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Advances in R/R Follicular Lymphoma: Diagnostic Approaches and Novel Therapeutic Options

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Disclosures

- **Erin Mulvey, MD:** Advisory Board – AbbVie, BeOne Medicines, Epizyme, Genentech-Roche, Genmab; Consultant – AbbVie, BeOne Medicines; Speaker's Bureau – ADC Therapeutics; Grant/Research Support – Epizyme, Genentech-Roche, Genmab

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Learning Objectives

- Describe best practices in the diagnostic evaluation of R/R FL to accurately confirm disease status and detect disease progression or histologic transformation
- Evaluate the current treatment landscape and the latest clinical trial data on approved and emerging treatments for R/R FL
- Apply interdisciplinary strategies to personalize treatment plans for patients with R/R FL, considering disease characteristics, prior therapies, and individual patient factors

R/R = relapsed/refractory; FL = follicular lymphoma.

Follicular Lymphoma

Generally considered incurable and chronic, median survival 15-20 years

Few biomarkers to guide therapy

No need to treat if asymptomatic

Key focus

- "All-comer" trials developing novel approaches
  - Low vs high tumor burden
- About 20% die from disease – need biomarkers and new treatments
- About 80% die with disease – how do we optimize quality of life?
- Need a "cure"!

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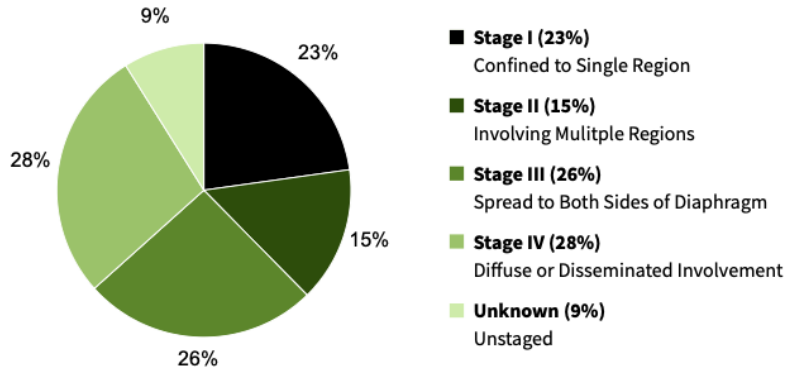
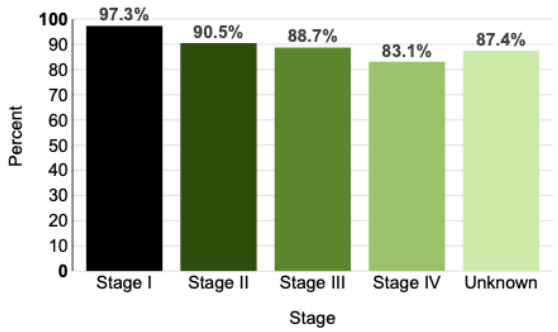
FL Epidemiology – SEER Stage and Survival

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Follicular Lymphoma

Percent of Cases by Stage

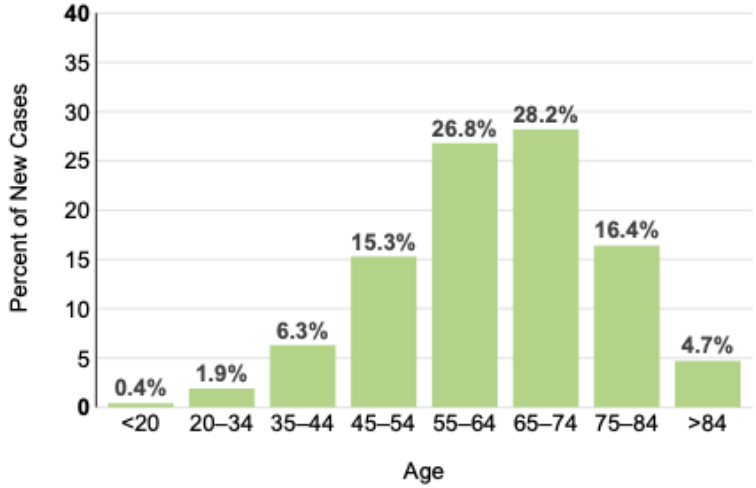


5-Year Relative Survival



SEER 17 2015–2021, All Races, Both Sexes by Ann Arbor Stage.
Statistics by stage only include cases coded as Lymhpoma or Lymphoma-CLL/SLL in EOD 2018 schema definitions.

Percent of New Cases by Age Group: Follicular Lymphoma



Follicular lymphoma is most frequently diagnosed among people aged 65–74.

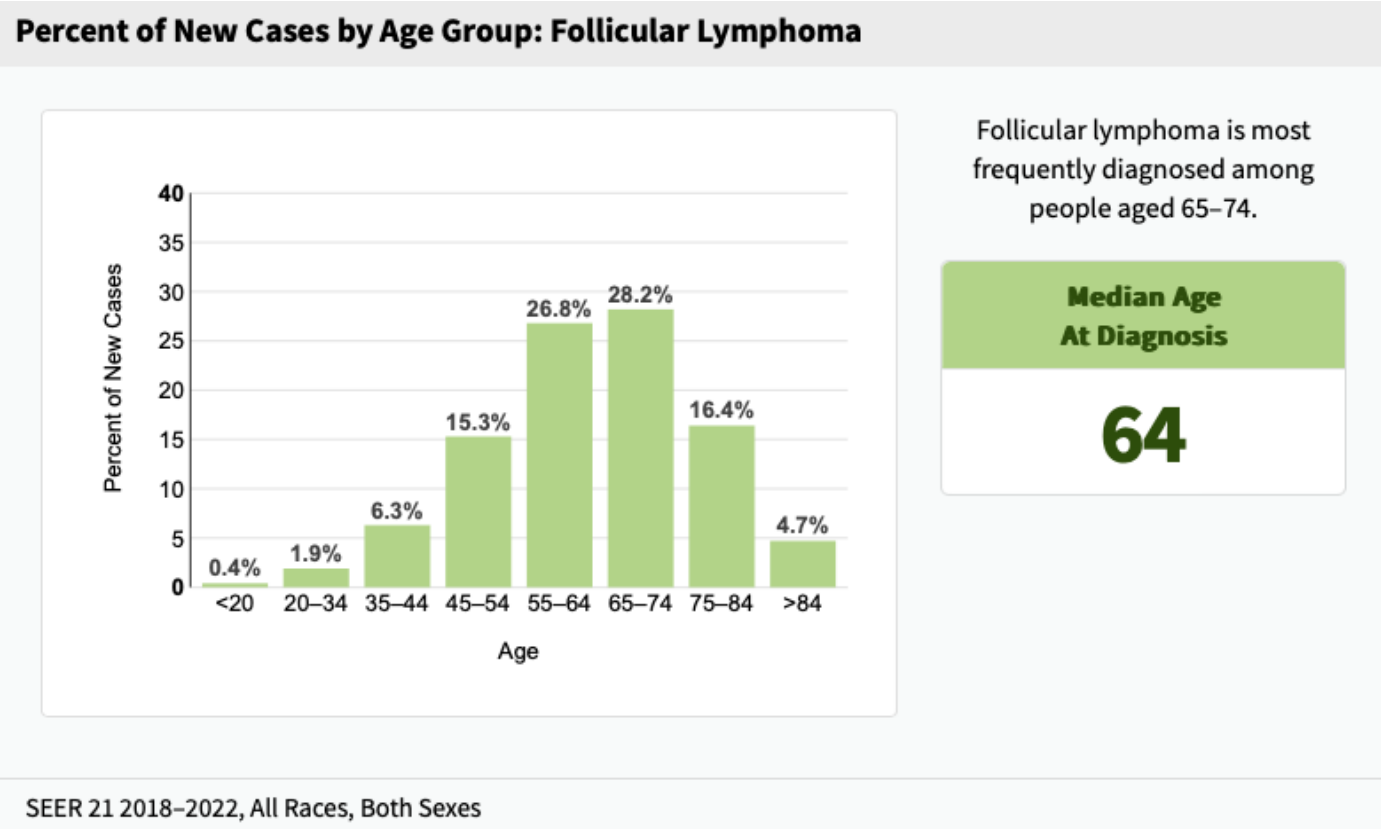
Median Age At Diagnosis

64

SEER 21 2018–2022, All Races, Both Sexes

Surveillance, Epidemiology, and End Results (SEER). Accessed October 13, 2025. https://seer.cancer.gov/statfacts/html/follicular.html.

FL Epidemiology – SEER Survival



Median life expectancy of a 64-year-old in NY state:

Male: 16.76 years
Female: 19.84 years

SEER. Accessed October 13, 2025. https://seer.cancer.gov/statfacts/html/follicular.html. New York State Department of Health. Accessed October 13, 2025. https://www.health.ny.gov/health_care/medicaid/publications/docs/adm/06adm-5att8.pdf.

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Cause of Death in Follicular Lymphoma in the First Decade of the Rituximab Era: A Pooled Analysis of French and US Cohorts

- 2 cohorts prospectively enrolled newly diagnosed patients with FL between 2001 and 2013, N=734 and N=920
- Median f/u 84 months
- 10-year OS comparable (80%)
- Lymphoma most common cause of death (10.3%), followed by TRM (3%), other cancer (2.9%), other (2.2%), unknown (3%)
- Conclusion – despite improvements in therapy, lymphoma is leading cause of death

OS = overall survival; TRM = treatment-related mortality.

Sarkozy C, et al. *J Clin Oncol*. 2019;37(2):144-152.

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Why Do We Treat Any Patient with Any Illness?

- Cure
- Live longer
- Feel better/quality of life

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Why Would We Choose to Treat a Patient with Follicular Lymphoma?

- Cure – no? (prior talk)
- Live longer – if symptomatic, but no advantage if asymptomatic
- Feel better/quality of life – not if asymptomatic, yes if symptomatic

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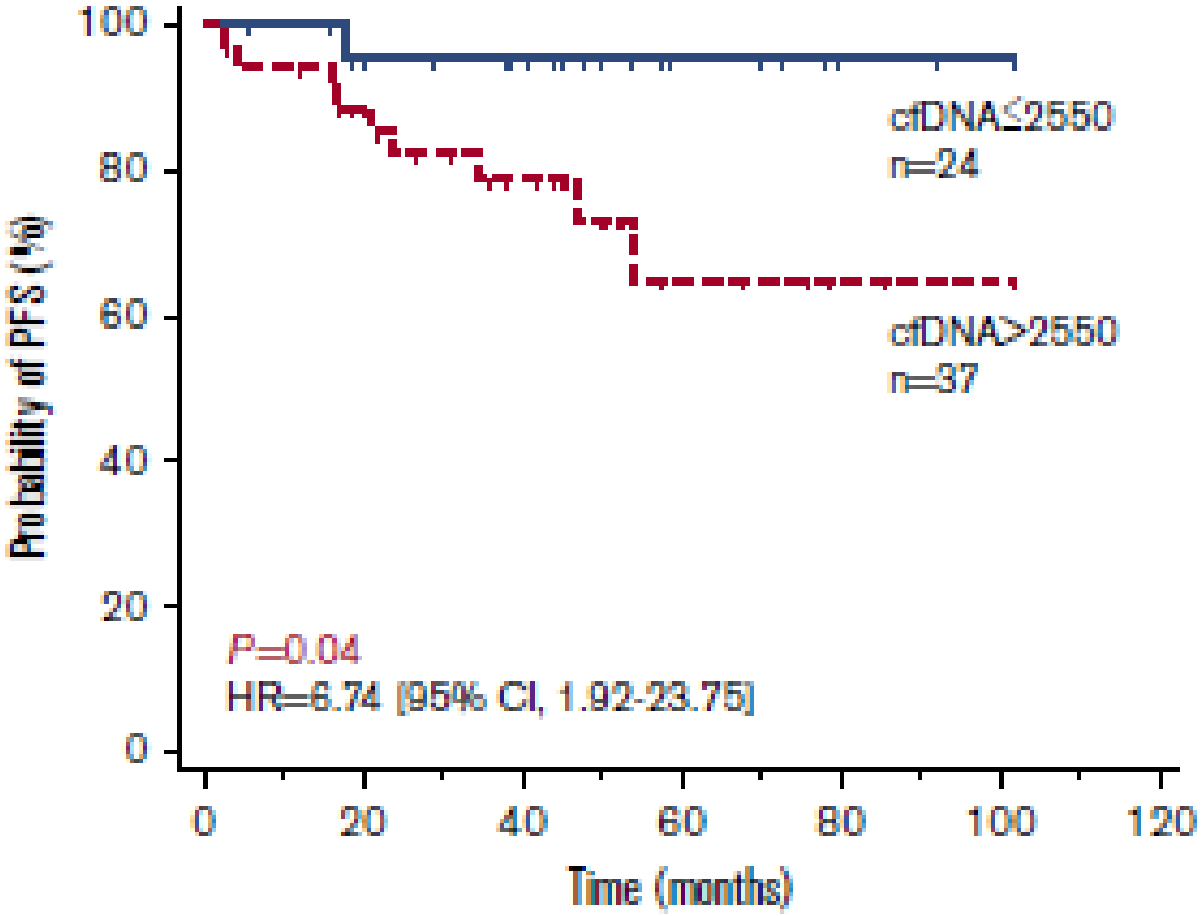
Approach to Following Patients with FL in Remission

- Tailor follow-up to risk of relapse (extent of prior disease, CR vs PR, possibility of occult transformation)
- Periodic history, physical exam, labs (every 4-6 months initially, longer interval over time)
- Minimize surveillance imaging in asymptomatic patients
- Encourage “return to normalcy” as much as possible

CR = complete response; PR = partial response.

Lower Levels of cfDNA at Diagnosis Can Be Associated with a Long Remission (PFS)

FL treated primarily with chemo-R and maintenance

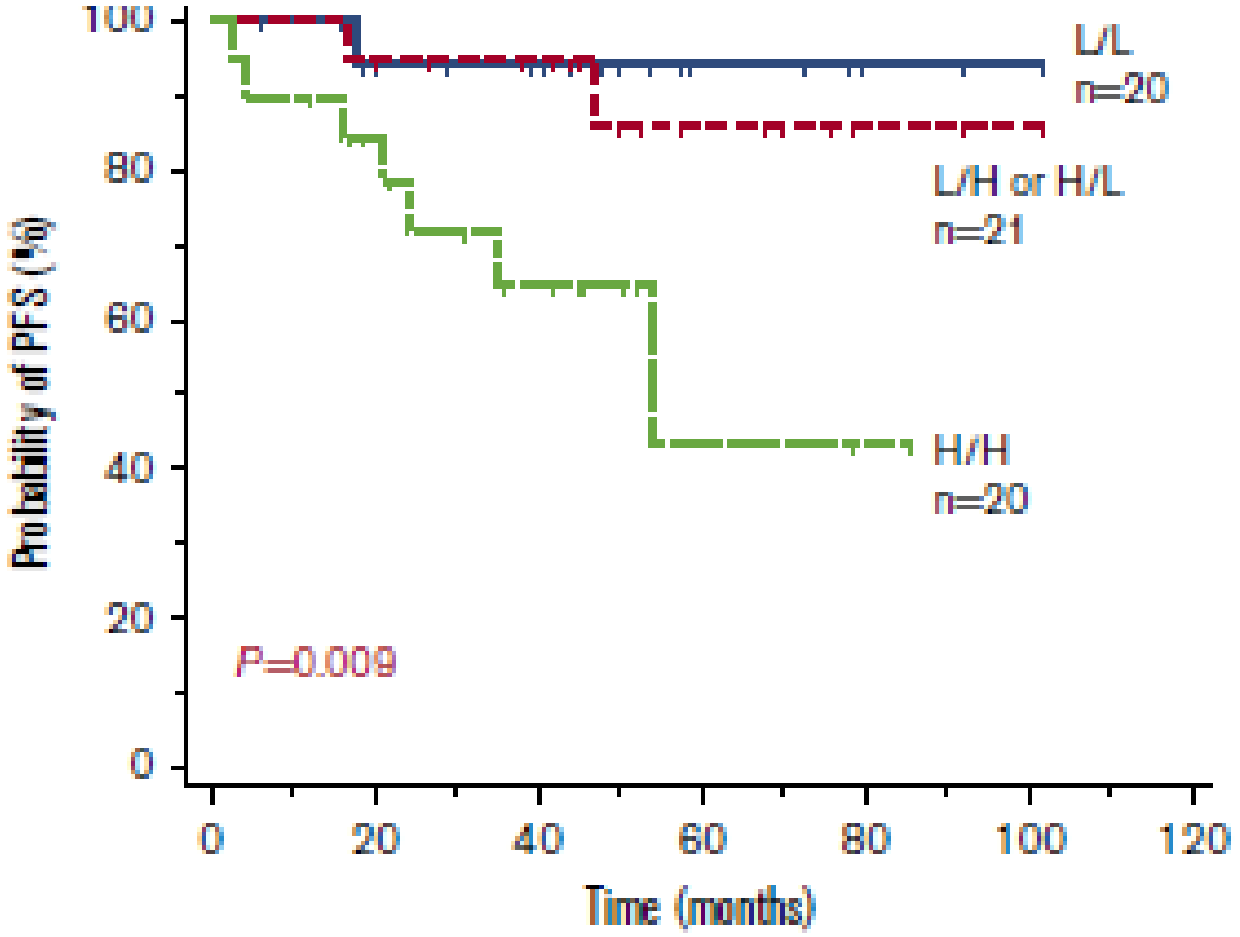


PFS = progression-free survival; R = rituximab.

Delfau-Larue MH, et al. *Blood Adv*. 2018;2(7):807-816.

Lower Levels of cfDNA + Lower MTV at Diagnosis Can Be Associated with a Long Remission (PFS)

FL treated primarily with chemo-R and maintenance

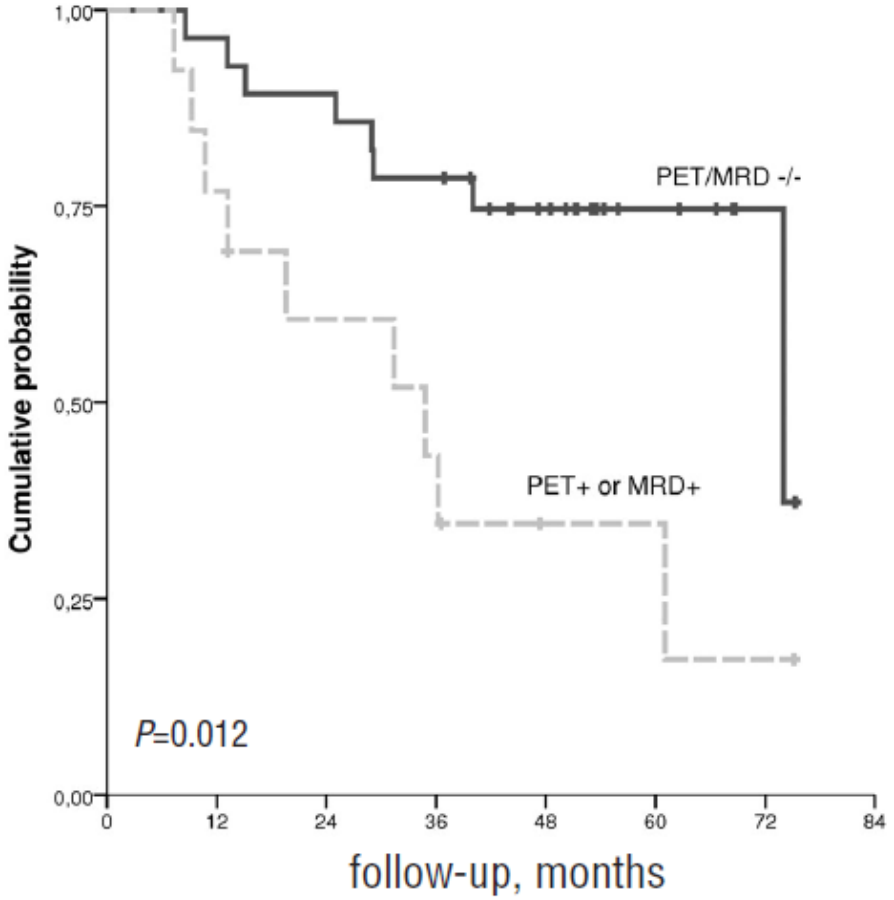


MTV = metabolic tumor volume.

Delfau-Larue MH, et al. *Blood Adv*. 2018;2(7):807-816.

PET-Negative, MRD-Negative (BCL2/IgH) Patients at End of Therapy Can Be Associated with a Long Remission (PFS)

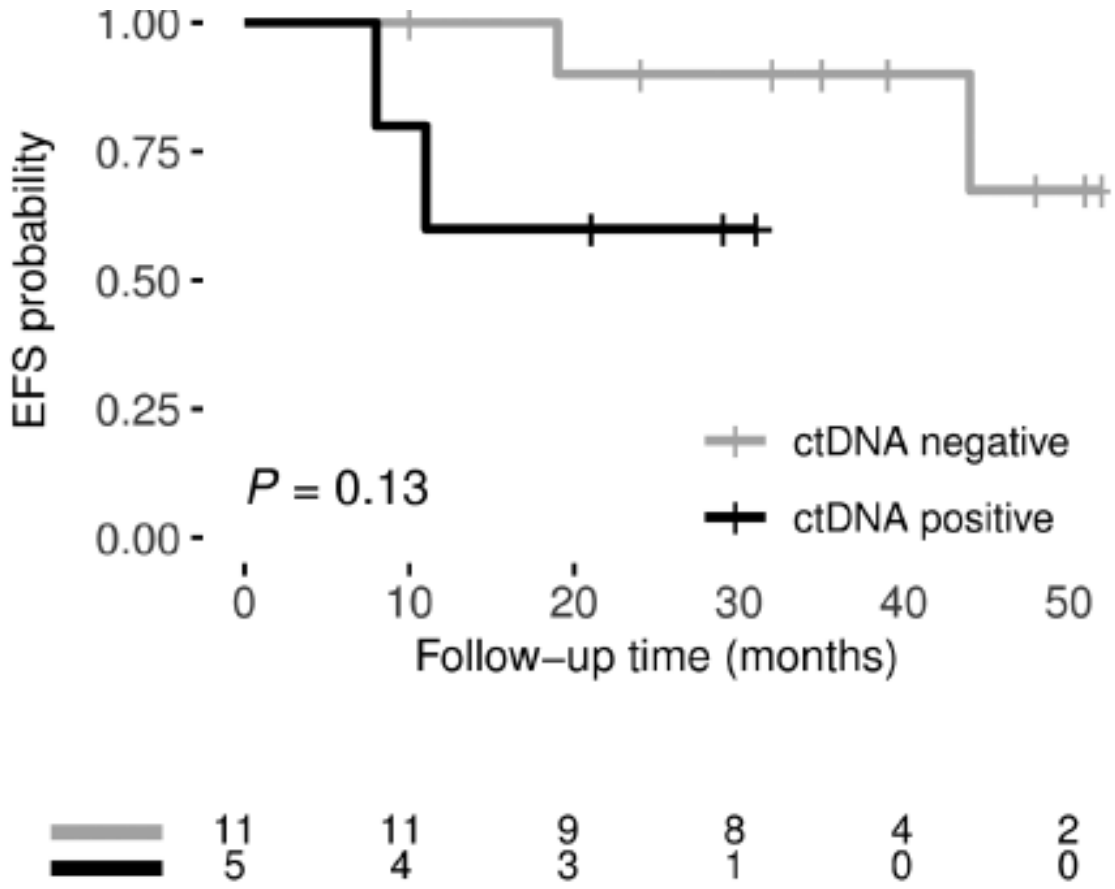
Advanced stage FL treated with chemo-R (FOLL05)



PET = positron emission tomography; MRD = minimal residual disease.

Luminari S, et al. *Haematologica*. 2016;101(2):e66-e68.

Lower Levels of NGS-Detectable ctDNA Mutations after Treatment Can Be Associated with a Long Remission (PFS)



NGS = next-generation sequencing.

Fernandez-Miranda I, et al. *Clin Cancer Res*. 2023;29(1):209-220.

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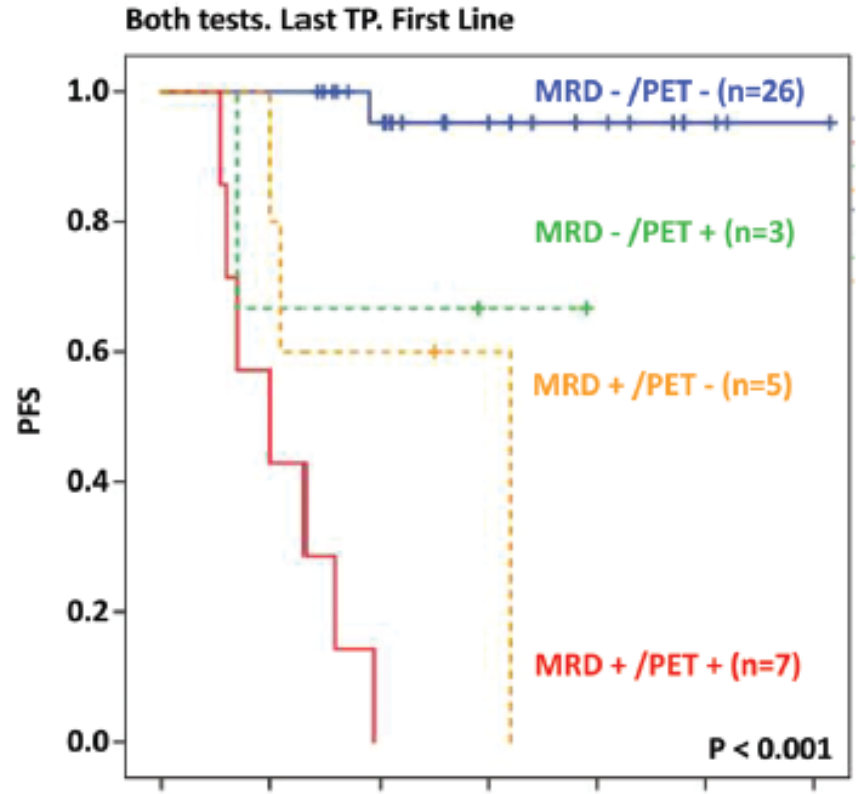
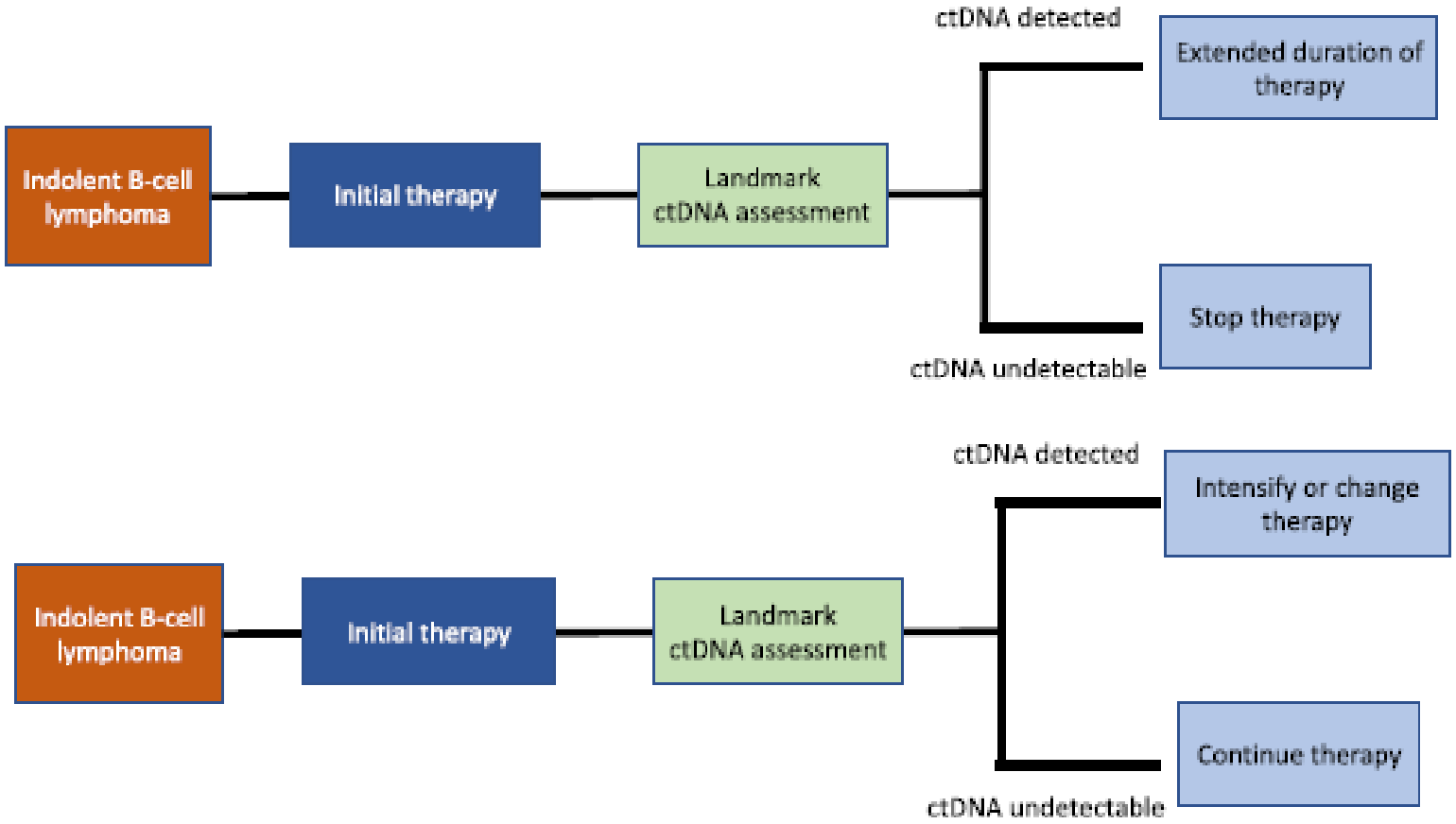
Lower Levels of NGS-Detectable ctDNA Mutations + PET-neg after Treatment Can Be Associated with a Long Remission (PFS)



Months	0	10	20	30	40	50	60
MRD - /PET -	26	26	20	13	8	3	1
MRD - /PET +	3	2	2	2	1	0	0
MRD + /PET -	5	5	3	2	0	0	0
MRD + /PET +	7	4	0	0	0	0	0

Jiminez-Ubieto A, et al. *Leukemia*. 2023;37(3):659-669.

How Might We Think about ctDNA Use in Practice in FL?



Lakhotia R, Roschewski M. *Semin Hematol*. 2023;60(3):164-172.

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What Patient with FL Has Most Likely Chance of Long-Term Remission?

- Low-risk FLIPI, EZH2-mutated
- Low tumor burden/MTV and/or limited stage
- Lower ctDNA at baseline
- Treated with chemo(?)immunotherapy and maintenance
- EOT PET-negative
- EOT ctDNA negative

FLIPI = Follicular Lymphoma International Prognostic Index; EOT = end of treatment.

QOL Data in Lymphoma Trials Is Often Not Collected or Reported

- Of the 103 eligible trials, QOL endpoints were collected in 53 (51%) trials, but were only reported in 25 (24%)

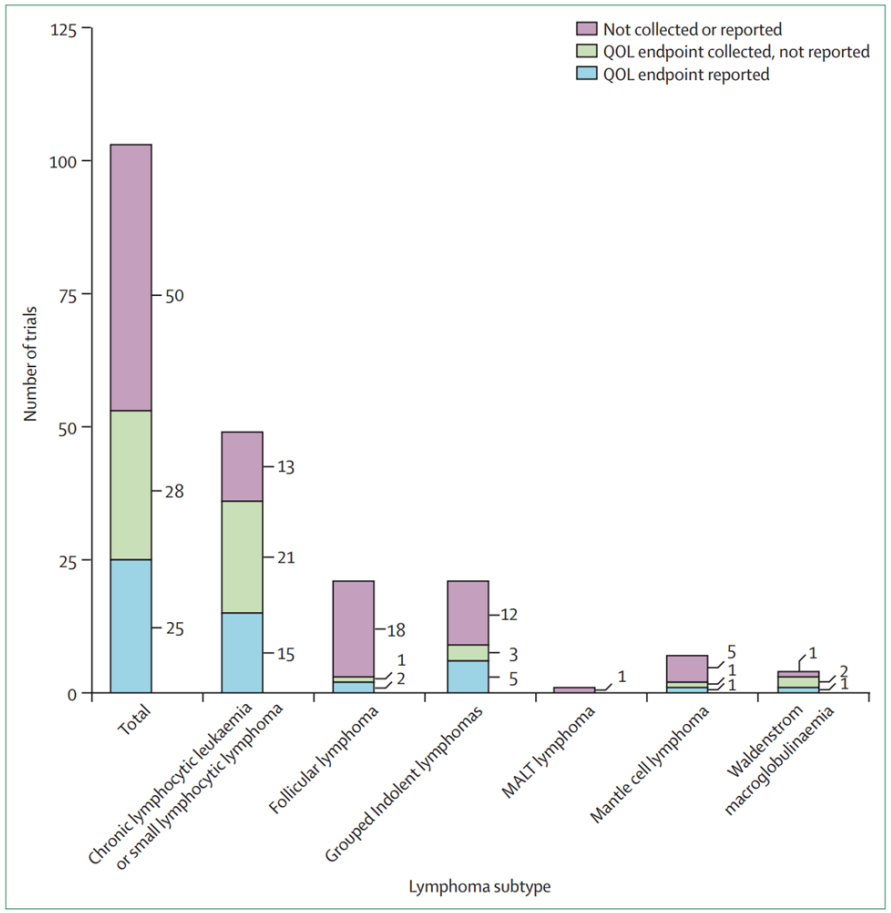

Figure 2: Eligible trials and reporting of quality of life by indolent lymphoma subtype

QOL = quality of life.

Milrod CJ, et al. *Lancet Haematol*. 2025;12(4):e312-e317.

Perceived Cognitive Function Issues in Patients with Lymphoma

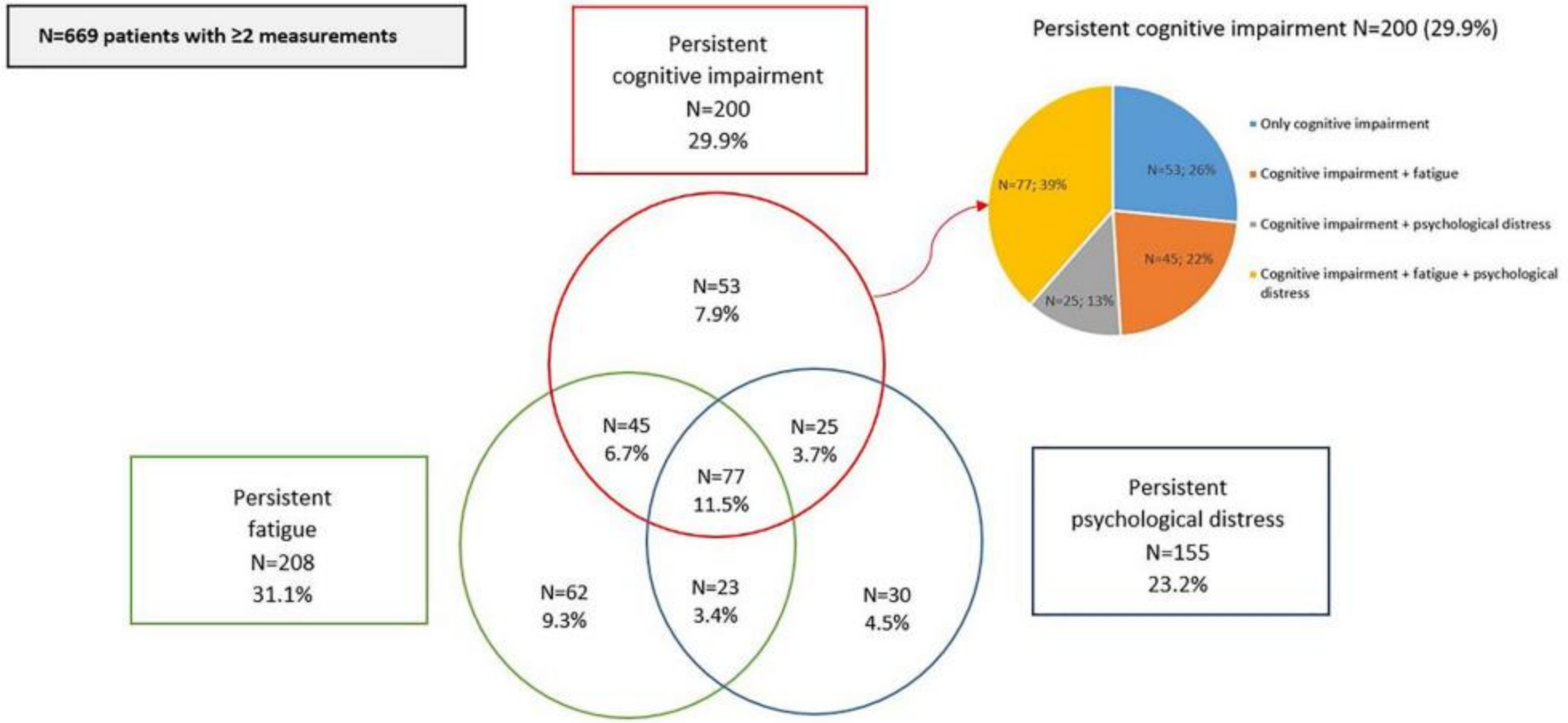

Fig. 2 Venn-diagram of the proportion of patients who reported persistent cognitive impairment, persistent fatigue and/or persistent psychological distress

Ekels A, et al. *J Cancer Surviv*. 2025;19(1):183-196.

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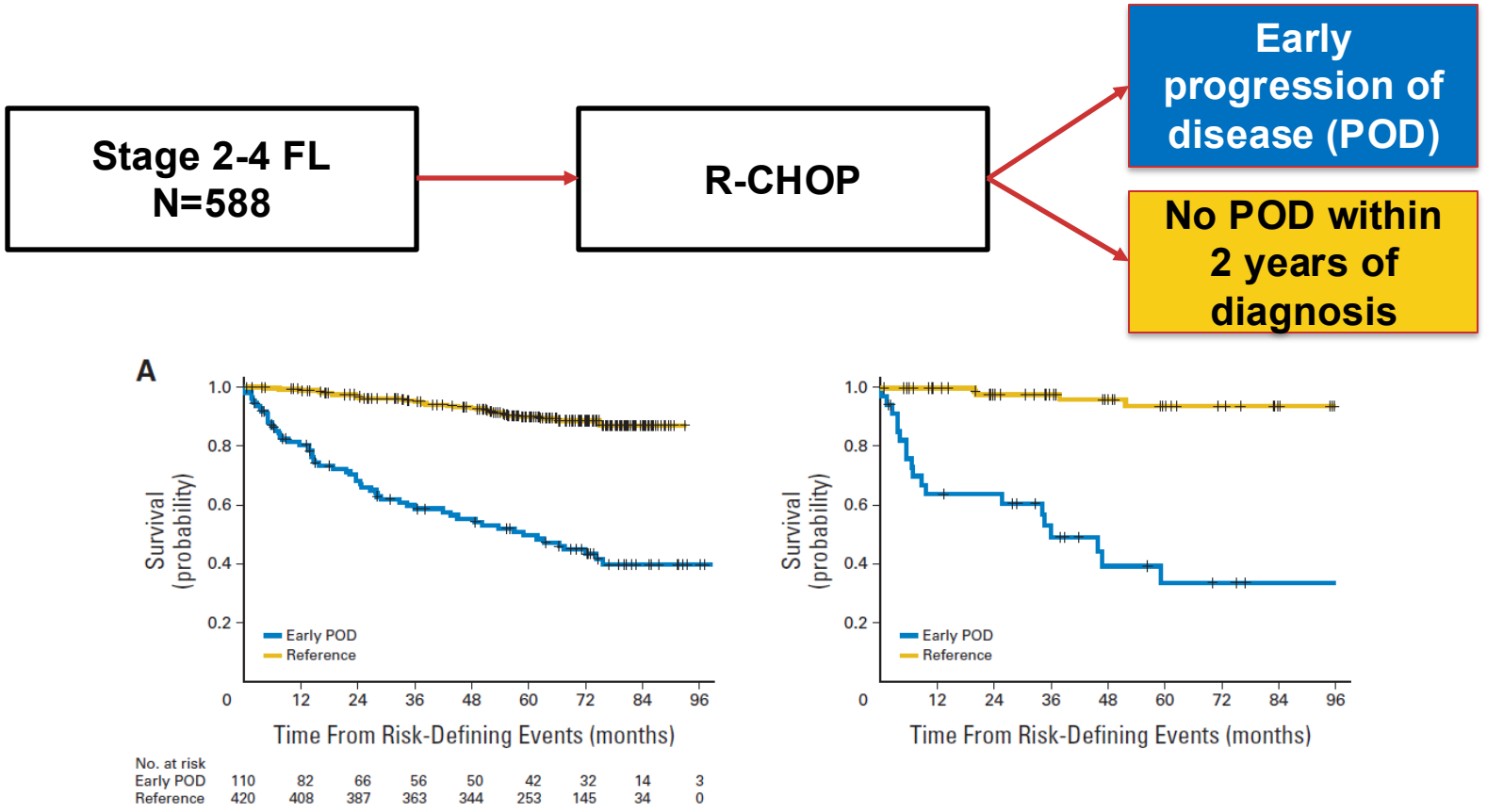
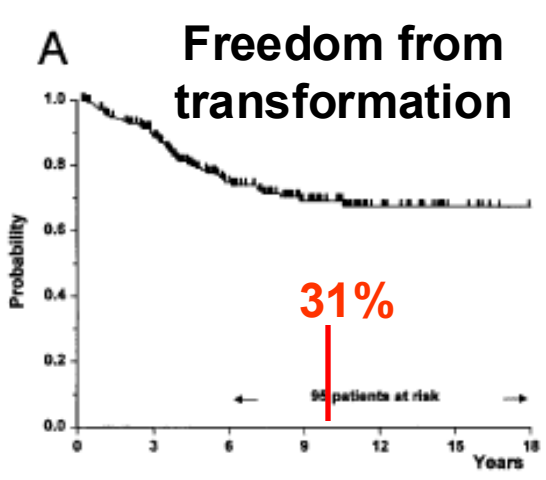
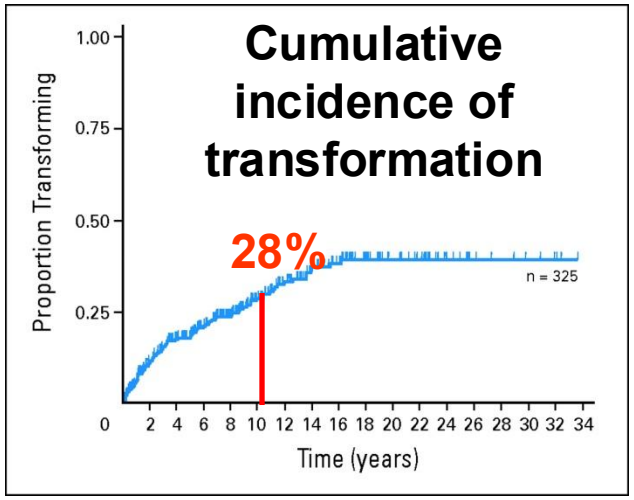
Early Relapse of FL Defines High-Risk Group Needing Better Therapies

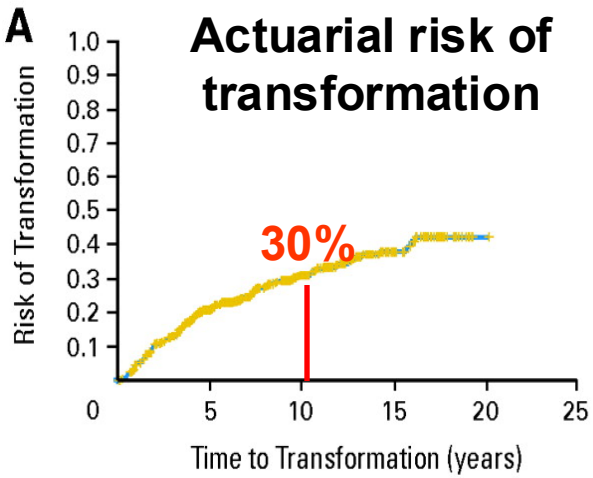


Casulo C, et al. *J Clin Oncol*. 2015;33(23):2516-2522.

Incidence of Transformed Lymphoma







Lyon: n=220 St. Barts: n=325 Vancouver: n=600

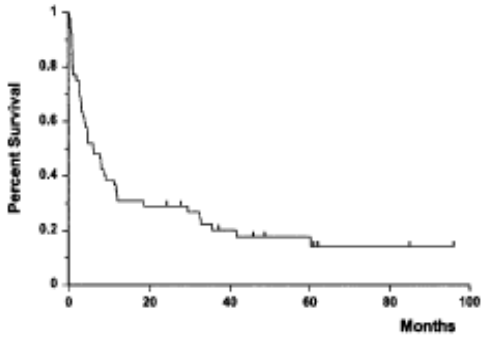
Transformation rate ~30% at 10 years

Bastion Y, et al. *J Clin Oncol*. 1997;15(4):1587-1594. Montoto S, et al. *J Clin Oncol*. 2007;25(17):2426-2433. Al-Tourah AJ, et al. *J Clin Oncol*. 2008;26(32):5165-5169.

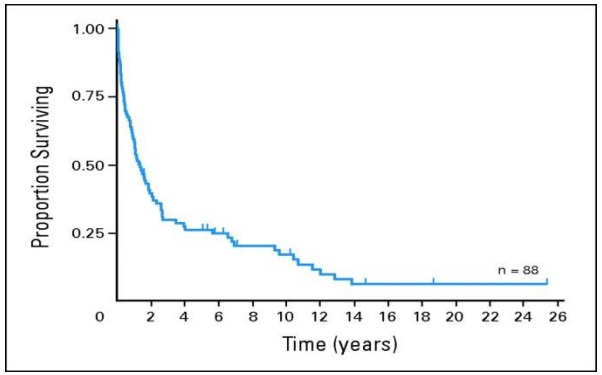
Historical Outcomes for Patients with TL

Median survivals range from 1-2 years

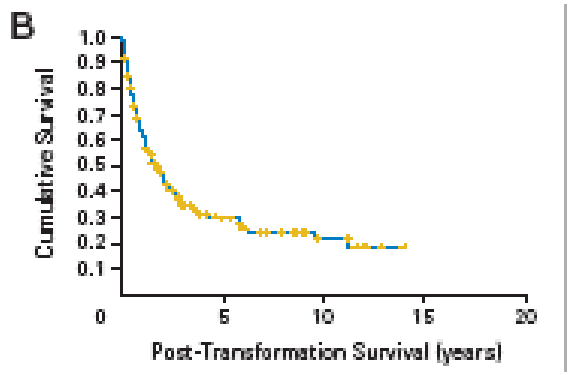
Lyon



St. Barts



Vancouver



Typically treated with DLBCL regimens and autoSCT

More favorable if “de novo transformation”

TL = transformed lymphoma; DLBCL = diffuse large B-cell lymphoma; SCT = stem cell transplantation.

Bastion Y, et al. *J Clin Oncol*. 1997;15(4):1587-1594. Montoto S, et al. *J Clin Oncol*. 2007;25(17):2426-2433. Al-Tourah AJ, et al. *J Clin Oncol*. 2008;26(32):5165-5169.

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Looking for Follicular Lymphoma Transformation

- Inexact process
- Signs of transformation
  - Rapid growth of one or more areas disproportionate to others
  - High LDH
  - High SUV on PET (debatable)
- If in doubt, biopsy (or re-biopsy after treatment)

LDH = lactate dehydrogenase; SUV = standardized uptake value.

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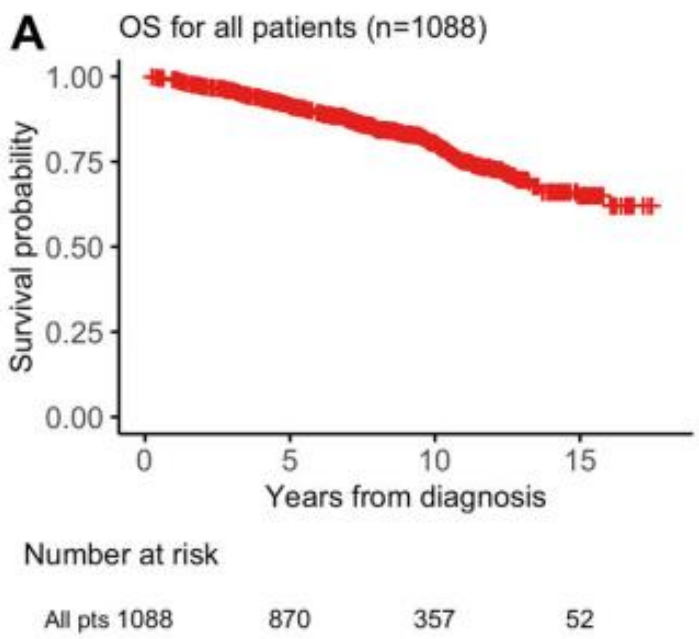
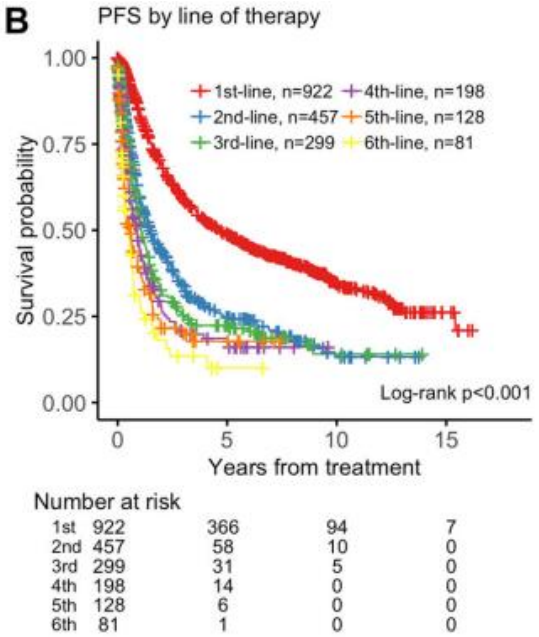
Advanced-Stage Lymphoma Outcomes with Serial Therapies

- 1088 patients, followed over serial therapies
- “While FL remains incurable, overall survival (OS) continues to improve due to improvements in diagnostic tools and supportive care, the development of the monoclonal anti-CD20 antibody rituximab, and the increasing number of FDA-approved therapies”





Batlevi CL, et al. *Blood Cancer J*. 2020;10(7):74.

Considerations in the Choice of Therapy for a Follicular/Indolent Lymphoma Patient at Diagnosis or Relapse

- Indications (reason) for therapy
- Bulk of disease
- Comorbidities
- Toxicity and practicality concerns
- Interest in and availability of clinical trials
- Risk of transformation to an aggressive type
- Grade (typically treat FL grade 1, 2, and 3A similarly)

SUGGESTED TREATMENT REGIMENS

SECOND-LINE THERAPY

Preferred regimens (in alphabetical order):

Bendamustine ± obinutuzumab or rituximab (not recommended if treated with prior bendamustine)
CHOP ± obinutuzumab or rituximab
CVP ± obinutuzumab or rituximab
Lenalidomide + rituximab
Tafasitamab-cxix + lenalidomide + rituximab (≥1 prior systemic therapy including an anti-CD20 mAb)

Other recommended regimens (in alphabetical order):

Lenalidomide (if not a candidate for anti-CD20 therapy)
Lenalidomide ± obinutuzumab
Obinutuzumab
Rituximab

SECOND-LINE THERAPY FOR OLDER OR INFIRM (if none of the therapies are expected to be tolerable in the opinion of treating physician)

Preferred regimens:

Rituximab (375 mg/m² weekly × 4 doses)
Tazemetostat (irrespective of EZH2 mutation status)

Other recommended regimen:

Cyclophosphamide ± rituximab

SECOND-LINE EXTENDED THERAPY (optional)

Preferred regimens:

Rituximab maintenance 375 mg/m² one dose every 12 weeks for 2 years (category 1)
Obinutuzumab maintenance for rituximab-refractory disease (1 g every 8 weeks for total of 12 doses)

SECOND-LINE CONSOLIDATION THERAPY (optional)

High-dose therapy with autologous stem cell rescue (HDT/ASCR)

Consider prophylaxis for tumor lysis syndrome (NHODG-B). See monoclonal antibody and adverse effect section (NHODG-B).

Footnotes on FOLL-B 4 of 6. See Third-Line and Subsequent Therapy on FOLL-B 3 of 6.

Note: All recommendations are category 2A unless otherwise indicated.

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SUGGESTED TREATMENT REGIMENS

THIRD-LINE AND SUBSEQUENT THERAPY

Subsequent systemic therapy options include second-line therapy regimens (**FOLL-B 2 of 6**) that were not previously given.

Preferred regimens (in alphabetical order):

- T-cell engager therapy
  - Bispecific antibody therapy
    - Epcoritamab-bysp
    - Mosunetuzumab-axgb
- Chimeric antigen receptor (CAR) T-cell therapy
  - Axicabtagene ciloleucel (CD19-directed)
  - Lisocabtagene maraleucel (CD19-directed)
  - Tisagenlecleucel (CD19-directed)

Other recommended regimens:

- EZH2 inhibitor
  - Tazemetostat (irrespective of EZH2 mutation status)
- BTK inhibitor
  - Zanubrutinib ± obinutuzumab
- Loncastuximab tesirine-lpyl + rituximab (category 2B)

THIRD-LINE CONSOLIDATION THERAPY

Useful in certain circumstances:

Allogeneic hematopoietic cell transplantation (HCT) in selected cases

Footnotes on FOLL-B 4 of 6.

Consider prophylaxis for tumor lysis syndrome *(NHODG-B).* See monoclonal antibody and viral reactivation *(NHODG-B).*

Note: All recommendations are category 2A unless otherwise indicated.

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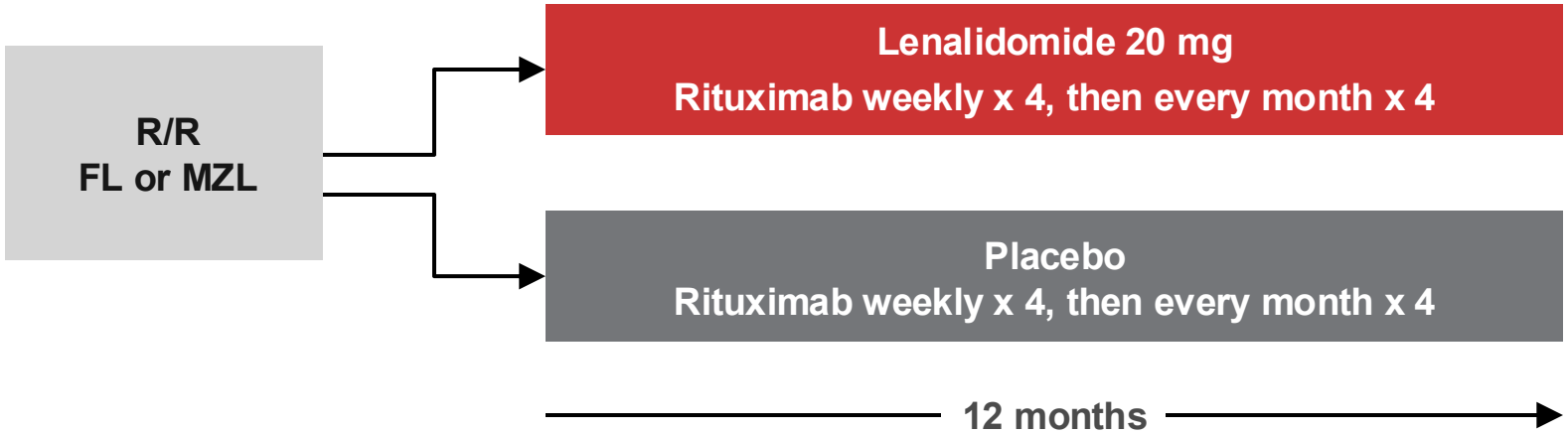
Key Agents and Regimens for Follicular Lymphoma

- Anti-CD20 mAbs (rituximab, obinutuzumab)
- Chemoimmunotherapy (bendamustine, CHOP)
- Radioimmunotherapy
- Lenalidomide
- BTK inhibitors (zanubrutinib)
- EZH2 inhibitors (tazemetostat)
- Bispecific antibodies (mosunetuzumab, epcoritamab)
- Auto/alloSCT
- CAR-T

NHL-007 (AUGMENT): R^2 vs Rituximab Monotherapy in R/R iNHL

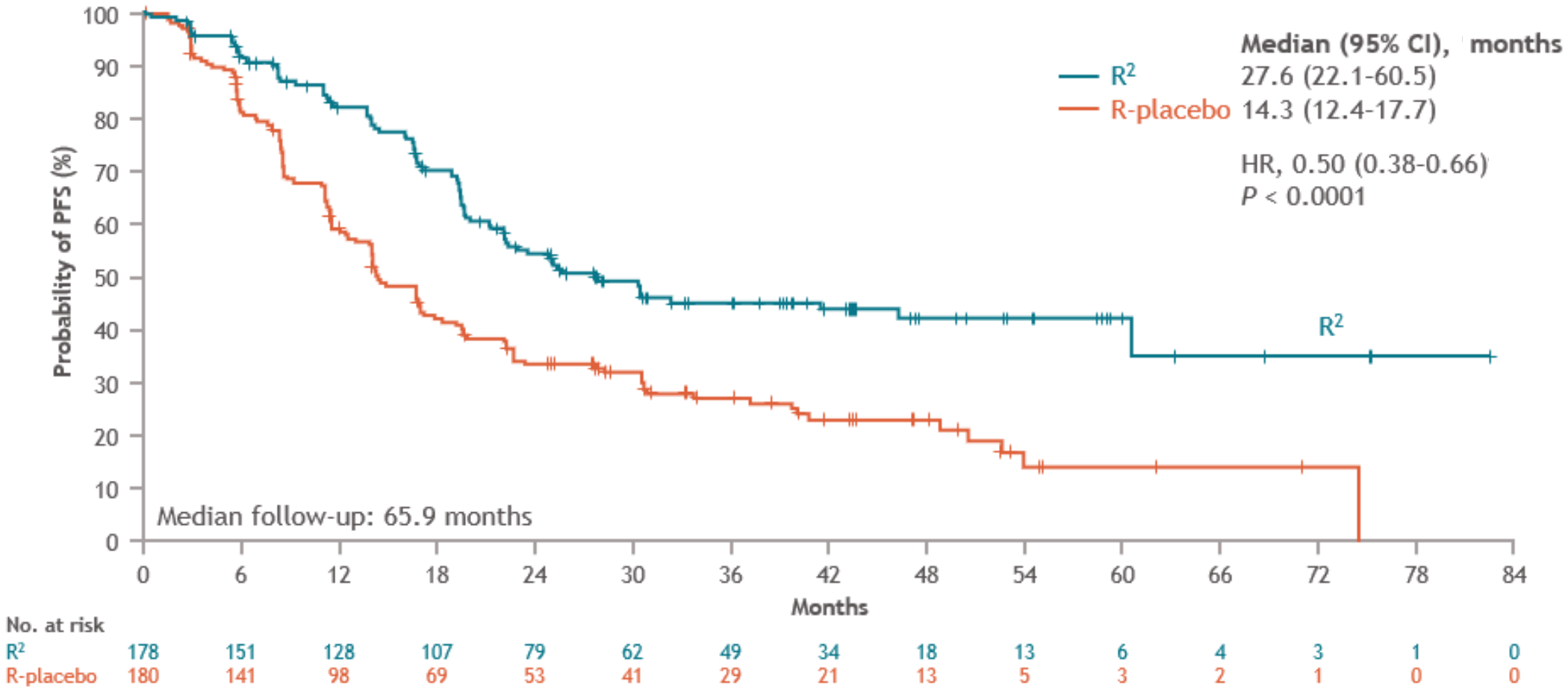


- Phase 3 study (registration)
- Eligible patients: rituximab-naïve or rituximab-sensitive R/R FL or MZL, grades 1, 2, or 3a
- Primary endpoint: PFS
- HR=1.6 (improvement of 6.7 months in median PFS)
  - Implies sample size of N=350

MZL = marginal zone lymphoma.

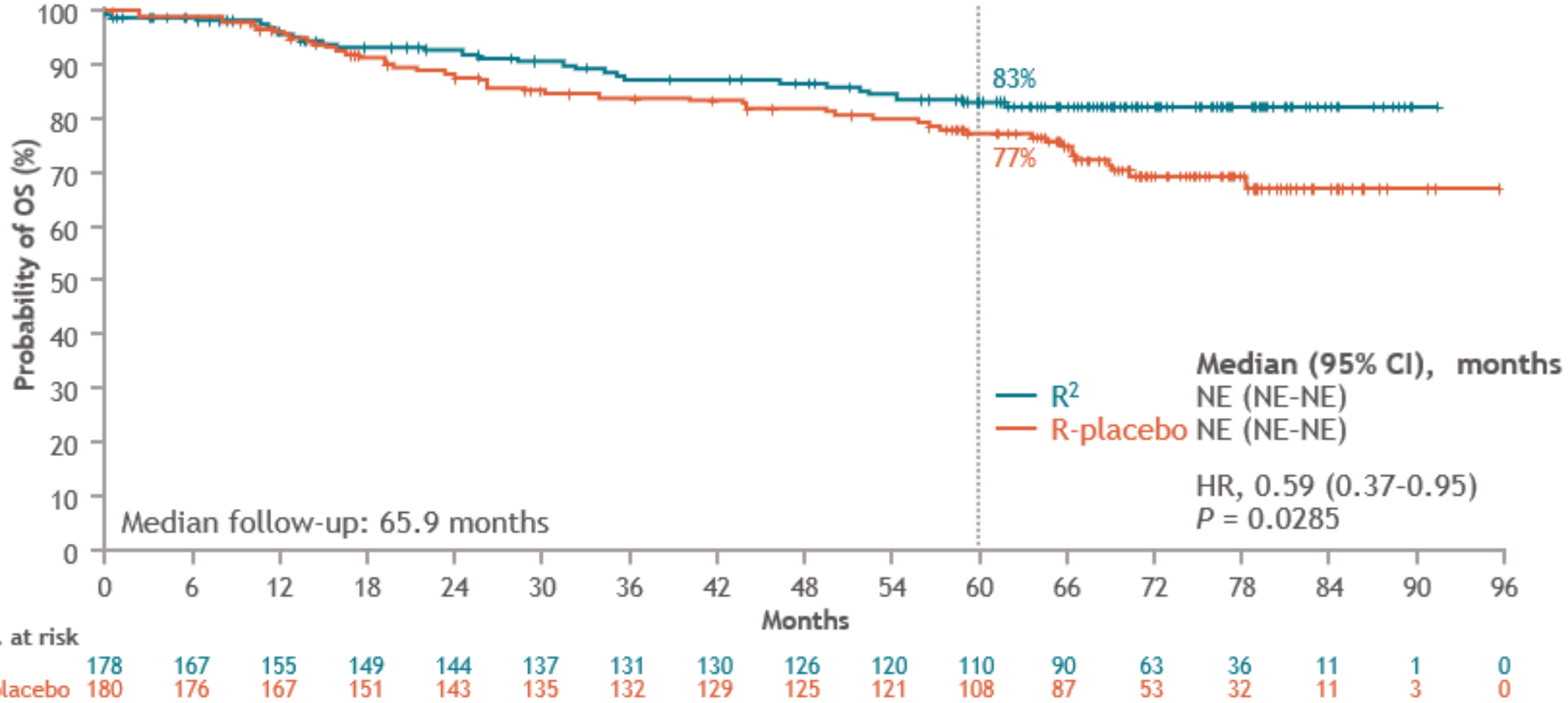
Leonard JP, et al. Presented at: American Society of Hematology (ASH) Annual Meeting; December 10-13, 2022; New Orleans, LA.

AUGMENT: Lenalidomide-Rituximab vs Rituximab in Recurrent FL: PFS



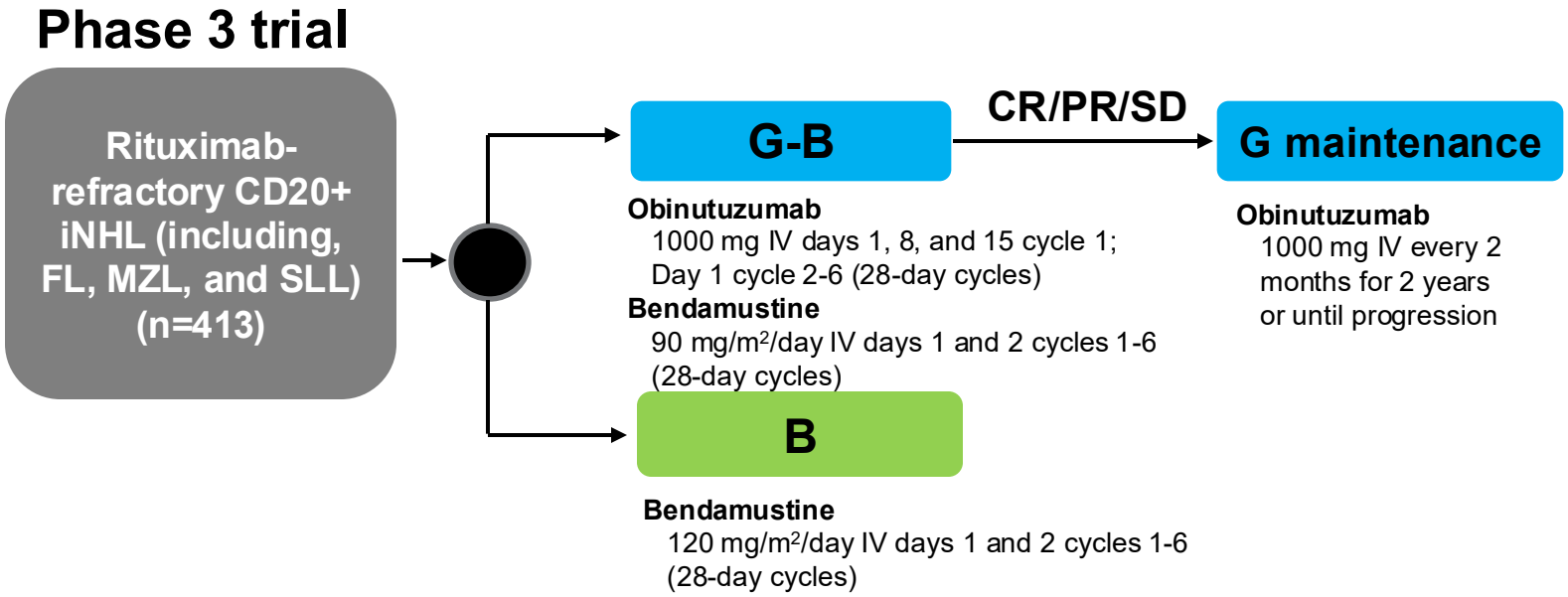
Leonard JP, et al. Presented at: ASH Annual Meeting; December 10-13, 2022; New Orleans, LA.

AUGMENT: Lenalidomide-Rituximab vs Rituximab in Recurrent FL: OS



Leonard JP, et al. Presented at: ASH Annual Meeting; December 10-13, 2022; New Orleans, LA.

GADOLIN: Study Design (NCT01059630)



- International, randomized, open-label study
- Response monitored by CT scan post-induction, then every 3 months for 2 years, then every 6 months

Stratification factors

- NHL subtype (FL vs other)
- Prior therapies (≤2 vs >2)
- Refractory type (R-mono vs R-chemo)
- Geographic region

NHL = non-Hodgkin lymphoma; SLL = small lymphocytic lymphoma; G = obinutuzumab; B = bendamustine; SD = stable disease; CT = computed tomography.

Sehn LH, et al. *J Clin Oncol*. 2015;33(30):3467-3474.

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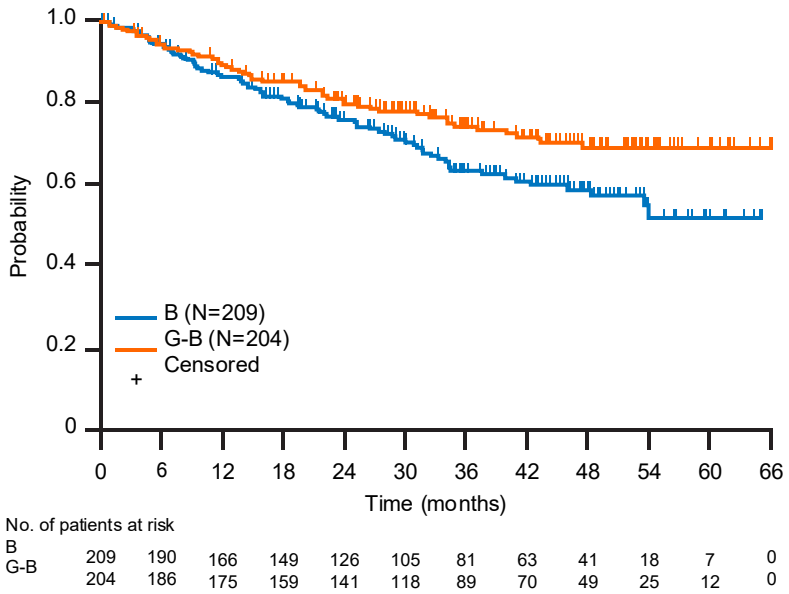
Obinutuzumab Has Improved OS in Recurrent iNHL When Added to Bendamustine

KM plot of OS by treatment arm (iNHL)



	G-B, n=204	***B, n=209***
Pts with event, n (%)	52 (25.5)	73 (34.9)
Median OS (mo)	NR (NR, NR)	NR (48.2, NR)
HR (95% CI), stratified *P*-value	0.67 (0.47, 0.96), *P*=0.0269	

Median follow-up: 31.8 months
(vs 21.1 months in primary analysis)

KM = Kaplan-Meier; NR = not reached; HR = hazard ratio; CI = confidence interval.

Sehn LH, et al. *J Clin Oncol*. 2015;33(30):3467-3474.

Considerations in the Choice of Therapy for a Follicular/Indolent Lymphoma Patient at Diagnosis or Relapse

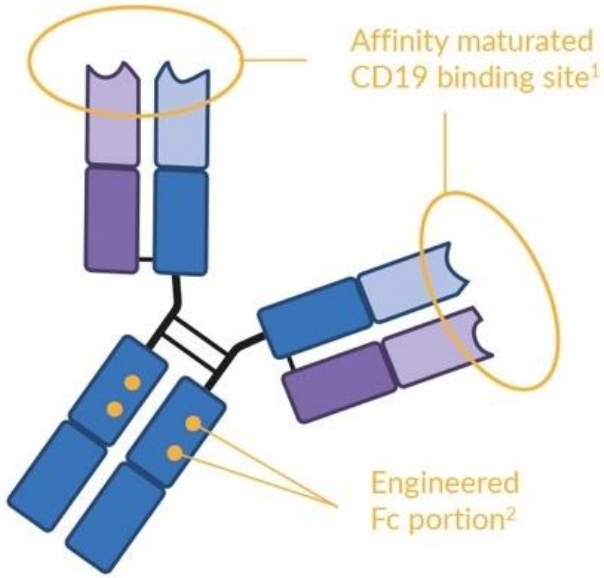
- Indications (reason) for therapy
- Bulk of disease
- Comorbidities
- Toxicity and practicality concerns
- Interest in and availability of clinical trials
- Risk of transformation to an aggressive type
- Grade (typically treat FL grade 1, 2, and 3A similarly)

Emerging Therapies in FL

- CD19 monoclonal antibodies: tafasitamab
- Antibody drug conjugates (ADCs): loncastuximab-tesirine
- Targeted therapies
  - EZH2 inhibitors: tazemetostat
  - BTK inhibitors: zanubrutinib
- Bispecific antibodies
  - Epcoritamab
  - Mosunetuzumab
  - Odronextamab
- CAR-T
  - Axi-cel
  - Liso-cel
  - Tisa-cel
- Other agents in development

CD19 mAb: Tafasitamab

- Humanized CD19-targeting monoclonal antibody (mAb)
- Induces direct cytotoxicity and enhances NK cell and macrophage immune-mediated mechanisms



Meisel A, et al. *Healthbook Times Oncol Hematol*. 2025;23(1):151-158.

inMIND Phase 3 Study: R^2 +/- Tafasitamab

- 548 pts with R/R FL1-3a, ≥1 prior systemic therapy (median = 1)
- Pts randomized 1:1 to receive tafa 12 mg/kg IV or placebo on D1, 8, 15, and 22 of C1-3, and D1 and D15 of C4-12 with standard dosing of R^2 for up to 12 28-day cycles
  - Median age 64 y; 55% male
  - 79% intermediate- or high-risk FLIPI
  - 83% high tumor burden per GELF criteria
  - 45% had ≥2 prior lines
  - 32% had POD24
  - 43% were refractory to anti-CD20 mAb

GELF = Groupe d'Etude des Lymphomes Folliculaires; POD24 = disease progression within 24 m.

Sehn LH, et al. *Blood*. 2024;144(Suppl 2):LBA-1.

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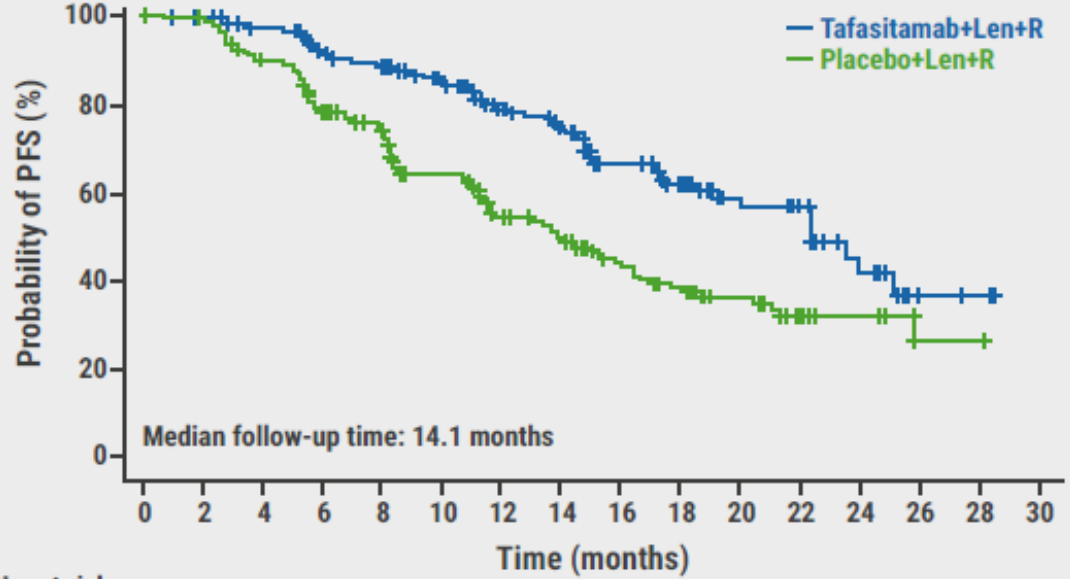
inMIND: Addition of Tafa to Len + R Significantly Lowers Risk of Progression, Relapse, or Death vs Placebo

- Median follow-up 14.1 m
- PFS: 22.4 m vs 13.9 m; hazard ratio [95% CI], 0.43 [0.32, 0.58]; *P*<0.0001
  - PFS benefit was seen in all prespecified subgroups: pts with POD24, pts refractory to prior anti-CD20 mAb, pts receiving multiple prior lines of tx
- PET-CR rate: 49.4% vs 39.8%; *P*=0.029
  - ORR 83.5% vs 72.4%; *P*=0.0014
- DOR: 21.2 m vs 13.6 m; HR [95% CI], 0.47 [0.33, 0.68]; *P*<0.0001
- TTNT: median NR vs 28.8 m; HR [95% CI], 0.45 [0.31, 0.64]; *P*<0.0001

	Tafasitamab + Len + R	Placebo + Len + R
Median PFS (95% CI), months	22.4 (19.2–NE)	13.9 (11.5–16.4)
HR (95% CI)	0.43 (0.32–0.58)	
P-value	P<0.0001	



No. at risk

Tafasitamab+Len+R	273	261	250	212	200	164	119	103	71	57	30	22	12	3	2	0
Placebo+Len+R	275	265	235	192	173	126	82	70	48	40	26	16	10	2	2	0

ORR = overall response rate; DOR = duration of response; TTNT = time to next treatment.

Sehn LH, et al. *Blood*. 2024;144(Suppl 2):LBA-1.

inMIND: Similar TEAEs between Arms

- Grade 3 or 4 AEs: 71% tafa arm vs 69.5% placebo
- TEAEs leading to discontinuation: 11% vs 7%
- Deaths: 15 pts (5.5%) in the tafa arm and 23 (8.5%) in the PBO arm
  - Including 5 (2%) vs 17 (6%) due to disease progression, and 6 (2%) in each arm due to fatal AEs

AE (Grade 3-4)	Tafasitamab + R2	Placebo + R2
Neutropenia	40%	38%
Pneumonia	8%	5%
Thrombocytopenia	6%	7%
COVID	6%	2%

TEAEs = treatment-emergent adverse events; PBO = placebo.

Sehn LH, et al. *Blood*. 2024;144(Suppl 2):LBA-1.

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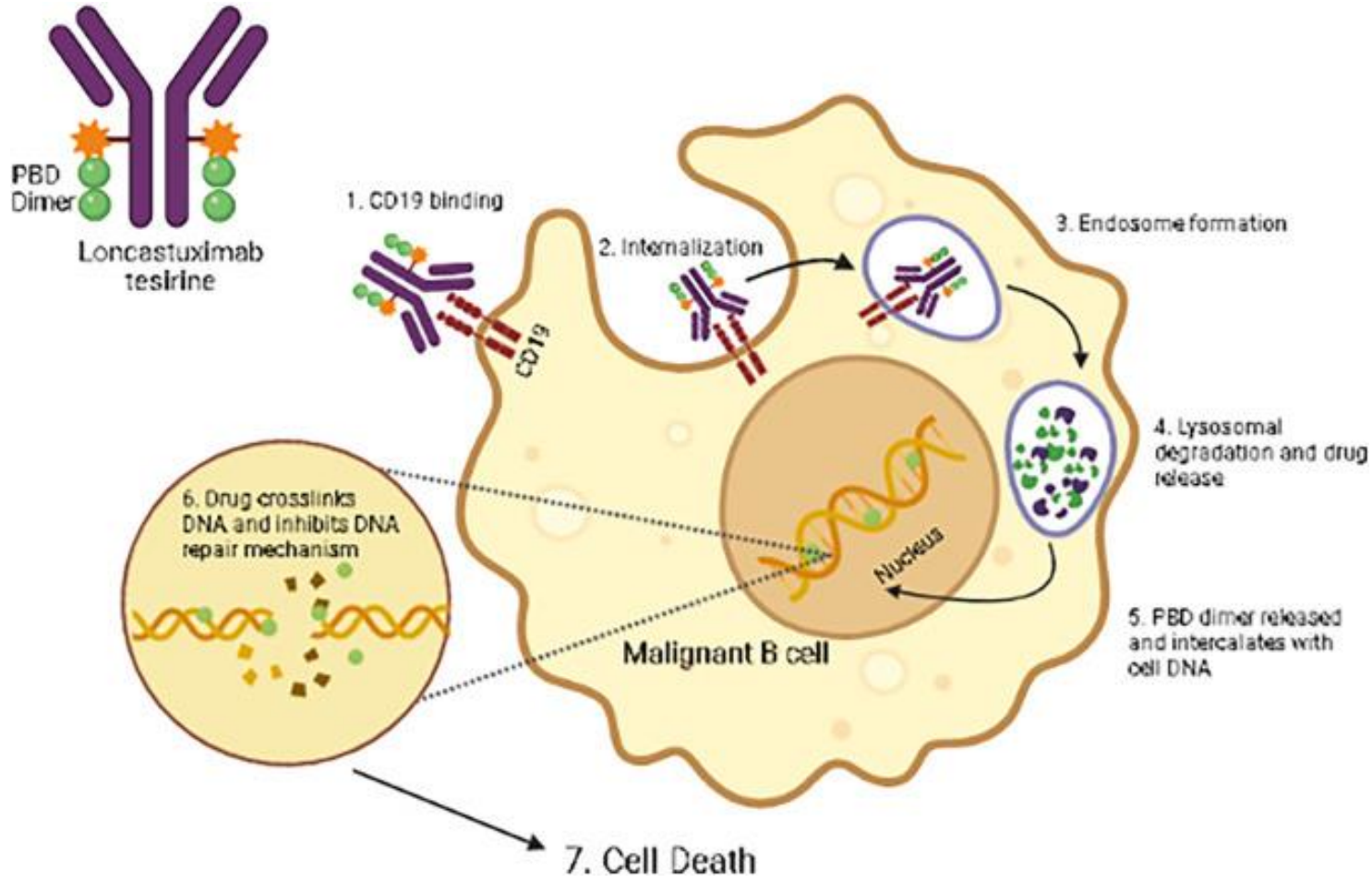
FDA approves tafasitamab-cxix for relapsed or refractory follicular lymphoma

On June 18, 2025, the Food and Drug Administration approved tafasitamab-cxix with lenalidomide and rituximab for adults with relapsed or refractory follicular lymphoma (FL).

FDA. Accessed October 13, 2025. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tafasitamab-cxix-relapsed-or-refractory-follicular-lymphoma.

Antibody Drug Conjugate: Loncastuximab Tesirine

- CD19-directed humanized monoclonal antibody linked to an alkylating agent, PBD



PBD = pyrrolobenzodiazepine.

Chu Y, et al. *Best Pract Res Clin Haematol*. 2023;36(1):101442.

Loncastuximab-Tesirine in FL

- Phase 1 study in R/R B-cell NHL
  - 180 pts total; 14 FL
  - ORR 78.6%, CR 64%

Adverse Reaction >10%	All Grades (%)
Fatigue	42
Edema	58
Rash	24
Pruritis	10.9
Photosensitivity Rxn	11.5
Pleural effusion	21

Laboratory Abnormalities	All grades (%)	Grade 3-4 (%)
Thrombocytopenia	58	17
Neutropenia	52	30
Anemia	51	10
GGT increase	57	21
AST increase	41	<1
ALT increase	34	3
Glucose increase	48	8
Albumin decrease	37	<1

GGT = gamma-glutamyl transferase; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Hamadani M, et al. *Blood*. 2021;137(19):2634-2645.

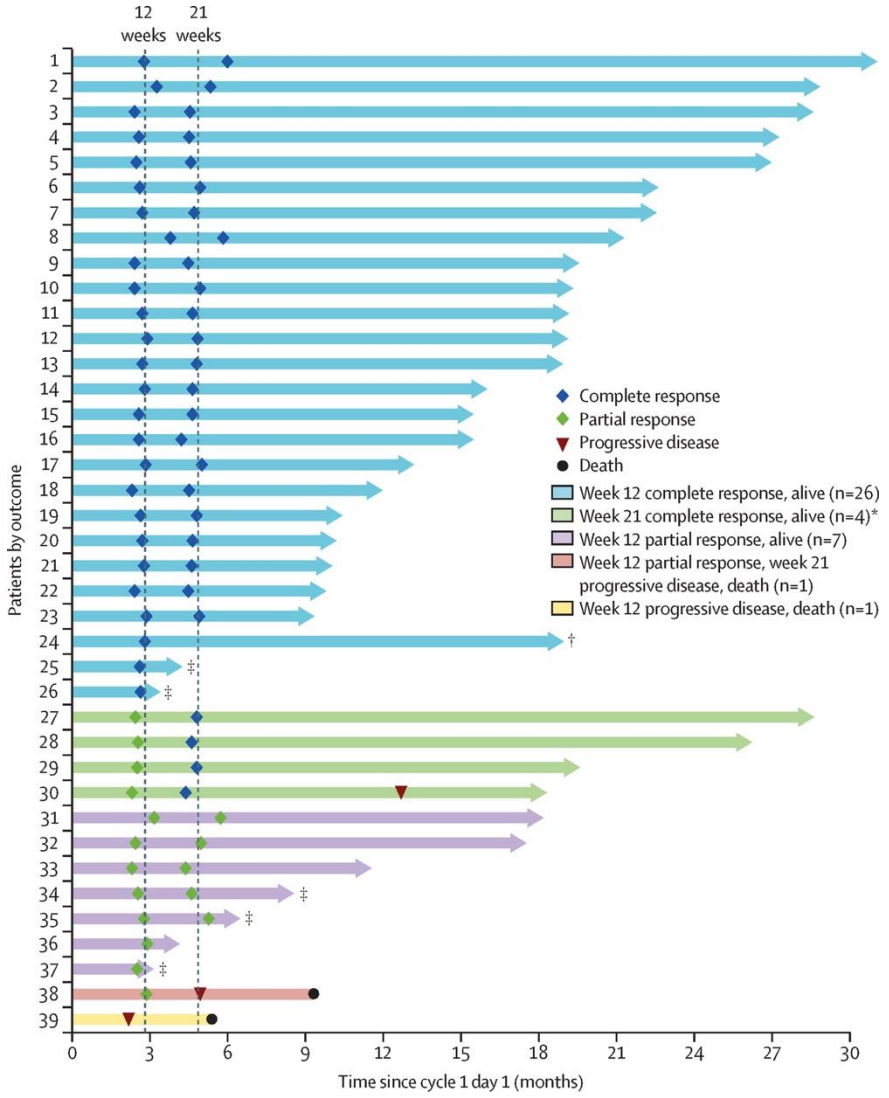
Loncastuximab Tesirine + Rituximab

- Single-center phase 2 study in 39 pts w/ R/R FL
  - Median age: 68 years (range 47 to 89), 53.8% male
  - 82% advanced-stage
  - 87.2% high-disease burden by GELF criteria
  - Median prior lines of therapy: 1
  - 51.3% POD24 after frontline immunochemotherapy (51.3%)
  - Median FLIPI score: 3
- Pts received rituximab 375 mg/m^2 IV x 4 weekly doses, followed by 1 dose every 8 weeks for a total of 5 doses, plus
- Loncastuximab 0.15 mg/kg IV every 3 weeks for 2 doses, followed by 0.075 mg/kg every 3 weeks for a total of 7 doses
  - Patients achieving CR by PET/CT by week 21 discontinued loncastuximab and received 2 more doses of rituximab every 8 weeks
- Premedication with dexamethasone 4 mg twice daily for 3 days was required with loncastuximab

Alderuccio JP, et al. *Lancet Haematol*. 2025;12(1):e23-e34.

Loncastuximab Tesirine + Rituximab Induces High Rates of CR in R/R FL

- Median follow-up 18.2 months
- Week 12 ORR: 97% (38 of 39)
- Week 12 CRR: 67% (n=26 of 39)
- Most common grade 3 or worse TEAE
  - Lymphopenia (8/39, 21%)
  - Neutropenia 5/39 (13%); febrile neutropenia 1/39
  - Generalized and peripheral edema mainly grade 1-2, all cases were treatable with diuretics
  - No fatal TEAEs occurred



CRR = complete response rate.

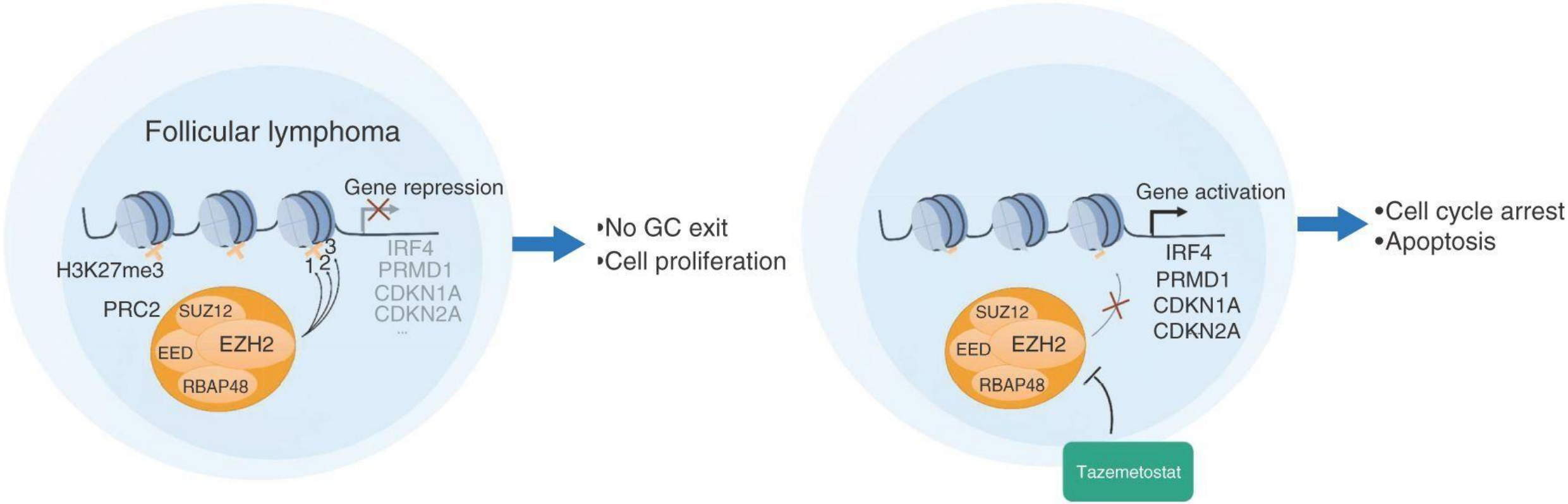
Alderuccio JP, et al. *Lancet Haematol*. 2025;12(1):e23-e34.

EZH2 in FL

- EZH2 is required for germinal center formation and plays a key role in lymphomagenesis
- EZH2 represses target genes involved in proliferation checkpoints, germinal center exit, and terminal differentiation
- Germinal center-derived lymphomas are reliant on wild-type EZH2 for their proliferation and survival, independent of somatic mutation
- EZH2 mutations and/or copy number gains seen in up to 30%

Beguelin W, et al. *Cancer Cell*. 2013;23(5):677-692.

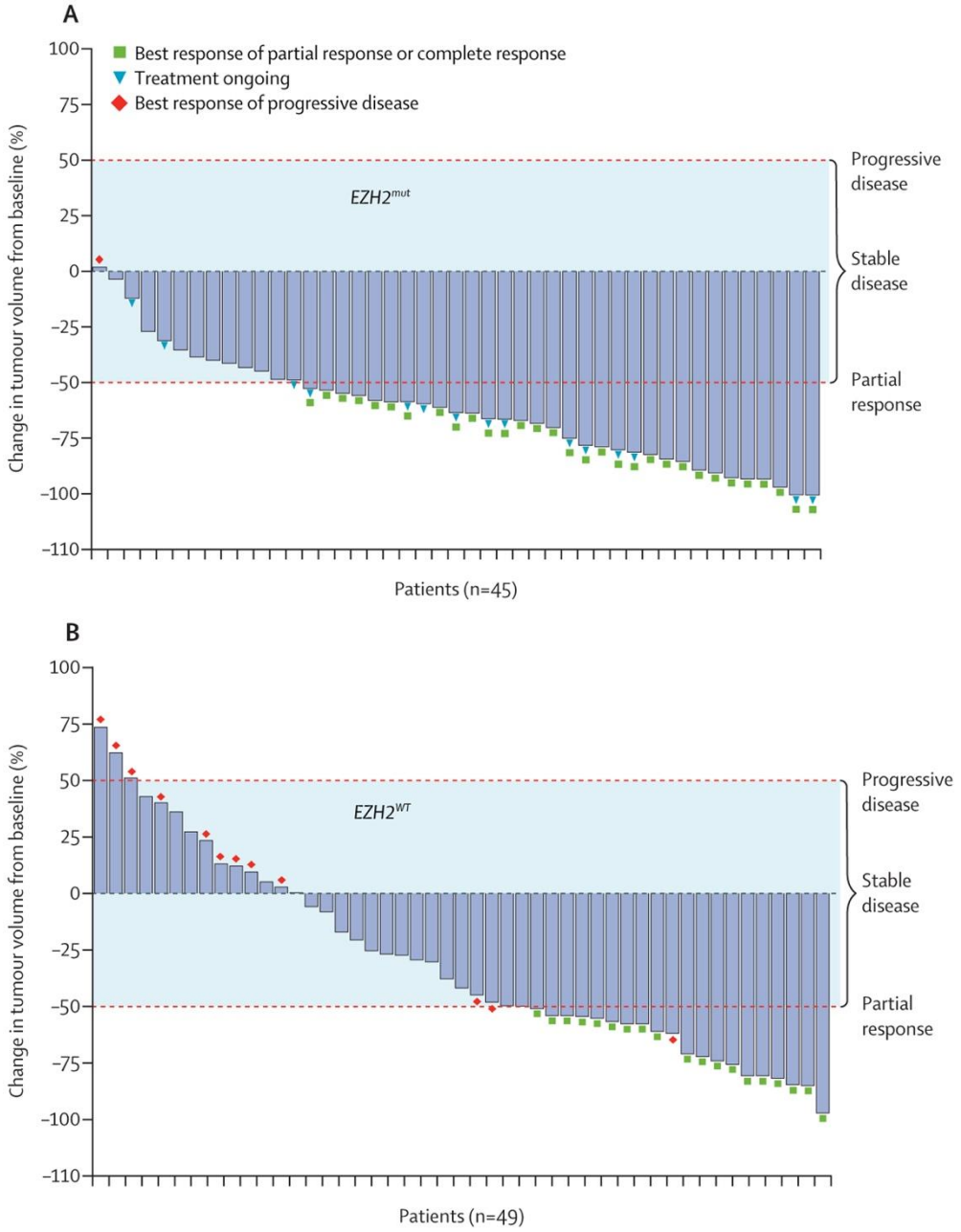
EZH2 Inhibition in Follicular Lymphoma



Julia E, Salles G. *Future Oncol*. 2021;17(17):2127-2140.

Tazemetostat in FL

	EZH2^{mut}	EZH2^{WT}
Objective response rate	69%	35%
Complete response	13%	4%
Partial response	56%	31%
Stable disease	29%	33%
Progressive disease	1%	22%
Overall disease control rate	98%	69%



Morschhauser F, et al. *Lancet Oncol*. 2020;21(11):1433-1442.

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Tazemetostat Safety Data

Common treatment-related adverse events

- **Fatigue**: 36%; grade 3-4: 5%
- **Hematologic**: anemia 50% (grade 3-4 8%); neutropenia 20% (grade 3-4 7%); thrombocytopenia 50% (grade 3-4 7%)
- **Gastrointestinal**: nausea 24% (grade 3-4: 1%); abdominal pain 20% (grade 3-4: 3%); diarrhea 18% (grade 3-4: 0%)
- **Infections**: upper respiratory tract (30%), lower respiratory tract (17%), urinary tract (11%) infections common; grade 3-4 infections rare (2%)
- Dose interruptions in 27%, dose reductions in 9%, treatment discontinuation due to AE 5%
- No treatment-related deaths reported

Secondary malignancies: potential risk for secondary malignancies due to the mechanism of action involving epigenetic regulation

- Rare cases of MDS, AML, B-ALL have been reported in adult patients
- T-cell lymphoblastic lymphoma (T-LBL) developed in 1 pediatric patient

MDS = myelodysplastic syndrome; AML = acute myeloid leukemia; B-ALL = B-cell acute lymphoblastic leukemia.

FDA. Accessed October 8, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/211723s005lbl.pdf.

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Tazemetostat in FL

FDA approval

- Patients with R/R FL who have received at least 2 prior systemic therapies and whose tumors are positive for an EZH2 mutation

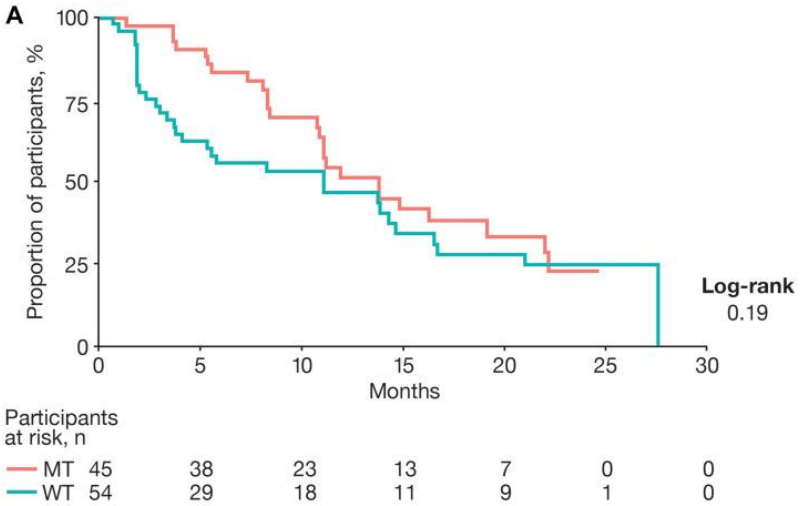
- Patients with R/R FL who have no satisfactory alternative treatment options

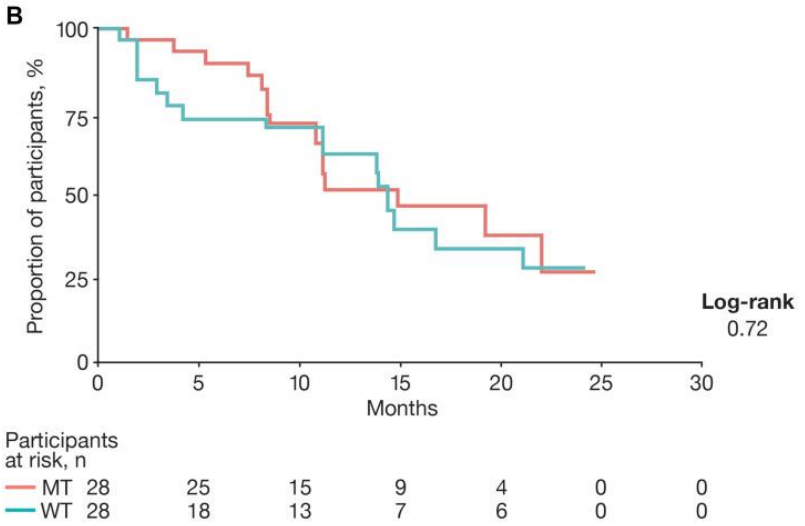
FDA. Accessed October 8, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/211723s005lbl.pdf.

Does EZH2 Mutational Status Matter?

- Propensity-matched analysis of E7438-G000-101 suggests that clinical disparities might have contributed to some of the differences in efficacy outcomes

Population	Before matching (n = 99)		Matched sample (n = 56)	
	Median (95% CI), mo	Median follow-up, mo	Median (95% CI), mo	Median follow-up, mo
All participants	11.9 (10.9–16.3)	—	14.3 (11.1–22.0)	—
MT *EZH2*	13.8 (11.1–22.1)	17.9	14.8 (10.7–∞)	19.2
WT *EZH2*	11.1 (5.4–16.7)	24.1	14.3 (11.1–∞)	24.4





Proudman DG, et al. *Oncotarget*. 2022;13:677-683.

EZH2 Combinations

- Given its favorable safety profile, tazemetostat is an appealing agent for combinations

- Due to MOA, there is rationale for enhanced activity of T-cell immunotherapies and/or other immunomodulatory agents

MOA = mechanism of action.

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SYMPHONY-1: Tazemetostat + Rituximab + Lenalidomide (R^2)

- As of July 2023, 44 patients were receiving TAZ + R^2
  - 81.8% $EZH2^{WT}$ (n=36); 18.2% $EZH2^{mut}$ (n=8)
  - 34.1% (n=15) rituximab-refractory
  - 27.3% (n=12) POD24

- ORR = 91%, 54.8% CR, 40.5% PR, 4.8% stable disease
  - $EZH2^{WT}$: ORR 89%
  - $EZH2^{mut}$: ORR 100%

- No new safety signals identified; the RP3D of TAZ was determined to be 800 mg BID in combination with R^2
  - Most common grade 3-4 TEAE = neutropenia 40.9%; n=18
  - AEs → drug interruption (70.5%), dose reduction (38.6%), treatment discontinuation (20.5%)

- Ongoing phase 3 study comparing tazemetostat + R^2 vs R^2 (NCT04224493)

Salles G, et al. *Blood*. 2023;142(Suppl 1):3035.

Tazemetostat + Other Combinations

- Tazemetostat + epcoritamab (R/R FL)
  - NCT06575686
- Tazemetostat + CAR-T (B-cell lymphomas)
  - NCT05934838
- Tazemetostat + mosunetuzumab (untreated FL)
  - NCT05994235

ClinicalTrials.gov. Accessed October 9, 2025. https://www.clinicaltrials.gov.

BTKi: Zanubrutinib

- Zanubrutinib approved in combination w/ obinutuzumab in R/R FL after 2 or more lines of therapy following ROSEWOOD study
  - Multicenter Phase 2 trial, randomized 2:1 (ZO vs O)
  - 2+ prior lines of therapy (median 3), including anti-CD20 + alkylator
  - 50% of ZO-treated subjects had POD24, 30% of O-treated subjects
  - Primary endpoint: overall response rate (ORR)

ZO = zanubrutinib plus obinutuzumab; O = obinutuzumab.

FDA. Accessed October 9, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/218785Original2s000lbl.pdf.

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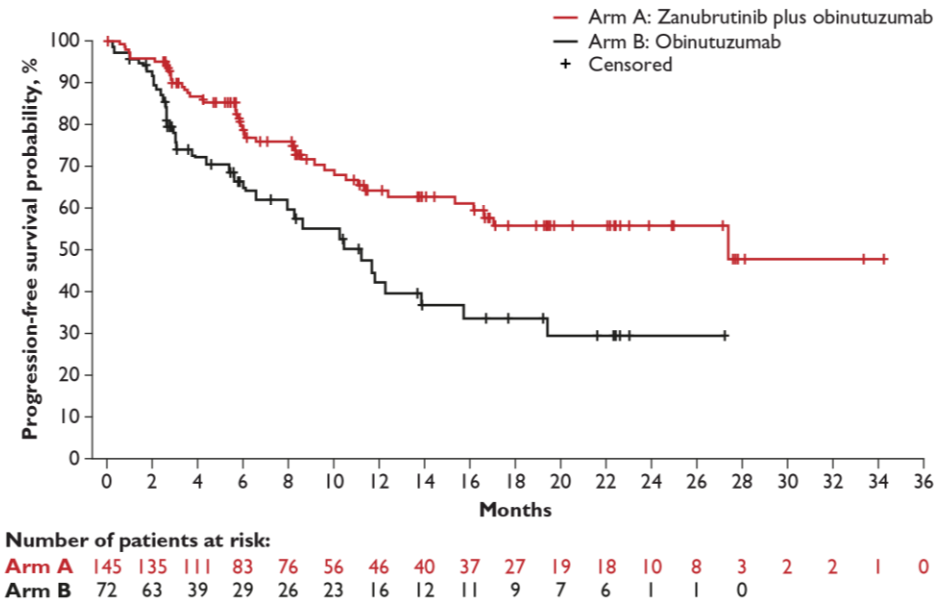
ROSEWOOD

- ORR: 68% ZO vs 43% O, *P*=0.001
- CR rate: 39% ZO vs 19% O
- PFS: 27.4 mo ZO vs 11.2 m O; *P*<0.001
- Duration of response (DOR): not reached ZO vs 26.5 mo O; *P*<0.001
- Time to next treatment: not estimable ZO vs 12.2 mo O

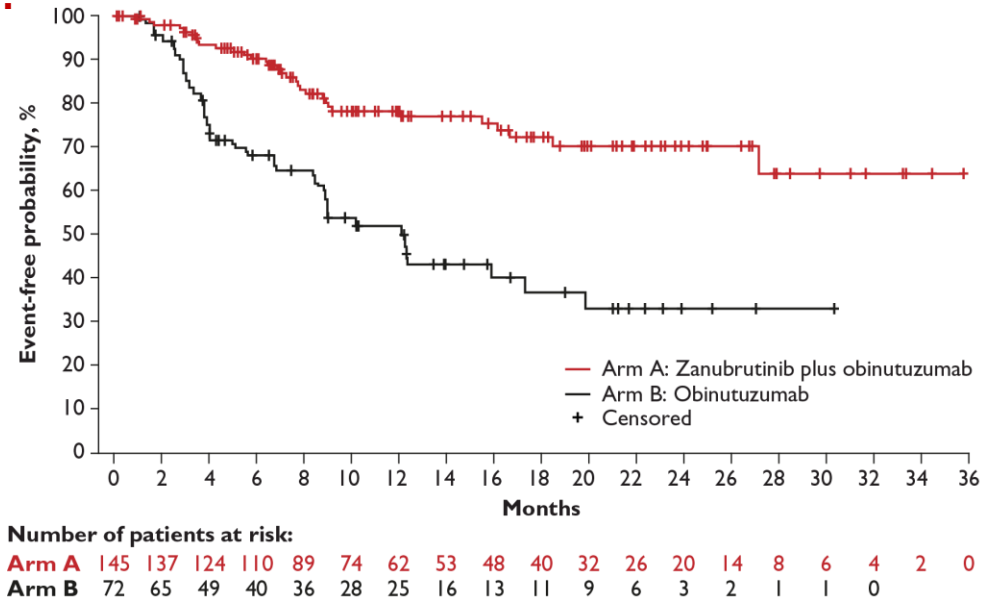
Median PFS (m):
27.4 Arm A vs
11.2 Arm B

Progression-Free Survival by ICR



Median TTNT (m):
NE (21.1, NE)
Arm A vs 12.1
(8.3, 19.8) Arm B

Time to Next Treatment



Zinzani PL, et al. *J Clin Oncol*. 2022;40(16):7510.

TABLE 3. Any Grade (>10% of patients) and Grade ≥3 (>5% of patients) TEAEs in the Safety Population

	ZO (n = 143)		O (n = 71)	
Adverse Event	Any Grade, No. (%)	Grade ≥3, No. (%)	Any Grade, No. (%)	Grade ≥3, No. (%)
≥1 TEAE	135 (94)	90 (63)	64 (90)	34 (48)
Thrombocytopenia[a]	51 (36)	22 (15)	17 (24)	5 (7)
Neutropenia[b]	42 (29)	35 (24)	20 (28)	16 (23)
Diarrhea	26 (18)	4 (3)	12 (17)	1 (1)
Fatigue	22 (15)	0 (0)	10 (14)	1 (1)
Constipation	19 (13)	0 (0)	6 (8)	0 (0)
Pyrexia	19 (13)	0 (0)	14 (20)	0 (0)
Cough	18 (13)	0 (0)	9 (13)	0 (0)
Pneumonia	17 (12)	14 (10)	5 (7)	3 (4)
Asthenia	17 (12)	1 (1)	6 (8)	0 (0)
Dyspnea	16 (11)	3 (2)	7 (10)	0 (0)
Back pain	15 (10)	1 (1)	4 (6)	1 (1)
Anemia	16 (11)	7 (5)	7 (10)	4 (6)
COVID-19	14 (10)	8 (6)	7 (10)	2 (3)

Abbreviations: O, obinutuzumab; TEAE, treatment-emergent adverse event; ZO, zanubrutinib plus obinutuzumab.
[a]Includes thrombocytopenia and platelet count decreased.
[b]Includes neutropenia and neutrophil count decrease.

Zinzani PL, et al. *J Clin Oncol*. 2023;41(33):5107-5117.

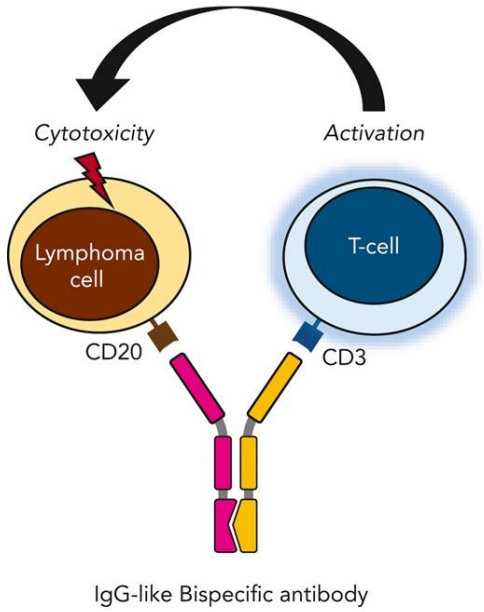
ROSEWOOD: Safety Data

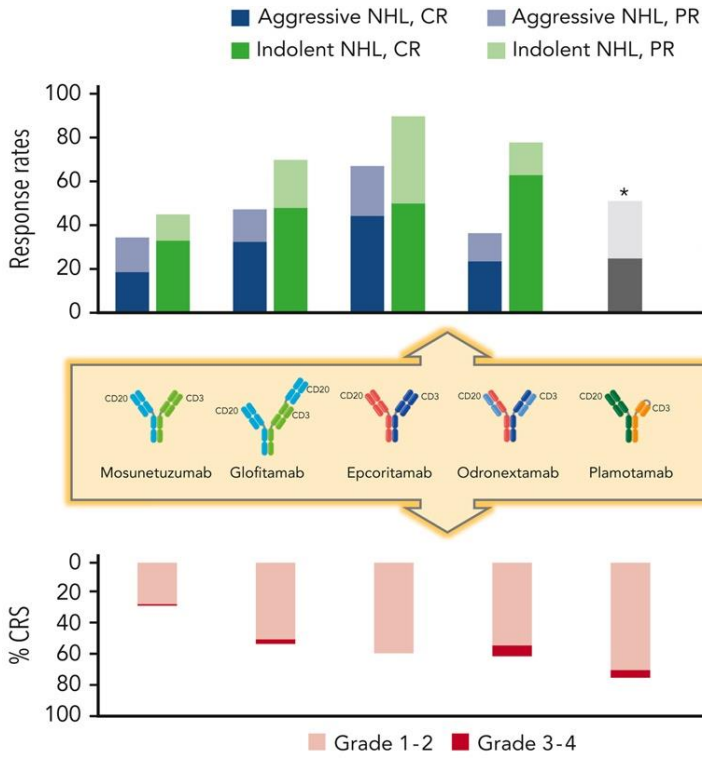
- TEAEs more common in ZO vs O
  - Petechiae (6.3% ZO vs 0% O)
  - Herpes zoster infection (6.3% ZO vs 0% O)

- TEAEs more common in O vs ZO
  - Pyrexia (19.7% O vs 13.3% ZO)
  - Infusion reactions (9.9% O vs 2.8% ZO)

Flowers C, et al. *J Clin Oncol*. 2023;41(16 Suppl):7545.

Bispecific Antibodies: Epcoritamab; Mosunetuzumab; Odronextamab*





Product name	Schematic depiction	Format	Technology	CD20:CD3 ratio	CD3 clone	CD20 clone	Fc silencing mutations*
Mosunetuzumab		IgG1	Knobs-into-holes (different Fabs)	1:1	UCHT1v9 (CD3δε)	2H7 (type 1 epitope, identical to rituximab)	N297G (no FcγR binding)
Epcoritamab		IgG1	Controlled Fab-arm exchange	1:1	huCACAO (SP34-der.) (CD3ε)	7D8 (type 1 epitope, shared by ofatumomab)	L234F,L235E,D265A (no FcγR,C1q binding)
Odronexamab		IgG4	Heavy chains with different affinity	1:1	REG1250 (CD3δε)	3B9-10 (type 1 epitope, shared by ofatumomab)	Modified IgG4 (no FcγRIII binding)

FDA-approved bispecific antibodies in 3rd-line FL

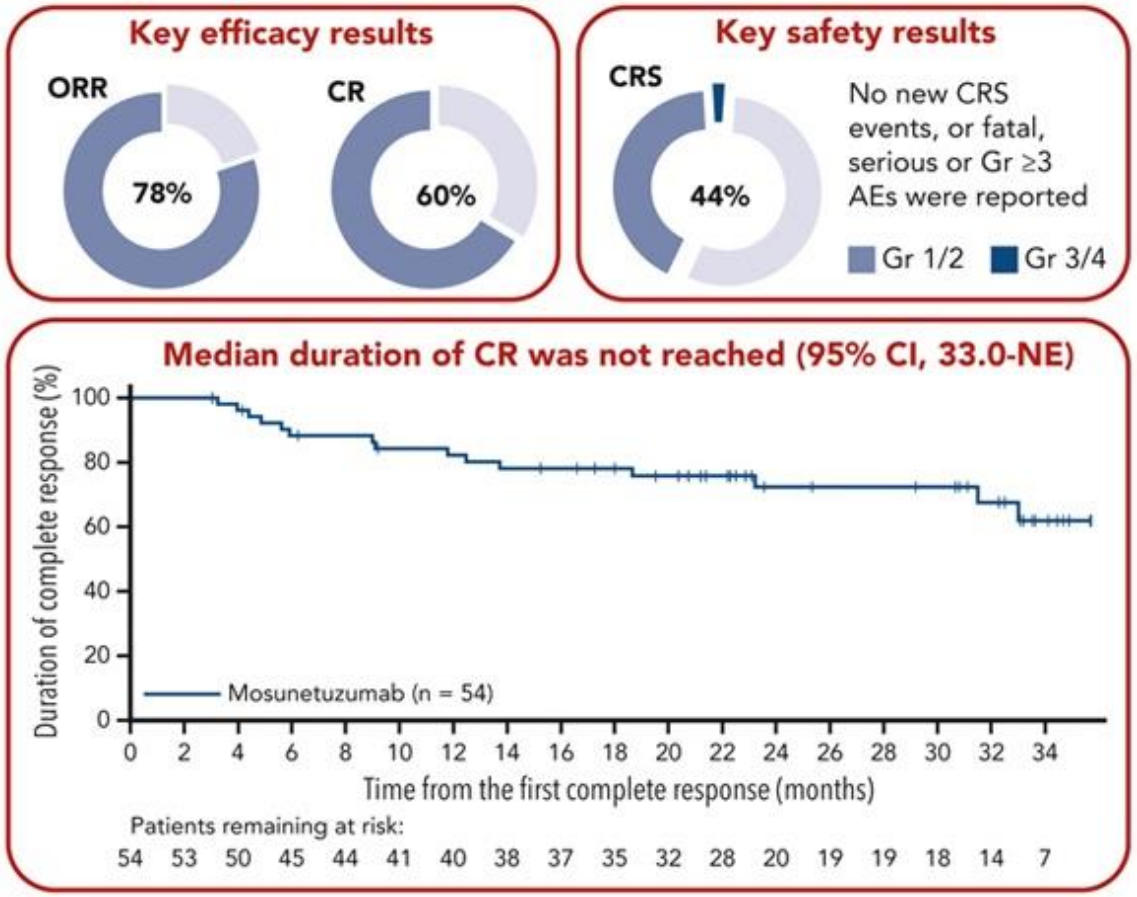
- Mosunetuzumab
- Epcoritamab

***Odronoextamab – EMA-approved; not FDA-approved.**

Falchi L, et al. *Blood*. 2023;141(5):467-480.

Mosunetuzumab

- FDA-approved for use in R/R FL after ≥2 prior therapies
- Phase 2 study – 3 years of follow-up demonstrate
  - High response rates: ORR 77.8%, CR 60%
  - Durable responses: median (DOR) 35.9 months
  - Manageable safety profile; no grade ≥3 CRS or ICANS
    - Low rates of discontinuation



CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome.

Sehn LH, et al. *Blood*. 2025;145(7):708-719.

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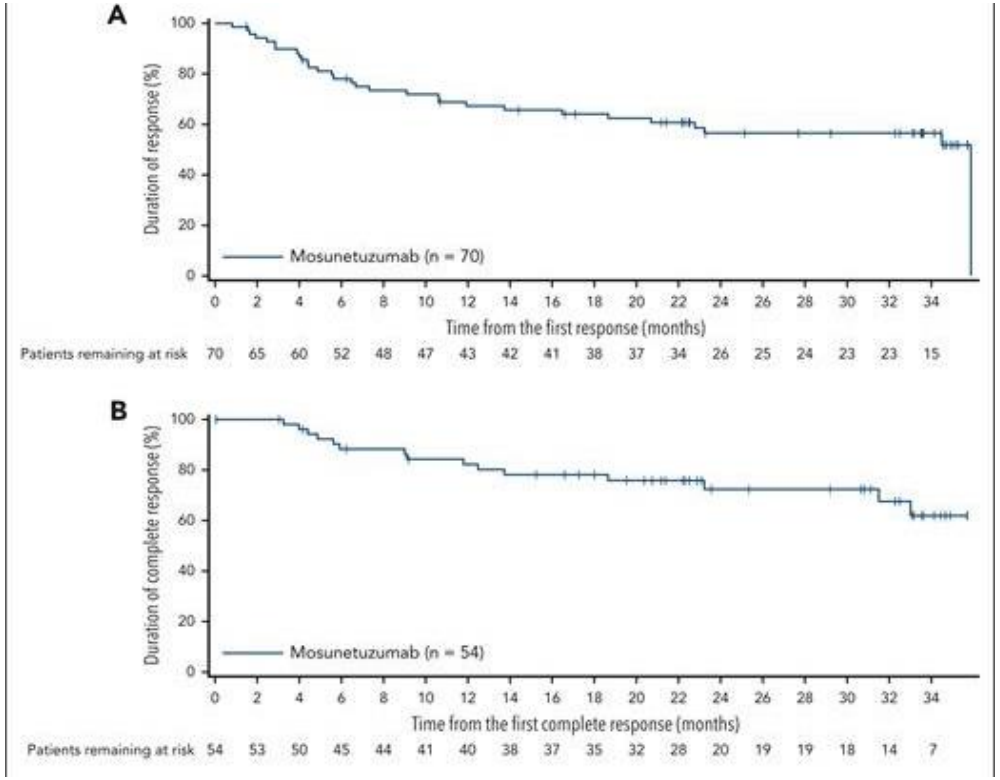
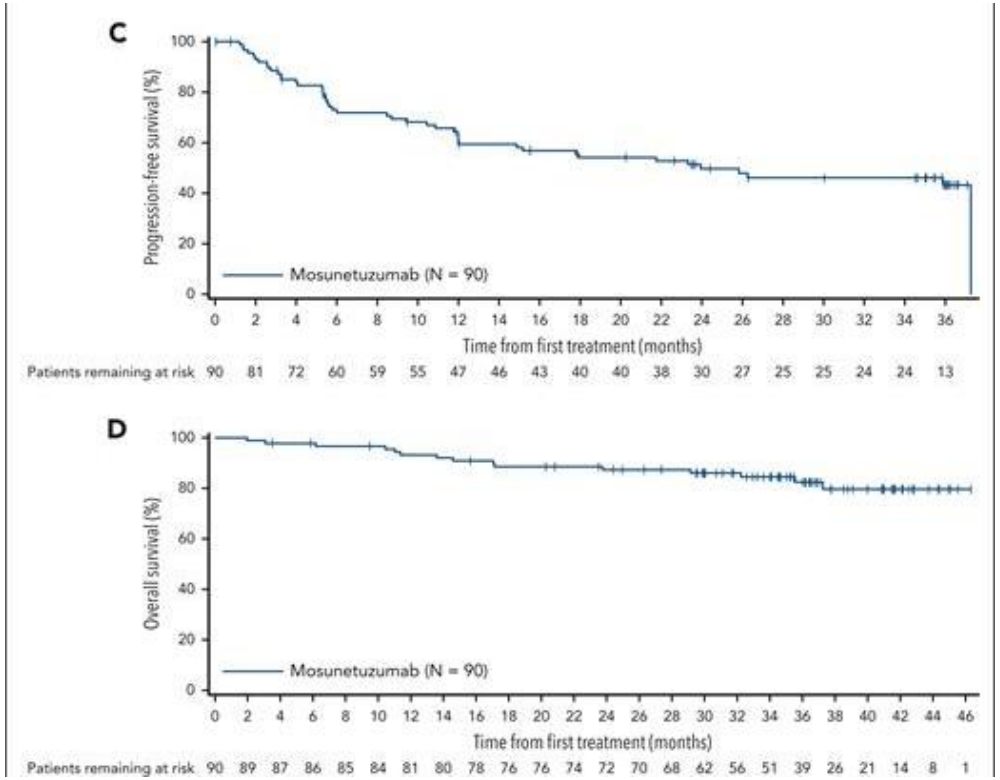
Mosunetuzumab DOR, PFS, OS





A: Median DOR – 39.4 m
B: Median DOR (CRs) – NR

C: Median PFS – 24 m
B: Median OS – NR

Sehn LH, et al. *Blood*. 2025;145(7):708-719.

Mosunetuzumab

- Off-the-shelf, fixed-duration treatment, administered in outpatient setting; IV infusion
  - Cycle 1: weekly (1 mg, 2 mg, 60 mg)
  - Cycle 2: 60 mg q21d
  - Cycle 3+: 30 mg q21d

- Premedications recommended: corticosteroid (C1-2; 3+ if prior CRS) + antihistamine + acetaminophen

- Patients achieving CR by C8 discontinue mosunetuzumab; patients with PR or SD continue up to 9 further cycles (17 cycles in total)
  - 5 patients received mosunetuzumab retreatment after disease relapse after CR
    - 3 achieved a second CR, 2 had stable disease as best response
    - 2 of 3 remained in CR, with ongoing responses at 20.6 and 8.8 months after initiation of retreatment, respectively; the third patient progressed 7.7 months after achieving a second CR
- Median time to recovery of CD19+ B-cells (to lower level of normal) 25.1 months from completion of C8

Sehn LH, et al. *Blood*. 2025;145(7):708-719.

Epcoritamab

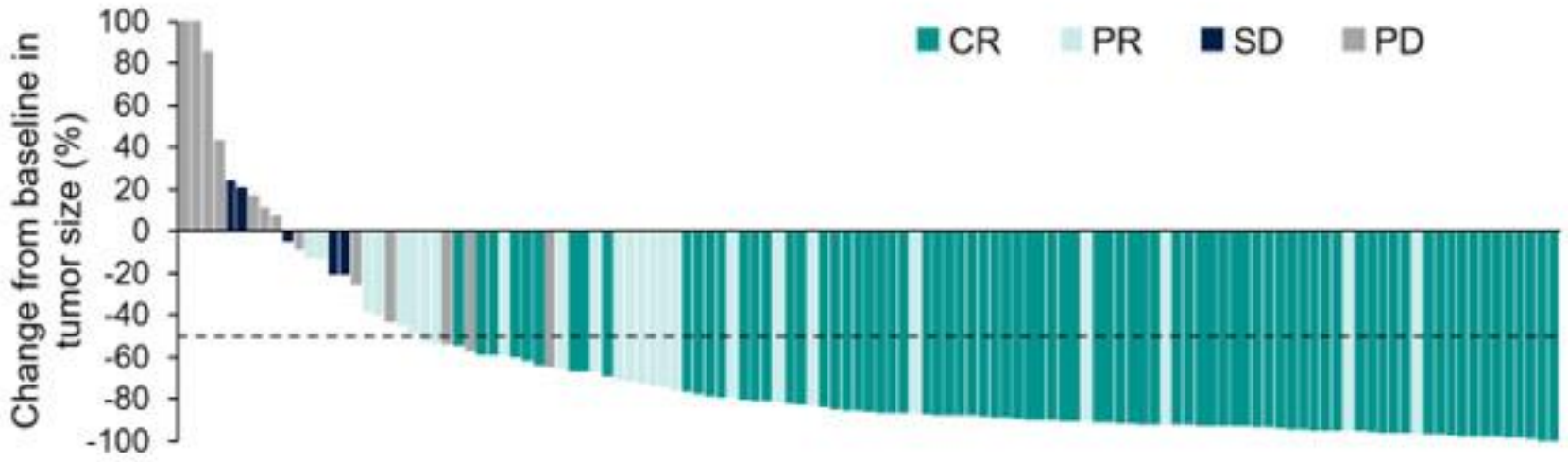
- FDA-approved for use in R/R FL after ≥2 prior systemic therapies

- Phase 2 study – 17.4 months of follow-up demonstrate
  - High response rates: ORR was 82% (95% CI: 74.1, 88.2), 62.5% CR
  - Durable responses: median DOR was not reached (95% CI: 13.7, NR)
  - 12-month DOR 68.4% (95% CI: 57.6%, 77.0%)

Linton K, et al. *Lancet Haematol*. 2024;11(8):e593-e605.

EPCORE 1

Figure. Antitumor activity



Two patients had a change from baseline in tumor size of >100%. Seven patients were not evaluable for change from baseline in tumor size.

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

ORR = 82%
CR = 63%

mPFS = 15.4 months
mDOR = NR
mOS = NR

Linton K, et al. *Blood*. 2023;142(Suppl 1):1655.

Epcoritamab

- Off-the-shelf, administered in outpatient setting, treat until progression; subQ dosing
  - Cycle 1-3: weekly (3 step-up doses)
  - Cycle 4-9: q2 weeks
  - Cycle 10+: q4 weeks until progression / unacceptable toxicity
- Premedications recommended: corticosteroid (C1; 2+ if prior CRS) + antihistamine + acetaminophen
- Manageable safety profile; low rates of discontinuation
  - In optimization cohort, a third step-up dose was included: 0.16 mg, 0.8 mg, 3 mg, 48 mg
  - CRS reported in 49% (42 of 86 pts)
    - 40% (34 pts) grade 1; 9% (8 pts) grade 2; 0 grade ≥3
    - 0 ICANS

Linton KM, et al. *Lancet Haematol*. 2024;11(8):e593-e605.

Odronextamab

- EMA-approved for use in R/R FL after ≥2 prior systemic therapies

- Phase 1 ELM-1 trial – 20.1 months of follow-up demonstrate
  - High response rates in FL: ORR was 91% (95% CI: 75, 98), 72% CR
  - Durable responses: median DOR 22.6 months
  - In POD24: ORR 81%, CR 73%

Kim TM, et al. *Ann Oncol*. 2024;35(11):1039-1047.

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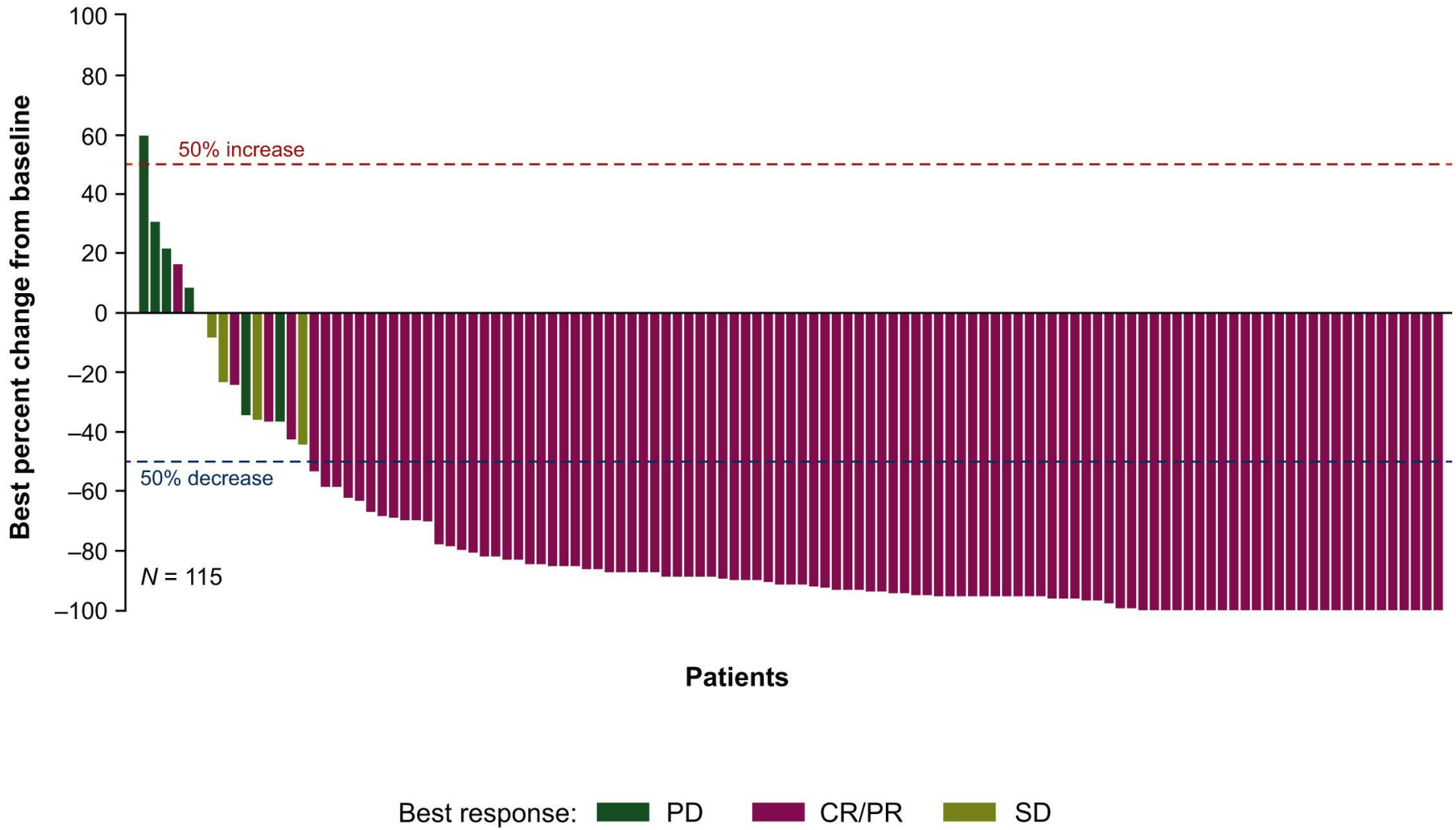
ELM-1



Kim TM, et al. *Ann Oncol*. 2024;35(11):1039-1047.

Odronextamab

- Off-the-shelf, treat until progression; IV dosing; study required hospitalization during step-up dosing, however, EMA label does not require (only if grade ≥2 CRS/ICANS)
- Premedications recommended: corticosteroid (throughout step-up dosing and continue until dose tolerated w/o CRS/ICANs) + antihistamine + acetaminophen
- Manageable safety profile; CRS in 56.3%, mainly low-grade
  - 1 pt w/ grade 3 CRS
  - 1 pt w/ grade 2 ICANS (grade 2)

Kim TM, et al. *Ann Oncol*. 2024;35(11):1039-1047.

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CRS and ICANS

	Epcoritamab	Mosunetuzumab	Odronextamab
Trial	EPCORE-NHL-1	Budde, et al (2022)	ELM-1
CRS (all gr)	49%; 88% of CRS during C1; 50% of CRS on C1D22 (second full dose)	44%; 33% of pts on C1D15 (first full dose); 15% of pts on C1D1 (first dose)	56%; 97% prior to second full dose
CRS (gr ≥3)	0%	2%	1 grade 3 event
ICANS (all gr)	0%	5%	1 grade 2 event
ICANS (gr ≥3)	0%	0%	0%

Linton K, et al. *Lancet Haematol*. 2024;11(8):e593-e605. Budde LE, et al. *Lancet Oncol*. 2022;23(8):1055-1065. Schuster SJ, et al. Presented at: ASH Annual Meeting; December 9-12, 2023; San Diego, CA. Kim TM, et al. *Ann Oncol*. 2024;35(11):1039-1047.

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Bispecific Antibody Combinations in FL under Investigation

- Epcoritamab + tazemetostat (NCT06575686)
- Epcoritamab + ibrutinib (NCT06536049)
- Epcoritamab + lenalidomide (NCT06112847; NCT05660967)
- Epcoritamab + rituximab (NCT05783609)
- Epcoritamab + rituximab + lenalidomide (NCT05409066)

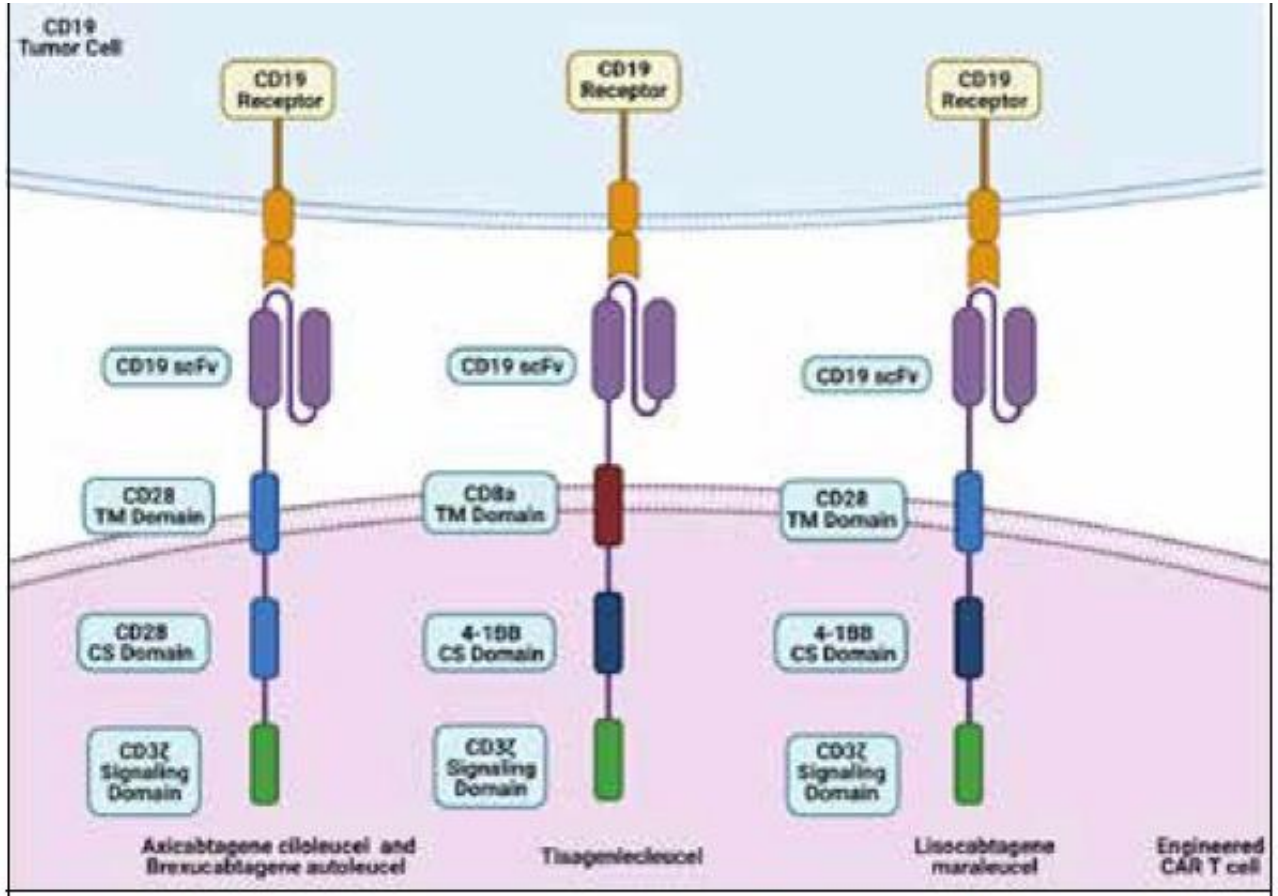
- Mosunetuzmab + lenalidomide (NCT04712097)
- Mosunetuzumab + polatuzumab (NCT06453044)
- Mosunetuzmab + loncastuximab tesirine (NCT05672251)

- Odronextamab + lenalidomide (NCT06149286)

ClinicalTrials.gov. Accessed October 9, 2025. https://www.clinicaltrials.gov.

CAR-T in FL

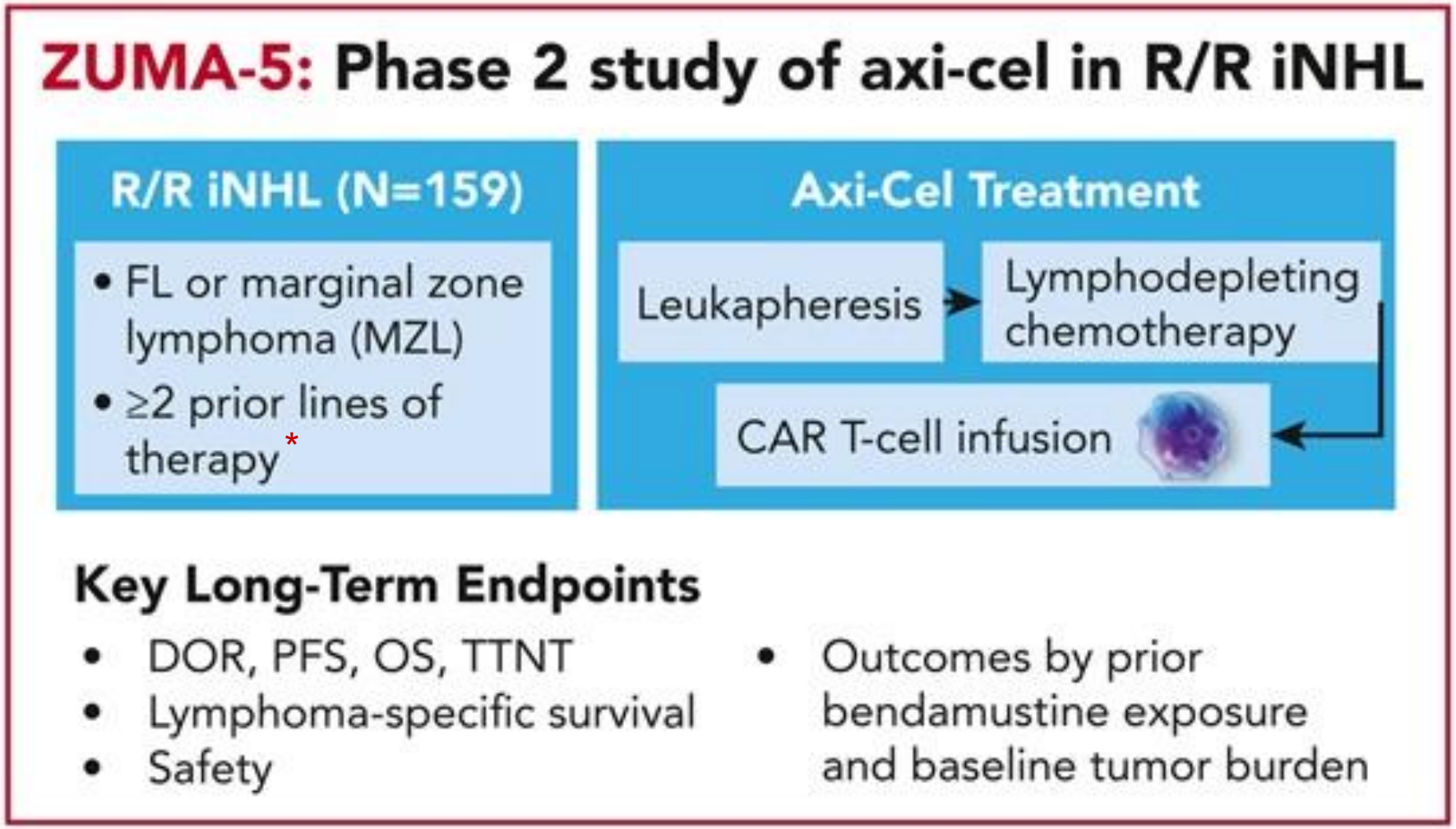
- Axi-cel – ZUMA-5
- Tisa-cel – ELARA
- Liso-cel – TRANSCEND



CAR indicates chimeric antigen receptor; CS, co-stimulatory; NHL, non-Hodgkin lymphoma; scFv, single-chain variable fragment; TM, transmembrane.

Wells DA, et al. *J Hematol Oncol Pharm*. 2022;12(1):30-42.

Axi-cel

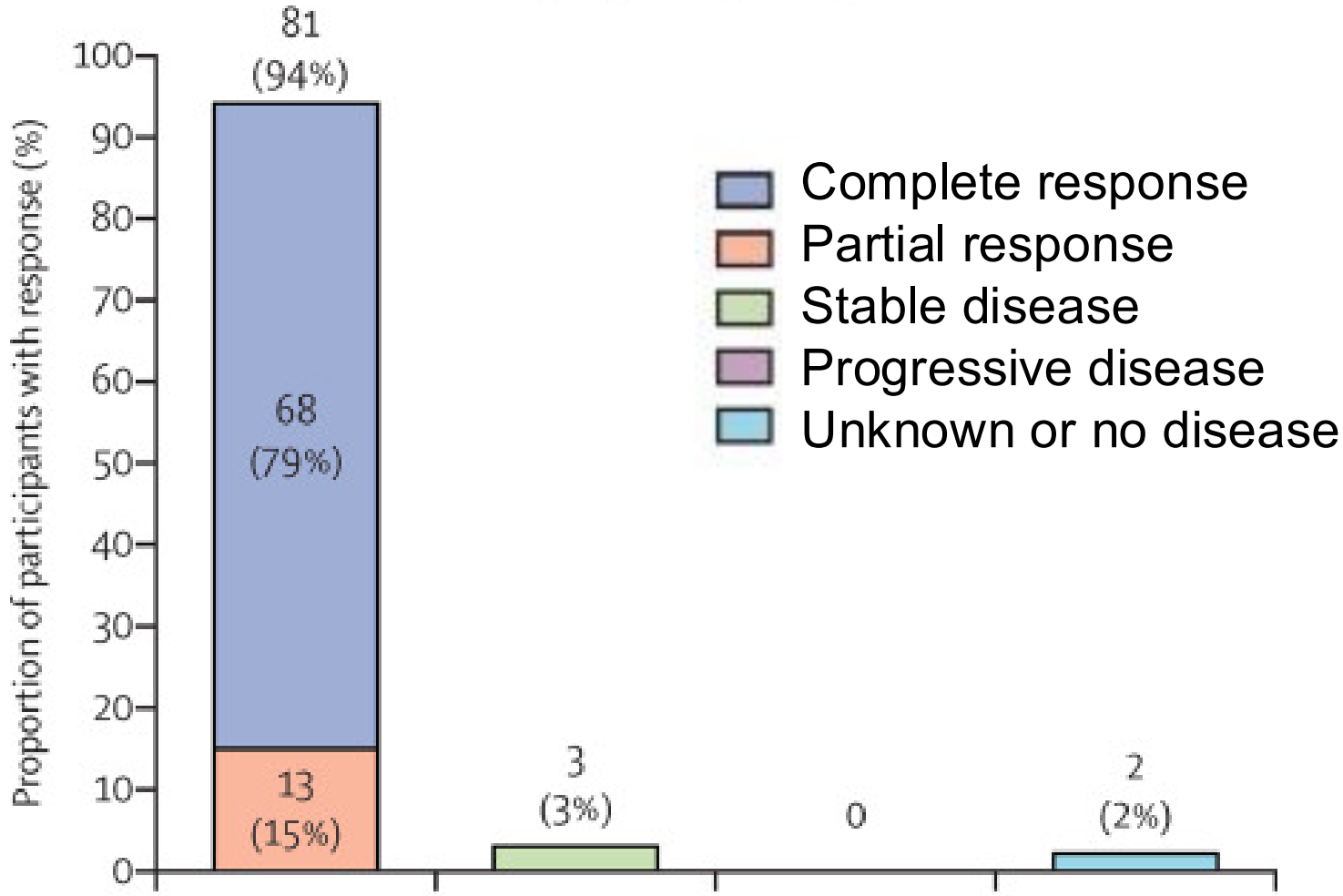


Including anti-CD20 mAb + alkylator

3% of patients received bridging chemotherapy

Wells DA, et al. *J Hematol Oncol Pharm*. 2022;12(1):30-42. Neelapu SS, et al. *Blood*. 2024;143(6):496-506.

94% of Pts with Relapsed FL Responded to Axi-cel



mDOR: 55.5 m

mDOCR: 60.4 m (FL/MZL)

Jacobson CA, et al. *Lancet Oncol*. 2022;23(1):91-103. Neelapu SS, et al. Presented at: ASH Annual Meeting; December 9-12, 2023; San Diego, CA. Neelapu SS, et al. *Blood*. 2024;143(6):496-506.

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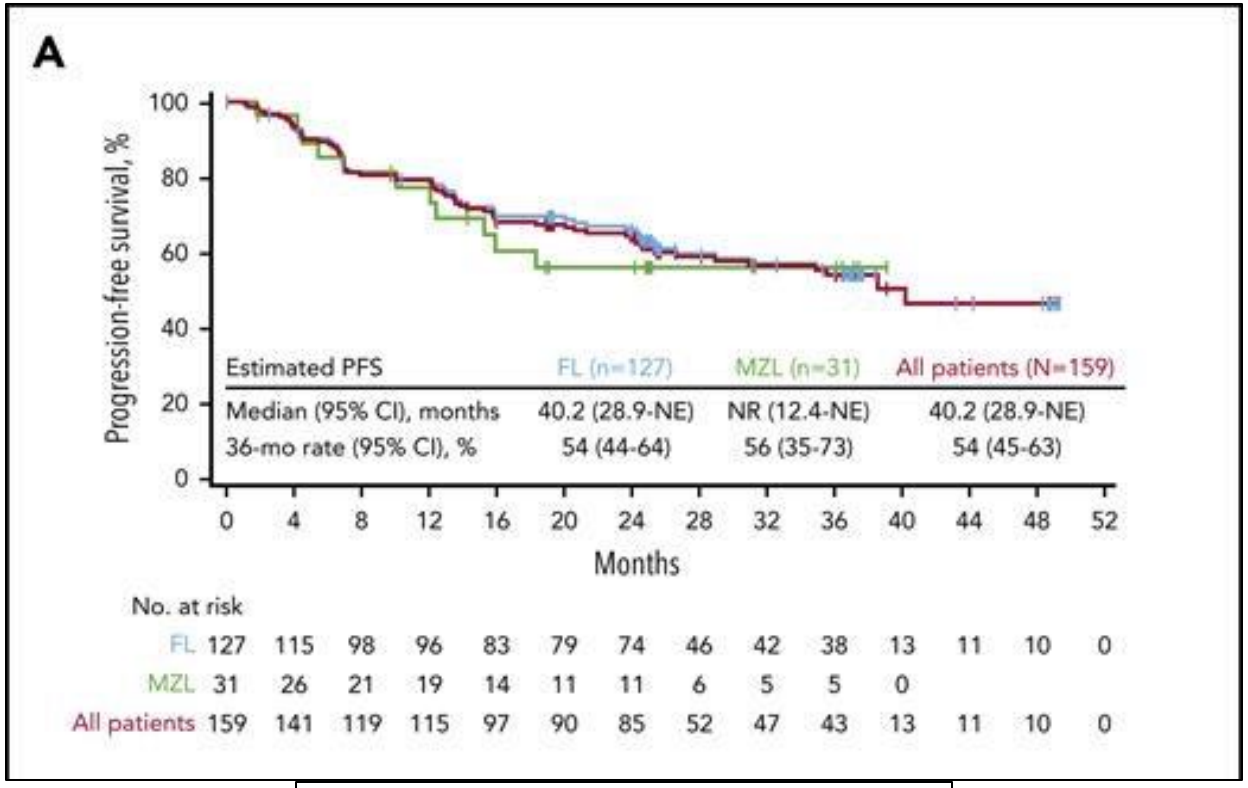
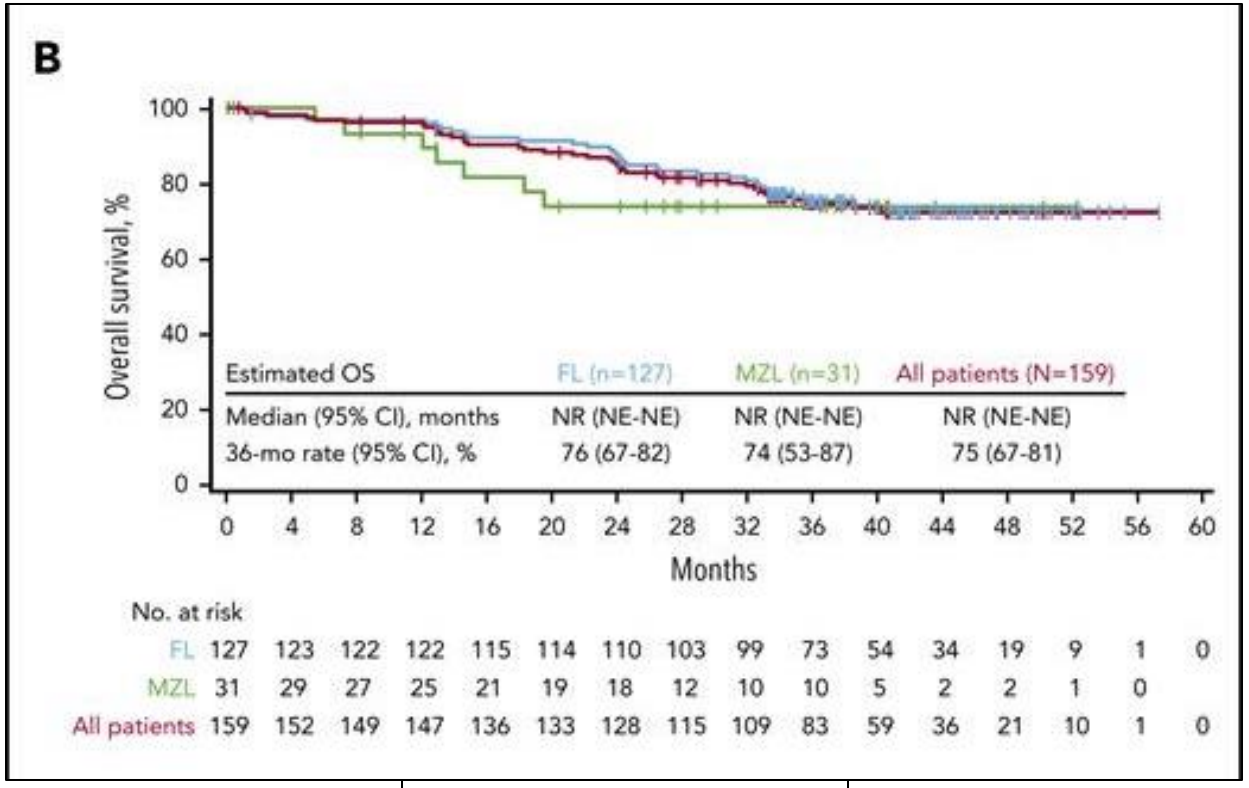
Responses to Axi-cel in Relapsed FL Are Durable



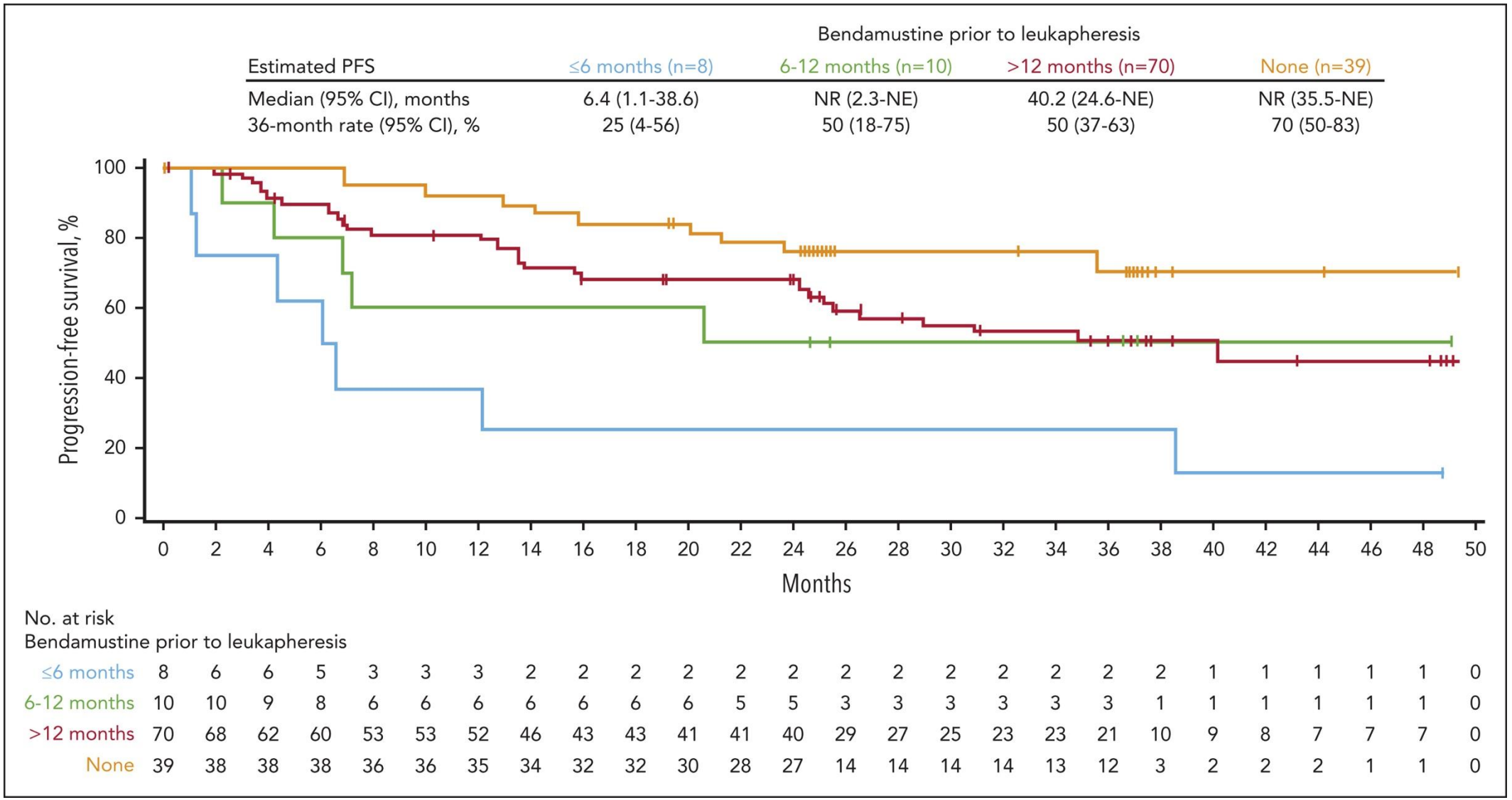


mPFS: 40.2 m
w/o POD 24: NR
w/ POD 24: 40.2 m
36 m PFS: 54%

mOS: NR
3y OS: 76%
4y OS: 72%

Jacobson CA, et al. *Lancet Oncol*. 2022;23(1):91-103. Neelapu SS, et al. Presented at: ASH Annual Meeting; December 9-12, 2023; San Diego, CA. Neelapu SS, et al. *Blood*. 2024;143(6):496-506.

PFS of Patients with FL Based on the Time Point of Bendamustine Use before Axi-cel Infusion



Neelapu SS, et al. *Blood*. 2024;143(6):496-506.

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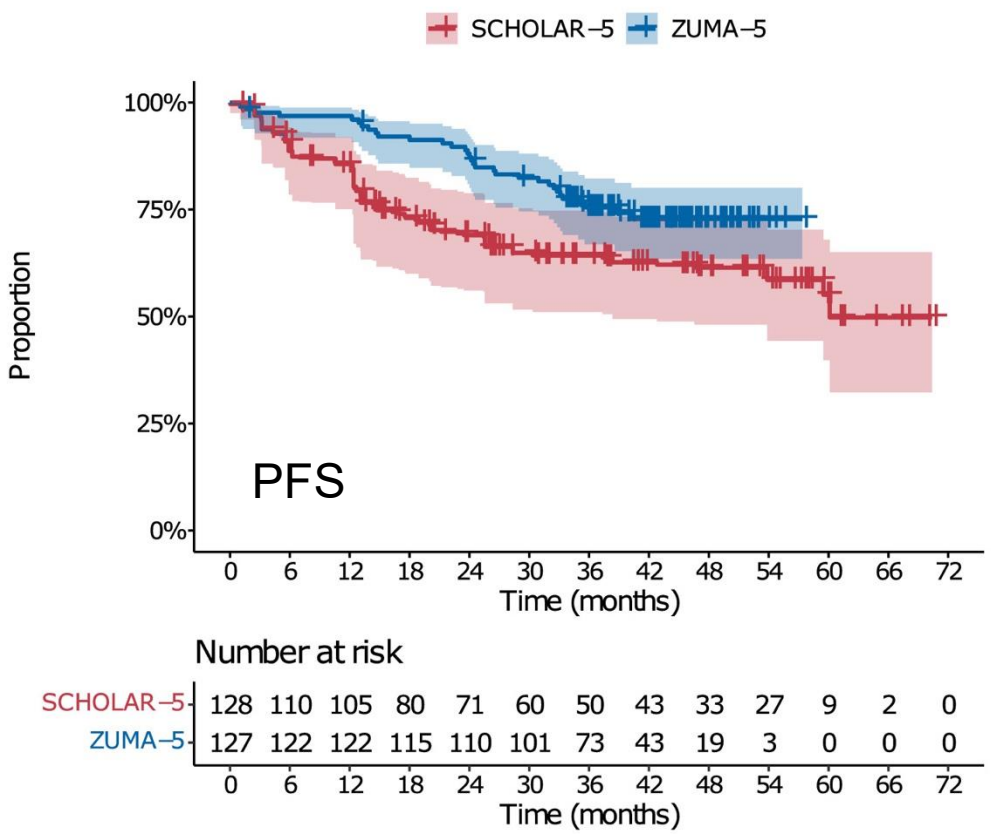
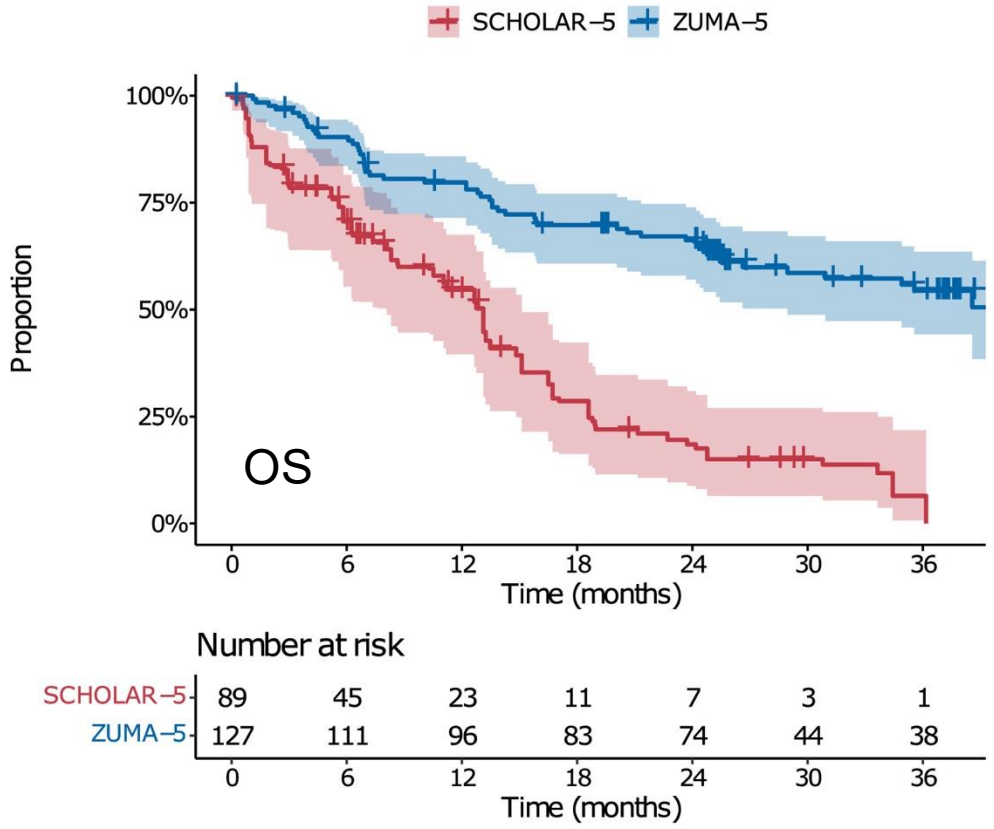
Axi-cel Has Improved PFS and OS Compared to Control





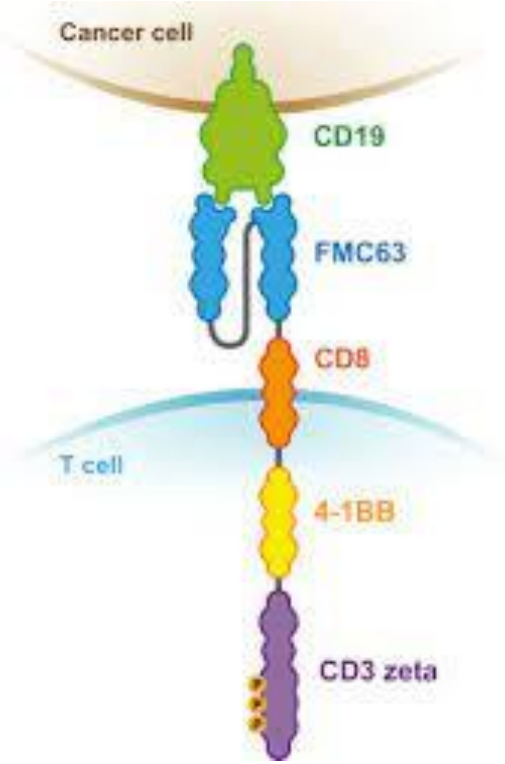
% pts with POD24: ZUMA-5: 57%; SCHOLAR-5: 56%

Ghione P, et al. *Blood*. 2022;140(8):851-860. Palomba ML, et al. *Expert Rev Anticancer Ther*. 2023;23(2):199-206.
Ghione P, et al. *Clin Lymphoma Myeloma Leuk*. 2024;24(5):e191-e195.e6.

Tisa-cel: ELARA

- Pts w/ R/R FL, meeting one or more of the following
  - Refractory to or relapsed <6 months after completion of 2L+ therapy
    - Must have received prior anti-CD20 mAb + alkylating agent
  - Relapsed during anti-CD20 maintenance following completion of 2L+ therapy
  - Relapsed after autologous HCT

FL pts enrolled = 127
FL pts with POD24 = 61 (63%)



Fowler NH, et al. *Nat Med*. 2022;28(2):325-332. Dreyling M, et al. *Blood*. 2024;143(17):1713-1725.

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Tisa-cel

BACKGROUND. The primary analysis of the Phase II ELARA trial (NCT03568461, median follow-up of 17 months) showed:

86%
Overall response rate (ORR)

69%
Complete response rate (CRR)

67%
12-mo progression-free survival rate

With a median follow-up of 29 months, high response rates were confirmed in patients with high-risk disease:

	ORR	CRR
POD24	82%	59%
High TMTV	75%	40%
Bulky Disease	86%	65%
High FLIPI	81%	61%
Double Refractory	85%	66%

POD24, progression of disease within 24 months from 1st immunochemotherapy TMTV, total metabolic tumor volume

45% of patients received bridging chemotherapy

Fowler NH, et al. *Nat Med*. 2022;28(2):325-332. Dreyling M, et al. *Blood*. 2024;143(17):1713-1725.

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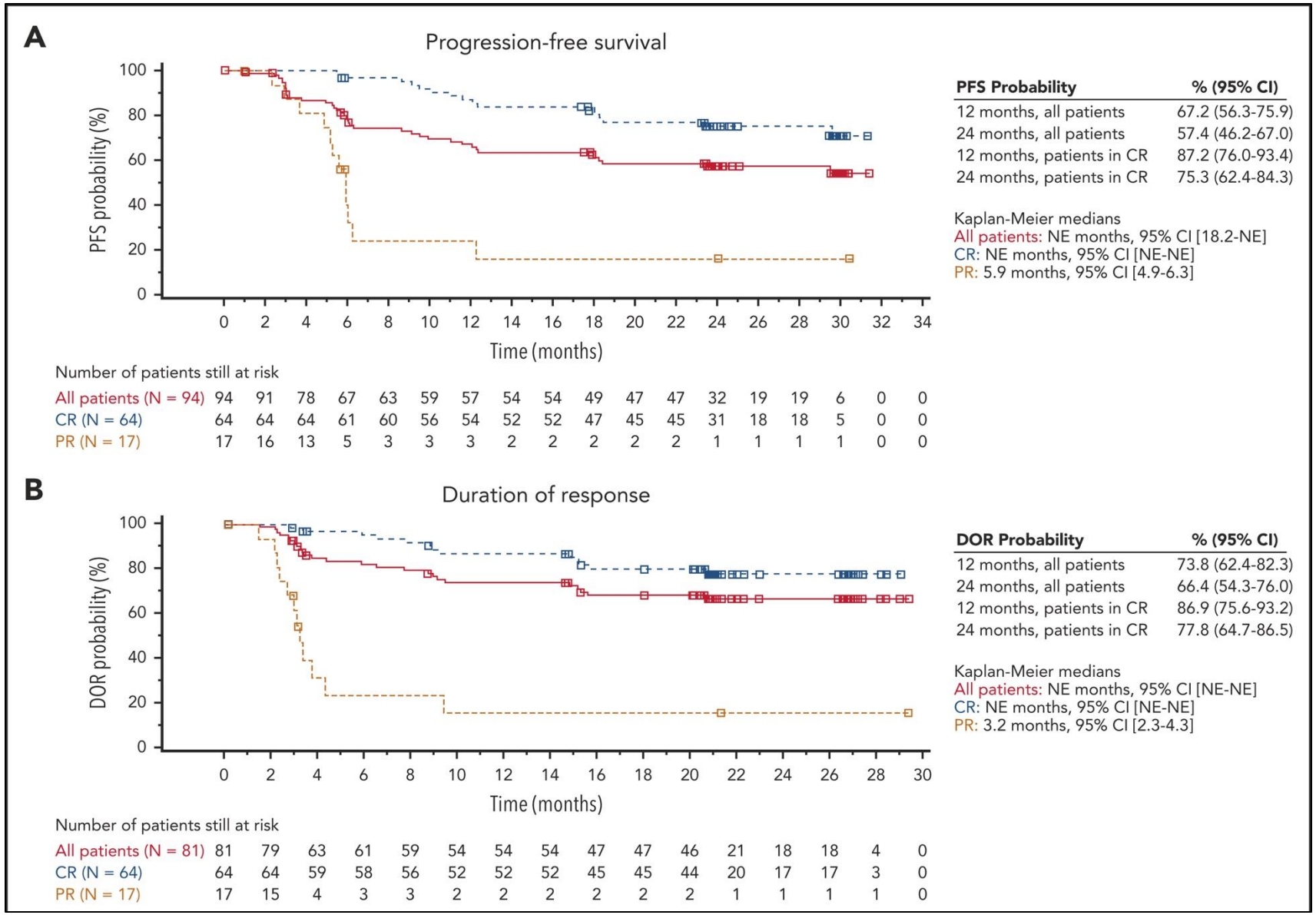
Responses to Tisa-cel Are Durable

24 m PFS: 57%



Fowler NH, et al. *Nat Med*. 2022;28(2):325-332. Dreyling M, et al. *Blood*. 2024;143(17):1713-1725.

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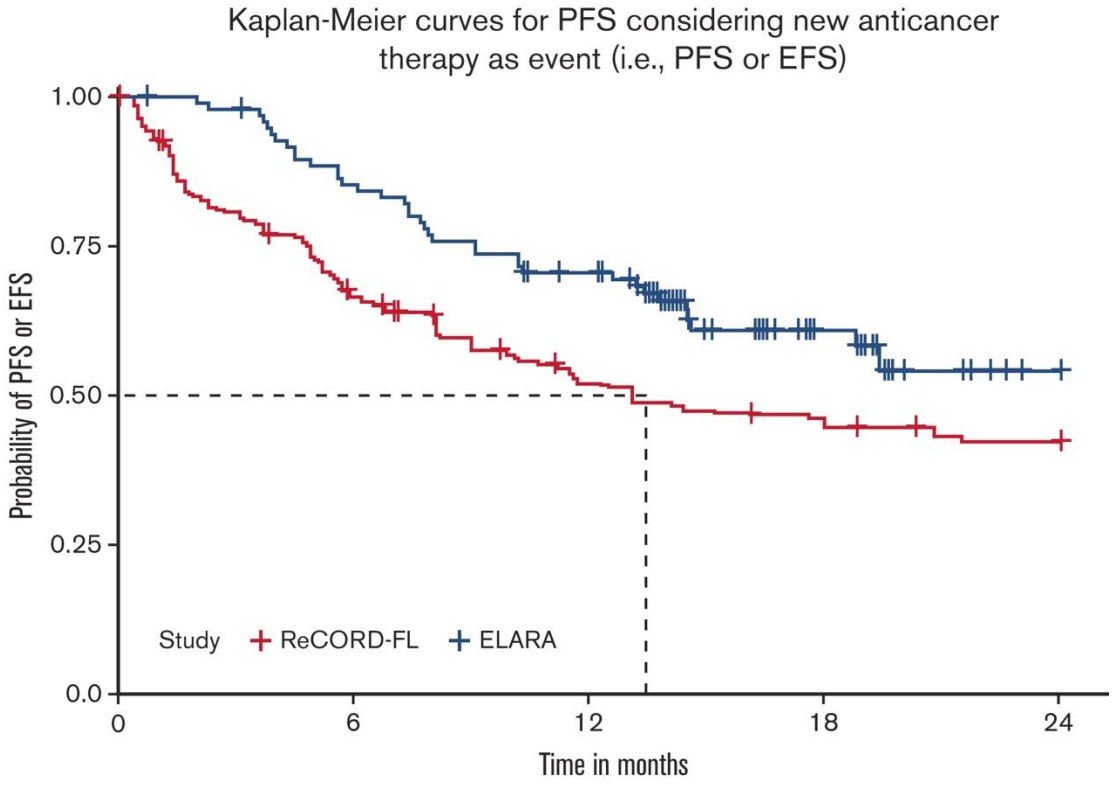
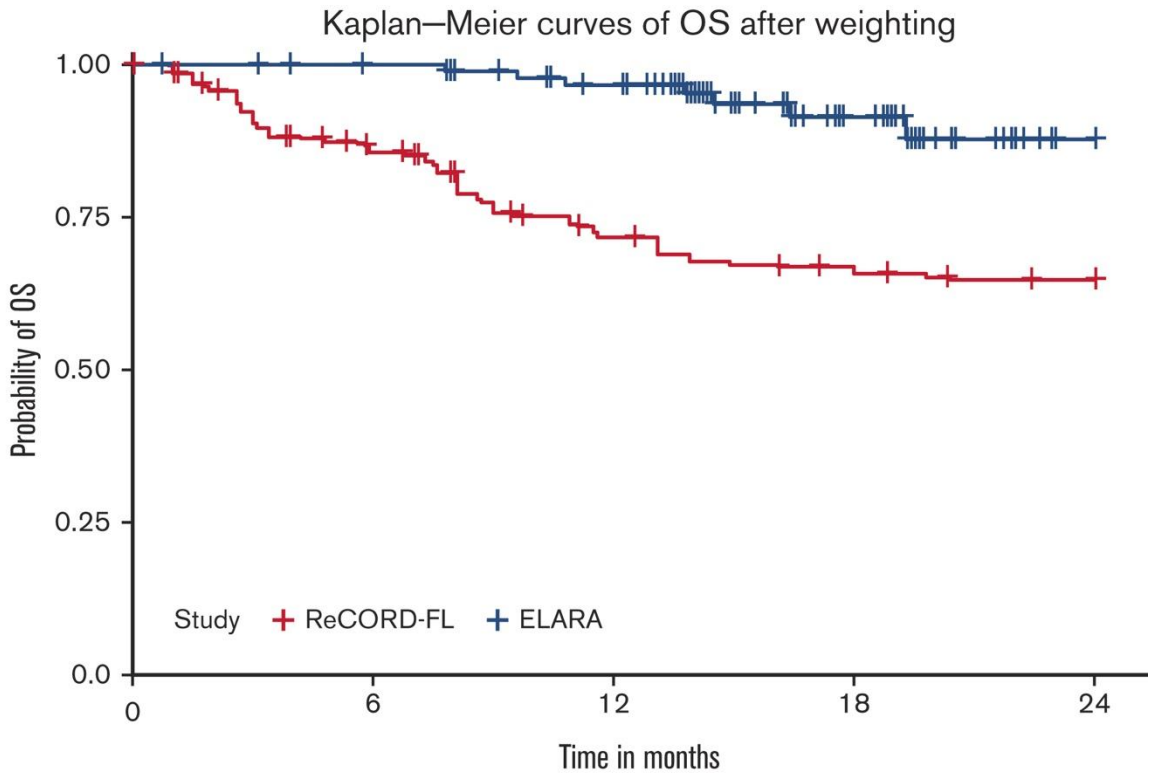
Tisa-cel Has Improved PFS and OS Compared to Control



Number at risk					
ReCORD-FL	99	64	46	40	35
ELARA	97	81	64	23	1



Number at risk					
ReCORD-FL	99	79	60	54	50
ELARA	97	93	83	34	2

% pts with POD24

- ELARA: 63%
- ReCORD-FL: 60%

Salles G, et al. *Blood Adv*. 2022;6(22):5835-5843.

Liso-cel (TRANSCEND FL)

- Patients with R/R FL treated in ~10 countries with liso-cel; N=130
- ≥2 lines of prior therapy including anti-CD20 mAb + alkylating agent OR ≥1 line of prior therapy if POD24 and/or ≥1 mGELF criteria met
- Bridging therapy received by 49 (38%) patients

	3L+ FL (n=107)	2L FL (n=23)	2L+ FL (n=130)
Median age (range), years	62 (23–80)	53 (34–69)	60 (23–80)
Male sex (biological attribute), *n* (%)	66 (62)	17 (74)	83 (64)
Primary race, *n* (%)			
Asian	10 (9)	2 (9)	12 (9)
Black or African American	3 (3)	1 (4)	4 (3)
White	60 (56)	9 (39)	69 (53)
Not collected or unknown[b]	34 (32)	11 (48)	45 (35)
ECOG PS at screening, *n* (%)			
0	65 (61)	17 (74)	82 (63)
1	42 (39)	6 (26)	48 (37)
FL subtype/grade at screening, *n* (%)			
Grade 1/2	81 (76)	17 (74)	98 (75)
Grade 3A	25 (23)	6 (26)	31 (24)
Unknown	1 (1)	0	1 (1)
Ann Arbor stage at screening, *n* (%)			
Stage I/II	12 (11)	6 (26)	18 (14)
Stage III	39 (36)	6 (26)	45 (35)
Stage IV	56 (52)	11 (48)	67 (52)
FLIPI at screening, *n* (%)			
Low risk (0–1)	12 (11)	11 (48)	23 (18)
Intermediate risk (2)	34 (32)	4 (17)	38 (29)
High risk (3–5)	61 (57)	8 (35)	69 (53)
SPD ≥50 cm^2 before LDC per IRC, *n* (%)	22 (21)	3 (13)	25 (19)
LDH>ULN before LDC, *n* (%)	47 (44)	6 (26)	53 (41)
mGELF criteria met at time of most recent relapse, *n* (%)	57 (53)	16 (70)	73 (56)

	3L+ FL (n=107)	2L FL (n=23)	2L+ FL (n=130)
Median prior lines of systemic therapy (range)	3 (2–10)	1 (1–1)	2 (1–10)
Prior HSCT[c], *n* (%)	33 (31)	0	33 (25)
Received prior rituximab and lenalidomide, *n* (%)	23 (21)	0	23 (18)
Prior bendamustine, *n* (%)			
No prior bendamustine	42 (39)	17 (74)	59 (45)
Prior bendamustine ≤6 months before leukapheresis	4 (4)	1 (4)	5 (4)
Prior bendamustine >6 months and ≤12 months before leukapheresis	4 (4)	2 (9)	6 (5)
Prior bendamustine >12 months before leukapheresis	57 (53)	3 (13)	60 (46)
Refractory to systemic therapy[d], *n* (%)	38 (36)	3 (13)	41 (32)
PD while on the last LOT or ≤6 months of completing the last LOT, *n* (%)	69 (64)	15 (65)	84 (65)
POD24 from diagnosis[e], *n* (%)	46 (43)	12 (52)	58 (45)
FL progression ≤24 months of first-line therapy with anti-CD20 antibody and alkylator, *n* (%)	58 (54)	15 (65)	73 (56)
Double refractory (anti-CD20 + alkylator)[f], *n* (%)	69 (64)	11 (48)	80 (62)
Median time-to-event analyses (range)			
Diagnosis to first PD, years	2.0 (0.25–16.5)	1.8 (0.5–11.2)	2.0 (0.25–16.5)
Initial treatment to first PD, years	1.5 (0.1–8.8)	1.4 (0.3–11.1)	1.5 (0.1–11.1)
Completion of last LOT to SD or PD[g], years	0.15 (0–9.6)	0.3 (0–8.8)	0.15 (0–9.6)
Diagnosis to liso-cel infusion, years	5.1 (0.7–35.3)	2.0 (0.8–11.4)	4.7 (0.7–35.3)
Most recent relapse to liso-cel infusion, years	0.4 (0–3.2)	0.3 (0.1–1.3)	0.3 (0–3.2)

Morschhauser F, et al. *Nat Med*. 2024;30(8):2199-2207.

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TRANSCEND FL: Initial Results

- 124 pts evaluable for efficacy
- 130 pts evaluable for safety

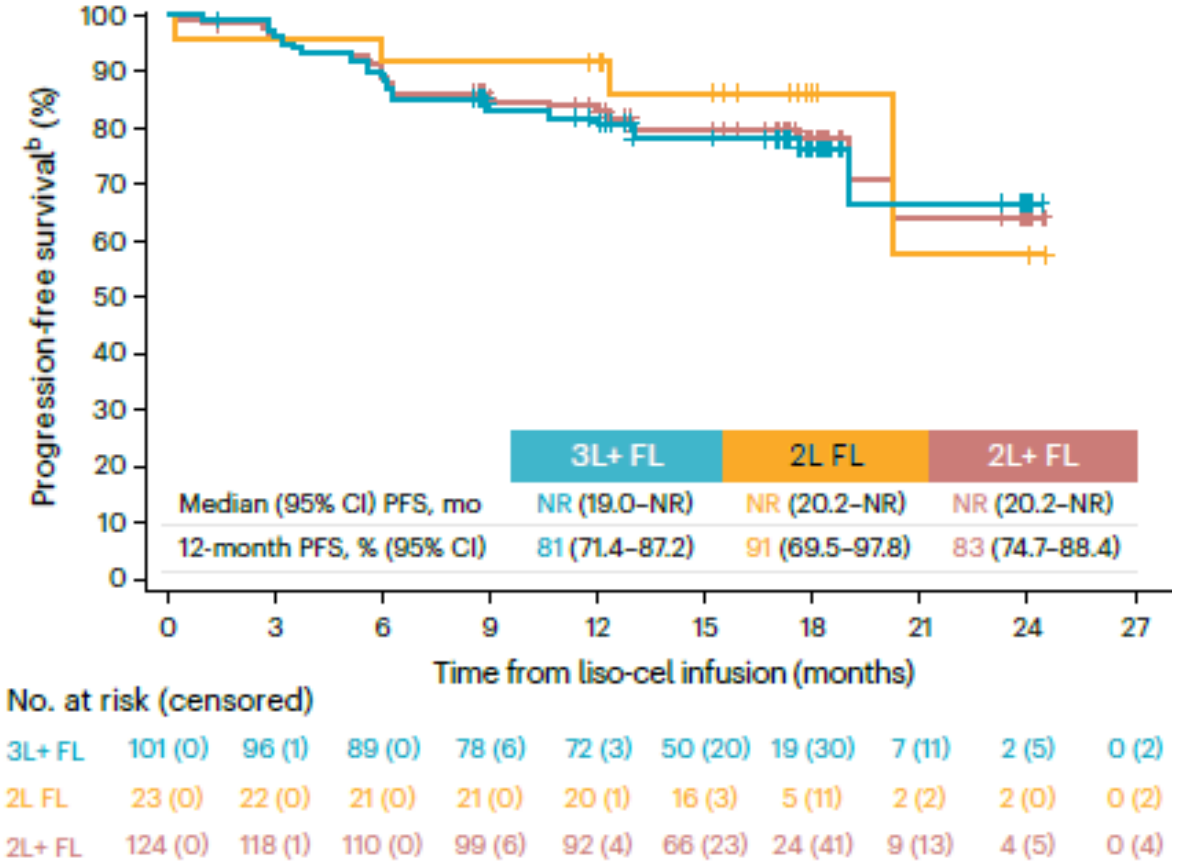
	ORR	CR rate
3L+ FL (n = 101)	97% (95% CI: 91.6–99.4) $P < 0.0001$[a]	94% (95% CI: 87.5–97.8) $P < 0.0001$[a]
2L FL (n = 23)	96% (95% CI: 78.1–99.9) $P < 0.0001$[b]	96% (95% CI: 78.1–99.9) $P < 0.0001$[b]
2L+ FL (n = 124)	97% (95% CI: 91.9–99.1)[c]	94% (95% CI: 88.7–97.7)[c]

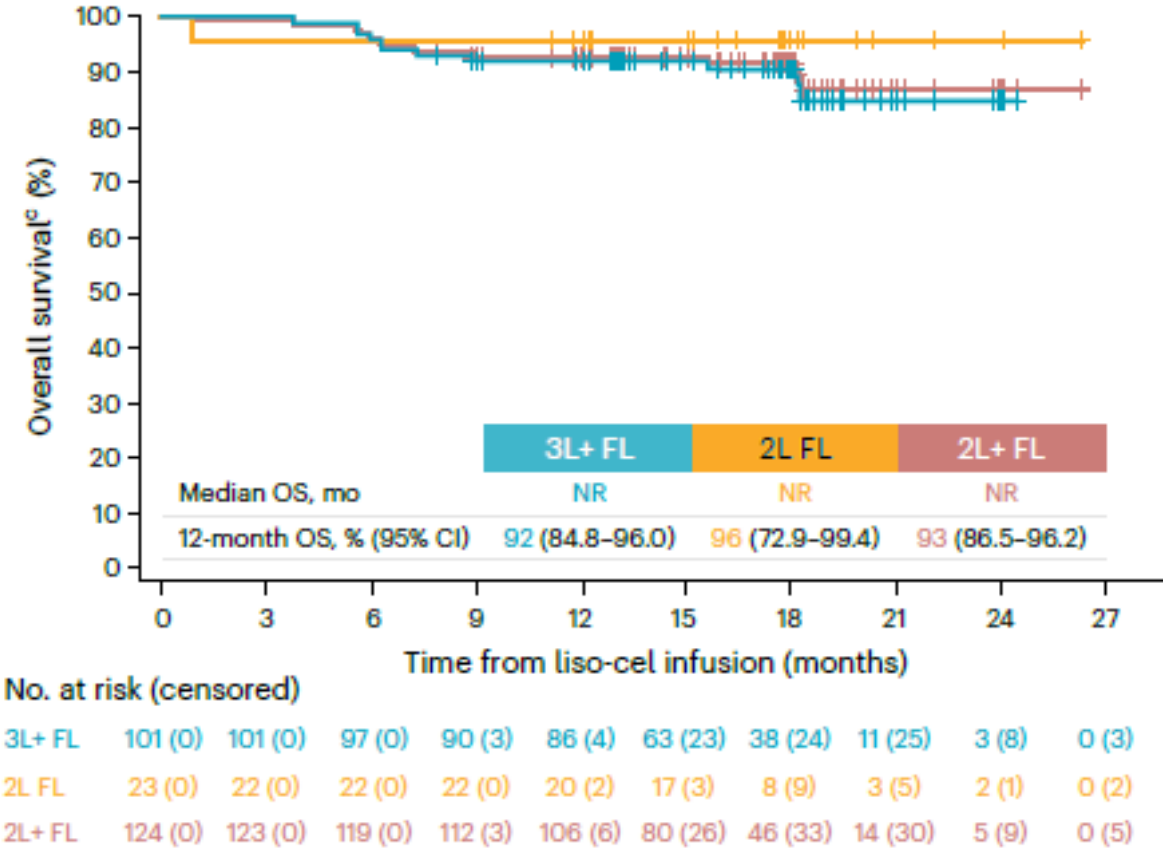
Toxicity	
Any grade CRS [n (%)]	75 (58%)
Grade ≥3 CRS [n (%)]	1 (1%)
Median time to onset of CRS [days (range)]	6 (1-17)
Median duration of CRS [days (range)]	3 (1-10)
Any grade ICANS [n (%)]	20 (15%)
Grade ≥3 ICANS [n (%)]	3 (2%)
Median time to onset of ICANS [days (range)]	8.5 (4-16)
Median duration of ICANS [days (range)]	3.5 (1-17)

[a]One-sided *P*-value using exact binomial test (H0 of ORR ≤60%; H0 of CR rate ≤30%); [b]One-sided *P*-value using exact binomial test (H0 of ORR ≤50%; H0 of CR rate ≤19%); [c]Not statistically tested (descriptive).

Morschhauser F, et al. *Nat Med*. 2024;30(8):2199-2207.

TRANSCEND FL: Follow-Up (Median 18.9 m)





12-month PFS:
2L – 91%
3L – 81%

12-month OS:
2L – 96%
3L – 93%

Morschhauser F, et al. *Nat Med*. 2024;30(8):2199-2207.

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Comparison between Products***

Baseline characteristics			
	Axi-cel	**Tisa-cel**	**Liso-cel (3L+)**
High-risk FLIPI	44%	60%	57%
High tumor bulk	52%	64%	
Median lines of therapy	3	4	3
Refractory to last therapy	68%	78%	64%
POD24	55%	63%	54%
Double refractory	29%	68%	64%
Bridging therapy	**3%**	**45%**	**38%**

***SLIDE FOR EDUCATIONAL PURPOSES; NO HEAD-TO-HEAD STUDIES HAVE BEEN CONDUCTED.

Jacobson CA, et al. *Lancet Oncol*. 2022;23(1):91-103. Fowler NH, et al. *Nat Med*. 2022;28(2):325-332. Morschhauser F, et al. *Nat Med*. 2024;30(8):2199-2207. Adapted from: Landsburg D, et al. Presented at: LL&M Congress; October 16-19, 2024; New York, NY.

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Comparison between Products***

Efficacy			
	Axi-cel	**Tisa-cel**	**Liso-cel (3L+)**
ORR	94%	87%	97%
CRR	79%	73%	94%
12 month PFS			81%
12 month OS			92%
24 month PFS		57%	
24 month OS		88%	
36 month PFS	54%		
36 month OS	76%		

***SLIDE FOR EDUCATIONAL PURPOSES; NO HEAD-TO-HEAD STUDIES HAVE BEEN CONDUCTED.

Jacobson CA, et al. *Lancet Oncol*. 2022;23(1):91-103. Fowler NH, et al. *Nat Med*. 2022;28(2):325-332. Morschhauser F, et al. *Nat Med*. 2024;30(8):2199-2207. Adapted from: Landsburg D, et al. Presented at: LL&M Congress; October 16-19, 2024; New York, NY.

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Comparison between Products***

Toxicity			
	Axi-cel	**Tisa-cel**	**Liso-cel**
Any grade CRS [n (%)]	97 (78%)	47 (49%)	75 (58%)
Grade ≥3 CRS [n (%)]	8 (6%)	0 (0%)	1 (1%)
Median time to onset of CRS [days (IQR/range)]	4 (2-6)	4 (2-7)	6 (1-17)
Median duration of CRS [days (IQR/range)]	6 (4-8)	4 (4-6)	3 (1-10)
Any grade ICANS [n (%)]	70 (56%)	4 (4%)	20 (15%)
Grade ≥3 ICANS [n (%)]	19 (15%)	1 (1%)	3 (2%)
Median time to onset of ICANS [days (IQR/range)]	7 (6-10)	9 (5-35)	8.5 (4-16)
Median duration of ICANS [days (IQR/range)]	14 (5-43)	2 (1-4)	3.5 (1-17)

*****SLIDE FOR EDUCATIONAL PURPOSES; NO HEAD-TO-HEAD STUDIES HAVE BEEN CONDUCTED.**

Jacobson CA, et al. *Lancet Oncol*. 2022;23(1):91-103. Fowler NH, et al. *Nat Med*. 2022;28(2):325-332. Morschhauser F, et al. *Nat Med*. 2024;30(8):2199-2207. Adapted from: Landsburg D, et al. Presented at: LL&M Congress; October 16-19, 2024; New York, NY.

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Novel T-Cell-Engaging Therapies in FL

- Glofitamab – CD20 x CD3 bispecific antibody
- Surovatamig (AZD0486) – CD19 x CD3 bispecific antibody (NCT06564038)
- RG6333 – CD19 x CD3 bispecific antibody (NCT05219513)
- RO7227166 – costimulatory bispecific antibody CD19 x 4-1BB (NCT04077723)
- PIT565 – anti-CD19, anti-CD3, anti-CD2 trispecific antibody (NCT05397496)

Hutchings M, et al. *J Clin Oncol*. 2021;39(18):1959-1970. ClinicalTrials.gov. Accessed October 9, 2025. https://www.clinicaltrials.gov.

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Key Learning Points

- PET/CT scan is a standard imaging modality used to evaluate for suspected transformation of R/R FL
- Early progression and transformation remain unmet needs
- Emerging strategies include novel targets (CD19, BTK, EZH2) and T-cell-engaging therapies (such as bispecific antibodies and CAR-T)
- Bispecific antibodies will likely be used in earlier lines
- Novel combinations of bispecific antibodies + targeted agents are likely to emerge
- Quality-of-life considerations and patient preferences will continue to drive treatment decisions

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Individualized Approach in R/R FL

Patient characteristics

- Age
- Comorbidities
- Tolerance of prior lines
- Risk tolerance
- ***Goals of care***
- ***Social determinants (support, access, ability to travel, etc)***

Disease characteristics

- Prior therapeutic exposure and response to previous LOTs
- Burden and tempo of disease
- Concern for transformation
- Disease biology (p53? EZH2?)

LOTs = lines of therapy.