ADVANCEMENTS IN AGGRESSIVE NON-HODGKIN LYMPHOMAS (NHL)

Joshua Brody, MD
Director, Lymphoma Immunotherapy Program
Icahn School of Medicine at Mount Sinai
Hess Center for Science and Medicine
New York, NY

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WELCOMING REMARKS

ADVANCEMENTS IN AGGRESSIVE NON-HODGKIN LYMPHOMAS (NHL)

Lizette Figueroa-Rivera, MA
Senior Director, Education & Support
The Leukemia & Lymphoma Society
Rye Brook, NY

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PRESENTATION

ADVANCEMENTS IN AGGRESSIVE NON-HODGKIN LYMPHOMAS (NHL)

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DISCLOSURES

ADVANCEMENTS IN AGGRESSIVE NON-HODGKIN LYMPHOMAS (NHL)

Joshua Brody, MD, receives research funding from:

- National Cancer Institute
- Cancer Research Institute
- Lymphoma Research Foundation
- Follicular Lymphoma Research Foundation
- Department of Defense
- AbbVie, ADC Therapeutics, AstraZeneca, BMS, Celldex, Genentech, Genmab, Merck, Oncovir, Seagen

4

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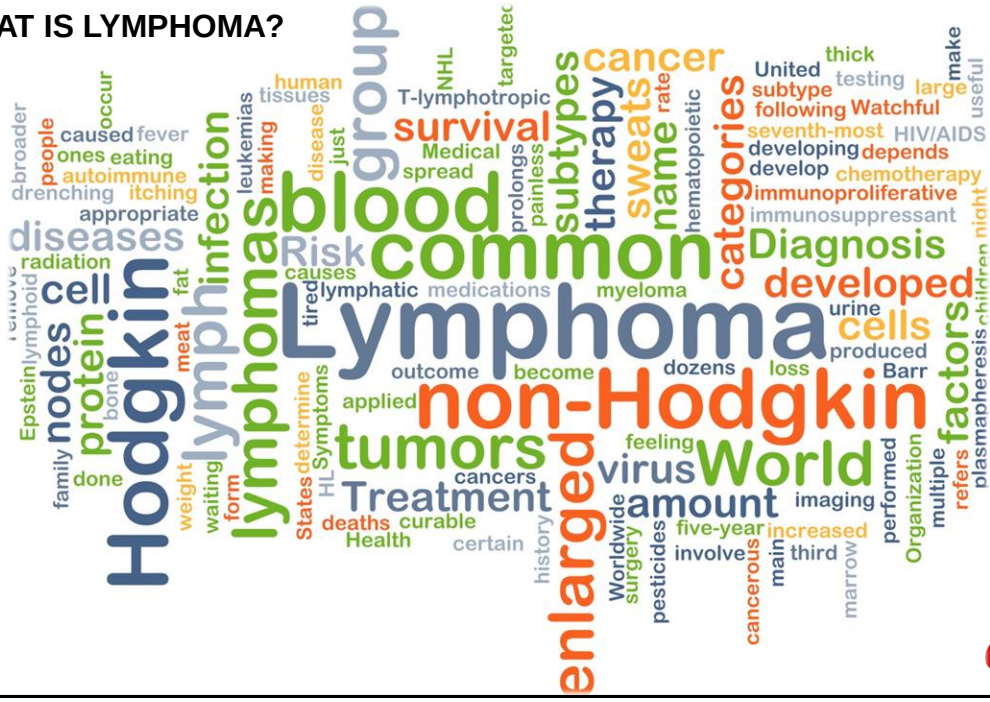
WHAT IS LYMPHOMA?



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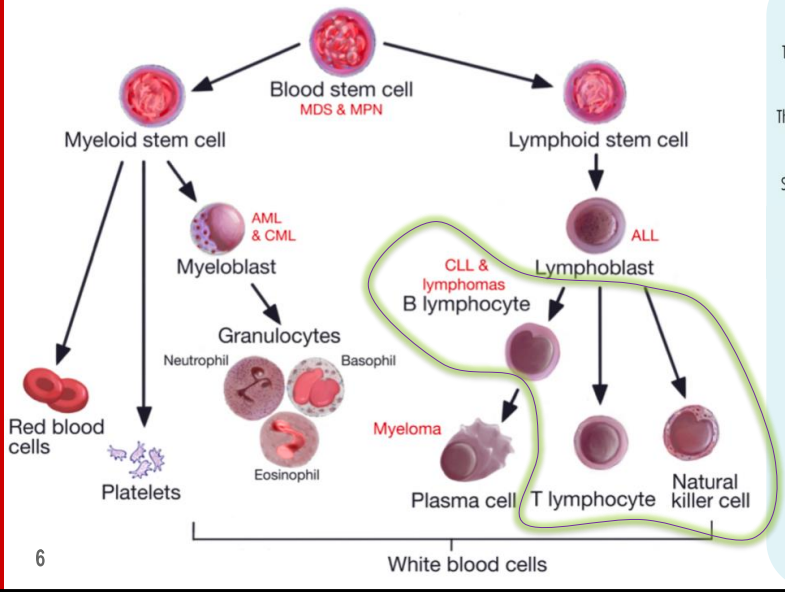
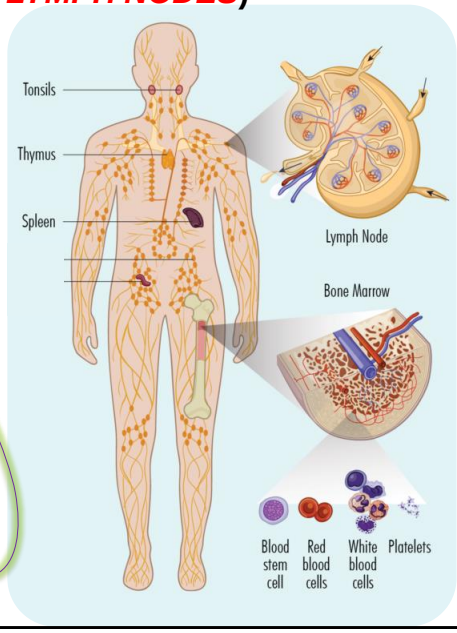
WHAT IS LYMPHOMA?
(CANCER OF *LYMPHOCYTES*, FREQUENTLY IN *LYMPH NODES*)





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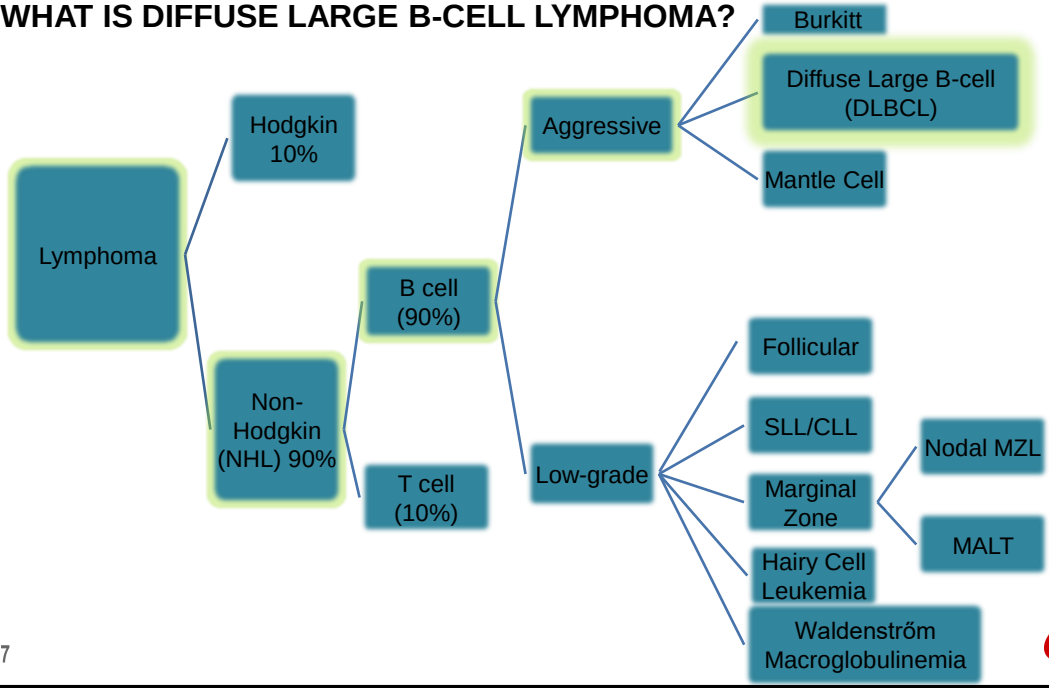
WHAT IS DIFFUSE LARGE B-CELL LYMPHOMA?



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WHAT IS DIFFUSE LARGE B-CELL LYMPHOMA?

(THE FULL LIST)

Mature B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic lymphoma/leukemia, unclassifiable*
Splenic diffuse red pulp small B-cell lymphoma*
Hairy cell leukemia variant*
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Heavy chain diseases
α Heavy chain disease
γ Heavy chain disease
μ Heavy chain disease
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma*
Follicular lymphoma
Pediatric follicular lymphoma*
Primary cutaneous follicle centre lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma (DLBCL), NOS
T-cell/histiocyte rich large B-cell lymphoma
Primary DLBCL of the CNS
Primary cutaneous DLBCL, leg type
EBV-positive DLBCL of the elderly*
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK-positive large B-cell lymphoma
Plasmablastic lymphoma
Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
Primary effusion lymphoma
Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte-depleted classical Hodgkin lymphoma
Histiocytic and dendritic cell neoplasms
Histiocytic sarcoma
Langerhans cell histiocytosis
Langerhans cell sarcoma
Interdigitating dendritic cell sarcoma
Follicular dendritic cell sarcoma
Fibroblastic reticular cell tumor
Intermediate dendritic cell tumor
Disseminated juvenile xanthogranuloma
Posttransplantation lymphoproliferative disorders (PTLDs)
Early lesions
Plasmacytic hyperplasia
Infectious mononucleosis–like PTLD
Polymorphic PTLD
Monomorphic PTLD (B- and T/NK-cell types)†
Classical Hodgkin lymphoma type PTLD†
Mature T-cell and NK-cell neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells*
Aggressive NK-cell leukemia
Systemic EBV-positive T-cell lymphoproliferative disease of childhood
Hydroa vacciniforme–like lymphoma
Adult T-cell leukemia/lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis–like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30+ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma*
Primary cutaneous CD4+ small/medium T-cell lymphoma*
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma, ALK-positive
Anaplastic large cell lymphoma, ALK-negative*

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WHAT IS DIFFUSE LARGE B-CELL LYMPHOMA?

Lymphomas: how to think about them

Diagnosis

Prognosis

Treatment

- Surgery
- Radiation
- Chemotherapy
- Passive immunotherapy (Antibodies, CARs)
- Kinase inhibitors
- Epigenetic modifiers
- Active immunotherapy

Like most veterinary students, Doreen breezes through chapter 9.

9

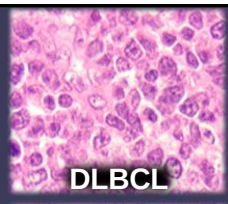
9

WHAT IS DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)?

Diagnosis

What does it look like: Diffuse, Large, B cells

Surface markers: CD19/CD20(+)

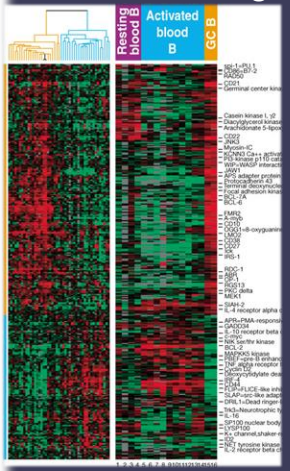


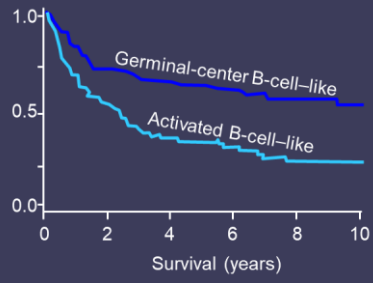
Prognosis: curable 65%

IPI:
- **Age**
- **Performance**
- **LDH**
- **Extranodal disease**
- **Stage**

DNA/RNA?

Transcriptome (Microarrays)





IPI, International Prognostic Index. Alizadeh AA et al. *Nature*. 2000;403:503-511.

10

HOW WE TREAT DLBCL:

Diagnosis

Prognosis

Treatment: **chemotherapy + anti-CD20 antibody +/- antibody drug conjugate**

=> (relapse) CAR-T cells or high-dose chemo + BMT

=> (relapse) bispecific antibodies or several others

11

TREATMENT OF FIRST-LINE DLBCL

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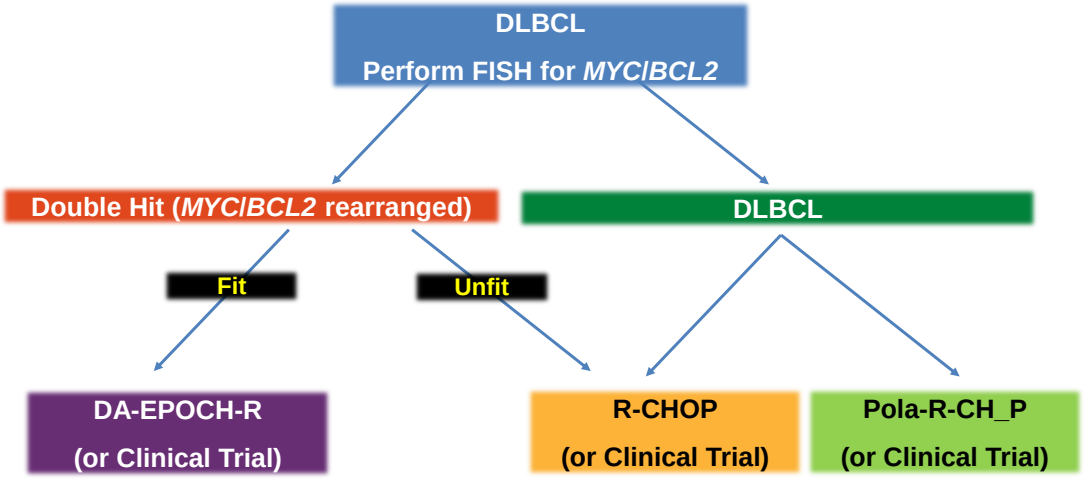
FIRST-LINE TREATMENT ALGORITHM FOR DLBCL



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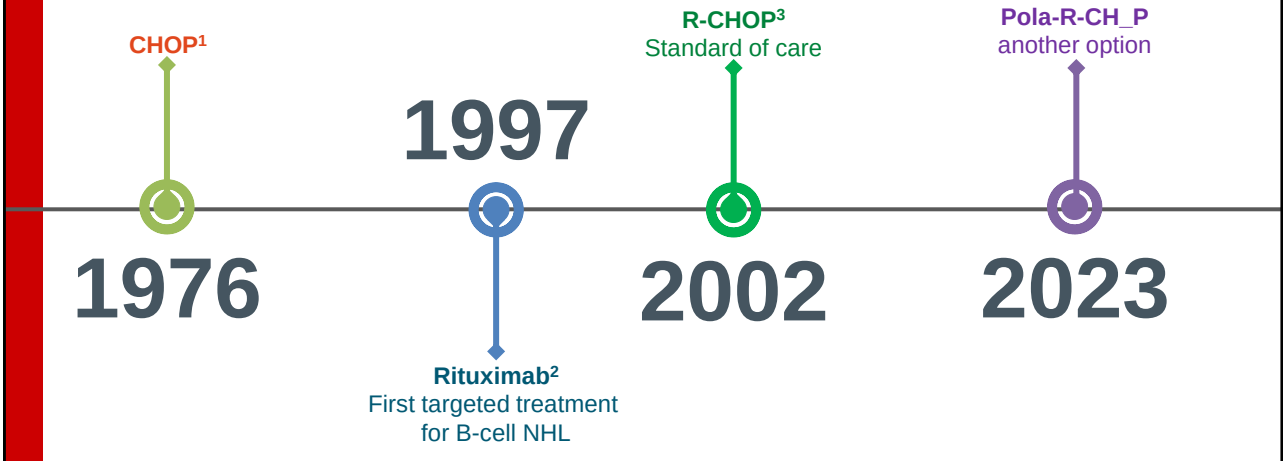
R-CHOP: FIRST-LINE IN DLBCL FOR 2 DECADES



14 1. McKelvey. *Cancer*. 1976;38:1484. 2. McLaughlin. *JCO*. 1998;16:2825. 3. Coiffier. *NEJM*. 2002;346:235.

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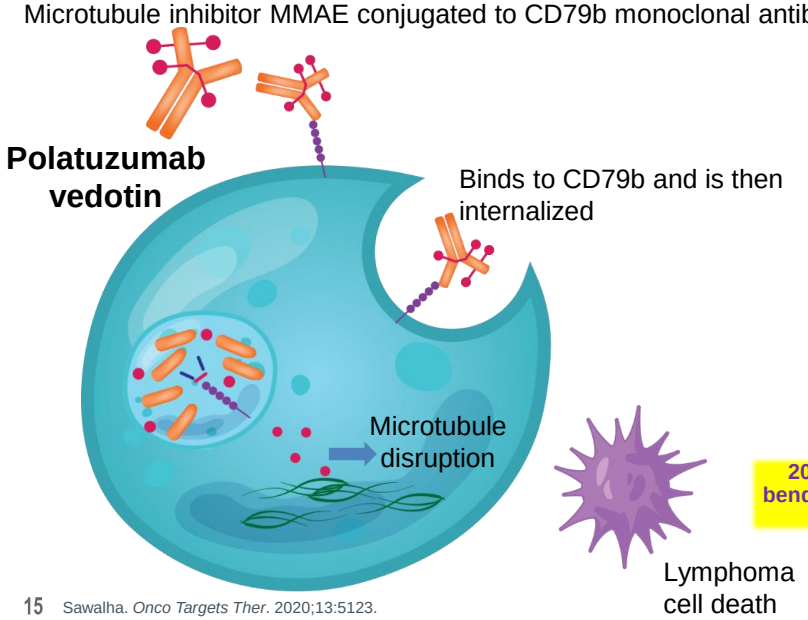
POLATUZUMAB VEDOTIN: MECHANISM OF ACTION

Microtubule inhibitor MMAE conjugated to CD79b monoclonal antibody via a cleavable linker



2019, FDA approval in combination with bendamustine and rituximab for DLBCL after ≥2 prior therapies

15 Sawalha. *Onco Targets Ther*. 2020;13:5123.

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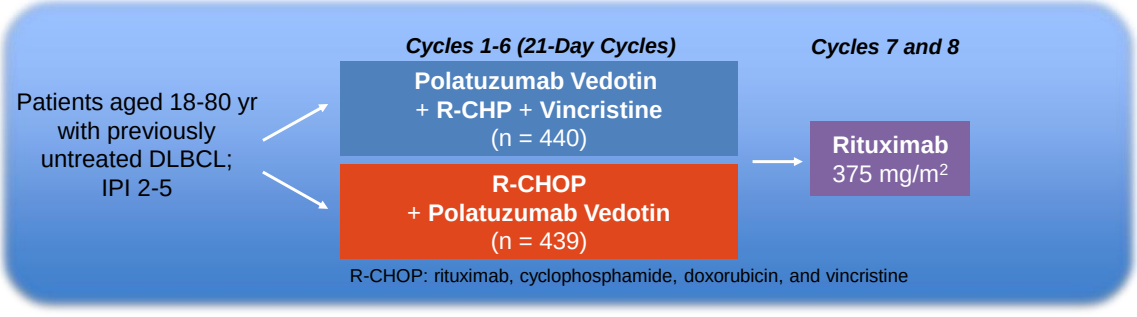
FIRST-LINE DLBCL TREATMENT: POLARIX TRIAL: POLATUZUMAB + R-CHP vs R-CHOP (PREVIOUSLY UNTREATED DLBCL)

- Multicenter, double-blind, placebo-controlled, phase 3 trial



- **Primary endpoint:** investigator-assessed progression-free survival (PFS)

16 IPI, International Prognostic Index. Tilly. ASH 2021. Abstr LBA1. Tilly. *NEJM*. 2022;386:351.

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FIRST-LINE DLBCL TREATMENT: POLARIX TRIAL: POLATUZUMAB + R-CHP vs R-CHOP (PREVIOUSLY UNTREATED DLBCL)

Baseline Characteristics

Characteristic	Polatuzumab vedotin + R-CHP (n = 440)	R-CHOP (n = 439)
Median age, yr (range)	65 (19-80)	66.0 (19-80)
Male, n (%)	239 (54)	234 (53)
ECOG PS 0/1, n (%)	374 (85)	363 (83)
Bulky disease (≥7.5 cm), n (%)	193 (44)	192 (44)
Elevated LDH, n (%)	291 (66)	284 (65)
Median time from diagnosis to treatment initiation, days	26	27
Ann Arbor stage III/IV, n (%)	393 (89)	387 (88)
Extranodal sites (≥2), n (%)	213 (48)	213 (49)

Characteristic, n (%)	Polatuzumab vedotin + R-CHP (n = 440)	R-CHOP (n = 439)
IPI score		
▪ 2	167 (38)	167 (38)
▪ 3-5	273 (62)	272 (62)
Cell of origin		
▪ **ABC**	**102 (31)**	**119 (35)**
▪ **GCB**	**184 (56)**	**168 (50)**
▪ **Unclassified**	**44 (13)**	**51 (15)**
MYC/BCL2 expression	139 (38)	151 (41)
MYC/BCL2/BCL6 rearrangement	26 (8)	19 (6)

17 IPI, International Prognostic Index. Adapted from Tilly. *NEJM*. 2022;386:351.

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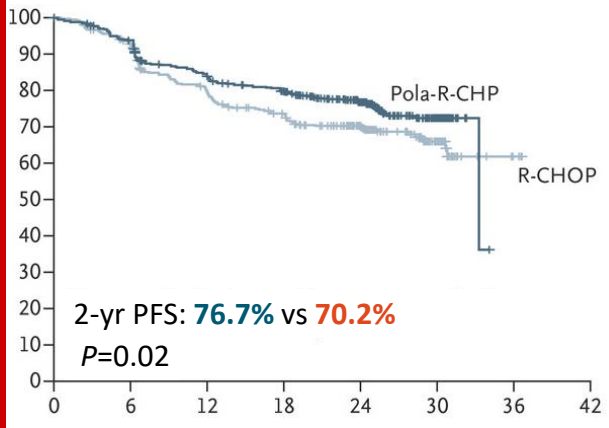
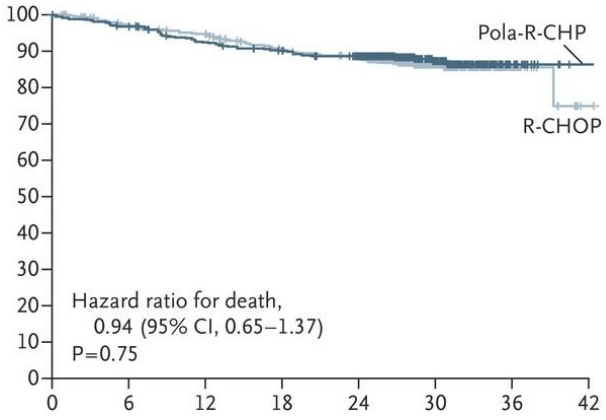
FIRST-LINE DLBCL TREATMENT: POLARIX TRIAL: POLATUZUMAB + R-CHP vs R-CHOP (PREVIOUSLY UNTREATED DLBCL)

Overall Response: **95.9 %** vs **94.1%**

Complete Response: **86.6%** vs **82.7%**

Median follow-up: 28.2 mo





months

18 Adapted from Tilly. *NEJM*. 2022;386:351.

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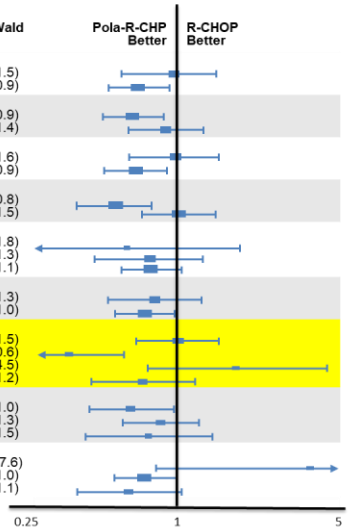
FIRST-LINE DLBCL TREATMENT:
POLARIX TRIAL: POLATUZUMAB + R-CHP vs R-CHOP (PREVIOUSLY UNTREATED DLBCL)
Subgroup Analysis of Progression-free Survival (PFS)

Baseline Risk Factors	Total N	Pola-R-CHP (N = 440) n	Pola-R-CHP (N = 440) 2-Yr Rate	R-CHOP (N = 439) n	R-CHOP (N = 439) 2-Yr Rate	HR	95% Wald CI
Age group, yr							
≤60	271	140	74.1	131	71.9	0.9	(0.6-1.5)
>60	608	300	77.9	308	69.5	0.7	(0.5-0.9)
Sex							
Male	473	239	75.9	234	65.9	0.7	(0.5-0.9)
Female	406	201	77.7	205	75.2	0.9	(0.6-1.4)
IPI score							
IPI 2	334	167	79.3	167	78.5	1.0	(0.6-1.6)
IPI 3-5	545	273	75.2	272	65.1	0.7	(0.5-0.9)
Bulky disease							
Absent	494	247	82.7	247	70.7	0.6	(0.4-0.8)
Present	385	193	69.0	192	69.7	1.0	(0.7-1.5)
Ann Arbor stage							
I-II	99	47	89.1	52	85.5	0.6	(0.2-1.8)
III	232	124	80.7	108	73.6	0.8	(0.5-1.3)
IV	548	269	72.6	279	66.1	0.8	(0.6-1.1)
Baseline LDH							
≤ ULN	300	146	78.9	154	75.6	0.8	(0.5-1.3)
> ULN	575	291	75.4	284	67.2	0.7	(0.5-1.0)
Cell of origin							
GCB	352	184	75.1	168	76.9	1.0	(0.7-1.5)
ABC	221	102	83.9	119	58.8	0.4	(0.2-0.6)
Unclassified	95	44	73.0	51	86.2	1.9	(0.8-4.5)
Unknown	211	110	73.8	101	64.3	0.7	(0.4-1.2)
Double expressor by IHC							
DEL	290	139	75.5	151	63.1	0.6	(0.4-1.0)
Non-DEL	438	223	77.7	215	75.7	0.9	(0.6-1.3)
Unknown	151	78	76.0	73	69.8	0.8	(0.4-1.5)
Double- or triple-hit lymphoma							
Yes	45	26	69.0	19	88.9	3.8	(0.8-17.6)
No	620	305	76.8	315	70.3	0.7	(0.5-1.0)
Unknown	214	109	78.5	105	66.4	0.6	(0.4-1.1)



Is there benefit in:

- Younger ≤60 yr?
- Females?
- IPI = 2?
- Bulky disease (≥7.5 cm)?
- GCB subtype?
- DH/TH DLBCL?

19 Adapted from Tilly. *NEJM*. 2022;386:351.

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FIRST-LINE DLBCL TREATMENT:
POLARIX TRIAL: POLATUZUMAB + R-CHP vs R-CHOP (PREVIOUSLY UNTREATED DLBCL)
Adverse Events

AEs, %	Pola + R-CHP (n = 435) Any Grade	Pola + R-CHP (n = 435) Grade 3/4	R-CHOP (n = 438) Any Grade	R-CHOP (n = 438) Grade 3/4
Peripheral neuropathy	52.9	1.6	53.9	1.1
Nausea	41.6	1.1	36.8	0.5
Neutropenia	30.8	28.3	32.6	30.8
Diarrhea	30.8	3.9	20.1	1.8
Anemia	28.7	12.0	26.0	8.4
Constipation	28.7	1.1	29.0	0.2
Fatigue	25.7	0.9	26.5	2.5
Alopecia	24.4	0	24.0	0.2
Dec appetite	16.3	1.1	14.2	0.7

AEs, %	Pola + R-CHP (n = 435) Any Grade	Pola + R-CHP (n = 435) Grade 3/4	R-CHOP (n = 438) Any Grade	R-CHOP (n = 438) Grade 3/4
Pyrexia	15.6	1.4	12.6	0
Vomiting	14.9	1.1	14.4	0.7
Febrile neutropenia	14.3	13.8	8.0	8.0
Headache	12.9	0.2	13.0	0.9
Cough	12.9	0	12.1	0
Dec weight	12.6	0.9	11.9	0.2
Asthenia	12.2	1.6	12.1	0.5
Dysgeusia	11.3	0	13.0	0

20 Tilly. *NEJM*. 2022;386:351.

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TREATMENT OF *SECOND-LINE* DLBCL:

Focus on Early Relapsed Disease

21

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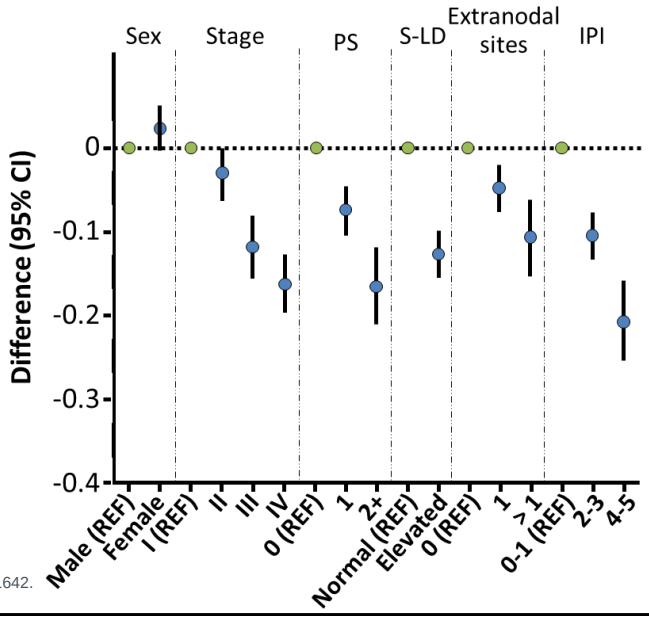
WHO IS AT RISK OF RELAPSE AFTER FIRST-LINE TREATMENT?

Predictors of Relapse



22 Ekberg. *Br J Cancer.* 2022;127:1642.

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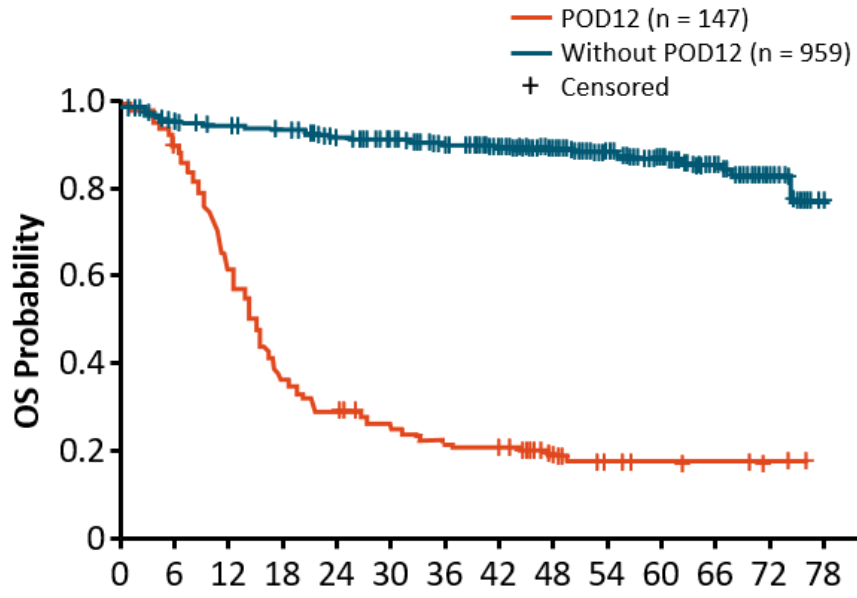
LATE RELAPSE IS MUCH BETTER THAN EARLY RELAPSE



23 Canales-Ruiz. *Clin Lymph Myeloma Leukemia*. 2022;8:e804.

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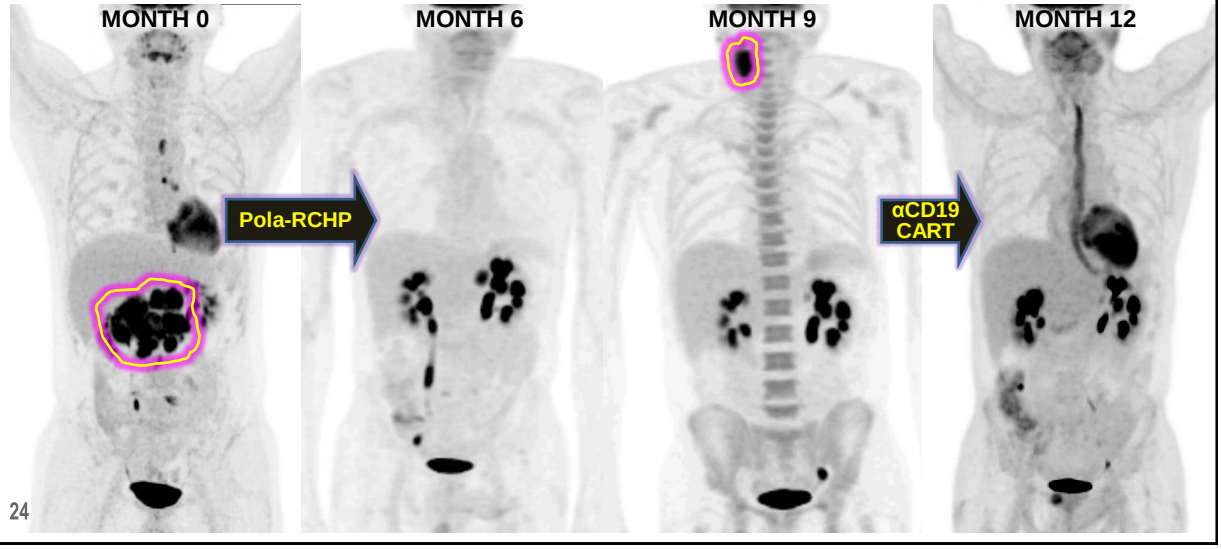
A SECOND-LINE DLBCL PATIENT

71-yo man w DM2, HTN, COPD, dx w DLBCL, non-GC → Pola-RCHP → CR x 6 months → relapse → XRT+ Liso-cel αCD19 CAR-T



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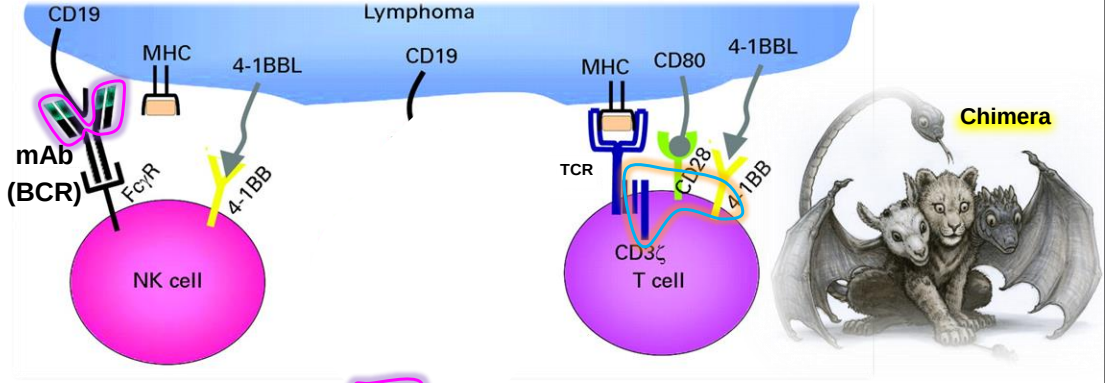
CAR: Chimera of 2 Antigen Receptors



-Antigen Receptor 1: antibody (recognition)

-Antigen Receptor 2: TCR (signaling)

-CAR-T: a T cell with a CAR shoved into it

25 Brody J, et al., *J Clin Oncol*. 2011.

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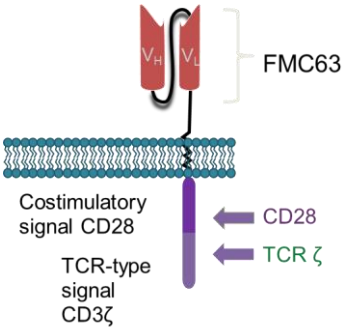
CD19-TARGETED CAR T-CELL PRODUCTS IN DLBCL

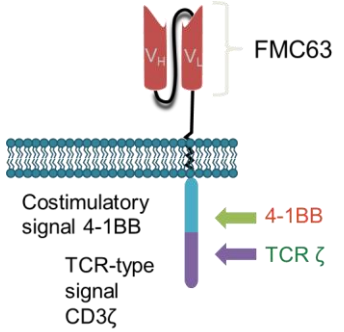
Axicabtagene ciloleucel (Axi-cel)

- CD28 costimulation
- Second generation



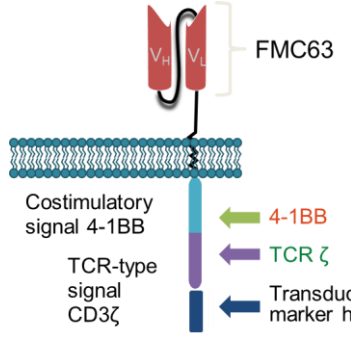
Tisagenlecleucel (Tisa-cel)

- 4-1BB costimulation
- Second generation



Lisocabtagene maraleucel (Liso-cel)

- 4-1BB costimulation
- Second generation



26 van der Stegen. *Nat Rev Drug Discov*. 2015;14:499.

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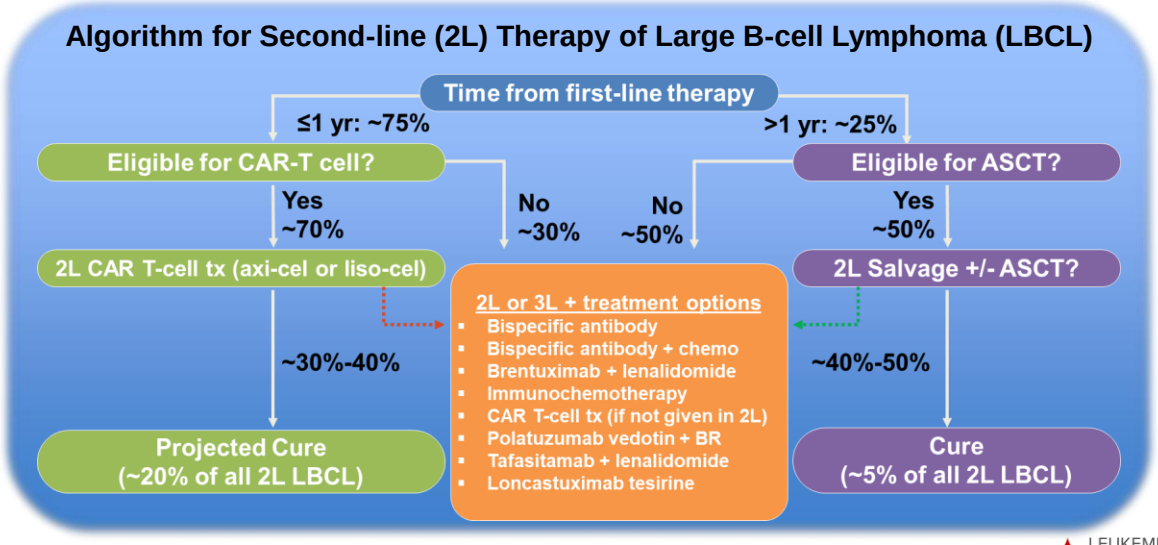
CAR-T THERAPY HAS *DICHOTOMIZED* TREATMENT OF RELAPSED/REFRACTORY (R/R) DLBCL



27 Westin. *Blood*. 2022;139:2737.

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ZUMA-7: AXICABTAGENE CILOLEUCEL (AXI-CEL) vs CHEMO + ASCT IN RELAPSED/REFRACTORY (R/R) DLBCL

Study Design

- Randomized phase 3 trial

Stratified by first-line treatment response, second-line age-adjusted IPI

Patients ≥18 years old;
ECOG PS 0-1;
R/R disease with ≤12 mo of first-line chemo
(N=359)

Axi-cel 2 x 10^6 CAR-T cells/kg after conditioning chemotherapy (n=180)

cyclophosphamide + fludarabine prior to CAR-T cells
Optional bridging therapy = only corticosteroids

SoC (2-3 cycles of investigator-selected, protocol defined, platinum-based CIT) (n=179)

CR/PR → **HDT-ASCT** (n=64)

No CR/PR → **Off-Protocol Tx**†

Chemo = R-GDP, R-DHAP, R-ICE, or R-ESHAP. †56% received subsequent cellular immunotherapy.

- Median follow-up: 24.9 mo

28 CIT, chemoimmunotherapy. Locke. *NEJM*. 2022;386:640; Locke. ASH 2021. Abstr 2.

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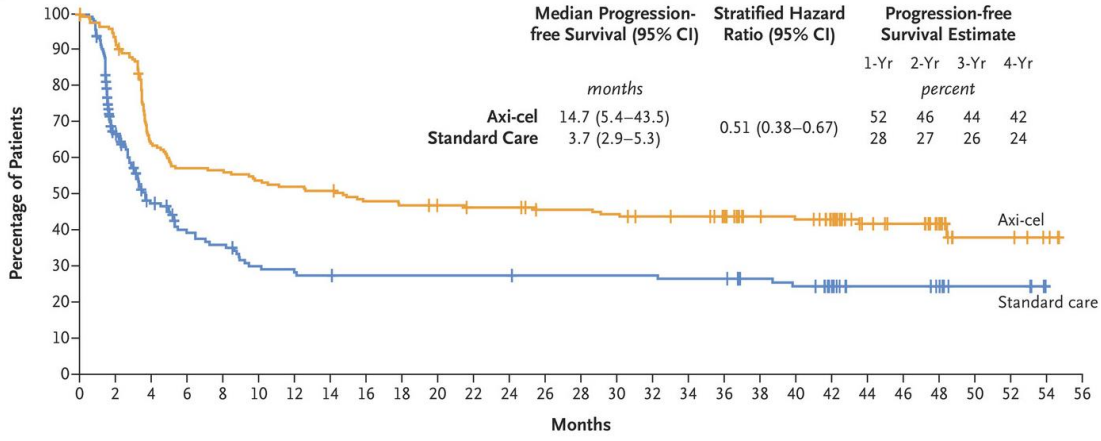
ZUMA-7: AXI-CEL vs CHEMO + ASCT IN R/R DLBCL

Efficacy

Response, %	Axi-cel (n = 180)	SoC (n = 179)	*P* Value
ORR	83	50	<.001
▪ CR	65	32	



29 Locke. *NEJM*. 2022;386:640; Westin. *NEJM*. 2023.

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ZUMA-7: AXI-CEL vs CHEMO + ASCT IN R/R DLBCL

Safety

	Axi-cel (N=170)		Standard Care (N=168)	
Event, n/N (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Febrile neutropenia	4/170 (2)	4/170 (2)	46/168 (27)	46/168 (27)
CRS	157/170 (92)	**11/170 (6)**	—	—
▪ Pyrexia	155/157 (99)	14/157 (9)	—	—
▪ Hypotension	68/157 (43)	18/157 (11)	—	—
▪ Sinus tachycardia	49/157 (31)	3/157 (2)	—	—
▪ Chills	38/157 (24)	0/157	—	—
▪ Hypoxia	31/157 (20)	13/157 (8)	—	—
▪ Headache	32/157 (20)	2/157 (1)	—	—
Neurologic events	102/170 (60)	**36/170 (21)**	33/168 (20)	1/168 (1)
▪ Tremor	44/170 (26)	2/170 (1)	1/168 (1)	0
▪ Confusional state	40/170 (24)	9/170 (5)	4/168 (2)	0
▪ Aphasia	36/170 (21)	12/170 (7)	0	0
▪ Encephalopathy	29/170(17)	20/170(12)	2/168 (1)	0
▪ Paresthesia	8/170 (5)	1/170 (1)	14/168 (8)	0
▪ Delirium	3/170 (2)	3/170 (2)	5/168 (3)	1/168 (1)

30 Locke. *NEJM*. 2022;386:640.

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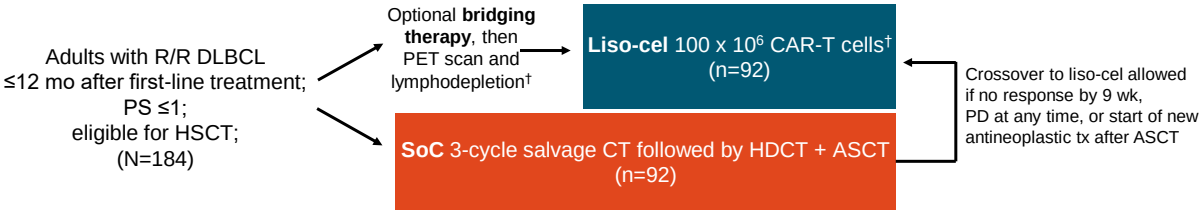
TRANSFORM: LISOCABTAGENE MARALEUCEL (LISO-CEL) vs CHEMO + ASCT IN RELAPSED/REFRACTORY (R/R) DLBCL

Study Design

- Randomized, multicenter, phase 3 study



- Primary refractory: 75% in both arms
- Double- or triple-hit lymphoma: 24%

31 Kamdar. *Lancet*. 2022;399:10343.

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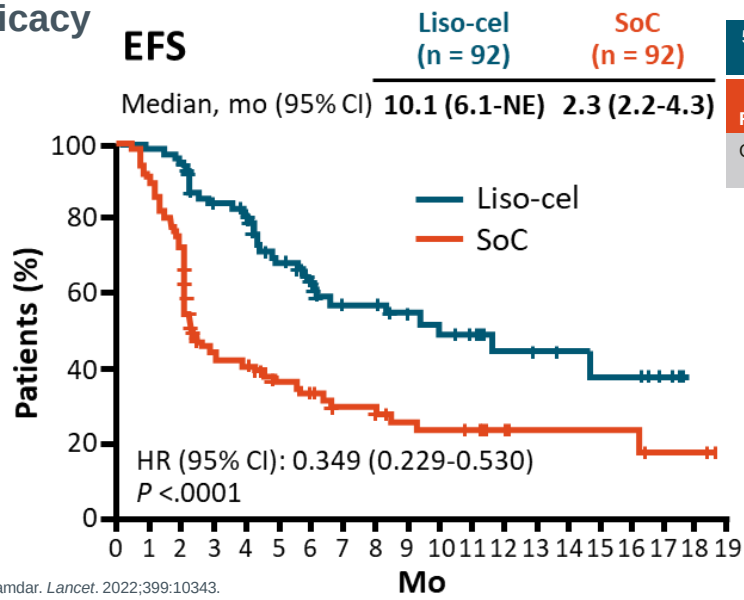
TRANSFORM: LISO-CEL vs CHEMO + ASCT IN R/R DLBCL

Efficacy



54% on SoC arm crossed over to liso-cel arm:
HR: 0.51 (95% CI: 0.26-1.00); *P*=0.026

Response	Liso-cel (n=92)	SoC (n=92)	*P* Value
ORR	86%	48%	<.0001
▪ CR	66%	39%	

- N = 184 (refractory dx: 75%; double- or triple-hit dx: = 23.4%)

32 Kamdar. *Lancet*. 2022;399:10343.

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TRANSFORM: LISO-CEL vs CHEMO + ASCT IN R/R DLBCL

Safety

Event	Liso-cel (n = 92)
Patients with ≥1 TEAE of special interest, n (%)	83 (90)
CRS	
▪ Any grade, n (%)	45 (49)
◦ Grade 1	34 (37)
◦ Grade 2	10 (11)
◦ **Grade 3**	**1 (1)**
◦ Grade 4-5	0
▪ Time to onset, days (range)	5 (3-8)
▪ Time to resolution, days	4 (2-5)
Neurological events	
▪ Any grade, n (%)	11 (12)
◦ Grade 1	5 (5)
◦ Grade 2	2 (2)
◦ **Grade 3**	**4 (4)**
◦ **Grade 4/5**	**0**
▪ Time to onset, days (range)	11 (10-17)
▪ Time to resolution, days (range)	6 (2-19)

	Liso-cel (n = 92)		Standard of Care (n = 91)	
Event, n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Febrile neutropenia	15 (16)	11 (12)	22 (24)	19 (21)

33 Kamdar. *Lancet*. 2022;399:10343.

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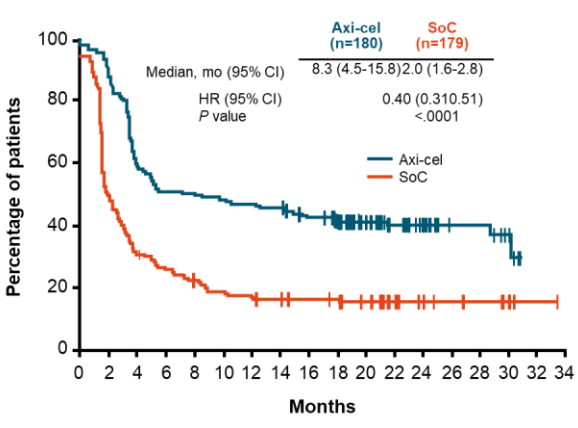
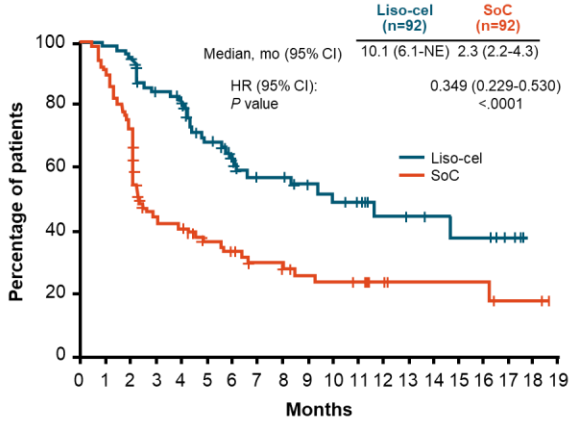
CAR-T CELLS: A NEW STANDARD IN EARLY RELAPSED DLBCL

ZUMA-7: Median Event-free Survival[1]



TRANSFORM: Median Event-free Survial[2]



34 1. Locke. *NEJM*. 2022;386:640. 2. Kamdar. *Lancet*. 2022;399:10343.

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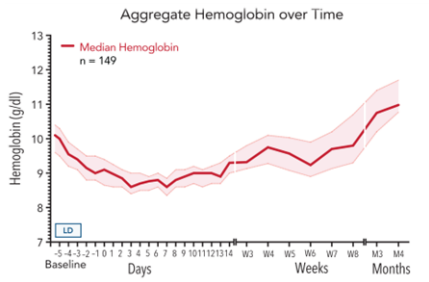
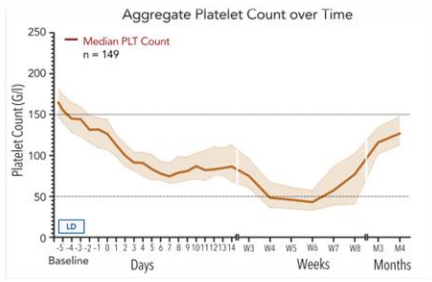
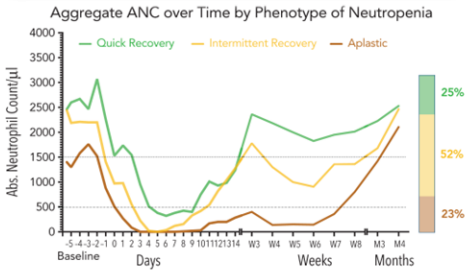
CAR-T CELLS: LATE TOXICITIES – CYTOPENIAS

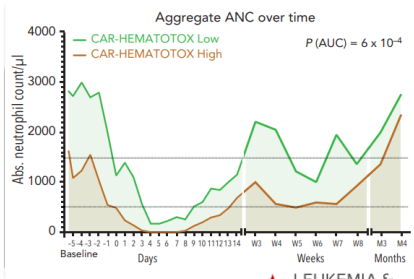
Platelet Count	< 75,000 /µl
Absolute Neutrophil Count (ANC)	< 1,200 /µl
Hemoglobin	< 9.0 g/dl
C-reactive protein (CRP)	< 3.0 mg/dl
Ferritin	> 2,000 ng/ml
CAR-HEMATOTOX score	6

Patient belongs to CAR-HEMATOTOX *high* risk group.









35 Rejeski K et al. *Blood*. 2021. www.german-lymphoma-alliance.de/Scores.html

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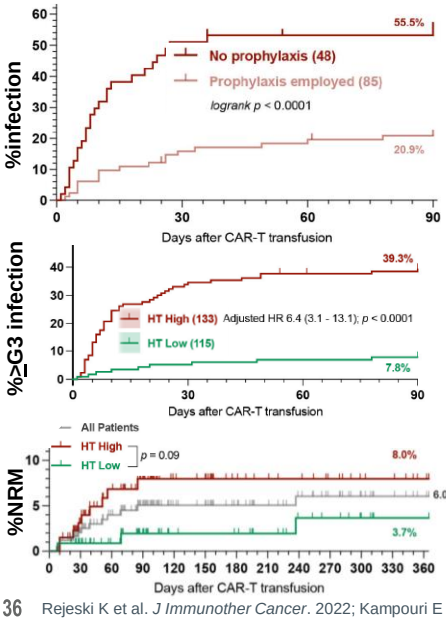
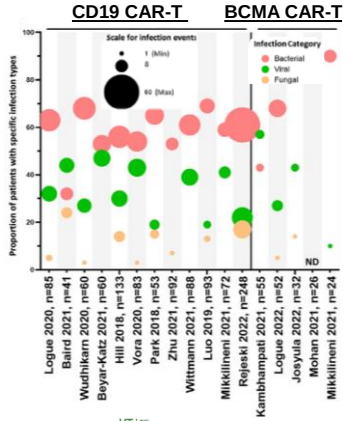
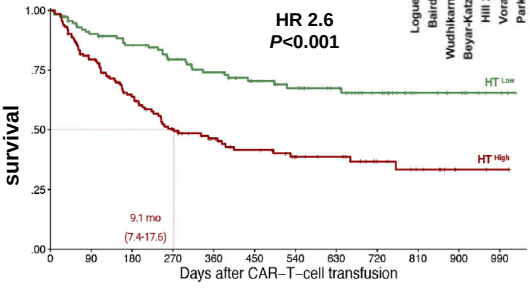
CAR-T CELLS: LATE TOXICITIES – INFECTIONS







36 Rejeski K et al. J *Immunother Cancer*. 2022; Kampouri E et al. *Transpl Infect Dis.* 2023.

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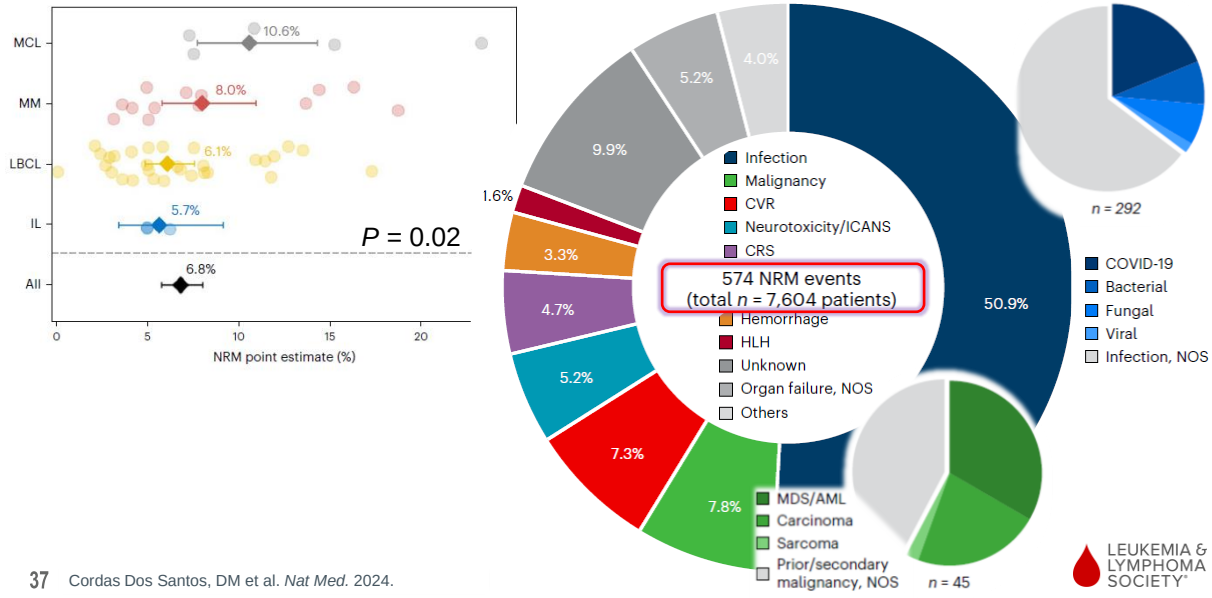
CAR-T CELLS: LATE TOXICITIES – INFECTIONS



37 Cordas Dos Santos, DM et al. *Nat Med.* 2024.

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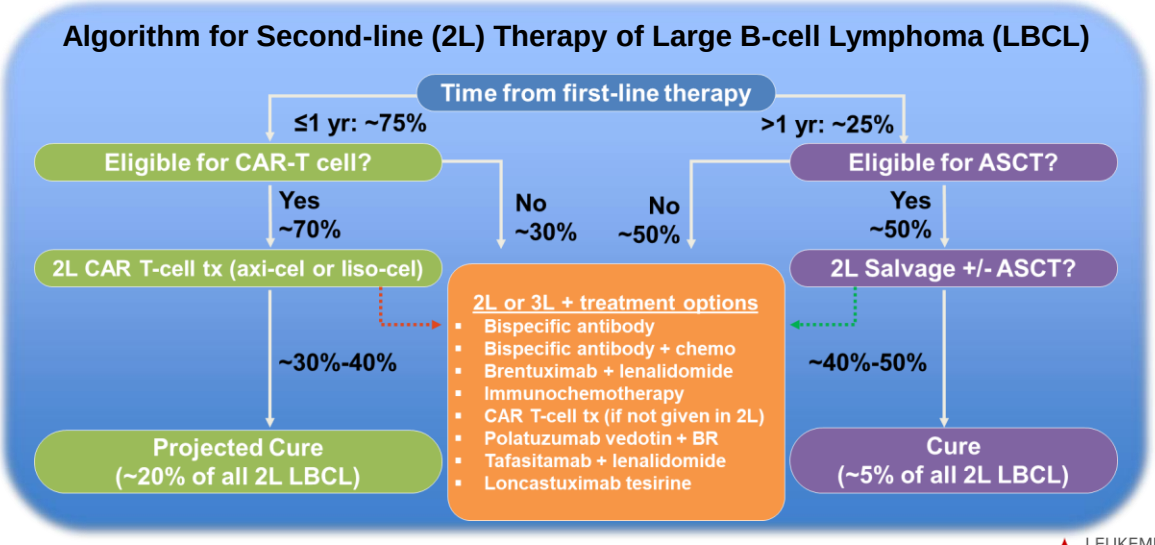
CAR-T THERAPY HAS *DICHOTOMIZED* TREATMENT OF RELAPSED/REFRACTORY (R/R) DLBCL



38 Westin. *Blood.* 2022;139:2737.

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TREATMENT OF ≥ THIRD-LINE DLBCL

39

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EFFICACY OF CAR-T IN ≥3 PRIOR LINES OF THERAPY

Characteristic	ZUMA-1 Axi-cel (n=101)	JULIET Tisa-cel (n=111)	TRANSCEND NHL 001 Liso-cel (n=269)
Median DoR, mo (95% CI)	NR (10.9-NE)	NR (10.0-NE)	NR (8.6-NR)
▪ 12-mo DoR, % (95% CI)	--	65 (49-78)	54.7 (46.7-62.0)
▪ 24-mo DoR, % (95% CI)	--	--	52.1 (43.6-49.8)
Median OS, mo (95% CI)	NR (12.8-NE)	11.1 (6.6-23.9)	21.1 (13.3-NR)
▪ 12-mo OS, % (95% CI)	59 (49-68)	48.2 (38.6-57.1)	57.9 (51.3-62.8)
▪ 24-mo OS, % (95% CI)	50.5 (40.2-59.7)	40.0 (30.7-49.1)	44.9 (36.5-52.9)
Median PFS, mo (95% CI)	5.9 (3.3-15.0)	NR	6.8 (3.3-14.1)
▪ 12-mo PFS, % (95% CI)	44 (34-53)	--	44.1 (37.3-50.7)
▪ 24-mo PFS, % (95% CI)	--	--	42.1 (35.0-48.9)
Median follow-up, mo	27.1	32.6	12.0-17.5

40 Westin. *Am J Hematol*. 2021;96:1295.

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FDA-APPROVED NOVEL AGENTS IN R/R DLBCL

Epcoritamab
Glofitamab
Polatuzumab vedotin + bendamustine and rituximab
Tafasitamab + lenalidomide
Loncastuximab tesirine
Selinexor

NOT YET FDA-APPROVED, BUT *IMPORTANT*

Glofitamab + Chemo (Gem-Ox) (Phase 3 STARGLO Trial)
Brentuximab + Lenalidomide + Rituximab (ECHELON-3 Trial)

41 Polatuzumab PI. 2020. Tafasitamab PI. 2020. Loncastuximab PI. 2021. Selinexor PI. 2019.

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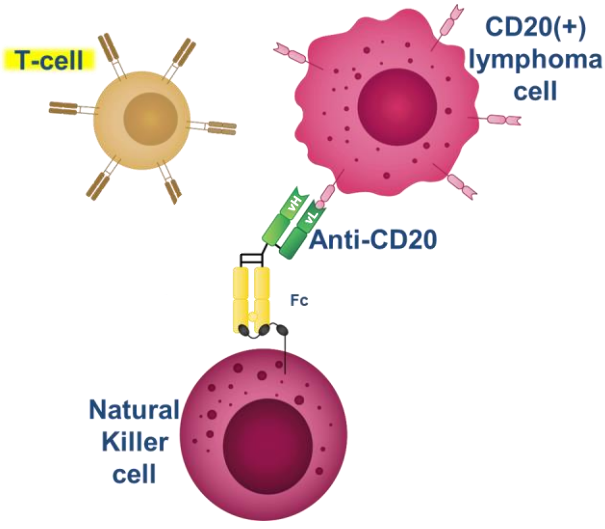
BISPECIFIC CD20xCD3 ANTIBODIES FOR R/R DLBCL



Bispecific antibodies bind **CD20 on tumor cells** and **CD3 on T cells**, bringing the two together. This then allows the T cell to initiate tumor cell lysis.

the "Kiss of Death"

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

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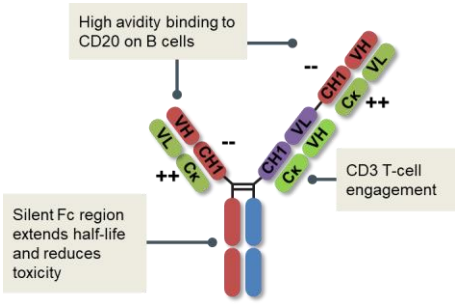
GLOFITAMAB (CD20xCD3) FOR R/R DLBCL

Schema



Phase 2 expansion in R/R DLBCL and ≥2 prior therapies

Key inclusion criteria

- DLBCL
- ECOG PS 0-1
- ≥ 2 prior therapies

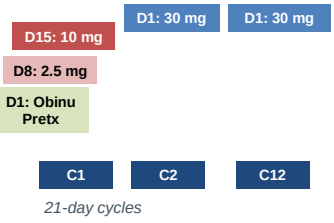
Glofitamab IV administration

Fixed-duration treatment

- max. 12 cycles

CRS mitigation

- Obinutuzumab pretreatment C1 step-up dosing
- Monitoring after first dose (2.5 mg)



43 Dickinson. EHA 2022. Abstr S220.

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GLOFITAMAB (CD20xCD3) FOR R/R DLBCL

Baseline Characteristics

Characteristic	Glofitamab (N = 154)
Median age, yr (range)	66.0 (21-90)
Male, n (%)	100 (64.9)
Ann Arbor stage, n (%)	
▪ I	10 (6.5)
▪ II	25 (16.2)
▪ III	31 (20.1)
▪ IV	85 (55.2)
NHL subtype	
▪ DLBCL	110 (71.4)
▪ Transformed from FL	27 (17.5)
▪ HGBCL	11 (7.1)
▪ PMBCL	6 (3.9)
Bulky disease, n (%)	
▪ >6 cm	64 (41.6)
▪ >10 cm	18 (11.7)

Characteristic	Glofitamab (N = 154)
Prior lines of therapy, median (range)	3 (2-7)
▪ 2 prior lines, n (%)	62 (40.3)
▪ ≥3 prior lines, n (%)	92 (59.7)
Prior therapy received, n (%)	
▪ Anti-CD20 antibody	154 (100)
▪ Anthracycline	149 (96.8)
▪ CAR T-cell therapy	51 (33.1)
▪ ASCT	28 (18.2)
Refractory disease, n (%)	
▪ To any prior therapy	139 (90.3)
▪ To last prior therapy	132 (85.7)
▪ Primary refractory	90 (58.4)
▪ To prior CAR T-cell therapy	46 (29.9)
▪ To any prior anti-CD20 antibody	128 (83.1)

44 Dickinson. EHA 2022. Abstr S220.

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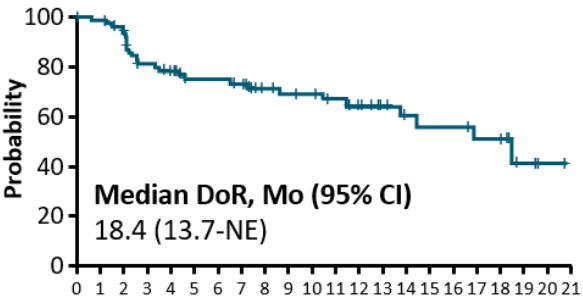
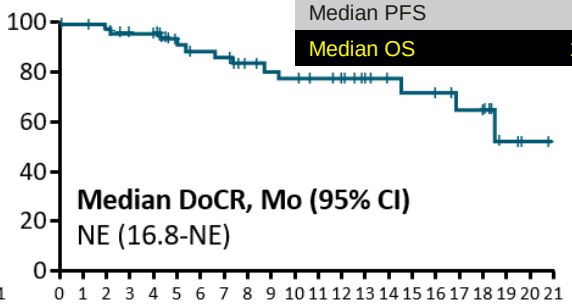
GLOFITAMAB (CD20xCD3) FOR R/R DLBCL

Efficacy

Response, %	N=155
▪ ORR	51.6
▪ CR	39.4
Subgroup CR rate	
▪ Post CAR-T	35
▪ Relapsed	70
▪ Refractory	34
Median PFS	4.9
Median OS	11.5





	N=80		n=61
Median DoR follow-up, mo (range)	10.6 (0-21)	Median DoCR follow-up, mo (range)	10.6 (0-21)
12-months DoR, % (95% CI)	63.6 (51.1 - 76.2)	12-months DoCR, % (95% CI)	77.6 (64.3 - 90.8)
Ongoing response at CCOD, n (%)	53 (66.3)	CRs ongoing at CCOD, n (%)	49 (80.3)

45 Dickinson. EHA 2022. Abstr S220.

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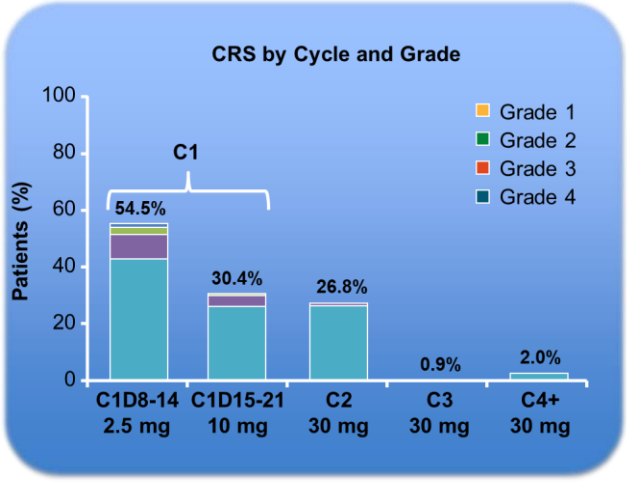
GLOFITAMAB (CD20xCD3) FOR R/R DLBCL

Adverse Effects

CRS Parameter	Glofitamab (N=154)
Any-grade CRS, n (%)	97 (63.0)
▪ Grade 1	73 (47.4)
▪ Grade 2	18 (11.7)
▪ **Grade 3**	**4 (2.6)**
▪ **Grade 4**	**2 (1.3)**
Median time to CRS onset from cycle 1 Day 8 dose, hr (range)	13.6 (6.2-51.8)
Corticosteroids given, n/N (%)	27/97 (27.8)
Tocilizumab given, n/N (%)	31/97 (32.0)
Any ICANS	12 (7.8)
▪ Grade ≥3	4 (2.6)



46 Dickinson. EHA 2022. Abstr S220.

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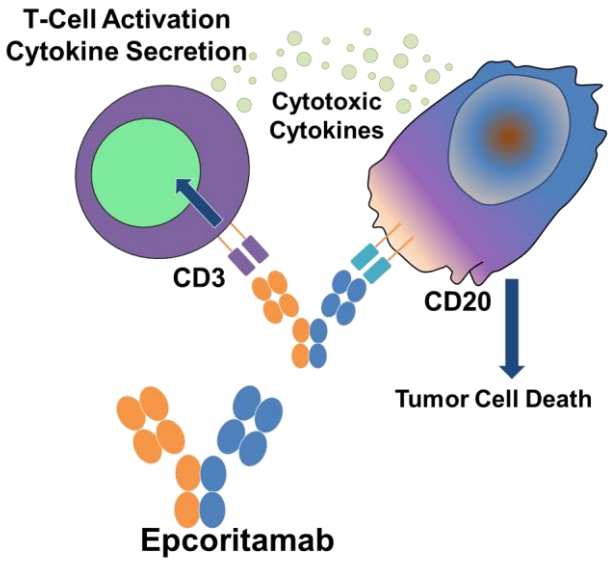
EPCORITAMAB (CD20xCD3) FOR R/R DLBCL

Schema



subcutaneously administered bispecific antibody

47 Hutchings. ASH 2020. Abstr 402. Engelberts. *EBioMedicine*. 2020;52:102625. Chiu. EHA 2020. Abstr EP1330.

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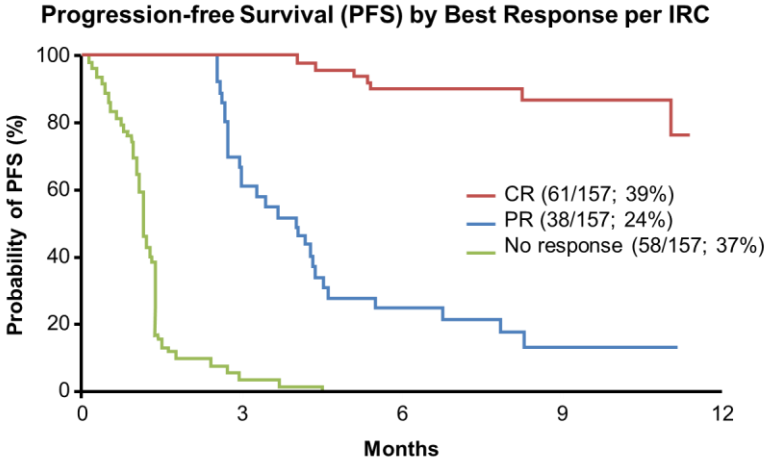
EPCORITAMAB (CD20xCD3) FOR R/R DLBCL

Efficacy



Best response rates
- CR: 39.0%
- ORR: 63.0%

Subgroup CR rate
- Post CAR T-cell: 34%
- Refractory 30%

Survival
- PFS: 4.4 mo
- OS: 57% at 12 mo

48 Thieblemont. EHA 2022. Abstr LB2364.

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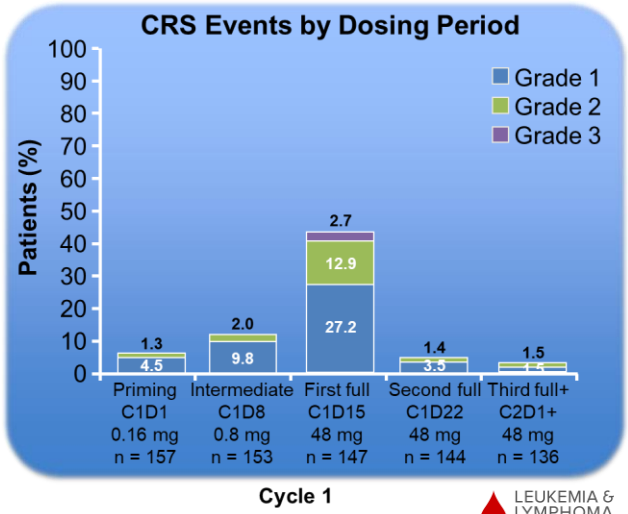
EPCORITAMAB (CD20xCD3) FOR R/R DLBCL

Adverse Effects

CRS	LBCL (N=157)
CRS events,* n (%)	78 (49.7)
▪ Grade 1	50 (31.8)
▪ Grade 2	24 (15.3)
▪ **Grade 3**	**4 (2.5)**
CRS resolution, n (%)	77 (98.7)
Median time to CRS onset from first full dose, days	0.8
Median days to CRS resolution from 1st full dose	2
CRS treatment	
▪ Tocilizumab	22 (14.0)
▪ Corticosteroids	16 (10.2)
CRS leading to treatment discontinuation, n(%)	1 (0.6)

- ICANS: 6.4%
  - All grade 1/2 except 1 case of grade 5 (with multiple confounders)



49 Thieblemont. EHA 2022. Abstr LB2364.

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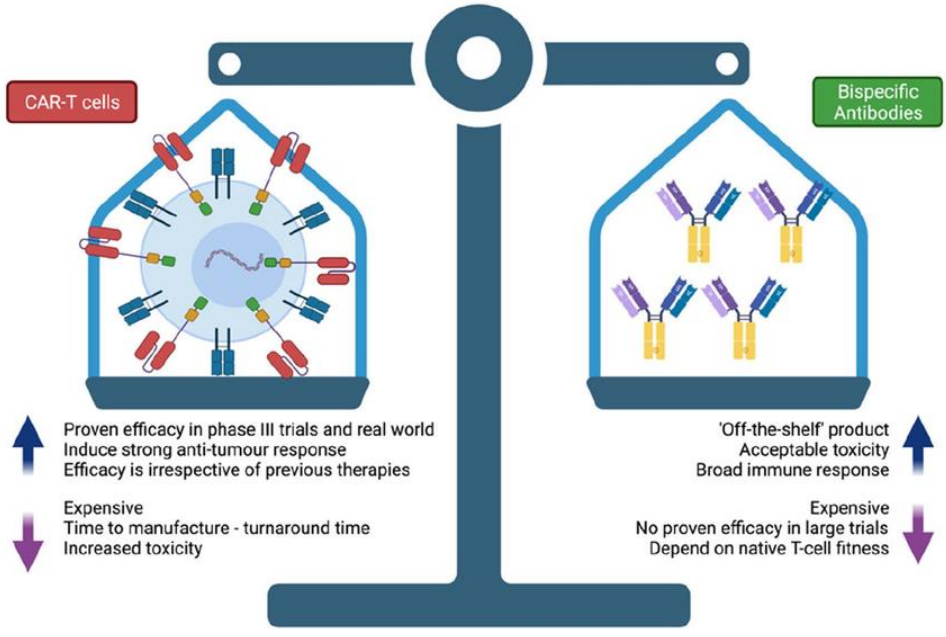
BISPECIFIC vs CAR-T THERAPIES



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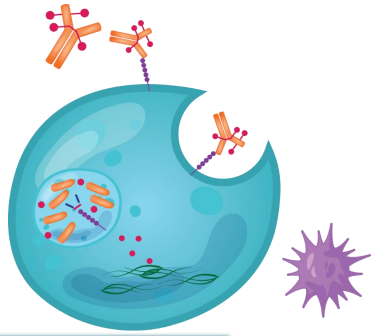
POLATUZUMAB VEDOTIN (POLA) + BENDAMUSTINE-RITUXIMAB (BR) vs BR FOR RELAPSED/REFRACTORY (R/R) DLBCL

Schema

- Polatuzumab vedotin: antibody-drug conjugate targeting CD79b with a toxic payload (MMAE)



Phase 2 trial

Stratified by duration of response (DoR) to last therapy (≤12 vs >12 mo)

Patients with R/R DLBCL; received ≥1 prior therapy; PS 0-2; (N=80)

Polatuzumab vedotin 1.8 mg/kg, D1 of each cycle + **Bendamustine** 90 mg/m^2 on D1,3 (C1), then D1,2 (each cycle) + **Rituximab** 375 mg/m^2, D1 (each cycle) (n=40)

Bendamustine 90 mg/m^2 on D1,3 (C1), then D1,2 (each cycle) + **Rituximab** 375 mg/m^2, D1 (each cycle) (n=40)

51 Sehn. *JCO*. 2020;38:155.

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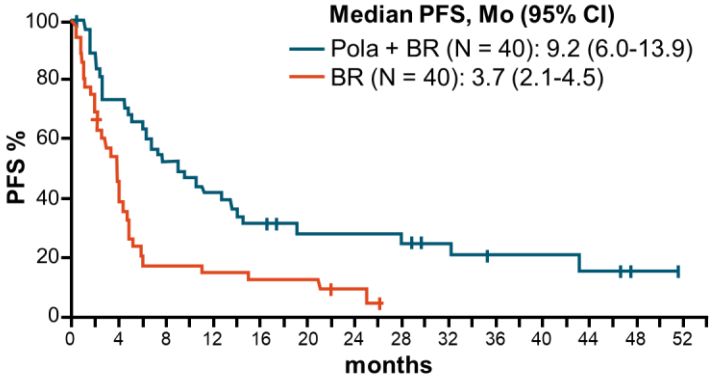
51

POLATUZUMAB VEDOTIN + BR vs BR FOR R/R DLBCL

Efficacy

Phase 2 Trial

Baseline Characteristic	BR (n=40)	Pola + BR (n=40)
Median age, yr (range)	71 (30-84)	67 (33-86)
IPI ≥3, n (%)	29 (73)	22 (55)
Median prior tx, no (range)	2 (1-5)	2 (1-7)
Outcome by IRC	**BR (n=40)**	**Pola + BR (n=40)**
CR at EoT, n (%)	7 (17.5)	17 (42.5)
Median PFS, mo	3.7	9.2
Median OS, mo	4.7	12.4



- **Notable toxicity:** Peripheral neuropathy with BR vs Pola + BR:
  - All grade: 7.7% vs 31.1%
  - Grade ≥3: 0 vs 2.0%

- **Generally avoid** prior to CAR-T cell

52 Sehn. *Blood Adv.* 2022. 6:533.

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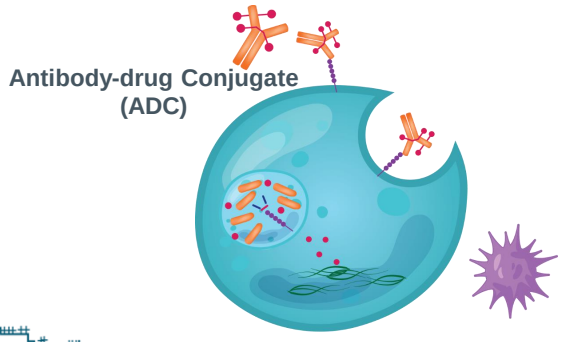
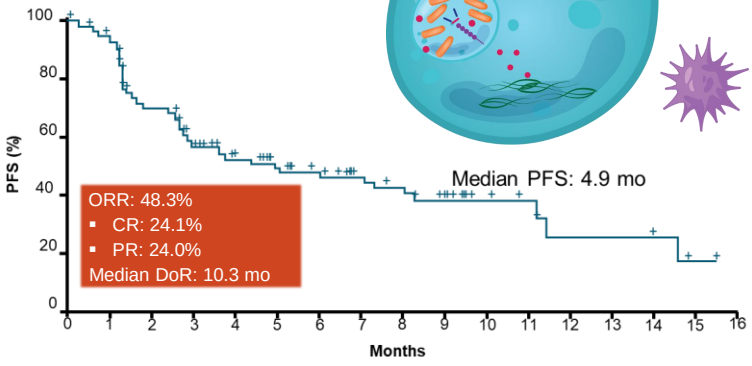
LONCASTUXIMAB TESIRINE (ANTI-CD19 ADC) IN RELAPSED/REFRACTORY (R/R) DLBCL

LOTIS-2 Phase 2 Study



Loncastuximab Tesirine Q3W

Baseline Characteristic	N = 145
Median age, yr (range)	66 (23-94)
Histology, n (%)	
▪ DLBCL NOS	127 (88)
▪ HGBCL	11 (8)
▪ PMBCL	7 (5)
Median prior tx (IQR)	3 (2-4)
Relapsed to prior tx, n (%)	43 (30)
Refractory to prior tx, n (%)	84 (58)
Prior CAR-T cells, n (%)	13 (9)



- Notable grade ≥3 AEs: Neutropenia (26%); thrombocytopenia (18%); edema/effusions (5%)

53 Caimi. *Lancet Oncol.* 2021;22:790.

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TAFASITAMAB + LENALIDOMIDE FOR R/R DLBCL (L-MIND TRIAL)

Efficacy

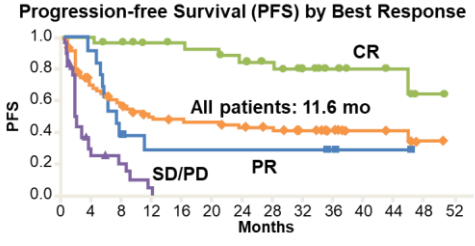
Patients with R/R DLBCL;
1-3 prior regimens;
PS 0-2;
primary refractory excluded
(N=81)

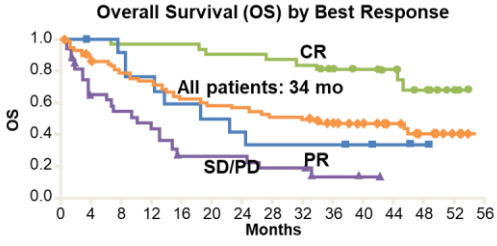
→ **Lenalidomide** D1-21 x 12 28D cycles
Tafasitamab weekly cycles 1-3 => bi- weekly

If no PD after 12 cycles →

Tafasitamab
12 mg/kg/wk
D1,15 until PD

ORR: 58% (40% CRs)





- **Notable toxicity (grade ≥3):** Neutropenia: 49.4% Thrombocytopenia: 17.3%

54 Salles. *Lancet Oncol*. 2020;21:978. Dull. ASCO 2021. Abstract 7513; Duell. *Haematologica*. 2021;106:2417.

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ASK A QUESTION

ADVANCEMENTS IN AGGRESSIVE NON-HODGKIN LYMPHOMAS (NHL)

Ask a question by phone:

Press star (*) then the number 1 on your keypad.

Ask a question by web:

Click “Ask a question”
Type your question
Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

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LLS EDUCATION & SUPPORT RESOURCES

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HOW TO CONTACT US:

To contact an **Information Specialist** about disease, treatment and support information, resources and clinical trials:

Call: (800) 955-4572
Monday to Friday, 9 a.m. to 9 p.m. ET

Chat live online: www.LLS.org/InformationSpecialist
Monday to Friday, 10 a.m. to 7 p.m. ET

Email: www.LLS.org/ContactUs

CLINICAL TRIAL SUPPORT CENTER
Work one-on-one with an LLS Clinical Trial Nurse Navigator who will help you find clinical trials and personally assist you throughout the entire clinical-trial process.
www.LLS.org/Navigation

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NUTRITION CONSULTATIONS
Our registered dietitian has expertise in oncology nutrition and provides free one-on-one consultations by phone or email.
www.LLSNutrition.org

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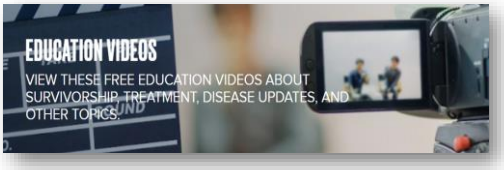
Online Chats

Online Chats are free, live sessions, moderated by oncology social workers. To register for one of the chats below, or for more information, please visit **www.LLS.org/Chat**.



Education Videos

View our free education videos on disease, treatment, and survivorship. To view all patient videos, please visit **www.LLS.org/EducationVideos**.

Patient Podcast

The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit **www.TheBloodline.org**.

57

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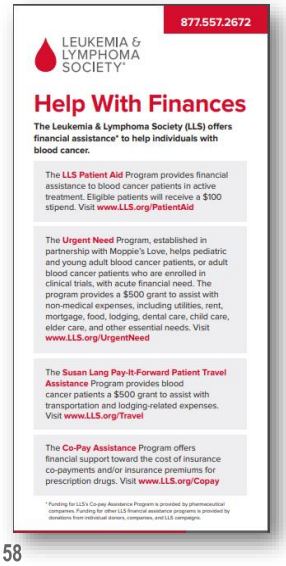
877.557.2672

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Help With Finances

The Leukemia & Lymphoma Society (LLS) offers financial assistance* to help individuals with blood cancer.

The **LLS Patient Aid** Program provides financial assistance to blood cancer patients in active treatment. Eligible patients will receive a $100 stipend. Visit **www.LLS.org/PatientAid**

The **Urgent Need** Program, established in partnership with Moppie's Love, helps pediatric and young adult blood cancer patients, or adult blood cancer patients who are enrolled in clinical trials, with acute financial need. The program provides a $500 grant to assist with non-medical expenses, including utilities, rent, mortgage, food, lodging, dental care, child care, elder care, and other essential needs. Visit **www.LLS.org/UrgentNeed**

The **Susan Lang Pay-It-Forward Patient Travel Assistance** Program provides blood cancer patients a $500 grant to assist with transportation and lodging-related expenses. Visit **www.LLS.org/Travel**

The **Co-Pay Assistance** Program offers financial support toward the cost of insurance co-payments and/or insurance premiums for prescription drugs. Visit **www.LLS.org/Copay**

* Funding for LLS's Co-pay Assistance Program is provided by pharmaceutical companies. Funding for other LLS financial assistance programs is provided by donations from individual donors, companies, and LLS campaigns.

58

The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers: **www.LLS.org/Finances**

To order free materials: **www.LLS.org/Booklets**

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THANK YOU
This program is supported by
Genentech
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Please complete our program evaluation
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We have one goal: A world without blood cancers

59