



# CAR-TALKING

News dal mondo CAR-T

Bologna, Royal Hotel Carlton  
14 aprile 2023

CAR-T nel linfoma  
follicolare

**Altri approcci terapeutici di  
salvataggio nel linfoma  
follicolare**

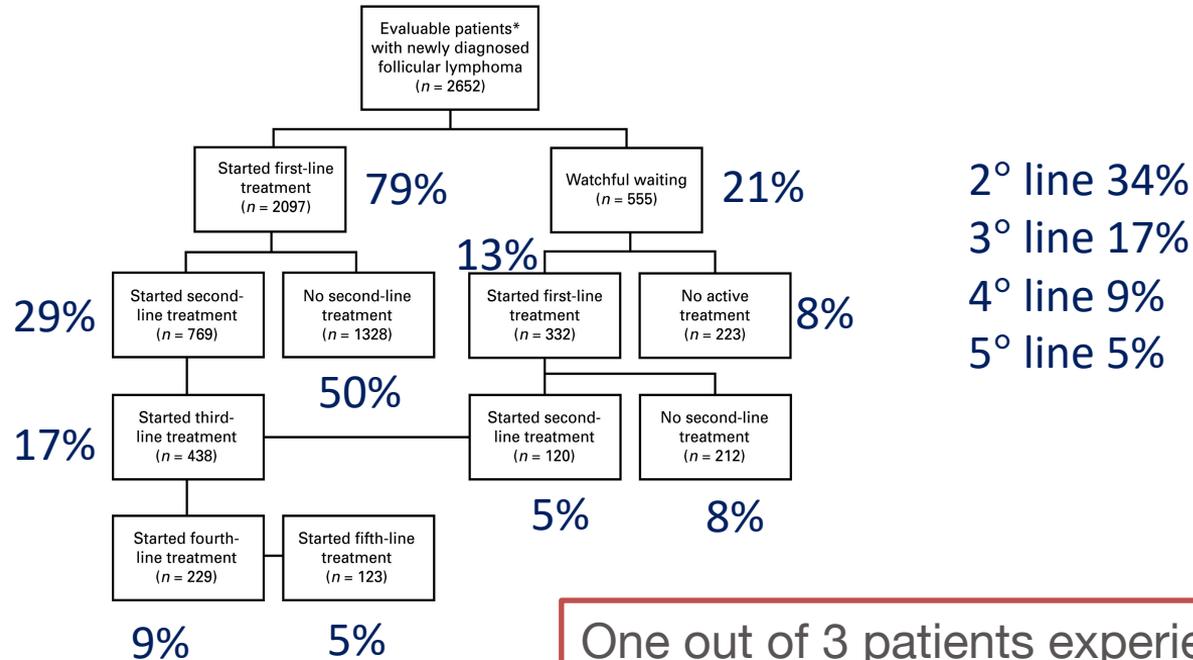
*Prof. Stefano Luminari  
Reggio Emilia*

# Conflict of Interest Disclosure

I hereby declare the following potential conflicts of interest concerning my presentation:

- » Consultancy: Roche, BMS, Regeneron, Abbvie, Janssen, Kite/Gilead, Beigene, Incyte, Beigene
  - » Research Funding: none
  - » Honoraria: none
  - » Patents and Royalties: none
  - » Membership on an Entity's Board of Directors or Advisory Committees: none
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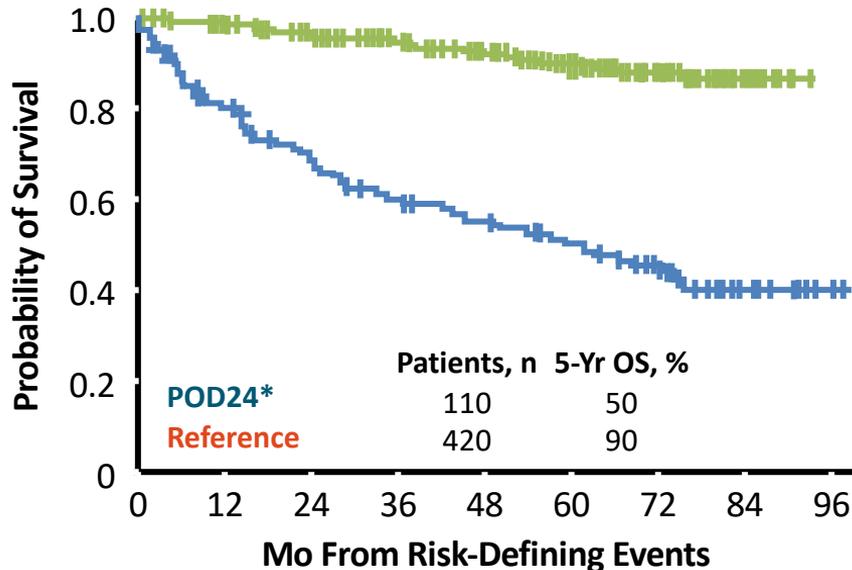
# Epidemiology and outcome after multiple relapses



One out of 3 patients experience more than 2 relapses

# Early relapsed patients represent an unmet need and lack consensus on their therapy

OS According to POD24\* (N = 588)



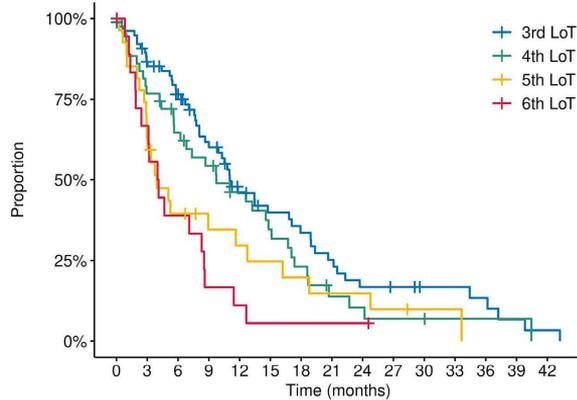
## POD24

- 15-20% after first line
- High risk of transformation (up to 80%) Freeman et al. blood 2019
- Chemorefractoriness
- Undefined role for ASCT Jurinovich et al. 2018
- Rapidly get to 3+ line of therapy

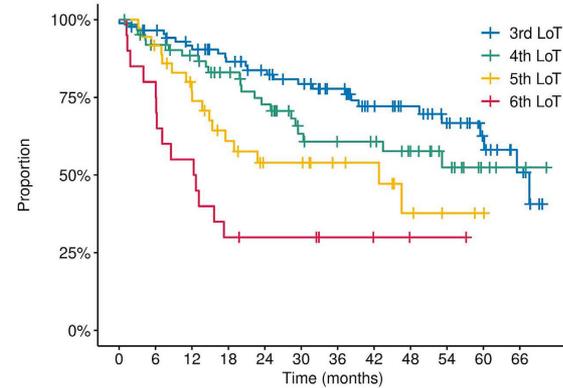
\*POD24: relapse within 24 mo after initial therapy. Given figure is of patients treated with 1L R-CHOP. Similar results found for independent validation set and for 1L R-CVP/R-fludarabine in exploratory analyses.

# Decreasing outcomes with additional lines of therapy (LOT): results from the international SCHOLAR-5 study

Progression-free survival



Overall survival

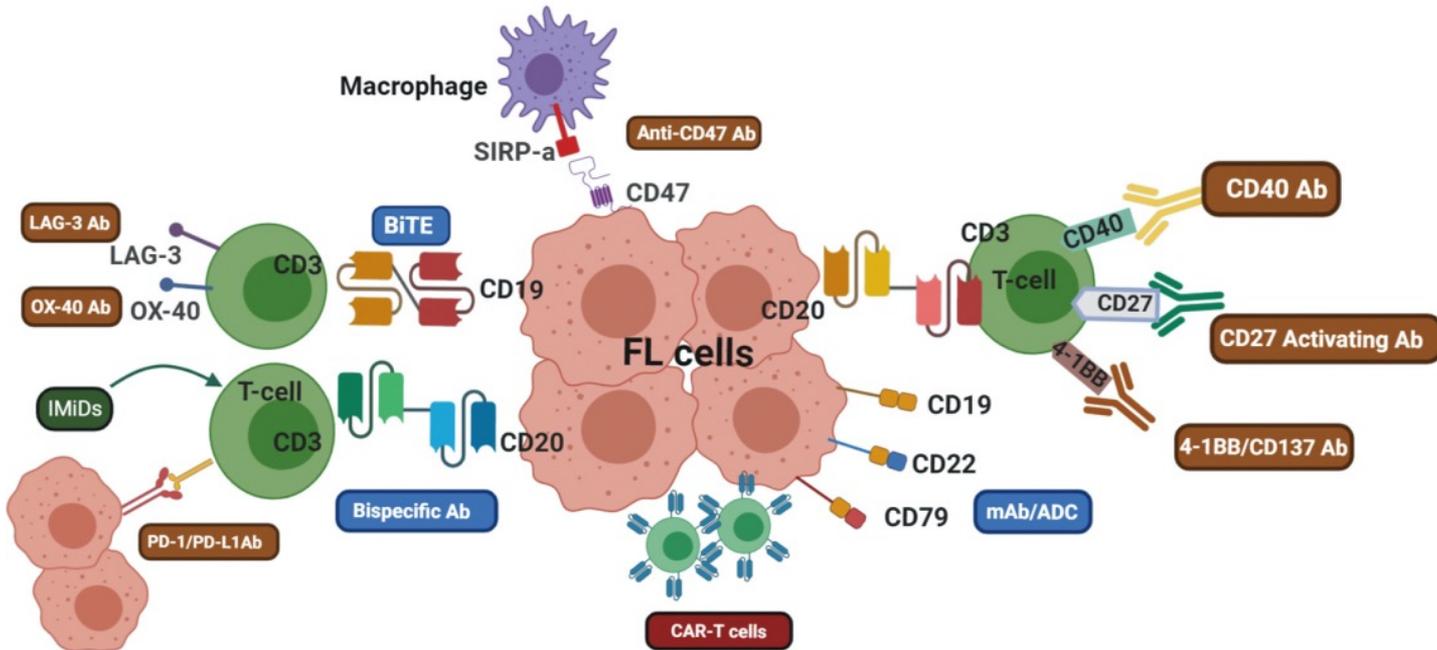


	3° LOT	4^ LOT	5+ LOT
ORR	68	63	37
CRR	44	27	22
5 yr OS	62%	52%	38%
mPFS	11	9.7	3.9
TTNT	20.1	17.9	7.1

# Few available options in RR FL outside trials

Option	ORR (CR)%	mPFS (months)	Note	Ref
ASCT (POD24)	NA	60	Retrospective series	Jurinovich bbmt 2018
G-Benda + G maint	69(11)	25.3	Improves OS vs B G-Benda 1° line	Cheson JCO 2018
Idelalisib	57(6)	11	Gr3+ AE 54%	Gopal Nejm 2014
Duvelisib	47(1.6)	9.5	Gr3+ AE 84%	Flinn JCO 2019
Copanlisib	61(17)	12.5	Gr3+ AE 56%	Dreyling JCO 2017
Umbralisib	45(-)	10.6	Gr3+ AE 54%	Fowler JCO 2021
Tazemetostat	69(13) EZH2 mut 35(4) EZH2 WT	13.8 11.1	FDA Only	Morschauer Lancet oncol 2020
Ibritumomab tiuxetan	-	10.4	Not Available	Horning JCO 2015

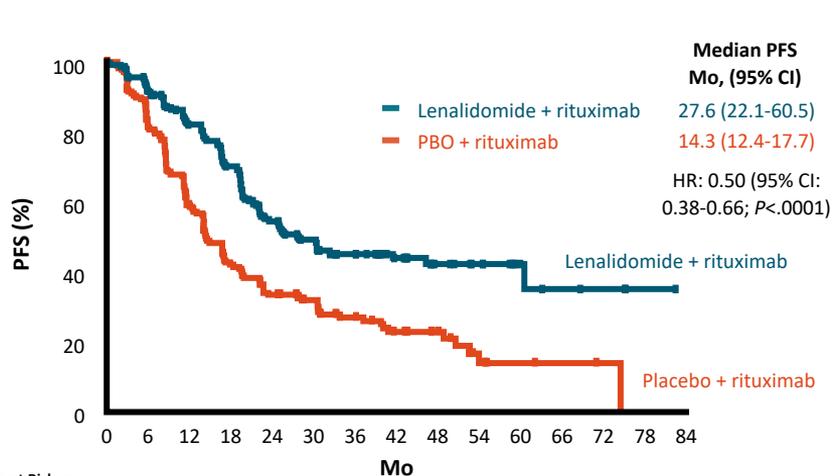
## Novel immunotherapy approaches in follicular lymphoma



BiTE, bispecific T-cell engager; IMiD<sup>®</sup>, immunomodulatory imide drug; mAb, monoclonal antibody; PD-1, programmed death-1; PD-L1, programmed death ligand 1; SIRP, signal regulatory protein.

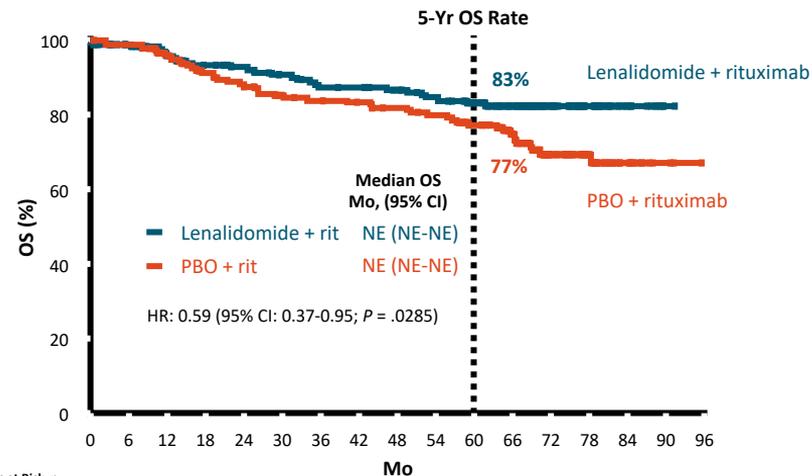
Adapted from: Khurana A, et al. Ann Lymphoma. 2021;5:9.

# AUGMENT: 5-Yr PFS and OS (ASH 2022)



**Patients at Risk, n**

Mo	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
Lenalidomide + rituximab	178	151	128	107	79	62	49	34	18	13	6	4	3	1	0
PBO + rituximab	180	141	98	69	53	41	29	21	13	5	3	2	1	0	0



**Patients at Risk, n**

Mo	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96
Lenalidomide + rituximab	178	167	155	149	144	137	131	130	126	120	110	90	63	36	11	1	0
PBO + rituximab	180	176	167	151	143	135	132	129	125	121	108	87	53	32	11	3	0

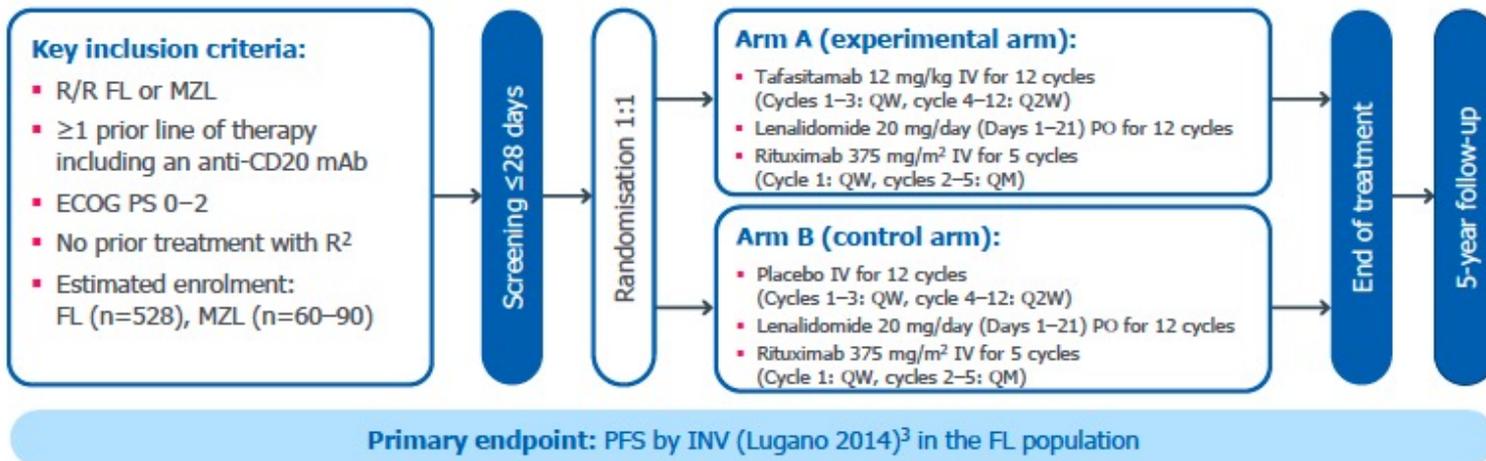
Median follow-up: 65.9 mo

# Antibody based therapies in follicular lymphoma

- **TAFASITAMAB** (ADCC, ADCP anti CD19)

## inMIND: PHASE 3 STUDY IN R/R FL AND MZL

PHASE 3 TRIAL OF TAFASITAMAB + LENALIDOMIDE + RITUXIMAB  
VERSUS PLACEBO + LENALIDOMIDE + RITUXIMAB FOR PATIENTS WITH R/R FL (GRADE 1–3A) OR MZL<sup>1,2</sup>



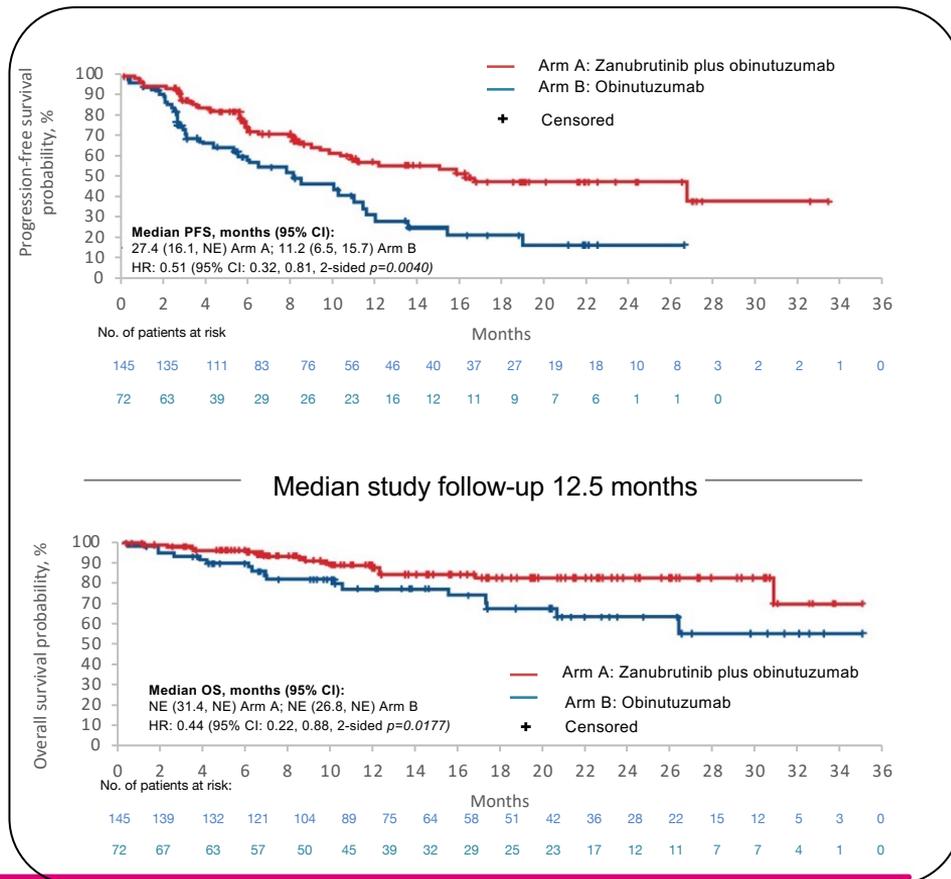
# ROSEWOOD: Response, PFS and OS

Disease Response by ICR			
	Zanubrutinib/ Obinutuzumab	Obinutuzumab	
<b>ORR (95% CI)</b>	<b>68.3% (60-75.7%)</b>	<b>45.8%</b>	<b><i>p=0.0017</i></b>
<b>Complete response</b>	<b>37.2%</b>	<b>19.4%</b>	
<b>Partial response</b>	<b>31%</b>	<b>26.4%</b>	
<b>Stable disease</b>	<b>17.2%</b>	<b>19.4%</b>	
<b>Disease progression</b>	<b>9%</b>	<b>20.8%</b>	

29 patients crossed over to Zanubrutinib/obinutuzumab

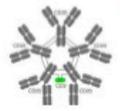


**ORR: 24.1% (CR: 6.9%)**



# Bispecific antibodies being explored in follicular lymphoma

Table 1. Comparative characteristics of CD20XCD3 BsAb currently in development

Product name	Schematic depiction	Format	Technology	CD20:CD3 ratio	CD3 done	CD20 clone	Fc silencing mutations*
Mosunetuzumab <sup>18</sup>		IgG1	Knobs-into-holes (different Fabs)	1:1	UCHT1v9 (CD3ε)	2H7 (type 1 epitope, identical to rituximab)	N297G (no FcγR binding)
Glofitamab <sup>15</sup>		IgG1	Head-to-tail fusion	2:1	SP34-der.(CD3ε)	By-L1 (type 2 epitope, identical to obinutuzumab)	IgG1-P329G-LALA (no FcγR binding)
Epcoritamab <sup>16</sup>		IgG1	Controlled Fab-arm exchange	1:1	huCACAO (SP34-der.)(CD3ε)	7D8 (type 1 epitope, shared by ofatumomab)	L234F,L235E,D265A (no FcγR,C1q binding)
Odronexamab <sup>17</sup>		IgG4	Heavy chains with different affinity	1:1	REG1250 (CD3ε)	3B9-10 (type 1 epitope, shared by ofatumomab)	Modified IgG4 (no FcγRIII binding)
Plamotamab <sup>20</sup>		IgG1	Fab-Fc x scFv-Fc	1:1	α-CD3_H1.30 (SP34-der.)(CD3ε)	C2B8_H1_L1 (type 1 epitope, shared by rituximab)	G236R, L328R (no FcγR binding)
IgM 2323 <sup>19</sup>		IgM	IgM + modified J chain	10:1	Not reported	Not reported	No

\*These Fc silencing mutations do not abolish the binding of BsAb to neonatal FcR.

# Mosunetuzumab monotherapy demonstrates durable efficacy with a manageable safety profile in patients with relapsed/refractory follicular lymphoma who received $\geq 2$ prior therapies: updated results from a pivotal phase II study

Pivotal, single-arm, multicenter, phase II expansion in patients with R/R FL and  $\geq 2$  prior therapies<sup>1</sup>

### Key inclusion criteria

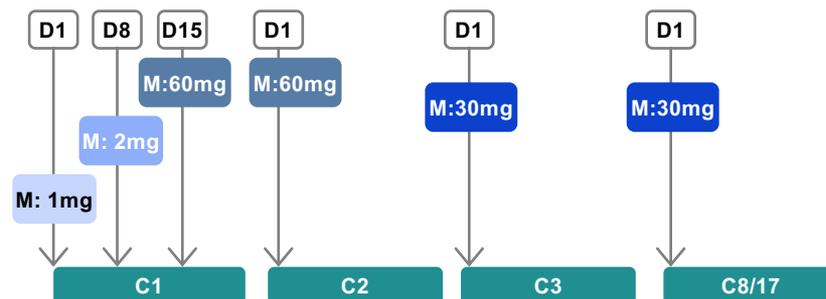
- FL grade 1–3A
- ECOG PS 0–1
- $\geq 2$  prior therapies including an anti-CD20 antibody and an alkylator

### Data analysis

- Study met its primary endpoint: 60% CR rate versus 14% historical control ( $p < 0.0001$ )<sup>2,3</sup>
- Updated efficacy and safety analysis with median **28.3 months of follow-up** (10 months after the previous report)

### Mosunetuzumab administration

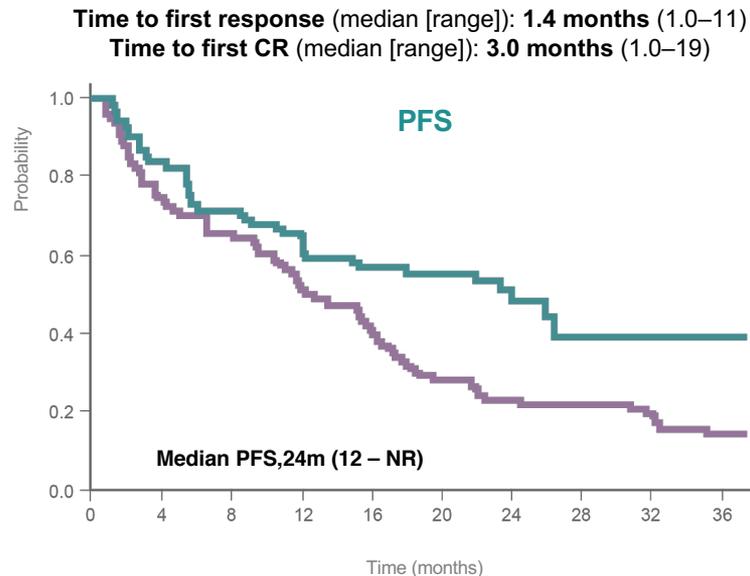
- IV mosunetuzumab administered in 21-day cycles with step-up dosing in C1
- Fixed-duration treatment: 8 cycles if CR after C8; 17 cycles if PR/SD after C8
- Re-treatment with mosunetuzumab permitted at relapse for patients who achieved CR
- No mandatory hospitalization



# Baseline characteristics and response

	N=90
Median age, years (range)	60 (29–90)
Male	61%
Ann Arbor stage	
I/II	23%
III/IV	77%
Median lines of prior therapy, n (range)	3 (2–10)
Refractory to last prior therapy	69%
Refractory to any prior anti-CD20 therapy	79%
Progression of disease within 24 months from start of first-line therapy (POD24)	52%
Double refractory to prior anti-CD20 and alkylator therapy	53%
Prior autologous stem cell transplant	21%

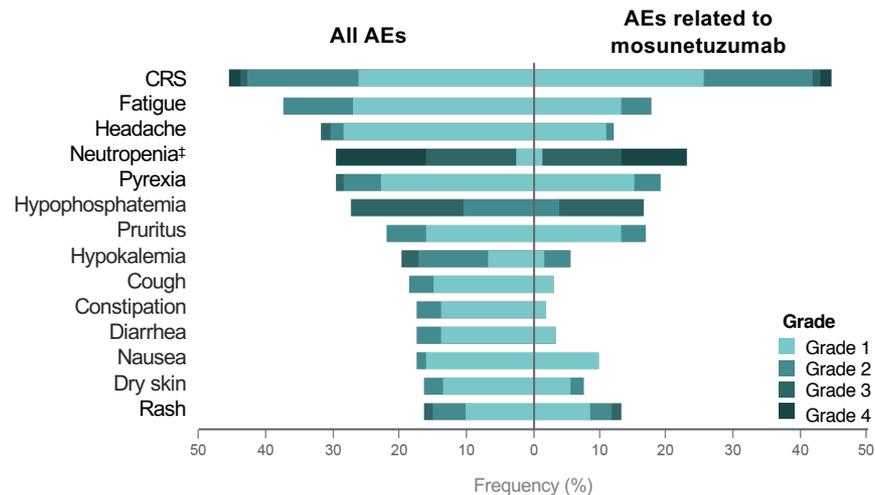
Efficacy endpoint in the overall population by investigator assessment	% (95% CI)
ORR	78% (68–86)
CR	60% (49–70)



# Safety profile

Adverse events (AEs)		N=90
<b>AE</b>		100%
Mosunetuzumab-related		92%
<b>Grade 3/4 AE</b>		70%
Mosunetuzumab-related		51%
<b>Serious AE</b>		47%
Mosunetuzumab-related		33%
<b>Grade 5 (fatal) AE</b>		2%*
Mosunetuzumab-related		0
<b>AE leading to treatment discontinuation</b>		4%†
Mosunetuzumab-related		2%

AEs (≥15%) by grade and relationship with mosunetuzumab



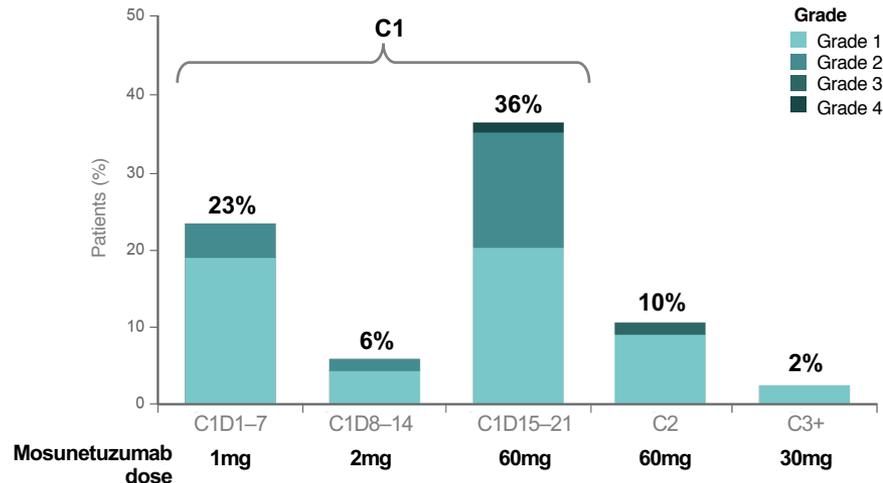
**No new serious AEs, grade ≥3 AEs, or treatment-related AEs were reported with 10 additional months of follow-up**

\*Malignant neoplasm progression (n=1) and unexplained death (n=1)  
 †Mosunetuzumab related: CRS (2 patients); mosunetuzumab unrelated: Epstein-Barr viremia and Hodgkin's disease (1 patient each)  
 ‡Grouped term including preferred term "neutropenia" and "neutrophil count decreased"  
 CRS: cytokine release syndrome

# CRS summary

CRS by ASTCT criteria <sup>1</sup>		N=90
CRS (any grade)		44%
Grade 1		26%
Grade 2		17%
Grade 3		1%
Grade 4		1%
<b>Median time to CRS onset, hours (range)</b>		
C1D1		5.2 (1.2–24)
	C1D15	27 (0.1–391)
<b>Median CRS duration, days (range)</b>		
		3 (1–29)
<b>Corticosteroids for CRS management</b>		11%
<b>Tocilizumab for CRS management</b>		8%
<b>Events resolved</b>		100%

CRS BY CYCLE AND GRADE

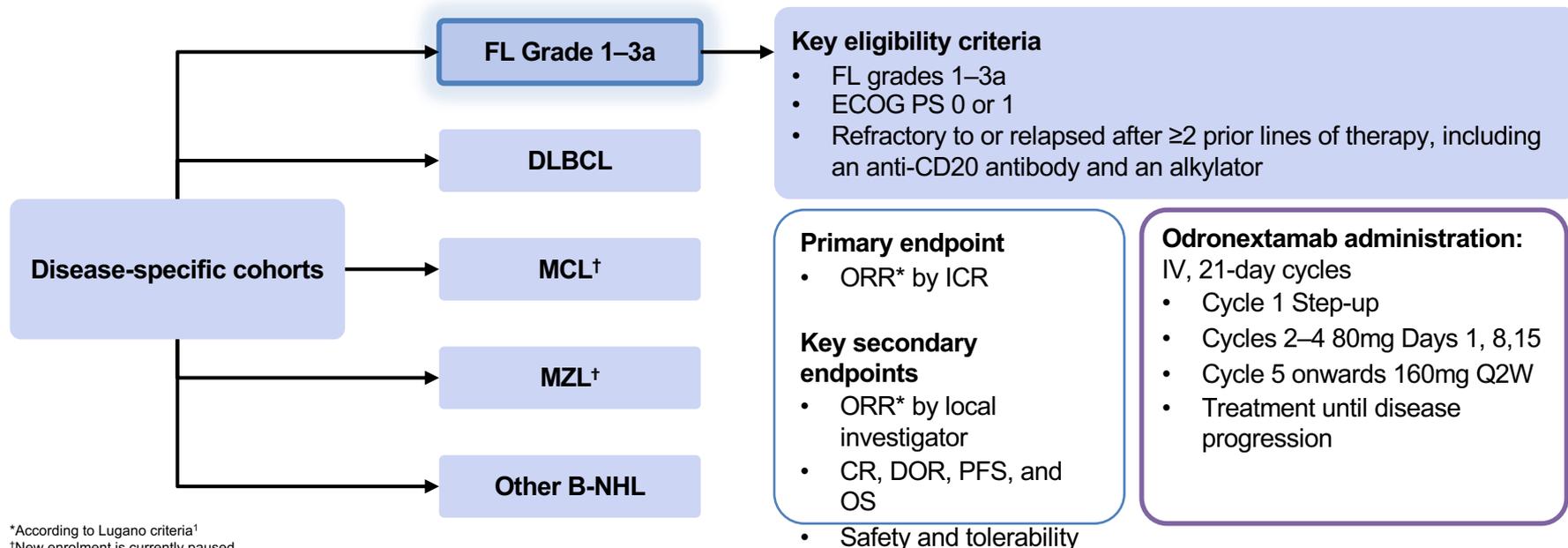


**CRS was predominantly low grade and during cycle 1**  
**All CRS events resolved; no new events were reported with 10 months of additional follow-up**  
**No correlation observed between the occurrence of CRS and tumor response**

<sup>1</sup>As per Lee DW, et al. Biol Blood Marrow Transplant 2019; 25: 625–638  
 ASTCT: American Society for Transplantation and Cellular Therapy

Mod. da: [Bartlett NL, et al. ASH 2022. Abstract 610](#)

# Odronextamab in Patients with Relapsed/Refractory (R/R) Follicular Lymphoma (FL) Grade 1–3a: Results from a Prespecified Analysis of the Phase 2 Study ELM-2



\*According to Lugano criteria<sup>1</sup>

<sup>†</sup>New enrolment is currently paused.

B-NHL, B-cell non-Hodgkin's lymphoma; CD, cluster of differentiation; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance score;

FL, follicular lymphoma; ICR, independent central review; IV, intravenous; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival;

R/R, relapsed/refractory; Q2W, every 2 weeks.

1. Cheson BD, et al. *J Clin Oncol*. 2014;32(27):3059–3068. Tae Min Kim et al. *ASH 2022*

# Odronextamab ELM2, RR FL, Baseline characteristics

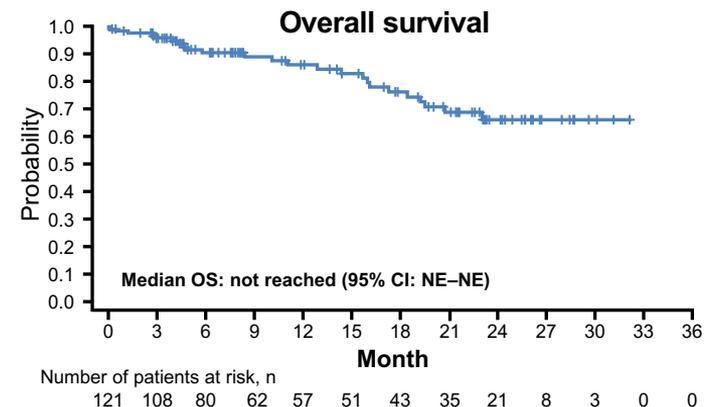
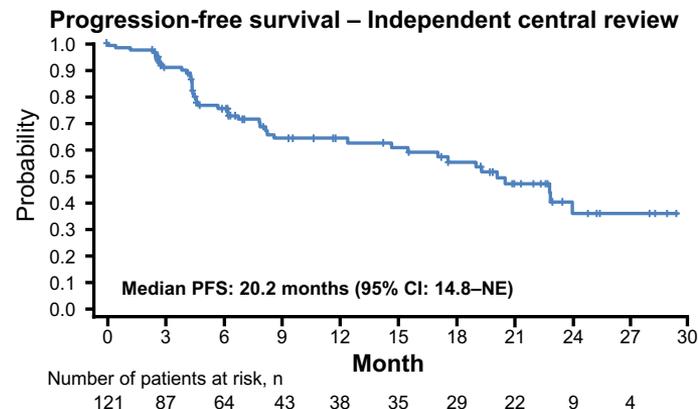
» Heavily pretreated, highly refractory patient population

Patient and disease characteristics	N=131
Median age, years (range)	61 (22–84)
Age ≥65	38.9%
Male	53.4%
Ann Arbor stage (I-II, III-IV)	15.3% / 84.7%
FLIPI risk score 0-1, 2, 3-5	14.5% / 26.7% / 58.8%
Bulky disease (investigator assessment)	13.7%
Median no. of prior lines, n (range)	3.0 (2–13)
Prior ASCT	30.5%
Prior PI3K inhibitor	13.7%
Prior R <sup>2</sup> (lenalidomide + rituximab)	13.7%
Refractory to last line of therapy	71.0%
Refractory to anti-CD20 antibody	74.8%
Double refractory to alkylator/anti-CD20 Ab	43.5%
POD24	48.1%

	N=131
Cycle 1 step-up regimen (1/20 mg) / (0/7/4/20 mg)	51.9% / 48.1%
Median duration of exposure, weeks (range)	22.1 (0.4–137.0)
Median number of doses (range)	19 (1–61)
Median number of cycles (range)	9.1 (0.1–66.5)
Completed cycle 1	95.4%
Completed ≥4 cycles	80.9%
Treatment ongoing	42.7%
Treatment discontinued	57.3%
Disease progression	19.8%
Patient or physician decision / withdrawal of consent	17.6%
Adverse event	9.9%
Death	9.9%

# Odronextamab efficacy

Independent central review	
<b>Best overall response</b>	<b>N=121*</b>
Objective response rate (ORR) <sup>†</sup>	<b>81.8%</b> [95% CI: 73.8–88.2%]
Complete response	<b>75.2%</b>
Partial response	6.6%
Stable disease	5.8%
Progressive disease	4.1%

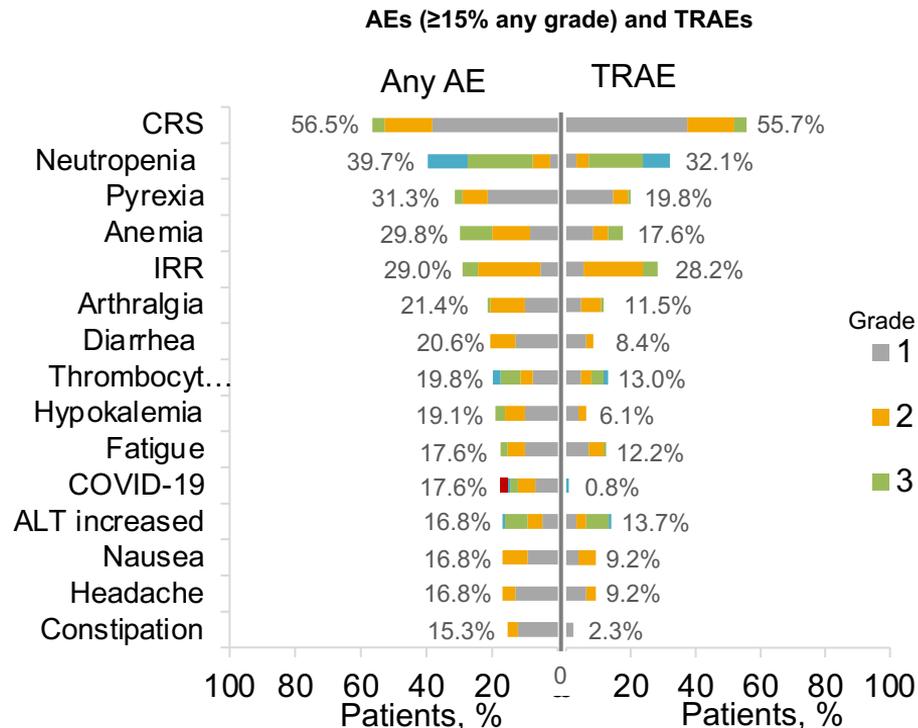


Data cut off date: Sep 15, 2022.  
 \*Efficacy evaluable (with an opportunity for assessment at 12 weeks); ORR = Complete responses + Partial responses.  
 CI, confidence interval; FL, follicular lymphoma; ORR, objective response rate; NE, not-evaluated.

# Odronextamab safety profile

Treatment-emergent adverse events, n (%)	Patients N=131	
	All events	TRAEs
Any TEAE	131 (100%)	118 (90.1%)
Grade ≥3 TEAE	102 (77.9%)	73 (55.7%)
Serious AE	81 (61.8%)	53 (40.5%)
Grade 5 TEAE	17 (13.0%)	3 (2.3%)
Related to COVID-19	7 (5.3%)	0
Other grade 5 events	10 (7.6%)	3 (2.3%)
TEAE leading to treatment discontinuation	15 (11.5%)	10 (7.6%)

- Grade 5 TRAEs: pneumonia, PML, systemic mycosis (n=1 each)
- TRAEs leading to treatment discontinuation: IRR (n=2); IRR and tremor (n=1); ALT increase; arthralgia; CRS; epilepsy; PML; viral bronchitis; weight decrease (n=1 each)



Data cut of date: Sep 15, 2022.

AEs per NCI-CTCAE v5.0. CRS per Lee 2019.

AE, adverse event; ALT, alanine aminotransferase; CRS, cytokine release syndrome; IRR, infusion related reaction; PML, Progressive multifocal leukoencephalopathy; TEAE, treatment-emergent adverse event; TRAE, treatment-related AE.

# Adverse events: Cytokine release Syndrome

n, (%)	1/20 regimen (N=68)	0.7/4/20 regimen (N=63)
CRS any Grade	38 (55.9%)	36 (57.1%)
Grade 1	22 (32.4%)	28 (44.4%)
Grade 2	12 (17.6%)	7 (11.1%)
Grade 3	4 (5.9%)	1 (1.6%)
Grade 4	0	0
Grade 5	0	0
Received corticosteroids	11 (16.2%)	17 (27.0%)
Received tocilizumab	9 (13.2%)	12 (19.0%)
Received vasopressors	4 (5.9%)	1 (1.6%)

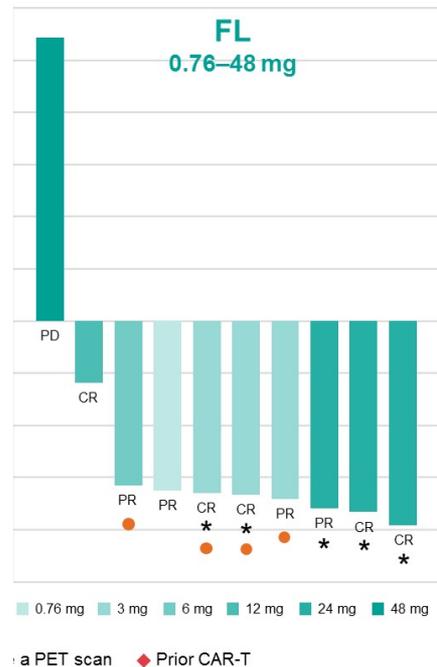
- 0.7/4/20 mg step-up regimen reduced the incidence of grade 2 and grade 3 CRS
- Approximately half of patients with R/R FL had CRS, mostly grade 1
- Only 1 case of grade 3 CRS with 0.7/4/20 mg step-up regimen and no grade 4 or higher CRS events
- All CRS events resolved with a median time to resolution of 2 days (range 1–51)
- No patients required mechanical ventilation or ICU admission for the management of CRS

# Subcutaneous epcoritamab in patients with relapsed/refractory FL results from the phase I study

N=12 (12-48-60mg)  
 Median age 73 (63-76)  
 Mean Previous lines 5 (2.5-8)  
 Refractory to last prior therapy 83%  
 Double refractory (antiCD and alkil) 75%  
 Prior ASCT 8%

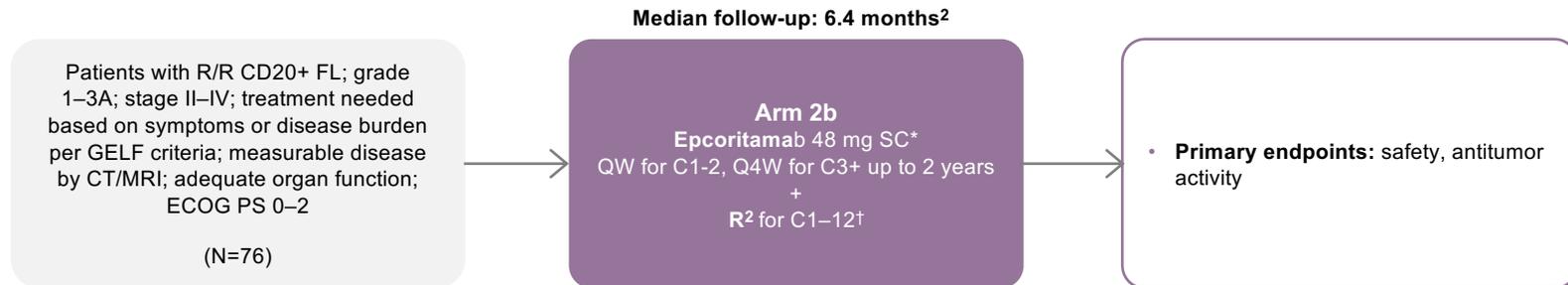
ORR 90%,  
 CRR 50%

AEs (DLBCL + FL + MCL N=68)  
 • pyrexia 69%,  
 • CRS; Steroids used in all cases% 59%, all grade 1-2  
 • Grade 3-4 neutropenia 27%  
 • No discontinuations due to Aes



# EPCORE NHL-2: study design

- Multicenter, open-label phase Ib/II trial (current analysis reported data from arm 6 and arm 2b)



\*Epcoritamab administered in 28-day cycles, with step-up dosing comprising priming and intermediate doses prior to first full dose, along with corticosteroid as CRS prophylaxis. †Rituximab 375 mg/m<sup>2</sup> IV QW for C1, Q4W for C2–6 (arm 6) or C2–5 (arm 2b); lenalidomide 20 mg PO QD x 21 days for C1–12.

GELF: Groupe d'Etude des Lymphomes Folliculaires

# EPCORE NHL-2: baseline characteristics

Characteristic		R/R FL <sup>2</sup> (N=76)
Median age, yr (range)		64 (30–79)
Female, N (%)		37 (49)
Median time from dx to first dose, weeks (range)		--
Ann Arbor stage, N (%)	I-II*	12 (16)
	III	19 (25)
	IV	45 (59)
Histologic grade, N (%)	1	6 (8)
	2	37 (49)
	3A	24 (32)
FLIPI, N (%) <sup>†</sup>	0-1	7 (9)
	2	24 (32)
	3–5	39 (51)
ECOG PS, N (%)	0	48 (63)
	1	25 (33)
	2	3 (4)

Characteristic	R/R FL <sup>2</sup> (N=76)
Median time from dx to first dose, months (range)	59 (4–331)
Median time from end of last line of tx to first dose, months (range)	16 (0.2–198)
Median no. prior lines of tx, n (range)	1 (1–9)
• 1 prior line, N (%)	41 (54)
• 2 prior lines, N (%)	21 (28)
• ≥3 prior lines, N (%)	14 (18)
Primary refractory <sup>‡</sup> disease, N (%)	29 (38)
Double refractory <sup>§</sup> disease, N (%)	30 (39)
POD24, <sup>  </sup> N (%)	32 (42)
Refractory <sup>‡</sup> to last line of tx, N (%)	29 (38)
Prior ASCT, N (%)	8 (11)
Prior CAR-T-cell therapy, N (%)	2 (3)

\*For R/R arm 2b, all patients stage II. †Unknown for 3 and 6 patients in 1L and R/R FL arms, respectively  
<sup>‡</sup>No response or relapse within 6 months after prior therapy. <sup>§</sup>Refractory to both anti-CD20 and an alkylating agent  
<sup>||</sup>Progression within 2 years of initiating first-line treatment including immunochemotherapy.  
 Dx: diagnosis; tx: treatment

# EPCORE NHL-2: safety

TEAE, N (%)	R/R FL <sup>2</sup> (N=76)
Median no. of epcoritamab cycles initiated (range)	6 (1–11)
Grade ≥3 TEAE	53 (70)
• Related to epcoritamab	29 (38)
Fatal TEAE*	3 (4)
Epcoritamab dose delay due to TEAE	40 (53)
• Related to epcoritamab	19 (25)
Epcoritamab discontinuation due to TEAE	5 (7)
• Related to epcoritamab	0

- No clinical TLS was observed
- 1 patient had grade 1 ICANS, which resolved in 7 days (R/R)

\*1 patient each with COVID-19 pneumonia and septic shock in 1L FL arm and 3 patients with COVID-19 in R/R FL arm  
 TLS: tumor lysis syndrome

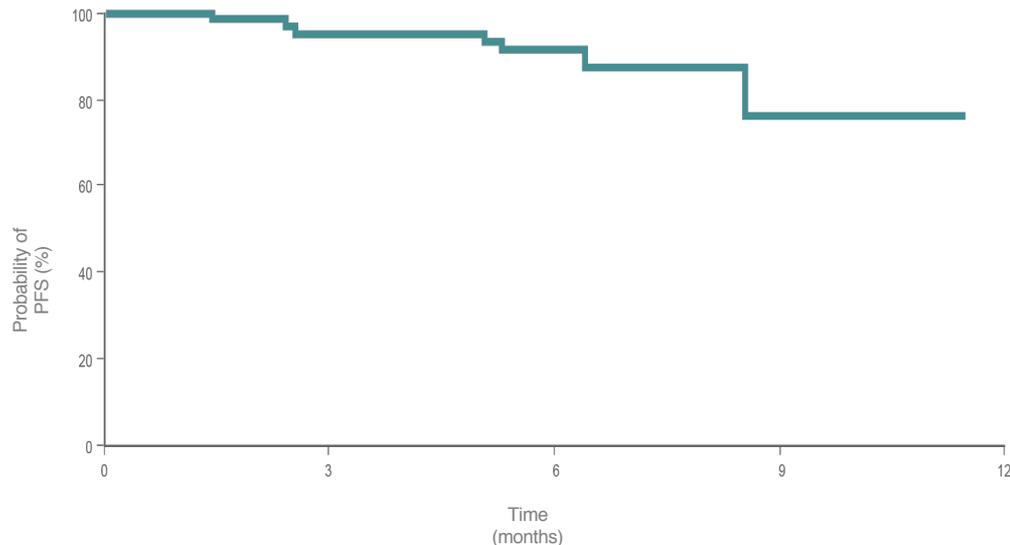
# EPCORE NHL-2: R/R FL

## RESPONSES ACROSS HIGH-RISK SUBGROUPS



Deep responses consistent across high-risk R/R FL subgroups

## PROGRESSION-FREE SURVIVAL



Median PFS not reached (95% CI, 8.5–not reached)

Data cutoff: September 16, 2022.

<sup>a</sup> Refractory indicates no response or relapse within 6 months after prior therapy

<sup>b</sup> Double refractory indicates refractory to both anti-CD20 and an alkylating agent

<sup>c</sup> Progression within 2 y of initiating first-line treatment that included immunochemotherapy

# Mosunetuzumab in Combination with Lenalidomide has a Manageable Safety Profile and Encouraging Activity in Patients with Relapsed/Refractory Follicular Lymphoma: Initial Results from a Phase Ib Study

N=29	
Age in years, median (range)	59 (30–79)
Male	13 (44.8%)
Ann Arbor stage at study entry	
I–II	2 (6.8%)
III–IV	27 (93.1%)
FLIPI risk factors at study entry	
0–1	7 (24.1%)
2	8 (27.6%)
3–5	14 (48.3%)
Number of prior lines of therapy, median (range)	1 (1–6)
1 prior line	16 (55.2%)
≥2 prior lines	13 (44.8%)
Refractory to any prior aCD20 therapy	9 (31.0%)
Refractory to any prior aCD20 therapy AND an alkylating agent (double refractory)	7 (24.1%)
POD24	3 (10.3%)

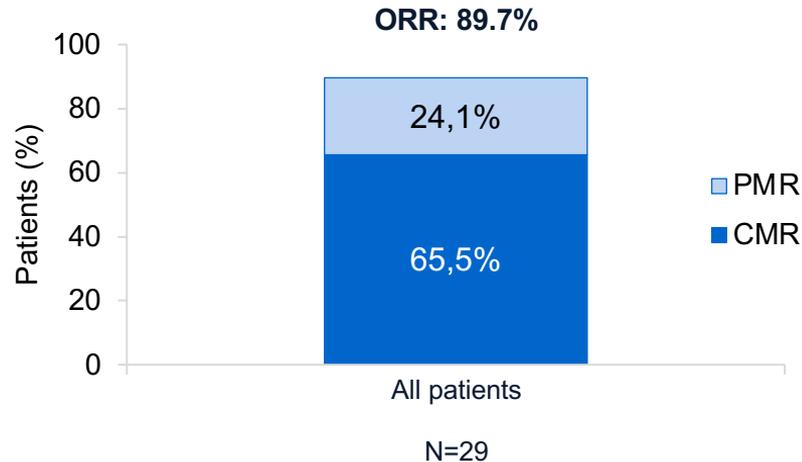
- **Most patients had advanced stage disease**
- **31.0% were refractory to aCD20 therapy**

All patients had Grade 1–3a FL at entry; ECOG PS at entry was 0 in 19 patients (67.9%) and 1 in 9 patients (32.1%); no patient had received prior lenalidomide; cut-off date: Sept 13, 2021; FLIPI, follicular lymphoma International Prognostic Index

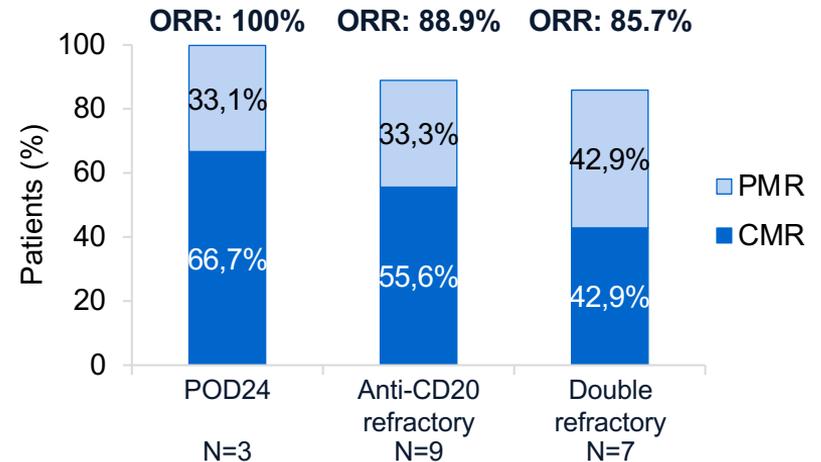
# Response

- Median time to first / best response: 2.5 mo (range: 1.4–5.3) / 2.5 mo (range: 1.4–10.7)

Best response by PET-CT in all patients\*



Best response by PET-CT in patient subgroups\*



- **High ORR and CMR rate in overall population and in patients with high-risk disease**

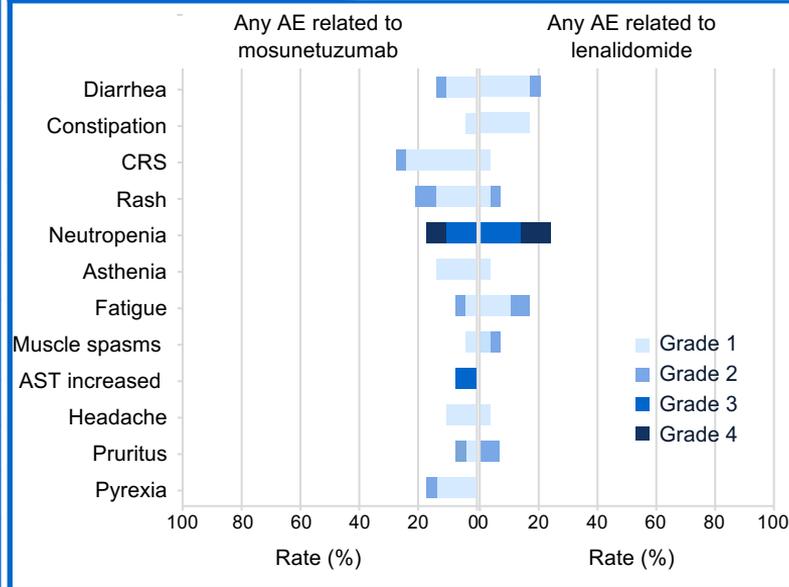
\*assessed by investigators using Lugano 2014 criteria<sup>1</sup>; CMR, complete metabolic response; mo, months; ORR, overall response rate; PET-CT, positron emission tomography-computed tomography; PMR, partial metabolic response

# Adverse event summary

- Median duration of follow-up: 5.4 months (range: 3–12)

	N=29
AE	29 (100%)
Related to mosunetuzumab / lenalidomide	27 (93.1%) / 23 (79.3%)
Grade 3–4 AE	13 (44.8%)
Related to mosunetuzumab / lenalidomide	1 (3.4%) / 1 (3.4%)
Serious AE	9 (31.0%)
Related to mosunetuzumab / lenalidomide	6 (20.7%) / 1 (3.4%)
Grade 5 (fatal) AE	0
AE leading to mosunetuzumab / lenalidomide discontinuation	0 / 1 (3.4%)
AE leading to mosunetuzumab dose delay	6 (20.7%)
AE leading to lenalidomide dose reduction	2 (6.9%)
AE leading to lenalidomide temporary dose interruption	6 (20.7%)
AE leading to lenalidomide dose reduction AND temporary dose interruption	4 (13.7%)

AEs with ≥15% incidence overall and corresponding rates of treatment-related events by Grade



- **M-Len had a favorable safety profile. No AEs led to mosunetuzumab discontinuation.**

# Altri approcci terapeutici di salvataggio nel linfoma follicolare

- » Numerose opzioni chemofree in arrivo per la malattia recidivata/refrattaria
  - » Approccio Standard:
    - Dati consolidati: R2
    - In futuro: Obino-Zanubrutinib (studio Mahogany), Tafa-R2 (studio inMIND)
  - » T-cell engagement oltre le CART:
    - In arrivo: Mosunetuzumab (3L+)
    - In futuro: Bites in mono or combo
  - » Come immaginare il futuro per la terapia dei LF RR?
    - dati di retreatment
    - dati di sequenza
    - Prima linea?
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