4th edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, March 26-27, 2026

Starhotels Majestic

Scientific board:
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First line treatment in high-risk follicular lymphoma

Stefano Luminari

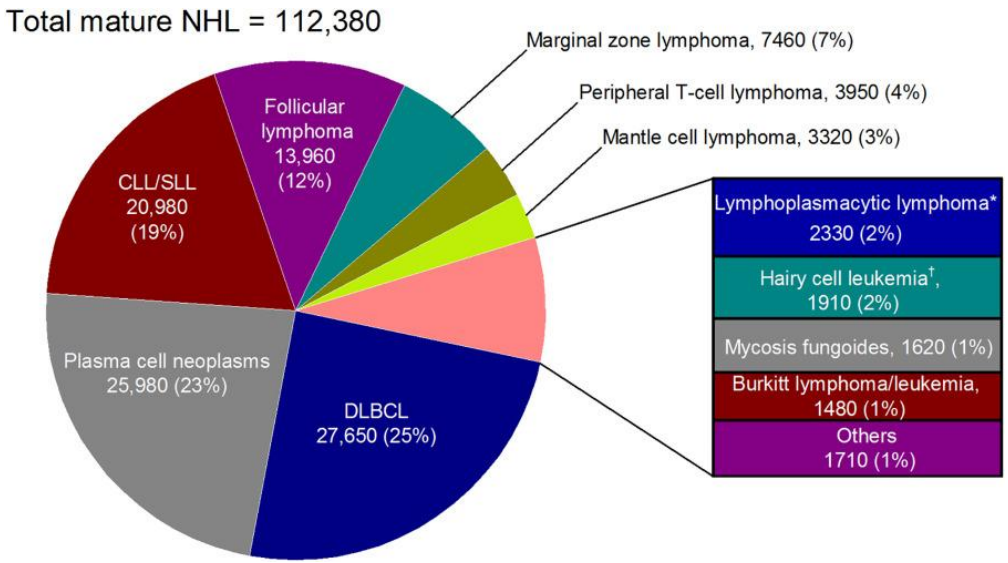
Conflict of interests

Type of affiliation / financial interet	Name of the commercial company
Receipt of grant / research supports	Beigene, Roche
Receipt of honoraria (including advisory board) or consultation fee:	Roche, Beigene, Kite, BMS, Novartis, Abbvie, Regeneron
Participation in a company-sponsored speaker’s bureau:	Roche, BMS, Kite, Abbvie
Stock shareholder:	None
Spouse / partner:	None
Other support (please specify):	None

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

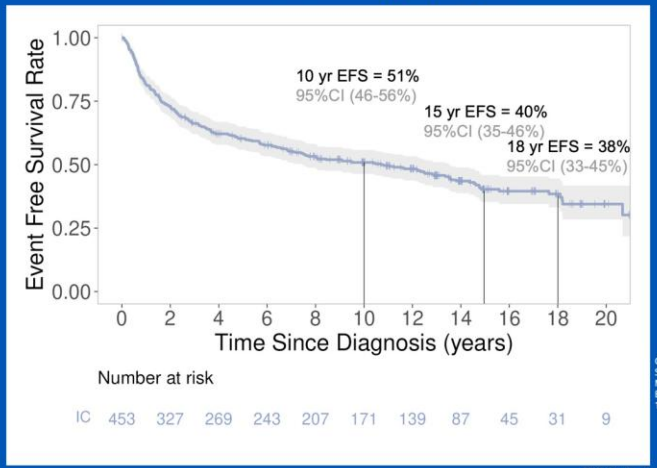
Distribution of NHL Subtypes



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

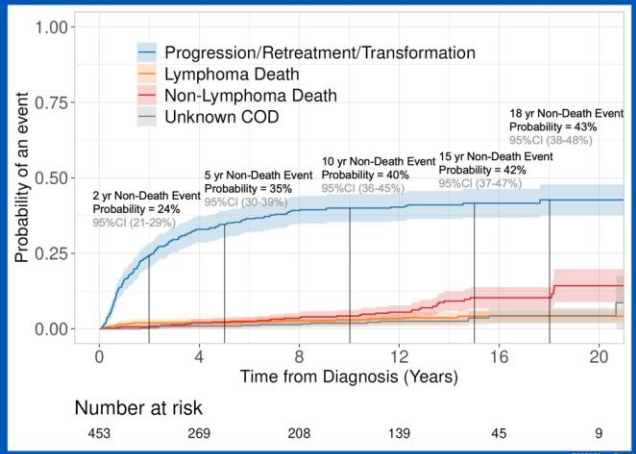
Outcomes in the 2° decade following FL diagnosis

FL: EFS – Immunochemotherapy (IC) Treated Patients



Comparisons Discussed:
Shadman M, et al. *J Clin Oncol.* 2018, Mar 1;36(7):697-703.
Bachy E, et al. *J Clin Oncol.* 2019 Nov 1;37(31):2815-2824.

Lymphoma Event Rate – IC treated patients

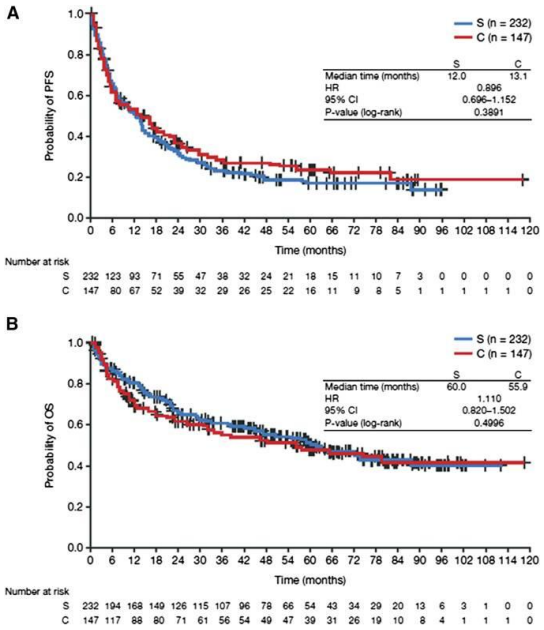


Median follow up 14 years: 18 year OS 55%

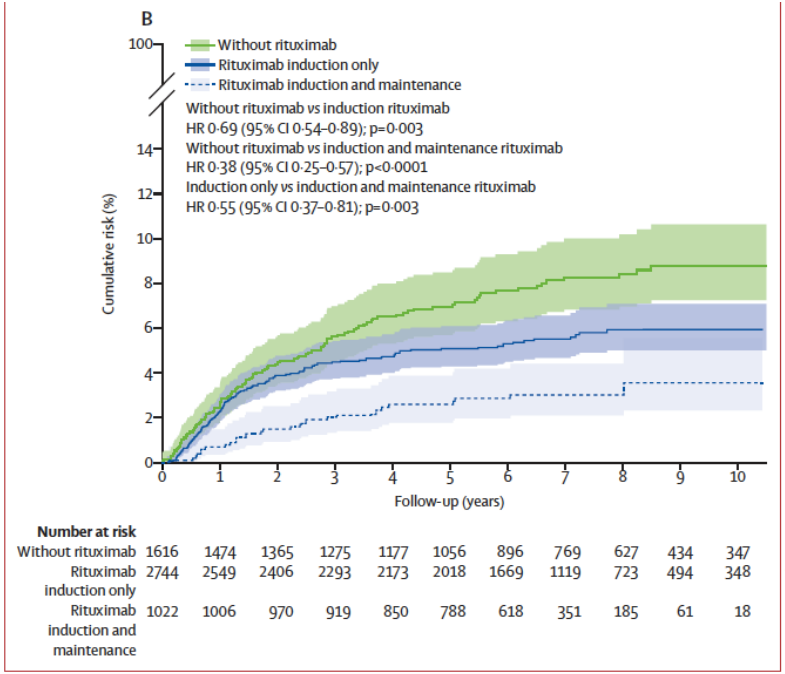
Day et al ASH 2025

Histological Transformation in FL

Survival from transformation (n=379)

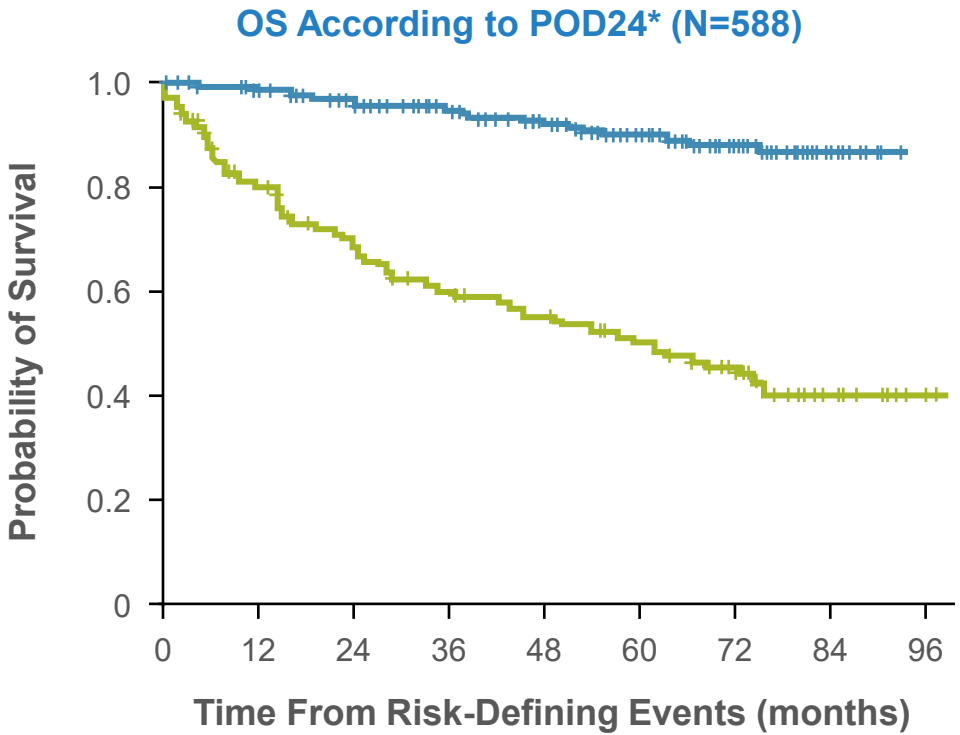


Wagner Johnson et al Blood 2015



Federico M. et al Lancet Hem 2018

Early Relapsed Patients Represent an Unmet Need and Lack Consensus on Their Therapy



POD24

- 15% to 20% after 1L
- High risk of transformation (up to 80%)
- Chemorefractoriness
- Rapidly gets to 3L+ of therapy

	Patients, n	5-year OS, %
POD24*	110	50
Reference	420	90

*POD24: relapse within 24 months after initial therapy. 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.

1L, 1st-line; 3L, 3rd-line; ASCT, autologous stem cell transplant; OS, overall survival; R, rituximab; R-CHOP, rituximab + cyclophosphamide + doxorubicin hydrochloride + vincristine + prednisolone; R-CVP, rituximab + cyclophosphamide + vincristine + prednisolone.
Adapted from: 1. Casulo C, et al. *J Clin Oncol.* 2015;33(23):2516-2522. 2. Casulo C, et al. *Biol Blood Marrow Transplant.* 2018;24:1163-1171. 3. Freeman CL, et al. *Blood.* 2019;134(9):761-764.

Clinical based prognostic indexes in FL

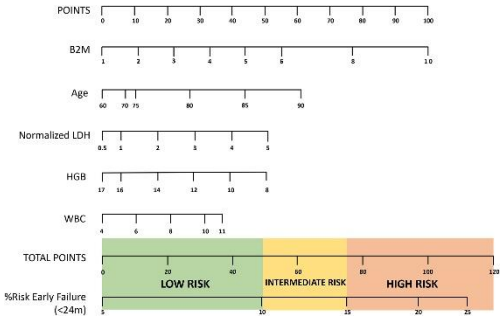
	FLIPI (0% R 2004)[1]	FLIPI2 (50%R 2009) [2]	PRIMA-PI (100% R adv stage 2018)[3]
Adv. Risk Factors (RF)	• **Age ≥60 y** • Stage III/IV • Hb <12 g/dL • LDH > UNL • >4 nodal sites	• **Age ≥60 y** • BM positive • Hb <12 g/dL • β-2m > UNL • LodLin (>6cm)	• BM positive • β-2m >3 mg/l
High risk def.	3-5 RF	3-5 RF	β-2m >3 mg/l
High risk (N=475)[4]	**46%**	**37%**	**30%**
All ages [4]			
5 yr PFS	**48**	**44**	**39**
Sens.	**66**	**58**	**43**
Spec.	**60**	**68**	**80**
> 60 yrs [4]			
5 yr PFS	**47**	**42**	**31**
Sens.	**84**	**82**	**53**
Spec.	**33**	**47**	**73**

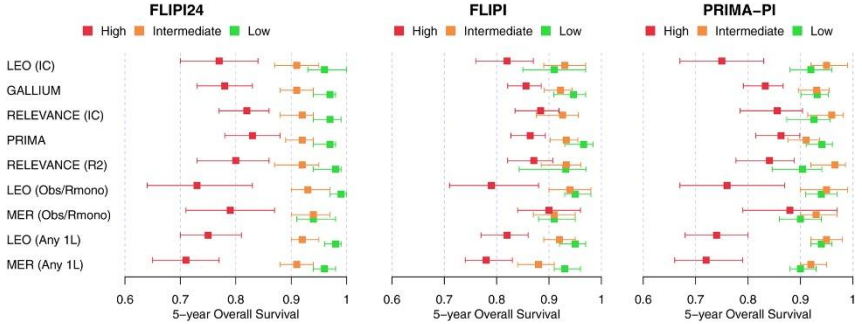
1 Solal-Céligny P, *et al*. Blood 2004;104:1258–126 **2** Federico M, *et al*. J Clin Oncol. 2009;27(27):4555-4562 **3** Bachy E, et al Blood. 2018;132(1): 49-58. **4** Alig S, et al Blood Adv. 2019; 3(7): 1033- 1037

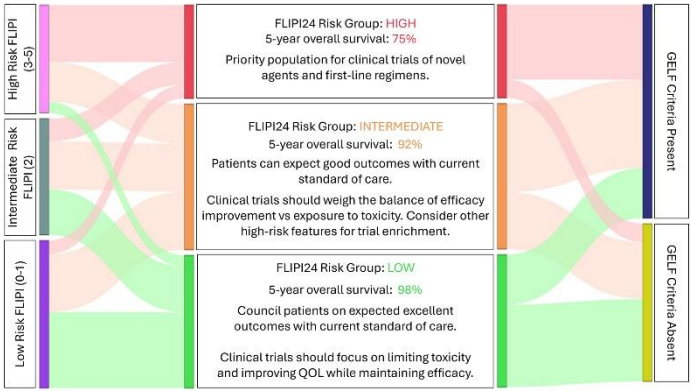
FLIPI24: A Modern Prognostic Model and Clinical Trial Enrichment Tool for Newly Diagnosed Follicular Lymphoma

N+3577 from observational cohorts: 3 RCT + LEO and MER Cohort for validation

Primary endpoint EFS24: Co-primary endpoint OS





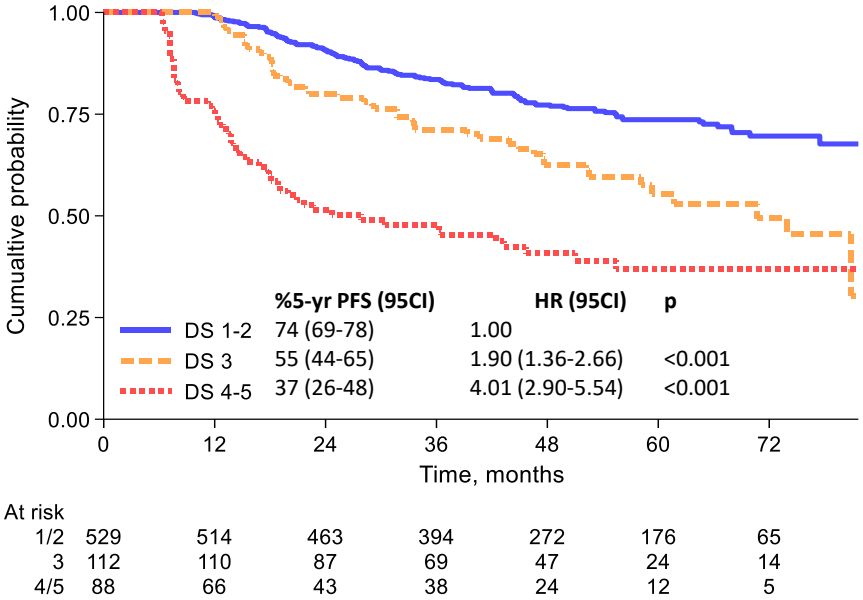


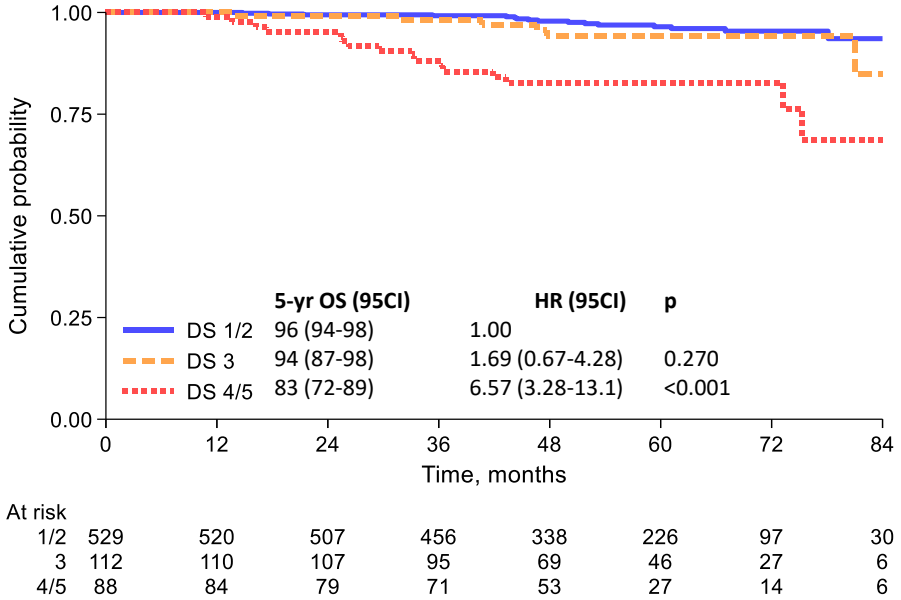
https://rtools.mayo.edu/flipi24calculator/

Maurer et al JCO 2025

How to best define metabolic response in FL

Deauville score – PFS from EoI (n=729)





Guerra et al. EJNM 2024

Available guidelines for the first line therapy of FL

	Low tumor burden	Low tumour burden	High tumour burden
	Stage I–II	Stage III–IV	
First line	ISRT 24-30 Gy +/- rituximab **In selected cases:** Watch and wait, rituximab, INRT 2x2 Gy	Watch and wait, **In selected cases:** rituximab	ImmunoChT (**G**/R-B, **G**/R-CHOP, **G**/R-CVP) CR/PR: discuss **Ab** maintenance **In select cases:** rituximab +/- lenalidomide[d]

CHOP (1/3):

- More frequently used in Young, High risk (FLIPI/FLIPI2), and FL g3a (Gallium, FOLL12)
- Cardiac toxicity

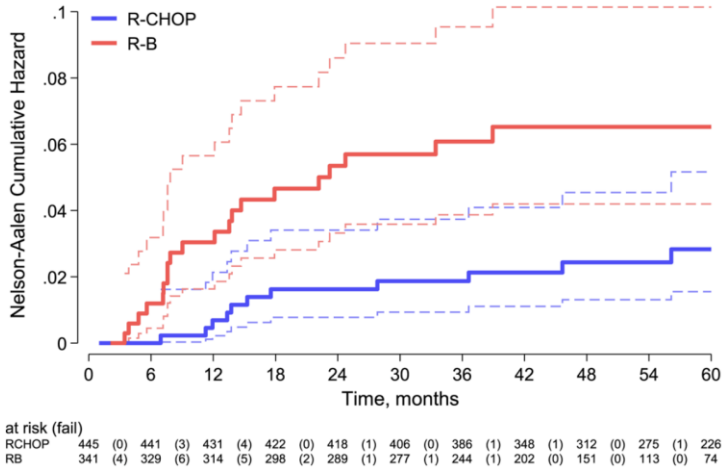
Bendamustine (2/3):

- More frequently used in Old, Low risk (Gallium, FOLL12)
- Profound and persisting T-Cell depletion (gallium)
- Higher risk of SM (Bright, FOLL12)

Adapted from Dreyling M et al. Newly Diagnosed and Relapsed Follicular Lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020:32;298-308.

R-Benda may not be enough to control the risk of tFL

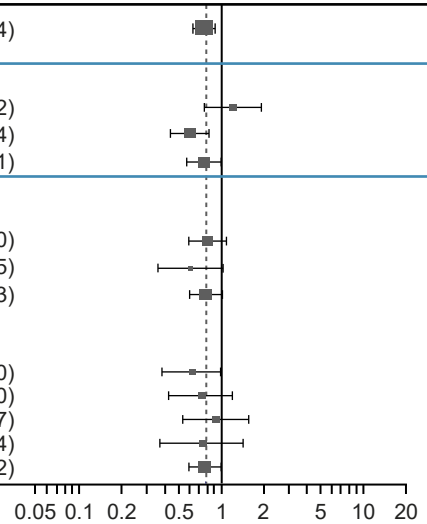
- POD24 occurred in 37 (13%) of BR-treated patients, with an elevated LDH ($P < .001$) at baseline being the only identifiable risk factor. The majority, 28/37 (76%), had transformed disease. Grade 3A was not associated with increased risk of POD24. (Freeman et al Blood 2019)
- A higher risk of tFL was observed in a non randomized comparison between R-CHOP and R-Benda (FOLL12 substudy Nizzoli et al 2023)



Nizzoli et al. Hematol Oncol 2023

PFS was favorable with G- vs R-chemo across the majority of subgroups

Characteristics at baseline	Total n	R-chemo (n=601) n	R-chemo (n=601) Events	G-chemo (n=601) n	G-chemo (n=601) Events	HR*	95% CI
All patients	1202	601	244	601	206	0.78	(0.65–0.94)
FLIPI							
Low	251	125	34	126	42	1.22	(0.77–1.92)
Intermediate	448	222	92	226	69	0.61	(0.45–0.84)
High	503	254	118	249	95	0.77	(0.59–1.01)
Chemotherapy regimen							
CHOP	399	203	93	196	76	0.81	(0.60–1.10)
CVP	117	57	30	60	26	0.62	(0.37–1.05)
Bendamustine	686	341	121	345	104	0.79	(0.61–1.03)
Geographic region							
Asia	185	93	42	92	31	0.63	(0.39–1.00)
Eastern Europe	157	79	39	78	26	0.73	(0.44–1.20)
North America	152	77	29	75	27	0.92	(0.54–1.57)
Other	127	65	20	62	17	0.74	(0.38–1.44)
Western Europe	581	287	114	294	105	0.78	(0.60–1.02)



PFS favored G-chemo vs R-chemo in patients with an intermediate-to-high-risk (2–5) FLIPI score

*Unstratified analysis

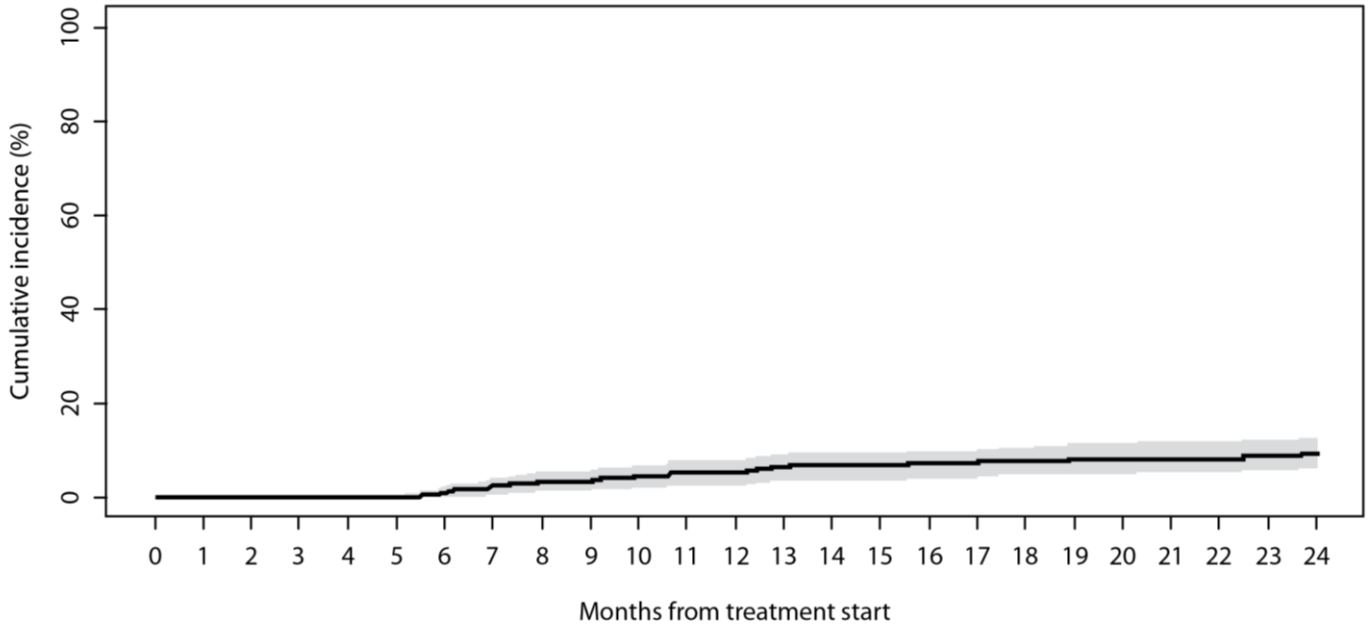
CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Marcus R. N Engl J Med. 2017;377:1331-44. Thowsend et al . ASH 2021

Progression of disease within 24 months

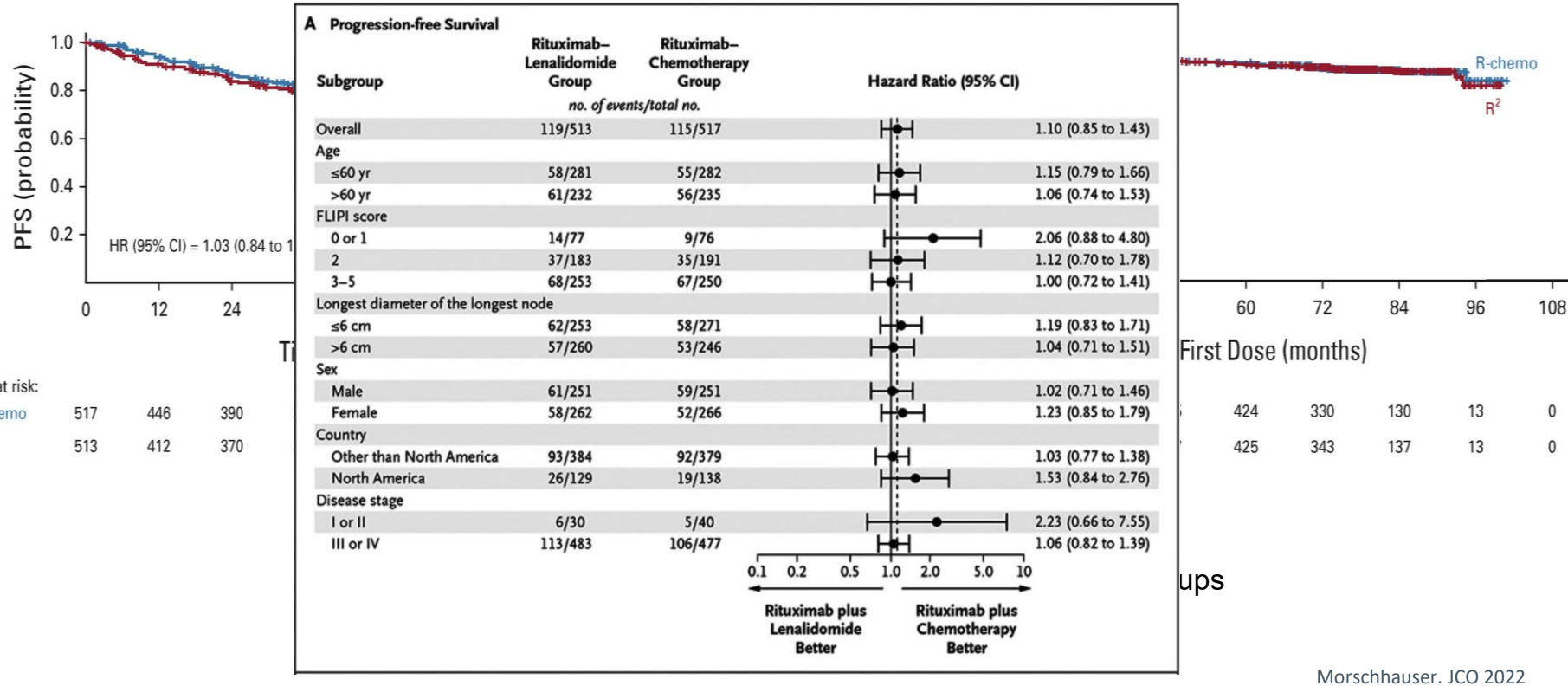
Among 281 evaluable patients, 25 experienced POD24 (8.9%; 95% CI: 5.8-12.9%), demonstrating a low rate of early progression consistent with GALLIUM trial results.

Figure 1. POD24 - Kaplan Meier and 95% CI[3]



Pinto A. et al, poster presentation ASH 2025; Blood (2025) 146 (Supplement 1): 5366.

Six-Year Results From RELEVANCE: Lenalidomide Plus Rituximab (R2) Versus Rituximab-Chemotherapy Followed by Rituximab Maintenance in Untreated Advanced Follicular Lymphoma



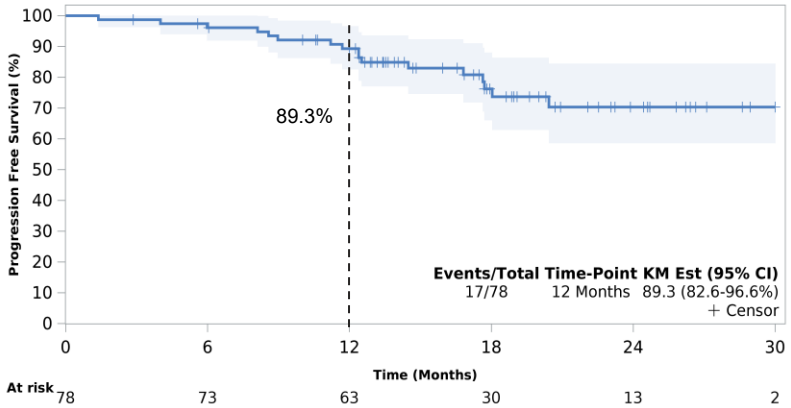
A Progression-free Survival

Subgroup	Rituximab–Lenalidomide Group	Rituximab–Chemotherapy Group	Hazard Ratio (95% CI)
	no. of events/total no.		
Overall	119/513	115/517	1.10 (0.85 to 1.43)
Age			
≤60 yr	58/281	55/282	1.15 (0.79 to 1.66)
>60 yr	61/232	56/235	1.06 (0.74 to 1.53)
FLIPI score			
0 or 1	14/77	9/76	2.06 (0.88 to 4.80)
2	37/183	35/191	1.12 (0.70 to 1.78)
3–5	68/253	67/250	1.00 (0.72 to 1.41)
Longest diameter of the longest node			
≤6 cm	62/253	58/271	1.19 (0.83 to 1.71)
>6 cm	57/260	53/246	1.04 (0.71 to 1.51)
Sex			
Male	61/251	59/251	1.02 (0.71 to 1.46)
Female	58/262	52/266	1.23 (0.85 to 1.79)
Country			
Other than North America	93/384	92/379	1.03 (0.77 to 1.38)
North America	26/129	19/138	1.53 (0.84 to 2.76)
Disease stage			
I or II	6/30	5/40	2.23 (0.66 to 7.55)
III or IV	113/483	106/477	1.06 (0.82 to 1.39)

Morschhauser. JCO 2022

Mosunetuzumab Demonstrates Encouraging Single-Agent Activity in 1L FL

- Humanized IgG1-like CD3xCD20 bispecific antibody,[1] administered IV[2,3] or SC[4], approved for 3L+ FL
- In the MITHIC-FL1 trial single-agent SC mosunetuzumab showed promising efficacy and manageable toxicity in 1L FL[5]
- 1L mosunetuzumab caused early expansion of CD8+ T-cells expressing activation and exhaustion markers (eg, PD-1, TIM-3)[6]
- T-cell exhaustion may represent a key mechanism of resistance to CD3xCD20 BsAb



1. Sun et al. *Sci Transl Med.* 2015;7:287; **2.** Budde et al. *Lancet Oncol* 2022;23:1055-1065; **3.** Sehn et al. *Blood* (2025) 145 (7): 708–719; **4.** Bartlett et al. *Blood* (2024) 144 (Supplement 1): 1645; **5.** Falchi et al. *Blood* (2024) 144 (Supplement 1): 340; **6.** Falchi et al. Blood (2023) 142 (Supplement 1): 6116

MorningSun: 1L HTB FL cohort (mosunetuzumab)

n (%), unless stated	All patients N=103	Patients who received maintenance treatment n=46
Median age, years (range)	64.6 (24–86)	64.6 (32–79)
Female	53 (51.5)	24 (52.2)
Race		
White	82 (79.6)	36 (78.3)
Asian	5 (4.9)	1 (2.2)
American Indian or Alaska Native	3 (2.9)	2 (4.3)
Black or African American	2 (1.9)	1 (2.2)
Not reported	8 (7.8)	5 (10.9)
Unknown	3 (2.9)	1 (2.2)
Ethnicity		
Not Hispanic or Latino	84 (81.6)	32 (69.9)
Hispanic or Latino	9 (8.7)	5 (10.9)
Not reported	5 (4.9)	5 (10.9)
Unknown	5 (4.9)	4 (8.7)
Patients with B-symptoms	23 (22.3)	9 (19.6)
Elevated LDH		
Yes	26 (25.2)	10 (21.7)
No	77 (74.8)	36 (78.3)

n (%), unless stated	All patients N=103	Patients who received maintenance treatment n=46
ECOG performance status		
0–1	101 (98.1)	46 (100)
2	2 (1.9)	0
FL grade		
Grade 1–2	82 (79.6)	37 (80.4)
Grade 3A	20 (19.4)	8 (17.4)
Missing	1 (1.0)	1 (2.2)
Ann Arbor stage		
II	9 (8.7)	3 (6.5)
III	38 (36.9)	18 (39.1)
IV	56 (54.4)	25 (54.3)
Extranodal involvement	40 (38.8)	18 (39.1)
Bulky disease		
Yes	41 (39.8)	19 (41.3)
No	54 (52.4)	22 (47.8)
Unknown	8 (7.8)	5 (10.9)
FLIPI score		
0–1	22 (21.4)	10 (21.7)
2	35 (34.0)	15 (32.6)
3–5	46 (44.7)	21 (45.7)

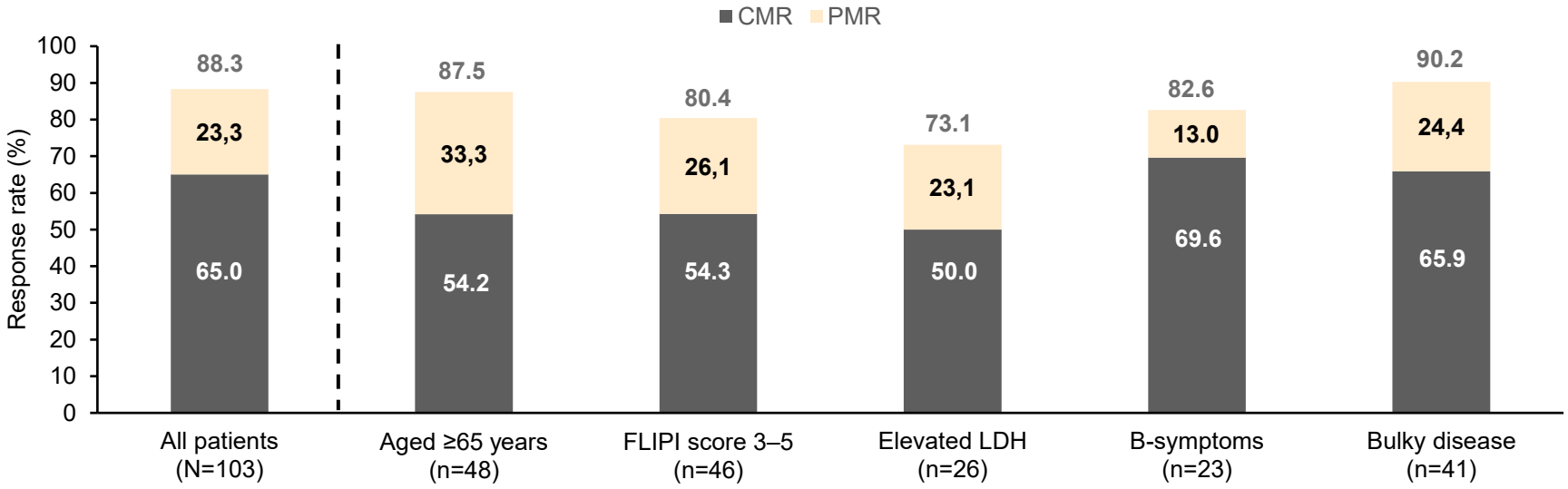
- A total of 82 patients were enrolled from community practices and 21 patients from academic sites

CCOD: February 10, 2025.

FLIPI, Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase.

Ghosh N. et al, oral presentation ASH 2025; Blood (2025) 146 (Supplement 1): 1020.

Efficacy: Response by high-risk subgroup



- Among patients with a response (n=91), median time to response was 2.7 months (range: 1.2–6.0)

Consistent response rates were seen among high-risk subgroups

CCOD: February 10, 2025.

Ghosh N. et al, oral presentation ASH 2025; Blood (2025) 146 (Supplement 1): 1020.

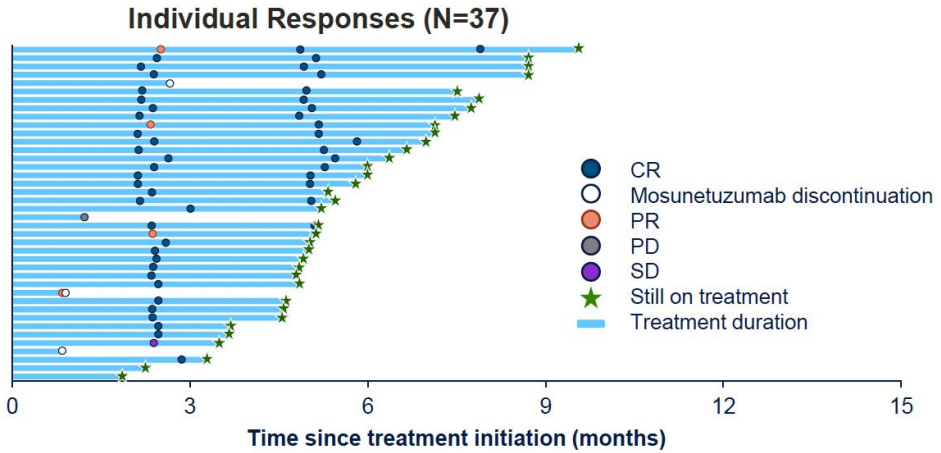
Mosunetuzumab + Lenolidamide in 1L FL

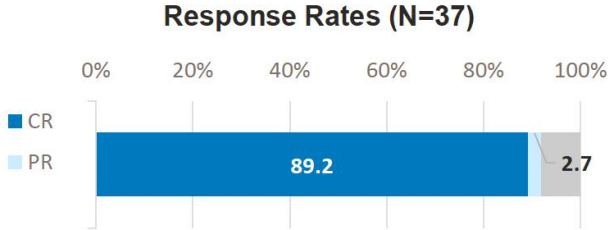
Phase 1b/2 CO41942

Phase 1b/2
(N=237)

→ **Mosunetuzumab (SC) + Len (PO)** in previously untreated FL

Events, %	N=40
AEs	100
Related to Mosun | Len	95.0 | 82.5
SAEs	32.5
Related to Mosun | Len	22.5 | 7.5
Gr 3-4 AEs	55.0
Serious Gr 3-4 AEs	7.5
Related to Mosun | Len	5.0 | 2.5
Most Common AEs	
Injection Site Reaction	
Rash	
CRS	

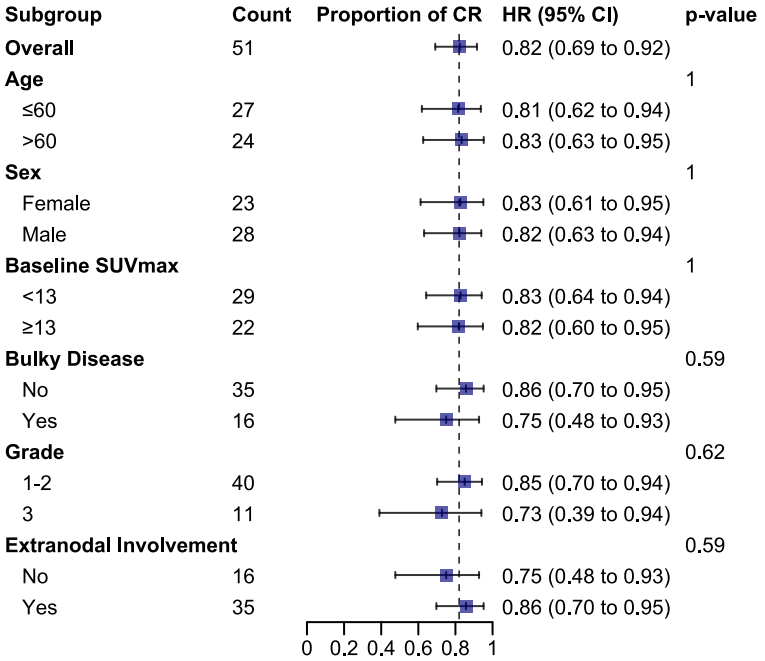




AE, adverse event; CR, complete response; CRS, cytokine release syndrome; FL, follicular lymphoma; Gr, Grade; L, line; len, lenalidomide; mosun; mosunetuzumab; PD, progressive disease; PO, oral; PR, partial response; SAE, serious AE; SC, subcutaneous; SD, stable disease.
Adapted from Morschhauser, et al. Oral #605. ASH Annual Meeting. Dec. 8-12, 2023.

Mosunetuzumab + Zanubrutinib Induced Deep Responses in Most Patients

Response Type	Response Evaluable (n=51)
Overall Response	47 (92%)
Complete Response	**42 (82%)**
Partial Response	5 (10%)
Stable Disease	1 (2%)
Progressive Disease	3 (6%)

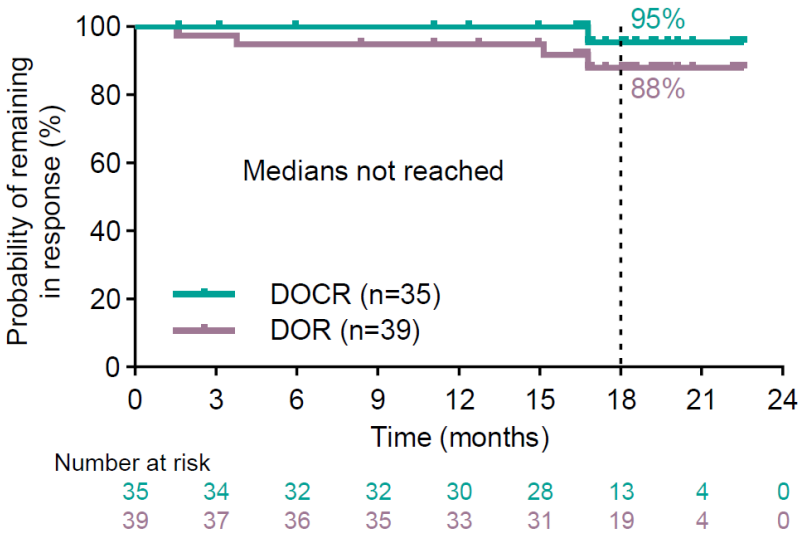


Data cutoff: November 14, 2025; response assessed per the 2014 Lugano criteria and integrated with the 2016 LYRIC criteria; evaluable = patients who received at least one dose of study drug and underwent at least one response assessment

Falchi et al ASH 2025

Arm 6 (1L FL): Epcoritamab + R2 continued to show deep and durable responses

	N=41[a]
Overall response, n (%)	39 (95)
Complete response, n (%)	35 (85)
Partial response, n (%)	4 (10)
Progressive disease, n	0
Median time to response, mo (range)	2.7 (1.2–5.5)
Median time to complete response, mo (range)	2.8 (1.4–11.4)



High rates of patients remaining in response and complete response were observed at 18 months

1L, previously untreated; DOCR, duration of complete response; DOR, duration of response; FL, follicular lymphoma; mo, month(s); R^2, rituximab + lenalidomide. Kaplan–Meier estimates of DOR and DOCR assessed by investigator. [a]A total of 2 patients were not evaluable.

Authors : Leslie L. A. et al., Oral Presentation, 7014, ASCO 2024

Ongoing Ph III trials for HTB 1l FL

	anti-CD20xCD3 bsAbs				anti-CD19xCD3 bsAb
	EPCORE FL-2[1]	**OLYMPIA-1[2*]**	**OLYMPIA-2[3*]**	**MorningLyte[4]**	**SOUNDTRACK-F1[5]**
Investigational	**Induction:**  **Epcor + R²**	 **Odron monotherapy**	 **Odron + CHOP/CVP**	 **Mosun + Len**	 **AZD0486 + R**
	Maintenance:  ± epcor maintenance	 + odron maintenance	 ± odron maintenance	 + mosun maintenance	 + R maintenance
	vs	vs	vs	vs	vs
Comparators	**Induction:** • R/G-CHOP • R/G-Benda • R²	• R-CHOP/CVP • R-Benda	• R-CHOP	• R/G-CHOP • R/G-Benda	• R-CHOP/CVP • R/Benda
	Maintenance:  + R maintenance	 + R maintenance	 + R maintenance	 + R maintenance	 + R maintenance (with R-CHOP/CVP only)
	Primary Endpoint(s): CR30, PFS	CR30	CR30	PFS	PFS

*Part 1 is a safety run-in, and all patients will receive odronextamab.

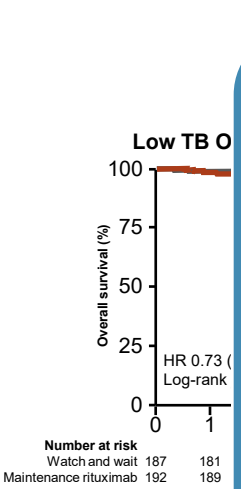
Benda, bendamustine; bsAb, bispecific antibody; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CVP, cyclophosphamide, vincristine, prednisone; CR30, CR rate at 30 weeks; epcor, epcoritamab; O, obinutuzumab; len, lenalidomide; mosun, mosunetuzumab; odron, odronextamab; PFS, progression-free survival; R, rituximab; R², rituximab + lenalidomide.

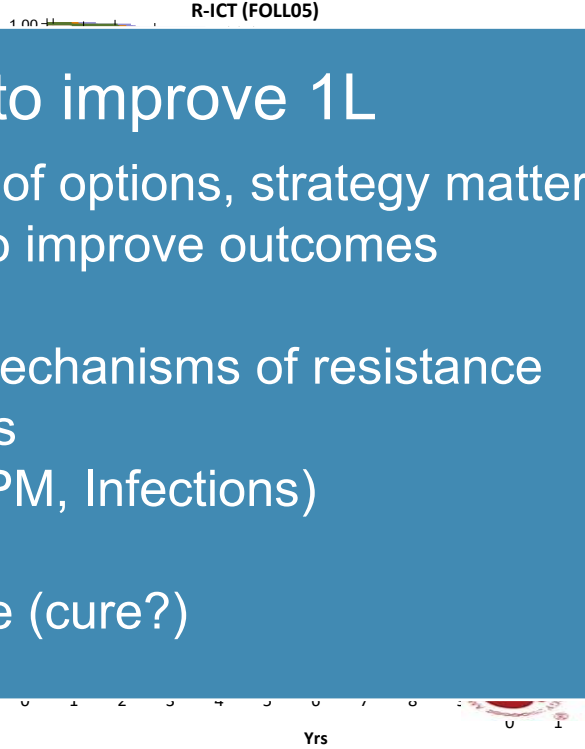
Images created with BioRender.com. Adapted from: 1. NCT06191744. 2. NCT06091254. 3. NCT06097364. 4. NCT06284122. 5. NCT06549595.

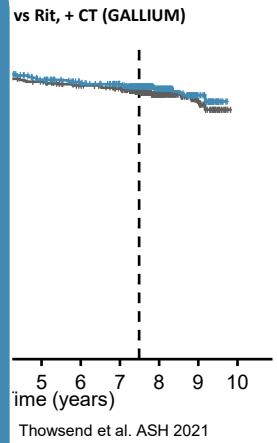
No further evidence of OS improvement since rituximab was added to first line

What do I ask to improve 1L

- Not just a matter of options, strategy matters
- Should be able to improve outcomes
  - OS?
  - Risk profiling/mechanisms of resistance
  - Transformations
  - Late events (SPM, Infections)
  - PROs
- Paradigm change (cure?)







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