“Relapsed Refractory FL.

What options do we have?”

Department of Hematology - FUNDALEU

Medical Director – CHP

GATLA

Buenos Aires, Argentina.

FUNDALEU

Centro de Hematología
PAVLOVSKY
Atención médica y laboratorio de alta complejidad

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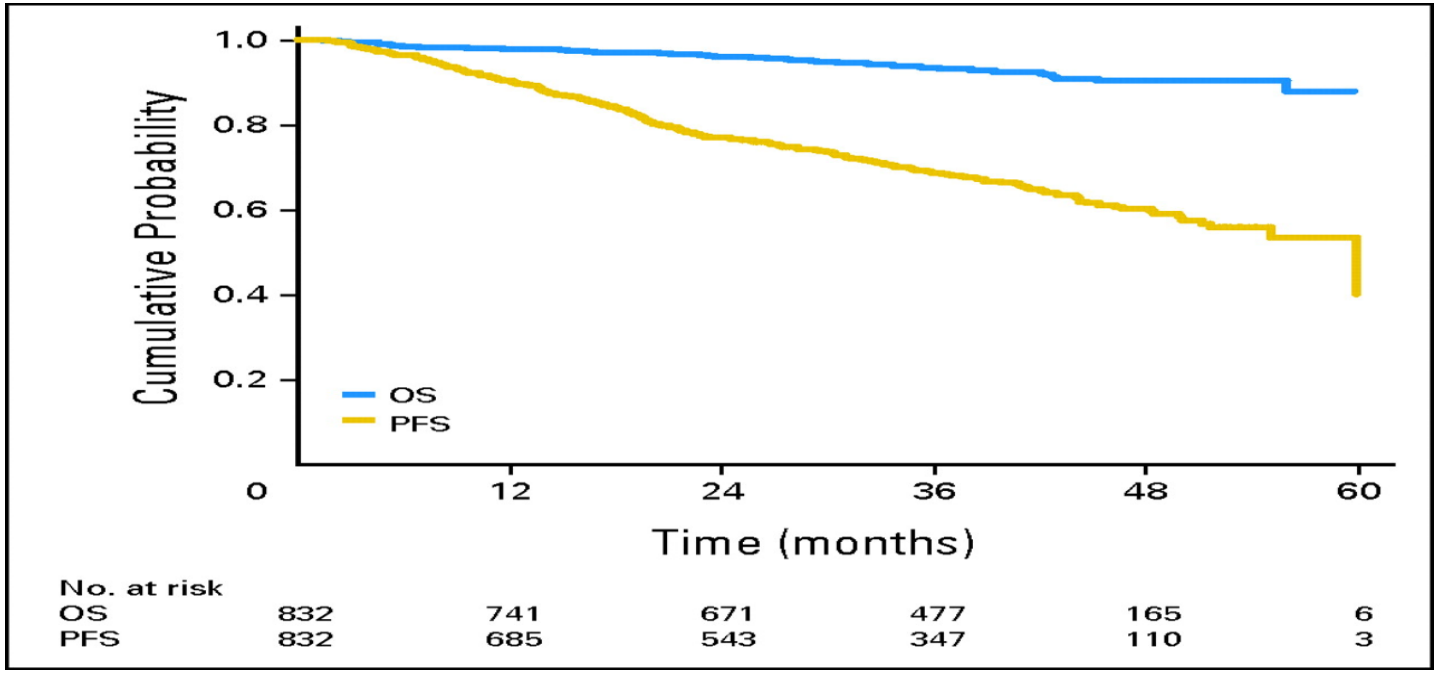
Follicular Lymphoma



Federico et al. JCO 2009;27:4555-4562

Prognostic models to predict outcome in 1L FL.

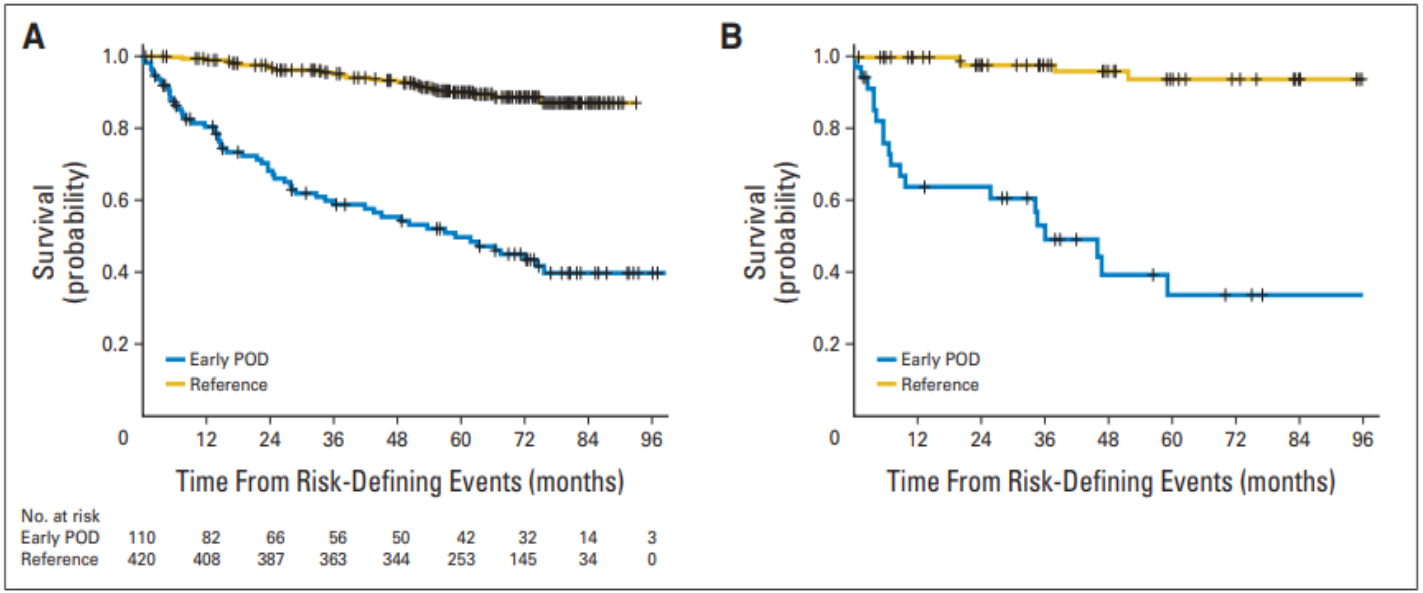
Table I. Prognostic models in FL

Model	Factors	Risk groups	OS	PFS
FLIPI	Age > 60 yearsStage III–IVHb < 120 g/lLDH > ULN>4 nodal sites	Low risk (0–1 factors)Intermediate risk (2 factors)High risk (3 or more factors)	5-year OS: 91%5-year OS: 78%5-year OS: 52%	–
FLIPI-2	Age > 60 yearsHb < 120 g/lElevated β2 MGMass >6 cmBone marrow involvement	Low risk (0–1 factor)Intermediate risk (2 factors)High risk (3 or more factors)	–	Low risk: 5-year PFS: 80%Intermediate risk: 5-year PFS: 51%High risk: 5-year PFS: 19%
PRIMA-PI	β2 MG > 3 g/lBone marrow involvement	Low risk (0 factors)Intermediate risk (1 factor)High risk (2 factors)		Low risk: 5-year PFS: 69%Intermediate risk: 5-year PFS: 55%High risk: 5-year PFS: 37%
m7-FLIPI	ECOG PS > 1FLIPI high riskMutations in: *EP300, CREBBP, CARD11, MEF2B, EZH2, ARID1A, FOXO1*	Low riskHigh risk		Low risk: 5-year FFS: 77·2%High risk: 5-year FFS: 38·2%

Casulo C. How I manage patients with follicular lymphoma. BJH. 2019. doi: 10.1111/bjh.16011

High risk FL defined as POD 24

(Progression of disease in first 24 months)



POD24= 19%

Patients with POD24 → 2-year and 5-year OS rates of 68% and 50%.

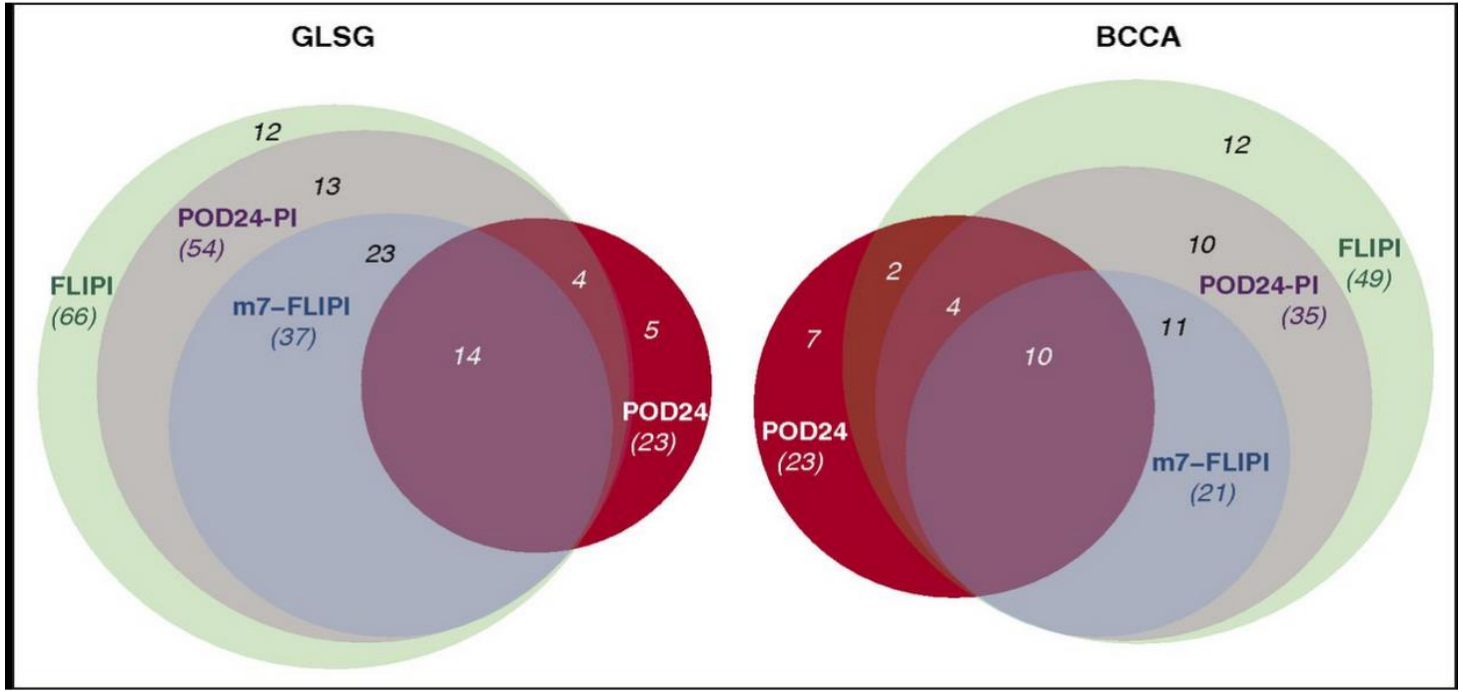
Patients without POD24 → 97% and 90%.

Casulo et al. JOURNAL OF CLINICAL ONCOLOGY. 2015

High risk at relapse. POD 24 in 20% pts.

- ✓ Around 20% of patients will progress within the first 24 months.
- ✓ These patients with early events after immuno-chemotherapy represent the greatest clinical need in FL, reproducible in several datasets.
- ✓ This newly defined **high-risk group** of patients represents a distinct population *warranting further exploration in precision studies of FL biology and treatment.*

Can we identify HR FL?



Jurinovic, Blood 2016

Prognostic models to predict outcome in 1L FL.

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PRIMA-PI	β2 M inv			5-year PFS: 69% iate risk: 5-year PFS: h risk: 5-year PFS: 37%
m7-FLIPI	ECO risk *CREBBP, CARD11, MEF2B,* *EZH2, ARID1A, FOXO1*			5-year FFS: 77·2% k: 5-year FFS: 38·2%

At this moment all FL are treated the same , no biomarkers to guide herapy, unable to adapt 1L treatment to those who will have an event within the first 24 months.

Casulo C. How I manage patients with follicular lymphoma. BJH. 2019. doi: 10.1111/bjh.16011

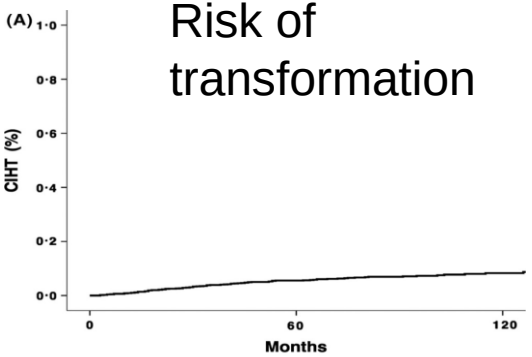
***THE* most important risk factor at relapse is histologic transformation.**

Histologic transformation.

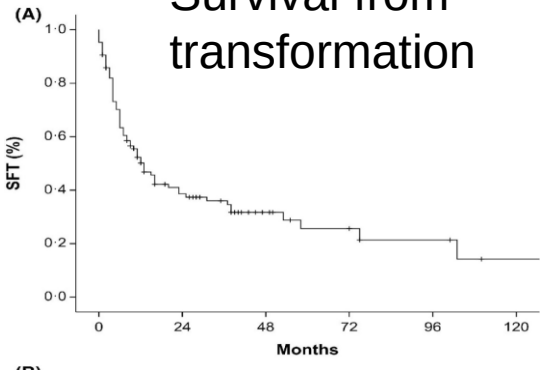
- A 10-year cumulative incidence of HT is10.3%.
- The majority of patients who die due to lymphoma have transformed disease.

Zinzani et al, Experimental Hematology, 2024

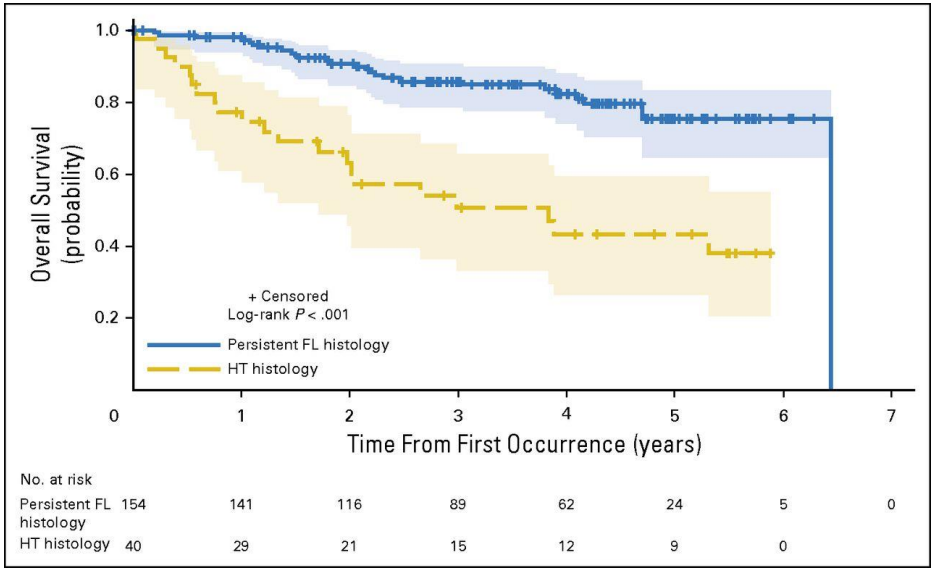
Misconception regarding POD24: Influence of histologic transformation?



Risk of transformation



Survival from transformation



Sarkozy C, J Clin Oncol 2016;34:2575-82

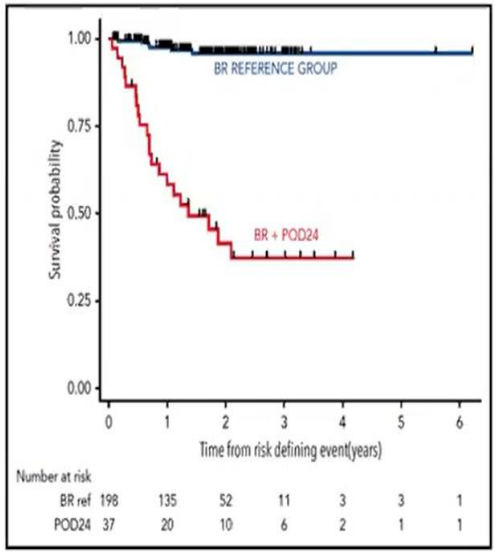
Alonso-Álvarez S, Br J Haematol 2017;178:699-708

Histologic transformation.

BR and maintenance R
N=296

13%
POD24

76%
HGT



HT is a frequent event in patients with POD 24

Freeman et al Blood, 2019

2L Therapy of *ALL* pts with RR FL.

- Always biopsy first!
- In ***ALL*** asymptomatic patients observation can be an option.
- In ***ALL*** pts chemoinmunotherapy can be an option.
- In ***ALL*** pts maintenance with Rituximab can be considered.

❖ Autologous HCT ***can*** be considered in selected POD24 patients.
(absence of randomized prospective data confirming benefit of AUTO in POD24)

Ladetto, Marco1,2;. HemaSphere, 2021
Zinzani, P.L. et al.. Exp Hematol Oncol, 2024
Tiqbal et al, Transplantation and Cellular Therapy,2024,

2nd line treatment in RR FL.

NCCN Guidelines for 2L therapy in FL.

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]

SECOND-LINE THERAPY[h]

Preferred regimens (in alphabetical order)
- Bendamustine[d,l] + obinutuzumab[j] or rituximab (not recommended if treated with prior bendamustine)
- CHOP + obinutuzumab[j] or rituximab
- CVP + obinutuzumab[j] or rituximab
- Lenalidomide + rituximab
- Tafasitamab-cxix[k] + lenalidomide + rituximab (≥1 prior systemic therapy including an anti-CD20 mAb)

Other recommended regimens (in alphabetical order)
- Lenalidomide (if not a candidate for anti-CD20 mAb therapy)
- Lenalidomide + obinutuzumab
- Obinutuzumab
- Rituximab

SECOND-LINE THERAPY FOR OLDER OR INFIRM
(if none of the therapies are expected to be tolerable in the opinion of treating physician)

Preferred regimens
- Rituximab (375 mg/m^2 weekly for 4 doses)
- Tazemetostat[l] (irrespective of *EZH2* mutation status)

Other recommended regimen
- Cyclophosphamide ± rituximab

SECOND-LINE EXTENDED THERAPY (optional)

Preferred regimens
- Rituximab maintenance 375 mg/m^2 one dose every 12 weeks for 2 years (category 1)
- Obinutuzumab maintenance for rituximab-refractory disease (1 g every 8 weeks for total of 12 doses)

SECOND-LINE CONSOLIDATION THERAPY (optional)

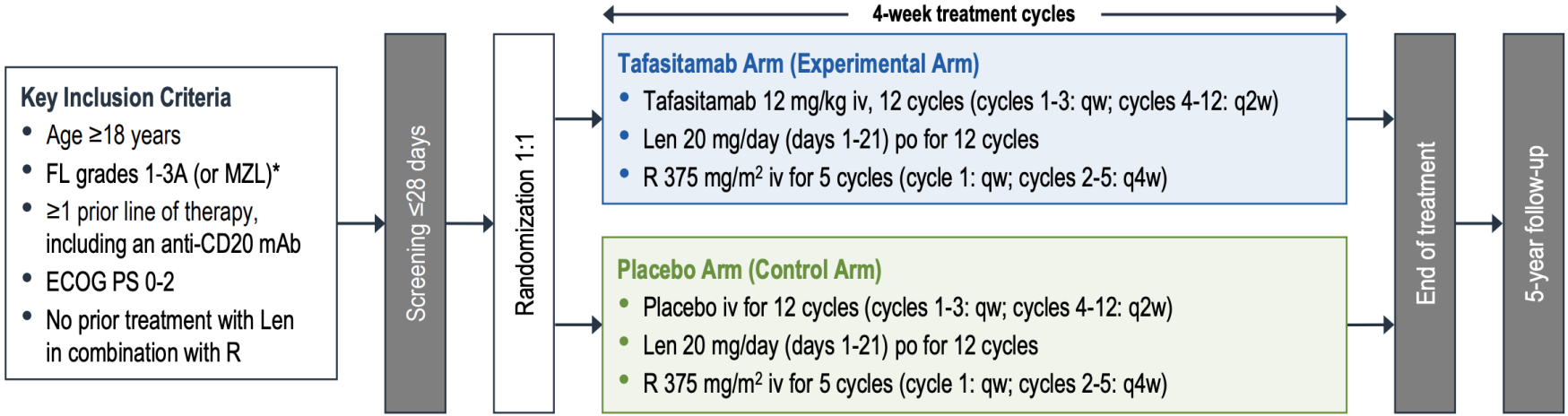
- High-dose therapy with autologous stem cell rescue (HDT/ASCR)

At the present time, **we have no reliable prognostic factors in which to base sequencing of treatment for RR FL**.

Parameters affecting these decisions include clinical presentation, patients fitness and previous therapies.

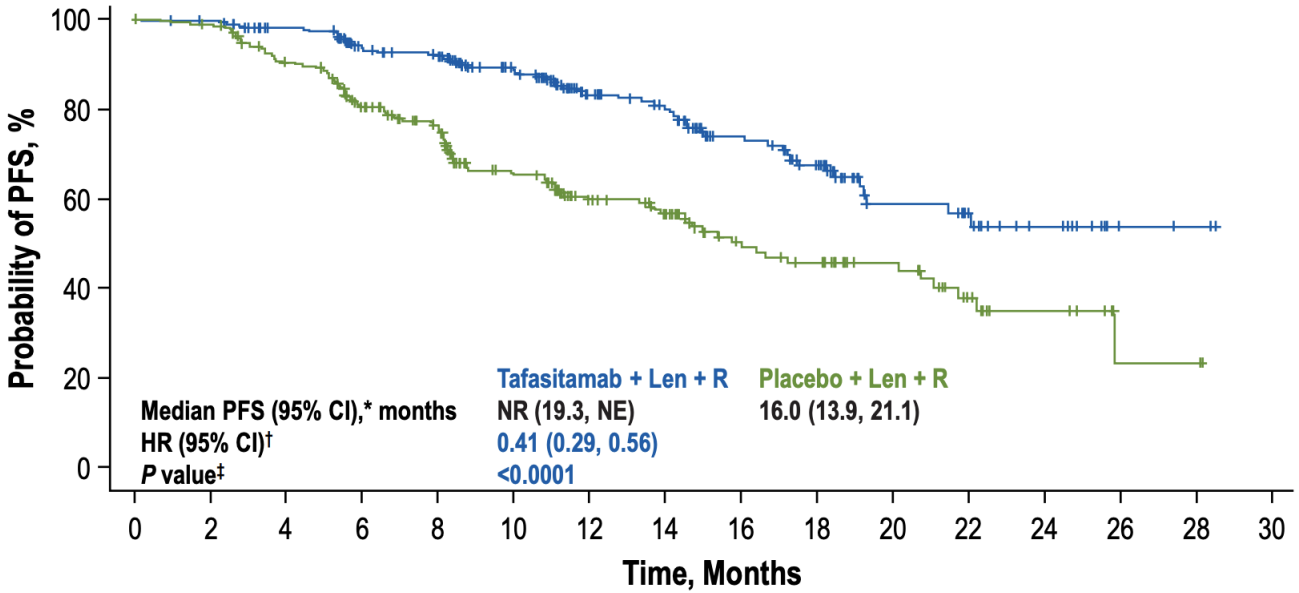
Guidelines recommend to treat patients according to clinical presentation or patient´s fitness.

InMIND: Phase III Tafasitamab + R2 vs R2 for R/R Follicular Lymphoma



Sehn L et Al. ICML 2025

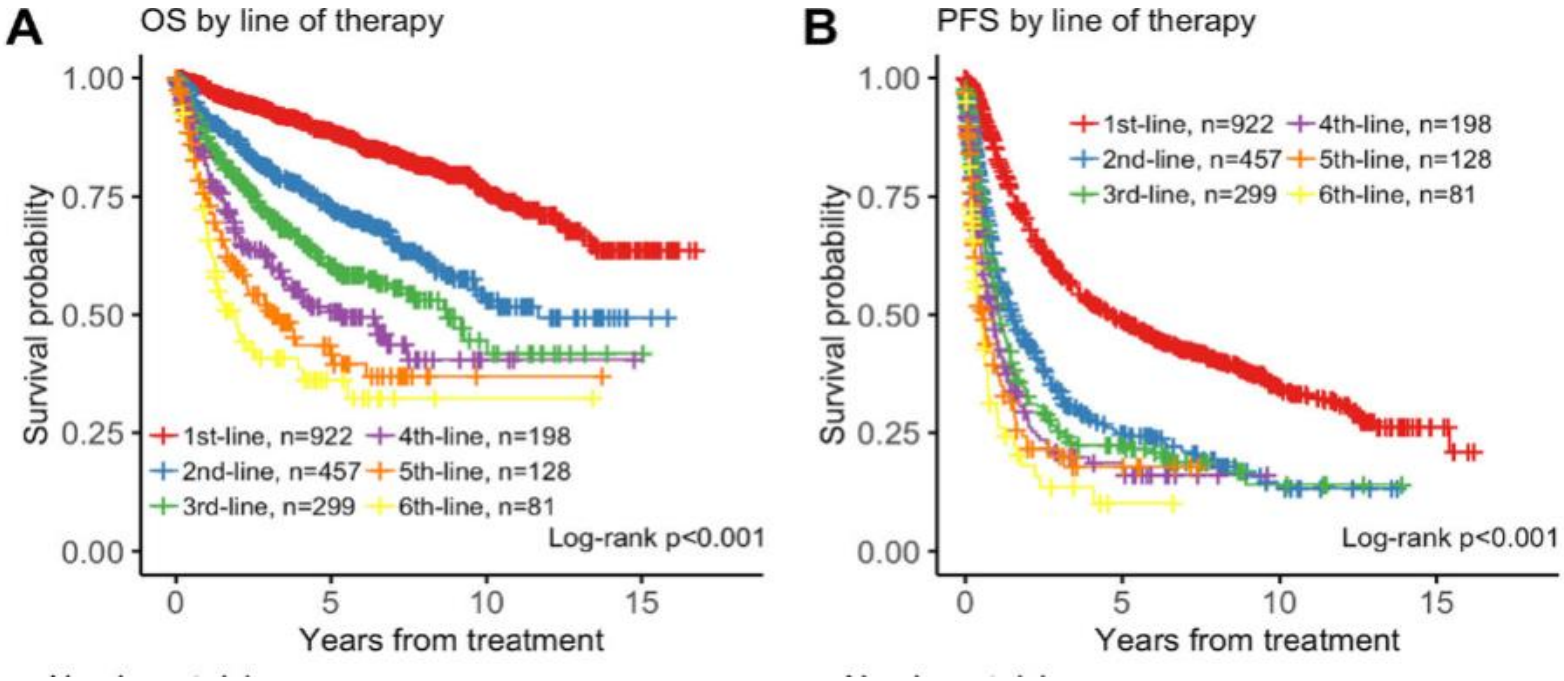
InMIND: Phase III Tafasitamab + R2 vs R2 for R/R Follicular Lymphoma



Sehn L et Al. ICML 2025

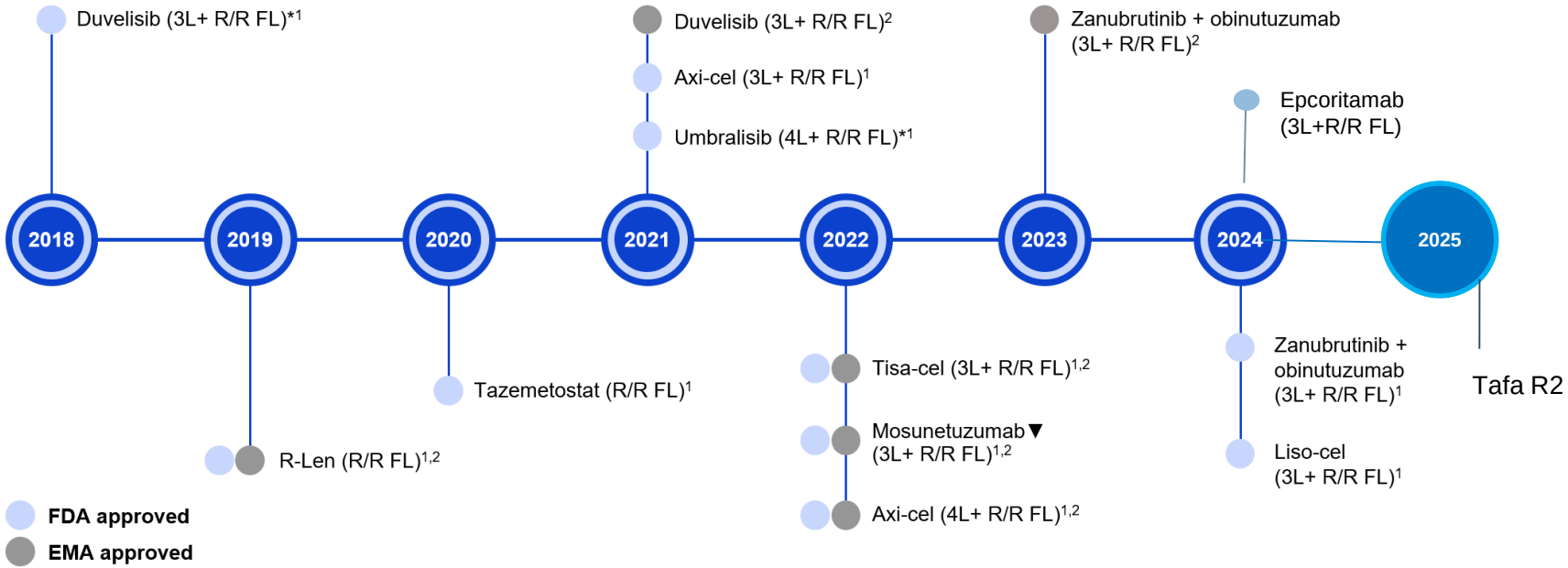
Double refractory or 3+L.
What are options are available?

Outcome after different lines of therapy.



Batlevi et al, BCA, 2020

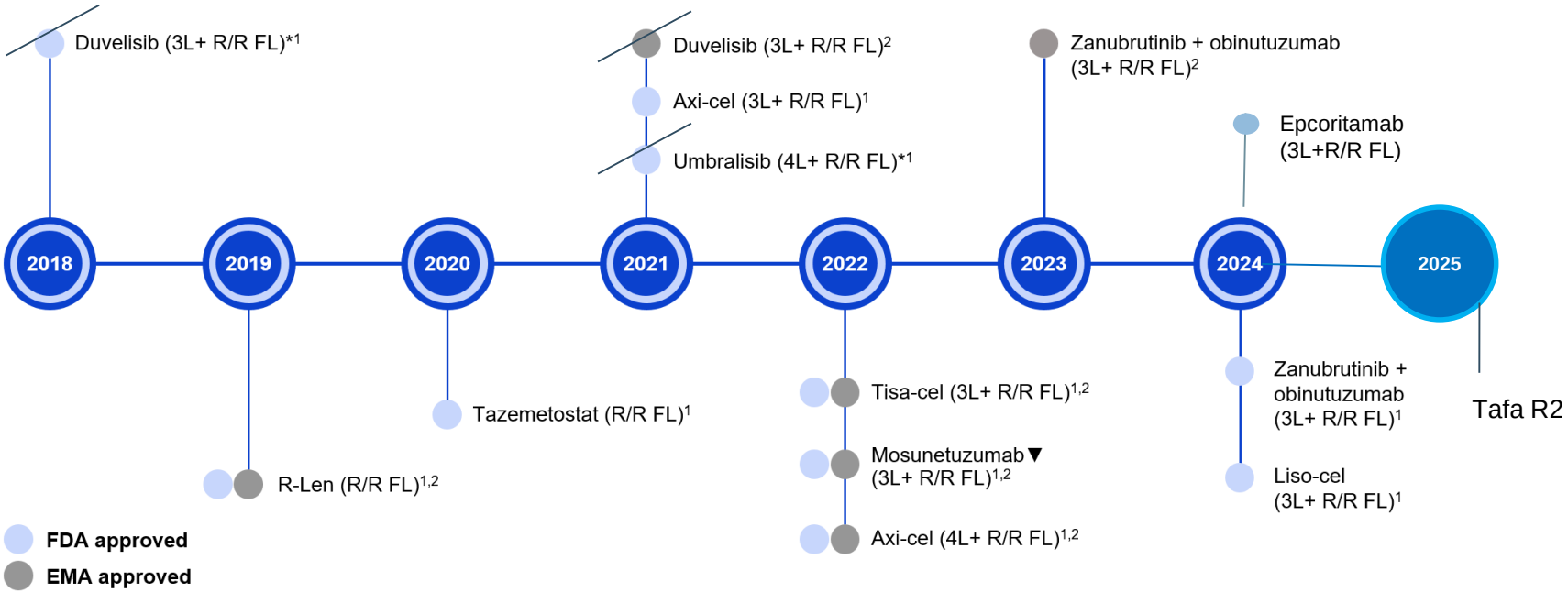
Treatment options in 3+L FL



▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information.Healthcare professionals are asked to report any suspected adverse reactions.
*FDA approval withdrawn in 2022.[3]
Axi-cel, axicabtagene ciloleucel; Len, lenalidomide; liso-cel, lisocabtagene maraleucel; tisa-cel, tisagenlecleucel.

1. US PI. Available from: www.accessdata.fda.gov/scripts/cder/daf/;
2. EU SmPC. Available from: www.ema.europa.eu/en/medicines;
3. FDA Federal Register. Available from: https://www.federalregister.gov/documents/2022/04/13/2022-07931/secura-bio-inc-withdrawal-of-approval-of-relapsed-or-refractory-follicular-lymphoma-indication-for.

Treatment options in 3+L FL



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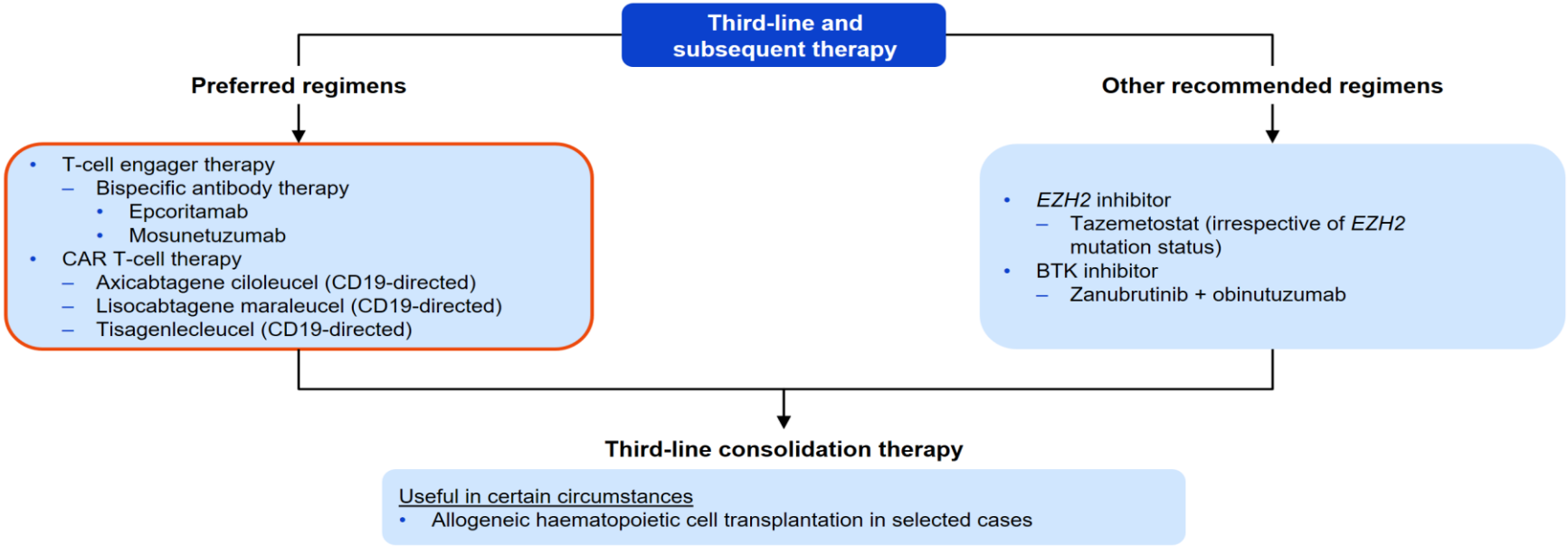
2. EU SmPC. Available from: www.ema.europa.eu/en/medicines;
3. FDA Federal Register. Available from: https://www.federalregister.gov/documents/2022/04/13/2022-07931/secura-bio-inc-withdrawal-of-approval-of-relapsed-or-refractory-follicular-lymphoma-indication-for.

NCCN Guidelines 2025 3+L .

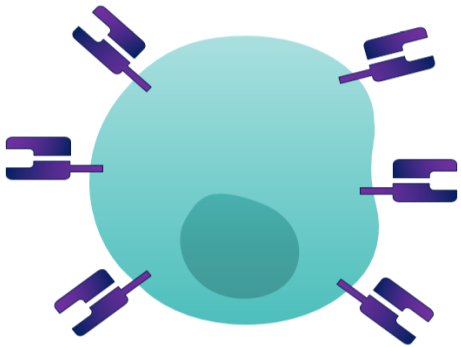


NCCN Guidelines for B Cell Lmphomas V 2.2025

Cellular therapy.

Two main classes of T-cell engaging therapies[1]

CAR T-cell therapies



Bispecific antibodies

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

1. Batlevi CL, et al. Nat Rev Clin Oncol 2016;13:25–40; 2. US PI. Available from: www.accessdata.fda.gov/scripts/cder/daf/; 3. EU SmPC. Available from: www.ema.europa.eu/en/medicines; 4. Sun LL, et al. Sci Transl Med 2015;7:287ra70.

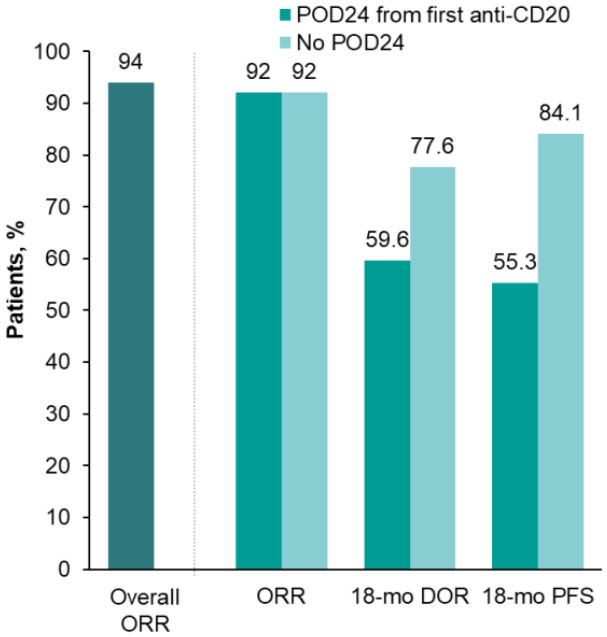
CAR T cell in RR FL.

High risk patients with not many good options at time of inclusión.

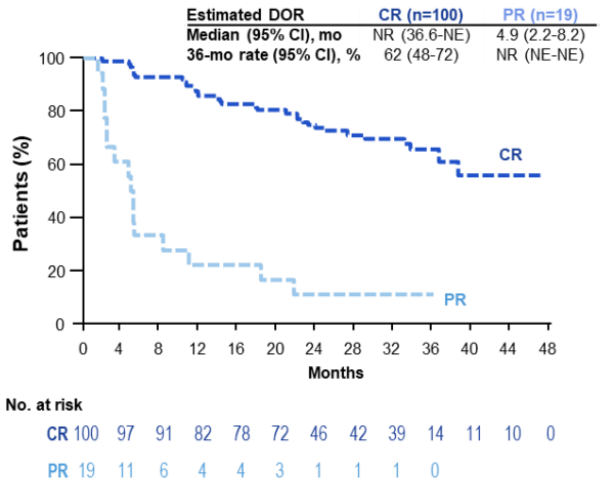
- 44-60% FLIPI 3
- Median lines of therapy 3-4
- 44-68% double refactory
- More than half POD24
- Mayority were refractory to last line of therpy

CAR T cell in RR FL.

Axi-cel[1]



Axi-cel[1]



Axi-cel[1]

Phase 2 ZUMA-5

N=127

ORR: 94%; CR: 79%

mDOR: 38.6 mo; 36-mo: 57%

mPFS: 40.2 mo; 36-mo: 54%

mOS: NR; 36-mo: 76%

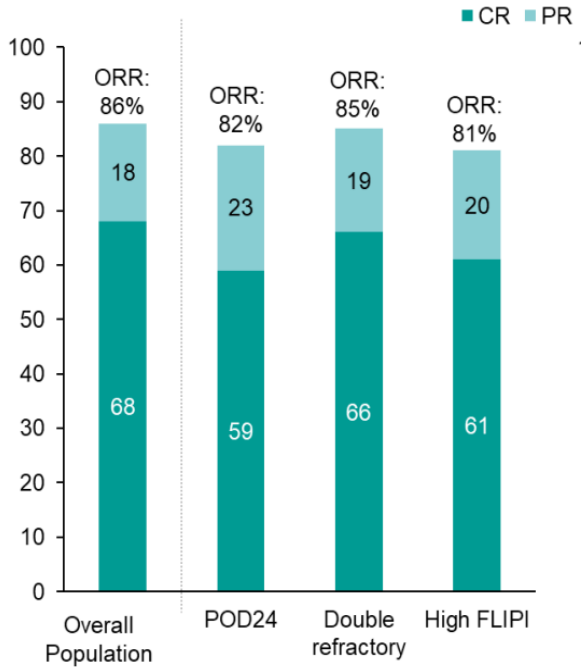
Median follow-up: 41.7 months

3L+ FL 2021

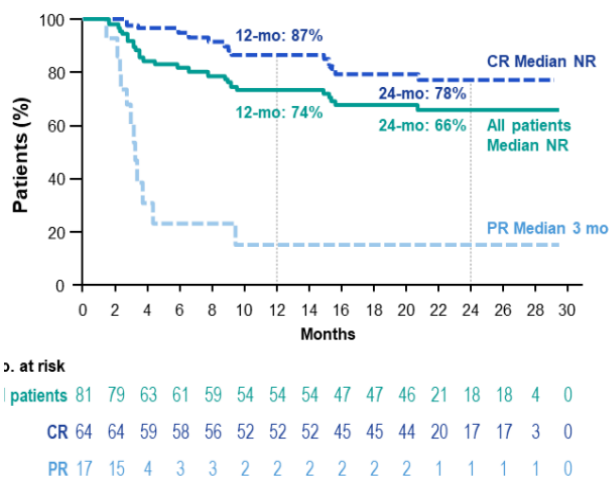
4L+ FL 2022

CAR T cell in RR FL.

Tisa-cel[2]



Tisa-cel[2]



Tisa-cel[2]

Phase 2 ELARA

N=94

ORR: 86.2%; CR: 68.1%

mDOR: NR

24-month DOR: 66.4%

mPFS: NR (24-month PFS: 57.4%)

mOS: NR; 24-mo OS: 87.7%

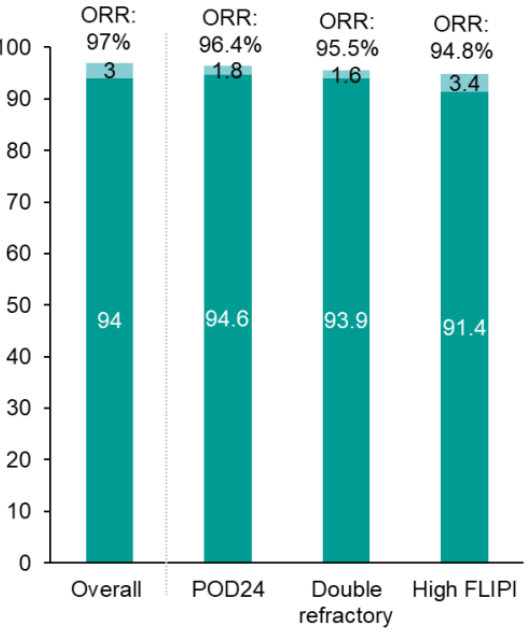
Median follow-up: 16.6 months

3L+ FL 2022

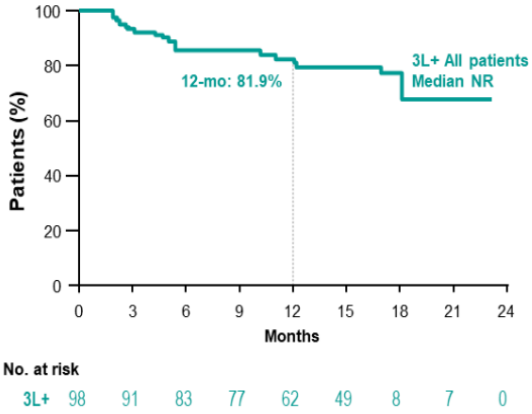
3L+ FL 2022

CAR T cell in RR FL.

Liso-cel[3]



Liso-cel[3]



Liso-cel[3]

Phase 2 TRANSCEND FL

N=101

ORR: 97%: CR: 94%

mDOR: NR

12-month DOR: 81.9%

mPFS: NR (12-month PFS: 80.7%)

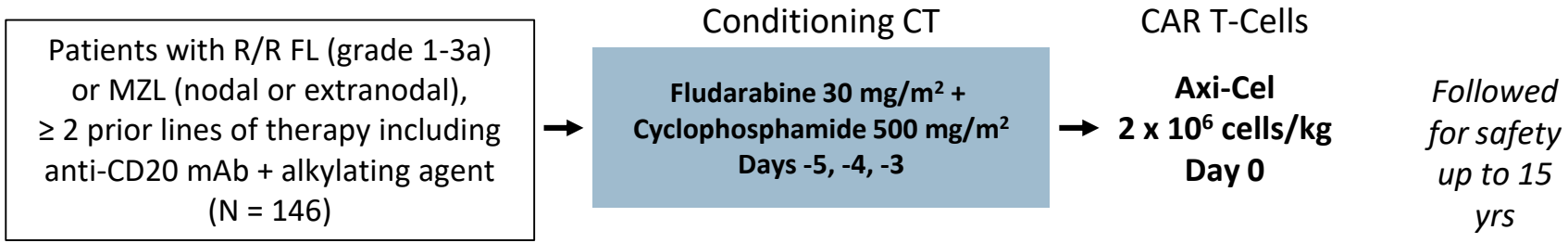
mOS: NR; 12-mo OS: 92.1%

Median follow-up: 17.9 months

3L+ May 15, 2024

Five-Year Follow-Up Analysis of ZUMA-5: Axicabtagene Ciloleucel in R/R Indolent Non-Hodgkin Lymphoma

- Multicenter, single-arm phase II trial



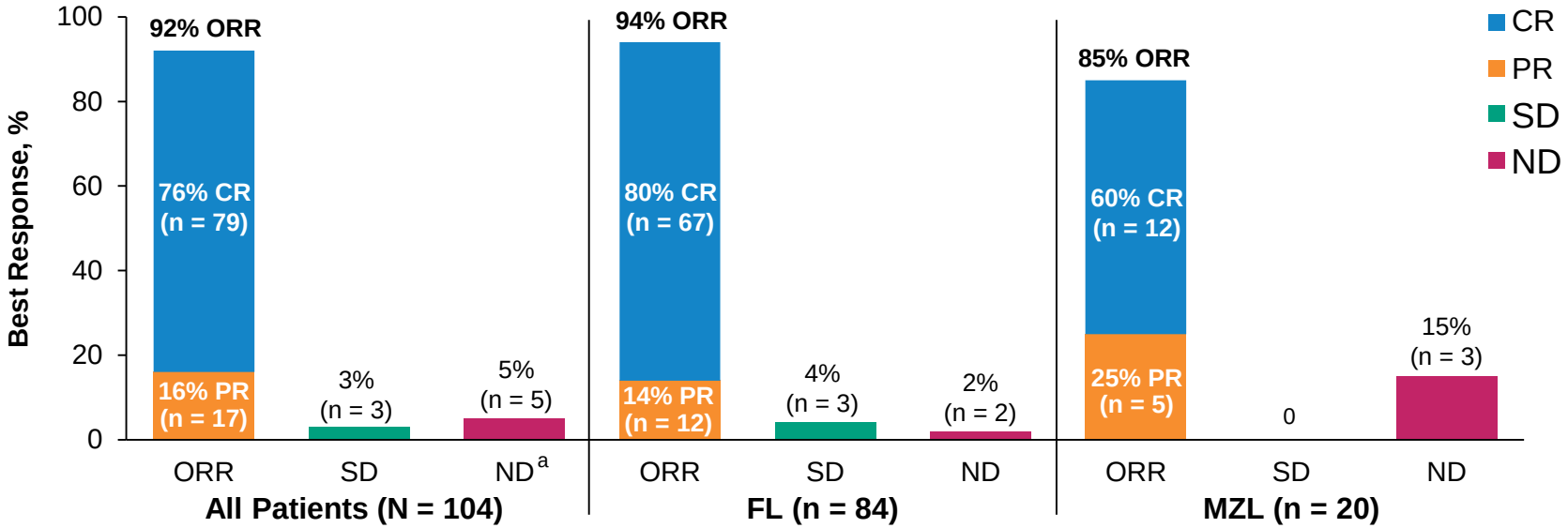
Patients with SD but no relapse > 1 yr from completion of last therapy ineligible. Single-agent anti-CD20 mAb not counted as line of therapy for eligibility. Median time to delivery of axi-cel: 17 days following leukapheresis.

Primary endpoint: ORR (IRRC-assessed per Lugano classification)

Key secondary endpoints: CR rate (IRRC-assessed), ORR (investigator-assessed), DoR, PFS, OS, AEs, CAR T-cell and cytokine levels

Jacobson. ASH 2020. Abstr 700. NCT03105336.
Neelapu, S, JCO, 2024

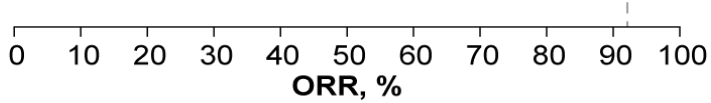
ZUMA-5: Efficacy (ORR and CR- Primary Endpoint)



- The median time to first response was 1 month (range, 0.8 – 3.1)
- Among the 25 patients with FL who initially had a PR, 13 (52%) subsequently converted to a CR after a median of 2.2 months (range, 1.9 – 11.2)

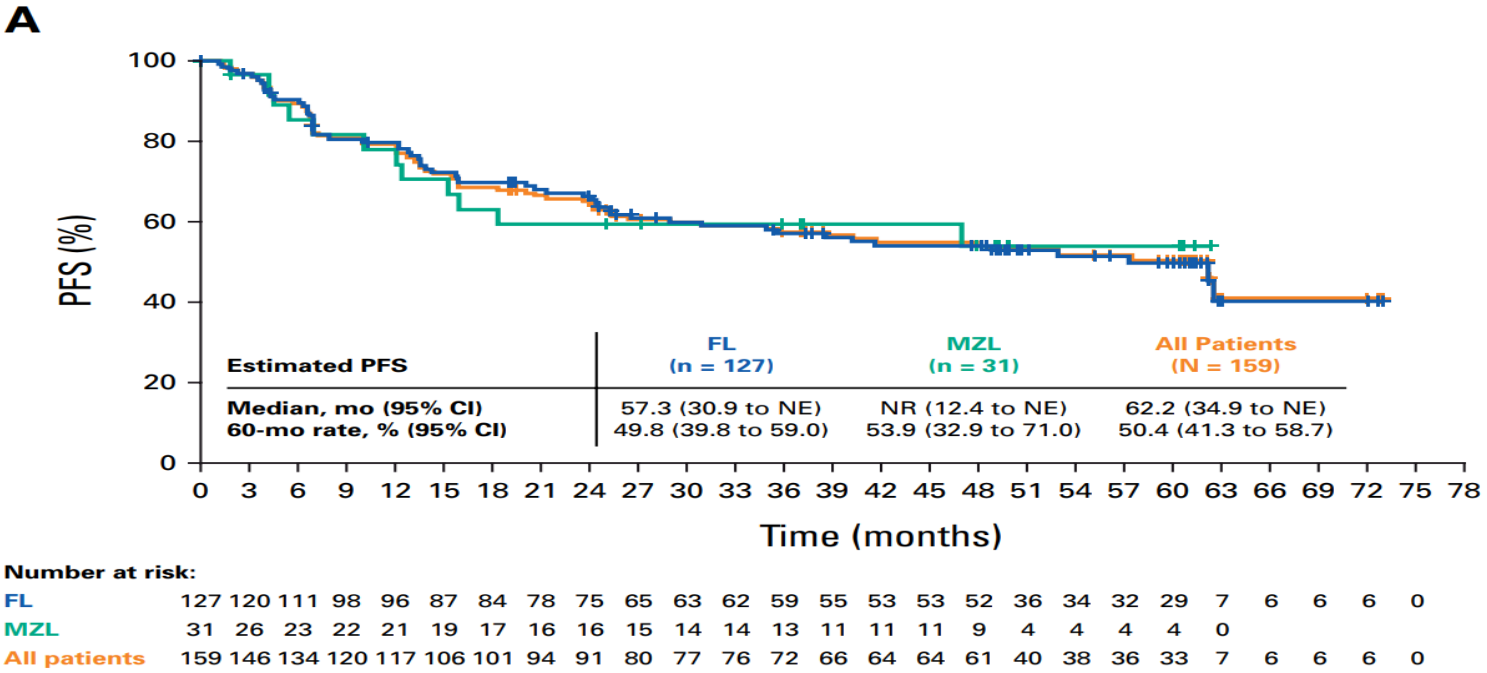
The investigator-assessed ORR (N = 104) was 95%, with a CR rate of 77%. Concordance between investigator-assessed and IRRC-assessed ORR was 91%. [a] For the 5 patients reported as ND, 4 (1 FL; 3 MZL) had no disease at baseline and postbaseline per IRRC but were considered with disease by the investigator; 1 patient with FL died before the first disease assessment.
CR, complete response; FL, follicular lymphoma; IRRC, Independent Radiology Review Committee; MZL, marginal zone lymphoma; ND, undefined/not done; ORR, overall response rate; PR, partial response;
SD, stable disease.

		Evaluable Patients	Responding Patients	ORR (95% CI)
Overall		104	96	92 (85 – 97)
Age	< 65	62	58	94 (84 – 98)
	≥ 65	42	38	90 (77 – 97)
Sex	Male	54	51	94 (85 – 99)
	Female	50	45	90 (78 – 97)
ECOG performance status	0	63	58	92 (82 – 97)
	1	41	38	93 (80 – 98)
FLIPI score	0 – 1	15	14	93 (68 – 100)
	2	36	32	89 (74 – 97)
	≥ 3	53	50	94 (84 – 99)
High tumor burden (GELF criteria)	Yes	49	47	96 (86 – 100)
	No	55	49	89 (78 – 96)
Number of prior therapies	2	32	28	88 (71 – 96)
	3	26	25	96 (80 – 100)
	≥ 4	46	43	93 (82 – 99)
Prior PI3K inhibitor	Yes	35	33	94 (81 – 99)
	No	69	63	91 (82 – 97)
Prior autologous SCT	Yes	23	21	91 (72 – 99)
	No	81	75	93 (85 – 97)
Relapsed/refractory subgroup	Relapsed	28	25	89 (72 – 98)
	Refractory	76	71	93 (85 – 98)
POD24 from initiating first anti-CD20 mAb–containing therapy	Yes	57	53	93 (83 – 98)
	No	36	33	92 (78 – 98)
CD19 status	Positive	83	76	92 (83 – 97)
	Negative	9	9	100 (66 – 100)
Corticosteroid and/or tocilizumab use	Yes	63	57	90 (80 – 96)
	No	41	39	95 (83 – 99)



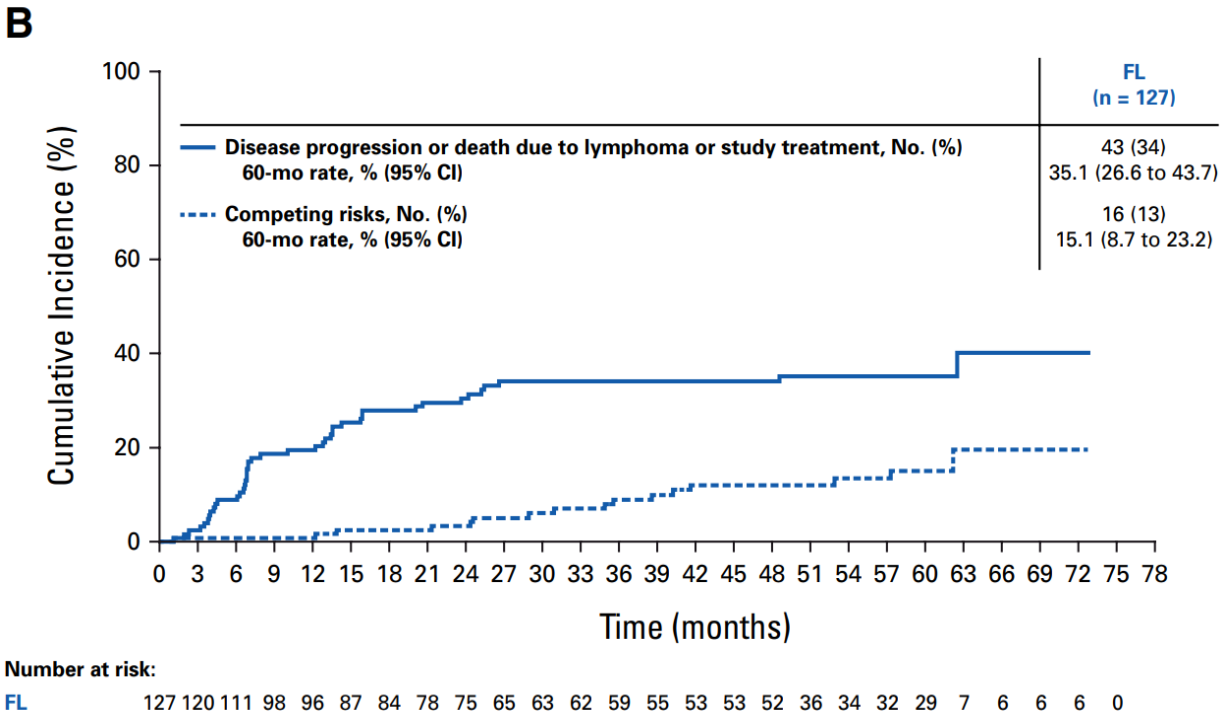
Jacobson C el Al. Lancet Oncology 2022

PFS after 5 years follow up



Neelapu, JCO, 2025

Cumulative incidence of DP or death due to lymphoma vs competing risk

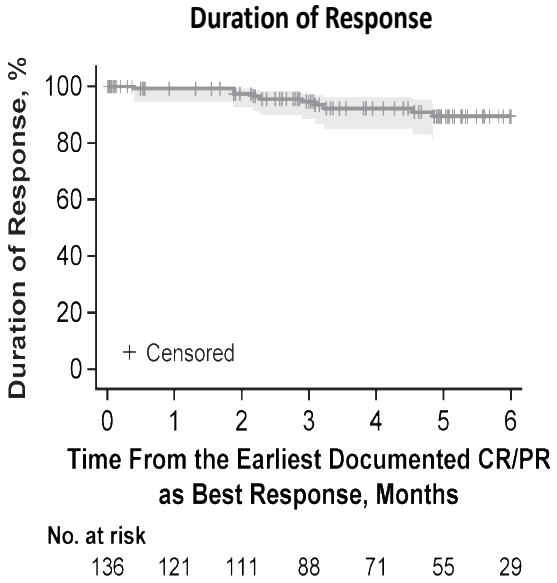


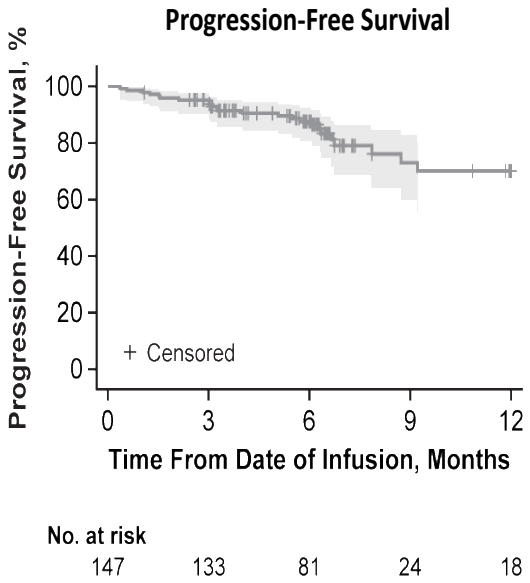
- Plateau after 2 years.
- Only 2 events after 30 m.

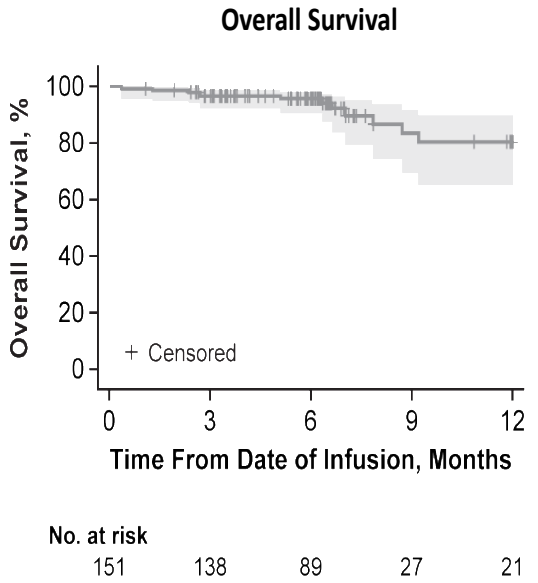
- **CURATIVE POTENTIAL?**

Neelapu, JCO, 2025

Real-Life Experience Axi-Cel: CIBMTR Analysis

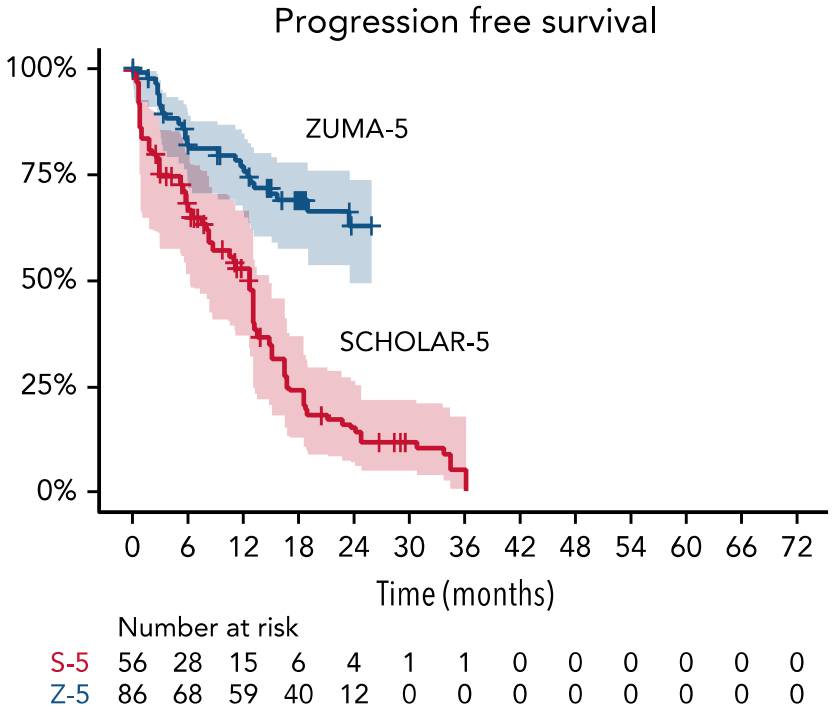


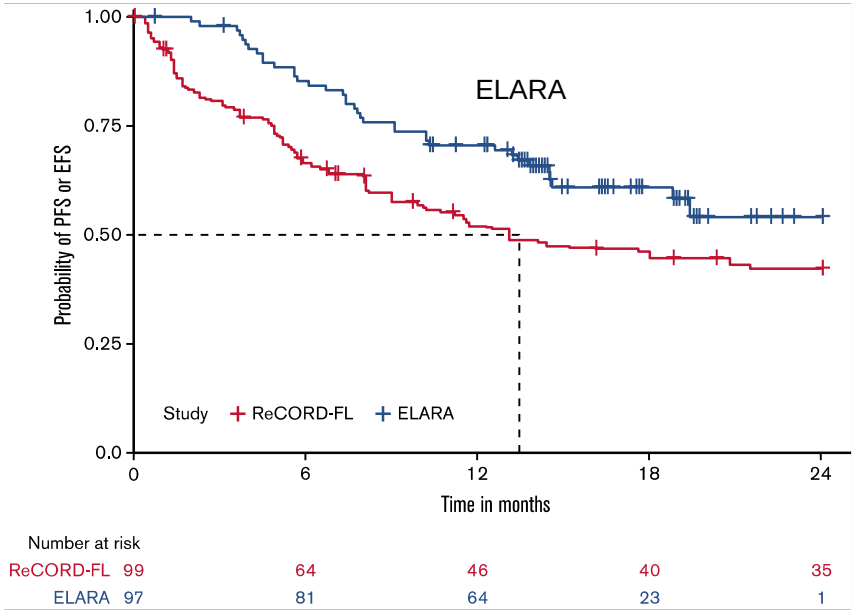




Jacobson C, et al. EHA;2023. Abstract: S223.

CAR-T compared with matched external cohort in R/R FL





Ghione P et al. Blood 2022, Salles G S et Al. Blood Advances 2023

Study of Axicabtagene Ciloleucel Versus Standard of Care Therapy in Participants With Relapsed/Refractory Follicular Lymphoma (ZUMA-22)

Inclusion Criteria

- Histologically-confirmed follicular lymphoma (FL) (Grade 1, 2, or 3a)
- Relapsed/refractory (R/r) disease after first-line chemoimmunotherapy and high-risk disease with relapse or progression within 24 months of the initial course of chemoimmunotherapy (ie, POD24), Or r/r disease after ≥ 2 prior systemic lines of therapy
- Clinical indication for treatment.
- At least 1 measurable lesion per the Lugano Classification {Cheson 2014}
- Adequate renal, hepatic, pulmonary, and cardiac function

Clinicaltrial. gov

R/R FL Subjects defined as: 1) POD24* after initiation of 1st line of therapy (2L POD24)
OR
2) All-comers after ≥ 2 prior lines of therapy (3L+ All-comers including POD24)

1:1 Randomization
n = Approximately 230, ~75 sites globally
Primary Endpoint: PFS

Stratification:

- 1 vs ≥ 2 prior lines
- POD24 vs Non-POD24
- US vs non-US site

Optional corticosteroid bridging

Axi-cel

Investigator Choice: R-CHOP, BR, or R2

Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study

Lihua E Budde, Laurie H Sehn, Matthew Matasar, Stephen J Schuster, Sarit Assouline, Pratyush Giri, John Kuruvilla, Miguel Canales, Sascha Dietrich, Keith Fay, Matthew Ku, Loretta Nastoupil, Chan Yoon Cheah, Michael C Wei, Shen Yin, Chi-Chung Li, Huang Huang, Antonia Kwan, Elicia Penuel, Nancy L Bartlett

Summary

Background Mosunetuzumab is a CD20×CD3 T-cell-engaging bispecific monoclonal antibody that redirects T cells to

Lancet Oncol 2022; 23: 1055–65

Epcoritamab monotherapy in patients with relapsed or refractory follicular lymphoma (EPCORE NHL-1): a phase 2 cohort of a single-arm, multicentre study

Kim M Linton, Umberto Vitolo, Wojciech Jurczak, Pieternella J Lugtenburg, Emmanuel Gyan, Anna Sureda, Jacob Haaber Christensen, Brian Hess, Hervé Tilly, Raul Cordoba, David John Lewis, Craig Okada, Martin Hutchings, Michael Roost Clausen, Juan-Manuel Sancho, Tara Cochrane, Sirpa Leppä, Martine E D Chamuleau, Diana Gernhardt, Işıl Altıntaş, Yan Liu, Tahamtan Ahmadi, Minh H Dinh, Daniela Hoehn, Elena Favaro, Brian Elliott, Catherine Thieblemont, Julie M Vose

Summary

Background A standard of care and optimal duration of therapy have not been established for patients with multiply relapsed or refractory follicular lymphoma. The aim of this study was to evaluate epcoritamab, a novel CD3×CD20 bispecific antibody, in the third-line and later setting of follicular lymphoma.

Lancet Haematol 2024
Published Online
June 15, 2024

Mosunetuzumab demonstrates durable responses in patients with relapsed and/or refractory follicular lymphoma who have received ≥2 prior therapies: updated analysis of a pivotal Phase II study

Laurie H. Sehn,[1] Nancy L. Bartlett,[2] Matthew Matasar,[3] Stephen J. Schuster,[4] Sarit Assouline,[5] John Kuruvilla,[6] Mazyar Shadman,[7] Chan Yoon Cheah,[8] Keith Fay,[9] Matthew Ku,[10] Loretta Nastoupil,[11] Michael C. Wei,[12] Shen Yin,[12] Iris To,[12] Nan Hu,[12] Juliana Min,[13] Elicia Penuel,[12] Anton Belousov,[14] Alexandre Coimbra,[12] Skander Jemaa,[12] Brendan Bender,[12] David Turner,[12] L. Elizabeth Budde[15]

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Presented at the 2023 International Conference Malignant Lymphoma (ICML) Annual Meeting | June 13–17, 2023

Baseline characteristics

	Patients with CR at EOT n=49	Patients without CR at EOT n=41	All patients N=90
Median age, years (range)	63 (29–90)	59 (35–83)	60 (29–90)
Female, %	47	29	39
ECOG PS, %			
0	61	56	59
1	39	44	41
Ann Arbor stage, %			
I/II	18	29	23
III/IV	82	71	77
Median lines of prior therapy, n (range)	3 (2–10)	3 (2–7)	3 (2–10)
Refractory to last prior therapy, %	55	85	69
Refractory to prior anti-CD20 therapy, %	71	88	79
Double refractory*, %	41	68	53
POD24, %	53	51	52
Prior autologous stem cell transplant, %	22	20	21
Prior bendamustine, %	59	73	66

Data cut-off date: July 8, 2022.

*Double refractory to prior anti-CD20 and alkylator therapy.

POD24, proportion of patients with progression of disease within 24 months after start of first-line therapy.

Longer follow-up data continue to demonstrate clinically meaningful outcomes

Pivotal Phase II study:
mosunetuzumab showed high rates of durable responses

Efficacy endpoint (best response)	IRF, N (%)
CR[1]	54 **(60%)**
ORR[1]	72 **(80%)**
24-month DoCR rate: 63%[2]	

Updated analysis:
high percentage of pts achieving CR at EOT*

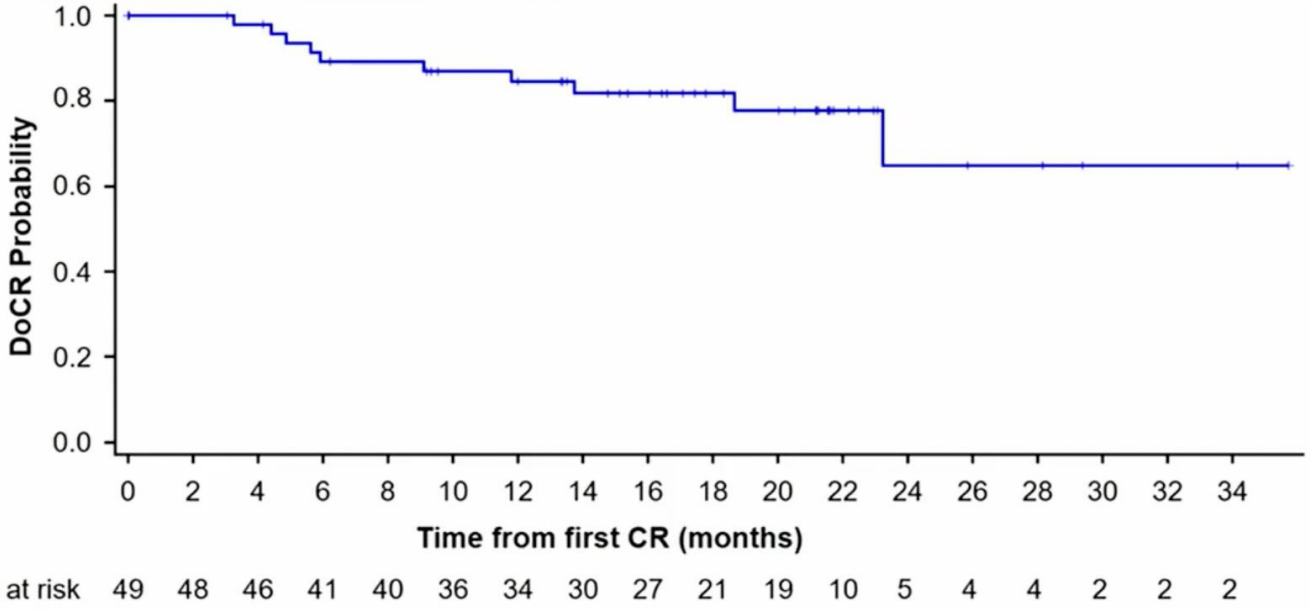
54 (60%) pts achieved CR as best response

- 49 pts (**54%**) achieved CR at EOT*
- 1 CR pt experienced PD in Cycle 8
  4 pts achieved CR after EOT due to delayed bone marrow confirmation of CR

Data cut-off date: July 8, 2022. *Defined as CR at the last assessment prior to EOT or within 30 days following EOT.
DoCR; duration of complete response; IRF, Independent Review Facility.

1. Budde LE, et al. Lancet Oncol 2022;23:1055–1065
2. Bartlett N, et al. ASH 2022; oral presentation.

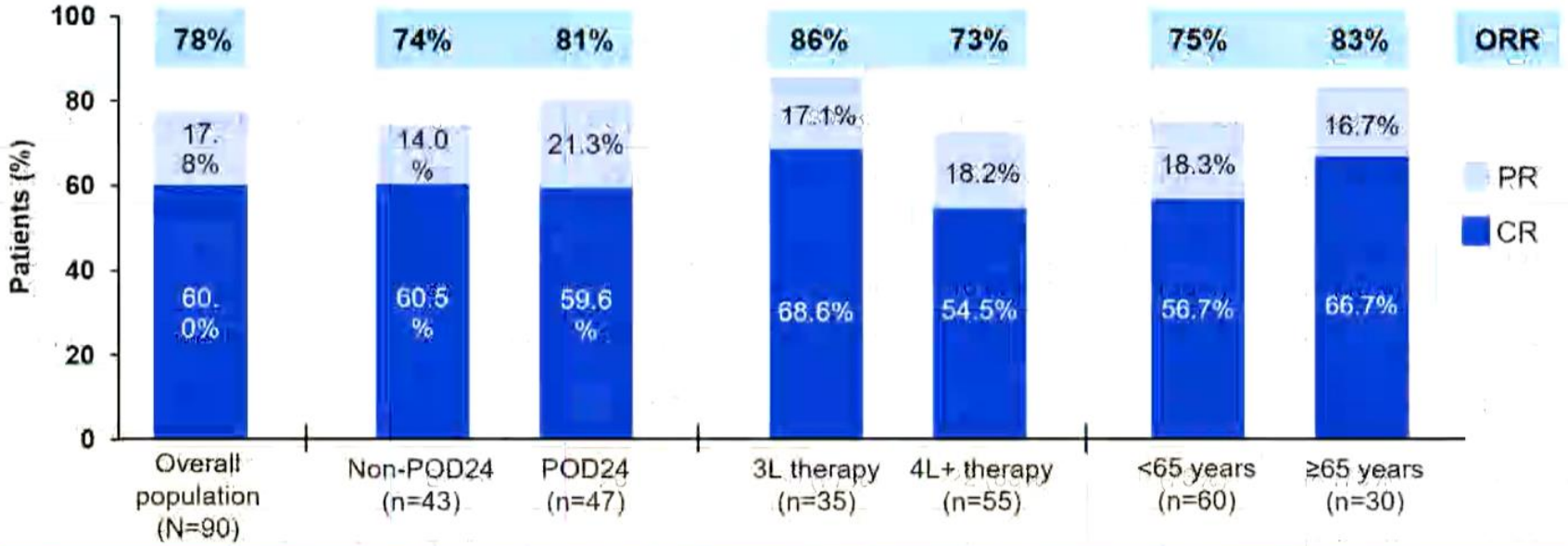
Durable responses were observed in patients who achieved a CR at EOT



	n=49
Median, months (95% CI)	**NE** (23.2–NE)
24-month DoCR, % (95% CI)	**65** (39.0–90.5)

Data cut-off date: July 8, 2022. NE, not estimable.

Efficacy summary: response rates

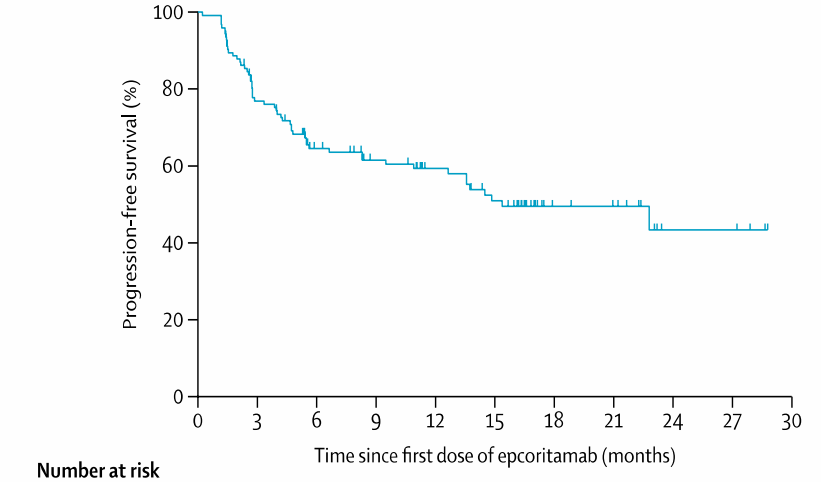


CR rates across high-risk subgroups were consistent with the overall population; higher CR rates were observed in patients who received mosunetuzumab in 3L than in the other subgroups

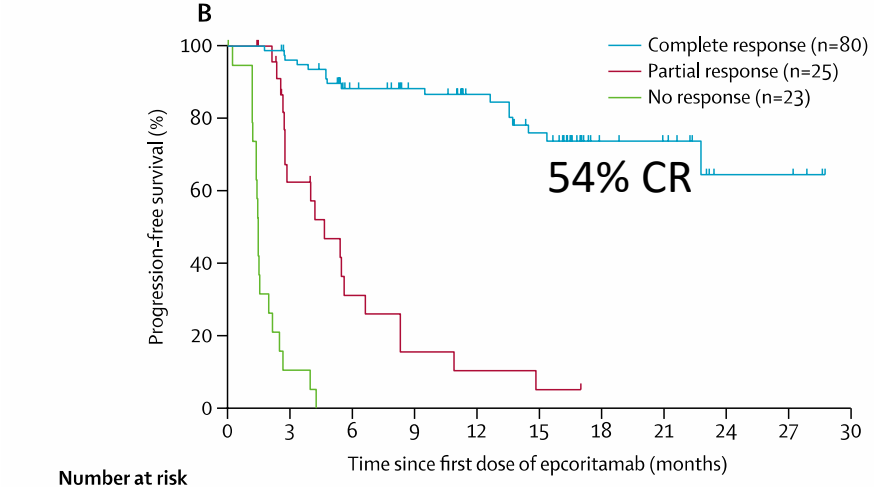
Conclusions

- Results after >3 years of follow-up demonstrate strong efficacy outcomes with fixed-duration mosunetuzumab treatment across high-risk subgroups in R/R FL
  - Durable remissions and PFS benefit in patients with POD24
  - Data suggest better DOCR and PFS outcomes with mosunetuzumab in earlier versus later lines of treatment
- The manageable safety profile was consistent across all subgroups, including patients aged ≥65 years
- Most infections occurred early; recovery of B cells and immunoglobulins was observed after completion of treatment
- Mosunetuzumab offers favorable benefit/risk to patients with R/R FL with a broad range of baseline and disease characteristics as an outpatient, fixed-duration therapy

EPCORITAMAB 3+L in RR FL



Number at risk (number censored)											
Pivotal cohort	128	90	67	57	43	35	14	12	4	4	0
	(0)	(10)	(19)	(26)	(38)	(40)	(60)	(62)	(69)	(69)	(73)



Number at risk (number censored)											
Complete response	80	75	61	54	41	34	14	12	4	4	0
	(0)	(2)	(10)	(17)	(29)	(31)	(50)	(52)	(59)	(59)	(63)
Partial response	25	13	6	3	2	1	0	0	0	0	0
	(0)	(4)	(5)	(5)	(5)	(5)	(6)	(6)	(6)	(6)	(6)
No response	23	2	0	0	0	0	0	0	0	0	0
	(0)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)

Grade 1-2 CRS in 65%, grade III in 2% in pivotal, and 49% in optimization cohort

FDA approvals for Bispecifics in FL

- On **December 22, 2022,** the Food and Drug Administration (FDA) granted accelerated approval to mosunetuzumab-axgb (Lunsumio, Genentech, Inc.), a bispecific CD20-directed CD3 T-cell engager for adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

- The target action date for the FDA decision is **March 31, 2024**. The FDA has granted odronextamab Orphan Drug Designation and Fast Track Designation for FL and DLBCL.

- On **June 26, 2024**, the Food and Drug Administration granted accelerated approval to epcoritamab-bysp (Epkinly, Genmab US, Inc.), a bispecific CD20-directed CD3 T-cell engager, for adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

. Autologous CAR-T offers high and durable CR rates
and is a **one-time potentially curative** option for selected 3L+ patients.

. Bispecific CD20×CD3 antibodies are now **approved, off-the-shelf options** with deep responses and durable remissions in heavily pretreated FL.

. Key unanswered questions: optimal sequencing, outpatient monitoring, access, and long-term immunosuppression/infection risk.

What other chemo free options available?

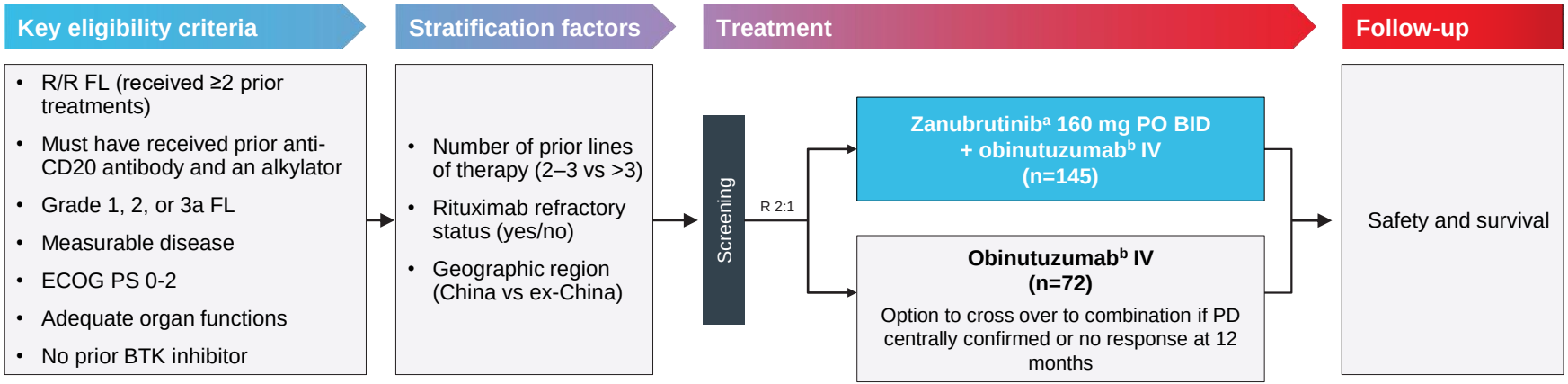
- Zanubrutinib + Obinutuzumab
- Tafa-Lena-Ritu en 2L

Zanubrutinib-Obinutuzumab. Rosewood study

Phase 2

Study Identifier: BGB-3111-212, NCT03332017

Primary Endpoint: ORR by ICR per Lugano Classification[3]
Key Secondary Endpoints: ORR by investigator, DOR and PFS by ICR, OS, CR and CMR rate



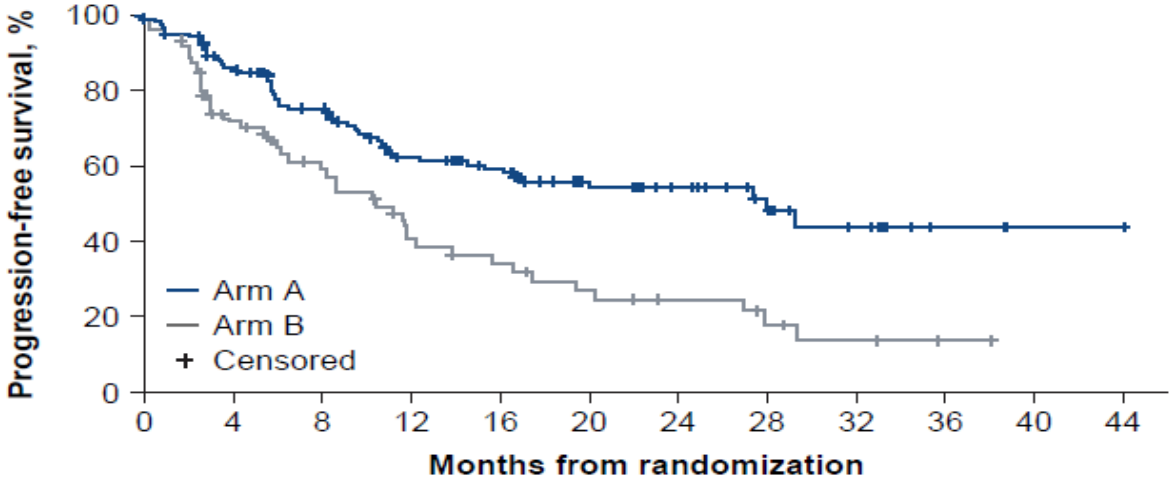
Zinzani PL et al. Journal of Clinical Oncology, 202359-3068.

Eficacy

Endpoint	Zanubrutinib + Obinutuzumab n = 145	Obinutuzumab n = 72	HR (95% CI)	2-sided P value
ORR by ICR, % (95% CI)	69 (61 to 76)	46 (34 to 58)	–	.001
CR, n (%)	57 (39)	14 (19)	–	.004
PR, n (%)	43 (30)	19 (26)	–	–
Median DOR by ICR, months (95% CI)	NE (25.3 to NE)	14.0 (9.2 to 25.1)	–	–
18-month rate, %	69 (58 to 78)	42 (23 to 60)	–	–
Median DO CR by ICR, months (95% CI)	NE (26.5 to NE)	26.5 (2.7 to NE)	–	–
18-month rate, % (95% CI)	87 (74 to 94)	51 (21 to 75)	–	–
Median PFS by ICR, months (95% CI)	28.0 (16.1 to NE)	10.4 (6.5 to 13.8)	0.50 (0.33 to 0.75)	< .001
Median TTNT, months	NE (33.4 to NE)	12.2 (8.5 to 17.3)	0.34 (0.22 to 0.52)	< .001
Median OS, months (95% CI)	NE (NE to NE)	34.6 (29.3 to NE)	0.62 (0.35 to 1.07)	.085
24-month rate, % (95% CI)	77 (68 to 84)	71 (58 to 81)	–	–

Zinzani PL et al. Journal of Clinical Oncology (2023)

PFS with Zanu-Obinu



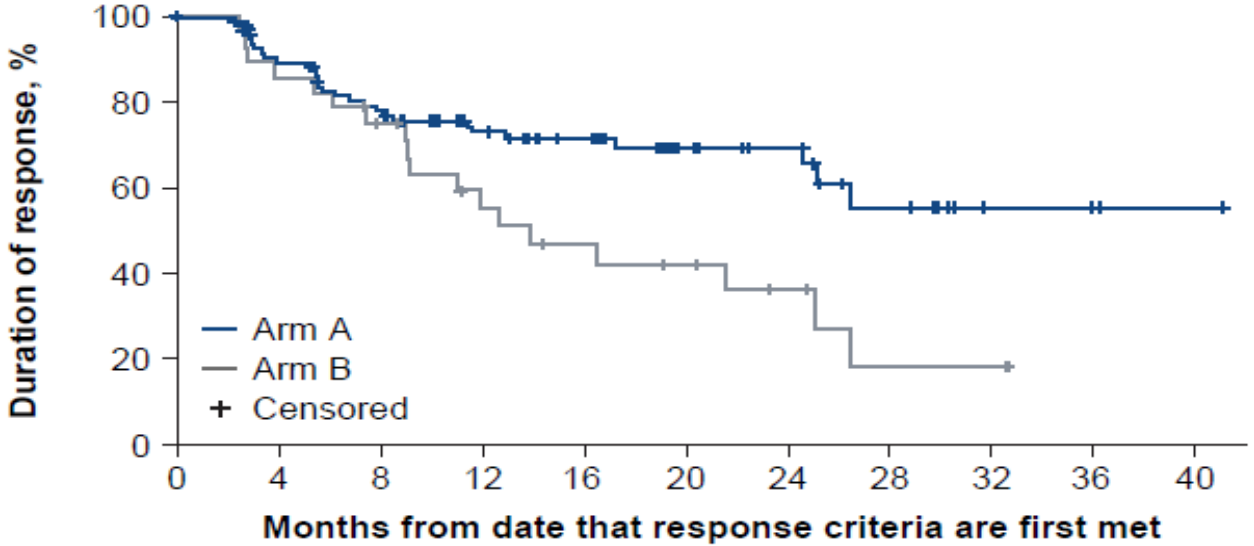
No. of patients at risk

Arm A	145	135	116	96	92	79	67	62	56	45	38	35	25	22	15	10	9	5	3	3	1	1	0
Arm B	72	63	42	34	30	27	19	16	15	12	11	9	8	8	5	3	3	2	1	1	0		

Median PFS by ICR, months (95% CI)	**28.0 (16.1 to NE)**	**10.4 (6.5 to 13.8)**	**0.50 (0.33 to 0.75)**	**< .001**

Zinzani PL et al. Journal of Clinical Oncology (2023)

Median duration of CR



No. of patients at risk

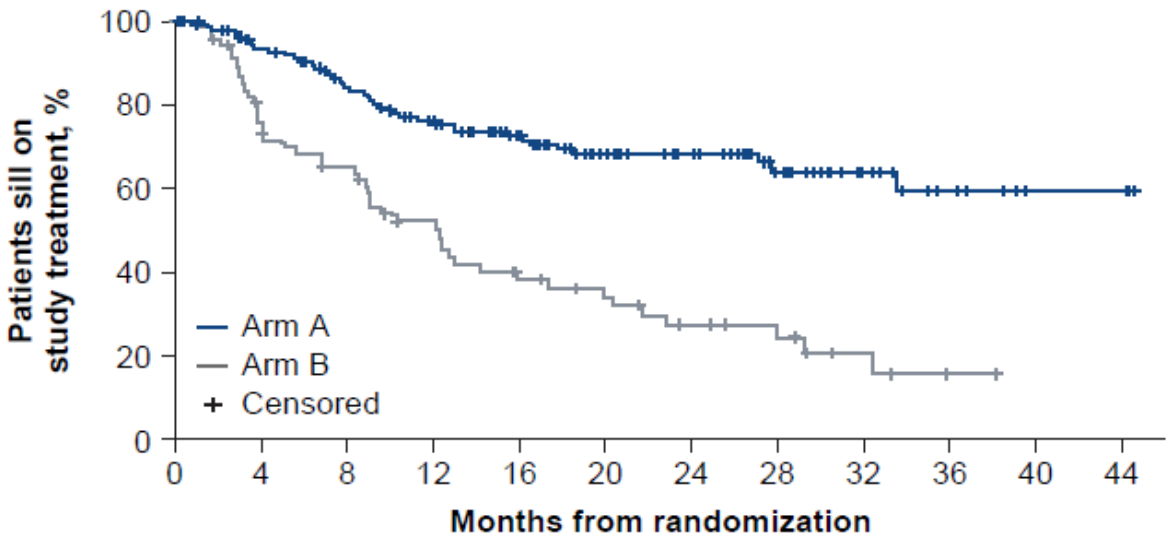
Arm A	100	97	82	73	68	59	51	43	40	33	23	21	19	12	10	7	3	3	2	1	1	0
Arm B	33	29	24	23	20	16	13	11	10	9	8	6	5	3	2	2	2	0				

Median DO CR by ICR, months (95% CI)	**NE (26.5 to NE)**	**26.5 (2.7 to NE)**	**–**	**–**

Zinzani PL et al. Journal of Clinical Oncology (2023)

Time to Next Antilymphoma Treatment

ROSEWOOD – Updated Analysis



No. of patients at risk

Arm A	145	137	125	118	107	98	91	80	71	62	53	47	44	40	29	22	17	12	10	6	3	3	3	0
Arm B	72	65	49	44	41	32	30	24	20	18	16	13	11	9	8	5	4	2	1	1	0			

- Time to next antilymphoma treatment was not estimable with zanubrutinib plus obinutuzumab versus 12.2 months with obinutuzumab
- For patients who did not crossover, median TTNT with obinutuzumab was 32.4 months (95% CI: 21.7, NE)
- After crossover, median TTNT was 18.2 months (95% CI: 10.7, NE)

Near future

-Combination of successful treatments.
    Bispecifics + Lena
    CART + combinations.

-New CART, new Bispecifics.

Fixed-Duration Epcoritamab Plus R² Drives Favorable Outcomes in Relapsed or Refractory Follicular Lymphoma

Context of Research

- Although R² is commonly used in R/R FL treatment, most patients experience relapse after R², and novel, chemotherapy-free treatments that lead to deep and durable responses, prolong time off treatment, and have manageable safety are needed
- Epcoritamab, a CD3xCD20 bispecific antibody, is approved as monotherapy for treatment of 3L+ FL and 3L+ DLBCL
- EPCORE NHL-2 arm 2 evaluated efficacy and safety of epcoritamab SC + R² in patients with 2L+ R/R FL

Patients and Methods

Key Inclusion Criteria: R/R CD20⁺ FL (grade 1–3A; stage II–IV) with ≥1 prior systemic treatment, including an anti-CD20 antibody

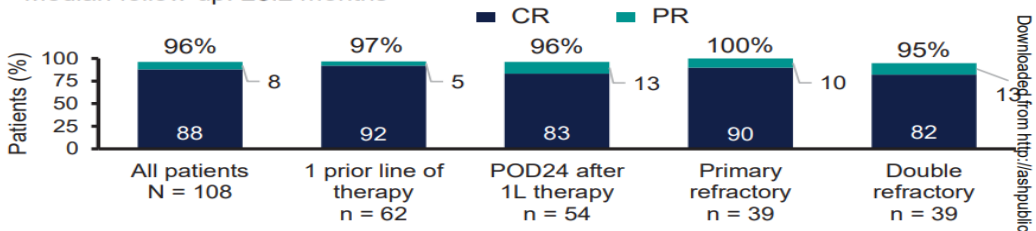
Primary Endpoint: ORR per investigator assessment

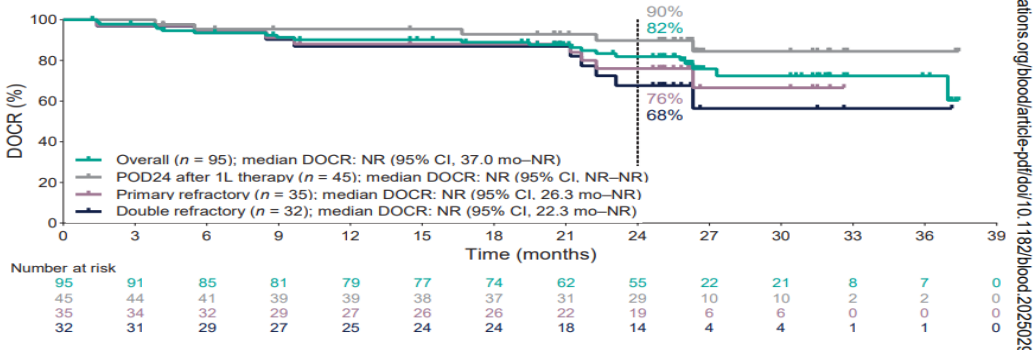
Fixed-duration epcoritamab SC 48 mg + rituximab IV + lenalidomide PO (28-day cycles up to 2 years)

Agent	Cycles					
	1	2	3	4–5	6–9	10+
Epcoritamab (2 SUD)						
Cohort A	QW			Q2W		Q4W
Cohort B	QW		Q4W			
Rituximab	QW	Q4W				
Lenalidomide	D1–21 of each cycle through C12					

Findings

- Median follow-up: 28.2 months





- The most common TEAEs were neutropenia (65%), COVID-19 (59%), and CRS (51%); CRS events were primarily low grade (49% grade 1–2, 2% grade 3), and all resolved; 1 ICANS event (grade 1) occurred

Conclusions: With more than 2 years of follow-up, fixed-duration epcoritamab plus R² showed deep, durable responses with favorable outcomes in R/R FL regardless of risk features, with manageable safety and no new safety signals. These results support further investigation of this combination in the phase 3 trial EPCORE FL-1, which is evaluating fixed-duration epcoritamab (1 year) plus R².

Falchi et al. DOI

Management of RR FL in 2025

- ✓ Chemo-inmunotherapy still has a role and novel approaches give new options.
- ✓ Patients have a long OS and possible “functional cure”.

Is 2025 offering a change in long standing paradigmas in RR FL?

- ✓ New therapies (CAR-T, bispecific CD20×CD3 antibodies, and zanubrutinib + obinutuzumab) have extended progression-free intervals in relapsed FL.
- ✓ Whether POD24 retains the same negative prognostic impact in the era of these agents remains uncertain.

The wide availability of new therapeutic agents, is improving prognosis of FL, and patients, **even high risk patients** may enjoy prolonged long-term survival.

The challenge is not to choose a winner, but to select the best treatment sequence in a personalized way.

Las cosas cambiaron … en algunas partes del mundo

- **En LATAM, los desafíos son distintos.**
  - Acceso limitado a terapias celulares o biespecíficas.
  - Necesitamos fortalecer los caminos de derivación, el diseño de estudios propios, y la articulación con el sistema de salud para que mas pacientes accedan a estas oportunidades.

Opinion de la oradora.

Estamos frente a la **etapa más transformadora del tratamiento del LNH**.

El progreso no será real hasta que esté **disponible, secuenciado con lógica clínica**, y adaptado a las **realidades locales**.

MUCHAS GRACIAS.

astridp@intramed.net

Thank you!

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Thank you!

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