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# Getting into trouble in Follicular and Mantle Cell Lymphoma: How targeted and Cellular Therapies can rescue us?

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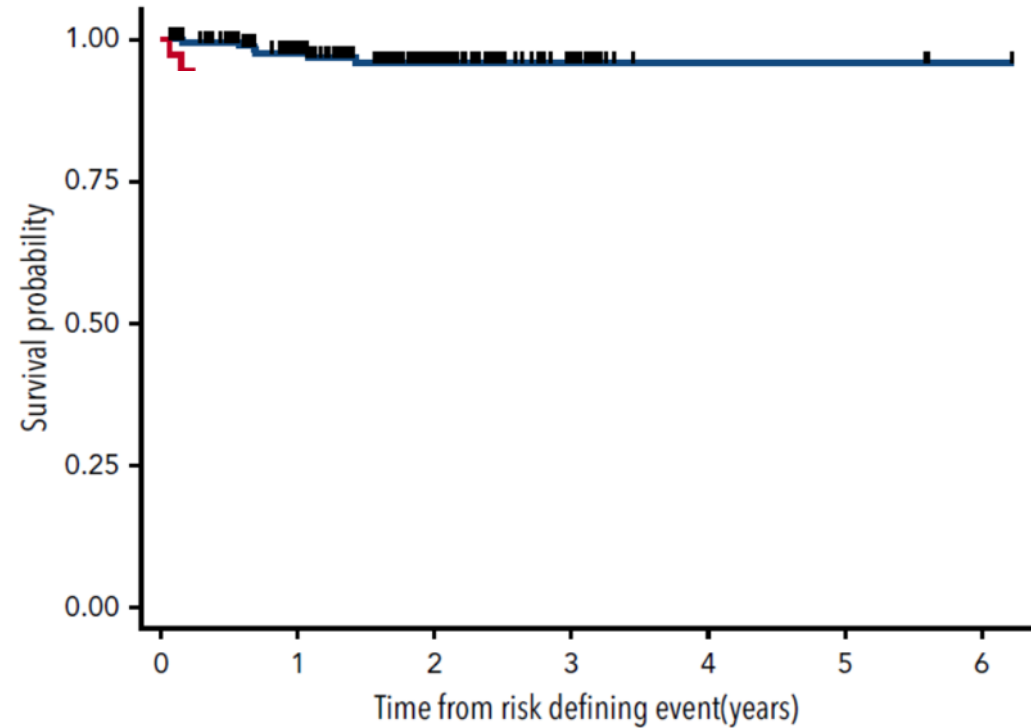
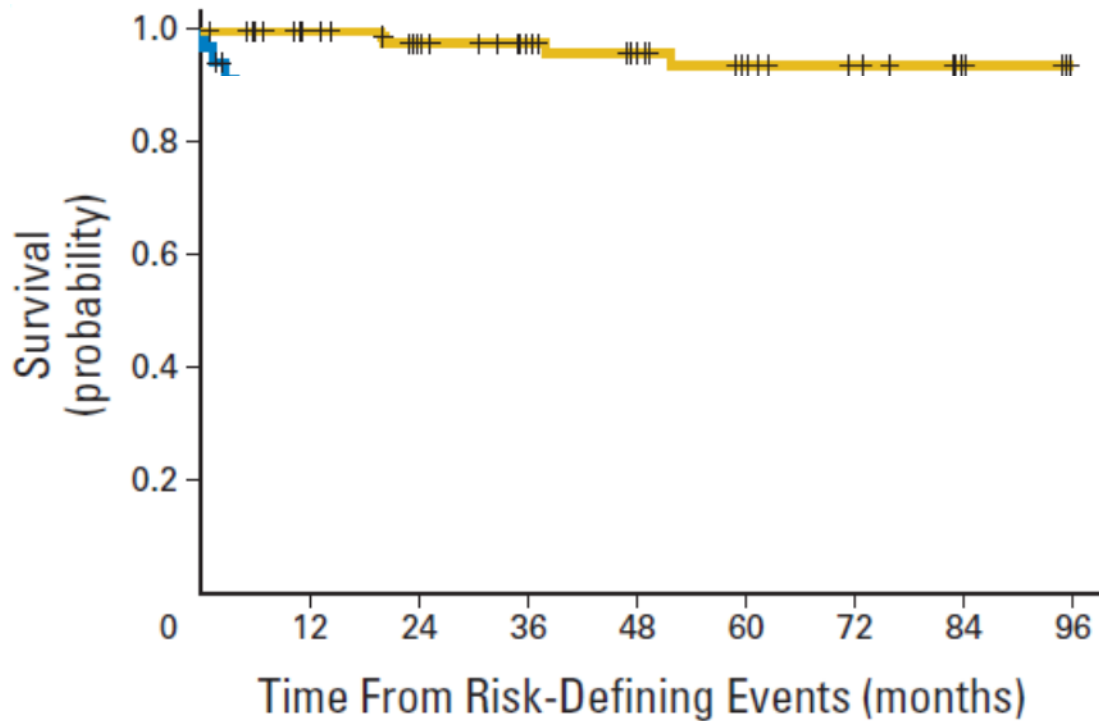
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## Relapsed FL:

We have many options and life expectancy is 10+ years  
Do we need cell therapies?

# Progression of disease > 24 months

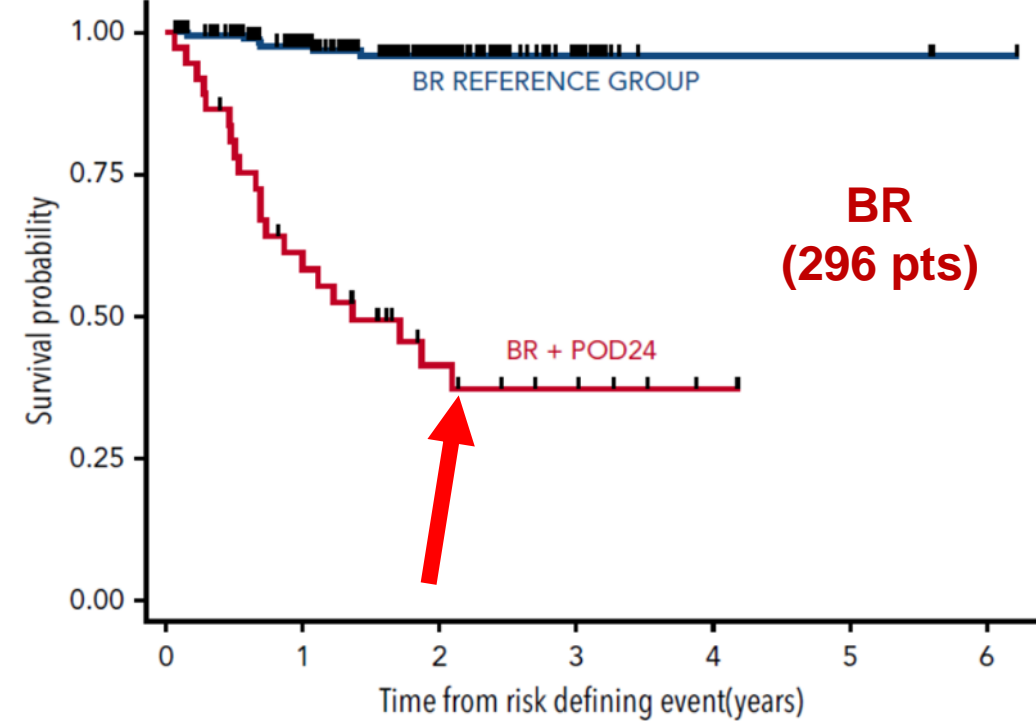
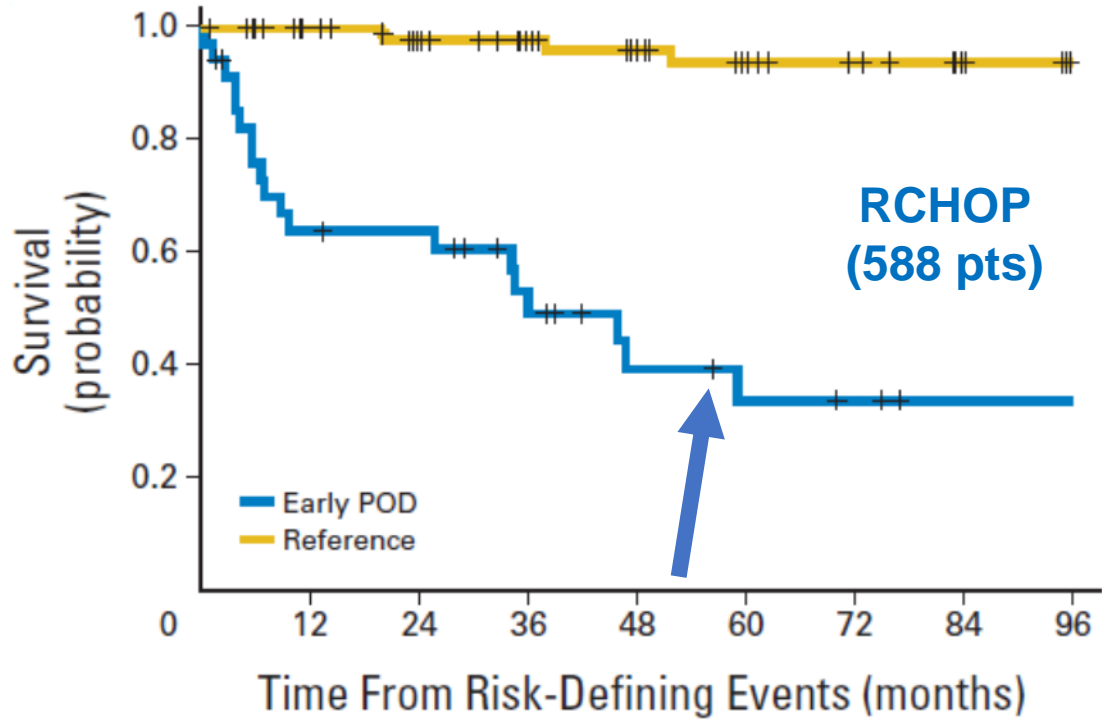


Number at risk

BR ref	198	135	52	11	3	3	1
POD24	37	20	10	6	2	1	1

***Casulo C et al, JCO 2015; Freeman CL et al, Blood 2019***

# Progression of disease < 24 months



Number at risk

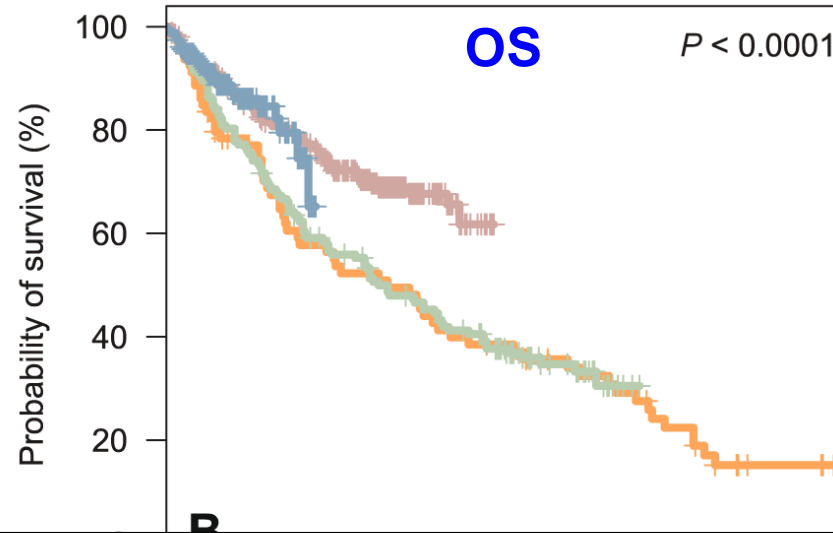
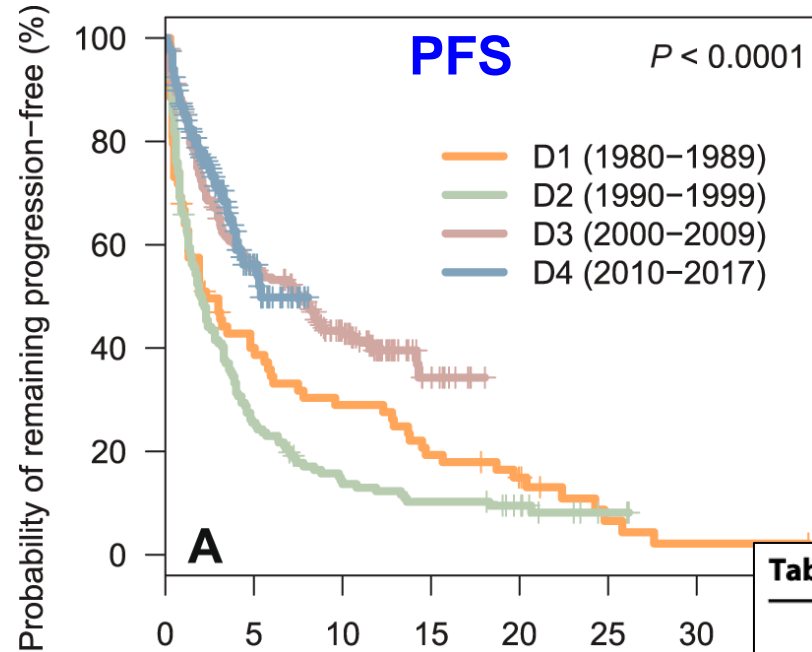
BR ref	198	135	52	11	3	3	1
POD24	37	20	10	6	2	1	1

*Casulo C et al, JCO 2015; Freeman CL et al, Blood 2019*

## **We are in trouble – now what?**

For early progressing relapsed or refractory FL –  
there is a real risk of death from lymphoma.  
We need effective treatment options

# Advanced stage FL is not curable! (except with allogeneic SCT)



**No. at risk:**

	0	5	10	15	20	25	30
D1 (1980–1989)	78	29	21	14	9	3	1
D2 (1990–1999)	158	40	21	15	10	2	0
D3 (2000–2009)	239	126	69	11	0	0	0
D4 (2010–2017)	198	29	0	0	0	0	0

**Table 3 Causes of death in the 204 patients who died within the first 10 years after diagnosis.**

	Entire cohort (n = 204)	Decade 1 (1980–1989) (n = 36)	Decade 2 (1990–1999) (n = 71)	Decade 3 (2000–2009) (n = 66)	Decade 4 (2010–2017) (n = 31)
Progression of FL (%)	111 (54)	22 (61)	47 (66)	28 (42)	14 (45)
Complications of therapy (%)	18 (9)	1 (3)	5 (7)	9 (14)	3 (10)
Other neoplasms (%)	31 (15)	3 (8)	9 (13)	16 (24)	3 (10)
Others/unknown (%)	44 (22)	10 (28)	10 (14)	13 (20)	11 (35)

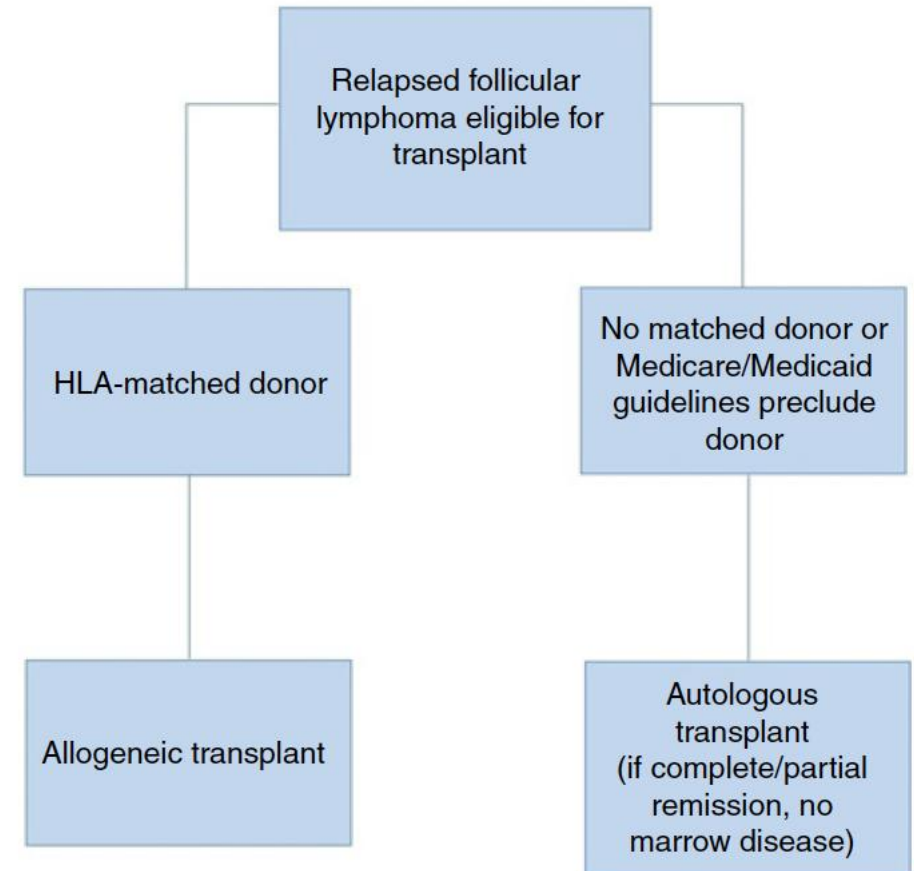
The Others/unknown group is composed of 23 patients (11%) dying of other causes (mainly geriatric complications and cardiovascular disease), and 21 patients (10%) for whom information concerning the exact cause of death was not available.

# Stem Cell Transplant

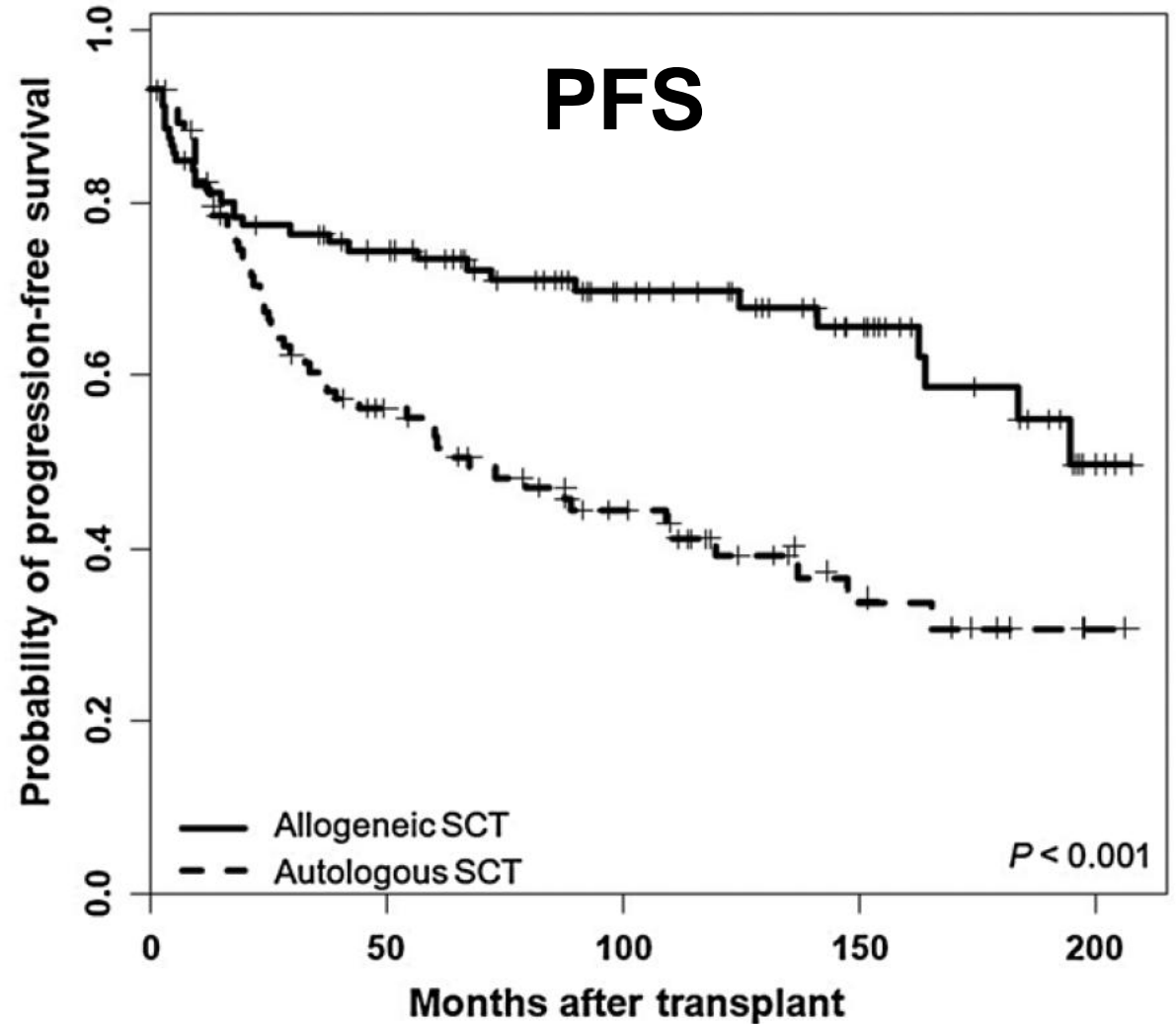
CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

## Nine-Year Follow-up of Patients with Relapsed Follicular Lymphoma after Nonmyeloablative Allogeneic Stem Cell Transplant and Autologous Transplant

Issa F. Khouri<sup>1</sup>, Denái R. Milton<sup>2</sup>, Alison M. Gulbis<sup>3</sup>, Elias J. Jabbour<sup>4</sup>, Loretta Nastoupil<sup>5</sup>, Celina Ledesma<sup>1</sup>, Paolo Anderlini<sup>1</sup>, Qaiser Bashir<sup>1</sup>, May Daher<sup>1</sup>, Jin S. Im<sup>1</sup>, Swaminathan P. Iyer<sup>5</sup>, David Marin<sup>1</sup>, Rohtesh S. Mehta<sup>1</sup>, Amanda L. Olson<sup>1</sup>, Uday R. Popat<sup>1</sup>, Muzaffar Qazilbash<sup>1</sup>, Neeraj Saini<sup>1</sup>, Felipe Samaniego<sup>5</sup>, Gabriela Rondon<sup>1</sup>, L. Jeffrey Medeiros<sup>6</sup>, and Richard E. Champlin<sup>1</sup>



Characteristic	Stem cell transplant type		P
	Allogeneic (n = 98)	Autologous (n = 96)	
Age			
Median	53 y	56 y	0.031
Range	29-71 y	33-77 y	
Age >60 y, No. (%)	24(24)	32(33)	0.21
Sex, No. (%)			
Male	49(50)	46(48)	0.78
Female	49(50)	50(52)	
HCT-CI >3, No. (%)	11(11)	18(19)	0.16
No. of prior therapies			
Median	3.0	2.0	<0.001
Range	1.0-9.0	1.0-9.0	
≤2, No. (%)	39(40)	59(61)	0.003
>3, No. (%)	59(60)	37(39)	
Prior treatment exposure, No. (%)			
R-CHOP induction at diagnosis	54(55)	66(69)	0.056
Anthracyclines	89(91)	82(85)	0.27
Rituximab	91(93)	96(100)	0.014
Ibrutinib	4(4)	0	0.12
Lenalidomide	7(7)	1(1)	0.06
autoSCT	7(7)	0	0.014
Relapse ≤2 y from induction, No. (%)	71(72)	61(64)	0.22
Timing of transplant, No. (%)			
First relapse	37(38)	56(58)	0.006
Second relapse or beyond	61(62)	40(42)	
Disease status at transplant, No. (%)			
CR	45(46)	49(51)	0.018
PR	37(38)	43(45)	
PD	16(16)	4(4)	



alloSCT	98	72	42	25	4
autoSCT	96	48	29	11	1

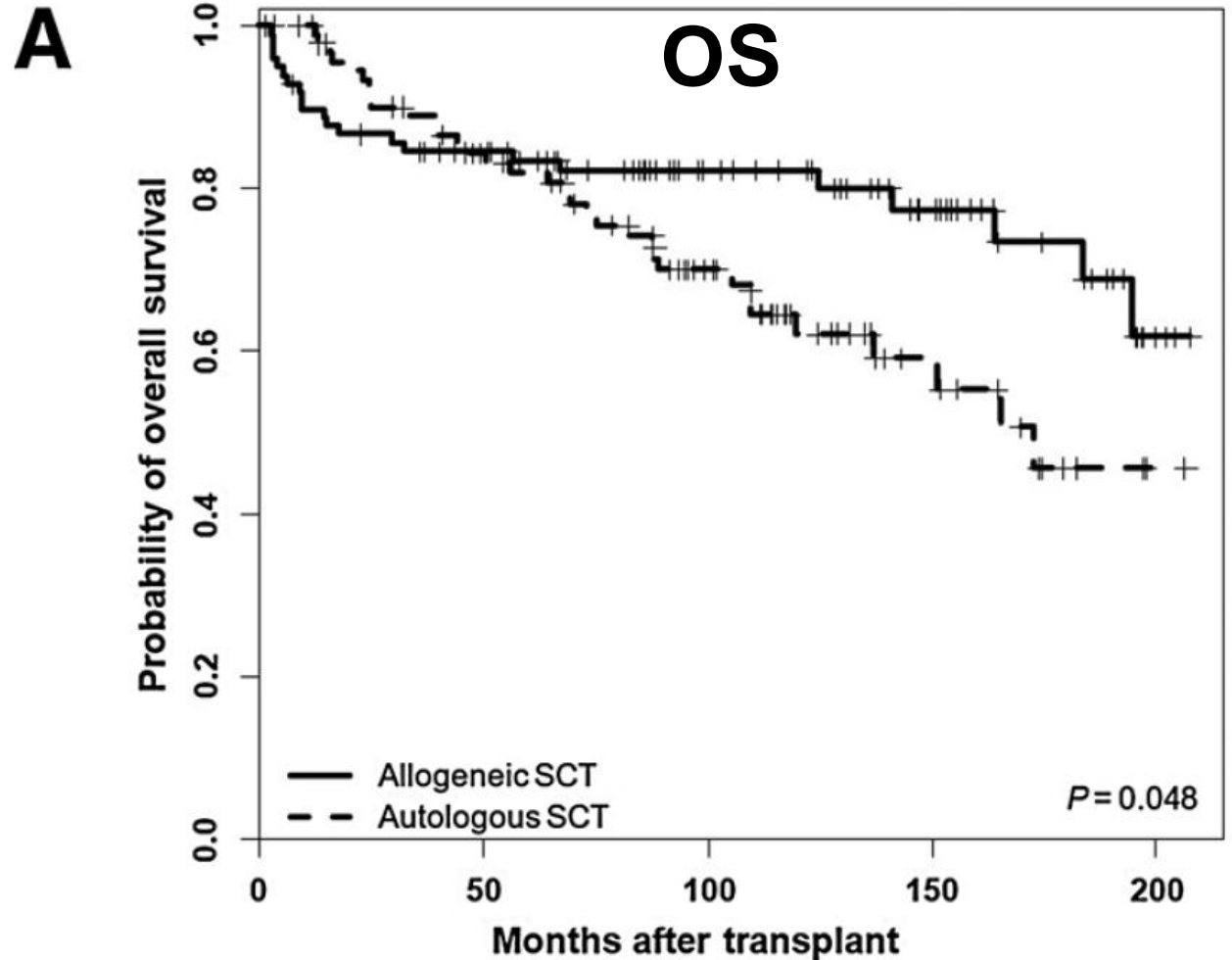
In the Allo group:

- 22 deaths
  - acute (n=3) or chronic (n=4) GVHD
  - infection (n=4)
  - disease progression (n=4)
  - unknown causes (n=6)

In the Auto group:

- 11 developed MDS
- 33 deaths
  - MDS (n =9)
  - disease progression (n=15)
  - infection (n = 3)
  - other (n=6)

NRM was allo 15% and auto 11%



alloSCT	98	76	45	27	4
autoSCT	96	70	43	16	1

# What targeted therapies may overcome bad FL?

CAR T-cells

Bispecific antibodies

# Bispecifics vs CAR T-cells in FL

CAR T-cells	Mosunetuzumab/Epcoritamab
Excellent efficacy with longer follow up	Excellent efficacy with shorter follow up
Requires 3-4 weeks of manufacturing	Off the shelf
Logistically more complex, \$\$\$	Logistically less complex, \$\$
"One and done" for life	Time-limited vs. indefinite (can be repeated (mosun only))
Needs lymphodepleting chemo	No lymphodepleting chemo
Higher risk of CRS (axi-cel) and neurotoxicity	Lower risk of CRS (as compared to axi-cel) and neurotoxicity
Usually inpatient	Usually outpatient

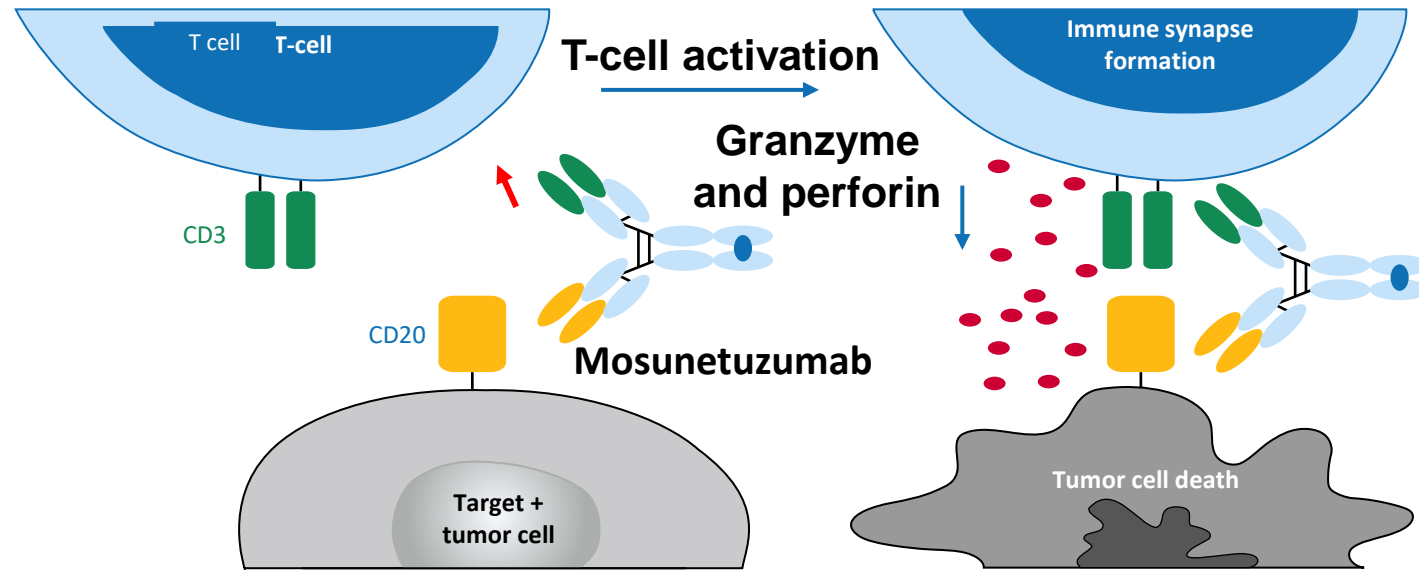
# Efficacy and Safety

Drug	N	ORR	CR	mPFS	CRS	Grade 3+	ICANS	Grade 3+
Mosunetuzumab	90	78%	60%	24 m	44.4%	2.2%	3%	0
Epcoritamab	128	82%	63%	49.4%*	65%	2%	6%	0
(Optimization)	86				49%	0%	N/A	
Odronextumab	68	81.8%	75.2%	20.7 m	56%	6%	N/A	
(Optimization)	60				56.7%	1.7%		
Axi-cel	127	94%	75%	62.2 m	82%	7%	59%	19%
Tisa-cel	97	86.2%	68.1%	57.4% <sup>+</sup>	49%	0%	4%	1%
Liso-cel	124	97%	94%	NR	58%	1%	15%	2%

\* 18 months

<sup>+</sup>24 months

**Mosun: CD20xCD3 T-cell engaging bispecific antibody redirects T cells to engage and eliminate B cells<sup>2,3</sup>**



# Mosunetuzumab Subgroup Analysis Study Schema

## Subgroup analysis from the updated analysis at ASH 2023 (median follow-up of 37.4 months)<sup>1</sup>

### Key inclusion criteria<sup>2</sup>

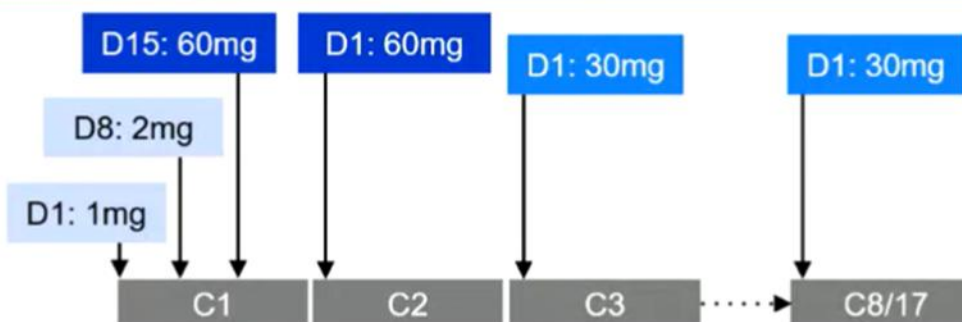
- R/R FL Grade 1–3a
- ≥2 prior therapies including an anti-CD20 antibody and an alkylator
- ECOG PS 0–1

### Data analysis

- Subgroups evaluated for investigator-assessed efficacy and safety:
  - History of POD24
  - 3L versus 4L+
  - Age <65 years versus ≥65 years

### Mosunetuzumab administration<sup>2</sup>

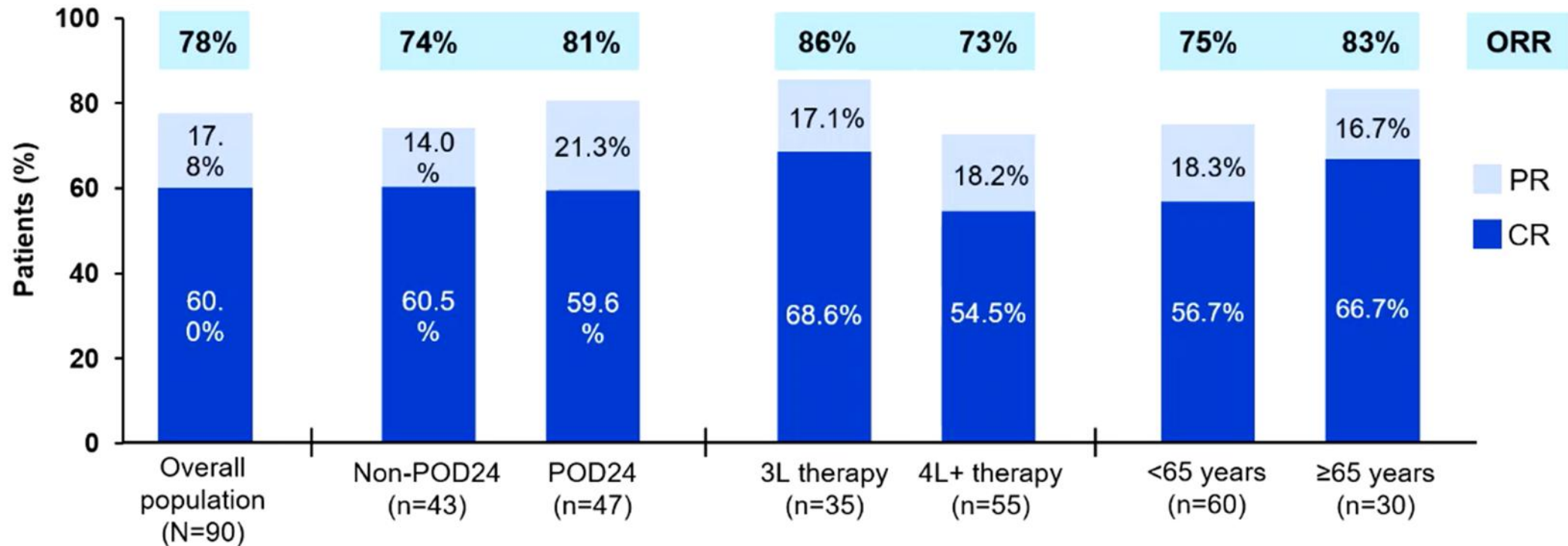
- Intravenous mosunetuzumab (21-day cycles); step-up dosing in C1
- Fixed-duration treatment: eight cycles (if CR after C8) or 17 cycles (if PR/SD after C8)
- No mandatory hospitalization



3L, third-line; 4L, fourth-line; C, cycle, D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; POD24, progression of disease within 24 months from start of 1L therapy; PR, partial response; SD, stable disease.

1. Schuster SJ, et al. ASH 2023; Oral presentation (abstract #603);  
2. Budde LE, et al. Lancet Oncol 2022;23:1055–65.

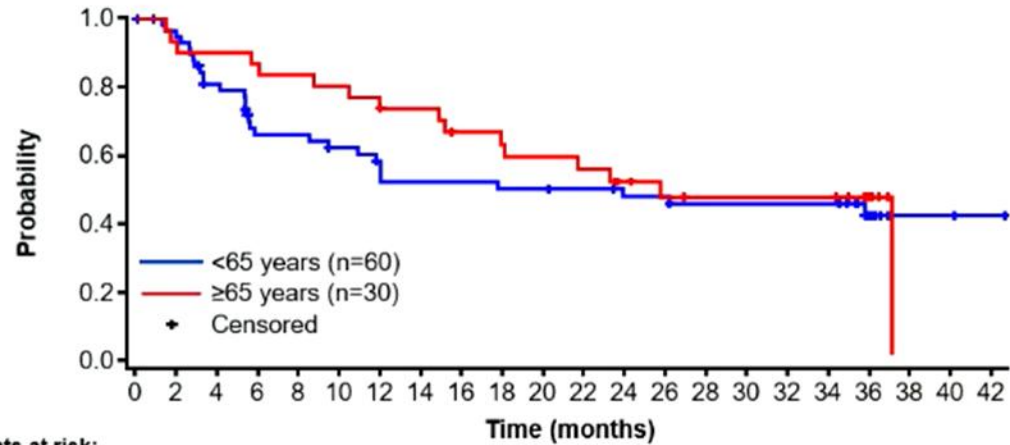
# Response Rates and Risk Group



**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**

# PFS and OS: <65 versus ≥65 years

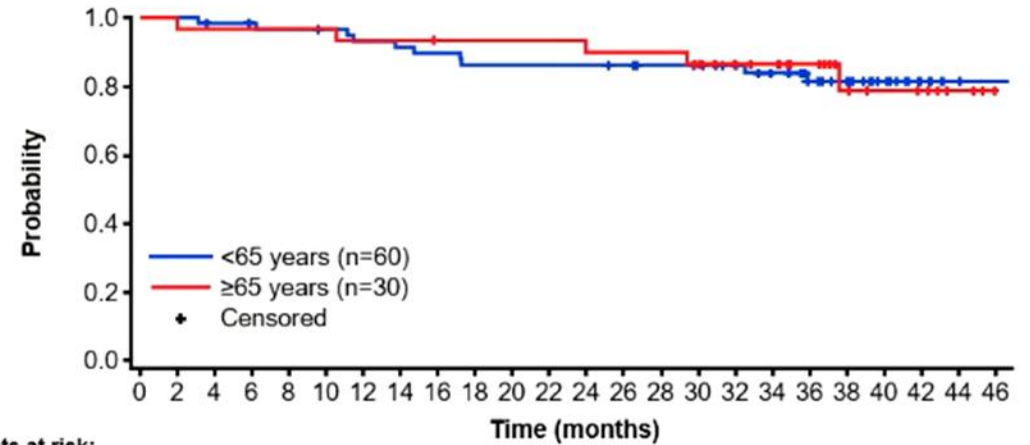
## PFS



Patients at risk:

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42
<65 years	60	54	44	34	34	31	25	25	25	24	24	23	21	21	19	19	19	19	19	10	2	1
≥65 years	30	27	27	26	25	24	22	21	18	17	16	15	12	10	9	9	9	9	6	NE	NE	NE

## OS



Patients at risk:

Time (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46
<65 years	60	60	58	57	56	55	53	52	51	49	49	49	49	48	46	44	39	36	30	25	17	11	4	1
≥65 years	30	29	29	29	29	29	28	28	27	27	27	27	26	26	26	22	20	19	15	9	8	5	3	NE

	Overall population (N=90)	<65 years (n=60)	≥65 years (n=30)
Median PFS, months (95% CI)	24.0 (12.0–NE)	17.8 (9.4–NE)	25.8 (15.2–NE)
36-month PFS, % (95% CI)	43 (31.8–54.7)	42 (27.3–55.8)	47 (28.1–65.8)

	Overall population (N=90)	<65 years (n=60)	≥65 years (n=30)
Median OS, months (95% CI)	NR (NE)	NR (NE)	NR (NE)
36-month OS, % (95% CI)	83 (74.6–91.2)	81 (70.6–91.9)	86 (74.0–98.8)

**36-month PFS and OS rates in patients ≥65 years were consistent with the overall population**

# CRS Rates

AE	Overall population (N=90)	POD24 status		Line of therapy		Age	
		Non-POD24 (n=43)	POD24 (n=47)	3L therapy (n=35)	4L+ therapy (n=55)	<65 years (n=60)	≥65 years (n=30)
<b>CRS by ASTCT<sup>1</sup></b>	40 (44%)	16 (37%)	24 (51%)	14 (40%)	26 (47%)	31 (52%)	9 (30%)
Grade 1	23 (26%)	10 (23%)	13 (28%)	9 (26%)	14 (26%)	17 (28%)	6 (20%)
Grade 2	15 (17%)	5 (12%)	10 (21%)	4 (11%)	11 (20%)	13 (22%)	2 (7%)
Grade 3	1 (1%)	1 (2%)	0	0	1 (2%)	0	1 (3%)
Grade 4	1 (1%)	0	1 (2%)	1 (3%)	0	1 (2%)	0
<b>Neutropenia</b>	26 (29%)	7 (16%)	19 (40%)	10 (29%)	16 (29%)	19 (32%)	7 (23%)
<b>Serious infections</b>	18 (20%)	5 (12%)	13 (28%)	8 (23%)	10 (18%)	13 (22%)	5 (17%)

**The incidence of serious infections in patients ≥65 years was consistent with the overall population**

# Mosunetuzumab

## Three-Year Follow-Up of Mosunetuzumab for the Treatment of Patients with Relapsed or Refractory Follicular Lymphoma (R/R FL) after $\geq 2$ Prior Therapies

### Context of Research

Mosunetuzumab is a CD20xCD3 T-cell engaging bispecific antibody that redirects T cells to eliminate malignant B cells

### Aim of This Study

ClinicalTrials.gov ID **NCT02500407** is an ongoing phase 1/2 dose-escalation study of mosunetuzumab as a single agent in patients with R/R FL

### Outcomes

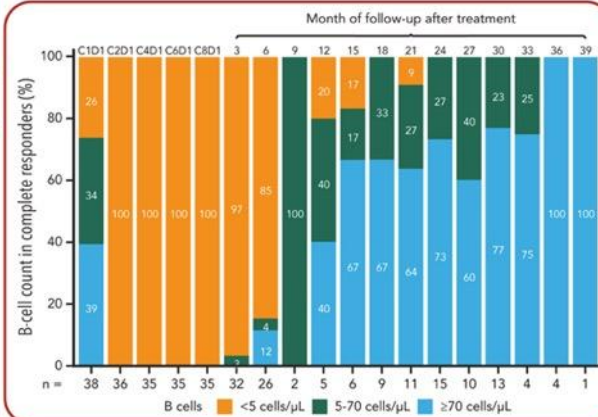
#### Key efficacy results



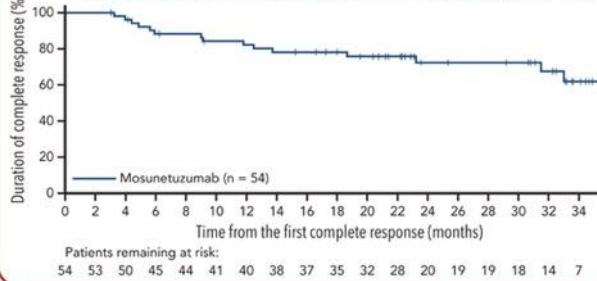
#### Key safety results



Median time to B-cell recovery was 18.4 months in patients who had a CR after 8 cycles of fixed-duration mosunetuzumab treatment

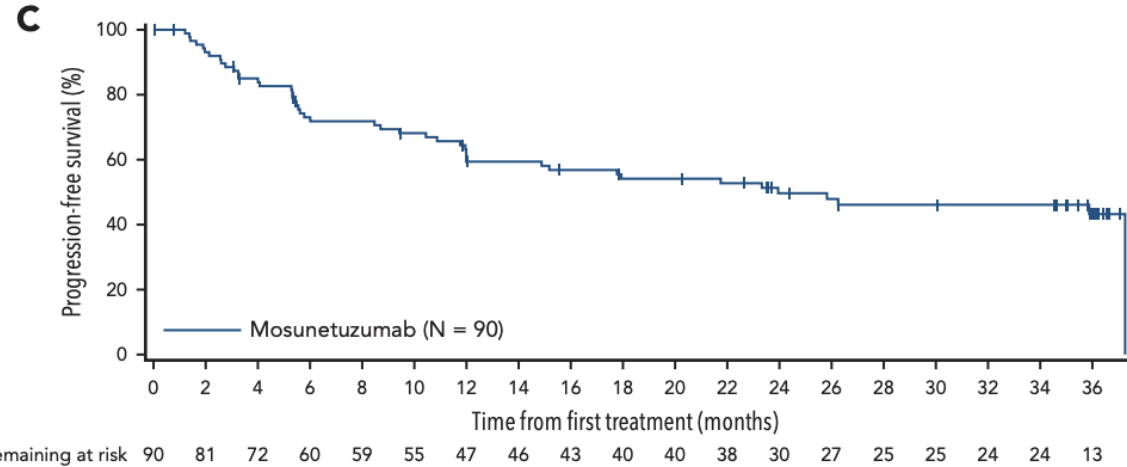


#### Median duration of CR was not reached (95% CI, 33.0-NE)



**Conclusion:** At a median follow-up of 37.4 months, fixed-duration mosunetuzumab demonstrated high response rates, durable remissions, and manageable safety in patients with R/R FL after  $\geq 2$  prior therapies.

Sehn et al. DOI: 10.1182/*blood*.2024025454



# Mosunetuzumab in 1L FL

Falchi et al. Abstract #30

## SC mosun in 1L FL

## Phase 2 study overview

### Endpoints:

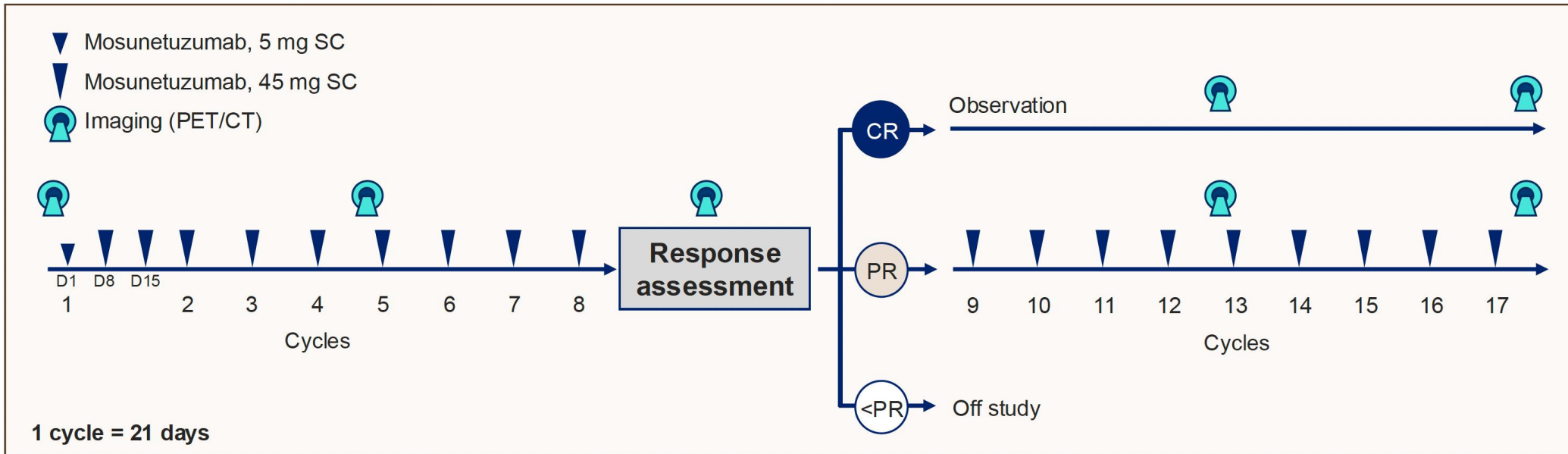
- **Primary:** CR rate per Lugano
- **Secondary:** ORR, safety, PFS, DOR, TTNT, OS
- **Exploratory:** PD, ctDNA monitoring

### Eligibility:

- ≥18 years; PS 0-2
- CD20+ previously untreated FL,
- G1-3A, stage II-IV
- **Need of therapy per GELF criteria**

### Outpatient administration:

- Dexamethasone, anti H2, acetaminophen in C1 (and C2 if prior CRS)
- VZV and PJP prophylaxis and GCSF support per treating physician



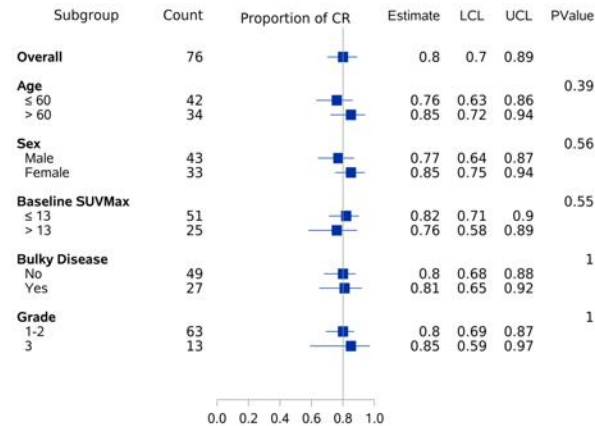
Patients who experience progression at any time point were taken off study; CR, complete response; ORR, overall response rate; PFS, progression-free survival; DOR, duration of response; OS, overall survival; PD, progressive disease; ctDNA, circulating tumor DNA; CRS, cytokine release syndrome; VZV, Varicella Zoster virus; PJP, *Pneumocystis Jirovecii* pneumonia; GCSF, granulocyte colony stimulating factor; PET/CT, positron emission tomography/computerized tomography; PR, partial response

# Mosunetuzumab in 1L FL

## SC mosun in 1L FL

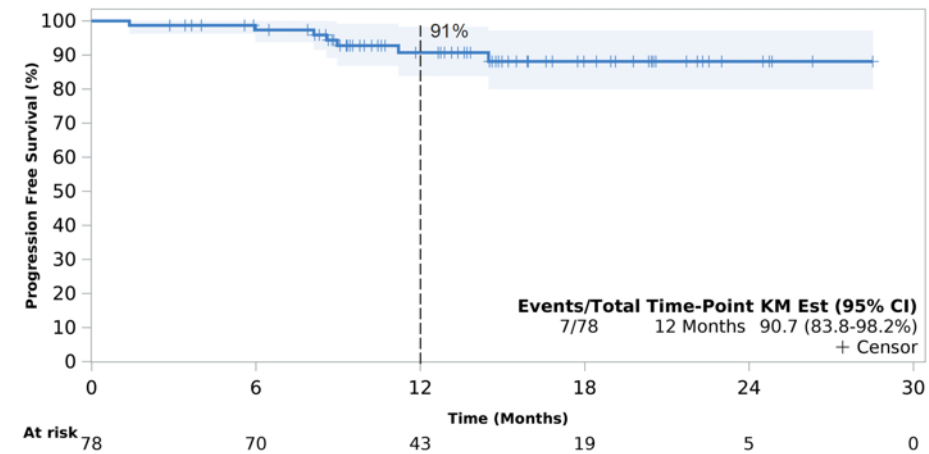
Complete response rates were consistently high

Response type	Response evaluable (N=76)	Intention-to-treat (N=78)
Overall response	96%	94%
Complete response	80%	78%
Partial response	16%	15%
Stable disease	3%	3%
Progressive disease	1%	1%
Non-evaluable	n/a	3%



## SC mosun in 1L FL

Progression Free Survival



- An estimated 91% of patients remained progression-free at 1 year
- 7 patients progressed:
  - 3 patients had CD20-POD with FL histology
  - 3 patients had transformation to CD20+ DLBCL (one 6 weeks after study entry); after chemoimmunotherapy all achieved CR

Data cutoff: November 1, 2024; response assessed per the 2014 Lugano criteria and integrated with the 2016 LYRIC criteria; evaluable = patients who received at least one dose of study drug and underwent at least one response assessment;

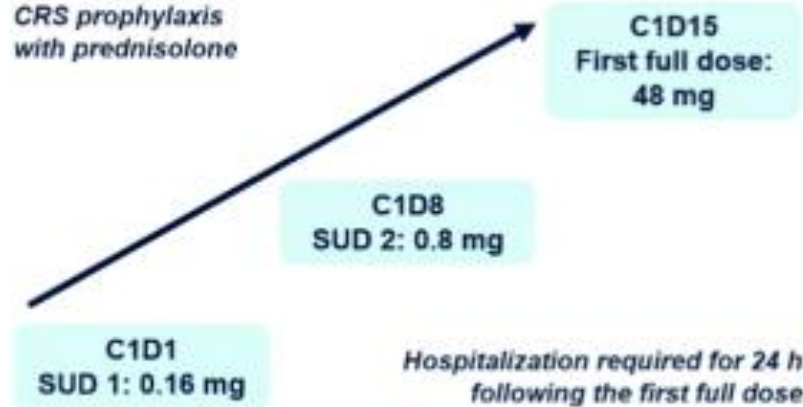
# Epcoritamab

## Key inclusion criteria

- R/R CD20<sup>+</sup> FL grade 1–3A
- ECOG PS 0–2
- ≥2 prior lines of antineoplastic therapy, including ≥1 regimen with an anti-CD20 mAb
- Prior treatment with an alkylating agent or lenalidomide
- FDG-avid disease by PET/CT
- Prior CAR T allowed

## Pivotal<sup>a</sup>

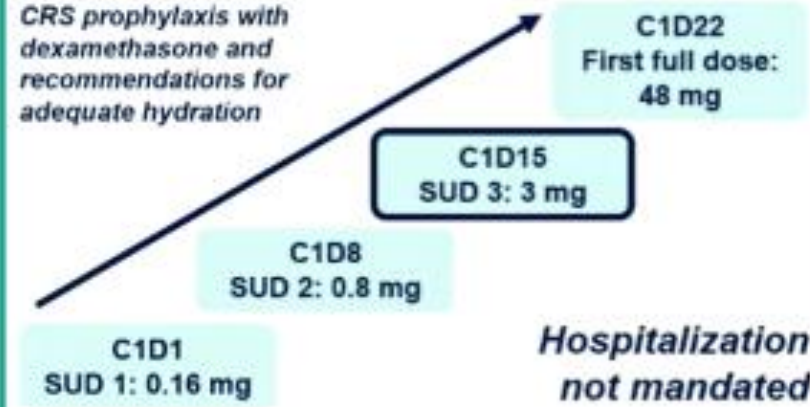
CRS prophylaxis with prednisolone



**Primary objective:** ORR by independent review committee  
**Data cutoff:** April 21, 2023  
**Median follow-up:** 17.4 mo

## C1 optimization<sup>a</sup>

CRS prophylaxis with dexamethasone and recommendations for adequate hydration

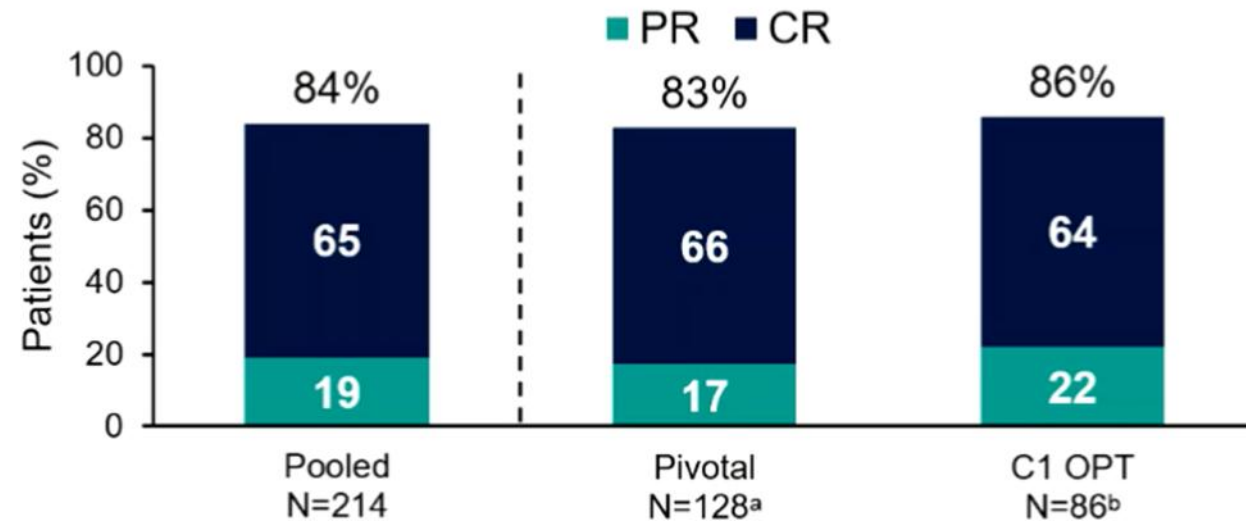


**Primary objective:** Assess incidence and severity of CRS  
**Data cutoff:** January 8, 2024  
**Median follow-up:** 5.7 mo

Phase 1/2 trial. C, cycle; CAR T, chimeric antigen receptor T-cell therapy; ECOG PS, Eastern Cooperative Oncology Group performance status; mAb, monoclonal antibody; MRD, minimum residual disease; OPT, optimization; ORR, overall response rate; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; SUD, step-up dose. <sup>a</sup>Patients received subcutaneous epcoritamab QW C1–3, Q2W C4–9, and Q4W C≥10 until progressive disease (≥2 measurable [by CT/MRI] and FDG PET–positive lesions) or unacceptable toxicity. Radiographic disease evaluation was performed every 6 wk for the first 24 wk (6, 12, 18, and 24 wk), then every 12 wk (36 and 48 wk), and every 6 mo thereafter. MRD was assessed in peripheral blood using the clonoSEQ<sup>®</sup> (Adaptive Biotechnologies, Seattle, WA) next-generation sequencing assay. ClinicalTrials.gov: NCT03625037; EudraCT: 2017-001748-36.

4

# EPCORE-NHL-1 Response Rates



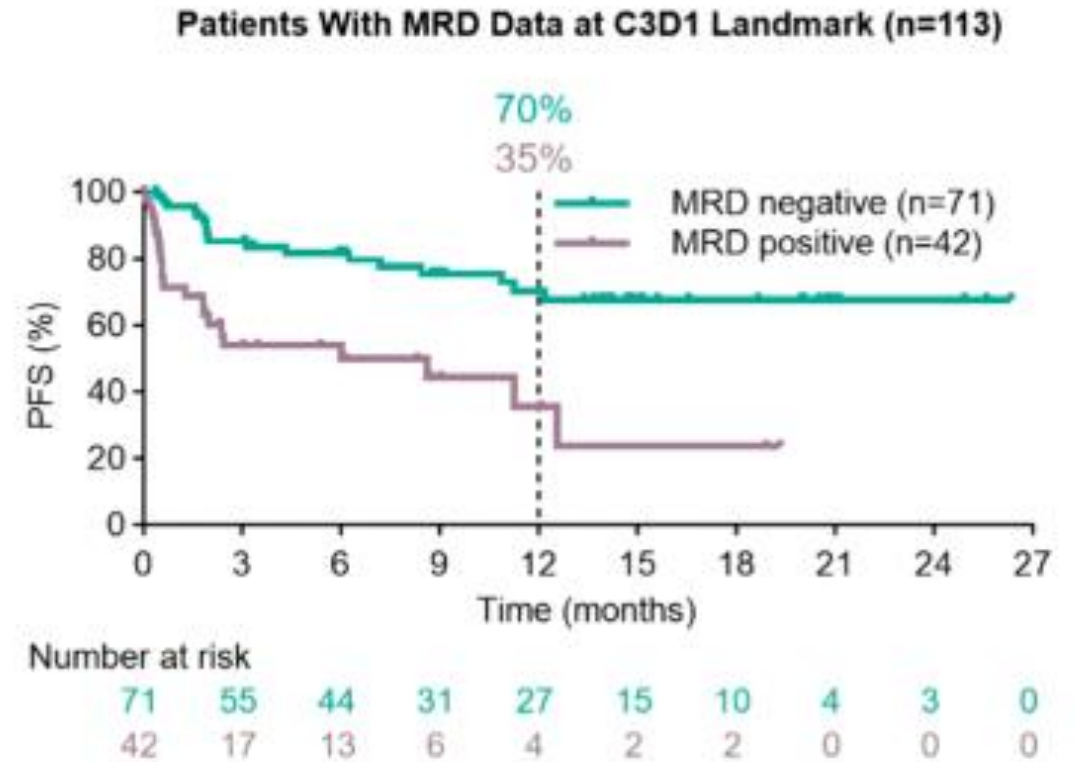
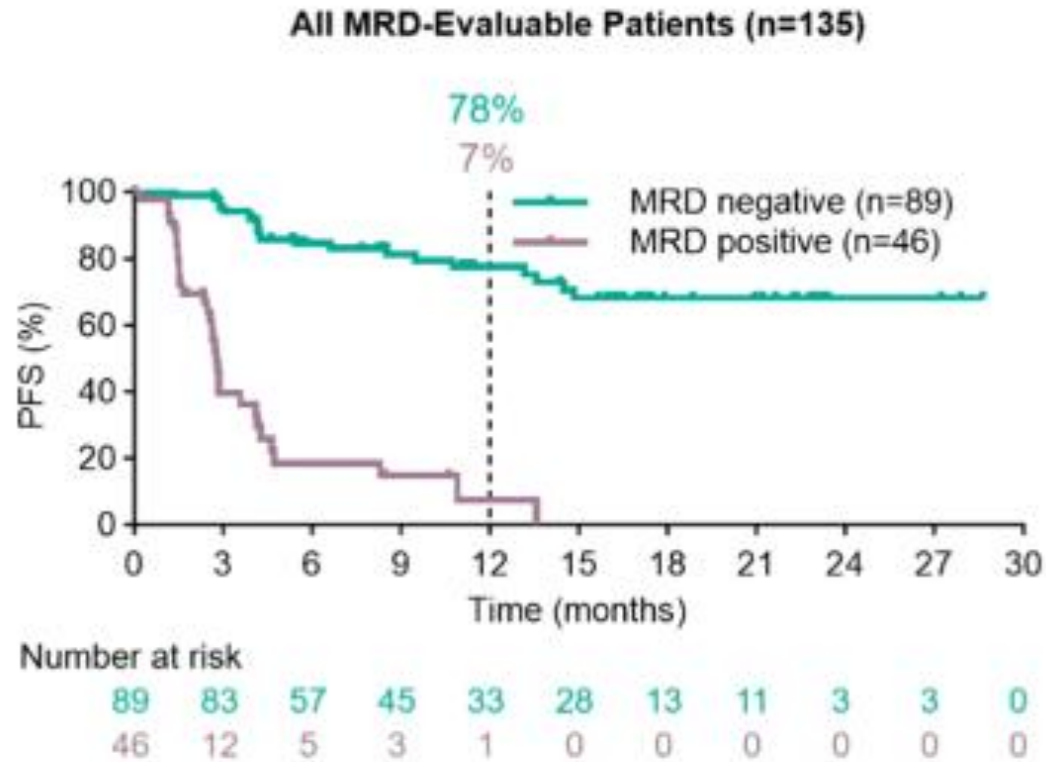
MRD-Negativity Rate	n (%)
Pooled (n=135)	89 (66)
Pivotal (n=91)	61 (67)
C1 OPT (n=44)	28 (64)

Based on MRD-evaluable population per clonoSEQ<sup>®</sup> PBMC assay with 10<sup>-6</sup> cutoff.

- No impact on time to response in C1 OPT
  - Median time to response was 1.4 mo in both cohorts<sup>c</sup>
  - Median time to complete response was 1.5 mo in both cohorts<sup>d</sup>

CR was complete metabolic response (ie, PET negativity). CR, complete response; PBMC, peripheral blood mononuclear cell; PR, partial response. <sup>a</sup>Three patients (2%) were not evaluable. <sup>b</sup>Five patients (6%) were not evaluable. <sup>c</sup>Range: 1.2–4.4 in C1 OPT, 1.0–3.0 in pivotal. <sup>d</sup>Range: 1.2–4.7 in C1 OPT, 1.2–11.1 in pivotal.

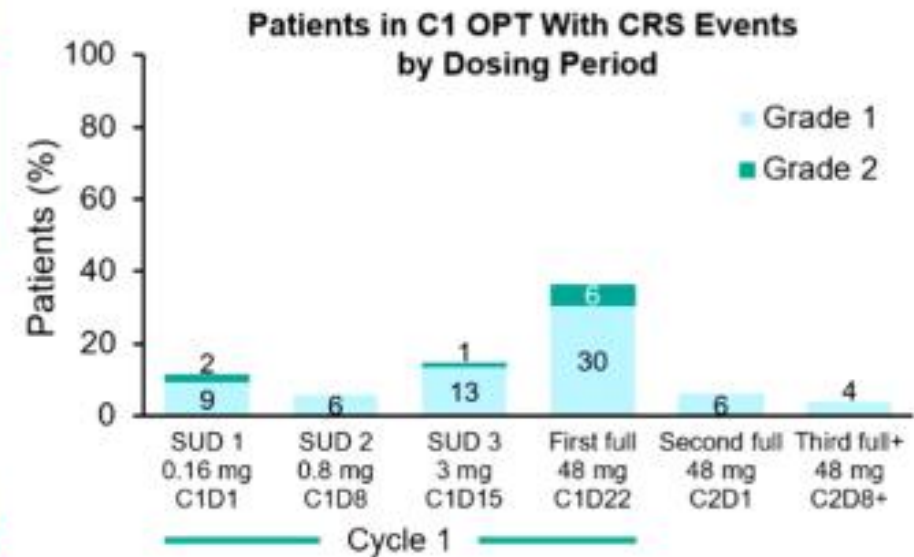
# EPCORE-NHL1 PFS and MRD



Median follow-up: 17.4 mo for pivotal cohort and 5.7 mo for C1 OPT cohort. PFS assessed by investigator. MRD was assessed in peripheral blood using the clonoSEQ<sup>®</sup> next-generation sequencing assay with  $10^{-4}$  cutoff. MRD negative was defined as having MRD negativity at any time point (left graph) or at any time point up to C3D1 (right graph).

# EPCORE-NHL1 CRS and Dose Optimization

	Pivotal N=128	C1 OPT N=86
CRS, <sup>a</sup> n (%)	85 (66)	42 (49)
Grade 1	51 (40)	34 (40)
Grade 2	32 (25)	8 (9)
Grade 3	2 (2)	0
Treated with tocilizumab, n (%)	31 (24)	10 (12)
Leading to epcoritamab discontinuation, n (%)	0	0
Median time to CRS onset after first full dose	15 hours	2.5 days
<b>CRS resolution, n/n (%)</b>	<b>85/85 (100)</b>	<b>42/42 (100)</b>
Median time to resolution, d (range)	2 (1–54)	2 (1–14)
ICANS, n (%)	8 (6) <sup>b</sup>	0



- In C1 OPT, with no mandatory hospitalization, 54% of patients who received first full dose (44/82) had outpatient monitoring for CRS
  - Regardless of hospitalization status at the first full dose, 77% of patients with CRS following the first full dose (23/30) had CRS onset in the outpatient setting; all were able to identify CRS signs/symptoms in a timely manner and receive adequate treatment
- In both cohorts, most CRS occurred after the first full dose and was primarily confined to C1

<sup>a</sup>Graded by Lee et al 2019 criteria. <sup>b</sup>All grade 1–2; none leading to discontinuation. 1. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-38.

# Study Design: EPCORE<sup>®</sup> NHL-2 Arm 2

## Key inclusion criteria

- R/R CD20<sup>+</sup> FL
  - Grade 1–3A
  - Stage II–IV
- ≥1 prior treatment, including an anti-CD20 antibody
- Need for treatment per GELF criteria<sup>1</sup>
- ECOG PS 0–2
- Measurable disease by CT or MRI
- Adequate organ function

**Data cutoff:** May 15, 2024

**Median follow-up:** 25.3 months

Concomitant fixed-duration epcoritamab 48 mg + R <sup>2</sup> (28-day cycles up to 2 years)							
Agent	C1	C2	C3	C4–5	C6–9	C10–12	C13+
Epcoritamab SC 48 mg							
Cohort A <sup>b</sup>	QW			Q2W		Q4W	
Cohort B <sup>b</sup>	QW		Q4W				
Rituximab IV 375 mg/m <sup>2</sup>	QW	Q4W					
Lenalidomide PO 20 mg/d	D1–21 of each cycle						

2-step-up-dose regimen<sup>a</sup> (Cohort A and B)

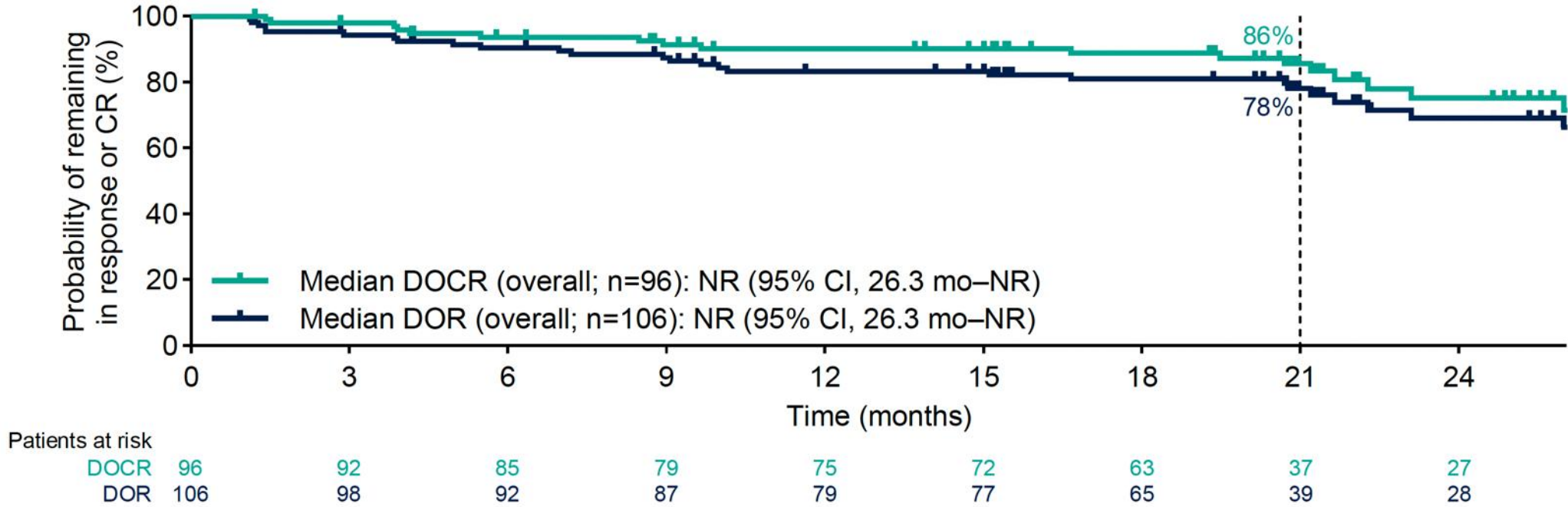
R<sup>2</sup> (Rituximab and Lenalidomide)

**Primary endpoint:** ORR per Lugano criteria<sup>c</sup>

**Key secondary endpoints:** CR rate, DOR, DOCR, PFS, TTNT, OS, MRD analysis,<sup>d</sup> and safety and tolerability

NCT04663347. <sup>a</sup>Patients received epcoritamab with 2 step-up doses (0.16 mg on C1D1 and 0.8 mg on C1D8) before the first full dose on C1D15, corticosteroid prophylaxis to mitigate CRS, and protocol-mandated hospitalization for 24 h after the first full dose. <sup>b</sup>Cohorts A and B enrolled 27 and 84 patients, respectively. <sup>c</sup>Tumor response was evaluated by PET-CT (or separate PET and CT/MRI when PET-CT was not available) obtained at 6, 12, 18, 24, 36, and 48 wk, and every 24 wk thereafter, until disease progression. <sup>d</sup>MRD was assessed in PBMCs using the clonoSEQ<sup>®</sup> assay (Adaptive Biotechnologies) with a cutoff of 10<sup>-6</sup>. 1. Brice P, et al. *J Clin Oncol.* 1997;15:1110-7.

# Durable Responses



- 93% (37/40) of patients with CR who completed treatment per protocol remained in CR<sup>a</sup>
- 81% (25/31) of patients with CR who discontinued epcoritamab treatment early due to reasons other than PD remained in CR<sup>b</sup>

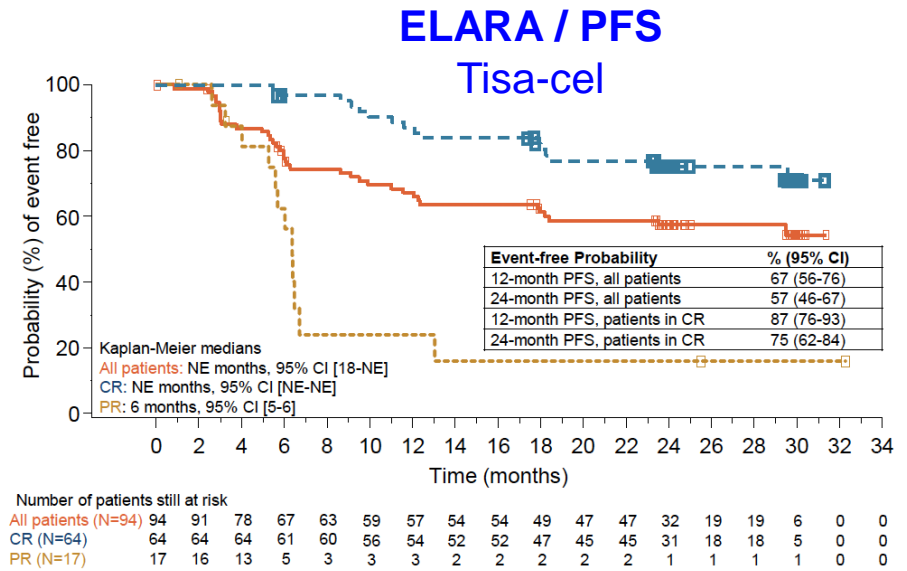
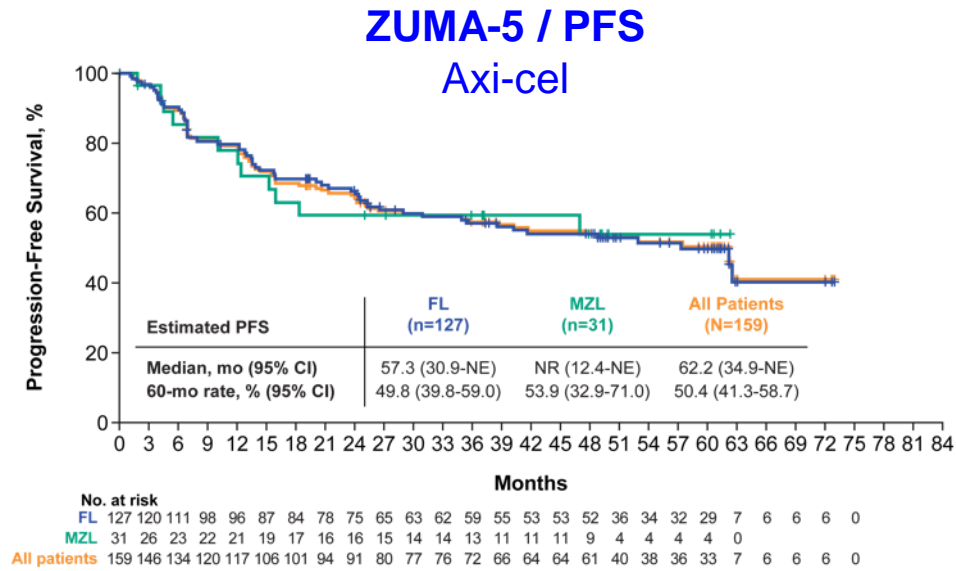
Data cutoff: May 15, 2024. Response-evaluable population. Median follow-up for DOR/DOCR: 21.0/20.9 months.

<sup>a</sup>17 of the 19 patients with CR at end of treatment and response evaluations after end of treatment (89%) remained in CR. <sup>b</sup>Median epcoritamab treatment duration: ~1 year.

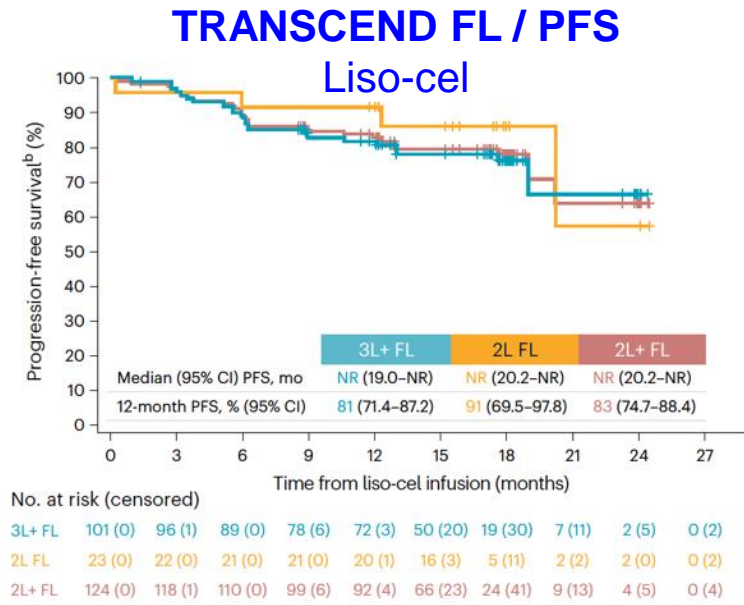
# What about CAR T-cell?



# PFS outcomes with CD19 CAR-T in R/R FL



- ORR ~95%
- CR rates 80-90%

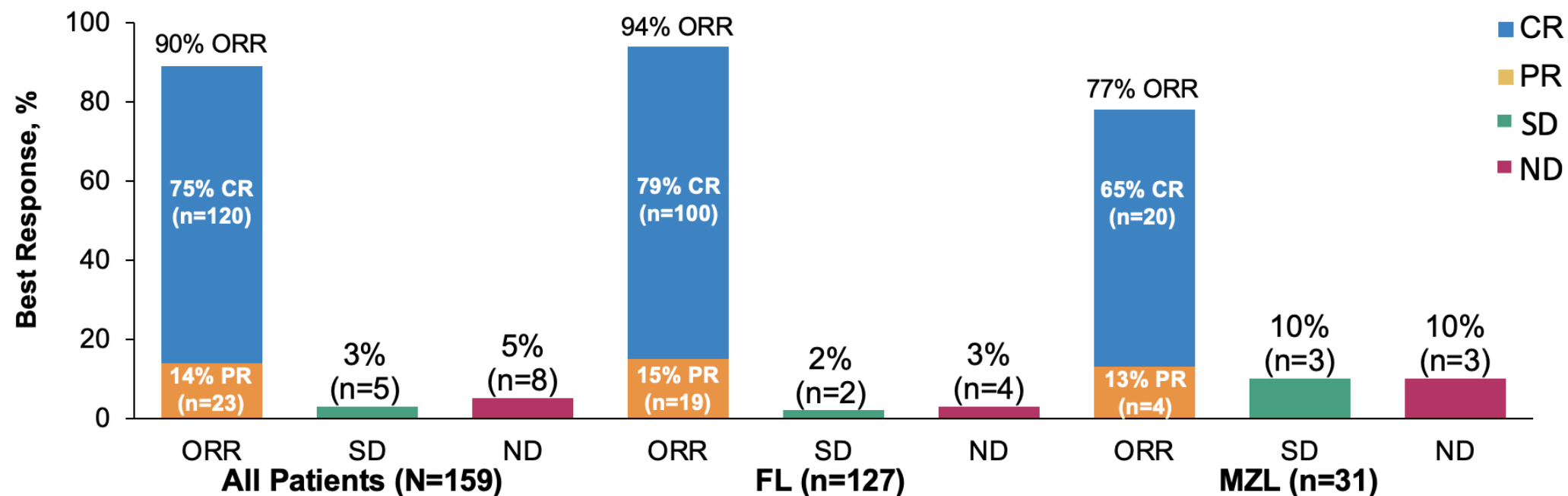


- Is CAR T cell therapy curative for FL?

Neelapu et al. *ASH 2024*, Abstract 864  
 Dreyling M et al. *ASH 2022*, Abstract 608  
 Morschhauser F et al. *Nat Med 2024* Aug;30(8):2199-2207

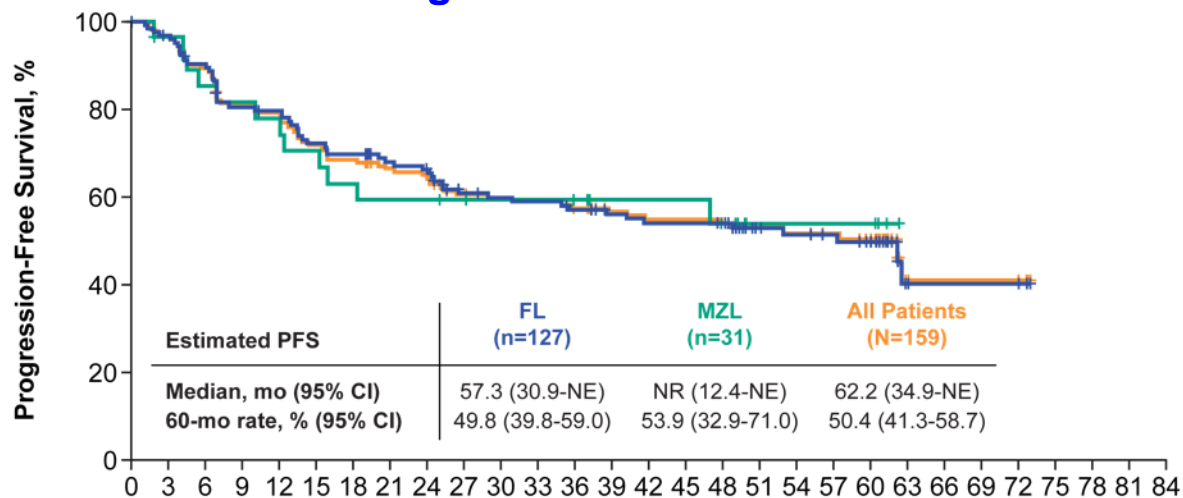
# ZUMA-5: Prior results

- Axi-cel is an autologous anti-CD19 CAR T-cell therapy approved for the treatment of patients with R/R FL based on the Phase 2 ZUMA-5 trial in March 2021



# ZUMA-5: PFS and Lymphoma-specific PFS

## Progression-Free Survival

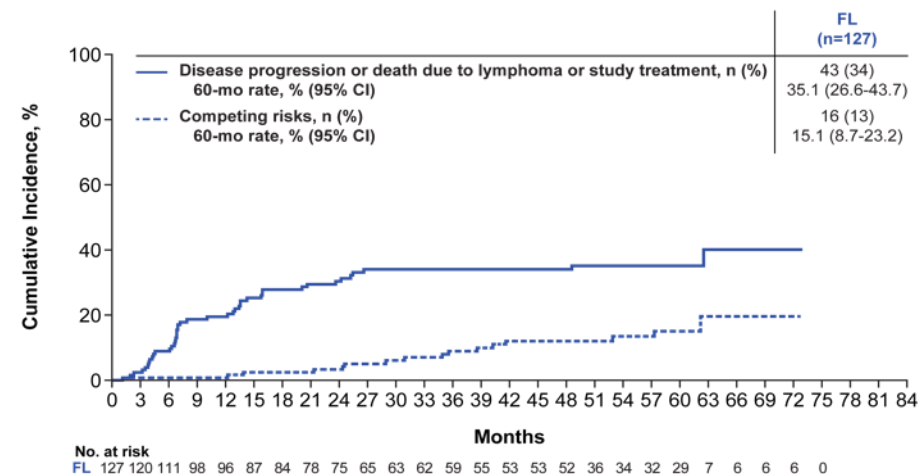


No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75	78	81	84
FL	127	120	111	98	96	87	84	78	75	65	63	62	59	55	53	53	52	36	34	32	29	7	6	6	6	0			
MZL	31	26	23	22	21	19	17	16	16	15	14	14	13	11	11	11	9	4	4	4	4	0							
All patients	159	146	134	120	117	106	101	94	91	80	77	76	72	66	64	64	61	40	38	36	33	7	6	6	6	0			

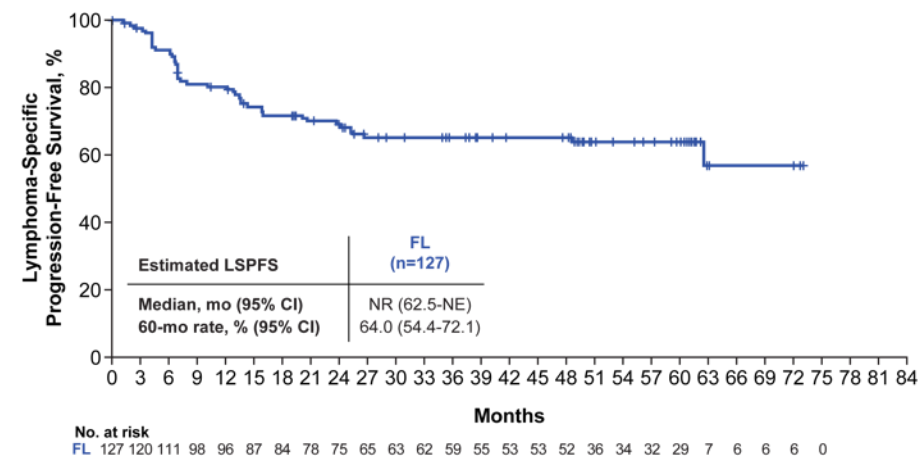
➤ 60-month PFS rate was 50.4%

- 60-month lymphoma-specific PFS was 64.0%

## Cumulative Incidence of Progression and Lymphoma-Specific Death in FL



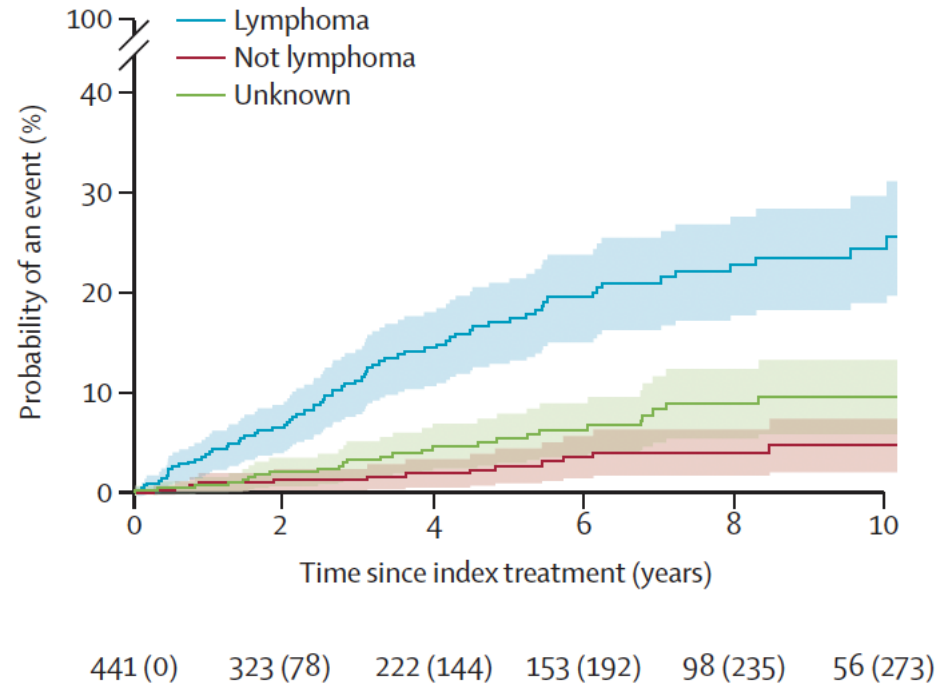
## Lymphoma-Specific PFS



# Cumulative incidence of lymphoma-specific death: ZUMA-5 vs. Historical

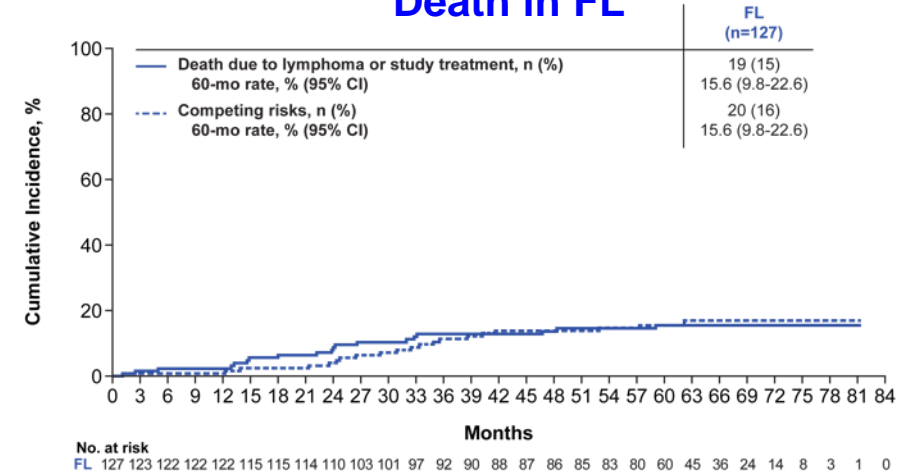
## Treatment patterns and outcomes of patients with relapsed or refractory follicular lymphoma receiving three or more lines of systemic therapy (LEO CReWE): a multicentre cohort study

Carla Casulo, Melissa C Larson, Julianne J Lunde, Thomas M Habermann, Izidore S Lossos, Yucai Wang, Loretta J Nastoupil, Christopher Strouse, Dai Chihara, Peter Martin, Jonathon B Cohen, Brad S Kahl, W Richard Burack, Jean L Koff, Yong Mun, Anthony Masaquel, Mei Wu, Michael C Wei, Ashwini Shewade, Jia Li, James Cerhan, Christopher R Flowers, Brian K Link, Matthew J Maurer

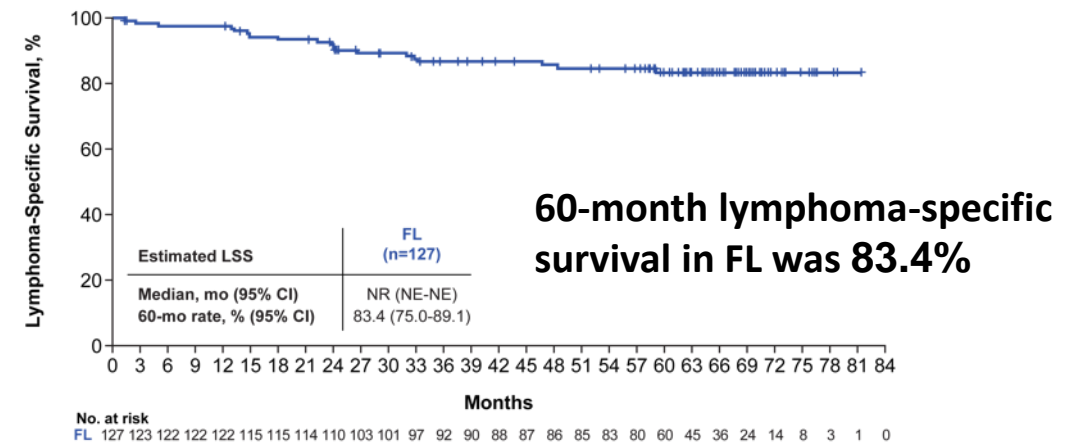


Casulo C et al. *Lancet Haematol* 2022 Apr;9(4):e289-e300

## Cumulative Incidence of Lymphoma-Specific Death in FL



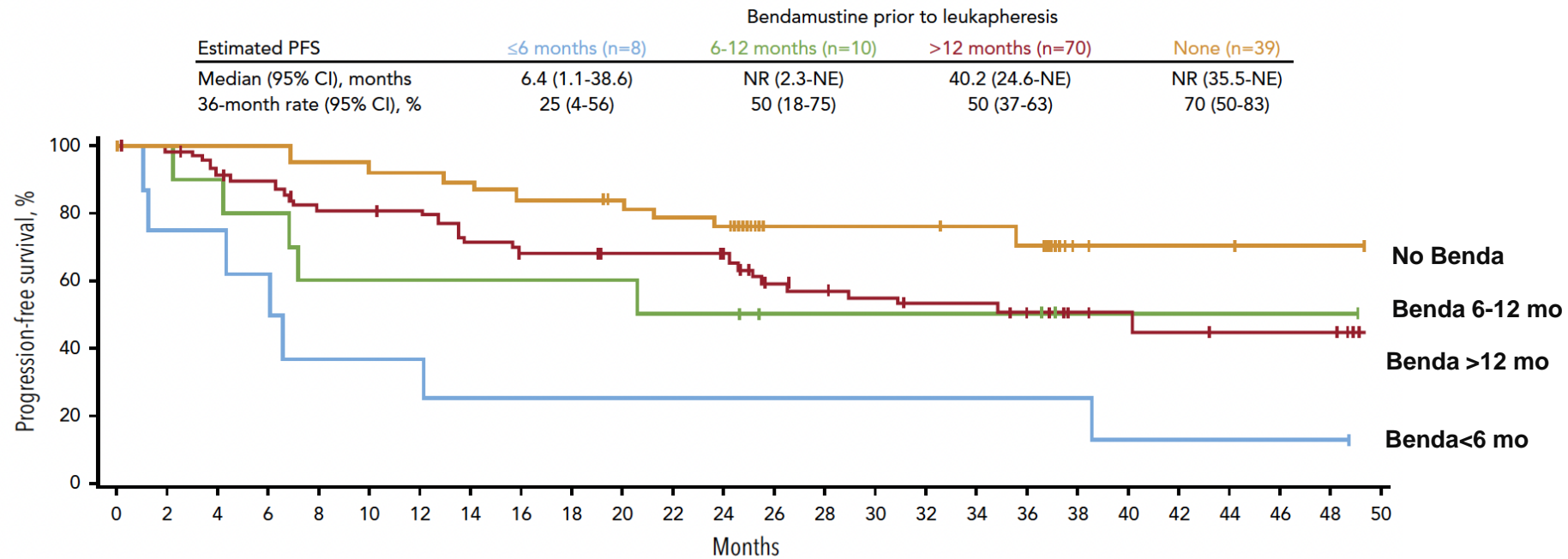
## Lymphoma-Specific Survival



Neelapu et al. ASH 2024, Abstract 864

# Impact of bendamustine exposure pre-apheresis in FL

## ZUMA-5: PFS in FL



No. at risk

Bendamustine prior to leukapheresis

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50
≤6 months	8	6	6	5	3	3	3	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	0
6-12 months	10	10	9	8	6	6	6	6	6	6	6	5	5	3	3	3	3	3	3	1	1	1	1	1	1	0
>12 months	70	68	62	60	53	53	52	46	43	43	41	41	40	29	27	25	23	23	21	10	9	8	7	7	7	0
None	39	38	38	38	36	36	35	34	32	32	30	28	27	14	14	14	14	13	12	3	2	2	2	1	1	0

# **MCL – what are the data for bispecific and CAR T-cell therapy?**



# Efficacy and Safety

Drug	N	ORR	CR	mPFS	mOS	CRS	Grade 3+	ICANS	Grade 3+
Glofitamab	61	85%	78.3%	16.8 m	29.9 m	75.7%	16.2%	5%	0
Mosun/Pola	20	75%	70%	15.8 m	17.9 m	45%	0%	4%	0
Brexu-cel	68	91%	68%	25.8 m	46.6 m	91%	15%	63%	31%
Liso-cel	83	86.5%	74.3%	15.3 m	18.2 m	61%	1%	31%	9%

# Glofitamab

## Study design<sup>1</sup>

- Multicenter, open-label, dose-escalation and dose-expansion study of glofitamab with Gpt

## Glofitamab IV administration

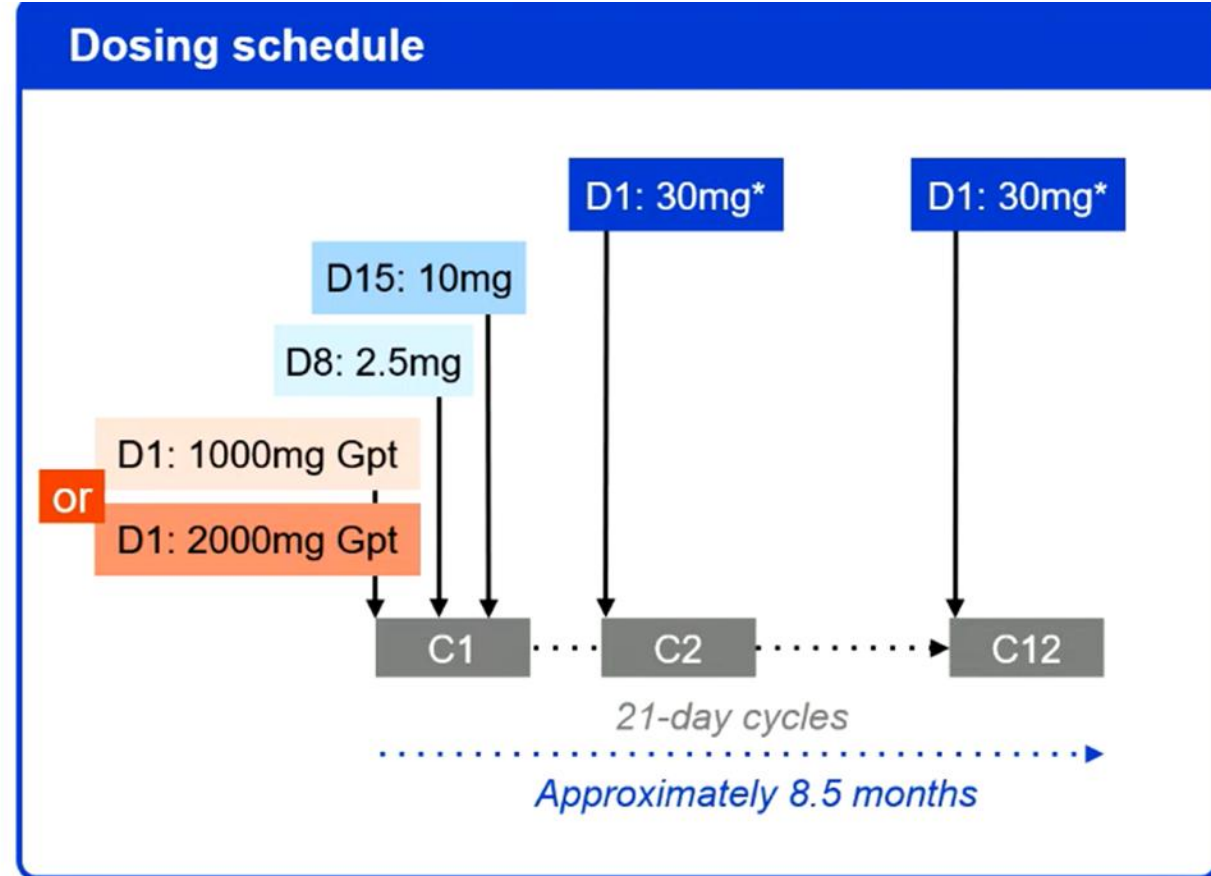
- Fixed-duration treatment: maximum 12 cycles

## Population characteristics

- Age ≥18 years
- ≥1 prior systemic therapy
- ECOG PS 0 or 1

## CRS mitigation

- Obinutuzumab pretreatment (1000mg or 2000mg)
- C1 step-up dosing
- Monitoring after first dose (2.5mg)



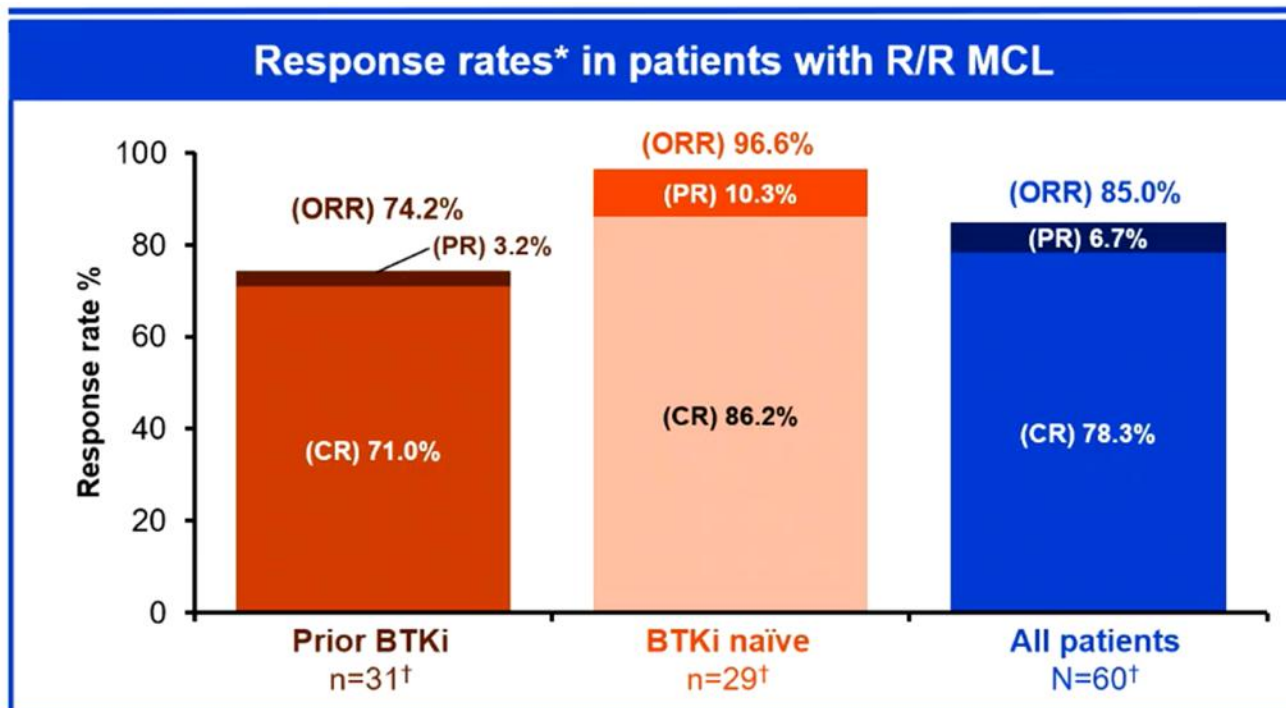
Clinical cut-off date: September 04, 2023.

\*In the 1000mg Gpt cohort, two patients had 16mg glofitamab as their target dose in the dose escalation phase.

C, cycle; CRS, cytokine release syndrome; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; Gpt, obinutuzumab pretreatment; IV, intravenous.

1. NCT03075696. Available at: <https://www.clinicaltrials.gov>.

# Response Rates and Prior BTKi Exposure



- Median time to first response among responders (n=51): **42 days** (95% CI: 42.0–45.0)

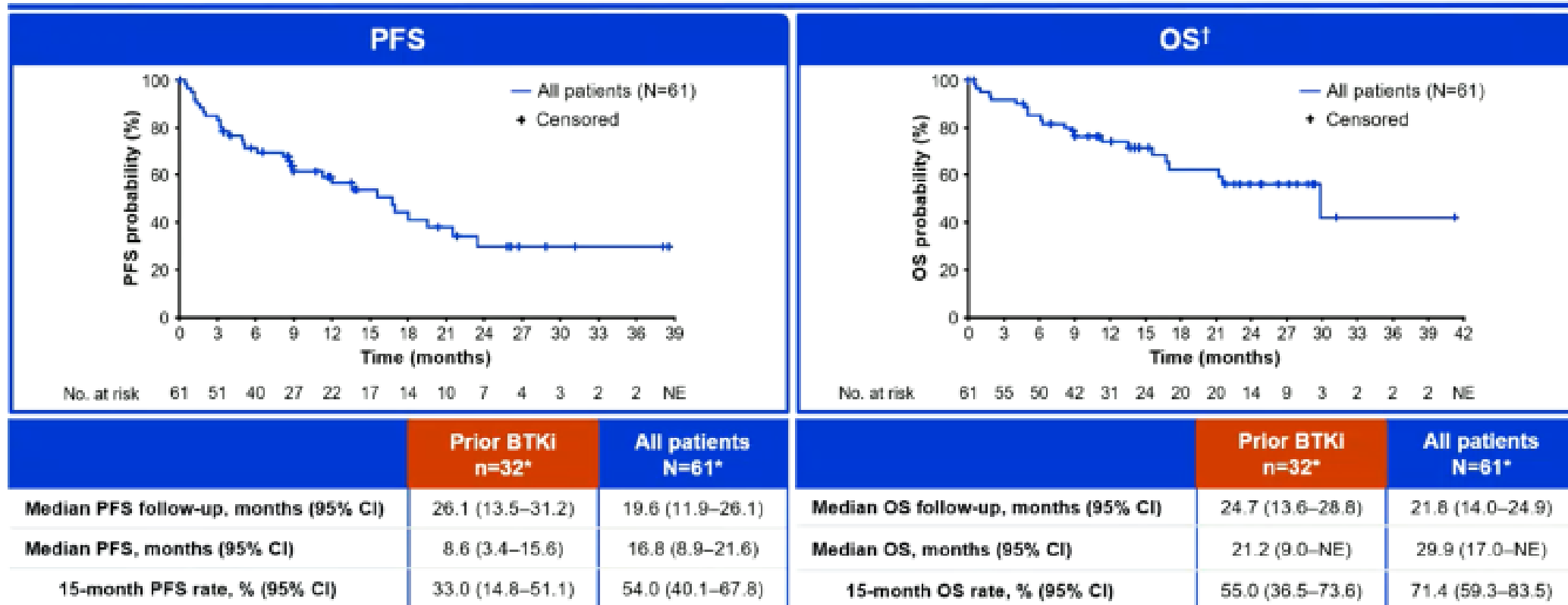
**High CR and OR rates were observed in the overall population and in both BTKi-naïve patients and those with prior BTKi therapy**

Clinical cut-off date: September 04, 2023.

\*Investigator-assessed. <sup>†</sup>Efficacy evaluable population.

CI, confidence interval; ORR, overall response rate; PR, partial response.

# Survival Outcomes: Glofitamab MCL



Clinically significant PFS and OS at 15 months were achieved with fixed-duration glofitamab

Clinical cut-off date: September 04, 2023. \*ITT population. †At the time of analysis, 22 patients had died, the majority due to PD (n=7) or COVID-19 (n=7); other causes of death were pneumonia (n=1), septic shock (n=1), cardiac arrest (n=1), and unknown/other (n=5). All patients who died due to COVID-19 had achieved a CR. ITT, intention to treat; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

# CRS Summary

n (%)	1000mg Gpt cohort (n=16)	2000mg Gpt cohort (n=44)	All patients (N=60)	n (%)	1000mg Gpt cohort (n=16)	2000mg Gpt cohort (n=44)	All patients (N=60)
<b>Any grade CRS*</b>	14 (87.5)	28 (63.6)	42 (70.0)	<b>CRS management</b>			
Grade 1	4 (25.0)	18 (40.9)	22 (36.7)	Tocilizumab	11 (68.8)	11 (25.0)	22 (36.7)
Grade 2	6 (37.5)	7 (15.9)	13 (21.7)	Corticosteroid	8 (50.0)	10 (22.7)	18 (30.0)
Grade 3	2 (12.5)	3 (6.8)	5 (8.3)	Tocilizumab and corticosteroids	6 (37.5)	7 (15.9)	13 (21.7)
Grade 4	2 (12.5)	0	2 (3.3)	ICU admission	5 (31.3)	4 (9.1)	9 (15.0)
<b>Serious AE of CRS†</b>	11 (68.8)	12 (27.3)	23 (38.3)				

The majority of CRS events were Grade 1/2, and a lower incidence of CRS was observed in the 2000mg versus 1000mg cohort

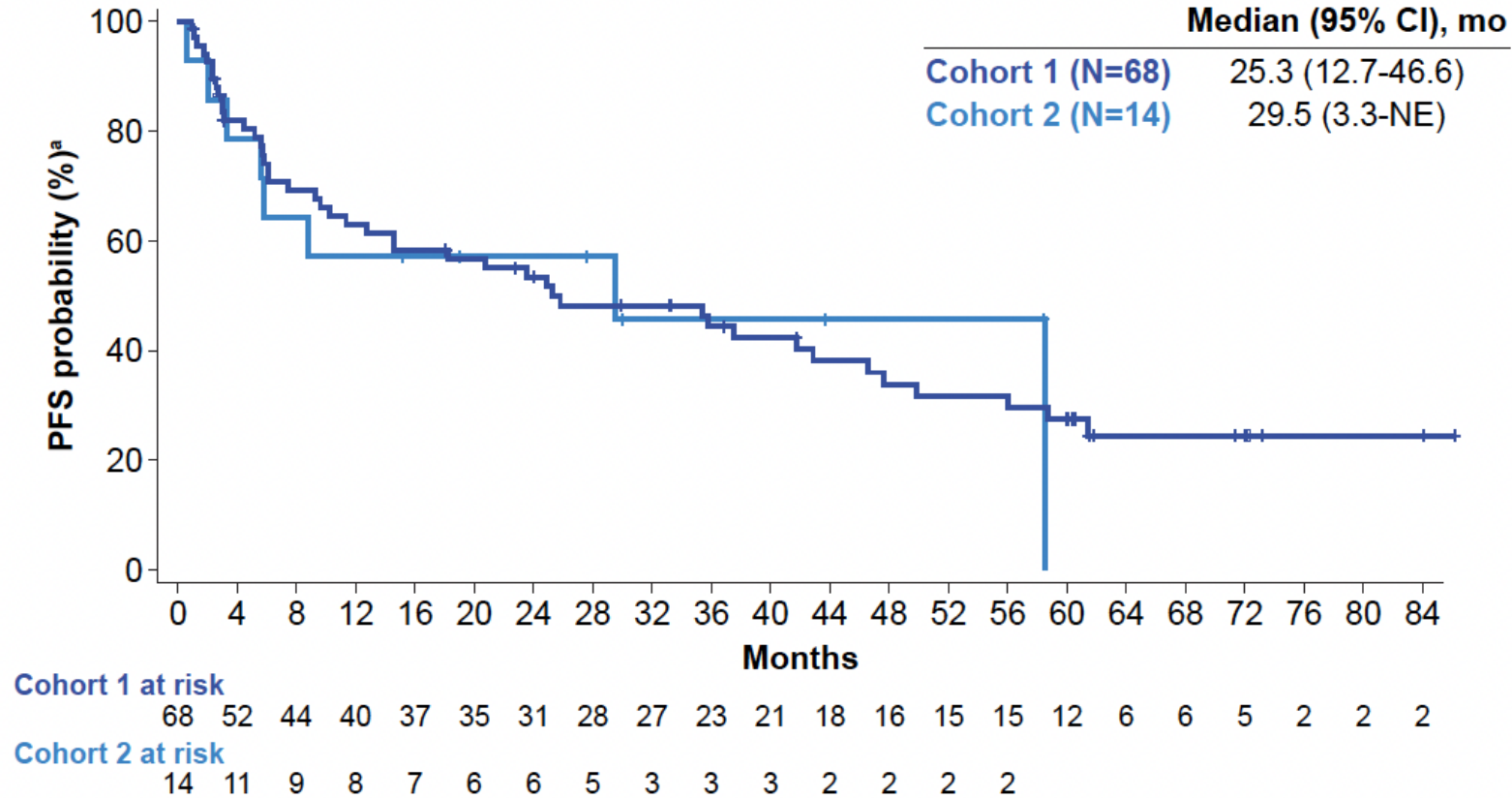
Clinical cut-off date: September 04, 2023. \*CRS by ASTCT consensus grading criteria.<sup>1</sup> †Serious AE of CRS is defined as per International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ASTCT, American Society for Transplantation and Cellular Therapy; ICU, intensive care unit.

1. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38.

# Brexucabtagene autoleucel

## Progression-Free Survival in ZUMA-2

## 5-Year Outcomes



- Median investigator-assessed PFS was 25.3 months (95% CI, 12.7-46.6; N=68) and 54-month PFS rate was 32% (95% CI, 20.0-44.2) in Cohort 1
- In Cohort 2, median PFS was 29.5 months (95% CI, 3.3-NE) and 54-month PFS rate was 46% (17.3-70.5; N=14)

<sup>a</sup> Per investigator assessment. NE, not estimable; PFS, progression-free survival.

# Adverse Events of Special Interest in ZUMA-2

AEs of Interest, n (%)	Cohort 1 (N=68)	Cohort 2 (N=14)
<b>Any CRS<sup>a</sup></b>	62 (91)	13 (93)
<b>Grade ≥3</b>	10 (15)	2 (14)
<b>Any neurologic event<sup>b</sup></b>	43 (63)	13 (93)
<b>Grade ≥3</b>	21 (31)	6 (43)
<b>Any thrombocytopenia</b>	50 (74)	7 (50)
<b>Grade ≥3</b>	36 (53)	6 (43)
<b>Any neutropenia</b>	59 (87)	11 (79)
<b>Grade ≥3</b>	58 (85)	11 (79)
<b>Any anemia</b>	47 (69)	7 (50)
<b>Grade ≥3</b>	36 (53)	6 (43)
<b>Any infection</b>	37 (54)	7 (50)
<b>Grade ≥3</b>	26 (38)	3 (21)
<b>Any hypogammaglobulinemia</b>	14 (21)	0
<b>Grade ≥3</b>	1 (1)	0

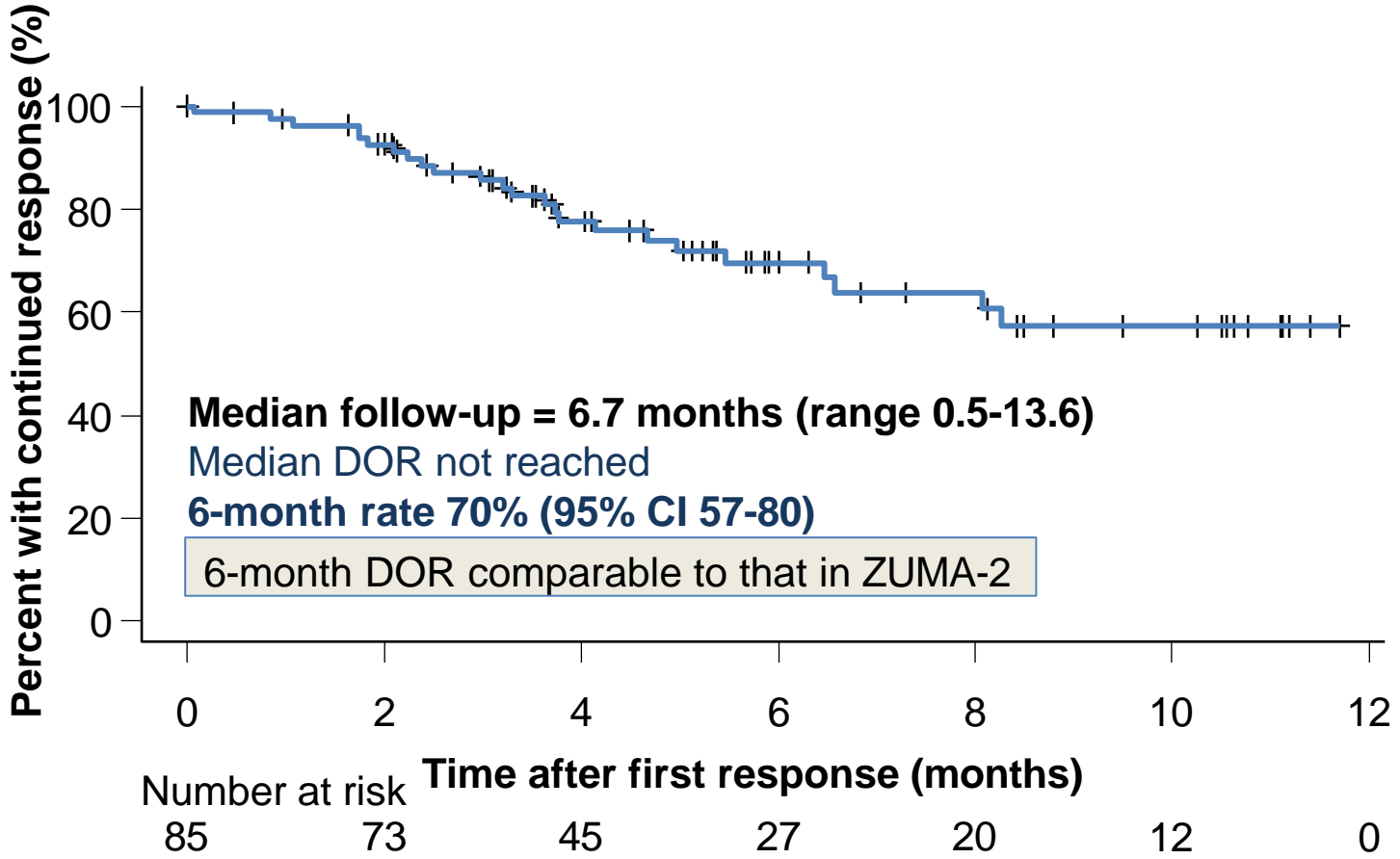
- Rates of Grade ≥3 CRS and neurological events were 15% and 31% in Cohort 1, and 14% and 43% in Cohort 2, respectively; no cases of Grade 5 CRS or neurological events occurred
- CRS and neurological events resolved within a median of 10 days and 15 days in Cohort 1, and 10 days and 17 days in Cohort 2, respectively

<sup>a</sup> CRS events were graded per the revised grading system of Lee et al. 2014.<sup>1</sup> <sup>b</sup> Neurologic events were identified based on Topp et al. 2015.<sup>2</sup> All other events were graded per CTCAE v.4.03.

<sup>1</sup> Lee DW, et al. *Blood* 2014. <sup>2</sup> Topp MS, et al. *Lancet Oncol.* 2015;16(1):57-66.

AE, adverse event; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events.

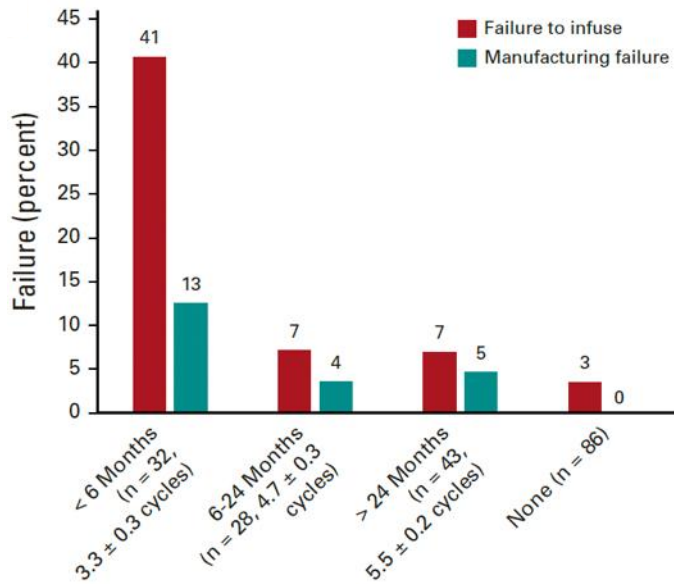
# Brexu-Cel real world evidence: Duration of response



Wang Y et al. ASH 2021, Abstr #744.

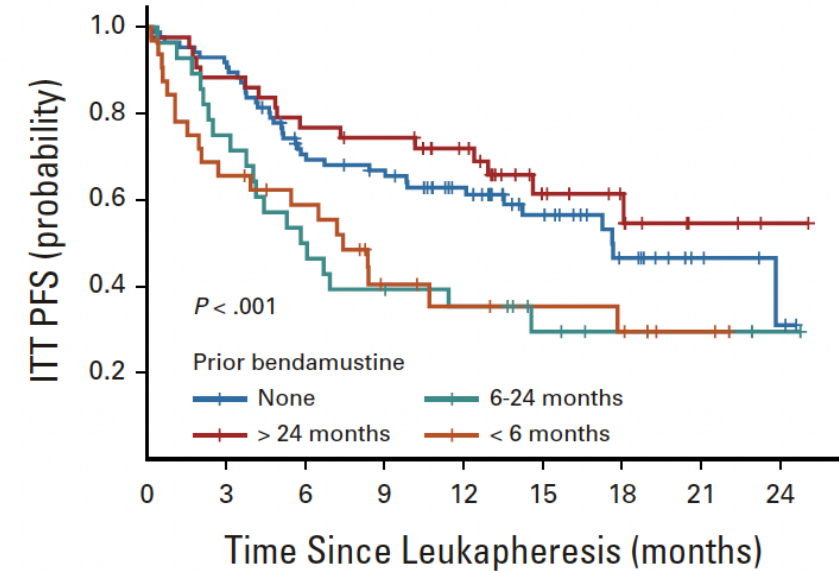
# Impact of bendamustine exposure pre-apheresis in MCL

## Brexu-cel: Failure to infuse or manufacturing failure



Prior Bendamustine Exposure

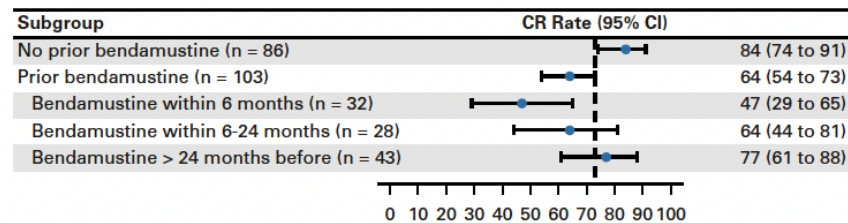
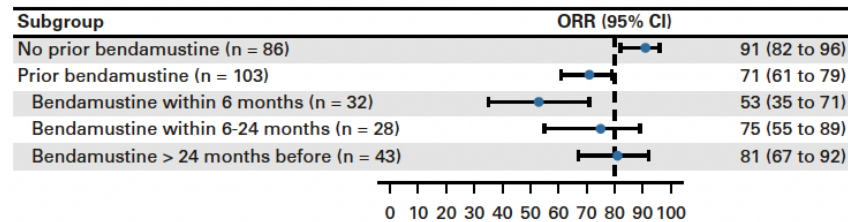
## PFS by prior benda



No. at risk:

	0	3	6	9	12	15	18	21	24
None	86	79	57	51	39	23	13	5	2
> 24 months	43	38	33	31	25	13	9	3	1
6-24 months	28	21	14	11	9	5	3	2	1
< 6 months	32	21	17	9	7	6	5	2	0

## ORR and CR rate by prior benda



# Conclusion

For patients with refractory or early relapsed FL and MCL

- FL:
  - Mosunetuzumab and Epcoritamab have shown impressive efficacy with lower toxicity than CAR T-cell therapy
  - Axi-cel, Tisa-cel, and Liso-cel have high efficacy but high complexity & cost
- MCL
  - Glofitamab has impressive efficacy but greater toxicity than bispecifics in FL
  - Brexu-cel and liso-cel have high efficacy but high neuro toxicity & cost



**Thank you!**  
**Obrigado!**

**Jason Westin, MD MS FACP FASCO**

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