Latest Management Updates in Diffuse Large B Cell Lymphoma (DLBCL)

Multidisciplinary Approaches to Cancer Symposium

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Swetha Kambhampati, MD

Assistant Professor, Lymphoma Division
Department of Hematology & Hematopoietic Cell Transplantation
City of Hope
Contact: skambhampati@coh.org

Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

Talk Outline

- Risk Assessment in DLBCL
- Frontline treatment for DLBCL: RCHOP and Pola-R-CHP
- Second-line therapies for DLBCL: second line CAR T
- Standard FDA approved third-line therapies: Tafa-Len, Lonca-T, Selinexor, R-Benda-Pola
- Emerging DLBCL therapies: bispecifics
- Summarize changing treatment landscape for DLBCL

Risk Assessment in DLBCL

Clinical Prognostic Scores: IPI, R-IPI, NCCN-IPI

Parameters Used By Each Scoring System[2]			
	IPI	**R-IPI**	**NCCN-IPI**
Age (years)	>60	≤60, >60	>40 to ≤60, >60 to <75, ≥75
Serum LDH	>normal	>normal	>1 to ≤3, >3
ECOG PFS	≥2	≥2	≥2
Stage	III or IV	III or IV	III or IV
Extranodal disease	>1 site	----	Presence in BM, CNS, liver/GI tract or lung

	Scoring Group	Estimated 5-Year OS (%)
IPI	Low	87.7
	Low-intermediate	76.1
	High-intermediate	67.0
	High	53.9
R-IPI	Very good	92.5
	Good	81.3
	Poor	60.9
NCCN-IPI	Low	92.1
	Low-intermediate	83.9
	High-intermediate	62.7
	High	49.0

Conclusions:

- IPI and NCCN-IPI slightly better at identifying poor-risk patients
- Either can be used outside of a clinical trial

Caveats:

- No score identified a very poor-risk group with 5-year OS <50% with rituximab-based treatment
- All were developed prior to identification of molecular high-risk groups (double-hit and triple-hit)

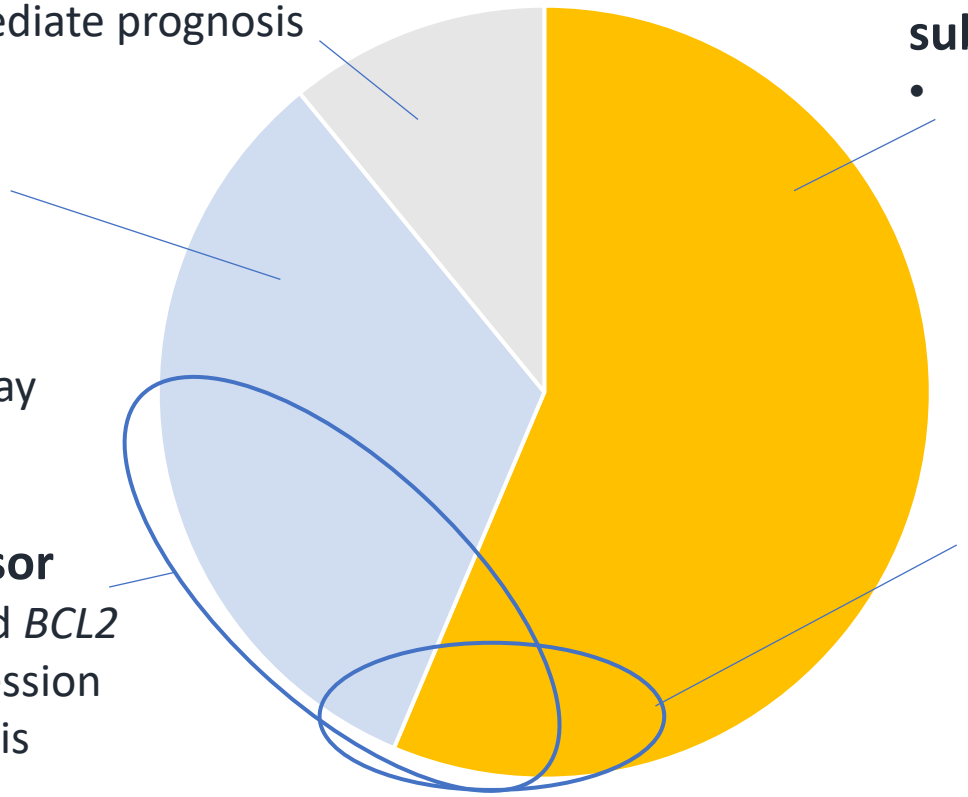
Ruppert AS et al. *Blood*. 2020;135(23):2041-2048.

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



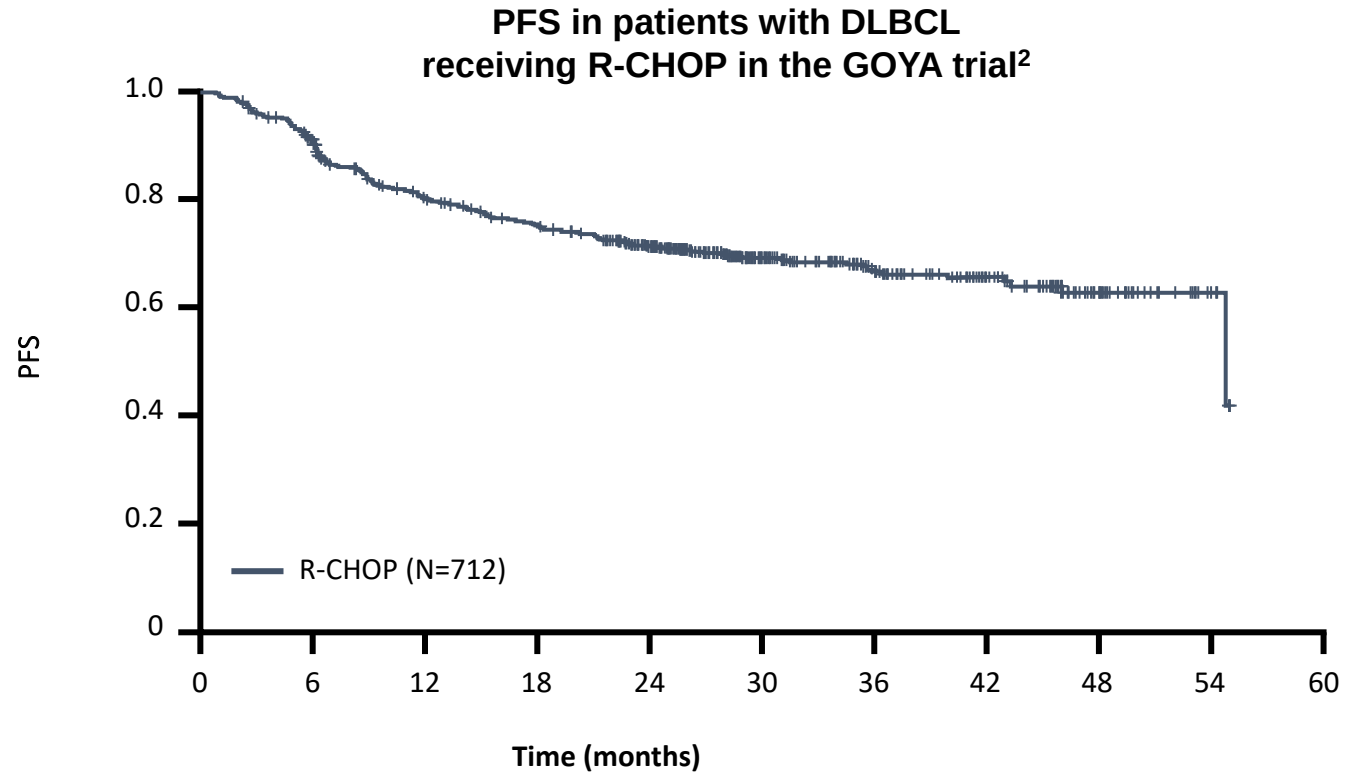
Double expressor
- High *MYC* and *BCL2* protein expression
- Poor prognosis

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.

Front-line DLBCL treatment

R-CHOP has been the standard of care in first-line DLBCL for over 20 years



- Only 60–70% of patients are cured with R-CHOP[1,2]
- An unmet need remains for patients with previously untreated DLBCL

1. Sehn LH and Salles G. N Engl J Med 2021
2. Vitolo U, et al. J Clin Oncol 2017

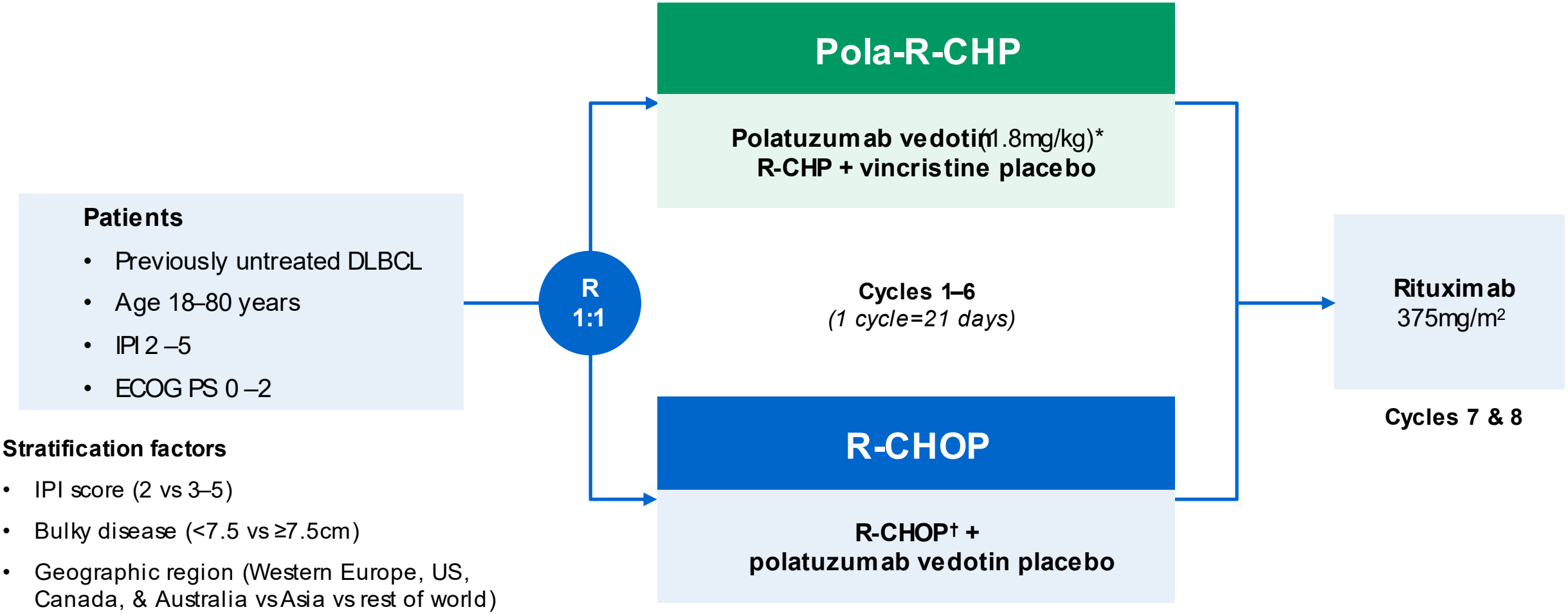
Improving R-CHOP: What has *not* worked

Phase III Trial	Subgroup	Outcome
GOYA[1] R-CHOP vs. G-CHOP (n = 1,418)	All	Negative
A50303[2] R-CHOP vs. R-EPOCH (n = 524)	All	Negative
PHOENIX[3] R-CHOP ± Ibrutinib (N= 838)	Non-GC by Hans	Negative
ROBUST[4] **and E1412**[5] R-CHOP ± Lenalidomide (n = 570) (n = 349)	ABC by GEP	Negative
REMoDL[6] R-CHOP ± Bortezomib (n = 1,128)	Stratified by GEP	Negative

R-CHOP 21 remains the standard of care for most patients with DLBCL

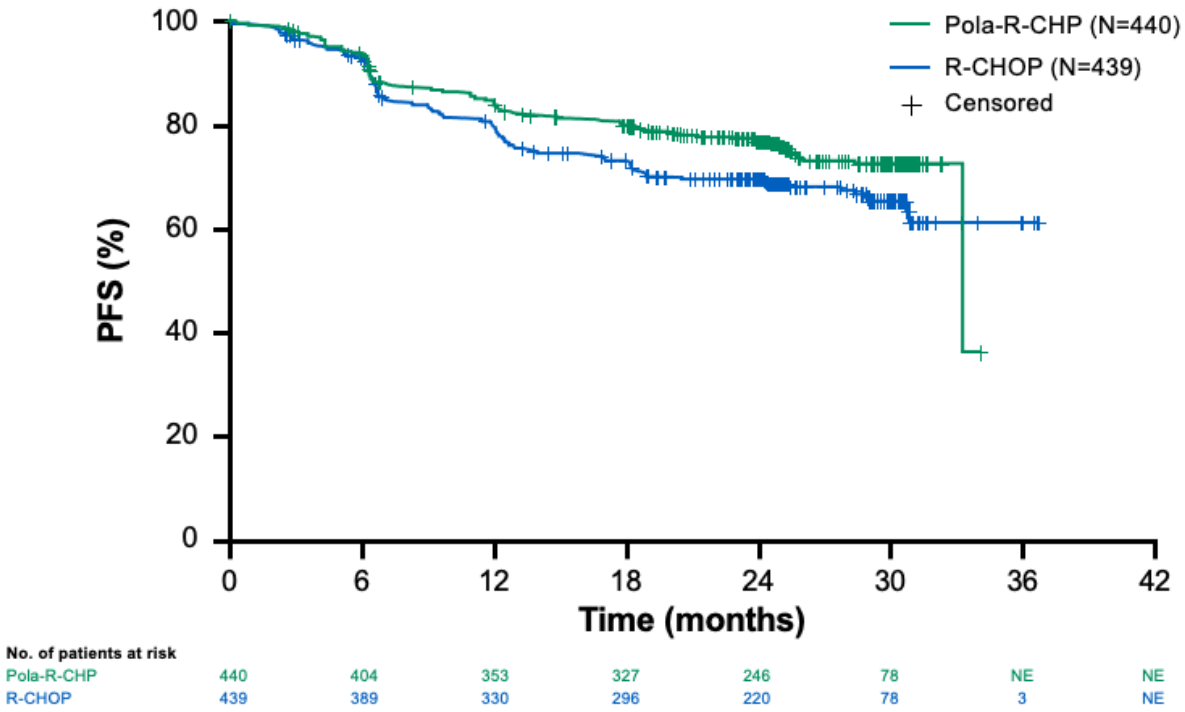
1. Sehn LH et al. *J Hematol. Oncol.* 2020;13(1):71. 2. Bartlett NL et al. *J Clin Oncol.* 2019;37(21):1790-1799. 3. Younes A et al. *J Clin Oncol*. 2019;37(15):1285-1295.4. Nowakowski GS et al. *J Clin Oncol.* 2021;39(12):1317-1328. 5. Nowakowski GS et al. *J Clin Oncol.* 2021;39(12):1329-1338. 6. Davies A et al. *Lancet Oncol.* 2019;20(5):649-662.

POLARIX: A randomized double-blinded study

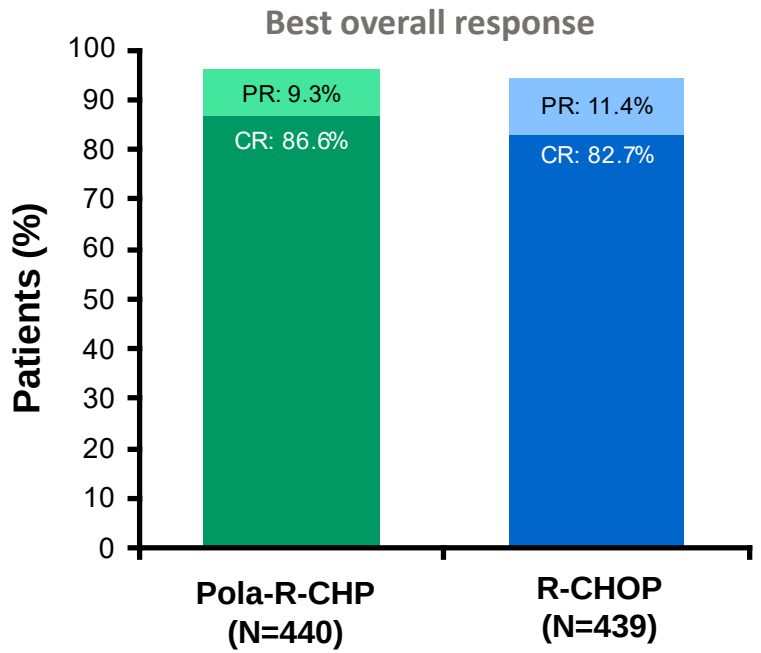


Tilly et al. NEJM January 2022

POLARIX: Pola-R-CHP improves PFS compared to R-CHOP



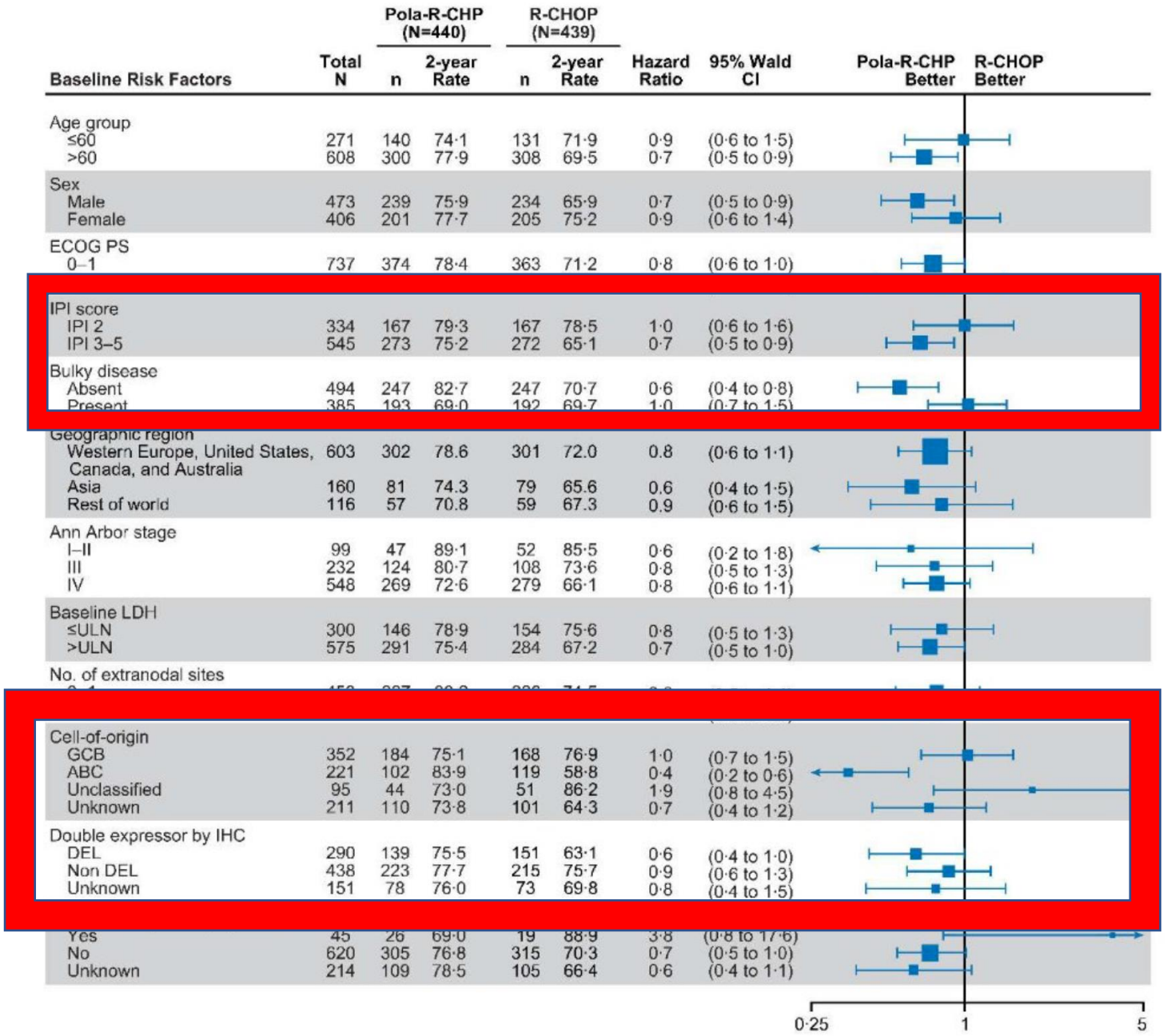
- Pola-R-CHP demonstrated a **27% reduction in the relative risk of disease progression, relapse, or death** versus R-CHOP
- **24-month PFS:**
  76.7% with Pola-R-CHP versus 70.2% with R-CHOP (**Δ=6.5%**)
- CR 86.6% vs 82.7%
- At median follow-up of 28.2 months, no OS benefit



Tilly et al. NEJM January 2022

POLARIX Sub-group analysis

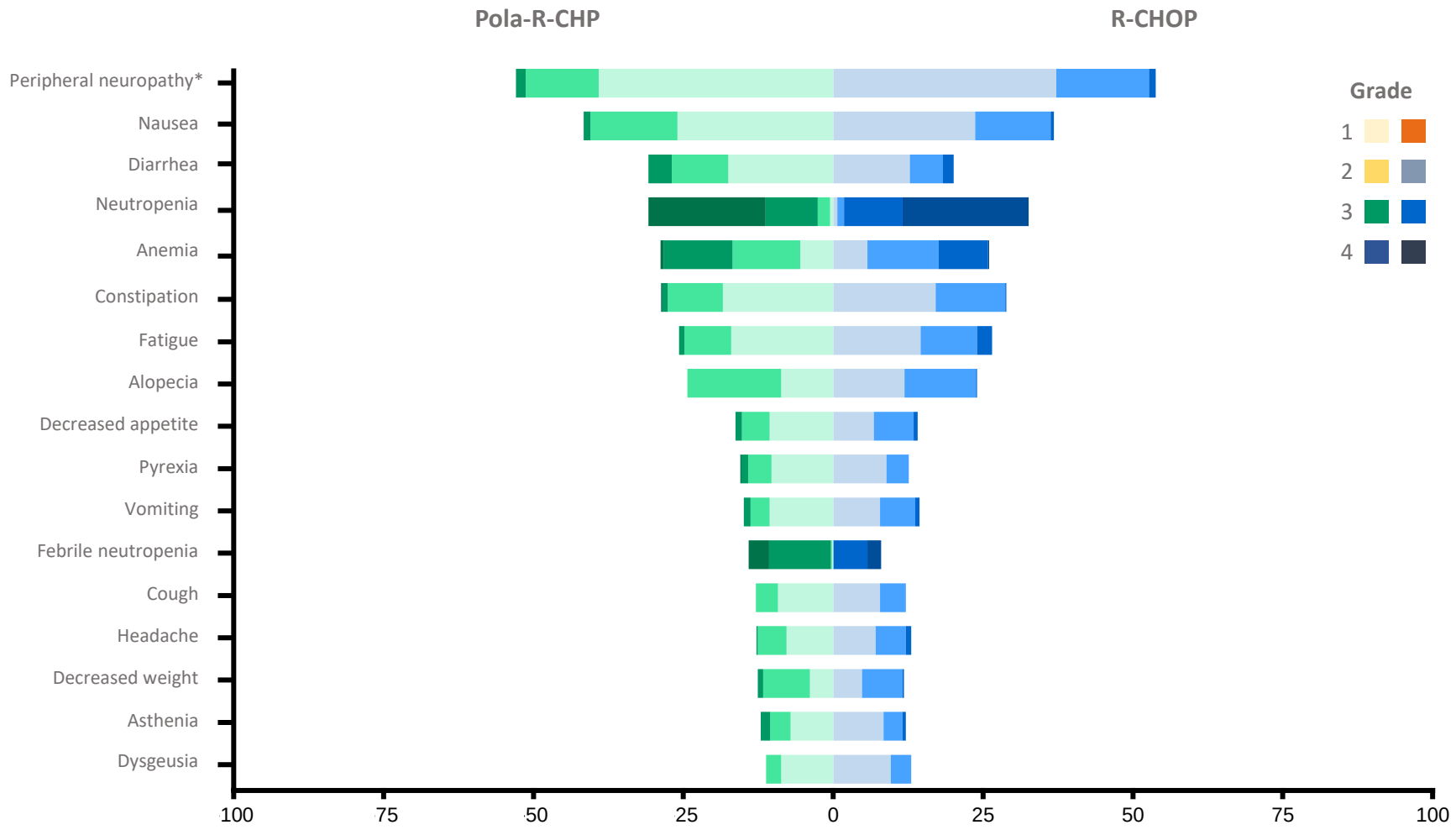
PFS Benefit in IPI 3-5, non-bulky disease, older male patients, and ABC subtype though study not powered for sub-group analysis



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)
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							
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)
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)

Tilly et al. NEJM January 2022

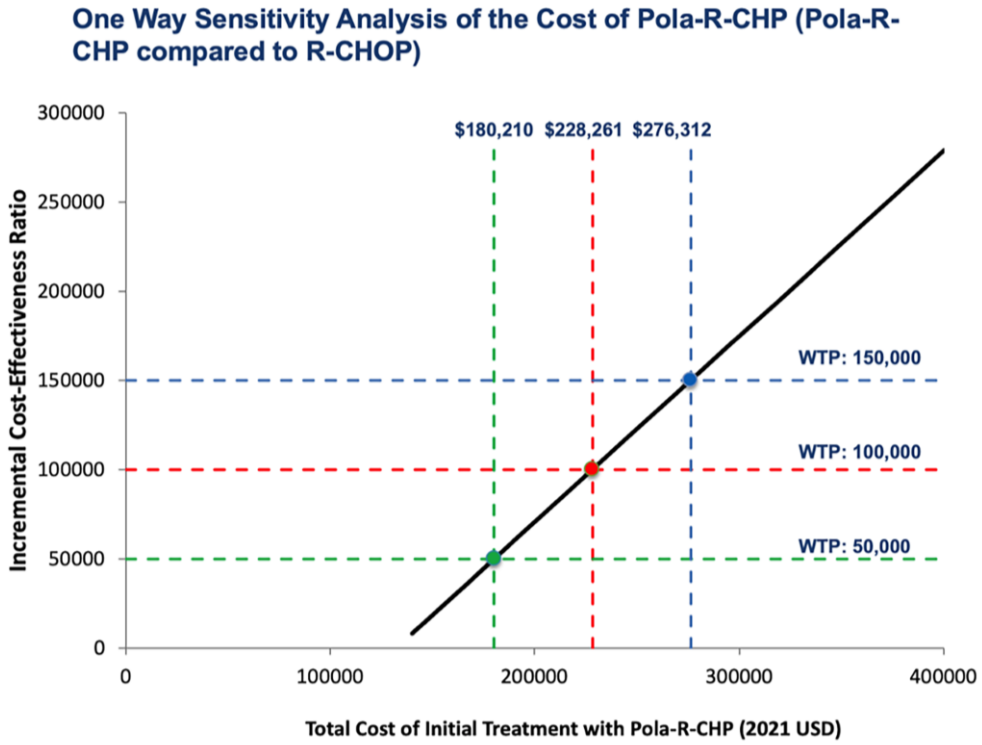
Common Adverse Events



Tilly et al. NEJM January 2022

Cost effectiveness of Pola-R-CHP depends upon long-term outcomes

- Routine use of pola-R-CHP will add significantly to healthcare expenditures
- Markov Model
  - Threshold willingness-to-pay 150K/QALY
  - If 5-year PFS > 66%, then cost-effective
- Identifications of subgroups that have maximal benefit would improve cost-effectiveness



Kambhampati et al. Blood June 2022

POLARIX: Pola-R-CHP vs R-CHOP

- Pola-R-CHP significantly prolongs PFS compared with R-CHOP (HR 0.73) in patients with intermediate and high-risk previously untreated DLBCL
  - 24-month PFS: 76.7% with Pola-R-CHP versus 70.2% with R-CHOP
- Benefit highest for patients age > 60, IPI 3-5, and ABC subtype? (study not powered for this)
- No overall survival benefit yet
- Safety profile of pola-R-CHP and R-CHOP comparable
- Cost-effective analysis demonstrates that pola-RCHP is cost effective (ICER $84,308/QALY) if 5-year PFS is at least 66.1%

Strengths	Concerns
• Enhanced PFS at 2-year follow-up • No toxicity differences • Higher risk patients appeared to disproportionately benefit • Cost-effective if long-term outcomes are maintained	• Small PFS difference (6%) at 2-year f/u • Certain subsets (GCB, double hit) appear to not benefit • Expensive • Uncertain impact on outcome of salvage treatments • No OS benefit at 2-year f/u

Tilly H et al. *N Engl J Med*. 2022;386(4):351-363.
Kambhampati et al. *Blood*. 2022

Frontline Diffuse Large B-cell Lymphoma
How we treat

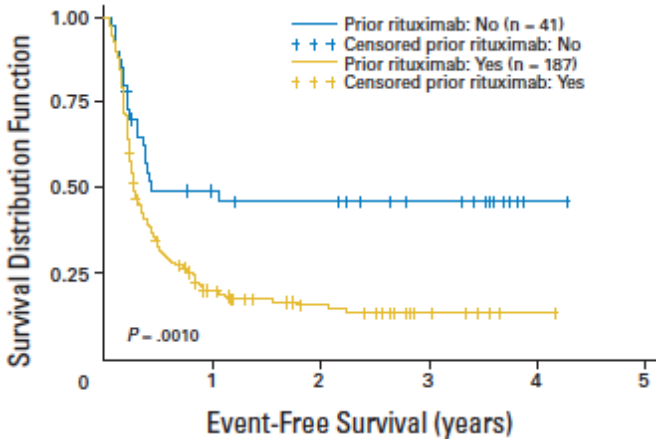
Factors	First-Line Therapy
DLBCL, NOS	**RCHOP**
DLBCL, with risk factors: age > 60y, IPI 3-5	**R-Pola-CHP** RCHOP
HGL, includes double hit(myc+/bcl2 or myc+/bcl6) Primary mediastinal B cell lymphoma	**DA-EPOCH-R**
DLBCL with cardiac dysfunction	**R-CEOP, R-GCVP**
Frail Patients or age >80y	**R-mini-CHOP**

Second-line DLBCL treatment

Salvage chemotherapy with high dose chemotherapy and ASCT

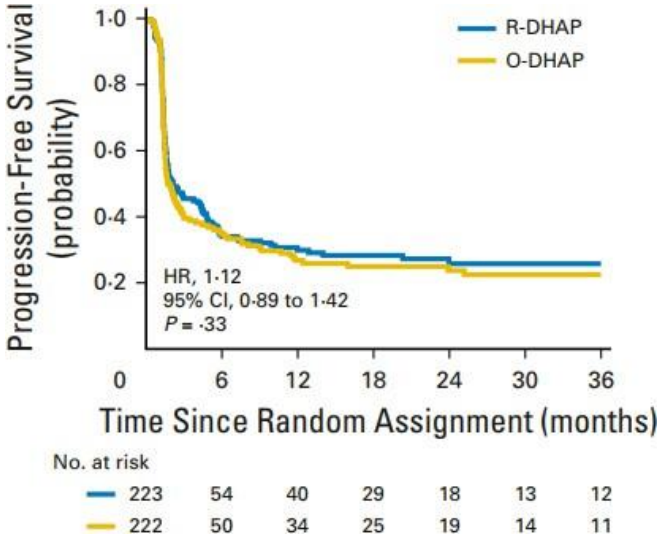
- Historical second-line treatment option
- However about 50% of patients relapse post ASCT
- About 3/4 of DLBCL relapsed happen within one year of frontline therapy, where outcomes with SOC are poor
- Plus, only half of relapsed DLBCL patients are candidates for HDT/ASCT in the first place due to age/comorbidities

CORAL



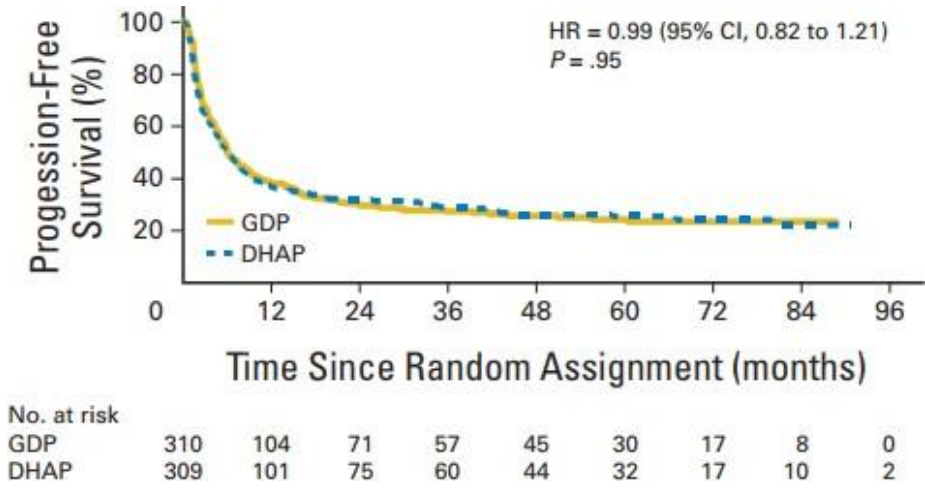
Gisselbrecht, et al. JCO 2010

ORCHAARD



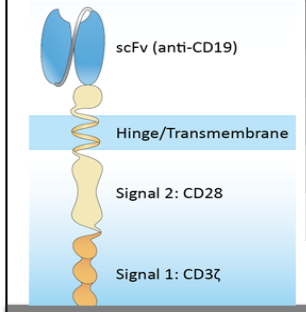
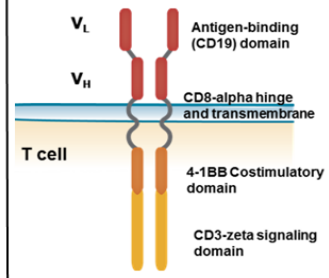
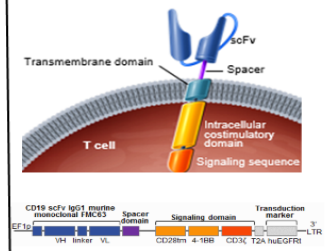
van Imhoff, et al. JCO 2017

NCIC-CTG LY.12



Crump, et al. JCO 2014

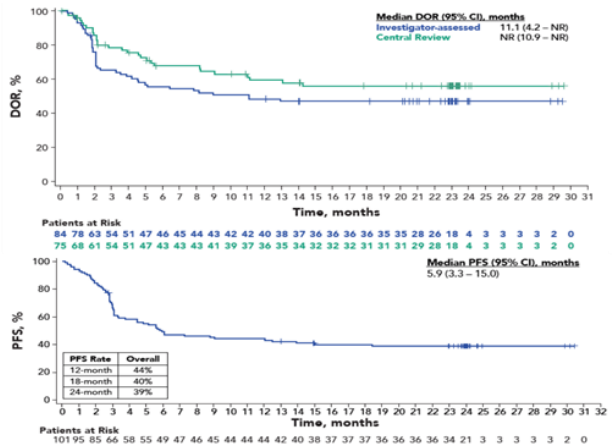
Three CD19 CAR T Products for R/R DLBCL

KTE-C19 *axicabtagene ciloleucel (axi-cel)*	CTL019 *tisagenlecleucel (tisa-cel)*	JCAR017 *lisocabtagene maraleucel (liso-cel)*
		
axi-cel	tisa-cel	liso-cel
scFv = anti-CD19	scFv = anti-CD19	scFv = anti-CD19
CD28-CD3ζ	4-1BB-CD3ζ	4-1BB-CD3ζ
ZUMA-1 trial	JULIET trial	TRANSCEND-NHL-001 trial

Durable remission in ~40% patients

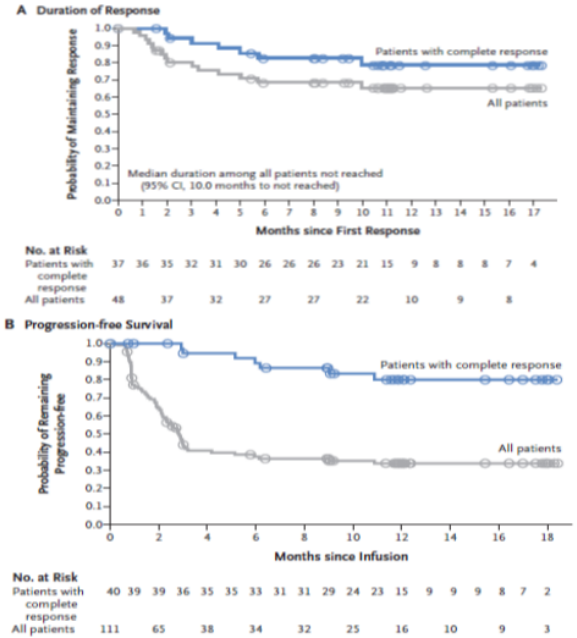
ZUMA-1 5-year OS rate was 42.6%
24-month EFS rate was 37.7%

ZUMA-1

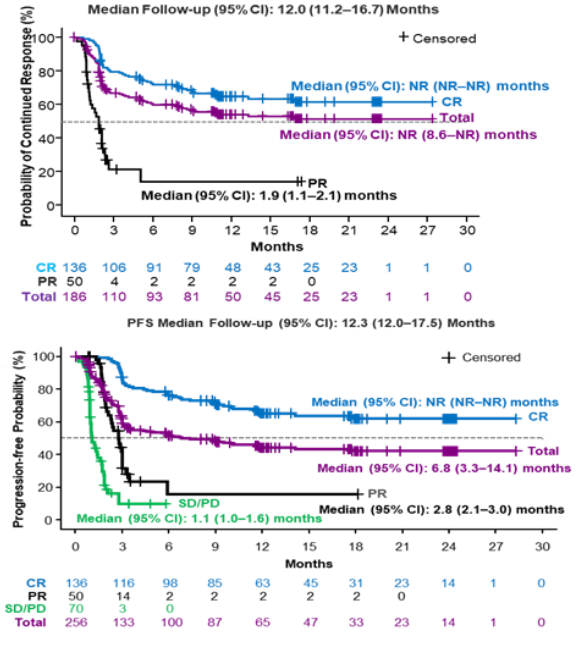


Locke et al Lancet Oncology 2019;20:31
Schuster et al NEJM 2018
Abramson et al ASH 2019

JULIET



TRANSCEND-001



Three randomized trials of CAR T cell therapy versus SOC in transplant- eligible DLBCL with early relapse or primary refractory disease

Clinical trials of CD19 CAR T cell therapies in 2L ≤ 12 months LBCL

ZUMA 7[1]
(N = 359)
Phase 3; axi-cel vs SOC

Primary Analysis of ZUMA-7: a Phase 3 Randomized Trial of Axicabtagene Ciloleucel versus Standard-of-Care Therapy in Patients with Relapsed/Refractory Large B-Cell Lymphoma

Frederick L. Locke, MD[1]; David B. Miklos, MD, PhD[2]; Caron A. Jacobson, MD, MMSc[3]; Miguel-Angel Perales, MD[4];

Positive study
Axi-cel approved second line

TRANSFORM[2]
(N = 184)
Phase 3; liso-cel vs SOC

TRANSFORM Study: Lisocabtagene Maraleucel, a CD19-Directed Chimeric Antigen Receptor T Cell Therapy, Versus Standard of Care with Salvage Chemotherapy Followed by Autologous Stem Cell Transplantation as Second-Line Treatment in Patients with Relapsed or Refractory Large B-Cell Lymphoma: Results from the Randomized Phase 3 TRANSFORM Study

Manali Kamdar,[1] Scott R. Solomon,[2] Jon Arnason,[3] Patrick B. Johnston,[4] Bertram Glass,[5] Veronika Bachanova,[6] Sami

Positive study
Liso-cel approved second-line

BELINDA[3]
(N = 322)
Phase 3; tisa-cel vs SOC

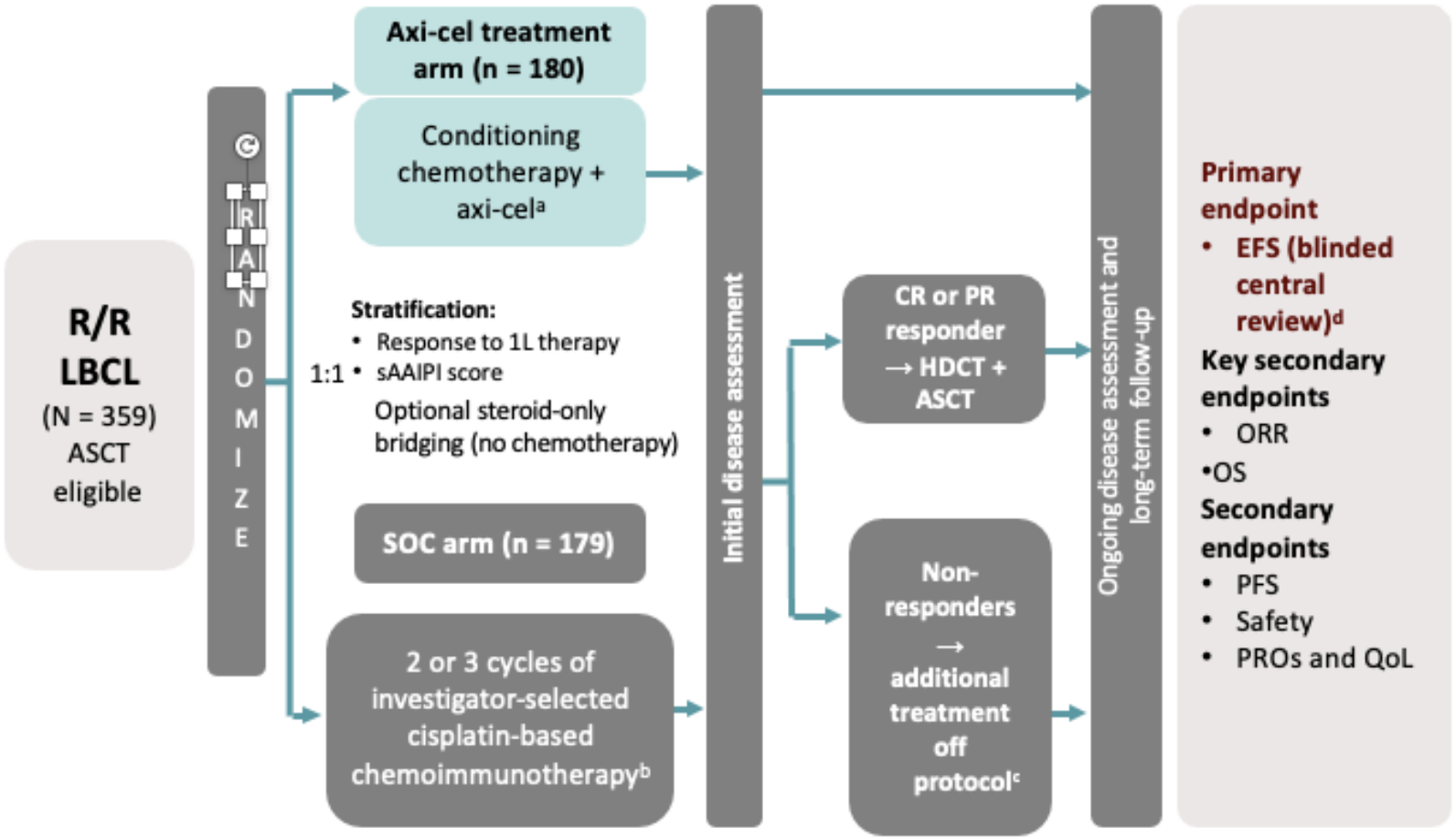
Tisagenlecleucel vs Standard of Care as Second-Line Therapy of Primary Refractory or Relapsed Aggressive B-Cell Non-Hodgkin Lymphoma: Analysis of the Phase III BELINDA Study

Michael R. Bishop,[1] Michael Dickinson,[2] Duncan Purtill,[3] Pere Barba,[4] Armando Santoro,[5] Nada Hamad,[6] Koji Kato,[7] Anne Sureda,[8] Richard Greil,[9]

Negative study
Tisa-cel not approved second-line

1. Locke FL, et al. N Engl J Med. 2022;386:640-54. 2. Kamdar M, et al. Oral presentation at ASH 2021; abstract 91. 3. Bishop MR, et al. N Engl J Med. 2022;386:629-39.

ZUMA-7: axi-cel vs SOC in 2L DLBCL



Characteristics	Axi-cel (n = 180)	SOC (n = 179)
Median age (range), years	58 (21–80)	60 (26–81)
Disease stage III-IV, n (%)	139 (77)	146 (82)
Primary refractory, n (%)	**133 (74)**	**131 (73)**
Relapse ≤ 12 months of 1L therapy, n (%)	**47 (26)**	**48 (27)**
HGBCL (incl. DHL/THL), n (%)	**31 (17)**	**25 (14)**
ECOG PS of 1	85 (47)	79 (44)
Elevated LDH level	101 (56)	94 (53)

Locke FL, et al. N Engl J Med. 2022;386:640-54. Locke FL, et al. Oral presentation at ASH 2021; abstract 2.

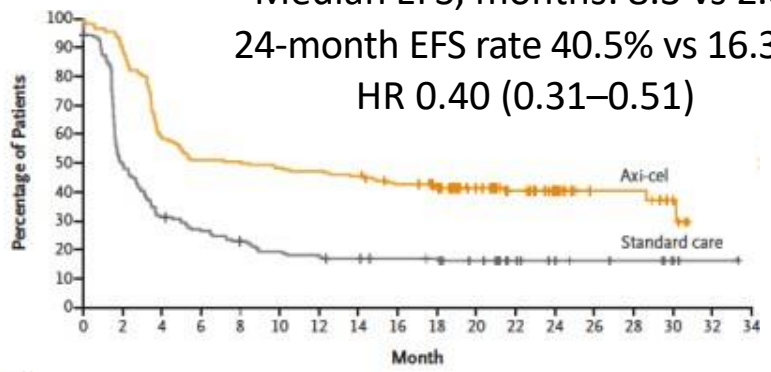
Axi-cel vs SOC as 2L therapy in primary refractory or early relapsed DLBCL

Median follow-up: 24.9 months

ORR: 83% vs 50%
CRR: 65% vs 32%

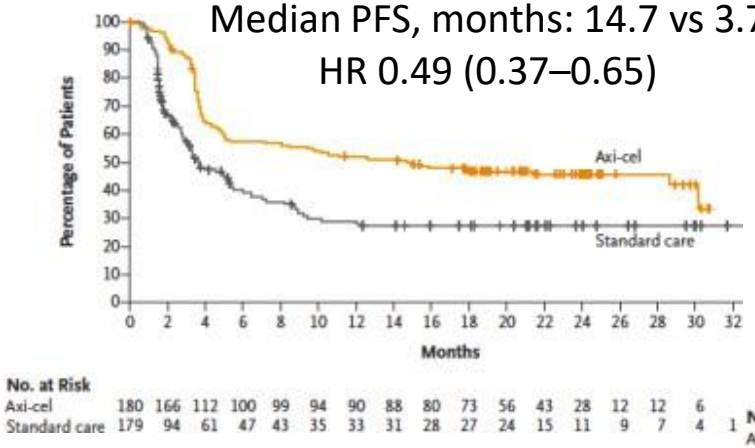
EFS

Median EFS, months: 8.3 vs 2.0
24-month EFS rate 40.5% vs 16.3%
HR 0.40 (0.31–0.51)



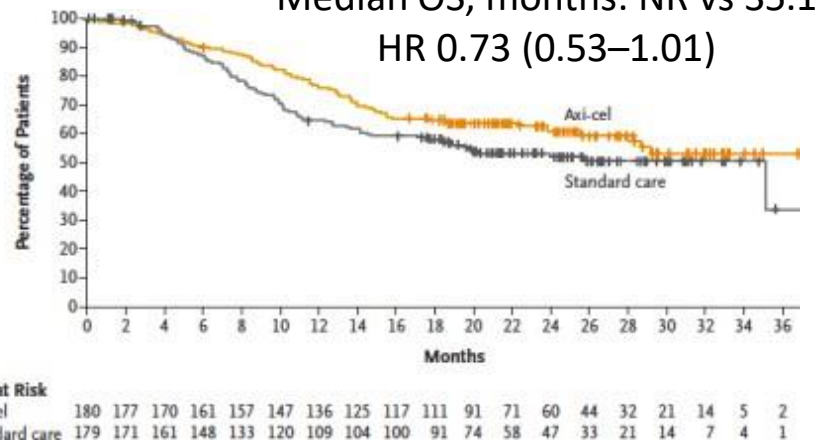
PFS

Median PFS, months: 14.7 vs 3.7
HR 0.49 (0.37–0.65)



OS

Median OS, months: NR vs 35.1
HR 0.73 (0.53–1.01)

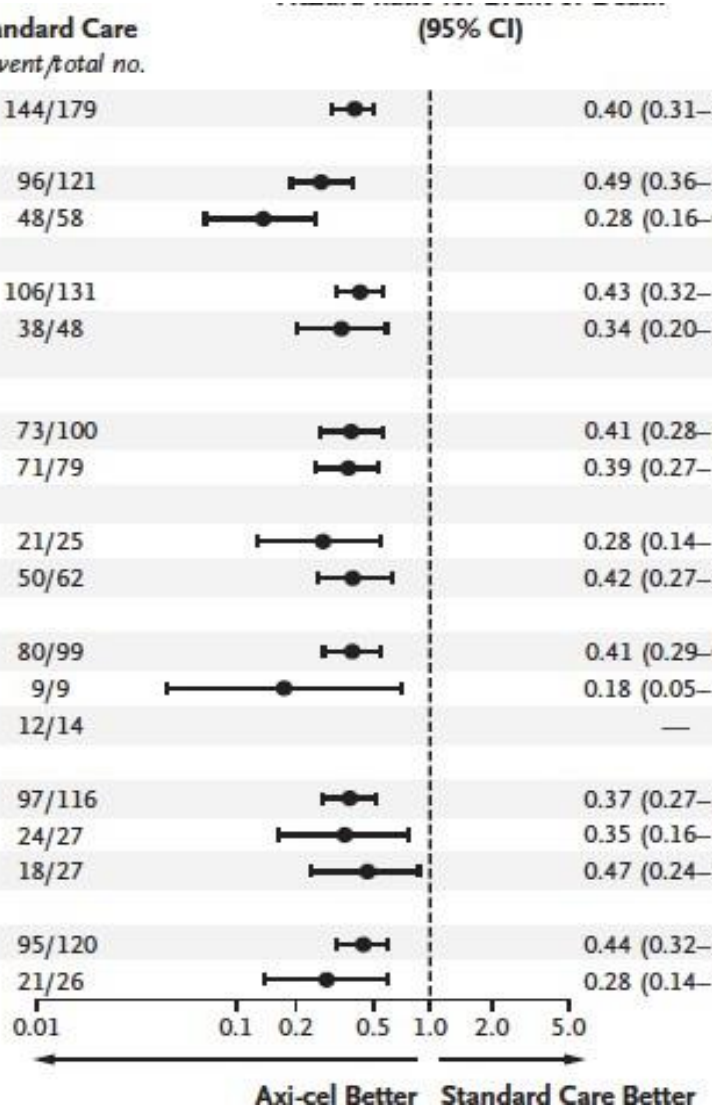


Axi-cel associated with improved QoL by PRO

Locke FL, et al. N Engl J Med. 2022;386:640-54.

EFS improvements with Axi-cel vs SOC were consistent among key patient subgroups

Subgroup	Axi-cel	Standard Care	(95% CI)
	no. of patients with event/total no.		
Overall	108/180	144/179	0.40 (0.31–0.51)
Age			
<65 yr	81/129	96/121	0.49 (0.36–0.67)
≥65 yr	27/51	48/58	0.28 (0.16–0.46)
Response to first-line therapy at randomization			
Primary refractory disease	85/133	106/131	0.43 (0.32–0.57)
Relapse ≤12 mo after initiation or completion of first-line therapy	23/47	38/48	0.34 (0.20–0.58)
Second-line age-adjusted IPI			
0 or 1	54/98	73/100	0.41 (0.28–0.58)
2 or 3	54/82	71/79	0.39 (0.27–0.56)
Prognostic marker according to central laboratory			
HGBL, double- or triple-hit	15/31	21/25	0.28 (0.14–0.59)
Double-expressor lymphoma	35/57	50/62	0.42 (0.27–0.67)
Molecular subgroup according to central laboratory			
Germinal center B-cell–like	64/109	80/99	0.41 (0.29–0.57)
Activated B-cell–like	11/16	9/9	0.18 (0.05–0.72)
Unclassified	8/17	12/14	—
Disease type according to investigator			
DLBCL, not otherwise specified	68/110	97/116	0.37 (0.27–0.52)
Large-cell transformation from follicular lymphoma	10/19	24/27	0.35 (0.16–0.77)
HGBL, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	23/43	18/27	0.47 (0.24–0.90)
Disease type according to central laboratory			
DLBCL	79/126	95/120	0.44 (0.32–0.60)
HGBL, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	15/31	21/26	0.28 (0.14–0.59)



Locke FL, et al. N Engl J Med. 2022;386:640-54.

Grade ≥3 CRS and Neurologic Events Were Generally Consistent With Third-Line Treatment of Patients

CRS Parameter	Axi-cel N=170
CRS, n (%)	
Any grade	157 (92)
Grade ≥3	11 (6)
Grade 5	0
Most common any-grade symptoms, n/n (%)	
Pyrexia	155/157 (99)
Hypotension	68/157 (43)
Sinus tachycardia	49/157 (31)
AE management[d], n (%)	
Tocilizumab	111 (65)
Corticosteroids	40 (24)
Vasopressors	11 (6)
Median time to onset, days	3
Median duration of events, days	7

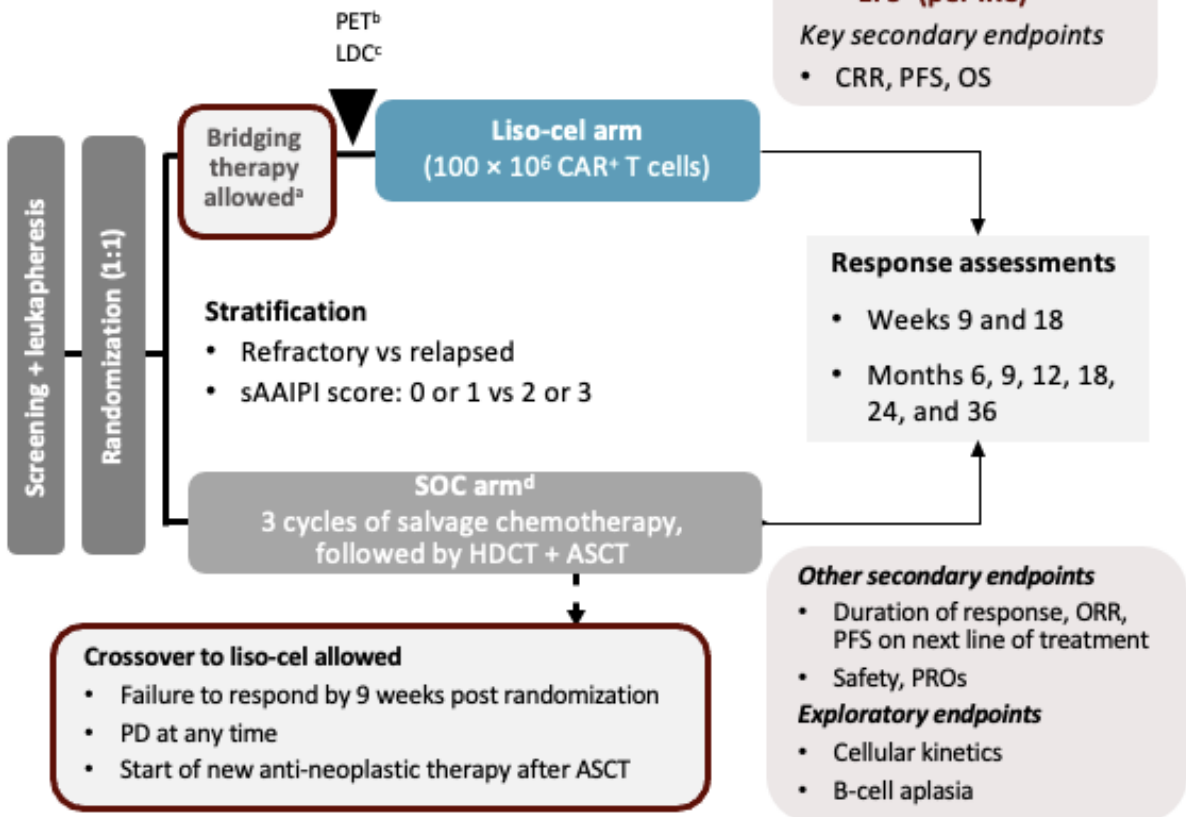
Neurologic Event Parameter	Axi-cel N-170	SOC N=168
Neurologic events, n (%)		
Any grade	102 (60)	33 (20)
Grade ≥3	36 (21)	1 (1)
Grade 5	0	0
Most common any-grade symptoms, n (%)		
Tremor	44 (26)	1 (1)
Confusional state	40 (24)	4 (2)
Aphasia	36 (21)	0
AE management[d], n (%)		
Corticosteroids	54 (32)	-
Median time to onset, days	7	23
Median duration of events, days	9	23

Locke FL, et al. N Engl J Med. 2022;386:640-54.

TRANSFORM: Liso-cel vs SOC in 2L DLBCL

Key eligibility

- Age 18–75 years
- Aggressive NHL
  - DLBCL NOS (de novo or transformed from iNHL), HGBCL (DHL/THL) with DLBCL histology, grade 3B FL, PMBCL, THRBCL
- R/R ≤ 12 months after 1L treatment containing an anthracycline and a CD20-targeted agent
- ECOG PS score ≤ 1
- Eligible for HSCT
- Secondary CNS lymphoma allowed
- LVEF > 40% for inclusion
- No minimum ALC



Characteristic	Liso-cel (n = 92)	SOC (n = 92)
Median age (range), years	60 (53.5–67.5)	58 (42–65)
LBCL subtypes, n (%)		
DLBCL NOS	53 (58)	49 (53)
HGBCL (incl. DHL/THL), n (%)	**22 (24)**	**21 (23)**
PMBCL	8 (9)	10 (11)
DLBCL transformed from iNHL	7 (8)	8 (9)
Primary refractory, n (%)	**67 (73)**	**68 (74)**
Relapsed, n (%)	**25 (27)**	**24 (26)**
sAAIPI score, n (%)		
0 or 1	56 (61)	55 (60)
2 or 3	36 (39)	37 (40)
ECOG PS score of 1, n (%)	44 (48)	35 (38)

Kamdar M, et al. Lancet 2022.

Liso-cel vs SOC as 2L therapy in primary refractory/early relapsed DLBCL

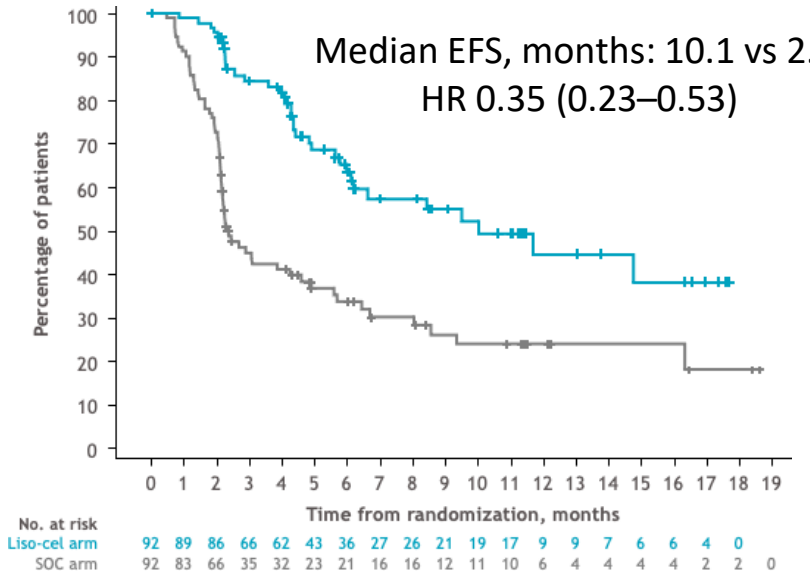
Median follow-up: 6.3 months

ORR: 86% vs 48%
CRR: 66% vs 39%

SOC crossed over to receive liso-cel: 54%

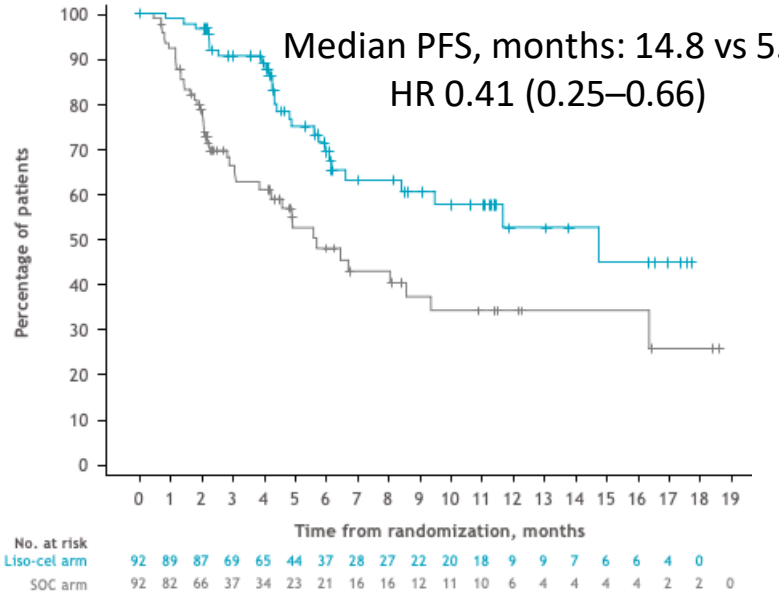
EFS

Median EFS, months: 10.1 vs 2.3
HR 0.35 (0.23–0.53)



PFS

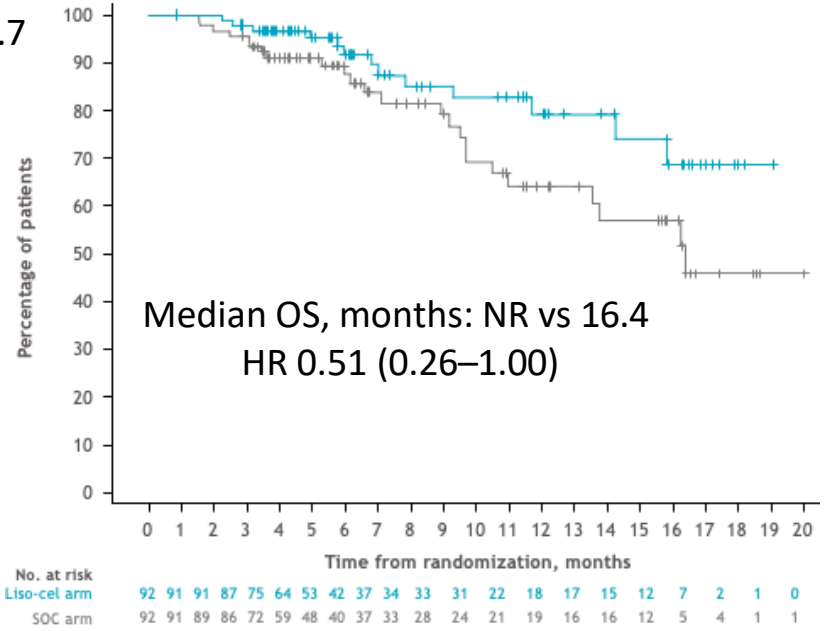
Median PFS, months: 14.8 vs 5.7
HR 0.41 (0.25–0.66)



QoL by PRO favored liso-cel

OS

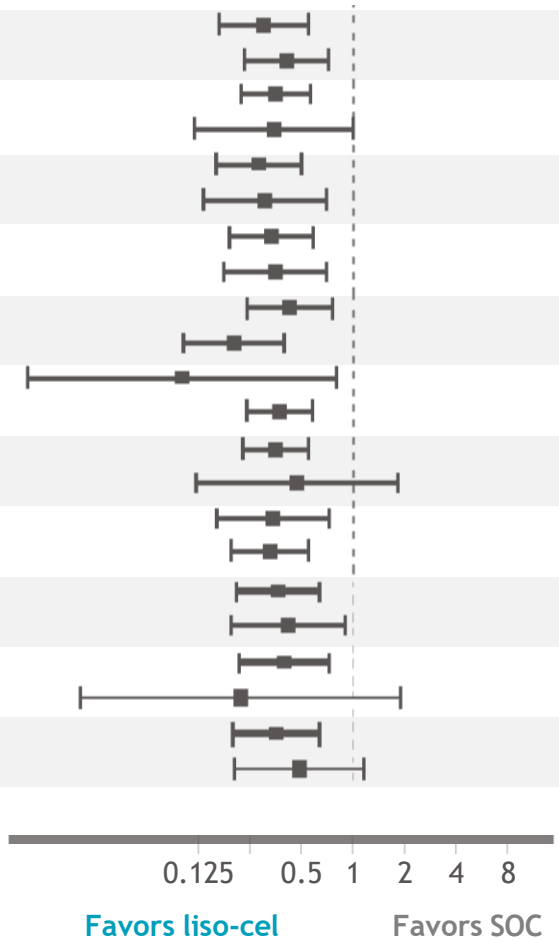
Median OS, months: NR vs 16.4
HR 0.51 (0.26–1.00)



Kamdar M, et al. Lancet 2022.

TRANSFORM: Event-Free survival by IRC by subgroup (ITT set)

Subgroup		Liso-cel arm n/N	SOC arm n/N	Stratified HR
sAAIPI	0 or 1	16/56	32/55	0.298
	2 or 3	19/36	31/37	0.404
Prior response status	Refractory	30/67	52/68	0.350
	Relapse to last prior therapy	5/25	11/24	0.343
Age group, years	< 65	17/56	46/67	0.277
	≥ 65 to < 75	18/36	15/23	0.301
Sex	Male	19/44	44/61	0.331
	Female	16/48	19/31	0.346
ECOG PS (at screening)	0	18/48	36/57	0.420
	1	17/44	27/35	0.201
SPD	> 50 cm^2	3/10	9/10	0.099
	≤ 50 cm^2	29/77	53/76	0.366
Lactate dehydrogenase	< 500 µ/L	30/79	53/81	0.350
	≥ 500 µ/L	4/10	10/11	0.460
Prior CT response status	Chemorefractory (PD, SD)	15/25	16/18	0.338
	Chemosensitive (PR, CR)	20/67	47/74	0.320
NHL type	DLBCL	21/60	36/57	0.357
	HGBCL	14/22	19/21	0.413
DLBCL subtype	DLBCL NOS de novo	19/53	30/49	0.395
	DLBCL transformed from indolent NHL	2/7	6/8	0.218
DLBCL subtype based on cell of origin	GCB	21/45	29/40	0.348
	ABC, non-GCB	7/21	22/29	0.477

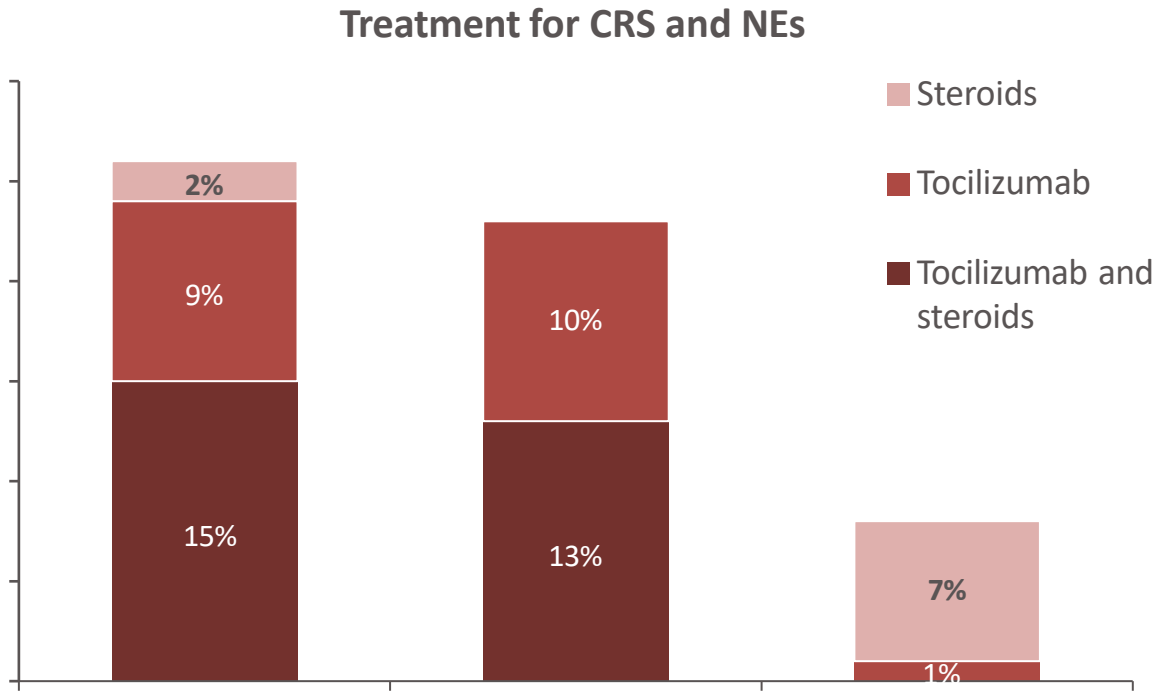


ABC, activated B-cell; GCB, germinal B-cell; SPD, sum of the product of perpendicular diameters.

Kamdar M, et al. Lancet 2022.

TRANSFORM: TEAEs of special interest

Patients with CRS and NEs	Liso-cel arm (n = 92)
CRS,[a] n (%)	
Any grade	45 (49)
Grade 1	34 (37)
Grade 2	10 (11)
Grade 3	**1 (1)[b]**
Grade 4/5	**0**
Time to onset, days, median (range)	5 (1–63)
Time to resolution, days, median (range)	4 (1–16)
NE,[c] n (%)	
Any grade	11 (12)
Grade 1	5 (5)
Grade 2	2 (2)
Grade 3	**4 (4)**
Grade 4/5	**0**
Time to onset, days, median (range)	11 (7–25)
Time to resolution, days, median (range)	6 (1–30)

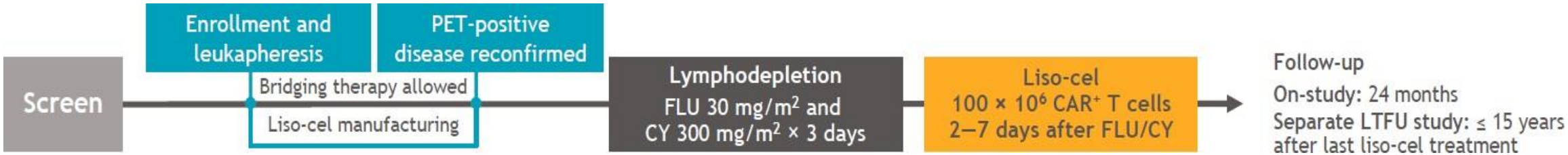


Other adverse events of special interest	Liso-cel arm (n = 92)	SOC arm (n = 91)
Prolonged cytopenia[d]	40 (43)	3 (3)
Grade ≥ 3 infection	14 (15)	19 (21)

Kamdar M, et al. Lancet 2022.

Not all patients are eligible for ASCT

PILOT study



Patient eligibility

- Age ≥ 18 years
- LBCL: DLBCL NOS (de novo; transformed from FL), HGBCL with rearrangements in *MYC* and *BCL2* and/or *BCL6* (double/triple hit), or FL3B
- One prior line of therapy containing an anthracycline and a CD20-targeted agent
- Not intended for HSCT by investigator and met ≥ 1 of the following TNI criteria: age ≥ 70 years, ECOG PS of 2, DLCO ≤ 60% (adjusted for sex-specific hemoglobin concentration), LVEF < 50%, CrCl < 60 mL/min (calculated using Cockcroft-Gault), and/or AST/ALT > 2 × ULN
- Adequate organ function[a]
- Patients with secondary CNS lymphoma were allowed

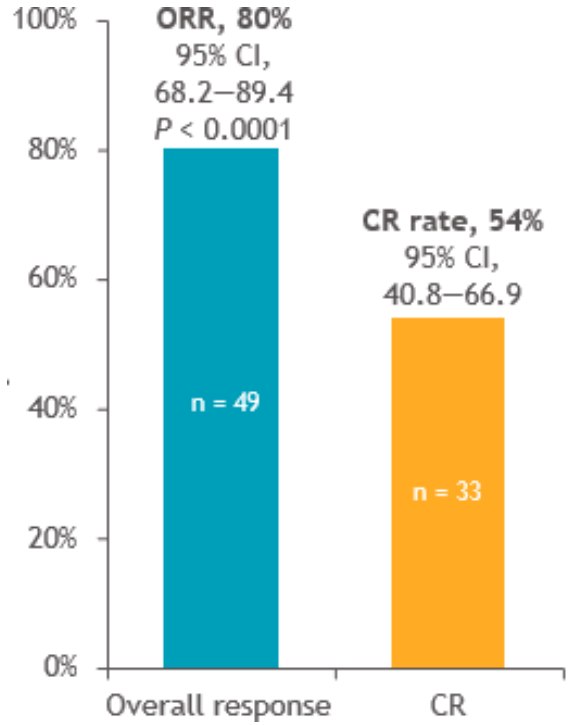
Endpoints

- **Primary**
  - Overall response rate (ORR) by independent review committee (IRC) per Lugano 2014 criteria[2]
- **Main secondary**
  - Adverse events (AE) and laboratory abnormalities
  - Complete response (CR) rate by IRC
  - Duration of response (DOR)
  - DOR for patients whose best overall response (BOR) was CR
  - Progression-free survival (PFS)
  - Event-free survival (EFS)[b]
  - Overall survival (OS)

Sehgal A, et al. Lancet 2022

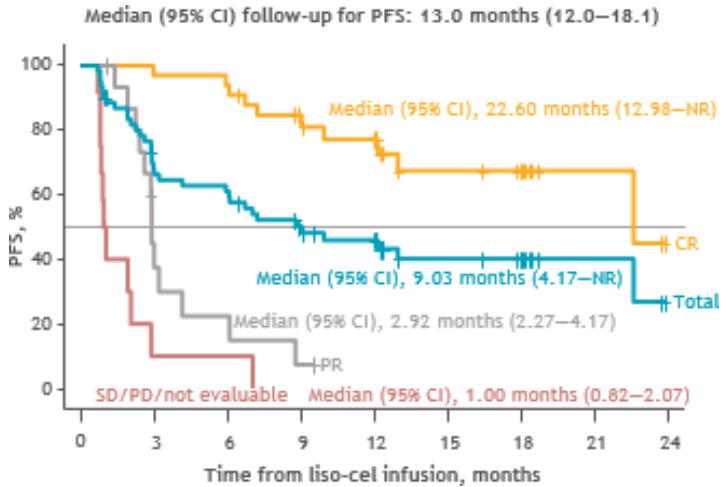
Demographics and disease characteristics in liso-cel patients

	Liso-cel–treated analysis set (n = 61)
Median (range) age, y	74 (53–84)
Histology, n (%) DLBCL NOS tFL HGBCL with DLBCL histology FL3B	 33 (54) 9 (15) 18 (30) 1 (2)
Double or triple hit,[c] n (%)	20 (33)
Less than CR to frontline therapy	33 (54%)
Relapsed within 1 year of first-line therapy	13 (21%)
Relapsed after 12 months of first-line therapy	15 (25%)
Frontline systemic therapy R-CHOP EPOCH-R Other	 51 (84%) 10 (16%) 8 (13%)

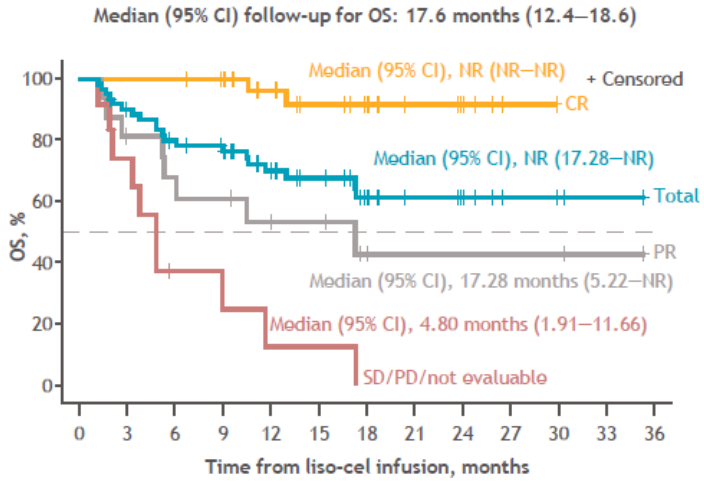


Median DOR 12 mo
(22 mo in CR pts)

PFS



OS



Sehgal A, et al. Lancet 2022

Summary of second line CAR T

- ZUMA 7 and TRANSFORM studies support the use of second-line CAR T therapy in high-risk DLBCL patients either primary refractory or early relapse < 12 months of CIT
- There were key differences between the study design including bridging therapy used, number of salvage therapies, ways in which EFS was defined, and whether crossover was allowed
- Liso-cel also approved as second-line for transplant ineligible patients who relapse > 12 months of CIT based on PILOT study
- Unclear if second line CAR will improve long-term responses given 24-month EFS is 40% similar to that when used in third-line setting and will need longer follow-up to further assess OS benefit
- HDT-ASCT remains standard of care option for transplant-eligible patients who progress later than one year after frontline therapy who then respond to salvage therapy

Third-line therapies for DLBCL

SADAL: Selinexor in Patients With Relapsed/Refractory DLBCL

ORR	CR	PR	SD	PD/NR
36 (28.3%)	15 (11.8%)	21 (16.5%)	11 (8.7%)	80 (63.0%)

Category	Median OS (months)
All Patients	9.1

Category	Median DOR (months)
All Responders	9.2
CR Patients	13.5
PR Patients	4.8

Median follow-up: 11.1 months

Kalakonda N et al. Lancet Haematology. 2020

Phase 2 SADAL: TEAE (≥ 20%)

	Grade 1–2	Grade 3	Grade 4
Thrombocytopenia	20 (16%)	39 (31%)	19 (15%)
Nausea	66 (52%)	8 (6%)	0
Fatigue	46 (36%)	14 (11%)	0
Anemia	26 (21%)	27 (21%)	1 (1%)
Decreased appetite	42 (33%)	5 (4%)	0
Diarrhea	41 (32%)	4 (3%)	0
Constipation	39 (31%)	0	0
Neutropenia	7 (6%)	20 (16%)	11 (9%)
Weight loss	38 (30%)	0	0
Vomiting	35 (28%)	2 (2%)	0
Pyrexia	23 (18%)	5 (4%)	0
Asthenia	21 (17%)	6 (5%)	0

Event	% (N)
TEAE-related discontinuations	17% (22)
Dose modification due to TEAE	57% (73)
Serious AEs	48% (61)
Death due to TEAE[a]	(5)

a None of the deaths in the study were considered related to selinexor by the investigator.

Kalakonda N et al. Lancet Haematology. 2020

L-MIND Study: Tafasitamab + Len in R/R DLBCL

	Tafasitamab + Lenalidomide (N=80)	
	Primary Analysis (cut-off November 30, 2018)	Follow-up Analysis (cut-off October 30, 2020)
ORR (CR + PR), %	60.0	57.5
CR, %	42.5	40.0
PR, %	17.5	17.5
SD, %	13.8	16.3
PD, %	16.3	16.3
mDOR, months	21.7	43.9
mPFS, months	12.1	11.6
mOS, months	NR	33.5

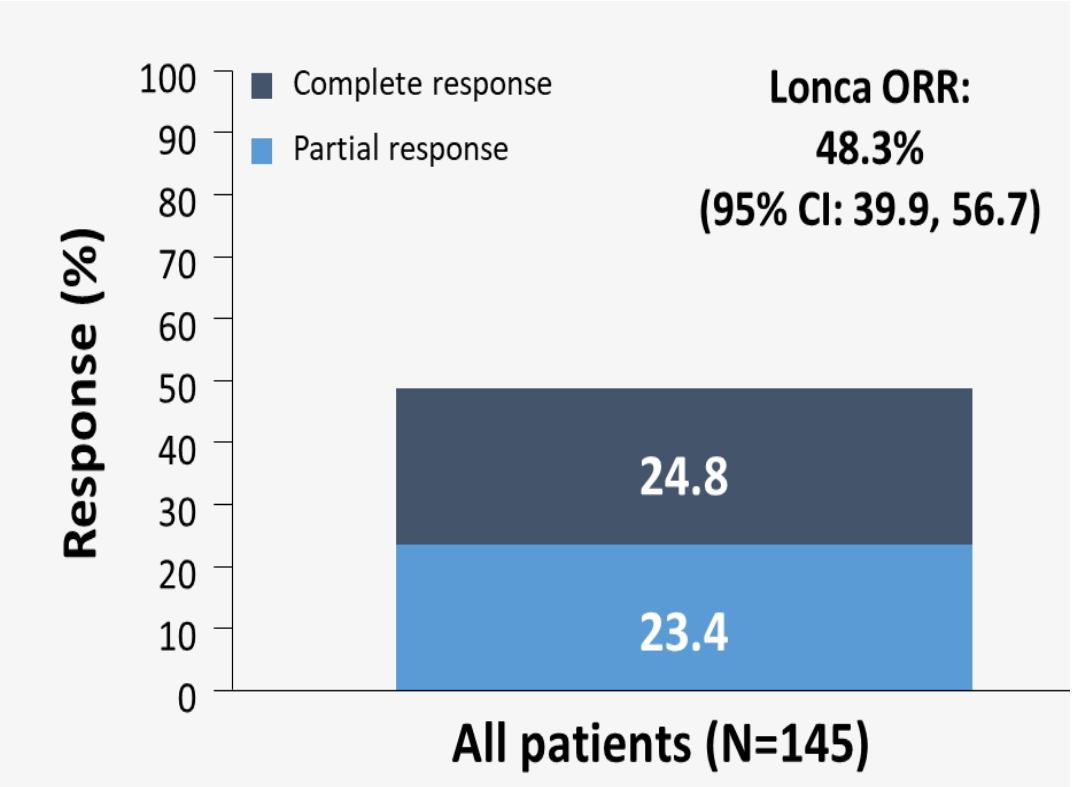
Duell J et al. *Haematologica*. 2021;106(9):2417-2426.

Phase 2 L-MIND: Select Adverse Events

Adverse Event	All Grade, %	Grade ≥ 3, %
Neutropenia	50.6	49.4
Anemia	37.0	7.4
Thrombocytopenia	30.9	17.3
Leukopenia	14.8	11.1
Febrile neutropenia	12.3	12.3
Diarrhea	35.8	1.2
Asthenia	24.7	2.5
Hypokalemia	18.5	6.2
Infective pneumonia	12.3	9.9
Urinary tract infection	12.3	2.5
Upper respiratory tract infection	9.9	2.5
Hypertension	8.6	3.7

Duell J et al. *Haematologica*. 2021;106(9):2417-2426.

LOTIS-2 Trial: Loncastuximab tesirine efficacy results



mDoR for the 70 responders:
12.58 months
(95% CI: 6.87, -)

Median PFS:
5.09 mo
(95% CI, 2.89-8.31)

mDoR for patients with a CR:
13.37 months
(95% CI: 12.58, -)

Median OS:
9.53 mo
(95% CI, 6.93-11.24)

Caimi PF et al. *Lancet Oncol.* 2021;22(6):790-800

LOTIS-2 Trial: Loncastuximab tesirine safety results

TEAEs in ≥20% of the all-treated population

Preferred term	Patients n (%)		
	<65 years (N=65)	≥65 (N=80)	Total (N=145)
Patients with any TEAE	65 (100)	78 (97.5)	143 (98.6)
GGT increased	33 (50.8)	27 (33.8)	60 (41.4)
Neutropenia	34 (52.3)	24 (30.0)	58 (40.0)
Thrombocytopenia	28 (43.1)	20 (25.0)	48 (33.1)
Fatigue	21 (32.3)	19 (23.8)	40 (27.6)
Anemia	23 (35.4)	15 (18.8)	38 (26.2)
Nausea	17 (26.2)	17 (21.3)	34 (23.4)
Cough	19 (29.2)	13 (16.3)	32 (22.1)
Alkaline phosphatase increased	18 (27.7)	11 (13.8)	29 (20.0)
Peripheral edema	11 (16.9)	18 (22.5)	29 (20.0)

Most common (≥10%) grade ≥3 TEAEs were:

- Neutropenia (38 patients; 26.2%)
- Thrombocytopenia (26 patients; 17.9%)
- GGT increased (25 patients; 17.2%)
- Anemia (15 patients; 10.3%)

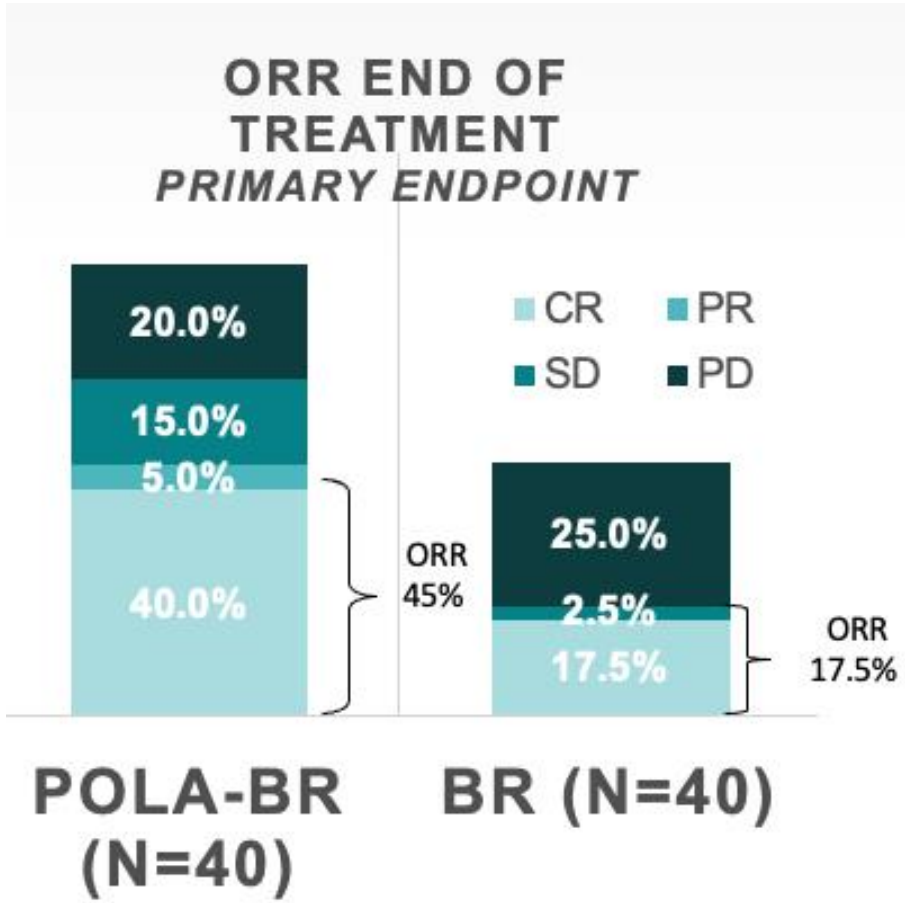
Treatment-related TEAEs leading to treatment discontinuation occurred in 26 (17.9%) patients, most commonly (≥2%):

- GGT increased (16 patients; 11.0%)
- Peripheral edema (4 patients; 2.8%)
- Localized edema (3 patients; 2.1%)

No increase in toxicity was seen in patients aged ≥65 years compared with younger patients

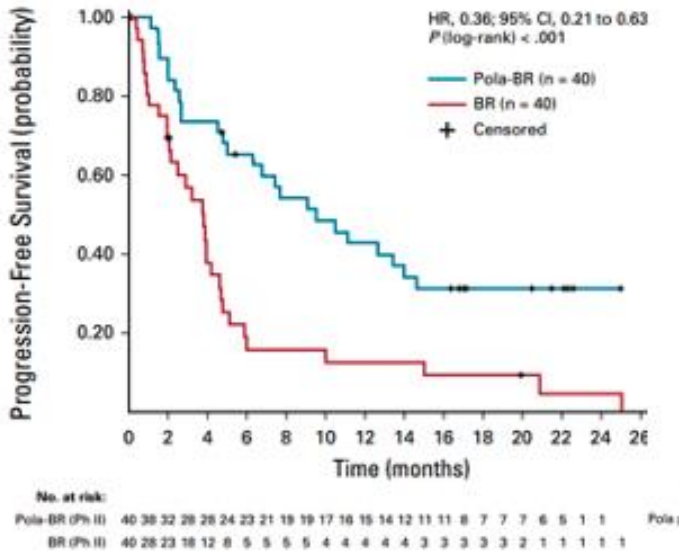
Caimi PF et al. *Lancet Oncol.* 2021;22(6):790-800

Ph2 Pola + BR Efficacy

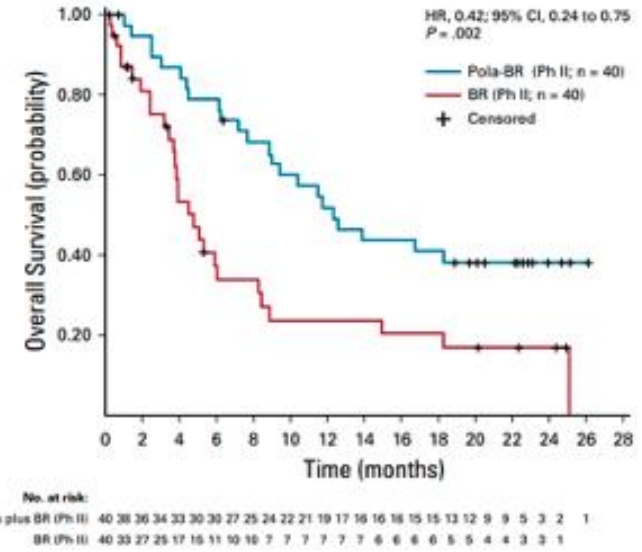


mDOR by IRC (Pola + BR vs BR): 12.6 mo vs 7.7 mo

mPFS
9.5 mo vs 3.7 mo



mOS
12.4 mo vs 4.7 mo



Sehn L. et al. JCO 2020

Ph2 Pola + BR Safety

	Pola-BR (n = 39)*		BR (n = 39)*	
Adverse Event	**All Grades, No. (%)**	**Grades 3-4, No. (%)**	**All Grades, No. (%)**	**Grades 3-4, No. (%)**
Blood and lymphatic system disorders				
Anemia	21 (53.8)	11 (28.2)	10 (25.6)	7 (17.9)
Neutropenia	21 (53.8)	18 (46.2)	15 (38.5)	13 (33.3)
Thrombocytopenia	19 (48.7)	16 (41.0)	11 (28.2)	9 (23.1)
Lymphopenia	5 (12.8)	5 (12.8)	0	0
Febrile neutropenia	4 (10.3)	4 (10.3)	5 (12.8)	5 (12.8)
GI disorders				
Diarrhea	15 (38.5)	1 (2.6)	11 (28.2)	1 (2.6)
Nausea	12 (30.8)	0	16 (41.0)	0
Constipation	7 (17.9)	0	8 (20.5)	1 (2.6)
General disorders and administration site conditions				
Fatigue	14 (35.9)	1 (2.6)	14 (35.9)	1 (2.6)
Pyrexia	13 (33.3)	1 (2.6)	9 (23.1)	0
Metabolism and nutrition disorders				
Decreased appetite	10 (25.6)	1 (2.6)	8 (20.5)	0
Peripheral neuropathy				
Peripheral neuropathy†	17 (43.6)	0	3 (7.7)	0

Sehn L. et al.
JCO 2020

Summary of approved DLBCL third-line therapies

	Loncastuximab teserine[1]	Selinexor[2]	Tafasitamab + Lenalidomide[3]	R-Bendamustine-Polatuzumab[4]
Characteristics of r/r DLBCL patients included	Median 3 prior lines, Excluded pts with bulky disease ≥ 10 cm, 6% of pts with bulky disease ≥ 7.5 cm, included HGDLBCL, transformed DLBCL, PMBCL	41% of pts with > 3 prior lines, Included transformed lymphoma, excluded PMBCL, required ≥ 60 days to have elapsed since EOT for pts who responded to their last-line therapy, and ≥ 98 days since end of last-line therapy for pts who did not have a response	Median 2 prior lines, Did not include double hit, triple hit, or primary refractory DLBCL, or > 3 prior lines, or prior CD-19 CAR T therapy, 50% had received 1 prior line	Median 2 prior lines, Did not include transformed pts, double hit, or triple hit DLBCL, 27% pts received 1 prior line
Safety	≥ Gr 3 TrAEs: neutropenia (26%), thrombocytopenia (18%), increased GGT (17%)	≥ Gr 3 TrAEs: thrombocytopenia (46%), neutropenia (24%), anemia (22%)	≥ Gr 3 TrAEs: Neutropenia (48%), thrombocytopenia (17%), febrile neutropenia (12%), rash (9%), hypokalemia (6%)	≥ Gr 3 TrAEs: Anemia (28%), neutropenia (46%), thrombocytopenia (41%)
ORR	48%	28%	60%	45%
Follow-up time (months)	7.3	14.7	17.3	27
PFS (months)	4.9	2.6	12.1	9.5
OS (months)	9.9	9.1	Not reached	12.4
DOR (months)	10.3	9.3	21.7	_

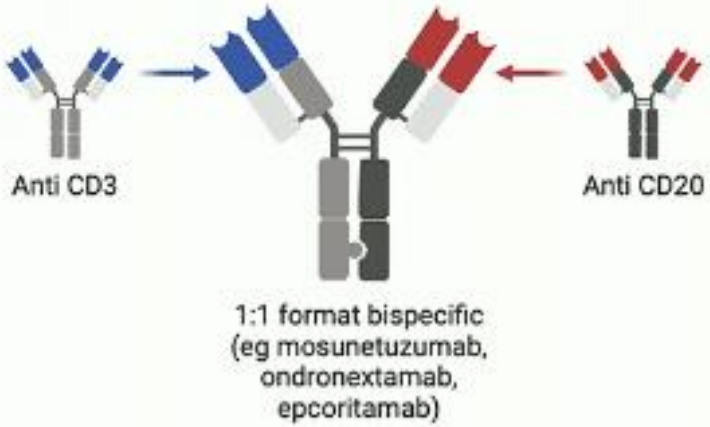
1. Caimi et al. Lancet 2021 2. Kalakonda et al. Lancet 2020 3. Salles et al. Lancet 2020 4. Sehn et al. JCO 2019

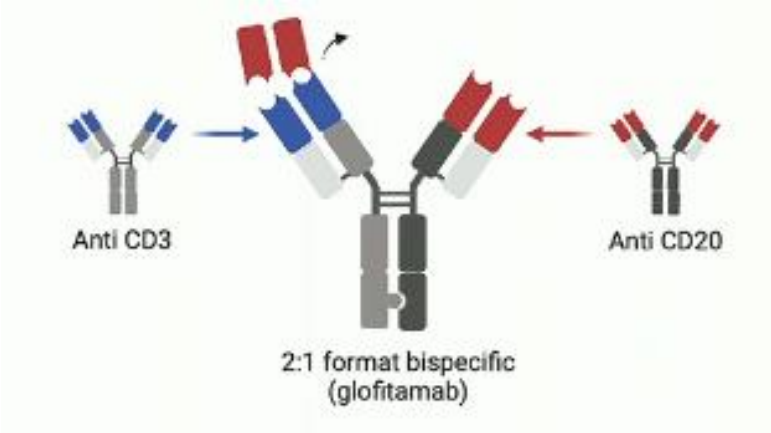
CD3 X CD20 Bispecifics: Emerging therapy

Mosunetuzumab, glofitamab, epcoritamab, odronextumab

Structural Features of the CD3 x CD20 Bispecific Abs

T-cell binding, activation, T-cell mediated target cell death at extremely low receptor occupancy





- CD3 on T cells
- CD20 on B cells (normal and malignant)
- Full length antibody
- FC modifications and silencing
- Long half life
- Alternate conformations (eg 2:1 structure of glofitamab)

Delivery and Scheduling

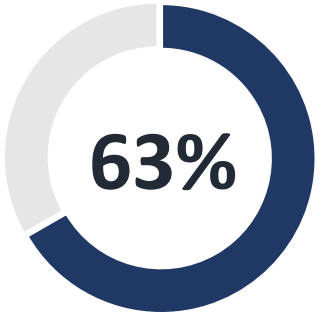
Treatment	Route	Cycles	Duration	CRS mitigation
Mosunetuzumab	IV/SC	Q21d: Weekly during C1 D1,8,15 Q3w starting C2 to C8 (if in CR), to C17 (if PR/SD)	Fixed	Step up
Glofitamab	IV	Q21d: 2 (weekly) steps to target then q3w to C12	Fixed	Obinutuzumab Step up Steroids
Epcoritamab	SC	Q28d: Weekly C1-3 Q2w C4-9 Q4w C10 onwards	Until PD	Step up Steroids
Ondronextamab	IV	Q21d: 6 doses C1, q1w doses C2-4 Then q14d maintenance	Until PD	Step up Split dosing Steroids

CD20-CD3 Bispecific Antibodies: Early Data in R/R DLBCL

Epcoritamab[1]

Phase 2 dose escalation trial (n=157)

CR = 34% in patients with prior CAR-T vs 42% in those without prior CAR-T

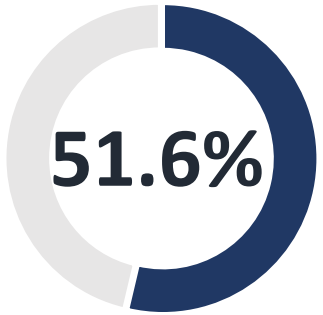


ORR
(95% CI, 55%–71%)

Glofitamab[2]

Phase 2 dose expansion trial (n=107)

CR = 35% in patients with prior CAR-T vs 42% in those without prior CAR-T

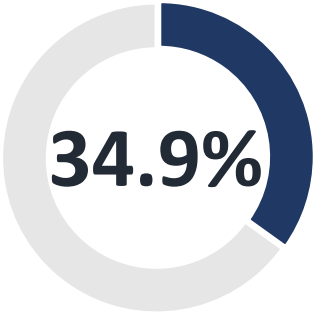


ORR
(95% CI, 43.5%–59.7%)

Mosunetuzumab[3]

Phase 1 dose escalation trial

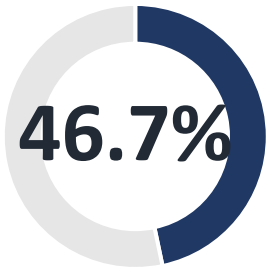
129 patients with aggressive B-cell NHL



ORR
(95% CI, 26.7%–43.8%)

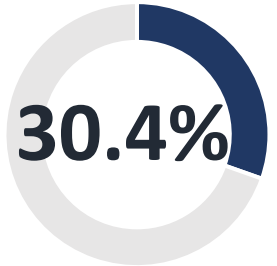
Odronextamab[4]

Phase 1 dose escalation and expansion trial (DLBCL cohort)



Without prior CAR-T ≥5-mg dose (n=30)

ORR



With prior CAR-T ≥5-mg dose (n=23)

1. Thieblemont C et al. Abstract LB2364 presented at EHA 2022; 2. Dickinson M et al. *J Clin Oncol*. 2022;40(16_suppl):7500; 3. Budde LE et al. *J Clin Oncol.* 2022;40:481-491;
4. Bannerji R et al. *Blood.* 2020;136(Suppl. 1):42.

Additional Efficacy Data in R/R DLBCL

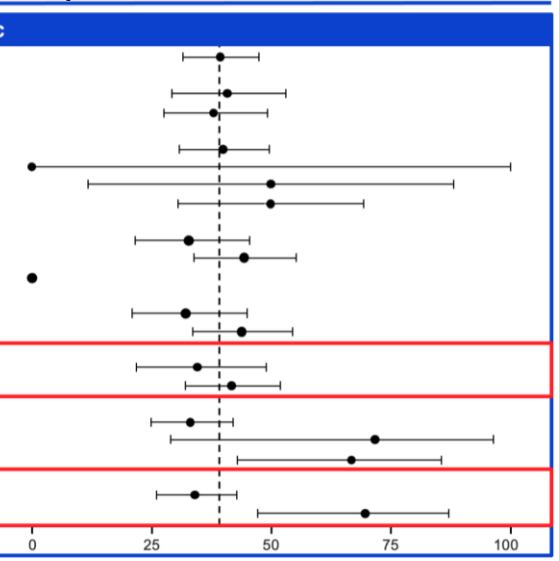
	Mosunetuzumab (n=129)[1]	Odronextamab (n=85)[2]	Epcoritamab (n=157)[3]	Glofitamab (n=154)[4]
Trial design	Phase 1/1b dose escalation and expansion	Phase 1 dose escalation and expansion	Phase 2 dose expansion	Phase 2 dose expansion
ORR	34.9%	39% (no prior CAR T), 33% (prior CAR T)	63%	51.6%
CR	19.4%	24% (no prior CAR T0, 24% (prior CAR T)	39%	39.4%
DOR (mos)	7.6	4.4 (no prior CAR T), 6.7 (prior CAR T)	12	18.4
DOR in patients with CR (mos)	22.8	10.3 (no prior CAR T), 7.4 (prior CAR T)	Not reached	34.2
PFS (mos)	1.4	11.5 (no prior CAR T), 2 (prior CAR T)	4.4	4.9
Follow-up (mos)	11.9	4.2	10.7	12.6

1. Budde et al. JCO. Feb 2022 2. Bannerji et al. Lancet May 2022 3. Thieblemont et al. EHA 2022 4. Dickinson et al. EHA 2022.

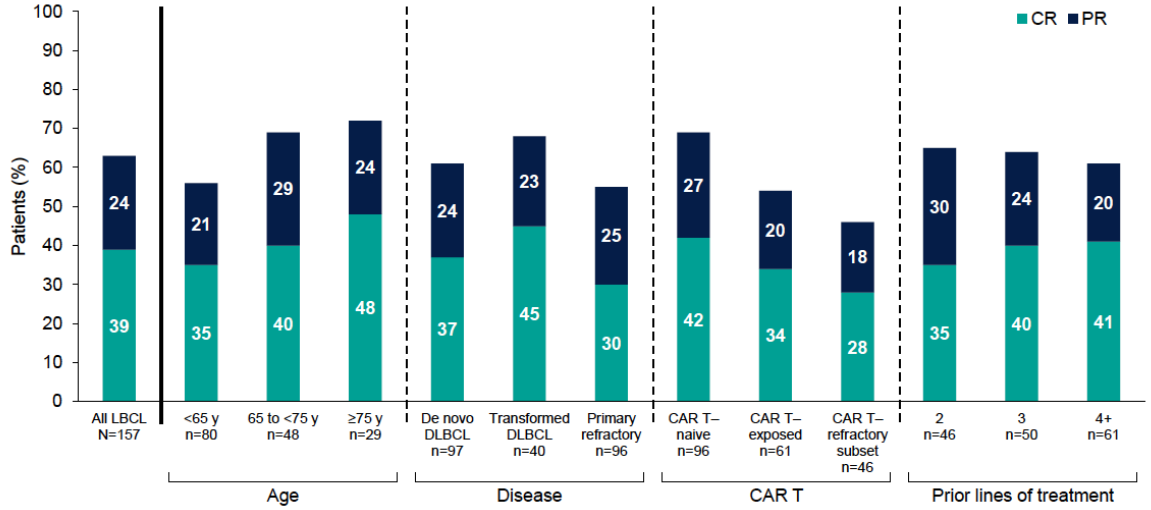
Responses seen across key subgroups

Glofitamab: Complete response rates by IRC in pre-specified subgroups

Subgroups	No. of patients	CR (95% CI) by IRC
Overall	155 (100%)	39% (32%, 48%)
Age group		
<65	71 (46%)	41% (29%, 53%)
≥65	84 (54%)	38% (28%, 49%)
NHL subtype at study entry		
DLBCL	110 (71%)	40% (31%, 50%)
HGBCL	11 (7%)	0%
PMBCL	6 (4%)	50% (12%, 88%)
trFL	28 (18%)	50% (31%, 69%)
Bulky disease >6cm		
Yes	64 (41%)	33% (22%, 46%)
No	90 (58%)	44% (34%, 55%)
Unknown/Missing	1 (1%)	0%
Number of prior line of therapies		
2	62 (40%)	32% (21%, 45%)
≥3	93 (60%)	44% (34%, 55%)
Prior CAR-T therapy		
Yes	52 (34%)	35% (22%, 49%)
No	103 (66%)	42% (32%, 52%)
Post ASCT		
No	127 (82%)	33% (25%, 42%)
Refractory	7 (5%)	71% (29%, 96%)
Relapsed	21 (14%)	67% (43%, 85%)
R/R to last prior therapy		
Refractory	132 (85%)	34% (26%, 43%)
Relapsed	23 (15%)	70% (47%, 87%)



Epcoritamab: Deep responses consistent across key subgroups

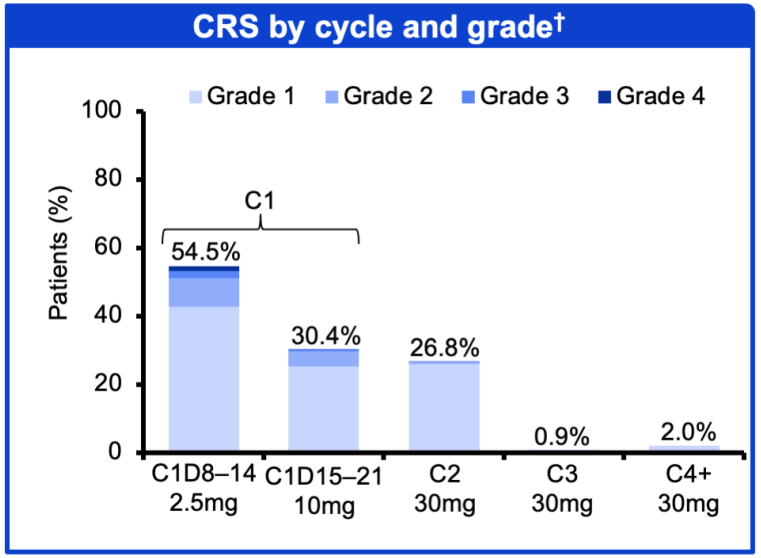


1.Thieblemont et al. EHA 2022 2. Dickinson et al. EHA 2022.

Safety of bispecifics

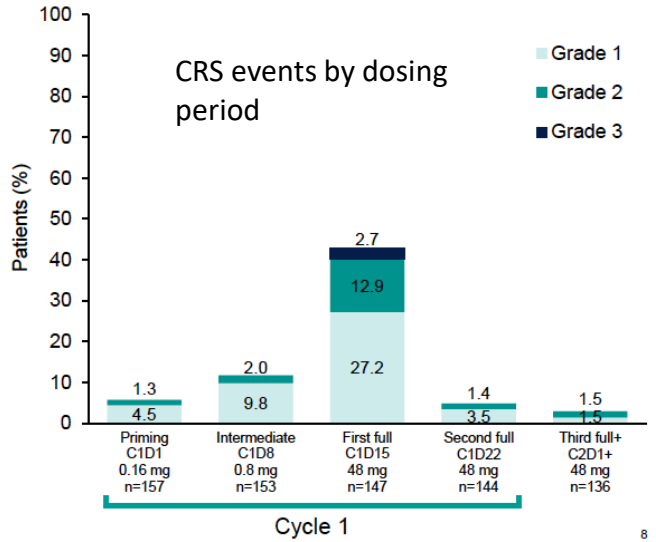
Glofitamab

n (%)	N=154
CRS (any grade)*	97 (63.0)
Grade 1 (fever)	73 (47.4)
Grade 2	18 (11.7)
Grade 3	4 (2.6)
Grade 4	2 (1.3)
Median time to CRS onset from C1D8 dose, hours (range)	13.6 (6.2–51.8)
Corticosteroids for CRS management	27/97 (27.8)
Tocilizumab for CRS management	31/97 (32.0)



Epcoritamab

	LBCL N=157
CRS events, n (%)[a]	78 (49.7)
Grade 1	**50 (31.8)**
Grade 2	24 (15.3)
Grade 3	4 (2.5)
Median time to onset from first full dose, d	**0.8 (20 h)**
CRS resolution, n (%)	77 (98.7)
Median time to resolution from first full dose, d	**2 (48 h)**
Treated with tocilizumab, n (%)	22 (14.0)
Treated with corticosteroids, n (%)	16 (10.2)
Leading to treatment discontinuation, n (%)	**1 (0.6)**



CRS mostly low grade with most events occurring during cycle 1 and mitigated with use of steroids

1.Thieblemont et al. EHA 2022 2. Dickinson et al. EHA 2022.

Advantages of Bispecifics

- Off the shelf
- Able to produce deep, durables responses in high-risk DLBCL patients (multiply refractory, post CAR T, etc)
- Ongoing studies evaluating bispecifics combined with established treatments in frontline and relapsed setting
- Several rational immunologic combinations

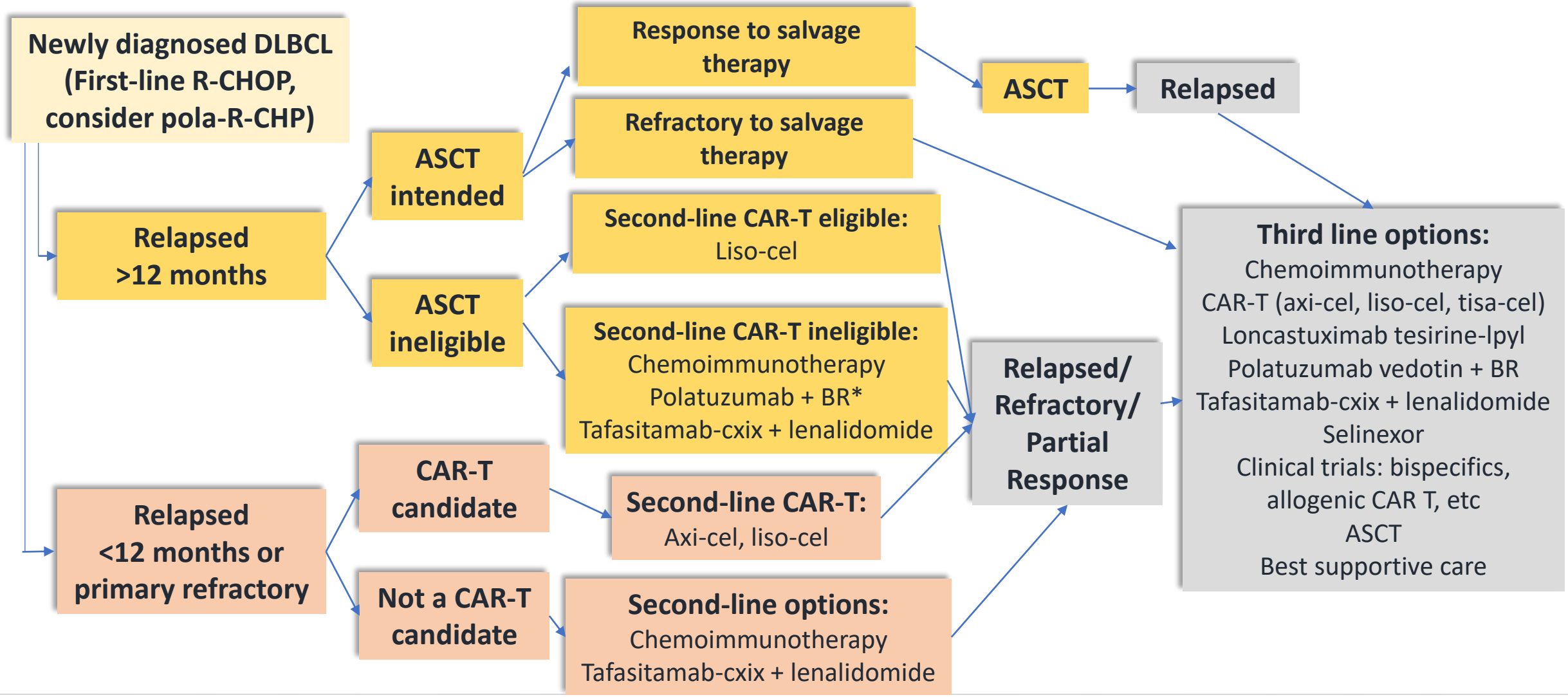
Setting	Bispecific	Partner	Design
2L DLBCL	Glofitamab	GemOx	Randomised v RGemOx
2L DLBCL	Epcoritamab	Mono	Randomised v RGem Ox or BR
NHL/ DLBCL	Glofitamab	CelMods / Len	Ph1/2
NHL	Epcoritamab	Len + ritux	Ph1/2
1L DLBCL	Epcoritamab	RCHOP	Ph2
1L DLBCL	Glofitamab	RCHOP RCHP Pola	Ph2
3L+ NHL	Glofitamab	"second signal" bispecifics	Ph1
3L+	Glofitamab	Polatuzumab Vedotin	Ph2

The Changing Treatment Landscape for DLBCL

Recent FDA Approvals in R/R DLBCL

Class	Agent	Line of therapy	Approval date	Full indication(s)
CD-19 directed CAR T-cell therapy (CAR-T)	Axicabtagene ciloleucel	Second line Third line	4/1/2022 10/18/2017	• LBCL refractory to or that relapses <12 months after first-line chemoimmunotherapy • R/R LBCL after ≥2 lines of systemic therapy
	Lisocabtagene maraleucel	Second line Third line	6/24/2022 2/5/2021	• LBCL refractory to or that relapses <12 months after first-line chemoimmunotherapy • LBCL refractory disease or relapsed after first-line chemoimmunotherapy and are not eligible for HSCT due to comorbidities or age • R/R LBCL after ≥2 lines of systemic therapy
	Tisagenlecleucel	Third line	5/1/2018	R/R LBCL after ≥2 lines of systemic therapy
Antibody or antibody drug conjugate	Loncastuximab tesirine-lpyl	Third line	4/23/2021	R/R LBCL after ≥2 lines of systemic therapy
	Tafasitamab-cxix + lenalidomide	Second line	7/31/2020	R/R DLBCL-NOS in patients who are not eligible for ASCT
	Polatuzumab vedotin-piiq + BR	Third line	6/10/2019	R/R DLBCL-NOS after ≥2 prior therapies
Targeted	Selinexor	Third line	6/22/2020	R/R DLBCL-NOS after ≥2 lines of systemic therapy

DLBCL: New Treatment Options in Context



*NCCN recommended but not an FDA approved option

Conclusion

- DLBCL treatment landscape is changing
- R-CHOP remains SOC but pola-R-CHP emerging option for high-risk patients (age > 60, IPI 3-5, and ABC subtype?)
- Second-line option for patients with primary refractory/early relapse DLBCL (within 12 months of CIT) is Axi-cel or Liso-cel CD19 CAR T
- ASCT remains SOC for transplant-eligible patients with relapse >12 months of initial CIT
- Post CAR T space is unmet need with multiple recently approved novel therapies: lonca-T, pola-BR, tafa-len, and selinexor
- Bispecifics in single agent and combination are emerging as novel therapy option with high efficacy and low CRS/ICANS
- Emerging question is how to sequence these novel therapies

Thank you for your attention!

Any Questions?

Please email me at
skambhampati@coh.org