GIORNATE EMATOLOGICHE VICENTINE

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Il ruolo degli anticorpi bispecifici e delle CAR-T nel linfoma follicolare

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Disclosures of Vittorio Ruggero Zilioli

Company name	Research support	Consultant	Speakers bureau	Advisory board	Other
Abbvie				X	
AstraZeneca				X	
Beigene					X
Incyte			X		
Janssen			X		X
Kite/Gilead	X			X	
Lilly			X		X
Novartis				X	
Roche		X		X	X
Sobi			X	X	
Takeda			X	X	X

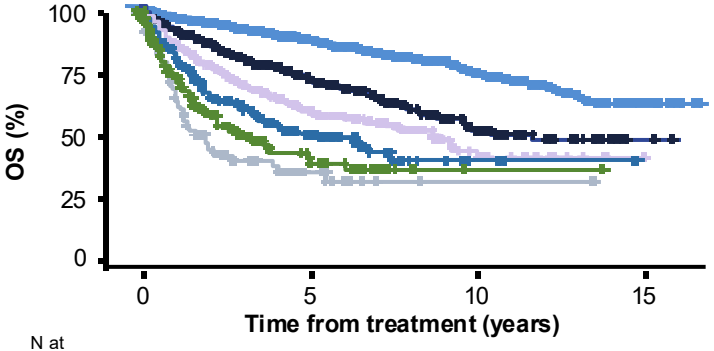
Epidemiology and outcomes

~20% of NHL patients globally[1]

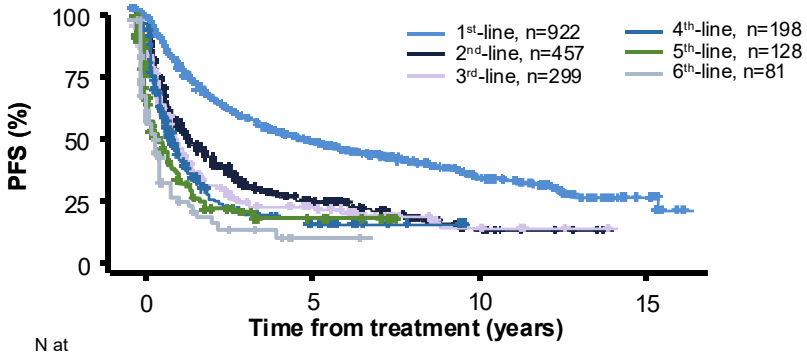
- Most common type of iNHL[2]
  - Overall incidence of 2.1-4.3/100,000[1]

64 Years – median age at diagnoses*[3]

- ~10% of patients are diagnosed as young adults (18-40 years)[4]



N at risk				
1st	922	673	244	30
2nd	457	203	45	2
3rd	299	99	16	1
4th	198	47	3	0
5th	128	23	1	0
6th	81	10	1	0



N at risk				
1st	922	366	94	7
2nd	457	58	10	0
3rd	299	31	5	0
4th	198	14	0	0
5th	128	6	0	0
6th	81	1	0	0

Figure adapted from Batlevi CL, et al. *Blood Cancer J.* 2020; 10:74.

1. Monga N, et al. *Ann Hematol.* 2019;98(1):175-183.
2. Nastoupil L et al. Community Oncol. 2012;9(11):S53-S60;
3. National Cancer Institute.SEER 22. https://seer.cancer.gov/statfacts/html/follicular.html. Accessed May 31, 2022.
4. Casulo C, et al. *Best Pract Res Clin Haematol.* 2018;31(1):15-223., 2022.

Epidemiology and outcomes

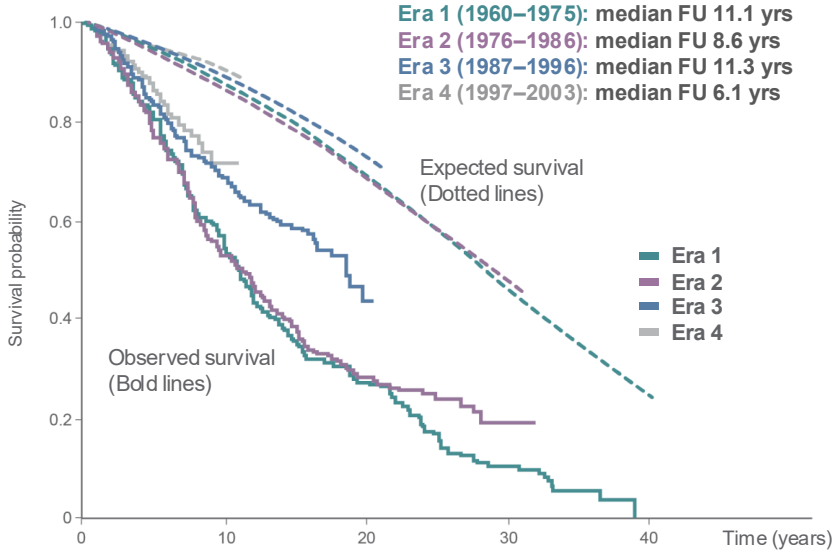


Figure modified from Tan D et al, Blood 2013; 122: 981-987

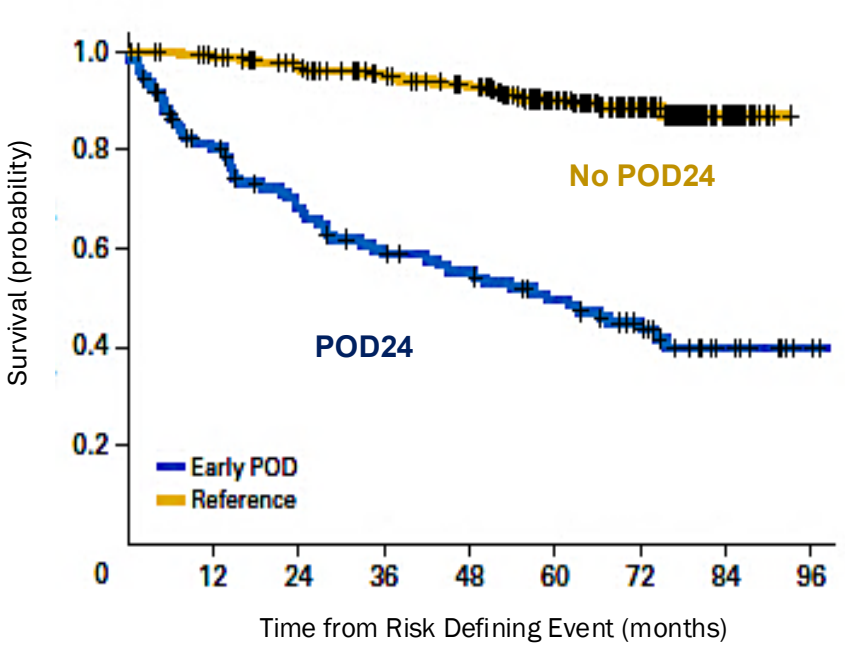
Improvements in OS exceeded improvements in survival in the general population in the same period

Prognosis

FLIPI-1 CRITERIA	FLIPI-2 CRITERIA
Age ≥60 years	Age ≥60 years
Stage III-IV	Bone marrow involvement
Hb <12 g/dL	Hb <12 g/dL
LDH >ULN	β2 macroglobulin > UNL
Nodal sites ≥5	Largest lymph node >6 cm

GELF Criteria
Involvement of ≥3 nodal sites, each with a diameter of ≥3 cm
Any nodal or extranodal tumor mass with a diameter of ≥7 cm
B-symptoms
Splenomegaly
Pleural effusions or peritoneal ascites
Cytopenias (leukocytes <1.0 × 10^9/L and/or platelets <100 × 10^9/L
Leukemia (>5.0 × 10^9/L malignant cells)

NCCN guidelines, B-cell lymphomas, v2,; Dreyling M, ESMO FL Guidelines 2020



	2-y OS	5-y OS
No POD24	97%	90%
POD24	68%	50%

Casulo C et al. L Clin Oncol. 2015

FIRST line

- The addition of Rituximab to chemotherapy extended PFS, DOR and OS
- Bendamustine plus rituximab (BR) improved PFS compared to R-CHOP
- Obinutuzumab-based therapy resulted in longer PFS than Rituximab-based therapy
- Rituximab-maintenance after remission prolongs PFS (and TTNT)

Hiddeman W et al. Blood. 2005;106: 3725-3732; Rummel M et al, Lancet 2013; 381: 1203 – 1210; Marcus R et al, NEJM 2017; 377: 1331 – 1344; Salles G al, Lancet 2010; 377: 42-51;

SECOND line

- ImmunoCT (preferably regimens not used in 1st line) still represents a valid tx option
- Obinu added to bendamustine improves PFS and OS in Rituximab-Refractory iNHL
- Rituximab plus lenalidomide induces demonstrated high PFS and OS in R/R FL treated

Is there still a role for ASCT in R/R FL?

The CUP trial: ASCT improves PFS and OS vs chemotherapy

Pre-R era

The German LG studies: ASCT improves PFS and OS in POD24 pts

R era

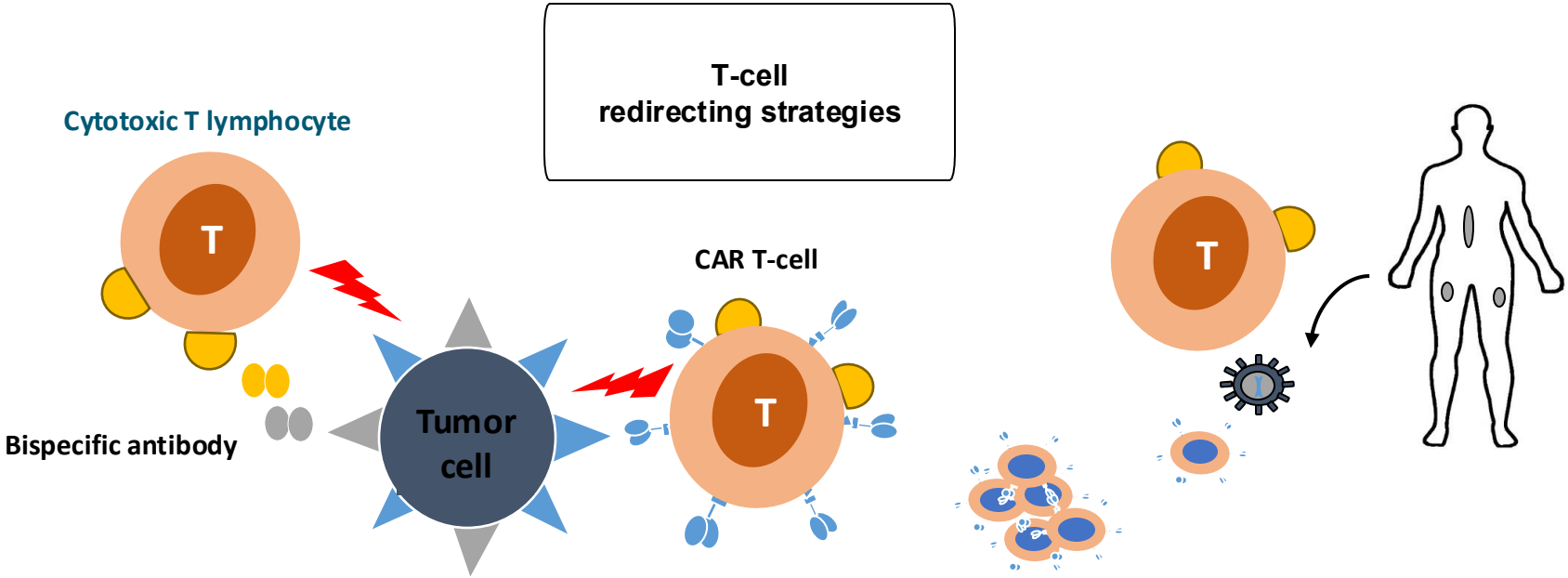
The FIL_FLAZ12 trial: no difference between ASCT and RIT

No difference even in POD24

ASCT more toxic

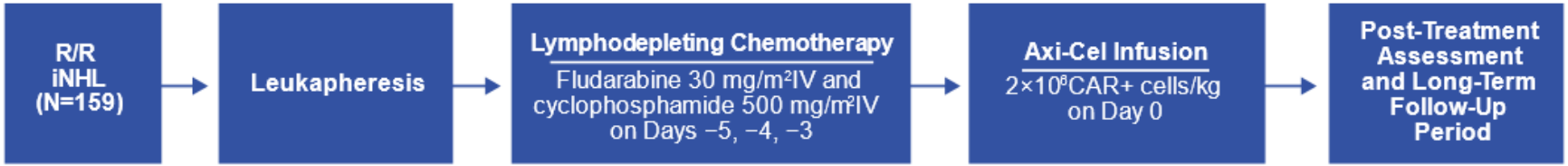
Cheson BD et al. J Clin Oncol. 2018; Leonard JP et al. J Clin Oncol. 2019; Leonard JP et al. Blood. 2022; Schouten HC, et al. J Clin Oncol 2003; Jurinovic V et al. Biol Blood Marrow Transplant. 2018; Ladetto M et al. Ann Oncol. 2024

THIRD line



Slide credit: clinicaloprions.com

Axi-cel (ZUMA-5)



Key ZUMA-5 Eligibility Criteria

- R/R FL (Grades 1-3a) or MZL (nodal or extranodal) [a]
- ≥2 prior lines of therapy that must have included an anti-CD20 mAb combined with an alkylating agent [b]

Primary Endpoint

- ORR (centrally assessed per Lugano[6])

Key Secondary Endpoints

- CR rate
- DOR, PFS, OS
- AEs
- CAR T-cell and cytokine levels

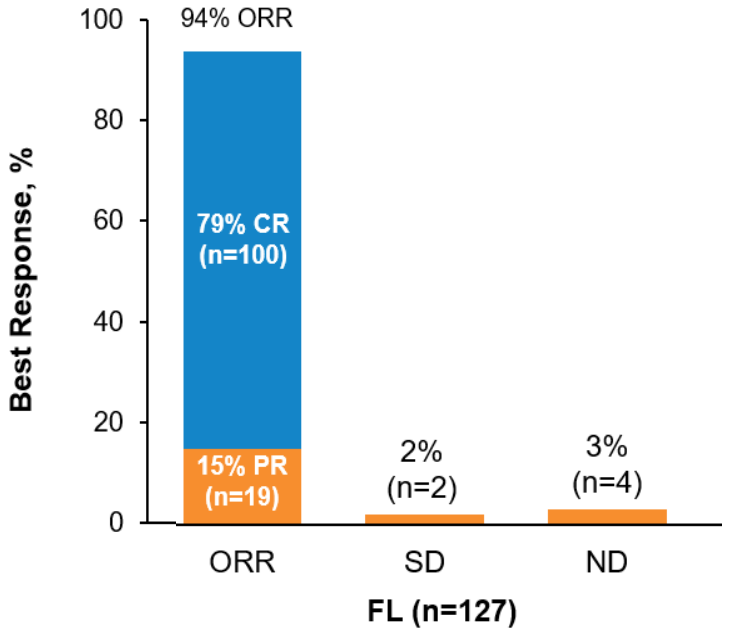
- ❑ FL= 124 pts
- ❑ Success in manufacturing in ALL patients
- ❑ Median time from leukapheresis to delivery: 17 days
- ❑ Bridge to 6 (4%) of total 148 pts (4 FL)

Jacobson CA et al, Lancet Oncol 2022; Neelapu SS et al, ASH 2023, #4868; Neelapu SS et al, ASH 2024

Axi-cel (ZUMA-5)

CRS grade ≥ 3 = 6%
ICANS grade ≥ 3 = 18%

Parameter	Infused FL patients (n = 124)
Median age, y	60 (53-67)
ECOG PS 1 before infusion, n (%)	**46 (37%)**
Stage at study entry III-IV, n (%)	106 (85%)
High tumor bulk (GELF criteria), n (%)	**64 (52%)**
FLIPI high (≥ 3) at study entry, n (%)	54 (44%)
Median no. of previous therapies (range)	**3 (2-4)**
POD24, n (%)	68 (55%)
Refractory disease to last line of therapy, n (%)	84 (68%)
Previous autologous HSCT, n (%)	30 (24%)

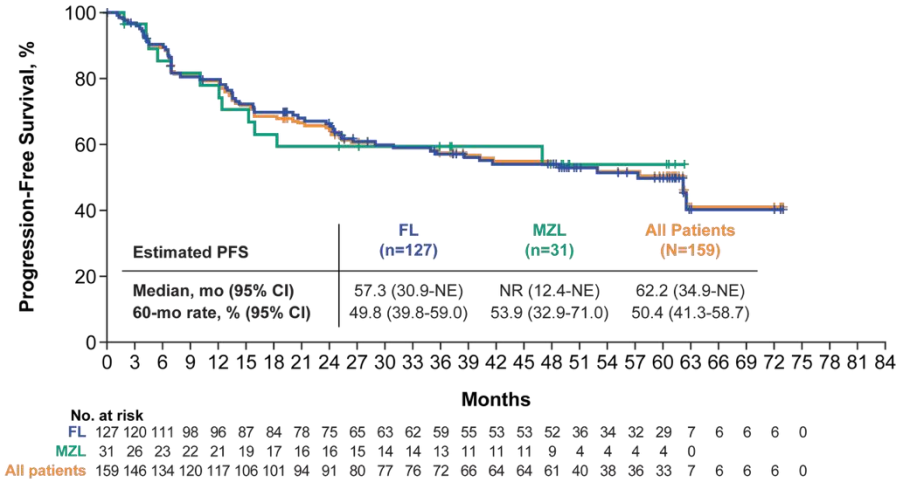


Jacobson CA et al, Lancet Oncol 2022; Neelapu SS et al, ASH 2023, #4868; Neelapu SS et al, ASH 2024

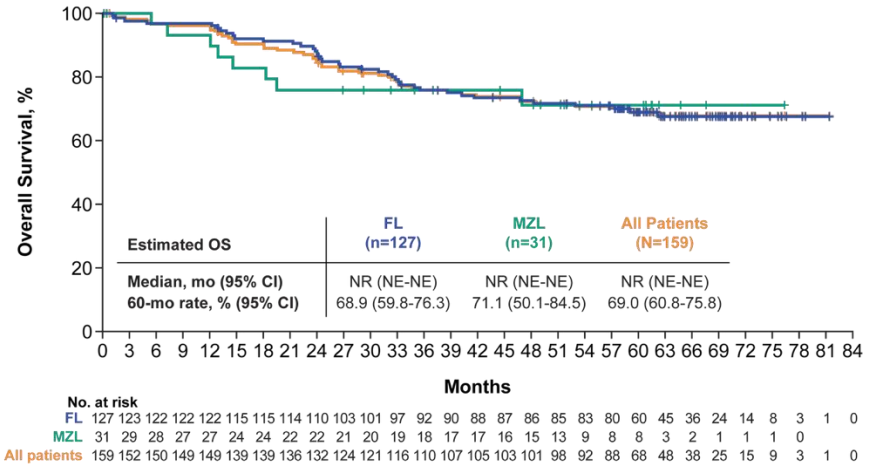
Axi-cel (ZUMA-5)

5y f-up

Progression-Free Survival



Overall Survival



60m PFS consistent regardless of HR factors (eg POD24)

60m PFS rate was 61.9% in CR pts (vs 9.1% in PR pts)

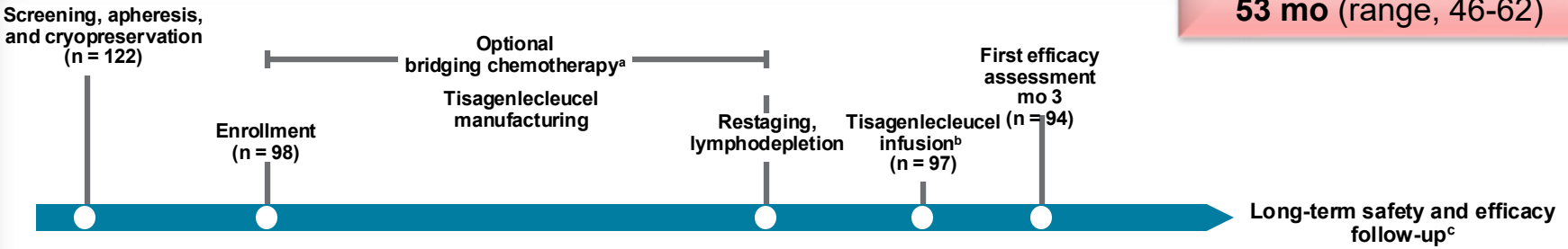
Median DOR: 80.4 months

Median TTNT: not reached

Jacobson CA et al, Lancet Oncol 2022; Neelapu SS et al, ASH 2023, #4868; Neelapu SS et al, ASH 2024

Tisa-cel (ELARA)

Median follow-up:
53 mo (range, 46-62)



Key eligibility criteria	Study treatment	End points
• ≥18 years of age • FL grade 1, 2, or 3A • Relapsed/refractory disease[d] • No evidence of histological transformation/FL3B • No prior anti-CD19 therapy or allogeneic HSCT	Tisagenlecleucel dose range (single IV infusion) was 0.6-6 × 10^8 CAR-positive viable T cells	**Primary:** CRR by IRC **Secondary:** ORR, DOR, PFS, OS, safety, cellular kinetics

- Bridging therapy was allowed during manufacturing and was followed by disease re-evaluation before tisagenlecleucel infusion
- Endpoints included CRR, ORR, DOR, PFS, OS, safety and cellular kinetics

Fowler NH et al, Nature Medicine 2022; Schuster SJ et al, ASH 2023, #601; Thieblemont et al, ASH 2024, #3034

Tisa-cel (ELARA)

CRS grade ≥ 3 = 1%
ICANS grade ≥ 3 = 1%

	Infused set (N = 97), n (%)
Median age (range), years	57.0 (29.0-73.0)
18 to <65 years	73.0 (75.0)
≥65 years	24.0 (25.0)
ECOG PS ≥1 prior to infusion	42.0 (43.0)
Stage at study entry III-IV	83.0 (86.0)
Bone marrow involvement	37.0 (38.0)
Bulky disease[a]	63.0 (65.0)
FLIPI high at study entry (≥3)	58.0 (60.0)
Median no. of prior therapies (range)	4.0 (2.0-13.0)
POD24 from first anti-CD20 mAb containing therapy	61.0 (63.0)
Refractory disease to last line of therapy	76.0 (78.0)
Refractory to ≥2 regimens	69.0 (71.0)
Double refractory: anti-CD20 mAb + alkylating agent	66.0 (68.0)
Refractory to PI3K inhibitors	14.0 (14.0)
Prior autologous HCT	35.0 (36.0)

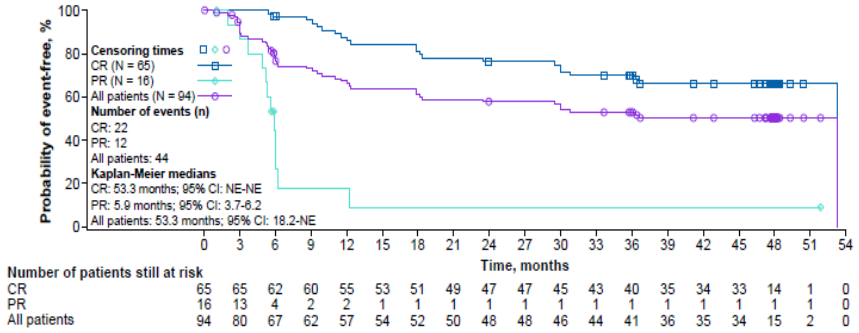
Endpoint in Efficacy Analysis Set (IRC Assessment)		% (95% CI) N=94
	CRR[a]	68 (58-77)[b]
	ORR[c]	86 (78-92)[b]

Disease Charact.	All Pts n (%) N=97	CRR % (95% CI)	ORR % (95% CI)
POD24	61 (63)	59 (46-71)	82 (70-91)
HighTMTV[d]	20 (21)	40 (19-64)	75 (51-91)
Bulky[e]	62 (64)	65 (51-76)	86 (74-93)
Double refr	65 (67)	66 (53-77)	85 (74-92)
FLIPI (≥3)	57 (59)	61 (48-74)	81 (68-90)

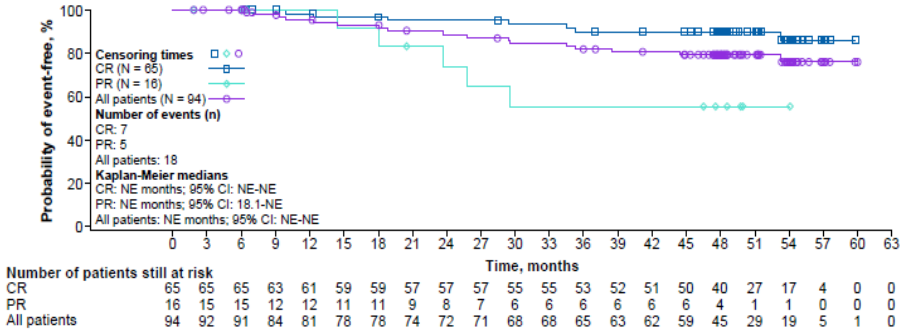
Fowler NH et al, Nature Medicine 2022; Schuster SJ et al, ASH 2023, #601; Thieblemont et al, ASH 2024, #3034

Tisa-cel (ELARA)

Progression-Free Survival



Overall Survival



Median PFS: 53 months

48-month PFS was 50% for all pts and 66% for pts with a CR

48-month PFS rates were consistent regardless of high-risk factors (POD24, FLIPI, bulky, double refract) except high tumor burden

Median OS: not reached

48-month OS rate was 79%

Median DOR: not reached

Median TTNT: not reached

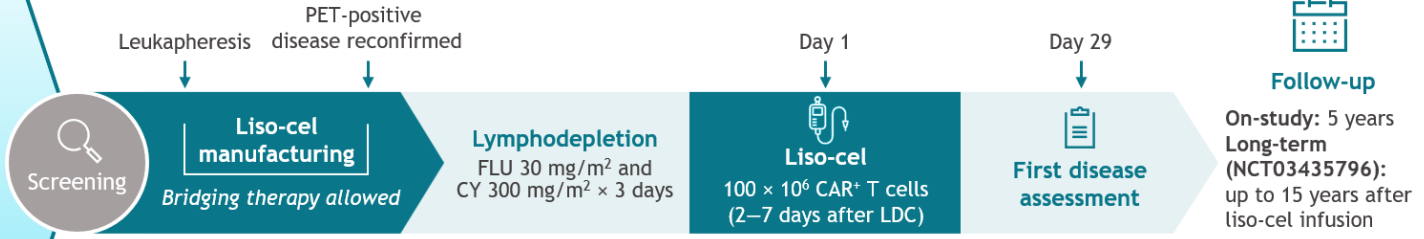
Fowler NH et al, Nature Medicine 2022; Schuster SJ et al, ASH 2023, #601; Thieblemont et al, ASH 2024, #3034

Liso-cel

Median follow-up:
24 months

Key FL eligibility criteria

- Age ≥ 18 years
- R/R FL
  - 4L+ cohort
  - 3L cohort
  - 2L cohort (POD24 and/or mGELF)[a]
- FL histologically confirmed ≤ 6 months before screening with PET-positive and measurable disease
- Received combination of anti-CD20 antibody and alkylator
- ECOG PS ≤ 1
- Adequate organ function



Primary endpoint (efficacy set)

- ORR (BOR of CR or PR) per IRC by PET/CT per Lugano 2014 criteria[1]

Secondary endpoints

- CR rate, DOR, DOR if BOR is CR, and PFS per IRC by PET/CT per Lugano 2014,[1] and OS
- Safety, cellular kinetics, HRQOL; B-cell aplasia (exploratory)

- Study endpoints of ORR and CR rate were tested hierarchically with null hypotheses in the following order at 1-sided α = 0.025 significance:
  - Sequence 1: 3L+ FL (ORR ≤ 60%), 4L+ FL (ORR ≤ 50%), 3L+ FL (CR rate ≤ 30%), and 4L+ FL (CR rate ≤ 20%); sequence 2: 2L FL (ORR ≤ 50%) and 2L FL (CR rate ≤ 19%)

ClinicalTrials.gov identifier: NCT04245839.

Morschhauser F et al, Nature Medicine 2024; Morschhauser F et al, ASH 2023, #602; Nastoupil LJ et al, ASH 2024, #4387

Liso-cel

CRS grade ≥ 3 = 1%
ICANS grade ≥ 3 = 2%

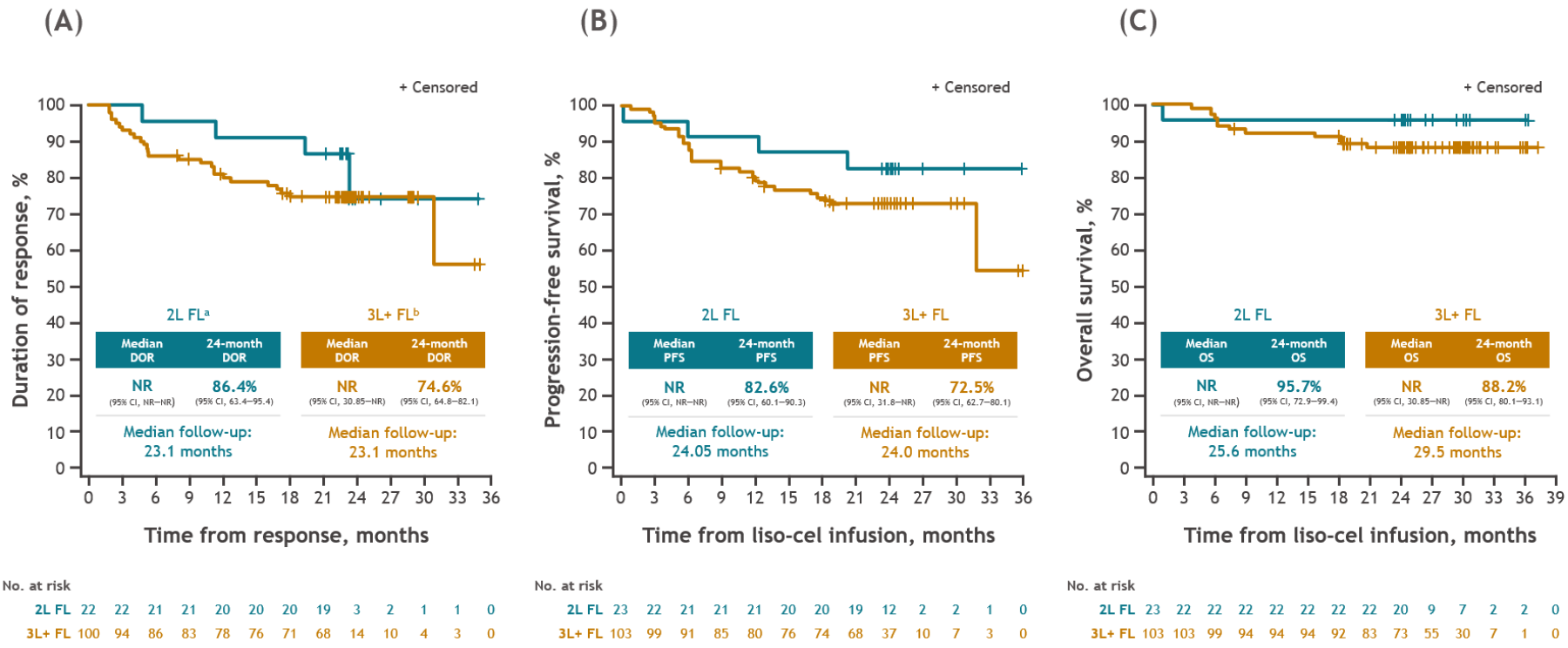
	2L FL (n = 23)	3L+ FL (n = 107)
Median (range) age, y		
Male, n (%)		
FL grade 1 or 2 / 3a at screening,[a] n (%)		
Ann Arbor stage at screening, n (%)		
Stage I/II		
Stage III/IV		
FL International Prognostic Index at screening, n (%)		
Low risk (0–1) / intermediate risk (2)	11 (48) / 4 (17)	12 (11) / 34 (32)
High risk (3–5)	8 (35)	61 (57)
LDH > ULN before lymphodepletion, n (%)	6 (26)	47 (44)
Met mGELF criteria at most recent relapse, n (%)	16 (70)	57 (53)
Symptoms attributable to FL	6 (26)	13 (12)
Threatened end-organ function/cytopenia secondary to lymphoma/bulky disease	7 (30)	24 (22)
Splenomegaly	0	4 (4)
Steady progression over at least 6 months	3 (13)	16 (15)
Median (range) prior lines of systemic therapy	1 (1–1)	3 (2–10)
Prior HSCT, n (%)	0	33 (31)
Received prior rituximab and lenalidomide, n (%)	0	23 (21)
Refractory to last systemic therapy,[b] n (%)	15 (65)	72 (67)
Double refractory (anti-CD20 and alkylator),[c] n (%)	11 (48)	69 (64)
POD24 from initial immunochemotherapy, n (%)	15 (65)	58 (54)
POD24 from diagnosis, n (%)	12 (52)	46 (43)
Received bridging therapy, n (%)	5 (22)	44 (41)

ORR 97%
CRR 97%

ORR 97%
CRR 94%

Morschhauser F et al, Nature Medicine 2024; Morschhauser F et al, ASH 2023, #602; Nastoupil LJ et al, ASH 2024, #4387

Liso-cel



Morschhauser F et al, Nature Medicine 2024; Morschhauser F et al, ASH 2023, #602; Nastoupil LJ et al, ASH 2024, #4387

Mosunetuzumab

Median follow-up:
49.8 months

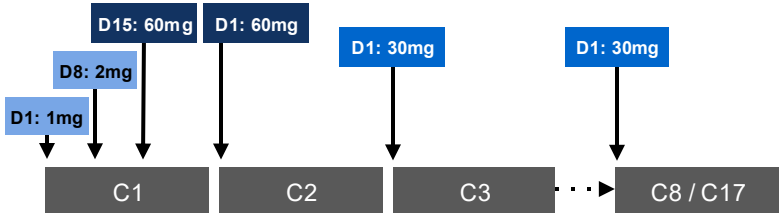
Pivotal cohort: single-arm, multicenter, Phase II expansion in patients with R/R FL and ≥2 prior therapies[1–3]

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



Fixed duration treatment
Retreatment permitted at relapse for pts 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

Budde LE et al. ASH 2021; Budde LE et al. Lancet Oncol 2022;23:1055-1065; Schuster SJ et al. ASH 2023.

Mosunetuzumab

CRS grade ≥ 3 = 2%
ICANS grade ≥ 3 = 0%

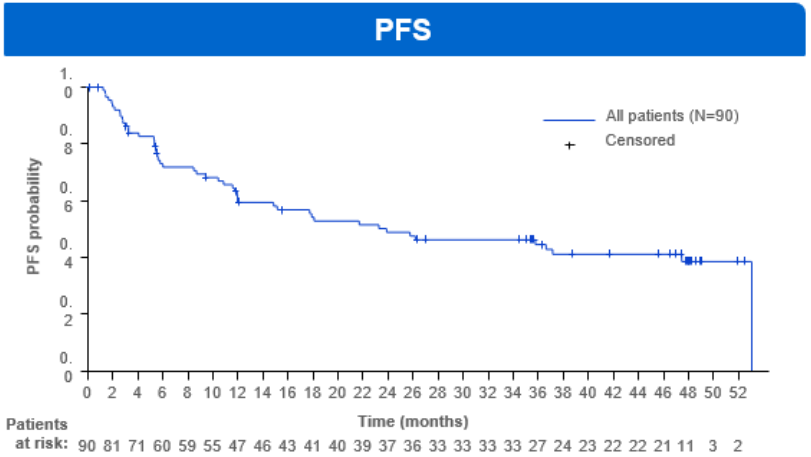
n (%), unless stated	N=90
Median age, years (range)	60 (29–90)
Male	55 (61)
ECOG PS	
0	53 (59)
1	37 (41)
Ann Arbor stage	
I/II	21 (23)
III/IV	69 (77)
Median lines of prior therapy, (range)	3 (2–10)
Prior autologous stem cell transplant	28 (31)*
Refractory to last prior therapy	62 (69)
Refractory to any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

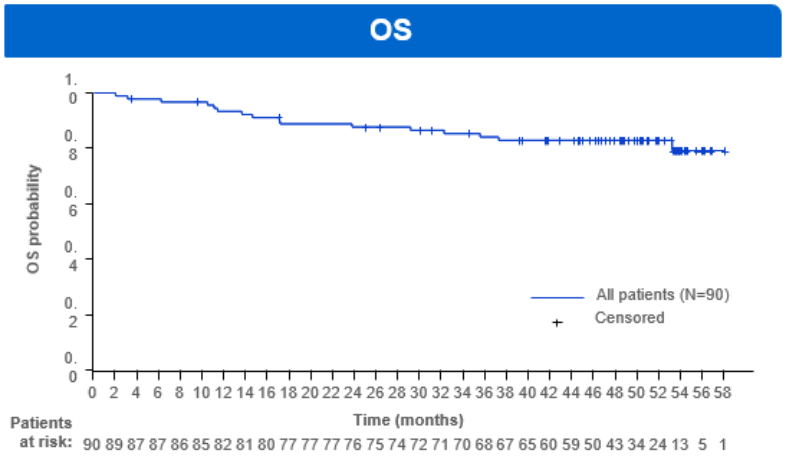
Efficacy endpoint; n (%) [95% CI]	IRF assessed N=90
CR	**54 (60)** [49–70]
ORR	**72 (80)** [70–88]

CRR and ORR were consistent regardless of high-risk factors (POD24, 3L vs 4L, double refract)

Budde LE et al. ASH 2021; Bartlett NL et al. ASH 2022. Schuster SJ et al. ASH 2023; Assouline et al. EHA 2024.

Mosunetuzumab





Median PFS: 24 months
48-month PFS was 38.6% for all pts

Median OS: not reached
48-month OS rate was 82,7%

Median DOR: 46.4 months (mDOCR: 51.8 months)
Median TTNT: 37.3 months

Budde LE. ASH 2021; Bartlett NL et al. ASH 2022. Schuster SJ et al. ASH 2023; Assouline et al. EHA 2024; Shadman M et al. ASH 2024.

Epcoritamab

Median follow-up:
17.4 months

Dose escalation

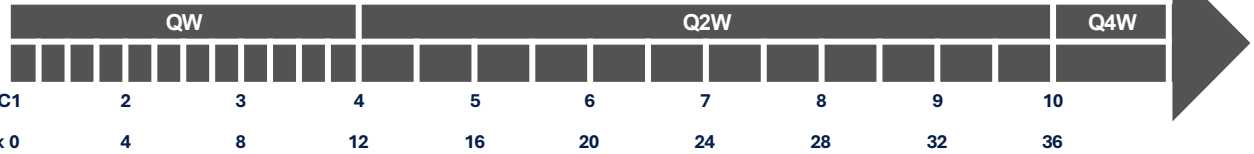
Dose expansion data cutoff: April 21, 2023
Median follow-up: 17.4 months

Key inclusion criteria:

- R/R CD20^{+} FL (grade 1–3A)
- ECOG PS 0–2
- ≥2 prior lines of antineoplastic therapy, including ≥1 anti-CD20 mAb
- Prior treatment with an alkylating agent or lenalidomide

Step-up dosing[a]

Epcoritamab SC RP2D 48 mg
Treatment until PD[b] or unacceptable toxicity
R/R FL grade 1–3A expansion cohort, N=128



- **Primary endpoint:** ORR by independent review committee (IRC)
- **Key secondary endpoints:** CR rate, TTR, TTCR, DOR, DOCR, PFS, OS, TTNT, MRD[c], and safety/tolerability

Linton KM et al. Lancet Haematol. 2024; Linton KM et al. ASH 2023.

Epcoritamab

CRS grade ≥ 3 = 2%
ICANS grade ≥ 3 = 0%

n (%), unless stated	N=128
Median age, years (range)	65 (39–84)
Male	79 (62)
ECOG PS	
0	77 (55)
1	51 (40)
Ann Arbor stage	
I/II	19 (15)
III/IV	109 (85)
Median lines of prior therapy, (range)	3 (2–9)
Prior R2	27 (21)
Refractory to last prior therapy	88 (69)
Refractory to any prior anti-CD20 therapy	101 (79)
POD24	54 (42)
Double refractory to prior anti-CD20 & alkylator therapy	90 (70)

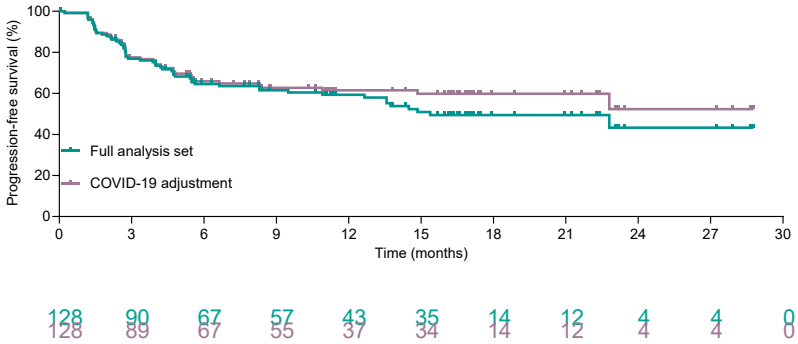
Efficacy endpoint; n (%) [95% CI]	IRC assessed N=128
CR	**80 (63)** [54–71]
ORR	**105 (82)** [74–88]

CRR and ORR were consistent regardless of high risk factors (POD24, 3L vs 4L, double refractory, high FLIPI)

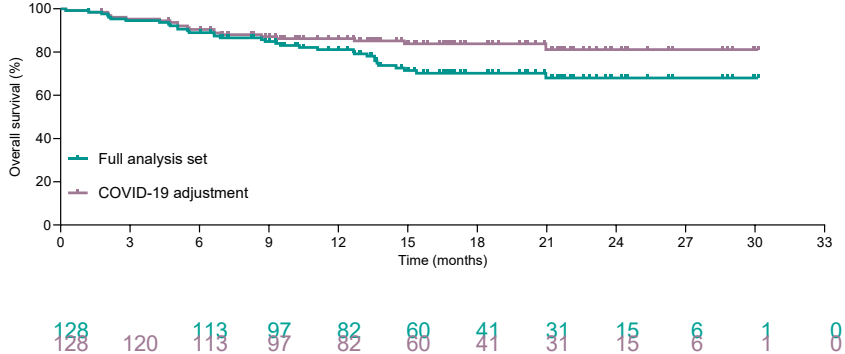
Linton KM et al. Lancet Haematol. 2024; Linton KM et al. ASH 2023.

Epcoritamab

Progression-Free Survival



Overall Survival



Median PFS: 16 months
18m PFS was 49.4% for all pts, 73.8% for pts with a CR

Median OS: not reached
18-month OS rate was 70.2%

Median DOR: not reached
Median TTNT: not reached

Linton KM et al. Lancet Haematol. 2024; Linton KM et al. ASH 2023.

Activity of single agentes BiAbs in R/R FL

Fixed Duration

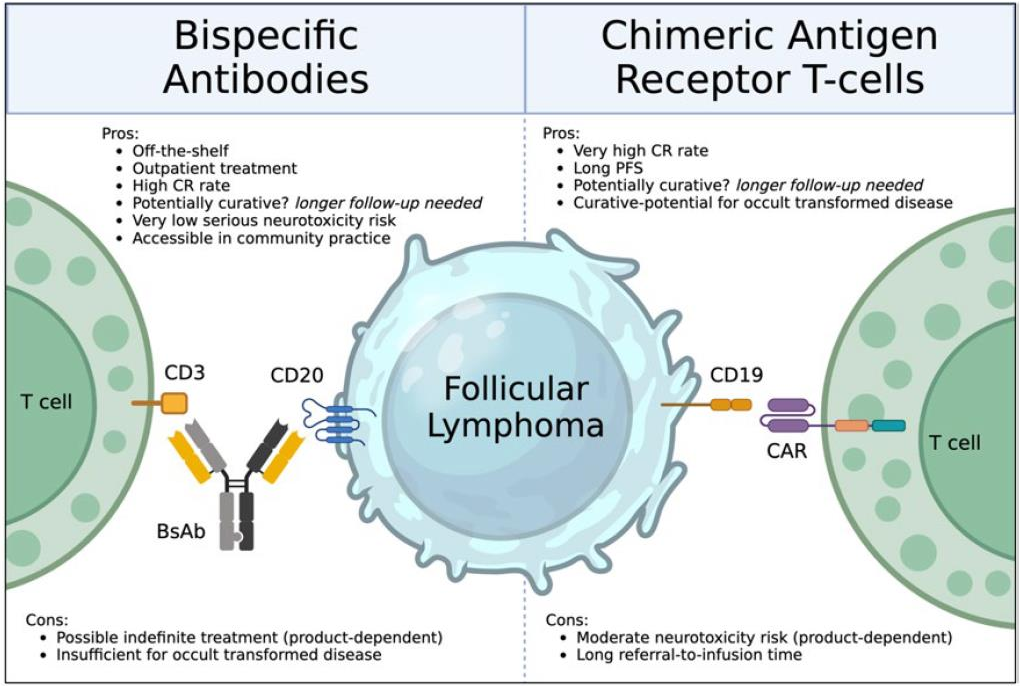
	N	Age range	ASCT/ POD24 %	mFU	ORR/ CRR (%)	mPFS (months)	CRS (all,G3+)	other
Mosunetuzumab	90	29-90	21/52	37.4m	78/60	24 mo	44%,2%	G5 AE 2% (0 related) Discont (AE). 4%

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.

CAR-T vs BiAbs



Russler-Germain DA et al, ASH Education Program 2024

FL… future treatment landscape

First-line Treatment Trials	R2 (RELEVANCE) Mosunetuzumab sc (phase 2) R2 plus Epcoritamab (phase2, phase 3 vs R-chemo) Odronextamab (phase 3, alone or plus chemo versus R-chemo)
R/R FL Treatment Trials	R2 plus Epcoritamab (phase 2 NHL-2) R2 + Mosu / Epco / Odro vs R2 (phase 3 CELESTIMO, M22-630, OLYMPIA 5) Axi-cel vs SOC (phase 3 ZUMA-22) Mosu + Zanubrutinib (phase 2 MOZART) Obinu + Zanubrutinib vs R2 (phase 3 MAHOGANY) R2 + tafasitamab vs R2 (phase 2 INMIND) R2 + tazemetostat vs R2 (phase 3 SYMPHONY-1)

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

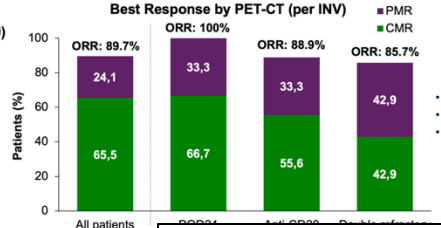
Lenalidomide PO 20 mg
- C2-12 D1-21 (11 total cycles)

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%

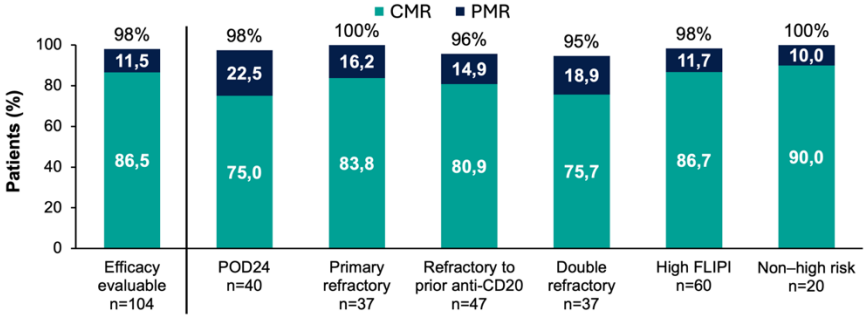
Median follow-up: 5.4 mo (range: 3–12)



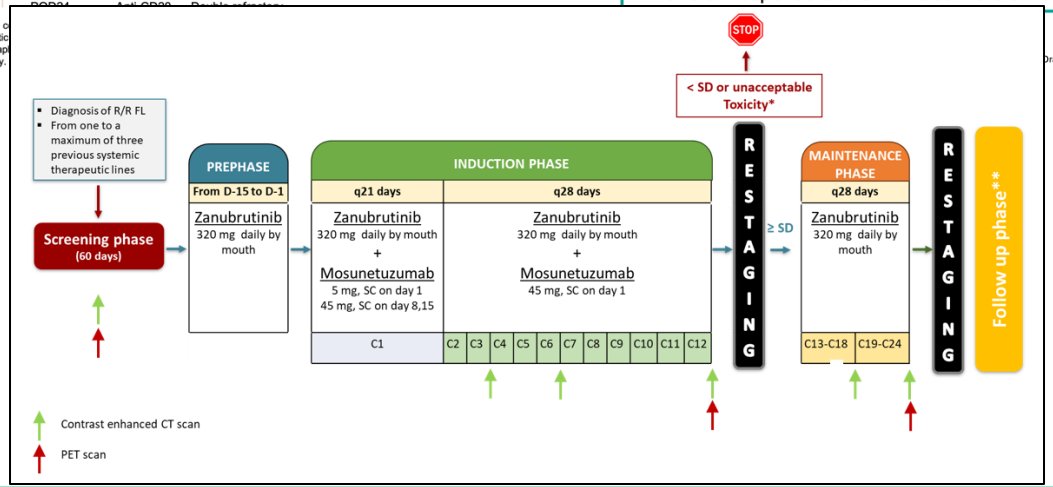
- 86.2% had ongoing response
- All patients in CMR were still in CMR
- 2 patients experienced deepening of response (at approximately 5 months and 10.5 months)

2L, second-line; C, cycle; CIT, chemoimmunotherapy; CMR, complete metabolic response; CT, c
performance status; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic
therapy; Mosun, mosunetuzumab; ORR, overall response rate; PET: positron emission tomograp
progression of disease within 24 months from the start of initial therapy; R/R, relapsed/refractory.
Morschhauser F, et al. ASH 2021. Abstract 129.

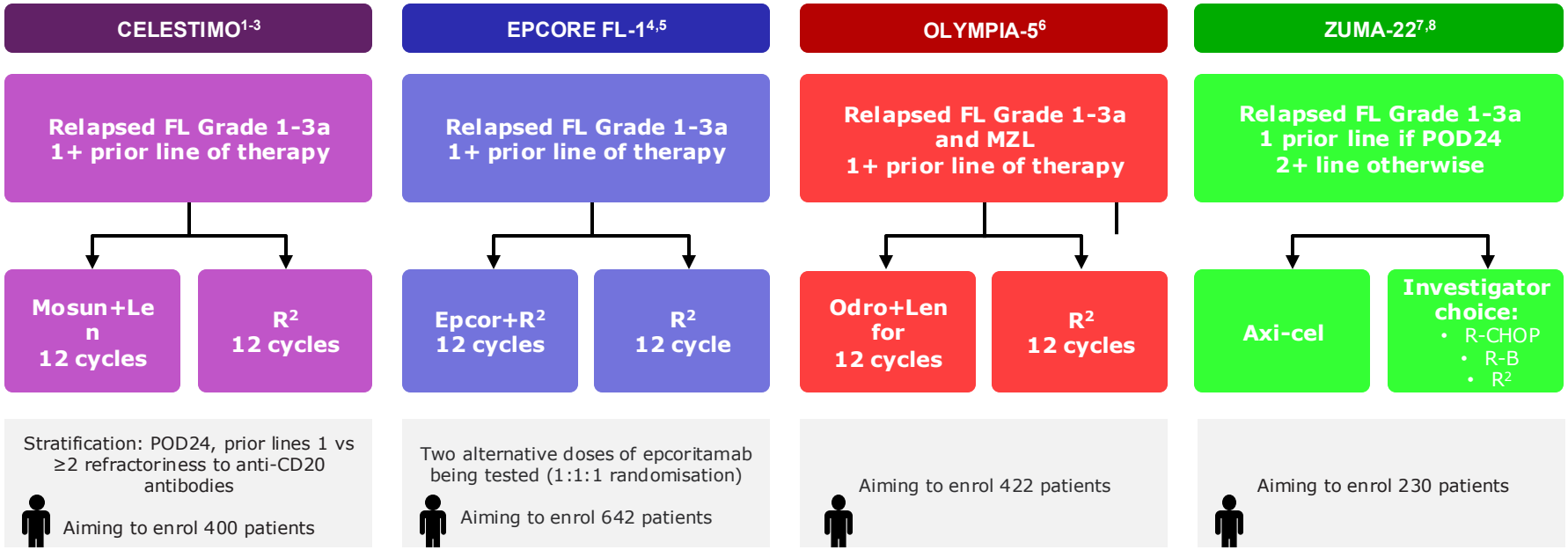
Epcoritamab + R² in R/R FL: Antitumor Activity in Subgroups



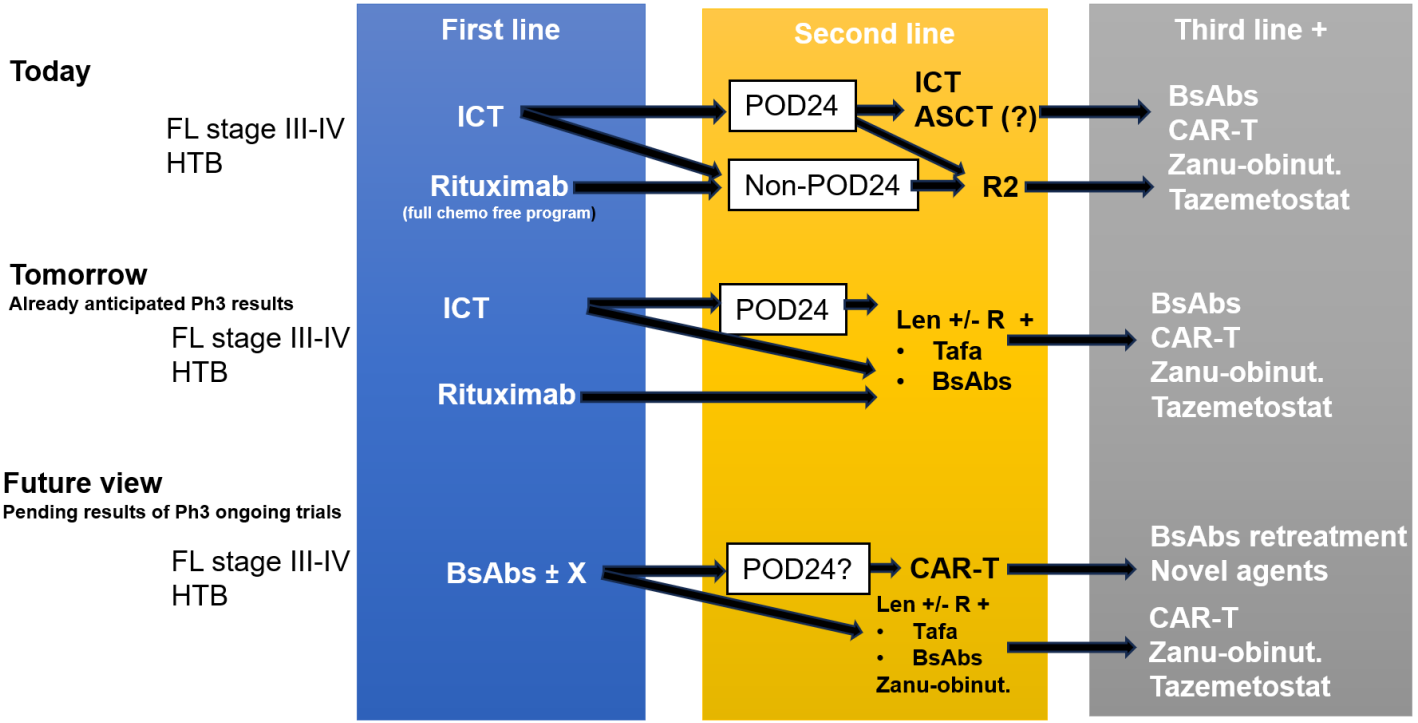
Overall response and CMR rates were consistently high across all subgroups



Ongoing phase 3 trials in R/R FL



Evolving paradigms in FL



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

Luminari S, BJH 2025 – slide credit: Stefano Luminari

Conclusions

- FL is still considered an incurable disease (but 20% of patients will not experience any disease recurrence)
- At the opposite extreme is the 15-20% of patients who experience an early disease recurrence (POD24), with a worse prognosis
- CAR-T and BiAbs (currently 3L+) have change the dogma of a lower efficacy associated with each subsequent therapeutic line and proved to be useful weapons even in groups traditionally with a poor prognosis (POD24, high FLIPI, double refractory, high tumor volume)
- The anticipation in first or second line of highly effective (chemo-free) strategies will further change the paradigm of FL treatment

Conclusions

- The number of cured patients is destined to increase, but equally important is the very marked increase of functionally cured patients

- It is time to change our approach in describing the path of the disease and treatment options
  - →shared choice with the patient of the "best therapy at that particular moment in her/his life“
  - →QoL (in the context of a pathology with these characteristics, progression and curability) should today represent at least a co-primary objective of clinical studies

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Thank you