

CONVEGNO INTERREGIONALE SIE

Delegazioni Umbria e Marche

Società Italiana di Ematologia

NOVITÀ TERAPEUTICHE NEI LINFOMI NON-HODGKIN E MIELOMA MULTIPLO: FOCUS SU ANTICORPI BISPECIFICI E CAR-T

Assisi, Sala Conciliazione, Comune di Assisi
4 Novembre 2026

Novità terapeutiche nei linfomi non-Hodgkin indolenti

Monia Capponi

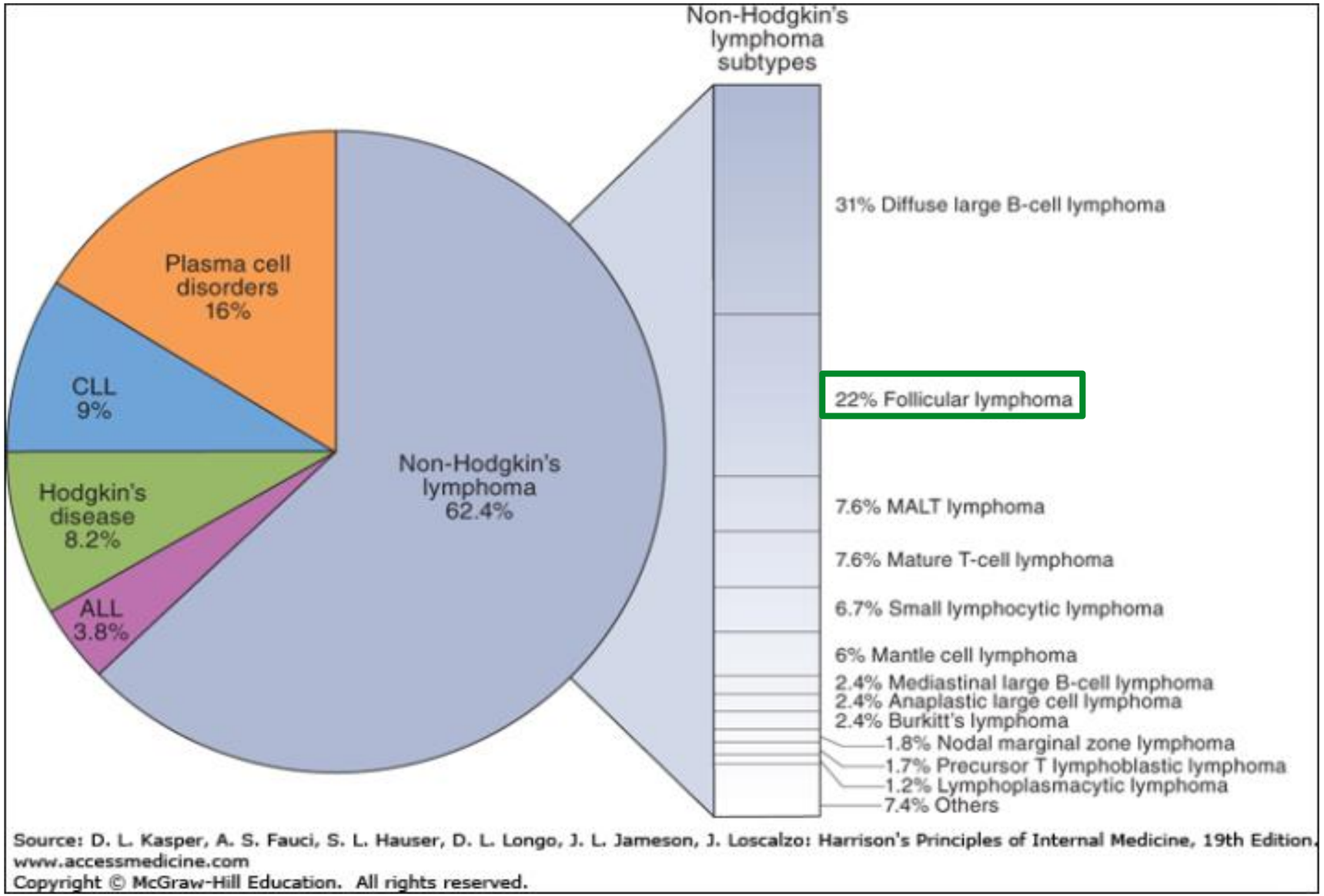
S.C. di Ematologia con trapianto

Azienda Ospedaliera di Perugia

Disclosures of Monia Capponi

Company name	**Research support**	**Employee**	**Consultant**	**Stockholder**	**Speakers bureau**	**Advisory board**	Other

B – cell lymphoprolipherative diseases



Source: D. L. Kasper, A. S. Fauci, S. L. Hauser, D. L. Longo, J. L. Jameson, J. Loscalzo: Harrison's Principles of Internal Medicine, 19th Edition.
www.accessmedicine.com
Copyright © McGraw-Hill Education. All rights reserved.

Considerations in Frontline FL

Frontline FL Treatment Guidelines

Lymphomas: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆ **Annals of Oncology, 2025; 36: 11**

Frontline is dominated by chemoimmunotherapy

1L

Symptomatic, Stage II-IV, HTB

- R/O-Benda
- $R^{2\dagger}$
- R/O-CHOP
- R
- R/O-CVP

Asymptomatic, Stage II-IV, LTB

- Rituximab
- Active Observation‡

Maintenance (optional)§

- Rituximab
- Obinutuzumab

B-Cell Lymphomas 3.2025

Featured Updates to the NCCN Guidelines

1L

Preferred, HTB

- R/O-Benda
- R/O-CHOP
- R/O-CVP
- R^2

Preferred, LTB, Older/Infirm

- Rituximab

Maintenance (optional)

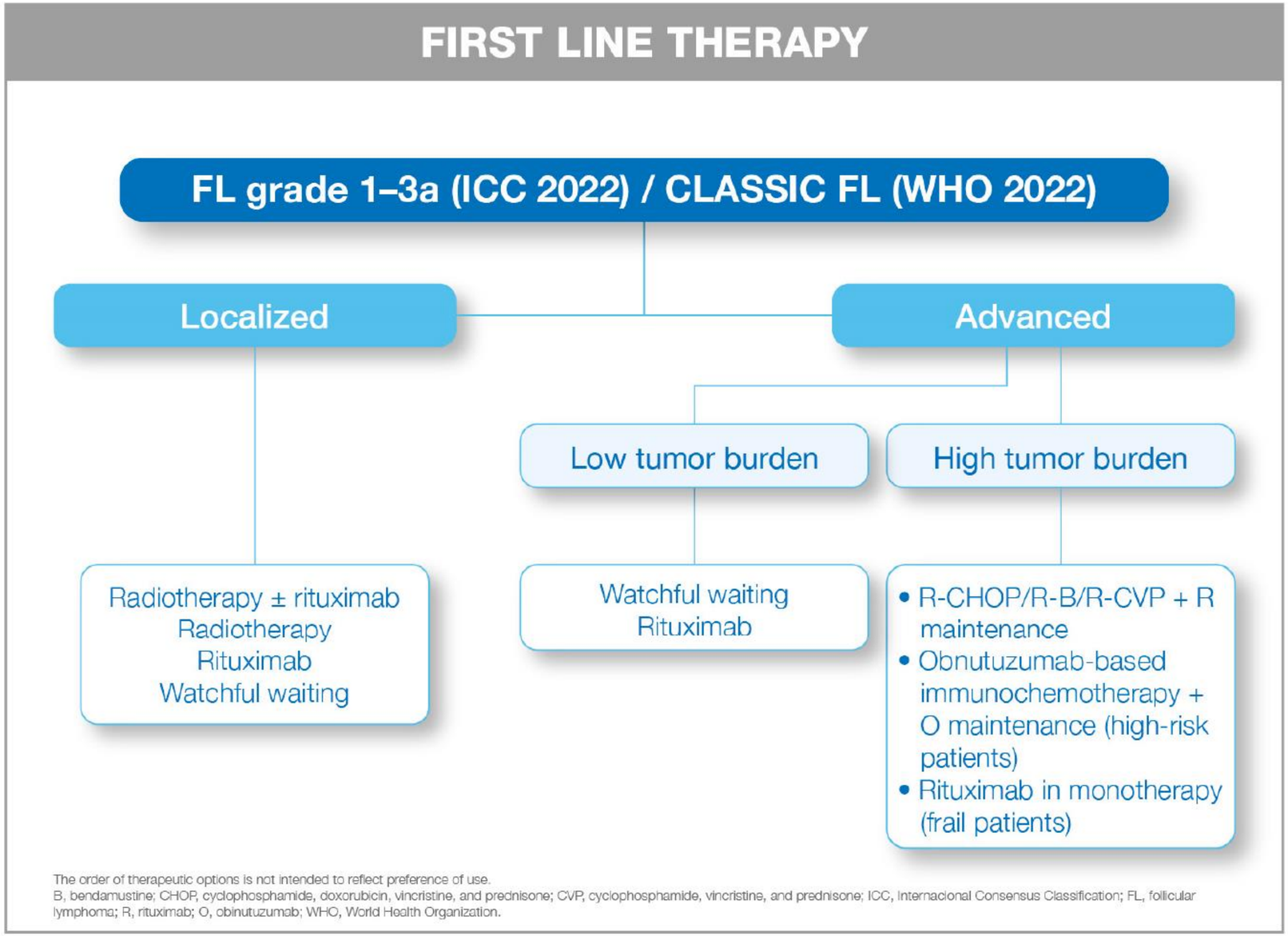
- Rituximab‖
- Obinutuzumab

There are no other targeted agents outside of anti-CD20 mAbs

*All recommendations are Category 1B unless otherwise indicated. †R^2 is not EMA or FDA approved. ‡Category 1A. §Category 1C; single-agent R ± R maintenance is Category 3B. ¶Recommendations are category 2A unless otherwise indicated. ‖Category 1. 1L, first line (of therapy); ASCT, allogeneic stem cell transplant; Benda, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine, Prednisone; CVP, cyclophosphamide, vincristine, prednisone; ESMO, European Society for Medical Oncology; FL, follicular lymphoma; HTB, high tumor burden; LTB, low tumor burden; mAbs, monoclonal antibodies; NCCN, National Comprehensive Cancer Network; O, obinutuzumab; R, rituximab; R^2, rituximab + lenalidomide; RIT, radioimmunotherapy; tafa, tafasitamab.

1. T A Eyre et al. Ann Oncol. 2025;36(11):1263-1284. 2. ESMO Lymphomas Living Guideline, v1.1 February 2026. https://www.esmo.org/guidelines/living-guidelines/esmo-living-guideline-lymphomas/follicular-lymphoma-fl. Accessed May 2026. 3. National Comprehensive Cancer Network, Inc. NCCN Guidelines for B-Cell Lymphomas V3.2026.

GELTAMO GUIDELINES 2025

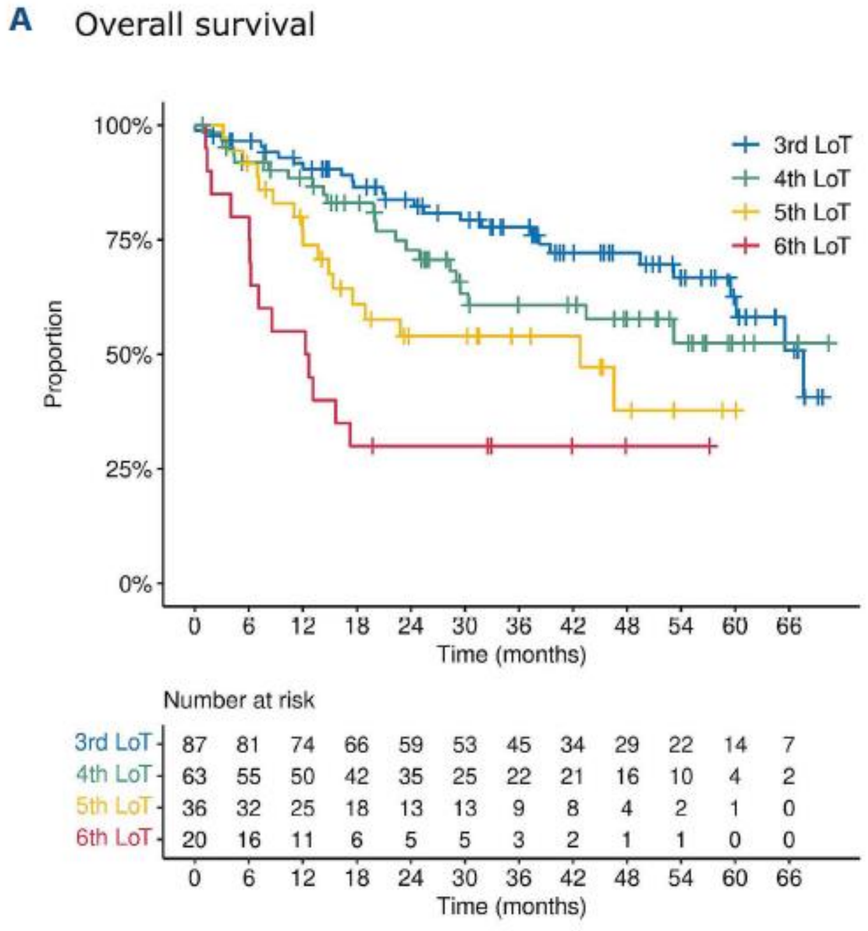


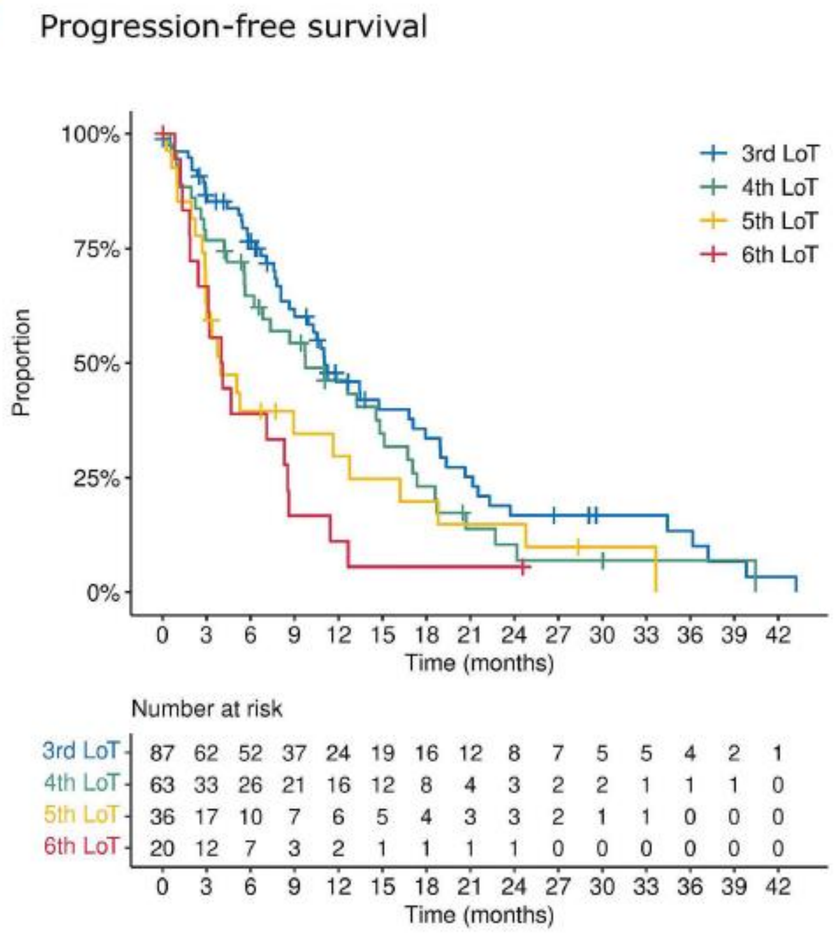
Cancers **2026**, *18*, 395

FOLLICULAR LYMPHOMA

SCHOLAR-5 study:

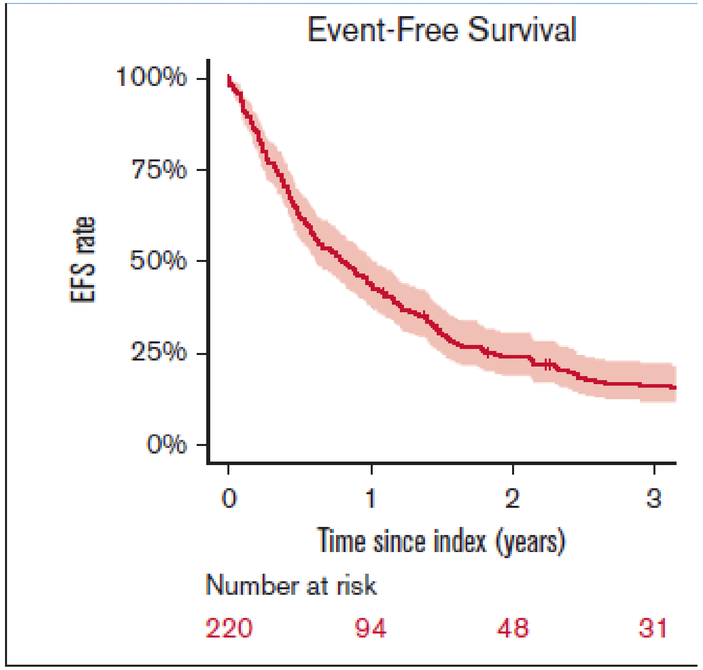
OS after 1° LoT is > 20 years, but this survival rate declines with each subsequent line of treatment



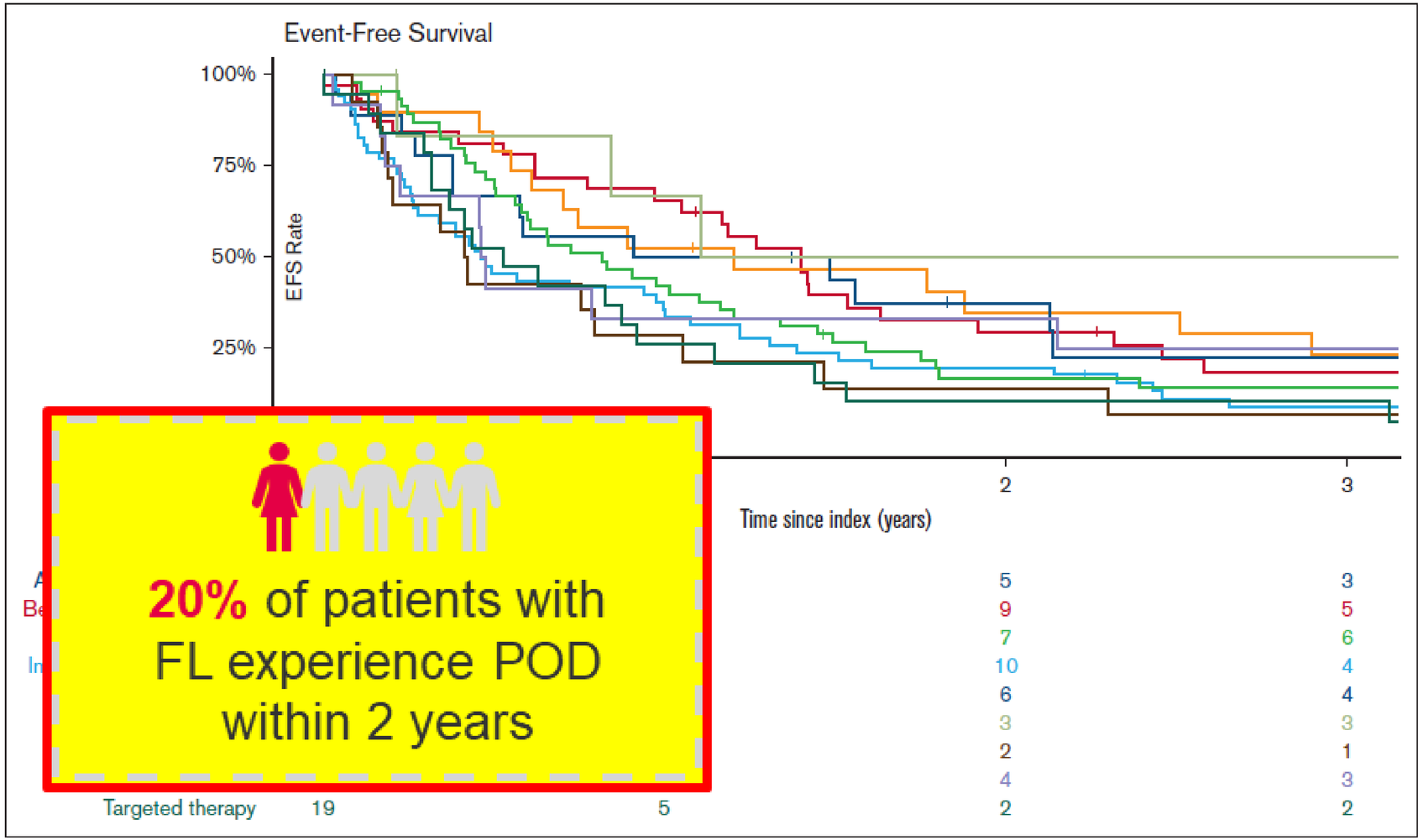


Ghione P, Palomba M.L. et al, Haematol. 2022; 108; 3: 822 - 832

OUTCOME IN FOLLICULAR LYMPHOMA WITH POD24: an analysis from the LEO Consortium

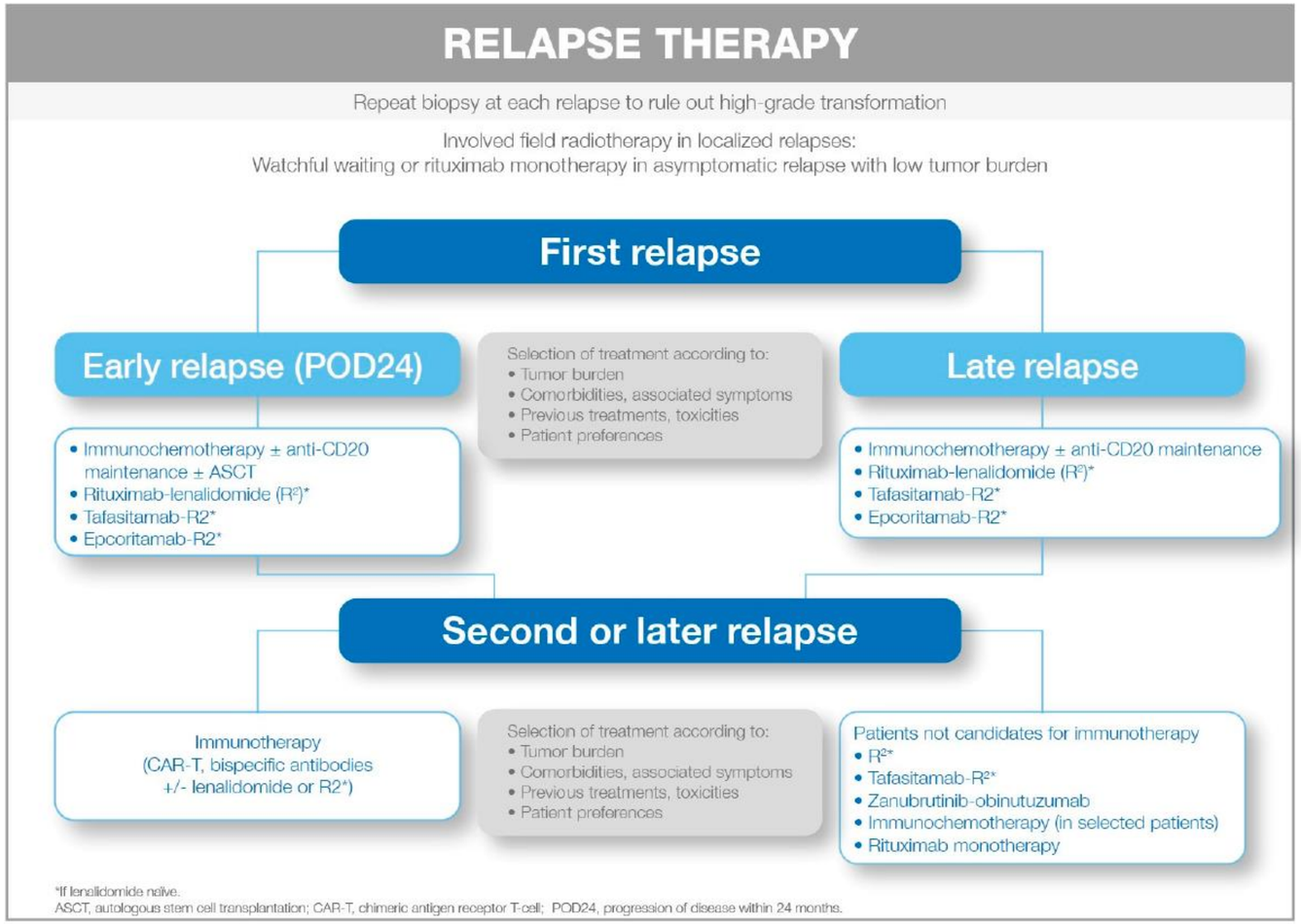


2 yrs EFS 24%
5 yrs EFS 12%
Median EFS 9,8 mths

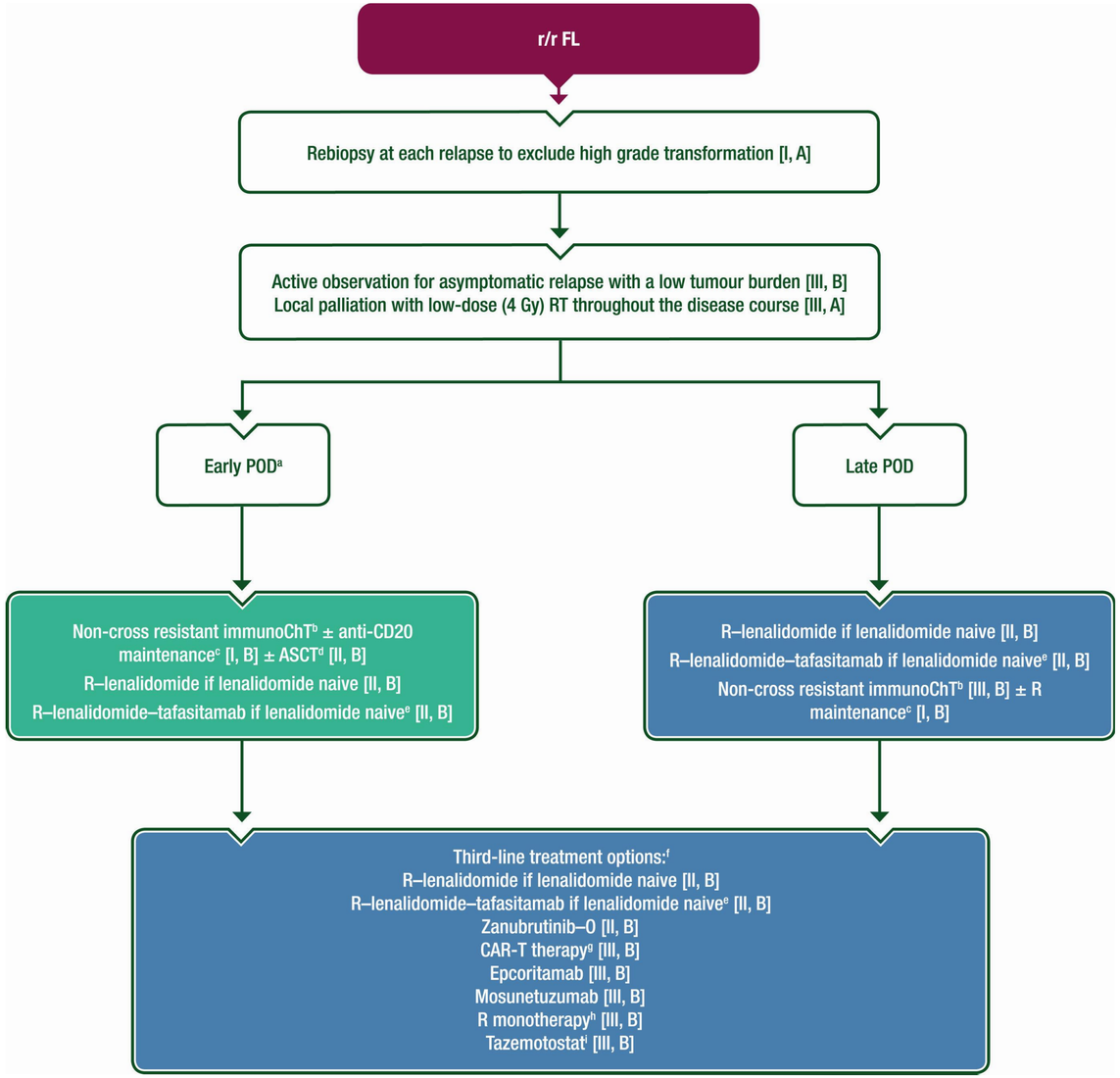


Day R. J., Larson M.C. et al, Blood Advances ; 11 March 2025; 9: 1013

GELTAMO GUIDELINES 2025



ESMO GUIDELINES 2025



NCCN Clinical Practice Guidelines in Oncology for B-Cell Lymphomas, Version 3.2025

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/m² 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/m² one dose every 12 we
- Obinutuzumab maintenance for rituximab-refractory dise

SECOND-LINE CONSOLIDATIO

- High-dose therapy with autologous stem cell rescue (HD

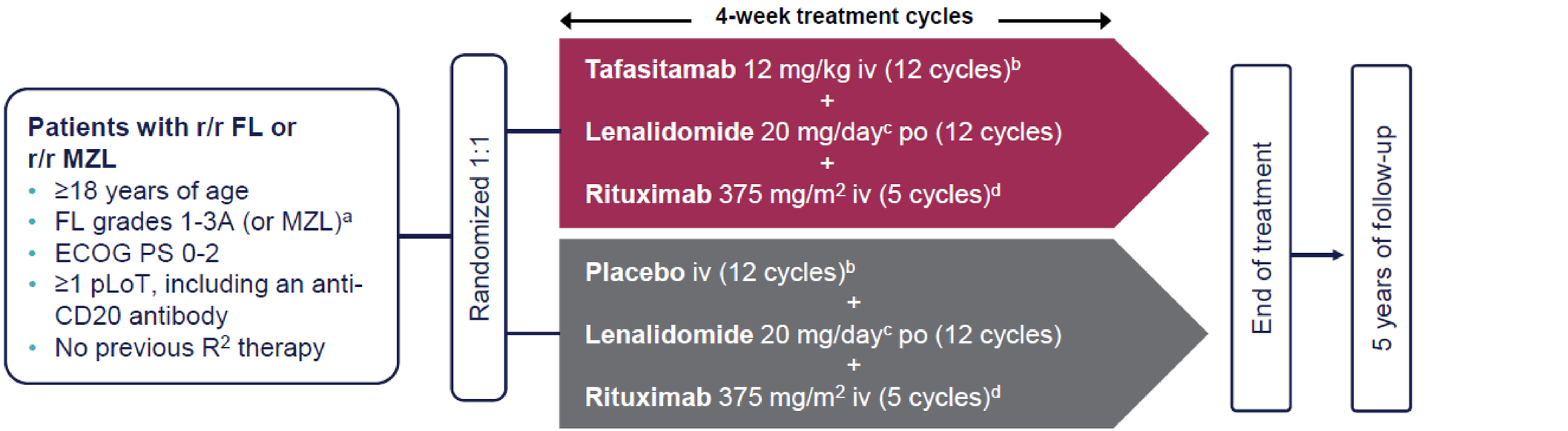
Version 3.2025 © 2025 National Comprehensive Cancer Network® (NCCN®). All rights reserved.
The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Clinical Practice Recommendations for Hematopoietic Cell Transplantation and Cellular Therapies in Follicular Lymphoma: A Collaborative Effort on Behalf of the American Society for Transplantation and Cellular Therapy and the European Society for Blood and Marrow Transplantation

1. The panel **recommends** autologous transplant as an option for consolidation therapy in eligible, relapsed POD24 FL patients who have achieved complete or partial remission after second line therapies.	19 (70)	8 (30)	Yes
2. The panel **DOES NOT** recommend autologous transplant as consolidation therapy in eligible, relapsed FL patients who do not achieve complete or partial remission after second or subsequent line therapies.	26 (96)	1 (4)	Yes

Transplantation and Cellular Therapy 30 (2024) 832–843

inMIND: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study



Study endpoints in the FL population (investigator-assessed unless specified)

• **Primary:**	**PFS**
• Key secondary:	PET-CR rate in the FDG-avid population, OS
• Select other secondary:	PFS by IRC, ORR, DoR, safety, QoL, MRD
• Exploratory:	TTNT, B-cell recovery, Ig levels, CD19 expression

Stratification factors (patients with FL)
- POD24-ID (yes or no)
- Refractoriness to previous CD20-directed mAb (yes or no)
- Number of pLoTs (1 or ≥2)

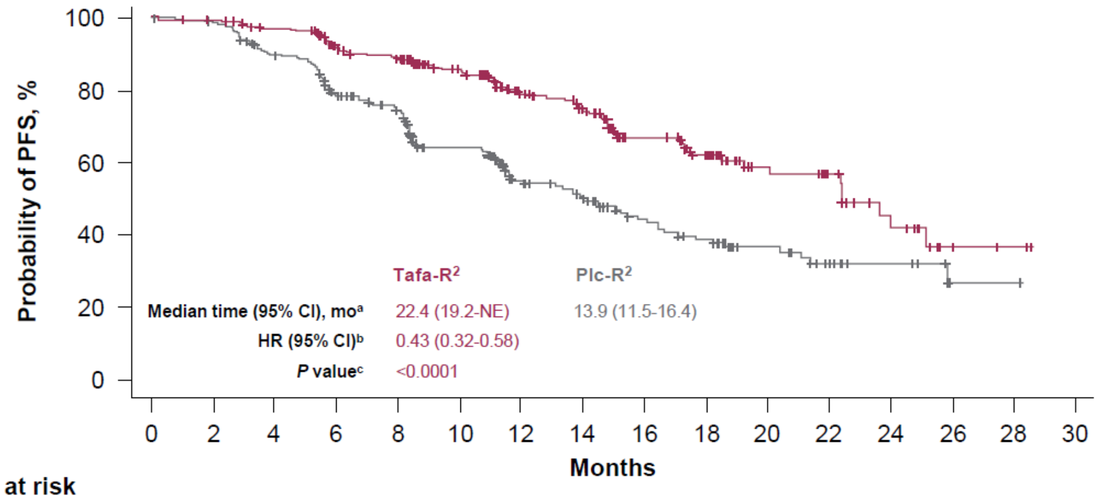
Sehn LH, et al. ASH 2024. Oral presentation LBA-1. 2. ClinicalTrials.gov. inMIND. Accessed Jun 2025

FL Patients' Baseline Characteristics

Characteristics	Tafa-R² (n=273)	Plc-R² (n=275)	POD24-IT-positive			POD24-IT-negative			Total (N=548)
			Tafa-R² (n=121)	Plc-R² (n=128)	Total (n=249)	Tafa-R² (n=142)	Plc-R² (n=140)	Total (n=282)	
Median age, years (range)	64.0 (36-88)	64.0 (31-85)	64.0 (36-88)	62.0 (31-84)	63.0 (31-88)	65.0 (38-88)	67.0 (31-85)	66.0 (31-88)	64.0 (31-88)
≥75, n (%)	54 (19.8)	54 (19.6)	27 (22.3)	19 (14.8)	46 (18.5)	27 (19.0)	34 (24.3)	61 (21.6)	108 (19.7)
Male sex, n (%)	150 (54.9)	149 (54.2)	72 (59.5)	65 (50.8)	137 (55.0)	73 (51.4)	79 (56.4)	152 (53.9)	299 (54.6)
Median time since initial FL diagnosis, years (range)	5.2 (0-34)	5.5 (1-33)	3.4 (0-34)	2.7 (1-33)	3.1 (0-34)	6.7 (2-25)	8.5 (2-33)	7.7 (2-33)	5.3 (0-34)
ECOG PS at screening, n (%)									
0	181 (66.3)	192 (69.8)	77 (63.6)	86 (67.2)	163 (65.5)	97 (68.3)	102 (72.9)	199 (70.6)	373 (68.1)
1-2	92 (33.7)	83 (30.2)	44 (36.4)	42 (32.8)	86 (34.5)	45 (31.7)	38 (27.1)	83 (29.4)	175 (31.9)
Bone marrow involvement, n (%)									
Yes	88 (32.2)	91 (33.1)	NA	NA	NA	NA	NA	NA	179 (32.7)
No	169 (61.9)	162 (58.9)	NA	NA	NA	NA	NA	NA	331 (60.4)
Unknown/missing	16 (5.9)	22 (8.0)	NA	NA	NA	NA	NA	NA	38 (6.9)
Ann Arbor stage, n (%)									
I or II	52 (19.0)	50 (18.2)	23 (19.0)	16 (12.5)	39 (15.7)	29 (20.4)	32 (22.9)	61 (21.6)	102 (18.6)
III or IV	221 (81.0)	225 (81.8)	98 (81.0)	112 (87.5)	210 (84.3)	113 (79.6)	108 (77.1)	221 (78.4)	446 (81.4)
FL grade, n (%)									
1 or 2	203 (74.4)	203 (73.8)	88 (72.7)	89 (69.5)	177 (71.1)	109 (76.8)	108 (77.1)	217 (77.0)	406 (74.1)
3A	67 (24.5)	71 (25.8)	31 (25.6)	38 (29.7)	69 (27.7)	32 (22.5)	32 (22.9)	64 (22.7)	138 (25.2)
B symptoms, n (%)	63 (23.1)	67 (24.4)	28 (23.1)	36 (28.1)	64 (25.7)	33 (23.2)	31 (22.1)	64 (22.7)	130 (23.7)
FLIPI score, n (%)									
0 or 1	57 (20.9)	57 (20.7)	22 (18.2)	21 (16.4)	43 (17.3)	35 (24.6)	36 (25.7)	71 (25.2)	114 (20.8)
2	79 (28.9)	67 (24.4)	33 (27.3)	30 (23.4)	63 (25.3)	42 (29.6)	36 (25.7)	78 (27.7)	146 (26.6)
3-5	137 (50.2)	150 (54.5)	66 (54.5)	77 (60.2)	143 (57.4)	65 (45.8)	67 (47.9)	132 (46.8)	287 (52.4)
GELF criteria, n (%)	222 (81.3)	232 (84.4)	97 (80.2)	109 (85.2)	206 (82.7)	117 (82.4)	117 (83.6)	234 (83.0)	454 (82.8)
Relapsed/refractory status to last therapy, n (%)									
Relapsed	148 (54.2)	164 (59.6)	49 (40.5)	59 (46.1)	108 (43.4)	97 (68.3)	101 (72.1)	198 (70.2)	312 (56.9)
Refractory	112 (41.0)	97 (35.2)	68 (56.2)	67 (52.3)	135 (54.2)	36 (25.4)	27 (19.3)	63 (22.3)	209 (38.1)
Undetermined	13 (4.8)	14 (5.1)	4 (3.3)	2 (1.6)	6 (2.4)	9 (6.3)	12 (8.6)	21 (7.4)	27 (4.9)
FL diagnosis confirmed by central pathology, n (%)	256 (93.8)	259 (90.5)	NA	NA	NA	NA	NA	NA	505 (92.2)
Refractory to prior CD20-directed therapy, n (%)	118 (43.2)	115 (41.8)	80 (66.1)	86 (67.2)	166 (66.7)	32 (22.5)	25 (17.9)	57 (20.3)	233 (42.5)

PFS by Investigator Assessment

Primary Endpoint (FL Population)[1,2]

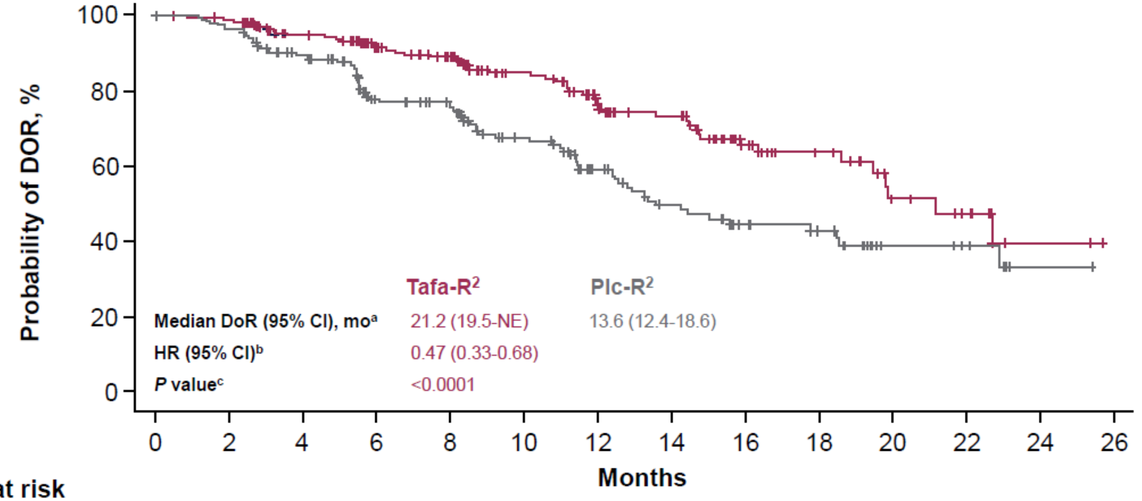


No. at risk																
Tafa-R2	273	261	250	212	200	164	119	103	71	57	30	22	12	3	2	0
Plc-R2	275	265	235	192	173	126	82	70	48	40	26	16	10	2	2	0

Significant improvement in PFS with tafa-R2 vs plc-R2, representing a 57% reduction in risk of progression, relapse or death[1,2]

Duration of Response

FL Population



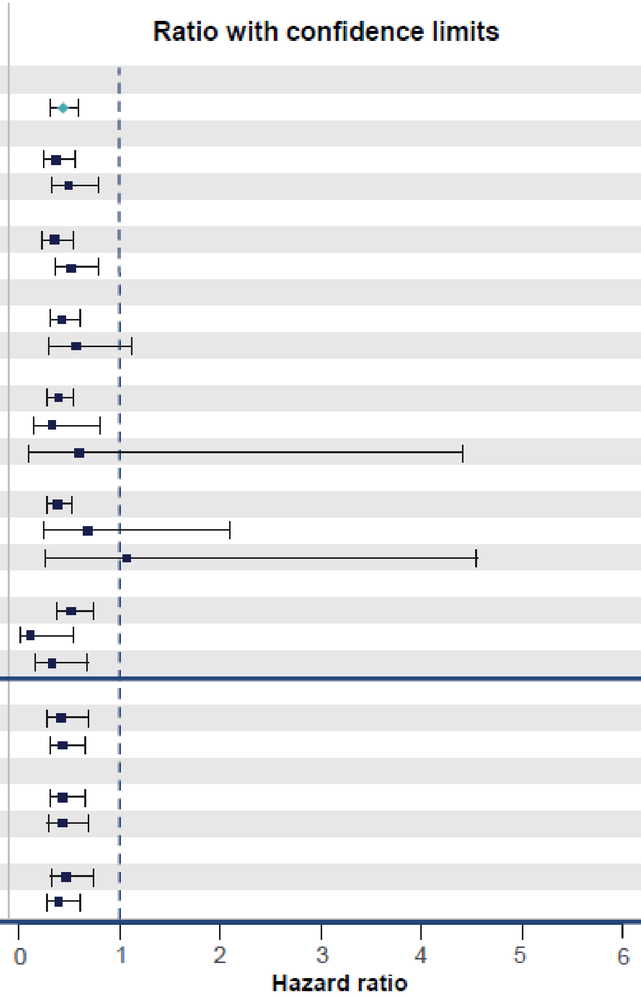
No. at risk														
Tafa-R2	228	219	185	155	140	105	81	66	37	27	14	10	3	0
Plc-R2	199	188	163	115	106	75	54	40	29	22	10	8	2	0

Significant improvement in DoR was observed with tafa-R2 vs plc-R2

PFS by Subgroups

FL Population[1,2]

Variable	Tafa+R² # Events/ # Patients censored	Plc-R² # Events/ # Patients censored	Hazard ratio (95% CI)
Subgroup			
All patients	75/198	131/144	0.43 (0.32-0.58)
Sex			
Male	40/110	78/71	0.38 (0.26-0.56)
Female	35/88	53/73	0.51 (0.33-0.80)
Age group 1			
<65	29/108	69/70	0.35 (0.23-0.55)
≥65	46/90	62/74	0.53 (0.35-0.80)
Age group 2			
<75	55/164	102/119	0.44 (0.31-0.61)
≥75	20/34	29/25	0.58 (0.30-1.12)
Race			
White	61/158	106/113	0.40 (0.29-0.55)
Asian	11/29	21/21	0.34 (0.14-0.81)
Other and missing	3/11	4/10	0.60 (0.08-4.41)
Ethnicity			
Not Hispanic or Latino	62/166	112/114	0.39 (0.28-0.53)
Hispanic or Latino	8/23	10/14	0.71 (0.24-2.10)
Other and missing	5/9	9/16	1.07 (0.25-4.56)
Geographic region			
Europe	52/124	88/105	0.53 (0.38-0.76)
North America	8/30	11/13	0.12 (0.02-0.55)
Rest of the world	15/44	32/26	0.33 (0.16-0.68)
POD24-ID			
Yes	29/56	52/36	0.43 (0.27-0.69)
No	46/142	79/108	0.45 (0.31-0.65)
Refractory to prior anti-CD20			
Yes	45/73	68/47	0.44 (0.30-0.65)
No	30/125	63/97	0.44 (0.28-0.68)
Number of pLoTs			
1 line	36/110	61/86	0.48 (0.32-0.74)
≥2 lines	39/88	70/58	0.41 (0.28-0.61)

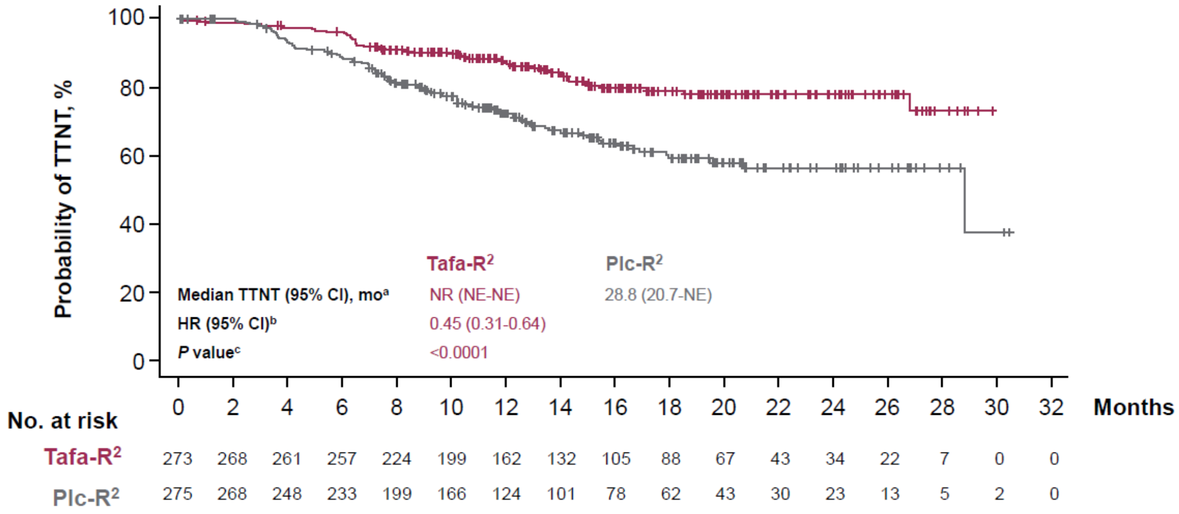


Improvement in PFS with tafa-R² vs plc-R² was reported in all subgroups analyzed, including:

- POD24-ID
- Refractory status
- 1 pLoT vs ≥2 pLoTs

Time to Next Treatment

FL Population



Median TTNT was not reached with tafa-R^2 and was 28.8 months with plc-R^2

Safety

Most Common Grade 3 or 4 TEAEs (≥5% in Any Group) in the FL Population

Preferred term, n (%)	Tafa-R^2 (n=274)[a]	Plc-R^2 (n=272)[b]	Total (N=546)
Neutropenia	109 (39.8)	102 (37.5)	211 (38.6)
Pneumonia	23 (8.4)	14 (5.1)	37 (6.8)
Thrombocytopenia	17 (6.2)	20 (7.4)	37 (6.8)
Neutrophil count decreased	16 (5.8)	18 (6.6)	34 (6.2)
Anemia	12 (4.4)	16 (5.9)	28 (5.1)
COVID-19	16 (5.8)	6 (2.2)	22 (4.0)
COVID-19 pneumonia	13 (4.7)	3 (1.1)	16 (2.9)

Safety

Dose Modifications in the FL Population

TEAEs leading to:

- **Dose delays or interruptions, n (%):**
  - Tafa-R^2: 203 (74%)
  - Plc-R^2: 190 (70%)
- **Discontinued study treatment, n (%):**
  - Tafa-R^2: 30 (11%)
  - Plc-R^2: 18 (7%)
- **Lenalidomide discontinuation, n (%):**
  - Tafa-R^2: 39 (14%)
  - Plc-R^2: 31 (11%)

Lenalidomide dose reduction

Median relative dose intensity, %:
- Tafa-R^2: 86%
- Plc-R^2: 87%

Dose modifications were similar between the tafa-R^2 and plc-R^2 groups

Phase 3 Study (inMIND) of Tafasitamab Plus Lenalidomide and Rituximab for Relapsed or Refractory Follicular Lymphoma: Clinical Characteristics and Outcomes of Patients Receiving Second-Line Treatment

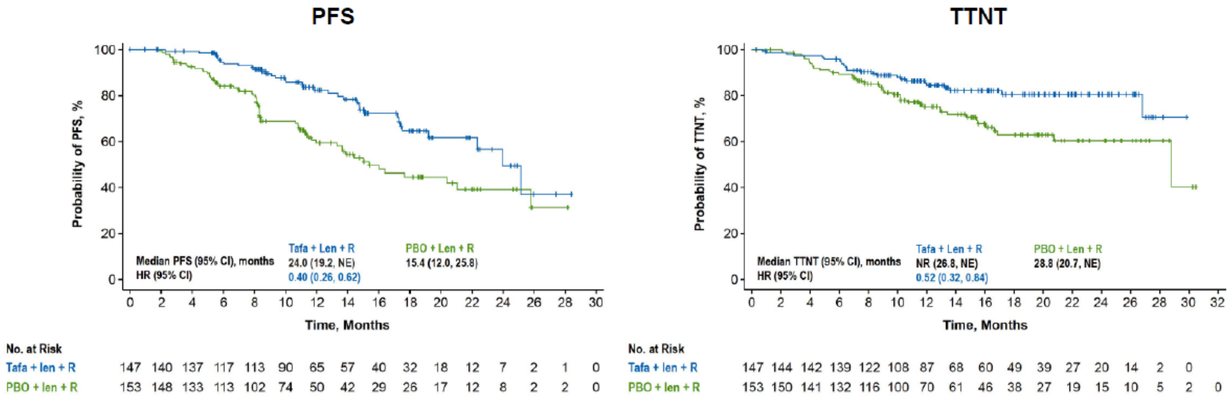
Ajay K. Gopal,[1] Marek Trneny,[2] Laurie H. Sehn,[3] **Julie Wu,**[4] Michael Arbushites,[4] Oscar Bortolami,[5] Stefano Luminari[6,7]

[1]Division of Medical Oncology/Fred Hutchinson Cancer Center, University of Washington, Seattle, WA, USA; [2]Charles University, General Hospital, Prague, Czech Republic; [3]BC Cancer Centre for Lymphoid Cancer and The University of British Columbia, Vancouver, BC, Canada; [4]Incyte Corporation, Wilmington, DE, USA; [5]Incyte International Biosciences Sàrl, Morges, Switzerland; [6]Azienda USL di Reggio Emilia – IRCCS, Reggio Emilia, Italy; [7]Surgical, Medical and Dental Department of Morphological Sciences related to Transplant, Oncology and Regenerative Medicine, University of Modena and Reggio Emilia, Reggio Emilia, Italy

Baseline Characteristics in 2L FL Patients From inMIND

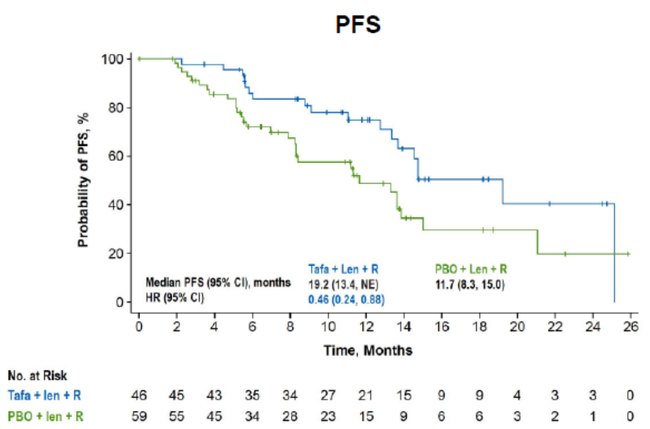
Variable	Overall 2L Population		
	Tafa + Len + R (n=147)	PBO + Len + R (n=153)	Total (n=300)
Median age (range), years	64.0 (36, 88)	65.0 (31, 85)	64.5 (31, 88)
Male sex, n (%)	83 (56.5)	85 (55.6)	168 (56.0)
Median time since initial diagnosis of FL (range), years	4.1 (0, 17)	3.9 (1, 33)	4.0 (0, 33)
ECOG PS at screening, n (%)			
0	99 (67.3)	115 (75.2)	214 (71.3)
1-2	48 (32.7)	38 (24.8)	86 (28.7)
Ann Arbor stage at study entry, n (%)			
I or II	29 (19.7)	27 (17.6)	56 (18.7)
III or IV	118 (80.3)	126 (82.4)	244 (81.3)
FL grade at study entry, n (%)*			
1 or 2	113 (76.9)	115 (75.2)	228 (76.0)
3A	33 (22.4)	38 (24.8)	71 (23.7)
FLIPI score, n (%)			
0-1	39 (26.5)	31 (20.3)	70 (23.3)
2	36 (24.5)	35 (22.9)	71 (23.7)
3-5	72 (49.0)	87 (56.9)	159 (53.0)
≥1 GELF criterion, n (%)	114 (77.6)	130 (85.0)	244 (81.3)

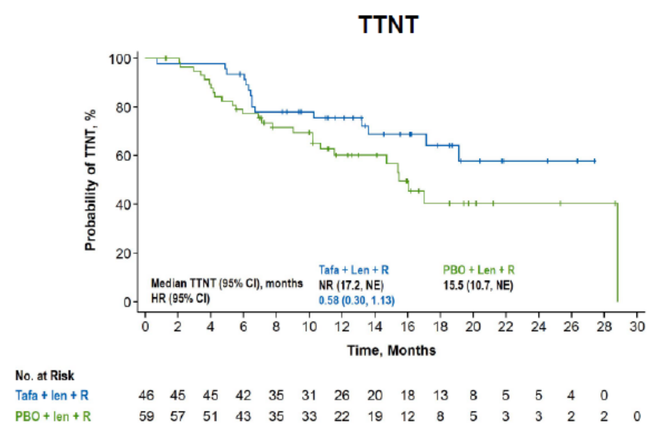
Results: PFS and TTNT in 2L FL Patients



Median PFS (95% CI), months HR (95% CI)	Tafa + Len + R 24.0 (19.2, NE) 0.40 (0.26, 0.62)	PBO + Len + R 15.4 (12.0, 25.8)

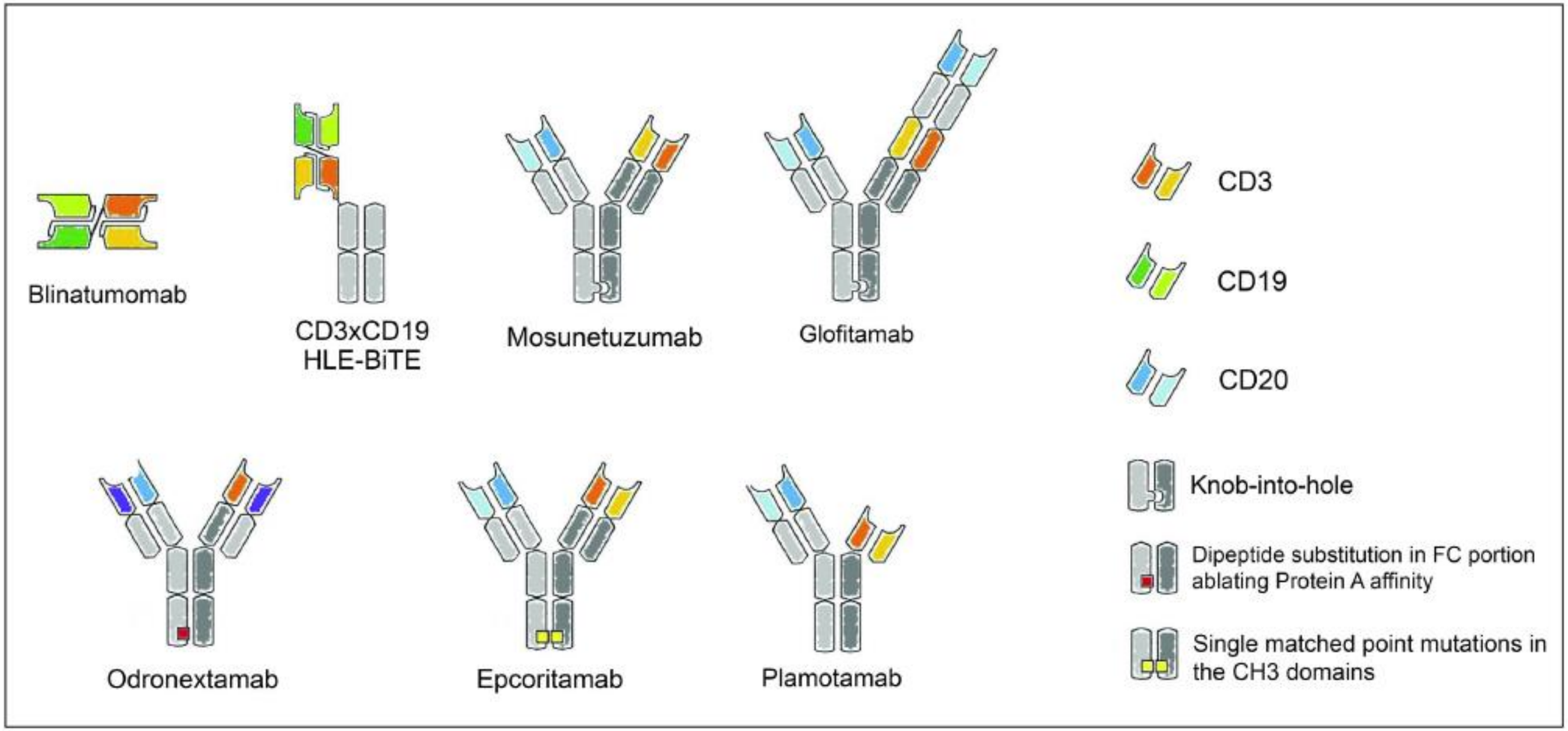
Results: PFS and TTNT in 2L FL Patients Who Received 1L Anti-CD20 + Chemotherapy With POD24





Median TTNT (95% CI), months HR (95% CI)	Tafa + Len + R NR (26.8, NE) 0.52 (0.32, 0.84)	PBO + Len + R 28.8 (20.7, NE)

BISPECIFIC ANTIBODIES



Nizamuddin I.A, Bartlett N.L., Haematologica 110 July 2025

ON-GOING STUDIES ON BISPECIFICS IN FL

	Epcoritamab[1]	Mosunetuzumab[2]	Odronextamab[3]
1L	**Ph3 EPCORE-FL-2**[4] Epcor + R-Len (R²) **Ph1b/2 EPCORE NHL-2**[5] **- Arm 3** Epcor + BR **- Arm 7** Epcor maintenance after SOC	**Ph2 MorningSun**[8] Mosun mono **Ph3 MorningLyte**[9] Mosun + Len (FLIPI 2-5)	**Ph 3 OLYMPIA-1**[12] Odro mono **Ph 3 OLYMPIA-2**[13] Odro + CHOP or Odro + CVP
2L	**Ph3 EPCORE FL-1**[6] Epcor + R-Len (R²) **Ph1b/2 EPCORE NHL-2**[5]**:** **- Arm 7** Epcor maintenance after SOC **- Arm 9** Epcor + Len (POD24 FL) **Ph1b/2 EPCORE NHL-5**[7]**:** **- Arm 5** Epcor + Golcadomide	**Ph3 CELESTIMO**[10] Mosun + Len **Ph1/2 BTCT4465A**[11] Mosun + Pola	**Ph3 OLYMPIA-5**[14] Odro + Len
3L			

EPCORE FL-1: Phase 3, Global, Randomized, Open-Label Study[1]

Fixed-Duration: 12 Cycles (28-Day Cycles)

Key eligibility criteria

- Histologically confirmed CD20+ R/R FL
- Grade 1–3a, Stage II–IV
- ≥1 prior treatment, including anti-CD20 mAb plus an alkylating agent
- Met ≥1 GELF criterion

Randomization 1:1

Epcoritamab (48 mg) plus R²

- **Epcoritamab**
  3-SUD cycle 1,[a] QW; cycles 2–3, QW; cycles 4–12, Q4W
- **Rituximab** (375 mg/m²)
  5 cycles: cycle 1, QW; cycles 2–5, Q4W
- **Lenalidomide** (20 mg)
  12 cycles QD, D1–21

R²

- **Rituximab** (375 mg/m²)
  5 cycles: cycle 1, QW; cycles 2–5, Q4W
- **Lenalidomide** (20 mg)
  12 cycles, QD, D1–21

Post Hoc Subgroup Analyses

Clinically relevant subgroups:

- Age (<70 vs ≥70 years)
- NHL-5 comorbidity index (low vs high/intermediate)[2]
- Prior LOTs (1 vs ≥2)
- FLIPI (0–2 vs 3–5)
- POD24 status[b]
- Bulky disease status[b,c]
- Double refractory status[b]

Len RDI subgroups: <50% vs ≤70% vs >70%

- **Dual primary endpoints: ORR per IRC and PFS per IRC**
- Select secondary endpoints: CR rate per IRC, OS, and safety

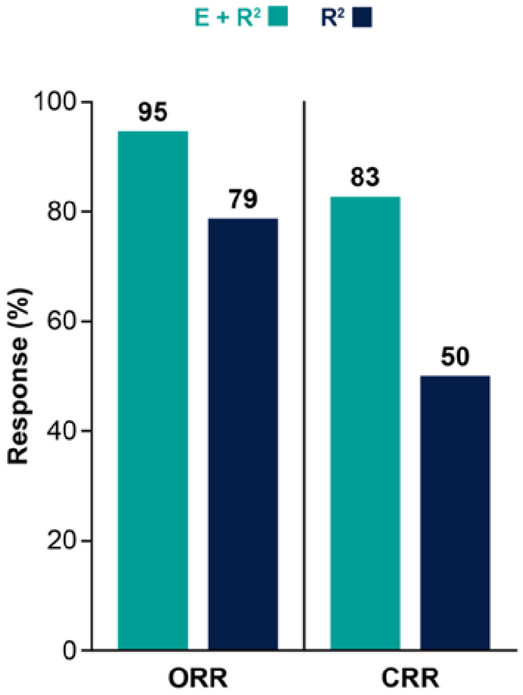
Data cutoff: May 24, 2025
Median follow-up: 14.8 months[d]
Enrollment period: Oct 2022 to Jan 2025

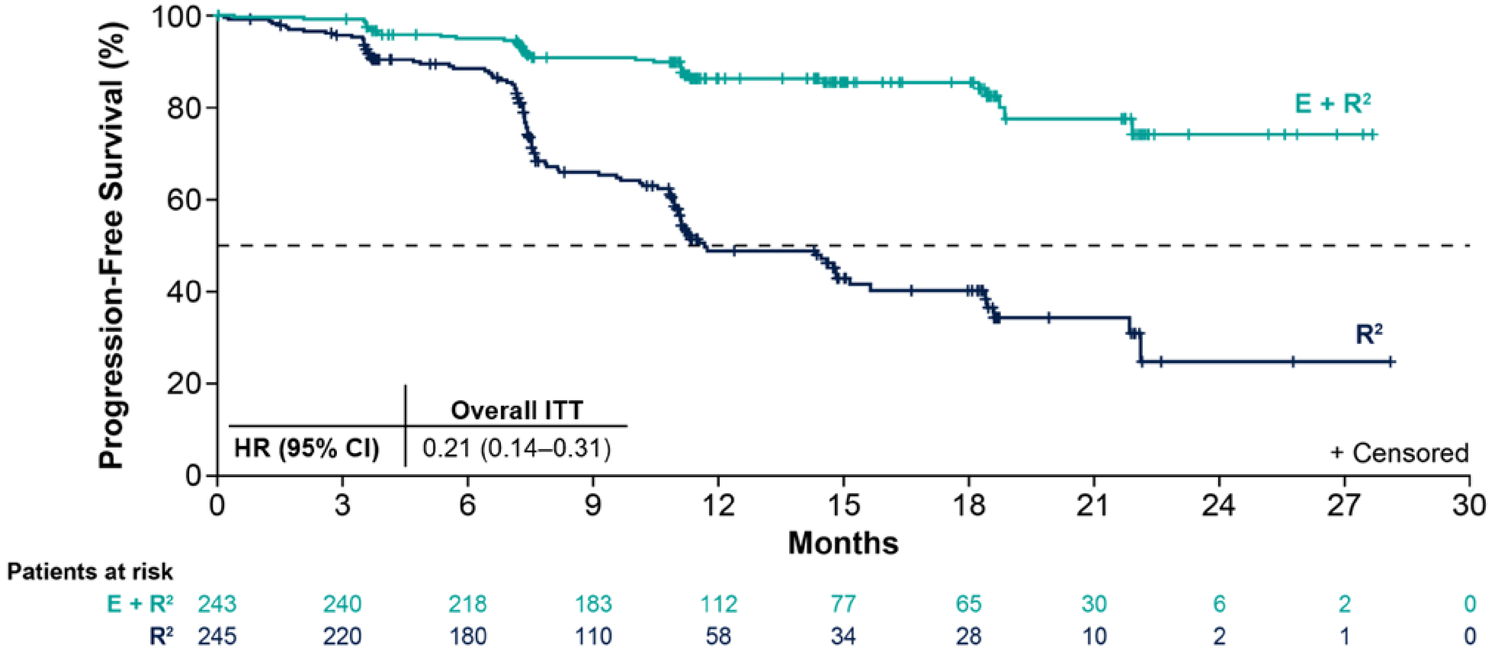
[a]Two SUD regimens were evaluated during cycle 1 to mitigate the risk of CRS: either a 2-SUD (0.16 mg on cycle 1 day 1, 0.8 mg on cycle 1 day 8), or 3-SUD (0.16 mg on cycle 1 day 1, 0.8 mg on cycle 1 day 8, 3 mg on cycle 1 day 15) regimen, followed by full dose 48 mg. The 3-SUD regimen was implemented after reduced CRS severity and incidence had been observed in the EPCORE NHL-1 FL trial (NCT03625037).[3] [b]Pre-specified subgroup per the study statistical analysis plan. [c]Bulky disease was defined by the presence of a lymph node ≥7 cm at baseline/screening. [d]The data presented here are from the second planned interim analysis (May 24, 2025) after 78% information fraction for PFS had occurred.

1. Falchi et al. *Lancet*. 2026;407:161-173. 2. Gordon MJ, et al. *JCO Clin Cancer Inform*. 2024;8:e2300223. 3. Vose J, et al. *J Clin Oncol*. 2024;42(16_suppl):7015.

CR, complete response; CRS, cytokine release syndrome; D, day; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; IRC, independent review committee; Len, lenalidomide; LOT, line of therapy; mAb, monoclonal antibody; NHL-5, non-Hodgkin lymphoma comorbidity score; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; POD24, progression of disease ≤2 years from the date of initiation of frontline therapy; Q4W, once every 4 weeks; QD, once daily; QW, once every week; R², lenalidomide and rituximab; RDI, relative dose intensity; R/R, relapsed/refractory; SUD, step-up dosing; TEAE, treatment-emergent adverse event.

Epcoritamab + R² Resulted in Superior Responses and PFS Compared With R² Alone in the Overall ITT Population



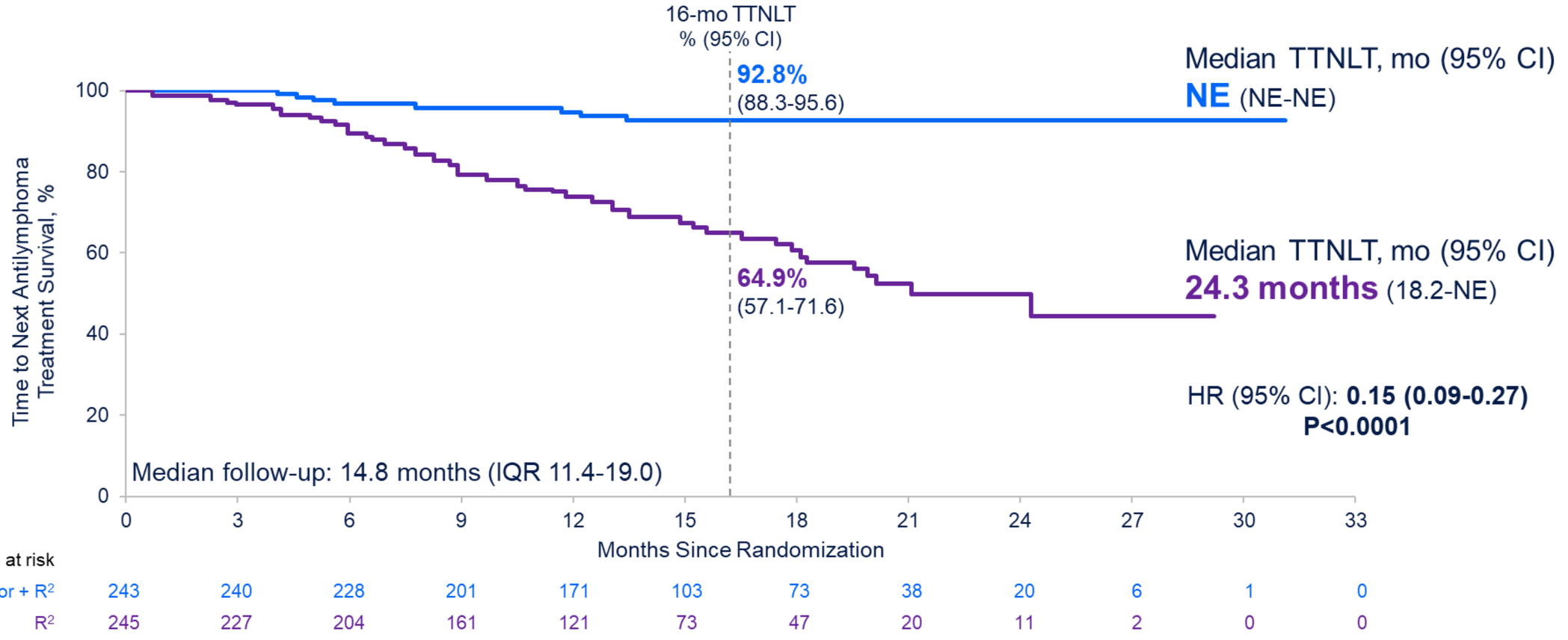


Patients at risk

E + R²	243	240	218	183	112	77	65	30	6	2	0
R²	245	220	180	110	58	34	28	10	2	1	0

The data were previously published (Falchi et al. *Lancet*. 2026;407:161-173) and reproduced with permission under the terms of the CC BY 4.0 license
CRR, complete response rate; E, epcoritamab; HR, hazard ratio; ITT, intent to treat; ORR, overall response rate; PFS, progression-free survival; R², lenalidomide and rituximab.

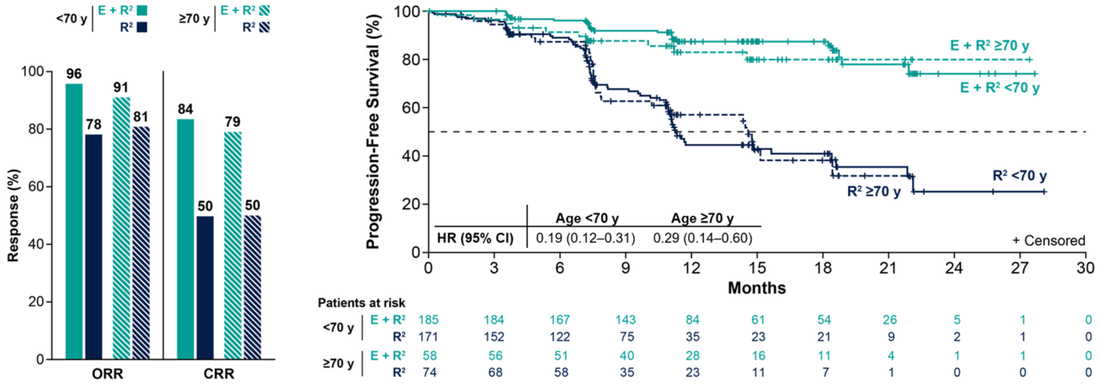
Time to Next Lymphoma Treatment



At 16 months, 92.8% of patients treated with epcoritamab+R^2 remained free from new anti-lymphoma treatment compared with 64.9% of patients treated with R^2.

CI, confidence interval; HR, hazard ratio; IQR, interquartile range; KM, Kaplan-Meier; Mo, month; NE, not evaluable; TTNLT, time to next lymphoma treatment.
Falchi L, et al. Lancet, 2025.

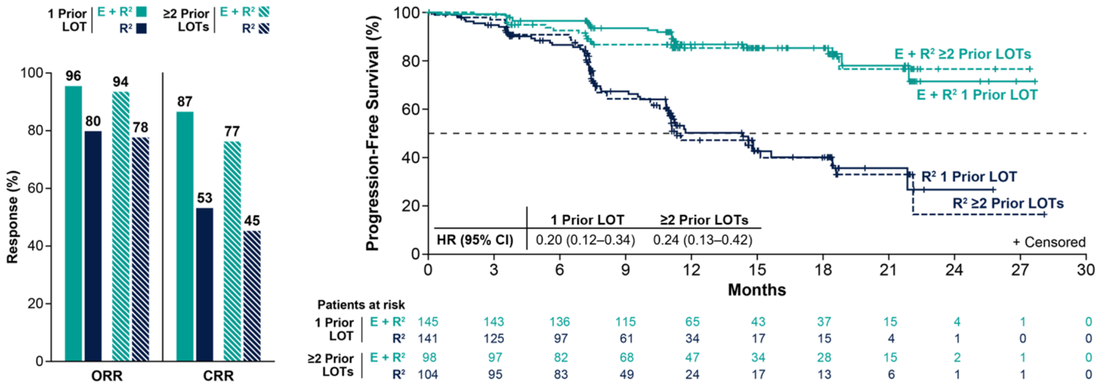
Efficacy Benefit With Epcoritamab + R² Was Maintained Across Patient Age Subgroups



CRR, complete response rate; E, epcoritamab; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival; R², lenalidomide and rituximab.

6

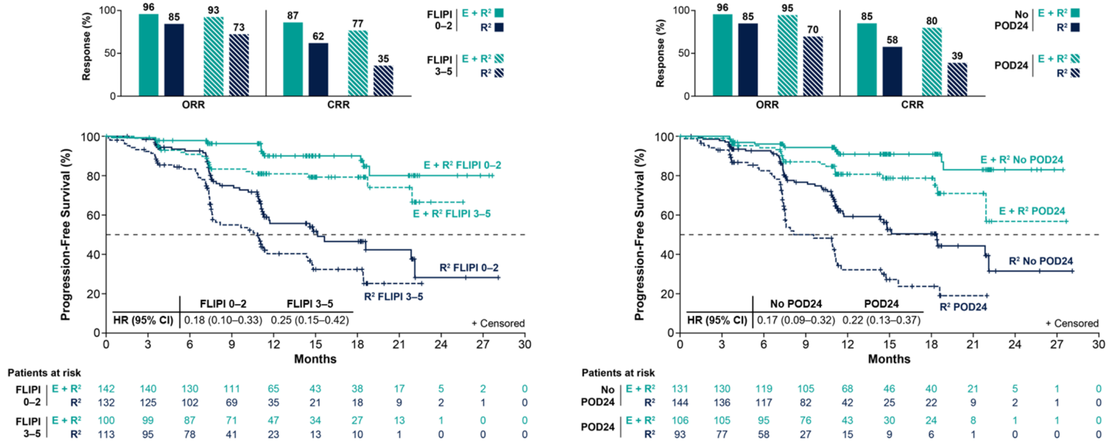
Epcoritamab + R² Showed Favorable Efficacy Over R² Across Prior LOT Subgroups



CRR, complete response rate; E, epcoritamab; HR, hazard ratio; LOT, line of therapy; ORR, overall response rate; PFS, progression-free survival; R², lenalidomide and rituximab.

10

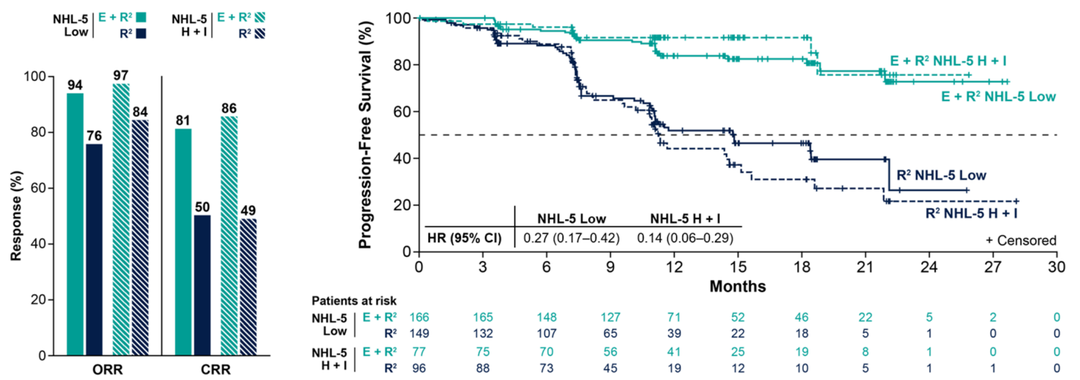
Baseline FLIPI Score or POD24 Status Did Not Influence the Treatment Benefit of Epcoritamab + R² Over R²



CRR, complete response rate; E, epcoritamab; FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival; POD24, progression of disease ≤2 years from the date of initiation of frontline therapy; R², lenalidomide and rituximab.

11

Regardless of Comorbidity Burden Epcoritamab + R² Resulted in Higher Response Rates and Improved PFS



- The NHL-5 comorbidity score[a] is a five-category score that classifies patients as low, intermediate, or high risk based on vascular disease, congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, and renal disease[1]

[a]*Comorbidity Score Sum, Range (0 – 5) and defined as 0 = low, 1 = intermediate, >=2 = high.* 1. Gordon MJ, et al. *JCO Clin Cancer Inform.* 2024;8:e2300223.
CRR, complete response rate; E, epcoritamab; H + I, high and intermediate; HR, hazard ratio; NHL-5, non-Hodgkin lymphoma comorbidity score; ORR, overall response rate; PFS, progression-free survival; R², lenalidomide and rituximab.

8

CELESTIMO Study

Randomised, open-label, multicentre Phase III study of mosunezutumab (IV) and lenalidomide compared with rituximab and lenalidomide in patients with R/R FL

Eligibility

- Age ≥18 years
- Grade 1–3a CD20+ FL
- ECOG PS 0–2
- ≥1 prior systemic anti-lymphoma therapy
- Target enrolment (Randomised cohort): 400

Stratification factors

- POD 24 status
- Prior lines of therapy (1 vs ≥2)
- Refractoriness to anti-CD20 therapy

Randomised 1:1*

Arm A

Mosunetuzumab + lenalidomide
- Mosunetuzumab IV on C1 [D1 (1 mg), D8 (2 mg), D15 (30 mg)] q3w and C2–12 D1 (30 mg) q4w
- Lenalidomide on C2–12 D1-21 (20 mg)

Arm B

Rituximab + lenalidomide
- Rituximab IV on C1 D1/D8/D15/22 and C3, 5, 7, 9. 11 D1 (375 mg/m²) q4w
- Lenalidomide on C1–12 D1-21 (20 mg)

Arm C

Mosunetuzumab + lenalidomide
(US extension cohort, n=54 pts)

1º endpoint

PFS (IRC-assessed) in ITT

Efficacy follow-up: 5 years from time of randomisation

Secondary and other endpoints†

- PFS (INV-assessed) in ITT, CR rate (by PET-CT), ORR, OS, DOR, DOCR, time to deterioration in physical functioning and fatigue by EORTC QLQC30, safety, PK, immunogenicity, biomarker

Non-randomized single arm US extension of CELESTIMO

Key inclusion criteria

- CD20+ FL Grade 1–3a
- ≥1 prior systemic therapy for FL
- ECOG PS 0–2

Endpoints

- Preliminary efficacy of Mosun-Len: INV-assessed ORR and CR (Lugano criteria[1])
- Safety: incidence and severity of AEs and CRS according to CTCAE v5.0 and ASTCT[2] criteria, respectively

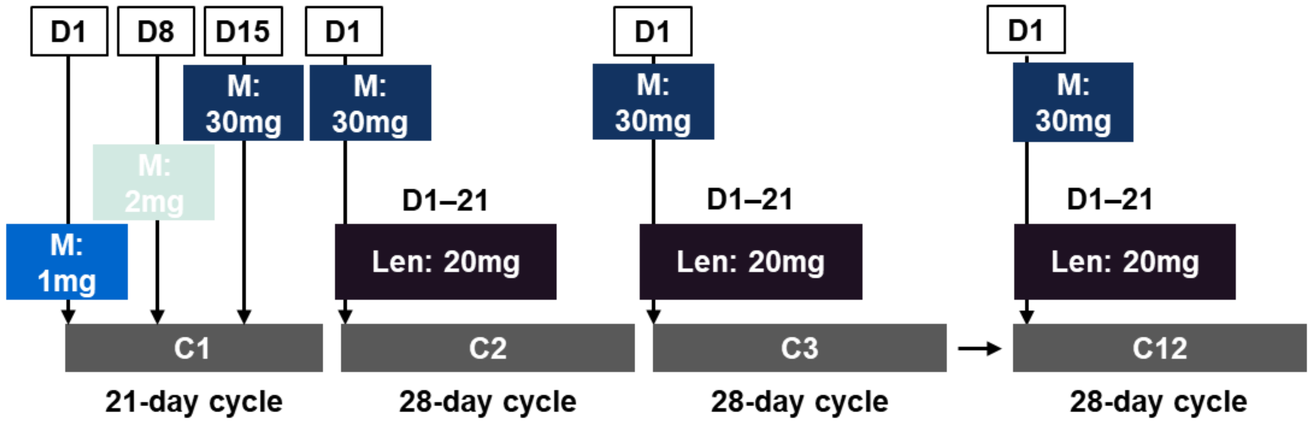
Mosun-Len administration

Mosunetuzumab

- IV administration for 12 cycles (C1: QW; C2–12: D1 of each cycle)
- C1 step-up dosing (CRS mitigation)
- No mandatory hospitalization

Lenalidomide

- Oral administration for 11 cycles (C2–12)



AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; C, Cycle; CR, complete response; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; D, Day; ECOG PS, Eastern Oncology Group performance status; INV, investigator; IV, intravenous; M, mosunetuzumab; ORR, objective response rate; QW, weekly.

1. Cheson BD, et al. J Clin Oncol 2014;32:3059–68;
2. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38.

Baseline characteristics

n (%), unless otherwise stated		2L+ FL US cohort (n=54)
Age, years	Median (range)	62.0 (37–82)
Sex	Male	32 (59.3)
Race	Asia Black or African American White Multiple* Unknown	3 (5.6) 2 (3.7) 47 (87.0) 1 (1.9) 1 (1.9)
Ethnicity	Hispanic or Latino Not Hispanic or Latino	12 (22.2) 42 (77.8)
ECOG PS	0 1 2	40 (74.1) 13 (24.1) 1 (1.9)
Ann Arbor stage	I/II III/IV	9 (16.7) 45 (83.3)

n (%)		2L+ FL US cohort (n=54)
FLIPI score		n=52†
	0/1	13 (25.0)
	2	18 (34.6)
	3	17 (32.7)
	4	3 (5.8)
	5	1 (1.9)
FL grade		n=47†
	1/2	28 (59.6)
	3a	19 (40.4)
POD24	Yes	16 (29.6)
Number of prior lines of therapy	1	30 (55.6)
	≥2	24 (44.4)
Refractory to prior CD20 therapy		n=48†
	Yes	19 (39.6)
Relapsed after prior CD20 therapy		n=48†
	Yes	17 (35.4)
Double refractory		n=53†
	Yes	9 (17.0)

Data cut-off: June 9, 2025. *American Indian or Alaska Native, White. †Missing or partial data. 2L+, at least one prior therapy; FLIPI, Follicular Lymphoma International Prognostic Index; POD24, progressive disease within 24 months of first systemic therapy.

Sano D, et al. ASH 2025; Poster presentation (abstract #1800).

Mosun-Len achieved high response rates in patients with R/R FL

n (%)	2L+ FL US cohort (n=54)
ORR	52 (96.3)
CR	47 (87.0)
PR	5 (9.3)
Stable disease	0
Progressive disease	2 (3.7)

The **median duration of follow-up** was **12.7 months** (range: 5–20)

Data cut-off: June 9, 2025.
PR, partial response.

Sano D, et al. ASH 2025; Poster presentation (abstract #1800).

Mosun-Len had manageable safety

n (%)	2L+ FL US cohort (n=54)
Any grade AE	54 (100)
Mosunetuzumab related	48 (88.9)
Lenalidomide related	50 (92.6)
AE leading to discontinuation of mosunetuzumab	6 (11.1)
AE leading to discontinuation of lenalidomide	10 (18.5)
Grade 3/4 AE	31 (57.4)
Grade 5*	1 (1.9)
Serious AE	15 (27.8)
Mosunetuzumab related	9 (16.7)
Lenalidomide related	4 (7.4)

n (%)	2L+ FL US cohort (n=54)
CRS by ASTCT grading	15 (27.8)
Grade 1	12 (22.2)
Grade 2	2 (3.7)
Grade 3	1 (1.9)
Infections†	31 (57.4)
Grade 1	2 (3.7)
Grade 2	24 (44.4)
Grade 3	3 (5.6)
Grade 4	1 (1.9)
Grade 5	1 (1.9)
Neutropenia/neutrophil count decreased	22 (40.7)
Grade 3/4	18 (33.3)
Febrile neutropenia (Grade 3)	2 (3.7)

CRS events were mainly low grade and all resolved
- Median duration of CRS: 4.0 days (range: 1.0–23.0)
- Median time to onset of first CRS event: 2.0 days (range: 1.0–27.0)

The most common AEs (any grade, by preferred term) were fatigue (57.4%), maculo-papular rash (42.6%), and constipation (42.6%)

Data cut-off: June 9, 2025. *Pneumonia, considered to be mosunetuzumab related. †The most common infections were: COVID-19, 20.4%; sinusitis, 18.5%; and upper respiratory tract infection, 16.7%; which were mainly Grade 2 (44.4%) in severity.

Sano D, et al. ASH 2025; Poster presentation (abstract #1800).

Preliminary data (ORR, 96.3%; CR, 87.0%) support the potential of Mosun-Len as a well-tolerated outpatient combination treatment for US patients with R/R FL

Sano D, et al. ASH 2025; Poster presentation (abstract #1800).

SUGGESTED TREATMENT REGIMENS[a,b,c]

THIRD-LINE AND SUBSEQUENT THERAPY

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

Preferred regimens (in alphabetical order)

- T-cell engager therapy
  - Bispecific antibody therapy[l,m]
    - ◊ Epcoritamab-bysp
    - ◊ Mosunetuzumab-axgb
  - Chimeric antigen receptor (CAR) T-cell therapy[n]
    - ◊ Axicabtagene ciloleucel (CD19-directed)
    - ◊ Lisocabtagene maraleucel (CD19-directed)
    - ◊ Tisagenlecleucel (CD19-directed)

Other recommended regimens

- EZH2 inhibitor
  - Tazemetostat[l] (irrespective of EZH2 mutation status)
- BTK inhibitor (BTKi)
  - Zanubrutinib[l] + obinutuzumab
- Loncastuximab tesirine-lpyl + rituximab (category 2B)[k]

THIRD-LINE CONSOLIDATION THERAPY

Useful in Certain Circumstances

- Allogeneic hematopoietic cell transplantation (HCT) in selected cases[o]

Footnotes on FOLL-B 4 of 6

Version 3.2025 © 2025 National Comprehensive Cancer Network® (NCCN®). All rights reserved.
The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Long-term 3-year follow-up of mosunetuzumab in relapsed or refractory follicular lymphoma after ≥2 prior therapies

Laurie H. Sehn,[1] Nancy L. Bartlett,[2] Matthew J. Matasar,[3] Stephen J. Schuster,[4] Sarit E. Assouline,[5] Pratyush Giri,[6] John Kuruvilla,[7] Mazyar Shadman,[8] Chan Yoon Cheah,[9] Sascha Dietrich,[10] Keith Fay,[11] Matthew Ku,[12] Loretta J. Nastoupil,[13] Michael C. Wei,[14] Shen Yin,[14] Iris To,[14] Derrick Kaufman,[14] Antonia Kwan,[14] Elicia Penuel,[14] Christopher R. Bolen,[14] and Lihua E. Budde[15]

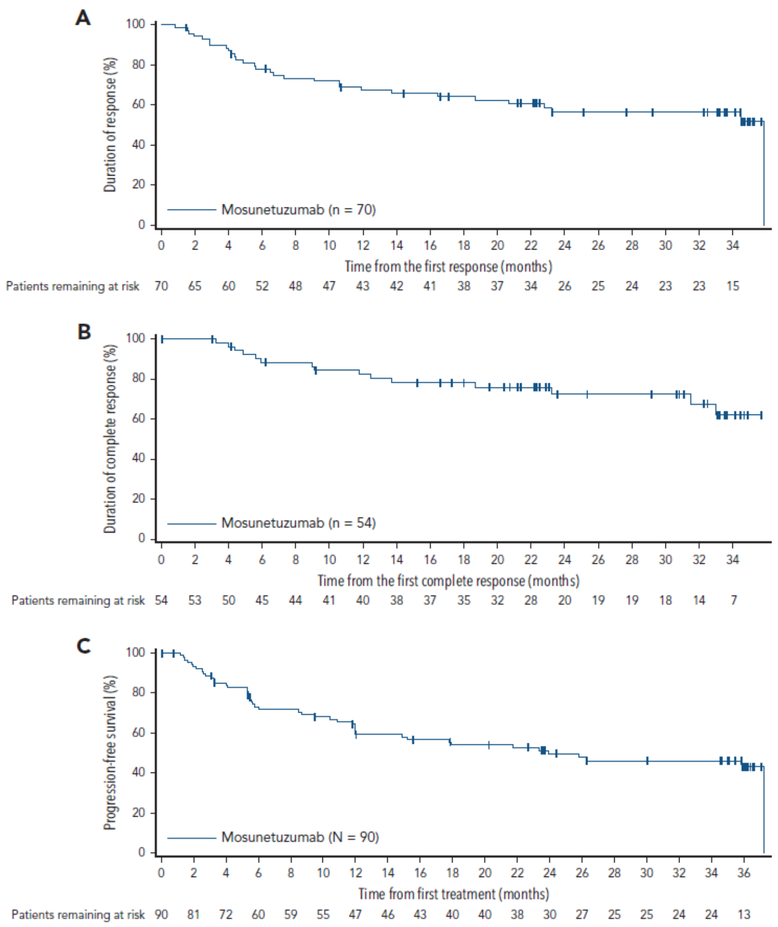


Table 2. Efficacy summary in the overall population (N = 90) with mosunetuzumab

INV-assessed efficacy end points	Mosunetuzumab (N = 90)
ORR* % (95% CI)	77.8 (67.8-85.9)
CR* % (95% CI)	60.0 (49.1-70.2)
Time to first response, mo, median (range)	1.4 (1-11)
Time to first CR, mo, median (range)	3.0 (1-19)
DOR, mo, median (95% CI) (n = 70)	35.9 (20.7-NE)
30-mo remission rate, % (95% CI)	56.6 (44.2-68.9)
DOCR, mo, median (95% CI) (n = 54)	NR (33.0-NE)
30-mo remission rate, % (95% CI)	72.4 (59.2-85.6)
PFS, mo, median (95% CI)	24.0 (12.0-NE)
36-mo PFS rate, % (95% CI)	43.2 (31.3-55.2)
OS, mo, median (95% CI)	NR (NE-NE)
36-mo OS rate, % (95% CI)	82.4 (73.8-91.0)
TTNT, mo, median (95% CI)	37.3 (18.0-NE)
36-mo TTNT rate, % (95% CI)	51.8 (40.8-62.8)

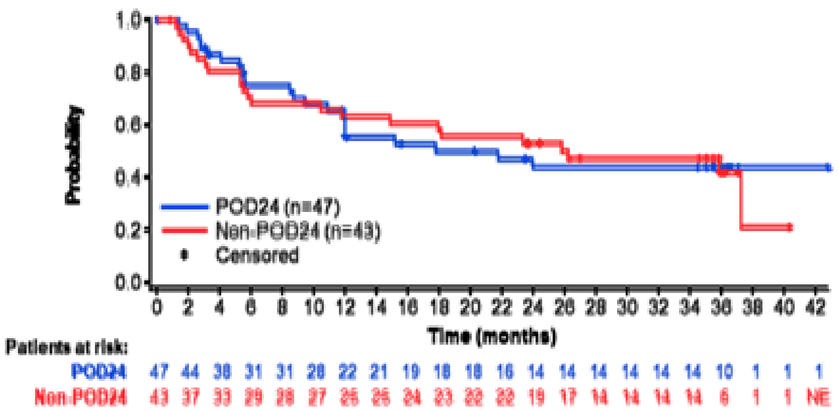
MOST COMMON Aes

	ANY GRADE	GRADE 3 - 4
CRS	40 (44.4)	2 (2.2)
FATIGUE	33 (36,7)	0
HEADACHE	28 (31,1)	1 (1,1)
NEUTROPENIA	26 (28,9)	24 (26,7)
PYREXIA	26 (28,9)	1 (1.1)
HYPOPHOSPH.	24 (26,7)	15 (16,7)
PRURITUS	19 (21,1)	0

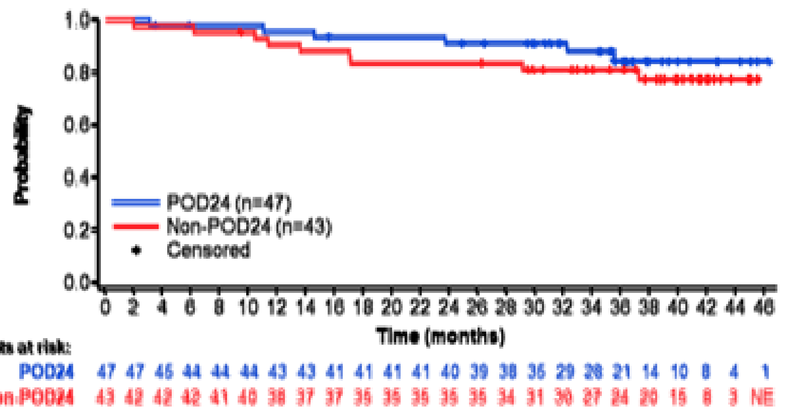
blood® 13 FEBRUARY 2025 | VOLUME 145, NUMBER 7

Mosunetuzumab In High-Risk Patients with Heavily Pre-Treated R/R FL After ≥3 Years of Follow-up: Subgroup Analysis of a Pivotal Phase II Study

PFS



OS



	Overall population (N=90)	Non-POD24 (n=43)	POD24 (n=47)
Median PFS, months (95% CI)	24.0 (12.0–NE)	26.3 (11.8–NE)	17.8 (12.0–NE)
36-month PFS, % (95% CI)	43 (31.8–54.7)	42 (25.0–59.0)	44 (28.2–59.5)

	Overall population (N=90)	Non-POD24 (n=43)	POD24 (n=47)
Median OS, months (95% CI)	NR (NE)	NR (NE)	NR (NE)
36-month OS, % (95% CI)	83 (74.6–91.2)	81 (69.1–92.9)	84 (72.1–96.3)

Similar PFS and OS benefit were observed in patients with non-POD24 and POD24

Assouline et al. Oral presentation EHA 2024

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

Lancet Haematol 2024; 11: e593–605

Published Online June 15, 2024 https://doi.org/10.1016/S2352-3026(24)00166-2

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

FIRST DATA PUBLISHED in 2024
- **Expansion Cohort : Median FU 17.4 m**
- **Cycle 1 Optimization Cohort: Median FU 5.7 m**

Vitolo et al, PF881, EHA 2025

Epcoritamab Demonstrates deep and durable responses at 3-years follow up in patients with relapse/refractory follicular Lymphoma

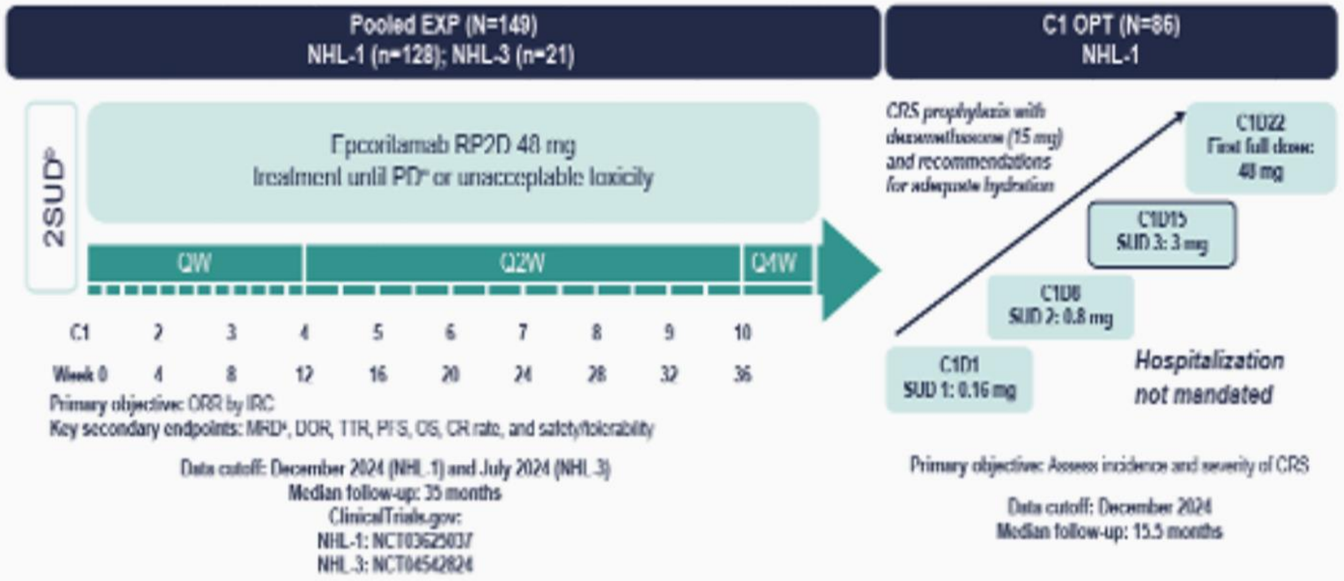
Vitolo et al, PF881, EHA 2025

LAST UPDATE in 2025
- **Pooled Expansion Cohort : Median FU 35 m**
- **Cycle 1 Optimization Cohort: Median FU 15.5 m**

STUDY DESIGN

Key inclusion criteria[a]:

- R/R CD20+ FL grade 1-3A
- HCOG PS score 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 cell therapy allowed



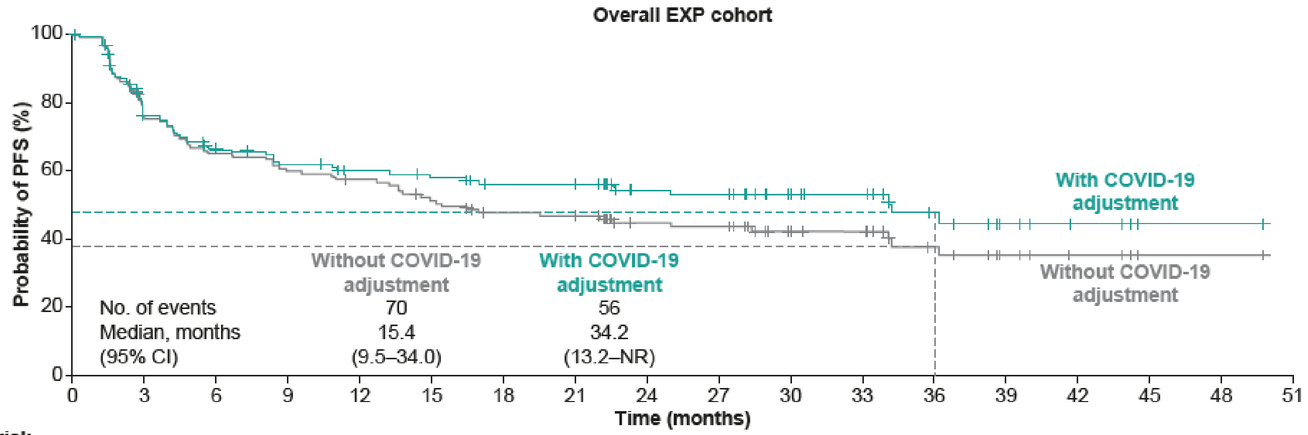
[a]Patients enrolled in this trial (and excluded from trials of other T-cell–engaging therapies) included those with worse anemia, lymphopenia, and/or renal function. [b]SUD (priming [SUD 1] 0.16 mg and intermediate [SUD 2] 0.8 mg dosing before first full dose) and corticosteroid prophylaxis were used to mitigate CRS. [c]≥2 measurable (by CT/MRI) and FDG PET–positive lesions; radiographic disease evaluation was performed every 6 weeks for the first 24 weeks (6, 12, 18, and 24 weeks), then every 12 weeks (36 and 48 weeks), and every 6 months thereafter. [d]MRD was assessed in PBMC using the clonoSEQ® next-generation sequencing assay.

- To increase diversity and expand the patient population, the EXP cohorts of NHL-1 and NHL-3 were pooled
- The approved SUD regimen is based on C1 OPT data, which showed reduced CRS and ICANS incidence and severity with mitigation strategies, and consistent response rates, supporting outpatient administration; time-to-event analyses in the C1 OPT cohort of NHL-1 are still maturing and not presented
- In the pooled EXP cohort, sensitivity analyses for PFS and OS were performed based on an adjusted population excluding deaths on study related to COVID-19; a conservative analysis was performed since the study was conducted during the COVID-19 pandemic (enrollment dates: NHL-1: June 2020–April 2023; NHL-3: January 2021–November 2021)

Vitolo et al, PF881, EHA 2025

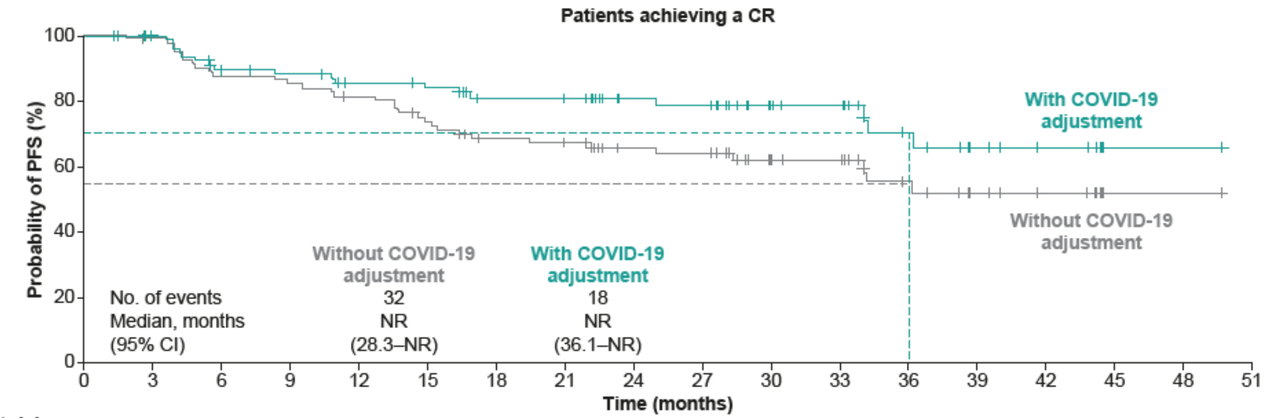
PFS and OS in the pooled exp Cohort

Sustained PFS With Epcoritamab in the Pooled EXP Cohort



Number at risk

Without COVID-19 adjustment	128	89	76	70	66	58	51	49	39	38	26	25	15	10	6	1	1	0
With COVID-19 adjustment	128	88	74	68	59	56	49	48	38	37	26	25	15	10	6	1	1	0



Number at risk

Without COVID-19 adjustment	84	80	70	68	64	57	50	48	39	38	26	25	15	10	6	1	1	0
With COVID-19 adjustment	84	79	68	66	57	55	48	47	38	37	26	25	15	10	6	1	1	0

Data cutoff: December 2024. Population based on the FDA-approved indication of epcoritamab (N=127) had a median PFS of 34.2 months (95% CI, 13.2–NR) with COVID-19 adjustment, and 15.4 months (95% CI, 9.5–34.2) without adjustment. A total of 56 and 69 events were reported in the adjusted and unadjusted analyses, respectively.

In the pooled EXP cohort median PFS was 15.4 mo
<u>However</u>
After adjustment for COVID-19 deaths it was 34.2 mo and NR in patients in CR

OS was NR regardless od COVID adjustment
The exstimated COVID- adjusted 30-month OS rate was 79%

Vitolo et al, PF881, EHA 2025

CRS Events in the Cycle 1 Optimization Cohort

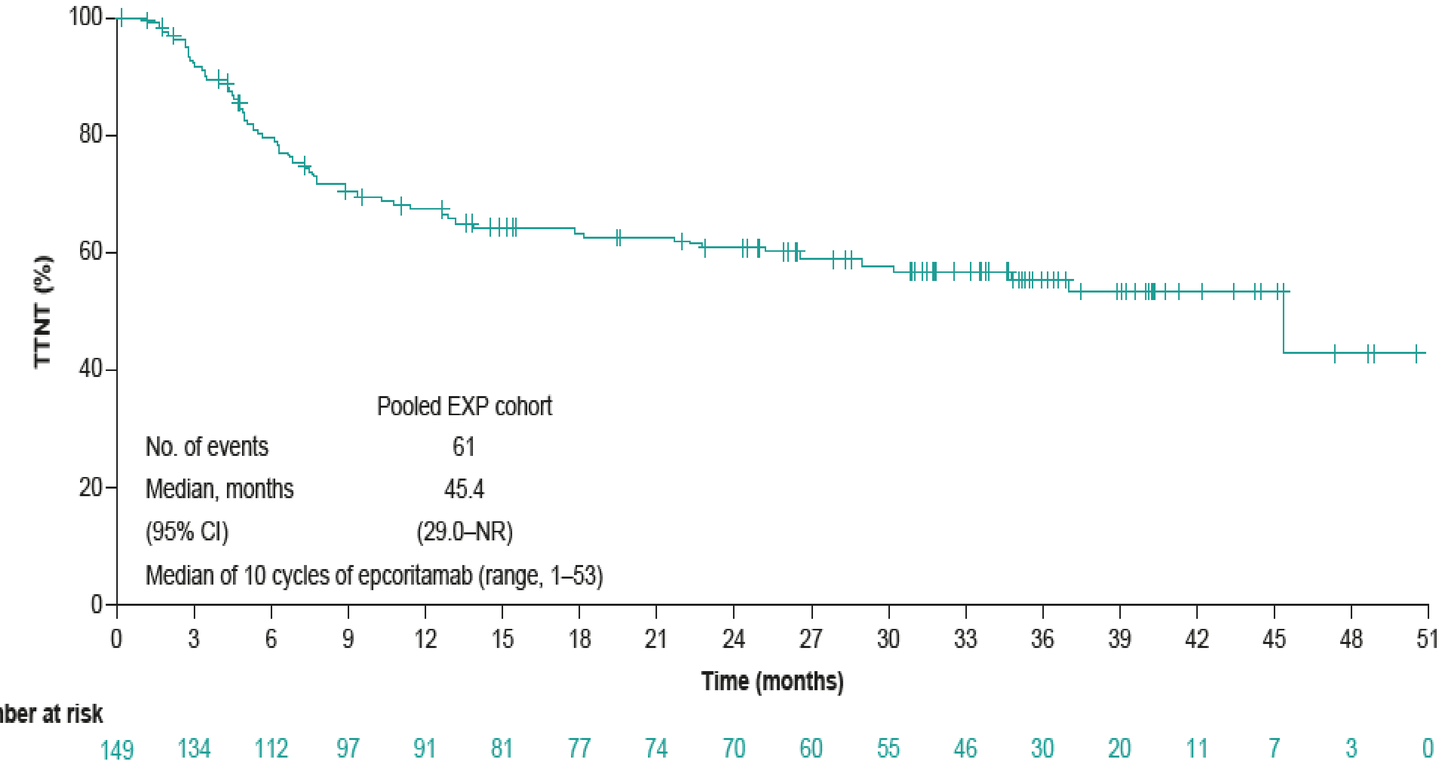
	C1 OPT (N=86)
Patients with ≥1 CRS event, n (%)	42 (49)
Grade 1	39 (45)
Fever	39 (45)
Grade 2	8 (9)
Fever	8 (9)
Hypotension	6 (7)
Hypoxia	2 (2)
Tocilizumab treatment, n (%)	11 (26)
CRS leading to epcoritamab discontinuation, n (%)	0
Median time to first CRS onset, days (range)	23 (1–52)
CRS resolution, n (%)	42 (100)
Median time to resolution, days (range)	2 (1–14)

Data cutoff: December 2024. CRS dynamics from the previous data cut are presented in Linton KM, et al. *Lancet Haematol* 2024;11(8):e593-e605. In the population based on the FDA-approved indication of epcoritamab (N=127), 99% had a TEAE, 73% had a grade ≥3 TEAE, 14% had a fatal TEAE, 28% had a TEAE leading to treatment discontinuation, 66% had CRS, and 6% had ICANS.

Vitolo et al, PF881, EHA 2025

Time to Next Treatment

Extended TTNT With Epcoritamab in the Pooled EXP Cohort



Data cutoff: December 2024. Population based on the FDA-approved indication of epcoritamab (N=127) had a median TTNT of 45.4 months (95% CI, 22.7–NR).

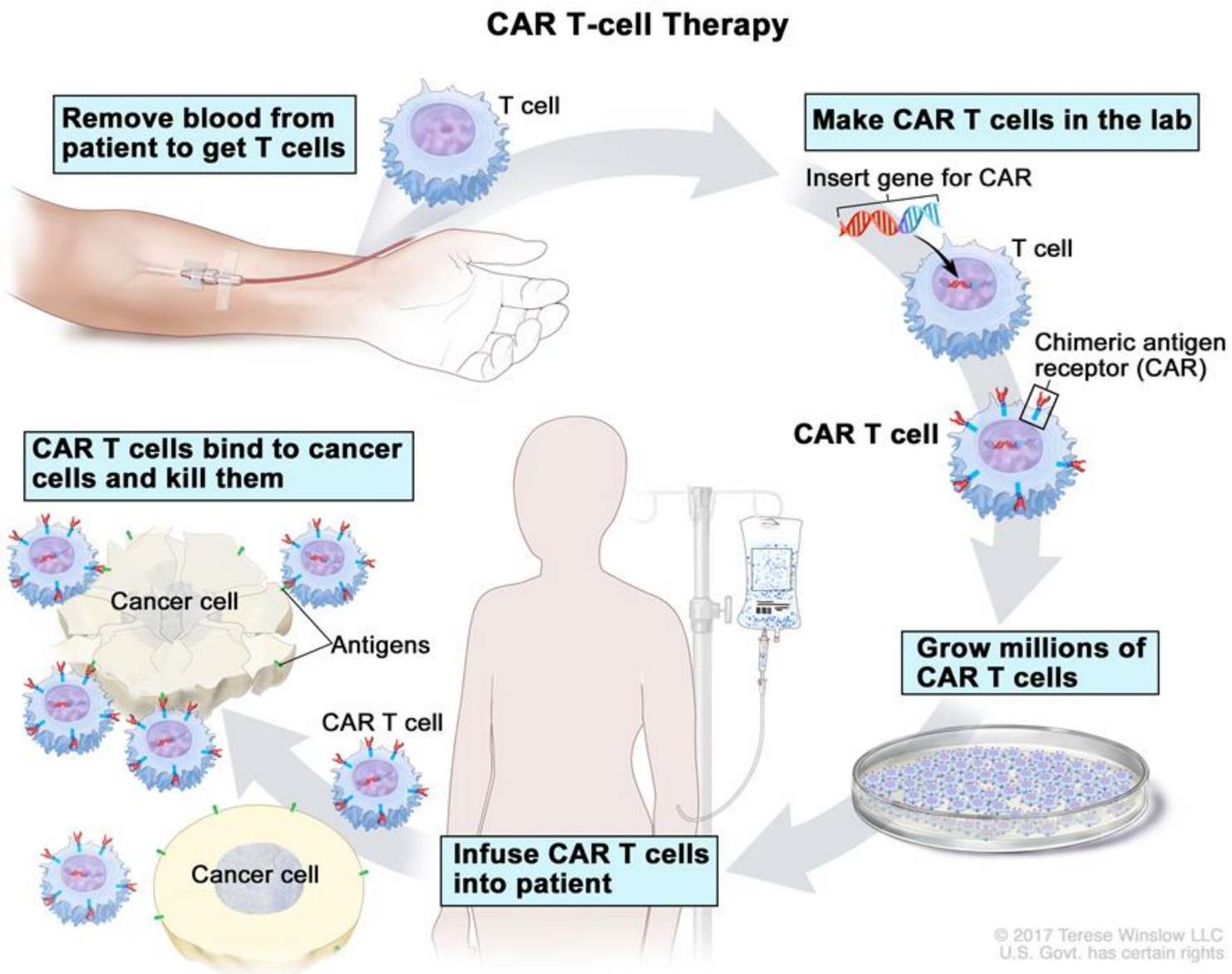
- **MEDIAN TTNT was 45 months with a median epcoritamab exposure of 9.7 months**

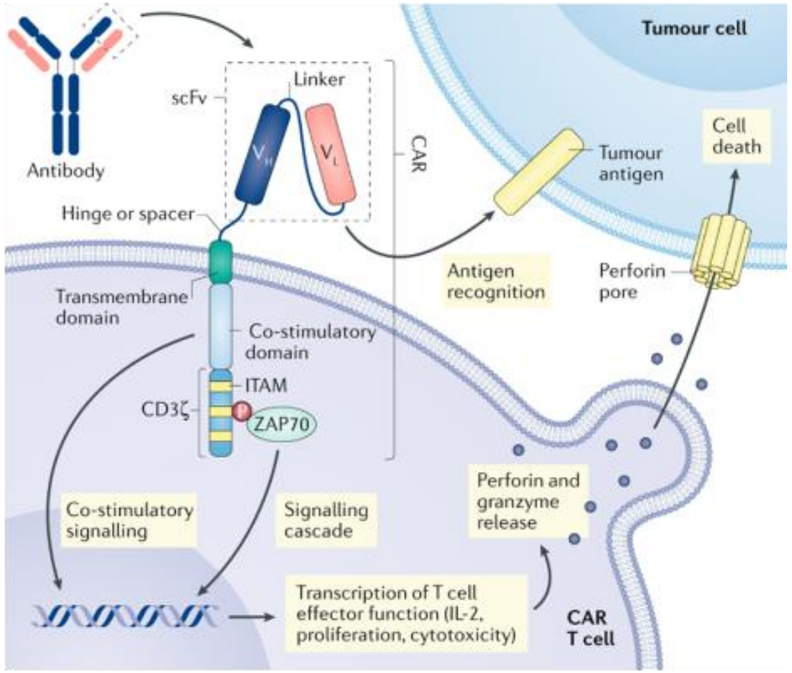
EFFICACY AND SAFETY OF BISPECIFIC ANTIBODIES IN R/R FL

Agent	Trial	N of patients	Median follow up in months	Response	Median PFS in months	Median DOR, DoCR in months	Median OS in months
Mosunetuzumab[18]	GO29781 (NCT02500407)	90	37	ORR 80%, CR 60%	24.0	35.9, NR	NR
Epcoritamab[15]	EPCORE NHL-1 (NCT03625037)	128	27	ORR 82%, CR 63%	15.4	NR, NR	NR

Agent	Trial	N of patients	Rate of CRS: any grade (grade ≥3), %	CRS: rates of tocilizumab use, %	Rate of ICANS: any grade (grade ≥3), %	Rate of neutropenia: any grade (grade ≥3), %	Rate of infections: any grade (grade ≥3), %	Treatment discontinuation rate due to adverse events, %
Mosunetuzumab[17]	GO29781 (NCT02500407)	90	44 (2)	8	5 (0)	29 (27)	51 (17)	4
Epcoritamab[15]	EPCORE NHL-1: pivotal cohort	128	66 (2)	24	6 (0)	29 (26)	NA	19
Epcoritamab[15]	EPCORE NHL-1: optimization cohort	86	49 (0)	12	0 (0)	20 (19)	NA	3

Nizamuddin I.A, Bartlett N.L., Haematologica 110 July 2025

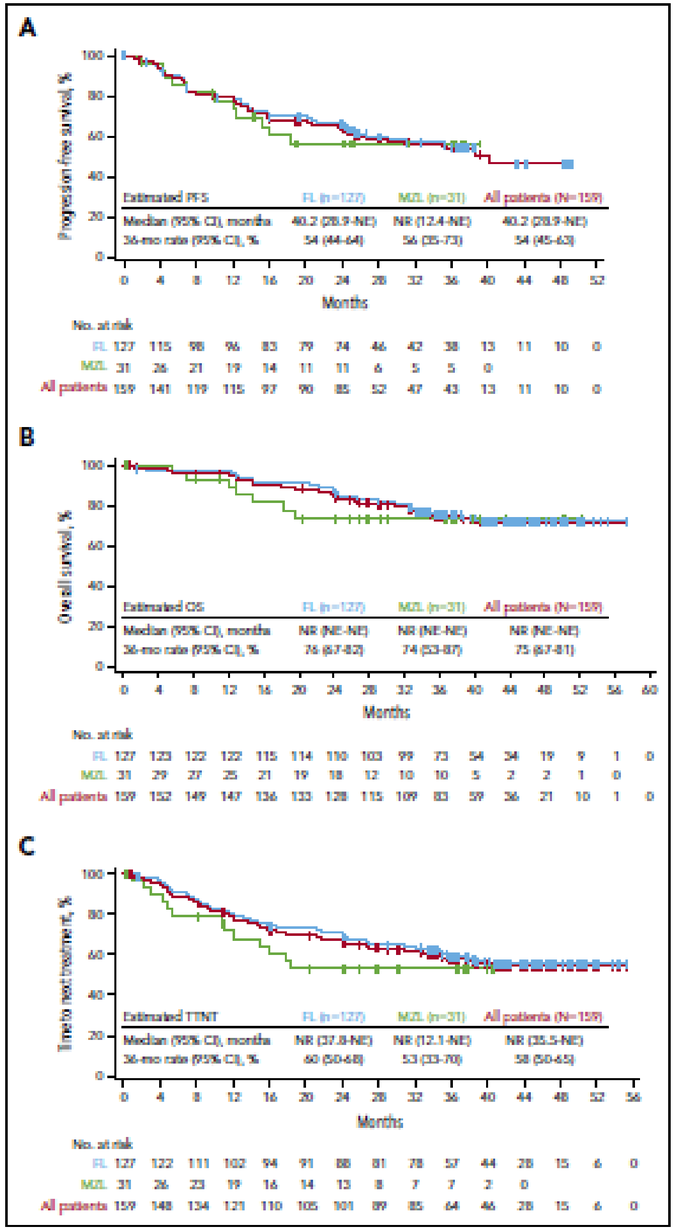

CAR T-cell Therapy
Remove blood from patient to get T cells
T cell
Make CAR T cells in the lab
Insert gene for CAR
T cell
Chimeric antigen receptor (CAR)
CAR T cell
CAR T cells bind to cancer cells and kill them
Cancer cell
Antigens
CAR T cell
Cancer cell
Grow millions of CAR T cells
Infuse CAR T cells into patient
© 2017 Terese Winslow LLC
U.S. Govt. has certain rights


Tumour cell
Antibody
scFv
Linker
CAR
Hinge or spacer
Tumour antigen
Cell death
Antigen recognition
Perforin pore
Transmembrane domain
Co-stimulatory domain
ITAM
CD3ζ
ZAP70
Co-stimulatory signalling
Signalling cascade
Perforin and granzyme release
Transcription of T cell effector function (IL-2, proliferation, cytotoxicity)
CAR T cell

Three-year follow-up analysis of axicabtagene ciloleucel in relapsed/refractory indolent non-Hodgkin lymphoma (ZUMA-5)

n (%)	FL (n = 124)		MZL (n = 28)		All patients (N = 152)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	20 (16)	10 (8)	10 (36)	7 (25)	30 (20)	17 (11)
Serious AEs	11 (9)	10 (8)	4 (14)	3 (11)	15 (10)	13 (9)
Cytopenias	3 (2)	2 (2)	5 (18)	5 (18)	8 (5)	7 (5)
CRS	0	0	3 (11)	0	3 (2)	0
Neurologic events	0	0	1 (4)	1 (4)	1 (1)	1 (1)
Infections	14 (11)	6 (5)	7 (25)	2 (7)	21 (14)	8 (5)
Hypogammaglobulinemia	1 (1)	0	1 (4)	0	2 (1)	0
Tumor lysis syndrome	0	0	0	0	0	0

	FL (n = 124)	MZL (n = 28)	All patients (N = 152)
Any second primary malignancy, n (%)	13 (10)	5 (18)	18 (12)
Nonmelanoma skin cancer	3 (2)	0	3 (2)
Melanoma	1 (1)	0	1 (1)
t-MDS/t-AML	5 (4)	3 (11)	8 (5)
Colorectal cancer	1 (1)	0	1 (1)
B-ALL/AML	1 (1)	0	1 (1)
Anal/rectal cancer	1 (1)	0	1 (1)
Prostate cancer	1 (1)	0	1 (1)
Neuroendocrine tumor	0	1 (4)	1 (1)
Breast cancer	0	1 (4)	1 (1)



Median f.up 41,7 mths

ORR 94%

Median DOR 38,6 mths

Median PFS 40,2 mths

Median OS not reached

Neelapu et al, Blood 2024

Real-World Effectiveness and Safety Outcomes by Age, Comorbidity, Frailty, and Treatments Prior to Infusion in Relapsed or Refractory Follicular Lymphoma Patients Treated With Axicabtagene Ciloleucel

Results: Patients

Table 1. Demographics and Baseline Characteristics

Characteristic	Analyzed Patients n=238
Median age at infusion, years (IQR)	61 (55-68)
≥65, n (%)	90 (38)
Male sex, n (%)	137 (58)
KPS prior to infusion, n (%)	
90-100	124 (54)
80	81 (35)
≤70	25 (11)
Clinically significant comorbidity, n (%)[a]	179 (75)
Cardiac	35 (15)
Hepatic	15 (6)
Pulmonary (moderate/severe)	43 (18)
Disease stage III-IV at diagnosis, n (%)[b]	159 (67)
Elevated LDH prior to axi-cel infusion, n (%)	61 (36)
Median prior lines of therapy, n (IQR)	4 (3-6)
Prior auto-HCT, n (%)	34 (14)
Prior bendamustine, n (%)	173 (74)
Bridging therapy, n (%)[c]	72 (32)
LD chemotherapy, n (%)	
Cyclophosphamide + fludarabine	221 (93)
Single-agent bendamustine	14 (6)

- A total of 238 patients with R/R FL who received axi-cel were included in this analysis (**Table 1**)
- Median follow-up was 24.1 months (95% CI, 23.7-24.2)
- Median time from leukapheresis to axi-cel infusion was 28 days (interquartile range [IQR], 26-34)

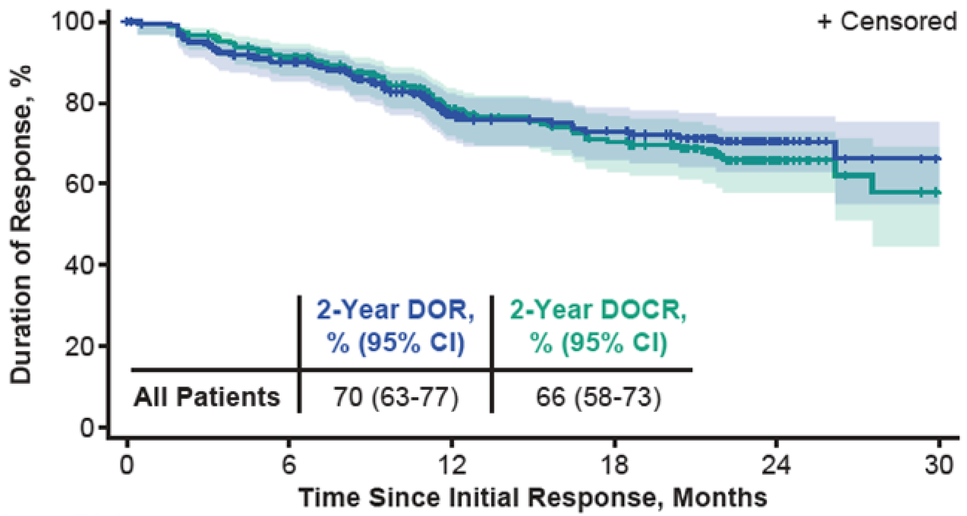
[a] Does not include all clinically significant comorbidities in the study. [b] Disease stage at diagnosis was not reported in 47 patients. [c] Presence or absence of bridging therapy was not reported in 14 patients.
Auto-HCT: autologous hematopoietic stem cell transplant; axi-cel: axicabtagene ciloleucel; FL: follicular lymphoma; IQR: interquartile range; KPS: Karnofsky performance score; LD: lymphodepletion; LDH: lactate dehydrogenase; R/R: relapsed or refractory.

Tun *et al.* ASH 2025 (Publication 5356; poster presentation)

Real-World Effectiveness and Safety Outcomes by Age, Comorbidity, Frailty, and Treatments Prior to Infusion in Relapsed or Refractory Follicular Lymphoma Patients Treated With Axicabtagene Ciloleucel

Aung M. Tun, MD[1]; Matthew J. Frank, MD, PhD[2]; Madiha Iqbal, MBBS, MD[3]; Alex F. Herrera, MD[4]; Mehdi Hamadani, MD[5]; Waleska S. Pérez, MPH[5]; Soyoung Kim, PhD[5]; Babatunde Adedokun, PhD, MBBS[6]; Constance Lau, MPH[6]; Zhen-Huan Hu, MPH[6]; Timothy Best, PhD[6]; Olga Nikolajeva, MD[6]; Grace Lee, PharmD, MAS[6]; Marcelo C. Pasquini, MD, MS[5]; and Caron Jacobson, MD, MMSc[7]

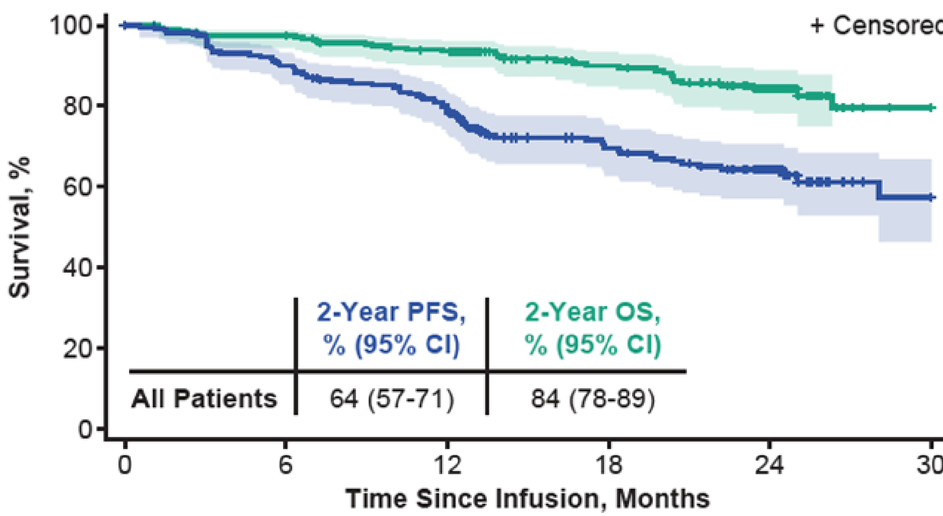
Duration of Response[b]



No. at Risk

DOR	229	194	120	98	31	11
DOCR	216	189	118	94	30	11

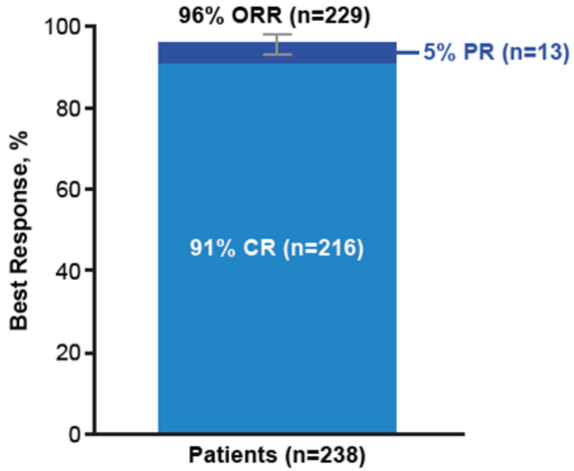
Progression-Free and Overall Survival[c]

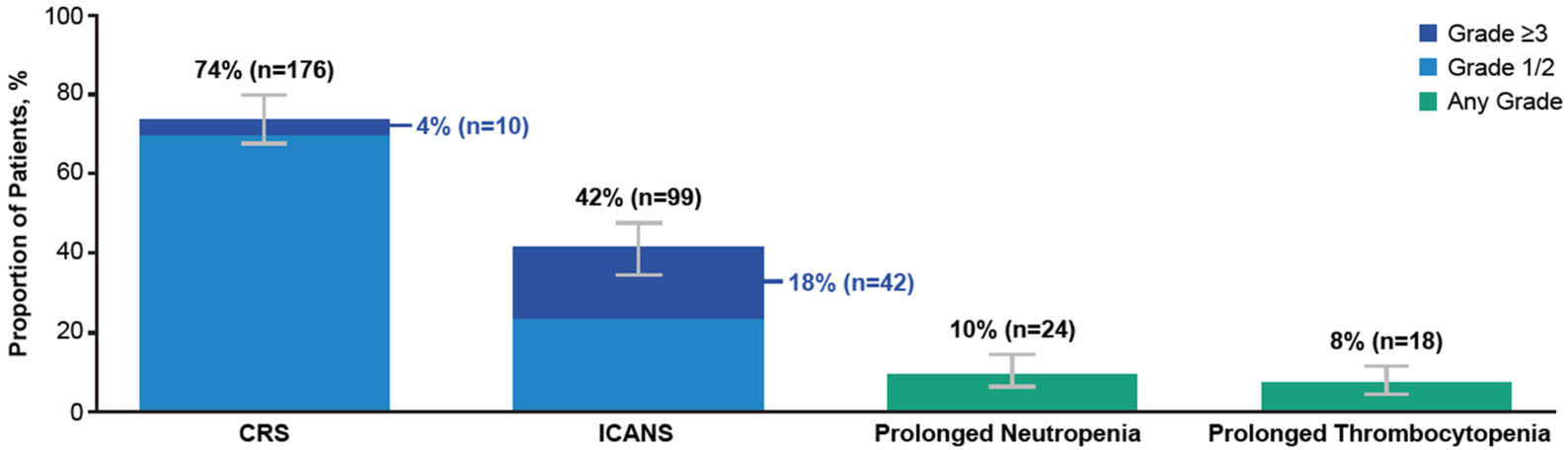


No. at Risk

PFS	238	208	179	107	75	15
OS	238	230	215	146	104	20

Response[a]



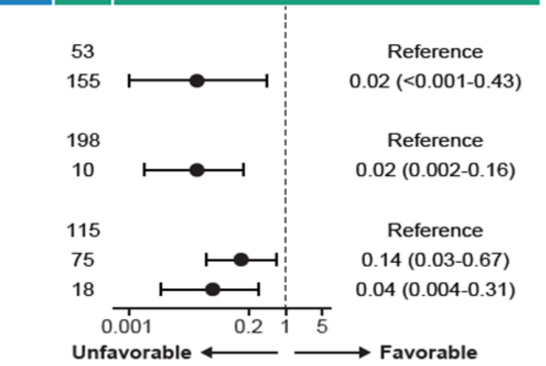


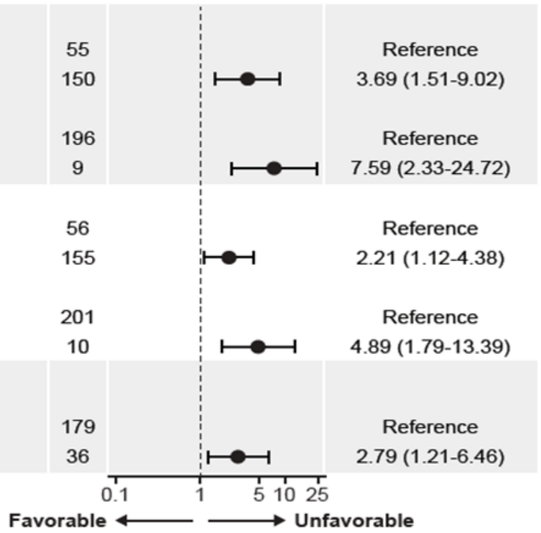
ASH 2025

Results: Effectiveness

Table 2. Univariate and Multivariable Analyses of Effectiveness Outcomes

Outcome	Variable	Univariate Analysis Estimate at 2 Years		Multivariable Analysis	
		n	Rate (95% CI)	n	OR/HR (95% CI)
CR Rate	**Prior bendamustine use[a]**				
	No	61	98 (91-100)	53	Reference
	Yes	173	88 (83-93)	155	0.02 (<0.001-0.43)
	Type of LD				
	Cyclophosphamide + fludarabine	221	93 (89-96)	198	Reference
	Bendamustine	14	57 (29-82)	10	0.02 (0.002-0.16)
	Karnofsky performance score				
	90-100	124	94 (89-98)	115	Reference
	80	81	89 (80-95)	75	0.14 (0.03-0.67)
	≤70	25	76 (55-91)	18	0.04 (0.004-0.31)
DOR	**Prior bendamustine use[a]**				
	No	61	89 (75-96)	55	Reference
	Yes	173	65 (57-73)	150	3.69 (1.51-9.02)
	Type of LD				
	Cyclophosphamide + fludarabine	221	73 (66-79)	196	Reference
	Bendamustine[b]	—	—	9	7.59 (2.33-24.72)
PFS	**Prior bendamustine use[a]**				
	No	61	84 (69-92)	56	Reference
	Yes	173	58 (49-66)	155	2.21 (1.12-4.38)
	Type of LD				
	Cyclophosphamide + fludarabine	221	66 (58-72)	201	Reference
	Bendamustine	14	48 (21-71)	10	4.89 (1.79-13.39)
OS	**Clinically significant comorbidities: Pulmonary (moderate or severe)**				
	No	195	87 (81-92)	179	Reference
	Yes	43	70 (51-83)	36	2.79 (1.21-6.46)





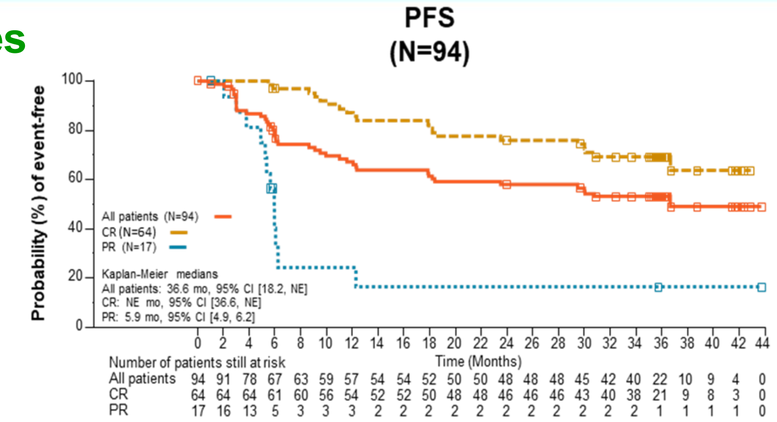
- Univariate and multivariable analysis demonstrated that prior bendamustine use was associated with reduced CR rates, and shorter DOR and PFS (**Table 2**)
  - Bendamusine LD was also associated with reduced CR rates, and shorter DOR and PFS (**Table 2**)
- Moderate or severe pulmonary comorbidity was associated with shorter OS
- Lower KPS was associated with reduced CR rates
- No other significant associations between key demographic or clinical variables with effectiveness were observed

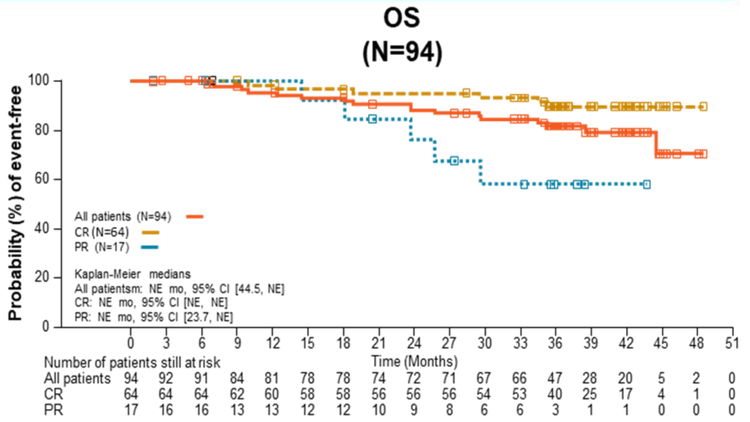
Conclusions

- With 2 years of follow-up, durable responses and manageable safety were observed with real-world axi-cel use in patients with R/R FL, similar to outcomes in ZUMA-5
- Outcomes among the elderly and those with comorbidities were generally comparable to the overall R/R FL population
- Age ≥65 years was associated with greater risk of any grade ICANS, but not Grade ≥3 ICANS
- Bendamustine LD was associated with reduced effectiveness, but these findings should be interpreted with caution given the small sample size (n=14) and warrant further investigation on appropriate washout period
- Prior bendamustine use was associated with fewer durable responses, though whether this is limited to recent administration prior to axi-cel infusion is unknown as these data were unavailable

ELARA study: 36-months PFS and OS rates

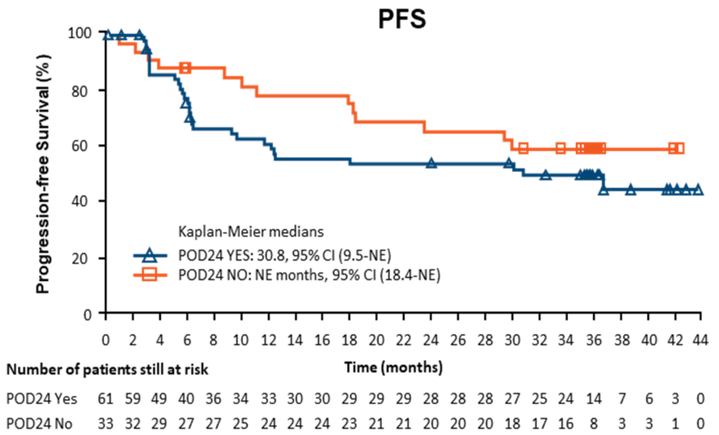
Baseline Patients Characteristics	Infused Patients (N=97)
ECOG PS ≥1 prior to infusion, n (%)	42 (43.3)
Stage at study entry III-IV, n (%)	83 (85.6)
Bone marrow involvement, n (%)	37 (38.1)
Bulky disease,[a] n (%)	63 (64.9)
FLIPI high at study entry (≥3), n (%)	58 (59.8)
Median no. of prior therapies (range)	4 (2-13)
≥3 lines	73 (75.2)
≥5 lines	27 (27.8)
POD24 from first anti-CD20 mAb-containing therapy,[b] n (%)	61 (62.9)
Refractory disease[c] to last line of therapy, n (%)	76 (78.3)
Best response SD/PD	
Refractory to ≥2 regimens, n (%)	69 (71.1)
Double refractory[d]: Anti-CD20 mAb + alkylating agent	66 (68.0)
Refractory to PI3K inhibitors	14 (14.4)
Prior autologous HSCT, n (%)	35 (36.1)
Relapsed ≤12 months after autologous HSCT	15 (15.5)
Median DOR from last line of therapy, months (n=35)	7.5
Received bridging chemotherapy	44 (45.4)

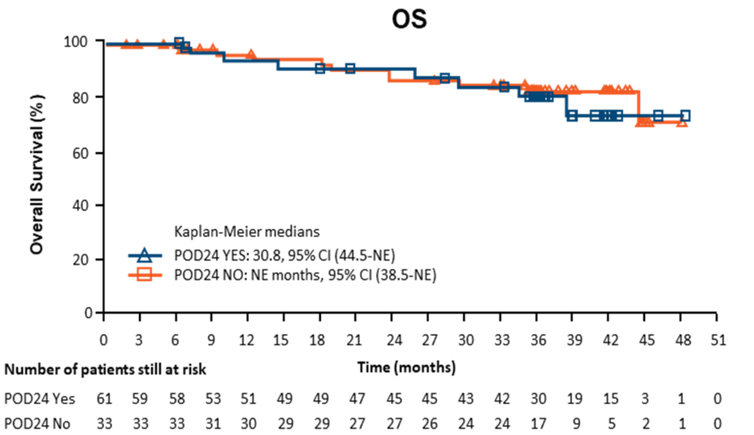




- Median PFS was 37 months among efficacy evaluable patients
- 36-month PFS was 53% for all patients and 69% for patients with a CR

- Median OS was not reached among efficacy evaluable patients
- 36-month OS rate was 82%





- 36-month PFS rate was 50% (95% CI; 35.8-61.9) in the POD24 subgroup and 59% (95% CI; 39.5-73.5) in patients without POD24

- 36-month OS rate was 83% (95% CI; 69.1-90.5) in the POD24 subgroup and 80% (95% CI; 60.9-90.6) in patients without POD24

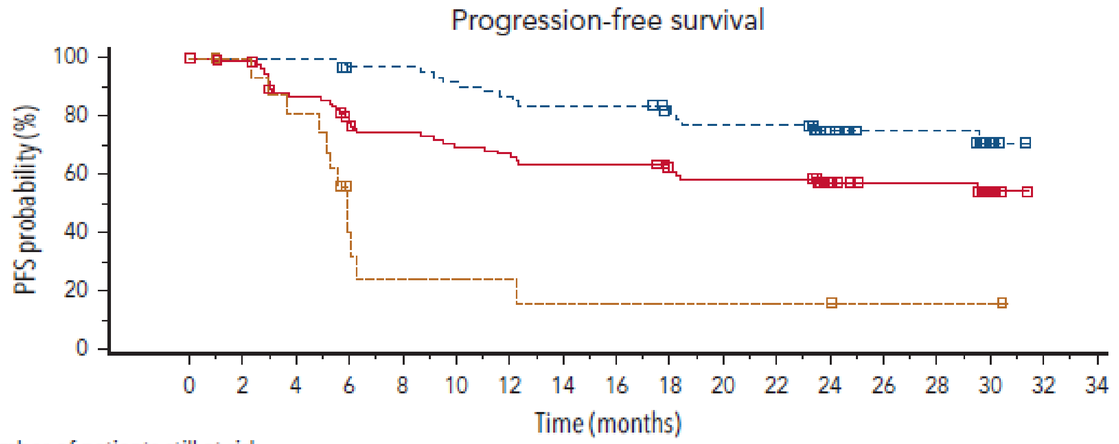
Stephen J. Schuster, ASH meeting 2023 Oral Abstract #601

Durable response after tisagenlecleucel in adults with relapsed/refractory follicular lymphoma: ELARA trial update

PFS Probability	% (95% CI)
12 months, all patients	67.2 (56.3-75.9)
24 months, all patients	57.4 (46.2-67.0)
12 months, patients in CR	87.2 (76.0-93.4)
24 months, patients in CR	75.3 (62.4-84.3)

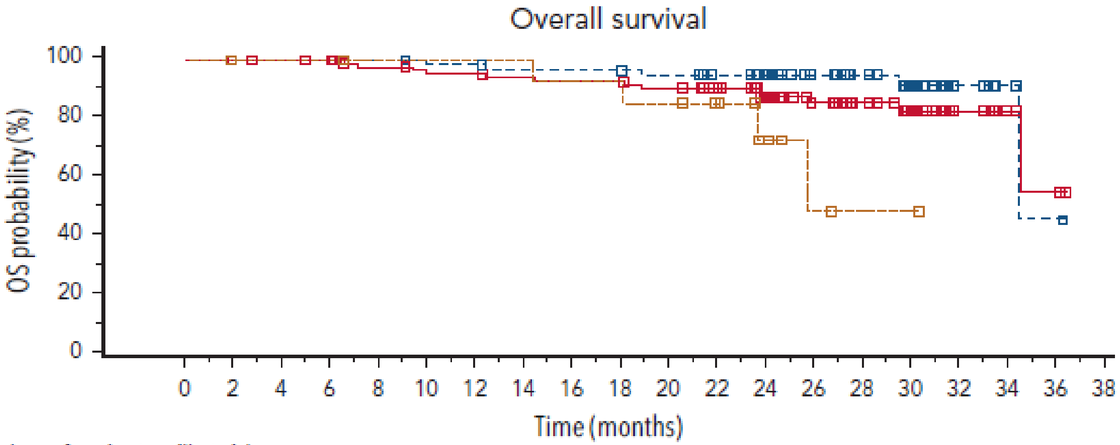
OS Probability	% (95% CI)
12 months, all patients	95.3 (88.1-98.2)
24 months, all patients	87.7 (78.3-93.2)
12 months, patients in CR	98.4 (88.9-99.8)
24 months, patients in CR	95.0 (85.3-98.4)

TTNT Probability	% (95% CI)
12 months, all patients	79.6 (69.6-86.7)
24 months, all patients	69.7 (58.7-78.3)
12 months, patients in CR	95.1 (85.6-98.4)
24 months, patients in CR	83.3 (71.2-90.7)



Number of patients still at risk

All patients (N = 94)	94	91	78	67	63	59	57	54	54	49	47	47	32	19	19	6	0	0
CR (N = 64)	64	64	64	61	60	56	54	52	52	47	45	45	31	18	18	5	0	0
PR (N = 17)	17	16	13	5	3	3	3	2	2	2	2	2	1	1	1	1	0	0

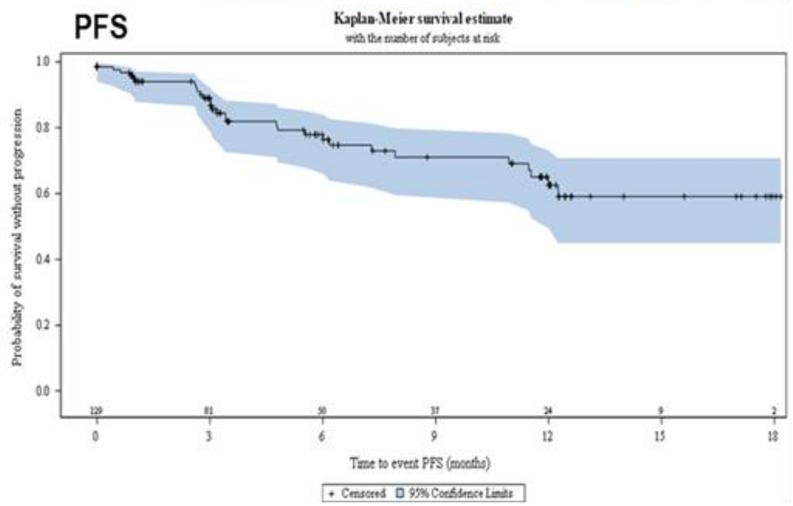


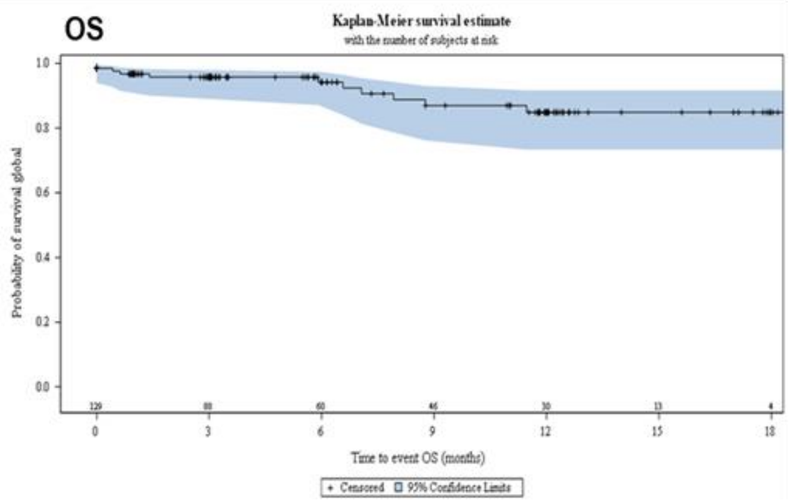
Number of patients still at risk

All patients (N = 94)	94	93	92	91	84	81	81	79	78	78	75	69	55	38	32	19	9	4	2	0
CR (N = 64)	64	64	64	64	62	60	60	58	58	58	56	52	45	32	27	16	7	3	1	0
PR (N = 17)	17	16	16	16	13	13	13	13	12	12	11	9	4	2	1	1	0	0	0	0

Dreyling M et al, Blood 2024

Real-world efficacy and safety of Tisagenlecleucel (CTL019) for relapse or refractory follicular lymphoma patients included in the Early Access Program through the French DESCAR-T registry





Conclusion

144 high-risk R/R FL patients:
77,9% Refractory disease
75% Relapsed during or within 6 months after completion of maintenance therapy
33,8% Relapsed after a hematopoietic stem cell transplantation

- Real-world use of Tisa-cel that confirms the efficacy outcomes reported in ELARA trial (ORR 86%; CR 68%):
  - **ORR: 98.3%**
  - **Complete response: 85.8%**
  - **PFS at 12 months: 62.6% [49.5 - 73.1]**
  - **OS at 12 months: 84.9% [73.3 - 91.7]**
- No new safety concerns were identified: very low rate of grade 3-4 CRS or ICANS

CRS	**gr. 1 – 2**	80	(75,5%)
	gr. 3 – 4	1	(0,9%)
ICANS	**gr. 1 – 2**	21	(19,8%)
	gr. 3 – 4	1	(0,9%)

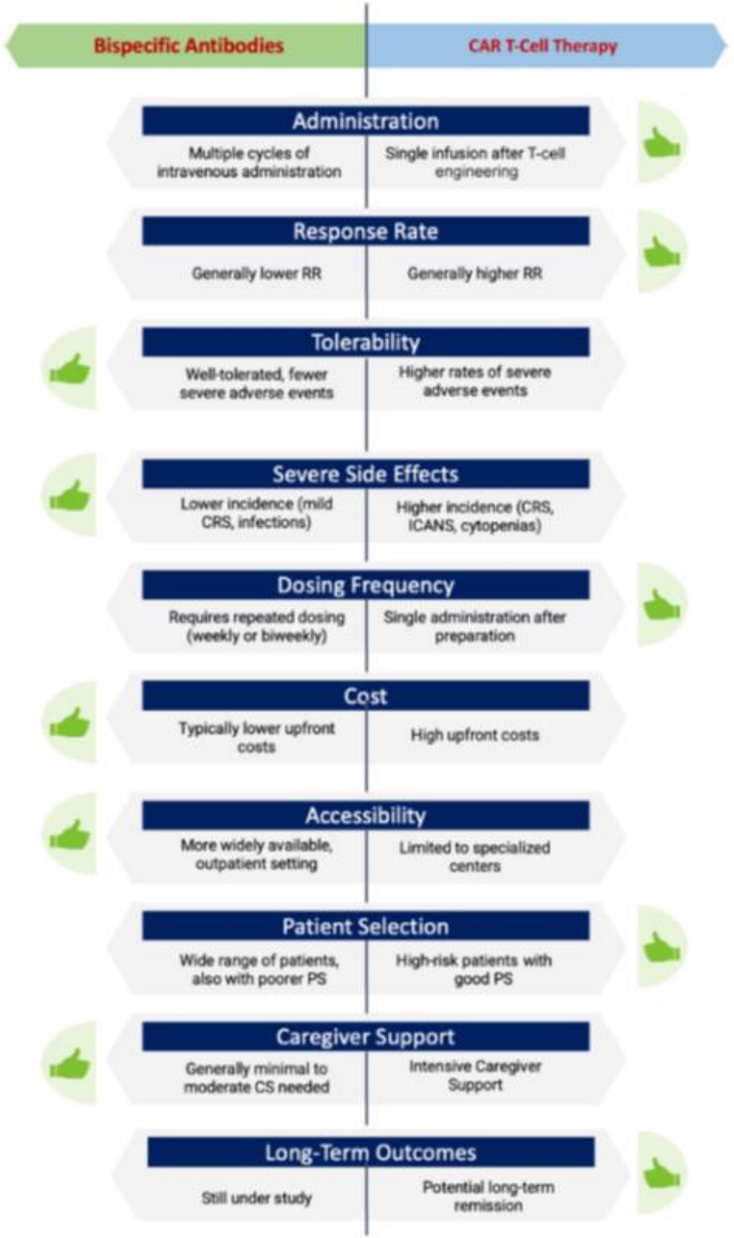
YSEBAERT L., ESMO meeting 2024 Oral Abstract #805MO

Comparative Analysis of Bispecific Antibodies and CAR T-Cell Therapy in Follicular Lymphoma

Fortunato Morabito[1] | Enrica Antonia Martino[2] | Maria Elena Nizzoli[3] | Annalisa Talami[3] | Stefano Pozzi[3] | Massimo Martino[4] | Antonino Neri[5] | Massimo Gentile[2,6]

[1]Gruppo Amici Dell'Ematologia Foundation—GrADE, Reggio Emilia, Italy | [2]Hematology Unit, Department of Onco-Hematology, AO of Cosenza, Cosenza, Italy | [3]Hematology Unit, Azienda USL-IRCSS di Reggio Emilia, Reggio Emilia, Italy | [4]Department of Hemato-Oncology and Radiotherapy, Hematology and Stem Cell Transplantation and Cellular Therapies Unit (CTMO), Grande Ospedale Metropolitano "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy | [5]Scientific Directorate, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy | [6]Department of Pharmacy, Health and Nutritional Science, University of Calabria, Rende, Italy

European Journal of Haematology, 2025; 114:4–16



Cost-effectiveness analysis:

- **Axi-cell is cost- effective versus mosun in r/r 3L+ FL**
  Oluwole O.O. et al, Vanderbilt University Center, Nashville

- **Mosun is more cost-effective compared to both axi-cel and tisa-cell at 1,2,5 and 10 yrs for treatment of R/R FL**
  Lin M et al, University of Michigan, Ann Arbor

SWOT CONSENSUS for CAR-T in FL

Patients with late relapses deserve a careful assessment of the available therapeutic options (included watchful wait)

In order to improve the dismal survival of patients who failed two prior lines and show refractory disease and/or early relapse, CAR-T therapy is strongly recommended, irrespectively of prior ASCT and of FLIPI or metabolic tumor volume at relapse

But a careful selection of patients is necessary!

Those patients who have been exposed to bendamustine in the last 6 months should better be considered for treatments alternative to CAR-T

In order to avoid unacceptable toxicity of immunotherapies, particularly long-term cytopenias and infections and neurologic toxicity, very elderly patients should be carefully screened with validated frailty tools before confirming their eligibility

Marchetti M, Corradini P, Arcaini L et al, Haemat Oncol 2025

Good Practice Reccomendations

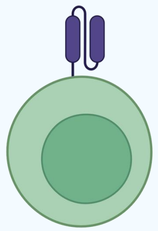
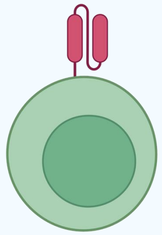
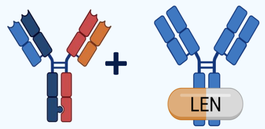
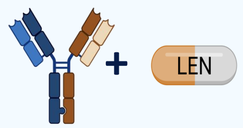
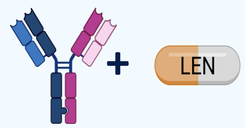
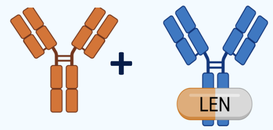
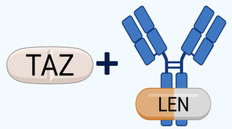
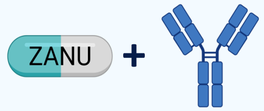
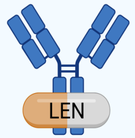
In order to foster an efficient journey-to-CAR-T, preliminary assessment of CAR-T eligibility items is recommended in FL patients who proved refractory to frontline therapy, incurred an early relapse (POD24), or showed a high disease burden at relapse (GELF mass criteria or metabolic tumor burden), provided that they are free of relevant comorbidities

In order to timely implement a possible use of CAR-T therapy in subsequent lines, hematology centers are recommended to settle a specific "CAR-T pathway" starting since the diagnosis in younger FL patients and in those showing a high disease burden (FLIPI/m7FLIPI, metabolic tumor burden)

In order to foster an efficient journey to CAR-T, early assessment of response is recommended in FL patients (see recommendation 2.1)

A CAR-T focused choice of second-line treatment is recommended in patients diagnosed at a young age, with a high disease burden, or with suboptimal response after frontline therapy

Study Designs in 2L FL

CAR T-cell therapies		anti-CD20xCD3 bsAbs			anti-CD19	Other targeted therapies	
ZUMA-22[1]	TRANSFORM FL[2]	EPCORE® FL-1[3]	Celestimo[4]	OLYMPIA-5[5]	inMIND[6]	SYMPHONY-1[7]	MAHOGANY[8]
axi-cel	liso-cel	epcoritamab + R^2	mosunetuzumab + len	odronextamab + len	tafasitamab + R^2	tazemetostat + R^2	zanubrutinib + R/O
							
		vs	vs	vs	vs	vs	vs
Comparator: R-chemo or R^2		R^2 					
Primary Endpoint(s): PFS	PFS	ORR PFS	PFS	PFS	PFS	PFS	PFS

- **Adapted from: 1. NCT05371093. 2. NCT06313996. 3. NCT05409066. 4. NCT04712097. 5. NCT06149286. 6. NCT04680052. 7. NCT04224493. 8. NCT05100862.**

Considerations in Frontline FL

Select Phase 3 Development in 1L FL

	anti-CD20xCD3 bsAbs				anti-CD19xCD3 bsAb
	EPCORE FL-2[1]	**OLYMPIA-1[2]**	**OLYMPIA-2[3]**	**MorningLyte[4]**	**SOUNDTRACK-F1[5]**
Investigational	**Epcor + R²**	**Odron monotherapy**	**Odron + CHOP/CVP**	**Mosun + Len**	**Surovatamig + R**
	± epcor maintenance	+ odron maintenance	± odron maintenance	± mosun maintenance[7]	± suro maintenance[8]
	vs	vs	vs	vs	vs
Comparators	• R/O-CHOP • R/O-Benda • R² + R/O maintenance[6]	• R-CHOP/CVP • R-Benda + R maintenance	• R-CHOP + R maintenance	• R/O-CHOP • R/O-Benda + R maintenance	• R-CHOP/CVP • R/Benda + R maintenance
Primary Endpoint(s)	CR30, PFS	CR30	CR30	PFS	PFS, ORR at EOI

1L, first line (of therapy); Benda, bendamustine; bsAb, bispecific antibody; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CVP, cyclophosphamide, vincristine, prednisone; CR30, complete response rate at 30 weeks; EOI, end of induction; pcor, epcoritamab; FL, follicular lymphoma; len, lenalidomide; mosun, mosunetuzumab; O, obinutuzumab; odron, odronextamab; ORR, overall response rate; PFS, progression-free survival; R, rituximab; R², rituximab + lenalidomide; suro, surovatamig. 1. ClinicalTrials.gov. NCT06191744. 2. ClinicalTrials.gov. NCT06091254. 3. ClinicalTrials.gov. NCT06097364. 4. ClinicalTrials.gov. NCT06284122. 5. ClinicalTrials.gov. NCT06549595. 6. Linton K et al. Abstract TPS7084. ASCO Annual Meeting 2024. 7. Lysarc Press Release. Available at: https://lymphoma-research-experts.org/wp-content/uploads/lysarc/pr-morninglyte-2024-eng.pdf. 8. Cheah CY et al. Abstract 3614. ASH Annual Meeting 2025.

REVIEW

Towards a chemo-free approach for follicular lymphoma

Stefano Luminari[1,2] | Emiliano Barbieri[1,3] | Maria Elena Nizzoli[1,3]

Br J Haematol. 2025;207:1755–1764.

It is time to change our approach in describing the path of the disease and treatment options shared choice with the patient of the "best therapy at that particular moment in her/his life“

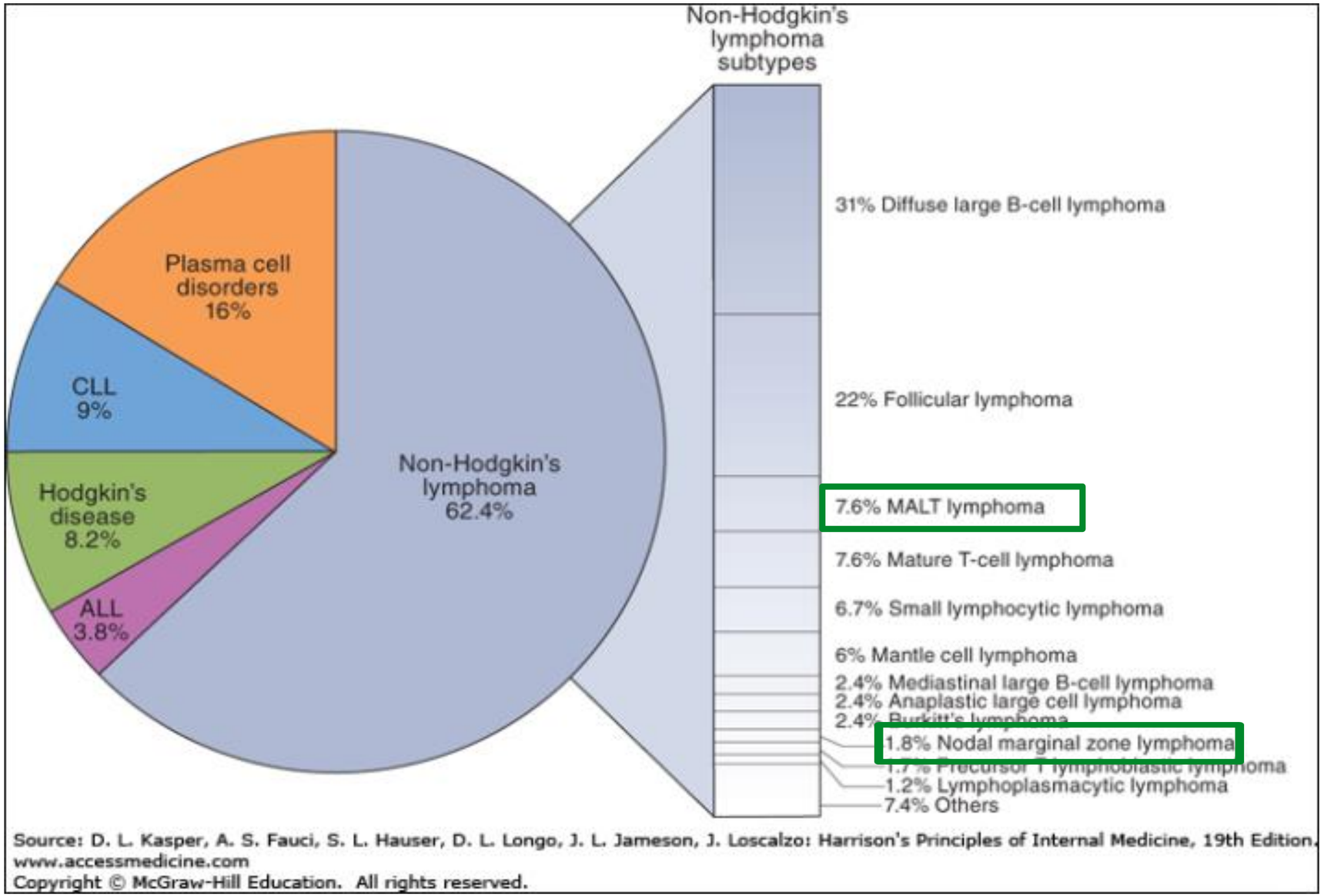
QoL (in the context of a pathology with these characteristics, progression and curability) should today represent at least a co-primary objective of clinical studies

	First line	Second line	Third line +
Today FL stage III-IV, HTB	• **ICT** • **Rituximab** (full chemo-free program)	POD24: • **ICT + ASCT (?)** • **R2** Non-POD24: • **R2**	• **BsAbs** • **CAR-T** • **Zanu-obinut.** • **Tazemetostat***
Tomorrow *Already anticipated Ph3 results* FL stage III-IV, HTB	• **ICT** • **Rituximab**	POD24 and non-POD24: • **Len ± R + Tafa/BsAbs**	• **BsAbs** • **CAR-T** • **Zanu-obinut.** • **Tazemetostat***
Future view *Pending results of Ph3 ongoing trials* FL stage III-IV, HTB	• **BsAbs ± X**	• **CAR-T** (POD24) • **Len ± R +Tafa/BsAbs** • **Zanu-obinut**	• **BsAbs** • **Novel agents** • **CAR-T** • **Zanu-obinut.** • **Len ± R +Tafa/BsAbs** • **Tazemetostat**

B – cell lymphoprolipherative diseases

MZL is the third most common subtype of B-cell non-Hodgkin lymphomas (B-NHL) and **the second most common indolent B-NHL:**

61% ENMZL
30% NMZL
9% SMZL



Effect of POD24 on the prognosis of follicular and other indolent B-cell non-hodgkin lymphomas

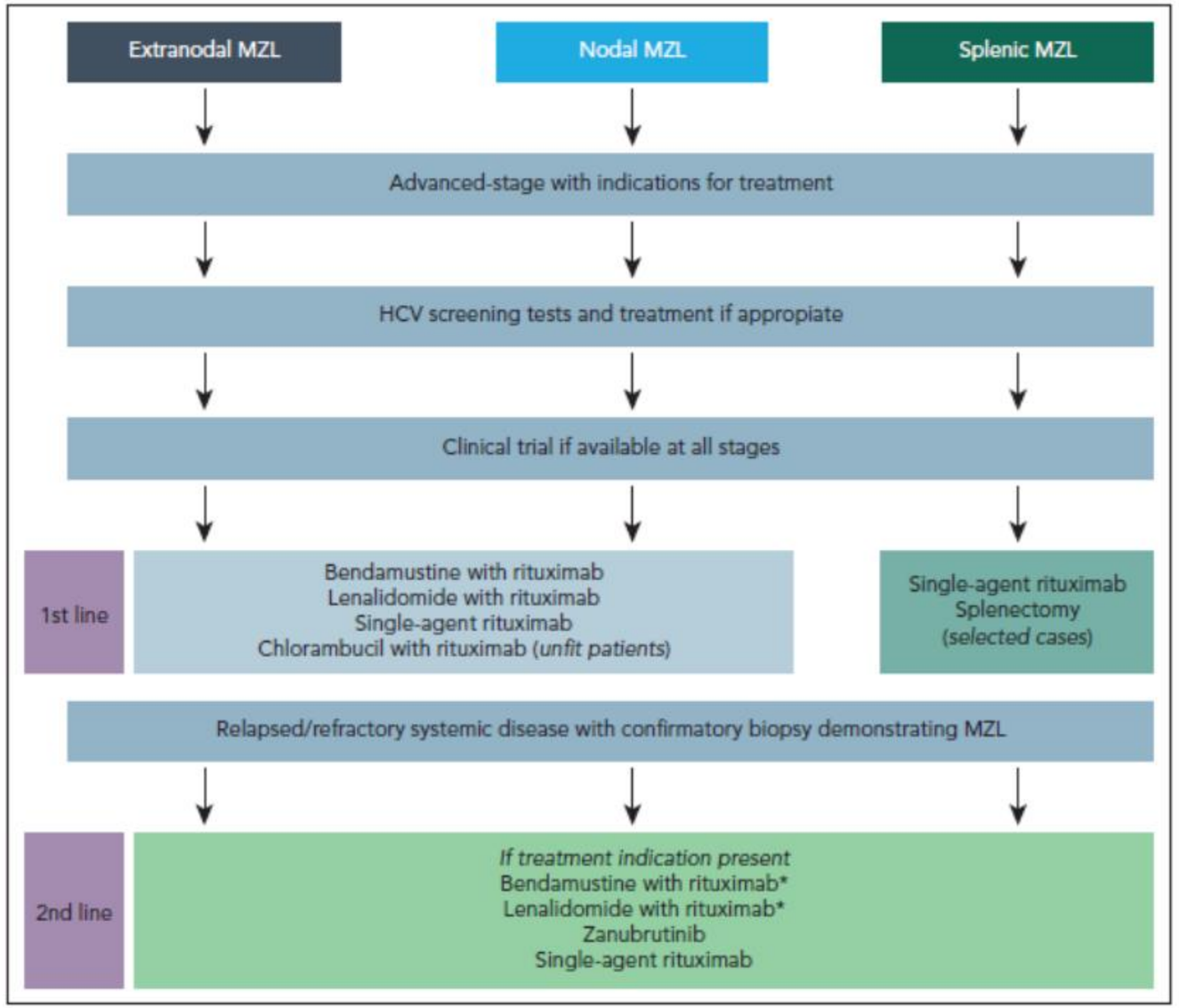
Xiaoyan Li[1] · Xin Wang[1]

Table 2 Differences in prognosis between patients with early versus late disease progression in patients with different subtypes of MZL

Study	*N*	Classification	Definition of POD24	Treatment	POD24 rate	OS(POD24)	OS(non-POD24)	HR/*P*
Luminar[48]	N = 321	MZL	POD24: POD occurred within 24 months after diagnosis	Alk-Mono (n = 16) ;R-Mono(n = 30);R-Alkylating(n = 83);R -CHOP(n = 48); BR (n = 112) ;R-Fludarabi-nen(= 3) ;Other(n = 21)	18%	53% (3years)	88% (3years)	HR = 19.5 p < 0.001
Conconi[49]	N = 401	MALT	POD2;progression within 24 months from the start of first-line treatment	Chemotherapy only(n = 131);Ritux-imab and chemotherapy(n = 132); R-Mono (n = 138)	18%	64% (10years)	85% (10years)	HR = 2.42
Lu[50]	N = 106	SMZL	POD24: POD occurred within 24 from diagnosis	CHOP/COP/ FC(n = 20); R + CHOP /COP/FC(n = 54); splenectomy (n = 11); R only(n = 4); combination of the proposed approaches (n = 17)	16.0%	-	-	HR = 20.116
Epperla[51]	N = 364	MZL	POD24: POD occurred within 24 from systemic therapy initiation	R-Mono	28%	75% (5years)	88% (5years)	p = 0.007
				ICT		69% (5years)	94% (5years)	p < 0.0001

Annals of Hematology (2025) 104:1427–1442

Treatment algorithm for newly diagnosed and R/R advanced stage MZL



Alderuccio and Noy, Blood 2026

Selected large clinical trials in MZL

MAGNOLIA study:

68 pz. R/R MZL

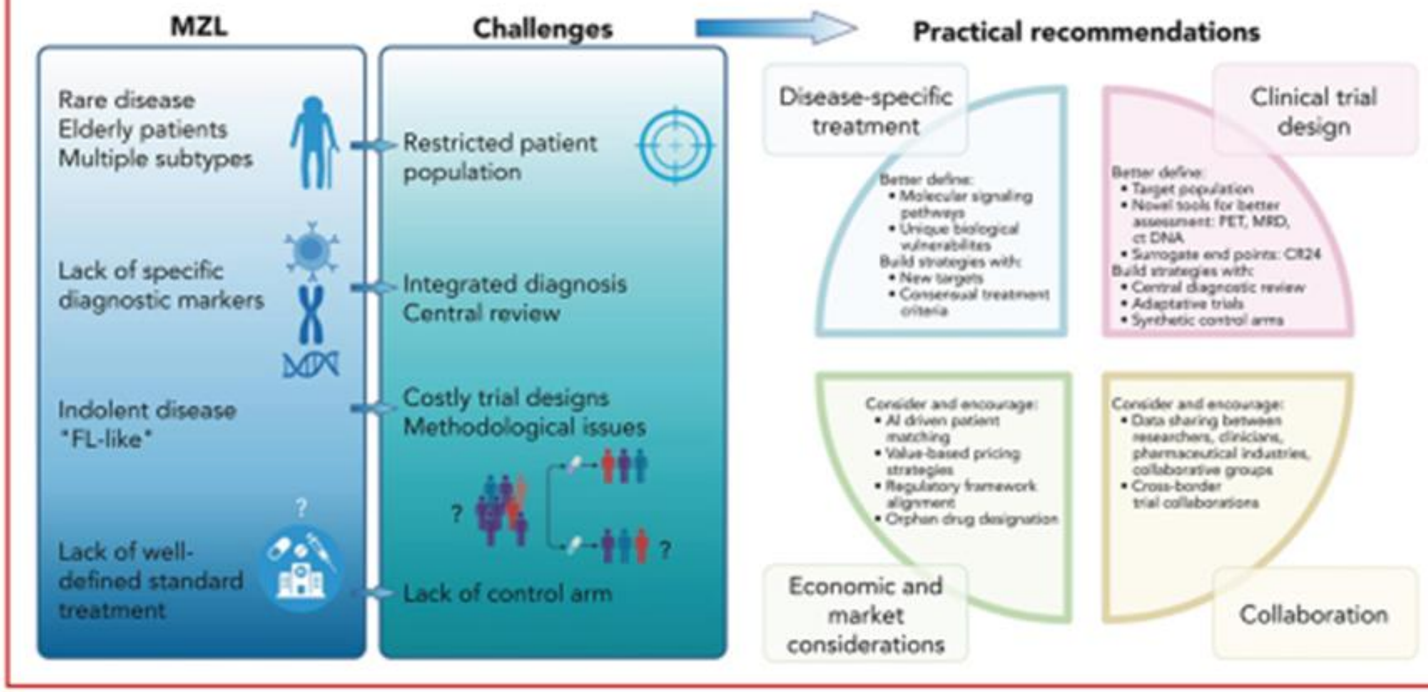
ORR 68,2%
CR 25,8%
2yrs PFS 70,9%

Zanobrutinb is the only new drug with regulatory approval in R/R MZL

Study	Agent(s)	Study, n	Primary end point	Primary end point population	MZL, n (%)	MZL end point
Randomized phase 3 studies						
SELENE[102]	Ibrutinib + BR/R-CHOP vs placebo + BR/R-CHOP	403	PFS	FL and MZL	40 (14)	Subgroup
AUGMENT[29]	R2 vs placebo + R	358	PFS	FL and MZL	64 (18)	Subgroup
GALLIUM[95]	O + B/CHOP/CVP vs R + B/CHOP/CVP	1401	PFS	FL	196 (14)	Subgroup
GADOLIN[101]	BO vs B	396	PFS	FL, MZL, SLL, and LPL	47 (12)	Subgroup
BRIGHT[27]	BR vs R-CVP/R-CHOP	447	CR	FL, MZL, LPL, SLL, MCL, and unclassified	44 (10)	Subgroup
STiL[28]	BR vs R-CHOP	549	PFS	FL, MZL, LPL, SLL, MCL, and unclassified	115 (12)	Subgroup
IELSG-19[84]	R vs C vs CwR	454	EFS	EMZL	454 (100)	Primary
Single-arm phase 2 studies						
PCYC-1121[17]	Ibrutinib	63	ORR	MZL	100	Primary
MAGNOLIA[103]	Zanubrutinib	68	ORR	MZL	100	Primary
ACE-LY-003 (part 2)[104]	Acalabrutinib	43	ORR	MZL	100	Primary
ZUMA-5[131]	Axicabtagene ciloleucel	153	ORR	FL	24 (16)	Subgroup
BRISMA/IELSG-36[86]	BR	56	CR	SMZL	100	Primary
MALT 2008-01[85]	BR	60	EFS	EMZL	100	Primary
AGMT MALT-2[49]	R2	46	Objective/histologic response	EMZL	100	Primary

Alderuccio and Noy, Blood 2026

Drug Development in Marginal Zone Lymphoma (MZL): Caring for the Forgotten Child



Conclusions: **Despite its heterogeneity and challenges in trial design, marginal zone lymphoma represents a unique setting to improve clinical trial methodology and enhance therapeutic innovation.**

*Thieblemont et al. DOI: 10.1182/**blood**.2024028270*

blood Visual Abstract



CONVEGNO INTERREGIONALE SIE

Delegazioni Umbria e Marche

Società Italiana di Ematologia

NOVITÀ TERAPEUTICHE NEI LINFOMI NON-HODGKIN E MIELOMA MULTIPLO: FOCUS SU ANTICORPI BISPECIFICI E CAR-T

Assisi, Sala Conciliazione, Comune di Assisi
4 Novembre 2026

Grazie per l'attenzione