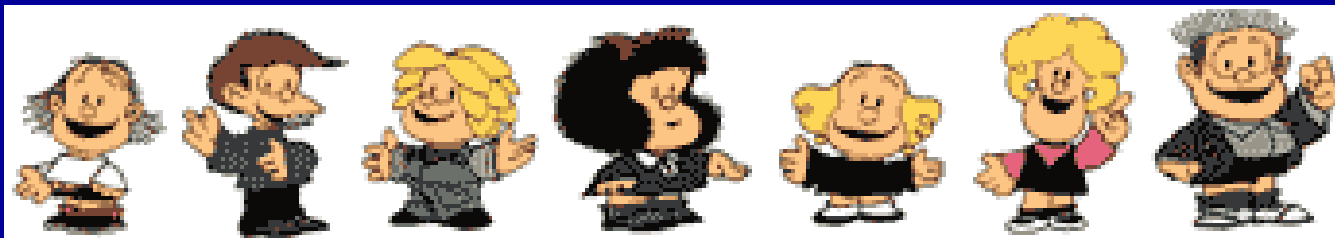


Valdivia 2009

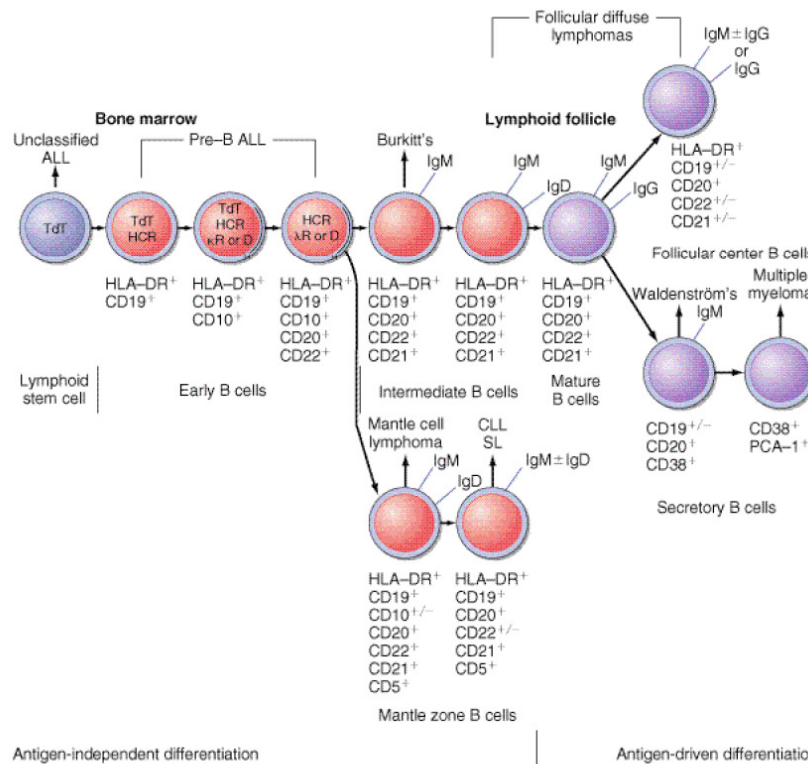


Leucemia Linfática Crónica

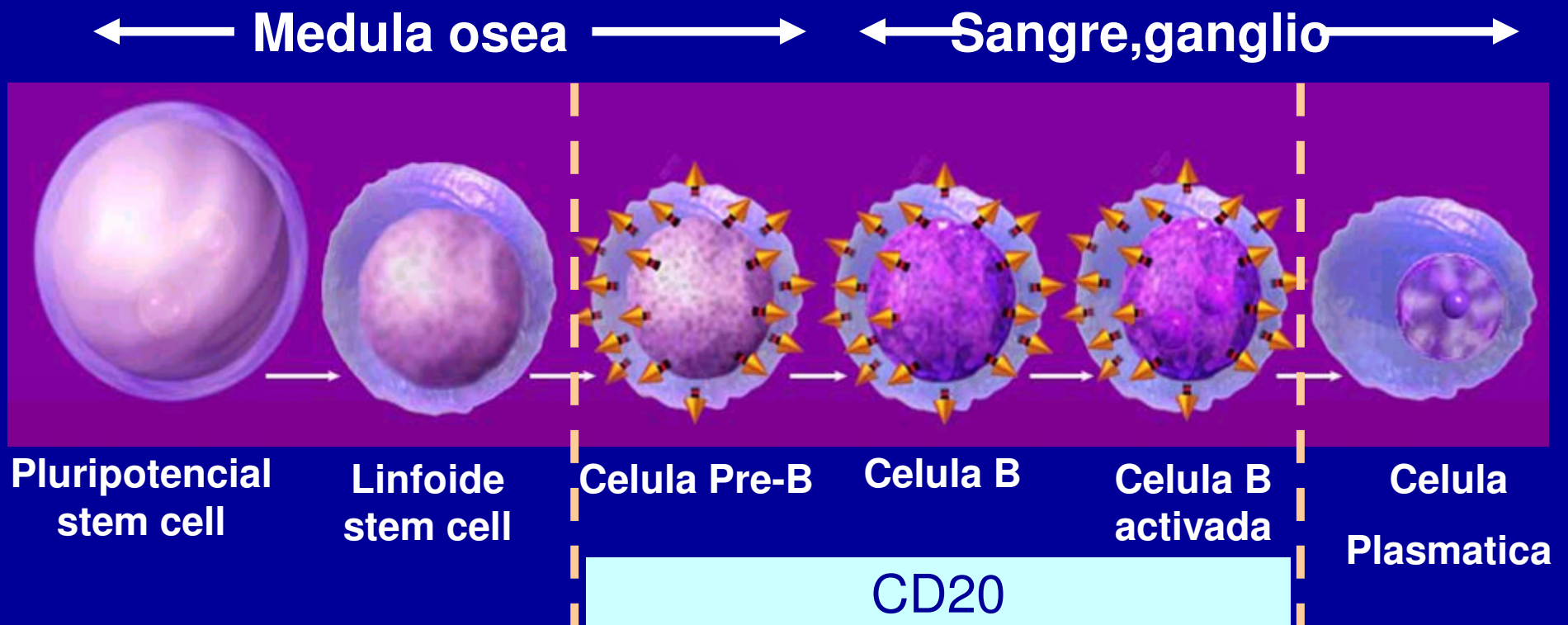
- LLC es una enfermedad Clonal
- Origen en células B post Germinales, con mejor pronóstico que células B pre germinales
- Linfoma de Linfocitos pequeños (no leucémico) es la contraparte de LLC
- Marcadores cromosómicos específicos tienen valor pronóstico

Diferenciación linfocitos B

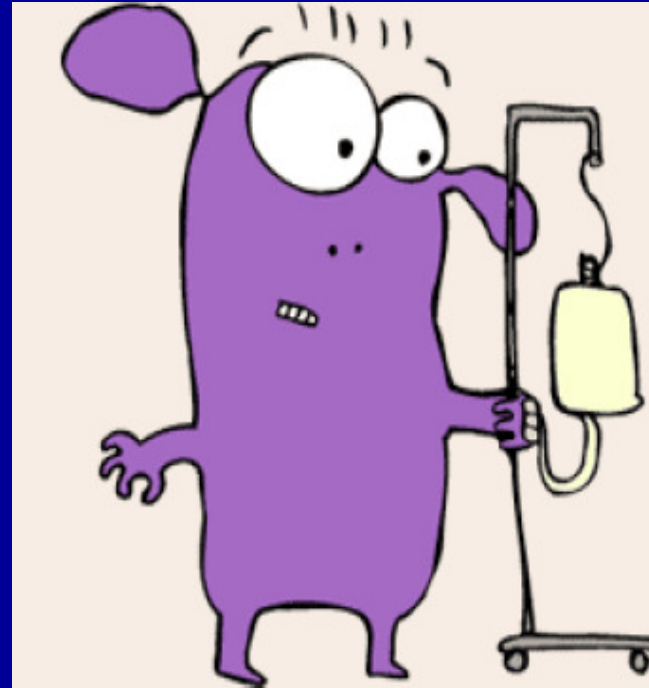
Figure 97-1



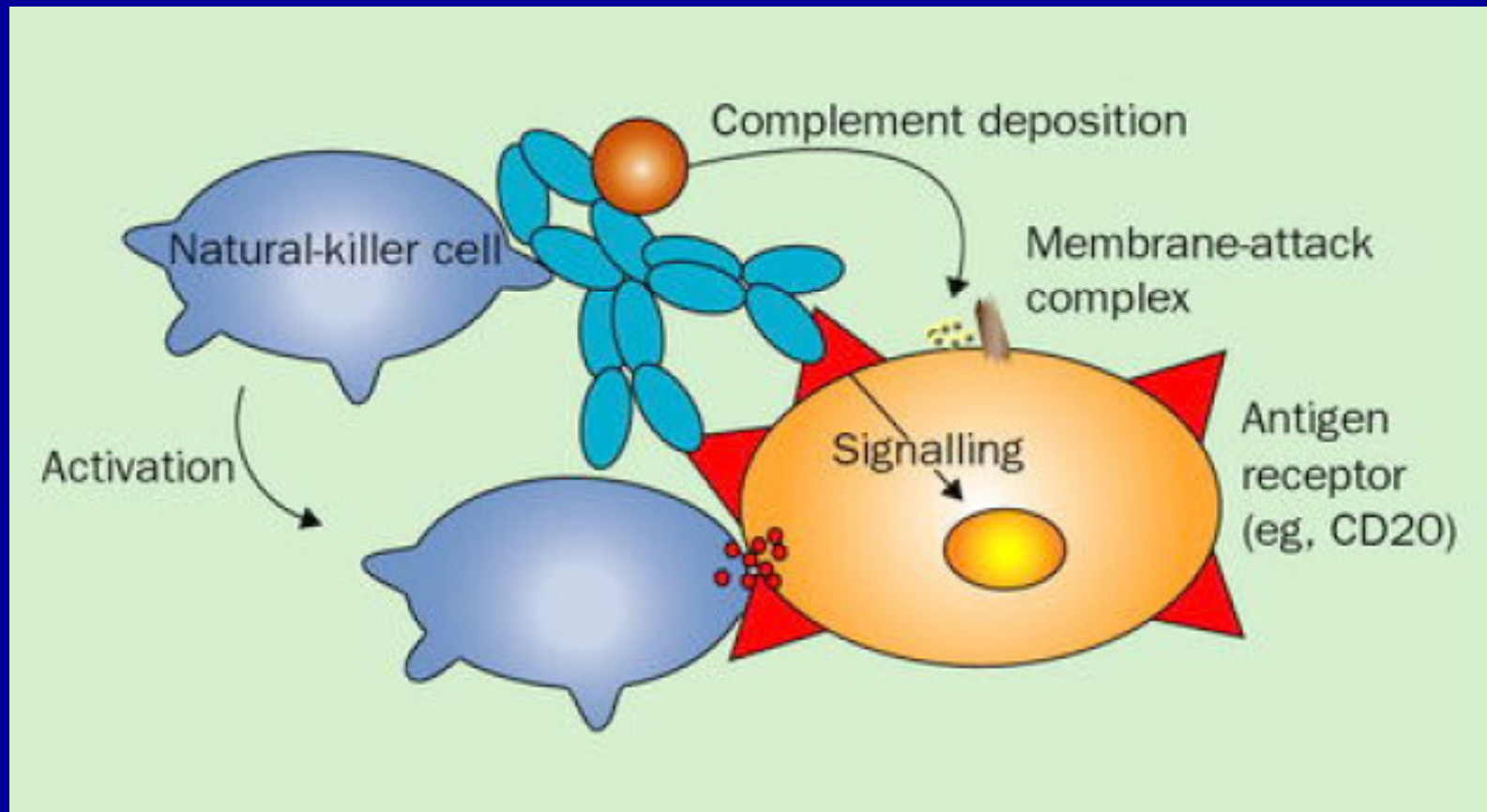
CD20 Expresión en desarrollo de células B



Opciones Terapéuticas

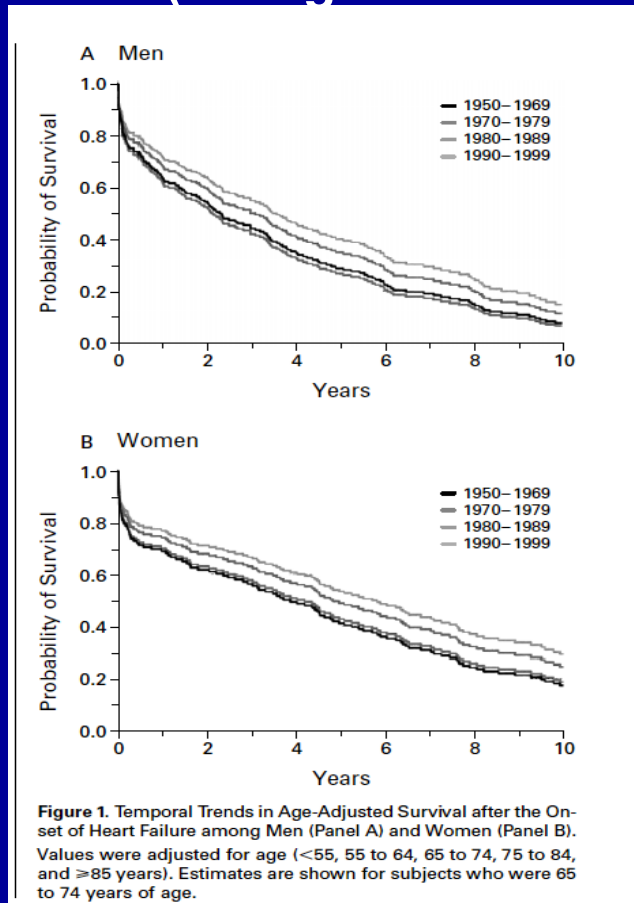


90' Nueva Estrategia: InmunoQuimioterapia



Sobrevida Desde Diagnostico

Insuficiencia Cardiaca (N Eng J Med 2002;347:1397-402)



Leucemia Linfática Crónica

- Objetivos Tratamientos???
- HIV
- Hipertensión arterial
- Insuficiencia Renal Crónica
- Insuficiencia Cardíaca
- Diabetes
- Leucemia Linfática Crónica.

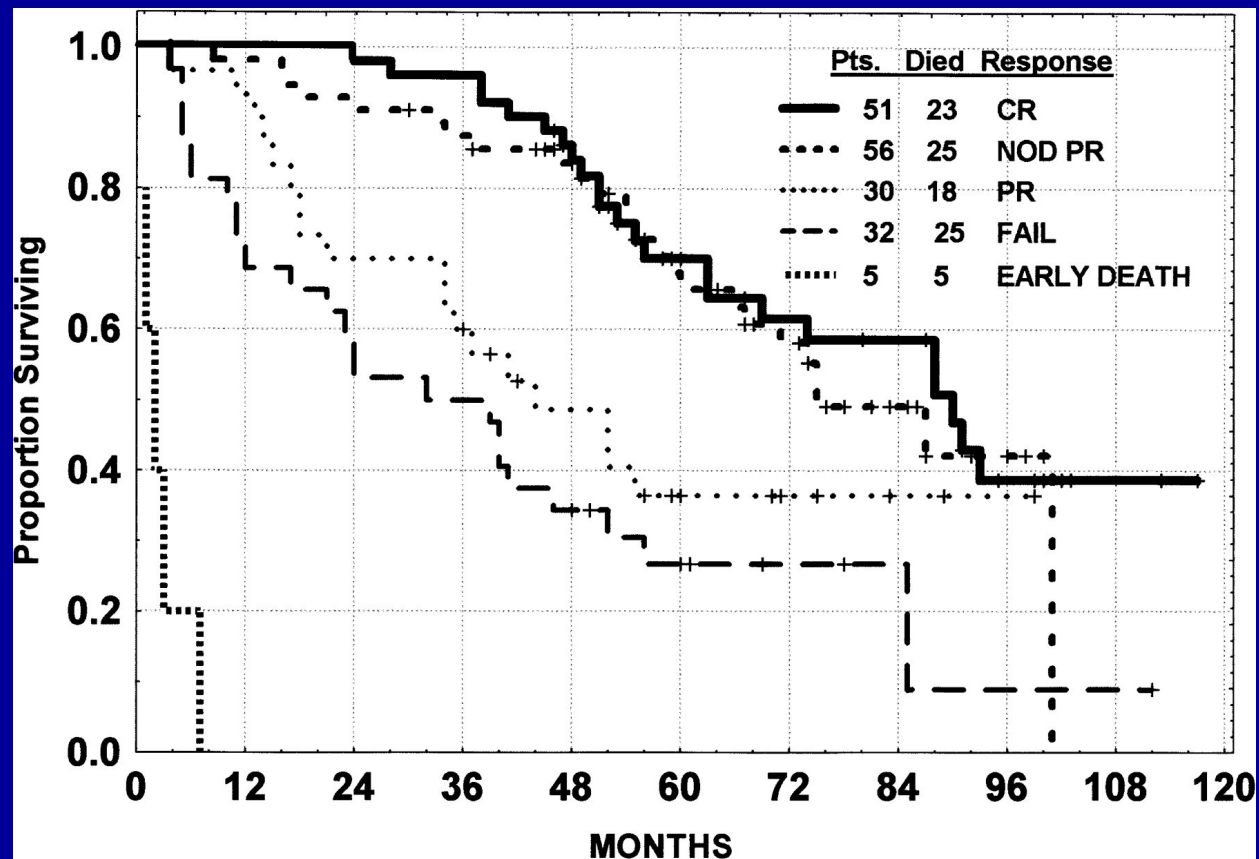
Leucemia Linfática Crónica

- Indicaciones Tratamiento ??
 - Etapas Avanzadas (Rai St III-IV, Binet St By C)
 - Experimental tratamiento en etapas precoces (edad).

Leucemia Linfática Crónica

- Tratamientos
 - Alquilantes
 - Cloranbucil
 - Ciclofosfamida
 - Bendamustine
 - Analogos Purinas
 - FLUDARABINA
 - Claribine
 - Pentostatina
 - Lenalidomide
 - Ac Monoclonales

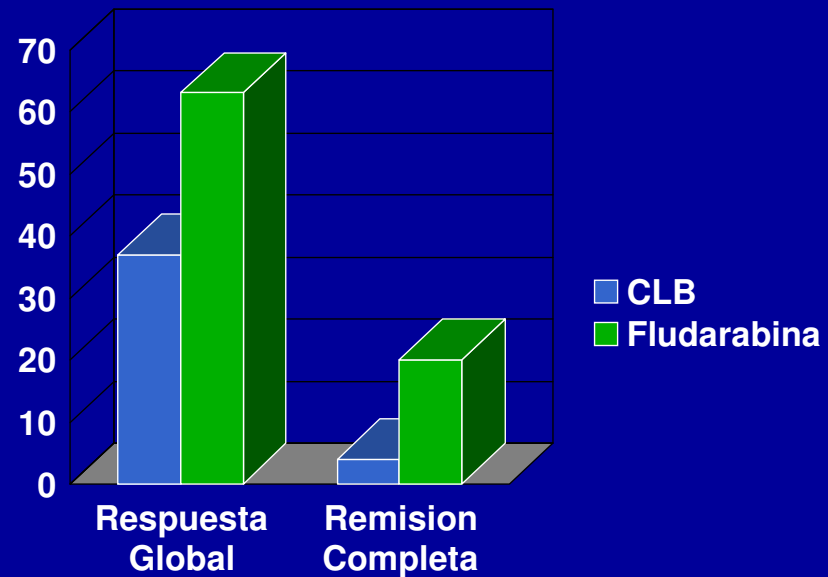
Algo Nuevo???: Fludarabina en LLC



Keating, M.J. et al. Blood 1998;92:1165-1171

Leucemia Linfática Crónica

- Estudio Randomizado CLB vs Flud
- Sobrevida Global Similar
- Respuesta recaída
CLB tratada con Flud = 46%
Flud tratada con CLB= 7%



NEJM 2000;343, 1750-1757

Fludarabina (F) + Ciclofosfamida (C) es superior a F en CLL sin previo tratamiento

Regimen N	Chl 387	F 194	FC 196	F 137	FC 141	F 182	FC 180
Med age	65	64	65	61	61	59	58
Rai Stage III- IV, Binet C (%)	31	29	30	42	44	41	39
Grade 3 / 4 ↓ ANC (%)	28	41	56	63	69	26	56
% CR	7	15	38	5	23	7	24
% OR	72	80	94	59	74	83	95
Med PFS (mo)	20	23	43	19.2	31.6	20	48

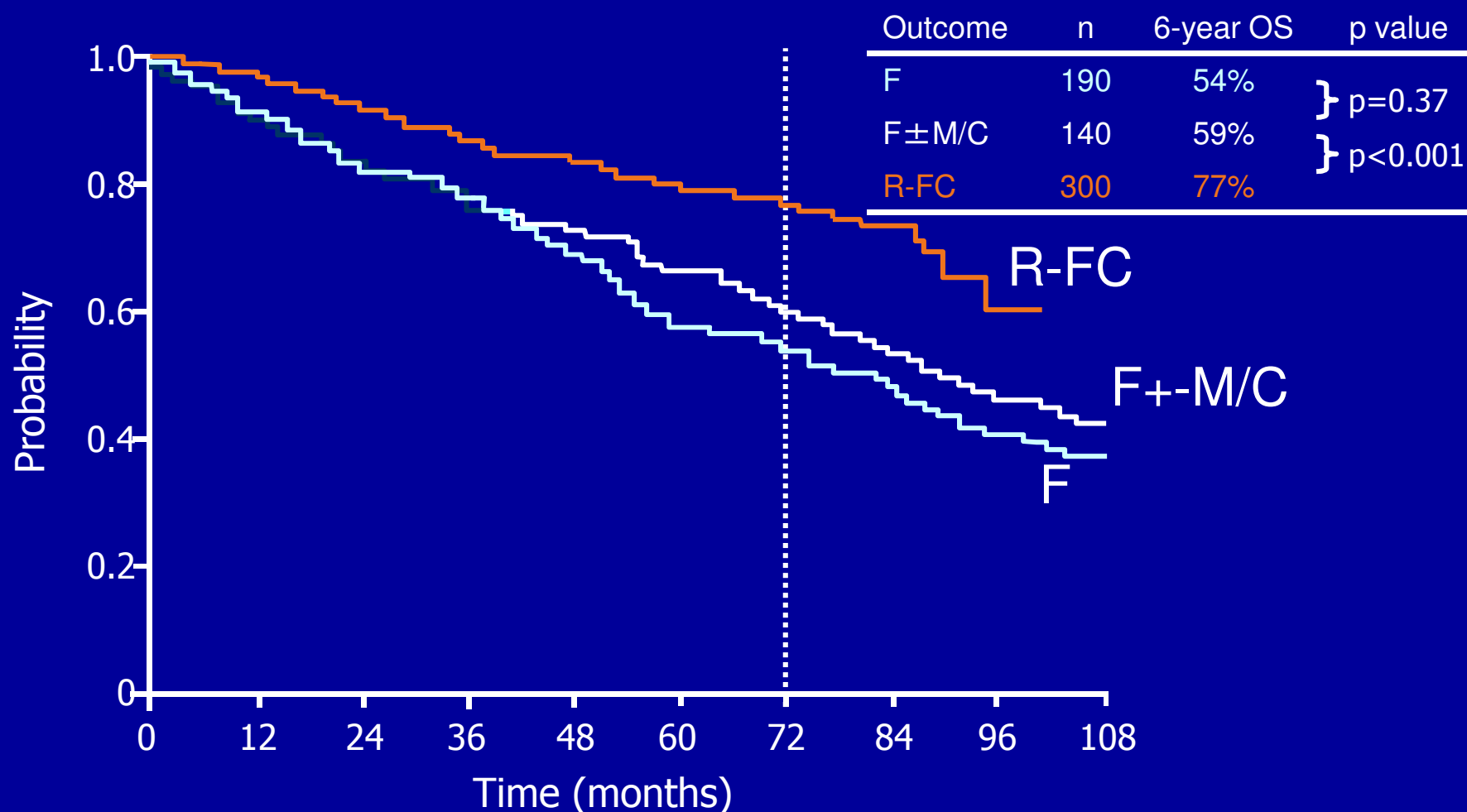
Catovsky D, et al. *Lancet*. 2007;370:230-239; Flinn FW, et al. *J Clin Oncol*. 2007;25:793-798;
Eichhorst BF, et al. *Blood*. 2006;107:885-891.

Anti CD20: Activo en LLC??

- Dosis Rituximab vs Respuesta.(JCO 19:2001,2165)
 - 375mg/m²/semana x4 = 5-14%
 - 375 mg/m²/ x3 veces/ semana x 4 = 45%
 - 500-825 mg/m² = 22%
 - 1000-1500 mg/m² = 43%
 - 2250mg/m²= 75%
- Rituximab-FC 375 mg/m² vs 500 mg/m² no se han comparado

FC + Rituximab

(MD Anderson Comparacion datos historicos, no randomizado)

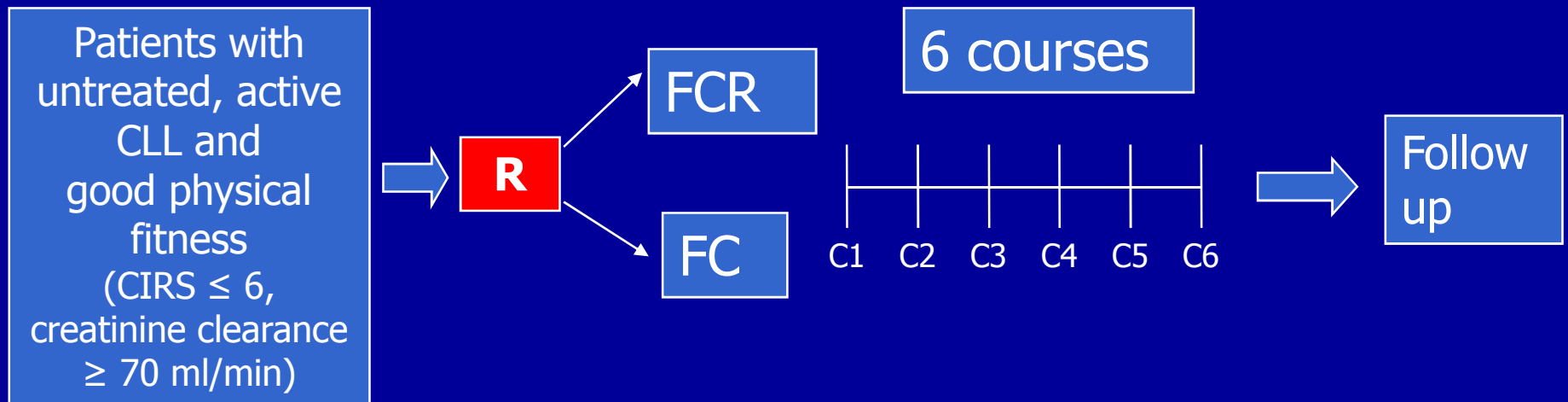


Chemoimmunotherapy with Fludarabine (F),
Cyclophosphamide (C), and Rituximab (R) (FCR)
versus Fludarabine and Cyclophosphamide (FC)
improves response rates and progression-free
survival (PFS) in previously untreated patients
(pts) with advanced chronic lymphocytic leukemia
(CLL8, ASH 2008)

Hallek M*, Fingerle-Rowson G, Fink A-M, Busch R, Mayer J, Hensel M, Hopfinger G, Hess G, von Grünhagen U, Bergmann M, Catalano J, Zinzani PL, Caligaris Cappio F, Seymour J, Berrebi A, Jäger U, Cazin B, Trneny M, Westermann A, Wendtner C-M, Eichhorst BF, Staib P, Boettcher S, Ritgen M, Stilgenbauer S, Mendila M, Kneba M, Döhner H, Fischer K on behalf of an international group of investigators and of the German CLL Study Group (GCLLSG).

*University of Cologne, Germany

CLL8 Study Design



Primary endpoint

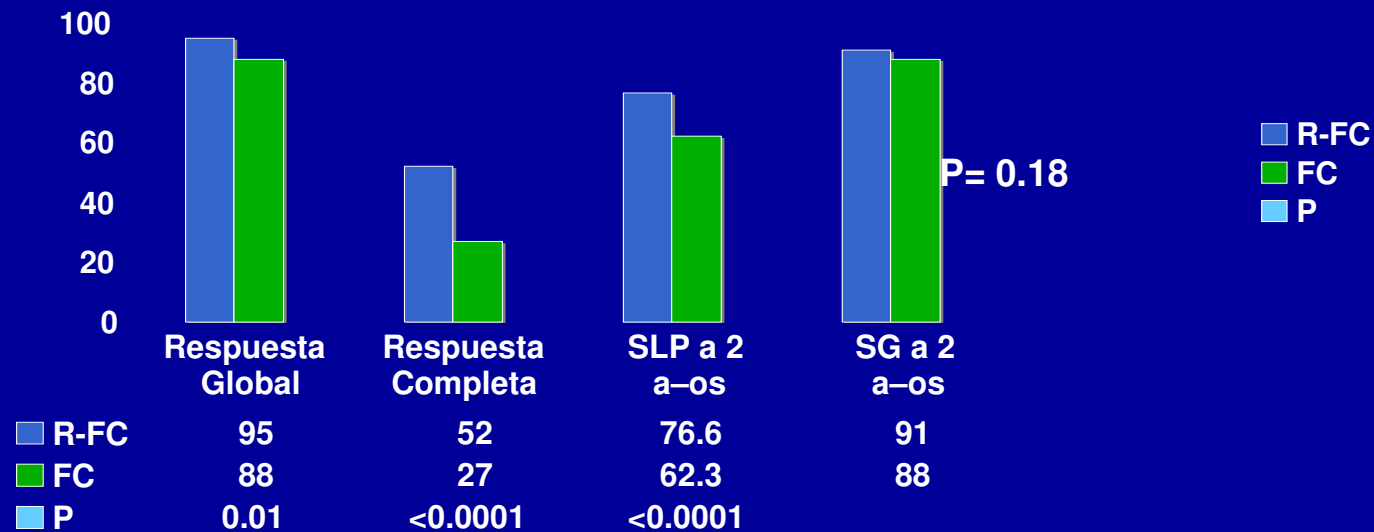
-Progression-free survival (PFS)

Secondary endpoints

- Overall survival
- Rates of molecular, complete and partial remission
- Rates of treatment-related adverse effects

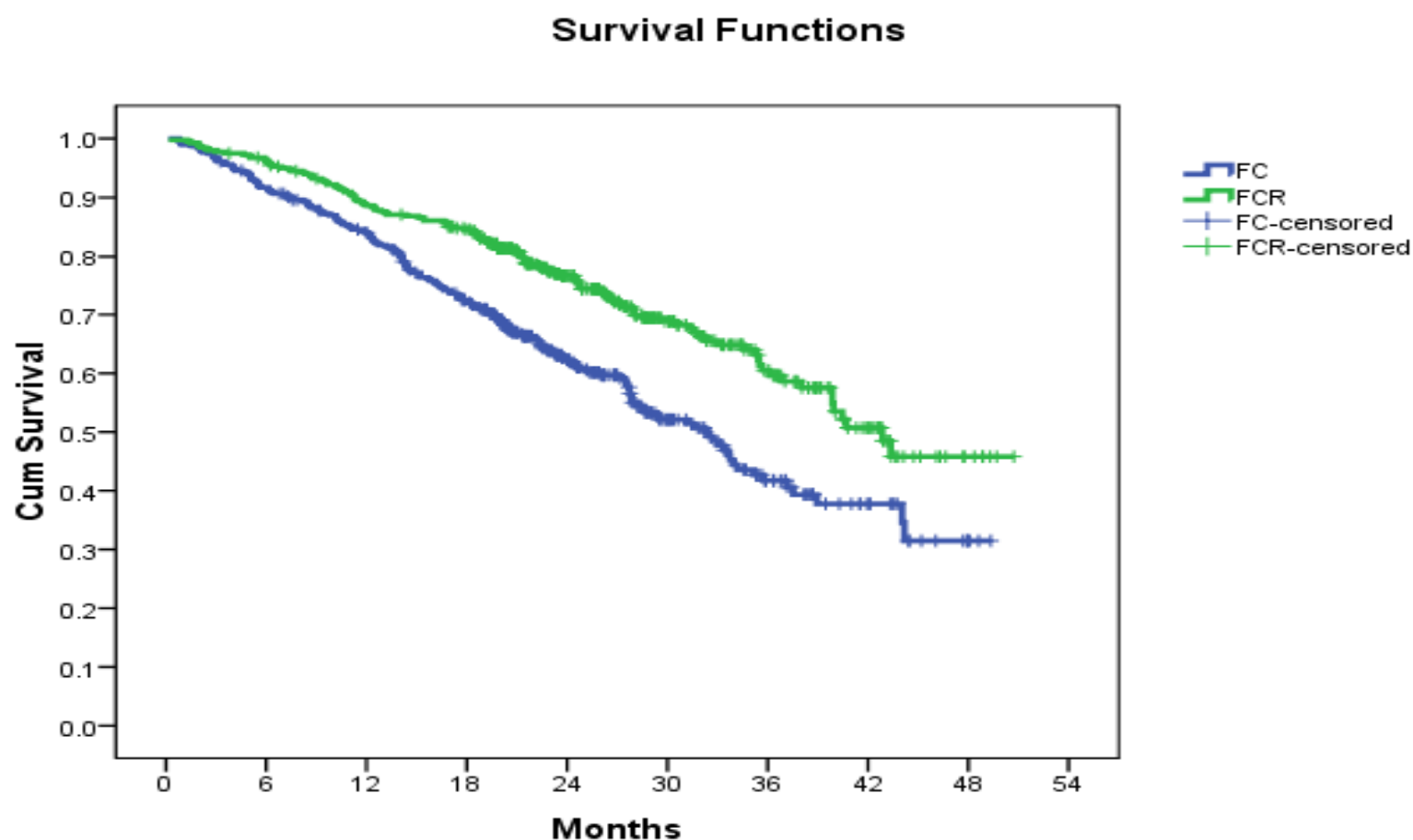
LLC: FC vs R-FC

- Terapia Primera Linea
- N= 761
- Respuesta depende de estado de LLC



Sobrevida Libre de Progresion: FCR versus FC

Median observation time 25.5 months

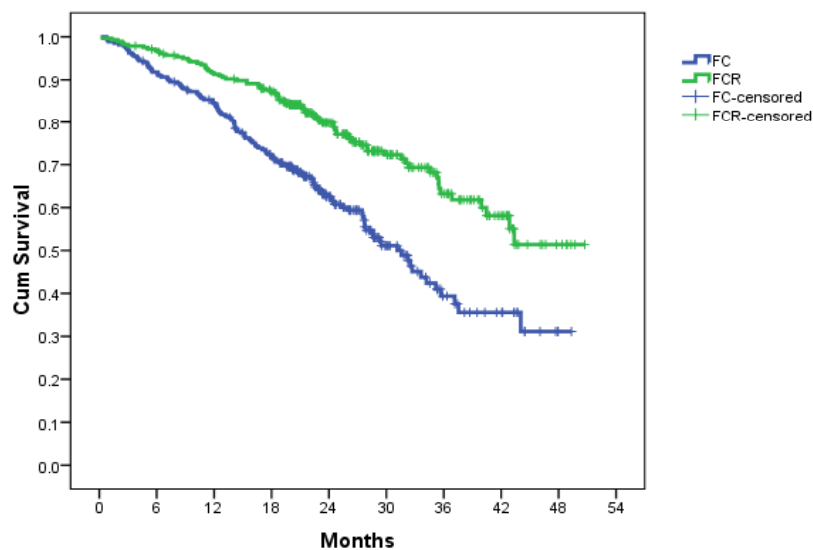


Numero de Respuestas Completas por Estadio.

Binet stage	CR Rate (%)
A	57,1
B	43,2
C	29,3

Sobrevida libre de progresión por estadio

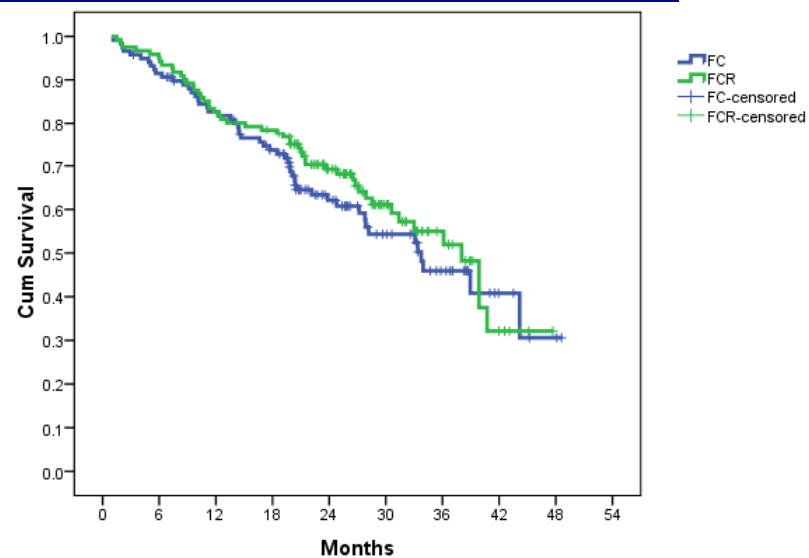
Binet stages A+B



$p < 0.000001$

ORR 93,3%

Binet stage C

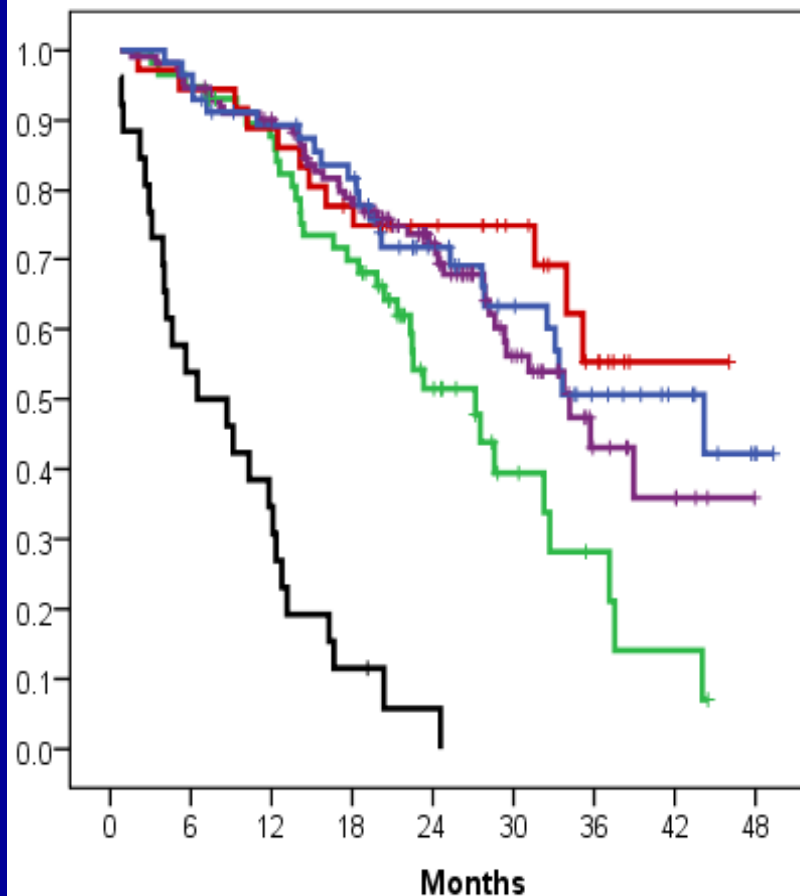


$p = 0.44$

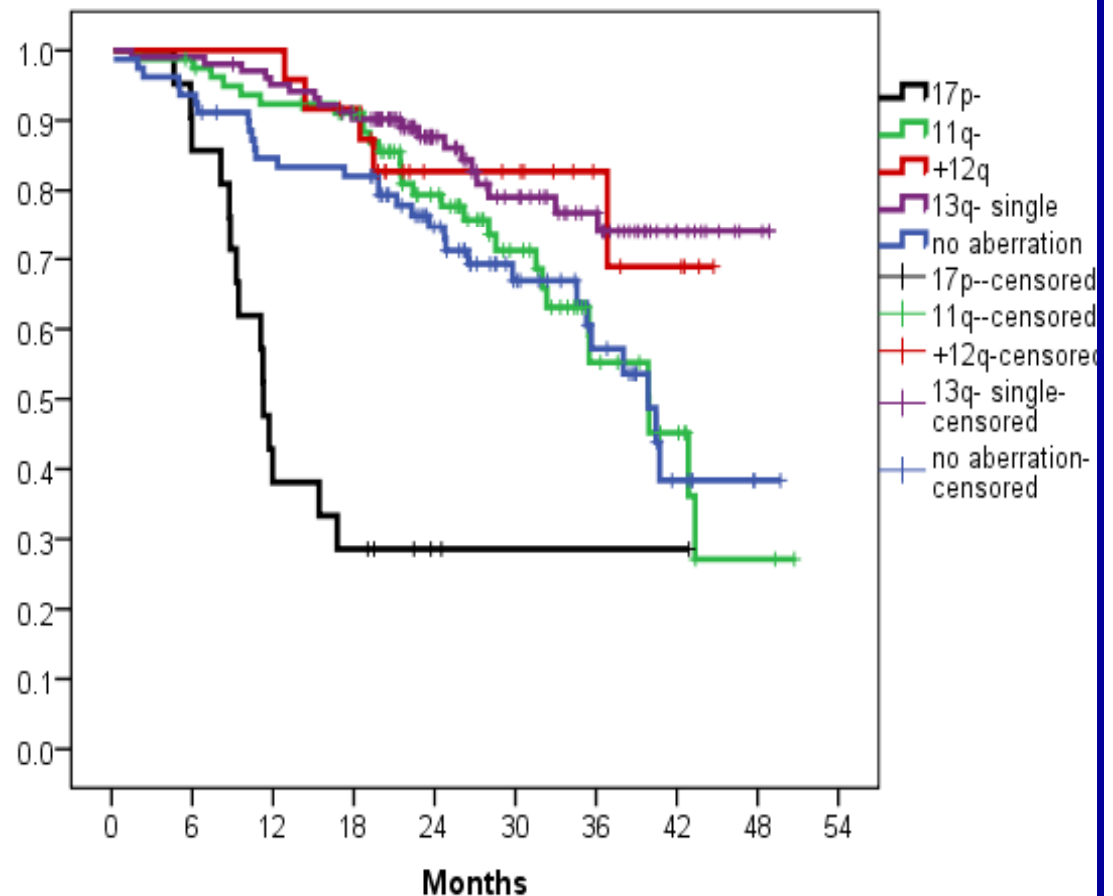
ORR 88,0%

CLL8 Genetic Analyses: PFS

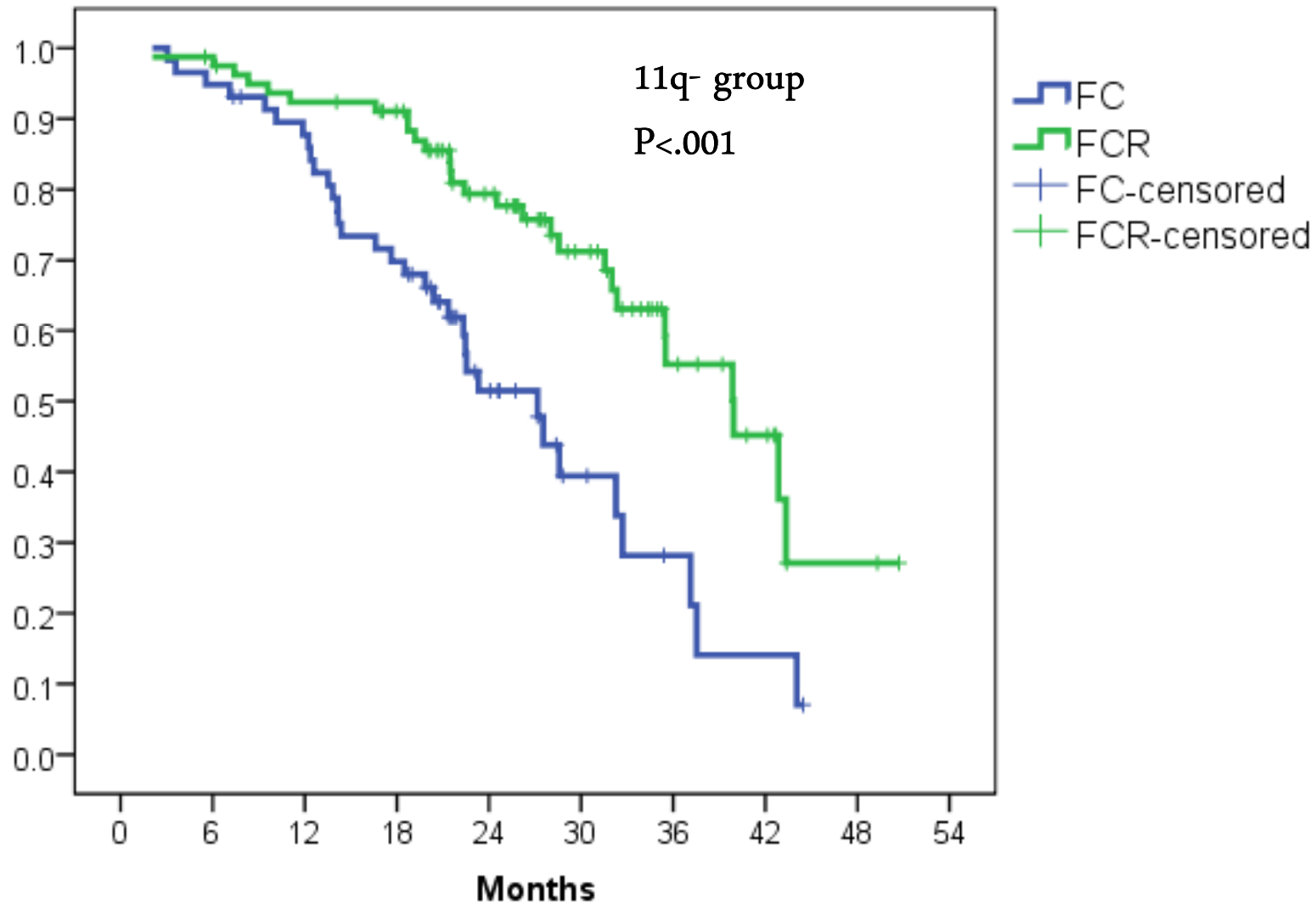
FC



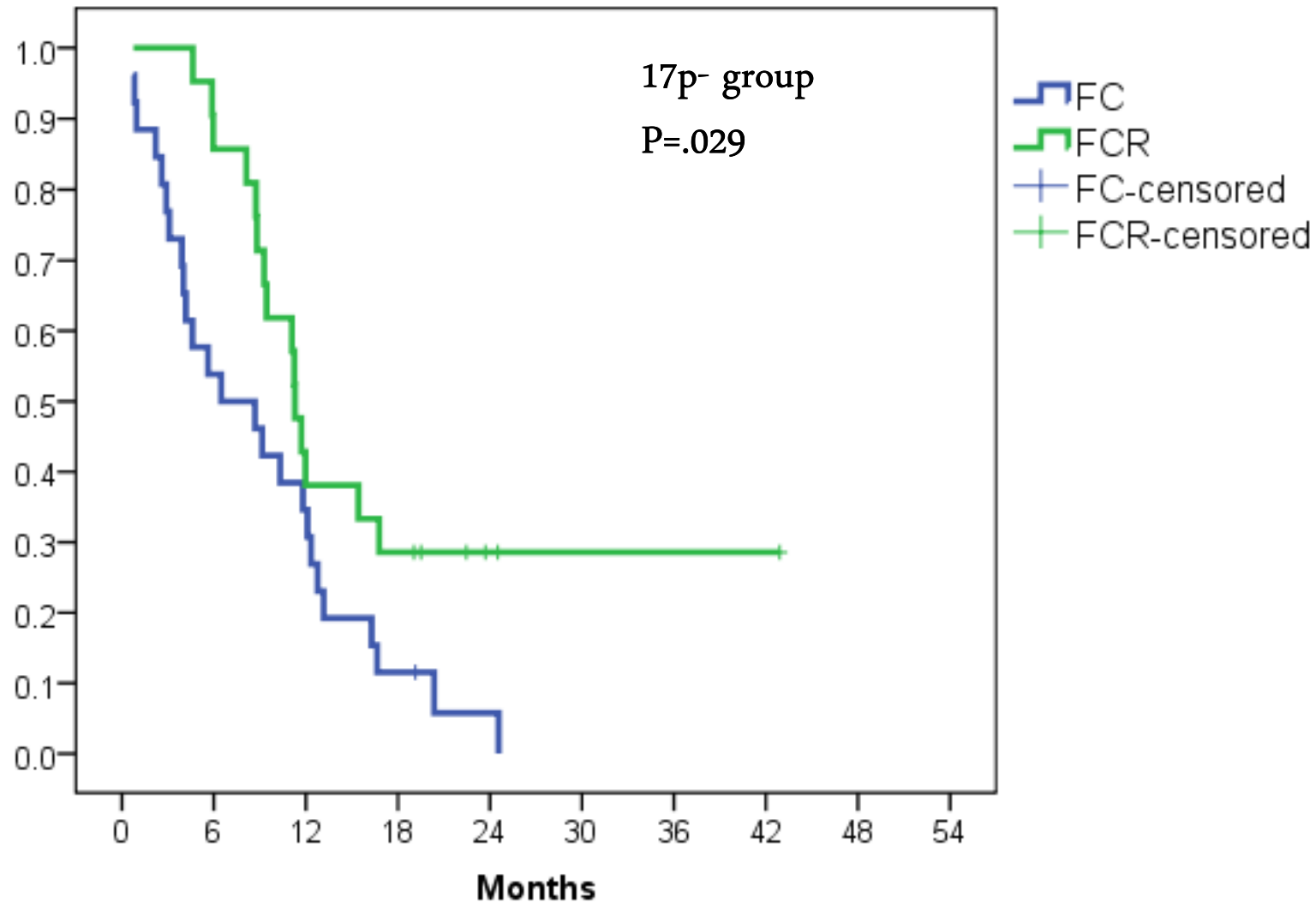
FCR



CLL8 Treatment Effect: PFS



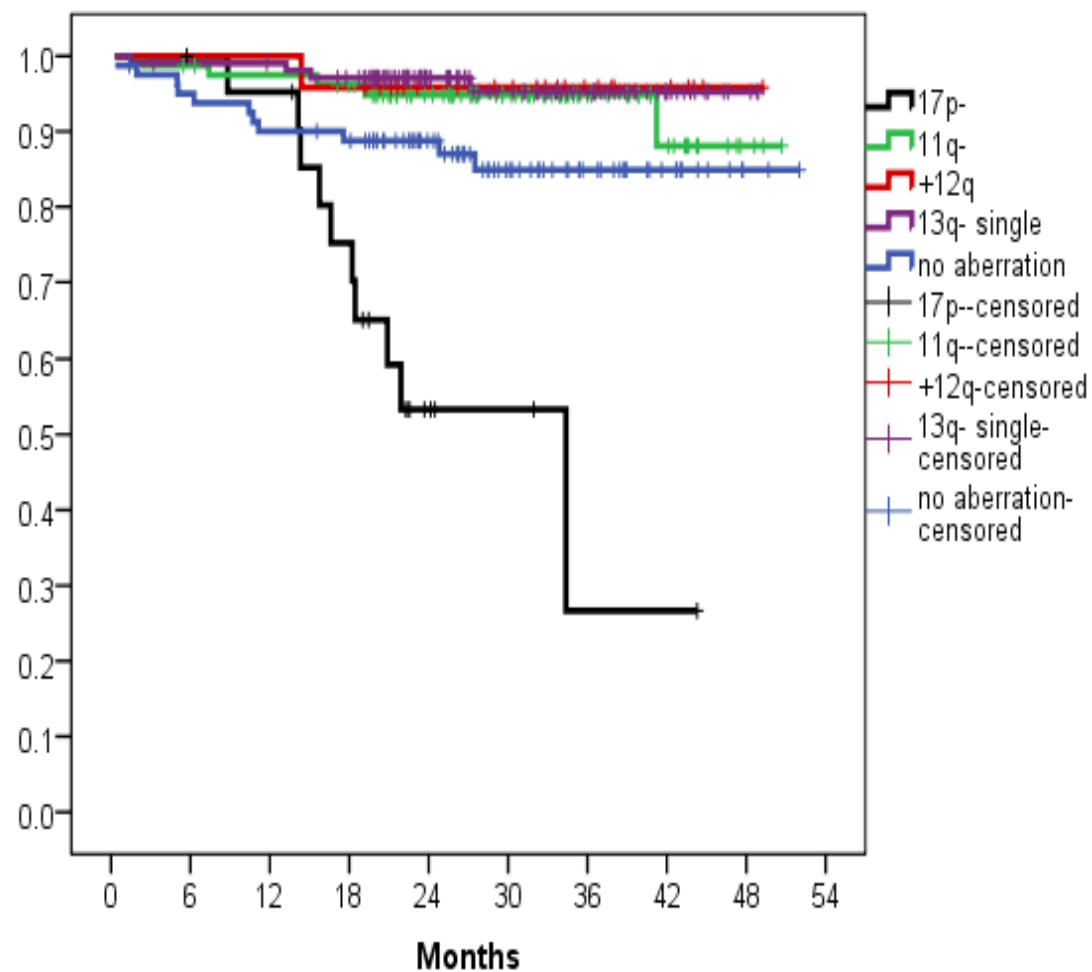
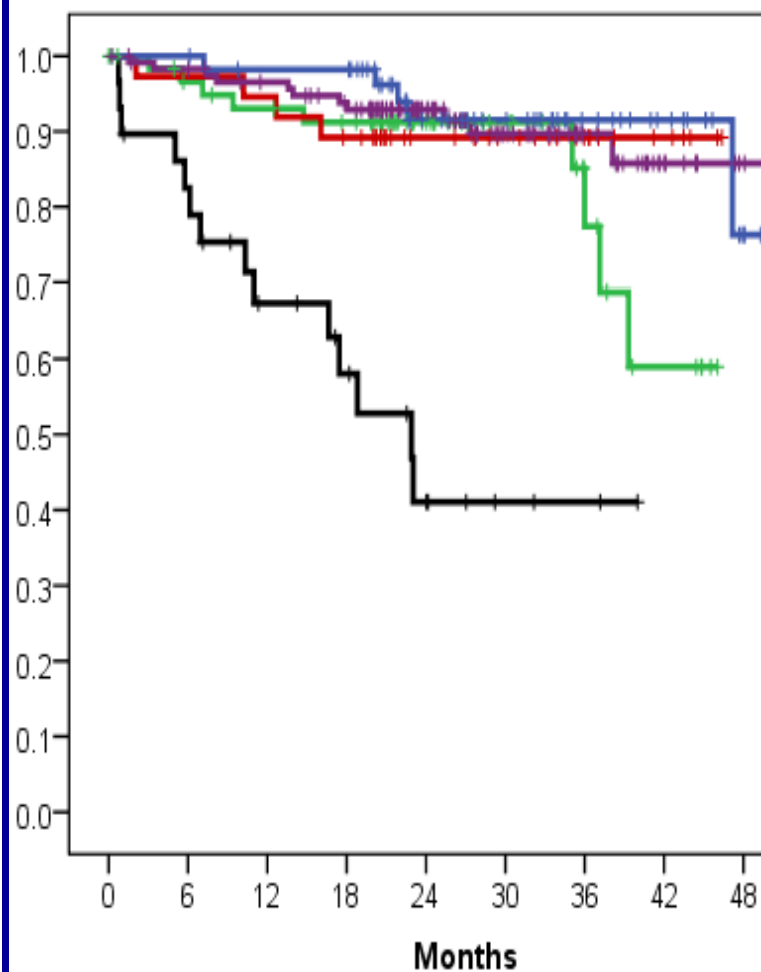
CLL8 Treatment Effect: PFS



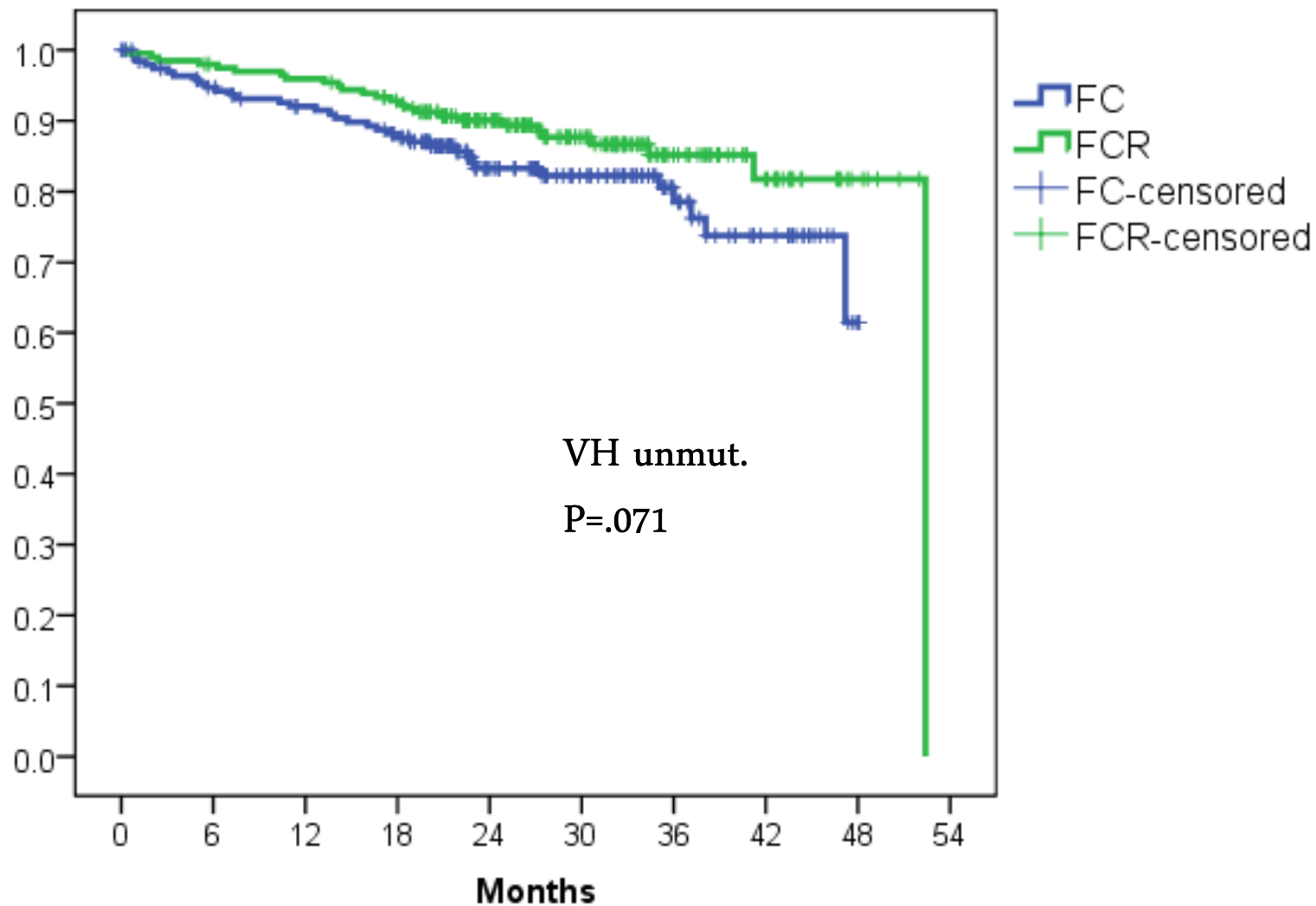
CLL8 Genetic Analyses: OS

FC

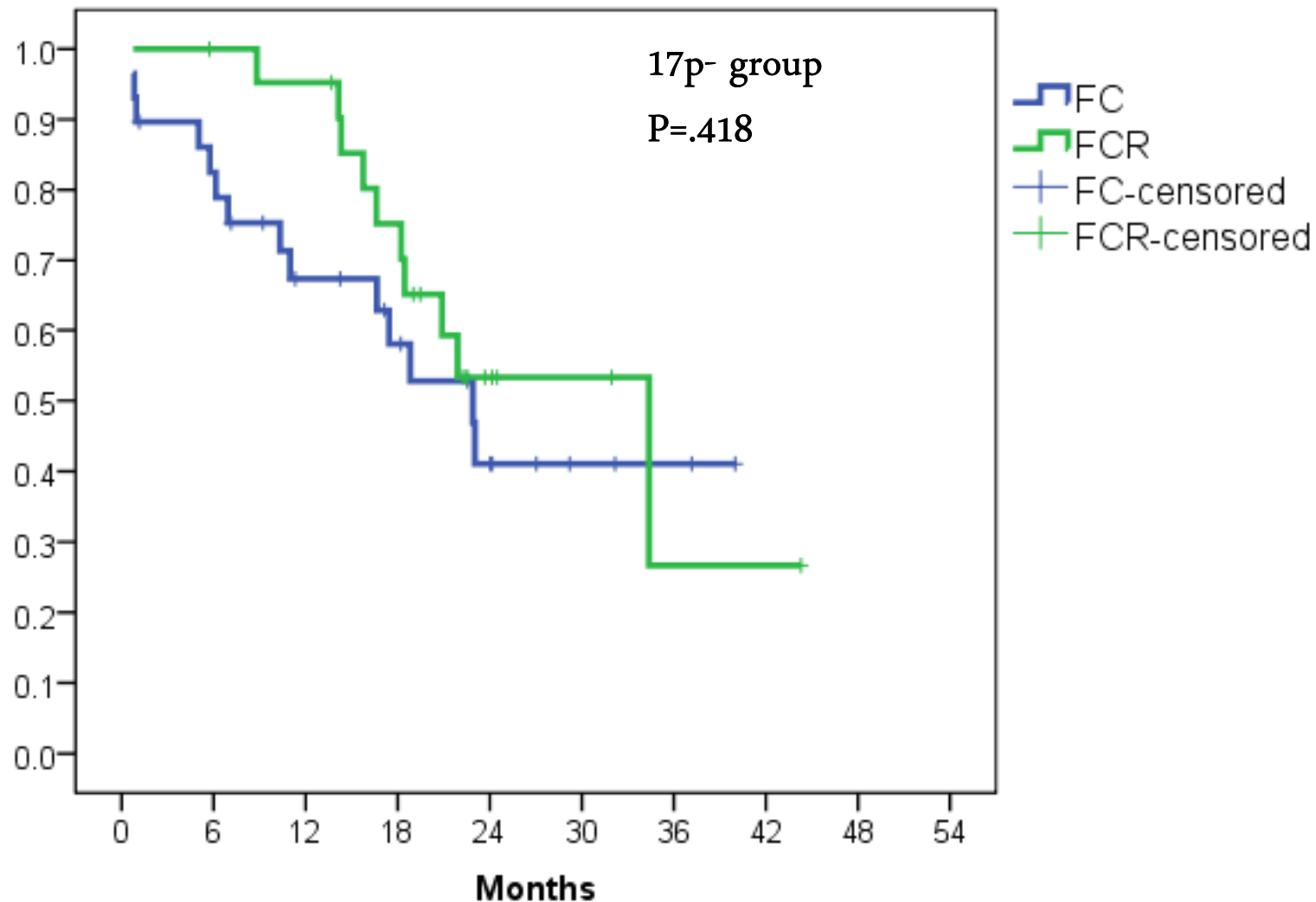
FCR



CLL8 Treatment Effect: OS



CLL8 Treatment Effect: OS

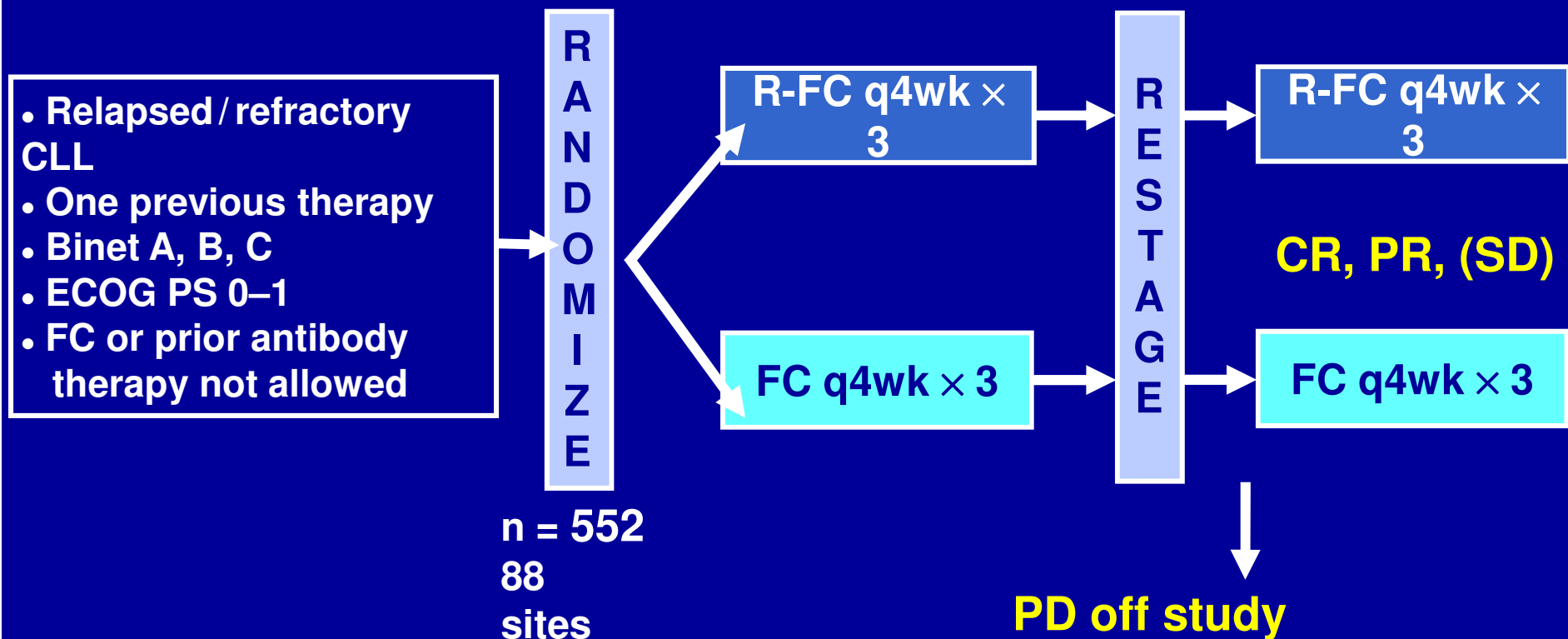


Rituximab plus Fludarabine and Cyclophosphamide (R-FC) vs. FC alone in Relapsed/Refractory CLL: Final Results of the REACH BO17072 trial

Tadeusz Robak, Sergey I Moiseev, Anna Dmoszynska,
Philippe Solal-Céligny, Krzysztof Warzocha, Javier Loscertales,
John Catalano, Boris V Afanasiev, Loree Larratt, Christian Geisler, Marco
Montillo, Peter Ganly, Caroline Dartigeas, András Rosta,
Ann Janssen, Myriam Mendila, Jörg Maurer, Michael K. Wenger

This study was sponsored by F. Hoffmann-La Roche Ltd.

REACH: Study Design – R-FC vs FC

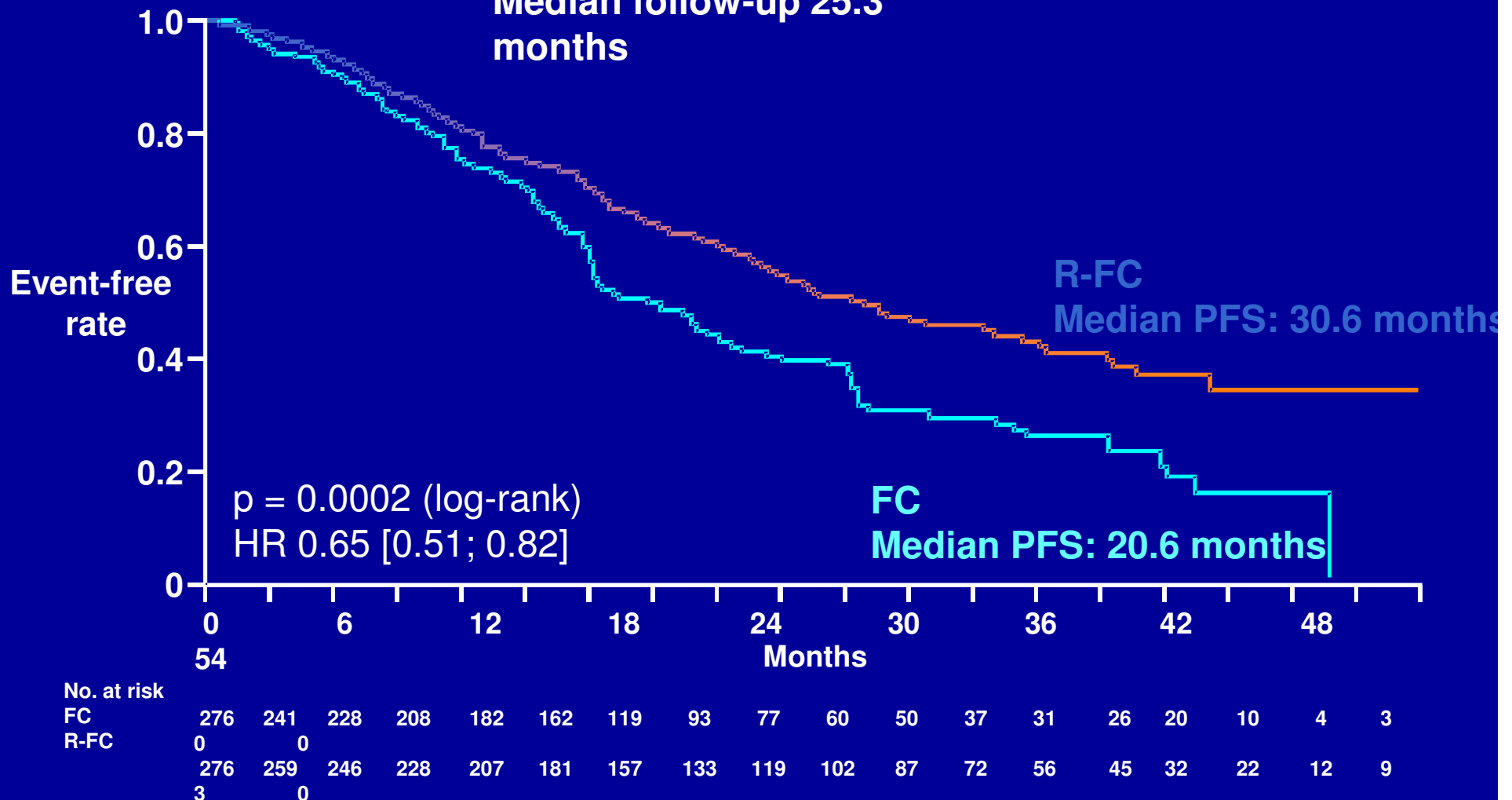


<u>Rituximab</u>		<u>Fludarabine</u>	<u>Cyclophosphamide</u>
Cycle 1	375 mg/m ² day 0	25 mg/m ² iv, day 1–3	250mg/m ² iv, day 1–3
Cycles 2–6	500 mg/m ² day 1		

REACH: Response Rates

	FC (%) n = 276	R-FC (%) n = 276	<i>p</i>
CR	13.0	24.3	0.0007
PR/nPR	44.9	45.7	0.8642
ORR	58.0	69.9	0.0034
SD	22.1	17.0	n.d.
PD	5.4	2.5	n.d.
*mainly patients with response that was not confirmed through a second assessment n.d.: not done			
not evaluable*	14.5	10.5	n.d.

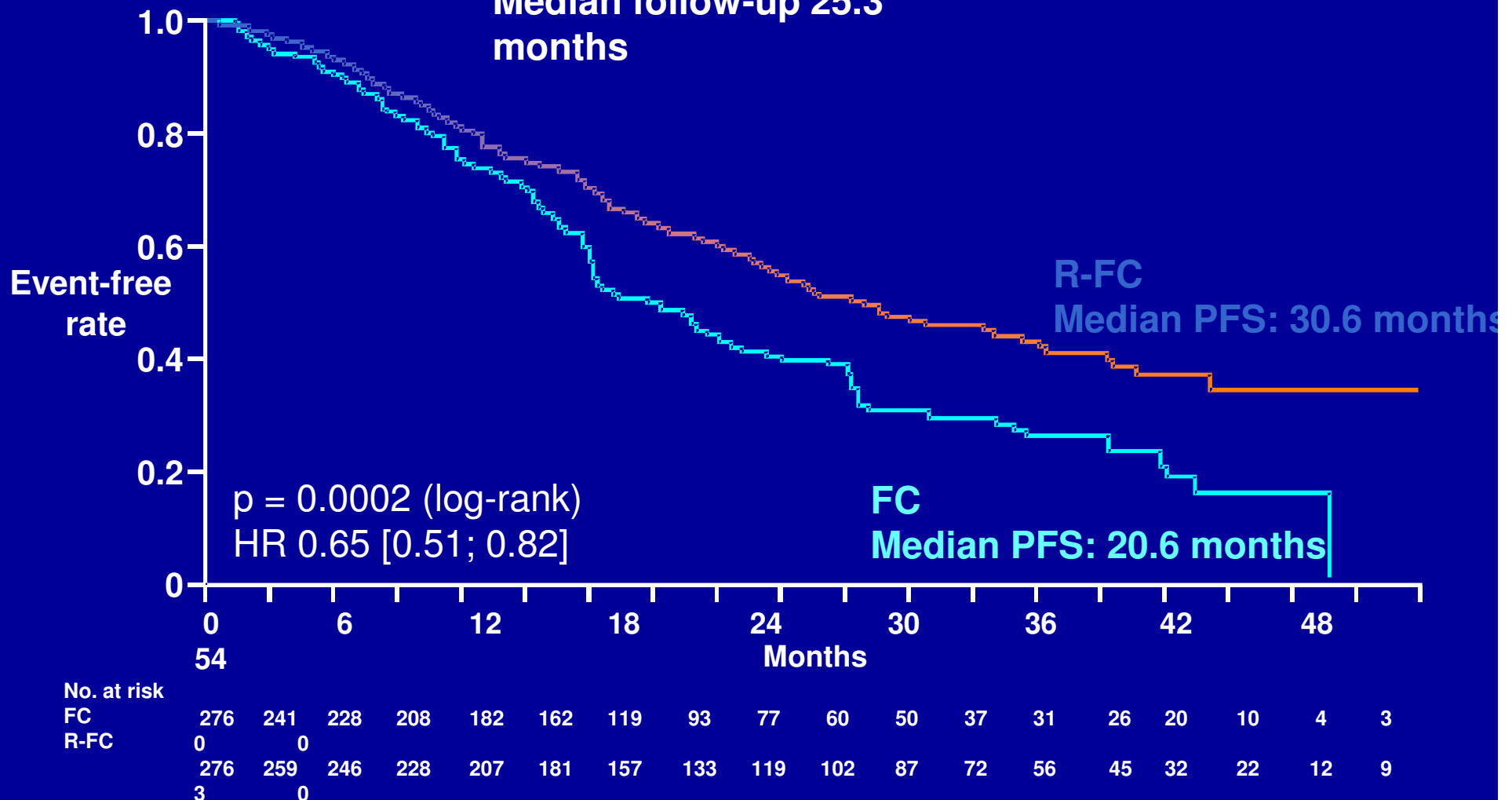
Median follow-up 25.3 months



REACH Binet Subgroups PFS – ITT

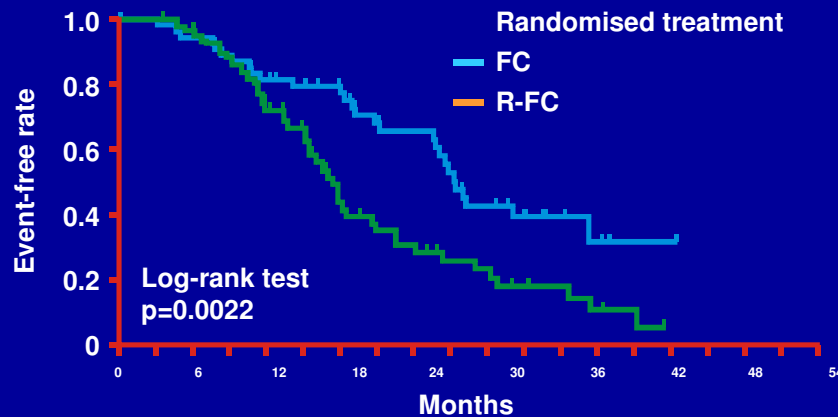
Binet stage	HR [95% CI] for PFS
A (n = 55)	0.75 [0.33; 1.72]
B (n = 326)	0.65 [0.47; 0.88]
C (n = 171)	0.61 [0.41; 0.90]

Median follow-up 25.3 months

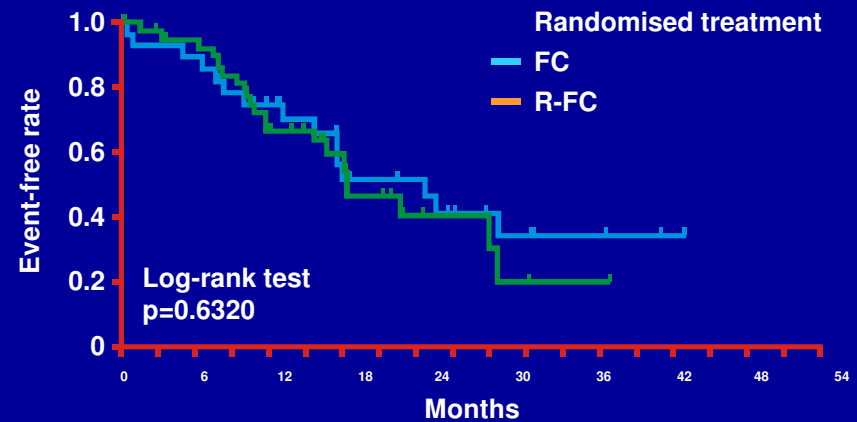


REACH: PFS by Cytogenetics – ITT

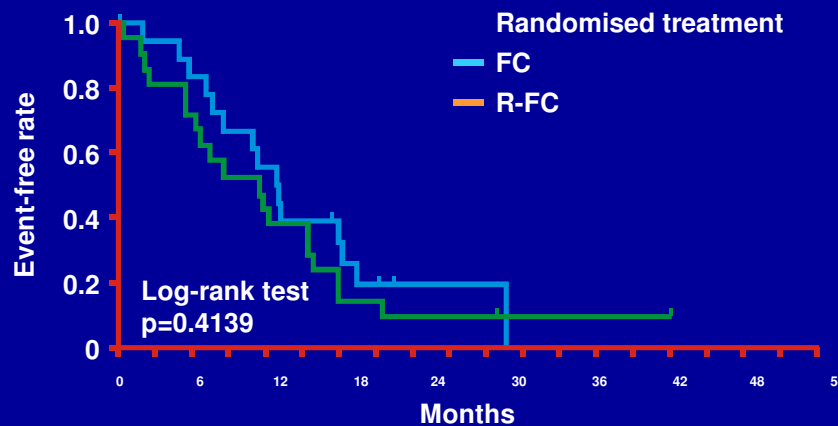
del11q (n=115)



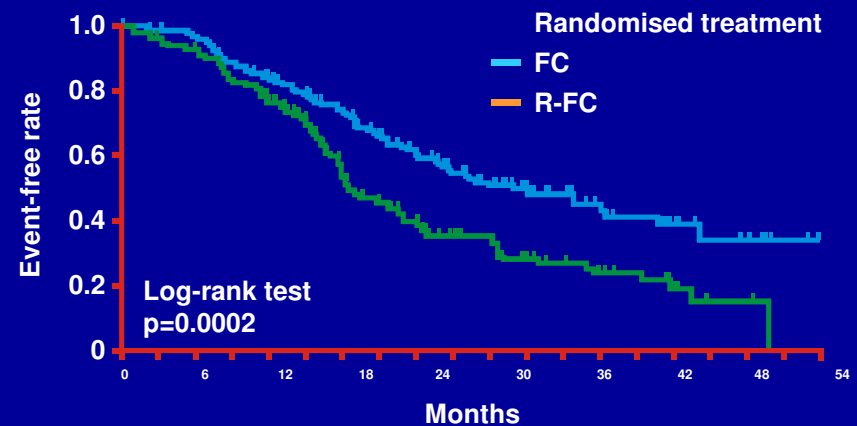
Trisomy 12 (n=69)



del17p (n=42)



del13q (n=309)



REACH: Resumen

- **Rituximab plus FC is significantly superior to FC alone in relapsed / refractory CLL patients**
- **Results were robust and consistent in subgroups and across secondary endpoints, including adverse prognostic groups**
 - **Binet C**
 - **11q–**
 - **unmutated IgVH, ZAP-70 positive**
- **R-FC showed a favorable risk-benefit profile with no new or unexpected safety findings**

LLC: A quien tratar???

- Falla Medular, compromiso EG, masas, gg??
- Marcadores citogenéticos y moleculares?
- Edad??
- Buscar un Índice Internacional similar a Linfoma??



VALDIVIA 2011

