Leucemia Linfocítica crónica

M. OCQUETEAU T

MAYO 2017

US Mortality, 2015

Rank	Cause of Death	No. of deaths	% of all deaths
1.	Heart Diseases	700,142	29.0
2.	**Cancer**	**553,768**	**22.9**
3.	Cerebrovascular diseases	163,538	6.8
4.	Chronic lower respiratory diseases	123,013	5.1
5.	Accidents (Unintentional injuries)	101,537	4.2
6.	Diabetes mellitus	71,372	3.0
7.	Influenza and Pneumonia	62,034	2.6
8.	Alzheimer's disease	53,852	2.2
9.	Nephritis	39,480	1.6
10.	Septicemia	32,238	1.3

Source: US Mortality Public Use Data Tape 2001, National Center for Health Statistics, Center for Disease Control and Prevention, 2003.

Epidemiología del Cáncer en el Mundo

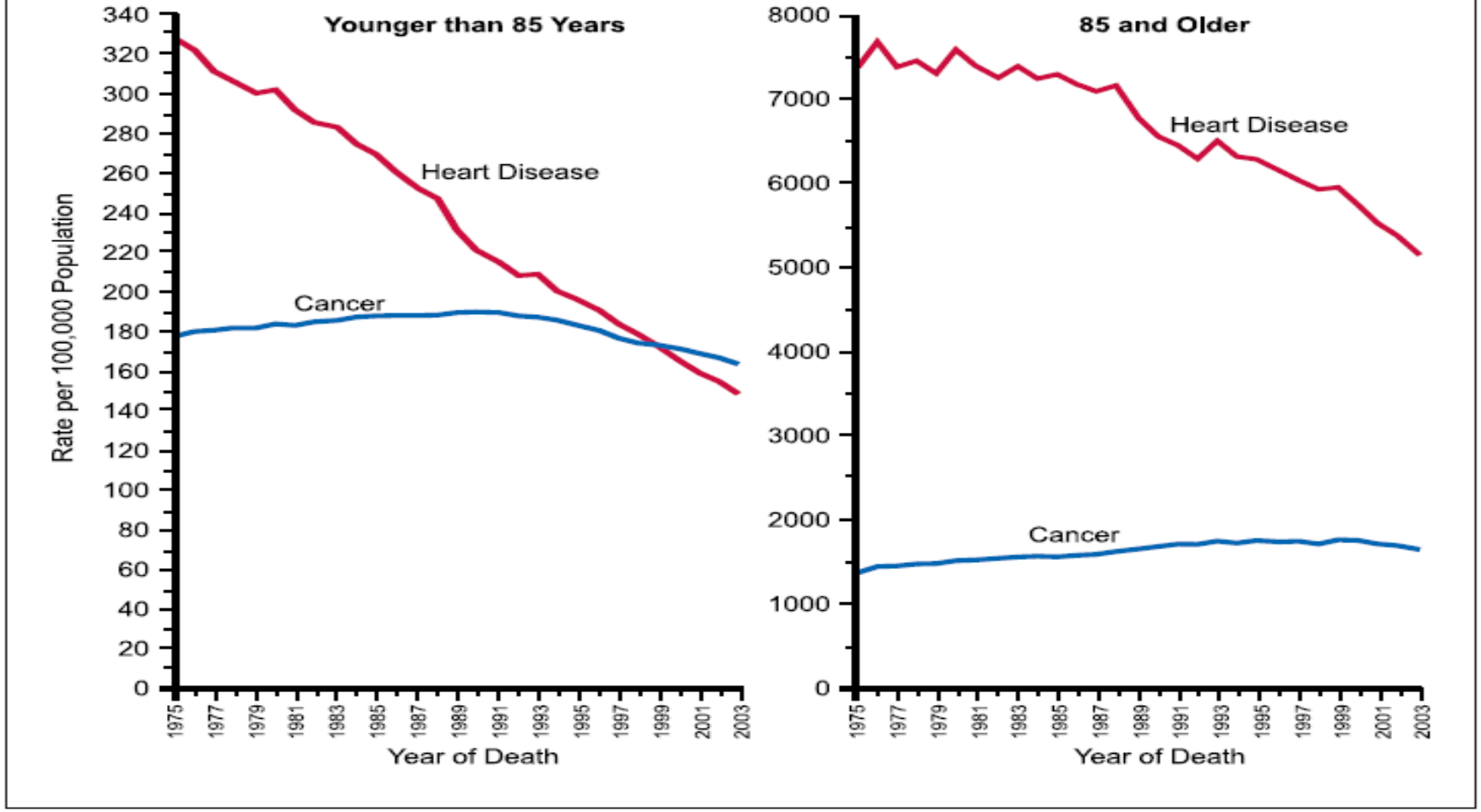


FIGURE 6 Death Rates* From Cancer and Heart Disease for Ages Younger Than 85 and 85 and Older.
*Rates are age-adjusted to the 2000 US standard population.
Source: US Mortality Public Use Data Tapes, 1960 to 2003, National Center for Health Statistics, Centers for Disease Control and Prevention, 2006.

Generalidades

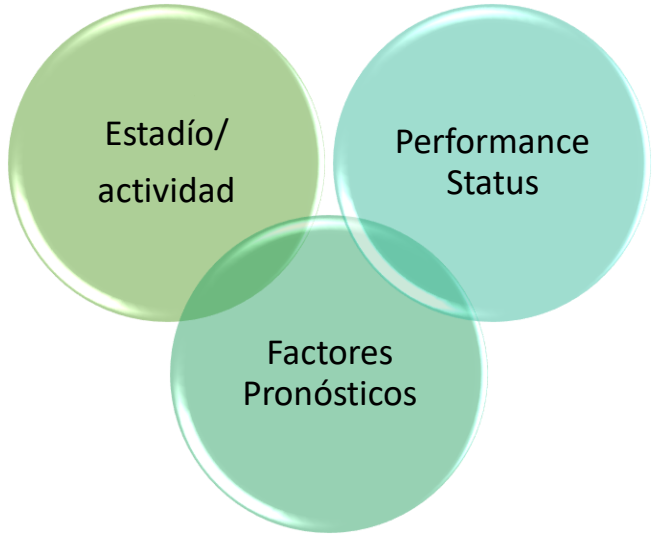
LLC gran variabilidad clínica

Sobrevida 2-20 años , media 10 años

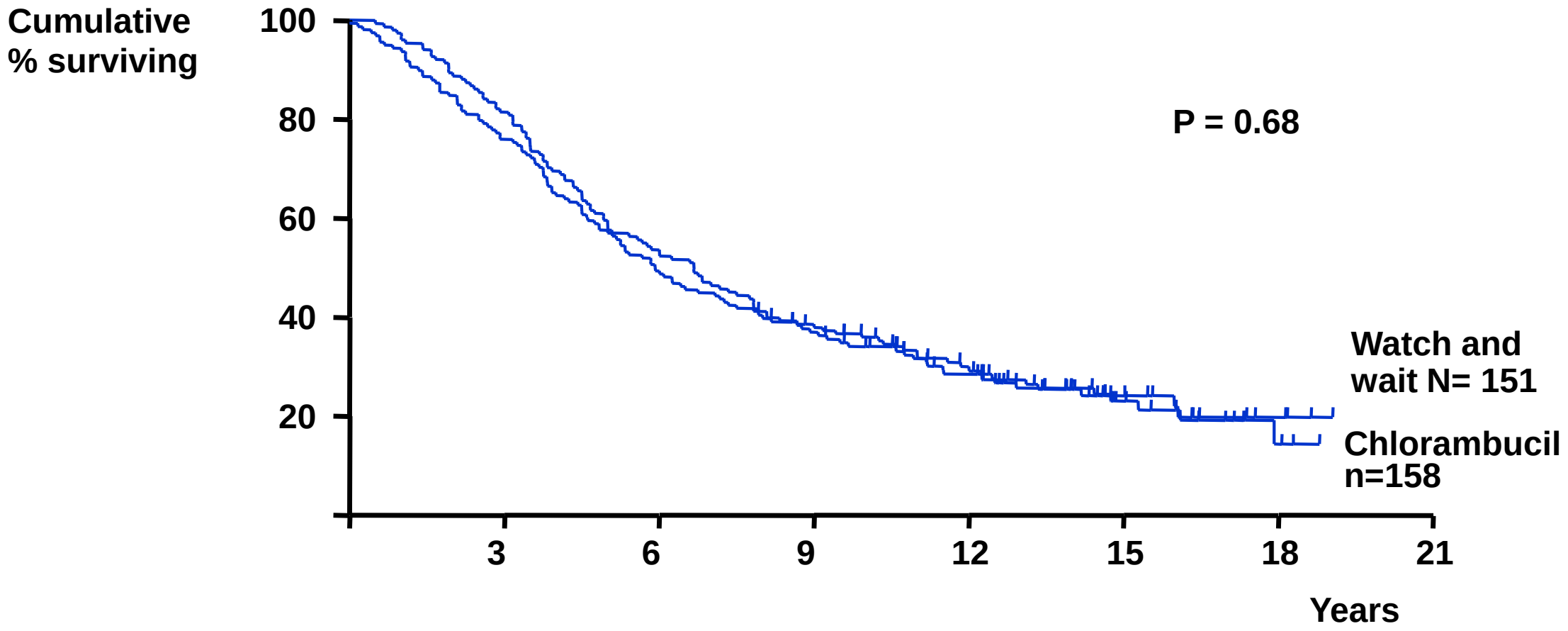
Indolente <30%

Agresiva : SV 2-3 años

Fase terminal 1-2 años, alta morbilidad



OVERALL SURVIVAL BY TREATMENT



Ardeshna et al. Lancet 2003;362:516-522.

CONCEPTO E INCIDENCIA

- LLC: enfermedad caracterizada por la proliferación y acumulaciónde linfocitos inmunoincompetentes de pequeño tamaño, aspecto maduro y fenotipo B

- Manifestaciones clínicas por infiltración progresiva de la medula ósea, ganglios linfáticos y otros tejidos . Además se presentan alteraciones inmunológicas

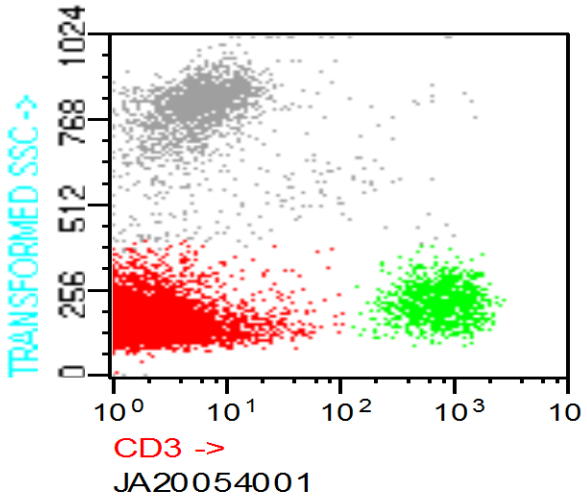
- Es la forma de leucemia más frecuente en los países occidentales, se presenta en personas de edad adulta y su incidencia es de 3 casos / 100,000 habitantes / año

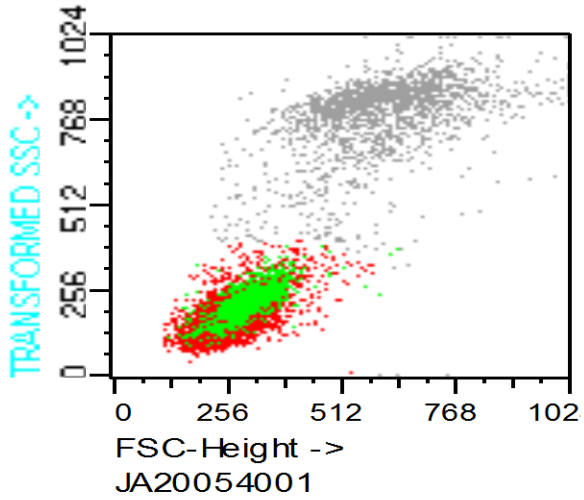
DIAGNOSTICO

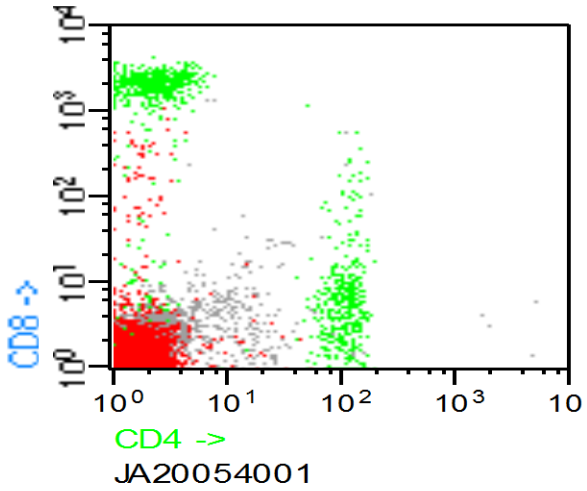
1. Linfocitos B >5 x109/L en sangre periférica durante más de 3 meses
2. Clonalidad de los linfocitos confirmada por citometría de flujo
3. Presencia de células atípicas (prolinfocitos, células hendidas) <50% de los linfocitos en sangre
4. Fenotipo compatible con LLC: expresión de cadenas kappa o lambda; SmIg de poca intensidad; positividad para los antígenos CD5, CD19, CD20 (débil), CD23 y CD200
5. La presencia de <5 x109/L linfocitos B, en ausencia de adenopatías, visceromegalias, citopenias o síntomas asociados, define la denominada linfocitosis B monoclonal (LBM), de significado clínico incierto

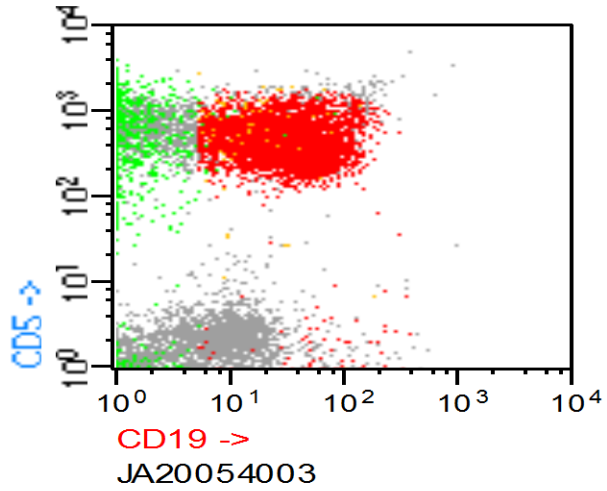
Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–W
Group 1996 guidelines. El término LLC de fenotipo T ha desaparecido de todas las clasificaciones actuales.

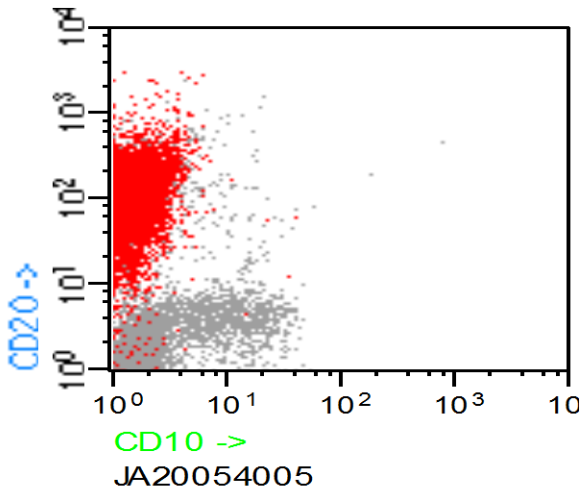
Caracterización Sd. Linfoproliferativo

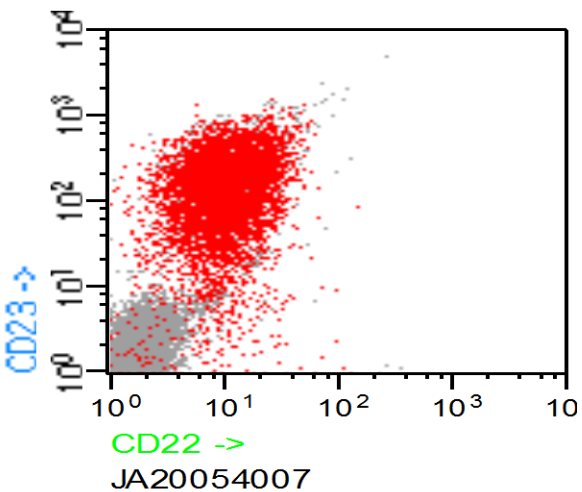


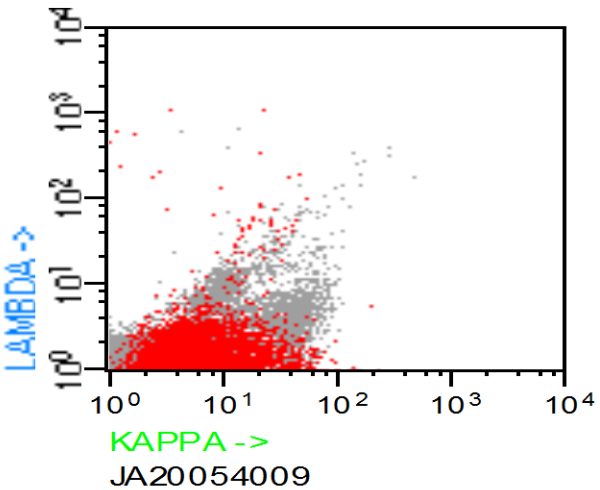












LLC: CLINICA

- Edad media 70 años (20% <65 años) y predomina en varones (1,5:1)
- 80% asintomáticos

Síntomas	Prevalencia	Características
Astenia	20%	A veces sin relación con el grado de actividad de la enfermedad
Síntomas B	10%	Fiebre (≥38 °C), pérdida de peso (≥10% en 6 meses), sudación nocturna. Su presencia debe hacer pensar en una transformación en linfoma de células grandes (síndrome de Richter)
Síndrome anémico	10%	Puede ser de origen infiltrativo, por anemia hemolítica autoinmune (15 – 30%) o por eritroblastopenia (<1%)
Plaquetopenia	10%	Puede ser de origen infiltrativo, por hiperesplenismo o autoinmune (<5%)
Infecciones	Fases avanzadas	Suelen ser bacterianas y de foco pulmonar. También son frecuentes las infecciones por herpes virus y agentes oportunistas
Transformación [1]	5 – 10% de casos	Transformación prolinfocitoide (>55% de prolinfocitos) o bien síndrome de Richter
Segundas neoplasias	5% de casos	Mayor riesgo de segundas neoplasias (piel, tracto digestivo, pulmón)
Otros síntomas	Raros	Reacciones alérgicas a picaduras de insectos

EXAMEN FISICO

- Normal en el 70% de pacientes al diagnóstico

—Adenopatías (20 – 30%) bilaterales y simétricas. Es excepcional la presencia de adenopatías mediastínicas así como la infiltración del anillo linfático de Waldeyer

— Esplenomegalia (20 – 30 %)

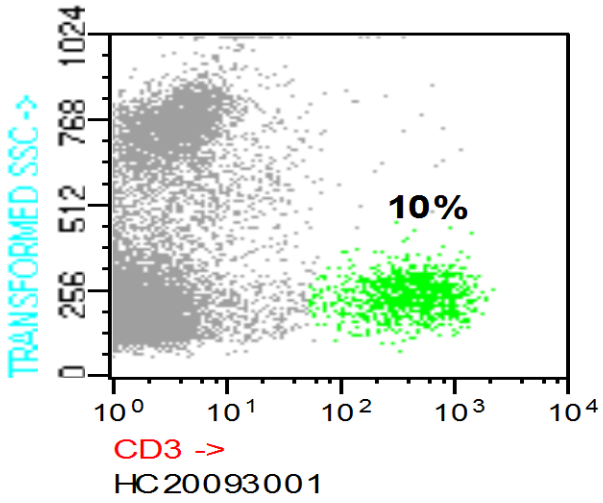
— Hepatomegalia (10 – 20%)

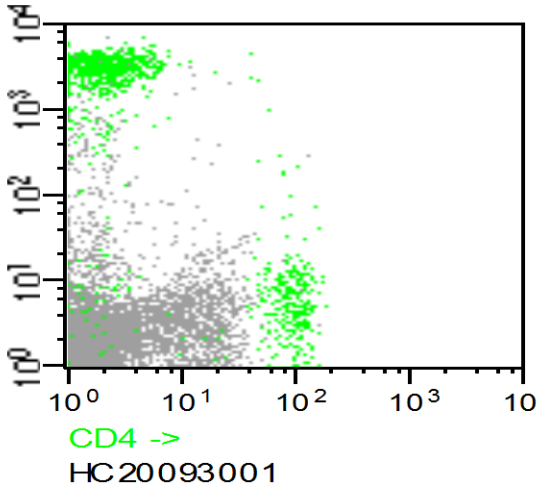
— La infiltración linfoide de piel, riñón, glándulas lagrimales o salivares, pulmón, etc. es excepcional

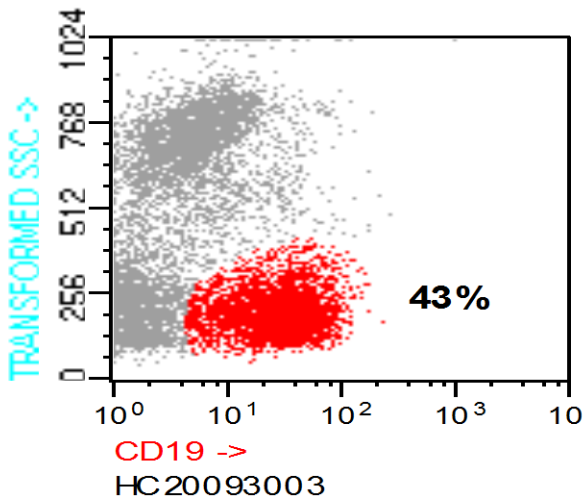
DIAGNOSTICO DIFERENCIAL

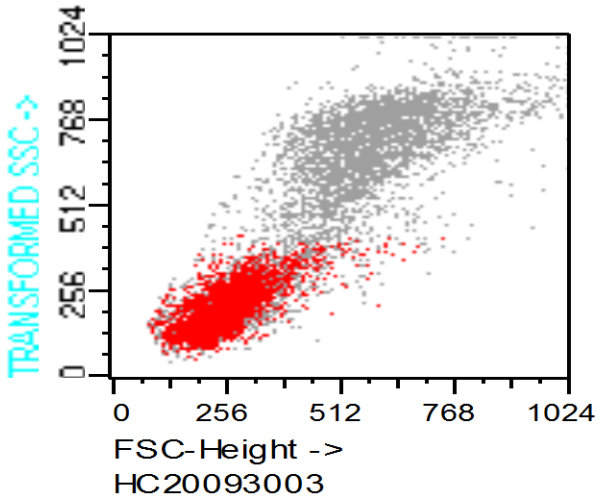
LEUCEMIA PROLINFOCÍTICA	— Linfocitosis extremas (>100 x109/L) con abundantes prolinfocitos (>55%) — SmIg intensa, FMC7+, CD23–
TRICOLEUCEMIA	— Morfología típica de tricoleucocito — SmIg intensa, CD25/CD11c/CD103+ — Formas variantes: leucocitosis, CD25 y CD103 negativas — Mutaciones de BRAF (>90%)
LINFOMAS FOLICULARES LEUCEMIZADOS	— Morfología centrofolicular — SmIg intensa, CD10/CD22+, CD5– — t(14;18)(q23;q32) en el 80%
LINFOMA DE CÉLULAS DEL MANTO	— SmIg intensa, CD5+, CD23 negativo del manto — t(11;14)(q13;q32) >90% pacientes — Expresión de Ciclina D1 en >90% casos
OTROS SÍNDROMES LINFOPROLIFERATIVOS	— Origen B: linfoma marginal esplénico, linfoma linfoplasmocitoide (macroglobulinemia de Waldenström) — Origen T: leucemia prolinfocítica, síndrome de Sézary, leucemia de linfocitos grandes granulares

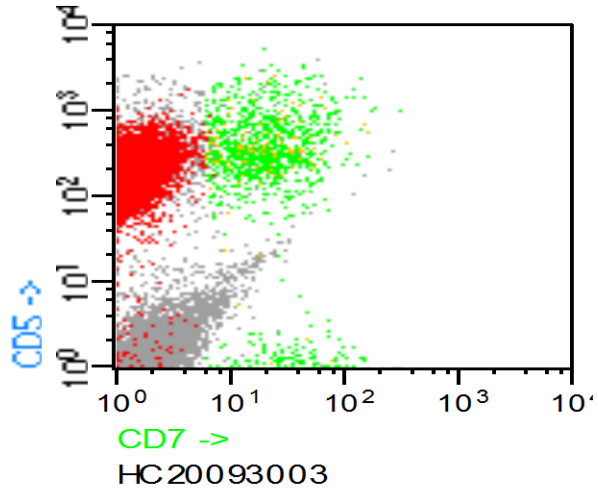
Caracterización Sd. Linfoproliferativo Médula Osea

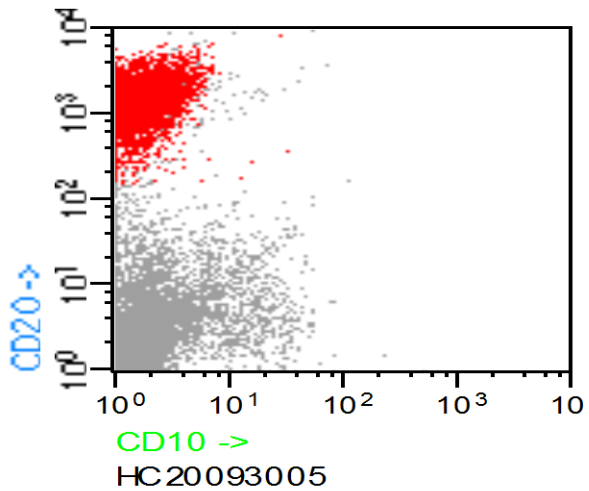


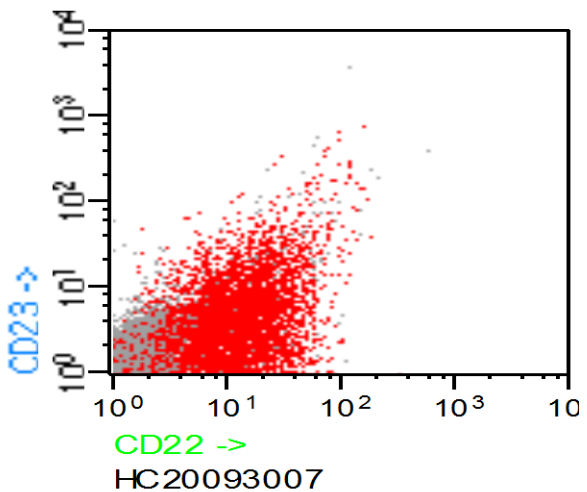


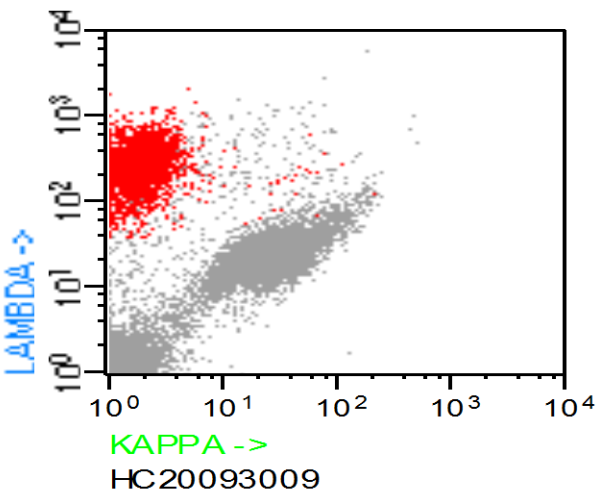












Etapificación

TABLE 2: Staging systems for CLL

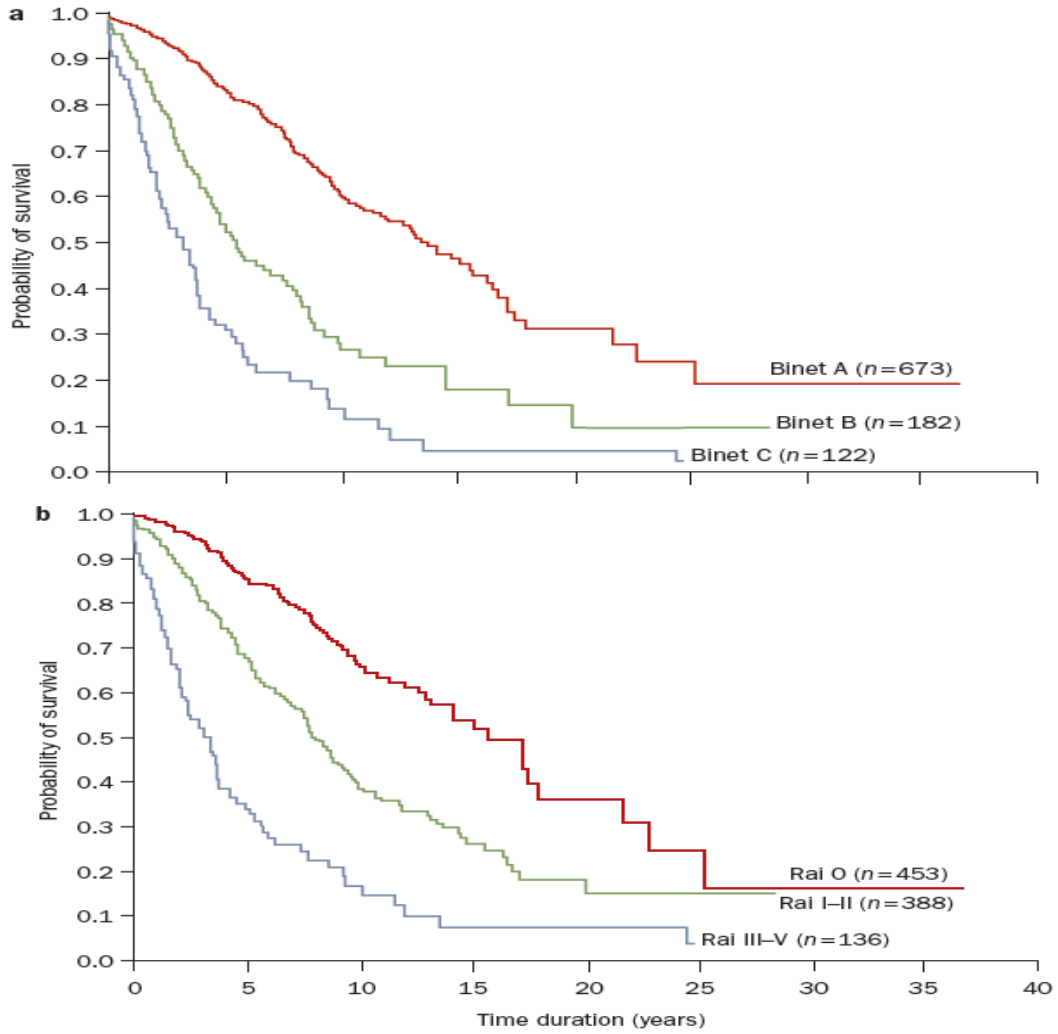
RAI SYSTEM

Rai stage	Modified Rai stage (risk)	Clinical characteristics	Median survival (yr)
0	Low	Lymphocytosis in peripheral blood and bone marrow only	> 10
I	Intermediate	Lymphocytosis and enlarged lymph nodes	6
II		Lymphocytosis and enlarged spleen and/or liver	
III	High	Lymphocytosis and anemia (hemoglobin < 11 g/dL)	2
IV		Lymphocytosis and thrombocytopenia (platelets < 100×10^9/L)	

BINET SYSTEM

Binet stage	Clinical characteristics	Median survival (yr)
A	Hemoglobin level ≥ 10 g/dL, platelet count ≥ 100×10^9/L, and < 3 areas involved	> 7
B	Hemoglobin level ≥ 10 g/dL, platelet count ≥ 100×10^9/L, and ≥ 3 areas involved	< 5
C	Hemoglobin level < 10 g/dL, platelet count < 100×10^9/L, or both (independent of areas involved)	< 2

OS- CLL according to Binet and Rai stages



Cramer, P. & Hallek, M. 2010*Nat. Rev. Clin. Oncol.*

¿Terapia?

Estadio	Manejo
Precoz (Rai 0, Binet A)	Monitorizacion sin tto hasta progresion
Intermedio (Rai I y II, Binet B)	Monitoreo hasta Enfermedad Activa
Avanzado (Rai III y IV, Binet C)	Requiere tratamiento

ENFERMEDAD ACTIVA

- Falla Medular progresiva
- Enfermedad Bulky (>10cm, esplenomegalia >6cm)
- Citopenias Autoinmune no controladas
- Tiempo Doblaje linfocitario rápido (<6meses o >50% en 2 meses)
- Síntomas B

Consideraciones

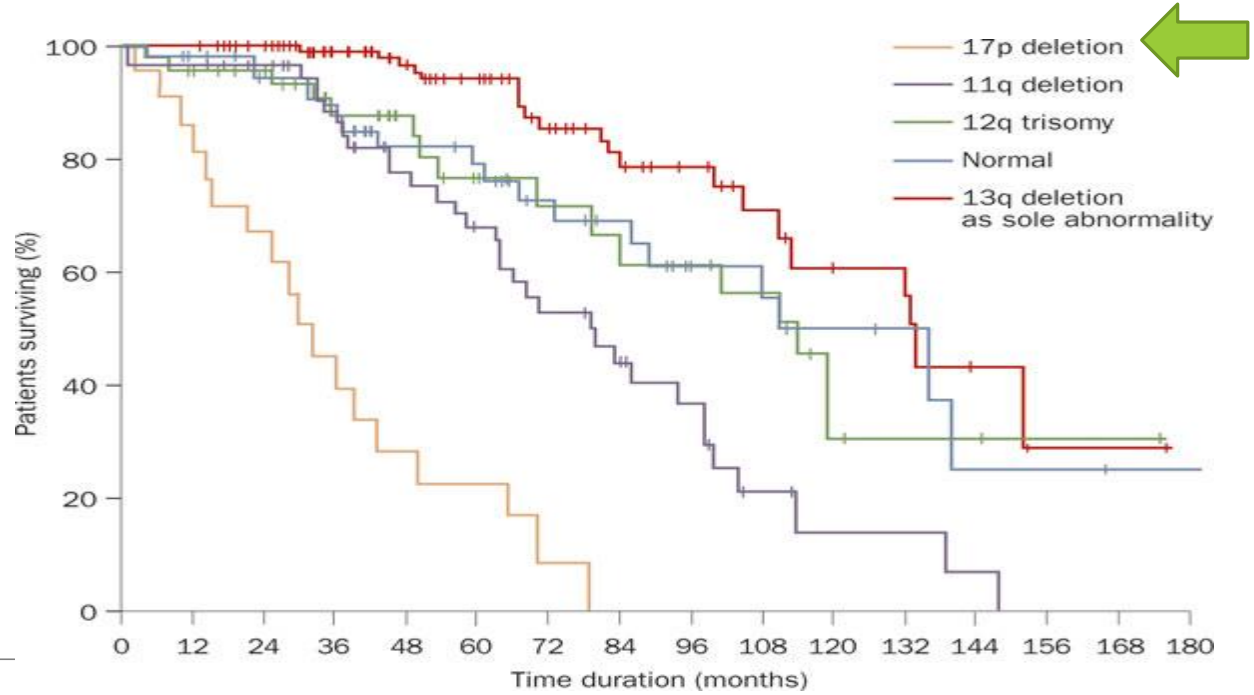
- TDL solo si RAL >30.000
- RAL no criterio unico de indicacion de tratamiento (Leucostasis/sintomas)
- No definen tratamiento: Hipogamaglobulinemia, componente monoclonal

No hay evidencia en iniciar terapia en etapa precoz y asintomático mejore SG, incluyendo pacientes de alto riesgo

Factores Pronosticos En Practica Clinica

Table Poor Prognostic Features in Chronic Lymphocytic Leukemia

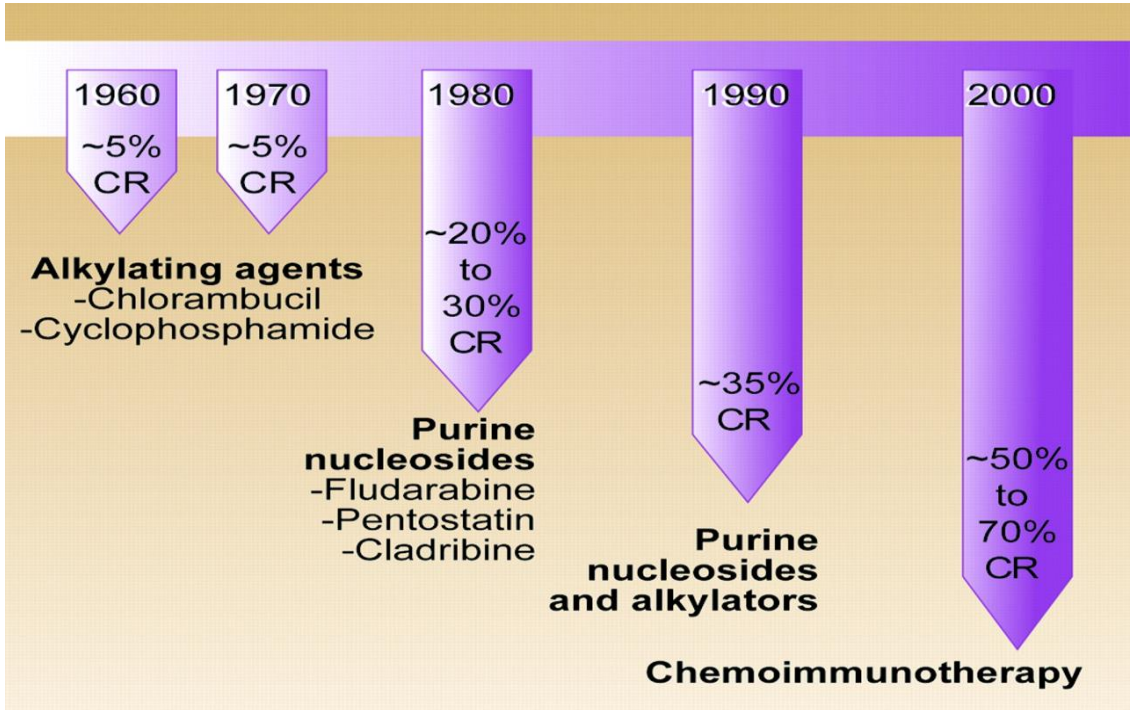
Rai stage III-IV or Binet stage C (presence of anemia and/or thrombocytopenia)
Lymphocyte doubling time < 12 months
Diffuse pattern of involvement on bone marrow examination
Serum beta 2 microglobulin > 3.5 mg/dL
Serum thymidine kinase > 5 U/L
CD38 expression > 30%
ZAP-70 expression > 20%
Immunoglobulin heavy chain (IgV_H) non-mutated
Deletion of 17p
Deletion of 11g
TP53 mutation
ATM mutation



La presencia de marcadores pronósticos de alto riesgo
No es sinónimo de enfermedad activa , ni necesidad de tratamiento

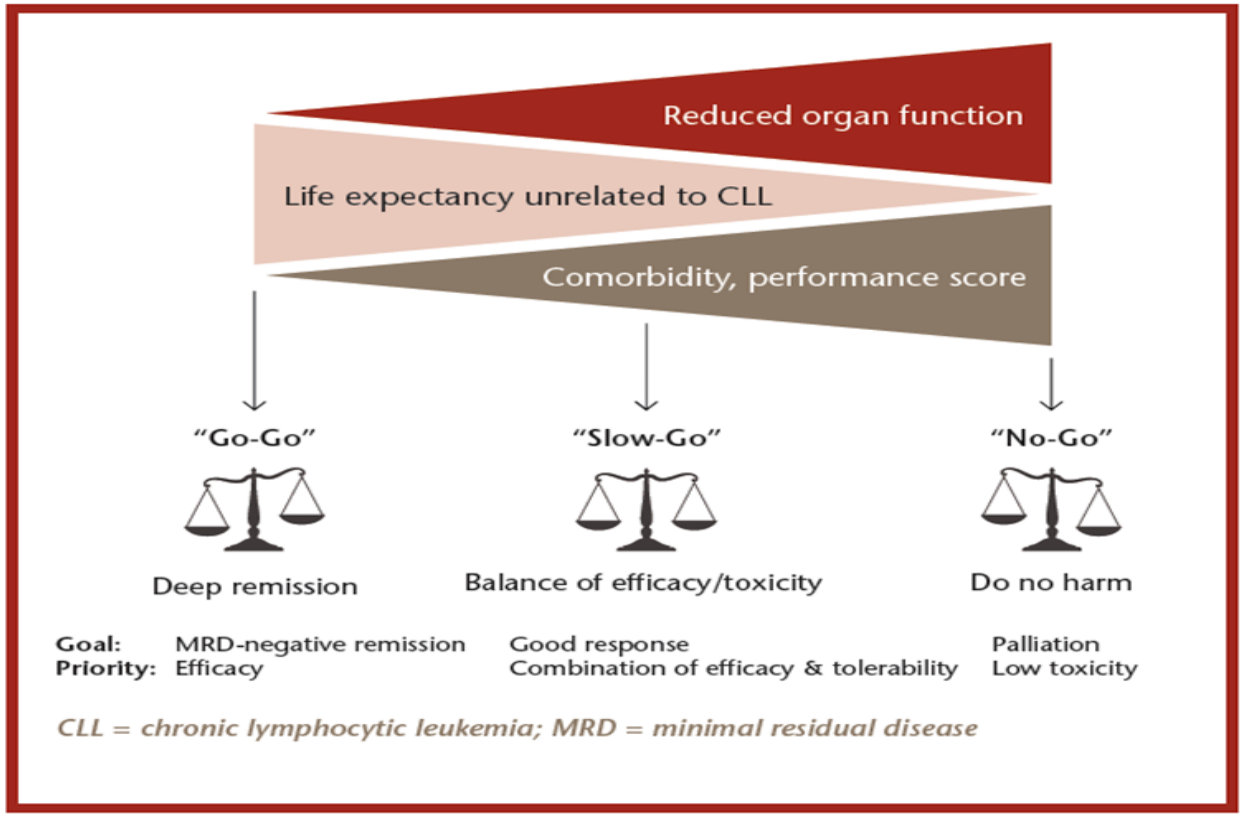
Cramer, P. & Hallek, M. (2010) Prognostic factors in chronic lymphocytic leukemia—what do we need to know?
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2010.167

LLC Evolucion Opciones terapeuticas



Neil E. Kay Blood 2006;107:848

Objetivos de tratamiento



Quimioinmunoterapia -1ª LINEA TRATAMIENTO

QIT Fludarabina
QIT Bendamustina
QIT Clorambucil

AC Monoclonal CD20
Rituximab
Ofatumumab
Obinutuzumab

Novel Agent

Table 1. Treatment Options for First-line Therapy

Trial	Regimen	N	Median Age	Median Follow-up	ORR	CR	PFS	OS
CLL8[5]								
	FCR	408	61 y; ≥65 y (31%)	5.9 y	90%	44%	46.8% at 5 y	78.7% at 5 y
	FC	409	61 y; ≥65 y (29%)		80%	22%	25.5% at 5 y	66.9% at 5 y
CLL10[7]								
	FCR	282	61.6 y; ≥65 y (30%)	37.1 mo	95%	40%	55.2 mo	91% at 3 y
	BR	279	61.6 y; ≥65 y (39%)		96%	31%	41.7 mo	92% at 3 y
CLL11[10,11]								
	Obinutuzumab + chlorambucil	333	73 y	39.0 mo	78%	21%	28.7 mo	Not reached
	Rituximab + chlorambucil	330			65%	7%	15.7 mo	Not reached
CLL11[10,11]								
	Obinutuzumab + chlorambucil	238	73 y	42.4 mo	77%	22%	31.1 mo	Not reached
	Chlorambucil	118			31% (PR)	N/A	11.1 mo	58.5 mo
COMPLEMENT 1[12]								
	FC + ofatumumab	226	69 y	29 mo	82%	12%	22.4 mo	Not reached
	Chlorambucil	221			69%	1%	13.1 mo	Not reached
RESONATE-2[17]								
	Ibrutinib	136	73 y ≥70 y (71%)	28.6 mo	92%	18%	89% at 2 y	95% at 2 y
	Chlorambucil	133	72 y ≥70 y (70%)		36%	N/A	34% at 2 y	84% at 2 y
PCYC-1102[14]								
	Ibrutinib	31	68 y ≥70 y (43%)	5 y	84%	29%	92% at 5 y	

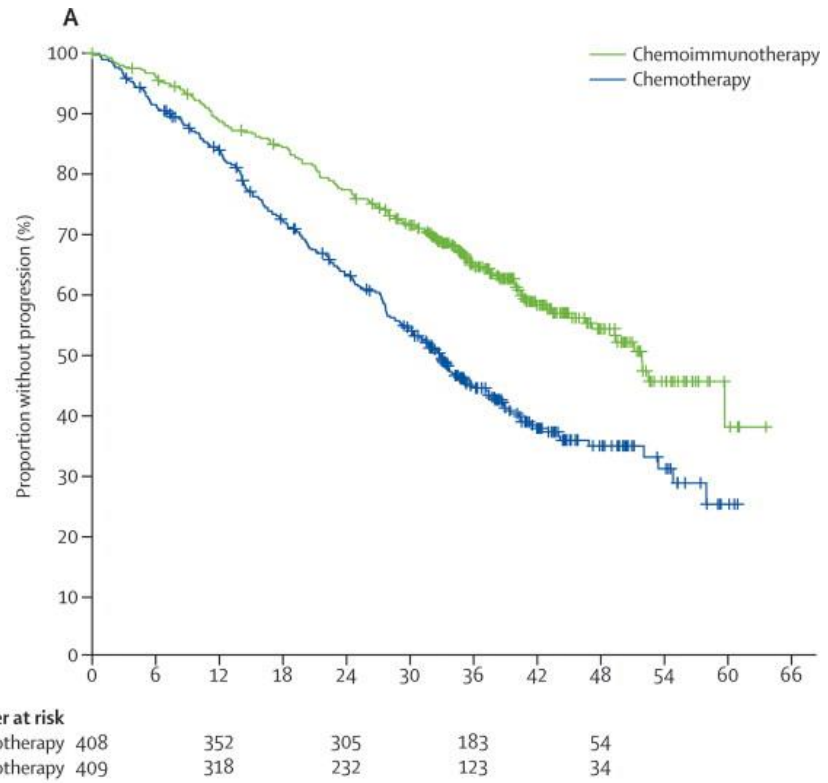
Addition of Rituximab to Fludarabine and Cyclophosphamide in patients with CLL: a randomised, open-label, phase 3 trial

CLL 8 TRIAL

LLC Naive
Binet B-C
PS 0-1
N= 817

FCR x 6 (408p)

FC x 6 (409p)



Rituximab
Cycle 1: 375 mg/m²
Cycles 2–6: 500 mg/m²

Fludarabine
25 mg/m² iv, days 1–3

Cyclophosphamide
250 mg/m² iv, days 1–3

1° Endpoint : PFS

Analisis IT

Edad media 61 años
31% Binet C
Del 17p 8,2 %
UMHV 63%

PFS 3 AÑOS
45% FC vs 65%FCR

M Hallek, K Fischer Volume 376, Issue 9747, 2010, 1164–1174

THE LANCET

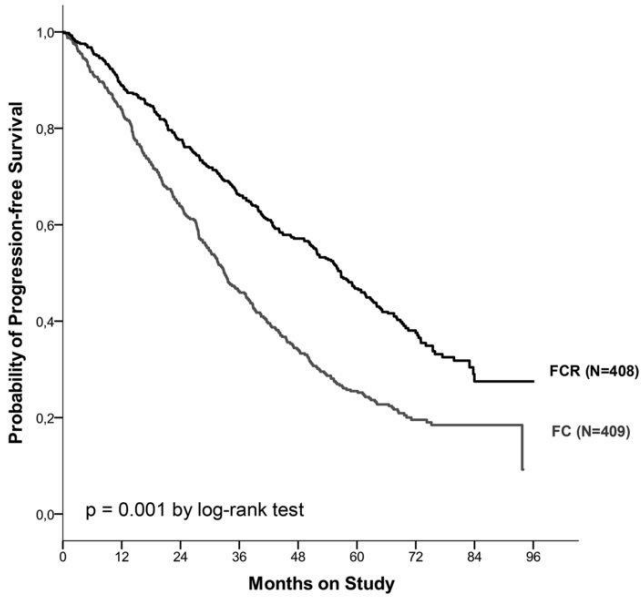
Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial

Seguimiento 5,9 años

	FC	FCR	
ORR	80 %	**90%**	**p <0,01**
RC	44%	**22%**	**p <0,01**
PFS	32,9m	**56,8m**	**p<0,001**
OS	86m	**NR**	**p<0,001**

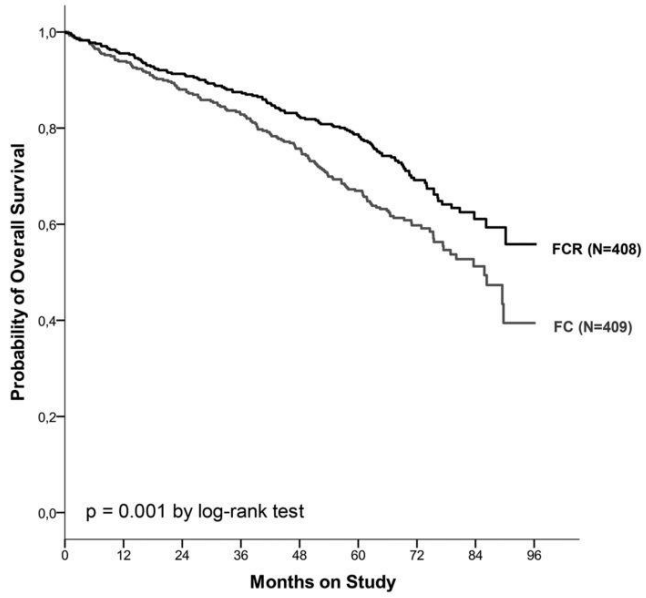
PFS y OS

A



Number at risk	0	12	24	36	48	60	72	84	96
FCR	408	358	310	261	222	178	76	18	1
FC	409	232	236	167	119	86	39	13	0

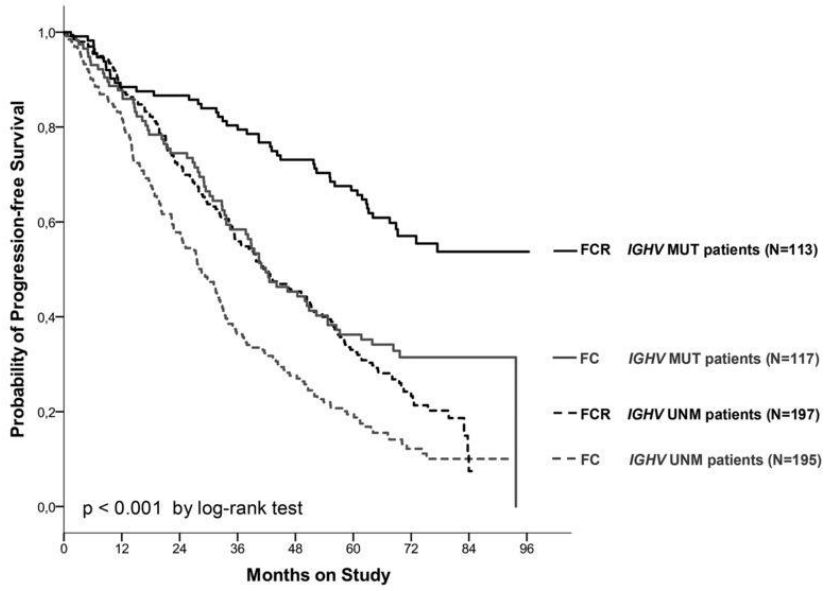
B



Number at risk	0	12	24	36	48	60	72	84	96
FCR	408	384	363	342	318	290	134	41	2
FC	409	360	232	297	262	220	100	33	1

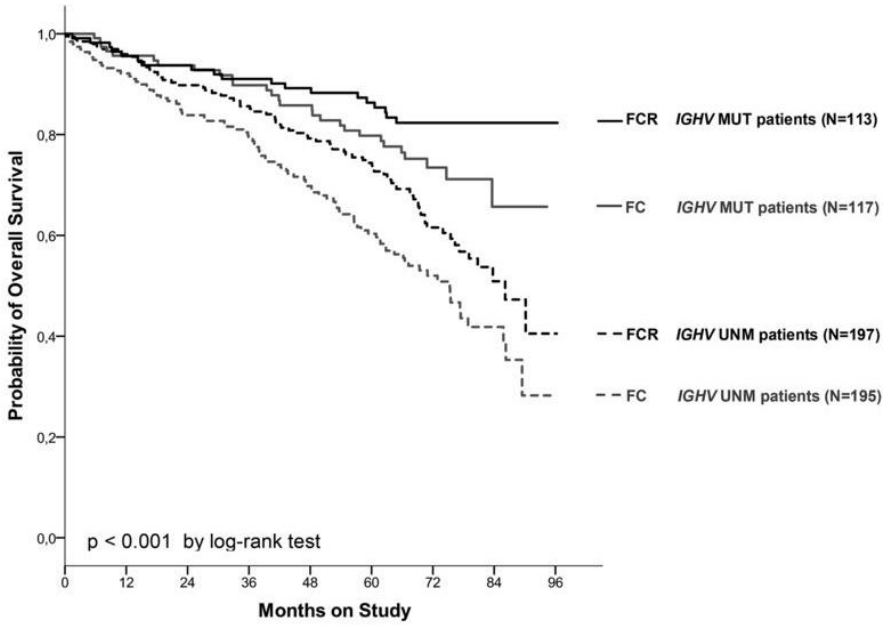
PFS and OS in both treatment arms and IGHV MUT/UNM patients.

A



Number at risk	0	12	24	36	48	60	72	84	96
FCR *IGHV* MUT	113	99	97	89	80	71	37	15	1
FC *IGHV* MUT	117	96	75	58	45	36	21	7	0
FCR *IGHV* UNM	197	173	140	106	85	61	25	2	0
FC *IGHV* UNM	195	153	105	65	45	30	12	4	0

B

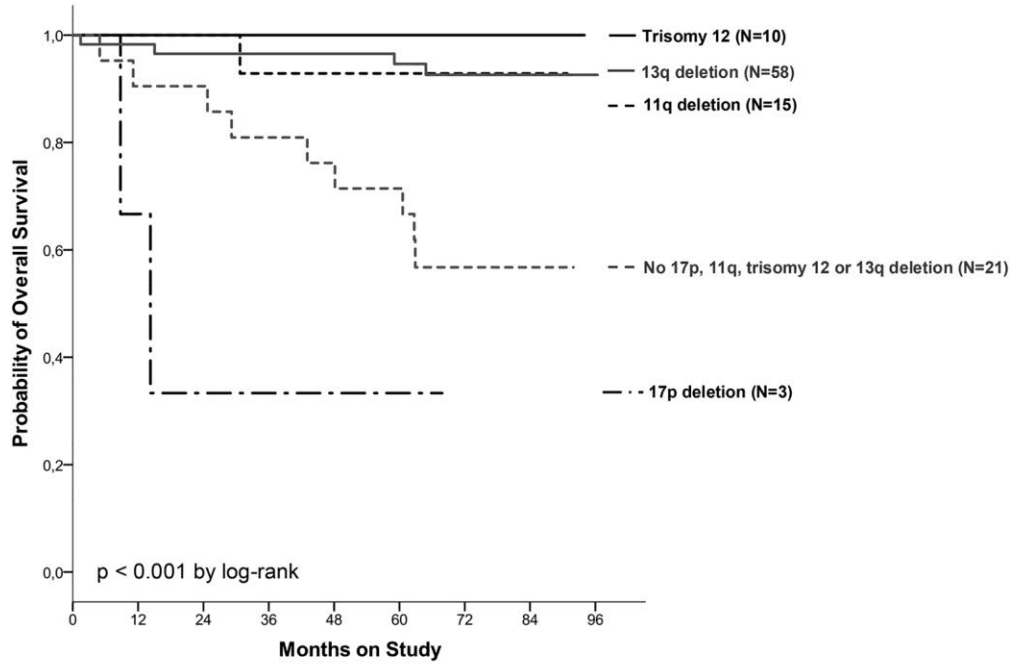


Number at risk	0	12	24	36	48	60	72	84	96
FCR *IGHV* MUT	113	106	104	100	96	89	47	20	1
FC *IGHV* MUT	117	105	96	91	86	76	38	12	0
FCR *IGHV* UNM	197	189	174	161	148	132	67	18	1
FC *IGHV* UNM	195	170	149	137	113	92	45	18	1

Kirsten Fischer et al. Blood 2016;127:208-215

blood

OS in genetic subgroups of IGHV MUT FCR patients (N = 107).



Number at risk	0	12	24	36	48	60	72	84	96
13q deletion	58	56	55	54	52	50	26	9	1
Normal[1]	21	19	19	17	16	15	8	3	0
Trisomy 12	10	10	10	10	10	9	5	3	0
11q deletion	15	14	14	13	13	11	8	5	0
17p deletion	3	2	1	1	1	1	0	-	-

[1]No 17p, 11q, Trisomy 12 or 13q deletion

Seguridad Largo Plazo

Neutropenia Grado III y IV

16,8% FCR vs 8,8 % FC p<0,007

Segundas neoplasias

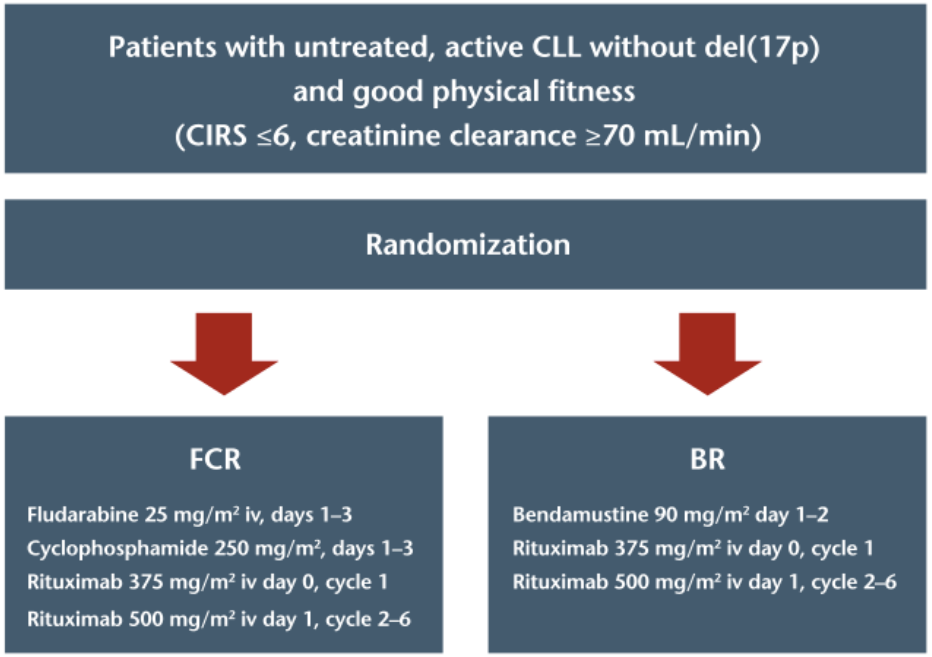
Richter

SMD /LMA

no diferencias

blood

First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced CLL (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial

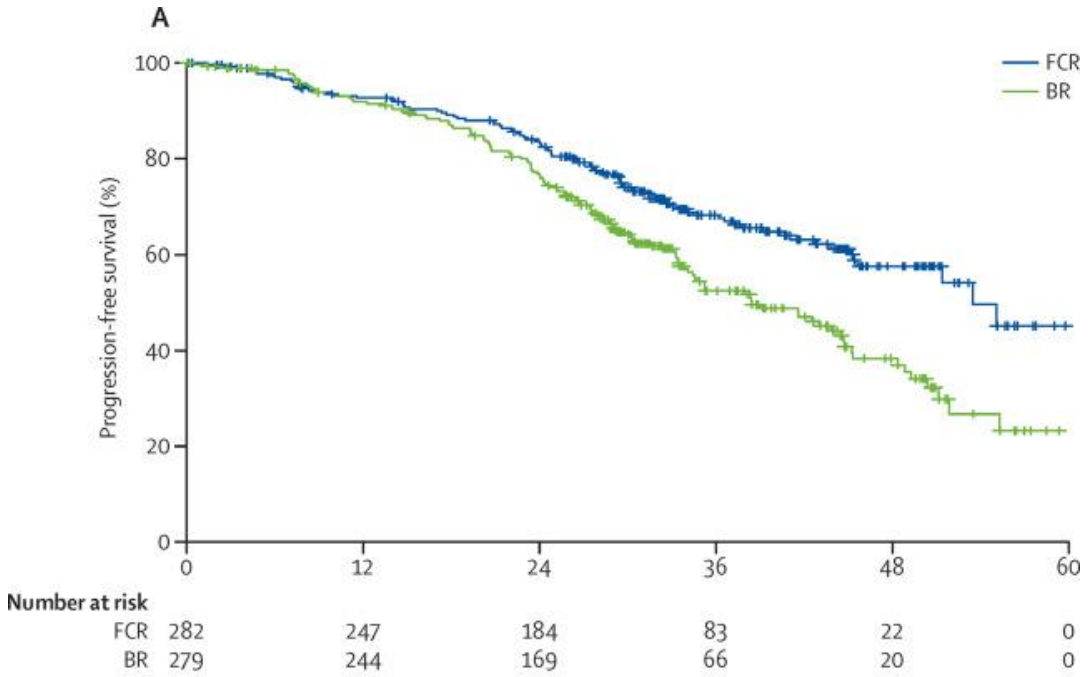


1° EP: No inferioridad BR vs FCR para PFS

Barbara Eichhorst et al . Volume 17, Issue 7, 2016, 928–942

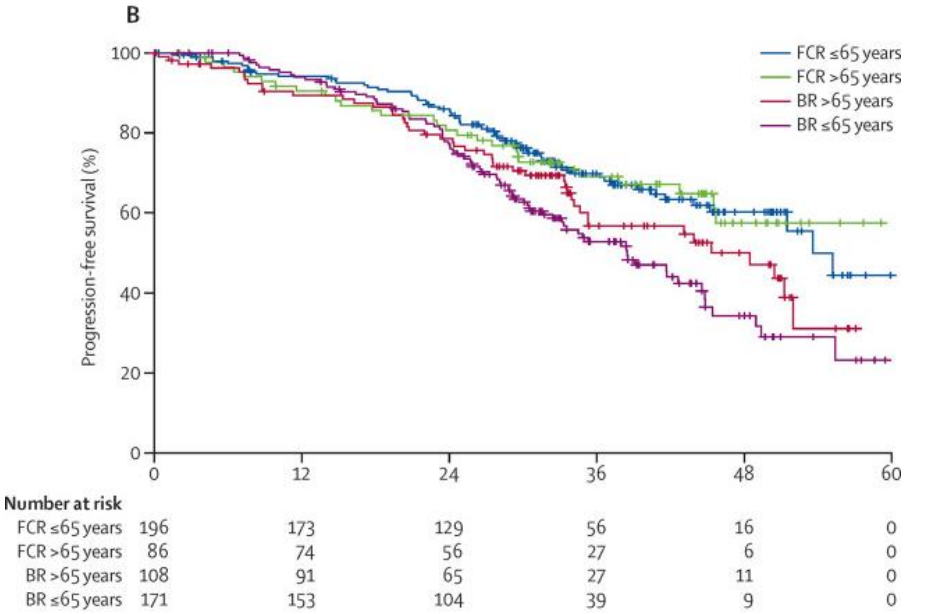
THE LANCET Oncology

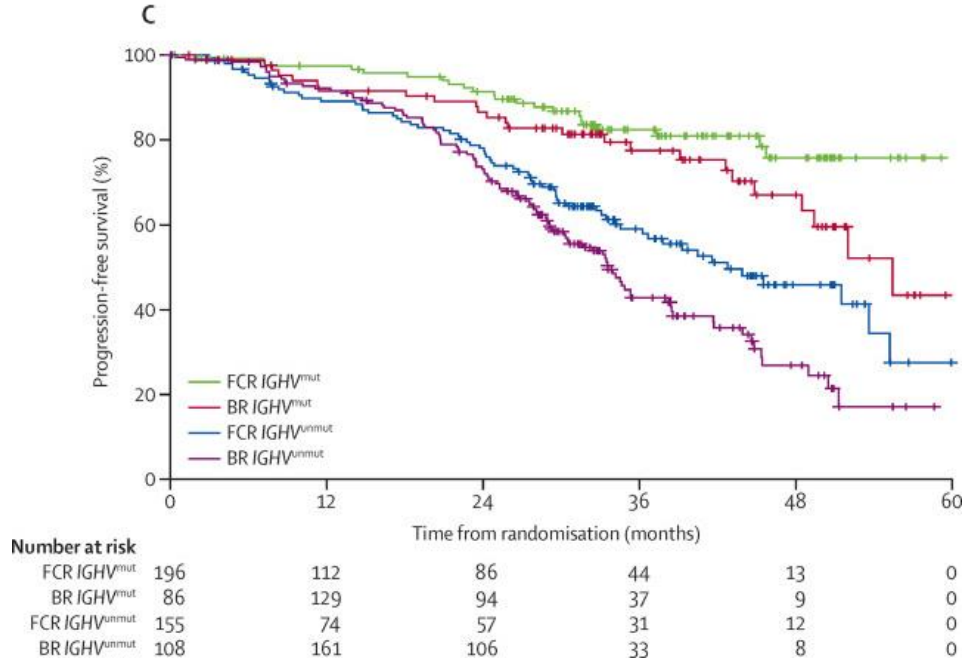
CLL 10 TRIAL



Media seguimiento 37,1 meses

	BR	FCR	
PFS	**41,7 m**	**55,2m**	**p = 0,0003**
ORR	**96%**	**95%**	
RC	**31%**	**40%**	**p=0,034**

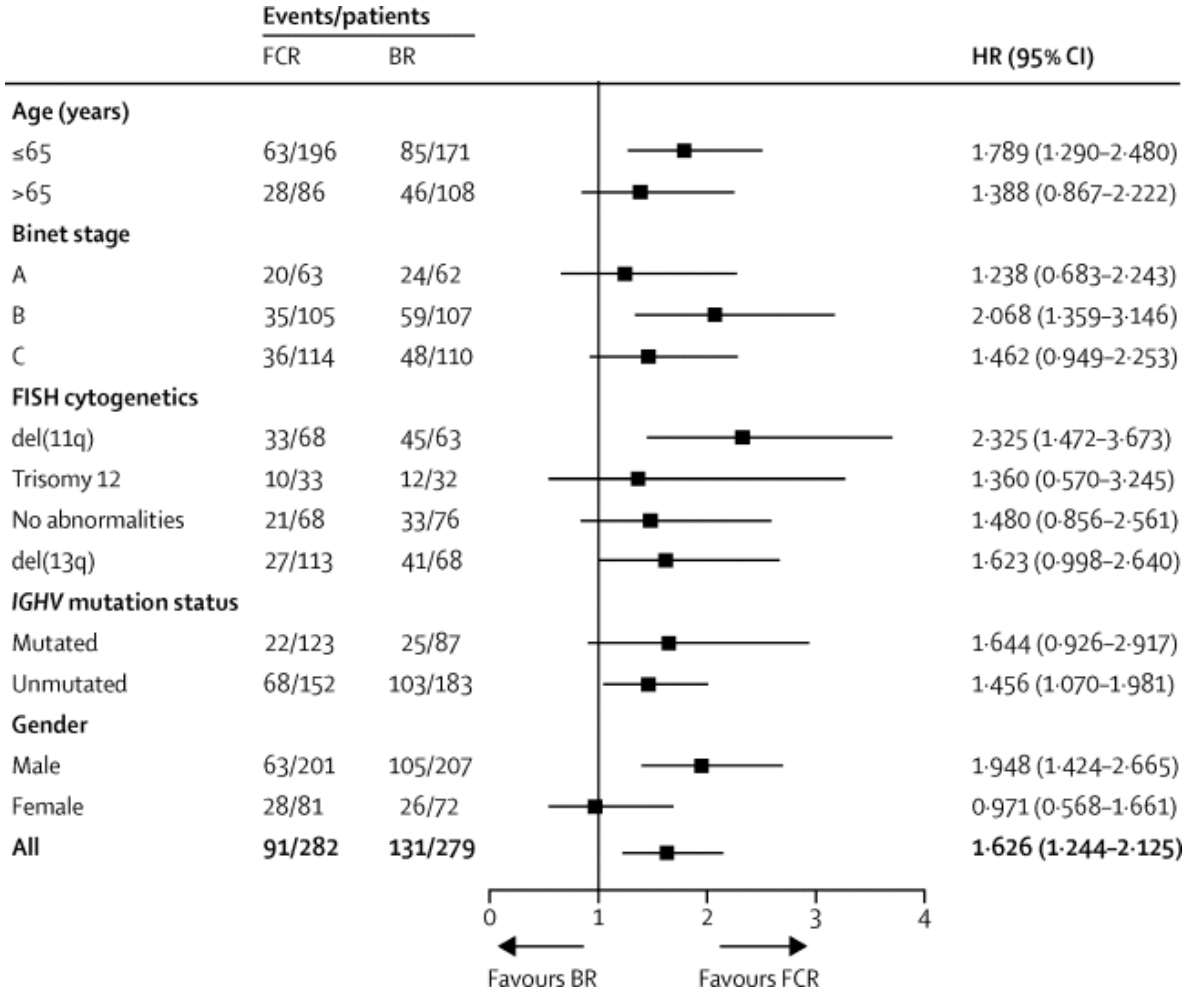




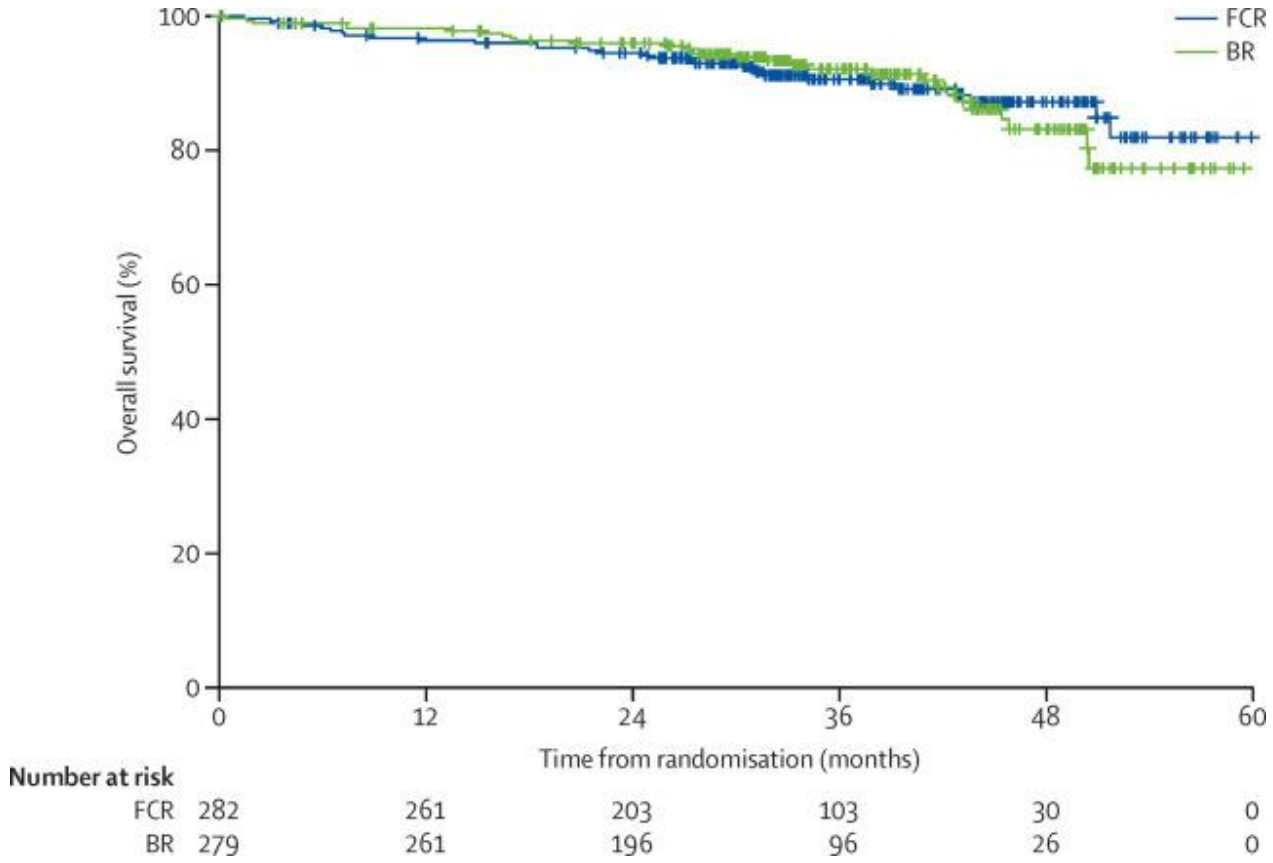
Barbara Eichhorst et al . Volume 17, Issue 7, 2016, 928–942

THE LANCET Oncology

PFS en subgrupos- FCR versus BR



Overall survival according to treatment group FCR=fludarabine, cyclophosphamide, and rituximab. BR=bendamustine and rituximab.

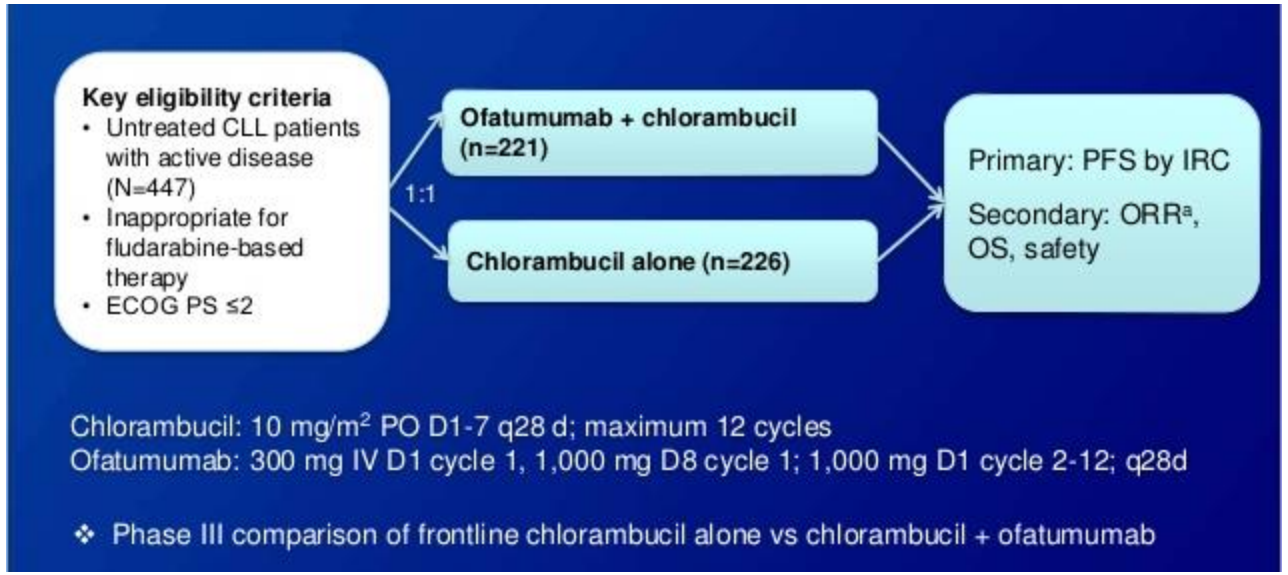


	BR	FCR	
SG 3 años	**92%**	**91%**	**ND**

Efectos Adversos
Infecciones mas frecuentes grupo FCR y adulto mayor

Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia ***(COMPLEMENT 1):*** *a randomised, multicentre, open-label phase 3 trial*

Dic 2008-Mayo 2011

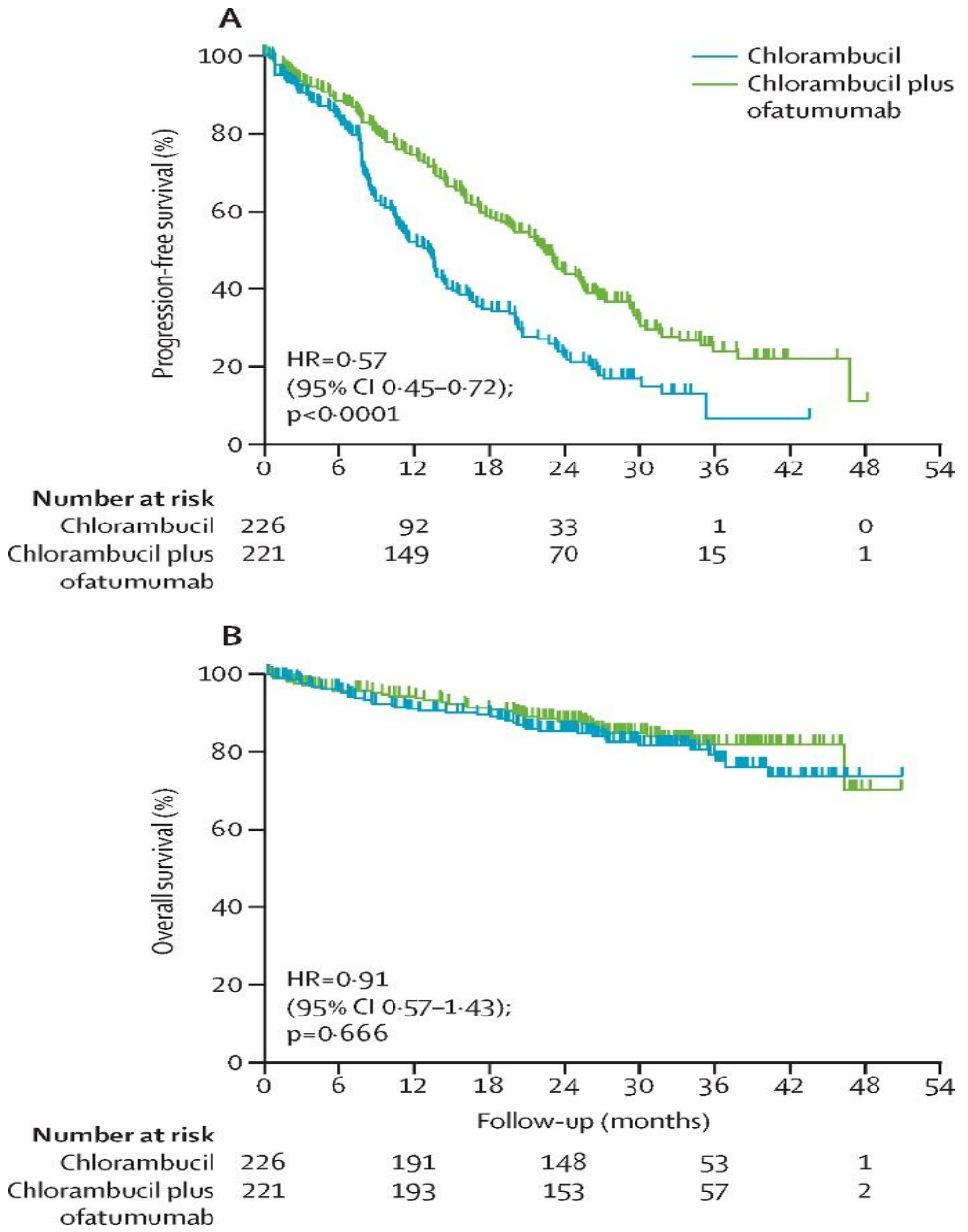


Edad media 69 años
69% (>65 años)
87% al menos 1 comorbilidad

Peter Hillmen, MB ChB, The Lancet Volume 385, Issue 9980, Pages 1873-1883 (May 2015)

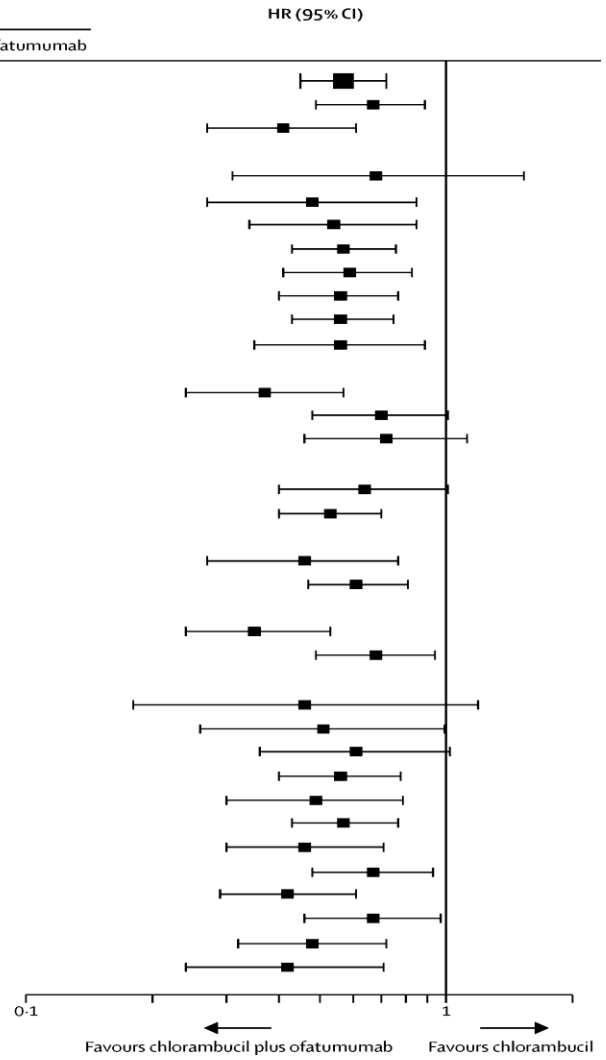
Media seguimiento 28,9 meses

	Clb	Clb + Ofatumumab
PFS	13,1m	**22,4m** p<0,0001
OS 3A	83%	85%
ORR	69%	**82%** p=0,001
RC	1%	**14%**



The Lancet 2015 385, 1873-1883DOI: (10.1016/S0140-6736(15)60027-7)

	Events/patients	
	Chlorambucil	Chlorambucil plus ofatumumab
All patients	**151/226**	**136/221**
Men	90/140	65/142
Women	61/86	41/79
Age (years)		
45–55	13/26	11/20
56–65	26/40	30/51
<65	42/71	38/69
≥65	109/155	98/152
<70	69/109	70/117
≥70	82/117	66/104
<75	109/163	103/165
≥75	42/63	33/56
Binet stage		
A	51/70	43/77
B	61/87	51/74
C	39/69	42/70
Comorbidities		
0 or 1	37/67	38/59
≤2	114/159	98/162
β_2-microglobulin		
≤3500 g/mL	32/48	33/61
>3500 g/mL	115/169	101/153
Immunoglobulin heavy chain status		
Mutated	65/90	38/87
Unmutated	73/113	87/114
Laboratory analysis		
17p	11/17	6/10
11q	18/24	30/39
17p or 11q	29/41	36/49
6q or +12q or 13q	76/111	71/119
No aberration	42/64	23/41
B-cell ZAP70-positive	72/110	72/100
B-cell ZAP70-negative	73/103	57/108
B-cell: T-cell ratio ZAP70-positive	96/135	93/137
B-cell: T-cell ratio ZAP70-negative	50/78	36/71
B-cell and B-cell: T-cell ratio ZAP70-positive	55/80	62/81
B-cell or B-cell: T-cell ratio ZAP70-positive	57/85	41/75
B-cell and B-cell: T-cell ratio ZAP70-negative	33/48	26/52



Efectos Adversos G3 50% (Clb+O)vs 43% (Clb)
Neutropenia 26%vs 14%
Infecciones GIII =

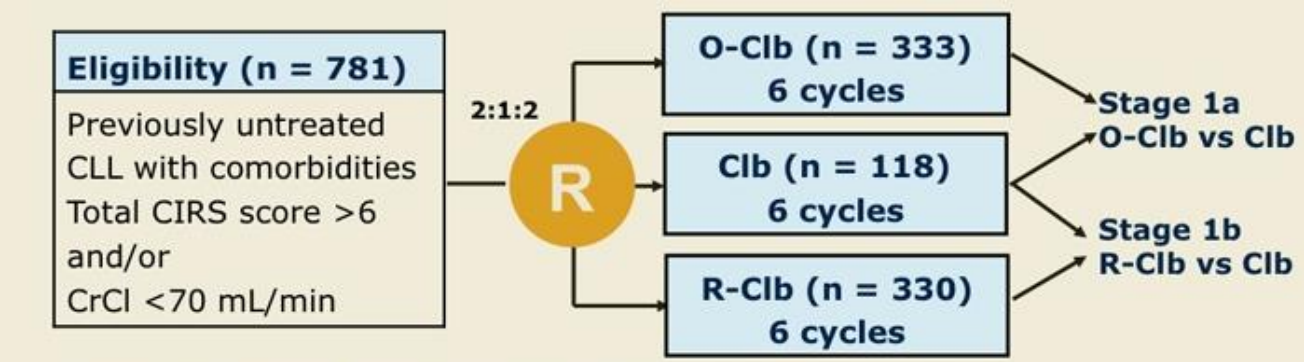
Reacciones infusionales 67%
GIII 10% vs 2%

The Lancet 2015 385, 1873-1883DOI: (10.1016/S0140-6736(15)60027-7)

ORIGINAL ARTICLE

CLL 11 TRIAL

Obinutuzumab plus Chlorambucil in Patients with CLL and Coexisting Conditions



CIRS = cumulative illness rating scale; CrCl = creatinine clearance

Obinutuzumab: IV, 1,000 mg on d1, 8, 15 (cycle 1); d1 (cycles 2-6), every 28 days

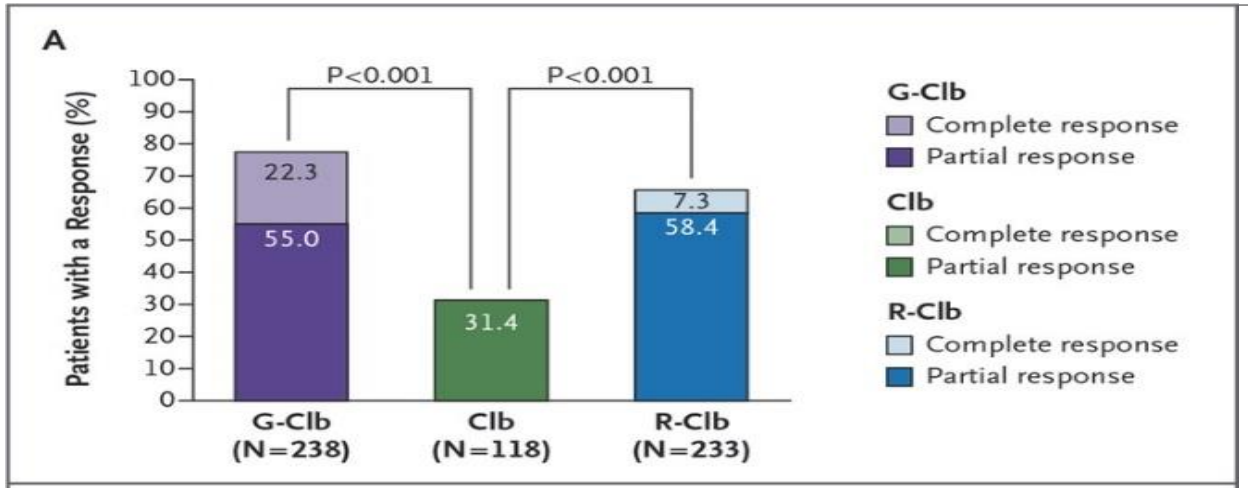
Rituximab: IV, 375 mg/m^2 d1 (cycle 1); 500 mg/m^2 d1 (cycles 2-6), every 28 days

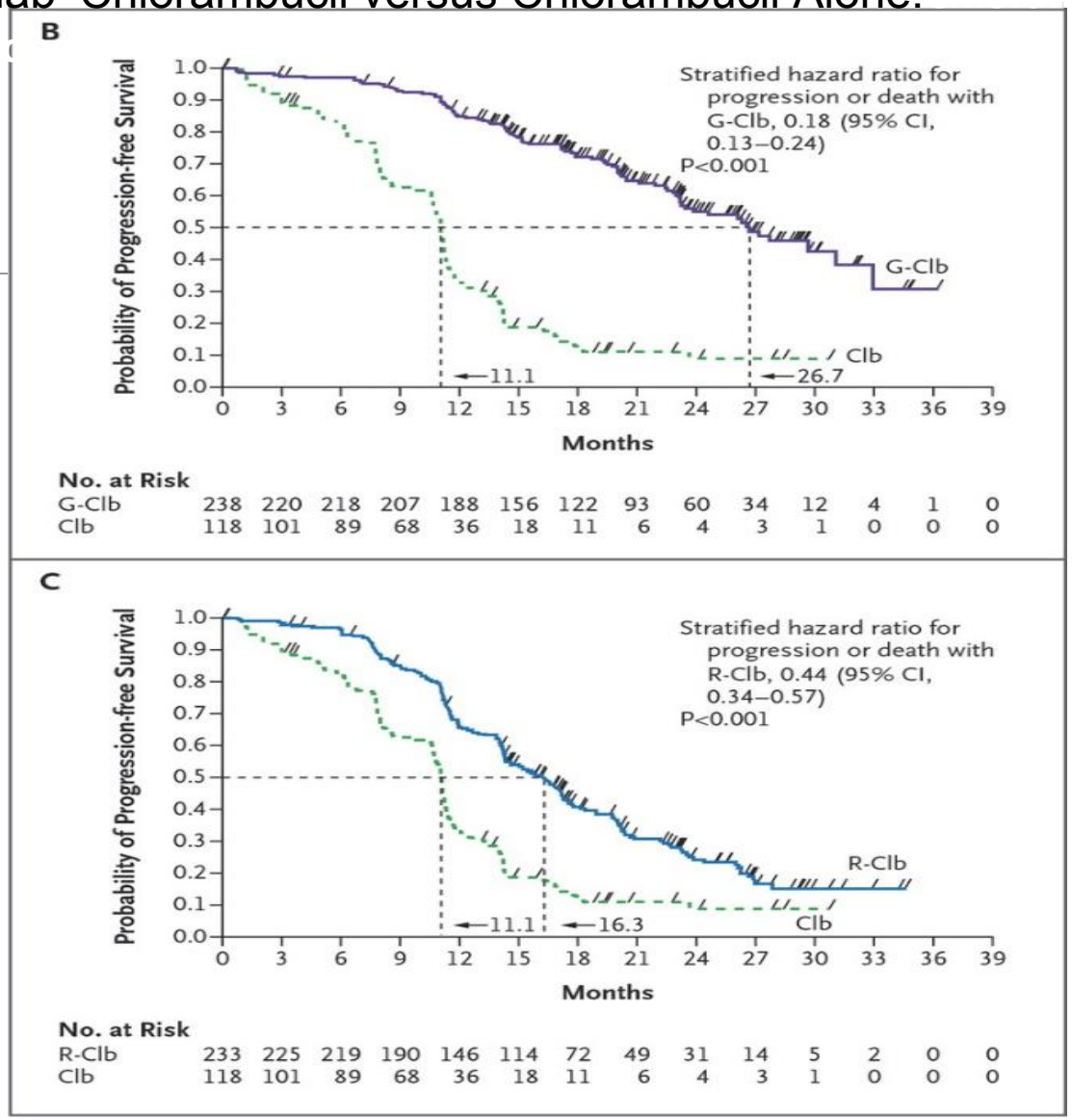
Clb: PO, 0.5 mg/kg d1, 15 (cycles 1-6), every 28 days

- **Stage 2 directly compares O-Clb to R-Clb**
- Patients with progressive disease in the Clb-alone arm were allowed to cross over to O-Clb.
- **Primary endpoint:** PFS

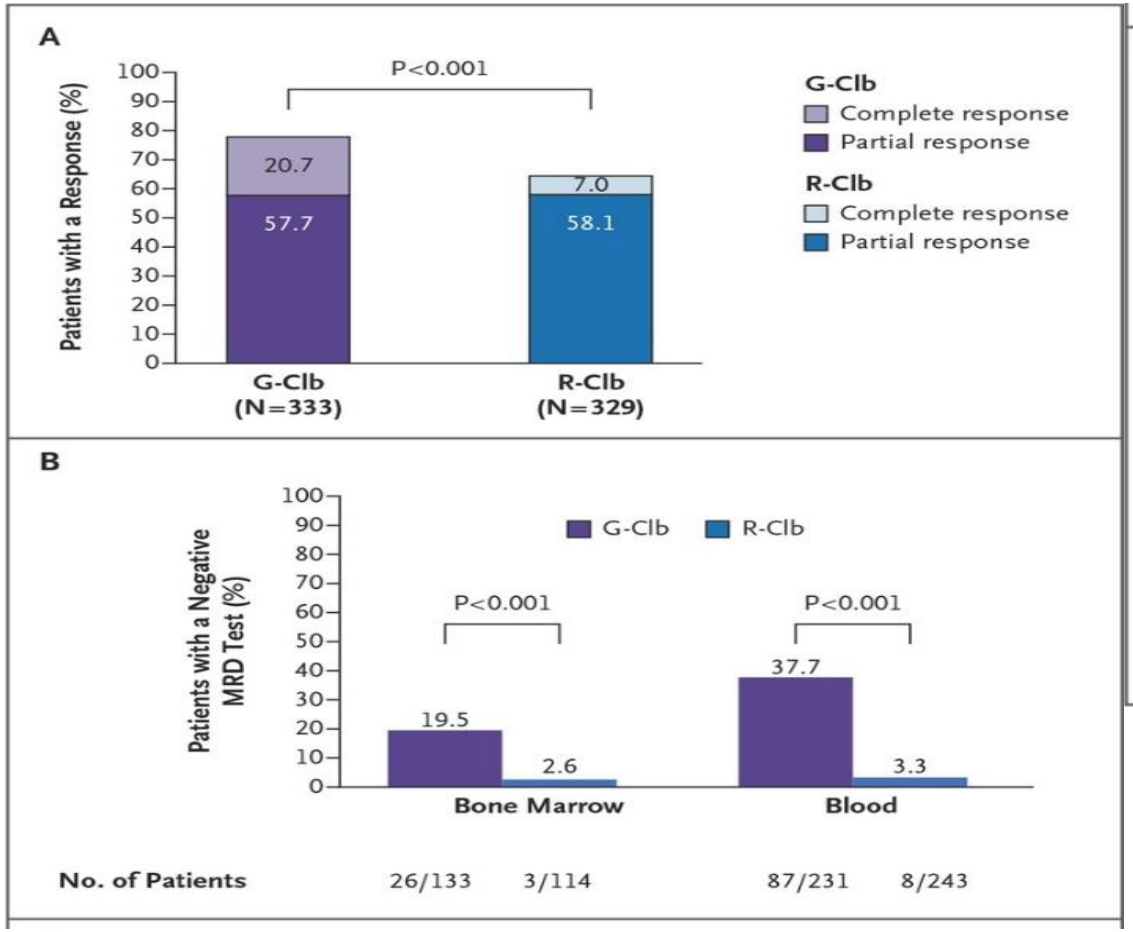
Goede V et al. *N Engl J Med* 2014;[Epub ahead of print].

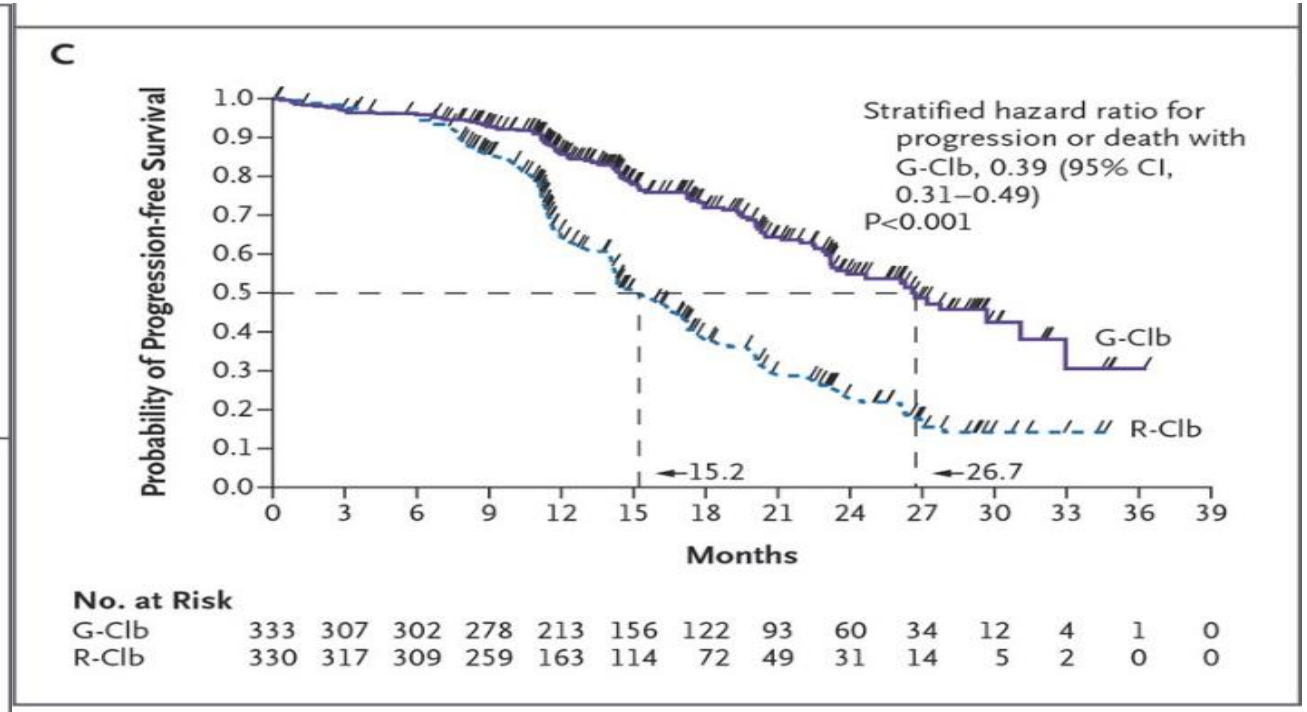
RR y PFS con Obinutuzumab–Chlorambucil or Rituximab–Chlorambucil versus Chlorambucil Alone.



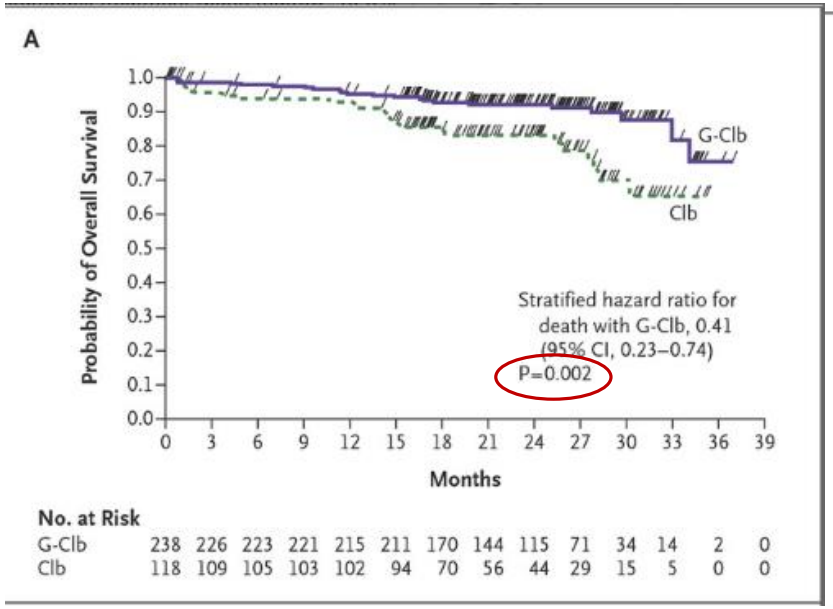


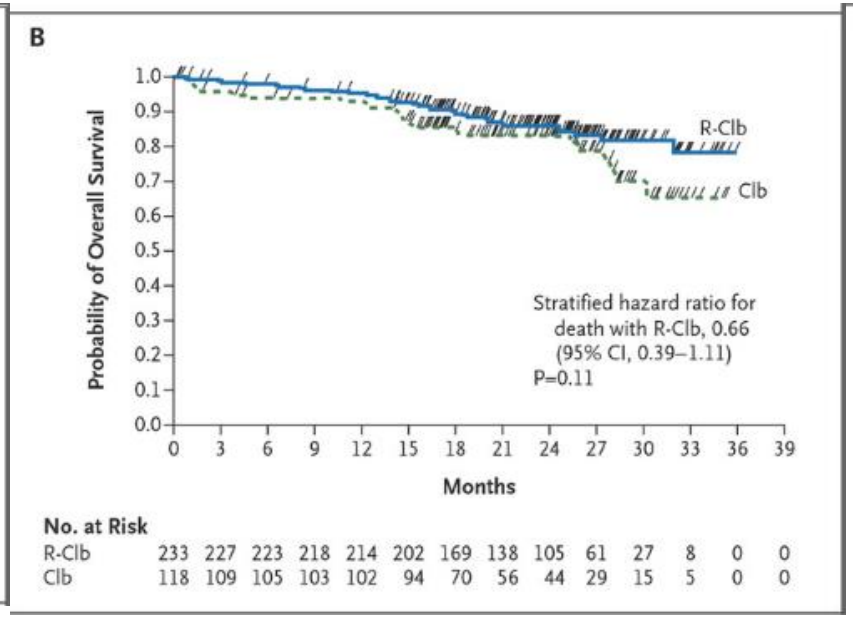
RR y PFS con Obinutuzumab–Chlorambucil versus Rituximab–Chlorambucil.

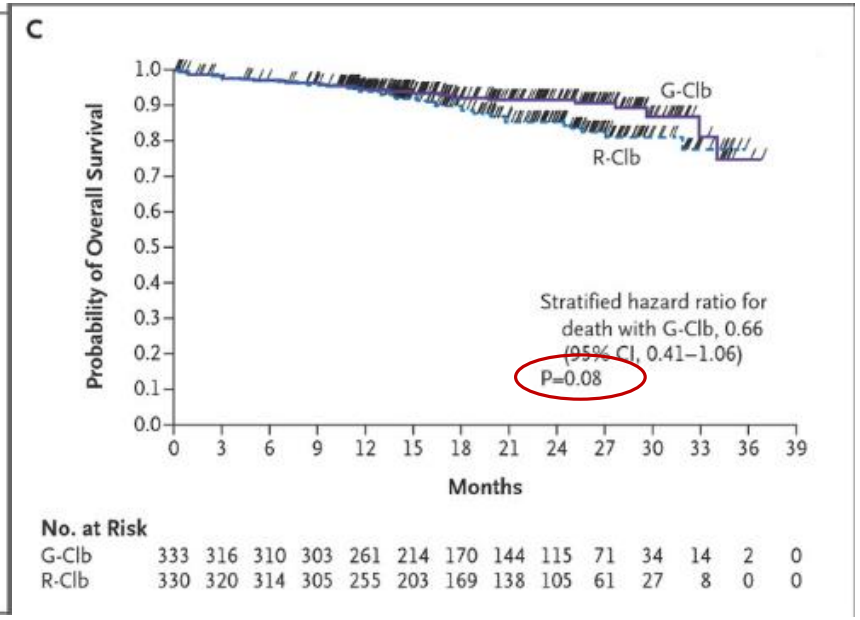




Overall survival







Nuevos Agentes Target

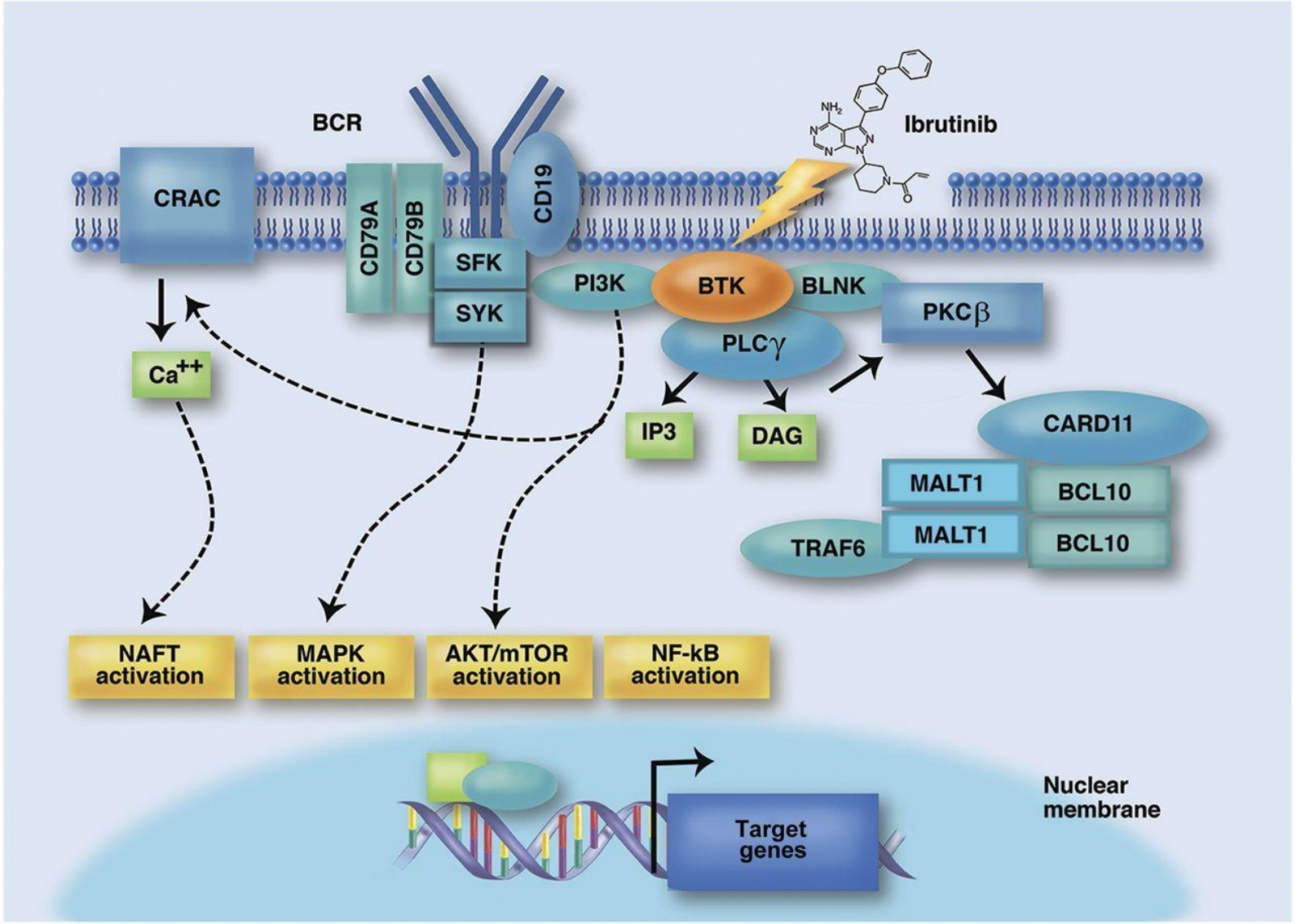
IBRUTINIB

Inhibidor selectivo, irreversible residuo cisteína 481 BTK

Bloquea señales intracelulares de proliferación y sobrevida generadas por activación BCR

Oral, 1 dosis día

- Induce apoptosis célula neoplásica
- Inhibe migración célula B a nichos de supervivencia y adhesión celular (redistribución)
- Regulación negativa CCL3 y CCL4



blood

ORIGINAL ARTICLE

Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia

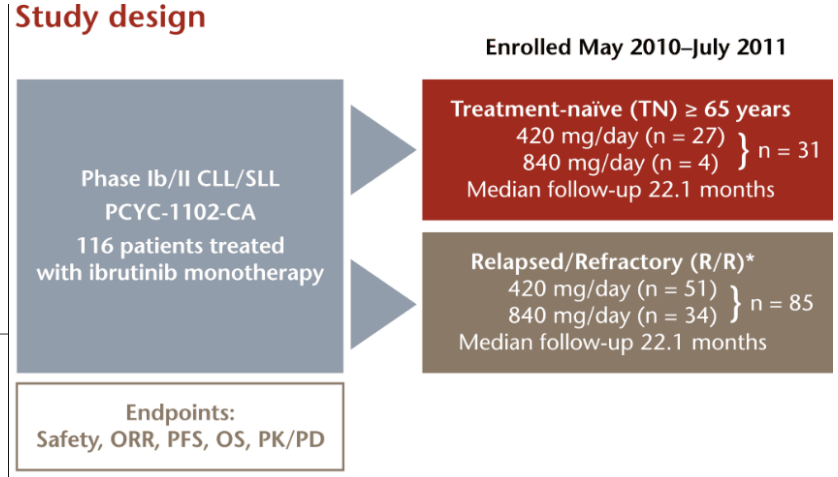
Fase 1b/2 abierto, multicentrico

LLC/SLL Recaído /refractario

Ibrutinib 420mg / 840mg

1° EP: safety : efectos Adversos

2° EP: eficacia :ORR, PFS, farmacocinética/dinamia



Mediana 66 años (35% >70 años)
76% masculino

Rai III-IV (65%)
Media terapias previas 4

UM- IgHV (81%)
Del 17p (33%)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia

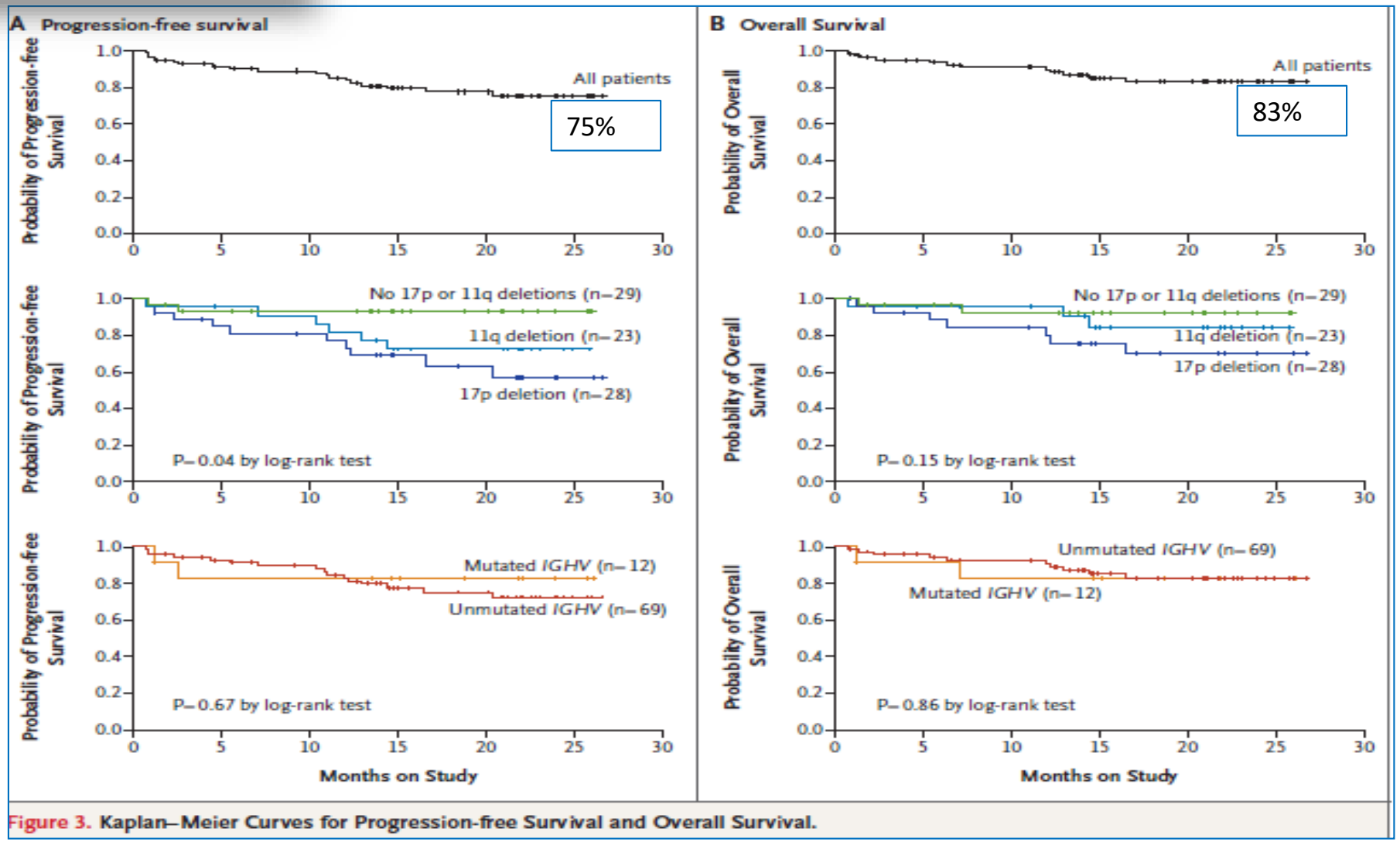


Figure 3. Kaplan–Meier Curves for Progression-free Survival and Overall Survival.

ORIGINAL ARTICLE

Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia

RESONATE TRIAL

Junio 2012-Abril 2013

Diseño Fase III

LLC /SLL R/R

>2 terapias

ECOG PS 0-1

Nodal disease CT

Ibrutinib 420mg vo/dia hasta PD o toxicidad (n=195)

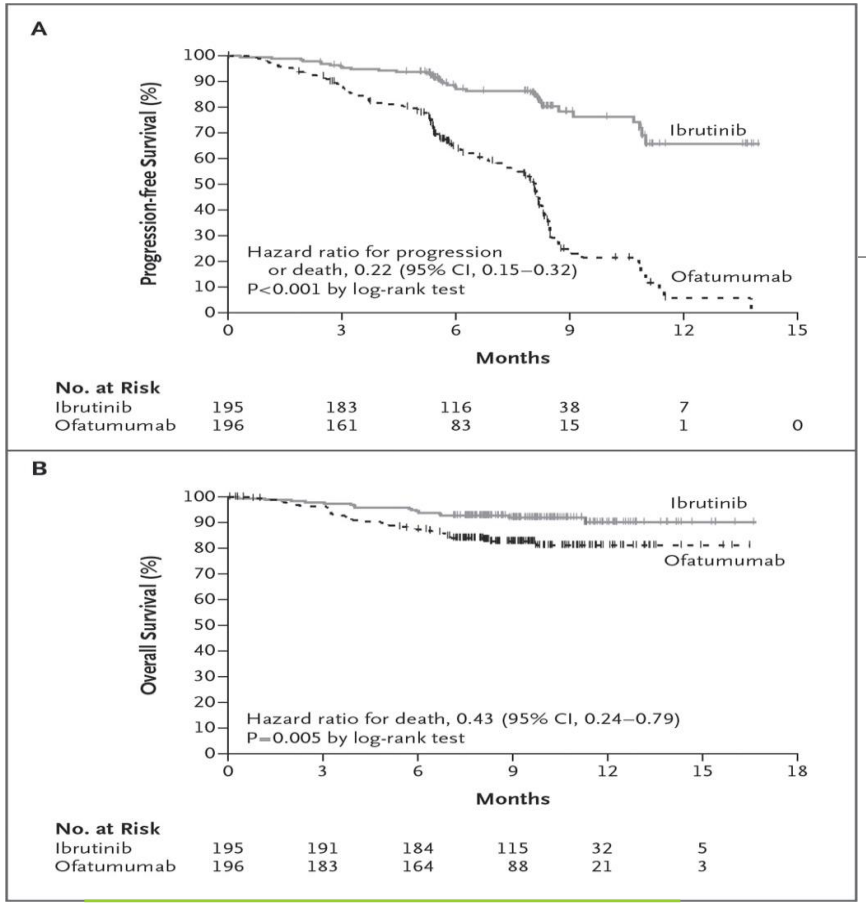
Ofatumumab IV 300mg inicial
Luego 2000mg /sem (n= 95)

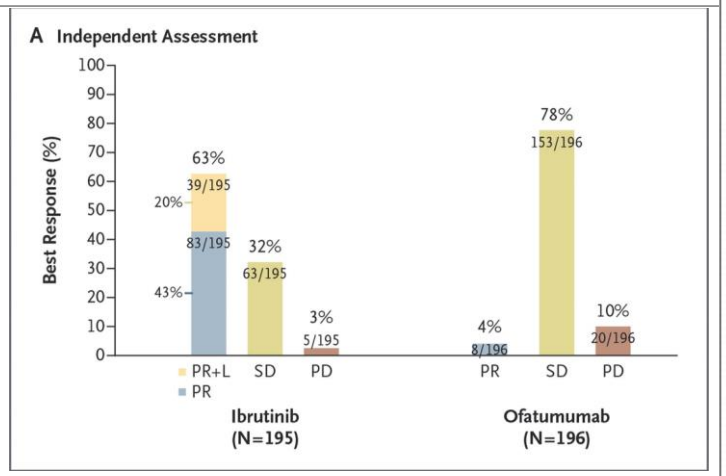
Crosover =122p
A ibrutinib 420mg /dia hasta PD

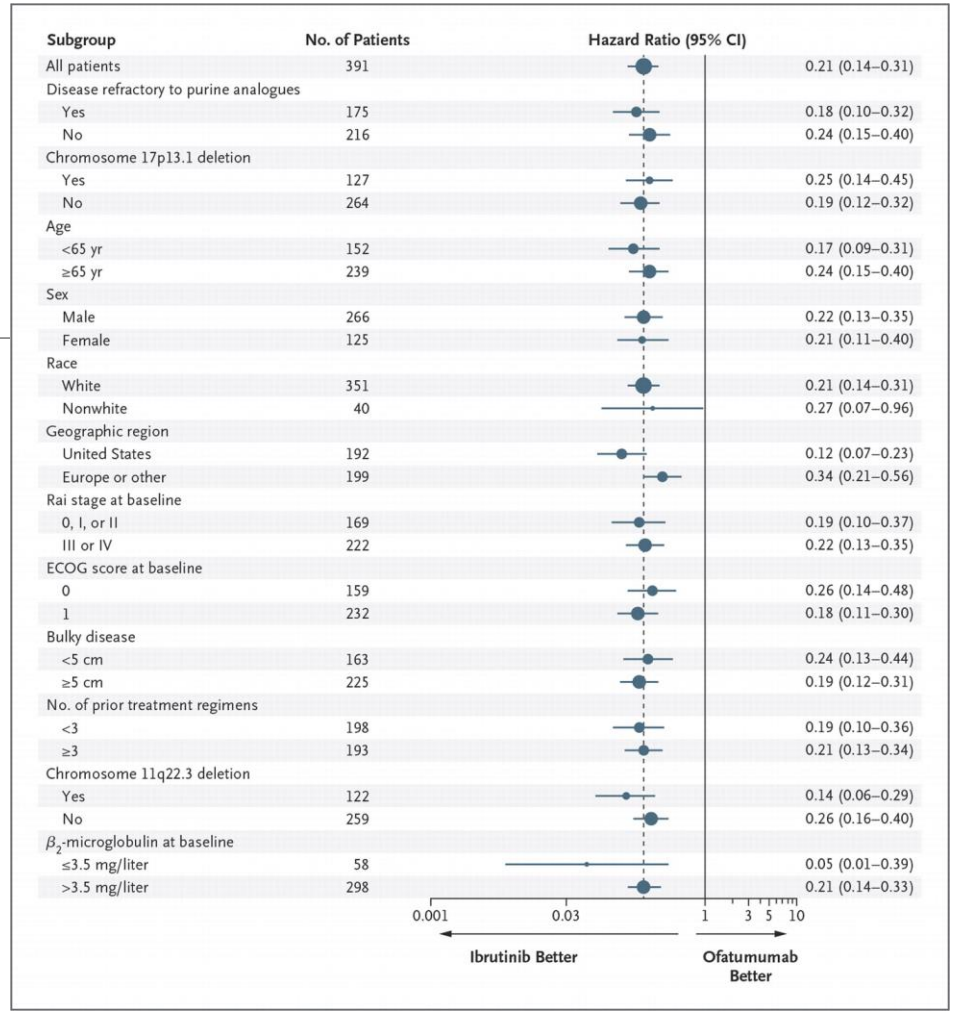
Pacientes:
391 P
M edad 70 años
66-70% masculino
30% Cl Crea <60ml/min
33% del 17p
45% R- analogos purina

1° Endpoint : PFS
2° EP: OS, ORR

Progression-free and Overall Survival.







	IBRUTINIB	OFATUMUMAB
PFS (m)	**NR**	8,1
OS 12 m	**90%**	81%
ORR	**43%**	4% (p<0,001)

Media seguimiento
9,4 meses

Aprobación FDA en LLC R/R

ORIGINAL ARTICLE

Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia

RESONATE -2 TRIAL

Marzo 2013

Diseño

Fase III

Multicentrico

LLC naive

>65 años

1:1

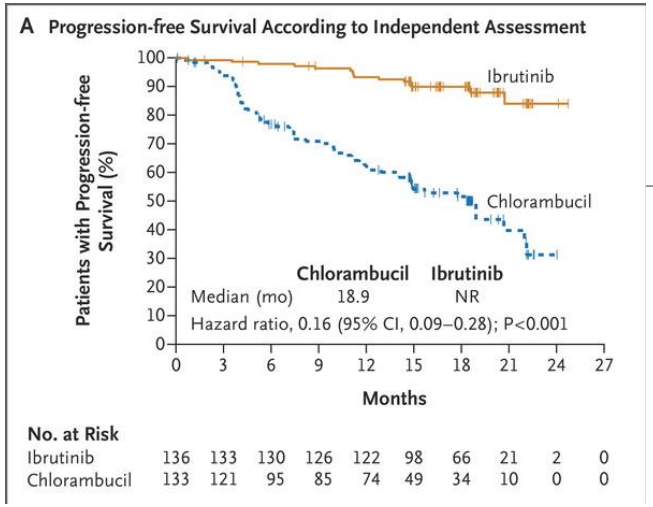
Ibrutinib
420mg vo/dia

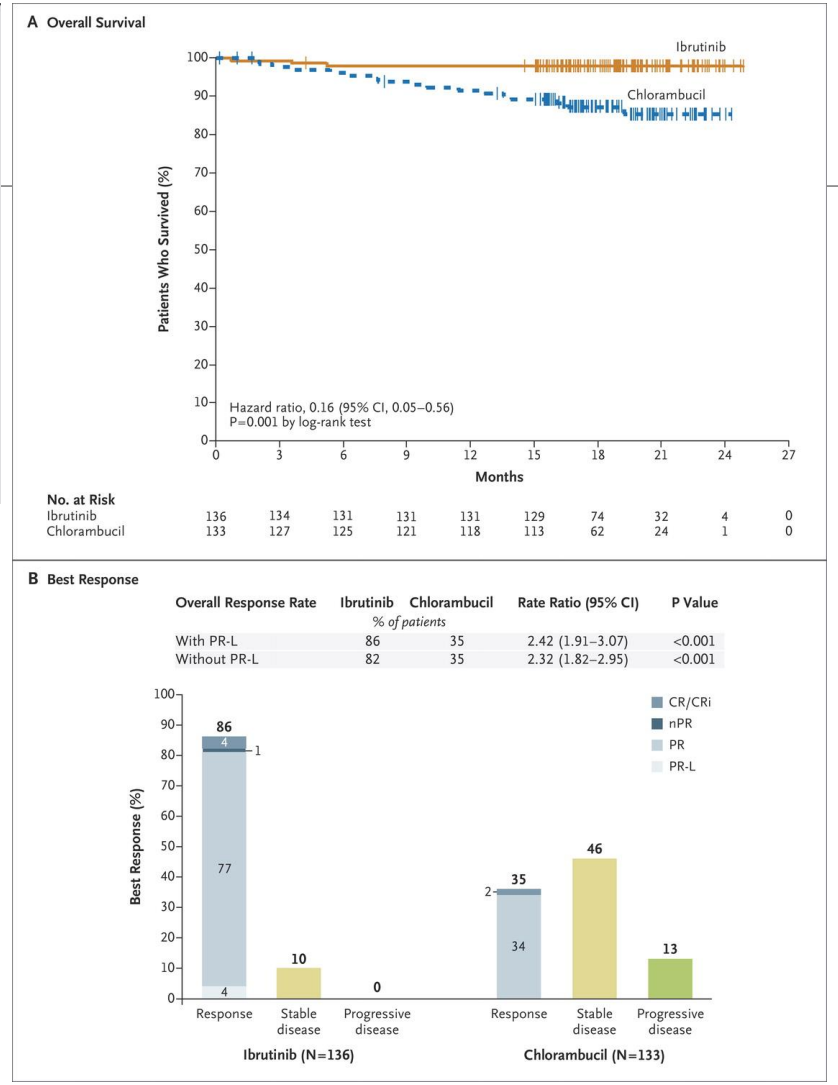
Clorambucil
0,5-0,8mg/kg x 15d/c28días
x12 ciclos

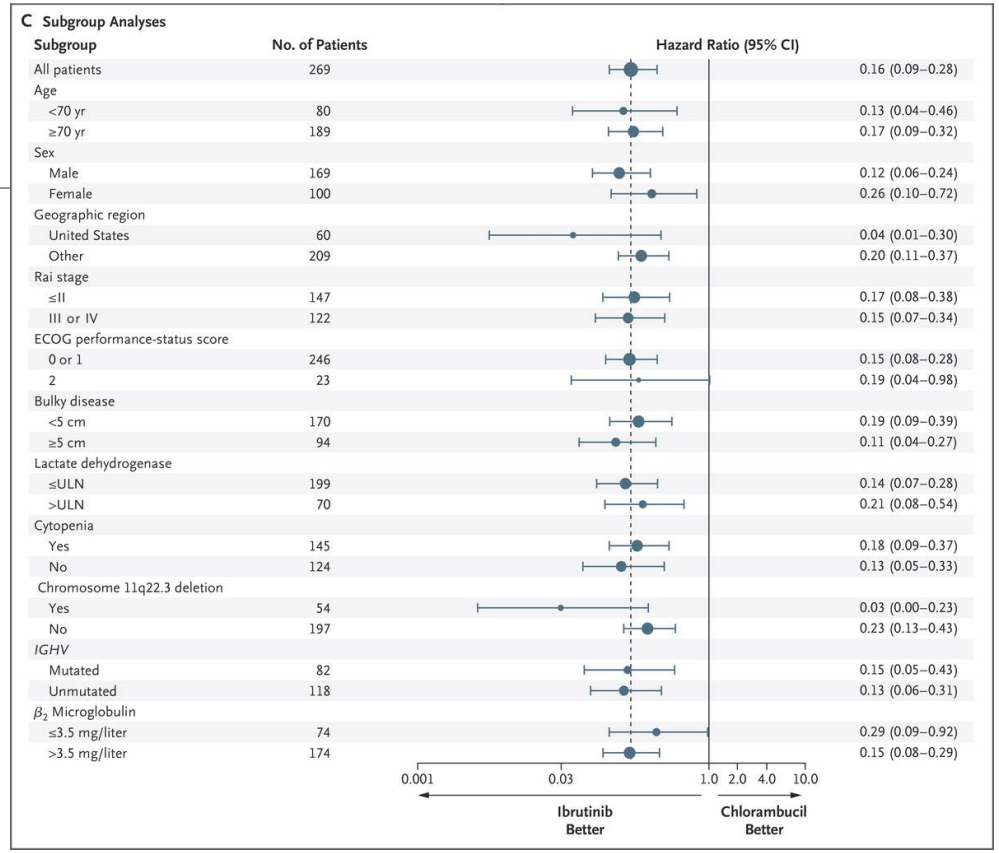
269 pacientes
Edad media 73 años
45% Rai III-IV
43% UM IGHV
20% del 11q

1° Endpoint : PFS
2° EP: OS, ORR, RH, seguridad

PFS y OS : Ibrutinib versus Chlorambucil.







	IBRUTINIB	Clorambucil
PFS (m)	NR	18,9
OS 24 m	98%	85%
ORR	82,4%	35,3% (p<0,001)

FDA Approval 2015 llc naive

Adverse Events and Duration of Treatment.

Table 2. Adverse Events and Duration of Treatment.

Variable	Ibrutinib (N=135)	Chlorambucil (N=132)
Duration of treatment — mo		
Median	17.4	7.1
Range	0.7–24.7	0.5–11.7
Most common adverse event of any grade — no. of patients (%)*		
Diarrhea	57 (42)	22 (17)
Fatigue	41 (30)	50 (38)
Cough	30 (22)	20 (15)
Nausea	30 (22)	52 (39)
Peripheral edema	25 (19)	12 (9)
Dry eye	23 (17)	6 (5)
Arthralgia	22 (16)	9 (7)
Neutropenia	21 (16)	30 (23)
Vomiting	18 (13)	27 (20)
Adverse event of grade ≥3 — no. of patients (%)†		
Neutropenia	14 (10)	24 (18)
Anemia	8 (6)	11 (8)
Hypertension	6 (4)	0
Pneumonia	5 (4)	2 (2)
Diarrhea	5 (4)	0
Maculopapular rash	4 (3)	2 (2)
Decreased platelet count	4 (3)	1 (1)
Abdominal pain	4 (3)	1 (1)
Hyponatremia	4 (3)	0
Thrombocytopenia	3 (2)	8 (6)
Febrile neutropenia	3 (2)	3 (2)
Upper respiratory tract infection	3 (2)	2 (2)
Pleural effusion	3 (2)	1 (1)
Cellulitis	3 (2)	0
Fatigue	1 (1)	7 (5)
Syncope	1 (1)	3 (2)
Hemolytic anemia	0	3 (2)
Serious adverse event — no. of patients (%)†		
Pneumonia	5 (4)	2 (2)
Basal-cell carcinoma	5 (4)	0
Hyponatremia	3 (2)	0
Pyrexia	1 (1)	5 (4)

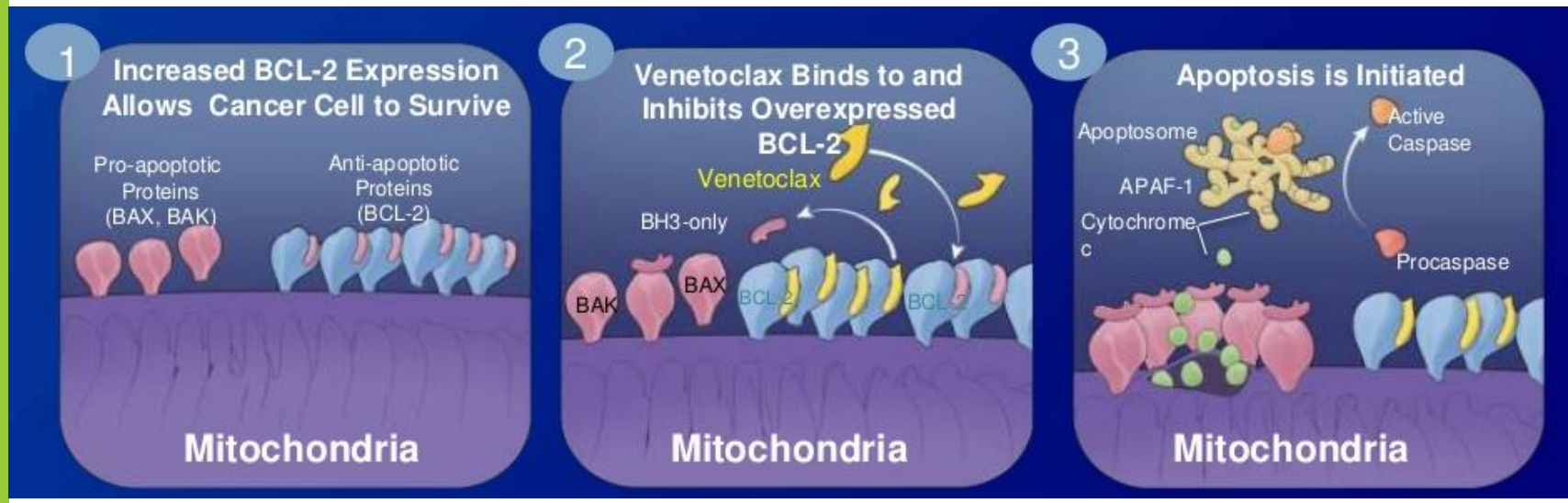
* The events listed are adverse events of any grade that occurred in at least 15% of patients in either treatment group and for which the frequency differed between treatment groups by at least 5%.

† The events listed are adverse events of grade 3 or higher or serious adverse events that occurred in at least 2% of the patients in either treatment group. One death due to toxic hepatitis in the chlorambucil group was considered by the investigator to be possibly related to the study treatment; no other deaths were considered by the investigator to be related to the study treatment.

Inhibidores BCL-2

Inhibidor selectivo BCL-2, oral

Induce apoptosis directa células LCC independiente p53

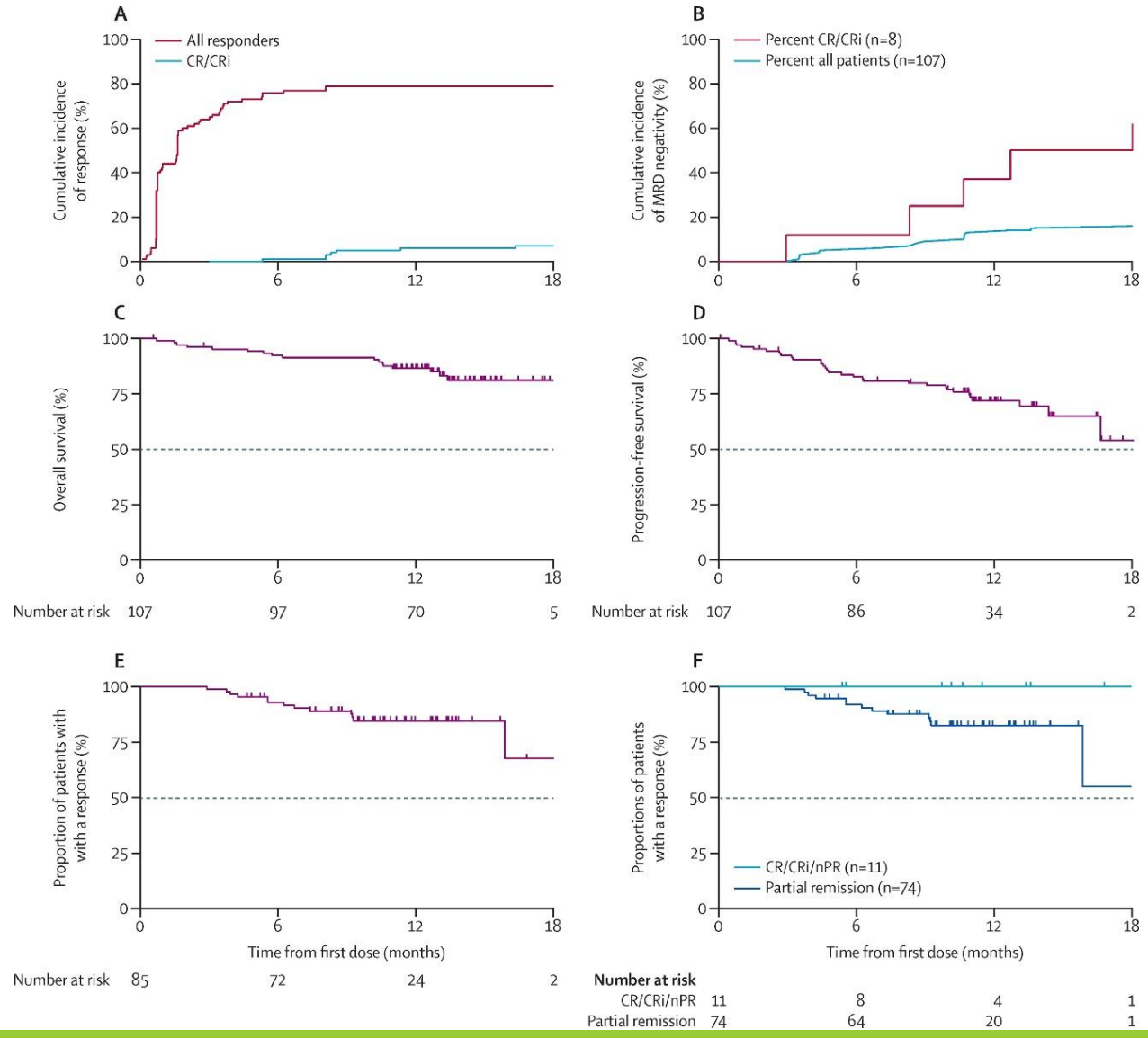


Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study S. Stilgenbauer, et al

Table 2.
Best response

	Independent review committee assessment (n=107)	Investigator assessment (n=107)
Overall response	85 (79%)	79 (74%)
Complete remission or complete remission with incomplete recovery of blood counts[-]	8 (8%)	17 (16%)
Nodular partial remission	3 (3%)	4 (4%)
Partial remission	74 (69%)	58 (54%)
Non-responder[†]	22 (21%)	..
Stable disease	..	24 (22%)
Disease progression	..	2 (2%)
Incomplete data[‡]	..	2 (2%)

Data are n (%).



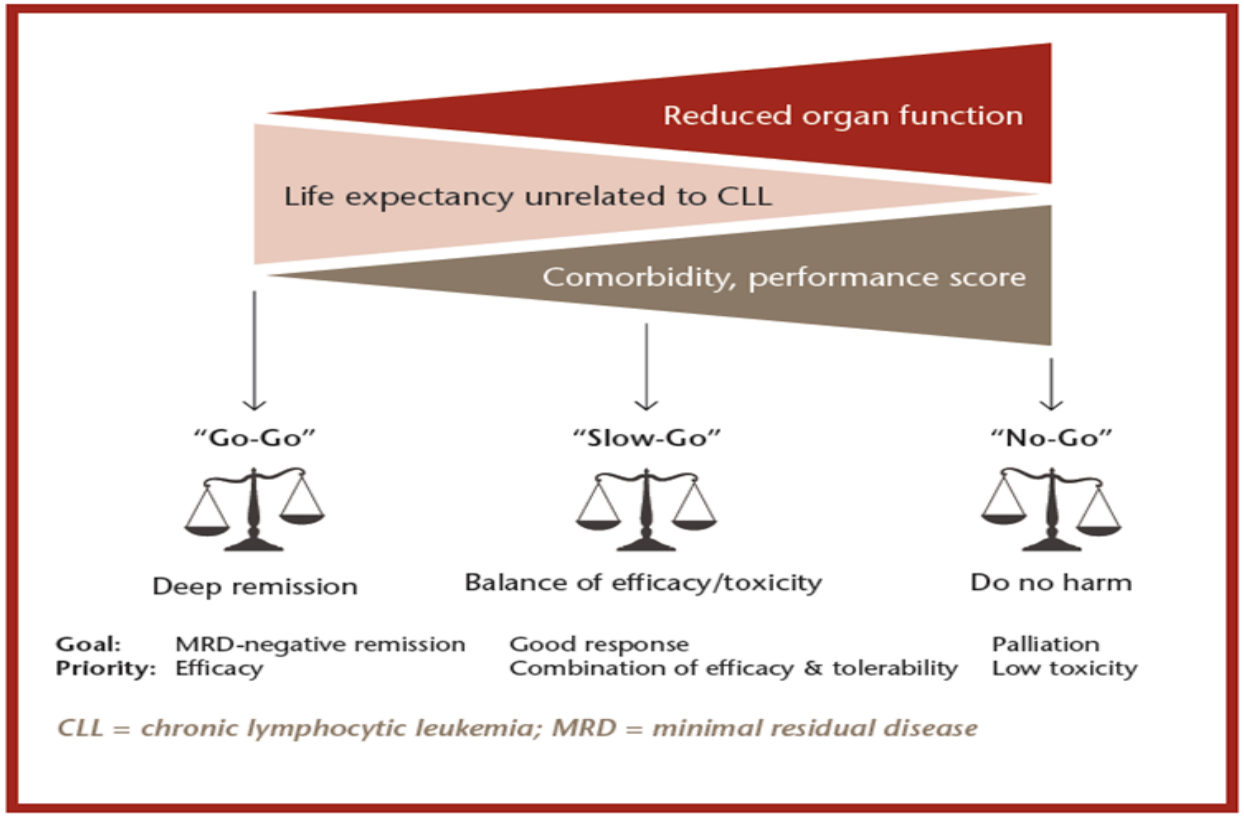
The Lancet Oncology 2016 17, 768-778DOI: (10.1016/S1470-2045(16)30019-5)

Table 2. Treatment Options for Relapsed/Refractory Therapy

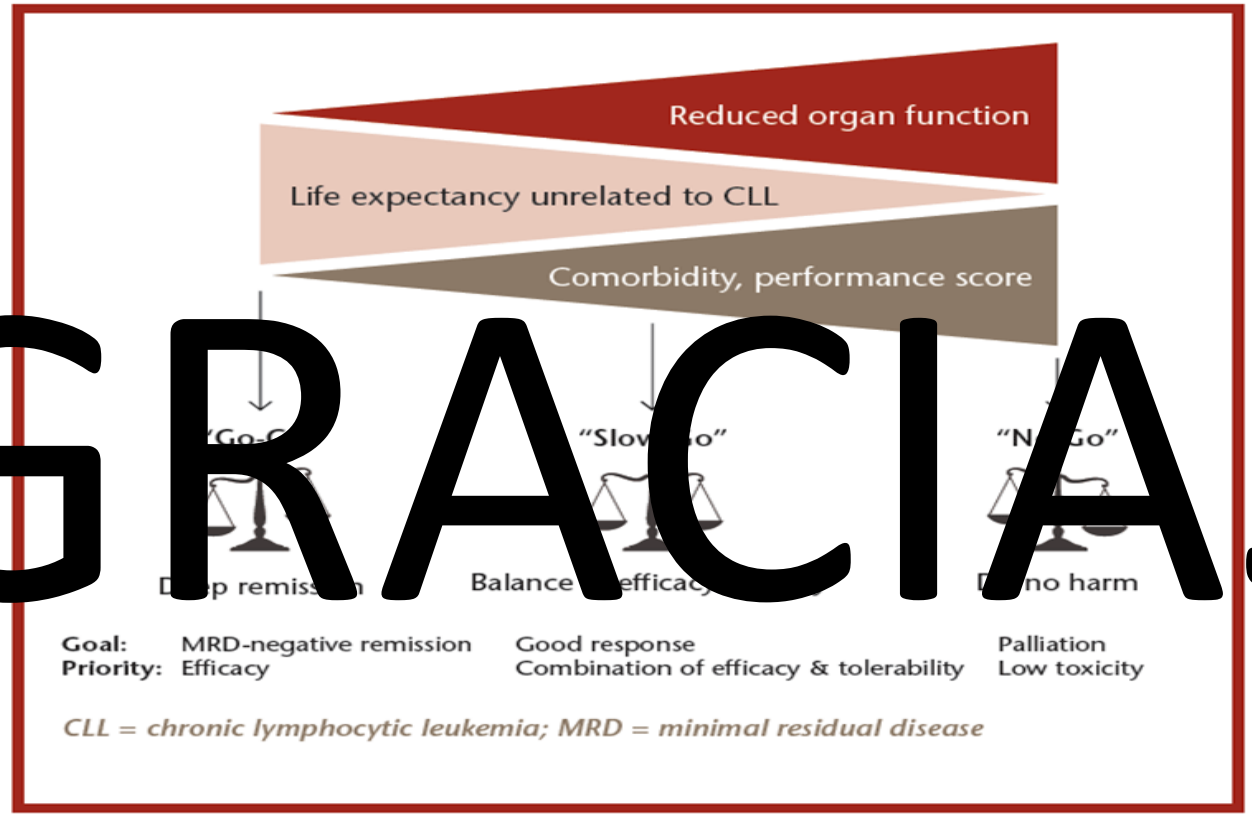
Trial	Regimen	N	Median Age	Median Follow-up	ORR	PFS	OS
RESONATE[19]							
	Ibrutinib	195	67 y ≥70 y (40%)	16 mo	90%	Not reached	85% at 18 mo
	Ofatumumab	196			25%	8.1 mo	78% at 18 mo
RESONATE-17[20]							
	Ibrutinib	144	64 y	27.6 mo	83%	63% at 24 mo	75% at 24 mo
PCYC-1102[14]							
	Ibrutinib	101	68 y ≥70 y (43%)	5 y	86%	43% at 5 y	
Furman et al[21]							
	Idelalisib + rituximab	110	71 y ≥65 y (78%)	24 wk	81%	93% at 24 wk	92% at 12 mo
	Chlorambucil	110			13%	46% at 24 wk	80% at 12 mo
Stilgenbauer et al[25]							
	Venetoclax	107	67 y ≥65 y (57%)	12.1 mo	79.4%	72% at 12 mo	86.7% at 12 mo

Abbreviations: ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Objetivos de tratamiento



Objetivos de tratamiento



GRACIAS