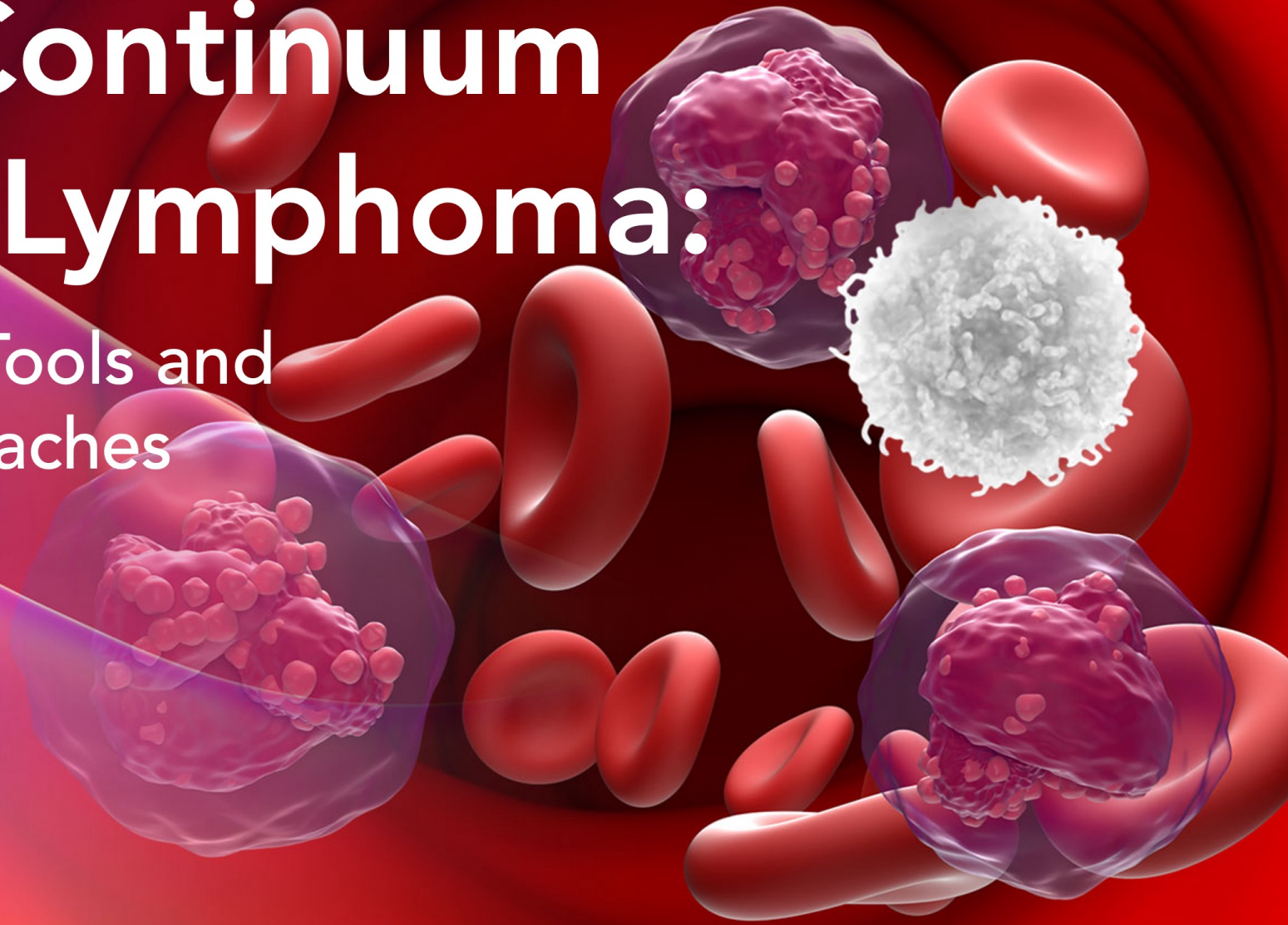
Pacing the Continuum of Follicular Lymphoma:

Integrating Prognostic Tools and Novel Treatment Approaches



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This taped Satellite Symposium is derived from the Society of Hematologic Oncology 2023 Annual Meeting, originally presented Friday, September 8, 2023. It is not sponsored or endorsed by the Society of Hematologic Oncology.

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Activity Overview

Target Audience

This activity is intended for hematologic oncology physicians, nurses, pharmacists, and advanced practice clinicians who provide care for individuals with hematologic malignancies, especially follicular lymphoma.

Educational Objectives

After completing this activity, the participant should be better able to:

- Apply prognostic tools to the evaluation and management of patients with FL, including patients with hallmarks of aggressive disease
- Compare and contrast mechanisms of action, efficacy data, and toxicity profiles for new and emerging therapies, including for third-line and later treatment settings in FL
- Select therapies for patients with RR FL in consideration of prior therapy, disease factors, patient factors, and treatment goals

Agenda

- Standard approaches to care in FL and implications of prognostic markers
- The latest clinical evidence and guideline recommendations for treatment decision-making in FL and common TRAEs (treatment-related adverse events)
- Patient-related factors that play an important role in access to novel therapies for FL and improved outcomes
- Q&A with Faculty

Accreditation Information

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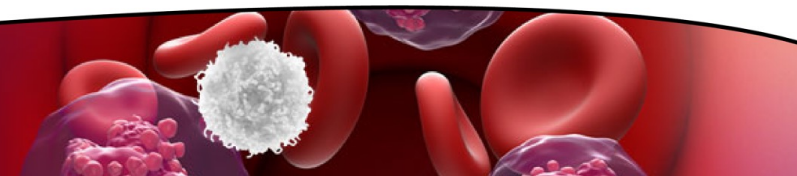
Universal Activity Number: JA0007322-9999-23-067-L01-P
Type of Activity: Application



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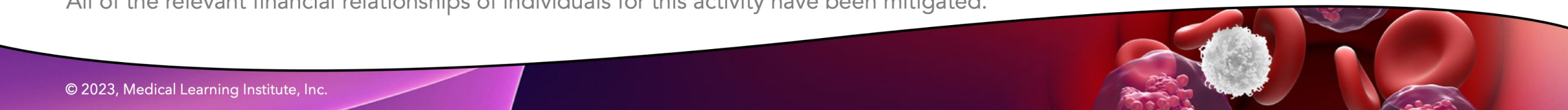

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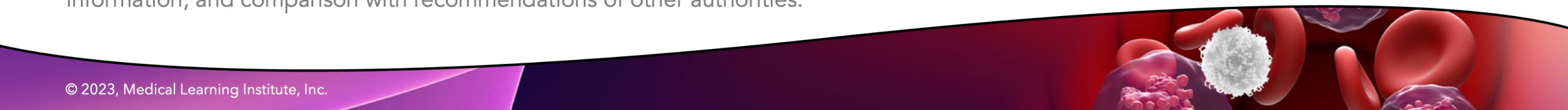
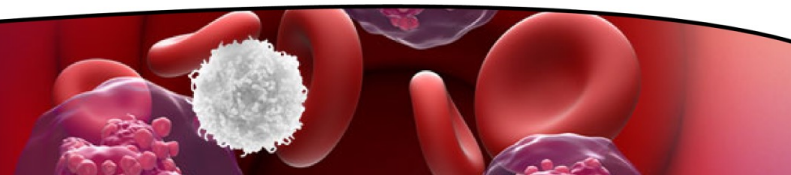


Advances in the Treatment of R/R Follicular Lymphoma

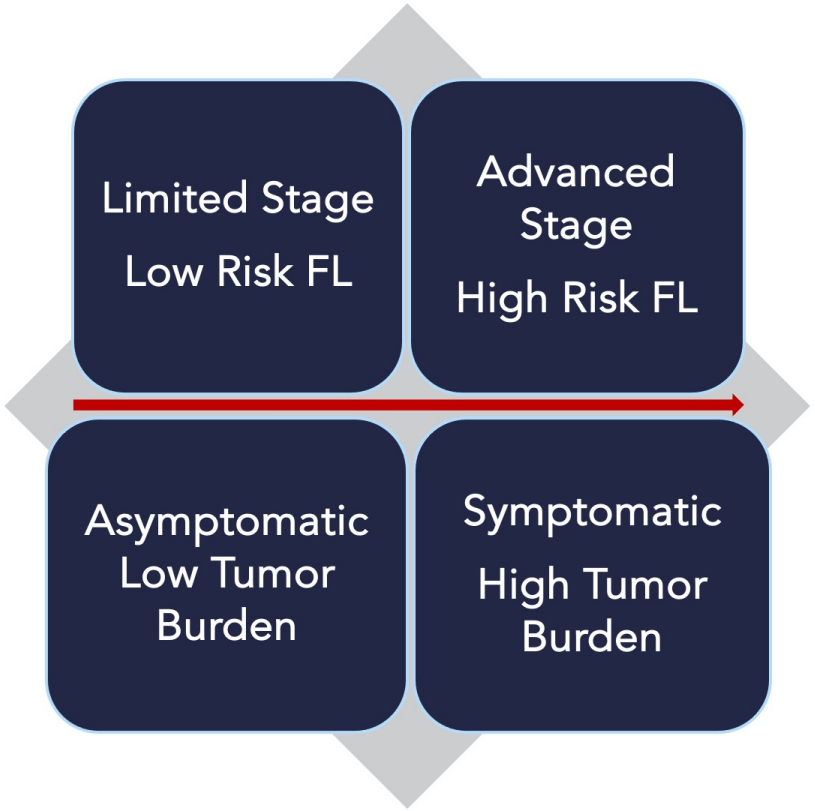
Challenges in FL Management and Treatment

- No formal standard of care
- Possibility of histological transformation
- Predicting prognosis
- Optimal sequencing of available therapies
- Rapidly evolving treatment landscape
- Patient QoL, preferences, and goals of therapy
- Lack of head-head studies of recently approved agents

Reference: Qualls D, Salles G. Haematologica. 2022;107(1):19-34.



The Clinical Spectrum of FL



- Second most common subtype of NHL
- Indolent and incurable
- Heterogenous disease
- PFS reduces with each relapse

Despite recent advances and improved OS, FL remains the leading cause of death in patients.

- Goals of treatment are to maximize efficacy, reduce risk of relapse, and limit toxicities to support patient QoL

FL, follicular lymphoma; NHL, non-Hodgkin lymphoma; OS, overall survival; PFS, progression-free survival; QoL, quality of life

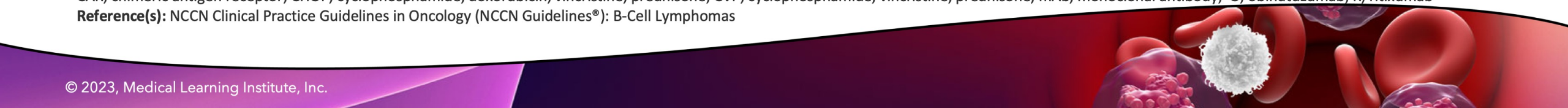
Reference(s): Batlevi CL, et al. *Blood Cancer J.* 2020; 10(7):74.2; Tun AM, et al. *Blood Adv.* 2022; 6 (17): 5210–5221.

NCCN Clinical Treatment Guidelines

First-line Therapy	• Bendamustine + obinutuzumab or rituximab • R-CHOP or O-CHOP • R-CVP or O-CVP • Lenalidomide + ritixumab	• Rituximab (375 mg/m^2 weekly) – consider for low tumor burden • Lenalidomide + obinutuzumab (category 2B)
Second-line Therapy	• Bendamustine + obinutuzumab or rituximab • R-CHOP or O-CHOP • R-CVP or O-CVP • Lenalidomide + ritixumab	• Rituximab or obinutuzumab • Lenalidomide + obinutuzumab • Lenalidomide + ritixumab • Lenalidomide (ineligible mAb)
Third-line/ Subsequent Therapy	• PI3K inhibitor: copanlisib • EZH2 inhibitor: tazemetostat • Anti-CD19 CAR T-cell therapy: axicabtagene ciloleucel and tisagenlecleucel • Bispecific T-cell engager therapy: monsunetuzumab	

CAR, chimeric antigen receptor; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CVP, cyclophosphamide, vincristine, prednisone; mAb, monoclonal antibody; O, obinutuzumab; R, ritixumab

Reference(s): NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): B-Cell Lymphomas



Criteria for Treatment Initiation: Which Patients Need Treatment?

GELF Criteria
High tumor bulk defined by: ▪ Tumor >7 cm ▪ 3 nodes in 3 distinct areas, each >3 cm ▪ Symptomatic splenic enlargement ▪ Organ compression ▪ Ascites or pleural effusion
Presence of systemic symptoms
Serum LDH or b2-microglobulin above the normal values

BNLI criteria
Rapid disease progression in the preceding 3 mo
Life-threatening organ involvement
Renal or liver infiltration
Bone lesions
Systemic symptoms or pruritus
Hb <10 g/dL or WBC <3.0 x 10^9/L or platelet count <100 x 10^9/L; related to marrow involvement

For advanced-stage FL without criteria for treatment initiation (asymptomatic disease), the recommendation is usually to propose therapeutic abstention with dynamic observation, or "Watch and Wait"

BNLI, British National Lymphoma Investigation; GELF, Groupe d'Etude des Lymphomes Folliculaires, Hb, hemoglobin; LDH, lactate dehydrogenase; WBC, white blood cell count

Reference(s): Brice P, et al. *J Clin Oncol*. 1997;15(3):1110-1117; Ardeshna KM, et al. *Lancet*. 2003;362(9383):516-522.

Advanced-stage, Low Tumor Burden FL: Single-Agent Rituximab v. "Watch and Wait"

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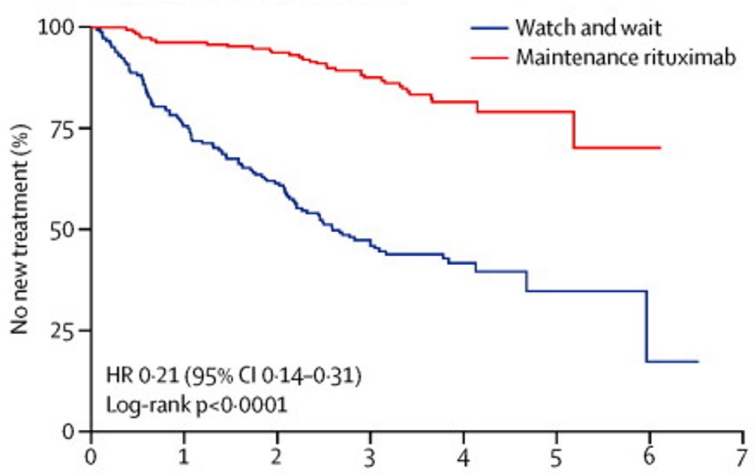
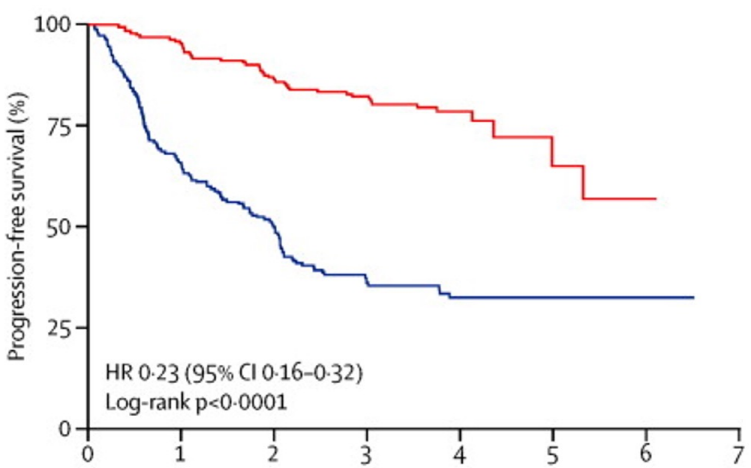
A. Time to start of new treatment



Number at risk

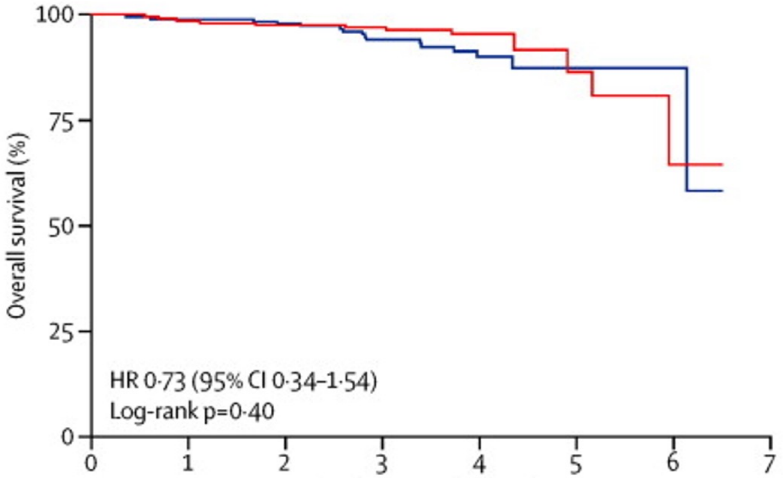
Watch and wait	187	139	111	66	33	6	1	0
Maintenance rituximab	192	184	176	146	59	10	1	0

B. Progression-Free Survival



	187	121	92	54	28	6	1	0
	192	183	165	138	56	9	1	0

C. Overall Survival



	187	181	175	130	68	18	4	0
	192	189	186	163	72	16	3	0

Reference: Ardeshna. Lancet Oncol. 2014;15:424.

RESORT Trial: Rituximab Maintenance v. Retreatment

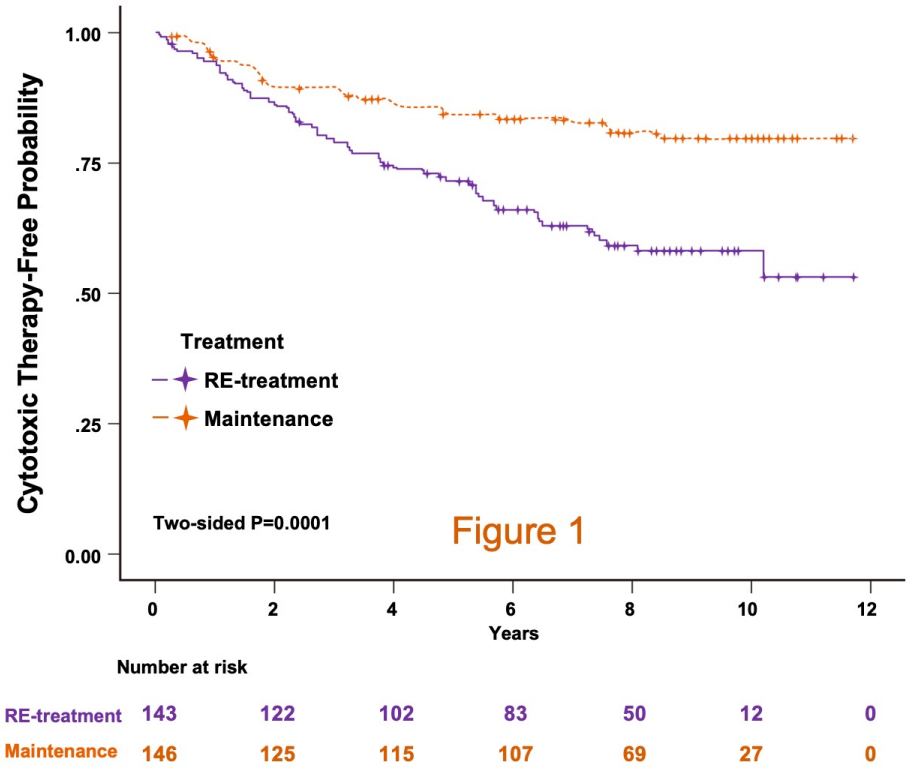


Figure 1

Number at risk

RE-treatment	143	122	102	83	50	12	0
Maintenance	146	125	115	107	69	27	0

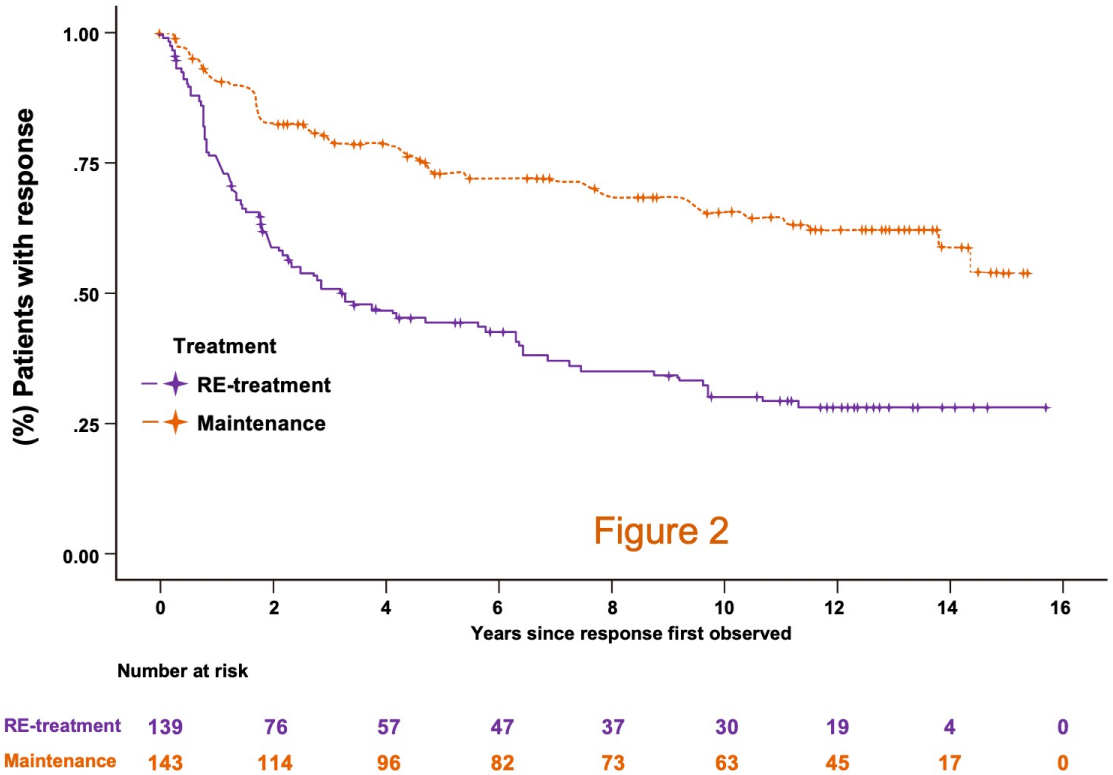


Figure 2

Number at risk

RE-treatment	139	76	57	47	37	30	19	4	0
Maintenance	143	114	96	82	73	63	45	17	0

In low-tumor burden FL, there was no difference OS or in health-related quality of life between maintenance vs. retreatment with ritixumab

Reference: Kahl BS, et al. *J Clin Oncol*. 2014;32(28):3096-3102; Brad S. Kahl, et al. *Blood.* 2021; 138 (Supplement 1): 815.

Prognostic Indices and Factors

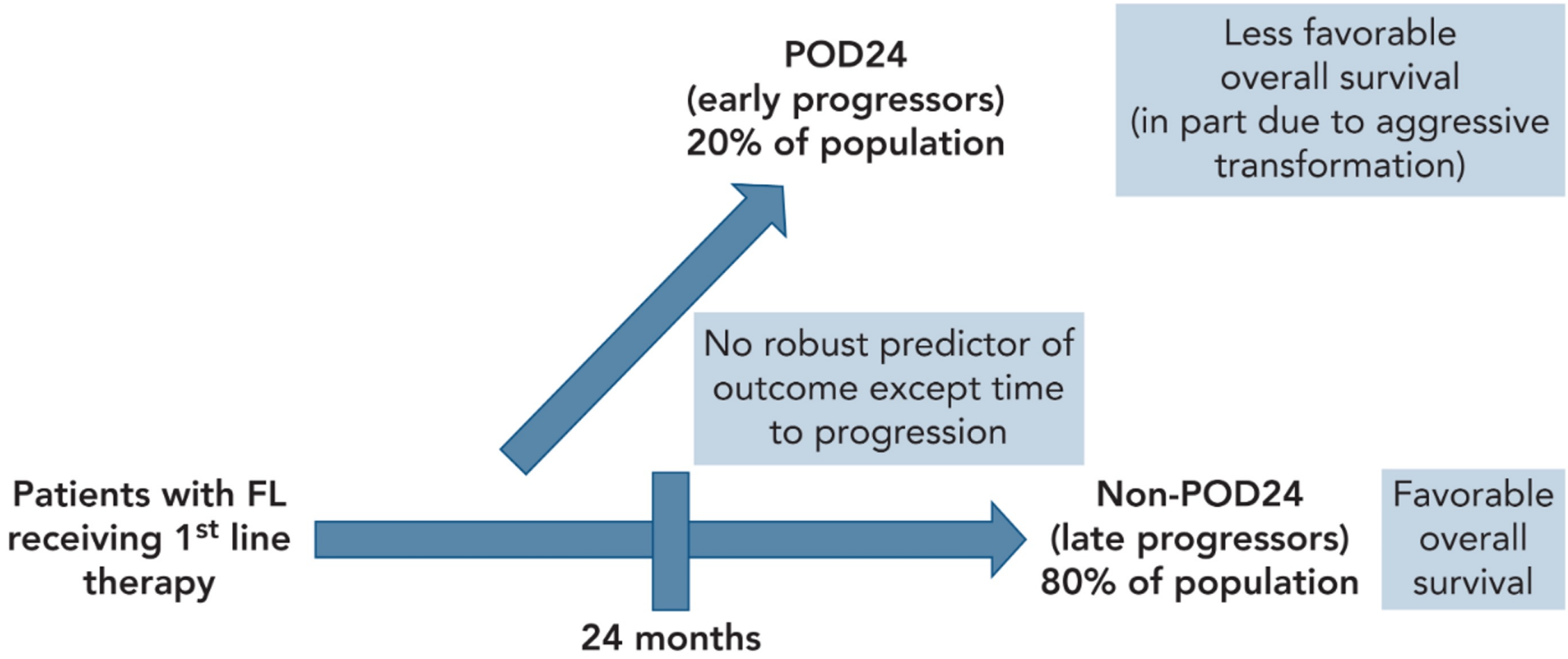
FLIPI		FLIPI-2	PRIMA-PI
▪ Age >60 years ▪ Serum LDH > ULN ▪ Hgb < 12 g/dL ▪ Ann Arbor stage III or IV ▪ Number of nodal sites >4		▪ Age >60 years ▪ Bone marrow involvement ▪ Hgb < 12 g/dL ▪ Tumor mass > 6 cm ▪ β-2 microglobulin > normal	▪ Bone marrow involvement ▪ β-2 microglobulin > 3mg/L
Risk Group	# risk factors	# risk factors	# risk factors
Low	0-1	0	β2m ≤ 3 mg/L and BM (-)
Intermediate	2	1-2	β2m ≤ 3 mg/L and BM (+)
High	3-5	3-5	β2m > 3 mg/L

Cytogenic adverse prognostic factors:
complex karyotype; *BCL2/MYC* rearrangement; del6q25-27; del117p and/or mutations of *TP53*

BM, bone marrow involvement; FLIPI, follicular lymphoma international prognostic index; Hgb, hemoglobin; LDH, lactate dehydrogenase

Reference: Jacobsen E. Am J Hematol. 2022;97(12):1638-1651; Cartron G, Trotman J. Haematologica 2022;107(1):7-18.

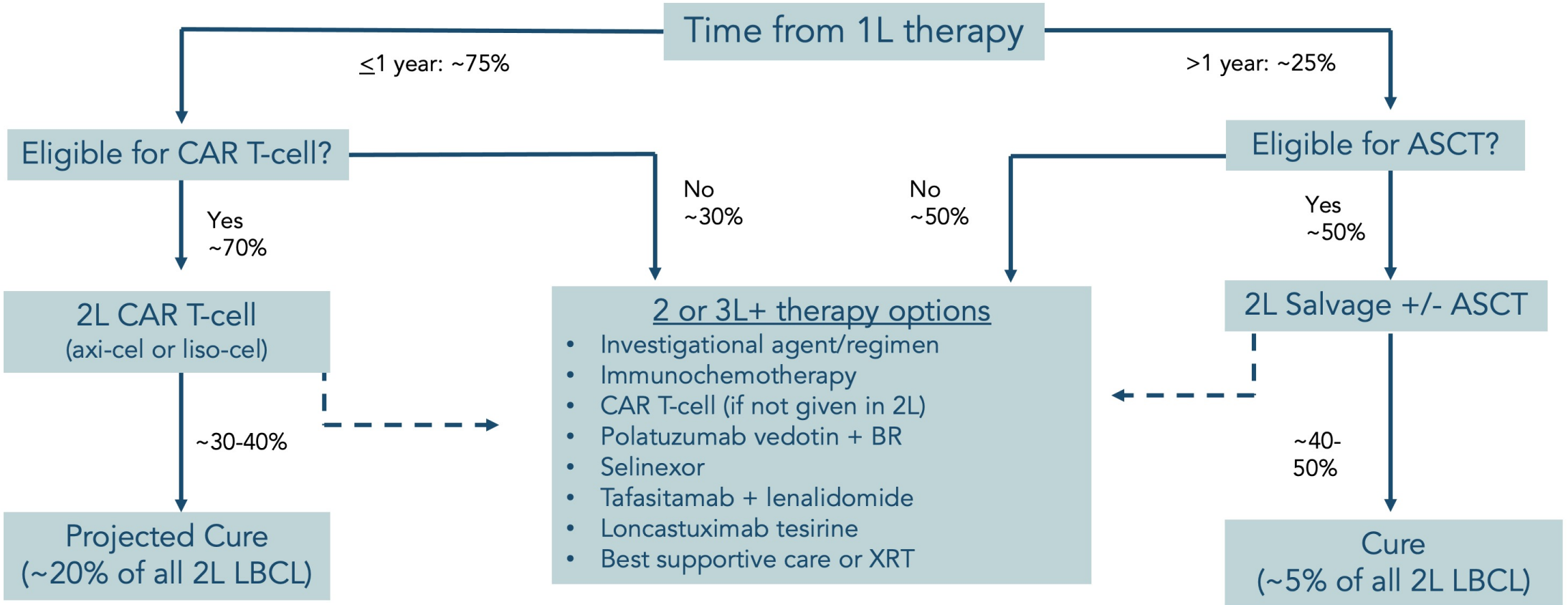
Progression of Disease within 2 years (POD24)



Reference: Leonard JP. Blood. 2022;139(11):1609-1610.

Transformed Lymphoma Treated as DLBCL: Eligibility Criteria for 2L Therapy

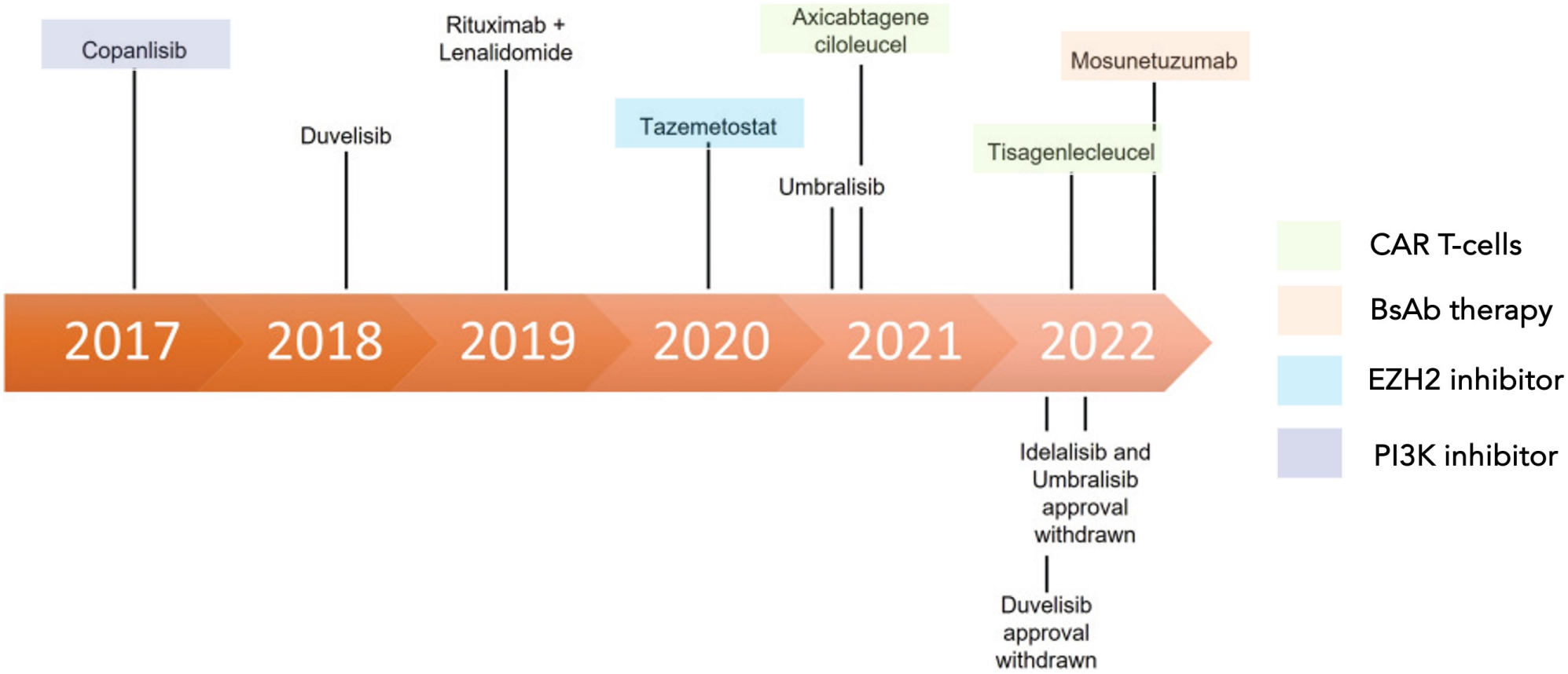
Algorithm for Second-line Therapy of LBCL



1L, first line; 2L, second line; ASCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; BR, bendamustine + rituximab; CAR, chimeric antigen receptor; LBCL, large B-cell lymphoma; liso-cel, lisocabtagene maraleucel; XRT, consolidation radiation therapy.

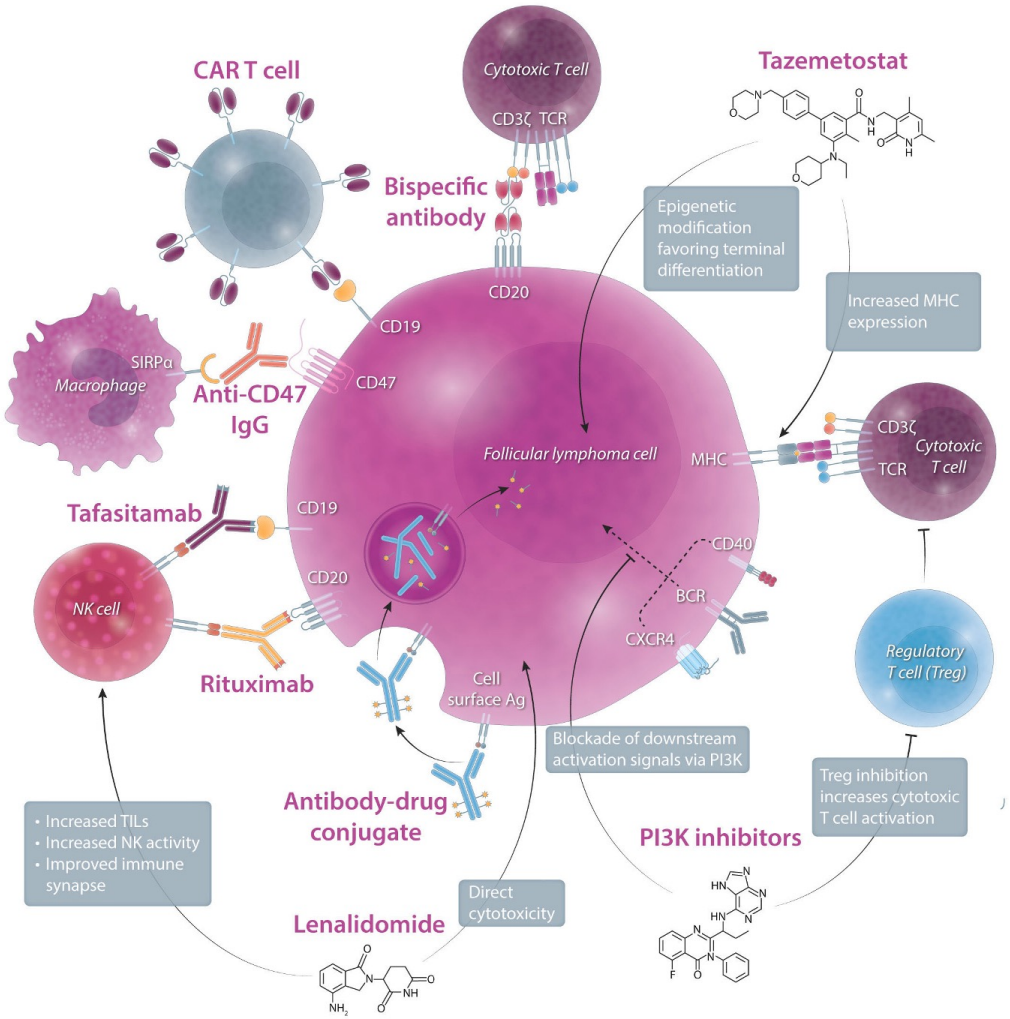
Reference: Westin J, Sehn LH. *Blood.* 2022;139(18):2737-2746.

Expanding Treatment Options in R/R FL



Reference: Lopedote P, et al. *Cancer Manag Res.* 2023;15:257-264.

Novel Mechanisms of in R/R FL

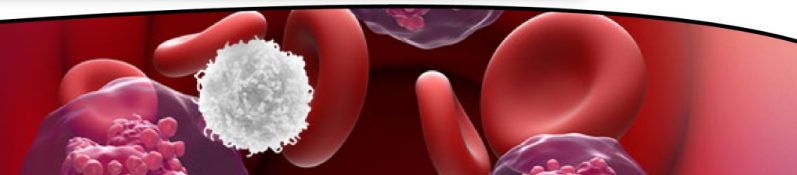


Reference: Qualls D, Salles G. Haematologica. 2022;107(1):19-34.

RAPID ROUND

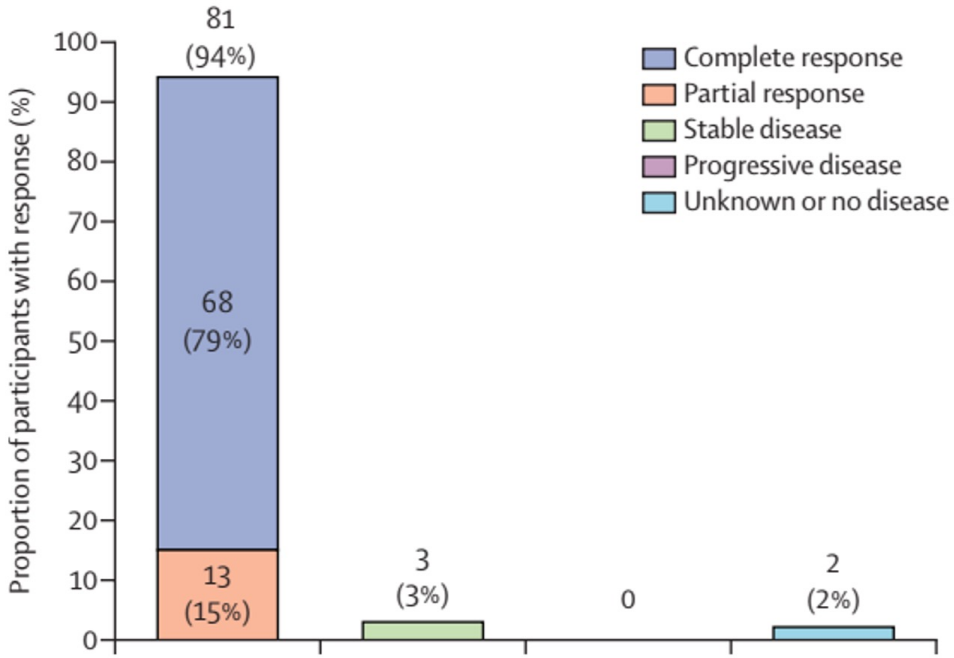
Which of the following descriptions correctly aligns (pairs) with the appropriate T-cell directed agent:

tisagenlecleucel	Emerging subq bsAb, deep and durable response, in combination with SOC
mosunetuzumab	CAR T, deep and durable response, more tolerable
odronextamab	CAR T, high efficacy, less tolerable
epcoritamab	FDA-approved bsAb in 3L setting
axicabtagene ciloleucel	Emerging bsAb, deep and durable response, as single agent



ZUMA-5: Axicabtagene ciloleucel (axi-cel)

Phase II, single-arm, multicenter study, evaluating the safety and efficacy of axi-cel (N=104) in patients with R/R indolent NHL, including FL (n=86)



Secondary Endpoints	Median (95% CI), mo
PFS	NR (23.5 – NE)
OS	NR (31.6 – NE)
CRS (All Grades v. Grade ≥3)	Neurotoxicity (All Grades v. Grade ≥3)
78% v. 6%	56% v. 15%

Median follow-up of 17.5 months

CRS, cytokine release syndrome; FL, follicular lymphoma, NHL, non-Hodgkin lymphoma; PFS, progression-free survival; OS, overall survival, R/R, relapsed/refractory

Reference: Jacobson CA, et al. *Lancet Oncol.* 2022;23(1):91-103.

ELARA: Tisagenlecleucel (tisa-cel)

Phase II, single-arm, multicenter, open-label study evaluating the safety and efficacy of tisa-cel (N=97) in patients with R/R follicular lymphoma

Table 2 | Best overall response in the EAS and per-protocol population[a]

Parameter	Per-protocol set, $n = 85$		EAS, $n = 94$	
	Local assessment	IRC assessment	Local assessment	IRC assessment
Best overall response, *n* (%)				
CR	64 (75.3); 95% CI, 64.7–84.0	62 (72.9); 95% CI, 62.2–82.0	68 (72.3); 95% CI, 62.2–81.1	65 (69.1); 95% CI, 58.5–78.3
PR	14 (16.5)	12 (14.1)	17 (18.1)	16 (17.0)
SD	2 (2.4)	3 (3.5)	3 (3.2)	3 (3.2)
PD	5 (5.9)	8 (9.4)	6 (6.4)	9 (9.6)
UNK				1 (1.1)
Overall response rate (CR + PR), *n* (%)	78 (91.8); 95% CI, 83.8–96.6	74 (87.1); 95% CI, 78.0–93.4	85 (90.4); 95% CI, 82.6–95.5	81 (86.2); 95% CI, 77.5–92.4

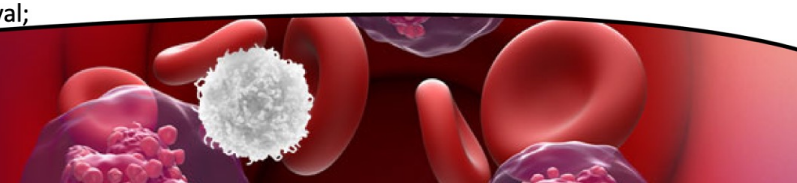
[a]The per-protocol set is a subset of patients in the primary analysis efficacy set with no major protocol deviations. UNK, unknown.

Secondary Endpoints	Median (95% CI), mo
PFS	NR (12.3 – NE)
OS	NR (NE – NE)
CRS (All Grades v. Grade ≥3)	**Neurotoxicity (All Grades v. Grade ≥3)**
48.5% v. 0%	4.1% v. 1.0%

Median follow-up of 16.6 months

CR, complete response; CRS, cytokine release syndrome; EAS, efficacy analysis set; IRC, independent review committee; PFS, progression-free survival; PR, partial response; OS, overall survival, SD, stable disease; PD, disease progression, UNK, unknown

Reference: Fowler NH, et al. *Nat Med.* 2022; 28, 325–332.



GO29781: Mosunetuzumab

Phase II, single-arm, open-label, multicenter, multicohort study evaluating the safety and efficacy of mosunetuzumab (N=90) in patients with R/R follicular lymphoma who received ≥2L of therapies

	Independent review committee assessment (n=90)	Investigator assessment (n=90)
Objective response rate*	72 (80·0% [70·3–87·7])	70 (77·8% [67·8–85·9])
Complete response rate*	54 (60·0% [49·1–70·2])	54 (60·0% [49·1–70·2])
Time to first response, months	1·4 (1·2–2·9)	1·4 (1·2–2·8)
Time to first complete response, months	3·0 (1·4–5·7)	3·0 (1·4–5·7)
Duration of response		
Patients with event	29/72 (40%)	27/70 (39%)
Median, months (95% CI)	22·8† (9·7–NR)	22·8† (18·7–NR)
12-month event-free rate	61·8% (50·0–73·7)	64·8% (53·1–76·5)
18-month event-free rate	56·9% (44·1–69·6)	62·5% (50·4–74·7)
Duration of response in complete responders		
Patients with event	16/54 (30%)	12/54 (22%)
Median, months (95% CI)	22·8† (18·7–NR)	22·8† (19·9–NR)
12-month event-free rate	76·4% (64·6–88·1)	84·3% (74·3–94·3)
18-month event-free rate	70·2% (56·7–83·8)	81·3% (70·0–92·5)
Duration of complete response		
Patients with event	16/54 (30%)	12/54 (22%)
Median, months (95% CI)	NR (14·6–NR)	NR (17·8–NR)
12-month event-free rate	71·4% (57·9–84·9)	80·4% (68·8–92·0)
18-month event-free rate	63·7% (48·0–79·4)	66·6% (45·5–87·8)

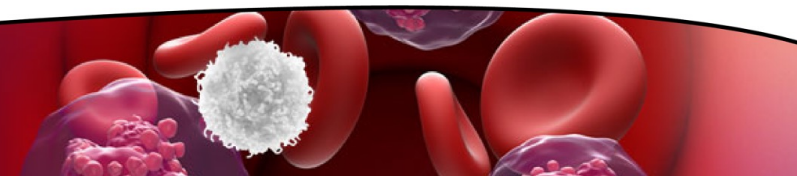
Median follow-up of 14.9 months

Secondary Endpoints	Median (95% CI), mo
PFS	17.9 (10.1– NR)
OS	NR (NR – NR)
CRS (All Grades v. Grade ≥3)	**Neurotoxicity (All Grades v. Grade ≥3)**
44% v. 2%	3% v. 0%

FDA-approved bispecific T-cell engager for adult patients with R/R FL after two or more lines of systemic therapy.

CRS, cytokine release syndrome; PFS, progression-free survival; OS, overall survival

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



ELM-2: Odronextamab

Phase II, open-label, multicenter, multicohort study evaluating the safety and efficacy of monotherapy odronextamab in patients with R/R B-NHL (N=131FL)

Best overall response	Independent central review (N=121)*	Investigator evaluation (N=121)*
Objective response rate (ORR) †	81.8% [95% CI: 73.8–88.2%]	81.8% [95% CI: 73.8–88.2%]
CR	75.2%	70.2%
PR	6.6%	11.6%
SD	5.8%	2.5%
PD	4.1%	5.8%

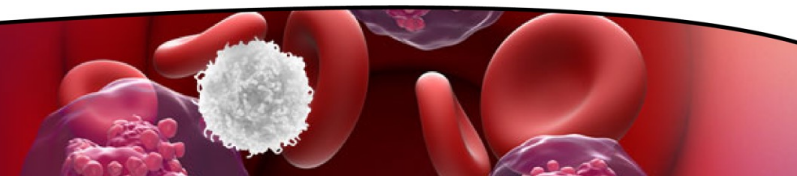
Secondary Endpoints	Median (95% CI), mo
PFS	20.2 (14.8–NE)
OS	NR (NE–NE)
CRS (All Grades v. Grade ≥3)	**Neurotoxicity (All Grades v. Grade ≥3)**
57.1% v. 1.6%	0%

0.7/4/20 mg step-up regimen reduced the incidence of grade 2 and grade 3 CRS

Median follow-up of 22.4 months

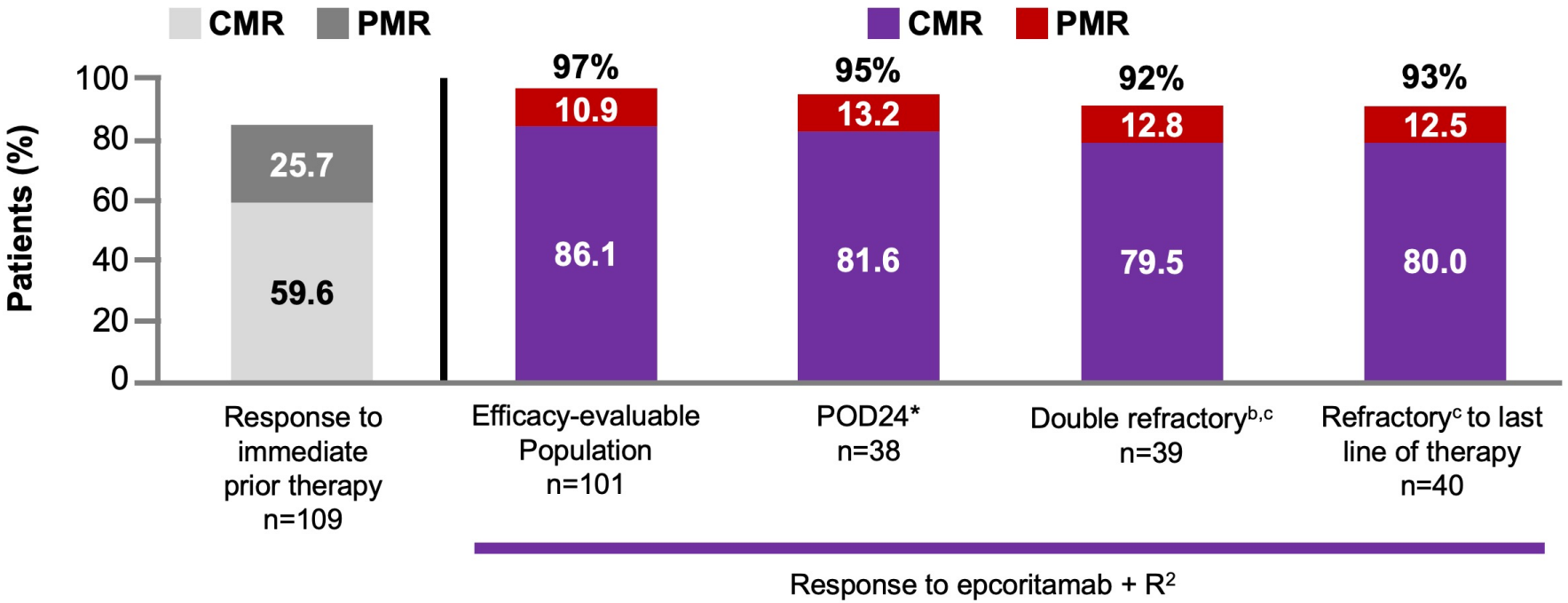
*Efficacy evaluable (with an opportunity for assessment at 12 weeks); †ORR = Complete responses + Partial responses

Reference: Kim TM, et al. *Blood.* 2022; 140 (Supplement 1): 1070–1071



EPCORE-NHL 2: Epcoritamab (SQ) + R²

Phase I/III, open-label, multicenter, multicohort study evaluating the safety and efficacy of SQ epcoritamab + R² in patients with R/R FL (N=109)



CRS (All Grades v. Grade ≥3)	48% v. 2%
Neurotoxicity (All Grades v. Grade ≥3)	0%

Median follow-up of 8.8 months

[a] POD24 indicates progression within 2y of 1L with chemoimmunotherapy [b] double refractory indicates refractory to both anti-CD20 and an alkylating agent [c] Refractory indicates no response or relapse within 6 mo after therapy
CMR, complete metabolic response; PMR, partial metabolic response, POD24, progression of disease within 2 years

Reference: Falchi L, et al. ASCO 2022 in Chicago, IL. Abstract 7524. Sureda A, et al. EHA 2023 in Frankfurt, Germany. Abstract S222.

CAR T-cell Therapy TEAEs

CRS median onset: 4 days
Duration: 4-7 days

LEUKEMIA & LYMPHOMA SOCIETY®

Non-Hematological

- CRS with ICANS
- Thrombocytopenia
- Neutropenia
- Anemia
- Gastrointestinal disorders
- Infections

Commonly occurs with:
- Axicabtagene ciloleucel
- Tisagenlecleucel

PREVENT

- Provide effective education at treatment start and throughout
- Assess prior treatment risk factors, which may place patient at increased risk (e.g., age, genetics, comorbidities)
- Understand mechanisms that contribute to inflammatory toxicities (e.g., activation of myeloid cells)

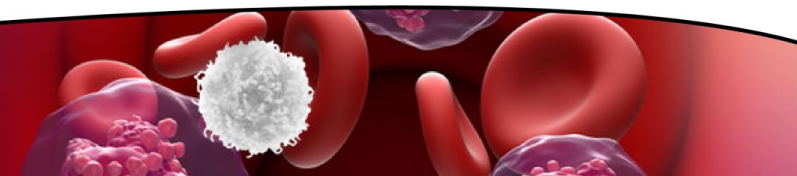
MONITOR

- Monitor and assess CRS and ICANs by grade
- Provide brain imaging for neurologic symptoms (MRI > CT)

MITIGATE SYMPTOMS

- Low-grade CRS and neurotoxicity can be managed by supportive care, corticosteroids, or small molecule inhibitors
- Provide prophylactic antiseizure medication if needed
- Provide monthly immunoglobulin G for patients at risk of infection

References: Jacobson CA, et al. *Lancet Oncol.* 2022;23(1):91-103. Fowler NH, et al. *Nat Med*. 2022; 28, 325–332. Adkins S. J Adv Pract Oncol. 2019(Suppl 3):21-28



Bispecific Antibody TEAEs

CRS median onset: 5 hours
Duration: 3 days

LEUKEMIA & LYMPHOMA SOCIETY®

Non-Hematological

- CRS with ICANS
- Fatigue
- Headache
- Pyrexia
- Neutropenia
- Hypophosphataemia

Commonly occurs with:

- Mosunetuzumab-axgb

PREVENT

- Provide effective education at treatment start and throughout
- Assess prior treatment risk factors, which may place patient at increased risk (e.g., age, genetics, comorbidities)
- Understand mechanisms that contribute to inflammatory toxicities (e.g., activation of myeloid cells)

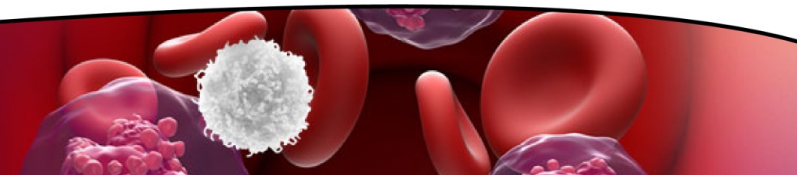
MONITOR

- Monitor and assess CRS and ICANs by grade
- Provide brain imaging for neurologic symptoms (MRI > CT)

MITIGATE SYMPTOMS

- Low-grade CRS and neurotoxicity can be managed by supportive care, corticosteroids, or small molecule inhibitors
- Administration of step-up dosing
- Provide prophylactic antiseizure medication if needed

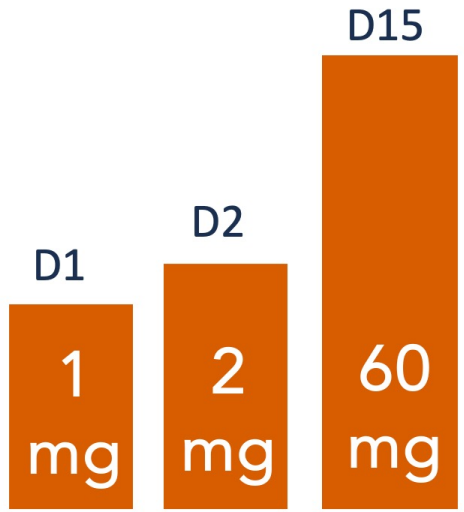
References: Budde LE, et al. *Lancet Oncol*. 2022;23(8):1055-1065.



Step-Up Dosing for CRS Mitigation

Mosunetuzumab (IV)

Step-up dosing

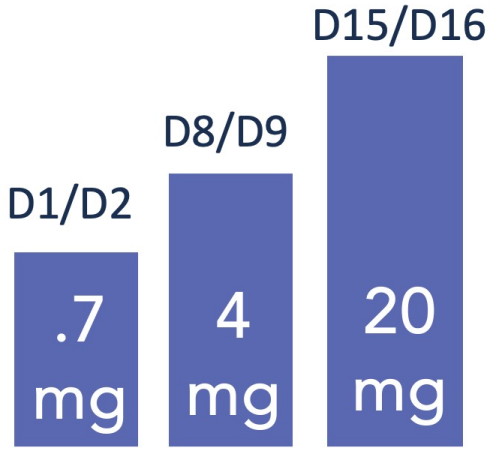


Cycle 1: 21 days

	Dose	Days
Cycle 2	60 mg	21
Cycle 3+	30 mg	21

Odronextamab (IV)

Step-up dosing

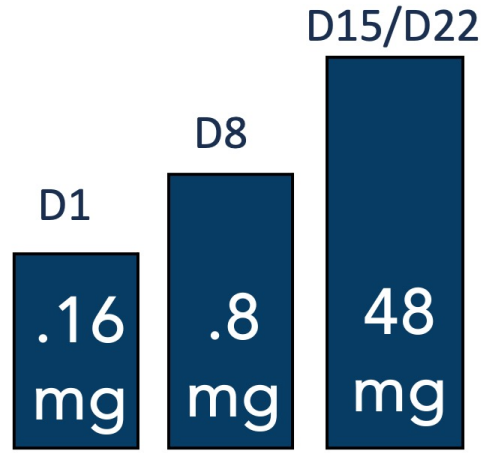


Cycle 1: 21 days

	Dose	Days
Cycle 2-4	80 mg	21
Cycle 5+*	160 mg	21

Epcoritamab (SQ)

Step-up dosing



Cycle 1: 28 days

	Dose	Days
Cycle 2-3	48 mg	28
Cycle 4-9*	48 mg	28

*** Q2W,** every other week

References: Monsunetuzumab. Product Information. Taszner, M, et al. EHA 2023. P1083. *HemaSphere.* 7:p e214536e. Thieblemont C, Phillips T, et al. *J Clin Oncol*. 2023. 41:12, 2238-2247.

Comparison of BsAb and CAR T- cell Therapy

Bispecific Antibody Therapy	CAR T-cell Therapy
Available off the shelf	Engineered for each patient
Fraction of cost for 1-2 cycles	Expensive and time consuming
Manufactured in large quantities	Requires sufficient peripheral counts
Required to be continued indefinitely	One-time infusion
≥3 adverse events: CRS and ICANS	

Toxicity associated with bispecific antibody therapy appears to be lower than that with CAR T-cells

Clinical trials have recently shown responses to bispecific antibody therapy after failure of CAR T-cell therapy

References: Subklewe M. Blood Adv. 2021;5(2):607-612. Abramson JS. American Society of Clinical Oncology Educational Book 40 (May 18, 2020) 302-313