Desayuno con L'Expert:
"Desafíos en el Tratamiento de Linfoma de Células del Manto en Pacientes Recaídos/Refractarios".

Dra. Carolina Mahuad
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Hora	Tema
08:00 - 08:10	**Bienvenida, Introducción y Contexto:**
	Bienvenida y descripción sobre la complejidad de la enfermedad en su fase de recaída
08:10 - 08:40	**Desafíos y Opciones de Tratamiento:**
	Discusión sobre la necesidad médica insatisfecha actual, su impacto en la calidad de vida del paciente y análisis de las opciones de nuevas alternativas terapéuticas y hallazgos de ensayos clínicos recientes
08:40 - 09:00	**Discusión Abierta y Cierre:**
	Espacio para interacción, preguntas y respuestas con la audiencia y reflexiones finales sobre las perspectivas futuras en el manejo de esta enfermedad

Viernes 4 de Abril – 08:00 – 09:00 am
Salón Peulla, Hotel Wyndham Puerto Varas

Desafíos en el tratamiento del linfoma del Manto recaído/refractario

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Hospital Alemán
Deutsches Hospital

HOSPITAL ACREDITADO
JOINT COMMISSION
INTERNATIONAL

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Conflictos de Interés

CATEGORÍA	
Empleado	No
Consultor	Takeda, BGB
Propiedad accionaria	No
Fondos de investigación	No
Honorarios por conferencia	Roche, Raffo, Janssen, Takeda, AZ, Sandoz, BGB, Abbvie
Formar parte del grupo de oradores	Takeda, Roche, AZ, Sandoz, Janssen, Abbvie
Formar parte del comité asesor	Takeda, Roche, Raffo, AZ, BGB, Abbvie
Fondos para un miembro de mi equipo de trabajo	No
Becas para asistencia a congresos/ actividades científicas formativas	Novartis, Roche, Takeda, Pfizer, Janssen, Abbvie, AZ, Sandoz
Otros	No

Agenda

Desafíos en el Tratamiento de Linfoma de Células del Manto en Pacientes Recaídos/Refractarios		
Hora	**Tema**	**Tiempo**
08:00 - 08:05	**Bienvenida y Presentación**	5 min
08:05 - 08:10	**Introducción y Contexto:** Bienvenida y descripción sobre la complejidad de la enfermedad en su fase de recaída	10 min
08:10 - 08:35	**Desafíos y Opciones de Tratamiento:** Discusión sobre la necesidad médica insatisfecha actual, su impacto en la calidad de vida del paciente y análisis de las opciones de nuevas alternativas terapéuticas y hallazgos de ensayos clínicos recientes	25 min
08:35 - 09:00	**Discusión Abierta y Cierre:** Espacio para interacción, preguntas y respuestas con la audiencia y reflexiones finales sobre las perspectivas futuras en el manejo de esta enfermedad	20 min

Conceptos importantes

- Aberraciones citogenéticas y moleculares que condicionan la desregulación de la respuesta al daño del DNA, la progresión del ciclo celular, fenómenos epigenéticos, apoptosis, proliferación
- A pesar de la respuesta inicial a la IQT, es una enfermedad que usualmente recae y se transforma en refractaria en el transcurso de pocos años
- Este curso natural de la enfermedad es el fundamento de inducción, consolidación y mantenimiento que se propone en el manejo del linfoma del manto a fin de evitar las recaídas tardías

El linfoma del manto sigue siendo hoy una enfermedad incurable

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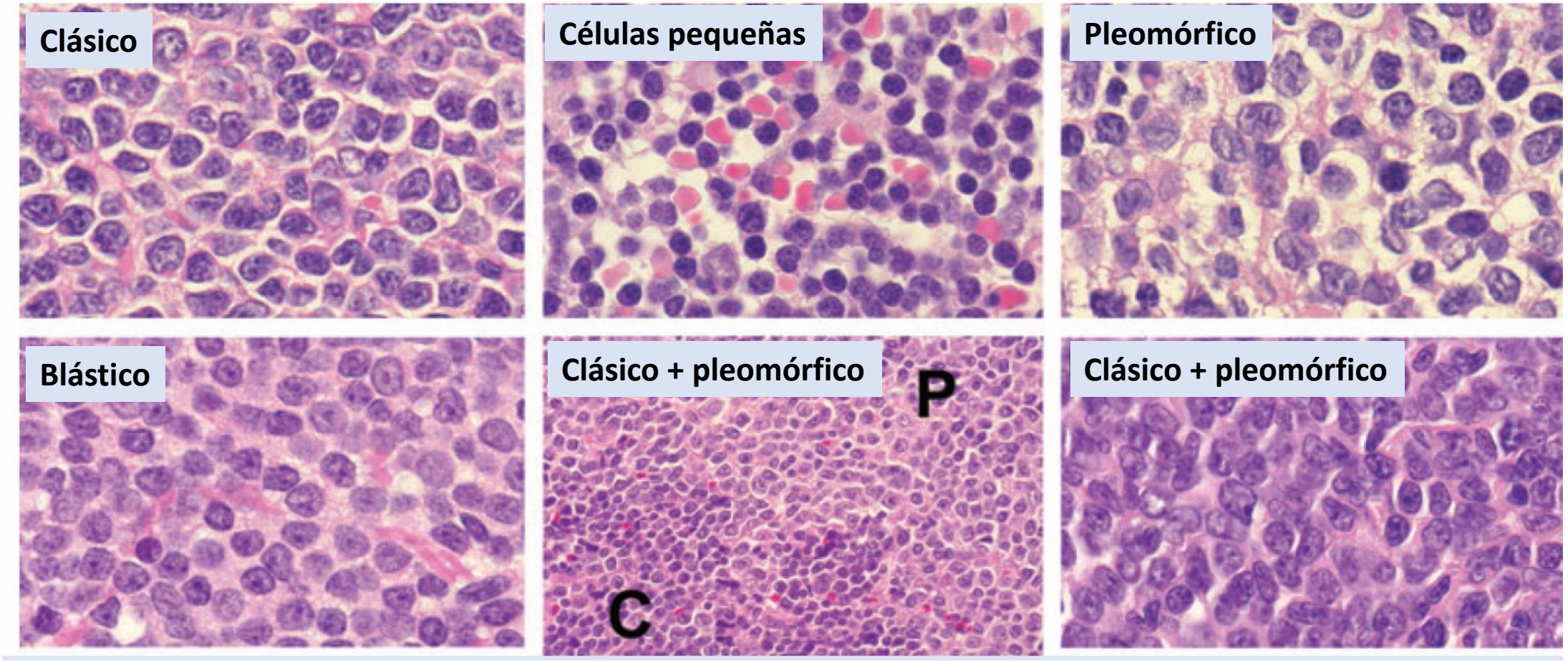
Telford C et al, https://doi.org/10.1016/j.clinthera.2019.09.012
Klener P. https://doi.org/10.1080/14728222.2020.1813718

Es una enfermedad con histología heterogénea



Tiemann, Br J Haematol 2005

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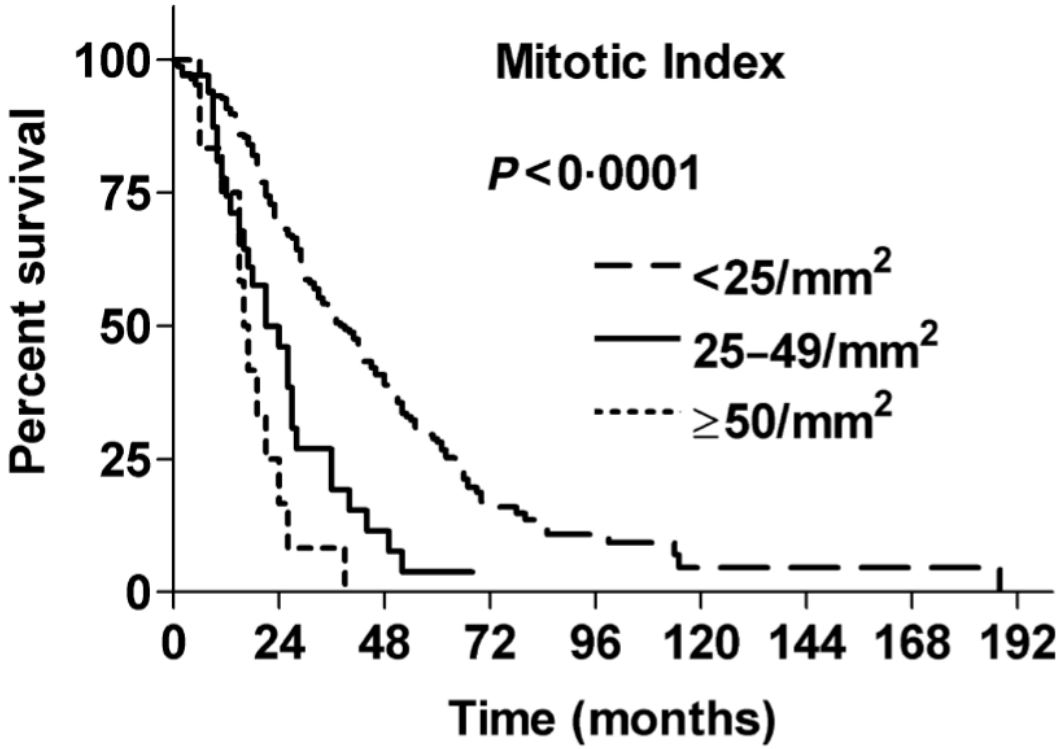
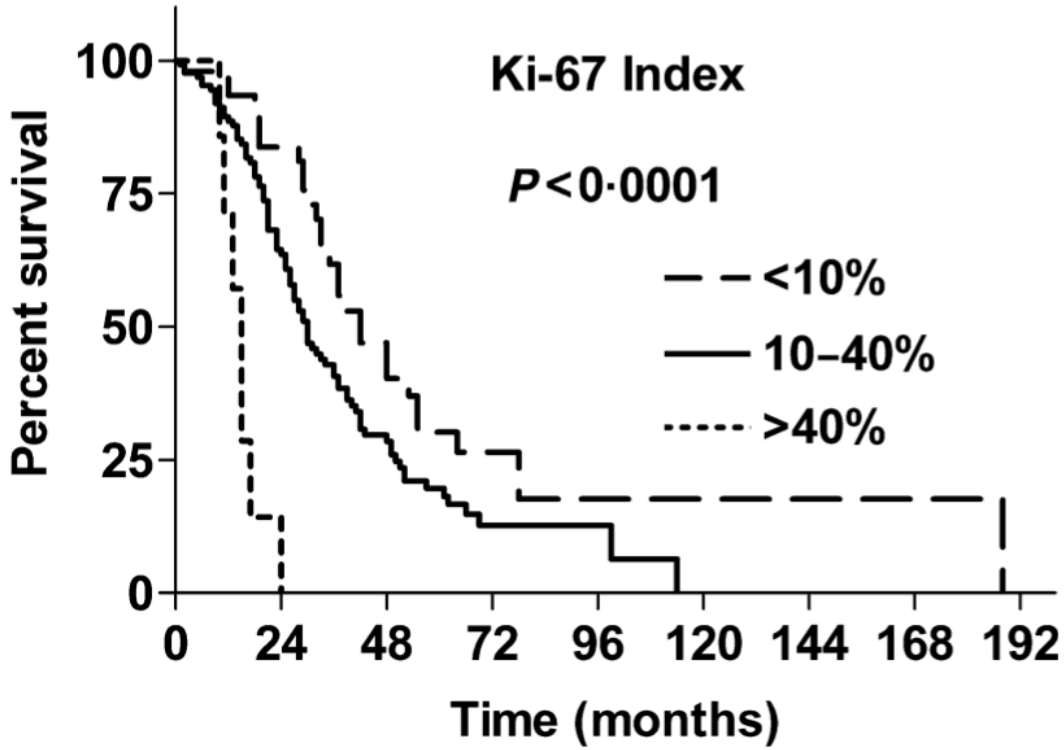
Enfermedad con comportamiento clínico heterogéneo y riesgo biológico heterogéneo: Correlación entre el índice mitótico y Ki67 con supervivencia





Tiemann, Br J Haematol 2005

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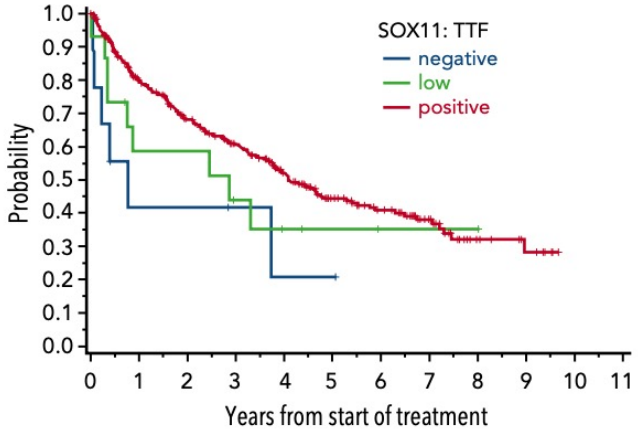
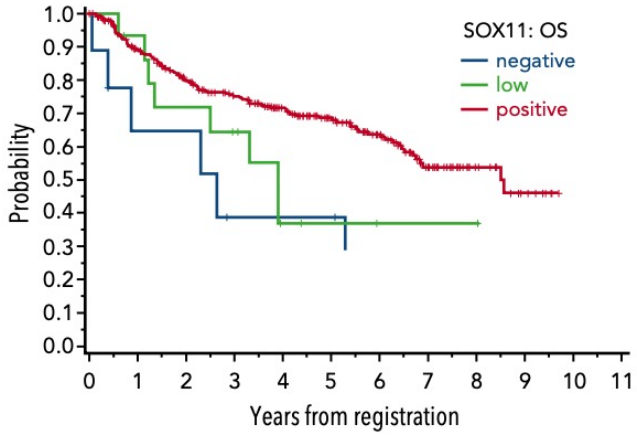
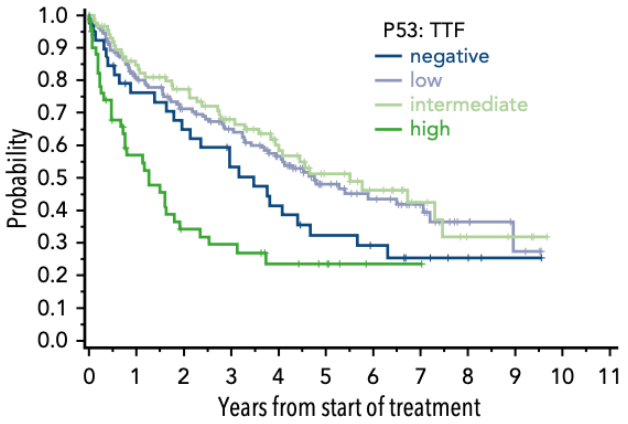
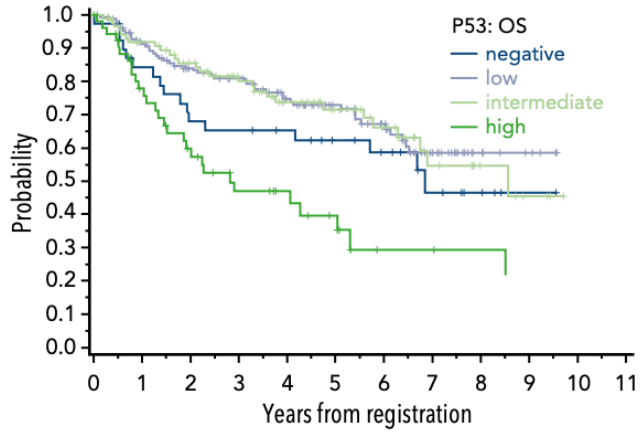
La expresión de TP53 por inmunohistoquímica (>50% células positivas) está asociada desenlace, en forma independiente al MIPI y Ki67 (Red Europea de MCL)









Multivariate analysis for OS using the parameters TP53 expression, Ki67 index, and MIPI score

Variable and comparison	*P*	HR	95% confidence interval	Events overall
TP53				
Negative vs low	.21	1.43	0.82-2.51	118/348
Intermediate vs low	.88	1.04	0.64-1.67	
High vs low	<.0001	3.01	1.87-4.83	
TP53				
Negative vs low	.19	1.52	0.81-2.87	96/276
Intermediate vs low	.58	0.86	0.50-1.47	
High vs low	.0043	2.20	1.28-3.78	
Ki-67 index				
+10%	.0002	1.20	1.09-1.32	
TP53				
Negative vs low	.17	1.56	0.82-2.94	96/276
Intermediate vs low	.28	0.74	0.43-1.27	
High vs low	.0068	2.09	1.23-3.55	
Ki-67 index				
+10%	.012	1.13	1.03-1.25	
MIPI score				
1	<.0001	2.00	1.46-2.74	

Aukema Blood 2018

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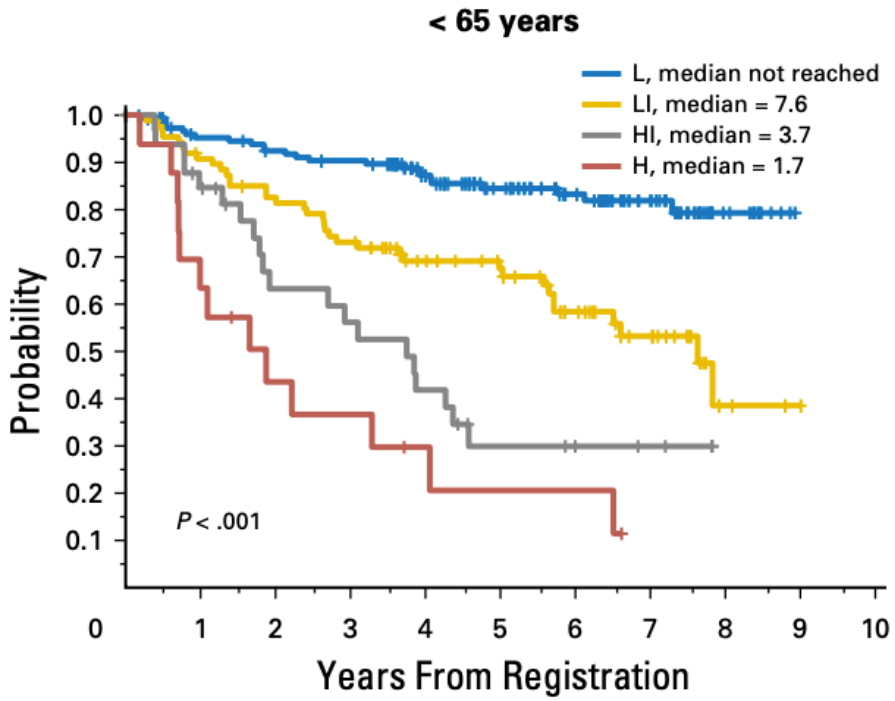
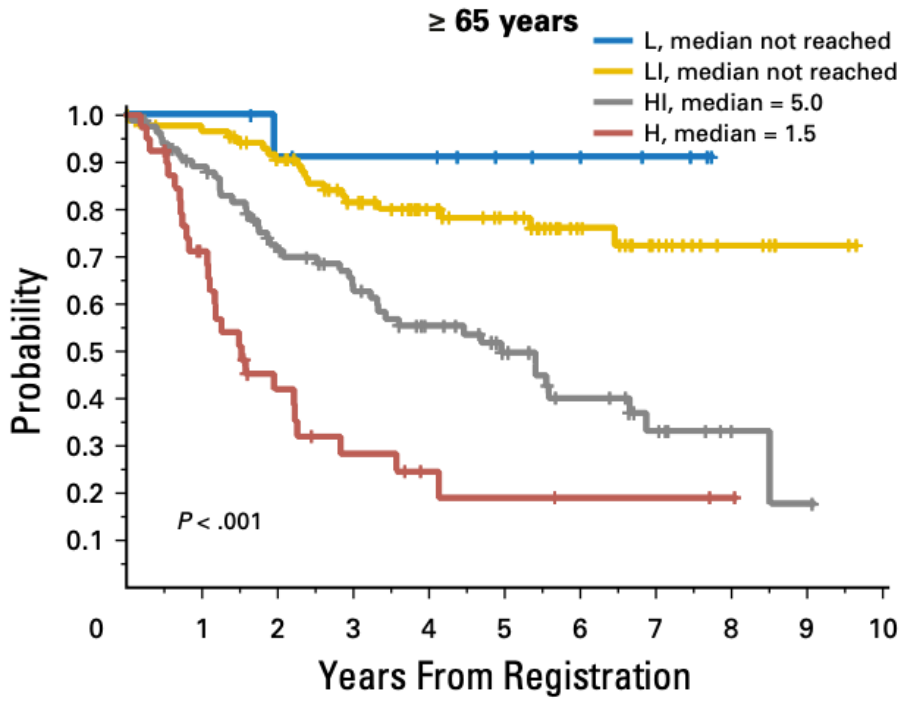
SG: MIPI-c





El uso del Ki-67 es superior al uso de la citología y el patrón de crecimiento como factores pronósticos en el manto

La combinación modificada (MIPI-c) del índice Ki-67 y MIPI mostró una estratificación de riesgo refinada, reflejando sus fuertes efectos pronósticos complementarios

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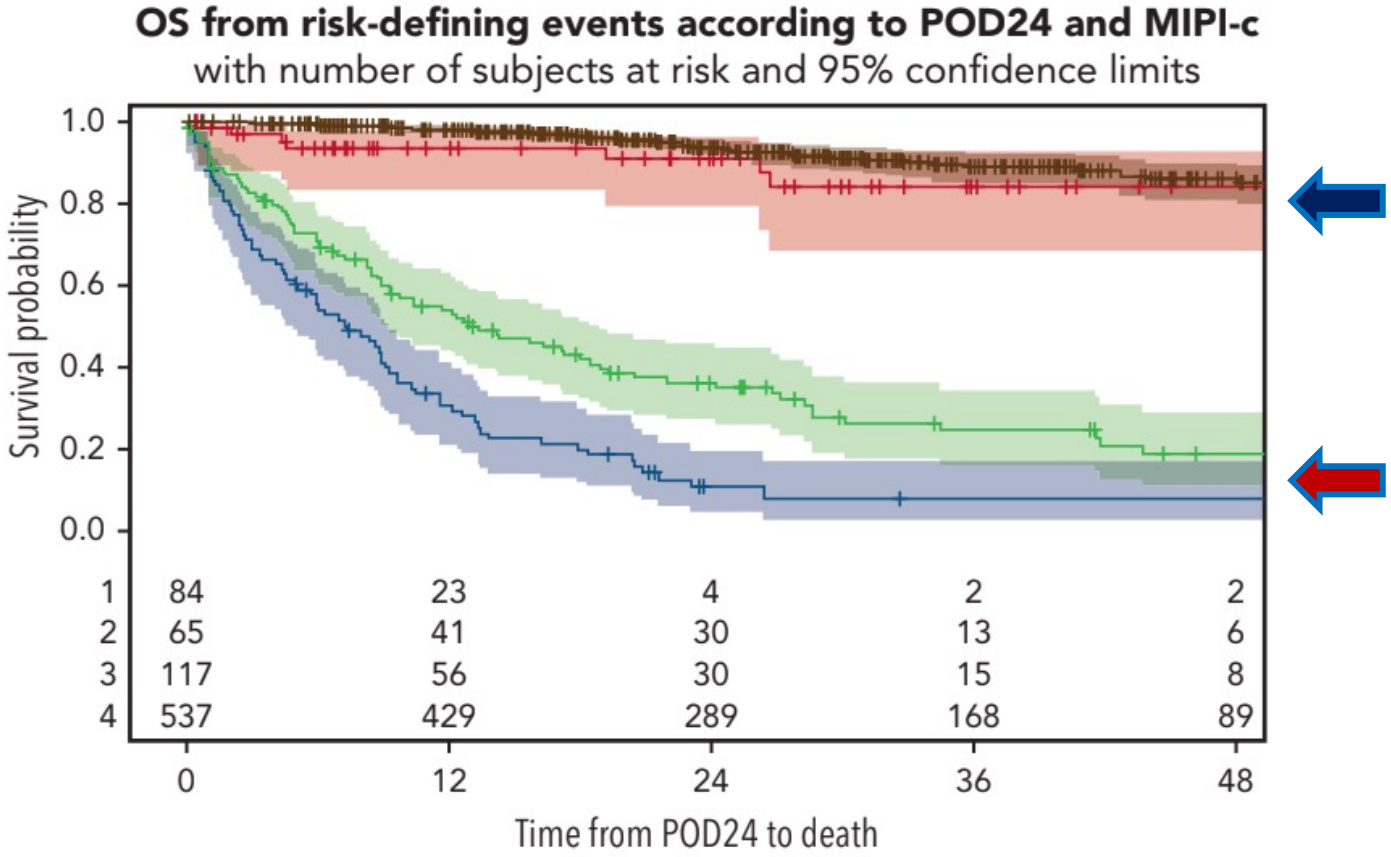
Hoster, JCO 2016

Relevancia del MIPI-c en la predicción de POD24



Silkenstedt E, Dreyling M. Blood 2025;145:673

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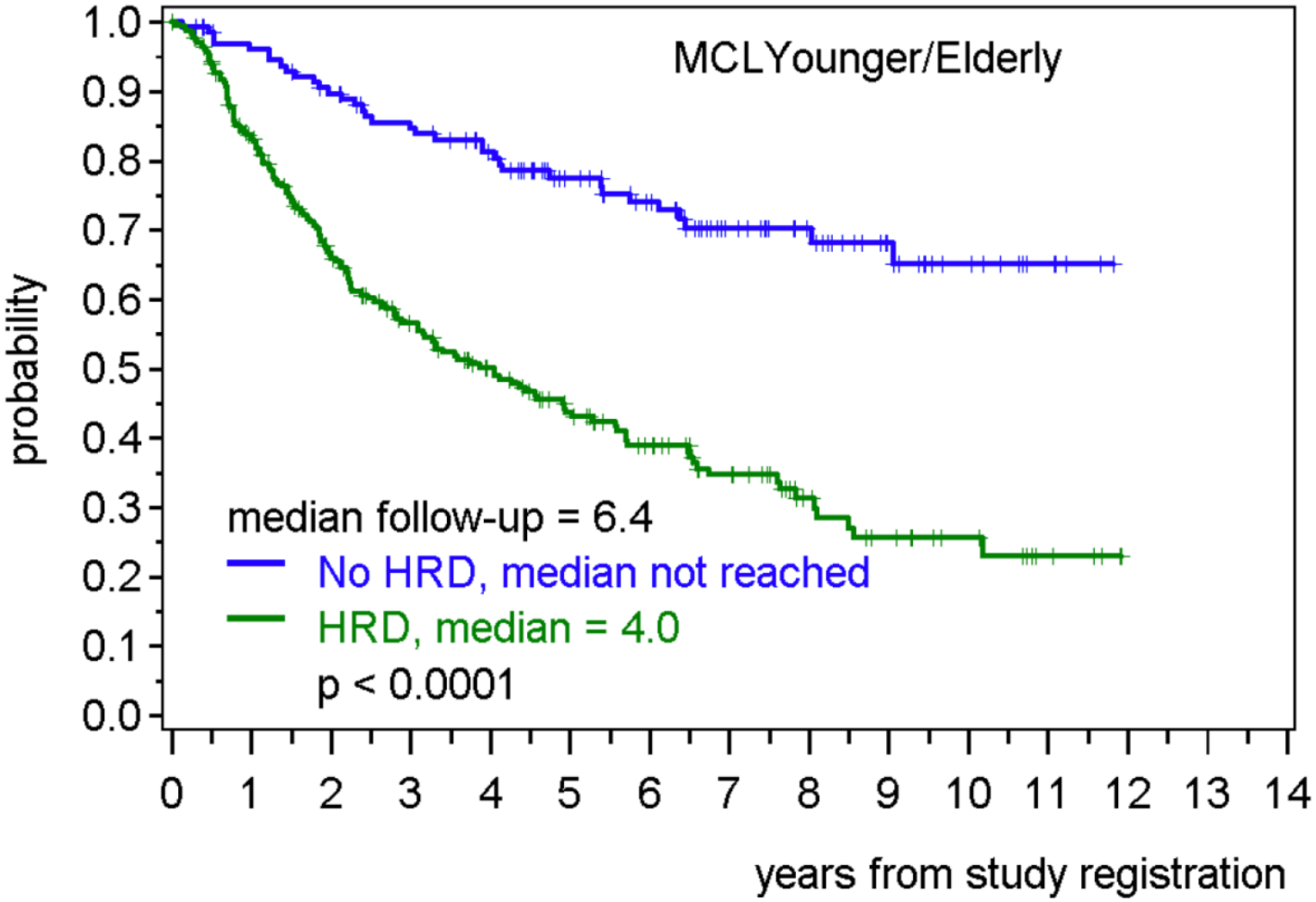
Manto de alto riesgo: Blastoide, Ki67 >30%, Mut TP53

SG



Dreyling, EHA 2020

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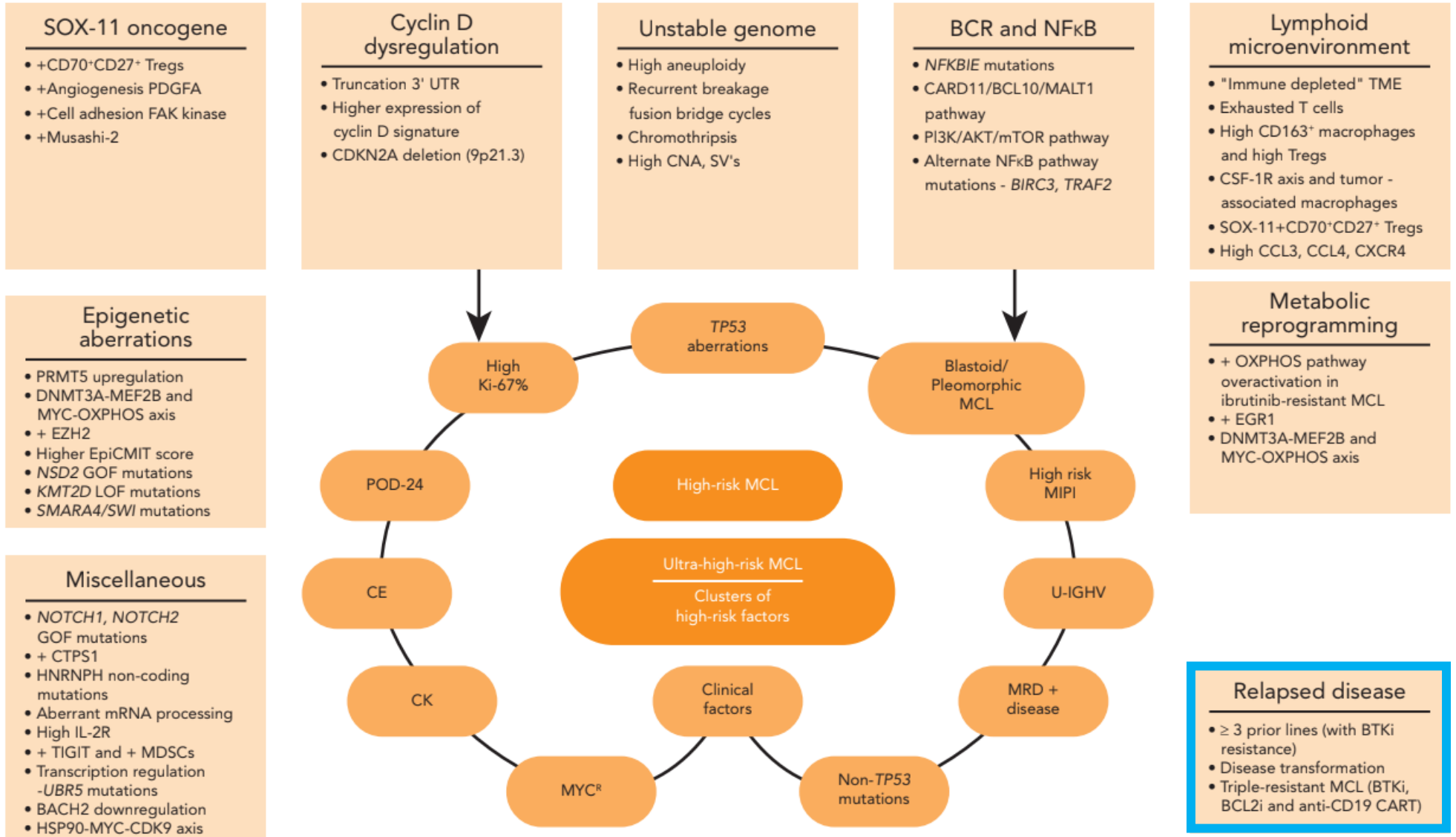
Factores patogénicos y pronósticos en el Manto de alto riesgo



Jain P, Wang M. Blood 2025;145:683

Supervivencia global promedio a 5 años: 50% en estadios avanzados, 70% en enfermedad localizada

SG 65–70% para pacientes jóvenes que reciben Ara-C y TAMO (50% para ancianos)

Predictors of indolent versus aggressive MCL (from Cohen et al. [20]).

Indolent	Aggressive
Asymptomatic	B-symptoms present
Good performance status	High risk MIPI score
Normal LDH	Elevated LDH
Ki67% < 30%	Ki67% > 30%
Early stage disease	Complex karyotype
Non-nodal, leukemic presentation	Blastoid variant, del 17p/TP53 mutation

LDH: lactate dehydrogenase.

Punctation for all factors and median survival for all risk group based on MIPI score [23,30].

Group of risk	MIPI score	Median survival
Low risk	0–3	Median survival not reached after median 32 months follow-up and 5-year OS rate of 83%
Intermediate risk	4–5	5-year OS: 63%
High risk	6–11	5-year OS: 34%

Median survival for all risk groups on combined MIPI [30].

Risk group	Overall survival (years)
Low	9.4
Low-intermediate	4.9
High-intermediate	3.2
High	1.8

Smolevsky P et al EXPERT OPINION ON PHARMACOTHERAPY
https://doi.org/10.1080/14656566.2019.1642871

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Características de alto riesgo en pacientes de reciente diagnóstico o enfermedad R/R

Features	Newly diagnosed MCL	R/R MCL*
Accepted ultra-high-risk features	De novo blastoid or pleomorphic histology with high-risk mutations[40] Ki-67% ≥50%† in involved tissue biopsy with blastoid or pleomorphic histology[12,41] ‡*TP53* mutation (R273) with other high-risk gene mutations (*KMT2D, NSD2, CCND1, NOTCH1, CDKN2A, NOTCH2,* or *SMARCA4* mutations) and extensive disease burden[42] CNS involvement with systemic disease[43]	Transformed blastoid or pleomorphic histology (transformed from classic histology; ie, disease resistant to BTKi, venetoclax, and anti-CD19 CART)[40] Primary BTKi-refractory disease [12] Refractory to ≥3 previous lines of standard therapy (including BTKi)[12] Triple-resistant MCL (disease resistant to BTKi, venetoclax, and anti-CD19 CART)[12,33]
Accepted high-risk features	Blastoid or pleomorphic histology[40] Ki-67 ≥50%† in involved tissues with classic histology[12,41] *TP53* mutation[14] and/or del(17p) by FISH, *TP53* overexpression by IHC, and/or non-*TP53* mutations (*NOTCH1/NOTCH2, KMT2D, NSD2,* and *SMARCA4* mutations)[44] CK[45] *MYC* rearrangement and/or amplification[46-50] *TP53* expression in >50% of cells or a high combined MIPI score Simplified MIPI score ≥6.2[51] Bulky disease‖	High-risk features for patients with newly diagnosed disease[12] ≤2 previous lines of standard therapy Progression within 24 months of first-line therapy[52] MRD$^+$ status after therapy§

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Jain P, Wang M. Blood 2025;145:683

Manto: un espectro de enfermedades

Indolente (15%) | ***Clásico (80%)*** | ***Transformado (5%)***

t(11;14)
Cyclin D1

RB1 | p27

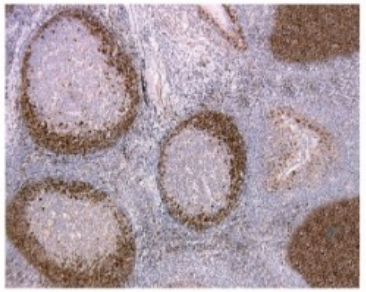

Figure 1 Tonsil: neoplastic cells are positive for cyclin D1 and located in the mantle zone of lymphoid follicles. At the upper and lower coins of the right side, primary follicles show numerous neoplastic cells (immunoperoxidase, anti-cyclin D1, ×100).

ATM
CHK2

↓

Complex karyotypes

INK4A/CDK4/RB1
ARF/MDM2/p53

↓

High proliferation

Dreyling, ESMO CR 2014

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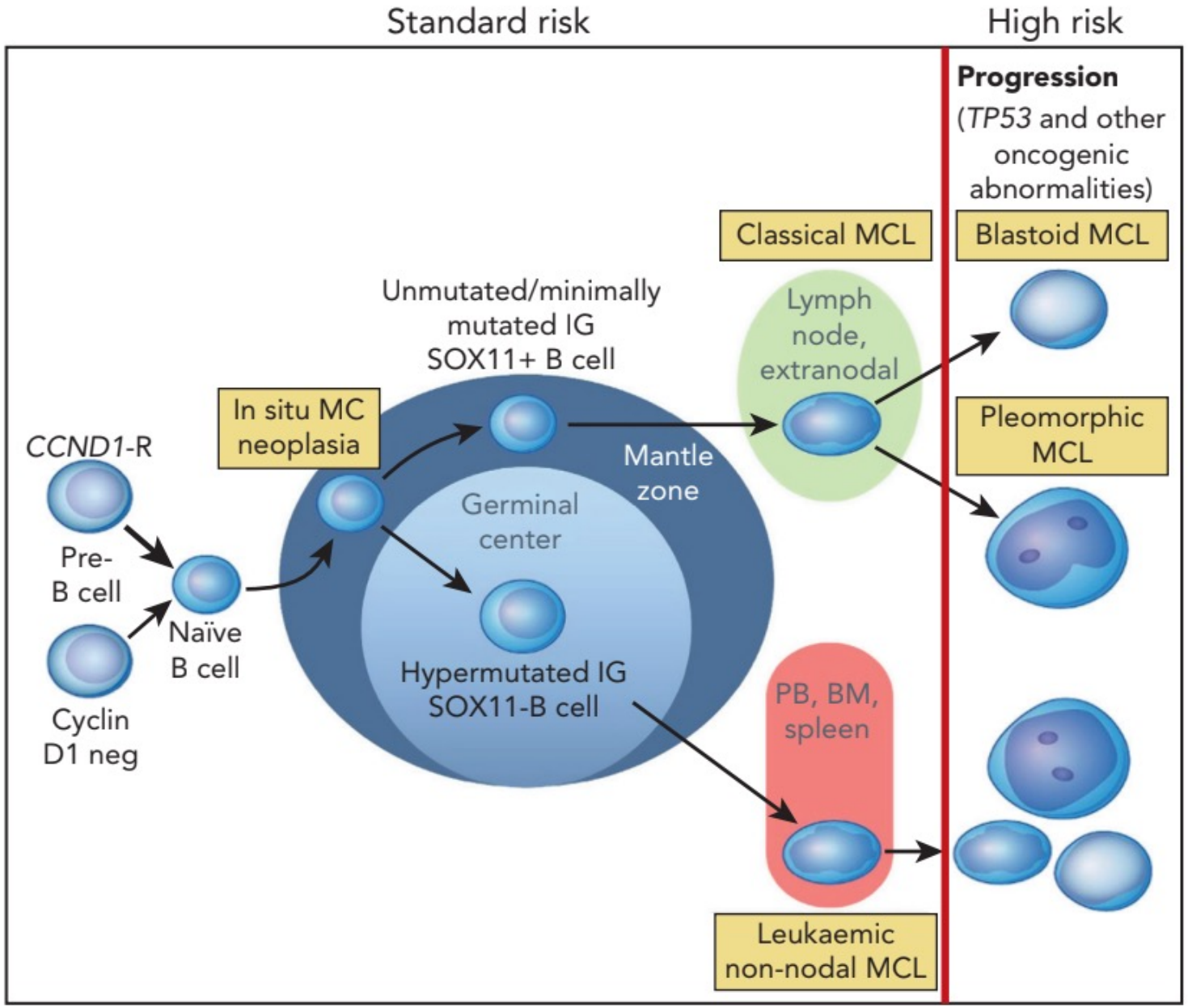
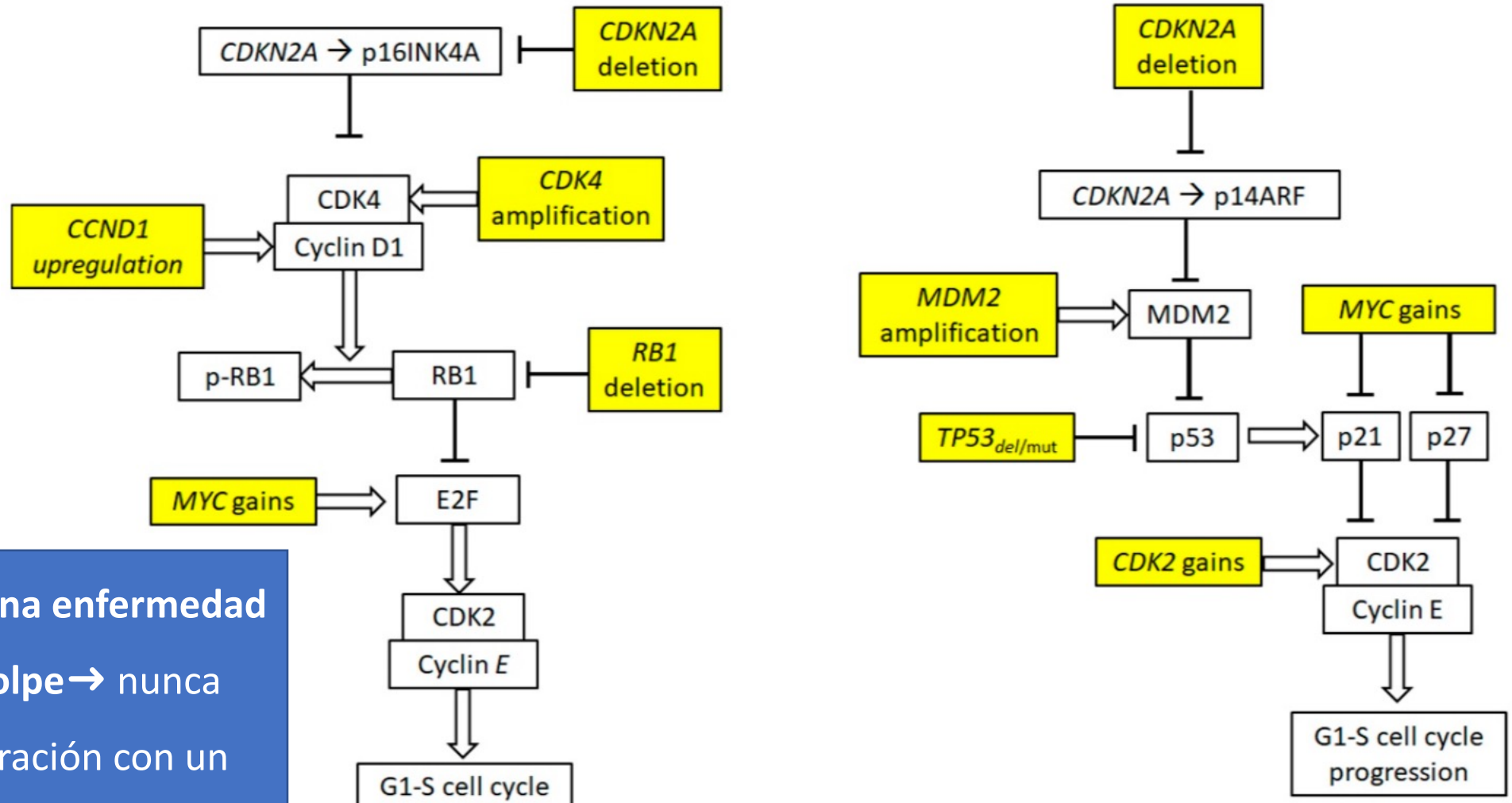
Manto: dos enfermedades diferentes



Dreyling, ESMO 2017
Silkenstedt E, Dreyling M. Blood 2025;145:673

Desregulación del ciclo celular en el linfoma del manto



El manto no es una enfermedad de un único golpe→ nunca alcanzará la curación con un único blanco terapéutico

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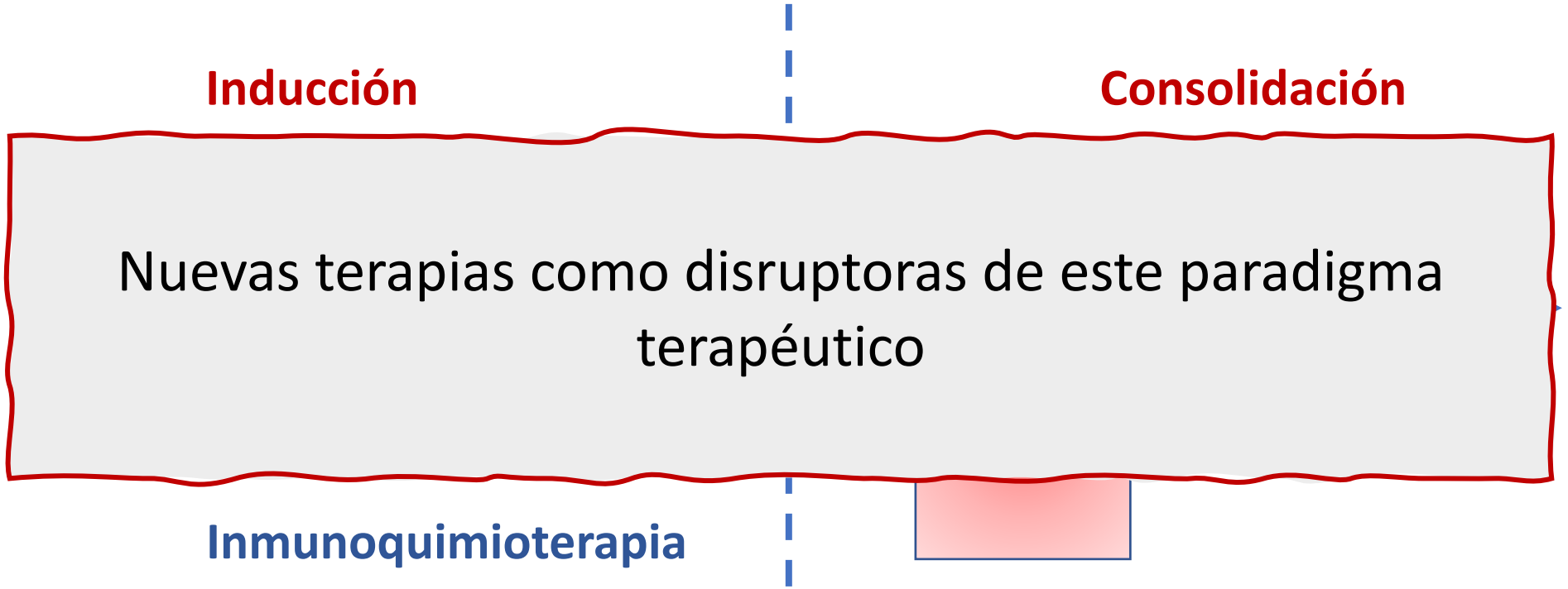
Klener P. Int. J. Mol. Sci. 2019, 20, 4417; doi:10.3390/ijms20184417

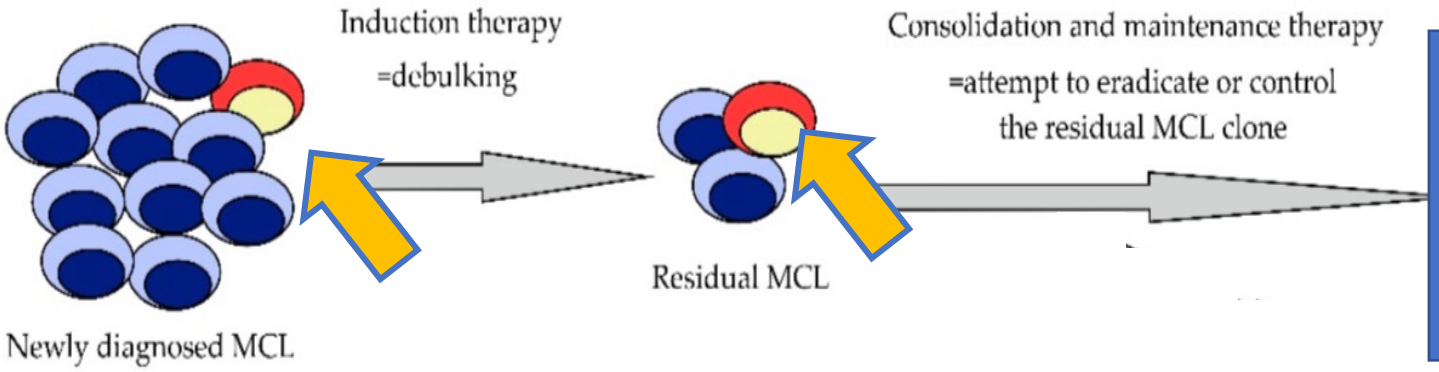
Concepción actual del tratamiento óptimo del LCM



➡ **Remisión del Linfoma**

➡ **Eliminación de la EMR**

¿Por qué iBTK en 1L?



Mejorar las respuestas a este nivel con blancos terapéuticos podría evitar la pérdida de respuesta posterior

Población R/R

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Ryan C et a. Blood 2025;145:663

Tratamiento óptimo del linfoma del manto

¿Vale el mismo tratamiento para todos los pacientes?

NO

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Algunas certezas…

- Tiempo a la primera recaída, consideración importante para la elección de la segunda línea
- Recaídas tempranas antes de los 24 meses→ pronóstico ominoso
- Enfermedad refractaria a primera línea → nuevos fármacos
- El mejor desempeño de **iBTK en 2da línea**
- La duración de la respuesta con iBTK depende de la profundidad de la respuesta
- Pacientes con mutación en TP53, respuesta menos robusta, no alcanzan RC (análisis de 370 pacientes enrolados en PCYC-1104, RAY trials y el estudio fase 2 SPARK)

Smolevsky P et al EXPERT OPINION ON PHARMACOTHERAPY
https://doi.org/10.1080/14656566.2019.1642871

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SUGGESTED TREATMENT REGIMENS[a,b]

INDUCTION THERAPY		
Stage I or Stage II nonbulky (contiguous or noncontiguous)[c] or Classical *TP53* wildtype: Stage II bulky noncontiguous; Stage III, IV	**Classical *TP53* wildtype: Stage II bulky noncontiguous; Stage III, IV**	**Classical *TP53* mutated: Stage II bulky noncontiguous; Stage III, IV**
Less Aggressive Induction Therapy **Preferred regimens** • Acalabrutinib[f,g] (continuous) + bendamustine + rituximab • Bendamustine + rituximab[d] • VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone) • RCHOP[e] • Lenalidomide (continuous) + rituximab **Other recommended regimen** • Acalabrutinib[f,g] (continuous) + rituximab	**Aggressive Induction Therapy** **Preferred regimens (in alphabetical order)** • LyMA regimen: RDHA (rituximab, dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) x 4 cycles followed by RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) for non-PET CR • NORDIC regimen: Dose-intensified induction immunochemotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone (maxi-CHOP) alternating with rituximab + high-dose cytarabine • Rituximab, bendamustine[h] followed by rituximab, high-dose cytarabine • TRIANGLE regimen (fixed duration): Alternating RCHOP + covalent BTKi[f]/RDHA (rituximab, dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) (category 2A for ibrutinib; category 2B for acalabrutinib or zanubrutinib) **Other recommended regimen** • HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab[i] (NOTE: There are conflicting data regarding the need for consolidation with HDT/ASCR) • RBAC500 (rituximab, bendamustine,[h] cytarabine)	**Suitable for all patients** • Zanubrutinib/obinutuzumab/venetoclax **Suitable for aggressive induction therapy:** • TRIANGLE regimen (fixed duration): Alternating RCHOP + covalent BTKi[f]/RDHA (rituximab, dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) (category 2A for ibrutinib; category 2B for acalabrutinib or zanubrutinib) **Not suitable for aggressive induction therapy:** • Less aggressive induction therapy regimens (as recommended for classical *TP53* wildtype)

SUGGESTED TREATMENT REGIMENS[a,b]

MAINTENANCE AFTER HDT/ASCR OR AGGRESSIVE INDUCTION THERAPY
• Covalent BTKi (fixed duration)[f] x 2 years[j] (category 2A for ibrutinib; category 2B for acalabrutinib or zanubrutinib) + rituximab every 8 weeks x 3 years
MAINTENANCE AFTER LESS AGGRESSIVE INDUCTION THERAPY
• Rituximab every 8 weeks for 2–3 years following RCHOP (category 1) or Bendamustine + rituximab ▸ Maintenance rituximab following VR-CAP or RBAC500 has not been evaluated

¿Qué hacer frente al la recaída?.....

¿Qué podemos hacer en nuestra región?

SECOND-LINE AND SUBSEQUENT THERAPY	
Preferred regimens (in alphabetical order) • Covalent BTKi (continuous)[f,k] ▸ Acalabrutinib[g] ▸ Zanubrutinib • Lenalidomide (continuous) + rituximab **Other recommended regimen** • Covalent BTKi (continuous)[f] ▸ Ibrutinib[l] ± rituximab	**Useful in Certain Circumstances (in alphabetical order)** • Bendamustine[h] + rituximab (not recommended if treated with prior bendamustine) • Bortezomib ± rituximab • DHA (dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) + rituximab (if not previously given) • GemOx (gemcitabine, oxaliplatin) + rituximab • Ibrutinib[f] (continuous) + venetoclax • RBAC500 (rituximab, bendamustine,[h] cytarabine) (not recommended if treated with prior bendamustine) • Venetoclax[f] (continuous) ± rituximab • Progressive disease after prior covalent BTKi ▸ Non-covalent BTKi (continuous) ◊ Pirtobrutinib[f,m] ▸ CAR T-cell therapy[n] ◊ Brexucabtagene autoleucel (CD19-directed) ◊ Lisocabtagene maraleucel (CD19-directed) • Progressive disease after CAR T-cell therapy and pirtobrutinib or ineligible for CAR T-cell therapy ▸ Glofitamab-gxbm[f,o] (category 2B)

¿Cómo responden los pacientes luego de la segunda recaída o posterior en la era moderna?

- Desenlace poco caracterizado luego de la segunda recaída
- Kumar et al: estudio retrospectivo de 404 pacientes tratados en forma consecutiva entre 2000 y 2014 en el Memorial Sloan Kettering Cancer Center
- Diagnóstico histológico centralmente confirmado, pacientes con seguimiento longitudinal desde el diagnóstico
- Mediana SG 9.7 años, SLP 4.0 años **luego de 1L**
- **2L→** mediana SG 41.1 meses y SLP 14.0 meses
- **3L→** 25.2 y 6.5 meses
- **4L →** 14.4 y 5.0 meses

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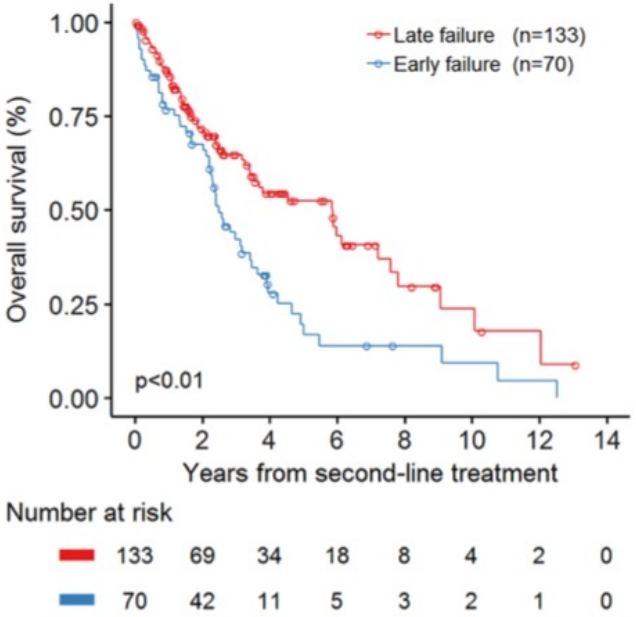
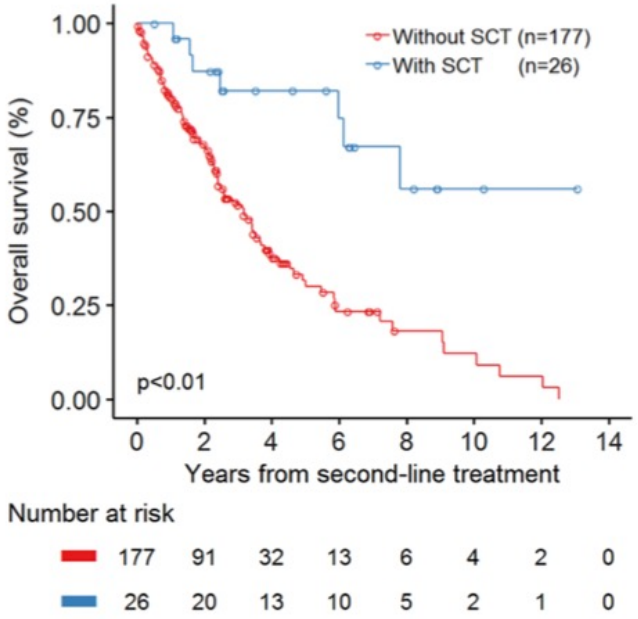
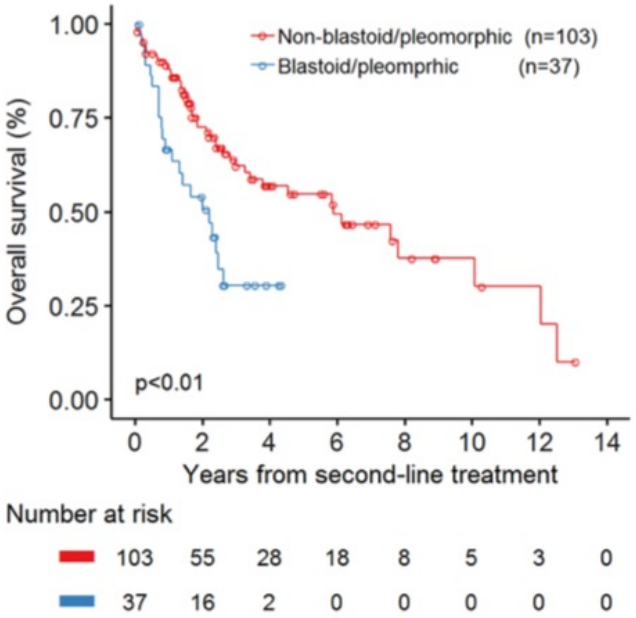
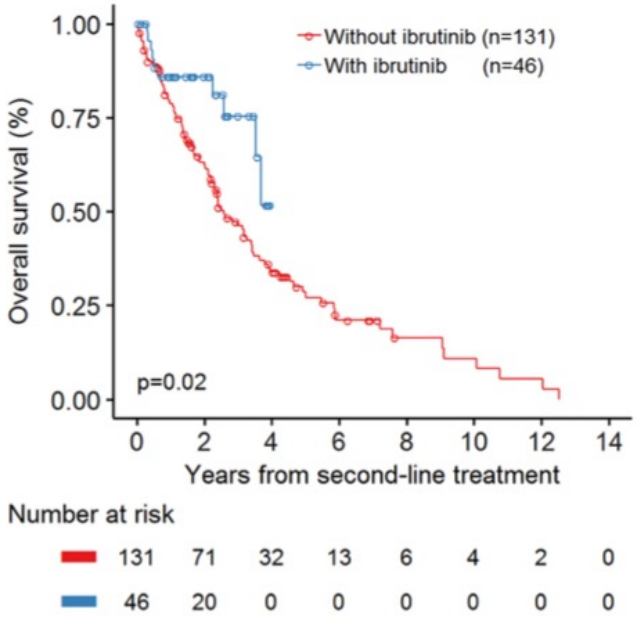
Kumar et al. Blood Cancer Journal (2019)9:50









77 pacientes con enfermedad R/R recibieron iBTK entre 2012 y 2018 → mediana de líneas previas 1 (rango 1–7)

iBTK **como 2L confiere mejor supervivencia** respecto de 3L o posterior (SG: HR, 0.27, P < 0.01; SLP: HR, 0.52; P = 0.03)

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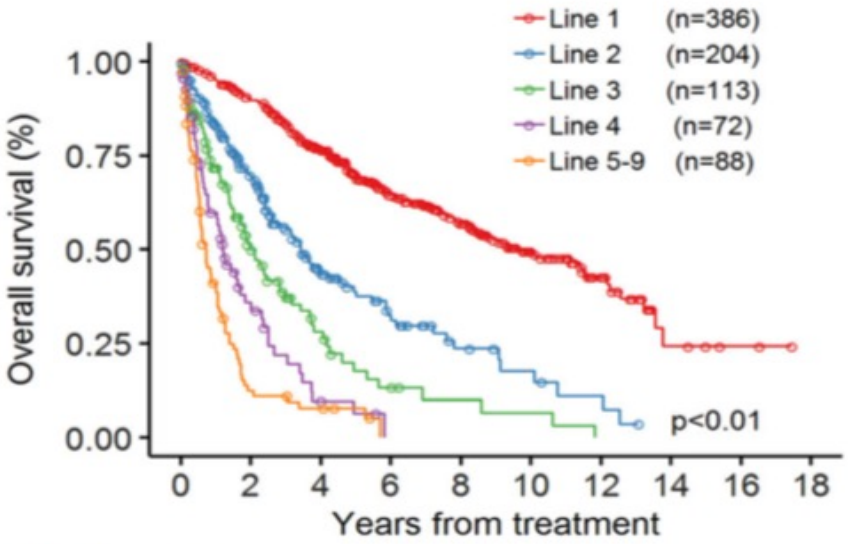
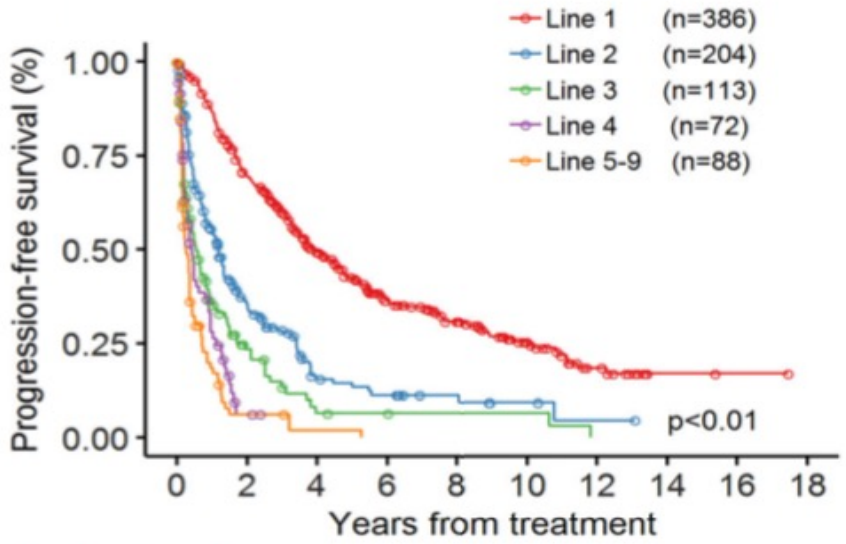
Kumar et al. Blood Cancer Journal (2019)9:50





- No hay consenso sobre la mejor estrategia terapéutica en manto R/R
- A pesar de las respuestas alentadoras con nuevas moléculas → **respuestas parciales y de corta duración**
- Necesidad clínica no cubierta: nuevas estrategias sobre todo en recaídas tempranas

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Kumar et al. Blood Cancer Journal (2019)9:50

Nordic MCL2 2000-2005
MCL3 2005-2009

Characterization of TP53 mutated MCLs

		TP53 unmutated (N=156)		TP53 mutated (N=20)		
	(N)	N	*%*	N	*%*	*p*
Baseline characteristics						
MIPI high risk	*(176)*	24	***15***	14	***70***	*<0.0001*
MIPI-c high risk	*(152)*	12	***9***	11	***58***	*<0.0001*
Blastoid morph.	*(176)*	19	***12***	12	***60***	*<0.0001*
KI67>30%	*(152)*	50	***38***	15	***79***	*0.001*
Treatment response						
CR pre-ASCT*	*(176)*	111	***71***	5	***25***	*0.0002*
CR post-ASCT*	*(176)*	141	***90***	9	***45***	*<0.0001*
No ASCT	*(176)*	8	***5***	5	***25***	*0.001*
MRD assesment						
MRD pos., pre-ASCT	*(99)*	32	***36***	7	***70***	*0.037*
MRD pos., post-ASCT	*(135)*	10	***8***	6	***50***	*<0.0001*

** CR or CRu.*

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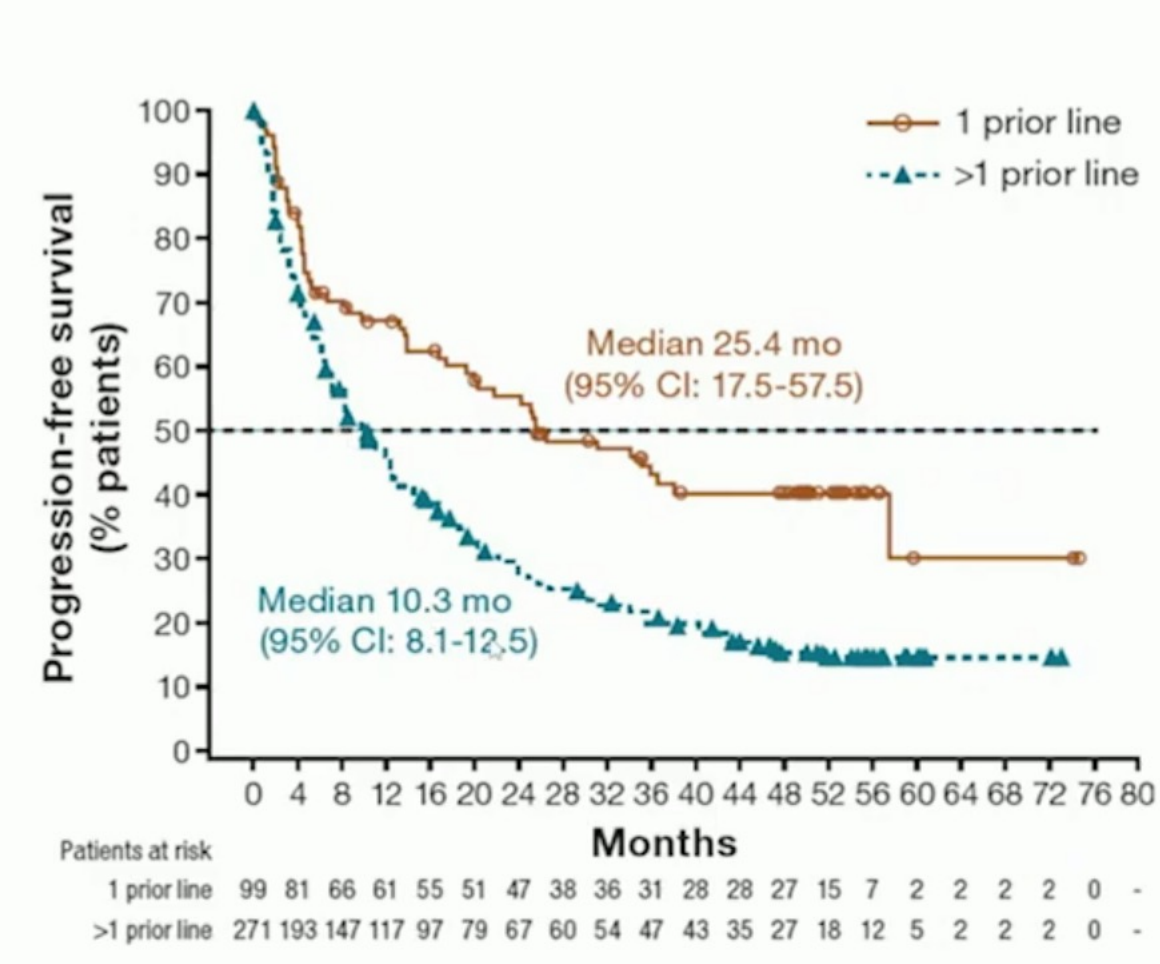
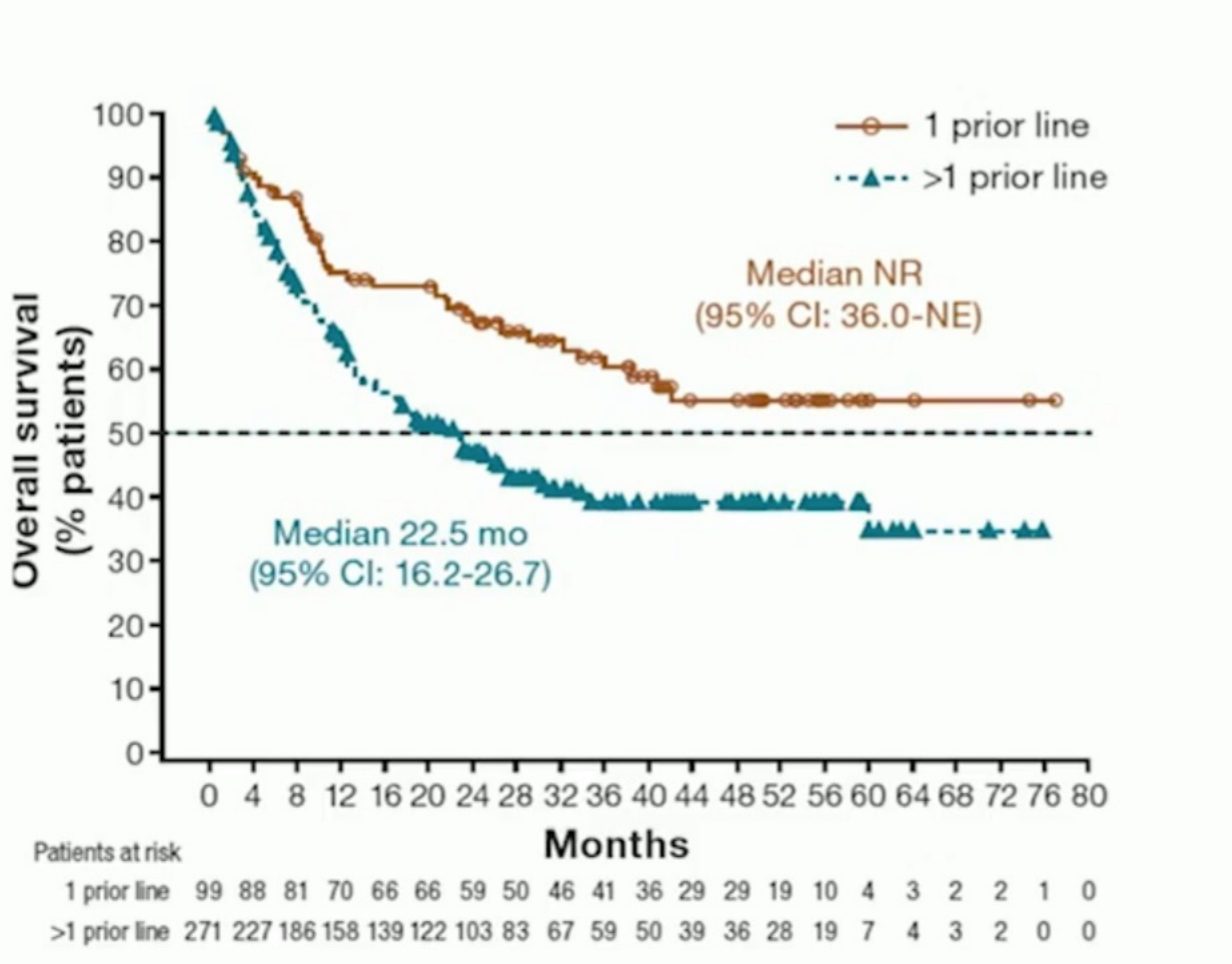
Eskelund et al, Blood 2017

iBTK son mejores como 2L





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Rule S, Haematologica 2019

Acalabrutinib en Linfoma del Manto: ACE-LY-004

- ACE-LY-004 estudio internacional, abierto de rama única, fase 2 para pacientes adultos con linfoma del manto R/R luego de 1-5 líneas terapéuticas
  - Confirmación de t(11;14)(q13;q32) y/o sobreexpresión de ciclina D1
  - Enfermedad medible
  - ECOG menor o igual a 2

Acalabrutinib monoterapia (100 mg cada 12 hs) hasta progresión o toxicidad limitante

Desenlace primario: respuesta global evaluada por el investigador (Criterios de respuesta de Lugano. Chesson 2014)

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Lancet. 2018 February 17; 391(10121): 659–667

Acalabrutinib en Linfoma del Manto: ACE-LY-004

- 124 pacientes incluídos en los análisis de eficacia y seguridad
- Edad media 68 años (rango = 42–90 años), 80% hombres,
- 75% Ann Arbor estadio IV
- 72% extranodal
- Febrero 12, 2018: mediana de seguimiento de 26 meses (rango = 0.3–35.1 meses)
- 40% (n = 49) aún en tratamiento

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Lancet. 2018 February 17; 391(10121): 659–667
Clin J Oncol Nurs. 2020 Aug 1;24(4):392-398

ACE-LY-004: Eficacia

Investigator-assessed and IRC-assessed responses

	Investigator-assessed response
Overall response (complete response + partial response)	100 (81%; 73–87)
Best response	
Complete response	49 (40%; 31–49)
Partial response	51 (41%; 32–50)
Stable disease	11 (9%; 5–15)
Progressive disease	10 (8%; 4–14)
Not evaluable	3 (2%; 1–7)

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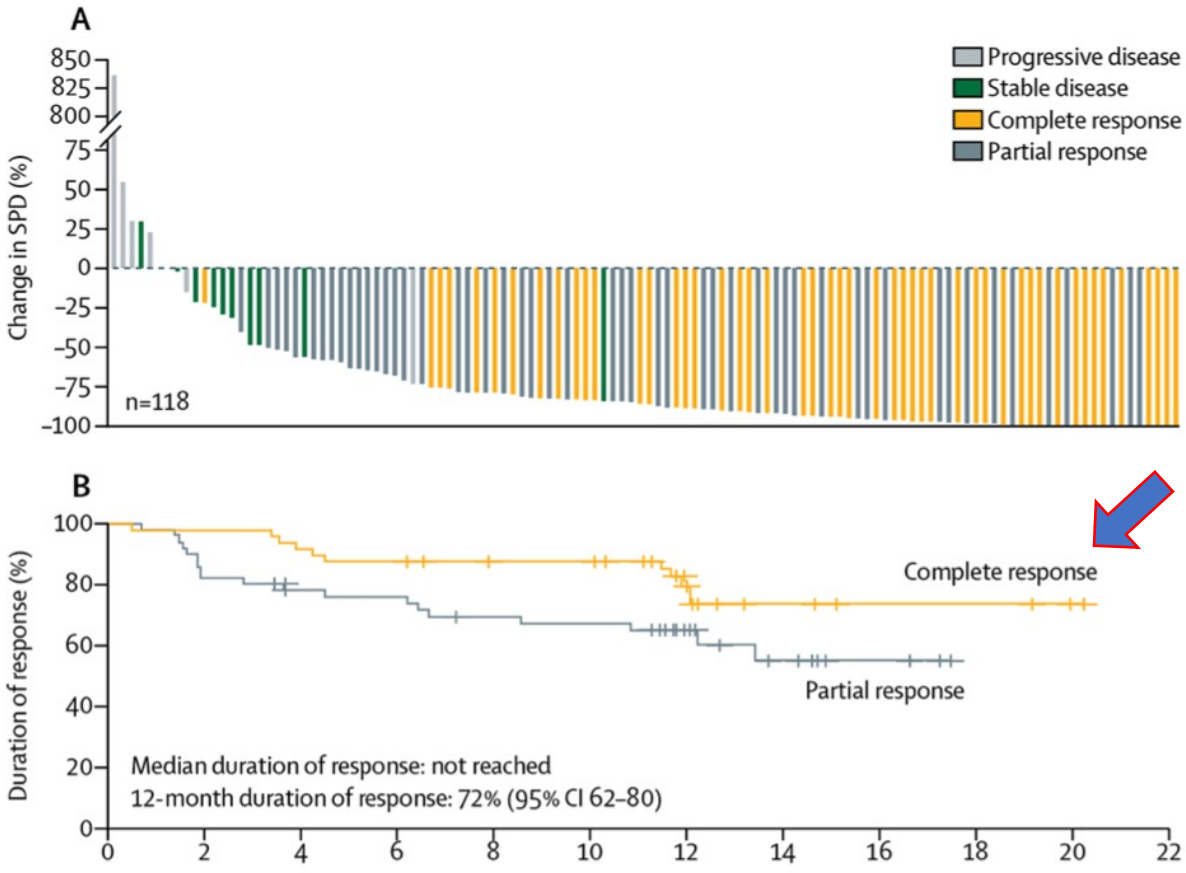
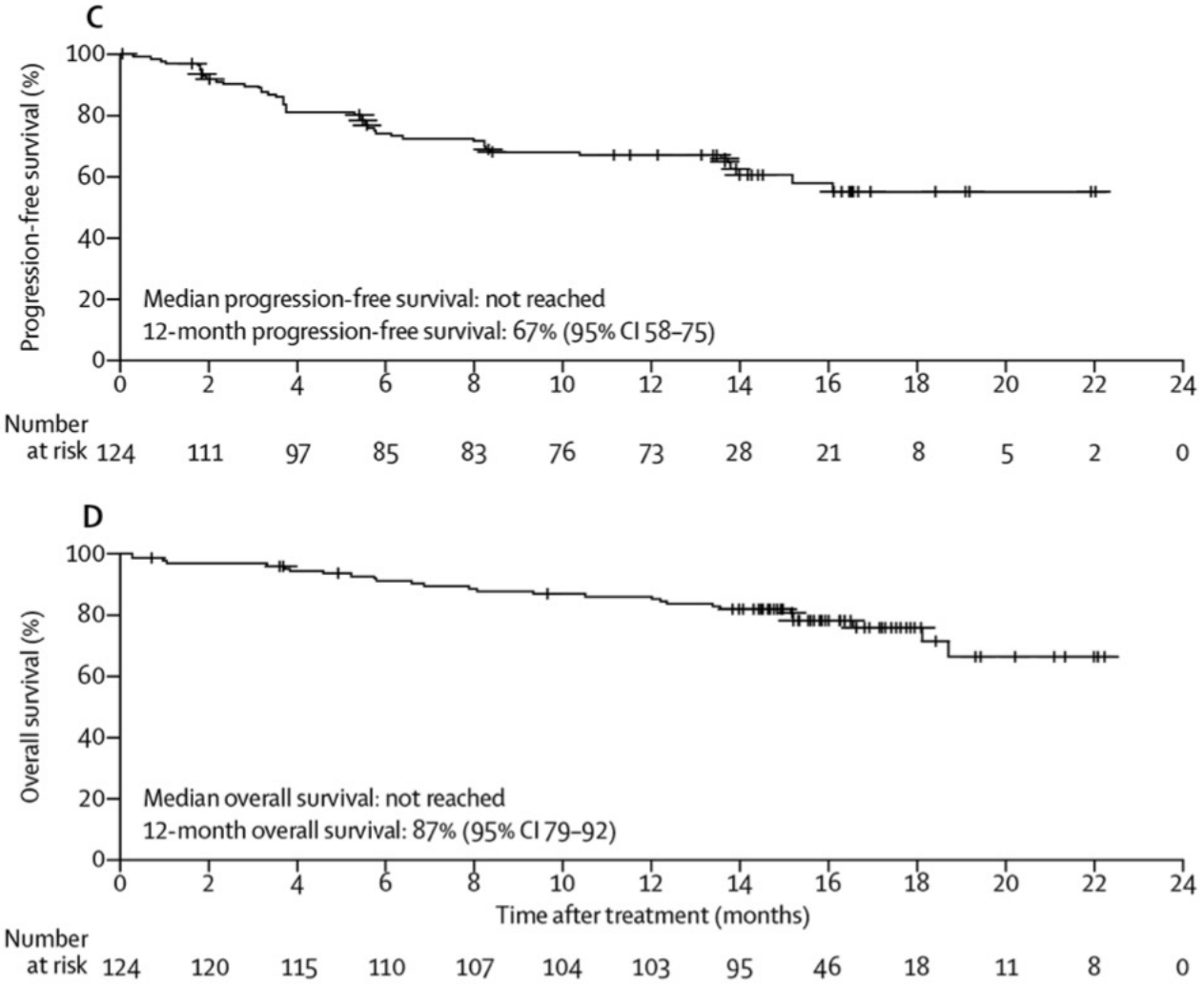
Lancet. 2018 February 17; 391(10121): 659–667

ACE-LY-004: Eficacia





SLP media 22 meses
Subgrupo blastoide/pleomórfico (n=26): SLP 15.2%

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Lancet. 2018 February 17; 391(10121): 659–667

ACE-LY-004: Seguridad

Eventos Adversos comunes

	Todos	Grado 1	Grado 2	Grado 3	Grado 4	Grado 5
Cefalea	47 (38%)	30 (24%)	15 (12%)	2 (2%)	0	0
Diarrea	38 (31%)	21 (17%)	13 (10%)	4 (3%)	0	0
Fatiga	34 (27%)	24 (19%)	8 (6%)	1 (1%)	0	0
Mialgia	26 (24%)	19 (15%)	6 (5%)	1 (1%)	0	0
Tos	24 (19%)	21 (17%)	3 (2%)	0	0	0
Nausea	22 (18%)	12 (10%)	9 (7%)	1 (1%)	0	0
Pirexia	19 (15%)	14 (11%)	5 (4%)	0	0	0

Lancet. 2018 February 17; 391(10121): 659–667
Clin J Oncol Nurs. 2020 Aug 1;24(4):392-398

ACE-LY-004: Seguridad

Eventos Adversos más comunes Grado 3 o más

	Todos	Grado 1	Grado 2	Grado 3	Grado 4	Grado 5
Anemia	15 (12%)	1 (1%)	3 (2%)	10 (8%)	1 (1%)	0
Neutropenia	13 (10%)	0	0	6 (5%)	7 (6%)	0
Neumonía	7 (6%)	0	1 (1%)	6 (5%)	0	0

Estudios previos con ibrutinib reportaron FA Grado 3 o más (6–9%), infección (14–29%) y sangrado (hasta 6%)

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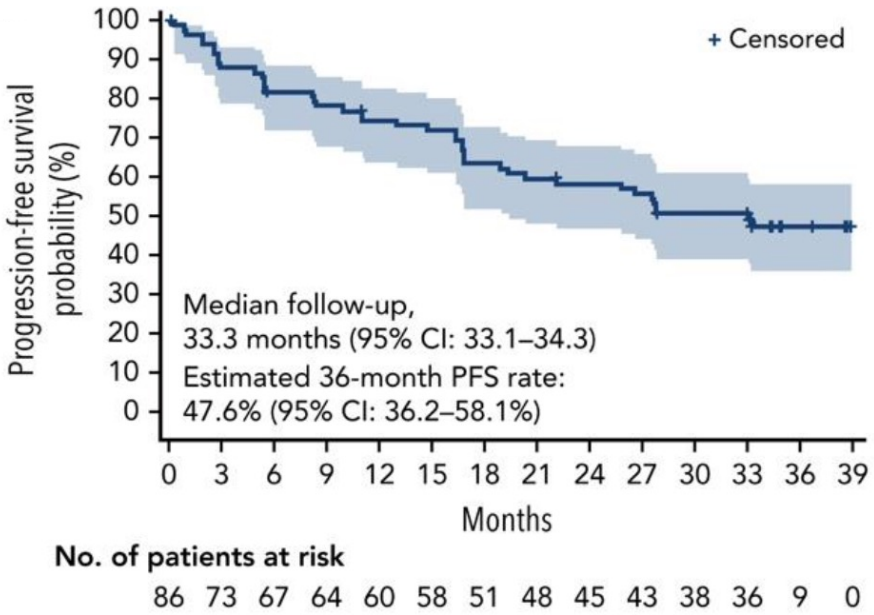
Lancet. 2018 February 17; 391(10121): 659–667
Clin J Oncol Nurs. 2020 Aug 1;24(4):392-398

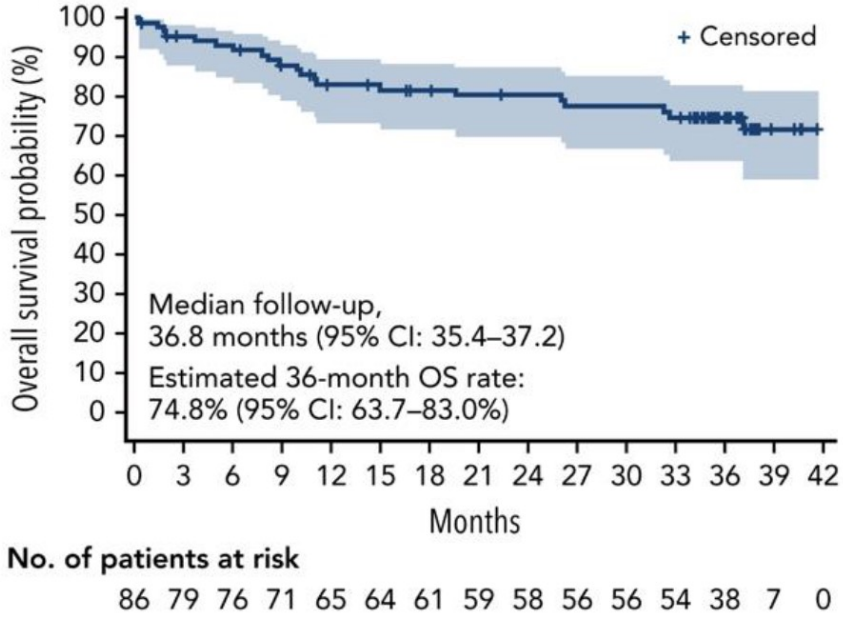
Acalabrutinib en manto

Opción terapéutica segura y eficaz con mejor perfil de toxicidad que ibrutinib

Lancet. 2018 February 17; 391(10121): 659–667
Clin J Oncol Nurs. 2020 Aug 1;24(4):392-398

Seguimiento a largo plazo del estudio Fase 2 de Zanubrutinib en Linfoma del manto R/R





- SLP media 31 meses
- SG media no alcanzada

- Hemorragia mayor (≥G3 o Hemorragia en SNC) 3.5%
- FA no reportada
- Eventos cardiovasculares G3 no registrados

n=83 (chinos)
RG 83.7%, RC 77.9%
SLP media 33 meses
Pacientes con mutTP53: SLP media 14.7 meses

Song Y et al. Blood 2022; 139 (21): 3148

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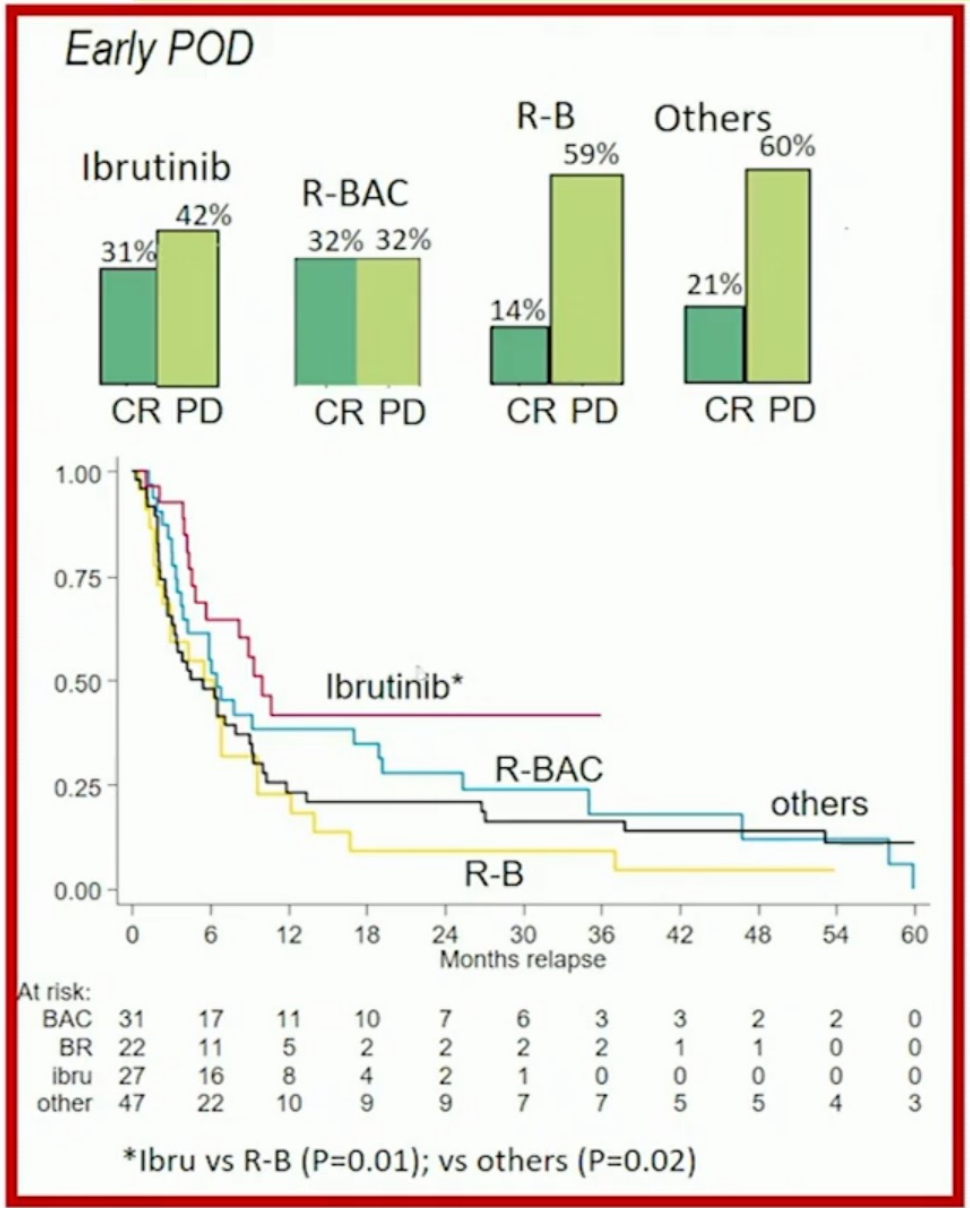
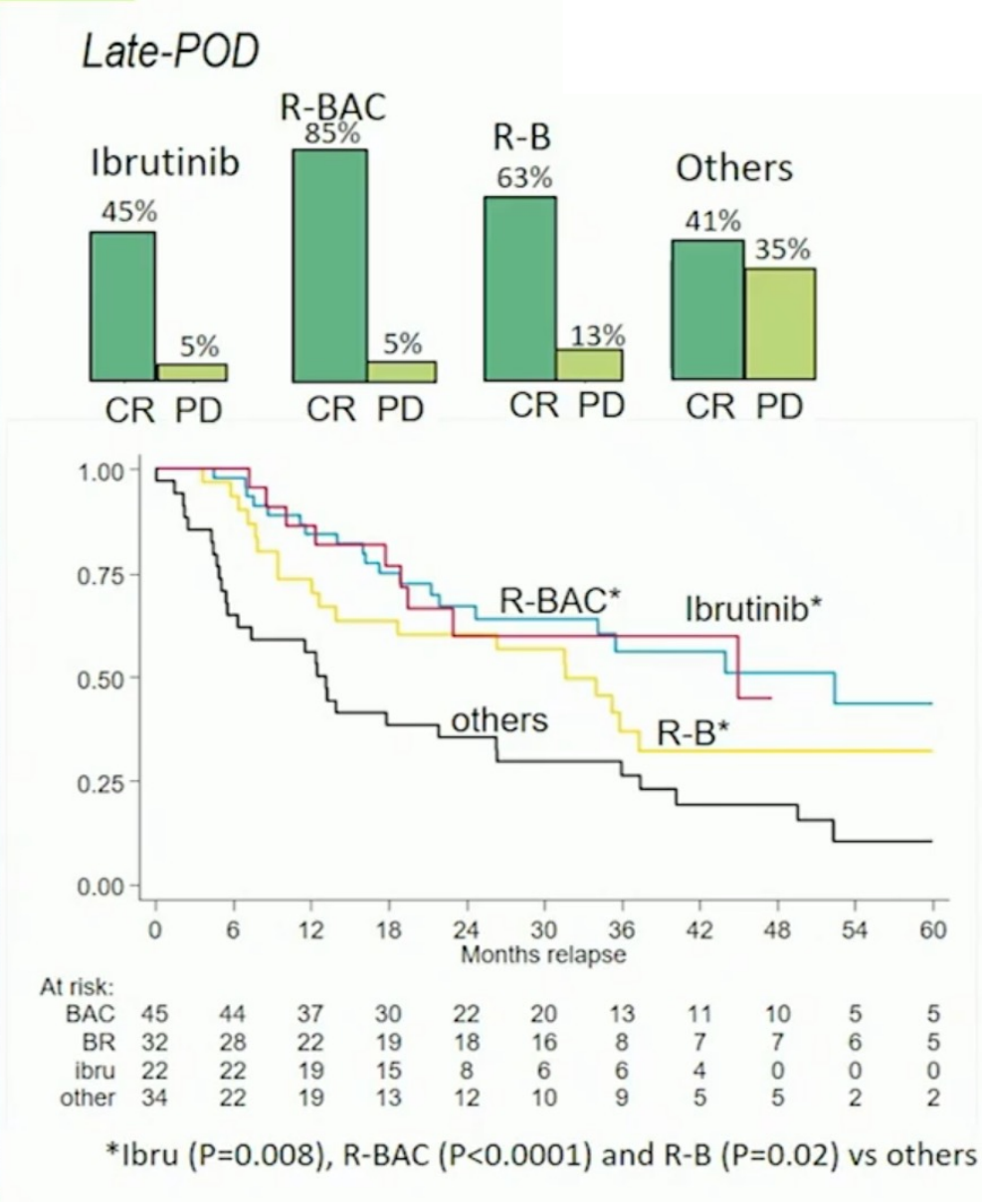
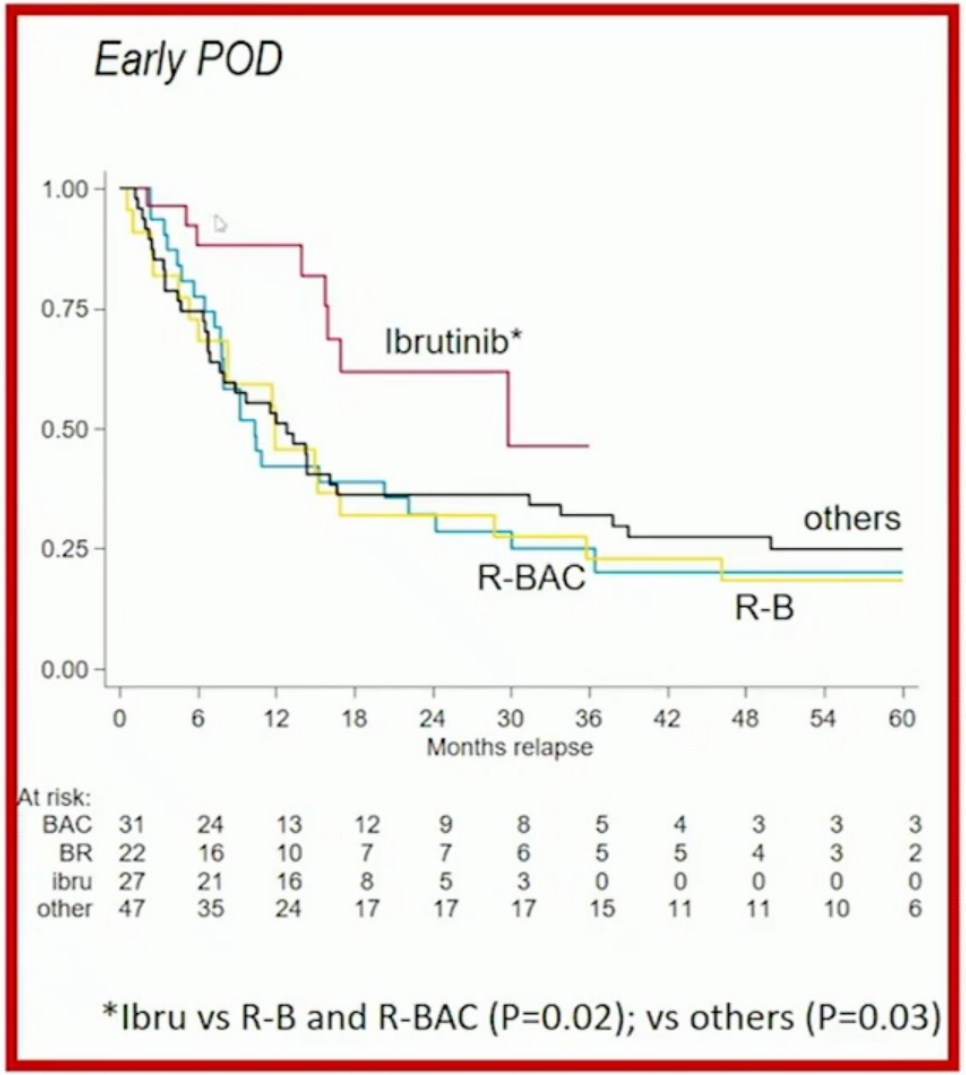
Ibrutinib en manto recaído (POD 24): SLP

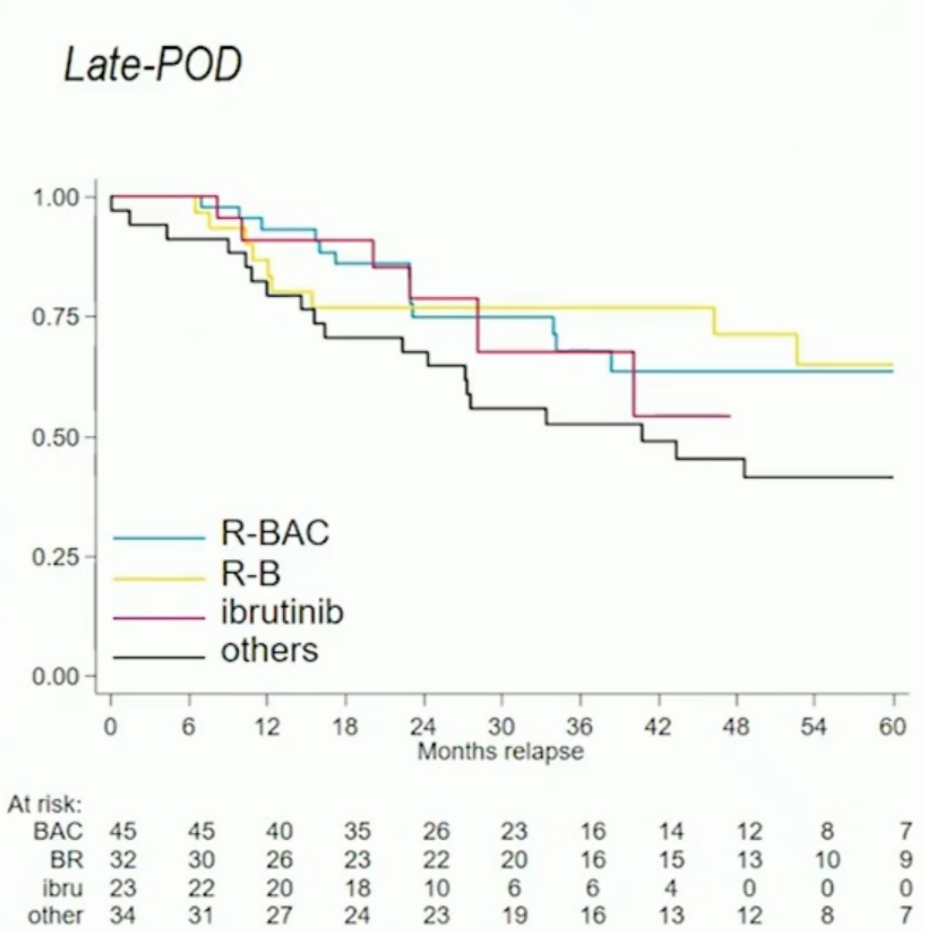




Visco, Leukemia 2020

Ibrutinib en manto recaído (POD 24): SG





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Visco, Leukemia 2020

iBTK covalentes en linfoma del Manto R/R

	Ensayo	Año	RG (RC)	SLP media
Ibrutinib	Fase 2 PCYC1104	2013	66% (17%)	13.9 meses
Acalabrutinib	Fase 2 LY-004	2017	81% (40%)	22 meses
Zanubrutinib	Fase 2 BGB-311-206/AU-003	2019	84% (59%) 84% (22%)	33 meses

Efficacy of R-BAC in relapsed, refractory mantle cell lymphoma post BTK inhibitor therapy

- Antecedentes:
  - El 40 % de los pacientes progresó en los 12 meses siguientes al inicio de BTKi ➜ alta frecuencia de mutaciones de TP53
  - Pocos datos que guíen el manejo clínico
  - Estudios retrospectivos ➜ tasas de respuesta a terapias sucesivas que oscilan entre el 29% y 53%, pocos pacientes sobreviven más de un año
  - Ningún tratamiento mostró clara superioridad ➜ NO hoy un tratamientos estándar luego de la falla a iBTK

- **Estudio de cohorte retrospectiva**, 36 pacientes con progresión luego de iBTK recibieron R-BAC (rituximab, bendamustina, cytarabina) ➜ citotoxicidad sinérgica entre bendamustina y cytarabina observadas *in vitro* en líeas celulares de MCL

RG 83% (RC 60%) y 31% puente a TALLO

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McCulloch R et al. doi: 10.1111/bjh.16416
Visco et al., 2012

Characteristic	
At initial diagnosis	
Median age, years (range)	61 (41–77)
Male	29 (80·6%)
Stage	
III or IV	36 (100·0%)
Histology (n = 36)	
Non-blastoid	29 (80·6%)
Blastoid	7 (19·4%)
MIPI at diagnosis (n = 30)	
Low risk	10 (33·3%)
Intermediate risk	6 (20·0%)
High risk	14 (46·7%)
Therapy before R-BAC	
Prior lines of therapy (n = 36)	
1	2 (5·6%)
2	30 (83·3%)
3	1 (2·8%)
4+	3 (8·3%)
Frontline therapy (n = 36)	
High dose cytarabine based regimen	23 (63·9%)
R-CHOP	9 (25·0%)
R-CVP	1 (2·8%)
Fludarabine + cyclophosphamide	1 (2·8%)
Rituximab + ibrutinib	2 (5·6%)
Autologous SCT consolidation	15 (41·7%)
Maintenance rituximab	10 (27·8%
Duration of response to frontline therapy	
<2 years	16 (44·4%)
≥2 years	20 (55·6%)
Prior BTK inhibitor therapy (n = 36)	
Ibrutinib	31 (86·1%)
Acalabrutinib	2 (5·6%)
Tirabrutinib	2 (5·6%)
M7583 (Merck)	1 (2·8%)
Duration of response to BTK inhibitor <1 year	22 (61%)
Previous allogeneic SCT*	2 (5·6%)
At start of R-BAC	
Median age, years (range)	66 (43–81)
Median white cell count, $\times 10^9$/L (range)	8·1 (1·0–305·0)
White cell count >15 $\times$ 10^9/L (n = 29)	10 (34·5%)
Median normalised LDH (range)	1·25 (0·61–8·91)
Normalised LDH > 1·5 (n = 28)	11 (39·3%)
ECOG > 1 (n = 35)	7 (20·0%)
MIPI (n = 26)	
Low risk	5 (19·2%)
Intermediate risk	6 (23·1%)
High risk	15 (57·7%)

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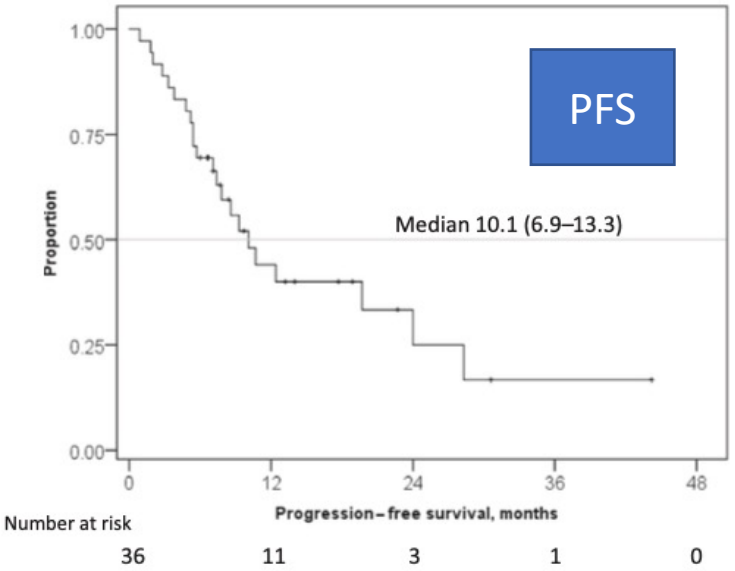
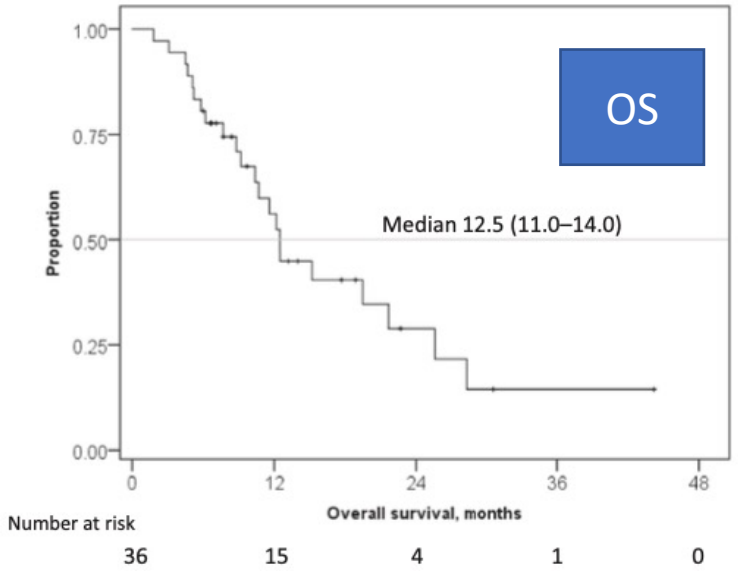
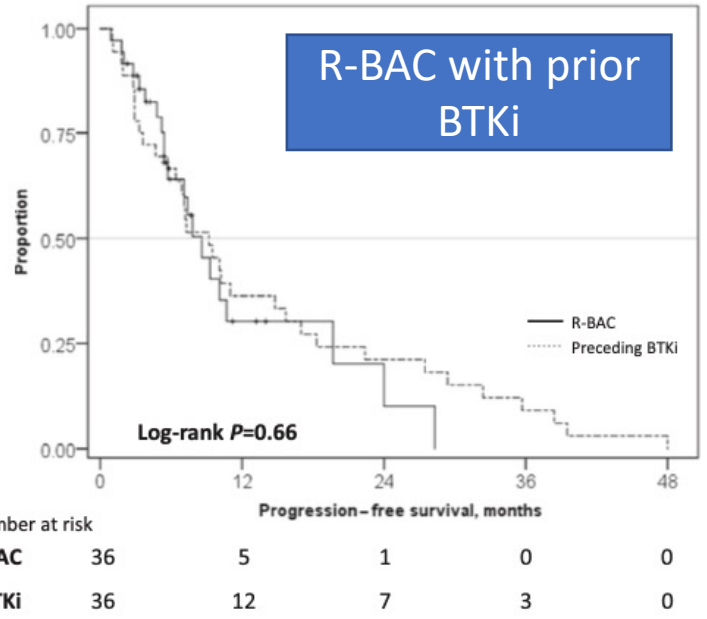
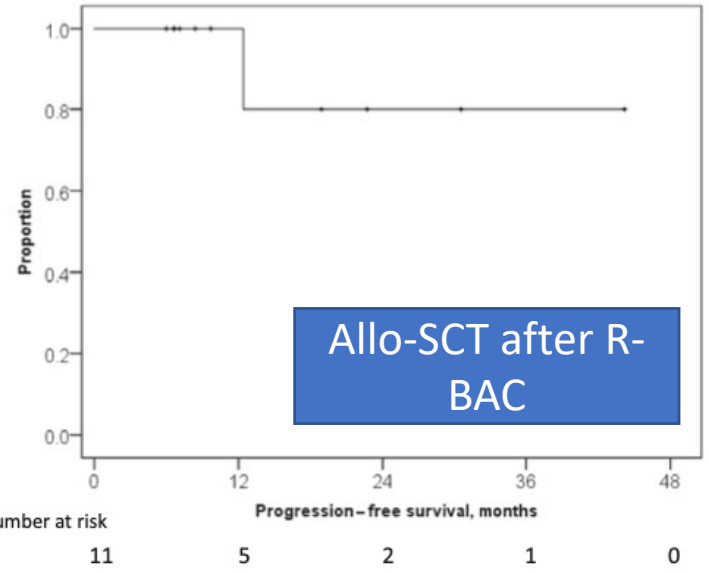
McCulloch R et al. doi: 10.1111/bjh.16416





Datos intrigantes en una población de alto riesgo → resaltan la necesidad de datos prospectivos en este contexto





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McCulloch R et al. doi: 10.1111/bjh.16416

Dr. Kelly Davison

Ibrutinib Combined with Venetoclax in Patients with Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis Results from the Randomized Phase 3 SYMPATICO Study

Michael Wang, Wojciech Jurczak, Marek Trněný, David Belada, Tomasz Wrobel, Nilanjan Ghosh, Mary-Margaret Keating, Tom van Meerten, Ruben Fernandez Alvarez, Gottfried von Keudell, Catherine Thieblemont, Frederic Peyrade, Marc Andre, Marc Hoffmann, Edith Szafer Glusman, Jennifer Lin, James P. Dean, Jutta K. Neuenburg, Constantine S. Tam

ASH 2023
Abstract (oral abstract): LBA-2

Ibrutinib and Venetoclax: acción sinérgica

- Ibrutinib ➜ aprobado en pacientes con LCM R/R ≥ 1 terapia previa[1]
- Venetoclax ➜ inhibidor BCL-2 aprobado en LLC y LMA[2]
- La combinación tiene mecanismos de acción complementarios que han demostrado evecto sinérgico antitumoral en modelos preclínicos de LCM[3,4]
- En pacientes con LCM R/R ➜ actividad clínica prometedora en estudios en fases tempranas[5,6]
- Estudio Fase 3 SYMPATICO ➜ evalúa eficacia y tolerabilidad de ibrutinib + venetoclax, comparado con ibrutinib + placebo, en pacientes con LCM R/R
    - Fase abierta de seguridad run-in demostró que el inicio concurrente es seguro y bien tolerado[6]

AML, acute myeloid leukemia; BCL-2, B-cell lymphoma 2 protein; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; R/R, relapsed/refractory.

1. IMBRUVICA [package insert]. South San Francisco, CA: Pharmcyclics LLC; 2023. 2. VENCLEXTA [package insert]. South San Francisco, CA: Genentech USA Inc; 2021. 3. Zhao X, et al. *Br J Haematol.* 2015;168:757-768. 4. Portell CA, et al. *Blood.* 2014;124:509. 5. Tam CS, et al. *N Engl J Med*. 2018;378:1211-1223. 6. Wang M, et al. *J Hematolg Oncol*. 2021;14:179.

Abstract reference: Wang et al. ASH 2023; abstract LBA-2 (Oral) https://ash.confex.com/ash/2023/webprogram/Paper191921.html

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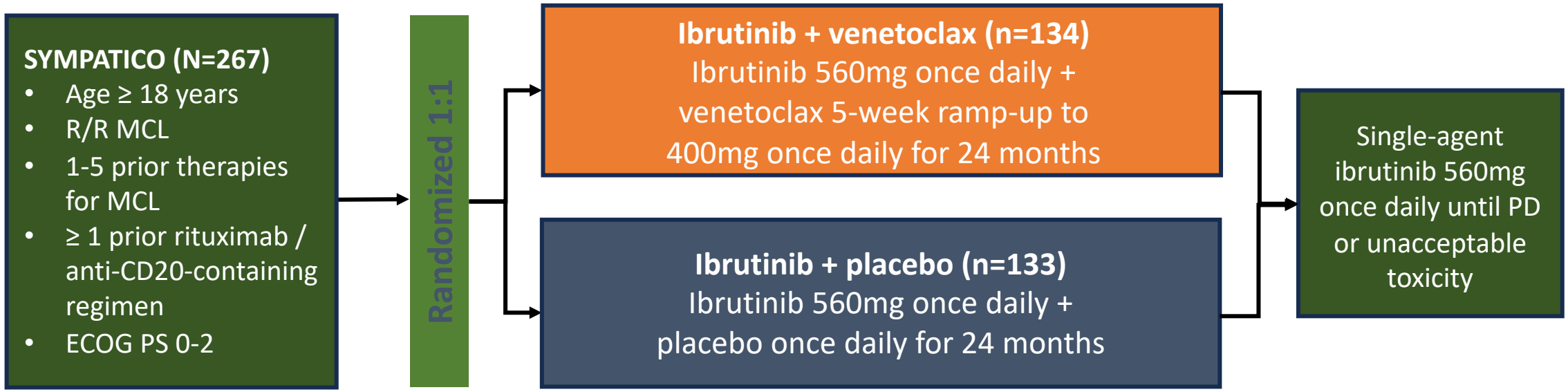
SYMPATICO: diseño del estudio

- SYMPATICO (NCT03112174) is a multinational, randomized, double-blind, placebo-controlled, phase 3 study



Stratification: ECOG PS, prior lines of therapy, TLS risk[a]

- **Primary endpoint:**
  - PFS by investigator assessment using Lugano criteria
- **Secondary endpoints (tested hierarchically in the following order):**
  - CR rate by investigator assessment
  - TTNT[b]
  - OS (interim analysis)
  - ORR by investigator assessment

[a]Increased TLS risk was defined as at least 1 lesion >10cm, or at least 1 lesion >5cm with circulating lymphocytes >25,000 cells/mm^3, and/or creatinine clearance <60mL/min. [b]For hierarchical testing per US FDA censoring, TTNT was tested after OS.

CD20, cluster of differentiate 20 protein; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MCL, mantle cell lymphoma; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R/R, relapsed/refractory; TLS, tumour lysis syndrome; TTNT, time to next treatment, US FDA; United States Food and Drug Administration.

Abstract reference: Wang et al. ASH 2023; abstract LBA-2 (Oral) https://ash.confex.com/ash/2023/webprogram/Paper191921.html

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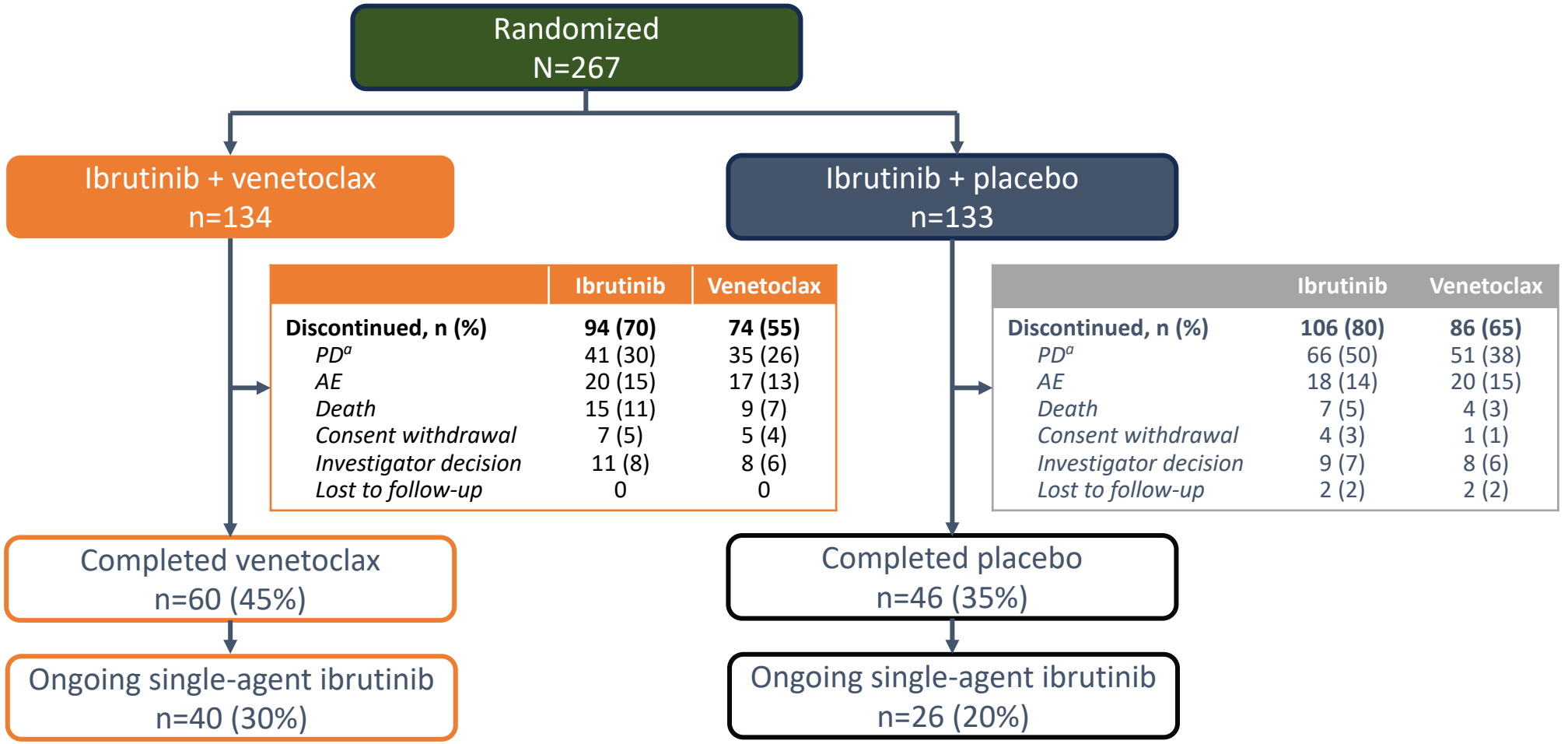
Disposición de los pacientes



	Ibrutinib	Venetoclax
Discontinued, n (%)	**94 (70)**	**74 (55)**
PD[a]	41 (30)	35 (26)
AE	20 (15)	17 (13)
Death	15 (11)	9 (7)
Consent withdrawal	7 (5)	5 (4)
Investigator decision	11 (8)	8 (6)
Lost to follow-up	0	0

	Ibrutinib	Venetoclax
Discontinued, n (%)	**106 (80)**	**86 (65)**
PD[a]	66 (50)	51 (38)
AE	18 (14)	20 (15)
Death	7 (5)	4 (3)
Consent withdrawal	4 (3)	1 (1)
Investigator decision	9 (7)	8 (6)
Lost to follow-up	2 (2)	2 (2)

- Median follow-up: 51.2 months (range, 0.1+ to 61.6) as of July 5, 2023
- Treatment discontinuations due to PD were more frequent in the ibrutinib + placebo arm
- Treatment discontinuations due to AEs were similar between arms

[a]PD per protocol criteria or clinical PD.

AE, adverse event; PD, progressive disease.

Abstract reference: Wang et al. ASH 2023; abstract LBA-2 (Oral) https://ash.confex.com/ash/2023/webprogram/Paper191921.html

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Características basales

Characteristic	Ibrutinib + venetoclax n=134	Ibrutinib + placebo n=133
Age		
Median (range), years	69 (42-84)	67 (44-88)
≥ 65 years, n (%)	93 (69)	86 (65)
ECOG PS, n (%)		
0	74 (55)	74 (56)
1-2	60 (45)	59 (44)
Prior lines of treatment, n (%)		
1	80 (60)	79 (59)
2	32 (24)	31 (23)
≥ 3	22 (16)	23 (17)
MCL histology, n (%)		
Typical	88 (66)	95 (71)
Blastoid	19 (14)	17 (13)
Pleomorphic	8 (6)	6 (5)
Round cell (CLL-like)	1 (1)	0
Other	18 (13)	15 (11)

Characteristic	Ibrutinib + venetoclax n=134	Ibrutinib + placebo n=133
Simplified MIPI score, n (%)		
Low risk	18 (13)	23 (17)
Intermediate risk	63 (47)	68 (51)
High risk	51 (38)	41 (31)
***TP53* status, n (%)**		
Mutated	40 (30)	37 (28)
Not mutated	66 (49)	57 (43)
Missing	28 (21)	39 (29)
Bulky disease, n (%)		
≥ 5cm	62 (46)	53 (40)
≥ 10cm	13 (10)	10 (8)
Extranodal disease, n (%)	64 (48)	61 (46)
BM involvement, n (%)	62 (46)	54 (41)
Splenomegaly, n (%)	42 (31)	33 (25)

BM, bone marrow; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index, TP53, tumour protein 53 gene.

Abstract reference: Wang et al. ASH 2023; abstract LBA-2 (Oral) https://ash.confex.com/ash/2023/webprogram/Paper191921.html

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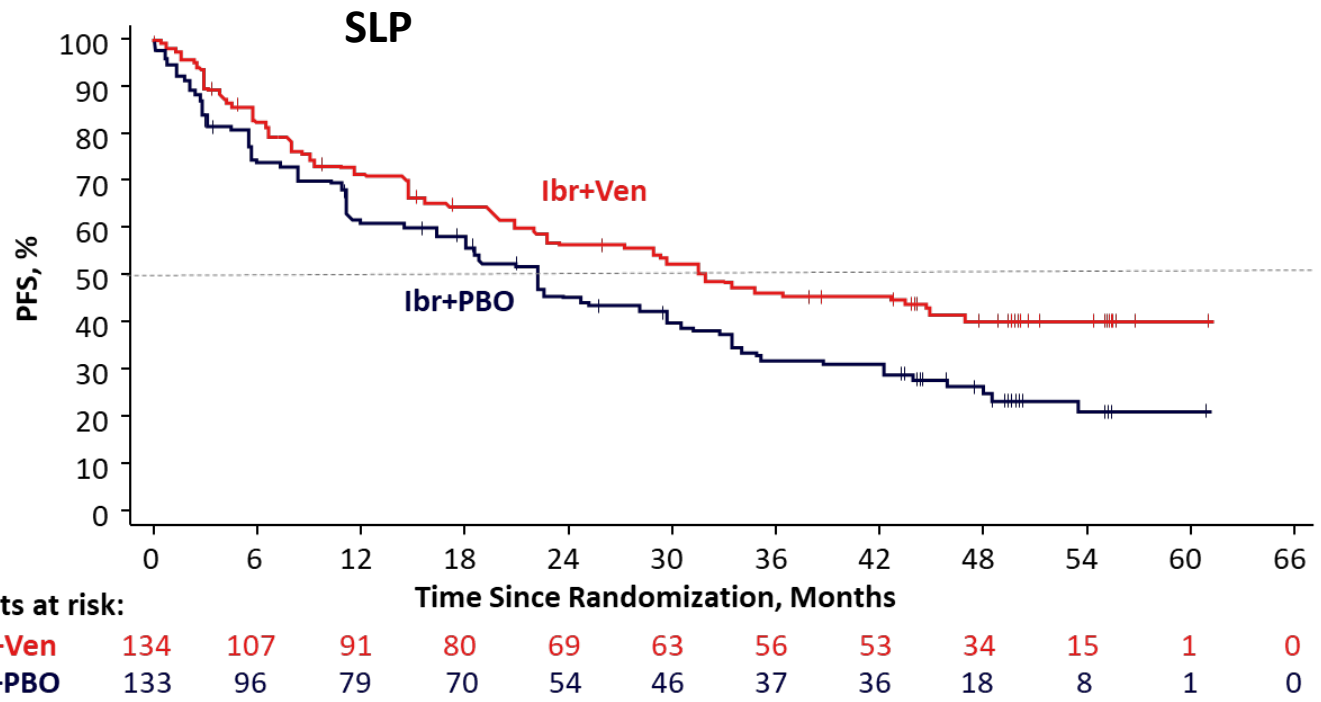
SLP evaluada por el investigador: Significativamente prolongada con Ibrutinib+Venetoclax vs Ibrutinib + Placebo



	Ibr+Ven (n=134)	Ibr+PBO (n=133)
PFS Events, n(%)	73 (54)	94 (71)
Median PFS, mo	31.9	22.1
HR (95% CI)	0.65 (0.47-0.88)	
Log-rank *P*-value[a]	0.0052	

Median PFS, mo	Global Censoring[b]				US FDA Censoring[c]			
	Ibr+Ven (n=134)	Ibr+PBO (n=133)	HR (95% CI)	Log-rank *P* value[a]	Ibr+Ven (n=134)	Ibr+PBO (n=133)	HR (95% CI)	Log-rank *P* value[a]
Investigator assessment	31.9	22.1	0.65 (0.47-0.88)	0.0052	42.6	22.1	0.60 (0.44-0.83)	0.0021
IRC assessment	31.8	20.9	0.67 (0.49-0.91)	0.0108	43.5	22.1	0.63 (0.45-0.87)	0.0057

[a]*P* values were determined by stratified log-rank test (stratification factors: prior lines of therapy [1-2 vs ≥3] and TLS risk category [low vs increased risk]). [b]Censoring at last non-PD assessment for patients without PD or death. [c]Patients were censored at last non-PD assessment before start of subsequent anticancer therapy or missing ≥2 consecutive visits prior to a PFS event, whichever occurred first.

CI, confidence interval; HR, hazard ratio; Ibr, ibrutinib; IRC, independent review committee; mo, months; PD, progressive disease; PFS, progression-free survival; PBO, placebo; TLS, tumour lysis syndrome; US FDA, United States Food and Drug Administration; Ven, venetoclax.

Abstract reference: Wang et al. ASH 2023; abstract LBA-2 (Oral) https://ash.confex.com/ash/2023/webprogram/Paper191921.html

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Seguridad consistente con el perfil de EA de cada agente por separado

- Duración media del tratamiento:
  - Ibrutinib + venetoclax, 22.2 meses (rango, 0.5-60.4)
  - Ibrutinib + placebo, 17.7 meses (rango, 0.1-58.9)

AE, n (%)	Ibrutinib + venetoclax n=134	Ibrutinib + placebo n=132
Grade ≥ 3 AEs	112 (84)	100 (76)
Serious AEs	81 (60)	79 (60)
AEs leading to discontinuation	41 (31)	48 (36)
Ibrutinib only	11 (8)	10 (8)
Venetoclax/placebo only	2 (1)	7 (5)
Both	28 (21)	31 (23)
AEs leading to dose reduction	48 (36)	29 (22)
Ibrutinib only	17 (13)	14 (11)
Venetoclax/placebo only	14 (10)	7 (5)
Both	17 (13)	8 (6)
AEs leading to death	22 (16)	18 (14)
Ibrutinib-related[a]	3 (2)	2 (2)
Venetoclax/placebo-related[a]	0	1 (1)
Tumour lysis syndrome		
Laboratory	7 (5)	3 (2)
Clinical	0	0

AE, n (%)	Ibrutinib + venetoclax n=134	Ibrutinib + placebo n=132
Most frequent any-grade AEs[b]		
Diarrhea	87 (65)	45 (34)
Neutropenia	46 (34)	19 (14)
Nausea	42 (31)	22 (17)
Fatigue	39 (29)	36 (27)
Anemia	30 (22)	16 (12)
Pyrexia	28 (21)	26 (20)
Cough	27 (20)	36 (27)
Muscle spasms	11 (8)	32 (24)
Most frequent ≥ grade 3 AEs[c]		
Neutropenia	42 (31)	14 (11)
Pneumonia	17 (13)	14 (11)
Thrombocytopenia	17 (13)	10 (8)
Anemia	13 (10)	4 (3)
Diarrhea	11 (8)	3 (2)
Leukopenia	10 (7)	0
MCL[d]	9 (7)	16 (12)
Atrial fibrillation	7 (5)	7 (5)
COVID-19	7 (5)	1 (1)
Hypertension	6 (4)	12 (9)

[a]Per investigator opinion. [b]Occurring in ≥ 20% of patients in either arm. [c]Occurring in ≥ 5% of patients in either arm. [d]Worsening of MCL without meeting criteria for PD.

AE, adverse event; COVID, coronavirus disease; MCL, mantle cell lymphoma; PD, progressive disease.

Abstract reference: Wang et al. ASH 2023; abstract LBA-2 (Oral) https://ash.confex.com/ash/2023/webprogram/Paper191921.html

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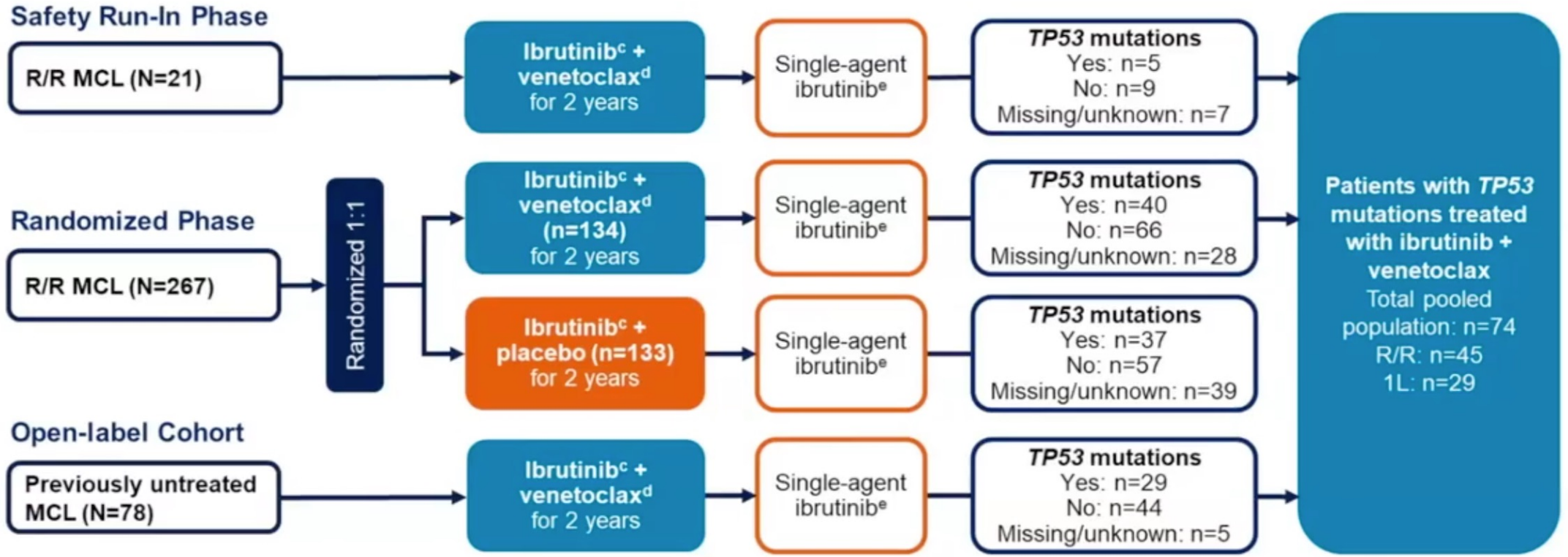
Efficacy and Safety of Ibrutinib Plus Venetoclax in Patients With Mantle Cell Lymphoma and *TP53* Mutations in the SYMPATICO Study

ASCO 2024

ERC multinacional, multicéntrico, Fase 3, controlado contra placebo
Se agruparon los datos (3 cohortes) de pacientes con mutación TP53 (sin deleciones) tratados con ibrutinib + venetoclax



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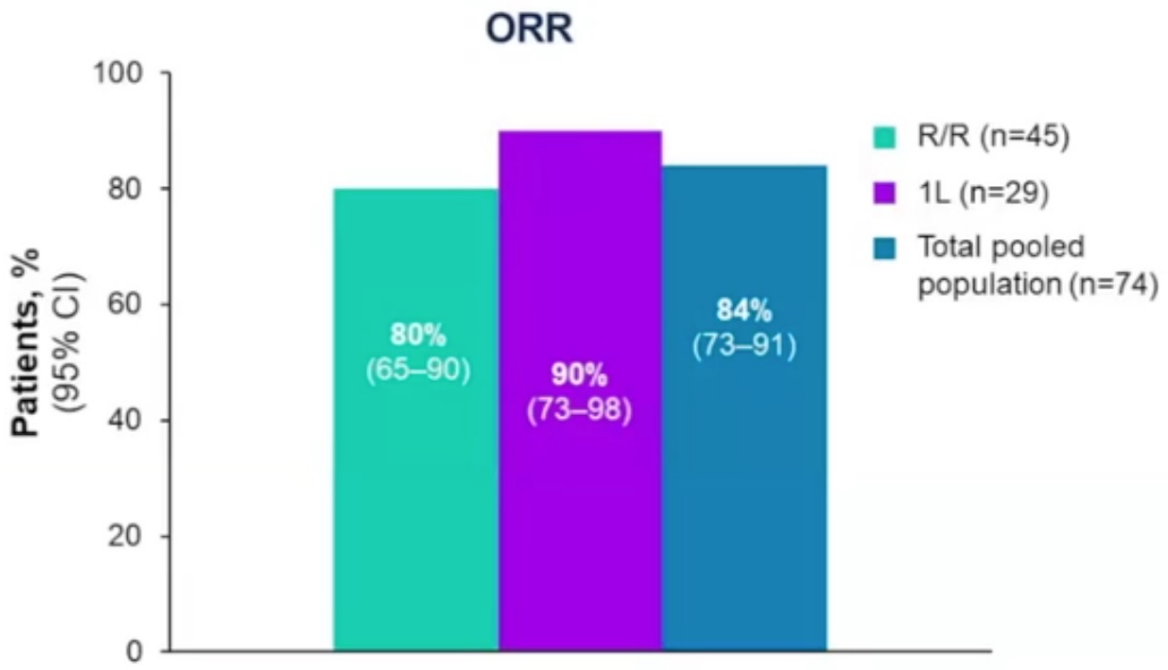
Wang M et al Lancet Oncol 2025 Feb;26(2):200-213

Altas tasas se RC y respuestas duraderas incluso en pacientes con mutaciones de TP53



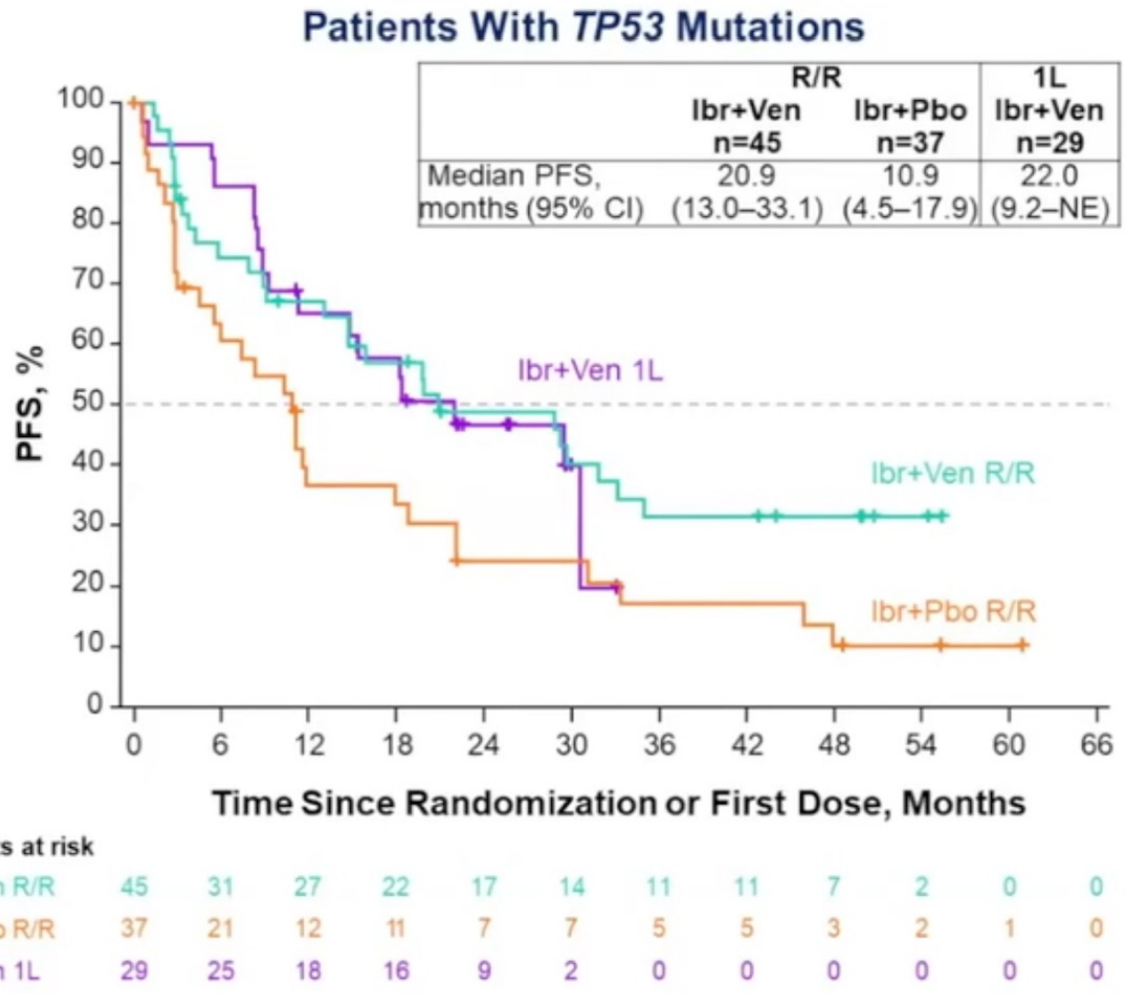
	R/R n=26	1L n=16	Total n=42
Median DOCR, months (95% CI)	NR (18.7–NE)	20.5 (5.4–NE)	32.2 (18.7–NE)

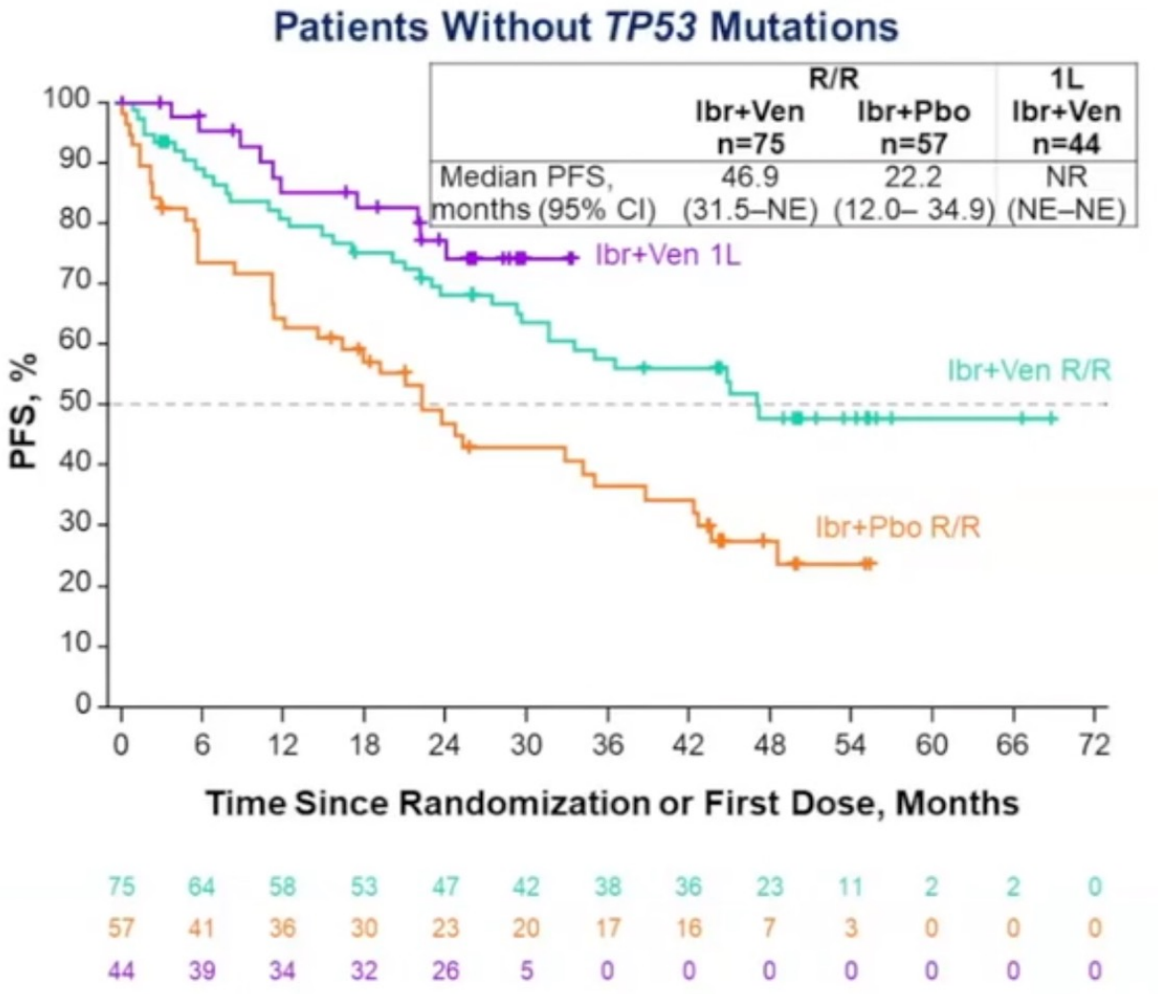
	R/R n=36	1L n=26	Total n=62
Median DOR, months (95% CI)	26.5 (16.8–NE)	20.5 (12.0–NE)	26.0 (16.8–32.2)

ASCO 2024

Wang M et al Lancet Oncol 2025 Feb;26(2):200-213

Beneficio en SLP en pacientes con y sin mutación de TP53

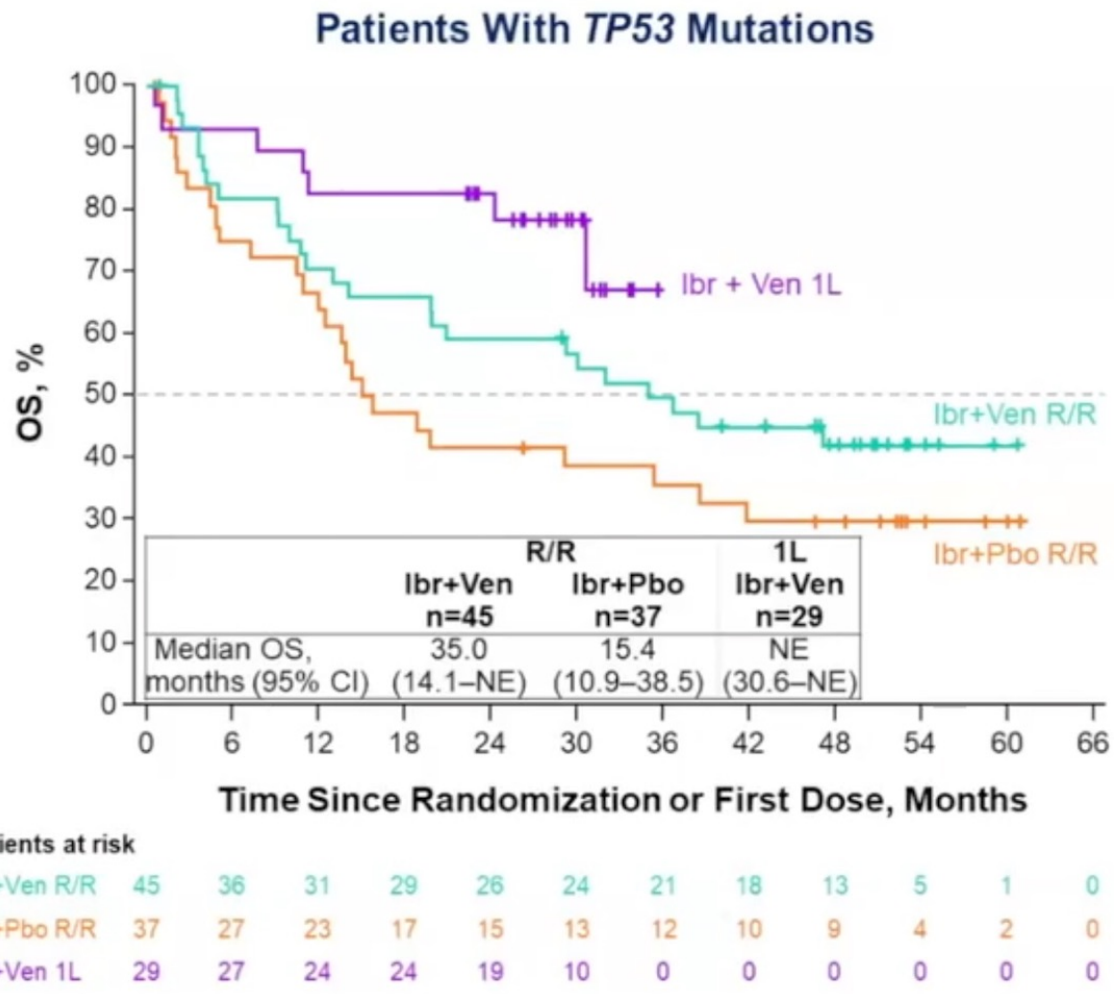


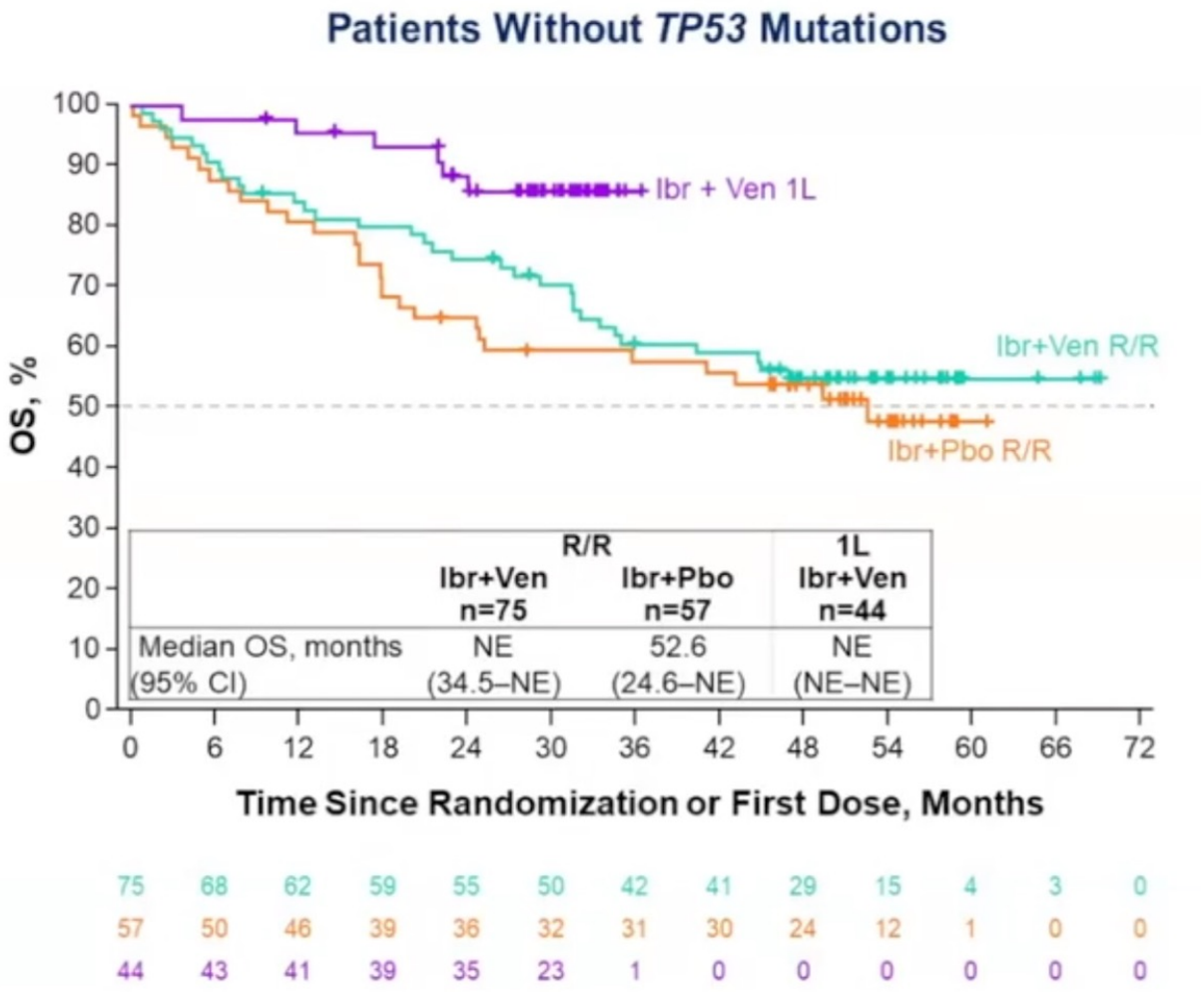


ASCO 2024

Wang M et al Lancet Oncol 2025 Feb;26(2):200-213

Beneficio en SG en pacientes con y sin mutación de TP53





ASCO 2024

Wang M et al Lancet Oncol 2025 Feb;26(2):200-213

Combinaciones con ibrutinib en linfoma del Manto R/R

Treatment	Study	N	Response	Median PFS, mo
Ibrutinib + rituximab	Phase 2	50	ORR, 88%; CR, 58%	43
Ibrutinib + bortezomib	Phase 1/2	71	ORR, 87.3%; CR, 44%	18.6
Ibrutinib + ixazomib	Phase 2	43	ORR, 77.1%; CR, 42.9%	2-y PFS, 44%
Ibrutinib + lenalidomide + rituximab	Phase 2	50	ORR, 76%; CR, 56%	16.0
Ibrutinib + venetoclax	Phase 2	24	ORR, 71%; CR, 71%	29.0
Ibrutinib + venetoclax vs ibrutinib	Phase 3	267	ORR, 82%; CR, 54% vs ORR, 74%; CR, 32	31.9 vs 22.1
Ibrutinib + venetoclax + obinutuzumab	Phase 1/2	24	ORR, 71%; CR, 67%	4-y PFS, 50%

Silkenstedt E, Dreyling M. Blood 2025;145:673

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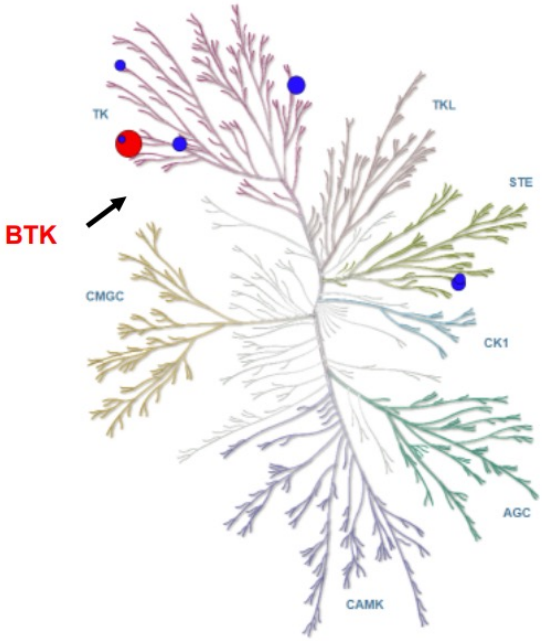
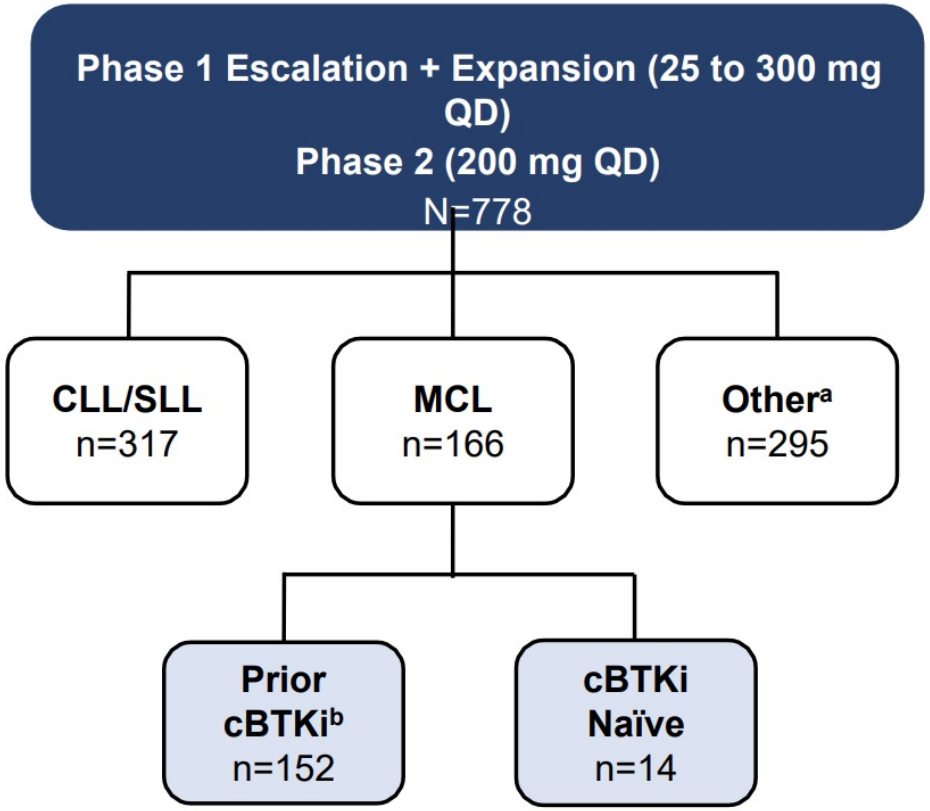
Pirtobrutinib en LCM R/R: Estudio BRUIN Fase 1/2



Pirtobrutinib inhibidor de BTK no covalente, altamente selectivo, non-covalent BTK
Efectivo post iBTK



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

- Age ≥18
- ECOG 0-2
- Active disease and in need of treatment
- Previously treated

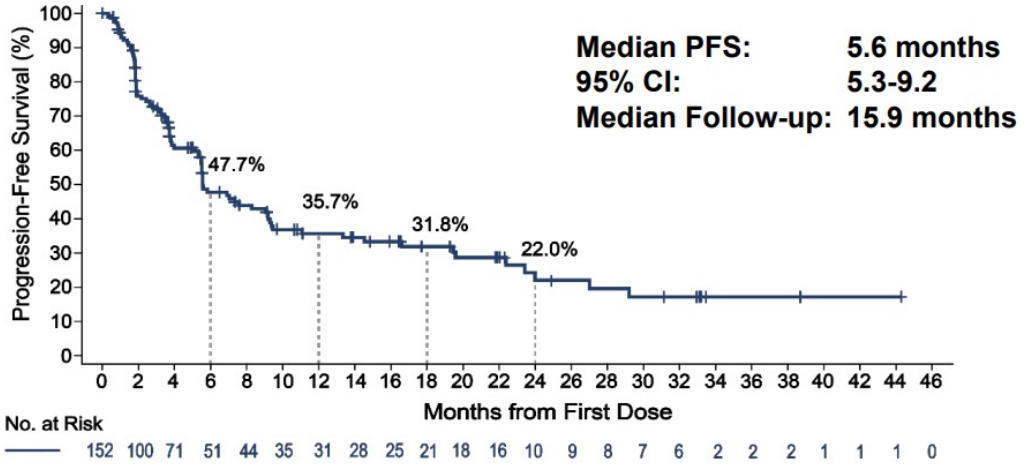
Key endpoints

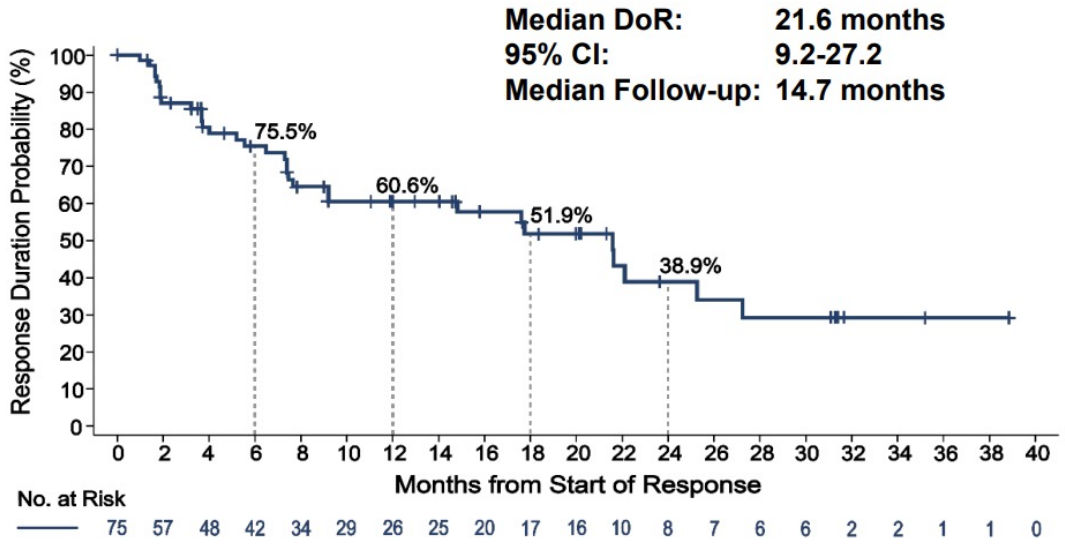
- Safety/tolerability
- Determine MTD and RP2D
- Pharmacokinetics
- Efficacy (ORR according to Lugano criteria, DoR, PFS, and OS)

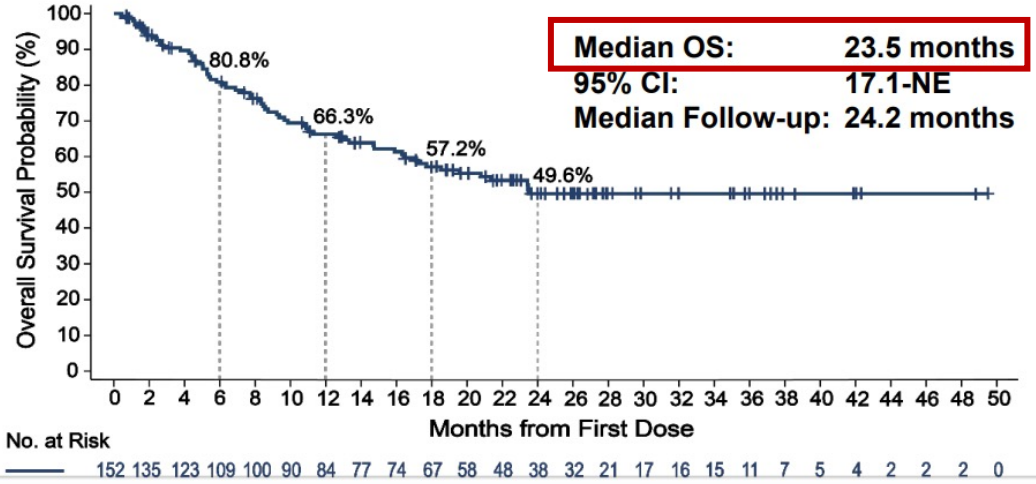
Mato et al. Lancet 2021; 397: 892–901.
Brandhuber et al. Clin Lymphoma Myeloma Leuk 2018; 18(Suppl.1):S216.
Wang et al. J Clin Oncol. 2023; 41:3988-3997

Pirtobrutinib en LCM R/R: Estudio BRUIN Fase 1/2

Prior cBTKi	n=152
ORR, % (95% CI)	49.3 (41.1-57.6)
Best Response, n (%)	
CR	24 (15.8)
PR	51 (33.6)







- 5 (3%) de los pacientes discontinuaron el tratamiento por EA
- 5 (3%) redujeron la dosis por EA

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ASH 2023 Abstract #981

Glofitamab Monotherapy in Patients with Heavily Pretreated Relapsed/Refractory (R/R) Mantle Cell Lymphoma (MCL): Updated Analysis from a Phase I/II Study

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n (%) of patients unless stated		Prior BTKi (n=31)*	BTKi naïve (n=29)*	All patients (N=60)*
Median age, years (range)		70.0 (41–84)	72.0 (52–86)	72.0 (41–86)
Male		23 (74.2)	21 (72.4)	44 (73.3)
Ann Arbor stage III/IV		28 (90.3)	24 (82.8)	52 (86.7)
MIPI score ≥6		7 (22.6)	8 (27.5)	15 (25.0)
Median no. of prior lines (range)		3.0 (1–5)	2.0 (1–4)	2.0 (1–5)
Median time since last prior therapy to first study treatment, months (range)		1.3 (0.1–53.2)	7.4 (1.1–132.5)	2.4 (0.1–132.5)
Median time since last anti-CD20 therapy to first study treatment, months (range)		15.1 (0.7–159.0)	25.1 (1.4–132.5)	16.3 (0.7–159.0)
Refractory status	Refractory to any prior therapy	30 (96.8)	20 (69.0)	50 (83.3)
	Refractory to 1L therapy	17 (54.8)	14 (48.3)	31 (51.7)
	Refractory to last prior therapy	27 (87.1)	17 (58.6)	44 (73.3)

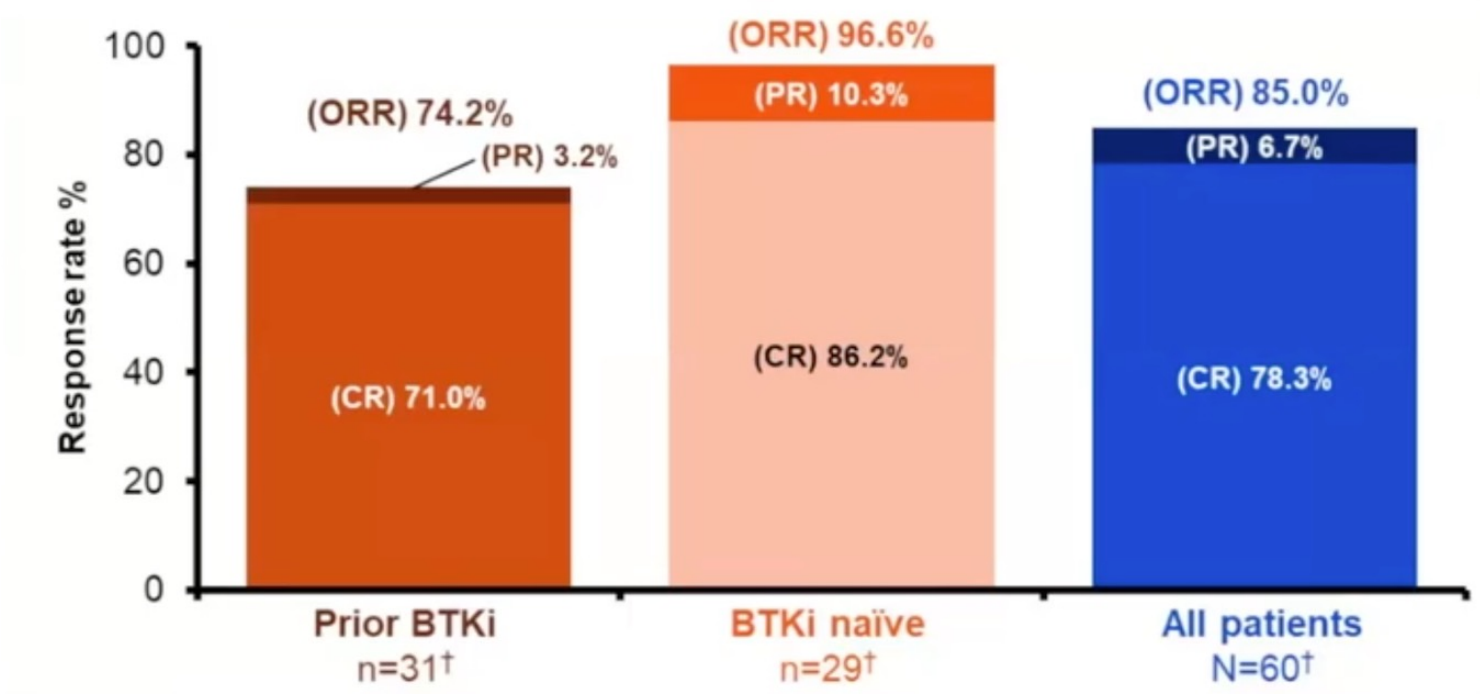
Patients with R/R MCL were heavily pretreated and highly refractory to their last prior therapy

A higher proportion of patients with prior BTKi therapy were refractory to their last prior therapy compared with BTKi-naïve patients

Pillips T et al ASCO 2024

Glofitamab Monotherapy in Patients with Heavily Pretreated Relapsed/Refractory (R/R) Mantle Cell Lymphoma (MCL): Updated Analysis from a Phase I/II Study

Respuesta evaluada por el Investigador



Tiempo medio de respuesta en los respondedores (51): 42 días IC95% 42-45

Altas tasas de RC y RG tanto en pacientes vírgenes de iBTK o expuestos

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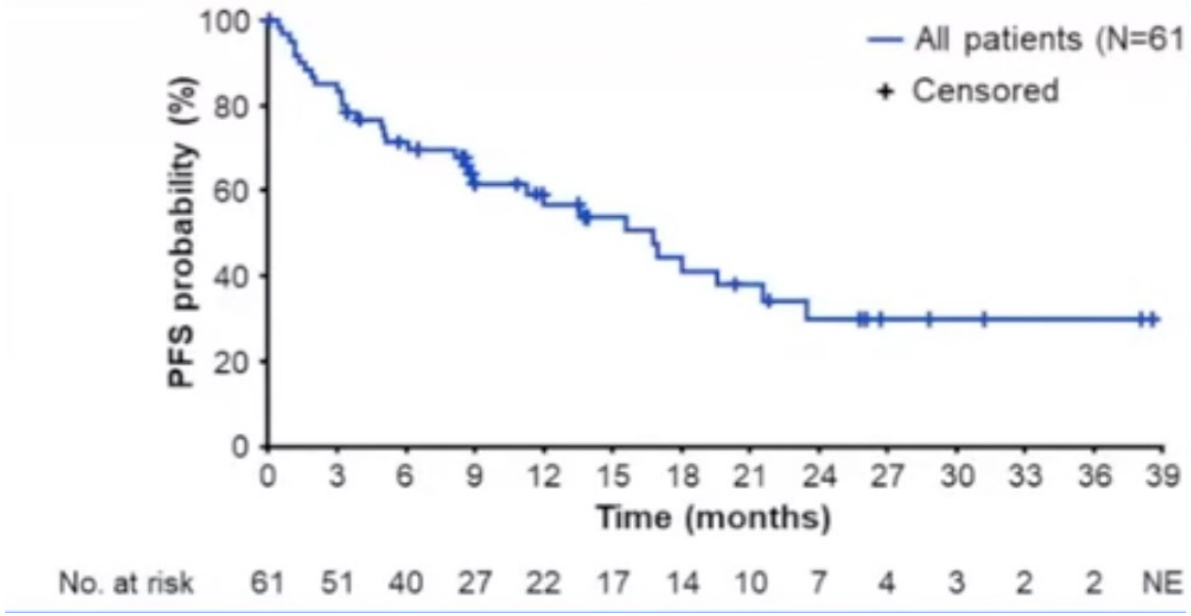
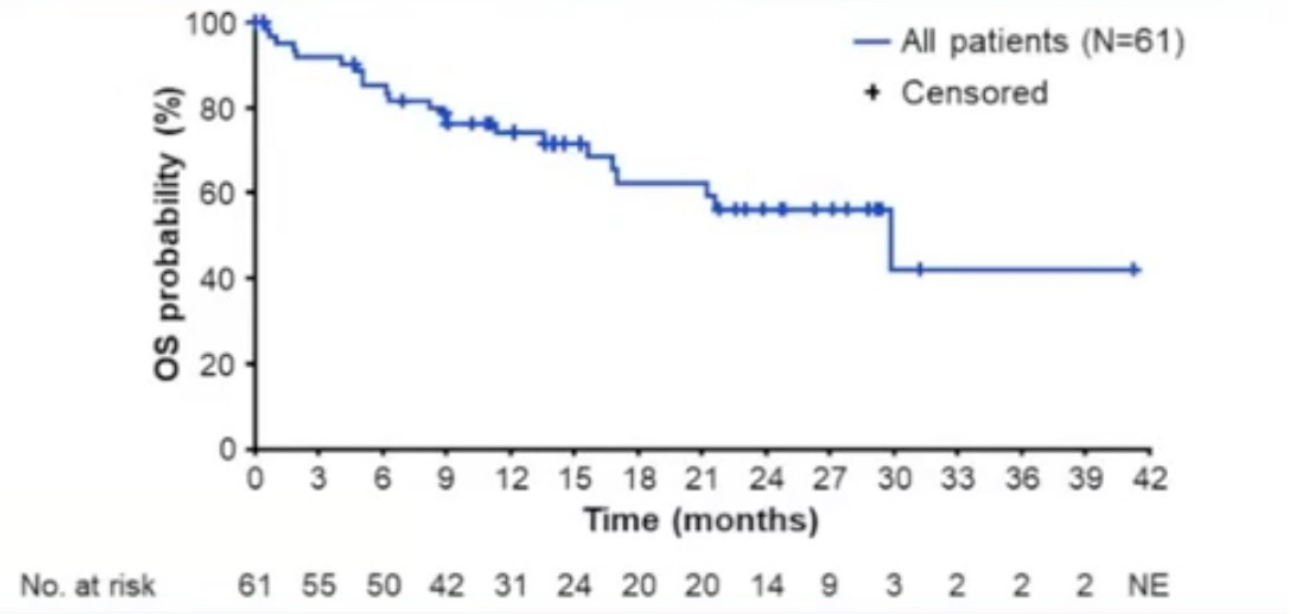
Pillips T et al ASCO 2024

SLP



SG



	Prior BTKi n=32*	All patients N=61*
Median PFS follow-up, months (95% CI)	26.1 (13.5–31.2)	19.6 (11.9–26.1)
Median PFS, months (95% CI)	8.6 (3.4–15.6)	16.8 (8.9–21.6)
15-month PFS rate, % (95% CI)	33.0 (14.8–51.1)	54.0 (40.1–67.8)

	Prior BTKi n=32*	All patients N=61*
Median OS follow-up, months (95% CI)	24.7 (13.6–28.8)	21.8 (14.0–24.9)
Median OS, months (95% CI)	21.2 (9.0–NE)	29.9 (17.0–NE)
15-month OS rate, % (95% CI)	55.0 (36.5–73.6)	71.4 (59.3–83.5)

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Pillips T et al ASCO 2024

Biespecíficos en el tratamiento del Manto R/R

Agent'	N	Activity
Epcoritamab[18]	4	One patient with CR, 1 PR, and 1 stable disease. Both responses occurred in patients with blastoid or pleomorphic MCL.
Glofitamab[21,22]	29	ORR 85%, CR 78.3%; mDOR 16.2 mo, mDOCR 15.4 mo
Mosunetuzumab + polatuzumab-vedotin[23,24]	20	ORR 75%, CRR 70%; mDOCR NR
Odronextamab[25]	12	ORR 50%, CRR 33%; mDOR 10.9 mo

CRR, complete response rate; NR, not reached.

Ensayos en curso con Biespecíficos (incluyendo 1L)

Setting	Agent(s)	NCT	Geography	Notes
R/R	Epcoritamab, ibrutinib	NCT05283720	Global	
R/R	Epcoritamab, ibrutinib, venetoclax			
Treatment naïve	Epcoritamab, ibrutinib, venetoclax			
R/R	Glofitamab, lenalidomide	NCT06192888	United States	Prior BTKi mandatory; prior lenalidomide acceptable if >12 months interval since treatment and previously sensitive
R/R	Glofitamab, pirtobrutinib	NCT05833763	Australia	Prior BTKi mandatory
		NCT06252675	United States	Must have responded to prior BTKi therapy
Treatment naïve	Glofitamab, ibrutinib	NCT06357676	United States	Either high-risk disease or ≥65 years old
R/R	Acalabrutinib, obinutuzumab, and glofitamab	NCT06054776	United States	Incorporates measurable residual disease testing
Treatment naïve	Glofitamab, obinutuzumab, venetoclax, and lenalidomide	NCT05861050	United States	At least one high-risk disease feature must be present
R/R	Glofitamab vs investigator's choice (rituximab-lenalidomide or rituximab-bendamustine)	NCT06084936	Global	Prior BTKi mandatory
	Mosunetuzumab	NCT05207670	United States	Prior BTKi mandatory
	Mosunetuzumab – polatuzumab-vedotin	NCT03671018	United States, Europe	≥2 prior lines of systemic therapy including BTKi, anti-CD20 MAb, and chemotherapy

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Hematology 2024, Ed. Program

Lisocabtagene maraleucel in patients with relapsed or refractory mantle cell lymphoma: subgroup analyses by number of prior systemic lines of therapy and by response to prior Bruton tyrosine kinase inhibitor from the TRANSCEND NHL 001 MCL cohort

M. Lia Palomba, MD,[1] Tanya Siddiqi, MD, MBBS,[2] Leo I. Gordon, MD,[3] Manali Kamdar, MD, MBBS,[4] Matthew Lunning, DO,[5] Alexandre V. Hirayama, MD,[6] Jeremy S. Abramson, MD,[7] Jon Arnason, MD,[8] Nilanjan Ghosh, MD, PhD,[9] Amitkumar Mehta, MD,[10] Charalambos Andreadis, MD, MS,[11] Scott R. Solomon, MD,[12] Ana Kostic, MD,[13] Ashvin Singh, MBS,[14] Ricardo Espinola, MD,[15] Rashmi Bhatnagar, MSc,[16] Anthony Raviele, PharmD,[14] Michael V

	Overall population (N = 83)	Number of prior lines of systemic therapy			Response to prior BTKi	
		≥ 2 (n = 81)	3–4 (n = 29)	5–11 (n = 26)	Not refractory (n = 35)	Refractory (n = 45)
DOR						
Median (95% CI),[a] months	15.7 (6.2–24.0)	14.5 (5.7–NR)	17.5 (3.3–NR)	6.7 (2.4–15.8)	24.0 (7.6–NR)	5.3 (2.3–15.8)
Median follow-up (95% CI),[b] months	22.8 (16.7–23.0)	22.6 (16.7–22.9)	22.8 (16.6–23.0)	22.8 (11.9–NR)	17.1 (11.7–23.0)	22.8 (16.6–22.8)
18-month rate, % (95% CI)[a]	42.7 (29.9–54.9)	43.0 (30.0–55.3)	45.6 (24.0–64.9)	24.5 (8.4–44.9)	58.0 (37.5–73.9)	28.6 (14.1–44.9)
PFS						
Median (95% CI),[a] months	15.3 (6.6–24.9)	12.3 (6.5–NR)	16.6 (2.6–NR)	7.4 (3.3–12.3)	24.0 (8.6–NR)	6.1 (3.1–16.5)
Median follow-up (95% CI),[b] months	23.5 (17.7–23.8)	23.5 (17.6–23.8)	23.7 (10.4–24.0)	18.0 (12.7–NR)	18.2 (12.4–24.0)	23.6 (17.6–23.7)
18-month rate, % (95% CI)[a]	43.9 (31.8–55.4)	44.2 (31.9–55.8)	46.0 (26.1–63.8)	23.5 (8.1–43.4)	58.0 (38.3–73.3)	30.2 (16.1–45.6)
OS						
Median (95% CI),[a] months	18.2 (12.9–36.3)	17.1 (11.1–36.3)	18.4 (6.7–NR)	13.5 (9.5–17.1)	36.3 (15.3–NR)	11.1 (6.1–17.1)
Median follow-up (95% CI),[b] months	24.0 (23.7–24.2)	24.0 (23.7–24.2)	23.7 (23.3–35.7)	35.2 (18.1–NR)	24.0 (18.1–26.8)	23.7 (23.6–24.0)
18-month rate, % (95% CI)[a]	50.8 (39.2–61.2)	49.5 (37.8–60.1)	57.2 (36.8–73.1)	28.2 (12.5–46.2)	68.9 (49.6–82.0)	34.3 (20.8–48.2)

La DOR, SLP y SG fue consistente a lo largo de todos los grupos aunque numéricamene menor en pacientes con ≥5 líneas y aquéllos refractarios a iBTK

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Abst #7016

Eficacia y toxicidad comparativa entre brexu-cel y liso-cel

Agent	ORR	CRR	Median follow-up (mo)	mDOR (mo)	mPFS (mo)	mOS (mo)	CRS. overall	CRS > grade 2	Neurotoxicity, overall	Neurotoxicity > grade 2
Brexu-cel (N = 68)[10]	91%	68%	35.6	28.2	25.8	46.6	91%	15%	63%	31%
Liso-cel (N = 83)[12]	83%	72%	16.1	15.7	15.3	18.2	61%	1%	31%	9%

CRR, complete response rate.

Comparando Terapias basadas en células T para MCL

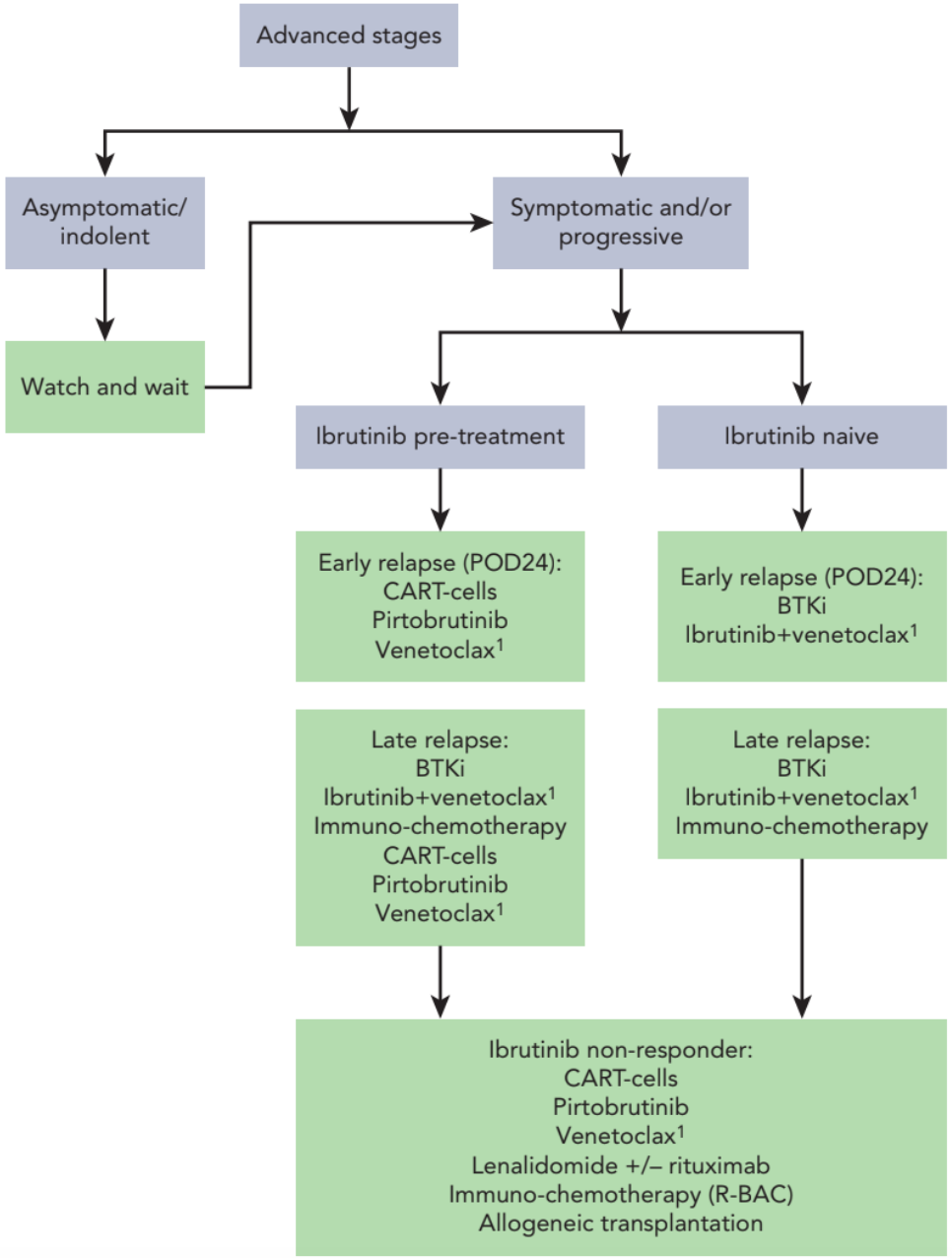
BiTes Pros:
- Off-the-shelf (pueden requierir anti CD20 para mitigar SLC)
- Comparativamente lenos inmunosupresión/infecciones a corto/largo plazo
- Mayor aplicación y monitoreo ambulatorio

CART Pros:
- Datos de eficacia a largo plazo disponibles
- Mayor confianza en la administración por los años de experiencia
- 2 constructos aprobados por FDA
- Puede ser curative en pacientes con DLBCL.y posiblemente pueda ser el caso del MCL

BiTes Cons:
- Actualmente investigacional
- Se desconoce la duración de la respuesta
- Potencial SLC/Neurotoxicidad
- Algunos riesgos de inmunosupresión
- Algunos eventos de progression en CD20-negativos

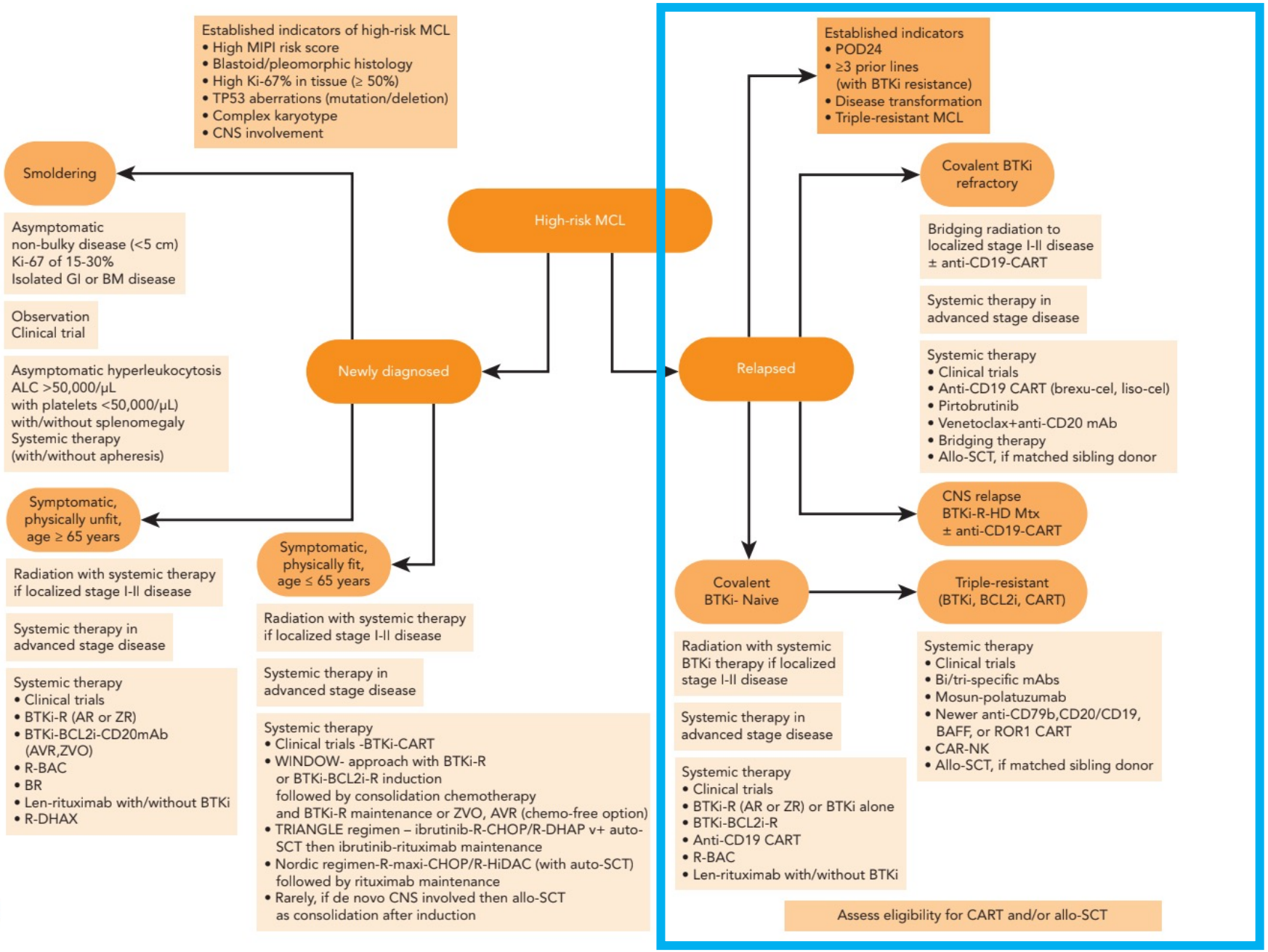
CART Cons:
- Mayores citopenias e inmunosupresión a largo plazo
- Mayor tiempo entre la aféresis y la administración
- Mayor riesgo de SLC/neurotoxicidad
- Administración en internación
- Series de casos con linfomas T subsecuentes

Algoritmo terapéutico en MCL (off label) (adaptado de Dreyling et al)



Silkenstedt E, Dreyling M. Blood 2025;145:673

Algoritmo terapéutico en MCL de alto riesgo



Jain P, Wang M. Blood 2025;145:683

Terapias blanco recomendadas

	First-line setting		Relapse setting	
Mode of action	**Approved**	**Off-label**	**Approved**	**Off-label**
BTKi		Rituximab + ibrutinib*; R-CHOP + ibrutinib/R-DHAP	Ibrutinib†; zanubrutinib‡; acalabrutinib‡; pirtobrutinib§	Ibrutinib + bortezomib; ibrutinib + lenalidomide + rituximab; ibrutinib + venetoclax; ibrutinib + venetoclax + obinutuzumab
Immunomodulator			Lenalidomide ± rituximab§	
Immunotherapy			Brexu-cel§	Glofitamab; loncastuximab tesirine
Others				Venetoclax

Silkenstedt E, Dreyling M. Blood 2025;145:673

Agentes nóveles en investigación activa

Name	Target and mechanism
NX-2127, BGB-16673	BTK-targeting PROTACs[129]
Epcoritamab	Bispecific antibody targeting CD20 and CD3; given subcutaneously
JNJ-80948543	Trispecific antibody targeting CD79b, CD20, and CD3
CART	CAR T-cells targeting CD19/CD20,[130] CD79b,[121] BAFF, SOX11, and ROR1. Efforts to improve the persistence of CART by modulating BCL2[131] and FOXO1[132] are being explored.
Sonrotoclax (BGB11417)	BCL2 antagonist
PRT-343 (NCT03886831)	PRMT5 inhibitor[133,134]
LP-284[135]	DNA-damaging agent that induces double-stranded DNA breaks. It has elevated potency in cancer cells with homologous recombination repair defects.
KIN-8194	Dual BTK/HCK inhibitor[136]
Luxeptinib (CG-806)[137]	Dual BTK/SYK inhibitor
TIGIT ab	Anti-TIGIT antibody
Miscellaneous	CDK inhibitors, MALT1,[138] BAFF,[139] ROR1[140,141]

Jain P, Wang M. Blood 2025;145:683

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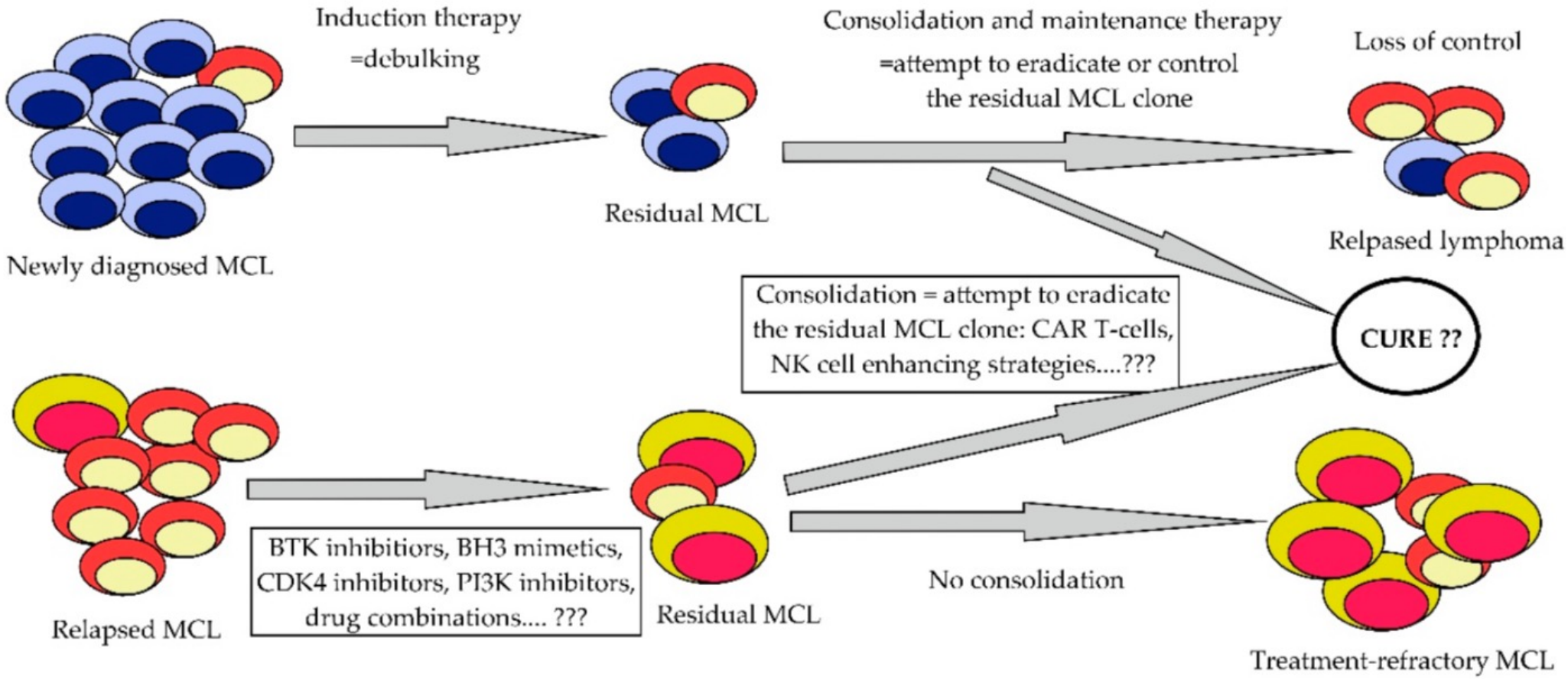
Perspectiva

- Tratamiento estratificado por riesgo, adaptado al paciente individual y a la respuesta
- Correcta definición de riesgo basado en perfil genético y molecular
    - Sumado a esquemas de rescate, rol de CAR19 T incluso en primera línea en pacientes de alto riesgo
    - BiTes y CAR19 T como consolidación luego de citorredución con combinación de nuevos agentes y anticuerpos monoclonales con o sin citostáticos → objetivo curación en pacientes de alto riesgo en quienes no puede pensarse la cura hoy en día

- Cambio de paradigma en los próximos años → intentar curación con el desarrollo de nuevos agentes o nuevas combinaciones en el marco de ensayos clínicos que sean eficaces en la erradicación de la EMR



Klener P. Int. J. Mol. Sci. 2019, 20, 4417; doi:10.3390/ijms20184417

Para llevarme a casa:

- El linfoma del manto continúa siendo una enfermedad incurable
- Esencial lograr mejoría en la eficacia de la 1L→ ¿combinación con nuevas moléculas?

  Objetivo: evitar desarrollo de clones refractarios, lograr EMR negativa
- Mejor definición de riesgo molecular y genético para adaptar el tratamiento al riesgo
- Combinación óptima y secuenciación más eficaz a definir en ensayos en curso/futuros
- Altamente improbable la cura con monoterapia → enfermedad genéticamente compleja

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