THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

High Grade B-cell Lymphoma

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Disclosures

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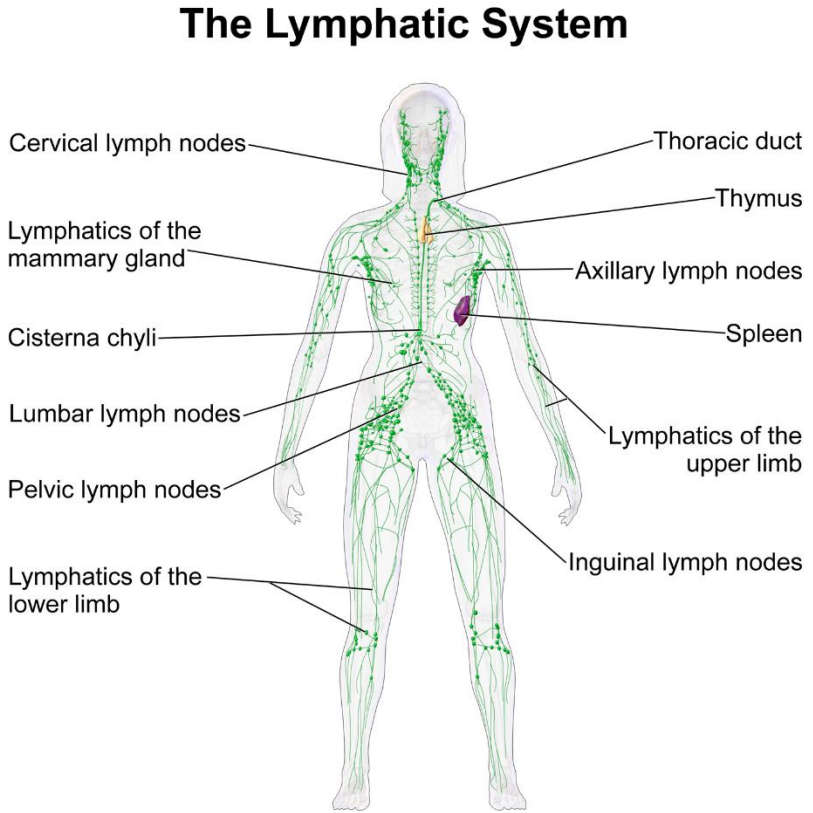
Outline

- Classification
- Frontline therapy
  - Is RCHOP the standard of care?
- Relapsed disease
  - Rapidly expanding treatment landscape
    - CAR T-cell therapy
    - Targeted therapy
- Q&A

Common Presentation of Lymphoma

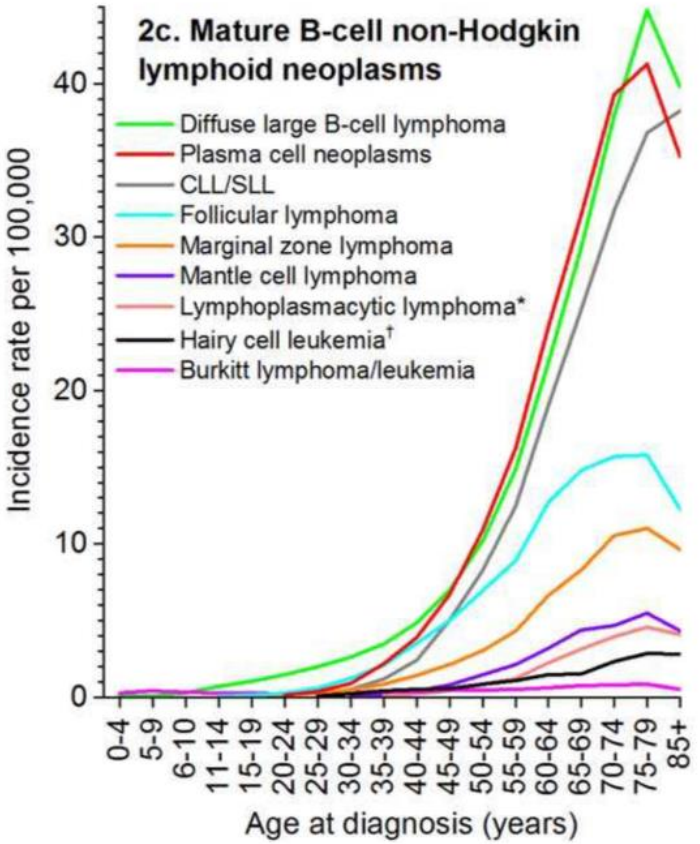


Symptoms:

- Painless enlargement of lymph nodes
- Fatigue
- Night sweats
- Fever and/or chills
- Weight loss

- No early detection or prevention strategies

Age-Specific Incidence Rates for NHL Subtypes



B Risk Factors for Development of DLBCL

Increased Risk	Family history; genetic susceptibility loci (TNF/LTA; 6p25.3; 6p21.33; 2p23.3; 8q24-21) Viruses: EBV, HIV, HHV8, hepatitis B, hepatitis C Solid-organ transplantation B-cell–activating autoimmune disorders (SLE, Sjögren's syndrome, celiac disease) Immunodeficiency Increased body-mass index (in young adults) Agricultural pesticides Ionizing radiation
Decreased Risk	Allergies (including hay fever) Blood transfusion Alcohol consumption Vegetable consumption Sun exposure
No Significant Effect	Type 2 diabetes

(1)Teras et. al. CA Cancer J Clin 2016

Sehn & Salles NEJM 2021

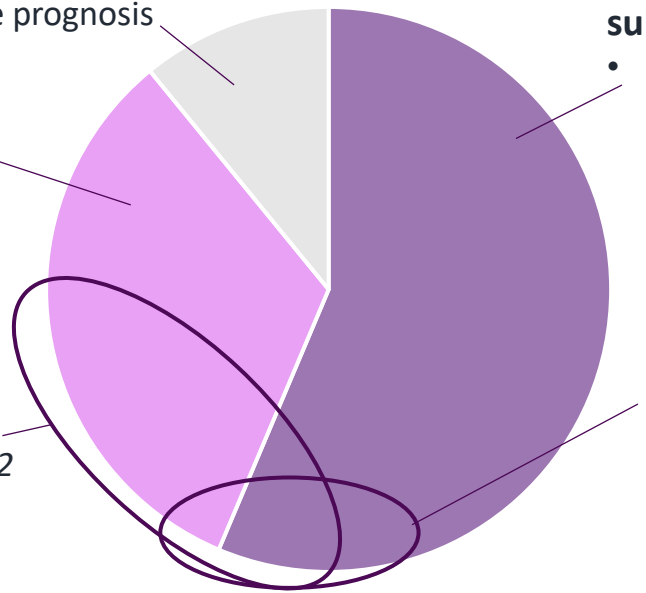
Cellular and Molecular Subtypes of DLBCL

Clinical and Prognostic Implications

Unclassifiable
- Heterogeneous
- Intermediate prognosis

Germinal center B subtype (GCB)
- Favorable prognosis compared with ABC

Activated B-cell-like subtype (ABC)
- Poor prognosis compared with GCB
- CNS involvement may be more likely

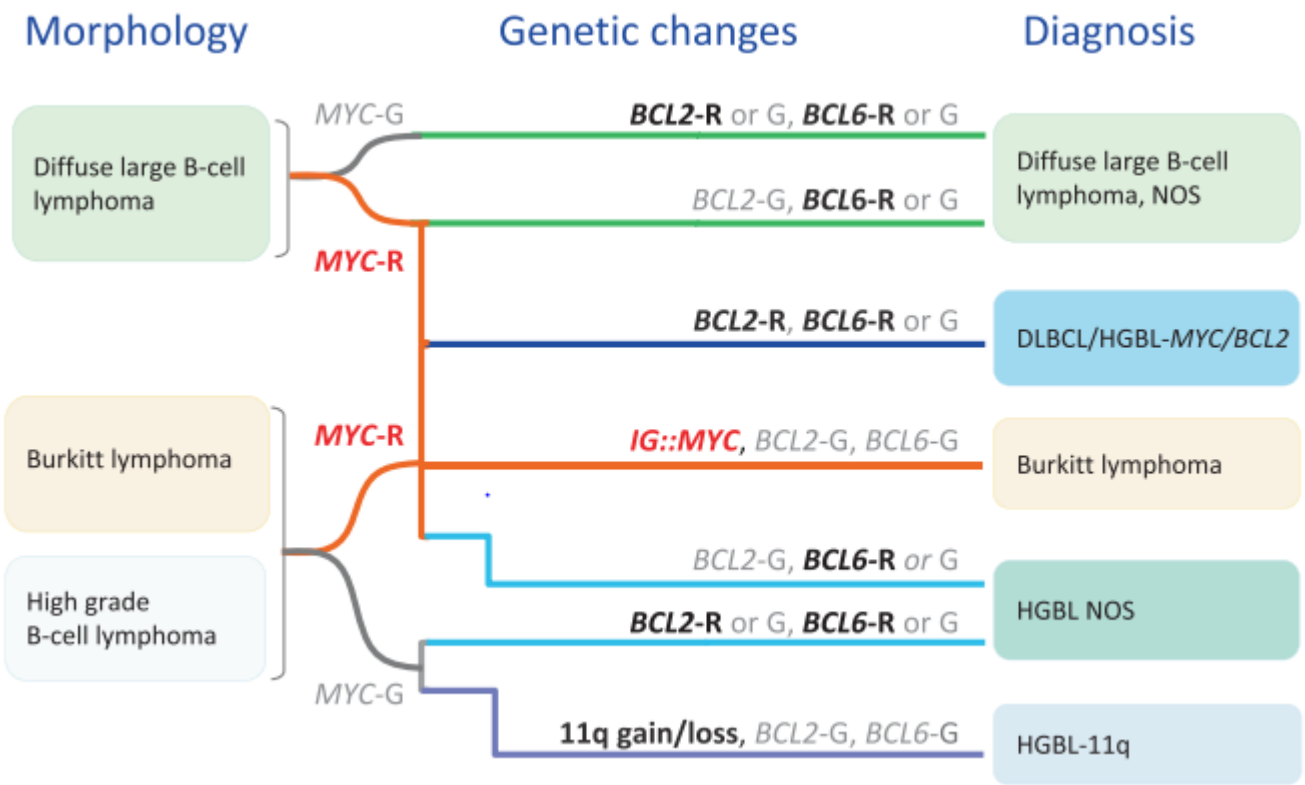


Double expressor
- High *MYC* and *BCL2* protein expression
- Poor prognosis

Double hit (*MYC* + *BCL2* or *BCL6*)
Triple hit (*MYC* + *BCL2* and *BCL6*)
- Gene rearrangements
- Classified as high-grade B-cell lymphoma
- Poor prognosis
- CNS involvement may be more likely
- Clinical trial or intensive treatment recommended

Friedberg JW. *Blood*. 2017;130(5):590-596; NCCN. Clinical Practice Guidelines in Oncology: B-Cell Lymphomas. Version 5.2022. July 12, 2022;
Sehn LH, Salles G. *N Engl J Med*. 2021;384(9):842-858.

Algorithm for Classification of Aggressive B-cell Lymphomas



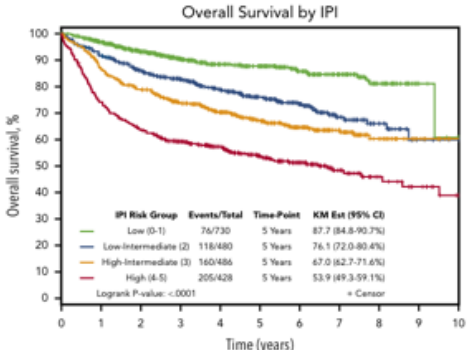
Alaggio Leukemia (2022) 36:1720–1748

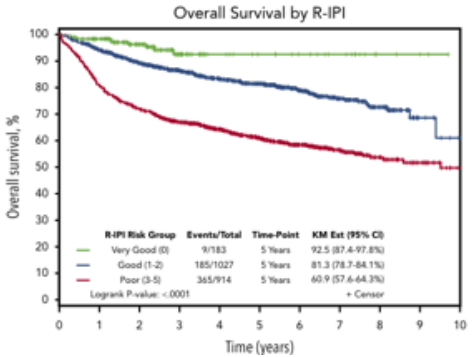
Risk Stratification

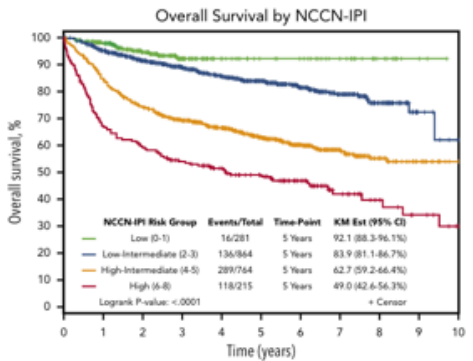
International Prognostic Index (1 point for each)
Age > 60 years
Serum LDH > ULN
ECOG PS 2-4
Stage III or IV
Extranodal involvement > 1 site

R-IPI (improve risk stratification post Rituximab era, 3 groups)

NCCN-IPI
Age classified into 4 groups (>75, >60, >40, ≤ 40)
LDH classified into 3 groups (> 3xULN, >1 x ULN, ≤1)
stage III/IV disease
ECOG PS 2-4
extra-nodal sites (bone marrow, CNS, liver/GI, or lung)

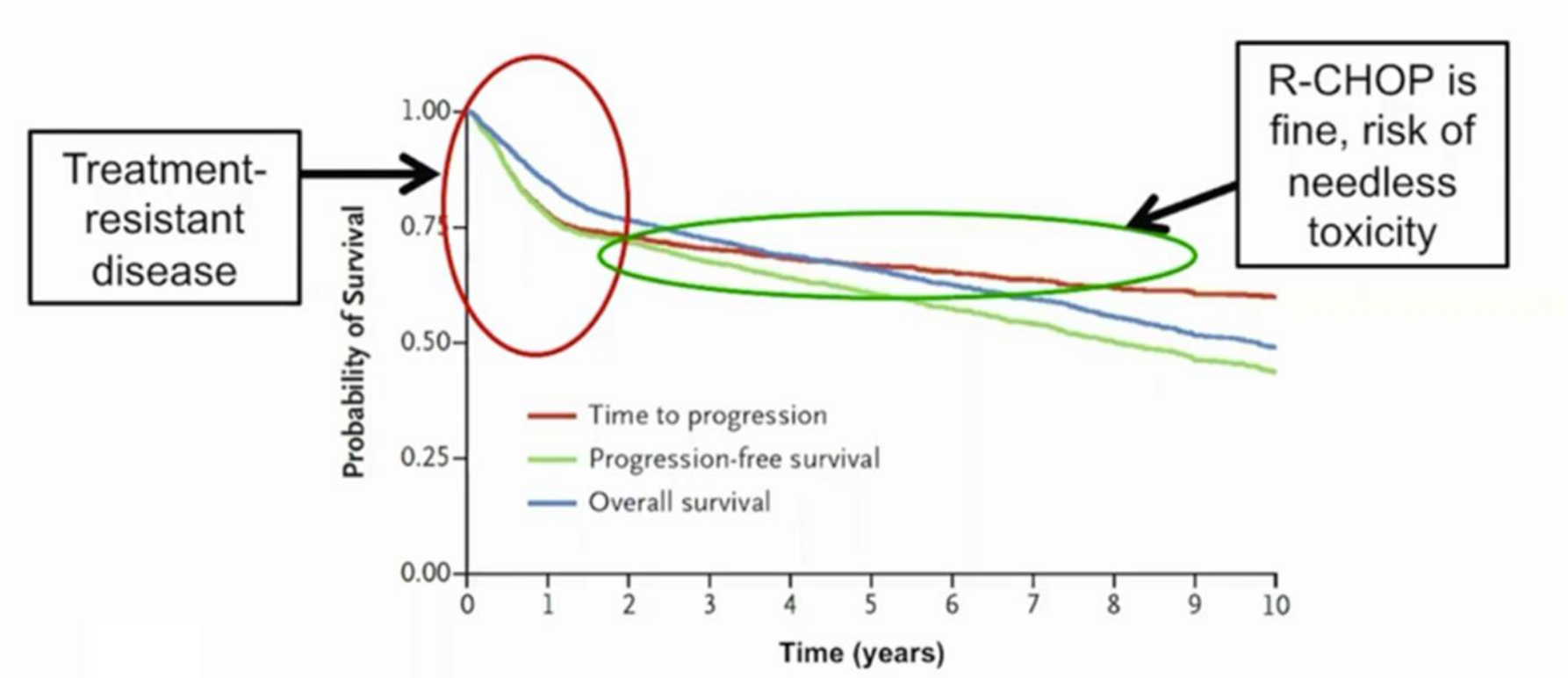






Ruppert Blood 2020

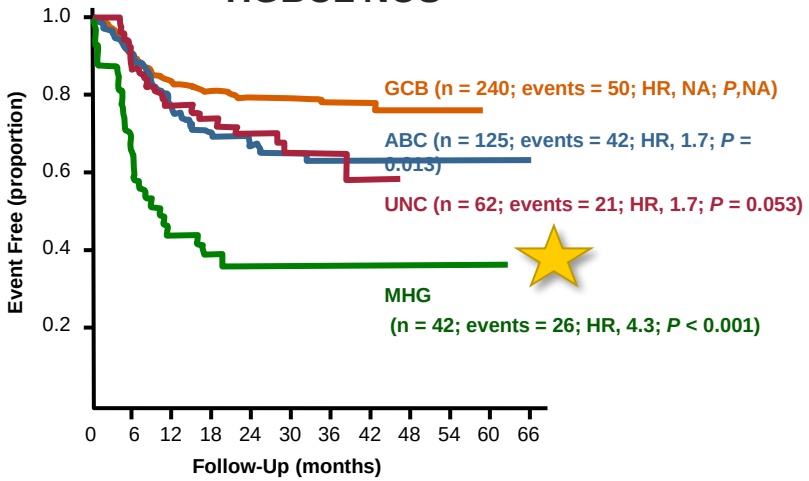
Can we improve upon RCHOP?



HGBCL: Prognosis

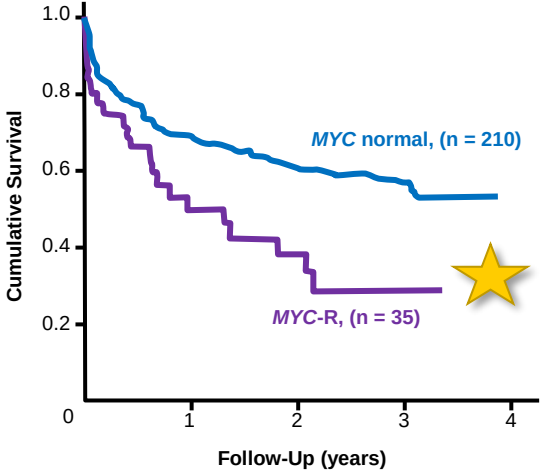
NOS and Double Hit Lymphomas

HGBCL NOS[1]



- Burkitt-like or blastoid morphology
  - Majority are GCB
  - 45% single hit *MYC* gene rearrangement
- Best frontline treatment is unknown: Burkitt-like regimens or DA REPOCH?

HGBCL/DHL[2]

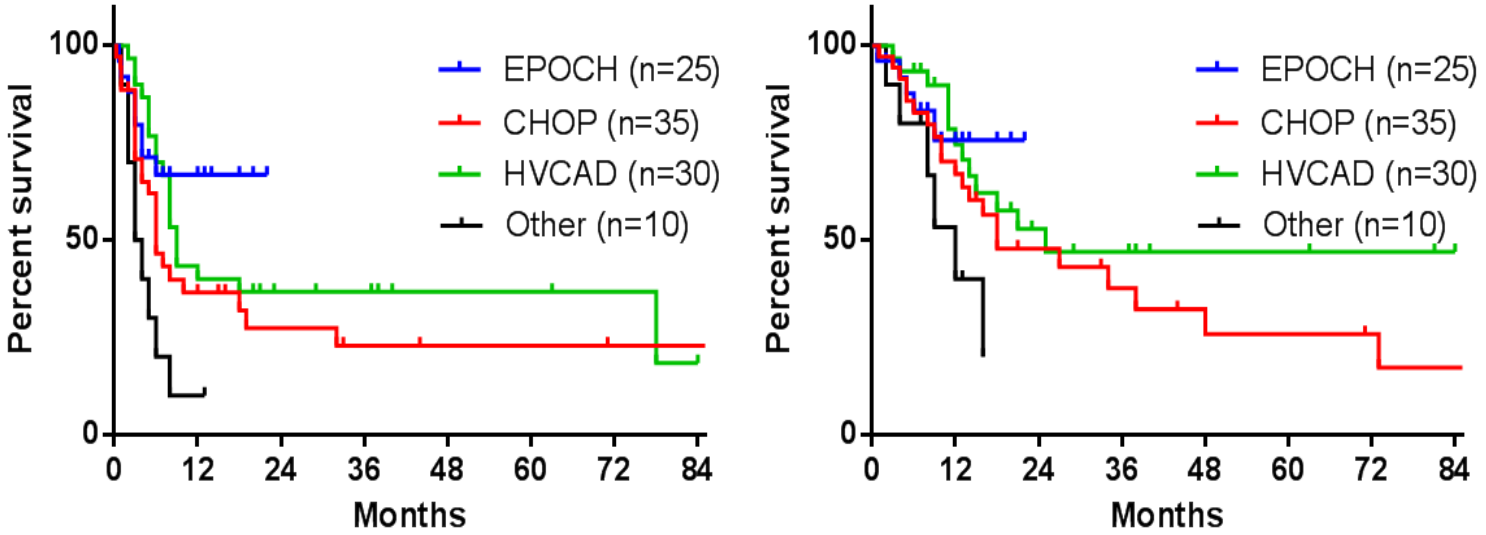


- >90% DHL are GCB-like
  - Most DEL are ABC-like
- DHL is associated with a poor outcome with RCHOP
  - DELs have an intermediate prognosis
  - Best frontline treatment is unknown: DA-REPOCH?

1. Sha C, et al. *J Clin Oncol*. 2019;37(3):202-212. 2. Barrans S, et al. *J Clin Oncol*. 2010;28(20):3360-3365.

Double Hit DLBCL in 100 MDACC Patients: A Retrospective Analysis

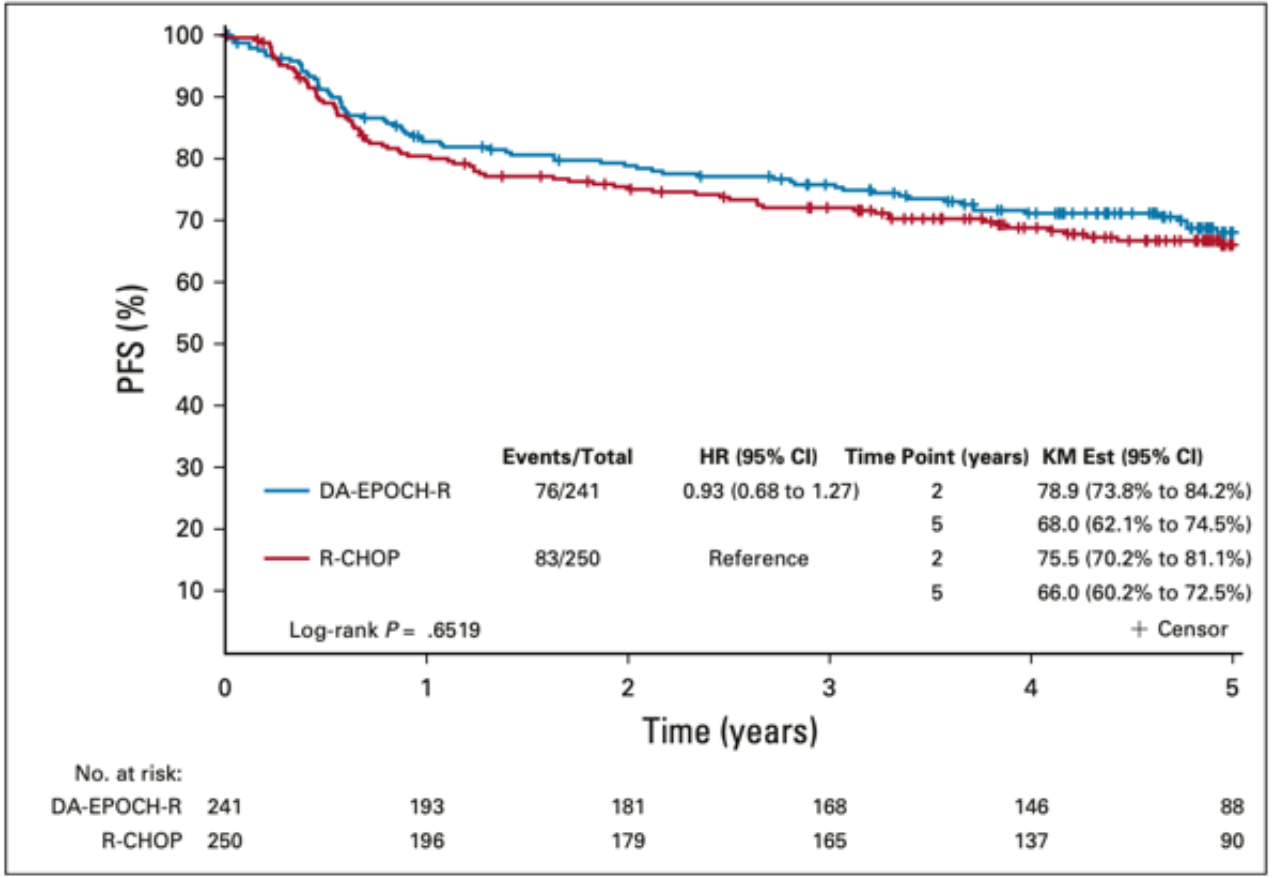
- CR rates: All 59%, CHOP ± R 49%, EPOCH ± R 50%, HCVAD ± R 60% (P=NS)
- 3 Year PFS (All pt) = 32%, OS = 41%. No diff by chemo regimen



Similar results for DA-EPOCH-R from NCI

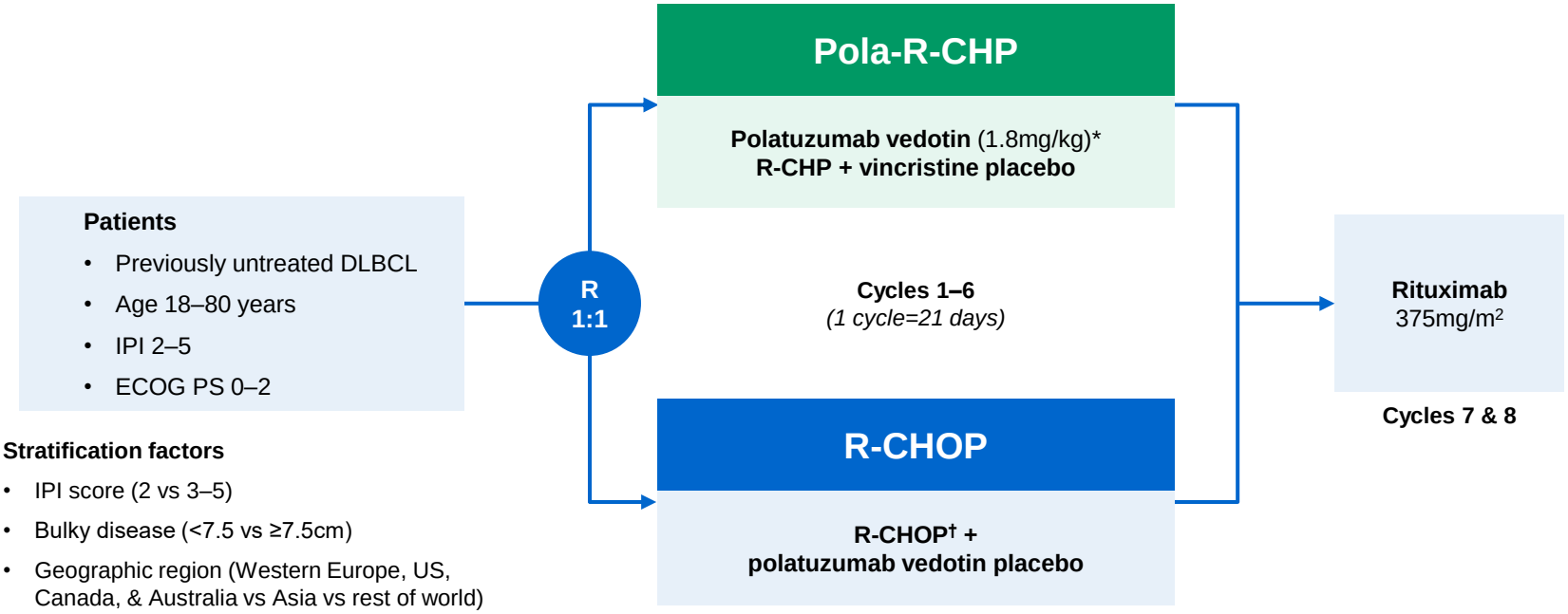
Oki et al. ASH 2013 #1776 Dunleavy et al. ASH 2013 #

DA-EPOCH-R is not superior to RCHOP



(7) Bartlett JCO 2019

POLARIX: A randomized double-blinded study



*IV on Day 1; †R-CHOP: IV rituximab 375mg/m², cyclophosphamide 750mg/m², doxorubicin 50mg/m², and vincristine 1.4mg/m² (max. 2mg) on Day 1, plus oral prednisone 100mg once daily on Days 1–5.
IPI, International prognostic index; ECOG PS, Eastern Cooperative Oncology Group performance status; R, randomized.

Hervé Tilly, et al., Presented at ASH2021; No. LBA-1

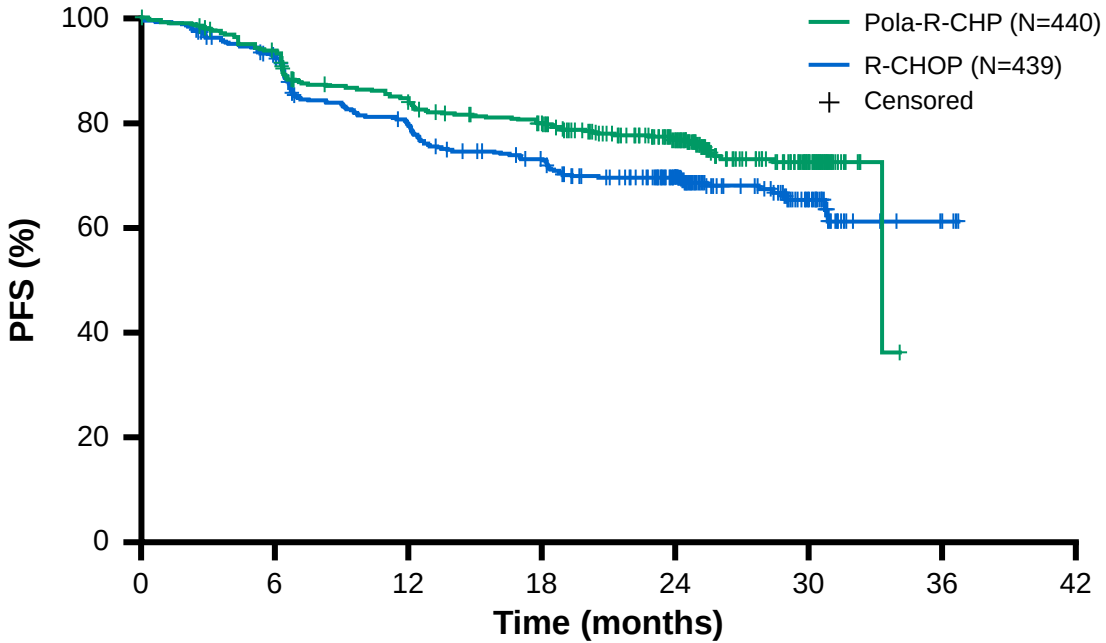
Baseline characteristics

ITT population		Pola-R-CHP (N=440)	R-CHOP (N=439)
Age	Median (range), years	65.0 (19–80)	66.0 (19–80)
Sex, n (%)	Male	239 (54)	234 (53)
ECOG PS, n (%)	0–1	374 (85)	363 (83)
	2	66 (15)	75 (17)
Bulky disease (≥7.5cm), n (%)	Present	193 (44)	192 (44)
Elevated LDH, n (%)	Yes	291 (66)	284 (65)
Time from diagnosis to treatment initiation	Median, days	26	27
Ann Arbor Stage, n (%)	III–IV	393 (89)	387 (88)
Extranodal sites, n (%)	≥2	213 (48)	213 (49)
IPI score, n (%)	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, n (%)*	Double expression	139 (38)	151 (41)
MYC/BCL2/BCL6 rearrangement, n (%)*	Double-/triple-hit	26 (8)	19 (6)

*In the Pola-R-CHP and R-CHOP groups, respectively, the numbers of patients evaluable for cell-of-origin were 330 and 338, with IHC for MYC/BCL2 expression were 362 and 366, and with FISH for *MYC/BCL2/BCL6* rearrangements were 331 and 334.
ABC, activated B-cell; FISH, fluorescence in situ hybridization; GCB, germinal center B-cell; LDH, lactate dehydrogenase.

Primary endpoint: Progression-free survival

Pola-R-CHP significantly improved PFS versus R-CHOP



No. of patients at risk

Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

HR 0.73 **(P<0.02)**

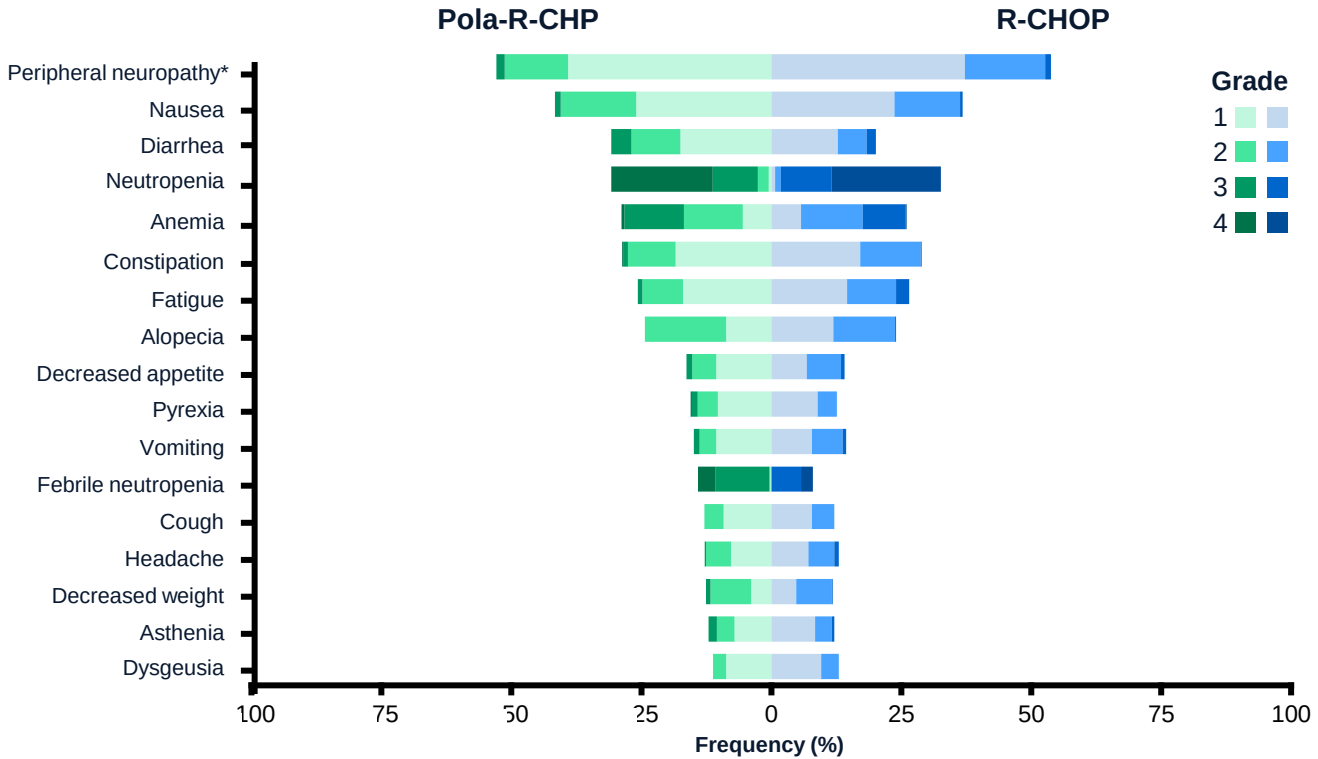
95% CI: 0.57, 0.95

- Pola-R-CHP demonstrated a **27% reduction in the relative risk of disease progression, relapse, or death** versus R-CHOP
- **24-month PFS:** 76.7% with Pola-R-CHP versus 70.2% with R-CHOP (Δ**=6.5%**)

ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up.
NE, not evaluable.

Hervé Tilly, et al., Presented at ASH2021; No. LBA-1

Common adverse events

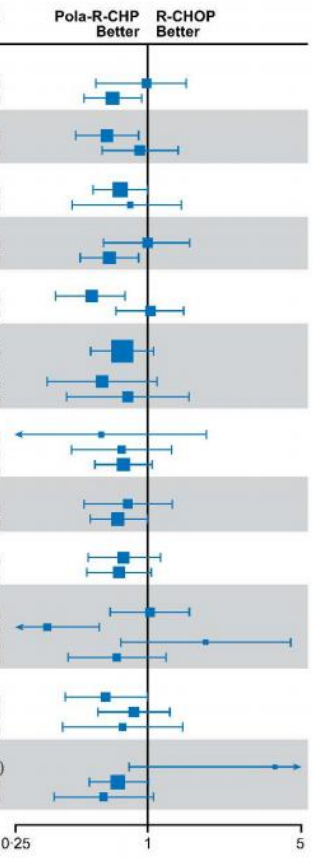


Data cut-off: June 28, 2021. Adverse events are Medical Dictionary for Regulatory Activities version 24.0 preferred terms; shown are all-grade adverse events occurring in ≥12% of patients in any treatment arm. *Peripheral neuropathy is defined by standard organ class group of preferred terms.

Hervé Tilly, et al., Presented at ASH2021; No. LBA-1

Exploratory Analyses

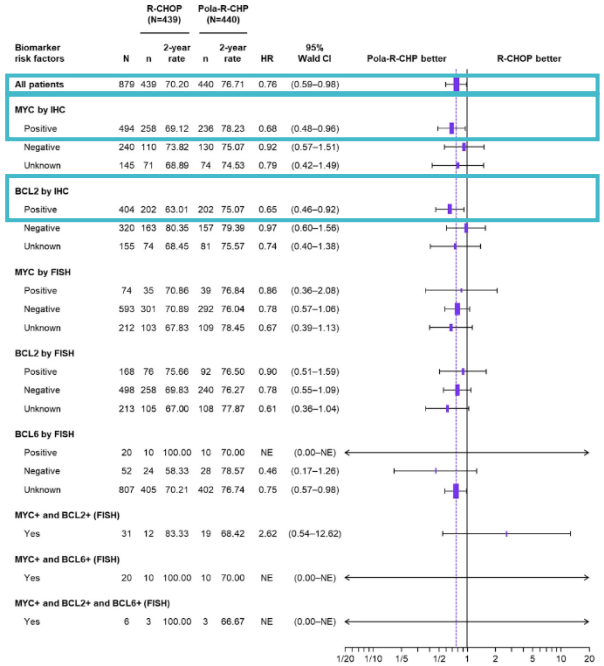
Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
Age group							
≤60	271	140	74·1	131	71·9	0·9	(0·6 to 1·5)
>60	608	300	77·9	308	69·5	0·7	(0·5 to 0·9)
Sex							
Male	473	239	75·9	234	65·9	0·7	(0·5 to 0·9)
Female	406	201	77·7	205	75·2	0·9	(0·6 to 1·4)
ECOG PS							
0–1	737	374	78·4	363	71·2	0·8	(0·6 to 1·0)
2	141	66	67·2	75	65·0	0·8	(0·5 to 1·4)
IPI score							
IPI 2	334	167	79·3	167	78·5	1·0	(0·6 to 1·6)
IPI 3–5	545	273	75·2	272	65·1	0·7	(0·5 to 0·9)
Bulky disease							
Absent	494	247	82·7	247	70·7	0·6	(0·4 to 0·8)
Present	385	193	69·0	192	69·7	1·0	(0·7 to 1·5)
Geographic region							
Western Europe, United States, Canada, and Australia	603	302	78.6	301	72.0	0.8	(0·6 to 1·1)
Asia	160	81	74.3	79	65.6	0.6	(0·4 to 1·5)
Rest of world	116	57	70.8	59	67.3	0.9	(0·6 to 1·5)
Ann Arbor stage							
I–II	99	47	89·1	52	85·5	0·6	(0·2 to 1·8)
III	232	124	80·7	108	73·6	0·8	(0·5 to 1·3)
IV	548	269	72·6	279	66·1	0·8	(0·6 to 1·1)
Baseline LDH							
≤ULN	300	146	78·9	154	75·6	0·8	(0·5 to 1·3)
>ULN	575	291	75·4	284	67·2	0·7	(0·5 to 1·0)
No. of extranodal sites							
0–1	453	227	80·2	226	74·5	0·8	(0·5 to 1·1)
≥2	426	213	73·0	213	65·8	0·7	(0·5 to 1·0)
Cell-of-origin							
GCB	352	184	75·1	168	76·9	1·0	(0·7 to 1·5)
ABC	221	102	83·9	119	58·8	0·4	(0·2 to 0·6)
Unclassified	95	44	73·0	51	86·2	1·9	(0·8 to 4·5)
Unknown	211	110	73·8	101	64·3	0·7	(0·4 to 1·2)
Double expressor by IHC							
DEL	290	139	75·5	151	63·1	0·6	(0·4 to 1·0)
Non DEL	438	223	77·7	215	75·7	0·9	(0·6 to 1·3)
Unknown	151	78	76·0	73	69·8	0·8	(0·4 to 1·5)
Double- or triple-hit lymphoma							
Yes	45	26	69·0	19	88·9	3·8	(0·8 to 17·6)
No	620	305	76·8	315	70·3	0·7	(0·5 to 1·0)
Unknown	214	109	78·5	105	66·4	0·6	(0·4 to 1·1)



Hervé Tilly, et al., NEJM 2021 Dec 14

Analyses From the POLARIX Phase 3 Trial of Pola-R-CHP vs R-CHOP in 1L DLBCL: Outcomes by BCL2 and MYC Expression/Rearrangements

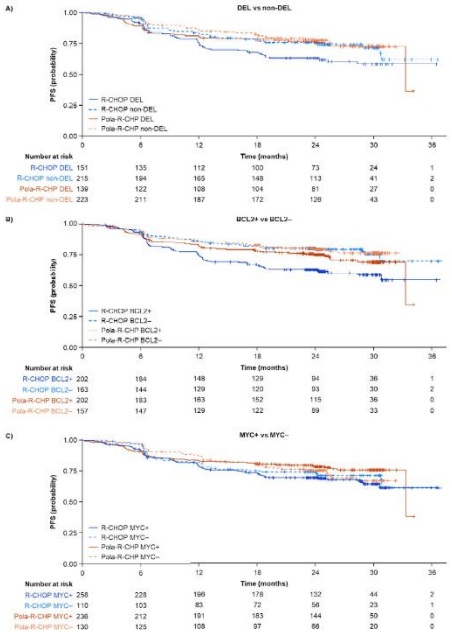
2-Year PFS (INV) and Univariate PFS HR by Biomarker Subgroup (ITT)



Pola-R-CHP vs R-CHOP

- Univariate results
  - BCL2+: HR 0.65 (95% CI 0.46-0.92)
  - MYC+: HR 0.68 (95% CI 0.48-0.96)
- Multivariate results
  - BCL2+: HR 0.60 (95% CI 0.43–0.86)
  - MYC+: HR 0.63 (95% CI 0.45–0.89)

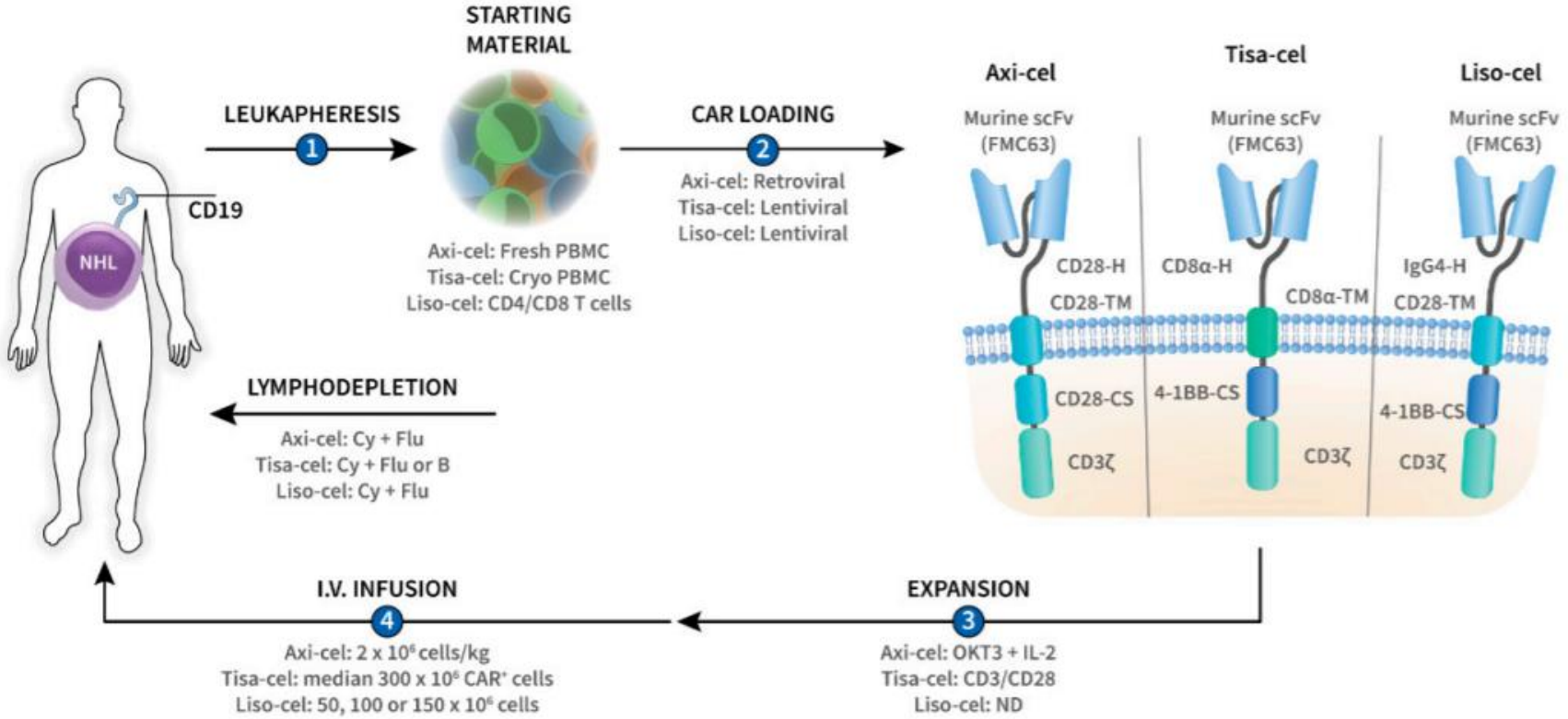
PFS in Subgroups Stratified by DEL vs non-DEL, BCL2+/-, MYC+/-



- Prognostic impact of DEL vs non-DEL was more pronounced with R-CHOP vs Pola-R-CHP
  - Univariate HR 1.53 (95% CI 1.06-2.21) vs HR 1.10 (95% CI 0.72-1.69)
  - Multivariate HR 1.29 (95% CI 0.88-1.91) vs HR 1.42 (95% CI 0.89-2.28)
- BCL2+ had inferior PFS vs BCL- with R-CHOP; no prognostic difference with Pola-R-CHP
  - Univariate HR 1.96 (95% CI 1.31-2.93)
  - Multivariate HR 1.74 (95% CI 1.14-2.66)
- No prognostic impact of MYC+ vs MYC- in either arm

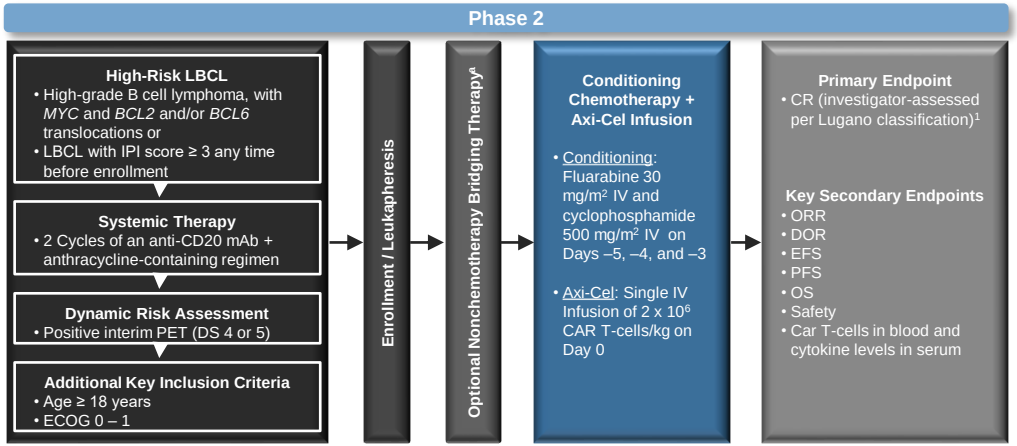
Morschhauser, F et al. ASCO 2022. Abstract 7517.

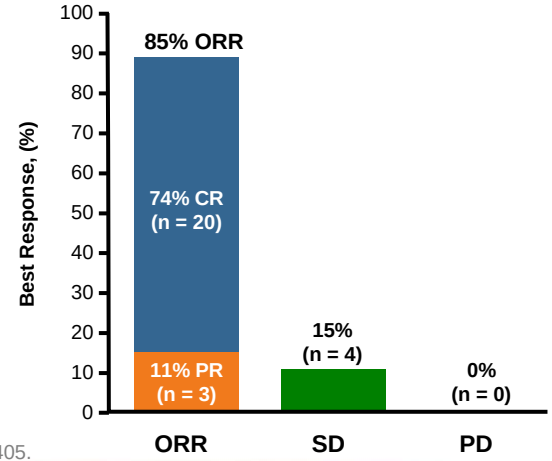
Auto CD19 CAR T-cell Products



Roex G, et al. Pharmaceutics. 2020;12:194.

Phase 2 ZUMA-12: CD19 CAR T-Cells in Frontline LBCL





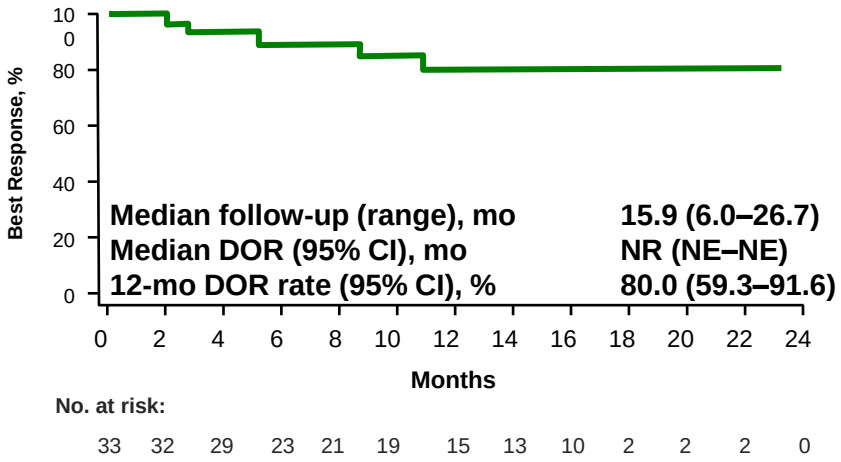
Parameter Median (Range)	ZUMA-12[a] (N = 32)	ZUMA-1 Cohort 1[b] (N = 77)
Total no. of T-cells infused x 10^6, n	306 (169 – 603)	295 (149 – 760)
Total no. of CAR T-cells infused x 10^6, n	17- (95 – 200)	160 (96 – 200)
Total no. of CCR7+CD45RA+T-cells infused x 10, n	105 (35 – 254)	40 (2 – 215)
CCR7+CD45RA+T-cells, %	34 (7 – 76)	14 (1 – 76)
Doubling time, days	1.6 (1.3 – 3.4)	1.5 (1.0 – 4.7)

	Response Evaluable N = 27[b]
Median follow-up (rang)e, months	9.3 (0.9 – 18.0)
Patients with ≥ 6-months follow-up, n (%)	19 (70)
Patients with ongoing response as of data cutoff	19 (70)
Median time to response (range), months	
Initial objective response	1.0 (0.9 – 3.1)
CR	1.0 (0.9 – 6.4)
Patients converted from PR / SD to CR, n (%)	5 (19)
PD to CR	4 (15)
SD to CR	1 (4)

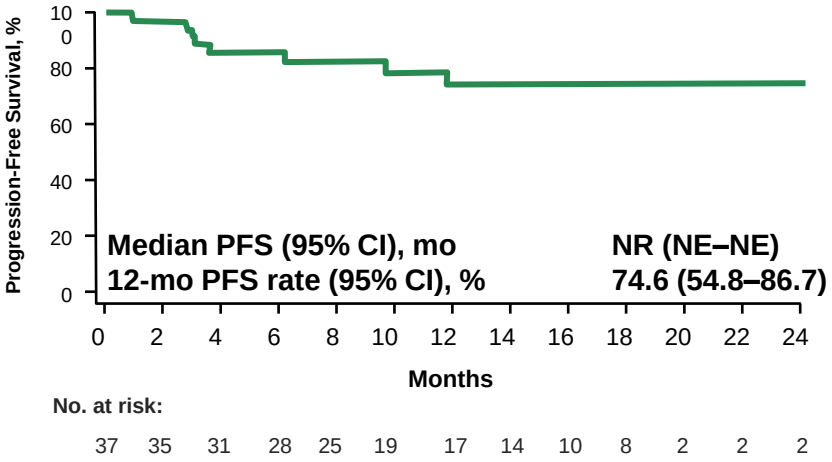
Neelapu, et al. ASH 2020; Abstract 405.

Phase 2 ZUMA-12: CD19 CAR T-Cells in Frontline LBCL

DOR



PFS

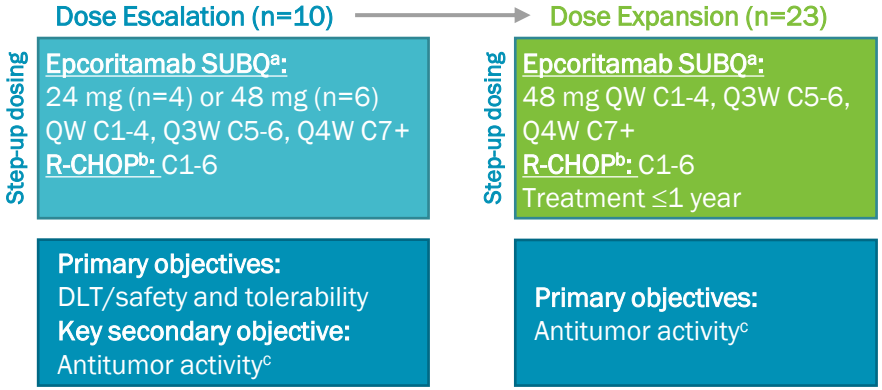


Analyses done in all treated patients with centrally confirmed disease type (double- or triple-hit lymphomas) or IPI score ≥3 who received ≥1x10^6 CAR T-cells/kg.
DOR, duration of response; EFS, event-free survival; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival.

EPCORE NHL-2 Phase 1/2 Study of Epcoritamab + R-CHOP in Patients With High-Risk DLBCL (Arm 1): Study Design and Patients

Key Eligibility Criteria (Arm 1)

- Newly diagnosed CD20+ DLBCL, including DLBCL NOS, T-cell/histiocyte-rich, double- or triple-hit, FL grade 3b
- IPI score ≥3
- ECOG PS 0-2



Patient Characteristics		N=33
Median age (range), years		66 (19-82)
ECOG PS, n (%)	0	13 (39)
	1	16 (48)
	2	4 (12)
Ann Arbor stage, n (%)	III	7 (21)
	IV	26 (79)
IPI score, n (%)	3	18 (55)
	4-5	10 (30)
DLBCL subtype, n (%)	De novo	28 (85)
	Transformed	5 (15)
MYC/BCL2/BCL6 rearrangements, n (%)	Double-hit lymphoma	3 (9)
	Triple-hit lymphoma	5 (15)
Median time from diagnosis to 1st dose (range), days		26 (5-70)

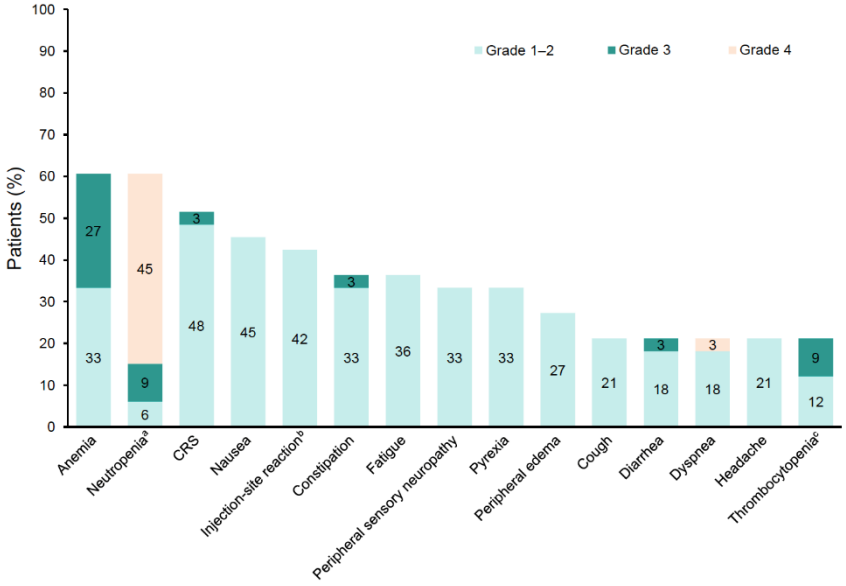
Data cutoff: March 25, 2022. [a] Patients received SUBQ epcoritamab with step-up dosing and corticosteroid prophylaxis to mitigate CRS. [b] R 375 mg/m^2 IV Q3W, cyclophosphamide 750 mg/m^2 IV Q3W, doxorubicin 50 mg/m^2 IV Q3W, vincristine 1.4 mg/m^2 IV Q3W (recommended maximum 2 mg), and prednisone 100 mg/d IV or orally on days 1-5. [c] Tumor response evaluated by PET-CT obtained at 6, 12, 18, 24, 36, and 48 weeks, and every 24 weeks thereafter until PD.
Falchi, L et al. ASCO 2022. Abstract 7523. Clausen MR, et al. EHA 2022. Abstract P1214.

EPCORE NHL-2 Phase 1/2 Study of Epcoritamab + R-CHOP in Patients With High-Risk DLBCL (Arm 1): Safety

Follow-up and Treatment Exposure		N=33
Median follow-up (range), months		6.9 (0.8-14.7)
Ongoing treatment, n (%)		24 (73)
Discontinued treatment, n (%)		6 (18)
PD		2 (6)
AE		1 (3)
Other reason		3 (9)
Completed treatment		3 (9)
Treatment exposure	Median cycles epcoritamab initiated (range), n	9 (1-15)[a]
	Median duration of treatment (range), months	6.3 (0.6-11.5)
	Epcoritamab dose delays due to TEAE, n (%)	17 (52)
	Completed 6 cycles of R-CHOP, n (%)	30 (91)

- No clinical TLS events
- One patient (3%) had grade 2 ICANS which resolved in 4 days

TEAEs (≥20%) by Grade



Data cutoff: March 25, 2022.

[a] 1 patient received an extra dose due to a repriming cycle causing maximum to be 15.

Falchi, L et al. ASCO 2022. Abstract 7523. Clausen MR, et al. EHA 2022. Abstract P1214.

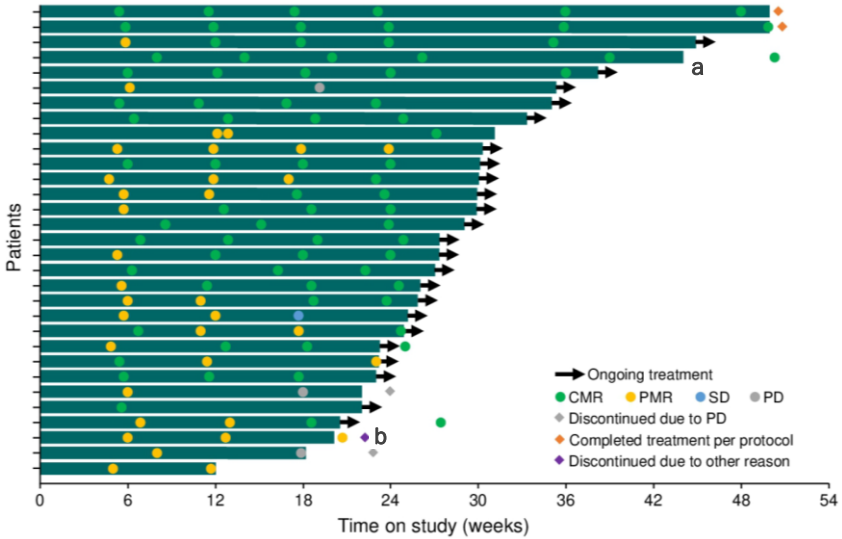
EPCORE NHL-2 Phase 1/2 Study of Epcoritamab + R-CHOP in Patients With High-Risk DLBCL (Arm 1): Efficacy and Summary

Best Overall Responses, n (%)	n=31
ORR	31 (100)
CMR	24 (77)
PMR	7 (23)
SD	0
PD	0

Authors' Conclusions

- Epcoritamab in combination with R-CHOP demonstrated efficacy, with an ORR of 100% and CMR of 77%, and a manageable safety profile, with low-grade CRS and events that resolved
- These data support further investigation of epcoritamab + R-CHOP in 1L DLBCL

Response Profile



Data cutoff: March 25, 2022.

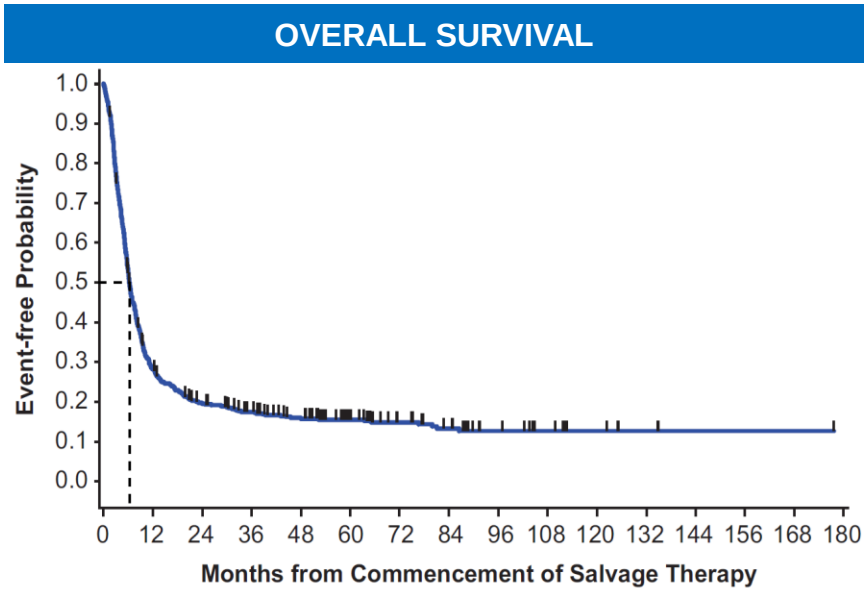
[a] This patient completed treatment per protocol. [b] Patient did not achieve CMR after completing 6 cycles of R-CHOP.

Falchi, L et al. ASCO 2022. Abstract 7523. Clausen MR, et al. EHA 2022. Abstract P1214.

SCHOLAR-1 (Retrospective Non-Hodgkin Lymphoma Research)

SCHOLAR-1, a retrospective, international, patient-level, multi-institution study with the largest reported analysis of outcomes in patients with refractory large B cell lymphoma

- N = 636 (post-rituximab era, 2000-2017)
- ORR = 26%
- CR rate = 7%
- Median OS = 6.3 months
- These results provided a benchmark for evaluation of new approaches



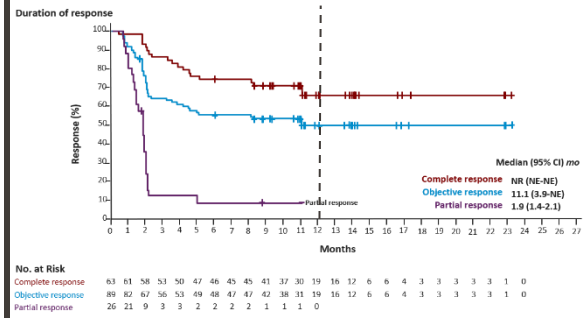
(22) Crump, Blood 2017

Duration of Response, CD19 CAR T-cell Therapies in DLBCL

ZUMA-1[1,2]

Axicabtagene ciloleucel

Median follow-up, 15.4 months

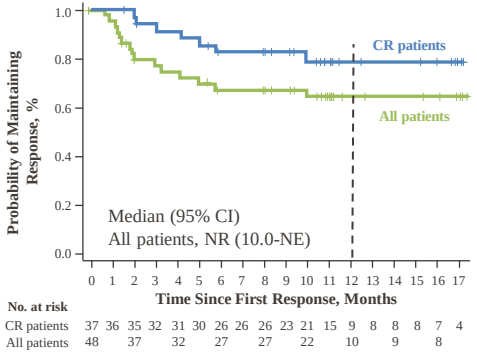


- 42% of patients had an ongoing response at long-term follow-up; 40% had CR
- 23 patients with either a PR (11/35) or SD (12/25) at the first tumor assessment (1 month post-axi-cel) achieved CR up to 15 months post infusion without additional therapy

JULIET[3]

Tisagenlecleucel

Median follow-up, 14 months

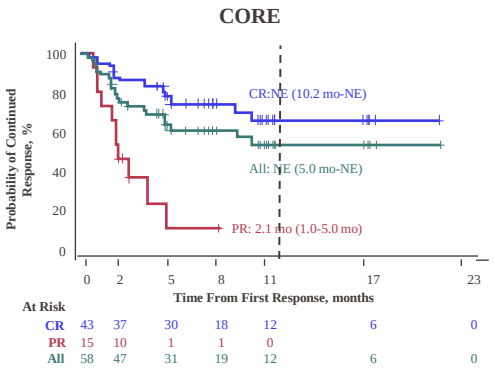


- 54% (13/24) patients converted from PR to CR, including 2 patients 15-17 months after initial response

TRANSCEND[4]

Lisocabtagene maraleucel*

Median follow-up, 8 months



- In CORE group, 88% of patients with CR at 3 months stayed in CR at 6 months; 93% of patients in CR at 6 months had ongoing response

*Lisocabtagene maraleucel is not TGA-registered and the efficacy and safety has not been evaluated by the TGA.

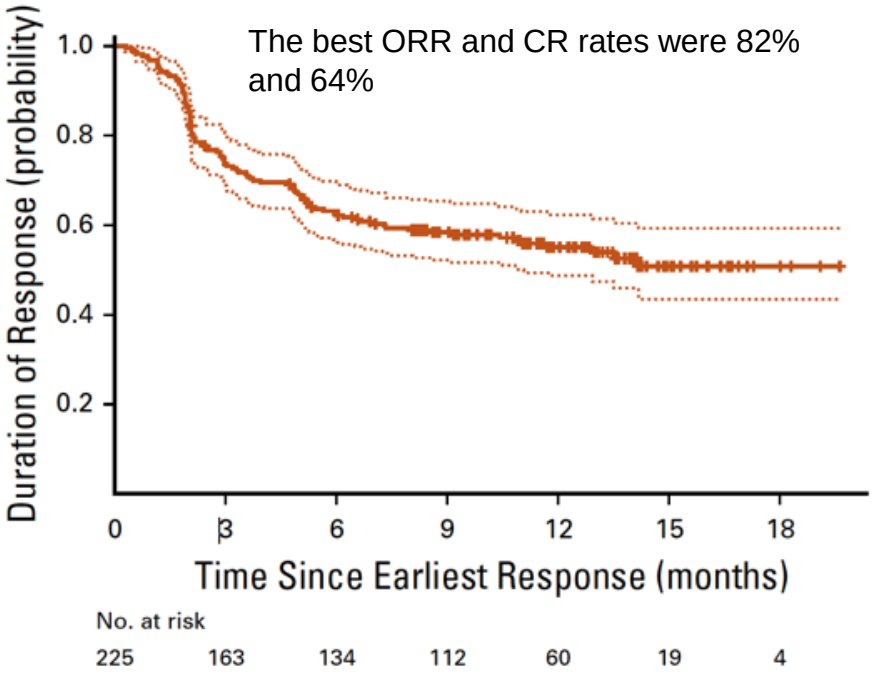
MD ANDERSON CANCER CENTER

1. Neelapu SS, et al. N Engl J Med. 2017;377:2531-2544. 2. Neelapu SS, et al. ASH 2017[Abst 578]. 3. Schuster SJ, et al. N Engl J Med 2019;380:45-56. 4. Abramson JS et al, ASCO 2018 [abstract 7505].

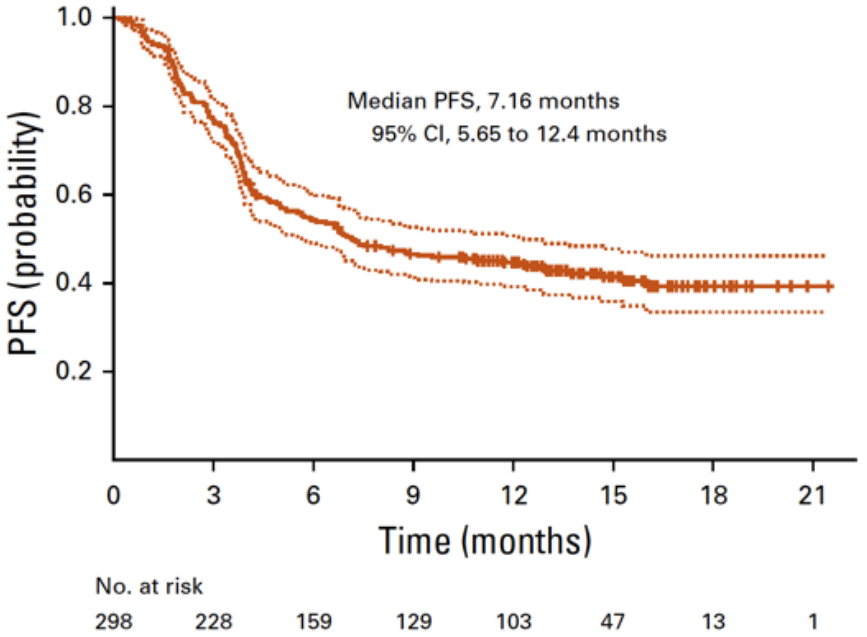
Efficacy of Axi-Cel in Clinical Practice

Duration of Response

The best ORR and CR rates were 82% and 64%



Progression Free Survival

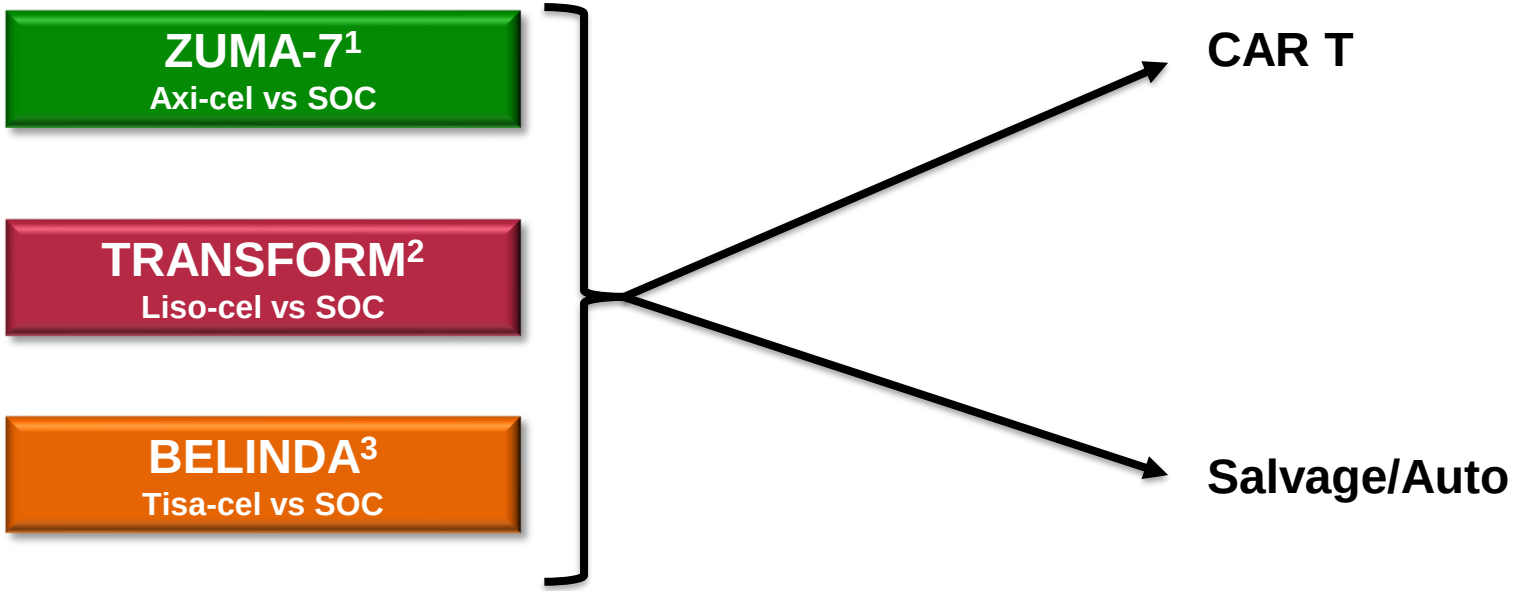


Nastoupil LJ, et al. J Clin Oncol. 2020;38:3119-3128.

Will CD19 CAR T-Cells Replace Auto-transplant?

High Risk DLBCL:

- Refractory to 1st-line tx
- Relapsed within 12m of 1st-line tx

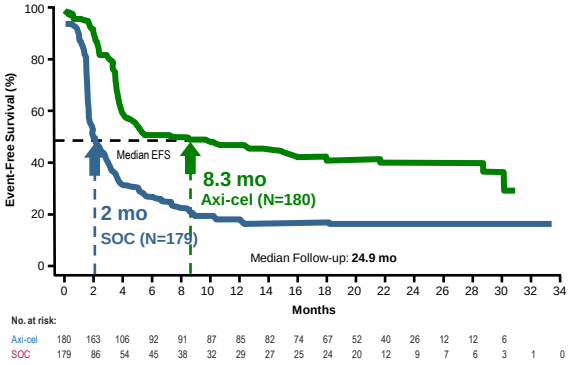


1. Locke, et al. ASH 2021: Abstract 2. 2.Kamdar M, et al. *Lancet*. 2022;399(10343):2294-2308 . 3. Bishop MR, et al. *N Engl J Med*. 2022;386(7):629-639.

ZUMA-7, TRANSFORM, & BELINDA: Survival & Responses

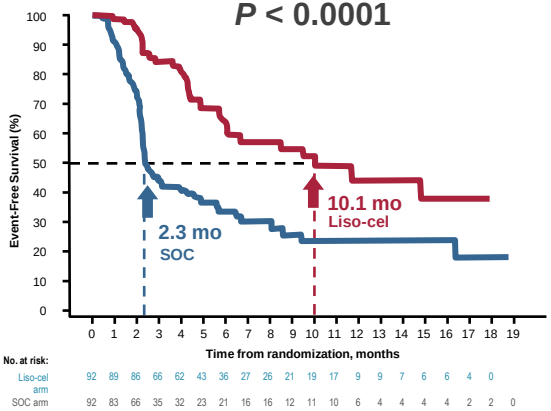
ZUMA-7[1]

HR 0.398 (95% CI, 0.308–0.514)
***P* < 0.0001**



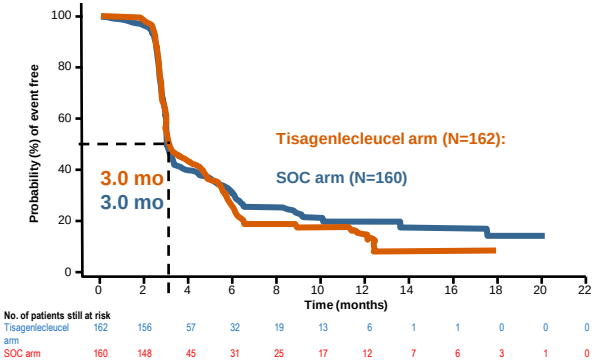
TRANSFORM[2]

HR 0.349 (95% CI, 0.229-0.530)
***P* < 0.0001**



BELINDA[3]

HR: 1.07 (95% CI, 0.82-1.40)
***P*=0.69**



	Axi-cel vs SOC	Liso-cel vs SOC	Tisa-cel vs SOC
ORR	83% vs 50%	86% vs 48%	46% vs 43%
CR	65% vs 32%	66% vs 39%	28% vs 28%
mOS	NR vs 35.1 mos HR: 0.73 (95% CI: 0.53-1.01) *P* = .0270	NR vs 16.4 mos HR: 0.51 (95% CI: 0.26-1.0)	NA

Cross-trial comparisons are for discussion purposes only
NR, not yet reached

1. Locke, et al. ASH 2021: Abstract 2. 2. Kamdar, et al. ASH 2021: Abstract 91. 3. Bishop MR, et al. *N Engl J Med*. 2022;386(7):629-639.

NCCN Guidelines: Second-line Regimens for Relapsed DLBCL <12 Months After Frontline Therapy or Primary Refractory

CAR-T eligible

- Axicabtagene ciloleucel (category 1)
- Lisocabtagene maraleucel

(with bridging therapy as clinically indicated)

CAR T-Cell Therapy Bridging Options

- DHA (dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) ± rituximab
- GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab
- GemOx (gemcitabine, oxaliplatin) ± rituximab
- ICE (ifosfamide, carboplatin, etoposide) ± rituximab
- Polatuzumab vedotin-piiq ± rituximab ± bendamustine (bendamustine should be considered/added only after leukapheresis)

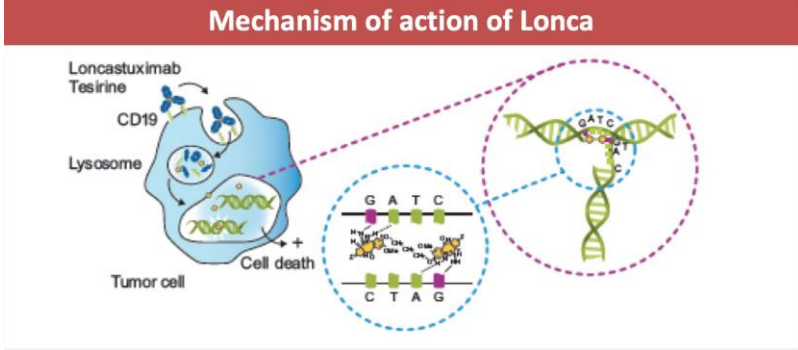
CAR-T ineligible

Clinical trial
OR
Second-line regimens (as on previous slide)
OR
Palliative ISRT
OR
Best supportive care

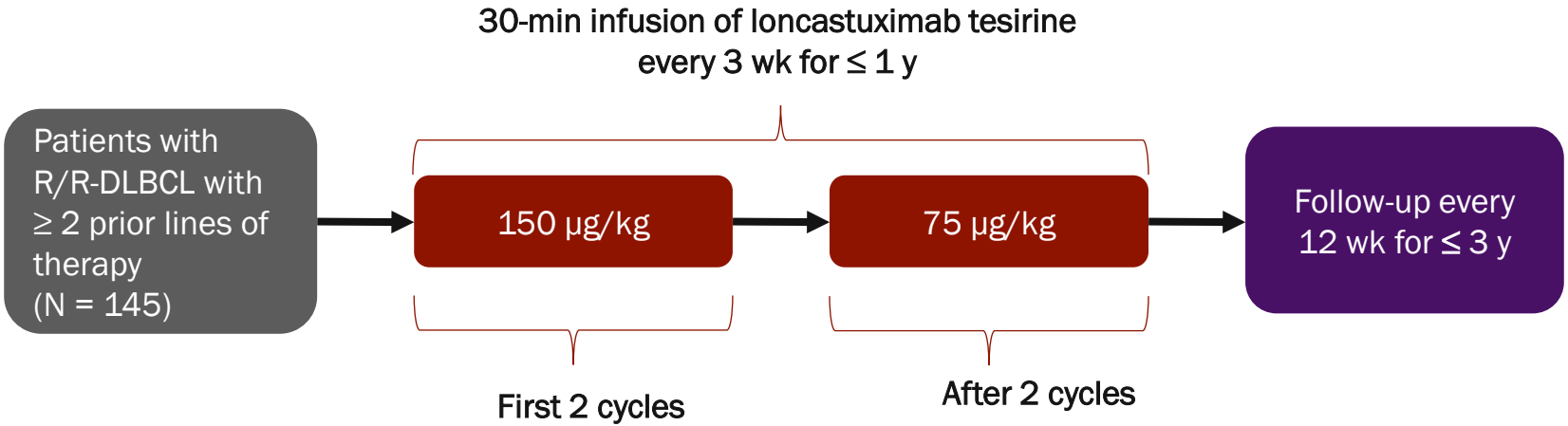
*High dose therapy with ASCT rescue, consider allogeneic HSCT in selected cases, ± ISRT. CR = complete response.

NCCN. Clinical Practice Guidelines in Oncology: B-Cell Lymphomas. Version 5.2022. July 12, 2022.

Loncastuximab Tesirine



- Phase 2 trial in R/R DLBCL after ≥ 2 prior lines of therapy



(28) Caimi Lancet Oncol. 2021

Loncastuximab Tesirine in R/R DLBCL
Baseline Characteristics

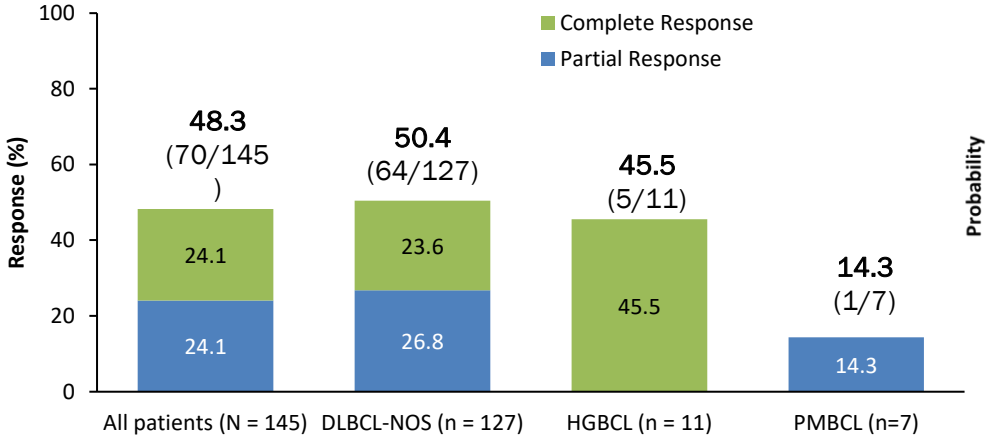
Patient Characteristic	Total (N = 145)
Sex, No. (%)	
Female	60 (41.4)
Male	85 (58.6)
Age, y, median (range)	66.0 (23–94)
Histology, No. (%)	
DLBCL	127 (87.6)
HGBCL	11 (7.6)
PMBCL	7 (4.8)
Double/triple hit, No. (%)	15 (10.3)
Double/triple expressor, No. (%)	20 (13.8)
Transformed disease, No. (%)	29 (20.0)
Stage, No. (%)	
I-II	33 (22.8)
III-IV	112 (77.2)

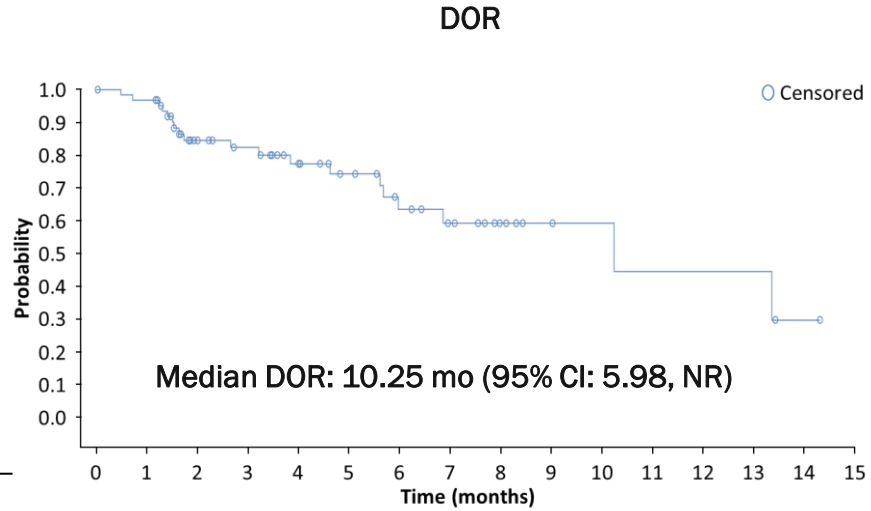
Patient Treatment History	Total (N = 145)
No. of prior systemic therapies,* median (range)	3 (2–7)
First-line systemic therapy response, No. (%)	
Relapse	99 (68.3)
Refractory†	29 (20.0)
Other‡	17 (11.7)
Last-line systemic therapy response,¶ No. (%)	
Relapse	43 (29.7)
Refractory†	84 (57.9)
Other‡	18 (12.4)
Refractory to all prior therapies, No. (%)	
Yes	25 (17.2)
No	115 (79.3)
Other‡	5 (3.4)
Prior SCT, No. (%)	
Allogeneic	2 (1.4)
Autologous	21 (14.5)
Both	1 (0.7)

Data cutoff: April 6, 2020. *Prior SCT is included. For patients who received an autologous transplant, the mobilization regimen was considered a line of therapy if it was chemotherapy based and distinct from the other previous lines of treatment. †Refractory disease defined as no response to therapy. ‡Other defined as unknown, not evaluable, or missing. ¶If SCT is the most recent line, the variable is defined as response to the therapy immediately preceding SCT.

Carlo-Stella C, et al. EHA 2020. Presentation S233.

Loncastuximab Tesirine in R/R DLBCL
Response by Histology





Carlo-Stella C, et al. EHA 2020. Presentation S233.

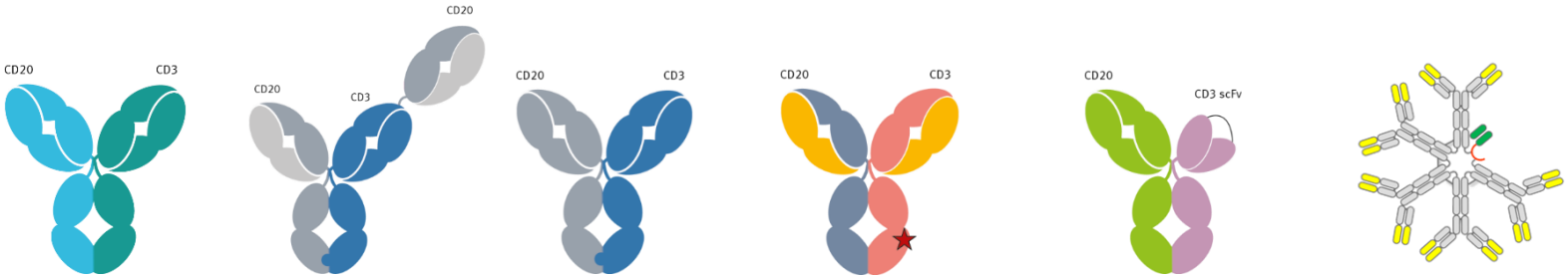
Loncastuximab Tesirine in R/R DLBCL
Safety Data

Preferred term, No. (%)	Patients (N = 145)
Patients with any TEAE	**143 (98.6)**
GGT increased	59 (40.7)
Neutropenia	57 (39.3)
Thrombocytopenia	48 (33.1)
Fatigue	40 (27.6)
Anaemia	38 (26.2)
Nausea	34 (23.4)
Cough	32 (22.1)
Alkaline phosphatase increased	29 (20.0)
Peripheral edema	29 (20.0)

- The most common grade ≥ 3 TEAEs (≥ 10% of patients) were:
  - Neutropenia (n = 37 patients; 25.5%)
    - Incidence of febrile neutropenia was low (n = 5 patients; 3.4%)
  - Thrombocytopenia (n = 26 patients; 17.9%)
  - GGT increased (n = 24 patients; 16.6%)
  - Anemia (n = 15 patients; 10.3%)

Carlo-Stella C, et al. EHA 2020. Presentation S233.

Overview of CD3xCD20 Bispecific Antibodies



Name of bispecific	Epcoritamab[1]	Glofitamab[2,3]	Mosunetuzumab[4,5]	Odronextamab[6]	Plamotamab[7]	IGM-2323[8]
Bispecific format	DuoBody IgG1	Fab-Fc x Fab-Fab-Fc Knob-into-hole (HC) XmAb (LC-HC)	Knob-into-hole (HC) IgG1	FcΔAdp IgG4	XmAb Fab-Fc x scFv-Fc	Proprietary IgM platform
CD3 Ab clone	huCACAO (SP34-der.) (CD3ε)	(SP34-der.) (CD3ε)	UCHT1v9 (CD3δε)	REG1250 (CD3δε)	α-CD3_H1.30 (SP34-der.) (CD3ε)	Not reported
CD20 Ab clone	7D8 (OFA epitope)	Obinutuzumab (Ritux epitope)	2H7 (Ritux epitope)	3B9-10 (OFA epitope)	C2B8_H1_L1 (Rituximab > Ritux epitope)	Not reported
Inert format	L234F,L235E,D265A (No FcγR,C1q binding)	IgG1-P329G-LALA (No FcγR binding)	N297G (No FcγR binding)	Modified IgG4 (No FcγRIII binding)	G236R, L328R (No FcγR binding)	IgM + modified J chain (10 CD-20 and 2 CD-3 binding domains)
Publications	Engelberts, et al. 2020	Bacac, et al. 2016 Bacac, et al. 2018	Sun, et al. 2015 Ferl, et al. 2018	Smith, et al. 2015	Patel, et al. ASH 2019 (abstract 4079)	Baliga, et al. ASH 2019 (abstract 1574)

1. Engelberts PJ, *et al. EBioMedicine* 2020; **52:**10262; 2. Bacac M, *et al. Clin Cancer Res* 2016; **13:**3286–97; 3. Bacac M, et al. Clin Cancer Res 2018; **19:**4785–4797; 4. Sun LL, *et al. Sci Transl Med* 2015; **287:**287ra70; 5. Ferl GZ, *et al. Clin Transl Sci* 2018; **3:**296–304; 6. Smith EJ, *et al. Sci Rep* 2015; **5:**17943; 7. Patel, et al. ASH 2019; Abstract 4079; 8. Baliga, et al. ASH 2019; Abstract 1574.

Pivotal Results From the Phase 2 Expansion Study of Glofitamab in Patients With R/R DLBCL: Study Design and Patients

Key Eligibility Criteria

- R/R DLBCL NOS, HGBCL, tFL, or PMBCL
- ECOG PS 0-1
- ≥2 prior therapies, including anti-CD20 mAb, anthracycline

Glofitamab IV Administration

- Fixed-duration treatment: ≤12 (21-day) cycles
- CRS mitigation
  - Obinutuzumab IV 1000 mg 7 days prior to glofitamab
  - C1 step-up dosing
  - Monitoring after first dose (2.5 mg)

Primary endpoint: CR (best response) rate by IRC[a]

Secondary endpoints: ORR rate (by IRC & INV), DoR, DoCR (by IRC & INV), PFS, OS

Patient Characteristics		N=154
Median age (range), years		66.0 (21-90)
ECOG PS, n (%)	0	69 (44.8)
	1	84 (54.5)
Ann Arbor stage, n (%)	III	31 (20.1)
	IV	85 (55.2)
NHL subtype, n (%)	DLBCL	110 (71.4)
	tFL	27 (17.5)
	HGBCL	11 (7.1)
	PMBCL	6 (3.9)
Bulky disease, n (%)	>6cm	64 (41.6)
	>10cm	18 (11.7)
Median prior lines of therapy (range), n		3 (2-7)
≥3 prior lines, n (%)		92 (59.7)
Prior CAR-T, n (%)		51 (33.1)
Refractory status, n (%)	Refractory to last prior therapy	132 (85.7)
	Primary refractory	90 (58.4)
	Refractory to prior CAR-T	46 (29.9)

Clinical cut-off date: March 14, 2022

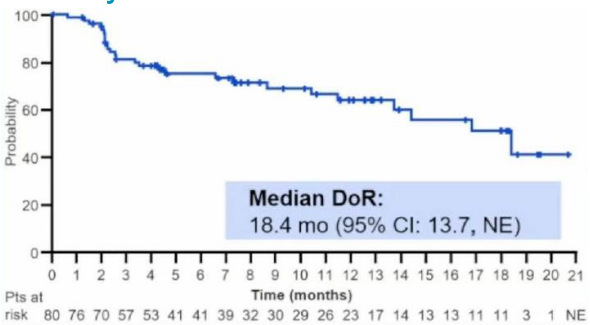
[a] By PET-CT (Lugano criteria).

Dickinson, M et al. ASCO 2022. Abstract 7500. EHA 2022. Abstract S220.

Pivotal Results From the Phase 2 Expansion Study of Glofitamab in Patients With R/R DLBCL: Efficacy

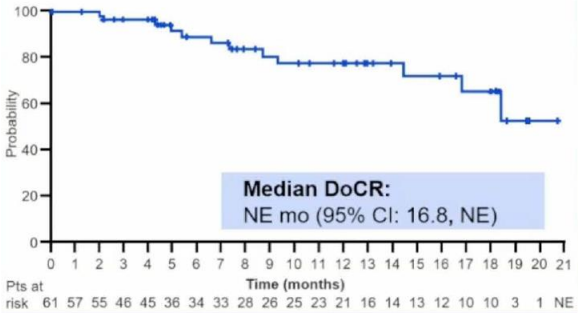
Efficacy	Glofitamab 2.5/10/30 mg (N=155)
ORR, n (%) [95% CI]	80 (51.6) [43.5, 59.7]
CR rate, n (%) [95% CI]	61 (39.4) [31.6, 47.5]
Median follow-up (range), months	12.6 (0-22)
Median time to first CR, days (95% CI)	42 (42, 44)
At primary analysis, primary endpoint was met in primary efficacy population (n=108): 35.2% CR rate was greater than 20% historical control CR rate (*P*<0.0001)	

DOR by IRC



DOR	n=80
Median follow-up (range), months	10.6 (0-21)
12-month DOR, % (95% CI)	63.6 (51.1, 76.2)
Responses ongoing at cutoff, n (%)	53 (66.3)

DoCR by IRC

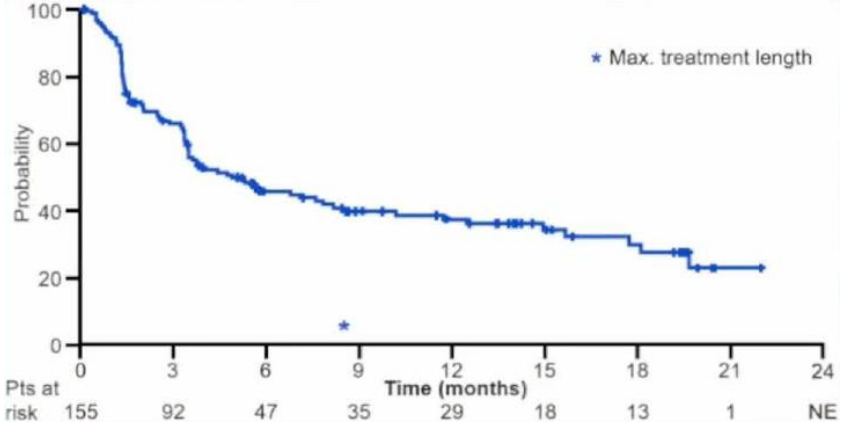


	n=61
Median follow-up (range), months	10.6 (0-21)
12-month DOCR, % (95% CI)	77.6 (64.3, 90.8)
CRs ongoing at cutoff, n (%)	49 (80.3)

Dickinson, M et al. ASCO 2022. Abstract 7500. EHA 2022. Abstract S220

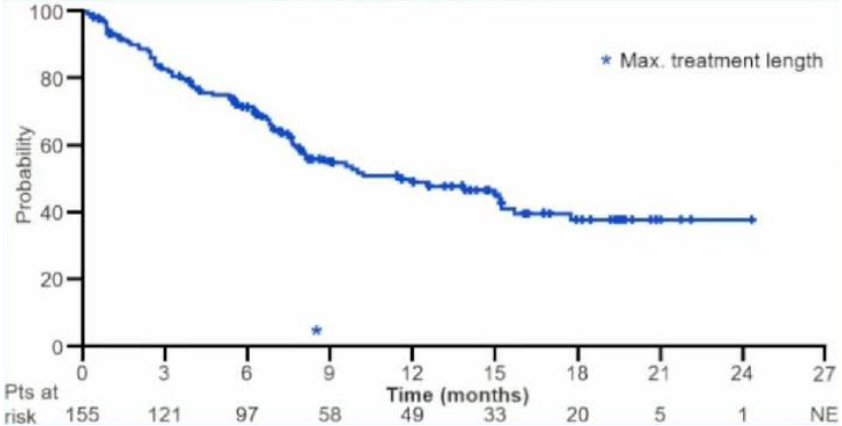
Pivotal Results From the Phase 2 Expansion Study of Glofitamab in Patients With R/R DLBCL With ≥2 Prior Therapies: Efficacy (Cont'd)

PFS by IRC



	N=155
Median PFS follow-up (range), months	12.6 (0-22)
Median PFS, months (95% CI)	4.9 (3.4, 8.1)
6-month event-free rate, % (95% CI)	45.5 (37.2, 53.8)
12-month event-free rate, % (95% CI)	37.1 (28.5, 45.8)

OS



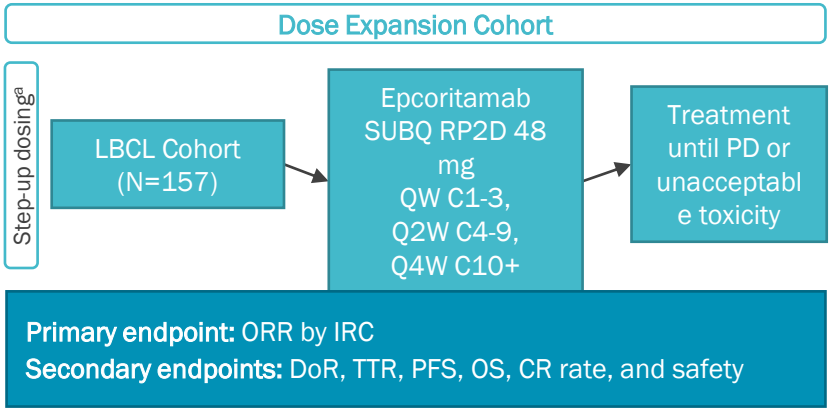
	N=155
Median OS, months (95% CI)	11.5 (7.9, 15.7)
12-month OS rate, % (95% CI)	49.8 (41.1, 58.5)

Dickinson, M et al. ASCO 2022. Abstract 7500. EHA 2022. Abstract S220

Pivotal Results From the EPCORE NHL-1 Phase 2 Study of Epcoritamab in Patients With R/R LBCL: Study Design and Patients

Key Eligibility Criteria

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



Patient Characteristics		N=157
Median age (range), years		64 (20-83)
≥75 years, n (%)		29 (18)
ECOG PS, n (%)	0	74 (47)
	1	78 (50)
	2	5 (3)
Disease type, n (%)	DLBCL	139 (89)
	HGBCL	9 (6)
	PMBCL	4 (3)
	FL grade 3b	5 (3)
Median time from initial diagnosis to first dose, years		1.6
Median prior lines of therapy (range), n		3 (2-11)
≥3 lines of therapy, n (%)		111 (71)
Primary refractory disease, n (%)		96 (61)
Refractory to ≥2 consecutive lines of therapy		119 (76)
Prior CAR T-cell therapy, n (%)		61 (39)
PD ≤6 months of CAR T-cell therapy, n (%)		46 (75)

Data cuttoff: January 31, 2022.

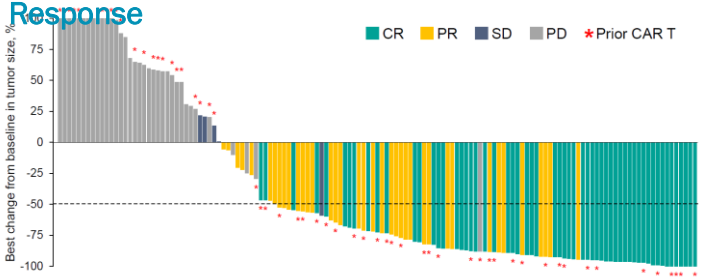
[a] Step-up dosing (priming 0.16 mg and intermediate 0.8 mg dosing before first full dose) and corticosteroid prophylaxis to mitigate CRS.

Thieblemont, C et al. EHA 2022. Abstract LBA2364.

Pivotal Results From the EPCORE NHL-1 Phase 2 Study of Epcoritamab in Patients With R/R LBCL: Efficacy

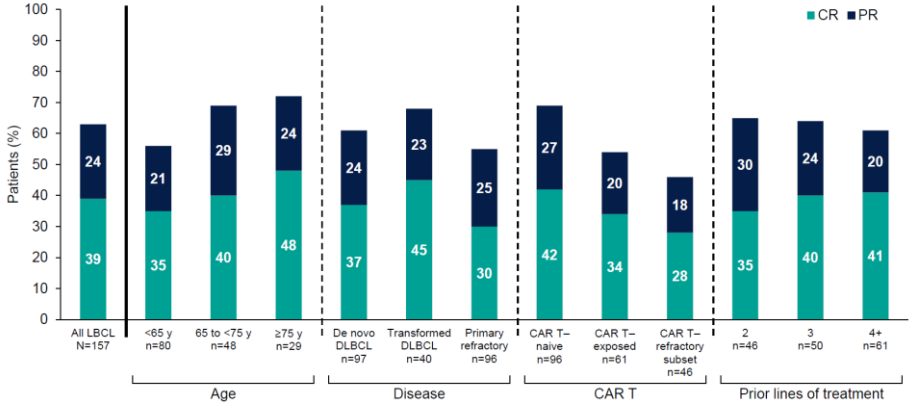
Best Overall Response by IRC	N=157
ORR, n (%) [95% CI]	99 (63) [55-71]
CR, n (%) [95% CI]	61 (39) [31-47]
PR, n (%)	38 (24)
SD, n (%)	5 (3)
PD, n (%)	37 (24)

Depth of Response



- Most CRs were achieved by the 1st/2nd assessment
- At ≥36 weeks, conversions from PR to CR were still observed

Response in Key Subgroups



Response Characteristics (range), months	
Median time to response	1.4 (1.0-8.4)
Median time to CR	2.7 (1.2-11.1)
Median DOR[a]	12 (0+ to 15.5+)
Median DOR for patients in CR	NR

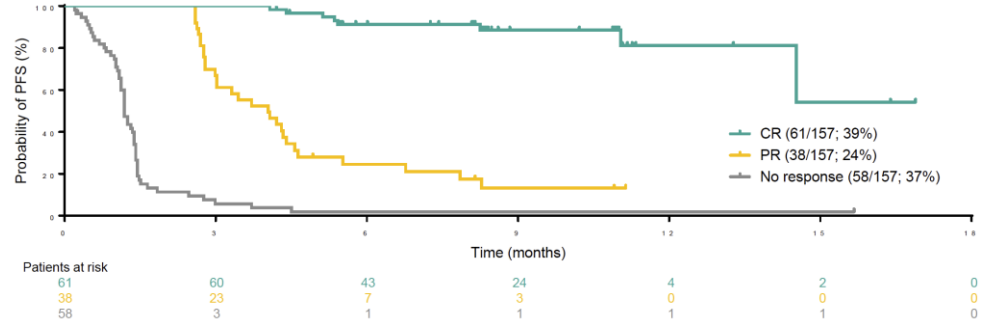
Data cutoff: January 31, 2022.

[a] Median DOR data not yet mature.

Thieblemont, C et al. EHA 2022. Abstract LBA2364.

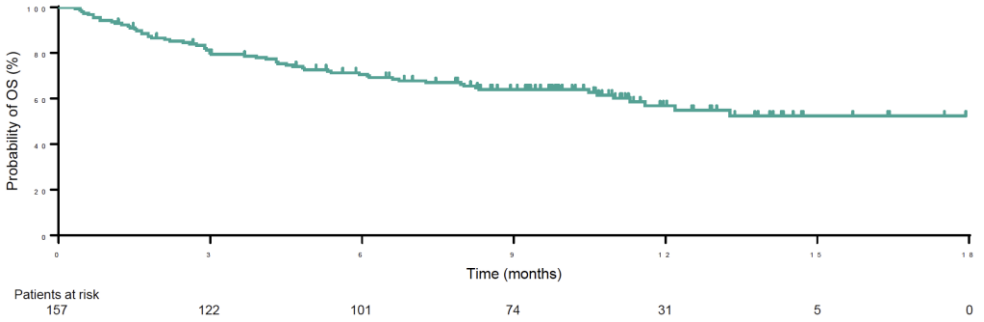
Pivotal Results From the EPCORE NHL-1 Phase 2 Study of Epcoritamab in Patients With R/R LBCL: Efficacy (cont'd)

PFS by Best Response per IRC



PFS	N=157
Median PFS in CRs	NR
CRs remaining in CR at 9 months, %	89
Median PFS, months (95% CI)	4.4 (3.0-7.9)
6-month PFS, % (95% CI)	43.9 (35.7-51.7)

OS



OS	N=157
Median OS	NR
6-month OS, % (95% CI)	70.6 (62.7-77.2)
12-month OS, % (95% CI)	56.9 (47.3-65.4)

Data cutoff: January 31, 2022.

Thieblemont, C et al. EHA 2022. Abstract LBA2364.

Management Considerations for Older Patients With DLBCL

At time of diagnosis

- Molecular testing for unfavorable risk characteristics
- Early supportive and palliative care
  - Symptom control
  - Define goals of therapy
- Consider prophylactic WBC growth factors
- Consider formal geriatric assessment

First-line regimens

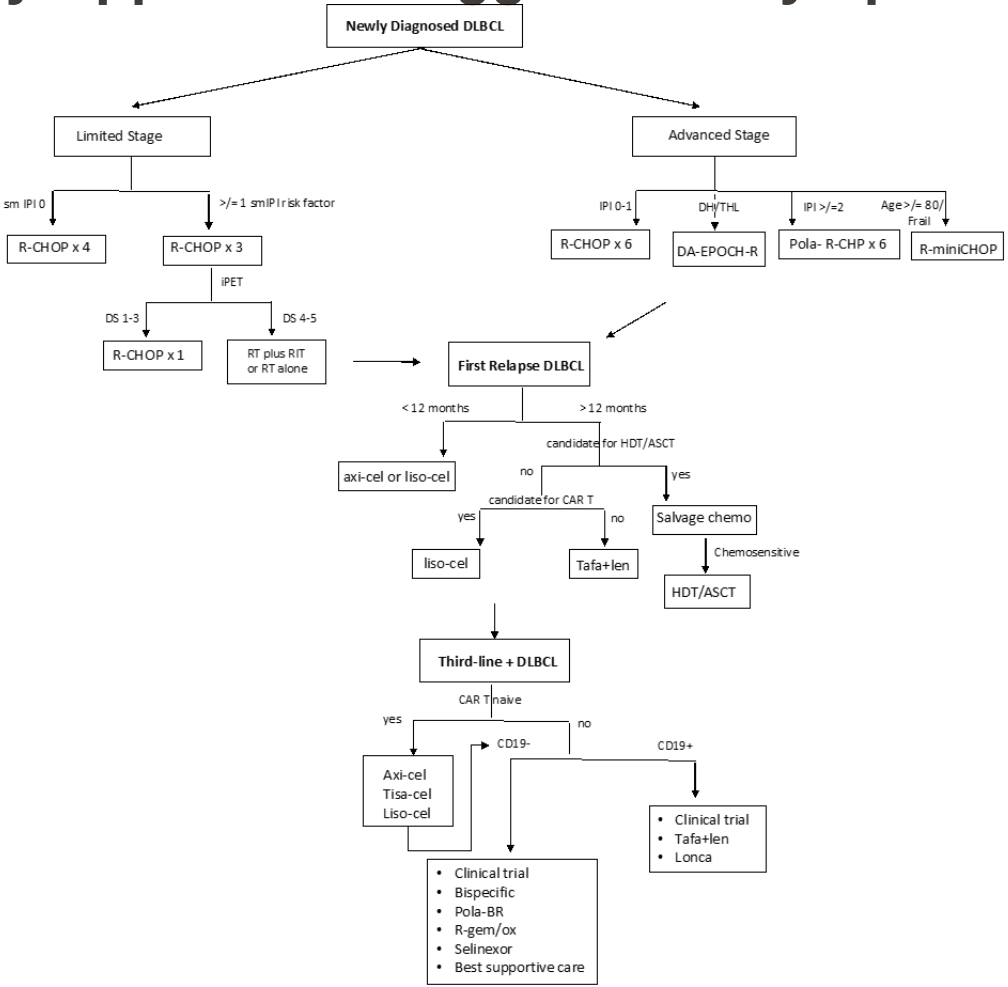
- Fit, older patients can benefit from R-CHOP with curative intent
- Cardiac comorbidities: consider non-anthracycline-containing regimens such as R-CEOP or R-GCVP
- Very frail or >80 years old with comorbidities: consider attenuated regimens such as R-mini-CHOP or R-GCVP

Relapsed/refractory disease

- The majority of older patients are not ASCT eligible
- May benefit from CAR-T cell therapy but higher risk of grade ≥3 neurotoxicity
- Consider newer FDA approved options: polatuzumab vedotin + BR or tafasitamab + lenalidomide
- Emerging chemotherapy-free regimens

R-CEOP = rituximab, cyclophosphamide, etoposide, vincristine, and prednisone; R-GCVP = rituximab, gemcitabine, cyclophosphamide, vincristine, prednisone; R-mini-CHOP = R-CHOP with attenuated doses of vincristine, doxorubicin, and cyclophosphamide; WBC = white blood cell.

Di M et al. *Oncologist.* 2021;26(2):120-132; NCCN. Clinical Practice Guidelines in Oncology: B-Cell Lymphomas. Version 5.2022. July 12, 2022.



Nastoupil & Bartlett JCO in press

Conclusions

Risk stratification
- IPI, R-IPI, NCCN-IPI (clinical characteristics)
- Molecular subtypes

Frontline approach
- Intensive induction
- Pola-RCHP for IPI >/=2?
- Clinical trial

Promising therapies in R/R HGBCL
- CAR T-cell therapy
- Lonca