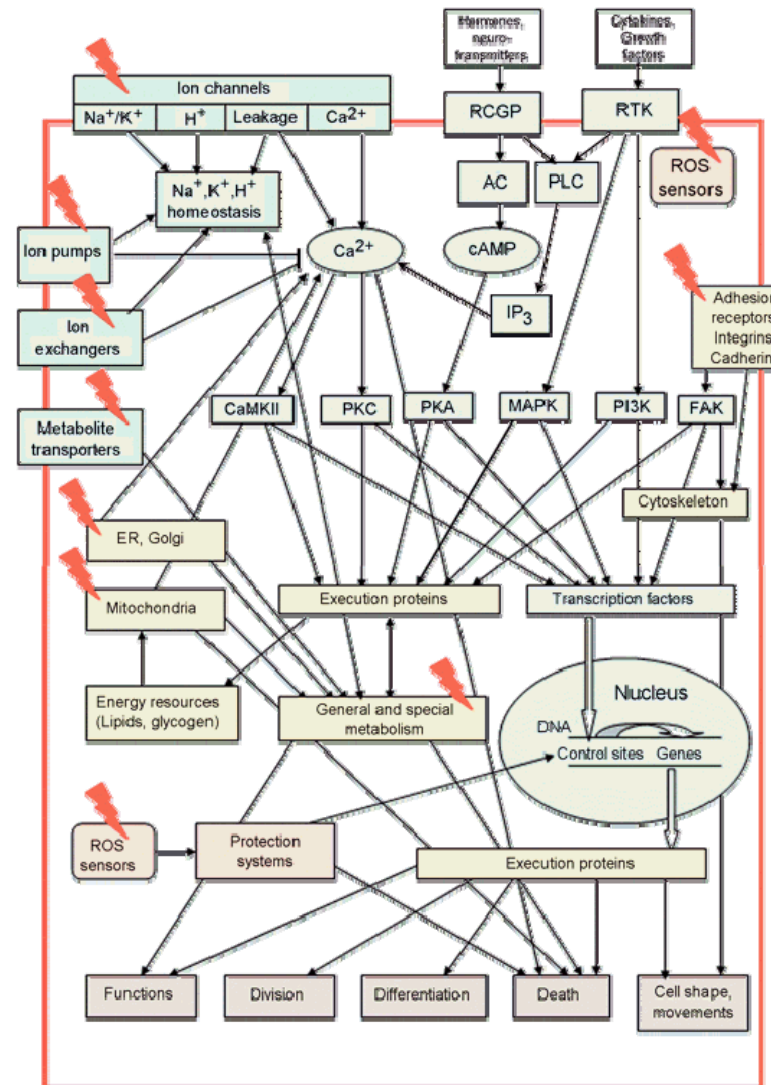
# Otras vías: 'terapia dirigida'

Figure 2 - Signaling Pathways in Malignant Lymphoma





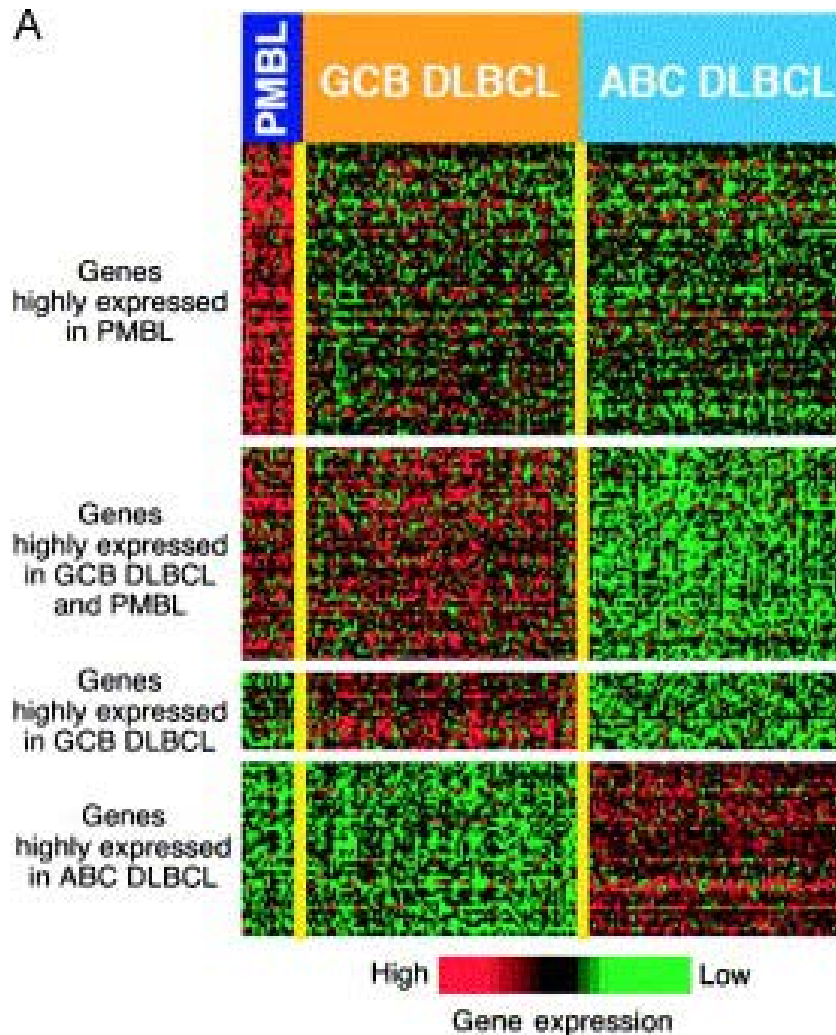
# Otras vías: 'terapia dirigida'



# *'Nuevos' fármacos*

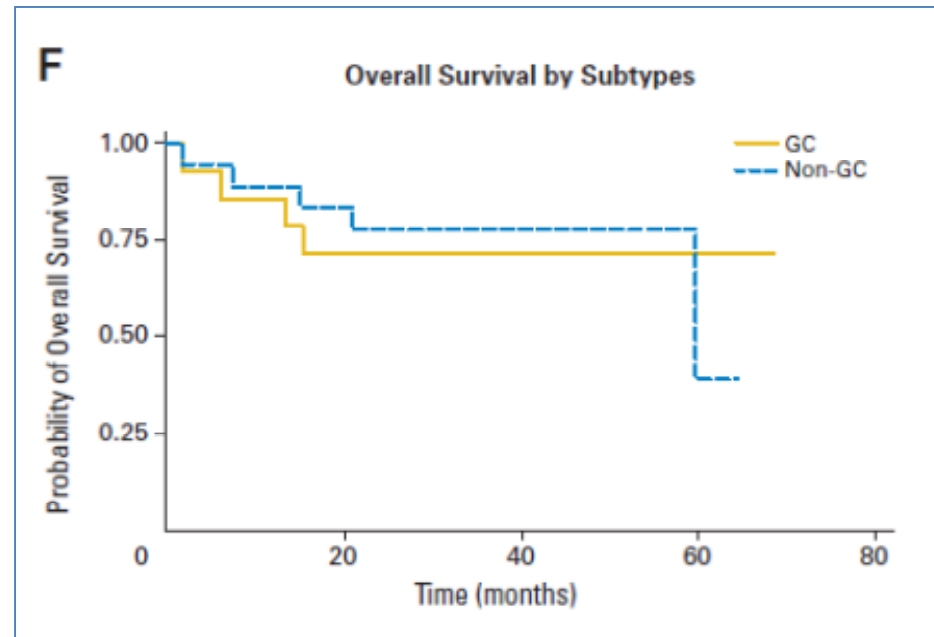
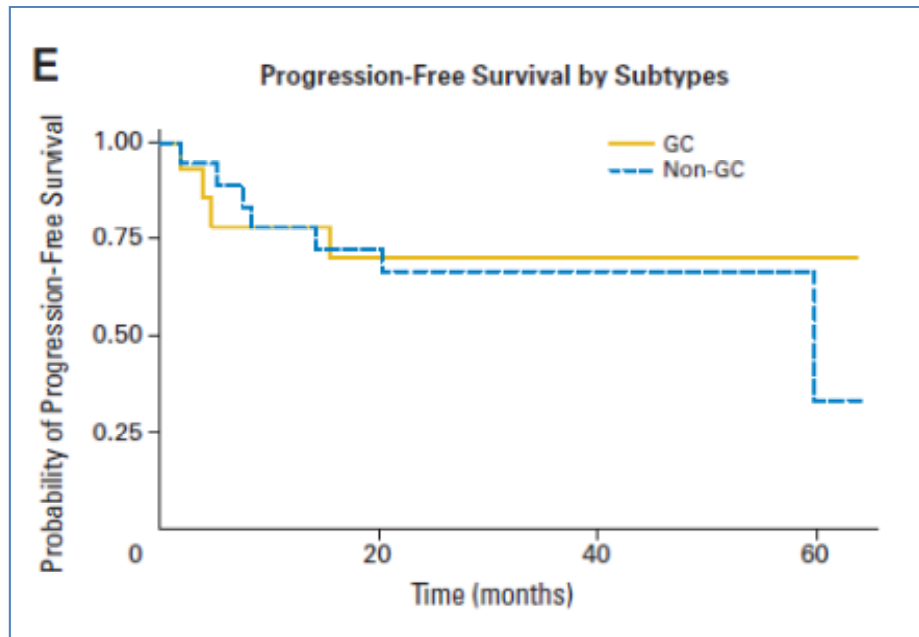
- Bortezomib
- Bendamustina
- Lenalidomida

# Bortezomib en LDCG-B: fundamento



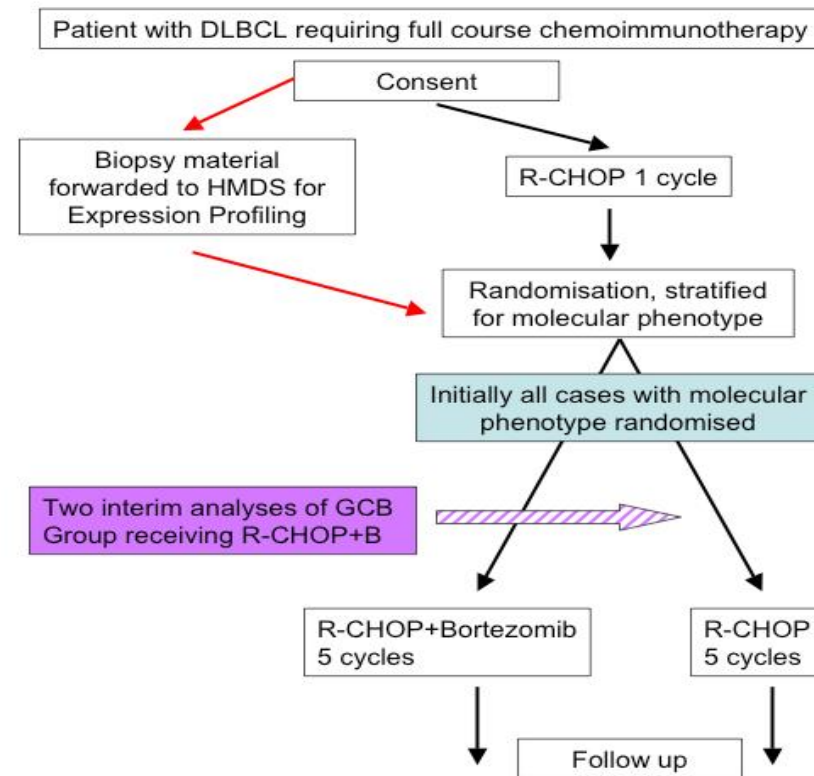
	GCB DLBCL	ABC DLBCL	PMBL
c-rel Amplification	16%	0	25%
BCL-2 Translocation	45%	0	18%
Gain Chr. 3q	0	24%	5%
Gain/amp Chr. 9p24	0	6%	43%
Constitutive NF-κB activation	-	+	+

# Bortezomib en LDCG-B



# *Bortezomib en LDCG-B: REMoDL-B*

## Trial Outline:



# *Bortezomib en LCM: RiPAD + C*

- 65-80 años
- Primera línea
- Rituximab, doxorubicina, DXM, CB
- Bortezomib bisemanal



- RR: 74%, RC/RCi: 59%
- Mediana de SLP: 26 meses
- Neuropatía periférica °3: 18%

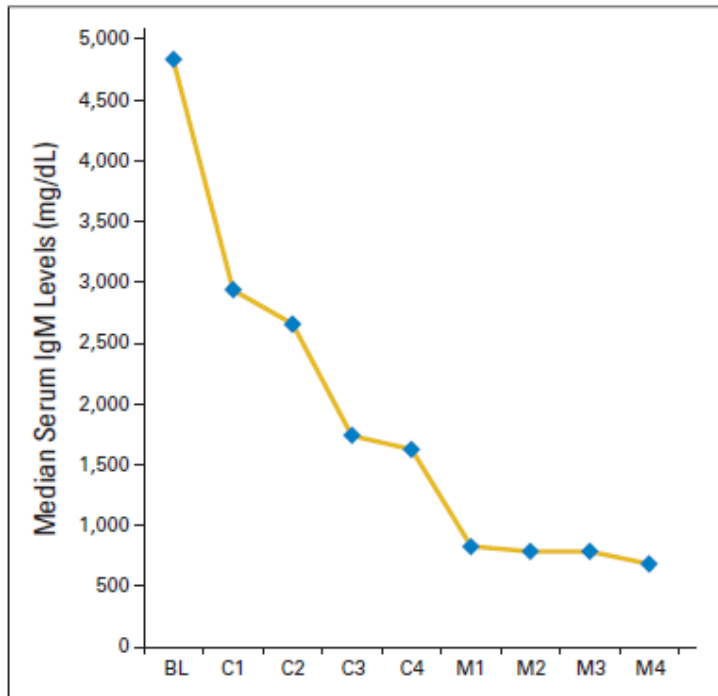
# Bortezomib en LF: BR-CVP

**Table 3.** Incidence of Neurotoxicity (n = 94)\*

Neuropathy	Grade (CTCAE v3)							
	1		2		3		4	
	No.	%	No.	%	No.	%	No.	%
After four cycles								
Motor neuropathy	1	1	3	3	0	0	0	0
Sensory neuropathy	45	48	12	13	3	3	0	0
Neuropathic pain	8	9	6	6	0	0	0	0
After eight cycles								
Motor neuropathy	4	4	5	5	0	0	0	0
Sensory neuropathy	41	44	24	26	5	5	0	0
Neuropathic pain	15	16	11	12	1	1	0	0

Response	No. of Patients	%	95% CI
Overall response	78	83	75.4 to 90.6
Complete response (CR/CRu)	46	49	38.8 to 59.0
Partial response	32	34	24.5 to 43.6
Stable disease	5	5	0.8 to 9.9
Progressive disease	8	9	2.9 to 14.2
Unevaluable	3	3	—

# Bortezomib en MW: BDR



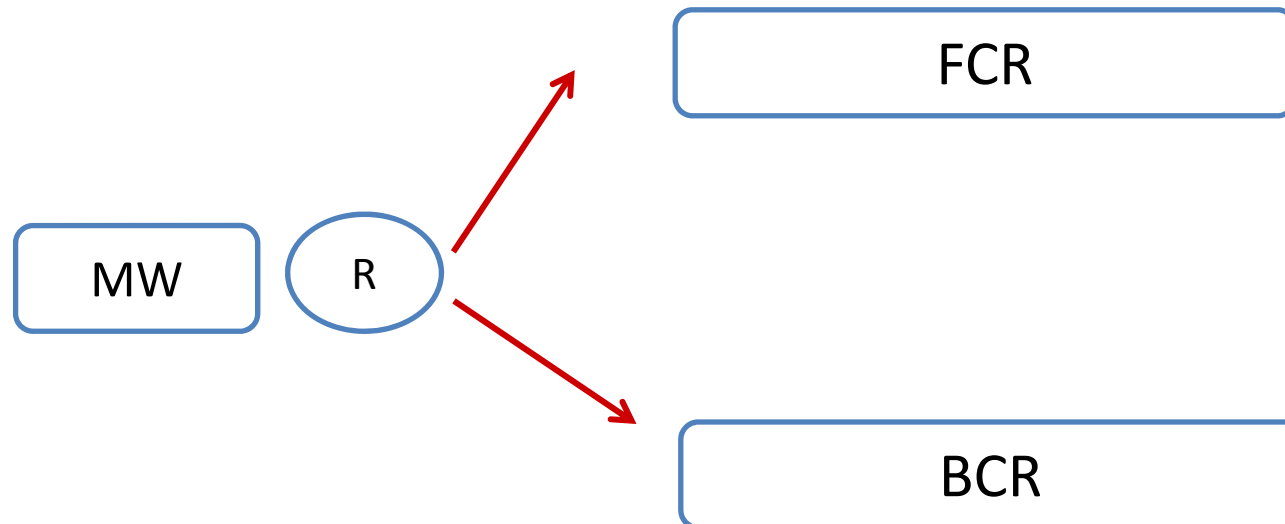
	<i>BDR</i> (bisemanal)	<i>BR</i> (semanal)
<i>Grado 3-4 neuropatía periférica</i>	30%	5%
<i>Cese bortezomib</i>	61%	16%

Treon S et al, J Clin Oncol, 2009

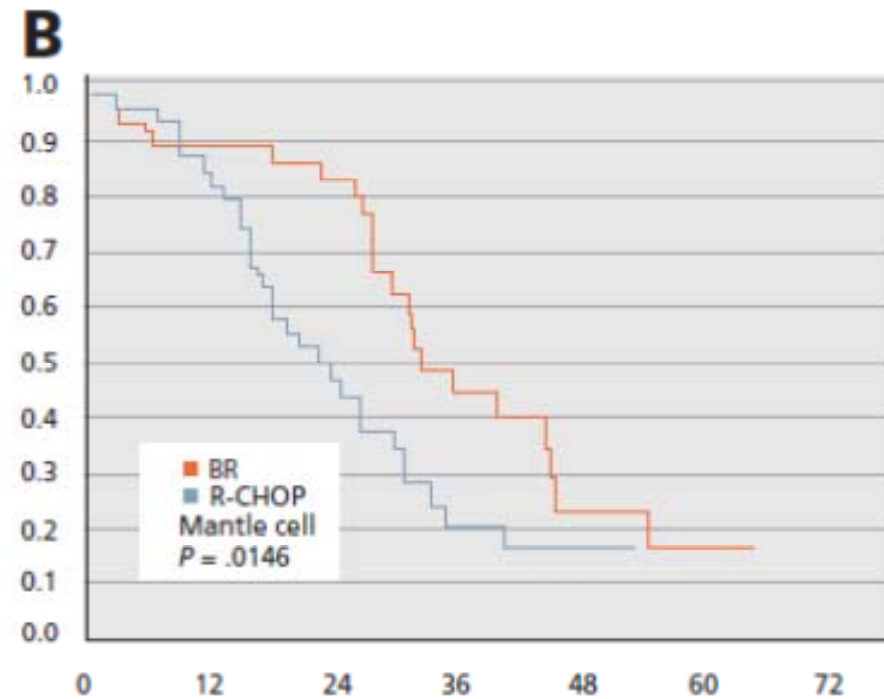
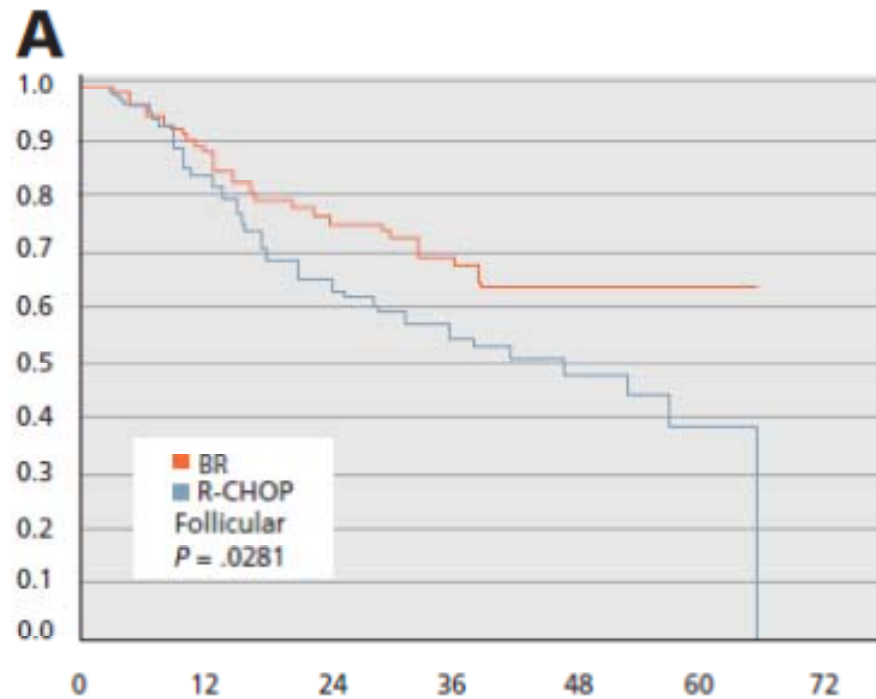


# *Bortezomib en MW: estudio R2W*

- Estudio randomizado, fase II
- Primera línea
- Bortezomib SC, semanal

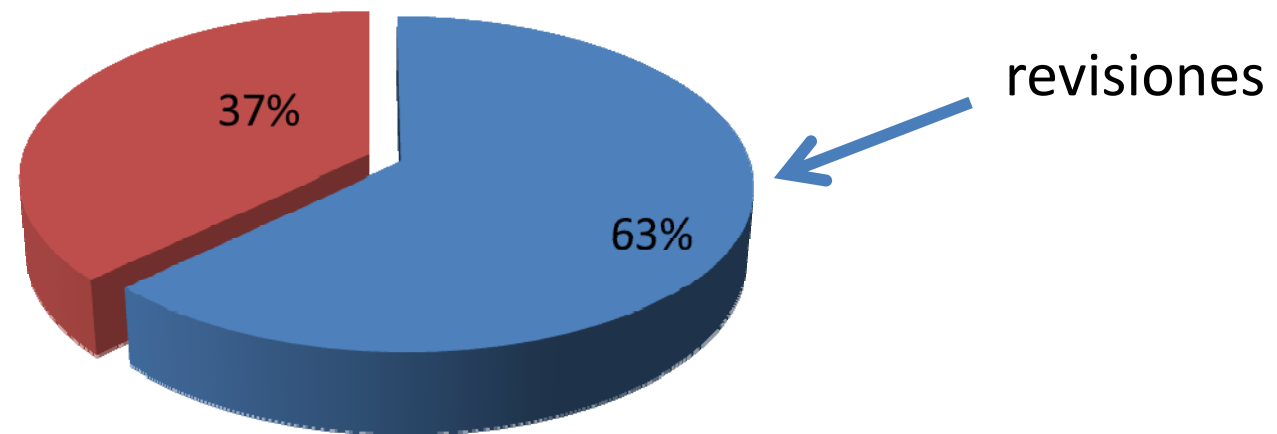


# Bendamustina en LF y LCM

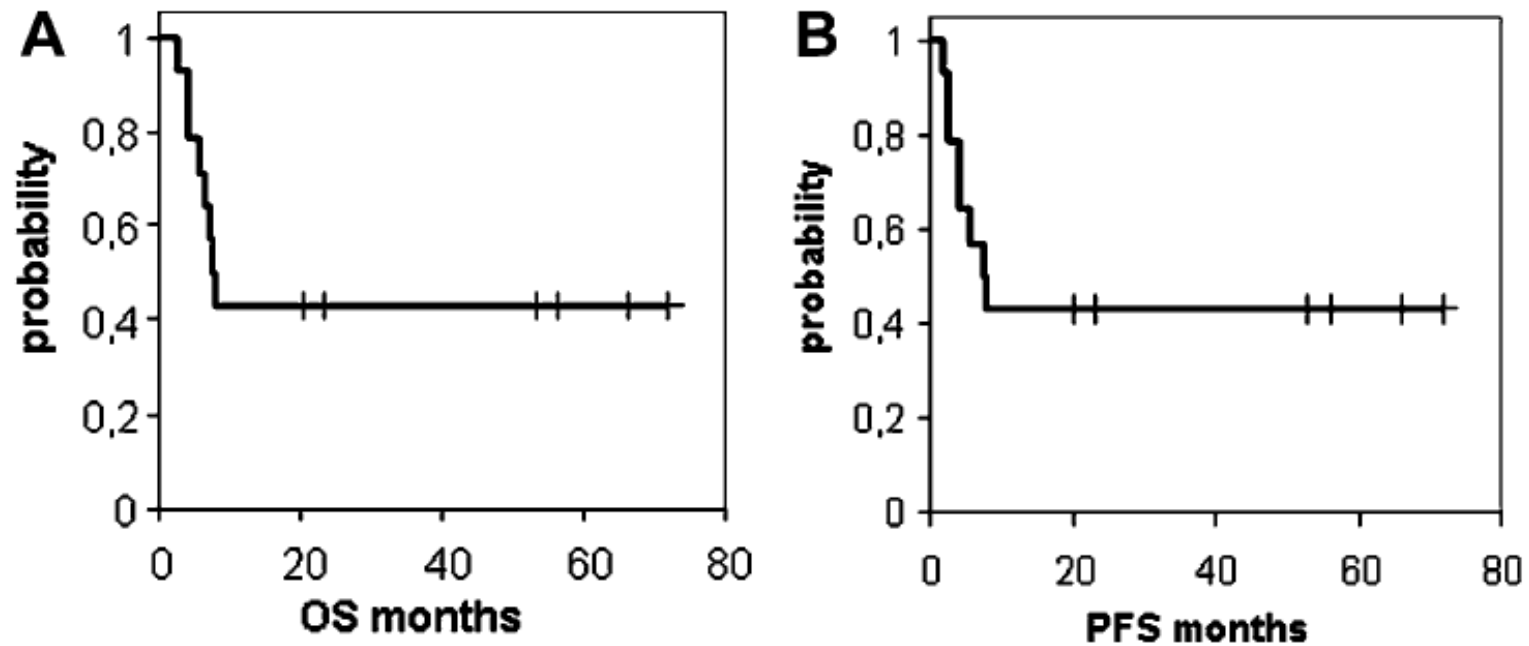


# *Información disponible sobre bendamustina*

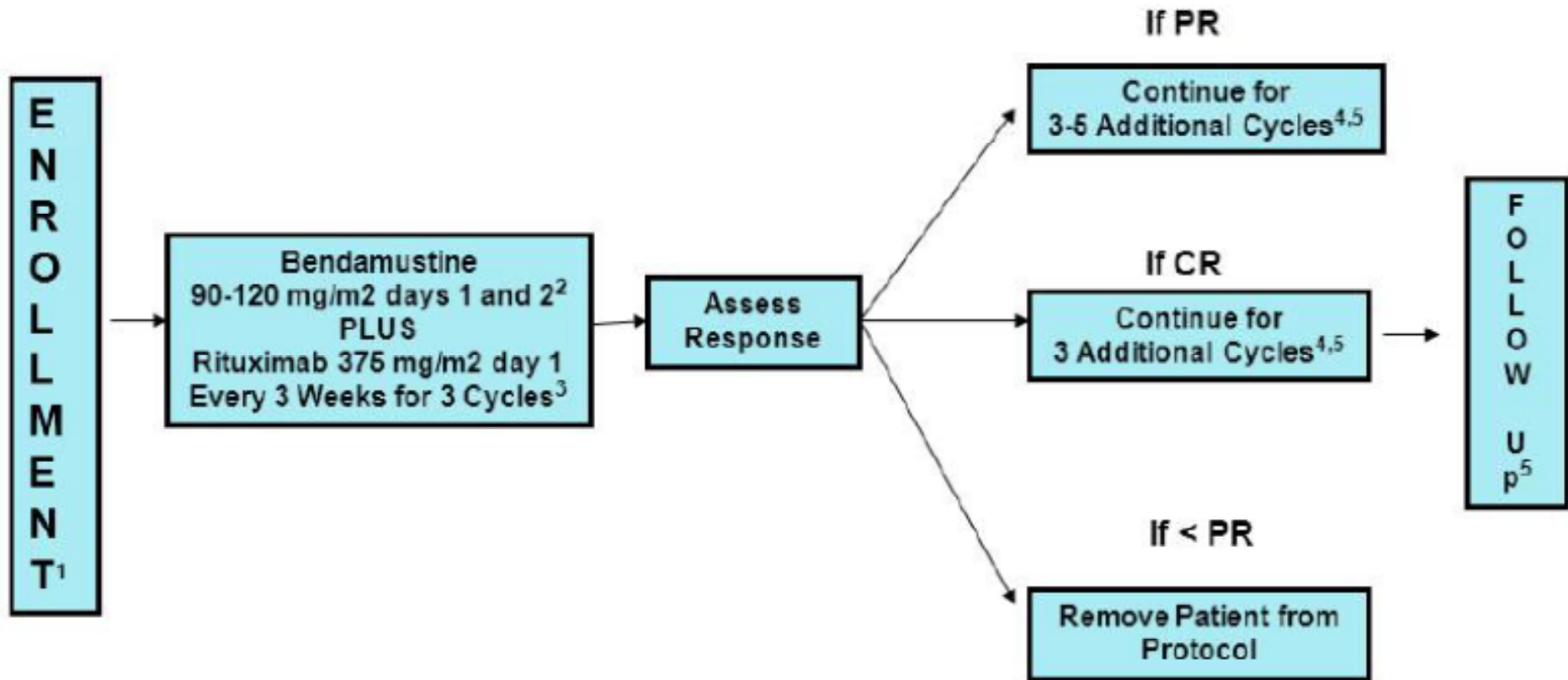
- PubMed: 'Bendamustine, indolent lymphoma' → 62 resultados



# *Bendamustina en LDCG-B*



# Bendamustina en LDCG-B



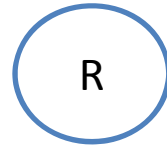
# *Lenalidomida-R en linfoma indolente*

Histology	Response Rates		
	CR/CRu	PR	ORR
FL (n = 30)	83%	10%	93%
SLL/CLL (n = 5)	40%	40%	80%
Marginal zone lymphoma (n = 13)	46%	16%	62%
Total (n = 48)	69%	14%	83%

# *Lenalidomida-R en LF*

Combined Rituximab and Lenalidomide Treatment for Untreated Patients  
With Follicular Lymphoma (RELEVANCE)

LF grado 1, 2 o 3a,  
Estadio II-IV  
LF sintomático  
Edad ≥18 years  
ECOG: 0-2



Lena-R

CHOP-R

CVP-R

Bendamustina-R

# Lenalidomida en LDCG-B

- Fase II
- 23 pacientes (>65 a) con LDCG-B en recaída
- Lenalidomida-rituximab x 4 → mantenimiento lenalidomida 8 meses
- Respuesta global: 7RC + 1RP (35%) → 10 mantenimiento: 8 RC

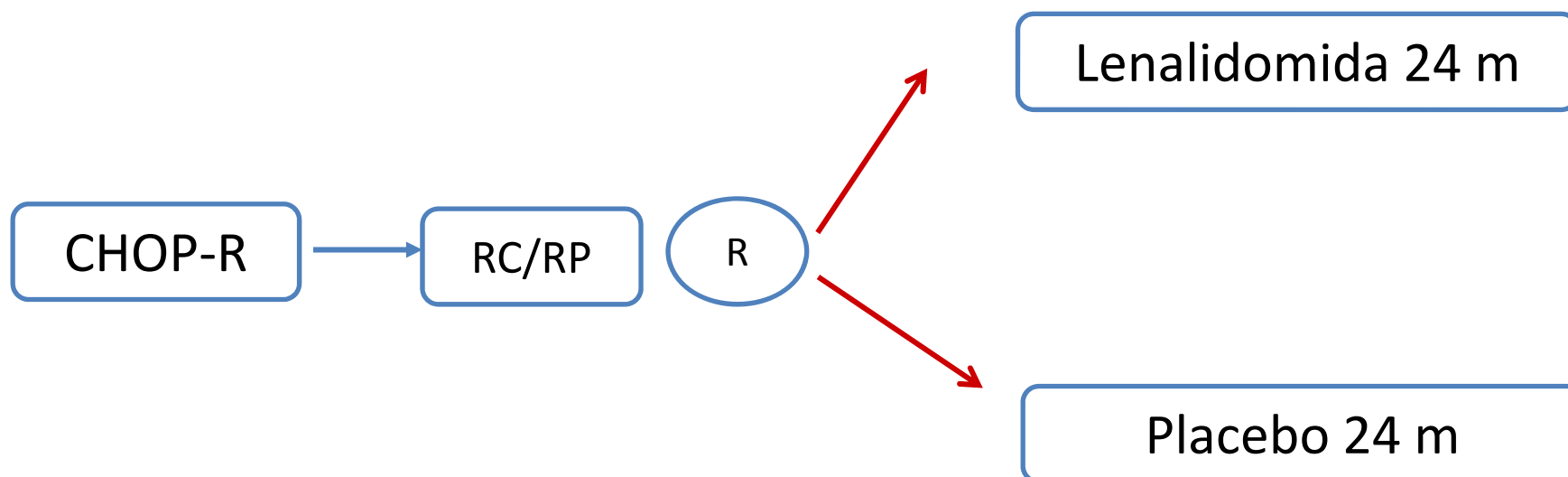
Previous Treatments	Status at Enrolment	Duration of Complete Response, Months
VNCOP-B-R; Ibritumomab tiuxetan	Relapsed	18
MACOP-B-R; IEV; ASCT; Ibritumomab tiuxetan	Refractory	18
VNCOP-B-R; Rituximab	Relapsed	17
R-CHOP; Ibritumomab tiuxetan; Gemcitabine	Relapsed	16
R-CHOP; IEV; Radiotherapy	Refractory	17
R-CHOP; IEV; ASCT	Relapsed	16
VNCOP-B-R; Rituximab; Gemcitabine	Relapsed	16
R-CHOP; Vincristine; Rituximab	Relapsed	14

*Zinzani PL et al, Clin Lymphoma Myeloma Leuk, 2011*

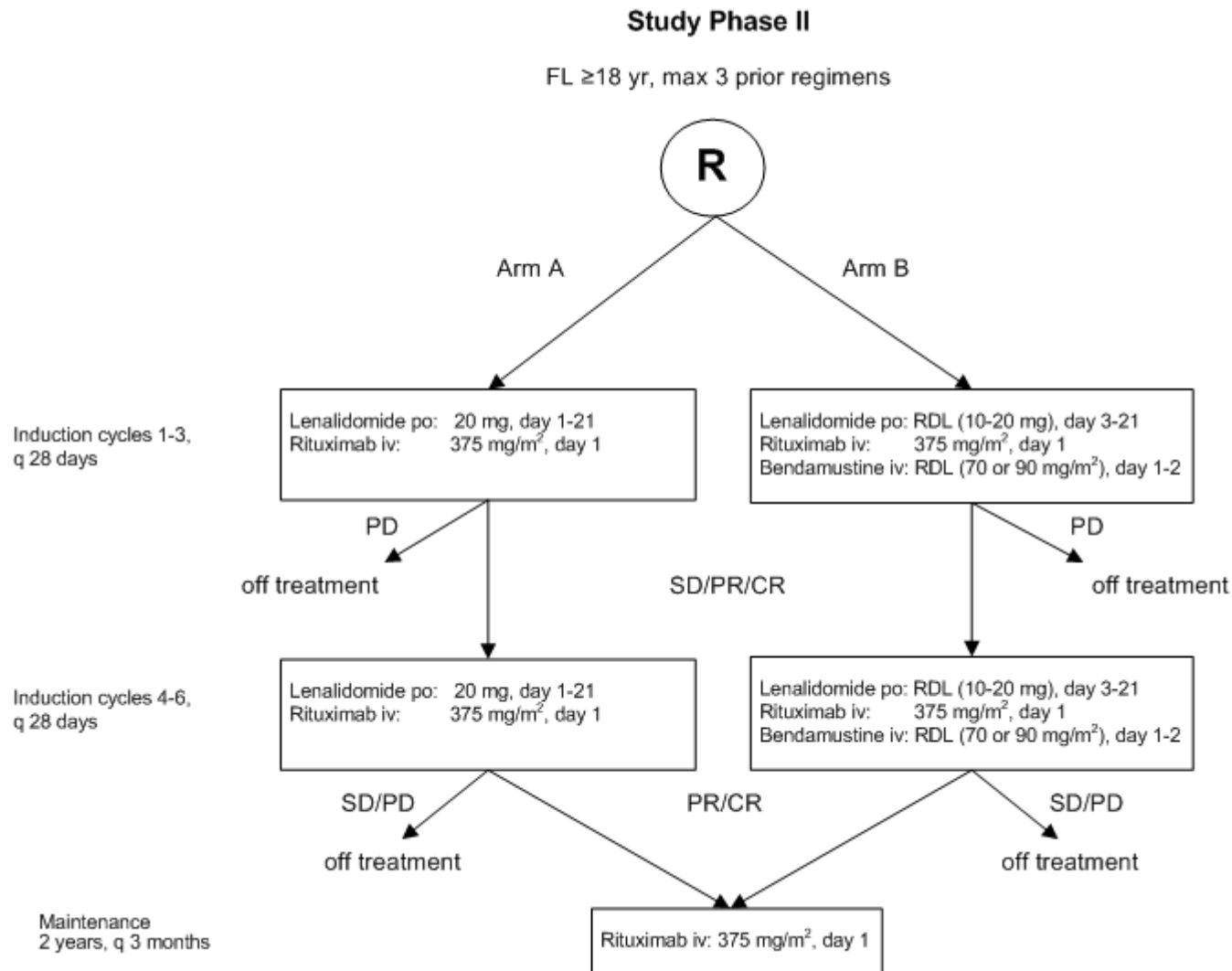


# *Lenalidomida en LDCG-B*

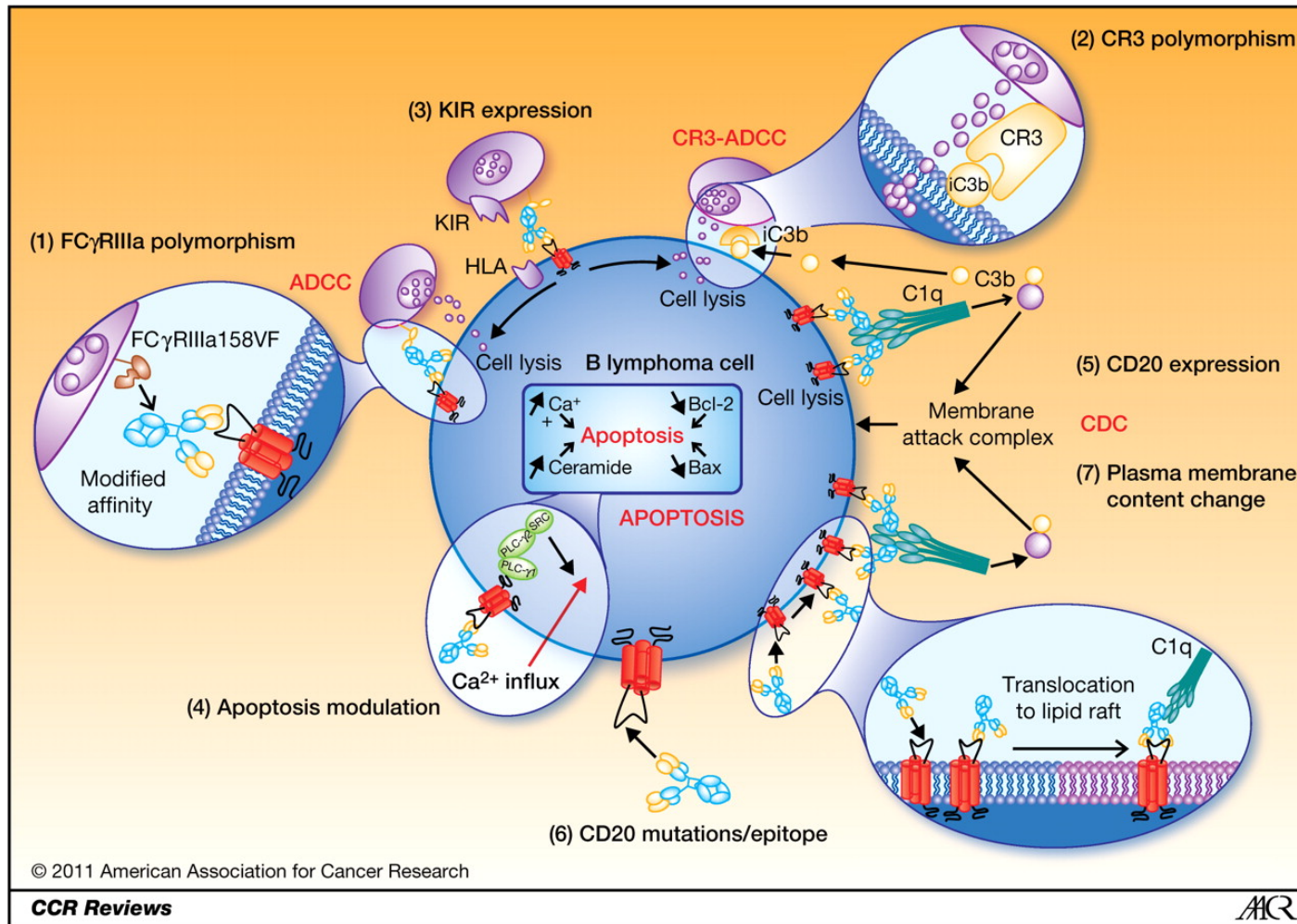
REMARCA: 1a línea, LDCG-B, 60-80 a



# *O en combinación...*

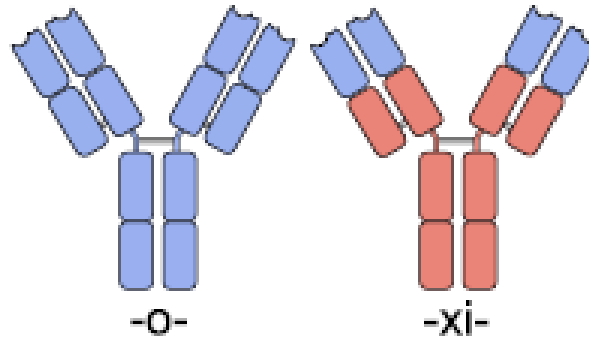


# Mejores anti-CD20: resistencia a rituximab

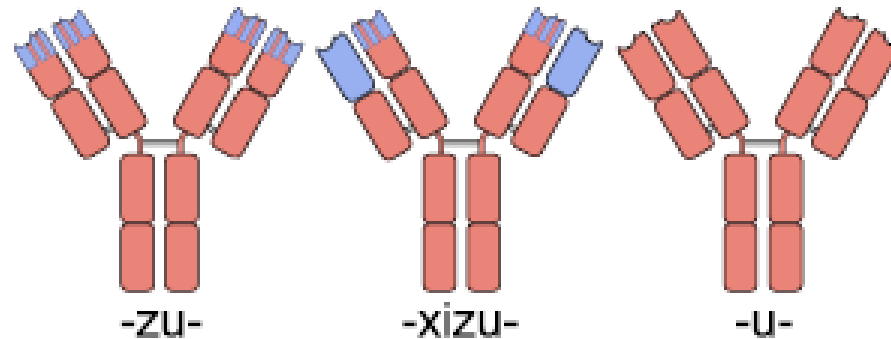


# 'Nuevos' anti-CD20

Murino:  
tositumOmab (B1)  
ibritumOmab tiuxetan



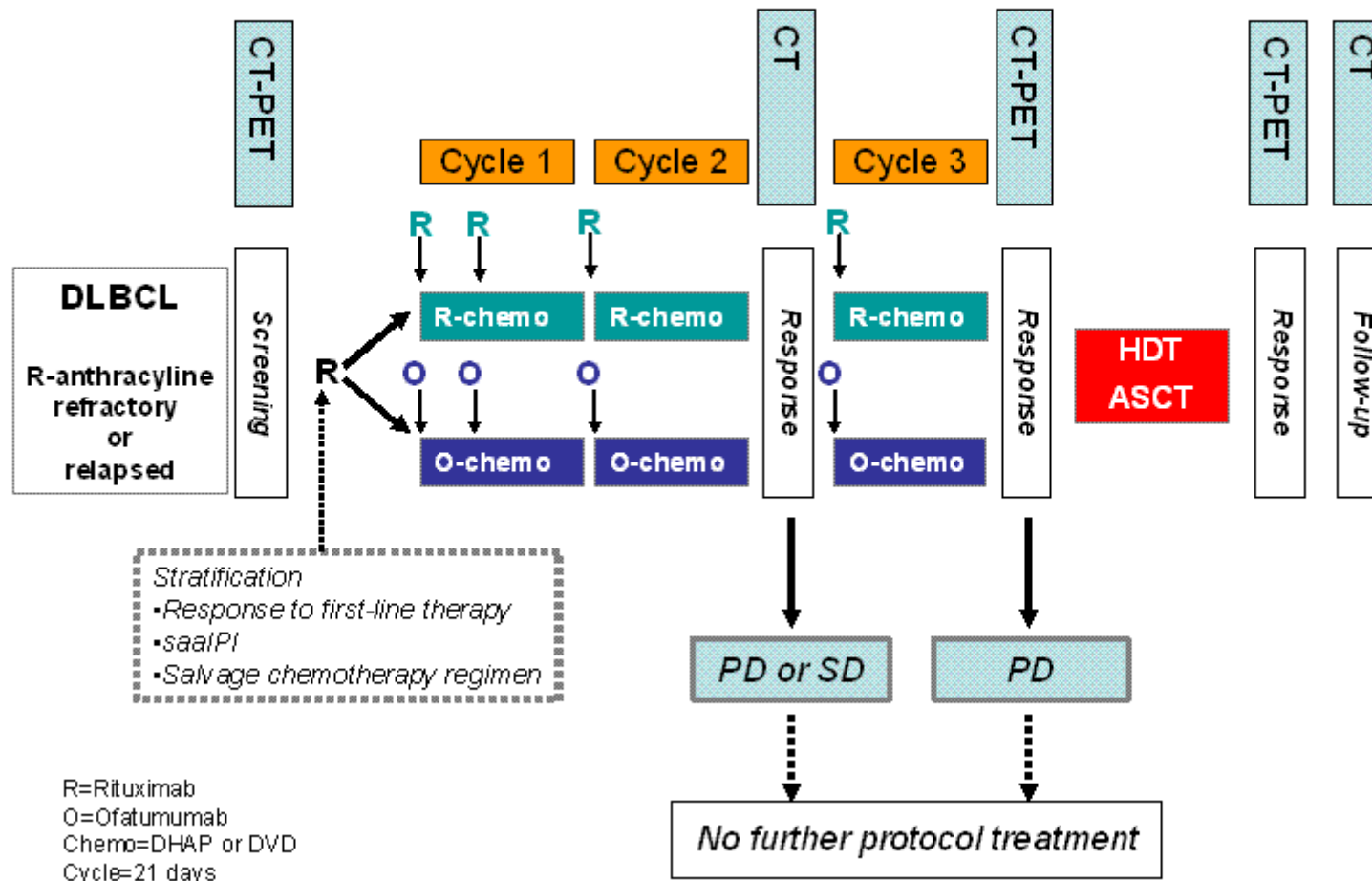
Quimérico: rituxImab



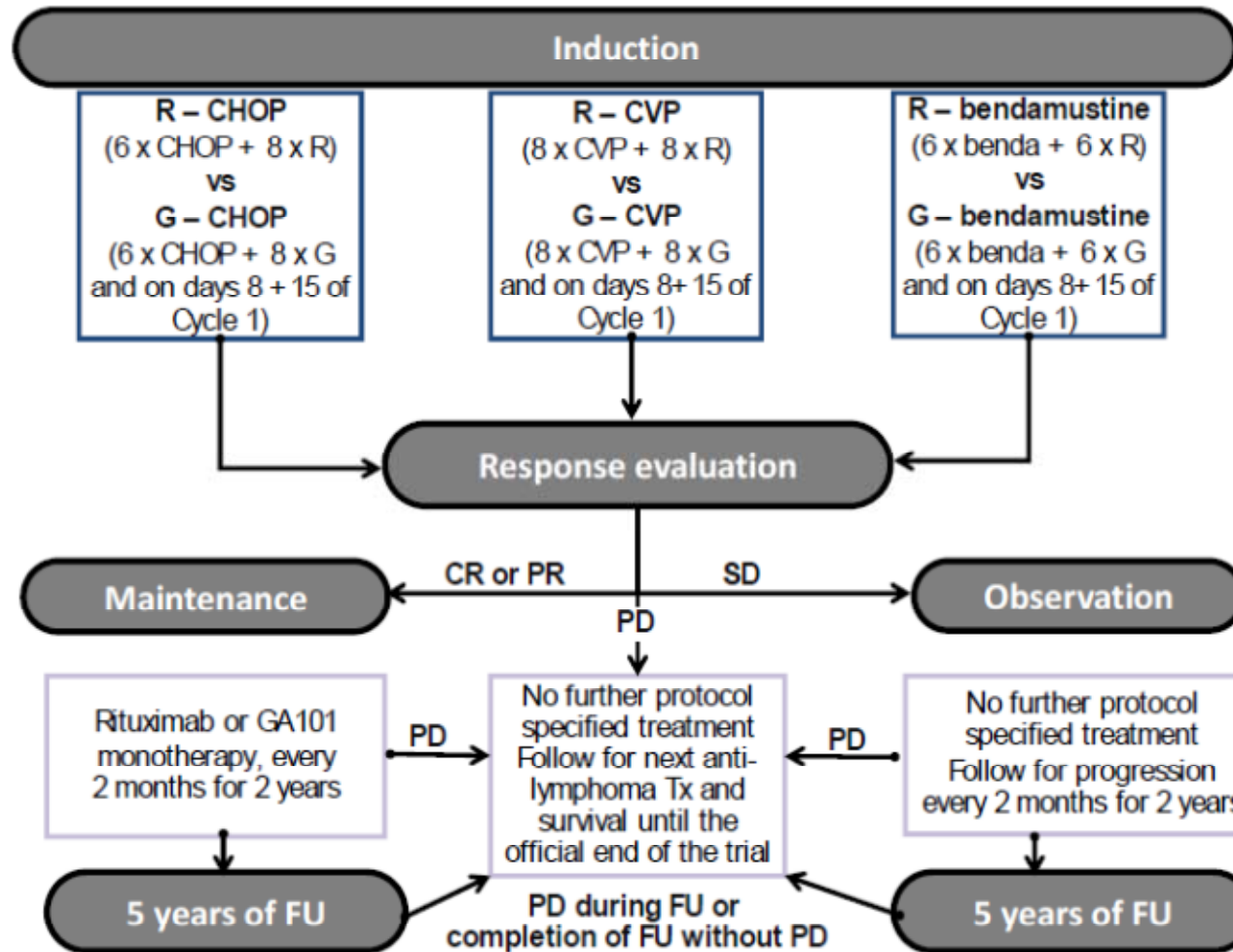
Humanizado:  
veltuZUmab (2a generación)  
obinutuZUmab: GA101 (3a generación)

Humano: ofatumUmab (2a generación)

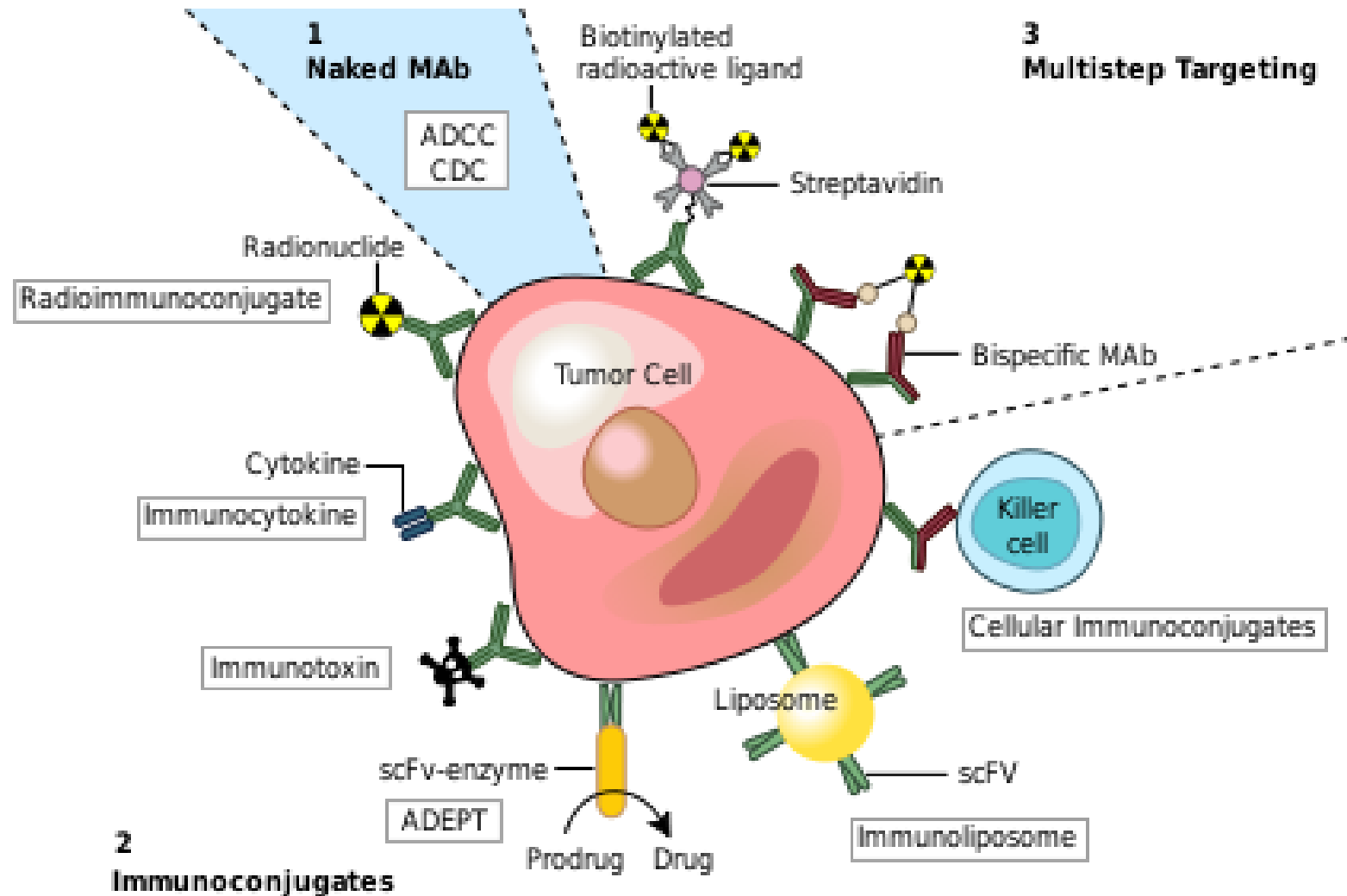
# Nuevos anti-CD20: ofatumumab



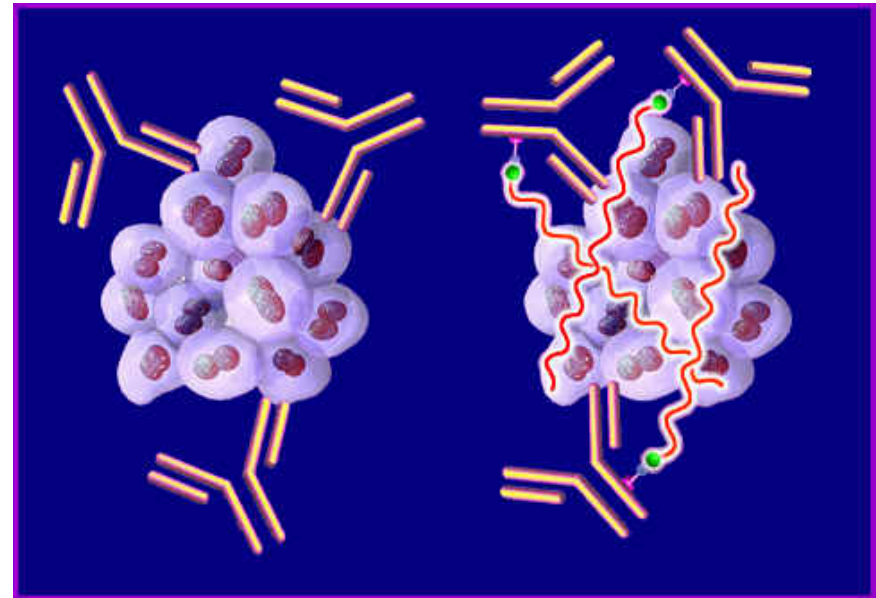
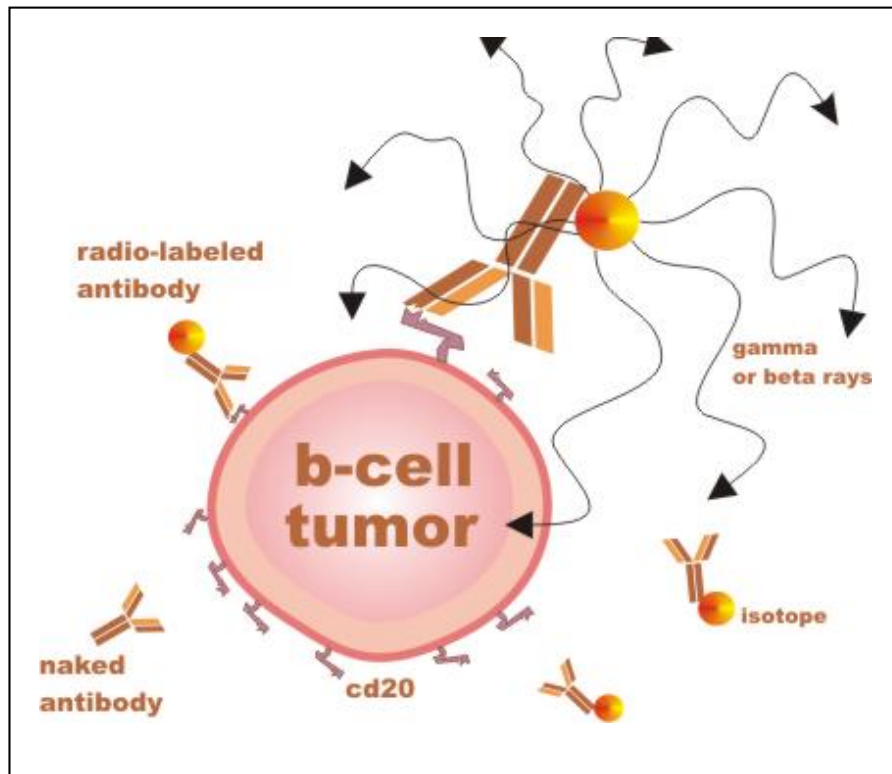
# Nuevos anti-CD20: obinutuzumab (GA-101)



# Algo más que un AcMo

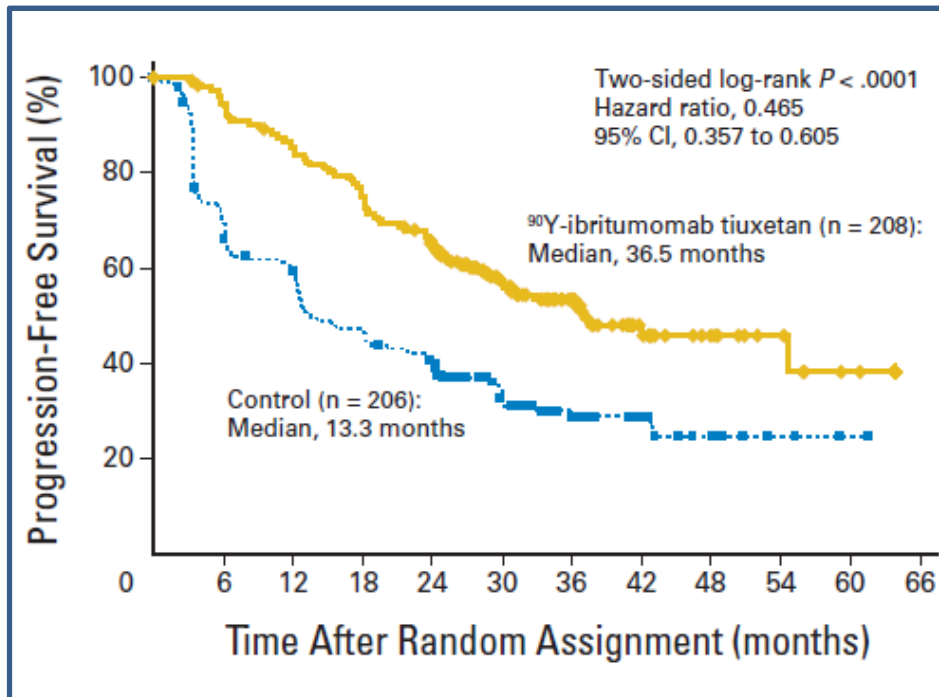


# *Radio-immunoterapia*

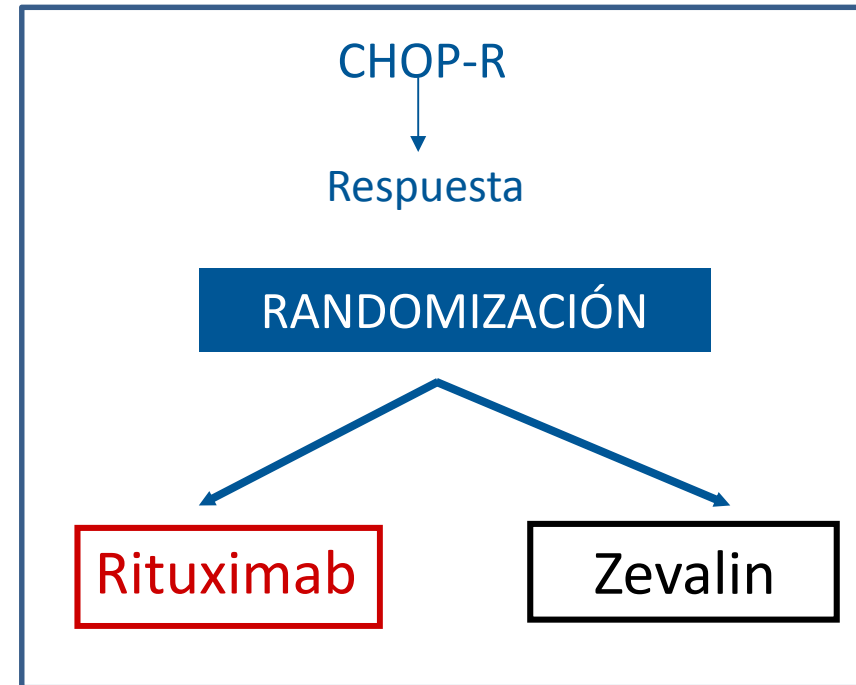




# RIT en LF

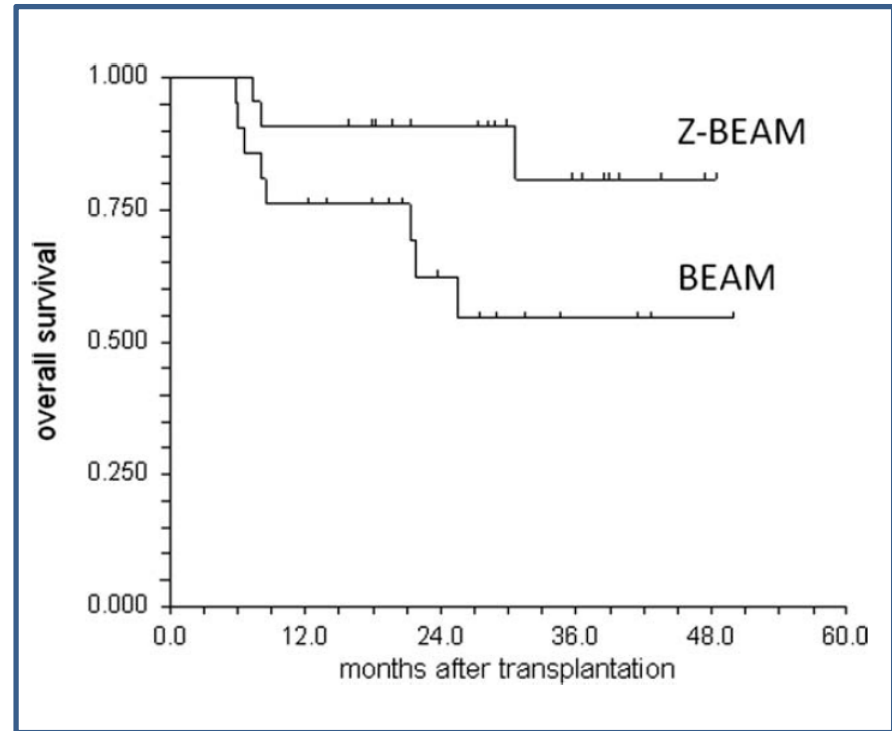
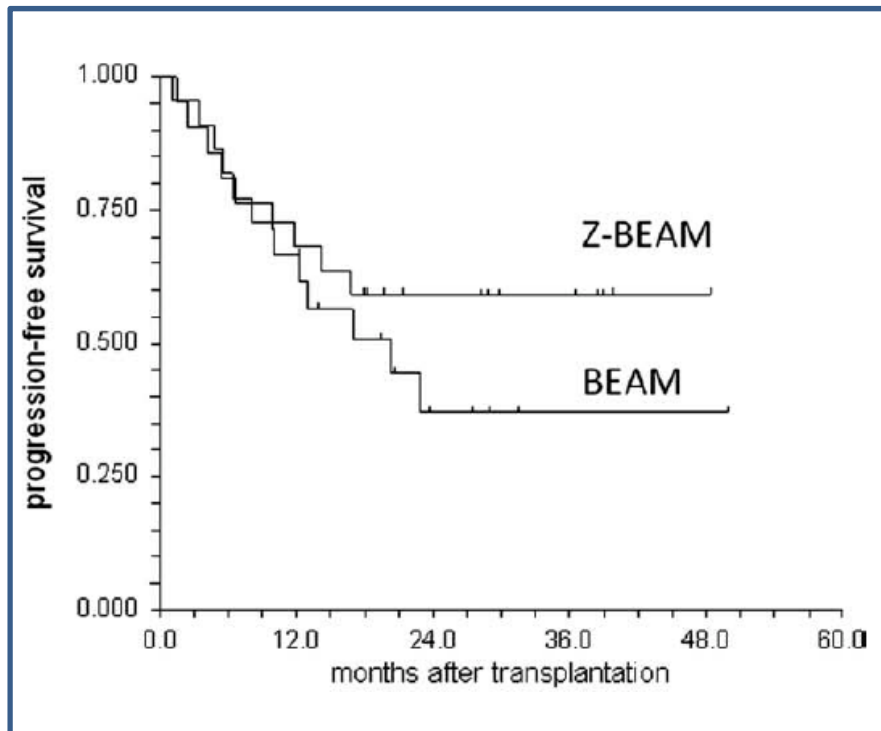


Morschhauser et al, J Clin Oncol, 2008

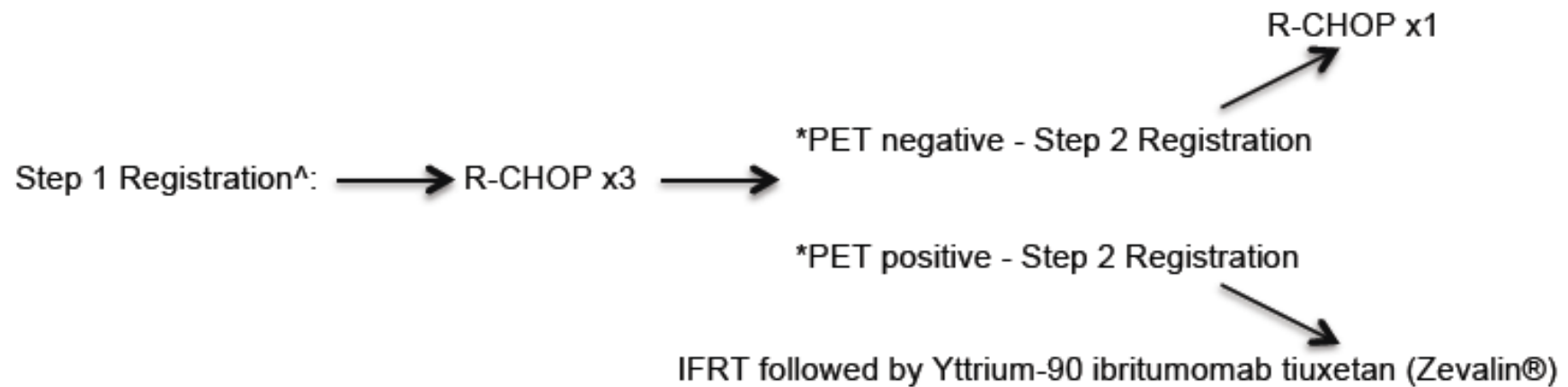


ZAR 2007

# RIT en LDCG-B



# *RIT en LDCG-B: SWOG S1001*



# *¿Y para el futuro?*

- Más AcMo
  - CMC-544
  - Blinatumomab
- Más 'terapia dirigida'
  - Inhibidores de BTK
  - Inhibidores de PI3K (CAL101)
  - Anti-BCL2

# *Conclusiones*

- Impacto de rituximab en el pronóstico de los pacientes con linfomas B
- Bendamustina, primera línea en LF
- ¿Bortezomib y lenalidomida, los siguientes en incorporarse a la 1a línea?