POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

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Verona
Palazzo della Gran Guardia
15-16-17 Febbraio 2024

LINFOMI INDOLENTI

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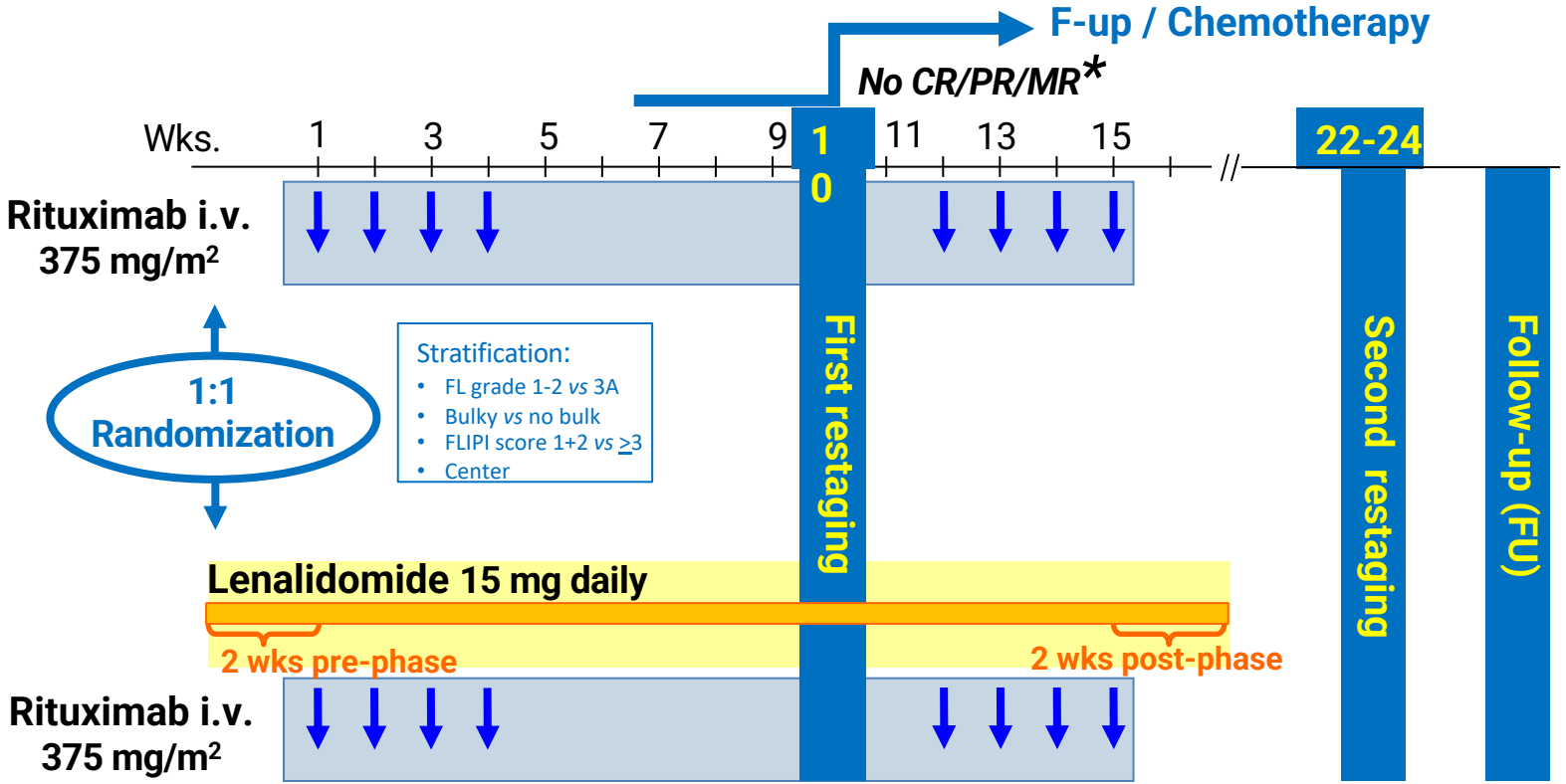
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche						x	
Beigene						x	
GIlead/Kite						x	
Jannsen						x	
Novartis						x	
Sobi						x	
Regeneron						x	
Abbvie						x	

Contributi sui linfomi indolenti all'ASH 2023 – Linfoma follicolare

STUDI RANDOMIZZATI

Long term results of the SAKK 35/10 Ph III trial of Rituximab vs Rituximab and Lenalidomide in FL in need of First Line therapy

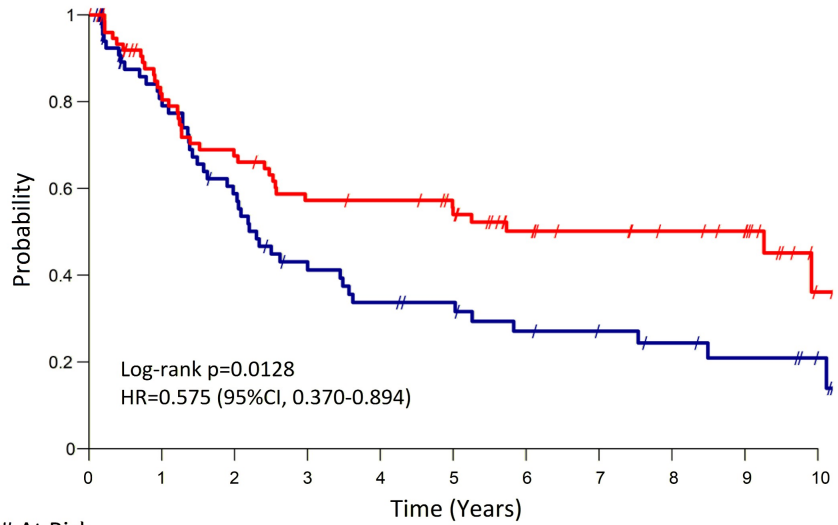


*MR >25% decrease in SPD

E. Zucca et al. ASH 2023

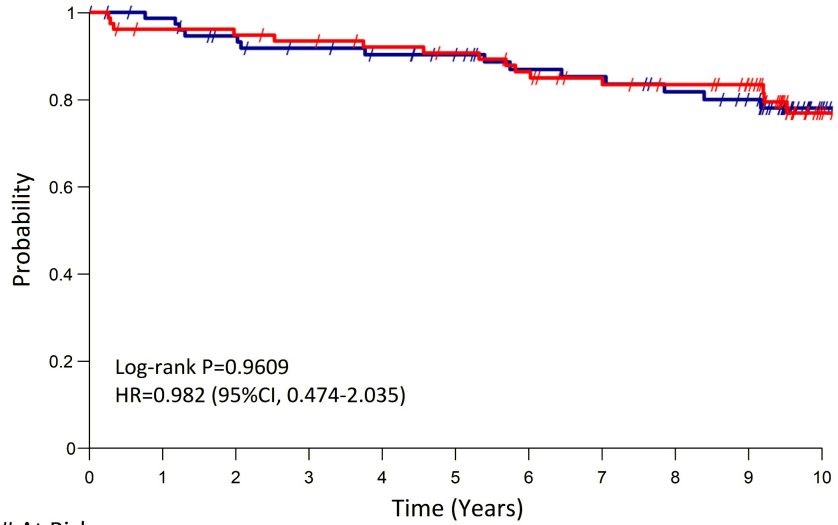
Long term results of the SAKK 35/10 Ph III trial of Rituximab vs Rituximab and Lenalidomide in FL in need of First Line therapy

Progression-free Survival



# At Risk											
R	77	48	34	23	18	16	12	10	8	6	3
R+L	77	57	47	39	38	33	24	20	17	15	3

Overall survival



# At Risk											
R	77	73	67	63	60	57	51	50	46	43	19
R+L	77	72	71	69	66	64	60	55	52	48	22

E. Zucca et al. ASH 2023

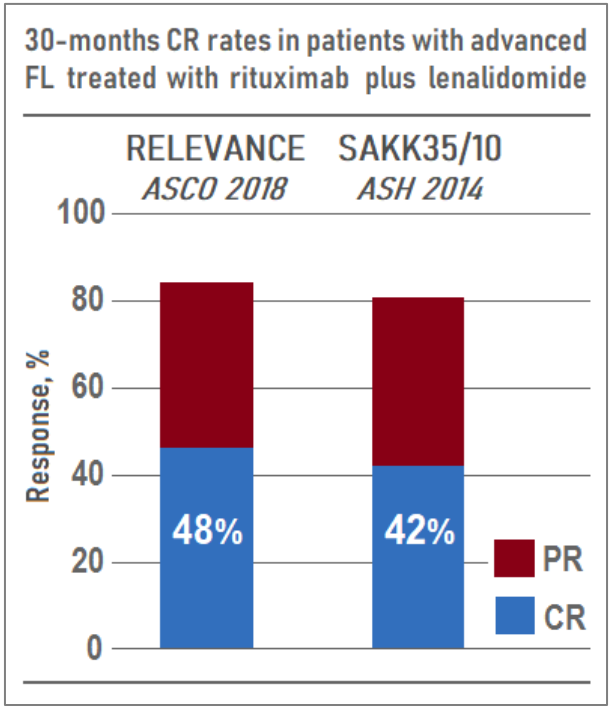
Comparison of different R+ L schedules

RELEVANCE[1]

R 375 mg/m2/wk in cycle 1, d1 on cycles 2-6, then q 8 wks x 12 cycles

L 20 mg/d d2-22 until CR/Cru at 6, 9 or 12 cycles then 10 mg/d (total 18 cycles)

6-yr OS, 89%
6-yr PFS, 60%



SAKK 35/10[2]

R 375 mg/m2/wk on wks 1-4 and 12-15

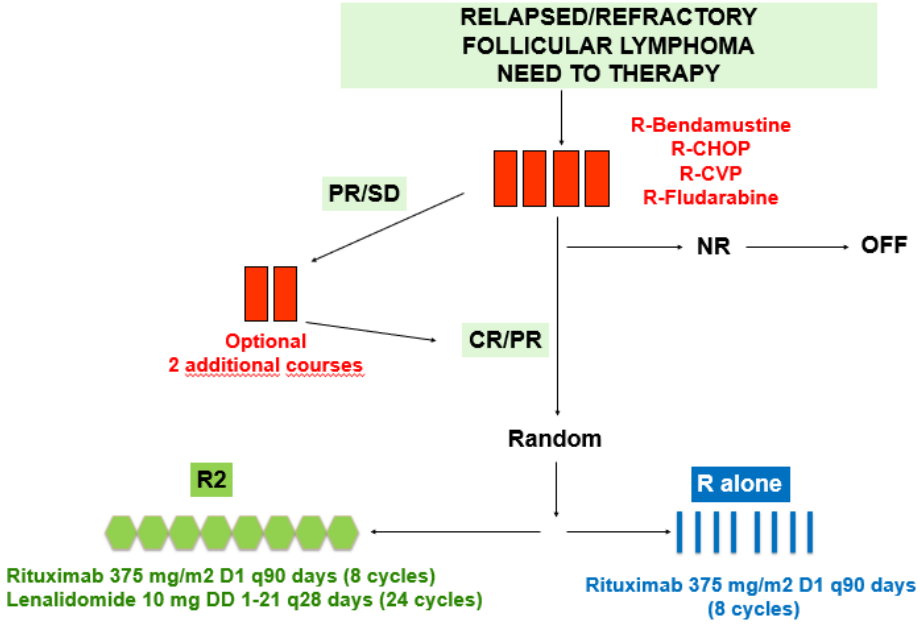
L 15 mg/d d1-28 x 6 months (total 6 cycles)

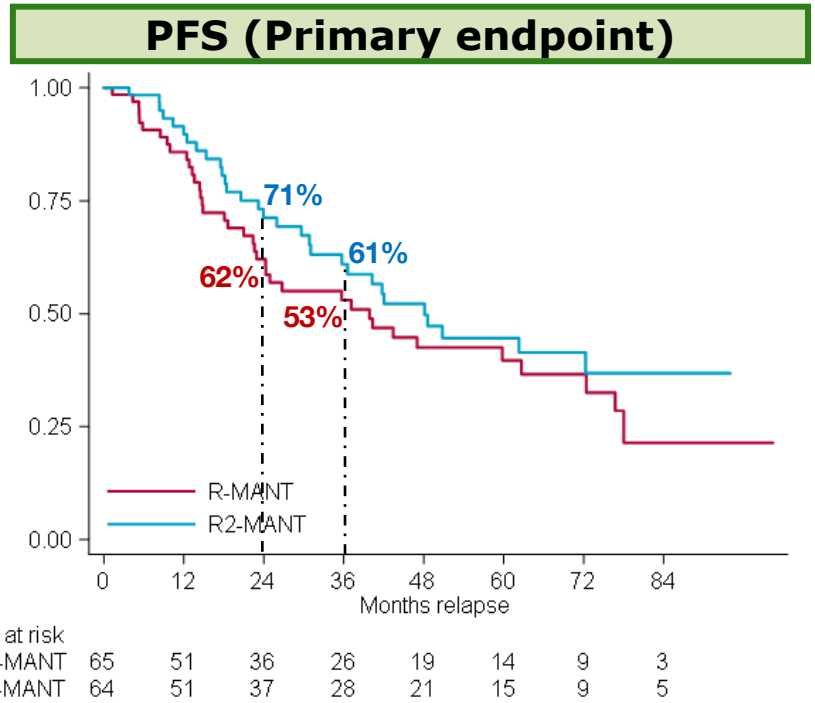
6-yr OS, 86%
6-yr PFS, 50%

[1] *Morschhauser et al. J Clin Oncol 2022*

[2] *Zucca et al. Blood 2019*

Rituximab and Lenalidomide (R2) Vs Rituximab Alone As Maintenance Treatment after Chemoimmunotherapy for Elderly Patients with Relapsed/Refractory Follicular Lymphoma (FL): Final Analysis of Renoir Phase III Study of the Fondazione Italiana Linfomi (FIL)

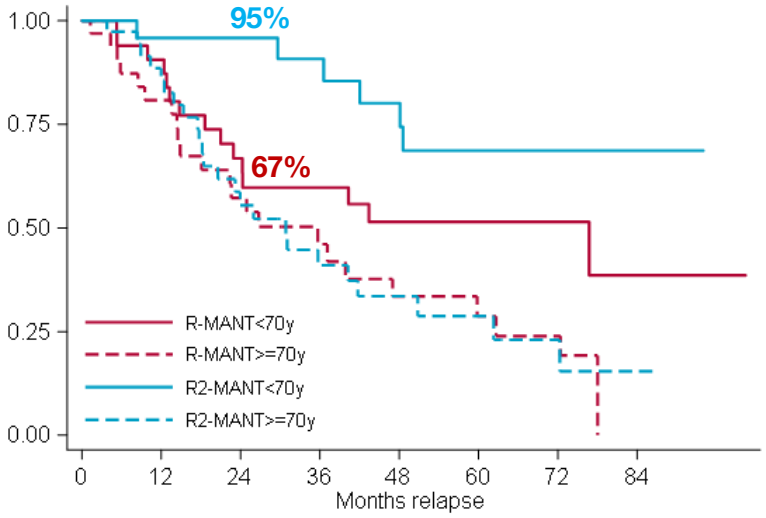




C. Boccomini et al. Oral Presentation ASH 2023

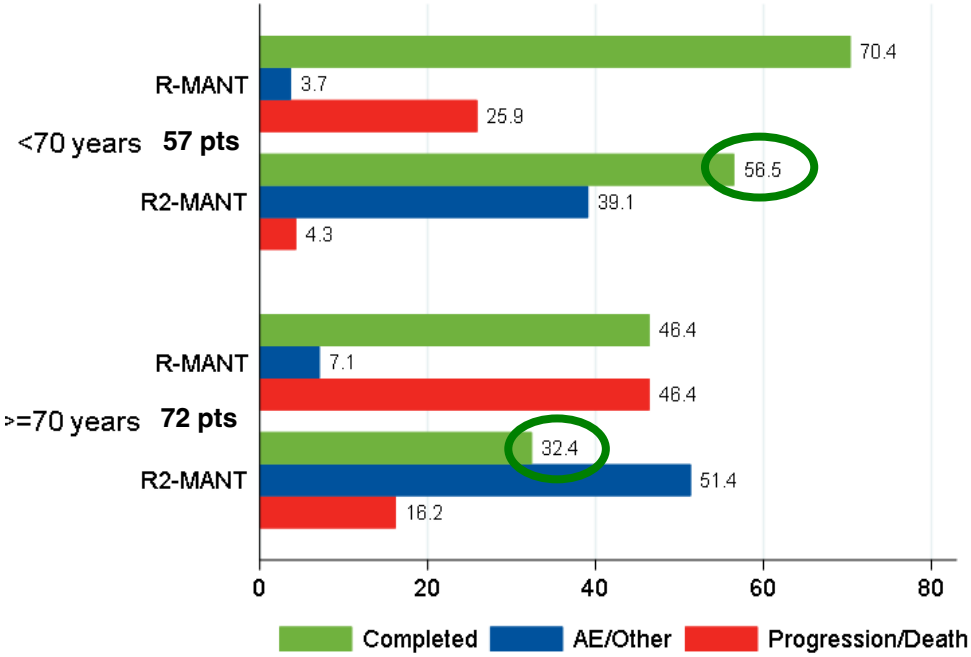
PFS R vs R2 Maintenance by Age: </≥ 70-yrs

2-yr PFS



Number at risk

R-MANT<70y	33	27	19	15	11	8	4	3
R-MANT>=70y	32	24	17	11	8	6	5	0
R2-MANT<70y	24	22	20	17	14	10	6	4
R2-MANT>=70y	40	29	17	11	7	5	3	1



C. Boccomini et al. Oral Presentation ASH 2023

Contributi sui linfomi indolenti all'ASH 2023 – Linfoma follicolare

STUDI NON RANDOMIZZATI

Ph II Study of Mosunetuzumab ev in RR FL PFS and OS; median follow-up >36 months

Pivotal, single-arm, Phase II expansion study in patients with R/R FL and ≥2 prior therapies (NCT02500407)

Key inclusion criteria

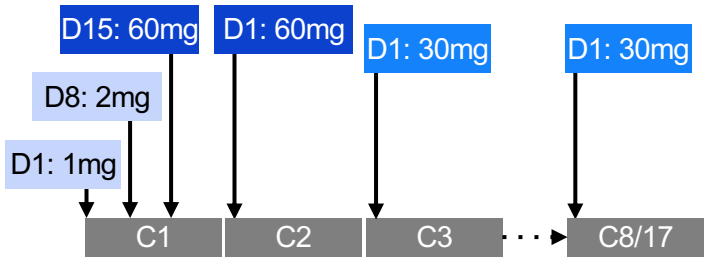
- FL Grade 1–3a
- ECOG PS 0–1
- ≥2 prior therapies including an anti-CD20 antibody and an alkylator

Data analysis

- Study met its primary endpoint: 60% CR rate versus 14% historic control ($p<0.0001$)[1,2]
- Updated efficacy and safety analysis with a median follow-up of 37.4 months

Mosunetuzumab administration

- IV mosunetuzumab administered in 21-day cycles with step-up dosing in C1
- Fixed-duration treatment: 8 cycles if CR after C8; 17 cycles if PR/SD after C8
- Retreatment with mosunetuzumab permitted at relapse for patients who achieved CR
- No mandatory hospitalization



D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; PR, partial response; SD, stable disease.

1. Dreyling M, et al. J Clin Oncol 2017;35:3898–905;
2. Budde LE, et al. Lancet Oncol 2022;23:1055–65.

Schuster et al., Oral presentation ASH 2023

Baseline patient characteristics

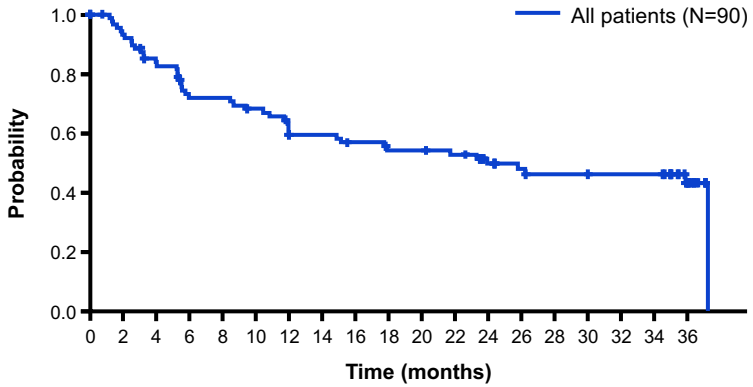
n, unless stated	N=90
Median age, years (range)	60 (29–90)
Male	55 (61%)
ECOG PS	
0	53 (59%)
1	37 (41%)
Ann Arbor stage	
I/II	21 (23%)
III/IV	69 (77%)
Median lines of prior therapy, (range)	3 (2–10)
Prior autologous stem cell transplant	28 (31%)*
Refractory to last prior therapy	62 (69%)
Refractory to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

*Data updated based on subsequent snapshot.

Schuster et al., Oral presentation ASH 2023

Ph II Study of Mosunetuzumab ev in RR FL PFS and OS; median follow-up >36 months

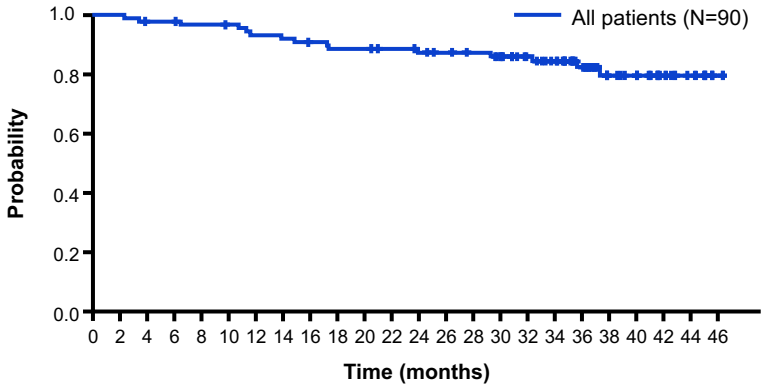
PFS



Patients at risk 90 81 72 60 59 55 47 46 43 40 40 38 30 27 25 25 24 24 13

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

OS



Patients at risk 90 89 87 86 85 84 81 80 78 76 76 74 72 70 68 62 56 51 39 26 21 14 8 1

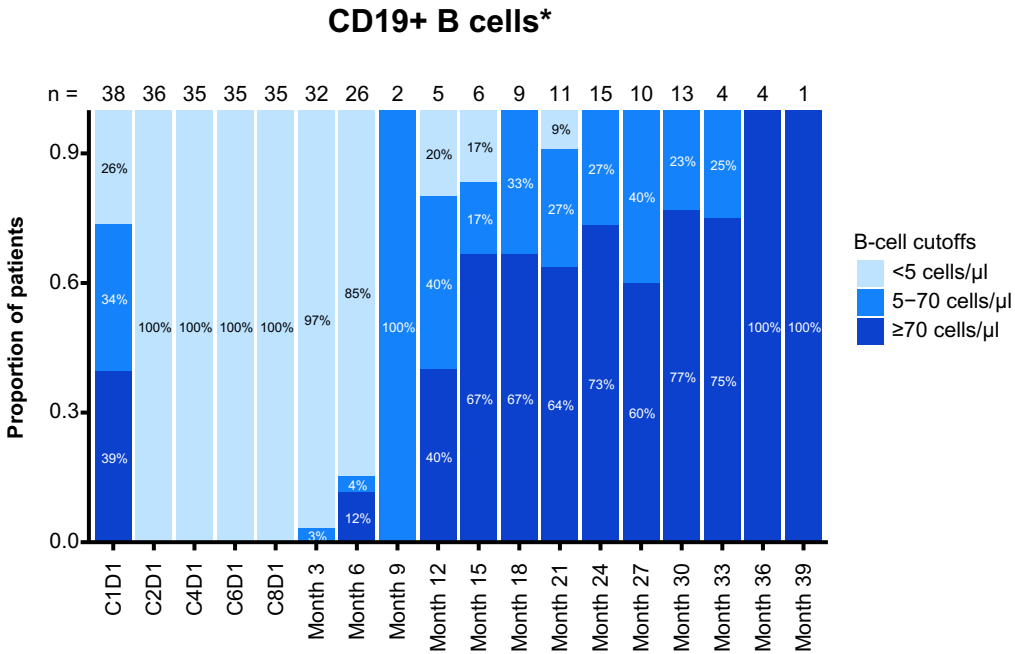
	N=90
Median OS, months (95% CI)	**NR** (NE–NE)
36-month OS, months (95% CI)	**82.4%** (73.8–91.0)

Robust and stable progression-free and overall survival rates at 3 years

OS, overall survival; PFS, progression-free survival.

Schuster et al., Oral presentation ASH 2023

B-cell depletion and recovery



- Peripheral blood B-cell depletion following treatment with mosunetuzumab occurred rapidly by the initiation of C2 dosing in all patients (n=74)
- Time-to-event analysis in patients with end-of-treatment (C8) and follow-up samples (n=38) was performed to assess B-cell recovery
  - Median time to recovery to quantitative levels was 18.4 months (95% CI: 12.8–25.0)
  - Median time to recover to the lower level of normal was 25.1 months (95% CI: 19.0–NE)

*CD19+ B cells were monitored by flow cytometry at C1, C2, C4, and C8, and every 3 months during follow-up or until progression or next lymphoma treatment. The lower limit of quantitation was 5 cells/µl and the lower limit of normal was 70 cells/µl. Depletion was analyzed in all patients with a pre-dose and at least one on-treatment sample. Recovery was analyzed in patients with a CR and at least one follow-up sample.

New anti-lymphoma therapy or retreatment with mosunetuzumab

n, unless stated	N=90
Median TTNT, months (95% CI)	37.3 (18.0–NE)
Any new anti-lymphoma therapy	36 (40%)
New systemic treatments	35 (39%)
Chemo +/- immunotherapy	20 (22%)
PI3K inhibitors +/- immunotherapy	10 (11%)
CAR T-cell therapy	9 (10%)
BTK inhibitors +/- venetoclax	5 (6%)
Lenalidomide +/- immunotherapy	4 (4%)
Radiotherapy	9 (10%)
Excision of tumor	2 (2%)
Allogeneic stem cell transplant	2 (2%)
Autologous stem cell transplant	2 (2%)

5 patients received mosunetuzumab retreatment

Response to mosunetuzumab retreatment; n	n=5
CR	3 (60%)
PR	0
SD	2 (40%)
PD	0

BTK, Bruton tyrosine kinase; CAR, chimeric antigen receptor; chemo, chemotherapy; PD, progressive disease; PI3K, phosphoinositide 3-kinase; TTNT, time to next therapy or death.

Schuster et al., Oral presentation ASH 2023

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

	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%
Epcoritamab	128	39-84	NA/42	17.4m	82/63	14.4 mo	48%,0%	G5 AE 13pts 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%

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. 4. **Shuster et al., ASH 2023 5. Linton et al., ASH 2023 6. Villasboas et al., ASH 2023**

Subcutaneous mosunetuzumab in 1L FL

Phase II trial

Eligibility:

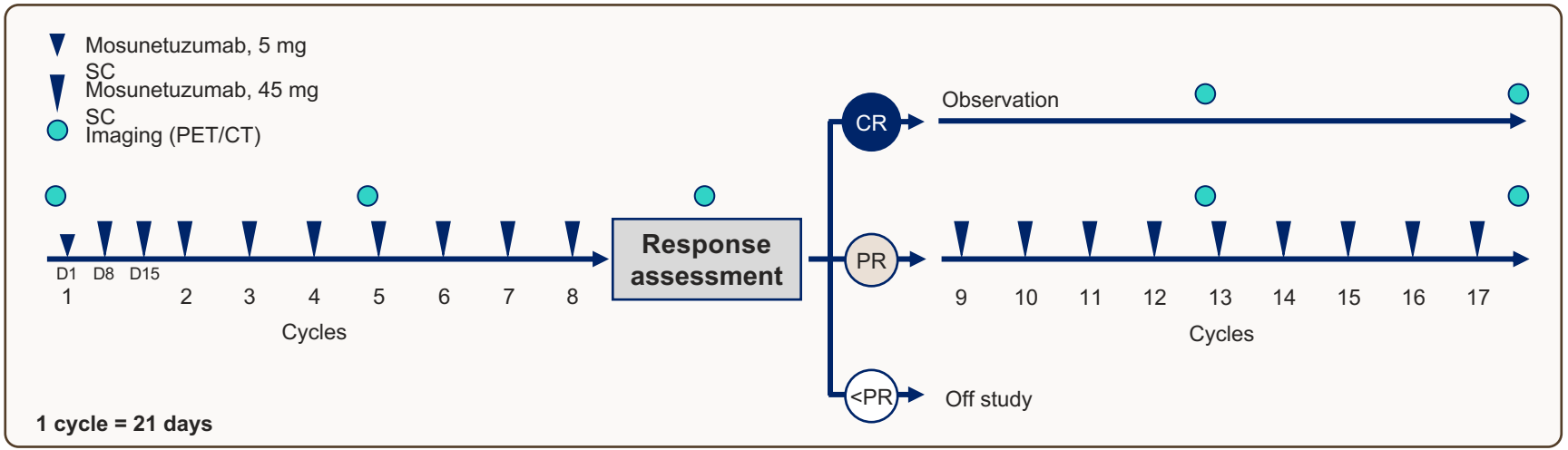
- ≥18 years; PS 0-2
- CD20+ FL, G1-3A, stage II–IV
- Need of therapy per GELF criteria
- Candidate for chemoimmunotherapy

Endpoints:

- **Primary:** CR per Lugano + LYRIC
- **Secondary:** ORR, TEAE, PFS, DOR, TTNT, OS
- **Exploratory:** PD, ctDNA monitoring

Premedication and supportive care:

- Dexamethasone, anti H2, acetaminophen during C1 (and C2 if prior CRS)
- Prophylactic hospitalization not required
- VZV and PJP prophylaxis and GCSF support per treating physician



Patients who experience progression at any time point were taken off study; CR, complete response; ORR, overall response rate; TEAE, treatment emergent adverse events; PFS, progression-free survival; DOR, duration of response; OS, overall survival; PD, progressive disease; ctDNA, circulating tumor DNA; CRS, cytokine release syndrome; VZV, Varicella Zoster virus; PJP, *Pneumocystis Jirovecii* pneumonia; GCSF, granulocyte colony stimulating factor; PET/CT, positron emission tomography/computerized tomography; PR, partial response

Patient characteristics: All had high-burden disease

Characteristic	All patients (N=54)
Median age, y (range)	58 (26 - 83)
Female, n (%)	22 (40.7%)
Race, n (%)	
White	43 (79.6%)
Asian	7 (13.0%)
Black	1 (1.8%)
Unknown	3 (5.6%)
Ethnicity, n (%)	
Non-Hispanic	47 (87.0%)
Unknown	7 (13.0%)
ECOG Status, n (%)	
0	44 (81.5%)
1	10 (18.5%)
B Symptoms, n (%)	10 (18.5%)

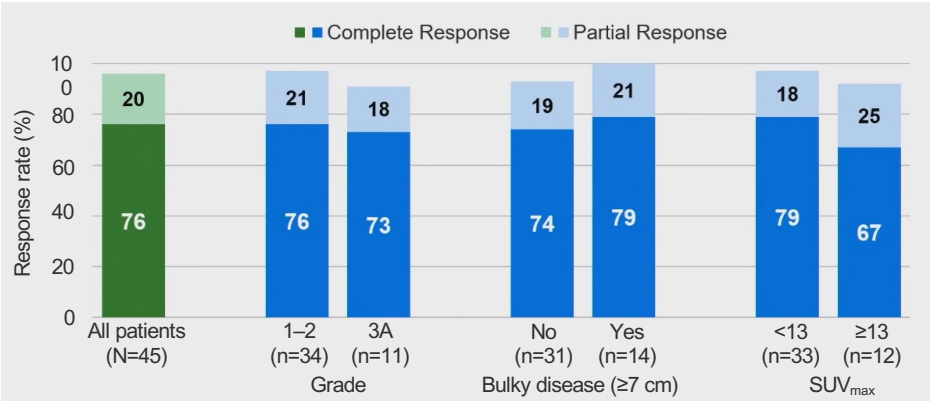
Characteristic	All patients (N=54)
ALC, median (range)	1.2 (0.5 - 7.9*)
Elevated LDH, n (%)	9 (16.7%)
Grade, n (%)	
1-2	41 (75.9%)
3A	13 (24.1%)
Stage, n (%)	
II	5 (9.3%)
III	10 (18.5%)
IV	39 (72.2%)
FLIPI, n (%)	
0-1	10 (18.5%)
2	30 (55.6%)
3-4	14 (25.9%)
Mass > 7 cm, n (%)	18 (33.3%)
Median SUV_{max} (range)	11.5 (3.7 - 41.1¶)

* Clonal B-cells 1700/mcl; ¶ DLBCL diagnosed 6 weeks after treatment initiation on a left axillary lymph node with baseline SUV 41 not previously biopsied; ALC, absolute lymphocyte count; LDH, lactate dehydrogenase; FLIPI, follicular lymphoma international prognostic index

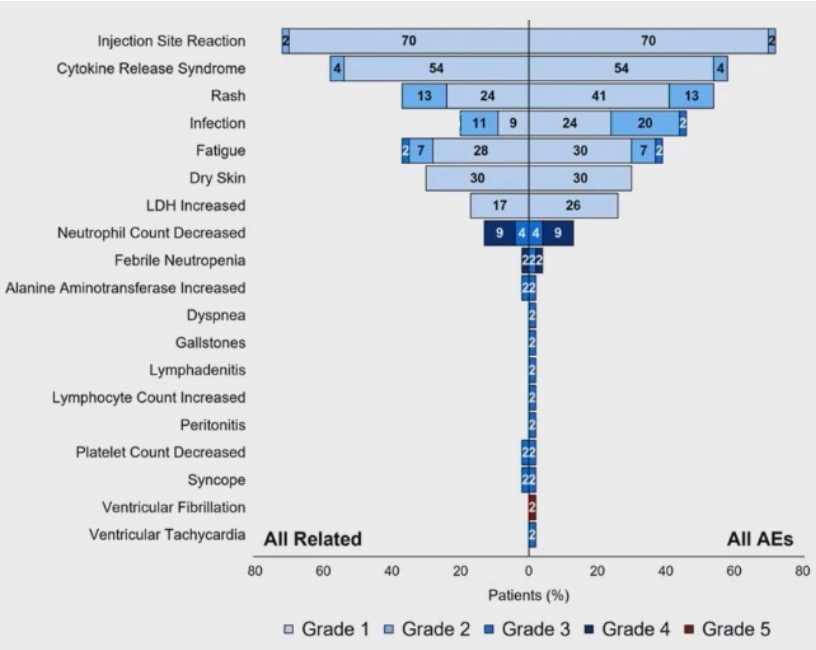
Subcutaneous mosunetuzumab in 1L FL

Phase II trial, median 5.8-month follow-up

The ORR with SC mosunetuzumab was 96%, with high response rates observed across high-risk subgroups



No new safety signals were observed



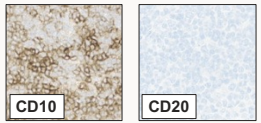
1L, first line; AE, adverse event; FL, follicular lymphoma; ORR, overall response rate; SC, subcutaneous.

Falchi L *et al*. Oral presentation 604 presented at American Society of Hematology 2023; San Diego, United States, December 9–12.

SC mosun in 1L FL

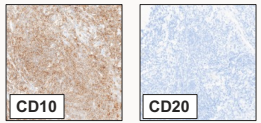
CD20-negative progressions after mosunetuzumab in 1L FL

Patient 1
Best response: PR
PET: Low-volume adenopathy
Histology: FL, G1-2
CD20 status: Negative



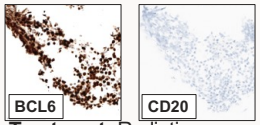
Treatment: Observation
Status: Stable disease

Patient 2
Best response: CR
PET: Low-volume adenopathy
Histology: FL, G1-2
CD20 status: Negative



Treatment: Observation
Status: Stable disease

Patient 3
Best response: CR
PET: Isolated, small lesion
Histology: FL, G1-2
CD20 status: Negative



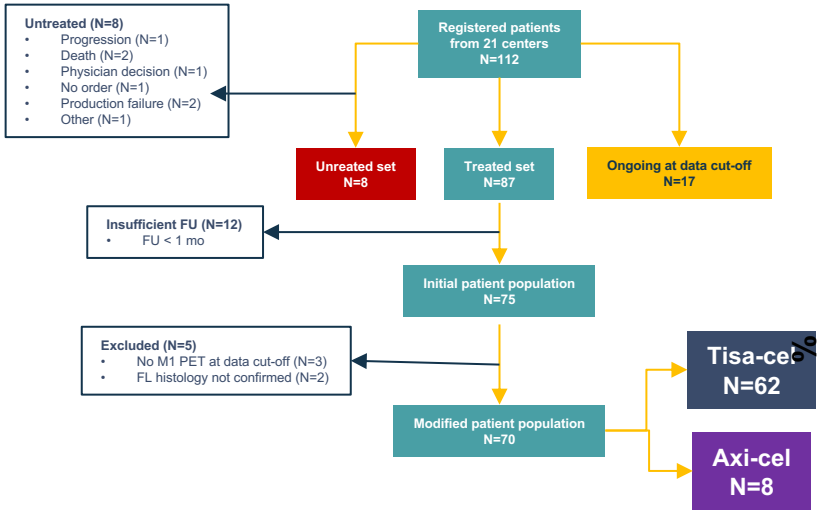
Treatment: Radiation therapy
Status: Pending assessment

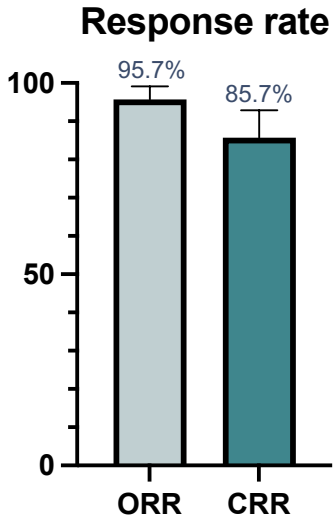
Treatment
Follow-up

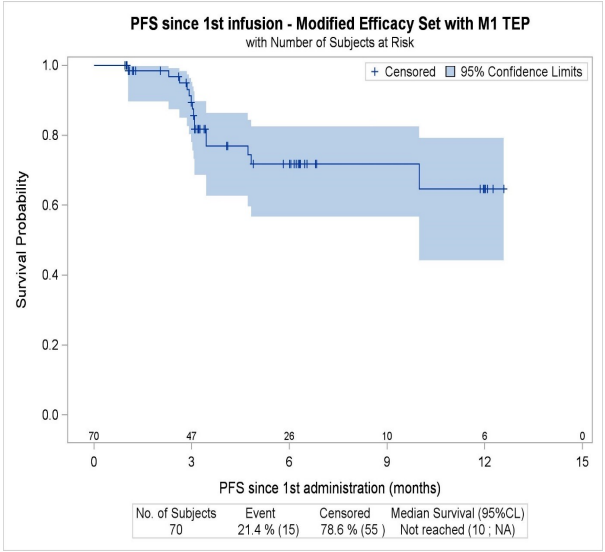
Baseline
6 months
9 months
12 months

Patient 4
Histology: DLBCL, GCB type
CD20 status: Positive
Treatment: R-CHOP x 6
Status: No evidence of disease
Notes: DLBCL on a left axillary lymph node with baseline SUV 41, not previously biopsied

CAR T-cells for relapsed/refractory follicular lymphoma : a DESCART registry analysis from the LYSA







Bachy et al. ASH 2023, Abstract #296

TAKE home messages

- We are living a therapeutic «storm» in FL
- What's new from San Diego
  - R2 well ideintified as a strong combination and IMIDs are strong partners for future combination
  - Bispecs: confirmatory data and anticipated future changes. Fixed duration, Subcute
  - CAR-T: confirmatory 3L+, Something new in 2L Liso-cel
  - New questions
    - Long term outcomes
    - Sequencing/retreatment
    - Mehcanisms of resistance
  - A strategy is needed