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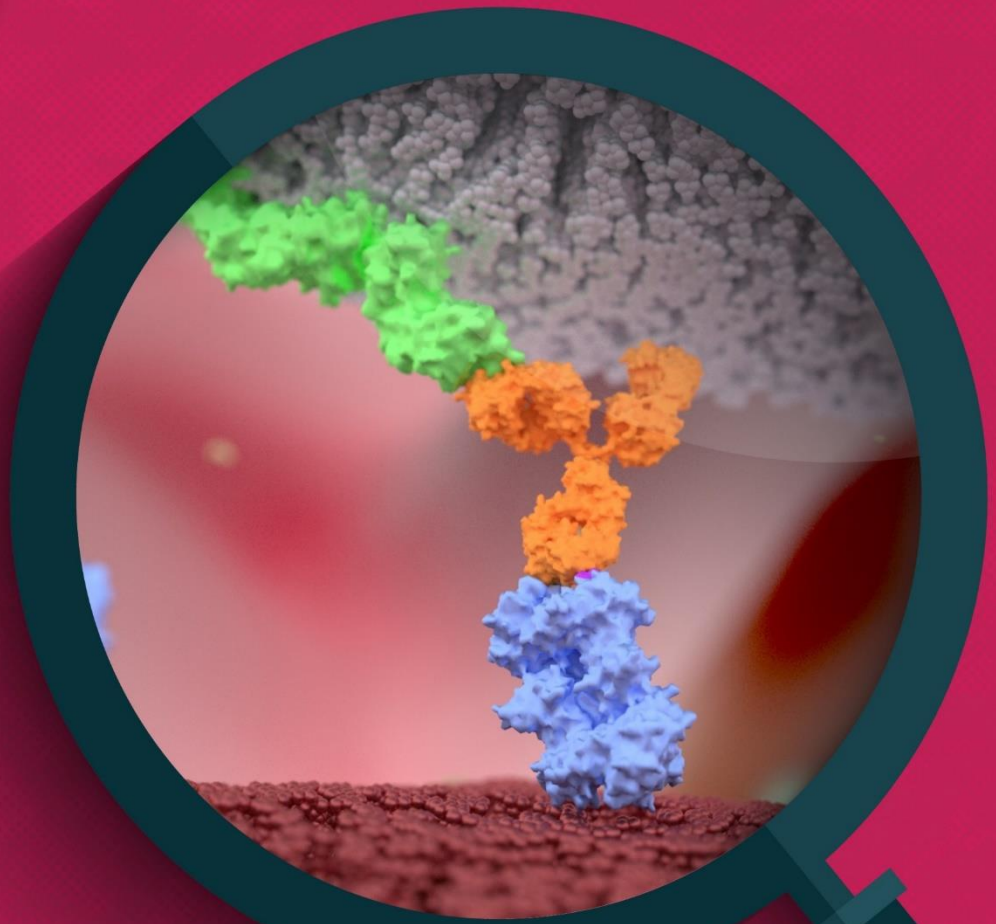
Exploring the Role of Novel Bispecific Antibodies in Relapsed/Refractory Diffuse Large B-Cell Lymphoma

A Clinical Transfers Activity



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This activity is supported by an educational grant from Genmab US, Inc. and AbbVie.

Refractory/Relapsed Diffuse Large B-Cell Lymphoma: Why is it Important?

DLBCL

- Most common type of NHL, accounting for 30% to 40% of cases
- Aggressive and heterogeneous disease
- More than 60% of patients are cured with first-line chemoimmunotherapy
- 5-year survival is 50% to 60%

R/R DLBCL

- 10% to 15% of patients with DLBCL are refractory to first-line therapy or relapse within 6 months of treatment
- 20% to 25% relapse after initial response, often within first two years
- Historical overall survival for patients with primary refractory disease is about 6 months
- Survival in patients who relapse after 2 years is better, but 5-year overall survival continues to be poor: around 20%

DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma; R/R, refractory or relapsed.

Atallah-Yunes SA, et al. *Front Immunol*. 2022;13:901365. Sehn LH, Salles G. *N Engl J Med*. 2021;384(9):842-58. Wang Y, et al. *J Clin Oncol*. 2019;37(21):1819-27.

Agenda

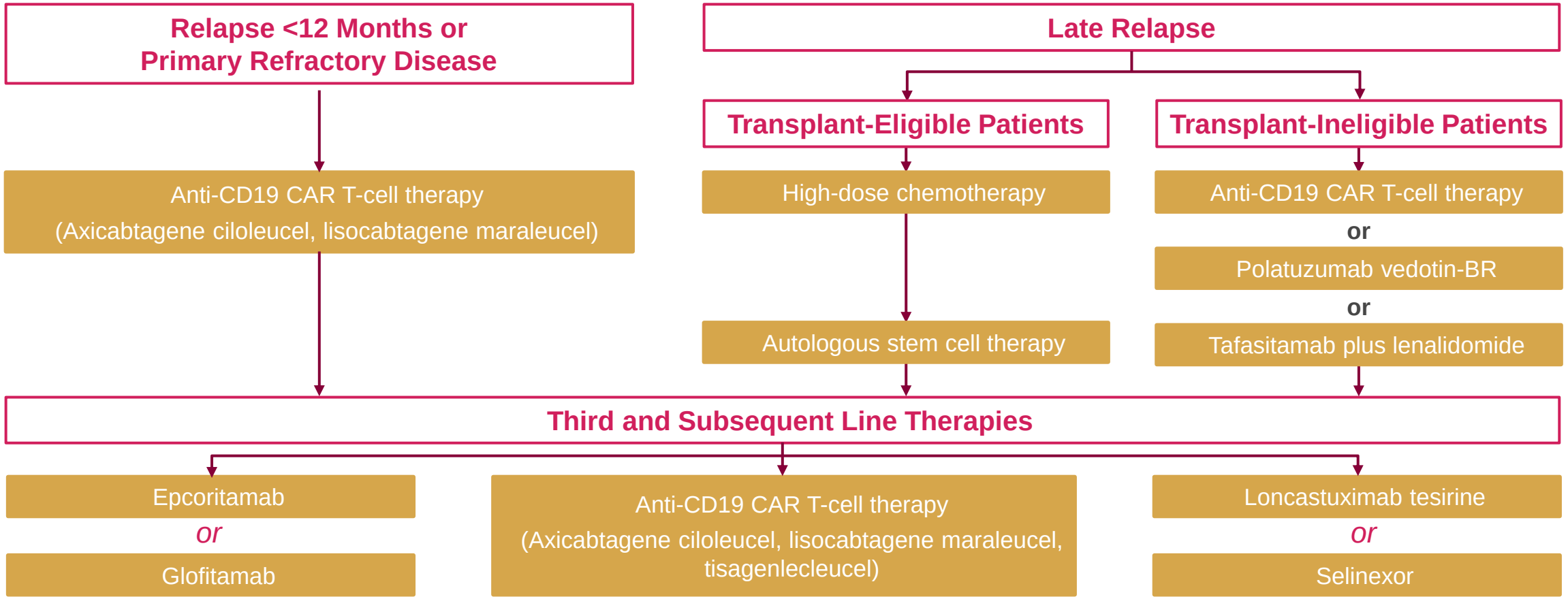
1. Taking Stock of the Current Treatment Landscape of R/R DLBCL
   Dr. Yasmin Karimi

2. Current and Emerging Role of Bispecific Antibodies for the Treatment of R/R DLBCL
   Dr. Allison Rosenthal

Taking Stock of the Current Treatment Landscape of R/R DLBCL

Dr. Yasmin Karimi

Overview of Current Therapies for R/R DLBCL



Treatment approaches should take patient characteristics and efficacy and toxicities into consideration.

BR, bendamustine-rituximab; CAR, chimeric antigen receptor.

NCCN Clinical Practice Guidelines in Oncology. B-cell Lymphomas Version 4.2023. June 2, 2023. www.nccn.org; FDA. Accessed June 27, 2023. https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications.

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Efficacy and Safety of Anti-CD19 CAR T-Cell Therapy in Third and Subsequent Line Treatment of R/R DLBCL: Phase 2 Clinical Trial Results

- Patients had received ≥2 prior lines of treatment (LOT)
- Rates of adverse events differed among CAR T therapies, with axi-cel having the highest rates of CRS and neurotoxicity
- Outcomes were similar among CAR T-cell therapies, with approximately 30% of patients achieving durable disease control

	Trial	n	ORR (%)	CR rate (%)	1-year EFS (%)	Median OS (months)	Grade ≥ 3 Toxicities (%)
Axicabtagene ciloleucel (axi-cel)	ZUMA-1	111	83	58	43	25.8	CRS, 11 Neurotoxicity, 32
Lisocabtagene maraleucel (liso-cel)	TRANSCEND NHL-001	344	73	53	44	27.3	CRS, 2 Neurotoxicity, 10
Tisagenlecleucel (tisa-cel)	JULIET	93	53	39	65	11.1	CRS, 23 Neurotoxicity, 1

CRS, cytokine release syndrome; CR, complete response; EFS, event-free survival; ORR, overall response rate.

Ngu H, et al. *Am Soc Clin Oncol Educ Book*. 2022;(42):629-42; Sehn LH, Salles G. *N Engl J Med*. 2021;384(9):842-58.

Efficacy and Safety of Anti-CD19 CAR T-Cell Therapy in Second-Line Treatment of R/R DLBCL: Phase 3 Clinical Trial Results

- Patients had primary refractory or early relapsing disease and were eligible for transplant
- Patients randomized to CAR T-cell therapy vs SOC salvage chemotherapy, followed by high-dose chemotherapy and ASCT
- Treatment with tisa-cel (BELINDA) did not meet primary endpoint
- **Initial data showed ZUMA-7 (axi-cel) and TRANSFORM (liso-cel) demonstrated significant improvement in PFS with CAR T-cell therapy compared to SOC**

	Trial	n	ORR (%)	CR rate (%)	Median Follow-up (months)	Median EFS (months)	Grade ≥ 3 Toxicities (%)
Axi-cel vs SOC	ZUMA-7	359	83 vs 50	65 vs 32	25	8.3 vs 2	91 vs 83 CRS, 6 Neurotoxicity, 21
Liso-cel vs SOC	TRANSFORM	184	86 vs 43	66 vs 39	6.2	10.1 vs 2.3	34 vs 43 CRS, 1 Neurotoxicity, 4
Tisa-cel vs SOC	BELINDA	322	46 vs 43	28 vs 28	10	3 vs 3	75 vs 86 CRS, 5 Neurotoxicity, 3

ASCT, autologous stem cell transplant; SOC, standard of care.

Ngu H, et al. *Am Soc Clin Oncol Educ Book*. 2022;(42):629-42. Duarte C, Kamdar M. *Am Soc Clin Oncol Educ Book*. 2023 Jan;43:e390802.

Safety and Efficacy of Axi-Cel vs SOC in Patients With R/R DLBCL: Final Results of Phase 3 ZUMA-7 Trial

359 patients with refractory or early relapsed LBCL and intention to proceed to HDT-ASCT were randomized 1:1

Axi-cel (n=180)
Conditioning chemotherapy + axi-cel

SOC (n=179)
2-3 cycles investigator-selected platinum-based chemoimmunotherapy

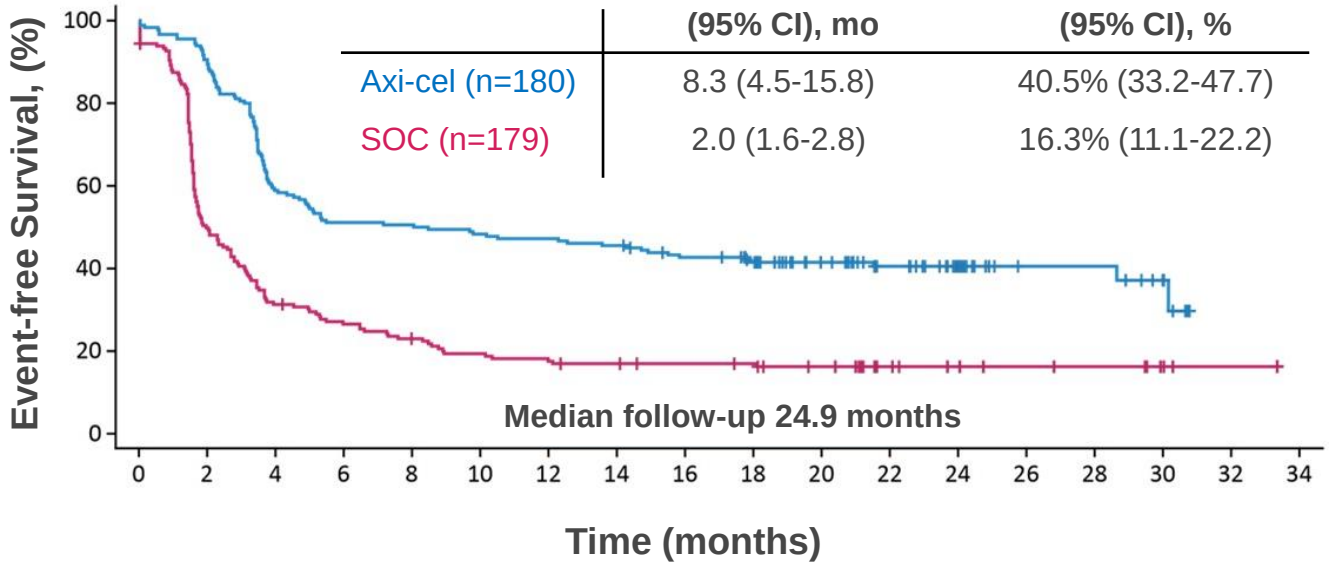
EFS Primary Analysis

Prespecified ITT OS primary analysis 5 years after randomization of first patient

PRIMARY ENDPOINT: EFS

HR 0.398 (95% CI, 0.308-0.514); P<.0001)

	Median EFS (95% CI), mo	24-month EFS Rate (95% CI), %
Axi-cel (n=180)	8.3 (4.5-15.8)	40.5% (33.2-47.7)
SOC (n=179)	2.0 (1.6-2.8)	16.3% (11.1-22.2)



Axi-cel, axicabtagene ciloleucel; ITT, intention to treat; HDT, high-dose therapy; HR, hazard ratio; mo, months; OS, overall survival.

Westin JR, et al. Presented at ASCO; June 2-6, 2023; Late-breaking abstract 107; Westin JR, et al. *N Engl J Med*. Published online June 5, 2023.

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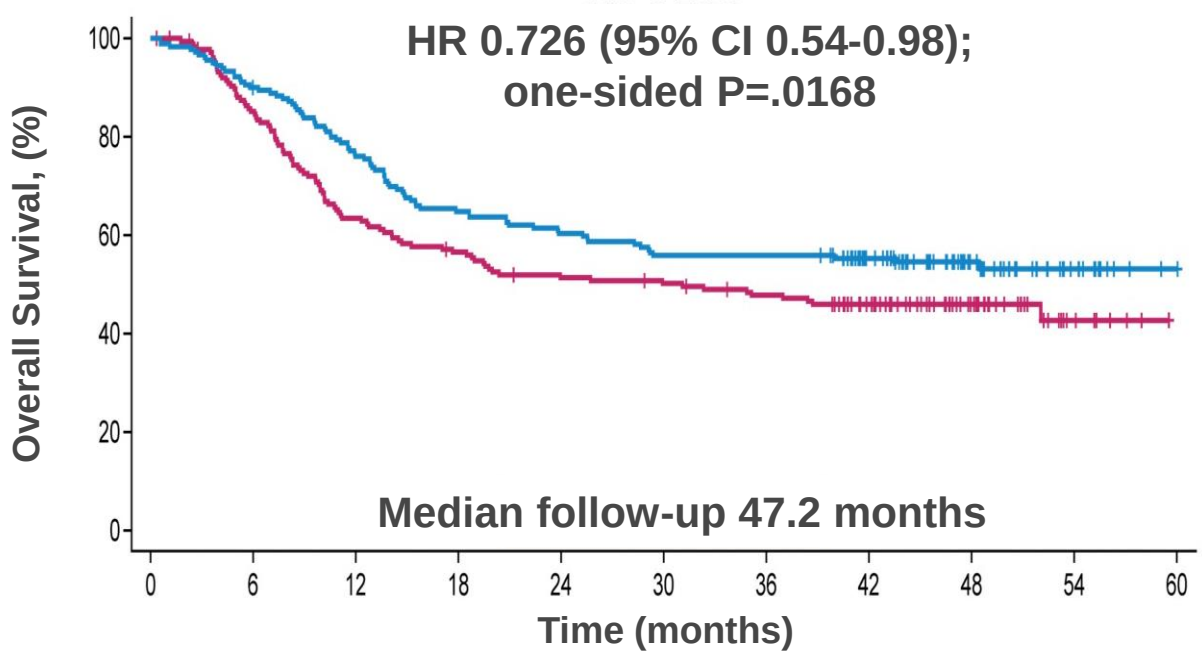
Safety and Efficacy of Axi-Cel vs SOC in Patients With R/R DLBCL: Final Results of Phase 3 ZUMA-7 Trial

- 57% (102/179) of SOC patients received subsequent cellular immunotherapy (off protocol)
- Median overall survival with axi-cel was not reached vs 31 months with SOC
- Survival benefit with axi-cel was similar across prespecified subgroups including age, response to first-line therapy, age-adjusted IPI or prognostic markers
- Grade ≥3 adverse events included CRS in 6%, neurotoxicity in 21%, cytopenia in 75%, and infections in 16%

KEY SECONDARY ENDPOINT: Overall Survival



IPI, international prognostic index.

Westin JR, et al. Presented at ASCO; June 2-6, 2023; Late-breaking abstract 107; Westin JR, et al. *N Engl J Med*. Published online June 5, 2023.

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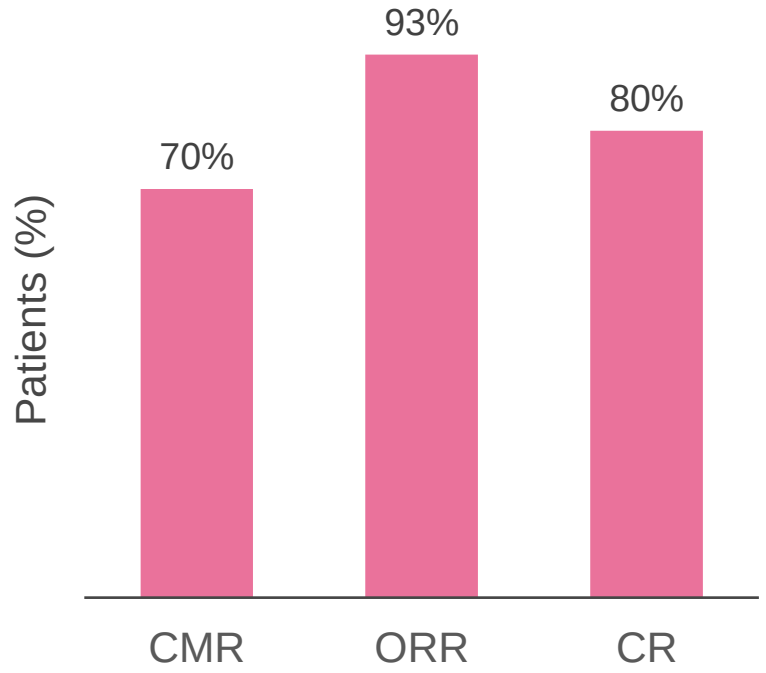
Safety and Efficacy of Axi-cel as Second-line Therapy for LBCL in Transplant-Ineligible Patients: Final Analysis of Phase 2 ALYCANTE Study

- Phase 2 ALYCANTE trial included 62 infused patients with R/R DLBCL in the 2nd line treatment setting
- Among 62 infused patients, 40 patients were included in analysis
- Patients were ineligible for HDCT/HSCT based on physician's assessment
- Complete metabolic response (CMR) at 3 months (primary endpoint) was 70% with axi-cel vs 12% with SOC based on historical control
- Adverse events included
  - CRS in 90% of patients (10% grade 3-4)
  - ICANS in 55% (20% grade 3-4)

Clinical Outcomes



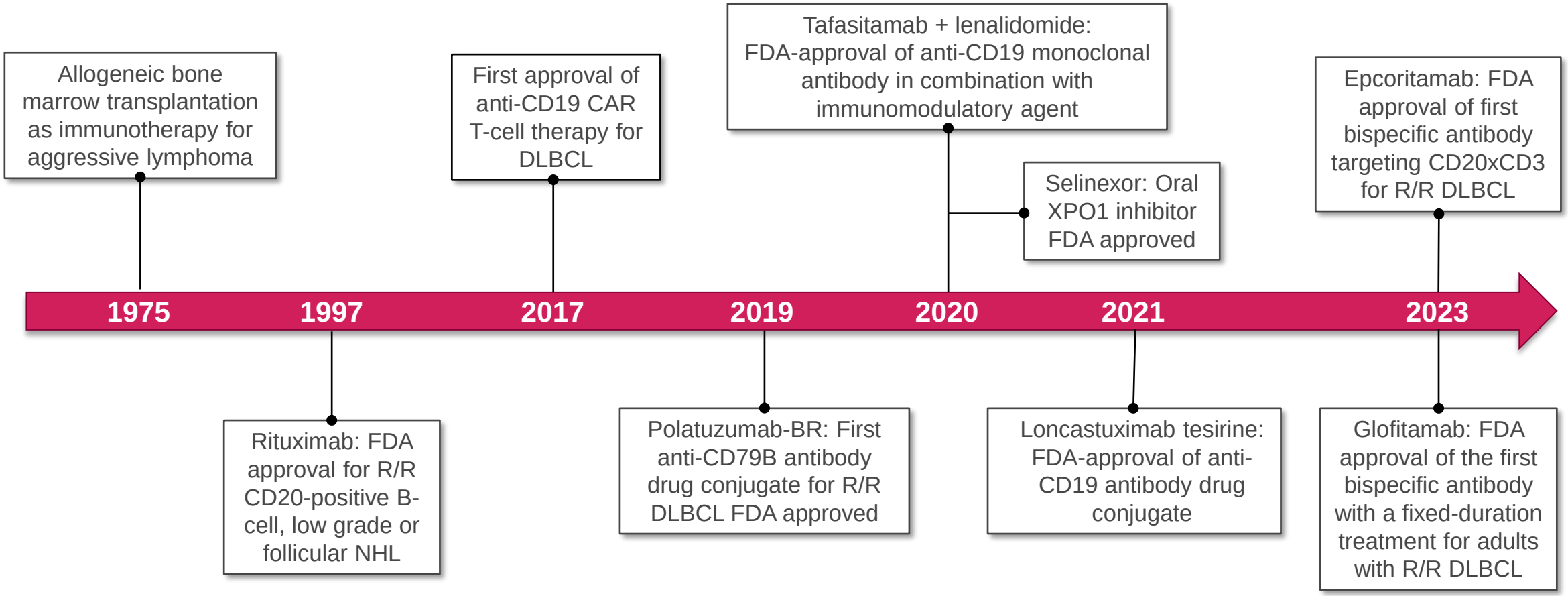
Houot R, et al. Presented at EHA; June 8-11, 2023; Abstract S233.

Challenges Associated With Anti-CD19 CAR T-Cell Therapy

- Toxicities, such as CRS and ICANS
- Appropriate bridging therapy may not be available for patients with quickly evolving disease
- Prognosis: Only 30% to 40% of patients achieve durable remission
- Logistics/access such as required travel to treatment center
- High cost of manufacturing CAR T cells

Sehn LH, Salles G. *N Engl J Med*. 2021;384(9):842-58. Atallah-Yunes SA, et al. *Front Immunol*. 2022;13:901365.

Timeline of FDA Approvals of Therapies for R/R DLBCL



Gambella M, et al. *Front Immunol*. 2022;13:837457. Falchi L, et al. *Blood*. 2023;141(5):467-80. Sawalha Y. *J Pers Med*. 2021;11(12):1345. FDA. Accessed June 27, 2023. https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications

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Efficacy of Novel FDA-Approved Therapies: Phase 2 Clinical Trial Results

- Novel therapies may benefit patients who do not have access to CAR T therapy or who progress post CAR T therapy
- **Response rates with novel therapies were *lower* compared to those with CAR T therapy**

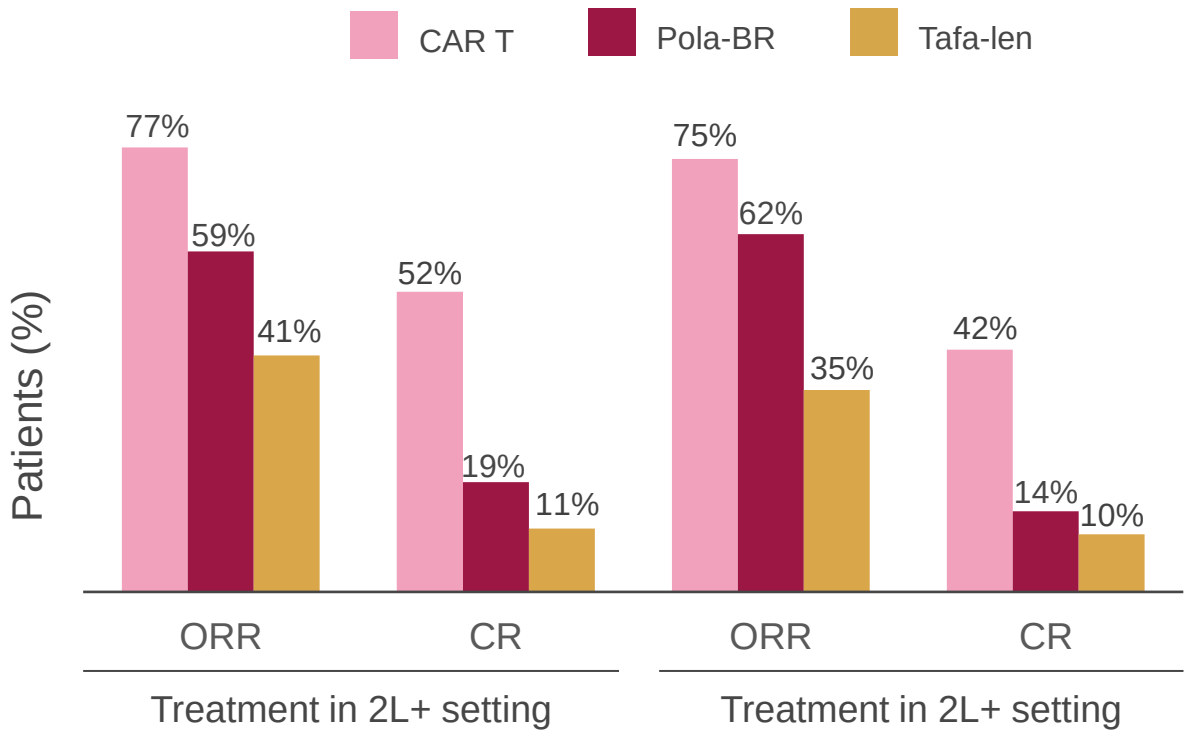
Therapy	Trial	n	Median Previous Lines of Therapy	ORR (%)	CR Rate (%)	Median PFS or EFS (months)	Median OS (months)
Polatuzumab vedotin-BR	NCT02257567	118	Two	45	40	9.5	12.4
Tafasitamab + lenalidomide	L-MIND	81	Two	58	43	11.6	33.5
Loncastuximab tesirine	LOTIS-2	184	Three	48	24	4.9	9.9
Selinexor	SADAL	127	Three	28	12	2.6	9.1

Duarte C, Kamdar M. *Am Soc Clin Oncol Educ Book*. 2023 Jan;43:e390802. Kalakonda N, et al. *Lancet Haematol*. 2020;7(7):e511-e522.

Real-World Outcomes With Novel Therapies in R/R DLBCL

- Retrospective analysis of 175 patients with R/R DLBCL and ≥1 prior LOT from COTA electronic health database
- Among these, 67% had ≥2 LOTs and 36% had ≥3 LOTs
- There was a trend toward inferior outcomes as patients moved through subsequent lines of therapy
- Outcomes in real-world setting were inferior to those in clinical trials
- **Response rates were *higher* with CAR T therapy than other therapies**

Clinical Outcomes



Pola-BR, polatuzumab + bendamustine and rituximab; Tafa-len, tafasitamab + lenalidomide.

Crombie JL, et al. Presented at ASCO; June 2-6, 2023. Abstract 7552.

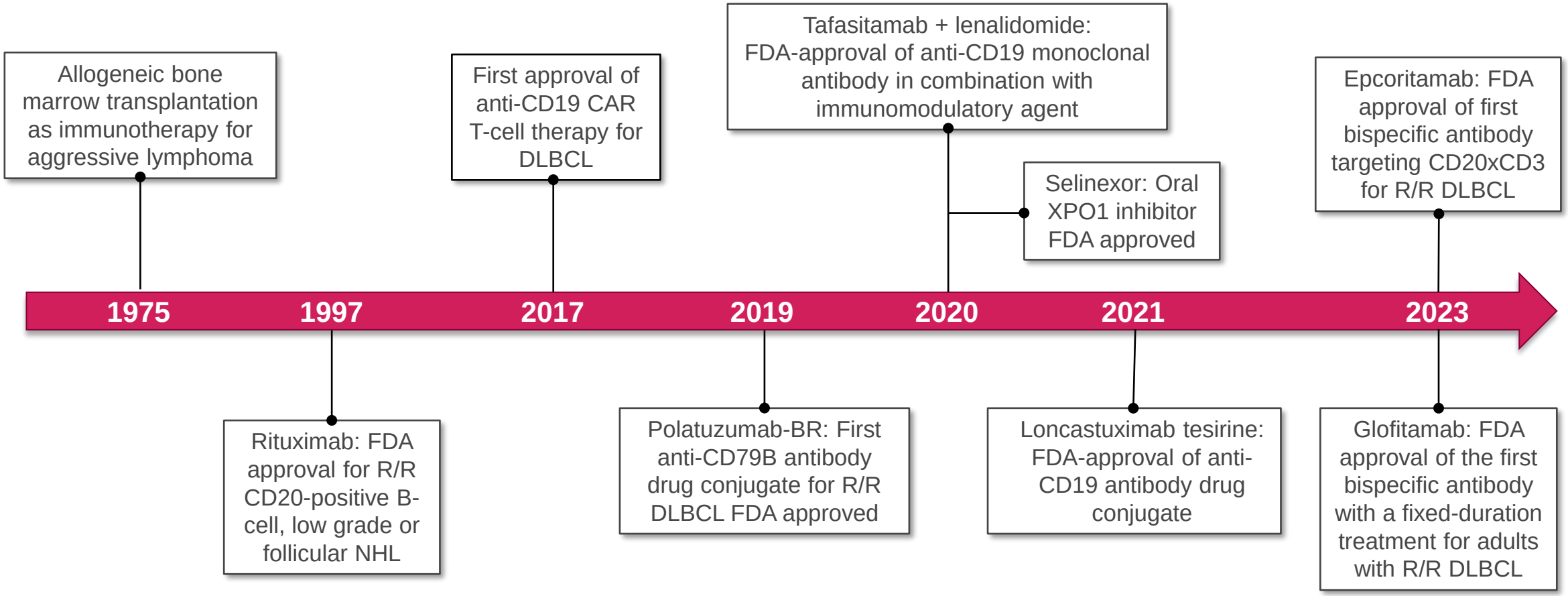
Summary

- About 30% to 40% of patients with DLBCL relapse
- Anti-CD19 CAR T-cell therapy is the recommended second-line treatment for early relapse and primary refractory DLBCL, and for patients ineligible for transplant
- However, access to CAR T-cell therapy remains limited due to potential toxicities and logistical challenges
- Novel treatment approaches such as monoclonal antibodies and antibody-drug conjugates are available, but have limited efficacy
- Prognosis of R/R DLBCL remains poor and novel therapies are needed for this patient population

Current and Emerging Role of Bispecific Antibodies for the Treatment of R/R DLBCL

Dr. Allison Rosenthal

Timeline of FDA Approvals of Therapies for R/R DLBCL



Gambella M, et al. *Front Immunol*. 2022;13:837457. Falchi L, et al. *Blood*. 2023.141(5):467-80; Sawalha Y. *J Pers Med*. 2021;11(12):1345. FDA. Accessed June 27, 2023. https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications.

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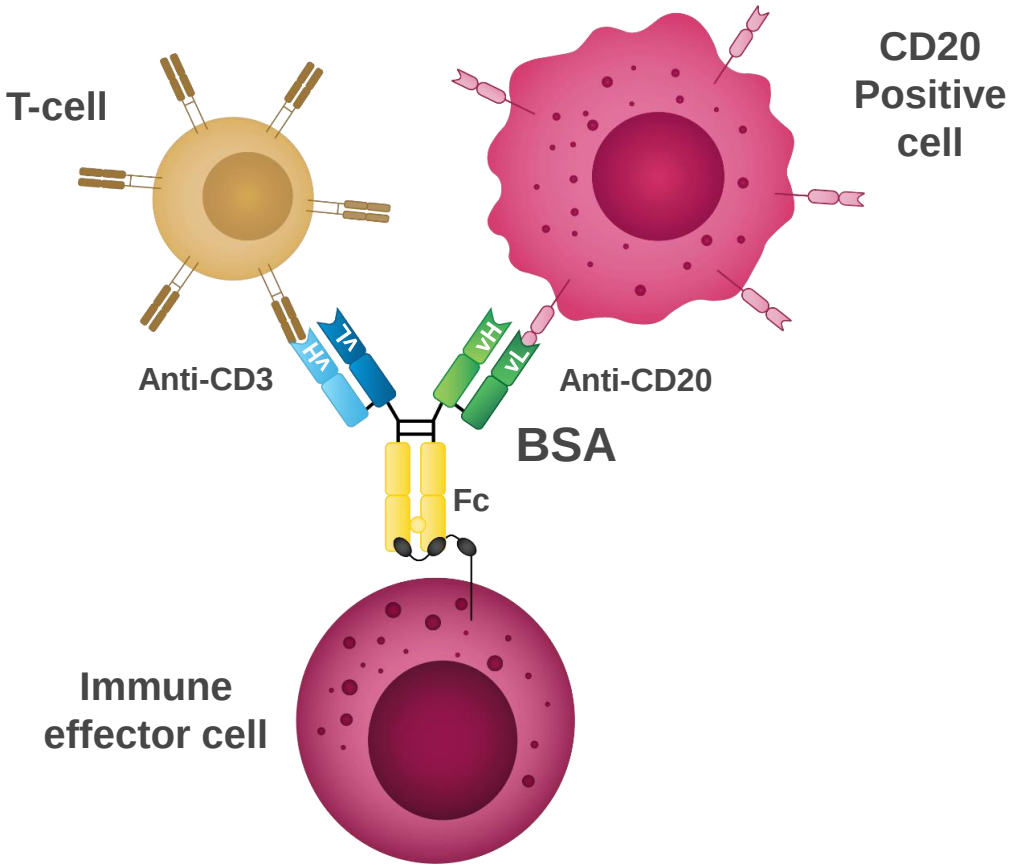
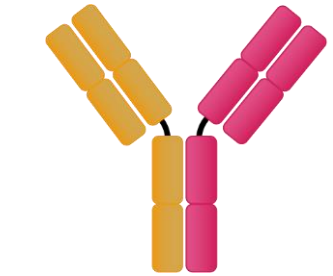
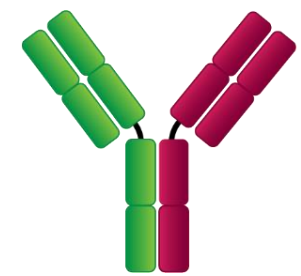
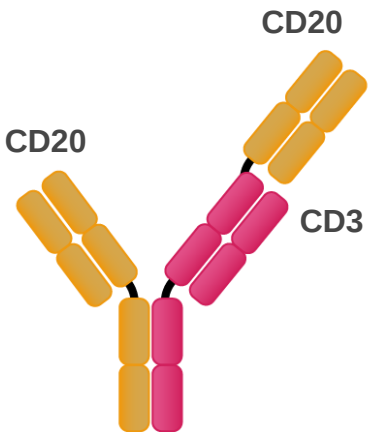
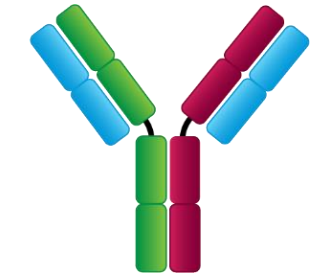
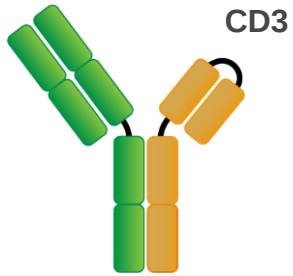
Rationale for Treating R/R DLBCL With Bispecific T-Cell Engaging Antibodies Targeting CD20 x CD3



- CD20 is widely expressed on cells of B-cell origin
- Bispecific antibodies bind to CD20 on tumor cells and CD3 on T cells, initiating T-cell engagement and malignant cell lysis
- Cytotoxicity occurs in MHC-independent manner
- Fc region stabilizes the molecule, giving it a half-life of 10 days, and it can be used to activate immune effector cells
- Bispecific antibodies have “off-the-shelf” availability
- Different bispecific antibodies bind different CD20 antigen epitopes, making combination therapies possible

Rampotas A, et al. *Ther Adv Hematol*. 2021;12:20406207211053120. Falchi L, et al. *Blood*. 2023;141(5):467-80.

Overview of Current and Emerging Bispecific T-Cell Engaging Antibodies for R/R DLBCL

					
	MOSUNETUZUMAB	**EPCORITAMAB**	**GLOFITAMAB**	**ODRONEXTAMAB**	**PLAMOTAMAB**
Status	FDA-approved for follicular lymphoma	FDA-approved for R/R DLBCL	FDA-approved for R/R DLBCL	Investigational	Investigational
Format	IgG1	IgG1	IgG1	IgG4	IgG1
CD20:CD3 ratio	1:1	1:1	2:1	1:1	1:1

Falchi L, et al. *Blood*. 2023;141(5):467-80. FDA. Accessed June 27, 2023. https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications.

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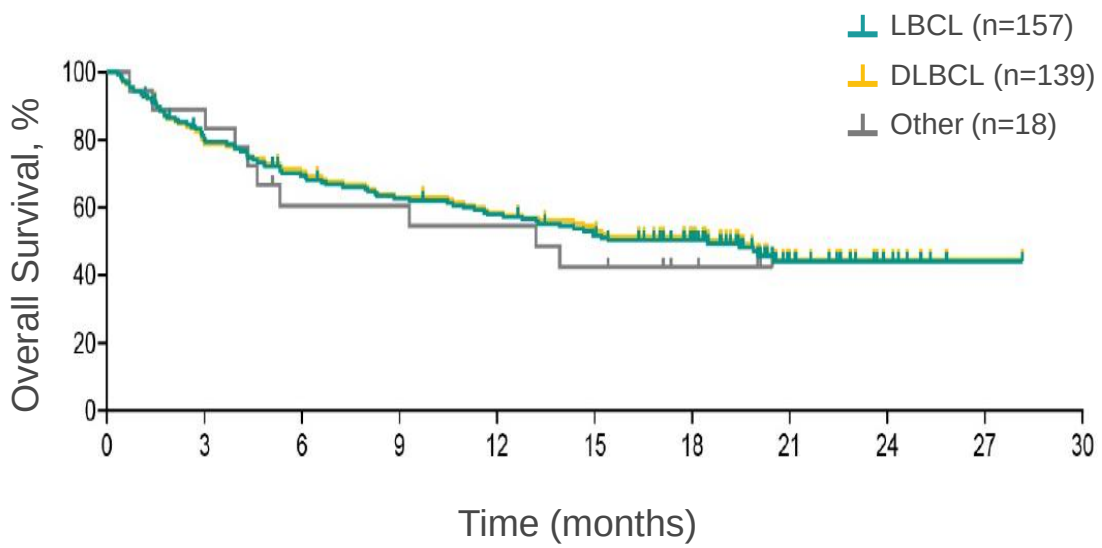
Efficacy and Safety of Epcoritamab Monotherapy in R/R LBCL: Updated Results of Phase 1/2 EPCORE NHL-1 Trial

- Patients with LBCL and ≥2 prior LOTs received step up dosing (0.16 mg and 0.8 mg) to epcoritamab SC 48 mg until PD or unacceptable toxicity
- Among 157 patients with LBCL, 139 had DLBCL and 9 HGBCL
- Median follow-up 20 months
- Primary endpoint: ORR

Best overall response, n (%) [95% CI]	DLBCL & HGBCL n=148	LBCL n=157
ORR	90 (61) [53-69]	99 (63) [55-71]
CR	57 (39) [31-47]	62 (39) [32-48]
PR	33 (22)	37 (24)
SD	5 (3)	5 (3)
PD	37 (25)	37 (24)

Overall Survival



Median OS 18.5 months (95% CI, 11.7-NR) for overall LBCL population and 19.4 months (95% CI, 11.7-NR) for patients with DLBCL

HGBCL, high-grade B-cell lymphoma; PD, progressive disease; PR, partial response; SC, subcutaneous; SD, stable disease.

Karimi Y, et al. Presented at ASCO; June 2-6, 2023; Abstract 7525. Jurczak W, et al. Presented at EHA; June 8-11; Abstract P1118.

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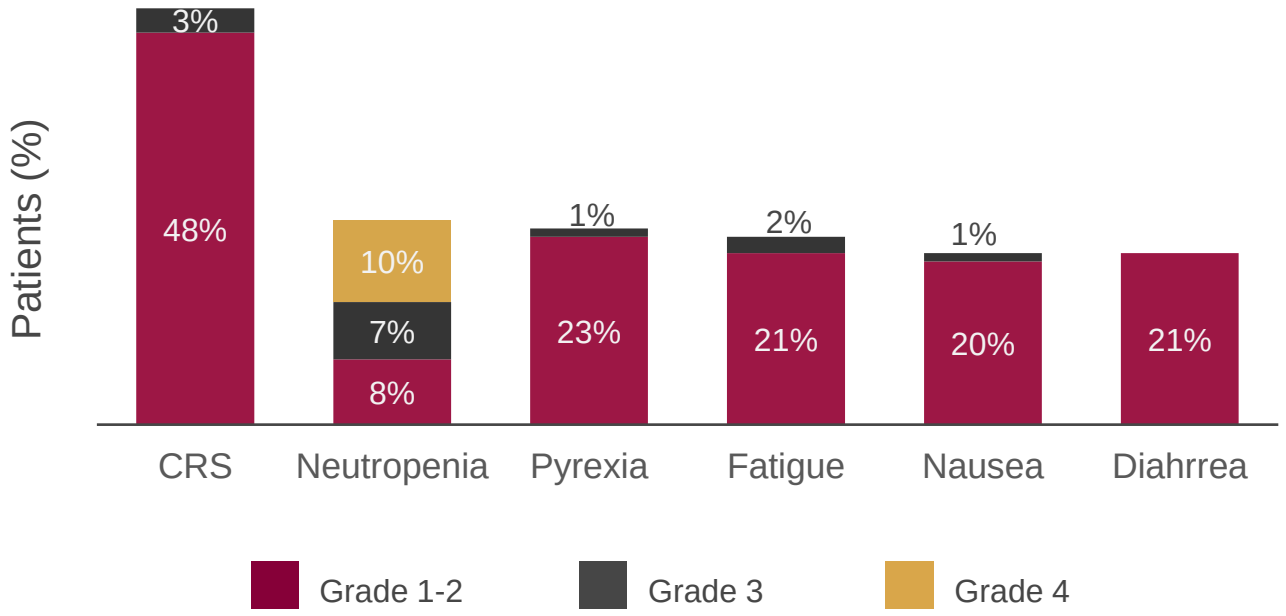
Efficacy and Safety of Epcoritamab Monotherapy in R/R LBCL: Updated Results of Phase 1/2 EPCORE NHL-1 Trial

- Among 157 patients with LBCL, fatal treatment-emergent adverse events (TEAE) occurred in 15 patients
- **CRS was predictable and primarily low-grade in patients with LBCL**
  - Five patients (3%) had grade 3 CRS
  - CRS occurred primarily following first full dose
  - Anticytokine therapy was most often administered for events after first full dose
  - 23 patients (15%) received anticytokine therapy

TEAE in ≥20% of Patients with LBCL

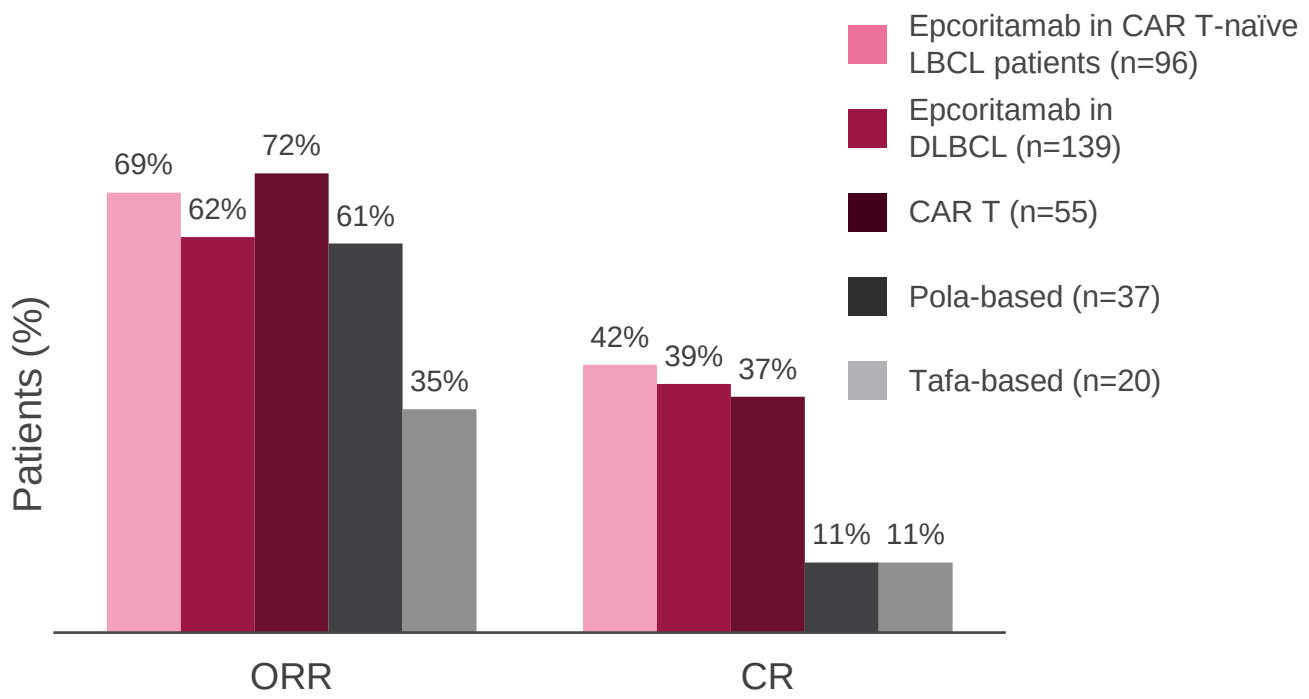


Karimi Y, et al. Presented at ASCO; June 2-6, 2023; Abstract 7525. Jurczaki W, et al. Presented at EHA; June 8-11; Abstract P1118.

Comparison of Efficacy of Epcoritamab vs CAR T Therapies, Polatuzumab- and Tafasitimab-Based Regimens

- Retrospective analysis included individual patient data from EPCORE NHL-1 trial and patients with R/R DLBCL and LBCL and ≥2 prior LOT from COTA electronic health database
- Cohorts were balanced on factors including prior CAR T exposure, number of prior LOTs, and refractoriness to last LOT
- Adjusted hazard ratio (95% CI) for OS:
  - 1.08 (0.70-1.69) for epcoritamab vs CAR T
  - 0.44 (0.32-0.62) for epcoritamab vs pola-based regimens
  - 0.53 (0.38-0.75) for epcoritamab vs tafa-based regimen
- **Epcoritamab provided significantly better efficacy vs pola-based and tafa-based regimens**

Clinical Outcomes

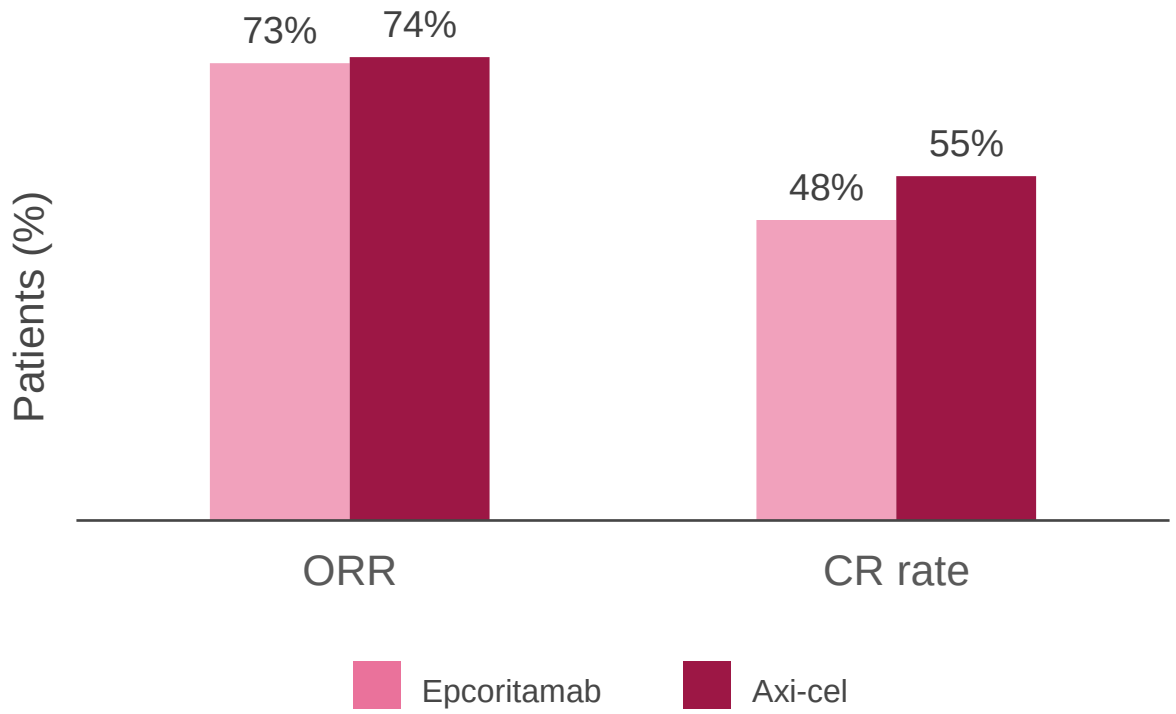


Rosenthal A, et al. Presented at EHA; June 8-11, 2023; Abstract P1149.

Indirect Comparison of Epcoritamab vs Axi-cel in R/R DLBCL CAR T-Naïve and CAR T-Eligible Patients

- Matching-adjusted analysis of 101 patients from ZUMA-1 trial who received axi-cel and 86 patients from EPCORE NHL-1 trial who received epcoritamab monotherapy
- Patients with prior CAR T therapy were excluded
- Analyses were adjusted for imbalances in baseline characteristics
- **There was no significant difference in response to axi-cel vs epcoritamab in overall CAR T-naïve patients or in subpopulation of CAR T-eligible patients**

Clinical Outcomes

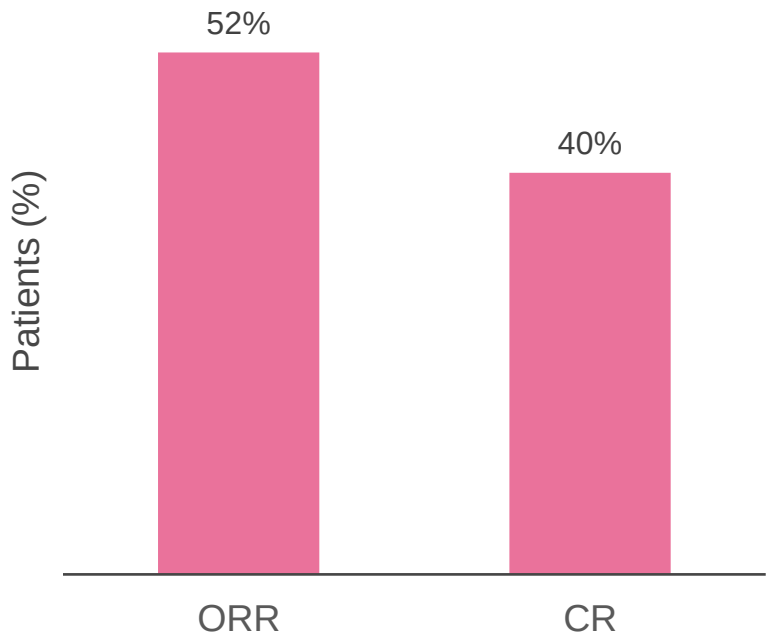


Thieblemont C, et al. Presented at EHA; June 8-11, 2023; Abstract P1154.

Efficacy and Safety of Glofitamab Monotherapy in Third and Subsequent Line Treatment of R/R LBCL: Updated Results from Phase 2 Trial

- Phase 2 trial included 155 patients with R/R LBCL and ≥2 prior LOTs treated with step up dosing (2.5 mg and 10 mg) to glofitamab IV 30 mg in 12 three-weekly cycles
- Patients were pretreated with obinutuzumab 1,000 mg seven days prior to first glofitamab dose
- Median follow-up 18.2 months
- Median duration of complete response 26.9 months (18.4-NE)
- Primary endpoint: CR rate as best overall result by IRC
- Most common adverse event was CRS, occurring in 64% of patients (4% grade ≥3)

Clinical Outcomes



IRC = independent review committee; NE, not estimable.

Falchi JR, et al. Presented at ASCO; June 2-6, 2023; Abstract 7550.

Summary

- Epcoritamab had an ORR of 63% and CR rate of 39% among 157 patients with R/R LBCL in the phase 2 EPCORE NHL-1 trial
  - CRS was most common treatment related adverse event, occurring in 48% of patients (3% with grade 3 CRS)
  - Comparison of EPCORE NHL-1 results with both clinical trials and real-world data showed similar efficacy between epcoritamab and CAR T-cell therapy
- Glofitamab showed an ORR of 52% and a CR rate of 40% among 155 patients with R/R DLBCL and ≥2 prior LOTs in a phase 2 trial
  - Most common adverse event was CRS, occurring in about 64% of patients (4% with grade ≥3 CRS)

Thank you!

Please take a moment to complete the posttest and evaluation to receive CME credit.