Best Practices for the Multidisciplinary Management of NHL Using Antibody Therapeutics

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Disclosures

- **Mehdi Hamadani, MD**, reports that he is a consultant for ADC Therapeutics, AbbVie, Omeros, BMS, Kite, Genmab, CRISPR, Autolus, Caribou and Forte 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

This activity is supported by an unrestricted educational grant from ADC Therapeutics America, Inc., and an educational grant from Genentech, a member of the Roche Group.

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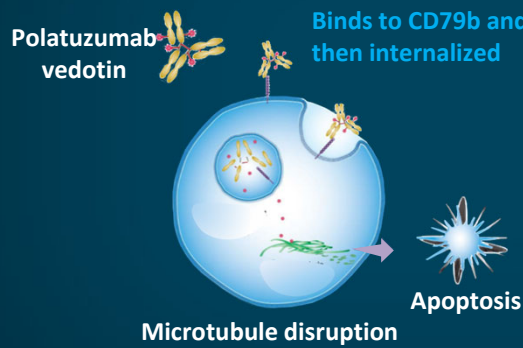
Learning Objectives

- Recognize the function of novel antibody therapeutics and combinations in the management of B-cell non-Hodgkin lymphoma (B-NHL)
- Evaluate contemporary clinical trial data informing the use and development of antibody therapeutics in B-NHL
- Assess potential adverse events associated with antibody therapeutics in B-NHL and best practices for the management of potential adverse events in the context of the multidisciplinary oncology care team

POLARIX: Polatuzumab Vedotin* vs Vincristine in R-CHOP

CD79B is ubiquitously expressed in B-cell NHL.

Polatuzumab vedotin is an anti-CD79b ADC, FDA-approved with bendamustine (BR) for R/R DLBCL.



Eligibility criteria
- Previously untreated DLBCL
- Aged 18 to 80 years
- IPI score 2 to 5
- ECOG PS 0 to 2

R 1:1

6 cycles: Pola-R-CHP	6 cycles: R-CHOP
2 additional cycles of rituximab	2 additional cycles of rituximab

Primary endpoint: Investigator-assessed PFS

Baseline characteristics
- Median age = 65 years
- Advanced stage = 89%
- IPI 3 to 5 = 62%
- DHL/THL = 8%
- DE = 38%

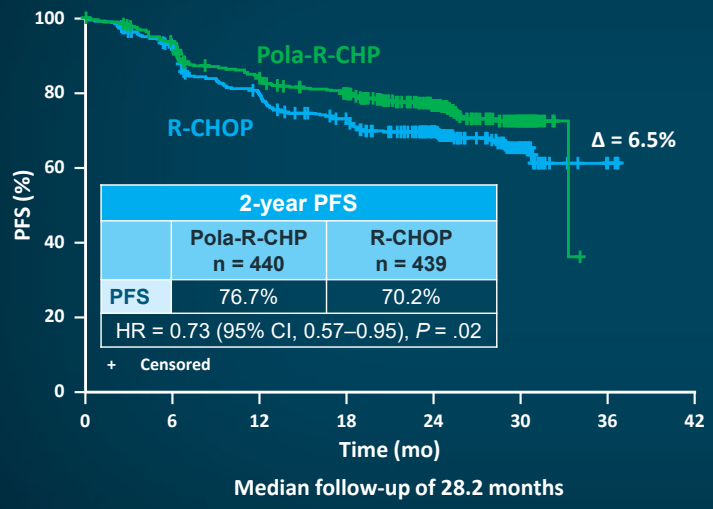
ADC = antibody-drug conjugate; DE = dual/double expresser; DHL = double-hit lymphoma; ECOG PS = Eastern Cooperative Oncology Group performance status; PFS = progression-free survival; Pola = polatuzumab; Pola-R-CHP = polatuzumab, rituximab, cyclophosphamide, doxorubicin, and prednisone; R =randomization; R/R = relapsed/refractory; THL = triple-hit lymphoma.

Tilly H, et al. *N Engl J Med*. 2022;386:351-363. Polatuzumab vedotin (Polivy®) prescribing information (PI) 2023 (www.gene.com/download/pdf/polivy_prescribing.pdf). Creative Biolabs. ADC development for NHL (www.creative-biolabs.com/adc/adc-development-for-nhl.htm). URLs accessed 2/24/2024.

*Polatuzumab is not FDA-approved for first-line DLBCL.

POLARIX—Primary Endpoint: PFS

Pola-R-CHP significantly improved PFS vs R-CHOP.

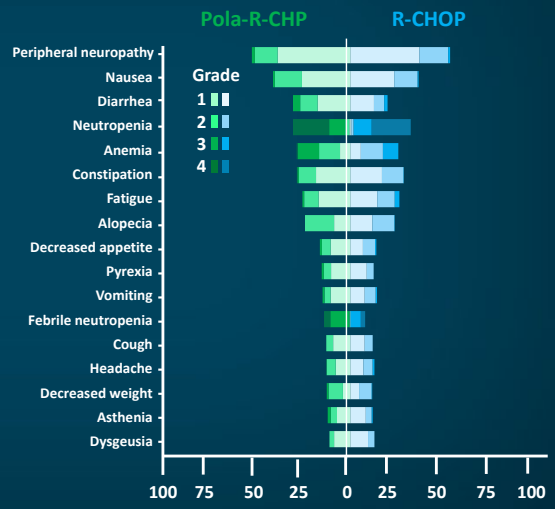


2-year PFS		
	Pola-R-CHP n = 440	R-CHOP n = 439
PFS	76.7%	70.2%
HR = 0.73 (95% CI, 0.57–0.95), *P* = .02		

\+ Censored

Median follow-up of 28.2 months

With no excess toxicity



CI = confidence interval; HR = hazard ratio.

Tilly H, et al. *N Engl J Med*. 2022;386:351-363.

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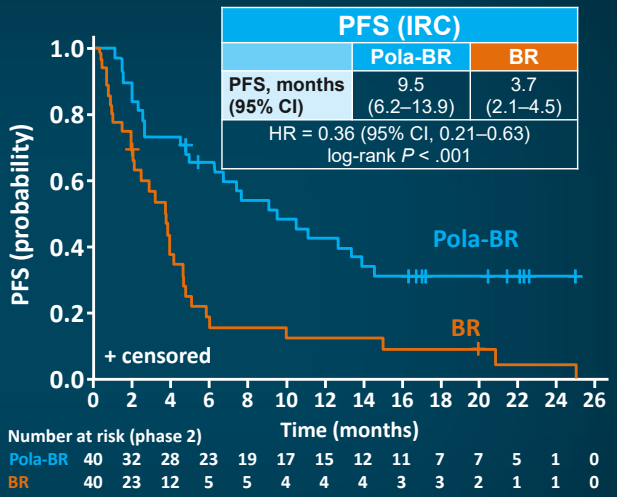
Randomized Phase 2 Trial of Polatuzumab-BR vs BR in R/R DLBCL

Patients received up to six 21-day cycles

Baseline characteristics	BR (n = 40)	Pola-BR (n = 40)
Median age, years	71 (30–84)	67 (33–86)
IPI ≥3, n (%)	29 (73)	22 (55)
Median prior treatment, n (range)	2 (1–5)	2 (1–7)
Prior BMT, n (%)	6 (15)	10 (25)

Response	BR (n = 40)	Pola-BR (n = 40)
ORR	17.5%	45.0%
CR	17.5%	40.0%



The primary toxicities of Pola-BR are peripheral sensory neuropathy and cytopenias.

BMT = bone marrow transplantation; IRC = independent review committee; ORR = overall response rate; Pola-BR = polatuzumab vedotin, bendamustine, and rituximab.

Sehn LH, et al. *J Clin Oncol*. 2020;38:155-165.

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Pola-BR's Activity in Double-Hit Lymphoma

Best response to Pola-BR	All patients (N = 133)	Prior CAR-T (n = 16)	DHL/THL (n = 14)	Transformed lymphoma (n = 31)	Stand alone treatment (n = 78)	Bridge to CAR-T (n = 40)	>1 prior lines of treatment (n = 86)
CR	42 (31.6%)	3 (18.8%)	3 (21.4%)	11 (35.5%)	31 (39.7%)	7 (17.5%)	21 (24.4%)
PR	31 (23.3%)	4 (25.0%)	2 (14.3%)	10 (32.3%)	19 (24.4%)	9 (22.5%)	19 (22.1%)
SD	13 (9.8%)	3 (18.8%)	2 (14.3%)	2 (6.5%)	5 (6.4%)	6 (15.0%)	11 (12.8%)
PD	42 (31.6%)	6 (37.5%)	6 (42.9%)	7 (22.6%)	21 (26.9%)	16 (40.0%)	32 (37.2%)
Missing	5 (3.8%)	0 (0.0%)	1 (7.1%)	1 (3.2%)	2 (2.6%)	2 (5.0%)	3 (3.5%)
ORR (95% CI)	57.0% (48.0–65.7%)	43.8% (19.8–70.1%)	38.5% (13.9–68.4%)	70.0% (50.6–85.3%)	65.8% (54.0–76.3%)	42.1% (26.3–59.2%)	48.2% (37.1–59.4%)

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

Northend M, et al. *Blood Adv*. 2022;6:2920-2926.

L-MIND Phase 2 Trial of Tafasitamab/Lenalidomide in R/R DLBCL

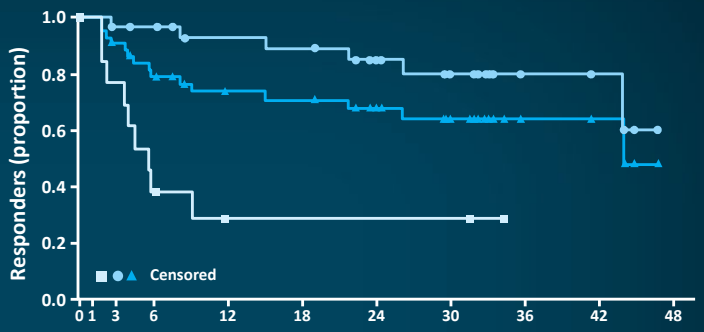
Tafasitamab: 12 mg/kg C1–3 D1, D8, D15, D22; C4+ D1 and 15, up to 12 cycles
Lenalidomide: 25 mg D1–21 (28-day cycles)

Baseline characteristics	N = 81
Median age, years	72 (41–86)
Primary refractory, n (%)	15 (18.5)
Median prior treatment, n (range)	2 (1–4)
Non–GCB-like, n (%)	22 (27)

Response (N = 80)			
	% or months		Months (95% CI)
ORR	57.5%	PR	5.6 (2.2–NR)
CR rate	40.0%	CR	NR (43.9–NR)
PFS	11.6 mo	PR/CR	43.9 (26.1–NR)
mDoR	43.9 mo	TTR	2.1 mo

C = cycle; D = day; DoR = duration of response; mDoR = median DoR; NR = not reached; PR = partial response; TTR = time to response.

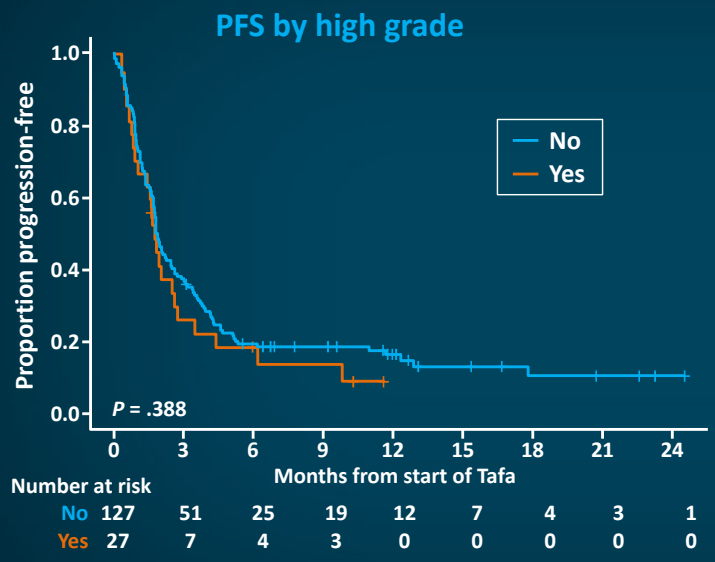
Duell J, et al. *Haematologica*. 2021;106:2417-2426.



This study included second-line DLBCL and excluded patients with primary refractory and DHL.

The primary toxicities of tafasitamab/lenalidomide are cytopenias and diarrhea.

Real-World Evidence of Tafa-Len's Activity in HGBCL and Post CAR T-Cell



TOLA study	
DHL/THL	n = 27
ORR	18%
CR rate	15%

Response to Tafa/Len according to CAR T-cell response		
DoR after CAR T-cell	≥6 months (n = 11)	<6 months (n = 15)
ORR	36%	7%
CR	36%	7%

Len = lenalidomide; Tafa = tafasitamab.

Qualls D, et al. *Blood*. 2023;142(26):2327-2331.

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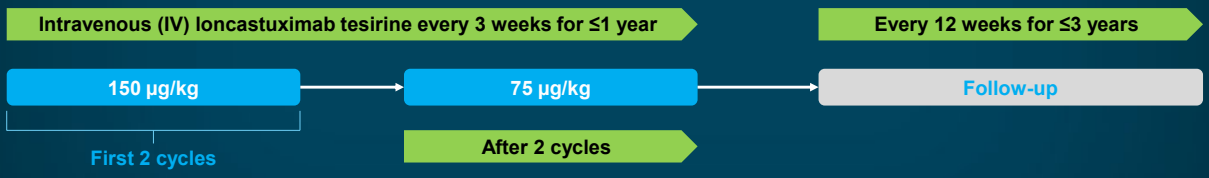
LOTIS-2 Study of Loncastuximab Teserine in R/R DLBCL

- Patients with R/R DLBCL for whom salvage chemotherapy/stem cell transplantation (SCT) is unsuccessful and who have a poor prognosis and limited treatment options[1,2]
- Loncastuximab tesirine comprises a humanized anti-CD19 antibody conjugated to a potent pyrrolobenzodiazepine (PBD) dimer toxin[3]
- LOTIS-2 is a multicenter, open-label, single-arm, phase 2 study in patients aged ≥18 years with pathologically defined R/R DLBCL and ≥2 prior systemic treatments[4-6]
  - Included patients with high-risk characteristics such as double-hit, triple-hit, transformed, or primary refractory DLBCL[4]



- Primary efficacy and safety data have been published (**≥6 months** since first dose)[4]
- Presented are updated results (**≥17 months** since first dose)

Study findings were previously presented as a poster at the International Conference on Malignant Lymphoma (ICML) Virtual Congress, June 18–22, 2021.

1. Crump M, et al. *Blood.* 2017;130:1800-1808. 2. Gisselbrecht C, et al. *Br J Haematol.* 2018;182:633-643. 3. Zammarchi F, et al. *Blood.* 2018;131:1094-1105. 4. Caimi PF, et al. *Lancet Oncol.* 2021;22:790-800. 5. Caimi PF, et al. American Society of Hematology (ASH) 2020; Abstract 1183. 6. Caimi PF, et al. American Society of Clinical Oncology (ASCO) 2021; Abstract 7546.

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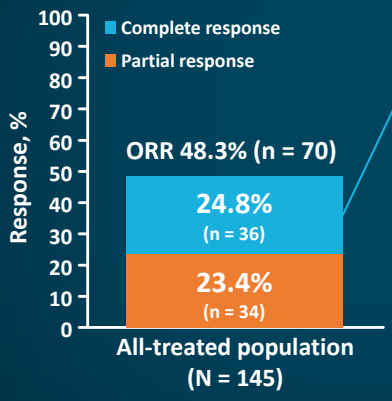
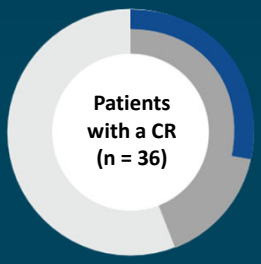
Overall Response Rate and Long-Term Responses Observed in the All-Treated Population





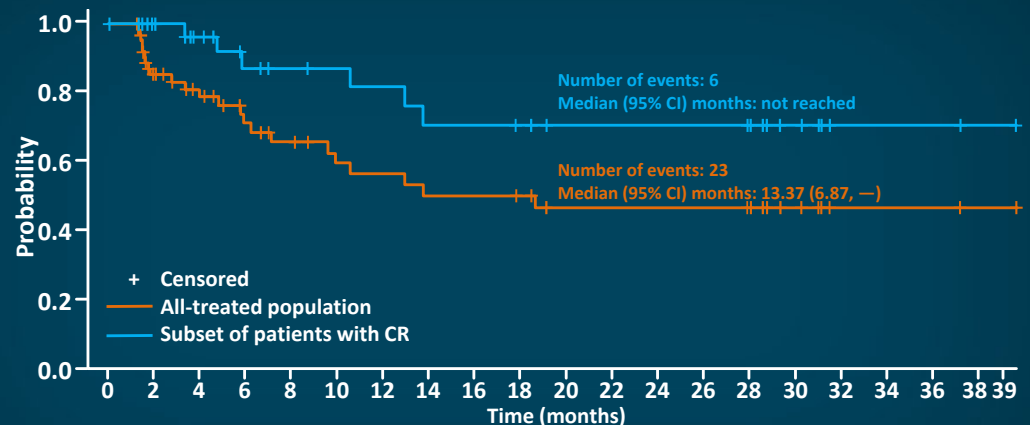
Of the patients with a CR, **44% (16 of 36)** were event-free for ≥1 year.

Of the patients with a CR, **31% (11 of 36)** were event-free for ≥2 years.

Median (range) number of treatment cycles	
All-treated population	3.0 (1–26)
Patients with a CR	8.0 (1–26)
Patients with a CR, event-free ≥1 year[a]	12.5 (1–26)
Patients with a CR, event-free ≥2 years[a]	13.0 (1–22)

Data cutoff: September 15, 2022.
The median duration of follow-up was 7.8 months (range, 0.3–42.6 months) in the all-treated population and 35.0 months (range, 4.4–42.6 months) in patients with a CR.
[a]Event-free is defined as no progressive disease or death starting from Day 1, Cycle 1 of Lonca treatment.
CR = complete response; Lonca = loncastuximab tesirine-lpyl; ORR = overall response rate.
Caimi PF, et al. *Haematologica*. 2023. (https://doi.org/10.3324/haematol.2023.283459). Accessed 2/26/2024.

DOR: All-Treated Population and Patients With a CR



Number at risk																				
All-treated population	70	42	33	25	21	18	17	15	15	13	11	11	11	11	7	5	2	2	2	1 0
Subset of patients with CR	36	30	25	20	18	17	16	14	14	12	11	11	11	11	7	5	2	2	2	1 0

The median (range) time to response was 41 (35–247) days in the all-treated population and 42 (36–247) days for patients with a CR.

Data cutoff: September 15, 2022.
CR = complete response; DOR = duration of response.
Caimi PF, et al. *Haematologica*. 2023. (https://doi.org/10.3324/haematol.2023.283459). Accessed 2/26/2024.

All-Grade and Grade ≥3 Adverse Events

TEAEs, any grade in ≥30% of patients	All-treated population N = 145	Patients with a CR n = 36
Patients with any TEAE	98.6%	100%
Increased GGT	42%	50%
Neutropenia	40%	42%
Thrombocytopenia	33%	36%
Anemia	26%	36%
Peripheral edema	20%	33%
Nausea	23%	31%

TEAEs, grade ≥3 in ≥10% of patients	All-treated population N = 145	Patients with a CR n = 36
Patients with any TEAE	73.8%	75%
Neutropenia	26%	28%
Thrombocytopenia	18%	19%
Increased GGT	17%	19%
Anemia	10%	8.3%
Leukopenia	9%	14%
Hypophosphatemia	6%	11%

No new safety signals were identified during the long-term follow-up.

Data cutoff: September 15, 2022.

GGT = gamma-glutamyltransferase; TEAE = treatment emergent adverse events.

Caimi PF, et al. *Haematologica*. 2023. (https://doi.org/10.3324/haematol.2023.283459). Accessed 2/26/2024.

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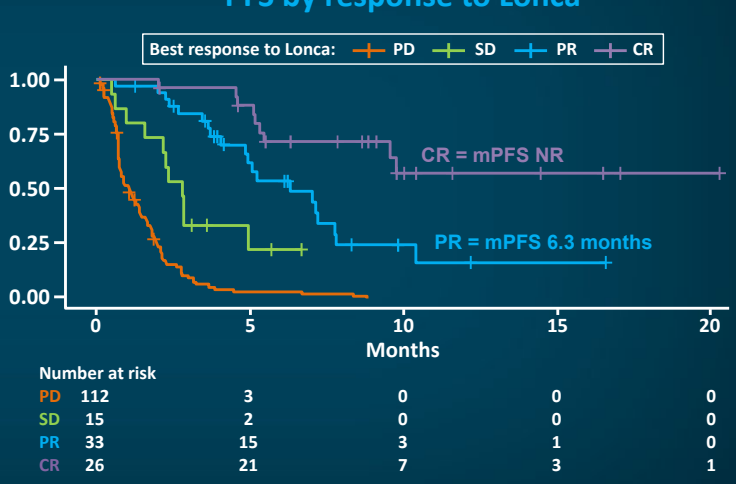
Real-World Data for Loncastuximab

N = 187	ORR (%)	CR (%)
Overall study population	**32**	**14**
CD19 status		
Positive	32	14
Negative	26	21
Bulky disease (N = 32)	16	0
Prior CAR T-cell		
Yes (N = 112)	30	15
No	35	12
Number of prior therapies		
<4	33	14
4+	30	13
Age >75 years		
Yes	32	14
No	26	21



Ayers E, et al. ASH 2023; Abstract 312.

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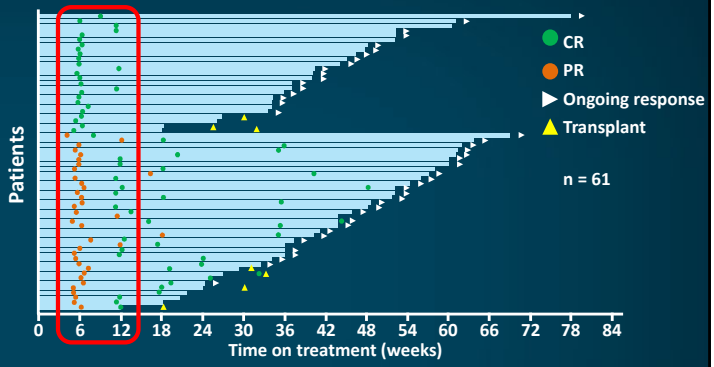
Epcoritamab in R/R LBCL: EPCORE NHL-1 LBCL Expansion Cohort

Step-up dosing protocol

Patient group	n	ORR, %	CR, %
All LBCL	157	63	39
• <65 years of age	80	56	35
• 65 to <75 years	48	69	40
• >75 years	29	72	48
• De novo DLBCL	97	61	37
• tDLBCL	40	68	45
• Primary refractory	96	55	30
• CAR T-cell therapy naïve	96	69	42
• CAR T-cell therapy exposed	61	54	34
• CAR T-cell therapy refractory	46	46	28
• 2 prior lines	46	65	35
• 3 prior lines	50	64	40
• 4 prior lines	61	61	41

Received FDA approval on May 19, 2023, for R/R DLBCL after 2 prior therapy lines



CRS parameter	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)
ICANS Grade 1 to 2	5.7%
ICANS Grade 3 or more	1 (0.6)

ICANS = Immune effector cell-associated neurotoxicity syndrome.

Thieblemont C, et al. *J Clin Oncol.* 2022;41:2238-2247.

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Glofitamab Monotherapy at RP2D Induces Durable Complete Responses

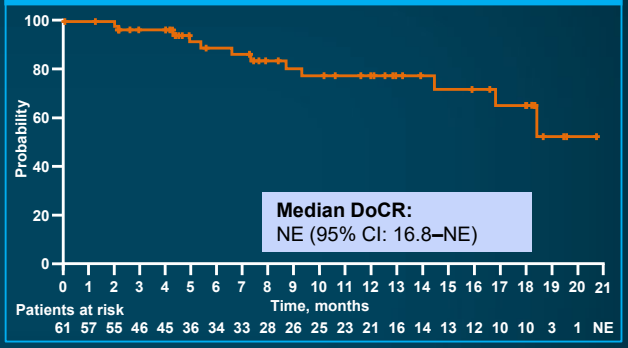
Heavily pretreated, highly refractory population

Pivotal phase 2 results presented at ASCO 2022

- DLBCL NOS, HGBCL, trFL or PMBCL; ≥2 prior therapies
- Glofitamab 2.5/10/30 mg (N = 155)
- Efficacy
  - CR rate: 39.4% (61/155)
  - ORR: 51.6% (80/155)

Received FDA approval on June 15, 2023, for R/R DLBCL after 2 prior therapy lines

Pivotal phase 2 cohort (ASCO 2022) – DoCR* by IRC



	N = 61
Median DoCR follow-up, months (range)	10.6 (0–21)
12-months DoCR, % (95% CI)	**77.6 (64.3–90.8)**
CRs ongoing at CCOD, n (%)	49 (80.3)

Clinical cutoff date: March 14, 2022. *Time from the initial occurrence of a CR until PD or death due to any cause, whichever occurs first.

CCOD = clinical cutoff date; CI = confidence interval; CRS = cytokine release syndrome; DoCR = duration of complete response; IRC = independent review committee; PD = progressive disease; PMBCL = primary mediastinal large B-cell lymphoma; RP2D = recommended phase 2 dose; trFL = transformed follicular lymphoma.

Dickinson MJ, et al. ASCO 2022; Abstract 7500. Dickinson M, et al. *N Engl J Med.* 2022;387:2220-2231.

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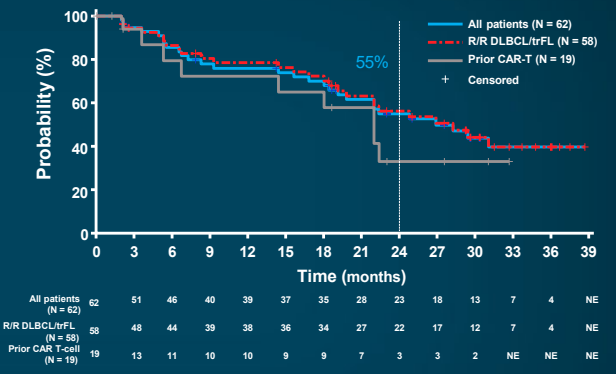
Response Rates and DoCR: Update Follow-Up
ASH 2023

	All patients (N = 155)*	R/R DLBCL/trFL (N = 132)†‡	Prior CAR T-cell (N = 52)†
ORR, n (%) [95% CI]	80 (52)	74 (56)	26 (50)
	[43.5–59.7]	[47.2–64.7]	[35.8–64.2]
CR rate, n (%) [95% CI]	62 (40)	58 (44)	19 (37)
	[32.2–48.2]	[35.3–52.8]	[23.6–51.0]
Median DoCR, months (95% CI)	26.9	28.3	22.0
	(19.8–NR)	(19.8–NR)	(6.7–NR)
24-month DoCR, % (95% CI)	55.0	56.2	33.1
	(41.1–68.8)	(41.9–70.4)	(7.2–59.0)
Median CR follow-up, months (range)	29.6	29.6	23.0
	(0–39)	(0–39)	(0–33)
Ongoing CRs, n/N (%)	34/62 (55)	32/58 (55)	10/19 (53)

DoCR by IRC



- Median time on study: 32.1 months (range: 0–43)

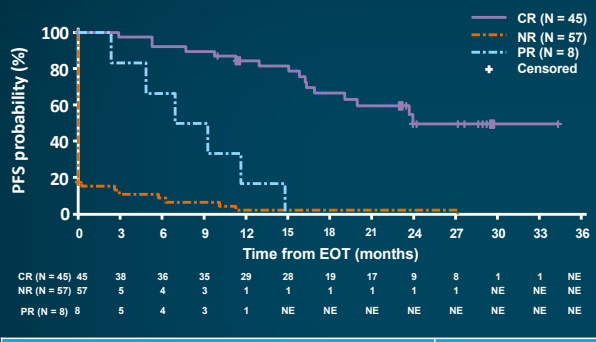
With 32 months median follow-up, glofitamab showed high response rates and durable remissions across subgroups.

*Intent-to-treat population (DLBCL, trFL, HGBCL, and PMBCL). †Patients in this subgroup had similar baseline characteristics to the overall population. ‡Primary efficacy population reported in the glofitamab USPI, all patients received at least 1 dose of glofitamab.
CI = confidence interval; NE = not estimable; NR = not reached; USPI = United States prescribing information.

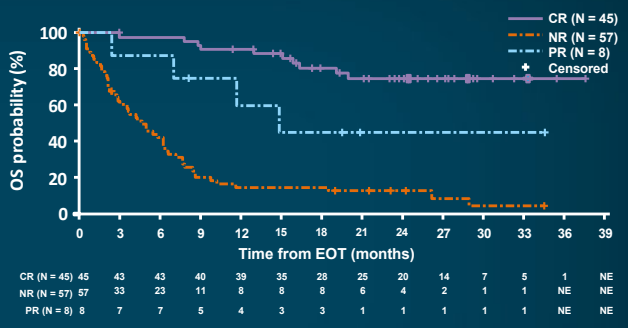
Glofitamab-gxbm (Columvi™) PI 2023 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761309s000lbl.pdf). Accessed 2/24/2024; Hutchins M et al. ASH 2023; Abstract 433.

Landmark Analysis by Response at EOT

PFS



OS



Landmark PFS from EOT in patients with CR at EOT*	N = 45
Median PFS, months (95% CI)	24.0 (19.1–NE)
18-month PFS rate, % (95% CI)	66.6 (51.0–82.2)

Landmark OS from EOT in patients with CR at EOT*	N = 45
Median OS, months (95% CI)	NE (NE)
18-month OS rate, % (95% CI)	80.7 (68.6–92.8)

The majority of patients with a CR at EOT remained progression-free and alive at 18 months after EOT.

*KM estimates.
EOT = end-of-treatment.

Interval Q&A

Use the "Raise a Hand" Feature or Post Your Question in the Chat!

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Case Studies

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Clinical Case 1: Presentation

- A 60-year-old male presented with left facial pain and swelling; no fevers, night sweats, or weight loss
- **Past medical history**
  - Lyme disease (remote), actinic keratosis, dyslipidemia
- **Social and family history**
  - Self-employed as a honeybee farmer
  - Father with coronary artery disease
- **Physical examination**
  - Large maxillary mass visible on exam
- **Laboratory values**
  - All other laboratory values within normal limits (WNL)
  - Hepatitis B and C and HIV: Negative

Test	Value	ULN
LDH	300 U/L	280 U/L
Hemoglobin	14.2 g/dL	15.1 gm/L
WBC	5.2 10e3/uL	11.2 10e3/uL
Platelet	180 10e3/uL	366 10e3/uL
Bilirubin	0.4 mg/dL	1.2 mg/dL
Creatinine	0.86 mg/dL	1.2 mg/dL

LDH = lactate dehydrogenase; ULN = ULN = upper limit of normal; WBC = white blood cells.

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Clinical Case 1: Work-Up

Diagnostic work-up

- Positron emission tomography/computed tomography (PET/CT) scan showed large left maxillary mass, adenopathy below diaphragm, and involvement of left lung and pleural surface
- Core needle biopsy of maxillary mass consistent with GCB DLBCL (CD20+, CD10+, *BCL6*+, MUM1+, Ki67 90%)
- FISH-negative for *MYC*; *BCL2* amplification but no rearrangement seen
- **ECOG PS = 1, Stage IV; IPI = 4**

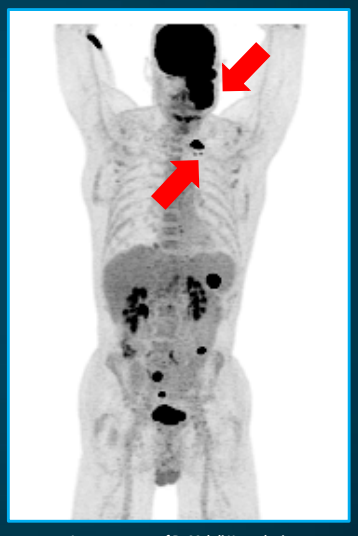

Image courtesy of Dr Mehdi Hamadani.

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Clinical Case 1: Question

What would be your initial approach to management of this patient?

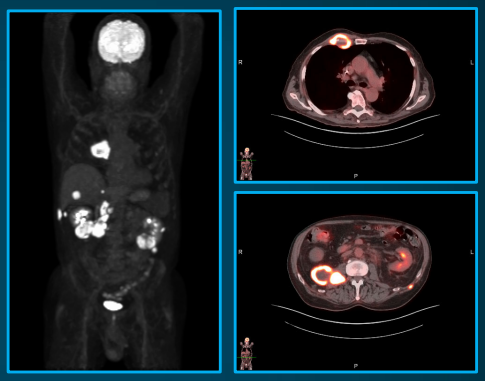
a) R-CHOP x 6 cycles
b) Rituximab with dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) x 6 cycles
c) Polatuzumab vedotin R-CHP x 6 cycles
d) R-CHOP x 3 cycles plus involved field radiation treatment
e) R-CHOP x 6 followed by rituximab maintenance for 2 years

Clinical Case 1:
Audience Discussion Questions

- What characteristics of this patient would lead you to consider the incorporation of polatuzumab vedotin into the first-line therapeutic regimen?
- What types of considerations would lead you to forego the incorporation of polatuzumab vedotin into the first-line regimen?

Clinical Case 2: Presentation

- A 72-year-old white male presented with an enlarging chest wall mass and 25-pound weight loss
- **Social and family history**
  - Retired computer software engineer
  - Brother passed away with myeloma
- **Past medical history**
  - GERD, dyslipidemia, BPV, hypertension, atrial fibrillation
- **Physical examination**
  - Chest wall mass palpable, no other lymph nodes palpable
- **Laboratory values**
  - No evidence of viral hepatitis or HIV



Test	Value	ULN
LDH	308 U/L	280 U/L
Hemoglobin	13.5 g/dL	17.5 gm/L
Bilirubin	0.8 mg/dL	1.2 mg/dL
Creatinine	1.1 mg/dL	1.2 mg/dL

BPV = benign positional vertigo; GERD = gastroesophageal reflux disease; HIV = human immunodeficiency virus.

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Clinical Case 2: Work-Up and Treatment

Diagnostic work-up

- Imaging studies
  - PET/CT images shown on previous slide
  - Chest wall mass core needle biopsy consistent with non-GCB DLBCL (CD20+, CD10-, BCL6-, MYC+++, BCL2+++, EBER– , Ki67 70%); FISH negative for *MYC*, and *BCL2* rearrangement
  - Bone marrow biopsy not done
  - CSF analysis negative
  - Stage IV; IPI = 4

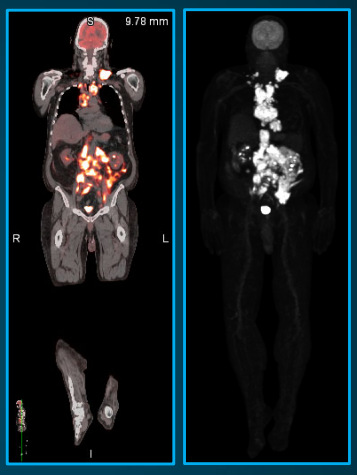

Image courtesy of Dr. Mehdi Hamadani

Initial treatment

- R-CHOP; CT C/A/P slowly responsive disease after 3 cycles; went on to receive 3 more cycles
- At end of treatment imaging, patient had primary progressive disease
- Repeat biopsy showed refractory B-cell lymphoma

C/A/P = chest, abdomen, pelvis.

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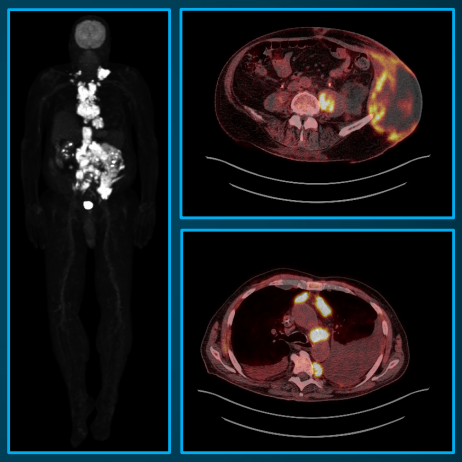
Clinical Case 2: Subsequent Therapy

- Patient received polatuzumab vedotin/rituximab bridging and underwent CD19-directed CAR T-cell treatment with axicabtagene ciloleucel (axi-cel) (bendamustine lymphodepletion)
- Patient continued to feel unwell; notice a rapidly enlarging abdominal soft tissue mass, a PET/CT showed no improvement, and large new metabolic active left flank mass
- Repeat biopsy to assess CD19 expression showed no CD19 loss via flow cytometry; LDH was 980/UL



27

Clinical Case 2: Question

What would be your next treatment choice in the management of this patient?

a) Chemotherapy and autologous transplant
b) Loncastuximab tesirine
c) Polatuzumab/bendamustine (BR)
d) Tafasitamab/lenalidomide
e) Bispecific antibody

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Clinical Case 2
Audience Discussion Questions

- If you selected a bispecific antibody for this patient, which one would you use and why?
- What patient characteristics would lead you to consider an ADC such as loncastuximab tesirine?

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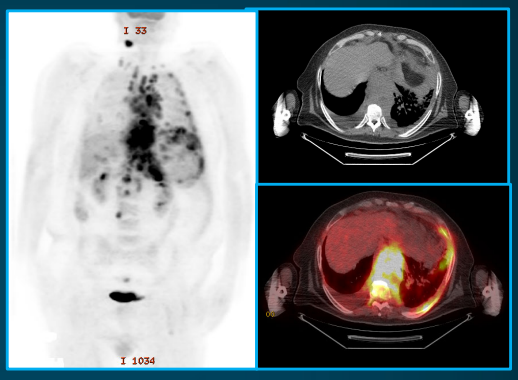
Clinical Case 3: Presentation

- A 45-year-old White male presented with dyspnea on exertion and marked fatigue
- **Past medical history**
  - DM-II, generalized anxiety disorder
- **Social and family history**
  - Single, worked in health insurance; quit smoking in 1998
  - Father had melanoma; maternal aunt had gastric cancer
- **Physical examination and imaging**
  - Cervical adenopathy
  - PET/CT showed pleural effusion, mediastinal mass with pleural, pulmonary, and skeletal involvement
- **Laboratory values**
  - No evidence of viral hepatitis or HIV



Test	Value	ULN
LDH	411 U/L	280 U/L
Hemoglobin	9.8 g/dL	17.5 gm/L
Bilirubin	1.1 mg/dL	1.2 mg/dL
Creatinine	1.5 mg/dL	1.2 mg/dL

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Clinical Case 3: Work-Up and Treatment

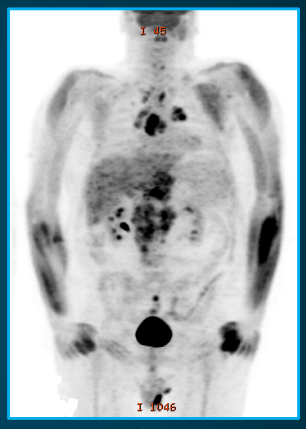

Image courtesy of Dr Mehdi Hamadani.

Diagnostic work-up

- Transbronchial biopsy of mediastinal mass
  - Large B cell lymphoma (CD20 positive, cyclin D1 negative, CD10 negative, *BCL6* few positive cells, *BCL2* several positive cells, MUM1 positive, Ki-67 of approximately 50%, EBER-ISH negative)
  - FISH analysis showed no MYC gene rearrangement, but extra copies of *MYC* were seen
  - Bone marrow biopsy negative
- Stage IV-B; IPI = 4

Treatment course

- First-line treatment R-CHOP x 6 intercalated with high-dose methotrexate x 3; response of CR
- ~16 months later presented with cord compression and large mass centered on T9
- Biopsy confirmed relapsed LBCL; patient achieved a CR with RICE, but stem cell collection failed but, unfortunately, shortly after collection failure he relapsed (late 2021; scan shows)

EBER-ISH = Epstein-Barr virus–encoded RNA-1 in situ hybridization.

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Clinical Case 3: Subsequent Course

- Patient next received bridging treatment with polatuzumab vedotin and underwent an experimental CD19.20 directed CAR T-cell therapy following fludarabine/cyclophosphamide (Flu/Cy) lymphodepletion
- Patient achieved a complete remission on Day 30, but a PET/CT at the 6-month mark showed evidence of recurrent disease (image)
- Repeat biopsy to assess CD19/CD20 expression showed no CD19 loss; CD20 was not detectable via flow cytometry or IHC

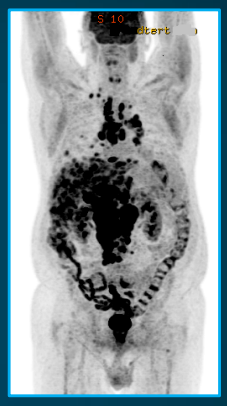

Image courtesy of Dr Mehdi Hamadani.

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Clinical Case 3: Question

What would be your next treatment choice in the management of this patient?

a) Polatuzumab/bendamustine (BR)
b) Loncastuximab tesirine
c) Tafasitamab/lenalidomide
d) CD20 directed bispecific antibody
e) Allogeneic transplant with active disease

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Clinical Case 3
Audience Discussion Questions

- What considerations would lead you to consider an antibody drug conjugate such as loncastuximab tesirine for this patient?
- What considerations would lead you to consider tafasitamab/lenalidomide for this patient?

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Thank you!

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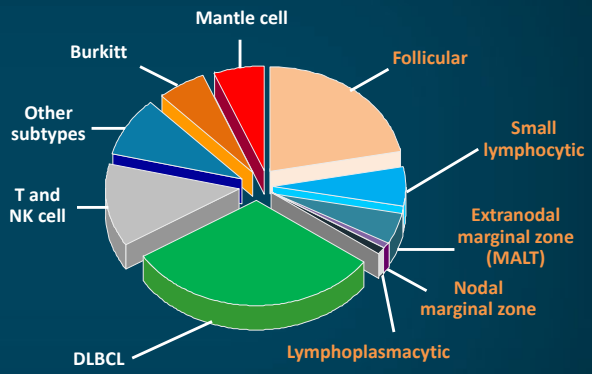
To receive your CME and CNE credit
please follow the links provided in the chat.

You will also receive this information
in your post-program email.

36

Most Common Subtypes of Non-Hodgkin Lymphoma (NHL)

- NHL accounts for 4% of all cancers in the US
- Expected ~81,000 new diagnoses of NHL in 2023; more than 20,000 deaths
- Highly heterogenous group of tumors affecting B lymphocytes
- Subtypes and approximate percentages of all cases
  - ***Diffuse large B-cell lymphoma* (DLBCL) is most common, accounting for 30% of cases**
  - **Follicular lymphoma (FL) = 20% to 22%**
  - Chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL) = 7%
  - Marginal zone lymphoma (MZL) = 7%
  - Mantle cell lymphoma (MCL) = 3%



BCL = B-cell lymphoma; MALT = mucosa-associated lymphoid tissue; NK = natural killer; US = United States.

American Cancer Society (ACS). Key statistics for non-Hodgkin lymphoma, 2023 (https://www.cancer.org/cancer/types/non-hodgkin-lymphoma/about/key-statistics.html). Accessed 2/24/2024; Leukemia and Lymphoma Society. NHL Subtypes. (https://www.lls.org/lymphoma/non-hodgkin-lymphoma/nhl-subtypes). Accessed 3/11/2024. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood.* 2016;127(20):2375-2390. Modified from Armitage JO, Weisenburger DD. *J Clin Oncol.* 1998;16:2780-2795.

Diffuse Large B-Cell Lymphoma

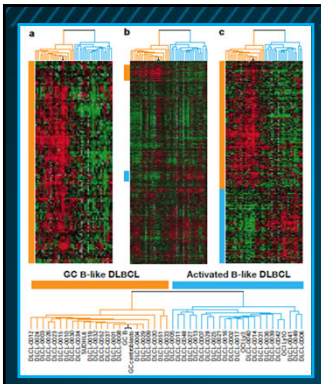
Most common NHL in United States and worldwide

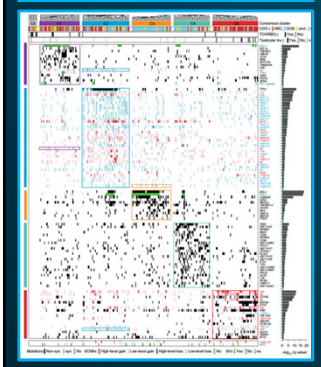
- Median age = 66 years
- Male = 55%
- Approximately half of patients present with advanced-stage disease
- Elevated LDH = ~50%
- Any extranodal involvement = ~70%
- Bone marrow involvement = 10% to 20%
- CNS involvement at diagnosis = ~1%
- Clinically and biologically heterogeneous

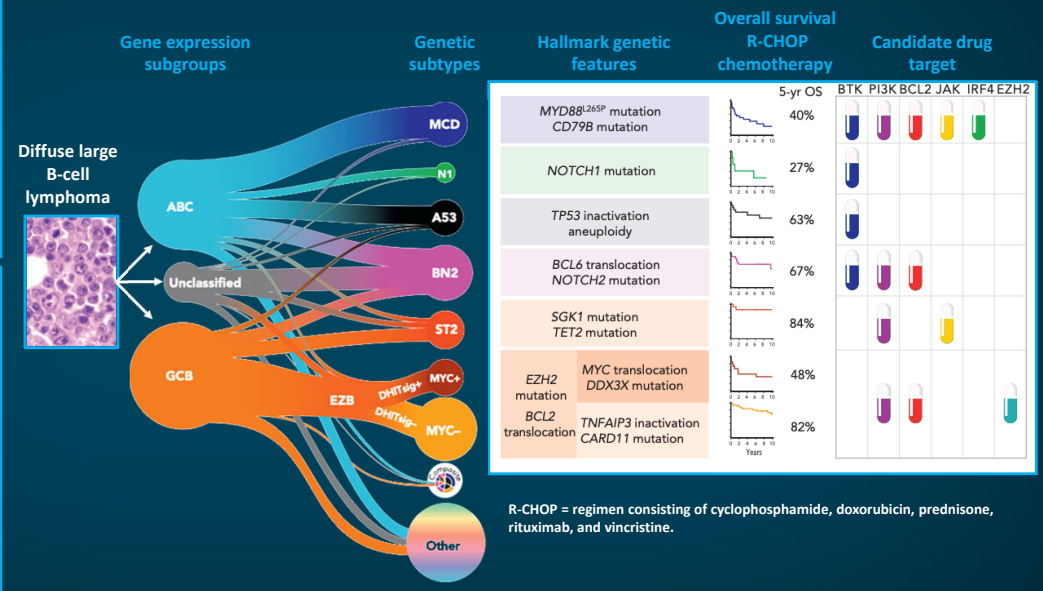
CNS = central nervous system; LDH = lactate dehydrogenase.

Abramson JS, Shipp MA. *Blood.* 2005;106:1164-1174. Armitage JO, Weisenburger DD. *J Clin Oncol.* 1998;16:2780-2795. Eyre TA, et al. *Lancet Oncol.* 2022;23:e416-e426. National Cancer Institute (NCI). Cancer stat facts: NHL—DLBCL (https://seer.cancer.gov/statfacts/html/dlbcl.html). Accessed 2/24/2024.

Genomic Heterogeneity



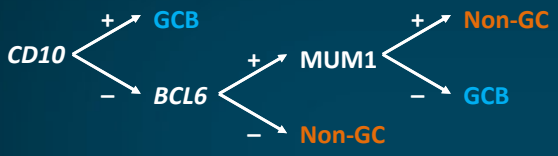




R-CHOP = regimen consisting of cyclophosphamide, doxorubicin, prednisone, rituximab, and vincristine.

Chapuy B, et al. *Nat Med*. 2018;24(8):1290-1291. Wright GW, et al. *Cancer Cell*. 2020;37(4):551-568. de Leval L, et al. *Blood*. 2022;24;140(21):2193-2227. Alizadeh AA, et al. *Nature*. 2000;403(6769):503-511.

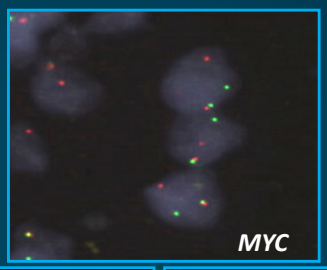
Integrating IHC/Flow Cytometry and Molecular Data

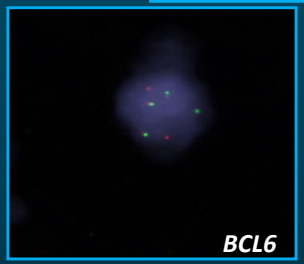


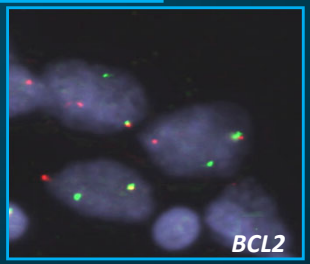
HGBCL with rearrangement of concurrent *MYC* and *BCL2* and/or *BCL6*

- 5% to 10% of newly diagnosed DLBCL
- Dismal prognosis with standard R-CHOP

FISH with dual color break-apart probes for *MYC*, *BCL2*, and *BCL6*







FISH = fluorescence in situ hybridization; GC = germinal center; GCB = germinal center B; HGBCL = high-grade B-cell lymphoma; IHC = immunohistochemistry; MUM1 = multiple myeloma oncogene-1; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Johnson NA, et al. *Blood*. 2009;114:2273-2279. Green TM, et al. *J Clin Oncol*. 2012;30:3460-3467. Petrich AM, et al. *Blood*. 2014;124:2354-2361.

Photos courtesy of V. Bedell, 63x Bioview imaging system.

International Prognostic Index (IPI)

IPI	Age-adjusted IPI (age ≤60 years)	Adverse factor
Age	—	≥60 years
Stage	Stage	III-IV
Performance status	Performance status	2 to 4
Serum LDH	Serum LDH	>ULN
Extranodal involvement	-	≥2 sites

Risk group	IPI	Age-adjusted IPI	IPI 5-year OS	Age-adjusted IPI 5-year OS	Rituximab-era 3-year OS
Low	0 to 1	0	73%	83%	91%
Low/intermediate	2	1	51%	69%	80%
High/intermediate	3	2	43%	46%	65%
High	4 or 5	3	26%	32%	59%

OS = overall survival; ULN = upper limit of normal.

Shipp MA, et al. *N Engl J Med*. 1993;329:987-994; Ziepert M, et al. *J Clin Oncol*. 2010;28(14):2373-2380.

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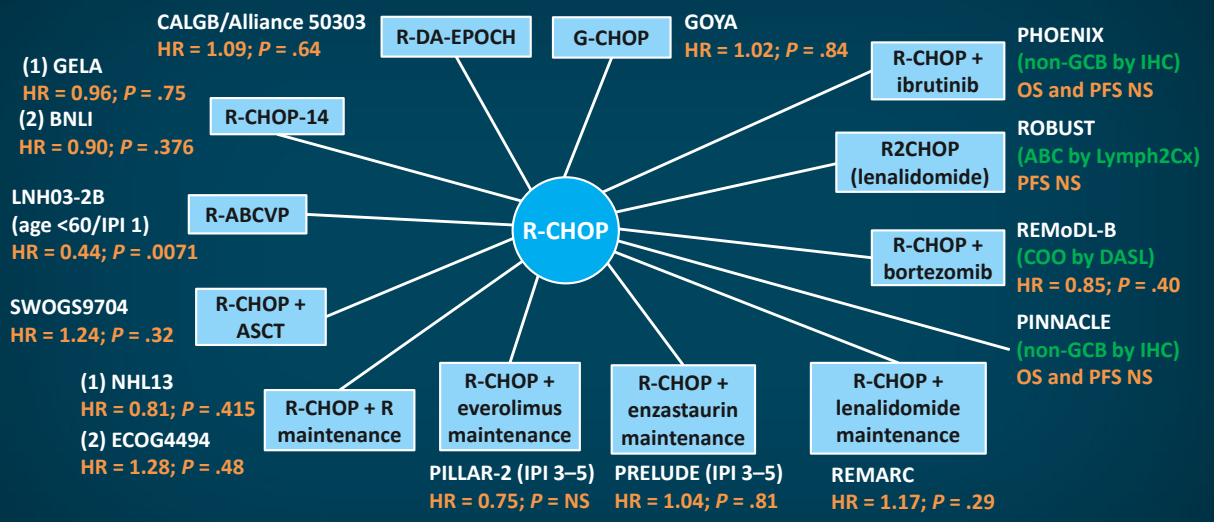
Unsuccessful Phase 3 Trials Trying to Improve Outcomes for DLBCL



ABC = activated B-cell (subtype); COO = cell of origin; DASL = whole-genome cDNA-mediated annealing, selection, extension, and ligation (assay); G-CHOP = obinutuzumab + CHOP; HR = hazard ratio; IHC = immunohistochemistry; NS = not significant; R = rituximab; R2CHOP = lenalidomide + R-CHOP; R-ABCVP = R + doxorubicin, bleomycin, cyclophosphamide, vindesine, prednisone.

Bartlett NJ, et al. *J Clin Oncol*. 2019;37:1790-1799. Crump M, et al. *Blood*. 2013;122(21):371. Cunningham D, et al. *J Clin Oncol*. 2011;29(suppl 15); Abstract 8000. Davies A, et al. *Lancet Oncol*. 2019;20:649-662. Habermann TM, et al. *J Clin Oncol*. 2006;24:3121-3127. Jaeger U, et al. *Haematologica*. 2015;100:955-963. Lamy T, et al. *Blood*. 2018;131:174-181. Lowry L, et al. *Radiother Oncol*. 2011;100(1):86-92. Nowakowski GS, et al. *J Clin Oncol*. 2021;39:1317-1328. Récher C, et al. *Lancet*. 2011;378:1858-1867. Sehn LH, et al. *J Hematol Oncol*. 2020;13:71. Stiff PJ, et al. *J Clin Oncol*. 2011;29; Abstract 8001. Thieblemont C, et al. *Blood*. 2020;136(suppl 1):30-31. Witzig TE, et al. *Ann Oncol*. 2018;29:707-714. Younes A, et al. *J Clin Oncol*. 2019;37:1285-1295.

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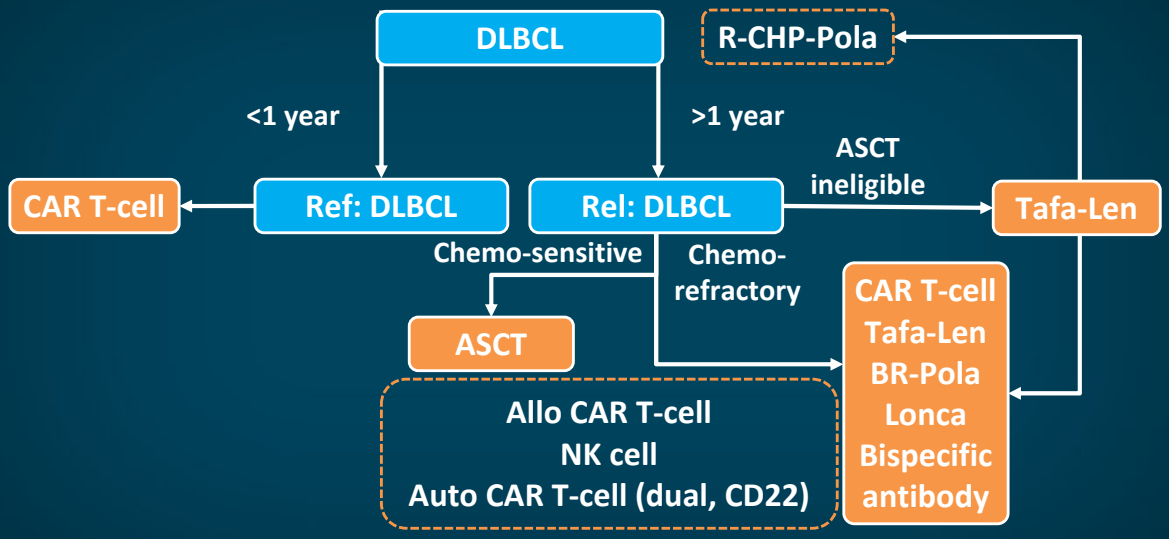
Treatment Landscape: DLBCL—The Relapsed/Refractory Setting



R-CHP-Pola is FDA-approved for DLBCL (not otherwise specified [NOS]) or high-grade B-cell lymphoma (HGBL).
allo = allogeneic; ASCT = autologous stem cell transplant; auto = autologous; BR-Pola = polatuzumab vedotin, bendamustine, and rituximab; Lonca = loncastuximab tesirine; R-CHP-Pola = rituximab, cyclophosphamide, doxorubicin, and prednisone plus polatuzumab vedotin; Ref = refractory; Rel = relapsed; Tafa-Len = tafasitamab plus lenalidomide.
Modified from National Comprehensive Cancer Network (NCCN) guidelines for B-cell lymphoma, V3.2023 (www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf). Accessed 2/24/2024.

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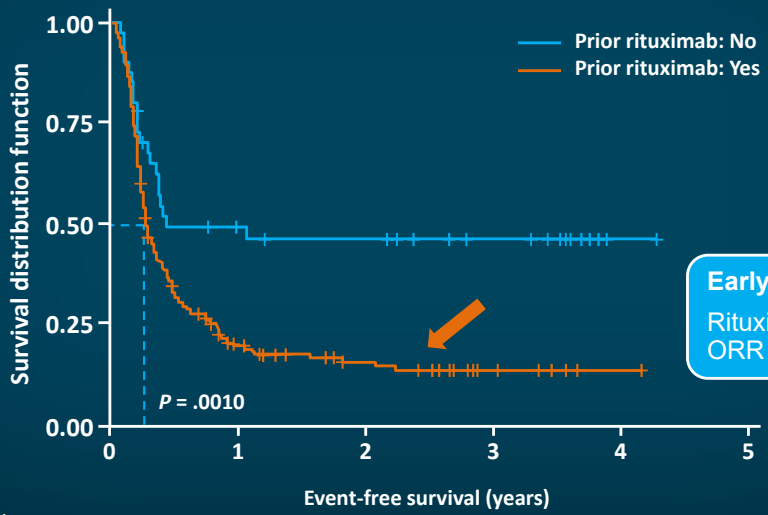
Early Relapse: Autologous HCT Is Often Not Applicable

Relapse within 1 year of "initial diagnosis"



Early relapse
Rituximab + chemotherapy
ORR = 46%

HCT = hematopoietic cell transplantation.
Gisselbrecht C, et al. *J Clin Oncol*. 2010;28:4184-4190.

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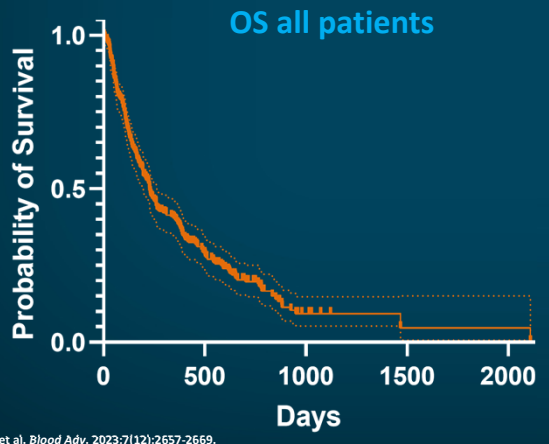
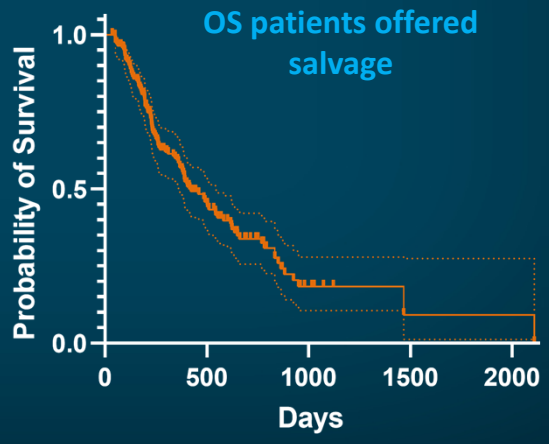
US Retrospective Analysis of Patients for Whom CAR T-Cell Therapy Failed (n = 284)

- From time of progression post-CAR T-cell
  - Median OS for all patients with PD: 7.5 months
  - Median OS for patients who received salvage: 13.6 months

*Median follow-up for surviving patients: **15.9 months** (range: 2.6–36.9)





Zurko JC, et al. *Blood Adv*. 2023;7(12):2657-2669.

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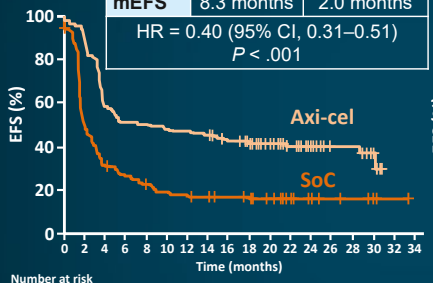
EFS in Randomized Trials of CAR T-Cells vs SoC as Second-Line Therapy

Primary Refractory or Early Relapsed DLBCL

Axi-cel vs SoC (N = 359)[1]

	axi-cel	SoC
mEFS	8.3 months	2.0 months

HR = 0.40 (95% CI, 0.31–0.51)
P < .001

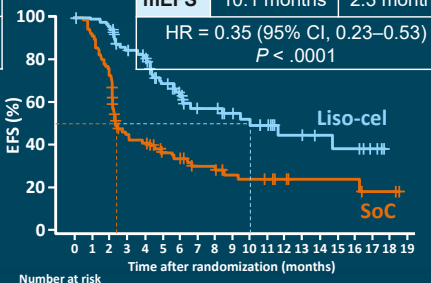


Number at risk
Axi-cel 180 163 106 92 91 87 85 82 74 67 52 40 26 12 12 6 0 0
SoC 179 86 54 45 38 32 29 27 25 24 20 12 9 7 6 3 1 0

Liso-cel vs SoC (N = 184)[2]

	liso-cel	SoC
mEFS	10.1 months	2.3 months

HR = 0.35 (95% CI, 0.23–0.53)
P < .0001

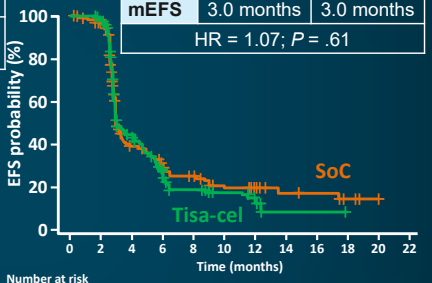


Number at risk
Liso-cel 92 89 86 66 62 43 36 27 26 21 19 17 9 9 7 6 6 4 0 0
SoC 92 83 66 35 32 23 21 16 16 12 11 10 6 4 4 4 2 2 0

Tisa-cel* vs SoC (N = 322)[3]

	tisa-cel	SoC
mEFS	3.0 months	3.0 months

HR = 1.07; *P* = .61



Number at risk
Tisa-cel 162 156 57 32 19 13 6 1 1 0 0 0
SoC 160 148 45 31 25 17 12 7 6 3 1 0

Median follow-up = 24.9 months	Median follow-up = 6.2 months	Median follow-up = 10 months
Grade ≥3 CRS/neurologic events		
6%/21%	1%/4%	5%/2%

axi-cel = axicabtagene ciloleucel; CRS = cytokine release syndrome; liso-cel = lisocabtagene maraleucel; mEFS = median EFS; SoC = standard of care; tisa-cel = tisagenlecleucel.

1. Locke FL, et al. *N Engl J Med*. 2022;386:640-654. 2. Kamdar M, et al. *Lancet*. 2022;399:2294-2308. 3. Bishop MR, et al. *N Engl J Med*. 2022;386:629-639.

*Tisa-cel is not FDA-approved as second-line treatment for DLBCL.

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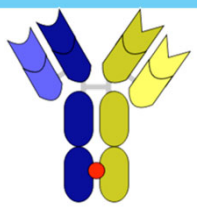
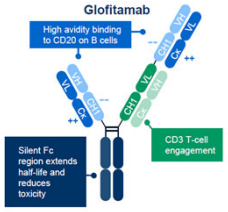
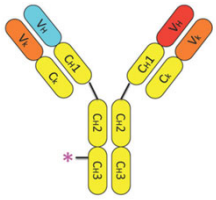
New and Emerging Bispecific Antibodies in Non-Hodgkin Lymphomas

Anti-CD20/CD3 bispecific monoclonal antibodies in the development for B-cell NHL

Epcoritamab[1]	Mosunetuzumab[2,3]	Glofitamab[4]	Odronextamab[5,6]
			
DuoBody—CD3 x CD20 Knobs-into-holes Fc BsAb SC	CD3 x CD20 Knobs-into-holes Fc BsAb IV/SC	CD3 (Fab) x CD20 (Fab x2) Fc BsAb IV	CD3 x CD20 common LC Fc BsAb IV

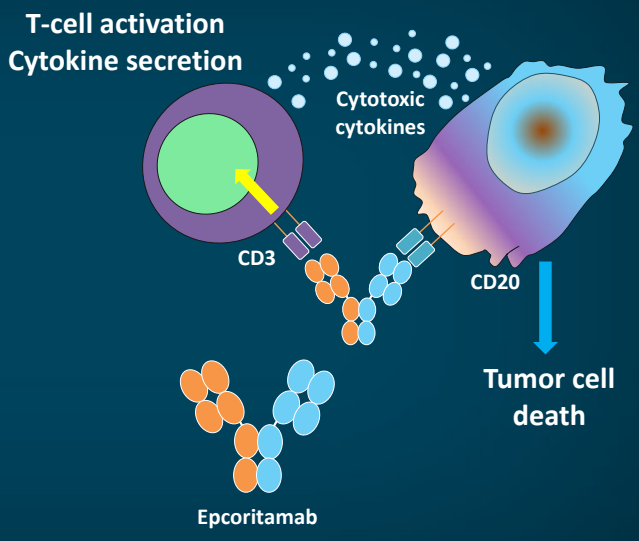
Odronextamab is an investigational therapy for the management of NHL.
Ab = antibody; BsAb = bispecific Ab; Fc = crystallizable fragment; FL = follicular lymphoma; Fab = fragment antigen binding; IV = intravenous; LC = liquid chromatography; SC = subcutaneous.

1. Hutchings M, et al. *Lancet*. 2021;398:1157-1169. 2. Budde LE, et al. *J Clin Oncol*. 2022;40:481-491. 3. Hosseini I, et al. *NPJ Syst Biol Appl*. 2020;6:28. 4. Minson A, Dickinson M. *Leuk Lymphoma*. 2021;62:3098-3108. 5. Zhu M, et al. *Clin Transl Sci*. 2022;15:954-966. 6. Smith EJ, et al. *Sci Rep*. 2015;5:17943.

Epcoritamab: CD3 x CD20 Bispecific Antibody (SC administration)

Epcoritamab: CD3 × CD20 bispecific antibody (humanized mouse IgG1-based)

- Induces T-cell activation by binding to CD3 on T cells and CD20 on malignant B cells
- Promotes immunologic synapse between bound cells, resulting in apoptosis of B cells
- Binds to a distinct epitope on CD20 differently from epitopes of rituximab or obinutuzumab
- Retains activity in the presence of CD20 monoclonal antibodies (mAbs)



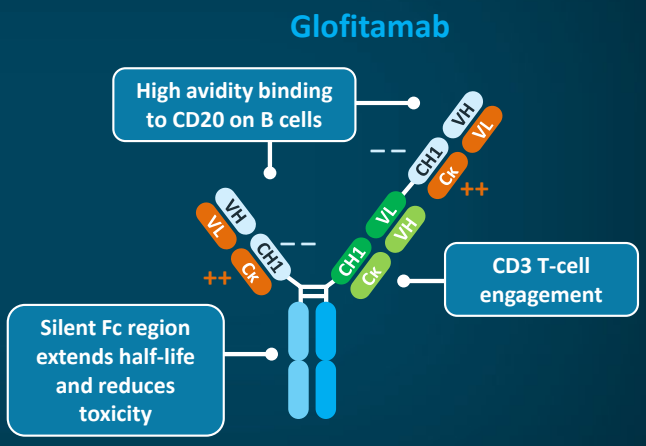
Epcoritamab is FDA-approved for refractory/relapsed (R/R) DLBCL.

Hutchings M, et al. *Blood*. 2020;136(suppl 1): Abstract 402. Engelberts PJ, et al. *EBioMedicine*. 2020;52:102625. Chiu C, et al. European Hematology Association (EHA) 2020: Poster EP1330. Hutchings M, et al. *Lancet*. 2021;398:1157-1169.

Glofitamab: Bispecific Antibody Targeting CD20 and CD3 in 2:1 Ratio

Glofitamab is CD3/CD20 bispecific antibody for DLBCL.

- Humanized mouse IgG1-based antibody
- Unique 2:1 molecular configuration allows "double binding" to CD20 (highlighted in blue zones)
- Advantages of 2:1 design
  - Associated with superior potency under experimental conditions as compared with 1:1 binding bispecific agents
  - Allows concomitant treatment with anti-CD20 antibodies—pre-dosing



Glofitamab is FDA-approved for R/R DLBCL.

Dickinson M, et al. *N Engl J Med.* 2022;387:2220-2231. Hutchings M, et al. *J Clin Oncol.* 2021;39:1959-1970.

Potential Adverse Events Considerations: Bispecific Antibodies

- Cytopenias are frequent and manageable; rates of neutropenic fevers are not high
- Infectious disease prophylaxis (eg, pneumocystis jirovecii pneumonia [PJP] prophylaxis, antivirals) and monitoring immunoglobulin levels are important supportive care considerations
- Important to recognize the unique adverse event (AE) profile of bispecific antibodies
  - Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are potential AEs associated with CAR T-cell therapy and bispecific T-cell engagers

Lee DW, et al. *Blood.* 2014;124(2):188-195. NCCN guidelines for B-cell lymphoma, V3.2023 (www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf). Accessed 2/24/2024. Hutchings M, et al. *Blood.* 2020;136(suppl 1):45-46. Hutchings M, et al. *Lancet.* 2021;398:1157-1691. Bannerji R, et al. ASH 2020. Engelberts PJ, et al. *EBioMedicine.* 2020;52:10262.

CRS and ICANS: Bispecifics

	N/disease	Grade 1 to 4 CRS	Grade ≥3 CRS	Grade 1 to 4 neurotoxicity	Grade ≥3 neurotoxicity
Glofitamab	N = 155/ DLBCL	63%	3% (Grade ≥2 12%)	8%	3%
Epcoritamab	N = 157/ LBCL	49.7%	2.5%	6.4%	0.6%

Odronextamab is an investigational therapy for the management of NHL.

Dickinson M, et al. *N Engl J Med*. 2022;387(24):2220-2231. Thieblemont C, et al. *J Clin Oncol*. 2023;41(12):2238-2247.

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Cytokine Release Syndrome

CYTOKINES INVOLVED

IMMEDIATE ONSET

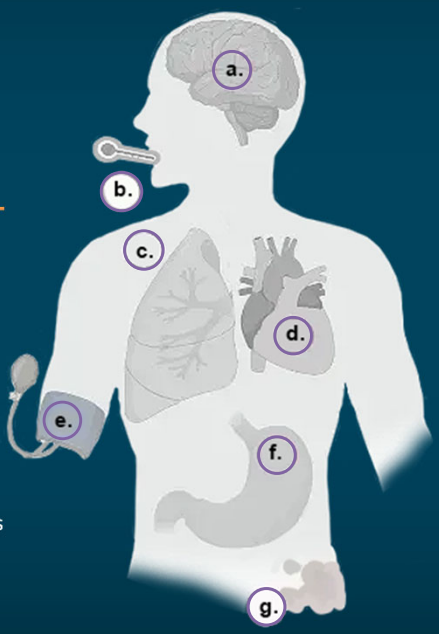
TNF IL-1β
IL-8 MCP-1

LATE ONSET

IL-6

ALSO IMPLICATED

IFN-α, IFN-β, IFN-γ
Colony stimulating factors



SYMPTOMS

a. Headache
b. Fever
c. Trouble breathing
d. Rapid heartbeat
e. Low blood pressure
f. Nausea
g. Rash

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Cytokine Release Syndrome: ASTCT Grading

ASTCT CRS Consensus Grading

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or†		
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 but they do not influence CRS grading.
* Fever is defined as temperature >38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia. † CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5° C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS. ‡ Low-flow nasal cannula is defined as oxygen delivered at <6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

ASTCT = American Society for Transplantation and Cellular Therapy.

Lee D, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

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Future Unmet Needs to Address

- Chemotherapy-free regimens in frontline setting for frail/elderly patients
- Enhancing the efficacy of frontline treatments
- Management and prevention of CAR T-cell failure
- Developing chemotherapy-free approaches in the R/R setting

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Study Overview[1]

Key inclusion criteria

- Previously untreated DLBCL
- Age ≥80 years OR age 65 to 79 years and considered ineligible* for CIT
- ECOG PS 0–2

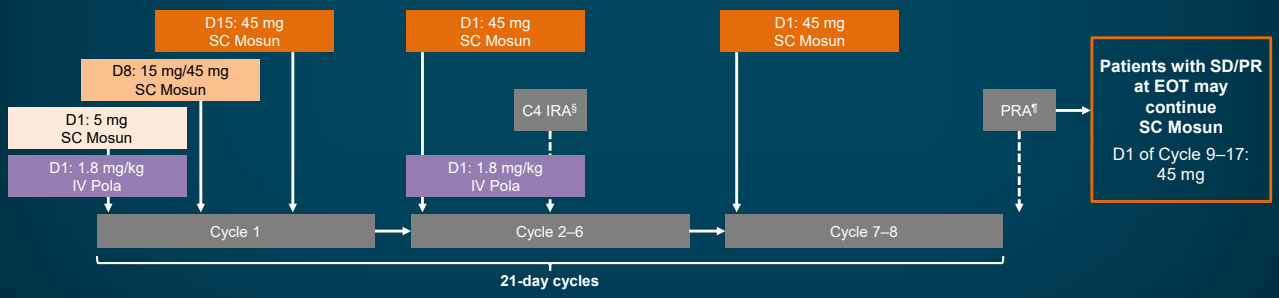
CRS mitigation strategies

- Step-up SC mosunetuzumab dosing in Cycle 1
- Pre-medication with dexamethasone in Cycle 1†
- Pre-medication with acetaminophen and diphenhydramine may also be given‡

Primary efficacy endpoint

- ORR by PET-CT at the PRA as assessed by IRC according to Lugano 2014 criteria[2]
- Additional objectives: Evaluation of safety, immunogenicity, pharmacokinetics, and pharmacodynamics

SC mosunetuzumab-polatuzumab administration: Cohort C1 (N = 7): 5/15/45 mg; Cohort C2 + C Expansion (N = 101): 5/45/45 mg (target dose cohort)**



*Per simplified geriatric assessment: Impairment in ≥2 ADL components and/or impairment in IADL components and/or CIRS-G score of at least one comorbidity with a severity score of 3–4 or a score of 2 in ≥8 comorbidities. **Note that this combination of agents is not FDA-approved for any indication. †Optional from C2+. ‡Optional from C1+. §In Cycle 4 between D14 and D21. ¶6–8 weeks after Cycle 8 D1 or the final dose of study treatment for those who discontinue prematurely. ADL = activity of daily living; CIRS-G = Cumulative Illness Rating Scale for Geriatrics; CIT = chemoimmunotherapy; CRS = cytokine release syndrome; D = Day; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = end of treatment; IADL = instrumental activity of daily living; IRA = interim response assessment; IRC = independent review committee; IV = intravenous; Mosun = mosunetuzumab; ORR = objective response rate; PET-CT = positron emission tomography–computed tomography; Pola = polatuzumab; PR = partial response; PRA = primary response assessment; SD = stable disease.

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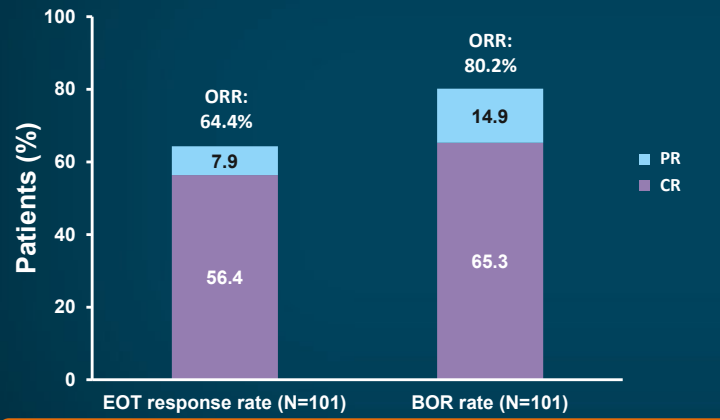
Investigator-Assessed EOT and BOR response rates

EOT response and BOR rates in Mosun-Pola target dose cohort



Response rate, n (%)	EOT N = 101	BOR N = 101
ORR	65 (64.4)	81 (80.2)
CR	57 (56.4)	66 (65.3)
PR	8 (7.9)	15 (14.9)
SD	4 (4.0)	4 (4.0)
PD	10 (9.9)	4 (4.0)
ND	22 (21.8)*	12 (11.9)†

- 6 of 8 patients with PR at EOT continued treatment beyond Cycle 8, and 3 of 6 patients converted from PR to CR during continuation
- The difference between BOR and EOT is attributed to 22 patients who did not reach the EOT visit due to AEs, death, and subject withdrawal, which reflects the frailty and high comorbidity burden of the study population

Mosun-Pola* induces encouraging response rates in elderly unfit or frail patients with previously untreated DLBCL.

Data cutoff: August 5, 2023. *6 patients withdrew consent, 14 discontinued early due to AEs, 1 discontinued due to investigator decision, and 1 had early PD in C1. †4 patients withdrew consent, 6 discontinued early due to AEs, 1 discontinued due to PI decision, 1 had early PD in C1. **Note that this combination of agents is not FDA-approved for any indication.
BOR = best overall response; CR = complete response; ND = not done or missing; PD = progressive disease.

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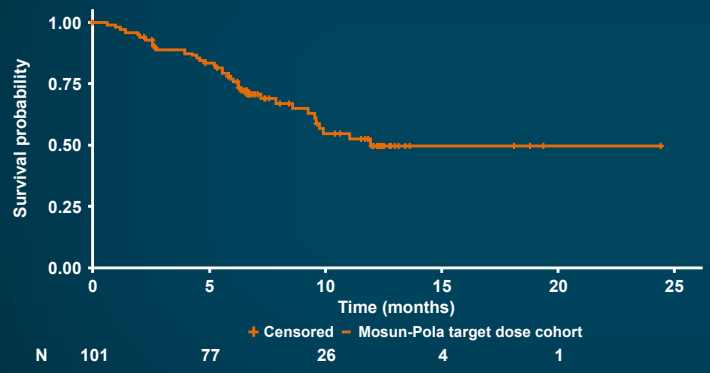
PFS in Mosun-Pola* Target Dose Cohort

KM curve of PFS in Mosun-Pola target dose cohort



	Mosun-Pola target dose cohort N = 101
Median PFS, months (95% CI)	11.9 (9.5, NE)
9-month PFS event-free rate, % (95% CI)	64.8 (54.2, 75.5)
12-month PFS event-free rate, % (95% CI)	49.7 (36.8, 62.5)
Patient disposition	
Censored/no event at CCOD	64 (63.4)
Event	37 (36.6)
Disease progression	12 (12)
Death	25 (25)

Early data show encouraging PFS with Mosun-Pola in elderly unfit or frail patients with previously untreated DLBCL.

Data cutoff: August 5, 2023. *Note that this combination of agents is not FDA-approved for any indication.

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Chemotherapy-Free Regimens in R/R DLBCL (EPCORE NHL-5) (NCT05283720)

Key inclusion criteria: Arm 1

- Adults ≥18 years
- Histologically confirmed CD20+ DLBCL[a]
  - DLBCL, NOS
  - High-grade B-cell lymphoma with *MYC* and *BCL-2* and/or *BCL-6* translocations
  - FL grade 3B
- R/R disease[b] with ≥1 prior anti-CD20 mAb–containing systemic therapy
- Prior CAR T-cell allowed, but prior CD3/CD20 bispecific antibodies not allowed
- ECOG PS 0–2

Dose escalation and dose expansion

Arm 1	Arm 2	Arm 3	Arms 4–5	Arms 6–7
Epcoritamab + lenalidomide (12 x 28-day cycles) R/R DLBCL	Epcoritamab + ibrutinib + lenalidomide R/R DLBCL	Epcoritamab + polatuzumab + R-CHP 1L DLBCL	Epcoritamab + CC-99282 (CELMoD) R/R DLBCL, R/R FL	Epcoritamab + ibrutinib ± venetoclax R/R MCL, 1L MCL

Epcoritamab dosing schedule

Step-up dosing (SUD)

- Cycle 1, day 1: SUD1 (0.16 mg)
- Cycle 1, day 8: SUD2 (0.8 mg)
- Cycle 1, days 15, 22: full dose (48 mg)
- Cycles 2–3, days 1, 8, 15, 22: full dose (48 mg)
- Cycles 4–12, day 1: full dose (48 mg)

Lenalidomide dosing schedule

Cycles 1–12: 25 mg once daily on days 1–21

Premedication and CRS prophylaxis

Diphenhydramine, acetaminophen, and corticosteroids were mandatory for CRS prophylaxis with the first 4 epcoritamab doses

- Current recommendation is dexamethasone 15 mg for 4 days[c]

Median follow-up: 8.2 months

Note that combined epcoritamab and lenalidomide is not FDA approved for any indication, and CC-99228 is an investigational agent that also has not been FDA-approved. [a]Per WHO 2016 classification.

[b]Relapsed disease is defined as disease that previously responded to therapy but progressed ≥6 months after completion of therapy. Refractory disease is defined as disease that either progressed during therapy, failed to achieve an objective response to prior therapy, or progressed within 6 months after completion of therapy (including maintenance therapy).

[c]Additional information can be found in the following presentation: Vose J, et al. ASH 2023; Abstract 1729.

Avivi Mazza, et al. ASH 2023; Abstract 438.

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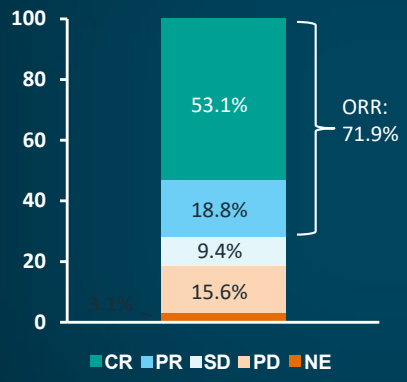
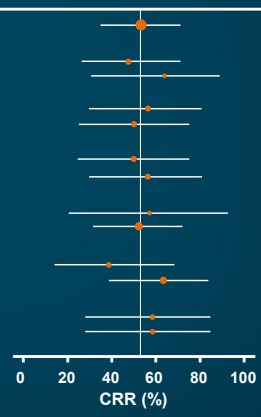
Frequent and Deep Responses Observed

Best overall response[a] (N = 32)



Complete response in subgroups (N = 32)

Subgroup	N	CRR, % (95% CI)
All patients	32	53.1 (34.7, 70.9)
Age		
<75 years	21	47.6 (25.7, 70.2)
≥75 years	11	63.6 (30.8, 89.1)
Prior lines of therapy		
1	16	56.3 (29.9, 80.2)
≥2	16	50.0 (24.7, 75.3)
Time from end of last therapy to first dose		
<6 months	16	50.0 (24.7, 75.3)
≥6 months	16	56.3 (29.9, 80.2)
Prior CAR T-cell therapy		
Yes	7	57.1 (18.4, 90.1)
No	25	52.0 (31.3, 72.2)
Primary refractory status		
Yes	13	38.5 (13.9, 68.4)
No	19	63.2 (38.4, 83.7)
Molecular classification		
GCB	12	58.3 (27.7, 84.8)
ABC/non-GCB	12	58.3 (27.7, 84.8)



Data cutoff: October 6, 2023.

[a]Based on response-evaluable population, defined as patients with measurable disease at baseline and ≥1 postbaseline disease evaluation, or who had died within 60 d of the first dose of study drug without a postbaseline assessment.

Note that combined epcoritamab and lenalidomide is not FDA-approved for any indication.

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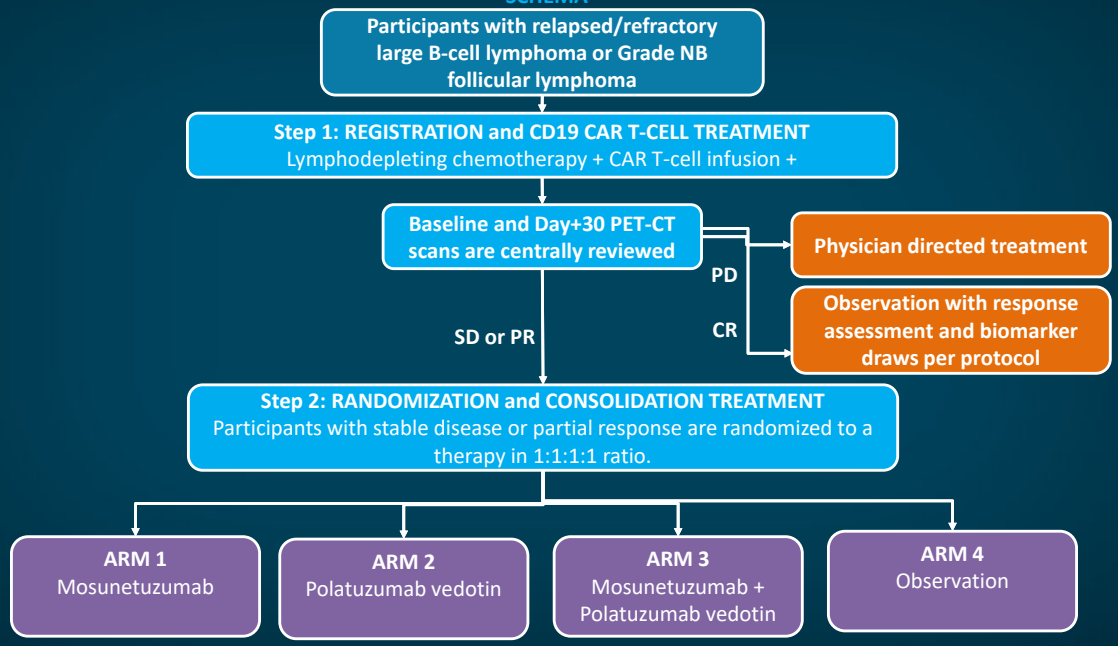
Preventing CAR T-Cell Failure: SWOG 2114

SCHEMA



SWOG clinical trial S2114 (https://www.swog.org/clinical-trials/s2114). Accessed 2/24/2024.

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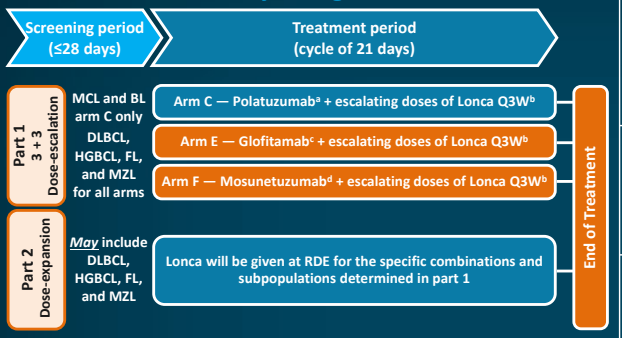
Chemotherapy-Free Combinations in R/R (LOTIS-7)

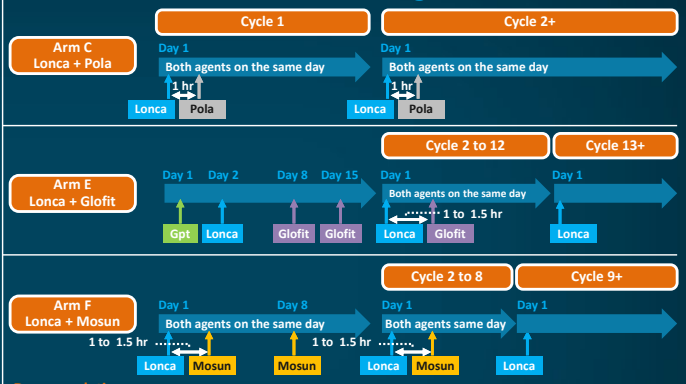
Study design



Participants may continue treatment for up to 1 year or until disease progression, unacceptable toxicity, or other discontinuation criteria, whichever occurs first. The follow-up period is for ≤2 years from the end of treatment.

a IV polatuzumab vedotin 1.8 mg/kg on day 1 of each 21-day cycle.
b Escalating doses of IV Lonca on day 1 of each cycle (C) at doses of 90, 120 and 150 µg/kg. Lonca will be administered on D1 of each cycle, 1 hour before combination drugs, with the exception of Arm E, which will be administered on C1D2. If the starting dose of loncastuximab tesirine is 120 µg/kg or higher, the dose will be reduced to 75 µg/kg from C3.
c Obinutuzumab pretreatment on C1D1; IV glofitamab 2.5 mg on C1D8, 10 mg on C1D15, and then 30 mg for cycles 2-12 on D1.
d Subcutaneous mosunetuzumab 5 mg on C1D1 and then 45 mg for C1D8, C1D15, and cycles 2-8 on D1.

Part 1 dosing



Dose escalation

Arm C	Arm E	Arm F
Lonca[a]: IV Q3W on D1 of all cycles	Lonca: IV Q3W on D2 of cycle 1 and D1 of cycle 2+	Lonca[a]: IV Q3W on D1 of all cycles
Pola: 1.8 mg/kg IV Q3W on D1 of all cycles	Glofit: 2.5 mg on cycle 1 D8; 10 mg on cycle 1 D15, and then 30 mg on D1 of cycle 2-12	Mosun: 5 mg on cycle 1 D1; 45 mg on cycle 1 D8 and D15 and then 45 mg on D1 of cycle 2-8

a Dose level 1, 90 µg/kg; dose level 2, 120 µg/kg; dose level 3, 150 µg/kg.
b If the starting dose of Lonca is ≥120 µg/kg, the dose will be reduced to 75 µg/kg from cycle 3.
c If a dose limiting toxicity (DLT) is clearly related to Pola, the DLT does not recur after a reduction of Pola, and Lonca has not been escalated to the 150-µg/kg level, dose-escalation of Lonca will be continued with a reduced Pola dose of 1.4 mg/kg.

BL = Burkitt lymphoma; D = day; DLBCL = diffuse large B-cell lymphoma; FL = folicular lymphoma; Glofit = glofitamab; Gpt = obinutuzumab; HGBCL = high-grade B-cell lymphoma; IN = intravenous; Lonca = loncastuximab tesirine; MCL = mantle cell lymphoma; Mosun = mosunetuzumab; MTD = maximum tolerated dose; MZL = marginal zone lymphoma; Pola = polatuzumab vedotin; Q3W = every 3 weeks; RDE = recommended dose for expansion; R/R = relapsed/refractory.

Note that the combinations of polatuzumab and loncastuximab; mosunetuzumab and loncastuximab; and glofitamab and loncastuximab are not FDA-approved for any indication.

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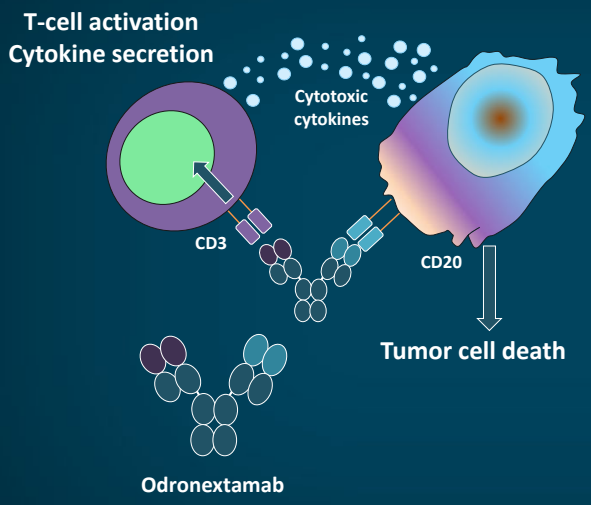
Odronextamab—Directing T-Cells to CD20+ Cells



- Odronextamab (REGN1979) is a CD20 x CD3 bispecific antibody
- Hinge-stabilized, fully human immunoglobulin G4 (IgG4)-based
- Binds to CD3 on T cells and CD20 on malignant B cells, triggering T-cell-mediated cytotoxicity independent of T-cell receptor recognition

Odronextamab is an investigational therapy for the management of NHL.

Smith EJ, et al. *Sci Rep*. 2015;5:17943. Bannerji R, et al. *Blood*. 2020;136(suppl 1); Abstract 400. Bannerji R, et al. *Lancet Haematol*. 2022;9:e327-e339.

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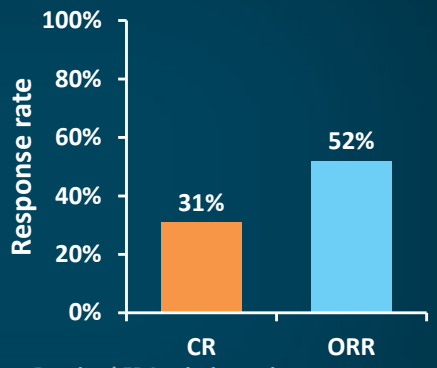
Odronextamab Efficacy and Safety in R/R DLBCL: ELM-2 Phase 2 Results

- Pivotal phase 2 results presented at ASH 2023*
  - R/R DLBCL after ≥2 prior LOT
  - Median follow-up was 26.2 months
  - Probability of CRs ongoing at 24 months was 48%
  - *Initial 1/20 step-up regimen revised to 0.7/4/20 to mitigate risk of CRS*
- Safety
  - Most common AEs were CRS, anemia, pyrexia, neutropenia, and hypokalemia
  - CRS was mostly low grade and further mitigated by revised step-up regimen

Odronextamab step-up regimen demonstrated clinical efficacy, durable CRs, and manageable safety profile; it also confirms the efficacy of odronextamab in hard-to-treat, highly aggressive R/R DLBCL.

Response to odronextamab in R/R DLBCL*



Received FDA priority review acceptance on September 29, 2023, for R/R DLBCL or R/R FL after 2 prior therapy lines

Odronextamab is an investigational therapy for the management of NHL.

*As of January 31, 2023.

CR = complete response; CRS = cytokine release syndrome; LOT = lines of therapy; mDOCR = median duration of complete response; ORR = objective response rate; R/R = relapsed/refractory.

Odronextamab is an investigational agent for the management of NHL.

Walewski J, et al. EHA 2023; Abstract P1115 (https://library.ehaweb.org/eha/2023/eha2023congress/385565/jan.walewski.odronextamab.in.patients.with.relapsed.refractory.diffuse.large.html?f=menu%3D16%2Abrowseby%3D8%2Asortby%3D2%2Ace_id%3D2489% 2Aot_id%3D27893% 2Atrend%3D4016%2Amarker%3D4178). Accessed 2/24/2024. Ayyapan S, et al. *Blood*. 2023;142(suppl 1):436.

Novel Bispecifics in Trials

Bispecific antibody	Trial ID	Phase	ORR (in DLBCL/ aggressive lymphomas)	Most common AE/ grade 3 or higher AE
TNB-486	NCT04594642	1	40%	CRS (59%)/ lymphopenia (26%)
GB261	NCT04923048	1/2	73%	COVID-19 infection (40%)/not reported
Imvotamab	NCT04082936	1	N/A	Not reported/ neutropenia (25%)
Plamotamab	NCT02924402	1	47.4%	CRS (72%)/anemia (19.4%)

The agents listed in this table are investigational and have not yet been FDA-approved for these indications.

Hou J-Z, et al. *Blood*. 2022;140(suppl 1):1474-1475. Song Y, et al. Blood. 2023;142(suppl 1):1719-1719. Budde E, et al. *Blood*. 2020;136:45-46. Patel K, et al. Blood. 2022;140(suppl 1):9470-9472.

Discussing Treatment Considerations With Patients

Best Practice in Discussing Therapeutic Options in Later-Line B-Cell Lymphoma Management

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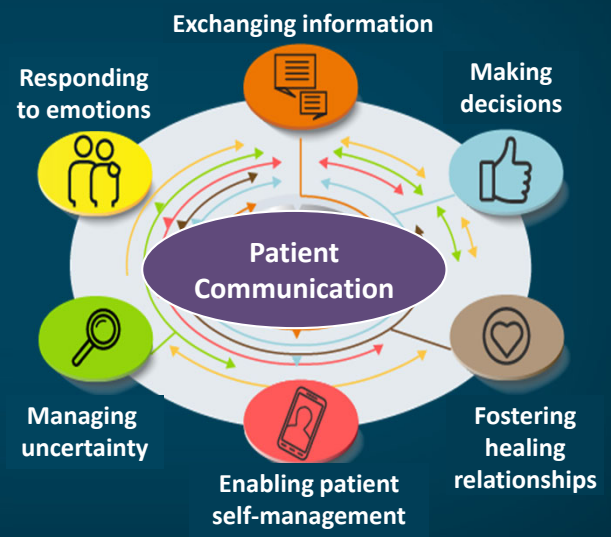
Patient-Centered Communication in Shared Decision-Making

Patient participation is key in medical decision-making and often leads to improved outcomes.

Shared decision-making can facilitate

- ↑ patient satisfaction
- ↑ productive conversations
- ↓ anxiety
- ↑ quality of patient-clinician relationships
- ↑ patient-reported outcomes following treatment decisions
- ↑ disease-related understanding



Perocchia RS, et al. *J Cancer Educ.* 2011;26:36-43. Research Triangle Institute (RTI) International. Advancing patient-centered communication in cancer care (https://www.rti.org/advancing-patient-centered-communication-cancer-care). National Cancer Institute (NCI). Communication in cancer care (PDQ®). Health professional version. Updated 6/22/2023 (www.cancer.gov/about-cancer/coping/adjusting-to-cancer/communication-hp-pdq). URLs accessed 2/24/2024. Shickh S, et al. *Am Soc Clin Oncol Educ Book.* 2023;43:e389516.

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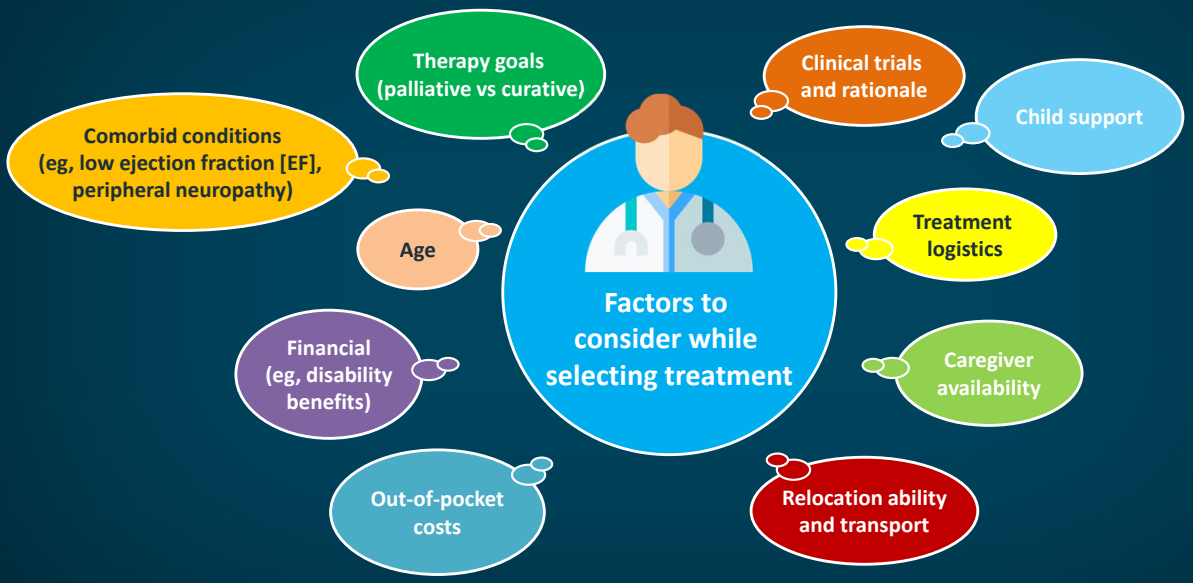
Key Considerations in Therapeutic Selection



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The Need for a Multidisciplinary Approach

- Multidisciplinary care is critical in patient care and treatment decision-making
- With their shared expertise, multidisciplinary teams help improve treatment outcomes
- The patient perspective is important to ensure treatment choices match patient goals of therapy

Negbenebor NA. *Cutis.* 2021;107:E22-E23. Cancer.net. The oncology team. Updated 9/20 (www.cancer.net/navigating-cancer-care/cancer-basics/cancer-care-team/oncology-team). CancerCare. Your health care team: understanding their roles. Updated 1/7/2021 (www.cancercare.org/publications/59-your_health_care_team_understanding_their_roles). American Cancer Society (ACS). Health professionals associated with cancer care. Updated 8/7/19 (www.cancer.org/content/dam/CRC/PDF/Public/6059.00.pdf). National Cancer Institute (NCI). People in health care. Updated 11/12/21 (www.cancer.gov/about-cancer/managing-care/services/providers). Memorial Sloan Kettering Cancer Center. Your cancer care team (www.mskcc.org/cancer-care/diagnosis-treatment/your-care-team). URLs accessed 2/24/2024. Ahmed HZ, et al. *Cureus*. 2023;15:e34693.

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