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

GELL Grupo de Estudio Latinoamericano de Linfoproliferativos

Inhibidores BTK en Linfomas Foliculares

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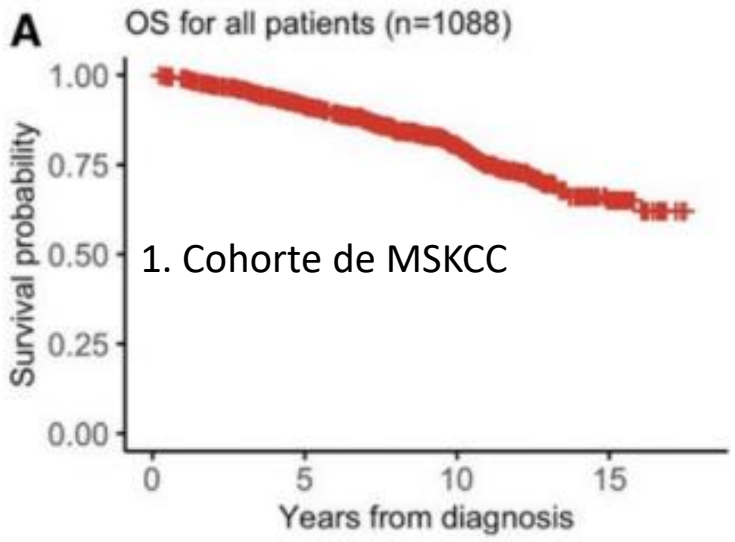
HOB ULHB

Con el Aval:

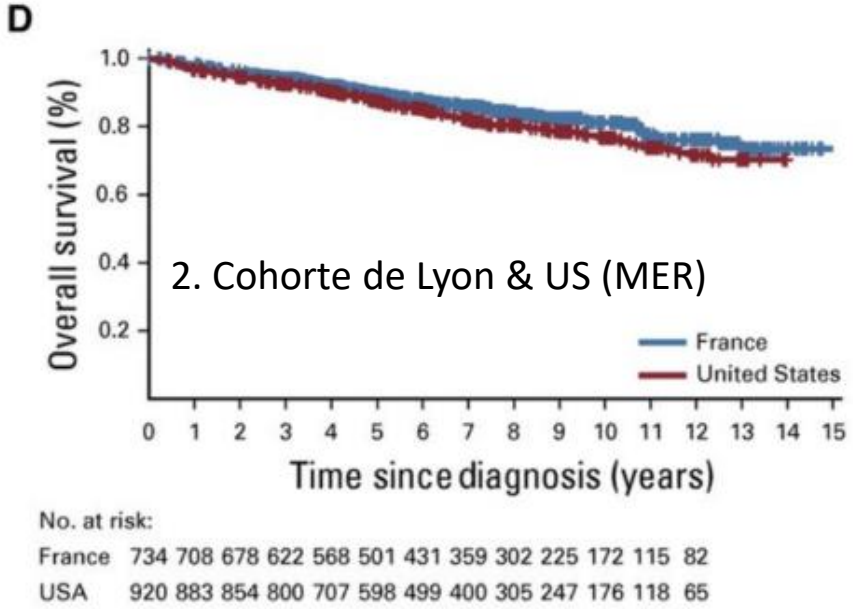
Linfoma Folicular

El linfoma Folicular (LF), representa el 20 % de los LNH B, con una mediana de SG de~ 15 años.

La recaída suele ocurrir en periodos prolongados a la inducción. Pero un 20% de los pacientes van a recaer antes de los 24 meses y los tratamiento subsiguientes son cada vez menos eficaces acortando la SLP.



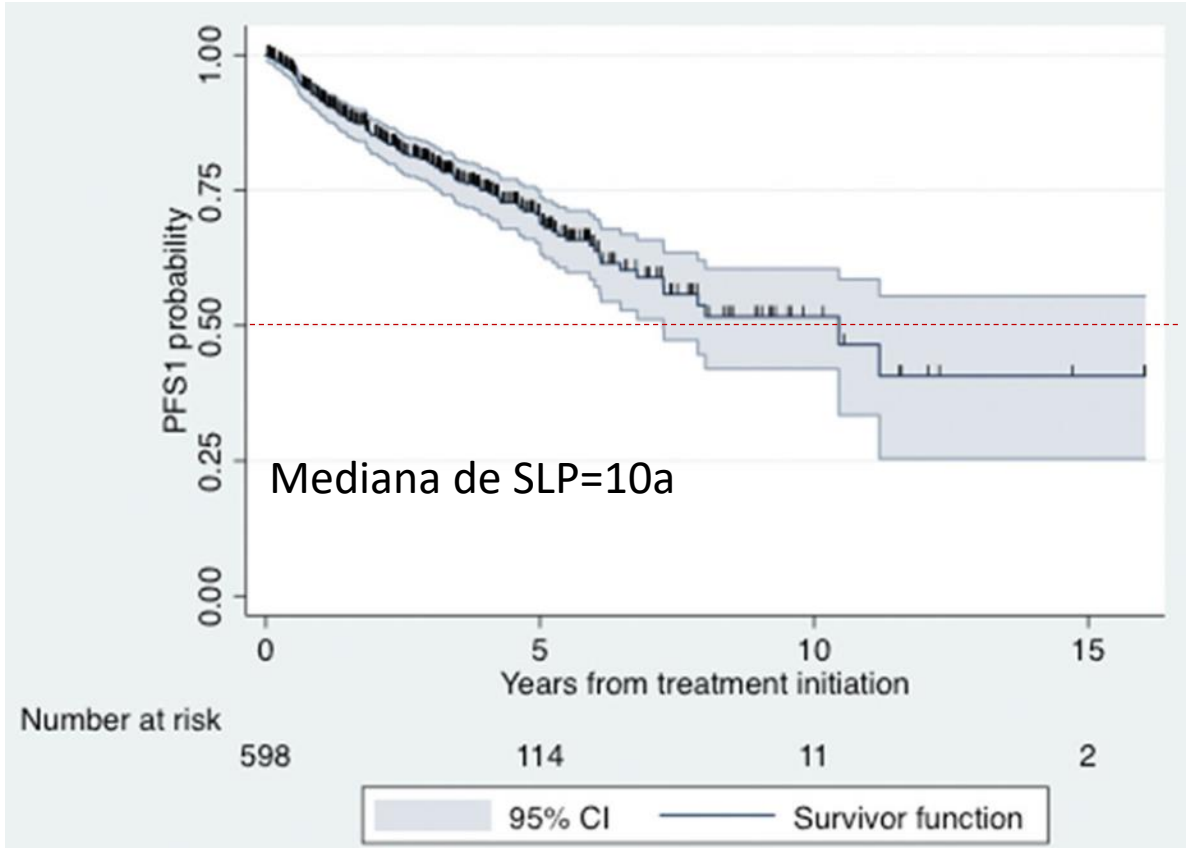
1. Cohorte de MSKCC



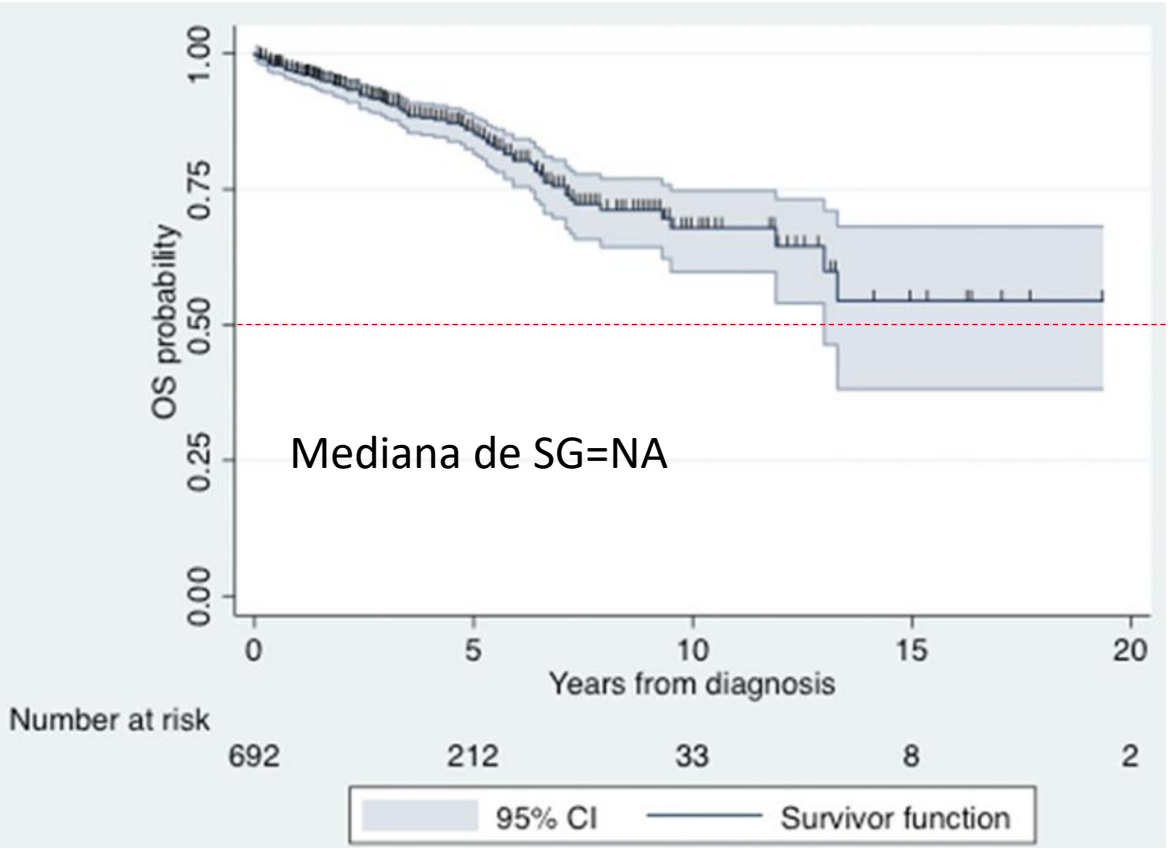
2. Cohorte de Lyon & US (MER)

Casulo C et al. Lancet 2022
1. Batlevi el al. Blood 2020
2. Sarkozy el al. JCO 2018

LF.GELL data



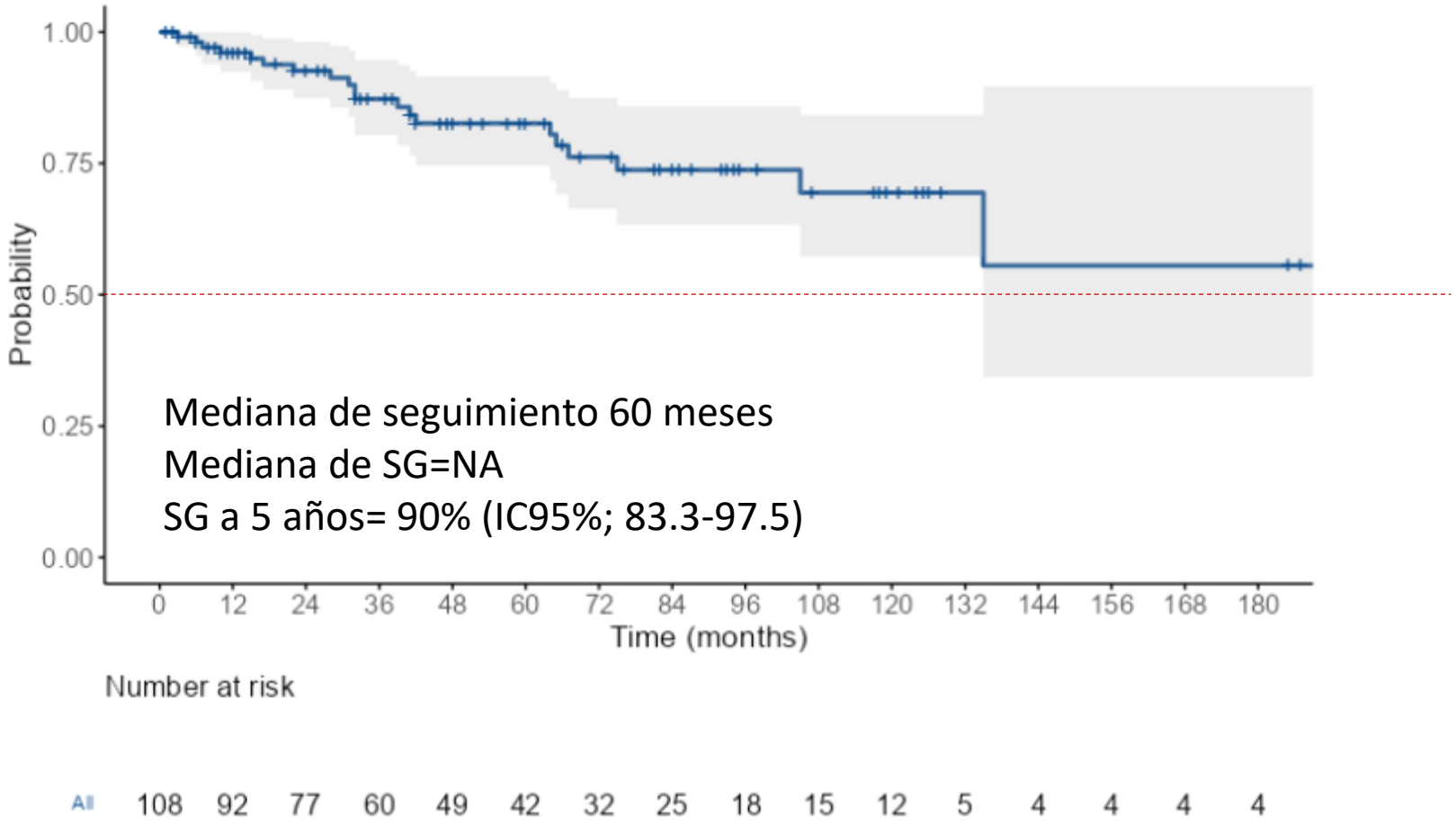
Mediana de SLP=10a



Mediana de SG=NA

Torres A et al. ASH 2020

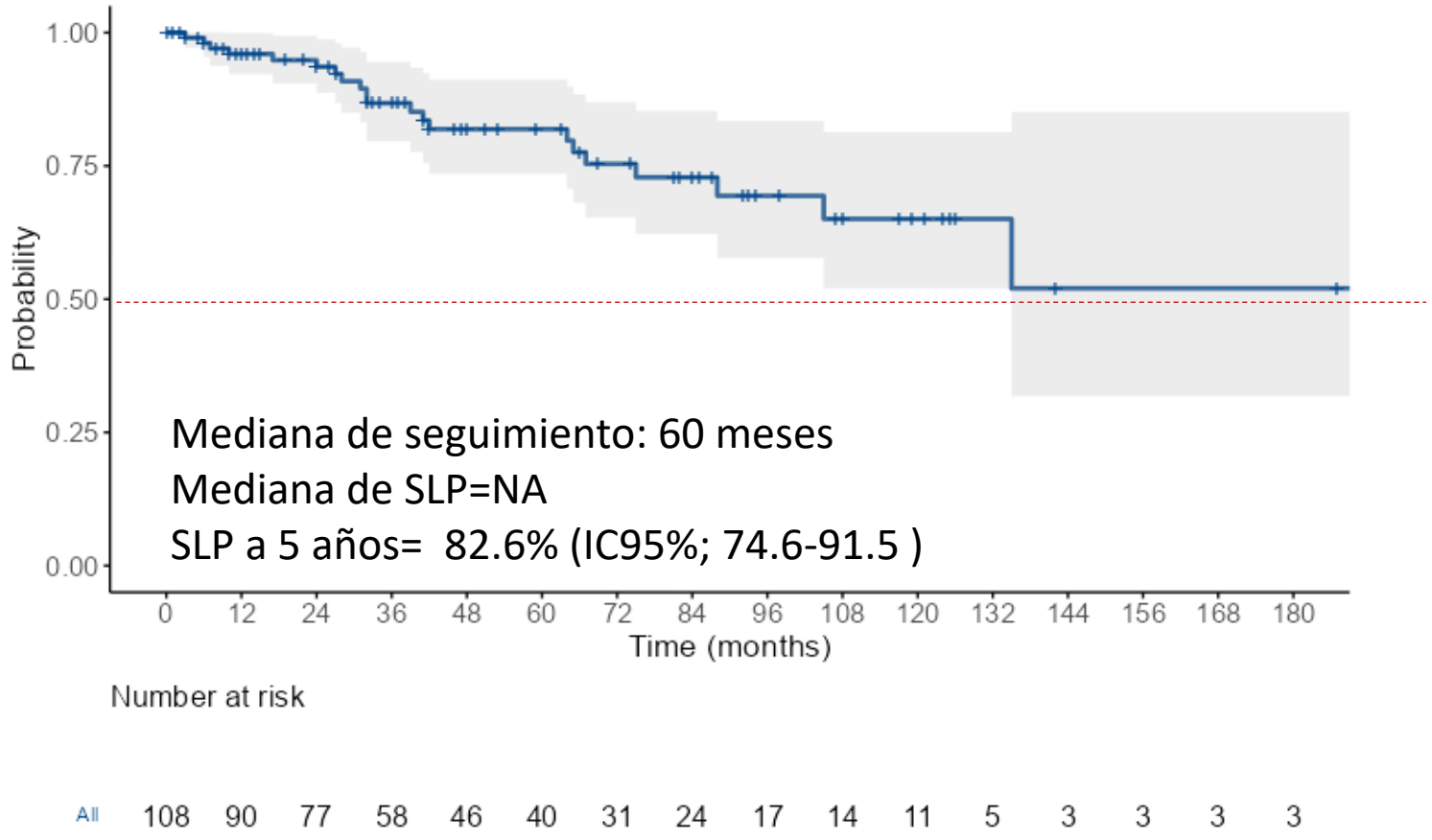
SG Población total.



Mediana de seguimiento 60 meses
Mediana de SG=NA
SG a 5 años= 90% (IC95%; 83.3-97.5)

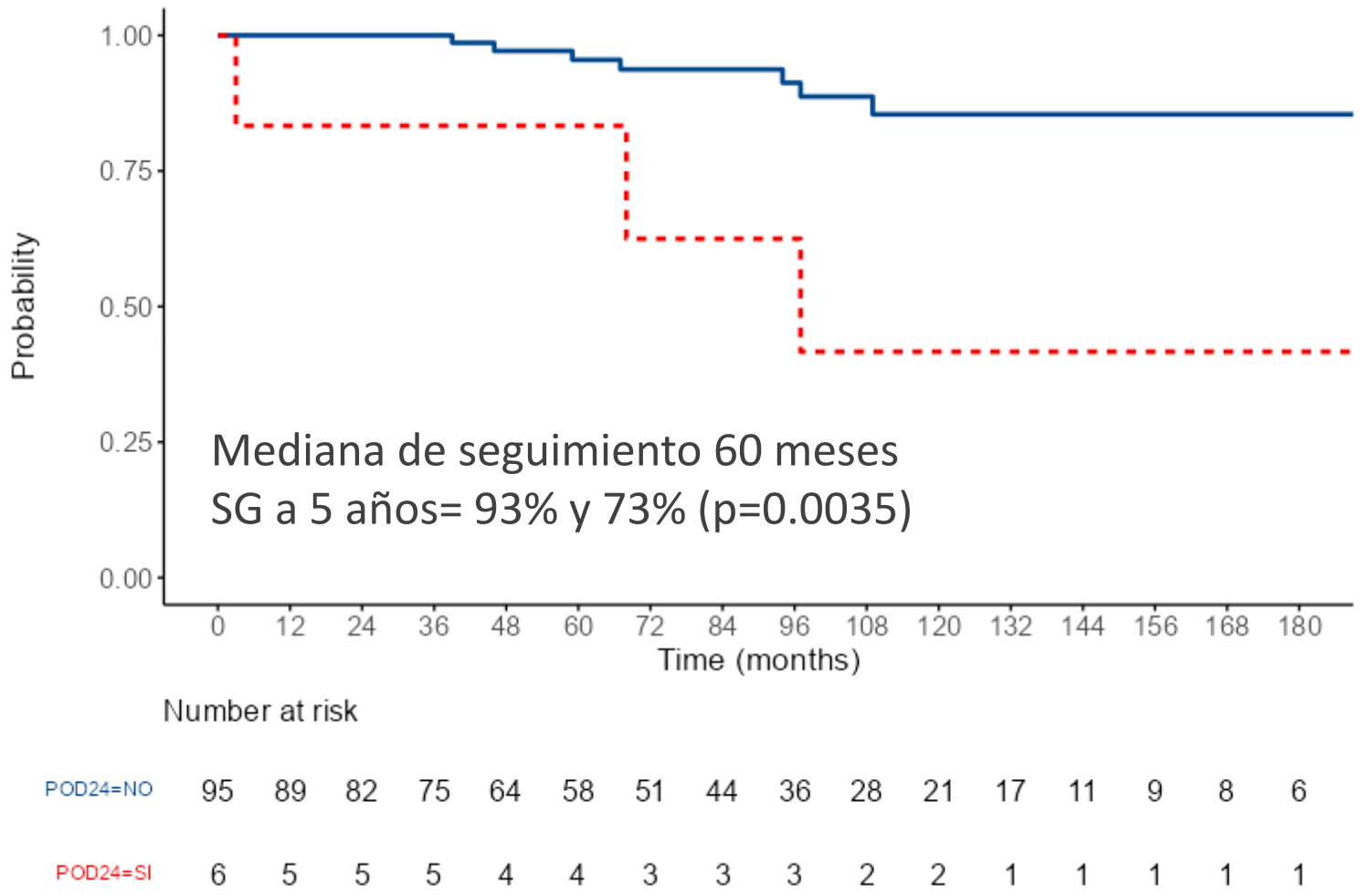
Rivarola S et al. ASH 2025

SLP. Población total.



Rivarola S et al. ASH 2025

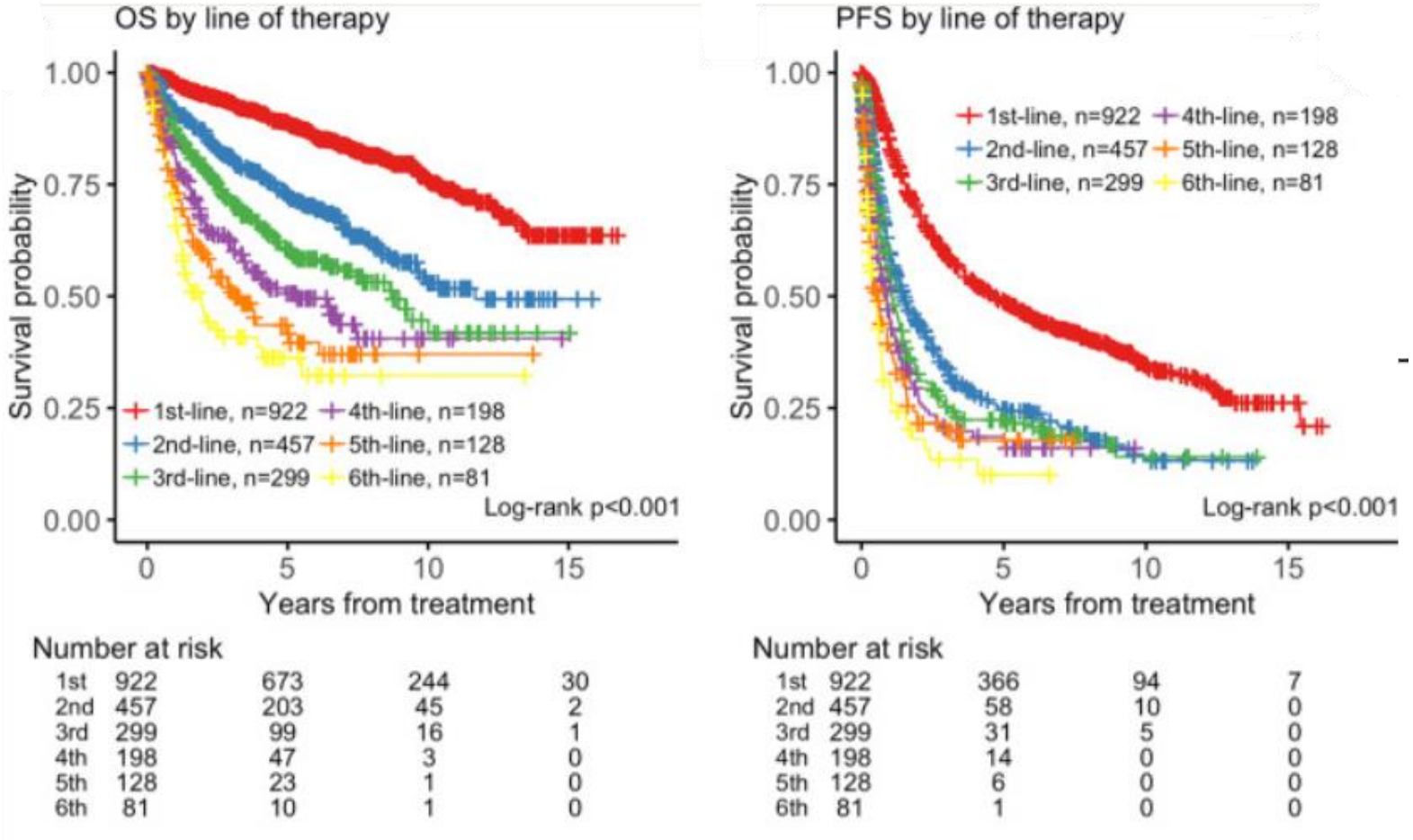
SG POD24.



Rivarola S et al. ASH 2025

LF. Más allá de la 1L

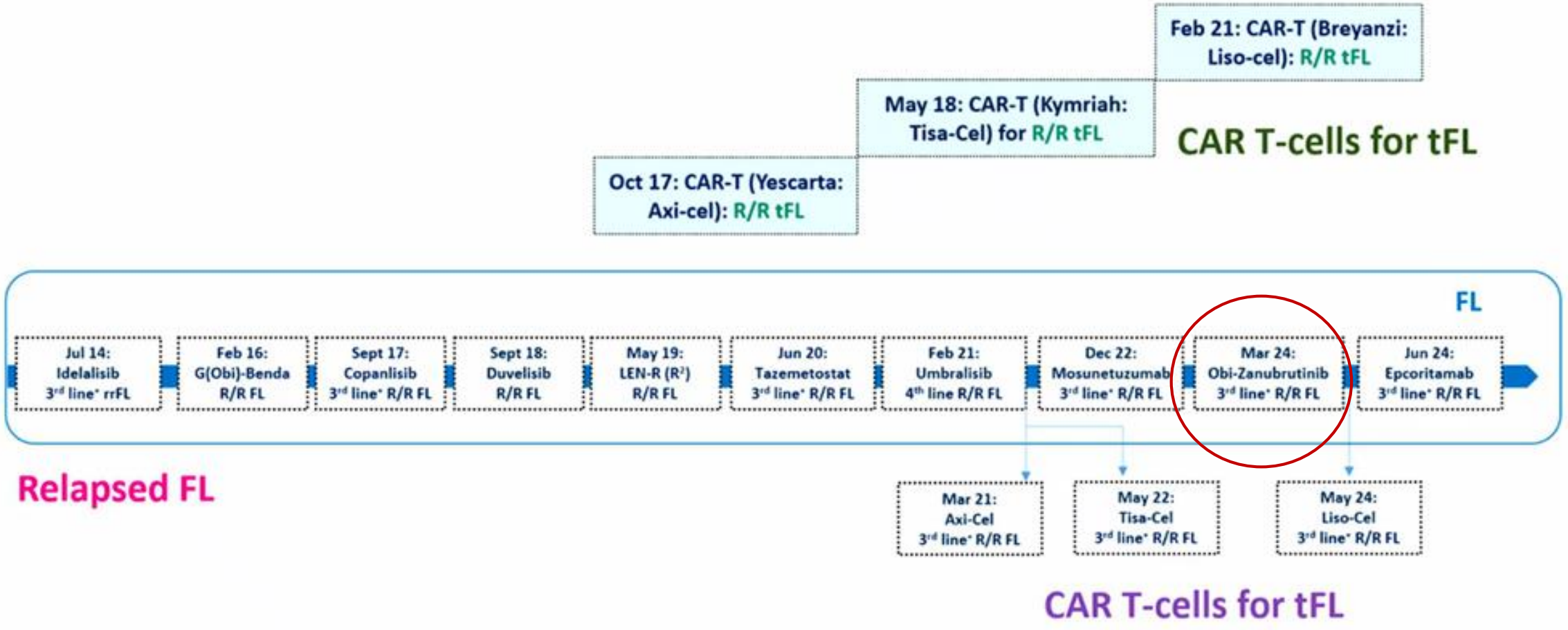
N=1053
La mediana de SG y SLP luego de :
2L: 11.7 y 5 años
3L: 8,8 y 2 años
4L: 5.3 a y 0.9 m
5L: 3.1 a y 0.6m



Batlevi et al. Blood 2020

Linfoma Folicular

Estrategias para mejorar los LF R/R



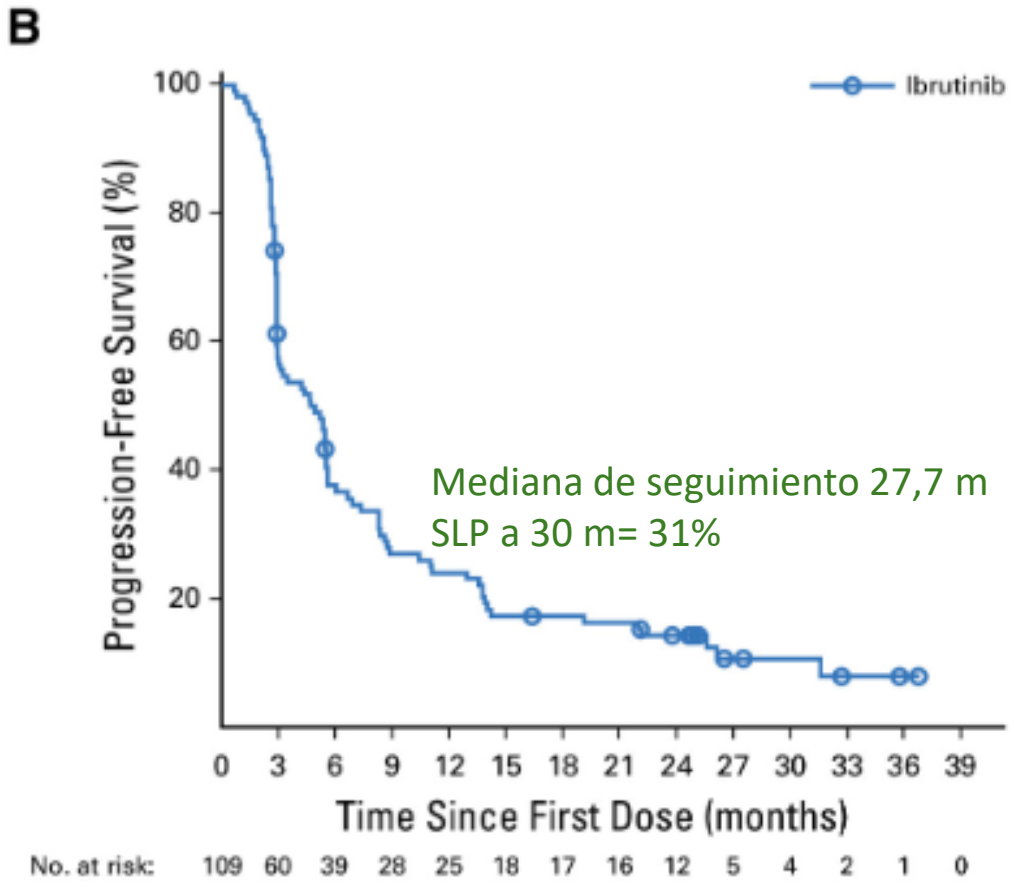
LF R/R
DAWN: Ibrutinib

Fase II
N=110
Objetivo primario: ORR
Objetivos secundarios: DoR, SLP, TTNT, valoración de marcadores.

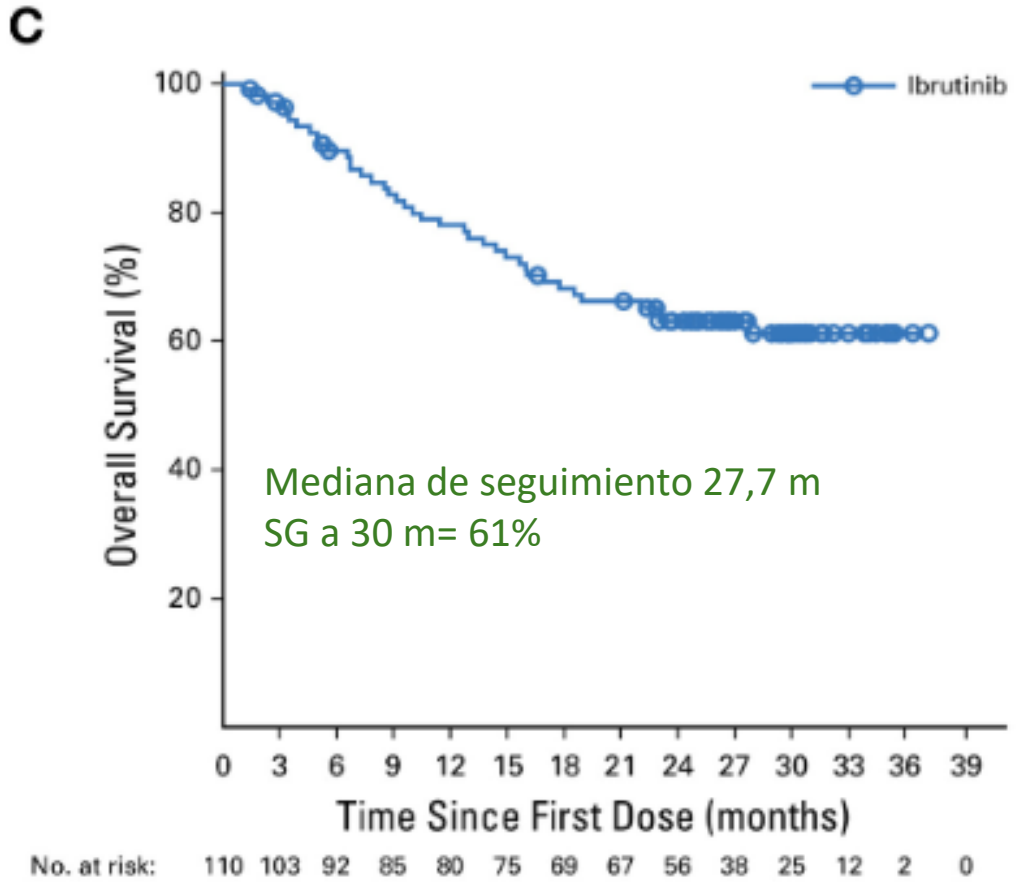
ORR	RC	mDOR
20,9%	11%	19,4 m

Gopal A et al. JCO 2018

LF R/R
DAWN: Ibrutinib



Mediana de seguimiento 27,7 m
SLP a 30 m= 31%

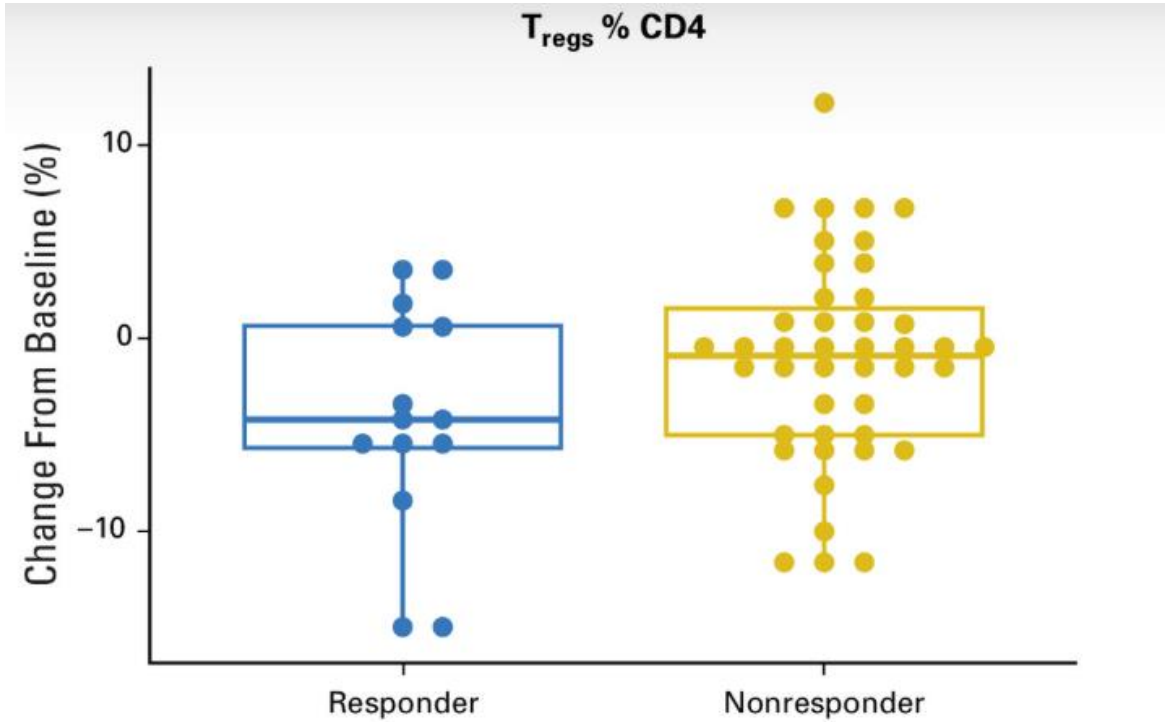


Mediana de seguimiento 27,7 m
SG a 30 m= 61%

Gopal A et al. JCO 2018

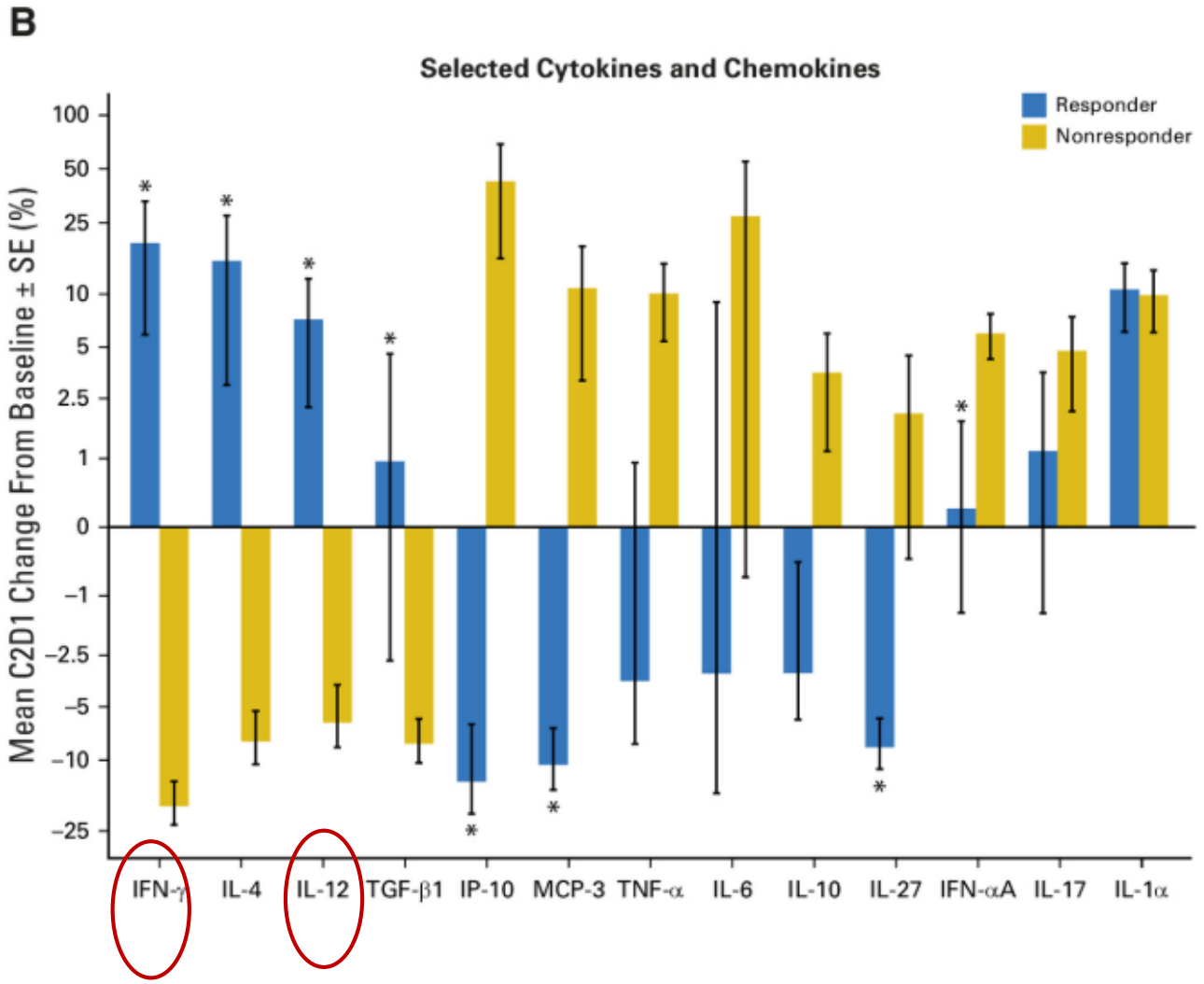
LF R/R
DAWN: Ibrutinib

Mediana de tiempo hasta la rta: 5,7 m
Mediana de TTNT: 16 m 66% requirió un nuevo tratamiento



Gopal A et al. JCO 2018

LF R/R
DAWN: Ibrutinib



Gopal A et al. JCO 2018

LF R/R
DAWN: Ibrutinib

Table 4. Most Common (≥ 10%) Adverse Events

Adverse Event, No. (%)	Safety Analysis Population (N = 110)		
	Grade 1 and 2	Grade 3 and 4	Grade 5
Diarrhea	51.0 (46.4)	5.0 (4.5)	0.0
Fatigue	38.0 (34.5)	6.0 (5.5)	0.0
Cough	39.0 (35.5)	0.0	0.0
Muscle spasms	35.0 (31.8)	0.0	0.0
Nausea	31.0 (28.2)	1.0 (0.9)	0.0
Peripheral edema	30.0 (27.3)	1.0 (0.9)	0.0
Pyrexia	25.0 (22.7)	2.0 (1.8)	0.0
Anemia	15.0 (13.6)	10.0 (9.1)	0.0
Thrombocytopenia	16.0 (14.5)	5.0 (4.5)	0.0
Headache	18.0 (16.4)	1.0 (0.9)	0.0
Upper respiratory tract infection	18.0 (16.4)	1.0 (0.9)	0.0
Rash	18.0 (16.4)	0.0	0.0
Decreased appetite	16.0 (14.5)	0.0	0.0
Neutropenia	1.0 (0.9)	15.0 (13.6)	0.0
Vomiting	15.0 (13.6)	0.0	0.0
Asthenia	13.0 (11.8)	1.0 (0.9)	0.0
Back pain	14.0 (12.7)	0.0	0.0
Constipation	14.0 (12.7)	0.0	
Dyspnea	11.0 (10.0)	3.0 (2.7)	0.0
Hypokalemia	11.0 (10.0)	3.0 (2.7)	0.0
Insomnia	14.0 (12.7)	0.0	0.0
Abdominal pain	11.0 (10.0)	2.0 (1.8)	0.0
Platelet count decreased	10.0 (9.1)	3.0 (2.7)	0.0
Pruritus	12.0 (10.9)	1.0 (0.9)	0.0
Bronchitis	12.0 (10.9)	0.0	0.0
Dizziness	12.0 (10.9)	0.0	0.0
Chills	11.0 (10.0)	0.0	0.0
Dry mouth	11.0 (10.0)	0.0	0.0
Myalgia	11.0 (10.0)	0.0	0.0
Pain in extremity	10.0 (9.1)	1.0 (0.9)	0.0
Pneumonia	3.0 (2.7)	7.0 (6.4)	1.0 (0.9)
Sinusitis	11.0 (10.0)	0.0	0.0

Gopal A et al. JCO 2018

LF R/R
Ibrutinib

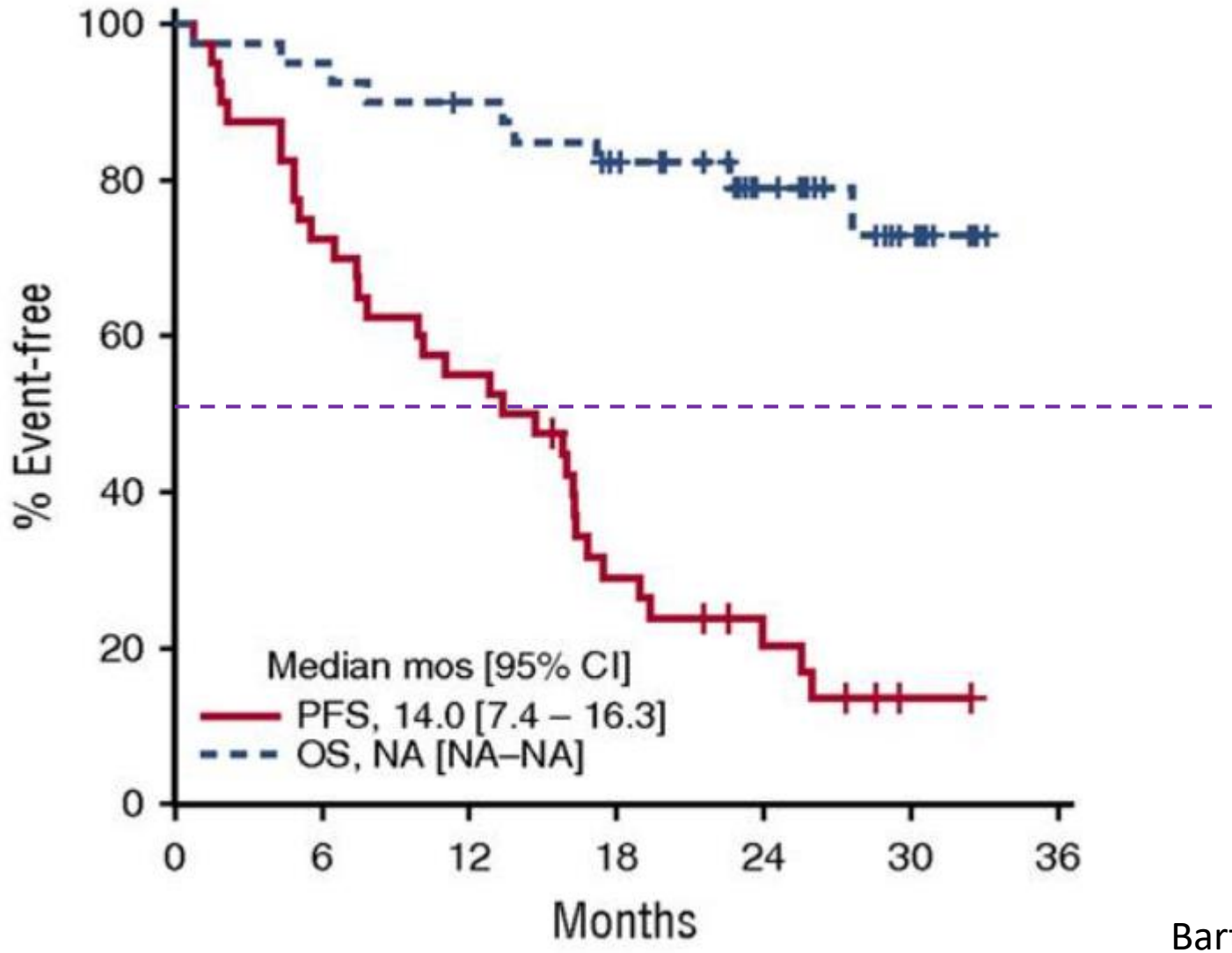
Fase II
N=40
Objetivo primario: ORR

ORR	RC	mDOR
37,5%	12,5%	13,9 m

Mejores ORR en paciente sensibles a R
(52,6% vs 16,7%)

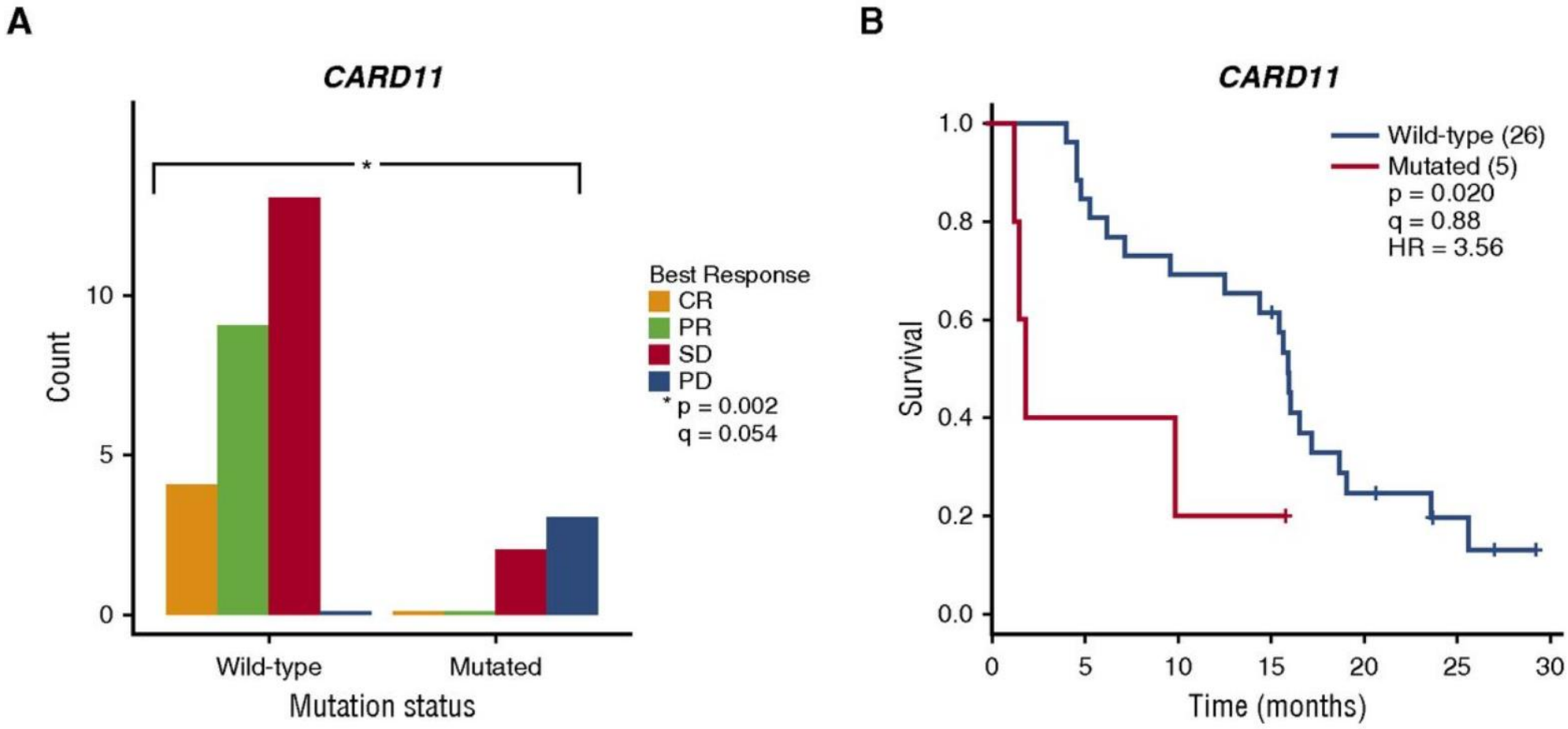
Bartlett N et al. Blood 2018

LF R/R
Ibrutinib



Bartlett N et al. Blood 2018

LF R/R
Ibrutinib



Bartlett N et al. Blood 2018

LF R/R
Ibrutinib

EA	EA G5
• Neutropenia:4 (10%) • Linfopenia: 3 (7,5%) • Hematoma 1 pte. • TSV 1 pte.	• Hemorragia digestiva 1 pte.

Bartlett N et al. Blood 2018

LF R/R

BGB-3111-AU-003: Zanubrutinib

Fase I/II

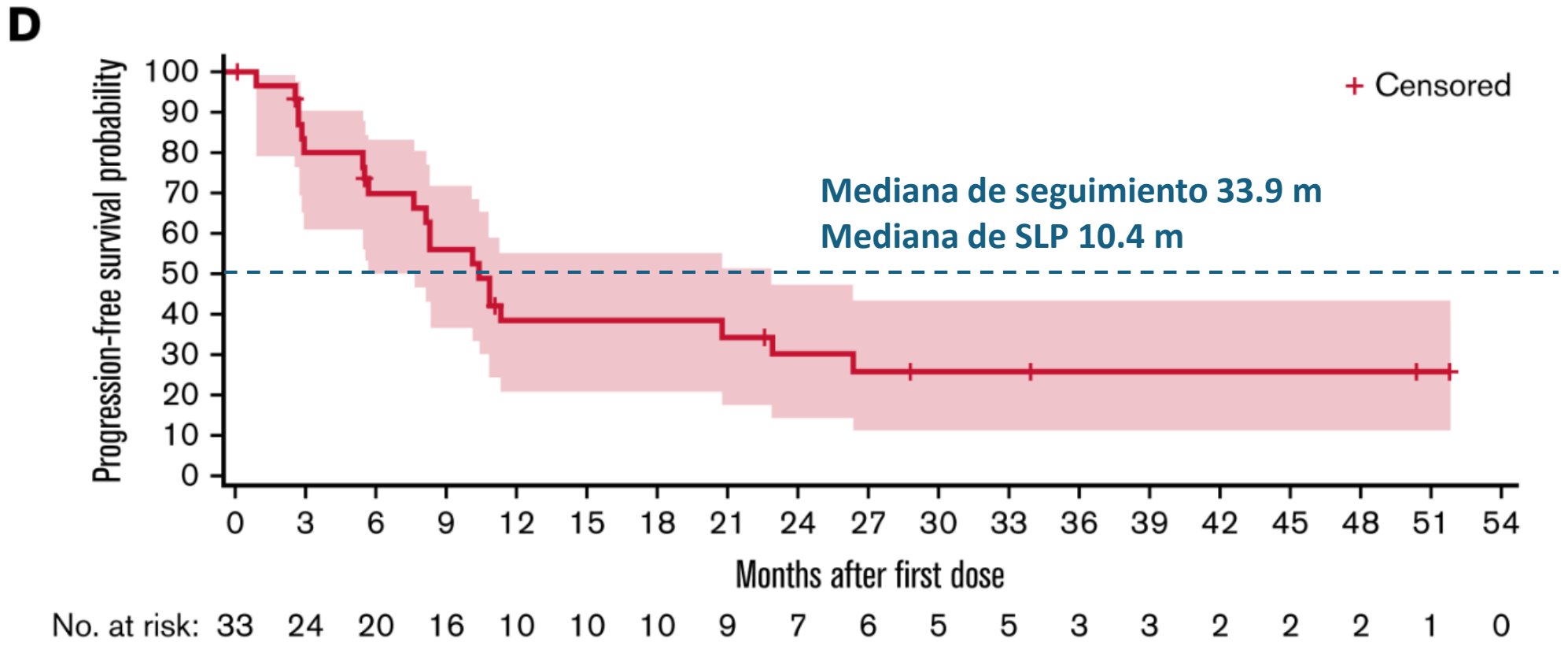
N=53-FL:33

ORR	RC	mDOR
36%	18%	NA

Phillips T et al. Blood 2022

LF R/R

BGB-3111-AU-003: Zanubrutinib



Phillips T et al. Blood 2022

LF R/R

BGB-3111-AU-003: Zanubrutinib

No se reportó FA

Interrupciones de tt= 4

Disminución de dosis= 2

Any grade/Grade ≥ 3 AESI, n (%)	MZL	FL
Patients with ≥ 1 AESI	19 (95)/10 (50)	28 (84.8)/17 (51.5)
Bleeding	12 (60)/1 (5)	18 (54.5)/1 (3)
Major hemorrhage*	2 (10)/1 (5)	1 (3)/1 (3)
Atrial fibrillation/flutter	0/0	0/0
Hypertension	1 (5)/1 (5)	2 (6.1)/2 (6.1)
Second primary malignancies	3 (15)‡/2 (10)	3 (9.1)/1 (3)
Skin cancers	1 (5)/0	1 (3)/0
Infections	15 (75)/4 (20)‡	21 (63.6)/10 (30.3)
Opportunistic infections	1 (5)/0	1 (3)/0
Tumor lysis syndrome	0/0	0/0
Anemia§	3 (15)/3 (15)	5 (15.2)/5 (15.2)
Neutropenia‖	6 (30)/4 (20)	6 (18.2)/6 (18.2)
Thrombocytopenia	3 (15)/2 (10)	3 (9.1)/1 (3)

Phillips T et al. Blood 2022

LF R/R

Ibrutinib y zanubrutinib Monoterapia

ORR	RC	mDOR
I: 20,9% Z: 36%	I:11% Z: 18%	I: 19.4m Z: NA

LF R/R

SELENE: Ibrutinib+IQT vs Placebo+IQT

Fase III

N=403

I+R-CHOP/RB vs R-CHOP/RB (RB:90%)

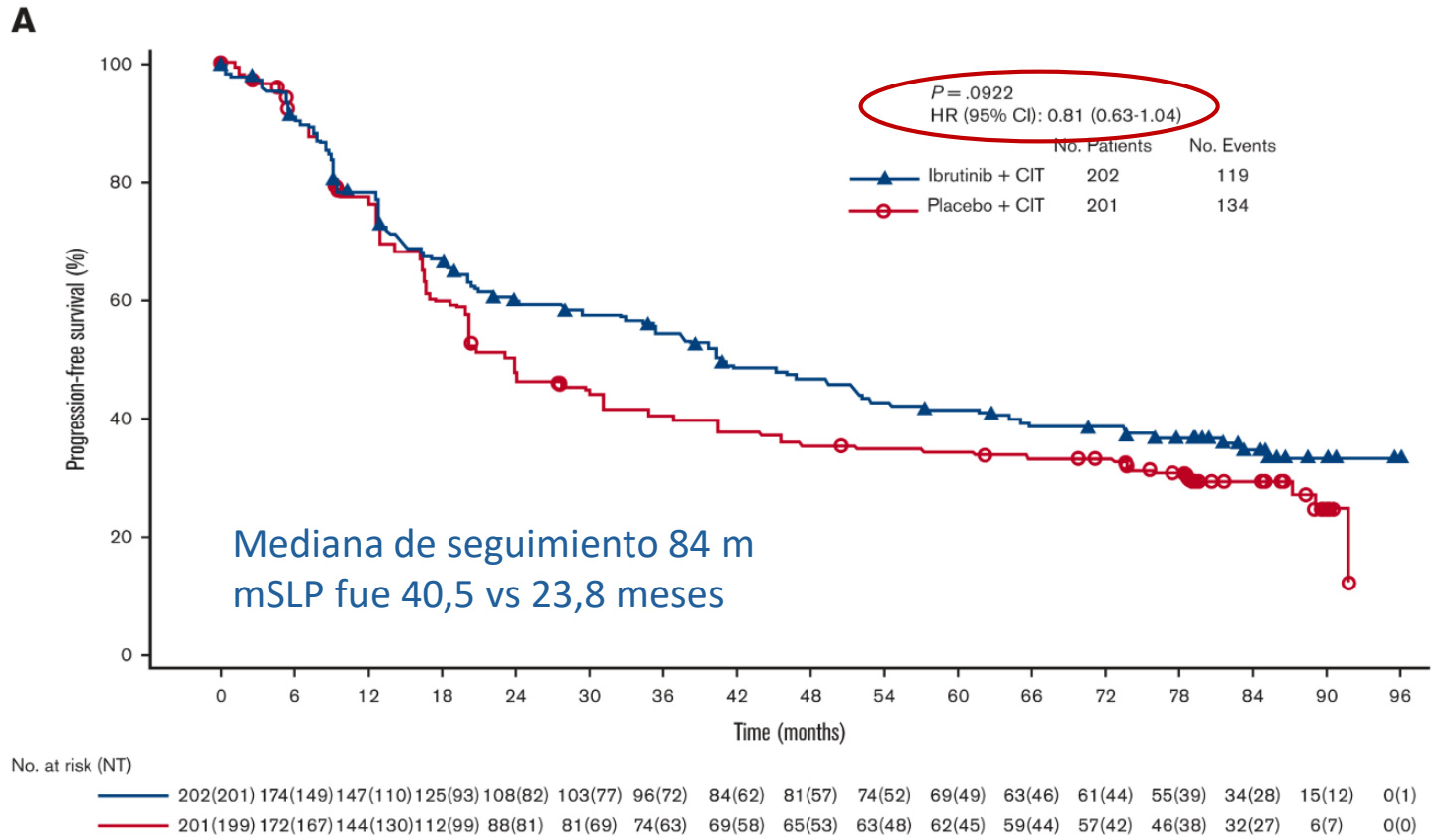
Objetivo primario: SLP

Objetivos secundarios: ORR, RC, DOR, seguridad

Nastoupil L et al. Blood 2023

LF R/R

SELENE: Ibrutinib+IQT vs Placebo+IQT



Nastoupil L et al. Blood 2023

LF R/R

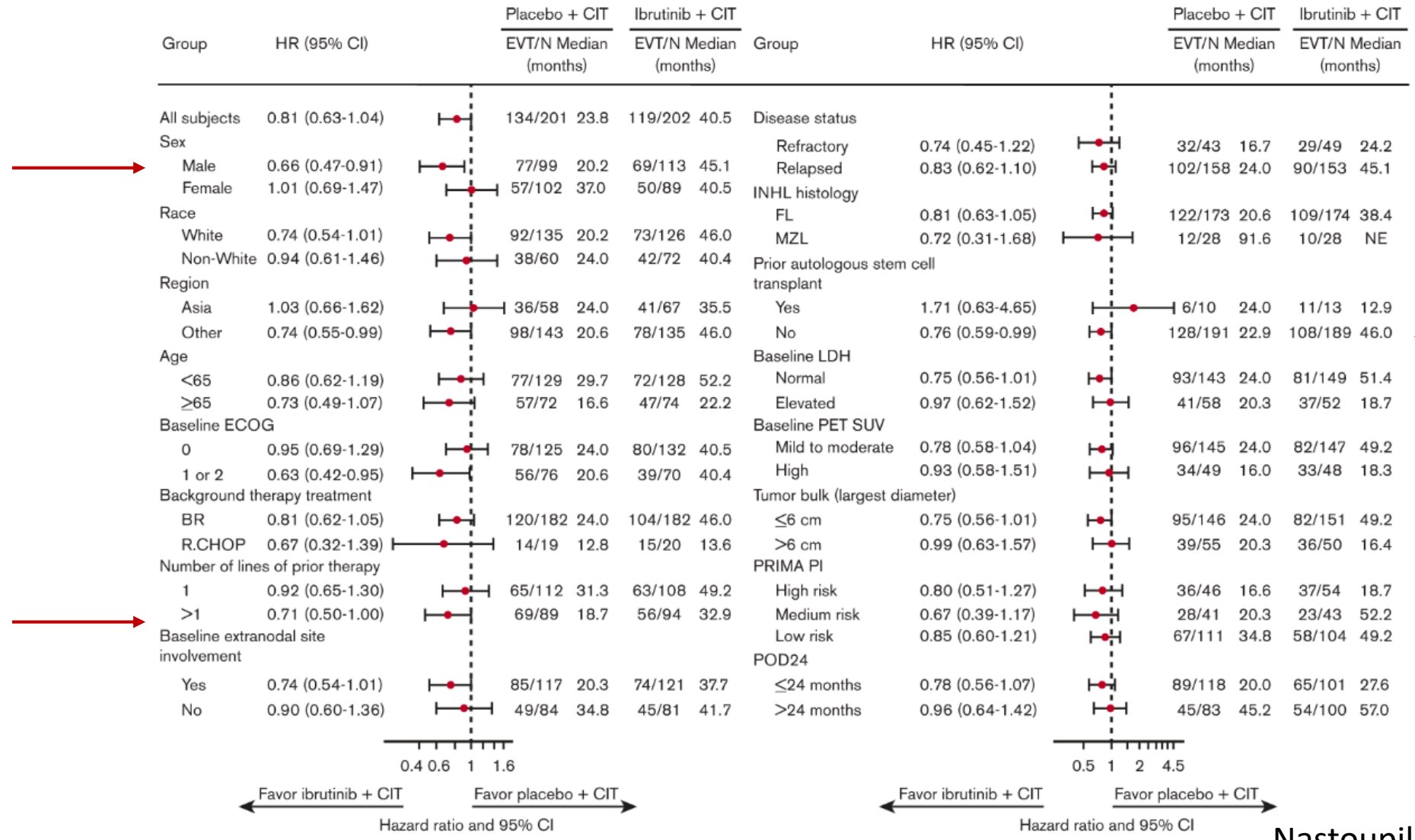
SELENE: Ibrutinib+IQT vs Placebo+IQT

ORR	RC	mDOR
I: 91.6%	I:55%	I:44.3m
P: 90.5%	P: 50.2%	P:21.7m

Nastoupil L et al. Blood 2023

LF R/R

SELENE: Ibrutinib+IQT vs Placebo+IQT



Nastoupil L et al. Blood 2023

LF R/R

SELENE: Ibrutinib+IQT vs Placebo+IQT

Rama I-IQT
FA: 13/201 (6.5%)
Hemorragia mayor: 6/201 (3%)

	Ibrutinib + CIT (n = 201)		Placebo + CIT (n = 199)	
Preferred term, no. (%)	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
Diarrhea	103 (51.2)	13 (6.5)	69 (34.7)	11 (5.5)
Nausea	103 (51.2)	6 (3.0)	79 (39.7)	3 (1.5)
Neutropenia	77 (38.3)	62 (30.8)	70 (35.2)	62 (31.2)
Fatigue	73 (36.3)	10 (5.0)	60 (30.2)	4 (2.0)
Rash	69 (34.3)	13 (6.5)	33 (16.6)	2 (1.0)
Pyrexia	66 (32.8)	6 (3.0)	49 (24.6)	4 (2.0)
Vomiting	58 (28.9)	8 (4.0)	41 (20.6)	3 (1.5)
Cough	57 (28.4)	5 (2.5)	41 (20.6)	0
Anemia	51 (25.4)	23 (11.4)	39 (19.6)	8 (4.0)
Upper respiratory tract infection	48 (23.9)	6 (3.0)	50 (25.1)	2 (1.0)
Thrombocytopenia	46 (22.9)	20 (10.0)	28 (14.1)	10 (5.0)
Decreased appetite	44 (21.9)	5 (2.5)	34 (17.1)	6 (3.0)
Constipation	33 (16.4)	0	54 (27.1)	1 (0.5)

Abbreviations: CIT, chemoimmunotherapy; TEAE, treatment-emergent adverse event.

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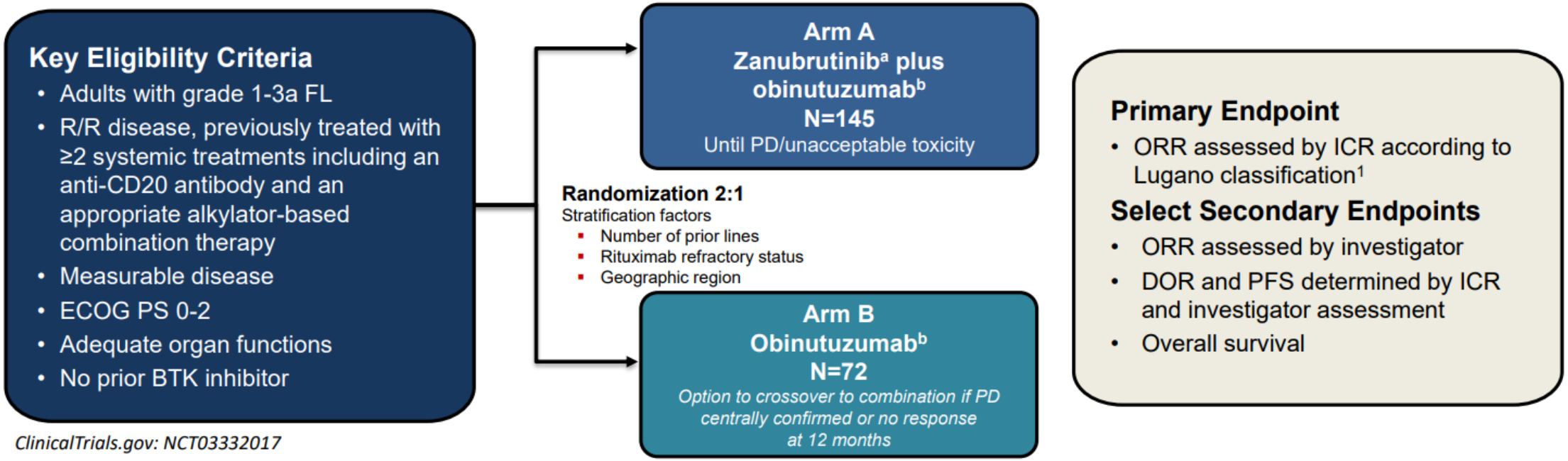
LF R/R
Rosewood: Zanubrutinib+O vs O
#chemofree



- Patients were randomized between November 2017 and June 2021
- Median study follow-up: 12.5 months

Zinzani PL et al. ASCO 2022

LF R/R
Rosewood: Zanubrutinib+O vs O
#chemofree

Characteristic	Zanubrutinib plus obinutuzumab N=145	Obinutuzumab N=72
Male sex, %	51.7	45.8
Median age, years (min, max)	63.0 (31, 84)	65.5 (32, 88)
FLIPI, %		
Low (0-1)	19.3	12.5
Intermediate (2)	24.8	33.3
High (≥3)	53.1	51.4
Missing	2.8	2.8
ECOG performance status ≥1, %	40.7	56.9
Bulky disease (≥5 cm), %	39.3	43.1
Elevated LDH, %	34.5	40.3
Elevated beta-2 microglobulin, %	44.8	51.4
Median prior lines of therapy, n (min, max)	3 (2, 11)	3 (2, 9)
Patients with >3 lines of therapy, %	28.3	25.0
Patients refractory to rituximab, %	53.8	50.0
Patients refractory to the most recent line of therapy, %	32.4	40.3
Patients with PD within 24 months of starting the first line of therapy, %	34.5	41.7

Zinzani PL et al. ASCO 2022

LF R/R

Rosewood: Zanubrutinib+O vs O

#chemofree

Response rate	Zanubrutinib plus obinutuzumab N=145	Obinutuzumab N=72
ORR, % (95% CI)	**68.3** (60.0, 75.7)	**45.8** (34.0, 58.0)
Risk difference, % (95% CI)	22.0 (8.3, 35.8)	
2-sided *P* value	**0.0017**	
Best Response, n (%)		
CR	54 (37.2)	14 (19.4)
PR	45 (31.0)	19 (26.4)
SD	25 (17.2)	14 (19.4)
Nonprogressive disease	3 (2.1)	4 (5.6)
PD	13 (9.0)	15 (20.8)
Discontinued prior to first assessment	4 (2.8)	6 (8.3)
NE	1 (0.7)	0 (0.0)
CR rate, % (95% CI)	**37.2** (29.4, 45.7)	**19.4** (11.1, 30.5)
2-sided *P* value	**0.0083**	

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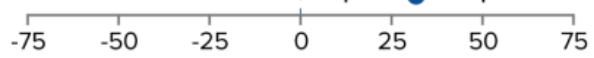
LF R/R

Rosewood: Zanubrutinib+O vs O

#chemofree

Subgroup		Response/Patients		Risk difference (95% CI)
		Obinutuzumab	Zanubrutinib plus obinutuzumab	
All patients in ITT		33 / 72	99 / 145	22.4 (8.7, 36.2)
Age, years	<65	14 / 32	57 / 83	24.9 (5.1, 44.8)
	≥65	19 / 40	42 / 62	20.2 (0.9, 39.6)
Sex	Male	14 / 33	53 / 75	28.2 (8.5, 48.0)
	Female	19 / 39	46 / 70	17.0 (-2.2, 36.2)
Geographic region	China	5 / 12	15 / 21	29.8 (-4.2, 63.7)
	Ex-China	28 / 60	84 / 124	21.1 (6.0, 36.1)
Prior lines of therapy	2-3	27 / 54	76 / 108	20.4 (4.5, 36.2)
	>3	6 / 18	23 / 37	28.8 (2.0, 55.6)
Baseline ECOG performance status	0	17 / 31	64 / 86	19.6 (-0.2, 39.4)
	≥1	16 / 41	35 / 59	20.3 (0.8, 39.8)
Bulky disease: any target lesion longest diameter ≥5 cm	Yes	15 / 31	30 / 57	4.2 (-17.6, 26.1)
	No	18 / 41	69 / 88	34.5 (17.1, 52.0)
Baseline FLIPI risk category	Low (0-1)	3 / 9	20 / 28	38.1 (3.0, 73.1)
	Intermediate (2)	13 / 24	27 / 36	20.8 (-3.6, 45.3)
	High (≥3)	17 / 37	49 / 77	17.7 (-1.6, 37.0)
Rituximab-refractory status	Refractory	14 / 36	46 / 78	20.1 (0.8, 39.4)
	Not refractory	19 / 36	53 / 67	26.3 (7.3, 45.3)
Refractory status to the most recent line of therapy	Refractory	11 / 29	29 / 47	23.8 (1.3, 46.2)
	Not refractory	21 / 42	65 / 93	19.9 (2.1, 37.7)
Progression of disease within 24 months of starting the first line of therapy	Yes	14 / 30	29 / 50	11.3 (-11.2, 33.8)
	No	15 / 35	55 / 74	31.5 (12.3, 50.6)



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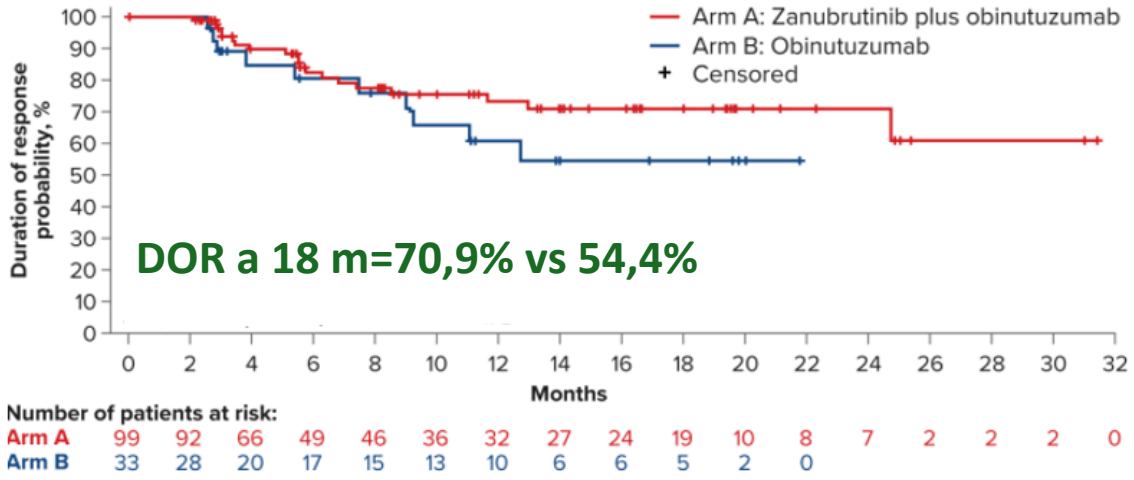
LF R/R

Rosewood: Zanubrutinib+O vs O

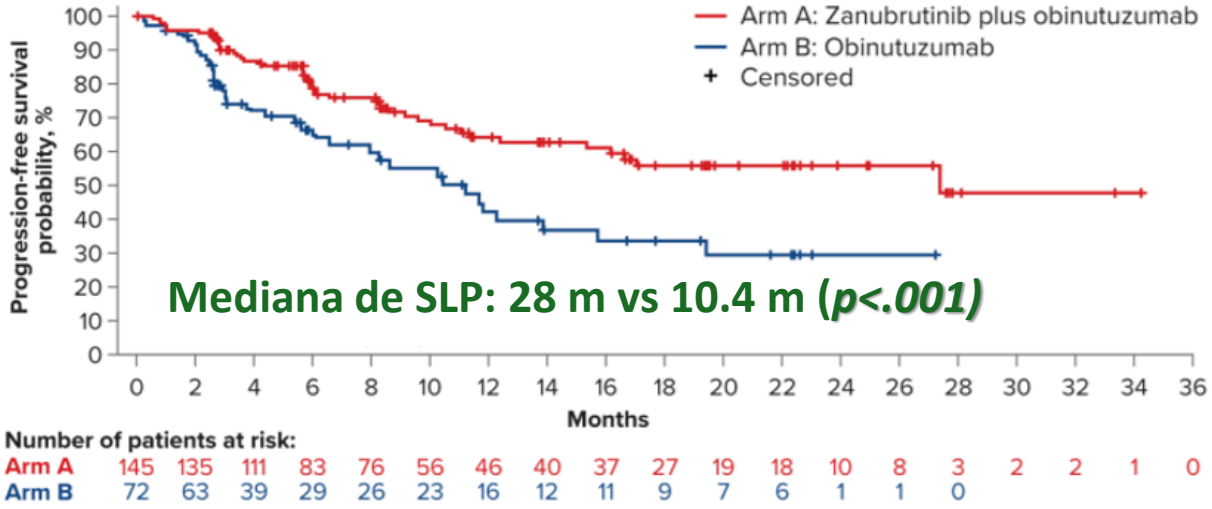
#chemofree

Duration of Response



DOR a 18 m=70,9% vs 54,4%

Progression-free survival



Mediana de SLP: 28 m vs 10.4 m (*p<.001*)

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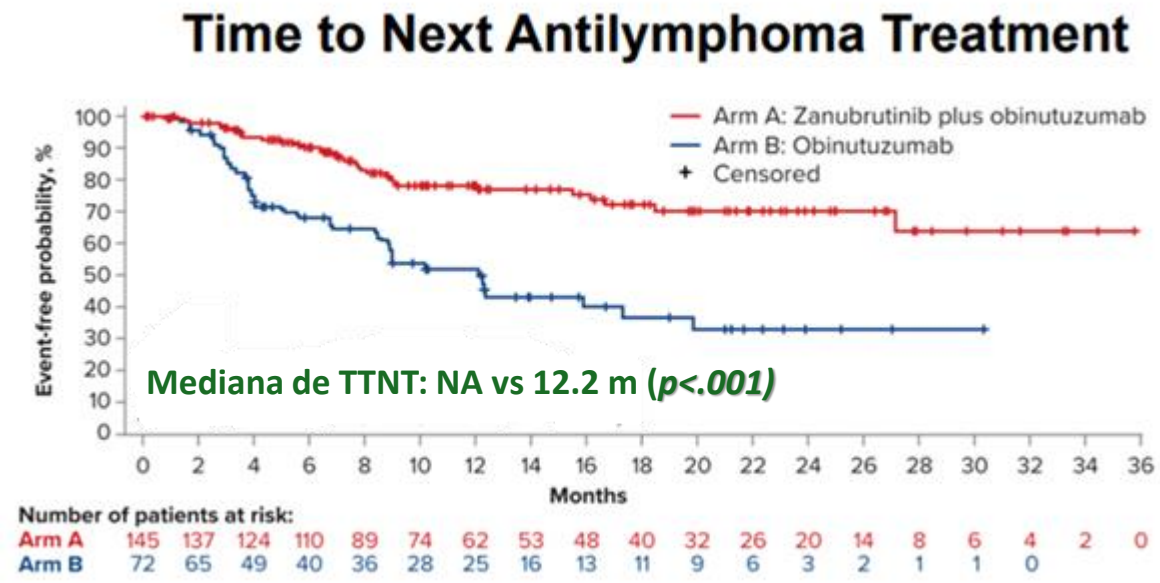
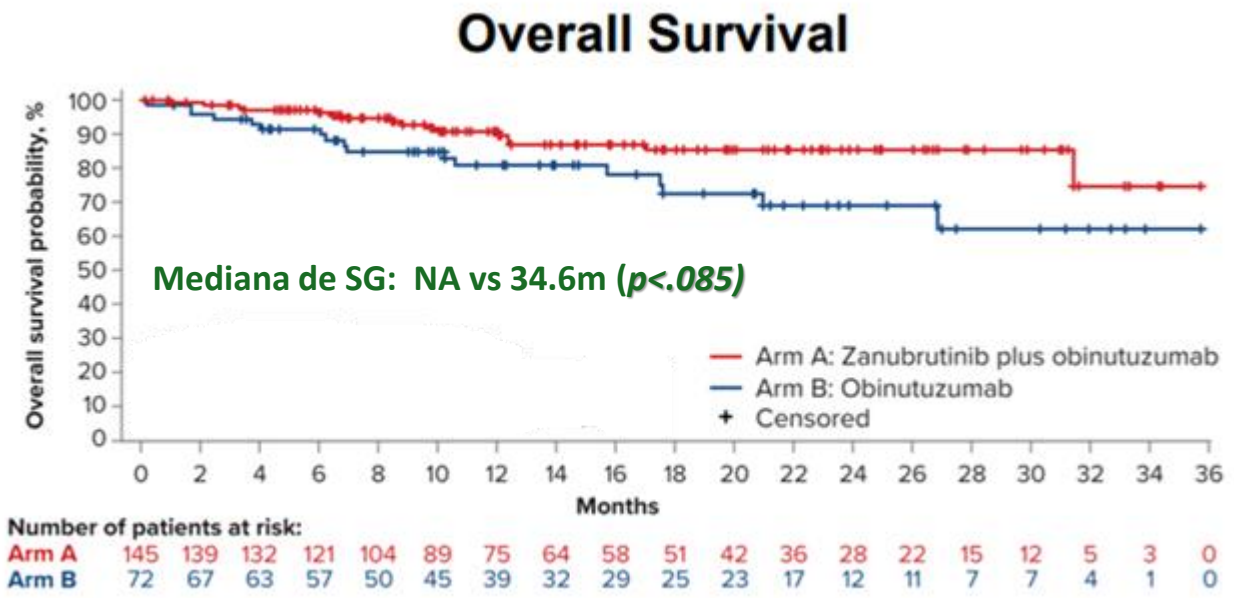
LF R/R

Rosewood: Zanubrutinib+O vs O

#chemofree





Zinzani PL et al. ASCO 2022

LF R/R

Rosewood: Zanubrutinib+O vs O

TEAE, %	Zanubrutinib plus obinutuzumab N=143		Obinutuzumab N=71	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Patients with at least 1 TEAE	92.3	53.8	88.7	47.9
Thrombocytopenia or platelet count decreased	34.3	14.0	23.9	7.0
Neutropenia or neutrophil count decreased	27.3	22.4	25.4	19.7
Diarrhea	16.1	2.8	16.9	0.0
Fatigue	14.0	1.4	11.3	0.0
Constipation	13.3	0.0	7.0	0.0
Cough	11.9	0.0	11.3	0.0
Pyrexia	11.2	0.0	19.7	0.0
Dyspnea	10.5	1.4	9.9	0.0
Anemia	9.1	4.2	9.9	5.6
Nausea	8.4	0.0	12.7	0.0
Pruritus	7.0	0.0	9.9	0.0
Infusion-related reaction	2.8	0.7	9.9	4.2
TEAEs of special interest				
Atrial fibrillation and flutter	2.1	0.7	1.4	0.0
Hypertension	3.5	0.7	4.2	1.4
Hemorrhage	26.6	1.4	8.5	0.0
Major hemorrhage	1.4	1.4	1.4	0.0
Infections	47.6	18.9	36.6	12.7
Secondary primary malignancies	6.3	3.5	2.8	0.0

Reducción de dosis: Z: 16(11%)
Discontinuación en :
Z: 23(16%)
O:8(11%)

Zinzani PL et al. ASCO 2022

¡Único iBTK aprobado en 2024 por FDA y EMA!

LF R/R

Rosewood: Zanubrutinib+O vs O

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2025
Classic Follicular Lymphoma

NCCN Guidelines Index
Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a,b,c]

THIRD-LINE AND SUBSEQUENT THERAPY
Subsequent systemic therapy options include second-line therapy regimens (FOLL-B 2 of 6) that were not previously given.

Preferred regimens (in alphabetical order)	**Other recommended regimens**
• T-cell engager therapy ▸ Bispecific antibody therapy[l,m] ◊ Epcoritamab-bysp ◊ Mosunetuzumab-axgb ▸ Chimeric antigen receptor (CAR) T-cell therapy[n] ◊ Axicabtagene ciloleucel (CD19-directed) ◊ Lisocabtagene maraleucel (CD19-directed) ◊ Tisagenlecleucel (CD19-directed)	• EZH2 inhibitor ▸ Tazemetostat[l] (irrespective of EZH2 mutation status) • BTK inhibitor (BTKi) ▸ Zanubrutinib[l] + obinutuzumab • Loncastuximab tesirine-lpyl + rituximab (category 2B)[k]

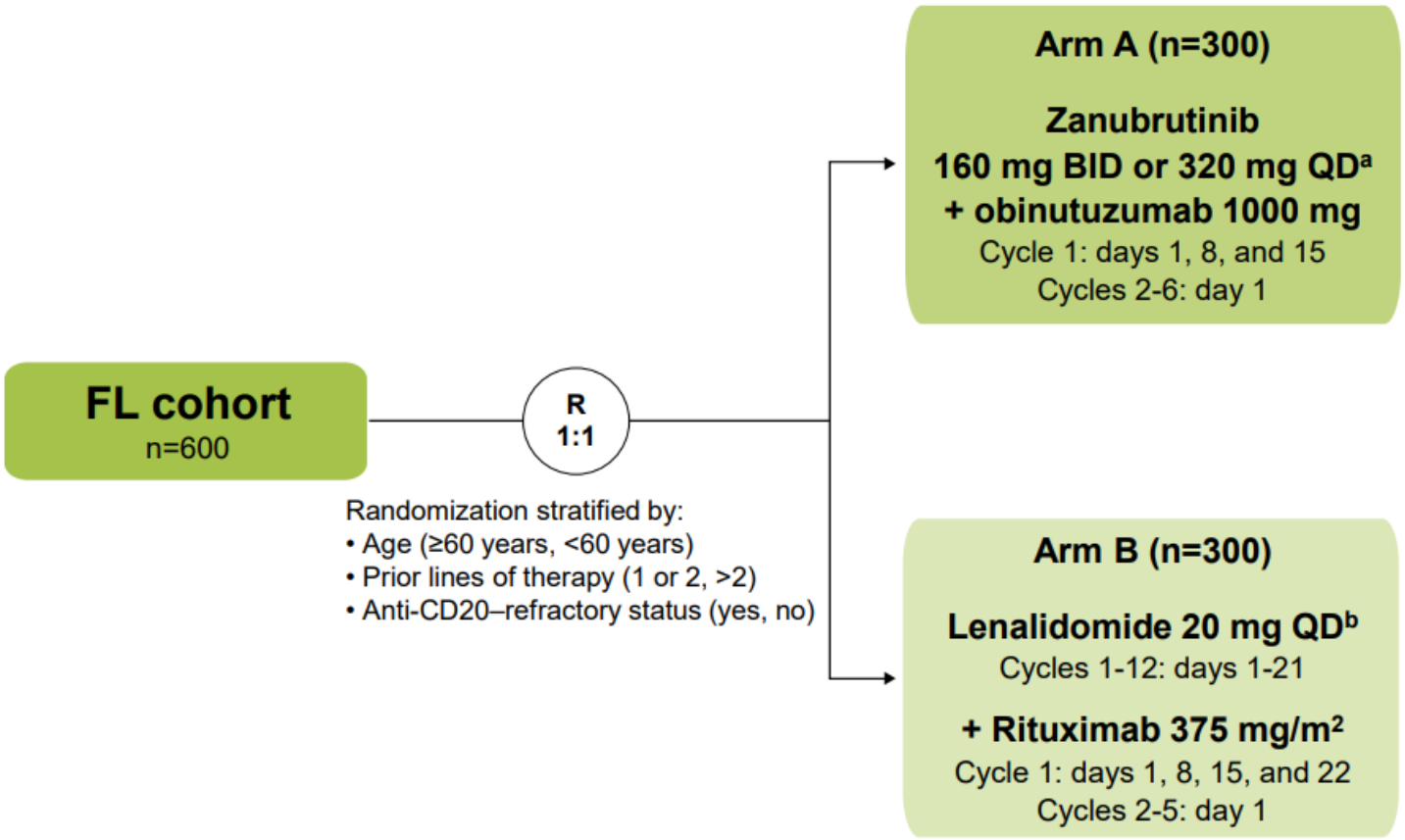
THIRD-LINE CONSOLIDATION THERAPY

Useful in Certain Circumstances
• Allogeneic hematopoietic cell transplantation (HCT) in selected cases[o]

Footnotes on FOLL-B 4 of 6

LF R/R

Mahogany: Zanubrutinib+O vs Len-R (Ongoing)



Primary endpoint
- PFS per IRC using PET/CT-based Lugano 2014 criteria[1]

Key secondary endpoints
- ORR per IRC using PET/CT-based Lugano 2014 criteria[1]
- OS

Secondary endpoints
- PFS and ORR per IA; DOR, CRR, and TTR per IRC and IA (all using PET/CT-based Lugano 2014 criteria[1])
- Time to next antilymphoma treatment
- Health-related QOL
- Safety

https://clinicaltrials.gov/study/NCT05100862

LF R/R

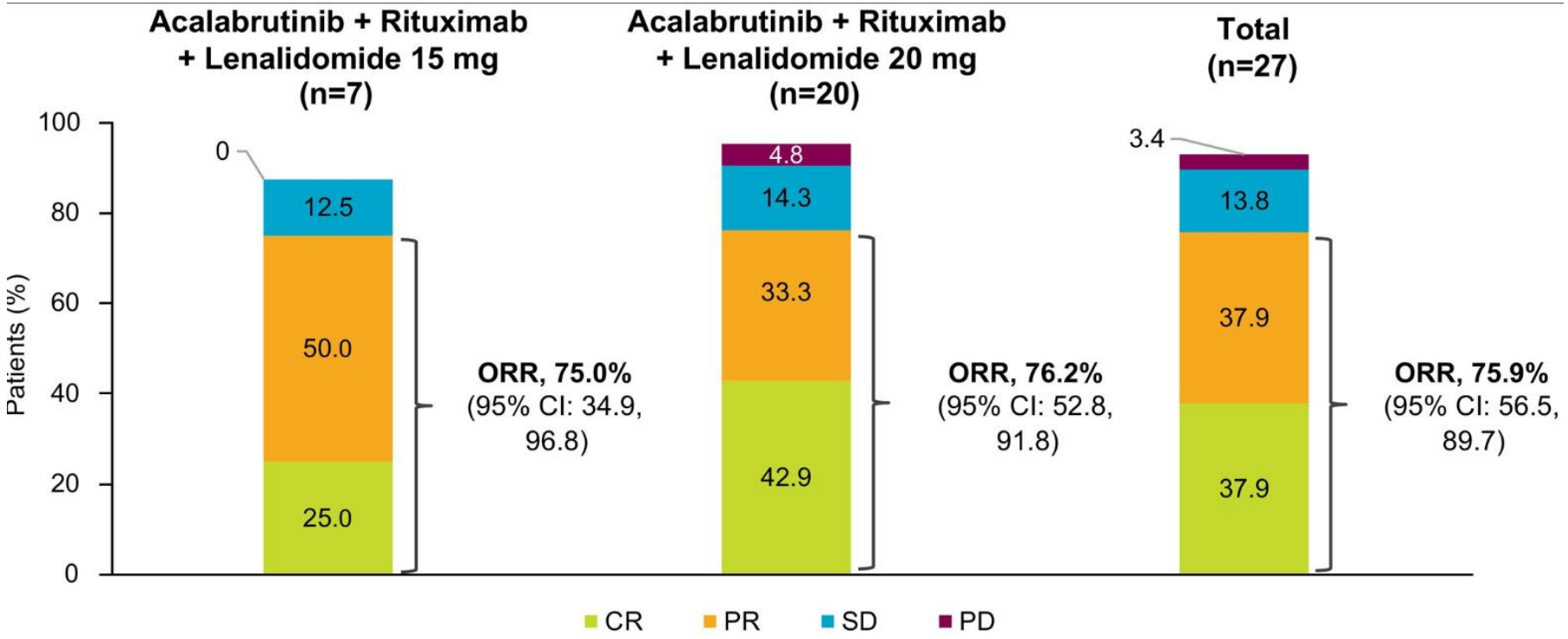
ACE-LY-003:Acalabrutinib-Len-R

#chemofree

Fase IB
N=29

Objetivo primario:
Seguridad.

Objetivos secundarios:
ORR, RC,S LP, SG.

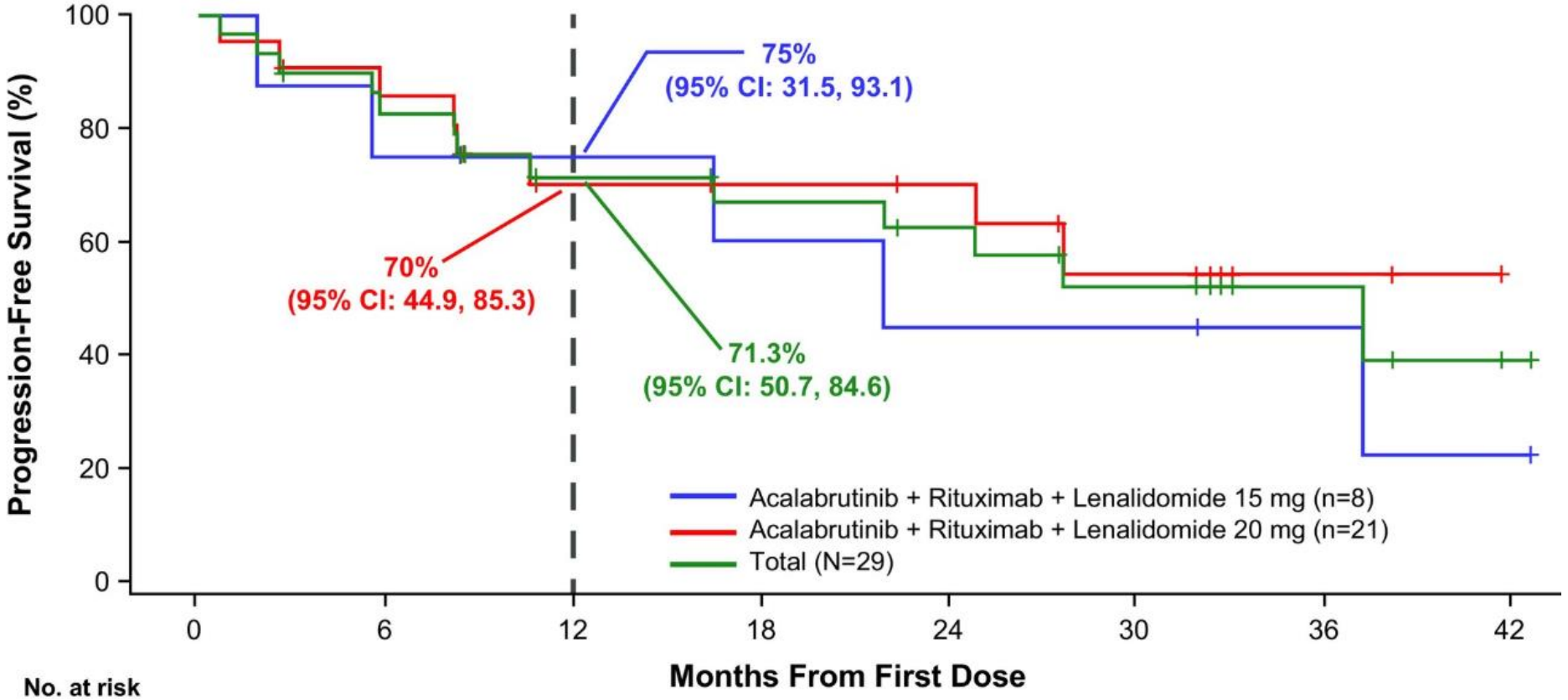


Paolo Strati et al. BJH 2024

LF R/R

ACE-LY-003:Acalabrutinib-Len-R

#chemofree



No. at risk															
Acalabrutinib + Rituximab + Lenalidomide 15 mg	8	7	6	5	5	5	4	4	3	3	3	2	2	1	1
Acalabrutinib + Rituximab + Lenalidomide 20 mg	21	18	17	14	12	12	11	11	10	9	6	3	2	1	0
Total	29	25	23	19	17	17	15	15	13	12	9	5	4	2	1

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LF R/R

ACE-LY-003:Acalabrutinib-Len-R

#chemofree

EA>3	EA de interés
• Neutropenia:11 (38%) • Neumonía COVID-19:4 (14%) • Otras NAC: 3(10%) • COVID-19: 3(10%)	• FA: 2 ptes. • HTA: 2 ptes.

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LF R/R
iBTK combinados

SELENE (I-IQT)	ROSEWOOD(ZO)	ACALA-LEN-R
ORR:91%-90% RC:55%-50% SLP 12m:80% vs 78%	ORR:68%-45% RC:54%-14% SLP 12m:70% vs 40%	ORR:76% RC:38% SLP 12m:75%

LF R/R

Respuesta con otras moléculas

Class	Agent	Trial	N	Demographics		Follow-up (months)	ORR (%)	CRR (%)	Survival outcomes	Duration of response
				POD24 (%)	Refractory to prior therapy					
Bispecific antibody	Mosunetuzumab	NCT02500407 (GO29781)	90	52	69	37	78	60	36-mo PFS: 43%	30-mo DOCR: 72%
Bispecific antibody	Epcoritamab	NCT03625037 (EPCORE NHL-1)	128[a]	42	69	17	82	63	Median PFS: 15.4 mo	18-mo DOCR: 72%
Bispecific antibody	Odronextamab	NCT02290951 (ELM-1)	128[b]	49	72	27	81	73	24-mo PFS: 45%	24-mo DOCR: 48%
CAR T cell	Axicabtagene-ciloleucel	NCT03105336 (ZUMA-5)	127	55	69	42	94	79	36-mo PFS: 54%	36-mo DOCR: 62%
CAR T cell	Tisagenlecleucel	NCT03568461 (ELARA)	97	63	78	29	86	68	24-mo PFS: 57%	24-mo DOCR: 78%
CAR T cell	Lisocabtagene-maraleucel	NCT04245839 (TRANSCEND FL)	107[c]	43	38	19	97	94	12-mo PFS: 81%	12-mo DOCR: 82%

[a]EPCORE NHL-1 FL study: N = 128 for efficacy and safety except for CRS and ICANS (N = 86 optimization cohort).

[b]ELM-2 study: N = 128 for efficacy and safety except for CRS and ICANS (N = 60 optimization cohort).

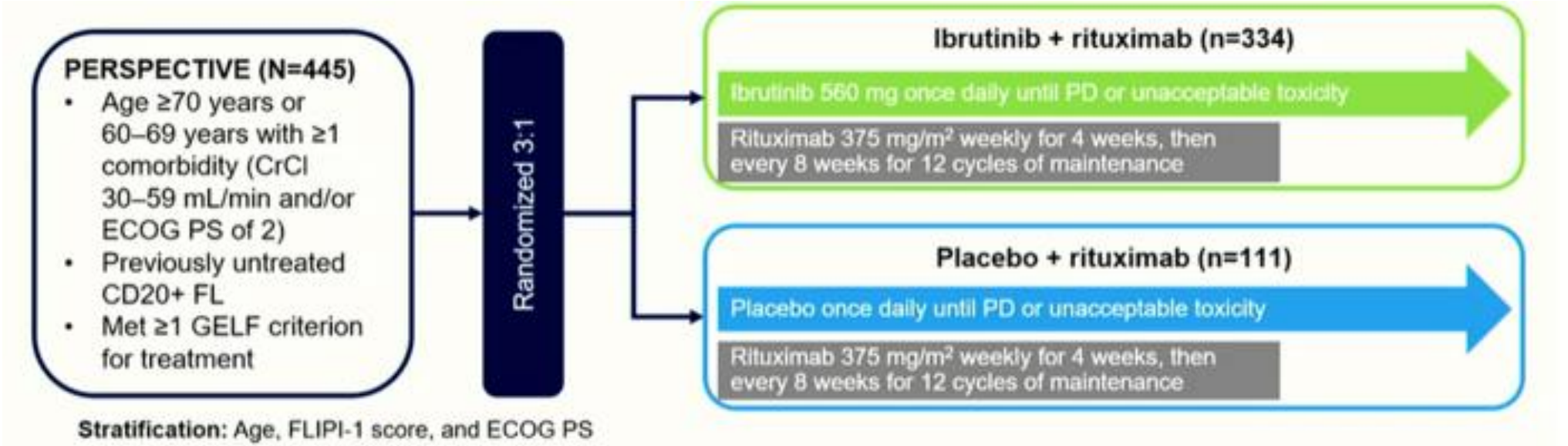
[c]TRANSCEND FL study: third-line or beyond FL for efficacy (N = 107), second-line or beyond FL for safety (N = 130).

CRR, complete response rate.

Barlett N, Russler-Germain D et al. Educacional ASH 2024

LF-Primera línea unfit

PERSPECTIVE: Ibrutinib+R vs R



- **Primary end point:**
  - PFS by investigator assessment per Cheson 2014 criteria using FDA censoring rules
    - Sensitivity analyses of PFS were performed based on IRC assessment and using global censoring rules

- **Secondary end points (tested hierarchically in the following order):**
  - ORR by investigator assessment per Cheson 2014 criteria
  - OS
  - IRR rates

Belada D et al. ICML 2025

LF-Primera línea unfit

PERSPECTIVE: Ibrutinib+R vs R

Characteristic	Ibrutinib + rituximab n=334	Placebo + rituximab n=111
Age		
Median (range), years	74 (60–87)	75 (61–88)
60–69 years, n (%)	69 (21)	22 (20)
≥70 years, n (%)	265 (79)	89 (80)
Sex, n (%)		
Male	151 (45)	58 (52)
Female	183 (55)	53 (48)
ECOG PS, n (%)		
0	120 (36)	37 (33)
1	130 (39)	47 (42)
2	84 (25)	27 (24)
CrCl, n (%)		
<30 mL/min	7 (2)	1 (1)
30 to <60 mL/min	108 (32)	36 (32)
≥60 mL/min	219 (66)	74 (67)
Median time since initial diagnosis (range), months	2.3 (0.4–176.0)	2.5 (0.1–114.0)

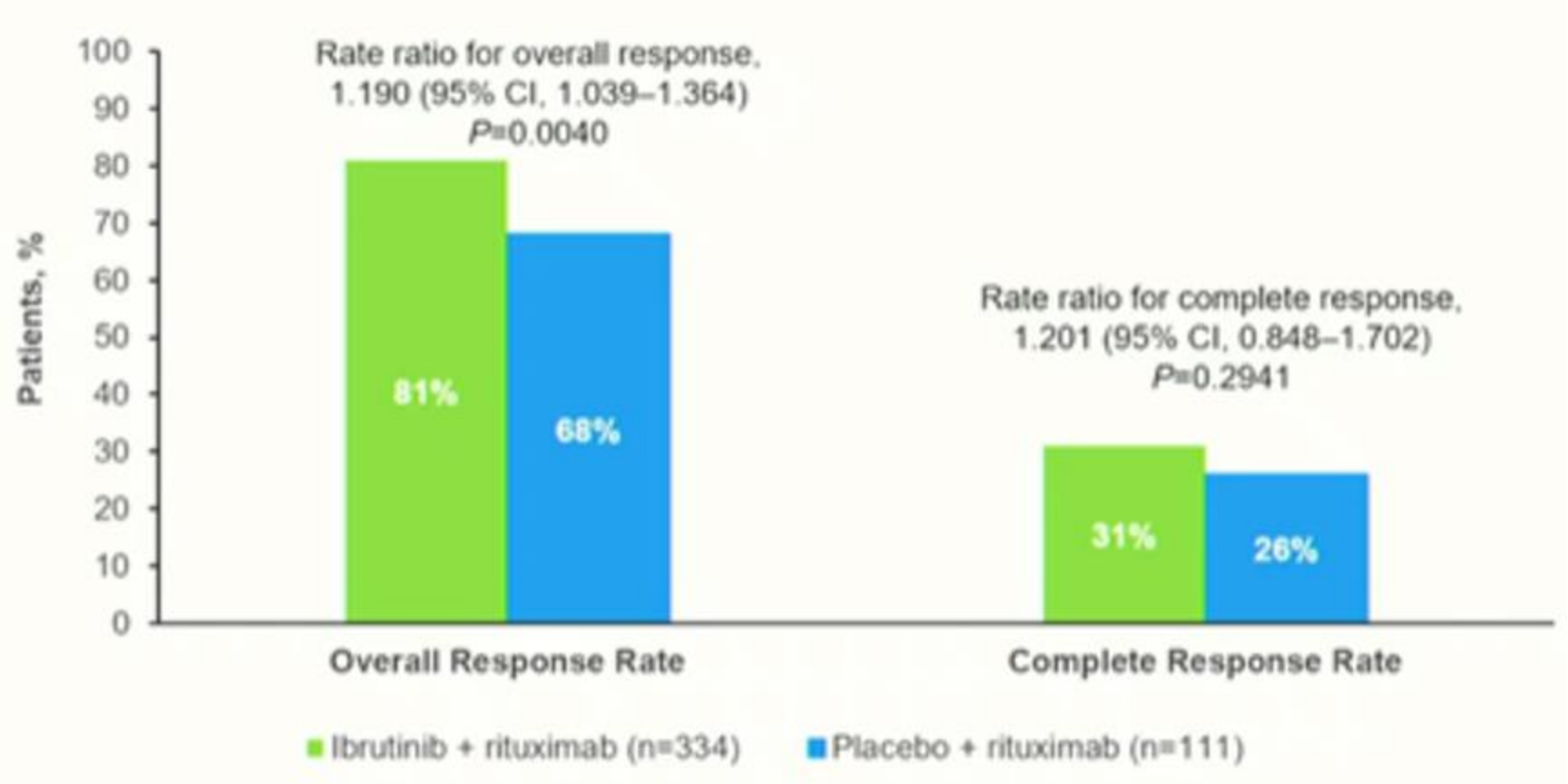
Characteristic	Ibrutinib + rituximab n=334	Placebo + rituximab n=111
FL WHO grade, n (%)		
1	100 (30)	37 (33)
2	157 (47)	53 (48)
3a	77 (23)	20 (18)
Missing	0	1 (1)
Ann Arbor stage, n (%)		
II	53 (16)	17 (15)
III	110 (33)	36 (32)
IV	171 (51)	58 (52)
FLIPI-1 score, n (%)		
Low (0–1)	30 (9)	7 (6)
Intermediate (2)	83 (25)	30 (27)
High (≥3)	221 (66)	74 (67)
Number of nodal areas involved, n (%)		
≤4	163 (49)	56 (50)
≥5	171 (51)	55 (50)
Bulky disease >7 cm, n (%)[a]	137 (41)	49 (44)

- An older patient population, per study design
- Meaningful proportion of patients with an ECOG PS score of 2
- Predominantly high FLIPI-1 score, Ann Arbor stage IV

Belada D et al. ICML 2025

LF-Primera línea unfit

PERSPECTIVE: Ibrutinib+R vs R



La media de DOR fue a favor de I+R : 44.3m vs 34.6m

Belada D et al. ICML 2025

LF-Primera línea unfit

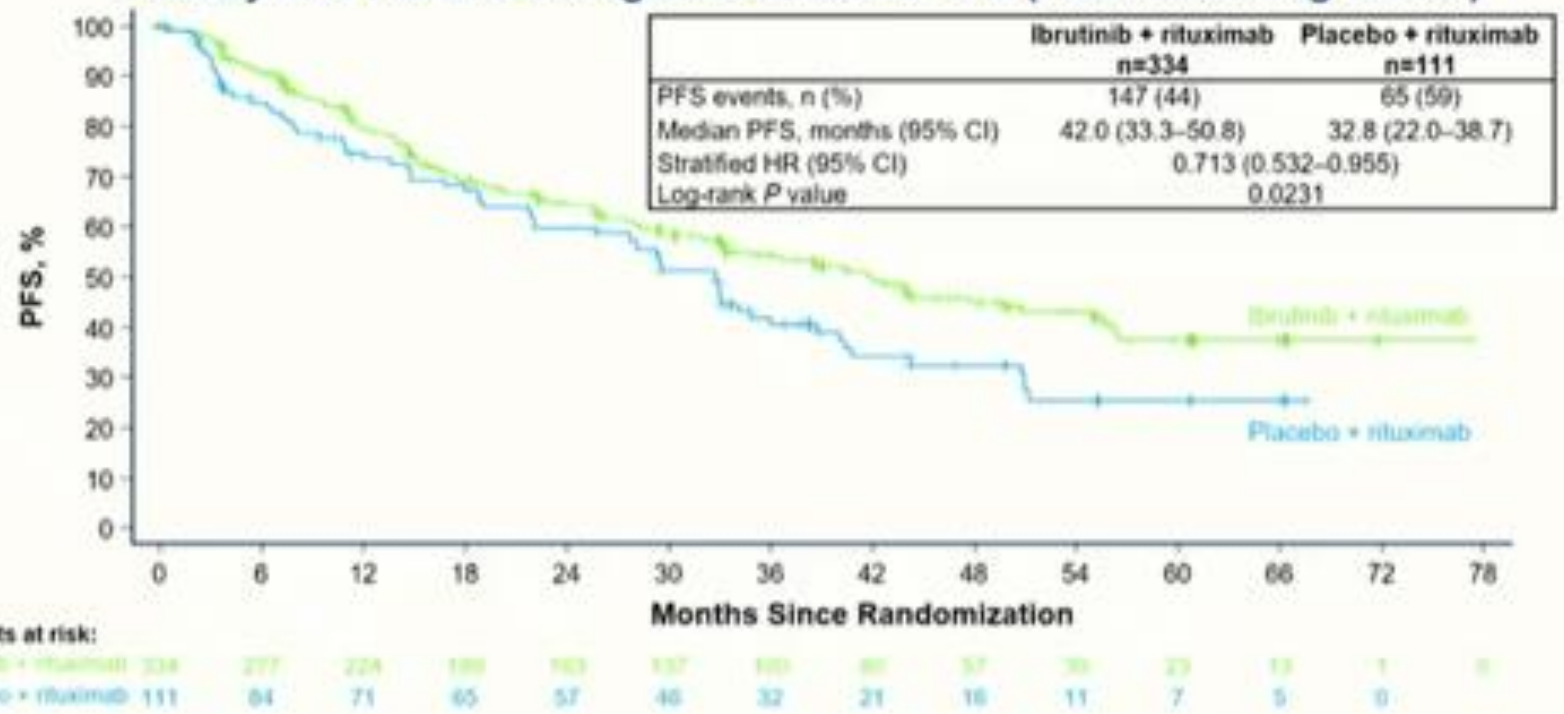
PERSPECTIVE: Ibrutinib+R vs R

SLP

- **Median follow-up:**
  - 53.7 months (range, 0.03–82.8)

Primary End Point: Investigator-Assessed PFS (FDA Censoring Rules[a])

	Ibrutinib + rituximab n=334	Placebo + rituximab n=111
PFS events, n (%)	147 (44)	65 (59)
Median PFS, months (95% CI)	42.0 (33.3–50.8)	32.8 (22.0–38.7)
Stratified HR (95% CI)	0.713 (0.532–0.955)	
Log-rank *P* value	0.0231	

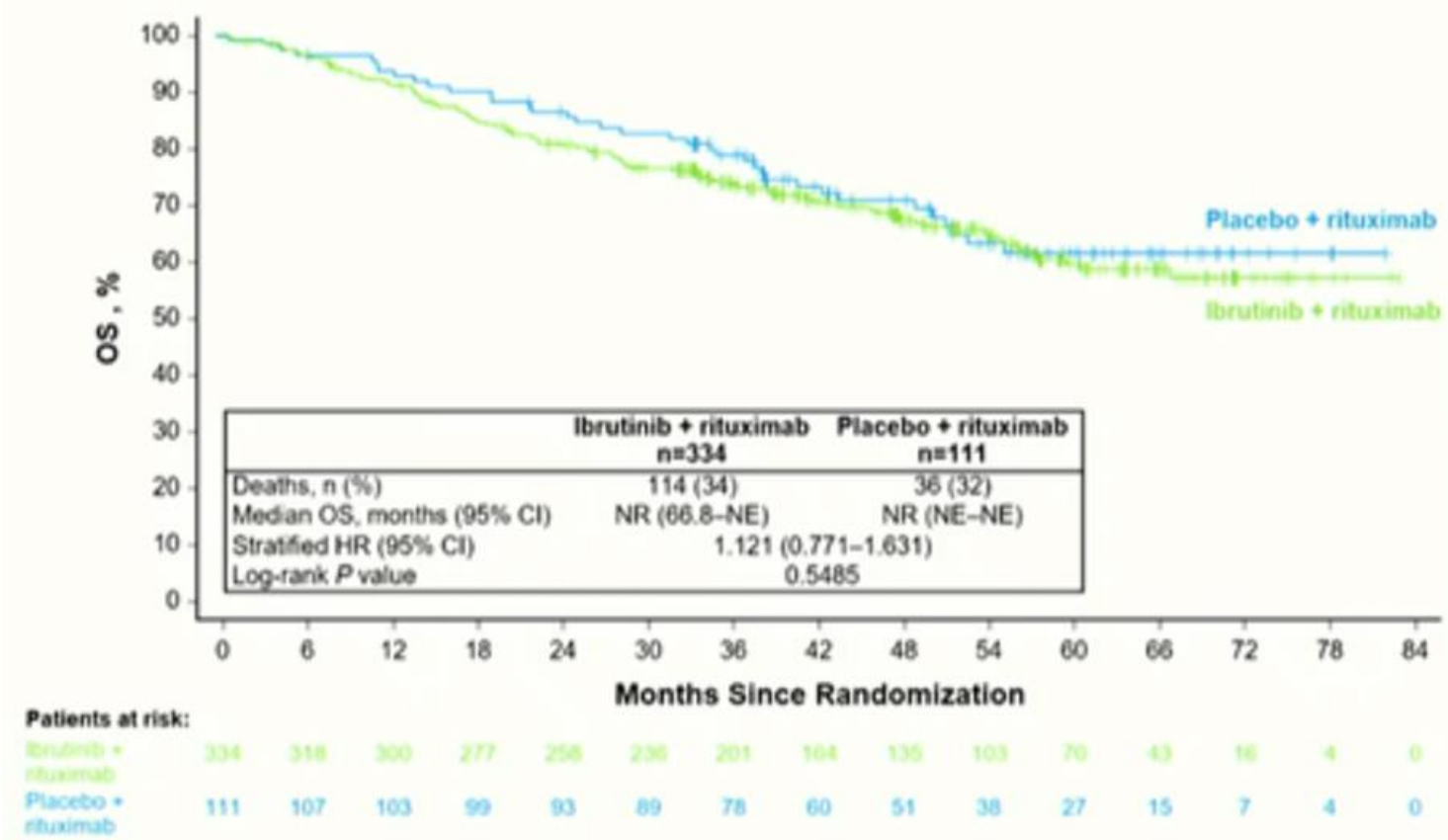


Belada D et al. ICML 2025

LF-Primera línea unfit

PERSPECTIVE: Ibrutinib+R vs R

SG



Causes of Death (ITT Population)

Deaths, n (%)	Ibrutinib + rituximab n=334	Placebo + rituximab n=111
All deaths	114 (34)	36 (32)
AE	47 (14)	8 (7)
Underlying disease	23 (7)	10 (9)
Unknown	14 (4)	7 (6)
Other[a]	30 (9)	11 (10)

Belada D et al. ICML 2025

LF-Primera línea unfit
Ibrutinib+R vs R

- **Median duration of treatment:**
  - Ibrutinib + rituximab: 22.1 months (range, 0.03–82.3)
  - Placebo + rituximab: 22.1 months (range, 0.4–71.2)

AE, n (%)	Ibrutinib + rituximab n=330	Placebo + rituximab n=111
Any AE	324 (98)	106 (95)
Grade ≥3 AEs	259 (78)	63 (57)
Serious AEs	204 (62)	45 (41)
AEs leading to death[a]	48 (15)	6 (5)
AEs leading to discontinuation	144 (44)	16 (14)
Ibrutinib/placebo only	84 (25)	6 (5)
Rituximab only	2 (1)	0
Both	58 (18)	10 (9)
AEs leading to dose reduction[b]		
Ibrutinib/placebo only	80 (24)	3 (3)

AE, n (%)	Ibrutinib + rituximab n=330	Placebo + rituximab n=111
Most frequent any-grade AEs[c]		
Diarrhea	120 (36)	16 (14)
COVID-19	83 (25)	23 (21)
Fatigue	73 (22)	14 (13)
Nausea	70 (21)	12 (11)
Neutropenia	68 (21)	11 (10)
Urinary tract infection	67 (20)	12 (11)
Most frequent grade ≥3 AEs[d]		
Neutropenia	52 (16)	8 (7)
Pneumonia	30 (9)	5 (5)
Hypertension	27 (8)	6 (5)
COVID-19	21 (6)	2 (2)
COVID-19 pneumonia	21 (6)	3 (3)
Diarrhea	21 (6)	2 (2)
Grade ≥3 atrial fibrillation	15 (5)	2 (2)

- In the ITT population, IRRs occurred in 21% of patients in the ibrutinib + rituximab arm versus 27% in the placebo + rituximab arm (rate ratio 0.787 [95% CI, 0.544–1.137])

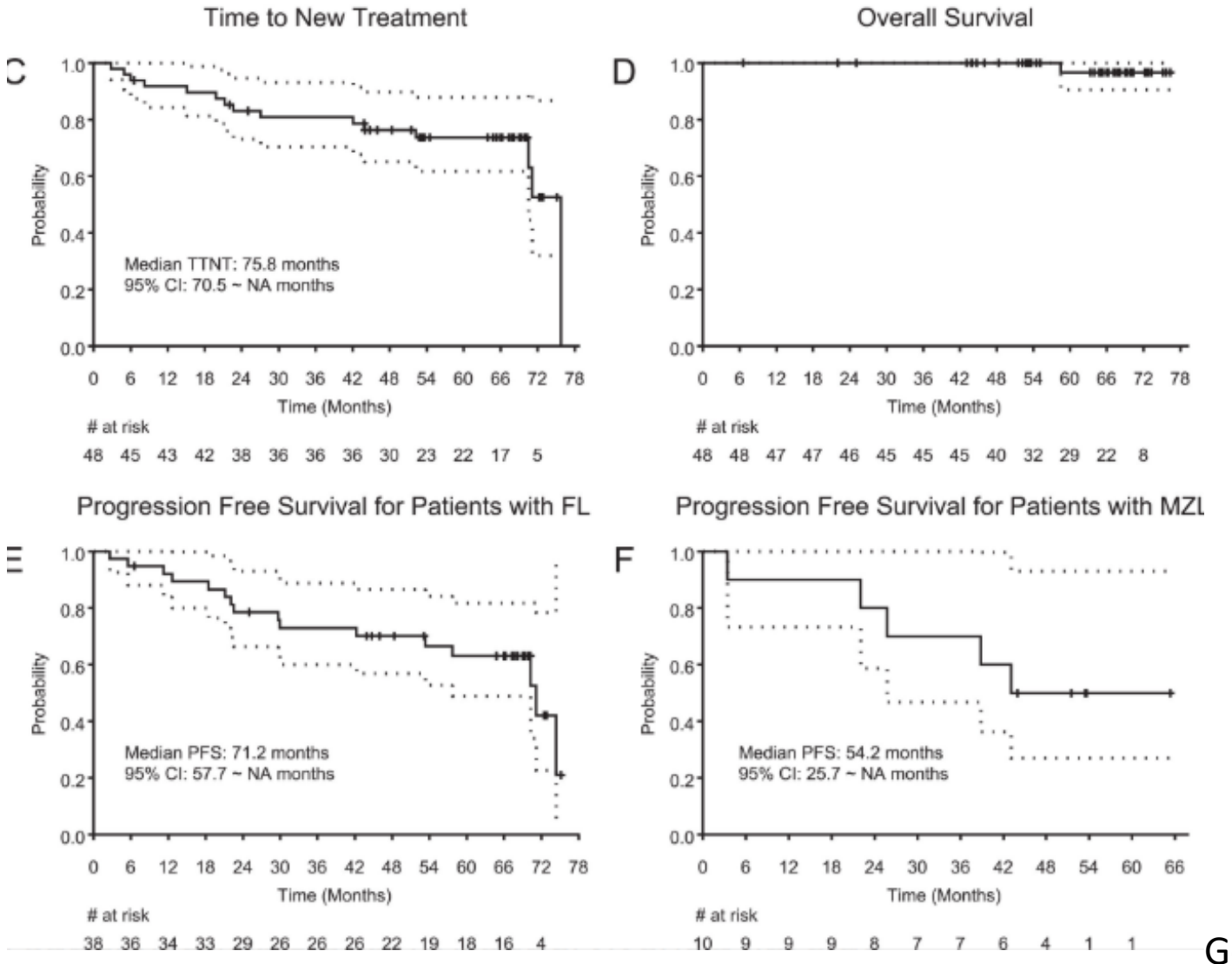
Belada D et al. ICML 2025

LF-Primera línea
Ibrutinib+R-Len

Fase II

N=48

OP:SLP



Gordon M et al. ACSJ 2023

LF-Primera línea
Acalabrutinib-Len-R

Fase II (2020-2021)

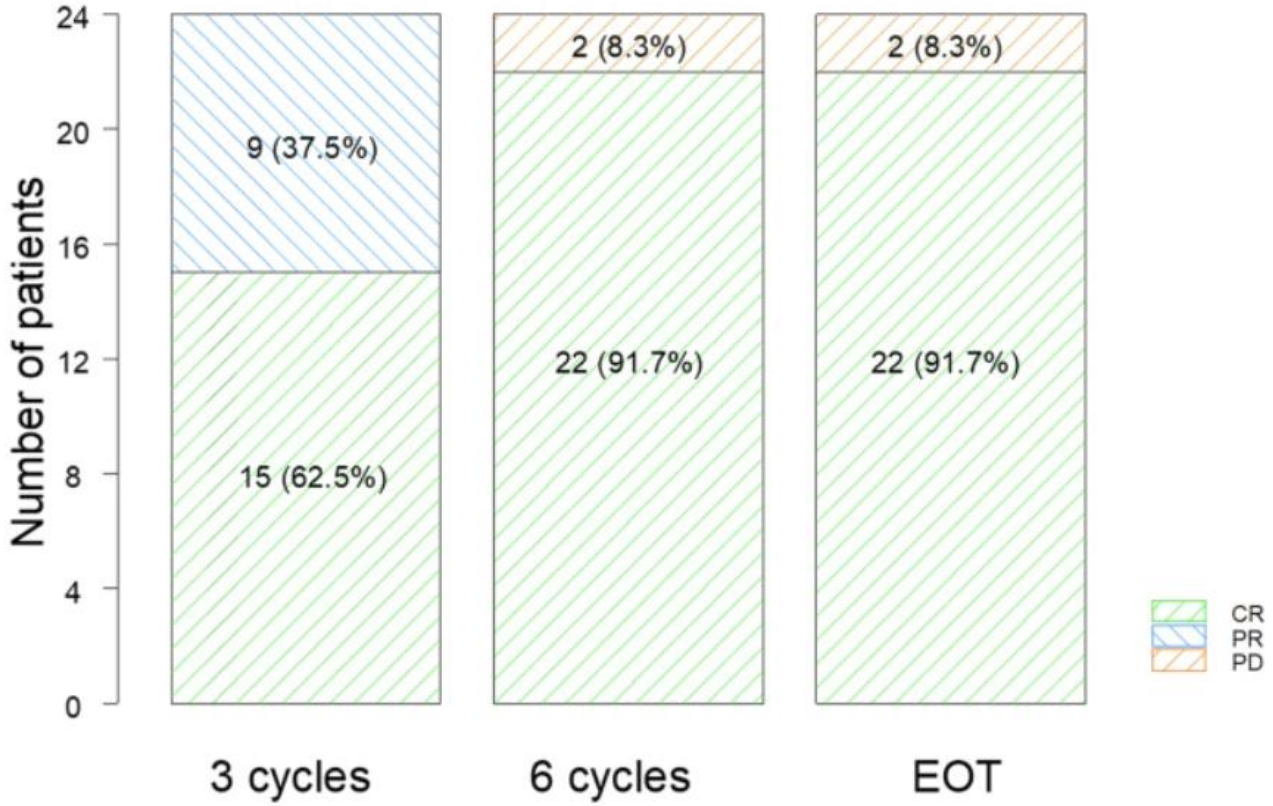
N=24

Objetivo Primario: RC

Objetivos secundarios :ORR, DoRC, POD24, SLP,SG, AE

Paolo Strati et al. Nature 2025

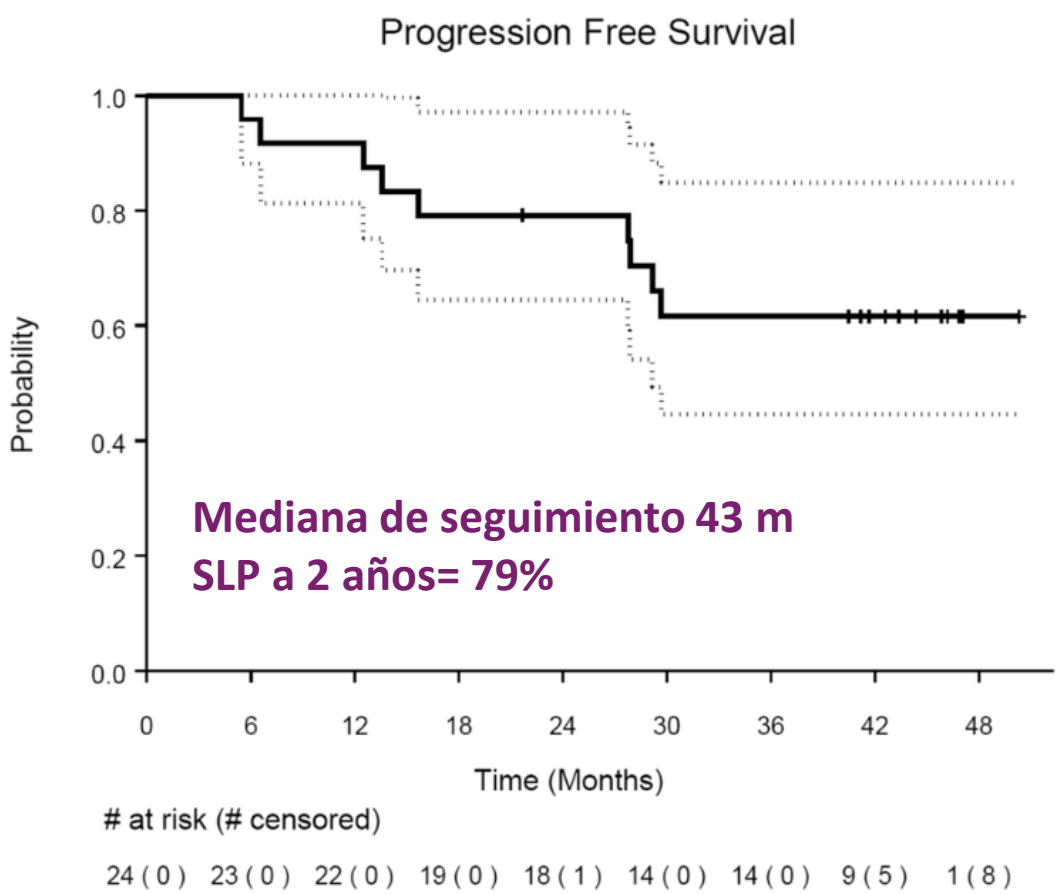
LF-Primera línea
Acalabrutinib-Len-R



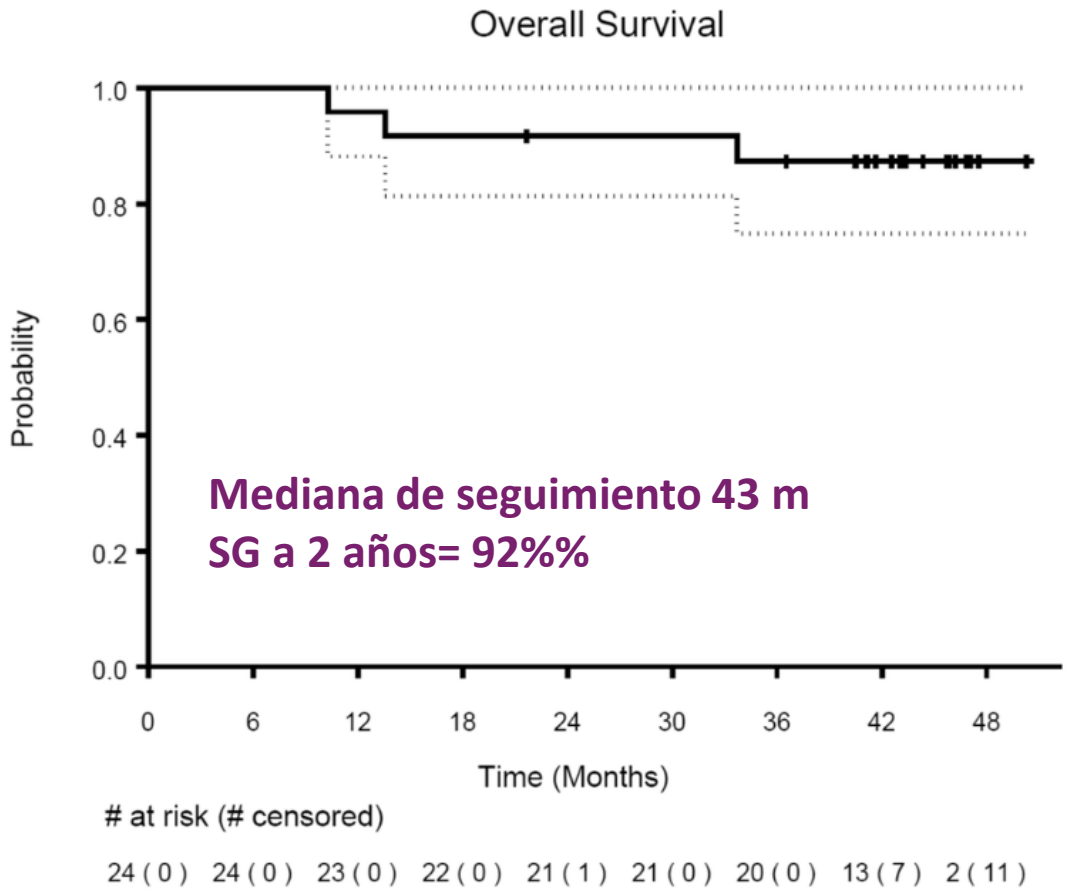
POD24=17%

Paolo Strati et al. Nature 2025

LF-Primera línea
Acalabrutinib-Len-R



Mediana de seguimiento 43 m
SLP a 2 años= 79%



Mediana de seguimiento 43 m
SG a 2 años= 92%%

Paolo Strati et al. Nature 2025

Conclusión

1. El uso de inhibidores de iBTK en monoterapia no ha demostrado ser una estrategia eficaz.
2. Sin embargo, las combinaciones de iBTK con otras moléculas, como lenalidomida o rituximab, han mostrado efectos sinérgico con toxicidad manejable y chemo-free, posicionándose como una alternativa razonable, especialmente en regiones como LATAM, donde el acceso a terapias como anticuerpos biespecíficos o células CAR-T resulta limitado.
3. La combinación de ibrutinib asociado a IQT, resultó fútil.
4. Si bien no existen estudios comparativos directos entre los distintos iBTK, y extrapolando la experiencia en leucemia linfocítica crónica (LLC), podría considerarse el uso preferente de iBTK de segunda generación en pacientes con alto riesgo de hemorragia o arritmias.
5. Las combinaciones en primera línea han mostrado buenos resultados, pero debemos tener en cuenta en LATAM si los cambios que producen la introducción de estas moléculas justifican la “toxicidad financiera” que producen.
6. Están pendiente los resultados del estudio MAHOGANY, el cual compara ZO vs el backbone “R2” y resulta de importancia para un cambios de estándar.

¡Muchas Gracias!

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ULHB

Con el Aval: