10th POSTGRADUATE

Lymphoma Conference

The transition from second line to first line “chemo-free” regimens: Will it be a winning concept? Will the “maintenance” regimen disappear/be permanently reduced?

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What defines a successful 1st line therapy in FL? (i.e., that can beat chemoimmunotherapy)

- ✓ High rates of deep responses (eg, MRD-negative)
- ✓ Longer PFS vs. CIT
- ✓ Lower transformation rates vs. CIT
- ✓ Leaves options for 2L+ therapy intact
- ✓ Favorable safety profile and limited long-term toxicity
- ✓ Limited duration of therapy
- ✓ Patient-centered schedule

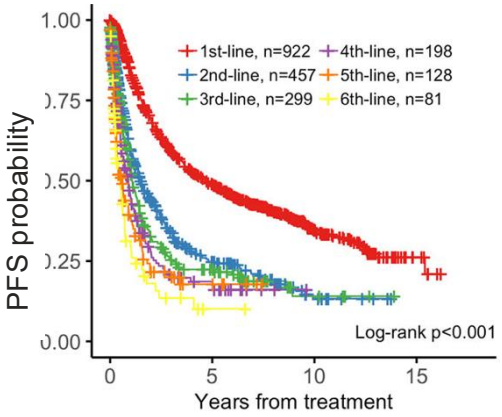
Do bispecific antibodies meet this definition?

Do BsAb have what it takes to be a 1st line FL therapy?

Searching for clues

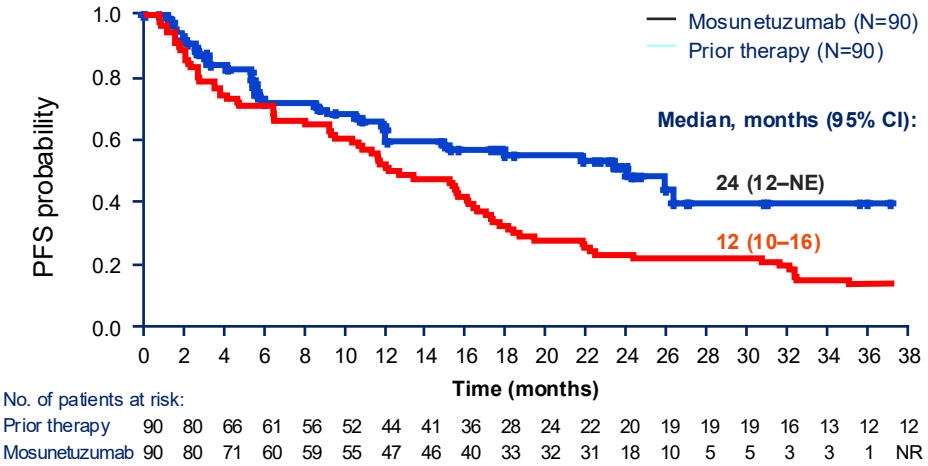
1st clue:
Bispecific antibodies are shifting historical paradigms

Old “dogma”



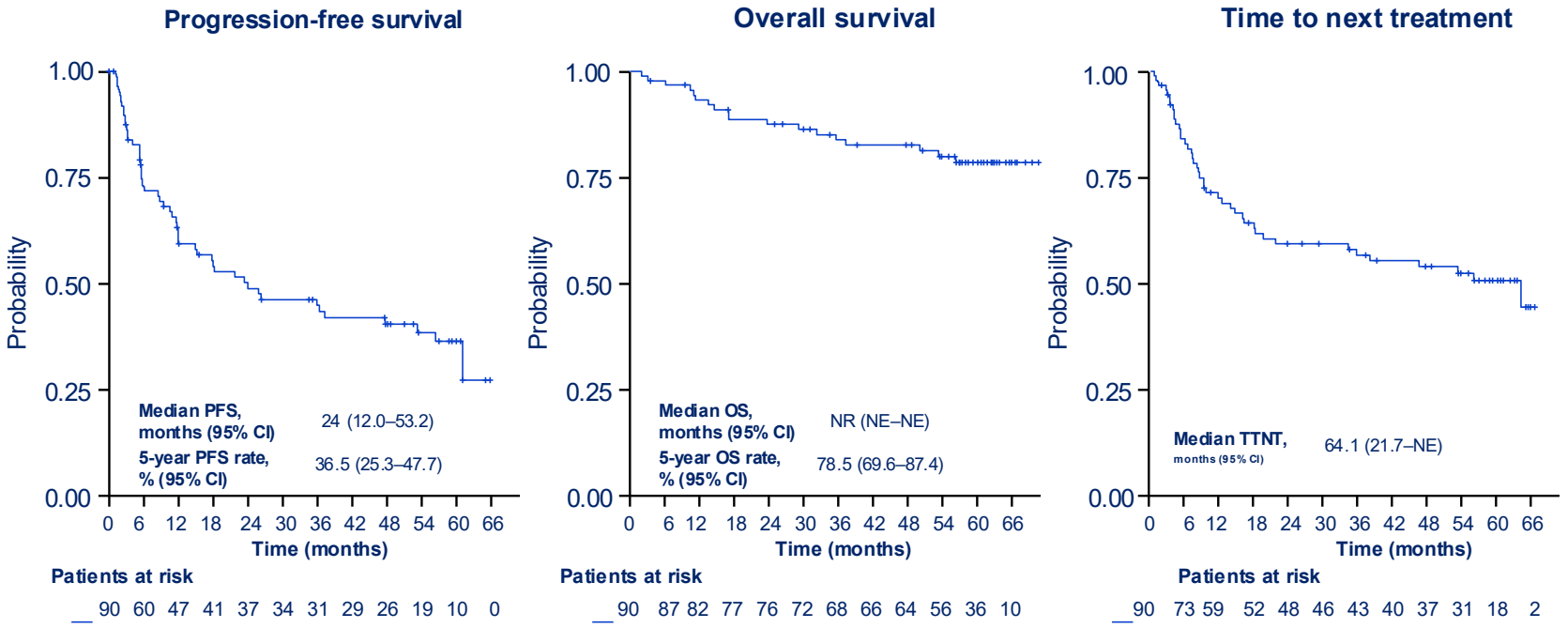
LOT	n	Median PFS (95% CI), y
1L	922	4.73 (3.93–5.71)
2L	457	1.51 (1.22–1.92)
3L	299	1.07 (0.93–1.39)
4L	198	0.90 (0.59–1.10)
5L	128	0.55 (0.33–0.92)
6L	81	0.48 (0.28–0.71)

New reality



Batlevi CL, et al. Blood Cancer J 2020;10:74. Bartlett NL, et al. ASH 2022; abstract #610).

2nd clue:
Favorable long-term outcomes for some patients: The mosunetuzumab experience

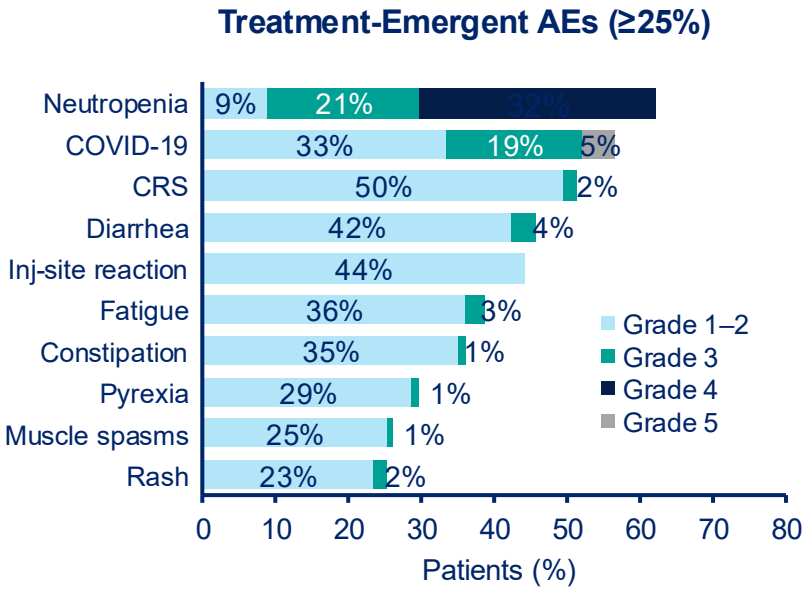


Budde E, et al. ASH 2025; abstract 5352

3rd clue:
BsAb combinations Drive Deep Responses in 2L+ FL with Manageable Safety: Epcoritamab + R2

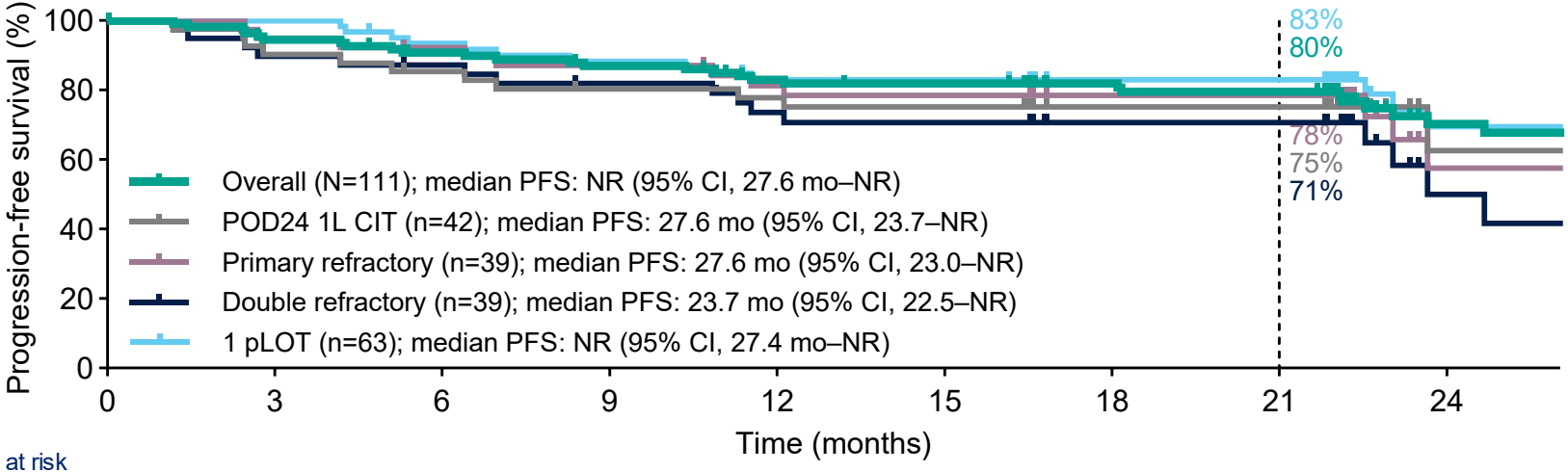
Best Response, n (%)[a]	N=111
Overall response	**107 (96)**
Complete response	**97 (87)**
Partial response	10 (9)
Progressive disease	2 (2)

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



Falchi et al. *Blood*. 2025 Nov 27;146(22):2629-2640

Progression-Free Survival and Duration of Response



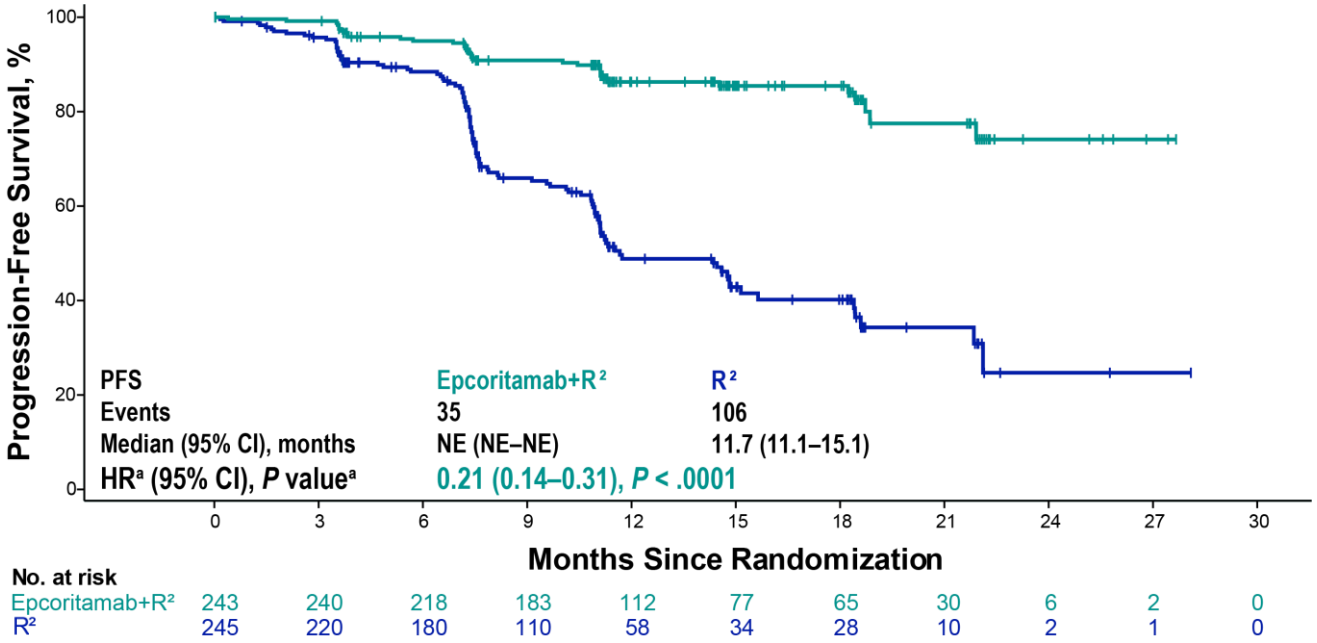
Patients at risk									
Overall	111	102	95	90	82	80	68	66	29
POD24 1L CIT	42	37	34	31	30	29	21	21	5
Primary refractory	39	37	35	32	28	27	22	22	7
Double refractory	39	35	33	30	26	25	18	18	6
1 pLOT	63	61	55	52	45	45	38	38	13

PFS in MRD- vs. MRD+ patients: 86% vs 44% at 21 months*

Data cutoff: May 15, 2024. PFS is among the full analysis population. Median follow-up for PFS: 22.3 months.

Falchi et al. *Blood* (2024) 144 (Supplement 1): 342 and Blood, online, ahead of print

4th clue:
Epcoritamab+R² Resulted in Superior PFS vs. R² (a therapy equivalent to CIT in 1L)



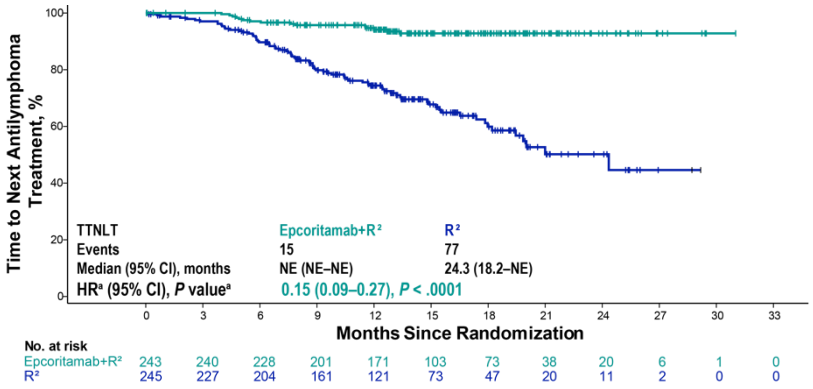
- The estimated 16-month PFS was 85.5% (95% CI: 79.7, 89.7) for epcoritamab+R² and 40.2% (95% CI: 31.8, 48.4) for R²

Median follow-up for PFS: epcoritamab+R² (14.4m), R² (11.5m). The first planned interim analysis (January 10, 2025) achieved statistical significance on PFS, HR 0.21 (95% CI 0.13, 0.33) $P < 0.0001$, with a 1-sided significance level of 0.0023. [a]Nominal P value is based on stratified log-rank test. Hazard ratio is estimated using stratified Cox proportional hazards model. This analysis was performed on the 78% information fraction.

Falchi L, et al. *Lancet*. 2026 Jan 10;407(10524):161-173

Epcoritamab+R^2 Extended Time to Next Treatment and Associated with Positive OS Trend

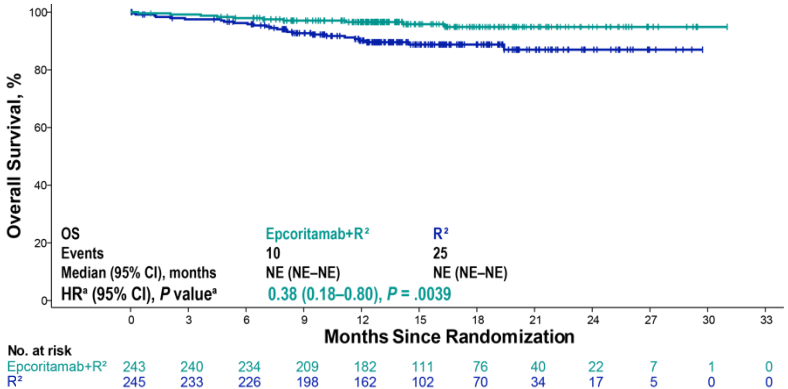
Time to next anti-lymphoma therapy



- At 16 months, 92.8% of patients treated with epcoritamab+R^2 remained free from new antilymphoma treatment compared with 64.9% of patients treated with R^2

Median follow-up for TTNLT: epcoritamab+R^2 (14.6m), R^2 (14.1m). TTNLT results are for descriptive purposes only. [a]Nominal *P* value is based on stratified log-rank test. Hazard ratio is estimated using stratified Cox proportional hazards model.

Overall survival

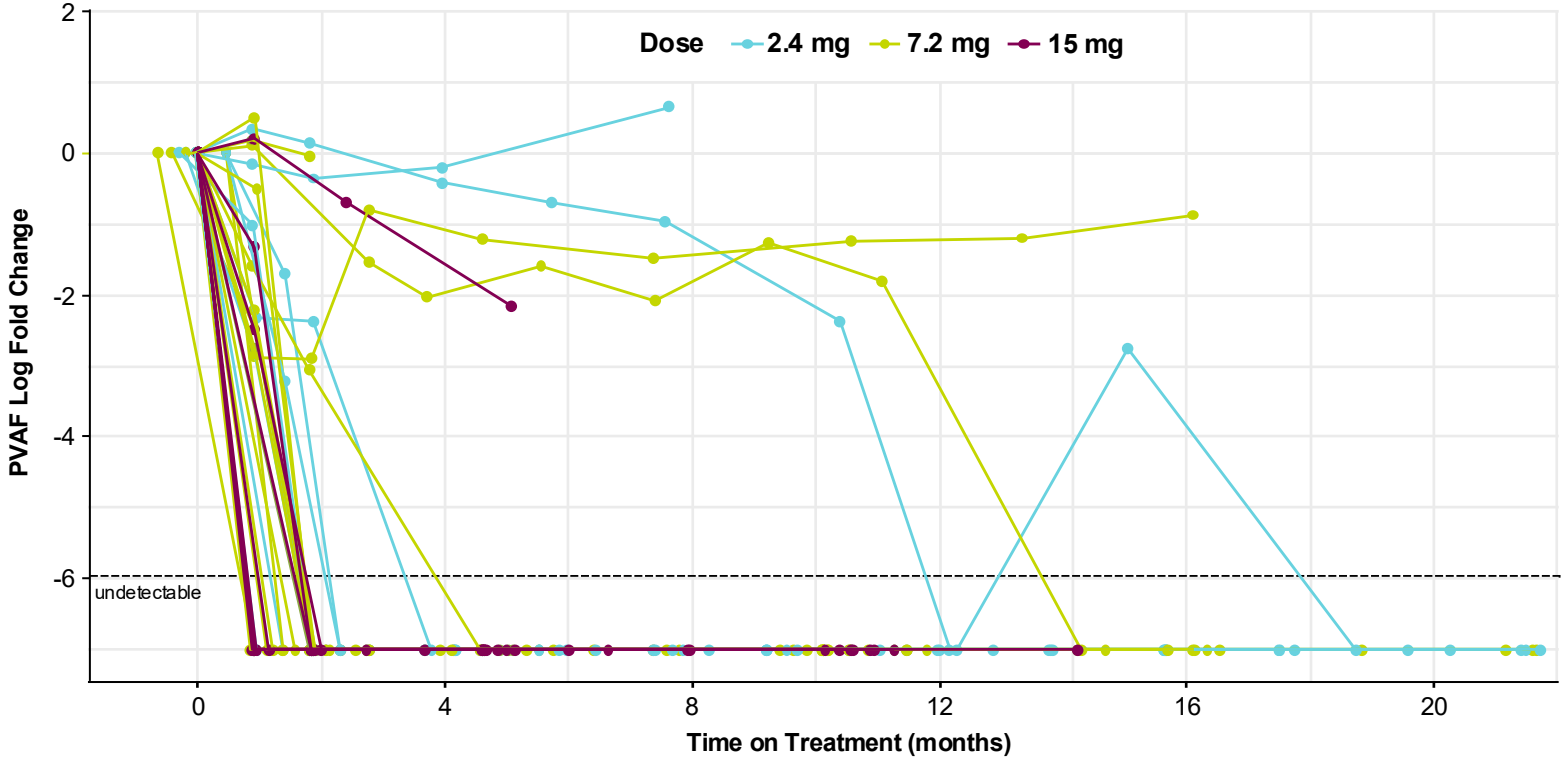


- The 16-month estimate for OS was 95.8% with epcoritamab+R^2 and 88.8% with R^2

Median follow-up for OS: epcoritamab+R^2 (14.8m), R^2 (14.6m). The OS data is based on the 24% (35/146 events) information fraction and has not yet reached statistical significance; additional analyses are forthcoming. [a]*P* value is based on stratified log-rank test with 1-sided significance level of 0.000005. Hazard ratio is estimated using stratified Cox proportional hazards model.

Falchi L, et al. *Lancet*. 2026 Jan 10;407(10524):161-173

5th clue:
BsAb Induce Rapid Clearance of MRD in most patients with 3L+ FL: Surovatamig (CD3xCD19 BsAb)



ctDNA assessed by PhasED-Seq

Hou J, et al. ASH 2025 Presentation P1005

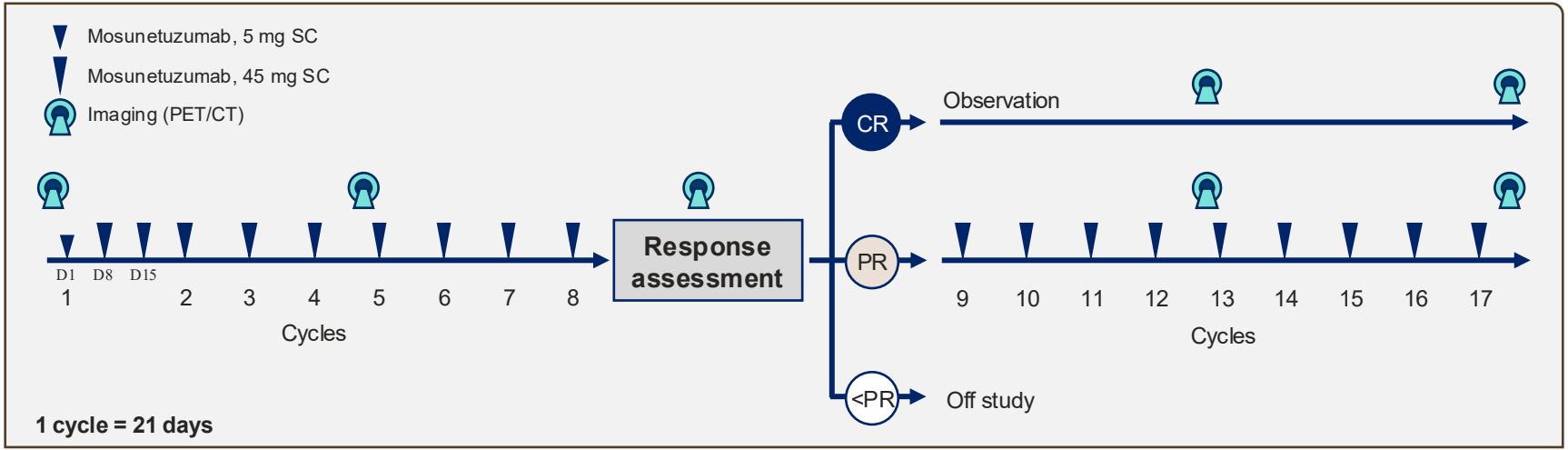
What is the evidence (so far) that BsAb are a valid candidate for 1st line FL therapy?

MITHIC-FL1: SC Mosunetuzumab in 1L FL: Multicenter Phase 2 Study Overview

Endpoints:
- **Primary:** CR per Lugano
- **Secondary:** ORR, safety, PFS, DOR, TTNT, OS
- **Exploratory:** PD, ctDNA monitoring

Eligibility:
- ≥18 years; ECOG PS 0-2
- CD20+ previously untreated FL,
- G1-3A, stage II–IV
- **Need of therapy per GELF criteria**

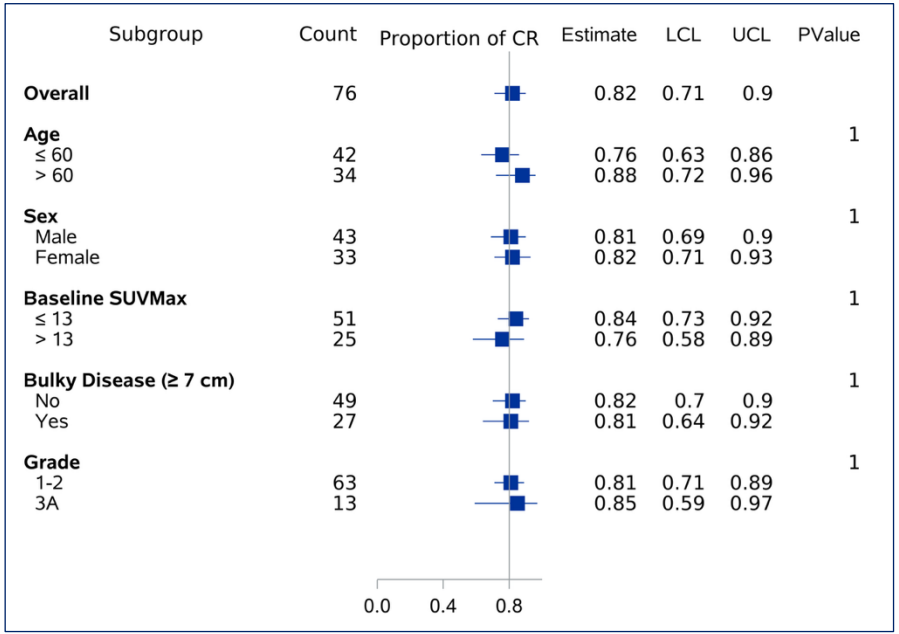
Outpatient administration:
- Prophylaxis: Dexamethasone, anti H2, acetaminophen in C1 (and C2 if prior CRS)
- VZV and PJP prophylaxis and GCSF support per treating physician



Patients who experience progression at any time point were taken off study; CR, complete response; ORR, overall response rate; 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

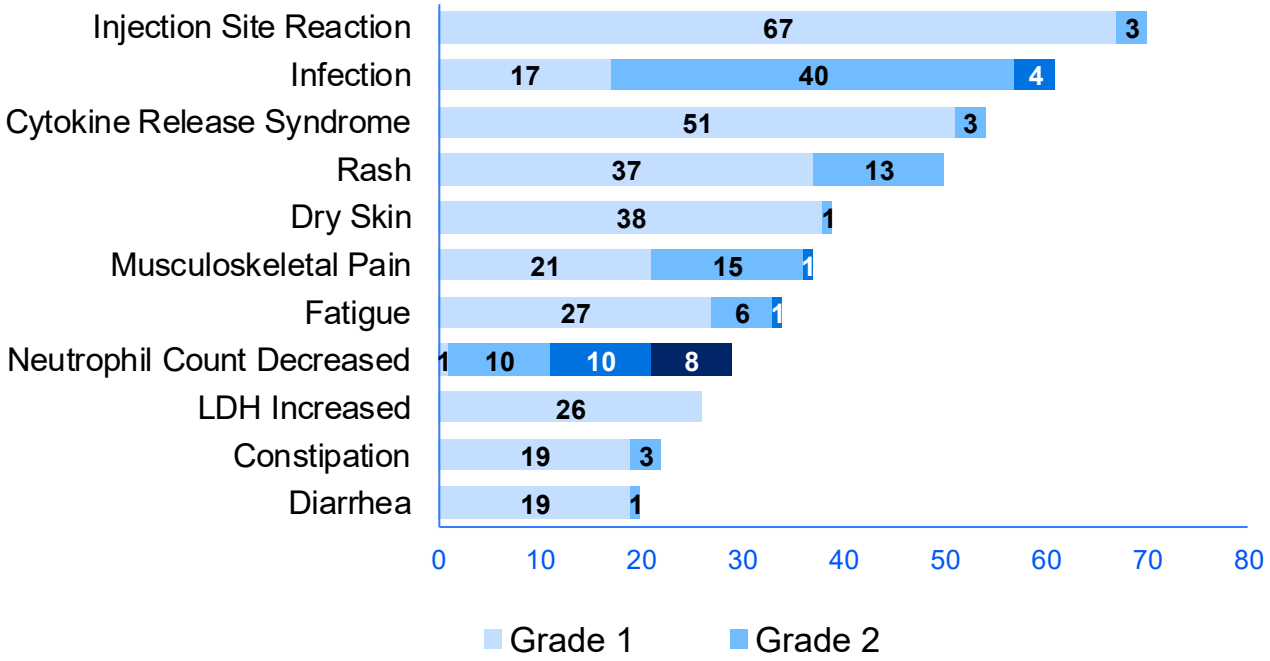
Responses Were Deep and Consistent Across Key Subgroups

Response type	Response evaluable (N=76)	Intention-to-treat (N=78)
Overall response	**95%**	92%
Complete response*	**82%**	79%
Partial response	13%	13%
Stable disease	3%	3%
Progressive disease	3%	3%
Non-evaluable	n/a	3%



Intention-to-treat group includes all patients who received at least one dose of mosunetuzumab. Response evaluable population includes all patients who had at least one radiographic response evaluation. *One patient's end-of-treatment response adjudication was updated from a partial response to a complete response after biopsy of the only persistent FDG-avid lesion after treatment demonstrated Schwannoma; this patient received a total of 17 mosunetuzumab cycles

Most Treatment-Emergent Adverse Events Were Mild

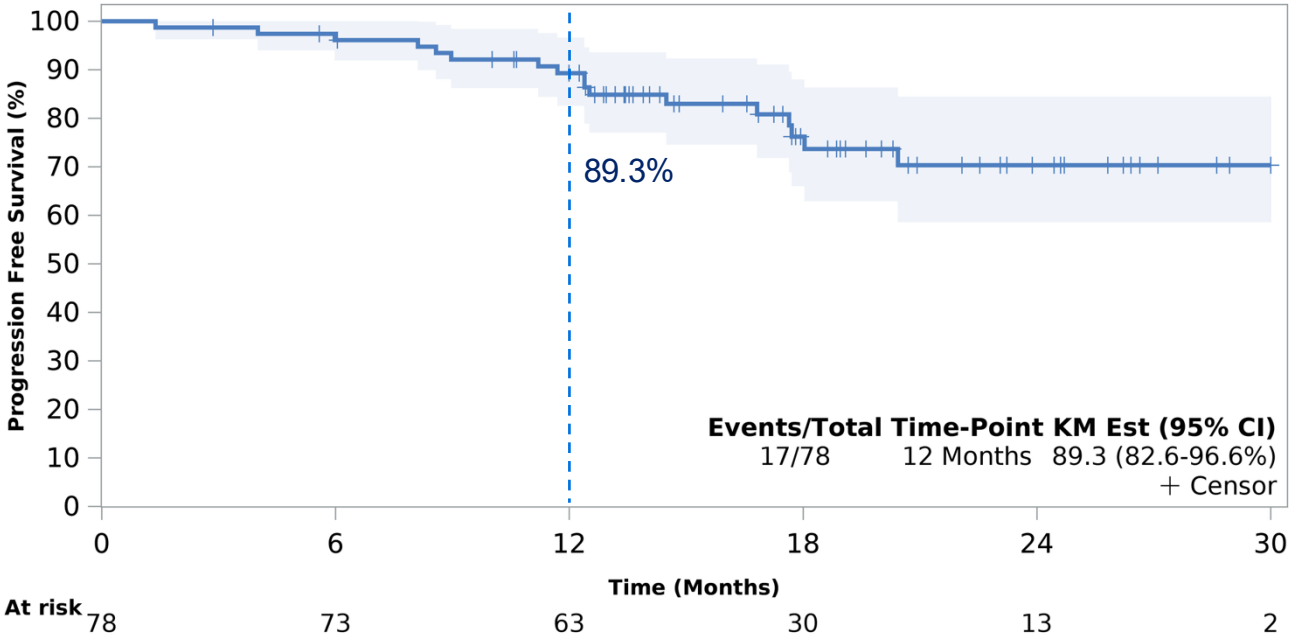


- **No new safety signal observed**
- No ICANS-like toxicities
- No tumor lysis syndrome
- One episode of G2 tumor flare reaction

Other AEs: Febrile neutropenia G3 (4%); ventricular tachycardia G5 (1%), dyspnea (G1-2 10%, G3 1%), platelet count decreased (G1-2 14%, G3 1%), syncope G3 (1%), hyperglycemia (G1-2 11%, G3 1%), ALC decreased (G1-2 3%, G3 1%), peritonitis (G3 1%), fracture (G3 1%), anemia (G1-2 12%, G3 1%).

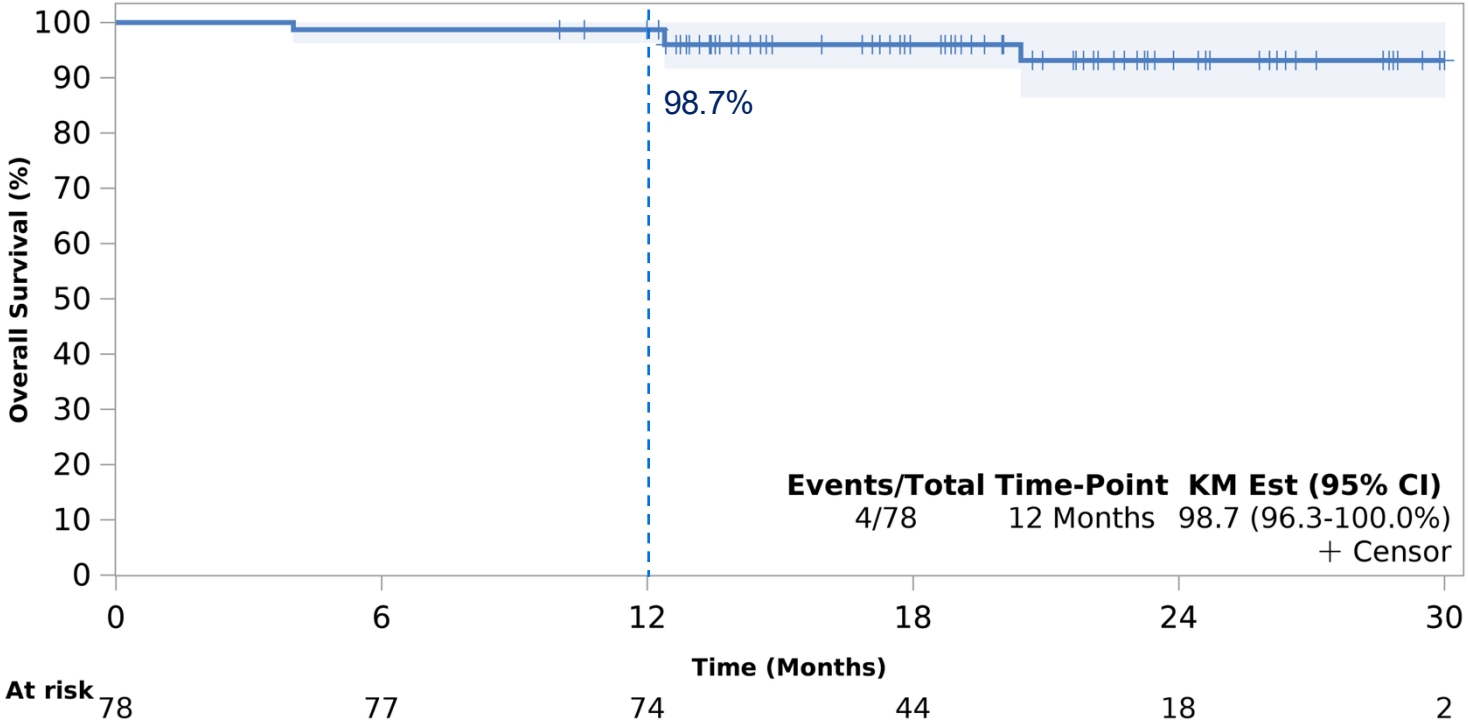
NOTE: Adverse events are stratified by CTCAE v5.0 grade. AEs of grade 1-2 occurring in at least 20% of patients and all AEs of grade ≥3 regardless of frequency are reported

Progression-Free Survival



- 13 Patients experienced PD:
  - 7 are on observation
  - 2 received radiation to a single site of PD
  - 4 had transformation and were treated with R-CHOP (all in continued CR)
- CD20 status by IHC at PD:
  - 8 CD20+
  - 3 CD20-
  - 2 not biopsied

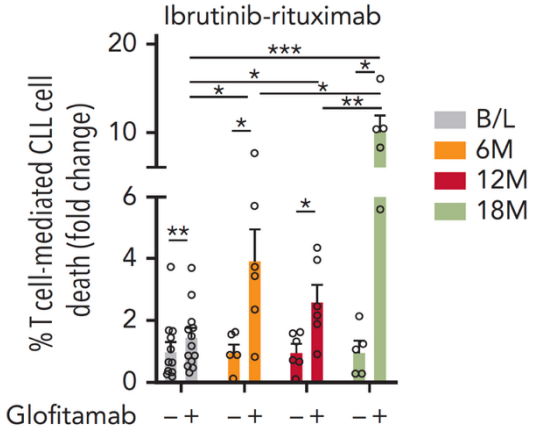
Overall Survival



One patient died while on study from complications of COVID-19 pneumonia at 4 months post study entry. Three patients died having been off study: one from a second cancer at 12 months, one from amyotrophic lateral sclerosis at 12 months, and one from sudden cardiac death at 20 months.

Zanubrutinib as Rational Combination Partner for Mosunetuzumab

- Second generation, covalent Bruton Tyrosine kinase inhibitor (BTKi) FDA approved for 3L+ FL in combination with obinutuzumab[1]
- *In vitro*, treatment with BTKi, including zanubrutinib, downregulated T-cell PD-1 expression.[2,3]
- BTKi increased the number of CD8+ T-cell immune synapses in patients with B-cell lymphoid malignancies[4]
- Co-culture of a BsAb and BTKi resulted in increased BsAb-mediated target cell killing.[4]

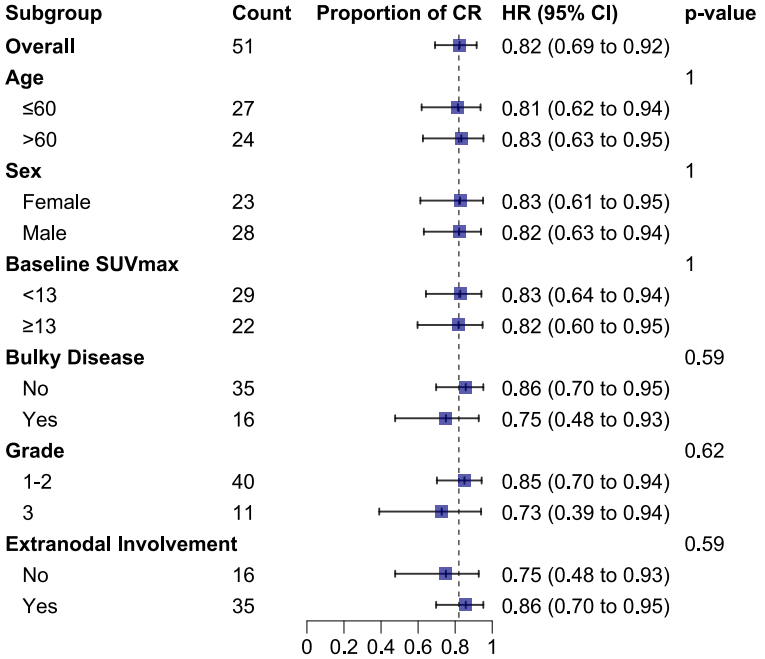


HYPOTHESIS: Adding zanubrutinib to mosunetuzumab may mitigate or reverse T-cell exhaustion, increase mosunetuzumab-mediated tumor killing, and improve clinical results.

1. Zinzani PL et al. J Clin Oncol J Clin Oncol 41:5107-5117; **2.** Zou YX, et al. Hematol Oncol. 2019;37(4):392-400; **3.** Svanberg R et al, haematologica 2021; 106(9); **4.** Papazoglou D et al Blood 2024 Jan 4;143(1):57-63.

Mosunetuzumab + Zanubrutinib Induced Deep Responses in Most Patients

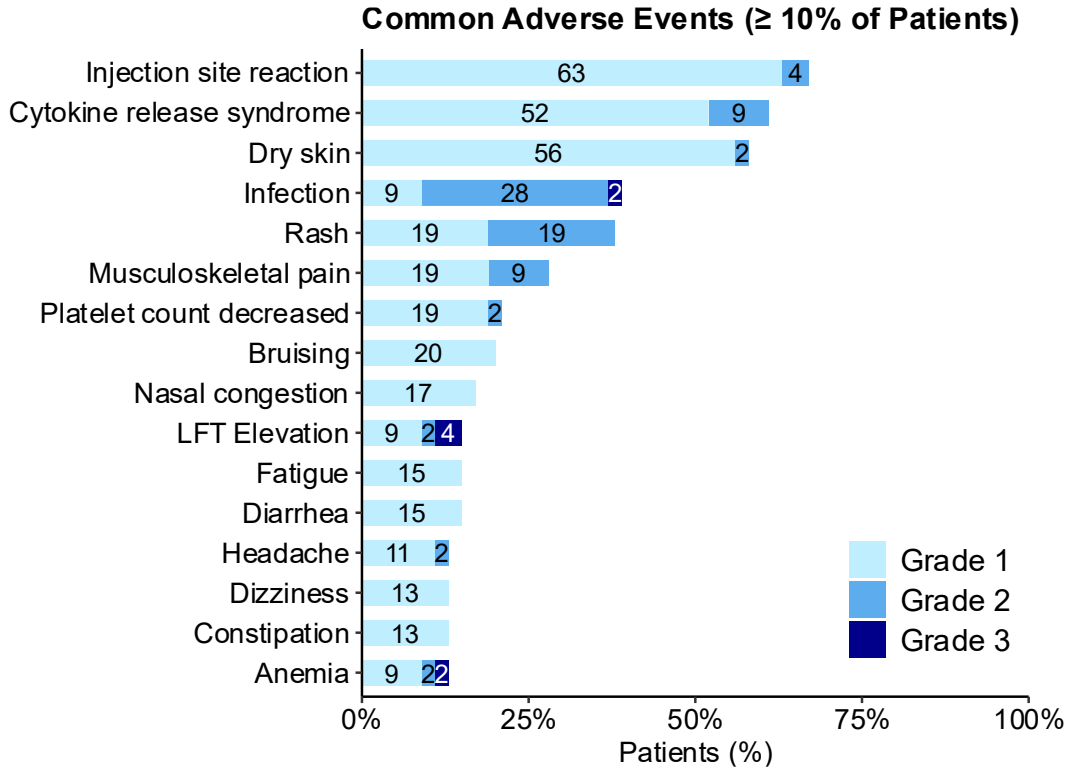
Response Type	Response Evaluable (n=51)
Overall Response	47 (92%)
Complete Response	**42 (82%)**
Partial Response	5 (10%)
Stable Disease	1 (2%)
Progressive Disease	3 (6%)



Data cutoff: November 14, 2025; response assessed per the 2014 Lugano criteria and integrated with the 2016 LYRIC criteria; evaluable = patients who received at least one dose of study drug and underwent at least one response assessment

Falchi et a. ASH 2025: Abstract 463

Most Adverse Events Were Low-Grade



- No safety signals were observed for mosunetuzumab or zanubrutinib
- Most AEs were grade 1-2
- No patient discontinued treatment due to AEs
- No neurotoxicity, clinical tumor lysis syndrome, or tumor flare reaction
- 11 patients had bruising (22%), all grade 1
- 2 patients had epistaxis (4%), all grade 1
- No episodes of atrial fibrillation
- One patient developed G5 EBV-associated HLH during Cycle 1. This patient had negative EBER staining on baseline biopsy and did not have detectable EBV viral load at baseline.

Other AEs of interest: 3 Patients had G3 (1) or G4 (2) neutropenia; 1 had G3 febrile neutropenia; 1 had G3 acute kidney injury in the setting of tumor ureteral compression; 1 had prostate cancer (G3), and 1 had G3 syncope

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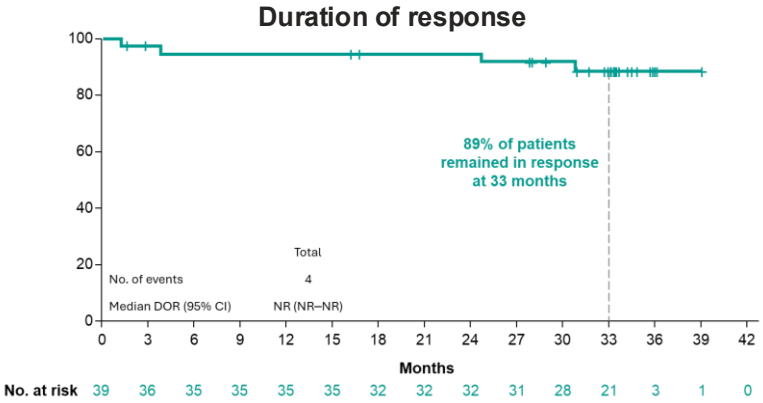
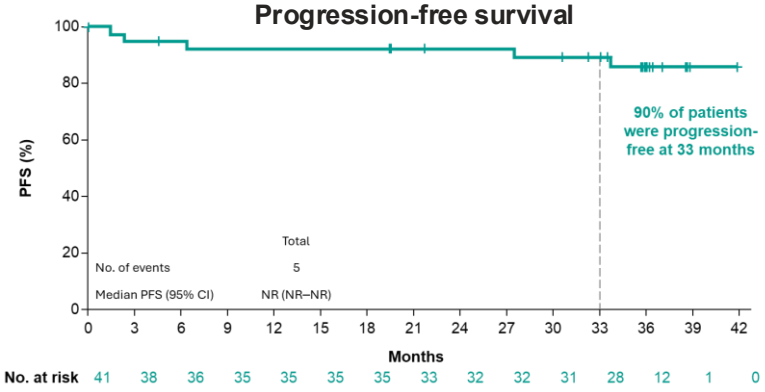
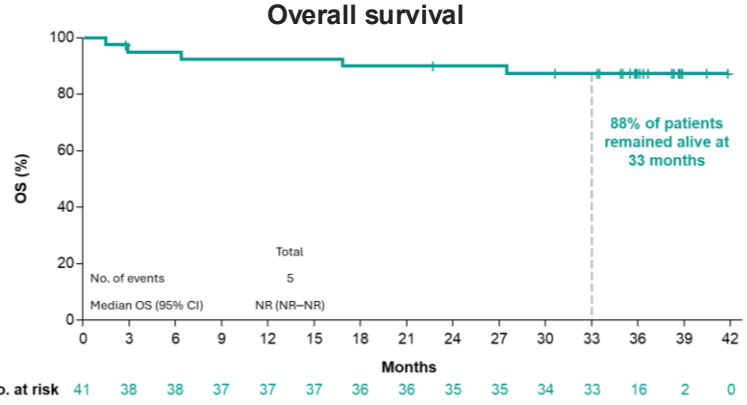
Epcoritamab + R² in 1L FL: 3y follow-up of EPCORE NHL-2 Arm 6

	Epcoritamab + R² N = 41
Overall response, n (%)	39 (95)
CR	36 (88)
PR	3 (7)
NE[a]	2 (5)

- Among 36 patients in CR, 9/10 who discontinued treatment for reasons other than PD or death[b] maintained CR[c]
- MRD negativity[e] (<10^{-6}):100% (26/26 MRD-evaluable patients





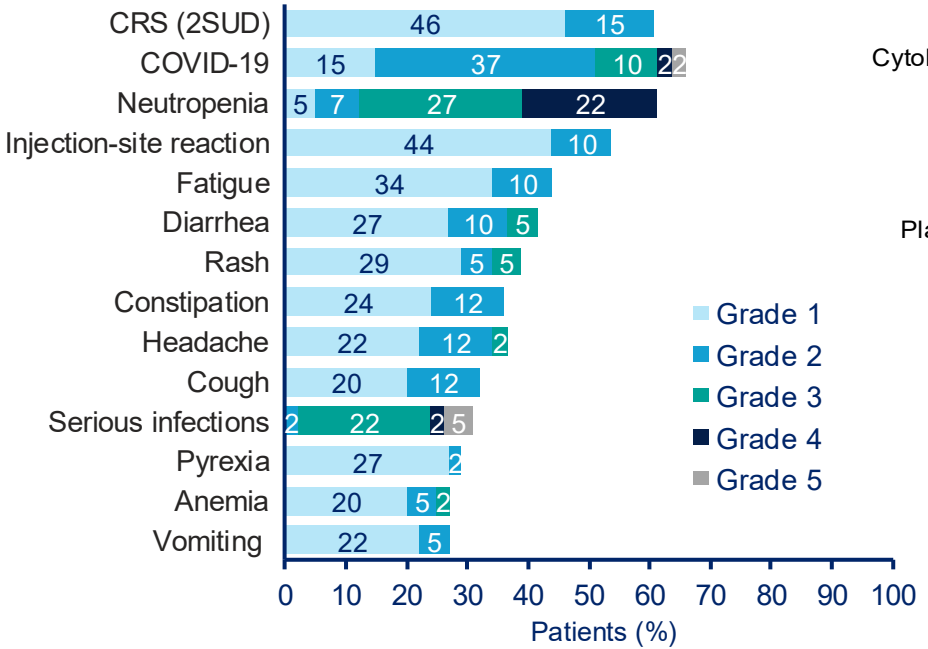


Median follow-up time for DOR was 33.2 months (95% CI, 33.0–33.5). [a]No post-baseline assessment in 2 patients; no patients had PD. [b]Median treatment duration of 13 months. [c]Median follow-up of 20 months post-treatment. [d]Median follow-up of 12.5 months post-treatment. [e]MRD was assessed by PBMC, using clonoSEQ assay. NE, not evaluable; NR, not reached.

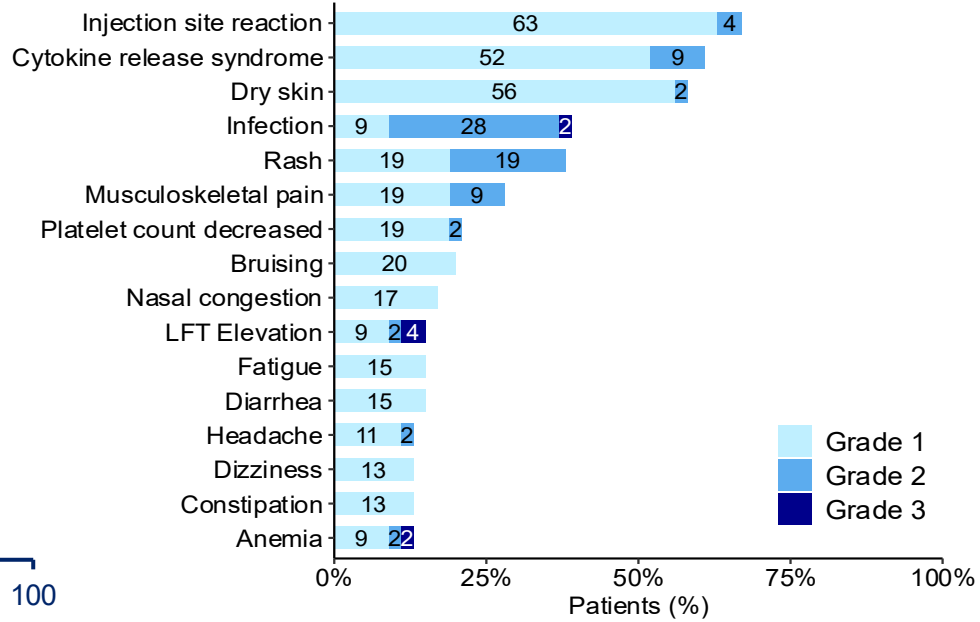
Leslie L et a. ASH 2025: Abstract 465

Safety of R-lenalidomide vs Zanubrutinib as BsAb partners

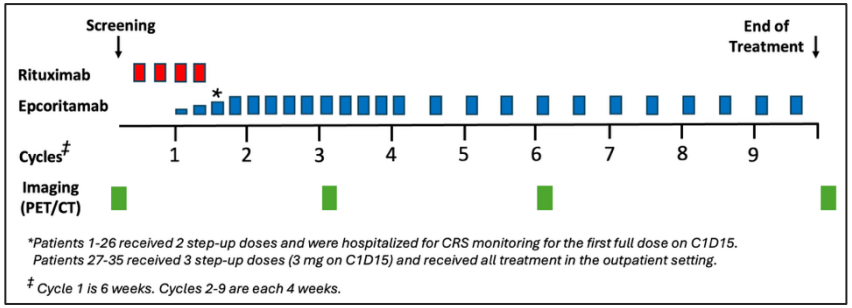
Epcoritamab, rituximab and lenalidomide (EPCORE NHL-2, Arm 6)



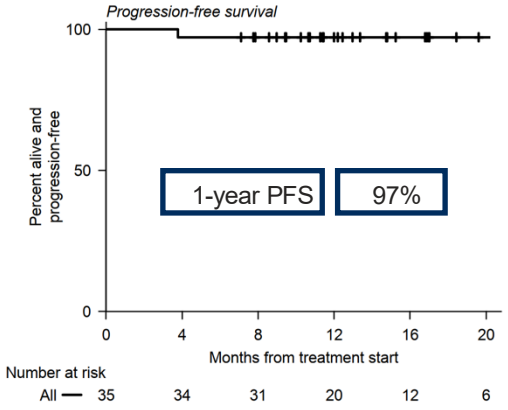
Mosunetuzumab and Zanubrutinib (MITHIC-FL2)

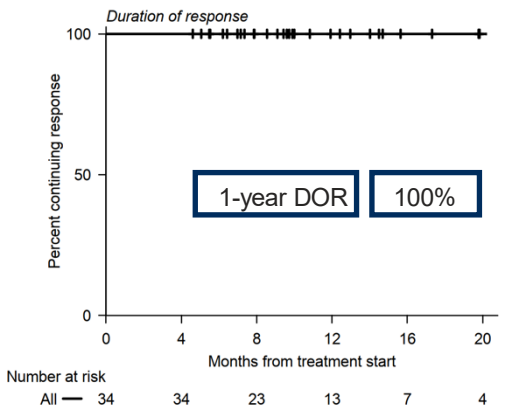


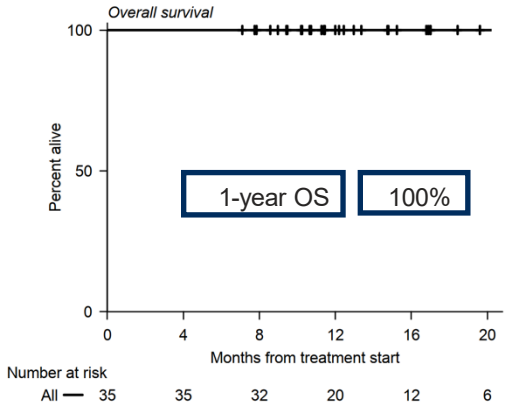
R-epcoritamab in 1L high-burden FL: Phase 2 trial (DFCI)



	C3D1	EOT*	Best Response
N	35	30	35
ORR	97%	97%	97%
CMR	86%	93%	94%







Merryman R et a. ASH 2025: Abstract 464

Ongoing randomized studies of bispecific antibody combinations in 1L FL

Regimen	Trial (Phase)	Patients (1L FL cohorts)*	Treatment duration and administration	Primary endpoint	Study status
Mosunetuzumab-Len versus R- / G-chemo	**MorningLyte** (Phase III)[1]	790[1]	**Mosunetuzumab** (SC) **Len** (oral)[1] 21 cycles	PFS (by IRC)[1]	Recruiting[1]
Odronextamab-chemo versus R-chemo	**OLYMPIA-2** (Phase III)[2]	733[2]	**Odronextamab** (IV) **CHOP/CVP** (IV)[2]	Part 1: DLTs and safety Part 2: CR30 (by ICR)[2]	Recruiting[2]
Epcoritamab-R-Len versus R- / G-chemo	**EPCORE FL-2** (Phase III)[3]	1095[3]	**Epcoritamab** (SC) **R** (IV) **Len** (oral)[3] 12 cycles +/- maintenance	CR30 (by IRC) PFS (by IRC)[3]	Recruiting[3]
Surovatamig plus R versus R-chemo	**SOUNDTRACK-F1** (Phase III)[4]	975[4]	**R-surovatamig** (IV) 7 cycles alone (arm A) or 17 cycles (arm B)	Safety run-in: RP3D safety Phase III: PFS by IRC[4]	Recruiting[4]

Products/indications are investigational and not approved. This slide is for educational purposes only
*Estimated enrollment.
CR30, complete response at 30 months; CVP, cyclophosphamide, vincristine and prednisone;
DLT, dose-limiting toxicity; BICR, blinded independent central review; ICR, independent central review;
RP3D, recommended Phase III dose.

1. NCT06284122. Available at: https://clinicaltrials.gov/study/NCT06284122;
2. NCT06097364. Available at: https://clinicaltrials.gov/study/NCT06097364;
3. NCT06191744. Available at: https://clinicaltrials.gov/study/NCT06191744;
4. NCT06549695. Available at: https://clinicaltrials.gov/study/NCT06549595.

Bispecifics in 1L FL: Take home messages

- **BsAb have shown remarkable activity in R/R FL with consistent efficacy and safety profile**
  - Long-term remissions are seen
  - Most responders achieve MRD negativity
  - Combinations increase CR rates and, potentially, improve PFS

- **BsAb achieve promising results in 1L in phase 2 trials**
  - Single-agent CR rates generally higher in 1L vs. 2L+
  - Combinations may achieve deeper response and have the potential to outcompete CIT

- **Do BsAb have a curative potential?**
  - Not clear for monotherapy
  - Longer follow up needed for combinations

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