The Evolving Landscape of R/R FL: Progress and Emerging Therapies

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Great Debates Hematologic Malignancies
from Lymphoma • Leukemia & Myeloma Congress

Faculty Disclosures

- **Andrew M. Evens, DO, MBA, MSc:** Consult—CRISPR Therapeutics, Genentech, Incyte, Novartis, Pfizer, Pharmacyclics; Advisory Board—Daiichi Sankyo, Genentech, Lymphoma Research Foundation, Novartis and Pharmacyclics (DSMC), Pfizer Inc., SAB and ASH Research Council; honoraria—Pfizer, Incyte, Genentech, CRISPR Therapeutics, Novartis, Pharmacyclics
- Presenter will be discussing drugs (in combinations) which are not yet approved in the United States

This CME activity includes brand names for participant clarity purposes only.
No product promotion or recommendation should be inferred.

Learning Objectives

- Summarize the current treatment landscape, considerations for risk stratification, and updated guidelines for R/R FL
- Evaluate the most recent clinical trial data associated with approved and emerging novel therapies for R/R FL
- Incorporate interdisciplinary team strategies to select personalized treatments for R/R FL tailored to disease grade, line of therapy, and individual patient needs

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R/R FL = relapsed/refractory follicular lymphoma.

Program Information

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- Supported by an educational grant from Incyte Corporation.

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Increasing Targeted Treatment Options for R/R FL

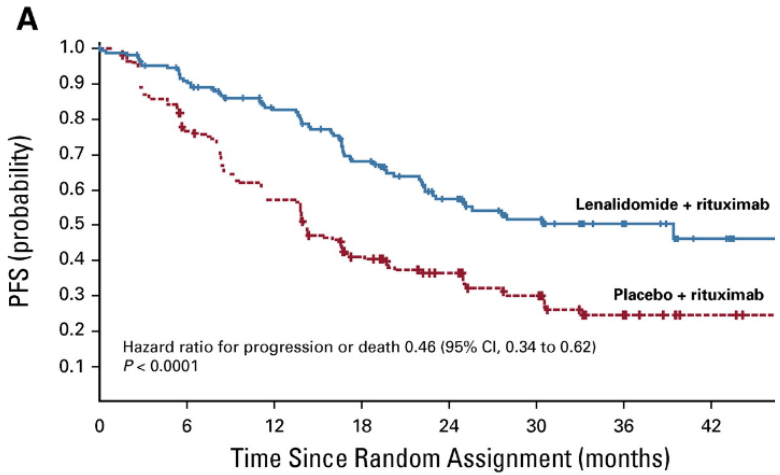
- CAR T cell therapy
- Monoclonal antibodies
- Bispecific antibodies
- Targeted agents
  - Lenalidomide
  - EZH2 inhibitor
  - BTK inhibitor

BTK = Bruton's tyrosine kinase.

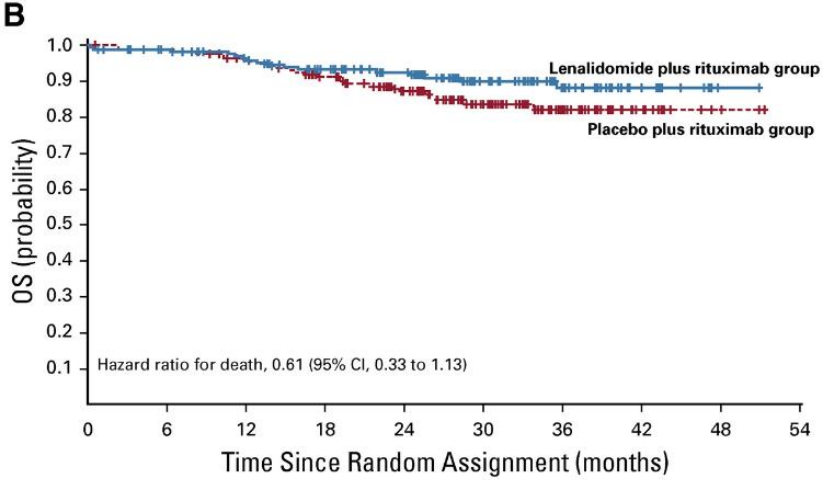
Immunomodulatory Agents in FL

Lenalidomide in R/R Follicular Lymphoma

AUGMENT



No. at risk:								
Lenalidomide + rituximab	178	148	124	91	59	39	20	7
Placebo + rituximab	180	132	92	58	40	26	10	4



No. at risk:										
Lenalidomide + rituximab	178	167	155	143	122	80	44	15	1	0
Placebo + rituximab	180	176	167	145	116	79	40	14	3	0

PFS = progression-free survival; OS = overall survival.

Leonard JP, et al. *J Clin Oncol.* 2019;37(14):1188-1199.

CD19 CAR-T Cell Therapy in FL

ZUMA-5 (Axicabtagene Maraleucel for Relapsed/Refractory iNHL)

Phase 2 (N ≈ 160 planned for enrollment)

R/R iNHL	FL: n ≈ 125 (with n ≥ 80 evaluable for efficacy) MZL: n ≈ 35

Key eligibility criteria

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

Conditioning regimen

- Fludarabine 30 mg/m^2 IV and cyclophosphamide 500 mg/m^2 IV on Days −5, −4, −3

Axi-cel: 2 × 10^6 CAR+ cells/kg

Primary endpoint

- ORR (IRRC-assessed per the Lugano classification[1])

Key secondary endpoints

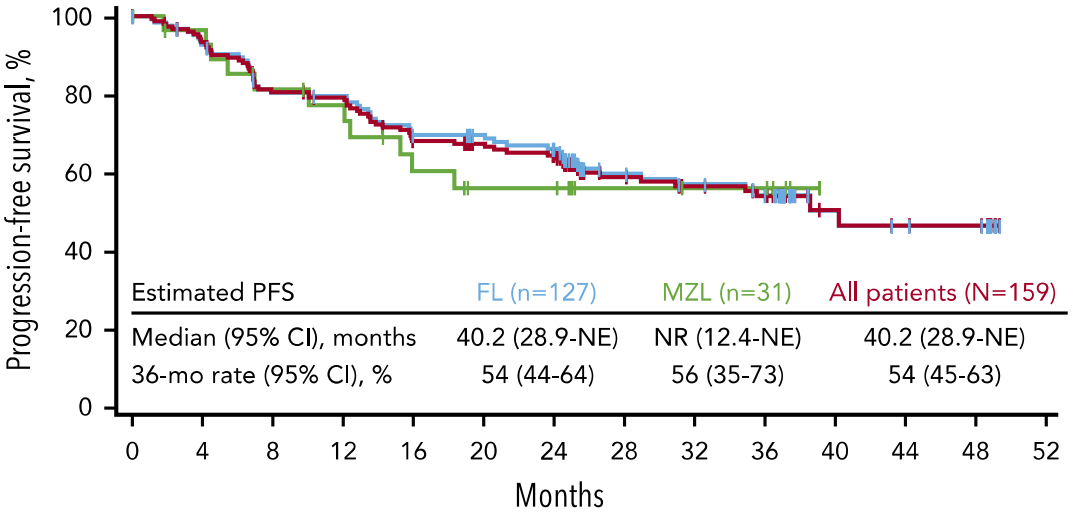
- CR rate (IRRC-assessed)
- DOR, PFS, OS
- AEs
- CAR T cell and cytokine levels

iNHL = indolent non-Hodgkin lymphoma; MZL = marginal zone lymphoma; mAb = monoclonal antibody; CAR = chimeric antigen receptor; ORR = objective response rate; IRRC = immune-related response criteria; CR = complete response; DOR = duration of response; AE = adverse event.

Jacobson CA, et al. *Lancet Oncol*. 2022;23(1):91-103. Neelapu SS, et al. *Blood*. 2024;143(6):496-506.

ZUMA-5: Efficacy

	FL (n = 127)
ORR, n (%)	119 (94)
CR	100 (79)
PR	19 (15)
SD, n (%)	2 (2)
PD, n (%)	2 (2)
Not done, n (%)	4 (3)
DOR, median (95% CI), mo	38.6 (29.0-NE)
Estimate at 36 mo (95% CI), %	57 (47-66)
Duration of CR, median (95% CI), mo	NR (35.4-NE)
Estimate at 36 mo (95% CI), %	62 (48-72)
Duration of PR, median (95% CI), mo	4.9 (2.2-8.2)
Estimate at 36 mo (95% CI), %	NR (NE-NE)



SD = stable disease; PD = progressive disease; PR = partial response; NR = not reached; NE = not estimable.

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

Tisagenlecleucel in the ≥3rd-Line FL Setting

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

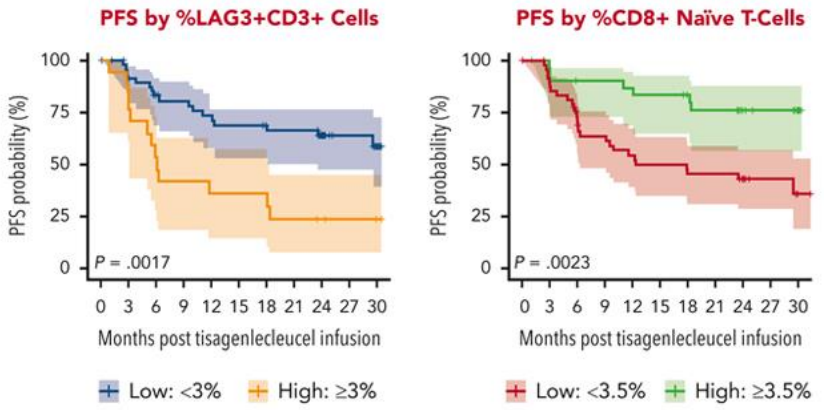
86%	69%	67%
Overall response rate (ORR)	Complete response rate (CRR)	12-mo progression-free survival rate

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

Low levels of exhausted T cells and high levels of naive T cells were significantly associated with improved outcomes:



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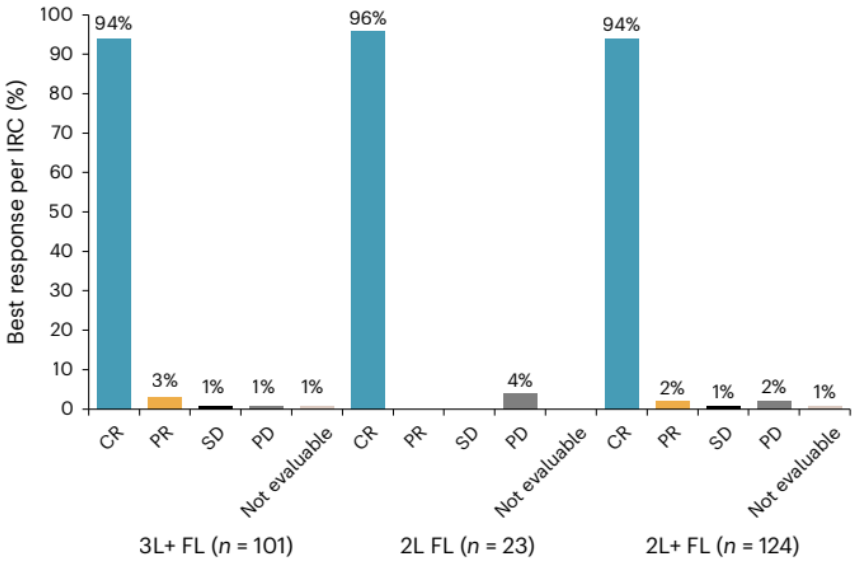
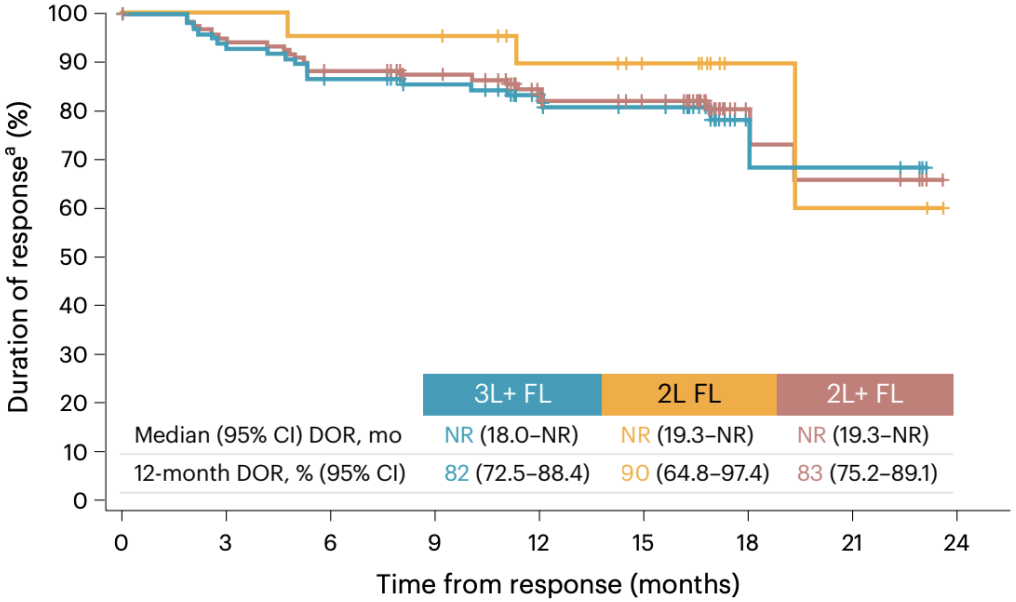
Fowler NH, et al. *Nat Med*. 2022;28(2):325-332. Dreyling M, et al. *Blood*. 2024;143(17):1713-1725.

Lisocabtagene Maraleucel in Relapsed/ Refractory FL: The Phase 2 TRANSCEND Trial





IRC = independent review committee.

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

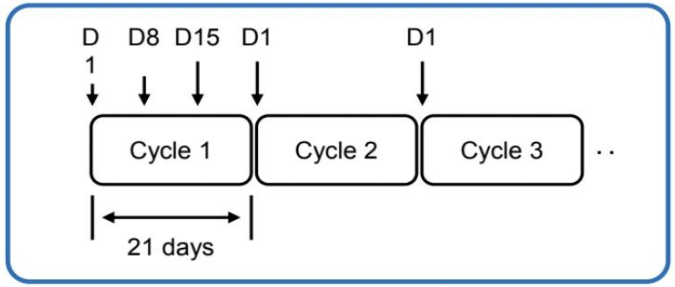
Key Toxicities of CD19 CART in FL

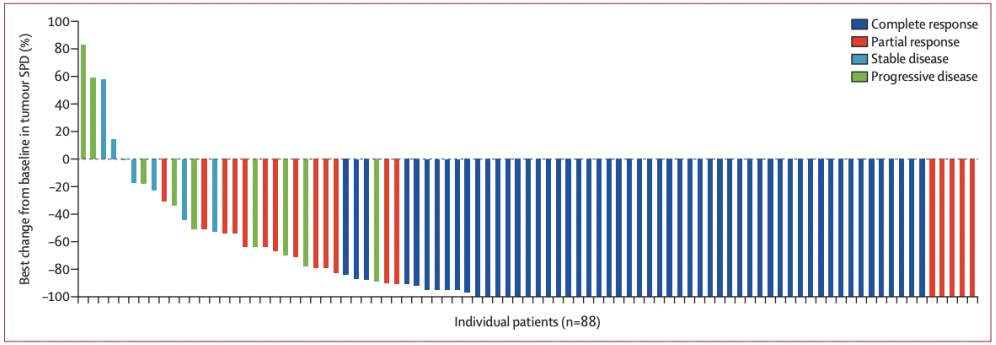
Therapy	CRS Incidence	CRS Severity	ICANS Incidence	ICANS Severity
Axicabtagene ciloleucel	High (~80-90%)	Frequently Grade 3+ (~10-20%)	Moderate (~15-30%)	Severe (Grade 3+) rare (~5-10%)
Tisagenlecleucel	Moderate (~50-60%)	Rarely Grade 3+ (~1-5%)	Low (~5-10%)	Severe ICANS rare or minimal (<5%)
Lisocabtagene maraleucel	Moderate (~40-50%)	Rarely Grade 3+ (<5%)	Low (~5-10%)	Rare severe ICANS (<3%)

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

Bispecific Antibodies in FL

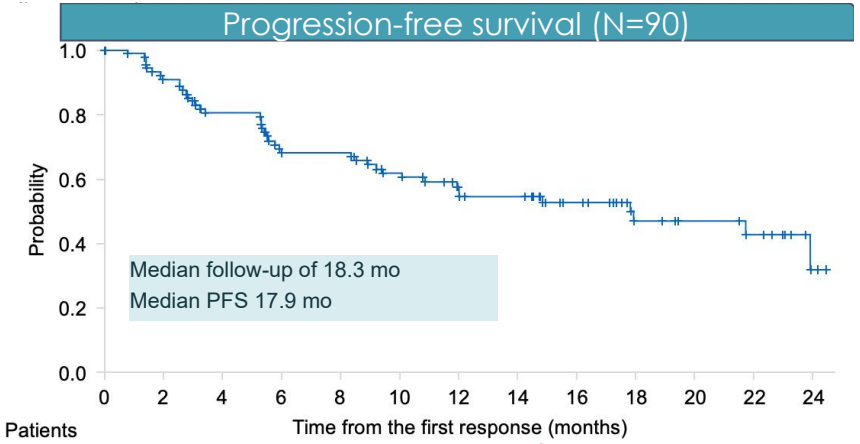
Mosunetuzumab in Relapsed/Refractory FL





Single agent

- Monotherapy as third-line or greater in FL: ORR 80%, CR 60%, median PFS 17.9 months, CRS primarily grade 1-2
- Monotherapy as second-line or greater: with subcutaneous step-up dosing, low CRS rates and ORR 80% in recurrent FL (Bartlett, et al., ASH 2021)



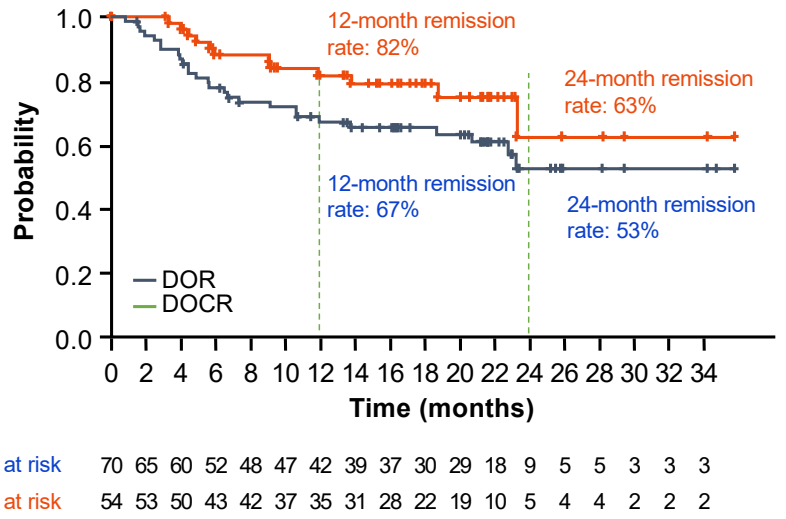
ASH = American Society of Hematology.

Bartlett NL, et al. *Blood*. 2023;7(17):4926-4935. Budde LE, et al. *Lancet Oncol*. 2022;23(8):1055-1065.

Mosunetuzumab: Durability

Efficacy endpoint by investigator assessment	N=90
Median DOR, months (range), n=70	NR (21–NR)
24-month DOR (95% CI)	53% (38–68)
Median DOCR, months (range), n=54	NR (23–NR)
24-month DOCR (95% CI)	63% (38–88)
Median PFS, months (range)	24 (12–NR)
24-month PFS (95% CI)	48% (36–60)
Median TTNT, months (range)	NR (18–NR)
24-month TTNT (95% CI)	56% (45–67)
Median OS, months (range)	NR (NR–NR)
24-month OS (95% CI)	87% (80–94)

DOR and DOCR



Durable responses: majority of patients in remission after 2 years

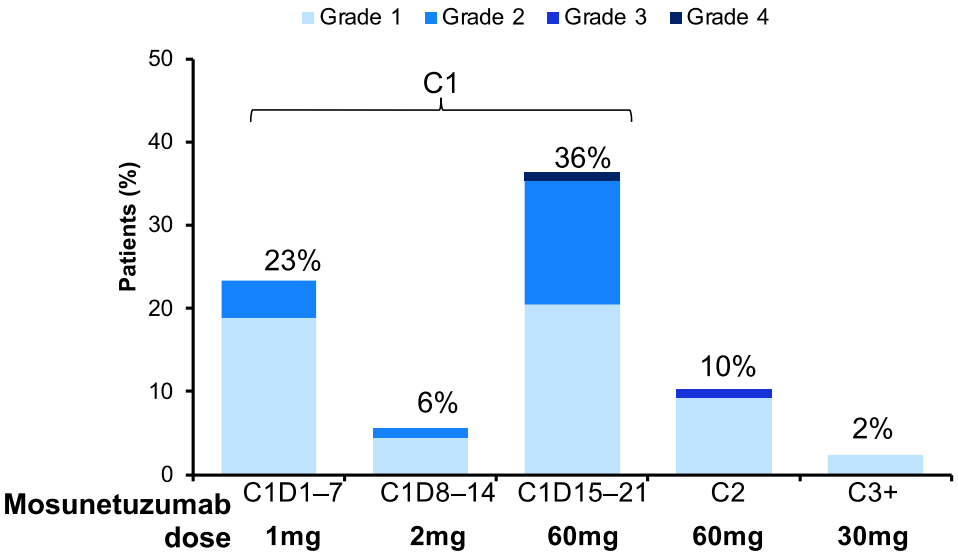
DOCR = duration of complete response; TTNT = time to next treatment.

Budde LE, et al. *Lancet Oncol*. 2022;23(8):1055-1065.

Mosunetuzumab FL CRS Summary

CRS by ASTCT criteria[1]	N=90
CRS (any grade)	44%
Grade 1	26%
Grade 2	17%
Grade 3	1%
Grade 4	1%
Median time to CRS onset, hours (range)	
C1D1	5.2 (1.2–24)
C1D15	27 (0.1–391)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management	11%
Tocilizumab for CRS management	8%
Events resolved	100%

CRS by cycle and grade



CRS was predominantly low grade and during Cycle 1
All CRS events resolved; no new events were reported with 10 months of additional follow-up

ASTCT = American Society for Transplantation and Cellular Therapy.

Budde LE, et al. *Lancet Oncol*. 2022;23(8):1055-1065.

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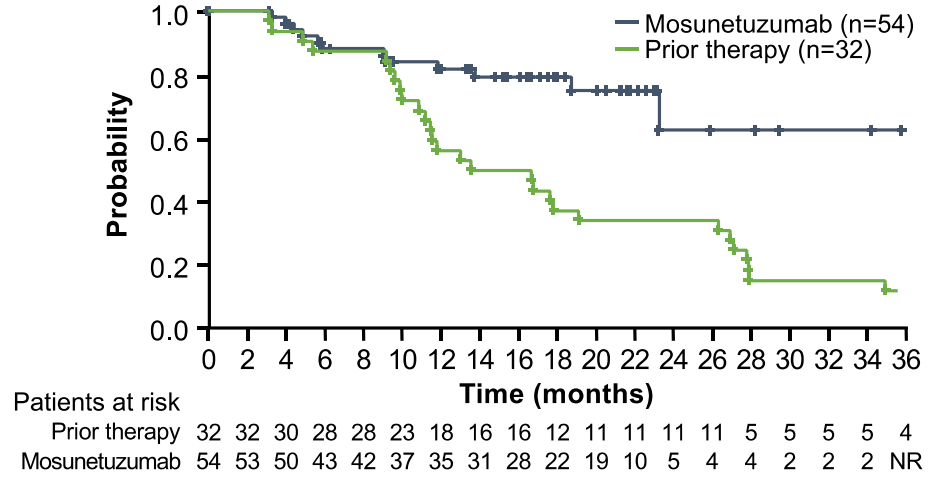
DOCR and PFS with Mosunetuzumab vs Last Prior Therapy

DOCR

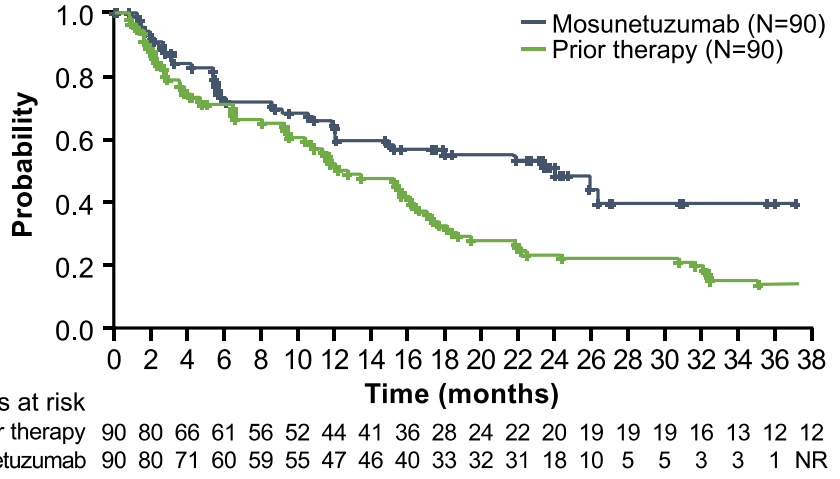


Patients at risk

Prior therapy	32	32	30	28	28	23	18	16	16	12	11	11	11	5	5	5	5	4
Mosunetuzumab	54	53	50	43	42	37	35	31	28	22	19	10	5	4	4	2	2	2	NR

	Mosunetuzumab (n=54)	Last prior therapy (n=32)
Median DOCR, months (95% CI)	NR (23–NR)	15 (11–26)

PFS



Patients at risk

Prior therapy	90	80	66	61	56	52	44	41	36	28	24	22	20	19	19	19	16	13	12	12
Mosunetuzumab	90	80	71	60	59	55	47	46	40	33	32	31	18	10	5	5	3	3	1	NR

	Mosunetuzumab (N=90)	Last prior therapy (N=90)
Median PFS, months (95% CI)	24 (12–NR)	12 (10–16)

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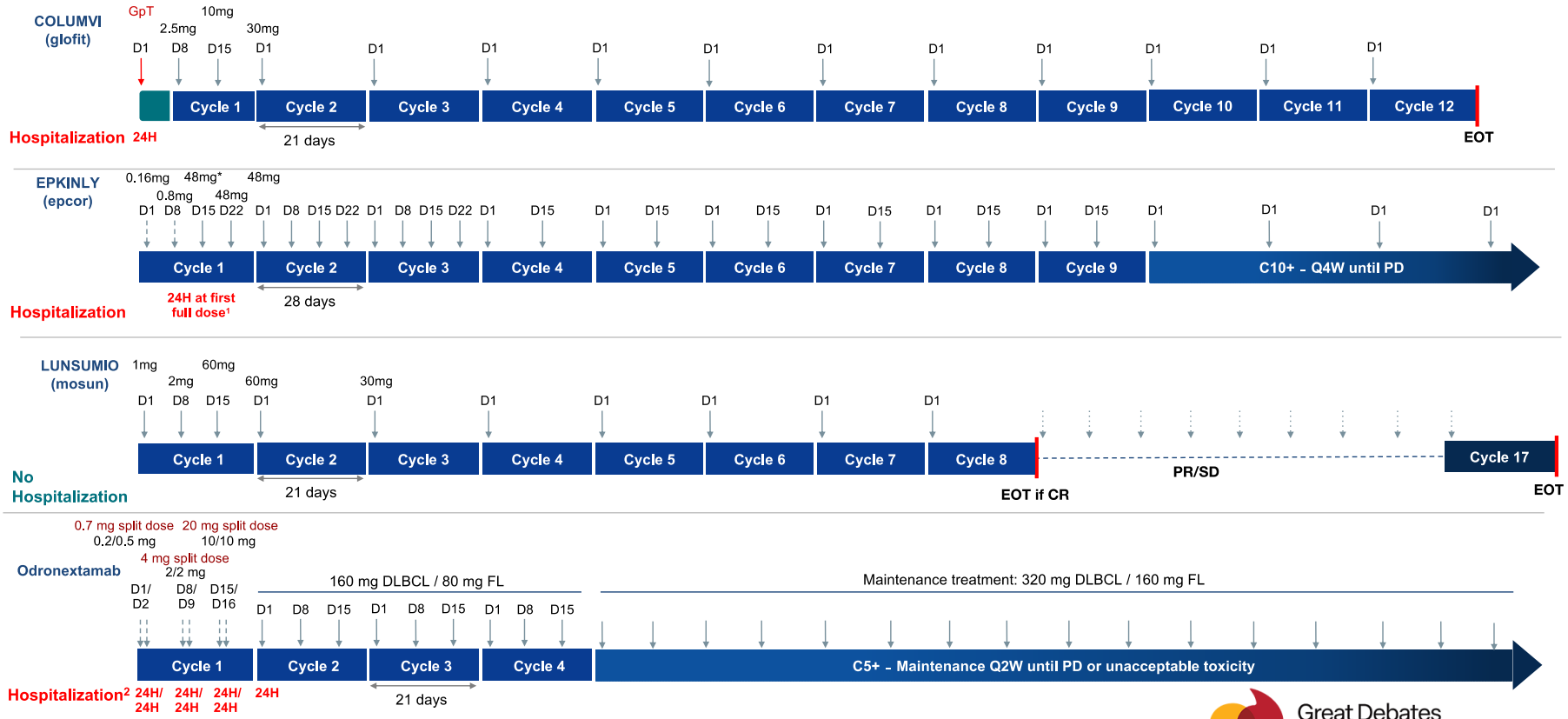
Budde LE, et al. *Lancet Oncol*. 2022;23(8):1055-1065.

Administration of Key CD20×CD3 Bispecific Antibodies in FL

Dosing Schedules and Hospitalization



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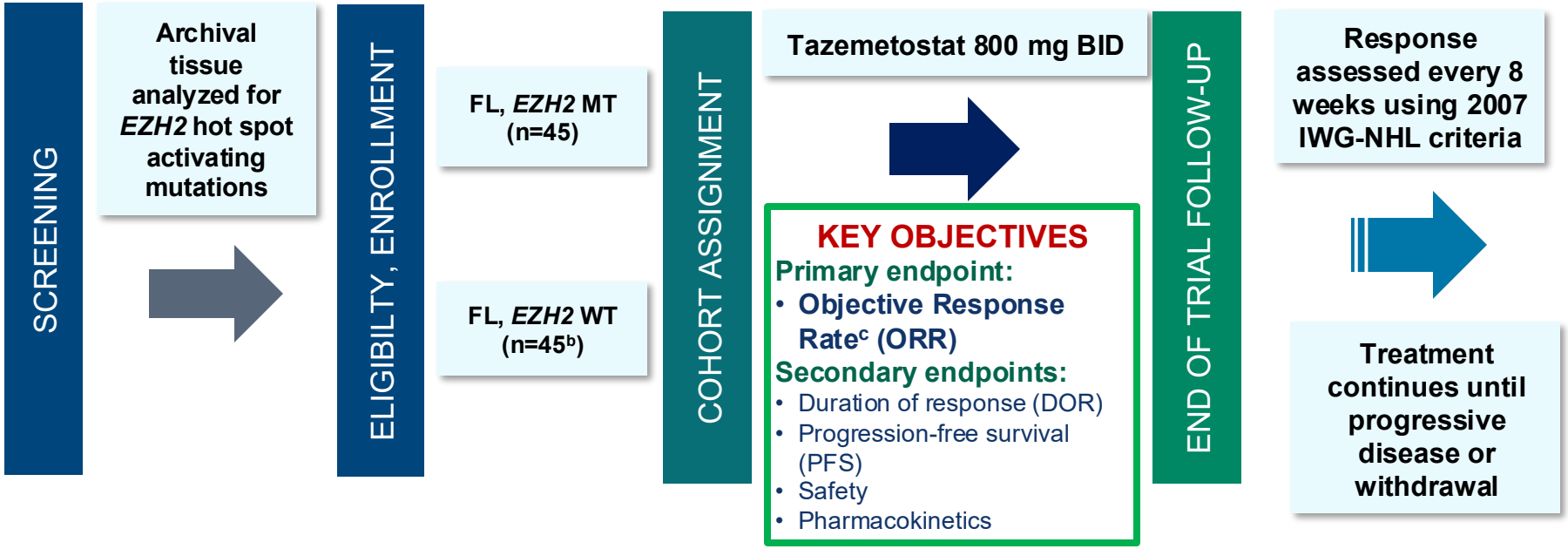
DLBCL = diffuse large B-cell lymphoma; EOT = end of treatment.

EZH2 Inhibitors in FL

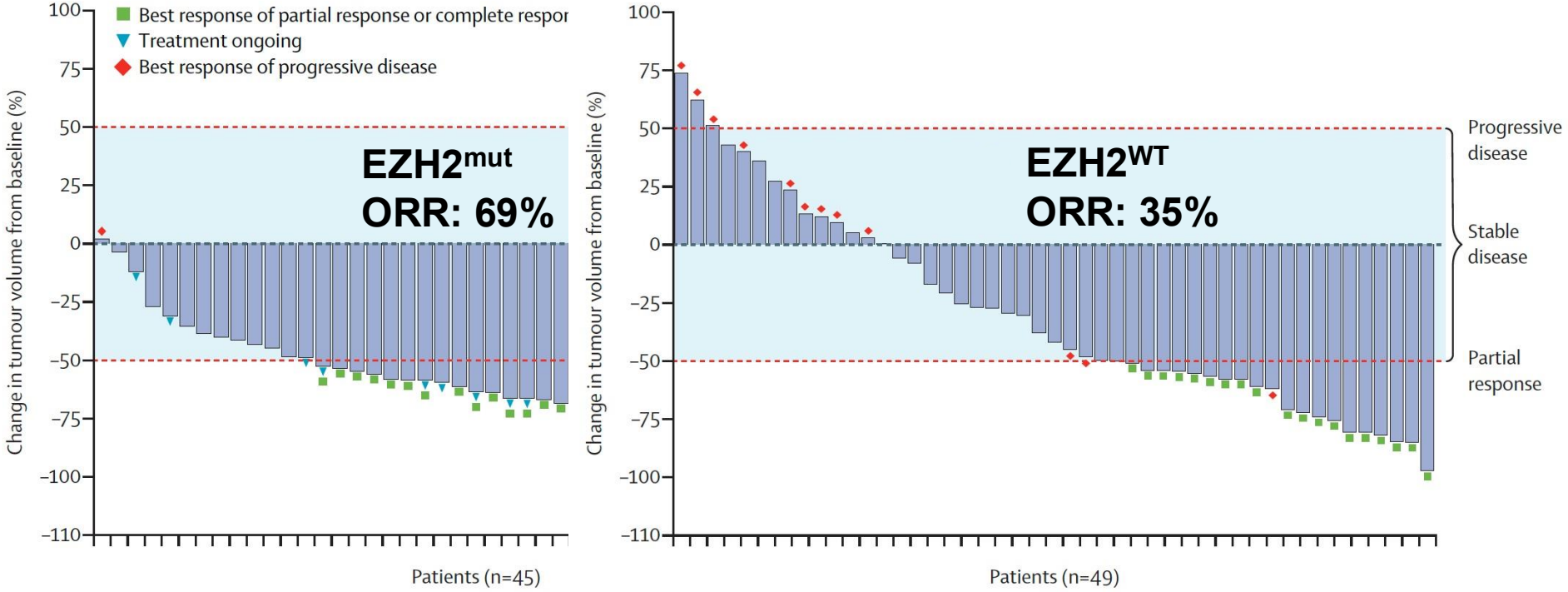
Tazemetostat in Multiply Relapsed Low-Grade Follicular Lymphoma



IWG-NHL = International Working Group for non-Hodgkin lymphoma; MT = mutant; WT = wild-type.

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

Response to Tazemetostat in Patients with R/R FL and EZH2- Mutated or EZH2 Wild-Type Tumors



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

Tazemetostat: Safety

Toxicity	Frequency	Severity (Grade 3-4)
Fatigue	Common (≥20%)	Rare
Nausea	Common (10-20%)	Rare
Decreased appetite	Common (10-20%)	Rare
Diarrhea	Common (10-20%)	Rare
Anemia	Common (≥20%)	Occasional
Thrombocytopenia	Less common (<10%)	Occasional
Neutropenia	Less common (<10%)	Occasional
Elevated liver enzymes	Common (10-20%)	Rare

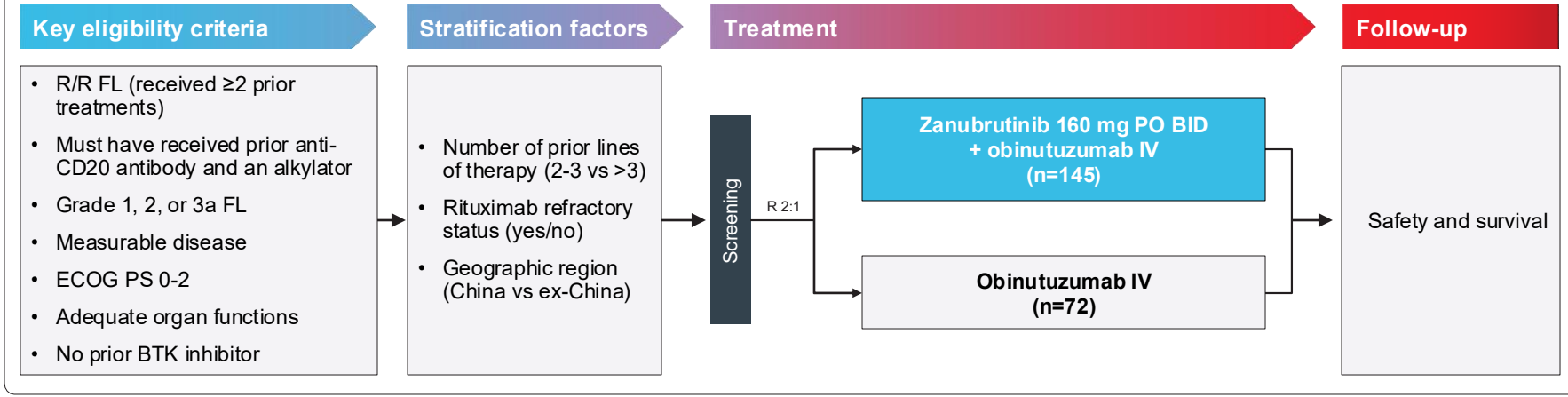
BTK Inhibitors in FL

Rosewood: Trial Design

Phase 2

Study Identifier: BGB-3111-212, NCT03332017

Primary Endpoint: ORR by ICR per Lugano Classification
Key Secondary Endpoints: ORR by investigator, DOR and PFS by ICR, OS, CR and CMR rate



ECOG PS = Eastern Cooperative Oncology Group performance status; CMR = complete molecular response.

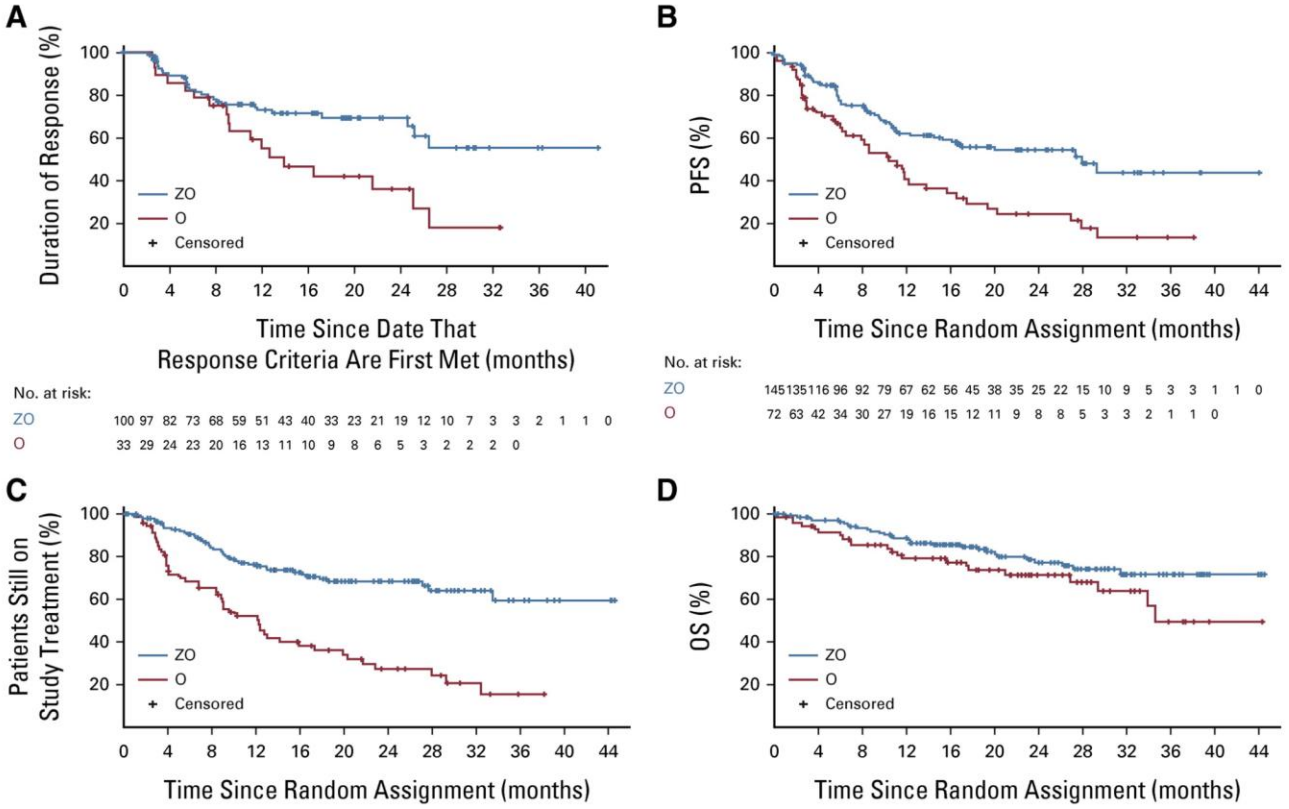
Zinzani PL, et al. *J Clin Oncol*. 2023;41(33):5107-5117.

Disease Response by Independent Central Review

End Point	ZO (n = 145)	O (n = 72)
ORR by ICR, % (95% CI)	69 (61 to 76)	46 (34 to 58)
CR, No. (%)	57 (39)	14 (19)
PR, No. (%)	43 (30)	19 (26)
DOR by ICR, months, median (95% CI)	NE (25.3 to NE)	14.0 (9.2 to 25.1)
18-month rate, %	69 (58 to 78)	42 (23 to 60)
Duration of CR by ICR, months, median (95% CI)	NE (26.5 to NE)	26.5 (2.7 to NE)
18-month rate, % (95% CI)	87 (74 to 94)	51 (21 to 75)

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

Outcomes



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

Any Grade (>10%) and Grade ≥3 (≥5% Pts) TEAEs

	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)

TEAE = treatment-emergent adverse event.

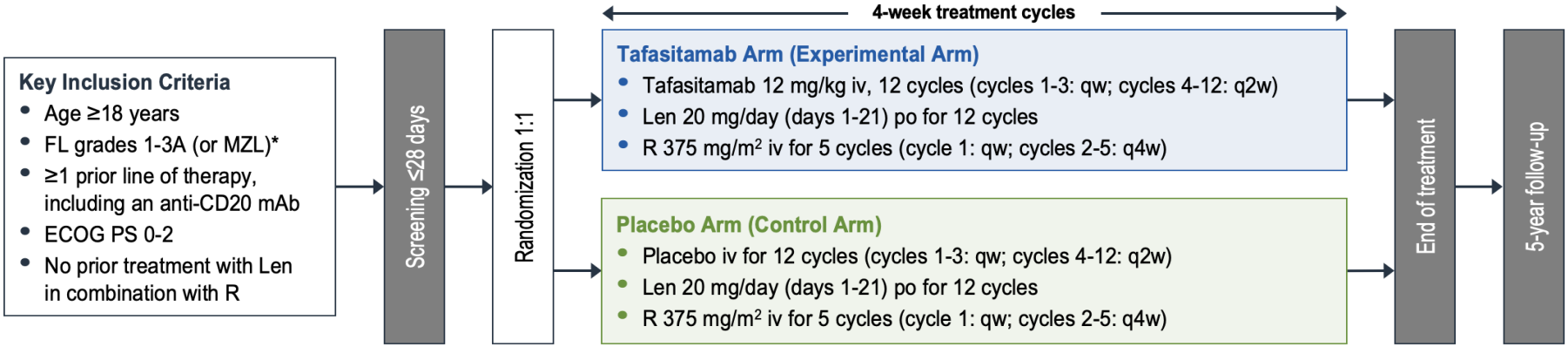
Zinzani PL, et al. *J Clin Oncol*. 2023;41(33):5107-5117.

What Are Next Steps in Relapsed FL?

- New agents (bispecifics, etc.) and new class approvals (eg, ADCs, etc.)
- Novel/novel combinations
- Critical analyses of HRQL, post-acute/late effects, and other important patient-reported outcomes and related toxicity
- Hopeful biomarker-based (precision) therapy

HRQL = health-related quality of life.

inMIND: Phase 3, Double-Blind, Placebo-Controlled, International, Multicenter Randomized Study



Stratification Factors (Patients With FL)

- POD24
- Refractoriness to prior anti-CD20 mAb therapy
- Number of prior lines of therapy (1 or ≥2)

Study Endpoints in FL Population (Investigator Assessed Unless Specified)

- **Primary study endpoint:** PFS
- **Key secondary:** PET-CR rate in the FDG-avid population, OS
- **Select other secondary:** PFS by IRC, ORR, DOR, safety, QoL, MRD
- **Exploratory:** TTNT, B-cell recovery, Ig levels, CD19 expression

- Powered to assess PFS in the FL population, triggered when 174 investigator-assessed events occurred
- OS analysis planned after 5 years of follow-up

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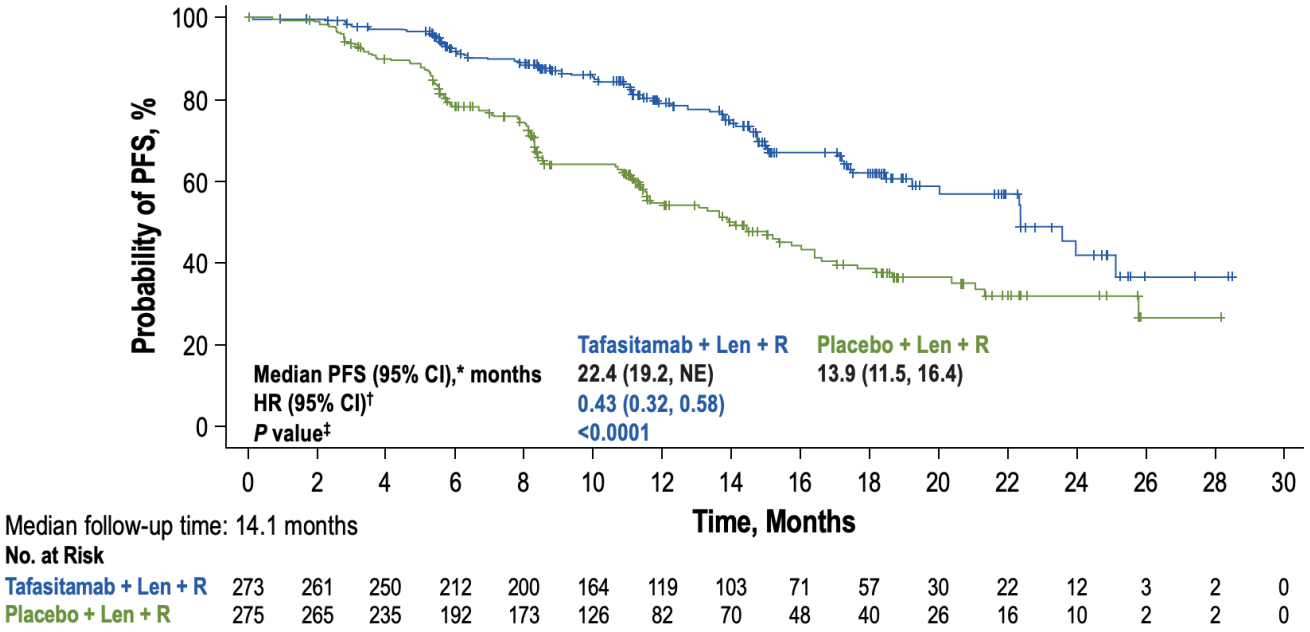
Sehn LH, et al. *Blood*. 2024;144(Suppl 2):LBA-1.

Primary Endpoint: PFS by Investigator Assessment



Significant improvement in PFS was observed with tafasitamab

Median PFS was improved by ~8 months with the addition of tafasitamab to lenalidomide + rituximab

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

Grade 3 or 4 TEAEs and Dose Modifications

Most Common Grade 3 or 4 TEAEs (≥5% in Any Group)

Preferred Term, n (%)	Tafasitamab + Len + R (n=274)*	Placebo + Len + R (n=272)†	Total (n=546)
Neutropenia	109 (39.8)	102 (37.5)	211 (38.6)
Pneumonia	23 (8.4)	14 (5.1)	37 (6.8)
Thrombocytopenia	17 (6.2)	20 (7.4)	37 (6.8)
Neutrophil count decreased	16 (5.8)	18 (6.6)	34 (6.2)
Anemia	12 (4.4)	16 (5.9)	28 (5.1)
COVID-19	16 (5.8)	6 (2.2)	22 (4.0)
COVID-19 pneumonia	13 (4.7)	3 (1.1)	16 (2.9)

- Tafasitamab and placebo dose interruptions or discontinuations due to TEAEs were similar between treatment arms, n (%):
  - Dose delay or interruption due to TEAEs: 203 (74%) vs 190 (70%)
  - Discontinued study treatment due to TEAEs: 30 (11%) vs 18 (7%)
- Len discontinuations due to TEAEs were similar between tafasitamab and placebo arms, n (%):
  - 39 (14%) vs 31 (11%)
- Len dose reductions were similar between tafasitamab and placebo arms
  - Median relative dose intensity: 86% vs 87%

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

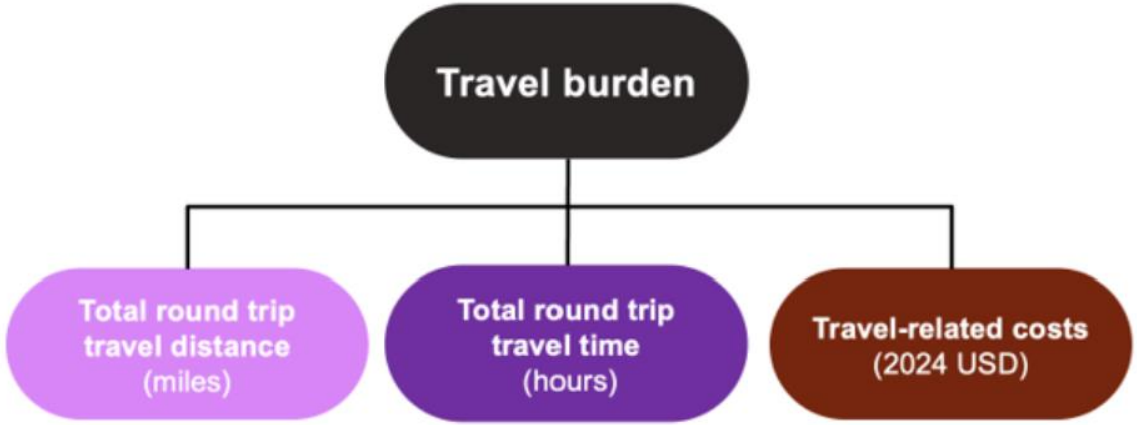
Individualized Approach to Relapsed/Refractory FL

- Patient characteristics
  - Age
  - Comorbidity
  - Tolerance of prior lines
  - Risk tolerance
  - Social determinants (support, access, travel, etc.)
  - Goals of care

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

LOT = line of therapy.

Methods: Real-World Data and an Economic Framework Were Used to Estimate Patient Travel Burden



- **Total driving distance** and **total travel time** were estimated using Google Maps and 5-digit zip codes for patient's residence and location of drug administration from the 100% FFS Medicare Dataset (January 1, 2022 – December 31, 2023)
- **Travel-related costs** were estimated based on driving costs (2024 IRS standard mileage rate[1]) and costs of work productivity loss (US Bureau of Labor Statistics 2024[2])

FFS, fee-for-service; IRS, Internal Revenue Service; USD, United States dollars.

1. IRS Standard Mileage Rates 2024. https://www.irs.gov/newsroom/irs-issues-standard-mileage-rates-for-2024-mileage-rate-increases-to-67-cents-a-mile-up-1-point-5-cents-from-2023. Accessed November 2024;
2. US Bureau of Labor Statistics 2024. https://www.bls.gov/news.release/empsit.t19.htm. Accessed November 2024.

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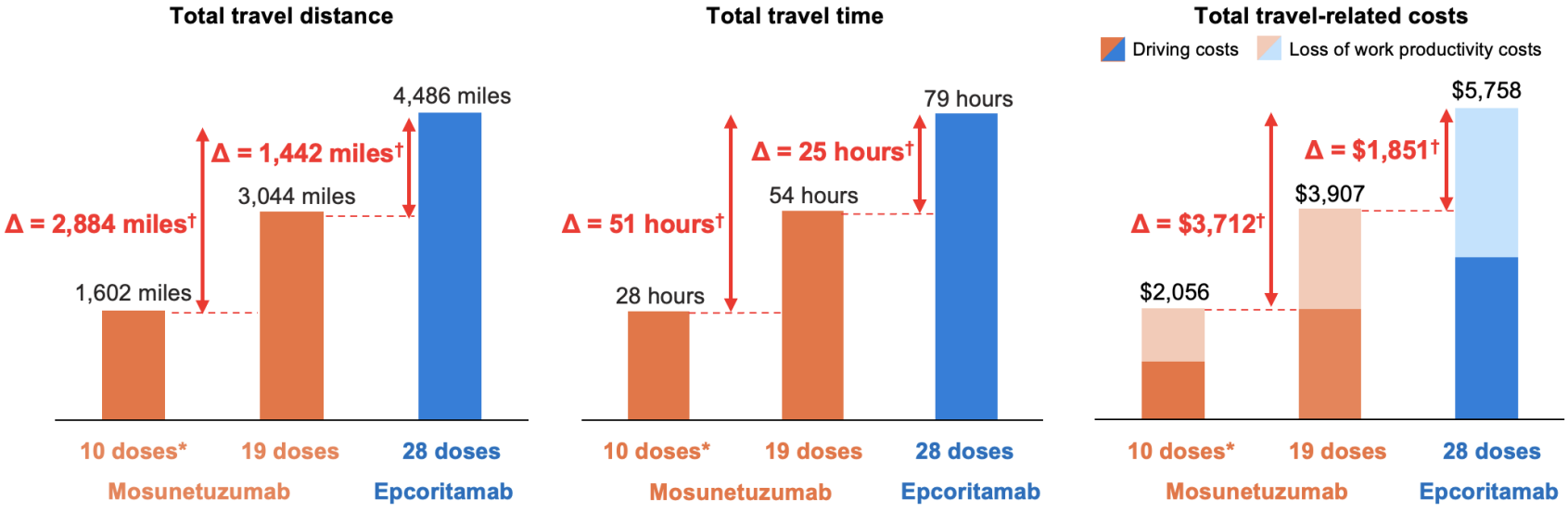
In FL, Mosunetuzumab's Less Frequent Administration Resulted in Lower Travel Distance, Time, and Related Costs versus Epcoritamab

Over a 1-year time horizon, fixed-duration mosunetuzumab treatment resulted in lower travel burden versus continuous epcoritamab treatment



*Patients who received mosunetuzumab and achieved CR after eight cycles required a total of 10 doses. †Differences shown are between epcoritamab and mosunetuzumab.

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Conclusions

In Medicare patients with NHL receiving BsAbs:

One-way travel distance: mean 80.1 miles; median 23.7 miles

One-way travel time: mean 84.5 minutes; median 40.0 minutes

The **less frequent dosing requirement** for fixed-duration **glofitamab and mosunetuzumab** treatment was associated with **lower travel burden** (distance, time and related costs) versus continuous epcoritamab treatment, which required more frequent administrations

Travel burden and travel costs associated with BsAb administrations may provide insight for patients and caregivers during **shared decision-making**

BsAb = bispecific antibody.

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Relapsed Follicular Lymphoma in 2025

- 1st relapse: rituximab/lenalidomide (+/- tafasitimab)
- 2nd relapse: CD19 CAR T-cell therapy versus CD3/CD20 bispecific antibody
- 3rd relapse: CD19 CAR T-cell therapy versus CD3/CD20 bispecific antibody
- 4th relapse and beyond: EZH2 inhibitor, BTK inhibitor/ obinutuzumab, chemotherapy, allogeneic SCT (highly select pts)
- OVERALL: Clinical trials, biomarker discovery, HRQL, and shared decision-making!!!

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SCT = stem cell transplantation.

Key Learning Points

- Targeted treatment options for R/R FL include CAR T cell therapy, monoclonal antibodies, bispecific antibodies, and targeted agents (eg, lenalidomide, EZH2 inhibitors, and BTK inhibitors)
- Lisocabtagene maraleucel is US Food and Drug Administration (FDA)-approved for R/R FL and demonstrated a complete response rate above 90% in clinical trials
- CRS incidence is moderate to high for patients treated with axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel
- Mosunetuzumab is now considered a standard, FDA-approved, non-chemotherapy option for third-line treatment in R/R FL
- Adding tafasitamab to lenalidomide and rituximab may extend median PFS by ~8 months in patients with R/R FL who have received at least two prior lines of therapy
- Shared decision-making and quality of life remain critical components in the treatment of R/R FL

Thank You!


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