Onkopedia Webinar, 23. Februar, 2024

Diffuse großzellige B-Zell Lymphome: was ist neu?

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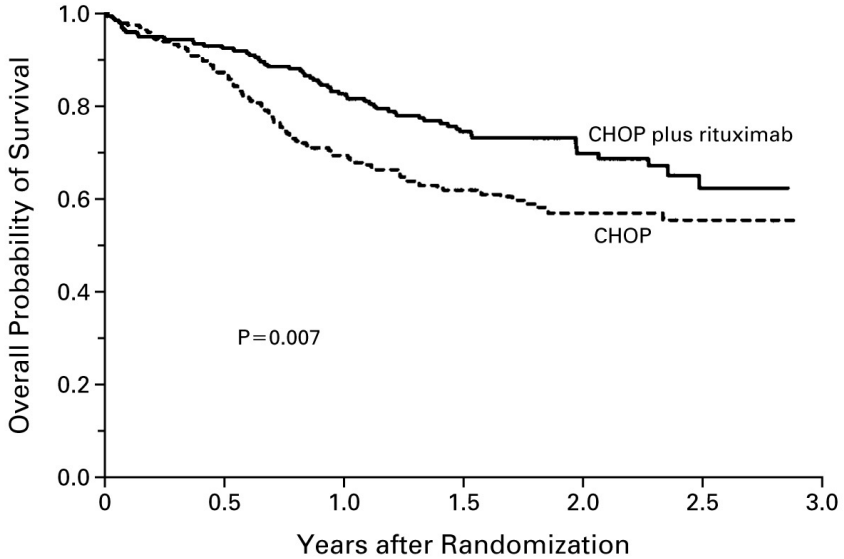
Potential conflicts of interest

Company	Conflict of interests
Roche	Advisory Board, invited speaker, research support
Gilead	Advisory Board, research support
Janssen	Advisory Board, invited speaker, research support
Bayer	Advisory Board, invited speaker, research support
Celgene	Advisory Board, invited speaker, research support
Novartis	Advisory Board, research support
AstraZeneca	Advisory Board, research support
Takeda	Advisory Board, invited speaker
BMS	Advisory Board, invited speaker
NanoString	Advisory Board
AbbVie	Advisory Board, invited speaker
Incyte	Advisory Board, invited speaker
MorphoSys	Advisory Board, invited speaker, research support
Genmab	Advisory Board
Karyopharm	Advisory Board
Constellation	Advisory Board
ADC	Advisory Board
Miltenyi	Advisory Board
PentixaPharm	Advisory Board
Sobi	Advisory Board, invited speaker
Immagene	Consultation
Genase	Consultation
Hexal/Sandoz	Advisory Board, invited speaker
Lilly	Consultation
BeiGene	Advisory Board
MSD GmbH	Advisory Board
Pierre Fabre Pharma GmbH	Advisory Board

Frontline therapy of patients with diffuse large B-cell lymphoma

Introduction of rituximab significantly improved outcome of DLBCL patients

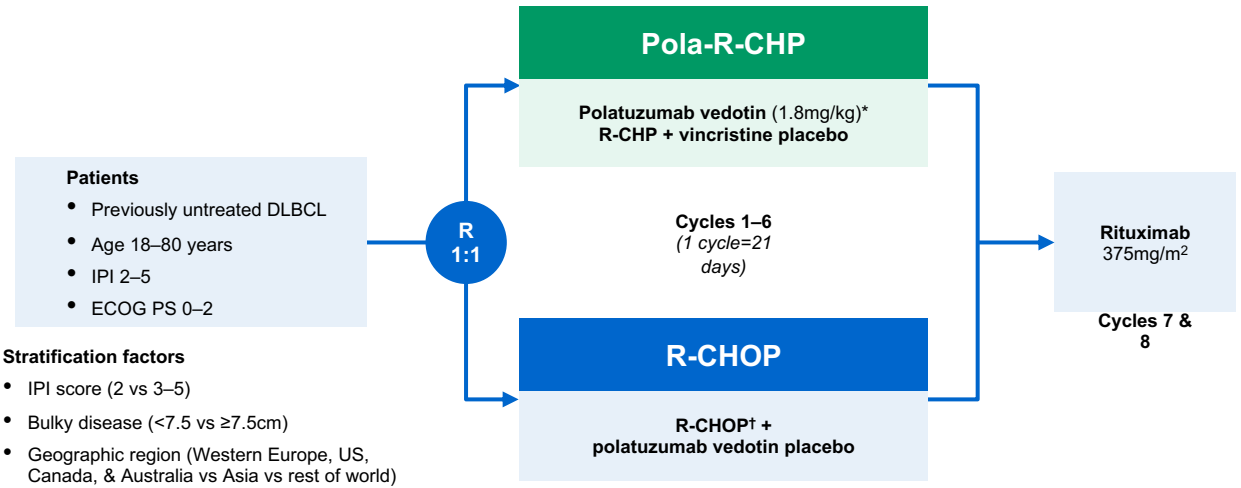


No. at Risk						
CHOP plus rituximab	202	187	167	118	64	21
CHOP	197	171	136	96	58	16

Coiffier et al., NEJM, 2002

The standard R-CHOP has been challenged!

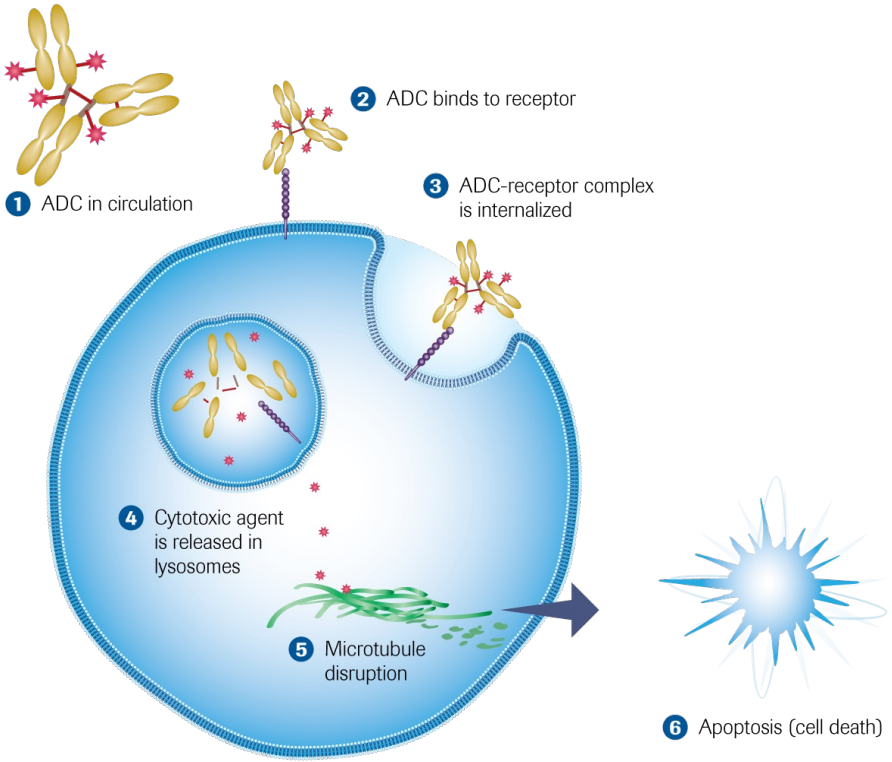
POLARIX: A randomized double-blinded study



*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.

Tilly et al., NEJM, 2022

Polatuzumab - mechanism of action

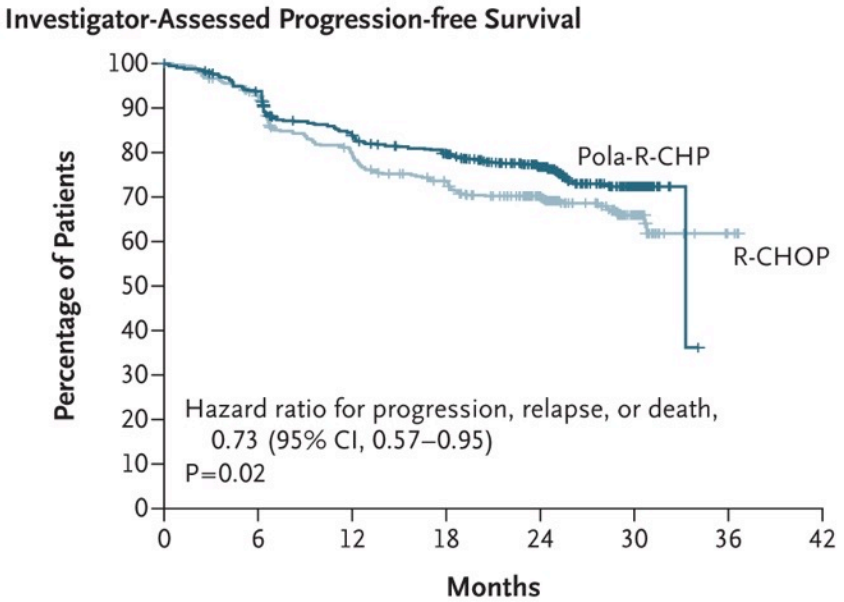


POLARIX-trial demographics

Table 1. Demographic and Clinical Characteristics at Baseline (Intention-to-Treat Population).*

Characteristic	Pola-R-CHP (N = 440)	R-CHOP (N = 439)
Median age (range) — yr	65 (19–80)	66 (19–80)
Age category — no. (%)		
≤60 yr	140 (31.8)	131 (29.8)
>60 yr	300 (68.2)	308 (70.2)
Female sex — no. (%)	201 (45.7)	205 (46.7)
Geographic region — no. (%)†		
Western Europe, United States, Canada, and Australia	302 (68.6)	301 (68.6)
Asia	81 (18.4)	79 (18.0)
Rest of world	57 (13.0)	59 (13.4)
Ann Arbor stage — no. (%)‡		
I or II	47 (10.7)	52 (11.8)
III or IV	393 (89.3)	387 (88.2)
No. of extranodal sites — no. (%)		
0 or 1	227 (51.6)	226 (51.5)
≥2	213 (48.4)	213 (48.5)
Bulky disease — no. (%)†§	193 (43.9)	192 (43.7)
ECOG performance status score — no. (%)¶		
0 or 1	374 (85.0)	363 (82.7)
2	66 (15.0)	75 (17.1)
Lactate dehydrogenase level — no. (%)‖		
Normal	146 (33.2)	154 (35.1)
Elevated	291 (66.1)	284 (64.7)
IPI score — no. (%)†**		
2	167 (38.0)	167 (38.0)
3 to 5	273 (62.0)	272 (62.0)
Median time from initial diagnosis to treatment initiation (IQR) — days	26 (16.0–37.5)	27 (19.0–41.0)
Cell of origin — no./total no. (%)††		
Germinal-center B-cell–like subtype	184/330 (55.8)	168/338 (49.7)
Activated B-cell–like subtype	102/330 (30.9)	119/338 (35.2)
Unclassified	44/330 (13.3)	51/338 (15.1)
Double-expressor lymphoma — no./total no. (%)††	139/362 (38.4)	151/366 (41.3)
Double-hit or triple-hit lymphoma — no./total no. (%)††	26/331 (7.9)	19/334 (5.7)

POLARIX - Efficacy

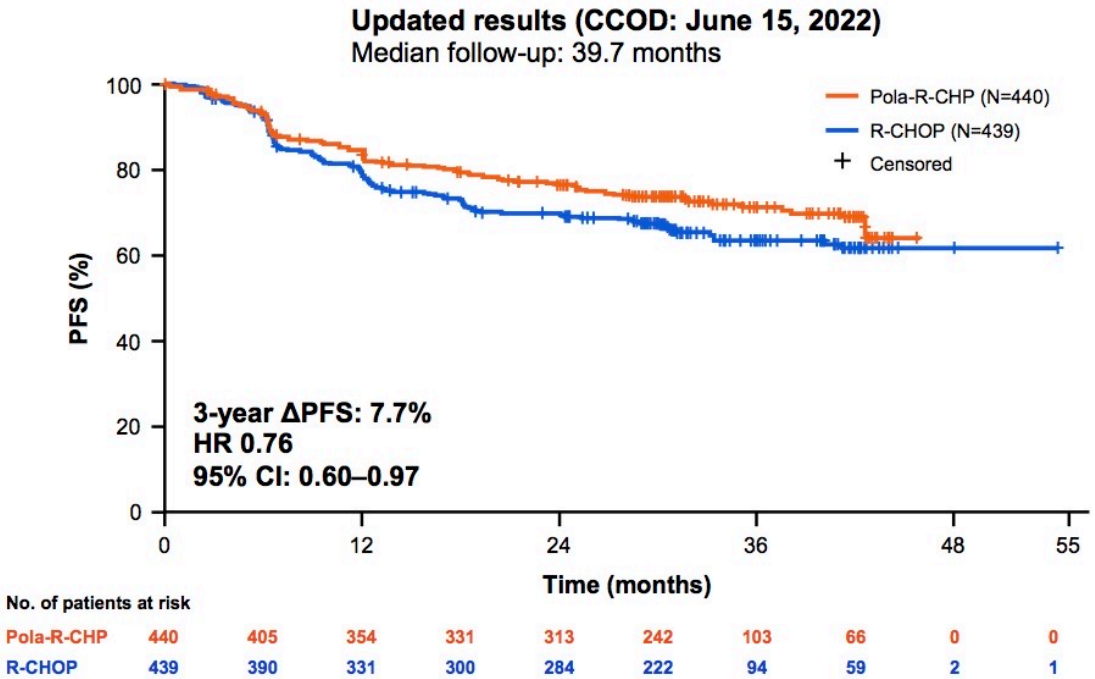


No. at Risk

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

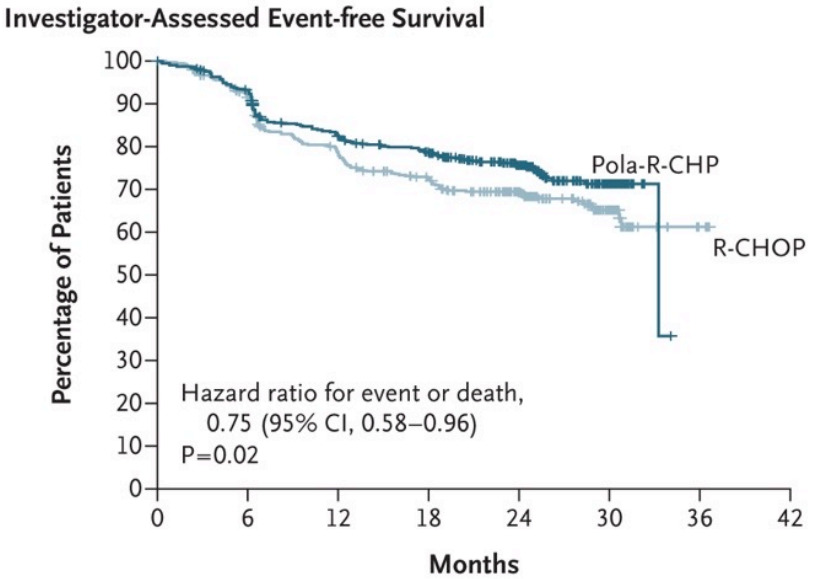
Tilly et al., NEJM, 2022

POLARIX - superior PFS maintained over time



Herrera et al., ASH, 2022

POLARIX - Efficacy

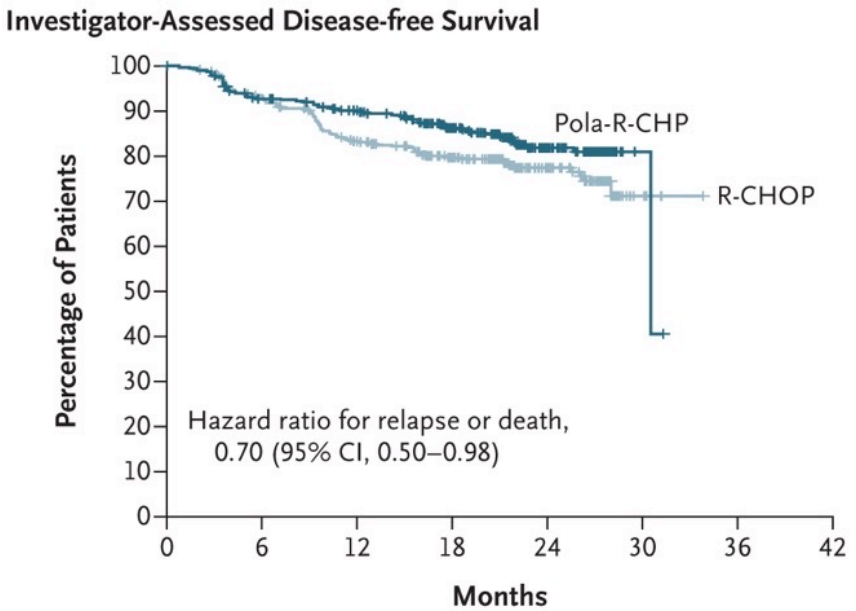


No. at Risk

Pola-R-CHP	440	402	348	323	243	78	NE	NE
R-CHOP	439	386	327	294	218	78	3	NE

Tilly et al., NEJM, 2022

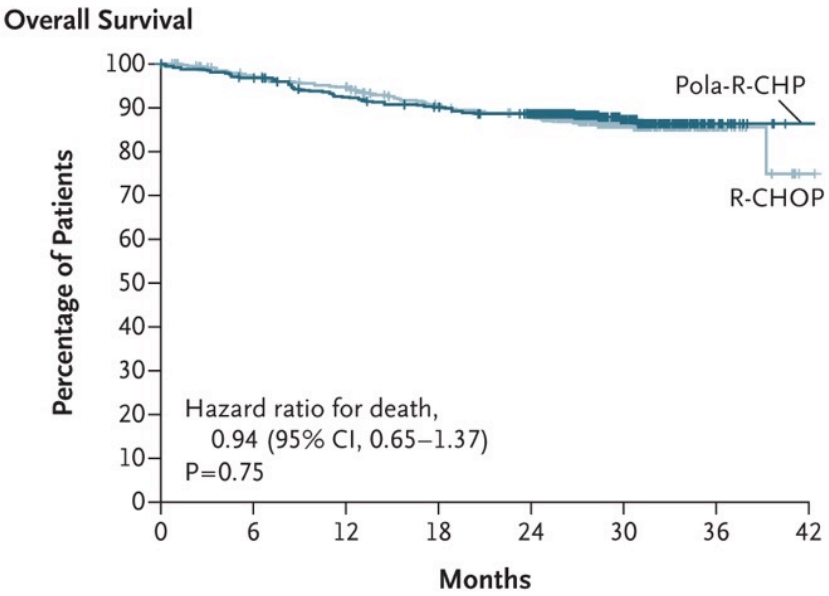
POLARIX - Efficacy



No. at Risk								
Pola-R-CHP	381	342	322	266	106	2	NE	NE
R-CHOP	363	326	282	238	96	5	NE	NE

Tilly et al., NEJM, 2022

POLARIX - Efficacy



No. at Risk

Pola-R-CHP	440	423	397	384	362	140	15	1
R-CHOP	439	414	401	376	355	132	20	1

Tilly et al., NEJM, 2022

POLARIX - Safety

Table 3. Adverse Events during the Treatment Period (Safety Population).*

Adverse Event	Pola-R-CHP (N=435)		R-CHOP (N=438)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Peripheral neuropathy†	230 (52.9)	7 (1.6)	236 (53.9)	5 (1.1)
Nausea	181 (41.6)	5 (1.1)	161 (36.8)	2 (0.5)
Neutropenia	134 (30.8)	123 (28.3)	143 (32.6)	135 (30.8)
Diarrhea	134 (30.8)	17 (3.9)	88 (20.1)	8 (1.8)
Anemia	125 (28.7)	52 (12.0)	114 (26.0)	37 (8.4)
Constipation	125 (28.7)	5 (1.1)	127 (29.0)	1 (0.2)
Fatigue	112 (25.7)	4 (0.9)	116 (26.5)	11 (2.5)
Alopecia	106 (24.4)	0	105 (24.0)	1 (0.2)
Decreased appetite	71 (16.3)	5 (1.1)	62 (14.2)	3 (0.7)
Pyrexia	68 (15.6)	6 (1.4)	55 (12.6)	0
Vomiting	65 (14.9)	5 (1.1)	63 (14.4)	3 (0.7)
Febrile neutropenia	62 (14.3)	60 (13.8)	35 (8.0)	35 (8.0)
Headache	56 (12.9)	1 (0.2)	57 (13.0)	4 (0.9)
Cough	56 (12.9)	0	53 (12.1)	0
Decreased weight	55 (12.6)	4 (0.9)	52 (11.9)	1 (0.2)
Asthenia	53 (12.2)	7 (1.6)	53 (12.1)	2 (0.5)
Dysgeusia	49 (11.3)	0	57 (13.0)	0

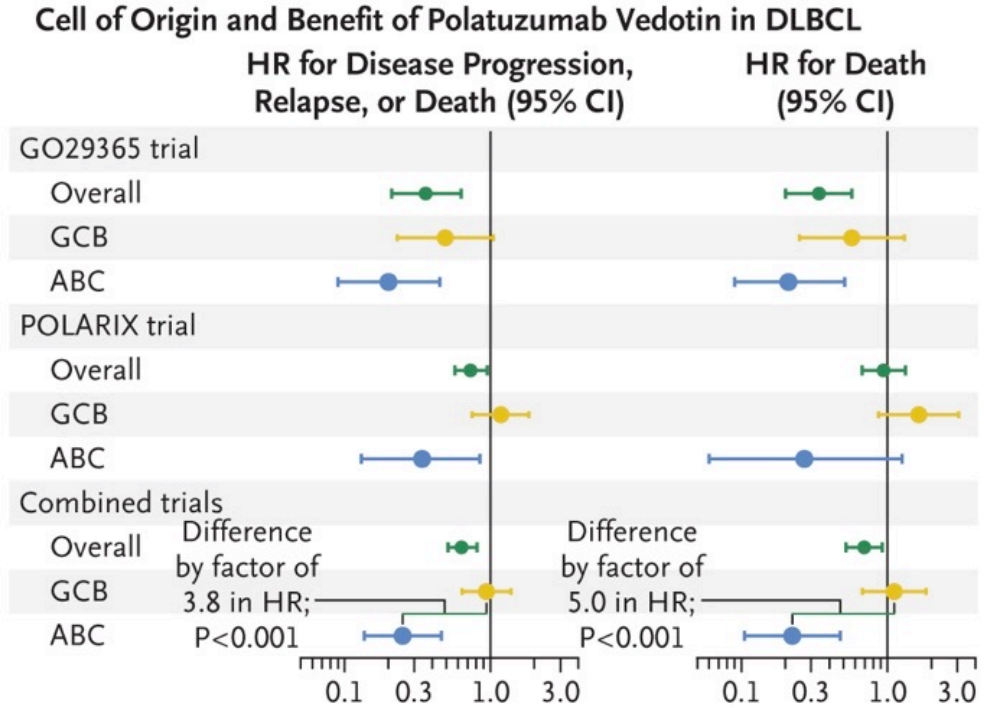
POLARIX - Efficacy

	Pola-R-CHP N = 440	R-CHOP N = 439
Total number of patients with at least one subsequent anti-lymphoma treatment, n (%)*	99 (22.5)	133 (30.3)
Total number of subsequent anti-lymphoma treatments (radiotherapy and systemic), n*	179	290
Total number of radiotherapy treatments, n	42	73
Patients with at least one radiotherapy treatment, n (%)	41 (9.3)	57 (13.0)
Total number of systemic therapy regimens, n (%)†	137	217
Patients who received at least one systemic therapy	75 (17.0)	103 (23.5)
Patients who received stem cell transplant	17 (3.9)	31 (7.1)
Patients who received CAR T-cell therapy	9 (2.0)	16 (3.6)

Tilly et al., NEJM, 2022

Does Polatuzumab work only in specific molecular subgroups?

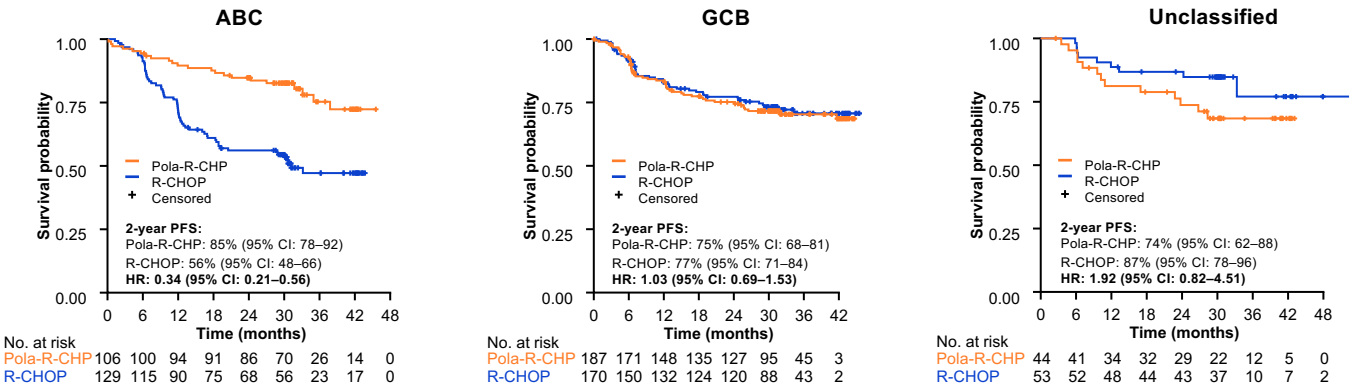
Polatuzumab in molecular subgroups



Palmer et al., NEJM, 2023

POLARIX study: PFS by COO subgroup

- COO status was determined in 689 patients in POLARIX (ABC, n=235; GCB, n=357; unclassified, n=97)
- Based on a data cutoff of June 15, 2022, with a median follow-up of 39.7 months, a **PFS difference between treatment groups** was observed in ABC-DLBCL, but not in GCB or the unclassified subgroups



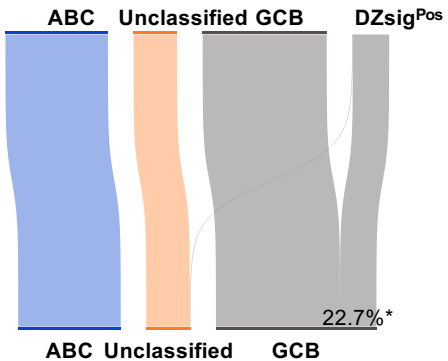
*Investigator-assessed disease progression and disease relapse or death from any cause were counted as events. ABC, activated B cell-like; COO, cell of origin; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B cell; HR, hazard ratio.

Morschhauser et al., ASH, 2023

Distribution of DZ signature status across COO subgroups in the overall POLARIX population

- GEP and COO data were available for 641 patients (Pola-R-CHP, n=318; R-CHOP, n=323)
  - **76 GCB and 1 unclassified tumors were found to be DZsig^{Pos}** (Pola-R-CHP, n=37; R-CHOP, n=40), accounting for 12.0% of all patients
  - 22.7% of GCB were re-classified to DZsig^{Pos}
  - **DZsig^{Pos} represent the majority of DHL/THL** (18/29 [62%] DHL/THL were DZsig^{Pos})
  - 3 ABC tumors that were DZsig^{Pos} remained to be assigned to the ABC group

Subgroups	Number (%) Total=641
ABC	214 (33.4)
Unclassified	91 (14.2)
GCB	259 (40.4)
DZsig^{Pos}	77 (12.0)

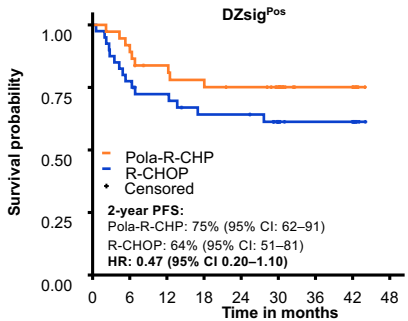


* Proportion of GCB re-classified to DZsig^{Pos}.

ABC, activated B cell-like; COO, cell of origin; DHL/THL, double-hit/triple-hit lymphoma; DLBCL, diffuse large B-cell lymphoma; DZsig^{Pos}, Dark Zone Signature positive; GCB, germinal center B cell; GEP, gene expression patterns.

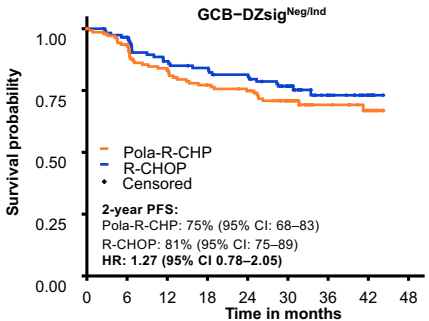
Morschhauser et al., ASH, 2023

POLARIX-Study: PFS by DZ signature subtype



Number at risk

POLA–R–CHP	37	34	29	27	25	21	7	6	0
R–CHOP	40	31	27	23	23	14	10	9	0



Number at risk

POLA–R–CHP	141	129	111	100	95	68	34	24	0
R–CHOP	118	110	97	93	89	68	30	16	0

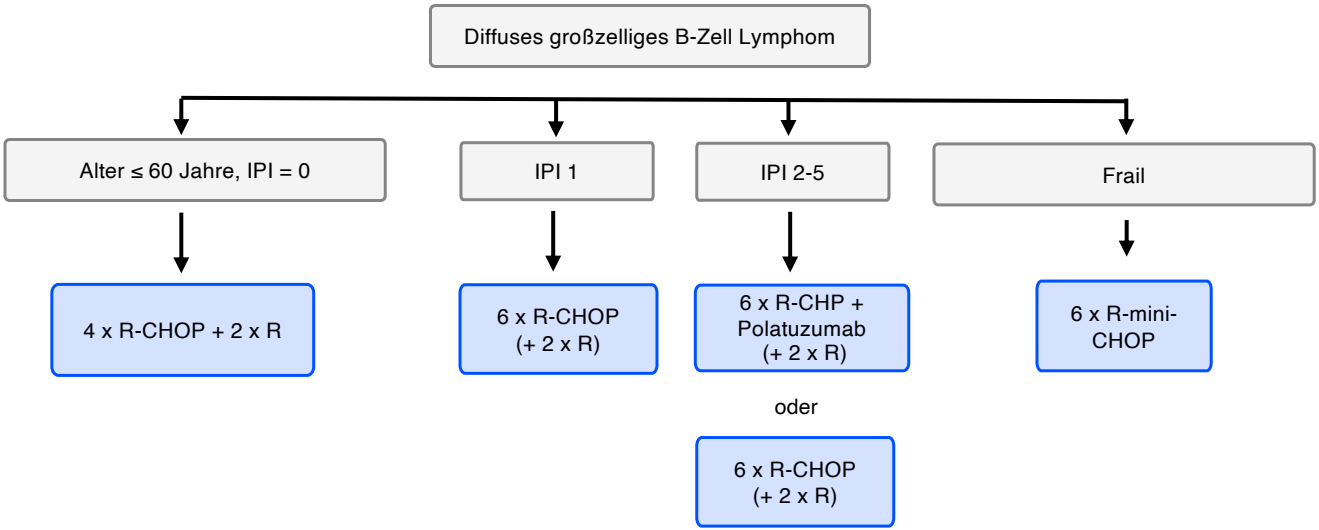
- In the R-CHOP arm, patients with DZsig^{Pos} DLBCL experienced shorter PFS vs those with DZsig$^{Neg/Ind}$ GCB-DLBCL (HR 2.04 [95% CI: 1.08–3.86]; 2-year PFS, 64% [95% CI: 51–81] vs 81% [95% CI: 75–89])
- In the Pola-R-CHP arm, no significant difference in PFS was observed between patients with DZsig^{Pos} DLBCL vs those with DZsig$^{Neg/Ind}$ GCB-DLBCL (HR 0.77 [95% CI: 0.37–1.58]; 2-year PFS, 75% [95% CI: 62–91] vs 75% [95% CI: 68–83])

A trend of higher 2-year PFS rate was observed in patients with DZsig^{Pos} DLBCL treated with Pola-R-CHP vs R-CHOP, but not in those with DZsig$^{Neg/Ind}$ GCB-DLBCL

*Investigator-assessed disease progression and disease relapse or death from any cause were counted as events.

ABC, activated B cell; CI, confidence interval; COO, cell of origin; DZsig$^{Neg/Ind}$, DZsig negative/indeterminate; DZsig^{Pos}, dark zone signature positive; GCB, germinal center B cell; HR, hazard ratio PFS, progression-free survival.

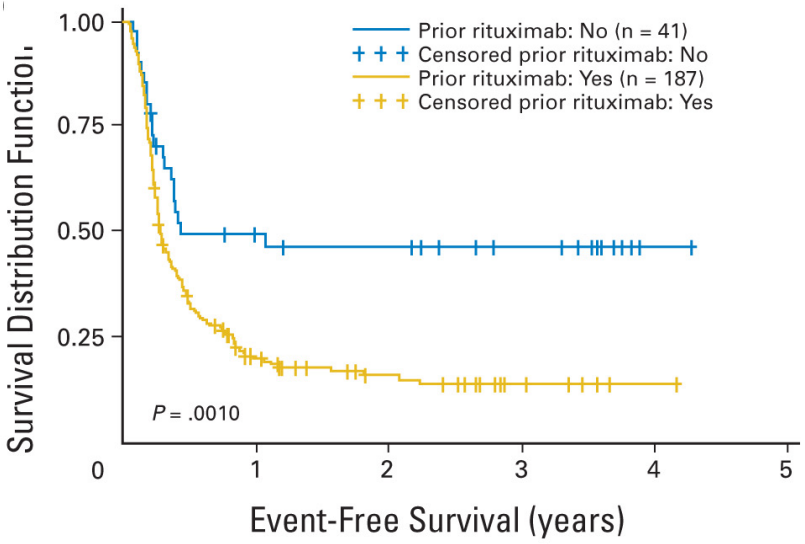
Morschhauser et al., ASH, 2023



Lenz et al., Onkopedia guideline, 2024

Relapsed/refractory DLBCL patients are characterized by adverse survival

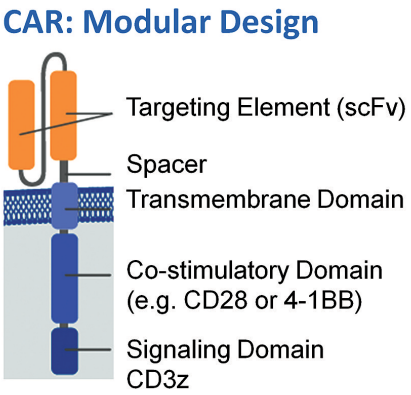
Patients with refractory disease and early relapse are characterized by poor survival

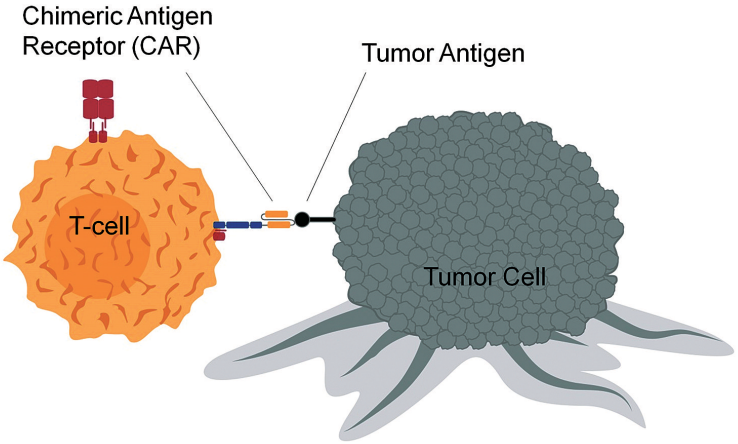


Gisselbrecht et al., JCO, 2010

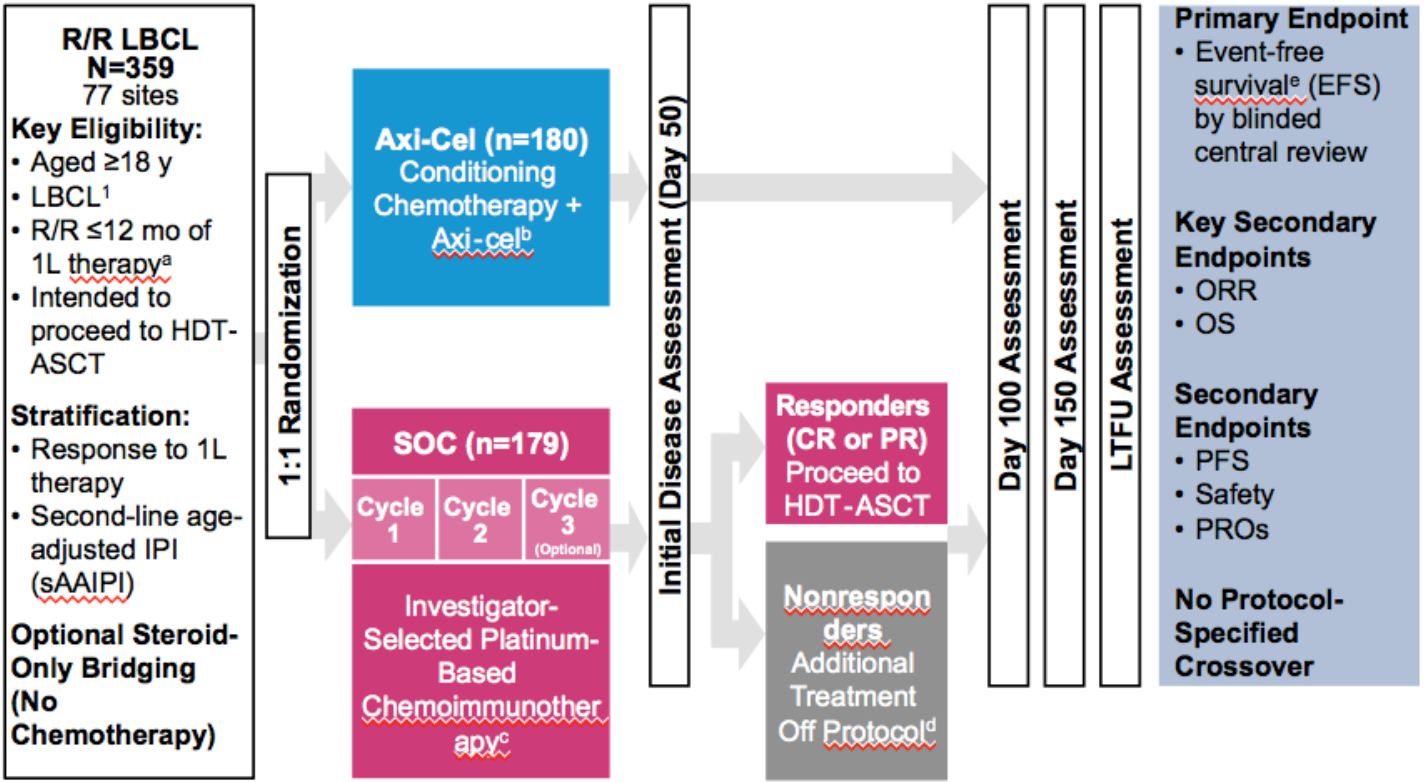
Are CAR-T-cells better than ASCT?

Chimeric antigen receptor (CAR) T-cells



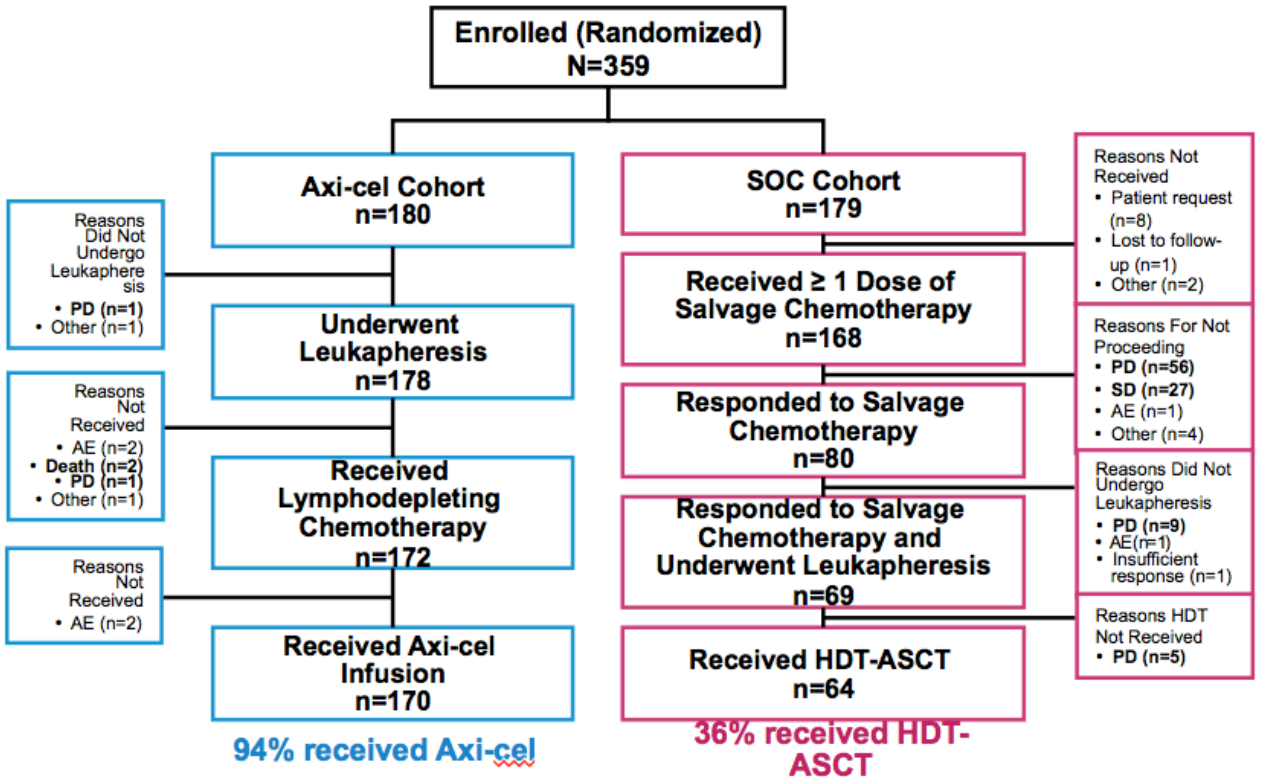


ZUMA-7 trial design



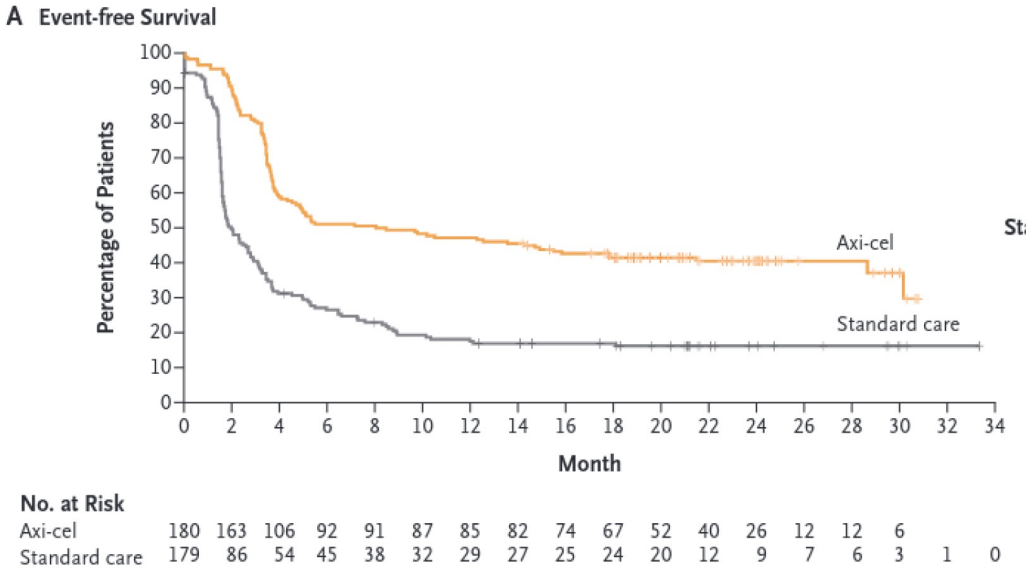
Locke et al., NEJM, 2022

Patients treated in the ZUMA-7 study



Locke et al., NEJM, 2022

ZUMA-7 primary endpoint EFS

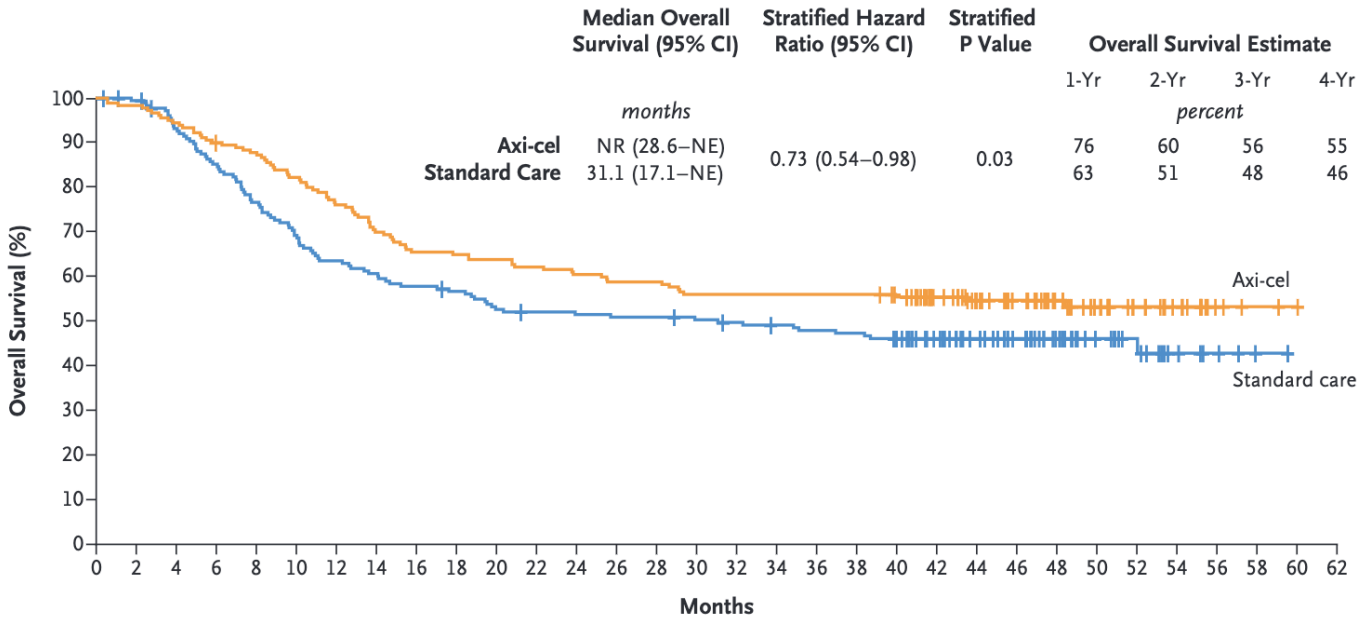


	No. of Patients	Median Event-free Survival (95% CI)
		mo
Axi-cel	180	8.3 (4.5–15.8)
Standard Care	179	2.0 (1.6–2.8)

Stratified hazard ratio for event or death, 0.40 (95% CI, 0.31–0.51)
P<0.001

Locke et al., NEJM, 2022

ZUMA-7 overall survival



No. at Risk

Axi-cel	180	177	170	161	157	147	136	125	117	116	114	111	108	105	105	100	100	100	100	100	96	80	67	54	41	29	20	14	4	2	1	0
Standard care	179	176	163	149	134	121	111	106	101	98	91	89	88	87	87	85	83	81	79	78	73	63	51	41	31	19	14	7	4	1	0	

Westin et al., NEJM, 2023

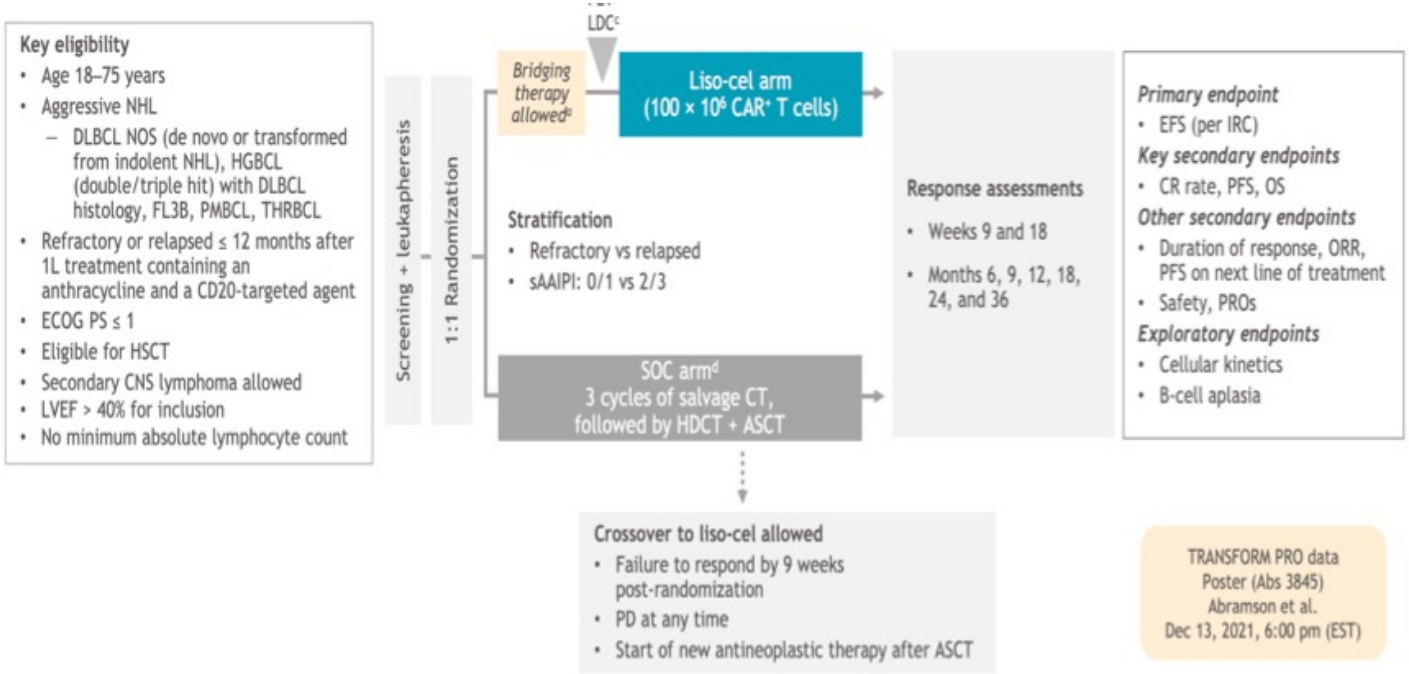
Lisocabtagene Maraleucel, a CD19-Directed Chimeric Antigen Receptor T Cell Therapy, Versus Standard of Care with Salvage Chemotherapy Followed by Autologous Stem Cell Transplantation as Second-Line Treatment in Patients with Relapsed or Refractory Large B-Cell Lymphoma: Results from the Randomized Phase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

Manali Kamdar,[1] Scott R. Solomon,[2] Jon Arnason,[3] Patrick B. Johnston,[4] Bertram Glass,[5] Veronika Bachanova,[6] Sami Ibrahimi,[7] Stephan Mielke,[8] Pim Mutsaers,[9] Francisco Hernandez-Ilizaliturri,[10] Koji Izutsu,[11] Franck Morschhauser,[12] Matthew Lunning,[13] David G. Maloney,[14] Alessandro Crotta,[15] Sandrine Montheard,[15] Alessandro Previtali,[15] Lara Stepan,[16] Ken Ogasawara,[16] Timothy Mack,[16] Jeremy S. Abramson[17]

[1]University of Colorado Cancer Center, Aurora, CO, USA; [2]Northside Hospital Cancer Institute, Atlanta, GA, USA; [3]Beth Israel Deaconess Medical Center, Boston, MA, USA; [4]Mayo Clinic, Rochester, MN, USA; [5]Helios Klinikum Berlin-Buch, Berlin, Germany; [6]University of Minnesota, Minneapolis, MN, USA; [7]University of Oklahoma Stephenson Cancer Center, Oklahoma City, OK, USA; [8]Center of Allogeneic Stem Cell Transplantation and Cellular Therapy (CAST), Karolinska Institutet and University Hospital, Stockholm, Sweden; [9]Erasmus University Medical Center, Rotterdam, The Netherlands, on behalf of HOVON/LLPC; [10]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [11]National Cancer Center Hospital, Tokyo, Japan; [12]Université de Lille, Centre Hospitalier Universitaire de Lille. ULR 7365, GRITA – Groupe de Recherche sur les formes Injectables et les Technologies Associées, Lille, France; [13]University of Nebraska Medical Center, Omaha, NE, USA; [14]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [15]Celgene, a Bristol-Myers Squibb Company, Boudry, Switzerland; [16]Bristol Myers Squibb, Princeton, NJ, USA; [17]Massachusetts General Hospital Cancer Center, Boston, MA, USA

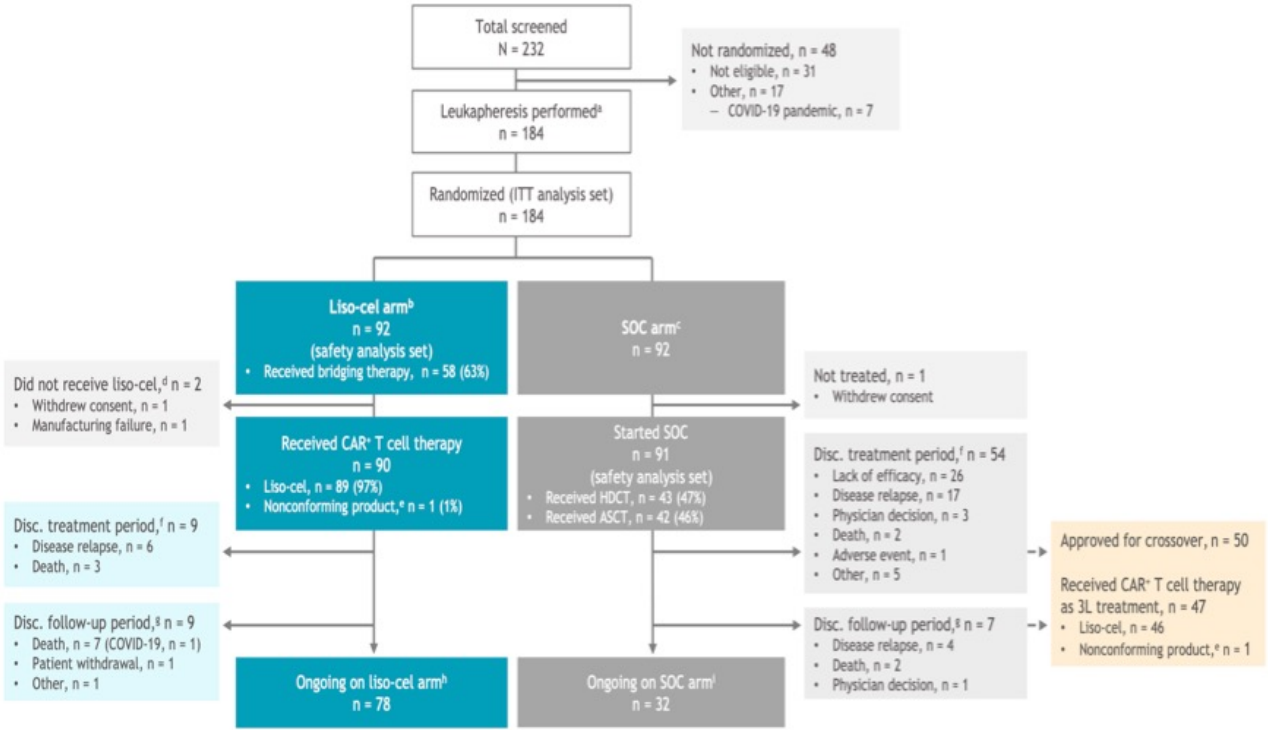
ASH 2021, Presentation Number 91

TRANSFORM study trial design



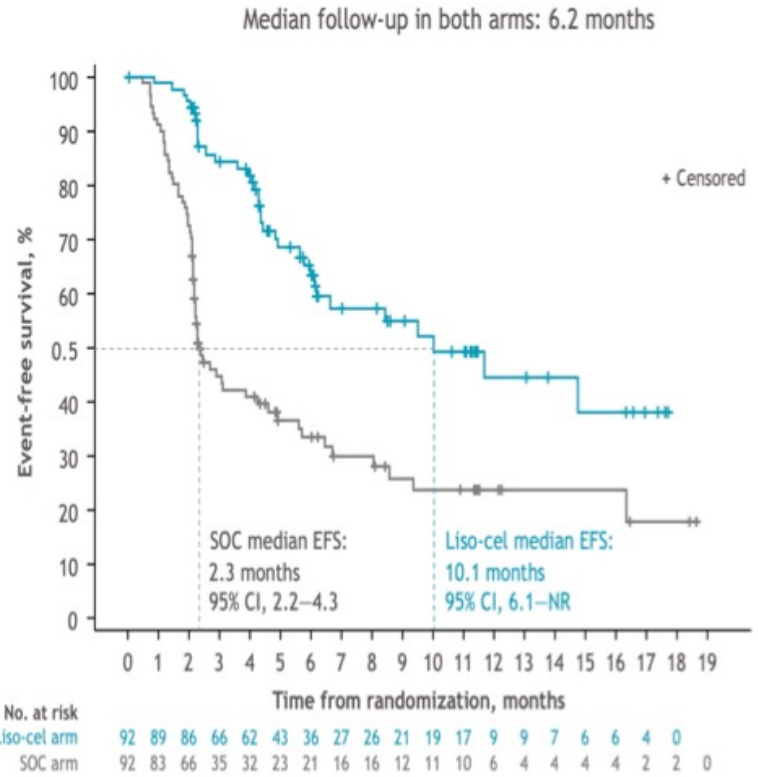
Kamdar et al., Lancet, 2022

TRANSFORM study consort diagram



Kamdar et al., Lancet, 2022

TRANSFORM study EFS

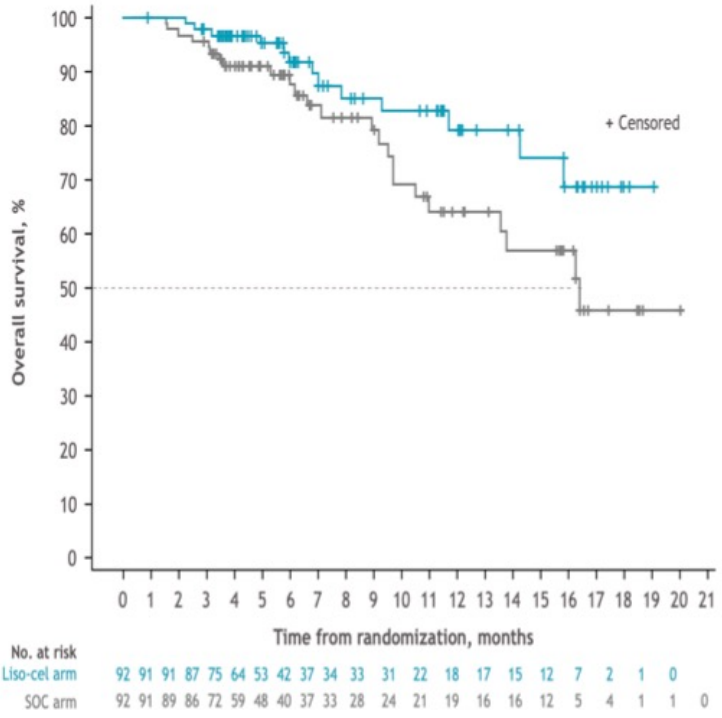


	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	35	63
Stratified HR (95% CI)	0.349 (0.229–0.530)	
	P < 0.0001	
6-month EFS rate, % (SE)	63.3 (5.77)	33.4 (5.30)
Two-sided 95% CI	52.0–74.7	23.0–43.8
12-month EFS rate, % (SE)	44.5 (7.72)	23.7 (5.28)
Two-sided 95% CI	29.4–59.6	13.4–34.1

One-sided *P* value significance threshold to reject the null hypothesis was < 0.012

Kamdar et al., Lancet, 2022

TRANSFORM study overall survival



	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	13	24
Stratified HR (95% CI)	0.509 (0.258–1.004) *P* = 0.0257	
Median OS (95% CI), months	NR (15.8–NR)	16.4 (11.0–NR)
6-month OS rate, % (SE)	91.8 (3.29)	89.4 (3.36)
Two-sided 95% CI	85.4–98.2	82.9–96.0
12-month OS rate, % (SE)	79.1 (6.13)	64.2 (6.99)
Two-sided 95% CI	67.1–91.1	50.5–77.9

Patients in the SOC arm that crossed over to receive liso-cel continue to be followed for OS in the SOC arm

One-sided *P* value significance threshold to reject the null hypothesis was < 0.012

Kamdar et al., Lancet, 2022

Third line treatment -

CAR T-cells

Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial

Frederick L Locke, Armin Ghobadi, Caron A Jacobson, David B Miklos, Lazaros J Lekakis, Olalekan O Oluwole, Yi Lin, Ira Braunschweig, Brian T Hill, John M Timmerman, Abhinav Deol, Patrick M Reagan, Patrick Stiff, Ian W Flinn, Umar Farooq, Andre Goy, Peter A McSweeney, Javier Munoz, Tanya Siddiqi, Julio C Chavez, Alex F Herrera, Nancy L Bartlett, Jeffrey S Wiezorek, Lynn Navale, Allen Xue, Yizhou Jiang, Adrian Bot, John M Rossi, Jenny J Kim, William Y Go, Sattva S Neelapu**

Locke et al., Lancet Oncol, 2019

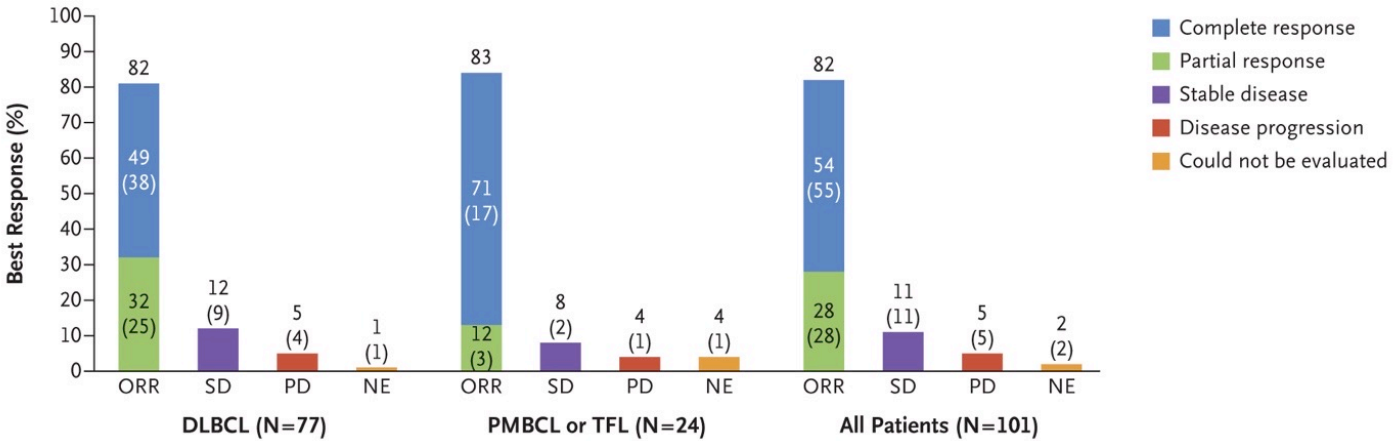
Efficacy of CAR T-cells in DLBCL

Table 1. (Continued.)

Variable	Patients with DLBCL	Patients with PMBCL or TFL	All Patients
Refractory subgroup at study entry — no. (%)			
Primary refractory	2 (3)	0	2 (2)
Refractory to second-line or subsequent therapy	59 (77)	19 (79)	78 (77)
Relapse after autologous stem-cell transplantation	16 (21)	5 (21)	21 (21)

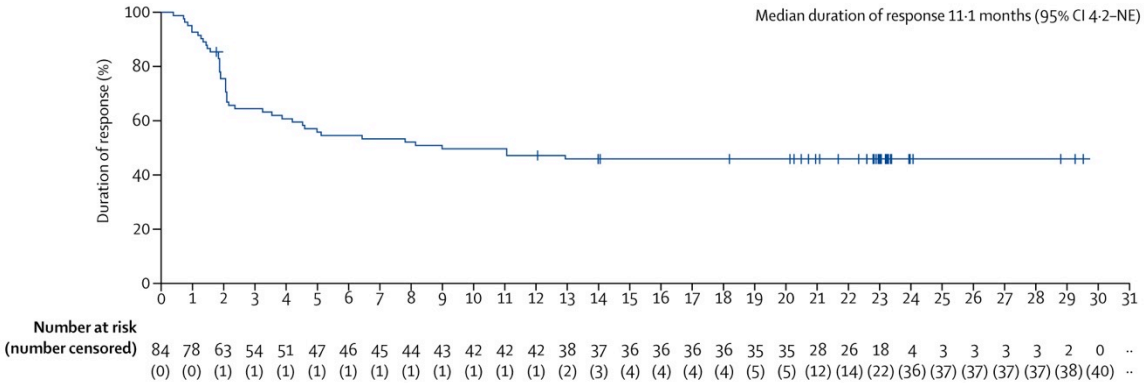
Neelapu et al., NEJM, 2017

Efficacy of CAR T-cells in DLBCL



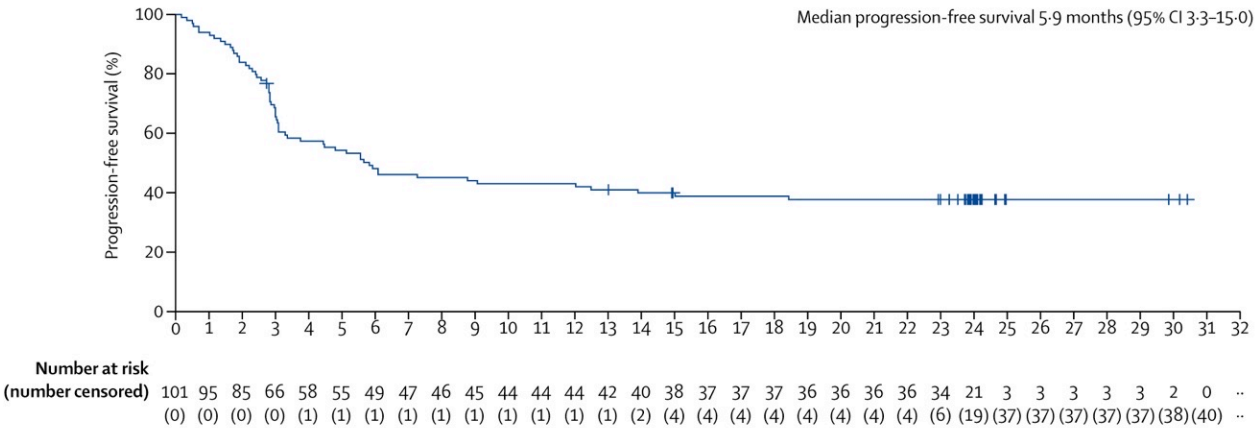
Neelapu et al., NEJM, 2017

Efficacy of CAR T-cells in DLBCL



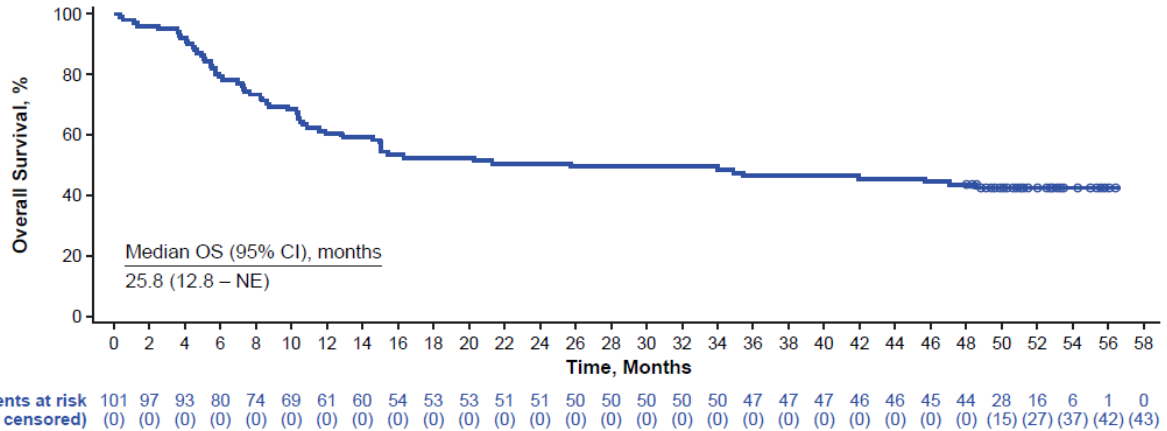
Locke et al., Lancet Oncol, 2019

Efficacy of CAR T-cells in DLBCL



Locke et al., Lancet Oncol, 2019

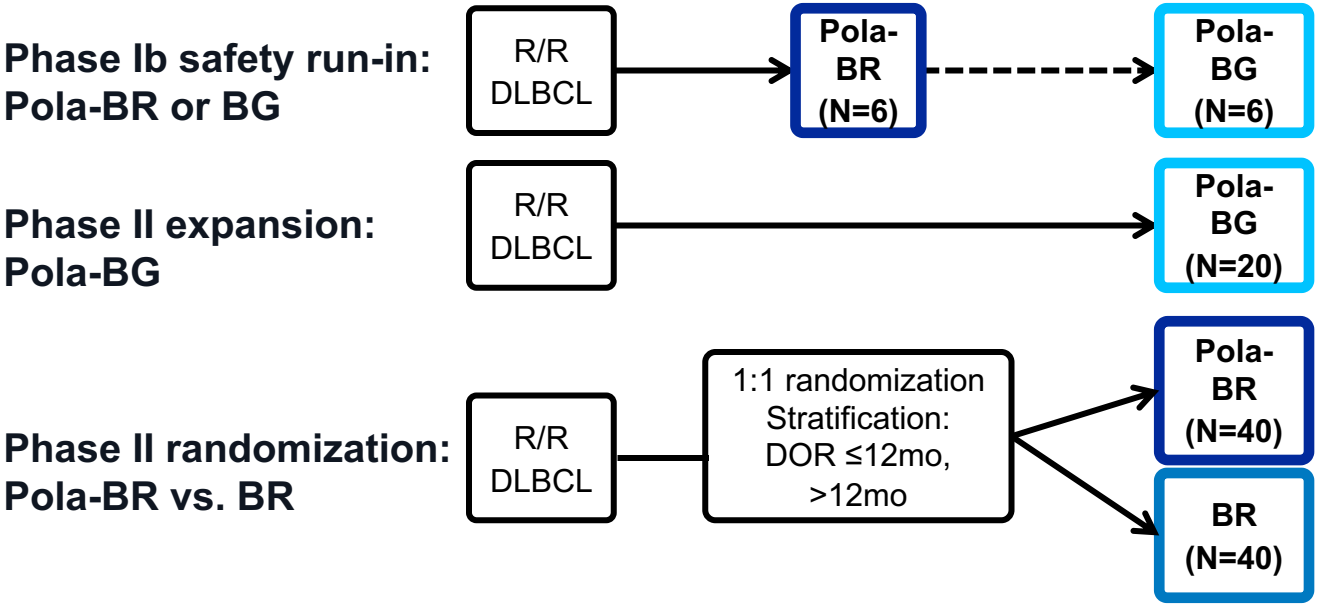
Efficacy of CAR T-cells in DLBCL



Jacobsen et al., ASH, 2020

Polatuzumab in the treatment of R/R DLBCL patients

Polatuzumab is active in DLBCL

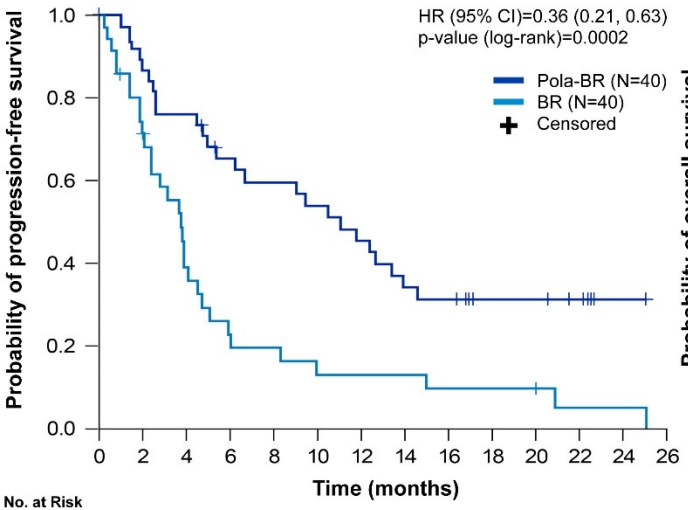


Treatment administered every 21 days x 6 cycles: Polatuzumab Vedotin: 1.8 mg/kg, C1D2, then D1 for C2+; Bendamustine (B): 90 mg/m^2, C1D2/3, then D1/2 for C2+; Obinutuzumab (G): 1000 mg, C1D1/8/15, then D1 for C2+; Rituximab (R): 375 mg/m^2, D1 for C1+.

Sehn et al., JCO, 2019

Efficacy

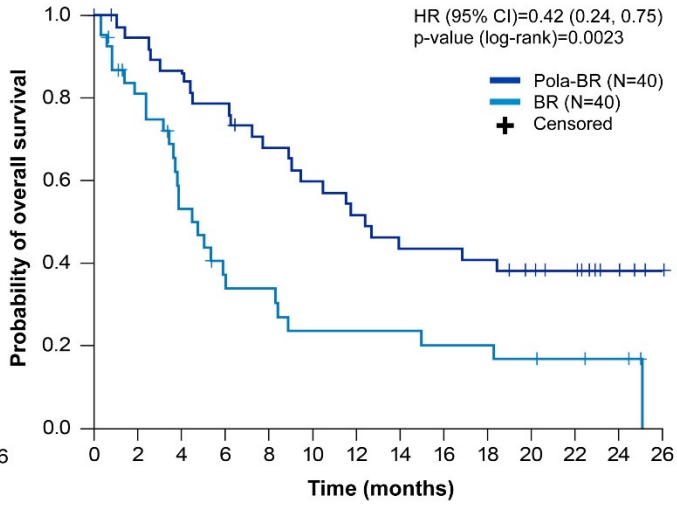
Figure 2. Progression-free survival (IRC)



No. at Risk

Pola-BR (Ph II)	40	38	33	29	29	25	23	21	21	21	19	18	16	14	12	11	11	8	7	7	7	6	5	1	1
BR (Ph II)	40	30	24	18	12	9	7	6	6	5	4	4	4	4	4	3	3	3	3	3	2	1	1	1	1

Figure 3. Overall survival



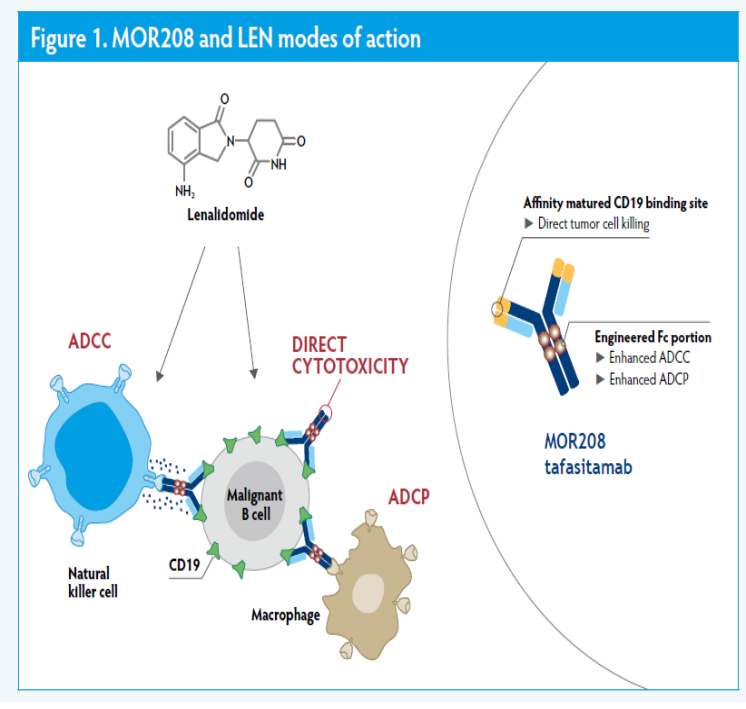
	40	38	36	34	33	30	30	27	25	24	22	21	19	17	16	16	16	15	15	13	12	9	9	5	3	2	1
	40	33	27	25	17	15	11	10	10	7	7	7	7	7	7	6	6	6	6	5	5	4	4	3	3	1	

Mod. Sehn LH et al. ASH 2018, Aggressive Lymphoma (Diffuse Large B-Cell and Other Aggressive B-Cell Non-Hodgkin Lymphomas) – Results from Prospective Clinical Trials: Poster I, Abstract No. 1683

Sehn et al., JCO, 2019

Tafasitamab

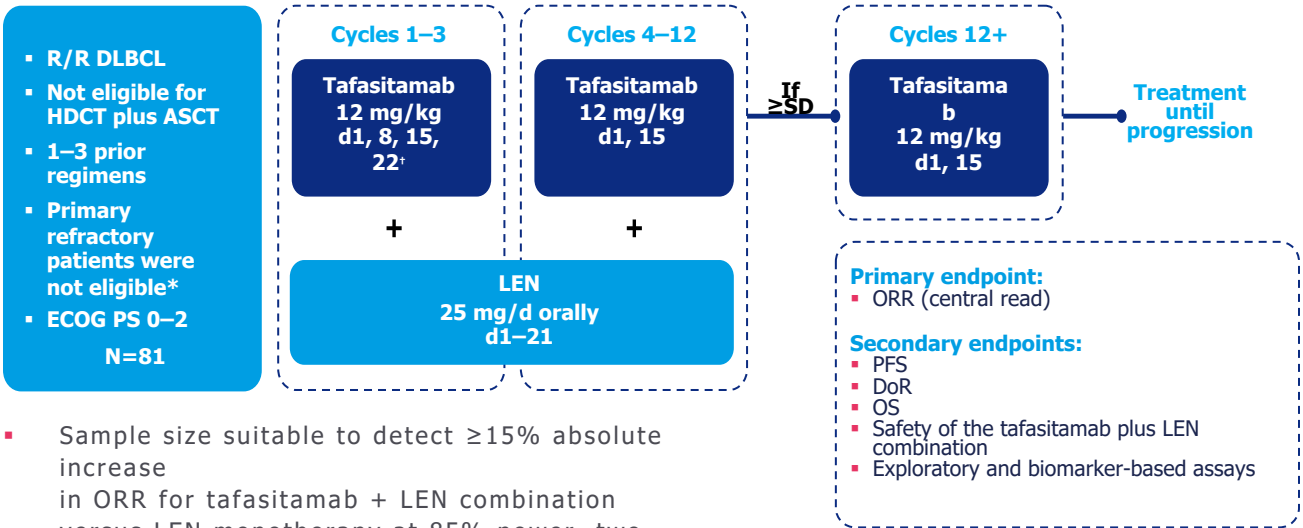
Efficacy of tafasitamab and lenalidomide in DLBCL patients



Maddocks et al., ASCO, 2019

L-MIND: STUDY DESIGN

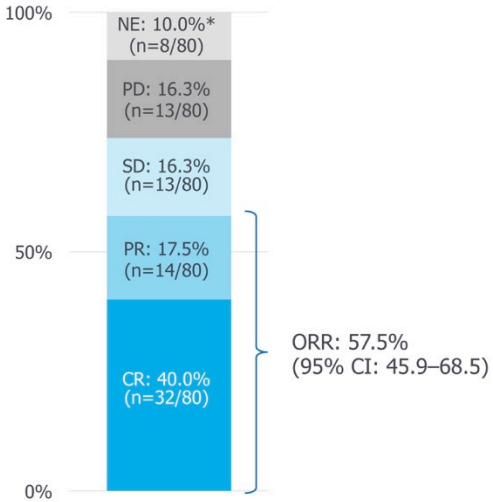
PHASE 2 SINGLE-ARM, OPEN-LABEL, MULTICENTRE STUDY (NCT02399085)



- Sample size suitable to detect ≥15% absolute increase in ORR for tafasitamab + LEN combination versus LEN monotherapy at 85% power, two-sided alpha of 5%

Salles et al., Lancet Oncology, 2020

PRIMARY ENDPOINT (ORR BY IRC)

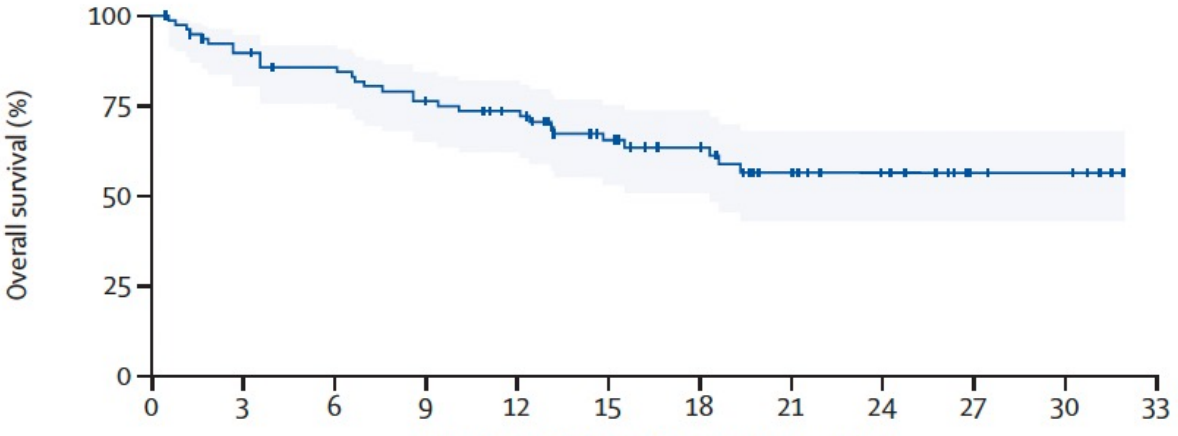


- ORR of 57.5% was consistent with the primary analysis and 2-year data
- A higher proportion of patients achieved a CR (40.0%) than a PR (17.5%)

N=80: full analysis set → patients receiving at least one dose of tafasitamab and LEN
*NE due to missing post-baseline tumour assessment

Salles et al., Lancet Oncology, 2020

Overall survival following tafasitamab and lenalidomide in DLBCL patients



Number at risk (number censored)												
All treated patients	80 (0)	69 (3)	64 (5)	57 (6)	50 (10)	35 (20)	29 (26)	20 (32)	14 (37)	6 (45)	5 (46)	0 (51)

Salles et al., Lancet Oncology, 2020

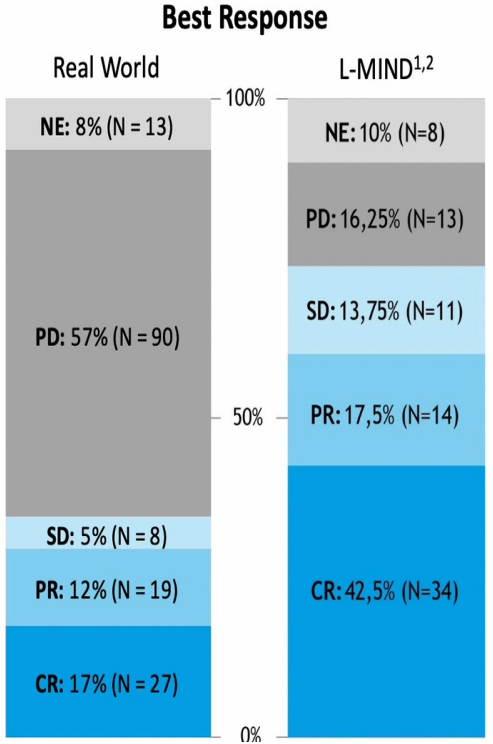
Real-world data for tafasitamab

Treatment exposure and responses

Treatment

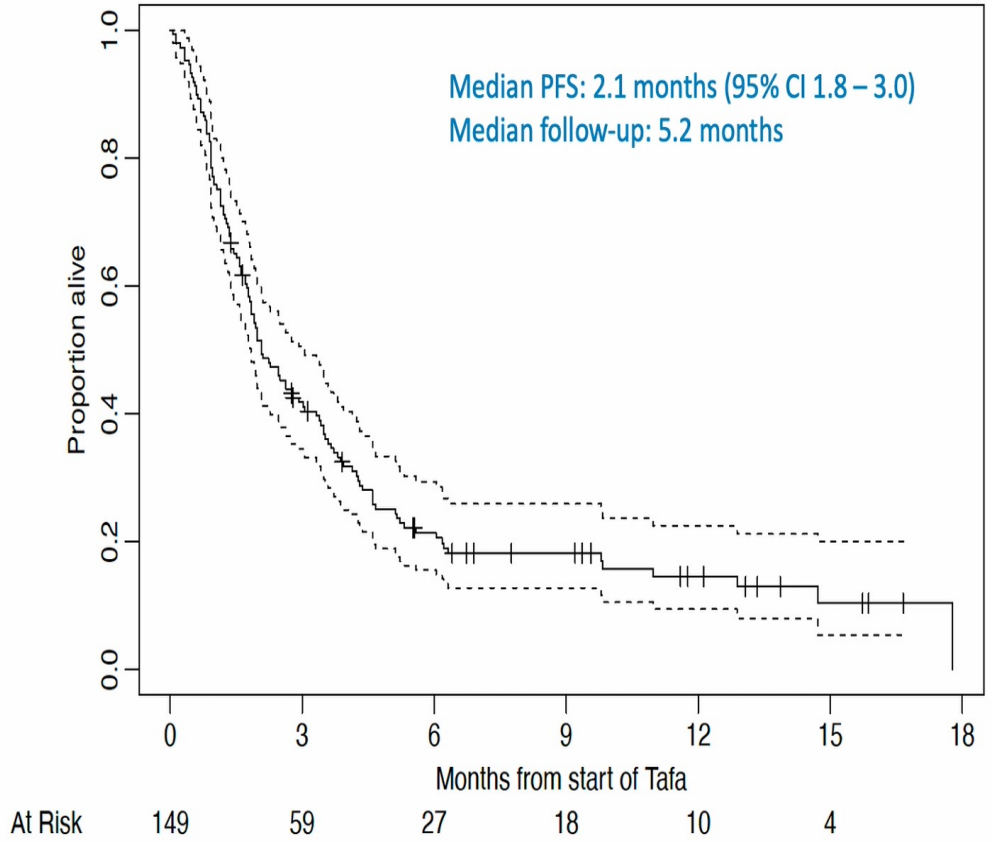
- All received at least 1 dose of tafasitamab and lenalidomide
- Median time on treatment: 59 days (IQR: 28-118 days)
- Lenalidomide dose delays in 45%
  - Median delay 7 days (IQR 4-20)
- Len dose reduction at initiation in 54%
  - Renal dysfunction (35%)
  - Frailty (18%)
  - Cytopenias (9%)
- Median len starting dose: 20 mg daily (IQR: 10–25 mg)

[1]Duell J et al., Haematologica 2021
[2]Duell J et al., presented at ASCO 2021



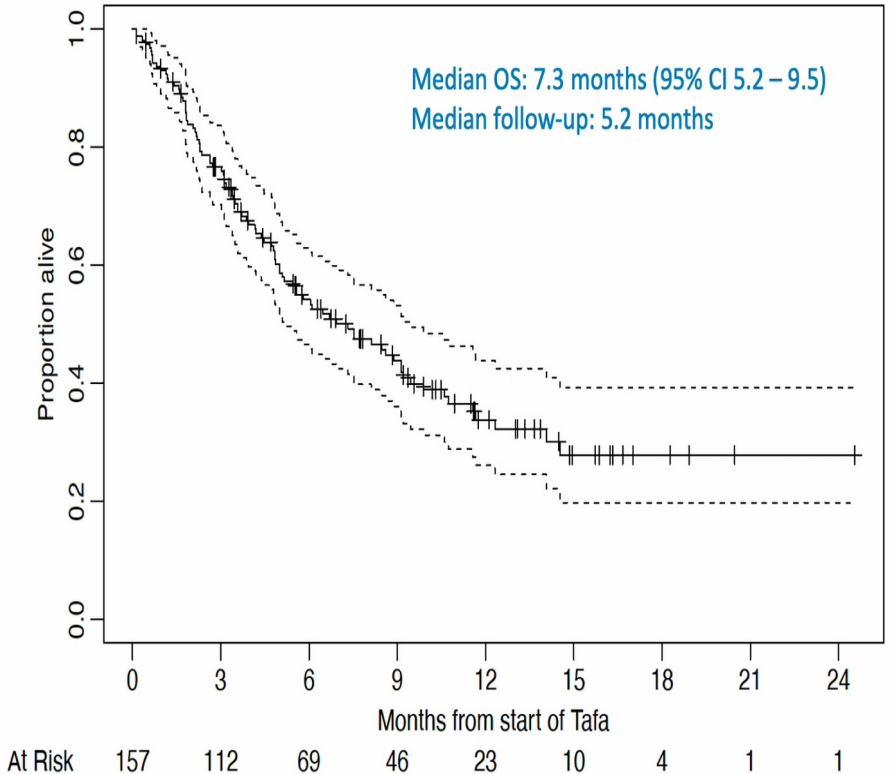
Qualls et al., Abstract #323, ASH 2022

Progression-Free Survival



Qualls et al., Abstract #323, ASH 2022

Overall Survival

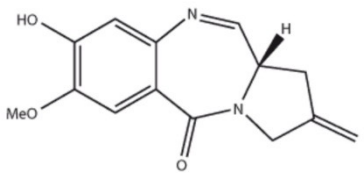


Qualls et al., Abstract #323, ASH 2022

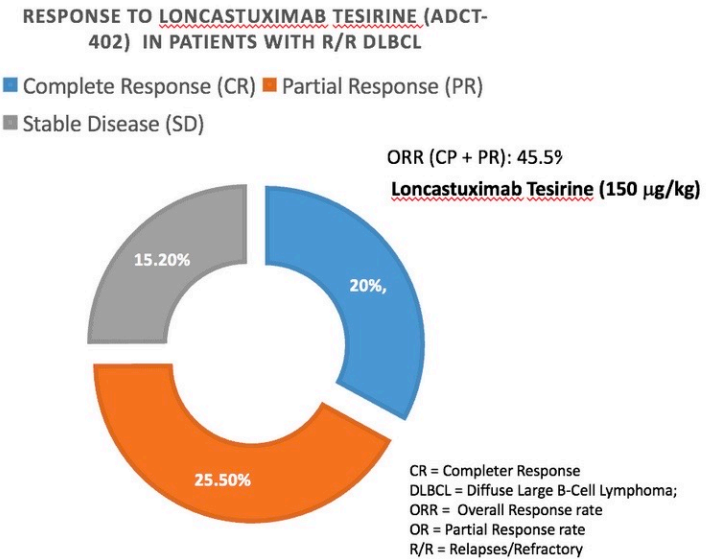
Third line treatment - Loncastuximab tesirine

Loncastuximab tesirine is active in relapsed/refractory DLBCL patients

Anti-CD19 antibody conjugated via a linker to Pyrrolobenzodiazepine (PBD)



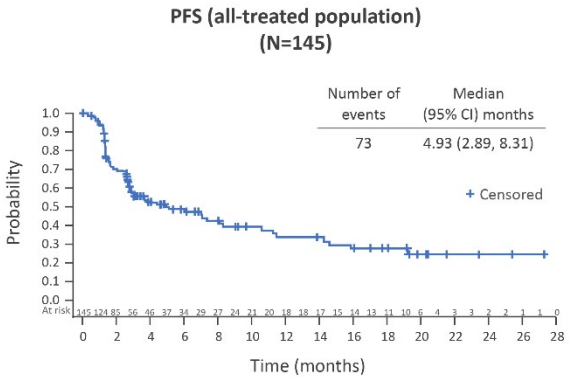
PBD



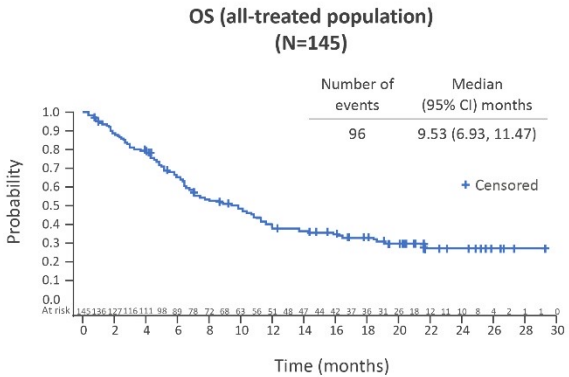
Carlo-Stella et al., EHA, 2020, Abstract # S233

Loncastuximab tesirine is active in relapsed/refractory DLBCL patients

LOTIS-2: OS and PFS



mPFS was **4.9 months**



mOS was **9.5 months**

Data cut-off: March 1, 2021. Patients with events after start of subsequent anticancer therapy or procedure, or progression free and alive at data cut-off, or who had unknown status were censored at last valid tumour assessment on or before start of subsequent anticancer therapy or procedure or data cut-off.
CI, confidence interval; m, median; OS, overall survival; PFS, progression-free survival.
Zinzani et al. ICML 2021; Caimi et al. *Lancet Oncol* 2021.

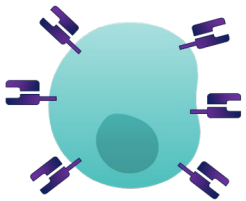
Caimi et al., Lancet Oncol., 2021

Efficacy of bispecific antibodies in patients with R/R aggressive lymphomas

Bispecific antibodies represent a novel therapeutic strategy

Two main classes of T-cell targeting therapy are under investigation for the treatment of lymphoma patients

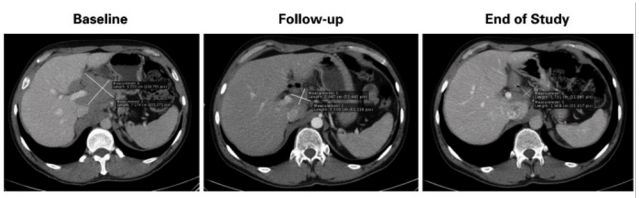
1 Chimeric antigen receptor T-cell (CAR-T) therapy

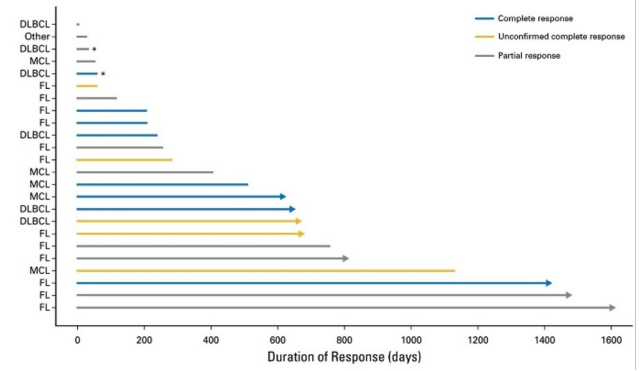


2 Bispecific antibodies

Without an Fc region eg Bispecific T-cell engagers (BiTE®)

With an Fc region





Batlevi CL, et al. Nat Rev Clin Oncol 2016;13:25–40

Goebeler et al., JCO, 2016

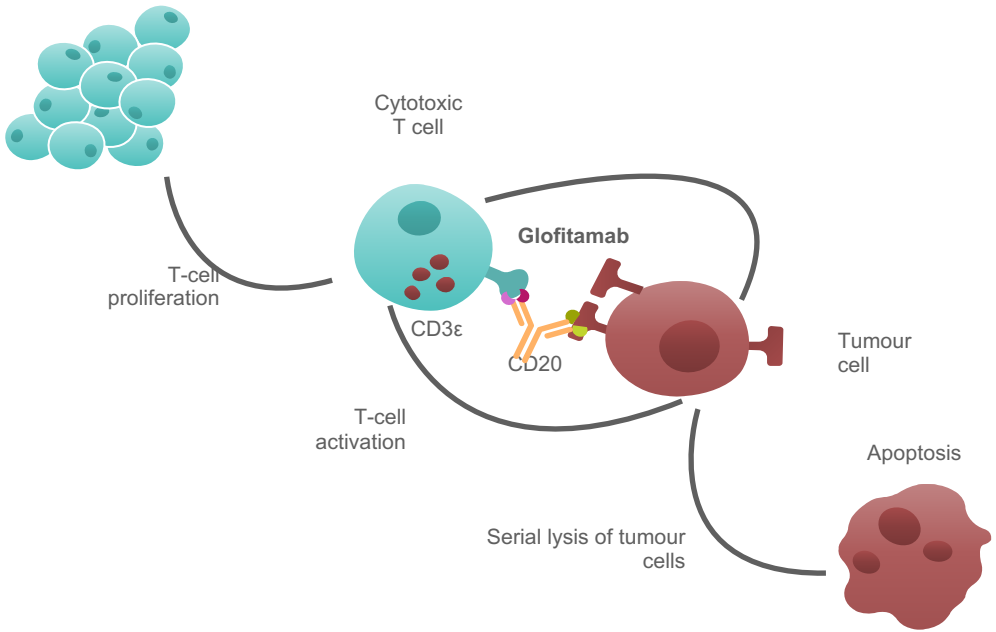
Glofitamab monotherapy in patients with relapsed/refractory large B-cell lymphoma: extended follow-up and landmark analyses from a pivotal Phase II study

Michael Dickinson,[1] Carmelo Carlo-Stella,[2] Franck Morschhauser,[3] Lorenzo Falchi,[4] Emmanuel Bachy,[5] Guillaume Cartron,[6] Cyrus Khan,[7] Monica Tani,[8] Joaquin Martinez-Lopez,[9] Nancy Bartlett,[10] Antonio Salar,[11] Joshua Brody,[12] Sirpa Leppä,[13] Estefania Mulvihill,[14] Linda Lundberg,[14] James Relf,[15] Yuying Xie,[16] Alessia Bottos,[14] Kathryn Humphrey,[15] Martin Hutchings[17]

[1]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and The University of Melbourne, Melbourne, VIC, Australia; [2]Humanitas University and IRCCS Humanitas Research Hospital, Milan, Italy; [3]Hôpital Claude Huriez and CHU de Lille, Lille, France; [4]Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [5]Centre Hospitalier Lyon-Sud, Lyon, France; [6]CHU de Montpellier, Montpellier, France; [7]Allegheny Health Network, Pittsburgh, PA, USA; [8]Ospedale Santa Maria delle Croci, Ravenna, Italy; [9]Department of Hematology, Hospital Universitario 12 de Octubre, Spanish National Cancer Research Center (CNIO), Complutense University Madrid, Madrid, Spain; [10]Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO, USA; [11]Department of Hematology, Hospital del Mar, Passeig Maritim, Barcelona, Spain; [12]Tisch Cancer Institute, New York, NY, USA; [13]University of Helsinki and Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland; [14]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [15]Roche Products Ltd, Welwyn Garden City, UK; [16]Hoffmann-La Roche Ltd, Mississauga, Canada; [17]Rigshospitalet, Copenhagen, Denmark

Presented at the 2023 International Conference Malignant Lymphoma (ICML) on June 13–17, 2023

Efficacy of glofitamab in patients with relapsed/refractory DLBCL



Study overview

Pivotal Phase II study in patients with R/R LBCL and ≥2 prior therapies

Key inclusion criteria

- DLBCL NOS, HGBCL, trFL, or PMBCL
- ECOG PS 0–1
- ≥2 prior therapies, including:
  - Anti-CD20 antibody
  - Anthracycline

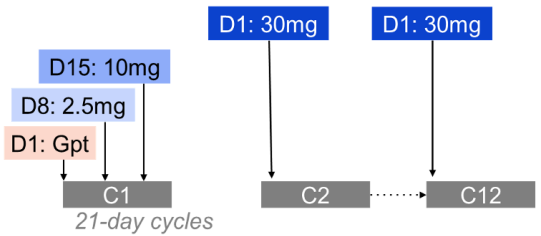
Glofitamab IV administration

Fixed-duration treatment

- Maximum 12 cycles

CRS* mitigation:

- Obinutuzumab pre-treatment (1 x 1000mg)
- C1 step-up dosing
- Monitoring after first dose (2.5mg)



Endpoints

- **Primary**: CR rate (as best response) by IRC†
- **Key secondary**: ORR‡, DoR, DoCR‡, PFS, OS

Landmark analyses

- PFS and OS post-hoc analysis were performed by response (landmark at C3, or EOT)

*By American Society for Transplantation and Cellular Therapy criteria.[1] †By PET-CT (Lugano criteria[2]). ‡By IRC and investigator.
C, cycle; CRS, cytokine release syndrome; D, day; DLBCL NOS, diffuse large B-cell lymphoma not otherwise specified; DoCR, duration of complete response; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end-of-treatment; Gpt, Obinutuzumab; HGBCL, high-grade B-cell lymphoma; IRC, independent review committee; IV, intravenous; ORR, overall response rate; OS, overall survival; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival; PMBCL, primary mediastinal large B-cell lymphoma; trFL, transformed follicular lymphoma.

1. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38;
2. Cheson BD, et al. J Clin Oncol 2014;32:3059–68.

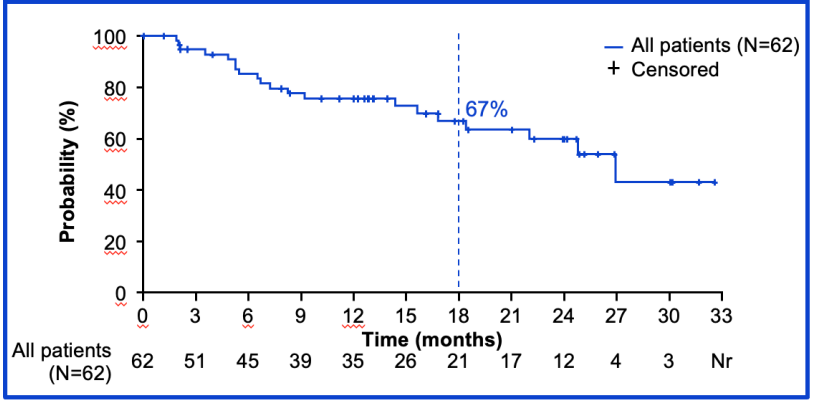
Dickinson et al., ICML, 2023

Complete responses remained durable

Glofitamab RP2D

	IRC (N=155)*
CR rate†, n (%) [95% CI]	62 (40) [32.2–48.2]
ORR, n (%) [95% CI]	80 (52) [43.5–59.7]
Median CR follow-up, months (range)	18.2 (0–33)
18 months DoCR, n (%) [95% CI]	67.0 (53.3–80.8)
Ongoing CRs, n/N (%)	42/62 (68)
Median DoCR, months (95% CI)	26.9 (18.4–NR)

DoCR by IRC (n=62)



- The median time on study was 21.2 months (range: 0–34)

An estimated 67% of patients with a CR at any time remained in remission at 18 months

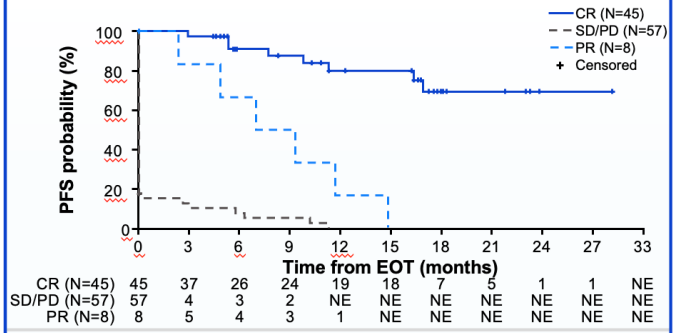
*Intent-to-treat population. †Best overall response. CI, confidence interval; NR, not reached.

Dickinson et al., ICML, 2023

Landmark analysis by response at EOT

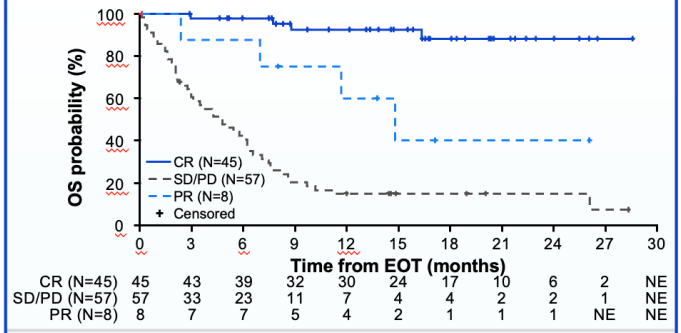
Glofitamab RP2D

PFS



PFS rate at 12 months: 80%

OS



OS rate at 12 months: 92%

- PFS analysis in patients with CR at EOT: six patients with PD and two deaths*

Majority of patients with a CR at EOT were alive 12 months after EOT

*Both due to COVID.

Dickinson et al., ICML, 2023

Safety summary

- **CRS remained the most common AE**
  - CRS occurred in 64% of patients
  - CRS events were mostly Grade 1 (48%) or Grade 2 (12%); Grade 3 (3%) and Grade 4 (1%) events were uncommon
- **The incidence of AEs and SAEs was stable compared with earlier analyses[1,2]**
  - One new Grade 3 AE (acute kidney injury)
  - Two new infections (Grade 4 COVID and Grade 2 pneumonia)
- **No glofitamab-related Grade 5 AEs**

Glofitamab RP2D

N (%)	N=154
AE Glofitamab-related	152 (99) 140 (91)
Grade ≥3 AE Glofitamab-related	99 (64) 68 (44)
SAE Glofitamab-related	75 (49) 46 (30)
Grade 5 (fatal) AE Glofitamab-related	9 (6) 0
AE leading to treatment discontinuation Glofitamab-related	14 (9) 5 (3)
AE leading to dose modification/interruption of glofitamab Glofitamab-related	29 (19) 16 (10)

Most patients did not experience new AEs since the previous analysis[1]

AE, adverse event; SAE, serious adverse event.

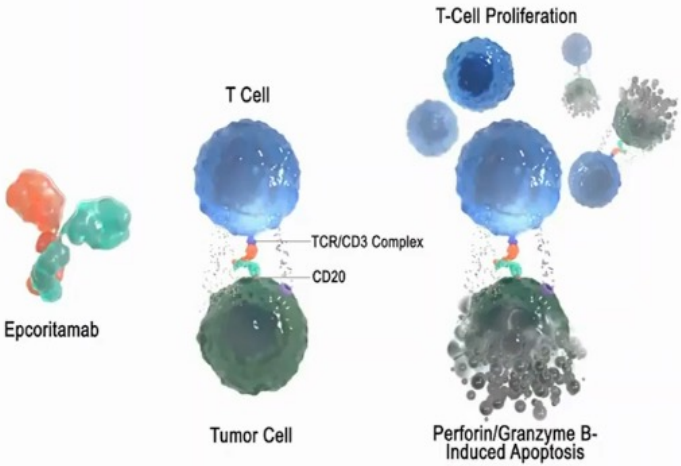
1. Dickinson MJ, et al. N Engl J Med 2022;387:2220–31;
2. Dickinson MJ, et al. J Clin Oncol 2022;40:7500.

Dickinson et al., ICML, 2023

Efficacy of epcoritamab in patients with relapsed/refractory DLBCL

Epcoritamab in B-cell non-Hodgkin Lymphoma

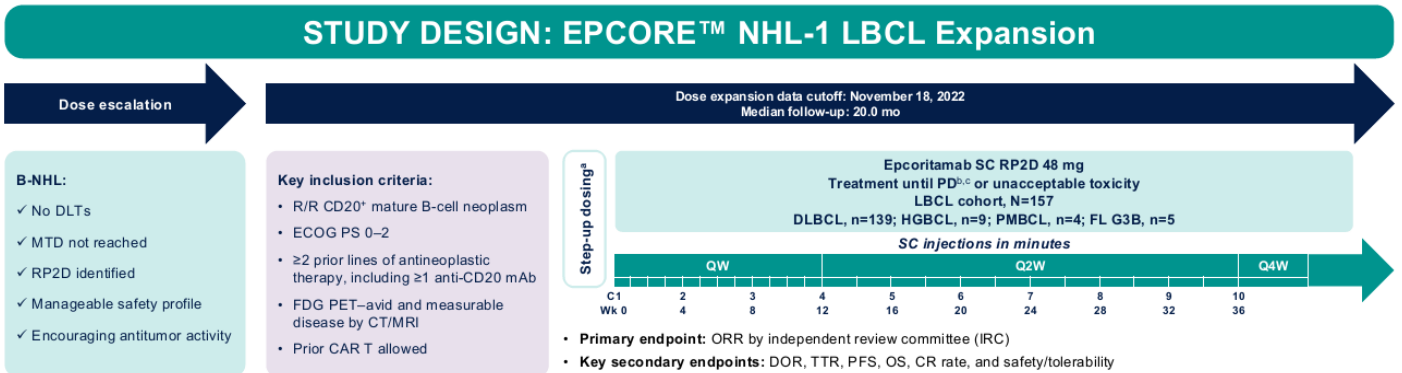
- Epcoritamab is a subcutaneous (SC) IgG1 bispecific antibody (bsAb) that binds CD20 and CD3, which harnesses the patient's immune system to induce T-cell–mediated killing of CD20-positive malignant B-cells[1]
- Epcoritamab key features:
  - SC formulation that allows more gradual increases and lower peaks in plasma cytokine levels as compared to an intravenous formulation, which may help mitigate cytokine release syndrome (CRS)
  - Potent T-cell–mediated killing even when CD20 expression levels are very low
  - Mutations to prevent off-target T-cell killing



1. Engelberts PJ, et al. *EBioMedicine*. 2020;52:102625.

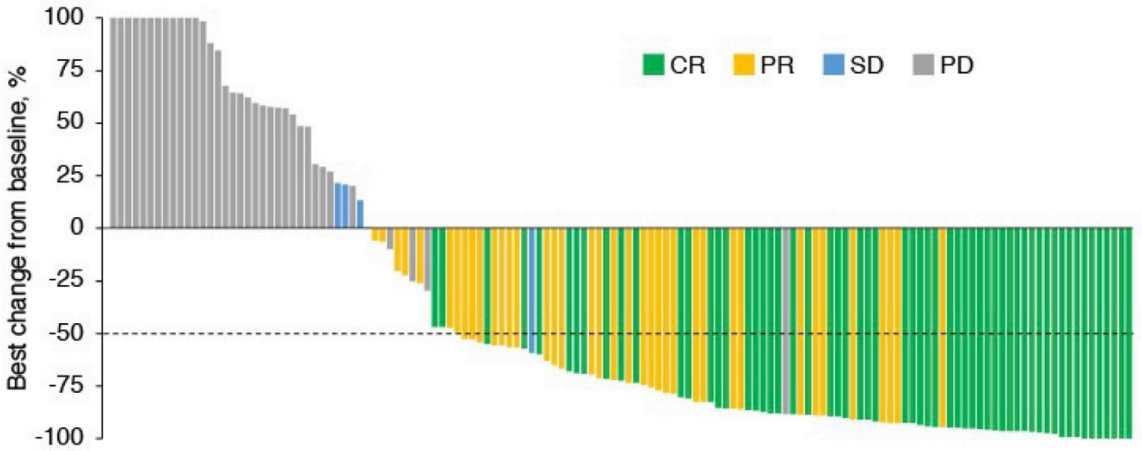
Hutchings et al., ICML, #016

Efficacy of epcoritamab in patients with relapsed/refractory DLBCL



Jurczak et al., EHA, 2023

Efficacy of epcoritamab in patients with relapsed/refractory DLBCL



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

Thieblemont et al., EHA, LB2364

Efficacy of epcoritamab in patients with relapsed/refractory DLBCL

High Rates of Complete Response

Best Overall Response, n (%)	To last therapy n=156[a]	DLBCL n=139[b]	LBCL N=157[b]	HGBCL n=9	PMBCL n=4	FL G3B n=5
Overall response	72 (46)	86 (62)	99 (63)	4 (44)	4 (100)	5 (100)
Complete response	31 (20)	55 (40)	62 (39)	2 (22)	2 (50)	3 (60)
Partial response	41 (26)	31 (22)	37 (24)	2 (22)	2 (50)	2 (40)
Stable disease	NA	4 (3)	5 (3)	1 (11)	0	0
Progressive disease	NA	33 (24)	37 (24)	4 (44)	0	0

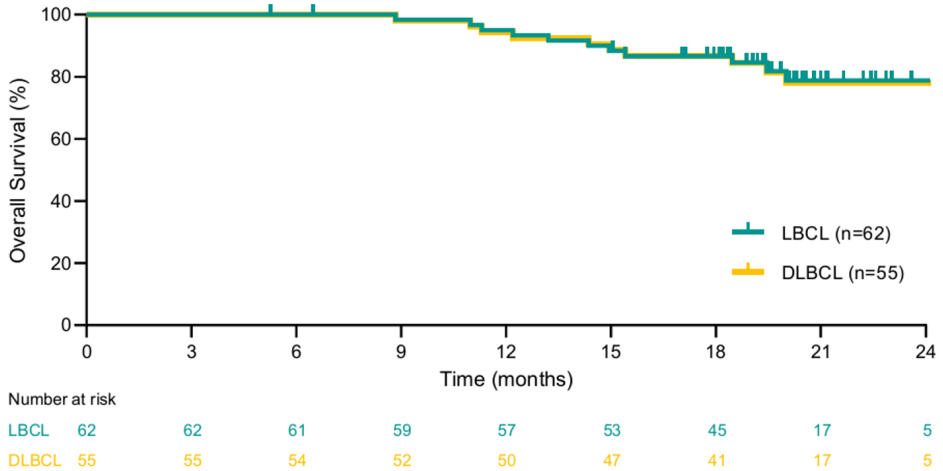
Based on IRC per Lugano criteria. NA, not available. [a]Response to last therapy not available for 1 patient. [b]16 patients were not evaluable.

- In LBCL patients:
  - Median time to response was 1.4 mo (range, 1.0–8.4);
  - median time to CR was 2.7 mo (range, 1.2–16.3)
  - 8 patients converted from partial response to CR at ≥36 wk
  - Median DOR was 15.5 mo (95% CI, 9.7–20.8); for patients previously treated with CAR T, median DOR was not reached

Jurczak et al., EHA, 2023

Efficacy of epcoritamab in patients with relapsed/refractory DLBCL

Overall Survival Among Complete Responders

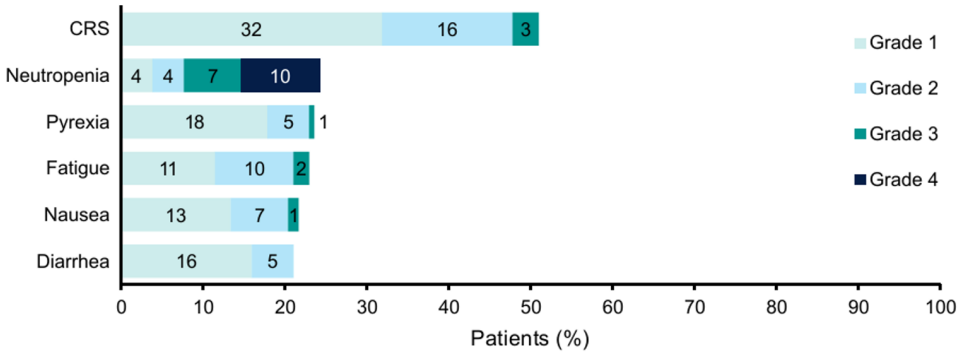


- Median OS was 18.5 mo (95% CI, 11.7–NR) for the overall LBCL population (N=157) and 19.4 mo (95% CI, 11.7–NR) for DLBCL patients (n=139)

Jurczak et al., EHA, 2023

Safety of epcoritamab in patients with relapsed/refractory DLBCL

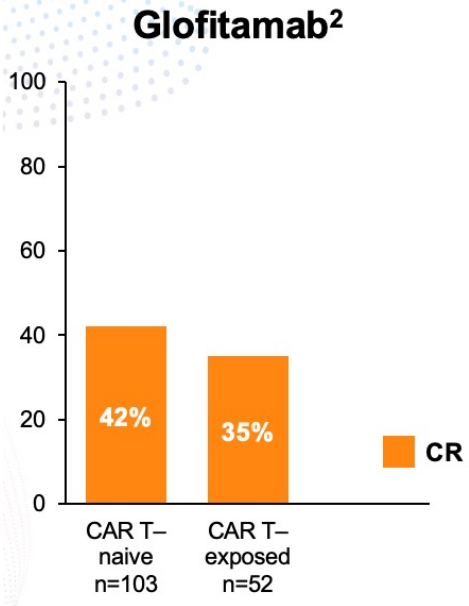
Treatment-Emergent Adverse Events (≥20%) of LBCL Patients

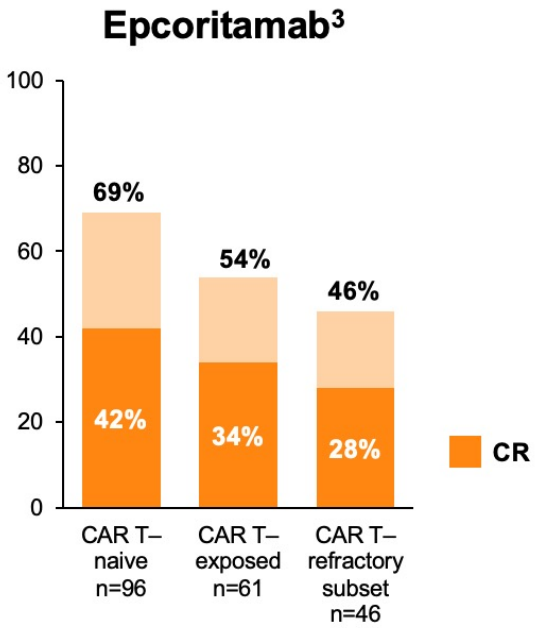


- Safety was consistent with previous findings
- Fatal TEAEs occurred in 15 patients
  - 2 were considered related events (COVID-19 pneumonia and ICANS [in a patient with several confounding factors])

Jurczak et al., EHA, 2023

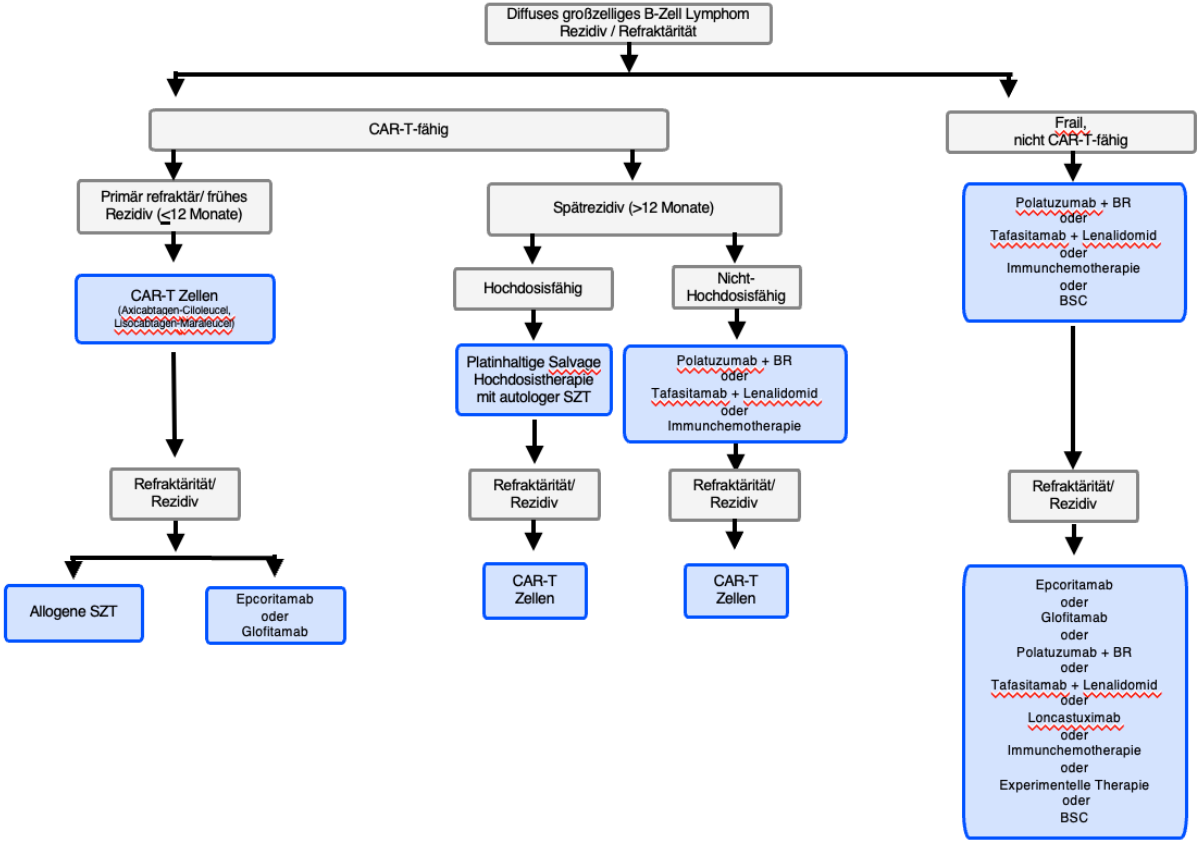
Bispecifics also work after CAR T-cell failure





Odronextamab, Glofitamab & Eporitamab are not approved in Switzerland.

Adapted from: 1. Kim SW, et al. Oral 444 ASH 2022. New Orleans, LA.
2. Dickinson MJ, et al. N Engl J Med. 2022;387(24):2220-2231.
3. Thieblemont C, et al. J Clin Oncol. 2023;41(12):2238-2247.



Lenz et al., Onkopedia guideline, 2024

Conclusions

- R-CHP-Pola replaces R-CHOP in DLBCL patient subgroups
- CAR T-cells are new standard in patients with early relapse as second-line treatment
- Different novel options for patients with R/R DLBCL
- Bispecific antibodies hold great promise for the treatment of R/R DLBCL patients