La rivoluzione terapeutica nel **linfoma** e nel **mieloma**

Napoli, Royal Hotel Continental • 14–15 Maggio 2026

III Sessione FCL
Le terapie consolidate alla diagnosi e alla recidiva

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Disclosures of Luigi Rigacci

Company name	Research support	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Gilead/Kyte				X	X	
Novartis				X	X	
Sandoz				X	X	
Abbvie				X	X	
Johnson & Johnson				X	X	
Incyte				X	X	
Takeda					X	
Astra Zeneca				X	X	
Eli Lilly					X	
Gentli				X		
GSK					X	

Let’s hope to be continued……

Agenda

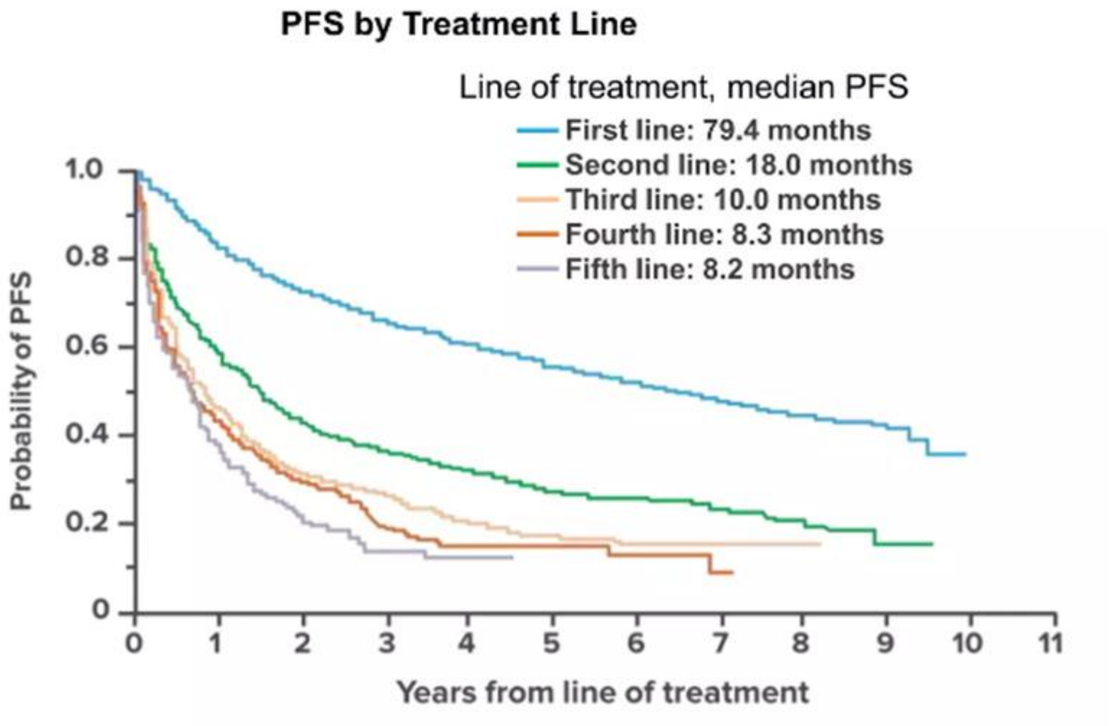
- Paradigm shift: no longer an incurable disease!
- First line with immunochemotherapy or immunotherapy without chemotherapy
- Maintenance is currently necessary
- In relapsed/refractory patients new drugs (immunotherapy) have significantly improved the prognosis (POD24 cancelled!)

Follicular Lymphoma has historically been considered an indolent B-cell lymphoma and incurable disease.

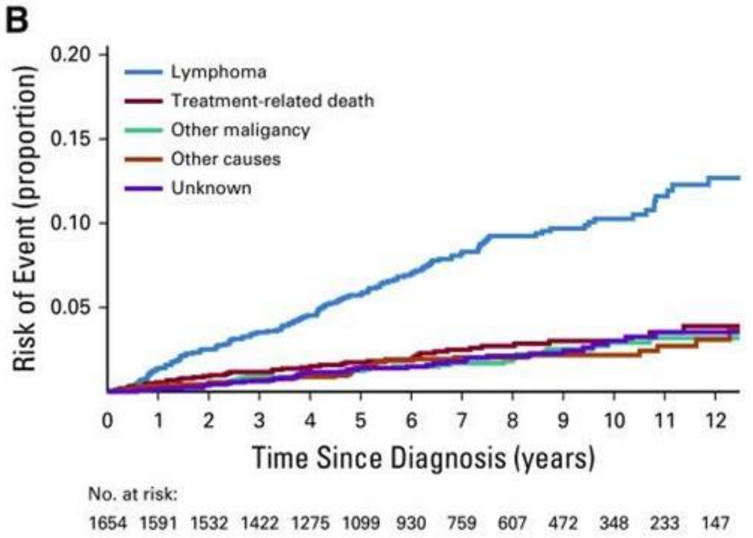
With more effective therapies, we advocate for a change in terminology.

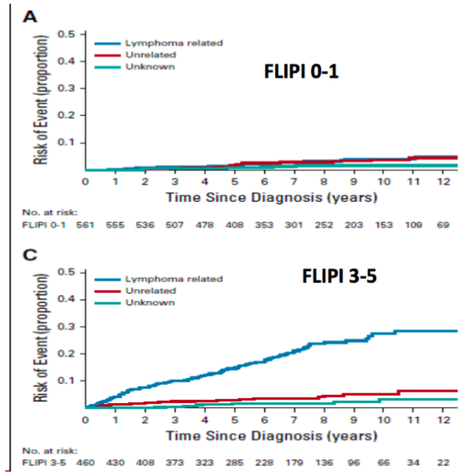
The new concept of ’functional cure’

SOME BASIC CONCEPTS



Cause of death

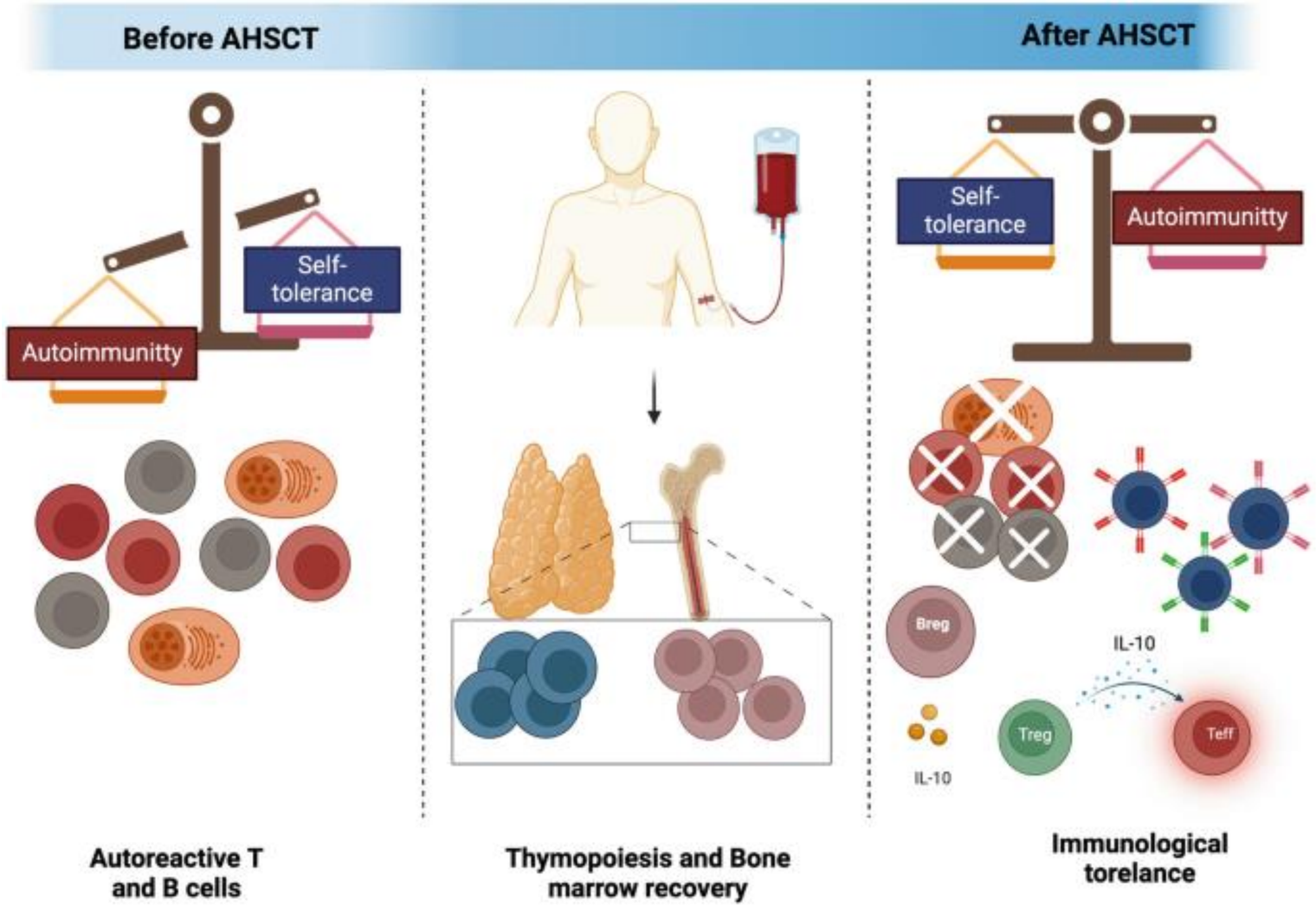




Kahl BS, et al. J Clin Oncol 2014; 32:3096–3102. Link et al. 2019. Casulo et al.2015. Sarkozy C. et al, J Clin Oncol. 2019;37:144-52.

ASCT in autoimmune diseases

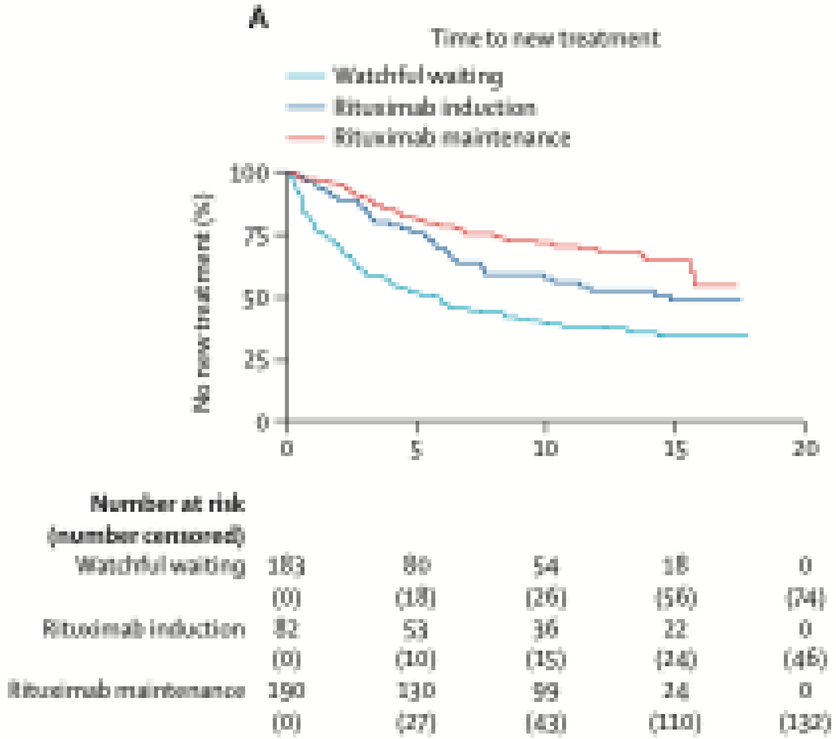
To reset immune system



Santana-Goncalves M. et al. T-cell recovery after autologous stem cell transplantation in autoimmune disease. Advances in Experimental Medicine and Biology 2025 vol. 1471

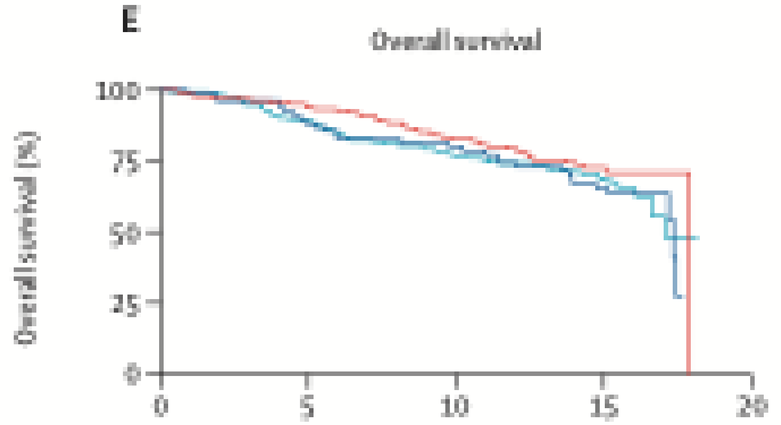
Early rituximab monotherapy versus watchful waiting for advanced stage, asymptomatic, low tumour burden follicular lymphoma: long-term results of a randomised, phase 3 trial

Michael Northend, William Wilson, Kushani Ediriwickrema, Laura Clifton-Hadley, Wendi Qian, Zaynab Rana, Tanya-Louise Martin, William Townsend, Moya Young, Fiona Miall, David Cunningham, Jan Walewski, Burhan Ferhanoglu, Kim Linton, Amanda Johnston, John F Seymour, David C Linch, Kirit M Ardeshna



Number at risk (number censored)					
Watchful waiting	183	80	54	18	0
	(0)	(18)	(26)	(56)	(74)
Rituximab induction	82	53	36	22	0
	(0)	(10)	(15)	(24)	(46)
Rituximab maintenance	190	130	99	34	0
	(0)	(27)	(43)	(110)	(132)

At 15 years 34% of patients in WW group had not started treatment

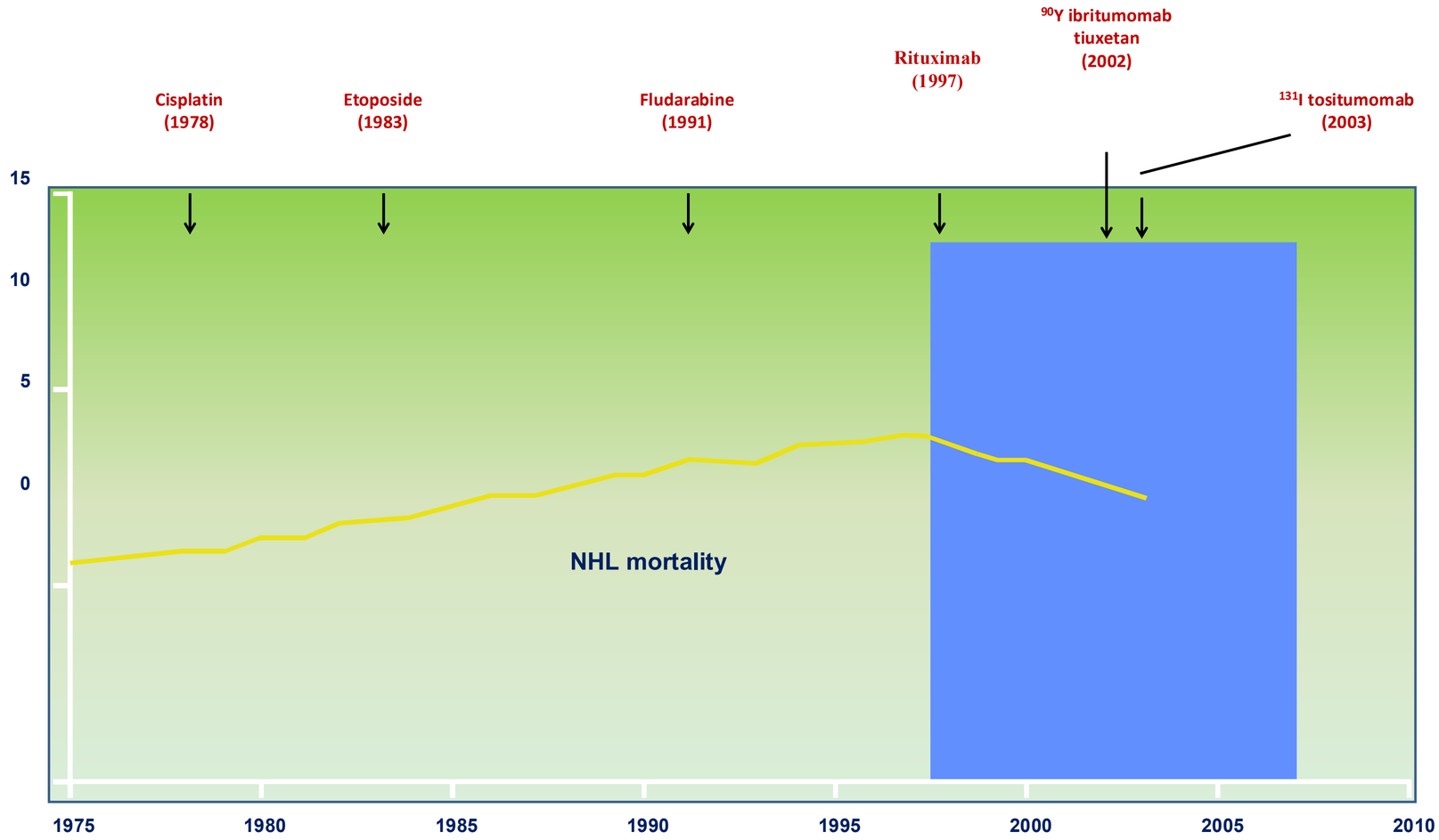


Number at risk (number censored)					
Watchful waiting	183	147	122	47	0
	(0)	(17)	(22)	(86)	(129)
Rituximab induction	82	65	57	40	0
	(0)	(8)	(10)	(17)	(53)
Rituximab maintenance	190	156	130	42	0
	(0)	(23)	(32)	(105)	(145)

At 15 years no significant differences in Overall Survival

Northend M. et al. Lancet Hematol 2025; 12: 335-345

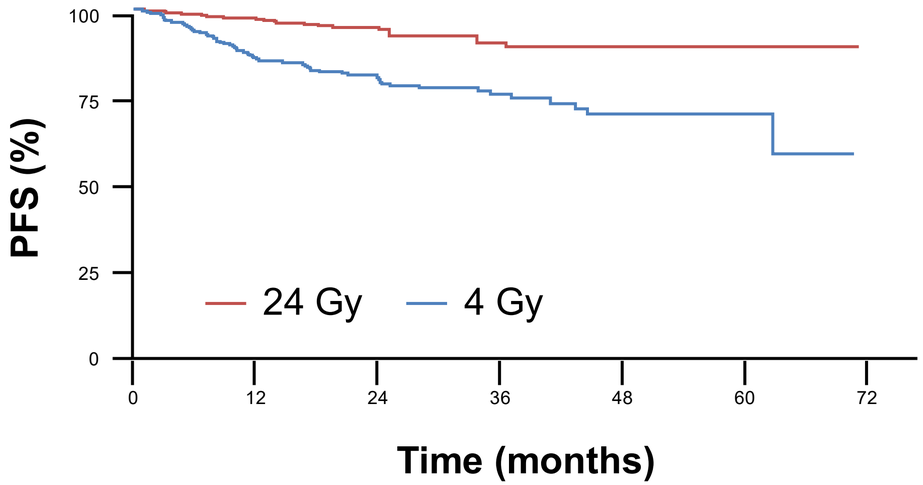
Immunotherapy has changed the clinical course of NHL

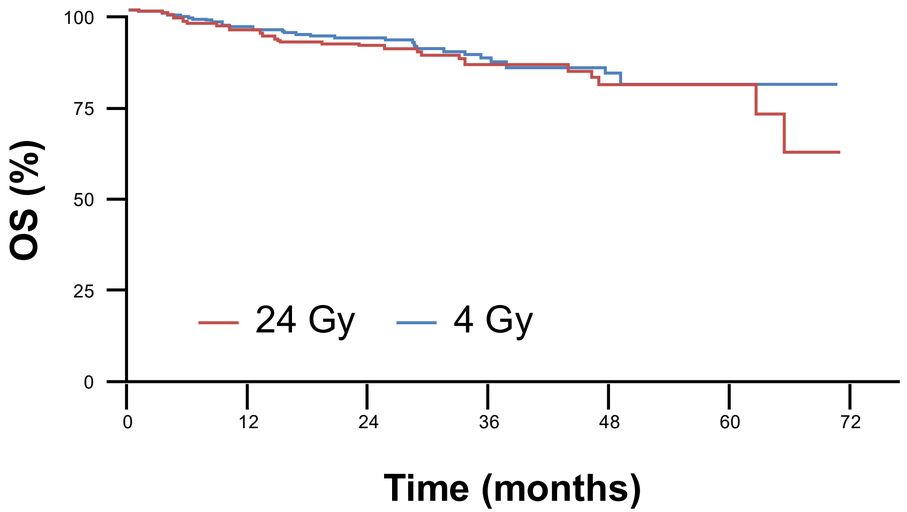


Adapted from Molina A. Annu Rev Med 2008; 59:237–250.

Radiotherapy for front-line treatment in localized Follicular Lymphoma

FORT: Randomised, open-label, Phase III trial in iNHL patients[a] who received no treatment for 1 month prior to study start (N=614)[1]



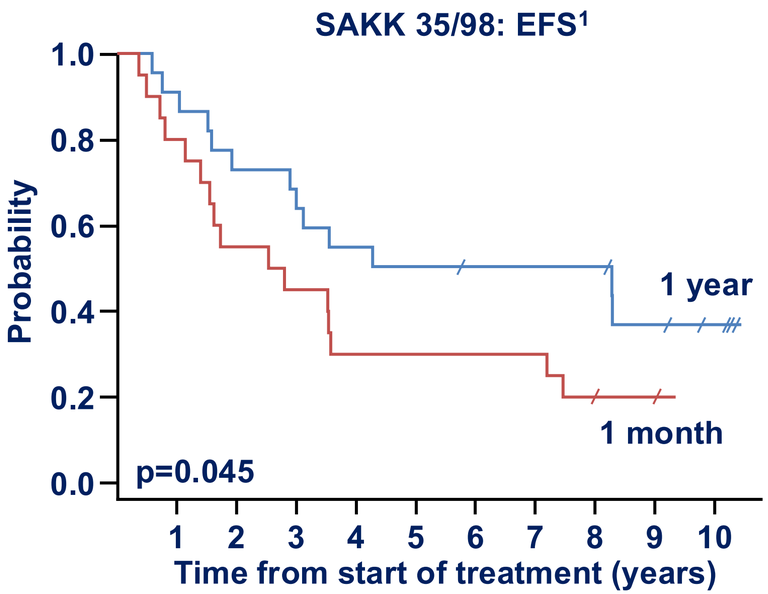


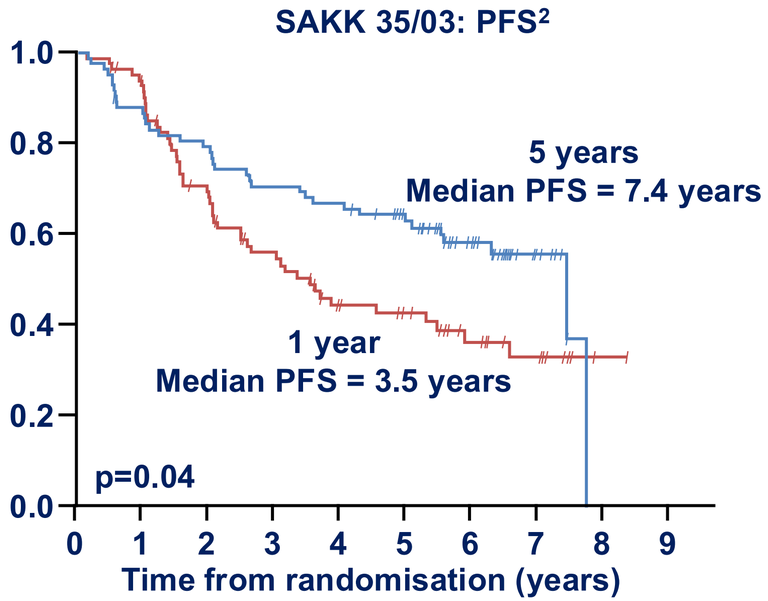
All patients (N=614)	24 Gy	4 Gy
Response rate, %	91	81
Local progression at 2 years, %	7	22
Acute or late toxic effects, %	4.2	2.6

1. Hoskin PJ, *et al. Lancet Oncol* 2014; 15:457–463. 2. Dreyling M, *et al. Ann Oncol* 2014; 25(Suppl 3):iii76–iii82.

Long-term outcomes may be improved with prolonged rituximab maintenance in first-line

High tumour burden, Stage III/IV





Increased EFS or PFS was seen with longer-term rituximab maintenance, without increased undue toxicity vs. short-term maintenance

1. Martinelli G, et al, J Clin Oncol 2010; 28:4480–4484. 2. Taverna C, et al. ASH 2013 (Abstract 508; oral presentation).

The benefit of adding rituximab to combination chemotherapy has been established

High tumour burden, Stage III/IV

	Regimens	OS	ORR	CR rate
Newly diagnosed FL (control vs. R-chemotherapy)				
Hiddemann *et al*.[1]	CHOP vs. R-CHOP	90% vs. 95% in 2 years (p=0.016)	90% vs. 96% (p=0.011)	17% vs. 20% (p=ns)
Herold *et al*.[2]	MCP vs. R-MCP	74% vs. 87% in 4 years (p=0.0096)	75% vs. 92% (p=0.0009)	25% vs. 50% (p=0.004)
Marcus *et al*.[3]	CVP vs. R-CVP	77% vs. 83% in 4 years (p=0.029)	57% vs. 81% (p<0.0001)	10% vs. 41% (p<0.0001)[b]
Salles *et al*.[4]	CHVP-I vs. R-CHVP-I	79% vs. 84% in 5 years[a]	50% vs. 67% (p=0.035)[b,c]	39% vs. 51% (p=0.035)[c]

1. Hiddemann W, et al. Blood 2005; 106:3725–3732. 2. Herold M, et al. J Clin Oncol 2007; 25:1986–1992. 3. Marcus R, et al. J Clin Oncol 2008; 26:4579–4586. 4. Salles G, et al. Blood 2008; 112:4824–4831. 5. Vidal L, et al. J Natl Cancer Inst 2011; 103:1799–1806.

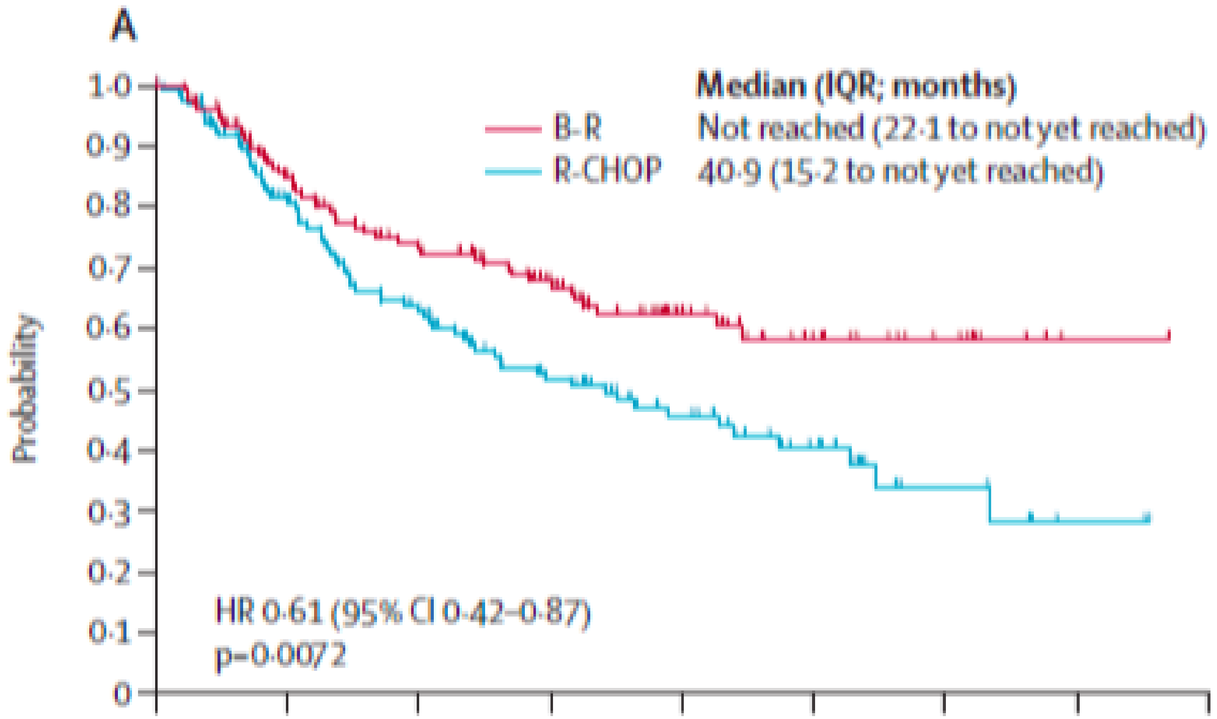
Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial

Mathias J Rummel, Norbert Niederle, Georg Maschmeyer, G Andre Banat, Ulrich von Grünhagen, Christoph Losem, Dorothea Kofahl-Krause, Gerhard Heil, Manfred Welslau, Christina Balser, Ulrich Kaiser, Eckhart Weidmann, Heinz Dürk, Harald Ballo, Martina Stauch, Fritz Roller, Juergen Barth, Dieter Hoelzer, Axel Hinke, Wolfram Brugger, on behalf of the Study group indolent Lymphomas (StiL)

	B-R (n=261)	R-CHOP (n=253)	p value
Alopecia	0	245 (100%)*	<0·0001
Paresthesia	18 (7%)	73 (29%)	<0·0001
Stomatitis	16 (6%)	47 (19%)	<0·0001
Skin (erythema)	42 (16%)	23 (9%)	0·024
Skin (allergic reaction)	40 (15%)	15 (6%)	0·0006
Infectious episodes	96 (37%)	127 (50%)	0·0025
Sepsis	1 (<1%)	8 (3%)	0·019

B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab. *Includes only patients who received three or more cycles.

Table 4: **All grades of non-haematological toxic events in patients receiving at least one dose of study treatment**



Rummel MS et al, Lancet 2013; Flinn IW et al, JCO 2019

Lenalidomide Plus Rituximab (R2) Followed by R Maintenance

Relevance Study

Figure 1. RELEVANCE Study Design

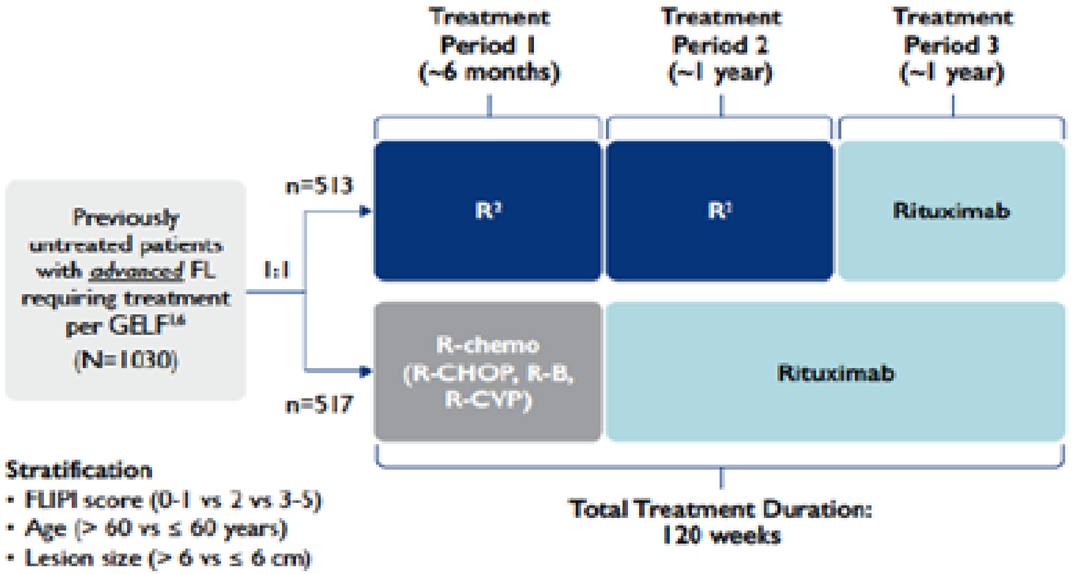


Figure 3: Progression-Free Survival by IRC, FDA Censoring Rules

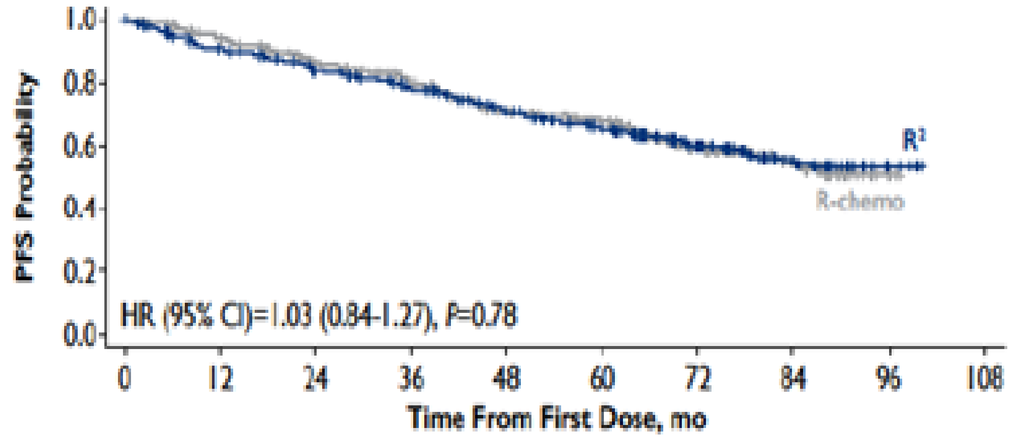
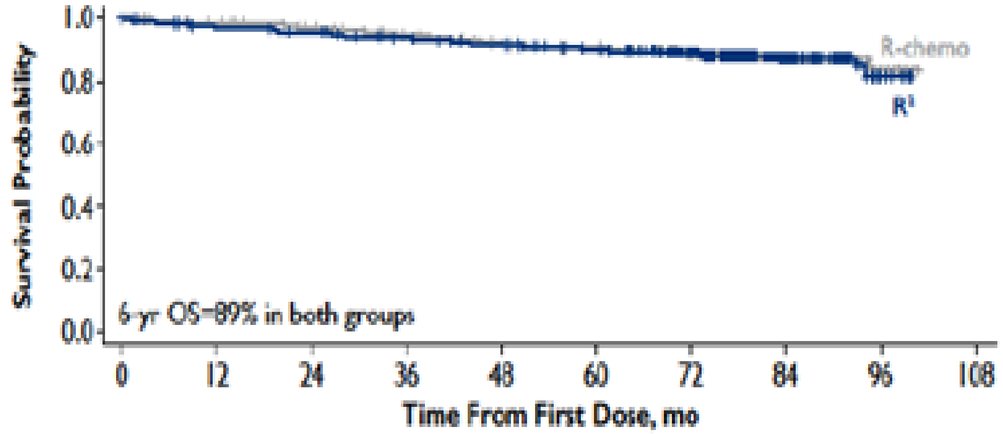


Figure 6: Overall Survival

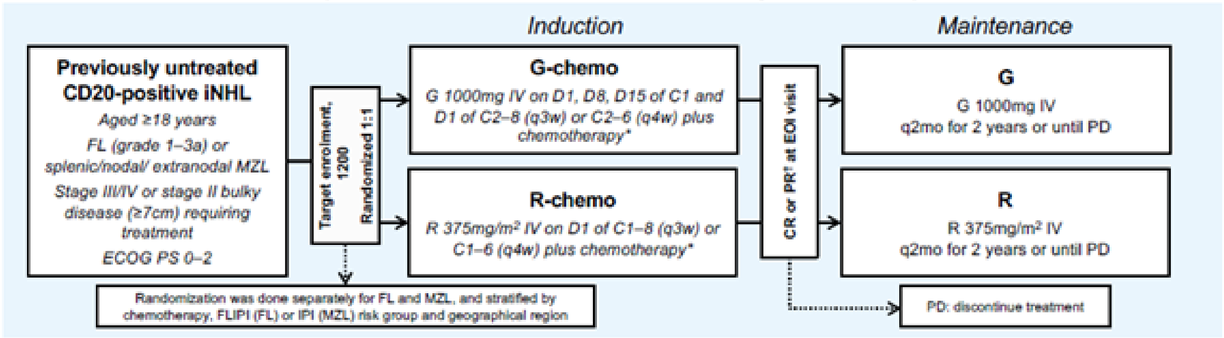


6 years updated results

Morschhauser F, et al JCO 2022;40:3239

R-Chemo vs G-Chemo in Untreated FL: GALLIUM Trial

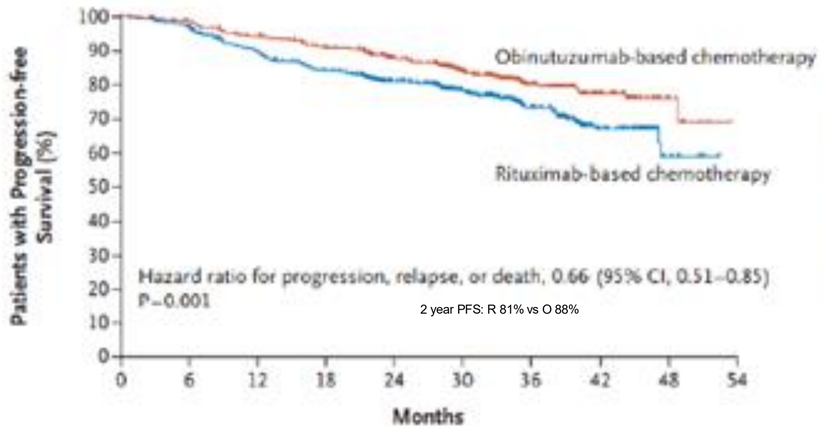
Global, open-label, randomized Phase 3 study in 1L iNHL patients



Median observation time: 7.9 (0.0–9.8) years

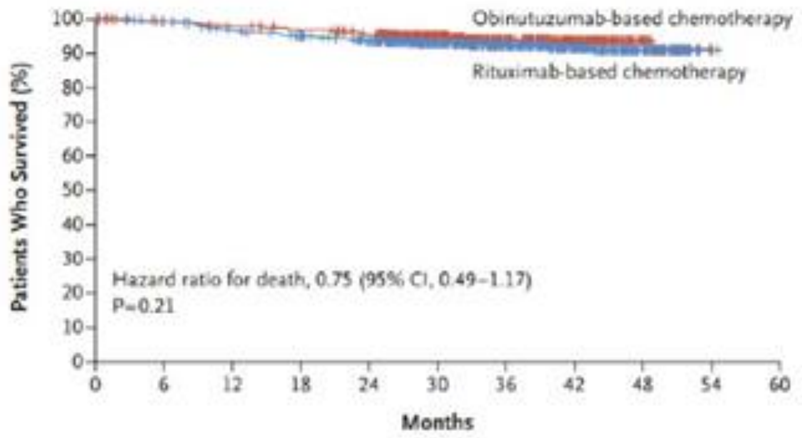
INV-assessed PFS	G-chemo (n=601)	R-chemo (n=601)
Patients with event, n (%)	206 (34.3)	244 (40.6)
7-year PFS, % (95% CI)	63.4 (59.0–67.4)	55.7 (51.3–59.9)
HR (95% CI)*	0.77 (0.64–0.93)	
P-value	0.006	

PFS



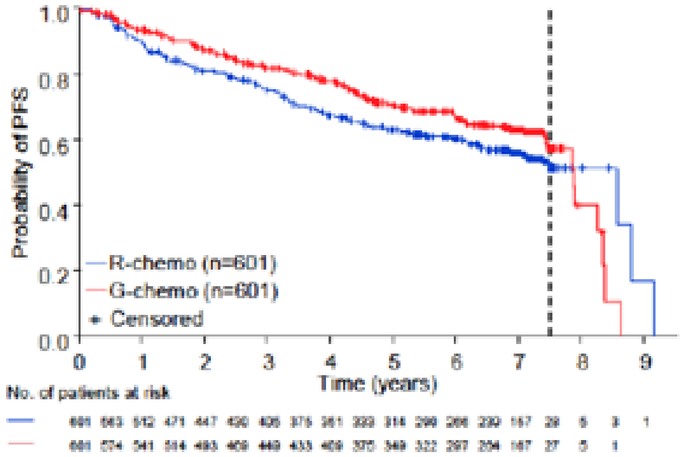
2 year PFS: R 81% vs O 88%

OS



- **Median follow-up: 34.5 months**

PFS by INV

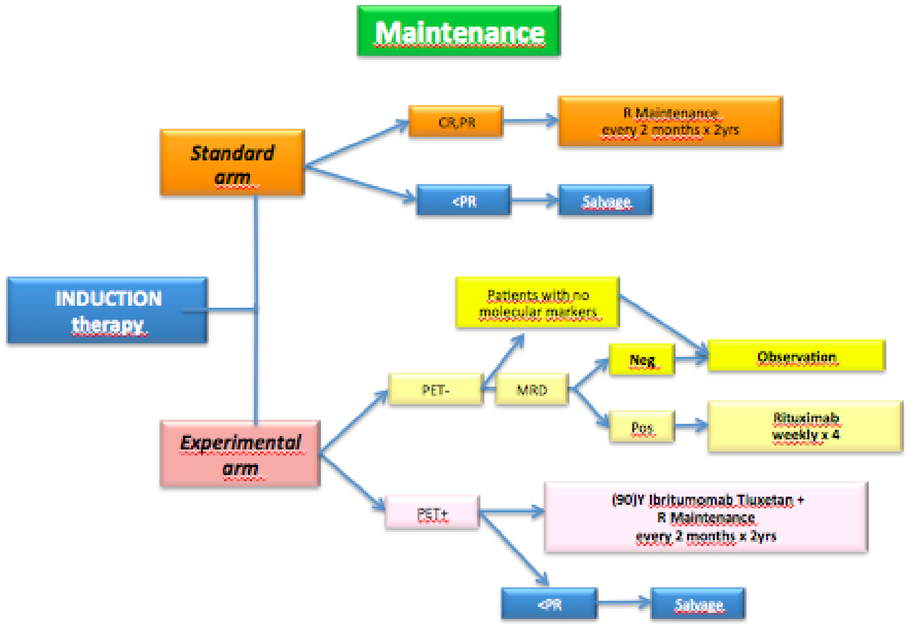


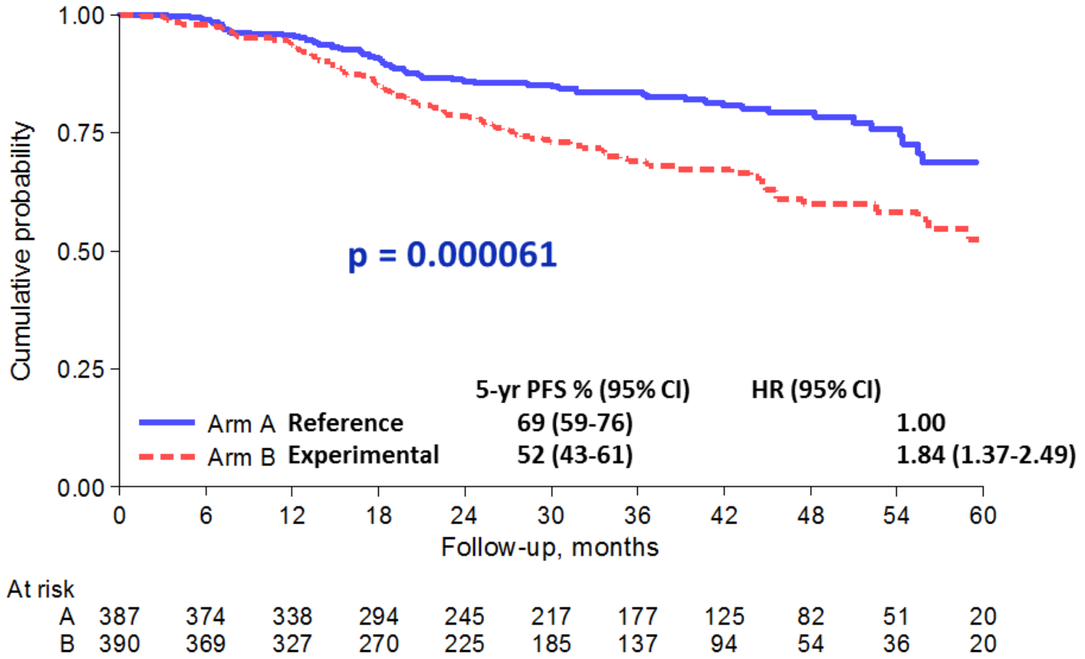
KM estimates became unreliable beyond 7.5 years, due to low numbers of patients at risk[1]

Marcus et al, NEJM 2017,377:1331. Hiddeman et al, JCO 2018. Townsend et al, EHA 2022. Townsend et al., HemaSphere, 7:e919 2023

R-Maintenance vs Response adapted post Induction Therapy

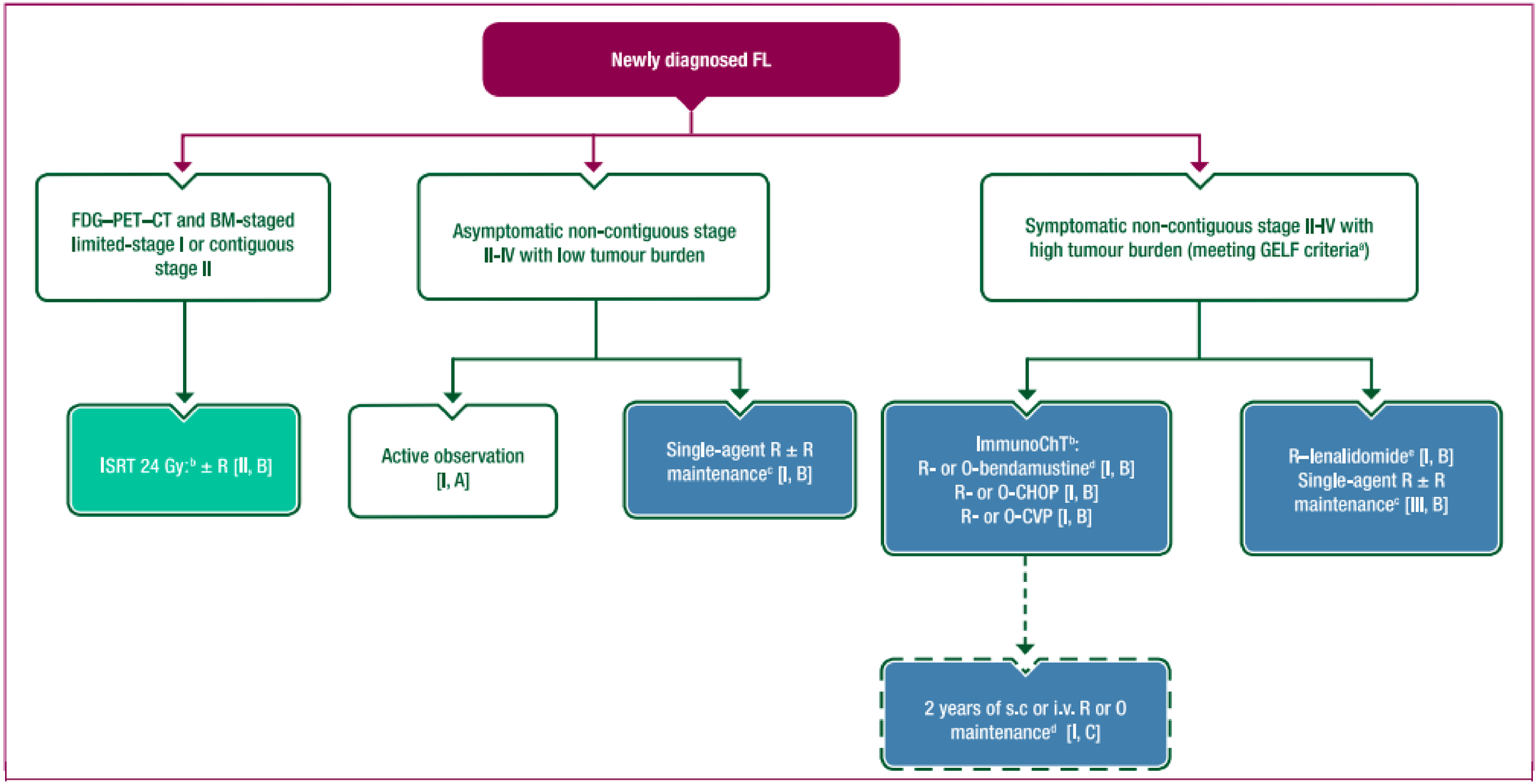
FOLL12 Phase III study





Superiority of standard maintenance therapy compared to an approach adapted to the post-induction response

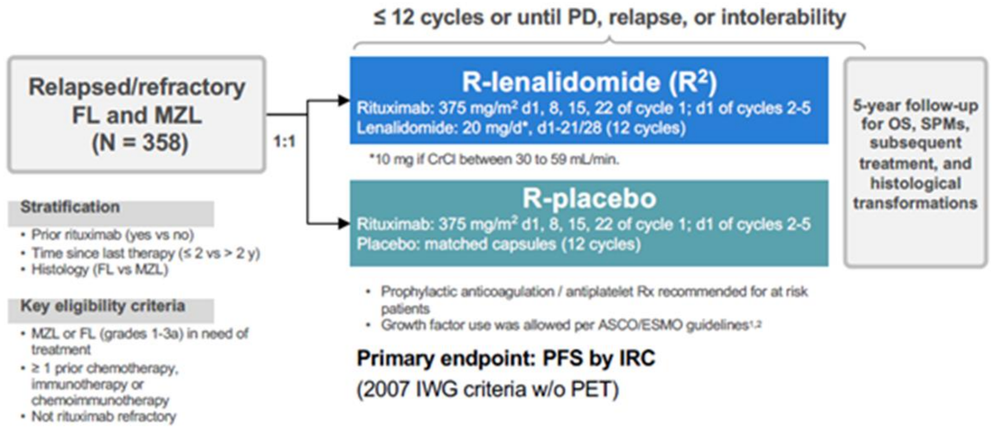
Luminari S et al, JCO 2021. 2022

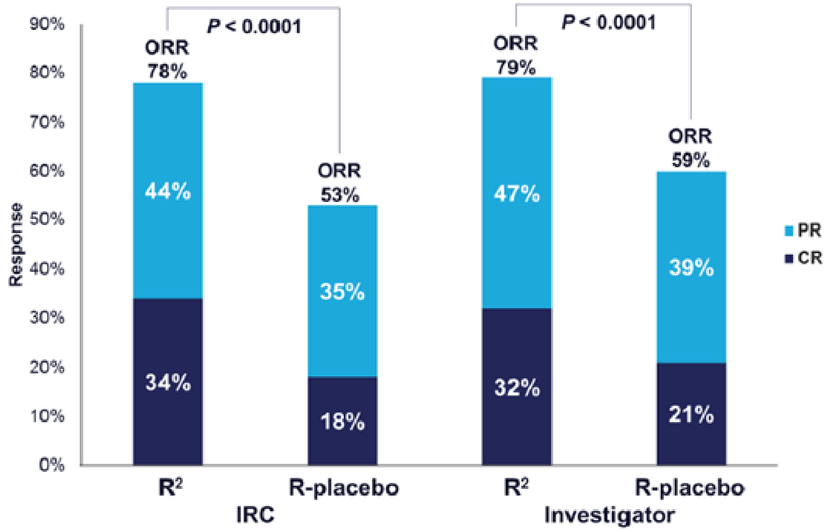


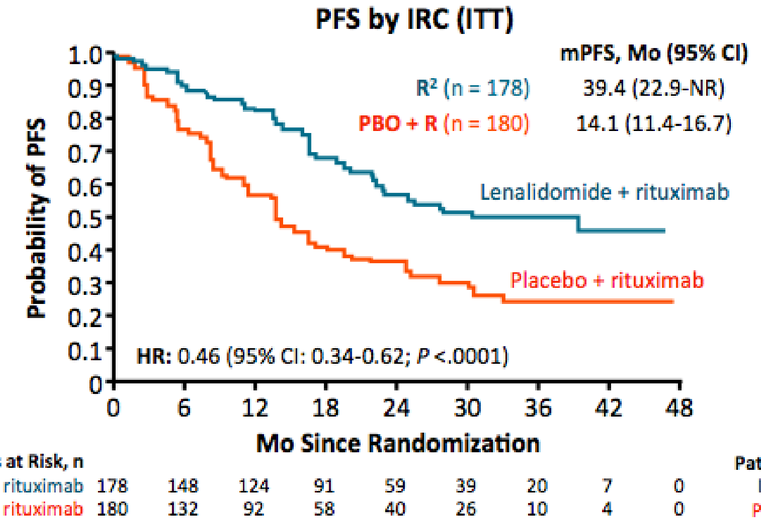
ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. July 2025

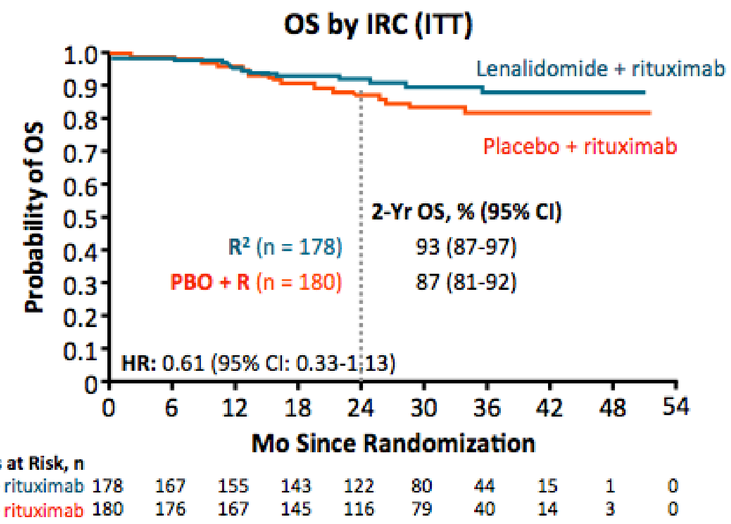
Key aspects in the management of Relapsed/Refractory Follicular Lymphoma

AUGMENT Study: R2 vs Rituximab Monotherapy in R/R iNHL









R²

- ORR: 78%; CR 34%
- Median DoR: 36.6 mo
- Median PFS: 39.4 mo
- Median OS: NR

Leonard. ASH 2022. Abstract #230. Leonard, et al; JCO 2019 371188-1199

The GADOLIN study design

Rituximab refractory iNHL (N = 413)

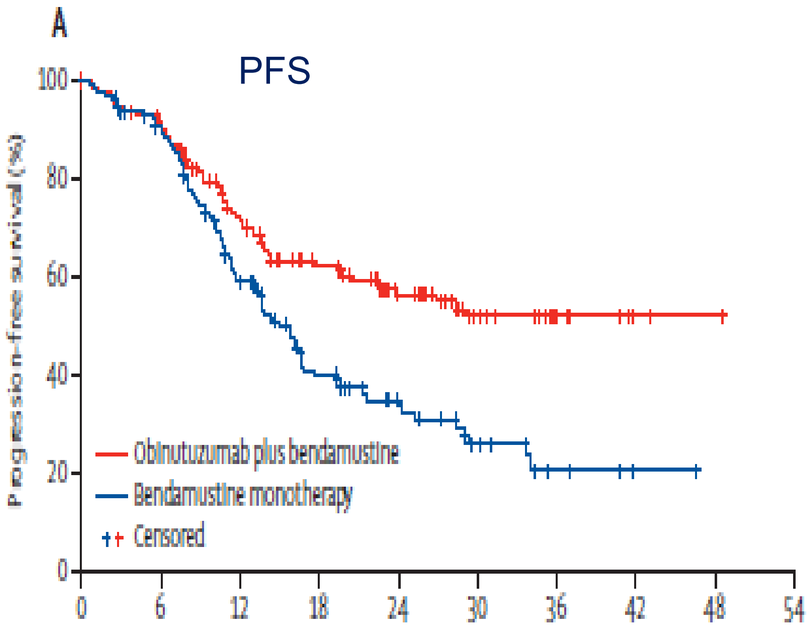
→ **Randomise 1:1**

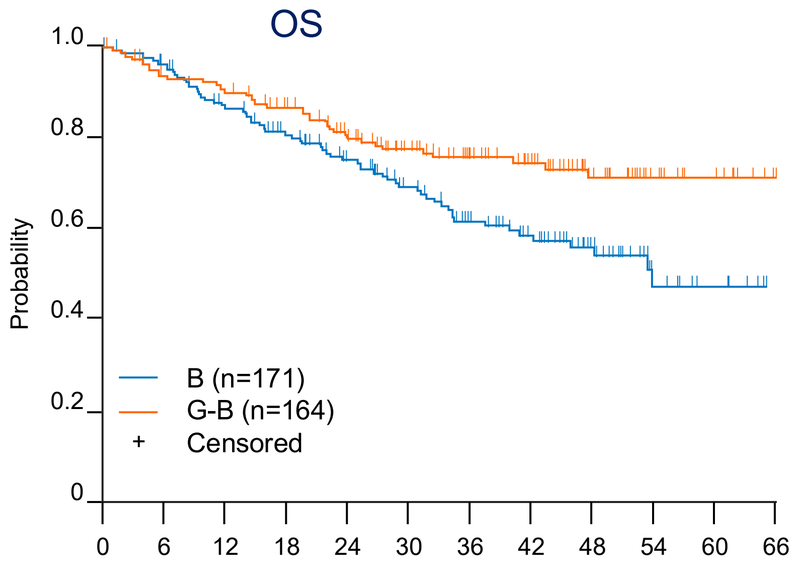
→ **Obinutuzumab 1,000 mg + bendamustine 90 mg/m²/day x 6 cycles**

→ **Obinutuzumab maintenance 1,000 mg every 2 months for 2 years or until progression**

→ **Bendamustine 120 mg/m²/day up to 6 cycles**

complete response, partial response *or* stable disease





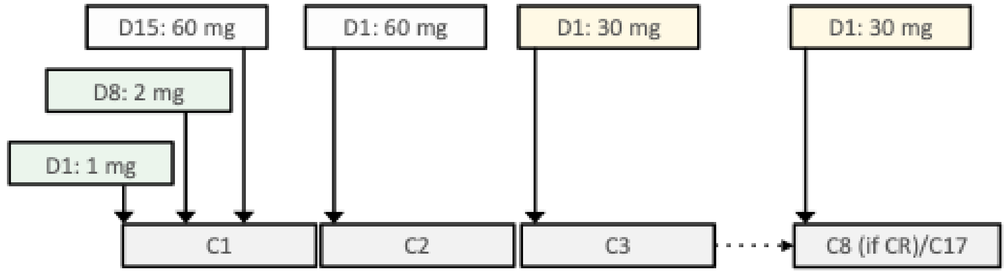
Sehn, Lancet Oncol 2016

Bispecific antibodies used in Follicular Lymphoma

Different BsAbs developed in FL 3L+

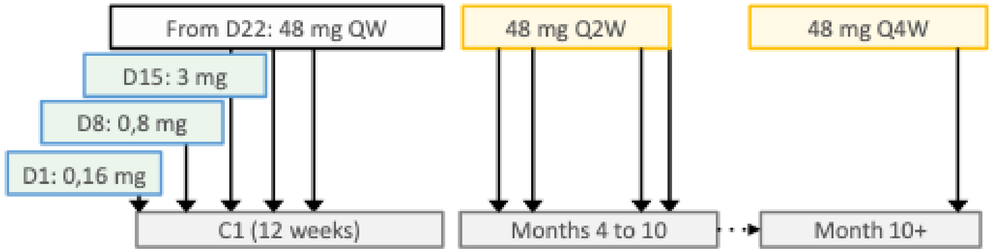
Mosunetuzumab

- IV mosunetuzumab administered weekly during C1 and then in 21-day cycles
- Step-up dosing in C1
- Fixed-duration treatment
- No mandatory hospitalization



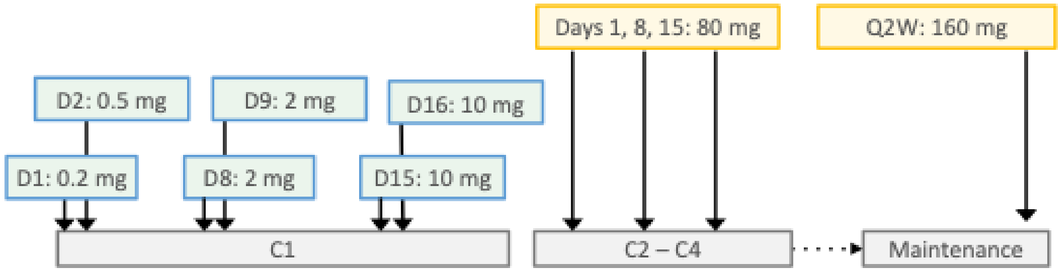
Epcoritamab

- SC epcoritamab administered weekly for 8 weeks then monthly
- Optimized Step-up dosing in C1 (4, 12, 48 mg)
- Treatment until progression
- Steroid prophylaxis
- Hospitalization at D22



Odronextamab

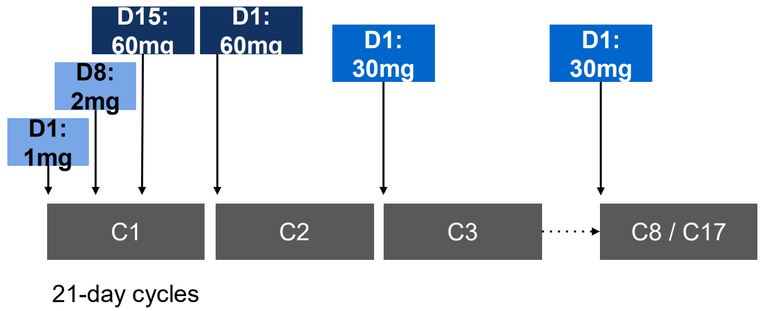
- IV odronextamab administered
- This was modified to 0.7/4/20 mg during C1 to further mitigate the risk of CRS
- Treatment until progression
- 48-hour hospital admission required at each split until nominal dose achieved



GO29781: Phase II expansion of mosunetuzumab in 3L+ FL

Mosunetuzumab administration (N=90)

- Q3W IV administration
  - 8 cycles if CR after C8
  - 17 cycles if PR/SD after C8



21-day cycles

n (%), unless stated	N=90
Median age, years (range)	60 (29–90)
Male	55 (61)
ECOG PS	
0	53 (59)
1	37 (41)
Ann Arbor stage	
I/II	21 (23)
III/IV	69 (77)
Median lines of prior therapy, (range)	3 (2–10)
Prior autologous stem cell transplant	28 (31)*
Refractory to last prior therapy	62 (69)
Refractory to any prior anti-CD20 therapy	71 (79)
POD24	47 (52)
Double refractory to prior anti-CD20 and alkylator therapy	48 (53)

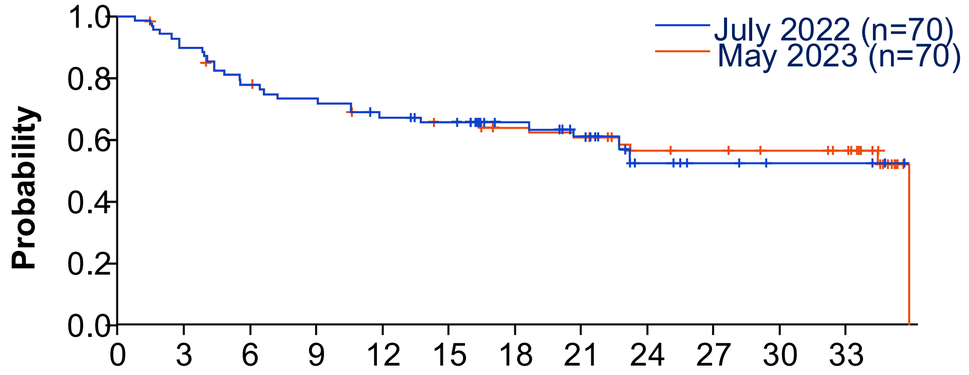
Efficacy endpoint	Investigator assessed N=90	IRF assessed N=90
CR*	54 (60) [49–70]	**54 (60)** [49–70]
ORR*	70 (78) [68–86]	**72 (80)** [70–88]

Median time on study: 37.4 months

Time to first response (median [range]): **1.4 months** (1.0–11)
Time to first CR (median [range]): **3.0 months** (1.0–19)

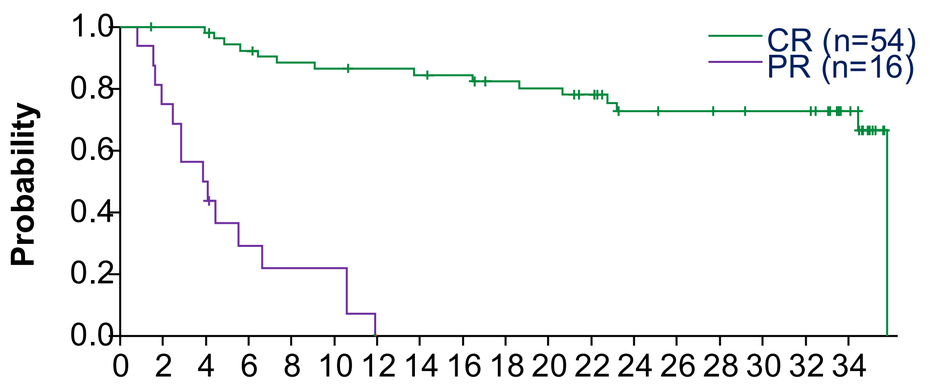
Schuster SJ, et al. ASH 2023.

DOR (July 2022 vs May 2023 data cut-off)



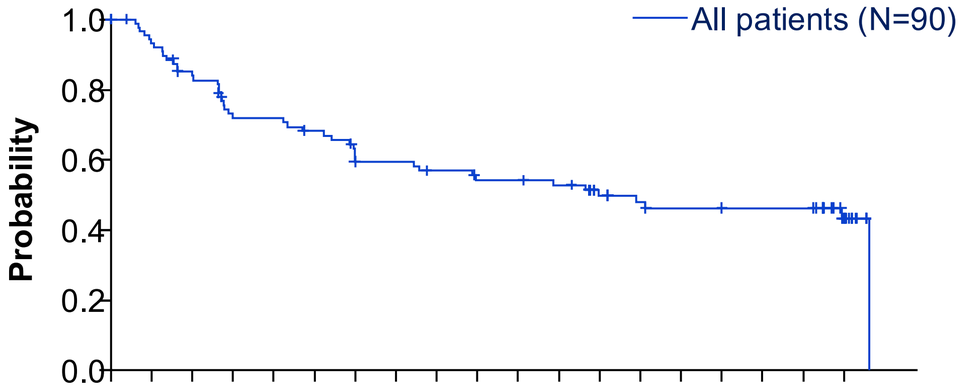
	n=70
Median DOR, months (95% CI)*	35.9 (20.7–NE)
30-month DOR rate, % (95% CI)†	56.6 (44.2–68.9)

DOR for CR vs PR (May 2023 data cut-off)



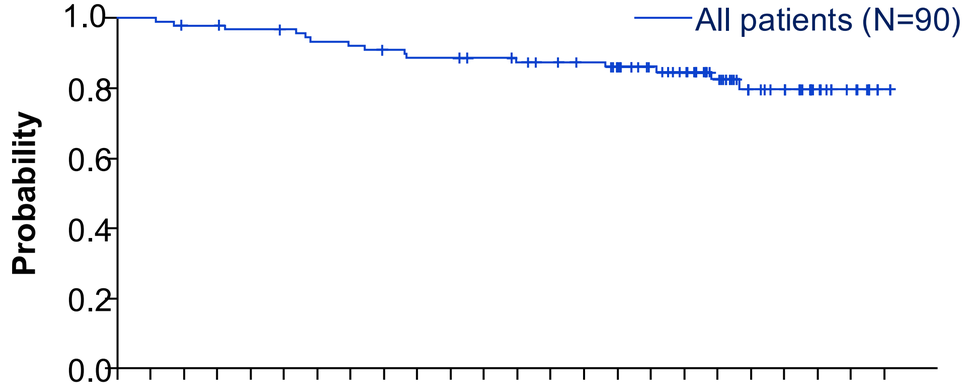
Median DOR in patients with CR, months (95% CI), n=54*	35.9 (NE–NE)
Median DOR in patients with PR, months (95% CI), n=16*	4.0 (2.5–6.7)

PFS



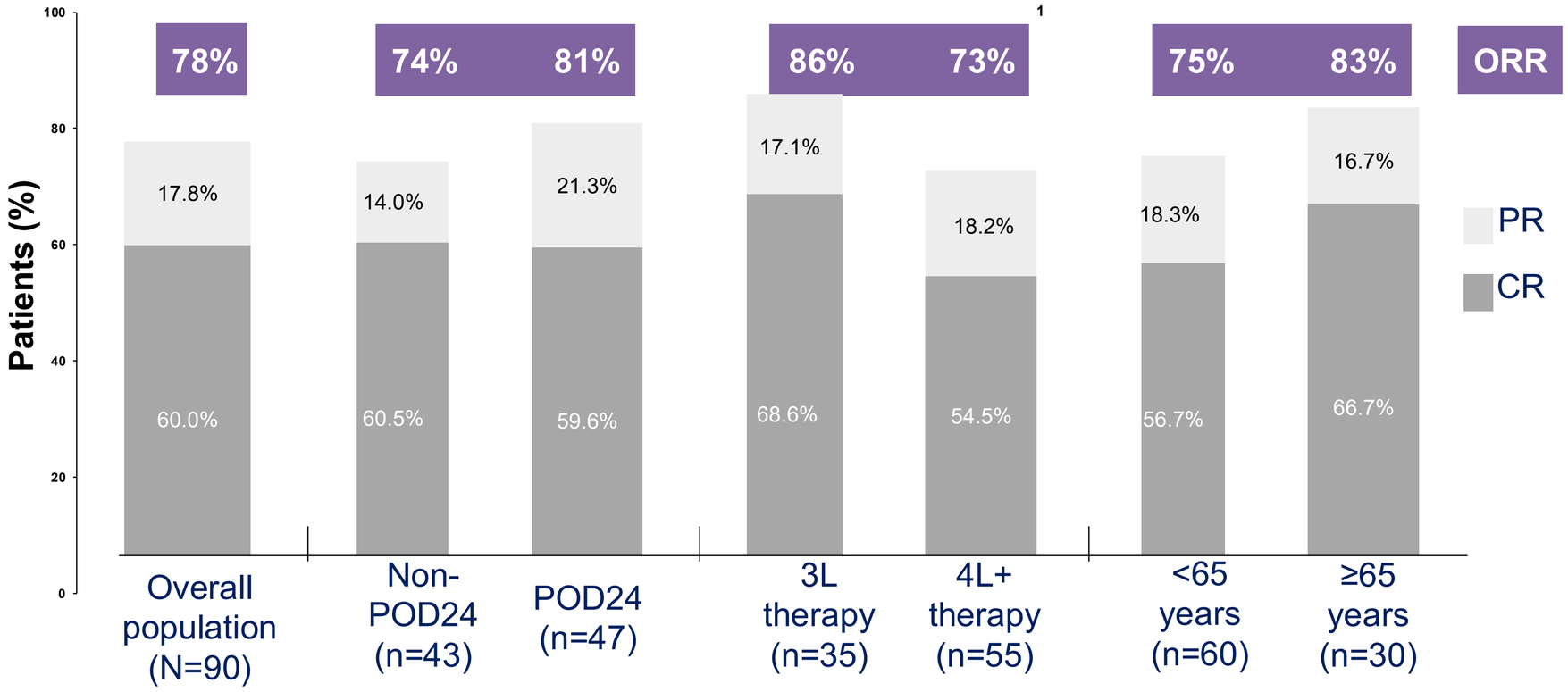
	N=90
Median PFS, months (95% CI)	**24.0** (12.0–NE)
36-month PFS, %(95% CI)	**43.2%** (31.3–55.2)

OS



	N=90
Median OS, months (95% CI)	**NR** (NE–NE)
36-month OS, % (95% CI)	**82.4%** (73.8–91.0)

Long follow-up Efficacy summary: response rates



CR rates across high-risk subgroups were consistent with the overall population; higher CR rates were observed in patients who received Mosunetuzumab in 3L than in the other subgroups

Assouline et al. Oral presentation EHA 2024

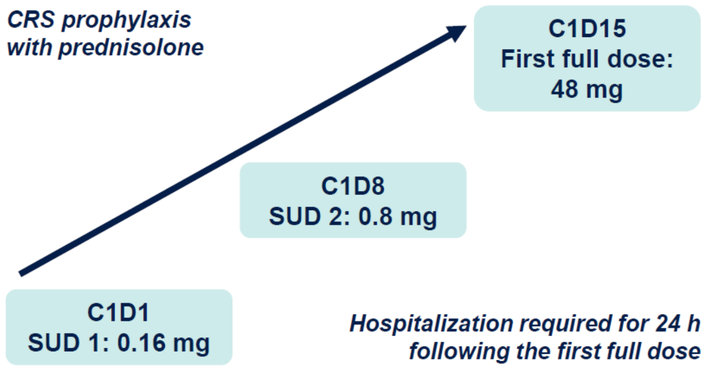
Epcoritamab in R/R FL

First C1 OPT–Focused Data Disclosure From EPCORE® NHL-1

Key inclusion criteria

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

Pivotal[a]

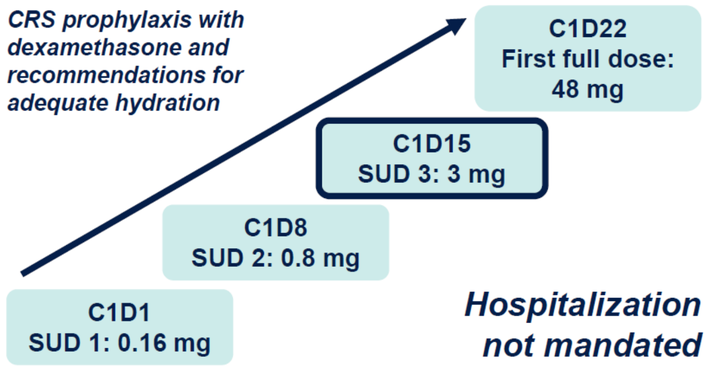


Primary objective: ORR by independent review committee

Data cutoff: April 21, 2023

Median follow-up: 17.4 mo

C1 optimization[a]



Primary objective: Assess incidence and severity of CRS

Data cutoff: January 8, 2024

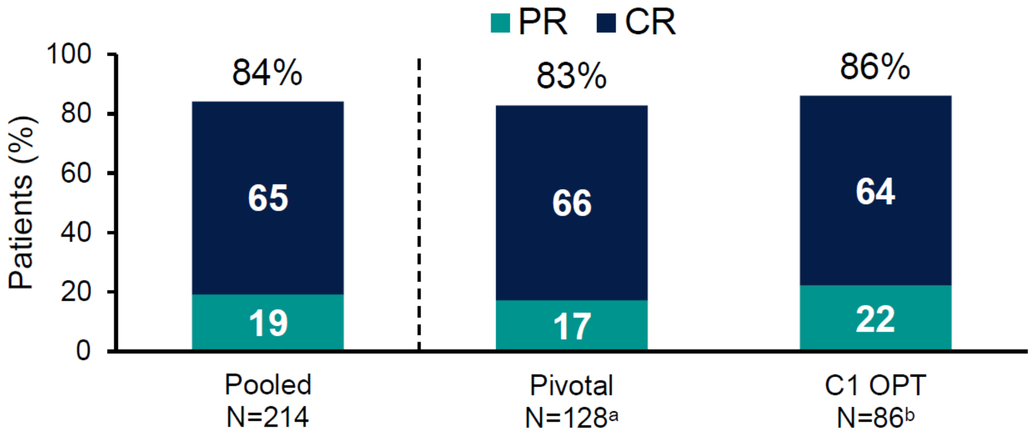
Median follow-up: 5.7 mo

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

Vitolo U. et al. EHA 2024

Epcoritamab in R/R FL

High Rates of Complete Response and MRD Negativity



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

Based on MRD-evaluable population per clonoSEQ® PBMC assay with 10^{-6} cutoff.

- No impact on time to response in C1 OPT
  - Median time to response was 1.4 mo in both cohorts[c]
  - Median time to complete response was 1.5 mo in both cohorts[d]

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

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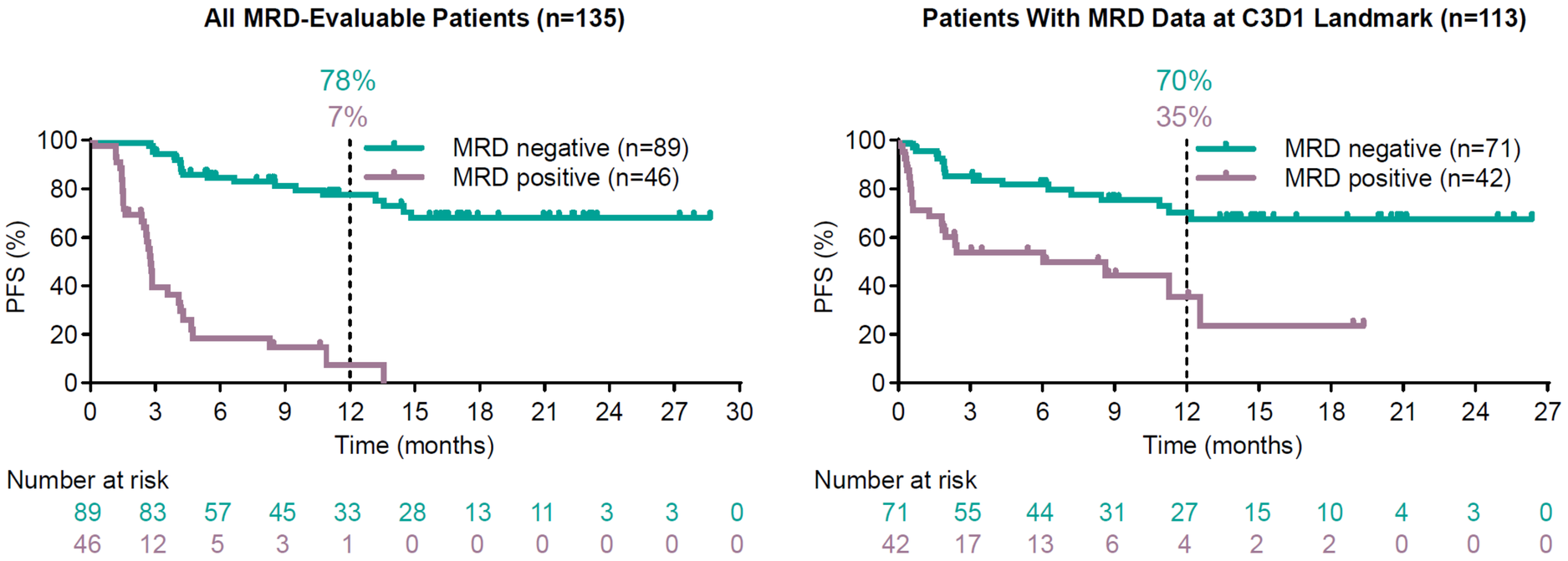
Epcoritamab in R/R FL

Overall and C3D1 MRD Negativity Associated With Favorable PFS



Median follow-up: 17.4 mo for pivotal cohort and 5.7 mo for C1 OPT cohort. PFS assessed by investigator. MRD was assessed in peripheral blood using the clonoSEQ® next-generation sequencing assay with 10^{-6} cutoff. MRD negative was defined as having MRD negativity at any time point (left graph) or at any time point up to C3D1 (right graph).

Vitolo U. et al. EHA 2024

Comparison of different bispecifics in Follicular Lymphoma

Activity of single agent BsAbs in RR FL (Phase II studies in 3L+)

Fixed Duration

	N	Age range	ASCT/ POD24 %	mFU	ORR/ CRR (%)	mPFS (months)	CRS (all,G3+)	other
Mosunetuzumab	90	29-90	21/52	37.4m	78/60	24 mo	44%,2%	G5 AE 2% (0 related) Discont (AE). 4%

TX until PG/tox

	N	Age range	ASCT/ POD24 %	mFU	ORR/ CRR (%)	mPFS (months)	CRS (all,G3+)	other
Epcoritamab	128	39-84	NA/42	17.4m	82/63	14.4 mo	48%,0%	G5 AE 6 pts Discont (AE) 19%
Odronextamab	131	22-84	31/48	26.6m	82/75	20.7mo	57%,2%	G5 AE 13% (2% related) Discont (AE). 11.5%

1. Dreyling M, et al. *J Clin Oncol*. 2017;35(35):3898-3905. 2. Budde LE, et al. *Lancet Oncol*. 2022;23(8):1055-1065. 3. Kim T-M, et al. Presented at: ASH 2022.

Summary of CAR-T cells Outcomes in RR-FL (≥3L)

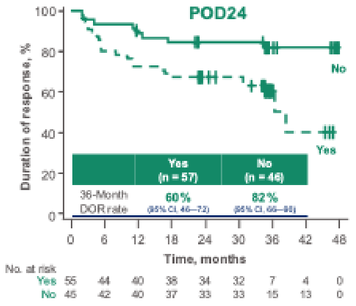
	Lisocabtagene Maraleucel TRANSCEND-FL	Tisagenlecleucel ELARA	Axicabtagene Ciloleucel ZUMA-5
n	107	94	124
Median # prior lines	3	4	3
Chemorefractory	67%	78%	68%
POD24	54%	60%	55%
CR rate	94%	69%	79%
Median PFS, m	NR	53 mo	57 mo
PFS	68% at 36m	50% at 60m	50% at 60m
PFS in POD24	58% at 36m	41% at 60m	50% at 60m
CRS (Any/severe) %	58/1	49/0	82/7
NT (Any/severe) %	15/2	4/1	59/15
References	Morschhauser, et al. Nature Med 2024 Ahmed, et al. Proc ASH 2025	Fowler, et al. Nat Med 2022. Schuster, et al.Proc ASH 2025	Jacobson, et al. Lancet Onc 2022 Neelapu, et al. JCO 2025

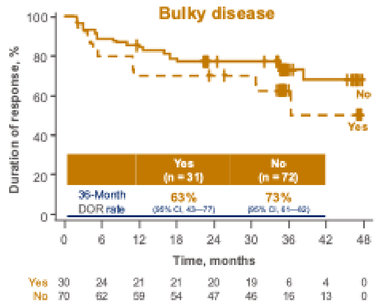
TRANSCEND FL: Sustained Benefit Across High-Risk

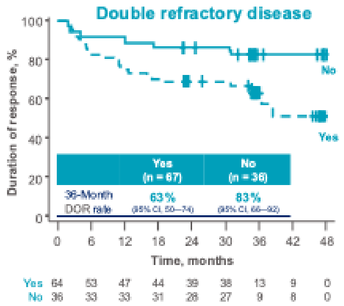
ELARA: Sustained PFS Across High-Risk Subgroups

ZUMA-5: Sustained PFS Across High-Risk Subgroups

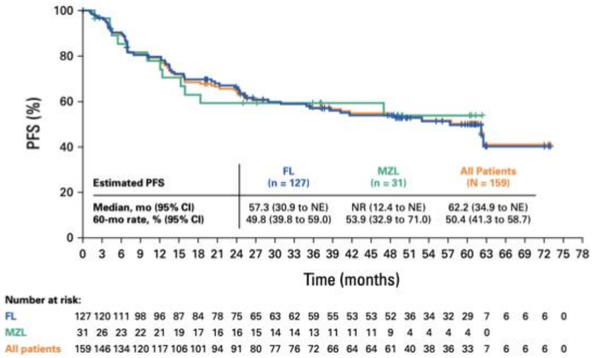
Summary of CAR-T cells Outcomes in RR-FL (≥3L)



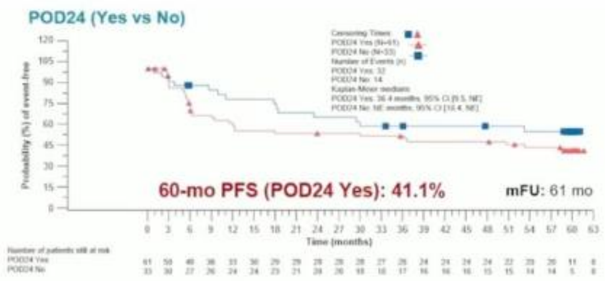


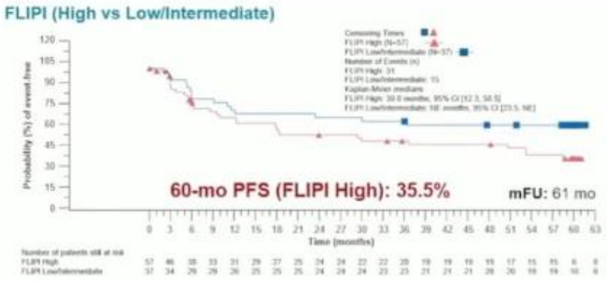


Trascend
Liso-cell



Zuma-5
Axi-cell





Elara
Tisa-cell

Comparison of efficacy of CAR T-cell therapy in patients with R/R FL

Car-T cell product	Ref.	N. of Pts	ORR (%)	CR (%)	Median PFS (mo)	Median OS	Median DOR (mo)
Axi-cel	ZUMA-5 (4y update)	124	94	79	57.3	NR	55
Tisa-cel	ELARA (3 y update)	97	86	68	37	NR	NR
Liso-cel	TRANSCEND-FL	101	97	94	12 mo, 81%	NR	12 mo, 82%

Jacobs et al. Frontiers in Oncology 2024

Conclusions: what we know in FL!

- Immunochemotherapy has changed the view of incurable disease
- The chemotherapy-free treatment, already started with immunotherapy, is proving to be very effective even in the first line
- High-dose therapy with autologous transplantation.....
- In R/R, new therapies with CAR-T and bispecifics certainly represent the treatment of choice from the third line onwards