

CD20 X CD3 Bispecifics—Redefining Treatment for Patients with R/R DLBCL/LBCL in the Community Setting



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Learning Objectives

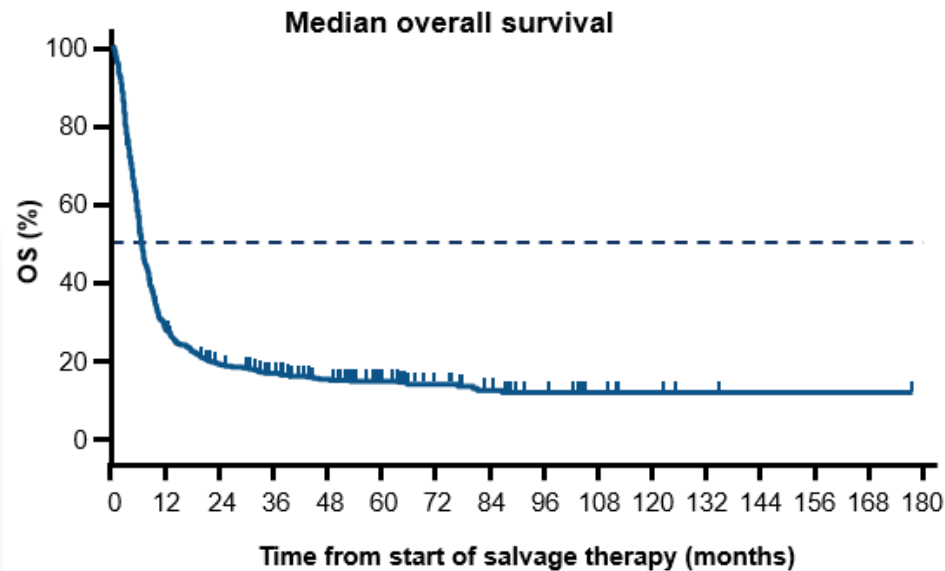
Upon completion of this activity, participants should be better able to:

- Evaluate the novel MOA of CD20 X CD3 bispecific antibodies, how these agents are delivered, and the differences among and between these agents and CAR T-cell therapies for R/R DLBCL
- Summarize updated clinical efficacy/safety data associated with the use of CD20 X CD3 bispecific antibodies for R/R DLBCL/LBCL
- Develop team-based, multidisciplinary treatment plans that involve shared decision-making tactics for selected patients with R/R DLBCL/LBCL and include CD20 X CD3 bispecific antibodies based on clinical evidence, disease- and patient-related characteristics, and patient goals and preferences
- Integrate team-based management and care coordination strategies for adverse events, including CRS and ICANS, related to the use of CD20 X CD3 bispecific antibodies for R/R LBCL/DLBCL

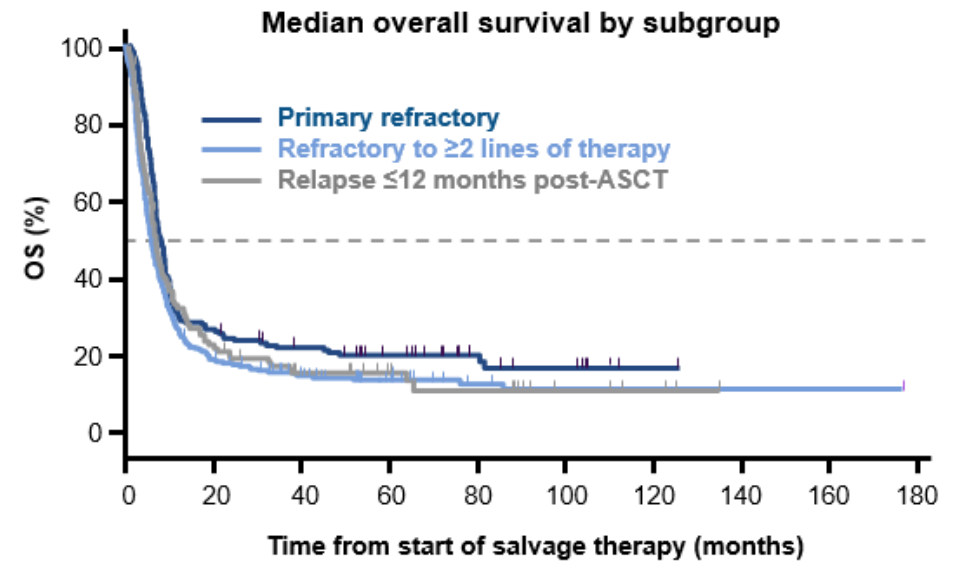
Rel/Ref LBCCL: Where We've Come From

Poor Outcomes in Rel/Ref LBCL Post 1st Line

Scholar-1: Retrospective analysis of outcomes in patients with R/R DLBCL (N = 636)



	Median OS (months)	2-yr survival
All	6.3	20%

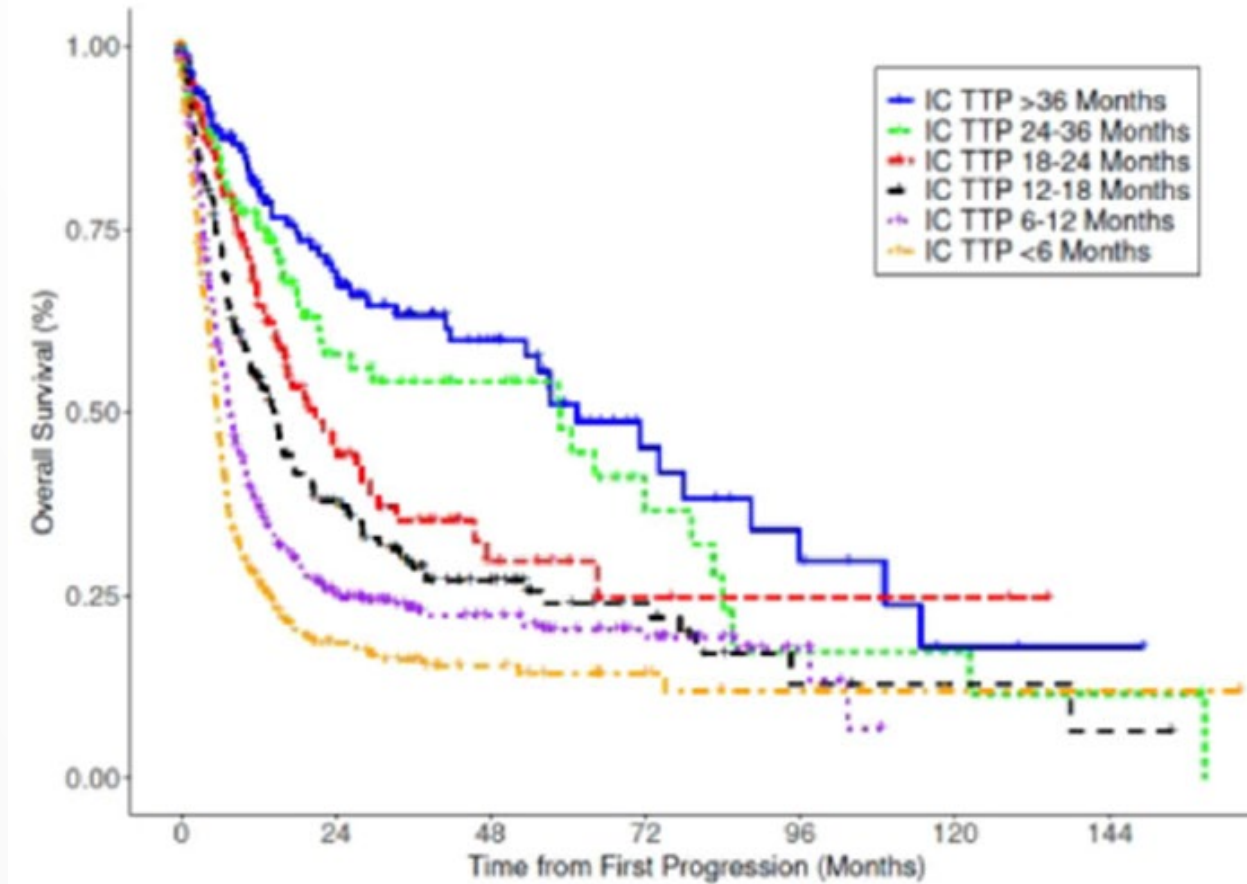


	Median OS (months)	2-yr survival
Primary refractory	7.1	24%
Refractory to ≥ 2 lines of therapy	6.1	17%
Relapse ≤ 12 months post-ASCT	6.2	19%

Crump M, et al. *Blood*. 2017;130(16):1800-1808.

ASCT, autologous stem cell transplant; DLBCL, diffuse large B-cell lymphoma; LBCL, large B-cell lymphoma; OS, overall survival; Rel/Ref, relapsed/refractory.

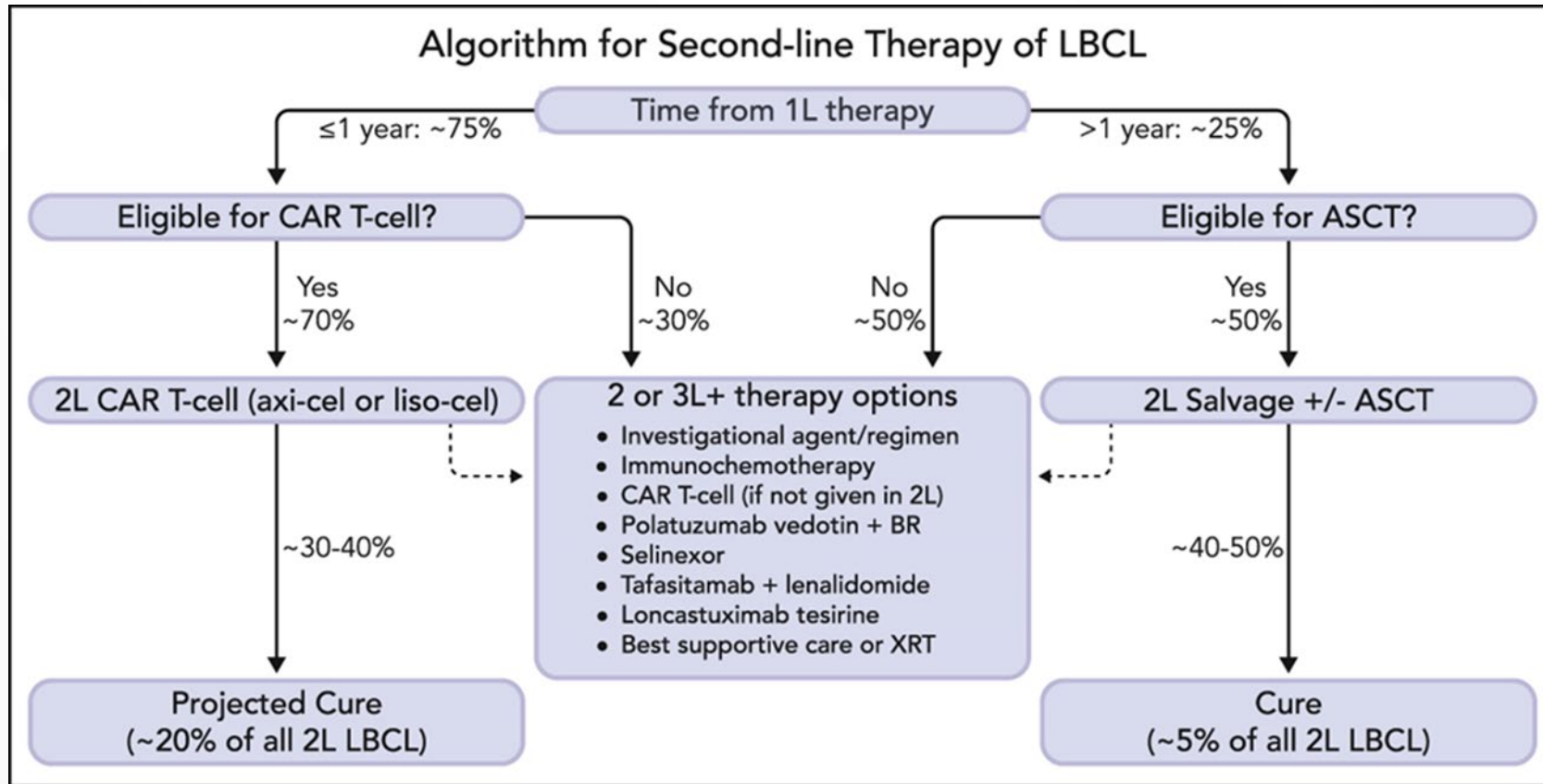
Timing Matters: Poor Outcomes in Rel/Ref LBCL Post 1st Line



Maurer MJ, et al. *Am J Hematol.* 2021;96(5):599-605.

IC, immunochemotherapy; LBCL, large B-cell lymphoma; Rel/Ref, relapsed/refractory; TTP, time to disease progression.

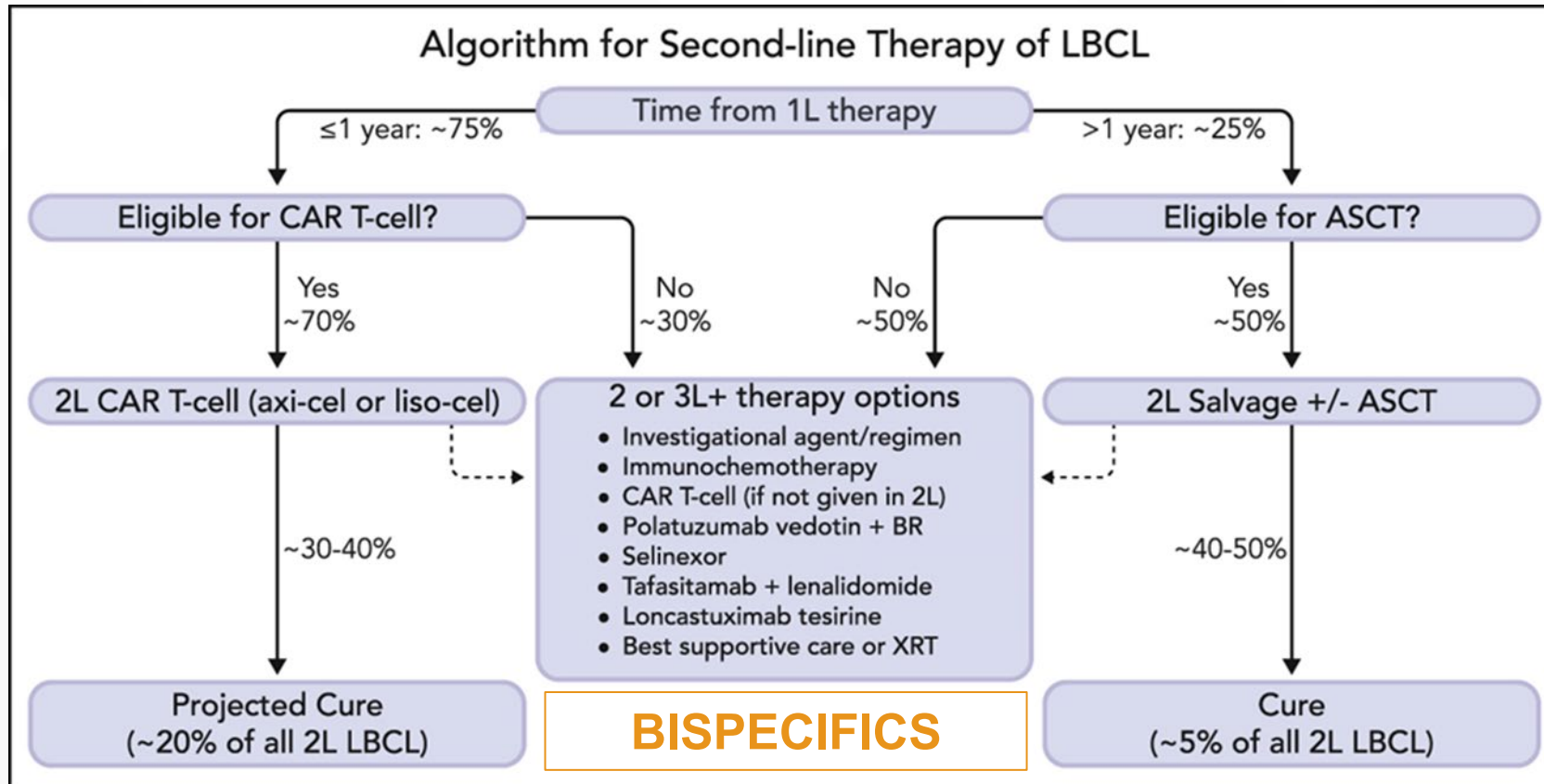
Rel/Ref LBCL: Chaos Driven By Clinical Trials



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

1L/2L/3L, first-line/second-line/third-line; ASCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; BR, bendamustine and rituximab; CAR, chimeric antigen receptor; LBCL, large B-cell lymphoma; liso-cel, lisocabtagene maraleucel; Rel/Ref, relapsed/refractory; XRT, radiation therapy.

Rel/Ref LBCL: Chaos Driven By Clinical Trials

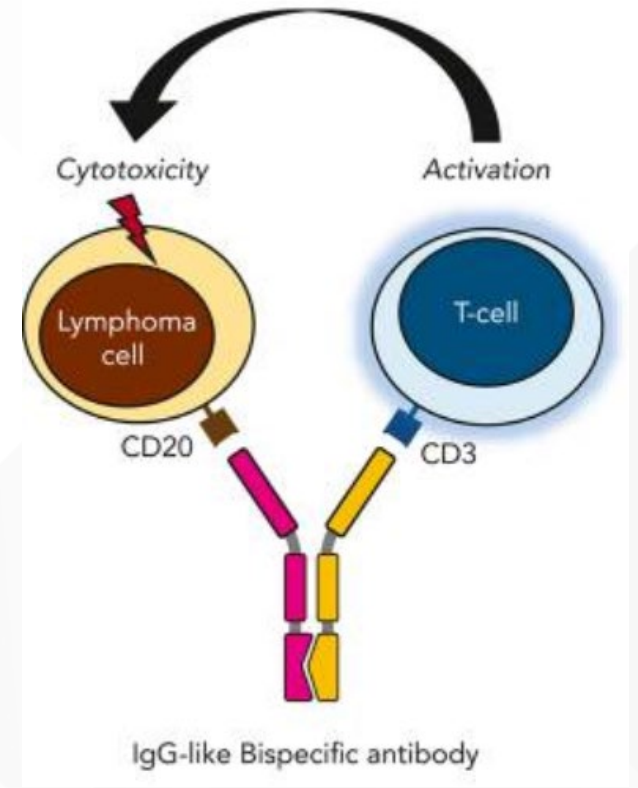


Westin J, Sehn LH. *Blood*. 2022;139(18):2737-2746.

1L/2L/3L, first-line/second-line/third-line; ASCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; BR, bendamustine and rituximab; CAR, chimeric antigen receptor; LBCL, large B-cell lymphoma; liso-cel, lisocabtagene maraleucel; Rel/Ref, relapsed/refractory; XRT, radiation therapy.

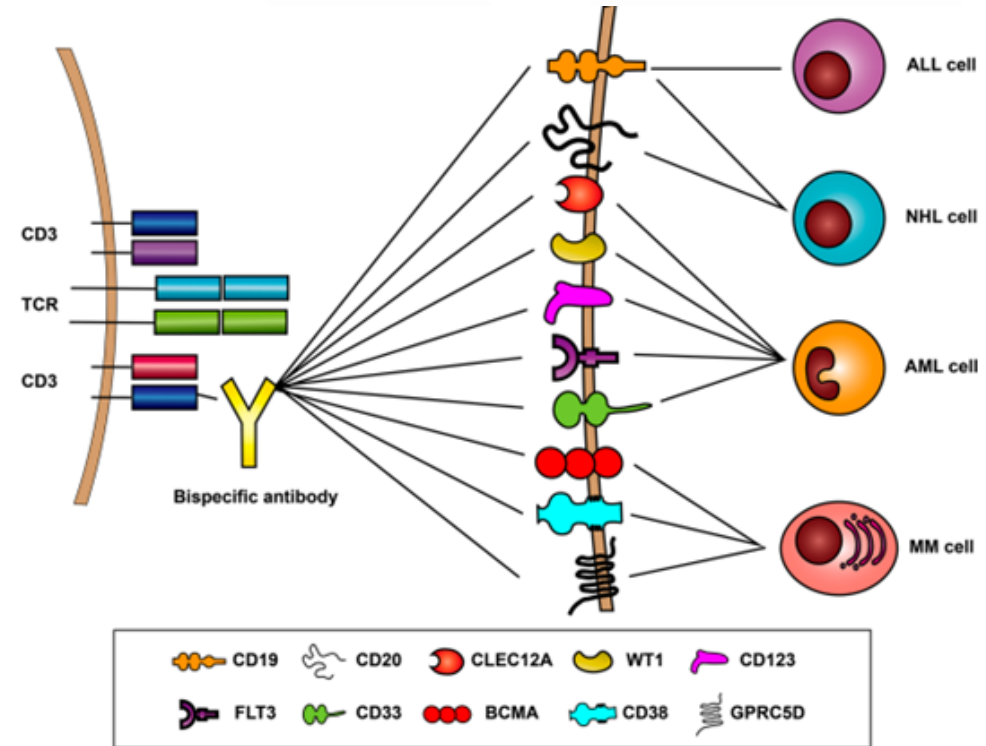
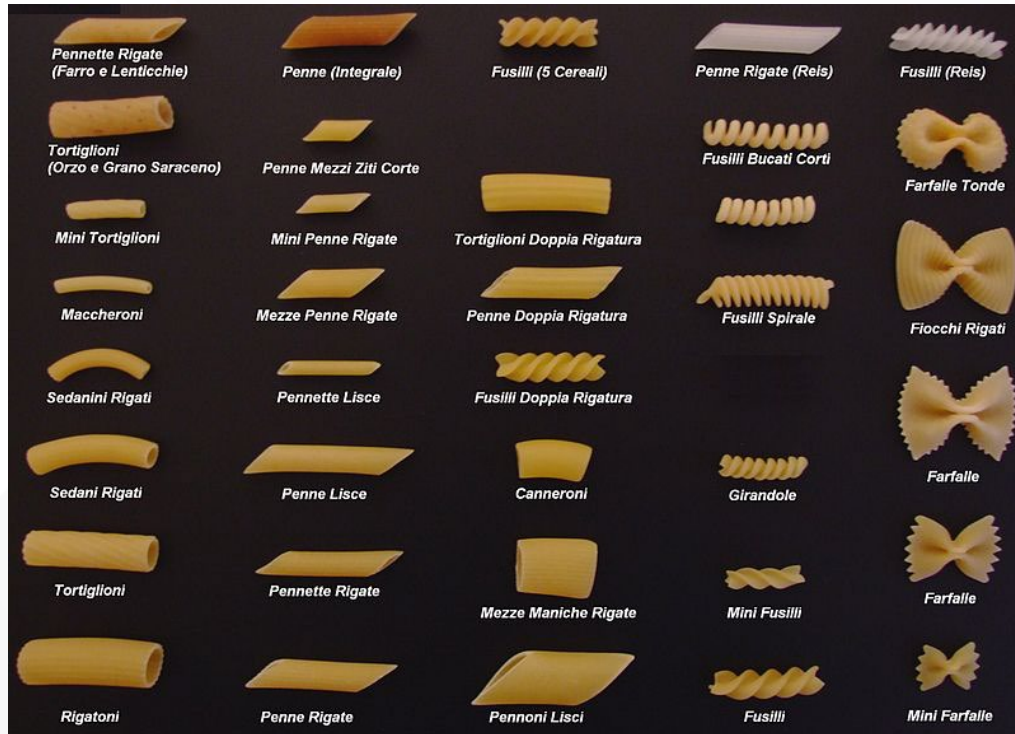
Factors That Differentiate CD20 X CD3 Bispecific Antibodies

Patient Facing: Keep it Simple



Falchi L, et al. *Blood*. 2023;141(5):467-480.
CD, cluster of differentiation; IgG, immunoglobulin G.

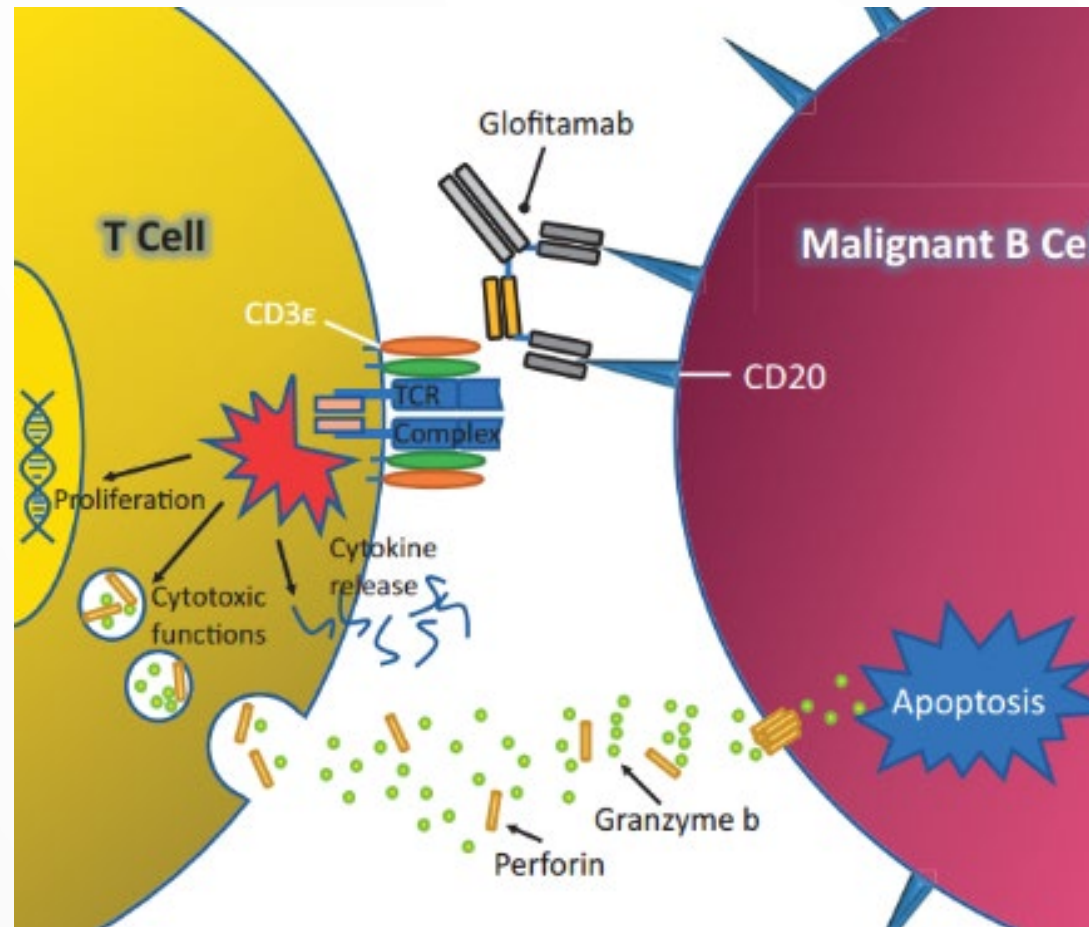
Provider Facing: Many Targets



Tian Z, et al. *J Hematol Oncol.* 2021;14(1):75.

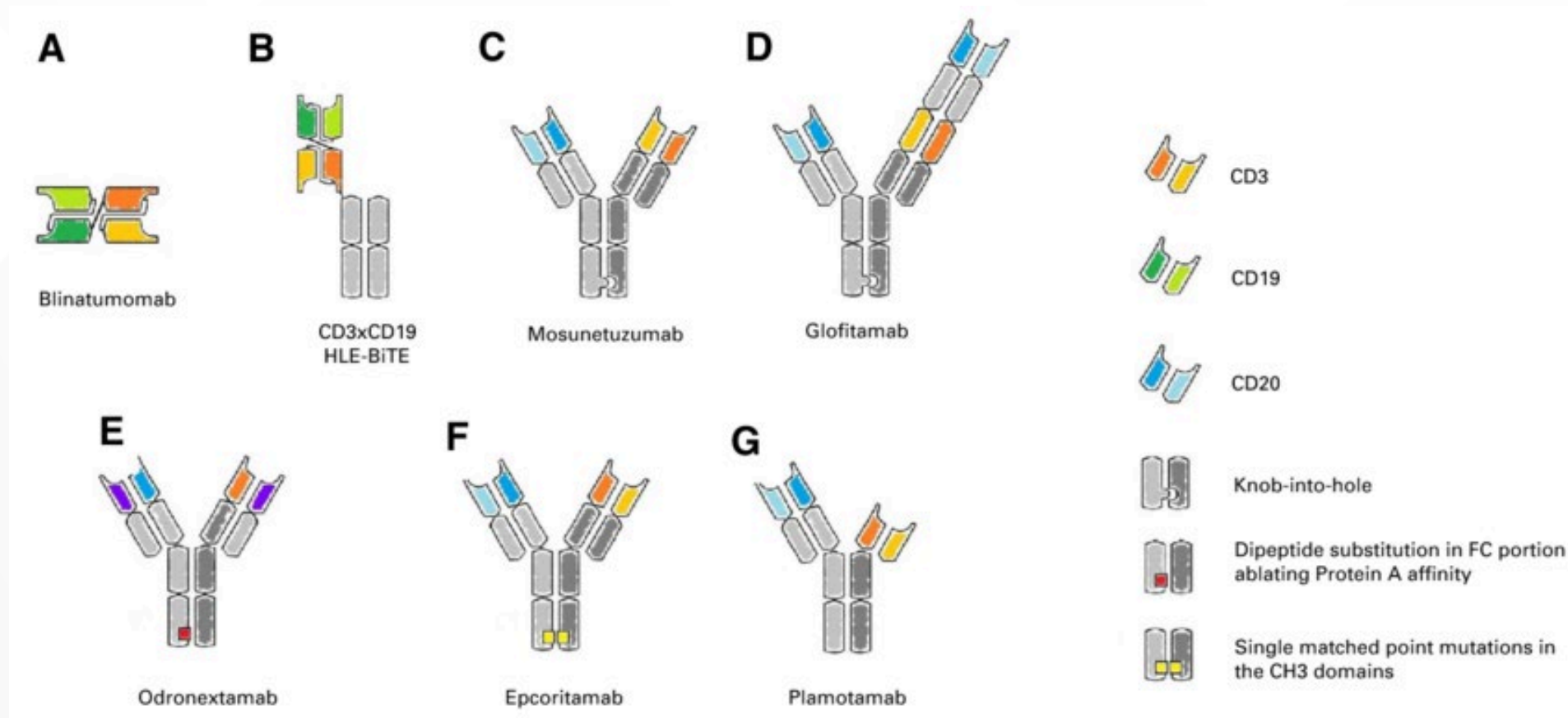
ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BCMA, B cell maturation antigen; CD, cluster of differentiation; CLEC12A, C-Type Lectin Domain Family 12 Member A; FLT3, Fms related receptor tyrosine kinase 3; GPRC5D, G protein-coupled receptor class C group 5 member D; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; TCR, T-cell receptor; WT, wild type.

Provider Facing: Way More Complex



Minson A, Dickinson M. *Leuk Lymphoma*. 2021;62(13):3098-3108.
CD, cluster of differentiation; TCR, T-cell receptor.

History of Bispecific T-Cell Engagers



Lussana F, et al. *J Clin Oncol*. 2021;39(5):444-455.

CD, cluster of differentiation; CH3, constant heavy chain 3; FC, fragment crystallizable.

Bispecific T-Cell Engagers: Same But Different

Agent	Epcoritamab	Glofitamab	Mosunetuzumab	Odronextamab	Plamotamab
Configuration CD20:CD3	1:1	2:1	1:1	1:1	1:1
Administration	SC	IV	IV	IV	IV
Dosing	Step-up	Step-up	Step-up	Step-up	Step-up
CD20 Ab lead-in**	No	Yes	No	No	No
Fixed or Continuous	Cont	Fixed	Fixed	Cont	Cont
Post-dose Steroids	Yes	No	No	No	No
Inpatient Stay in Cycle 1***	Yes	Yes	No	Unknown	Unknown
FDA Approval	Rel/ref DLBCL after ≥2 lines of therapy	Rel/ref DLBCL after ≥2 lines of therapy	Rel/ref FL after ≥2 lines of therapy	-	-

Slide courtesy of Matthew Lunning, DO, FACP.

*Under investigation, not approved.

**Lead-in requirement prior to step-up dosing as a side effect/CRS mitigation strategy.

***Because of the risk of CRS and ICANS.

Ab, antibody; CD, cluster of differentiation; FDA, Food and Drug Administration; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IV, intravenous; SC, subcutaneous.

Advantages of Bispecific Antibodies

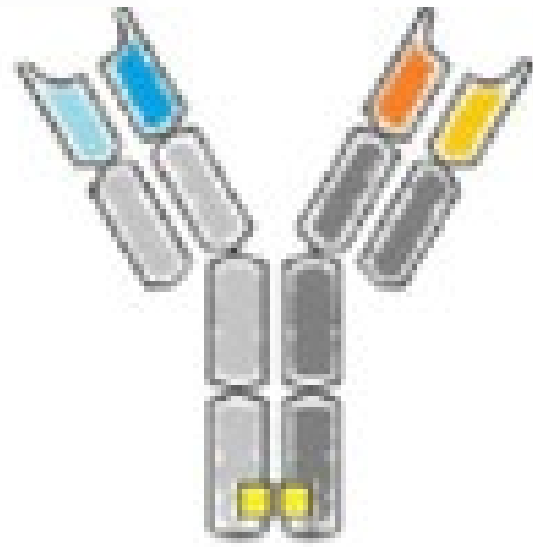
Readily available, "off-the-shelf" products	<p>CAR T-cell therapy: treatment delay due to the time needed for leukapheresis and CAR T-cell manufacturing</p> <p>BsAbs: do not require bridging therapy; administered SC or IV</p>
Lower rates of severe side effects	<p>CAR T-cell therapy: associated with severe CRS and neurological symptoms, which limits their use in older, more clinically vulnerable patients</p> <p>BsAbs: lower rates of grade ≥ 3 CRS and neurotoxicity; can easily be discontinued in case of severe toxicity</p>
Activity in a patient population that had previously rel/ref DLBCL after receiving CAR T-cell therapy	<ul style="list-style-type: none">• BsAbs are a promising choice, particularly for older patients and those with multiple prior lines of therapy• BsAbs may be particularly important for patient who are not eligible for CAR T-cell therapies

Bispecific T-Cell Engagers: Challenges

Logistics	Outpatient→Inpatient→Outpatient dosing <ul style="list-style-type: none">• Transition from academic to community• Transition from community to academic
Dosing	Deliver treatment in the center, but supportive measures are only available in the hospital (next door or miles away) <ul style="list-style-type: none">• Tocilizumab availability (who buys & who stores)
Toxicity Management	<ul style="list-style-type: none">• Product-specific pre-medications and post-dose supportive measures• Time-of-event specific• Severity of event• Location of patient

Clinical Efficacy/Safety Data of CD20 X CD3 Bispecific Antibodies

Epcoritamab



Bispecifics in 3rd line + LBCL: Epcoritamab

Key Eligibility:

- DLBCL, HGBCL, transformed FL, PMBCL, FL3b
- ECOG PS 0–2
- ≥2 prior therapies
- Prior CAR-T allowed

Treatment Duration

- Continuous
- SC administration

CRS mitigation

- Steroid day of X 3 days post-dose for cycle (C) 1
 - No CD20 Ab lead-in
- C1 step-up dosing (SUD)

Epcoritamab schedule

C1D1: 0.16 mg
 C1D8: 0.8 mg
 C1D15 & D22: 48 mg (full dose)

 C 2 & 3 weekly: 48 mg
 C 4-9 every 2 weeks: 48 mg
 C10 and beyond monthly: 48 mg

Primary Endpoint: Overall response rate

Key Characteristics		Subjects (N=157)
Median age, y (range)		64 (20–83)
NHL subtype, n (%)	DLBCL	139 (89)
	DeNovo	97 (70)
	tNHL	40 (29)
	Known DH/TL	13/99 (13)
Median no. of prior lines (range), n		3 (2–11)
Refractory to last prior therapy, n (%)		130 (83)
Prior CAR-T, n (%)		61 (39)
Refractory to prior CAR-T, n (%)		46 (75)*

*Progressed within 6 months of CAR T-cell therapy.

1. Thiebelmont, C et al. *J Clin Oncol*. 2023; 41(12):2238-2247. 2. Thieblemont C, et al. EHA 2022. Abstract LB2364. 3. Jurczak W, et al. EHA 2023. Abstract P1118.
 Ab, antibody; CAR-T, chimeric antigen receptor T-cell therapy; CD, cluster of differentiation; CRS, cytokine release syndrome; DH/TL, double-hit/triple-hit lymphoma; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FL, follicular lymphoma; FL3b, Follicular lymphoma grade 3B; HGBCL, high-grade B-cell lymphoma; LBCL, large B-cell lymphoma; NHL, non-Hodgkin lymphoma; PMBCL, primary mediastinal large B-cell lymphoma; SC, subcutaneous; tNHL, transformed non-Hodgkin lymphoma.

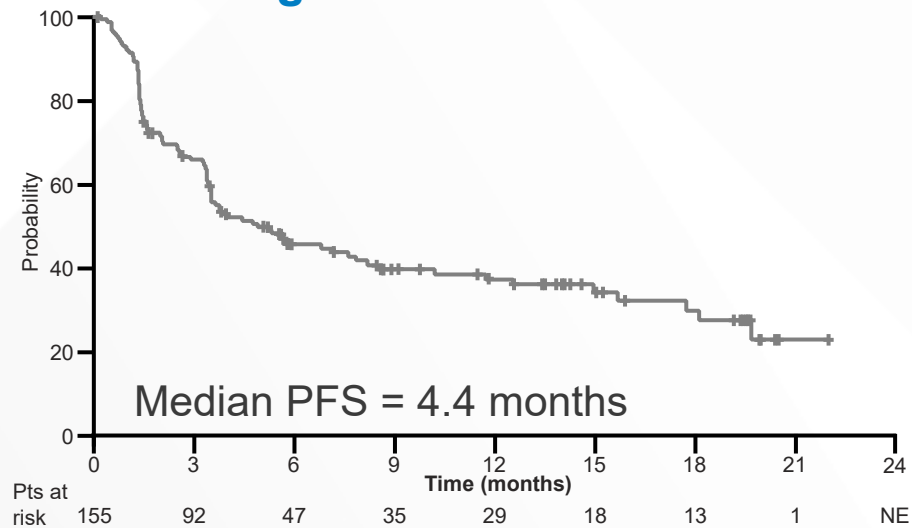
Bispecifics in 3rd line + LBCL: Epcoritamab

Efficacy	All patients (N = 157)
ORR	63%
CR rate	39%
Median Time to response	1.4 months
Median Time to CR	2.7 months
Median DOR	12 months
Median DoCR	Not Reached

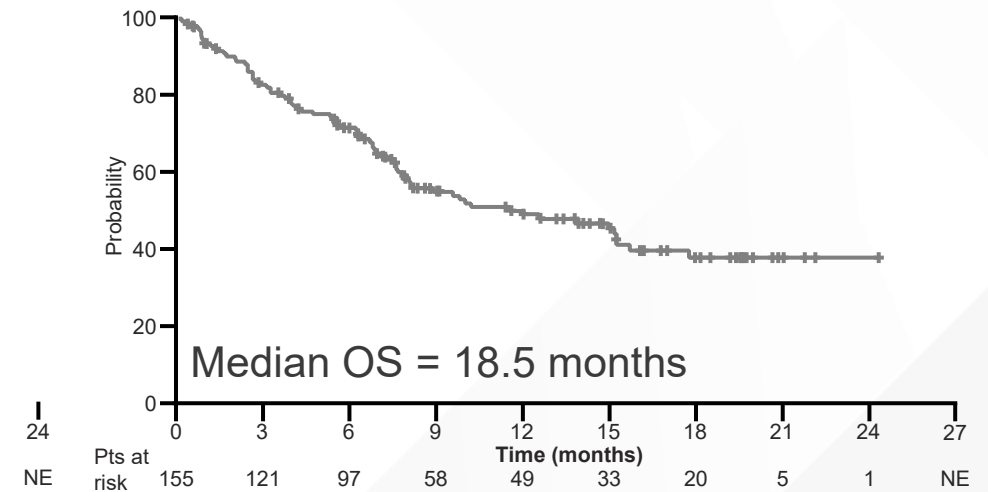
1. Thieblemont, C et al. *J Clin Oncol*. 2023; 41(12):2238-2247. 2. Thieblemont C, et al. EHA 2022. Abstract LB2364. 3. Jurczak W, et al. EHA 2023. Abstract P1118. CR, complete response; DoCR, duration of complete response; DOR, duration of response; LBCL, large B-cell lymphoma; ORR, overall response rate.

Bispecifics in 3rd line + LBCL: Epcoritamab

Progression-Free Survival



Overall Survival

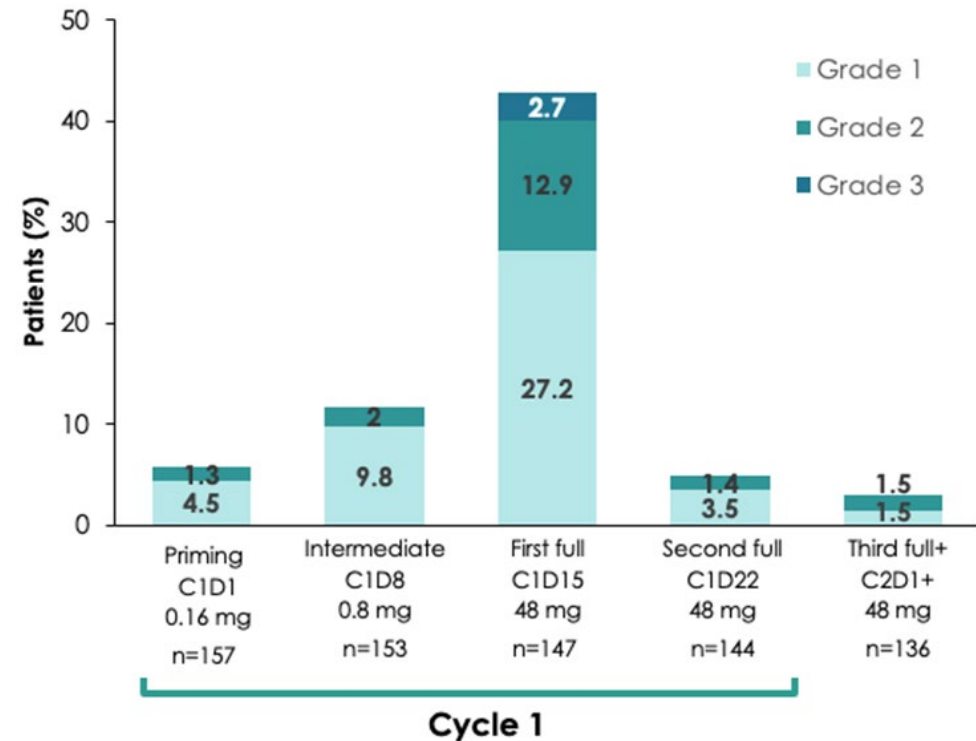


1. Thieblemont, C et al. *J Clin Oncol*. 2023; 41(12):2238-2247. 2. Thieblemont C, et al. EHA 2022. Abstract LB2364. 3. Jurczak W, et al. EHA 2023. Abstract P1118. LBCL, large B-cell lymphoma; OS, overall survival; PFS, progression-free survival.

Bispecifics in 3rd line + LBCL: Epcoritamab

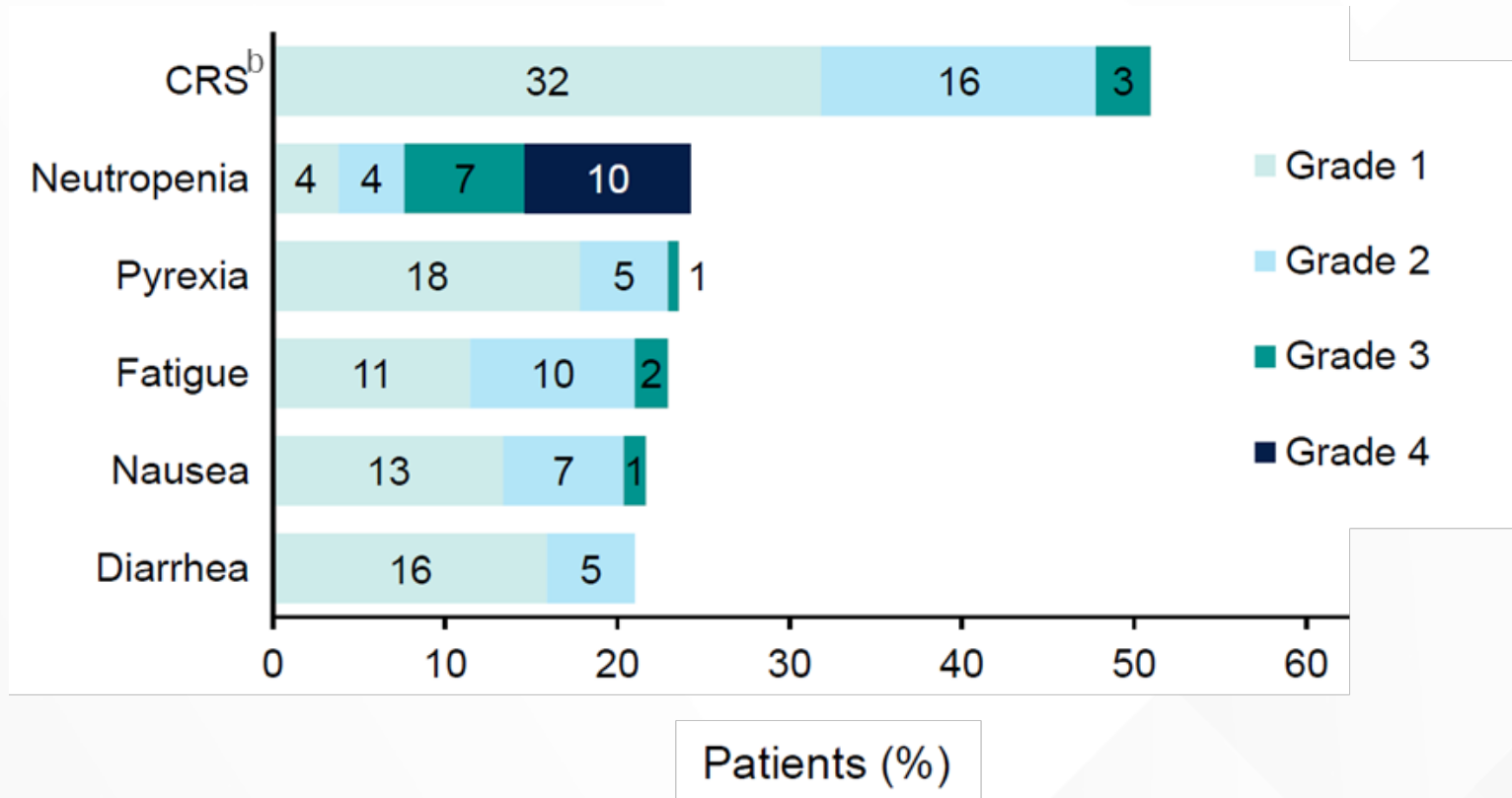
Safety Summary	All patients (N=157)
All grade CRS	50%
Grade 1	32%
Grade 2	14%
Grade 3	3%
Grade 4	0%
Grade 5	0%
Epcoritamab-related	0%

CRS Events by Dosing Period



1. Thiebelmont, C et al. *J Clin Oncol*. 2023; 41(12):2238-2247. 2. Thieblemont C, et al. EHA 2022. Abstract LB2364. 3. Jurczak W, et al. EHA 2023. Abstract P1118. CRS, cytokine release syndrome; LBCL, large B-cell lymphoma.

Epcoritamab: Beyond CRS



Karimi Y, et al. ASCO 2023. Abstract 7525.
CRS, cytokine release syndrome.

Epcoritamab: FDA Approval

- May 2023: accelerated approval for relapsed or refractory DLBCL not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after two or more lines of systemic therapy
 - Based on results of EPCORE NHL-1 trial
- Administered subcutaneously in 28-day cycles until disease progression or unacceptable toxicity
 - Recommended dose is step-up dosing in Cycle 1 followed by fixed dosing weekly during Cycles 2 through 3, every other week during Cycle 4 through 9, and then every four weeks on Day 1 of subsequent cycles
- Boxed Warning
 - Serious or life-threatening CRS
 - Life-threatening or fatal ICANS
- Warnings and precautions
 - Infections and cytopenias
- Should only be administered by a qualified healthcare professional with appropriate medical support to manage severe reactions such as CRS and ICANS
- Because of the risk of CRS and ICANS, patients should be **hospitalized for 24 hours after the Cycle 1 Day 15 dosage of 48 mg**

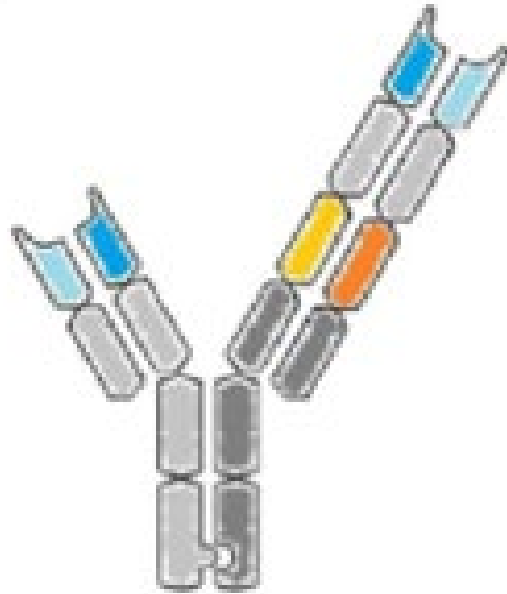
Epcoritamab: Ongoing Trials

Trial	Phase	Treatment	Setting
EPCORE NHL-2 NCT04663347	1/2	Epcoritamab in combination with other SOC agents	B-NHL, 10 different treatment arms
EPCORE DLBCL-1 NCT04628494	3	Epcoritamab vs investigator's choice chemotherapy	R/R DLBCL who have failed or are ineligible for HDT-ASCT
EPCORE DLBCL-2 NCT05578976	3	Epcoritamab in combination with R-CHOP vs R-CHOP	Newly diagnosed DLBCL
EPCORE DLBCL-3 NCT05660967	2	Epcoritamab +/- lenalidomide	Newly diagnosed elderly patients with DLBCL who cannot tolerate anthracycline therapy
NCT05733650	Expanded access program	Epcoritamab	R/R LBCL who have a high unmet medical need with no other treatment options
NCT05283720	2	To evaluate adverse events and change in disease activity of subcutaneous epcoritamab in combination with anti-neoplastic agents	NHL

ClinicalTrials.gov. <https://www.clinicaltrials.gov/study/NCT04663347>. ClinicalTrials.gov. <https://www.clinicaltrials.gov/study/NCT04628494>. ClinicalTrials.gov. <https://www.clinicaltrials.gov/study/NCT05578976>. ClinicalTrials.gov. <https://www.clinicaltrials.gov/study/NCT05660967>. ClinicalTrials.gov. <https://www.clinicaltrials.gov/study/NCT05733650>. ClinicalTrials.gov. <https://www.clinicaltrials.gov/study/NCT05283720>.

B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; HDT-ASCT, high-dose chemotherapy and autologous stem cell transplant; LBCL, large B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R/R, relapsed/refractory; SOC, standard of care.

Glofitamab



Bispecifics in 3rd line + LBCL: Glofitamab

Key Eligibility:

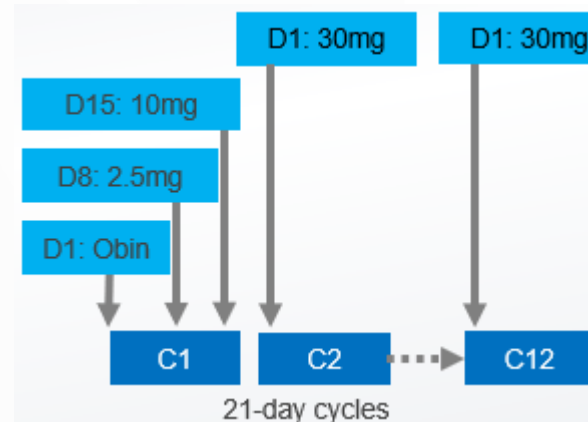
- DLBCL-NOS, HGBCL, transformed FL, or PMBCL
- ECOG PS 0–1
- ≥2 prior therapies
- Prior CAR-T allowed

Treatment Duration

- Fixed up to 12 cycles
- IV administration

CRS mitigation

- Obinutuzumab (Obin)
 - C1D1 1000 mg IV
- Cycle (C)1 step-up dosing (SUD)



Key Characteristics		Subjects (N=154)
Median age, y (range)		66 (21–90)
NHL subtype, n (%)	DLBCL	110 (71)
	tFL	28 (18)
	HGBCL	10 (7)
	PMBCL	6 (4)
Median no. of prior lines (range), n		3 (2–7)
Refractory to last prior therapy, n (%)		131 (85)
Prior CAR-T, n (%)		51 (33)
Refractory to prior CAR-T, n (%)		46 (90)

Primary Endpoint: Complete response rate (best response) by PET/CT Lugano Criteria

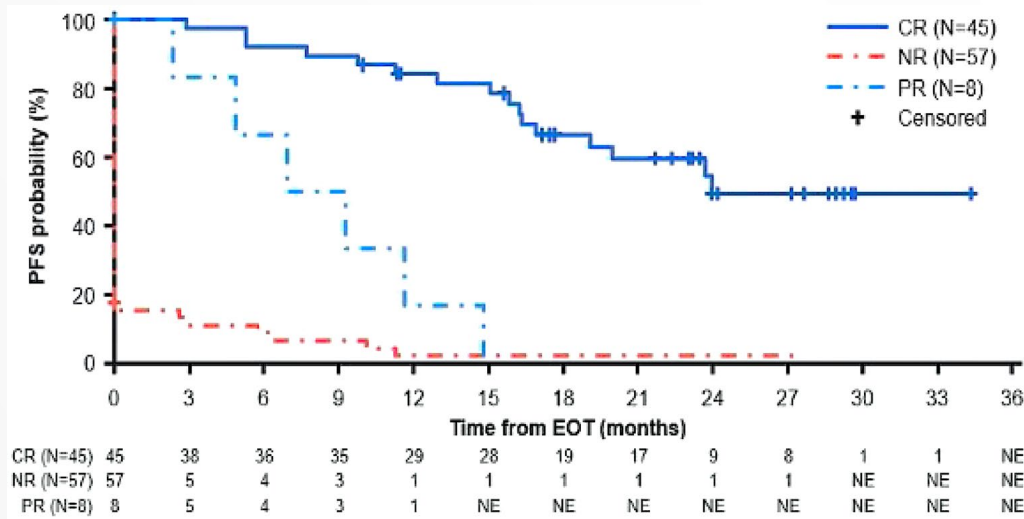
Hutchings M, et al. ASH 2023. Abstract 433.

CAR-T, chimeric antigen receptor T-cell therapy; CRS, cytokine release syndrome; CT, computed tomography; DLBCL-NOS, diffuse large B-cell lymphoma, not otherwise specified; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; IV, intravenous; LBCL, large B-cell lymphoma; NHL, non-Hodgkin lymphoma; PET, positron emission tomography; PMBCL, primary mediastinal large B-cell lymphoma; tFL, transformed follicular lymphoma.

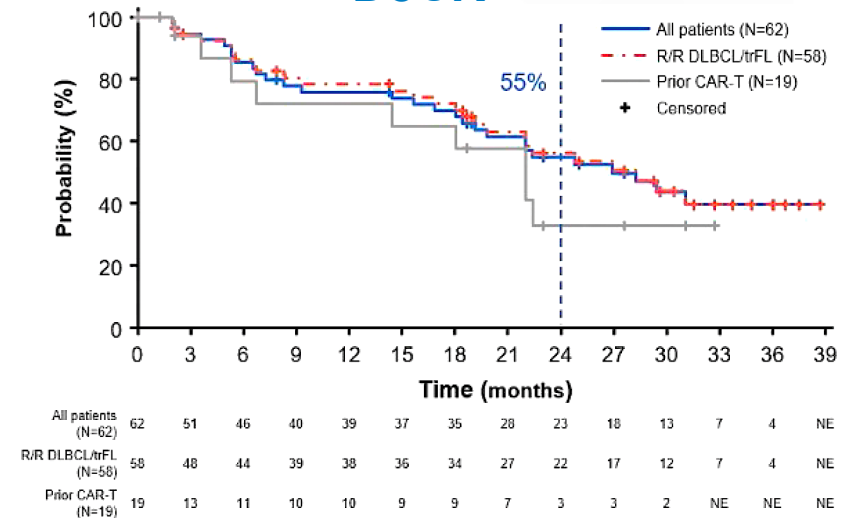
Bispecifics in 3rd line + LBCL: Glofitamab

Efficacy	All patients (N=155)	R/R DLBCL/tFL (N=132)	Prior CAR-T (N=51)
ORR	52%	56%	50%
CR rate	40%	44%	37%
Median CR f/u (range), months	29.6 (0–39)	29.6 (0–39)	23.0 (0–33)
Median DoCR, months	26.9	28.3	22.0
24-month DoCR	55.0%	56.2%	33.1%

PFS at End of the Treatment



DoCR

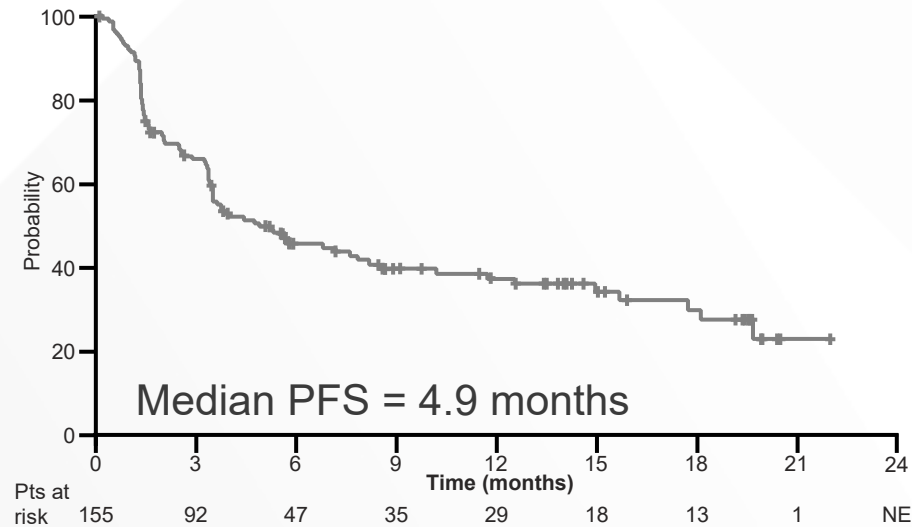


Hutchings M, et al. ASH 2023. Abstract 433.

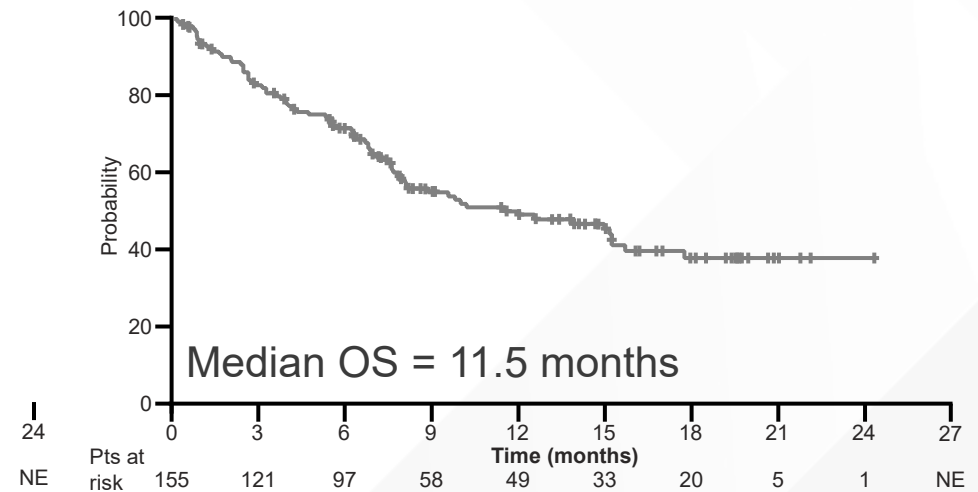
CAR-T, chimeric antigen receptor T-cell therapy; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DoCR, duration of complete response; EOT, end of trial; LBCL, large B-cell lymphoma; NE, not evaluable; NR, no response; ORR, overall response rate; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory; tFL, transformed follicular lymphoma.

Bispecifics in 3rd line + LBCL: Glofitamab

Progression-Free Survival

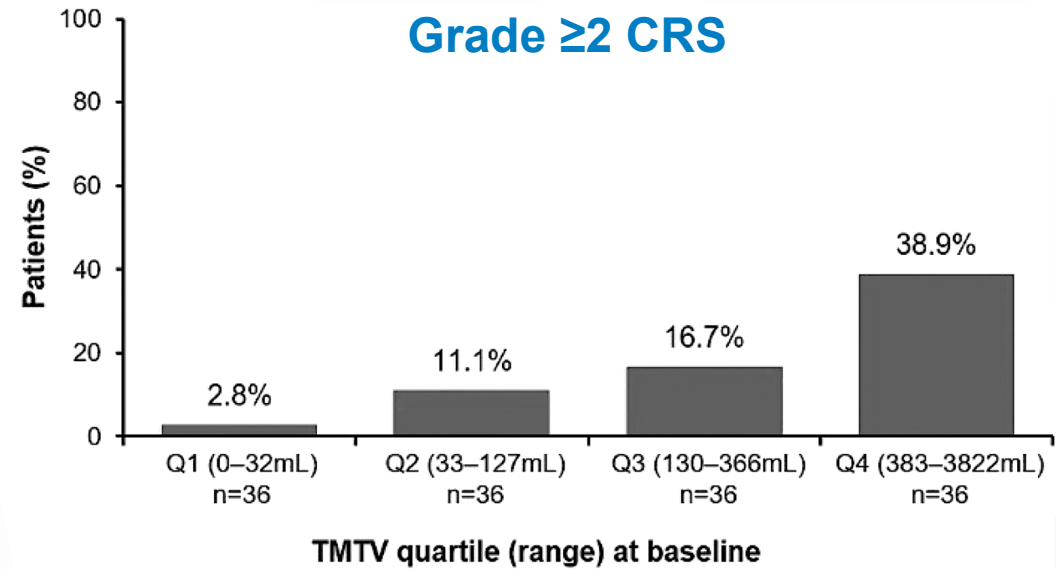


Overall Survival



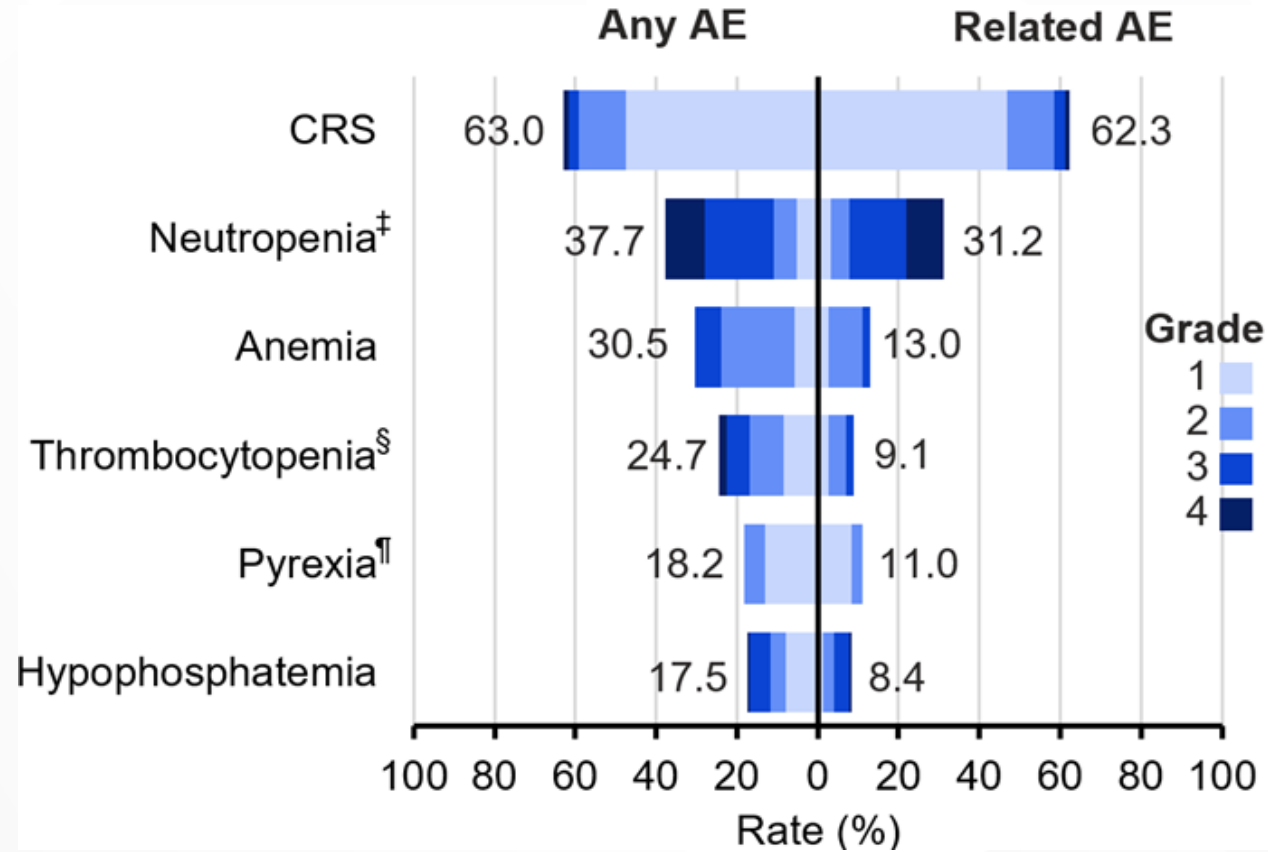
Bispecifics in 3rd line + LBCL: Glofitamab

Safety Summary	All patients (N=154)
All grade CRS	64%
Grade 1	48%
Grade 2	12%
Grade 3	3%
Grade 4	1%
Grade 5	7%
Glofitamab-related	0%



- Most grade ≥ 2 CRS was seen with first dose of glofitamab (C1D8)
- Higher baseline TMTV may be prognostic for increased risk of experiencing a grade ≥ 2 CRS event and lower PFS

Glofitamab: Beyond CRS



Dickinson M, et al. ASCO 2022. Abstract 7500.
AE, adverse event; CRS, cytokine release syndrome.

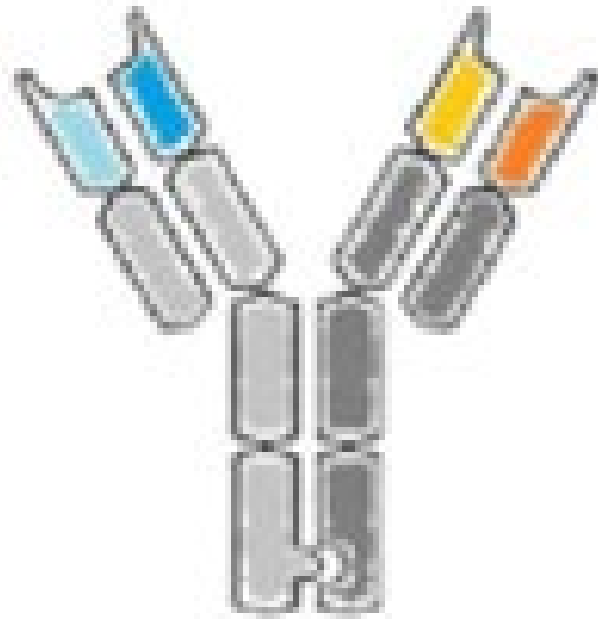
Glofitamab: FDA Approval

- June 2023: accelerated approval for relapsed or refractory DLBCL-NOS or LBCL arising from follicular lymphoma, after two or more lines of systemic therapy
 - Based on results of NP30179 trial
- Following a single 1,000 mg dose of obinutuzumab on Cycle 1 Day 1 to deplete circulating and lymphoid tissue B cells, glofitamab-gxbm is administered by IV infusion according to a step-up dosing schedule, then 30 mg on Day 1 of each subsequent cycle for a maximum of 12 cycles
 - Cycle length is 21 days
 - Refer to the prescribing information for complete dosing information
- Boxed Warning
 - Serious or fatal CRS
- Other Warnings and Precautions
 - Neurologic toxicity including ICANS, serious infections, and tumor flare
- Should only be administered by a healthcare professional with appropriate medical support to manage severe reactions, including CRS
- Because of the CRS risk, patients should be **hospitalized during and for 24 hours after the first step up dose**, and for the second step up dose if any grade CRS occurs
 - For subsequent doses, patients who experience Grade ≥ 2 CRS with their previous infusion should be hospitalized during and for 24 hours after the completion of the next infusion

Glofitamab: Ongoing Trials

Trial	Phase	Treatment	Setting
COALITION NCT04914741	1/2	Glofitamab in addition to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin, and prednisone (RCHP)	Treatment-naïve younger patients with higher-risk DLBCL or high-grade B-cell lymphoma
NCT05364424	1	Glofitamab (glofit) in combination with rituximab plus ifosfamide, carboplatin, and etoposide (R-ICE)	Relapsed/refractory transplant or CAR-T therapy eligible diffuse B-cell lymphoma
NCT03467373	1b	Glofitamab + rituximab (R) or obinutuzumab (G) plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), or polatuzumab vedotin plus RCHP	R/R NHL or in participants with untreated DLBCL
SKYGLO NCT06047080	3	Glofitamab + polatuzumab vedotin + rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP) vs Pola-R-CHP	Previously untreated CD20-positive LBCL

Mosunetuzumab



Bispecifics in 3rd line + LBCL: Mosunetuzumab

Key Eligibility:

- DLBCL-NOS, HGBCL, transformed FL
- ECOG PS 0–1
- ≥2 prior therapies
- Prior CAR-T allowed

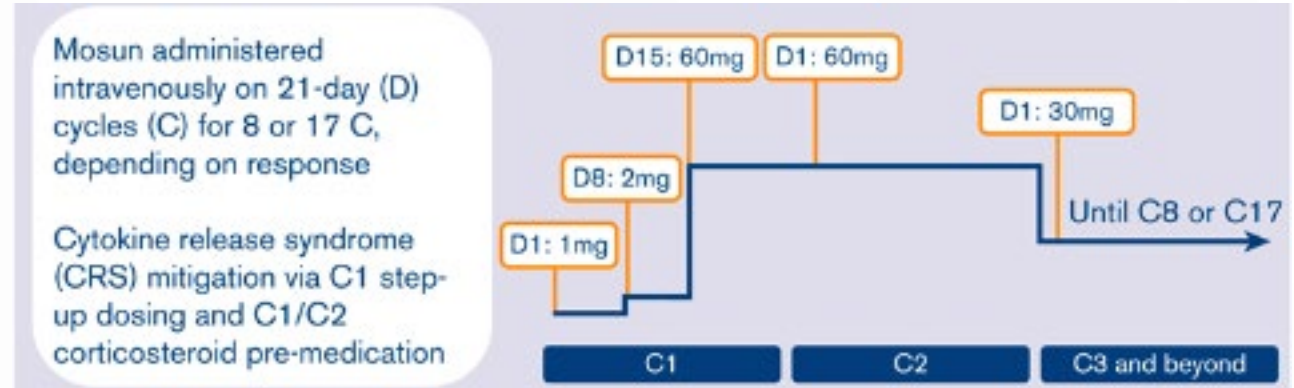
Treatment Duration

- Fixed
- IV administration

CRS mitigation

- Steroid with dose during C1
 - No CD20 Ab lead-in
- C1 step-up dosing (SUD)

Primary Endpoint: Overall response rate



Key Characteristics		Subjects (N=88)
Median age, y (range)		67 (24–96)
NHL subtype, n (%)	DLBCL	65 (74)
	tFL	23 (26)
Median no. of prior lines (range), n		3 (2–13)
Refractory to last prior therapy, n (%)		70 (80)
Prior CAR-T, n (%)		26 (30)
Refractory to prior CAR-T, n (%)		18 (70)*

*Progressed within 6 months of CAR T-cell therapy

Bartlett NL, et al. Blood Advances. 2021;7(17):4926-4935.

CAR-T, chimeric antigen receptor T-cell therapy; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; IV, intravenous; LBCL, large B-cell lymphoma; NHL, non-Hodgkin lymphoma; tFL, transformed follicular lymphoma.

Bispecifics in 3rd line + LBCL: Mosunetuzumab

Efficacy	All patients (N=88)
ORR	42%
CR rate	24%
Median CR f/u (range), months	29.6 (0–39)
Median DoCR, months	26.9
24-month DoCR	55.0%

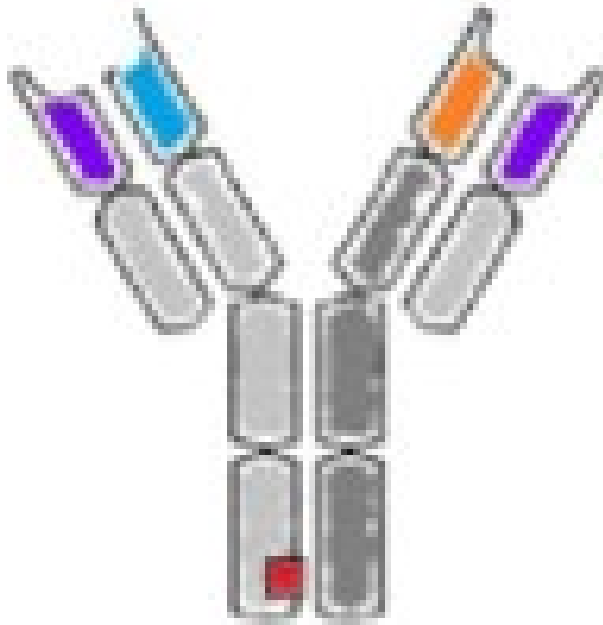
Bartlett NL, et al. *Blood Advances*. 2021;7(17):4926-4935.

CR, complete response; DoCR, duration of complete response; f/u, follow up; LBCL, large B-cell lymphoma; ORR, overall response rate.

Mosunetuzumab: FDA Approval

- December 2022: accelerated approval for adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy
 - Based on results of GO29781 trial
- Recommended dose is 1 mg on Cycle 1 Day 1, 2 mg on Cycle 1 Day 8, 60 mg on Cycle 1 Day 15, 60 mg on Cycle 2 Day 1, and 30 mg on Day 1 in subsequent cycles
 - Treatment cycle is 21 days
- Administered for 8 cycles unless patients experience unacceptable toxicity or disease progression
 - After 8 cycles, patients with a complete response should discontinue therapy
 - Patients with a partial response or stable disease should continue treatment up to 17 cycles unless they experience progressive disease or unacceptable toxicity
- Boxed Warning
 - Serious or life-threatening CRS
- Warnings and precautions
 - Neurologic toxicity, infections, cytopenias, and tumor flare

Odronextamab



Bispecifics in 3rd line + LBCL: Odronextamab

Key Eligibility:

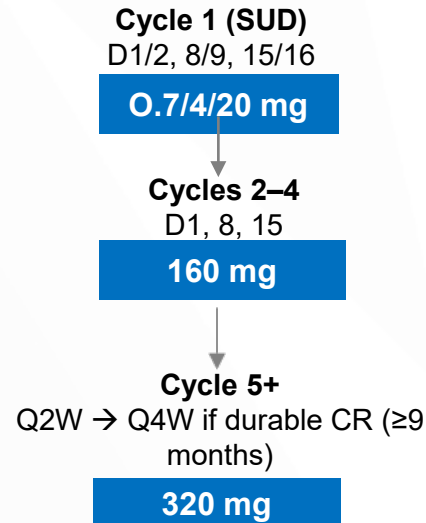
- DLBCL per WHO 2016
- ECOG PS 0–1
- ≥2 prior therapies

Treatment Duration

- Continuous

CRS mitigation

- Steroids/Benadryl premeds



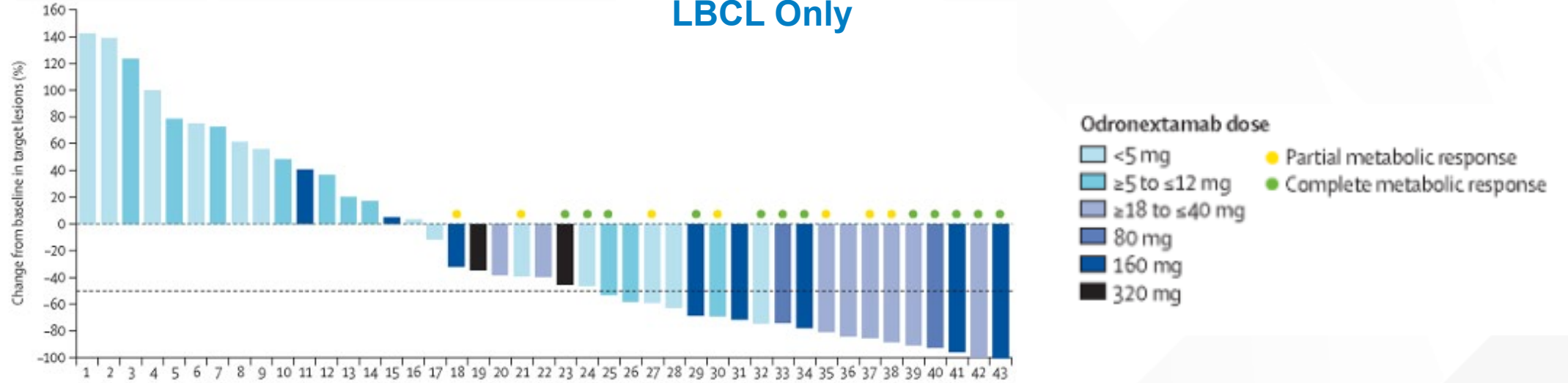
Primary Endpoint: Overall response rate by PET/CT Lugano Criteria

Key Characteristics

Key Characteristics		Subjects (N=127)
Median age, y (range)		66 (24–88)
NHL subtype, n (%)	DLBCL	83 (65)
	tNHL	25 (20)
	Known DH/TL	19 (15)
Median no. of prior lines (range), n		2 (2–8)
Refractory to last prior therapy, n (%)		111 (87)

Odronextamab: ELM-1

Best percentage change from baseline in target lesions LBCL Only



Subjects (80 mg or >)	ORR	CR
CAR-T Naïve (N=15)	53%	53%
CAR-T Exposed (N=30)	33%	23%

Bannerji R, et al. Lancet Haematol. 2022;9(5):e327-e339.

CAR-T, chimeric antigen receptor T-cell therapy; CR, complete response; LBCL, large B-cell lymphoma; ORR, overall response rate.

Bispecifics in 3rd line + LBCL: Odronextamab

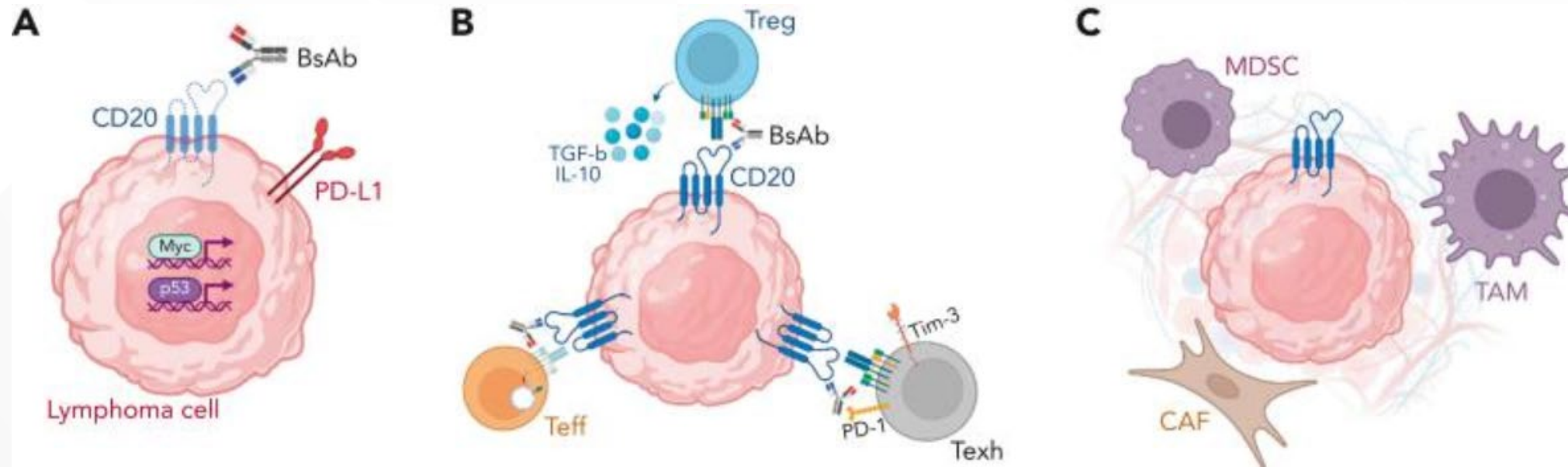
Safety Summary, n (%)	Subjects (N=127)
All grade CRS	55%
Grade 1/2	98%
Grade 3	2%
Grade 4	0%
Grade 5	0%
Odronextamab-related	0%

Odronextamab: Ongoing Trials

Trial	Phase	Treatment	Setting
ELM-1 NCT02290951	1	Odronextamab	CD20+ B-cell malignancies previously treated with CD20-directed antibody therapy
ELM-2 NCT03888105	2	Odronextamab	R/R B-cell NHL
ATHENA-1 NCT05685173	1	Odronextamab + REGN5837 (Anti-CD22 x Anti-CD28)	Aggressive B-cell NHL
OLYMPIA-1 NCT06091254	3	Odronextamab vs investigator's choice	Previously untreated FL
OLYMPIA-2 NCT06097364	3	Odronextamab + chemotherapy vs rituximab + chemotherapy	Previously untreated FL
OLYMPIA-3 NCT06091865	3	Odronextamab + CHOP vs rituximab + CHOP	Previously untreated DLBCL
OLYMPIA-4 NCT06230224	3	Odronextamab vs standard of care therapy	R/R aggressive B-cell NHL
OLYMPIA-5 NCT06149286	3	Odronextamab + lenalidomide vs rituximab + lenalidomide	R/R FL and marginal zone lymphoma

ClinicalTrials.gov. <https://www.clinicaltrials.gov/study/NCT02290951>. ClinicalTrials.gov. <https://www.clinicaltrials.gov/study/NCT03888105>. ClinicalTrials.gov. <https://www.clinicaltrials.gov/study/NCT05685173>. ClinicalTrials.gov. <https://www.clinicaltrials.gov/study/NCT06091254>. ClinicalTrials.gov. <https://www.clinicaltrials.gov/study/NCT06097364>. ClinicalTrials.gov. <https://www.clinicaltrials.gov/study/NCT06091865>. ClinicalTrials.gov. <https://www.clinicaltrials.gov/study/NCT06230224>. ClinicalTrials.gov. <https://www.clinicaltrials.gov/study/NCT06149286>.
 CD, cluster of differentiation; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma; R/R, relapsed/refractory.

Proposed Mechanisms of Resistance

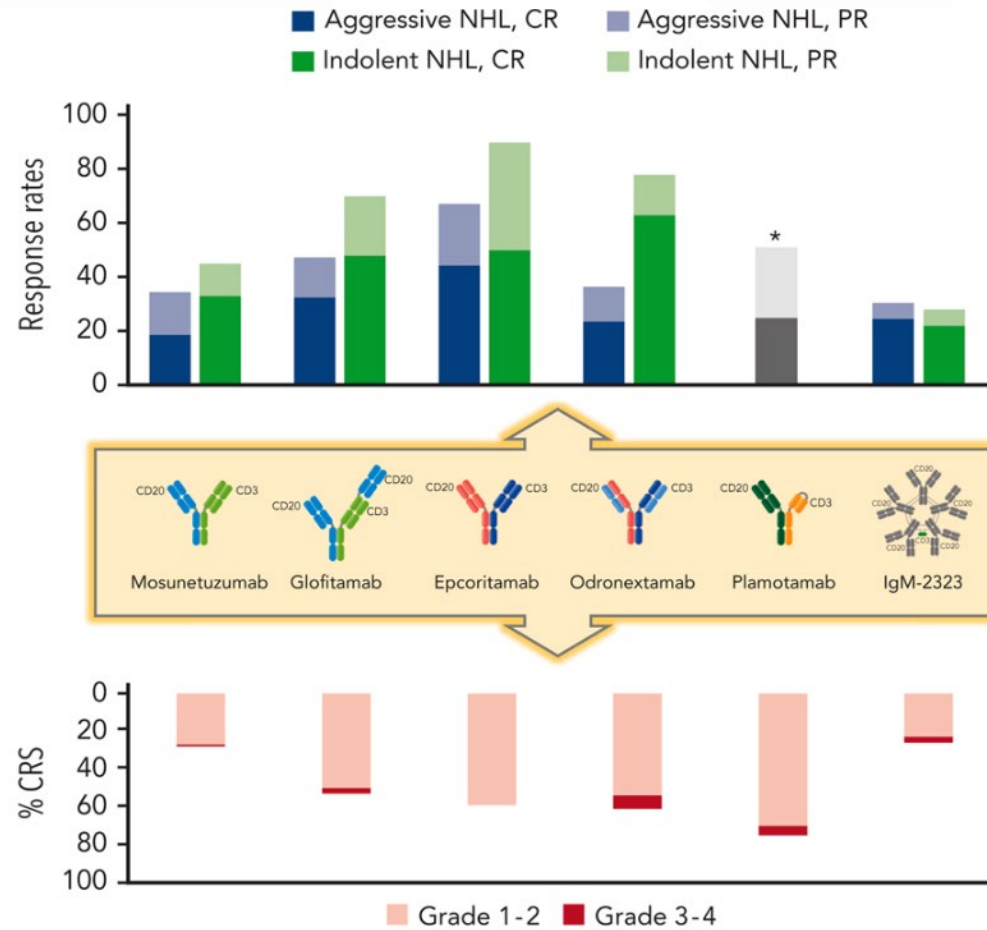


Falchi L, et al. Blood. 2023;141(5):467-480.

BsAb, bispecific antibody; CAF, cancer-associated fibroblast; CD, cluster of differentiation; IL-10, interleukin 10; MDSC, myeloid-derived suppressor cells; PD-L1, Programmed cell death-1 ligand-1; TAM, tumor associated macrophages; Teff, effector T cell; Texh, terminally exhausted; Tim-3, T-cell immunoglobulin mucin 3; TGF- β , transforming growth factor beta; Treg, regulatory T cell.

Patient Selection, Multidisciplinary Treatment Plans, and Sequencing Implications

Bispecific Antibodies in B-cell Lymphoma: Response Rates and CRS



- Other common adverse events (AE): Neutropenia, diarrhea, fatigue, anemia;
- ICANS-like syndrome, TLS, HLH: rare (<5%)
- * data for aggressive NHL and indolent NHL reported in aggregate

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

CR, complete response; CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell-associated neurotoxicity syndrome; NHL, non-Hodgkin lymphoma; PR, partial response; TLS, tumor lysis syndrome.

When to Consider Bispecific: Patient Selection

NOT eligible for CAR-T

- Comorbid conditions
- Access constraints
- Disease constraints

Post CAR-T

- Super Refractory: Relapse within 100 days (non-trial population for epcoritamab/glofitamab)
- Refractory: Relapsed within 6 months (trial population for epcoritamab/glofitamab)
- Relapse: >6 months from CAR-T

Patient preference

When to Consider Bispecific: Site Readiness

Management team

- Patient
- Caregiver
- Nurse Champions
- APP
- Physician
- Pharmacist
- Administrator

Bispecific Specific

- Outpatient vs inpatient dosing
- Timing of monitoring
- When to call
- Monitoring of vitals
 - BP cuff, thermometer, Pulse Ox
- Laboratory evaluation

Facility Logistics

- Communication with the hospital system
 - ER, Inpatient Unit, On-call team, Pharmacy
- Supportive meds availability
 - Steroids, Tocilizumab, etc
- Distance from tocilizumab
 - 30-60 minutes
- Patient-specific plan vs system plan

When to Consider Bispecific: Treatment Sequencing

CD20 exposure only	Multi-chemo refractory ex: Pola-R-CHP; R-ICE
Early CAR-T (2nd Line)	Chemo to CAR-T ex: R-CHOP to Liso-cel/Axi-cel
Late CAR-T (3rd Line)	Multi-chemo relapsed ex: R-CHOP, R-ICE → HDT-ASCR; CAR-T
Novel NO CAR-T (4th Line)	ex: mini-R-CHOP; Tafa-Len; Lonca-T

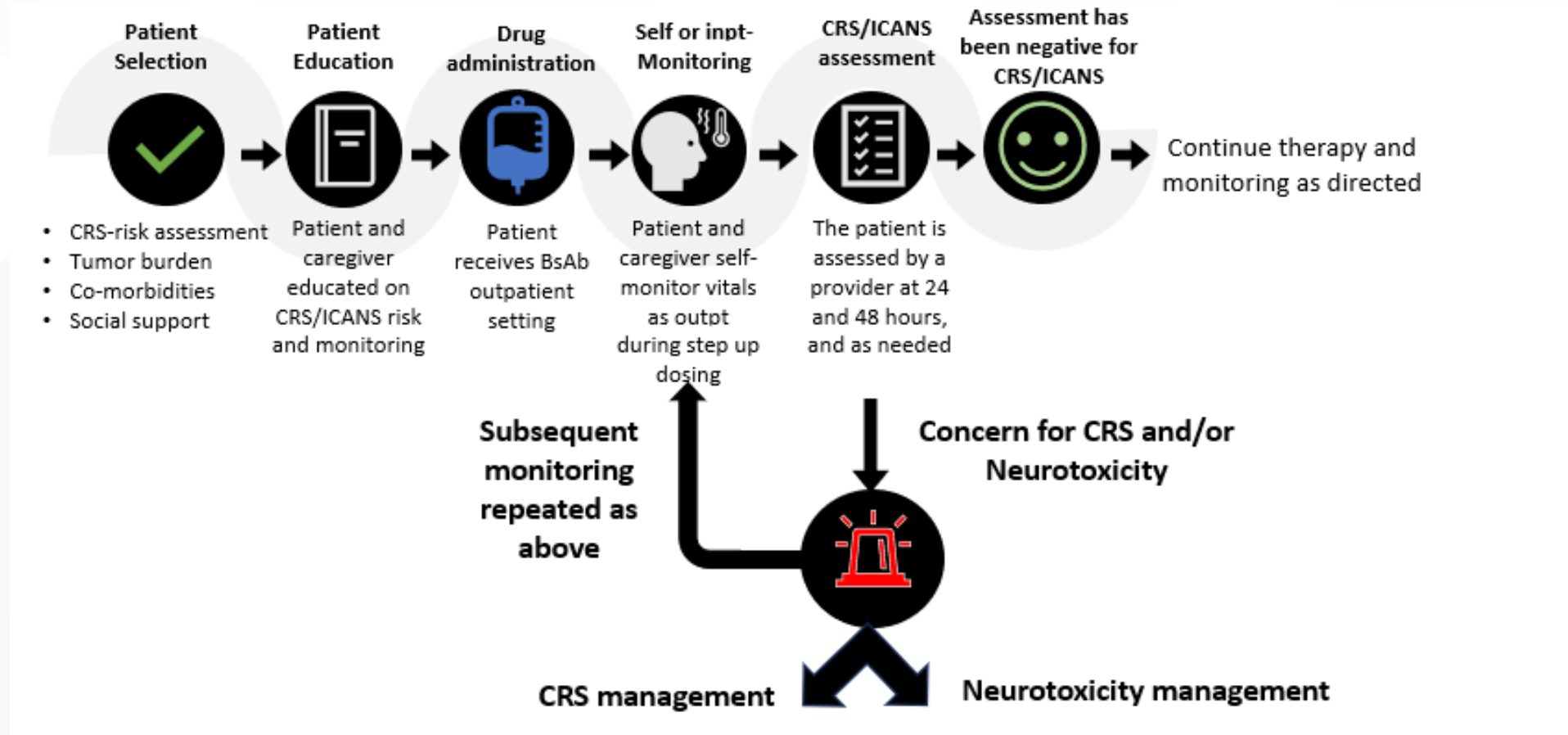
Axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T-cell therapy; CD, cluster of differentiation; HDT-ASCR, high-dose chemotherapy and autologous stem cell rescue; Liso-cel, lisocabtagene maraleucel; Lonca-T, loncastuximab tesirine; Pola, polatuzumab; R-CHP, rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone; R-ICE, rituximab plus ifosfamide, carboplatin, and etoposide; Tafa-Len, tafasitamab plus lenalidomide.

Coordinating Referrals/Transition and Follow-up Care

Establish Relationships and Referral Pathways	<p>Establish strong relationships between clinicians at academic and community cancer programs</p> <ul style="list-style-type: none">• Establishment of clear referral pathways and the transition from inpatient to outpatient administration; build on existing referral pathways (eg, for stem cell transplant or clinical trials)• Ensure office staff are familiar with referral process
Patient Education	<p>Create an online resource to help prepare patients to receive initial treatment at an academic medical center and follow-up care with a local oncologist</p> <ul style="list-style-type: none">• Website can guide patients through the process and help them understand what to expect <p>Create a patient information sheet that clearly outlines team members and their roles and responsibilities across the different sites of care</p> <ul style="list-style-type: none">• Community cancer program, local hospital, academic medical center, etc <p>Direct shared-decision making (SDM)</p>
Use Telehealth	<p>Use telehealth to provide follow-up care, remote vital sign monitoring, monitor for symptoms, and coordinate with local providers for patients who live further away from academic or tertiary care centers</p>
Connect Patients	<p>Connect patients with navigators who know how to coordinate logistics between community cancer programs and academic medical centers, if available</p> <ul style="list-style-type: none">• Many community cancer programs have navigators for common cancers; may not have navigators for less common hematologic malignancies

Team-Based Management Strategies for Adverse Events with CD20 X CD3 Bispecific Antibodies

When to Consider Bispecific: Plan is to Have a Plan



Discussion: Considerations for Managing Adverse Events

Planning	Knowledge and planning for the anticipated treatment-related AEs Step-up dosing
Challenges	Challenges of using new therapies Tolerability profile of bispecific antibodies based on frequency and severity
Assessment and monitoring	CRS and neurotoxicity: onset, rates, and severity Low blood cell counts Team-based strategies for anticipating, monitoring, managing, and coordinating care for potential AEs
Quality of Life (QoL)	Patient-reported improvements of lymphoma-related symptoms
Experience	Nuances will occur with more experience in the management of bispecific antibodies

AEs, adverse events; CRS, cytokine release syndrome.

Addressing Adverse Events with Bispecific Antibodies

**Strategies to
mitigate safety
and tolerability
concerns**

- Premedication (e.g., prophylactic corticosteroids)
- Step-up dosing
- Hospitalization for administration
- Slower infusion
- Alternate routes of administration (e.g., subcutaneous)

BsAbs Management Strategies: CRS

- Occurs mostly within the first **24 hours** following treatment initiation with continuous administration
- CRS events are typically confined to the step-up doses or first full dose with intermittent administration
- Typically occurs on the day of IV infusion and the day after SC administration
- SC formulations may reduce the risk of severe CRS
 - Result in a more gradual increase in serum concentration and reduce the peak plasma levels of the antibodies

Supportive Care

- Prompt administration of IL-6 receptor-blocking antibodies (tocilizumab) or steroids
- Antipyretics (acetaminophen)
- Intravenous fluid administration
- Oxygen supplementation
- Withhold drug or permanently discontinue

Strategies to Reduce Risk of CRS

- **Step-up dosing**
- **Pre-medication strategies (including steroids)**
- Pretreatment with obinutuzumab for glofitamab
- Co- and post-administration of prednisone for epcoritamab
- Coordinate with local emergency departments and clinics and have on-call physicians
- Develop a structured training program for staff including hospital nurses, ICU staff, and neurologists (and ER)
- Develop a central repository of treatment protocols and algorithms, including toxicity management plans
- Share with local community hospitals and those in the cancer program network to ensure a consistent approach
- Educate patients and caregivers on the signs and symptoms of CRS; wallet card

ACCC. <https://www.accc-cancer.org/docs/projects/bispecific-antibodies/bispecific-antibodies-brief.pdf>.

Hutchings M. *Hematol Oncol*. 2023;41(S1):107-111.

van de Donk NWCJ, Zweegman S. *The Lancet*. 2023;402(10396):142-158.

BsAbs, bispecific antibodies; CRS, cytokine release syndrome; ER, emergency room; ICU, intensive care unit; IL-6, Interleukin-6; IV, intravenous; SC, subcutaneous.

BsAbs Management Strategies: Neurotoxicity/ICANS

- Higher incidence with CD19-directed agents (CAR-T)
- Typically develops concurrently or shortly after CRS
 - Can also occur independently
- Characterized by headaches, tremors, ataxia, aphasia, confusion, hallucinations, and seizures

Prevention

- Step-up dosing and premedication
- Monitor patients for neurological signs or symptoms during treatment

Supportive care

- Tocilizumab if concurrent with CRS
- Steroids (dexamethasone)
- Anti-epileptic drugs
- Withhold drug or permanently discontinue

van de Donk NWCJ, Zweegman S. *The Lancet*. 2023;402(10396):142-158.

ACTEMRA (tocilizumab). Prescribing information. Genentech; 2022.

BsAbs, bispecific antibodies; CAR-T, chimeric antigen receptor (CAR) T-cell therapy; CD, cluster of differentiation; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

BsAbs Management Strategies

Infections

- Monitor patients for signs and symptoms of infection prior to and during treatment
- Provide PJP prophylaxis prior to initiating treatment
- Initiate antiviral prophylaxis against herpes virus prior to treatment
- Withhold or consider permanent discontinuation of treatment based on severity

Cytopenias

- Monitor complete blood counts throughout treatment
- Consider prophylactic granulocyte colony-stimulating factor
- Based on the severity of cytopenias, temporarily withhold or permanently discontinue treatment

Improving Management of CRS in Patients Treated with BsAbs

Dosage and Administration	Step-up dosing
	Interrupting therapy and providing supportive care
	Pre-medication strategies (including steroids)
Training	Ensure ED staff and hospitalists are aware that an on-call physician is available to help manage any patient who may present with CRS
	Develop a structured training program for staff
	Include hospital nurses, ICU staff, and neurologists in conversations about CRS and neurotoxicity
Coordination	Develop a central repository of treatment protocols and algorithms, including toxicity management plans
	Share with local community hospitals (and those in the cancer program network) to ensure that a consistent approach is delivered wherever the patient is treated
Patient Education	Remind patients and their caregivers about signs and symptoms of CRS
	Caregivers may be the first ones who recognize symptoms and should be prepared to call the cancer care program for assistance

Practical Application: Case-Based Learning Lab

Case Study

Presentation

- 78-year-old man presents with LBP and diffuse adenopathy on exam
- Excisional bx: DLBCL-NOS
- IHC based evaluation; non-GCB
- FISH: Negative for MYC rearrangement
- PET/CT demonstrates stage IV disease based on avid bone lesions
- BM bx deferred (CBC normal)
- LDH 250 (ULN: 192)
- ECOG PS 1
- IPI 3

Medical History

PMH:

- HTN

Medications:

- HCTZ/lisinopril

Social History:

- Retired lawyer
- Works as a mower at local golf club
- Cigars at the 19th hole
- Bourbon 1-2 times per week

BM, bone marrow; bx, biopsy; CBC, complete blood count; CT, computed tomography; DLBCL-NOS, diffuse large B-cell lymphoma, not otherwise specified; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FISH, fluorescence in situ hybridization; GCB, germinal center B-cell like; HCTZ, hydrochlorothiazide; HTN, hypertension; IHC, immunohistochemistry; IPI, International Prognostic Index; IV, intravenous; LBP, low blood pressure; LDH, lactate dehydrogenase; PET, positron emission tomography; PMH, past medical history.

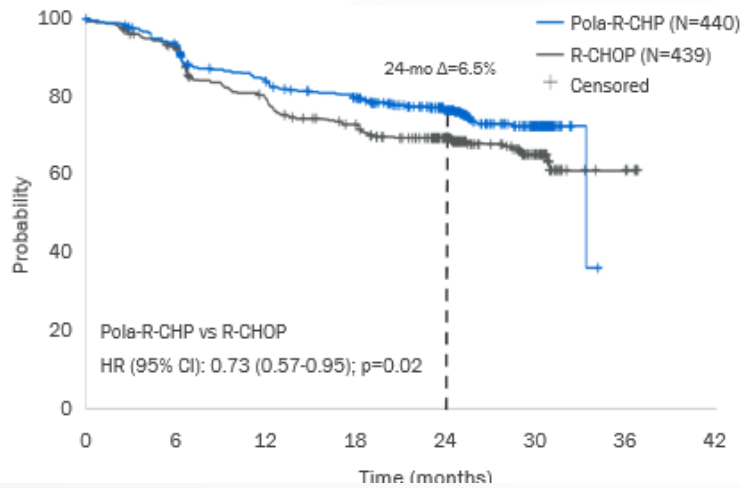
Case Study Question #1

What would be your initial induction therapy?

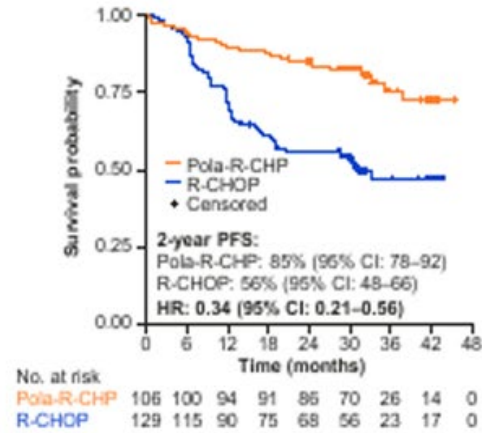
- a) R-CHOP
- b) Mini-R-CHOP
- c) Pola-R-CHP
- d) DA-EPOCH-R
- e) Unsure

Rationale for Answer #1

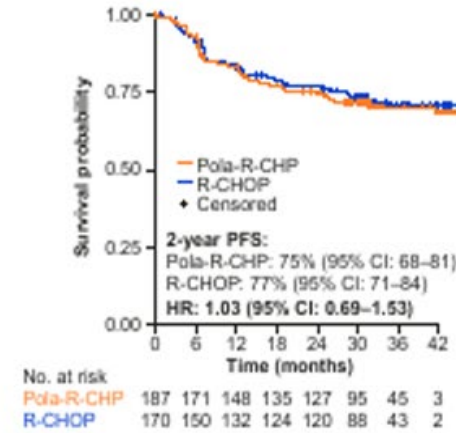
PFS



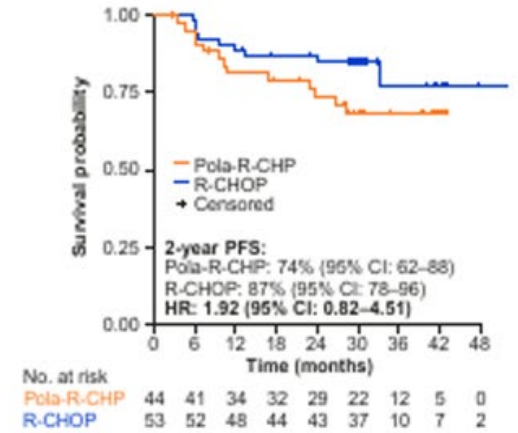
ABC



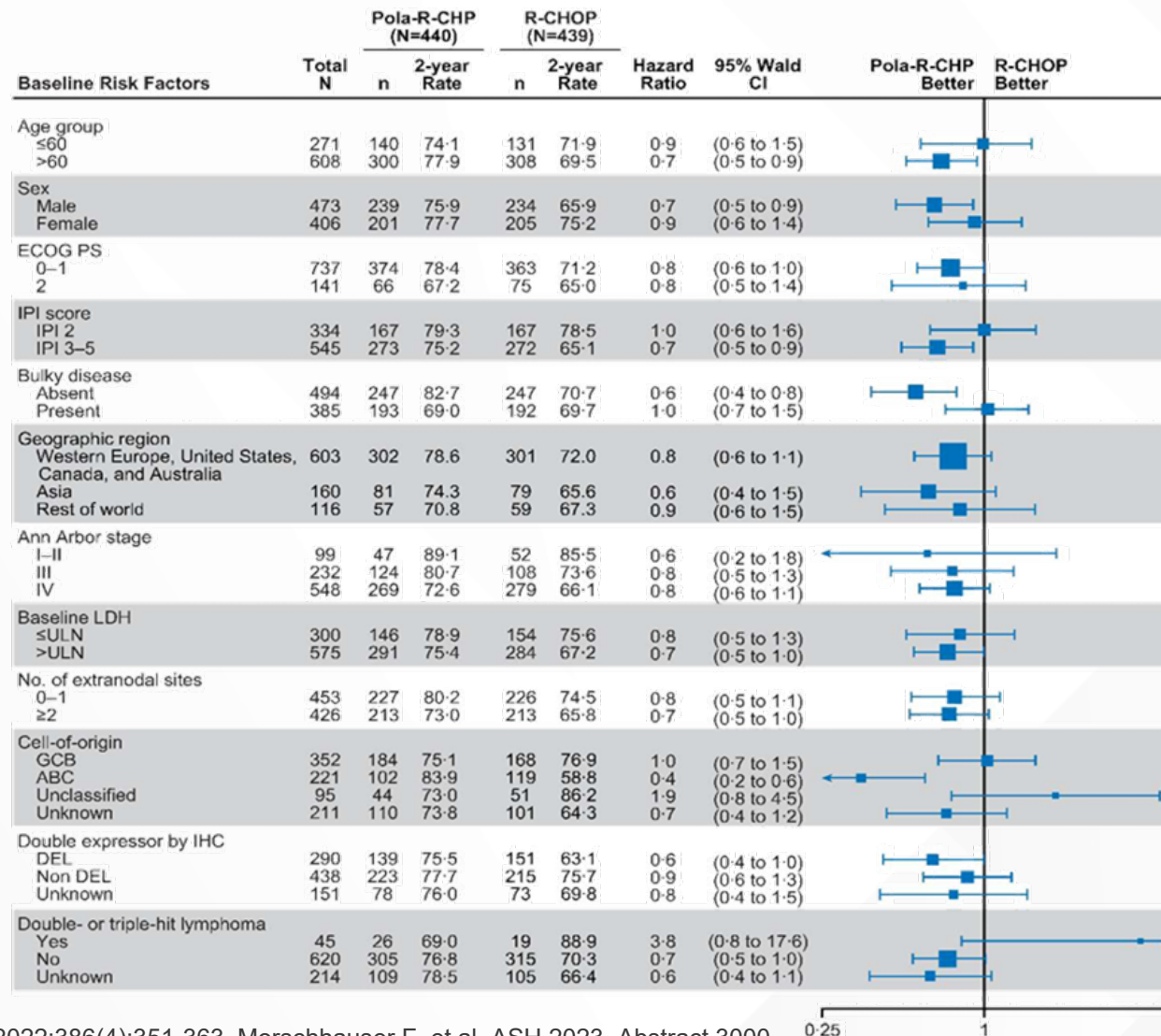
GCB



Unclassified



Rationale for Answer #1, Continued



Tilly H, et al. N Engl J Med. 2022;386(4):351-363. Morschhauser F, et al. ASH 2023. Abstract 3000.

ABC, activated B-cell like; DEL, double-expressor lymphoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GCB, germinal center B-cell like; IHC, immunohistochemistry; IPI, International Prognostic Index; LDH, lactate dehydrogenase; Pola, polatuzumab; R-CHP, rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone; ULN, upper limit of normal.

Case Study Follow Up

- Patient tolerates Pola-R-CHP X 6 with grade 1 peripheral neuropathy
- EOT evaluation notes PET/CT negative but MRD positive
- 5 months post completion of Pola-R-CHP, he has recurrence of LBP with PET/CT findings consistent with relapse
- Biopsy confirms DLBCL-NOS with involvement of marrow
- LDH elevated
- Mild anemia
- CrCl is 50 ml/min, LVEF 50-55%, and O2 sats 95%
- ECOG PS 1

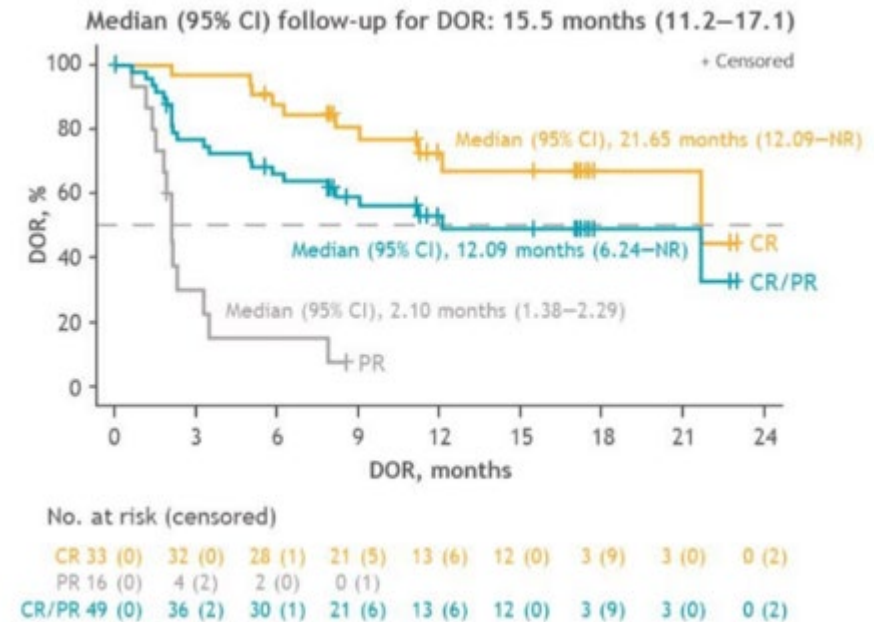
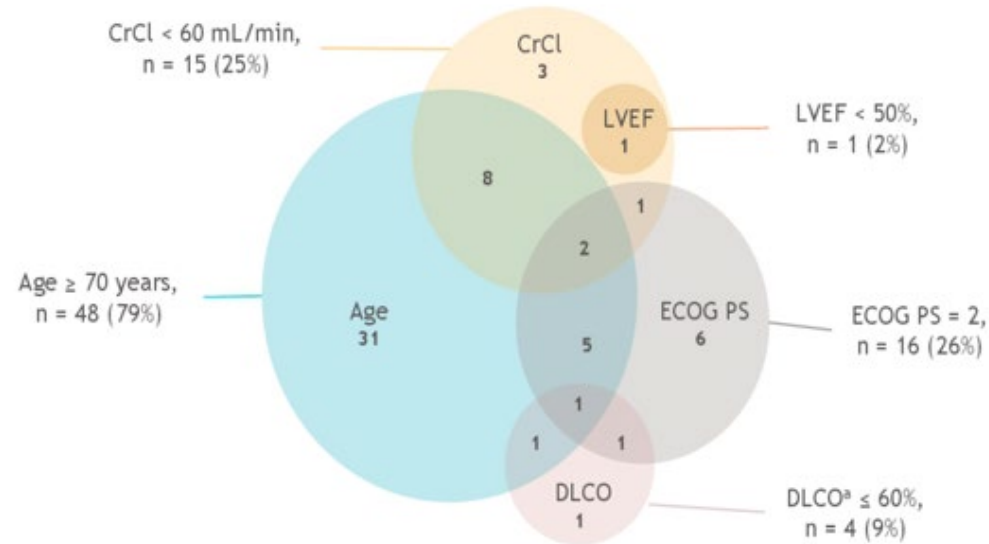
Case Study Question #2

How would you manage this patient?

- a) Tafasitamab + lenalidomide (25 mg)
- b) Loncastuximab teserine
- c) Liso-cel (CD19 CAR-T)
- d) R-Gem-ox
- e) Unsure

Rationale for Answer #2

PILOT Trial: liso-cel



Sehgal A, et al. ASCO 2022. Abstract 7062.

CR, complete response; CrCl, creatinine clearance; DLCO, diffusing capacity of the lungs for carbon monoxide; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; liso-cel, lisocabtagene maraleucel; LVEF, left ventricular ejection fraction; PR, partial response.

Case Study Follow Up

- Patient tolerates liso-cel with Grade 1 CRS without ICANS
- Day +100 PET/CT with evidence of POD
- Biopsy confirms DLBCL-NOS now CD19 negative by flow cytometry and IHC, but remains CD20 positive
- ECOG PS 1

Case Study Question #3

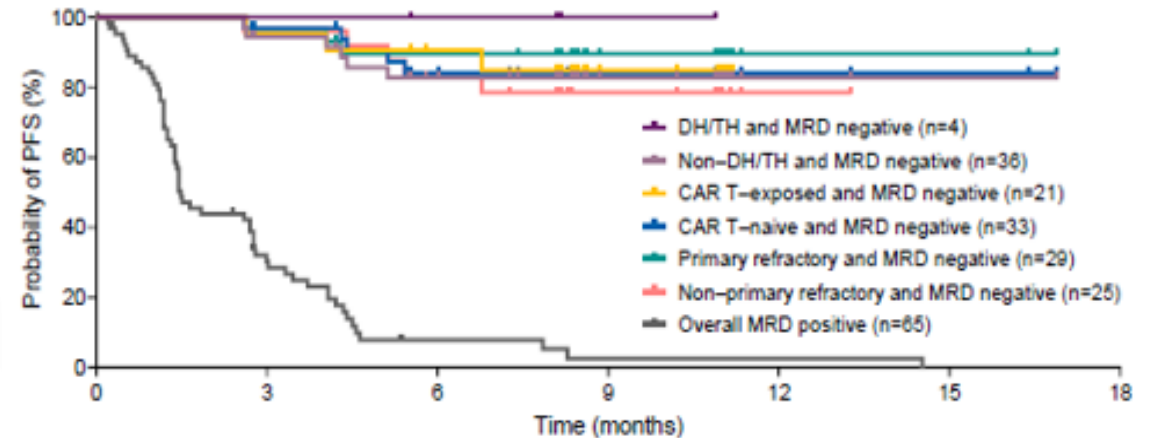
How would you manage this patient?

- a) Tafasitamab + lenalidomide (25 mg)
- b) Loncastuximab teserine
- c) R-Gem-ox
- d) Epcoritamab
- e) Unsure

Rationale for Answer #3

EPCORE NHL-1 Trial: Epcoritamab

Prior Treatments	LBCL, N=157
Median time from initial diagnosis to first dose, y	1.6
Median time from end of last therapy to first dose, mo	2.4
Median prior lines of therapy (range)	3 (2–11)
≥3 Lines of therapy, n (%)	111 (71)
Primary refractory ^c disease, n (%)	96 (61)
Refractory ^c to last systemic therapy, n (%)	130 (83)
Refractory ^c to ≥2 consecutive lines of therapy, n (%)	119 (76)
Prior ASCT, n (%)	31 (20)
Prior CAR T therapy, n (%)	61 (39)
Refractory ^c to CAR T therapy	46/61 (75)



Phillips T, et al. ASH 2022. Abstract 4251.

ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor T-cell therapy; DH/TH, double-hit/triple-hit lymphoma; MRD, minimal residual disease.

Key Takeaways

- LBCL remains a curable disease in the 1st line, 2nd line, and 3rd line setting but with diminishing odds
- There are multiple targeted therapies, either single agents or in combination
- Strategic considerations are necessary in the rel/ref LBCL space regarding the timing of CAR-T, CD19 engaging agents, and CD3XCD20 bispecific
- Consideration of capabilities for local administration vs shared administration vs referral for the administration of CD3XCD20 bispecifics

CD20 X CD3 Bispecifics—Redefining Treatment for Patients with R/R DLBCL/LBCL in the Community Setting

