The front lines of the near future (one, one hundred, one thousand): can we consider differentiated choices based on “different” patients?

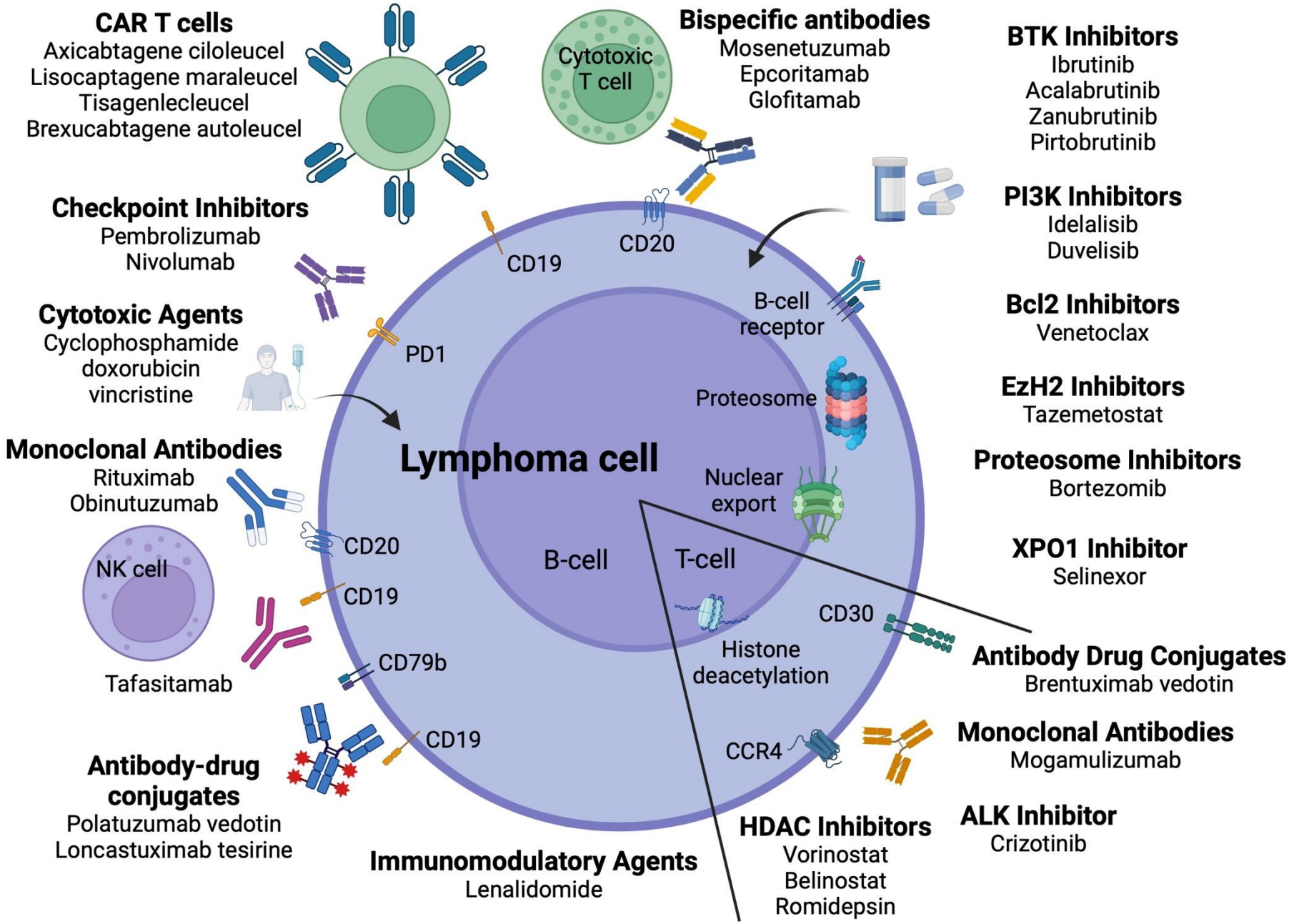
Stephen M. Ansell, MD, PhD
Dorotha W. and Grant L. Sundquist Professor in Hematologic Malignancies Research
Chair, Division of Hematology
Deputy Director, Mayo Clinic Comprehensive Cancer Center

Disclosures for Stephen Ansell, MD, PhD

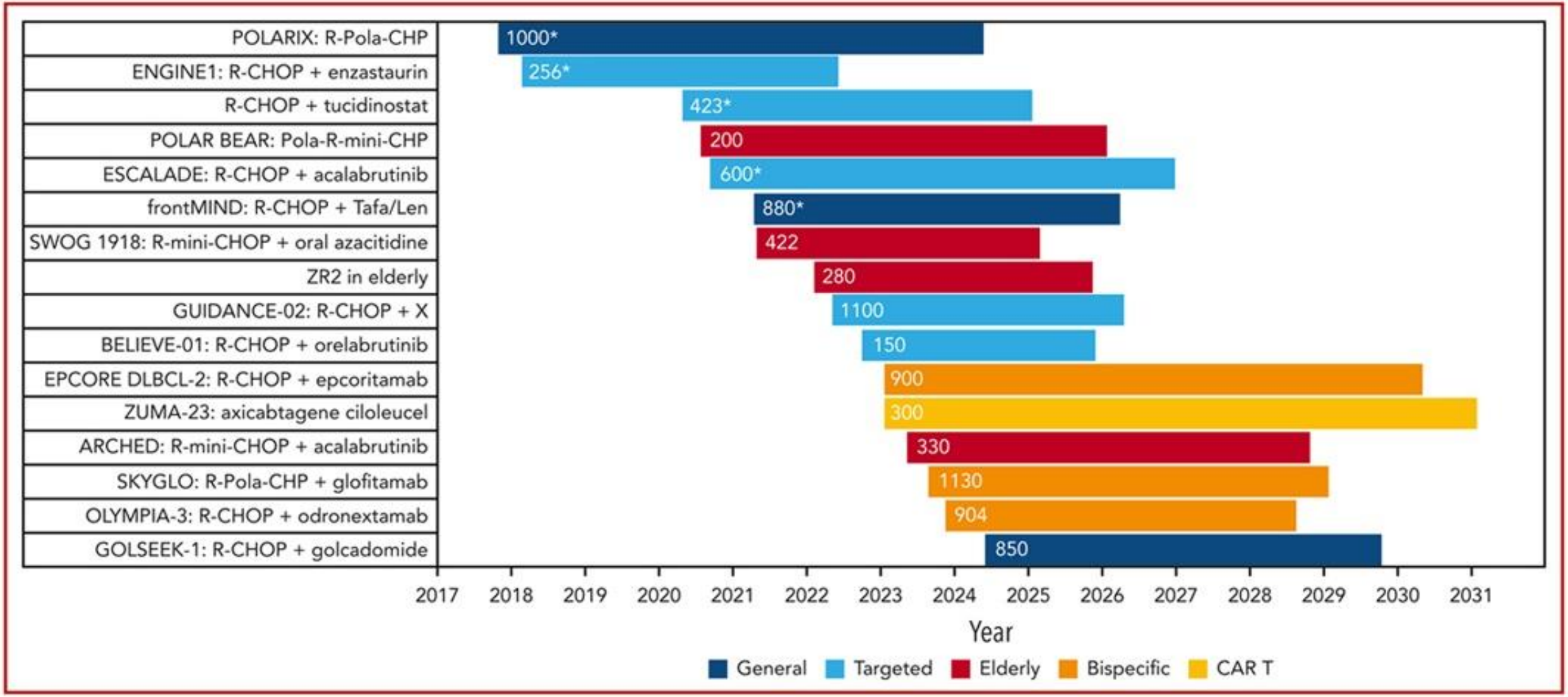
In compliance with ACCME policy, Mayo Clinic requires the following disclosures to the activity audience:

Research Support/P.I.	PI – BMS, Takeda, Affimed, Regeneron, AI Therapeutics, Pfizer, AstraZeneca, ADC Therapeutics for clinical trials
Employee	N/A
Consultant	N/A
Major Stockholder	N/A
Speakers' Bureau	N/A
Scientific Advisory Board	N/A

N/A = Not Applicable (no conflicts listed)


CAR T cells
Axicabtagene ciloleucel
Lisocaptagene maraleucel
Tisagenlecleucel
Brexucabtagene autoleucel
Cytotoxic T cell
Bispecific antibodies
Mosenetuzumab
Epcoritamab
Glofitamab
BTK Inhibitors
Ibrutinib
Acalabrutinib
Zanubrutinib
Pirtobrutinib
PI3K Inhibitors
Idelalisib
Duvelisib
Checkpoint Inhibitors
Pembrolizumab
Nivolumab
CD19
CD20
B-cell receptor
Bcl2 Inhibitors
Venetoclax
Cytotoxic Agents
Cyclophosphamide
doxorubicin
vincristine
PD1
Proteosome
EzH2 Inhibitors
Tazemetostat
Lymphoma cell
Proteosome Inhibitors
Bortezomib
Monoclonal Antibodies
Rituximab
Obinutuzumab
Nuclear export
B-cell
T-cell
XPO1 Inhibitor
Selinexor
CD20
NK cell
CD19
CD30
Histone deacetylation
Antibody Drug Conjugates
Brentuximab vedotin
Tafasitamab
CD79b
CD19
CCR4
Monoclonal Antibodies
Mogamulizumab
Antibody-drug conjugates
Polatuzumab vedotin
Loncastuximab tesirine
HDAC Inhibitors
Vorinostat
Belinostat
Romidepsin
ALK Inhibitor
Crizotinib
Immunomodulatory Agents
Lenalidomide

Ongoing frontline trials in DLBCL



Qualls et al. Blood (2025) 145 (2): 176–189.

Pivotal phase 3 clinical trials in first-line LBCL treatment

Name	Trial	Enrollment goal	Patients	Eligible histologies	Lead-in treatment permitted?	Primary outcome
General						
POLARIX[2,3] (NCT03274492)	Pola-R-CHP vs R-CHOP (Double Blind)	1000	Age 18-80 y IPI 2-5 ECOG 0-2	Included: DLBCL, HGBCL, TCHRLBL, EBV-positive, ALK-positive, HHV8-positive Excluded: PMBCL, FL3B, t-iNHL, GZL, PEL, leg type, CNSL, RT	Steroid prephase only	PFS (investigator)
frontMIND[4] (NCT04824092)	R-CHOP + tafasitamab + lenalidomide vs R-CHOP (Double Blind)	880	Age 18-80 y IPI 3-5 (if >60 y) aaIPI 2-3 (if ≤60 y) Diagnosis to treatment interval <28 y ECOG 0-2	Included: DLBCL, HGBCL, t-iNHL, FL3B, TCHRLBL, EBV-positive, ALK-positive, HHV8-positive Excluded: PMBCL, GZL, PEL, leg type, CNSL, RT	Steroid prephase only	PFS (investigator)
SKYGLO[5] (NCT06047080)	Pola-R-CHP + glofitamab vs Pola-R-CHP (Open Label)	1130	Age 18-80 y IPI 2-5 (IPI 2 capped at 35%) ECOG 0-2	Included: LBCL (further detail not specified) Excluded: FL3B, t-iNHL, PMBCL, GZL, CNSL, Primary testis, PEL, leg type	Steroid prephase only	PFS (IRC)
OLYMPIA-3[6] (NCT06091865)	R-CHOP + odronextamab vs R-CHOP (Open Label)	904	Age ≤75 y IPI 2-5 (part 2)	Included: LBCL, (further detail not specified) Excluded: CNSL	None	PFS (IRC)
EPCORE DLBCL-2[7] (NCT05578976)	R-CHOP + epcoritamab vs R-CHOP (Open Label)	900	Age 18-79 y IPI 2-5 (IPI 2 capped at 35%) ECOG 0-2	Included: DLBCL, HGBCL (DH/TH), TCHRLBCL, EBV-positive, FL3B, tFL Excluded: HGBCL-NOS, PMBCL, BL, Plasmablastic, HHV8-positive	Steroid/ vincristine prephase only	PFS (IRC) in patients with IPI 3-5
ZUMA-23[8] (NCT05605899)	Axicabtagene ciloleucel vs R-CHOP or R-EPOCH (Open Label)	300	Age ≥18 y IPI 4-5	Included: DLBCL or HGBCL, tFL tMZL Excluded: TCHRBCL, CNSL, PMBCL, GZL, BL	Yes (1 cycle R-CHOP or R-EPOCH)	EFS (central) defined as: time to POD, death, new lymphoma Rx, or residual disease at 6 mo
GOLSEEK-1 (NCT06356129)	R-CHOP + golcadomide vs R-CHOP (Double Blind)	850	Age 18-80 y IPI 3-5 (or IPI 1-2 with LDH ≥1.3 × ULN, or single lesion ≥7 cm size)	Included: DLBCL, HGBCL, TCHRLBCL, EBV-positive Excluded: PMBCL, leg-type, FL3B, t-iNHL, ALK-positive, PEL, BL	Not available	PFS (investigator)

Qualls et al. Blood. 2025 Jan 9;145(2):176-189.

Pivotal phase 3 clinical trials evaluating targeted therapies in first-line LBCL treatment

Name	Trial	Enrollment goal	Patients	Eligible histologies	Lead-in treatment permitted?	Primary outcome
R-CHOP ± tucidinostat[9] (NCT04231448)	R-CHOP + tucidinostat vs R-CHOP (double blind)	423	Age 18-80 y IPI 2-4 ECOG 0-2	Included: DLBCL with MYC and BCL2 expression by IHC only Excluded: HGBCL with DH or TH, CNSL, PMBCL, PEL, GZL, leg type, t-iNHL, BL, plasmablastic, HHV8-positive, primary testis	None	EFS: time to POD, relapse, new lymphoma Rx, or death
ESCALADE (ACE-LY-312)[10] (NCT04529772)	R-CHOP + acalabrutinib vs R-CHOP (double blind)	600	Age 18-75 y IPI 1-5 ECOG 0-2	Included: DLBCL (non-GCB by GEP) Excluded: HGBCL, CNSL, PMBCL, RT, t-iNHL	1 cycle R-CHOP before randomization	PFS (IRC)
GUIDANCE-02 (NCT05351346)	R-CHOP-X vs R-CHOP (open label)	1100	Age 18-80 y IPI 2-5 (or IPI 1 with "bulky disease"; bulk definition not available) ECOG 0-2	Included: LBCL Excluded: CNSL, PMBCL	Not available	PFS
BELIEVE-01 (NCT05234684)	R-CHOP + orelabrutinib vs R-CHOP (double blind)	150	Age 18-80 y IPI 2-5 ECOG 0-2	Included: DLBCL, MCD subtype by molecular profiling only Excluded: PMBCL, t-iNHL, CNSL	Steroid prephase only	PFS (IRC) CRR (IRC)
ENGINE-1[11] (NCT03263026)	R-CHOP + enzastaurin vs R-CHOP (double blind)	256	Age ≥18 y IPI 3-5 ECOG 0-2	Included: DLBCL, HGBCL (DH/TH) Excluded: t-iNHL, PMBCL, GZL, BL, CNSL	Steroid prephase only	OS in patients possessing DGM1 biomarker

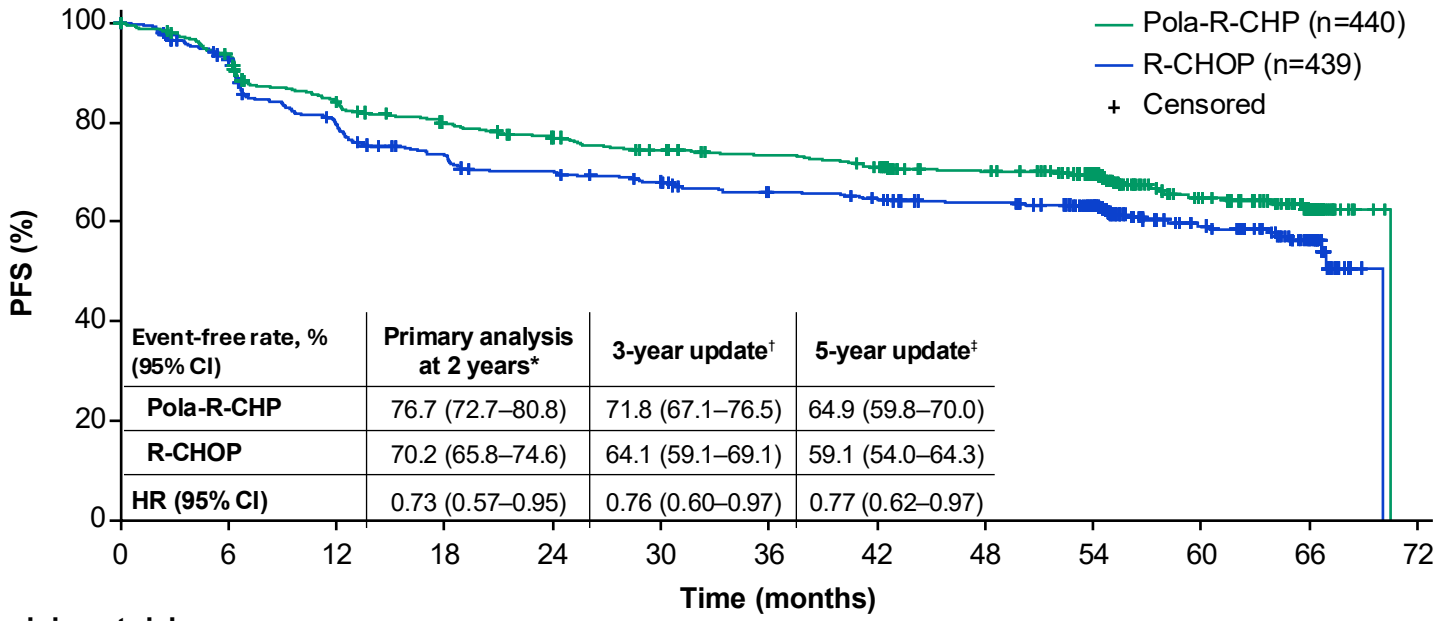
Qualls et al. Blood. 2025 Jan 9;145(2):176-189.

How are new agents going to improve frontline therapy?

1. Additional cytotoxicity to the malignant B-cell – ADCs
2. Target a specific mutation or molecular profile, or inhibit a pathway on which the lymphoma depends – BTK inhibitors, PI3 kinase inhibitors, bcl-2 inhibitors, XPO1 inhibitors
3. Engage the immune system – bispecific antibodies, monoclonal antibodies
4. Disrupt the tumor immune environment - IMiDs, CelMods
5. Replace cytotoxic chemotherapy

1. Polarix: Initial PFS benefit of Pola-R-CHP over R-CHOP is maintained at 5 years

PFS in the global ITT population



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

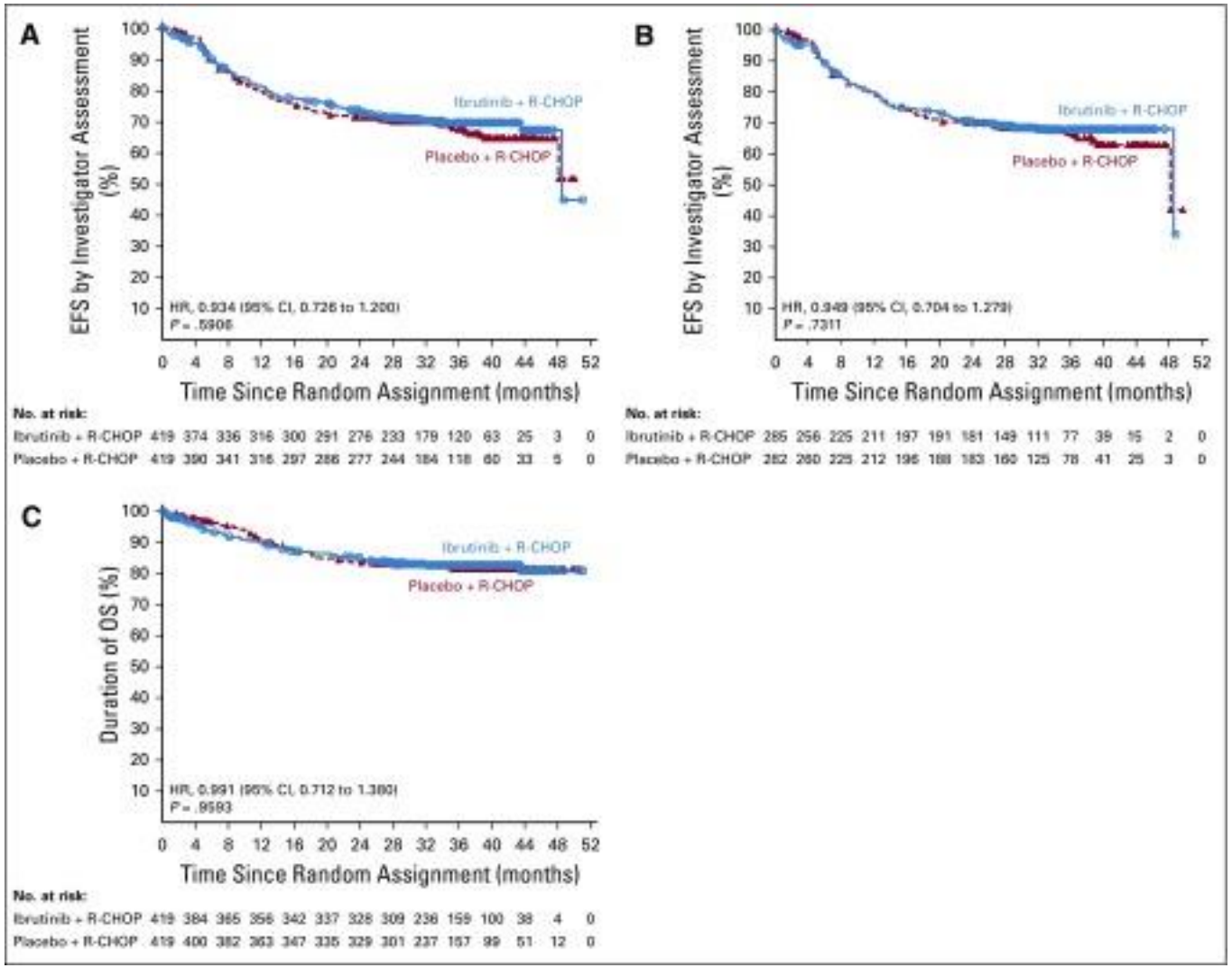
Pola-R-CHP	440	407	357	335	318	303	292	280	258	213	100	56	NE
R-CHOP	439	391	332	302	287	274	258	251	240	192	95	54	NE

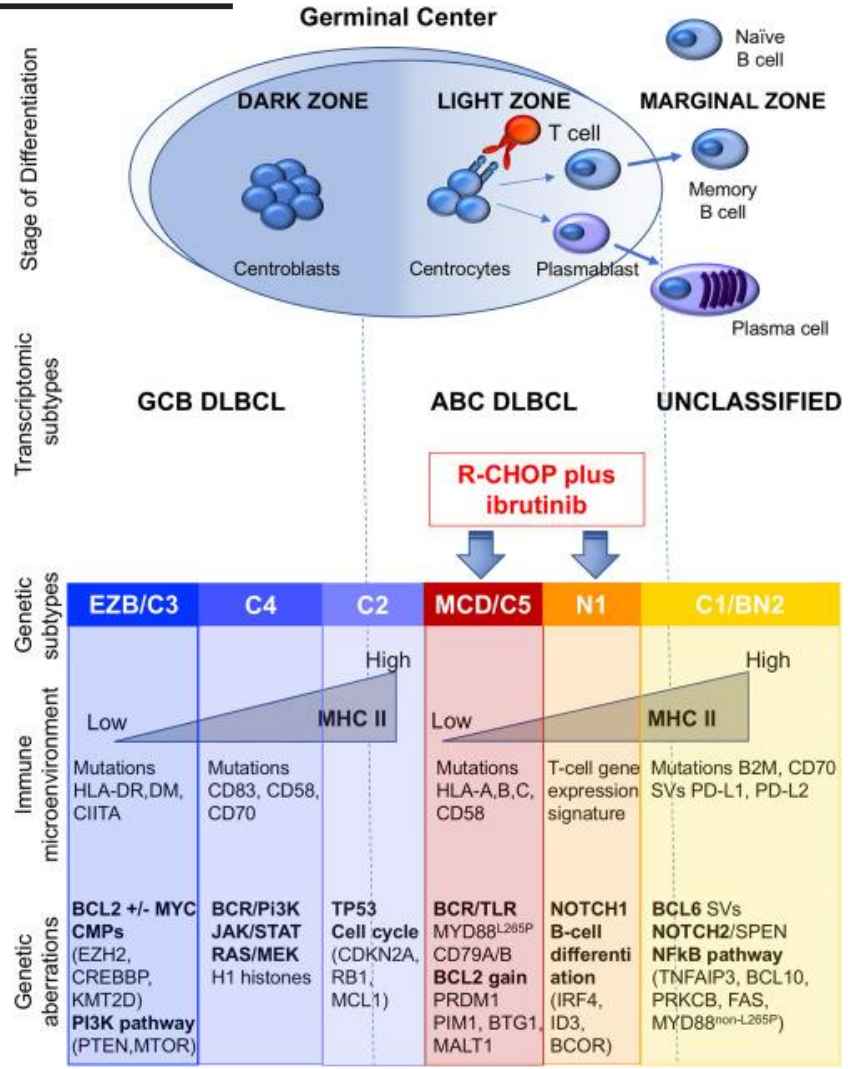
At the 5-year follow up, Pola-R-CHP had a **sustained and significant PFS benefit**, confirming results from the primary analysis of PFS at 2 years of follow up (HR 0.73).[1]

*Data cut-off: June 28, 2021; †Data cut-off: June 15, 2022; ‡Data cut-off: July 5, 2024.
CI, confidence interval; HR, hazard ratio; NE, not evaluable.

1. Tilly H, et al. N Eng J Med 2022;386:351–63.
Salles et al. ASH 2024;Abstract 469.

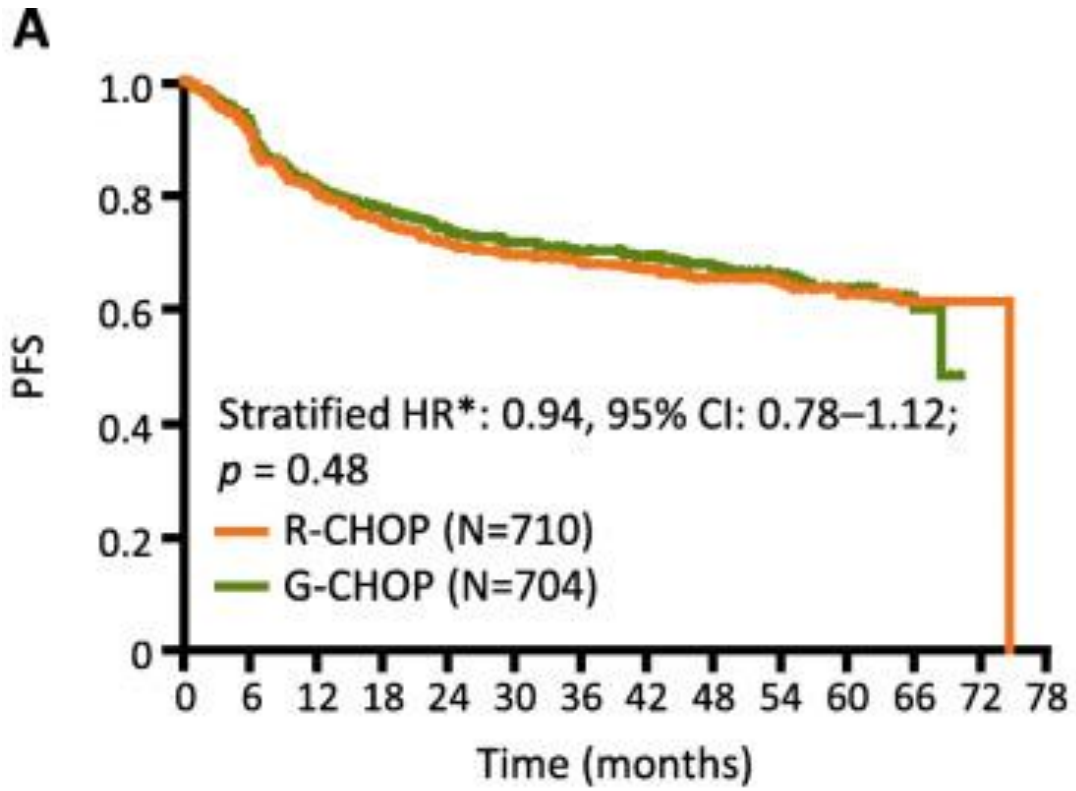
2. Phoenix: Effect of BTKi with R-CHOP chemotherapy in genetic subtypes of DLBCL





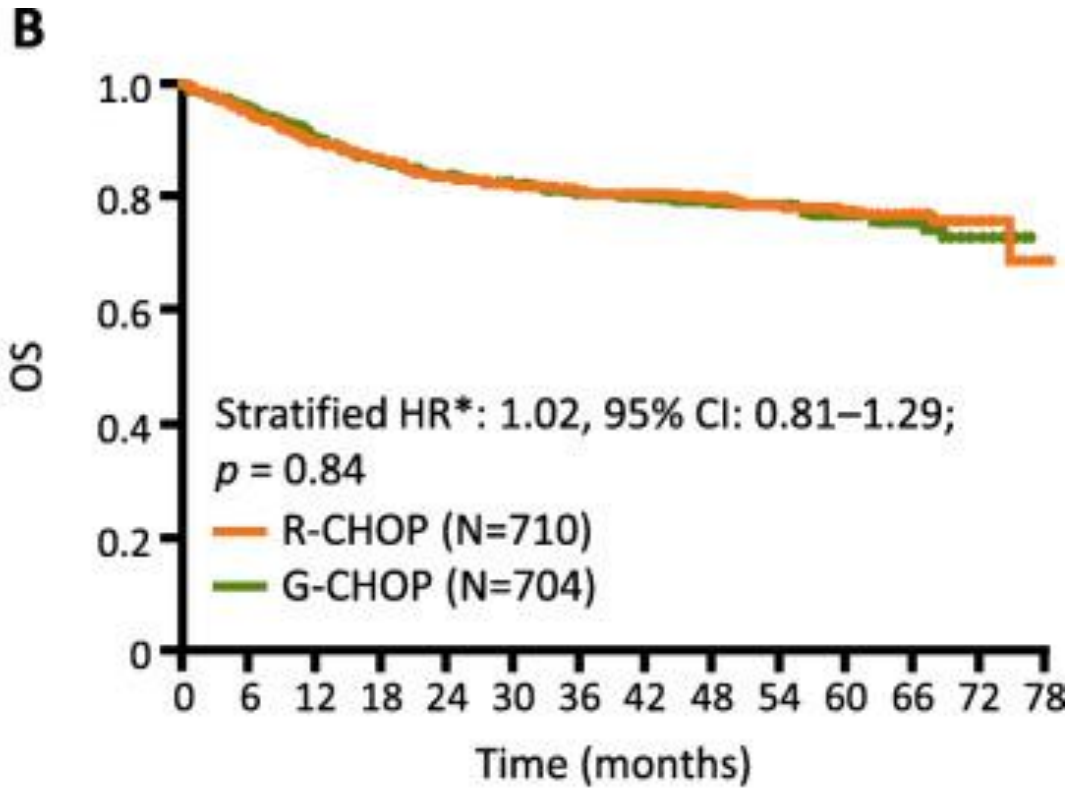
Younes et al. J Clin Oncol. 2019 May 20;37(15):1285-1295.
Mondello, Ansell. Cancer Cell. 2021 Dec 13;39(12):1570-1572.

3. GOYA: Obinutuzumab or rituximab plus CHOP in patients with previously untreated diffuse large B-Cell lymphoma



No. of patients at risk:

R-CHOP	710	613	531	495	462	434	408	379	240	124	71	27	1	–
G-CHOP	704	621	542	508	475	449	430	389	263	137	85	34	–	–

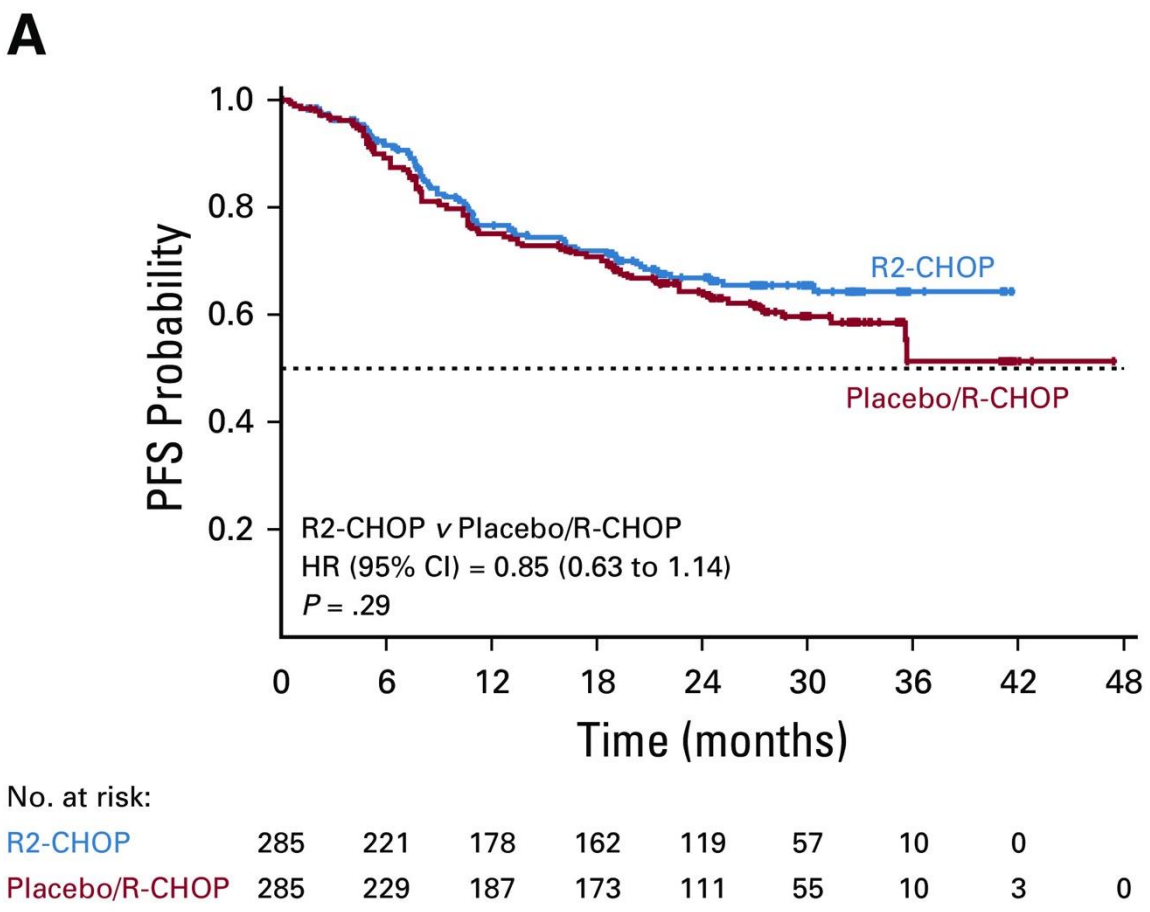


No. of patients at risk:

R-CHOP	710	656	612	582	553	540	522	493	342	212	136	89	26	1
G-CHOP	704	655	614	582	564	546	529	499	354	217	141	81	26	–

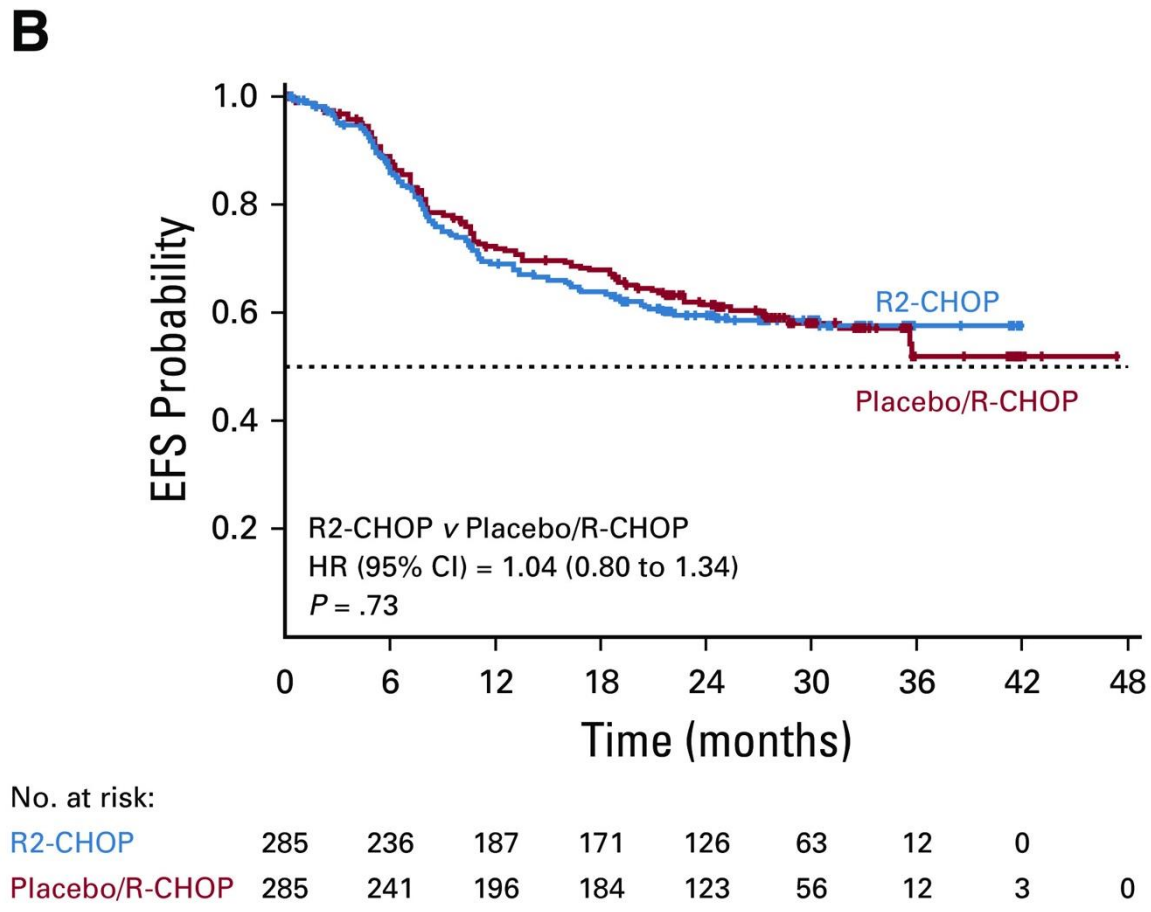
Sehn et al. J Hematol Oncol. 2020 Jun 6;13(1):71.

4. ROBUST: Lenalidomide Plus R-CHOP Versus Placebo Plus R-CHOP in Untreated Patients With ABC-Type Diffuse Large B-Cell Lymphoma



No. at risk:

R2-CHOP	285	221	178	162	119	57	10	0	
Placebo/R-CHOP	285	229	187	173	111	55	10	3	0

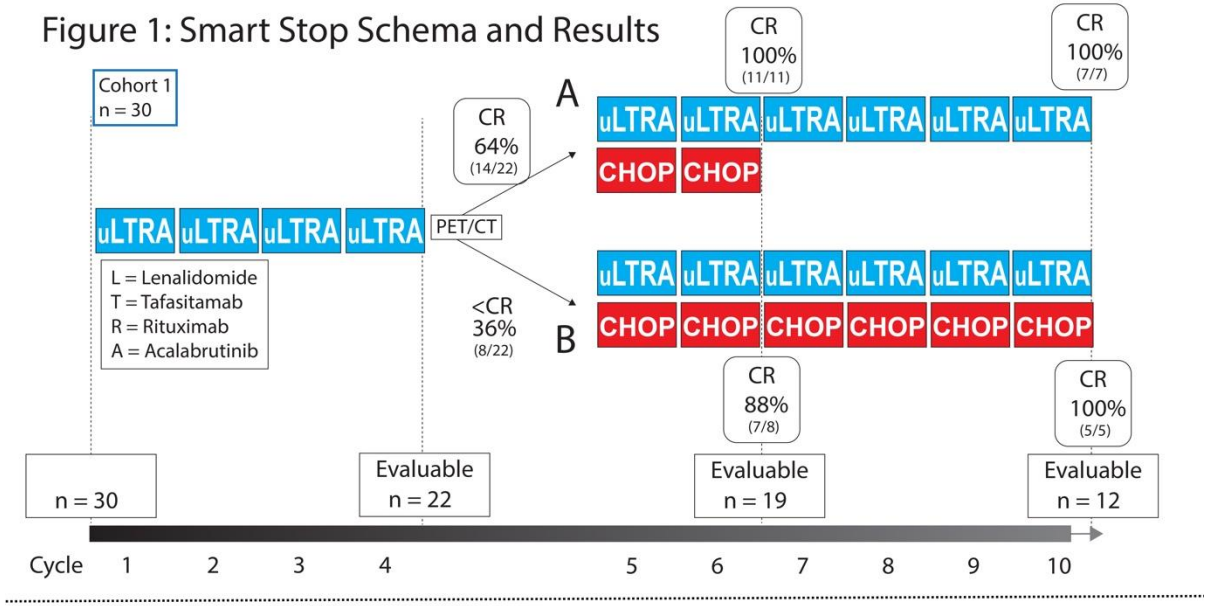


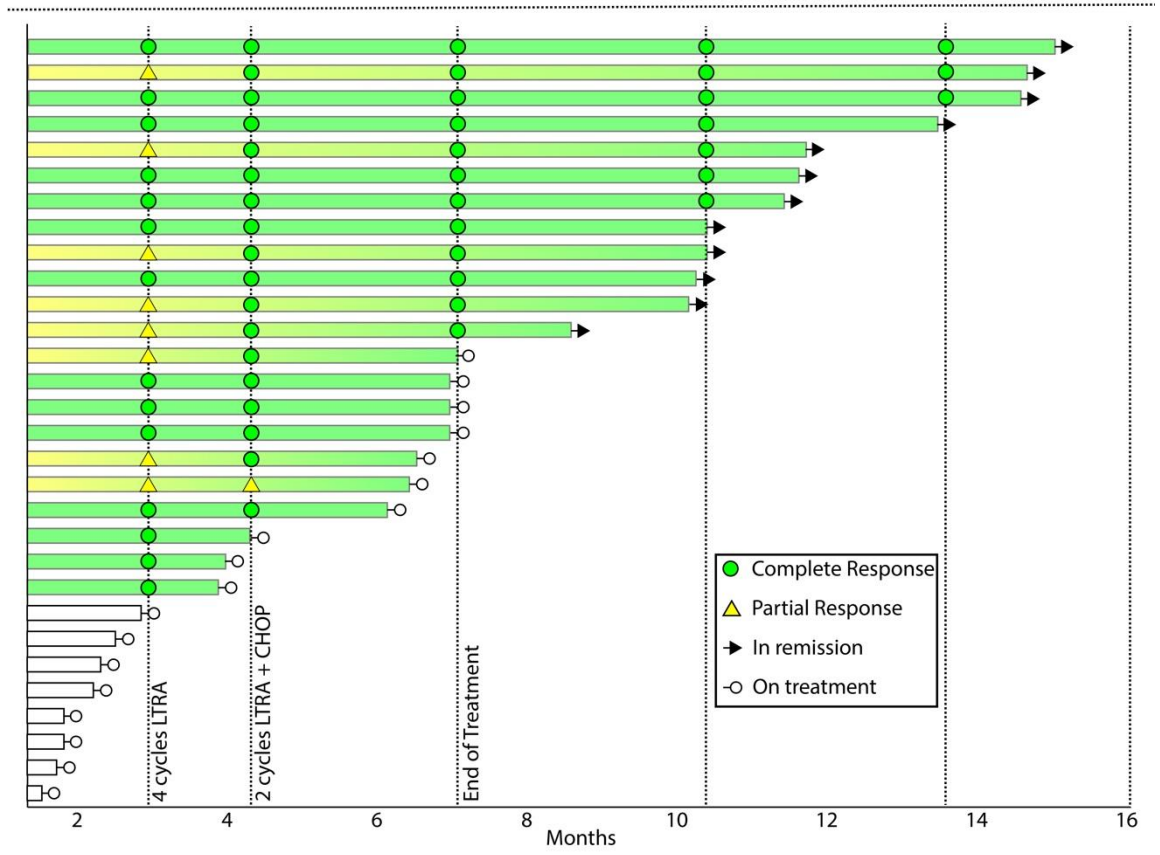
No. at risk:

R2-CHOP	285	236	187	171	126	63	12	0	
Placebo/R-CHOP	285	241	196	184	123	56	12	3	0

Nowakowski et al. J Clin Oncol. 2021 Apr 20;39(12):1317-1328.

5. Smart Stop: Lenalidomide, Tafasitamab, Rituximab, and Acalabrutinib Alone and with Chemotherapy for DLBCL



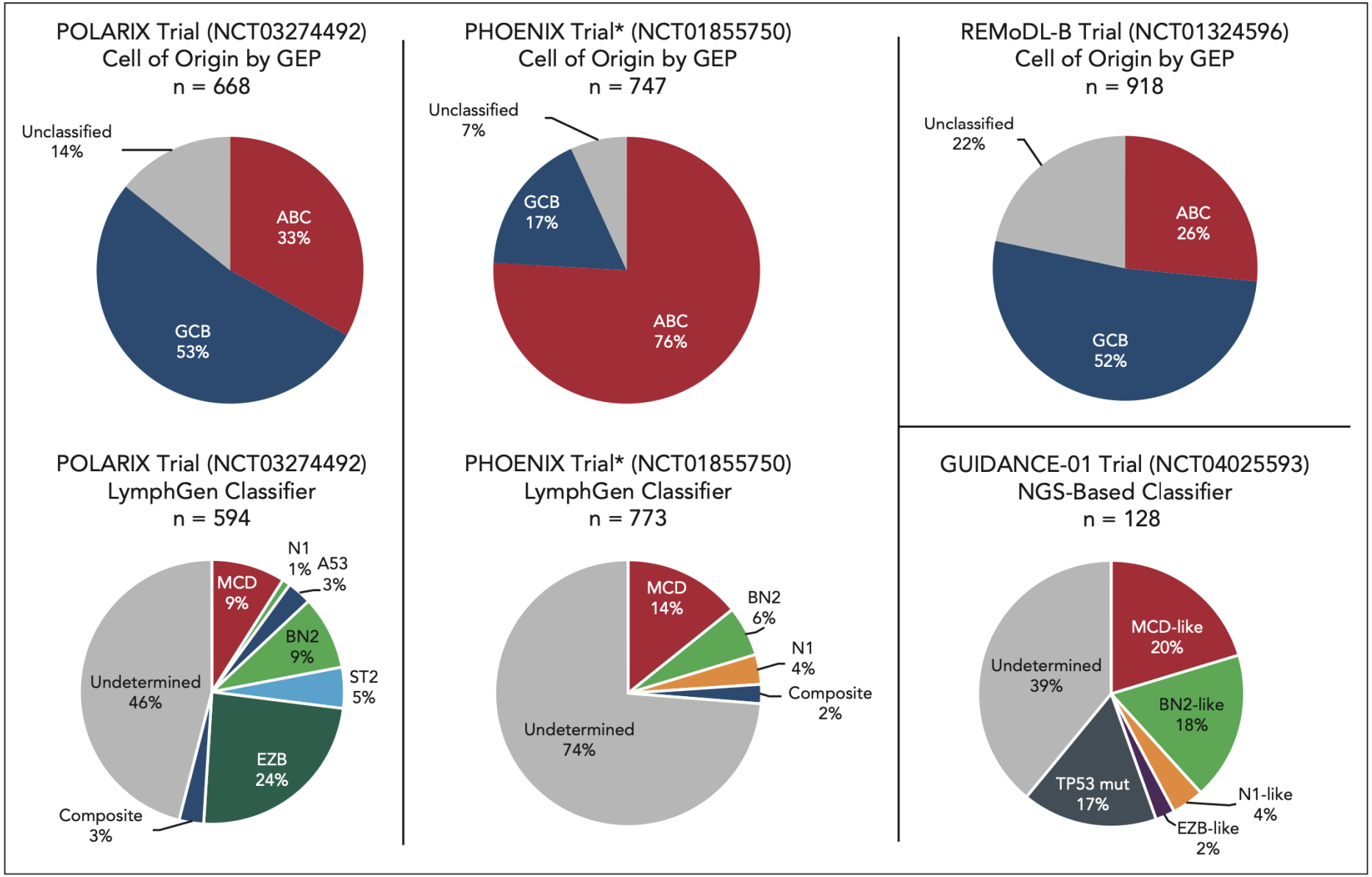


Westin et al. **Blood (2023) 142 (Supplement 1): 856.**

Questions that may influence which novel agents are included

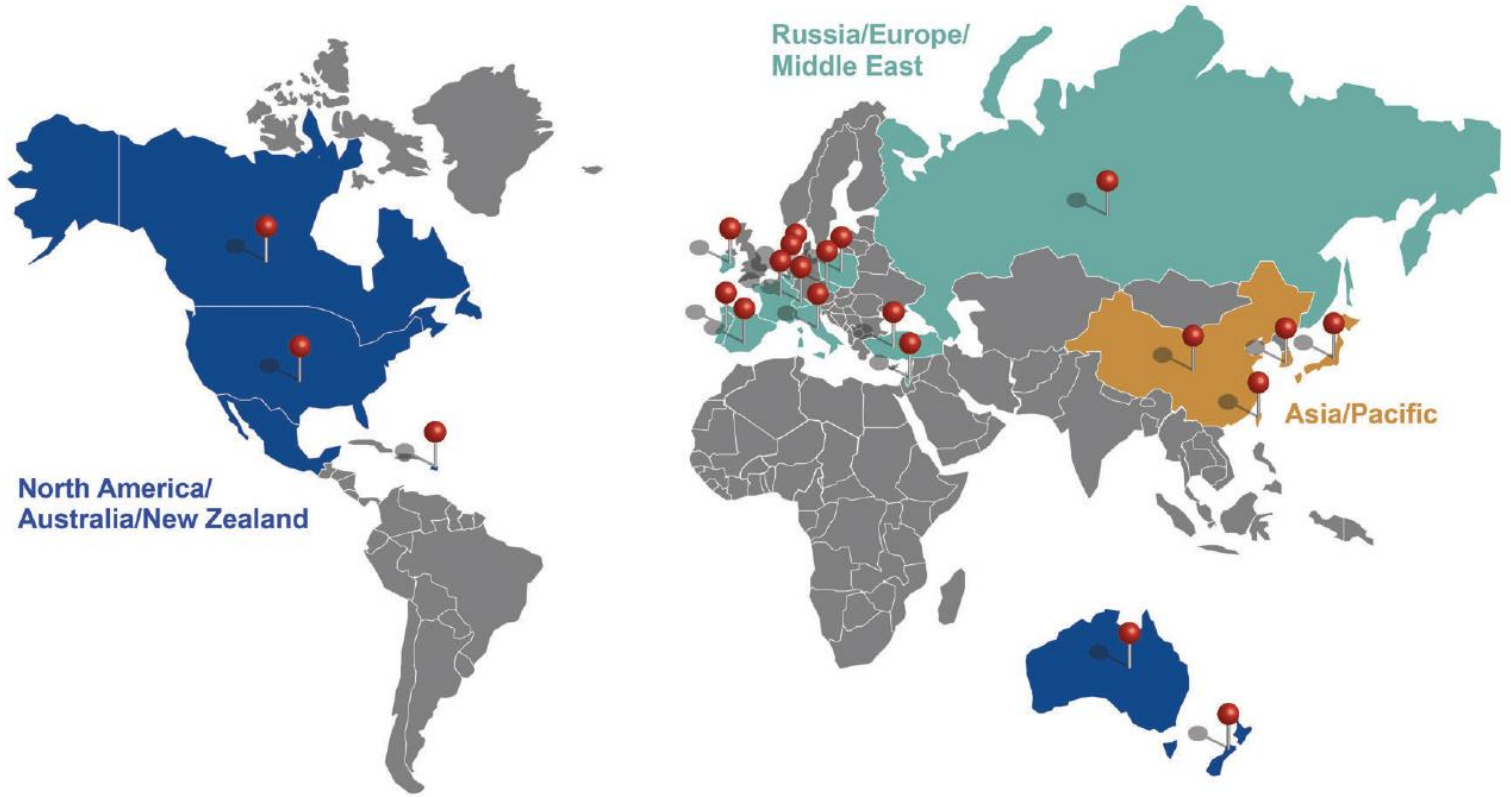
1. Do you believe lymphoma cells/lymphoma subtype are vulnerable to a specific inhibitor or more cytotoxic agents?
2. Can you measure a biomarker on a timeous fashion and does your geographical population contain enough patients?
3. Do you think the immune system can be appropriately activated?
4. Does timing of the new agent matter?
5. Are toxicities from the combination likely to impact the results?

1. Are lymphoma cells/lymphoma subtypes vulnerable?



Qualls et al. Blood (2025) 145 (2): 176–189.

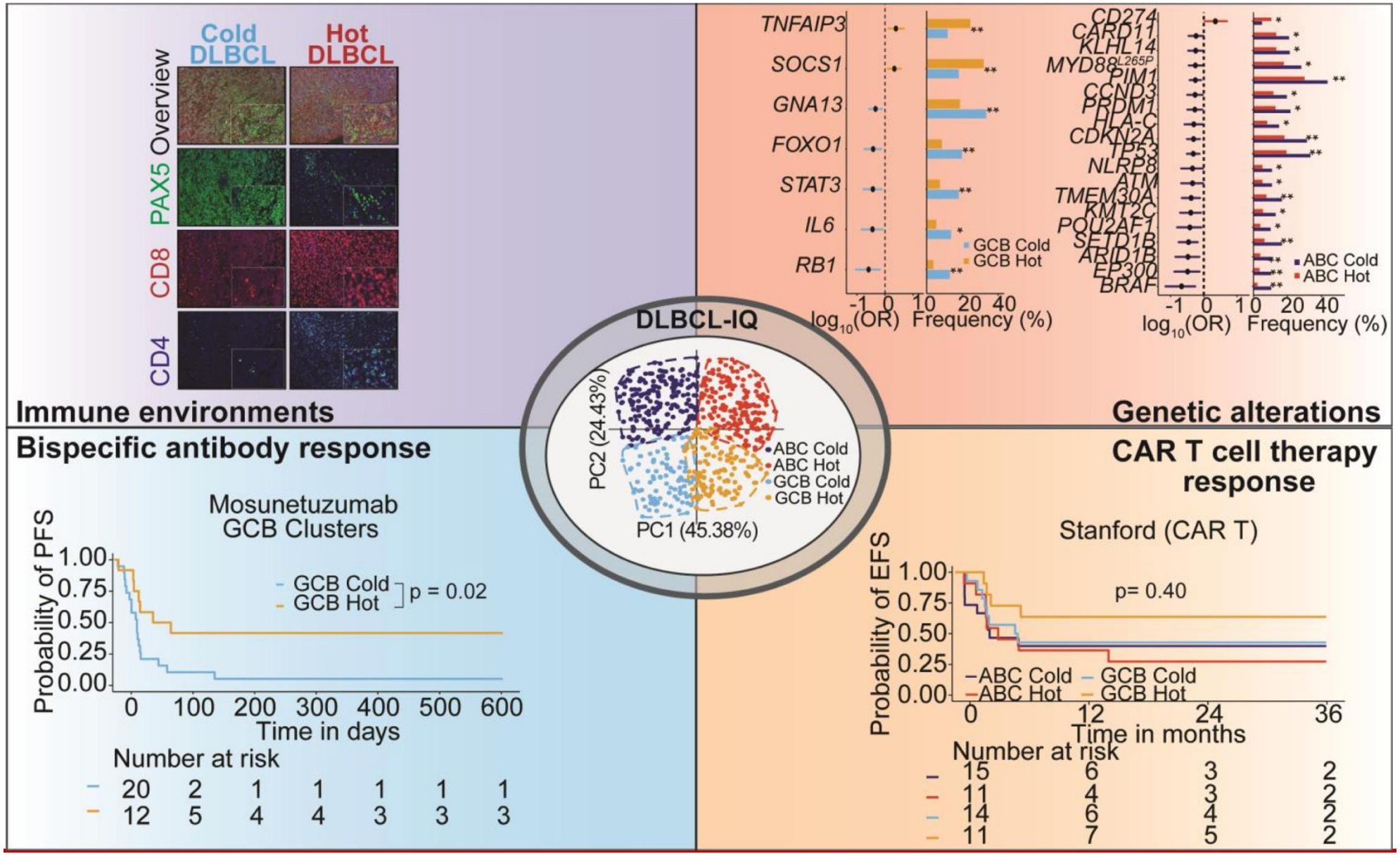
2. Does your geographical population contain enough patients?



Region	ABC-Type, % (n/n)	Non-ABC-Type, % (n/n)
Asia/Pacific (China, Japan, South Korea, Taiwan)	60% (241/404)	40% (163/404)
Russia/Europe/Middle East (Belgium, Czech Republic, France, Ireland, Israel, Italy, Netherlands, Poland, Portugal, Russia, Spain, Switzerland, Turkey)	40% (441/1105)	60% (664/1105)
North America/Australia/New Zealand (United States, Canada, Australia, New Zealand)	37% (106/289)	63% (183/289)

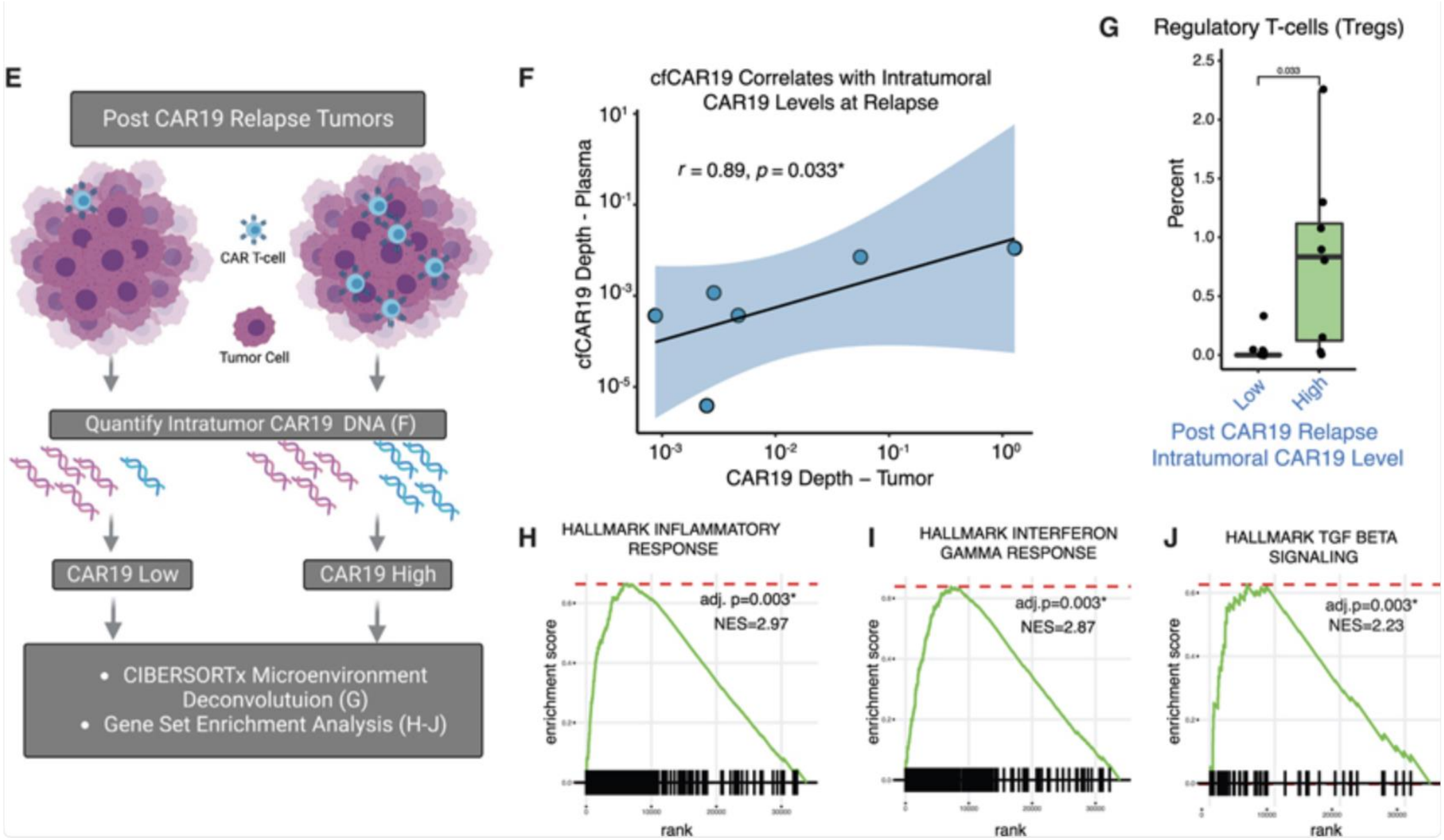
Nowakowski et al. Haematologica. 2020 Jan 31;105(2):e72-e75.

3. Can the immune system be appropriately activated?



Tumuluru et al. Blood. 2025 Jan 27:blood.2024025355.

3. Can the immune system can be appropriately activated?

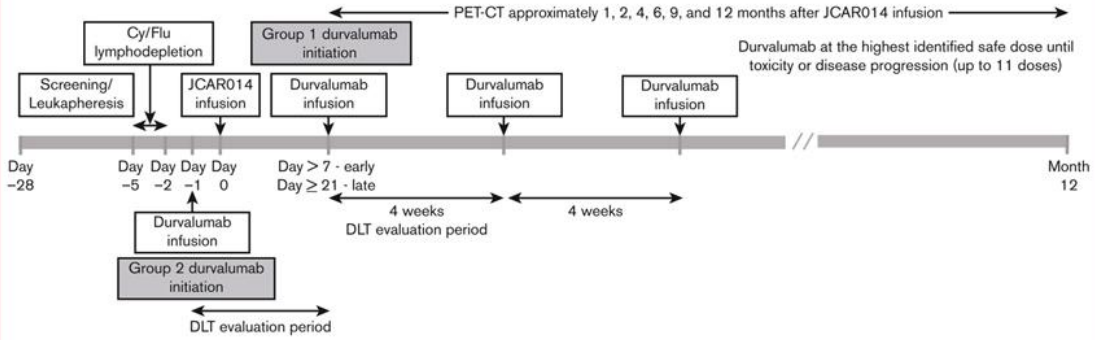


Sworder et al. Cancer Cell. 2023 Jan 9;41(1):210-225.e5.

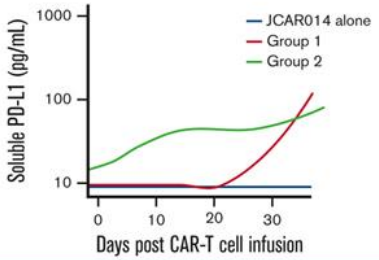
4. Does the timing of the new agent matter?

Timing of PD-1 blockade matters with CART therapy

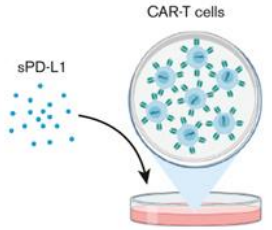
Phase 1 clinical trial of JCAR014 CD19-targeted 4-1BB-costimulated CAR-T cells combined with escalating doses of the anti-PD-L1 monoclonal antibody, durvalumab, in adults with R/R LBCL



Patients in Group 1 had an early increase in soluble PD-L1 (sPD-L1) levels that coincided with CAR-T cell expansion

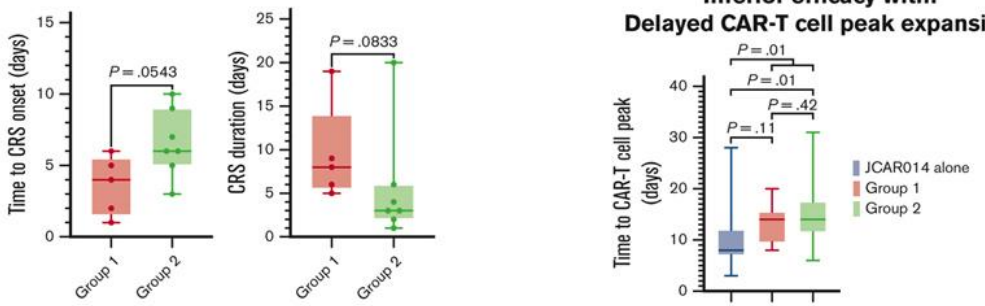


sPD-L1 induced dose-dependent suppression of CAR-T cell effector function



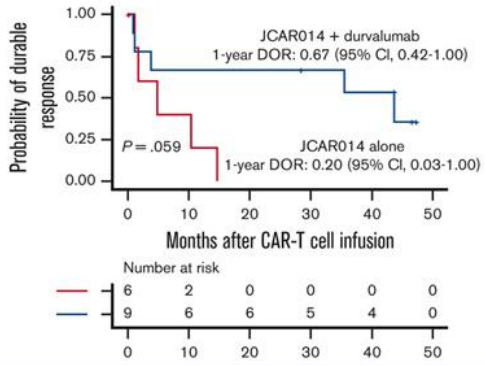
Patients in Group 2 who started durvalumab before JCAR014 infusion had:

Inferior efficacy with:
Delayed CAR-T cell peak expansion



Later onset and shorter duration of CRS ↓ Concentration of inflammatory cytokines

Ongoing durvalumab therapy was associated with re-expansion of CAR-T cells and enhanced duration of response



- **Timing of initiation of durvalumab in relation to CD19 CAR-T cell infusion affects efficacy and toxicity of CAR-T cell therapy in LBCL**
- **Durvalumab-induced increase in soluble PD-L1 mediates suppression of CD19 CAR-T cell effector function during the time of maximal expansion**

Hirayama et al. Blood Adv. 2024 Jan 23;8(2):453-467.

5. Will toxicities from the combination impact the results?

Trial	Treatment	Grades 3-4 toxicity*	Other notable toxicities*	Grade 5 AE rate
POLARIX[2] Phase 3	R-CHOP	NP 31% Anemia 8% F&N 8% Infection 13%	Neuropathy 54% (G3-4, 1%)	2.3%
	R-pola-CHP	NP 28% Anemia 12% F&N 14% Infection 15%	Neuropathy 53% (G3-4, 2%) Diarrhea 31% (G3-4, 4%)	3.0%
1L glofitamab + R-CHOP[35] Phase 1b	Glofitamab-R-CHOP	NP 48% Infection 22%	ICANS 0% CRS 11% (G3-4, 0%)	7.1%
1L glofitamab + pola-R-CHP[36] Phase 1b	Glofitamab-pola-R-CHP	NP 63% Infection 17%	ICANS 0% CRS 8% (G3-4, 0%)	4.2%
EPCORE NHL-2[37] Phase 1/2	Epcoritamab-R-CHOP	NP 62% F&N 13% Anemia 28%	CRS 60% (G3-4, 2%) ICANS 4% (G3-4, 0%)	N/A
FIRST-MIND[38] Phase 1b	Tafasitamab + R-CHOP	NP 58% Anemia 21% TCP 12% F&N 18% Infection 21%	Hypokalemia 21% (G3-4, 9%)	9.1%
	Tafasitamab + lenalidomide + R-CHOP	NP 85% TCP 36% F&N 18% Infection 27%	Diarrhea 33% (G3-4, 6%) Hypokalemia 30% (G3-4, 6%)	6.1%
ACCEPT[39] Phase 1b/2	Acalabrutinib + R-CHOP	NP 37% F&N 13% Infection 7%	Diarrhea (G3-4, 11%)	N/A
CC-220-DLBCL-001[40] Phase 1	Golcadomide + R-CHOP	NP 77% TCP 32% F&N 14% Infection 15%	Venous thromboembolism 8%	N/A
ZUMA-12[41,42] Phase 2	Axi-cel (in patients with DS 4-5 after 2 cycles of chemotherapy)	NP 53% Anemia 30% TCP 15% Infection 15%	CRS 100% (G3-4, 8%) Neuro AE 73% (G3-4, 23%)	2.5%
Aza-R-CHOP[43] Phase 1	Oral azacitidine + R-CHOP	NP 63% Anemia 17% TCP 14% F&N 25%	Diarrhea 56% (G3-4, 7%) Pulmonary embolism (G3-4, 7%)	1.7%

Qualls et al. Blood (2025) 145 (2): 176–189.

Issues that may influence which novel agents are included

1. Lymphoma cells/lymphoma subtype need to be vulnerable to a specific inhibitor or to additional cytotoxic agents
2. You need measure the biomarker on a timeous fashion and the population needs to contain enough of these patients
3. You need evidence that the immune system can be appropriately activated
4. Timing of administration of the new agent may be important
5. Additional toxicities from the new drug added to the combination may impact the results