

# Rol de anti-CD20 en el tratamiento de LLC en primera línea

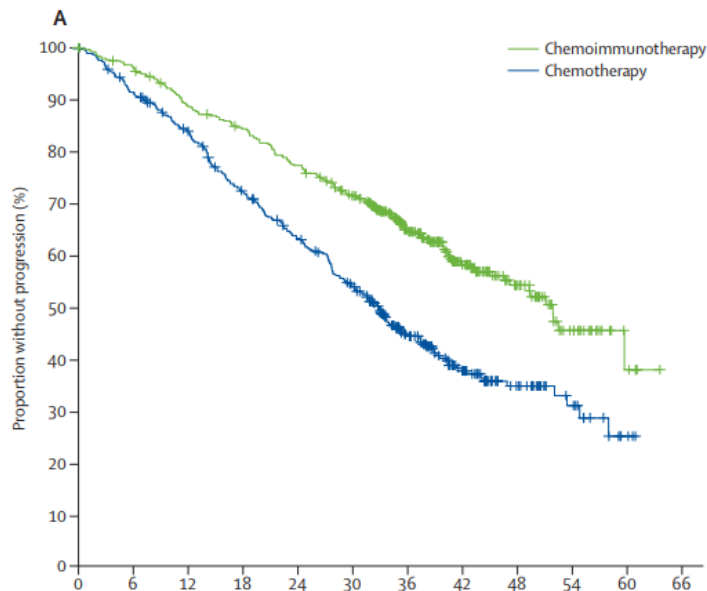
MIGUEL A PAVLOVSKY

Director Medico y Cientifico

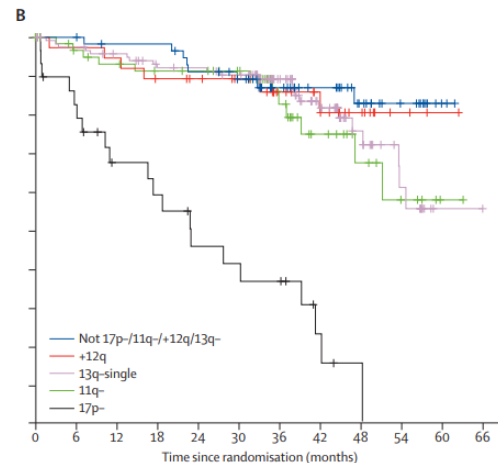
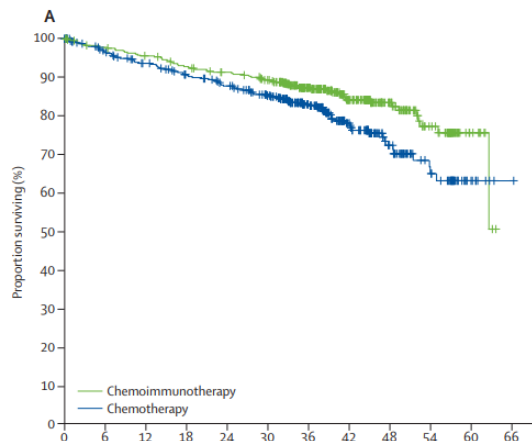
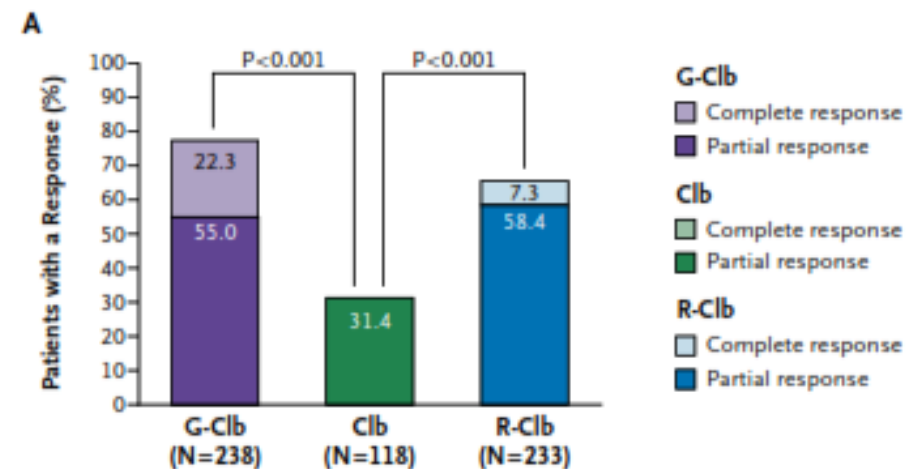
FUNDALEU

# Superioridad de quimio-antiCD20 vs quimio en estudios randomizados (CLL8 and CLL11)

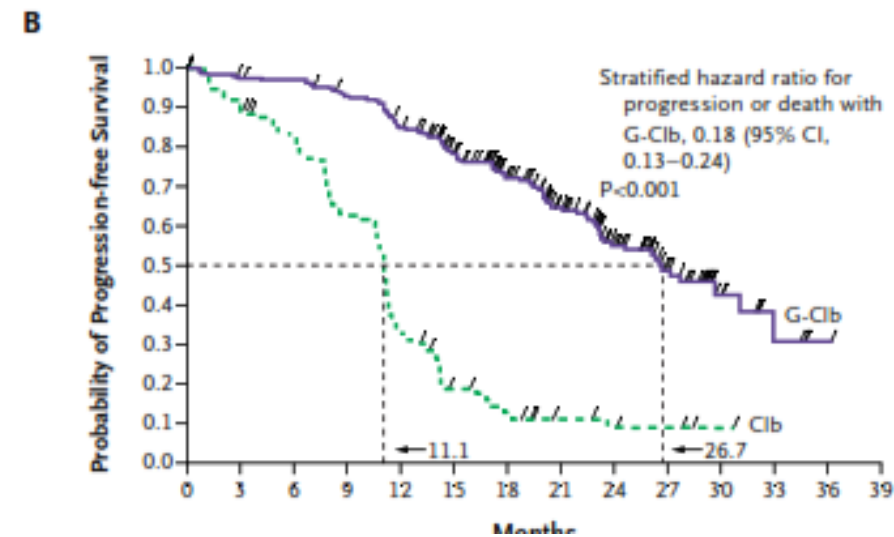
CLL8



CLL11



Number at risk	0	6	12	18	24	30	36	42	48	54	60	66
Chemoimmunotherapy	408	383	359	247	88							
Chemotherapy	409	357	320	207	66							



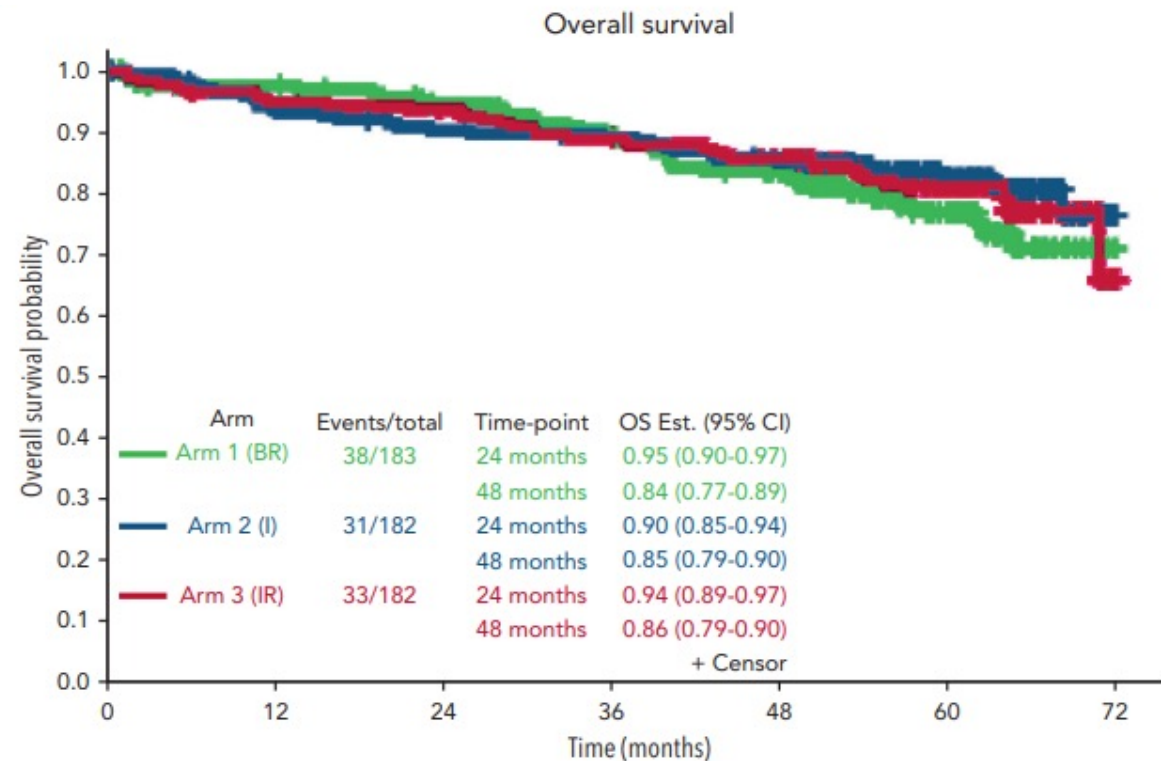
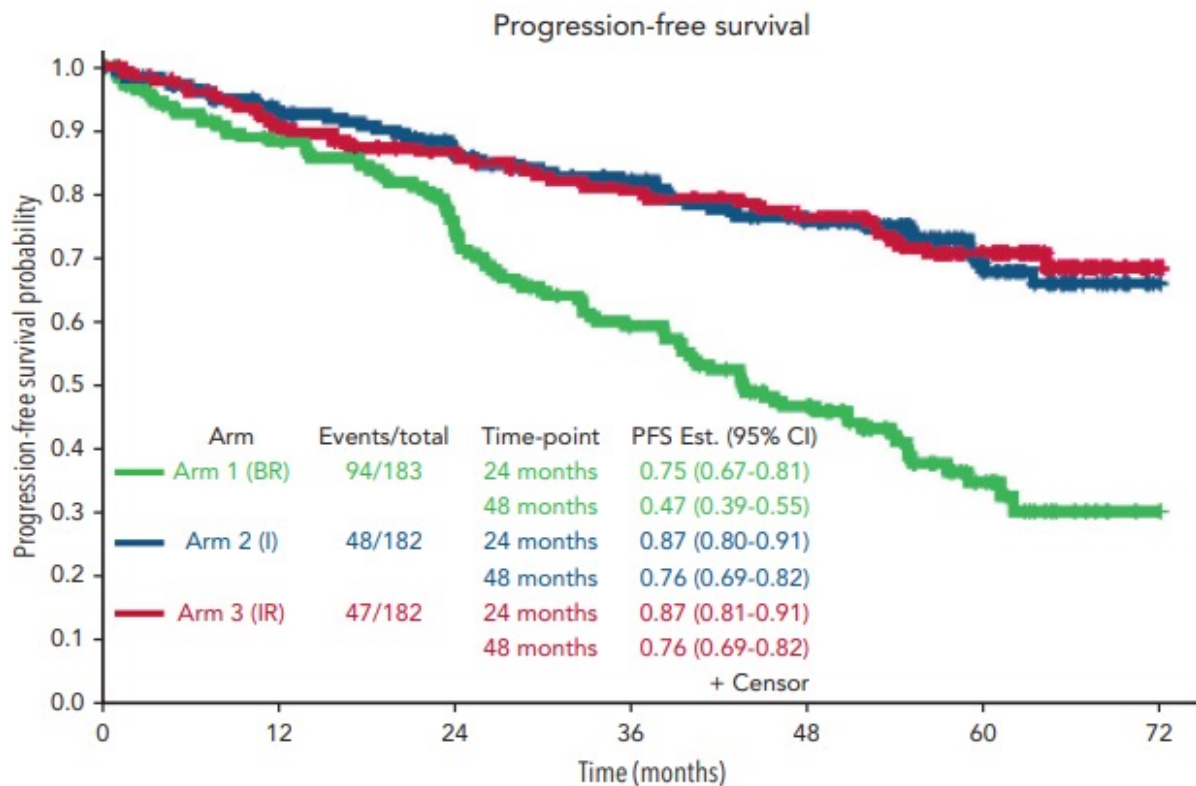
- Hallek et al. Lancet 2010; 376: 1164-74 .
- Goede Vet al. N Engl J Med. 2014 Mar 20;370(12):1101-10.

# Superioridad de ibrutinib vs CIT

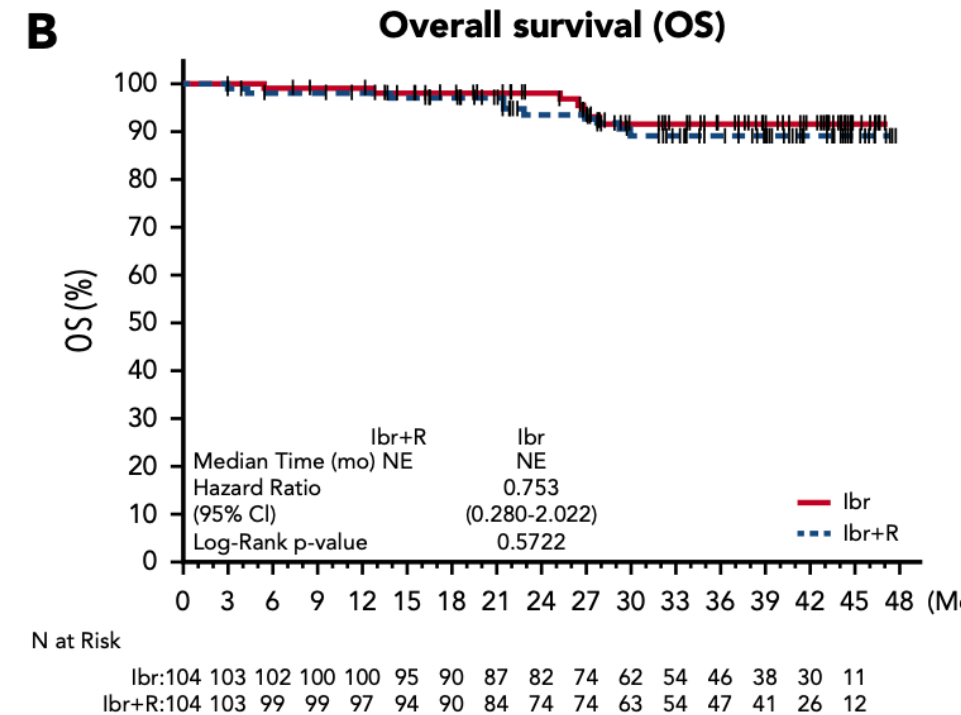
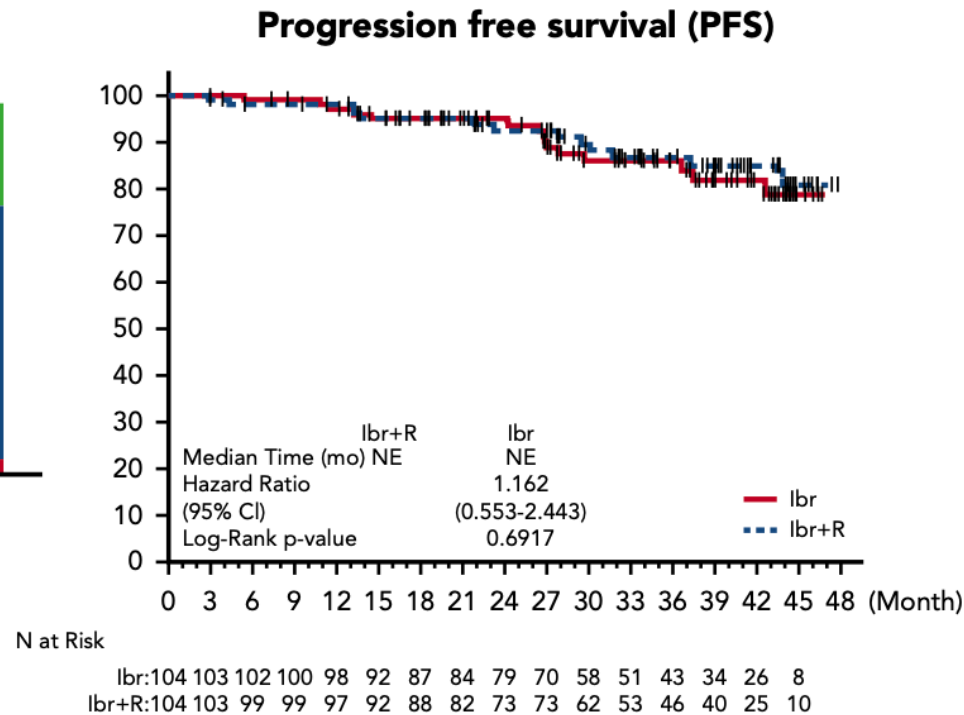
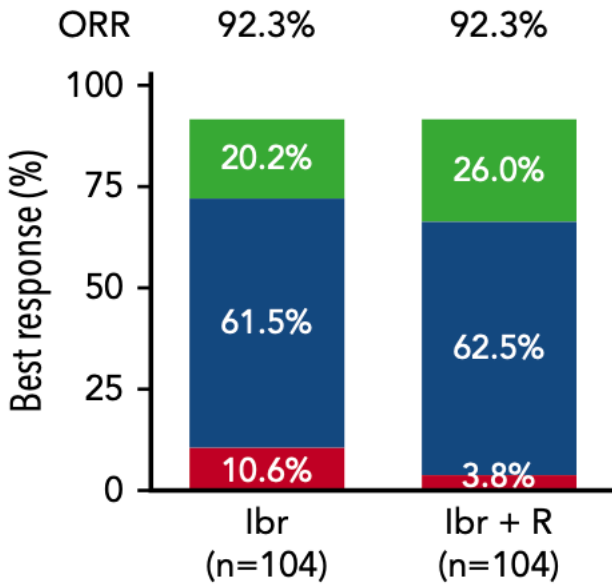
FIT	MODERATELY FIT	UNFIT
<p data-bbox="524 382 766 482"><b>E1912: FCR vs IR<sup>1</sup></b></p> <p data-bbox="473 586 817 601"><small>THE NEW ENGLAND JOURNAL OF MEDICINE</small></p> <p data-bbox="555 654 736 672"><small>ORIGINAL ARTICLE</small></p> <p data-bbox="354 725 937 789"><b>Ibrutinib–Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia</b></p> <p data-bbox="354 811 937 889"><small>T.D. Shanafelt, X.V. Wang, N.E. Kay, C.A. Hanson, S. O'Brien, J. Barrientos, D.F. Jelinek, E. Braggio, J.F. Leis, C.C. Zhang, S.E. Coutre, P.M. Barr, A.F. Cashen, A.R. Mato, A.K. Singh, M.P. Mullane, R.F. Little, H. Erba, R.M. Stone, M. Litzow, and M. Tallman</small></p>	<p data-bbox="1144 382 1574 475"><b>ALLIANCE: Ibrutinib ± R vs BR<sup>2</sup></b></p> <p data-bbox="1281 615 1457 634"><small>ORIGINAL ARTICLE</small></p> <p data-bbox="1082 686 1658 746"><b>Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL</b></p> <p data-bbox="1090 768 1651 868"><small>J.A. Woyach, A.S. Ruppert, N.A. Heerema, W. Zhao, A.M. Booth, W. Ding, N.L. Bartlett, D.M. Brander, P.M. Barr, K.A. Rogers, S.A. Parikh, S. Coutre, A. Hurria,<sup>†</sup> J.R. Brown, G. Lozanski, J.S. Blachly, H.G. Ozer, B. Major-Elechi, B. Fruth, S. Nattam, R.A. Larson, H. Erba, M. Litzow, C. Owen, C. Kuzma, J.S. Abramson, R.F. Little, S.E. Smith, R.M. Stone, S.J. Mandrekar, and J.C. Byrd</small></p>	<p data-bbox="1854 382 2262 532"><b>iLLUMINATE: GA101-Ibrutinib vs GA101-CBL<sup>3</sup></b></p> <p data-bbox="1742 672 2288 775"><b>Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial</b></p> <p data-bbox="1742 789 2288 825"><small>Conf. Moreno, Richard Graf, Felix Danneberg, Alessandro Tesei, Bernhard Arita, Lorenz Lamert, Martin Zinzmeister, Olga Semadeni, Jan Nisnev, Doro Beer, Vikas Khaitan, Venugop. Venkatesh, John C. Gibbins, Emily Hsu, Cath. Jiang, Cathy Zhou, Frank Jans, David F. James, Jan. Tighi, for iLLUMINATE</small></p>

1. Shanafelt T et al. NEJM. 2019.
2. Woyach JA et al. NEJM. 2018.
3. Moreno C et al. Lancet Oncol.2019

# Alliance trial: Updated results no benefit of IR vs Ibrutinib



# Estudio randomizado de ibrutinib vs ibrutinib plus rituximab (MDAnderson)

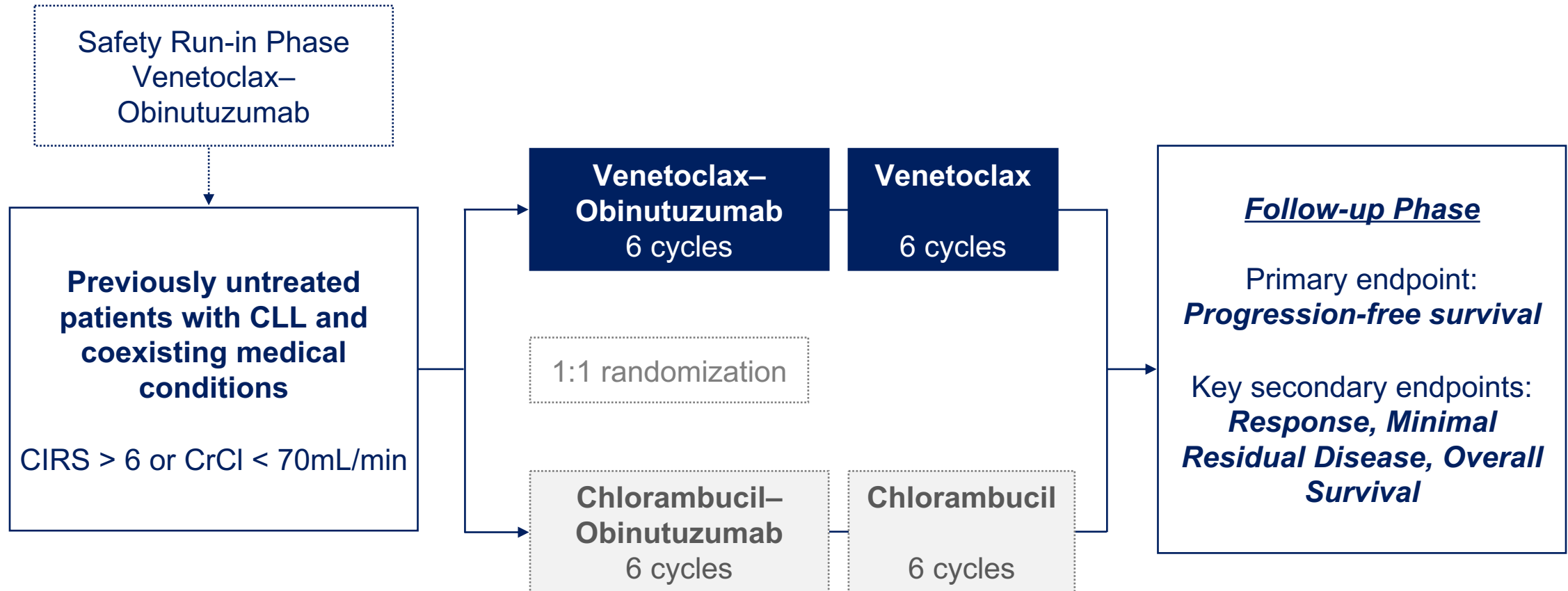


**RITUXIMAB**



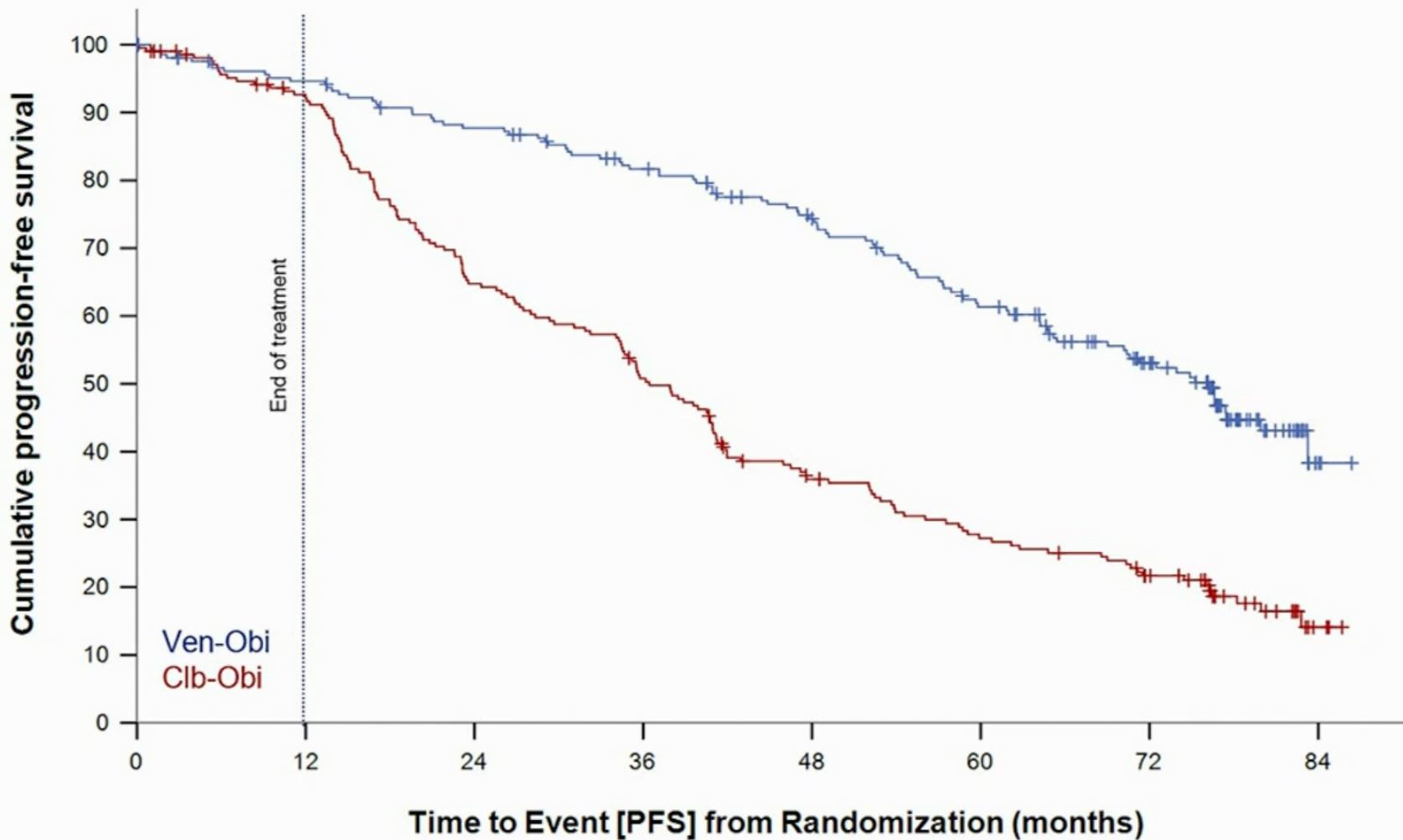
# Rol del Obinutuzumab para LLC

# CLL14: Frontline Ven-Obin vs. Chl-Obin



## PROGRESSION-FREE SURVIVAL

Investigator-assessed PFS



### Median PFS

Ven-Obi: 76.2 months

Clb-Obi: 36.4 months

### 6-year PFS rate

Ven-Obi: 53.1%

Clb-Obi: 21.7%

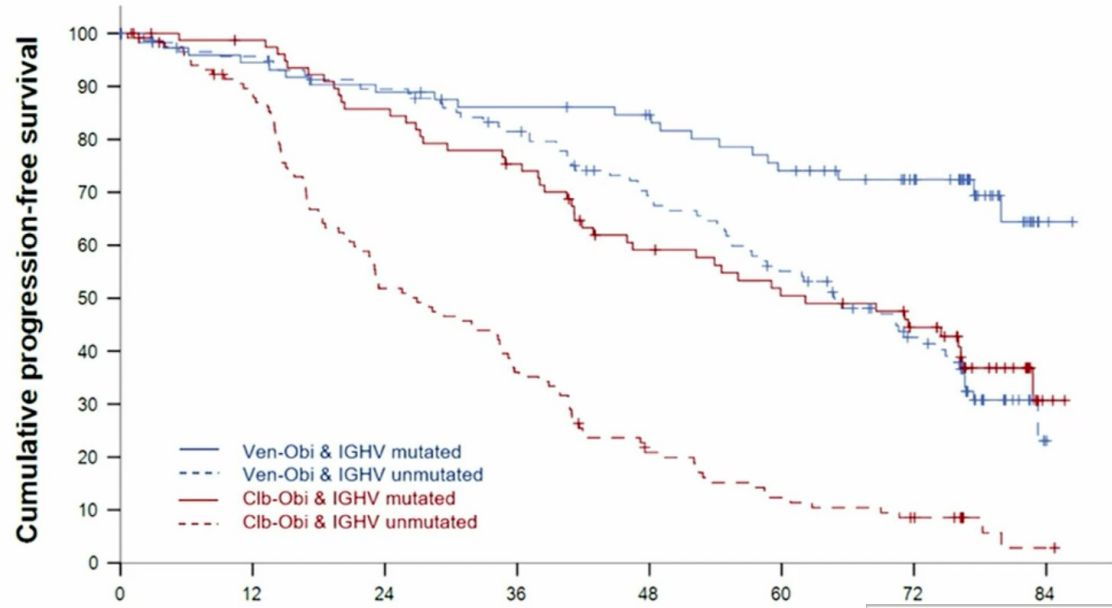
HR 0.40, 95% CI [0.31-0.52]

P<0.0001

Ven-Obi	216	193	177	160	139	112	79	3
Clb-Obi	216	185	130	101	67	50	36	3

## PROGRESSION-FREE SURVIVAL – IGHV status

Median observation time 76.4 months



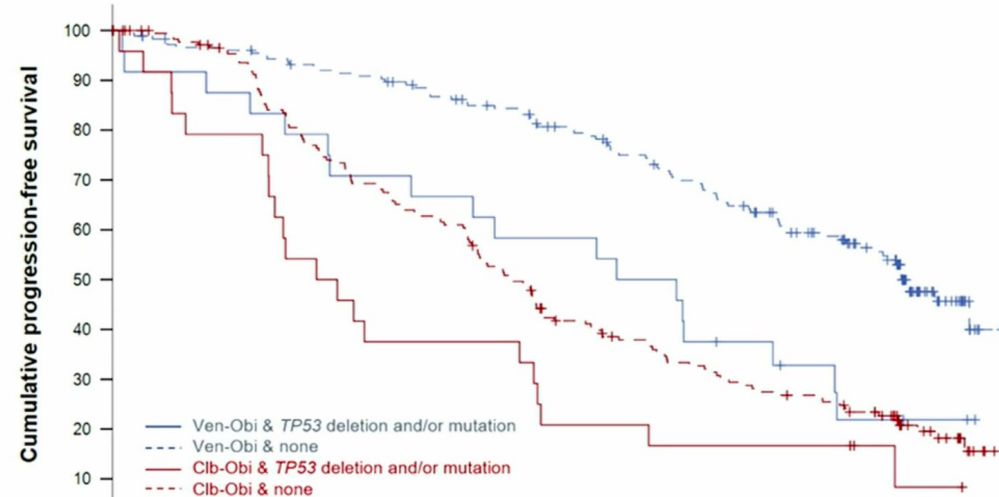
### Median PFS

Ven-Obi & IGHVmut: NR  
 Ven-Obi & IGHVunmut: 64.8 m  
*HR 0.38, 95%CI [0.23-0.61], p<0.001*

Clb-Obi & IGHVmut: 62.2 m  
 Clb-Obi & IGHVunmut: 26.9 m  
*HR 0.33, 95% CI [0.23-0.47], p<0.001*

## PROGRESSION-FREE SURVIVAL – TP53 status

Median observation time 76.4 months



### Median PFS

Ven-Obi & no TP53del/mut: 76.6 m  
 Ven-Obi & TP53del/mut: 51.9 m  
*HR 2.29, 95% CI [1.37-3.83], p=0.001*

Clb-Obi & no TP53del/mut: 38.9 m  
 Clb-Obi & TP53del/mut: 20.8 m  
*HR 1.66, 95% CI [1.05-2.63], p=0.03*

# MOST FREQUENT ≥ GRADE 3 ADVERSE EVENTS

CLL14

Venetoclax-obinutuzumab  
(N=212)

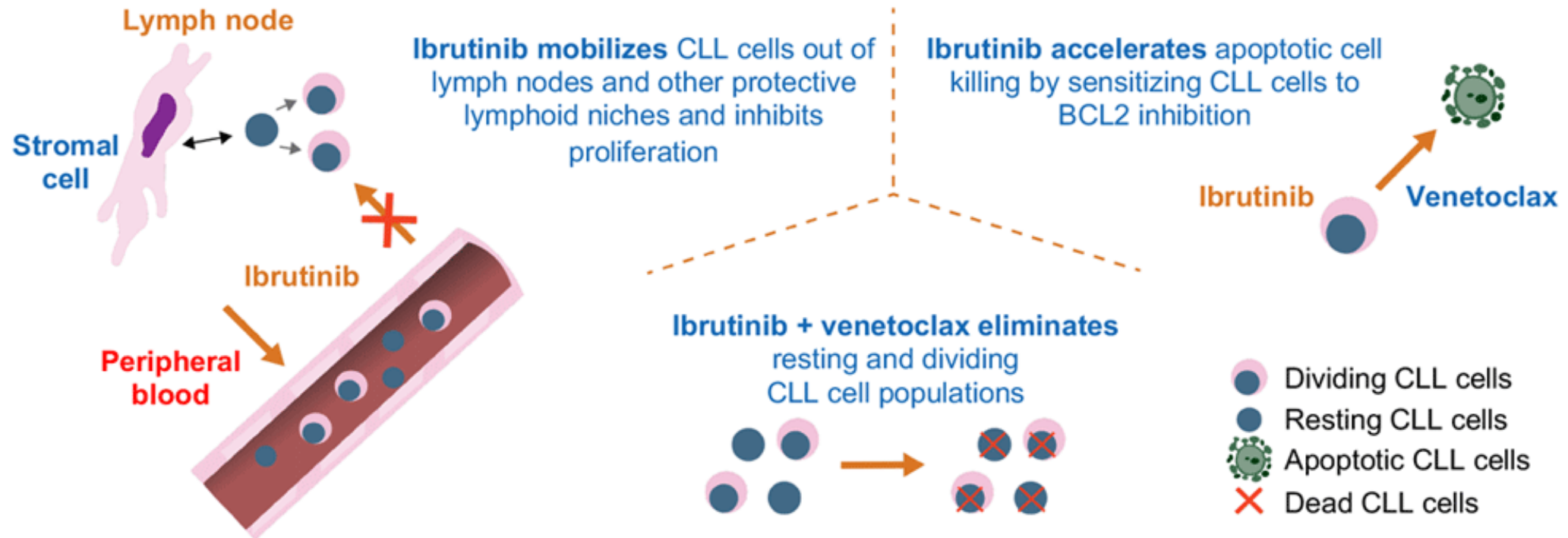
Chlorambucil-obinutuzumab  
(N=214)

	During Treatment	After Treatment	During Treatment	After Treatment
Neutropenia	51.9%	4.0%	47.2%	1.9%
Thrombocytopenia	13.7%	0.5%	15.0%	0.0%
Anemia	7.5%	1.5%	6.1%	0.5%
Febrile neutropenia	4.2%	1.0%	3.3%	0.5%
Infusion-related reaction	9.0%	0.0%	9.8%	0.5%
Tumour lysis syndrome	1.4%	0.0%	3.3%	0.0%
Neoplasms	1.4%	6.4%	1.4%	1.9%

Terapias combinadas orales:  
iBTK + iBCL2

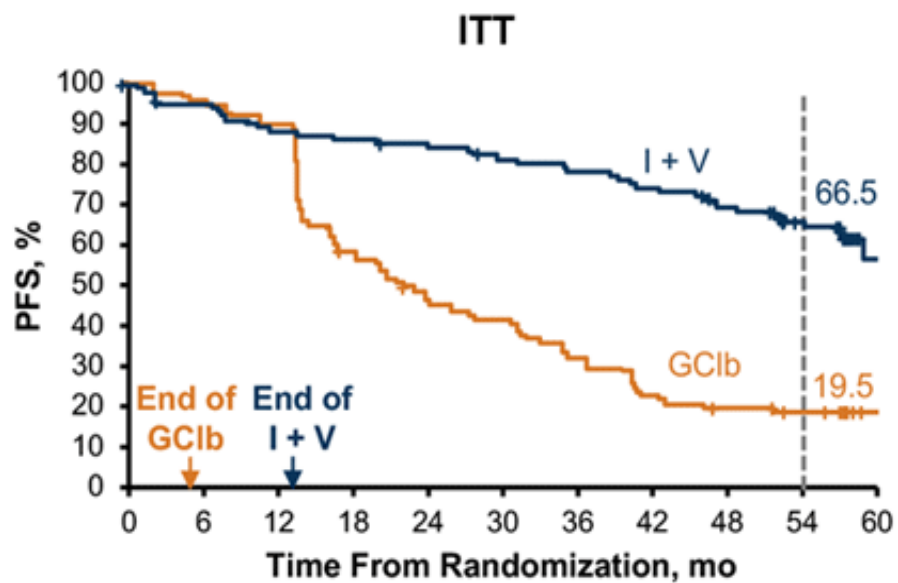
# Rationale for BTKi/BCL2i Combinations

## Distinct and Complimentary Mechanisms of Action for Ibrutinib and Venetoclax in CLL<sup>1-4</sup>



# Phase 3 GLOW Study: Ibru + Ven vs Clb + Obinutuzumab

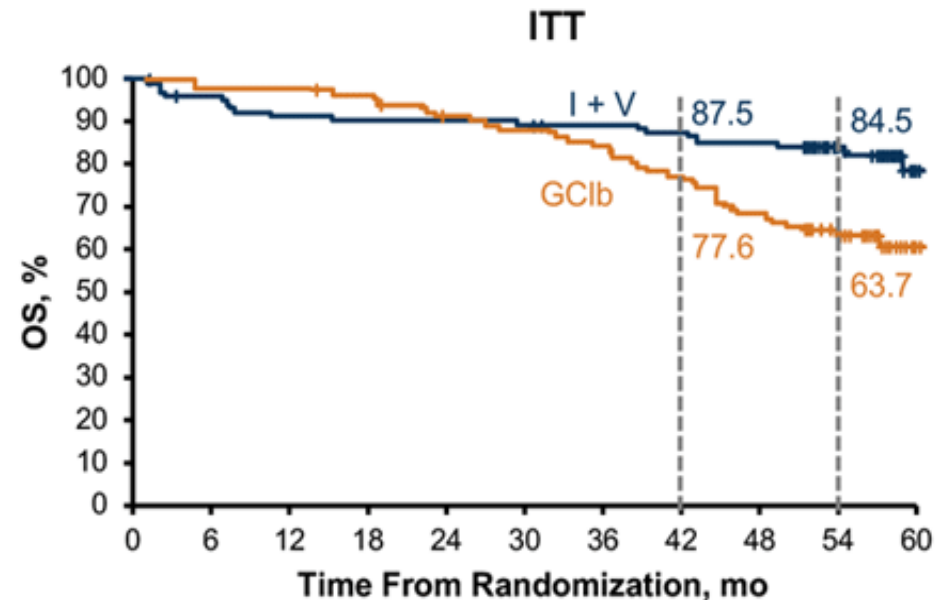
Prior results led to EMA approval of I + V for adults with previously untreated CLL<sup>1</sup>; updated findings recently reported after up to 5 years of follow-up<sup>2</sup>



No. at Risk		0	6	12	18	24	30	36	42	48	54	60
I+V	106	99	92	90	88	83	80	75	68	55	11	
GC1b	105	101	95	61	50	43	33	24	20	15	2	

I + V reduced the risk of progression or death by 74% vs GC1b

- HR (95% CI): 0.256 (0.172-0.382);  $P < .0001$



No. at Risk		0	6	12	18	24	30	36	42	48	54	60
I+V	106	100	95	94	94	93	91	89	87	74	19	
GC1b	105	103	103	100	93	90	86	79	70	57	17	

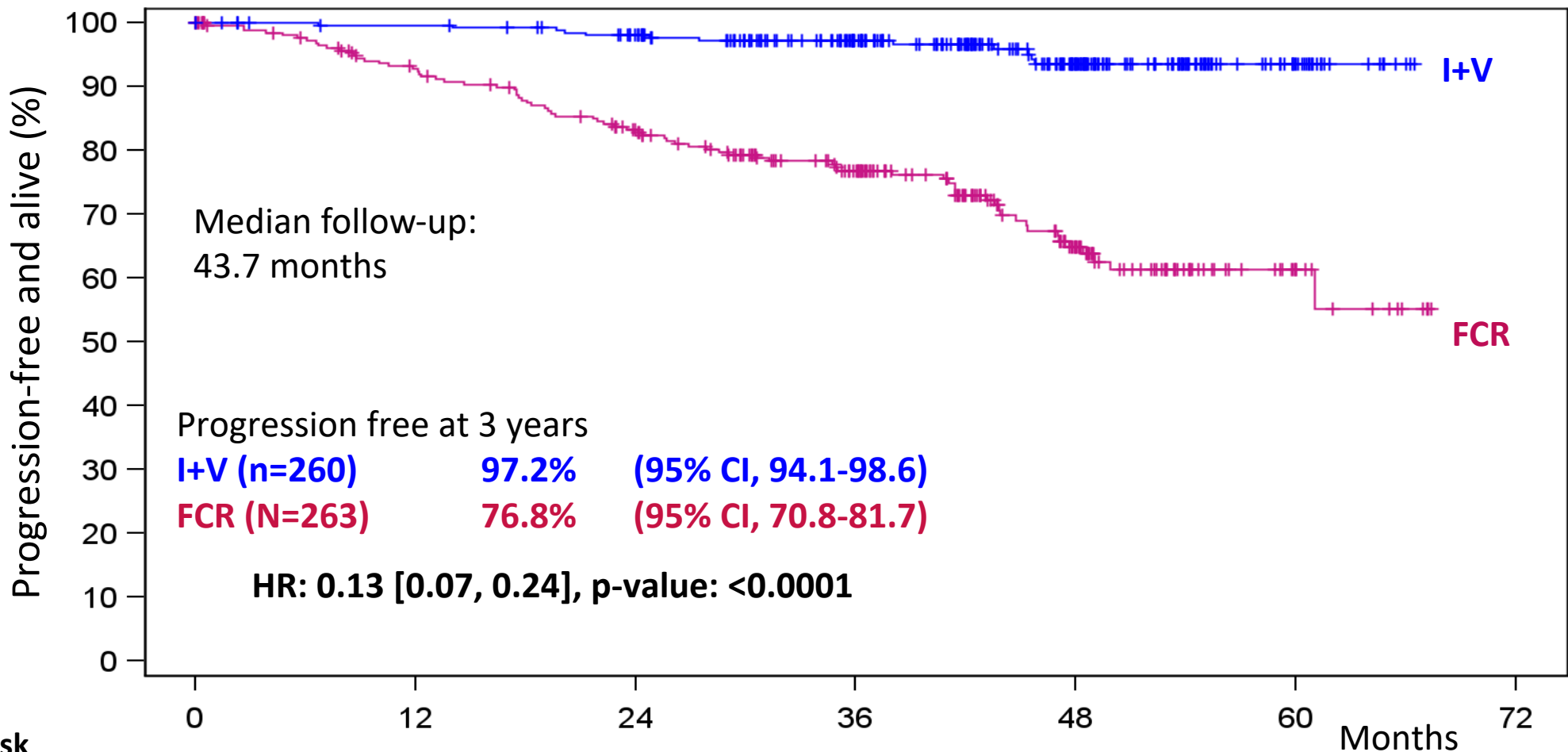
I + V reduced the risk of death by 55% vs GC1b

- HR (95% CI): 0.453 (0.261-0.785);  $P = .0038$

1. Kater A et al. *NEJM Evid.* 2022;1. 2. Moreno C et al. ASH 2023. Abstract 634.

# Flair

## Primary end-point: PFS for FCR versus I+V



No. at risk

I+V

260

253

239

183

99

21

0

FCR

263

227

194

145

68

12

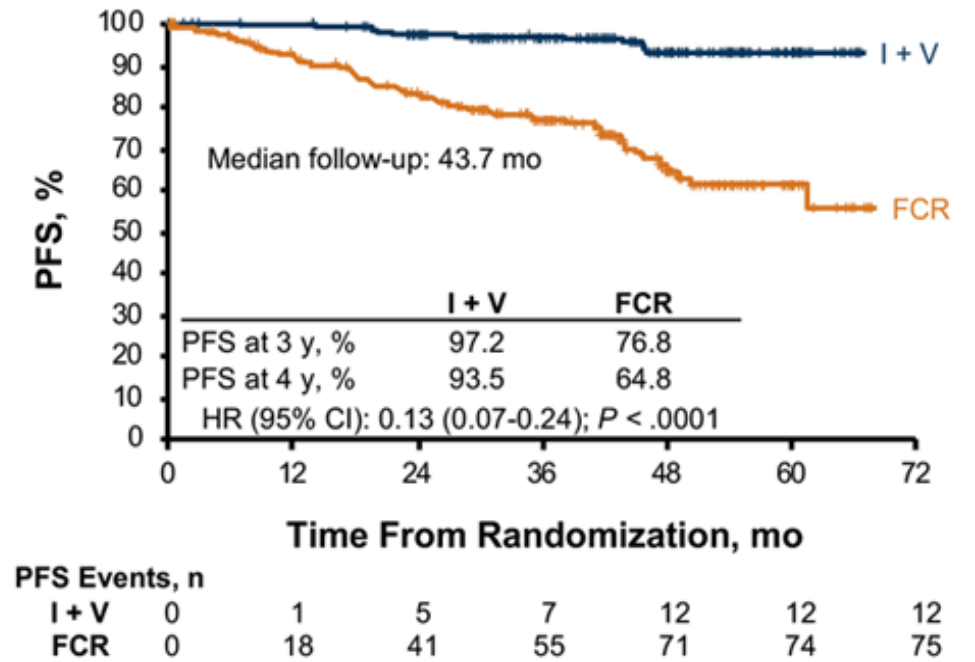
0

Months

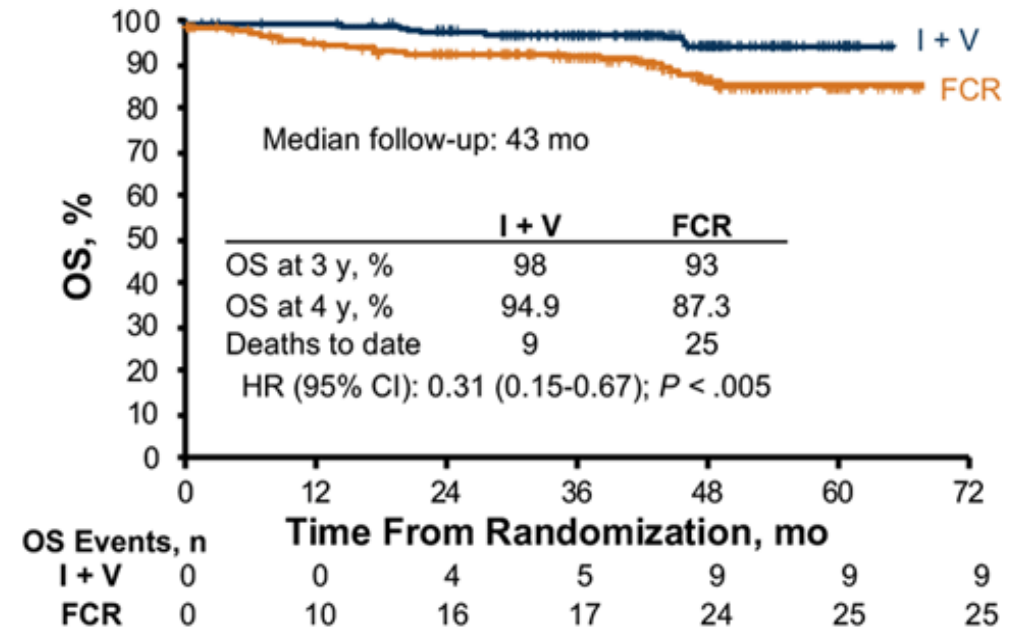
# FLAIR Study: Ibru + Ven vs FCR improved PFS and OS with MRD directed therapy

Using MRD to direct duration of I + V maximizes outcome with a PFS of 97.2% at 3 years<sup>a</sup>

Primary Analysis of PFS in FCR vs I + V

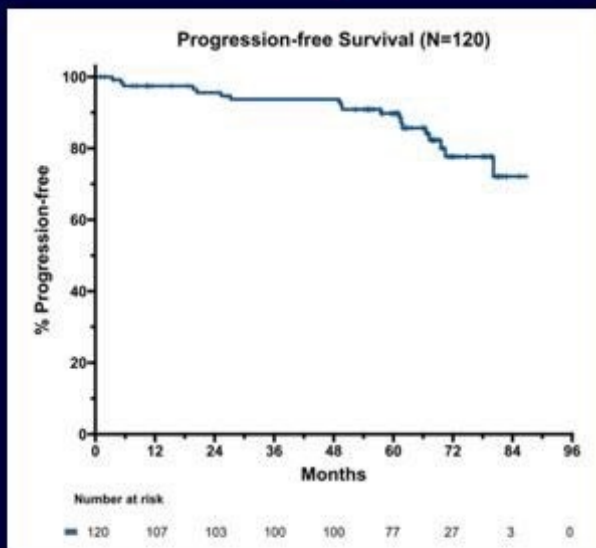


OS in FCR vs I + V



# I + V Regimen Comparisons, ASH 2023

## MDACC, I+V 24 cycles

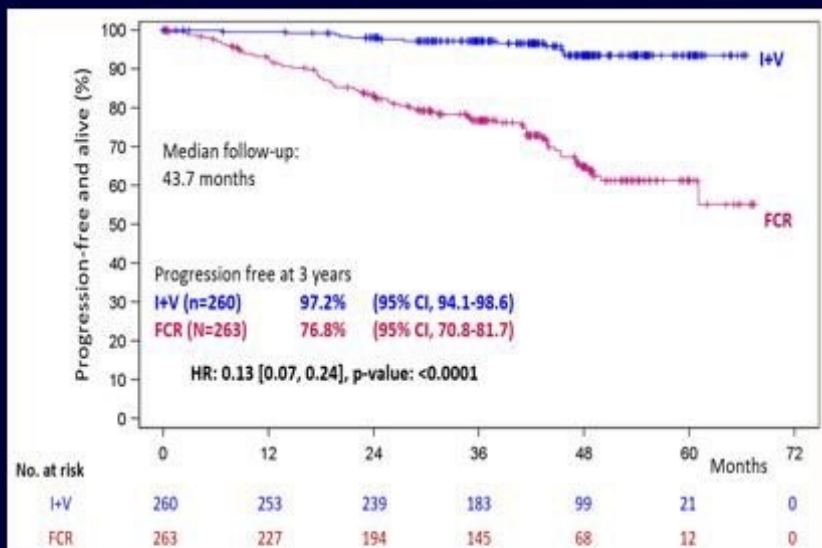


N=120  
 Median age = 64.5 yrs  
 IGHV-UM = 86%  
 Del(17p) / TP53-m = 23%

**5 yr PFS = 89.8%**

Jain, ASH 2023

## FLAIR, UK, I+V 2-6 years

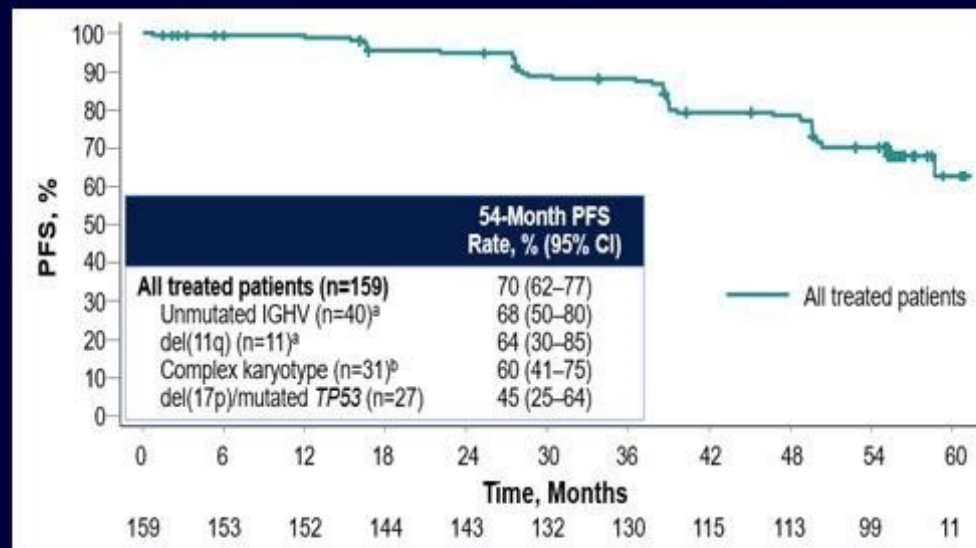


N=260  
 Median age = 62 yrs  
 IGHV-UM = 48%  
 Del(17p) = excluded

**3 yr PFS = 97.2%**

Hillmen, ASH 2023

## CAPTIVATE, I+V 12 cycles



N=159  
 Median age = 60 yrs  
 IGHV-UM = 56%  
 Del(17p) / TP53-m = 17%

**4.5 yr PFS = 70%**

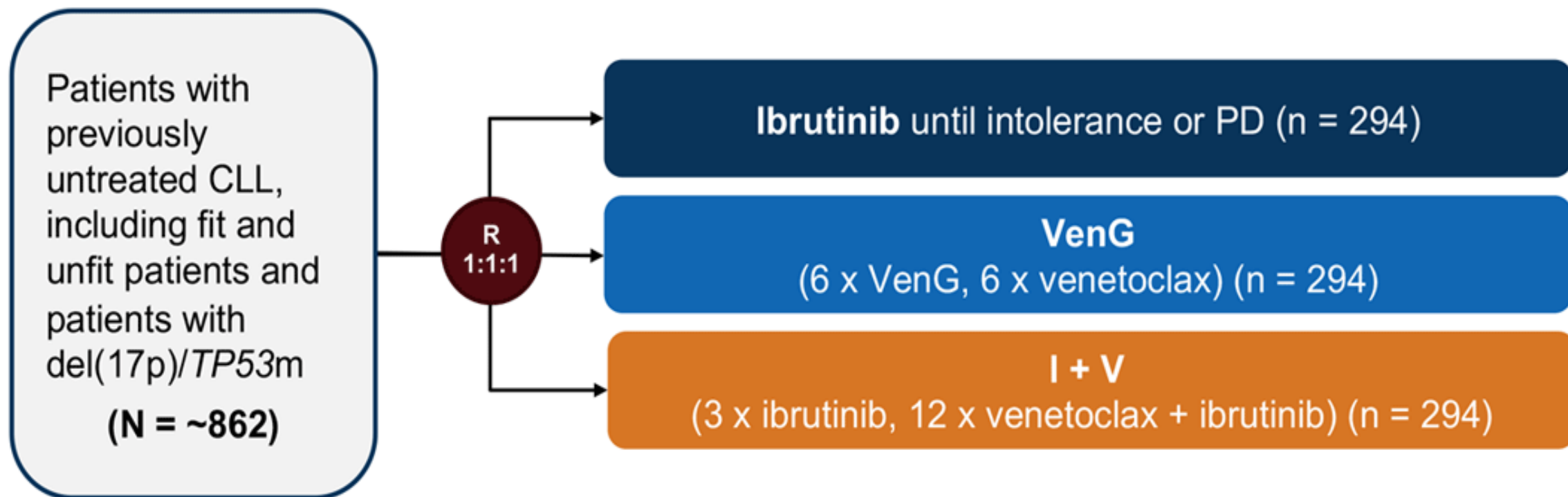
Ghia, ASH 2023

# 5-year PFS in Firstline CLL

		Approx 5-year PFS	
		IGHV-M	IGHV-UM
RESONATE 2	Ibrutinib	80%	70%
ELEVATE TN	Acalabrutinib	80%	70%
	Acalabrutinib + Obin	84%	82%
CLL14	Ven + Obin (1yr)	74%	55%
MDACC	Ibr + Ven (2yr)	86%	90%
CAPTIVATE	Ibr + Ven (1yr)	80%	56%
FLAIR	Ibr + Ven (2-6yr)	94% (3-yr)	98% (3-yr)
GLOW	Ibr + Ven (1yr)	90%	59%



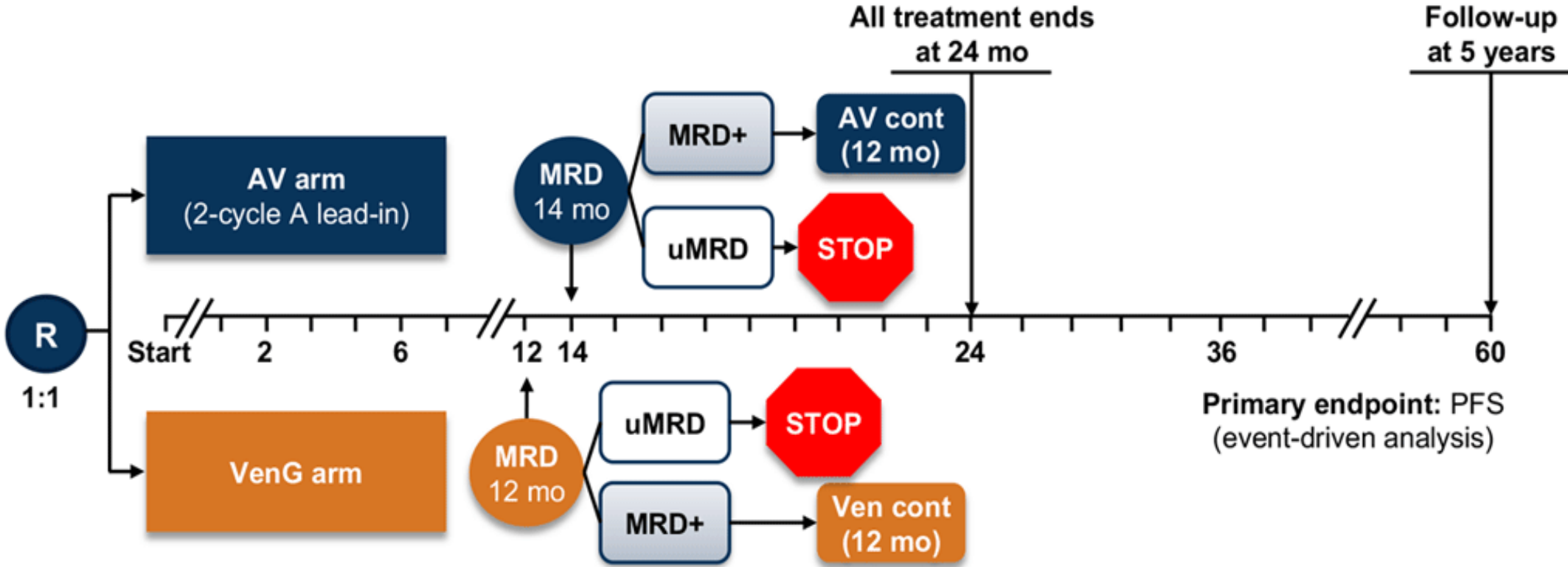
# CLL17 Is Testing Time-Limited Targeted Combinations Versus Continuous BTKi Therapy in TN CLL<sup>1</sup>



- **Primary endpoint:** PFS
- **Key secondary endpoints:** response, MRD, and OS

# MAJIC Phase 3 Study Will Test Acalabrutinib + Venetoclax Combination in an All-Comer CLL/SLL Population<sup>1</sup>

- |  |   |
|--|---|
| <ul style="list-style-type: none"> <li>• ~750 patients to be recruited</li> <li>• 40 sites around the world</li> </ul> | <p><b>Key eligibility criteria</b></p> <ul style="list-style-type: none"> <li>• TN CLL/SLL requiring treatment per 2018 iwCLL guidelines</li> <li>• ECOG PS 0-2</li> <li>• Antithrombotic agents permitted except for warfarin or equivalent vitamin K antagonists</li> </ul> |
|--|---|





# Terapia Finitas como elijo

**Ven + iBTK  
(voy suave)**

- ▽ Toxicidad CV
- ✓ Terapia enteramente oral  
(facil inicio)
- ✓ SLP muy Buena
- ✓ FLAIR mejor SLP a la fecha  
adapatado a EMR !!



**Ven + Obinu  
(agresivo)**

- ▽ Internacion
- ▽ Manjeo de SLT
- ▽ Reacciones infusionales Obinu  
grado 3/4
- ▽ Neutropenia / plaquetopenia
- ✓ Evitamos toxicidad CV
- ✓ Reservo iBTK para recaida
- ✓ Mayor EMR

# Conclusiones (como trato)

- Los estudios muestran que no hay beneficio de Rituximab en el tratamiento de LLC en la era de las terapias target
- **Rituximab NO**
- **Obinutuzumab** mas eficaz, pero mas toxico y requiere internaciones para manejo de reacciones infusionales
- Prefiero combinaciones orales para pacientes más jóvenes (I+V o A+V)
- Monoterapia oral continua con iBTK de 2G para pacientes mayores
- Pacientes con 17p/P53 iBTK continuo
- Aguardar estudios CLL17 y MAJIC (tratamiento guiado x EMR)

**C**hronic  
**L**ymphocytic  
**L**eukemia

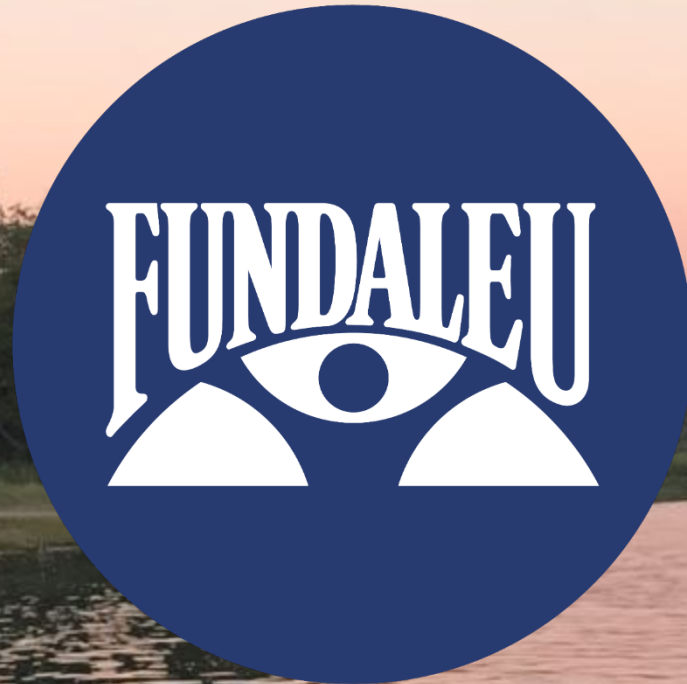
# Let's Level Up



**#WCLLD24**  
#LetsLevelUp  
#CLL

Health equity **for all** CLL patients

Gracias



# 6<sup>TH</sup> LAG-CLL 2026

Latin American Group on Chronic Lymphocytic Leukemia  
ARGENTINA



Mendoza, April 2026.



**President of honor**  
Guillermo Dighiero



# FUNDALEU - PROTOCOLOS DE INVESTIGACION ABIERTOS AL ENROLAMIENTO 3-2025



Patología	Protocolo	Diseño	Investigador Principal
LLC RR	MK1026-003 (MK-1026)	Fase 2 para evaluar eficacia y seguridad de MK-1026, inhibidor no covalente de BTK (Nemtabrutinib) en LLC RR con tratamiento previo con BTKi covalente irreversible y un BCL2i.	Miguel Pavlovsky
MM RECAIDO	64407564MMY3009 MonumenTAL-6	Fase 3, aleatorizado, compara talquetamab - pomalidomida (Tal-P), talquetamab - teclistamab (Tal-Tec) y la elección del investigador de elotuzumab, pomalidomida y dexametasona (EPd) o pomalidomida, bortezomib y dexametasona (PVd) en MM RR que han recibido de 1 a 4 L previas, incluido un anticuerpo anti-CD38 y lenalidomida	Guillermina Remaggi
LMA	ONCOPRECISION	Plataforma de oncología de precisión para la selección de tratamientos en LA	M. José Mela Osorio
cGVHD	EFC17757 ROCKnrol	Fase 3, aleatorizado, doble ciego, evalúa eficacia y seguridad de belumosudil en combinación con corticosteroides vs placebo en combinación con corticosteroides en pacientes con Dx reciente de enfermedad de injerto contra huésped crónica.	Gonzalo Bentolilla

# PROTOCOLOS DE INVESTIGACION PROXIMOS A INICIAR EN 2025



Patología	Protocolo	Diseño	Investigador Principal
Linfoma del Manto	14117- 302	Fase 3, abierto, randomizado de Zanubrutinib hasta progresión/ intolerancia + Sonrotoclax x 24 ciclos comparado Zanubrutinib hasta progresión/ intolerancia + placebo x 24 ciclos en pacientes con Linfoma del Manto RR.	Miguel Pavlovsky
LLC	16673-302	Fase 3, abierto, randomizado de BGB-16673 comparado con la elección del investigador (Idelalisib + Rituximab o Bendamustine+ Rituximab o Venetoclax + Rituximab) en pacientes con LLC o LLP previamente expuestos a iBTK y iBCL2	Carolina Pavlovsky
LDCGB	Olympia 4	Fase 3, abierto, evalúa eficacia y seguridad de Odronextamab (REGN1979), Biespecífico Anti CD20xAntiCD30 vs SOC en pacientes con LDCGB RR	Astrid Pavlovsky