V JORNADA GELL 2025
CLÍNICA DEL GRUPO DE ESTUDIO LATINOAMERICANO DE LINFOPROLIFERATIVOS

GELL Grupo de Estudio Latinoamericano de Linfoproliferativos

Enfermedad residual medible en LLC Realmente necesitamos medirla en LATAM?

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Uruguay

GULi Grupo Uruguayo de Linfoma

Con el Aval:

Conflictos de interes

Honorarios por conferencia: Abbvie, Roche

Honorarios advisory board: Abbvie, Roche

EMR

Concepto vs Utilidad clínica

Concepto

ERM traduce profundidad de respuesta y por tanto de ”potencia” del tratamiento

Predictor potente de resultados (PFS) en tratamientos de duración finita.

End point primario o secundario de varios ensayos clínicos.

No utilidad como predictor pronóstico en tratamientos prolongados basados en iBTK.

Métodos para determinar EMR

Table 1
Currently applied methods for MRD assessment

Method	Features	Advantages	Disadvantages
Flow cytometry	Detection of surface markers by established antibody panels, for example, CD5/CD19, CD20/CD38, CD81/CD22,CD79b/CD43[13] Sensitivity with 4-color flow 10^{-4}, with 6-color flow 10^{-5}	ERIC consensus guidelines available, widely accessible, relatively affordable, results with quantification relatively quick.	Fresh (<48 h) PB or BM samples necessary. Sufficient number of cells required to achieve sensitivity (≥ post-treatment cytopenia can be challenging). Sensitivity lower than PCR or NGS.
ASO PCR	Quantification based on allele- and patient-specific primers for hypervariable CDR3 of IgH. Sensitivity 10^{-5}	Good sensitivity, usage of DNA (instead of fresh material). Quantitative results.	Patient-specific primers required, baseline reference sample necessary, relatively time and labor intensive.
NGS	Measurement of CLL-specific IgH sequences based on consensus primers. Sensitivity 10^{-6}	High sensitivity, usage of DNA, tracking of clones possible, quantitative results.	Relatively expensive, baseline reference sample necessary, not widely used yet.

Método más frecuentemente utilizado
Estandarizado. Panel (ERIC)
Cutoff habitual 1 x 10^{-4}

Requiere primers específicos para cada paciente
Muestra inicial.

Costoso. Requiere muestra inicial

Tomado de Al Sawaf O et al. Hematol Oncol Clin N Am 2021

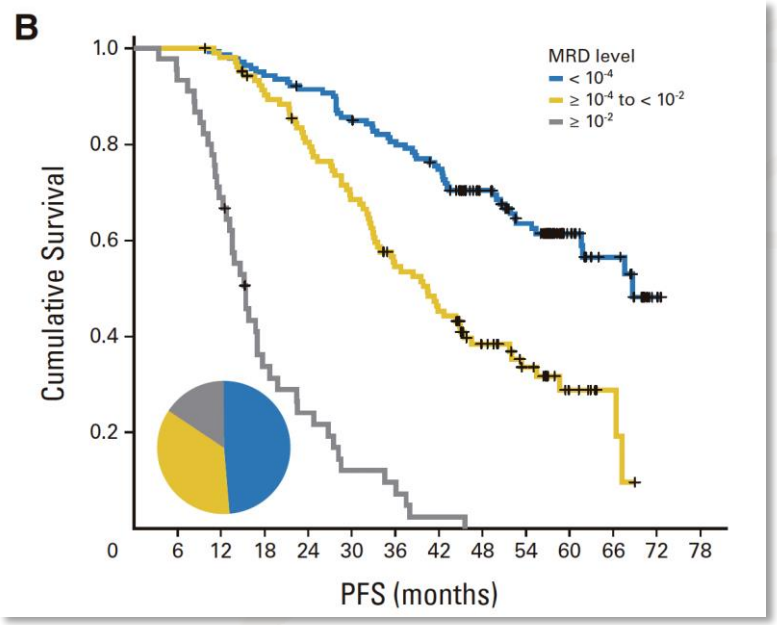
Utilidad clínica

Para qué medir ERM?

Pronóstico

Guiar el tratamiento

Valor pronóstico en la era QIT (CLL-8)



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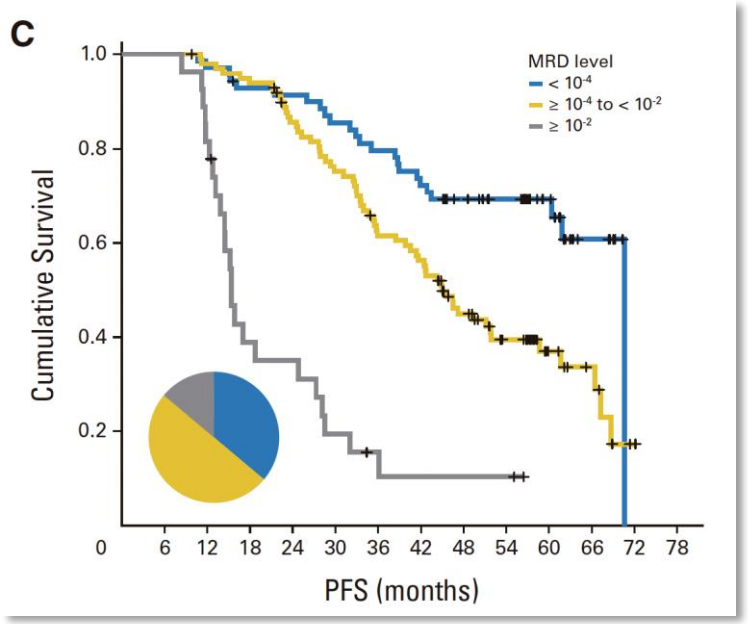
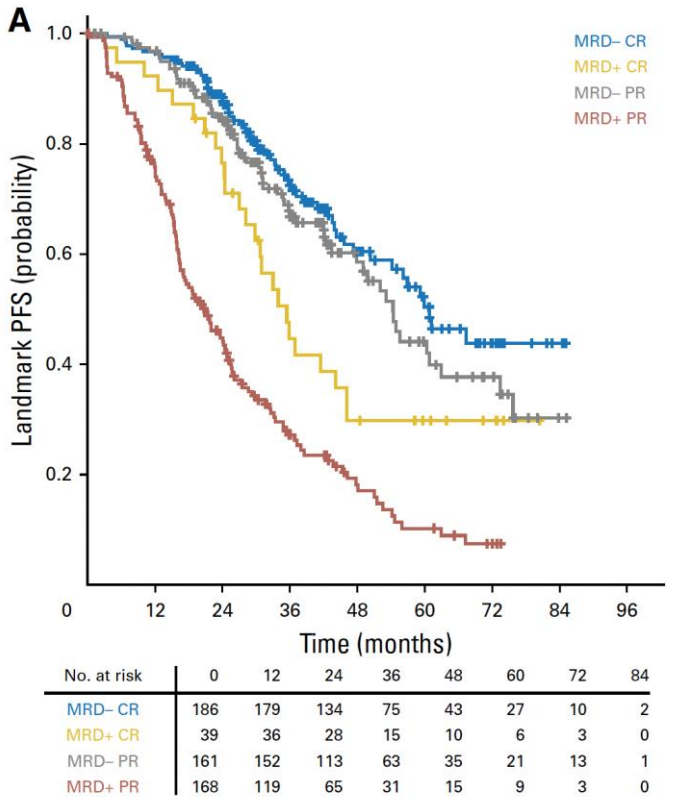


MO

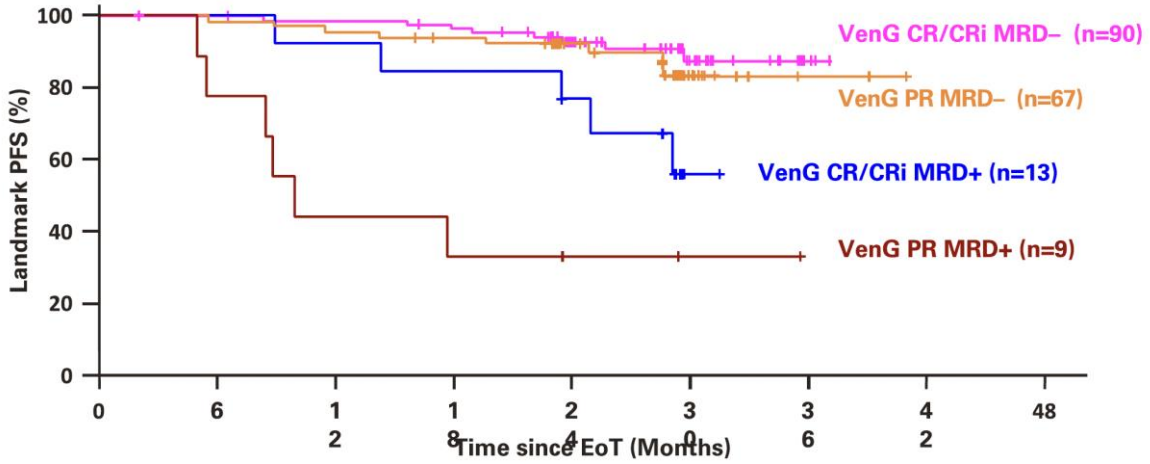
Böttcher S et al. J Clin Oncol 2012;30(9):980-988

Relación entre uEMR y respuesta por iWCLL

CLL-8 / CLL-10



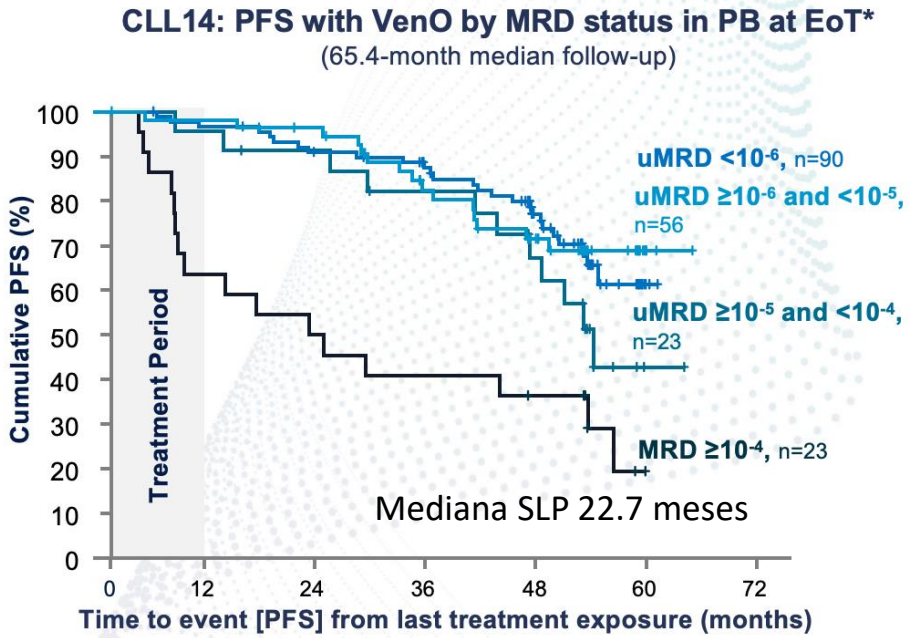
No. at risk	0	12	24	36	48	60	72	84
MRD– CR	186	179	134	75	43	27	10	2
MRD+ CR	39	36	28	15	10	6	3	0
MRD– PR	161	152	113	63	35	21	13	1
MRD+ PR	168	119	65	31	15	9	3	0

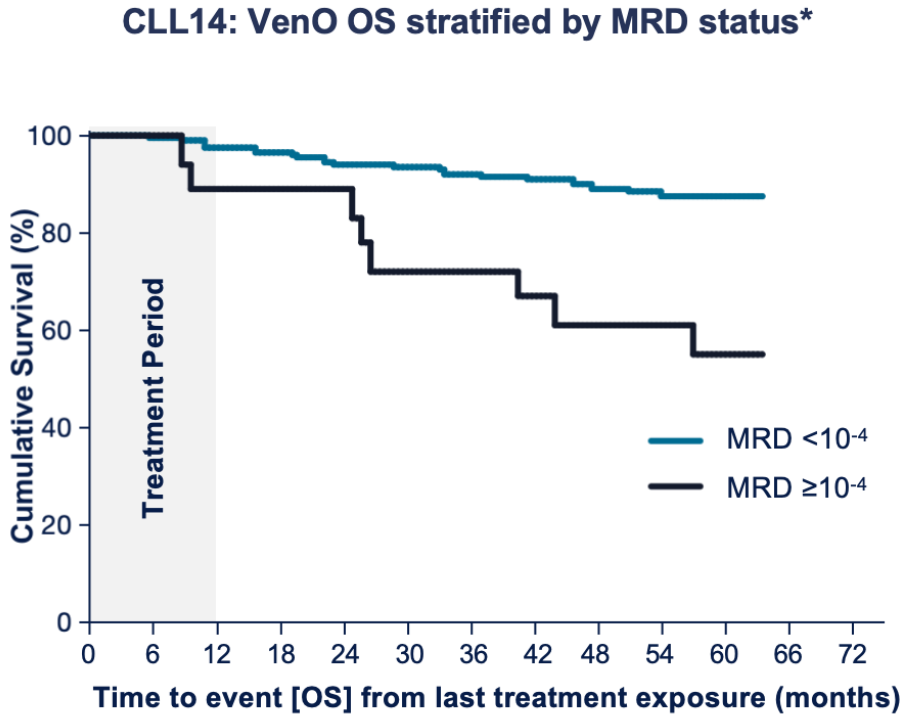


Kovacs G et al. J Clin Oncol 2016 Al-Sawaf O, et al. *Lancet Oncol*. 2020

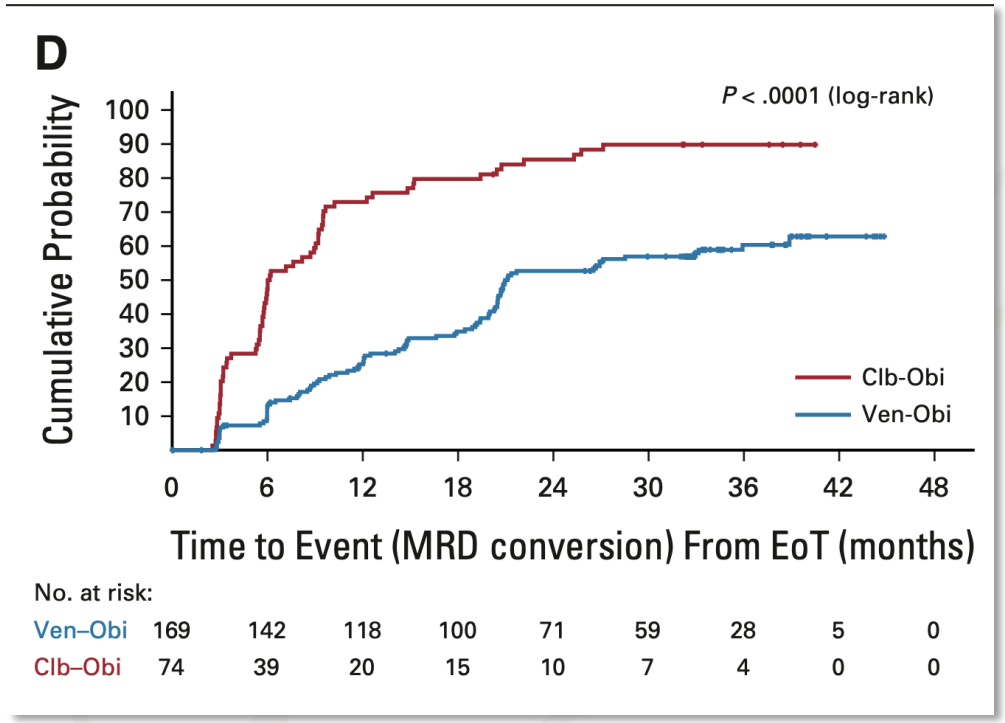
Con el Aval:

Valor pronóstico en la era terapias dirigidas

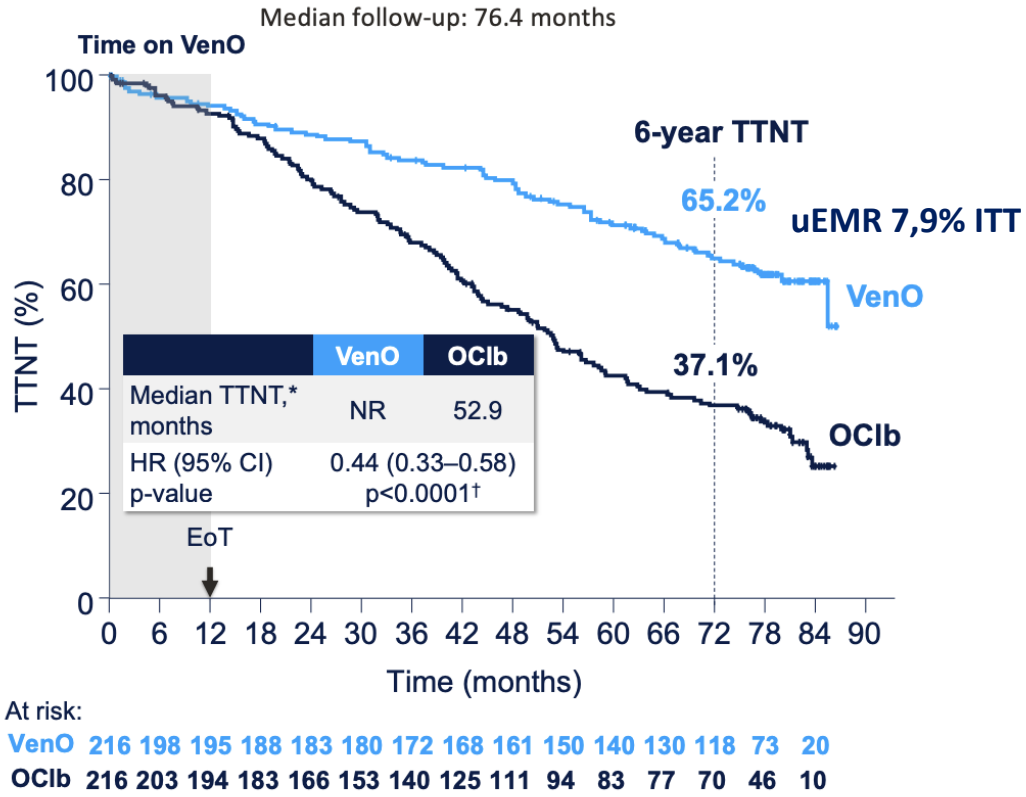




Al Sawaf O, et al. Nat Commun. 2023;14:21. Al Sawaf el at. Blood 2024 ;144(18)

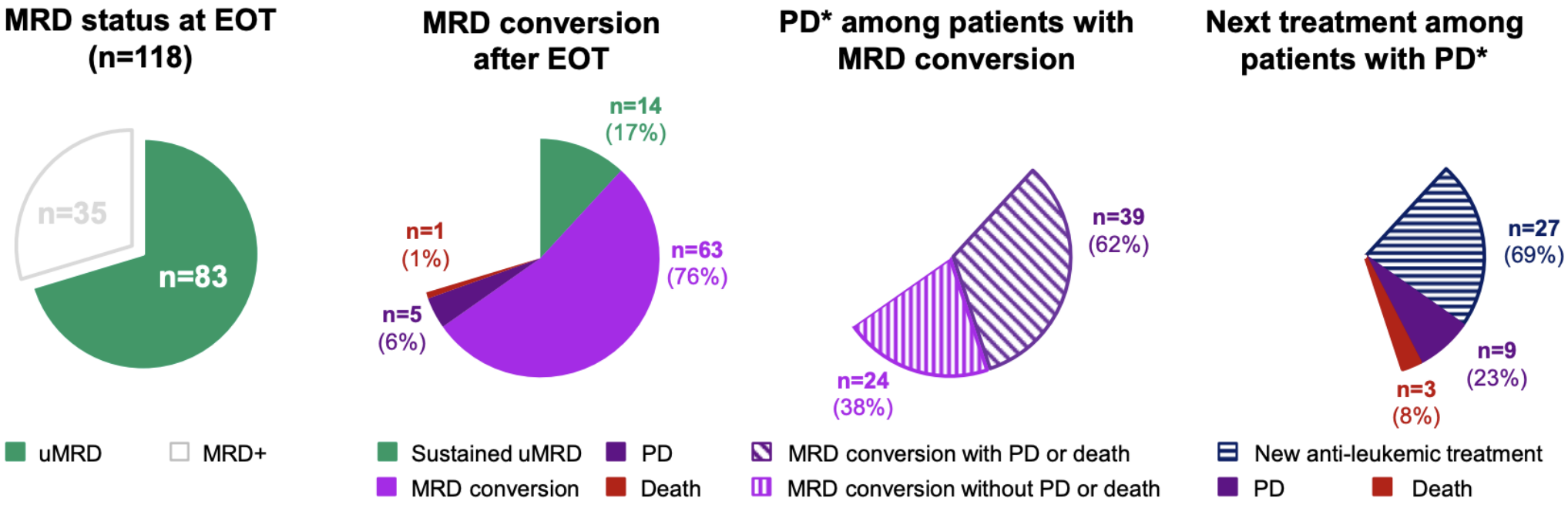


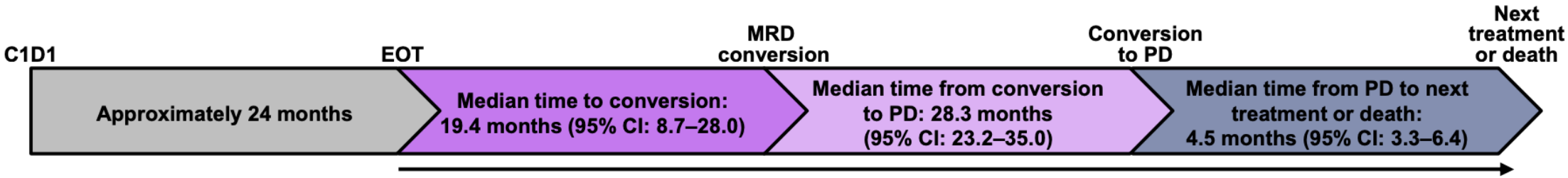
Mediana de tiempo a la conversión de EMR por NGS (EMR < 10^{-4} EoT a > 10^{-4}) 21 meses



Al Sawaf O et al. J Clin Oncol 2021:39(36). Al Sawaf O et al Blood 2024:144(18)

Dinámica de la EMR

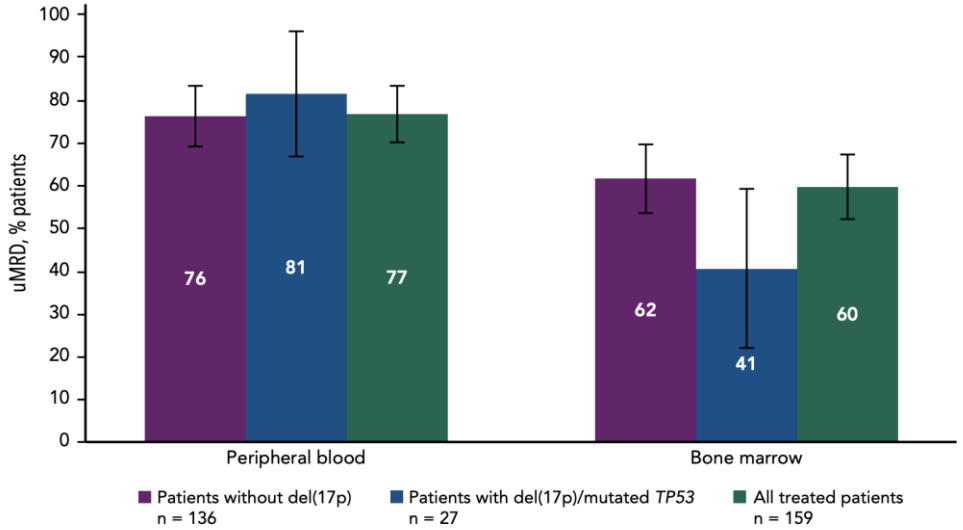




4 años libres de tratamiento

Kater A, et al. EHA 2023. Abstract S201 (Oral) Seymour JF, et al. Blood 2022; 140:839–850

CAPTIVATE: FD I + VEN



	CR*		PR†	
	uMRD in BM n = 51	Detectable MRD in BM n = 24	uMRD in BM n = 33	Detectable MRD in BM N = 29
24-month PFS rate, % (95% CI)	100 (100-100)	100 (100-100)	100 (100-100)	97 (78-99.5)

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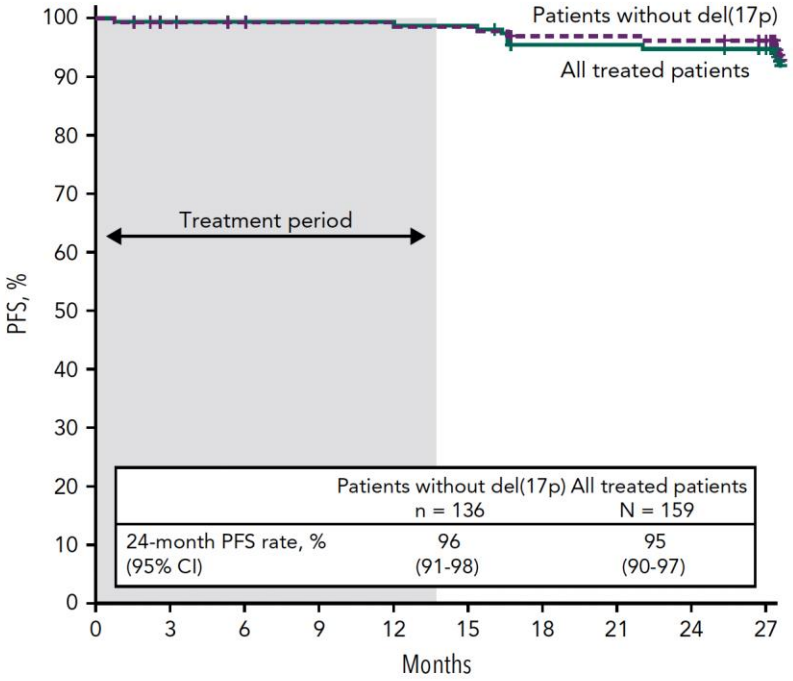
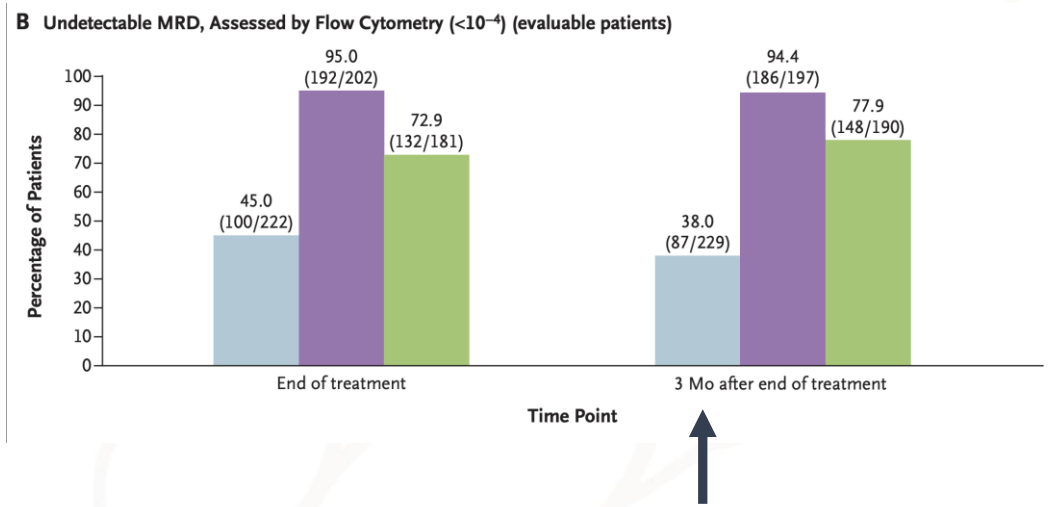
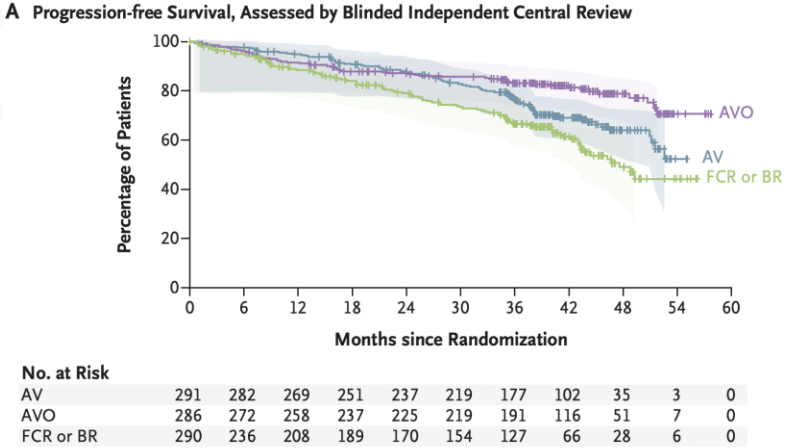


SLP estimada a 30 meses > 95%

AMPLIFY





No. at Risk											
AV	291	282	269	251	237	219	177	102	35	3	0
AVO	286	272	258	237	225	219	191	116	51	7	0
FCR or BR	290	236	208	189	170	154	127	66	28	6	0

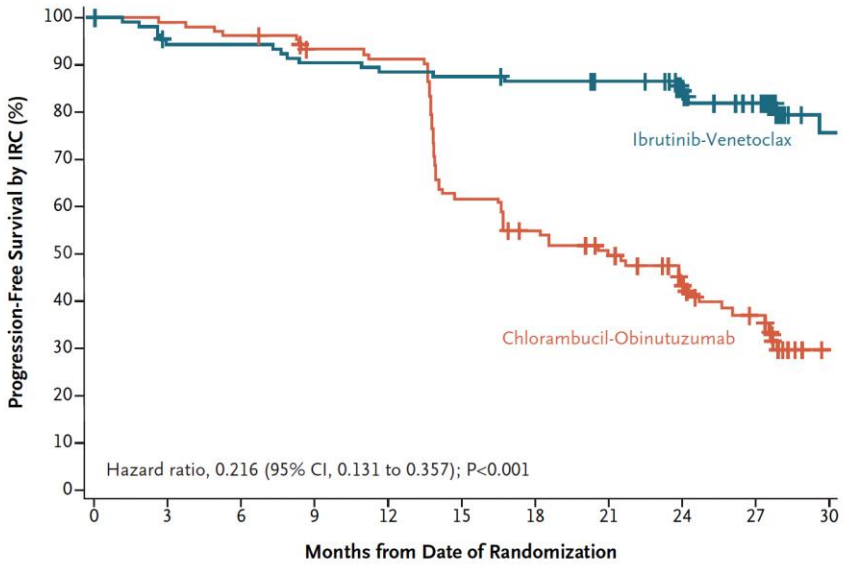
	No. of Events/ Total No. of Patients	Median Progression-free Suvival	Progression-free Survival at 36 Months
		mo	%
AV	89/291	NC	76.5
AVO	56/286	NC	83.1
FCR or BR	95/290	47.6	66.5

	Hazard Ratio for Disease Progression or Death (95% CI)	P Value
AV vs. FCR or BR	0.65 (0.49–0.87)	0.004
AVO vs. FCR or BR	–	<0.001

Brown J et al. N Engl J Med 2025

GLOW

A



No. at Risk											
Ibrutinib-Venetoclax	106	98	98	94	92	91	89	87	71	59	20
Chlorambucil-Obinutuzumab	105	104	101	95	93	63	54	47	36	25	6

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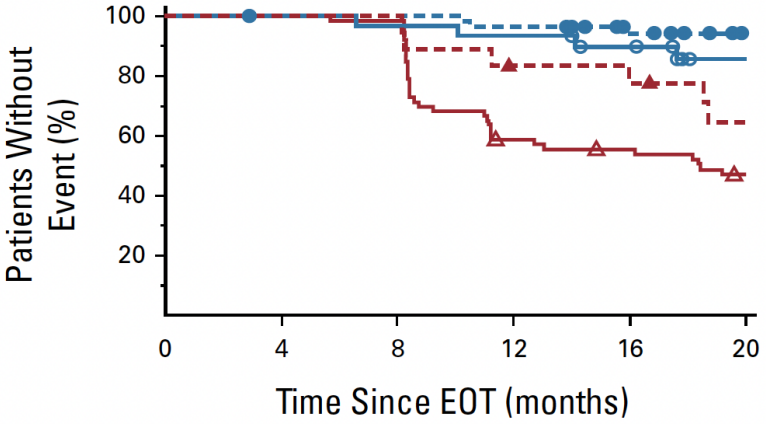


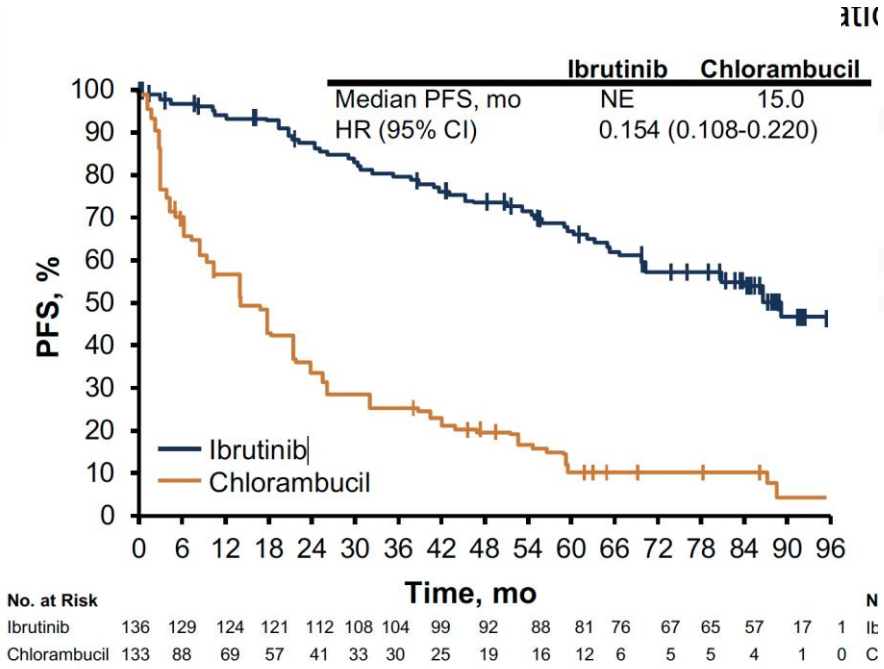
No. at risk:						
MRD ≥ 10^{-4}, ibrutinib + venetoclax	30	30	29	28	24	14
MRD < 10^{-4}, ibrutinib + venetoclax	55	54	54	52	46	25
MRD ≥ 10^{-4}, chlorambucil + obinutuzumab	63	63	62	36	33	27
MRD < 10^{-4}, chlorambucil + obinutuzumab	18	18	18	14	13	10

MRD ≥ 10^{-4}, ibrutinib + venetoclax
MRD < 10^{-4}, ibrutinib + venetoclax
MRD ≥ 10^{-4}, chlorambucil + obinutuzumab
MRD < 10^{-4}, chlorambucil + obinutuzumab

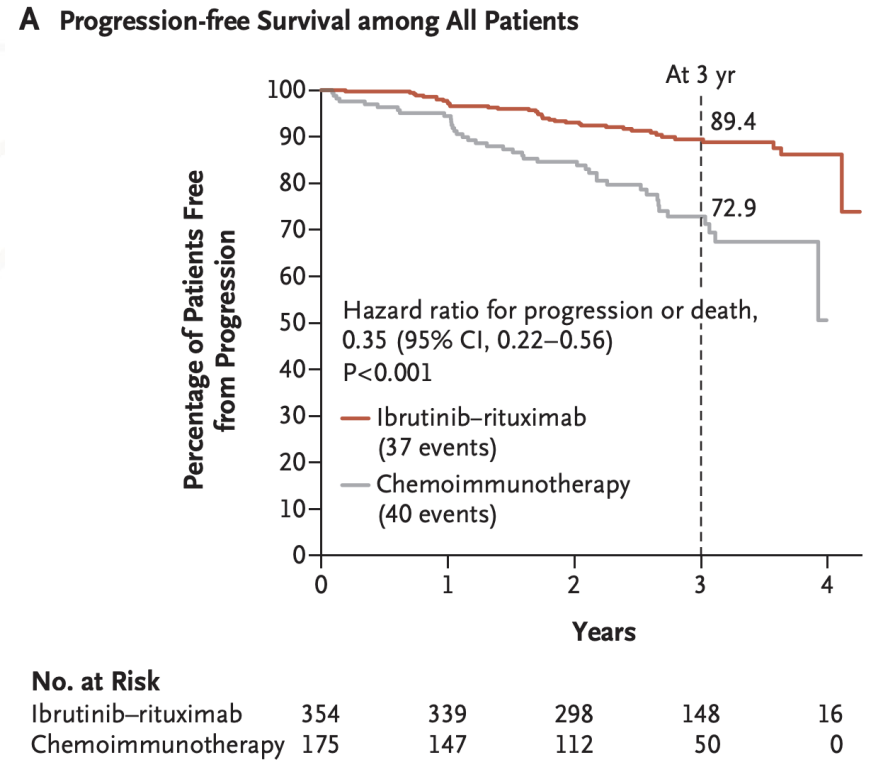
No diferencia en SLP con Ven +I según EMR en MO a 3 meses pTTO

Kater A et al. NEJM Evid 2022;1(7) Munir T et al. J Clin Oncol 2023;41

Con terapias basadas en iBTK pronóstico independiente de EMR



20% RC a 3 años
30% 8 años



uEMR 8,9% vs 58,9%

Barr PM et al. Blood Adv 2022. Shanafelt TD et al. N Engl J Med 2019;381:432-443

Conclusiones 1

uEMR valor pronóstico a fin de tratamiento en esquemas finitos

En todos? Parece claro en esquemas Ven + anti CD20

No tan claro en combinación Ven + iBTK

Tiempo libre de tratamiento prolongado incluso en pacientes que han convertido a EMR +

Qué hacemos con esa información?

Adaptamos el tratamiento ?

Modificamos el seguimiento ?

NO

Costo en LATAM
Entre 180-500 USD

Utilidad clínica

Pronóstico

Para qué medir ERM?

Guiar el tratamiento

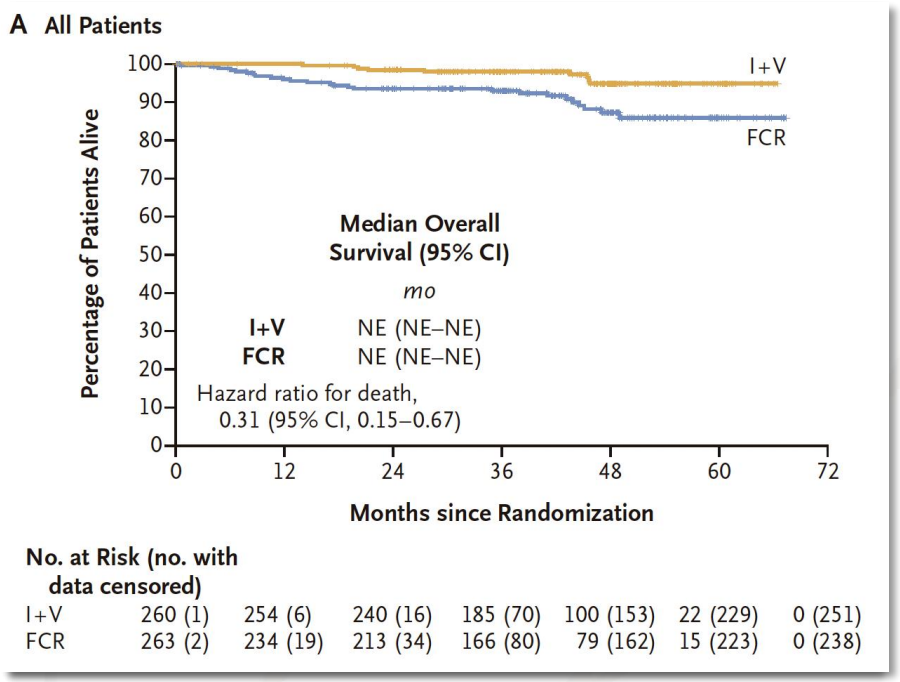
EMR como guía terapéutica

Terapias finitas o terapias limitadas?
Cuánto tiempo de tratamiento necesita CADA paciente??

Varias estrategias para usar EMR como guia para tto (individualizar tiempo de tratamiento de acuerdo a la respuesta alcanzada)

Ensayo				
FLAIR	Fase III 1L	IV	Tiempo a uEMR (duplicando)	CF SP (MO)
CAPTIVATE-mrd	Fase II 1L	IV	EMR fin de tto uEMR placebo vs IB EMR+ IV vs I	CF SP y MO
AMPLIFY (LLC alto riesgo)	Fase II 1L	AVO	Suspensión si uEMR en MO C16 o C24	CF en MO
CLL-2 GiVE	Fase II 1L del17p	Ven-Ib + O	Si EMR+ ciclo 15 IB hasta ciclo 36	CF en SP
CLL2-BAAG	Fase II R/R	Acala-Ven-Ob	Suspension si RC + uEMR en SP x 2	CF en SP

FLAIR



SLP estimada a 3 años 97%

EMR por CF (cutoff 10^{-4})
En SP a 12 meses
Cada 6 meses hasta uEMR
uEMR en SP ⟶ EMR en MO a 6 meses
Tiempo de tratamiento doble del requerido para uEMR

A 2 años 29% suspensión de tratamiento
A 3 años 58% suspensión de tratamiento
A 6 años 78% suspensión

Mediana ciclos Ven-IB 25 (1-70)

Munir T et al. New Engl J Med 2024:390

CAPTIVATE- MRD

3 meses

Ibrutinib

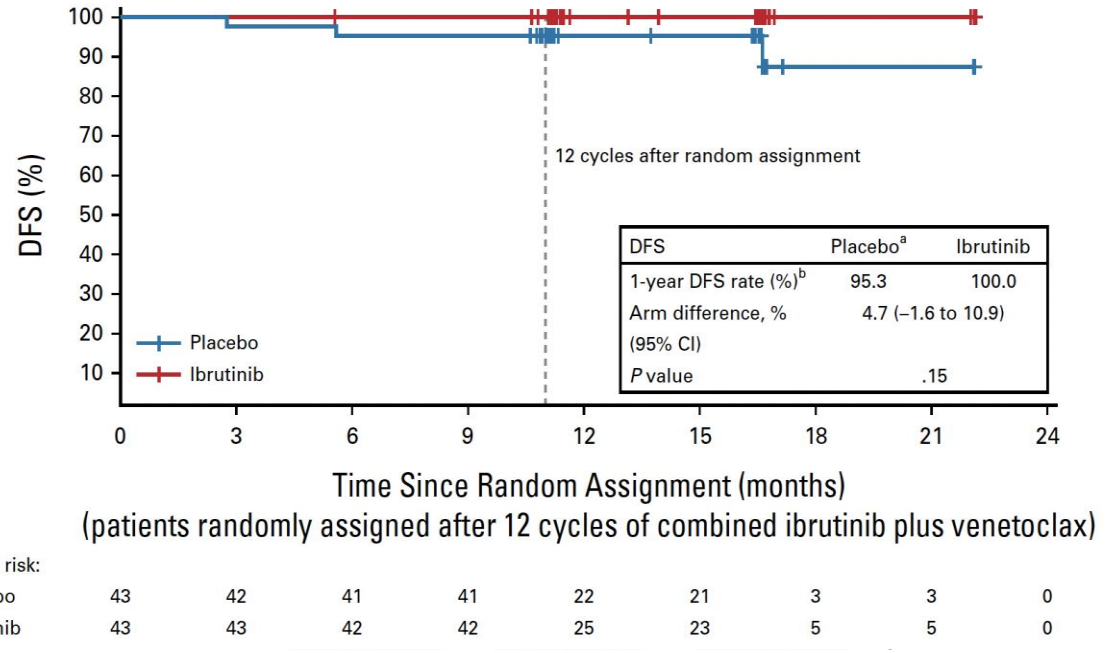
12 meses

Venetoclax

uEMR en SP y MO (2 determinaciones separadas 3 meses)

R: Placebo vs Ibrutinib (hasta conversión EMR o progresión)

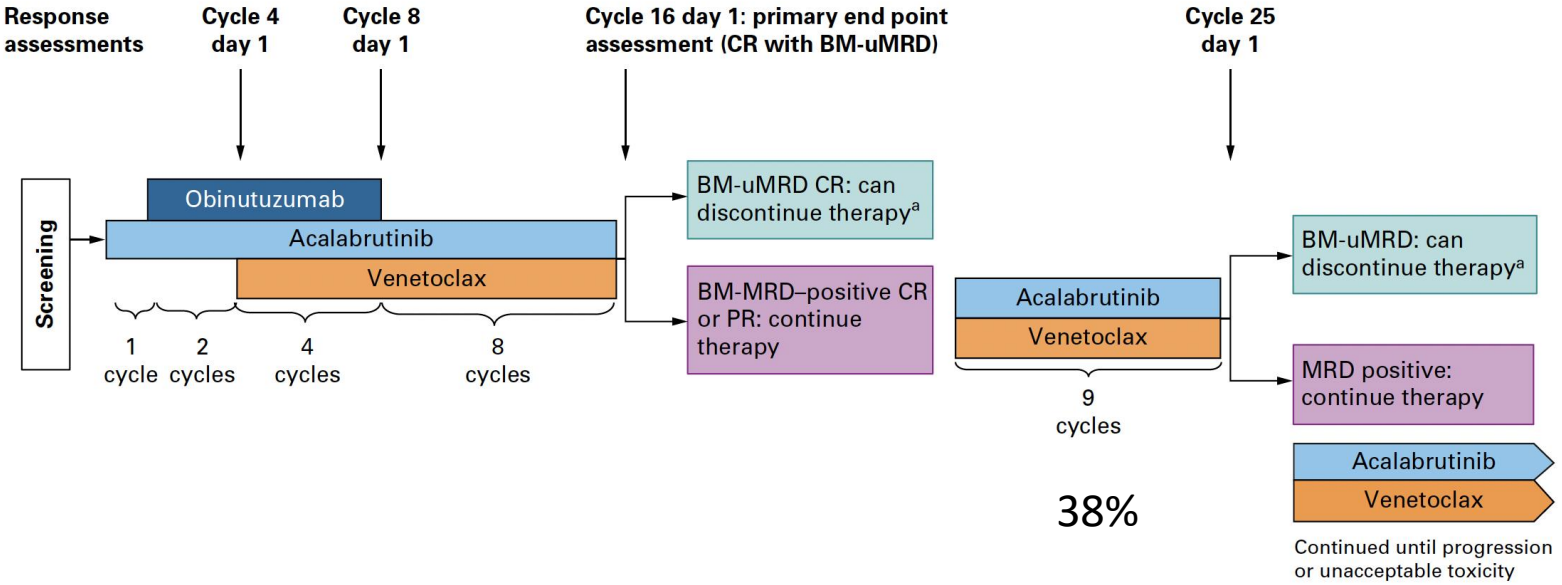
End point: DFS a 12 meses (conversion a EMR+, progresión, muerte)



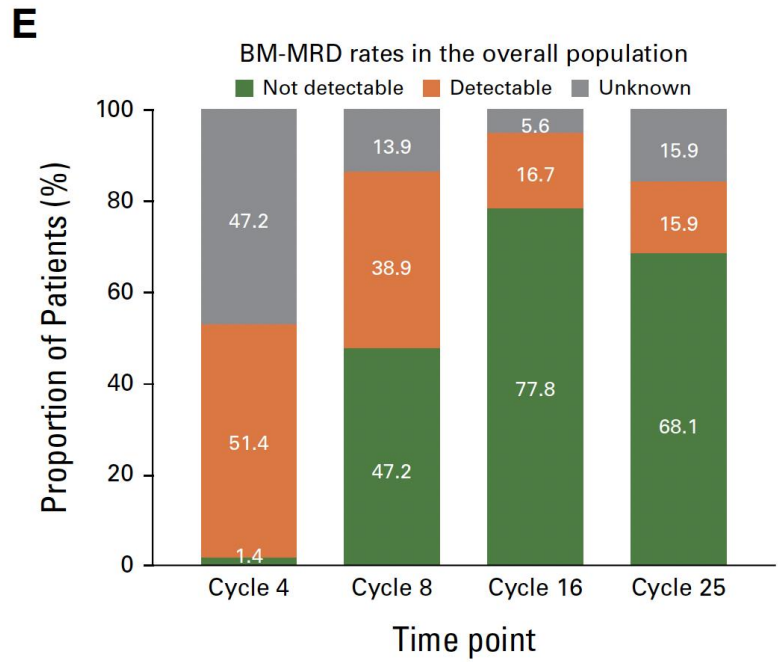
Wierda W et al. J Clin Oncol 2021

AVO (alto riesgo)

N=72 (45 mut p53, 28 CC, 72 IgVH NM)



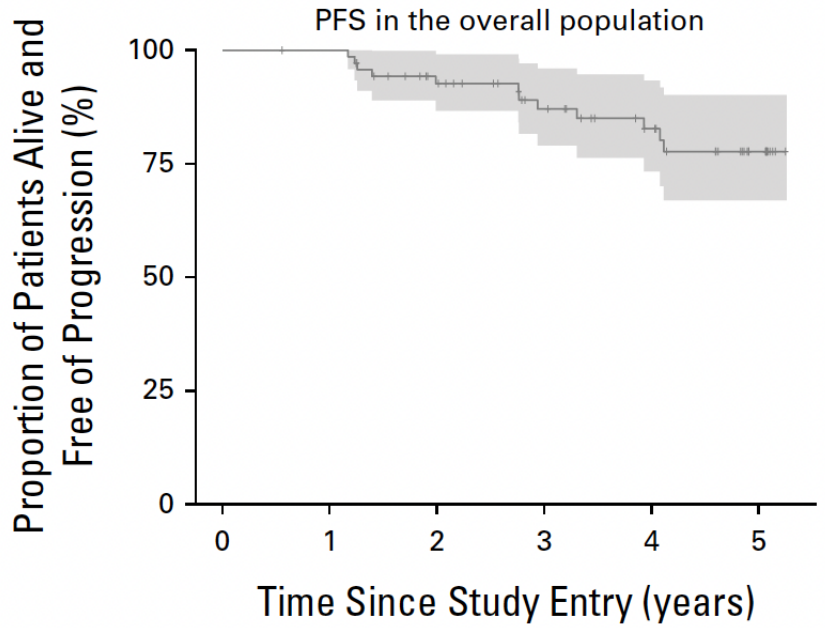
38%



Mediana de ciclos de tratamiento 25

11%

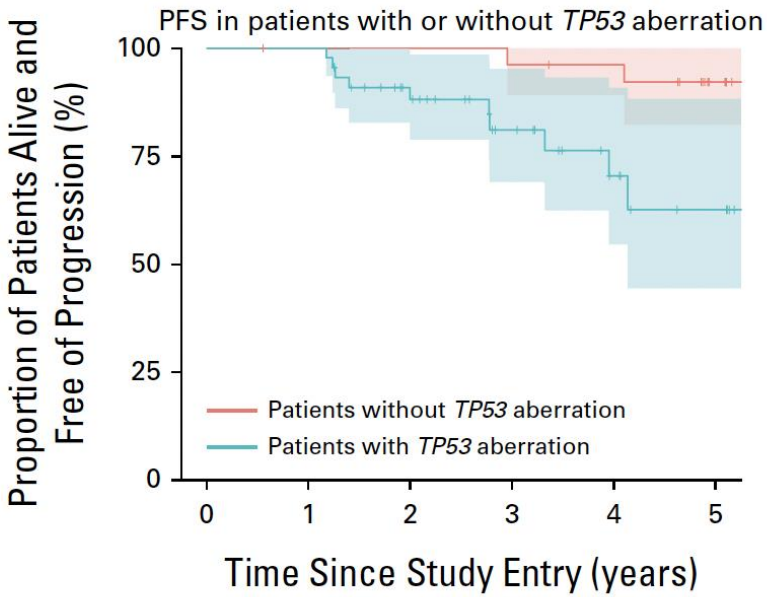
A



Number at risk:

All	72	71	58	45	35	21

B



Number at risk:

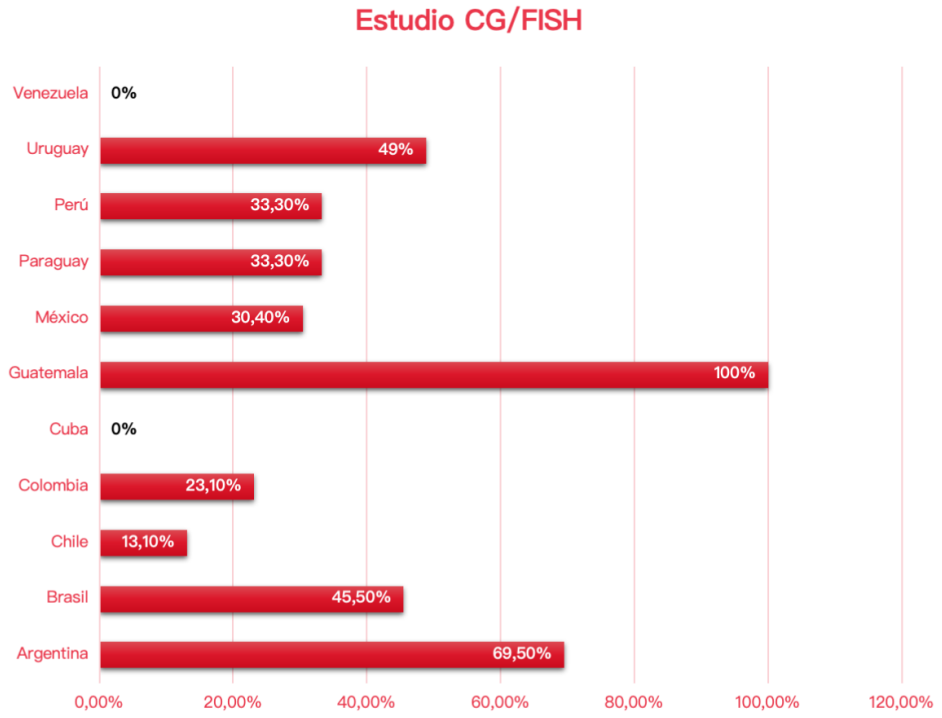
Patients without *TP53* aberration	27	26	26	25	24	15
Patients with *TP53* aberration	45	45	32	20	11	6

SLP 4 años
96% vs 70%

Nuestra realidad en LATAM

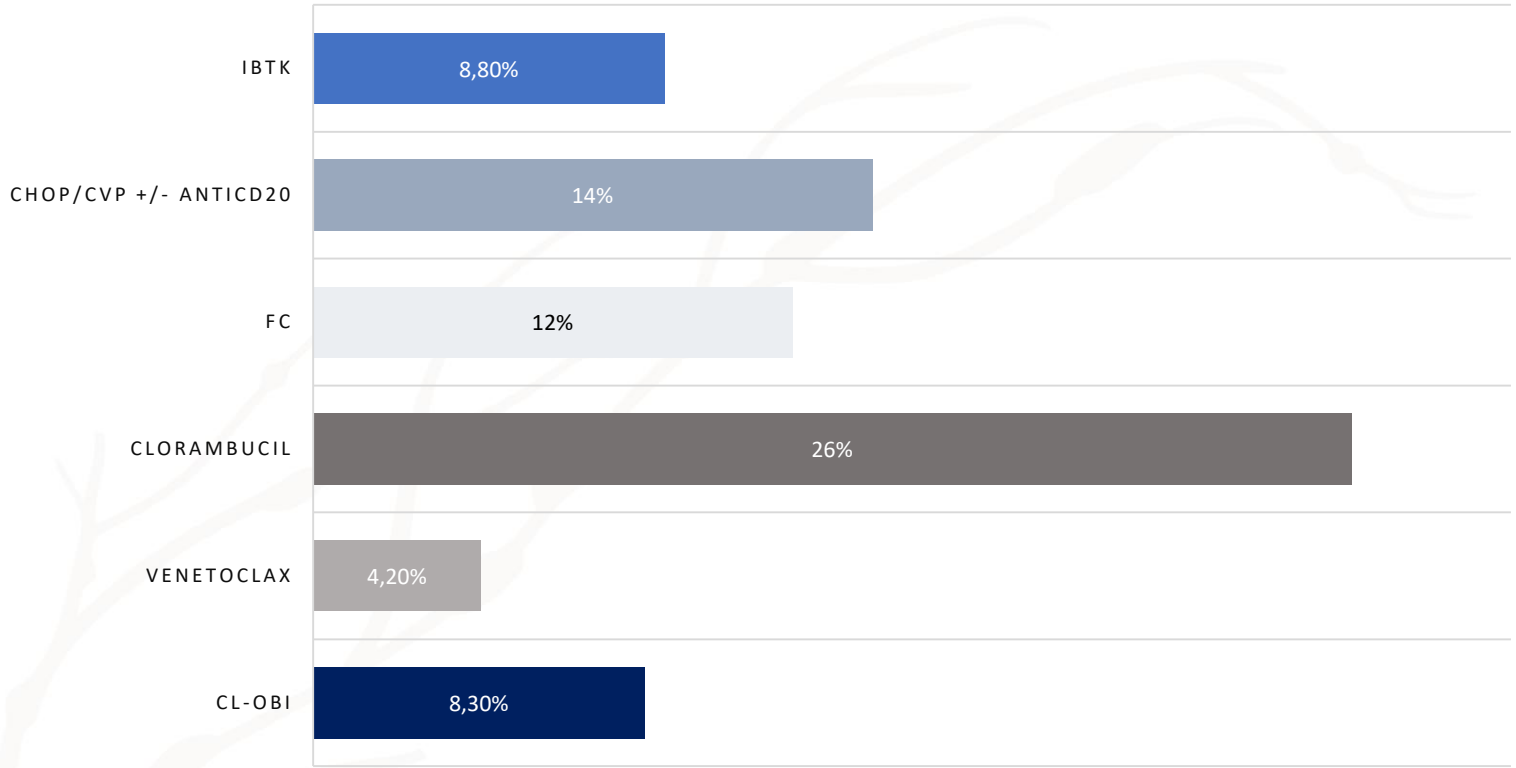
- 910 (44%) patients who received treatment have a previous cytogenetic/FISH analysis

- According to country:
  - Argentina: 69.5%
  - Brasil: 45.5%
  - Chile: 13.1%
  - Colombia: 23.1%
  - Cuba 0%
  - Guatemala: 100%
  - México: 30.4%
  - Paraguay 33.3%
  - Perú: 33.3%
  - Uruguay: 48.9%
  - Venezuela: 0%



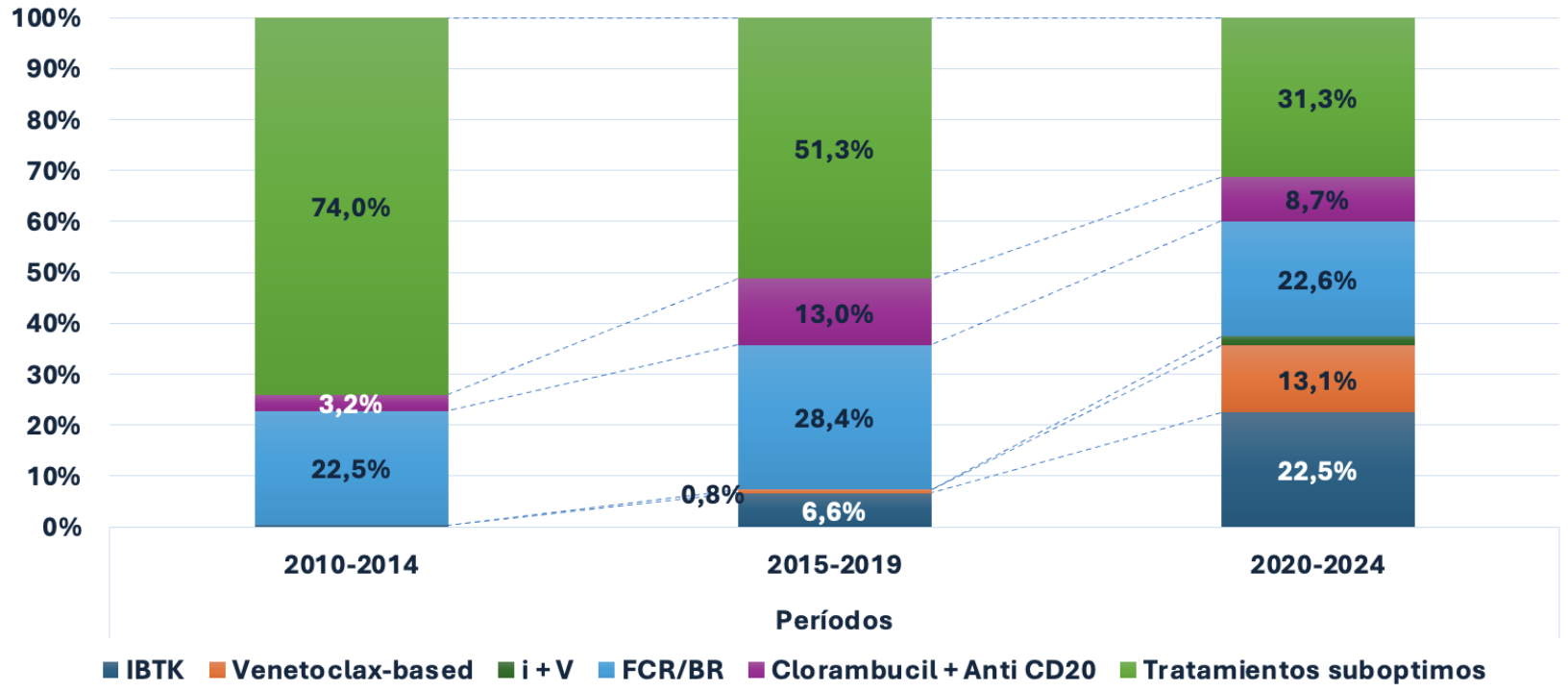
Oliver C et al. ASH 2025

TRATAMIENTO 1L (2010-2024) N=2133



Arrais C et al. ASH 2025

Evolución de los tratamientos de 1L en el tiempo



Current Oncology Reports (2024) 26:136–146

Practical Implications of MRD

Given the large body of evidence demonstrating the correlation between end-of-treatment MRD and long-term clinical outcomes, MRD can be considered an informative biomarker in routine clinical care. Multiple studies have demonstrated that patients who remain MRD-positive $> 10^{-4}$ in peripheral blood have a high risk of early relapses within 2–3 years after treatment [20••, 33••, 70]. Hence, testing of MRD in peripheral blood at the end of treatment by flow cytometry can provide valuable information in some patients for the sake of prognostication. Since so far there is no randomized evidence suggesting a benefit of MRD-guided treatment extension, the MRD status should not be used to modify treatment outside of clinical studies. Likewise, serial MRD assessments currently do not have clinical implications in routine clinical care, as the decision to treat a progressive CLL should be guided by iwCLL criteria for treatment indication [34].

Stumpf J, Al Sawaf O

Chronic Lymphocytic Leukemia: 2025 Update on the Epidemiology, Pathogenesis, Diagnosis, and Therapy

Michael Hallek[1,2,3,4,5]

Collectively, there is overwhelming evidence to suggest that MRD quantification allows for improved PFS prediction in both patients who achieve a PR and CR, supporting its application in all responders. Although evaluation of MRD is still not generally recommended for routine clinical practice [5], I anticipate that MRD assessment will be highly relevant to guide the duration of therapies with novel inhibitors [82]. In my practice, I use MRD levels at increased frequency for the following treatment decisions: (A) Should I continue therapy in a high-risk patient? (B) Should I stop therapy with targeted inhibitors? These questions are also being addressed in trials such as the FLAIR and the CLL18 protocols. These studies use uMRD as guidance to determine treatment duration [76].

Am j Hematol 2025

CONCLUSIONES 2

Cuáles son las necesidades de los pacientes con LLC en LATAM ?

1. Valor pronóstico de medición de EMR al finalizar el tratamiento **NO** tiene implicancias terapéuticas

   A MENOS que se utilicen esquemas guiados por EMR.

2. Con esquemas finitos utilizando nuevos agentes, **EXCELENTES** tasas de SLP y tiempo libre de tratamiento independientemente de ERM

3. Priorizar acceso a agentes dirigidos, idelamente en **TODOS** los pacientes, como **MINIMO** en pacientes con IgVH NO o del17p. ➡ Mejorar el acceso a estudios (IgVH, FISH/molecular para mut p53)

GELL
Grupo de Estudio Latinoamericano de Linfoproliferativos

Muchas gracias