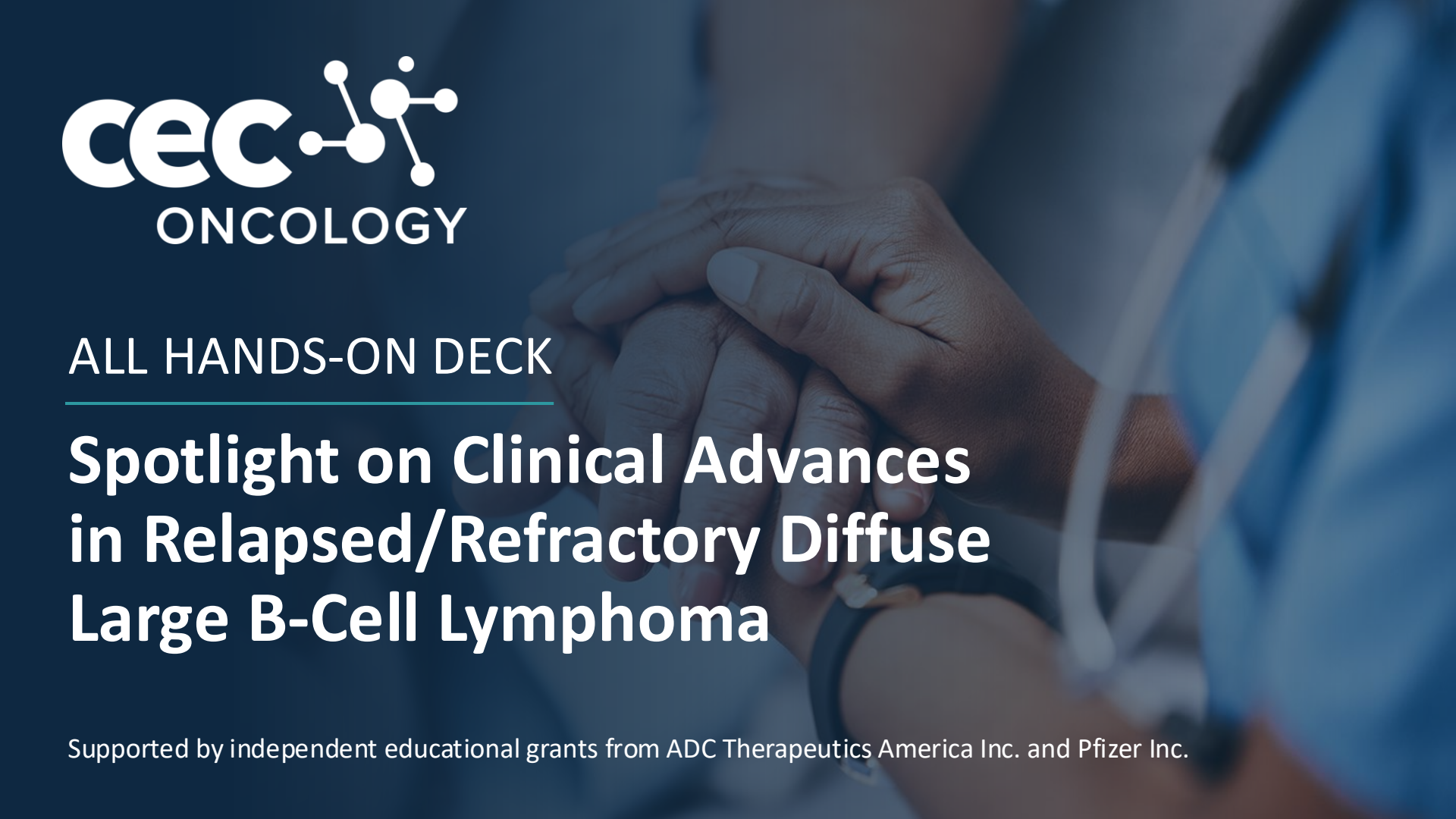

ALL HANDS-ON DECK

Spotlight on Clinical Advances in Relapsed/Refractory Diffuse Large B-Cell Lymphoma

Supported by independent educational grants from ADC Therapeutics America Inc. and Pfizer Inc.

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Disclosures

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- *Advisory Board:* NeoGenomics Laboratories
  Consultant: AbbVie Inc.; Adaptive Biotechnologies; AstraZeneca; BeiGene; Genentech, Inc.; Janssen Pharmaceuticals, Inc.; Lilly; Merck & Co., Inc. (DMSB Chair); and Pharmacyclics
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Learning Objectives

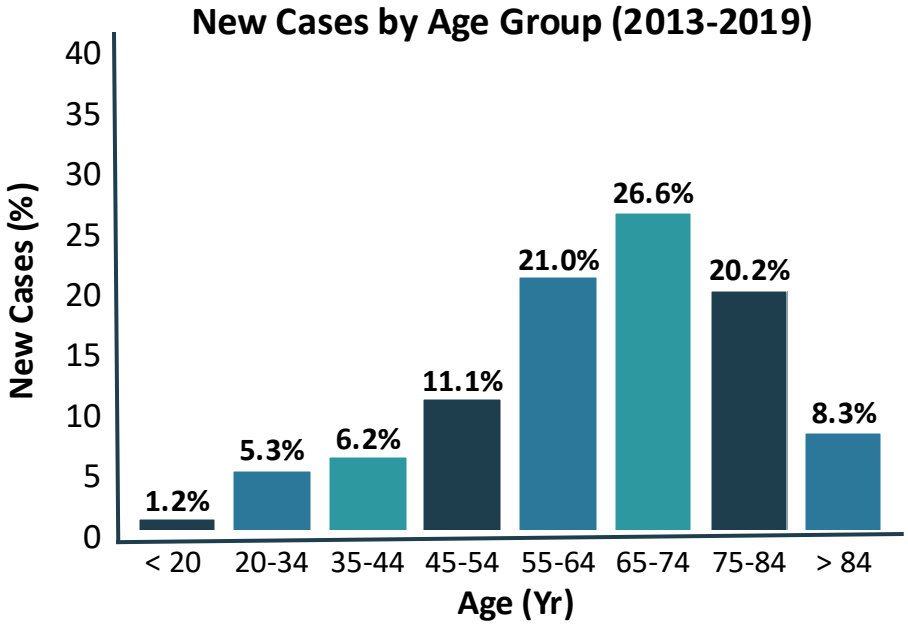
- Integrate diagnostic and prognostic biomarkers for DLBCL in order to develop personalized treatment strategies for patients
- Utilize an evidence-based approach for personalizing treatment for patients with R/R DLBCL, taking into consideration efficacy, safety, and patient-specific factors to optimize patient outcomes
- Develop strategies to identify and mitigate the impact of AEs associated with novel therapies used in the treatment of patients with R/R DLBCL

AE = adverse event; DLBCL = diffuse large B-cell lymphoma; R/R = relapsed refractory

Epidemiology of DLBCL: Age, Presentation, and Survival Rates

At Diagnosis:

- Median age at diagnosis: 66 yr
- Presenting with stage III/IV DLBCL: 55%
- With systemic B symptoms: ~30%
- With elevated LDH: ~62%
- With extranodal involvement: 40%
- With BM involvement: 11%-34%
- With CNS involvement: 4.2% (~2% at relapse)



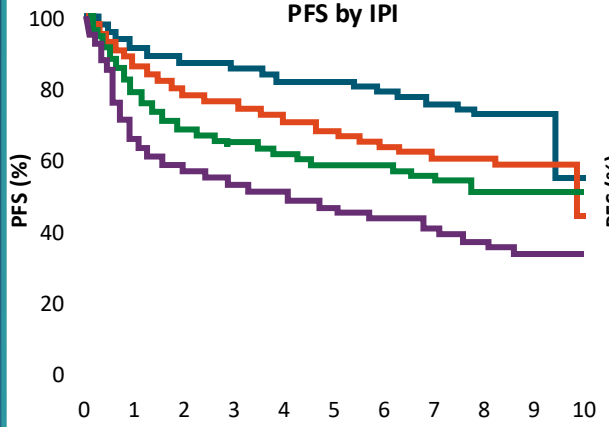
5-yr relative survival rate: 64.7%

BM = bone marrow; CNS = central nervous system; LDH = lactate dehydrogenase.

National Institutes of Health [NIH]. *Cancer Stat Facts: NHL — Diffuse Large B-cell Lymphoma (DLBCL).* SEER Website. 2021. https://seer.cancer.gov/statfacts/html/dlbcl.html. Mamgain J, et al. *Family Med Prim Care*. 2022;11:4151. Yao Z, et al. *Leukemia*. 2017;32(2):353-363. Al-Mansour M, et al. Asian Pac J Cancer Prev. 2023;24(2):623-631. Vodicka P, et al. ASH. 2023. Abstract No. 3140. https://ash.confex.com/ash/2023/webprogram/Paper186207.html.

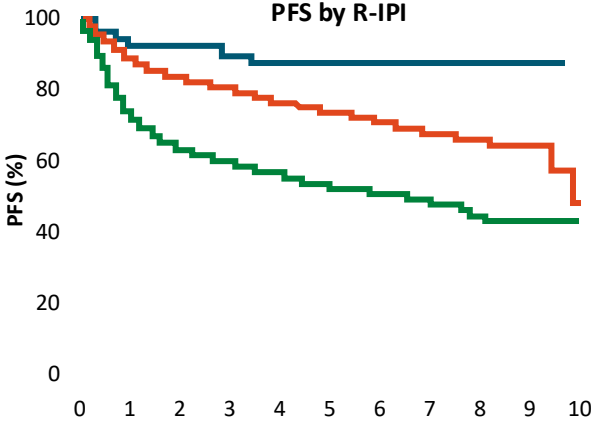
Comparison of Clinical Prognostic Indexes

- N = 2,124 patients with DLBCL who received R-CHOP from 1998-2009 across 7 multicenter, randomized clinical trials
- Compared with IPI, NCCN-IPI better discriminated low-risk and high-risk subgroups



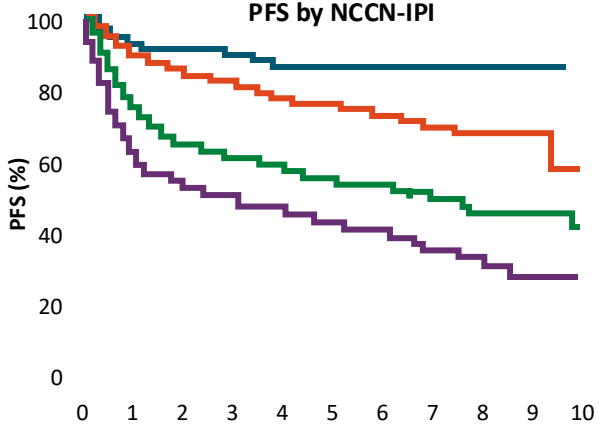
IPI Risk Group	Time Point, Yr	KM Est (95% CI)
Low (0-1)	5	81.4 (78.0-84.9)
Low-intermediate (2)	5	67.0 (62.5-71.8)
High-intermediate (3)	5	58.4 (53.9-63.1)
High (4-5)	5	45.8 (41.1-51.0)

Log-rank *P* <.0001



R-IPI Risk Group	Time Point, Yr	KM Est (95% CI)
Very good (0)	5	86.7 (79.8-94.3)
Good (1-2)	5	73.6 (70.6-76.7)
Poor (3-5)	5	52.5 (49.2-56.0)

Log-rank *P* <.0001 + Censor



NCCN-IPI Risk Group	Time Point, Yr	KM Est (95% CI)
Low (0-1)	5	86.0 (80.2-92.2)
Low-intermediate (2-3)	5	75.3 (72.1-78.6)
High-intermediate (4-5)	5	54.3 (50.7-58.2)
High (6-8)	5	42.8 (36.5-50.2)

Log-rank *P* <.0001

IPI = international prognostic index; NCCN = National Comprehensive Cancer Network; PFS = progression-free survival.

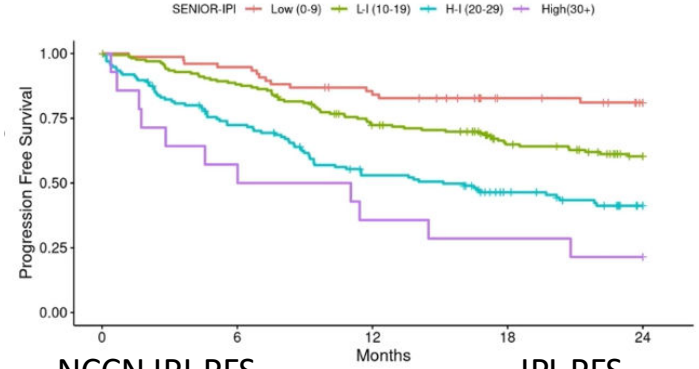
Ruppert S, et al. *Blood*. 2020;135(23):2041-2048.

Senior IPI for Elderly Receiving CIT

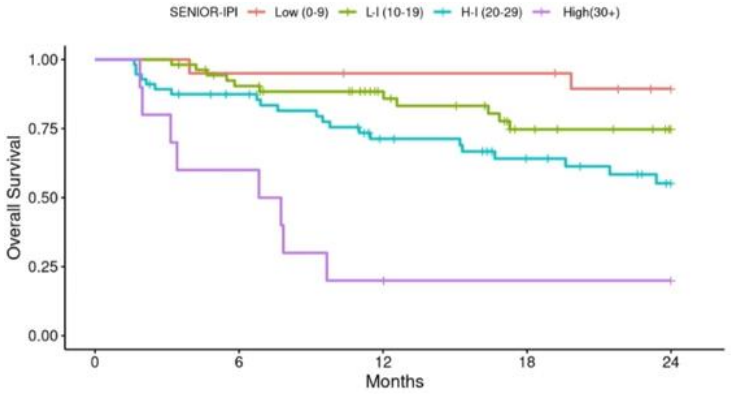
SENIOR-IPI: **number of years > 80 years old + number of aaIPI predictors + LDH > 3N + albumin < 35g/L**

Each x 6

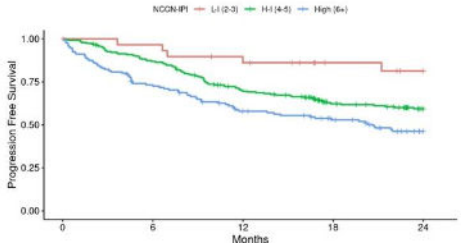
Senior IPI-PFS



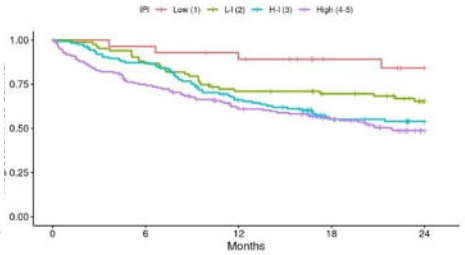
Senior IPI-OS



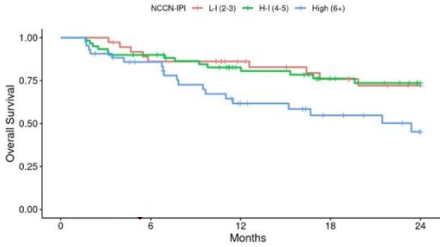
NCCN IPI-PFS



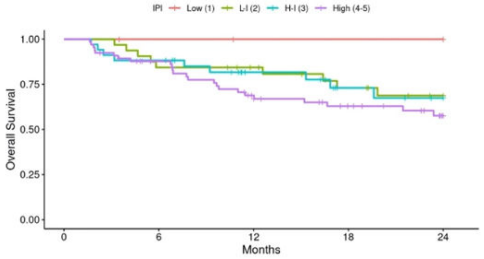
IPI-PFS



NCCN IPI-OS



IPI-OS

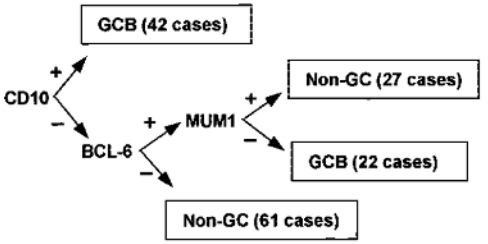


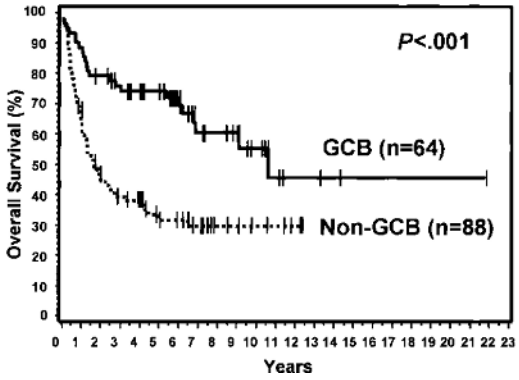
aaIPI = age-adjusted International Prognostic Index; OS = overall survival.

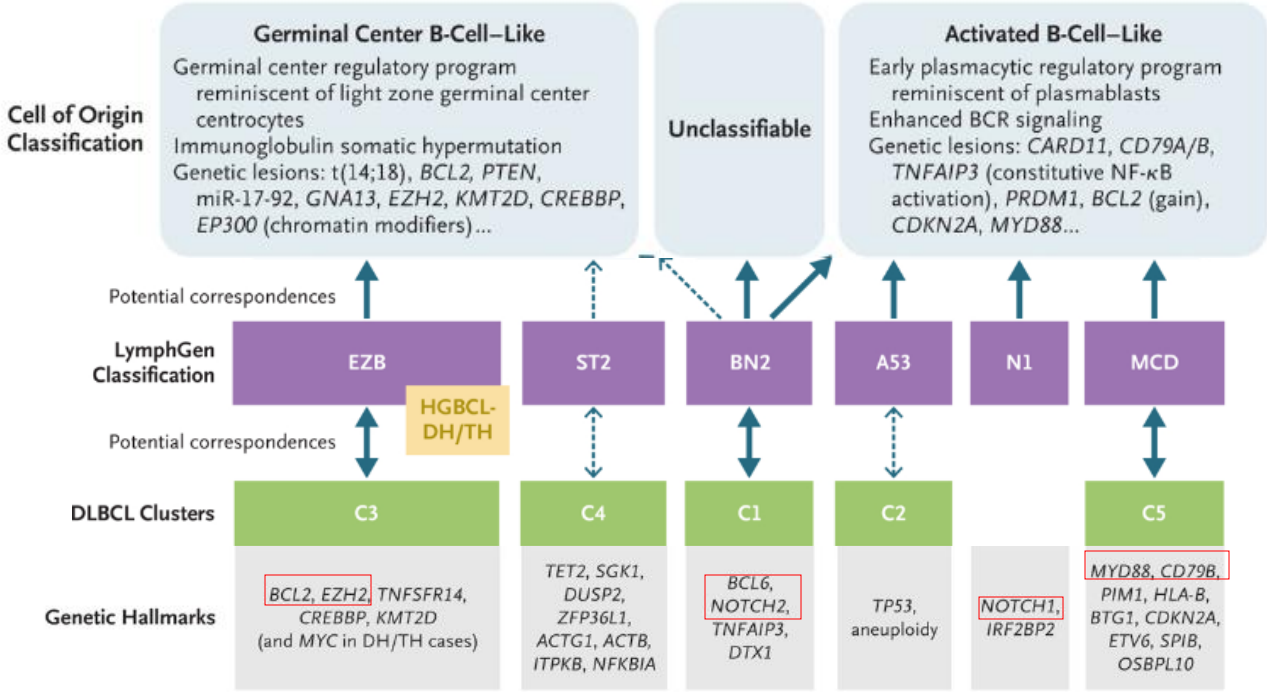
Dubois S, et al. *Blood*. 2024;144(1):649.

How do Diagnostic and Prognostic Biomarkers for DLBCL Fit in Clinical Practice?

Evolving Classification of COO Incorporating Gene Expression Profiles and Genomic Aberrations

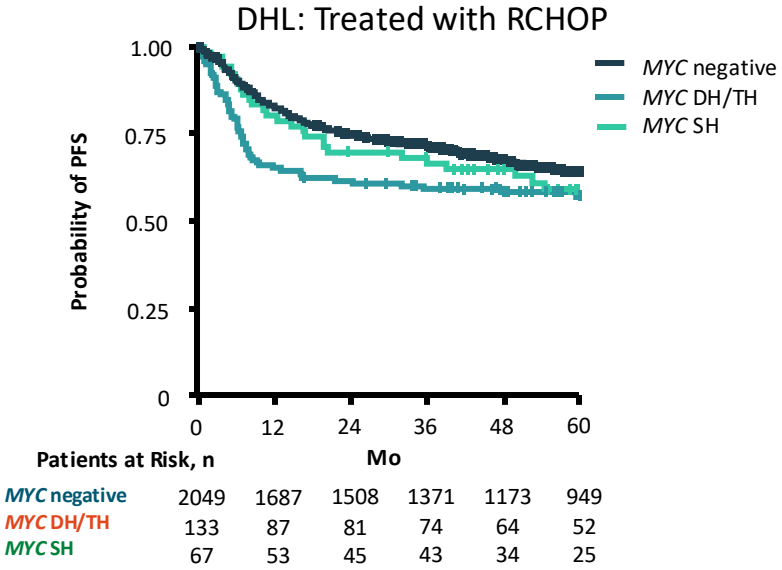




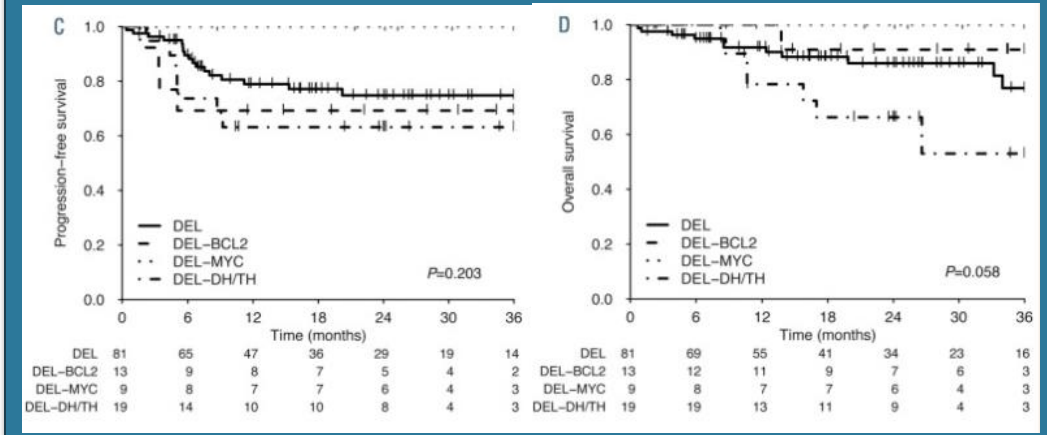


Schmitz R, et al. *N Engl J Med*. 2018;378(15):1396-1407.

PFS in Patients With DLBCL Treated With R-CHOP vs. REPOCH According to Rearrangements by FISH



DEL or DHL Treated with DA-REPOCH: PFS & OS



"Double hit" lymphoma or also known as high grade Bcell lymphoma with MYC and BCL2 rearrangement remain and unmet need with no SOC approach. Even in the age of polatuzumab based therapies REPOCH remains common.

DEL = double-expressor lymphoma; DH = double-hit; DHL = double-hit lymphoma; SH = single hit.

Rosenwald A, et al. *J Clin Oncol*. 2019;37(35):3359-3368. Dodero A, et al. *Haematologica*. 2022;107(5):1153–1162.

Assessing the Latest Evidence for Current and Emerging Treatment Options for R/R DLBCL

NCCN Guidelines Second Therapy Strategies

Second-Line Therapy
(intention to proceed to transplant)

Preferred regimens (in alphabetical order)
- DHA (dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) ± rituximab
- GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab
- ICE (ifosfamide, carboplatin, etoposide) ± rituximab

Other recommended regimens (in alphabetical order)
- ESHAP (etoposide, methylprednisone, cytarabine, cisplatin) ± rituximab
- GemOx (gemcitabine, oxiplatin) ± rituximab
- MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab

Second-Line Therapy
(relapsed disease > 12 mo or primary refractory disease)

- CAR T-cell therapy
  - Axicabtagene ciloleucel (CD19-directed) (category 1)
  - Lisocabtagene maraleucel (CD19-directed) (category 1)

Bridging Therapy Options
(typically 1 or more cycles as necessary until CAR T-cell product is available)

- DHA + platinum (carboplatin, cisplatin, or oxaliplatin) ± rituximab
- GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab
- GemOx ± rituximab
- ICE ± rituximab
- Polatuzumab vedotin-pilq ± rituximab ± bendamustine (bendamustine should be considered/added only after leukapheresis)
- ISRT (can be used as monotherapy or sequentially with systemic therapy)

Second-Line Therapy
(no intention to proceed to transplant)

Preferred regimens (in alphabetical order)
- CAR T-cell therapy (CD19-directed) (if eligible)
  - Lisocabtagene maraleucel
- Glofitamab-gxbm + GemOx
- Polatuzumab vedotin-pilq ± bendamustine ± rituximab
- Polatuzumab vedotin-piiq + mosunetuzumab-axgb
- Tafasitamab-cxixl + lenalidomide

Other recommended regimens (in alphabetical order)
- CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab
- DA-EPOCH ± rituximab
- GDP ± rituximab or gemcitabine, dexamethasone, carboplatin) ± rituximab
- GemOx ± rituximab
- Rituximab
- Useful in certain circumstances
- Brentuximab vedotin for CD30+ disease
- Ibrutinib (non-GCB DLBCL)
- Lenalidomide ± rituximab (non-GCB DLBCL)

Note: All recommendations are category 2A unless otherwise indicated

CAR T-cell = chimeric antigen receptor T-cell.

NCCN Guidelines. B-Cell Lymphomas: NCCN Evidence Blocks. (Version 1.2025). https://www.nccn.org/login?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/b-cell_blocks.pdf.

NCCN Guidelines Third Line and Later Strategies

Suggested Regimen Treatments

Third-Line and Subsequent Therapy
(no intention to proceed to transplant)

Preferred regimens

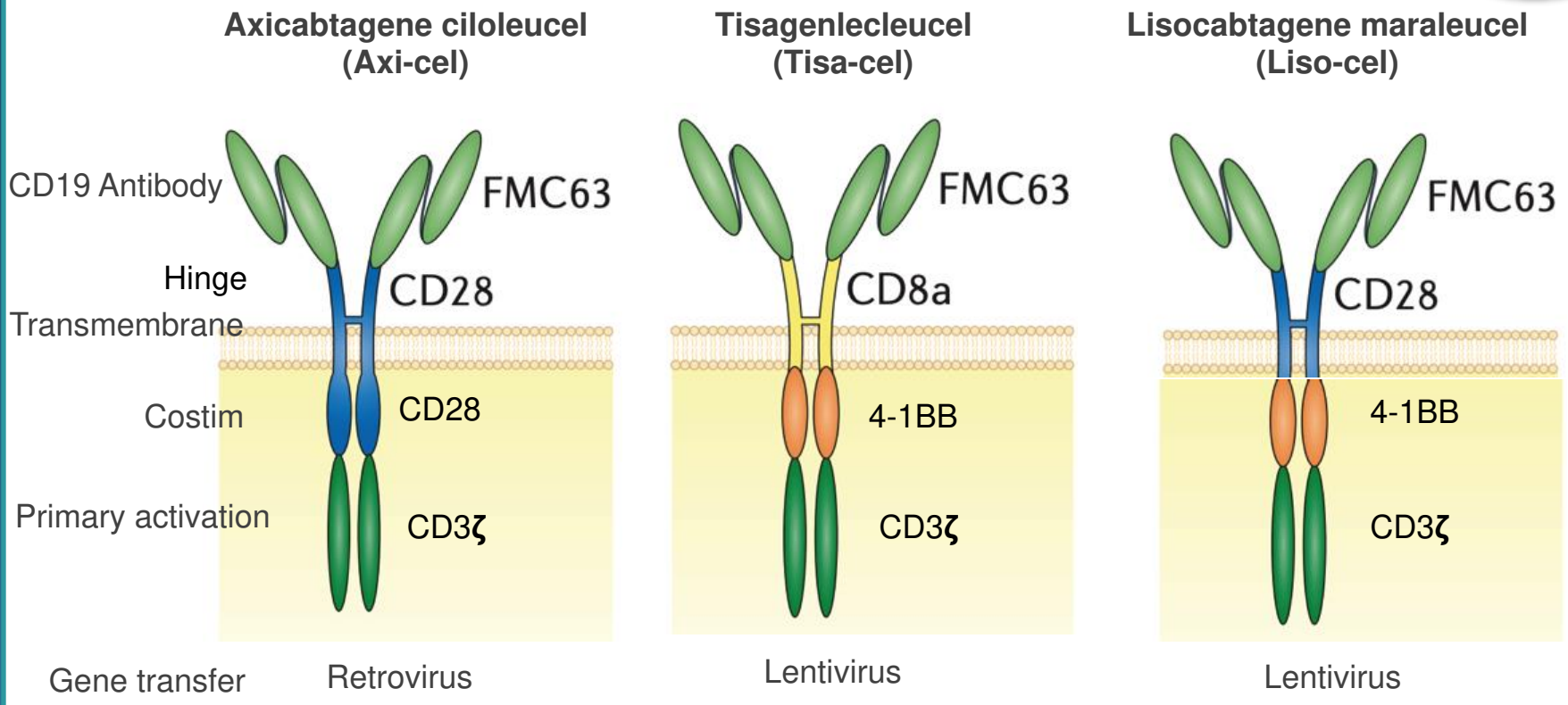
- T-cell engager therapy
  - CAR T-cell therapy (preferred if not previously given) (in alphabetical order)
    - Axicabtagene ciloleucel (CD19-directed)
    - Lisocabtagene maraleucel (CD19-directed)
    - Tisagenlecleucel (CD19-directed)
  - Bispecific antibody therapy (only after at least two lines of systemic therapy; including patients with disease progression after transplant or CAR T-cell therapy) (in alphabetical order)
    - Epcoritamab-bysp
    - Glofitamab-gxbm

Other recommended regimens

- Brentuximab vedotin + lenalidomide + rituximab (for CD30+ disease)
- Loncastuximab tesirine-lpyl
- Selinexor (including patients with disease progression after transplant or CAR T-cell therapy)

NCCN Guidelines. B-Cell Lymphomas: NCCN Evidence Blocks. (Version 1.2025). https://www.nccn.org/login?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/b-cell_blocks.pdf.

CD19-Directed CAR T Cells in the Clinic: LBCL



*Defined ratio of CD4:CD8. LBCL = large B-cell lymphoma.

van der Stegen SJ, et al. *Nat Rev Drug Discov*. 2015;14(7):499–509.

CD19-Directed CAR T-Cell Products for LBCL

	Axicabtagene Ciloleucel[1]	Tisagenlecleucel[2]	Lisocabtagene Maraleucel[3]
Construct	Anti–CD19-CD28-CD3z	Anti–CD19-41BB-CD3z	Anti–CD19-41BB-CD3z
Dose	2 x 10^6/kg (max 2 x 10^8)	0.6 to 6.0 x 10^8/kg	50 to 150 x 10^6
Lymphodepletion	Flu/Cy 30/500 x 3 days	Flu/Cy 25/250 x 3 days, or bendamustine x 2 days	Flu/Cy 30/300 x 3 days
FDA approval status	• 3rd line and beyond for R/R DLBCL, HGBCL, primary mediastinal B-cell lymphoma, FL • 2nd line if R/R within 12m	• 3rd line and beyond for R/R pediatric ALL, R/R DLBCL, HGBCL, FL	• 3rd line and beyond for R/R DLBCL, HGBCL, FL grade 3B, primary mediastinal B-cell lymphoma • 2nd line for R/R LBCL within 12m or at any time if transplant ineligible

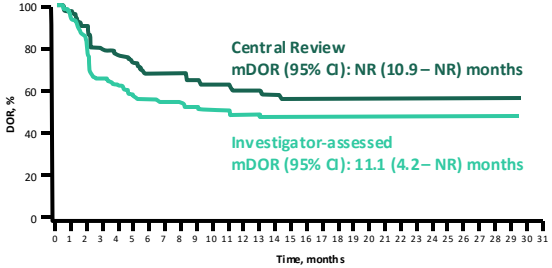
FL = follicular lymphoma; Flu/Cy = fludarabine and cyclophosphamide; HGBCL = high-grade B-cell lymphoma.

1. Axicabtagene ciloleucel [package insert]. https://www.fda.gov/media/108377/download. 2. Tisagenlecleucel [package insert]. https://www.fda.gov/media/107296/download. 3. Lisocabtagene maraleucel [package insert]. https://www.fda.gov/media/145711/download.

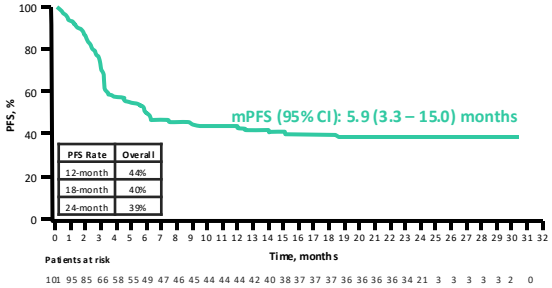
CD19 CAR T-Cells for DLBCL: 40% Durable Remission Rate

ZUMA-1 (Axi-cel)[1]

DOR

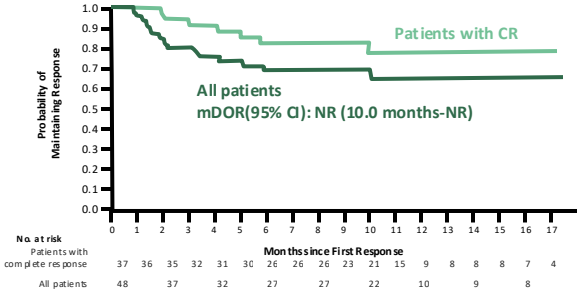


PFS



JULIET (Tisa-cel)[2]

DOR



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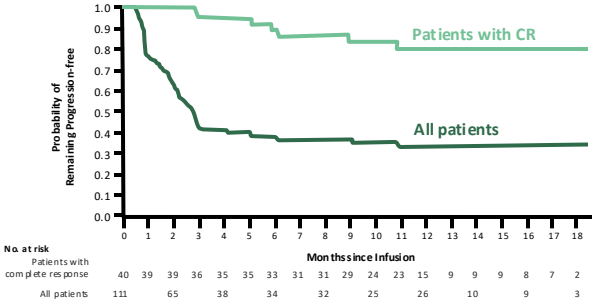
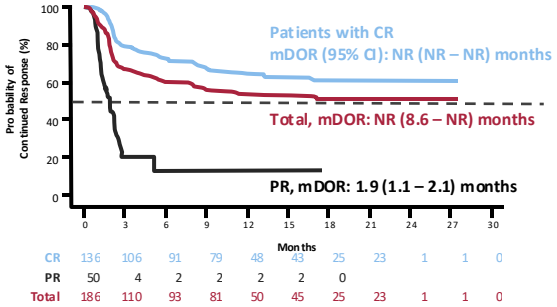
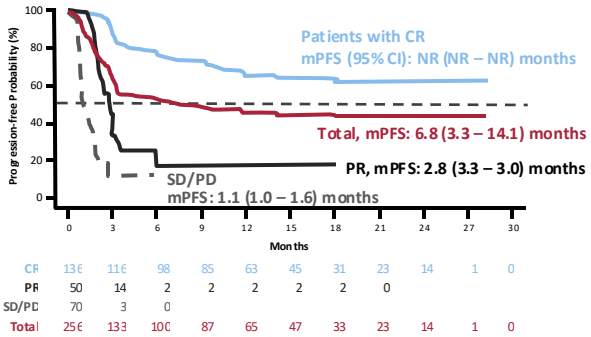


TRANSCEND-001 (Liso-cel)[3]

DOR



PFS



Cross-trial comparisons are for discussion purposes only

CR = complete response; DOR = duration of response; mDOR = median duration of response; mPFS = median progression free survival; NR = no response; PR = partial response.

1. Locke FL, et al. *Lancet Oncol*. 2019;20(1):31-42. 2. Schuster S, et al. *N Engl J Med*. 2019;380(1):45-56. 3. Abramson JS, et al. *Lancet*. 2020;396(10254):839-852.

CAR T-Cell Toxicity in LBCL

	ZUMA-1[1,2]	JULIET[3,4]	TRANSCEND CORE[5]
Product	**Axi-cel**	**Tisa-cel**	**Liso-cel**
# treated	101	111	269
CRS (%)	93	58	42
Gr 3+ CRS (%)	13	22*	2
ICANS (%)	64	21	30
Gr 3+ ICANS (%)	28	12	10
CRS Onset/Duration	1d/7d	3d/8d	5d/NR
ICANS Onset/Duration	4d/17d	6d/14d	9d/NR

Cross-trial comparisons are for discussion purposes only

*UPenn CRS grading

CRS = Cytokine release syndrome; Gr = grade; ICANS = Immune effector cell-associated neurotoxicity syndrome.

1. Jacobson, et al. *Blood*. 2020;136 (Supplement 1): 40–42. 2. Locke FL, et al. *Lancet Oncol*. 2019;20(1):31-42. 3.Schuster S, et al. *N Engl J Med*. 2019;380(1):45-56. 4. Maziarz RT, et al. *Blood Adv*. 2020;4(4):629-637. 5. Abramson JS, et al. *Lance*t. 2020;396(10254):839-852.

ZUMA-7, TRANSFORM, & BELINDA

	ZUMA-7 [1]	TRANSFORM [2]	BELINDA [3]
Product	**Axi-cel vs. SOC**	**Liso-cel vs. SOC**	**Tisa-cel vs. SOC**
ORR (%)	83% vs. 50%	87% vs. 49%	75% vs. 68%
CR (%)	65% vs. 32%	74% vs. 43%	46% vs. 44%
mEFS	10.8 vs. 2.3 mos	NR vs. 2.4 mos	3.0 vs. 3.0 mos
EFS rate	4-year: 39% vs. 17%	18-month: 53% vs. 21%	---
mPFS	14.7 vs. 3.7 mos	NR vs. 6.2 mos	---
PFS rate	4-year: 42% vs. 24%	18-month: 58% vs. 29%	---
mOS	NR vs. 31.1 mos	NR vs. 29 mos	---

Cross-trial comparisons are for discussion purposes only

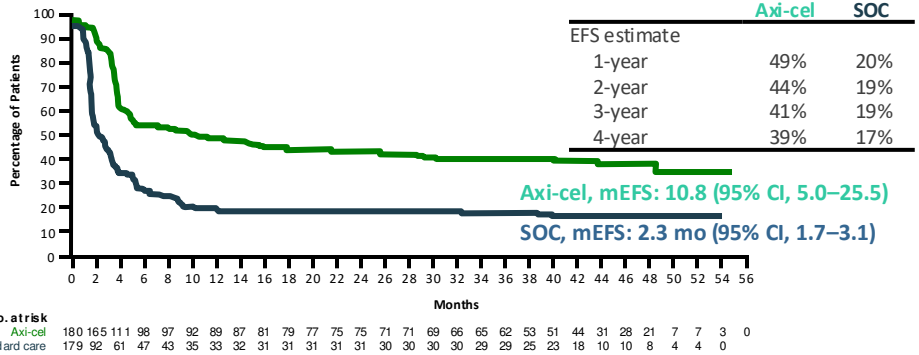
EFS = event-free survival; mEFS = median event-free survival; mOS = median overall survival; SOC = standard of care.

Locke FL, et al. *N Engl J Med.* 2022; 386(7):640-654. Westin JR, et al. *N Engl J Med.* 2023; 389(2):148-157.
Bishop MR, et al. *N Engl J Med.* 2021;386(7):386:629-639

ZUMA-7, TRANSFORM: EFS and OS

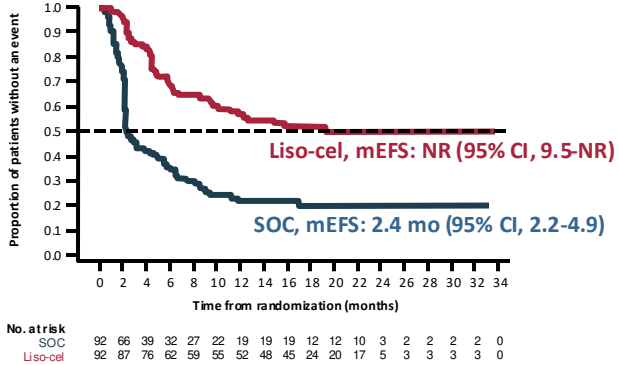
EFS

Stratified HR (hazard ratio), 0.42 (95% CI, 0.33-0.55)



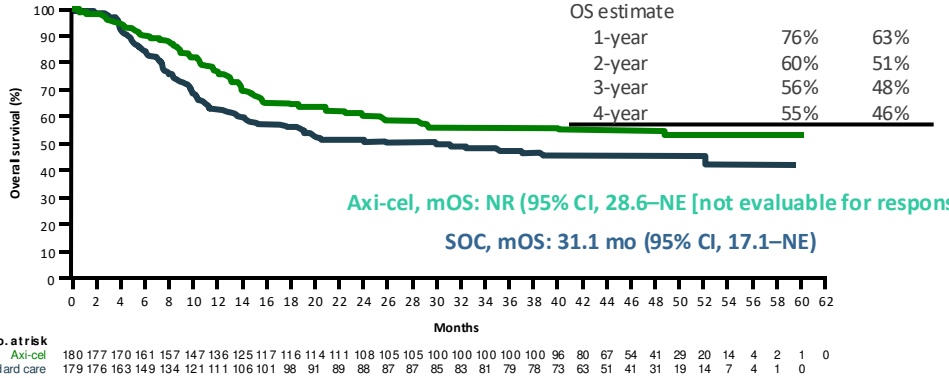
EFS estimate	Axi-cel	SOC
1-year	49%	20%
2-year	44%	19%
3-year	41%	19%
4-year	39%	17%

Stratified HR, 0.356 (95% CI, 0.243-0.522)



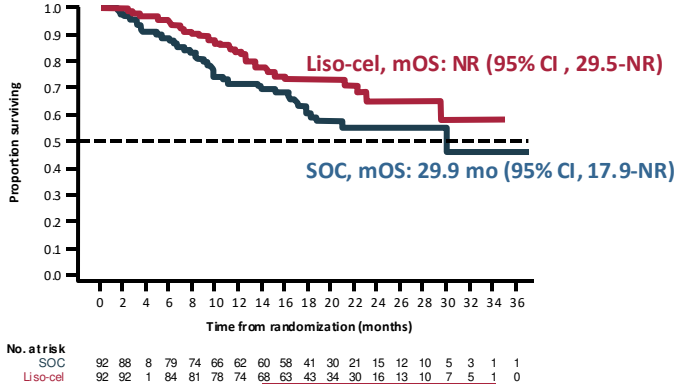
OS

Stratified HR, 0.73 (95% CI, 0.54-0.98); *P* = 0.03



OS estimate	Axi-cel	SOC
1-year	76%	63%
2-year	60%	51%
3-year	56%	48%
4-year	55%	46%

Stratified HR, 0.724 (95% CI, 0.443-1.183); *P* = 0.0987



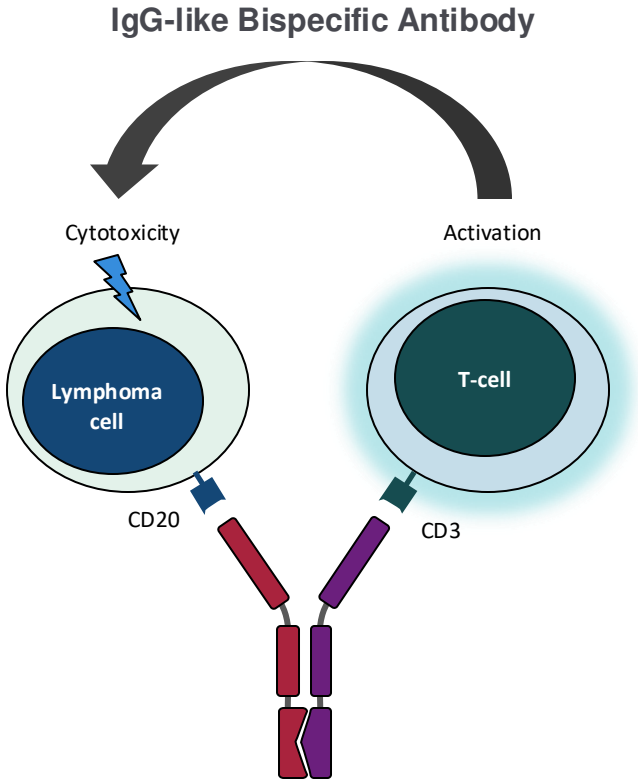
Cross-trial comparisons are for discussion purposes only

ZUMA-7

TRANSFORM

Westin JR, et al. *N Engl J Med*. 2023; 389(2):148-157. Abramson JS, et al. *Blood*. 2023; 141(14):1675-1684.

CD20 Bispecifics: Mechanism of Action

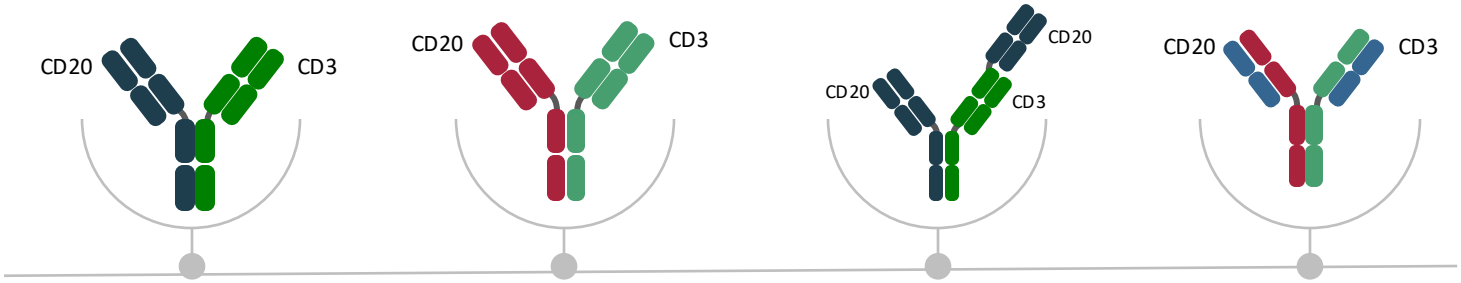


- Bivalent IgG-like, full-length Ab co-targeting CD20 (B-cells) and CD3 (pan-T-cell marker)
- Off-the-shelf availability
- Target different epitopes on CD20 (potential for co-administration with anti-CD20 antibodies)
- Fc mutations to avoid: ADCC, CDC, or fratricidal killing of anti-tumor T-cells
- Preserved neonatal FcR binding for prolonged half-life
- Cytotoxicity occurs in an MHC-independent manner
- Share pharmacokinetic properties with mAbs

FcR = FC receptor; IgG = immunoglobulin G; MHC = major histocompatibility complex.

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

Comparison of CD20 Bispecifics: Structure and Function



Bispecific Ab:	Mosunetuzumab	Epcoritamab	Glofitamab	Odronextamab
Status:	Approved for 3+L FL	Approved for 3+L LBCL and FL	Approved for 3+L LBCL	(Approved in EU for DLBCL and FL)
Format:	IgG1	IgG1	IgG1	IgG4
Technology:	Knobs-into-holes (different Fabs)	Controlled Fab-arm exchange	Head-to-tail fusion	Heavy chains with different affinity
CD20:CD3 ratio:	1:1	1:1	2:1	1:1

EU = Europe.

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

Comparison of CD20 Bispecifics: Safety and Efficacy

	Glofitamab[1,2]	Epcoritamab[3,4]	Odronextamab[5]	Mosunetuzumab[6]
Trial	(NCT03075696)	**GEN3013** (NCT03625037)	**ELM-2**	**GO29781** (NCT02500407)
Status	Phase II; **FDA approved for LBCL in the 3rd line and beyond**	Phase I/II; **FDA approved for LBCL in the 3rd line and beyond**	Phase II	Phase I/II
LBCL Patient Population	N = 155	N = 157	N = 130	N = 129
Median Prior Therapies	3	3	3	3
ORR	52%	59%	49%	35%
CRR	40%	41%	31%	19%
PFS	Median: 4.9m	Median 4.2m	Median: 4.4m	Median: 1.4m
Median DoCR	29.8m	36.1m	18m (CAR T naïve pts) NR (Post-CAR T pts)	22.8m
Any grade CRS/NT	64%/*15%	50%/6%	54%/0%	27%/NR
Grade ≥ 3 CRS	4%	3%	7%	1%
Grade ≥ 3 NT	3%	1%	0%	1%

Cross-trial comparisons are for discussion purposes only

DoCR = duration of complete response; NT = neurologic toxicities

1. Falchi, et al. *J Clin Oncol*. 2023;41(16):144-146. 2. Dickinson MJ, et al. American Society of Hematology (ASH). 2024. Abstract No. 865. https://ash.confex.com/ash/2024/webprogram/Paper194333.html
3. Thieblemont C, et al. *J Clin Oncol*. 2023; 41(12): 2238–2247. 4. Vose M, et al. American Society of Hematology (ASH). 2024. Abstract No. 4480. https://ash.confex.com/ash/2024/webprogram/Paper198714.html
5. Kim WS, et al. American Society of Hematology (ASH). 2024. Abstract No. 444. Budde LH, et al. *J Clin Oncol*. 2022; 40(5):481-491.

Enhancing Bispecific Antibodies: Synergistic Benefits of Combination Therapies

ECHELON-3 - Brentuximab Vedotin Combination

Randomized, double-blind, multicenter, phase III study (n=230); Compared BV + Len + R (n=112) vs placebo + Len + R (n=118) with a median follow-up of 16.4 months

Key Eligibility Criteria

- R/R DLBCL - after ≥ 2 prior therapy
- Patients must be HSCT/CAR-T cell therapy ineligible
- ECOG PS ≤ 2

Primary endpoint: Overall Survival

Secondary endpoints: PFS, ORR

Safety Run-in period
6 patients will receive brentuximab, lenalidomide, and rituximab; safety and PK data from at least 3 patients will be randomized portion of study

Randomized 1:1;CCI

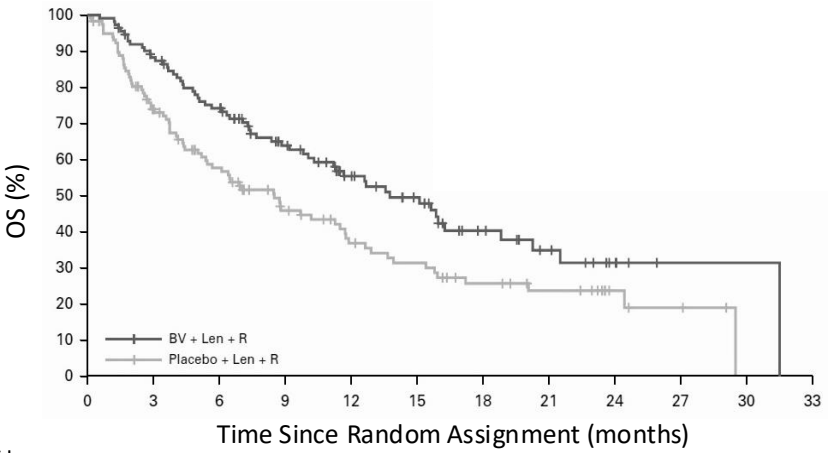
Brentuximab vedotin 1.2 mg/kg every 3 weeks, lenalidomide 20 mg daily, and rituximab on Cycle 1 followed by rituximab and hyaluronidase human beginning Cycle 2 for every 3 weeks

Placebo every 3 weeks, lenalidomide 20 mg daily, and rituximab on Cycle 1 followed by rituximab and hyaluronidase human beginning Cycle 2 for every 3 weeks

PET*/CT
Blinded central review
Scan at baseline, then every 6 weeks from randomization until Week 48 (± 7 days), then every 12 weeks (± 7 days) thereafter, unless progression is suspected.

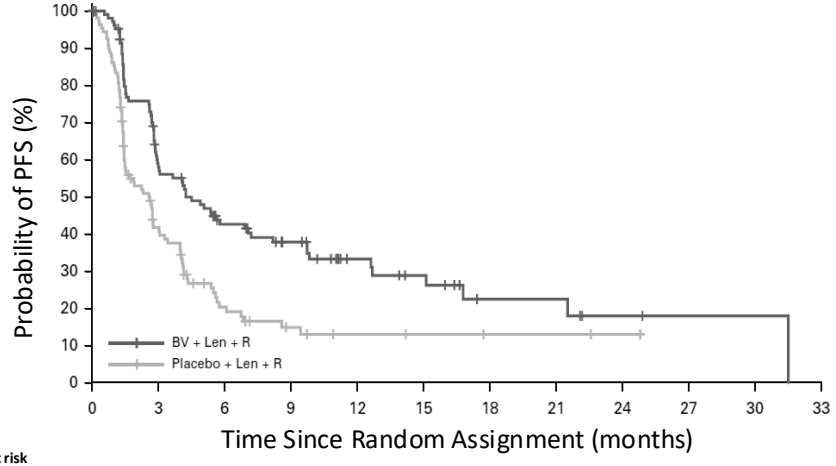
Bartlett NL, et al. *J Clin Oncol*. 2025;CO2402242.

ECHELON-3 – Response Rates



No. at risk												
BV + Len + R	112	96	79	57	40	30	17	11	5	1	1	0
Placebo + Len + R	118	81	58	39	28	23	16	12	5	3	0	0

BV + Len + R demonstrated significant OS benefit vs. placebo + Len + R, with △ORR of 22% and △CR of 21%



No. at risk												
BV + Len + R	112	58	38	27	15	11	5	5	2	1	1	0
Placebo + Len + R	118	40	16	8	4	3	2	2	1	0	0	0

BV + Len + R had a PFS of 4.2 months vs. placebo + Len + R of 2.6 months ($p < 0.001$)

Bartlett NL, et al. *J Clin Oncol*. 2025;CO2402242.

ECHELON-3 – Safety Summary

Patients	BV + Len + R (n = 112), No. (%)		Placebo + Len + R (n = 116), No. (%)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any adverse event	109 (97)	99 (88)	113 (97)	89 (77)
Neutropenia	52 (46)	48 (43)	37 (32)	32 (28)
Thrombocytopenia	36 (32)	28 (25)	25 (22)	22 (19)
Diarrhea	35 (31)	5 (4)	27 (23)	2 (2)
Anemia	32 (29)	25 (22)	31 (27)	24 (21)
Fatigue	27 (24)	7 (6)	20 (17)	3 (3)
COVID-19	26 (23)	8 (7)	18 (16)	6 (5)
Asthenia	24 (21)	4 (4)	14 (12)	3 (3)
Peripheral sensory neuropathy	22 (20)	5 (4)	9 (8)	0
Pneumonia	19 (17)	12 (11)	8 (7)	6 (5)
Constipation	19 (17)	2 (2)	21 (18)	0
Decreased appetite	19 (17)	1 (1)	11 (9)	0
Nausea	17 (15)	1 (1)	19 (16)	1 (1)
Pyrexia	17 (15)	2 (2)	17 (15)	1 (1)
Hypokalemia	15 (13)	6 (5)	9 (8)	3 (3)
Febrile neutropenia	10 (9)	10 (9)	11 (9)	11 (9)
Neutrophil count decreased	9 (8)	9 (8)	7 (6)	7 (6)
COVID-19 pneumonia	8 (7)	8 (7)	4 (3)	4 (3)

Most common TEAEs are neutropenia, thrombocytopenia, diarrhea, and anemia

Bartlett NL, et al. *J Clin Oncol*. 2025;CO2402242.

STARGLO: Glofit + GemOx vs R-GemOx in 2L Transplant-Ineligible DLBCL

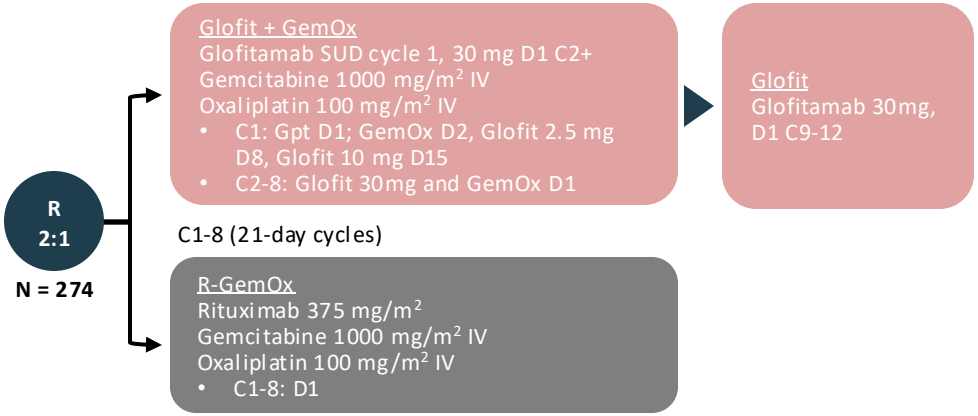
Study Design and Patient Characteristics

Study Design (Phase III)

Key Eligibility Criteria

- R/R DLBCL NOS after ≥ 1 prior therapy
- Patients with 1 prior LOT must be ASCT ineligible
- ECOG PS 0-2

- Primary endpoint: OS
- Secondary endpoints: PFS, CR, DOCR (all by IRC), AEs



Patient Characteristics		Glofit + GemOx (n = 183)	R-GemOx (n = 91)
Median age (range), years		68.0 (22-88)	68.0 (20-84)
Age ≥ 65 years, n (%)		116 (63.4)	56 (61.5)
ECOG PS, n (%)	0	72 (40.0)	44 (50.0)
	1	89 (49.4)	36 (40.9)
	2	19 (10.6)	8 (9.1)
Ann Arbor stage, n (%)	I/II	60 (32.8)	20 (22.0)
	III/IV	123 (67.2)	70 (76.9)
Prior LOT, n (%)	1	115 (62.8)	57 (62.6)
	≥ 2	68 (37.2)	34 (37.4)
Refractory status, n (%)	Primary	106 (57.9)	47 (51.6)
	To last therapy	112 (61.2)	54 (59.3)
Bulky disease (≥ 10cm), n (%)		23 (12.6)	14 (15.4)
COO at initial diagnosis, n (%)	GCB	60 (32.8)	29 (31.9)
	Non-GCB (including ABC)	103 (56.3)	50 (54.9)
Prior CAR T-cell therapy, n (%)		13 (7.1)	8 (8.8)

Abramson J, et al. EHA 2024. Abstract No. LBA3438.

STARGLO: Glofit + GemOx vs R-GemOx in 2L Transplant-Ineligible DLBCL

Efficacy and Safety

Efficacy

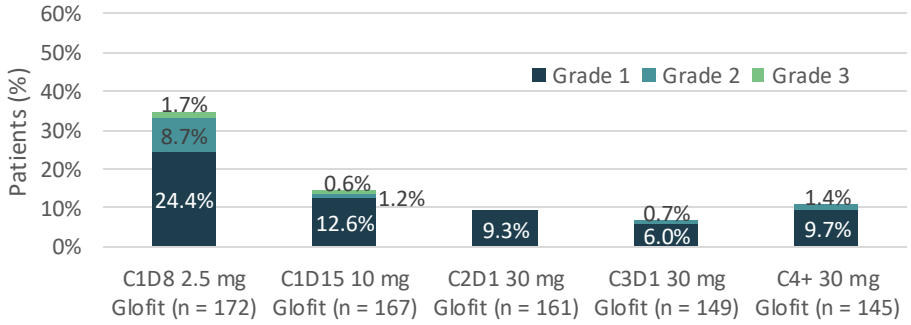
Response rates, %	Glofit + GemOx (n = 183)	R-GemOx (n = 91)
Overall response rate	68	41
CR	59	25
PR	10	15

OS Analyses	Glofit + GemOx (n = 183)	R-GemOx (n = 91)
Median (95% CI), months	25.5 (18.3-NE)	12.9 (7.9-18.5)
24-month (95% CI), %	52.8 (44.8-60.7)	33.5 (22.2-44.9)
Median follow-up	20.7 months	

PFS Analyses	Glofit + GemOx (n = 183)	R-GemOx (n = 91)
Median (95% CI), months	13.8 (8.7-20.5)	3.6 (2.5-7.1)
12-month (95% CI), %	51.7 (44.0-59.4)	25.2 (13.6-36.9)
Median follow-up	16.1 months	

Safety

Safety Summary	Glofit-GemOx (n = 180)	R-GemOx (n = 88)
Median cycles (range), n	11 (1-13)	4 (1-8)
Any grade AEs, n (%)	180 (100)	84 (95.5)
R/Glofit related	149 (82.8)	58 (65.9)
Serious AEs, n (%)	98 (54.4)	15 (17.0)
R/Glofit related	62 (34.4)	7 (8.0)
Grade 3-5 AEs, n (%)	140 (77.8)	36 (40.9)
R/Glofit related	85 (47.2)	20 (22.7)
Grade 5 AEs, n (%)	15 (8.3)	4 (4.5)
R/Glofit related	5 (2.8)	1 (1.1)
AE leading to tx discontinuation	48 (26.7)	11 (12.5)



Abramson J, et al. EHA 2024. Abstract LBA3438.

EPCORE NHL-2 (Arm 5): Epcor + GemOx in 2L Transplant-Ineligible DLBCL

Study Design and Patient Characteristics

Study Design (Phase I/II)

Key Eligibility Criteria

- R/R CD20+ DLBCL[a]
- Eligible for GemOx
- Ineligible for ASCT or prior ASCT failure
- ECOG PS 0-2

- Primary endpoint: Assess antitumor activity
- Secondary endpoints: DOR, DOCR, TTR, PFS, OS, TEAEs

Epcor SC + GemOx IV, 28-day cycles
C1-3: Epcor SC 48 mg QW,[b] GemOx[c] IV Q2W
C4: Epcor SC 48 mg Q2W,[b] GemOx[c] IV Q2W
C5-9: Epcor SC 48 mg Q2W[b]
C10+ until progression[d]: Epcor SC 48 mg Q4W[b]

[a]De novo or histologically transformed from FL or nodal marginal zone lymphoma based on World Health Organization 2016 classification. [b]SUD 1: priming, 0.16 mg; SUD 2: intermediate, 0.8 mg. [c]GemOx, gemcitabine 1000 mg/m^2 IV + oxaliplatin 100 mg/m^2 IV. [d]Tumor response evaluated by PET-CT obtained at 6, 12, 18, 24, 36, and 48 wk, and every 24 wk thereafter. [e]Refractory disease is defined as disease that either progressed during therapy or progressed within 6 mo of completion of therapy.

Patient Characteristics

	N = 103
Median age (range), years	72 (20-87)
ECOG PS, n (%)	
0	33 (32)
1	57 (55)
2	13 (13)
Ann Arbor stage III/IV, n (%)	81 (79)
Median lines of prior therapy (range)	2 (1-6)
Prior ASCT, n (%) Relapsed ≤ 12 mo after ASCT, n/n (%)	10 (10) 5/10 (50)
Primary refractory[e] disease, n (%)	54 (52)
Refractory[e] to last systemic therapy, n (%)	72 (70)
Refractory to ≥ 2 consecutive lines of therapy, n (%)	38 (37)
Prior CAR T therapy, n (%)	29 (28)

Brody J, et al. ASCO 2024. Abstract No. 7037. Córdoba R, et al. EHA 2024. Abstract No. P1152.

EPCORE NHL-2 (Arm 5): Epcor + GemOx in 2L Transplant-Ineligible DLBCL

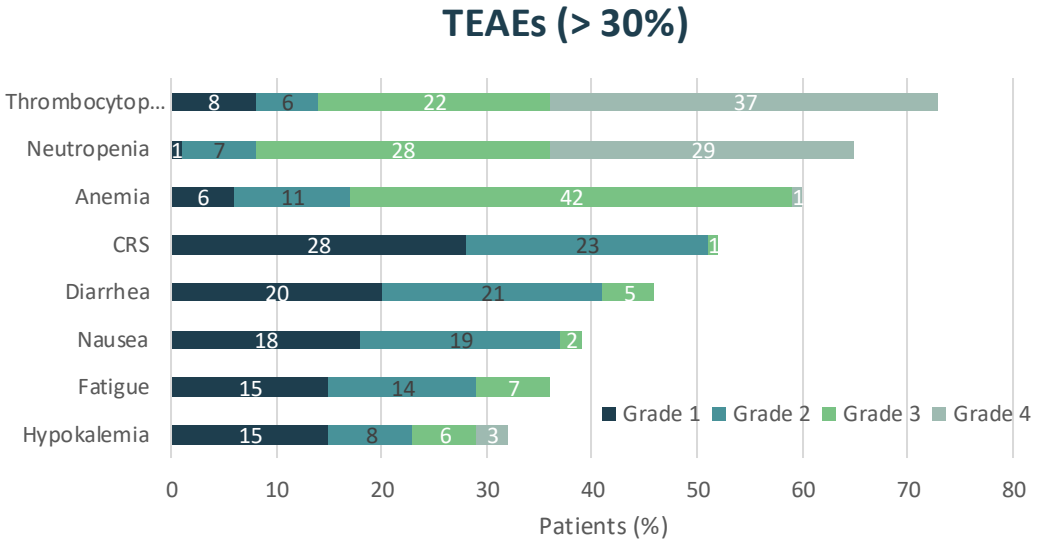
Efficacy and Safety

Efficacy

Best Overall Response (ICR), %	IRC Assessment N = 103[b]
Overall response rate	85
CR	61
PR	24
Median time to response (range), mo	1.5 (0.9-3.0)
Median time to CR (range), mo	2.6 (1.3-22.1)

Efficacy among complete responders	n = 63
PFS rates	
9-mo PFS rate, %	85
15-mo PFS rate, %	57
OS rates	
9-mo OS rate, %	94
15-mo OS rate, %	77
Probability of remaining in CR	
9-mo probability, %	73
15-mo probability, %	56

[a]Five patients were not evaluable for response per investigator.
[b]Four patients were not evaluable for response per IRC.



- ICANS was reported in 3 patients (grade 1-3, n = 1 each); all events resolved and 1 patient discontinued treatment due to ICANS
- There were no instances of clinical tumor lysis syndrome
- 13 patients experienced grade 5 TEAEs
- CRS was primarily low grade (52% overall, 28% grade 1, 23% grade 2, 1% grade 3) and had predictable timing, with most events occurring following the first full dose (median time to onset after first full dose, 2 days)
- CRS events all resolved (median time to resolution, 2.5 days) and did not lead to epcoritamab discontinuation

Brody J, et al. ASCO 2024. Abstract No. 7037. Córdoba R, et al. EHA 2024. Abstract No. P1152.

Redefining Treatment: Novel Agents in Chemo-Free Regimens

Mosunetuzumab plus Polatuzumab

Objectives

- Efficacy and safety of Mosun-Pola
- Primary endpoint: Best ORR1 by IRC

R† 1:1

†Stratified by no. of prior therapies (1 vs ≥ 2)

Mosun (SC)-Pola (N = 40)

	C1	C2	C3 – C6	C7 – C8
Mosun	D1 5mg; D8 45mg; D15 45mg	D1 45mg	D1 45mg	D1
Pola	Pola	Pola	Pola	

R-Pola (N = 40)

	C1	C2	C3 – C6	C7 – C8
	D1	D1	D1	D1
	Rituximab	Rituximab	Rituximab	Rituximab
	Pola	Pola	Pola	

Chavez JC, et al. *Blood*. 2024;144(1):989.

Mosunetuzumab plus Polatuzumab (cont.)

Baseline characteristics and prior treatment exposure

n (%), unless stated	Mosun-Pola (n = 40)	R-Pola (n = 40)
Median age, years (range)	71.5 (36-87)	67.5 (24-92)
Gender, male	25 (62.5)	24 (60.0)
Race		
Asian	1 (2.5)	0
Native Hawaiian or other	0	1 (2.5)
White	38 (95.0)	39 (97.5)
Unknown	1 (2.5)	0
Ethnicity		
Hispanic or Latino	5 (12.5)	11 (27.5)
Not Hispanic or Latino	35 (87.5)	25 (62.5)
Not stated/unknown	0	4 (10.0)
IPI score*		
0-1	9 (22.5)	8 (20.0)
2-3	22 (55.0)	24 (60.0)
4-5	9 (22.5)	8 (20.0)
ECOG PS*		
0	17 (42.5)	20 (50.0)
1-2	23 (57.5)	19 (47.5)
Histology		
DLBCL	27 (67.5)	33 (82.5)
HGBCL	10 (25.0)	6 (15.0)
FL Grade 3b	3 (7.5)	1 (2.5)
trFL	5 (12.5)†	9 (22.5)‡

n (%), unless stated	Mosun-Pola (n = 40)	R-Pola (n = 40)
Ann Arbor stage III-IV	31 (77.5)	34 (85.0)
Cell-of-origin	n = 37	n = 39
GCB	22 (59.5)	25 (64.1)
Non-GCB (by GEP or IHC)	14 (37.8)	11 (28.2)
Unknown	1 (2.7)	3 (7.7)
Double/triple-hit status	n = 37	n = 39
Double/triple-hit	8 (21.6)	3 (7.7)
Non-double/triple-hit	29 (78.4)	36 (92.3)
Bulky disease, > 7.5 cm	8 (20.0)	10 (25.0)
Extranodal involvement	24 (60.0)	29 (72.5)
Number of prior lines of therapy		
Median (range)	2 (1-5)	3 (1-9)
1	13 (32.5)	12 (30.0)
≥ 2	27 (67.5)	28 (70.0)
Prior ASCT	6 (15.0)	9 (22.5)
Prior CAR T-cell therapy△	14 (35.0)	15 (37.5)
Refractory to CAR T-cell therapy▲	10 (71.4)	12 (80.0)
Primary refractory#	20 (50.0)	24 (60.0)
Early relapse**	5 (12.5)	4 (10.0)

The **median number of cycles** received for each drug were: Mosun, 8 (range: 1-8) plus **Pola**, 6 (range 1-6); **R,** 4 (range: 1-8) plus **Pola**, 4 (range: 1-6)

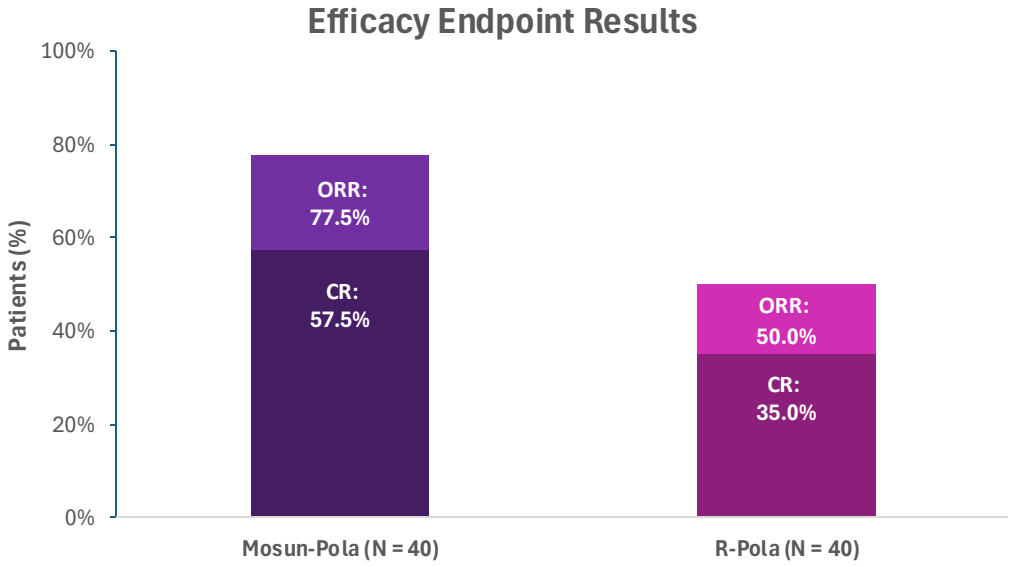
*For one patient in the Mosun-Pola arm, IPI and ECOG PS data were captured after the snapshot. †Four parts with DLBCL and one pt with HGBCL had trFL. ‡Eight pts with DLBCL and one pt with HGBCL had trFL. △Pts were eligible for the study if CAR T-cell therapy was > 30 days from start of treatment. ▲Defined as relapse < 6 months from CAR T-cell therapy. #Relapse < 6 months after 1L therapy. **Relapse 6-12 months after 1L therapy.

1l = first line; ASCT = autologous stem cell transplant; CAR = chimeric antigen receptor; ECOG PS = Eastern Cooperative Oncology Group performance status; GCB, germinal-derived B cells; IPI = international Prognostic Index; GEP = gene expression profiling; IHC = immunohistochemistry.

Chavez JC, et al. *Blood*. 2024;144(1):989.

Mosun plus Pola - Response Rates

Best response rates by IRC assessment



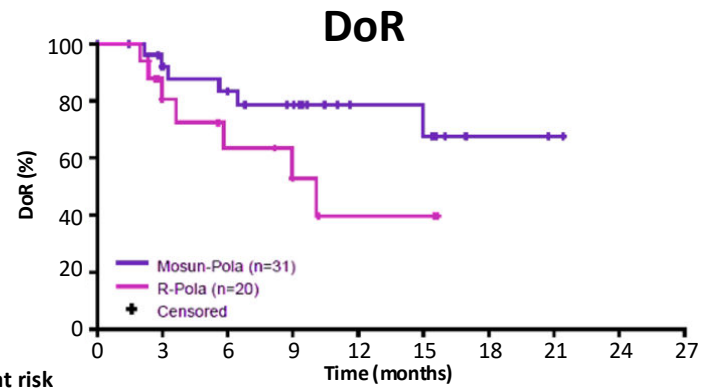
Mosun-Pola demonstrated improved efficacy vs. R-Pola, with △ORR of 27.5% and △CR of 22.5%

Data cut-off date: January 30, 2024. PR = partial response.
Mosun-Pola = mosunetuzumab plus polatuzumab vedotin; R-Pola = rituximab plus polatuzumab vedotin

Chavez JC, et al. *Blood.* 2024;144(1):989.

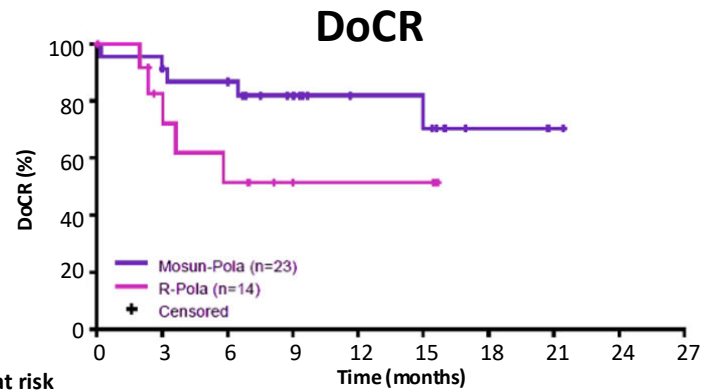
Mosun plus Pola - Response Rates (cont.)

DoR and DoCR by IRC assessment



No. at risk										
Mosun-Pola	31	22	19	15	7	6	2	1	NE	NE
R-Pola	20	10	7	5	2	2	NE	NE	NE	NE

	Mosun-Pola (N = 31)	R-Pola (N = 20)
Median DoR, months (95% CI)	NE (15.0 – NE)	10.1 (3.6 – NE)
Hazard ratio (95% CI), *p*-value*	0.40 (0.13 – 1.19), *p* = 0.0869	
6-month event-free rate, % (95% CI)	83.4 (68.4 – 98.3)	63.4 (37.1 – 89.8)
9-month event-free rate, % (95% CI)	78.7 (62.1 – 95.4)	52.8 (23.9 – 81.8)



No. at risk										
Mosun-Pola	23	20	19	13	7	6	2	1	NE	NE
R-Pola	14	8	5	3	2	2	NE	NE	NE	NE

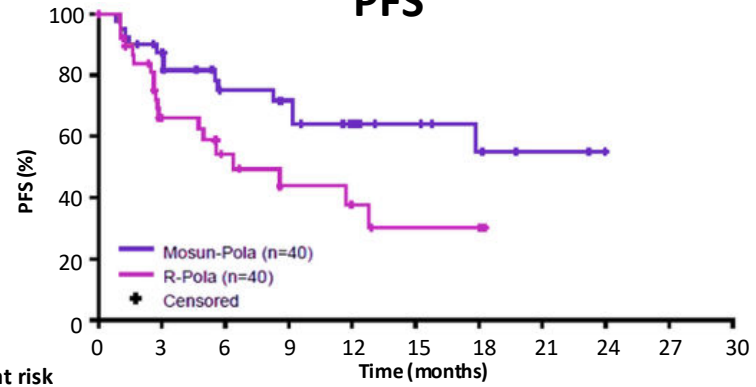
	Mosun-Pola (N = 23)	R-Pola (N = 14)
Median DoCR, months (95% CI)	NE (15.0 – NE)	NE (3.0 – NE)
Hazard ratio (95% CI), *p*-value*	0.38 (0.11 – 1.32), *p* = 0.1130	
6-month event-free rate, % (95% CI)	86.7 (72.8 – 100.0)	51.6 (20.6 – 82.5)
9-month event-free rate, % (95% CI)	81.9 (65.8 – 98.0)	51.6 (20.6 – 82.5)

Mosun-Pola demonstrated durable responses versus R-Pola (median follow-up† 18 months);data are still immature and longer follow-up is needed

Data cut-off date: January 30, 2024. *P-values are two sided and descriptive. †The median follow-up was estimated using the reverse KM method for OS.
DoR = duration of response; KM = Kaplan-Meier; NE = non evaluable; OS = overall survival.
Chavez JC, et al. *Blood.* 2024;144(1):989.

Mosun plus Pola - PFS and OS Outcomes

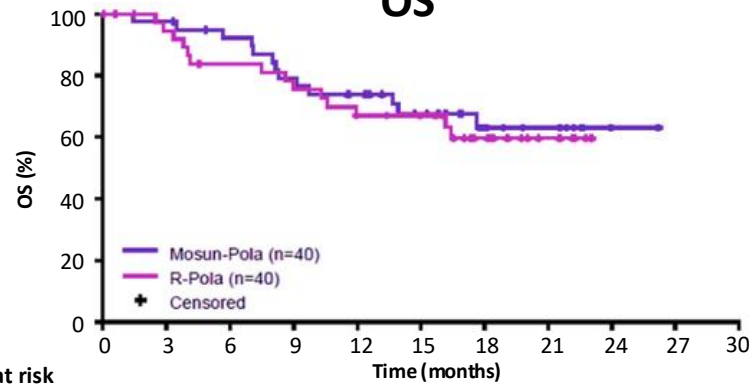
PFS



No. at risk											
Mosun-Pola	40	32	22	19	13	9	6	2	NE	NE	NE
R-Pola	40	18	11	7	5	3	3	NE	NE	NE	NE

	Mosun-Pola (N = 40)	R-Pola (N = 40)
Median PFS, months (95% CI)	NE (9.2 – NE)	6.4 (4.7 – NE)
Hazard ratio (95% CI), *p*-value†	0.45 (0.22 – 0.92), *p* = 0.0250	
9-month event-free rate, % (95% CI)	71.7 (56.6 – 86.8)	43.8 (24.4 – 63.3)
12-month event-free rate, % (95% CI)	64.2 (47.4 – 80.9)	37.6 (17.4 – 57.7)

OS



No. at risk											
Mosun-Pola	40	39	35	30	27	21	12	7	1	NE	NE
R-Pola	40	35	30	27	23	21	12	5	NE	NE	NE

	Mosun-Pola (N = 40)	R-Pola (N = 40)
Median OS, months (95% CI)	NE (17.6 – NE)	NE (16.2 – NE)
Hazard ratio (95% CI), *p*-value†	0.85 (0.40 – 1.80), *p* = 0.6644	
9-month event-free rate, % (95% CI)	79.1 (66.2 – 92.0)	75.4 (61.4 – 89.4)
12-month event-free rate, % (95% CI)	73.8 (59.9 – 87.8)	67.0 (51.7 – 82.3)

Encouraging PFS and OS rates were observed at 12 months

Data cut-off: January 30, 2024. *Results from pts who crossed over from R-Pola to Mosun-Pola were not censored. In total, 20 pts on R-Pola received crossover treatment with Mosun-Pola.
†P-values are double sided and descriptive.
Chavez JC, et al. *Blood*. 2024;144(1):989.

Mosun plus Pola - Safety and CRS Summary

AE Summary, N (%)	Mosun-Pola (N = 40)	R-Pola (N = 39)
AE Treatment -related	40 (100.0) 37 (92.5)	39 (100.0) 33 (84.6)
Grade 3/4 AE Treatment-related	22 (55.0) 11 (27.5)	20 (51.3) 11 (28.2)
Grade 5 AE* Treatment-related	2 (5.0) 1 (2.5)	1 (2.6) 0
AE leading to treatment discont.† Treatment-related	3 (7.5) 1 (2.5)	2 (5.1) 2 (5.1)
SAE Treatment-related	13 (32.5) 4 (10.0)	10 (25.6) 0

CRS by ASTCT Criteria	Mosun-Pola (N = 40)
Any grade, N (%)** Grade 1 Grade 2 Grade ≥ 3	4 (10.0) 3 (7.5) 1 (2.5) 0
Median CRS duration, days (range)	3 (2 – 5)
Median time to onset, days (range)	2 (2 – 3)
CRS Management, N (%) Corticosterouds Tocilizumab Low-flow oxygen	 4 (10.0) 1 (2.5) 1 (2.5)
Events resolved, %	100

Diarrhea, neutropenia and fatigue are the common AEs see in both groups and had a few treatment-related discontinuations

CRS rates with Mosun-Pola were infrequent, of low grade, and limited to Cycle 1

Data cut-off date: January 30, 2024. *Two pts on Mosun-Pola with COVID-19 (one treatment related), and one patient on R-Pola with hepatic failure (non-treatment related). †Three pts on Mosun-Pola: two pts with peripheral neuropathy (both grade 2; one Pola related) and one with Grade 5 COVID-19 pneumonia; two pts on R-Pola: one patient with peripheral neuropathy (Grade 1, treatment related) and one patient with pain in extremity and peripheral neuropathy (both Grade 2, the latter treatment related).**All events occurred during Cycle 1

AE = adverse event; ASTCT = American Society for Transplantation and Cellular Therapy; SAE = serious adverse event.

Chavez JC, et al. *Blood*. 2024; 144 (1):989, Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-38

Glofitamab plus Polatuzumab

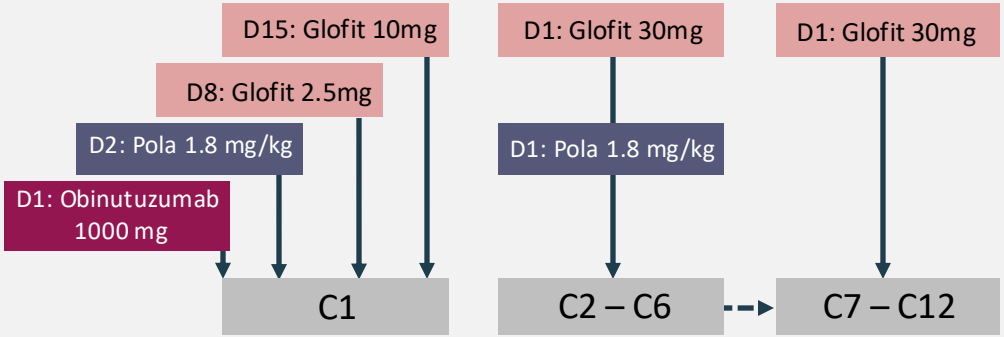
Key Inclusion Criteria

- DLBCL, HGBCL, trFL, or PMBCL
- ECOG PS 0 – 2
- ≥ 1 prior therapies, including anti-CD20 antibody, CAR T-cell therapy

Glofitamab IV Administration

Fixed-duration treatment:
- Up to 12 cycles

CRS mitigation:
- Obinutuzumab IV pre-treatment
- C1 step-up dosing
- 24-hour hospitalization with first glofit dose (C1D8)



Baseline characteristics

n (%), unless stated	N=129
Median age, years (range)	67.0 (23–84)
Gender, male	82 (63.6)
ECOG PS	
0–1	122 (94.6)
2	7 (5.4)
Disease type	
DLBCL	57 (44.2)
HGBCL*	44 (34.1)
DHL/THL†	29 (22.5)
trFL	26 (20.2)
PMBCL	2 (1.6)
Ann Arbor stage III–IV	99 (76.7)
Cell-of Origin†	
GCB	62 (48.1)
Non-GCB (by IHC or GEP)	39 (30.2)
Unknown	28 (21.7)

n (%), unless stated	N=129
Bulky disease >7.5cm	38 (29.5)
IPI score	
0–1	26 (20.2)
2–3	70 (54.3)
4–5	33 (25.6)
Median lines of prior therapy, n (range)	2 (1.0–7.0)
1	53 (41.1)
2+	76 (58.9)
Prior anti-CD20 therapy	127 (98.4)
Refractory to prior anti-CD20 therapy	97 (75.2)
Prior CAR T-cell therapy	28 (21.7)
Refractory to prior CAR T-cell therapy	22/28 (78.5)
Refractory to any prior therapy	102 (79.1)
Primary refractory‡	80 (62.0)
Refractory to last line of prior therapy	92 (71.3)
Early relapse§	6 (4.7)

The patient population was heavily pre-treated and highly refractory to prior therapy. Median number of treatment cycles received: Glofit 10.5 (range 1 – 17), Pola 6 (range 1 – 12)

HGBCL – high-grade B-cell lymphoma; PMBCL = primary mediastinal B-cell lymphoma

Hutchings M, et al. *Blood*. 2024;144(suppl 1):988.

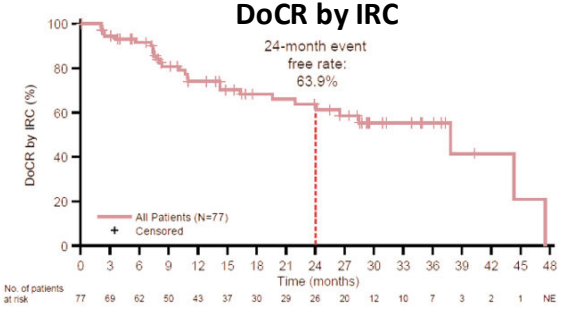
Glofit plus Pola - Response Rates

64% of complete responders **had ongoing response** and a **PFS rate of > 40%** at 24 months

N (%) [95% CI]	By INV N = 129	By IRC N = 129
ORR	104 (80.6) [72.7 – 87.1]	101 (78.3) [70.2 – 85.1]
CR	80 (62.0) [53.1 – 70.4]	77 (59.7) [50.7 – 68.2]
PR	24 (18.6) [12.3 – 26.4]	24 (18.6) [12.3 – 26.4]
PD	16 (12.4) [7.3 – 19.4]	16 (12.4) [7.3 – 19.4]
DOR, median (months) [95% CI]	24.3 [15.0 – 37.8]	26.4 [10.9 – 44.3]

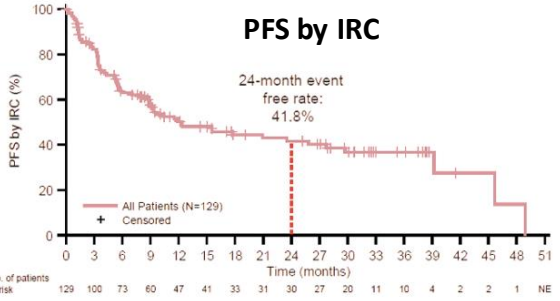
Impressive responses observed (66% CR) amongst patients with HGBCL

DoCR by IRC



	N = 77
Median DoCR, months (95% CI)	37.8 (24.1 – NE)
24-month DoCR event-free rate, % (95% CI)	63.9 (51.4 – 76.4)

PFS by IRC



	N = 129
Median PFS, months (95% CI)	12.3 (8.8 – 27.7)
24-month PFS event-free rate, % (95% CI)	41.8 (32.2 – 51.5)

Hutchings M, et al. Blood. 2024;144(suppl 1):988.

Glofit plus Pola - Safety and CRS Summary

AE profile is consistent with known toxicity profiles of individual drugs

AE summary, n (%)	N = 129
AE	128 (99.2)
Grade 3–4 AE	76 (58.9)
Grade 5 (fatal) AE*	12 (9.3)
AE leading to treatment discontinuation	
Glofit	16 (12.4)
Pola	11 (8.5)
Serious AE	79 (61.2)

CRS, neutropenia and diarrhea are the commonly reported AEs (in ≥10% of patients) and is consistent with known toxicity profiles of individual drugs.

Clinical cut-off date: September 2, 2024. * COVID-19 (n = 3 [2.3%]), Covid-19 pneumonia (n = 2 [1.6%]), progressive multifocal leukoencephalopathy, sepsis, adenocarcinoma pancreas, adenocarcinoma gastric, lung adenocarcinoma, acute myeloid leukemia, CRS (n = 1 [0.8%] each).

CRS events were mainly low-grade, occurred early during step-up dosing, and resolved within ~ 2 days

N (%)	N = 126*
CRS by grade†	**56 (44.4)**
Grade 1	35 (27.8)
Grade 2	19 (15.1)
Grade 3	1 (0.8)
Grade 4	0
Grade 5	1 (0.8)‡
Median time to CRS after glofitamab dose, hours (range)	
2.5 mg	16.3 (5.4-42.1)
10 mg	34.6 (8.9-86.0)
30 mg	36.2 (18.5-55.9)
CRS management	
Tocilizumab	19 (33.9)
Corticosteroids	8 (14.3)
Fluids	13 (23.2)
Single pressor	2 (3.6)
Low flow oxygen	11 (19.6)
High flow oxygen	1 (1.8)
Intensive care unit	3 (5.4)

Clinical cut-off date: September 2, 2024. *Glofitamab exposed patients. †By ASTCT grade. ‡Occurred in the context of unresolved infection, patient declined further CRS management at Grade 3.

CRS events were low-grade, occurred early during step-up dosing, and resolved within 2 days

Hutchings M, et al. Blood. 2024;144(suppl 1):988.

EPCORE NHL-5 Trial - Epcoritamab Plus Lenalidomide

Multicenter, open-label phase Ib/II study; current analysis of arm 1 after median follow-up of 11.5 months

Key endpoints: dose-limiting toxicities (DLTs), overall response rate (ORR), complete response (CR) rate, duration of response (DOR), time to response, and safety

Variable	Total N = 46
Age, median (range), y	71 (26-85)
≥ 75 y, n (%)	16 (35)
Male, n (%)	25 (54)
Race, N (%)	
White	36 (78)
Asian	9 (20)
Black/African American	1 (2)
Ethnicity, n (%)	
Non-Hispanic or Latino	44 (96)
Hispanic or Latino	2 (4)
Ann Arbor stage, n (%)	
I-II	15 (33)
III	8 (17)
IV	23 (50)
NHL subtype, n (%)	
DLBCL	42 (91)
FL grade 3b	3 (7)
Triple-hit lymphoma	1 (2)
Refractory disease, n (%)	
Primary refractory	28 (61)
Refractory to ≥ consecutive lines of anticancer therapy	15 (33)

Variable	Total N = 46
Extranodal disease at screening, n (%)	30 (65
ECOG PS, n (%)	
0	31 (67)
1	14 (30)
2	1 (2)
R-IPI, n (%)	
0	2 (4)
1-2	18 (39)
3-5	22 (48)
Unknown or missing	4 (9)
Prior lines of anticancer therapy, n (%)	
1	20 (43)
2	16 (35)
3	7 (15)
≥ 4	3 (7)
Number of prior lines of anticancer Therapy, median (range)	2 (1-4)
Time from end of last prior anticancer therapy to first epcoritamab dose, median (range), mo	4.6 (0.6-150.6)
Prior systemic therapies, n (%)	
Prior CAR T therapy	12 (26)
Prior stem cell transplant	5 (11)

*Percentages may not add up to 100 due to rounding.
Date cutoff July 5, 2024.

ECOG PS = Eastern Cooperative Oncology Group Performance Status Scale; R-IPI = Revised International Prognostic Index.

Gurion R, et al. *Blood*. 2024;144(1):3110.

EPCORE NHL-5 - Response Rates

Response rate[a], %	N = 45
ORR	64.4
CR	46.7
PR	17.8
SD	8.9
PD	22.2
NE	4.4

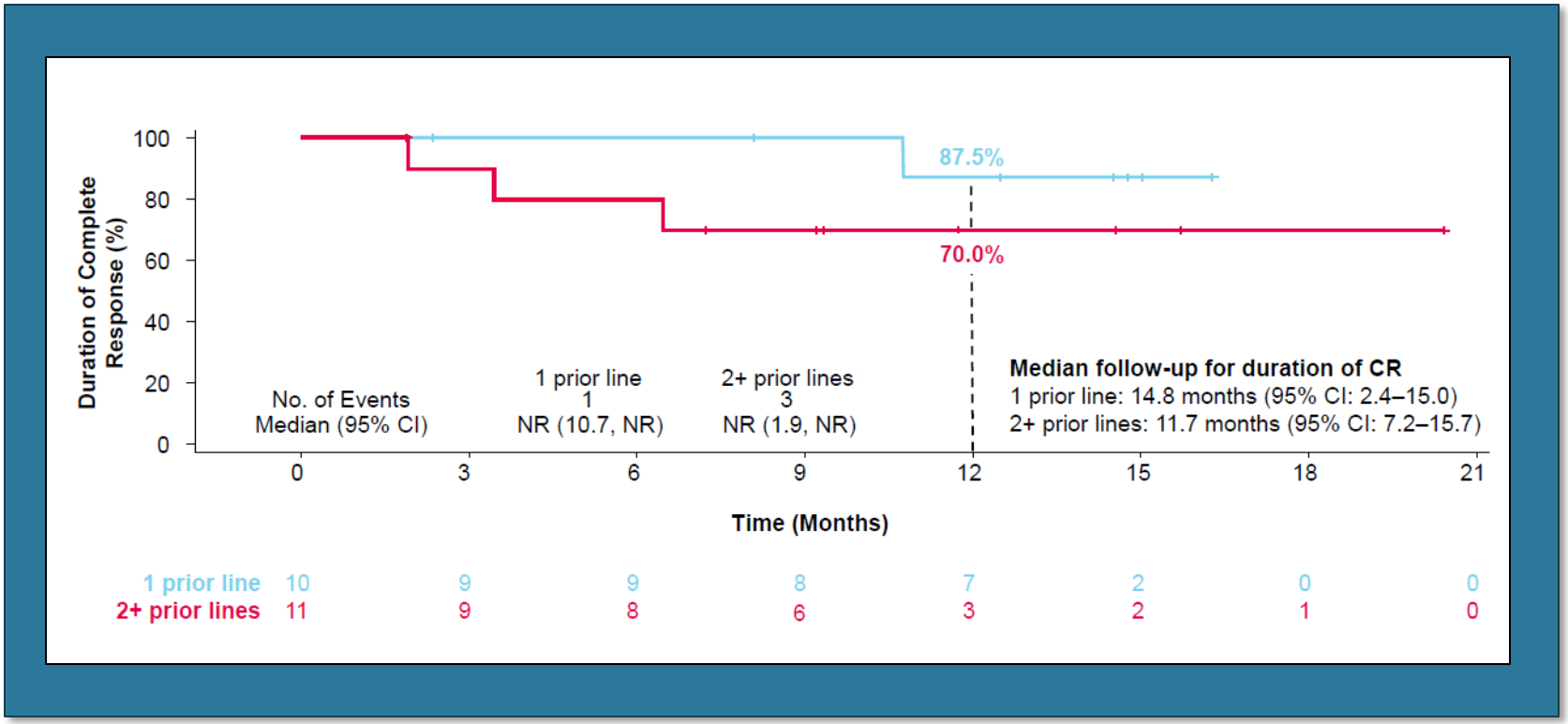
Data cutoff: July 5, 2024.
[a]Based on response-evaluable population, defined as patients with measurable disease at baseline and ≥1 postbaseline disease evaluation or who had died within 60 days of the first dose of study drug without a postbaseline assessment.

Subgroup	Patients, n	CR rate[a], % (95% CI)
All patients	45	46.7 (31.7-62.1)
Age		
< 75	30	40.0 (22.7-59.4)
≥ 75	15	60.0 (32.3-83.7)
Prior lines of therapy		
1 line	19	52.6 (28.9-75.6)
≥ 2 lines	26	42.3 (23.4-63.1)
Prior CAR T experience		
Yes	12	50.0 (21.1-78.9)
No	33	45.5 (28.1-63.6)
Primary refractory status		
Yes	27	37.0 (19.4-57.6)
No	18	61.1 (35.7-82.7)

Clinically meaningful responses were observed

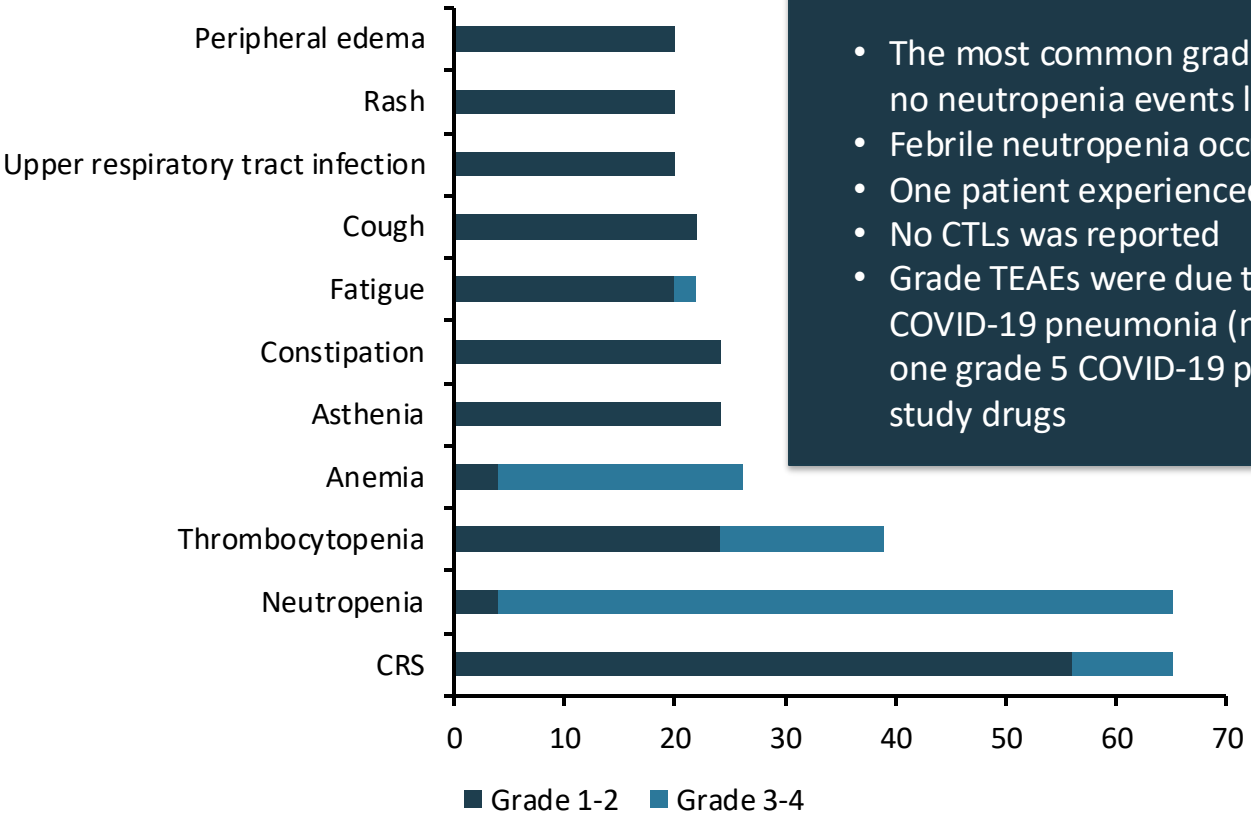
CI = confidence intervals; ORR = overall response rate; PD = progressive disease; SD = standard disease.
Gurion R, et al. *Blood*. 2024;144(1):3110.

EPCORE NHL-5 - Response Rates



Gurion R, et al. *Blood*. 2024;144(Supplement 1):3110.

CRS Events with Epcoritamab Plus Lenalidomide were Mainly Low Grade and Less Frequent with Prophylactic Dexamethasone (DEXA) vs. Other Corticosteroid



- The most common grade ≥ 3 TEAE was neutropenia (61%); no neutropenia events let to epcoritamab discontinuation
- Febrile neutropenia occurred in 2 (4%) patients
- One patient experienced grade 3 ICANS, which resolved
- No CTLs was reported
- Grade TEAEs were due to disease progression (n = 4), COVID-19 pneumonia (n = 1), and septic shock (n = 1); one grade 5 COVID-19 pneumonia was considered related to study drugs

CTLs = cytotoxic T lymphocytes; TEAEs = treatment emergent adverse events.

R. Gurion, et al. *Blood*. 2024;144(1):3110-3110.

LOTIS-7 Trial

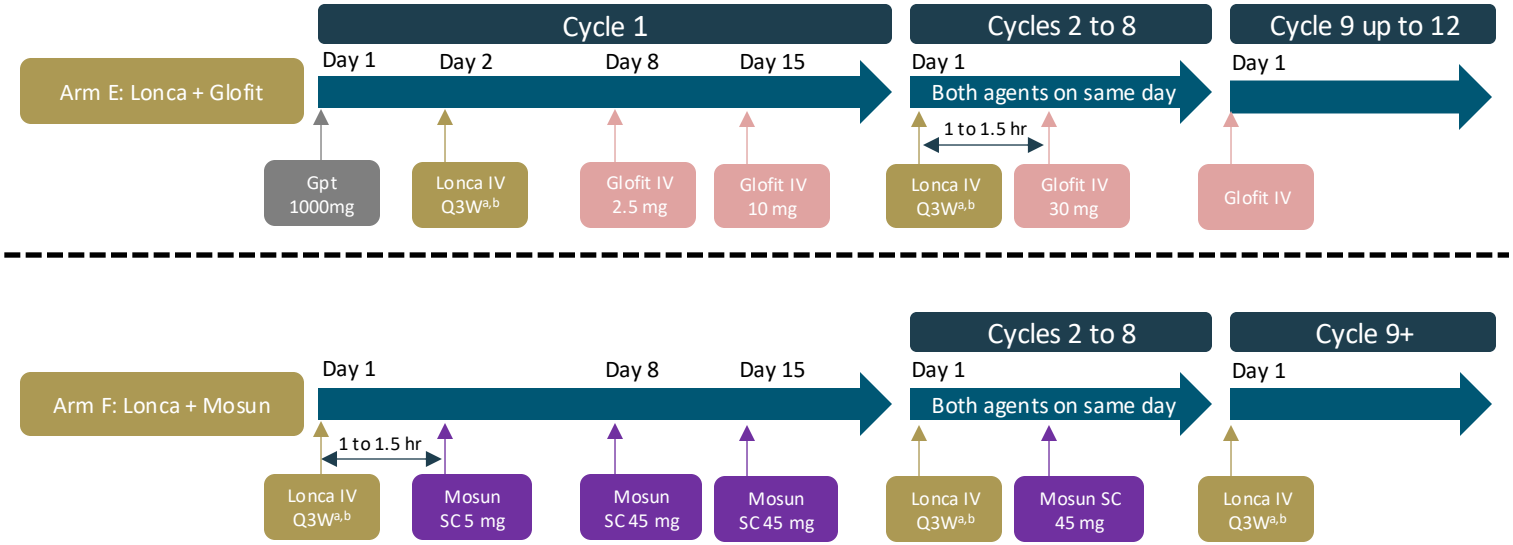
Phase Ib trial of **loncastuximab** in combination with other anticancer agents in R/R B-NHL

Primary Endpoints

- Safety and tolerability of loncastuximab in combination with glofitamab or mosunetuzumab
- MTD and/or RDE for the combination of agents (dose-escalation, part 1)

Secondary Endpoints

- Efficacy: ORR, DOR, CRR, PFS, RFS, OS
- Pharmacokinetics
- Immunogenicity



[a]Dose level 1 µg/kg; dose level 2, 120 µg/kg; and 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.

PR Newswire. 2024. https://www.prnewswire.com/news-releases/adc-therapeutics-announces-positive-initial-data-from-lotis-7-clinical-trial-evaluating-zynlonta-in-combination-with-bispecific-antibody-in-patients-with-relapsedrefractory-diffuse-large-b-cell-lymphoma-302328090.html/.

LOTIS-7 Trial

Baseline characteristics	n = 29
Median age (years (range)) Sex, n (%) Male	73 (26,88) 20 (69%)
ECOG Performance Status 0 1 2	 17 (58.6%) 12 (41.4%) 0
LBCL Histology DLBCL trFL HGBCL FL Grade 3b	 14 (48.3%) 6 (20.7%) 4 (13.8%) 1 (3.4%)
IPI Score 0/1/2 3/4/5	 15 (51.7%) 14 (48.3%)
Ann Arbor stage I/II III/IV Missing	 5 (17.2%) 23 (79.3%) 1 (3.4%)
Bulky disease > 6cm > 10cm	 7 (24.2%) 1 (3.4%)
Median prior lines of therapy 1 ≥ 2	2(1-5) 11 (37.9%) 18 (62.1%)
Prior CAR-T Therapy	7 (24.1%)
Refractory to primary therapy	15 (51.7%)
Refractory to last prior therapy	18 (62.1%)

trFL = transformed follicular lymphoma.

PR Newswire. 2024. https://www.prnewswire.com/news-releases/adc-therapeutics-announces-positive-initial-data-from-lotis-7-clinical-trial-evaluating-zynlonta-in-combination-with-bispecific-antibody-in-patients-with-relapsedrefractory-diffuse-large-b-cell-lymphoma-302328090.html/

LOTIS-7 Trial - Initial Efficacy Results

	120 µg/kg		150 µg/kg		Total	
	n = 9	%	N = 9	%	N = 18	%
ORR (CR + PR)	**8**	89%	**9**	100%	**17**	94%
Complete Response (CR)	**6**	67%	**7**	78%	**13**	72%
Partial Response (PR)	**2**	22%	**2**	22%	**4**	22%
Stable Disease	**1**	11%	0	0%	**1**	6%
Progressive Disease	**0**	0%	0	0%	**0**	0%

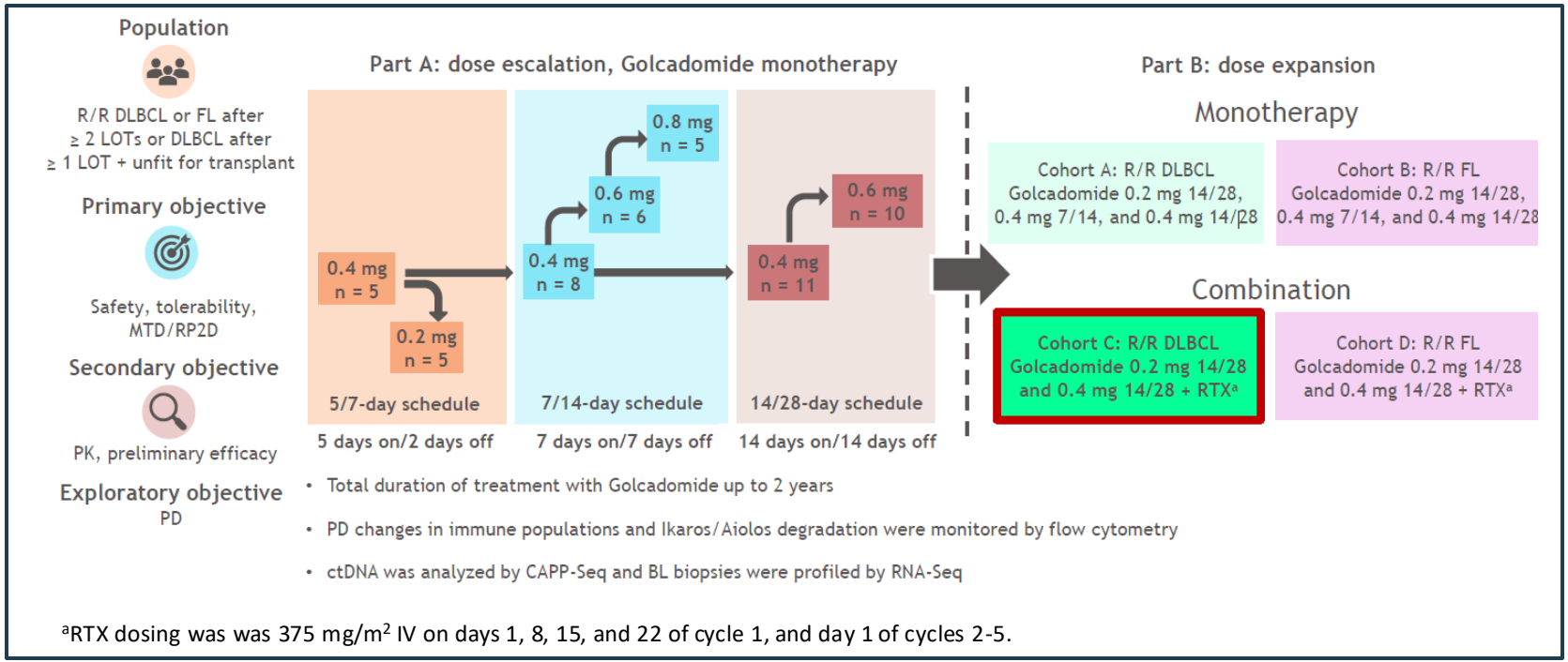
As of data cut off 20 Nov 2024. Note: Data extracted from live clinical database. Data is subject to change.

- Early efficacy data supports the combination of lonca with glofitamab in 2L+ DLBCL
- Encouraging efficacy data was observed across patients with different numbers of lines and types of prior treatments and across different histologies
- Next steps include fully enrolling 20 patients in each dosing arm

PR Newswire. 2024. https://www.prnewswire.com/news-releases/adc-therapeutics-announces-positive-initial-data-from-lotis-7-clinical-trial-evaluating-zynlonta-in-combination-with-bispecific-antibody-in-patients-with-relapsedrefractory-diffuse-large-b-cell-lymphoma-302328090.html/.

CC-99282-NHL-001 – Golcadomide ± Rituximab

Phase 1/2, multicenter, open-label, first-in-human, dose-escalation and expansion study evaluating golcadomide, a cereblon E3 ligase modulator (CELMoD™) agent ± rituximab in patients with relapsed/refractory diffuse large B-cell lymphoma.



[a]RTX dosing was was 375 mg/m^2 IV on days 1, 8, 15, and 22 of cycle 1, and day 1 of cycles 2-5.

BK = Burkitt lymphoma; CAPP-Seq = Cancer Personalized Profiling by deep Sequencing; ctDNA = circulating tumor DNA; LOT = line of therapy; MTD = maximum tumor diameter; PK = pharmacokinetics; RNA-seq = ribonucleic acid sequencing; RP2D = recommended phase 2 dose;RTX = rituximab.

Michot JM, et al. American Society of Hematology (ASH). 2024. Abstract No. 869. https://ash.confex.com/ash/2024/webprogram/Paper203163.html.

CC-99282-NHL-001 – Golcadomide ± Rituximab

Cohort C enrolled a heavily pretreated patient population

Characteristic	Golcadomide 0.2 mg + RTX (N = 39)	Golcadomide
Age, median (range), years	65.0 (20-86)	68.5 (21-78)
Sex, male, n (%)	24 (62)	24(63)
Diagnosis, n (%)		
DLBCL	39 (100)	37 (97)
Double-hit[a] / triple-hit[b]-positive	6 (16)	13 (34)
FL grade 3b	-	1 (3)
Stage III-IV	30 (77)	31 (82)
Cell of origin, n (%)		
GCB	11 (28)	7 (18)
ABC / non-GCB	4 (10)	3 (8)
Unknown	24 (62)	28 (74)
ECOG PS score, n (%)		
0	12 (31)	16 (42)
1	24 (62)	17 (45)
2	3 (8)	5 (13)
Treatment history		
No. of prior LOTs, median (range)	4 (1-11)	4 (1-11)
Prior stem cell transplant, n (%)	4 (10)	7 (18)
Prior CAR T cell therapy, n (%)	21 (54)	20 (53)
Prior TCE, n (%)	11 (28)	10 (26)
Prior lenalidomide treatment, n (%)	10 (26)	10 (26)
Best response to last regimen		
CR or PR	12 (31)	15 (39)
Never achieved objective response	19 (49	15 (39.5)
Unknown	8 (21)	8 (21.1)

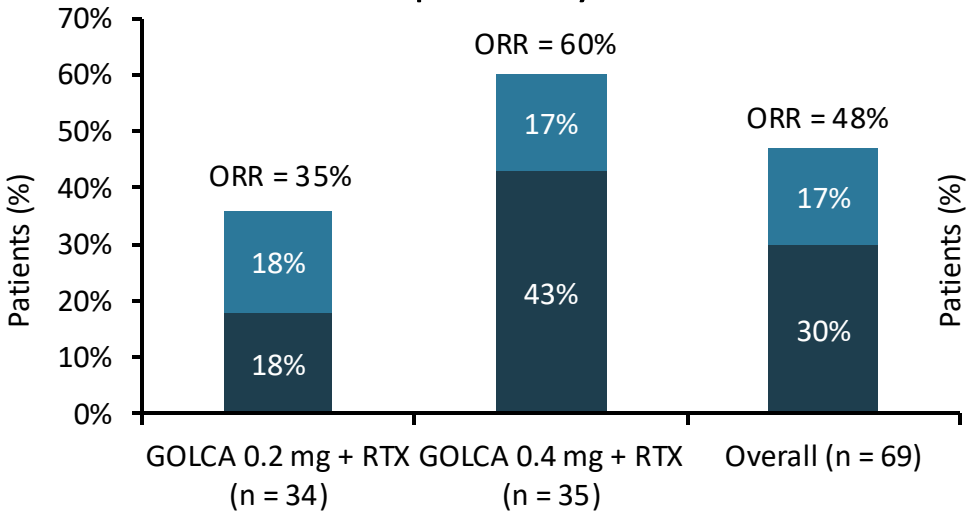
Data cutoff: September 13, 2024. Data are from the safety population of n = 77. [a]Double hit is defined as positive case of MYC + BCL2 or MYC + BCL6determined by FISH. [b] Triple hit is defined as positive case of MYC + BCL2 + BCL6 determined by FISH.

Michot JM, et al. American Society of Hematology (ASH). 2024. Abstract No. 869. https://ash.confex.com/ash/2024/webprogram/Paper203163.html.

CC-99282-NHL-001 – Golcadomide ± Rituximab

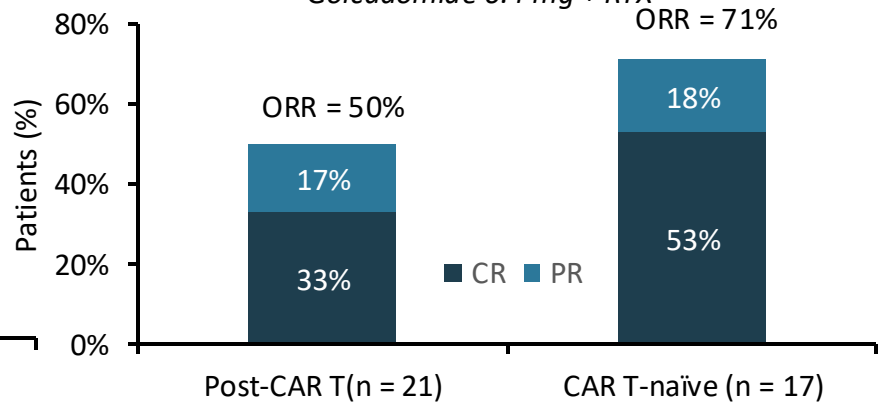
High ORR and CR was achieved with golcadomide + RTX in a heavily pre-treated patient population

Overall response by dose level[a]



Overall response by CAR-T cell therapy exposure[a]

Golcadomide 0.4 mg + RTX



- Median duration of golcadomide treatment in responders was 8 months (range, 3-24.2)
- Median follow-up in the efficacy-evaluable population was 5.85 months (range, 1.0-28.5)

Data cutoff: September 13, 2024. [a]Efficacy-evaluable population consisting of patients who completed ≥ 1 cycle of golcadomide (taking ≥ 75% of assigned doses) and having baseline and ≥ 1 post-baseline tumor assessments.

Michot JM, et al. American Society of Hematology (ASH). 2024. Abstract No. 869. https://ash.confex.com/ash/2024/webprogram/Paper203163.html.

CC-99282-NHL-001 – Golcadomide ± Rituximab

- Golcadomide-related AEs were mainly hematologic (neutropenia, anemia, thrombocytopenia) with low rates of non-hematologic AEs
- Neutropenia was managed with G-CSF administration and/or dose interruption
- Mean relative dose intensity was 91.3% with golcadomide 0.2 mg and 89.6% with golcadomide 0.4 mg

G-CSF = granulocyte colony-stimulating factor.

Michot JM, et al. American Society of Hematology (ASH). 2024. Abstract No. 869. https://ash.confex.com/ash/2024/webprogram/Paper203163.html.

CRS/ICANS Management for Lonca +Glofit

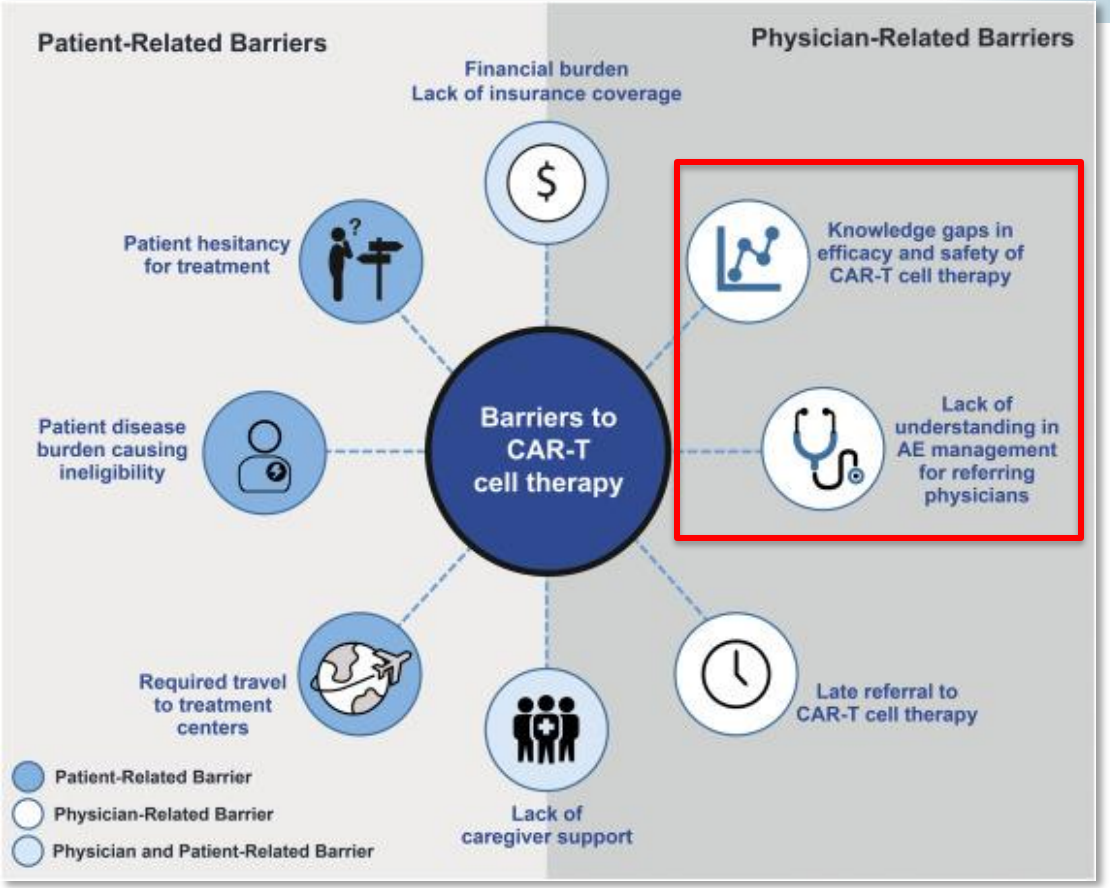
	90 µg/kg n=3	120 µg/kg n=13	150 µg/kg n=13	All n = 29
Cytokine Release Syndrome*				
Any grade	0	6 (46.2%)	4 (30.8%)	10 (34.5%)
Grade 1	0	5 (38.5%)	3 (23.1%)	8 (27.6%)
Grade 2	0	1 (7.7%)	1 (7.7%)	2 (6.9%)
Grade 3	0	0	0	0
ICANS *				
Any grade	0	1 (7.7%)	1 (7.7%)	1 (7.7%)
Grade 1	0	0	0	0
Grade 2	0	1 (7.7%)	1 (7.7%)	2 (6.9%)
Grade ≥3	0	0	0	0

*As per investigator reported adverse events

Data cutoff: 20 Nov 2024. Data extracted from live clinical database. Data is subject to change.

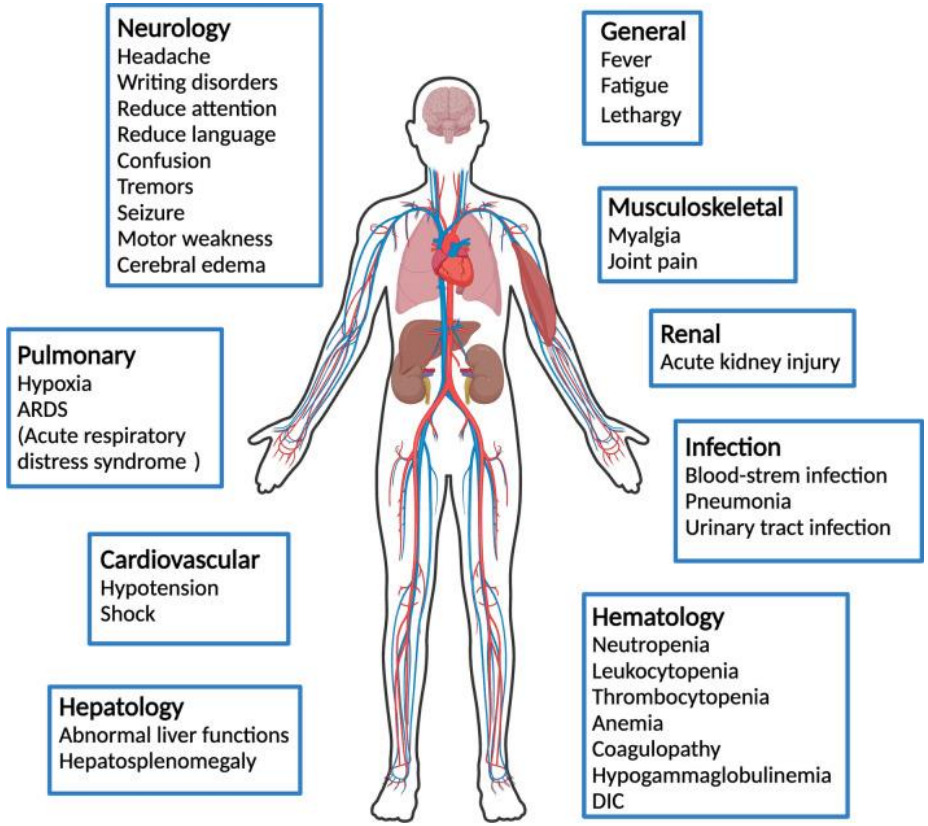
Challenges in AE Management as Part of Novel Treatments for R/R DLBCL

Barriers to CAR T-cell Therapy



Hoffmann, MS, et al. *Transplant Cell Ther*. 2023; 29:440-444

Immunotherapy Associated AEs



Systemic AEs

- Cytokine release syndrome (CRS)
- Immune effector cell associated neurotoxic syndrome (ICANS)
- Immune effector cell-associated hemophagocytic lymphohistiocytosis (HLH)-like syndrome (IEC-HS)
- Immune effector cell associated hematological toxicity (ICAHT)

Characterized by

- cytokine storm
- hyperinflammation

Differ mechanistically

- Variable cytokines and immune cells that drive pathophysiology

DIC = disseminated intravascular coagulation.

Yang C, Nguyen J, Yen Y. *J Biomed Sci*. 2023 Oct 21;30(1):89. Rejeski, K. et al. *Blood* (2021)138 (24):2499-2513.

Cytokine Release Syndrome (CRS)

- Grade 1: fever without hypotension or hypoxia, can be associated with constitutional symptoms such as myalgia and malaise.
- Grade 2: fever with hypotension and/or hypoxia requiring minimal support, such as fluids and low-flow nasal cannula, respectively.
- Grade 3: hypotension requiring one vasopressor and/or respiratory distress requiring high-flow nasal cannula or facemask.
- Grade 4: hypotension requiring more than one vasopressor (excluding vasopressin) and/or hypoxia requiring positive pressure ventilation including intubation
- Grade 5: death

ASTCT consensus statement includes fever as a necessary feature of all grades of CRS, and the maximum severity of hypotension or hypoxia defines the grade

ASTCT = The American Society for Transplantation and Cellular Therapy.

Lee DW, et al. *Biol Blood Marrow Transplant.* 2019;25(4):625–638. Santomasso BD, et al. 2021. *J Clin Oncol.* 39(35):3978–3992.

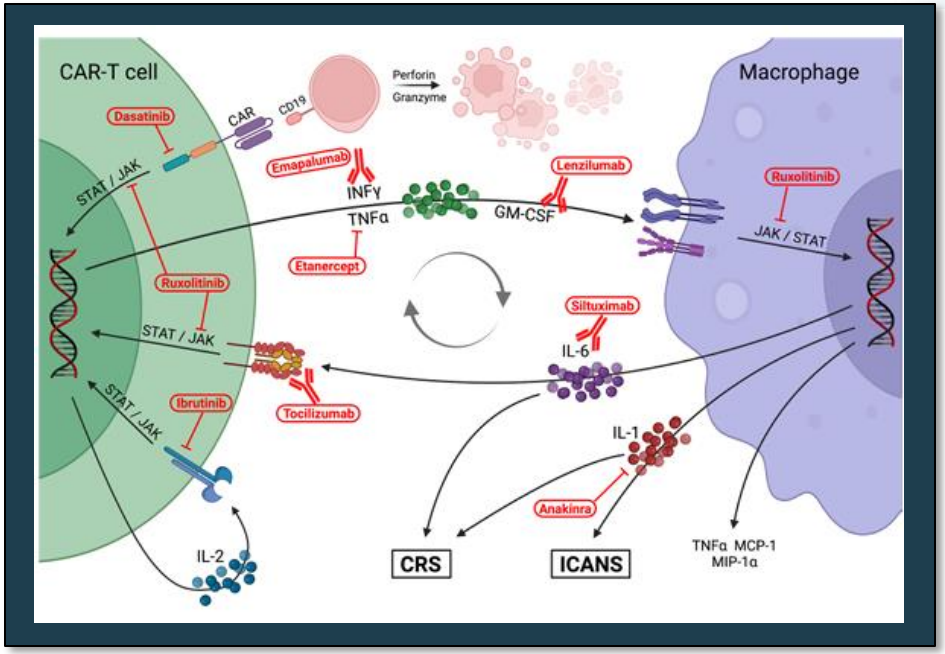
Immune Effector Cell-Associated Neurotoxicity (ICANS)

- Grade 1: ICE score > 6 with preserved alertness
- Grade 2: ICE score 3-6, mild somnolence but awakens to voice
- Grade 3: ICE score 0-2, somnolence responsive to tactile stimulation, brief seizure responsive to intervention, and/ or limited cerebral edema on imaging
- Grade 4: ICE score 0, profound somnolence, life-threatening prolonged seizure or status epilepticus, diffuse cerebral edema, and/or symptomatic intracranial hypertension
- Grade 5: death

Important risk factors for severe ICANS include high pre-infusion disease burden, history of neurologic disease, and development of severe CRS

Lee DW, et al. *Biol Blood Marrow Transplant.* 2019;25(4):625–638. Santomasso BD, et al. 2021. *J Clin Oncol.* 39(35):3978–3992.

Pathophysiology of CRS and ICANS



- Pathophysiology of CRS and ICANS caused by cross-talk between CAR-T cells and macrophages
- Several of the current and emerging therapies for CRS and ICANS are shown in their mechanism of action

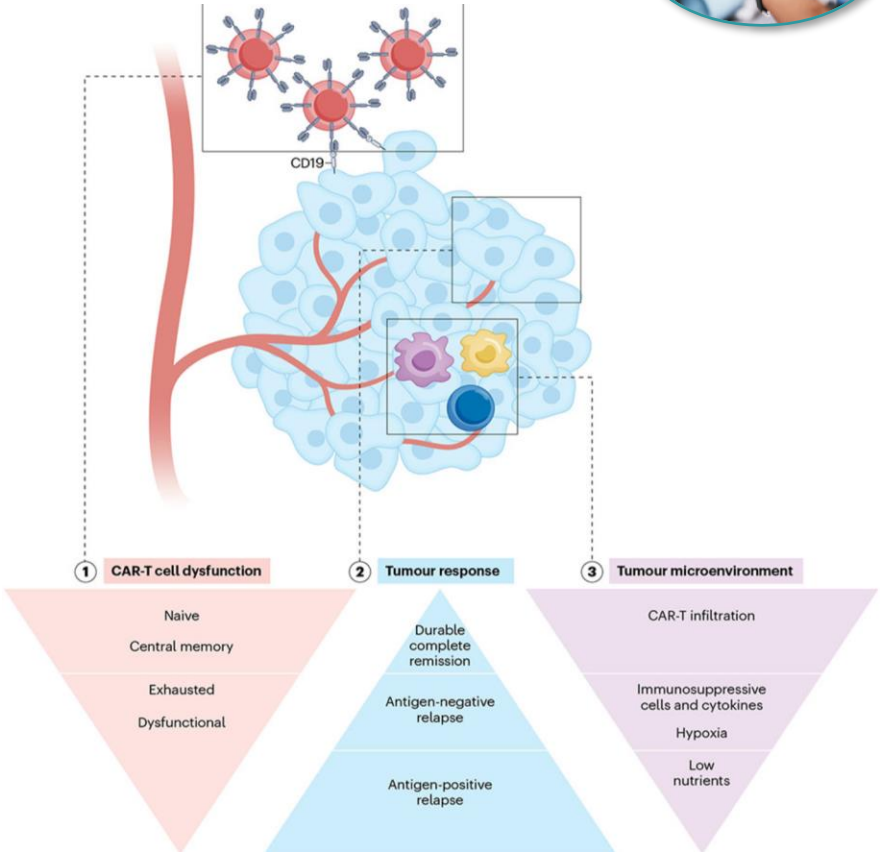
GM-CSF = Granulocyte-macrophage colony-stimulating factor; IL = interleukin; INFY = Interferon upsilon; JAK = janus kinase inhibitors; STAT = signal transducer and activator of transcription; TNFα = Tumor necrosis factor alpha.

Hughes AD, et al. *Semin Immunopathol*. 2024;46(3-4):5.

CAR T-cell Mechanisms of Resistance

Broadly related to CAR-T cell dysfunction

- Tumor-intrinsic resistance
- The surrounding immunosuppressive tumor microenvironment
- CAR-T cells from responders are characterized by a more naive and central memory phenotype, as opposed to exhausted or dysfunctional CAR-T cells from non-responders
    - A ‘hot’ tumor microenvironment with high CAR-T cell infiltration, polarization and trafficking is usually predictive of a better response



Ruella M, et al. *Nat Rev Drug Discov*. 2023;22(12):976–995.

Bispecific T-Cell Engager (BiTE) AEs

BUACC Management of Bispecific T-Cell Engager (BiTE) & CAR-T Toxicities

Lymphoma BiTEs		Epocoritamab[1,2]	Glofitamab [3]	Mosunetuzumab[4]
Treatment Details	REMS Program	NO	NO	NO
	Indication	DLBCL	DLBCL	Follicular Lymphoma
	Route	Subcutaneous	Infusion	Infusion
	Cycle Length	28 Days	21 Days	21 Days
	Inpatient Admission	Pt Specific, C1D15	Pt Specific, C1D8	Not Required
	Duration of Treatment	Until progression of unable to tolerate	Fixed-Duration	Fixed-Duration
	Length of Infusion Appt (schedule no later than)	C1 +/- CRS: 3Hr (1200) C2+: 1Hr (1530)	C1-2 +/- CRS: 6Hr (0900) C3+: 4Hr (1200)	C1-2 +/- CRS: 6Hr (0900) C3+: 4Hr (1200)
Standard Supportive Care	TLS Prophylaxis	NO	YES	NO
	Anti-Infectives	Acyclovir, SMZ/TMP (Trimethoprim / Sulfamethoxazole), Azole	Acyclovir, SMZ/TMP, Azole	Acyclovir, SMZ/TMP, Azole
	Dexamethasone PO	Cycle 1: Dex16mg QD x 3day after doses 1-4	N/A	N/A
Treatment Parameters	ICE Score (BH 9393) Required	YES, thru Cycle 2	YES, thru Cycle 3	YES, Cycle 3
	Post-Dose Observation	Not required per PI	Not required per PI	Not required per PI
	Dose Modifications	See PI for details	See PI for details	See PI for details
	Tociluzumab Procurement	YES, thru Cycle 2 (8mg/kg, MAX 800mg)	YES, thru Cycle 3 (8mg/kg, MAX 800mg)	YES, Cycle 3 (8mg/kg, MAX 800mg)
REQUIRED PRE-Medications (Complete steroid 60 minutes prior to giving BiTE)	1. Dexamethasone IV (ONLY)	Cycle 1	Cycles 1-3	Cycles 1-3
	2. Diphenhydramine IV/PO	Cycle 1	Cycles 1-3	Cycles 1-3
	3. Famotidine IV/PO	Cycle 1	Cycles 1-3	Cycles 1-3
	4. APAP 650-1000mg	Cycle 1	Cycles 1-3	Cycles 1-3
	5. IV Hydration	Cycle 1	Cycles 1-3	Cycles 1-3

1. Epcoritamab [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761324s000lbl.pdf
2. Vose, et al. American Society of Hematology (ASH). 2023. Abstract No. 1729. https://ash.confex.com/ash/2023/webprogram/Paper180333.html
3. Glofitamab [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761309s000lbl.pdf
4. Mosunetuzumab [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761263s000lbl.pdf

Bispecific T-Cell Engager (BiTE) Treatment Initiation

Lymphoma BiTEs		Epcoritamab[1,2]		Glofitamab [3]		Mosunetuzumab[4]	
TREATMENT SCHEDULE							
Step-Up Dosing Schedule	Cycle 1	C1D1	0.16mg Inj	C1D1 Obinutuzumab 1000mg		C1D1	1 mg
		C1D8	0.8mg	***C1D8 Inpatient***	2.5mg IVPB	C1D8	2 mg
		C1D15 Inpatient	**48mg**	C1D15 - 4 Hour	10mg	C1D15 - 4 Hr Infusion	60 mg
		C1D22	48mg	N/A		N/A	
	Cycle 2	D1, D8, D15, D22	48mg	C2D1 - 2 Hour	30mg	C2D1 - 2 Hr Infusion	60 mg
	Cycle 3	D1, D8, D15, D22	48mg	C3D1	30mg	C3D1 - 2 Hr Infusion	30 mg
	C4+ Schedule	C4-9: D1, D15 every 28D		C4-C8: D1 every 21D		C4-C8: D1 every 21D, CR > Stop	
		C10+: D1 every 28D		C8-17: D1 every 21D		If PR, C9-C17: D1 every 21D	

1. Epcoritamab [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761324s000lbl.pdf
2. Vose, et al. American Society of Hematology (ASH). 2023. Abstract No. 1729. https://ash.confex.com/ash/2023/webprogram/Paper180333.html
3. Glofitamab [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761309s000lbl.pdf
4. Mosunetuzumab [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761263s000lbl.pdf

Established Therapies for CRS

	Agent	Rationale	Comments
First Line	Tocilizumab	IL-6 is released by macrophages in CRS	• Well established as frontline treatment for CRS • Early treatment shown to be more effective than late • Can repeat doses q8h if insufficient response to first dose
Second Line	Corticosteroids (CS)	CS achieve broad immunosuppression	• Evidence mounting that steroids do not impair CAR-T efficacy, but conflicting reports remain • Methylprednisolone preferred for more severe CRS • Dexamethasone preferred with concomitant ICANS • Earlier start of CS associated with lower cumulative doses required
Third Line	Anakinra	IL-1 found to play a primary role in mediating CRS	• Increasing use for all CAR-T-related toxicities. • Attractive safety profile • Dose can be modulated to effect, which allows for • weaning off with recovery

Hughes, AD, et al. *Seminars in Immunopathology*. 2024;46:5.

Emerging Therapies for CRS

Agent	Rationale	Comments
Emapalumab	• IFNγ shown to mediate CRS/ICANS in preclinical model	• Successfully used in small numbers of patients with refractory CRS
Siltuximab	• Role of IL-6 well established in CRS	• Scattered reports of use for higher grade CRS refractory to tocilizumab
Dasatinib	• Tyrosine kinase inhibitor that blocks signal transduction through T cell receptor, shown in preclinical study to suppress CAR-T cell activation	• Clinical trial currently accruing (NCT04603872) testing dasatinib combined with CART therapy • Also being studied as an agent to "rest" CAR-T to reverse exhaustion
Ibrutinib	• Tyrosine kinase inhibitor that blocks IL-2 signaling, reduces cytokine release by T cells	• Concurrent administration of ibrutinib with CD19 CAR-T in small number of patients with CLL resulted in lower CRS severity without statistical difference in CART expansion or disease control
Ruxolitinib	• JAK/STAT mediates signaling by several pro-inflammatory cytokines important in CRS	• Case reports have demonstrated activity of ruxolitinib in refractory CRS
Etanercept	• TNFα elevated during CRS	• Since case report of treatment of CRS after BCMA CART showing efficacy and no impedance of CART activity

BCMA = B-cell maturation antigen.

Hughes, AD, et al. *Seminars in Immunopathology*. 2024;46:5.

Emerging Preemptive Therapies for CRS

Agent	Rationale	Comments
Tocilizumab	• Earlier tocilizumab administration results in less severe CRS, therefore, pre-emptive treatment may have an even greater effect	• Single arm trial administered tocilizumab with onset of grade 1 CRS for patients with higher tumor burden getting CTL019 and found near 50% reduction in severe CRS without impacting efficacy or CAR-T persistence compared to historical controls
Anakinra	• Preclinical model demonstrated that IL-1 inhibition prevented severe CRS and ICANS	• Clinical trial currently underway (NCT04148430) studying anakinra for prevention of CRS and ICANS in adults receiving CD19-directed CAR-T
Lenzilumab	• GM-CSF elevations found to correlate with severe CRS and neurotoxicity on ZUMA-1	• Administration before CAR-T infusion in a small number of patients resulted in very low rates of CRS and ICANS

Hughes, AD, et al. *Seminars in Immunopathology*. 2024;46:5.

Established Therapies for ICANS

	Agent	Rationale	Comments
First Line	Corticosteroids (CS)	• Global immunosuppression with CS currently has the most evidence of efficacy; antibody-based therapies such as tocilizumab do not cross the BBB.	• Dexamethasone preferred due to CNS penetration; however package insert for FDA-approved CD19 CART recommends dexamethasone or methylprednisolone. • High-dose methylprednisolone recommended for severe toxicity. • Prophylactic steroid administration found to be effective in preventing higher grade CRS and ICANS
Second Line	Anakinra	• IL-1 plays a major role in CAR-T-mediated toxicity • Anakinra crosses the BBB.	• Increasingly being used for ICANS, however steroids still considered first line • Increasing interest in utility for prophylaxis of toxicities with evidence particularly for ICANS mitigation

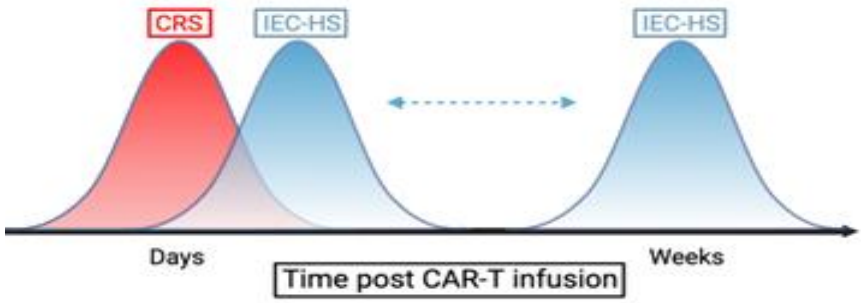
Hughes, AD, et al. *Seminars in Immunopathology*. 2024;46:5.

Established and Emerging Therapies for ICANS

Agent	Rationale	Comments
Intrathecal corticosteroids +/- chemotherapy	• Decrease CNS inflammation directly, no interference from the BBB	• LP may be challenging in severely ill patients, often who have thrombocytopenia
Intrathecal chemotherapy (MTX, Ara-C)	• Ablate CAR-T cells in the CNS, no interference from the BBB	• Effective for refractory ICANS in a small number of patients • Likely to destroy CAR-T cells, at least in CNS
ATG	• Direct elimination of T cells to abrogate CAR-T toxicity	• Single case reported • Indiscriminate T cell targeting would be expected to eliminate CAR-T, however long-term persistence reported • Significant infection risk associated with ATG
Defibrotide	• Stabilization of the endothelium, which is disrupted in ICANS	• Phase 2 trial ended early for lack of efficacy using prophylactic defibrotide

Hughes, AD, et al. *Seminars in Immunopathology*. 2024;46:5.

Evolving Grading Criteria for IEC-HS



Some patients with severe CRS develop a state of hyperinflammation that is accompanied by hyperferritinemia, cytopenia's, hypofibrinogenemia, and multiorgan dysfunction – analogous to HLH. Time to onset is later than CRS

Grade	Symptoms
Grade 1	Mild symptoms including fever, but clinical stability not requiring intervention
Grade 2	mild to moderate symptoms such as hypotension responsive to fluids alone and/or hypoxia requiring low- flow nasal cannula, asymptomatic hypofibrinogenemia
Grade 3	More severe symptoms including hypotension responsive to a vasopressor, respiratory distress requiring non-invasive support, coagulopathy with bleeding symptoms
Grade 4	Severe, life-threatening toxicities including respiratory distress requiring intubation, hypotension requiring multiple vasopressors, and/or dialysis
Grade 5	Death

HLH = hemophagocytic lymphohistiocytosis; IEC-HS = immune effector cell-associated HLH-like syndrome.

Hines MR, et al. *Transplant Cell Ther*. 2023. 29(7):438 e1–438 e16. Ragoonanan D, et al. *Nat Rev Clin Oncol.* 2021;18(7):435–453.

Established Therapies for IEC-HS

	Agent	Rationale	Comments
First Line	Corticosteroid (CS)	• Widely acting immunosuppressive effects, historically first line (in combination) for pHLH and sHLH	• CAR-T cell compromise continues to be a concern • Side effects include infection risk, hypertension, metabolic derangements
	Anakinra	• IL-1b is upregulated in IEC-HS, often used first-line with CS in MAS	• Successful use in IEC-HS. Good side effect profile, can be titrated to effect
Second Line	Ruxolitinib	• Blocks signaling through multiple cytokine receptors	• Successful use in refractory IEC-HS. Risk of worsening cytopenias and viral reactivation
	Emapalumab	• IFNγ is elevated in primary and secondary HLH, animal models show essential role for IFNγ in HL	• Successful use in CAR-T toxicity and in small pediatric cohort. Evidence supports that emapalumab does not impede CAR-T efficacy

MAS = Macrophage activation syndrome.

Hughes AD, et al. *Semin Immunopathol* 2024;46(3-4):5.

Emerging therapies for IEC-HS

Agent	Rationale	Comments
Tocilizumab/ Siltuximab	• IL-6 blockade effective in CRS, all cases of IEC-HS have followed or accompanied CRS	• Use discouraged in absence of CRS, may have a role in preventing severe toxicities such as IEC-HS when used pre-emptively
Etoposide	• Topoisomerase inhibitor that induces apoptosis in proliferating T cells	• Relatively extensive use in pHLH and sHLH, and has been used successfully in refractory IEC-HS • Proposed as second-line therapy. However, it is a cytotoxic agent with nontrivial side effect profile and risk for secondary malignancy
Alemtuzumab	• CD52 is present on mature lymphocytes including T lymphocytes used in the production of CAR-T	• Has been used in primary HLH, in particular for refractory disease • Increased risk for infectious complications and very hard to obtain in United States

Hughes AD, et al. *Semin Immunopathol* 2024;46(3-4):5.

Emerging therapies for IEC-HS

Agent	Rationale	Comments
Antithymocyte globulin (ATG)	• Horse or rabbit-derived antibodies against T lymphocytes and thymocytes to target CAR-T cells	• Limited experience in HLH, increased risk for infectious complications
Canakinumab	• IL-1b is upregulated in IEC-HS, often first line with CS in MAS	• Limited experience with HLH, has been used for refractory MAS/HLH; antibody therapy less likely to cross blood brain barrier
Tadekinig alfa	• IL-18 elevated in patient with HLH and MAS, is a potent inflammatory cytokine and enhances IFNg secretion	• Interest based on limited experience in XIAP deficiency causing pHLH
Etanercept/ Infliximab	• TNFα is elevated in HLH and mediates systemic damage	• Clinical experience limited

HLH, hemophagocytic lymphohistiocytosis.
Hughes AD, et al. *Semin Immunopathol.* 2024;46(3-4):5.

Estimating Risk for Hematologic Toxicity : CAR-HEMATOTOX

Prior to lymphodepleting chemotherapy (day -5)

→ Determine patient-individual risk of heme-tox and infections using the **CAR-HEMATOTOX score**

- Leniency time period for lab values: 3 days

Features	0 Point	1 Point	2 Points
Platelet count	> 175.000/µl	75.000 - 175.000/µl	< 75.000/µl
Absolute neutrophil count (ANC)	> 1200/µl	≤ 1200/µl	-
Hemoglobin	> 9.0 g/dl	≤ 9.0 g/dl	-
C-reactive protein (CRP)	< 3.0 mg/dl	≥ 3.0 mg/dl	-
Ferritin	< 650 ng/ml	650-2000 ng/ml	> 2000 ng/ml
Low: 0-1 **High: ≥2**			

Low risk (HT 0-1)

Risk profile	LBCL (n = 235)	MCL (n = 103)	MM (n = 113)
Median duration of severe neutropenia (ANC<500/µL, D0-60)	5.5 days (95% CI 5-8 days)	6 days (95% CI 5-7 days)	3 days (95% CI 2-5 days)
Aplastic phenotype	2.6%	0%	3%
Severe infection rate	8%	5%	5%
Severe bacterial infection rate	0.9%	5%	3%

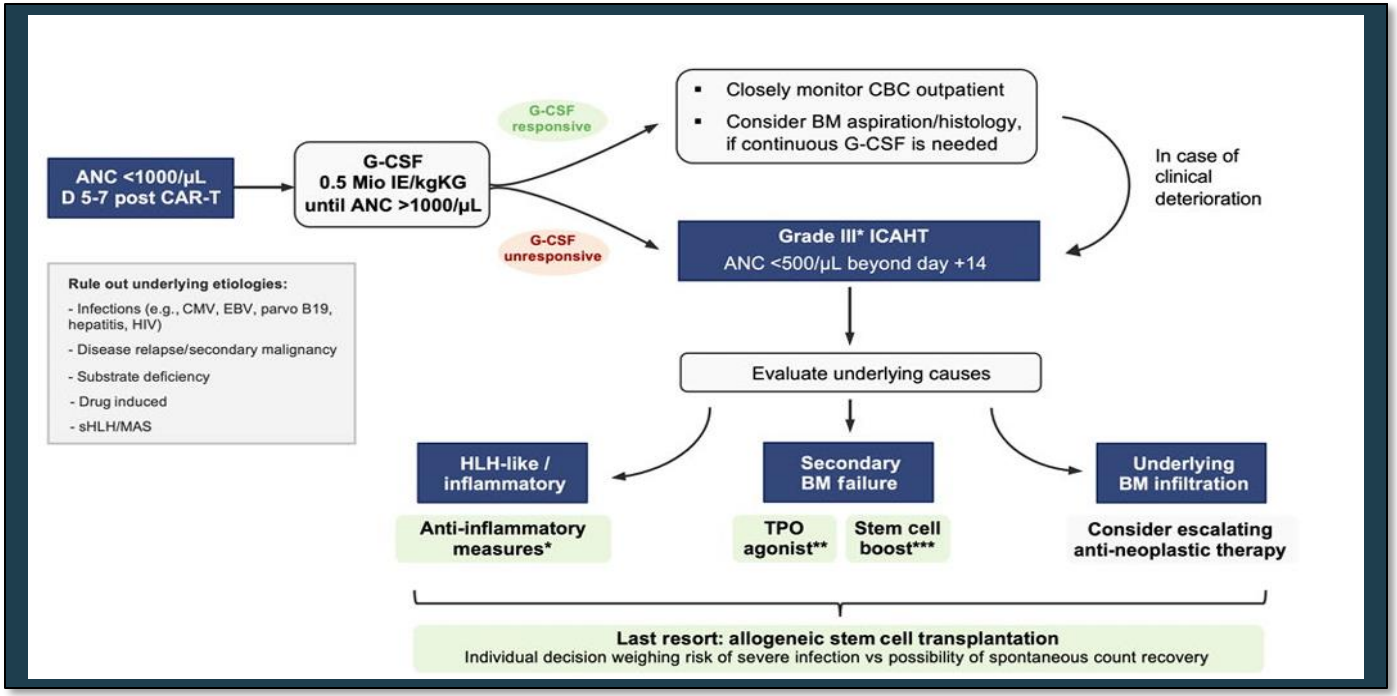
High risk (HT 2-7)

	LBCL (n = 235)	MCL (n = 103)	MM (n = 113)
Duration of severe neutropenia (ANC<500/µL, day 0-60)	12 days (95% CI 10-16 days)	14 days (95% CI 9-18 days)	9 days (95% CI 7-13 days)
Aplastic phenotype	36%	47%	32%
Severe infection rate	40%	30%	40%
Severe bacterial infection rate	27%	28%	34%

MCL = Mantle cell lymphoma; MM = multiple myeloma.

Rejeski K, et al. *Hematology Am Soc Hematol Educ Program.* 2023;2023(1):198-208.

Treatment Algorithm for Immune Effector Cell Associated Hematotoxicity



Treatment algorithm for immune effector cell associated hematotoxicity. *Consider dexamethasone-pulse (20 mg over 4 days) or anticytokine-therapy (e.g., anakinra or tocilizumab). **Consider eltrombopag (e.g., 50 mg × 7 days). ***If available, contact apheresis unit

ANC = absolute neutrophil count; CBC = complete blood count; CMV = cytomegalovirus; EBV = Epstein-Barr virus; HIV = human immunodeficiency virus. HLH = hemophagocytic lymphohistiocytosis; ICAHT = immune effector cell-associated haematotoxicity; sHLH = secondary hemophagocytic lymphohistiocytosis; TPO = thrombopoietin.

Rejeski K, et al. *Hematology Am Soc Hematol Educ Program*. 2023;2023(1):198-208.

Evaluating Hematologic Toxicity Post CAR-T

Diagnostic Category	Included Diagnostic Tests	When to Initiate	Additional Comments
Basis workup (tier 1)	• Check for myelotoxic medications • Rule out active infections: blood cultures, procalcitonin • Vitamin deficiency: B12, folic acid • Consider secondary HLH/MAS: serum ferritin • Bone marrow aspiration and biopsy	• ANC < 500/µL > day +7 after CAR-T infusion	Low threshold to per form (minimal workup)
Advanced workup in case of severe ICAHT (tier 2)	• Bone mar row aspiration and biopsy • Advanced viral studies (parvovirus B19, • CMV)	• Grade 3 or higher ICAHT beyond day +14	Especially in patients with underlying marrow infiltration
Clinical suspicion for therapy-related myeloid neoplasm	• Immunohistochemistry, flow cytometry, cytogenetics; NGS myeloid panel	• Bone marrow aplasia > 1 month Unclear and/or new-onset cytopenia • Cytopenia refractory to therapeutic measures	t-MN after CAR-T therapy is an emerging field of study*

*Incidence rate as high as 6% of t-MN after CAR T-cell infusion (see Gurney et al., EHA 2023; abstract number S26387)

NGS = next-generation sequencing; TGS = therapy-related myeloid neoplasms

Rejeski K, et al. *Hematology Am Soc Hematol Educ Program*. 2023;2023(1):198-208.

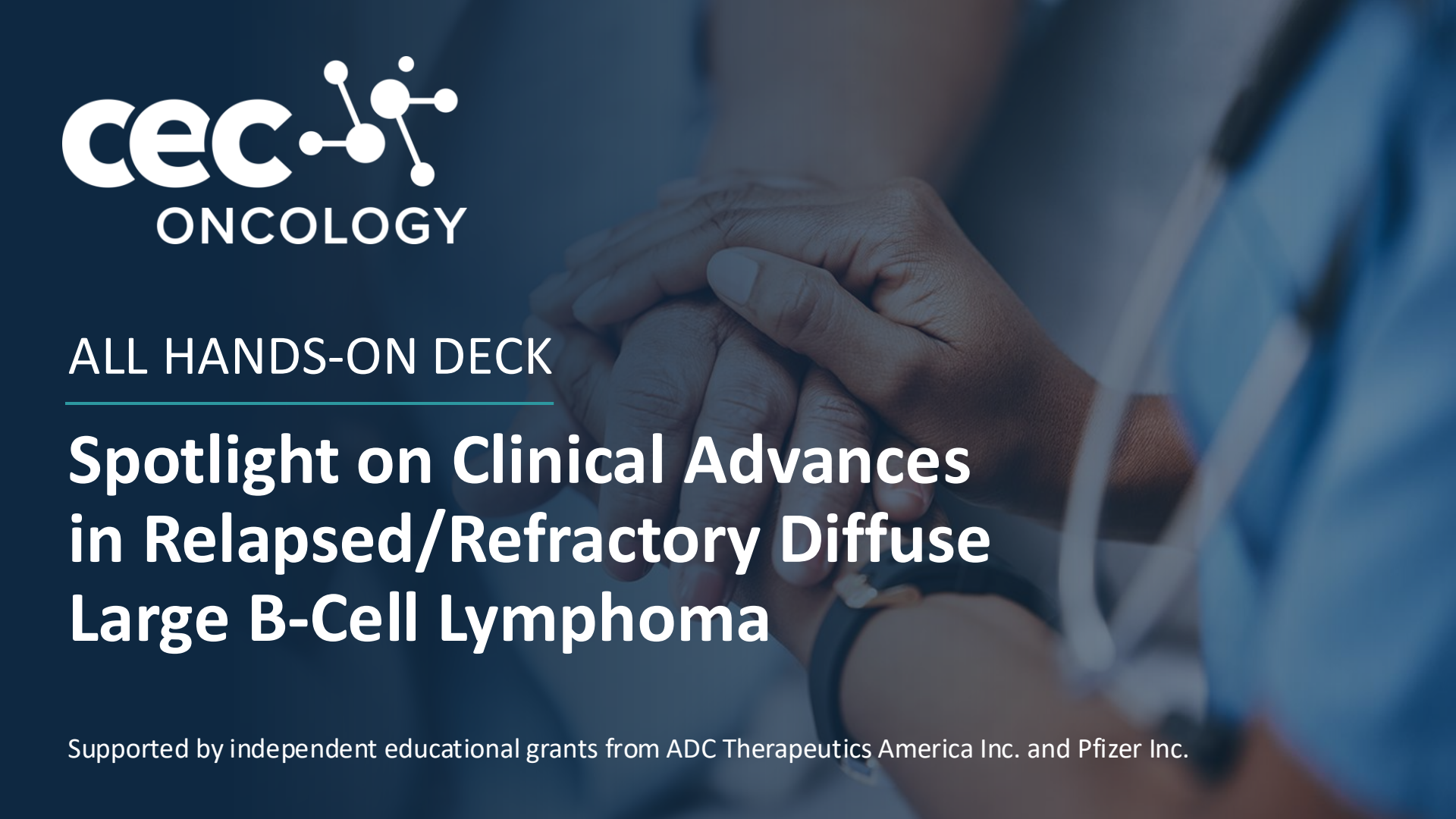
Put information into action!

Takeaways from this program can be implemented into your practice to improve patient care.

- Integrating biomarkers is crucial for personalizing DLBCL treatment.
- Evidence-based approaches ensure the best patient outcomes through tailored strategies.
- Research in biomarker discovery and novel treatment modalities continue to evolve.
- Effective AE management enhances treatment adherence and overall quality of life.

Claim Credit

Scan the QR code, create an account, complete the pre-evaluation and the post-evaluation and then claim credit. Thank you for your participation!



ALL HANDS-ON DECK

Spotlight on Clinical Advances in Relapsed/Refractory Diffuse Large B-Cell Lymphoma

Supported by independent educational grants from ADC Therapeutics America Inc. and Pfizer Inc.