Key Updates in Bispecific Antibodies in Non-Hodgkin Lymphoma Management—Unmet Needs and Opportunities for Improved Management in Later-Line Management

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Disclosures

- **Mehdi Hamadani, MD**, reports that he is a consultant for Incyte Corporation, MorphoSys, Seagen, Gamida Cell, Novartis, Legend Biotech, Kadmon, ADC Therapeutics, Omeros, AbbVie, Genmab, and Caribou Biosciences; he also is a speaker for Sanofi, AstraZeneca, BeiGene, ADC Therapeutics, and Kite Pharma and provides contract research funding to ADC Therapeutics and Spectrum Pharmaceuticals

All relevant financial relationships have been mitigated.

During this lecture Dr. Hamadani may mention the use of medications for both US Food and Drug Administration (FDA)-approved and non-FDA-approved indications.

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Learning Objectives

- Recognize approaches to use of novel bispecific antibody therapies in the management of non-Hodgkin lymphoma (NHL)
- Analyze the latest outcomes of clinical trials in NHL incorporating bispecific antibody therapy
- Summarize the latest data concerning potential adverse events associated with novel bispecific antibodies in NHL

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Pre-Read Slides

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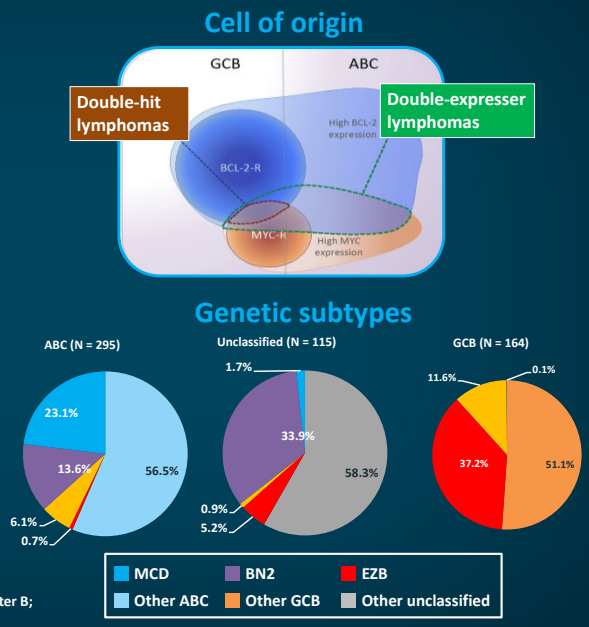
Diffuse Large B-Cell Lymphoma

- Most common NHL in US and worldwide
- Typically occurs in 6th decade of life, more common in males (55% males)
- Approximately half of patients present with advanced-stage disease
  - Elevated LDH ~40%
  - Any extranodal involvement 40% to 70%
  - Bone marrow involvement 10% to 20%
  - CNS involvement <1% (~3% during entire course of disease)
- Clinically and biologically heterogeneous based on cell of origin (eg, GCB, ABC, or unclassified)
- Typically, CD20-positive



ABC = activated B-cell like; CD = cluster of differentiation; CNS = central nervous system; GCB = germinal center B; LDH = lactate dehydrogenase.

Abramson JS, Shipp MA. *Blood.* 2005;106:1164-1174. Dunleavy K. *Curr Treat Options Oncol.* 2015;16:58. Schmitz R, et al. *N Engl J Med.* 2018;378:1396-1407. ACS. Key statistics for non-Hodgkin lymphoma, 2023 (https://www.cancer.org/cancer/types/non-hodgkin-lymphoma/about/key-statistics.html statistics). Accessed 9/1/23.

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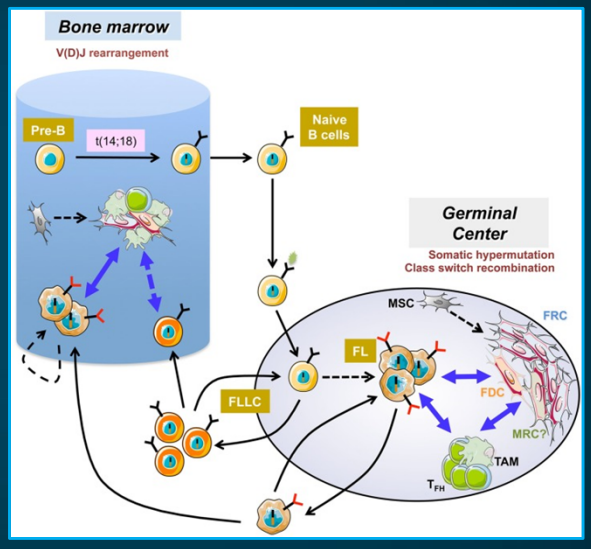
Follicular Lymphoma

- Follicular lymphoma (FL) is the most common indolent lymphoma subtype, with ~13,000 cases diagnosed each year; FL is slightly more common in males than females
- Relative 5-year survival rate = 90.6%
- However, outcomes are poorer in patients with relapsed/refractory disease within 12 months of diagnosis
- Recognizing early clinical failure and appropriate management is important in optimizing clinical outcomes
- Follicular Lymphoma International Prognostic Index (FLIPI)



Mourcin F, et al. *Front Immunol.* 2012;3:280.

Cerhan JR. *Hematol Oncol Clin North* Am. 2020;34:631-646. National Cancer Institute (NCI). Cancer stat facts: NHL—follicular lymphoma (https://seer.cancer.gov/statfacts/html/follicular.html). Accessed 9/1/23.

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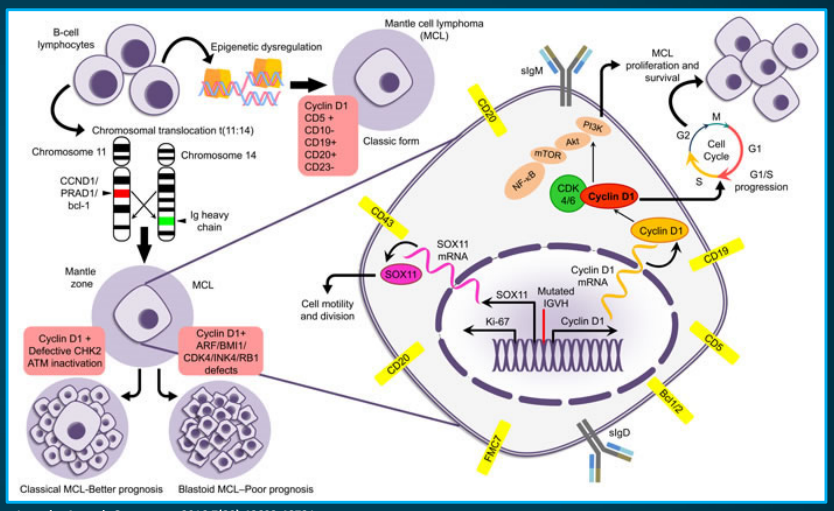
Mantle Cell Lymphoma (MCL)

- MCL is a rare subtype of lymphoma, accounting for ~6% of all NHL
- Median age is 60 to 70 years
- MCL is 3 times more common in males than in females
- Pathology: Mantle zone expansion, CD5+, CD23–, cyclin D1 overexpression, t(11;14)(q13;q32)



Inamdar A, et al. *Oncotarget*, 2016;7(30):48692-48731.

Armitage JO, Weisenburger DD. *J Clin Oncol.* 1998;16:2780-2795. Lynch DT, et al. Mantle cell lymphoma. StatPearls (www.ncbi.nlm.nih.gov/books/NBK536985/). Accessed 9/1/23.

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Epcoritamab: EPCORE NHL-1 LBCL Expansion Cohort

Dose escalation → **Dose-expansion data cutoff: January 31, 2022; median follow-up: 10.7 months**

B-cell NHL
- ✓ No DLTs
- ✓ MTD not reached
- ✓ RP2D identified
- ✓ Manageable safety profile
- ✓ Encouraging antitumor activity

Key inclusion criteria
- R/R CD20+ mature B-cell neoplasm
- ECOG PS 0 to 2
- ≥2 prior lines of antineoplastic therapy, including ≥1 anti-CD20 mAb
- FDG PET-avid and measurable disease by CT/MRI
- Prior CAR T-cell therapy allowed

Step-up dosing

Epcoritamab SC RP2D 48 mg QW cycle 1–3, Q2W cycle 4–9, Q4W cycle 10+ → **Treatment until PD or unacceptable toxicity** → **LBCL cohort N = 157** DLBCL, HGBCL, PMBCL, and FL grade 3b

- To ensure patient safety and better characterize CRS, inpatient monitoring was required at first full dose for 24 hours in this part of the study
- **Primary endpoint**: Objective response rate (ORR) by independent review committee (IRC)
- **Key secondary endpoints**: Duration of response (DOR), TTR, PFS, OS, CRR, and safety/tolerability

Demographics	LBCL (N = 157)
Median age (range), years	64 (20-83)
Median prior lines of therapy (range)	3 (2-11)
Refractory to last systemic therapy, n (%)	130 (83)
Prior ASCT, n (%)	31 (20)
Prior CAR T-cell therapy, n (%)	61 (39)
Progressed within 6 months of CAR T-cell therapy	46/61 (75)

	LBCL (N = 157)
CRS events, n (%)*	78 (49.7)
Grade 1 to 2	74 (47.1)
Grade 3	4 (2.5)
Median time to resolution from first full dose, days	2
Treated with tocilizumab, n (%)	22 (14.0)
Treated with corticosteroids, n (%)	16 (10.2)
Leading to treatment discontinuation, n (%)	1 (0.6)

*Graded by criteria in Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.
CCR = complete clinical remission; CT = computed tomography; CRS = cytokine release syndrome; DLT = dose-limiting toxicity; FDG = fluorodeoxyglucose; LBCL = large B-cell lymphoma; MRI = magnetic resonance imaging; MTD = maximum tolerated dose; Q4W = every 4 weeks; PET = positron emission tomography; TTR = time-to-treatment relapse.
Thieblemont C, et al. *J Clin Oncol.* 2022;41:2238-2247.

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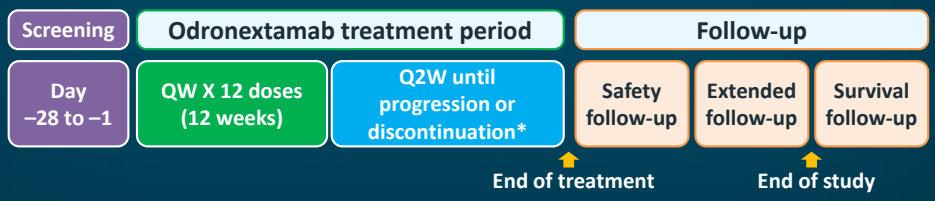
Odronextamab: ELM-2 (NCT03888105) Phase 2 in R/R NHL

Patient subgroups

- Relapsed/refractory disease-specific cohorts
- Independent parallel enrollment

- FL Grade 1–3a (n = 112)
- DLBCL (n = 146)
- MCL after BTKi therapy (n = 78)
- MZL (n = 78)
- **Other B-NHL,** excluding FL grade 1 to 3a, DLBCL, MCL, WM (n = **67**)

Patient study flow



*All patients with durable complete responses of 9 months will transition from Q2W to Q4W dosing.

B-NHL = B-cell NHL; BTKi = Bruton tyrosine kinase inhibitor; QW = once weekly; Q2W = once every two weeks; Q4W = once every 4 weeks; WM = Waldenstrom macroglobulinemia. Odronextamab is an investigational therapy for the management of NHL.

Kim TM, et al. *Blood.* 2020;136(suppl 1):28-29. NCT03888105 (https://clinicaltrials.gov/ct2/show/NCT03888105). Accessed 9/1/23.

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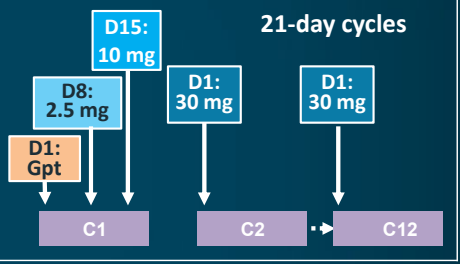
Pivotal Phase 2 Expansion Trial of Glofitamab in R/R DLBCL and ≥2 Prior Therapies

Key inclusion criteria

- DLBCL NOS, HGBCL, transformed FL, or PMBCL
- ECOG PS 0 to 1
- ≥2 prior therapies, including anti-CD20 antibody and anthracycline

Glofitamab administration

- **Fixed-duration treatment**
  - Maximum of 12 cycles
- **CRS mitigation**
  - Obinutuzumab pretreatment (1000 mg)
  - C1 step-up dosing
  - Monitoring after first dose (2.5 mg)



- **Primary endpoint:** CR (best response) rate by IRC*
- **Secondary endpoints:** ORR, DoR, DoCR, PFS, and OS

*By PET-CT (Lugano criteria).

Glofitamab is FDA-approved for R/R DLBCL.

C = cycle; D = day; DoCR = duration of complete response; Gpt = obinutuzumab pretreatment; HGBCL = high-grade BCL; NOS = not otherwise specified; PMBCL = primary mediastinal large BCL.

Dickinson M, et al. *N Engl J Med.* 2022;387:2220-2231.

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Glofitamab in R/R DLBCL: Baseline Characteristics

n (%)		N = 154*
Median age, years (range)		66.0 (21–90)
Male		100 (64.9)
ECOG PS†	0	69 (44.8)
	1	84 (54.5)
Ann Arbor stage	I	10 (6.5)
	II	25 (16.2)
	III	31 (20.1)
	IV	85 (55.2)
NHL subtype	DLBCL	110 (71.4)
	trFL	27 (17.5)
	HGBCL	11 (7.1)
	PMBCL	6 (3.9)
Bulky disease	>6 cm	64 (41.6)
	>10 cm	18 (11.7)

n (%)	N = 154*
Prior lines, median n (range)	3 (2–7)
≥3 prior lines	92 (59.7)
Prior anti-CD20 antibody (Ab)	154 (100.0)
Prior anthracycline	149 (96.8)
Prior CAR T-cell therapy	51 (33.1)
Prior ASCT	28 (18.2)
Refractory to any prior therapy	139 (90.3)
Refractory to last prior therapy	132 (85.7)
Primary refractory	90 (58.4)
Refractory to prior CAR T-cell therapy	46 (29.9)
Refractory to any prior anti-CD20	128 (83.1)

Heavily pretreated, highly refractory population

*Safety-evaluable population (all treated patients); †ECOG PS 2, n = 1 (0.6%).
Glofitamab is FDA-approved for R/R DLBCL.
HGBCL = high-grade B-cell lymphoma; PMBCL = primary mediastinal large B-cell lymphoma; trFL = transformed follicular lymphoma.

Dickinson M, et al. *J Clin Oncol.* 2022;40(16 suppl); Abstract 7500. Dickinson M, et al. *N Engl J Med.* 2022;387:2220-2231.

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Summary of Bispecific Antibody Studies in R/R MCL

Bispecific	Number	ORR%	CR %	CRS/ICANS (Grade 3/4)
Glofitamab[1]	37	83.8	73	16%/0%
Mosunetuzumab[2]	13	31	23	Not reported
Odronextamab[3]	12	50	33	Not reported
Epcoritamab[4]	5	60	20	Not reported

Philips TJ, et al. *Blood.* 2022;140(suppl 1):178-180. Budde LE, et al. *J Clin Oncol.* 2022;40(5):481-491; 1055-1065. Bannerji R, et al. *Lancet Haem.* 2022;9:e327-e339. Hutchings M, et al. *Lancet.* 2021;398:1157-1169.

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