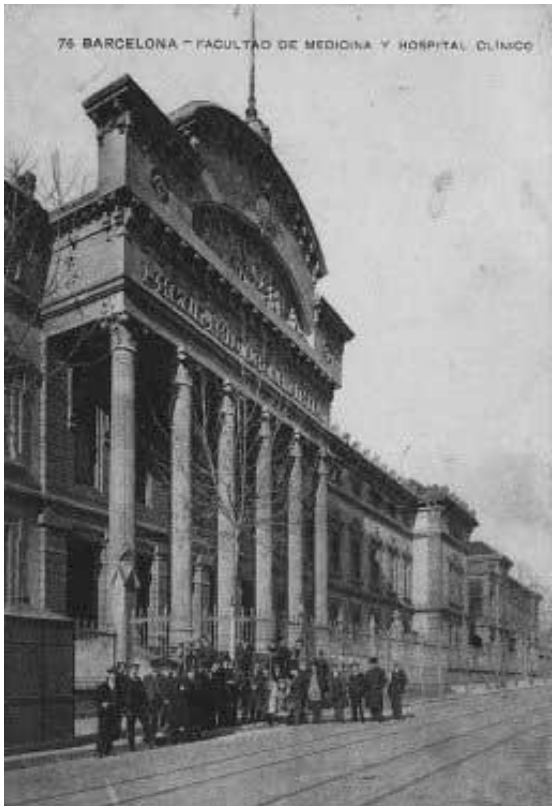


Sociedad Española de Hematología y Hemoterapia

Programa de formación

TRATAMIENTO ANTINEOPLÁSICO EN HEMATOLOGÍA: MUCHO QUE APRENDER, MUCHO QUE RECORDAR

Combinaciones quimioterápicas en hemopatías malignas:

Linfomas no Hodgkin

Armando López-Guillermo
Servicio de Hematología
Hospital Clínic

Clasificación de los linfomas (OMS 2008)

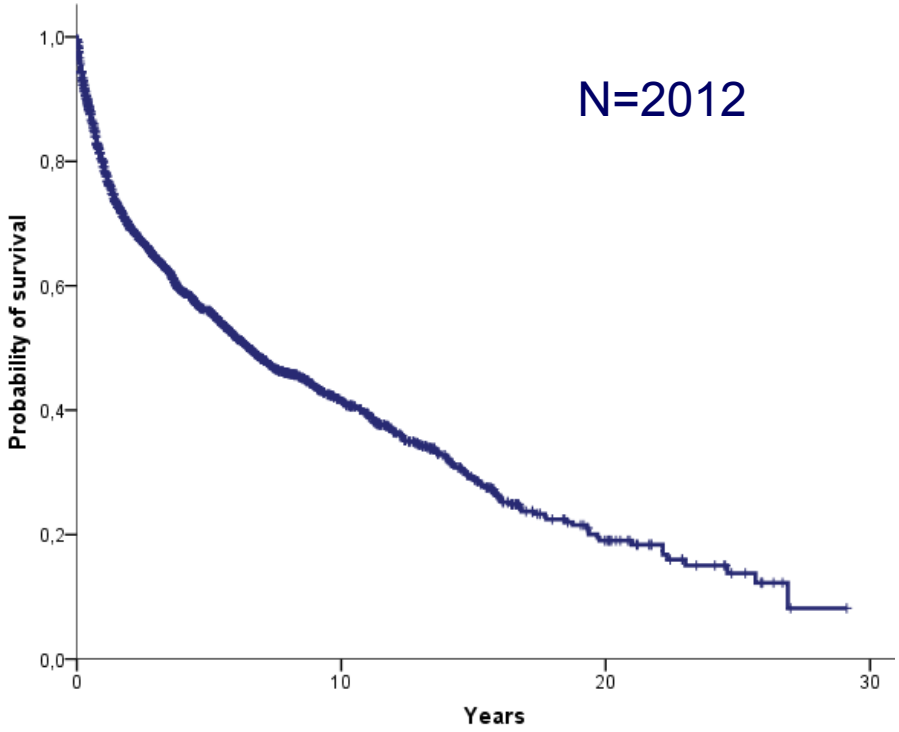
NEOPLASIAS DE PRECURSORES LINFOIDES
- L leucemia linfoblástico B, NOS
- L leucemia linfoblástico con alter. genéticas recurrentes
- L leucemia linfoblástico T

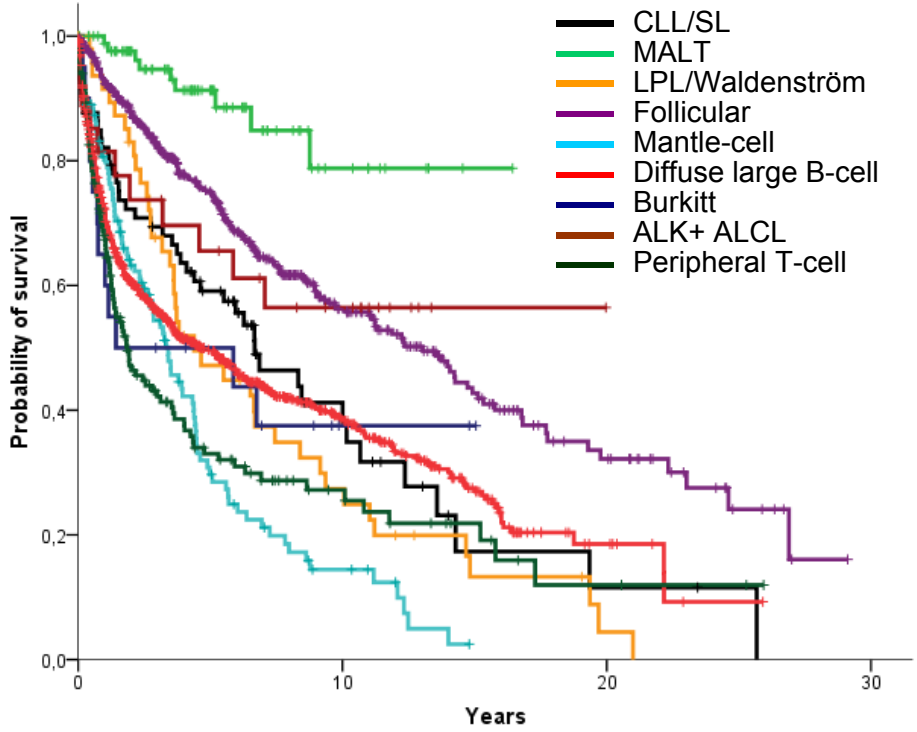
NEOPLASIAS DE CÉLULAS B MADURAS
- LLC/linfoma linfocítico
- Leucemia prolinfocítica B
- L esplénico de la zona marginal
- Tricoleucemia
- L linfoplasmocitoide
- Neoplasias de células plamáticas (MM, MGUS, …)
- L MALT
- L zona marginal ganglionar
- L folicular
- L células del manto
- L difuso de células grandes (reconocidos 11 subtipos y variantes)
- L Burkitt
- L intermedio células grandes y Hodgkin
- L intermedio células grandes y Burkitt

NEOPLASIAS DE CÉLULAS T Y NK MADURAS
- Leucemia prolinfocítica T
- Leucemia de linfocitos grandes granulares T
- Síndrome linfoproliferativo crónico de células NK
- Leucemia agresiva de células NK
- Síndrome linfoproliferativo T de la infancia EBV+
- L linfoma T del adulto
- L extraganglionar NK/T de tipo nasal
- L T periférico asociado a enteropatía
- L T hepato-esplénico
- L T subcutáneo de tipo paniculitis
- Mycosis fungoides
- Síndrome de Sézary
- L primarios cutáneos CD30+
- L primarios cutáneos subtipos raros (3)
- L T periférico, NOS
- L angioinmunoblástico
- L anaplásico de células grandes ALK+
- L anaplásico de células grandes ALK-

LINFOMA DE HODGKIN
- L Hodgkin predominio linfocítico nodular
- L Hodgkin clásico
  - L Hodgkin predominio linfocítico
  - L Hodgkin esclerosis nodular
  - L Hodgkin celularidad mixta
  - L Hodgkin depleción linfoide

Overall survival of patients with lymphoma





Clínic Barcelona, 2013

WHO Classification Principles

Malignant Lymphomas as Disease Entities

- Non- overlapping (mutually exclusive)
- Stratified according to cell lineage

Morphology
Phenotype
Genetic
Molecular alterations

Epidemiology
Etiology
Pathogenesis
Clinical presentation
Evolution
Prognostic parameters
Therapy

Non-Hodgkin lymphoma: treatment

- Before 1950: i
- 1955: chloram
- 1950/70: othe
- 1970s: combi
- 1990s:
  - Purine ana
  - Intensifica
  - Interferon
- 1998: Rituxim
- 2000s: targete

XRT

↓

CT (CHOP)

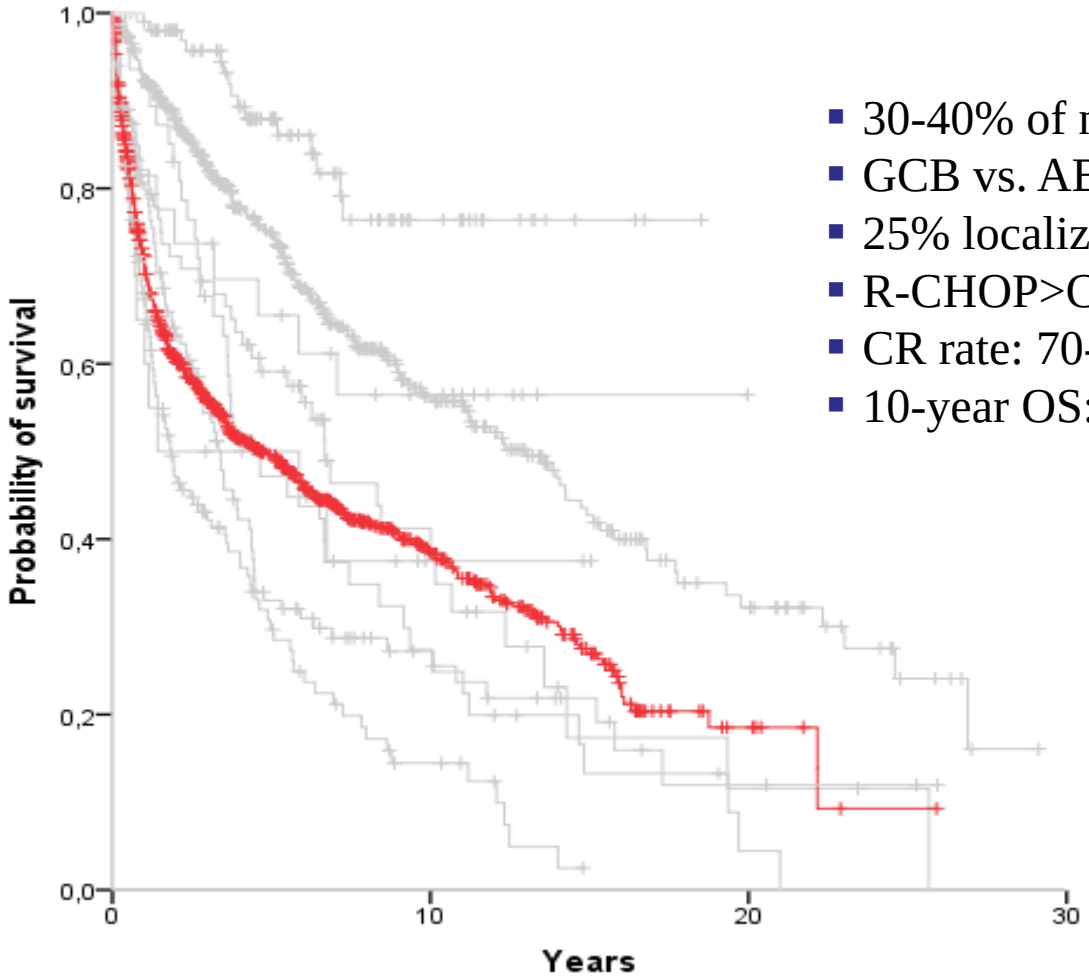
↓

Immuno-CT (R-CHOP)

↓

Targeted therapies?

Diffuse large B-cell lymphoma



- 30-40% of non-Hodgkin's lymphomas
- GCB vs. ABC; myc
- 25% localized disease
- R-CHOP>CHOP
- CR rate: 70-80%
- 10-year OS: 50-60%

Clínic Barcelona, 2013

ADVANCED DIFFUSE HISTIOCYTIC LYMPHOMA, A POTENTIALLY CURABLE DISEASE

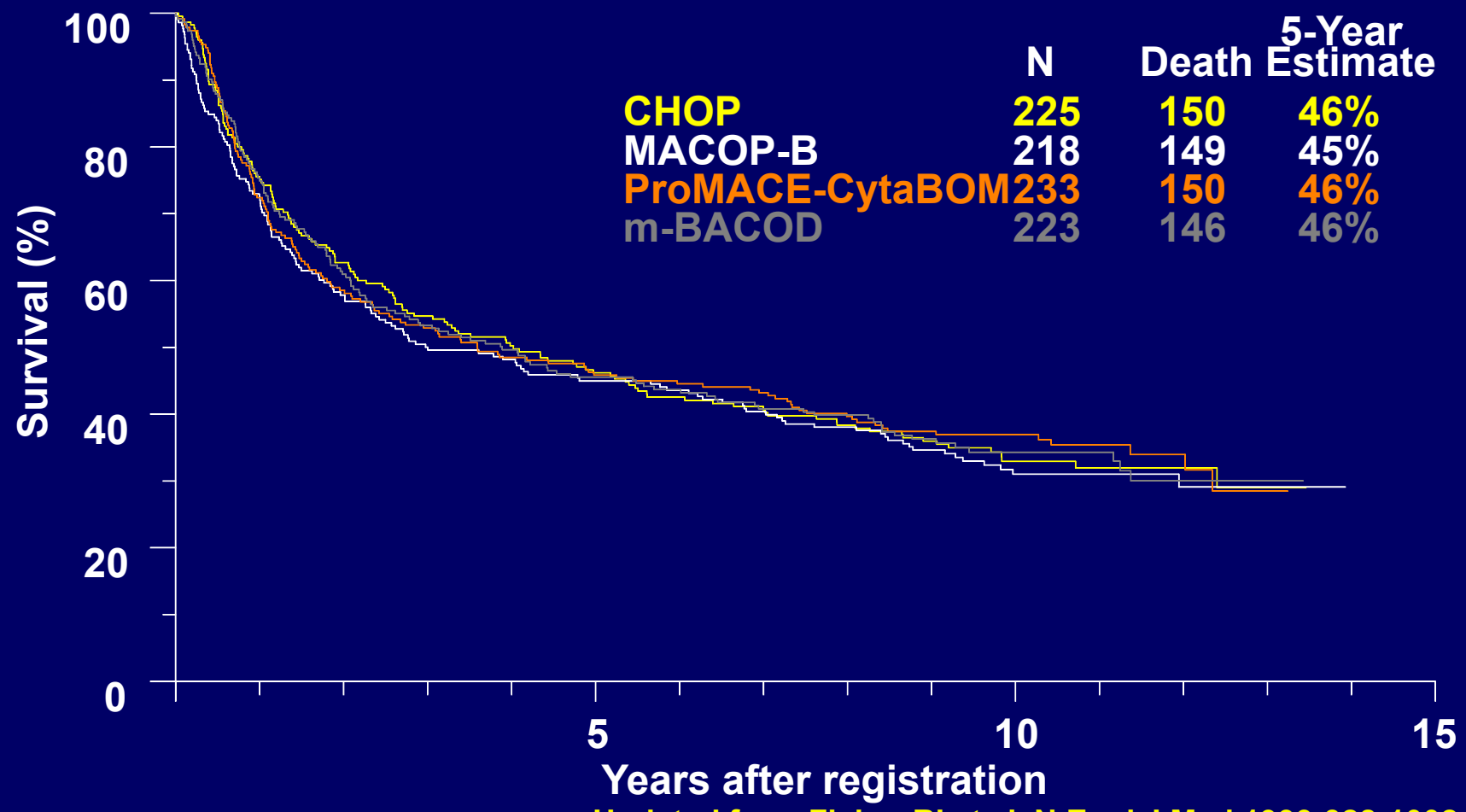
RESULTS WITH COMBINATION CHEMOTHERAPY

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

Medicine Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014, U.S.A.

Lancet, February 1, 1975

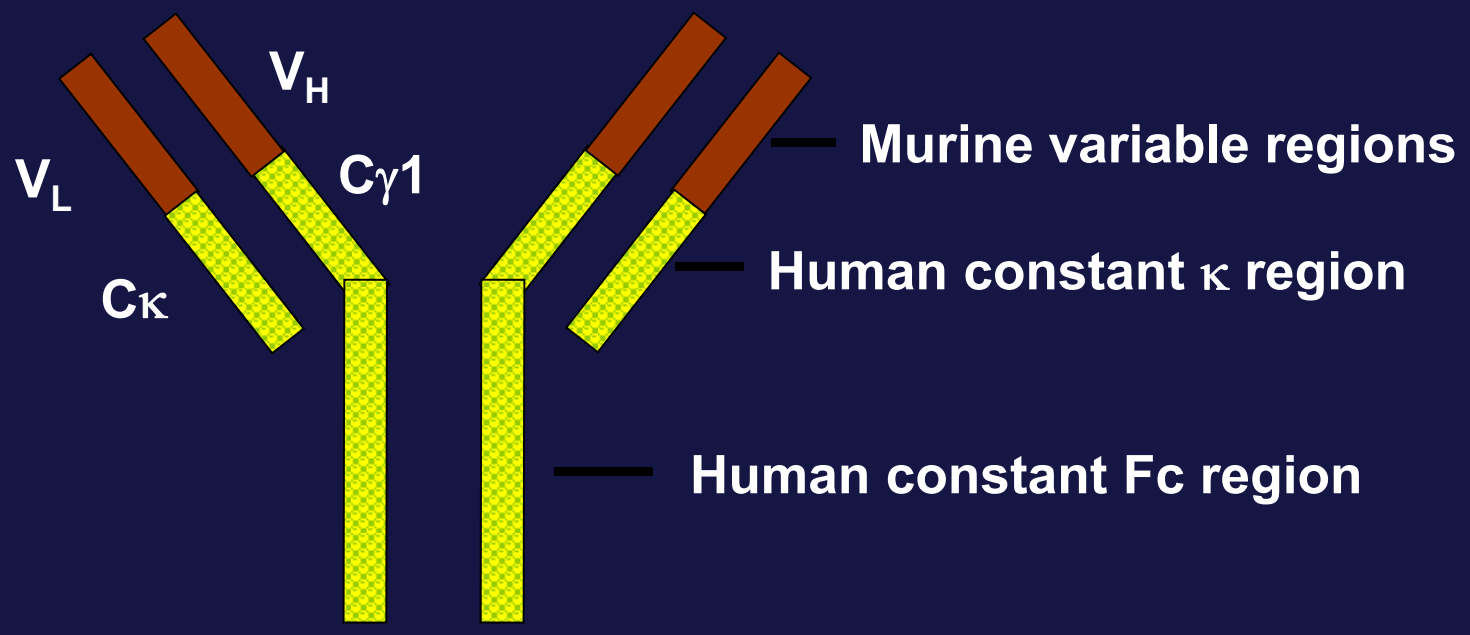
SWOG 8516 randomised trial in advanced stage aggressive NHL



Updated from Fisher RI et al. N Engl J Med 1993;328:1002

Rituximab: structure

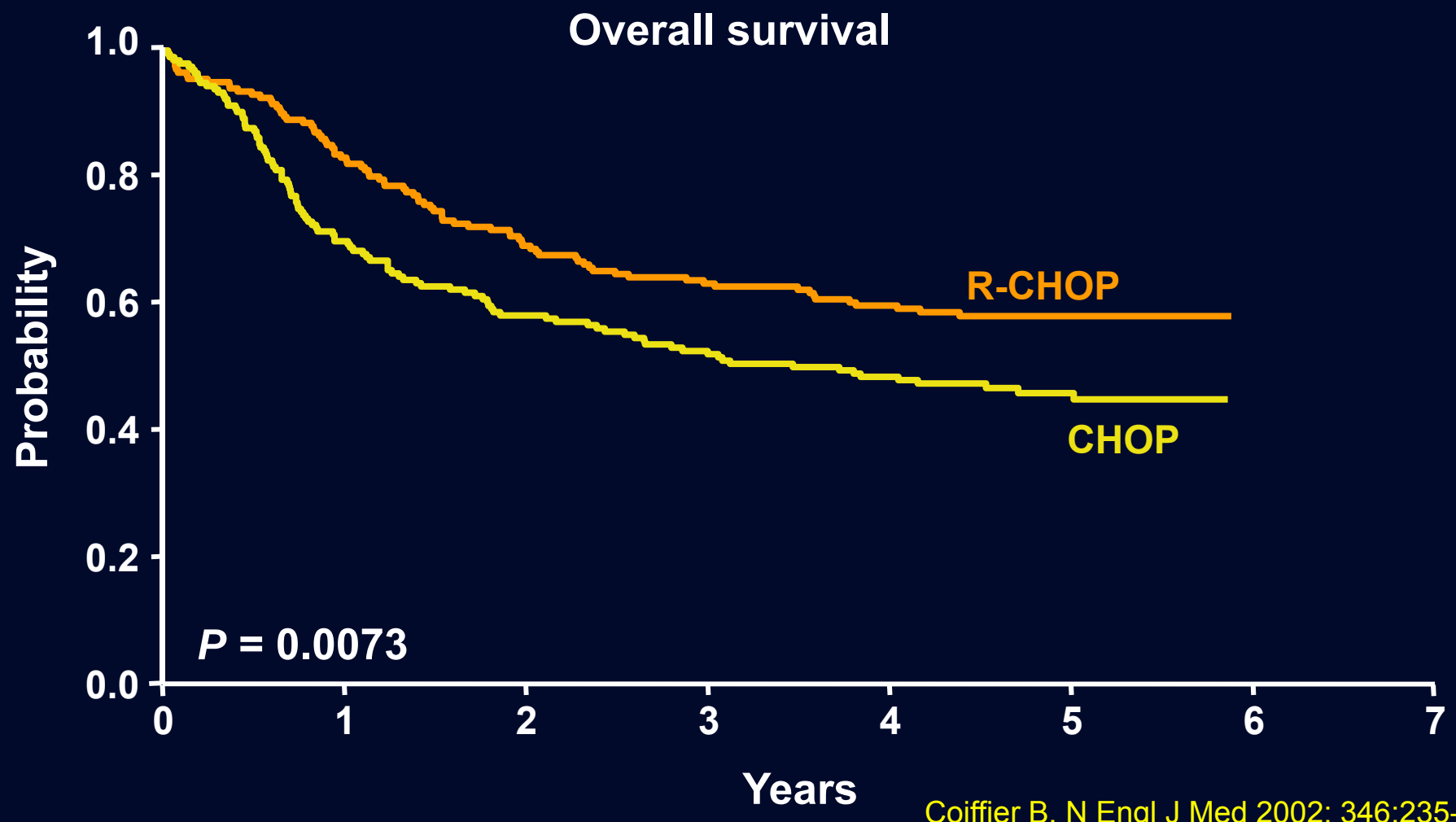
Chimeric anti-human CD20 monoclonal antibody



Variable region: murine IgG1 kappa anti-CD20

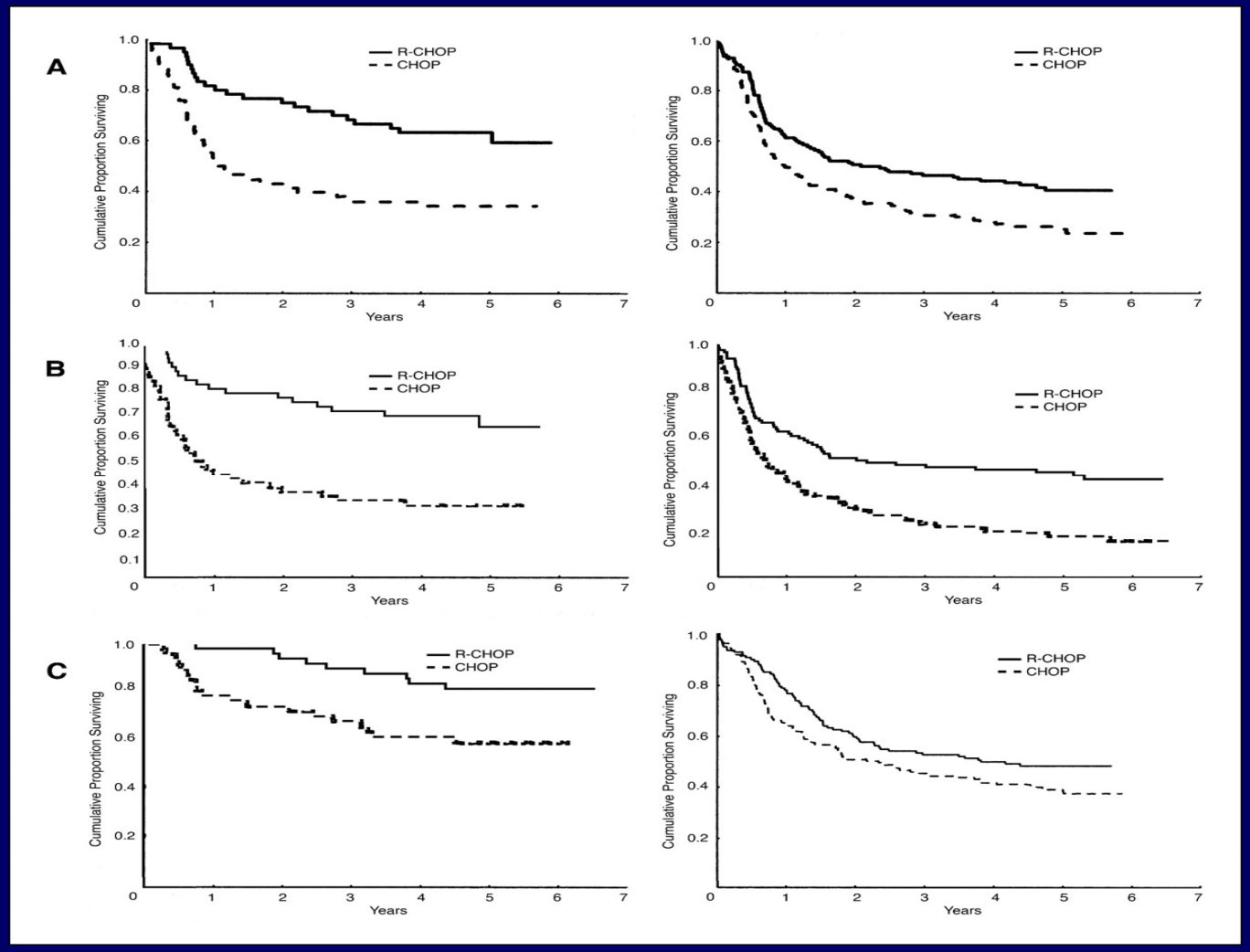
Constant region: human IgG1 heavy chain and kappa light chain

GELA 98.5: Improving CHOP-21 by adding rituximab



Coiffier B, N Engl J Med 2002; 346:235-42
Feugier P, J Clin Oncol 2005; 23:4117–26
Coiffier B, Blood 2010; 116: 2040-5

Event-free survival (A), progression-free survival (B), and overall survival (C) according to age-adjusted International Prognostic Index score: (1) low-risk patients (scores 0 and 1); (2) high-risk patients (scores 2 and 3)



Feugier, P. et al. J Clin Oncol; 23:4117-4126 2005

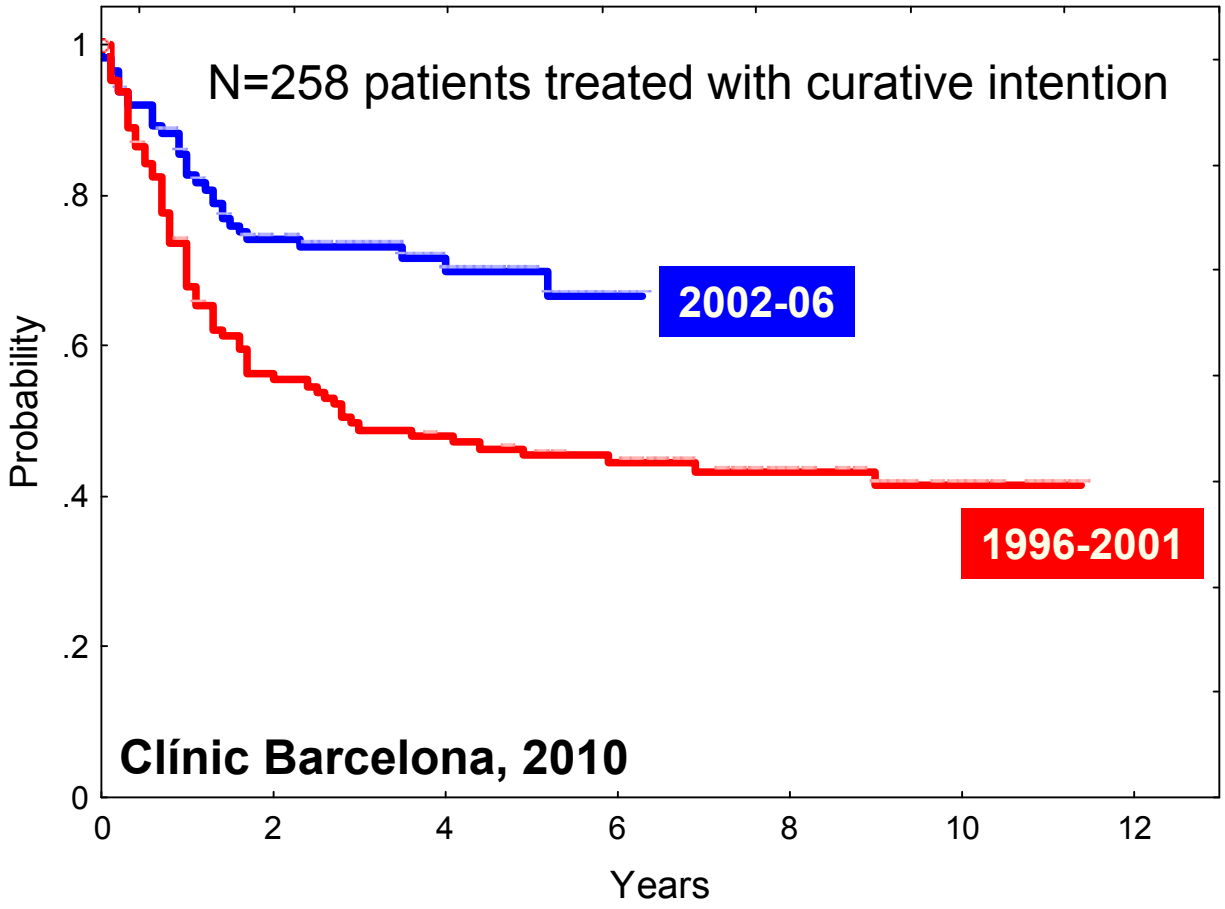
R-chemotherapy vs. chemotherapy alone in DLBCL

↑ CR, ↑ PFS and ↑ OS in different settings:

- GELA/LNH 98.5 (60-80 years)[1,2]
- ECOG 4494 (60-80 years; maintenance arm)[3]
- MINT (young low-risk patients)[4]
- RICOVER (CHOP-14)[5]
- HOVON (CHOP-14)[6]

Coiffier, NEJM 2002 (1)
Feugier, JCO 2005 (2)
Habermann, JCO 2006 (3)
Pfreundschuh, Lancet Oncol 2006 (4)
Pfreundschuh, Lancet Oncol 2008 (5)
Sonneveld, ASH 2006 (#210); JCO 2012 (in press) (6)

DLBCL: survival according to the date of diagnosis



Diffuse large B-cell lymphoma

Frontline treatment

How to improve the results of R-CHOP?

- ↑ “Density”
- ↑ Intensity
- Transplantation (auto, allo)
- New drugs (“targeted” therapy)

DLBCL: front-line treatment

- R-CHOP14 > R-CHOP21?

	N	CR (%)	EFS (2-yr)	OS (2-yr)
Cunningham[1]				
RCHOP14	540	58	75%	83%
RCHOP21	540	63	75%	81%
Delarue[2]				
RCHOP14	304	67	56*	67
RCHOP21	298	75	60*	70

*at 3 years

(1) Cunningham D, Lancet 2013:381:1817-26
(2) Delarue R, Lancet Oncol 2013;14:525-33

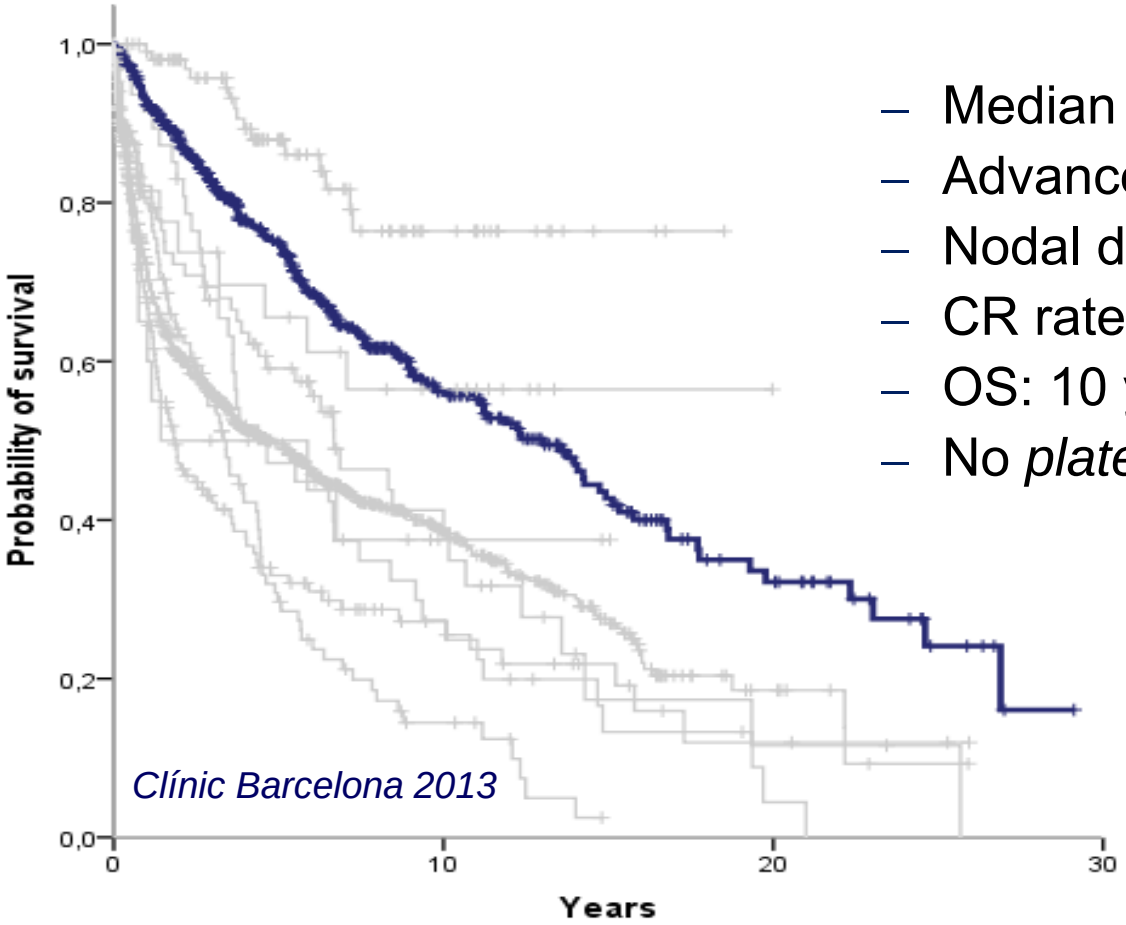
Current approaches in young patients with high-risk DLBCL

- R-Chemo (or somewhat more intensive?)
- Early assessment: “response-adapted therapy” (PET scan)
- Intensification
  - All patients
  - Only those with insufficient response
- New drugs

Next steps in DLBCL

- Differential approaches for biological groups (i.e., GCB vs. ABC)
- New monoclonal antibodies
  - new anti-CD20 and other targets (CD22, CD30, CD40 …) alone or combined
- Targeted therapies (“Small molecules”)
  - Proteasome inhibitors (bortezomib in ABC?)
  - Anti-apoptotic
  - M-TOR inhibitors
  - Tyrosin kinase inhibitors
  - Immunomodulators (lenalidomide)

Follicular lymphoma

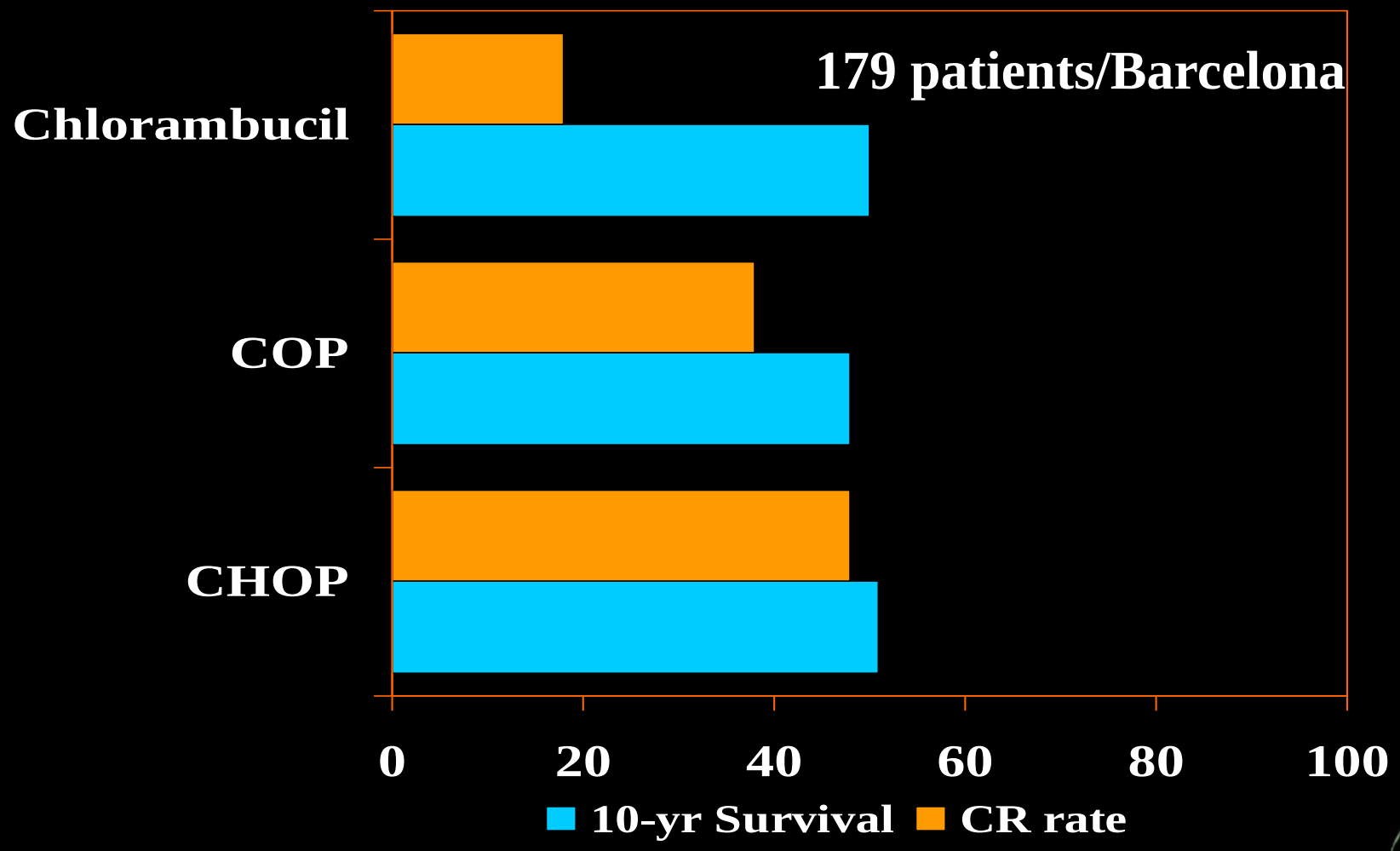


- Median age: 60 years
- Advanced stage: 80%
- Nodal disease; BM+
- CR rate: 10-80%
- OS: 10 years (↑)
- No *plateau* in PFS or OS curves

Linfoma folicular: tratamiento

Follicular Lymphoma

Response and survival according to treatment



Rituximab plus chemo in first-line FL: overall survival benefit across all studies

Study	Regimen	Follow-up	Overall survival (%)		
			Control	MabThera	*p*-value
M39021[1]	CVP ± Rituximab	4 years	77	83	0.029
GLSG[2,3]	CHOP ± Rituximab	5 years	84	90	0.0493
M39023[4,5]	MCP ± Rituximab	4 years	74	87	0.0205
FL2000[6]	CHVP + IFN ± Rituximab	5 years	79	84	0.025 (high-risk pts)

1. Marcus R, et al. J Clin Oncol 2008; 26:4579–4586
2. Hiddemann W, et al. Blood 2005; 106:3725–3732
3. Buske C, et al. Blood 2008; 112:Abstract 2599
4. Herold M, et al. J Clin Oncol 2007; 25:1986–1992
5. Herold M, et al. Ann Oncol 2008; 19(Suppl 4):Abstract 329
6. Salles G, et al. Blood 2008; 112:4824–4831

Rituximab combinations in FL

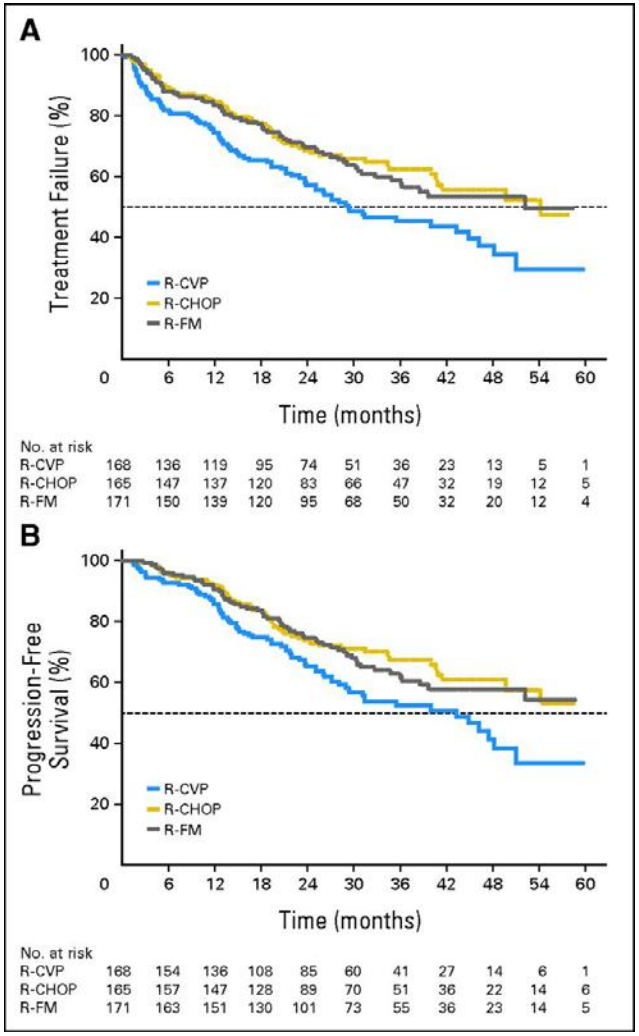
	CR rate	Toxicity
R-CVP	↓	↓
R-CHOP	↑	↓
R-FC/FCM/FMD	↑↑	↑↑
R-CT+ASCT		
R-Other MoAb		

R-BENDA > R-CHOP?[1]

R-CHOP>R-COP>R-FC?[2]

1- Rummel, Lancet 2013; 2- Federico, J Clin Oncol 2013

Kaplan-Meier analysis of probability of (A) time to treatment failure and (B) progression-free survival according to intention-to-treat principle.

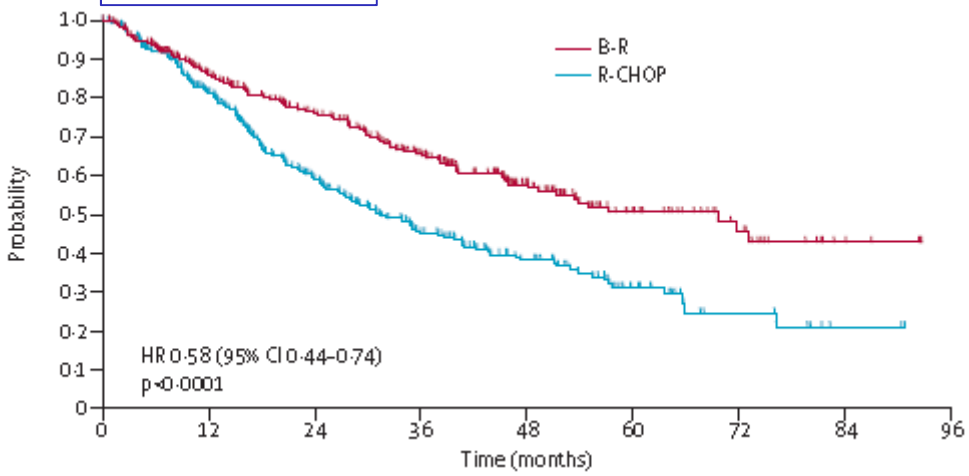


Federico M et al. JCO 2013;31:1506-1513

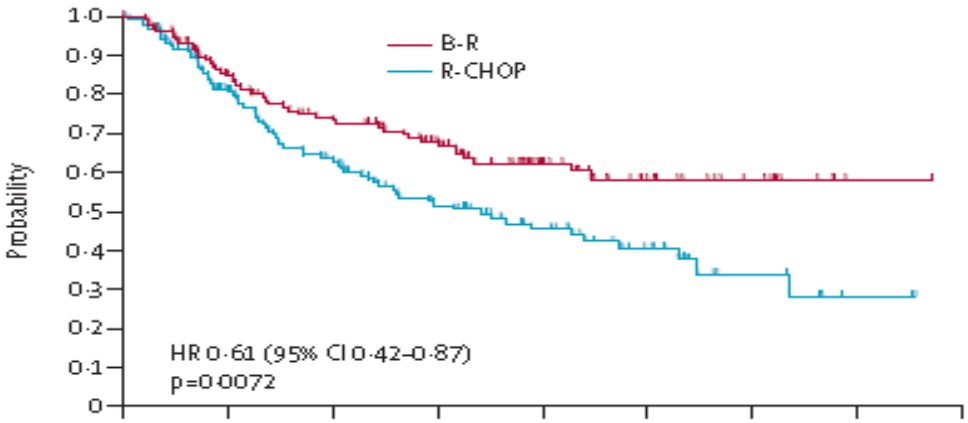
JOURNAL OF CLINICAL ONCOLOGY ASCO

Bendamustine plus rituximab (B-R) versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial

All patients



Follicular lymphoma

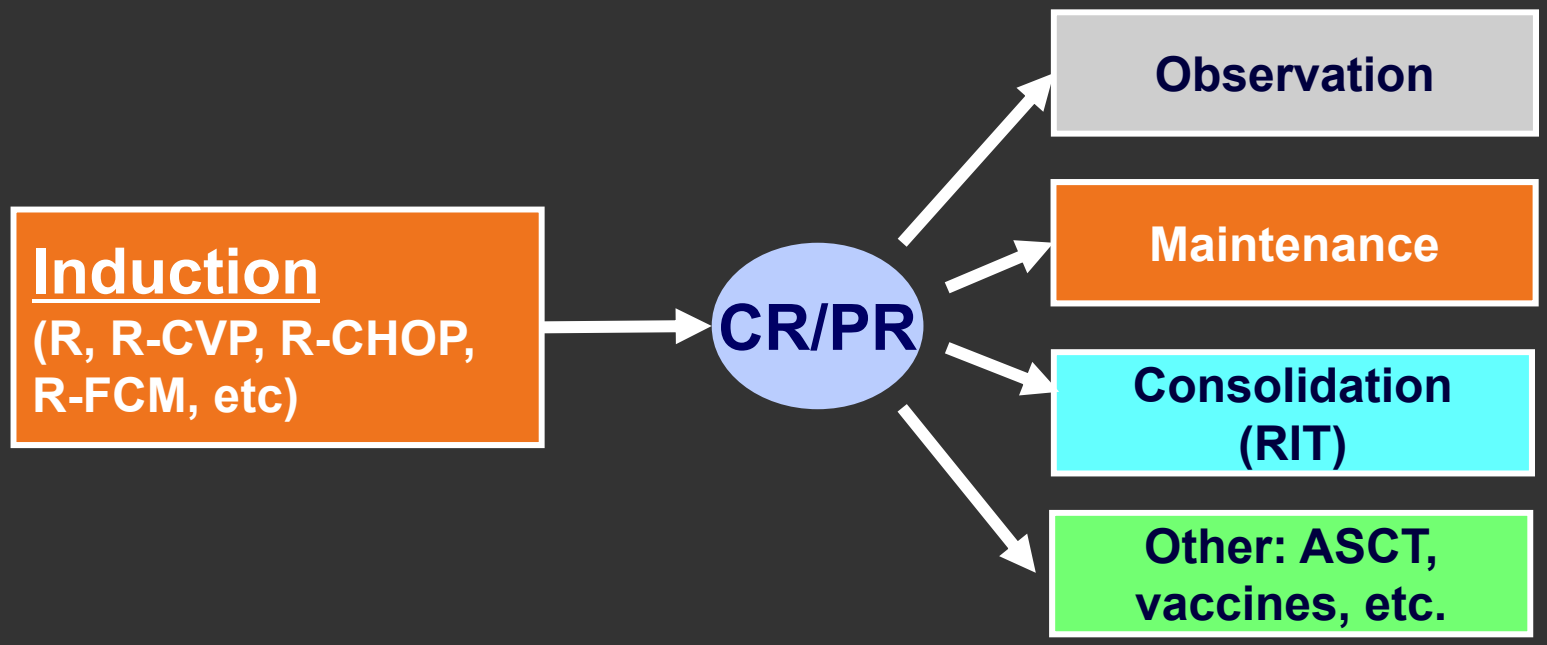


Benda-R:

- Higher CR rate
- Longer PFS / EFS
- ≈OS (at present)
- Less toxicity

Rummel MJ, Lancet 2013;381:1184

How can we improve positive response in patients after induction?



Benefits of rituximab maintenance in patients with FL

Relapsed disease

Induction treatment	PFS	Overall survival
Rituximab alone[1]	↑	=
Chemo alone[2,3]	↑	↑
R-chemo[2–4]	↑	↑ =

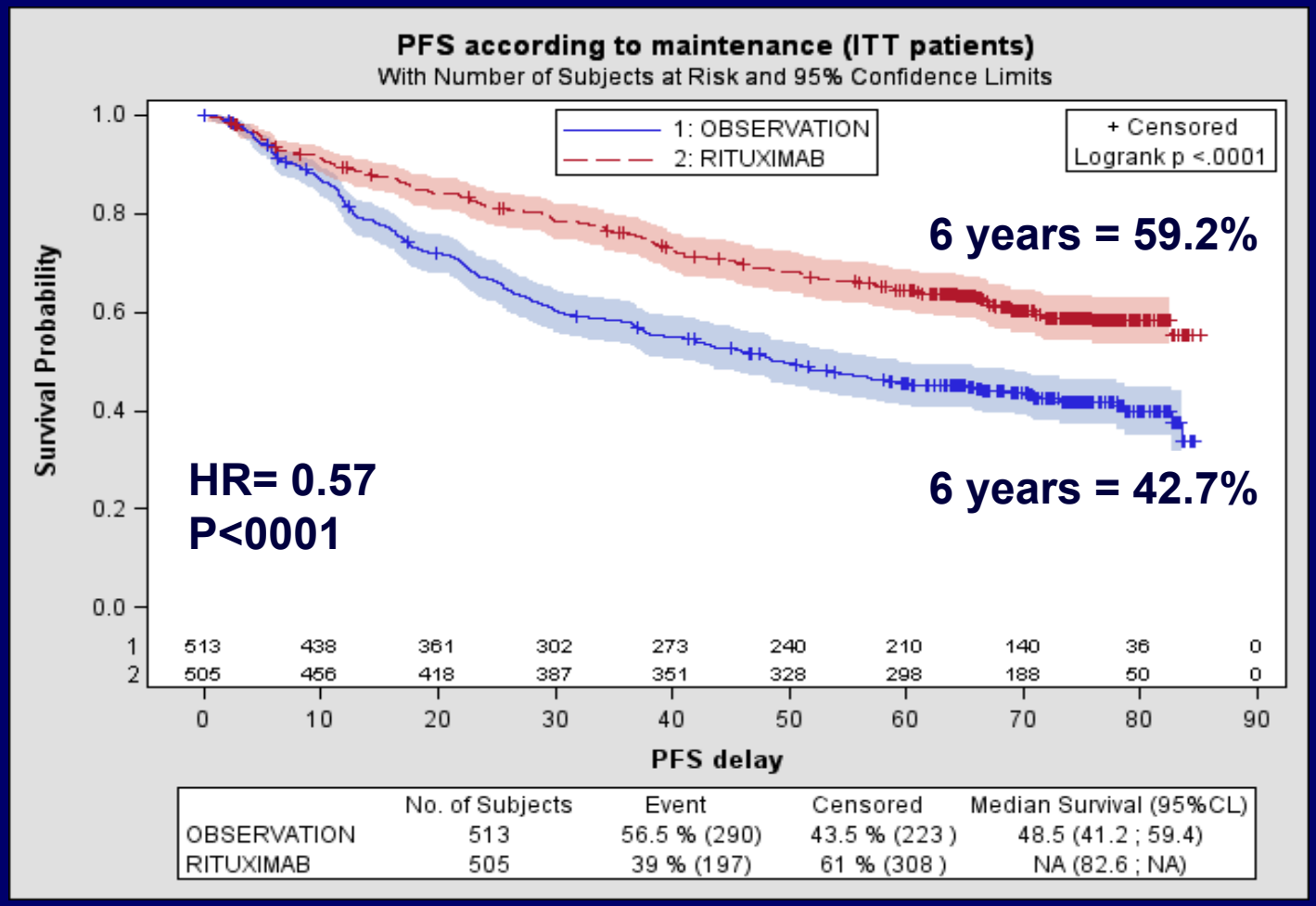
Initial treatment

Induction treatment	PFS	Overall survival
Rituximab alone[1]	↑	=
Chemo alone[5]	↑	↑ *
R-chemo (PRIMA)	↑	=

*p = 0.08

1. Ghielmini M, *et al. Blood* 2004; 103:4416–4423.
2. van Oers MHJ, *et al. Blood* 2006; 108:3295–3301. 3. van Oers MHJ, *et al. J Clin Oncol* 2010; 28:2853–2858.
4. Forstpointner R, *et al. Blood* 2006; 108:4003–4008. 5. Hochster H, *et al. J Clin Oncol* 2009; 27:1607–1614.

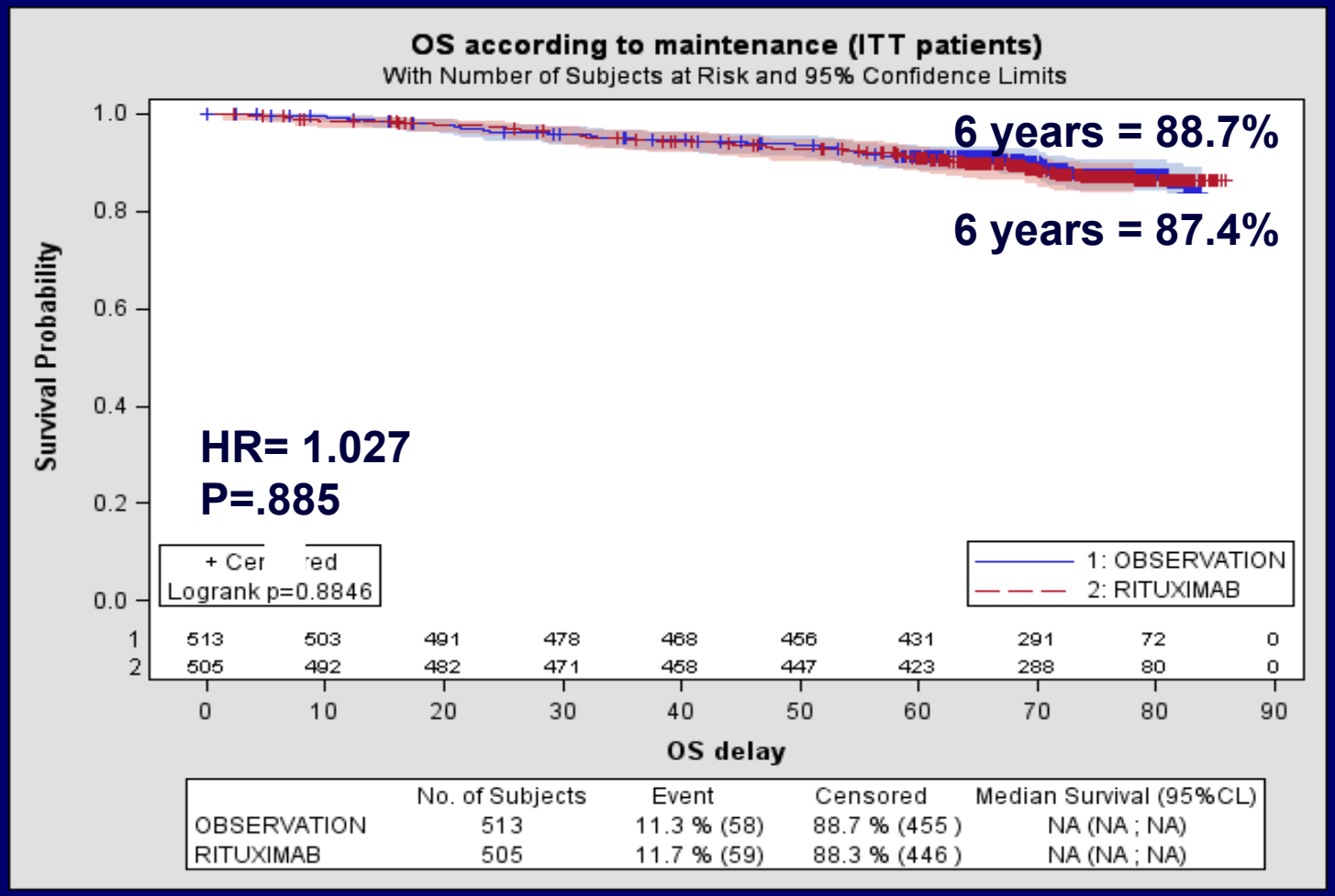
PRIMA 6 years follow-up
Progression free survival from randomization



	No. of Subjects	Event	Censored	Median Survival (95%CL)
OBSERVATION	513	56.5 % (290)	43.5 % (223)	48.5 (41.2 ; 59.4)
RITUXIMAB	505	39 % (197)	61 % (308)	NA (82.6 ; NA)

Median follow-up since randomization : 73 months

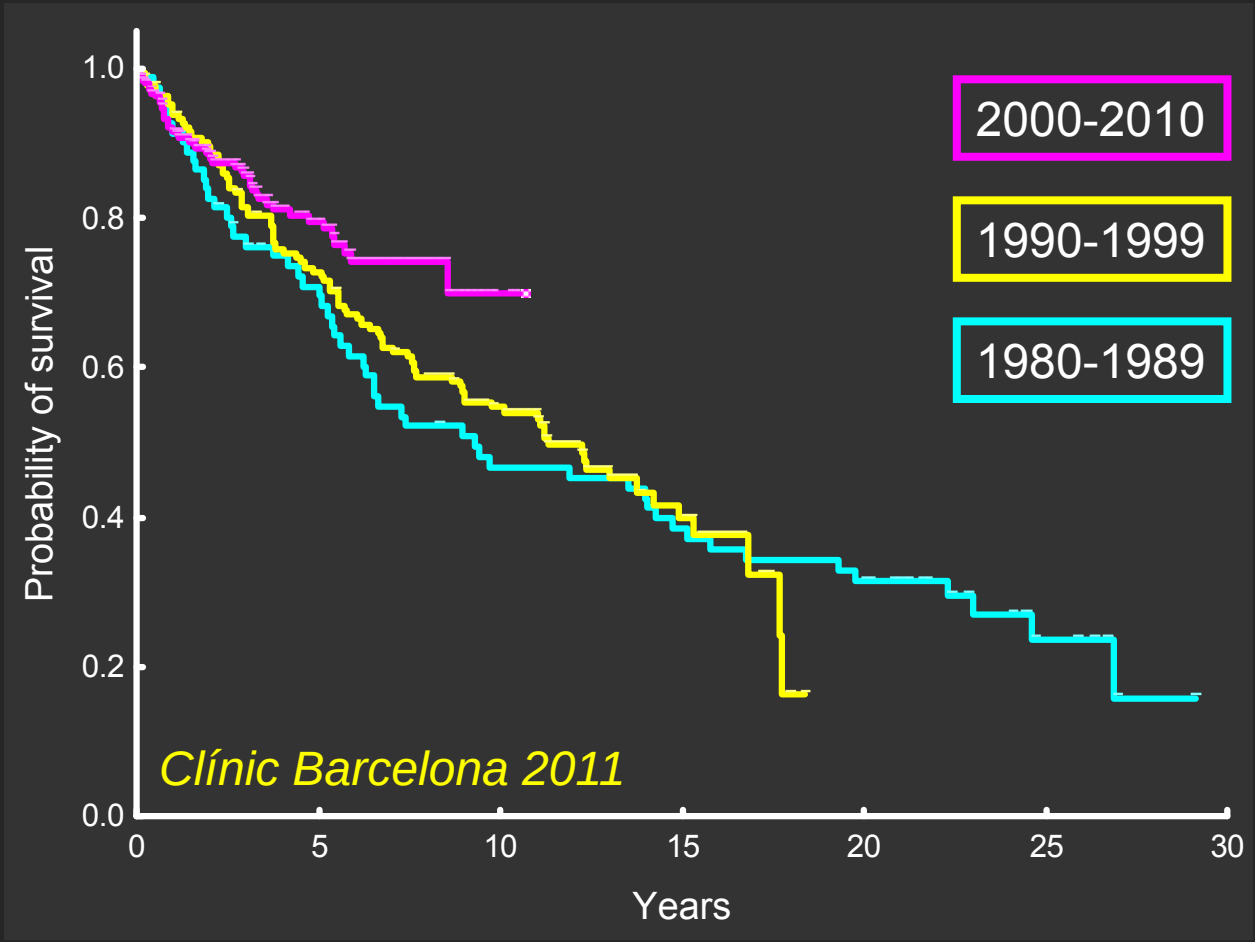
PRIMA 6 years follow-up
Overall survival



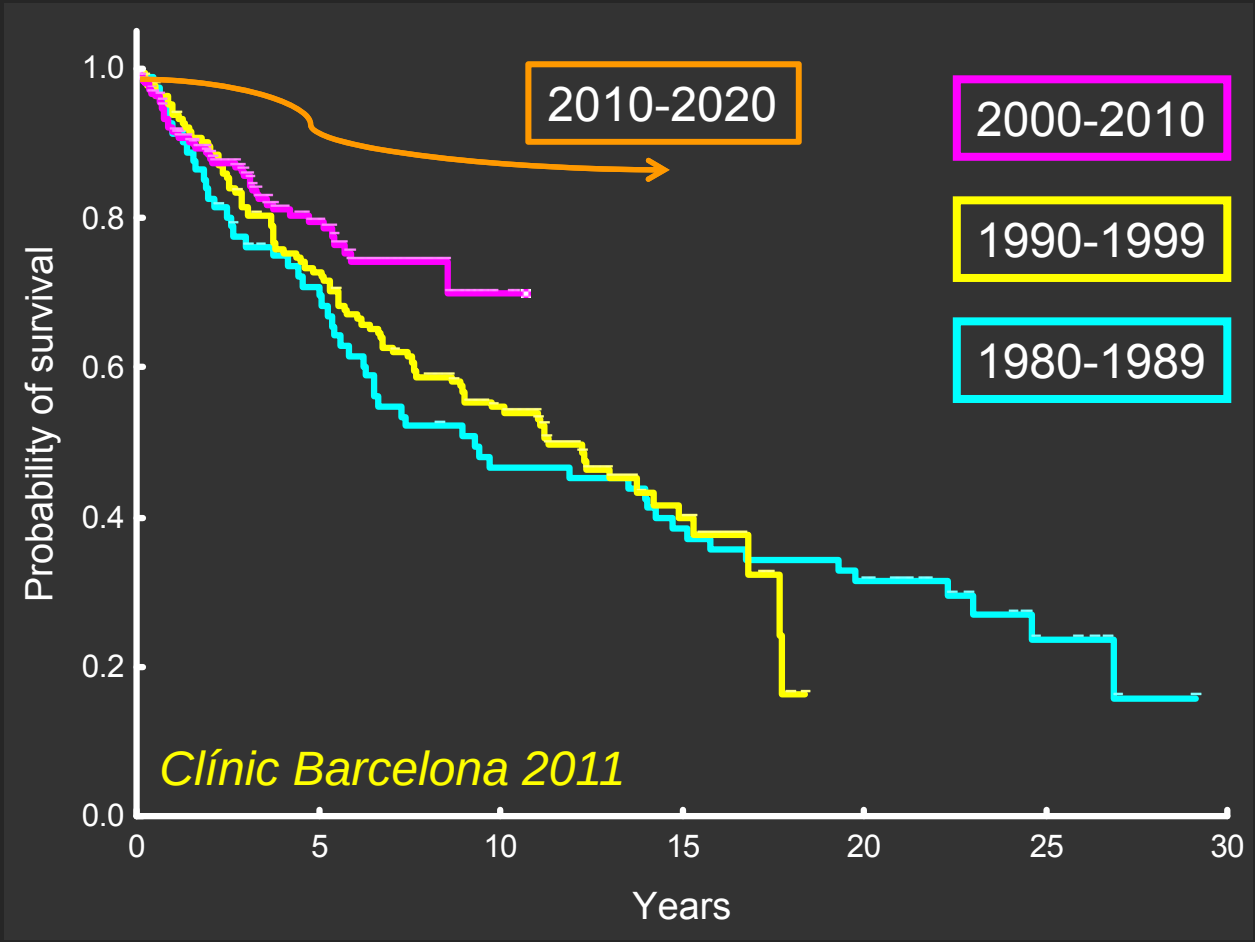
	No. of Subjects	Event	Censored	Median Survival (95%CL)
OBSERVATION	513	11.3 % (58)	88.7 % (455)	NA (NA ; NA)
RITUXIMAB	505	11.7 % (59)	88.3 % (446)	NA (NA ; NA)

Median follow-up since randomization : 73 months

Follicular lymphoma: survival by the date of diagnosis



Follicular lymphoma: survival by the date of diagnosis

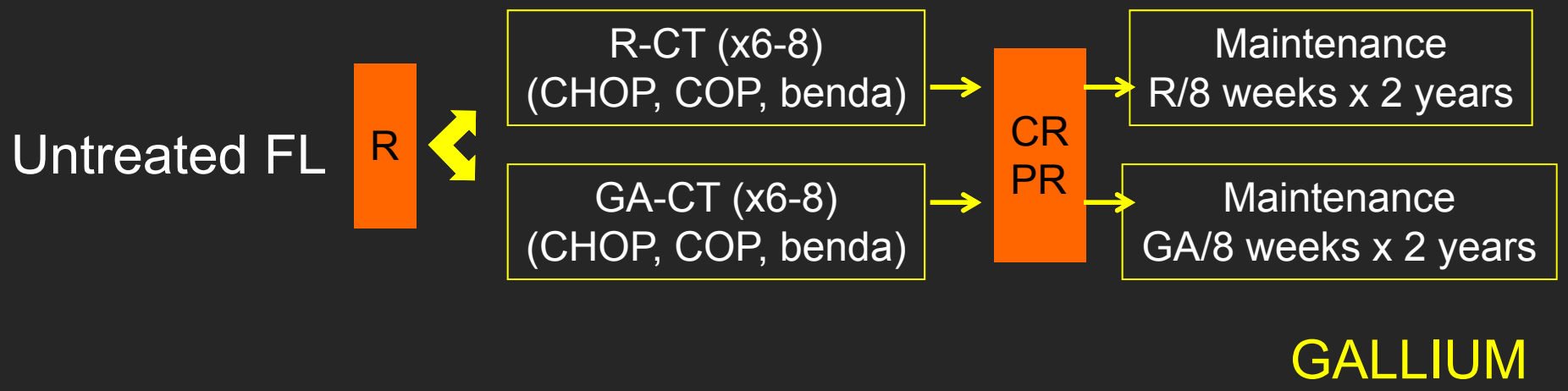


Siguientes pasos:

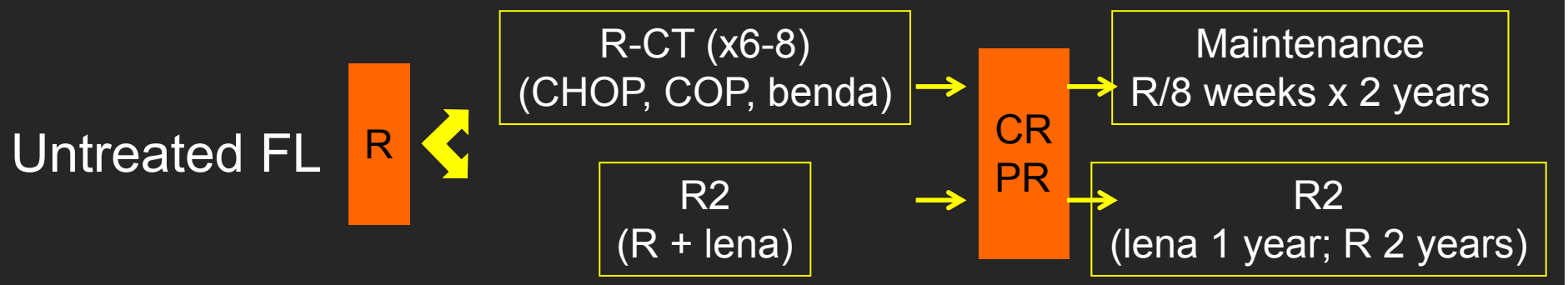
Nuevos regímenes que serán combinaciones de algunos de los fármacos anteriores:

- En tipos específicos de linfomas (esencial el conocimiento biológico)
- Dianas terapéuticas específicas
- Mecanismos de acción sinérgicos
- Sin aumento significativo de toxicidad
- +/- Inmuno-quimioterapia

Phase 3 trials in follicular lymphoma



GALLIUM



RELEVANCE