LBCL: algoritmo di trattamento

Antonello Pinto

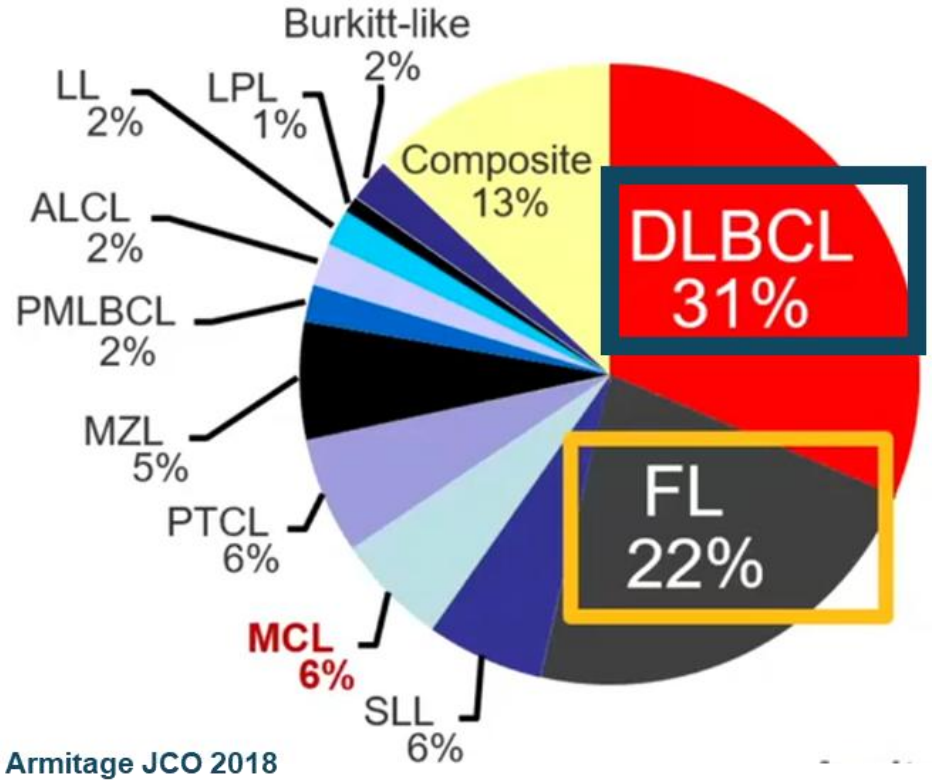
Dipartimento di Ematologia Oncologica,
Istituto Nazionale Tumori, IRCCS, Fondazione G. Pascale, Napoli

CAR-T:
e la storia continua...
migliorando

Roma, 9 Aprile 2025
Starhotels Metropole

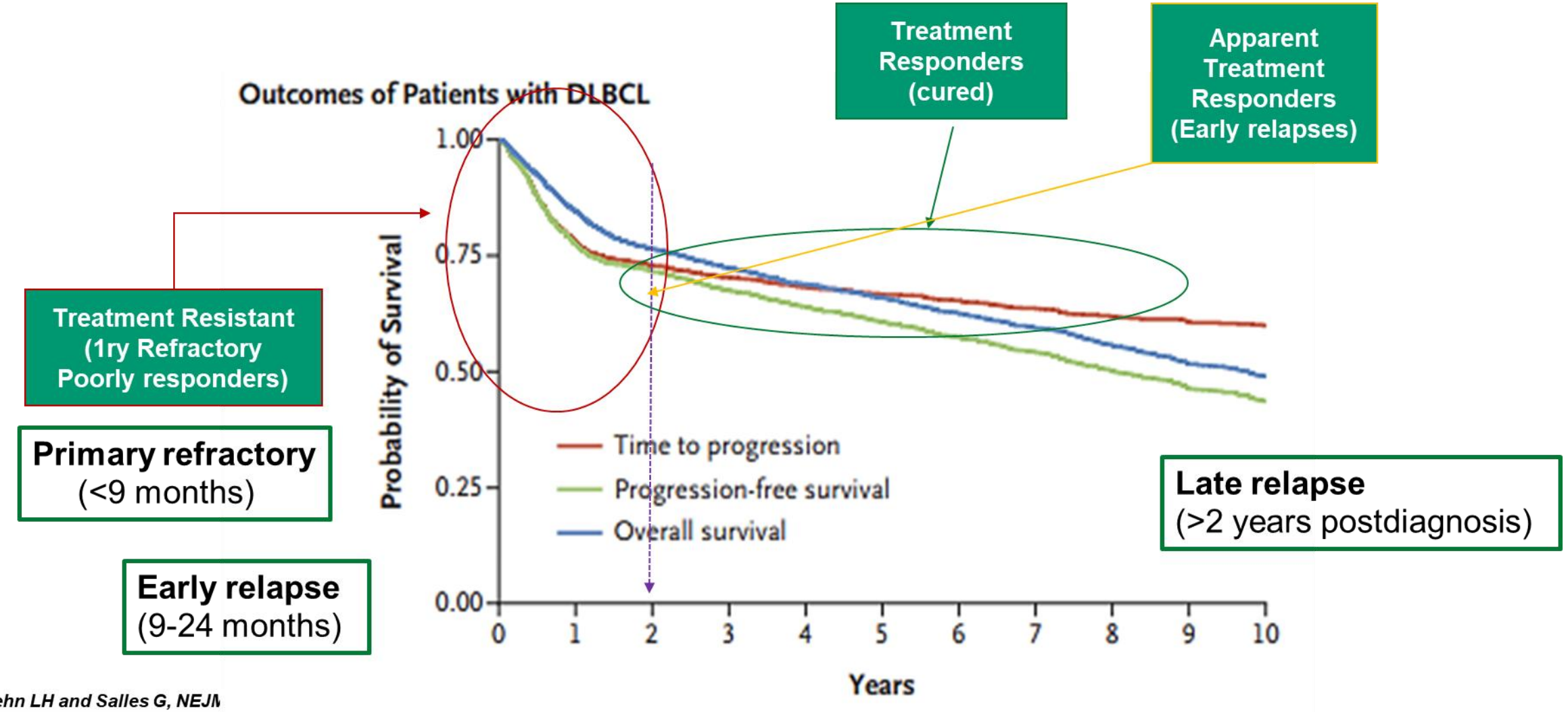
Disclosures for Antonello Pinto

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche			X		X	X	
BMS						X	
Eli Lilly			X		X	X	
Beigene						X	
SOBI					X	X	
MSD						X	
Autolus Ther.				X			
IGM BioSci.				X			
Incyte			X		X		
Takeda						X	
Abbvie					X		



Armitage JCO 2018

Yesterday, love was such an easy game to play...



Sehn LH and Salles G, NEJM

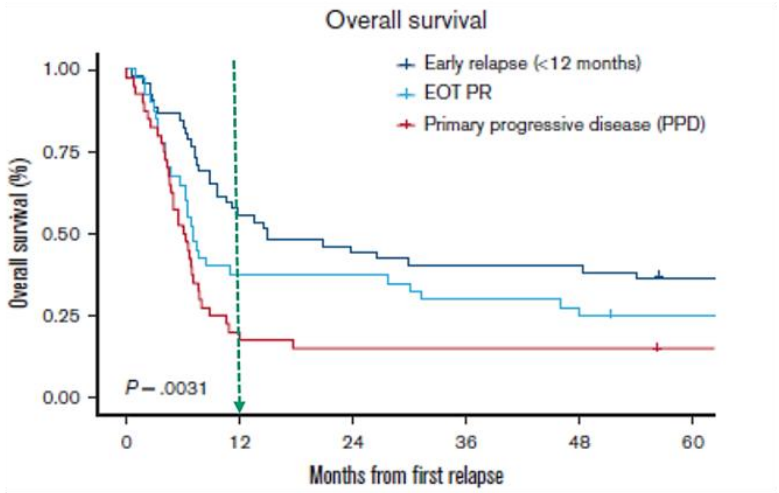
Hilton LK, et al. J Clin Oncol 2023; 41:4164

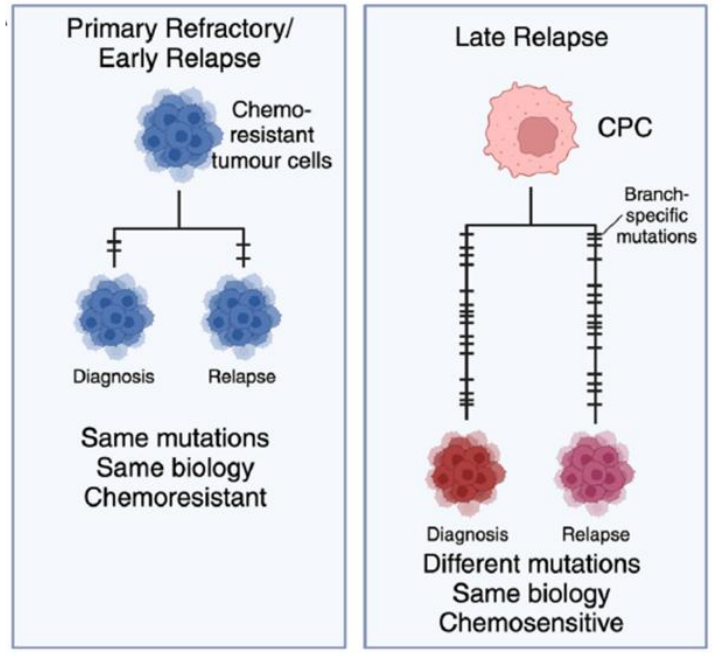
Redefining *Primary Refractoriness:* to what ? (R-CHOP)

Defining primary refractory large B-cell lymphoma

Key Points

- Patients with SD/PD to 1L therapy have lower responses to 2L therapy and poor OS compared with other subgroups of primary refractory disease.
- We advocate for the following definition of primary refractory LBCL: patients with SD or PD during, or by the end of, 1L treatment.





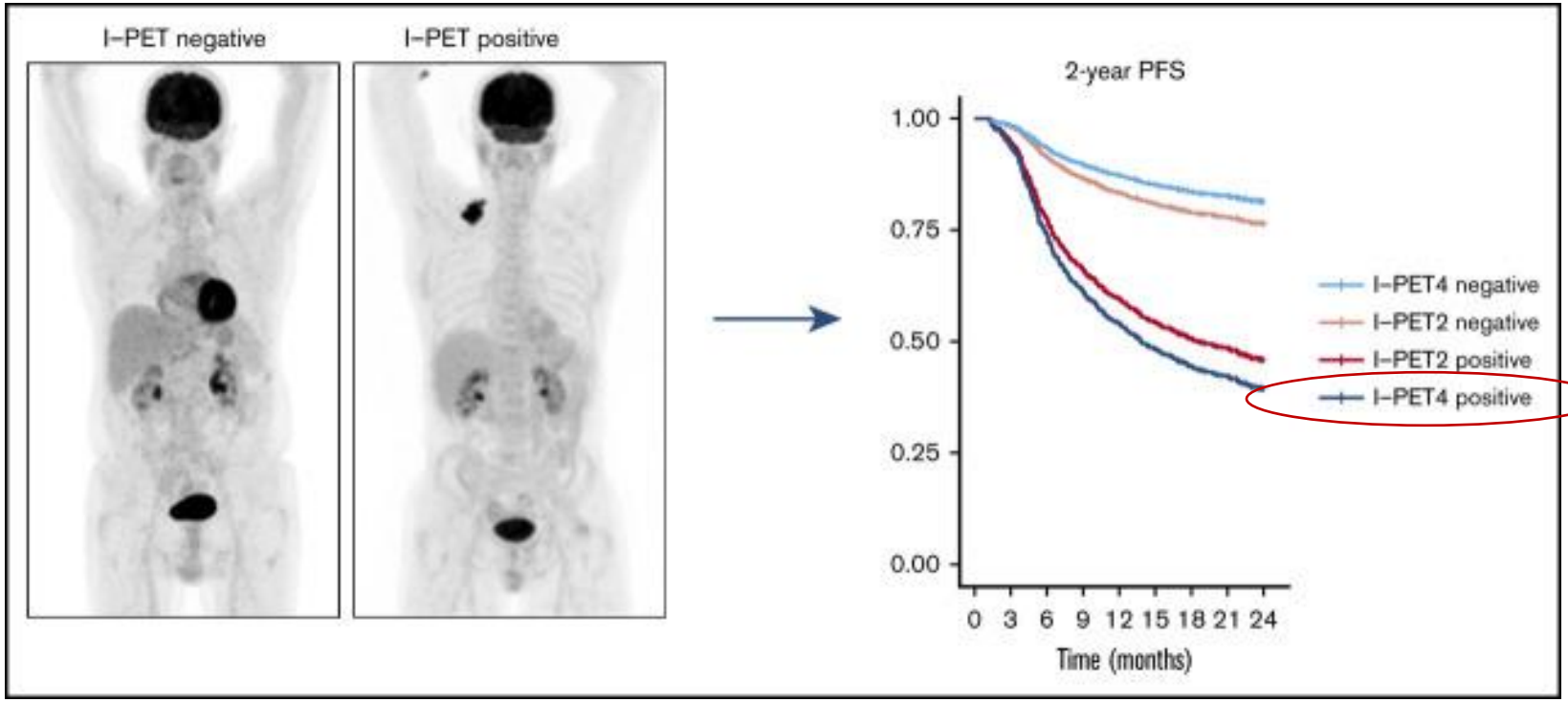
Hilton et al. (2023) Semin Hematol. 60(5):267

Patients with stable (SD) or progressive disease (PD) during or by the EOT are defined as "primary refractory LBCL". This is the group of patients with clear chemoresistance and most in need of better treatment options.

Patients with inadequate response or EOT PR (ie, PR as best response by EOT) and early relapse (ie, relapse within 12 months) have similar outcomes and may be better grouped as "early relapse"

Bock AM, *et al.* Blood Adv. 2024;8(13):3402-3415

Timing of response assessment



Eertink JJ et al. Optimal timing and criteria of interim PET in DLBCL: a comparative study of 1692 patients. *Blood Adv*. 2021;5(9):2375

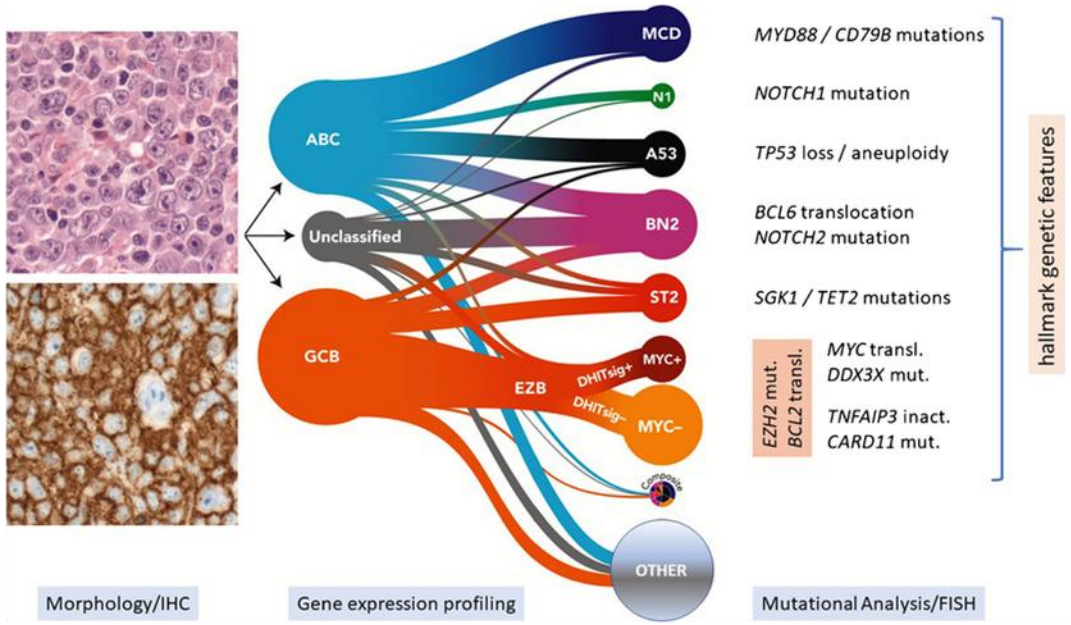
Early activation of the CAR-T pathway (eligible pts.)

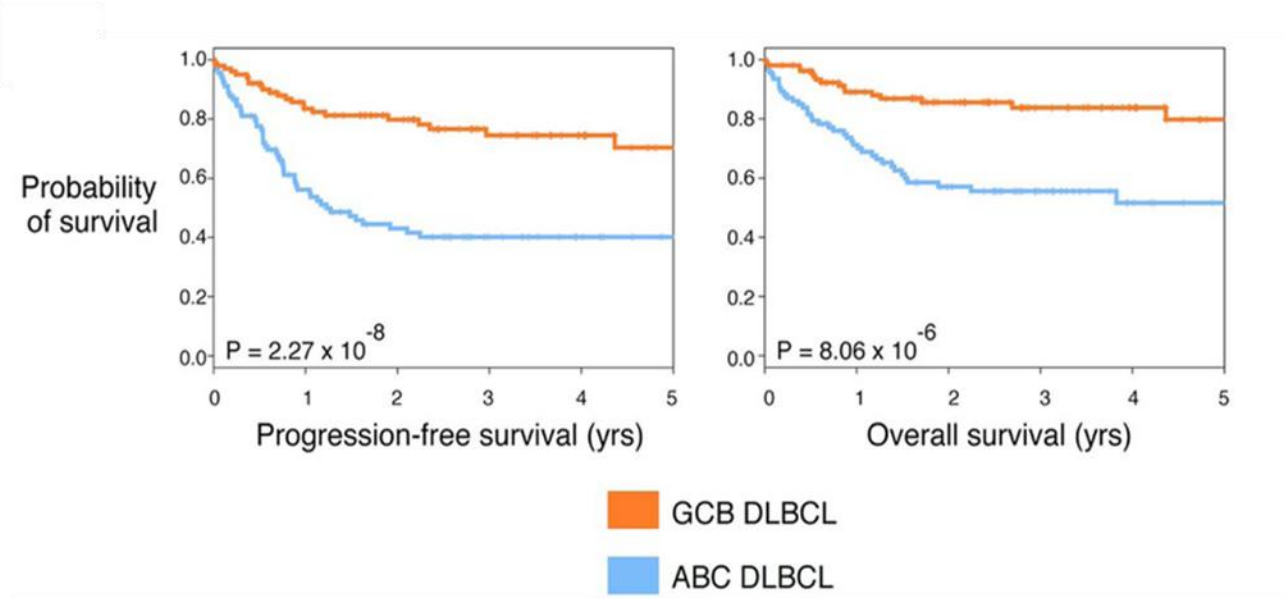
Early activation of a non-chemotherapy salvage pathway:

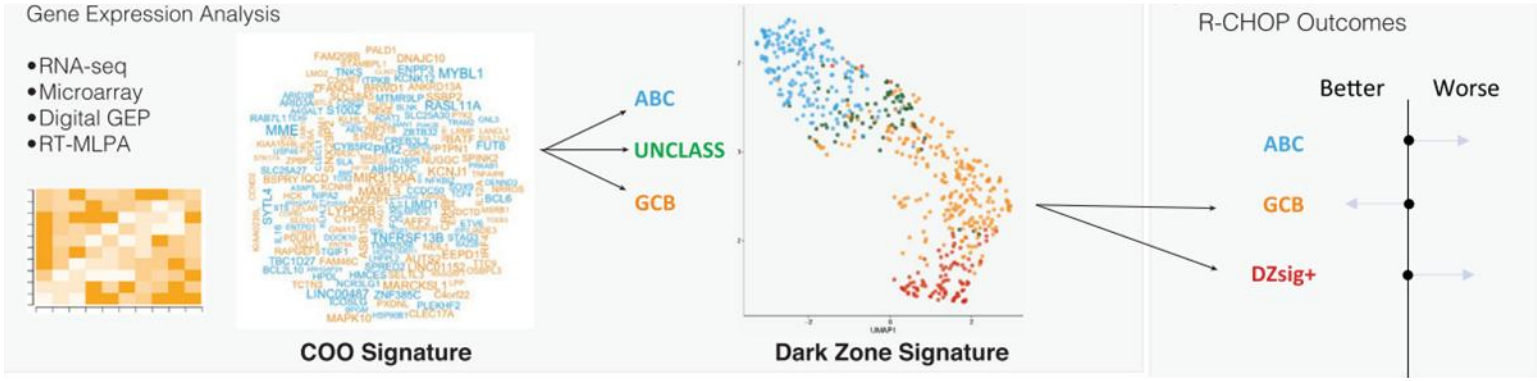
a) Bispecifics (regulatory issues)

b) Short-chemo (?) plus bispecifics

- *I. Stem cells collection*
- *II. Deferred CAR-T patwhay*
- *III. ASCT*
- *IV. Bispecifics-only salvage*

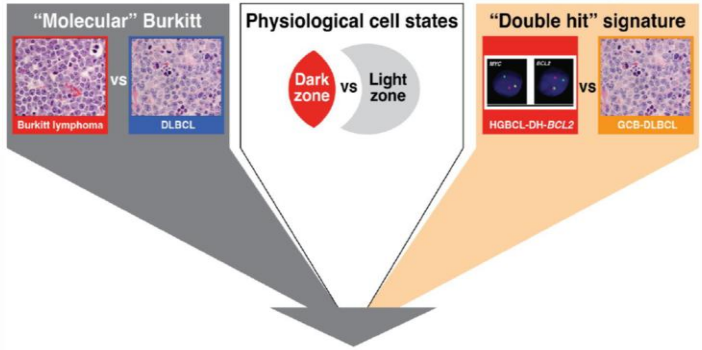






He, M.Y., Kridel, R., *Leukemia* 35, 2151–2165 (2021)
Hilton LK, Scott DW, Morin RD.; Semin Hematol. 2023;60(5):267-276.
Dunleavy K, Grant C, Wilson WH.; Ther Adv Hematol. 2013;4(1):43-57

Dark zone lymphomas: converging evidence



Dark zone lymphoma

An umbrella term encompassing lymphomas that phenocopy B cells from the germinal center dark zone

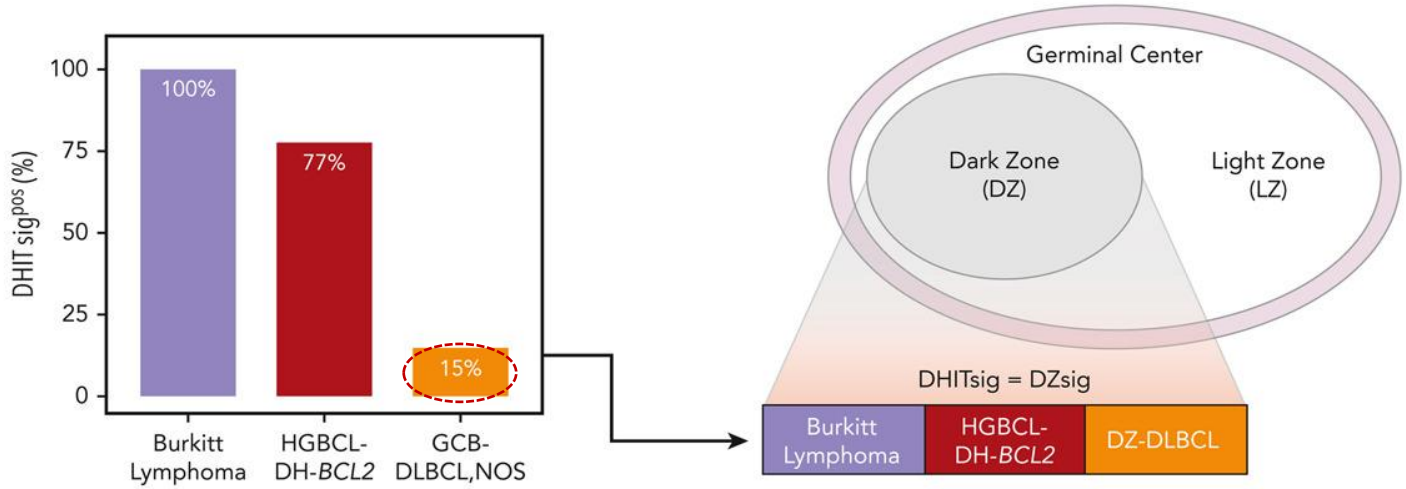
Defined ICC/WHO entities:

- All Burkitt lymphoma
- Most HGBCL-DH-*BCL2* ("double hit")

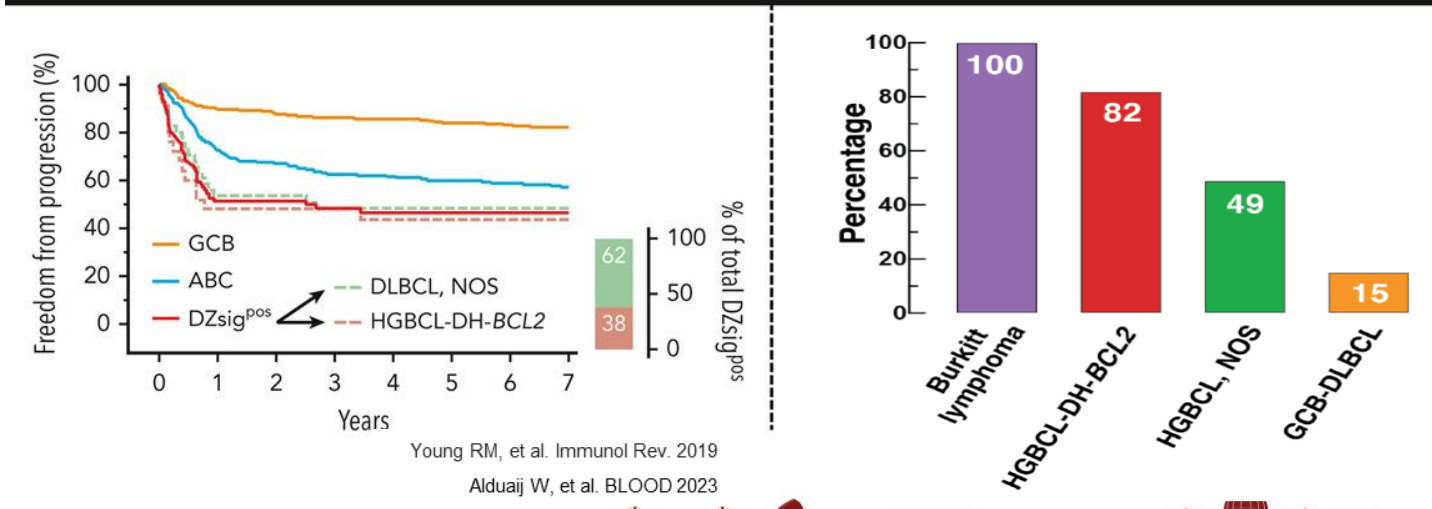
Not otherwise specified groups:

- Half of high-grade B-cell lymphoma, NOS
- 15% of GCB-DLBCL, NOS

1. DHITsig expression extends beyond HGBCL-DH-*BCL2* to identify dark zone lymphomas, and was thus renamed the "dark zone signature" (DZsig)

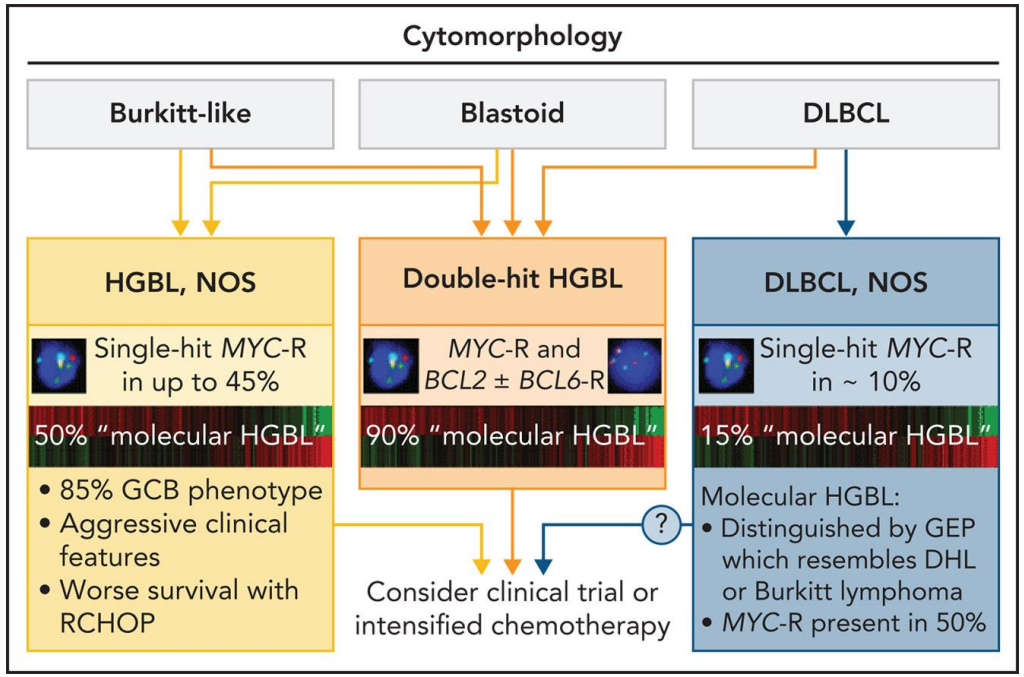


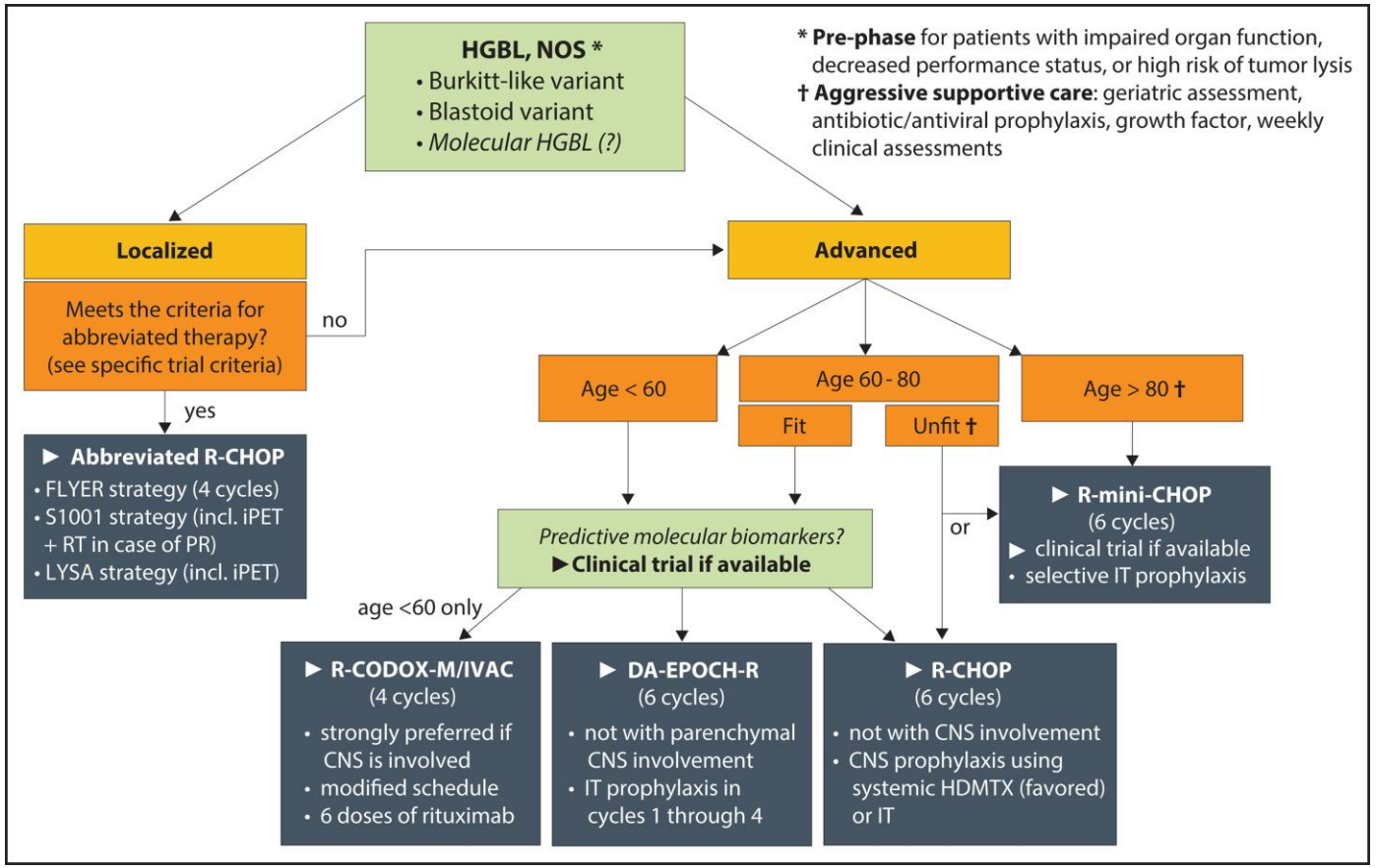
2. Among tumors of DLBCL morphology, gene expression profiling-defined molecular subgroups are associated with outcomes and diagnosis-to-treatment interval



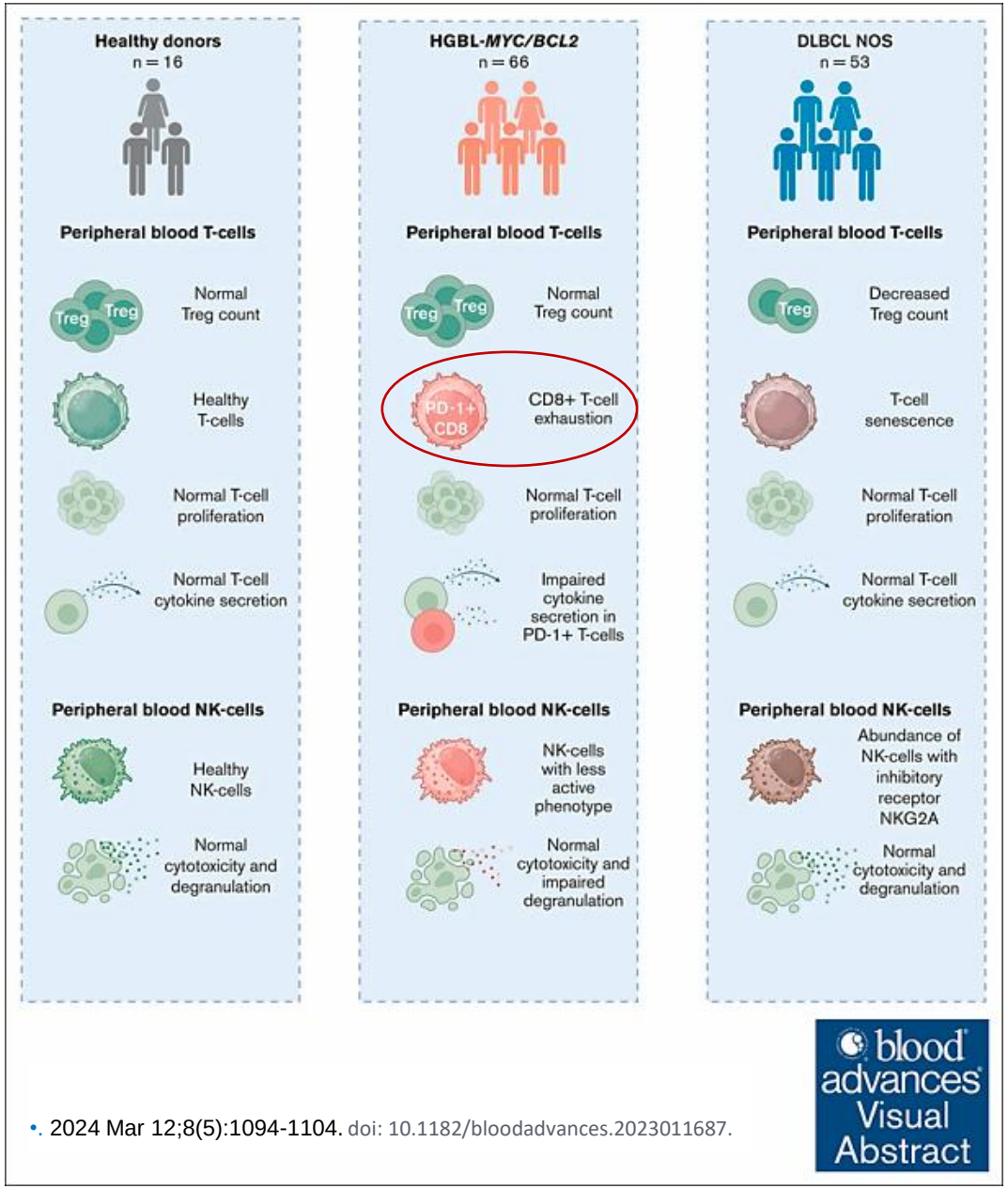
Young RM, et al. Immunol Rev. 2019

Alduaij W, et al. BLOOD 2023



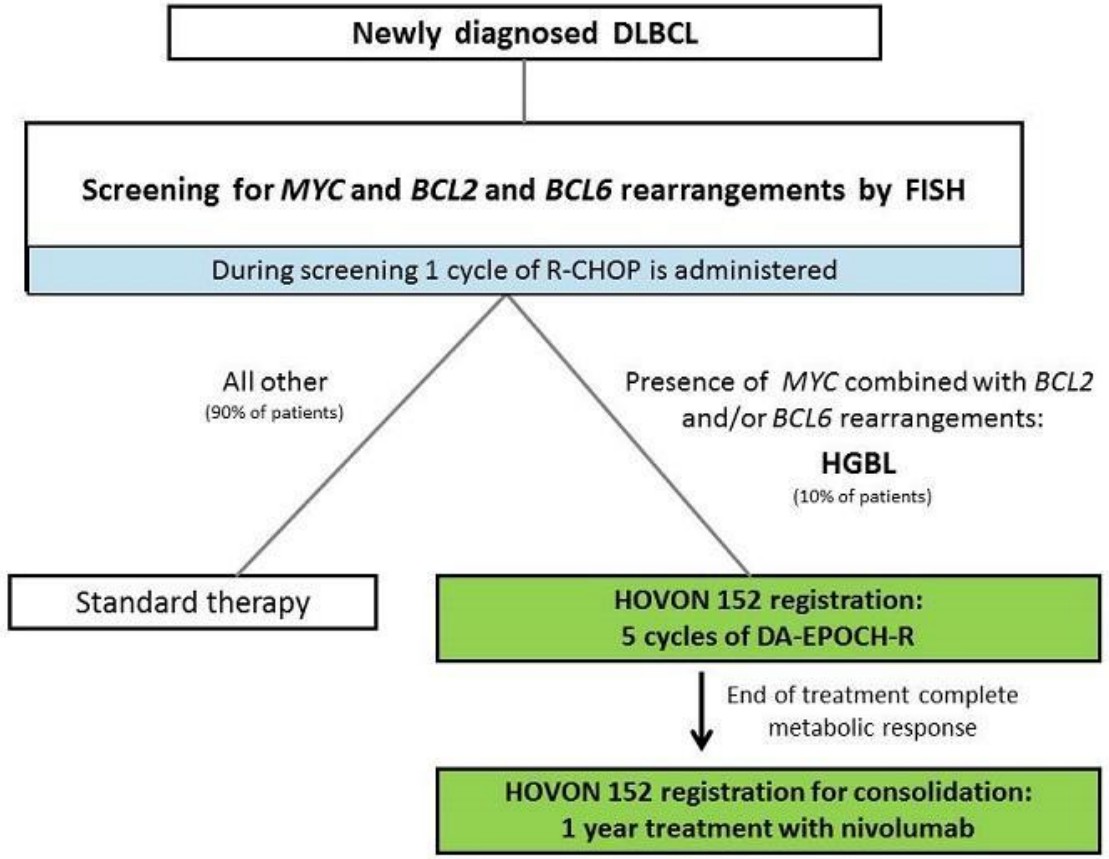


Olszewski AJ, et al. Blood (2022)



•. 2024 Mar 12;8(5):1094-1104. doi: 10.1182/bloodadvances.2023011687.

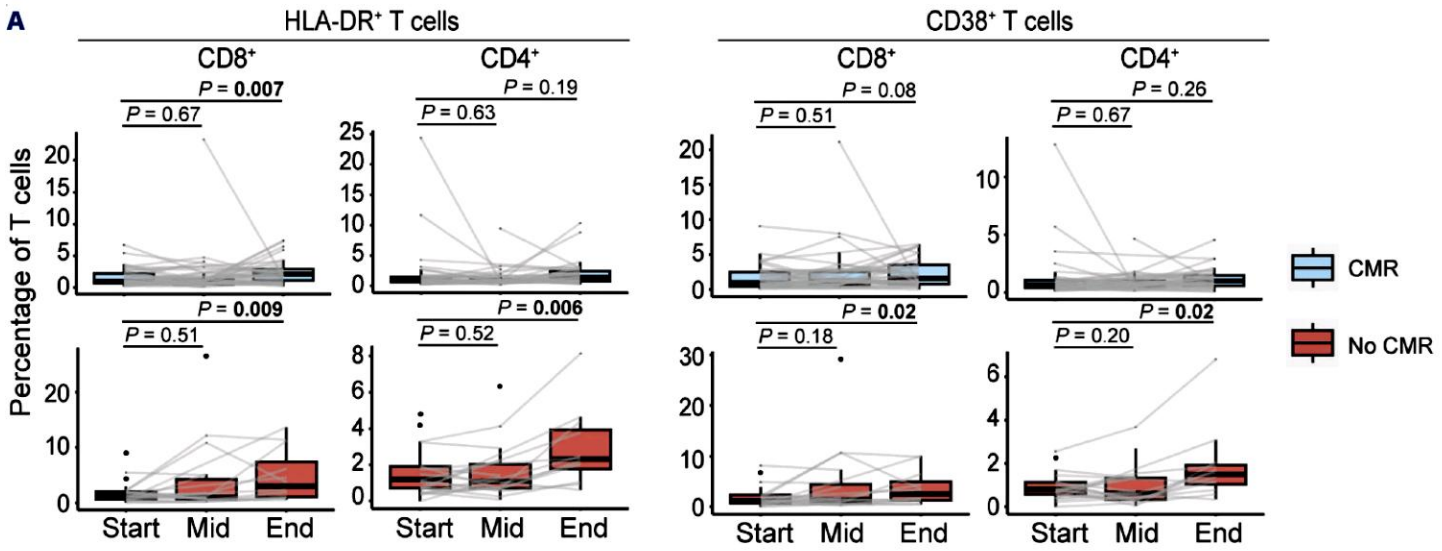
HOVON-152 Trial

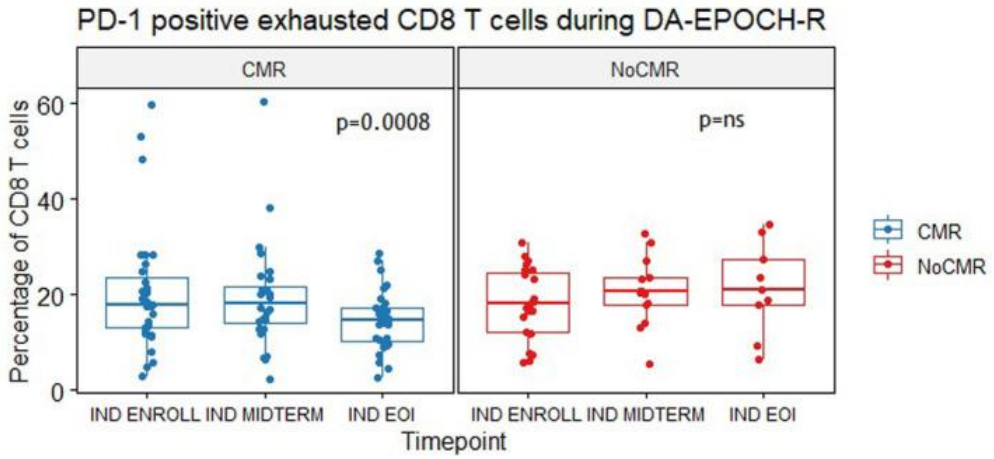


66% (95% CI 55%-75%) of the patients with HGBL-DH/TH achieve CMR after DAEPOCH-R.

Response to DA-EPOCH-R is associated with activation of ‘fitter’ cytotoxic T cells in patients with newly diagnosed double and triple hit high-grade B-cell lymphoma

HOVON-152 Phase II Trial





66% (95% CI 55%-75%) of the patients with HGBL-DH/TH achieve CMR after DAEPOCH-R.

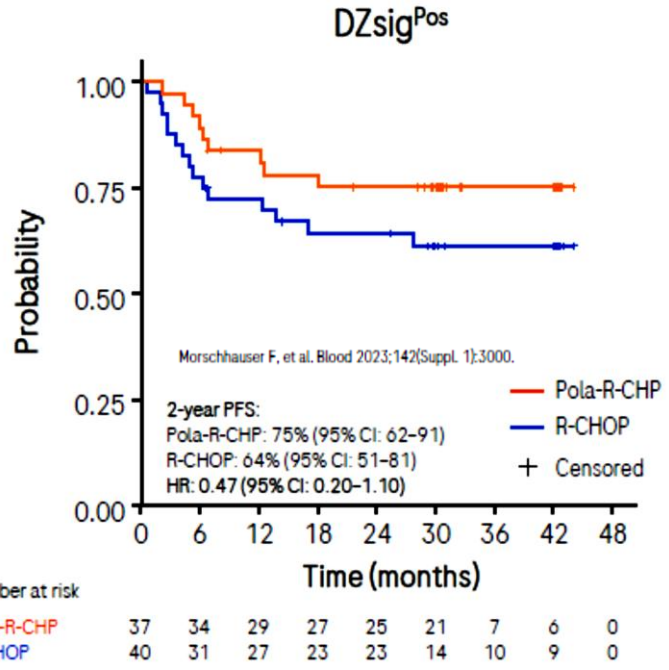
Are we improving in 1L ?

Five-year analysis of the POLARIX study: Prolonged follow-up confirms positive impact of polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP) on outcomes

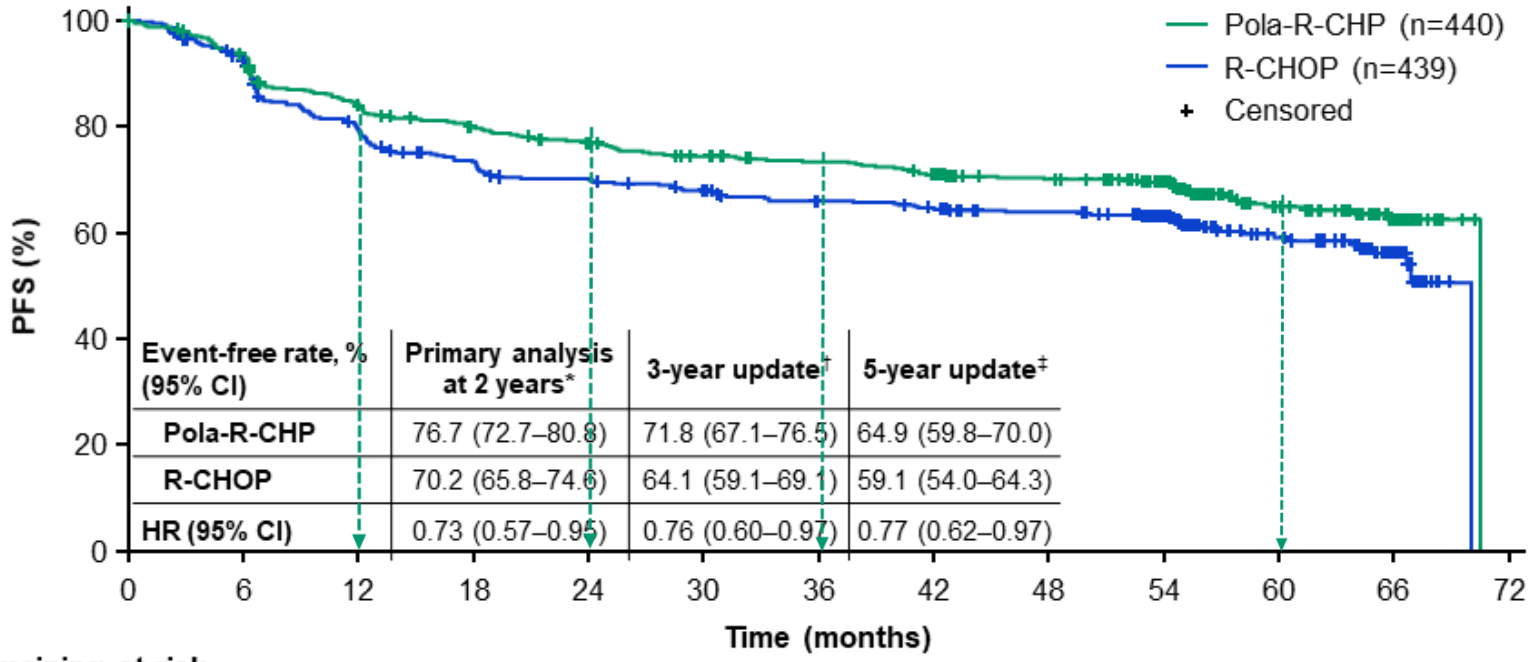
Gilles Salles[1], Franck Morschhauser[2], Laurie H. Sehn[3], Alex F. Herrera[4], Jonathan W. Friedberg[5], Marek Trněný[6], Georg Lenz[7], Jeff P. Sharman[8], Charles Herbaux[9], John M. Burke[10], Matthew Matasar[11], Graham P. Collins[12], Yuqin Song[13], Antonio Pinto[14], Shinya Rai[15], Koji Izutsu[16], Calvin Lee[17*], Saibah Chohan[18], Matthew Sugidono[17], Yanwen Jiang[17], Connie Lee Batlevi[17], Mark Yan[18], Jamie Hirata[17*], Hervé Tilly[19], Christopher R. Flowers[20]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]University of Lille, Lille, France; [3]BC Cancer Centre for Lymphoid Cancer and the University of British Columbia, Vancouver, BC, Canada; [4]City of Hope, Duarte, CA, USA; [5]Wilmot Cancer Institute, University of Rochester, Rochester, NY, USA; [6]Charles University, Prague, Czech Republic; [7]University Hospital Münster, Münster, Germany; [8]Willamette Valley Cancer Institute and Research Center, Florence, OR, USA; [9]University of Montpellier, Montpellier, France; [10]Rocky Mountain Cancer Centers/US Oncology, Aurora, CO, USA; [11]Rutgers Cancer Institute, New Brunswick, NJ, USA; [12]Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom; [13]Peking University Cancer Hospital, Beijing, China; [14]National Cancer Institute, Fondazione G. Pascale, IRCCS, Naples, Italy; [15]Department of Hematology and Rheumatology, Kindai University, Faculty of Medicine, Osaka-Sayama City, Japan; [16]National Cancer Center Hospital, Tokyo, Japan; [17]Genentech, Inc., South San Francisco, CA, USA; [18]Hoffmann-La Roche Ltd, Mississauga, Canada; [19]Centre Henri-Becquerel and University of Rouen, Rouen, France; [20]M.D. Anderson Cancer Center, Houston, TX, USA

*This affiliation was active at the time of the analysis



Initial PFS benefit of Pola-R-CHP over R-CHOP is maintained at 5 years



Event-free rate, % (95% CI)	Primary analysis at 2 years*	3-year update†	5-year update‡
Pola-R-CHP	76.7 (72.7–80.8)	71.8 (67.1–76.5)	64.9 (59.8–70.0)
R-CHOP	70.2 (65.8–74.6)	64.1 (59.1–69.1)	59.1 (54.0–64.3)
HR (95% CI)	0.73 (0.57–0.95)	0.76 (0.60–0.97)	0.77 (0.62–0.97)

Patients remaining at risk

Pola-R-CHP	440	407	357	335	318	303	292	280	258	213	100	56	NE
R-CHOP	439	391	332	302	287	274	258	251	240	192	95	54	NE

Are we improving in 1L ?

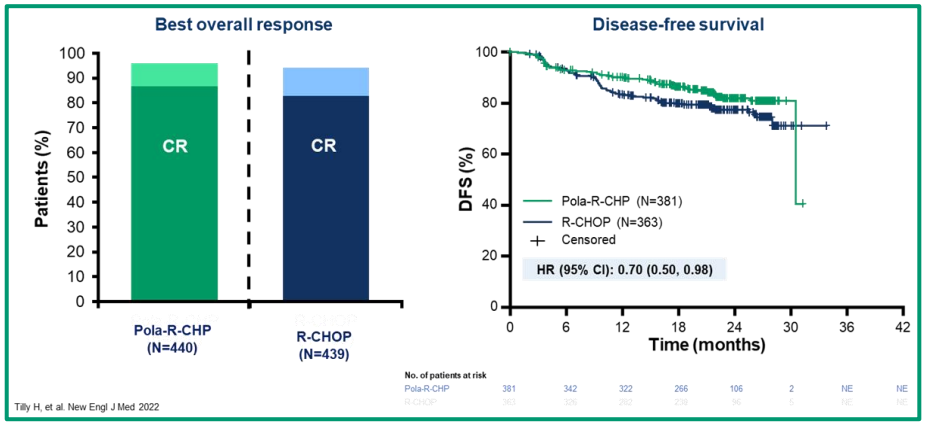
Five-year analysis of the POLARIX study: Prolonged follow-up confirms positive impact of polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP) on outcomes

Gilles Salles[1], Franck Morschhauser[2], Laurie H. Sehn[3], Alex F. Herrera[4], Jonathan W. Friedberg[5], Marek Trněný[6], Georg Lenz[7], Jeff P. Sharman[8], Charles Herbaux[9], John M. Burke[10], Matthew Matasar[11], Graham P. Collins[12], Yuqin Song[13], Antonio Pinto[14], Shinya Rai[15], Koji Izutsu[16], Calvin Lee[17*], Saibah Chohan[18], Matthew Sugidono[17], Yanwen Jiang[17], Connie Lee Batlevi[17], Mark Yan[18], Jamie Hirata[17*], Hervé Tilly[19], Christopher R. Flowers[20]

[1]*Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [2]*University of Lille, Lille, France;* [3]*BC Cancer Centre for Lymphoid Cancer and the University of British Columbia, Vancouver, BC, Canada;* [4]*City of Hope, Duarte, CA, USA;* [5]*Wilmot Cancer Institute, University of Rochester, Rochester, NY, USA;* [6]*Charles University, Prague, Czech Republic;* [7]*University Hospital Münster, Münster, Germany;* [8]*Willamette Valley Cancer Institute and Research Center, Florence, OR, USA;* [9]*University of Montpellier, Montpellier, France;* [10]*Rocky Mountain Cancer Centers/US Oncology, Aurora, CO, USA;* [11]*Rutgers Cancer Institute, New Brunswick, NJ, USA;* [12]*Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom;* [13]*Peking University Cancer Hospital, Beijing, China;* [14]*National Cancer Institute, Fondazione G. Pascale, IRCCS, Naples, Italy;* [15]*Department of Hematology and Rheumatology, Kindai University, Faculty of Medicine, Osaka-Sayama City, Japan;* [16]*National Cancer Center Hospital, Tokyo, Japan;* [17]*Genentech, Inc., South San Francisco, CA, USA;* [18]*Hoffmann-La Roche Ltd, Mississauga, Canada;* [19]*Centre Henri-Becquerel and University of Rouen, Rouen, France;* [20]*M.D. Anderson Cancer Center, Houston, TX, USA*

**This affiliation was active at the time of the analysis*

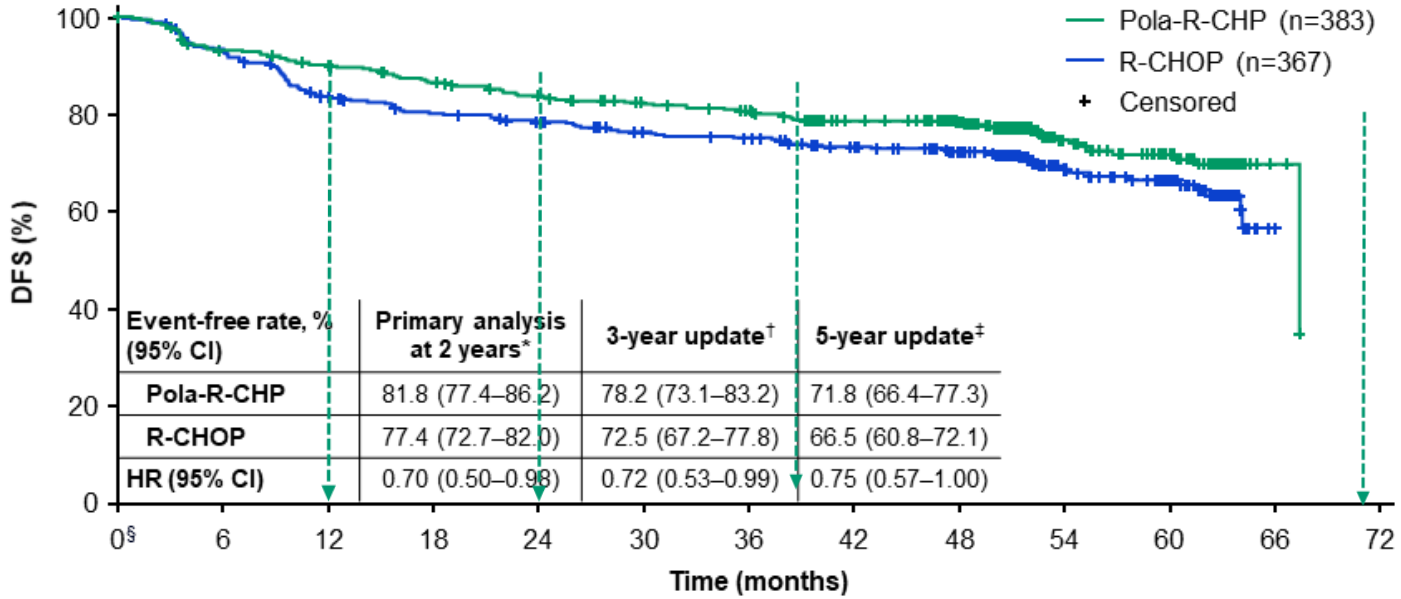
Presented at the 66th ASH Annual Meeting | December 7–10, 2024



Tilly H, et al. New Engl J Med 2022

Complete remission obtained after Pola-R-CHP treatment is maintained with 5-year follow-up

DFS (DoCR) in the global ITT population



Event-free rate, % (95% CI)	Primary analysis at 2 years*	3-year update†	5-year update‡
Pola-R-CHP	81.8 (77.4–86.2)	78.2 (73.1–83.2)	71.8 (66.4–77.3)
R-CHOP	77.4 (72.7–82.0)	72.5 (67.2–77.8)	66.5 (60.8–72.1)
HR (95% CI)	0.70 (0.50–0.98)	0.72 (0.53–0.99)	0.75 (0.57–1.00)

Patients remaining at risk

Pola-R-CHP	383	347	333	317	301	286	277	251	222	105	79	3	NE
R-CHOP	367	336	295	279	268	253	247	230	206	98	72	NE	NE

FDA Approval Summary: Polatuzumab Vedotin in the First-Line Treatment of Select Large B-Cell Lymphomas

Maryam Sarraf Yazdy[1], Yvette L. Kasamon[1], Wenjuan Gu[1], Lisa R. Rodriguez[1], Susan Jin[1], Vishal Bhatnagar[1], Nicholas C. Richardson[1], Marc R. Theoret[1,2], Richard Pazdur[1,2], and Nicole J. Gormley[1]

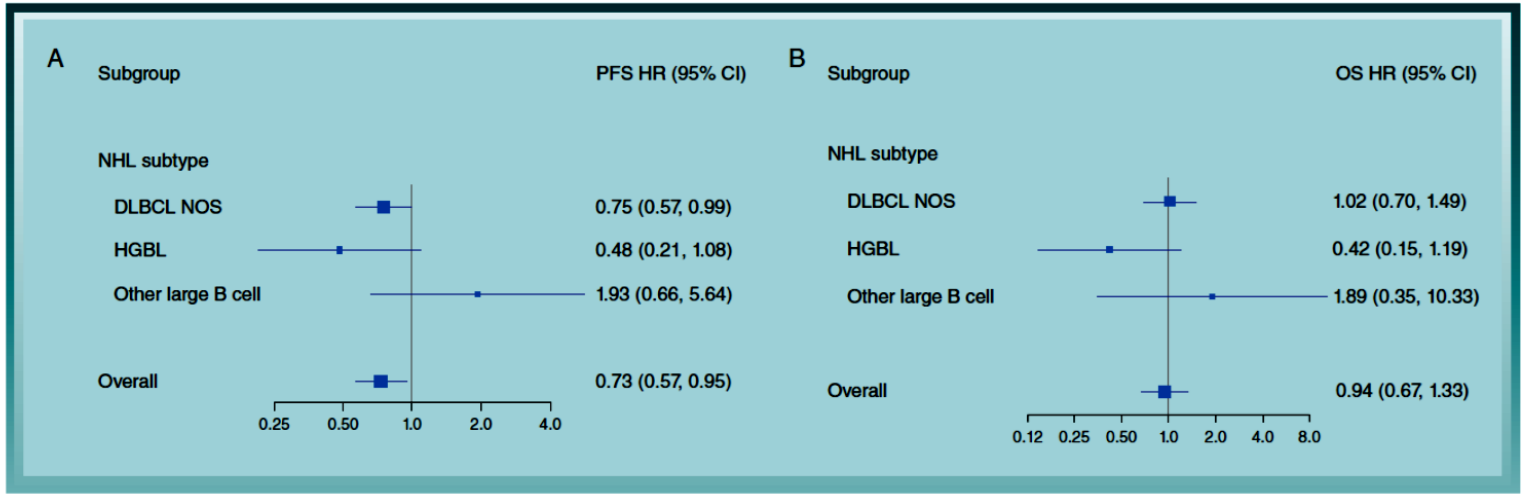
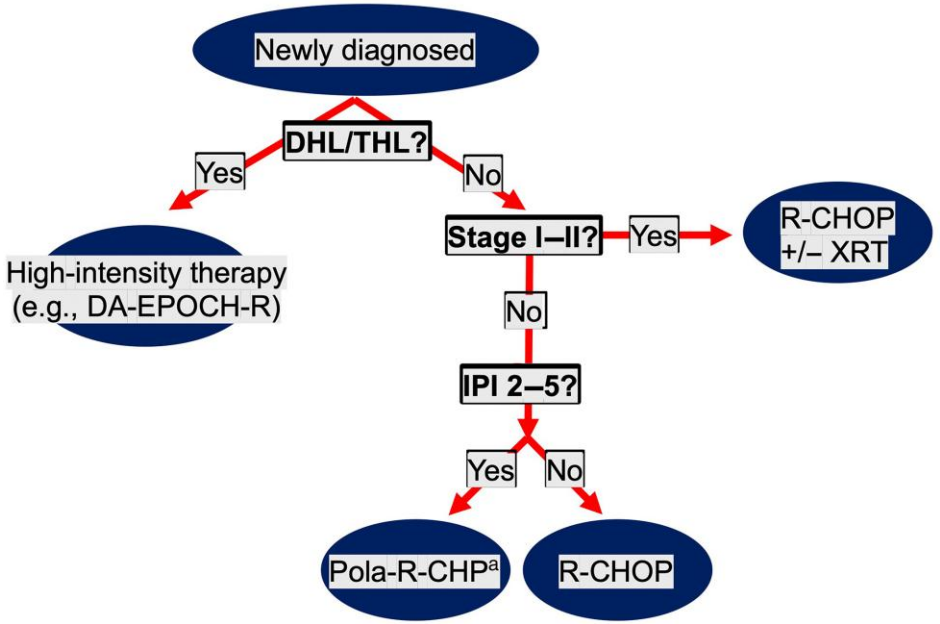


Figure 2.
Forest plots of PFS (**A**) and OS (**B**) by the type of non–Hodgkin lymphoma. NHL, non–Hodgkin lymphoma. Source: FDA analysis.



Tavakkoli et al. Am J Hematol (2023)

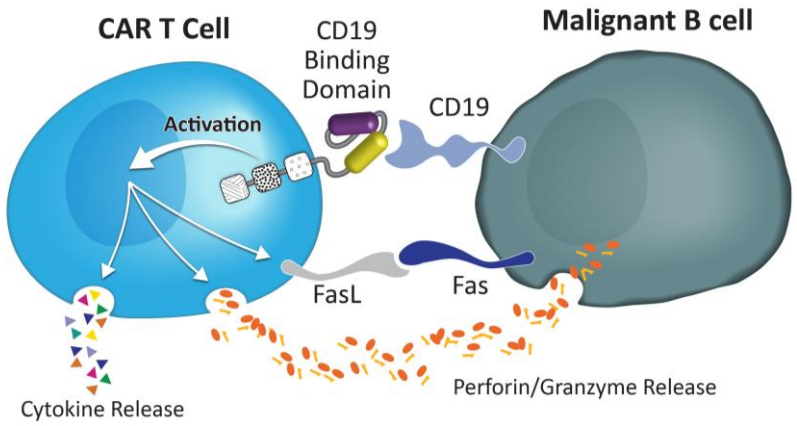
Based on the PFS rate and supported by modified EFS in a randomized phase 3 study, pola+R-CHP has clinically meaningful efficacy in patients with previously untreated DLBCL, NOS, or HGBL and who have an IPI score of 2 or greater.

Clin Cancer Res 2024;30:5521–6

1st Line				
IPI 0	IPI 1-2	IPI 3-5	HGBL-DzSig+	'Old'/unfit/frail
4 x R-CHOP (+2R ?)	6 x R-CHOP (+2R ?)	6 x Pola-R-CHP	DA-EPOCH-R BL-like CIT, Pola-R-CHP	R-*mini*-CHOP, Polar-Bear-like, R-CEOP/COMP, Non-anthr. CT ?
2nd Line				

T-cell Redirection strategies are changing the scenario

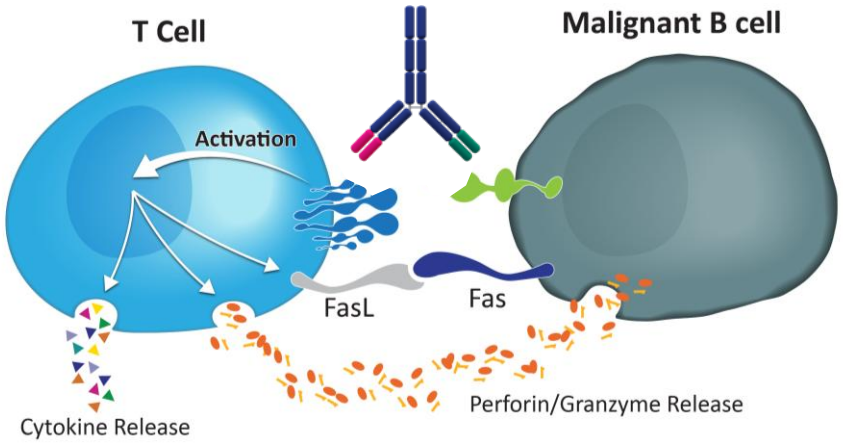
CAR T



Similarities

- **Both CAR Ts and bsAbs bring together T cells and B cells**
- **Interaction causes activation of the T cell and release of cytokines, granzyme, and perforin**
- **Results in T cell mediated killing of the tumor cell**

Bispecific Antibody



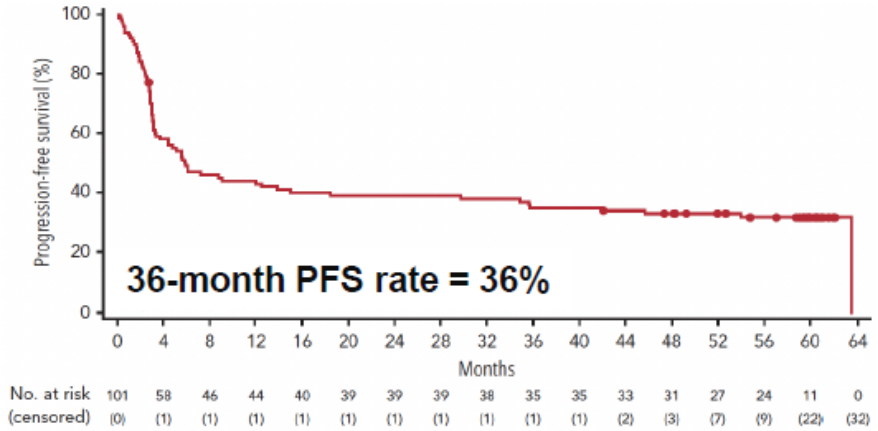
Differences

CAR T therapy **modifies the extracellular antigen-binding domain** on T cells	**Binding**	Bispecific antibodies **induce effector T cell binding to the tumor cell**
CAR T therapies rely on **ex vivo activated and expanded T cells**	**T-cell**	Bispecific antibodies use **the patient's endogenous T cells**
Yes	**2nd Signal**	**No (…not yet…)**

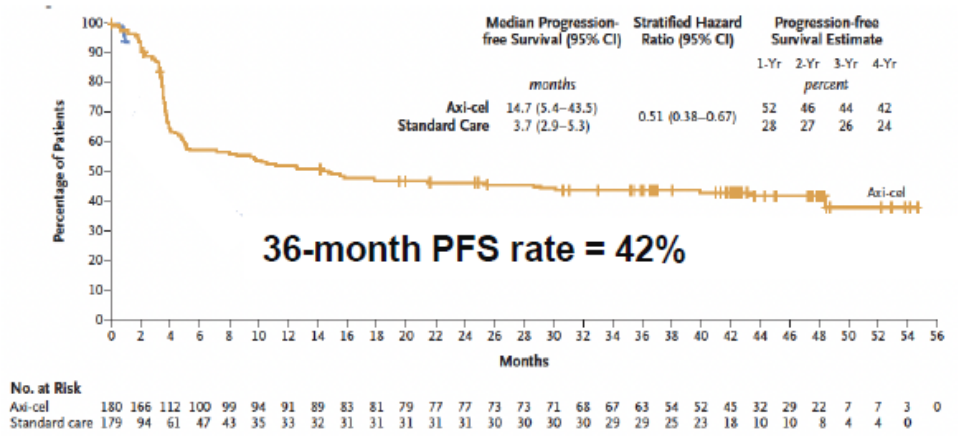
bsAb, bispecific antibody; CAR T, chimeric antigen receptor T-cell; MOA, mechanism of action.

Adapted from: Zhukovsky EA, et al. *Curr Opin Immunol.* 2016;40:24-35.

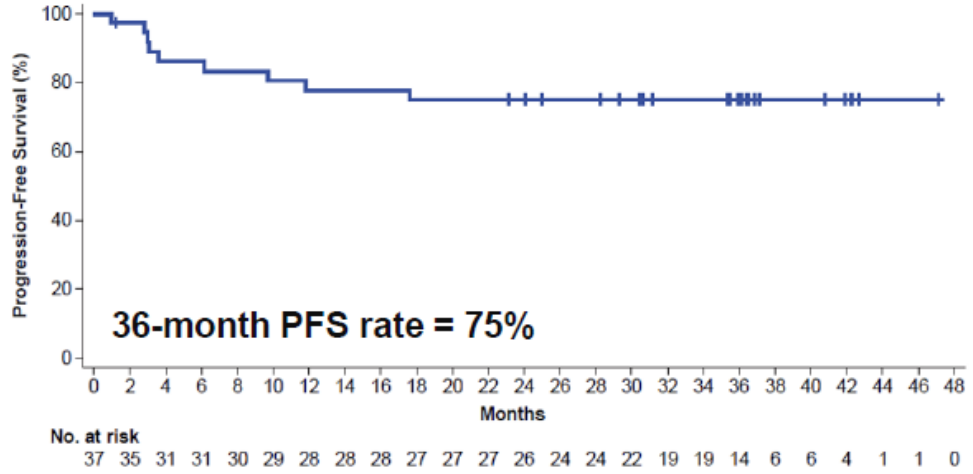
ZUMA-1: Axi-cel in ≥3rd line



ZUMA-7: Axi-cel in 2nd line



ZUMA-12: Axi-cel in 1st line



Neelapu et al, *Blood* 2023; 141(19):2307-2315
Westin JR et al. *N Eng J Med* 2023; 389(2):148-157
Neelapu et al, *Blood* 2025 Feb 12

How many LBCL can we cure with CAR T cells?

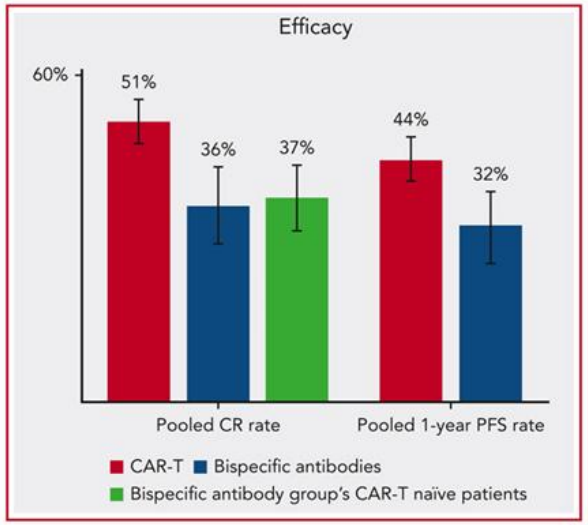
It depends

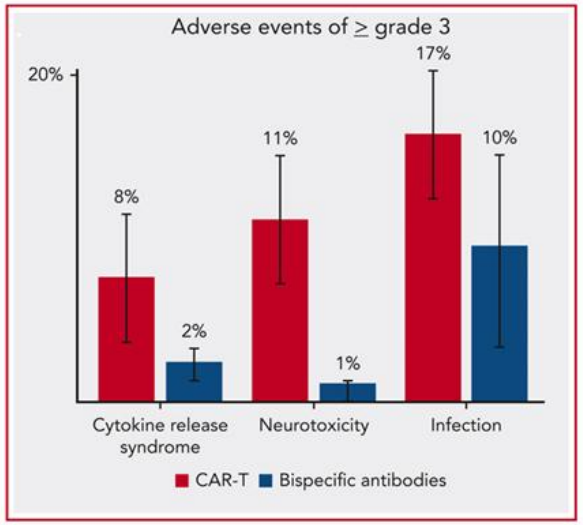
	Category	% Cured
3rd line	All LBCLs treated with CAR-T	~40%
	PMBCL and tFL	~60%
	DLBCL-NOS and HGBCL	~30%
	THRLBCL	0%
	2nd line LBCL	~40-50%
	1st line high-risk LBCL	~75%
	All 3rd line R/R LBCL (up to 40% treated with CAR-T)	~15%

Sattva S. Neelapu 2025

Comparison of CAR T-Cell Therapy and Bispecific Antibodies As Third-Line or Later Treatment for Diffuse Large B-Cell Lymphoma (DLBCL): A Meta-Analysis

CAR-T cell therapy: 10 studies including 742 patients
Bispecific antibodies: 6 studies including 605 patients

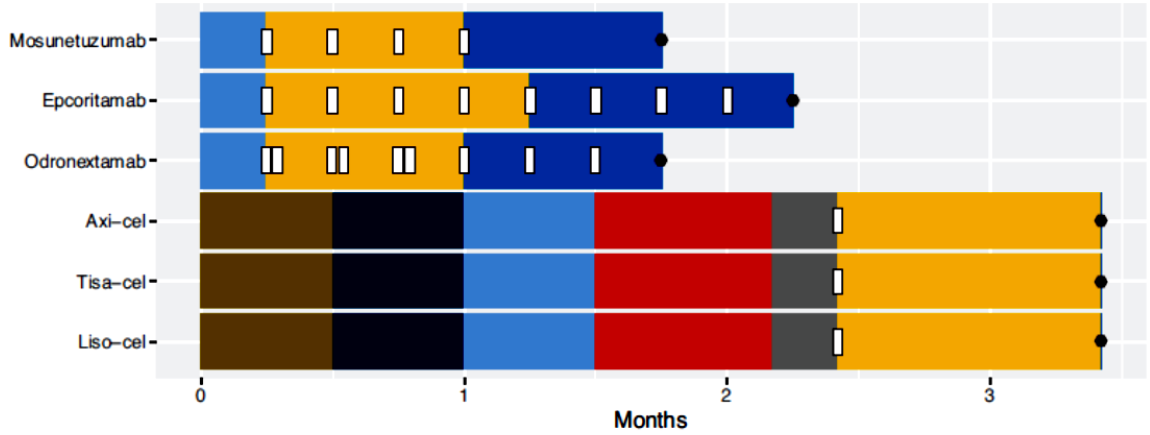




Conclusion: **In patients with relapsed/refractory DLBCL, CAR-T cell therapy has demonstrated superior efficacy compared to bispecific antibodies, although with a higher incidence of severe adverse effects.**

*Kim et al. DOI: 10.1182/**blood**.2023023419*

blood Visual Abstract



Phase of Care

- Cycle 2
- Cycle 1
- Pre-treatment
- Preparation (line placement, apheresis, production ± lead-in or bridging therapy)
- Insurance Authorization
- Pre-testing (TTE, PFTs, labs, SW assessment)
- Referral
- PET/CT
- BsAb or CAR-T Administration

David A. Russler-Germain and Nancy L. Bartlett -Hematology 2024 | ASH Education Programt

1st Line

IPI 0	IPI 1-2	IPI 3-5	HGBL-DzSig+	'Old'/unfit/frail
4 x R-CHOP (+2R ?)	6 x R-CHOP (+2R ?)	6 x Pola-R-CHP	DA-EPOCH-R BL-like CIT, Pola-R-CHP	R-*mini*-CHOP, Polar-Bear-like, R-CEOP/COMP, Non-anthr. CT ?

2nd Line

1ry Ref./Early Rel. (≤ 12 Mos.)	1ry Ref./Early Rel. (≤ 12 Mos.)	Late Relapse ≥ 12 Months	
CAR-T Eligible	CAR-T Ineligible/not-available	HDT-ASCT Eligible	CAR-T Ineligible/not available
CAR-T Axicel/Lisocel	Clinical study - ASCT - ???	Plat./based Salvage / ASCT	Tafa/Lena, Pola-BR, R-GemOx, R2

Clinical study

Tafasitamab and Lenalidomide

L-MIND trial: Phase 2 single-arm, open-label, multicentre study

- R/R DLBCL
- Not eligible for HDCT plus ASCT
- 1–3 prior regimens
- Primary refractory patients were not eligible*
- ECOG PS 0–2

N=81

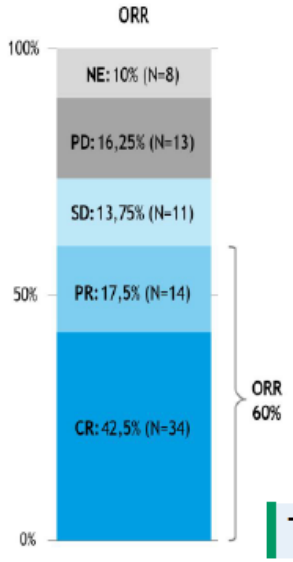
Cycles 1–3: Tafasitamab 12 mg/kg d1, 8, 15, 22† + LEN 25 mg/d orally d1–21

Cycles 4–12: Tafasitamab 12 mg/kg d1, 15 + LEN 25 mg/d orally d1–21

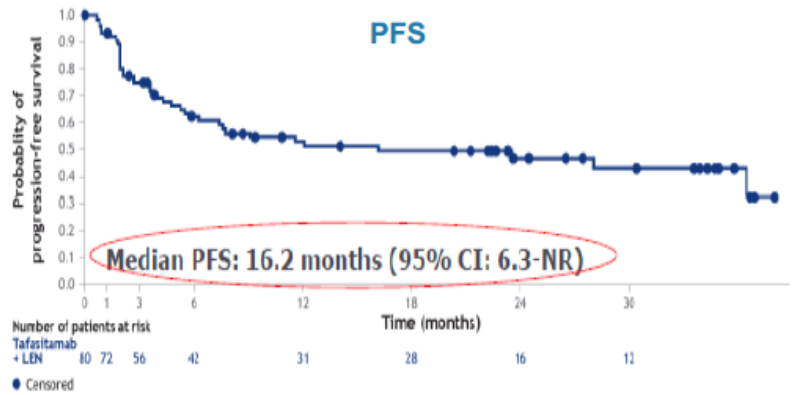
If ≥SD → **Cycles 12+**: Tafasitamab 12 mg/kg d1, 15 + LEN 25 mg/d orally d1–21 → Treatment until progression

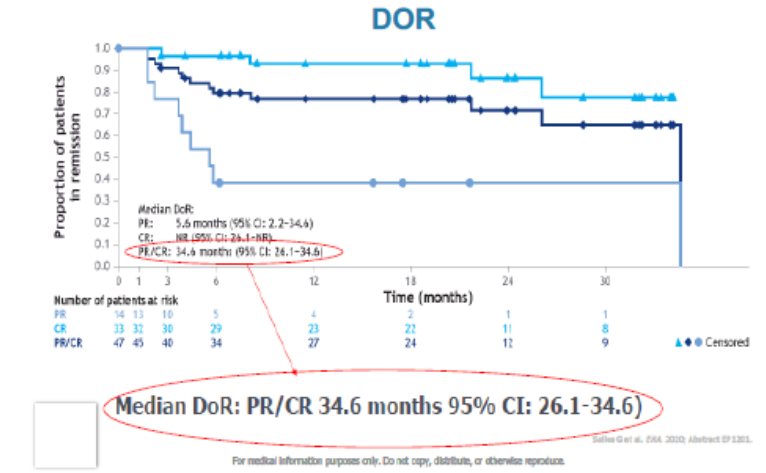
Primary endpoint:
- ORR (central read)

Secondary endpoints:
- PFS
- DoR
- OS
- Safety of the tafasitamab plus LEN combination
- Exploratory and biomarker-based assays



- ORR 60.0% (95% CI 48.4% - 70.8%)
- CR-rate 42.5%
  - 82% of CRs PET-confirmed
  - 18% of CRs based on CT only





Tafa-len received regulatory approvals for transplant ineligible R/R DLBCL

Salles G, et al. Lancet Oncol. 2020

ARTICLE OPEN

Check for updates

Autologous transplant vs. CAR-T therapy in patients with DLBCL treated while in complete remission

Mazyar Shadman[1,2], Kwang W. Ahn[3,4], Manmeet Kaur[3,4], Lazaros Lekakis[5], Amer Beitinjaneh[5], Madiha Iqbal[6], Nausheen Ahmed[7], Brian Hill[8], Nasheed M. Hossain[9], Peter Riedell[10], Ajay K. Gopal[1,2], Natalie Grover[11], Matthew Frigault[12], Jonathan Brammer[13], Nilanjan Ghosh[14], Reid Merryman[15], Aleksandr Lazaryan[16], Ron Ram[17,18], Mark Hertzberg[19], Bipin Savani[20], Farrukh Awan[21], Farhad Khimani[16], Sairah Ahmed[22,23], Vaishalee P. Kenkre[24], Matthew Ulrickson[25], Nirav Shah[3,26], Mohamed A. Kharfan-Dabaja[6], Alex Herrera[27], Craig Sauter[8] and Mehdi Hamadani[3,26]✉

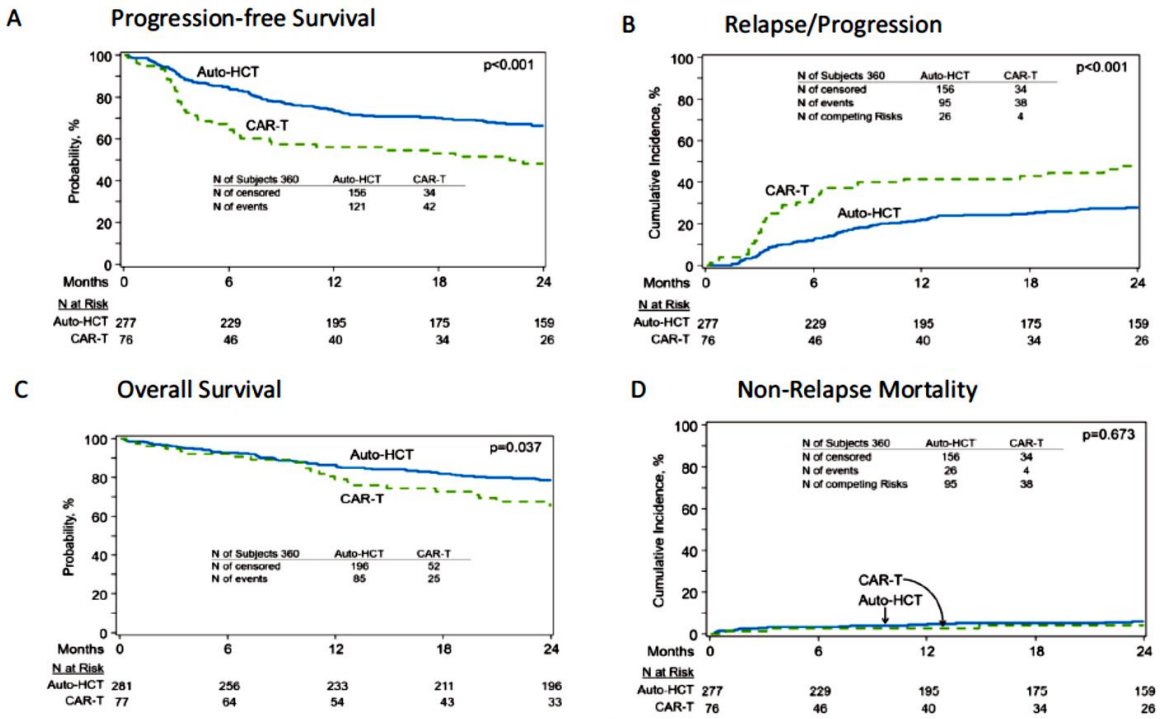
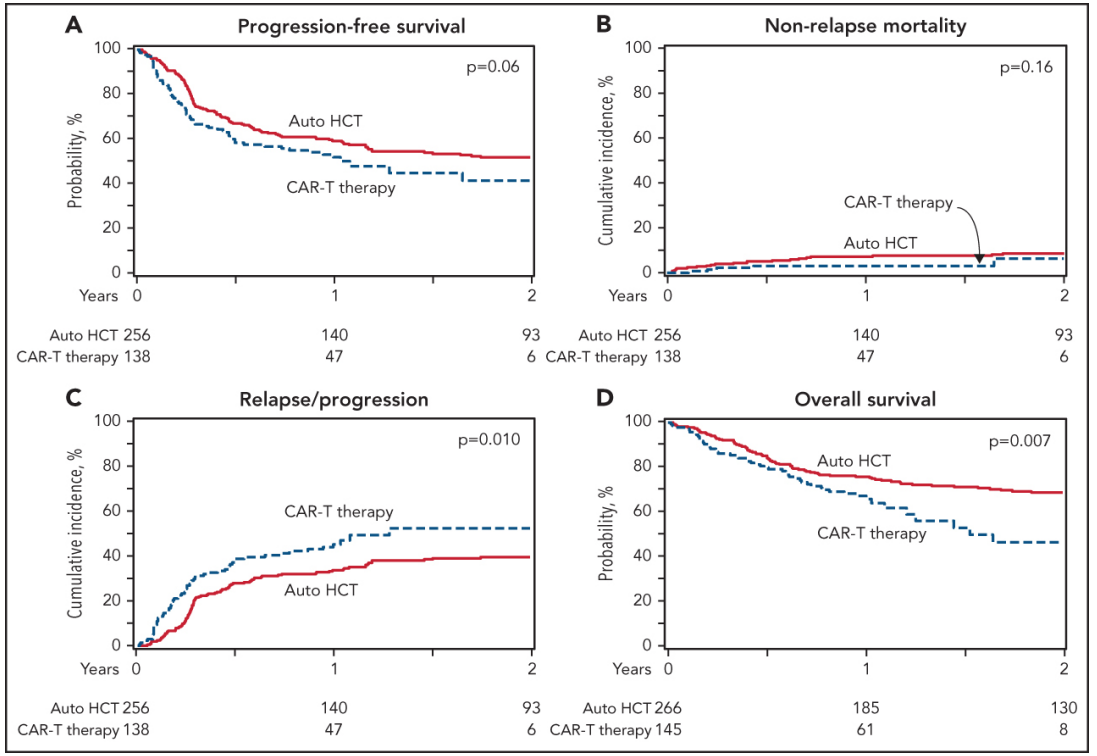


Fig. 1 Auto-HCT vs CAR-T in patients with DLBCL in CR. A progression-free survival. **B** Cumulativeincidence of relapse. **C** Overall survival. **D.** Non-relapse Mortality.

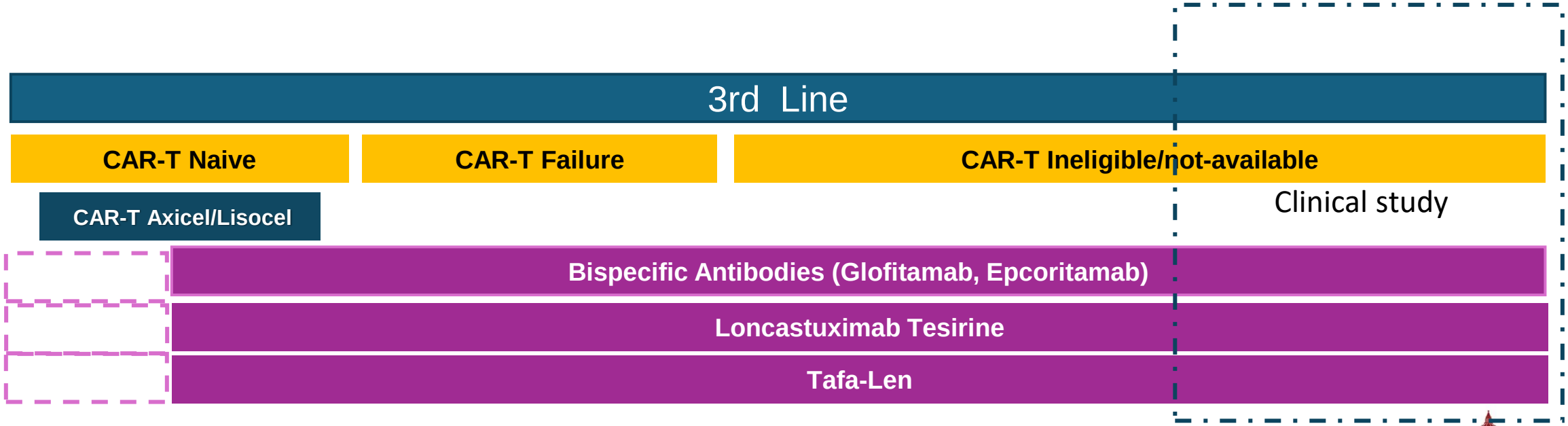
Blood Cancer Journal (2024)14:108 ; https://doi.org/10.1038/s41408-024-01084-w

Autologous transplant vs chimeric antigen receptor T-cell therapy for relapsed DLBCL in partial remission

Mazyar Shadman,[1,2] Marcelo Pasquini,[3] Kwang Woo Ahn,[3,4] Yue Chen,[3] Cameron J. Turtle,[1,2] Peiman Hematti,[5] Jonathon B. Cohen,[6] Farhad Khimani,[7] Siddhartha Ganguly,[8] Reid W. Merryman,[9] Jean A. Yared,[10] Frederick L. Locke,[7] Nausheen Ahmed,[8] Pashna N. Munshi,[11] Amer Beitinjaneh,[12] Patrick M. Reagan,[13] Alex F. Herrera,[14] Craig S. Sauter,[15,16] Mohamed A. Kharfan-Dabaja,[17] and Mehdi Hamadani[3,18]

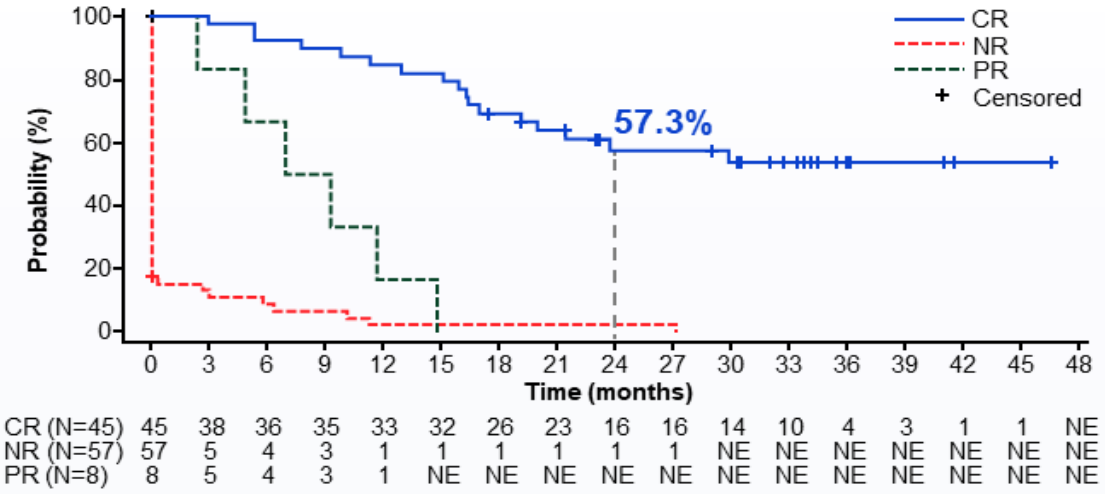


blood® 3 MARCH 2022 | VOLUME 139, NUMBER 9

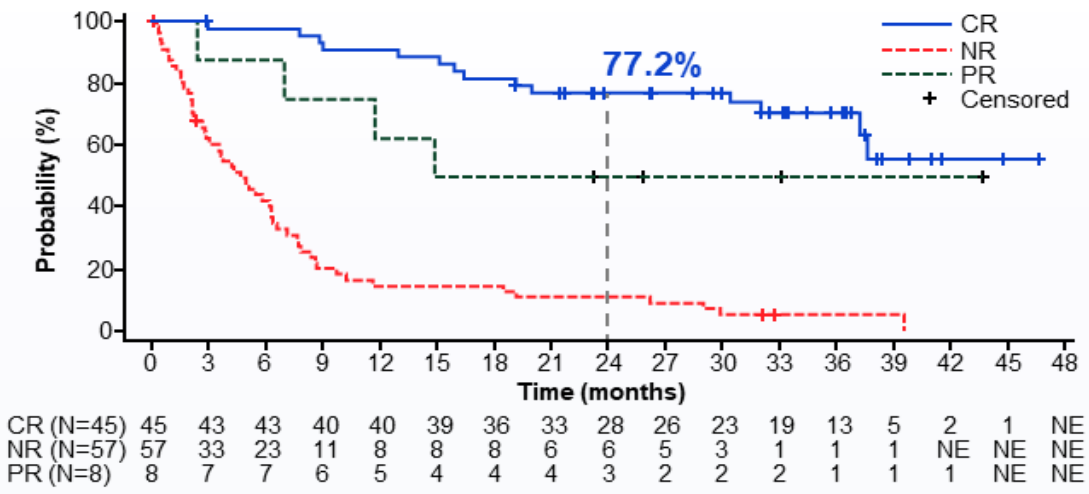

3rd Line
CAR-T Naive
CAR-T Failure
CAR-T Ineligible/not-available
CAR-T Axicel/Lisocel
Clinical study
Bispecific Antibodies (Glofitamab, Epcoritamab)
Loncastuximab Tesirine
Tafa-Len

Fixed-duration glofitamab monotherapy continues to demonstrate durable responses in patients with relapsed or refractory large B-cell lymphoma: 3-year follow-up from a pivotal Phase II study

PFS



OS



Landmark PFS from EOT in patients with CR at EOT*	N=45
Median PFS, months (95% CI)	NE (20.0–NE)
24-month PFS rate, % (95% CI)	57.3 (41.2–73.4)

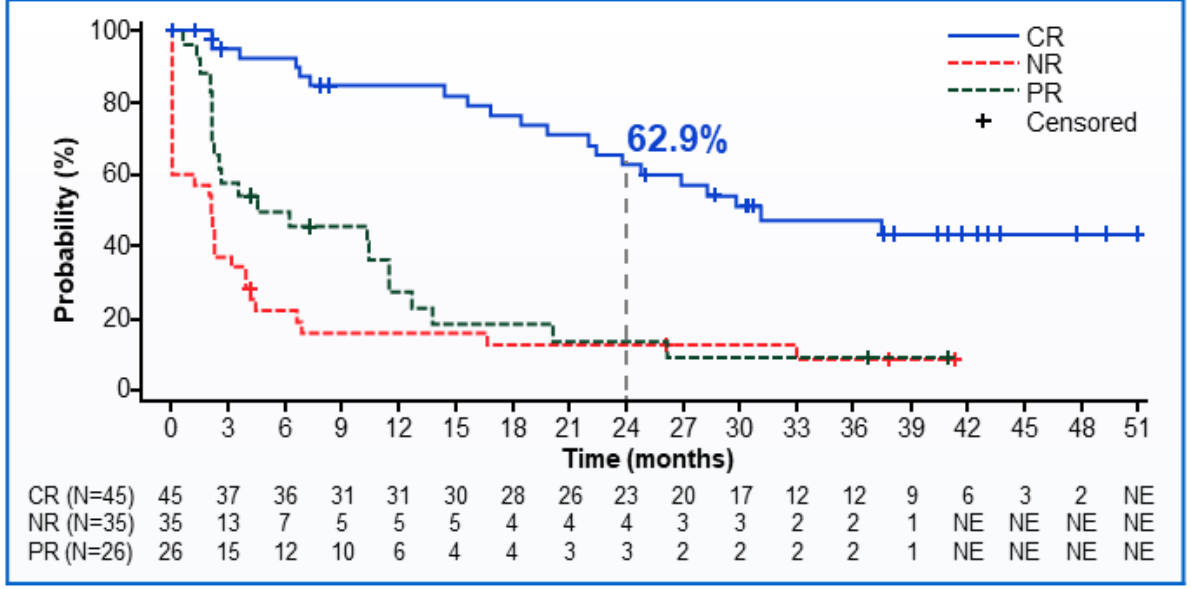
Landmark OS from EOT in patients with CR at EOT*	N=45
Median OS, months (95% CI)	NE (37.2–NE)
24-month OS rate, % (95% CI)	77.2 (64.8–89.6)

Most patients with a CR at EOT remained progression-free and alive at 24 months after EOT

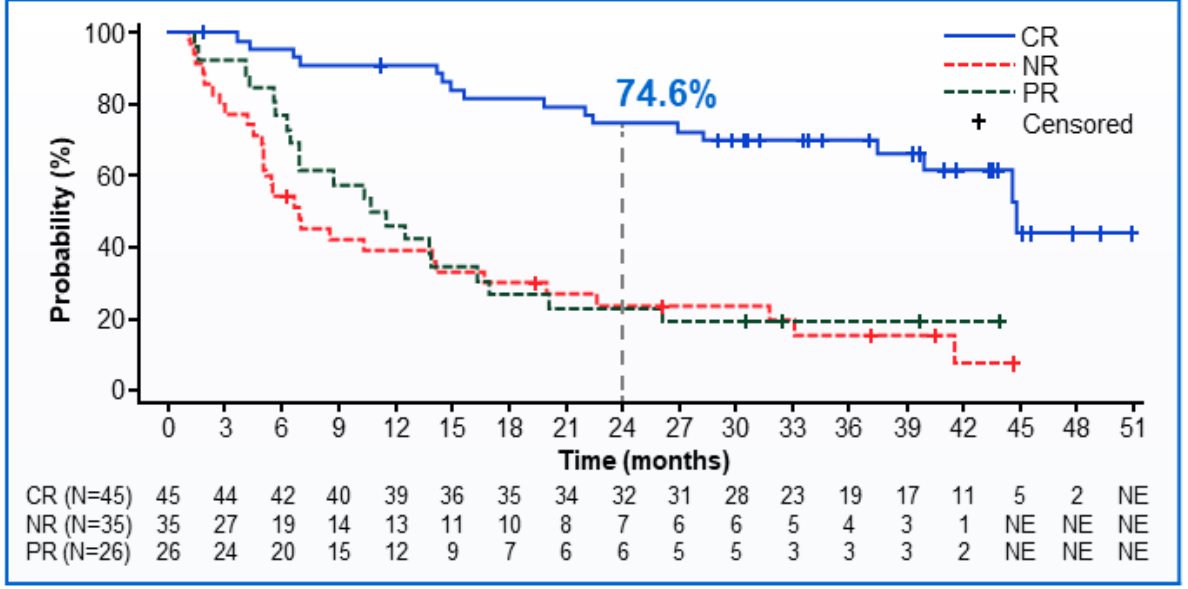
Dickinson, et al. ASH 2024

Landmark analysis by response at Cycle 3

PFS



OS



Landmark PFS from C3 in patients with CR at C3*	N=45
Median PFS, months (95% CI)	31.1 (23.8–NE)
24-month PFS rate, % (95% CI)	62.9 (47.5–78.4)

Landmark OS from C3 in patients with CR at C3*	N=45
Median OS, months (95% CI)	44.8 (40.0–NE)
24-month OS rate, % (95% CI)	74.6 (61.6–87.6)

Most patients with a CR at C3 remained progression-free and alive after 24 months

Epcoritamab in aggressive LBCL

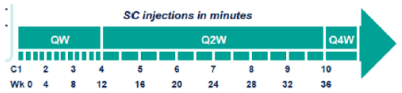
Dose escalation → **Dose expansion data cutoff: April 21, 2023**
Median follow-up: 25.1 mo

B-NHL:
- ✓ No DLTs
- ✓ MTD not reached
- ✓ RP2D identified
- ✓ Manageable safety profile
- ✓ Encouraging antitumor activity

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

Step-up dosing[a] → **Epcoritamab SC RP2D 48 mg** QW C1–3, Q2W C4–9, Q4W C10+ → **Treatment until PD or unacceptable toxicity** → **LBCL Cohort N=157** DLBCL, HGBCL, PMBCL, and FL Gr3B

- To ensure patient safety and better characterize CRS, inpatient monitoring was required at first full dose for 24 h in this part of the study
- **Primary endpoint:** ORR by Investigator Review Committee (IRC)
- **Key secondary endpoints:** DOR, TTR, PFS, OS, CR rate, and safety/tolerability

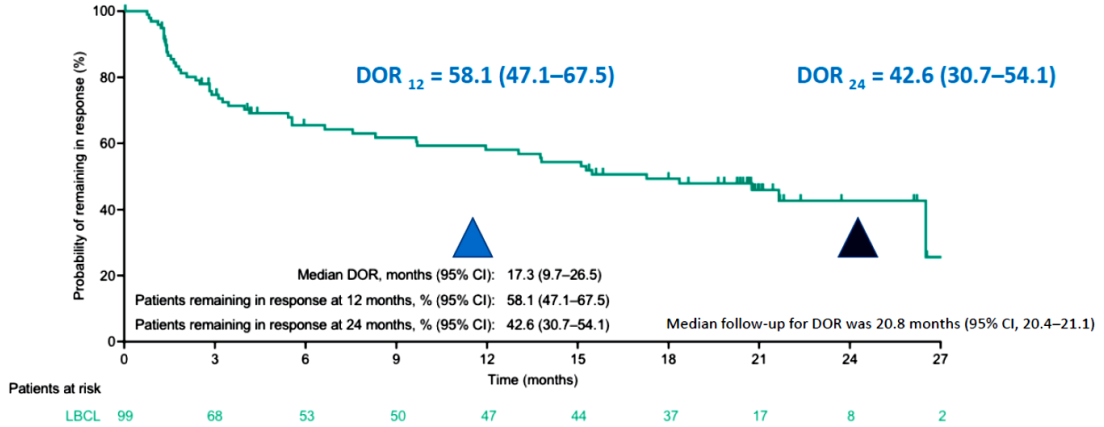


[a] C1D1 0.16 mg, C1D8 0.8 mg, C1D15 48 mg

Thieblemont C., J Clin Oncol, 2022, 41:2238-2247.

Duration of Response

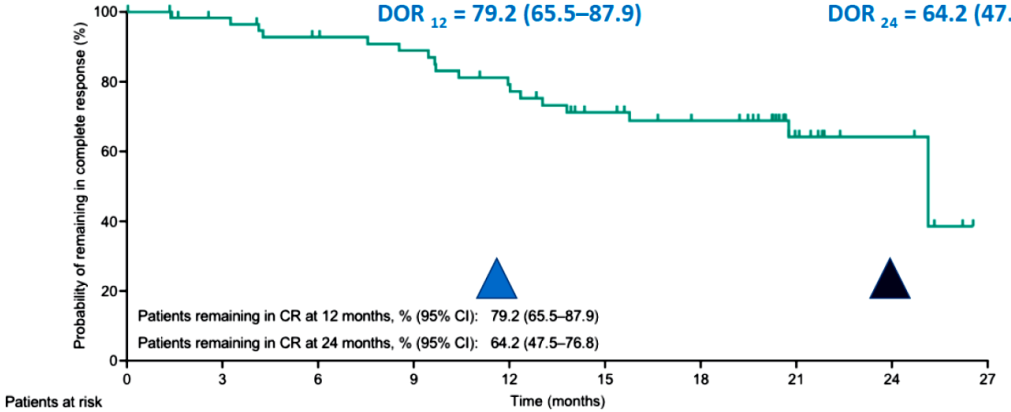
Median **DOR** was **17.3 months** (95% CI, 9.7–26.5)



Patients at risk

LBCL	99	68	53	50	47	44	37	17	8	2

Duration of Complete Response

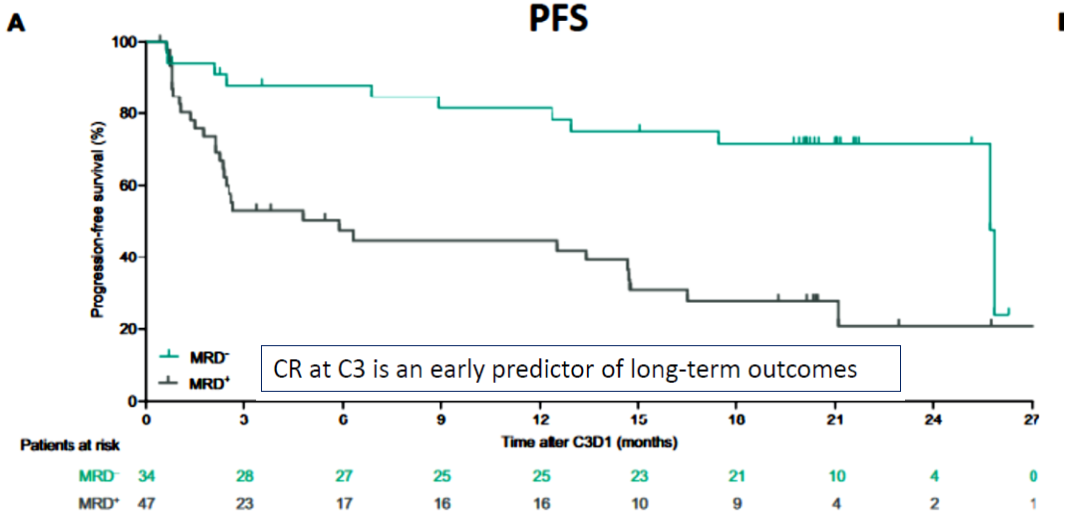


Patients at risk

LBCL	63	54	49	46	40	32	27	12	6	0

An estimated **64.2%** of complete responders remained in **CR at 24 months**

PFS

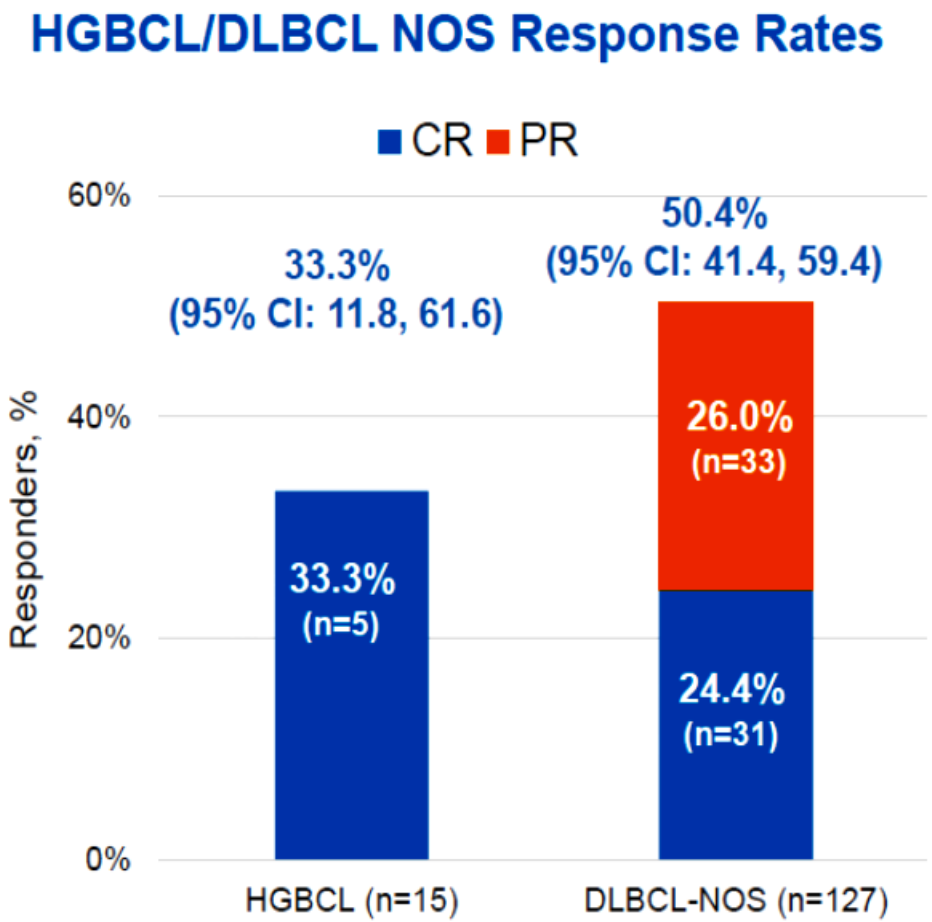


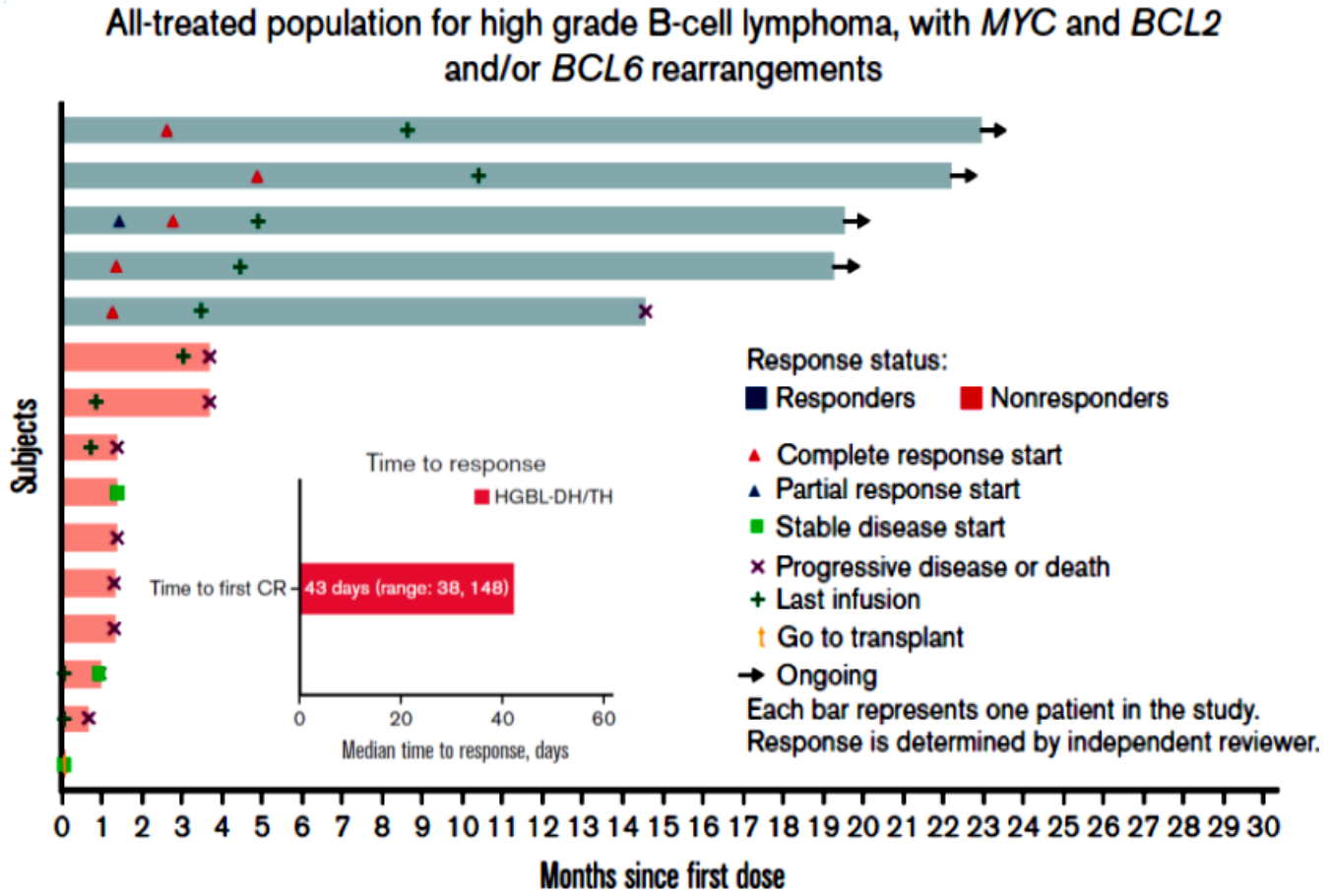
Patients at risk

MRD⁻	34	28	27	25	25	23	21	10	4	0
MRD⁺	47	23	17	16	16	10	9	4	2	1

Thieblemont, *Leukemia 2024*

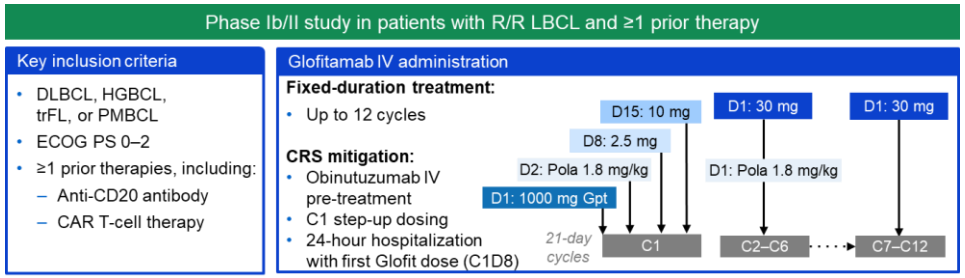
Loncastuximab tesirine activity in HGBCL (LOTIS-2 subset analysis)

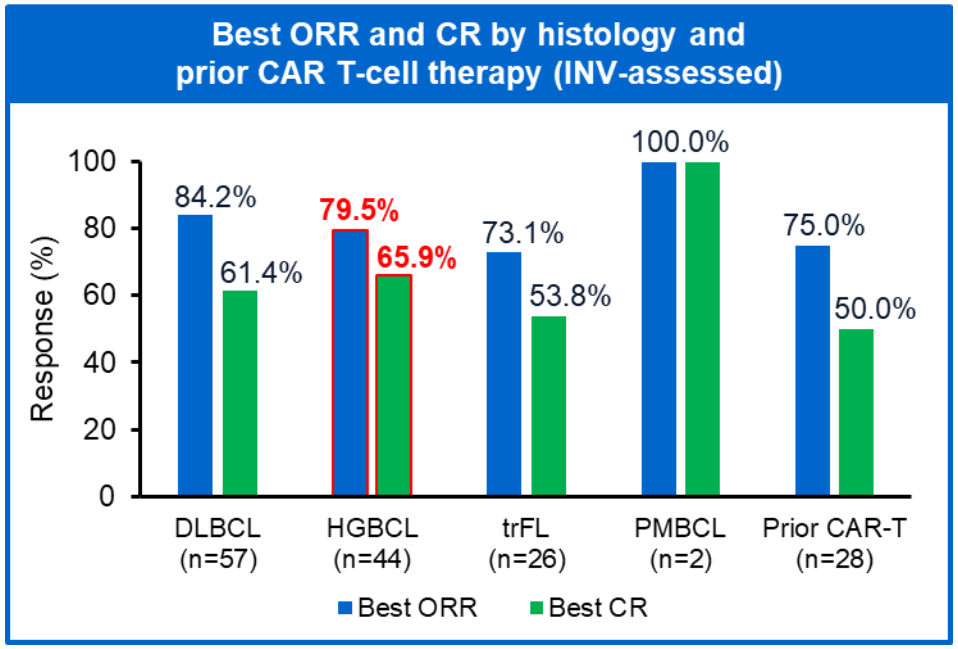


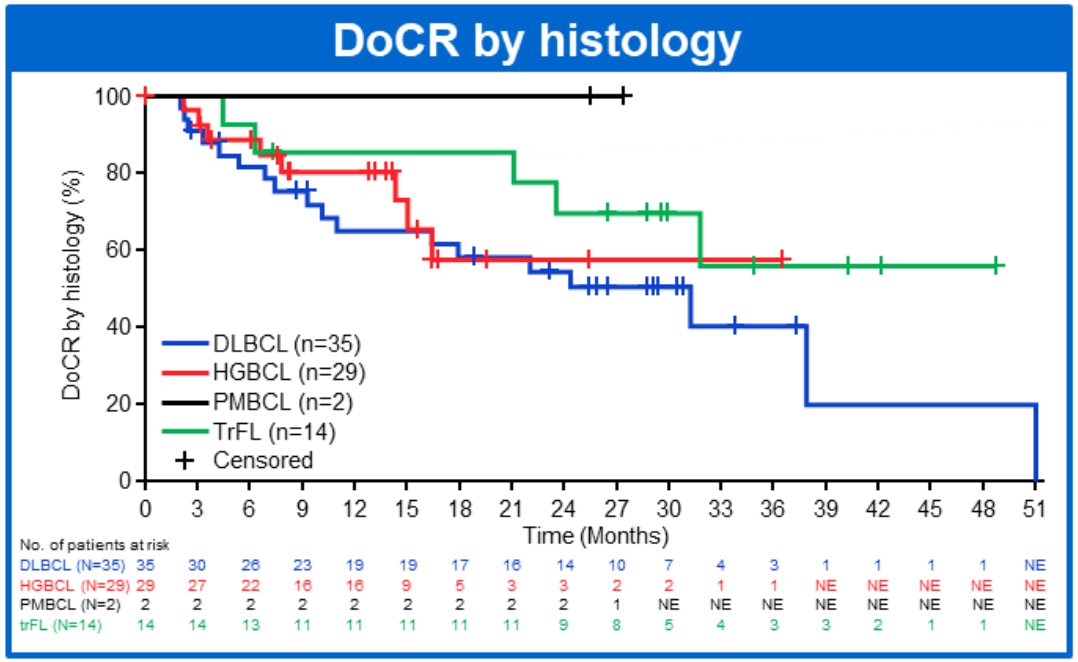


Alderuccio et al. Blood Adv. 2022;6(16):4736-9

Glofitamab in combination with polatuzumab vedotin maintains durable responses and a manageable safety profile in patients with heavily pre-treated relapsed/refractory (R/R) large B-cell lymphoma (LBCL) including high-grade B-cell lymphoma (HGBCL): extended follow-up of a Phase Ib/II study





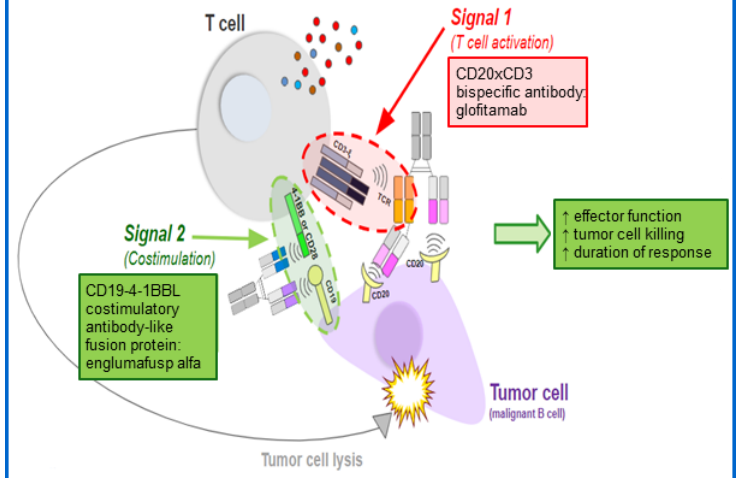


Median DoCR by histology, months (95% CI)	
DLBCL	31.2 (10.9–NE)
HGBCL	NE (15–NE)
trFL	NE (23.5–NE)
PMBCL	NE (NE–NE)

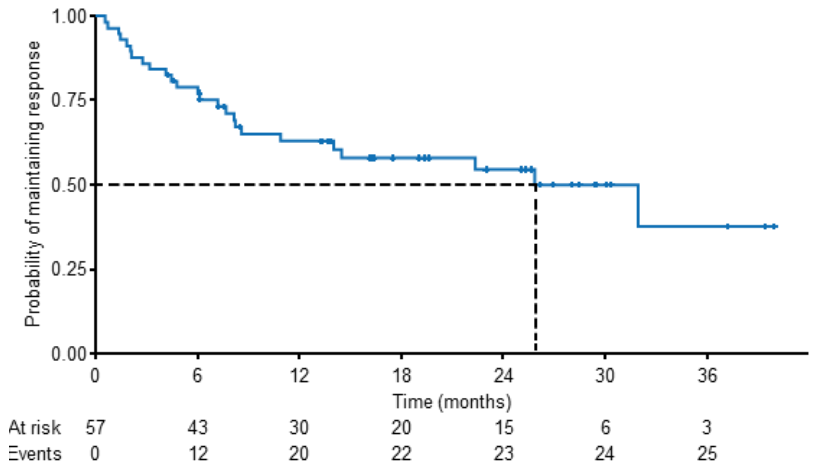
Clinical cut-off date: September 2, 2024.

Englumafusp Alfa (CD19-4-1BBL) Combined with Glofitamab is Safe and Efficacious in Patients with R/R B-NHL: Extended Follow-Up Analysis of the Dose-Escalation Part of Phase I Trial BP41072

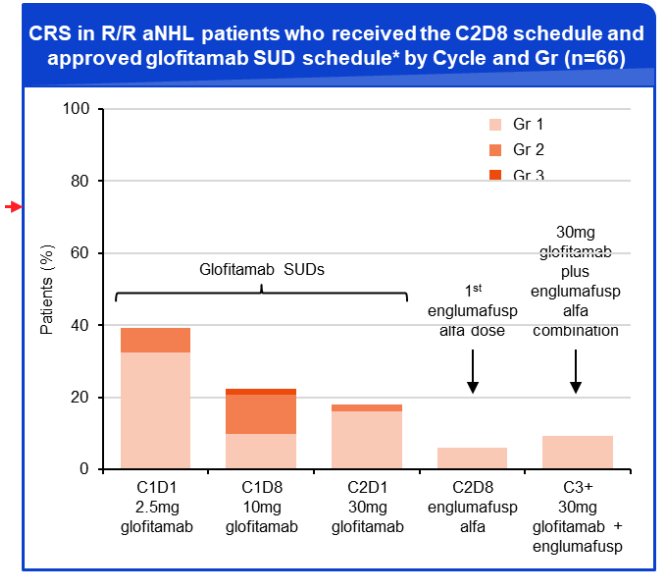
Englumafusp alfa mechanism of action[3]



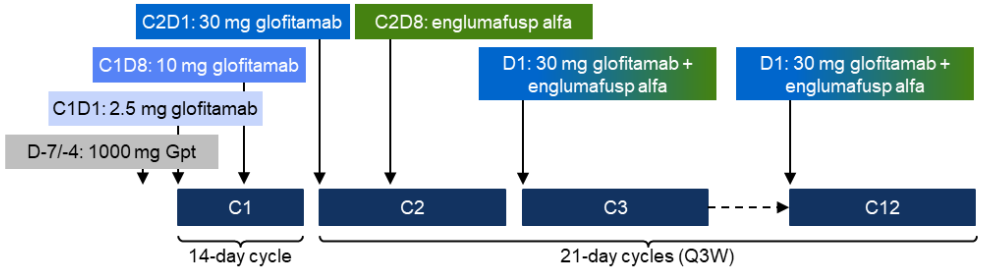
DOR* in R/R aNHL patients (C2D8 schedule)#



CRS in R/R aNHL patients who received the C2D8 schedule and approved glofitamab SUD schedule* by Cycle and Gr (n=66)

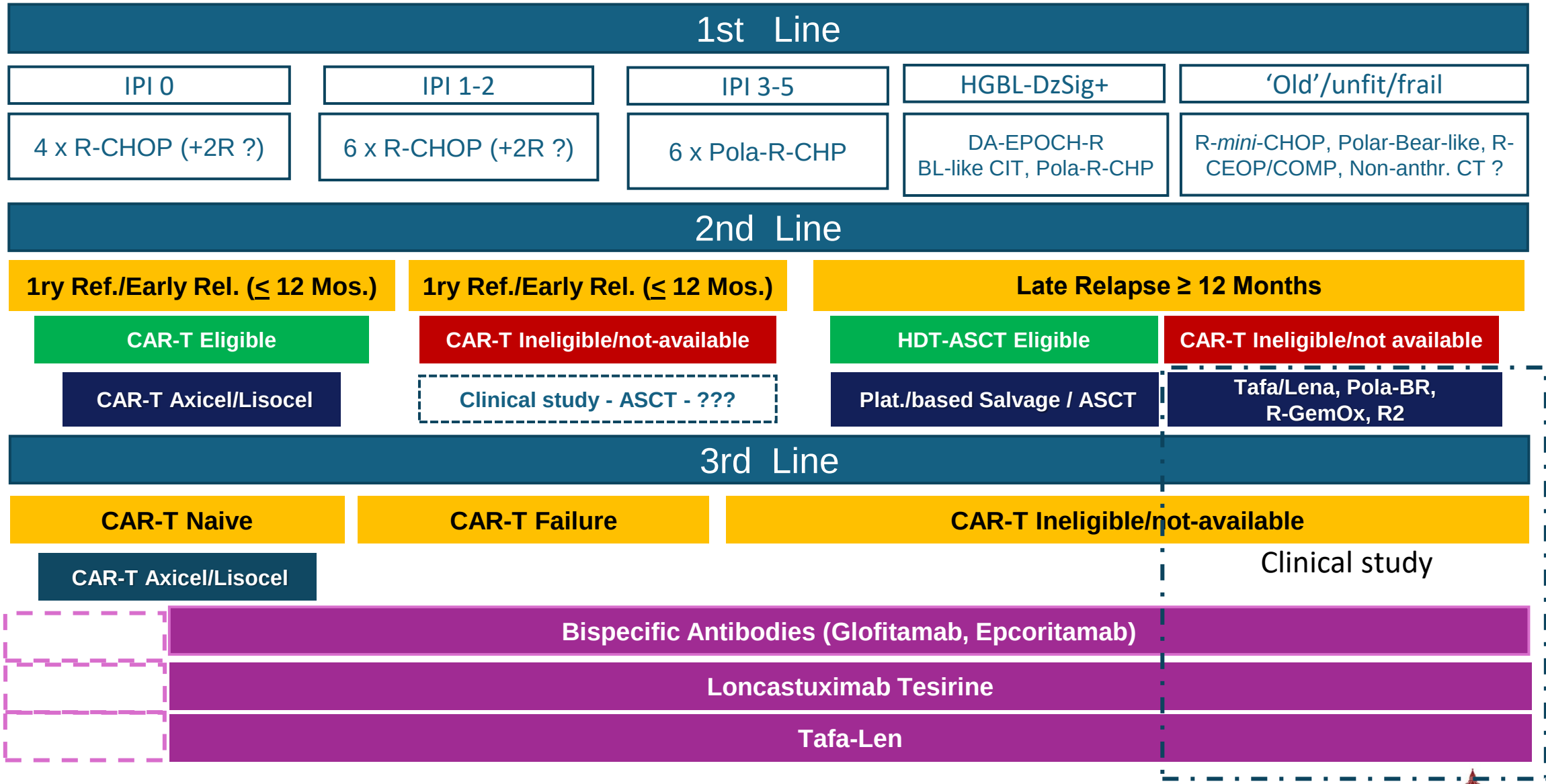


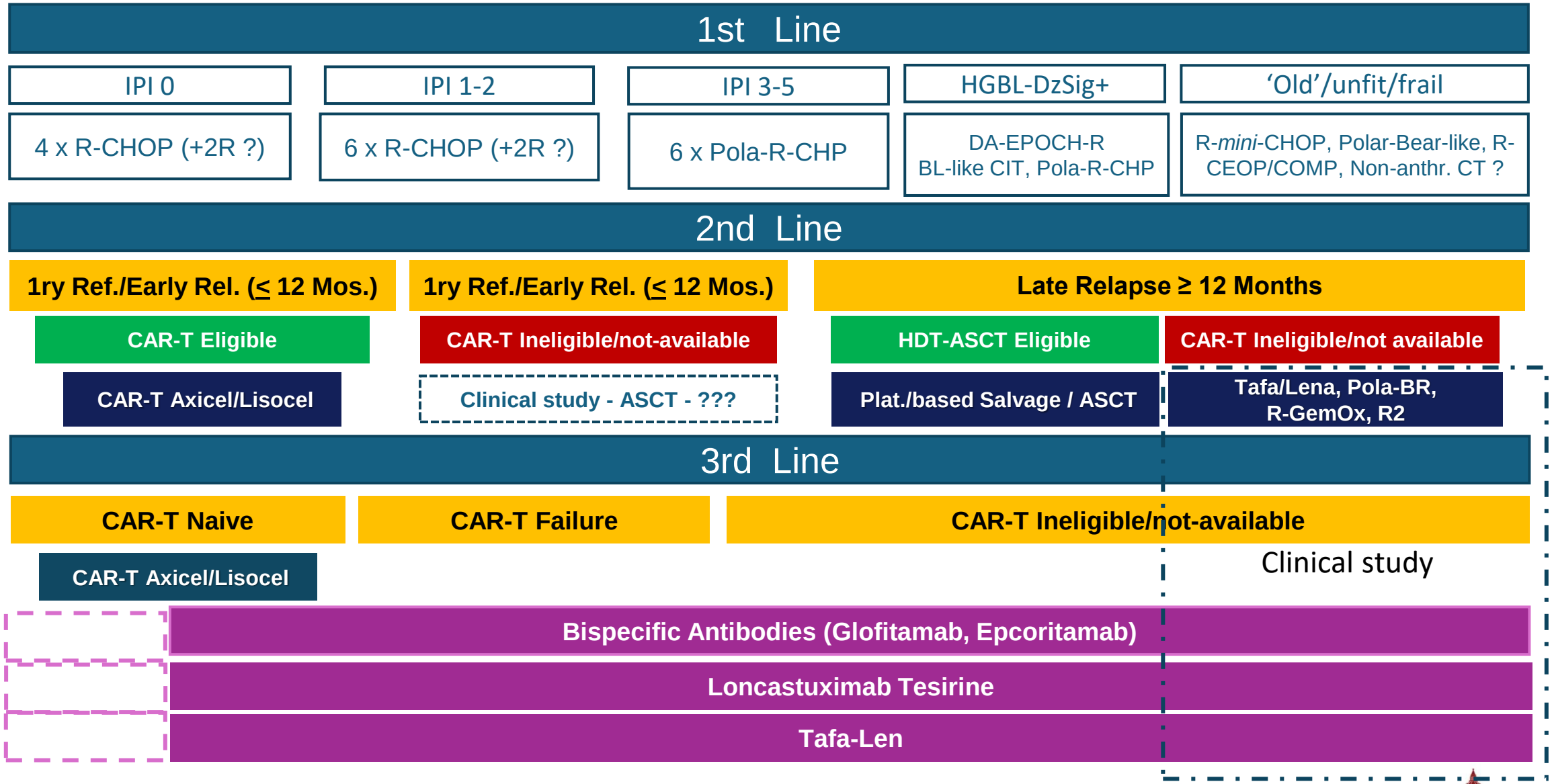
C2D8 englumafusp alfa dosing schedule at escalating dose levels of 0.36–75 mg*



n (%), C2D8 schedule	BOR	CMR	mDOR (95% CI)
R/R aNHL (n=83)*	**57 (68.6)**	**47 (56.6)**	**25.9 months (7.2, NE)**
3L+ (n=70)	47 (67.2)	37 (52.9)	14.3 months (8.2, 32.0)
2L (n=13)	**10 (76.9)**	**10 (76.9)**	**NE (NE, NE)**
Prior CAR-T (n=42)‡	27 (64.4)	20 (47.6)	14 months (6.1, NE)
No prior CAR-T (n=41)§	**30 (73.2)**	**27 (65.9)**	**32 months (14.5, NE)**

32/57 (56.1%) responders in response at data cut-off*

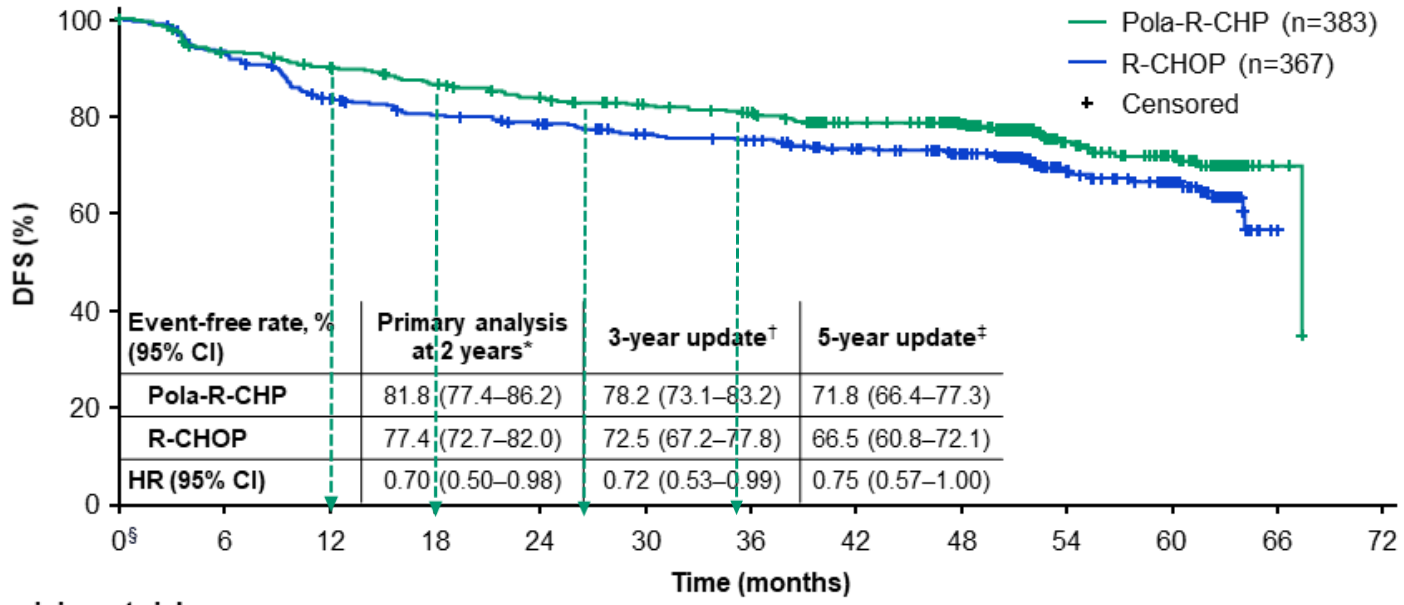

1st Line
IPI 0
IPI 1-2
IPI 3-5
HGBL-DzSig+
'Old'/unfit/frail
4 x R-CHOP (+2R ?)
6 x R-CHOP (+2R ?)
6 x Pola-R-CHP
DA-EPOCH-R
BL-like CIT, Pola-R-CHP
R-mini-CHOP, Polar-Bear-like, R-CEOP/COMP, Non-anthr. CT ?
2nd Line
1ry Ref./Early Rel. (≤ 12 Mos.)
1ry Ref./Early Rel. (≤ 12 Mos.)
Late Relapse ≥ 12 Months
CAR-T Eligible
CAR-T Ineligible/not-available
HDT-ASCT Eligible
CAR-T Ineligible/not available
CAR-T Axicel/Lisocel
Clinical study - ASCT - ???
Plat./based Salvage / ASCT
Tafa/Lena, Pola-BR, R-GemOx, R2
3rd Line
CAR-T Naive
CAR-T Failure
CAR-T Ineligible/not-available
CAR-T Axicel/Lisocel
Clinical study
Bispecific Antibodies (Glofitamab, Epcoritamab)
Loncastuximab Tesirine
Tafa-Len



A. Pinto (2025 - Personal view)

Complete remission obtained after Pola-R-CHP treatment is maintained with 5-year follow-up

DFS (DoCR) in the global ITT population



Event-free rate, % (95% CI)	Primary analysis at 2 years*	3-year update†	5-year update‡
Pola-R-CHP	81.8 (77.4–86.2)	78.2 (73.1–83.2)	71.8 (66.4–77.3)
R-CHOP	77.4 (72.7–82.0)	72.5 (67.2–77.8)	66.5 (60.8–72.1)
HR (95% CI)	0.70 (0.50–0.98)	0.72 (0.53–0.99)	0.75 (0.57–1.00)

Patients remaining at risk

Pola-R-CHP	383	347	333	317	301	286	277	251	222	105	79	3	NE
R-CHOP	367	336	295	279	268	253	247	230	206	98	72	NE	NE

Complete remissions are durable and sustained with longer follow-up.

*Data cut-off: June 28, 2021; †Data cut-off: June 15, 2022; ‡Data cut-off: July 5, 2024; §CR assessment occurred at the 0-month timepoint.
CR, complete remission; DFS, disease-free survival; DoCR, duration of complete remission.

Salles G et al, Oral Presentation ASH 2024 (abstract #469).

Epcoritamab in aggressive LBCL

Dose escalation

Dose expansion data cutoff: April 21, 2023
Median follow-up: 25.1 mo

B-NHL:
- ✓ No DLTs
- ✓ MTD not reached
- ✓ RP2D identified
- ✓ Manageable safety profile
- ✓ Encouraging antitumor activity

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

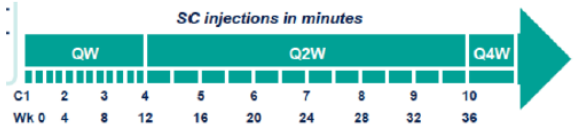
Step-up dosing[a]

Epcoritamab SC RP2D 48 mg
QW C1–3, Q2W C4–9, Q4W C10+

→ **Treatment until PD or unacceptable toxicity**

→ **LBCL Cohort N=157**
DLBCL, HGBCL, PMBCL, and FL Gr3B

- To ensure patient safety and better characterize CRS, inpatient monitoring was required at first full dose for 24 h in this part of the study
- **Primary endpoint:** ORR by Investigator Review Committee (IRC)
- **Key secondary endpoints:** DOR, TTR, PFS, OS, CR rate, and safety/tolerability

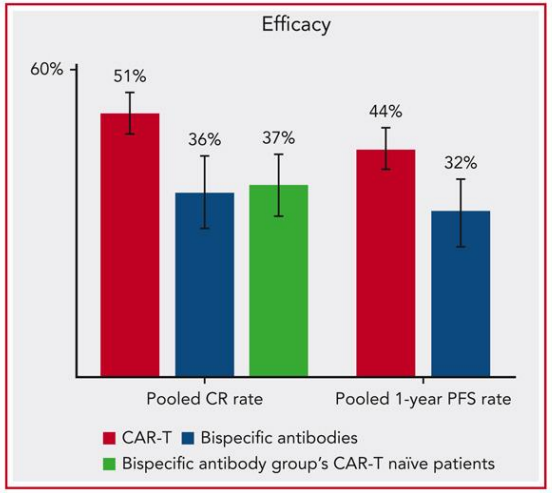


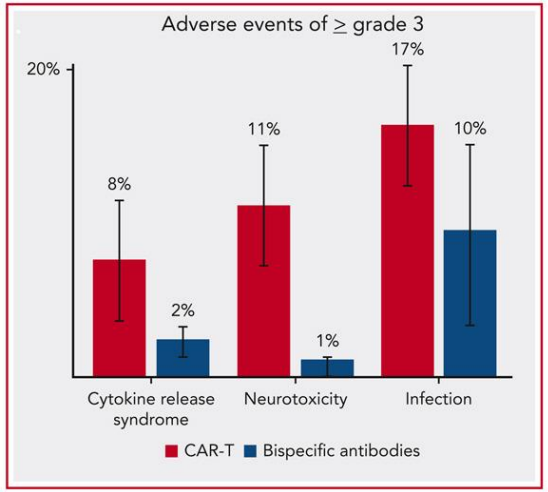
[a] C1D1 0.16 mg, C1D8 0.8 mg, C1D15 48 mg

Thieblemont C., J Clin Oncol, 2022, 41:2238-2247.

Comparison of CAR T-Cell Therapy and Bispecific Antibodies As Third-Line or Later Treatment for Diffuse Large B-Cell Lymphoma (DLBCL): A Meta-Analysis

CAR-T cell therapy: 10 studies including 742 patients
Bispecific antibodies: 6 studies including 605 patients





Conclusion: In patients with relapsed/refractory DLBCL, CAR-T cell therapy has demonstrated superior efficacy compared to bispecific antibodies, although with a higher incidence of severe adverse effects.

*Kim et al. DOI: 10.1182/**blood**.2023023419*

blood Visual Abstract