Algoritmo di trattamento nel linfoma follicolare

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ASL LATINA

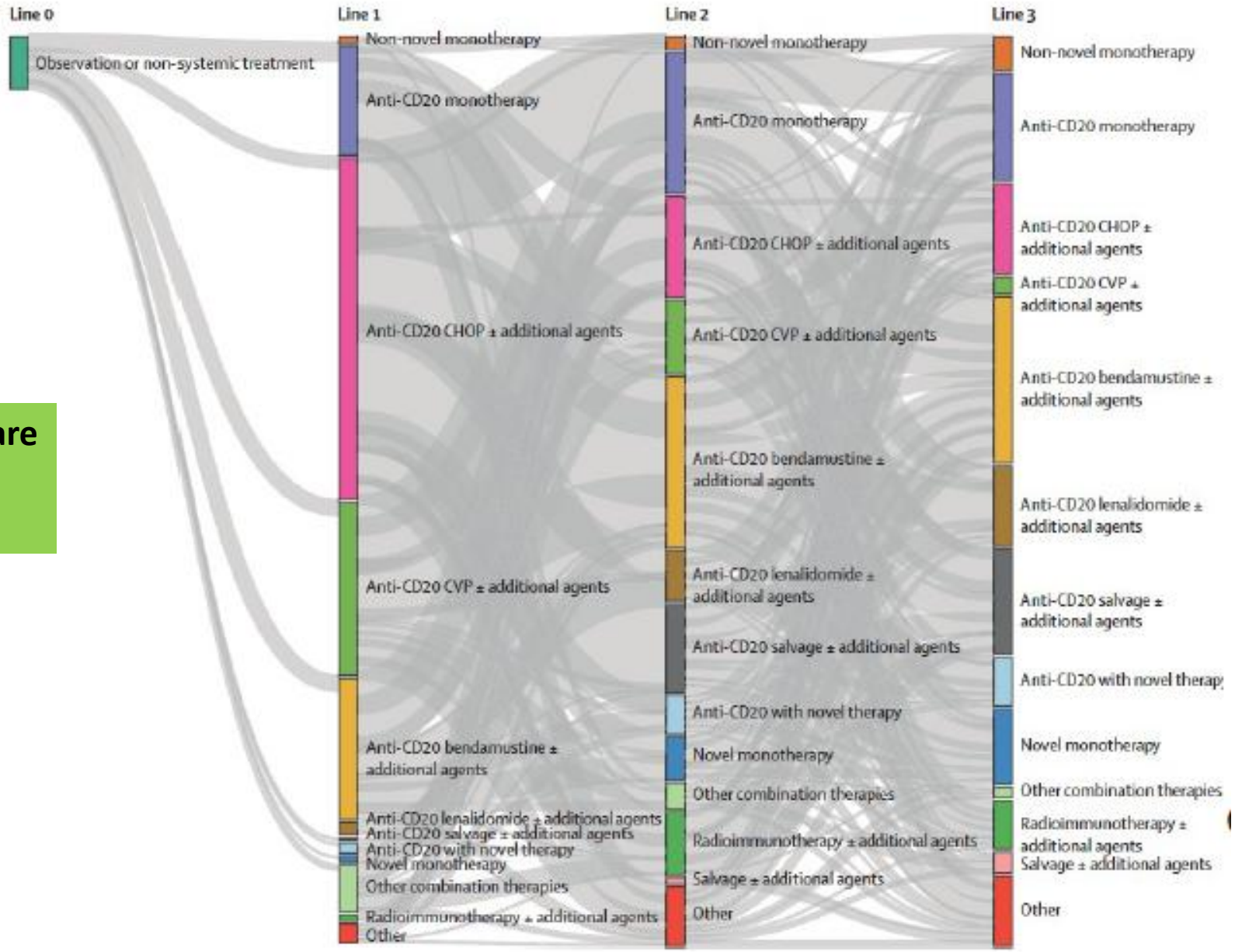
SAPIENZA
UNIVERSITÀ DI ROMA

Disclosures of Alessandro Pulsoni

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
ROCHE					x	x	
MERK SHARP &DOME					x		
PFIZER					x	x	
SANDOZ					x		
TAKEDA					x	x	
GILEAD					x	x	
BRISTOL MEIER SQUIBB						x	
JANSSEN					x		

Algoritmo di trattamento nel linfoma follicolare

Abbiamo le idee chiare?



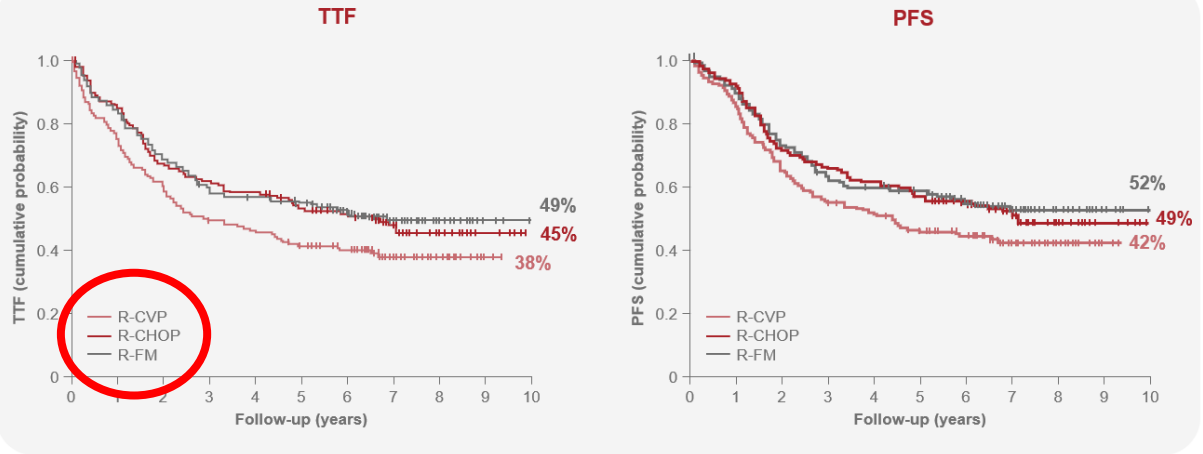
Casulo et al Lancet Haematol 2022;9:e289;

terapia di prima linea OGGI

Randomized Trials of Rituximab and Chemotherapy in Untreated FL

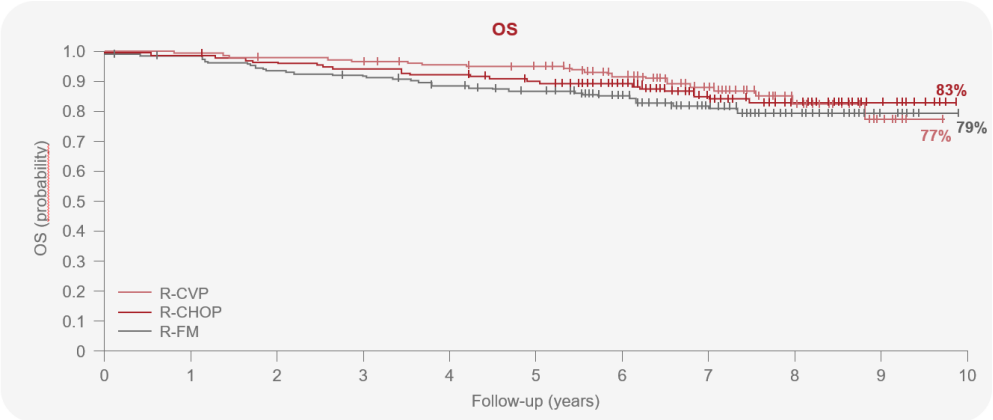
Trial	Patients	Treatment	Results
Marcus *J Clin Oncol 2008*	n = 321	CVP vs R-CVP	Improved TTP and OS
Hiddemann *Blood 2005*	n = 428	CHOP vs R-CHOP	Improved TTF and OS
Herold *J Clin Oncol 2007*	n = 201	MCP vs R-MCP	Improved EFS and OS
Salles, Foussard *Blood 2008*	n = 358	CHVP/IFN vs R-CHVP/IFN	Improved EFS and OS (high risk)

Long-term follow-up of the FOLL05 trial confirms the favourable outcome of advanced stage FL treated with immunochemotherapy



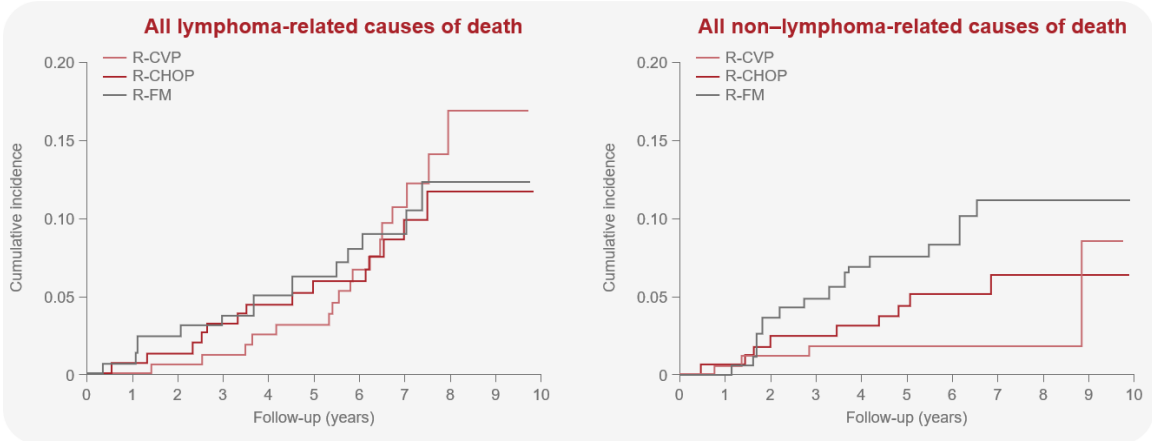
Median follow-up of 7 years
Luminari, et al. 2018

Long-term follow-up of the FOLL05 trial confirms the favourable outcome of advanced stage FL treated with immunochemotherapy



Median follow-up of 7 years
OS, overall survival
Luminari, et al. 2018

In FOLL05, risk of death from lymphoma was comparable among arms but risk of death from NLR causes was higher with R-FM vs R-CVP



Median follow-up of 7 years
NLR, non-lymphoma-related
Luminari, et al. 2018

Bendamustine-Rituximab (B-R) vs CHOP-R in Untreated Indolent Lymphoma

StiL NHL 1-2003

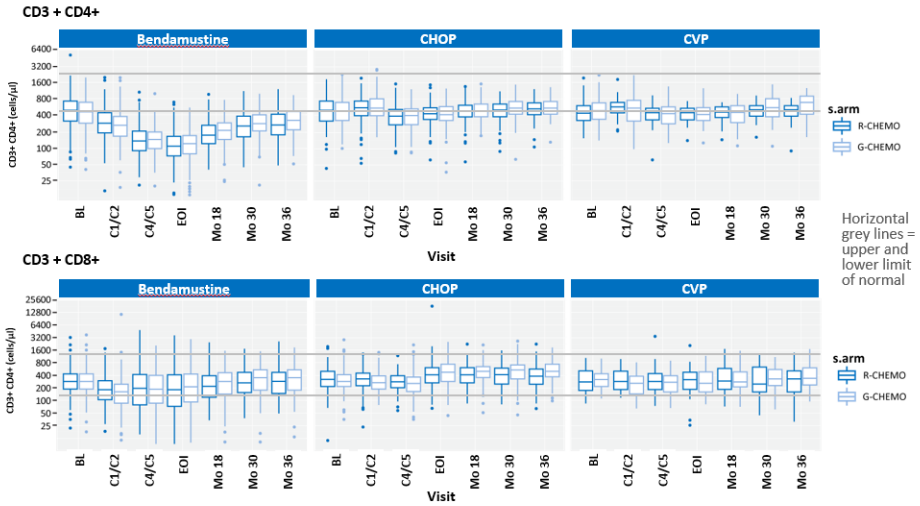
Follicular
Waldenström's
Marginal zone
Small lymphocytic
Mantle cell (elderly)

→ R

Bendamustine-Rituximab
- Bendamustine 90 mg/m² day 1+2
- Rituximab 375 mg/m² day 1

CHOP-Rituximab
- Cyclophosphamide 750 mg/m² day 1
- Doxorubicin 50 mg/m² day 1
- Vincristine 1.4 mg/m² day 1
- Prednisone 100 mg days 1-5
- Rituximab 375 mg/m² day 1

T-cell counts over time

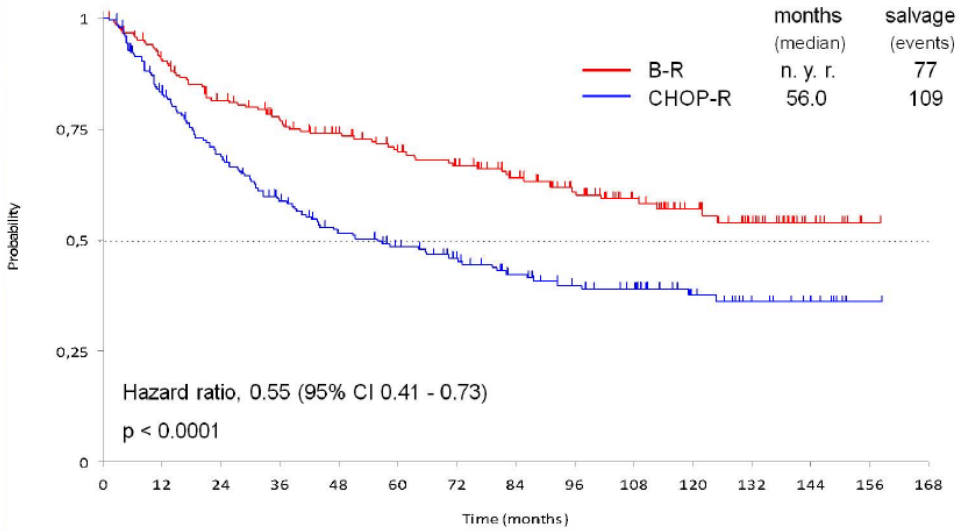


Horizontal grey lines = upper and lower limit of normal

Low T-cell count at baseline	R-benda, n=341	G-benda, n=345	R-CHOP, n=203	G-CHOP, n=196	R-CVP, n=57	G-CVP, n=60
CD3+/CD4+ cell count of ≤200/mm³	36 (12.5%)	36 (11.4%)	12 (7.2%)	9 (5.1%)	2 (4.4%)	4 (7.4%)

Hiddemann et al; presented at ICML 2017 and EHA 2017 http://onlinelibrary.wiley.com/doi/10.1002/hon.2437_106/full

STIL-1: Nine Year Updated Results Time-to-Next-Treatment

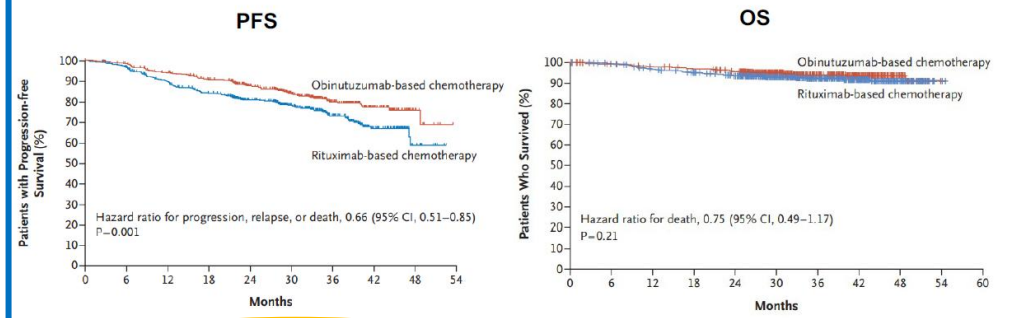


Rummel et al, ASCO 2016

*** No difference in OS or secondary malignancies**

MIGLIORE ANTI CD20 DA ASSCIARE ALLA CHEMIO?

Gallium Trial: Rituximab *v* Obinutuzumab



- Obinutuzumab: ↑ IRRs and neutropenia
- Most benefit in intermed-high risk FLIPI

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

Marcus et al, NEJM 2017;
Hiddemann et al, JCO 2018

Overview of safety

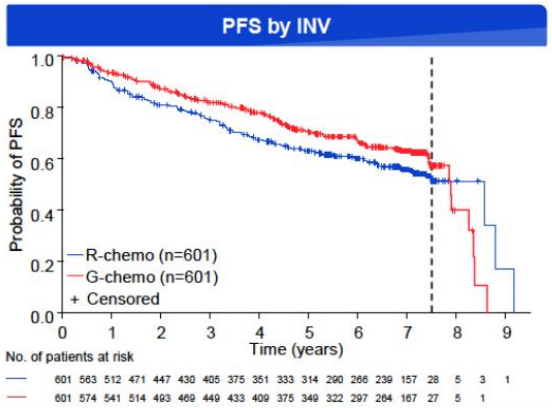
	R-benda (n=338)	G-benda (n=338)	R-CHOP (n=203)	G-CHOP (n=193)	R-CVP (n=56)	G-CVP (n=61)
Total number of patients with ≥1 event (AE/death)	331 (97.9%)	338 (100.0%)	201 (99.0%)	191 (99.0%)	56 (100.0%)	61 (100.0%)
Total number of deaths	37 (10.9%)	28 (8.3%)	9 (4.4%)	28 (8.3%)	6 (10.7%)	3 (4.9%)
Total number of Grade 3-5 AE	601	732	666	727	89	104
Total number of patients with ≥1:						
AE with fatal outcome	**16 (4.7%)**	**20 (5.9%)**	4 (2.0%)	3 (1.6%)	1 (1.8%)	1 (1.6%)
Grade 3–5 AE	228 (67.5%)	233 (68.9%)	**151 (74.4%)**	**171 (88.6%)**	30 (53.6%)	42 (68.9%)
Serious AE	160 (47.3%)	176 (52.1%)	67 (33.0%)	76 (39.4%)	19 (33.9%)	26 (42.6%)
AE leading to withdrawal from any treatment	48 (14.2%)	52 (15.4%)	31 (15.3%)	32 (16.6%)	9 (16.1%)	11 (18.0%)
AE leading to any dose reduction	46 (13.6%)	43 (12.7%)	38 (18.7%)	51 (26.4%)	11 (19.6%)	13 (21.3%)
AE leading to any dose interruption	194 (57.4%)	217 (64.2%)	114 (56.2%)	135 (69.9%)	29 (51.8%)	44 (72.1%)

- Study not designed or powered to compare differences between R-chemo and G-chemo within chemo groups

- Bendamustine: ↑ infections & fatal AEs?

Marcus et al, NEJM 2017;
Hiddemann et al, JCO 2018

PFS benefit was maintained with G- vs R-chemo after 8 years of follow-up



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

Median observation time: 7.9 (0.0–9.8) years

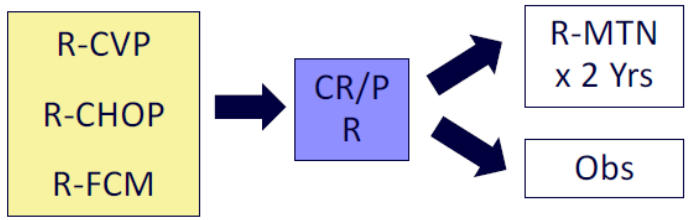
INV-assessed PFS	G-chemo (n=601)	R-chemo (n=601)
Patients with event, n (%)	206 (34.3)	244 (40.6)
7-year PFS, % (95% CI)	63.4 (59.0–67.4)	55.7 (51.3–59.9)
HR (95% CI)*	0.77 (0.64–0.93)	
P-value	0.006	

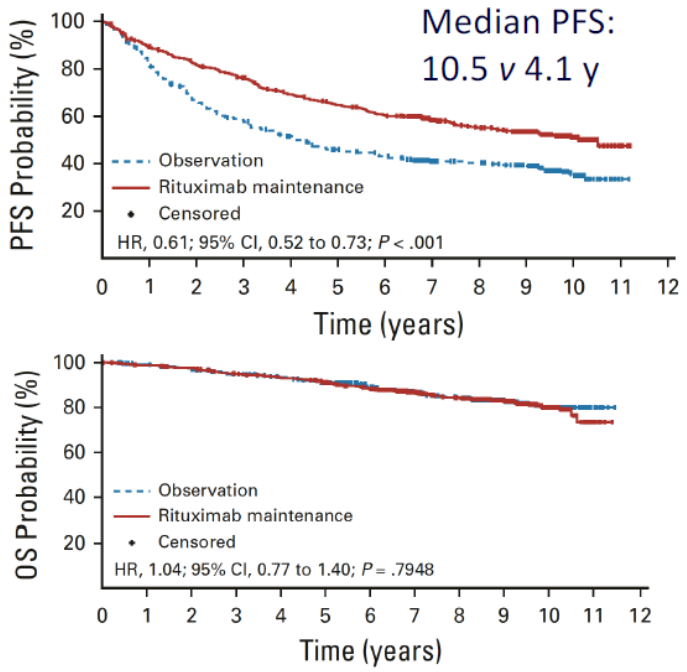
No new safety signals, ? higher grade ≥3 neutropenia and infection with Obinutuzumab

Townsend et al, EHA 2022

RUOLO DEL MANTENIMENTO R

PRIMA Trial: R-Maintenance after R-Chemo





Bachy E et al, JCO 2019

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Immuno-chemio + mantenimento

R/O	CVP CHOP BENDA	mantenimento R/O

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

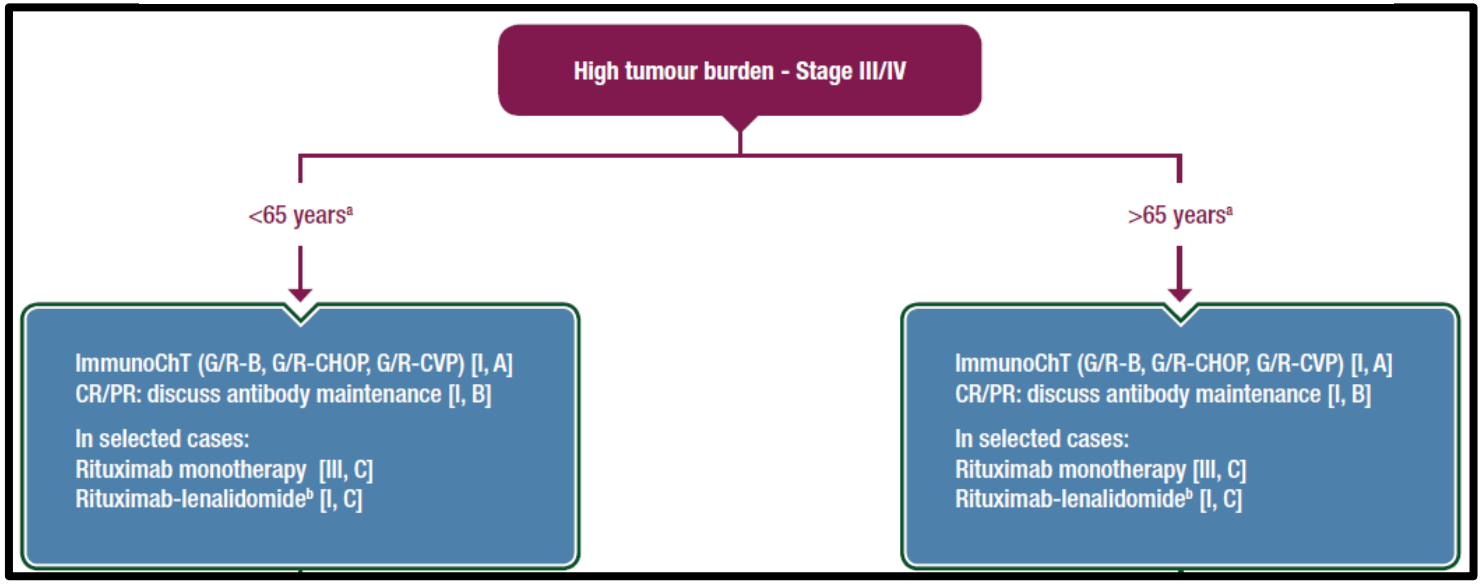
ANNALS OF ONCOLOGY driving innovation in oncology

2020

SPECIAL ARTICLE

Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†☆

M. Dreyling[1], M. Ghielmini[2], S. Rule[3], G. Salles[4,5], M. Ladetto[6], S. H. Tonino[7], K. Herfarth[8], J. F. Seymour[9] & M. Jerkeman[10], on behalf of the ESMO Guidelines Committee*



Alternativa chemo-free presente già oggi, anche se non disponibile in Italia

Six-Year Results from the Phase 3 RELEVANCE Study: Similar Outcomes for Previously Untreated FL Receiving Lenalidomide Plus Rituximab (R^2) versus R-Chemotherapy Followed by R Maintenance

Figure 1. RELEVANCE Study Design

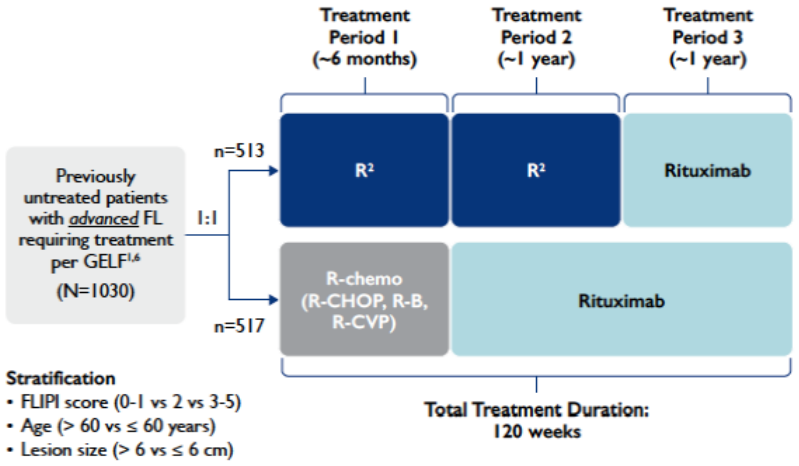


Figure 3: Progression-Free Survival by IRC, FDA Censoring Rules

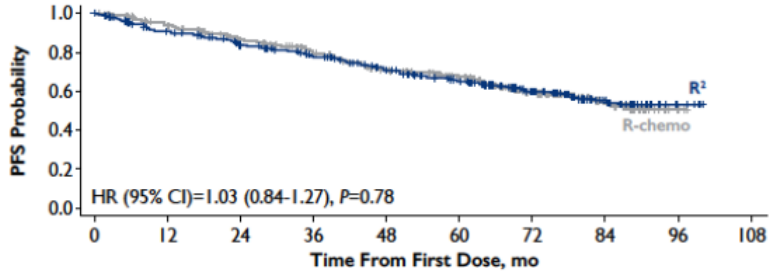
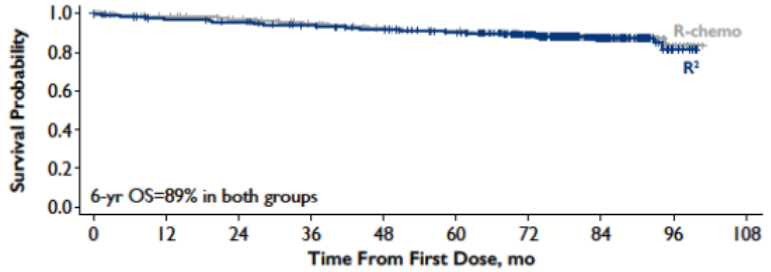


Figure 6: Overall Survival



- More patients died from lymphoma in R^2 arm
- No difference in transformation rate

Morschhauser F, et al JCO 2022

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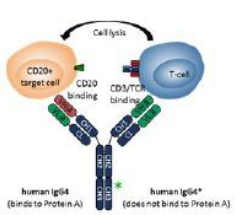
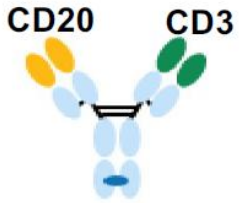
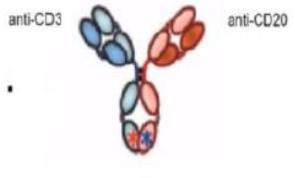
CD20/CD3 Bispecific Antibodies in B-cell lymphomas



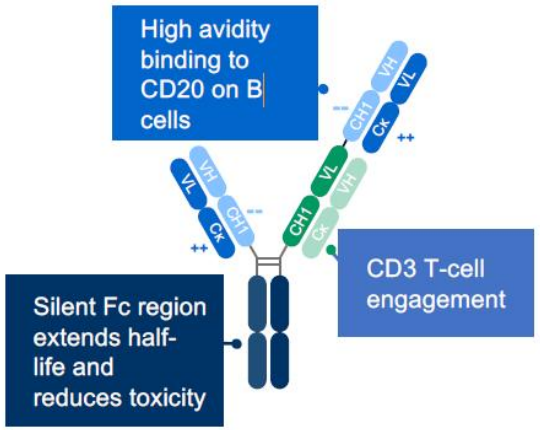
Odronextamab
(IV)
(REGN1979)
IgG4



Mosunetuzumab
(IV/SC)



Epcoritamab
(SC)
Duobody
GEN3013



Glofitamab (IV)
CD20-TCB

- A differenza delle CAR-T gli anticorpi bispecifici si prestano alla ***combinazione***

Sia con chemioterapia che con agenti chemo-free

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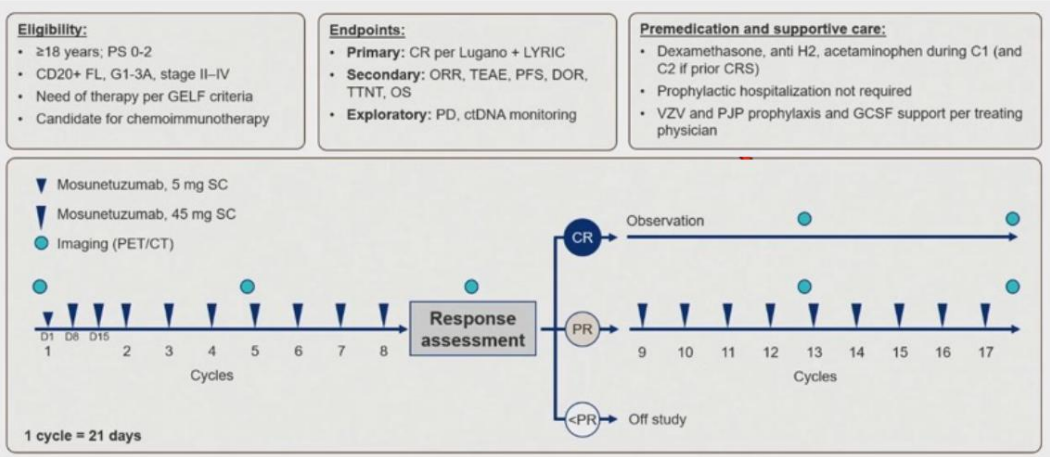
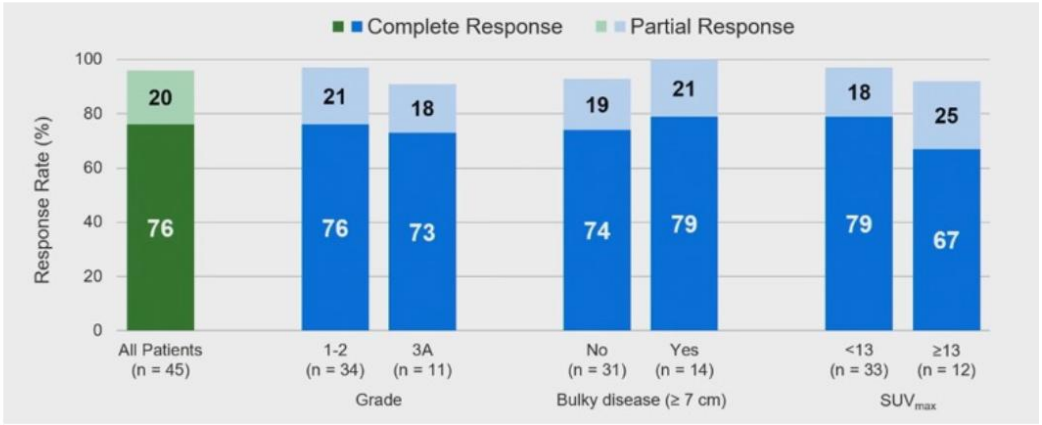
Phase 2 Trial of Subcutaneous Mosunetuzumab As First-Line Therapy in FL



Mosunetuzumab in FL
Response Rates by Risk Group



CO41942: Mosunetuzumab SC + Len in 1L FL

Open-label, multicenter, Phase Ib/II study of mosunetuzumab SC + lenalidomide in 1L FL

Key inclusion criteria

- CD20+ FL Grade 1–3a
- Previously untreated and require systemic therapy*
- ECOG PS 0–2

Objectives

- Primary: Safety and tolerability of Mosun-Len
- Other: Efficacy (response assessed every 3 cycles,† durability of response), biomarkers, and PK

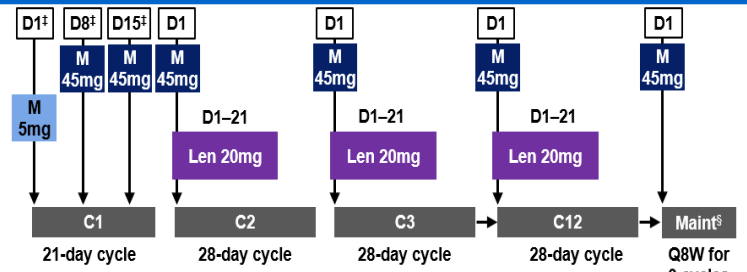
Mosun-Len administration

Mosun

- SC administration for 12 cycles (C1: Q3W; C2–12: Q4W)
- C1 step-up dosing (CRS mitigation)
- No mandatory hospitalization

Len

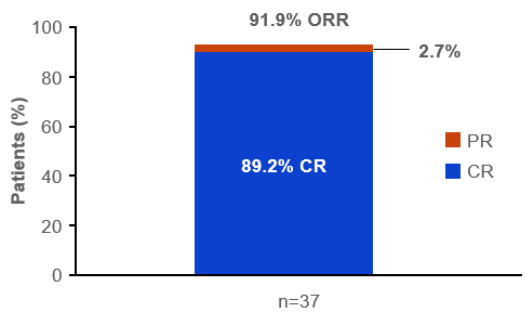
- Oral administration for 11 cycles (C2–12)



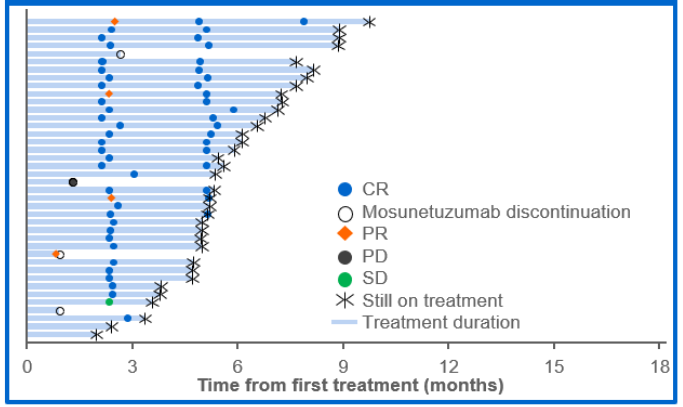
Response

- Median duration of follow-up: 5.2 months (range: 1–10); most patients (95%) had 3–9 months of follow-up at CCOD

Best overall response*

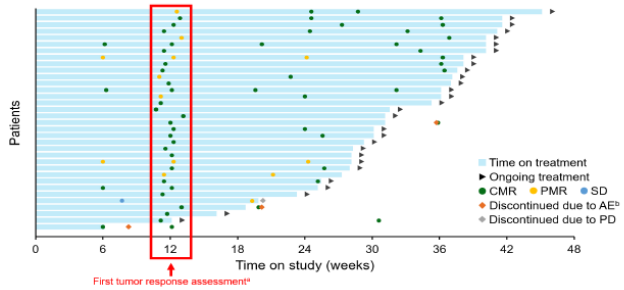


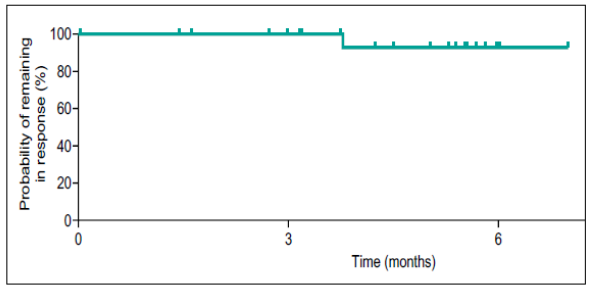
Response timing and duration†



ORR and CR rates were high. All patients who responded were still in response at the CCOD

Epcoritamab + R^2 in Untreated FL





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ORR 94%; CR 86%
CRS 39% G1; 15% G2

Falchi, L et al ASH 2022

Randomized Phase 3 Trials in FL

	Trial	Sponsor	N	Setting	Agent	Primary Endpoint	Key Secondary Endpoints
NCT06191744	EPCORE-FL2	AbbVie	900	Untreated	EpcorR2 vs CIT vs R2	CR30	PFS, OS, MRD, CR, EFS, DOR, TTNT, QOL (EORTC, FACT)
NCT06097364	OLYMPIA-2	Regeneron	733	Untreated	Odro-chemo vs R-chemo	CR30	PFS, EFS, OS, DOR, TTNT, QOL (EORTC, FACT)
NCT06284122	MorningLyte	LYSARC	790	Untreated	Mosun/len vs CIT	PFS	ORR, CMR, POD24, EFS, TTNLT, DOR, QOL (EORTC, FACT)
NCT06091254	OLYMPIA-1	Regeneron	478	Untreated	odro vs r-chemo	CR30	PFS, EFS, OS, DOR, TTNT, QOL (EORTC, FACT)
NCT06313996	TRANSFORM-FL	BMS	300	R/R	Liso-cel vs CIT/R2	PFS	CR, OS, OR, DOR, EFS, TTNLT, PFS2, QOL (EORTC)
NCT06149286	OLYMPIA-5	Regeneron	470	R/R	Odro-len vs R2	PFS	ORR, DOR, CR, OS, EFS, QOL (EORTC,FACT)
NCT05888493	LEDA	Novartis	108	R/R	tisa-gen vs (R2/R-CHOP)	PFS	CR, ORR, OS, TTNT, DOR,
NCT04224493	SYMPHONY-1	Epizyme	540	R/R	taz/R2 vs R2	PFS	ORR, DOR, OS, ECOG PS
NCT04712097	Celestimo	Roche	474	R/R	mosun/len vs R2	PFS	CR, ORR, OS, DOR, DOCR, QOL (EORTC, FACT), TTLT
NCT05371093	ZUMA-22	Kite	230	R/R	axi-cel vs CIT/R2	PFS	OS, CR, ORR, DOR, DOCR, TTNT, QOL (EORTC, NHL-LD20, EQ-5D)
NCT05100862	MAHOGANY	BeiGene	750	R/R	zan/O vs R2	PFS	DOR, ORR, CR, TTNLT, OS, QOL (EORTC)
NCT05409066	EPCORE-FL1	AbbVie	500	R/R	EpcorR2 vs R2	PFS	CR, OS, MRD
NCT04680052	InMIND	Incyte	654	R/R	tafa-len vs R2	PFS	CR, MRD, OS, CR, ORR, DOR, QOL

Slide courtesy M. Maurer

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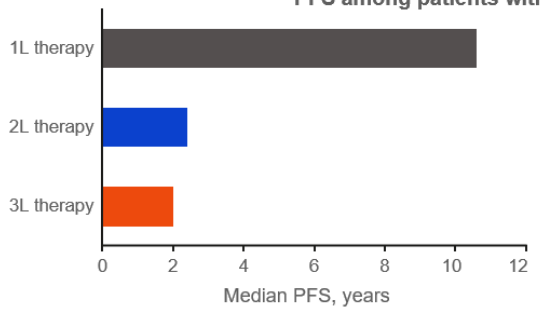
In ricaduta lo scenario è diverso:

PFS among patients with FL by line of therapy[3]

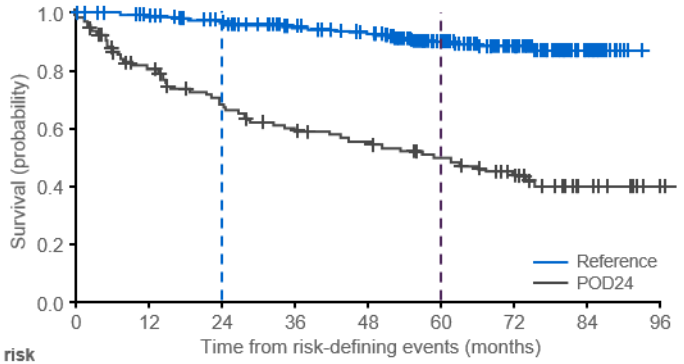


Line of therapy	n	Median PFS, years	5-year PFS
1L	348	10.6	61%
2L	111	2.4	35%
3L	41	2.0	23%

first line; 2L, second line; 3L, third line, FL, follicular lymphoma; PFS, progression-free survival.

1. Teras LR, et al. CA Cancer J Clin 2016;66:443–59;
2. Freedman A & Jacobsen E. Am J Hematol 2019;95:316–27;
3. Rivas-Delgado A, et al. Br J Haematol 2019;184:753–59.

OS by POD24 status (National LymphoCare Study database)*[3]



No. at risk

Early POD	110	82	66	56	50	42	32	14	3
Reference	420	408	387	363	344	253	145	34	0

	POD24 (n=110)	Reference (n=420)
2-year OS, % (95% CI)	68 (58.2–76.3)	97 (94.6–98.1)
5-year OS, % (95% CI)	50 (39.4–59.2)	90 (86.2–92.4)

Median follow-up: 7 years

*Analysis of 530 patients with previously untreated FL who received R-CHOP.
CI, confidence interval; FL, follicular lymphoma; OS, overall survival; POD, progression of disease; POD24, progression of disease within 24 months; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisolone.

1. Bachy E, et al. Blood Adv 2021;5:1729–32;
2. Seymour JF, et al. Haematologica 2019;104:1202–8;
3.Casulo C, et al. J Clin Oncol 2015;33(23):2516–22.

- **PFS dopo seconda linea decisamente inferiore**
- **Ruolo POD 24**

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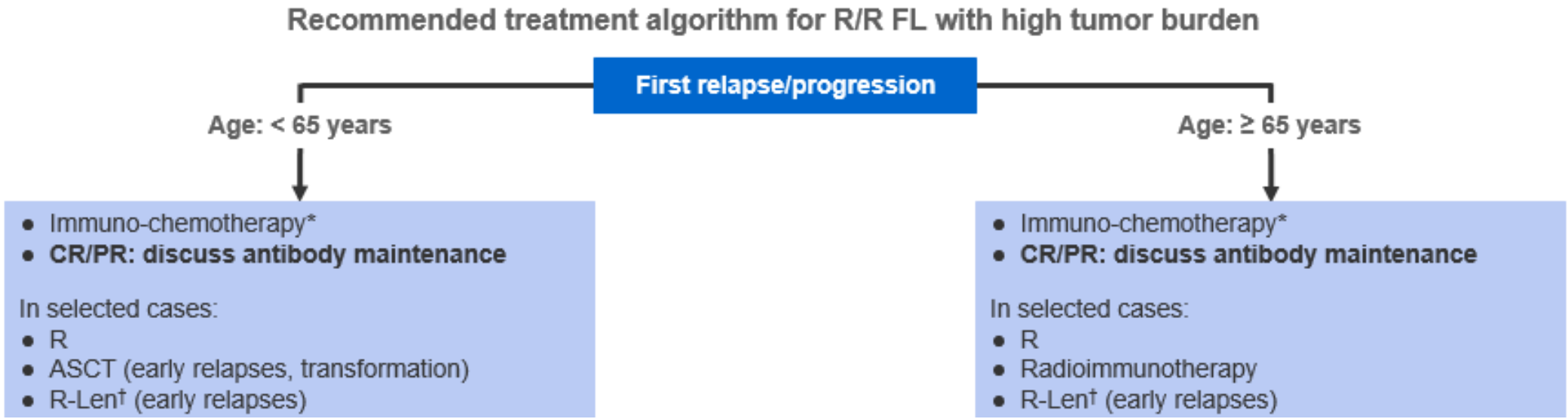
ESMO/EHA treatment algorithm (2021)[1,2]



AUGMENT (NCT01938001)

: R2 vs placebo-R

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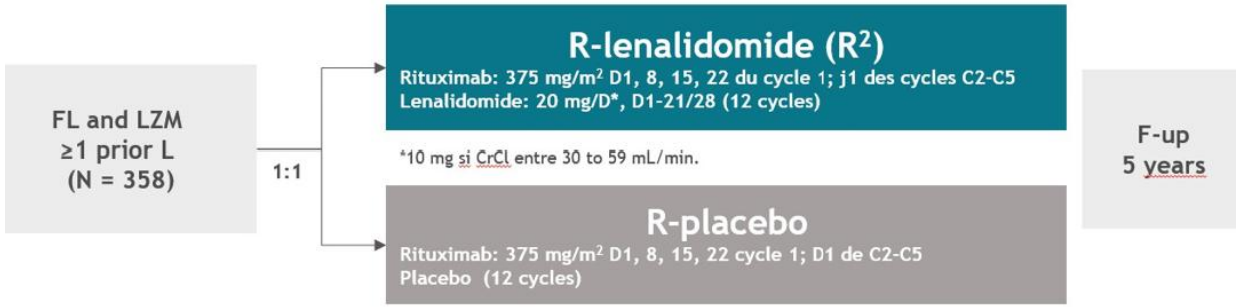
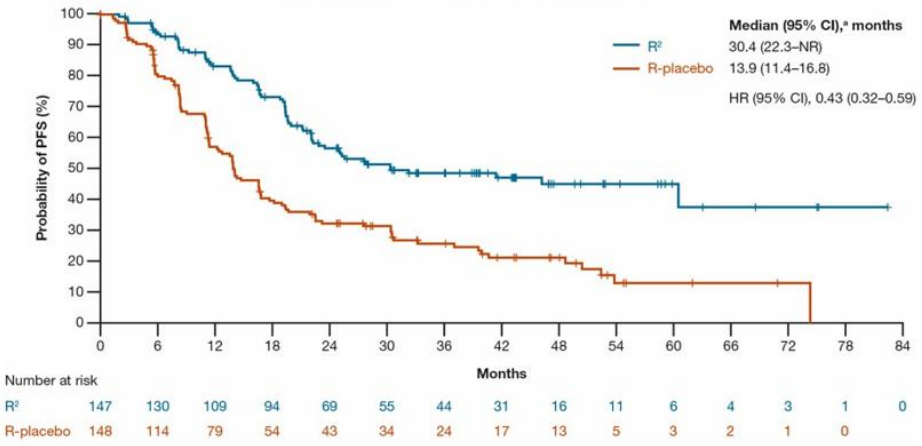
double-blind, phase III trial, 1:1



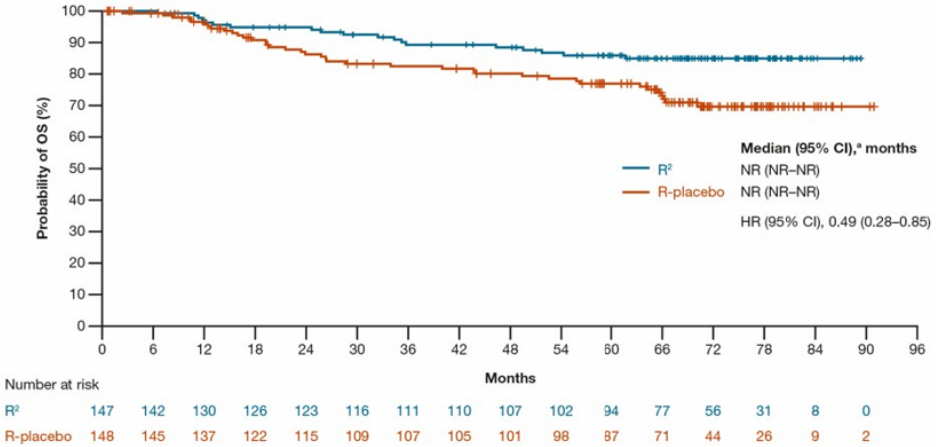
median follow-up of 65.9 months



FL population

median follow-up of 65.9 months

overall survival



C’è ancora un ruolo oggi per ASCT nel linfoma follicolare?

- ***SI, <u>oggi,</u> per pazienti giovani, fit, soprattutto se POD24 in molti centri viene ancora utilizzato in 2 linea***
- ***Il prossimo probabile avanzamento di terapie T-cell engagers in 2 linea ne ridurrà ulteriormente l’indicazione***

Terapia di 2 linea DOMANI

Studi in corso 2+ linea

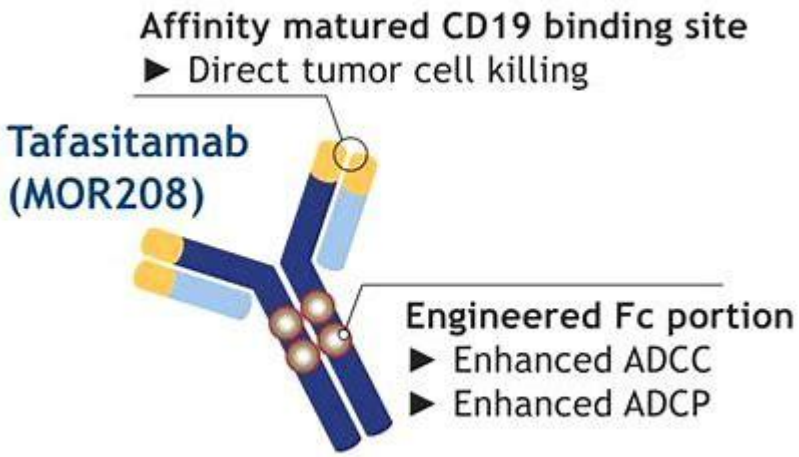
- In mind
- Mosu-lena
- Celestimo
- Epcore NHL2

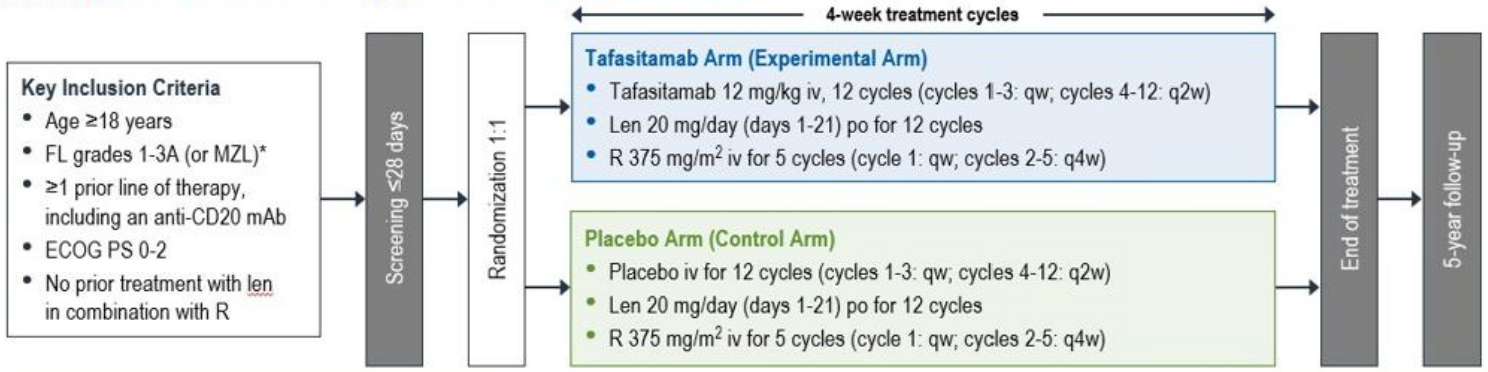
..

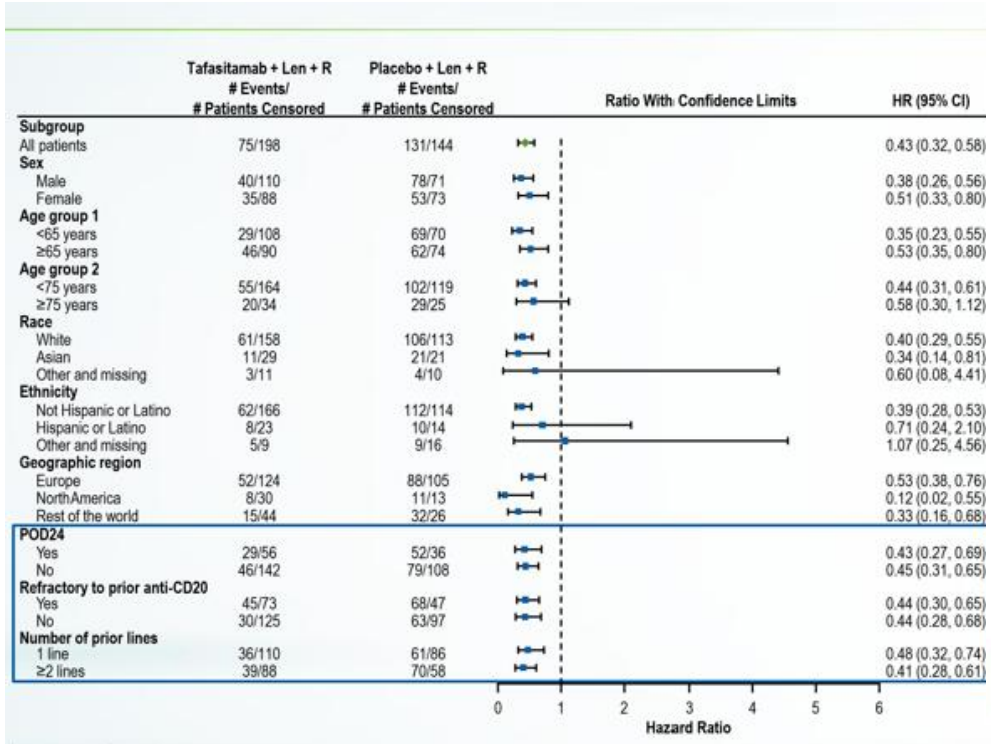
Terapia di 2 linea DOMANI

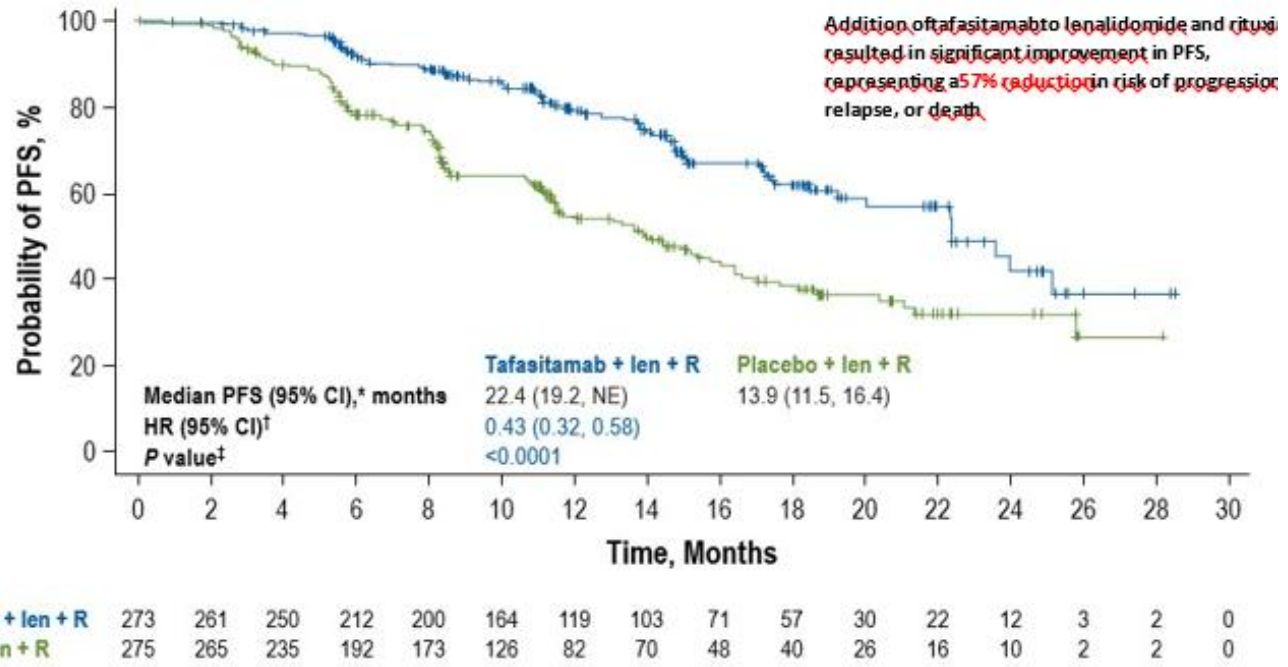
inMIND (NCT04680052)

inMIND (NCT04680052) : Tafa-R2 vs placebo-R2









Significant improvement in PFS was observed with tafasitamab

MOSU-Lena

Terapia di 2 linea DOMANI

Key inclusion criteria

- CD20+ FL Grade 1–3a
- R/R to ≥1 prior chemo-immunotherapy regimen including an aCD20 antibody; prior lenalidomide allowed
- ECOG PS 0–2

Objectives

- Primary: safety and tolerability of M-Len
- Other: efficacy (response, durability of response) and pharmacokinetics

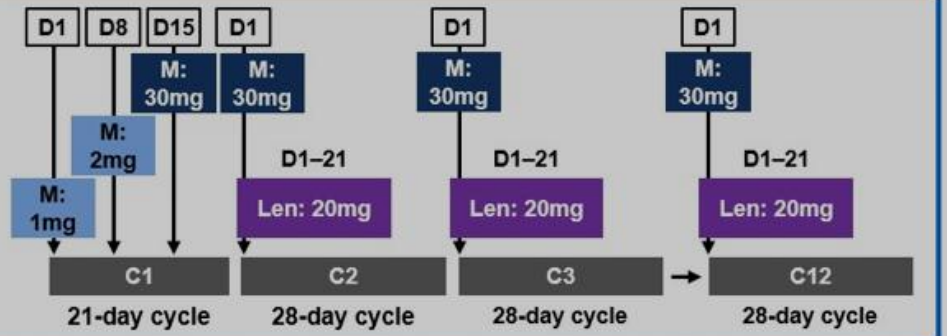
M-Len administration

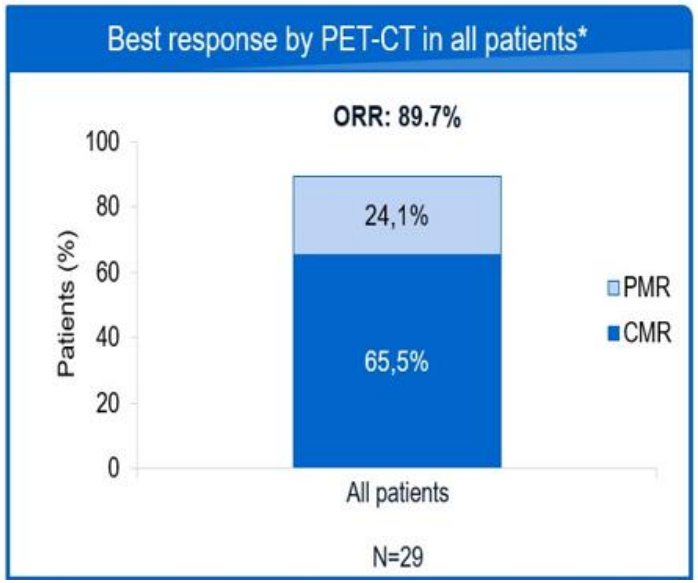
Mosunetuzumab

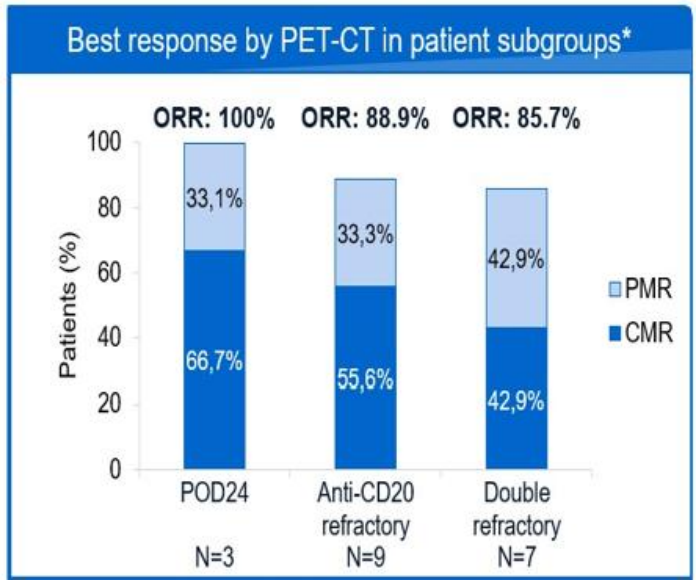
- IV administration for 12 cycles (C1: Q3W; C2–12: Q4W)
- C1 step-up dosing (CRS mitigation)
- No mandatory hospitalization

Lenalidomide

- Oral administration for 11 cycles (C2–12)







RR FL dalla 2 linea

- ORR 90%
- CR 65%
- Risultati invariati nei POD24
- Low CRS solo c1-2

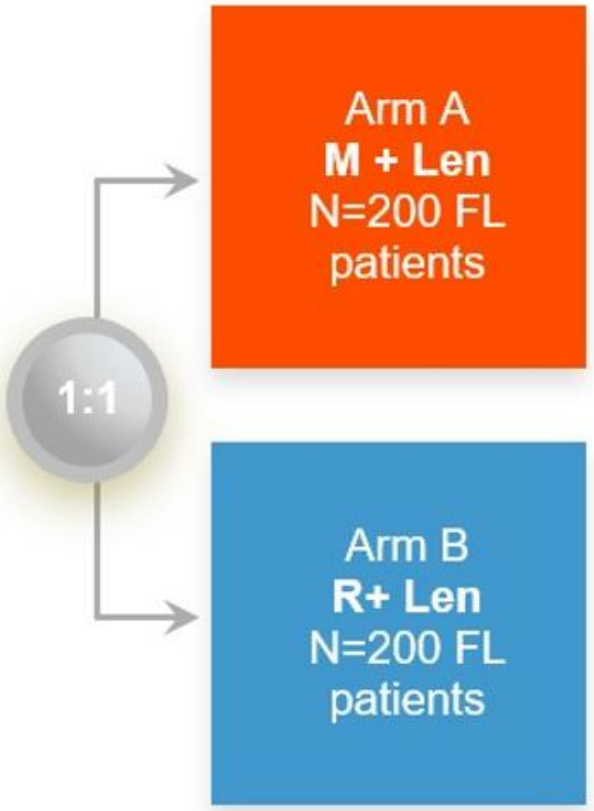
CELESTIMO Mosu-lena vs R-lena

Eligibility

- Histologically confirmed diagnosis of FL (Grade 1, 2 or 3a)
- >=1 prior systemic therapy for FL

Stratification:

- POD24 vs non POD24
- 1 prior therapy vs >1 prior therapy
- CD20 therapy refractory vs not



Terapia di 2 linea DOMANI

EPCO+R2

Study Design: EPCORE® NHL-2 Arm 2

Key inclusion criteria

- R/R CD20+ FL
  - Grade 1–3A
  - Stage II–IV
- ≥1 prior treatment, including an anti-CD20 antibody
- Need for treatment per GELF criteria[1]
- ECOG PS 0–2
- Measurable disease by CT or MRI
- Adequate organ function

Data cutoff: May 15, 2024
Median follow-up: 25.3 months

Concomitant fixed-duration epcoritamab 48 mg + R²
(28-day cycles up to 2 years)

	Agent	C1	C2	C3	C4–5	C6–9	C10–12	C13+
2-step-up-dose regimen[a]	Epcoritamab SC 48 mg							
	Cohort A[b]	QW			Q2W		Q4W	
	Cohort B[b]	QW		Q4W				
R²	Rituximab IV 375 mg/m²	QW	Q4W					
	Lenalidomide PO 20 mg/d	D1–21 of each cycle						

Primary endpoint: ORR per Lugano criteria[c]

Key secondary endpoints: CR rate, DOR, DOCR, PFS, TTNT, OS, MRD analysis,[d] and safety and tolerability

Terapia di 2 linea DOMANI

EPCO+R2

Baseline Characteristics	N=111
Median age, y (range)	65 (30–80)
Male sex at birth, n (%)	56 (50)
Race, n (%)[a]	
White	80 (72)
Asian	2 (2)
Black or African American	2 (2)
Other	2 (2)
Ethnicity, n (%)[b]	
Hispanic or Latino	3 (3)
Not Hispanic or Latino	23 (21)
Ann Arbor stage, n (%)[c]	
III	24 (22)
IV	68 (61)
Histologic grade, n (%)[d]	
1–2	77 (69)
3A	29 (26)
FLIPI, n (%)[e]	
0–2	46 (41)
3–5	65 (59)
Bulky disease (≥7 cm), n (%)	31 (28)

Treatment History	N=111
POD24 (any 1L treatment), n (%)[f]	55 (50)
POD24 (1L CIT), n (%)[g]	42 (38)
Primary refractory, n (%)[h]	39 (35)
Double refractory, n (%)[i]	39 (35)
Median time from diagnosis to first dose, mo (range)	63 (2–331)
Median time from end of last line of therapy to first dose, mo (range)	19 (0.6–198)
Median number of prior lines of therapy (range)	1 (1–7)
1 prior line, n (%)	63 (57)
≥2 prior lines, n (%)	48 (43)
Prior systemic therapies, n (%)[j]	
Anti-CD20	111 (100)
Alkylating agents	103 (93)

Best Response, n (%)[a]	N=111
Overall response	107 (96)
Complete response	97 (87)
Partial response	10 (9)
Progressive disease	2 (2)

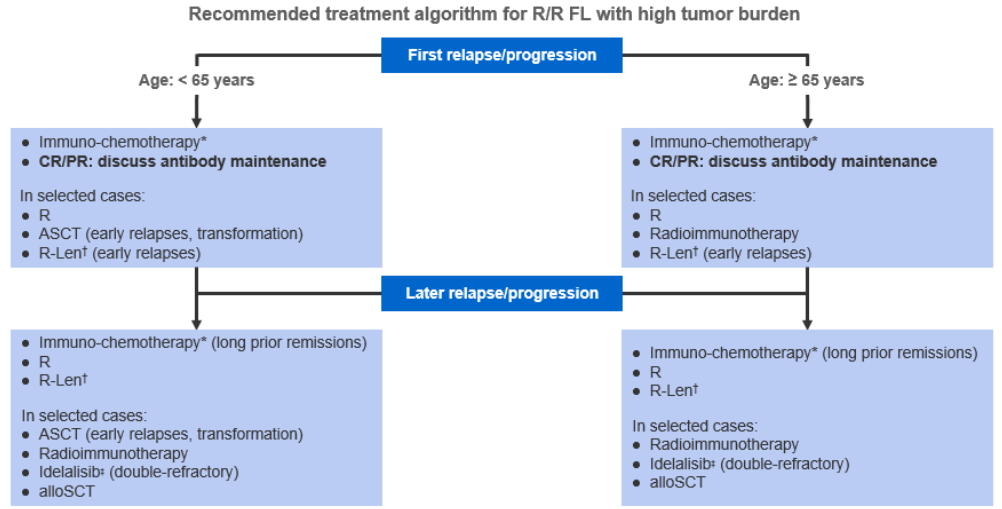
MRD Negativity, n/n (%)	MRD Evaluable
MRD negativity at any time[b]	66/75 (88)
MRD negative and complete response[c]	63/68 (93)
MRD negativity in high-risk subgroups[d]	
POD24 (1L CIT)	26/30 (87)
Primary refractory	25/28 (89)
Double refractory	23/27 (85)

- **CR in 2L = 92%**
- **CR in POD24 = 87%**
- **MRD negativity =88% (correlating with PFS)**
- **Low-Grade CRS and ICANS With 2 Step-Up Doses**

Falchi L et al. ASH 2024

terapia di terza linea OGGi

ESMO/EHA treatment algorithm (2021)[1,2]



NCCN Guidelines for 3L+ R/R FL (V2.2024)

Third-line and subsequent therapy*

Preferred regimens

- T-cell engager therapy
  - Bispecific antibody therapy
    - Epcoritamab†
    - Mosunetuzumab†
- CAR T-cell therapy:‡
  - Axicabtagene ciloleucel (CD19-directed)
  - Lisocabtagene maraleucel (CD19-directed)
  - Tisagenlecleucel (CD19-directed)

Other recommended regimens

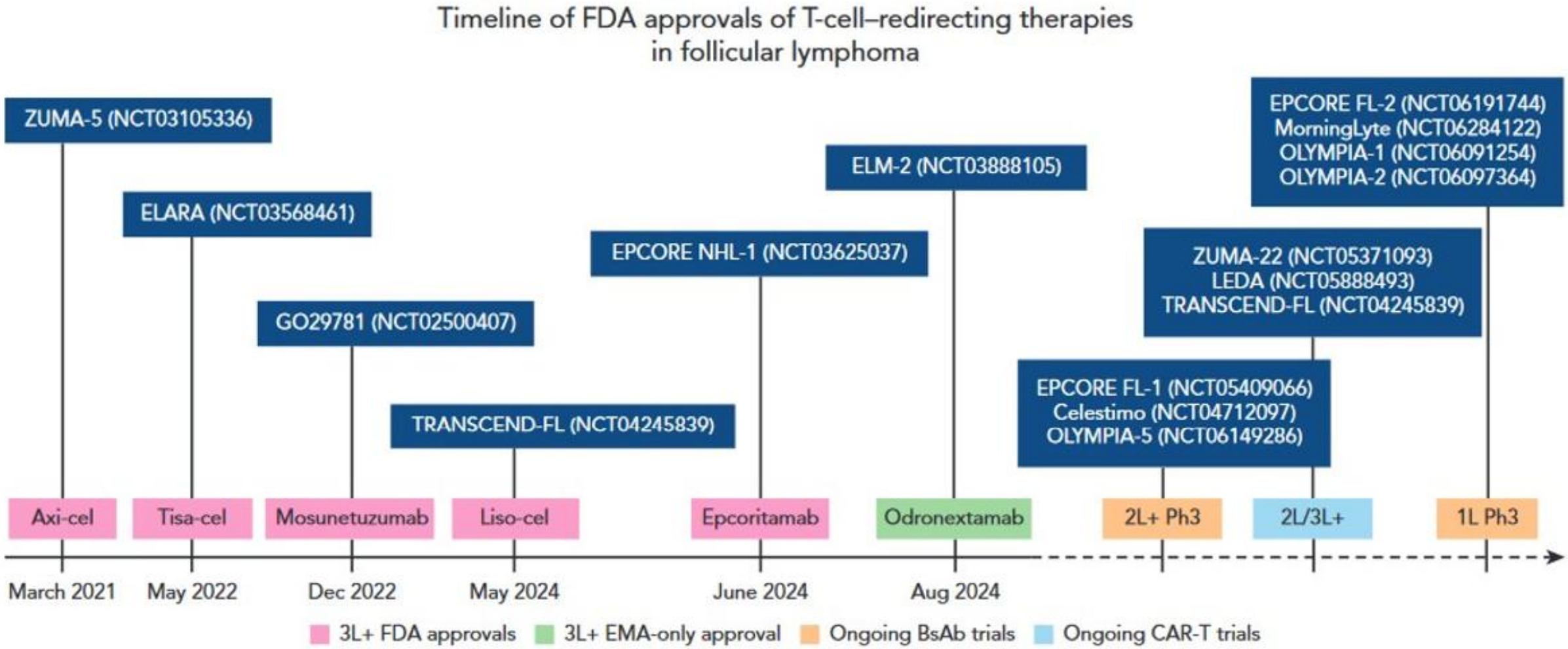
- *EZH2* inhibitor
  - Tazemetostat† (irrespective of *EZH2* mutation status)
- BTK inhibitor
  - Zanubrutinib† + obinutuzumab

Third-line consolidation therapy

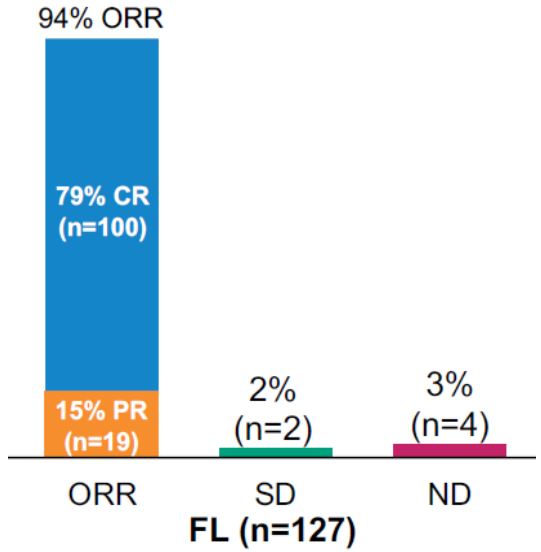
Useful in certain circumstances:

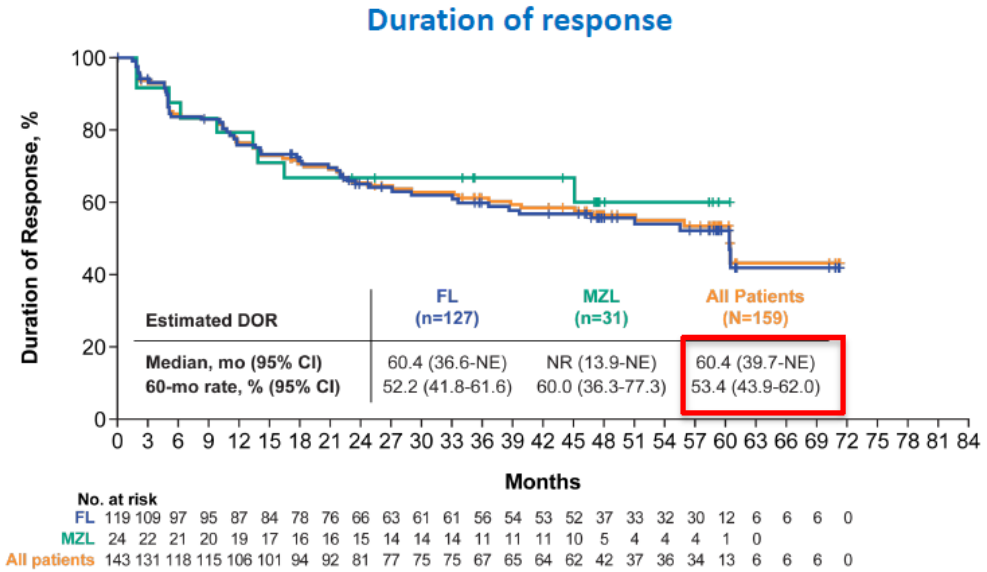
- Allogeneic haematopoietic cell transplantation in selected cases¶

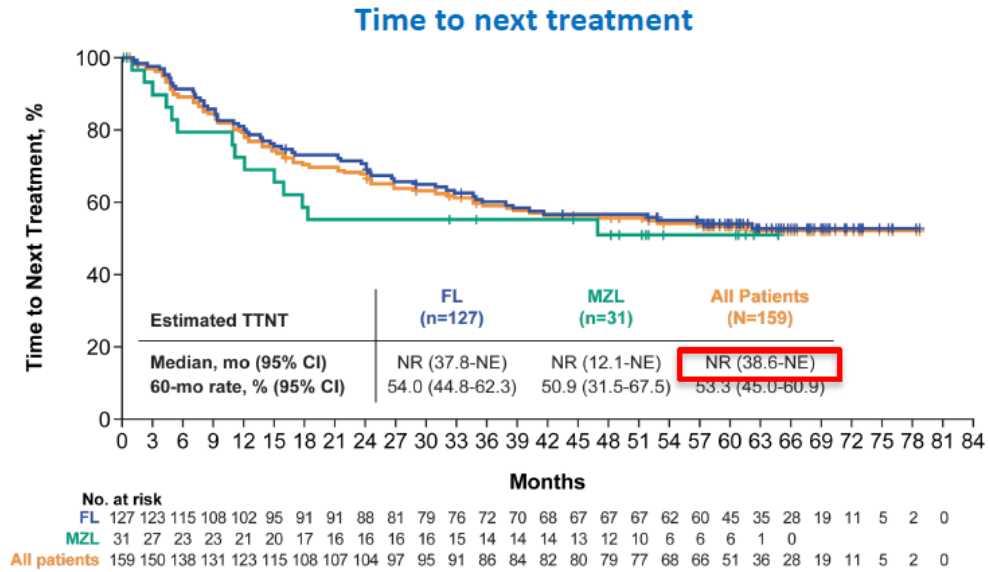
terapia di terza linea OGGi		*terapia di terza linea DOMANI*
	CAR T	
AXI CELL (ZUMA 5) TISACELL (ELARA)		LISOCELL (TRASCEND)
	BISPECIFICI	
MOSUNETUZUMAB		EPCORITAMAB ODRONEXTAMAB
	ALTRO	
		ZANUBRUTINIB TAFASITAMAB TAZEMETOSTAT


Timeline of FDA approvals of T-cell–redirecting therapies in follicular lymphoma
ZUMA-5 (NCT03105336)
ELARA (NCT03568461)
GO29781 (NCT02500407)
TRANSCEND-FL (NCT04245839)
EPCORE NHL-1 (NCT03625037)
ELM-2 (NCT03888105)
EPCORE FL-2 (NCT06191744)
MorningLyte (NCT06284122)
OLYMPIA-1 (NCT06091254)
OLYMPIA-2 (NCT06097364)
ZUMA-22 (NCT05371093)
LEDA (NCT05888493)
TRANSCEND-FL (NCT04245839)
EPCORE FL-1 (NCT05409066)
Celestimo (NCT04712097)
OLYMPIA-5 (NCT06149286)
Axi-cel
Tisa-cel
Mosunetuzumab
Liso-cel
Epcoritamab
Odronextamab
2L+ Ph3
2L/3L+
1L Ph3
March 2021
May 2022
Dec 2022
May 2024
June 2024
Aug 2024
3L+ FDA approvals
3L+ EMA-only approval
Ongoing BsAb trials
Ongoing CAR-T trials

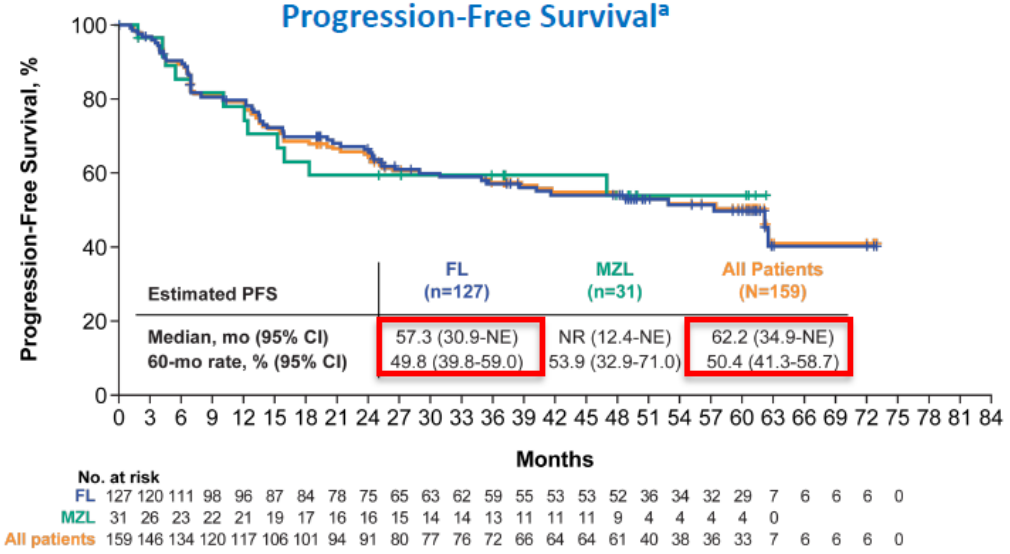
864. 5-Year Follow-up Analysis from ZUMA-5: A Phase 2 Trial of Axicabtagene Ciloleucel (Axi-Cel) in Patients with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma. *Neelapu S.S. et al*. Oral presentation.



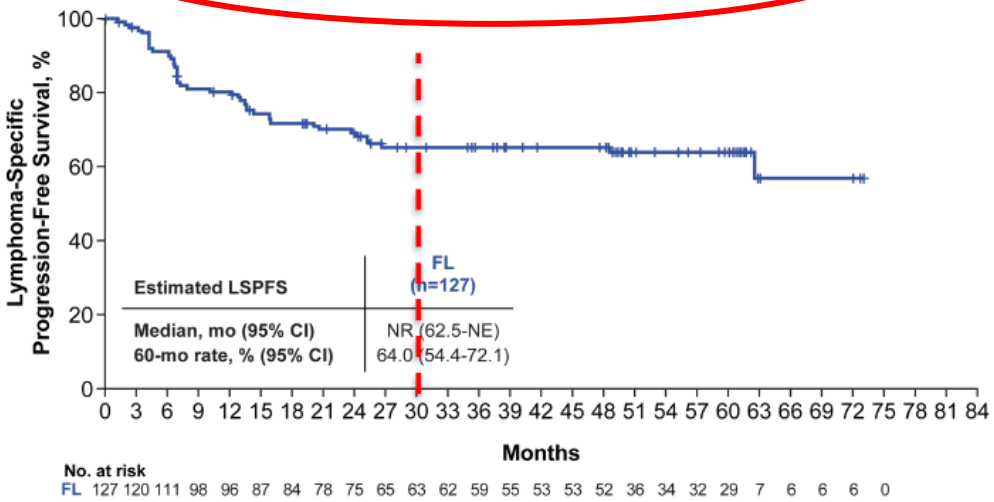




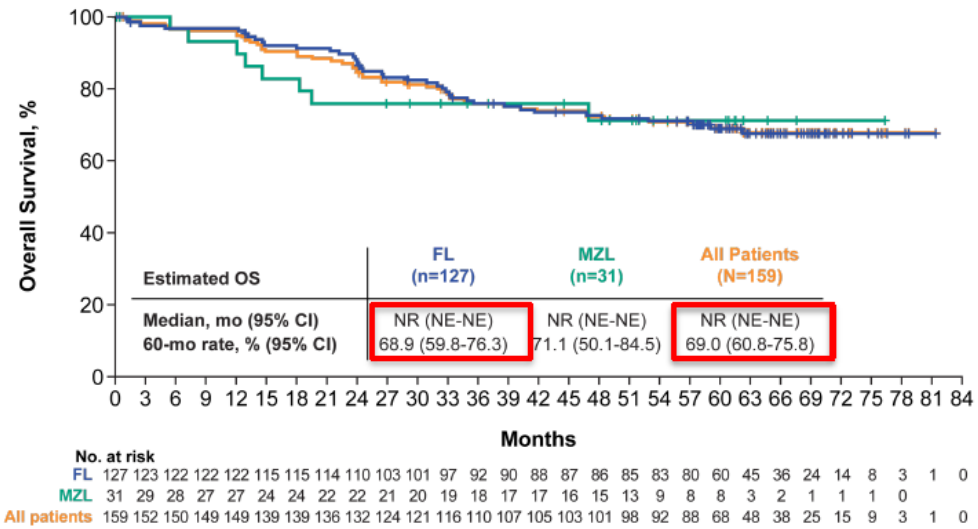
Progression-Free Survival[a]



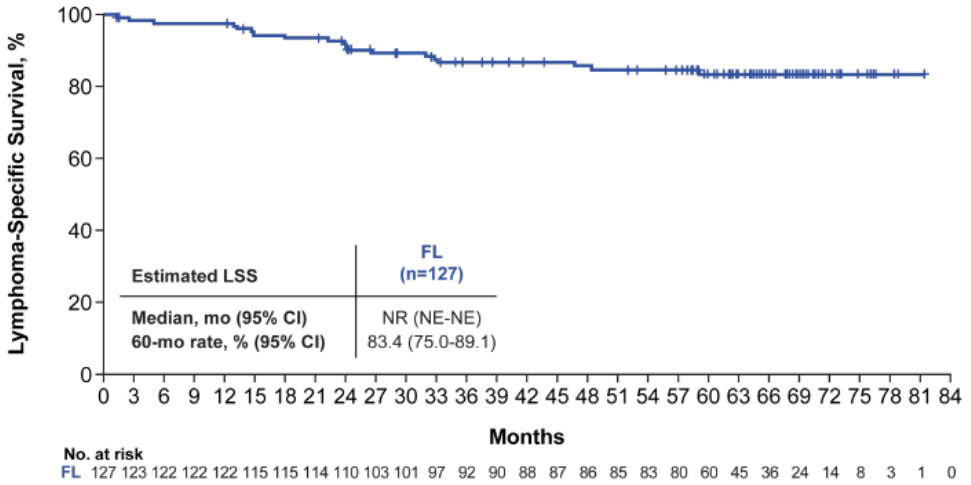
Lymphoma Specific Progression-Free Survival[a,b]



Overall Survival



Lymphoma Specific Survival[a]



Three CAR T-cell products for 3rd line + follicular lymphoma

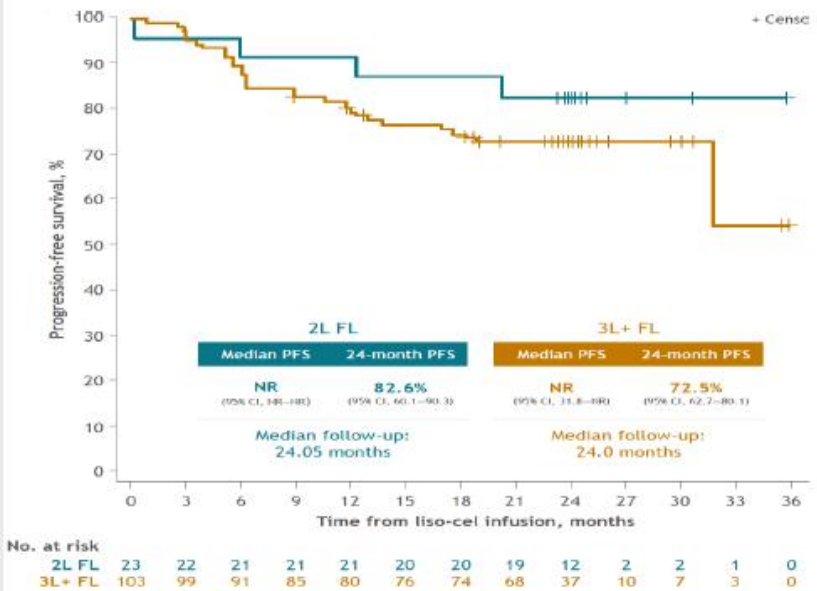
	Lisocabtagene Maraleucel TRANSCEND-FL	Tisagenlecleucel ELARA	Axicabtagene Ciloleucel ZUMA-5
n	107	94	124
Median # prior lines	3	4	3
Chemorefractory	67%	78%	68%
POD24	54%	60%	55%
CR rate	94%	69%	79%
Median PFS, m	NR	53 mo	57 mo
PFS	73% at 24m	50% at 60m	50% at 60m
CRS (Any/severe) %	58/1	49/0	82/7
NT (Any/severe) %	15/2	4/1	59/19
References	Morschhauser, et al. Nature Med 2024 Nastoupil, et al. Proc ASH 2024	Fowler, et al. Nat Med 2022. Thieblemont, et al.Proc ASH 2024	Jacobson, et al. Lancet Onc 2022 Neelapu, et al. Proc ASH 2024

DOMANI

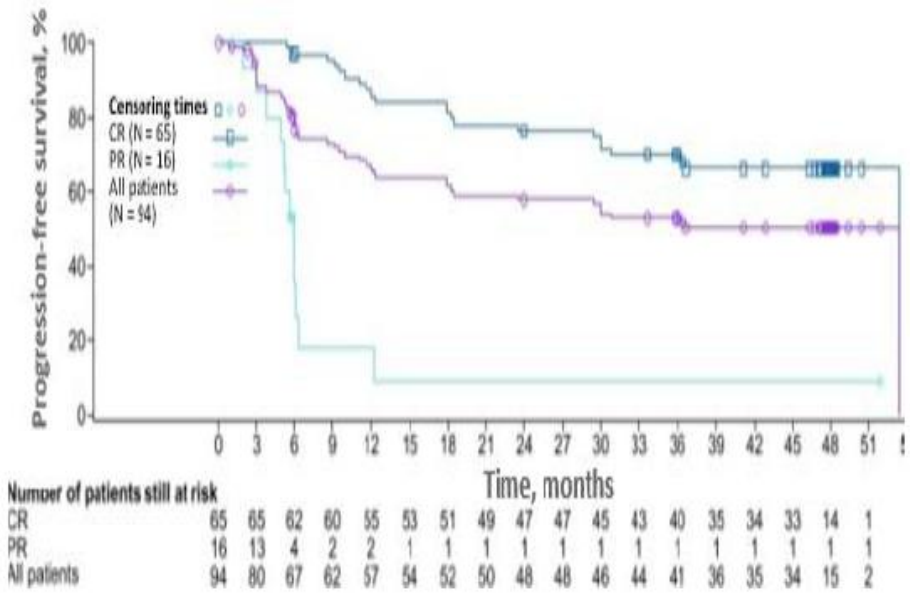
OGGI
Approvati in Italia

PFS for CAR T-cells in 3rd line or later FL

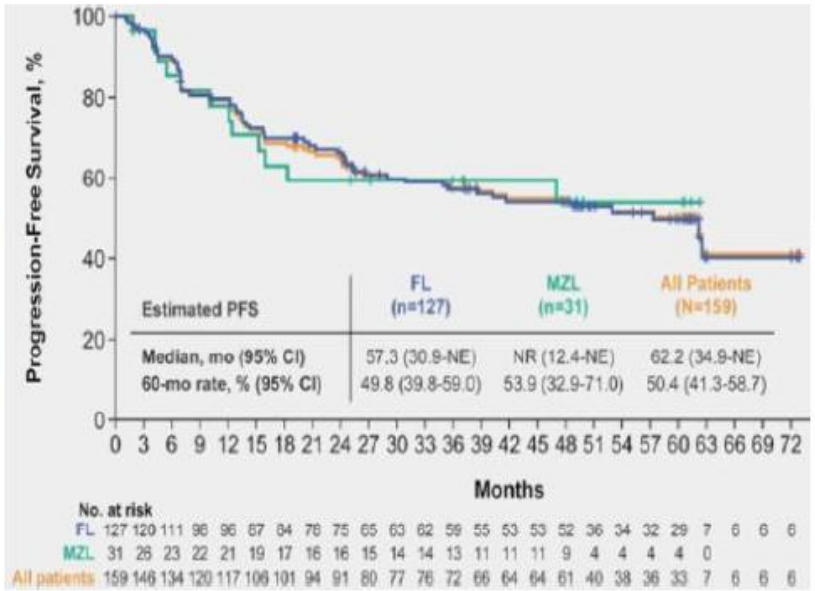
Liso-cel



Tisa-cel



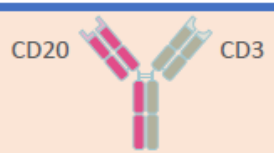
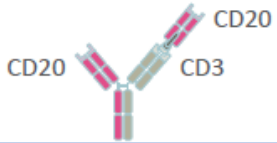
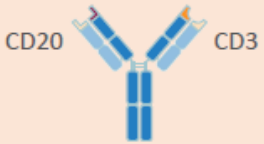
Axi-cel



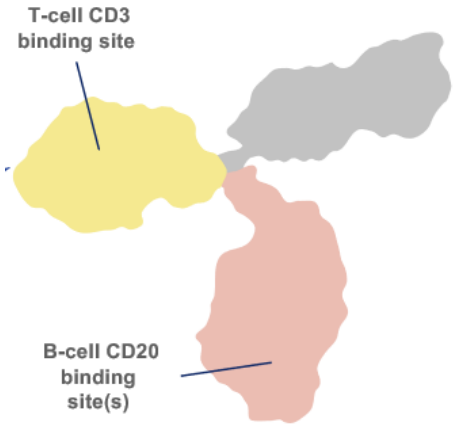
73% at 24m | **50% at 60m** | **50% at 60m**

BsAbs Being Explored in FL

Comparative Characteristics of CD20xCD3 BsAbs Currently in Development

Product Name	Schematic Depiction	Format	Technology	CD20:CD3 Ratio	CD3 Clone	CD20 Clone	Fc Silencing Mutations
Mosunetuzumab		IgG1	Knobs-into-holes (different Fabs)	1:1	UCHT1v9 (CD3δε)	2H7 (type 1 epitope, identical to rituximab)	N297G (no FcγR binding)
Glofitamab		IgG1	Head-to-tail fusion	2:1	SP34-der (CD3ε)	By-L1 (type 2 epitope, identical to obinutuzumab)	IgG1-P329G-LALA (no FcγR binding)
Epcoritamab		IgG1	Controlled Fab-arm exchange	1:1	huCACAO (SP34- der) (CD3ε)	7D8 (type 1 epitope, shared by ofatumumab)	L234F, L235E, D265A (no FcγR, C1q binding)
Odronextamab		IgG4	Heavy chains with different affinity	1:1	REG1250 (CD3δε)	3B9-10 (type 1 epitope, shared by ofatumumab)	Modified IgG4 (no FcγRIII binding)
Plamotamab		IgG1	Fab-Fc × scFv-Fc	1:1	α-CD3_H1_30 (SP34-der) (CD3ε)	C2B8_H1_L1 (type 1 epitope, shared by rituximab)	G236R, L328R (no FcγR binding)
IgM 2323		IgM	IgM + modified J chain	10:1	Not reported	Not reported	No

Not intended to be a cross-trial comparison. These Fc-silencing mutations do not abolish the binding of BsAb to neonatal FcR.
BsAb, bispecific antibody; Fab, fragment antigen binding; Fc, fragment crystallizable; FcR, Fc receptor; FcγR, Fcγ receptor; FcγRIII, Fcγ receptor III; IgG, immunoglobulin G; IgM, immunoglobulin M.
Adapted from Falchi L, et al. *Blood*. 2023;141(5):467-480.



Mosunetuzumab monotherapy 3L+ FL

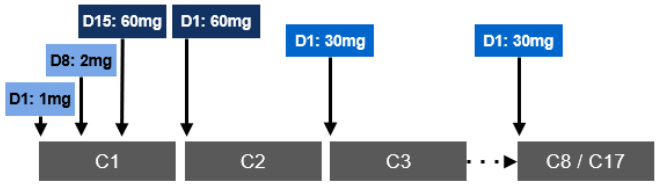
Pivotal cohort: single-arm, multicenter, Phase II expansion in patients with R/R FL and ≥2 prior therapies[1–3]

Eligibility

- FL (Gr 1–3a)
- ECOG PS 0–1
- R/R to ≥2 prior regimens, including:
  - ≥1 anti-CD20 antibody
  - ≥1 alkylating agent

Mosunetuzumab administration (N=90)

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



21-day cycles

- Fixed duration treatment
- C1 step-up dosing for for CRS mitigation
- Retreatment with mosunetuzumab permitted at relapse for patients who achieved CR
- Hospitalization was not mandatory*

Endpoints

Primary:
- IRF-assessed[4] CR rate (as best response)

Secondary:
- ORR
- DOR (DORC)
- PFS
- DOCR
- OS
- Safety
- PROs

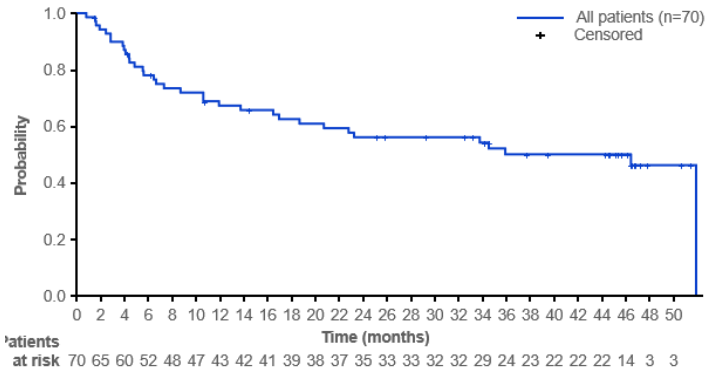
*Hospitalization not required routinely for all patients per-protocol or by licensed indication.[5,6]
Abbreviations in notes.

1. Budde LE, et al. ASH 2021; Oral presentation (abstract #127); 2. Budde LE, et al. Lancet Oncol 2022;23:1055–65; 3. Schuster SJ, et al. ASH 2023; Oral presentation (abstract #603); 4. Cheson J, et al. J Clin Oncol 2007;25:579–86; 5. LUNSUMIO™ EU SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/lunsumio-epar-product-information_en.pdf (Accessed December 2023); 6. LUNSUMIO™ US PI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761263s000lbl.pdf (Accessed December 2023).

Efficacy endpoint; n (%) [95% CI]	**Investigator assessed[1–3] N=90**	**IRF assessed[1,2] N=90**
CR*	54 (60) [49–70]	**54 (60)** [49–70]
ORR*	70 (78) [68–86]	**72 (80)** [70–88]

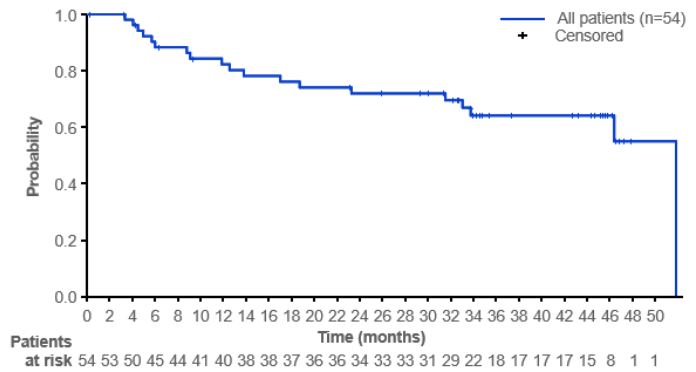
Time to first response (median [range]): **1.4 months** (1.0–11)[3]
Time to first CR (median [range]): **3.0 months** (1.0–19)[3]

DOR



	n=70
Median DOR, months (95% CI)*	46.4 (18.7–NE)
45-month DOR rate, % (95% CI)	50.1% (37.5–62.6)

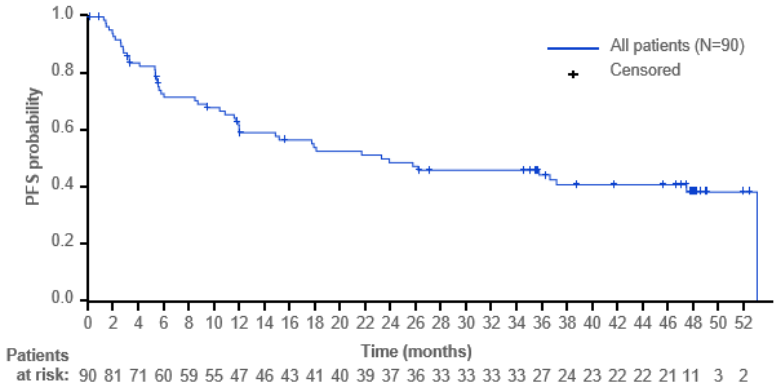
DOCR



	n=70
Median DOCR, months (95% CI)†	51.8 (46–NE)
45-month DOCR rate, % (95% CI)	64% (50.1–78.0)

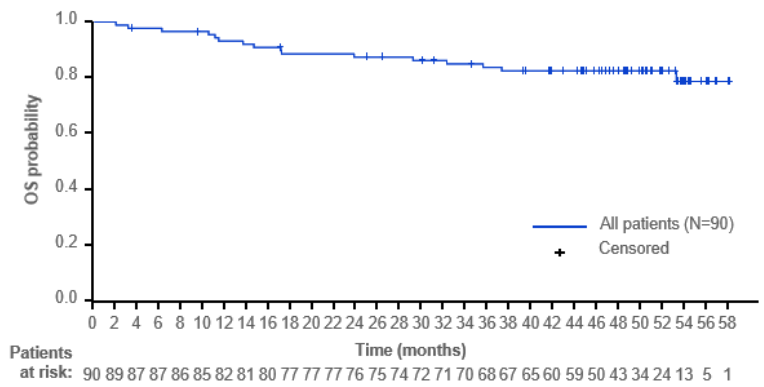
With a median follow up of 49.4 months, 2 out 3 patients (64%) with a CR are progression free

PFS



	N=90
Median PFS, months (95% CI)	**24.0** (12.0–NE)
48-month PFS, % (95% CI)	**38.6%** (27.1–50.2)

OS

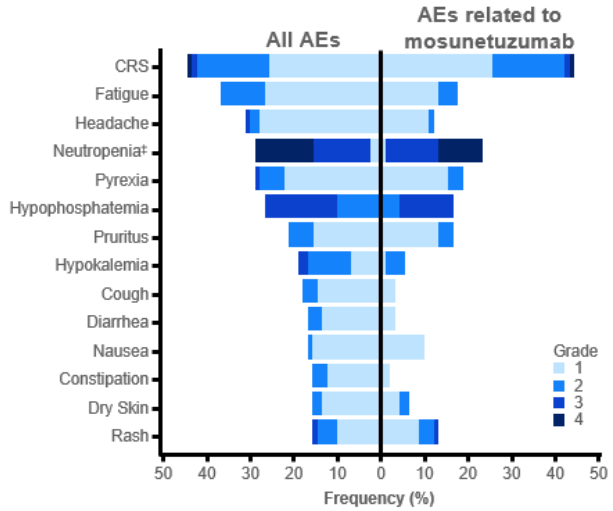


	N=90
Median OS, months (95% CI)	**NR** (NE–NE)
48-month OS, % (95% CI)	**82.7%** (74.7–90.7)

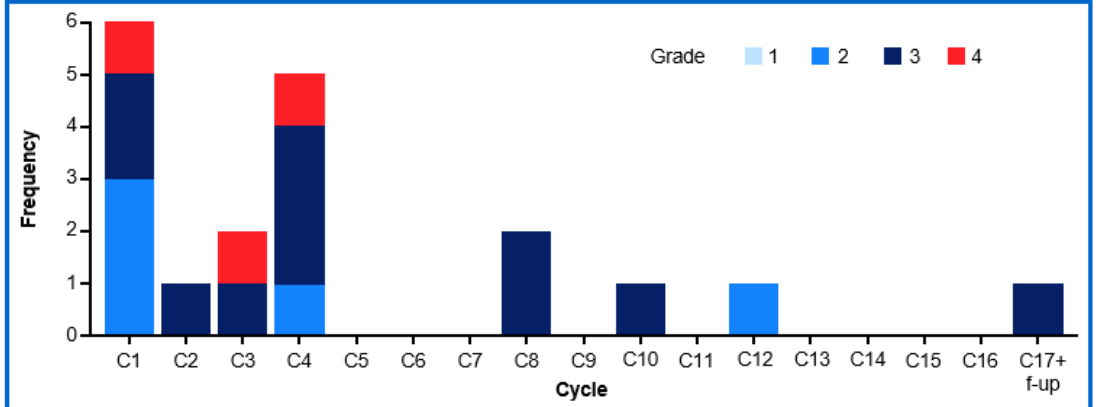
OS remained high after 4 years of follow up

AEs, n (%)	N=90
AE	90 (100)
Mosunetuzumab-related	83 (92)
Grade 3/4 AE	63 (70)
Mosunetuzumab-related	46 (51)
Serious AE	42 (47)
Mosunetuzumab-related	30 (33)
Grade 5 (fatal) AE	2 (2)*
Mosunetuzumab-related	0
AE leading to treatment discontinuation	4 (4)†
Mosunetuzumab-related	2 (2)

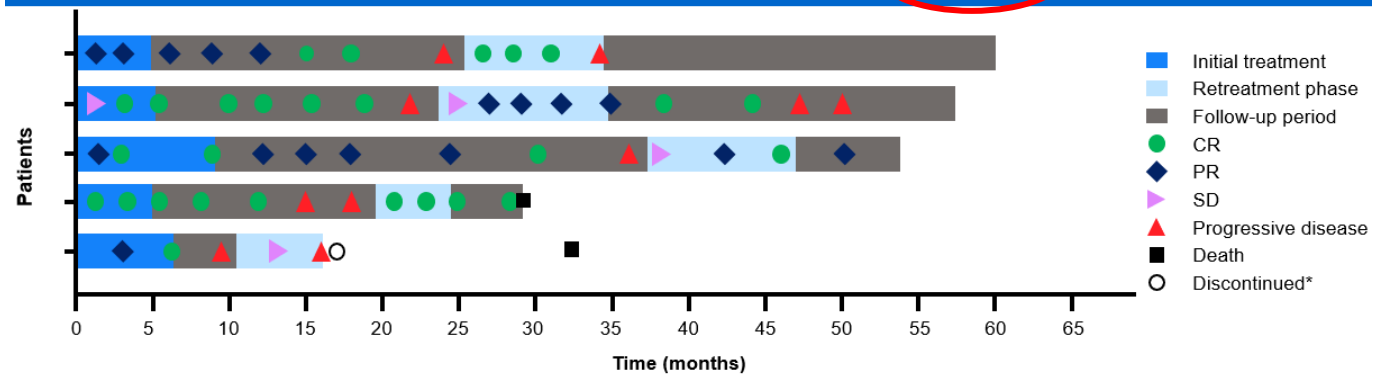
AEs (≥15%) by grade and relationship with mosunetuzumab



Serious infections by grade and cycle[2]



Response time to first treatment and retreatment

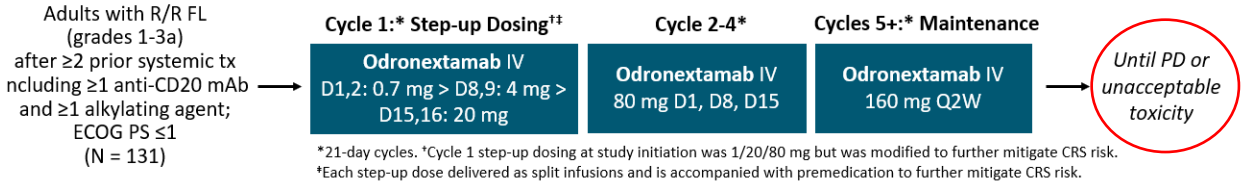


- Interval between the end of initial treatment to start of retreatment: 4.8–29.0 months

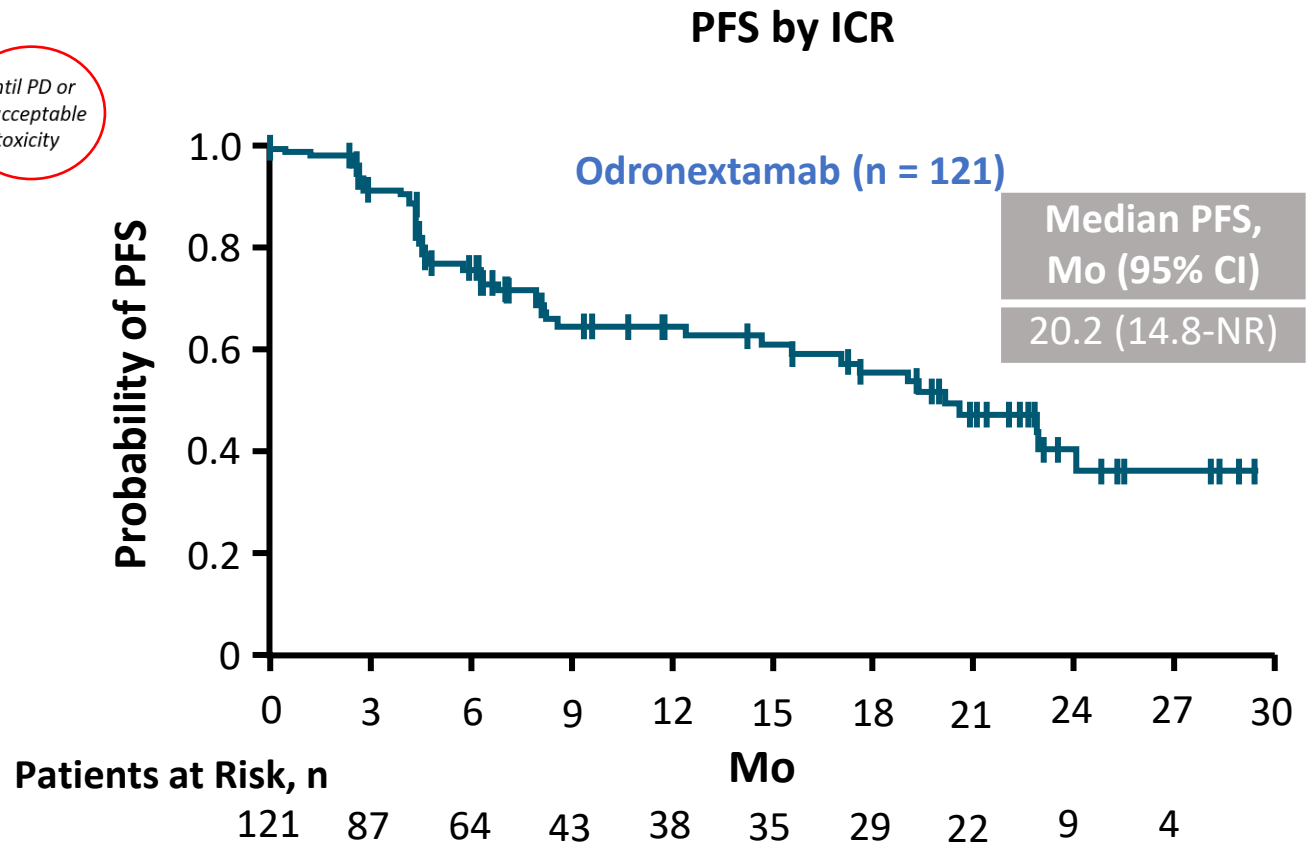
Of the 5 patients who received retreatment, 4 had a CR and 1 had SD following retreatment

ELM-2: Odronextamab Monotherapy in R/R FL

- Multicohort, open-label phase II study in R/R B-cell NHL
  - Current analysis reports FL cohort
  - Other disease-specific cohorts include DLBCL, MCL, MZL, other B-cell NHL subtypes



Best Overall Response	ICR (n = 121*)	Investigator (n = 121*)
ORR, % (95% CI)	81.8 (73.8-88.2)	81.8 (73.8-88.2)
▪ CR	75.2	70.2
▪ PR	6.6	11.6
SD	5.8	2.5
PD	4.1	5.8



EPCORE NHL-1: Epcoritamab in R/R B-Cell NHL

- Phase I/II open-label, dose escalation/expansion study

Patients with R/R CD20+ B-cell NHL after ≥2 previous lines of tx and ≥1 anti-CD20 mAb; ECOG PS 0-2; FDG PET-avid; measurable disease by CT/MRI; previous CAR T-cell therapy allowed (planned N = 700)

→

Cycle 1 Step-Up Dosing*

Epcoritamab SC
D1: 0.16 mg
D8: 0.8 mg
D15: 48 mg
D22: 48 mg

*With corticosteroid prophylaxis. To mitigate CRS.

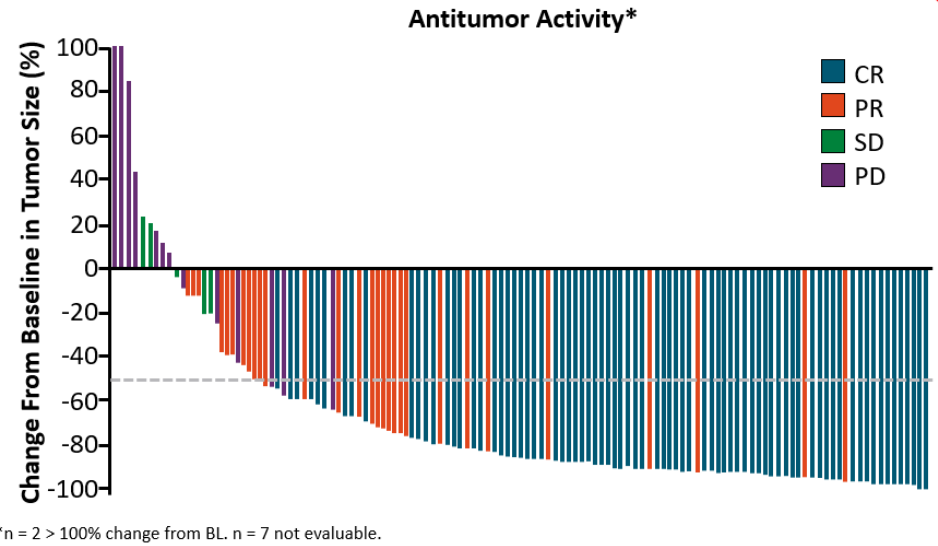
→

Epcoritamab 48 mg SC in 28-day cycles
QW cycles 2-3,
Q2W cycles 4-9,
Q4W cycles 10+

FL (grade 1-3A) cohort, n = 128
Median lines of tx:
3 (range: 2-9);
31% with ≥4
POD24: 42%

→ *Until PD or unacceptable toxicity*

- **Primary endpoint:** ORR by IRC
- **Secondary endpoints:** DoR, TTR, PFS, OS, CR rate, safety



*n = 2 > 100% change from BL. n = 7 not evaluable.

- ORR: 82%; CR: 63%
- Median PFS: 15.4 mo
- Median OS: NR
- CRS
  - Any grade: 66%
  - Grade 1: 40%
  - Grade 2: 25%
  - Grade 3: 2%
- ICANS in 8 patients

Pivotal trials for CAR-Ts and BsAbs in 3L+ FL

	CAR-Ts			BsAbs		
	Axi-cel	Tisa-cel	Liso-cel	Mosunetuzumab	Epcoritamab	Odronextamab
Main characteristics						
References	(25-27)	(28, 29)	(30)	(46-48)	(49)	(50)
Primary end point	ORR	CRR	ORR	CRR	ORR	ORR
Route	IV	IV	IV	IV	SC	IV
Duration	Single	Single	Single	Fixed	Indefinite	Indefinite
Apheresis, N	127	98	114	—	—	—
Treated, N	124	97	107	90	128	128
Median age, y*	60 (53-67)	57 (49-64)	62 (23-80)	60 (53-67)	65 (39-84)	61 (22-84)
Male, n (%)	73 (59%)	64 (66%)	66 (62%)	55 (61%)	79 (62%)	53%
POD24, n (%)†	68 (56%)	61 (63%)	58 (54%)	47 (52%)	42%	49%
Stage III-IV, n (%)	106 (85%)	83 (86%)	95 (89%)	69 (77%)	85%	85%
High-risk FLIPI (≥3), n (%)	54 (44%)	58 (60%)	61 (57%)	40 (44%)	61%	58%
Prior HCT, %	24%	36%	31%	21%	19%	31%
Prior lines, median	3	4	3	3	3	3
Bridging, n (%)	4 (3%)	44 (45%)	44 (41%)	—	—	—
FU, months	53.7	28.9	17.6	37.4	17.7	22.4

Iacoboni G and Morschhauser F. Blood 2025

	CAR-Ts			BsAbs		
	Axi-cel	Tisa-cel	Liso-cel	Mosunetuzumab	Epcoritamab	Odronextamab
Efficacy						
ORR (%)	94%	86%	97%	80%	82%	81%
CRR (%)	79%	68%	94%	60%	63%	73%
PFS, median (mo)	57.3	NR	NR	24	15.4	20.7
DoR, median (mo)	55.5	NR	NR	35.9	NR	22.6
TTNT, median (mo)	62.2	NR	NR	37.3	NR	—
OS, median (mo)	NR	NR	NR	NR	NR	NR

	CAR-Ts			BsAbs		
	Axi-cel	Tisa-cel	Liso-cel	Mosunetuzumab	Epcoritamab	Odronextamab
Safety						
CRS, any (%)	78%	49%	59%	44%	66%	57%‡
CRS G ≥3 (%)	6%	0	1%	2%	2%	2%‡
ICANS, any (%)	56%	4%	15%	6%	6%	2%‡
ICANS G ≥3 (%)	15%	1%	2%	0	0	0

Zanubrutinib Plus Obinutuzumab Versus Obinutuzumab in Patients With R/R Follicular Lymphoma: Updated Analysis of the ROSEWOOD Phase 2 Study

ROSEWOOD Study design[1]

Key eligibility criteria
- Age ≥18 years
- Grade 1-3A R/R FL
- Previous treatment with ≥2 lines of therapy, including an anti-CD20 antibody and an alkylating agent
- Measurable disease
- ECOG PS of 0-2
- Adequate organ function
- No prior BTK inhibitor

127 sites; 17 countries/regions
Randomized November 2017 to June 2021

Arm A
Zanubrutinib[a] + obinutuzumab[b] (N=145)
Until PD or unacceptable toxicity

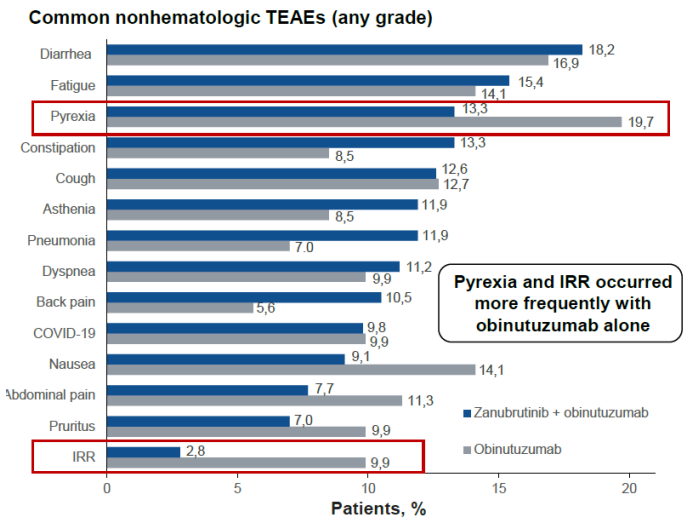
Randomization 2:1
Stratification factors
- Number of prior lines of treatment
- Rituximab-refractory status
- Geographic region

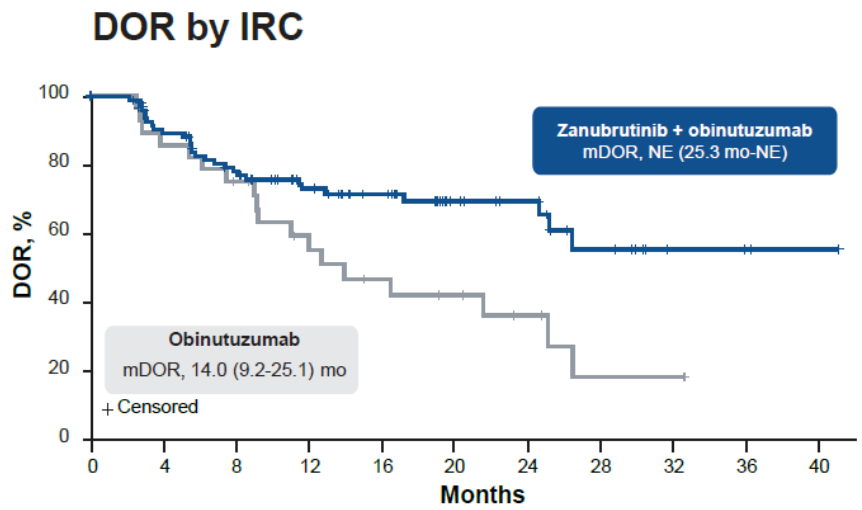
Arm B
Obinutuzumab[b] (N=72)
Option to cross over to combination if PD is centrally confirmed or if there is no response at 12 months

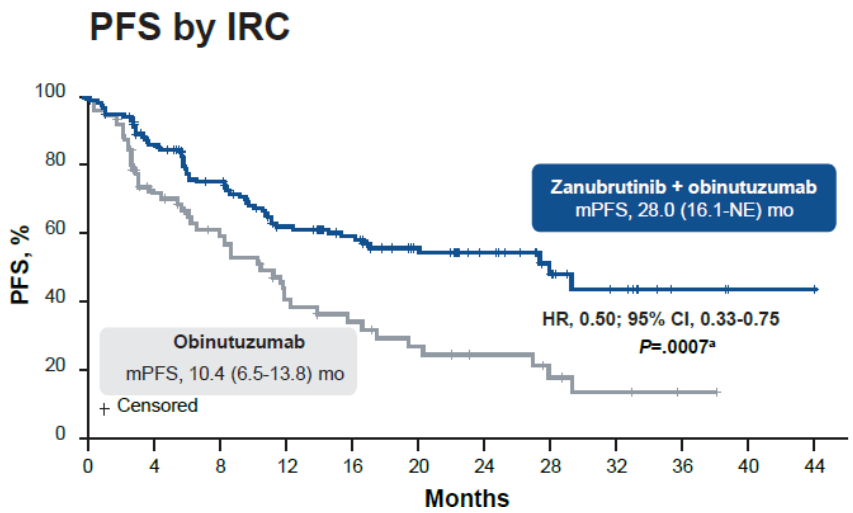
Primary endpoint
- ORR by IRC according to Lugano 2014 classification[2]

Other endpoints
- DOR by IRC[c]
- PFS by IRC[c]
- OS[c]
- TTNT
- Safety (AEs)[c]

Endpoint	Zanu + Obi (n=145)	Obi (n=72)	2-sided *P* value
ORR by IRC[a] (95% CI), %	**69.0** (60.8-76.4)	**45.8** (34.0-58.0)	.0012
CR	**39.3**	**19.4**	.0035
PR	29.7	26.4	–
DOR by IRC			
Median (95% CI), months	NE (25.3-NE)	14.0 (9.2-25.1)	–
18-month DOR rate (95% CI), %	**69.3** (57.8-78.2)	**41.9** (22.6-60.1)	–
DOCR by IRC			
Median (95% CI), months	NE (26.5-NE)	26.5 (2.7-NE)	–
18-month DOCR rate (95% CI), %	**87.4** (73.8-94.2)	**51.1** (21.0-74.9)	–







Tazemetostat is a first-in-class, selective, oral inhibitor of mutant and wild-type EZH2, an epigenetic regulator

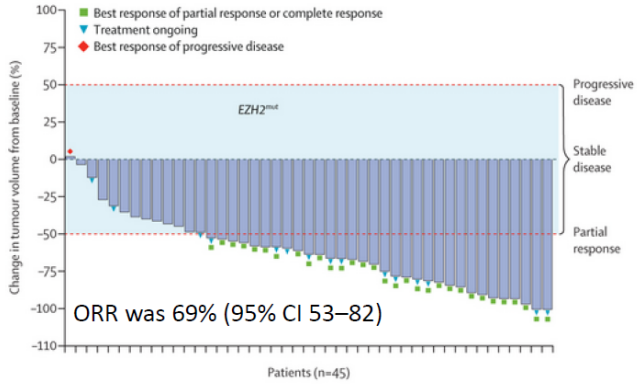
Activating mutations of EZH2 are present in approximately 20% of patients with follicular lymphoma.

Tazemetostat in R/R FL follicular lymphoma

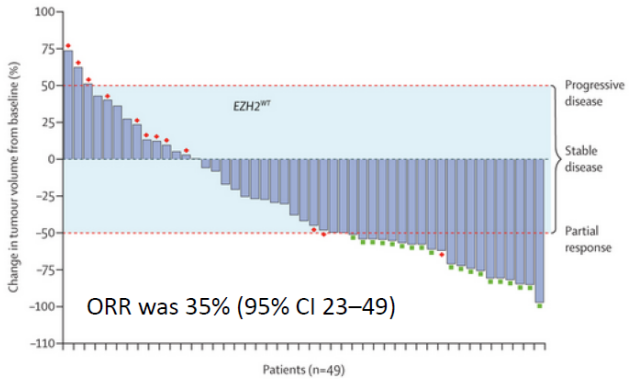
open-label, single-arm, multicentre, phase 2 trial

median follow-up
22·0 months (IQR 12·0-26·7) for the EZH2^{mut} cohort
35·9 months (24·9-40·5) for the EZH2^{WT} cohort

EZH2mut cohort

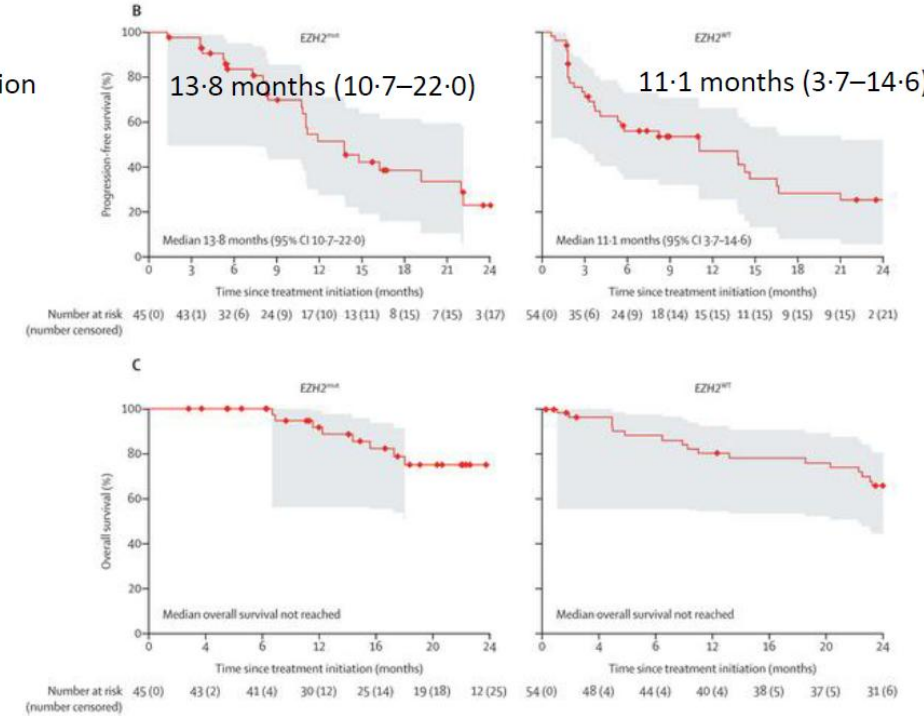


EZH2WT cohort



Morschhauser et al. Lancet Oncol . 2020 Nov;21(11):1433-1442

median progression free survival



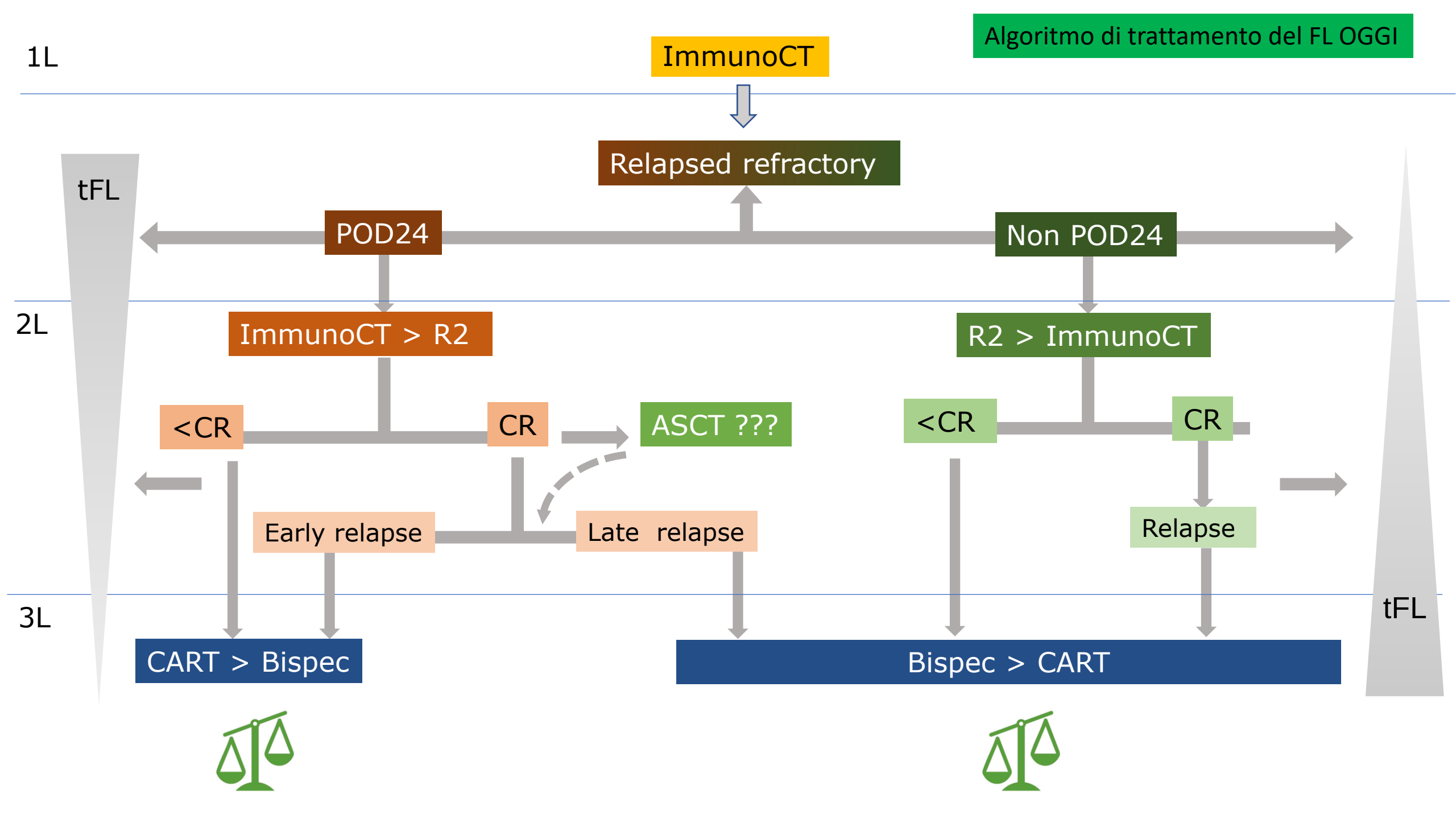
SYMPHONY-1 phase 1b trial design

Dose-escalating 3+3 design

Patients with R/R FL (N=44)

TAZ (12 cycles):
400/600/800 mg PO BID*
Rituximab (5 cycles):
375 mg/m^2 IV†
Lenalidomide (12 cycles):
20/10 mg PO QD‡

RP3D:
800 mg BID
TAZ (24 cycles)§

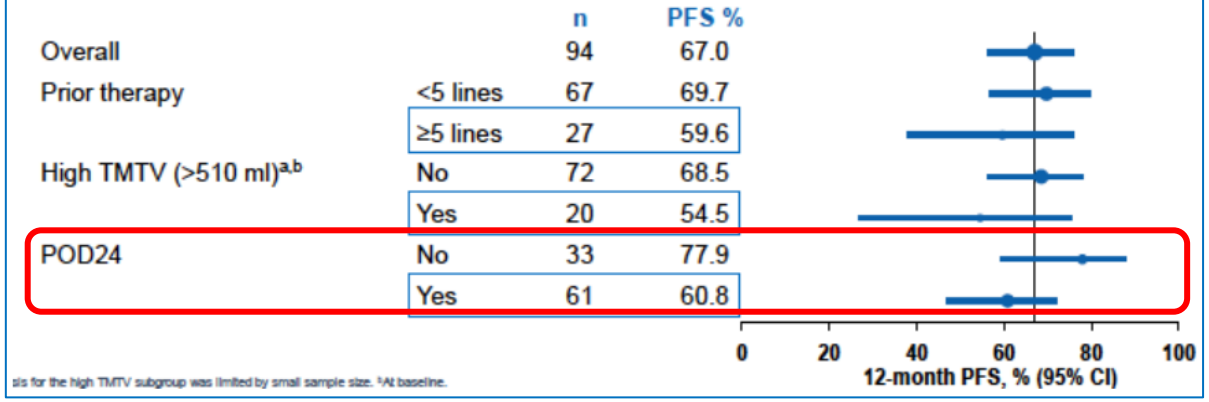

Algoritmo di trattamento del FL OGGI
1L
ImmunoCT
Relapsed refractory
tFL
POD24
Non POD24
2L
ImmunoCT > R2
R2 > ImmunoCT
<CR
CR
ASCT ???
<CR
CR
Early relapse
Late relapse
Relapse
3L
tFL
CART > Bispec
Bispec > CART

POD24: Efficacia CAR-T e Bispecifici

ZUMA-5 Outcomes by POD24 Status

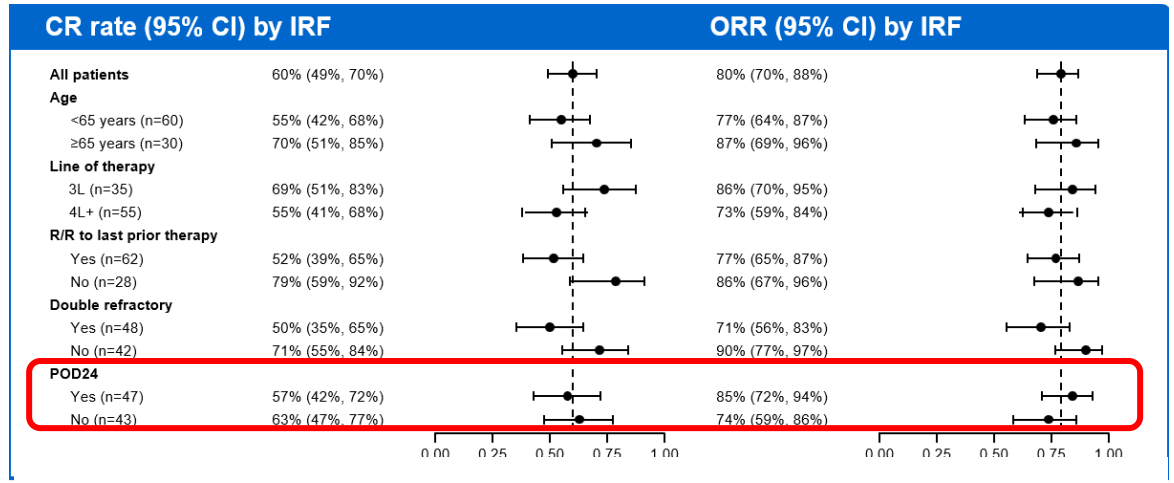
Parameter (95% CI)	Follicular Lymphoma (n=78)[a]	
	With POD24 (n=49)	Without POD24 (n=29)
Median DOR, months	38.6 (14.5–NE)	NR (24.7–NE)
24-month rate, %	61.1 (44.3–74.3)	72.4 (50.2–85.9)
Median PFS, months	39.6 (13.1–NE)	NR (25.7–NE)
24-month rate, %	57.3 (41.2–70.4)	73.0 (51.1–86.2)
Median OS, months	NR (39.6–NE)	NR (NE–NE)
24-month rate, %	77.6 (63.1–86.9)	85.9 (66.7–94.5)

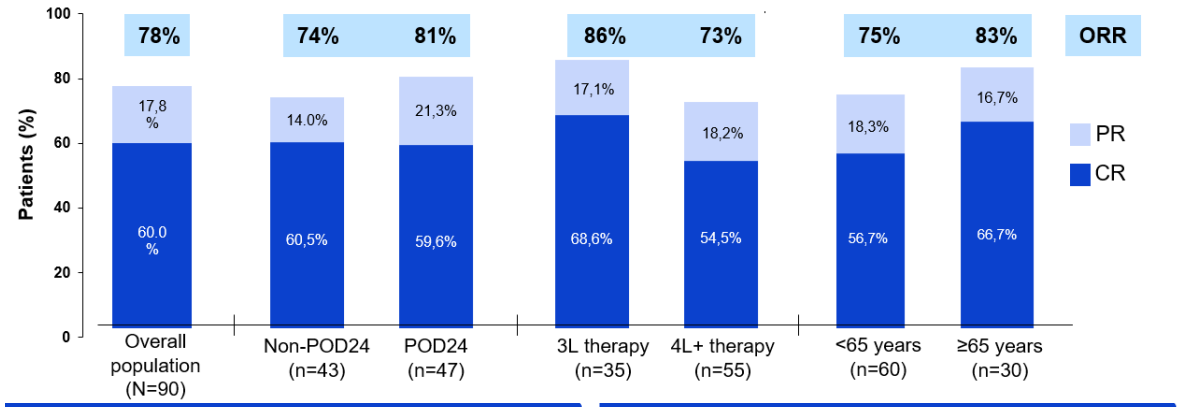
ELARA: Predictors of Outcome

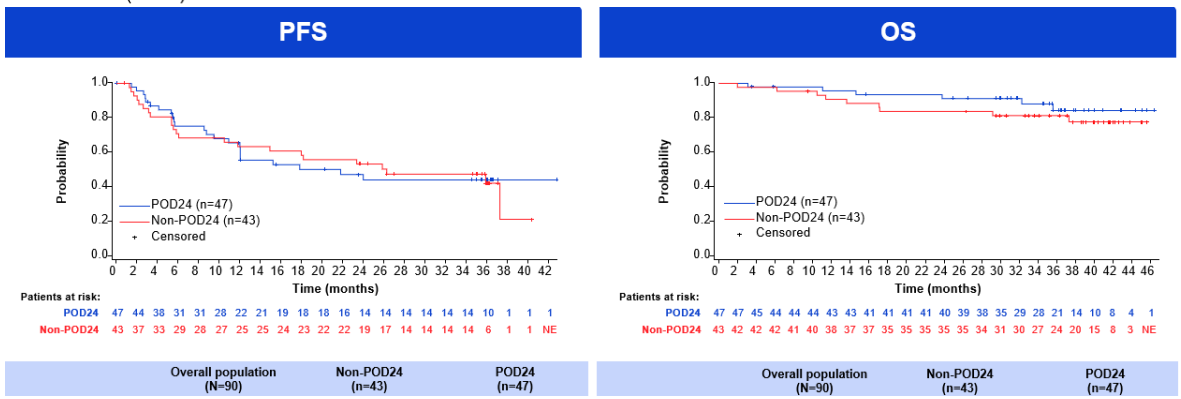


sis for the high TMTV subgroup was limited by small sample size. [a]At baseline.

mosunetuzumab in 3L+ FL







Vantaggi CAR-T

- Elevata efficacia nel FL (CR, PFS > Bispe)
- Terapia ONE SHOT
- Efficacia nei POD24
- Plateau?

Vantaggi BISPECIFICI

- Minore CRS/ICANS
- Pronti all'uso, anche in centri non CAR-T
- Terapia OUT-PATIENT
- Efficacia nei POD24
- Costi più accessibili
- Possibilità di combinazione con agenti chemo/chemo-free

Algoritmo di trattamento del FL DOMANI

1L

ImmunoCT

R2

BISPEC ± x

Relapsed refractory

2L+

R2
BISPEC + X
TAFA+ R2
CART

BISPEC
CART
(ImmunoCT)

CART
TAFA
ZANU
(ImmunoCT)

TAKE HOME MESSAGE

- Il panorama terapeutico del LF è in rapida evoluzione, con molti promettenti studi sia in fase avanzata che in 1L
- BsAbs, da soli o in combinazione, saranno utilizzati in più precoci fasi di trattamento
- I risultati condurranno potenzialmente alla eliminazione della chemioterapia e gli algoritmi di trattamento dovranno essere totalmente ridisegnati sia in fase avanzata che in 1L
- ***T-cell engagers inseriti da soli o in combinazione nei vari algoritmi di trattamento avvicinano l'obbiettivo della CURA del LF***

grazie