

Session: Lymphomas with good prognosis: do not harm



Bispecific antibodies in indolent lymphomas

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ROMA

HEMATOLOGY CONFERENCE

the lymphomas

Rome

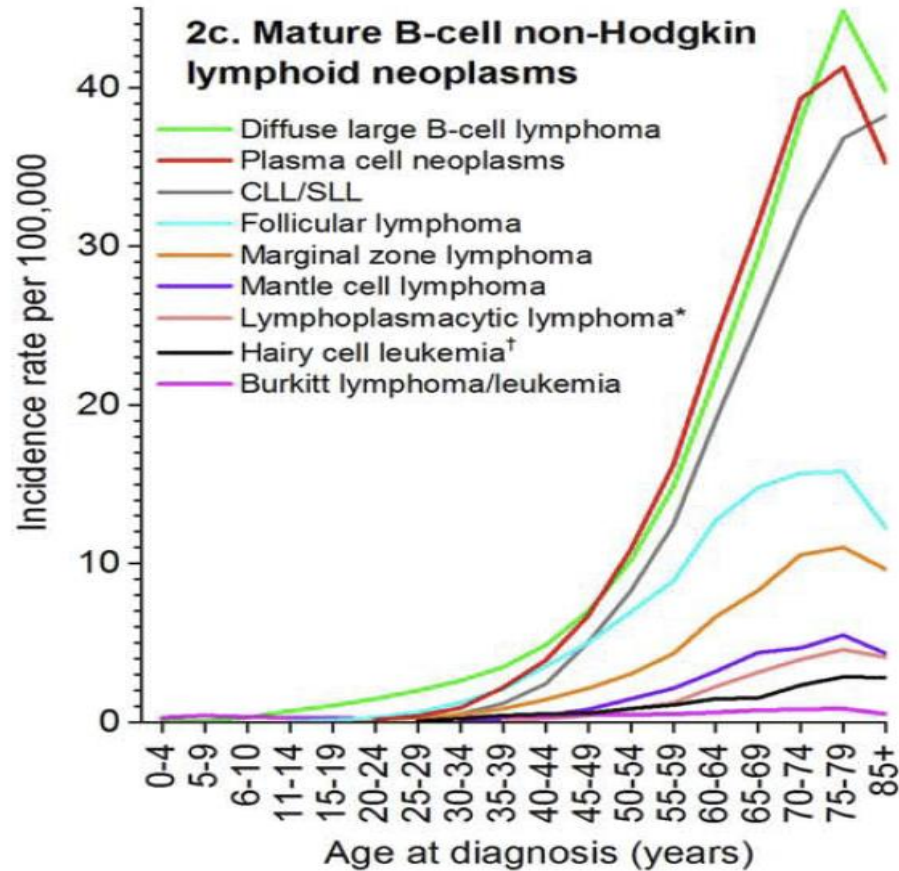
October 15-16, 2026

Hotel nhow Roma

Disclosure: Annarita Conconi

Company name	Speakers bureau	Advisory board
Roche		X
Gilead		X
Novartis	X	X
Janssen	X	
Abbvie	X	
Incyte	X	X
Takeda	X	

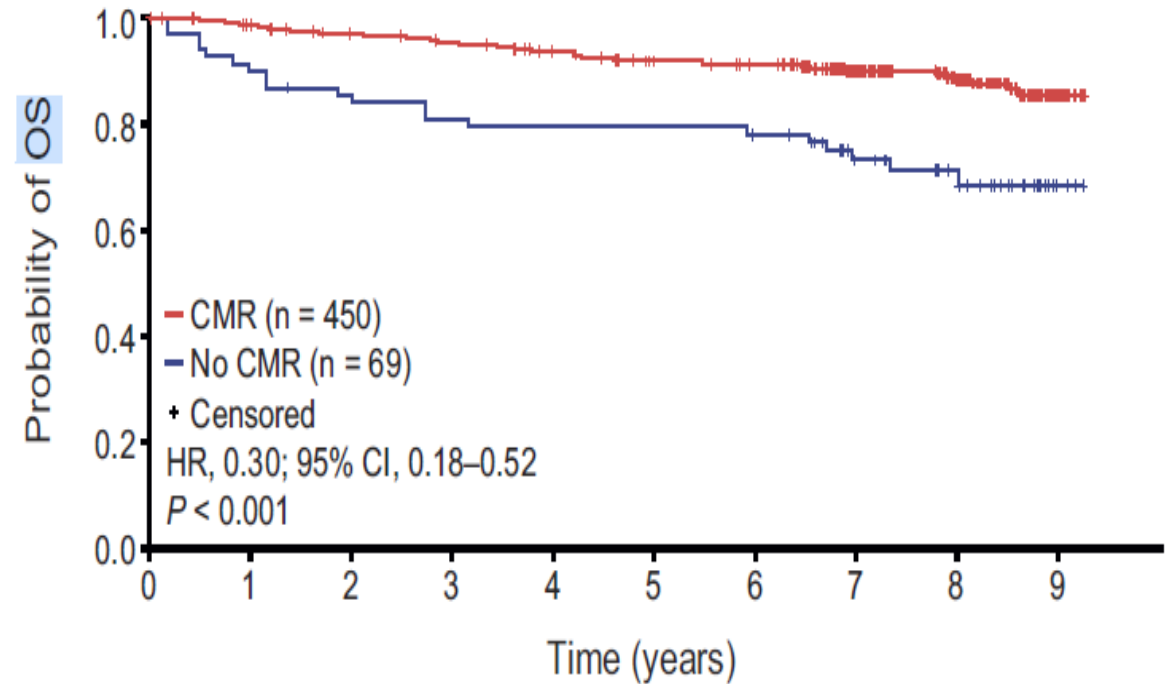
Epidemiology of FL



Incidence increases from about 30 to 70 years of age

Functional cure for FL

Final analysis of the Gallium study

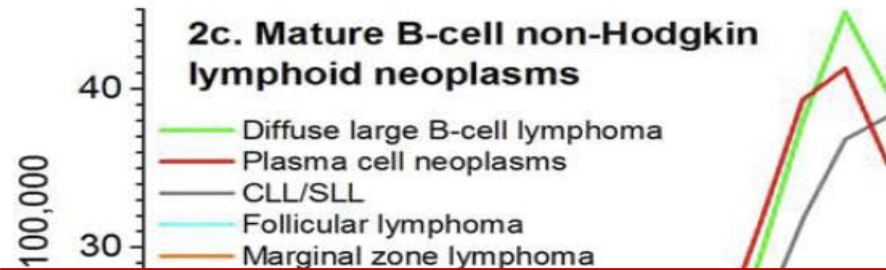


No. of patients at risk																			
CMR	450	444	438	428	423	419	414	410	398	391	382	380	374	359	308	217	139	79	21
No CMR	69	65	62	59	57	57	55	54	54	54	54	54	52	51	40	33	25	17	3

For patients in CMR after immunochemotherapy
estimated 90% to 91% 7-yr OS

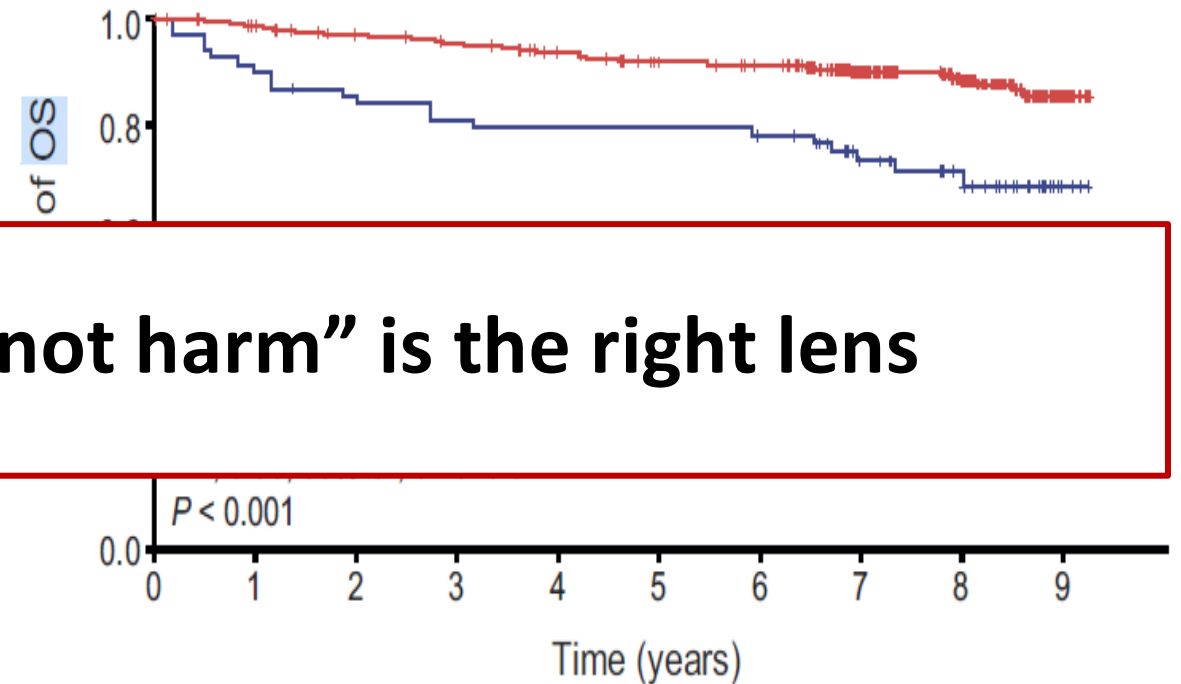
Townsend W et al. Hemasphere. 2023;7(7):e919 Teras LR, CA Cancer J Clin. 2016;66(6):443-459.

Epidemiology of FL



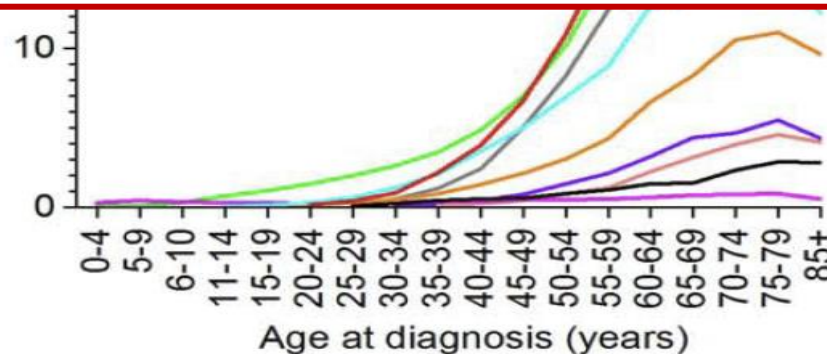
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No CMR	69	65	62	59	57	57	55	54	54	54	54	54	52	51	40	33	25	17	3

Bispecifics in FL: why “do not harm” is the right lens



Incidence increases from about 30 to 70 years of age

For patients in CMR after immunochemotherapy
estimated 90% to 91% 7-yr OS

Townsend W et al. Hemasphere. 2023;7(7):e919 Teras LR, CA Cancer J Clin. 2016;66(6):443-459.

Main issues to discuss

- Acute toxicity
 - immune mediated adverse events - CRS, ICANS
 - infections
- Long term toxicity
 - B cell aplasia
- Effects on subsequent lines of therapy
 - loss of CD20 antigen

Four fields to be explored

1

**Follicular
lymphoma
3rd line and beyond**

Mosunetuzumab and
epcoritamab monotherapy

2

**Follicular
lymphoma
2nd line**

Epcoritamab +
lenalidomide + rituximab
(EPCORE FL-1)

3

**Marginal zone
lymphomas**

First data with bispecifics

4

**Beyond the first
cycles**

Long-term effects, CD20
loss and the next line

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**Beyond the first
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Long-term effects, CD20
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CD20×CD3 bispecifics available for FL in Europe

Agent	Route	Duration	EU indication in FL
→ Mosunetuzumab	IV or SC	Fixed: 8 cycles if CR, otherwise 17	R/R FL after ≥2 systemic therapies
→ Epcoritamab	SC	Monotherapy: until progression With R2: fixed, 12 cycles	Monotherapy after ≥2 lines With R2: R/R FL (EC, July 2026)
Odronextamab	IV	Until progression (dosing interval extended in durable CR)	R/R FL after ≥2 systemic therapies



Duration is a safety variable:

in a disease where patients live for decades, every extra month of T-cell redirection adds infection exposure

1

Third line and beyond

Mosunetuzumab and epcoritamab monotherapy

Mosunetuzumab: 5-year FU of fixed-duration therapy

78%

Overall response rate

60%

Complete response rate

24 mo

Median PFS, all patients

61 mo

Median PFS,
in complete responders



GO29781 pivotal cohort, n = 90, ≥2 prior lines, median follow-up 60.2 months

- **Treatment stops** after 8 or 17 cycles, so most patients live most of these 5 years off therapy
- **B-cell and IgM recovery observed** and sustained in complete responders; no new safety signals
- Outcomes in **POD24** patients similar to the whole cohort

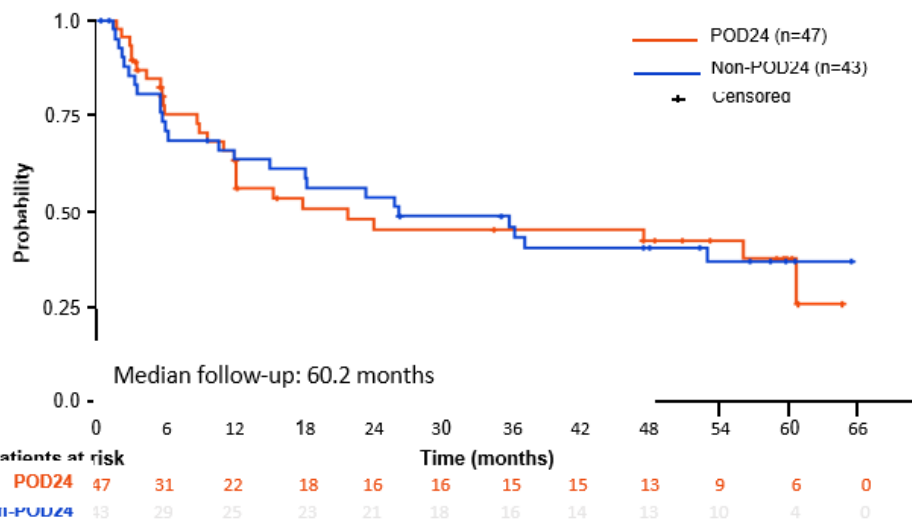
Budde LE et al. Lancet Oncol 2022;23:1055; Budde LE et al. ASH 2025 (Blood 2025;146 suppl), 5-year update.

Mo PFS and OS: POD24 vs non-POD24

78

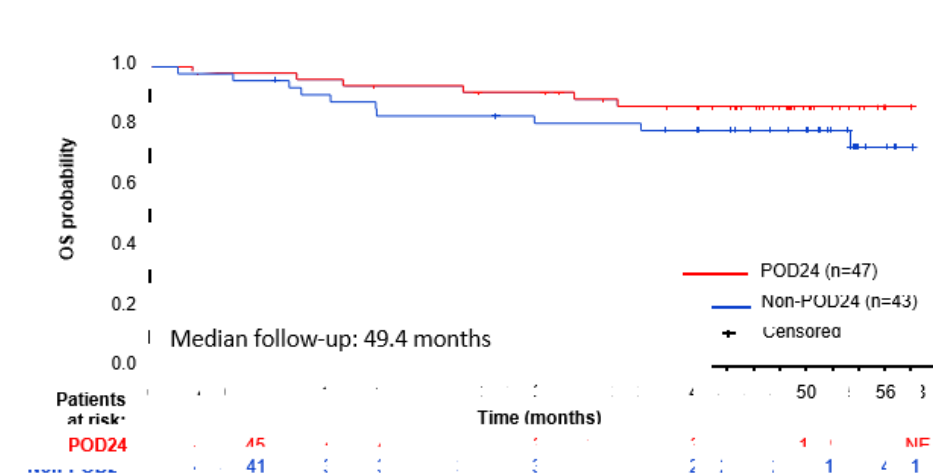
Over

PFS²



	Overall population (N=90)	Non-POD24 (n=43)	POD24 (n=47)
Median PFS ² , months (95% CI)	24.0 (12.0-53.2)	26. (11.8-NE)	22 (11.6-61.0)
5-year PFS ² , % (95% CI)	36.5 (25.3-47.7)	36.0 (20.4-51.5)	36.9 (20.7-53.1)

OS¹



	Overall population (N=90)	Non-POD24 (n=43)	POD24 (n=47)
Median OS ² , months (95% CI)	NR (NE)	NR (NE)	NR (NE)

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

Data cut-off: May 13, 2024 (1); Data cut-off: May 1, 2025. (2)

1. Shadman, et al. ASH 2024; Poster presentation (abstract #4407); 2. Budde, et al. ASH 2025; Poster presentation (abstract #5352).



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Epcoritamab: 3-year FU, deep responses, given until progression

82%

ORR, pivotal cohort (n = 128)

63%

CR rate, pivotal cohort

34 mo

Median PFS at 3 years (pooled)

92% / 73%

ORR / CR, optimisation cohort
(n = 86)



Treat to progression

Weekly, then every 2 weeks, then every 4 weeks. Exposure, B-cell aplasia and infection risk continue as long as the patient responds.

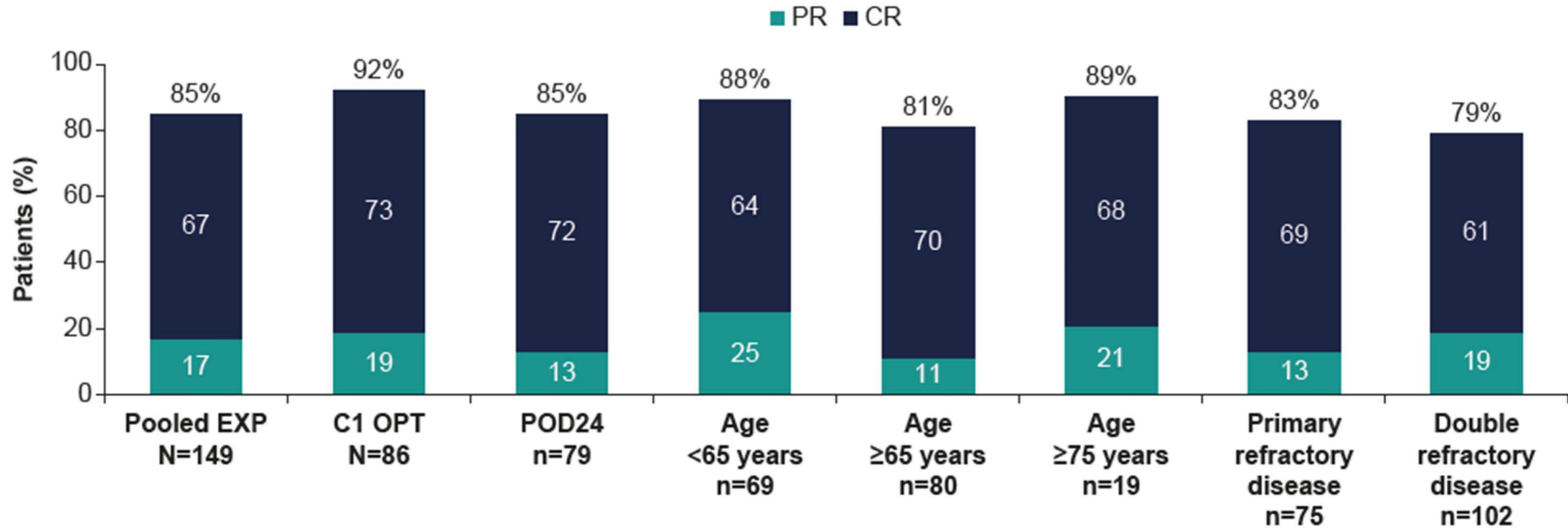


Can we stop in CR?

35 patients in CR stopped epcoritamab for a reason other than PD or death: 94% (33/35) had sustained CR after treatment discontinuation (median 13.1 mo, range: 0.4-28.3 mo)

Linton KM et al. Lancet Haematol 2024; pooled EPCORE NHL-1/NHL-3 3-year update (EHA 2025, n = 149, median follow-up 35 mo); C1 optimisation cohort (ASCO/EHA 2024–25).

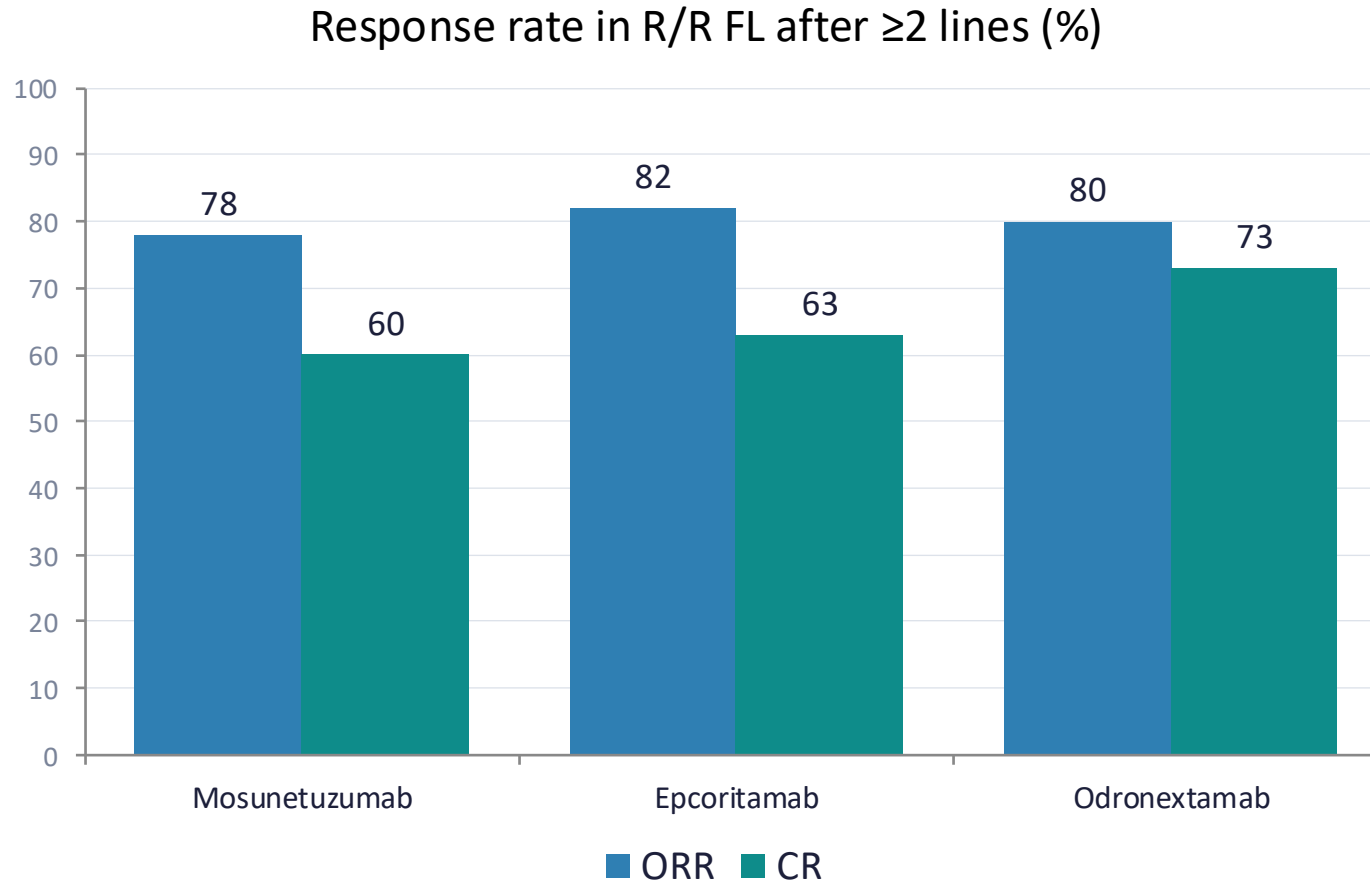
Epcoritamab: 3-year FU, deep responses, given until progression



^aSubgroups were evaluated in the pooled EXP cohort.

Data cutoff: December 2024. Population based on the FDA-approved indication of epcoritamab (N=127) had an ORR of 83%, including a CR rate of 65% and a PR rate of 17%.

Similar efficacy across agents: a cross-trial view

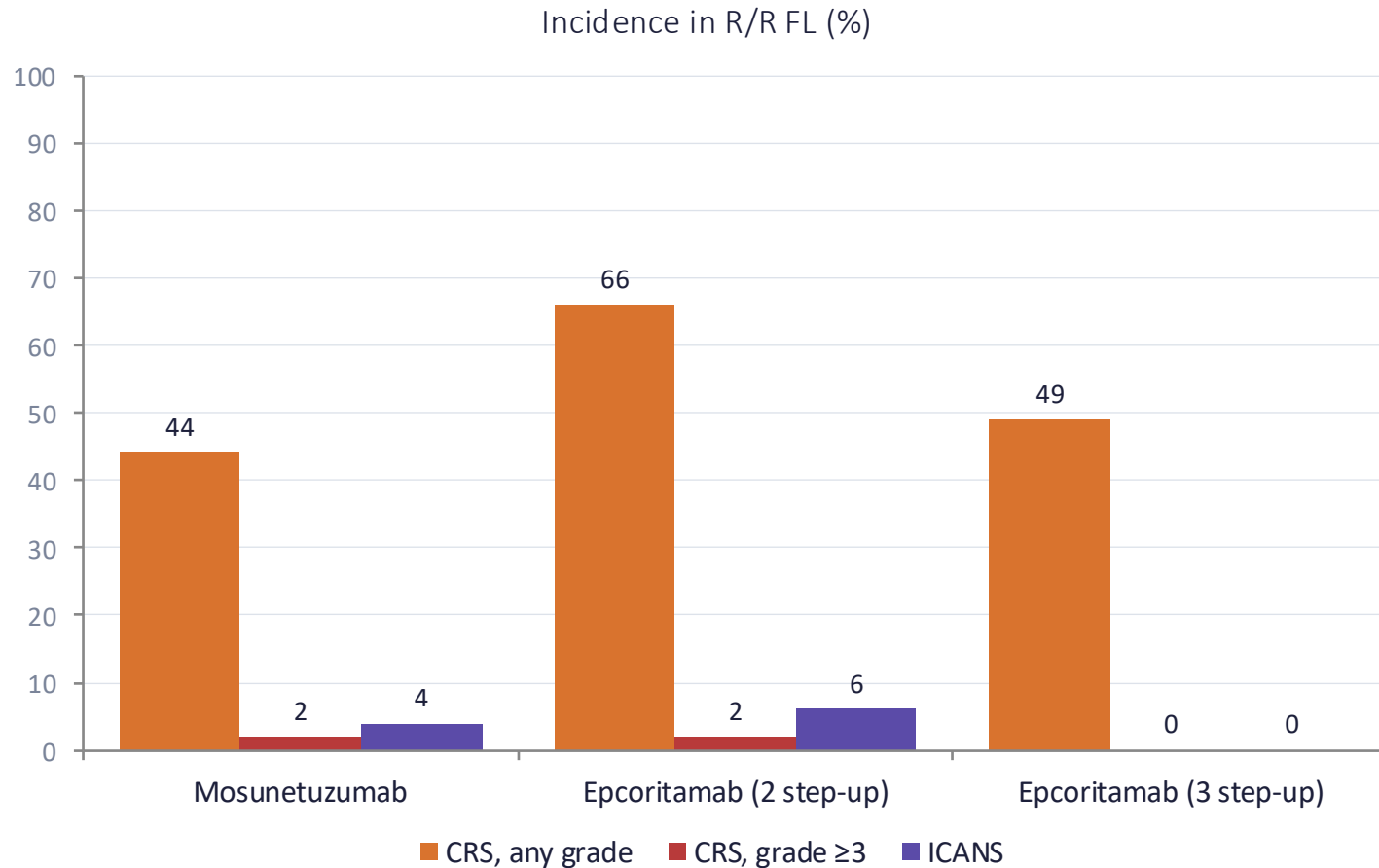


Read with caution

- Single-arm trials, no head-to-head data
- Different populations, follow-up and response assessment
- **Choose on schedule, route, duration and logistics, not on CR rate**

Mosunetuzumab: GO29781 5-year update; epcoritamab: EPCORE NHL-1 pivotal FL cohort; odronextamab: ELM-2 FL cohort (Taszner M et al. EHA 2024).

CRS and ICANS: frequent, early, mostly low grade



Timing

Concentrated in cycle 1, around step-up and first full doses



Severity

Grade ≥ 3 CRS in $\leq 2\%$; none with the 3-step-up schedule



ICANS

Uncommon, low grade and reversible

Budde LE et al. Lancet Oncol 2022; Linton KM et al. Lancet Haematol 2024 EPCORE NHL-1 C1 optimisation cohort.

Mitigating acute toxicity is now routine



Step-up dosing

Gradual exposure in cycle 1 is the main CRS safeguard; a third step-up dose further lowered CRS with epcoritamab.



Corticosteroid premedication

Dexamethasone around early doses in the optimisation cohort; hydration and antipyretics.



Ready to treat

Tocilizumab on site, ASTCT grading and a written CRS/ICANS algorithm shared with the patient and emergency team.



Outpatient monitoring

54% of patients in the epcoritamab optimisation cohort were monitored as outpatients after the first full dose.

Budde LE et al. ASH 2025; EPCORE NHL-1 3-year pooled analysis (EHA 2025)

Infection is the main threat, not CRS

44%

Any-grade infections,
pooled bispecific trials

3%

Fatal infections (79 of
1,774 patients)

4.2%

Non-relapse mortality in
NHL

72%

Of non-relapse deaths
caused by infection



In indolent lymphoma, one infectious death outweighs many months of PFS

- Rates of $\geq$ grade 3 infections did not differ significantly between mosu/epco/odro
- Significant proportion of serious and fatal events of viral etiology. Epcoritamab monotherapy in FL: fatal infections 6%, mostly COVID-19 during the pandemic
- Higher rate of fatal adverse reactions, mainly infections, in patients aged ≥ 65 years
- Non-relapse mortality is higher in real-world series than in trials

Reynolds GK et al. Blood Adv 2024;8:3555; Tix T et al. Mol Ther 2025;33:3163;).

Fixed duration versus treatment to progression



Fixed duration

- Mosunetuzumab: 8 or 17 cycles
- Epcoritamab + R2: 12 cycles
- Treatment-free interval, B-cell and IgM recovery
- Retreatment at relapse is feasible



Until progression

- Epcoritamab and odronextamab monotherapy
- Cumulative exposure and persistent B-cell aplasia
- Hypogammaglobulinaemia and late infections
- Stopping in sustained CR deserves prospective study

Budde LE et al. ASH 2025; EPCORE NHL-1 3-year pooled analysis (EHA 2025).

Third line and beyond: the balance tips toward benefit

Benefit

- CR in 60–73%, including POD24 and double-refractory
- Durable remissions, including POD24
- Median PFS 2–3 years, about 5 years in CR
- Off-the-shelf, outpatient, chemo-free



Risk

- Grade ≥ 3 CRS $\leq 2\%$, ICANS rare
- Infections drive non-relapse mortality ($\sim 4\%$)
- CD20 loss and fewer options later
- Logistics, monitoring and cost
- Duration of exposure matters

In 3L+ FL, where alternatives are limited and toxic, bispecifics have a favourable benefit–risk profile. Infection prevention is the lever we control.

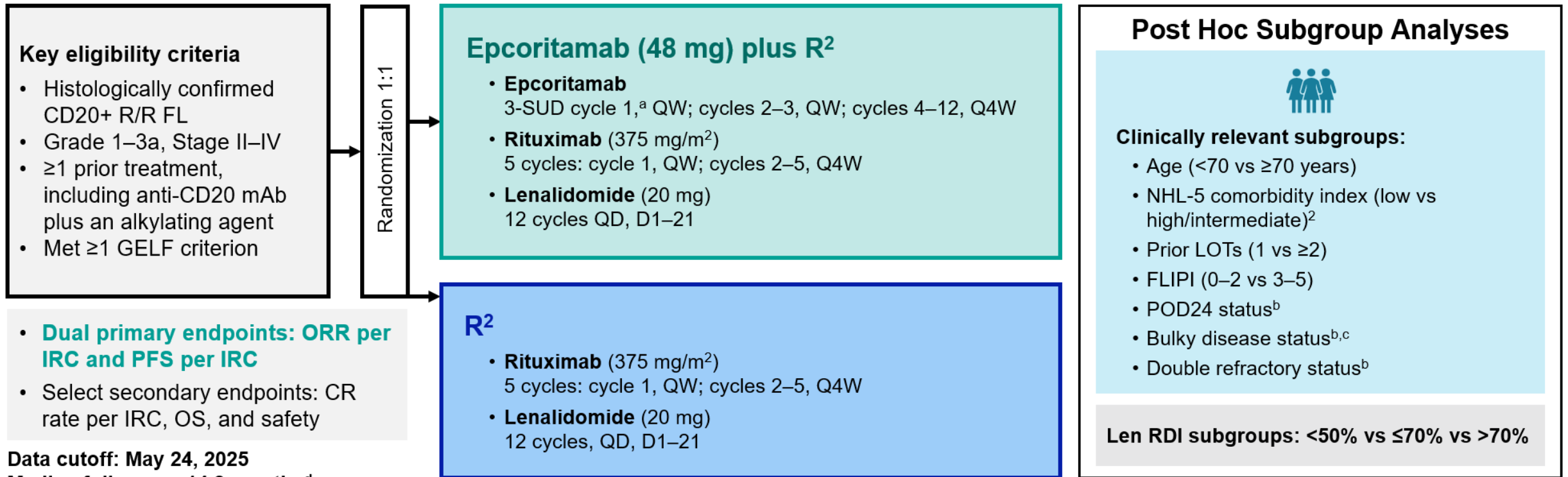
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Second line: earlier T-cell redirection

Epcoritamab + lenalidomide + rituximab (EPCORE FL-1)

EPCORE FL-1: Phase III, Global, Randomized, Open-Label Study

Fixed-Duration: 12 Cycles (28-Day Cycles)



- **Dual primary endpoints: ORR per IRC and PFS per IRC**

- Select secondary endpoints: CR rate per IRC, OS, and safety

Data cutoff: May 24, 2025

Median follow-up: 14.8 months^d

Enrollment period: Oct 2022 to Jan 2025

Epcoritamab given subcutaneously with 3 step-up doses in cycle 1; outpatient administration.

Falchi L et al. Lancet 2026 (EPCORE FL-1); ASH 2025 oral presentation, Nijland M et al. EHA 2026



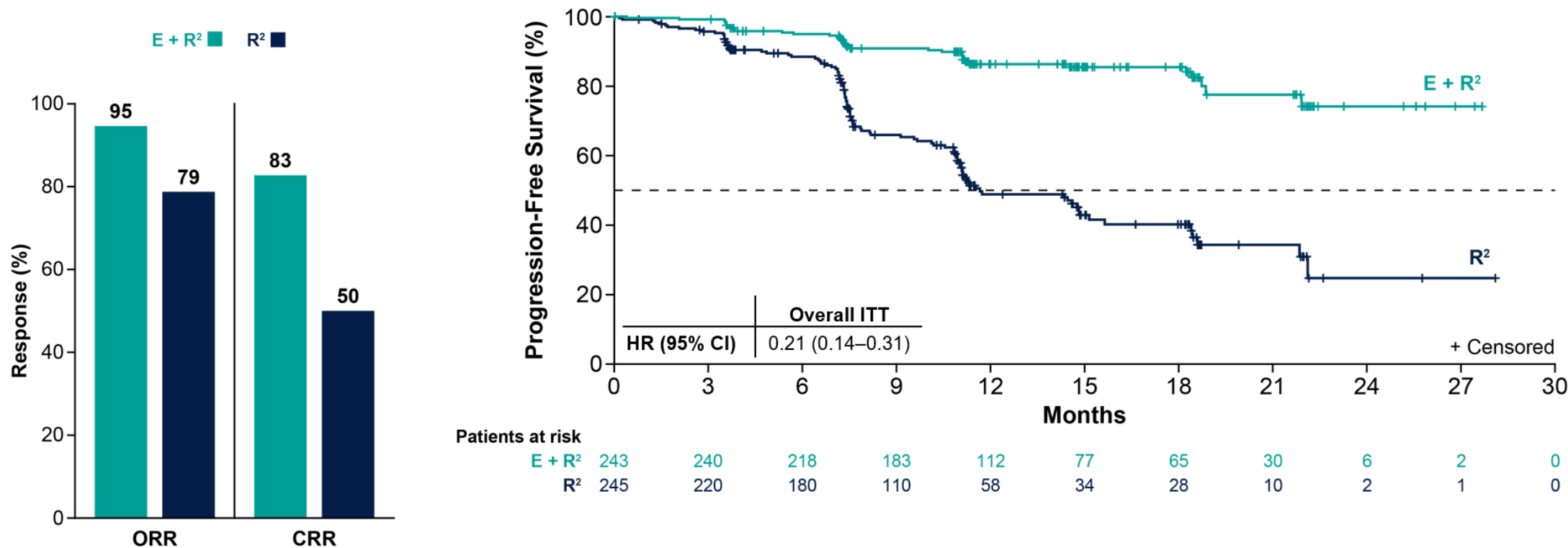
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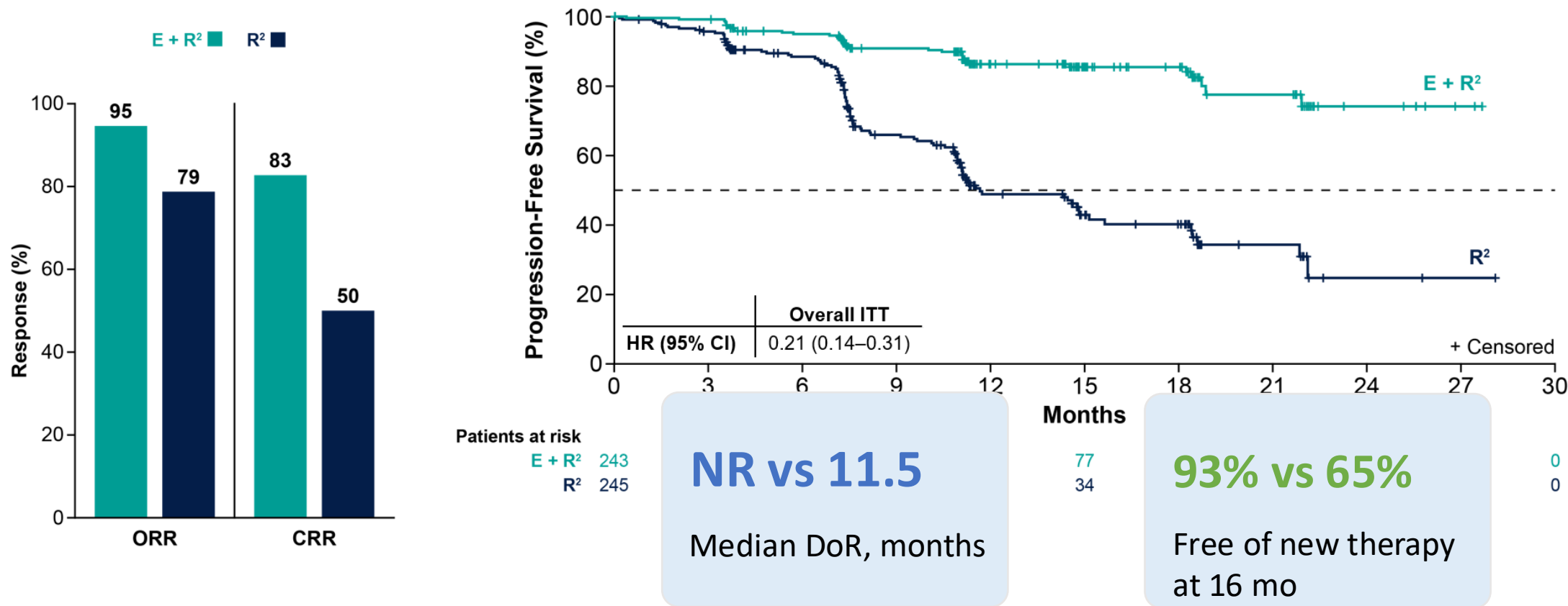
EPCORE FL-1: EPCO + R2 resulted in superior responses and PFS in the overall ITT population



Benefit consistent across subgroups, including POD24 and refractory disease

Nijland M et al. EHA 2026

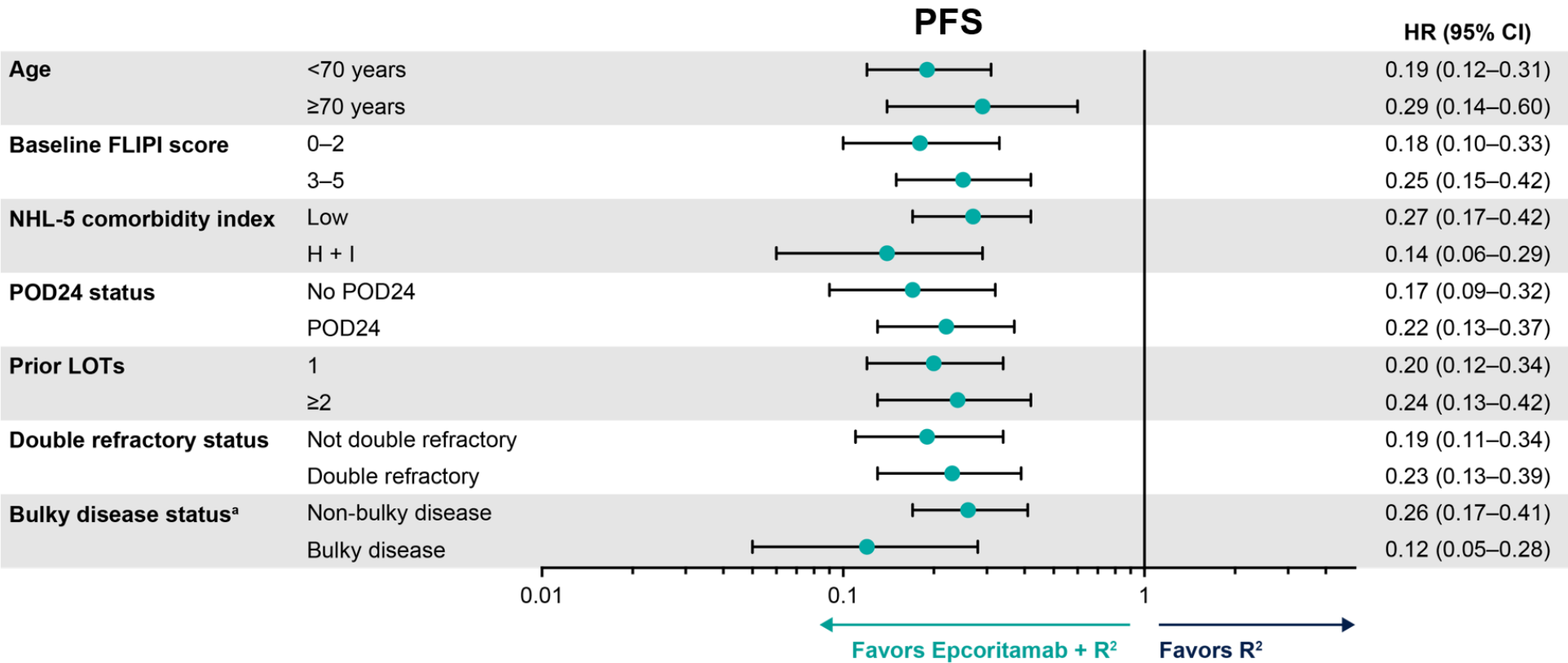
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Nijland M et al. EHA 2026

Both low- and high-risk clinically relevant subgroups showed improved PFS



HRs were determined by unstratified Cox proportional hazards model.
^aBulky disease was defined by the presence of a lymph node ≥7 cm at baseline/screening.
FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio; LOT, line of therapy; NHL-5, non-Hodgkin lymphoma comorbidity score; PFS, progression-free survival; POD24, progression of disease ≤2 years from the date of initiation of frontline therapy; R², lenalidomide and rituximab.

EPCORE FL-1 safety: the price is paid in infections

	Epcoritamab plus R ² (n=243)		R ² (n=238)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event	242 (>99%)	219 (90%)	235 (99%)	161 (68%)
Adverse event related to study drug	236 (97%)	203 (84%)	213 (90%)	129 (54%)
Serious adverse event	135 (56%)	..	69 (29%)	..
Adverse event leading to treatment discontinuation	46 (19%)	..	29 (12%)	..
Epcoritamab	21 (9%)	..	..	..
Rituximab	7 (3%)	..	12 (5%)	..
Lenalidomide	45 (19%)	..	29 (12%)	..
Adverse event of special interest ≥20%				
Infections*	188 (77%)	81 (33%)	125 (53%)	37 (16%)
Neutropenia	180 (74%)	167 (69%)	123 (52%)	100 (42%)
Cytokine release syndrome	85 (35%)	0	1 (<1%)	0
Anaemia	68 (28%)	19 (8%)	41 (17%)	11 (5%)
Thrombocytopenia	67 (28%)	23 (9%)	44 (18%)	15 (6%)
Pyrexia	58 (24%)	1 (<1%)	33 (14%)	3 (1%)
Rash	58 (24%)	19 (8%)	53 (22%)	9 (4%)
COVID-19	54 (22%)	7 (3%)	32 (13%)	4 (2%)

Data are n (%). The safety population consisted of all participants who received at least one dose of the study drug.
 *Events were in the MedDRA system organ class "Infections and Infestations".

Table 3: Adverse events and selected events of clinical interest (safety population)



What it means

- Grade ≥3 infections double (33% vs 16%)
- Grade ≥3 neutropenia in 7 of 10 patients
- No excess of fatal events

Falchi L et al. Lancet 2026; ASH 2025

Reading EPCORE FL-1 through the “do not harm” lens

Strengths

- Randomized, large, independent review
- PFS HR 0.21, consistent in POD24 and refractory
- Fixed duration, chemo-free, outpatient

Open questions

- OS immature; open-label design
- R2 is one of several 2L options in Europe
- More grade ≥ 3 infections and neutropenia
- Effect on later lines and CD20 status unknown

Ongoing 2 line trial

Celestimo
Olympia 5

Phase III Mosu+lana vs R2
Phase III Odro+lana vs R2

Falchi L et al. Lancet 2026



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Second line: choosing the patient, not just the regimen



Strong candidates

- POD24 or early relapse
- Refractory to anti-CD20
- Rapidly progressing histologically confirmed FL
- Unfit for, or wishing to avoid, chemotherapy
- Centre with infection prophylaxis and monitoring



Think twice

- Late relapse after a long first remission
- Frailty or major comorbidity
- Recurrent infections or hypogammaglobulinaemia
- Limited access to close follow-up

3

Marginal zone lymphoma

First data with CD20×CD3 bispecifics

MZL: early signals of high complete response rates

Odronextamab · ELM-2

Relapsed/refractory MZL

n = 34 (29 evaluable), median 2 prior lines,
53% anti-CD20 refractory, median FU:11 mo

79%

ORR = CR

69%

PFS at 36 mo

- CRS 53%, all grade 1–2 with optimised step-up
- No ICANS
- Grade ≥ 3 infections 24%, none fatal

Kim TM et al. ASH 2024, abstract 862 (ELM-2 MZL cohort)).

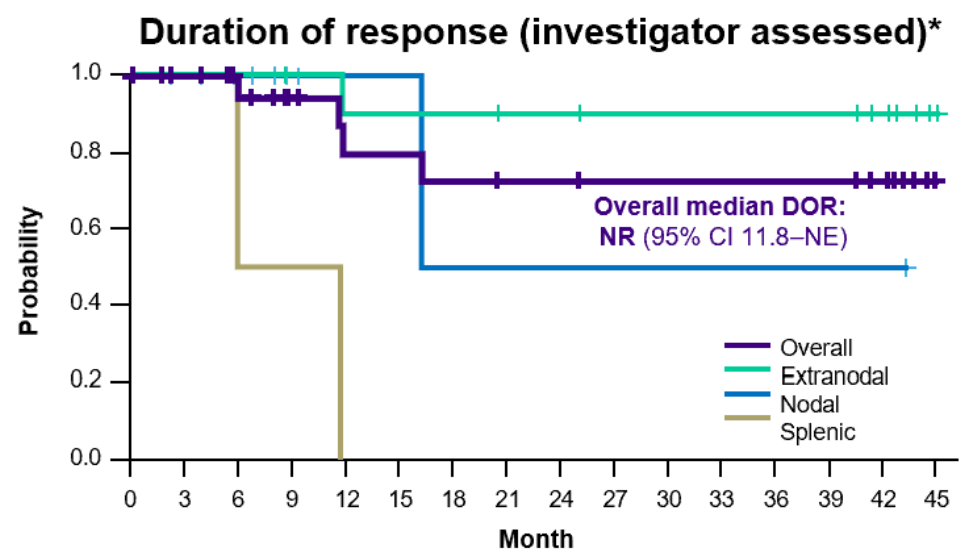
MZL: Odronextamab in R/R marginal zone lymphomas: Elm-2 trial

Odro
Relapse
n = 34 (
53% an

79%

ORR =

• CRS
• No IC
• Grad

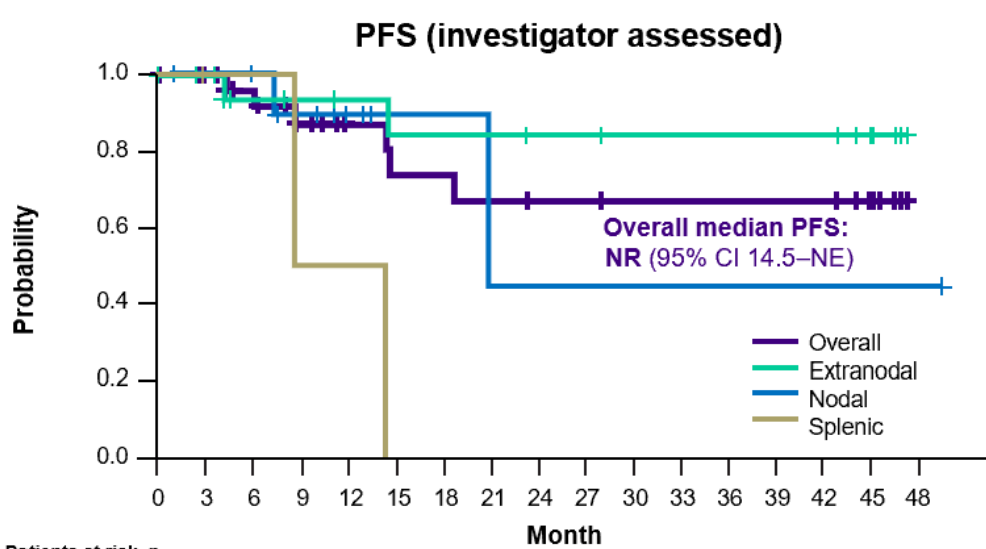


Patients at risk, n

Overall	27	22	18	14	11	11	10	9	9	8	8	8	8	6	0
Extranodal	15	12	11	10	9	9	9	8	8	7	7	7	7	5	0
Nodal	9	8	6	3	2	2	1	1	1	1	1	1	1	1	0
Splenic	3	2	1	1	0										

12-month PFS rate (95% CI):

	Overall	Extranodal	Nodal	Splenic
12-mo DOR (95% CI)	80.2 (49.6–93.3)	90.0 (47.3–98.5)	100 (100–100)	0.0 (NE-NE)



Patients at risk, n

Overall	35	28	23	18	13	11	11	10	9	9	8	8	8	8	5	0
Extranodal	19	16	12	11	10	9	9	9	8	8	7	7	7	7	4	0
Nodal	12	10	9	6	2	2	2	1	1	1	1	1	1	1	1	0
Splenic	3	2	2	1	1	0										

12-month PFS rate (95% CI):

	Overall	Extranodal	Nodal	Splenic
12-mo PFS (95% CI)	87.5 (65.9–95.8)	93.3 (61.3–99.0)	88.9 (43.3–98.4)	50.0 (0.6–91.0)

Median follow-up for efficacy population: 11.1 months (95% CI 6.2–42.8)

Kim TM et al. ASH 2024, abstract 862 (ELM-2 MZL cohort)).



MZL: early signals of high complete response rates

Odronextamab · ELM-2

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- No ICANS
- Grade ≥ 3 infections 24%, none fatal

SC mosunetuzumab · MorningSun

Previously untreated MZL

n = 36, median age 69, up to 17 cycles
median follow-up 18 mo

78%

ORR

64%

CR

- Mostly low-grade CRS and infections
- No fatal infections
- 6 of 36 stopped for adverse events

Kim TM et al. ASH 2024, abstract 862 (ELM-2 MZL cohort); Graff T et al. SOHO 2025 (MorningSun, NCT05207670).

MZL: promising, but keep it in clinical trials



MZL-specific issues

- Heterogeneous: splenic, nodal, extranodal
- Often older patients, autoimmune features, infection related diseases
- Variable FDG avidity complicates response assessment
- Only preliminary results

Ongoing trials



OLYMPIA-5 · phase 3

Odronextamab + lenalidomide vs R2 in R/R FL and MZL



NCT06796998 · phase 2

Epcoritamab in newly diagnosed MZL

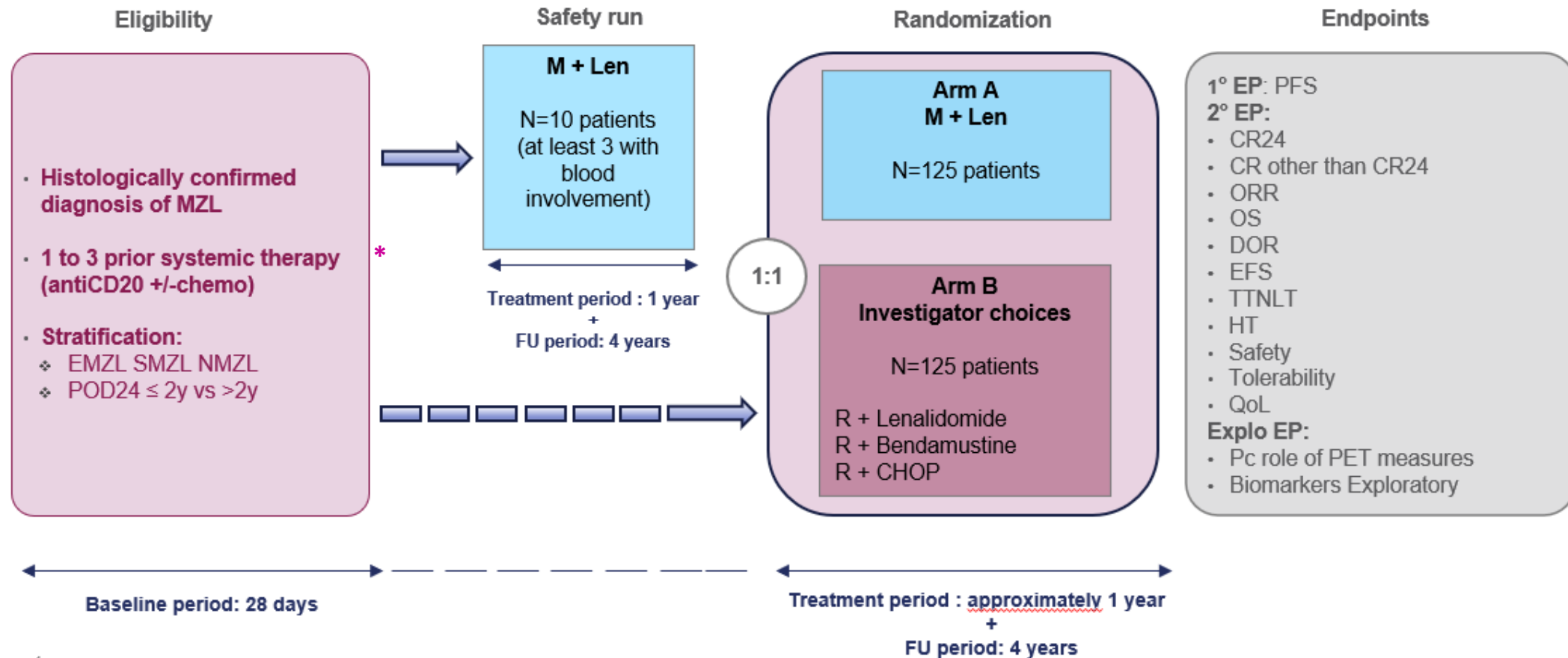


NCT06563596 · phase 2

Epcoritamab + zanubrutinib + rituximab in R/R FL and MZL



Marsun trial: study design/overview



4

Beyond the first cycles

Long-term immune effects, CD20 loss and the next line of therapy

Long-term immune effects: a prevention bundle



Immunoglobulins

Check IgG at baseline and regularly;
IVIg for recurrent or severe infections
with hypogammaglobulinaemia



Anti-infective prophylaxis

PJP and HSV/VZV prophylaxis; HBV
screening with antiviral prophylaxis or
monitoring



Vaccination

Vaccinate before starting (COVID-19,
influenza, pneumococcus); responses
are blunted on therapy



Vigilance

CMV and opportunistic infections;
PML has been reported



Recovery

With fixed-duration mosunetuzumab,
B cells and IgM recover in complete
responders

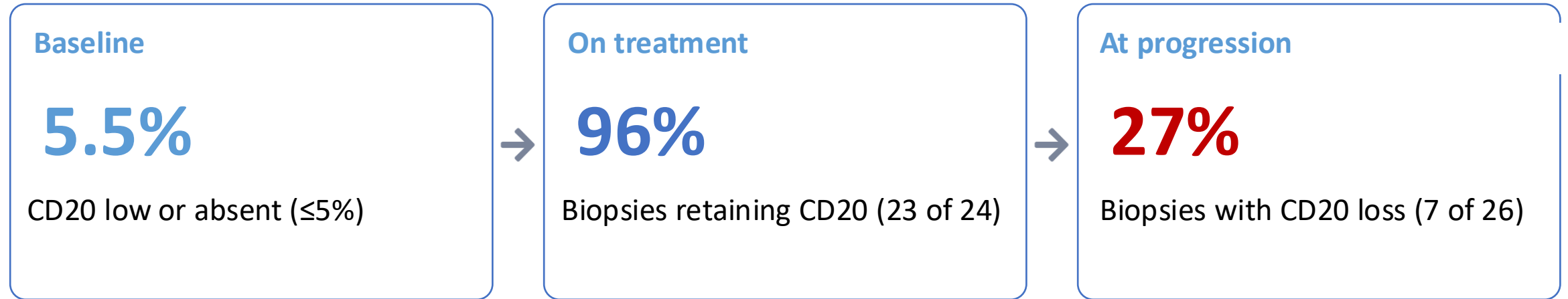


Patient education

Fever card, early contact, prompt
antibiotics

Budde LE et al. ASH 2025; Reynolds GK et al. Blood Adv 2024.

CD20 loss: a real mechanism of escape



Mechanisms

- Reduced MS4A1 transcription and truncating MS4A1 mutations explain most cases
- Extracellular-domain missense variants can block binding while CD20 is still detected
- Most progressions retain CD20: T-cell dysfunction and the microenvironment also matter

Schuster SJ et al. Blood 2024;143:822

What bispecifics may take away from the next line



Re-biopsy at progression

Confirm CD20 by IHC and flow; exclude transformation



CD20-negative

Avoid CD20-directed re-challenge; switch to CD19-directed options (CAR-T, tafasitamab, loncastuximab, surovatamig-based...)



CD20-positive after fixed duration

Retreatment with the same bispecific is feasible, with high response rates in small series



CAR-T after a bispecific

Limited FL data; small series. T-cell fitness and timing matter

Schuster SJ et al. Blood 2024; GO29781 extended follow-up (retreatment); CUBIC consortium real-world series (n = 8 CAR-T after bispecific); Braun A et al. ASH poster 2025.



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Take-home messages



3L+ FL: favourable benefit–risk.

CR 60–73% with manageable, early, mostly low-grade CRS



2L FL: epcoritamab + R2 sets a new PFS benchmark,
at the cost of more infections and neutropenia



MZL: high CR rates in small studies; keep bispecifics in trials



Infection, not CRS, drives non-relapse mortality: prevention is mandatory



Consider treatment **duration**;
re-biopsy at relapse, as CD20 loss reshapes the next line

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Thanks for your attention



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