

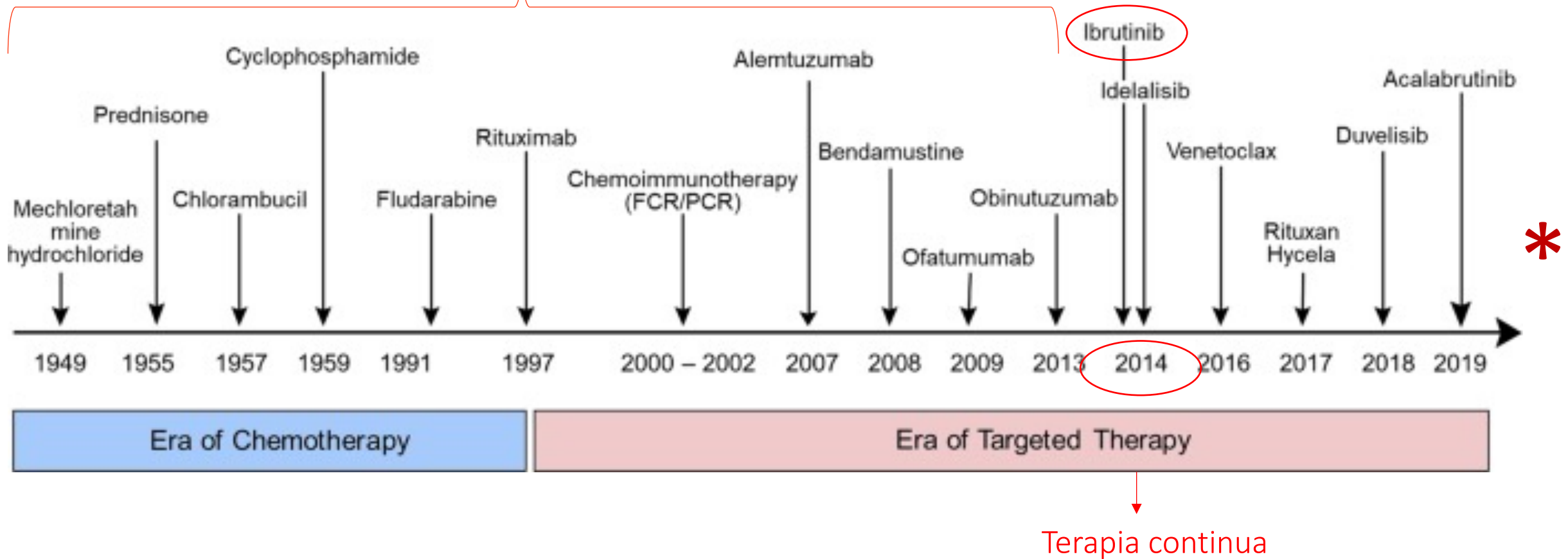


Leucemia linfóide crónica.
Tratamiento finito, siempre?

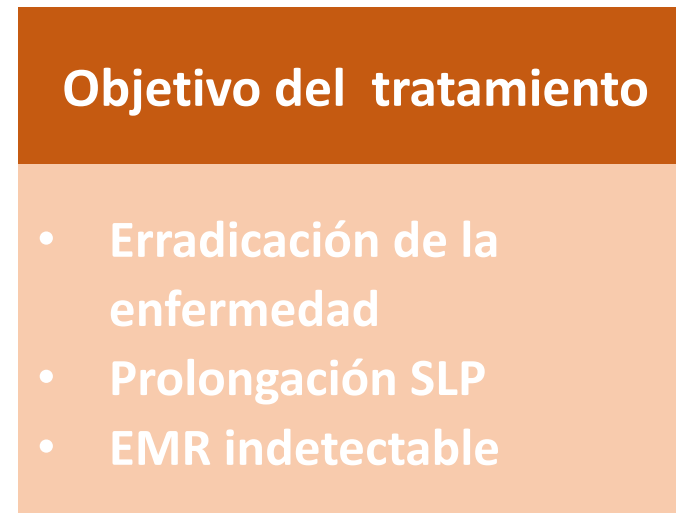
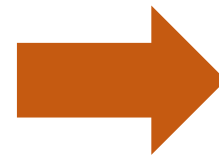
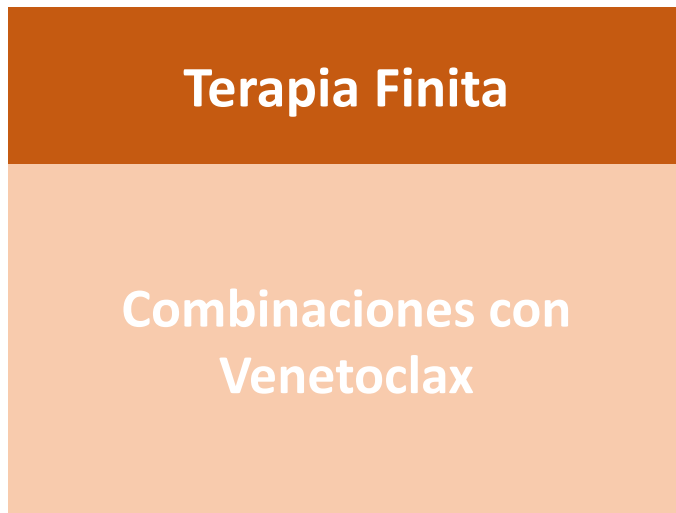
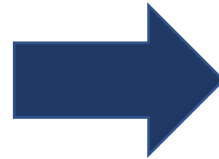
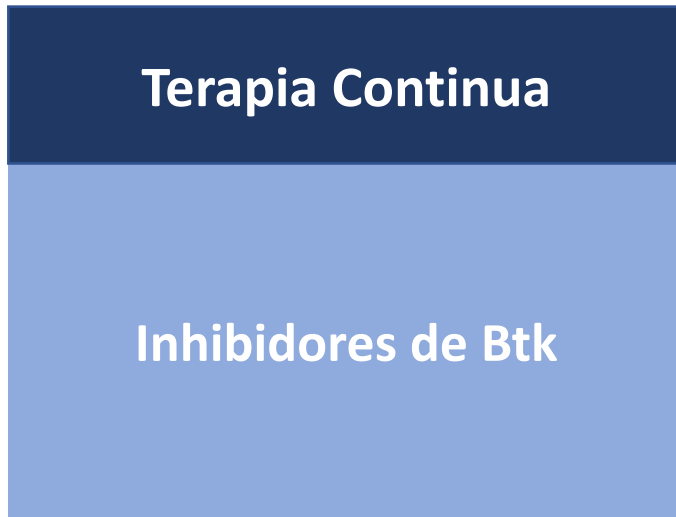
Dra. Victoria Irigoín
Montevideo-Uruguay

Evolución en el tratamiento de la LLC

Tratamiento finito



* Zanubrutinib/ Pirtobrutinib/ Nemtabrutinib/ CART. Bi terapia con agentes dirigidos/ tripletes



Tratamiento finito



Al momento de definir el tratamiento

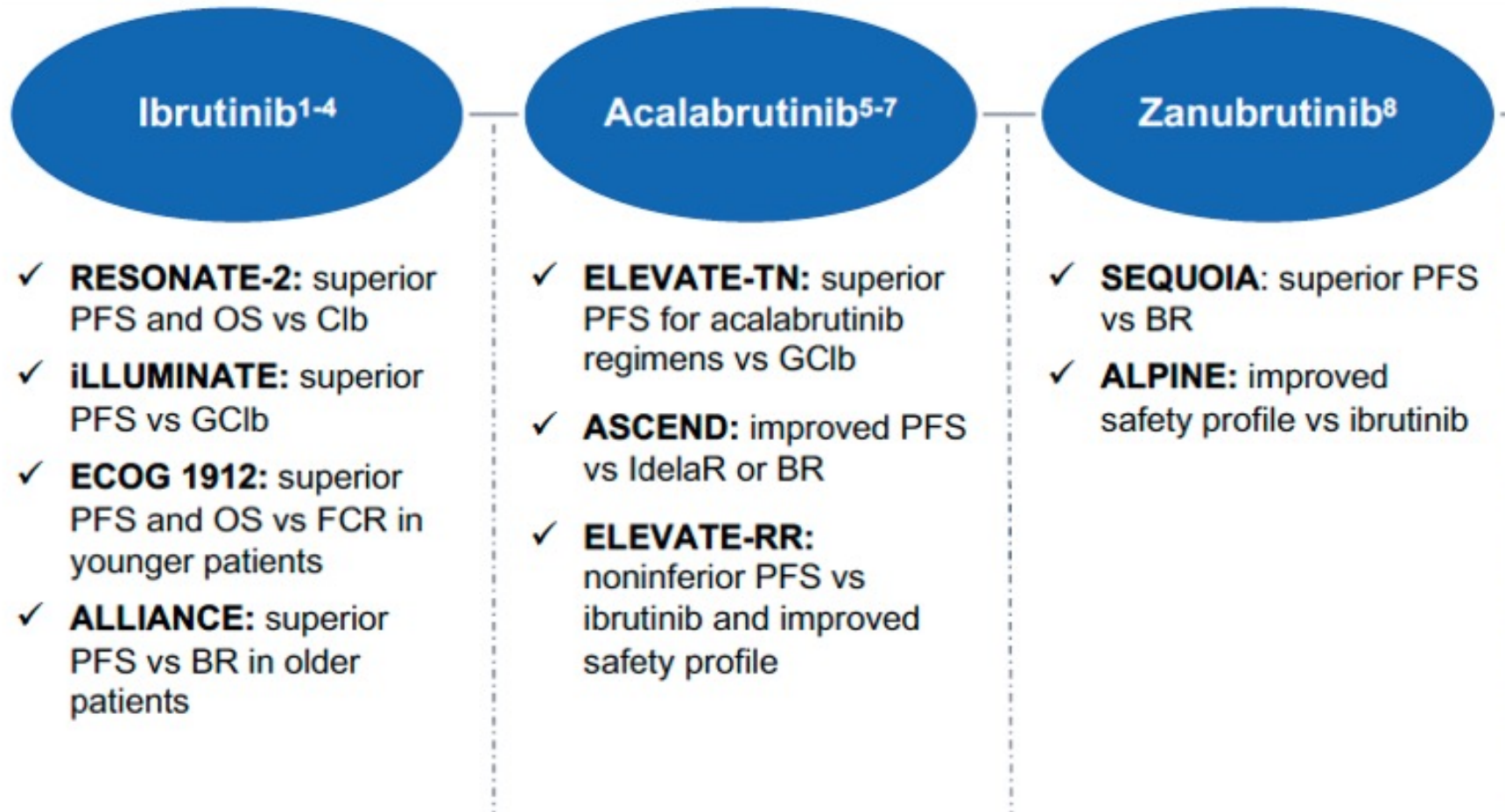
Edad
Comorbilidades
Medicación
adicional

Riesgo de la
enfermedad



Deseos del paciente
Estilo de vida
Practicidad/ comodidad
Soporte familiar
Cercanía a centro de atención
Calidad de vida

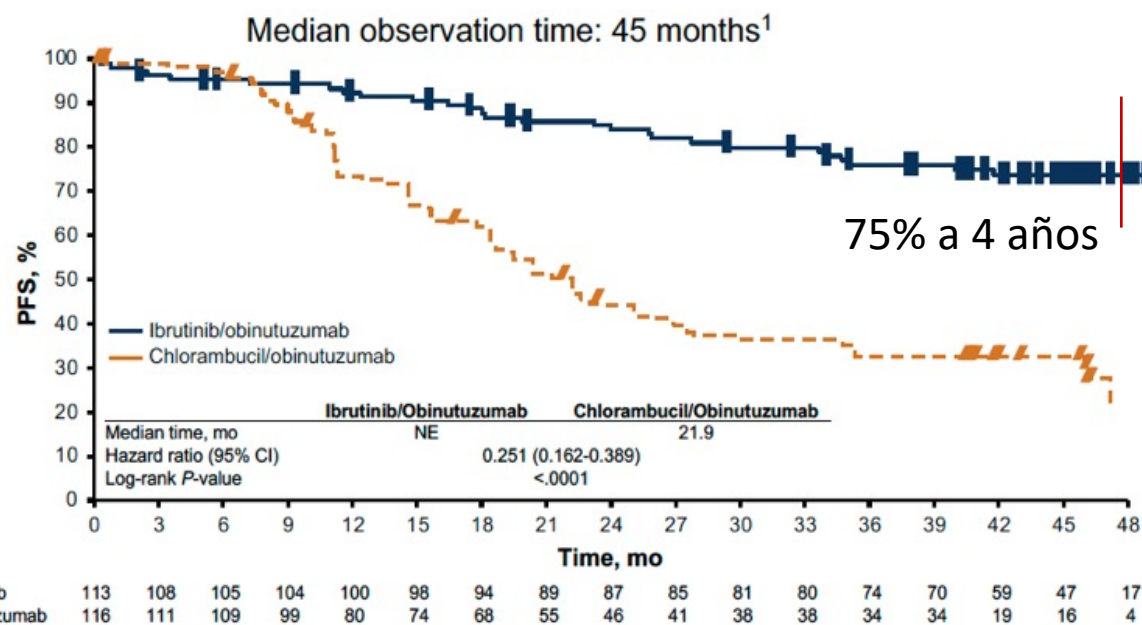
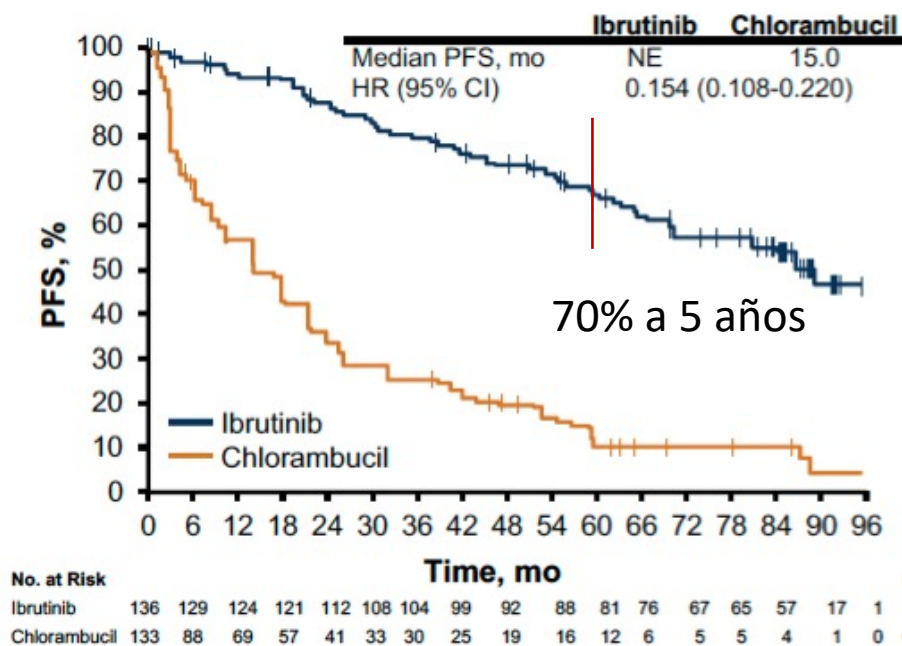
Principales ensayos Fase III de inh BTK en tto continuo en 1L y R/R



1. Shanafelt TD et al. N Engl J Med. 2019;381:432-443. 2. Woyach JA et al. N Engl J Med. 2018;379:2517-2528. 3. Moreno C et al. Lancet Oncol. 2019;20:43-56. 4. Burger JA et al. Leukemia. 2020;34:787-798. 5. Sharman JP et al. Lancet. 2020;395:1278-1291. 6. Ghia P et al. J Clin Oncol. 2020;38:2849-2861. 7. Byrd JC et al. J Clin Oncol. 2021;39:3441-3452. 8. Tam C et al. ASH 2021. Abstract 396.

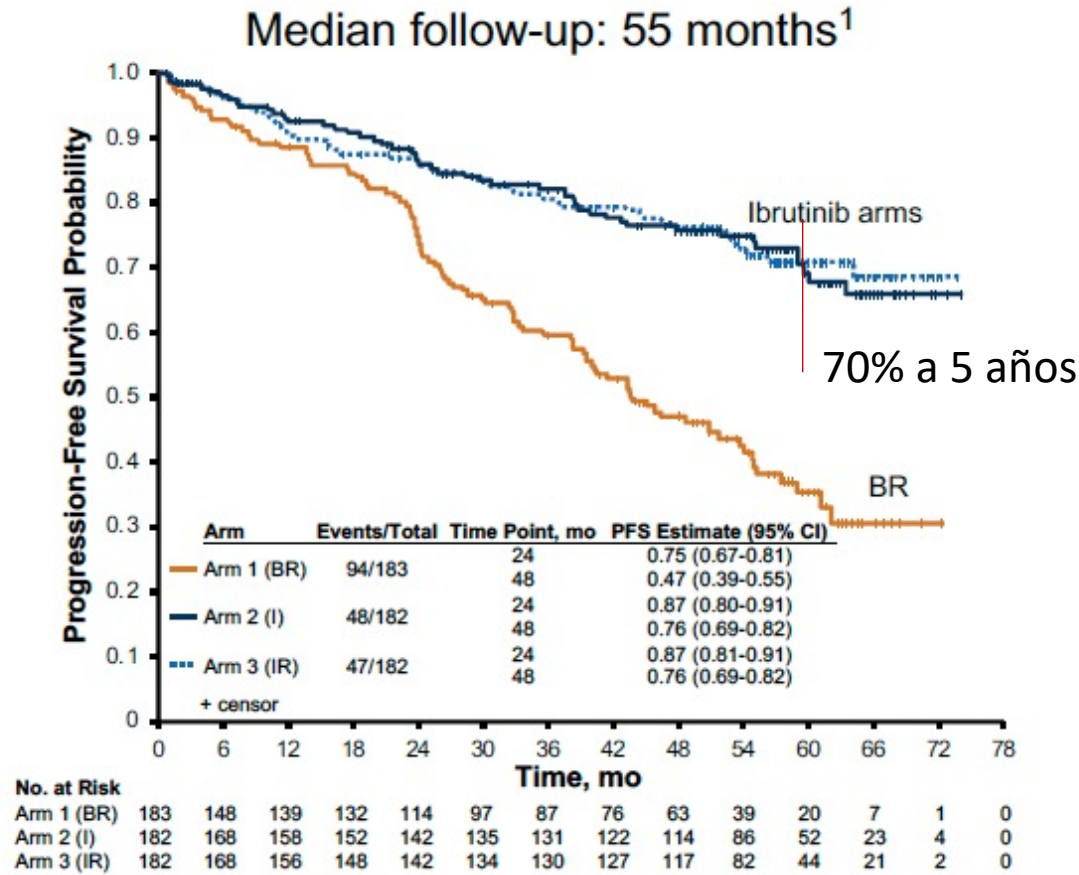
RESONATE-2: Ibrutinib vs Clorambucil en > 65 a Seguimiento a 7 años

ILLUMINATE: Ibrutinib/ Obinutuzumab vs Clorambucil/ Ob en > 65 a

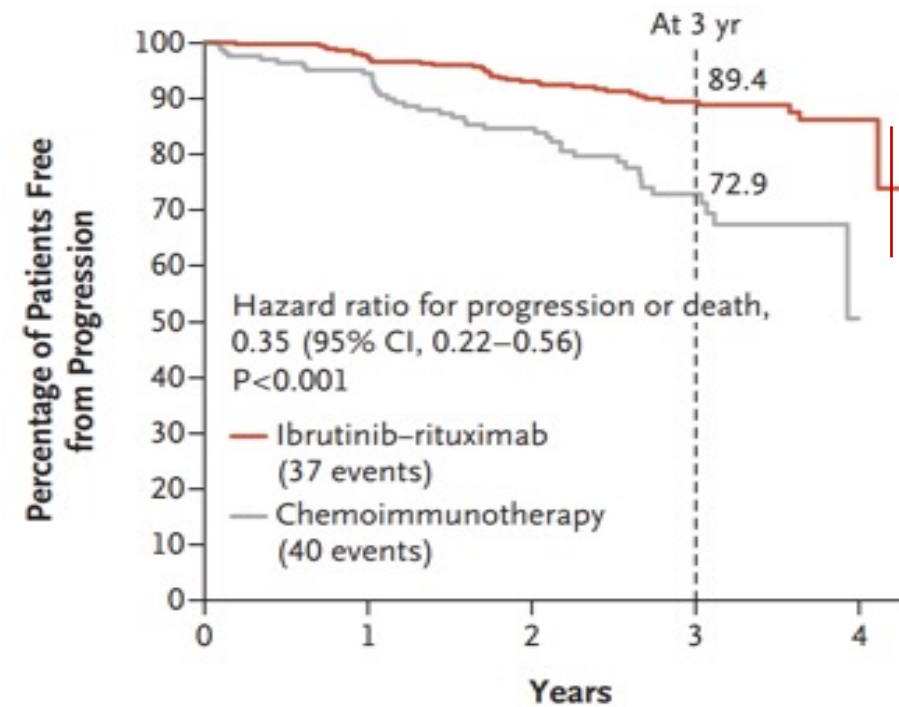


Alliance: Ibrutinib +/-Rituximab vs Bendamustina-Rituximab

ECOG 1912 Ibrutinib + R vs FCR en < 70 años



PFS among all patients



k	0	1	2	3	4
Ibrutinib-rituximab	354	339	298	148	16
Chemoimmunotherapy	175	147	112	50	0

Inconvenientes con los inh BTK

- Efectos adversos
- Resistencia
- Costo de tratamientos prolongados

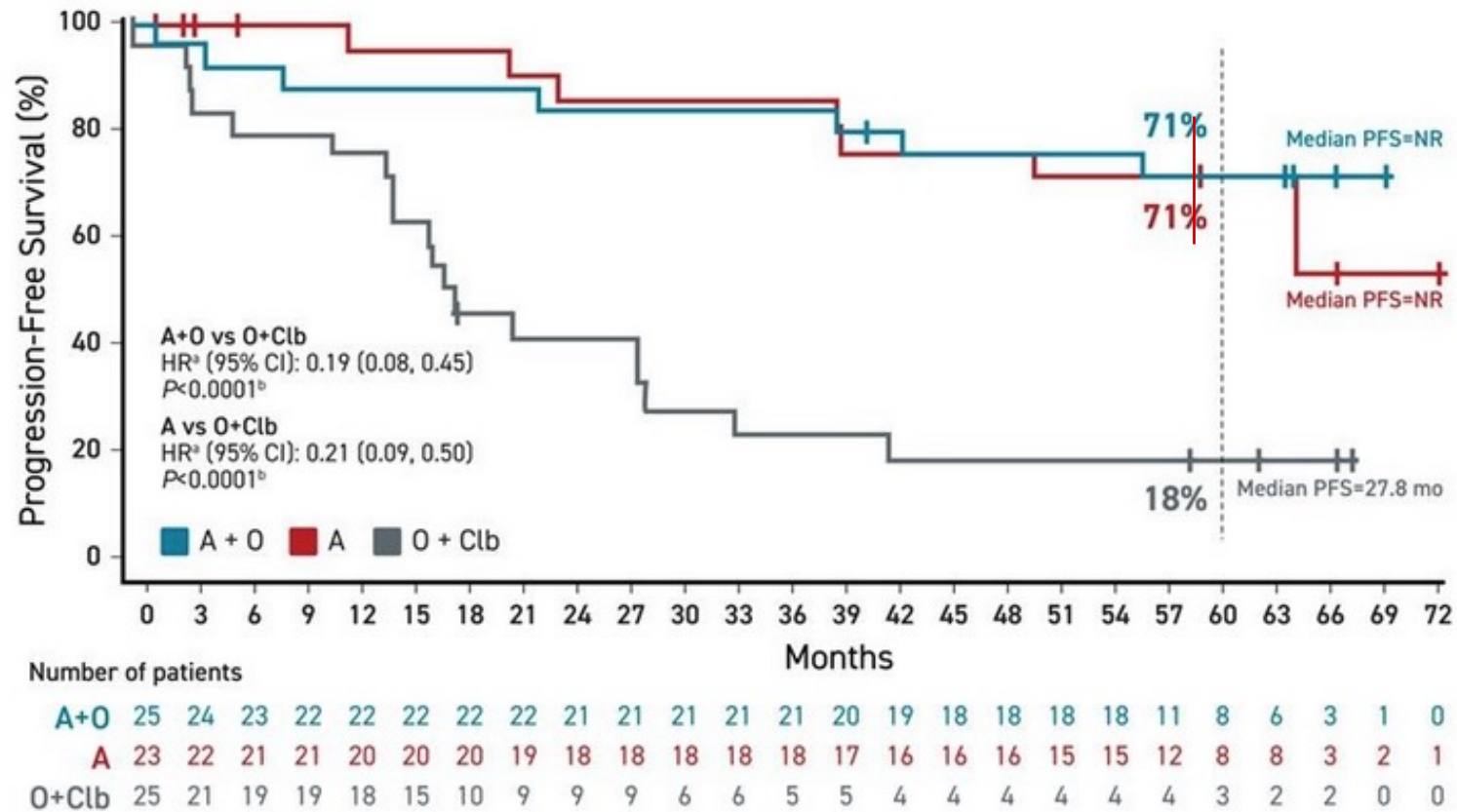


Toxicidad de inhibidores de BTK

AE ≥ CTC Grade 3	Ibrutinib		
	E1912 (I + Rituximab) ¹	RESONATE-2 ²	ALLIANCE ³
Median observation time, mo	70	60	38
Hypertension, %	11.4	8	29
Cardiac, %	7.7	N/A	N/A
AF, %	4.5	5	9
Neutropenia, %	28.4	13	15
Infection, %	11.4	12 ^a	19

Shanafelt TD et al. Blood. 2022;140:112-120. 2. Barr PM et al. Blood Adv. 2022;6:3440-3450. 3. Woyach JA et al. N Engl J Med. 2018;379:2517-2528. 4. Sharman JP et al. Lancet. 2020;395:1278-1291. 5. Tam C et al. ASH 2021. Abstract 396.

ELEVATE-TN: Acalabrutinib +/- Obinutuzumab vs Cl /Obinutuzumab



SEQUOIA: Zanubrutinib Prolonga la SLP vs BR en 1L

Mediana seguimiento 44 m

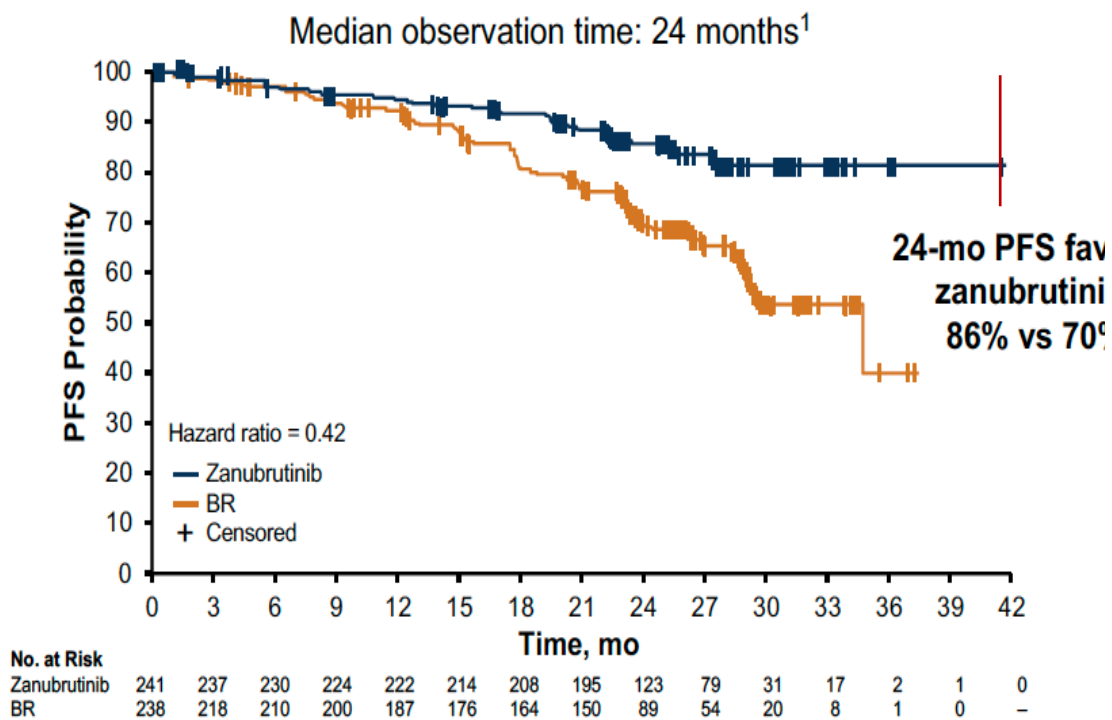
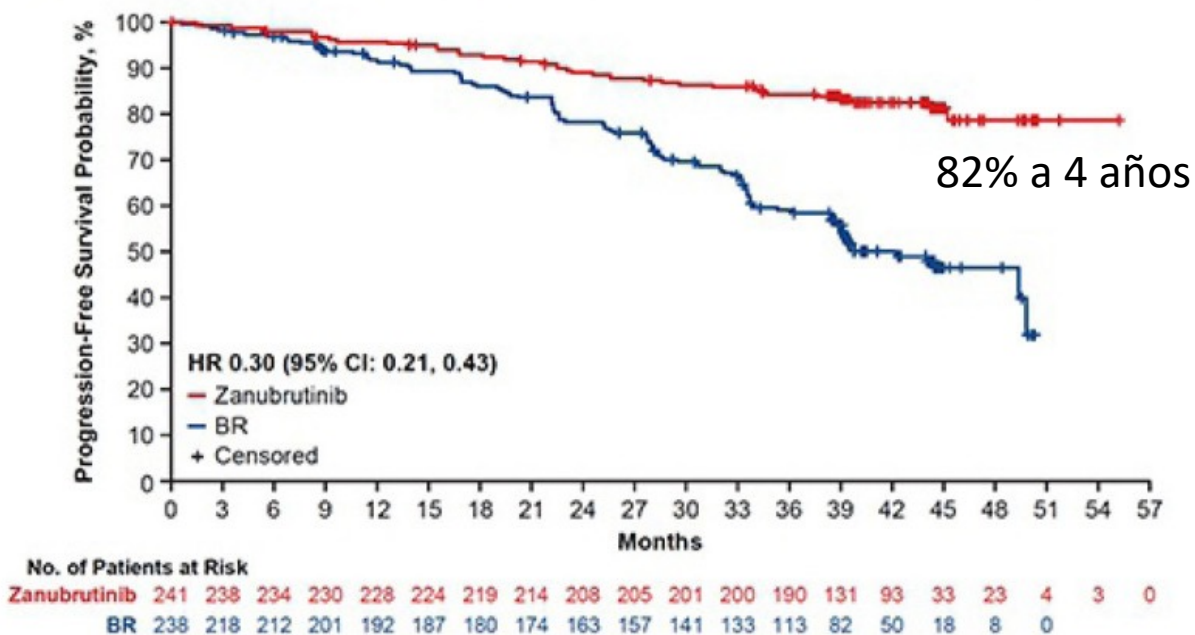
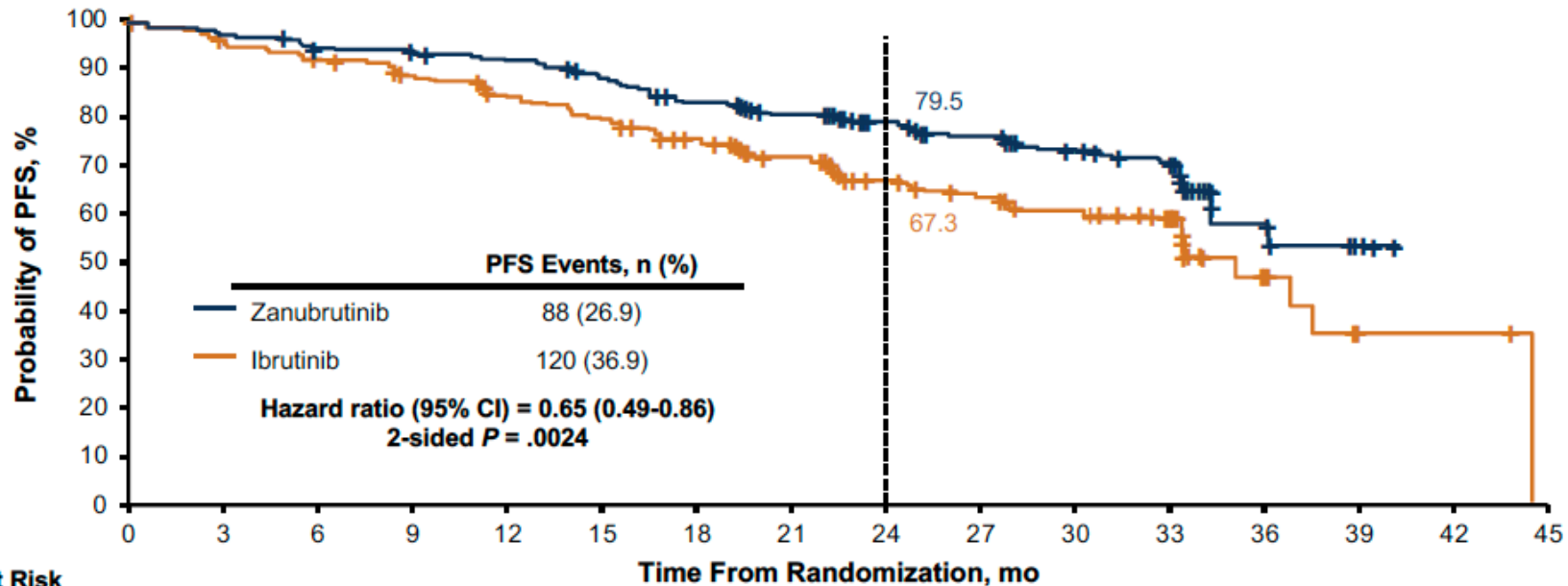


Figure: Progression-Free Survival by Investigator Assessment



ALPINE. Zanubrutinib vs Ibrutinib en R/R

After a median follow-up of 29.6 months, improved PFS with zanubrutinib



No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
Zanubrutinib	327	315	304	301	294	280	263	226	172	161	125	113	14	2	0	-
Ibrutinib	325	305	293	277	260	246	228	191	133	123	98	87	9	2	2	0

AF/Flutter

	Incidence, %
Zanubrutinib	2.5
Ibrutinib	10.1
2-sided P = .0014	

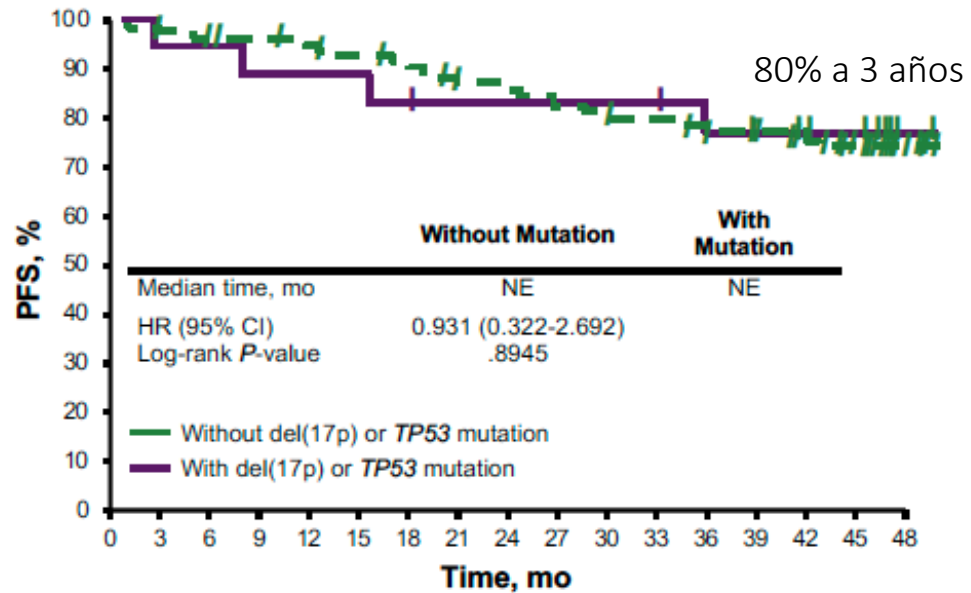
HTA sin diferencia

Inhibidores de BTK en monoterapia, en tratamiento continuo son efectivos en tratamiento de LLC en 1L en pacientes unfit y fit con > SLP que QT convencional.

Qué pasa con los pacientes de alto riesgo??

Ibrutinib en pacientes con del(17p)/mut TP53

iLLUMINATE

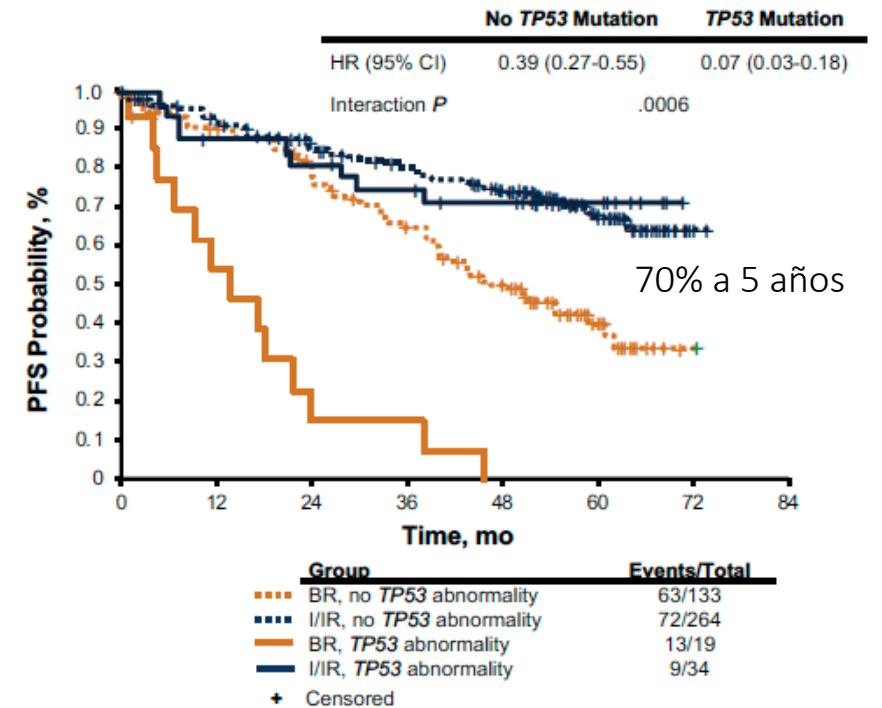


No. at Risk

Without mutation	95	91	88	88	84	83	80	75	73	71	67	67	62	60	52	41	15
With mutation	18	17	17	16	16	15	14	14	14	14	14	13	12	10	7	6	2

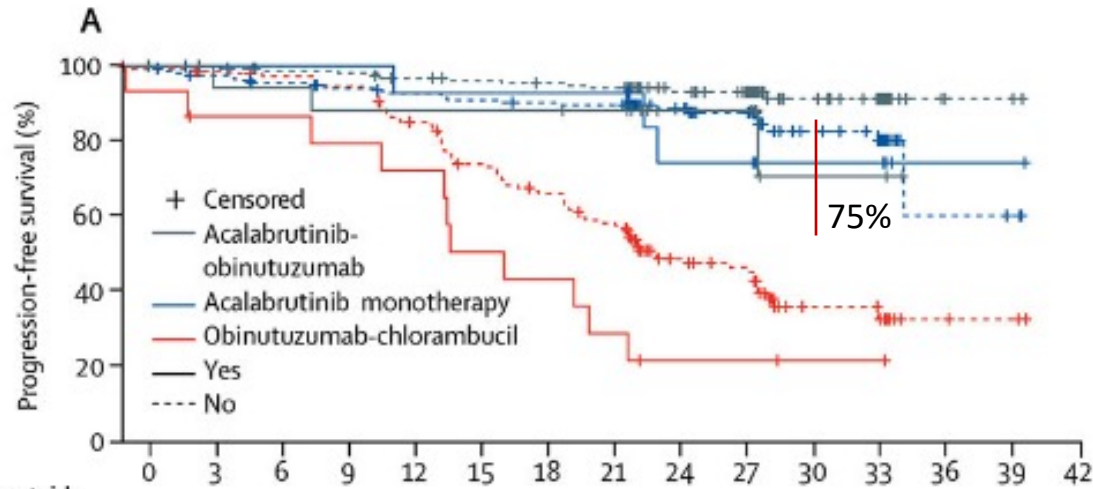
ALLIANCE

Ibrutinib ± R vs BR



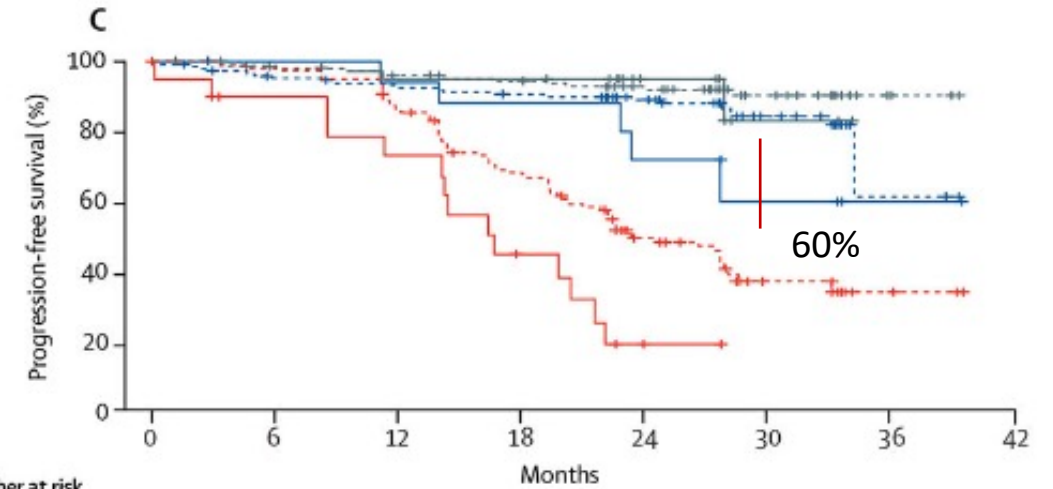
ELEVATE-TN. Subanálisis de pacientes de alto riesgo

Del 17p



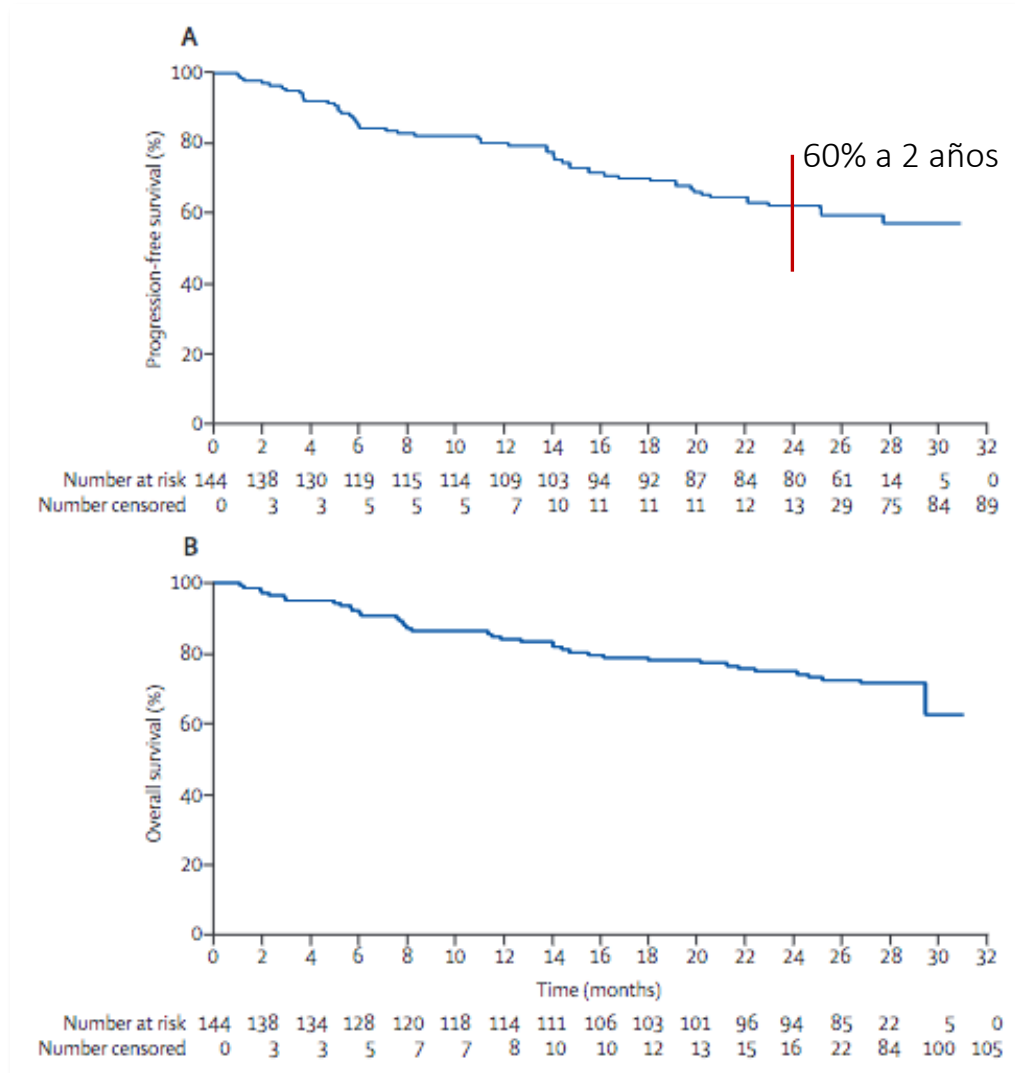
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
Number at risk (number censored)															
Acalabrutinib-obinutuzumab															
Yes	17	17	16	15	15	15	15	14	8	8	2	2	0		
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(7)	(7)	(12)	(12)	(14)		
No	162	159	154	153	148	145	144	141	101	96	44	39	4	2	
	(0)	(3)	(7)	(7)	(9)	(11)	(11)	(12)	(51)	(56)	(107)	(112)	(147)	(149)	
Acalabrutinib monotherapy															
Yes	16	14	14	14	13	13	13	13	8	8	5	5	1	1	
	(0)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(5)	(5)	(8)	(8)	(12)	(12)	
No	163	152	147	143	140	137	135	134	95	86	38	35	3	2	
	(0)	(7)	(9)	(11)	(12)	(12)	(13)	(13)	(51)	(59)	(104)	(107)	(137)	(138)	
Obinutuzumab-chlorambucil															
Yes	16	12	12	11	10	7	6	4	2	2	1	1	0		
	(0)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(3)	(3)	(4)	(4)	(5)		
No	160	149	144	139	125	105	95	81	43	38	12	12	3	2	
	(0)	(10)	(13)	(13)	(14)	(17)	(18)	(19)	(46)	(49)	(68)	(68)	(76)	(77)	

Mutacion p53

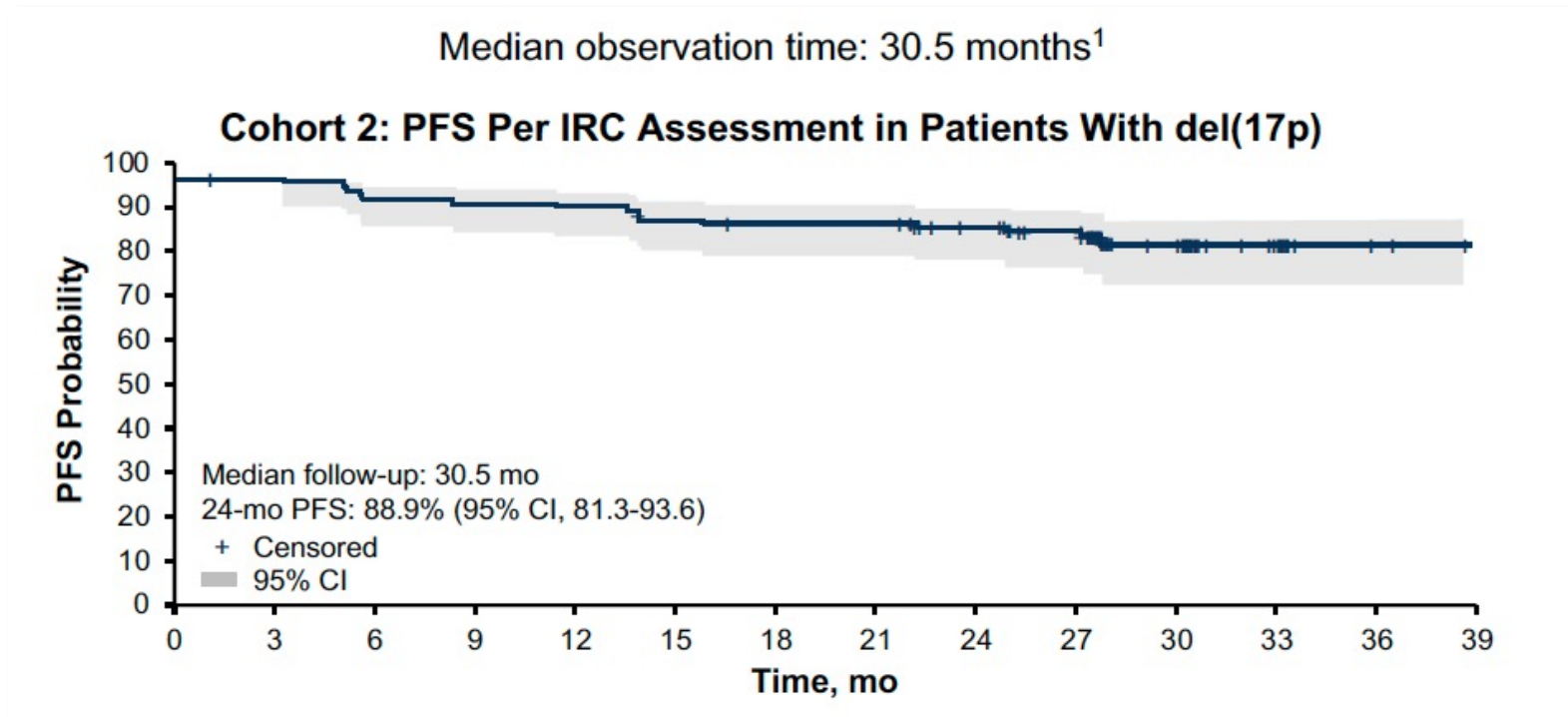


	0	6	12	18	24	30	36	42
Number at risk (number censored)								
Acalabrutinib-obinutuzumab								
Yes	21	20	19	19	12	5	0	
	(0)	(1)	(1)	(1)	(8)	(14)	(19)	
No	158	150	144	140	97	41	4	
	(0)	(6)	(8)	(10)	(50)	(105)	(142)	
Acalabrutinib monotherapy								
Yes	19	17	16	15	9	5	1	
	(0)	(2)	(2)	(2)	(6)	(9)	(13)	
No	160	144	137	133	94	38	3	
	(0)	(9)	(12)	(13)	(50)	(103)	(136)	
Obinutuzumab-chlorambucil								
Yes	21	16	13	7	1	0		
	(0)	(3)	(3)	(4)	(6)	(7)		
No	155	140	122	94	44	13	3	
	(0)	(12)	(13)	(16)	(43)	(65)	(74)	

RESONATE-17. Ibrutinib en pacientes con LLC R/R con del17p

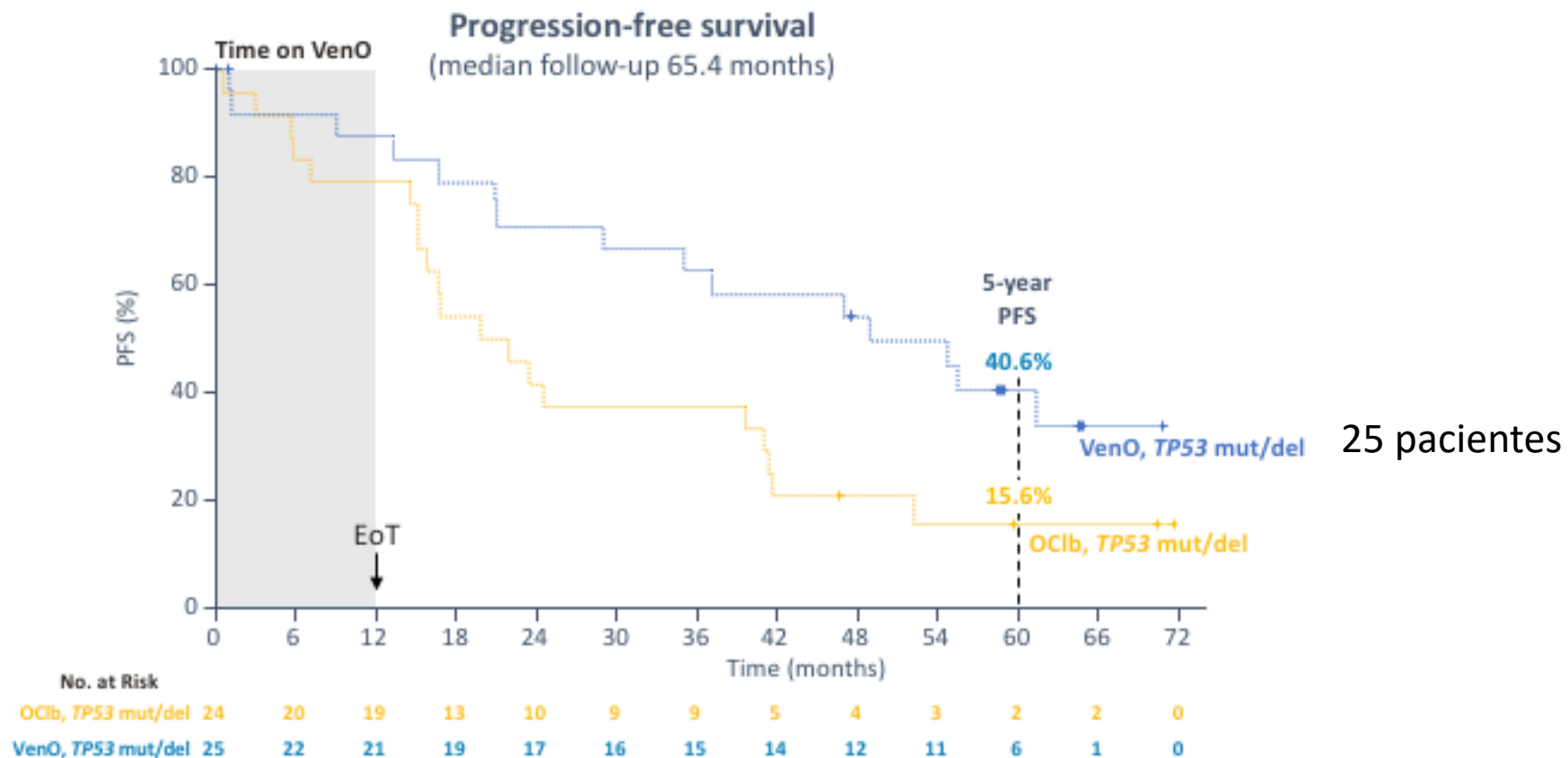


SEQUIOIA

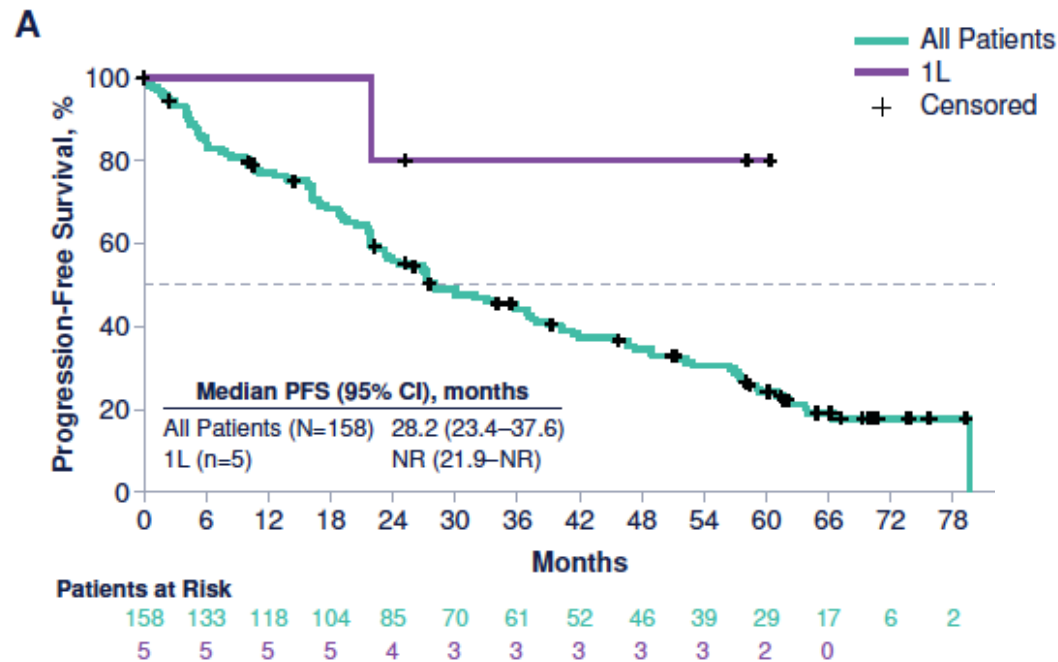


Mediana seguimiento 48 meses SLP estimada a 42 meses 79%

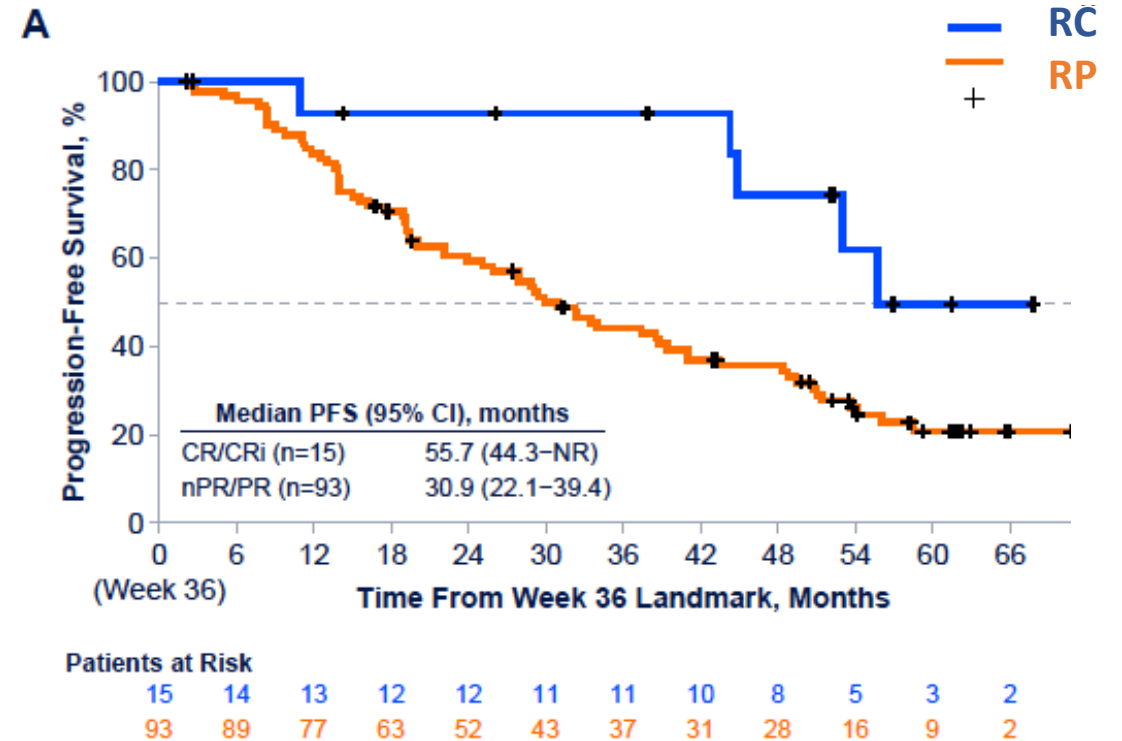
CLL-14. Subanálisis de pacientes con mut p53



Tratamiento continuo sólo con BTKi ?

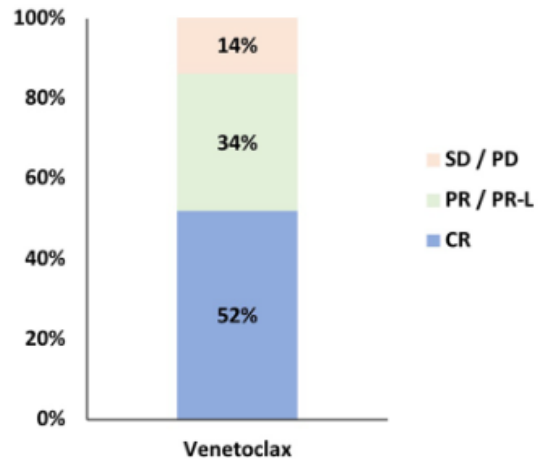


Ven monoterapia

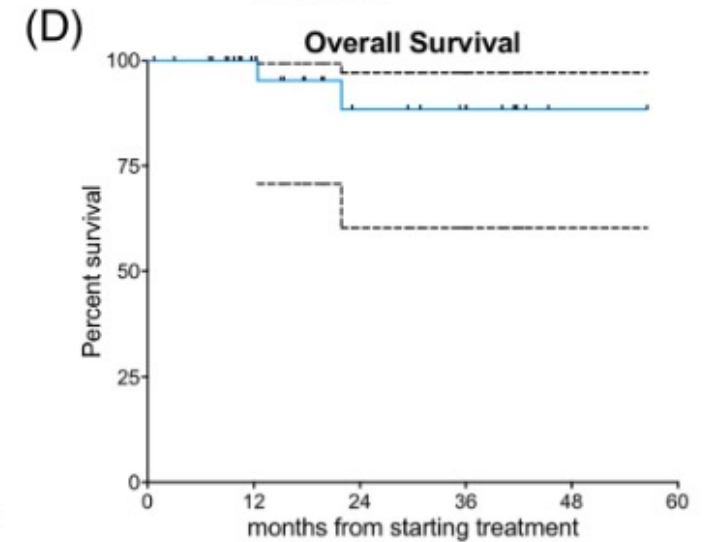
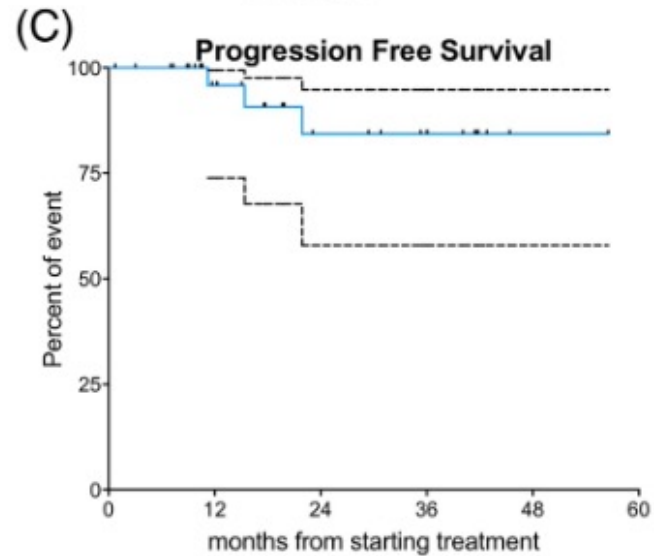
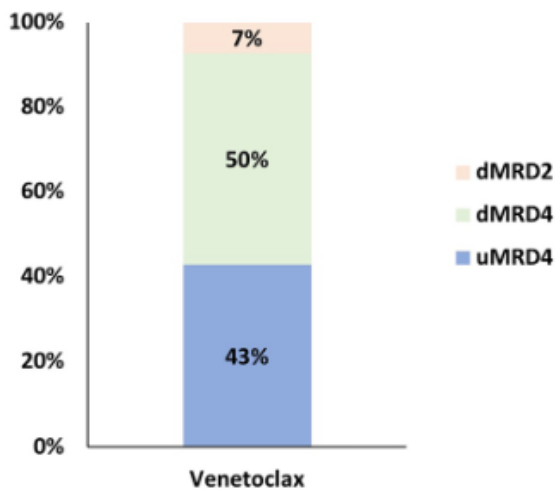


Venetoclax monoterapia. Tratamiento continuo en 1L con del 17p

(A) Overall response rates



(B) Measurable residual disease



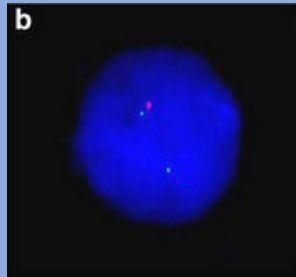
CONCLUSIONES

Terapia finita SI, pero no en todos los pacientes

- Identificar pacientes "óptimos" para terapias finitas o terapias continuas
- Definir el objetivo del tratamiento

Edad
Comorbilidades
Medicación
adicional

Riesgo citogenético



Deseos del paciente
Estilo de vida
Practicidad/ comodidad
Soporte familiar
Cercanía a centro de atención
Calidad de vida

- Accesibilidad
- Costo

Sin del17p

FIRST-LINE THERAPY ^e		
Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
<ul style="list-style-type: none"> • Acalabrutinib^{f,g,*} ± obinutuzumab (category 1) • Venetoclax^{f,h} + obinutuzumab (category 1) • Zanubrutinib^{f,g,*} (category 1) 	<ul style="list-style-type: none"> • Ibrutinib^{f,g,i,*} (category 1) • Ibrutinib^{f,g,*} + obinutuzumab (category 2B) • Ibrutinib^{f,g,*} + rituximab^j (category 2B) • Ibrutinib^{f,g,*} + venetoclax^{f,h} (category 2B) 	<ul style="list-style-type: none"> • Consider for IGHV-mutated CLL in patients aged <65 y without significant comorbidities <ul style="list-style-type: none"> ▶ FCR (fludarabine, cyclophosphamide, rituximab)^{k,l} • Consider when BTKi and venetoclax are not available or contraindicated or rapid disease debulking needed <ul style="list-style-type: none"> ▶ Bendamustine^m + anti-CD20 mAb^{n,o} ▶ Obinutuzumab ± chlorambucil^p ▶ High-dose methylprednisolone (HDMP) + anti-CD20 mAbⁿ (category 2B; category 3 for patients <65 y without significant comorbidities)

Con del 17p

FIRST-LINE THERAPY ^e		
Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
<ul style="list-style-type: none"> • Acalabrutinib^{f,g,*} ± obinutuzumab (category 1) • Venetoclax^{f,h} + obinutuzumab (category 1) • Zanubrutinib^{f,g,*} (category 1) 	<ul style="list-style-type: none"> • Ibrutinib^{f,g,i,*} (category 1) • Ibrutinib^{f,g,*} + obinutuzumab (category 2B) • Ibrutinib^{f,g,*} + rituximab^j (category 2B) • Ibrutinib^{f,g,*} + venetoclax^{f,h} (category 2B) 	<ul style="list-style-type: none"> • Consider for IGHV-mutated CLL in patients aged <65 y without significant comorbidities <ul style="list-style-type: none"> ▶ FCR (fludarabine, cyclophosphamide, rituximab)^{k,l} • Consider when BTKi and venetoclax are not available or contraindicated or rapid disease debulking needed <ul style="list-style-type: none"> ▶ Bendamustine^m + anti-CD20 mAb^{n,o} ▶ Obinutuzumab ± chlorambucil^p ▶ High-dose methylprednisolone (HDMP) + anti-CD20 mAbⁿ (category 2B; category 3 for patients <65 y without significant comorbidities)

Stage	Del (17p) or TP53 mut	Fitness	IGHV	Therapy
Inactive disease, Binet A-B, Rai 0-II	Irrelevant	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III-IV	Yes	Irrelevant	Irrelevant	Ibrutinib / acalabrutinib ^a or venetoclax + obinutuzumab or idelalisib-rituximab (if contraindications for other options)
	No	Go go	M	FCR (BR > 65 years) or ibrutinib / acalabrutinib ^a
			U	Ibrutinib / acalabrutinib ^a or venetoclax + obinutuzumab or FCR (BR > 65 years)
		Slow go	M	Venetoclax + obinutuzumab or ibrutinib / acalabrutinib ^{a,b} or chlorambucil-obinutuzumab
U	Venetoclax + obinutuzumab or ibrutinib / acalabrutinib ^{a,b} or chlorambucil-obinutuzumab			

Muchas gracias