



Relapsed/Refractory Follicular Lymphoma

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Outline

- NCCN updates for R/R FL
- BsAb-based regimens for R/R FL
 - Single-agent mosunetuzumab and epcoritamab
 - Combination regimens
- CAR-T
 - Overview of 3 available agents
 - Review of Transcend data
- BsAb vs CAR-T
- Zanubrutinib + obinutuzumab
- In the pipeline
 - Other combinations with early data and active trials

2nd line therapy for R/R Follicular Lymphoma

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NCCN Guidelines Version 4.2026 Classic Follicular Lymphoma

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

SUGGESTED TREATMENT REGIMENS^{a,b,c}

SECOND-LINE THERAPYⁱ

Preferred (in alphabetical order)

- Bendamustine^{d,j} + Obinutuzumab^{e,f} or Rituximab (not recommended if treated with prior Bendamustine)
- CHOP + Obinutuzumab^{e,f} or Rituximab
- CVP + Obinutuzumab^{e,f} or Rituximab
- Lenalidomide + Rituximab + Epcoritamab-bysp^{k,l} (category 1)
- Lenalidomide + Rituximab + Tafasitamab-cxix^{l,m} (≥1 prior systemic therapy including an anti-CD20 mAb) (category 1)

Other recommended (in alphabetical order)

- Lenalidomide (if not a candidate for anti-CD20 mAb therapy)
- Lenalidomide + Obinutuzumab or Rituximab
- 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

- Rituximab (375 mg/m² weekly for 4 doses)

SECOND-LINE EXTENDED THERAPY (optional)

Preferred

- 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)

3L+ Therapies for R/R Follicular Lymphoma



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[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

SUGGESTED TREATMENT REGIMENS^{a,b,c}

THIRD-LINE AND SUBSEQUENT THERAPY	
Second-line therapy regimens (FOLL-B 2 of 6) that were not previously given can also be used as options for third-line and subsequent therapy	
Preferred (in alphabetical order) • T-cell mediated therapy^k ▶ Bispecific antibody therapy^l ◊ Epcoritamab-bysp ◊ Mosunetuzumab-axgb (IV or SC)^m ▶ Chimeric antigen receptor (CAR) T-cell therapy^{n,o} ◊ Axicabtagene ciloleucel (CD19-directed) ◊ Lisocabtagene maraleucel (CD19-directed) ◊ Tisagenlecleucel (CD19-directed)	Other recommended • BTK inhibitor (BTKi) ▶ Zanubrutinib^l + Obinutuzumab • Loncastuximab tesirine-lpyl^{l,n} + Rituximab (category 2B)

THIRD-LINE CONSOLIDATION THERAPY

Useful in Certain Circumstances

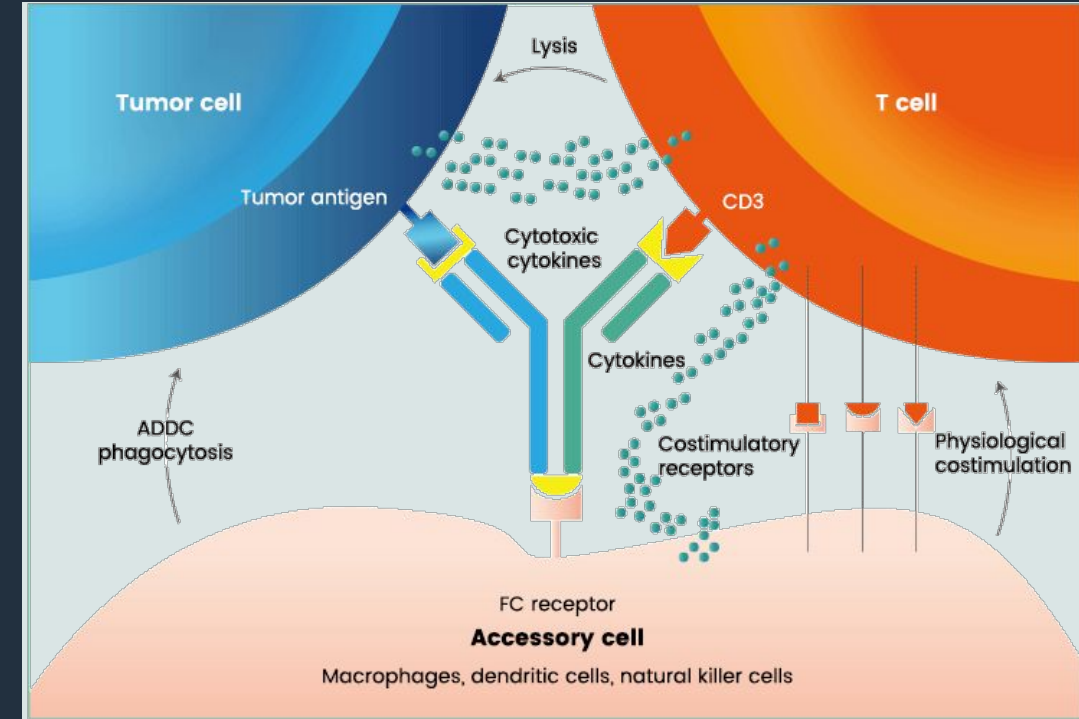
- Allogeneic hematopoietic cell transplantation (HCT) in selected cases^p

General trends in R/R FL

- Reducing the use of cytotoxic chemotherapy
- Increased use of T cell-directed therapies
- BsAb more easily administered in the outpatient setting for FL compared to HGBCL
- CAR-T showing more favorable toxicity profiles for FL compared to HGBCL
- Combination therapies using oral agents such as BTKi and iMiD

Bispecific T Cell Engaging Antibodies (BsAbs)

- “off the shelf” T-cell activating therapy
- More accessible than CAR-T therapy
- Incidence & severity of CRS/ICANS lower than CAR-T
- Primarily outpatient administration
 - No inpatient dose ramp-up for FL
- Efficacy may be lower than CAR-T
 - Combination regimens > single-agent therapy
 - Relapse after CAR-T
 - Loss of CD20 at high risk for BsAb failure



<https://www.sinobiological.com/resource/antibody-technical/bispecific-antibody>

CD3:CD20 Bispecific Antibody toxicities¹

- Cytokine release syndrome (CRS)
- Immune effector cell associated neurotoxicity syndrome (ICANS)
- Infections
 - Hypogammaglobulinemia
 - low CD4
- Cytopenias -> holding parameters per PI
 - When used in combination, consider reducing other agents first if more likely to be contributing
 - Consider gcsf
- Tumor lysis syndrome (TLS)
 - Prophylaxis (uric acid-reducing, hydration, lab monitoring)
- Tumor flare
 - Consider steroids, may be able to continue therapy
 - Consider radiating high risk sites

1. Perez Perez et al., FLASCO Consensus: Best Practices to Operationalize Bispecifics for Lymphoma in a Community Setting

CRS & ICANS Management

- Most CRS & ICANS events occur during cycle 1 ramp-up
 - Admission for C1D8 Glofit & C1D15 Epcoritamab
- For CRS symptoms, important to consider & rule-out infection if deemed necessary
- CNS imaging should be considered for ICANS that doesn't resolve or >G1
- Triage/infusion/clinic team education
- Patient/caregiver education
 - Review symptoms. Advise thermometer, BP cuff and pulse ox at home
 - For patients with underlying cognitive or motor impairment, important to obtain baseline assessment
 - Median time to onset increases during ramp-up & events can occur after first cycle
- Wallet cards for patients (e.g. ER/urgent care) & available oncologist on-call 24/7
- Outside provider education (e.g., PCP, ER, hospitalist)

Cytokine Release Syndrome (CRS)

	Fever	Hypotension	Hypoxia	Admission?	Treatment
Grade 1	Yes	No	No	Not required	Acetaminophen vs Dexamethasone
Grade 2	Yes	Yes (No pressors)	Yes (≤ 6L NC)	Consider**	Dexamethasone +/- Tocilizumab
Grade ≥ 3	Yes	Yes (Pressors)	Yes (> 6L NC)	Yes	Tocilizumab + Dexamethasone

Immune effector cell associated neurotoxicity (ICANS)

	ICE score	LOC	Admission?	Management
Grade 1	7-9	Awakens spontaneously	Consider	Supportive care, consider Dex 10mg x 1
Grade 2	3-6	Awakens to voice	Yes	Dex 10mg q12h
Grade ≥ 3	0-2	Requires tactile stimulus or any seizure activity or cerebral edema	Yes, <u>ICU</u>	Dex 10mg q6h Neurology consult Antiepileptics Consider anakinra

Perez Perez et al., FLASCO Consensus: Best Practices to Operationalize Bispecifics for Lymphoma in a Community Setting

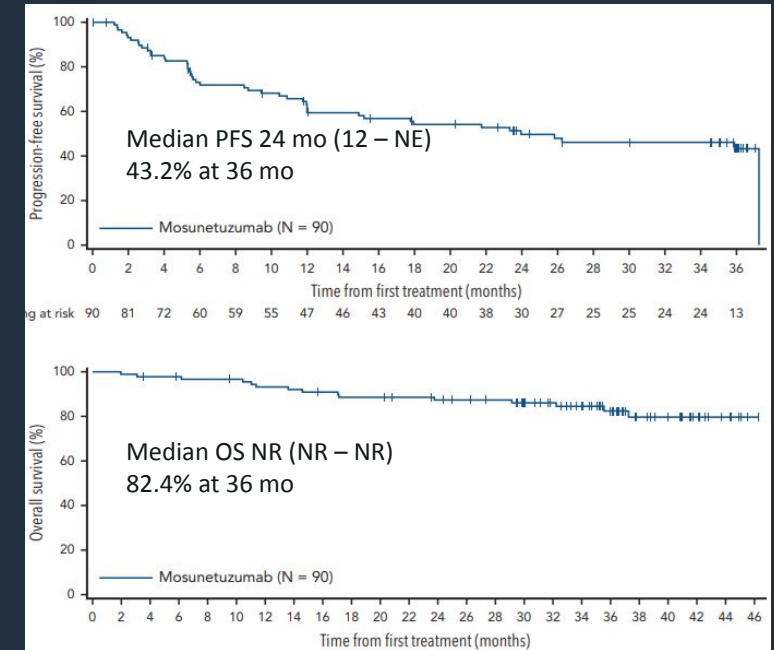
Infection prophylaxis & management

- BsAb therapy associated with increased risk of opportunistic/respiratory infx
 - COVID-19 PNA, PJP, UTIs, VZV, GI infx
- Screen for HepB, treat latent HBV infx during therapy
- VZV prophylaxis in all patients
- PJP prophylaxis in all patients
 - may need up to 6 months post-tx (delayed CD4 recovery)
 - monitor CD4 periodically, continue prophylaxis if < 200
- Monitor Ig levels periodically
 - IVIG for IgG < 400 w/ recurrent/severe infections
- Vaccinations against COVID, PNA, flu prior to tx if possible vs between cycles
 - Avoid live vaccines
 - Vaccine response may be impaired during therapy

1. Perez Perez et al., FLASCO Consensus: Best Practices to Operationalize Bispecifics for Lymphoma in a Community Setting

Mosunetuzumab and Epcoritamab in 3L+ Follicular lymphoma

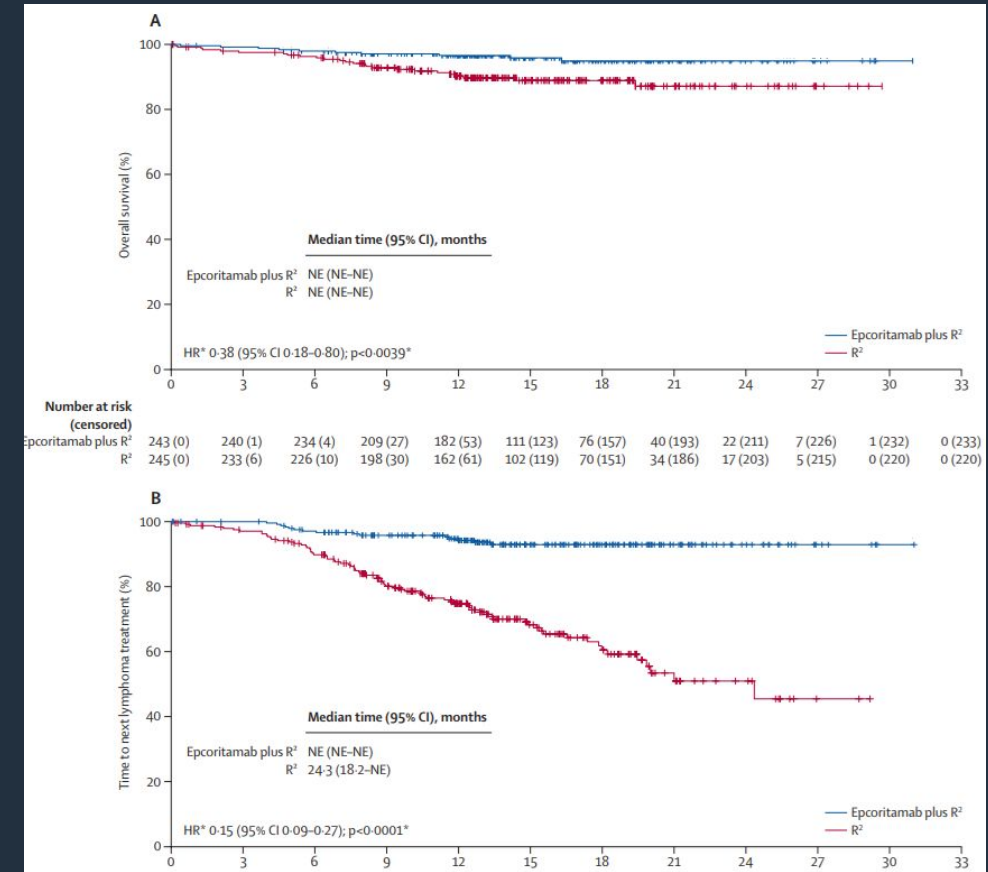
- Mosunetuzumab (Budde et al., *Lancet Oncol* 2022)
 - 3L+ as single-agent
 - weekly ramp-up (outpt) during C1, continue q3w for 8 (CR) or 17 (PR) cycles
 - 44% CRS, G3 x 2
 - 27% G3-4 neutropenia
- Epcoritamab (Linton et al., *Lancet Haematol* 2024)
 - 3L+ as single-agent
 - weekly ramp-up (outpt) during C1, weekly C1-3, q2w C4-9, q4w C10+, continuous
 - 65% G1-2 CRS, G3 x 2
 - 6% G1-2 ICANS
 - 25% G3-4 neutropenia
 - ORR 82%, CR 63%
 - 2-yr PFS 76%, OS 90%



Budde et al., *Lancet Oncol* 2022

Bispecific combinations in 2L+ Follicular lymphoma

- Epcoritamab + lenalidomide/rituximab
 - 2L+ FL
 - Finite regimen, 12 cycles, q28d
 - Epcoritamab weekly ramp-up (outpt) with weekly rituximab during C1
 - Epcoritamab weekly C1-3, then q4w C4-12
 - Continue rituximab q4w C2-5
 - Lenalidomide days 1-21 x 12 cycles
 - 35% CRS, all G1-2
 - Increased neutropenia & infx compared to Len/ritux
 - G3-4 neutropenia 69% vs 42%
 - ORR 95%, CR 88%
 - 2 yr PFS 76%, OS 90%

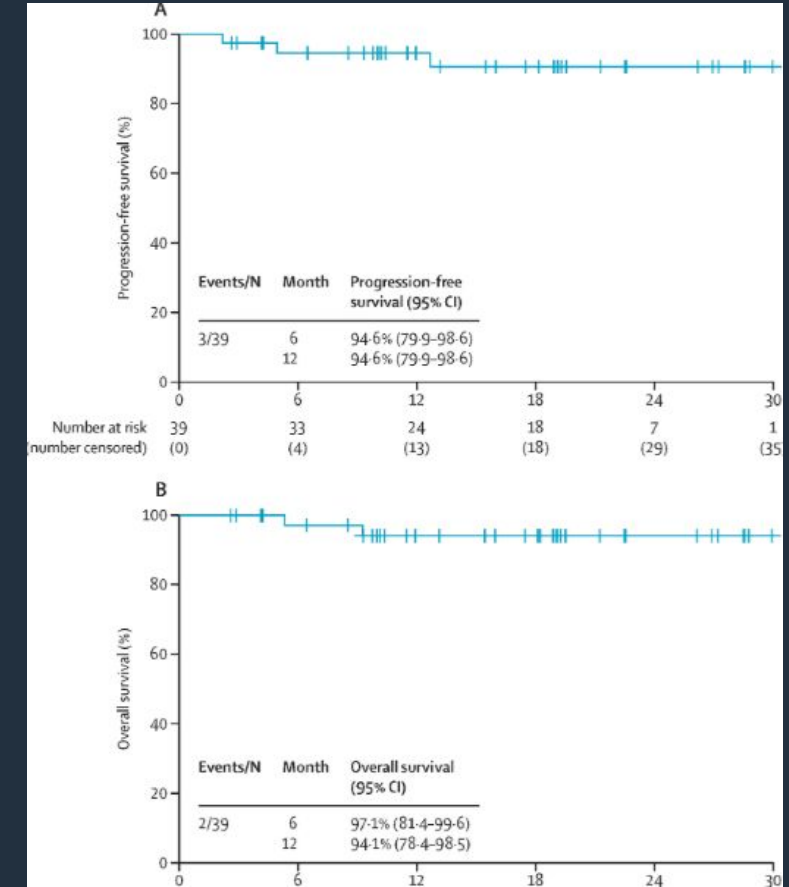


Falchi et al., *Lancet* 2026

Other combinations in 2L+ High Risk Follicular lymphoma

Loncastuximab + Rituximab in R/R FL

- 39 patients, median age 68 yo, all POD24
- Lonca q21days, rituximab weekly x 4 then q8weeks
- If CR at week 21, lonca d/c'd then ritux x 2
- If PR at week 21, continued both meds another 18 weeks
- 13% G2 neutropenia, 1 G3 febrile neutropenia
- Generalized & peripheral edema predominantly G1-2, all effectively treated
- 67% CR at week 12, 77% at week 21
- 12 month PFS & OS 94%

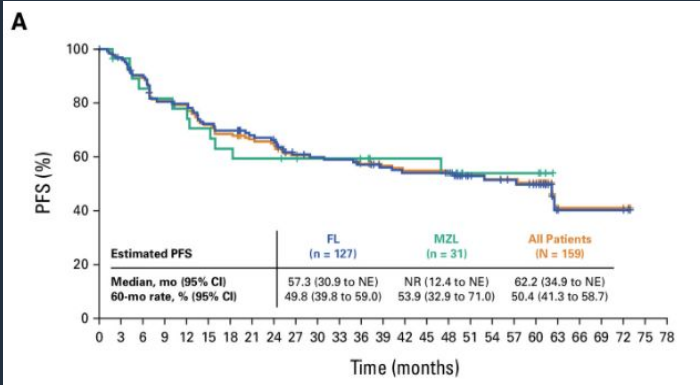


Alderuccio et al., Lancet 2025

CAR-T for R/R Follicular Lymphoma

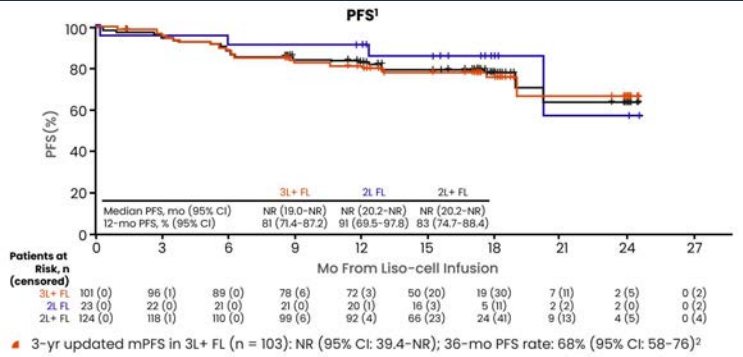
All 3 commercial CD19 CAR-T products have 3L+ FL indications

Zuma-5 Five-year: Axicel
mPFS 57.3m



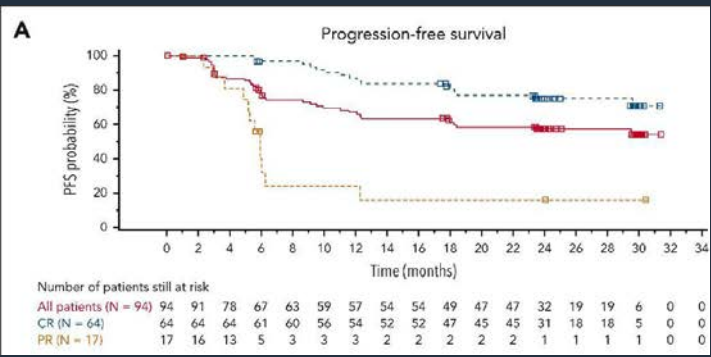
Neelapu. JCO. 2025;43:3573

Transcend Three-year: Lisocel
mPFS NR



Thieblemont. ASH 2025

ELARA Five-year: Tisacel
mPFS NR

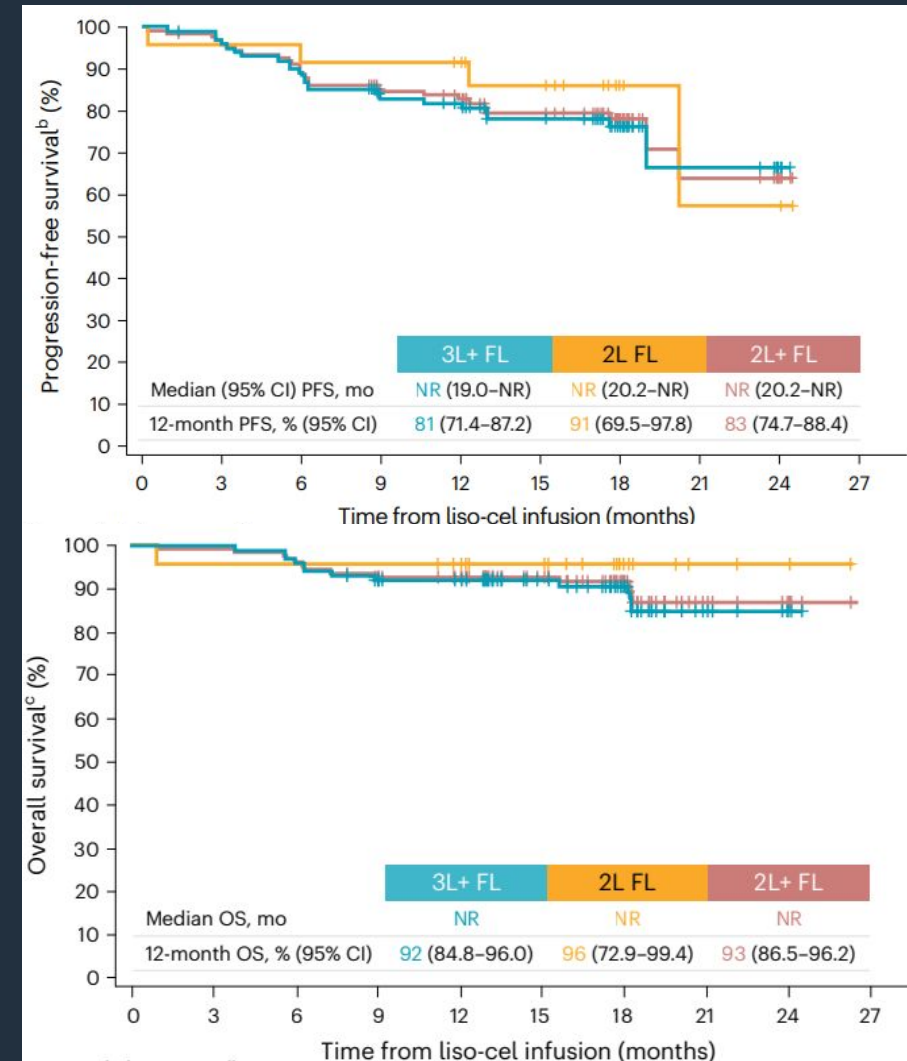


Ahmed. ASH 2025

Liso-cel in R/R Follicular Lymphoma

Transcend trial (Morschhauser et al., *Nat Med* 2024)

- 139 patients with r/r FL (25 pts in 2L), 130 rec'd cells
- Median age 60 yo, 86% stage III/IV, 53% high risk FLIPI
- Median follow-up 18.9 months
- 3L+ -> 97% ORR, 94% CR
- 2L -> 96% ORR, all responders achieved CR
- 58% CRS, 42% G1, 1 G3 event
- 15% neurologic AE's, 3 G3 events
- 5% $\geq$ G3 infections, 22% $\geq$ G3 prolonged cytopenias



CAR-T vs BsAb therapy

CAR-T therapy

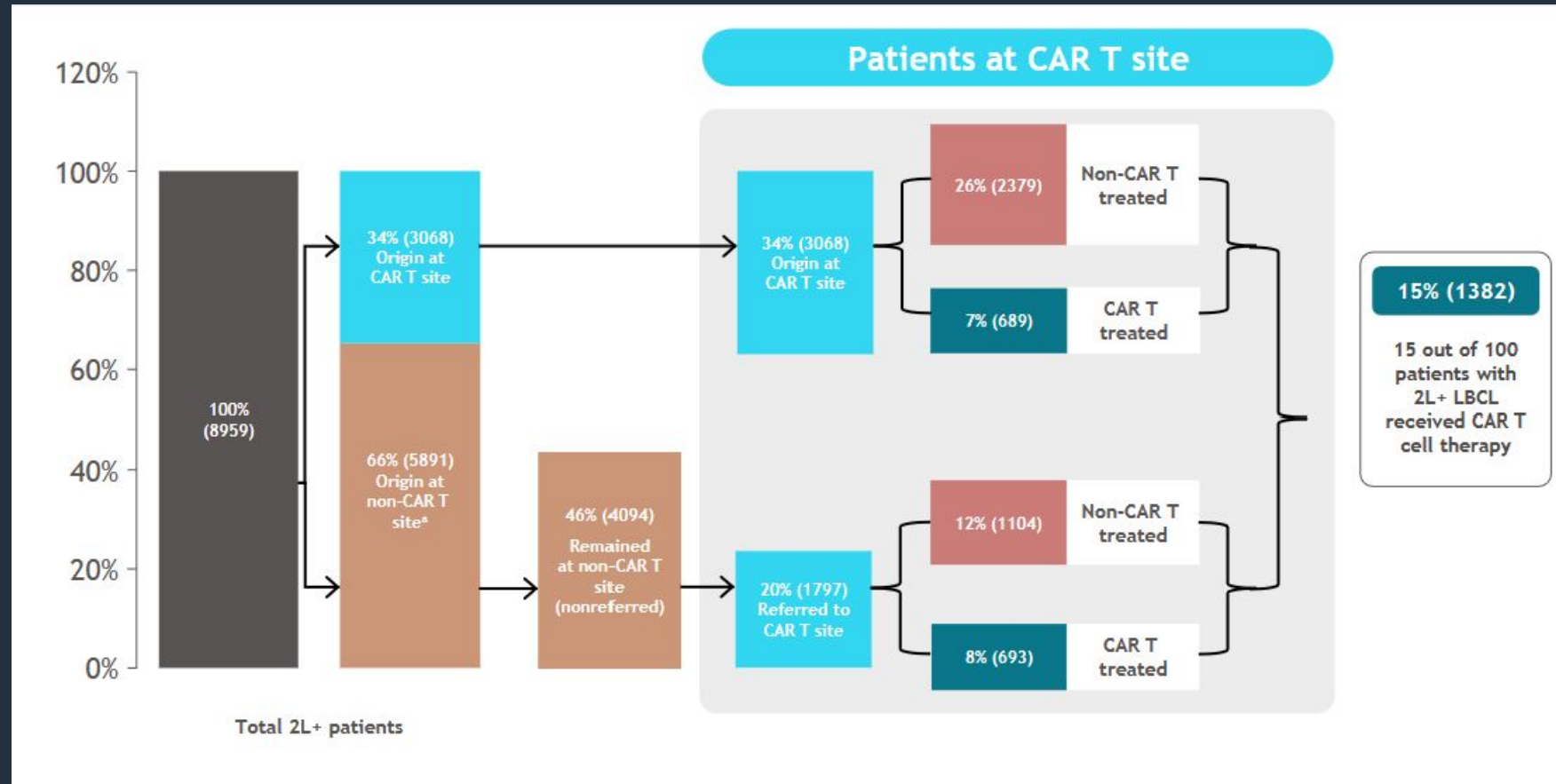
- Potentially curative
- Generally higher rates of toxicities
 - Transcend trial showing low overall tox
- Patient factors limiting eligibility
 - Frailty/comorbidities
 - Insurance coverage
 - Caregiver support
- Limited access to CAR-T centers
- Autologous product, manufacturing delays possible

Bispecific Antibodies

- “off the shelf”, readily available
- Lower toxicity profile
- Outpatient administration
- Single-agent data with likely lower responses than CAR-T
- Epcoritamab + lenalidomide/rituximab
 - Appears to have much higher ORR/CR with durable responses thus far
- Longer treatment duration, may be continuous

CAR-T vs BsAb therapy

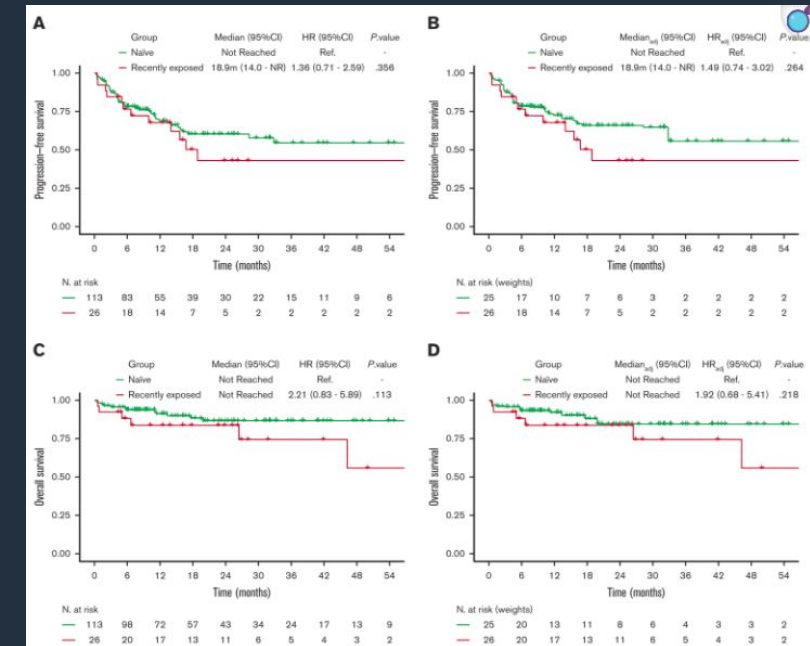
Access to CAR-T therapy isn't universal



Shadman ASH 2025

CAR-T vs BsAb therapy, prior bendamustine exposure

- Prior bendamustine is known to decrease CAR-T expansion & efficacy
- For BsAb, bendamustine exposure within 24 mo was compared to naïve patients
 - No significant difference in DOR, PFS or OS
 - Small cohort of patients with bendamustine exposure within 12 mo (n = 12) also showing no difference
- If concern for high grade transformation, consider CHOP-based in 1L
- Higher risk patients at risk for early relapse
 - May end up on BsAb-based therapy prior to CAR-T
 - Given other options in 1L, may consider avoiding bendamustine



Iacoboni et al., *Blood Adv* 2026

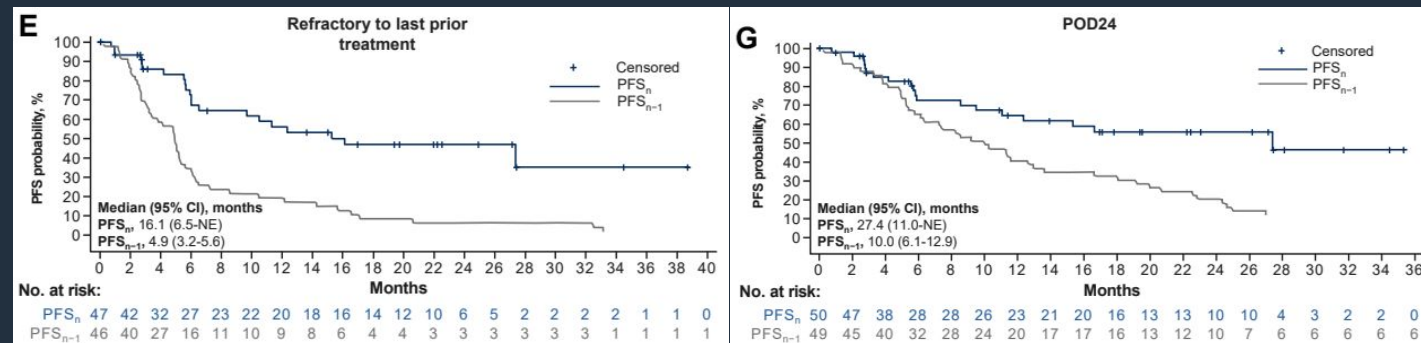
Zanubrutinib + Obinutuzumab in 3L+ Follicular Lymphoma

ROSEWOOD trial (Zinzani et al., JCO 2023)

- Zanubrutinib + obinutuzumab vs Obinutuzumab single-agent in r/r FL after 2+ prior LOT
- Continuous Zanubrutinib until progression/toxicity
- PFS 28 months vs 10.4 months
- 3% afib, 1% major hemorrhage in the ZO arm

Post-hoc analyses of comparative efficacy (Trotman et al., ESMO Open 2026)

- Significant benefit of ZO vs O for pts refractory to last LOT, heavily pretreated & POD24



In the Pipeline

- Golcadomide +/- rituximab in r/r FL (Chavez et al., ASH 2024)
 - 93% ORR, 67% CR for golca at 0.4mg + ritux, responses seen in pts with prior T-cell-directed therapy
 - 2 pts with febrile neutropenia & PNA, non heme AE's predominantly low grade
 - Golca + ritux being evaluated in 1L setting as well
- Surovatamig (CD19:CD3 BsAb) in r/r FL (Hou et al., ASH 2025)
 - NHL patients with ≥ 2 prior LOT, 61 pts with r/r FL
 - 51% CRS, all G1-2, 2 pts with G1-2 ICANS
 - Median f/u 16 mo, ORR 96%, CR 92%, 12 mo PFS 88%
- BTK degrader BGB16673 in r/r NHL (Guize et al., ASH 2025)
 - FL and MZL patients with ≥ 2 prior LOT (median 3 prior LOT)
 - ORR 41% for FL (7/17) with 3 pts achieving reponses > 6 mo
 - Major hemorrhages noted in MZL group

In the Pipeline

Novel 1L therapies for FL

- Mosunetuzumab with response-adapted Polatuzumab/Obinutuzumab in 1L FL & MZL (Lynch et al., JCO 2026)
 - 42 pts, median age 60, 93% stage III/IV, 88% had FL
 - Mosunetuzumab x 8 cycles -> those not in a CR rec'd Polatuzumab + obinutuzumab x 6 cycles
 - 64% CRS, all G1
 - 100% ORR, 71% CR after mosun, 2 yr PFS 89%, OS 100%
- Acalabrutinib + lenalidomide/rituximab in 1L FL with high tumor burden (Strati et al., Nat Commun 2025)
 - 24 pts, median age 62 yo, all stage III/IV
 - 58% G3-4 neutropenia
 - Best ORR 100%, CR 92% after 6 cycles per PET/CT, 2 yr PFS 79%, 3 yr PFS 62%

Summary

- The landscape for FL therapy in the r/r setting has changed significantly
- Bispecific Ab-based regimens now available in 2L+ with active studies evaluating 1L
- CAR-T is a potentially curative option with some data showing very manageable toxicity profiles
 - Significant barriers remain for many patients to receive CAR-T
- Sequencing CAR-T and BsAb should be based on patient factors and prior LOT
 - Patient fitness, comorbidities, access to CAR, prior bendamustine exposure
- Newer combination strategies with targeted therapies providing more low-intensity options
 - BTK inhibition, iMID
- Novel treatments for r/r FL in the pipeline
 - CD19:CD3 BsAb, CELMoD, BTK degraders
- Novel chemo-free combinations also moving into the 1L space



Thank you