Società Italiana di Ematologia

FORMAZIONE SIE

I linfomi: un nome con almeno 40 sfaccettature!

25 giugno 2026

Bologna
Royal Hotel
Carlton

Linfomi Follicolari

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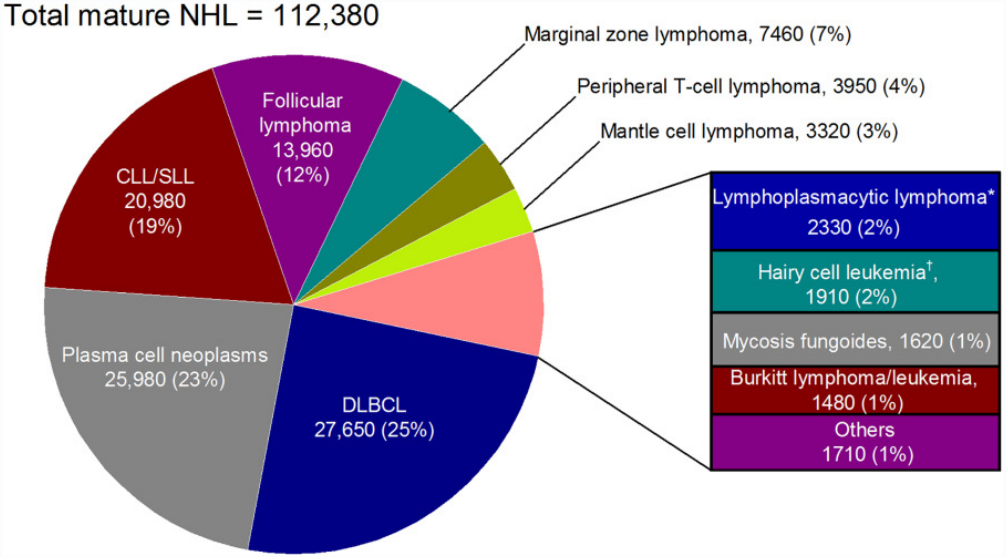
Disclosures of Stefano Luminari

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
ROCHE	x				x		
ABBVIE					x	x	
INCYTE					x	x	
BeOne	x				x	x	
Novartis					x	x	
Regeneron					x	x	
KITE					x		
BMS					x		

Features of follicular lymphomas

- Most frequent among indolent lymphomas
- Can be asymptomacic
- Relapsing remitting course
- Impact on life expectancy low with exceptions
- Can transform into more aggressive lymphomas

Distribution of NHL Subtypes

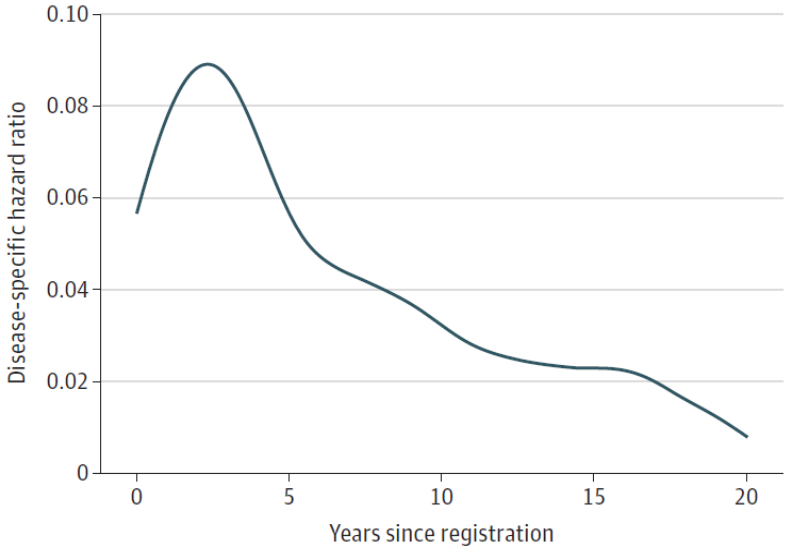


Teras. CA Cancer J Clin. 2016;66:443.

Is cure in FL possible?

Characteristic	Cure estimate, % (95% CI)
Overall	42 (33–52)
FLIPI score	
Low (0–1)	47 (30–65)
Intermediate (2)	46 (33–60)
High (3–5)	30 (17–48)
β2M	
Low	55 (44–66)
High	31 (20–46)

Hazard curve*



*The cause-specific hazard curve represents the smoothed rate of lymphoma progression or lymphoma-related death as a function of time. The decline suggests that the risk of lymphoma-related events diminishes with prolonged follow-up, approaching the level of the general population by 20 years, supporting the idea of cure in some patients.
β2M, beta-2 microglobulin; CI, confidence interval; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index.

Shadman M, et al. JAMA Oncol 2026; doi:10.1001/jamaoncol.2026.0042.

Prognostic models at diagnosis

	FLIPI[1,2]	FLIPI2[3–5]	PRIMA PI[6]	M7-FLIPI[7]
Component	Age, stage, haemoglobin, LDH, nodal sites	β2M, diameter lymph node, BMI, haemoglobin, age	β2M, BMI	FLIPI, ECOG PS, mutation status of seven genes†
OS by risk group (5-year unless specified)	Low: 91% High: 53%	Low: 96% High: 67%	Low: 93%* High: 81%	Low: 84–90% High: 42–65%

	FLEX score[8]	FLIPI-24‡[9,10]	POD24-PI[2]
Component	Male sex, sum of lesion dimension, Grade 3a, extranodal sites, ECOG PS, haemoglobin, β2M, NK cell count, LDH	Age, hemoglobin, white blood cell count, β2M	High-risk FLIPI, mutation status of three genes¶
OS by risk group (5-year unless specified)	Low: 97% (3-year) High: 87% (3-year)	Low: – High: 65%§	Low: 89–91% High: 48–71%

*Low/intermediate risk category; †*ARID1A*, *CARD11*, *CREBBP*, *EP300*, *EZH2*, *FOXO1*, *MEF2B*; ‡Very low risk: 0–0.10 and very high risk: >0.40; §Patients were treated with rituximab monotherapy, radiation or other non-immunochemotherapy regimen; ¶*EP300*, *EZH2*, *FOXO1*.
BMI, bone marrow infiltration; ECOG PS, Eastern Cooperative Oncology Group performance status; NK, natural killer; OS, overall survival; POD24, progression of disease within 24 months.

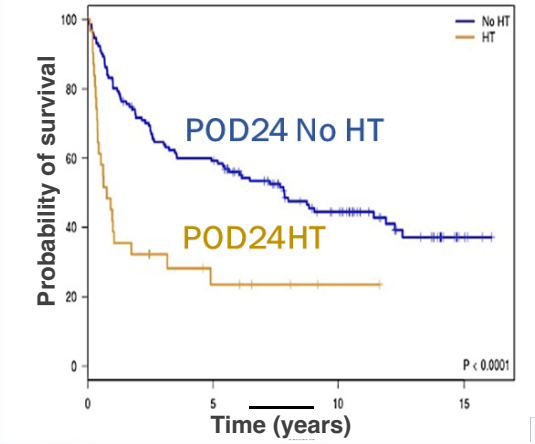
1. Solal-Céligny P, et al. Blood 2004;10[illegible]
Trněný M, et al. Blood 2016;128:1112–20;
3. Terol MJ, et al. Blood 2010;116:3128; 4. Rodríguez-Sevilla JJ, et al. Blood Adv 2023;7:1606–14;
5. Federico M, et al. J Clin Oncol 2009;27:4555–62; 6. Bachy E, et al. Blood 2018;132:49–58;
7. Pastore A, et al. Lancet Oncol 2015;16:1111–22; 8. Mir F, et al. Am J Hematol 2020;95:1503–10;
9. Casulo C, et al. ASH 2023; Abstract (abstract #1657); 10. Maurer MJ, et al. Blood 2022; 140:2292–95.

POD24 and histologic transformation

- FL with POD24 and HT is associated with high mortality
- Earliest events irrespective of HT had the strongest impact on prognosis

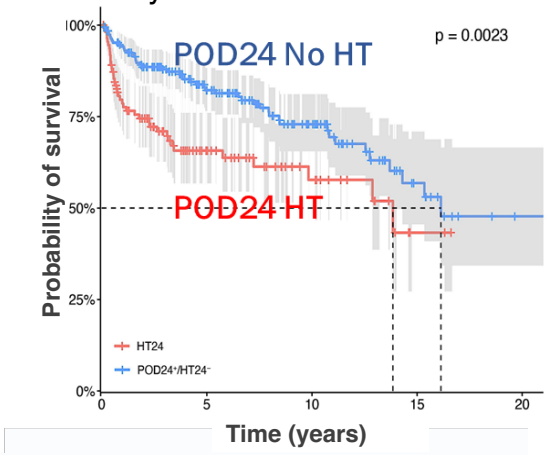
GELTAMO

10-year OS: 24% vs 44%[1]



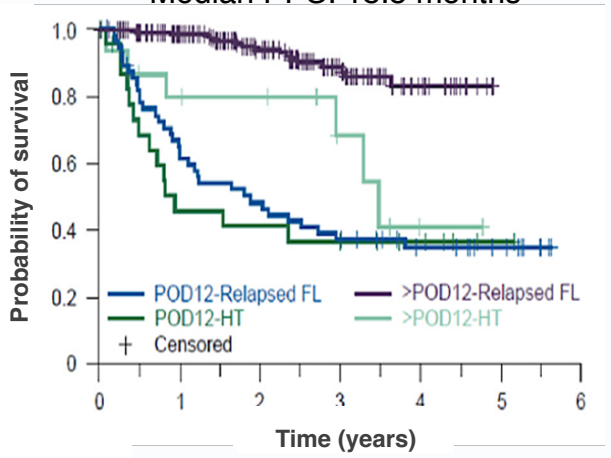
MSKCC

5-year OS: 66% vs 75%[2]



GALLIUM

Median PPS: 18.5 months[3]



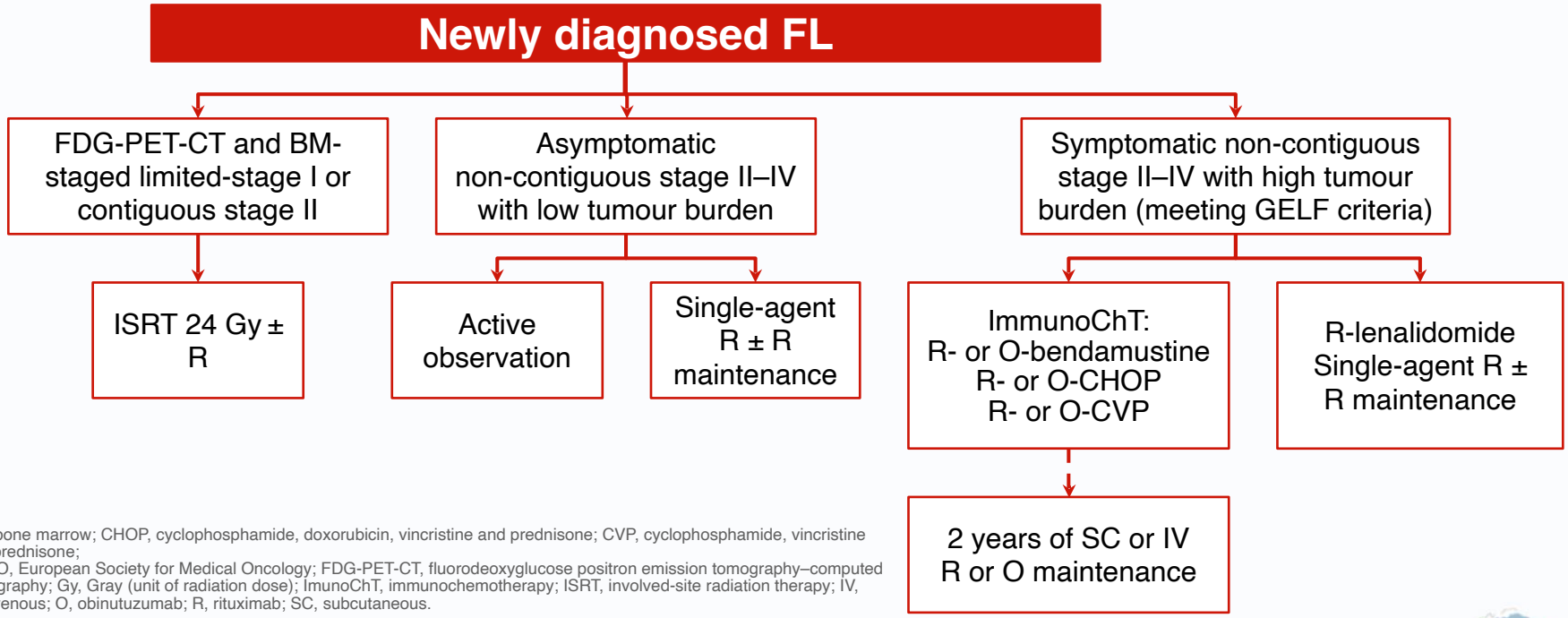
1. Muntañola A, et al. Br J Haematol 2022;200:306–14;
2. Luttwak E, et al. Blood 2023;142:3023;
3. Casulo C, et al. Clin Lymphoma Myeloma Leuk 2022;23:40–8.

HT, histological transformation; PPS, post-progression survival.

Key decision points for 1L therapy

- Is treatment needed?
- What are the risks for the patient (transformation, early failure, death)?
- Which therapy is available?
- How is the patient and what are his/her thoughts?
- Is cure a likely goal of therapy?

ESMO treatment guidelines for newly diagnosed FL (2025)



BM, bone marrow; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CVP, cyclophosphamide, vincristine and prednisone;
ESMO, European Society for Medical Oncology; FDG-PET-CT, fluorodeoxyglucose positron emission tomography–computed tomography; Gy, Gray (unit of radiation dose); ImunoChT, immunochemotherapy; ISRT, involved-site radiation therapy; IV, intravenous; O, obinutuzumab; R, rituximab; SC, subcutaneous.

Eyre TA. et al. Ann Oncol 2025;36:1258-84.

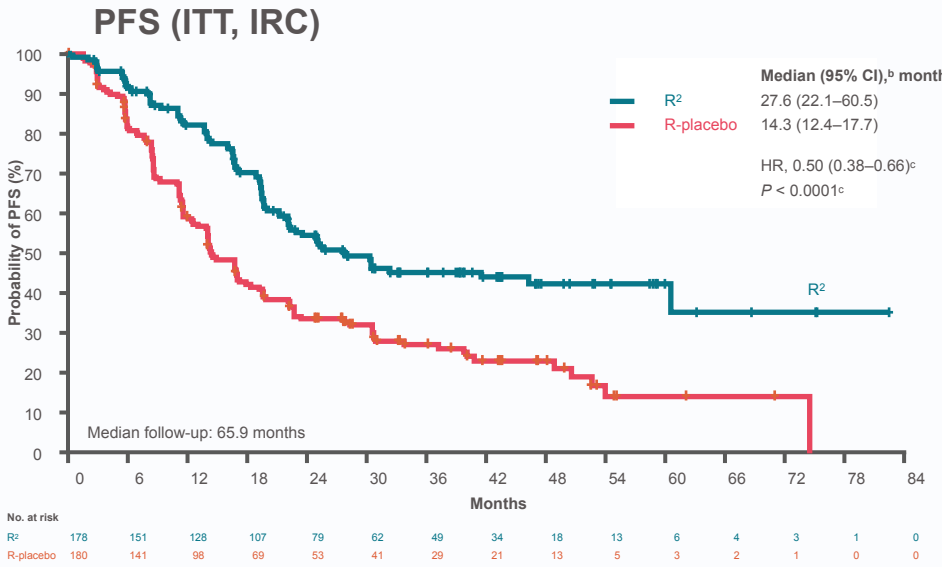
Anti-CD20 plus chemo and historic targeted therapies in R/R FL

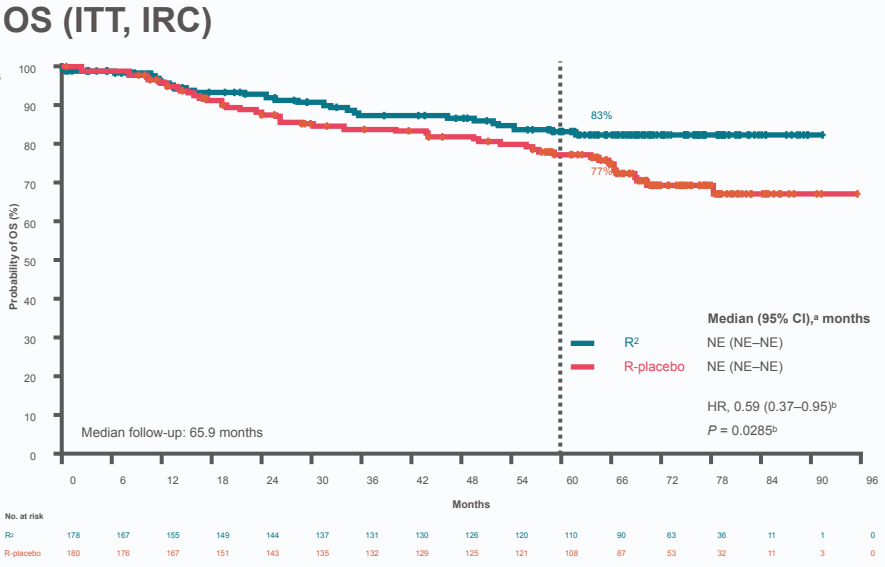
Therapy	Target	N	CR rate, %	ORR, %	Median DOR, months	Median PFS, months
Rituximab[1]	CD20	70	16	56	12.1	–
Obinutuzumab + benda[2,3]	CD20 + chemo	164	17	67.7	NR	25.3
^{90}Y ibritumomab tiuxetan[4]	CD20/RIT	59	64	80	29.4	–
Idelalisib[5]	PI3Kδ	72	6	57	12.5	11
Copanlisib[6]	PI3Kαδ	104	14	59	12.2	11.2
Ibrutinib[7]	BTK	40	12.5	37.5	13.9	14

*Drug withdrawn.[9]
Benda, bendamustine; BTK, Bruton's tyrosine kinase; CR, complete response; DOR, duration of response;
NR, not reached; ORR, overall response rate; PI3K, phosphoinositide 3-kinase; R/R, relapsed/refractory;
RIT, radioimmunotherapy.

1. Witzig T, et al. J Clin Oncol 2002;20:2453–63; 2. Cheson BD, et al. J Clin Oncol 2018;36:2259–66;
3. Sehn LH, et al. Lancet Oncol 2016;17:1081–93; 4. Witzig T, et al. Cancer 2007;109:1804–10;
5. Gopal A, et al. N Engl J Med 2014;370:1008–18; 6. Dreyling M, et al. J Clin Oncol 2017;35:3898–905;
7. Bartlett NL, et al. Blood 2018;131:182–90; 8. Italiano A, et al. Lancet Oncol 2018;19:649–59;
9. Ipsen voluntarily withdraws Tazverik. Ipsen press release 2026; Available at: https://www.ipsen.com/press-release/.

AUGMENT: PFS and OS advantage for R² in r/r FL





Median age for R2 arm: 64y (26–86)

ITT, intention to treat; NR, not reached

Source: Leonard JP, et al. AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. J Clin Oncol. 2019;37:1188-99. Updated at ASH 2022

Recently approved treatment options for R/R FL (3L+) based on the ESMO 2025 guidelines

	Treatment	Trial*
Bispecific antibodies	Mosunetuzumab IV[1]	GO29781
	Mosunetuzumab SC[2]	GO29781
	Epcoritamab[3,4]	EPCORE NHL-1
	Odronextamab[5]	ELM-2
CAR T-cell therapy	Axi-cel[6]	ZUMA-5
	Tisa-cel[7]	ELARA
Targeted	Liso-cel[8]	TRANSCEND FL
	Zanubrutinib + obinutuzumab[9]	ROSEWOOD

*All trials were Phase II trials and included patients with R/R FL after ≥2 prior therapies.
CAR, chimeric antigen receptor.

1. Budde LE, et al. ASH 2025; Poster presentation (abstract #5352); 2. Assouline S. et al. ASH 2025; Poster presentation (abstract #5353); 3. Linton K, et al. Lancet Haematol 2024;11:e593–e605; 4. Vitolo U et al, EHA 2025; Poster presentation (abstract #PF881); 5. Villasboas Bisneto J, et al. ASH 2025; Poster presentation (abstract #3588); 6. Neelapu SS, et al. J Clin Oncol 2025;43:3573–7; 7. Schuster SJ, et al. ASH 2025; Oral presentation (abstract #468); 8. Ahmed S, et al. ASH 2025; Oral presentation (abstract #467); 9. Zinzani PL, et al. ASH 2025; Oral presentation (abstract #227).

Novel therapies and combinations have significantly improved clinical outcomes in 3L+ R/R FL

	Treatment	Trial*	N	ORR/CR, %	Median DOR, months (95% CI)	Median DOCR, months (95% CI)	Median PFS, months (95% CI)
Bispecific antibodies	**Mosunetuzumab IV**[1]	GO29781	90	78 / 60	46.4 (18.7–NE)	5-year rate: 52%	24 (12.0–53.2)
	Mosunetuzumab SC[2]	GO29781	94	74 / 63	25.1 (21.0–39.2)	33.6 (21.8–NE)	18.5 (11.3–28.3)
	Epcoritamab[3,4]	EPCORE NHL-1	128	82 / 63	31.6 (13.7–NE)†	NR (31.1–NE)†	15.4 (9.4–34.0)†
	Odronextamab[5]	ELM-2	128	80 / 74†	26.0 (18.8–42.6)‡	35.2 (21.7–53.1)‡	24.1 (17.7–34.5)‡
CAR T-cell therapy	**Axi-cel**[6]	ZUMA-5	127	94 / 79	60.4 (36.6–NE)	60.5	57.3 (30.9–NE)
	Tisa-cel[7]	ELARA	94§	86 / 68	NR (35.8–NE)	4-year rate: 71%	53.2 (18.2–NE)
Targeted	**Liso-cel**[8]	TRANSCEND FL	103§	97 / 94	NR (38.5–NE)	NR	NR (39.4–NE)
	Zanubrutinib + obinutuzumab[9]	ROSEWOOD	145	70 / 42	32.9 (19.6–43.1)‡	44.2 (28.4–NE)‡	22.1 (16.1–34.0)‡

*All were Phase II trials and included patients with R/R FL after ≥2 prior therapies. †Population based on the FDA-approved indication (N=127); ‡Per IRC; §Efficacy evaluable population.

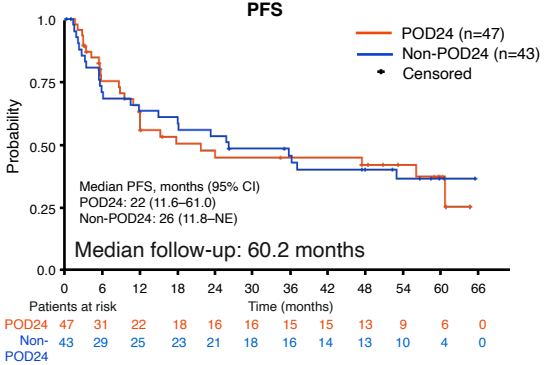
3. Linton K, et al. Lancet Haematol 2024;11:e593–e605; 4. Vitolo U et al, EHA 2025; Poster presentation (abstract #PF881);
5. Villasboas Bisneto J, et al. ASH 2025; Poster presentation (abstract #3588); 6. Neelapu SS, et al. J Clin Oncol 2025;43:3579–7;
7. Schuster SJ, et al. ASH 2025; Oral presentation (abstract #468); 8. Ahmed S, et al. ASH 2025; Oral presentation (abstract #467);
9. Zinzani PL, et al. ASH 2025; Oral presentation (abstract #227).

Bispecific antibodies and CAR T-cell therapies in the POD24 population

GO29781: Mosunetuzumab IV[1]

52% POD24

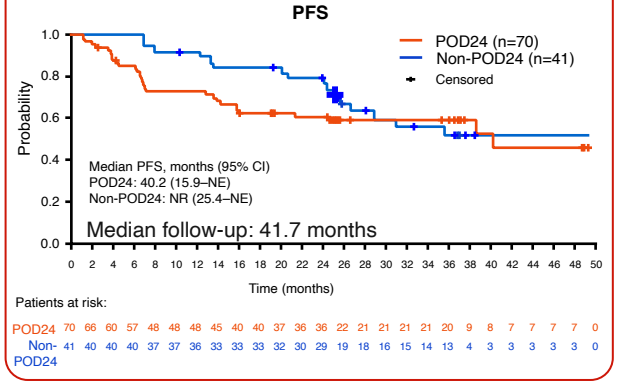
- 5-year PFS (non-POD24): 36%
- 5-year PFS (POD24): 37%



ZUMA-5: Axi-cel[2]

56% POD24

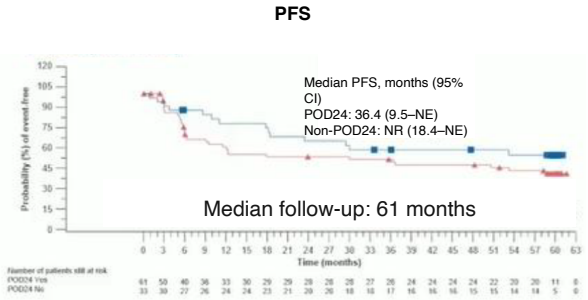
- 3-year PFS (non-POD24): 52%
- 3-year PFS (POD24): 59%



ELARA: Tisa-cel[3]

63% POD24

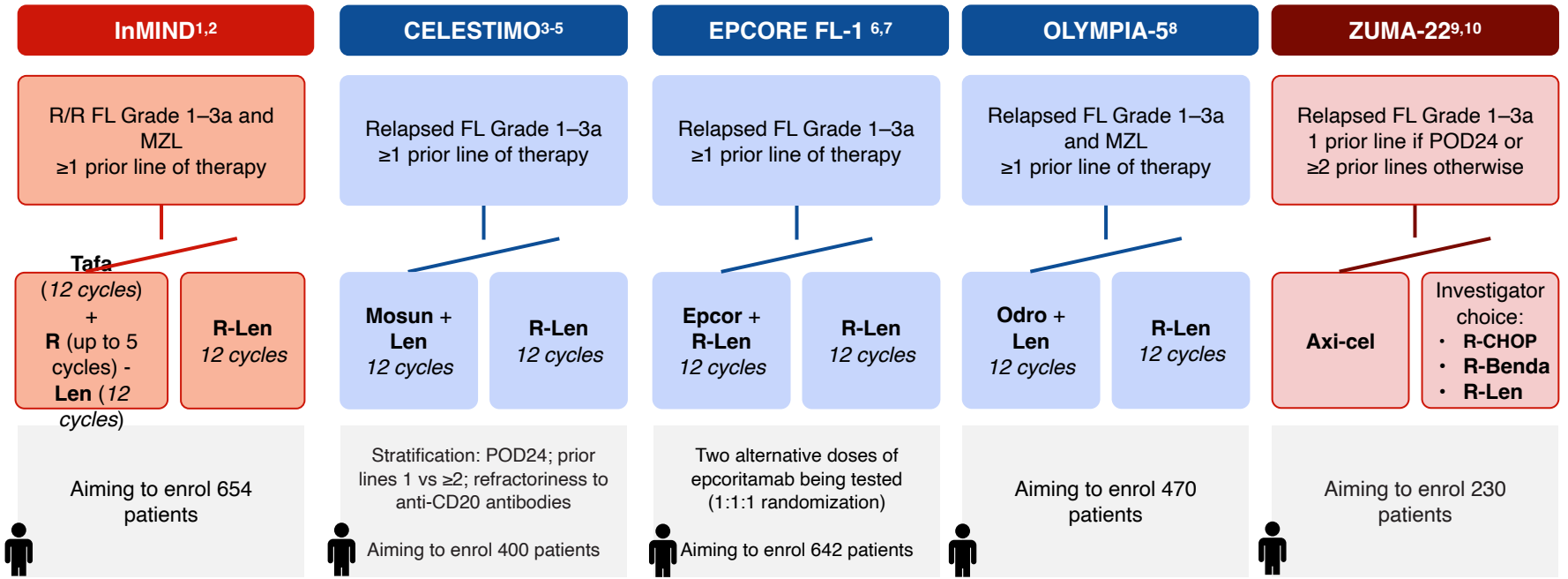
- 5-year PFS: 46%
- 5-year PFS (POD24): 41%



T-cell engaging therapies have improved outcomes for patients with 3L+ R/R FL with POD24

1. Budde LE, et al. ASH 2025. Poster presentation (abstract #5352); 2. Neelapu SS, et al. Blood 2024;143:496–506;
3. Schuster SJ, et al. ASH 2025. Oral presentation (abstract #468).

Ongoing Phase III trials with bispecific antibodies and CAR T-cell therapies in R/R FL

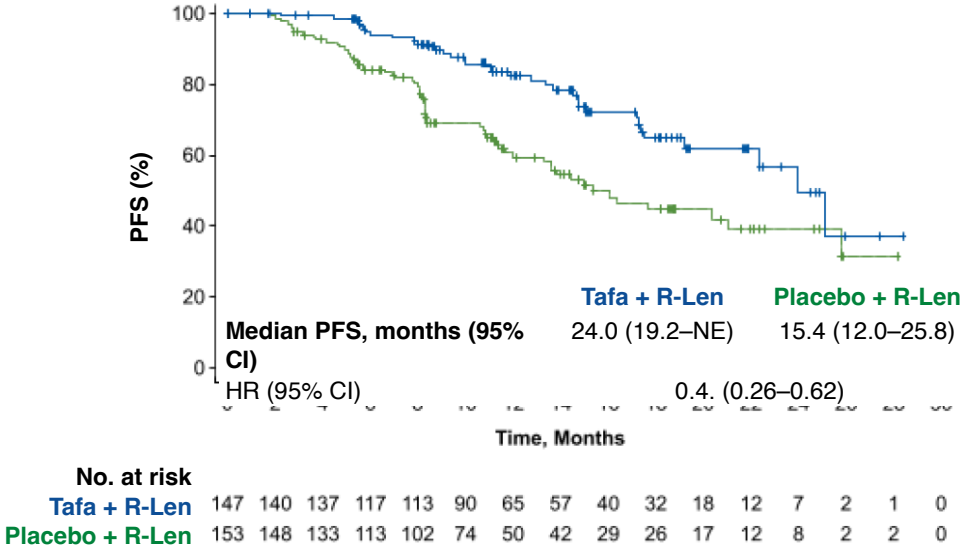


Ecor, epcoritamab; Mosun, mosunetuzumab; Odro, odronextamab.

1. NCT04680052. Available at: https://clinicaltrials.gov/study/NCT04680052; 2. Gopal AK, et al. ASH 2025; Poster presentation (abstract#1819); 3. NCT04712097. Available at: https://www.clinicaltrials.gov/study/NCT04712097; 4. Nastoupil LJ, et al. J Clin Oncol 2022;40(Suppl 16):TPS7588; 5. Sano D, et al. ASH 2025; Poster presentation (abstract #1800); 6. NCT05409066. Available at: https://clinicaltrials.gov/study/NCT05409066; 7. Falchi L, et al. Blood. 2022;140(Suppl 1):9338–9; 8. NCT06149286. Available at: https://www.clinicaltrials.gov/study/NCT06149286; 9. NCT05371093. Available at: https://www.clinicaltrials.gov/study/NCT05371093; 10. Flinn IW, et al. J Clin Oncol 2023;41(Suppl 16):TPS75798.

InMIND study in 2L R/R FL: Tafa + R-Len vs placebo + R-Len

Primary endpoint: PFS by investigator assessment



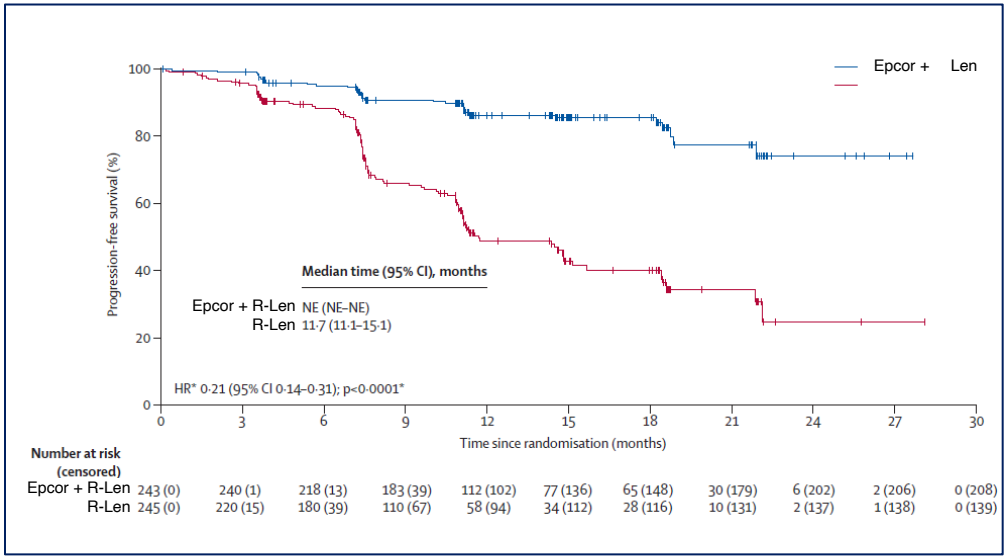
Safety summary, n (%)	Tafa + R-Len (n=147)	Placebo + R-Len (n=153)
Grade 3/4 AE	101 (68.7)	94 (61.4)
Fatal AE*	3 (2.0)	3 (2.0)
Neutropenia	69 (46.9)	60 (39.2)
Diarrhoea	55 (37.4)	47 (30.7)
Constipation	45 (30.6)	46 (30.1)

Significant improvement in PFS was observed with tafasitamab without any significant increase in toxicity

Intention-to-treat population for primary endpoint.
*None considered related to study treatment.

EPCORE FL-1 trial in 2L R/R FL: Epcor + R-Len vs R-Len

PFS per IRC



Efficacy summary	Epcor + R-Len (n=243)	R-Len (n=245)
ORR, n (%) CR rate, n (%) PR rate, n (%)	231 (95) 201 (83) 30 (12)	194 (79) 122 (50) 72 (29)
SD, n (%)	1 (<1)	17 (7)
PD, n (%)	7 (3)	16 (7)
12-month DOR, % (95% CI)	89 (84–93)	49 (39–58)
Safety summary, n (%)	**Epcor + R-Len (n=243)**	**R-Len (n=238)**
Grade 3/4 AE	219 (90)	161 (68)
CRS	85 (35)	1 (<1)
Neutropenia	180 (74)	123 (52)
Infections	188 (77)	125 (53)
ICANS	1 (<1)	0

Addition of Epcor to R-Len regimen resulted in superior PFS with a manageable safety profile

Median follow-up: 14.8 months for Epcor + R-Len; 14.6 months for R-Len. Intention-to-treat population for efficacy; safety population for safety table.
IRC, independent review committee.

Randomised studies of bispecific antibody combination therapy in 1L FL are ongoing

Regimen	Trial (Phase)	Patients (1L FL cohorts)*	Treatment duration and administration	Primary endpoint	Study status	Primary completion (estimated)
Mosunetuzumab-Len vs R- / G-chemo	**MorningLyte** (Phase III)[1]	790	**Mosunetuzumab** (SC) 21 cycles **Len** (oral) 11 cycles	PFS (by IRC)	Recruiting	November 2028
Odronextamab monotherapy vs R-chemo	**OLYMPIA-1** (Phase III)[2,3]	822	**Odronextamab** (IV) 6 cycles	Part 1: DLTs, TEAEs, Part 2: CR30 (by ICR)	Recruiting	February 2028
Odronextamab-chemo vs R-chemo	**OLYMPIA-2** (Phase III)[4,5]	733	**Odronextamab** (IV) 6 cycles **CHOP/CVP** (IV) 6 cycles	Part 1: DLTs and safety Part 2: CR30 (by ICR)	Active, not recruiting	July 2029
Epcoritamab-R-Len vs R- / G-chemo	**EPCORE FL-2** (Phase III)[6,7]	1095	**Epcoritamab** (SC) 21 cycles **R** (IV) 6 cycles **Len** (oral) 12 cycles	CR30 (by IRC) PFS (by IRC)	Recruiting	November 2037
Surovatamig plus R vs R-chemo	**SOUNDTRACK-F1** (Phase III)[8,9]	1018	**Surovatamig plus R** 7 cycles†	Safety, RP3D, PFS, ORR	Recruiting	November 2031

surovatamig monotherapy in patients achieving a PR or CR after the first 7 cycles.
CR30, complete response at 30 months; DLT, dose-limiting toxicity;
ICR, independent central review; RP3D, recommended Phase III dose.

5. Hardin C, et al. ASCO 2024; Abstract (abstract #TPS7099); 6. NCT06191744. Available at: https://clinicaltrials.gov/study/NCT06191744;
7. Linton KM, et al. ASCO 2024; Abstract (abstract #TPS7084); 8. NCT06549595. Available at: https://clinicaltrials.gov/study/NCT06549595;
9. Cheah C, et al. ASH 2025; Abstract (abstract #3615).

Visual Abstract

Evolving Paradigms in Follicular Lymphoma

PATIENT POPULATION
Stage III-IV, HTB (High Tumor Burden)

Luminari et. al BJH 2026

	FIRST LINE	SECOND LINE	THIRD LINE +
Today Current Standards of Care	• ICT • Rituximab	→ • ICT + ASCT (?) POD24 • R² NON-POD24	→ • BsAbs • CAR-T • Zanu-obinut.
Tomorrow Already anticipated Ph3 results	• ICT • Rituximab	→ • R² POD24 & NON-POD24 • Len ± R + Tafa/BsAbs	→ • BsAbs • CAR-T • Zanu-obinut.
Future view Pending results of Ph3 trials	• BsAbs ± X	→ • CAR-T POD24 • Len ± R + Tafa/BsAbs • Zanu-obinut	→ • BsAbs • Novel agents • CAR-T • Zanu-obinut. • Len ± R + Tafa/BsAbs

Abbreviations: ICT: Immunochemotherapy; R²: Rituximab + Lenalidomide; BsAbs: Bispecific Antibodies; Tafa: Tafasitamab; Zanu-obinut: Zanubrutinib + Obinutuzumab;