My experience managing 3L+ patients with follicular lymphoma

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- **Travel & Accomodations**:
  - Gilead/Kite, Janssen, Roche, Takeda

Follicular lymphoma: core principles

- Patient outcomes are continually improving in FL
  - 10-yr survival rate 64% to 92%; median survival is ~ 20 years
  - 50% still relapse or die within 10 years
- A subset of patients has remarkably poor outcome regardless of treatment approach
  - Early relapse (POD24) is predictive for shorter OS (5-yr OS <50%)
  - Upfront identification of these patients remain a high priority
- Shorter PFS is common with subsequent therapies
- Limited data regarding optimal sequencing due to introduction of new drugs and modalities

Treatment outcomes in 3L R/R FL: real-world evidence

	LEO-CReWE[1] n=411 Median f/u 6 years	SCHOLAR-5[2] n=128 Median f/u 7 years	ReCORD-FL[3] n=187 Median f/u 9 years
ORR	70%	68%	69.5%
CRR	47%	44%	37%
TTNT [median, mo (95%CI)]	23 (19-27)	20 (16-40)	13 (11-19)
2-y TTNT	48%	42%	-
5-y TTNT	29%	23%	-
PFS [median, mo (95%CI)]	17 (15-19)	11 (9-18)	12 (10-17)
2-y PFS	40%	17%	40%*
5-y PFS	24%	-	-
OS [median, mo (95%CI)]	169 (14-NE)	68 (60-NE)	134 (78-232)
2-y OS	90%	84%	93.5%*
5-y OS	75%	63%	-

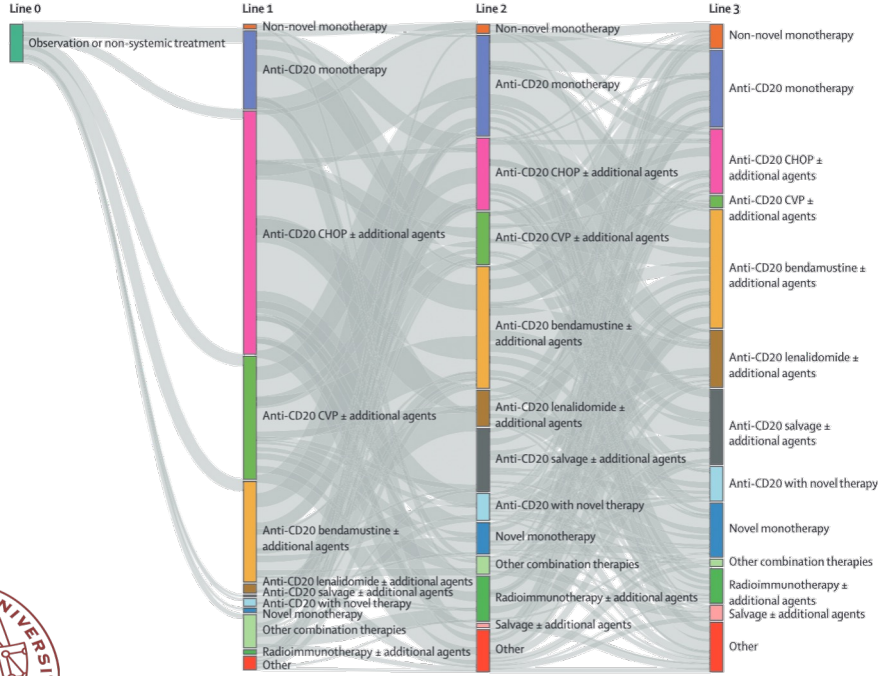
*18-month rates

1. Casulo C, et al. Lancet Haematol 2022;9:e289–300
2. Ghione P, et al. Haematologica 2023;108:822–32
3. Salles G, et al. HemaSphere 2022;6:e745

Treatment of FL exhibits significant heterogeneity

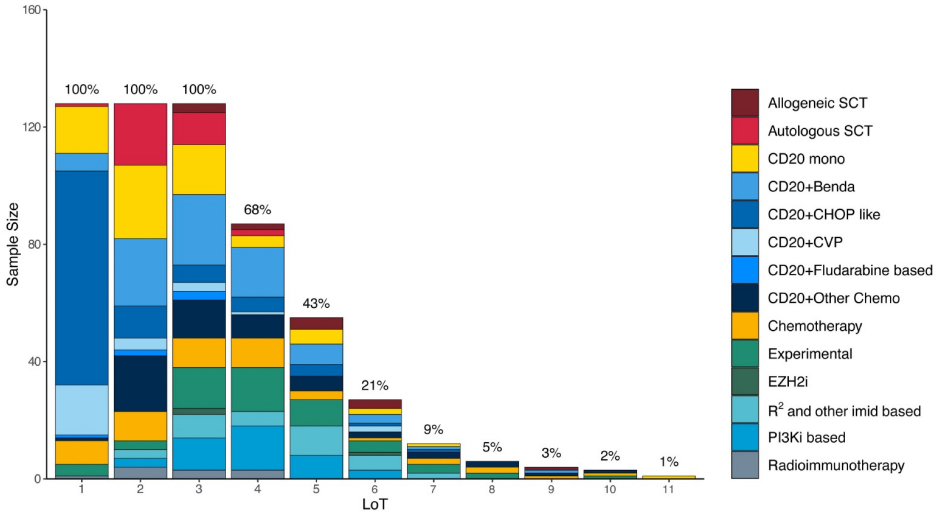
LEO CReWE study[1]

n=441, FL 1-3a, 2002-2018



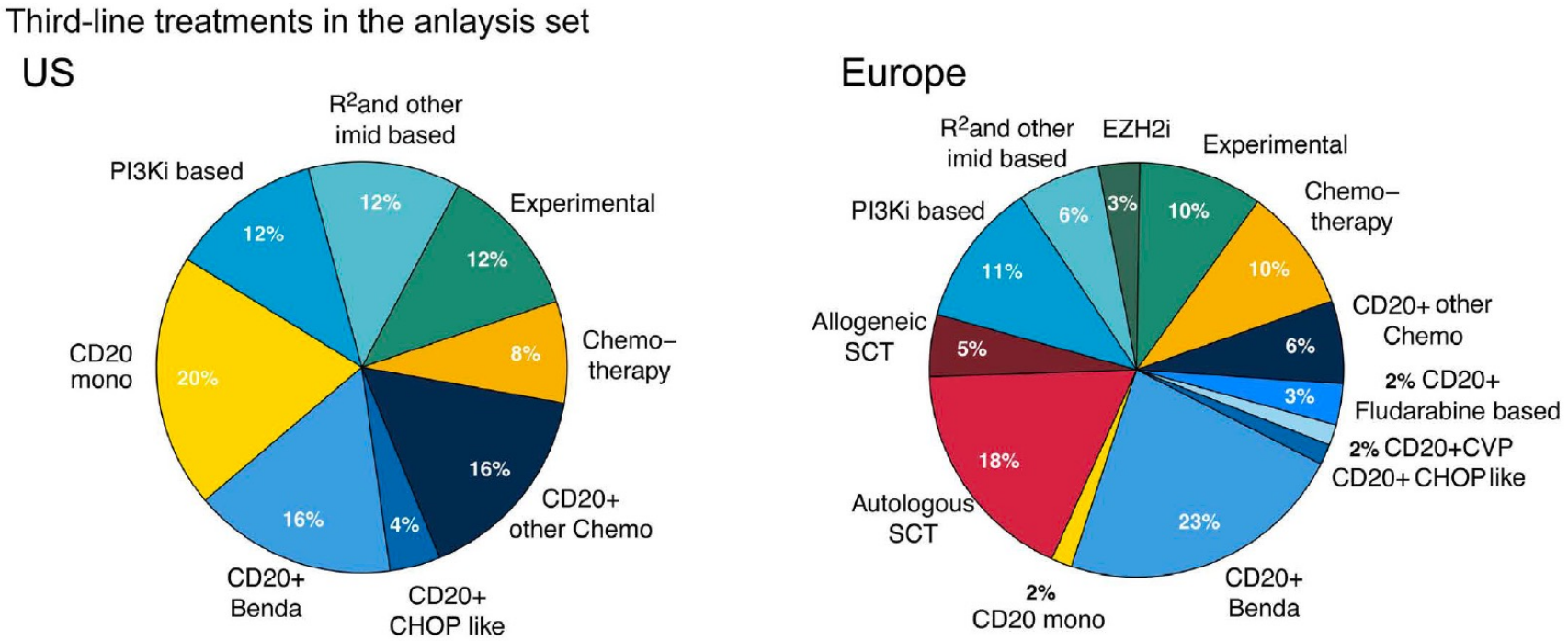
SCHOLAR-5 study[2]

n=128, FL 1-3a, after 2014



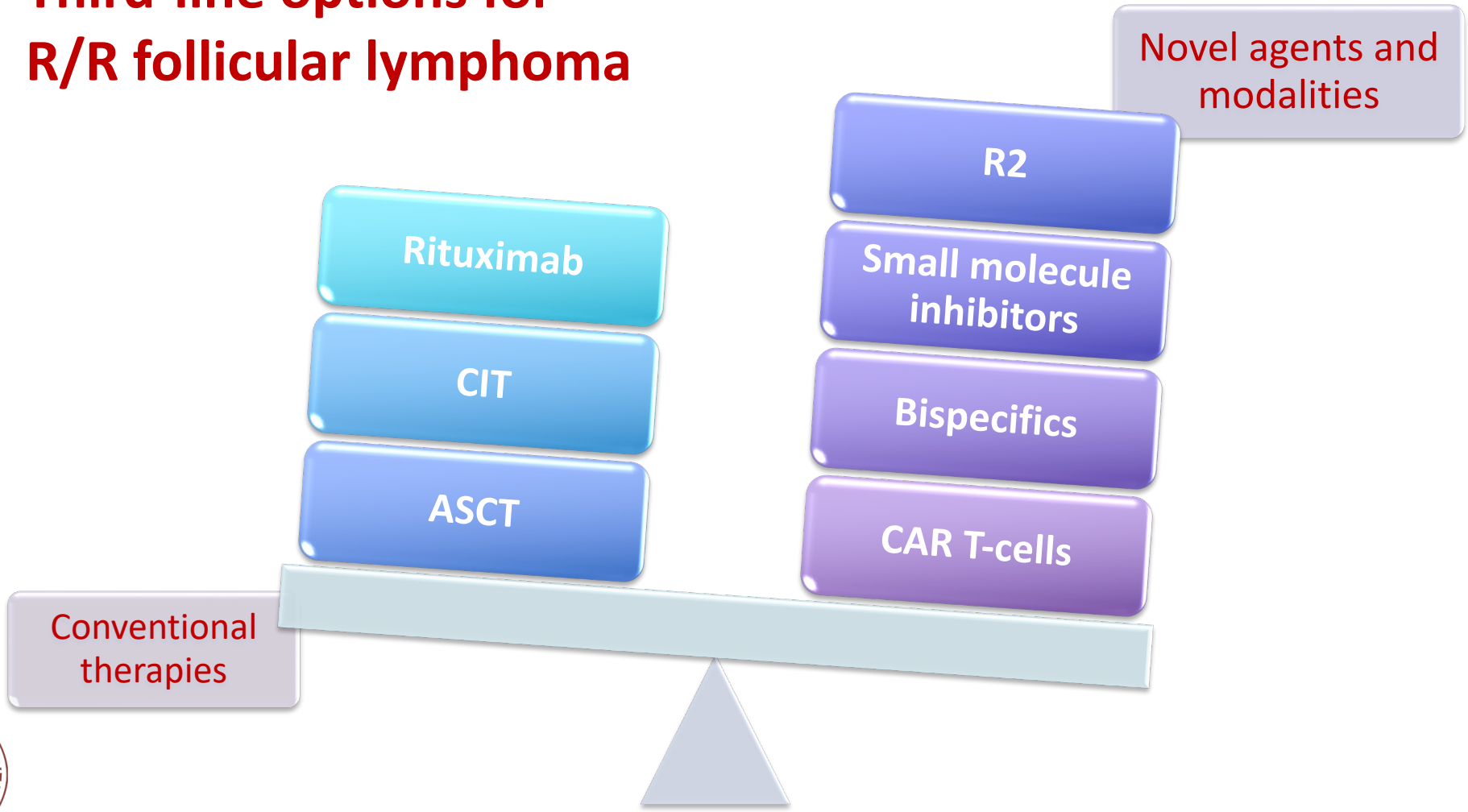
1. Casulo C, et al. Lancet Haematol 2022;9:e289–300
2. Ghione P, et al. Haematologica 2023;108:822–32

SCHOLAR-5: treatment patterns in 3L FL



Ghione P, et al. Haematologica 2023;108:822–32

Third-line options for R/R follicular lymphoma



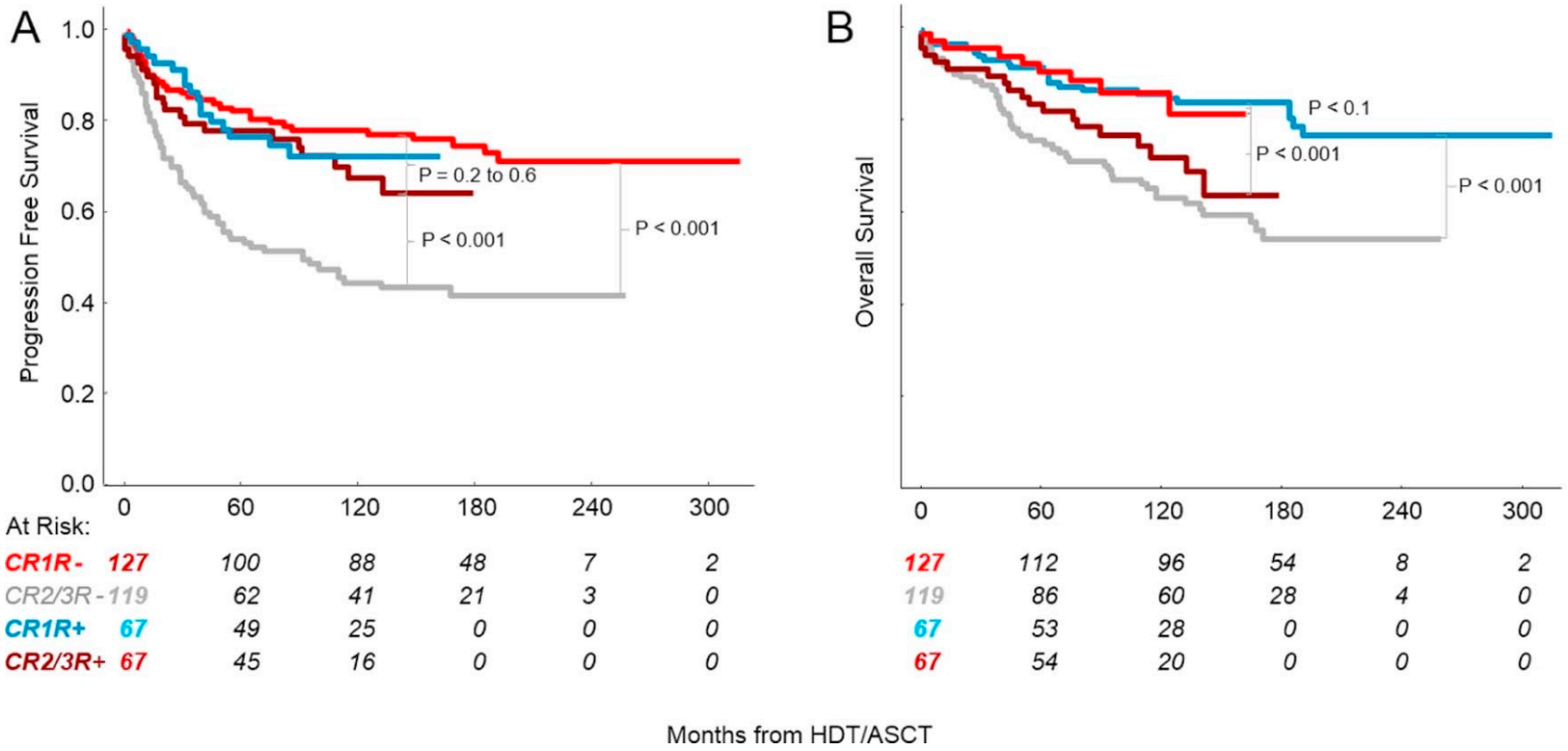
Chemoimmunotherapy in R/R follicular lymphoma

Study, regimen	Key patient characteristics	Outcomes
BR, Ph II[1]	1-3 prior regimens, **rituximab sensitive**	• ORR: 90% • mPFS: 24 mo
BR, Ph II[2]	1-4 prior regimens, **rituximab sensitive**	• ORR: 92% • mPFS: 23 mo
BR + R maint (StiL NHL-2-2003, Ph III)[3]	iNHL (FL 51%) and MCL Median 1 prior regimen, **rituximab sensitive**	• ORR: 82% • mPFS: 54.5 mo (FL)
BO + O maint (GADOLIN, Ph III)[4]	iNHL (FL 80%) Median 2 prior regimens, **rituximab refractory**	• ORR: 79% • mPFS: 24 mo (FL)

Bendamustine-based regimens yield mPFS of 2 years

1. Rummel MJ, et al. J Clin Oncol 2005; 23: 3383–9
2. Robinson KS, et al. J Clin Oncol 2008; 26: 4473–9
3. Rummel M, et al. Lancet Oncol 2016;17:57–66
4. Cheson BD, et al. J Clin Oncol 2018;36:2259–66

Does transplant still have a role in R/R FL?



Jimenez-Ubieto A, et al. Biol Blood Marrow Transplant 2017;23:1631–40

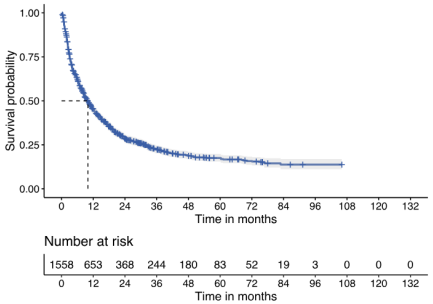
Longer survival in 3L R/R FL patients undergoing SCT

Representatitve cohorts:
- LymphoCare. *Link et al. Br J Haematol 2019*
- US single-center. *Batlevi et al. Blood Cancer J 2020*
- Japan multicenter. *Fuji et al. Ann Hematol 2020*

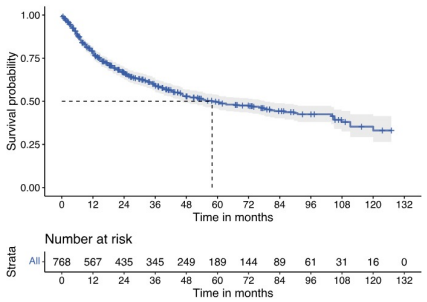
Pooled KM curves for supplemental model including only SCT studies

- SCT study populations tended to be significantly younger and healthier
- Risk of immortal time bias

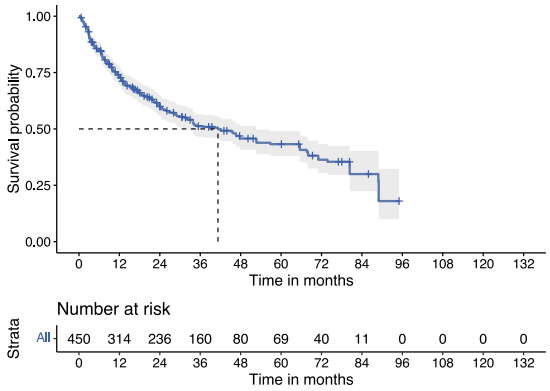
Representative cohorts progression-free survival, ≥3rd line



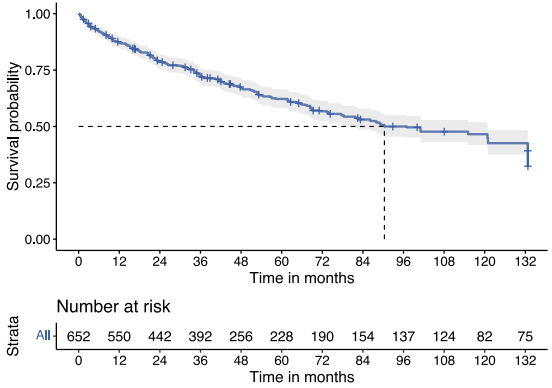
Representative cohorts overall survival, ≥3rd line



PFS 3rd line plus

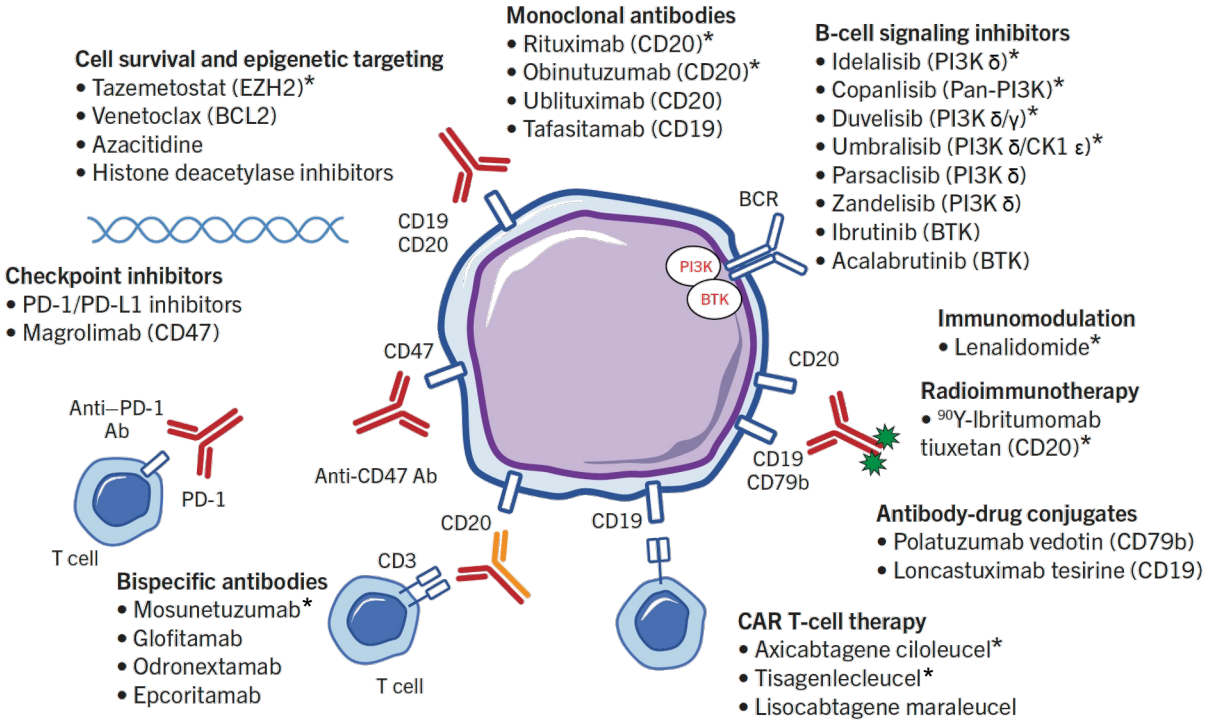


OS 3rd line plus



Kanters S, et al. BMC Cancer 2023;23:74

Approved* and investigational targeted agents in FL



Modified from Cahill KE, Smith SM. Oncology (Williston Park) 2022;36:97–106

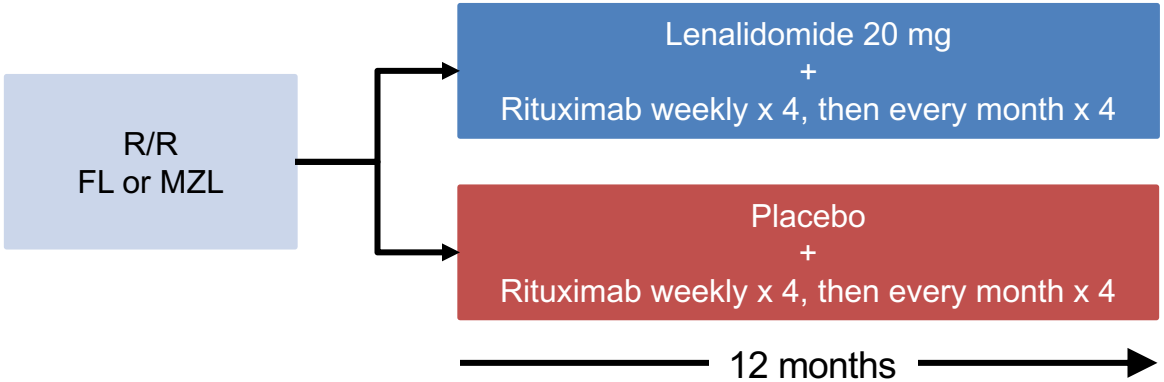
Drug development in R/R FL: focusing on both the tumor and TME

Target	Drug	Trial	ORR	CR	mDoR (months)	mPFS (months)
Cereblon	Lenalidomide + rituximab	AUGMENT[1] MAGNIFY[2]	80% 72%	35% 42%	36.6 NR	39.4 51.1
PI3K	Idelalisib Duvelisib Copanlisib Umbralisib Parsaclisib Zandelisib	DELTA[3] DYNAMO[4] CHRONOS-1[5] UNITY-NHL[6] CITADEL-203[7] TIDAL[8]	56% 42% 59% 45% 78% 70%	14% 1.2% 20% 5% 19% 35%	12.5 10 14.1 11.1 14.7 NA	11 9.5 12.5 10.6 15.8 NA
EZH2	Tazemetostat	NCT01897571[9]	69%	13%	10.9	13.8

1. Leonard JP, et al. J Clin Oncol 2019;37:1188–99; 2. Lansigan F, et al. HemaSphere 2022; 6: 1043–4 (P1156); 3. Salles G, et al. Haematologica 2017;102:e156–9; 4. Flinn IW, et al. J Clin Oncol 2019;37:912–22; 5. Dreyling M et al. Am J Hematol 2020;95:362–71; 6. Fowler NH, et al. J Clin Oncol 2021;39:1609–18; 7. Trneny M, et al. eClinicalMedicine 2023;63:102130; 8. Zelenetz AD, et al. HemaSphere 2022;6:S3 (S208); 9. Morschhauser F, et al. Lancet Oncol 2020;21:1433–42

AUGMENT study design

R2 vs. rituximab monotherapy in R/R iNHL



- Phase III study (registration)
- Eligible pts: rituximab-naïve or rituximab-sensitive R/R FL or MZL, Grades 1, 2 or 3a
- **Primary endpoint:** IRC-assessed PFS
- HR=1.6 (improvement of 6.7 months in median PFS)
  - Implies sample size of N=350

Leonard JP, et al. J Clin Oncol 2019;37:1188–99

AUGMENT: basal characteristics (ITT)

Characteristic, n (%)	R^2 (n = 178)	R-placebo (n = 180)
Number of prior systemic antilymphoma regimens		
1	102 (57)	97 (54)
2	31 (17)	42 (23)
≥ 3	45 (25)	41 (23)
Prior rituximab treatment	152 (85)	150 (83)
Prior rituximab-containing chemotherapy regimen	130 (73)	129 (72)
≤ 2 years since last antilymphoma therapy	89 (50)	92 (51)
Relapse ≤ 2 years of initial diagnosis	56 (31)	61 (34)
≤ 2 years of initial therapy	66 (37)	75 (42)
Refractory to last regimen*	30 (17)	26 (14)

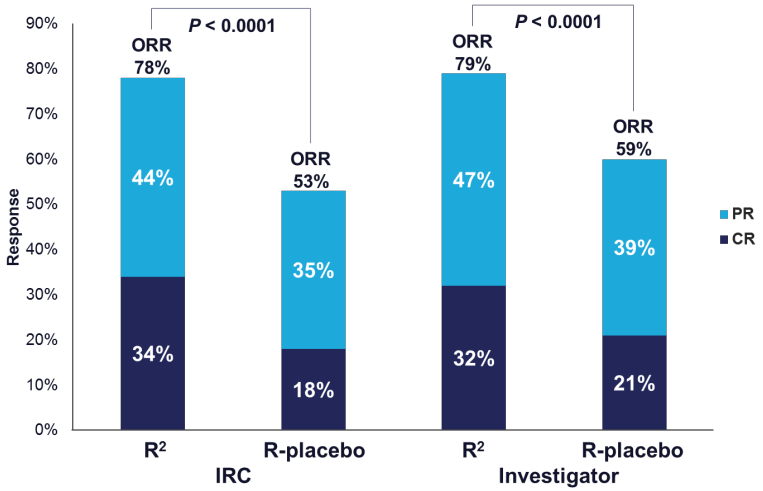
*Refractory defined as no response or progressive disease < 6 months after last dose.

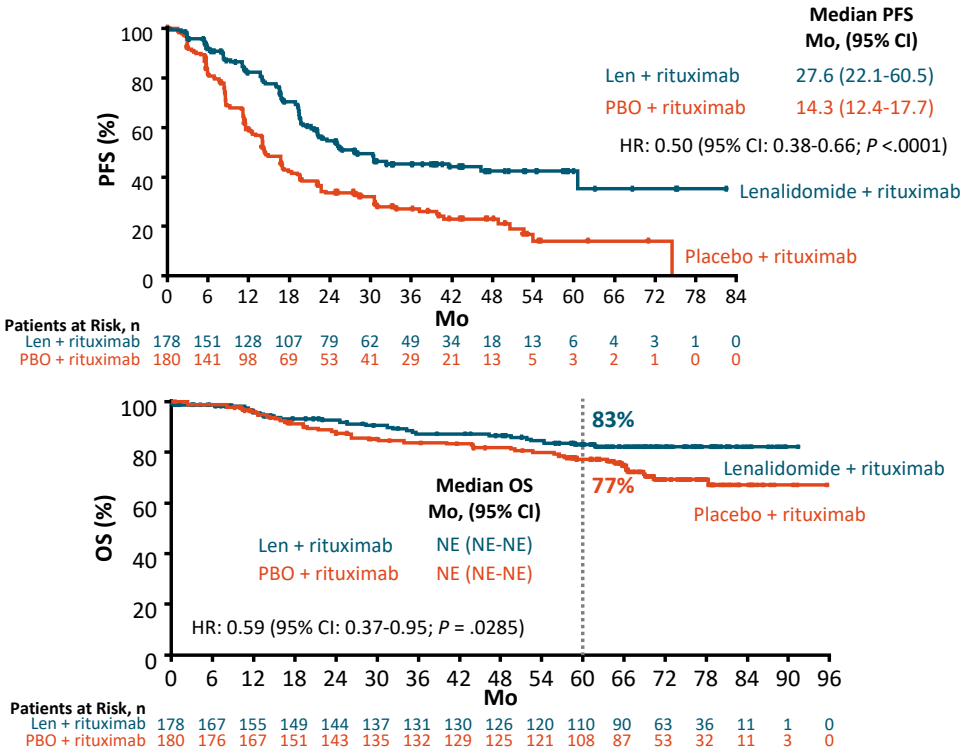
Most common prior last regimens were R-CHOP (R^2 37%, R-placebo 38%), combination chemotherapy (R^2 33%, R-placebo 31%,) and rituximab monotherapy (R^2 21%, R-placebo 23%)

Leonard JP, et al. J Clin Oncol 2019;37:1188–99

AUGMENT: 5-year survival update

Rituximab + Lenalidomide in R/R FL and MZL





Median follow-up: 65.9 months

Leonard JP, et al. J Clin Oncol 2019;37:1188–99
Leonard JP, et al. Blood 2022;140(Suppl 1):561–3

MAGNIFY: efficacy for R-Lenalidomide induction

- Relapsed / refractory FL grade 1-3a and MZL
- Median of 2 prior therapies (94% prior rituximab-containing)

	ORR, n (%)	CR/CRu, n (%)	DOR, median (95% CI), mo	PFS, median (95% CI), mo*
All FL gr 1–3a + MZL, N = 394	279 (71)	164 (42)	NR (43.9–NR)	50.5 (39.4–NR)
Histology				
FL gr 1–3a, n = 318	230 (72)	134 (42)	NR (45.8–NR)	51.1 (38.7–NR)
MZL, n = 76	49 (64)	30 (39)	39.0 (29.4–NR)	41.2 (29.9–NR)
R-refractory				
Yes, n = 140	84 (60)	47 (34)	NR (34.7–NR)	27.4 (18.1–38.4)
No, n = 254	195 (77)	117 (46)	NR (43.9–NR)	NR (49.7–NR)
Double refractory				
Yes†, n = 85	43 (51)	21 (25)	27.4 (17.7–NR)	18.1 (15.5–25.9)
No, n = 309	236 (76)	143 (46)	NR (45.8–NR)	NR (41.6–NR)
Early relapse				
Yes‡, n = 133	86 (65)	43 (32)	37.0 (24.9–NR)	27.4 (20.3–41.6)
No, n = 261	193 (74)	121 (46)	NR (NR–NR)	NR (41.4–NR)

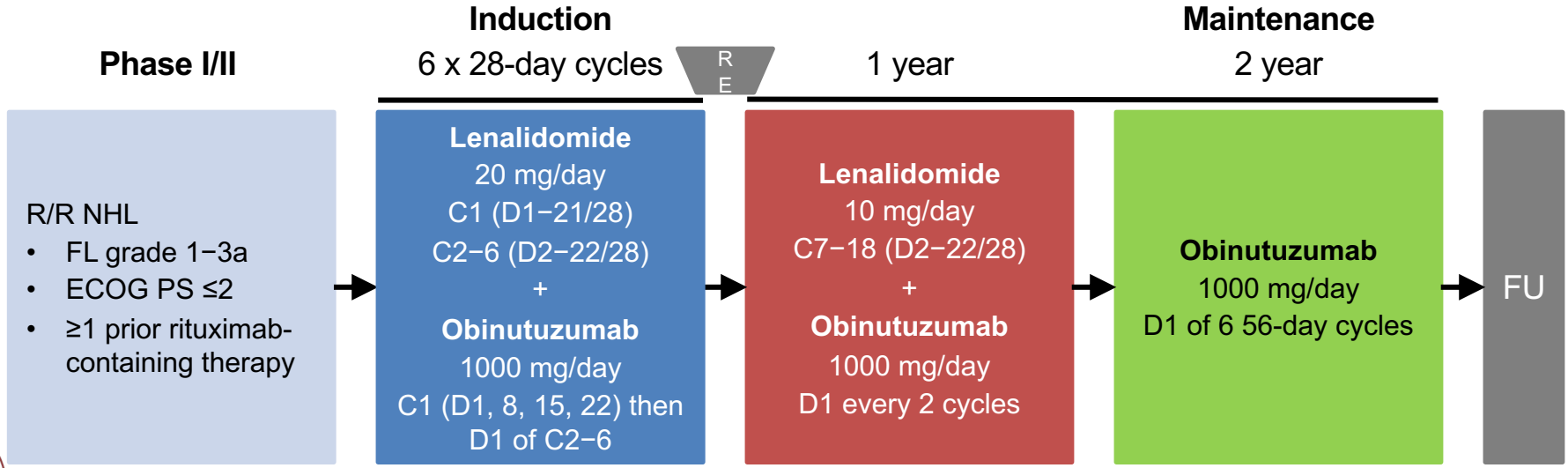
*If patients in maintenance at cutoff, response assessments also contributed to PFS.
†Refractory to both rituximab (monotherapy or combo) and alkylating agent.
‡Progressed or relapsed ≤ 2 y of initial diagnosis after 1L systemic treatment.

Lansigan F, et al. HemaSphere 2022; 6: 1043–4

GALEN study

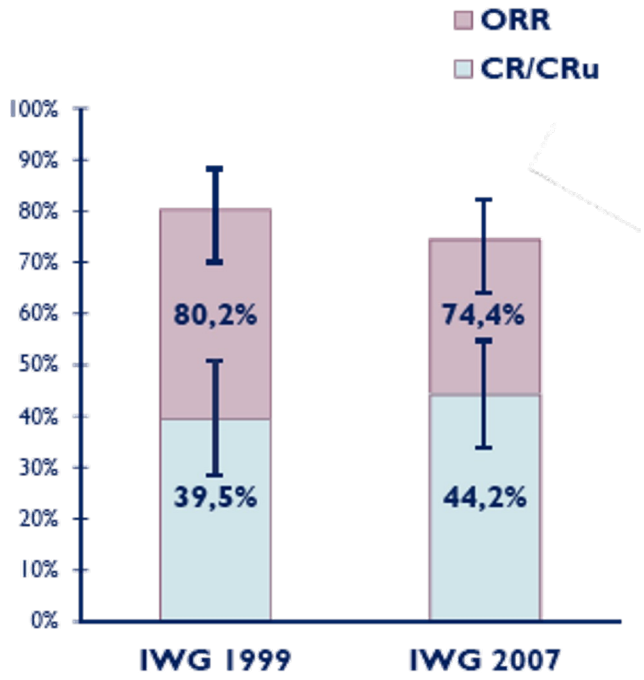
Lenalidomide + obinutuzumab in R/R FL

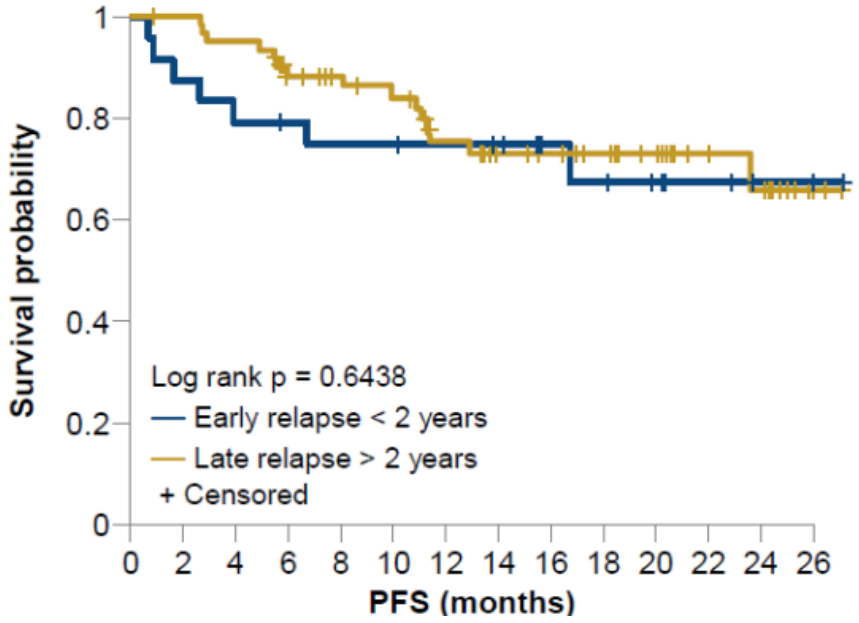
- Relapsed / refractory FL grade 1-3a
- ≥ 1 prior R-containing regimen (median 2, range 1-7)
  - Progression of disease within 24 mo. of 1st line start (POD24): 28%
  - Refractory to R-containing and / or last treatment: 27%



Morschhauser F, et al. Lancet Haematol 2019;6:e429–37

Towards a chemo-free regimen in R/R FL?

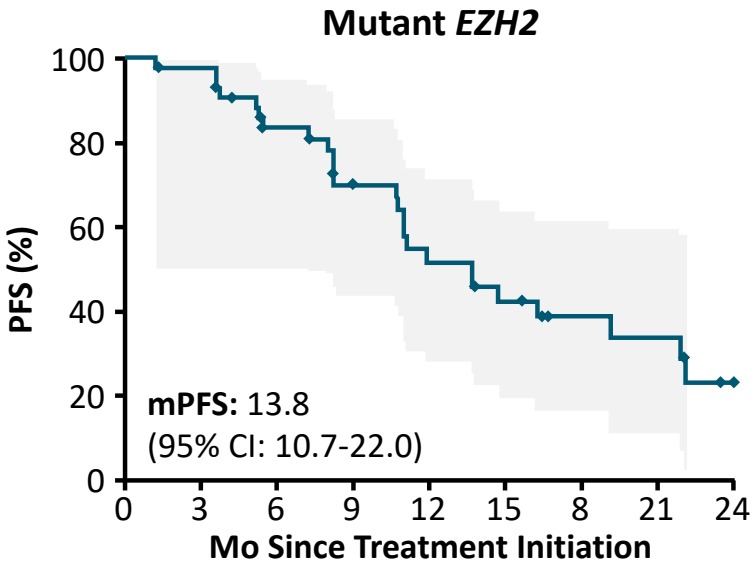




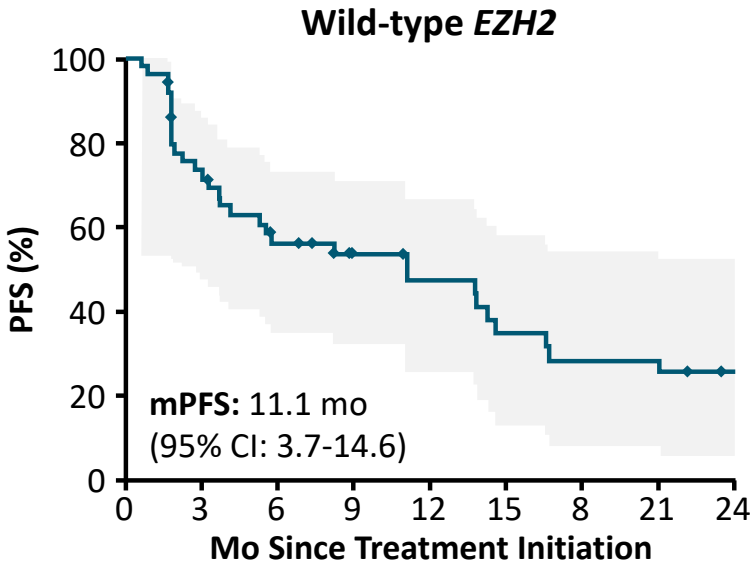
Median follow-up: 18.1 months

Morschhauser F, et al. Lancet Haematol 2019;6:e429–37

Efficacy of tazemetostat regardless of *EZH2* status



Patients at Risk, n (number censored)	45 (0)	43 (1)	32 (6)	24 (9)	17 (10)	13 (11)	8 (15)	7 (15)	3 (17)



Patients at Risk, n (number censored)	**54** (0)	**35** (6)	**24** (9)	**18** (14)	**15** (15)	**11** (15)	**9** (15)	**9** (15)	**2** (21)

Morschhauser F, et al. Lancet Oncol 2020;21:1433–42

Tazemetostat + R2

SYMPHONY-1 (phase 1b)

Median prior lines of therapies: 1 (1-4)
1 prior line: 68%

Response	Overall (n = 41)	*EZH2* WT (n = 33)	*EZH2* Mut (n = 7)	Rituximab Refractory (n = 14)	Rituximab Sensitive (n = 26)	POD24 (n = 11)	Non-POD24 (n = 30)
BOR, n (%)							
• ORR	40 (**97.6**)	32 (97.0)	7 (100)	14 (100)	25 (96.2)	11 (100)	29 (96.7)
• CR	21 (**51.2**)	15 (45.5)	5 (71.4)	7 (50.0)	13 (50)	4 (36.4)	17 (56.7)
• PR	19 (46.3)	17 (51.5)	2 (28.6)	7 (50.0)	12 (46.2)	7 (63.6)	12 (40.0)
• SD	1 (2.4)	1 (3.0)	0	0	1 (3.8)	0	1 (3.3)
PFS outcome	**(n = 44)**	**(n = 35)**	**(n = 7)**	**(n = 15)**	**(n = 28)**	**(n = 12)**	**(n = 32)**
Estimated 12-mo PFS, %	**84.8**	84.8	83.3	81.8	85.8	77.8	86.4

Median follow-up: 11.2 months

Batlevi CL, et al. Blood 2022;140(Suppl 1):2296–8

SYMPHONY-1 study update (ASH 2023)

Response	ITT (n = 44)	EZH2 WT (n = 36)	EZH2 Mut (n = 7)	Rituximab Refractory (n = 15)	POD24 (n = 12)
ORR, n (%)	40 (90.9) (55% CR)	32 (88.9)	7 (100)	14 (93.3)	11 (91.7)

- Median DoR: NR
  - 18-mo DoR (ITT): 81%
  - 18-mo DoR (800-mg cohort*): 100%
- Median PFS: NR
  - 18-mo PFS (ITT): 79.5%
  - 18-mo PFS (800-mg cohort*): 94.4%

Median follow-up: 22.5 mo. *n = 19.

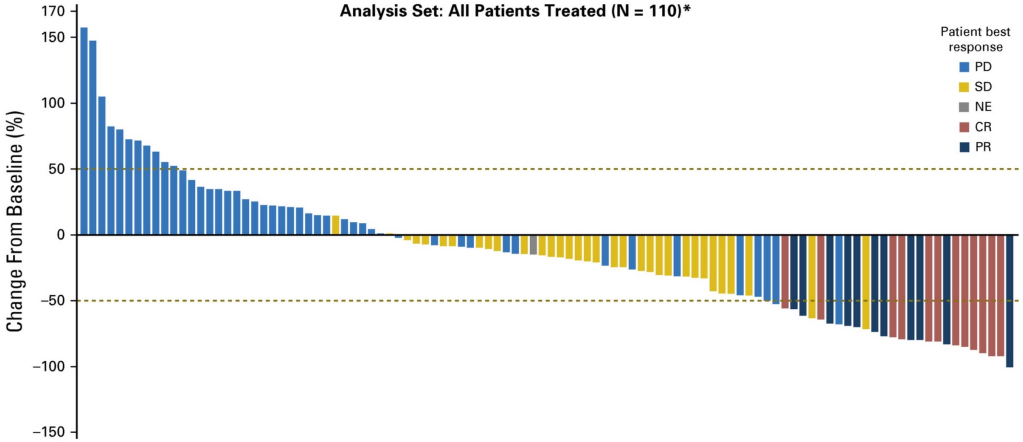
Salles G, et al. Blood 2023;142(Suppl 1):3035

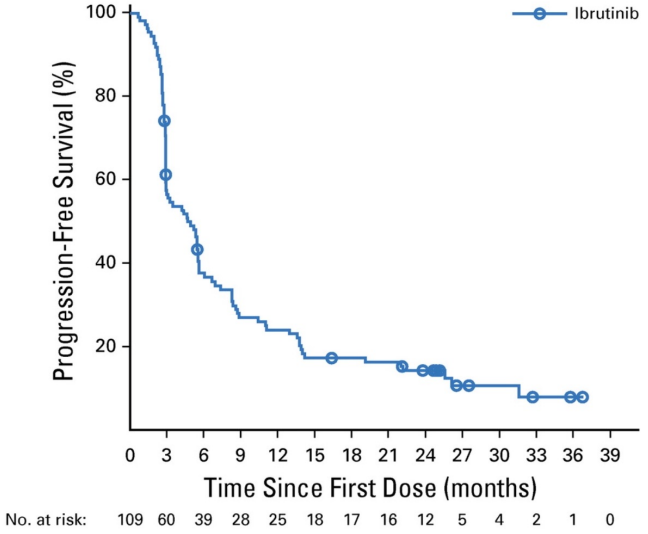
Ibrutinib in R/R FL: DAWN study

n=110

ORR: 20.9%, CR rate 11%

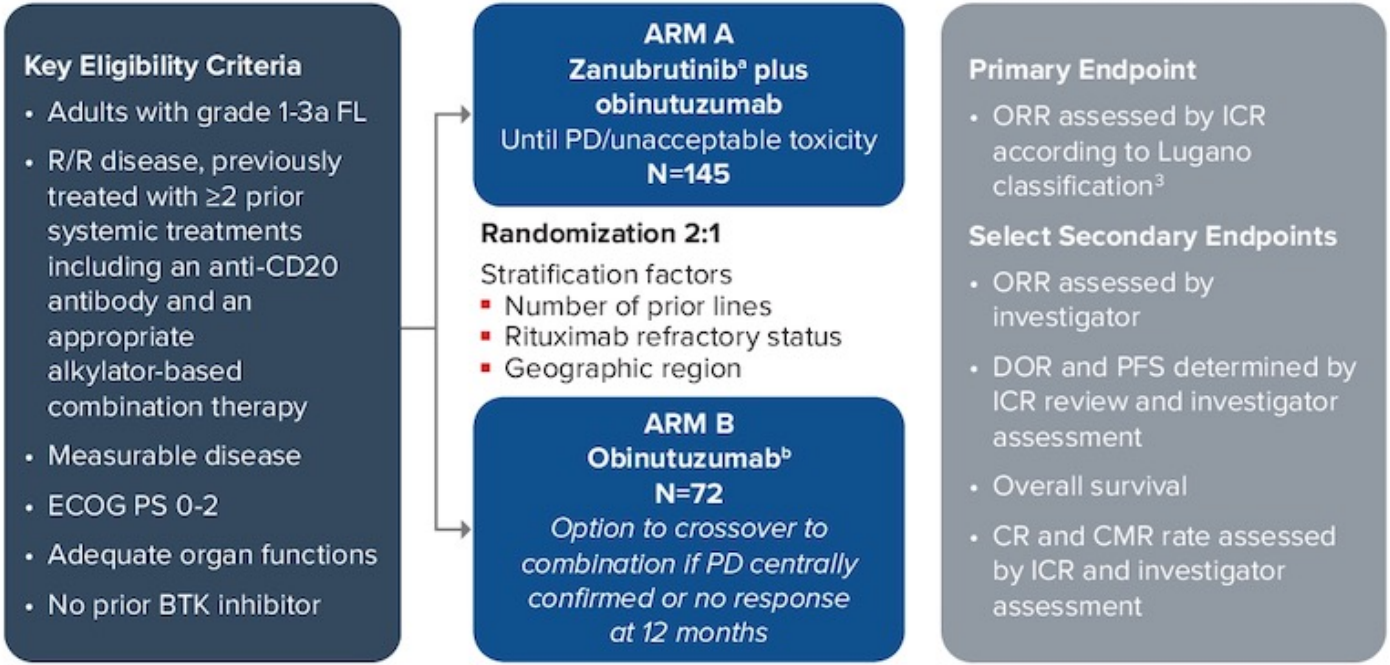
Median PFS: 4.6 months





Gopal AJ, et al. J Clin Oncol 2018;36:2405–12

ROSEWOOD trial: study design



ClinicalTrials.gov: NCT03332017

[a]Zanubrutinib was given orally at 160 mg twice a day; [b]Obinutuzumab (1000 mg) was given in both arms on days 1, 8, and 15 of cycle 1, day 1 of cycles 2-6, and then every 8 weeks up to 20 doses maximum.

Zinzani PL, et al. J Clin Oncol 2023;41:5107–19

ROSEWOOD trial: baseline characteristics

Characteristic	Zanubrutinib plus obinutuzumab N=145	Obinutuzumab N=72
Male sex, %	51.7	45.8
Median age, years (min, max)	63.0 (31, 84)	65.5 (32, 88)
FLIPI, %		
Low (0-1)	19.3	12.5
Intermediate (2)	24.8	33.3
High (≥3)	53.1	51.4
Missing	2.8	2.8
ECOG performance status ≥1, %	40.7	56.9
Bulky disease (≥5 cm), %	39.3	43.1
Elevated LDH, %	34.5	40.3
Elevated beta-2 microglobulin, %	44.8	51.4
Median prior lines of therapy, n (min, max)	3 (2, 11)	3 (2, 9)
Patients with >3 lines of therapy, %	28.3	25.0
Patients refractory to rituximab, %	53.8	50.0
Patients refractory to the most recent line of therapy, %	32.4	40.3
Patients with PD within 24 months of starting the first line of therapy, %	34.5	41.7

Zinzani PL, et al. J Clin Oncol 2023;41:5107–19

ROSEWOOD

Zanubrutinib + Obinutuzumab in R/R FL

n=217

ORR: 69% vs. 46%

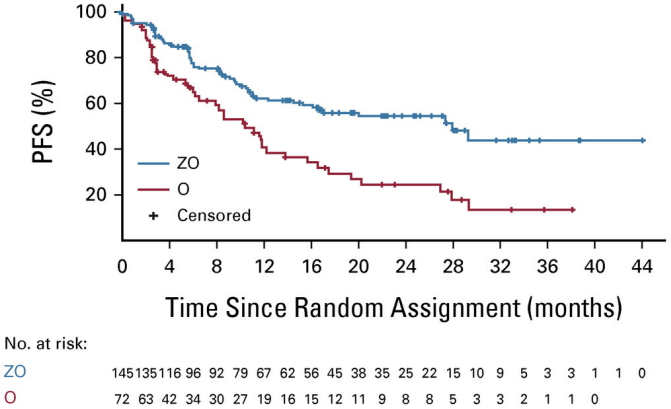
CRR: 39% vs. 19%

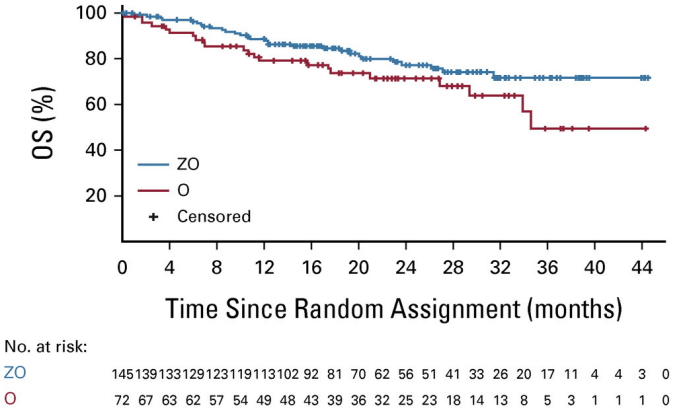
Median PFS: 28 vs. 10 months

- HR 0.50 (0.33 to 0.75), p<0.001

Median TTNT: NE vs. 12 months

- HR 0.34 (0.22 to 0.52), p<0.001





Zinzani PL, et al. J Clin Oncol 2023;41:5107–19

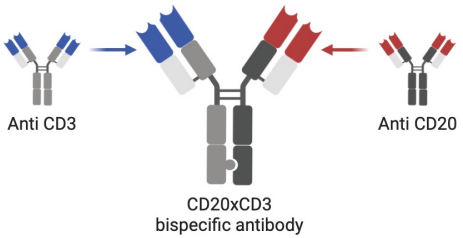
ROSEWOOD trial: safety analysis

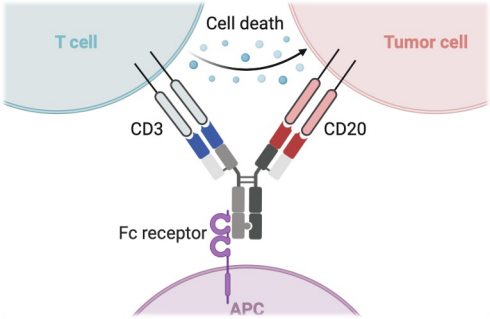
	Zanubrutinib/Obinutuzumab		Obinutuzumab	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Infections	47.6%	18.9%	36.6%	12.7%
Thrombocytopenia	34.3%	14%	23.9%	7%
Neutropenia	27.3%	22.4%	25.4%	19.7%
Hemorrhage	26.6%	1.4%	8.5%	0
Major bleeding	1.4%	1.4%	1.4%	0
Hypertension	3.5%	0.7%	4.2%	1.4%
Atrial fibrillation and flutter	2.1%	0.7%	1.4%	0

Zinzani PL, et al. J Clin Oncol 2023;41:5107–19)

T-cell engaging bispecific (TCEB) antibodies

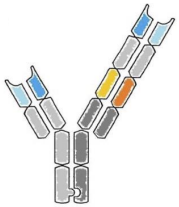
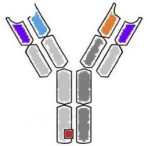
- Effector target: CD3 on T-cells
- Tumor target: B cell-specific (CD19, CD20, CD22) or plasma cell-specific (BCMA, GPRC5D, FcRH5) antigens [FcγR- and MHC-independent]
- Full length antibody
- Fc modifications and silencing; retains binding to neonatal Fc receptor
- Long half-life





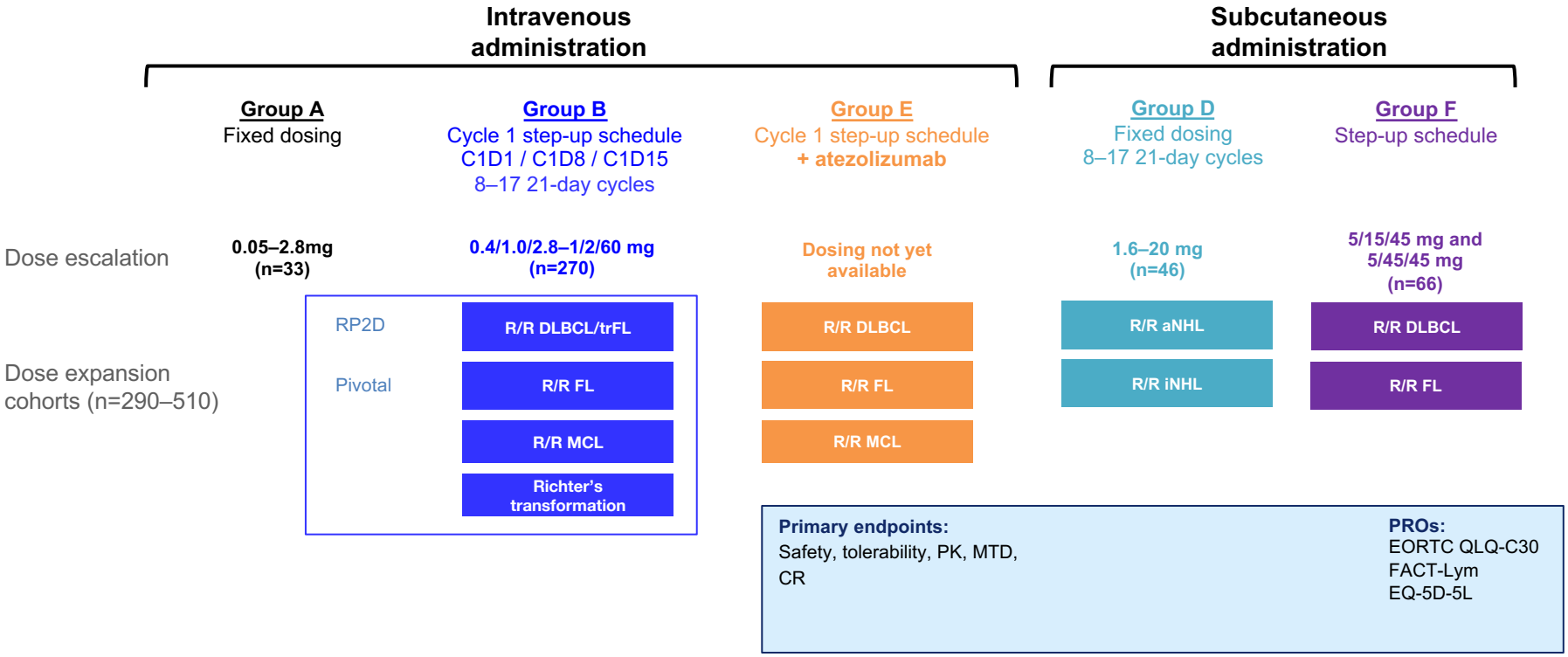
Created in BioRender.com

CD20 × CD3 biespecifics: structure and function

Biespecific	Mosunetuzumab	Glofitamab	Epcoritamab	Odronextamab	Plamotamab
					
Status	Approved for FL 3L+	Approved for LBCL 3L+	Approved for LBCL 3L+	Investigational	Investigational
Format	IgG1	IgG1	IgG1	IgG4	IgG1
Technology	Knobs into holes (different Fabs)	Head-to-tail fusion	Controlled Fab-arm exchange	Heavy chains with different affinity	Fab-Fc x scFv-Fc
CD20:CD3 ratio	1:1	2:1	1:1	1:1	1:1
CD20 clone	Type 1 epitope, identical to rituximab	Type 2 epitope, identical to obinutuzumab	Type 1 epitope, shared by ofatumomab	Type 1 epitope, shared by ofatumomab	Type 1 epitope, shared by rituximab

Lussana F, et al. J Clin Oncol 2021;39:444–55
Falchi L, et al. Blood 2023;141:467–80

Mosunetuzumab: GO29781 study



NCT02500407

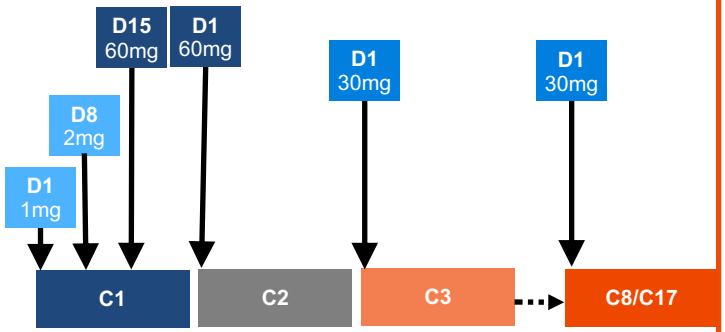
Mosunetuzumab: pivotal phase 2 study design

Key inclusion criteria

- R/R FL (Grade 1–3a)
- ≥2 prior therapies, including an anti-CD20 antibody and an alkylating agent
- ECOG PS 0–1

Mosunetuzumab administration

- IV mosunetuzumab (21-day cycles) with step-up dosing in C1
- Hospitalisation for monitoring following mosunetuzumab infusion not required
- **Fixed-duration treatment**: 8 cycles (CR after C8) / 17 cycles (PR/SD after C8)*
- As of July 8, 2022, 90 pts had received ≥1 dose of mosunetuzumab



Data analysis

- **Primary endpoint:** IRC-determined CR rate (as best response), by Cheson 2007 criteria[1]
- CRS graded using ASTCT criteria[2]
- Exploratory analyses assessed the association between TMTV at baseline, and clinical efficacy and safety
- TMTV derived from PET images at study entry using artificial intelligence-based model[3]

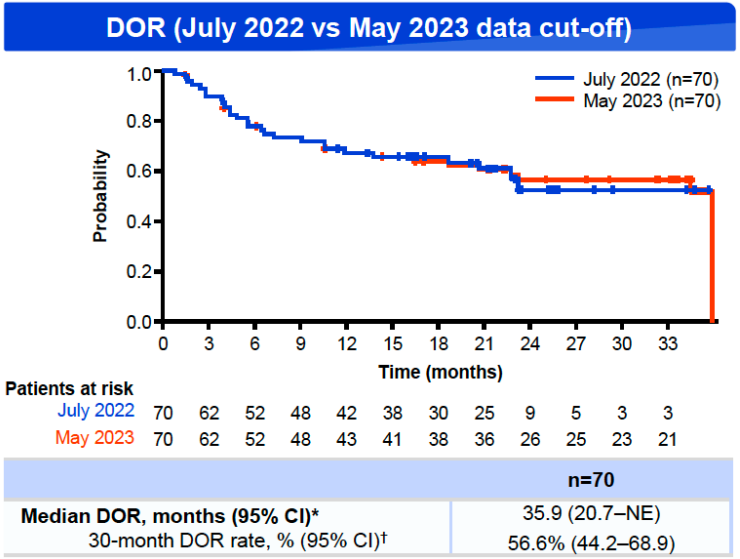
*Premedication with corticosteroids (IV dexamethasone 20mg or IV methylprednisolone 80mg) was administered 1 hour before each dose of mosunetuzumab in C1 and C2 and was optional from C3 onwards.

ASTCT, American Society for Transplantation and Cellular Therapy; C, cycle; CRS, cytokine release syndrome; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; IV, intravenous; PR, partial response; Pts, patients; PET, positron emission tomography; SD, stable disease; TMTV, total metabolic tumour volume.

1. Cheson BD, et al. J Clin Oncol 2007;25:579–86
2. Lee DW, et al. BBMT 2019;25:625–638
3. Jemaa S, et al. Cancer Imaging 2022;22:39

Mosunetuzumab in 3L+ follicular lymphoma

	RP2D (1/2/60/30 mg) n=90
Median age, years (range)	60 (29-90)
Prior LoT, median Refractory to last therapy Prior ASCT Prior CAR T-cell therapy	3 (2-10) 62 (69%) 28 (31%) 3 (3%)
ORR, % (95% CI) CR	78 (68-86) 60 (49-70)
CRS, all grades CRS G3+ Neurotoxicity, all grades ICANS G3+ Neutropenia G3+	44.4% 2.2% 4.4% 0 26.7%



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

Estimated 30-month DOCR rate was 72.7% (95%CI:60-8-86.9)

Budde LE, et al. Lancet Oncol 2022;23:1055–65
Schuster SJ, et al. Blood 2023;142(Suppl 1):603

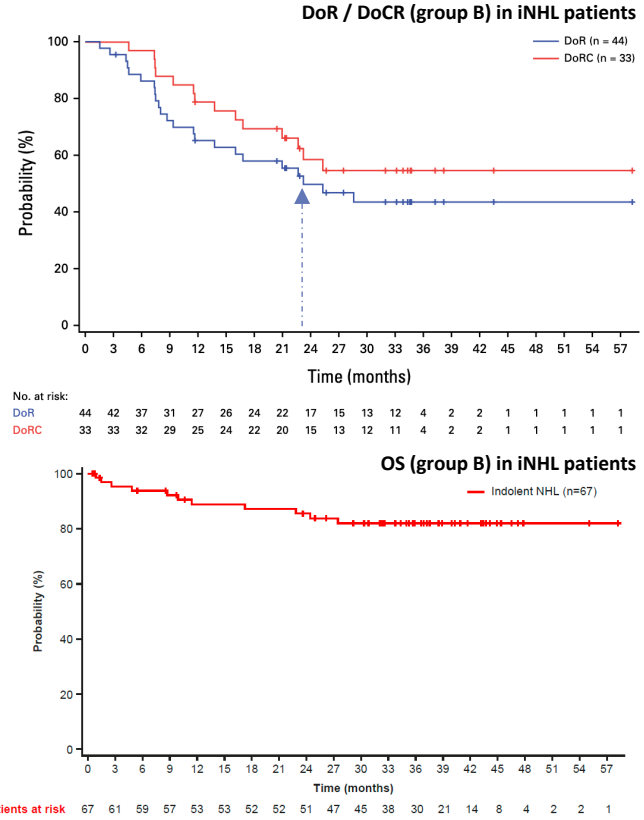
GO29781 (group B): outcomes (dose-escalation)

Patients	**129 aNHL** (79 DLBCL, 29 tFL, 13 MCL)	**67 iNHL** (64 FL)
Median age, years (range)	64 (19-91)	60 (27-85)
Prior LoT, median	3 (1-14)	3 (1-9)
Refractory to any therapy	124 (96%)	59 (88%)
Refractory to last therapy	113 (88%)	50 (75%)
Prior ASCT	33 (26%)	9 (13%)
Prior CAR T-cell	15 (12%)	4 (6%)
ORR | CRR (*)	36.4% | 21.7%	65.7% | 49.3%
Prior CART ORR | CR	36.8% | 26.3%	
CRS (ASTCT), all grades	26.4%	19.4%
CRS G3+	1%	
Neurotoxicity G3+	1%	
Neutropenia G3+	25.4%	

Median follow-up: 3.5 years

(*) Cheson 2007 response criteria

NCT02500407



Budde E, et al. J Clin Oncol 2022;40:481–91

Budde E, et al. J Clin Oncol 2024. doi: 10.1200/JCO.23.02329

Characteristics of patients who achieved a CR at EOT

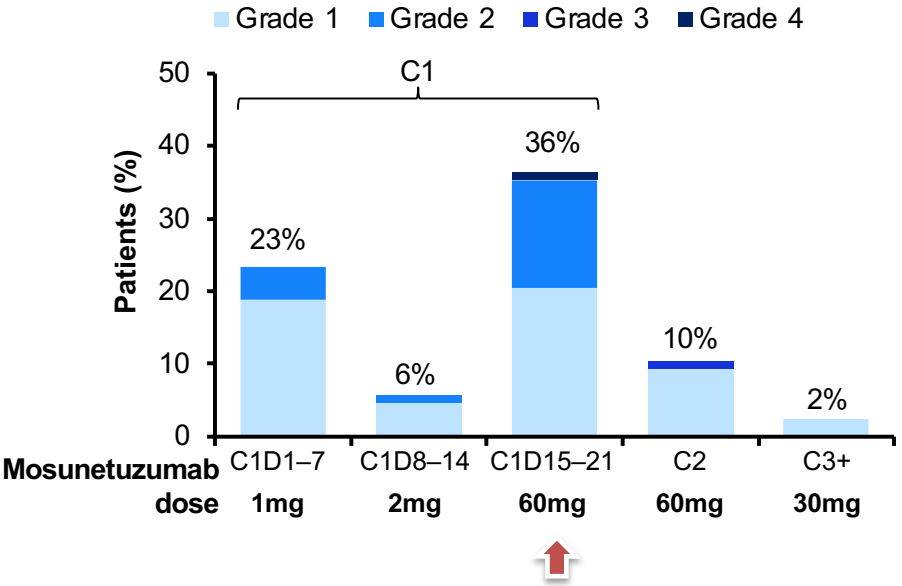
	Patients with CR at EOT n=49	Patients without CR at EOT n=41	All patients N=90
Median age, years (range)	63 (29–90)	59 (35–83)	60 (29–90)
Female, %	47	29	39
ECOG PS, %			
0	61	56	59
1	39	44	41
Ann Arbor stage, %			
I/II	18	29	23
III/IV	82	71	77
Median lines of prior therapy, n (range)	3 (2–10)	3 (2–7)	3 (2–10)
Refractory to last prior therapy, %	55	85	69
Refractory to prior anti-CD20 therapy, %	71	88	79
Double refractory*, %	41	68	53
POD24, %	53	51	52
Prior autologous stem cell transplant, %	22	20	21
Prior bendamustine, %	59	73	66

Sehn LH, et al. Hematol Oncol 2023;41(suppl 2):122-125

Mosunetuzumab in FL: CRS summary

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

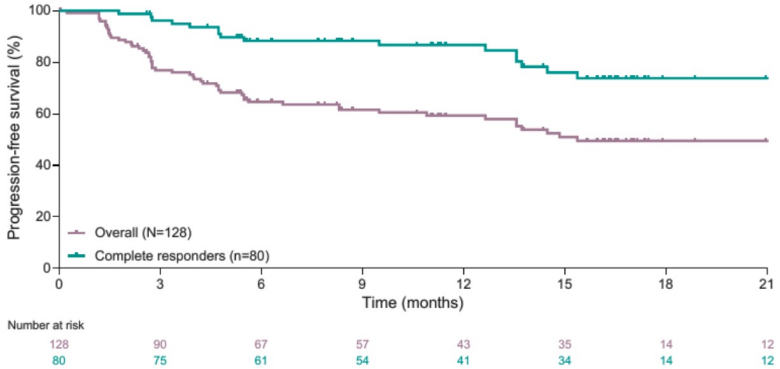
CRS by cycle and grade



Bartlett NL, et al. Blood 2022;140(Suppl 1):1467–70

Epcoritamab in 3L+ follicular lymphoma

	(0.16/0.8/48 mg) n=128
Median age, years (range)	64 (39-84)
Prior LoT, median Refractory to last therapy Primary refractory Double refractory	3 (2-9) 88 (69%) 69 (54%) 90 (70%)
ORR, % CR	82 63
CRS, all grades CRS G3+ Neurotoxicity, all grades ICANS G3+ Neutropenia G3+	66% 2% 6.25% 0 26%



Median PFS: 15.4 mo (95%CI: 10.9-NR)

Linton KM, et al. Blood 2023;142(Suppl 1):1655

EPCORE-NHL-2, arm 2b

Epcoritamab + R2 in R/R FL

A phase 1b/2, open-label trial evaluating the safety and antitumor activity of epcoritamab + R² in adults with R/R FL[a]

Key inclusion criteria

- R/R CD20⁺ FL
  - Grade 1, 2, or 3A
  - Stage II–IV
- Need for treatment based on symptoms or disease burden, as determined by GELF criteria[1]
- ECOG PS 0–2
- Measurable disease by CT or MRI
- Adequate organ function

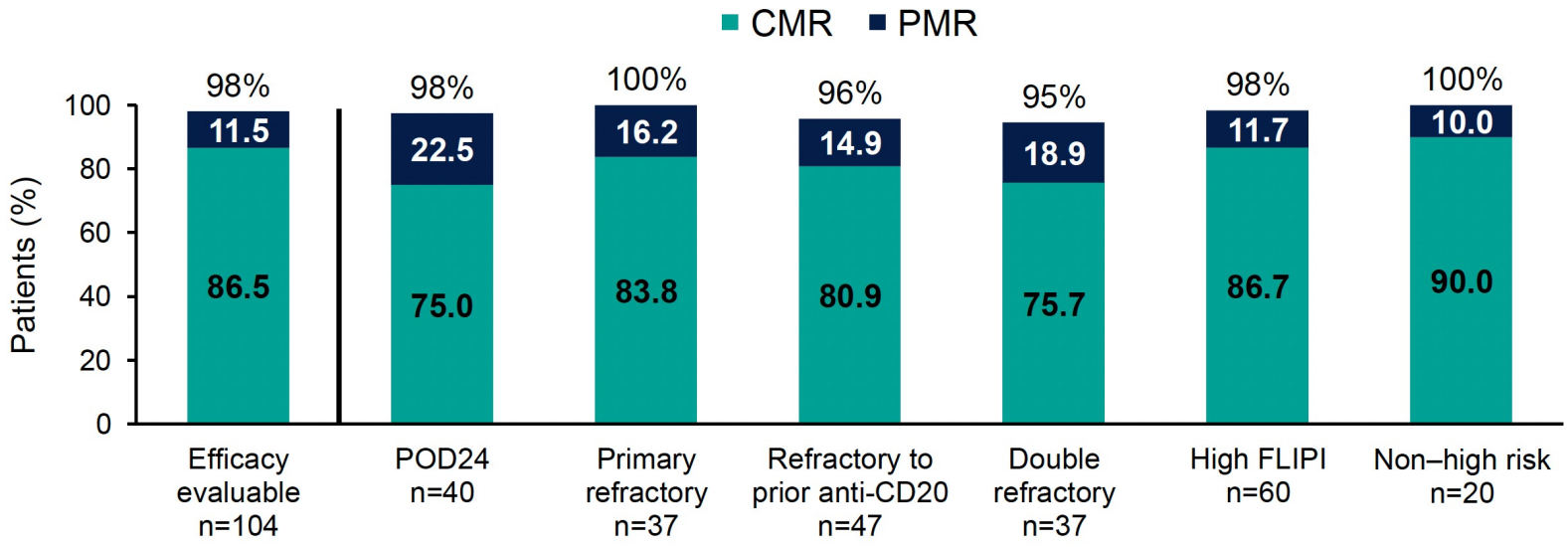
Data cutoff: September 16, 2022
Median follow-up: 6.4 mo

		Treatment Regimen Epcoritamab SC 48 mg + R²						
	Agent	**C1**	**C2**	**C3**	**C4**	**C5**	**C6–C12**	**C13+**
	Epcoritamab SC 48 mg	QW	QW	Q4W	Q4W	Q4W	Q4W	Q4W Up to 2 years
R²	Rituximab IV 375 mg/m²	QW	Q4W	Q4W	Q4W	Q4W		
R²	Lenalidomide oral 20 mg	Daily for 21 d (for 12 cycles)						

Primary objective: Safety and antitumor activity[b]

Belada D, et al. Hematol Oncol 2023;41(Suppl S2):125–7

Epcoritamab + R2 in R/R FL (EPCORE-NHL-2)



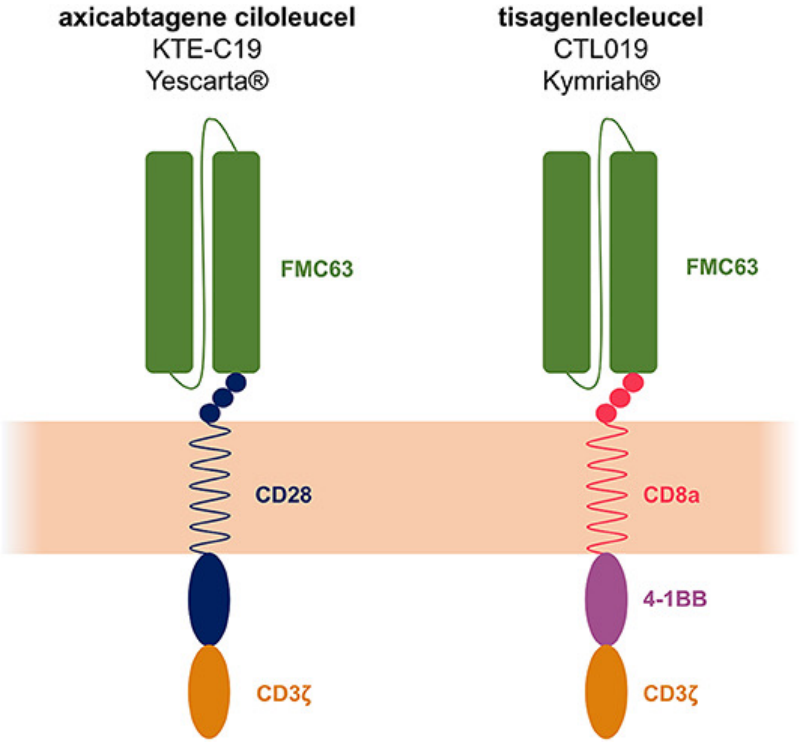
High overall response and CMR rates regardless of subgroup

Data cutoff: January 31, 2023. Median follow-up: 11.4 mo (range, 2.1–22.1). Definitions for all subgroups available in Study Design and Patient Disposition.

Belada D, et al. Hematol Oncol 2023;41(Suppl S2):125–7

CD19 CAR T-cells in R/R FL patients after ≥2 prior lines of therapy

ZUMA-5 **Axicabtagene ciloleucel**
FL (127) / MZL (31)
Anti–CD19-**CD28**-CD3z 2 x 10^6/kg (max 2 x 10^8)
Flu/Cy **30/500** mg/m^2 x 3 days
Patients apheresed / infused 153 / 148
Bridging 100%
Primary end-point: ORR (IRC)
Median prior LoT **3 (1-10)**



ELARA **Tisagenlecleucel**
FL (98)
Anti–CD19-**41BB**-CD3z 0.6-6.0 x 10^8/kg
Flu/Cy **25/250** mg/m^2 x 3 days, or **bendamustine x 2 days**
Patients apheresed / infused 98 / 97
Optional bridging
Primary end-point: CRR (IRC)
Median prior LoT **4 (2-13)**

Cerrano M, et al. Front Immunol 2020;11:888
Jacobson CA, et al. Lancet Oncol 2022;23:91–103
Fowler NH, et al. Nat Med 2022;28:325–32

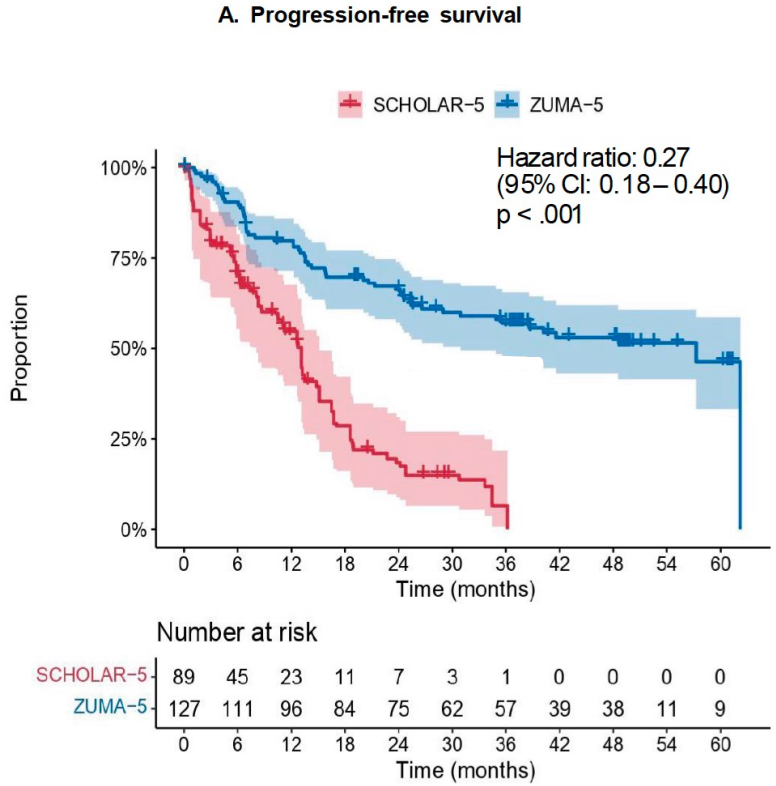
Outcomes of CD19 CART-cells in 3L+ FL patients

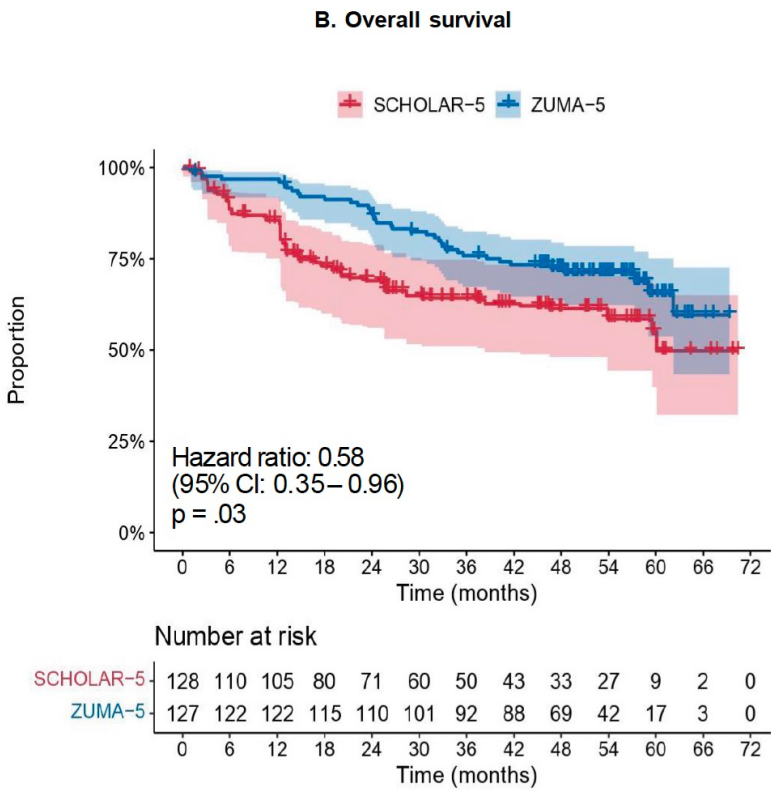
	ZUMA-5[1]	ELARA[2]
ORR	94%	84%
CRR	79%	66%
DoR median, months	39	NR
3-year	57%	63%
DoCR median, months	NR	NR
3-year	62%	73%
PFS median, months	40	37
3-year	54%	53%
OS median, months	NR	NR
3-year	76%	82%

Median follow-up: 41 months
NR: Not reached

1. Neelapu SS, et al. Blood 2024;143:496–506
2. Schuster SJ, et al. Blood 2023;142(Suppl 1):601

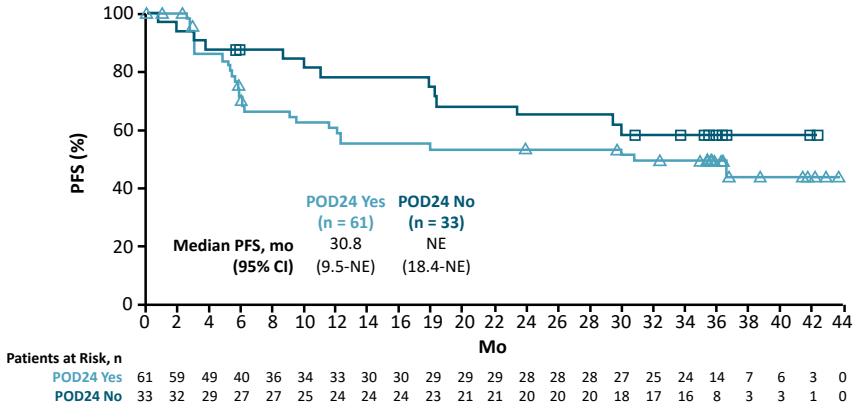
ZUMA-5 vs. SCHOLAR-5 in 3L+ FL patients (updated comparison at 4-year follow-up)

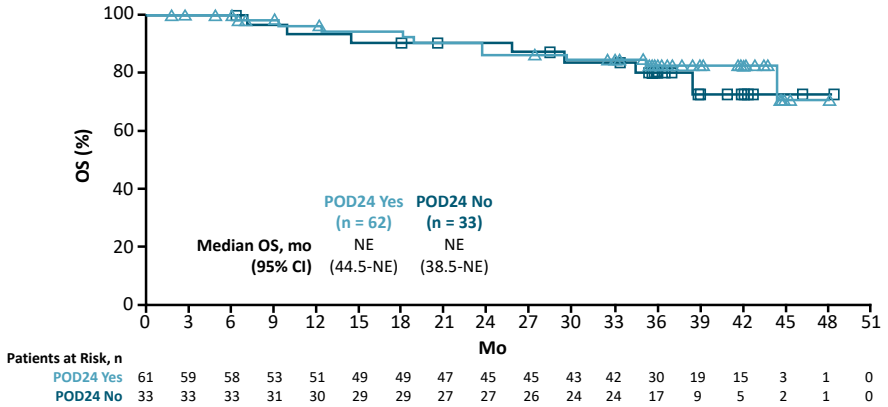




Gribben JG, et al. Blood 2023;142(Suppl 1):4869

ELARA: time-to-event outcomes by POD24 status





<u>36-month PFS in POD24</u>:

50% (95%CI, 35.8-61.9) vs. 59% (95% CI, 39.5-73.5)

<u>36-month OS in POD24</u>:

83% (95%CI, 69.1-90.5) vs. 80% (95% CI, 60.9-90.6)

Median follow-up: 41 months

Schuster SJ, et al. Blood 2023;142(Suppl 1):601

Considerations in choosing between CAR T-cells and bispecifics

CAR T-cells	Bispecifics
Excellent efficacy with longer follow up	Excellent efficacy, but shorter follow up
Requires 3-4 weeks of manufacturing	Off the shelf
Logistically more complex	Logistically less complex
“One and done”	8-17 cycles (mosun) or continuous (epco)
Needs lymphodepleting chemo	No lymphodepleting chemo
Higher risk of CRS and neurotoxicity (tisa-cel better than axi-cel), and cytopenias	Lower risk of CRS, neurotoxicity, and cytopenias
Usually inpatient	Usually outpatient

Ongoing phase 3 clinical trials in R/R FL

Study	N	Arms	Key eligibility criteria	Primary endpoint	Primary completion
CELESTIMO NCT04712097	400	• **Mosunetuzumab** + Lenalidomide • R2	LF grade 1-3a ≥1L, need of treatment	PFS	2025
EPCORE FL-1 NCT05409066	500	• **Epcoritamab** + R2 • R2	LF grade 1-3a ≥1L	PFS	2026
MAHOGANY NCT05100862	750	• **Zanubrutinib** + Obinutuzumab • R2	LF grade 1-3a ≥1L, need of treatment	PFS	2029
SYMPHONY-1 NCT04224493	540	• **Tazemetostat** + R2 • Placebo + R2	LF grade 1-3a ≥1L	PFS	2029
ZUMA-22 NCT05371093	230	• **Axi-cel** • SOC (R2, R-CHOP or BR)	LF grade 1-3a ≥2L or ≥1L POD24, need of treatment	PFS	2029
LEDA NCT05888493	108	• **Tisa-cel** • SOC (R2 or R-CHOP)	LF grade 1-3a ≥2L, need of treatment	PFS	2029

Conclusions

- Multiple effective therapies are now available for R/R FL patients, even in the third-line setting
- Treatment sequencing is still being optimized, but chemotherapy-free options are increasingly preferred
- Mosunetuzumab exhibits a high CR rate at EOT, long-lasting response, and predominantly low-grade and predictable CRS
- Ongoing clinical trials are paving the way for the best treatment sequence, potentially revolutionizing FL therapy in coming years

Acknowledgments

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