SINTOMA'25

8 A 10 DE MAIO

HOTEL INTERCONTINENTAL | SÃO PAULO

PARCERIA soho society of hematologic oncology

APOIO INSTITUCIONAL bp Educação e Pesquisa

SINTOMA'25

PARCERIA soho society of hematologic oncology

APOIO INSTITUCIONAL bp Educação e Pesquisa

What do I consider when deciding on second-line therapy in mantle cell lymphoma?

O que considero quando decido sobre a terapia de segunda linha no linfoma do manto?

DANIELLE LEÃO

Hematologista e Pesquisadora Clínica

BP – A Beneficência Portuguesa de SP

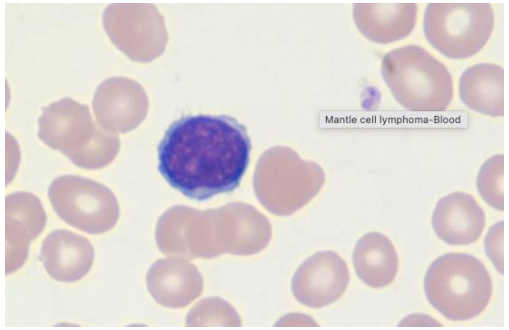
CROMA Oncologia

DISCLOSURES - DECLARAÇÃO DE CONFLITOS DE INTERESSE

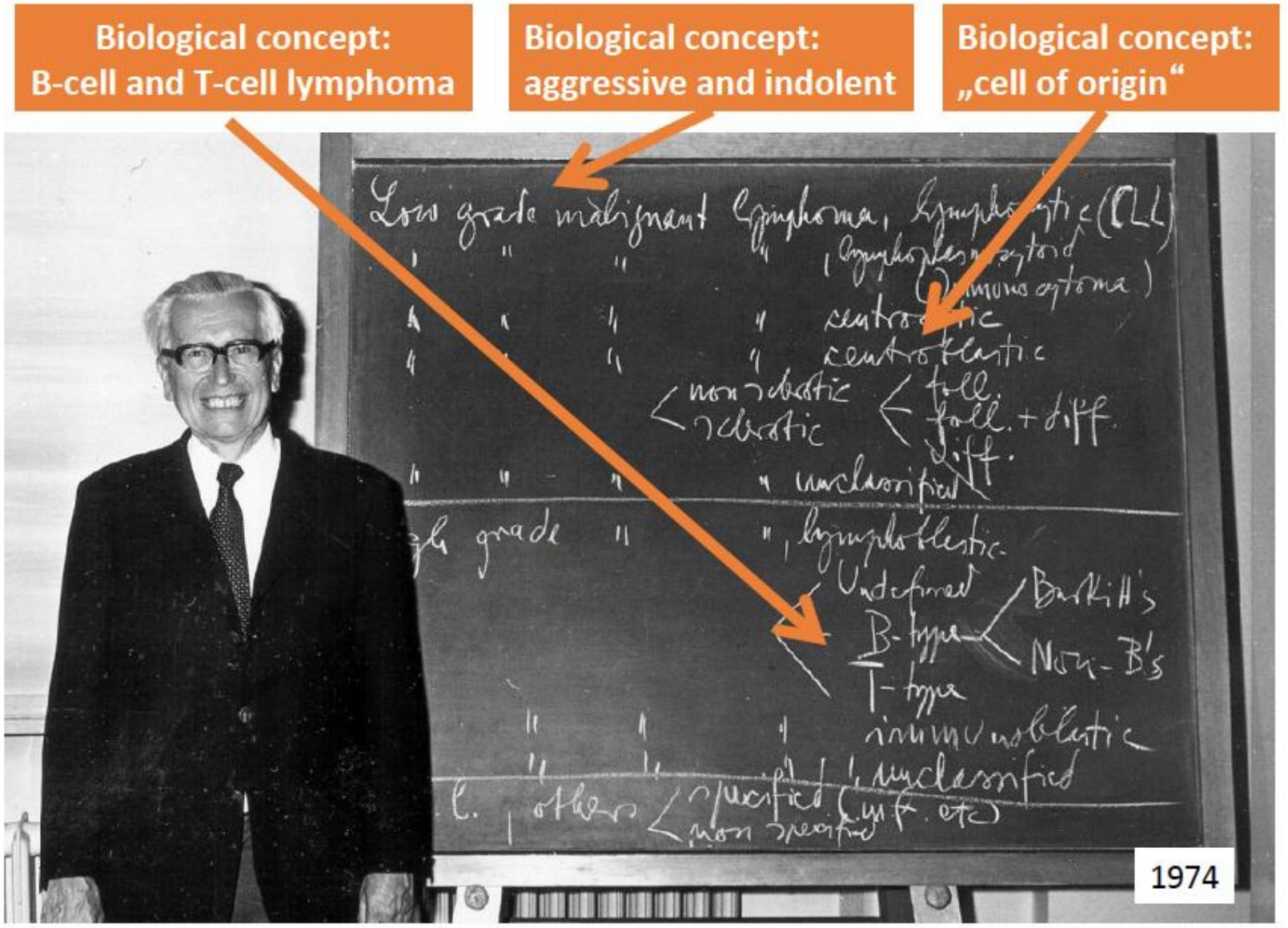
Patrocínio para esse evento	Sem fee / Patrocínio da AstraZeneca para SINTOMA 2025
Instituição	BP - Beneficencia Portuguesa de Sao Paulo e CROMA Oncologia
Participação em estudos clínicos (Indústria farmacêutica)	Roche, Novartis, GSK, Janssen, Millenium Takeda, ABBVIE, Daichii Sankyo, Pfizer, Celltrion, BMS, AstraZeneca, Viracta, Sandoz, AGIOS, Astellas, MEDAC, Onconova, MSD, Sanofi, Regeneron, Lilly, ADC Therapeutics, Libbs, Beigene
Participação em estudos clínicos (ITT, RWE ou registros)	T-Cell Project, HOLA registry, MMyBrave registry, REALITY WW, , Brazilian Group of CLL, Brazilian Group of Multiple myeloma, AML-Brazil, Coalizão COVID Brazil,
Palestrante	Janssen, AstraZeneca, Zodiac, Roche, Novartis, Takeda, AMGEN, Roche, Libbs, BMS, Celgene, Pfizer, ABBVIE, Sanofi, Pintfarma, Knight Therapeutics/United Medical
Membro de Advisory Board	Kite/Gilead, Knight Therapeutics/United Medical, Janssen, Novartis, AMGEM, Takeda, Roche, BMS, ABBVIE, Libbs, Celgene, Eurofarma,
Membro de Steering Committee	Janssen
Membro de Independent Data Monitoring Committee	Libbs /Mabxcience
Afiliação	ASH, EHA, ESO, IMS, CDCN (Castleman disease), ABHH (Associaçao Brasileira de Hematologia), Coordinator of Clinical Research Committee at ABHH, Myeloma Committee (ABHH), CLL Committee (ABHH), Lymphoma Committee (ABHH)

Dr. Karl Lennert

Department of Pathology of the Christian-Albrechts University in Kiel



Blood Images, 2018



https://www.society-for-hematopathology.org/web/about-memoriam-lennert.php

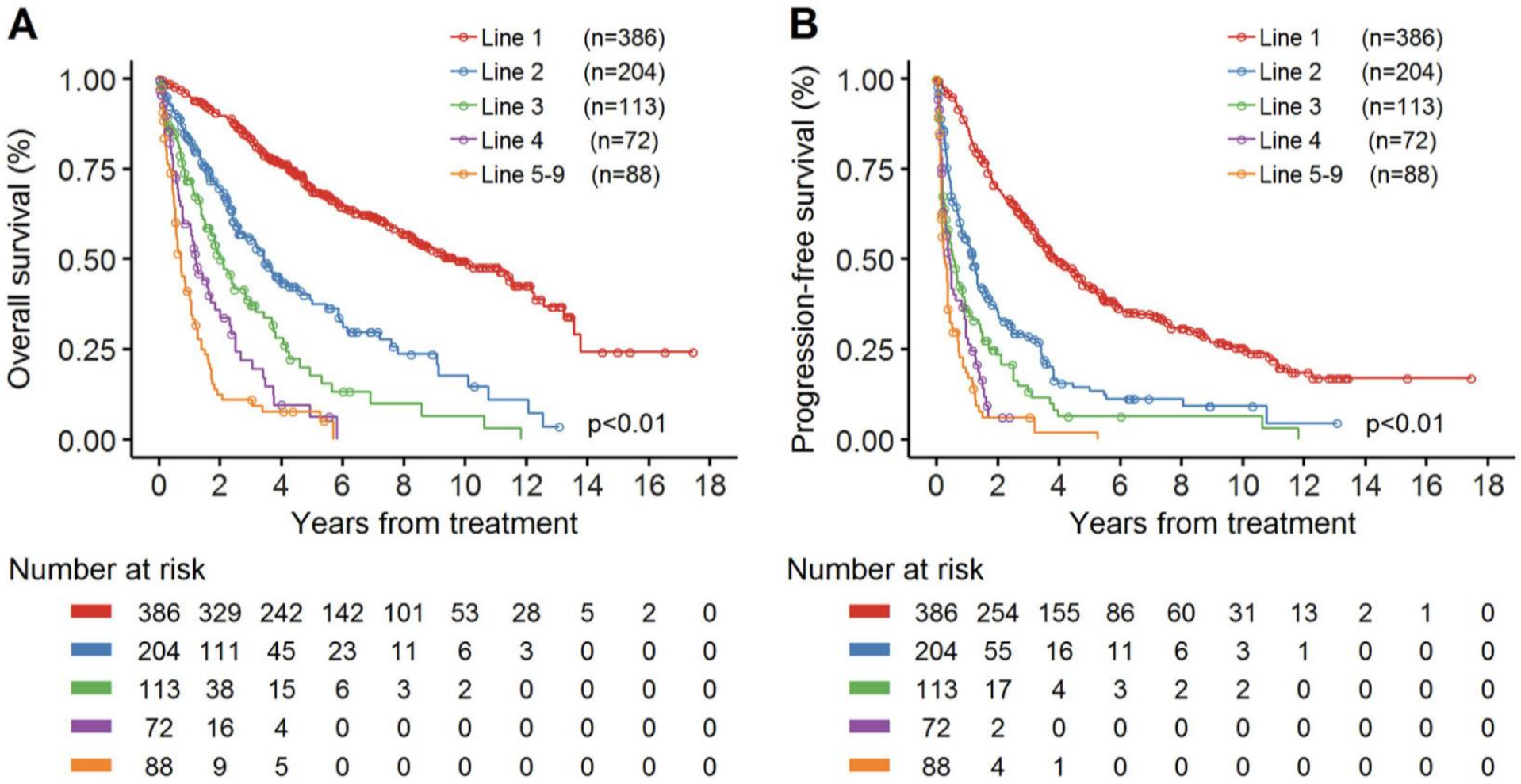
http://imagebank.hematology.org/image/61761/mantle-cell-lymphomablood. Acesso de ambas em 20/08/22

MANTLE CELL LYMPHOMA

"Virtually all patients will eventually experience refractory or relapsed disease, with a virulent course of resistance and serial relapses, making treatment challenging"

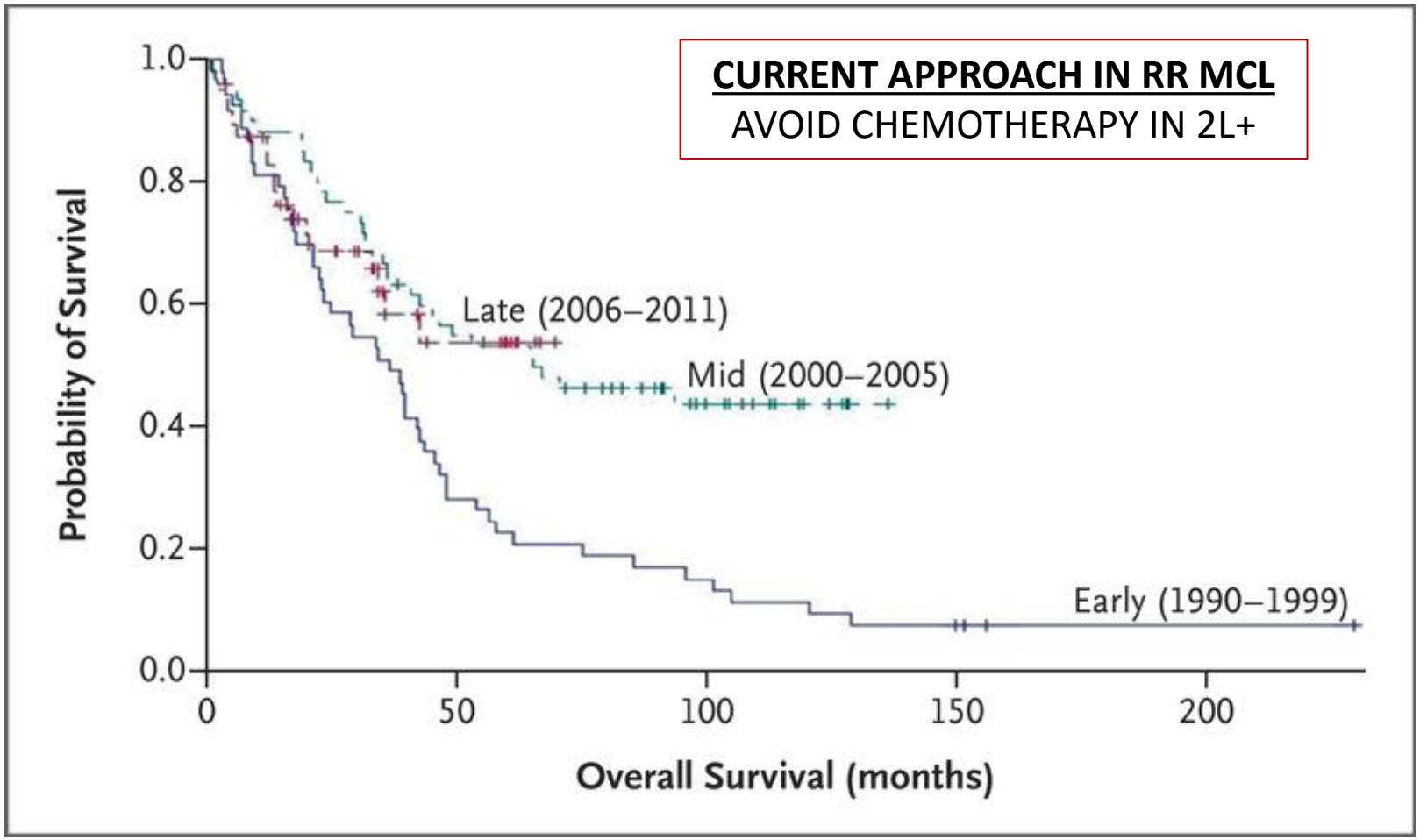
Burkart M & Karmali R. J Pers Med 2022 Mar 1;12(3):376

MCL SURVIVAL – LINES OF THERAPY



Kumar A. *et al.* Blood Cancer J 2019; 9(6):50

IMPROVEMENT IN MCL SURVIVAL WITH NEW DRUGS



Armitage JO and Longo DL. N Engl J Med 2022; 386:2495-2506

NEW DRUGS - ON LABEL IN BRAZIL - 2L+

2+ lines

MONOTHERAPY

-COVALENT BTKi

- 1st generation – ibrutinib
- 2nd generation – acalabrutinib, zanubrutinib

NEW DRUGS ASSOCIATION

- BTKi + BCL2i

Ibrutinib + venetoclax (SYMPATICO)

3+ lines

MONOTHERAPY

- BTKi

Pirtobrutinib (label – after 2+ lines of therapy and a covalente BTKi

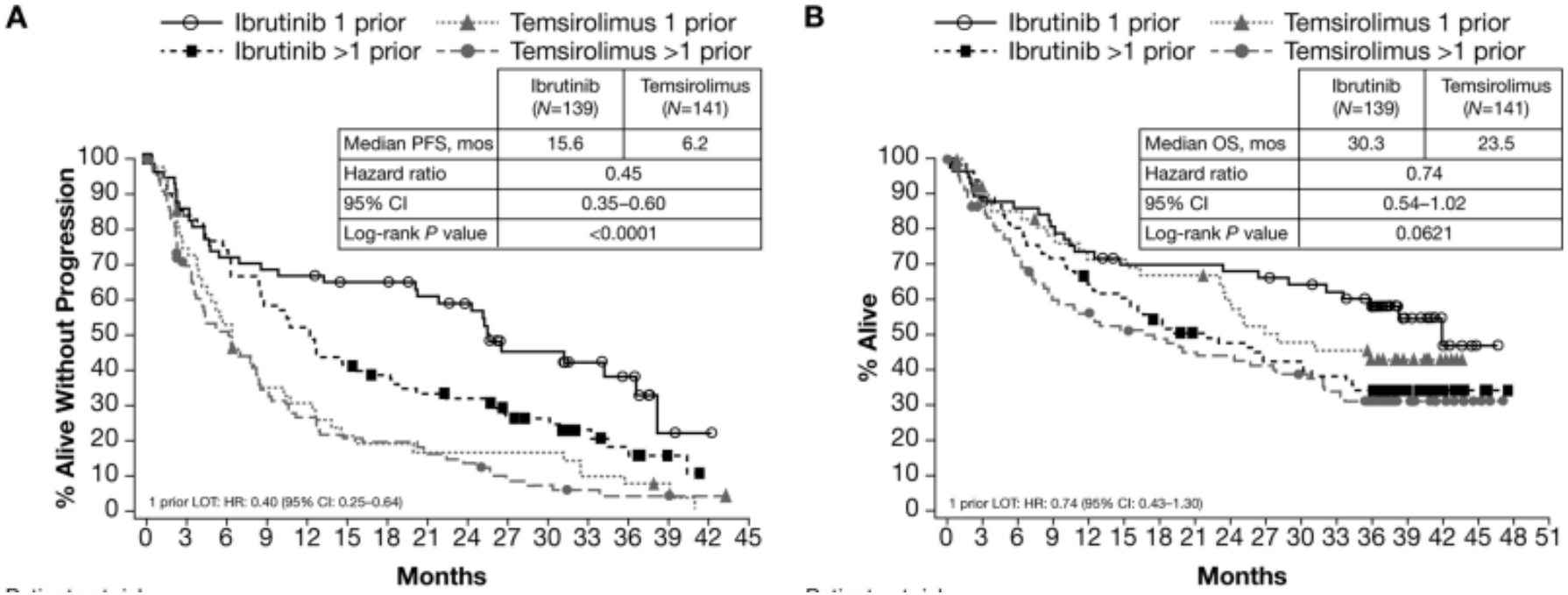
OBS- Not in the scope of the lecture, but, in fit patients ALWAYS consider/ discuss alloSCT

(debatable - Auto SCT if the only option and not previously done)

IT IS NOT CLL!! (unfortunately.....☹)

Slide by the author

Ibrutinib – estudo RAY



RESUMO CARACT. PACIENTES

- Med 68 anos (≥65 anos 62%)
- Med 2 linhas prévias (1-9)
- Dç refratária 26% Ibrut vs 33% Tensir
- Blastoide 12%

Leukemia 2018;32:1799-1803

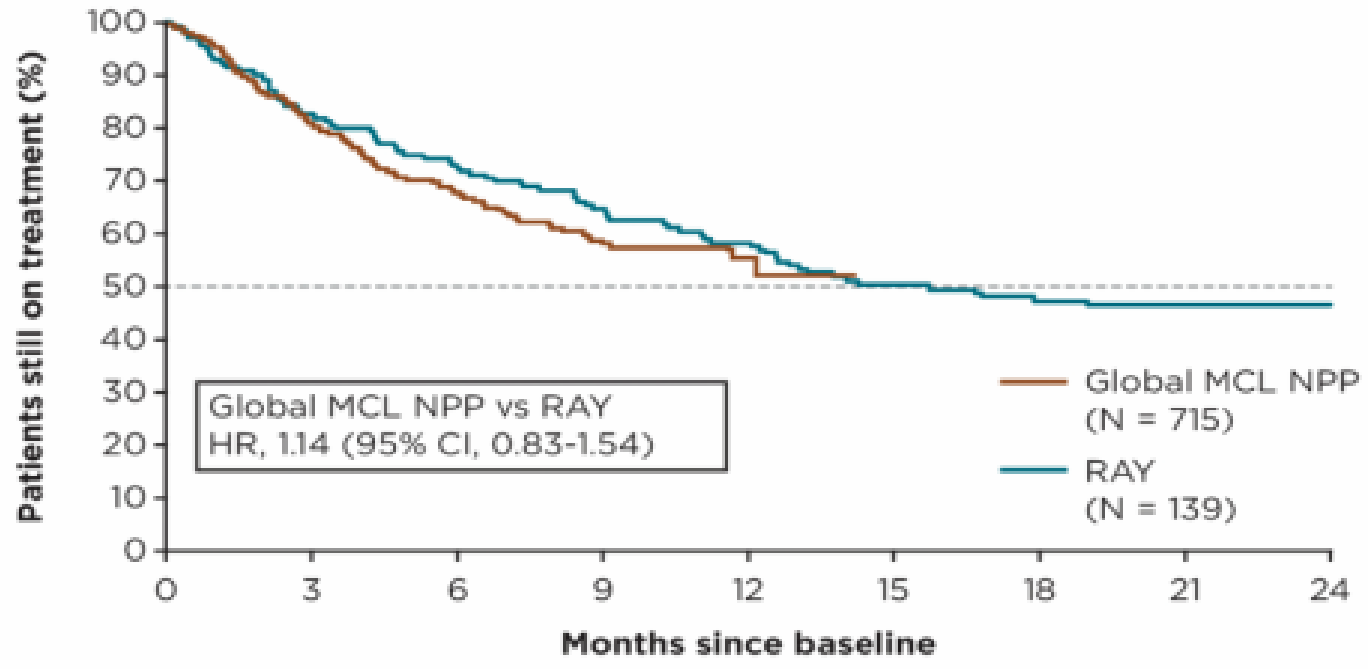
Real-World Experience of Ibrutinib In > 700 Patients With Mantle-Cell Lymphoma: Data From a Global Named Patient Program

Simon Rule,[1] Joris Diels,[2] Nollaig Healy,[3] Wafae Iraqi,[4] Johan Aschan,[5] and Mark Wildgust[6]

[1]Derriford Hospital, Plymouth, UK; [2]Janssen EU HEMAR Statistics & Modeling, Beerse, Belgium; [3]Janssen-Cilag EMEA Medical Affairs, Dublin, Ireland; [4]Janssen Pharmaceuticals, Paris, France; [5]Janssen-Cilag EMEA Medical Affairs, Solletuna, Sweden; [6]Janssen Research & Development, Raritan, NJ, USA

- 52,3% em tratamento p/ 12 meses
- RAY – 57,6%

Figure 1. Time on Treatment for Global MCL NPP Versus RAY



HR, hazard ratio.

Rule et al. Poster EHA 2016

Acalabrutinib – ACE-LY-004

Estudo aberto, de fase 2, braço único, multicêntrico

Pacientes com LCM r/r

Principais critérios de inclusão

- ≥18 anos*
- PS ECOG ≤2
- Translocação t(11;14)(q13;q32) e/ou superexpressão de ciclina D1
- Doença mensurável (≥1 lesão ≥2cm
- LCM r/r com 1 a 5 terapias anteriores

Critérios de exclusão

- Doença cardíaca significativa
- Creatinina 2,5x acima do limite de normalidade
- Uso de antagonista de vit. K
- Uso anterior de BCRi ou BCL2i
- Neutrófilos <0,75x10^9/L
- Plaquetas <50x10^9/L

Se envolvimento medular:

- Neutrófilos <0,50x10^9/L
- Plaquetas <30x10^9/L

Acalabrutinibe 100mg via oral, duas vezes ao dia, em ciclos de 28 dias, até progressão ou toxicidade inaceitável (n=124)

TC com contraste após ciclos 2, 4 e 6 e, após, a cada 3 ciclos.
PET-CT após ciclos 2 e 6.
Aspirado de medula ou endoscopia do TGI foram realizados quando aplicável.

40 centros em 10 países

RESUMO CARACT. PACIENTES

- **Med 68 anos**
- **Med 2 linhas prévias (1-5)**
- **Dç refratária 24%**

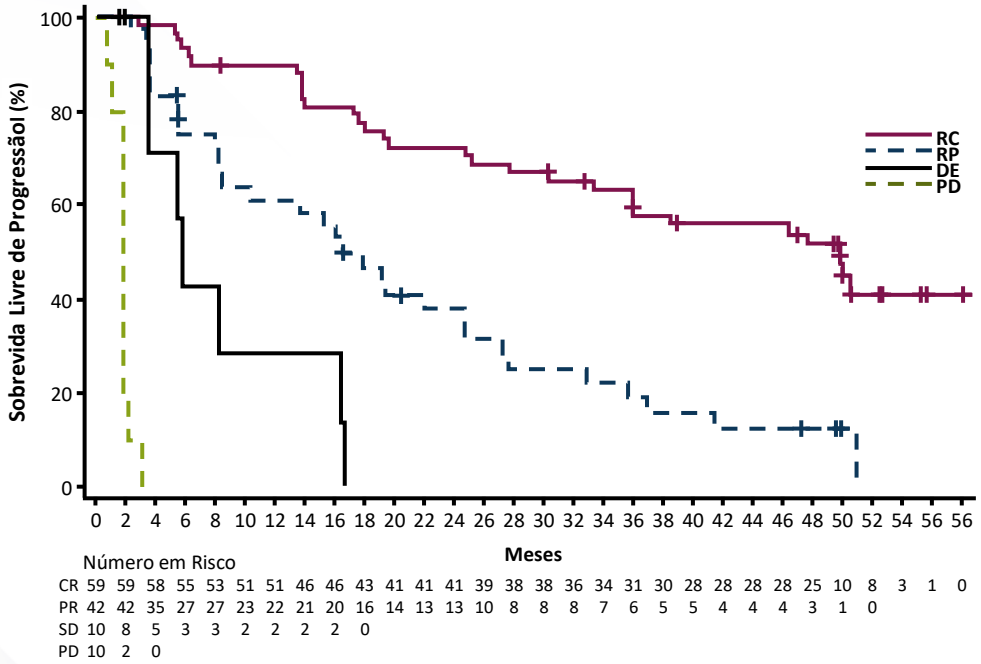
Desfecho Primário: Taxa de resposta,
Desfechos Secundários: Duração de resposta, SLP, SG, segurança, farmacocinética e farmacodinâmica. Taxa de resposta, duração de resposta e SLP por Revisão de Comitê Independente por critério de Lugano 2014.

Lancet. 2018;391(10121):659-67

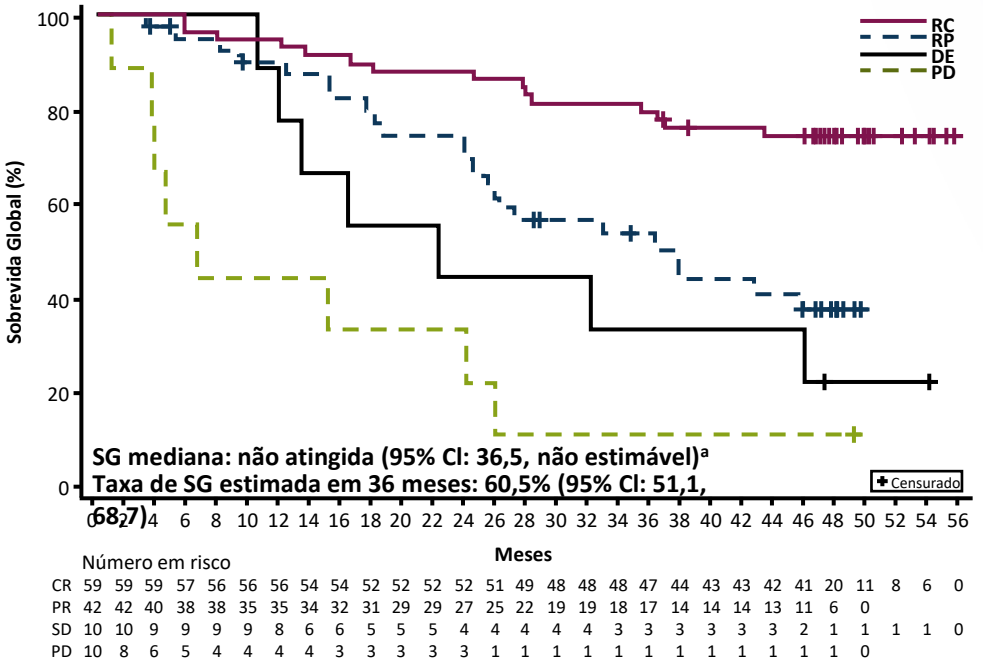
ACE-LY-004

Mais de um terço dos pacientes estava sem progressão de doença em 36 meses

Sobrevida Livre de Progressão



Sobrevida Global



Med SLP : 22,0 meses (95% CI: 16,6, 33,3)[a]

Med SG : Não atingida -FUP 26M

Taxa de SLP estimada em 36 meses: 37,2% (95% CI: 28,2, 46,1)

. Wang M, et al. Leukemia. 2019;33(11):2762-6.
2. Wang M, et al. Poster presented at: ASH; Dec 5-8, 2020; Poster #2040.

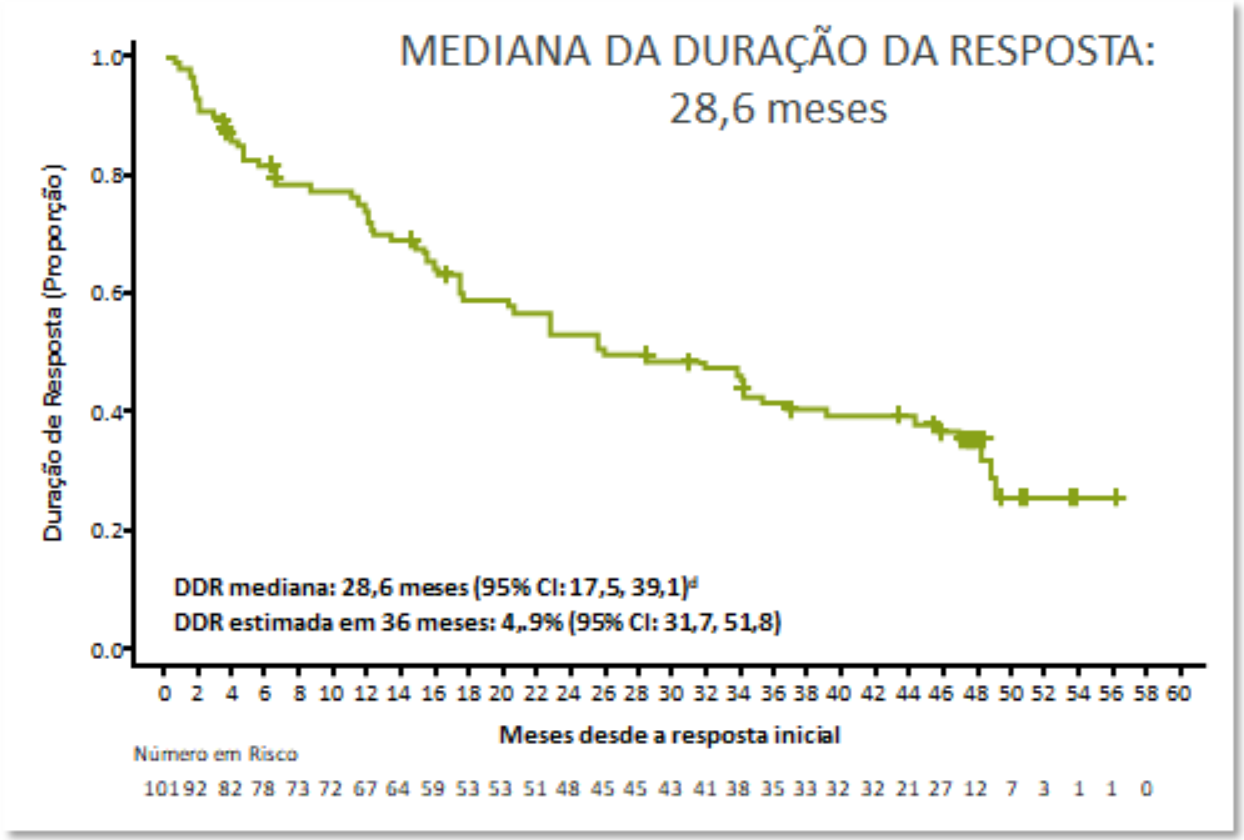
Atualização 38 Meses ACE-LY-004: Manutenção da Resposta

Todos os pacientes (N=124)				
Desfechos	Seguimento de 26 meses[1]		Seguimento de 38 meses[2]	
	n (%)	95% CI	n (%)	95% CI
TRO[b] (RC + RP)	100 (81)	73, 87	101 (81)	74, 88
Melhor Resposta				
RC	53 (43)	34, 52	59 (48)	39, 57
RP	47 (38)	29, 47	42 (34)	26, 43
DE	11 (9)	5, 15	10 (8)	4, 14
PD	10 (8)	4, 14	10 (8)	4, 14
Não avaliável[c]	3 (2)	1, 7	3 (2)	1, 7

MEDIANA DA DURAÇÃO DA RESPOSTA: 28,6 meses

Ki67 < 50%- 36,7 meses

Ki67 ≥ 50%- 15,3 meses



[a]De acordo com a classificação de Lugano. [b]Definido como a proporção de pacientes que alcançaram RP ou melhor de acordo com a classificação de Lugano. [c]Inclui pacientes sem qualquer avaliação adequada da doença pós baseline.[2] [d]DDR mediano no seguimento de 26 meses: 26 meses (IC de 95%: 17,5, não atingido).[1]

DDR: duração de resposta; DE: doença estável; IC: intervalo de confiança; (m): meses; PD: progressão de doença; RC: resposta completa; RP: resposta parcial; TRO: taxa de resposta objetiva.

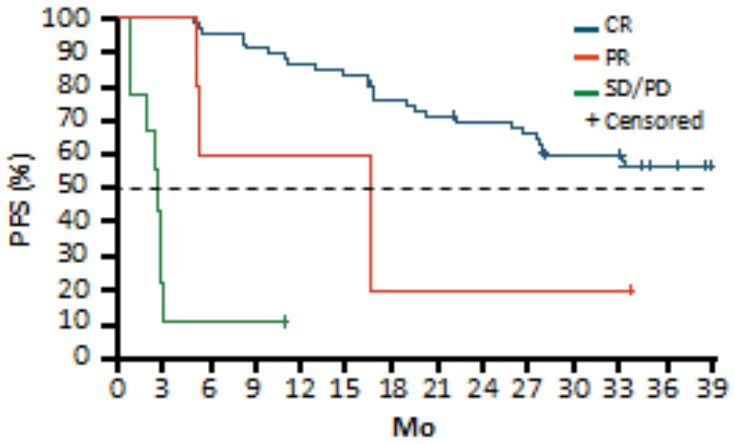
1. Wang M, et al. Leukemia. 2019;33(11):2762-6. 2. Wang M, et al. Poster presented at: ASH; Dec 5-8, 2020; Virtual Meeting. Poster 42040.

BGB-3111
Efficacy

BGB-3111 Phase II Study
Zanubrutinib monotherapy RR MCL

Efficacy Variable (INV Assessed)	N = 86
ORR (CR+PR), % (95% CI)	83.7 (74.2-90.8)
Best response, n (%)	
CR	67 (77.9)
PR	5 (5.8)
SD	1 (1.2)
PD	8 (9.3)
Discontinued before first assessment	5 (5.8)
Median follow-up, mo	30.6
Median DOR, mo (95% CI)	NR (24.9-NE)
Median PFS, mo (95% CI)	33.0 (19.4-NE)
36-mo PFS, % (95% CI)	47.6 (36.2-58.1)
36-mo OS, % (95% CI)	74.8 (63.7-83.0)

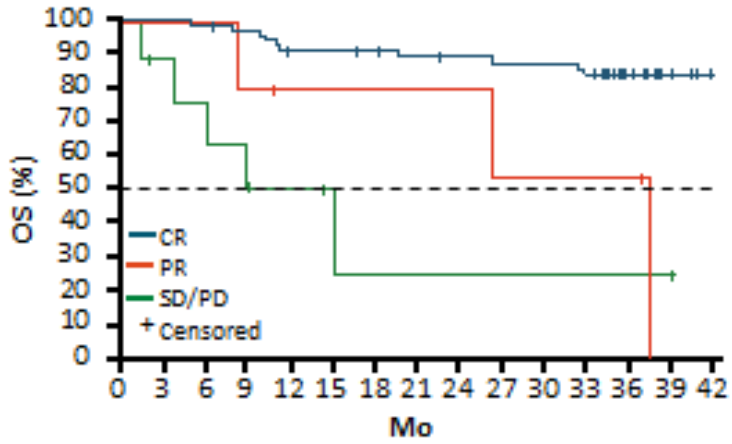
PFS



No. of patients at risk

CR	67	67	63	60	57	55	50	47	44	42	37	35	9	0	
PR	5	5	3	3	3	3	1	1	1	1	1	1	0	0	
SD/PD	9	1	1	1	0	0	0	0	0	0	0	0	0	0	

OS



No. of patients at risk

CR	67	67	66	64	59	59	57	55	54	53	53	51	35	7	0	
PR	5	5	5	4	3	3	3	3	3	2	2	2	2	0	0	
SD/PD	9	7	5	3	3	2	1	1	1	1	1	1	0	0	0	

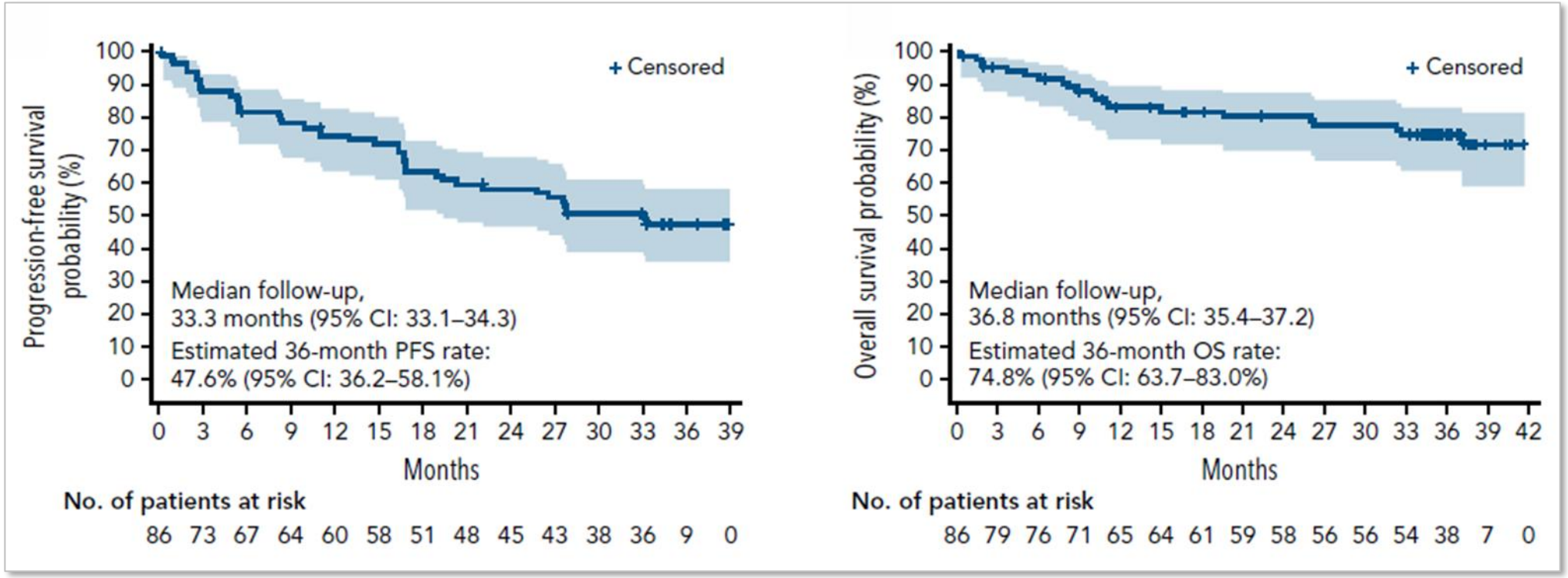
Median time to respose: 2.7m
45.3% pts continued on treatment
Median treatment duration: 27.6m

Song. Blood. 2022;139:3148.

Zanubrutinib in Relapsed/Refractory Mantle Cell Lymphoma Treatment

BGB-3111-206[2]

Efficacy



Kaplan-Meier curves of survival and response analyses. PFS as determined by investigator assessment. Shaded area indicates 95% CI. / OS. Shaded area indicates 95% CI.

Zodiac
Uma empresa Adium
Hematologia

1. Song Y.Blood. 2022; 139(21): 3148-3158.

Adapted from Song Y. Blood 2022

AND AFTER cBTKi?

PIRTOBRUTINIB EFFICACY IN MCL AFTER cBTKi

Does "Kinase Dead" mean that signal transduction is abrogated?

L528 and C481F/R/Y "kinase dead" → prevent the autophosphorylation of BTK (required for BTK kinase activation)

Class	Drug	Binding site	Half-life	Specificity	Toxicity	BTK mutations
First generation	Ibrutinib	Irreversible at C481	Short	Low	Bleeding, cardiac	C481S
Second generation	Acalabrutinib	Irreversible at C481	Short	High	Reduced	C481x, T474x
Next generation	Zanubrutinib	Irreversible at C481	Short	High	Reduced	C481x, L528W
Reversible	Pirtobrutinib	Reversible	Long	Very high	Reduced	T474, L528W, V416L, A428D, M477I, M437R, kinase-dead C481
Reversible	Nemtabrutinib	Reversible	Long	Low	Insufficient information	Not reported

Brown JR, et al. Oral presentation at EHA 2023. Abstract #S146.

BUT **DOES NOT** prevent downstream signal transduction proteins from being activated through phosphorylation.

Tam and Thompson Blood Advances 2024

PIRTOBRUTINIB EFFICACY IN MCL AFTER COVALENT BTKi

	Ibrutinib (n=59)	Acalabrutinib (n=31)	Zanubrutinib (n=6)
Overall response rate, % (95 CI)	59.3% (45.7-71.9)	58.1% (39.1-75.5)	50.0% (11.8, 88.2)
Best overall response, n (%)			
Complete response	13 (22.0)	5 (16.1)	1 (16.7)
Partial response	22 (37.3)	13 (41.9)	2 (33.3)
Stable disease	7 (11.9)	4 (12.9)	2 (33.3)
Progressive disease	11 (18.6)	4 (12.9)	1 (16.7)
Not evaluable[a]	6 (10.2)	5 (16.1)	0
Duration of response			
Patients with a response, n	35	18	3
Patients with censored data, n (%)	24 (68.6)	8 (44.4)	3 (100.0)
Median duration of response, mo (95% CI)	NR (7.46-NR)	6.93 (3.22-NR)	NR (NR-NR)
Median follow-up, mo	11.93	8.21	5.78

WANG´S DISCUSSION:

Notably, similar efficacy was observed in patients previously treated with ibrutinib, acalabrutinib, or zanubrutinib,

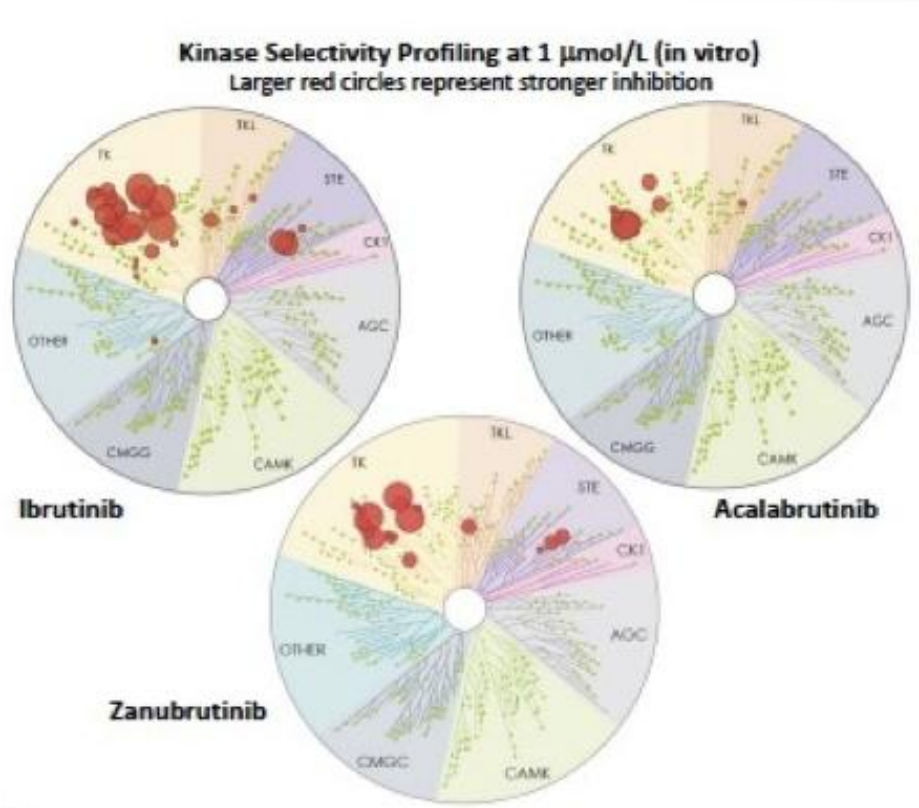
Wang ML, et al. J Clin Oncol. 2023

HOW TO CHOOSE THE cBTKI MONOTHERAPY FOR 2nd LINE?

- EFFICACY SIMILAR
- ESPECIFICITY FOR BTK
- SAFETY
- SPECIFIC PATTERN OF TOXICITY FOR EACH DRUG

BTKi Safety peculiarities

Adverse events	Cell type	Kinase	Ibrutinib	Acalabrutinib	Zanubrutinib
Infection	B-lymphocyte	BTK	⊣	⊣	⊣
		TEC	⊣	n.i.	⊣
	T-lymphocyte	ITK	⊣	n.i.	n.i.
		TEC	⊣	n.i.	⊣
		RLK/TXK	⊣	⊣	⊣
	Macrophage Neutrophil	BTK	⊣	⊣	⊣
		TEC	⊣	n.i.	⊣
** Bleeding	Thrombocyte	BTK	⊣	⊣	⊣
		TEC*	⊣	n.i.	⊣
			minor bleeding		
Atrial fibrillation	Cardiomyocyte	HER2	⊣	n.i.	n.i.
		HER4	⊣	⊣	⊣
		TEC*	⊣	n.i.	⊣
		atrial fibrillation:	frequent	less frequent	rare



Jpers Med 2021. K Lewis. Imagem: Adapted fron Estupiñán, 2021.

Adaptado de Front Oncol. 2021;11:668162

WHAT ABOUT COMBINATIONS?

DESENHO DO ESTUDO[1]

SYMPATICO (NCT03112174)

Um estudo multinacional, randomizado, duplo-cego, controlado por placebo, de fase 3

SYMPATICO (n=267)
- Idade ≥18 anos
- R/R MCL
- 1–5 terapias anteriores para MCL
- ≥1 esquema prévio contendo rituximabe /anti-CD20
- ECOG PS 0–2

Randomizado 1:1

IMBRUVICA® + venetoclax (n = 134)
Ibrutinibe 560 mg uma vez ao dia + venetoclax 5 semanas ramp-up para 400 mg uma vez ao dia por 24 meses

IMBRUVICA® + placebo (n=133)
Ibrutinibe 560 mg uma vez ao dia + placebo uma vez ao dia por 24 meses

Agente único IMBRUVICA® 560mg **uma vez ao dia até DP ou toxicidade inaceitável**

Estratificação: ECOG PS, linhas anteriores de terapia, risco de TLS[a]

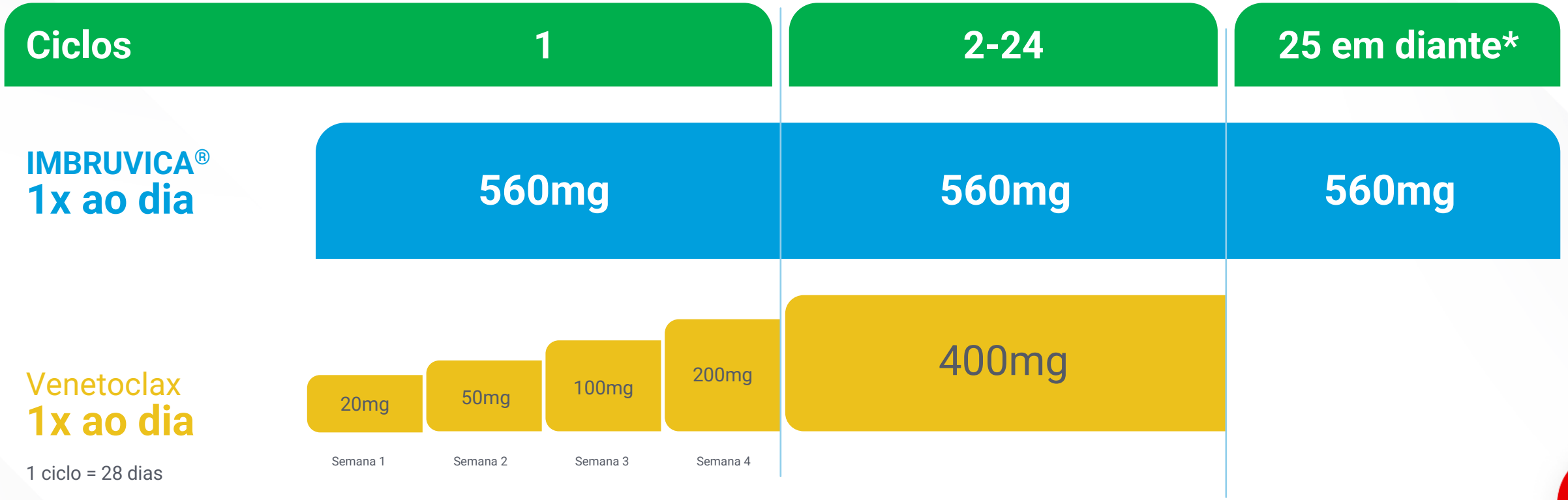
Endpoints Primário
- **Sobrevida Livre de Progressão (SLP)** por avaliação do investigador usando critérios de Lugano

Endpoints secundários
- **Taxa de reposta completa (RC)** avaliada pelo investigador
- Tempo até o **próximo tratamento**
- Sobrevida Global **(SG)**
- Taxa de resposta global (TRG) **avaliada pelo investigador**

Adaptado de: Wang M, et al. Blood.2023:142(Suppl.2): LBA-2

1. Wang M, Jurczak W, Trneny M, et all. Ibrutinin combined With Venetoclax in patients with Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis Results from the Randomized Phase 3 Sympatico Study. Blood. 2023;142 (suppl2);LBA-2

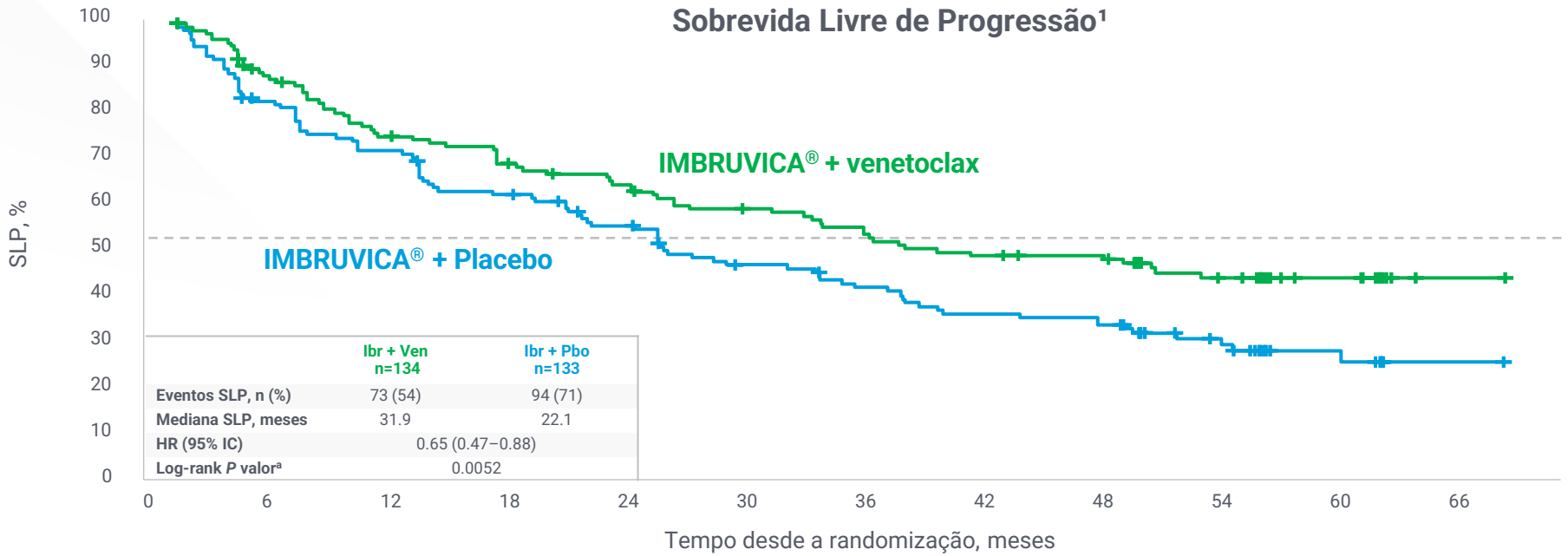
POSOLOGIA I+V EM LCM R/R[1]



*Até progressão de doença ou toxicidade inaceitável

Adaptado de: Wang M. et al Blood. 2023:142(Suppl.2):LBA-2
Referência: 1. Kater AP, et al. Fixed-Duration Ibrutinib-Venetoclax in Patients with Chronic Lymphocytic Leukemia and Comorbidities. NEJM Evidence. 2022; doi:10.1056/EVIDoa2200006. 2; Wang M, Jurczak W, Trneny M, et all. Ibrutinin combined With Venetoclax in patients with Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis Results from the Randomized Phase 3 Sympatico Study. Blood. 2023;142 (suppl2);LBA-2

SOBREVIDA LIVRE DE PROGRESSÃO[1]



Pacientes em risco

Ibr+Ven	134	107	91	80	69	63	56	53	34	15	1	0
Ibr+Pbo	133	96	79	70	54	46	37	36	18	8	1	0

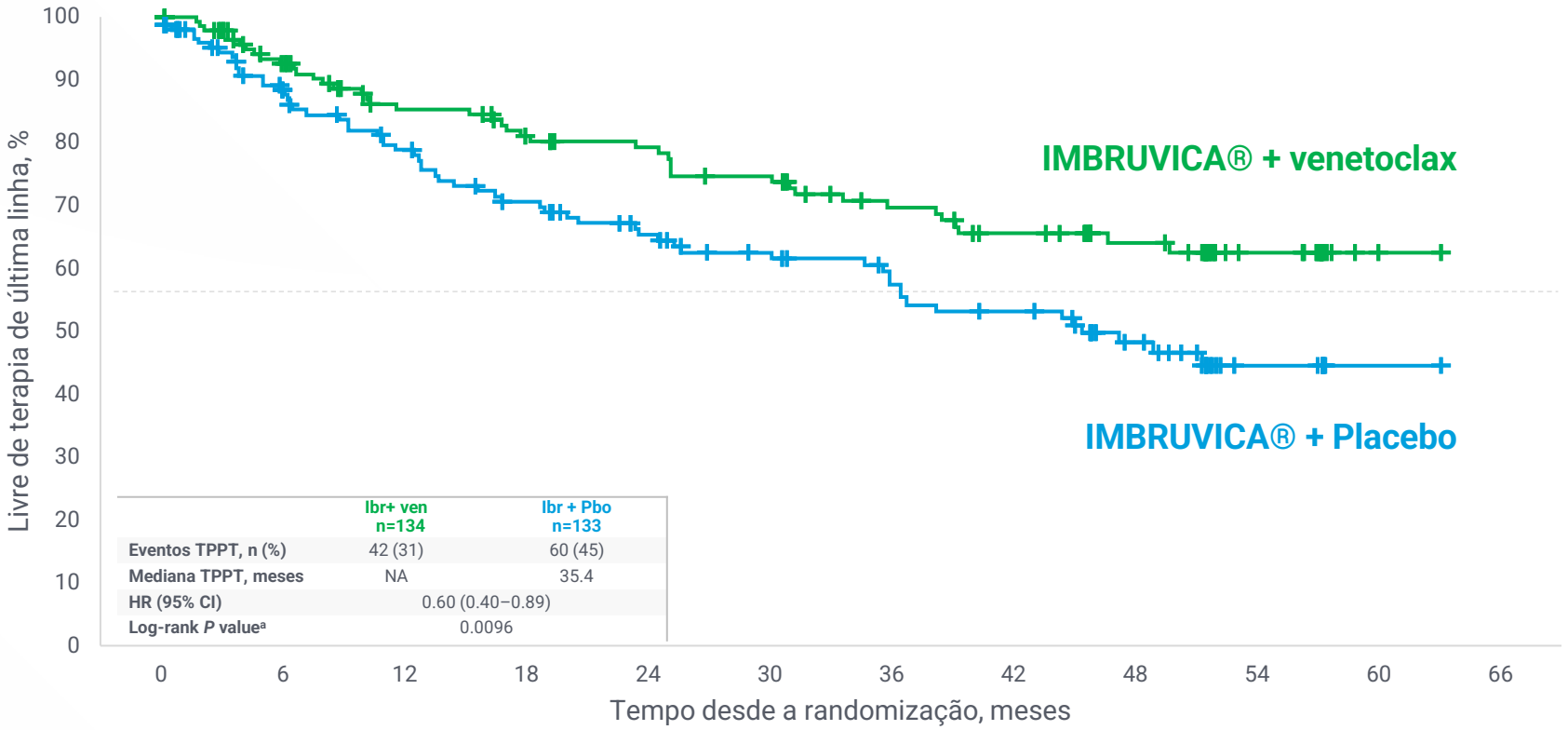
SLP mediana, meses	Dados do Global Censoring*			
	Ibr+Ven n=134	Ibr+Pbo n=133	HR (95% CI)	Log-rank *P* value[a]
Avaliação do investigador	31.9	22.1	0.65 (0.47–0.88)	0.0052
Avaliação de IRC	31.8	20.9	0.67 (0.49–0.91)	0.0108

mSLP = 31,9 meses

IMBRUVICA® + venetoclax aumentou em quase **10 meses a SLP** quando comparado a monoterapia independente do perfil do paciente

Adaptado de: Wang M, et al. Blood.2023:142(Suppl.2): LBA-2.
HR, Taxa de risco Ibr, ibrutinibe; Pbo, placebo; Ven, venetoclax
a.Os valores de P foram determinados pelo teste log-rank estratificado (fatores de estratificação: linhas anteriores de terapia [1–2 vs ≥3] e categoria de risco TLS [risco baixo vs aumentado])
*Método Global Censoring : at last non-PD assessment for patients without PD or death
1. Wang M, Jurczak W, Trneny M, et all. Ibrutinin combined With Venetoclax in patients with Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis Results from the Randomized Phase 3 Sympatico Study. Blood. 2023;142 (suppl2);LBA-2

TEMPO PARA O PRÓXIMO TRATAMENTO[1]



	Ibr+ ven n=134	Ibr + Pbo n=133
Eventos TPPT, n (%)	42 (31)	60 (45)
Mediana TPPT, meses	NA	35.4
HR (95% CI)	0.60 (0.40–0.89)	
Log-rank *P* value[a]	0.0096	

Pacientes em risco

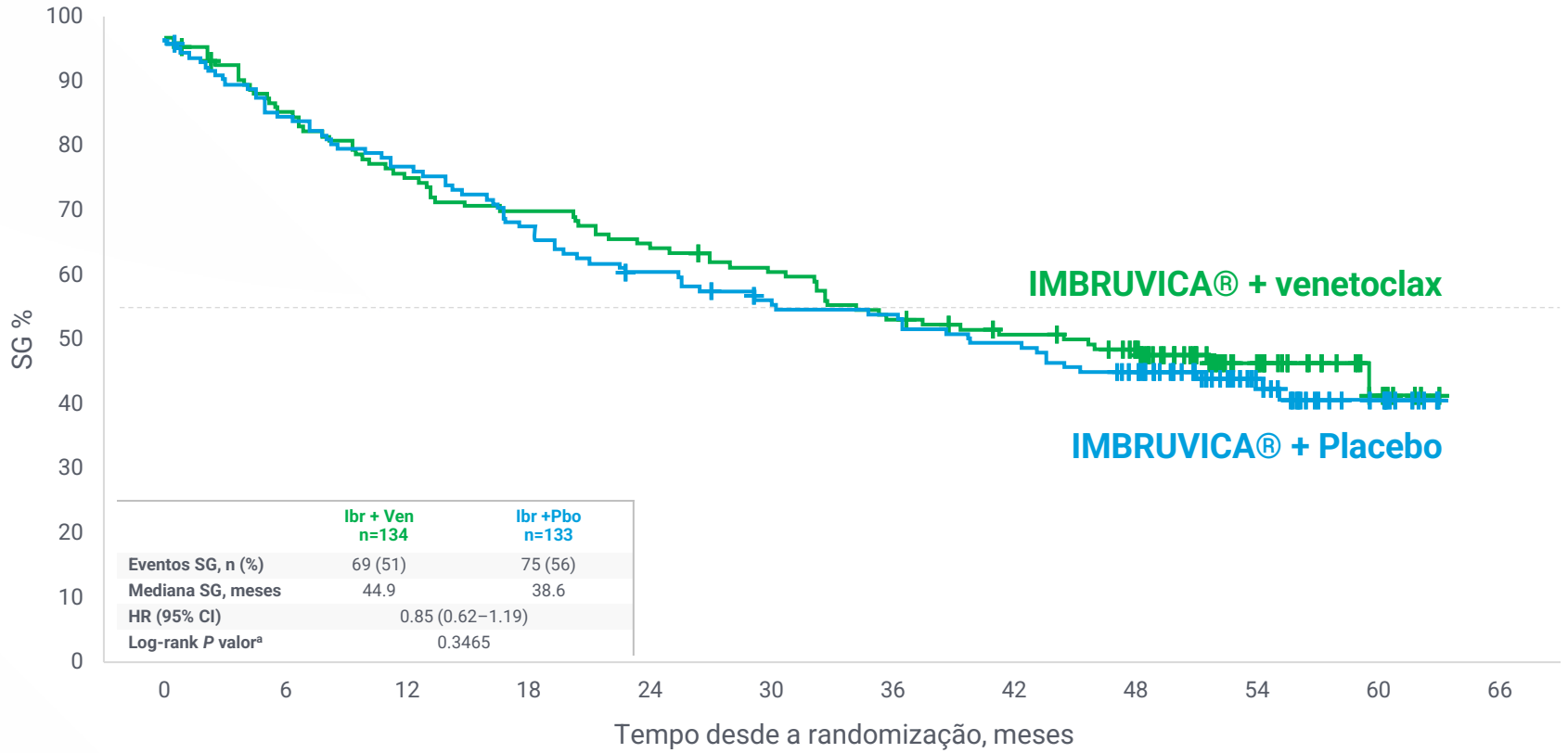
Ibr+Ven	134	107	92	82	76	65	59	52	35	16	1	0
Ibr+Pbo	133	96	83	71	58	50	42	39	20	8	1	0

Em 51.2 meses a **mediana de TPPT não foi atingida[1]**

IMBRUVICA® + venetoclax proporcionou **uma redução de 40% do risco de necessidade de um próximo tratamento[1]**

Adaptado de: Wang M, et al. Blood. 2023:142(Suppl.2):LBA-2
NA, não alcançado.
a. Os valores de aP foram determinados pelo teste de log-rank estratificado (fatores de estratificação: linhas anteriores de terapia [1–2 vs ≥3] e categoria de risco TLS [risco baixo vs aumentado]).
1. Wang M, Jurczak W, Trneny M, et all. Ibrutinin combined With Venetoclax in patients with Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis Results from the Randomized Phase 3 Sympatico Study. Blood. 2023;142 (suppl2);LBA-2

SOBREVIDA GLOBAL[1]



	Ibr + Ven n=134	Ibr +Pbo n=133
Eventos SG, n (%)	69 (51)	75 (56)
Mediana SG, meses	44.9	38.6
HR (95% CI)	0.85 (0.62–1.19)	
Log-rank *P* valor[a]	0.3465	

Pacientes em risco

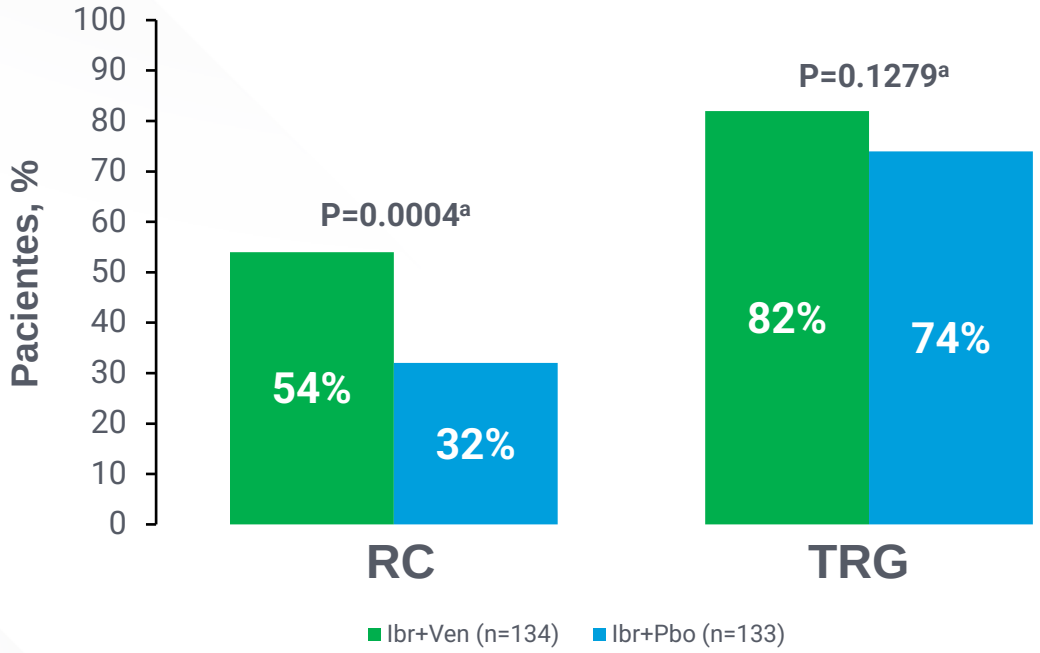
Ibr+Ven	134	116	102	95	87	81	70	65	48	20	3	0
Ibr+Pbo	133	115	103	88	80	70	66	61	46	20	4	0

No tempo de seguimento do estudo **não foi observada diferença estatisticamente significatica na SG** de pacientes com LCM tratados com I+V vs braço comparador[1]

Adaptado de: Wang M, et al. Blood. 2023:142(Suppl.2):LBA-2
HR, Taxa de risco Ibr, ibrutinibe; Pbo, placebo; Ven, venetoclax
a. Os valores de P foram determinados pelo teste log-rank estratificado (fatores de estratificação: linhas de terapia anteriores [1–2 vs ≥3] e categoria de risco de SLT [risco baixo vs aumentado]).
1. Wang M, Jurczak W, Trneny M, et all. Ibrutinin combined With Venetoclax in patients with Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis Results from the Randomized Phase 3 Sympatico Study. Blood. 2023;142 (suppl2);LBA-2

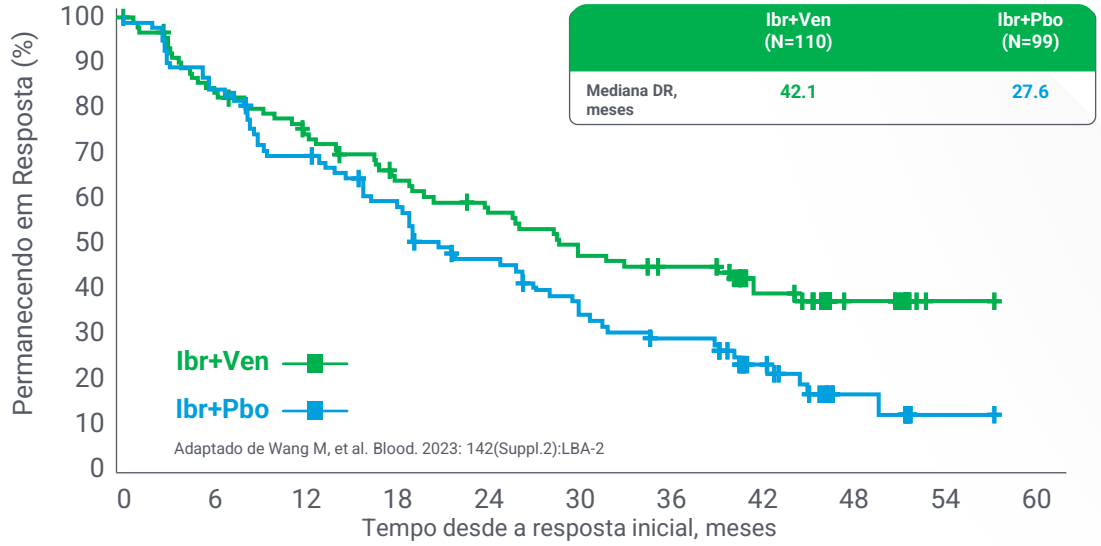
TAXA DE RESPOSTA PROFUNDAS E DURADOURAS[1]

Taxa de resposta



RC: Resposta Completa / **TGR** :Taxa de Resposta Global
Adaptado de Wang M, et al. Blood. 2023: 142(Suppl.2):LBA-2

Duração da resposta[b]



	Ibr+Ven (N=110)	Ibr+Pbo (N=99)
Mediana DR, meses	42.1	27.6

Pacientes em risco

1 LTP	110	93	83	72	66	58	52	37	15	1	0
>1 LTP	99	85	72	62	50	42	35	22	8	1	0

As taxas de resposta completa foram de **22% maiores** em pacientes com uso de I+V[1]

Respostas duradouras com o uso de IMBRUVICA® + venetoclax[1]

Os valores de a P foram determinados pelo teste de log-rank estratificado (fatores de estratificação: linhas anteriores de terapia [1–2 vs ≥3] e categoria de risco TLS [risco baixo vs aumentado]).

1. Wang M, Jurczak W, Trneny M, et all. Ibrutinin combined With Venetoclax in patients with Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis Results from the Randomized Phase 3 Sympatico Study. Blood. 2023;142 (suppl2);LBA-2

Phase 1b/2 Study of Venetoclax, Ibrutinib, Prednisone, Obinutuzumab, and Lenalidomide (ViPOR) in Relapsed/Refractory and Treatment-Naïve Mantle Cell Lymphoma: Preliminary Analysis of Safety, Efficacy, and Minimal Residual Disease

Christopher Melani[1], Rahul Lakhotia[1], Stefania Pittaluga[2], James D. Phelan[1], Jagan R. Muppidi[1], Max Gordon[1], Yandan Yang[1], Weihong Xu[1], Theresa Davies-Hill[2], Da Wei Huang[1], Craig J. Thomas[3], Michele Ceribelli[3], Frances A. Tosto[3], Anna M. Juanitez[1], Amynah Pradhan[1], Candis Morrison[1], Atekelt Tadese[1], Colleen Ramsower[4], Lisa M. Rimsza[4], Allison P. Jacob[5], Heidi Simmons[5], Seth M. Steinberg[6], Elaine S. Jaffe[2], Mark Roschewski[1], Louis M. Staudt[1], and Wyndham H. Wilson[1]

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Melani C et al. Blood (2024) 144 (Supplement 1): 750

CONCLUSÕES

- New drugs made a revolution

BUT

Mantle cell lymphoma isn´t CLL....

Slide by the author

CONCLUSIONS

- Prepare your patient for a relapse

- Use better drugs early!

- Always think ahead!

A marathon, not a 100 m run....

(suggestion: keep an HLA matched donor in your pocket!!

Slide by the author

LET´S LOOk FORWARD AND WORK HARD TO FIND THE CURE!!

Meanwhile....

Obrigada! Gracias! Thank you!

CONFIRA O CONTEÚDO ATUALIZADO
MOC-Hemato 2024

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