FONDAZIONE ITALIANA LINFOMI

IMMUNOTERAPIA E FARMACI BIOLOGICI NEL TRATTAMENTO DEI LINFOMI E LLC: ATTUALITÀ E FUTURO

Nuovi algoritmi terapeutici nei Linfomi follicolari recidivati/refrattari, in era Bispecifici e CAR-T

Stefano Luminari

Ematologia, Azienda USL IRCCS, Reggio Emilia
Università di Modena e Reggio Emilia

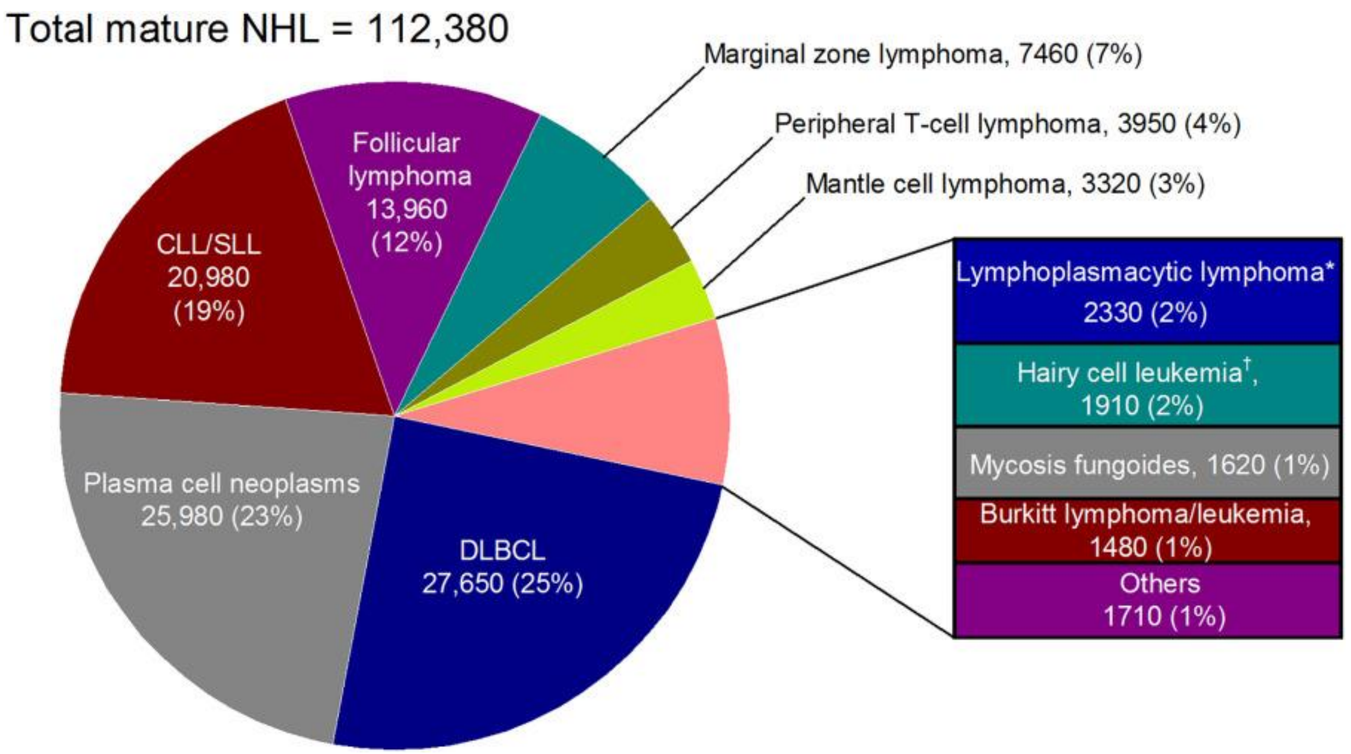
Disclosures of Name Surname

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

Features of follicular lymphomas

- Most frequent among indolent lymphomas
- Can be asymptomacic
- Relapsing remitting course
- Impact on life expectancy low with exceptions
- Can transform into more aggressive lymphomas
- Late events (infections, 2nd malign.)

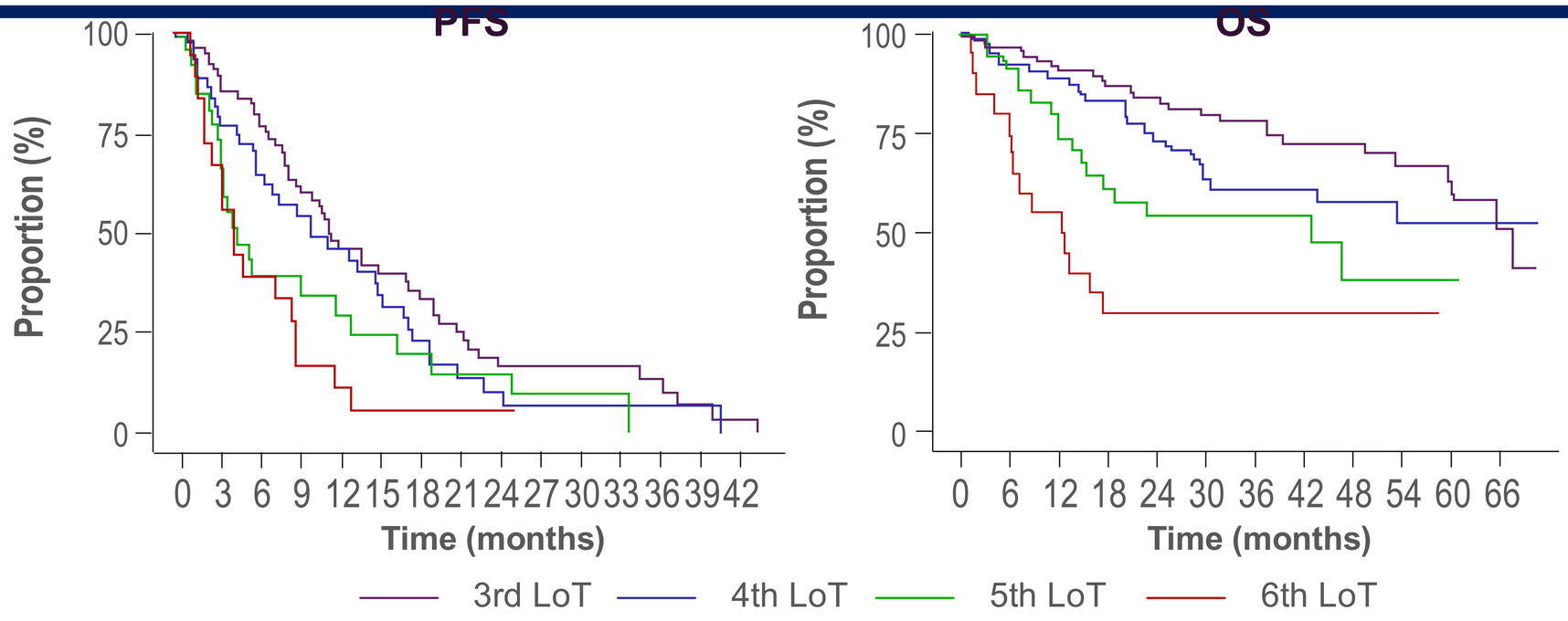
Distribution of NHL Subtypes



Teras. CA Cancer J Clin. 2016;66:443.

Worsening Outcomes With Additional Lines of Therapy: Results From the International SCHOLAR-5 Study

Ghione, et al. (SCHOLAR-5)	
N	128
Median age, years (range)	65 (36–86)
Stages 3–4	86%
FLIPI 3–5	39%
POD24	27%
Prior ASCT	18%
Prior anti-CD20+ alkylating agent	89%



	3rd LoT	4th LoT	5th+ LoT
ORR (%)	68	63	37
CRR (%)	44	27	22
5-year OS (%)	62	52	38
mPFS (median mo)	11	9.7	3.9
TTNT (median mo)	20.1	17.9	7.1

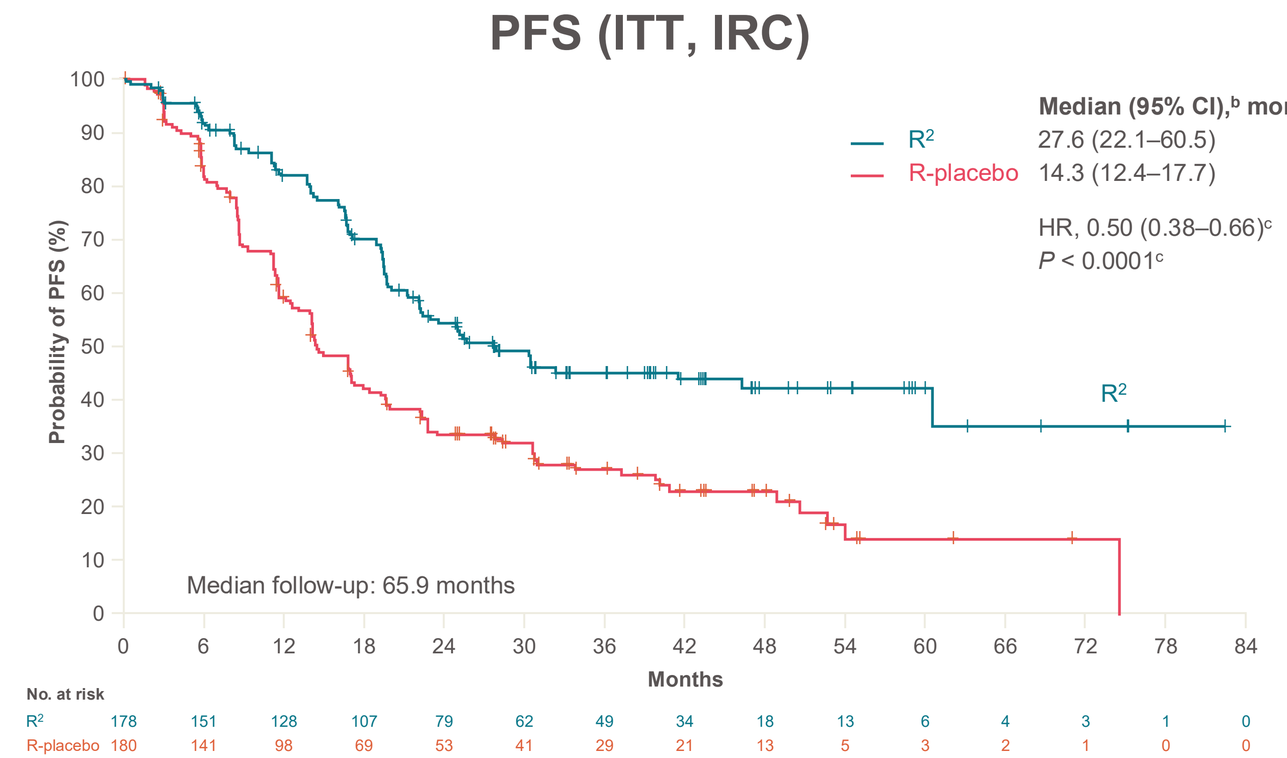
ASCT, autologous stem cell transplant; CRR, complete response rate; FLIPI, Follicular lymphoma international prognostic index; LoT, lines of therapy; mo, months; mPFS, median PFS; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; POD24, progression of disease within 24 months; TTNT, time to next treatment.

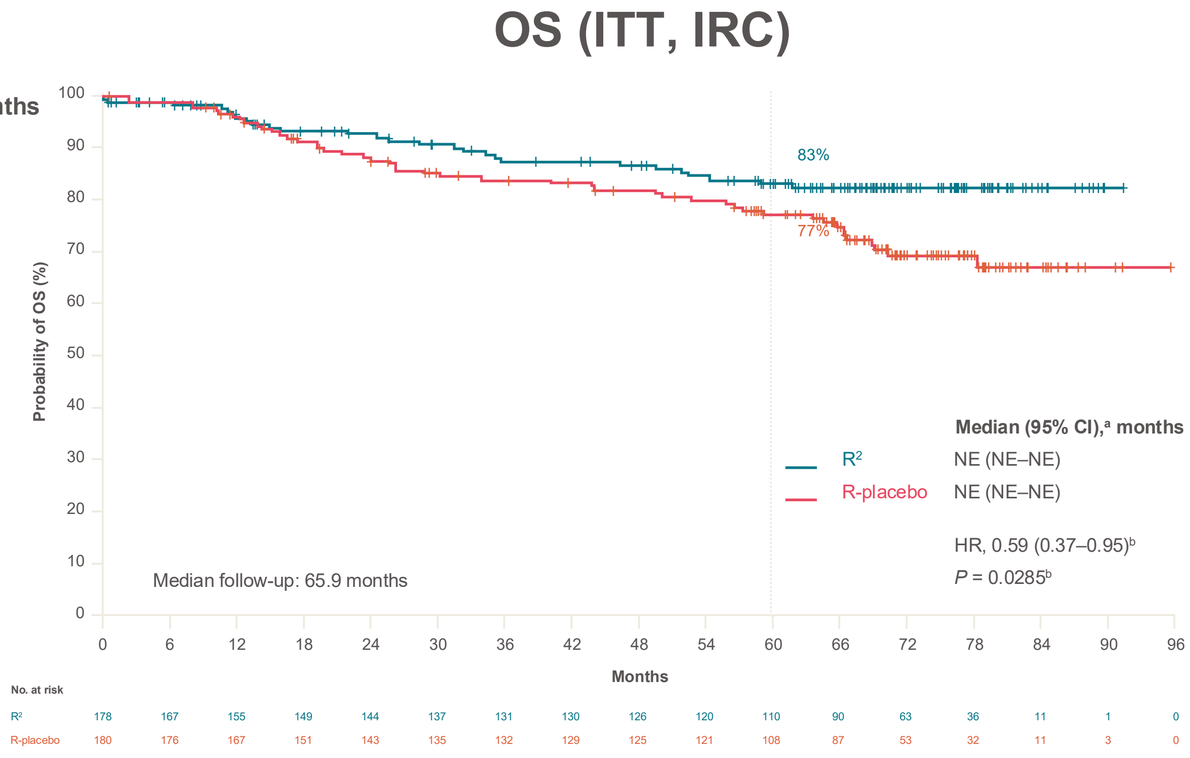
Adapted from Ghione P, et al. *Haematologica*. 2023;108(3):822-832.

Key aspects in the management of r/r FL

- Risk is heterogeneous but prognostic indexes are missing in the r/r setting
- Key decisional factors
  - duration of response (POD24), tumour burden, prior therapy
  - patients' age and comorbid conditions
  - availability of active drugs/therapies
- New therapies are revolutionizing old paradigms
  - No more ASCT
  - 2nd line is the entry door into the chemo free world
  - TCE and CART rapidly moving to early lines

AUGMENT: PFS and OS advantage for R² in r/r FL



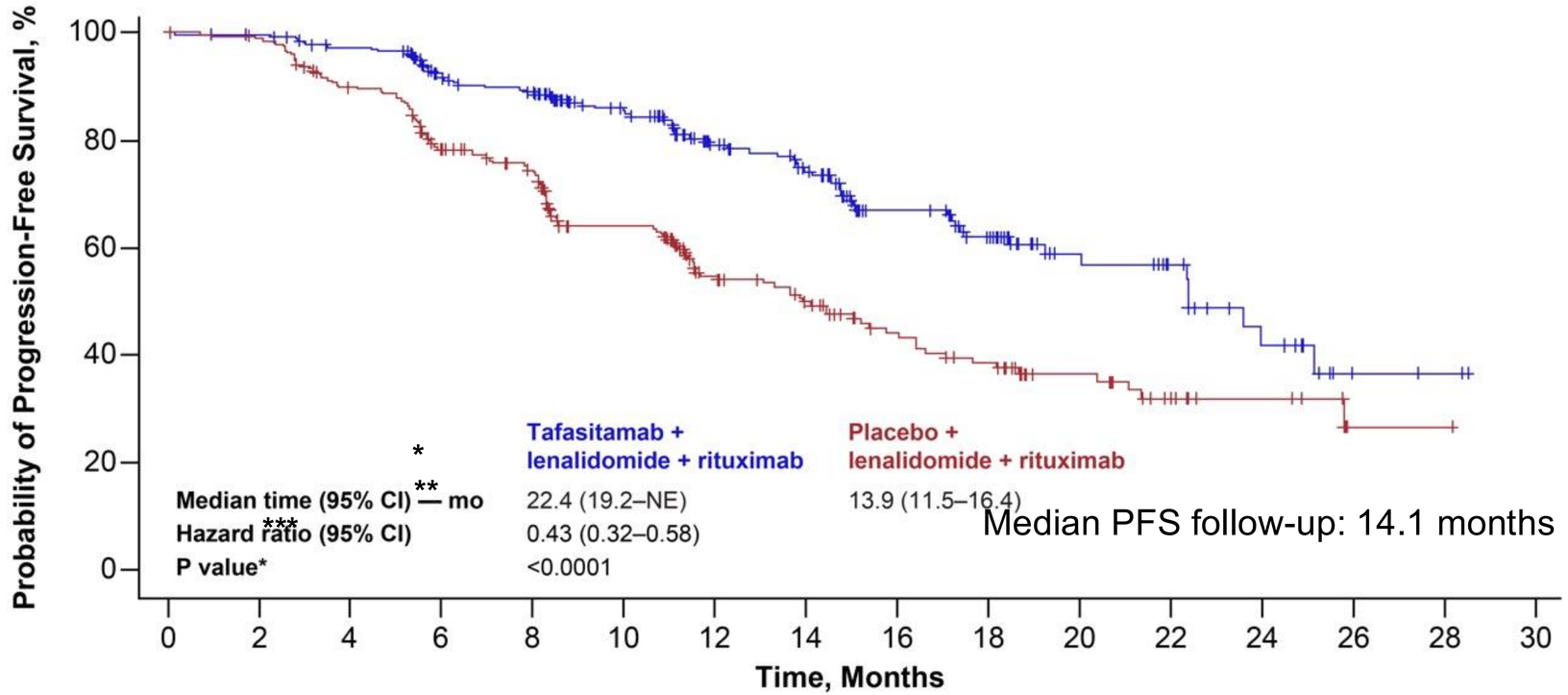


Median age for R2 arm: 64y (26–86)

ITT, intention to treat; NR, not reached

Source: Leonard JP, et al. AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. J Clin Oncol. 2019;37:1188-99. Updated at ASH 2022

INMIND Primary Endpoint: PFS by Investigator Assessment



Median PFS follow-up: 14.1 months

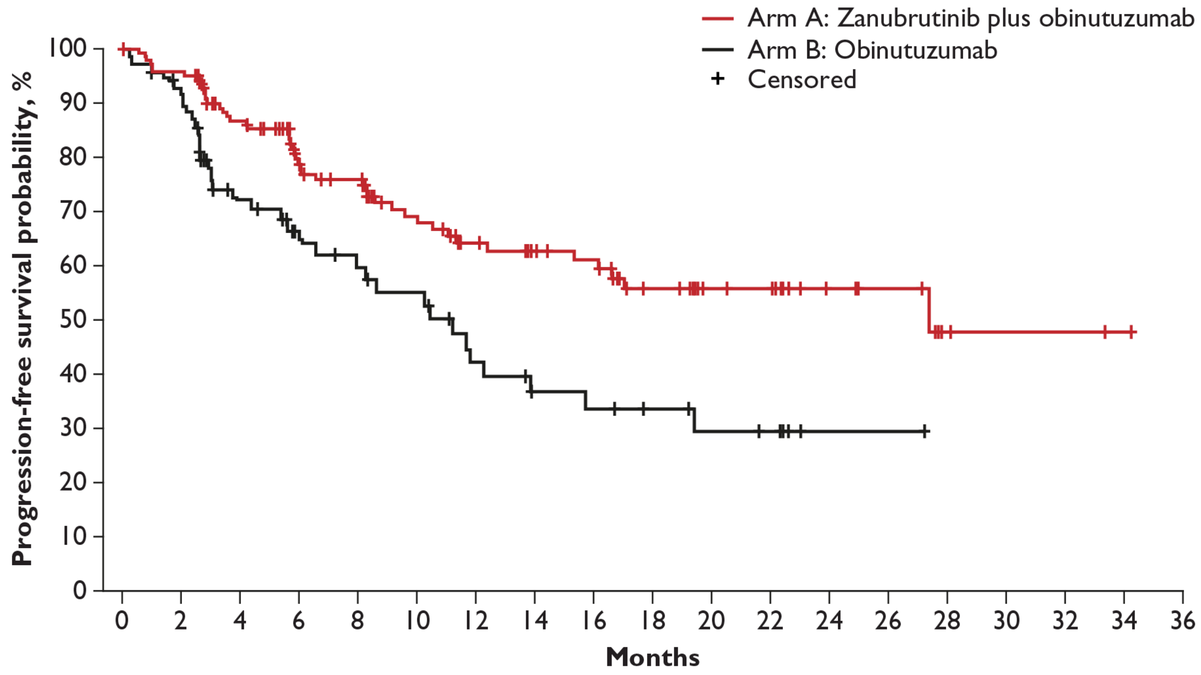
No. at Risk																
Tafasitamab + lenalidomide + rituximab	273	261	250	212	200	164	119	103	71	57	30	22	12	3	2	0
Placebo + lenalidomide + rituximab	275	265	235	192	173	126	82	70	48	40	26	16	10	2	2	0

Significant improvement in PFS was observed with tafasitamab without any significant icrease of Toxicity

ITT population.
*Estimated using Kaplan-Meier method. **Estimated using a stratified Cox proportional hazard model. ***Stratified log-rank test with a 1-sided significance level of 2.5%.
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mo, months; NE, not evaluable; PFS, progression-free survival.

ROSEWOOD: Selected Secondary Efficacy Endpoints

Progression-Free Survival by ICR



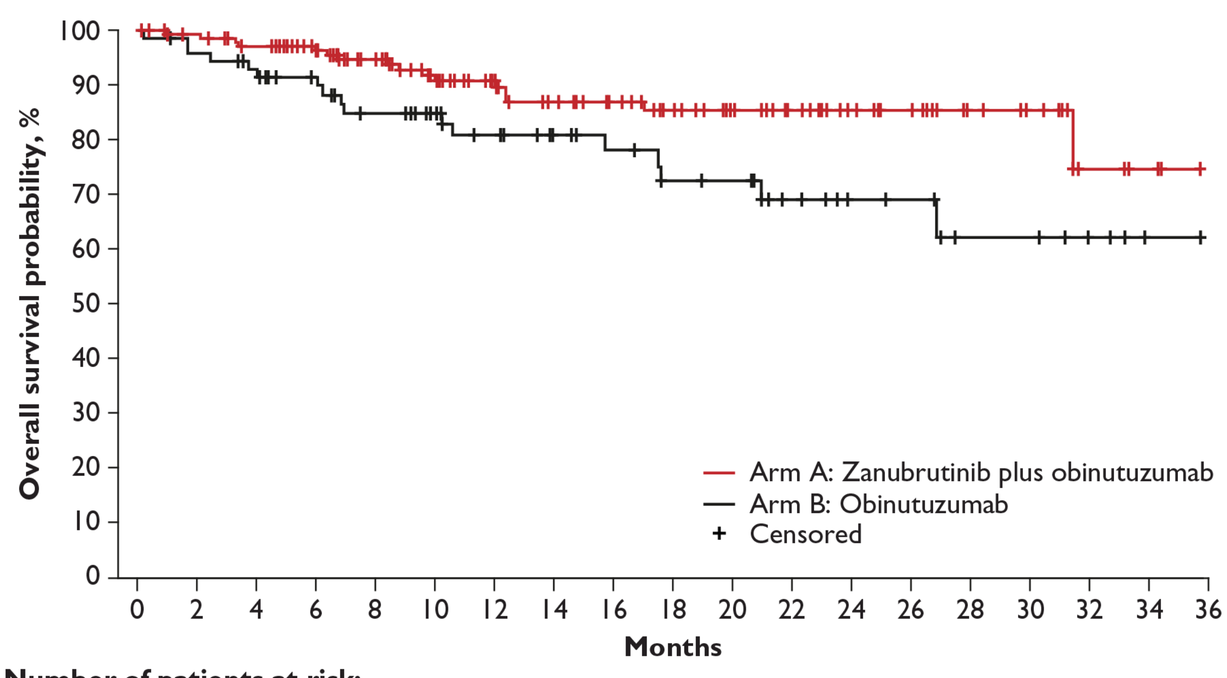
Number of patients at risk:

Arm A	145	135	111	83	76	56	46	40	37	27	19	18	10	8	3	2	2	1	0
Arm B	72	63	39	29	26	23	16	12	11	9	7	6	1	1	0				

Median PFS, months (95% CI):

27.4 (16.1, NE) Arm A vs 11.2 (6.5, 15.7) Arm B

Overall Survival



Number of patients at risk:

Arm A	145	139	132	121	104	89	75	64	58	51	42	36	28	22	15	12	5	3	0
Arm B	72	67	63	57	50	45	39	32	29	25	23	17	12	11	7	7	4	1	0

Median OS, months (95% CI):

NE (31.4, NE) Arm A vs NE (26.8, NE) Arm B

Study was not powered to detect OS difference

CI=confidence interval, DoR=duration of response, ICR=independent central review, NE=not evaluable, PD=progressive disease, PFS=progression-free survival.

Zinzani et al. ASCO 2022. Abstract: 7510.

Mosunetuzumab in 3L+ RR FL

Subgroup analysis from the updated analysis at ASH 2023 (median follow-up of 37.4 months)[1]

Key inclusion criteria[2]

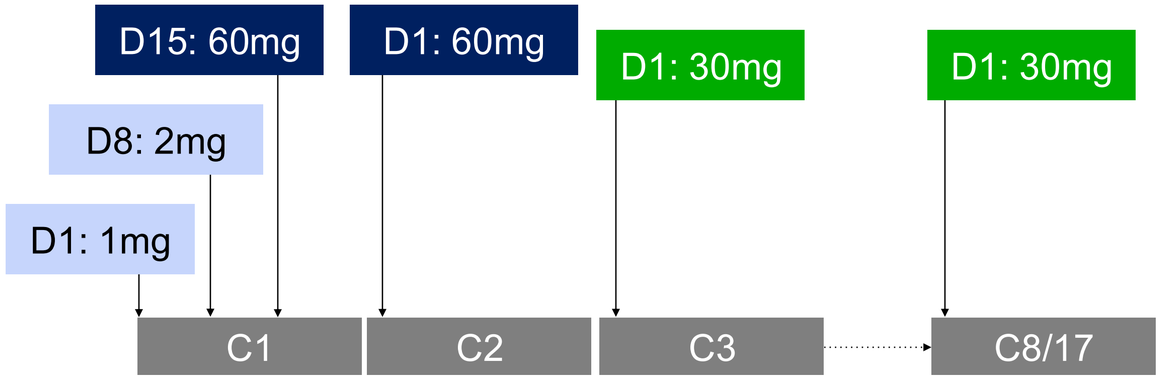
- R/R FL Grade 1–3a
- ≥2 prior therapies including an anti-CD20 antibody and an alkylator
- ECOG PS 0–1

Data analysis

- Subgroups evaluated for investigator-assessed efficacy and safety:
  - History of POD24
  - 3L versus 4L+
  - Age <65 years versus ≥65 years

Mosunetuzumab administration[2]

- Intravenous mosunetuzumab (21-day cycles); step-up dosing in C1
- Fixed-duration treatment: eight cycles (if CR after C8) or 17 cycles (if PR/SD after C8)
- No mandatory hospitalization



3L, third-line; 4L, fourth-line; C, cycle, D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; POD24, progression of disease within 24 months from start of 1L therapy; PR, partial response; SD, stable disease.

1. Schuster SJ, et al. ASH 2023; Oral presentation (abstract #603);
2. Budde LE, et al. Lancet Oncol 2022;23:1055–65.

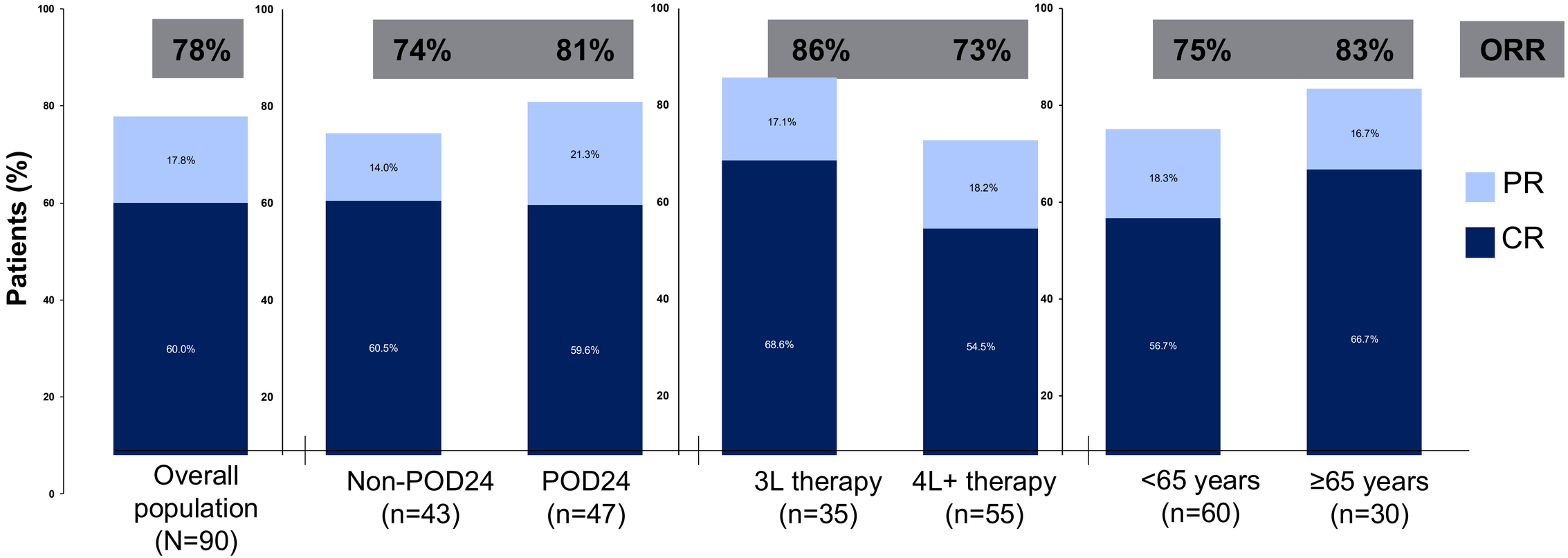
Baseline patient characteristics

n, unless stated	N=90
Median age, years (range)	60 (29–90)
Male	55 (61%)
ECOG PS 0 1	 53 (59%) 37 (41%)
Ann Arbor stage I/II III/IV	 21 (23%) 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

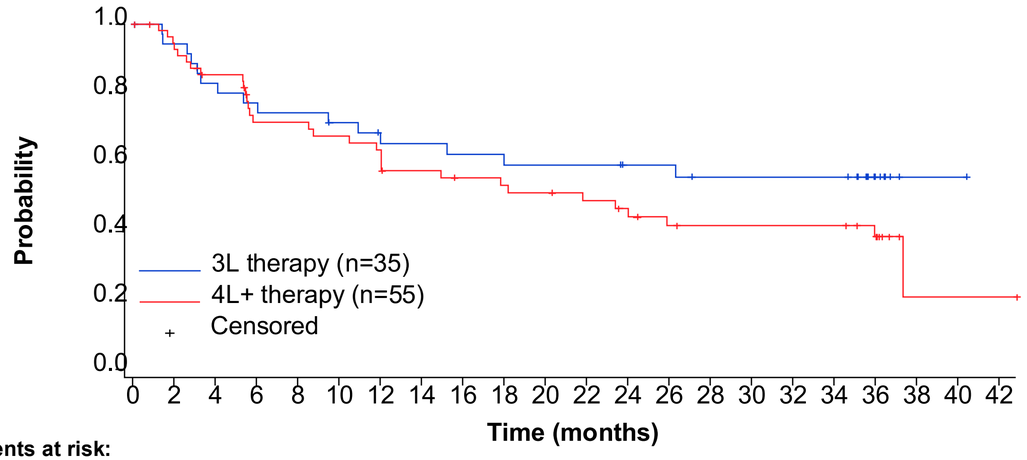
Efficacy summary: response rates



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

PFS and OS: 3L versus 4L+ therapy

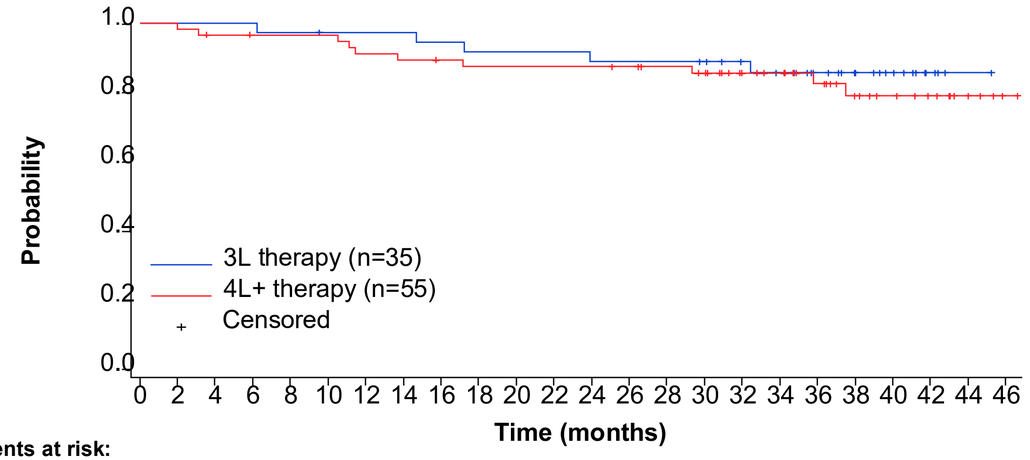
PFS



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

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 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)

	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+

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.

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

Fixed Duration

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

TX until PG/tox

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

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

Bsabs combos are highly active in RR FL

IV Mosunetuzumab + Lenalidomide in 2L+ FL: Study Design, Patients, Efficacy

NCT04246086

Eligibility
- CD20+ FL Grade 1-3a
- R/R to ≥1 prior CIT regimen including anti-CD20 antibody
- Prior len allowed
- ECOG PS 0-2

C1: 21-day cycle; C2-12: 28-day cycles

Mosunetuzumab IV
- C1 step-up dosing: D1: 1 mg, D8: 2 mg, D15: 30 mg
- C2-12 D1: 30 mg

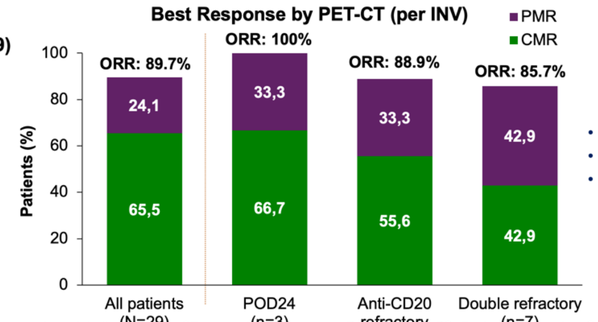
Lenalidomide PO 20 mg
- C2-12 D1-21 (11 total cycles)

Primary Objective
- Safety/tolerability of mosun-len

Other Objectives
- Efficacy (response, durability of response), PK

Select Baseline Characteristics (N=29)
- **Age, median (range):** 59 y (30–79)
- **FLIPI score 3-5:** 48.3%
- **Prior LOT, median (range):** 1 (1-6)
- **Double refractory:** 24.1%
- **POD24:** 10.3%

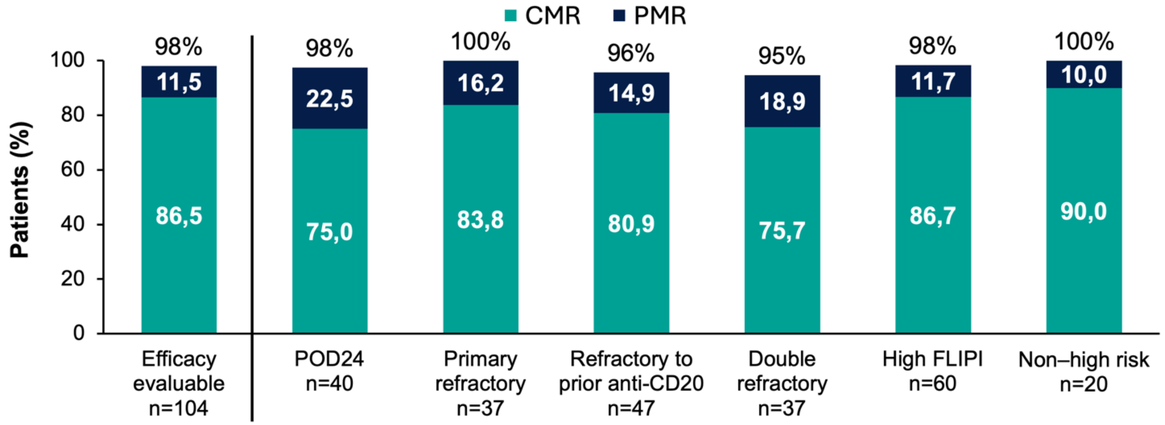
Median follow-up: 5.4 mo (range: 3–12)



- 86.2% had ongoing response
- All patients in CMR were still in CMR
- 2 patients experienced deepening of response (at approximately 5 months and 10.5 months)

2L, second-line; C, cycle; CIT, chemoimmunotherapy; CMR, complete metabolic response; CT, computed tomography; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; INV, investigator assessed; IV, intravenous; Len, lenalidomide; LOT, line of therapy; Mosun, mosunetuzumab; ORR, overall response rate; PET: positron emission tomography; PK, pharmacokinetics; PMR, partial metabolic response; PO, oral; POD24, progression of disease within 24 months from the start of initial therapy; R/R, relapsed/refractory.
Morschhauser F, et al. ASH 2021. Abstract 129.

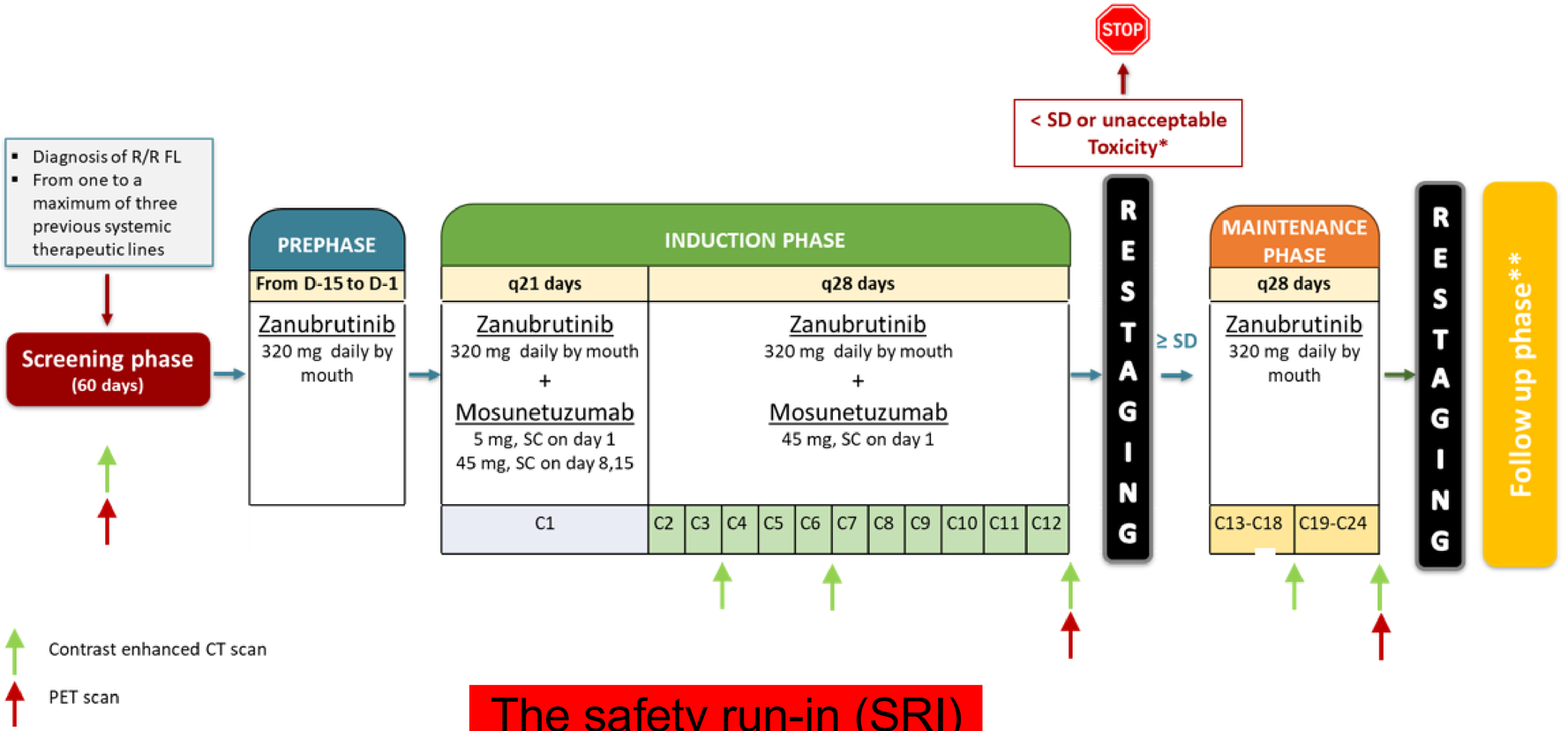
Epcoritamab + R^2 in R/R FL: Antitumor Activity in Subgroups



Overall response and CMR rates were consistently high across all subgroups

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

MOZART phase II trial - Flow chart



The safety run-in (SRI) phase is completed

*Patients with progressive disease at any time during protocol treatment will discontinue it and will be addressed to salvage therapy at clinician discretion.
**Follow-up visits will occur every 12 weeks for the first year, every 24 weeks for the next two years. In the last 2 years visits will occur every 24 weeks to assess disease status, survival status (alive, dead, lost to follow-up), second neoplasia and long-term toxicity.

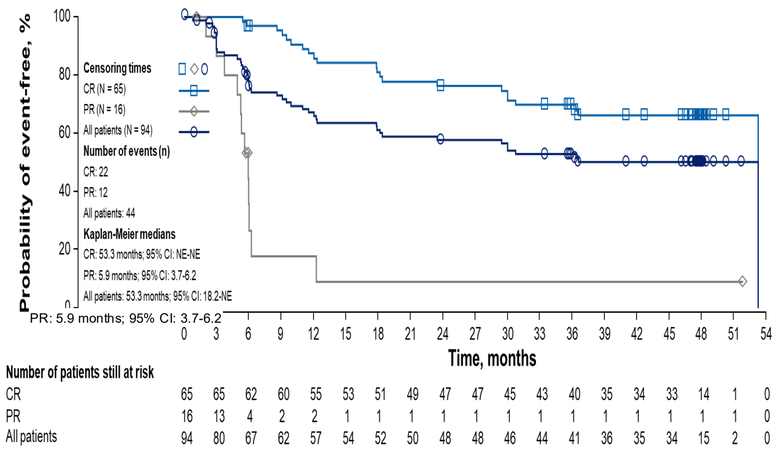
Efficacy and Safety of Patients With R/R FL Receiving Tisacel (ELARA), Axicel (ZUMA-5) or Lisocel (TRANSCEND FL)

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)

ORR: 86%
CRR: 69%

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



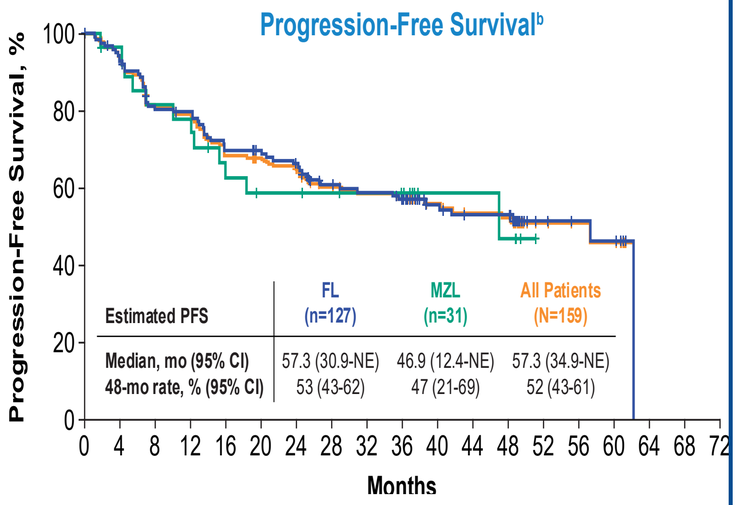
Thieblemont EHA 2025

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)

ORR: 94%
CRR: 79%

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



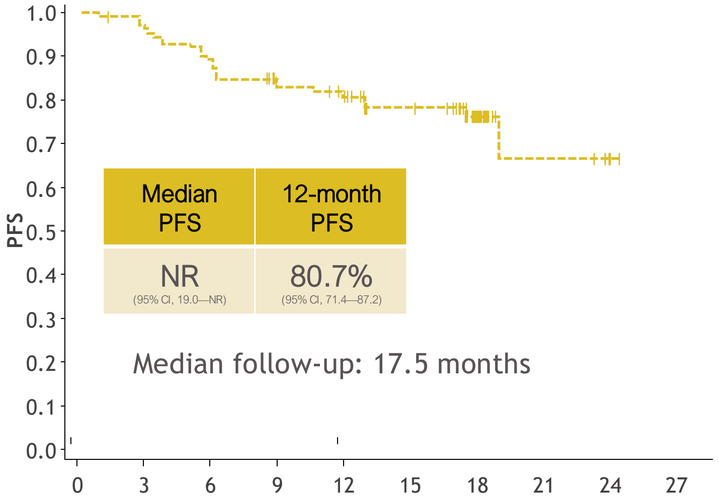
Neelapu. ASH 2023.

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)

ORR: 97%
CRR: 94%

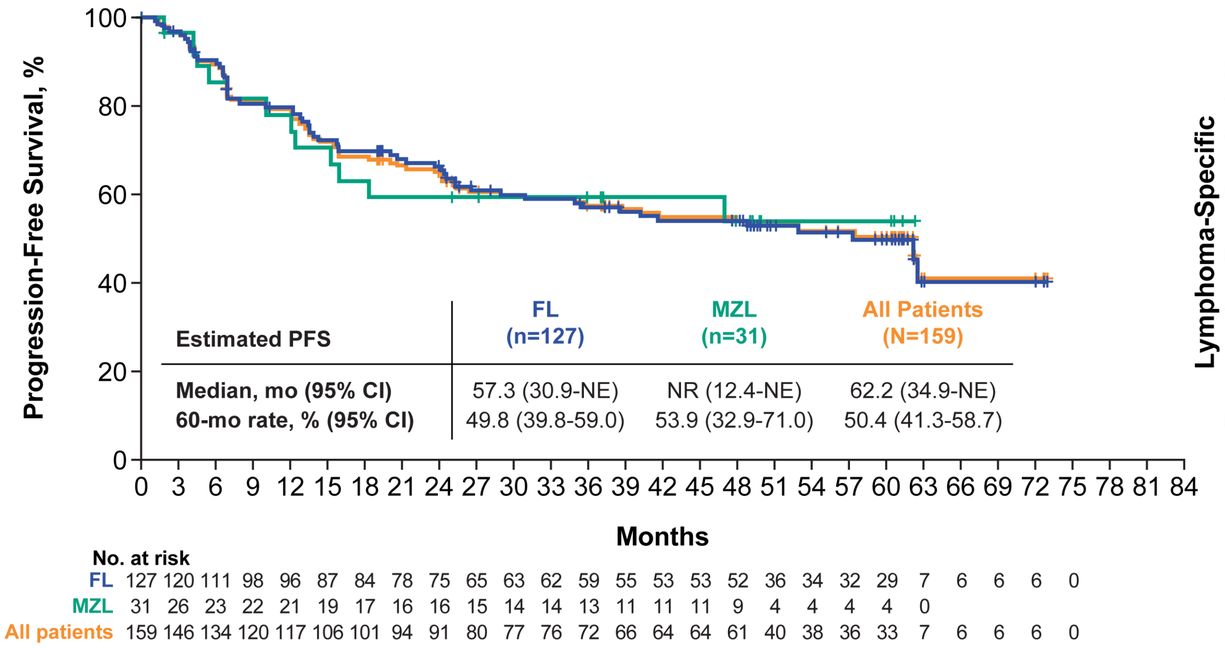
TEAEs of interest	Axi-cel
Grades ≥3 CRS, n (%)[a]	1 (1)
Grades ≥3 neurological toxicity, n (%)	2 (2)



Morschauser et al ASH 2023.

Is there a curative potential of the novel agents?

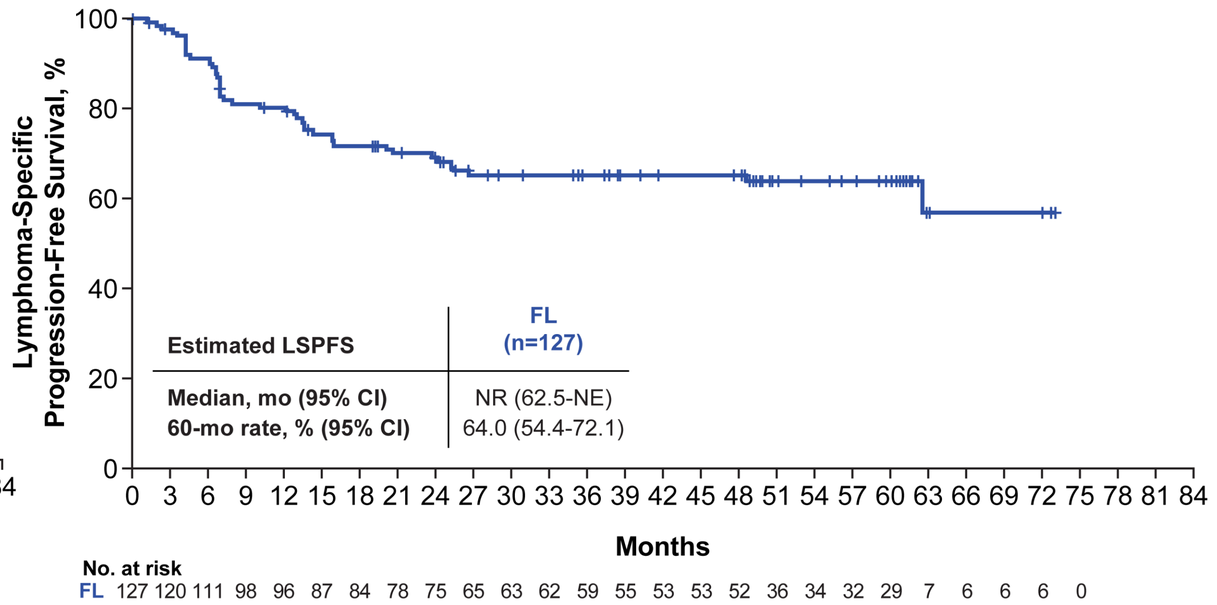
Progression-Free Survival[a]



No. at risk

FL	127	120	111	98	96	87	84	78	75	65	63	62	59	55	53	53	52	36	34	32	29	7	6	6	6	0
MZL	31	26	23	22	21	19	17	16	16	15	14	14	13	11	11	11	9	4	4	4	4	0				
All patients	159	146	134	120	117	106	101	94	91	80	77	76	72	66	64	64	61	40	38	36	33	7	6	6	6	0

Lymphoma-Specific Progression-Free Survival[a,b]



No. at risk

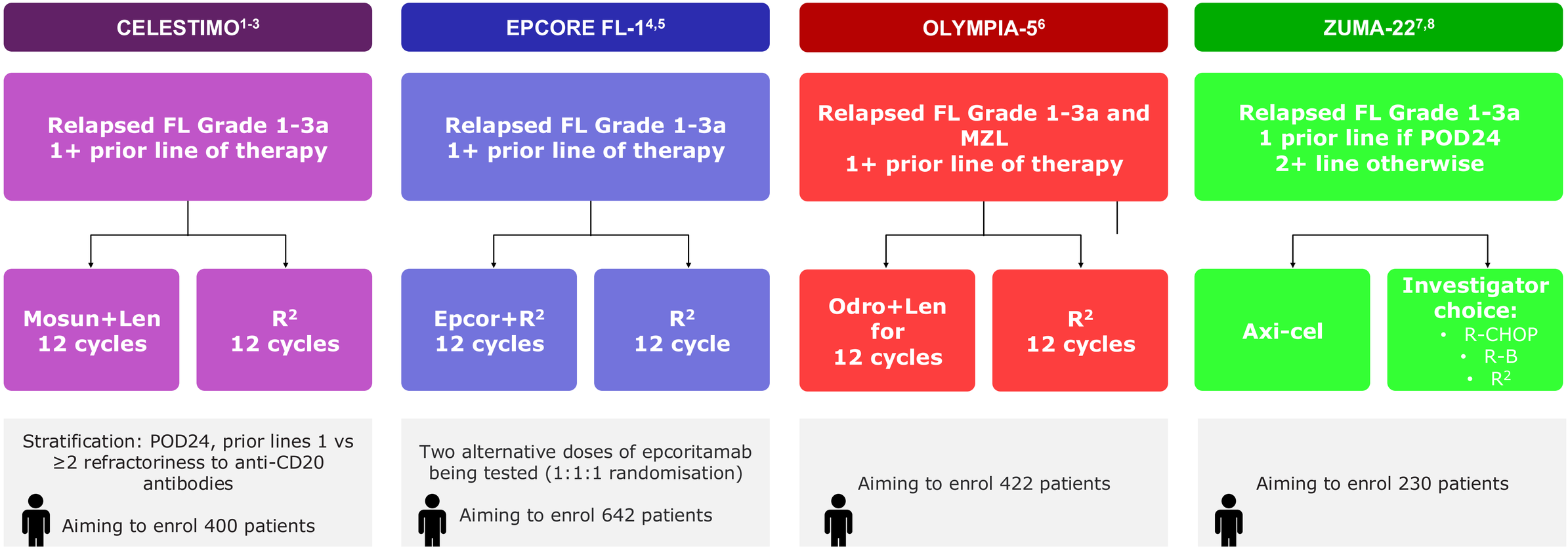
FL	127	120	111	98	96	87	84	78	75	65	63	62	59	55	53	53	52	36	34	32	29	7	6	6	6	0

- Only 4 patients progressed >24 months post-leukapheresis; 2 patients progressed >30 months post-leukapheresis

ZUMA 5, 5 year follow up update

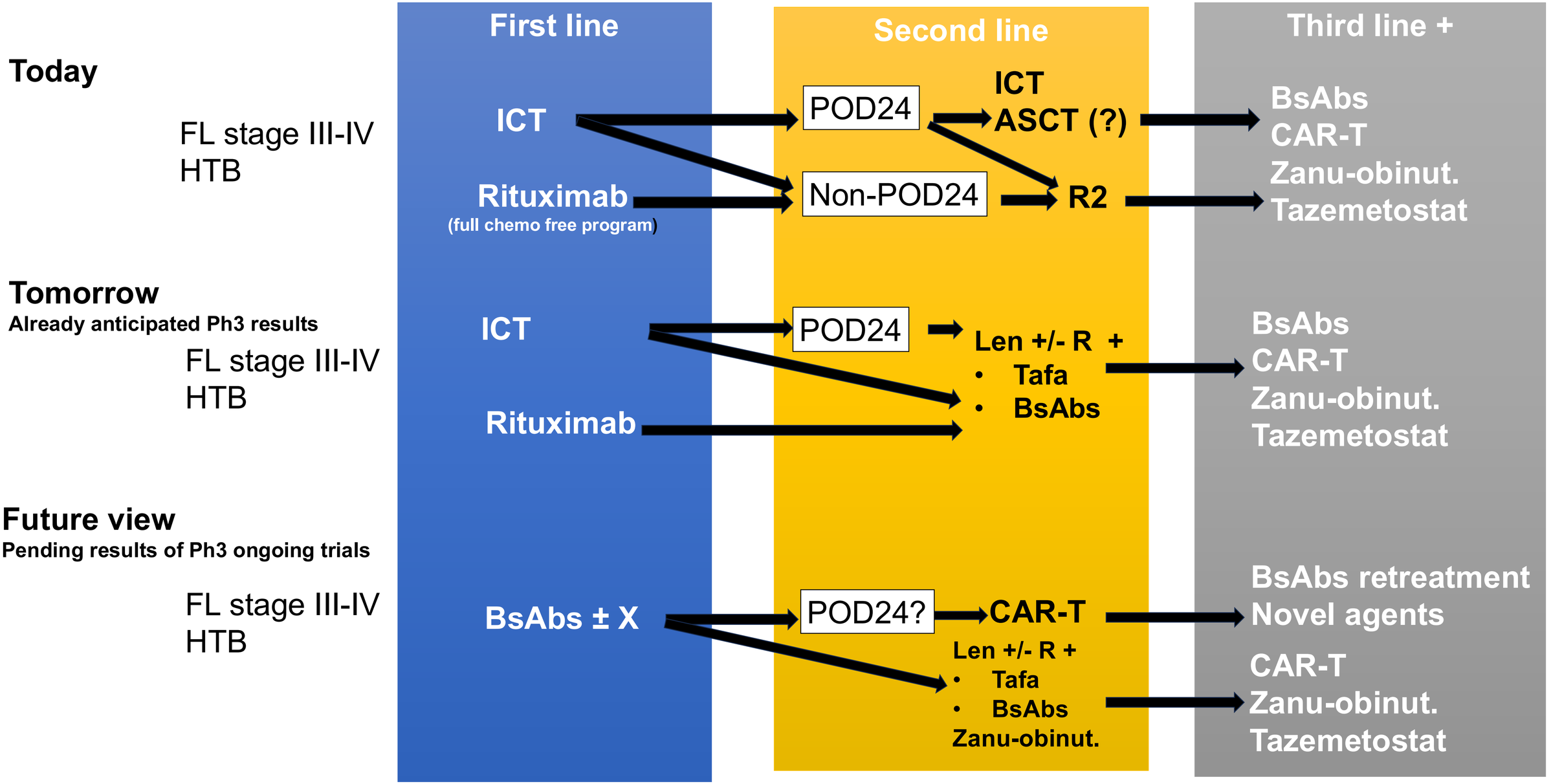
Neelapu *et al.* ASH 2024

Ongoing Phase 3 trials in R/R FL



axi-cel, axicabtagene ciloleucel; B, bendamustine; CHOP, cyclophosphamide+hydroxydaunomycin+oncovin+prednisone; epcor, epcoritamab; mosun, mosunetuzumab; odro, odronextamab.

Evolving paradigms in FL therapy



FL, follicular lymphoma; HTB, high tumor burden; ICT, immunochemotherapy; ASCT, autologous stem cell transplantation; R2, rituximab-lenalidomide; BsAbs, bispecific antibodies; Zanu-obinu, zanubrutinib obinutuzumab; TafaR2, tafasitamab-rituximab-lenalidomide; Mosu-len, mosunetuzumab-lenalidomide

S. Luminari BJH 2025