Stefano Luminari

Il paziente giovane con Linfoma Follicolare ricaduto/refrattario: CAR-T vs bispecifici CONS CART

Ematologia, Azienda USL IRCCS di Reggio Emilia

Università di Modena e Reggio Emilia

Disclosures of Stefano Luminari

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche						x	
Beigene	x					x	
Incyte						x	
Kite						x	
Novartis						x	
Abbvie			x			x	
BMS						x	
Regeneron			x			x	

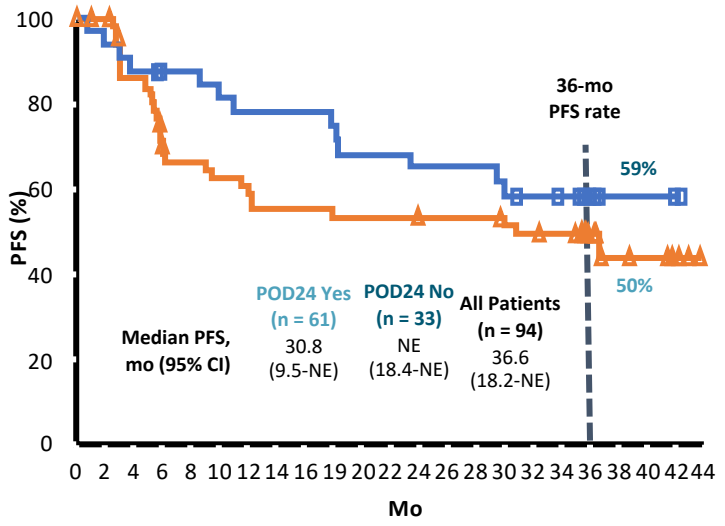
Efficacy and Safety of Patients With R/R FL Receiving Tisacel (ELARA), Axicel (ZUMA-5) or Lisocel (TRANSCEND FL)

ELARA

Characteristics	Patients (N=97)
Median age, years, (range)	57 (49–64)
Median prior lines, n (range)	4 (2–13)
Refractory to last line of therapy, n (%)	76 (78.4)
Prior HSCT, n (%)	35 (36.1)

TEAEs of Interest	Tisa-cel
Grades ≥3 CRS, %[a]	0
Grades ≥3 neurological toxicity, n (%)	3 (3.1)

ORR: 86%
CRR: 69%



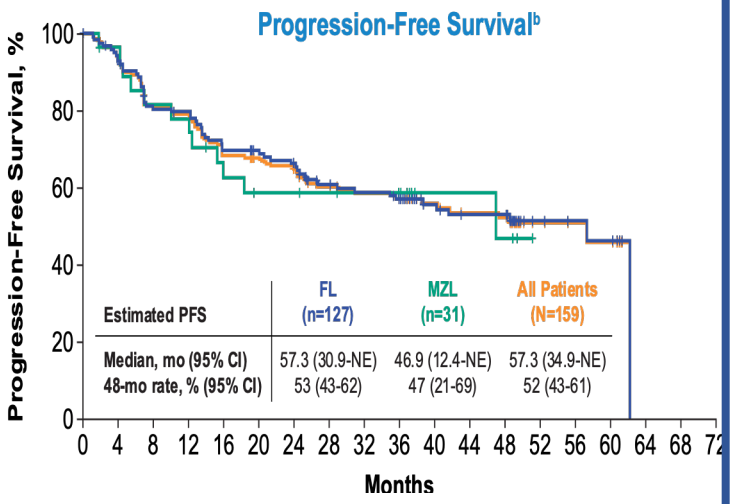
Schuster. ASH 2023. Abstr 601.

ZUMA5

Characteristics	Patients (N=148)
Median age, years (range)	60 (53–67)
Median prior lines, n (range)	3 (2–4)
Refractory disease, n (%)	84 (68)
Prior HSCT, n (%)	33 (22)

TEAEs of interest	Axi-cel
Grades ≥3 CRS, n (%)[a]	8 (6)
Grades ≥3 neurological toxicity, n (%)	19 (15)

ORR: 94%
CRR: 79%



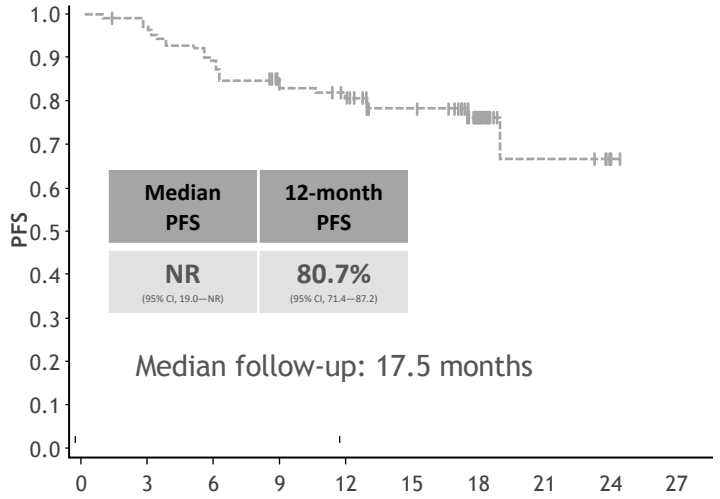
Neelapu. ASH 2023..

TRANSCEND FL

Characteristics	Patients (N=107)
Median age, years (range)	62 (23- 80)
Median prior lines, n (range)	3 (2–10)
Refractory disease, n (%)	69(74)
Prior HSCT, n (%)	33 (31)

TEAEs of interest	Axi-cel
Grades ≥3 CRS, n (%)[a]	1 (1)
Grades ≥3 neurological toxicity, n (%)	2 (2)

ORR: 97%
CRR: 94%



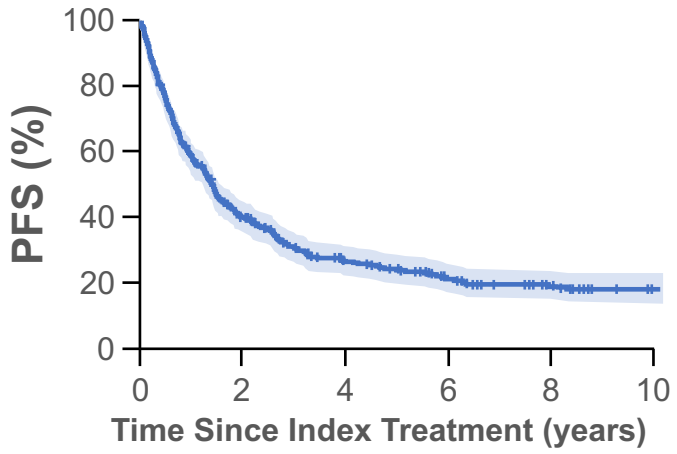
Morschauser et al ASH 2023.

High Heterogeneity of Treatment and Poor Outcomes in 3L R/R FL

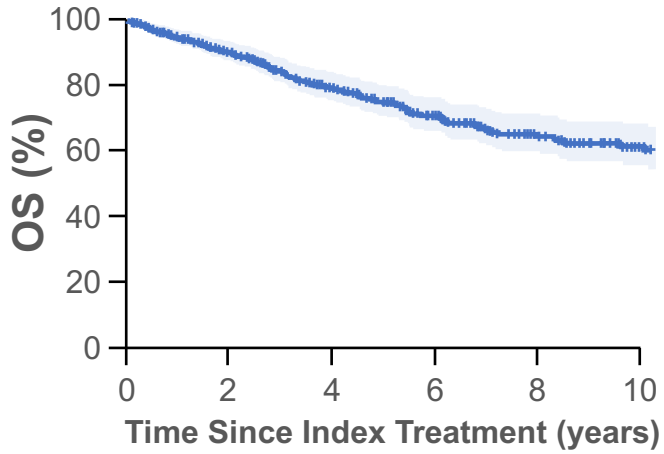
Administered Therapies as 3L

Immuno-chemotherapy	30%
BR	18%
R-CHOP	9%
R-CVP	2%
Other	2%
SCT	21%
Len ± R	8%
PI3K inhibitor ± R	6%
Off label	9%
Other	14%
Clinical trial	23%

- **ORR 70%; CRR 47%**



mPFS: 17 mo (15–19)



mOS: NA

Adverse Prognostic Factors for 5-Year OS (Univariate)

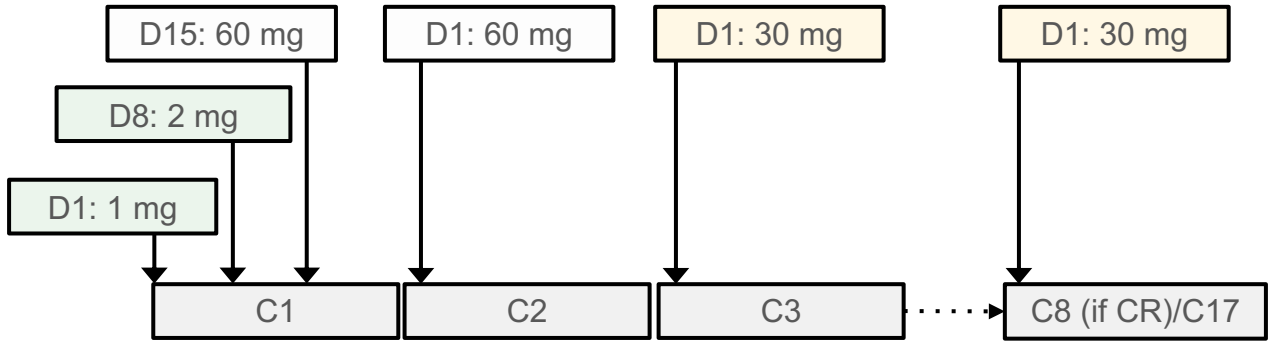
Age ≥60 years	HR 2.17 (1.5–3.15)
GELF criteria	HR 1.46 (1.01–2.13)
FLIPI 3–5	HR 2.09 (1.19–3.67)
<36 months from diagnosis	HR 1.89 (1.31–2.72)
Refractory to alkylating agent	HR 1.60 (1.04–2.46)

3L, 3rd-line; FL, follicular lymphoma; FLIPI, Follicular lymphoma international prognostic index; GELF, Groupe d'Etude des Lymphomes Folliculaires; HR, hazard ratio; Len, lenalidomide; mOS, median OS; mPFS, median PFS; NA, not available; OS, overall survival; ORR, overall response rate; PI3K, phosphoinositide 3-kinase; PFS, progression-free survival; POD24, progression of disease within 24 months; R, rituximab; R-CHOP, rituximab + cyclophosphamide + doxorubicin hydrochloride + vincristine + prednisolone; R-CVP, rituximab + cyclophosphamide + vincristine + prednisolone; R/R, relapsed/refractory; SCT, stem cell transplant. Adapted from Casulo C, et al. *Lancet Haematol*. 2022;9(4):e289-e300.

Three BsAbs available (EU) in RR FL

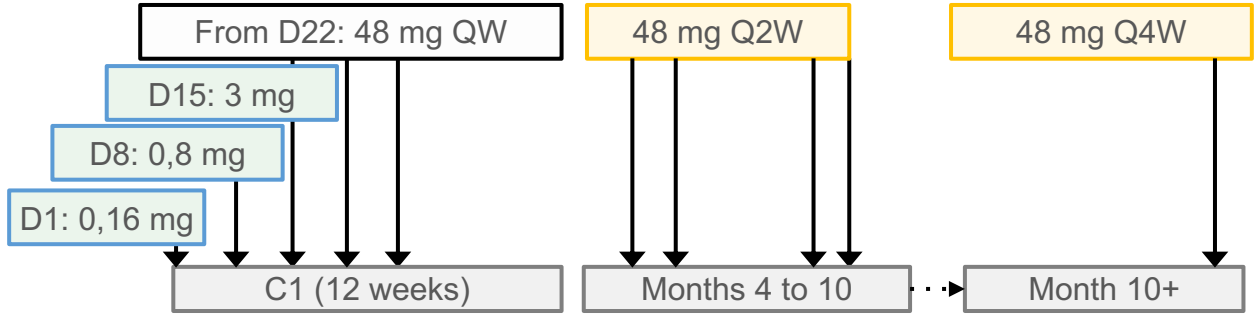
Mosunetuzumab

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



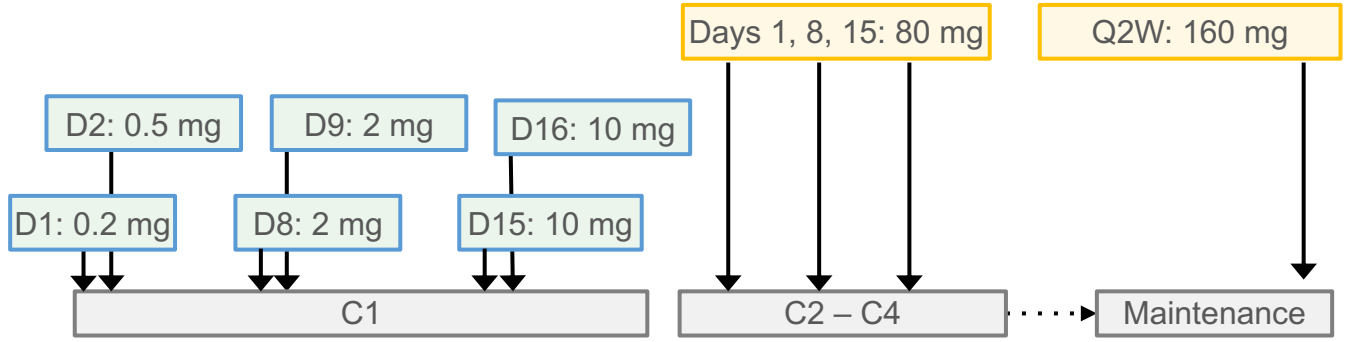
Epcoritamab

- 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



BsAb, bispecific antibody; C, cycle; CRS, cytokine release syndrome; D, day; FL, follicular lymphoma; IV, intravenous; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, every week; SC, subcutaneous.

Adapted from: 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.

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

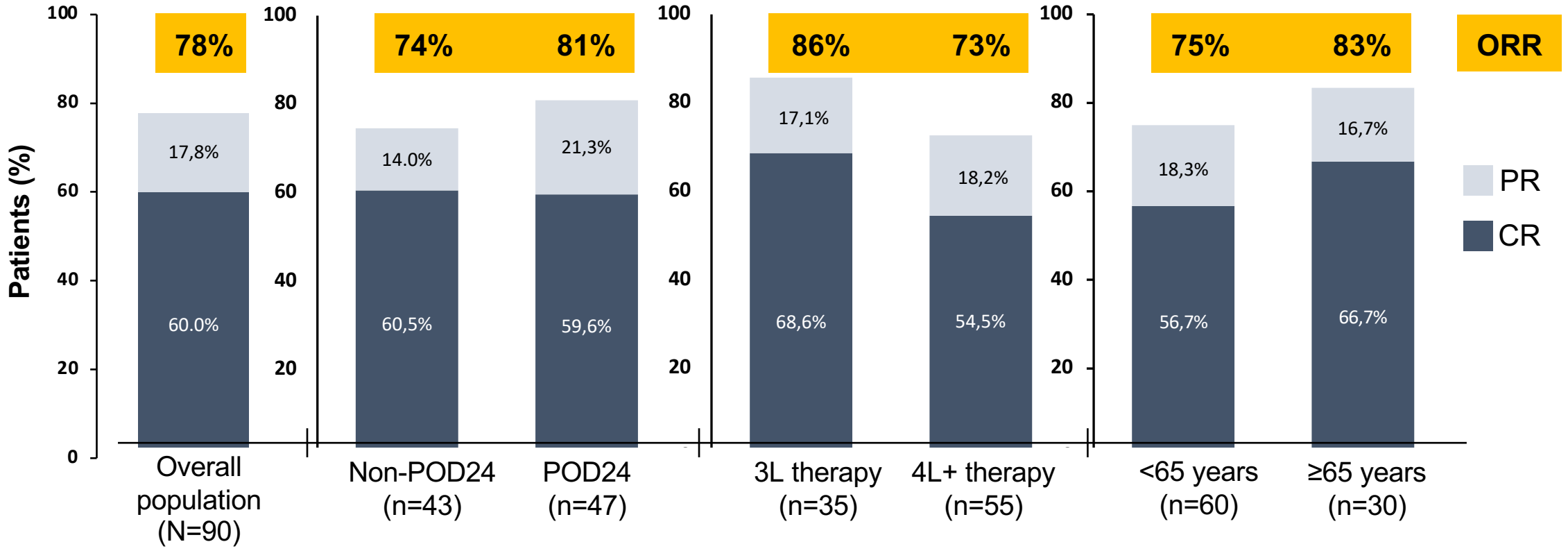
Fixed Duration

	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). 15.6%

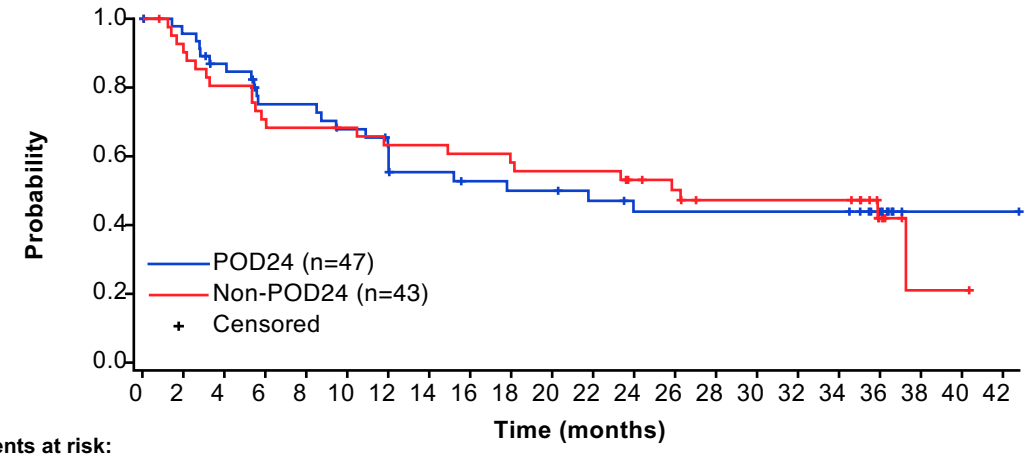
Efficacy summary: response rates (mosunetuzumab)



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

PFS and OS: non-POD24 versus POD24 (mosunetuzumab)

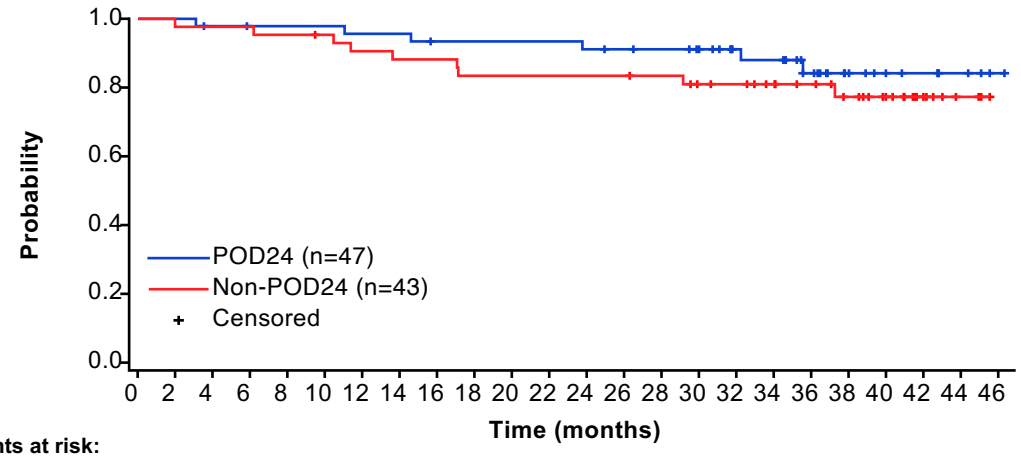
PFS



Patients at risk:

POD24	47	44	38	31	31	28	22	21	19	18	18	16	14	14	14	14	14	14	10	1	1	1
Non-POD24	43	37	33	29	28	27	25	25	24	23	22	22	19	17	14	14	14	14	6	1	1	NE

OS



Patients at risk:

POD24	47	47	45	44	44	44	43	43	41	41	41	41	40	39	38	35	29	28	21	14	10	8	4	1
Non-POD24	43	42	42	42	41	40	38	37	37	35	35	35	35	35	34	31	30	27	24	20	15	8	3	NE

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

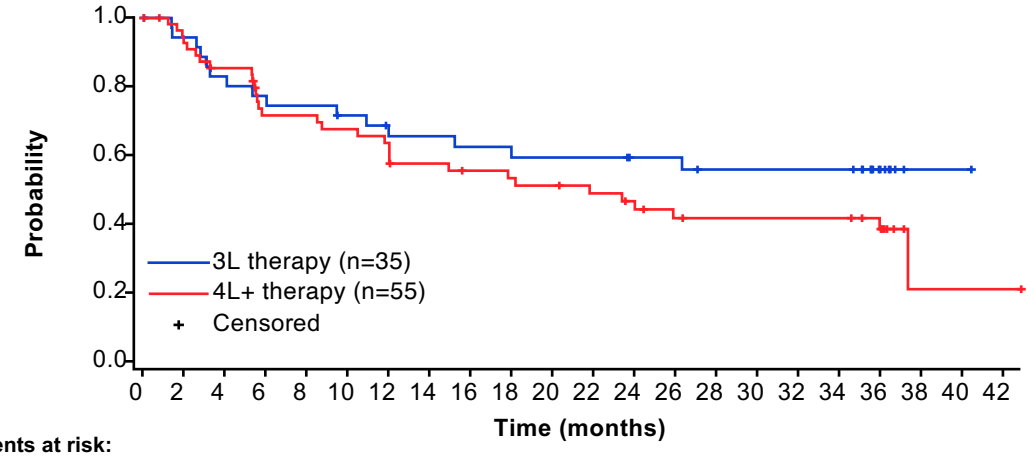
	Overall population (N=90)	Non-POD24 (n=43)	POD24 (n=47)
Median OS, months (95% CI)	NR (NE)	NR (NE)	NR (NE)
36-month OS, % (95% CI)	83 (74.6–91.2)	81 (69.1–92.9)	84 (72.1–96.3)

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

PFS, progression-free survival.

PFS and OS: 3L versus 4L+ therapy (mosunetuzumab)

PFS

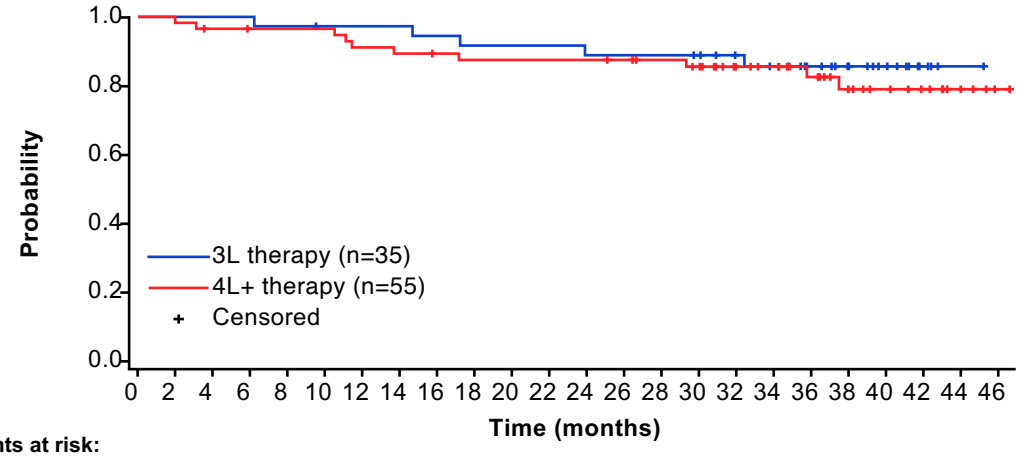


Patients at risk:

3L therapy	35	32	28	26	25	23	20	20	19	18	18	18	16	16	14	14	14	14	6	1	1	NE
4L+ therapy	55	49	43	34	34	32	27	26	24	23	22	20	17	15	14	14	14	14	10	1	1	1

	Overall population (N=90)	3L therapy (n=35)	4L+ therapy (n=55)
Median PFS, months (95% CI)	24.0 (12.0–NE)	NR (12.0–NE)	18.1 (11.8–37.3)
36-month PFS, % (95% CI)	43 (31.8–54.7)	54 (37.0–71.5)	36 (21.8–50.7)

OS



Patients at risk:

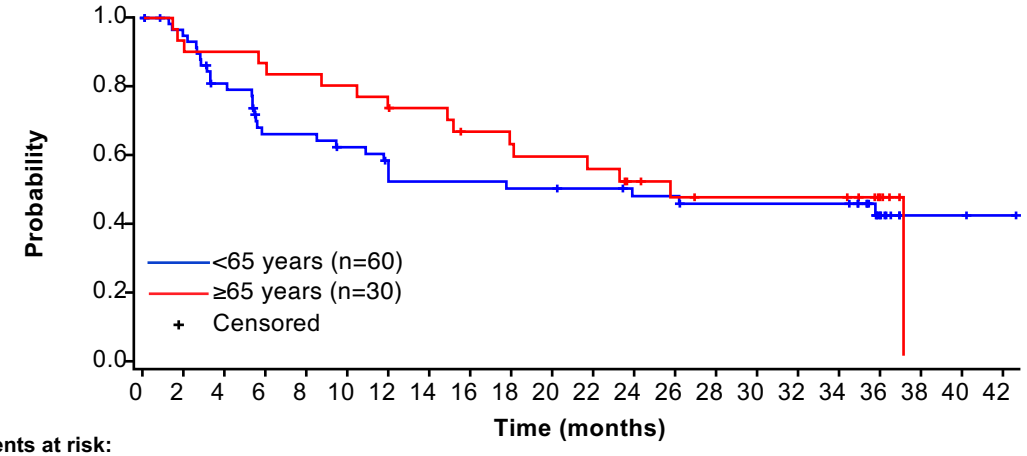
3L therapy	35	35	35	35	34	33	33	33	32	31	31	31	30	30	30	28	26	24	19	14	10	3	1	NE
4L+ therapy	55	54	52	51	51	51	48	47	46	45	45	45	45	44	42	38	33	31	26	20	15	13	6	1

	Overall population (N=90)	3L therapy (n=35)	4L+ therapy (n=55)
Median OS, months (95% CI)	NR (NE)	NR (NE)	NR (NE)
36-month OS, % (95% CI)	83 (74.6–91.2)	85 (72.7–97.2)	82 (70.5–92.8)

Numerically higher PFS benefit in patients who received mosunetuzumab in 3L versus 4L+

PFS and OS: <65 versus ≥65 years (mosunetuzumab)

PFS

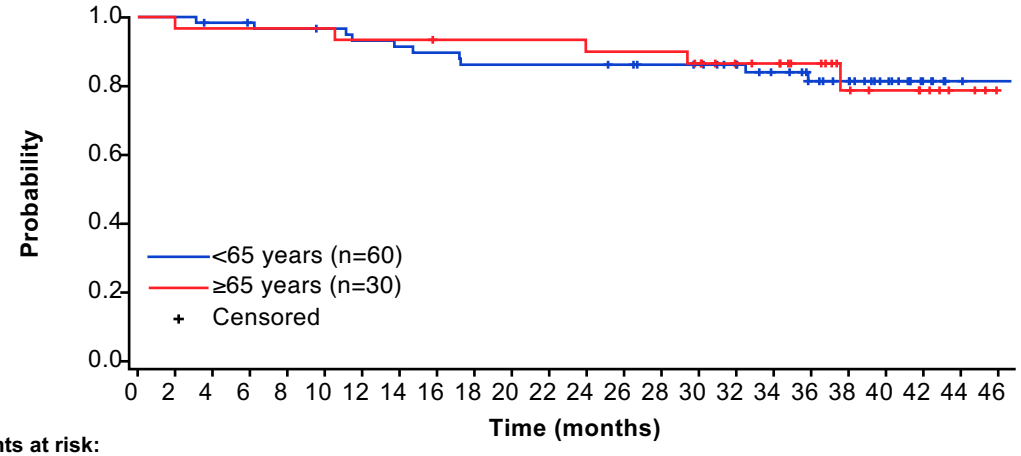


Patients at risk:

<65 years	60	54	44	34	34	31	25	25	25	24	24	23	21	21	19	19	19	19	10	2	2	1
≥65 years	30	27	27	26	25	24	22	21	18	17	16	15	12	10	9	9	9	9	6	NE	NE	NE

	Overall population (N=90)	<65 years (n=60)	≥65 years (n=30)
Median PFS, months (95% CI)	24.0 (12.0–NE)	17.8 (9.4–NE)	25.8 (15.2–NE)
36-month PFS, % (95% CI)	43 (31.8–54.7)	42 (27.3–55.8)	47 (28.1–65.8)

OS



Patients at risk:

<65 years	60	60	58	57	56	55	53	52	51	49	49	49	49	48	46	44	39	36	30	25	17	11	4	1
≥65 years	30	29	29	29	29	29	28	28	27	27	27	27	26	26	26	22	20	19	15	9	8	5	3	NE

	Overall population (N=90)	<65 years (n=60)	≥65 years (n=30)
Median OS, months (95% CI)	NR (NE)	NR (NE)	NR (NE)
36-month OS, % (95% CI)	83 (74.6–91.2)	81 (70.6–91.9)	86 (74.0–98.8)

36-month PFS and OS rates in patients ≥65 years were consistent with the overall population

AEs of interest

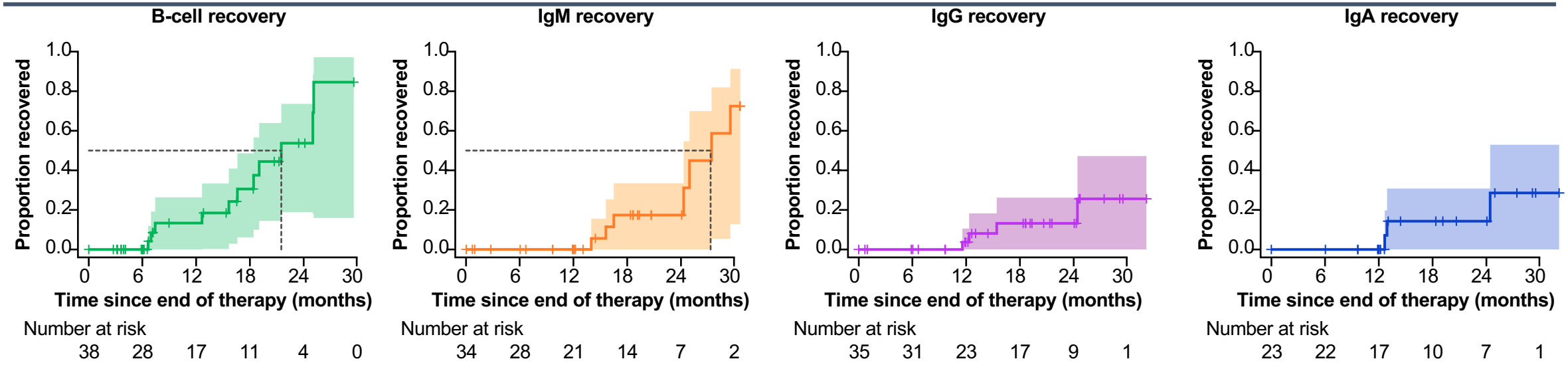
AE	Overall population (N=90)	POD24 status		Line of therapy		Age	
		Non-POD24 (n=43)	POD24 (n=47)	3L therapy (n=35)	4L+ therapy (n=55)	<65 years (n=60)	≥65 years (n=30)
CRS by ASTCT[1]	40 (44%)	16 (37%)	24 (51%)	14 (40%)	26 (47%)	31 (52%)	9 (30%)
Grade 1	23 (26%)	10 (23%)	13 (28%)	9 (26%)	14 (26%)	17 (28%)	6 (20%)
Grade 2	15 (17%)	5 (12%)	10 (21%)	4 (11%)	11 (20%)	13 (22%)	2 (7%)
Grade 3	1 (1%)	1 (2%)	0	0	1 (2%)	0	1 (3%)
Grade 4	1 (1%)	0	1 (2%)	1 (3%)	0	1 (2%)	0
Neutropenia	26 (29%)	7 (16%)	19 (40%)	10 (29%)	16 (29%)	19 (32%)	7 (23%)
Serious infections	18 (20%)	5 (12%)	13 (28%)	8 (23%)	10 (18%)	13 (22%)	5 (17%)

The incidence of serious infections in patients ≥65 years was consistent with the overall population

ASTCT, American Society for Transplantation and Cellular Therapy.

1. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38.

B-cell levels and immunoglobulin changes over time



- Recovery of B cells and immunoglobulins were evaluated after completion of treatment in patients with a CR
- Immunoglobulin treatment was used in 9% of all patients

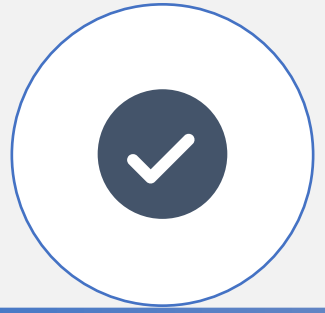
B-cell and immunoglobulin recovery were observed in patients with a CR after completion of fixed-duration treatment

Thresholds for recovery: B cells, ≥70 cells/µL; IgG, ≥8g/L; IgM, ≥0.5g/L; IgA, ≥1g/L.
IgA, immuglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M.

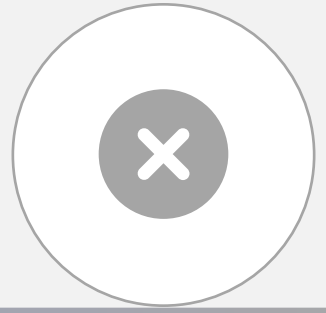
Bispecs vs CAR T for 3L+ FL

No cell manipulation
High rates of response
Can be administered Outpt./SC
Ability to mitigate CRS with SUD
Retreatment possible

High rates of response
One-time treatment
Works in aggressive Lymphomas

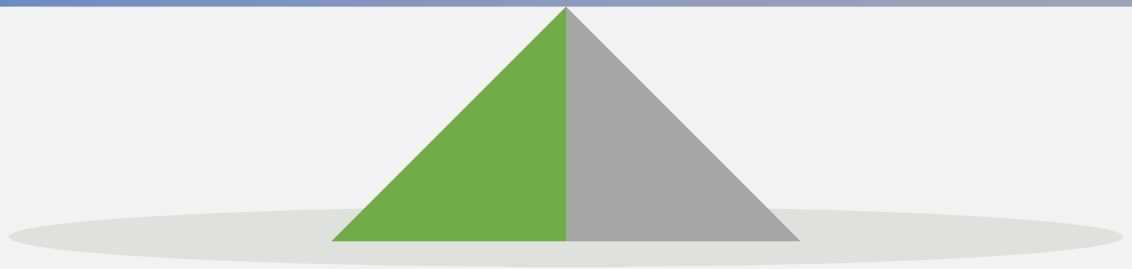


PT selection Sequence?



Bispecs

CART



Require multiple treatments
CRS can occur
Immunosuppression

Cell manipulation
Accessibility, Cost
Immunosuppression
Rates of CRS and ICANS
Second malignancies

Male 46yo, RR FL, POD24

Nov 2019:

FL g3a, stage IV (BM+) FLIPI3 (stage, LDH, LN)

6xR-CHOP + 2R → PR (BM neg) → R maint

Apr 2020 (+7 m):

1^ Relapse (FL g3a)

4xR-DHAP → CR → ASCT (Jul 2021)

Male 50 yo, RR FL, POD24, ASCT

Jan 2023 (+38m, +18 da ASCT):

2^ Relapse (FL), Stage IV (BM, Spleen, LN)

INCMOR trial: R2 +Tafasitamab/Placebo (Best response PR)

Aug 2023 (+46m):

Male 50 yo, RR FL, POD24, ASCT

Nov 2023 (+46m):

3^ Relapse: Stage IV, FL (G3a, CD19+)

Tisacel (4L), G1 CRS (fever), no ICANS Best response PR

HUMANITAS CANCER CENTER

Feb 2024 (+49m)

4^ Relapse (5L), FL G2-3, BM+, Spleen, ECOG 1

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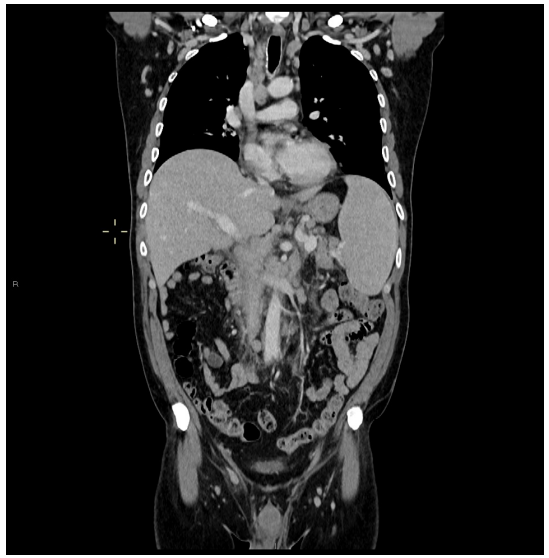
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Reggio Emilia
IRCCS Istituto in tecnologie avanzate e modelli assistenziali in oncologia

OECI COMPREHENSIVE Cancer Centre

Male 51 yo, RR FL, POD24, ASCT, CART

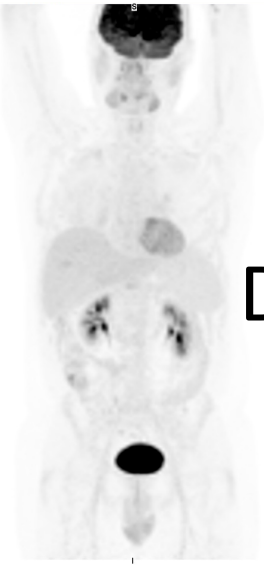
Mar 2024



Jul 2024 (C4)

DS3

Sep 2024 (C8)



DS2

BMB neg

Mosunetuzumab

Pre tx
Hb 11.5g/dl
WBC 4170/mmc
Plt 37K/mmc

In hospital C1 (21d)
CRS G2 (Toci)
Neutropenia G3 (G-CSF)
Low Plts G4 (3 UCP)

Outpatient c2+
Skin rash g1, Sc Ig

Both CARTs and Bispecs are available options for RR FL

- CARTs and Bispecs equally active in RR FL pts (overall and subgroups)
- None of the options is life saving (vs. DLBCL, more follow up needed)
- CARTs seem the best option for High Risk Pts (early relapsers, accelerate FL, suspect of tFL) ~ 10-15%
- Bispecs can be offered to a broder population vs CART
    - any age
    - logistic issues,
    - borderline pts conditions (PS, LAB, etc.)
- Sequencing is feasible (Bisepcs less affected by previous therapies)
- Brighter future for Bispecs vs CART

Ongoing trials: interest on BsAb and CAR-T

1L

- Phase 2
  - Morningsun: **Mosun sc**
  - EPCO NHL2 arm 6: **Epcoritamab + R2**
- Phase 3
  - M22-003: **EpcoR2** vs R-Chemo vs R2
  - OLYMPIA 1: **Odro** vs R+CT
  - OLYMPIA 2: **Odro+CT** vs R+CT

2L+

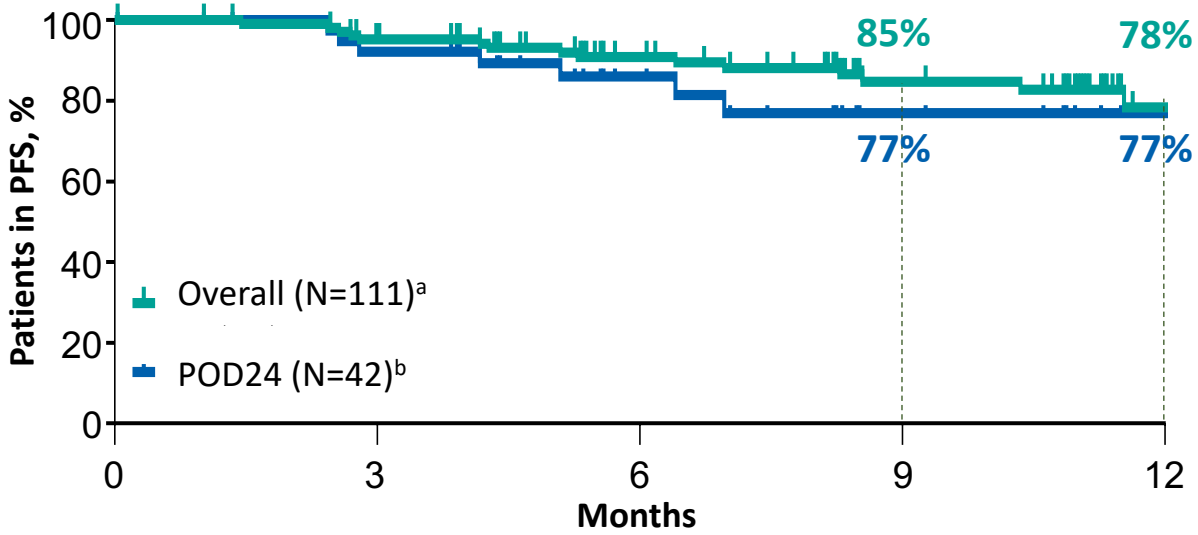
Phase 2

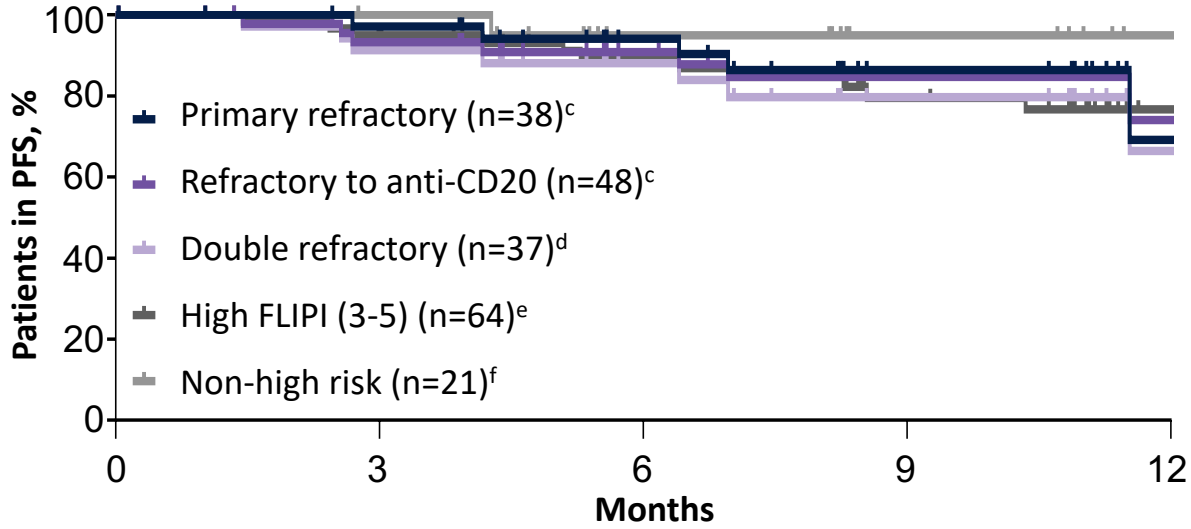
- **Mosu + Lenalidomide**
- **Mosu + Zanubrutinib**
- EPCO NHL-2 arm2b **Epcoritamab + R2**

Phase 3

- M22-638: **Epco R2** vs R2
- CELESTIMO: **Mosu+Len** vs R2
- OLYMPIA5: **Odro** vs R2 (
- ZUMA22 **Axi-cel** vs SOC (2L POD24 or 3L)
- LEDA **Tisa-cel** vs SOC (3L+)
- INCMOR R2 +/- **tafasitamab**
- Mahogany R2 vs **Obinu+zanubrutinib**

Epcoritamab + R^2 in R/R FL: PFS Overall and in Subgroups





No. at risk

111	96	70	44	17
42	35	20	10	3

38	34	25	15	4
48	41	31	19	7
37	31	21	14	5
64	54	41	29	11
21	20	13	8	3

- Median PFS NR for overall population and subgroups

[a]Median follow-up: 11.4 mo (range, 2.1–22.1). [b]Median follow-up: 9.5 mo (range, 2.4+ to 19.4). [c]Median follow-up: 10.4 mo (range, 3.0–19.4). [d]Median follow-up: 10.1 mo (range, 3.0–19.4). [e]Median follow-up: 12.5 mo (range, 2.1–22.1). [f]Median follow-up: 11.2 mo (range, 3.7–19.0).

1. Merryman RW, et al. ASCO 2023. Oral 7506. 2. Sureda A, et al. EHA 2023. Oral S222. 3. Belada D, et al. ICML 2023. Oral 84.

Bispecifics in FL: efficacy data from phase 2 trials

	MOSUNETUZUMAB [1] Trial GO29781	EPCORITAMAB [2] Trial Epcore NHL-1	ODRONEXTAMAB [3] Trial ELM-2
ENROLLED PTS	90	128 dose expansion 86 optimization cohort	128 ELM-2
AGE	29-90 (IQR 53-67)	39-84 (IQR 55-72)	22-84 (IQR NA)
PREV. LINES	2-4 (median 3)	2-4 (median 3)	2-13 (median 3)
POD24	52%	42%	49%
DOUBLE REFRACTORY	53%	65%	41%
Key criteria	cl.Creatinine >60 mL/min (AIFA > 30 mL/min)	Included creat.cl. 45-60 mL/min	Included creat.cl. <,15xULN or >50 mL/min
mFUP	37,4 m	17,4 m	20,1 m
ORR, CR	**78%, 60%**	**82%, 62,5%**	**80,5%, 73,4%**
mTTR	1,4 months	1,4 months	1,2 months
mPFS	24 m	14,4 m	20,7 m
mDOR	35,9 m NR in CR	NA	25,1m in CR

1. Budde LE, Lancet 2022; Schuster SJ ASH 2023; 2. Linton KM Lancet 2024 3. Kim TM Annals of Oncology 2024

Bispecifics in FL: safety data

	MOSUNETUZUMAB [1]	EPCORITAMAB [2]	ODRONEXTAMAB [3]
CRS all	44%	48%	57%
CRS grade 3-4	2%	2% (0 in optimiz.cohort)	6% (1,7% in opt cohort)
ICANS	3% (grade 1-2)	6% (grade 1-2) (0 in optimiz.cohort)	0,7% (grade 2)
TLS	2,2%	0	0,7%
Neutropenia grade 3-4	26%	23%	NA
Infection grade 3-5	14%	14%	40%
AE leading to discontinuation	4,4%	19%	15,6%

1. Budde LE, Lancet 2022; 2. Linton KM Lancet 2024 3. Kim TM Annals of Oncology 2024

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%