# DLBCL: A New Era—Emerging Therapies in First-Line Treatment

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Great Debates
Hematologic Malignancies
from Lymphoma · Leukemia & Myeloma Congress

# Faculty Disclosures

**Sarah C. Rutherford, MD:** Consultant—AbbVie, ADC Therapeutics, BMS, Genmab, Incyte, Karyopharm, Kite, Pfizer/Seagen; Data and Safety Monitoring Board—Karyopharm; research funding—Constellation, Genentech/Roche, Karyopharm

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# Program Information

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# Learning Objectives

- Describe the **mechanisms of action and key clinical data** for available and emerging **first-line therapies in DLBCL**
- Evaluate how **novel and targeted treatment** approaches can be **integrated into frontline DLBCL management**, including patient selection criteria and safety considerations
- Assess **future directions in DLBCL**, including ongoing trials, minimal residual disease monitoring, and evolving treatment strategies for high-risk patients

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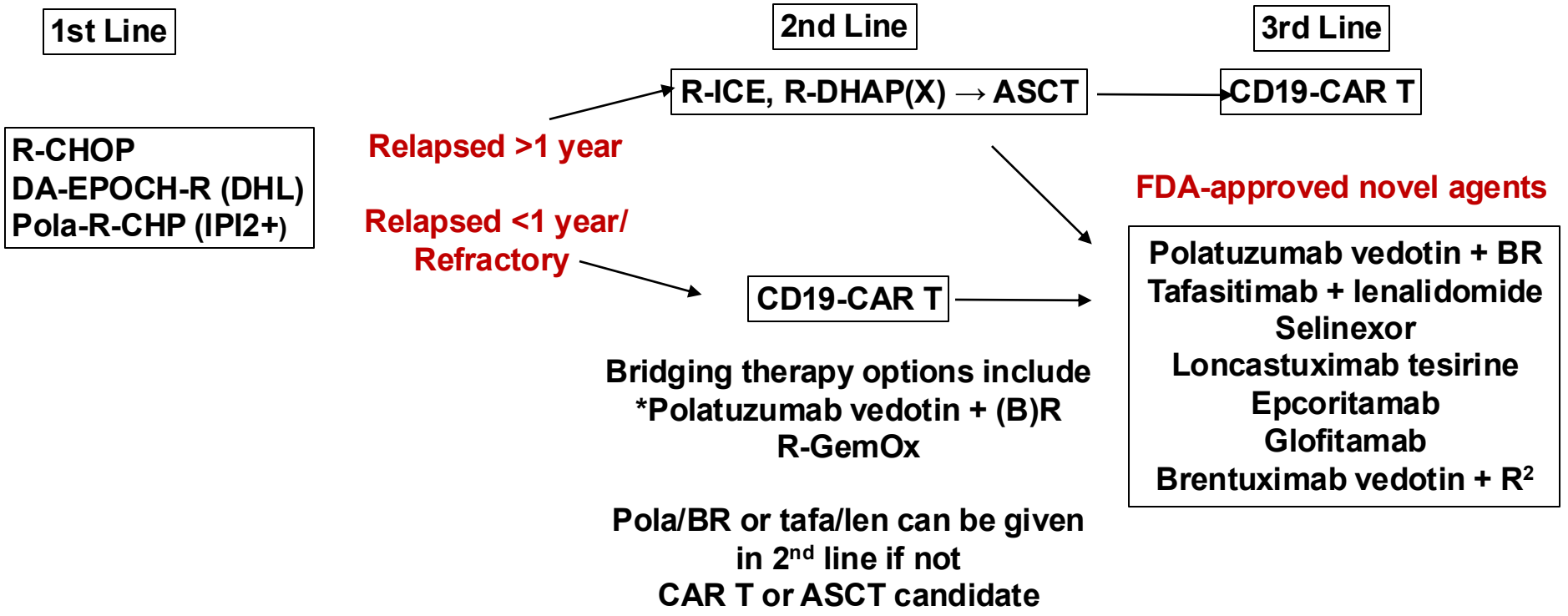
**DLBCL = diffuse large B-cell lymphoma.**

# Evolving DLBCL Treatment Algorithm




R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine sulfate, prednisone; DA-EPOCH-R = etoposide phosphate, prednisone, vincristine sulfate, cyclophosphamide, doxorubicin, and rituximab; pola-R-CHP = polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, prednisolone; R-ICE = rituximab, ifosfamide, carboplatin, etoposide; R-DHAP (X) = rituximab, dexamethasone, high-dose cytarabine, cisplatin; R-GemOx = rituximab gemcitabine oxaliplatin; BR = bendamustine, rituximab; tafa/len = tafasitamab, lenolidomide; FDA = US Food and Drug Administration; ASCT = autologous stem cell transplantation.

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# Outline: New Strategies in First-Line DLBCL

- Polatuzumab vedotin
- Chimeric antigen receptor T cells
- Bispecific antibodies
- Novel regimens in older patients
- Treatment by genetic subtype
- ctDNA to guide management

ctDNA = circulating tumor DNA.

# Case Presentation

44-year-old female with left knee pain, found to have soft tissue/bone mass

- Biopsy of soft tissue/bone: diffuse large B cell lymphoma, GCB subtype
- FISH: MYC rearrangement, no BCL2 rearrangement
- PET/CT: lymphadenopathy above/below diaphragm, LLE soft tissue/bone lesion
- Labs: normal CBC, CMP, LDH elevated at 316

## How should she be treated?

**GCB = germinal center B cell; FISH = fluorescence in situ hybridization; PET = positron emission tomography; CT = computed tomography; LLE = left lower extremity; CBC = complete blood count; CMP = comprehensive metabolic panel;; LDH = lactate dehydrogenase.**

# Polatuzumab Vedotin in Frontline DLBCL

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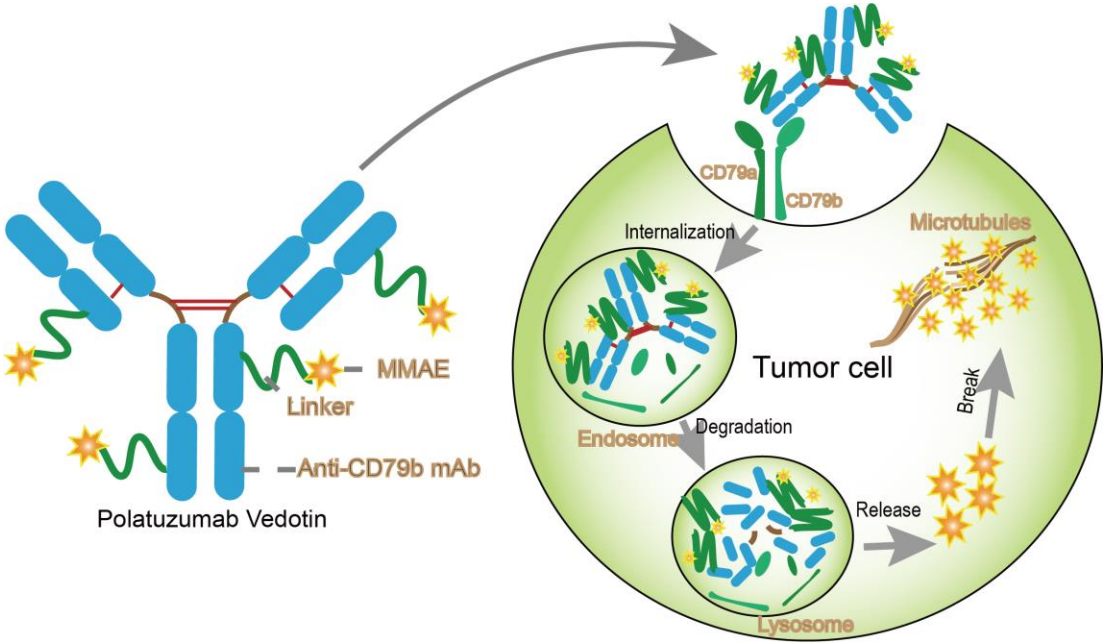
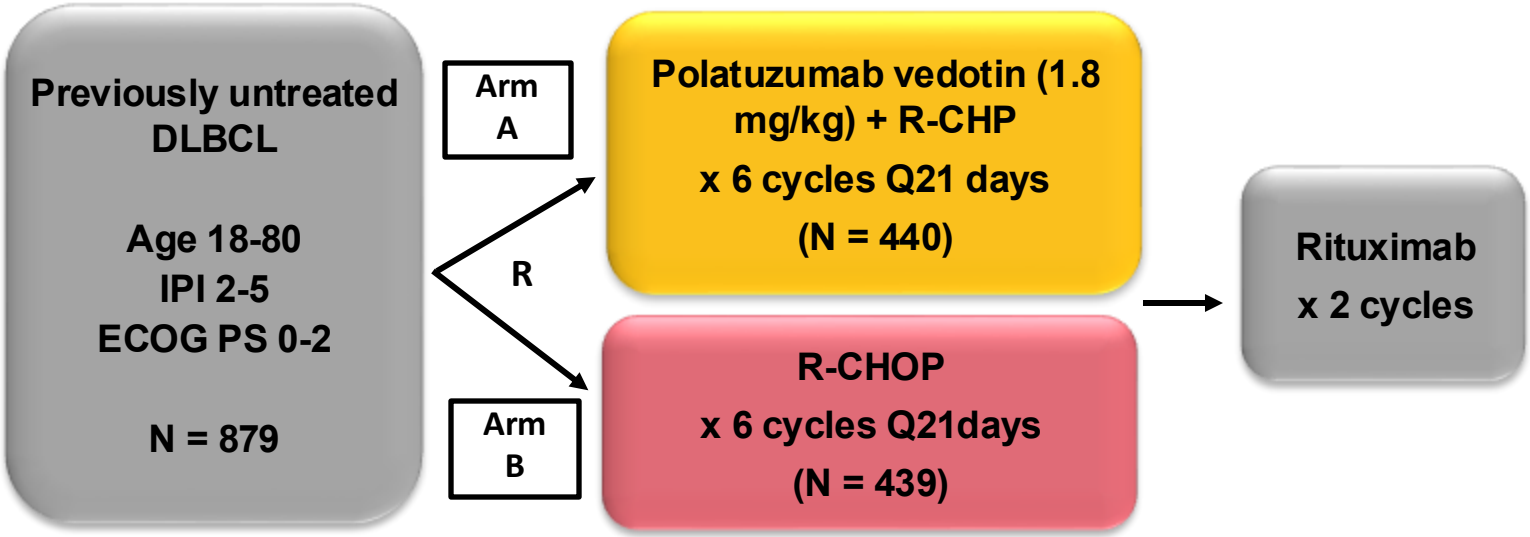
# Polatuzumab Vedotin




Both ABC and GCB subtypes of DLBCL are sensitive to MMAE payload.
ABC subtypes uniquely benefit due to reliance on B-cell receptor signaling.

**ABC = activated B-cell; GCB = germinal center B-cell; MMAE = monomethyl auristatin E.**
**Pfeifer M, et al. *Leukemia*. 2015;29(7):1578-1586. Creative Biolabs [www.creativebiolabs.net]. https://www.creativebiolabs.net/polatuzumab-vedotin-overview.htm.**

# POLARIX Study Design




| | | Pola-R-CHP | R-CHOP | Total | Median PFS follow-up | Median OS follow-up |
|---|---|---|---|---|---|---|
| **Global population** | ITT‡ | 440 | 439 | 879 | 54.9 months | 64.1 months |
| | Safety evaluable§ | 435¶ | 438# | 873 | | |

Primary endpoint: **PFS**

IPI = International Prognostic Index; ECOG PS = Eastern Cooperative Oncology Group performance status; ITT = intention-to-treat; PFS = progression-free survival; OS = overall survival.

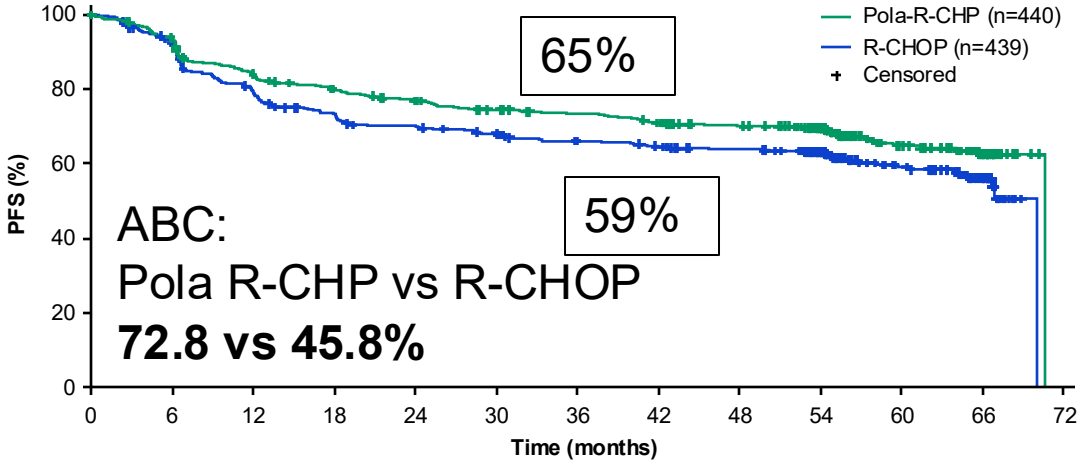
Tilly H, et al. *N Engl J Med*. 2022;386(4):351-363. Salles G, et al. *Blood*. 2024;144(Suppl 1):469.

# Patient Baseline Characteristics

| n (%), unless otherwise stated | | Global population | |
|---|---|---|---|
| | | Pola-R-CHP (n=440) | R-CHOP (n=439) |
| **Age** | Median, years (min–max)<br>≥65 years | 65.0 (19-80)<br>231 (52.5) | 66.0 (19-80)<br>236 (53.8) |
| **Sex** | Male | 239 (54.3) | 234 (53.3) |
| **ECOG PS** | 0-1<br>2 | 374 (85.0)<br>66 (15.0) | 363 (82.7)*<br>75 (17.1) |
| **IPI at screening** | 2<br>3-5 | 167 (38.0)<br>273 (62.0) | 167 (38.0)<br>272 (62.0) |
| **Bulky disease** | ≥7.5cm | 193 (43.9) | 192 (43.7) |
| **Baseline LDH** | >1x upper limit of normal | 291 (66.1) | 284 (64.7) |
| **Ann Arbor stage** | III or IV | 393 (89.3) | 387 (88.2) |
| **Number of extranodal sites** | ≥2 | 213 (48.4) | 213 (48.5) |
| **NHL histologic diagnosis reported by investigators** | DLBCL, ABC, GCB<br>HGBCL, DHL/THL<br>Other large B-cell lymphoma | 373 (84.8)†<br>43 (9.8)<br>24 (5.5) | 367 (83.6)<br>50 (11.4)<br>22 (5.0) |
| **COO centrally reported by NanoString‡** | n<br>ABC by NanoString<br>GCB by NanoString<br>Unclassified by NanoString<br>Unknown | 330<br>102 (30.9)<br>184 (55.8)<br>44 (13.3)<br>110 | 338<br>119 (35.2)<br>168 (49.7)<br>51 (15.1)<br>101 |

***ECOG PS was not reported for one patient in the R-CHOP arm; †The total percentage for NHL histologic diagnosis in the pola-R-CHP arm may exceed 100% due to rounding; ‡Based on central review, and percentages are based on biomarker evaluable population (ie, by excluding patients with unknown status).**
**NHL = non-Hodgkin lymphoma; COO = cell-of-origin. DHL = double-hit lymphoma; HGBCL = high-grade B-cell lymphoma; NOS = not otherwise specified; THL = triple-hit lymphoma.**
**Tilly H, et al. *N Engl J Med*. 2022;386(4):351-363. Salles G, et al. *Blood*. 2024;144(Suppl 1):469.**

# 5-Year PFS Higher with Pola-R-CHP than R-CHOP




**Patients remaining at risk**

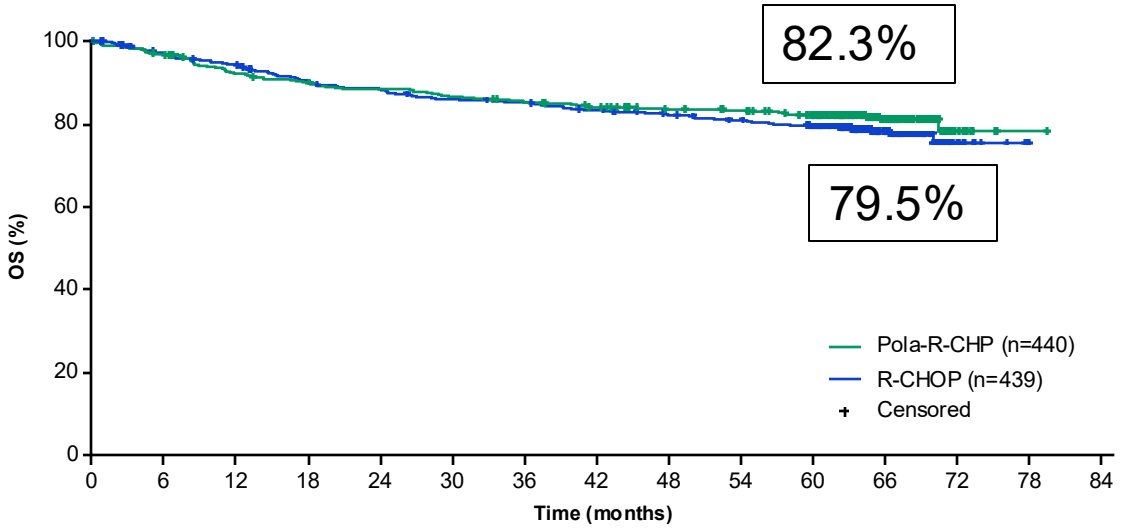
| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pola-R-CHP | 440 | 407 | 357 | 335 | 318 | 303 | 292 | 280 | 258 | 213 | 100 | 56 | NE |
| R-CHOP | 439 | 391 | 332 | 302 | 287 | 274 | 258 | 251 | 240 | 192 | 95 | 54 | NE |

| 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) |

*Data cutoff: June 28, 2021. †Data cutoff: June 15, 2022; ‡Data cutoff: July 5, 2024.

Tilly H, et al. *N Engl J Med*. 2022;386(4):351-363. Salles G, et al. *Blood*. 2024;144(Suppl 1):469. Hu B, et al. *Blood Adv*. 2025;9(10):2489-2499.

# 5-Year OS Favors Pola-R-CHP over R-CHOP




**Patients remaining at risk**

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pola-R-CHP | 440 | 424 | 399 | 389 | 381 | 373 | 366 | 355 | 343 | 338 | 319 | 124 | 12 | 1 | NE |
| R-CHOP | 439 | 415 | 403 | 382 | 372 | 361 | 357 | 347 | 338 | 329 | 311 | 128 | 13 | 1 | NE |

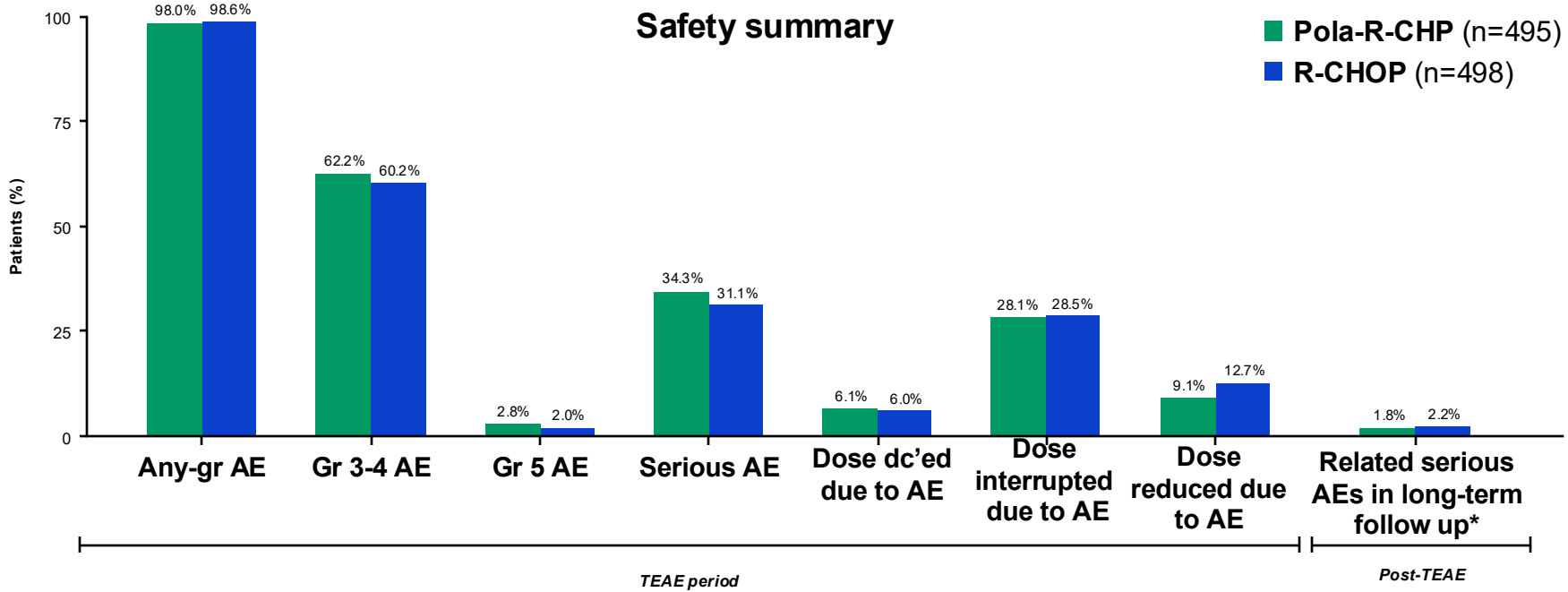
| Deaths, n§ | Pola-R-CHP (n=440) | R-CHOP (n=439) |
|---|---|---|
| 5-year update* | 79 | 91 |

| Event-free rate, % | 5-year update* |
|---|---|
| Pola-R-CHP | 82.3 (78.7-85.9) |
| R-CHOP | 79.5 (75.7-83.4) |
| HR (95% CI) | 0.85 (0.63-1.15) |

*Data cutoff: July 5, 2024; §In addition to the known deaths, there were two patients (one in the pola-R-CHP arm and one in the R-CHOP arm) who died due to an unknown cause and an unknown death date and were not counted as death events in the OS analysis.

Tilly H, et al. *N Engl J Med*. 2022;386(4):351-363. Salles G, et al. *Blood*. 2024;144(Suppl 1):469.

# Pola-R-CHP and R-CHOP Have Similar AE Profile




Data cutoff: July 5, 2024. *TEAEs are defined as new or worsening AE from the first dose of study drug through 90 days after the last dose of any study drug or prior to non-protocol-specified anti-lymphoma treatment (NALT), whichever is earlier. After this TEAE period, the post-TEAE period (ie, long-term safety follow-up) reporting requirement is only for serious AEs that the investigator believes to be related to prior study drug treatment.
TEAE = treatment-emergent adverse event; dc = discontinued.

Tilly H, et al. *N Engl J Med*. 2022;386(4):351-363. Salles G, et al. *Blood*. 2024;144(Suppl 1):469.

# Select Adverse Events of Particular Interest in the Expanded Population

| Patients, n (%) | Pola-R-CHP (n=495) | R-CHOP (n=498) |
|---|---|---|
| **Peripheral neuropathy** | | |
| All grade | 249 (50.3) | 261 (52.4) |
| Grade 3-5 | 7 (1.4) | 5 (1.0) |
| **Neutropenia** | | |
| All grade | 240 (48.5) | 228 (45.8) |
| Grade 3-5 | 216 (43.6) | 205 (41.2) |
| **Infections** | | |
| All grade | 237 (47.9) | 219 (44.0) |
| Grade 3-5 | 75 (15.2) | 66 (13.3) |
| **Anemia** | | |
| All grade | 165 (33.3) | 150 (30.1) |
| Grade 3-5 | 56 (11.3) | 49 (9.8) |

| Patients, n (%) | Pola-R-CHP (n=495) | R-CHOP (n=498) |
|---|---|---|
| **Thrombocytopenia** | | |
| All grade | 89 (18.0) | 86 (17.3) |
| Grade 3-5 | 32 (6.5) | 31 (6.2) |
| **Cardiac arrythmias** | | |
| All grade | 18 (3.6) | 26 (5.2) |
| Grade 3-5 | 3 (0.6) | 5 (1.0) |
| **Carcinogenicity** | | |
| All grade | 5 (1.0) | 12 (2.4) |
| Grade 3-5 | 5 (1.0) | 9 (1.8) |

There was a <5% difference in hematological toxicities and infections in the Pola-R-CHP versus R-CHOP arm. Fewer secondary malignancies were observed with Pola-R-CHP versus R-CHOP.

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Tilly H, et al. *N Engl J Med*. 2022;386(4):351-363. Salles G, et al. *Blood*. 2024;144(Suppl 1):469.

# Chimeric Antigen Receptor (CAR) T in Frontline DLBCL

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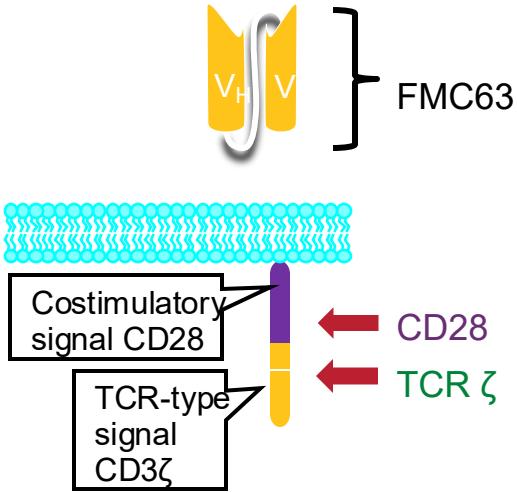
# CD19-Directed CAR T Cell Products

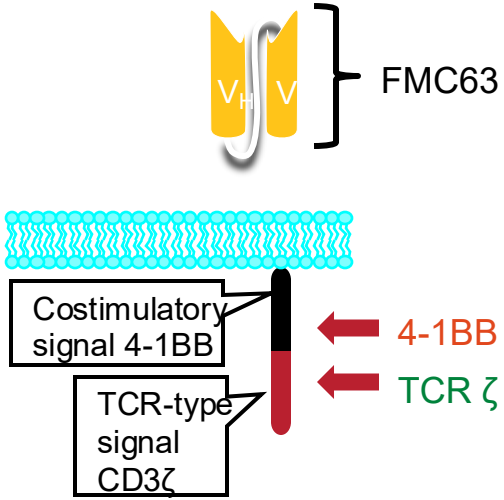
## Axicabtagene ciloleucel (Axi-cel)

- CD28 costimulation
- Second generation



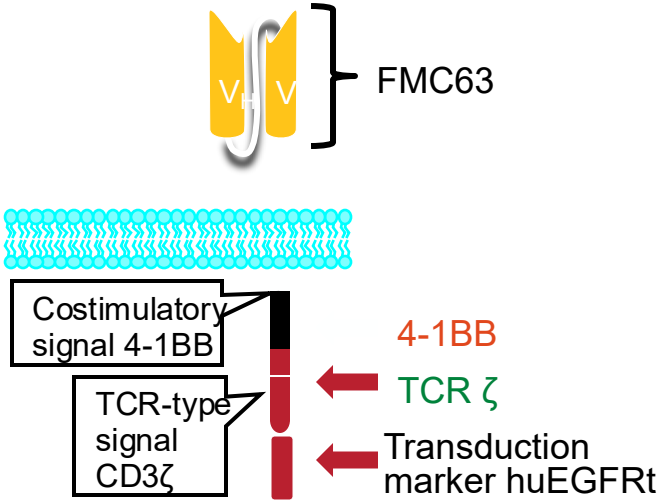

## Tisagenlecleucel (Tisa-cel)

- 4-1BB costimulation
- Second generation




## Lisocabtagene maraleucel (Liso-cel)

- 4-1BB costimulation
- Second generation




**TCR = T cell receptor; huEGFRt = truncated human epidermal growth factor receptor polypeptide.**

**Van der Stegen SJC, et al. *Nat Rev Drug Discov*. 2015;14(7):499-509.**

# CAR T in Frontline High-Risk DLBCL: ZUMA-12

## Phase 2

**High-Risk LBCL**
- HGBL, with *MYC* and *BCL2* and/or *BCL6* translocations (double- or triple-hit), or
- LBCL with IPI score ≥3 any time before enrollment

+

**Dynamic Risk Assessment**
- Positive interim PET (DS 4 or 5) after 2 cycles of an anti-CD20 mAb + anthracycline-containing regimen

+

**Additional Key Inclusion Criteria**
- Age ≥18 years
- ECOG 0-1

→ **Enrollment/Leukapheresis** →

**Optional Nonchemotherapy Bridging Therapy[a]** →

**Conditioning Chemotherapy + Axi-Cel Infusion**
- Conditioning: Fludarabine 30 mg/m$^2$ IV and cyclophosphamide 500 mg/m$^2$ IV on days -5, -4, and -3
- Axi-Cel: Single IV infusion of 2x10$^6$ CAR T cells/kg on day 0

**Primary Endpoint**
- CR (investigator-assessed per Lugano 2014 classification)

**Key Secondary Endpoints**
- ORR
- DOR
- EFS
- PFS
- OS
- Safety
- CAR T cells in blood and cytokine levels in serum

[a]Administered after leukapheresis and completed prior to initiating conditioning chemotherapy. Therapies allowed were corticosteroids, localized radiation, and HDMP+R. PET-CT was required after bridging.
CR = complete response; ORR = objective response rate; DOR = duration of response; EFS = event-free survival; HDMP+R = high-dose methylprednisolone, rituximab.
Figure adapted from Neelapu SS, et al. Presented at: American Society of Hematology (ASH) Annual Meeting; December 11-14, 2021; Atlanta, Georgia. Abstract 739. Neelapu SS, et al. *Nat Med*. 2022;28(4):735-742. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068. Chavez JC, et al. *Blood*. 2025;145(20):2303-2311.

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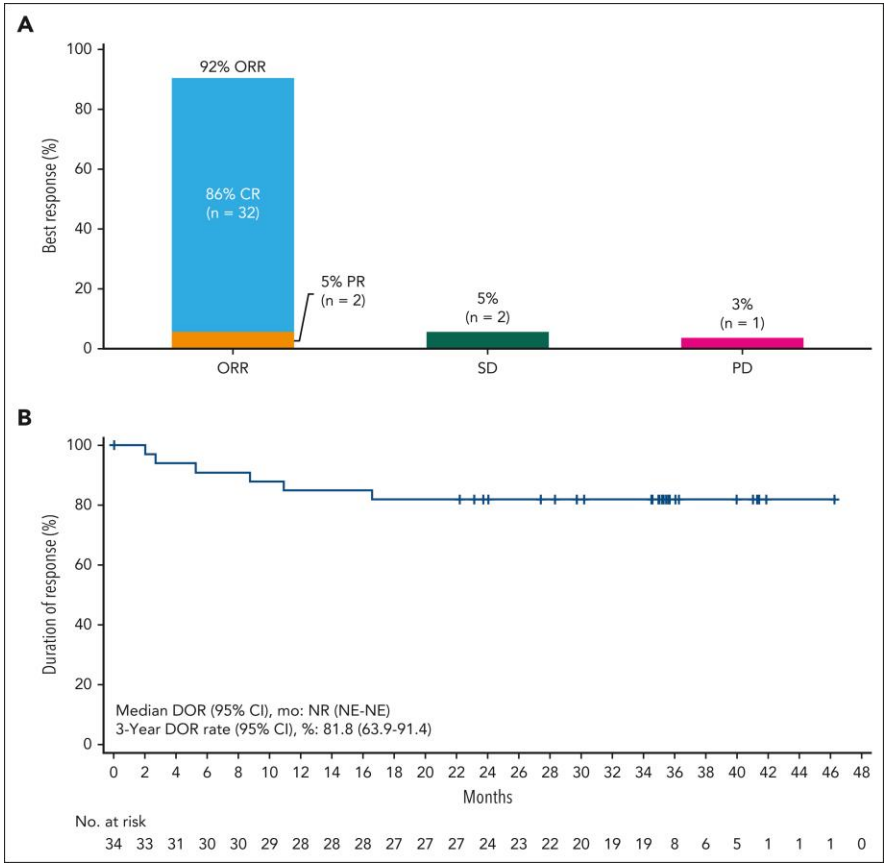
# High CR Rate and 3-Year DOR




Median f/u
47 months

ORR 92%
CRR 86%

3-yr

DOR 82%
EFS 73%
PFS 75%
OS 81%

f/u = follow-up; SD = stable disease; PD = progressive disease; NR = not reached; NE = not estimable.

Neelapu SS, et al. *Nat Med*. 2022;28(4):735-742. Chavez JC, et al. *Blood*. 2025;145(20):2303-2311.

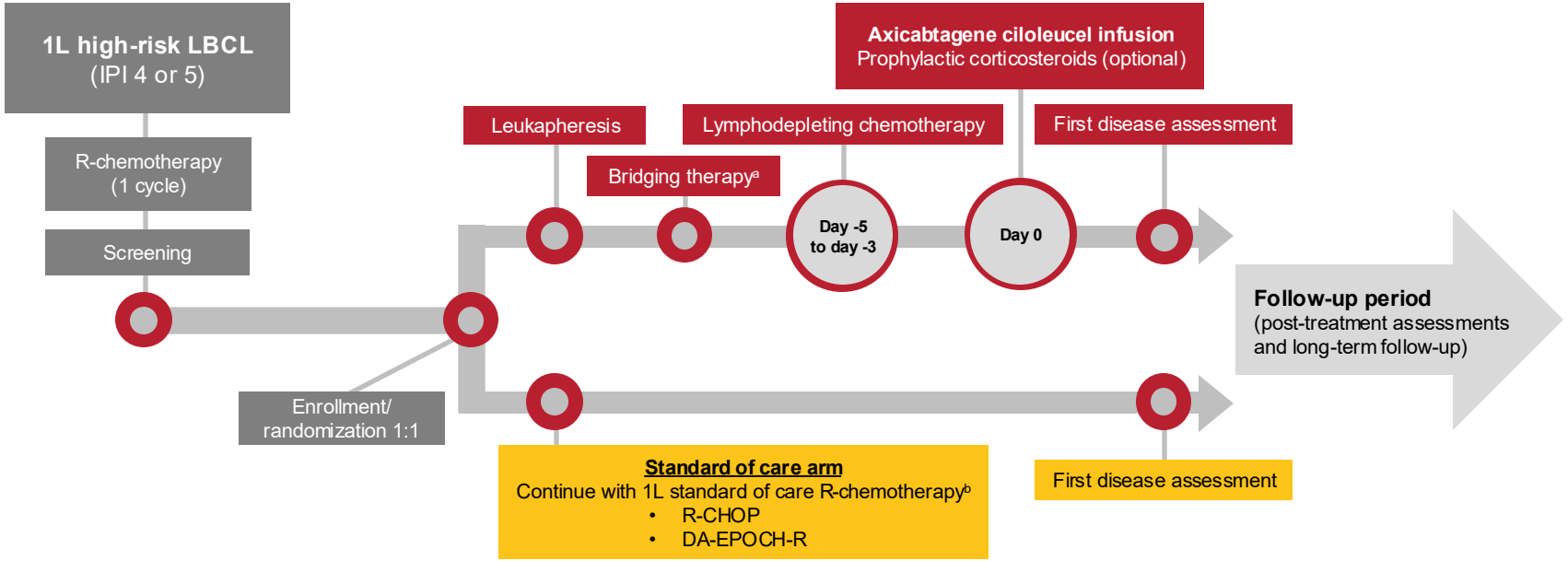
# CRS Was Mainly Low-Grade; One-Fourth of Pts Had Grade ≥3 Neurologic Events

| Adverse event[a], *n* (%) | Grade 1 | Grade 2 | Grade ≥3 | Total |
|---|---|---|---|---|
| **Subjects with any CRS[a]** | **27 (68)** | **10 (25)** | **3 (8)** | **40 (100)** |
| Pyrexia | 8 (20) | 28 (70) | 4 (10) | 40 (100) |
| Hypotension | 7 (18) | 5 (13) | 0 (0) | 12 (30) |
| Chills | 9 (23) | 1 (3) | 0 (0) | 10 (25) |
| Hypoxia | 2 (5) | 2 (5) | 5 (13) | 9 (23) |
| Sinus tachycardia | 6 (15) | 0 (0) | 0 (0) | 6 (15) |
| **Subjects with any neurologic events** | **14 (35)** | **6 (15)** | **9 (23)** | **29 (73)** |
| Confusional state | 7 (18) | 2 (5) | 2 (5) | 11 (28) |
| Encephalopathy | 2 (5) | 2 (5) | 6 (15) | 10 (25) |
| Tremor | 8 (20) | 2 (5) | 0 (0) | 10 (25) |

- No deaths from CRS or NE
- 2 grade 4 NE

[a]Adverse events include those with onset on or after axi-cel infusion date and coded using MedDRA v.23.1. Neurologic events were identified using the modified blinatumomab registrational study. CRS was graded according to Lee, et al. The severity of all adverse events, including neurologic events and symptoms of CRS, was graded according to CTCAE v.5.0.
CRS = cytokine release syndrome; NE = neurological event; CTCAE = Common Terminology Criteria for Adverse Events.
Neelapu SS, et al. *Nat Med*. 2022;28(4):735-742. Chavez JC, et al. *Blood*. 2025;145(20):2303-2311.

# CAR T in Frontline High-Risk DLBCL: ZUMA-23




**Primary endpoint**
- Event-free survival

**Secondary endpoints**
- Progression-free survival
- Overall survival
- Complete remission rate
- Patient-reported outcomes/quality of life
- Safety

**[a]Bridging therapy with R-CHOP or DA-EPOCH-R will be administered during the cell manufacturing period. [b]Participants will receive the investigator's choice of either R-CHOP or DA-EPOCH-R for a total of 6 cycles (21-day cycle). [c]By both blinded central assessment and investigator assessment.**

**ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated May 18, 2025. Accessed July 29, 2024. https://clinicaltrials.gov/study/NCT05605899.**

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# Bispecific Antibodies (BsAb) in Frontline DLBCL

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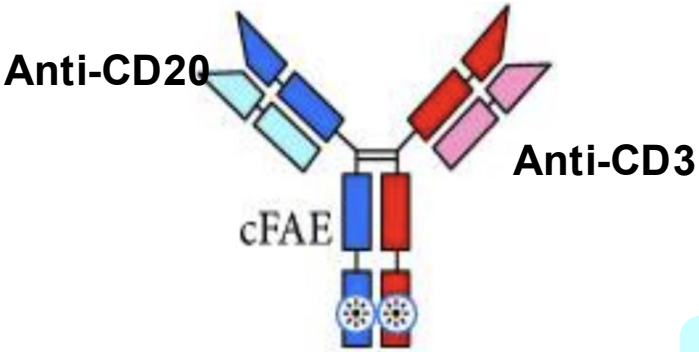
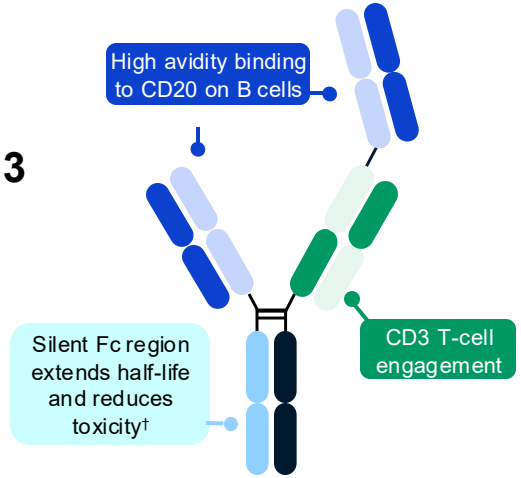
# CD20 x CD3 BsAb

**Epcoritamab**




**Glofitamab**




- Currently approved after 2+ lines of therapy in DLBCL
- Under investigation in frontline setting



Lewis KL, Cheah CY. *Leuk Lymphoma*. 2024;65(6):720-735.

# BsAb in Frontline DLBCL: EPCORE® NHL-2 Arm 1

**Key inclusion criteria**

- Newly diagnosed CD20+ DLBCL[a]
  - DLBCL, NOS
  - T-cell/histiocyte-rich DLBCL
  - Double-hit or triple-hit DLBCL[b]
  - FL grade 3B
- IPI score ≥3
- ECOG PS 0-2
- Measurable disease by CT or MRI
- Adequate organ function

**Treatment regimen: concomitant fixed-duration epcoritamab 48 mg + R-CHOP[c]**

| | Agent | C1-4 | C5-6 | C7+ |
|---|---|---|---|---|
| | Epcoritamab SC 48 mg | QW | Q3W | Q4W Up to 1 year |
| R-CHOP | Rituximab IV 375 mg/m$^2$ | Q3W | | |
| R-CHOP | Cyclophosphamide IV 750 mg/m$^2$ | Q3W | | |
| R-CHOP | Doxorubicin IV 50 mg/m$^2$ | Q3W | | |
| R-CHOP | Vincristine[d] IV 1.4 mg/m$^2$ | Q3W | | |
| | Prednisone IV or oral 100 mg/d | D1-5 of each cycle | | |

- **Primary endpoint:** Overall response rate[e]
- **Key secondary endpoints:** CR rate, time to response, time to CR, DOR, DOCR, PFS, OS, MRD negativity, and safety/tolerability
  - MRD was assessed using the exploratory AVENIO ctDNA method

**Data cutoff: May 15, 2024**
**Median follow-up: 27.4 mo**

NCT04663347. [a]De novo or histologically transformed from follicular lymphoma (FL) or nodal marginal zone lymphoma. [b]Classified as HGBCL, with *MYC* and *BCL2* and/or *BCL6* translocations. [c]Patients received epcoritamab with 2 step-up doses (0.16 mg and 0.8 mg) before the first full dose and corticosteroid prophylaxis to mitigate CRS. Cycles 1-6 were 21 d (epcoritamab + R-CHOP). Subsequent cycles of epcoritamab were 28 d. [d]Recommended maximum 2 mg. [e]Tumor response was evaluated by PET-CT obtained at 6, 12, 18, 24, 36, and 48 wk, and every 24 wk thereafter, until PD.
C = cycle; MRI = magnetic resonance imaging; DOCR = duration of complete response; MRD = measurable residual disease.
Falchi L, et al. *Blood.* 2024;144(Suppl 1):581.

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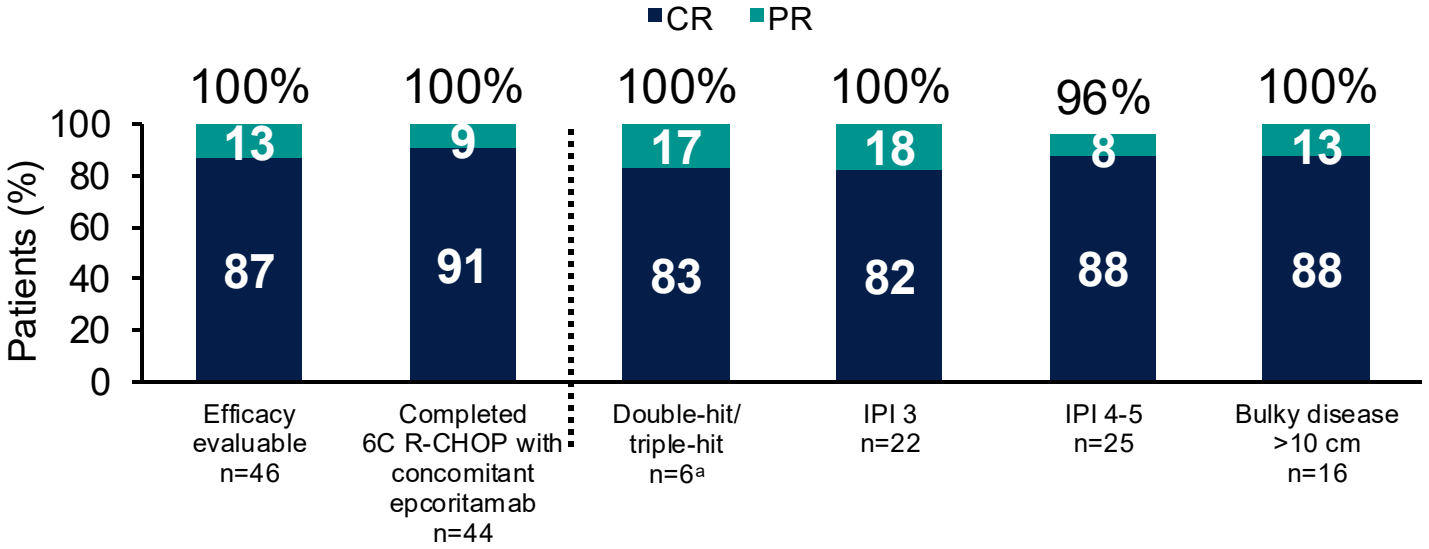
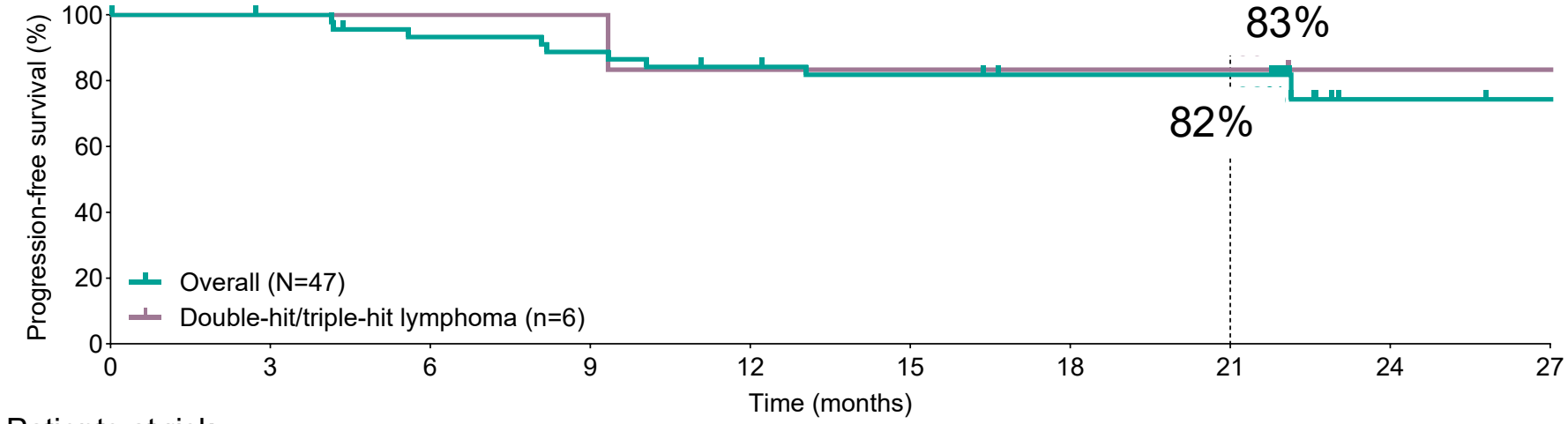
# High CRR across High-Risk Subgroups




- Median duration of 11.5 mo of epcoritamab (range, 0.6-13.2)
- Median relative dose intensity of R-CHOP 95%-98% for all individual components
  - Three patients did not complete 6C (withdrawal of consent, PD, and grade 5 COVID-19)

**CRR = complete response rate; PR = partial response.**
**Falchi L, et al. *Blood*. 2024;144(Suppl 1):581.**

# High Rates of Progression-Free Survival




Patients at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 47 | 45 | 41 | 39 | 36 | 34 | 32 | 32 | 16 | 15 |
| 6 | 6 | 6 | 6 | 5 | 5 | 5 | 5 | 3 | 3 |

**Median f/u for PFS: 22.9 months. Kaplan-Meier estimated probability of remaining progression-free.**
**Falchi L, et al. *Blood*. 2024;144(Suppl 1):581.**

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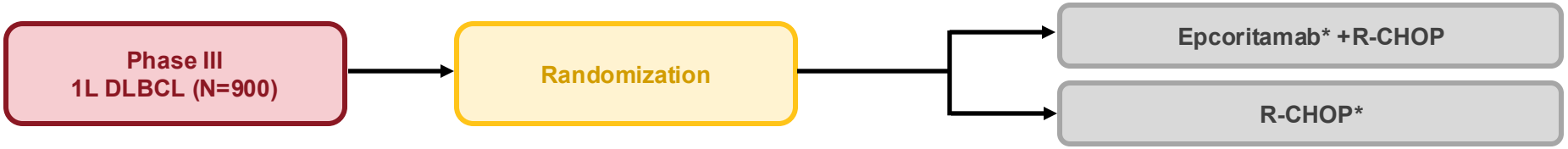
# EPCORE® DLBCL-2: Epcoritamab + R-CHOP vs R-CHOP in 1L DLBCL




## Objectives

**Epcoritamab* +R-CHOP**
- PFS in patients with IPI 3-5

**Secondary**
- PFS
- EFS
- CR
- OS
- MRD negativity

## Key Inclusion Criteria

- Planned to receive treatment with 6 cycles of R-CHOP per investigator determination
- Newly diagnosed, histologically confirmed CD20+ DLBCL (de novo or histologically transformed from a diagnosis of FL)†
- Availability of archival or freshly collected tumor tissue at screening‡
- IPI score 2-5§
- ECOG PS 0-2 prior to initiating R-CHOP treatment‖
- ≥1 target lesion¶
- Laboratory values meeting the criteria laid out in the protocol
- LVEF ≥50% by multi-gated acquisition or transthoracic echocardiography at screening

***21-day cycles. †Including: DLBCL NOS, high-grade B-cell lymphoma with MYC and BCL-2 and/or BCL-6 rearrangement with DLBCL morphology, T-cell/histiocyte-rich large B-cell lymphoma, Epstein Barr virus-positive DLBCL NOS, FL grade 3b. Note: The local pathology report must be available at screening to support CD20+ DLBCL histology. ‡Archival paraffin-embedded tissue must be obtained within 8 weeks prior to cycle 1 day 1. §The number of participants with IPI 2 will be capped at approximately 30% of the overall sample size. ‖Note that participant with an initial ECOG PS ≥3 may be screened if pre-phase treatment is planned. Participant may be eligible if ECOG PS were to improve to 0-2 during pre-phase treatment. ¶Defined as: ≥1 measurable nodal lesion (long axis >1.5 cm) or ≥1 measurable extra-nodal lesion (long axis >1 cm) on CT scan or MRI *and* PET-positive on PET-CT scan.**
**1L = first line; LVEF = left ventricular ejection fraction.**
**ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated January 23, 2025. Accessed August 26, 2024. https://clinicaltrials.gov/study/NCT05578976.**

# GO44145 (SKYGLO): Pola-R-CHP + Glofit vs Pola R-CHP in 1L DLBCL

**Patients**
- Previously untreated CD20+ LBCL
- Age 18-80
- IPI 2-5
- ECOG 0-2

**N=1130 (estimated enrollment)**

R
1:1

**Pola-R-CHP + Glofitamab**

**Pola-R-CHP**

**Primary Endpoint**
- PFS determined by IRF

**Secondary Endpoints**
- PFS determined by investigator
- PFS in IPI 3-5 patients determined by investigator and IRF
- EFS
- CR rate
- ORR
- DOR
- DOCR
- DFS
- OS

**IRF = independent review facility; DFS = disease-free survival.**
**ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated June 8, 2025. https://clinicaltrials.gov/study/NCT06047080.**

# Other Novel Combinations in Frontline DLBCL

- FrontMIND: Tafasitimab/lenalidomide/R-CHOP vs R-CHOP (NCT04824092)
- OLYMPIA-3: Odronextamab-CHOP vs R-CHOP (NCT06091865)
- GOLSEEK-1: Golcadamide-R-CHOP vs R-CHOP (NCT06356129)

# Frontline Treatment in Older Adults

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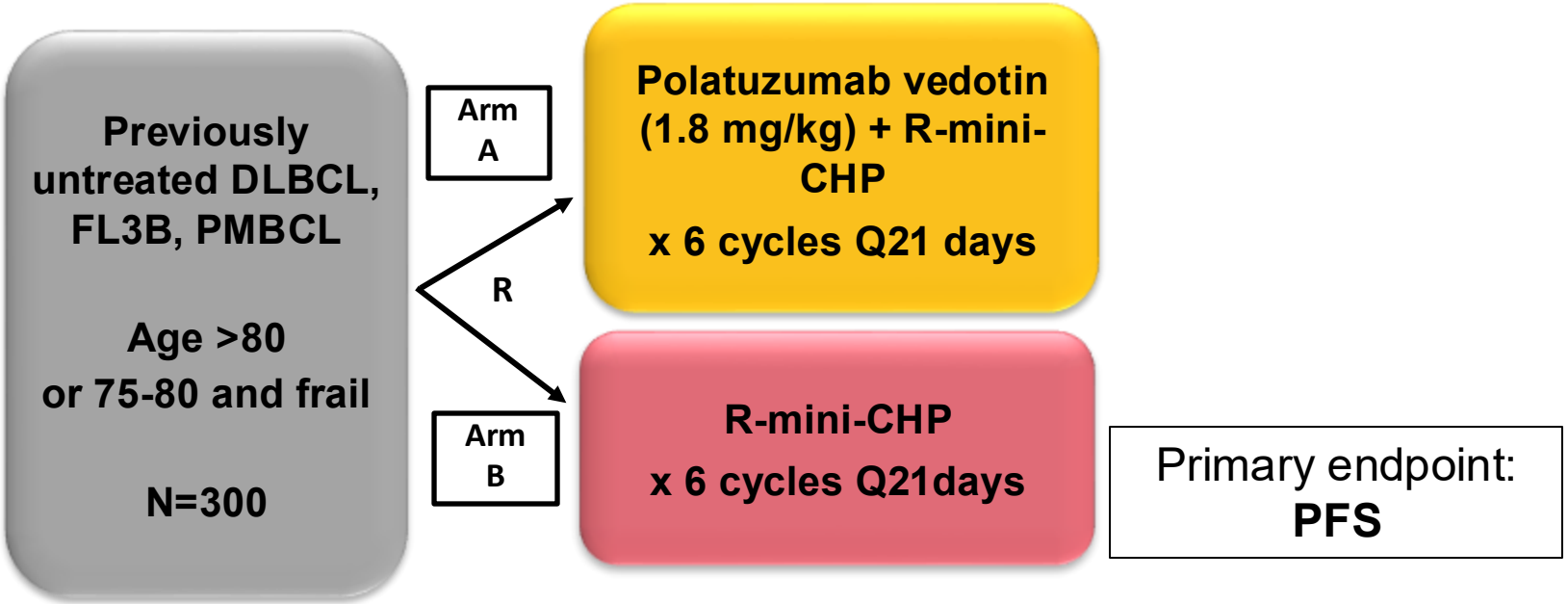
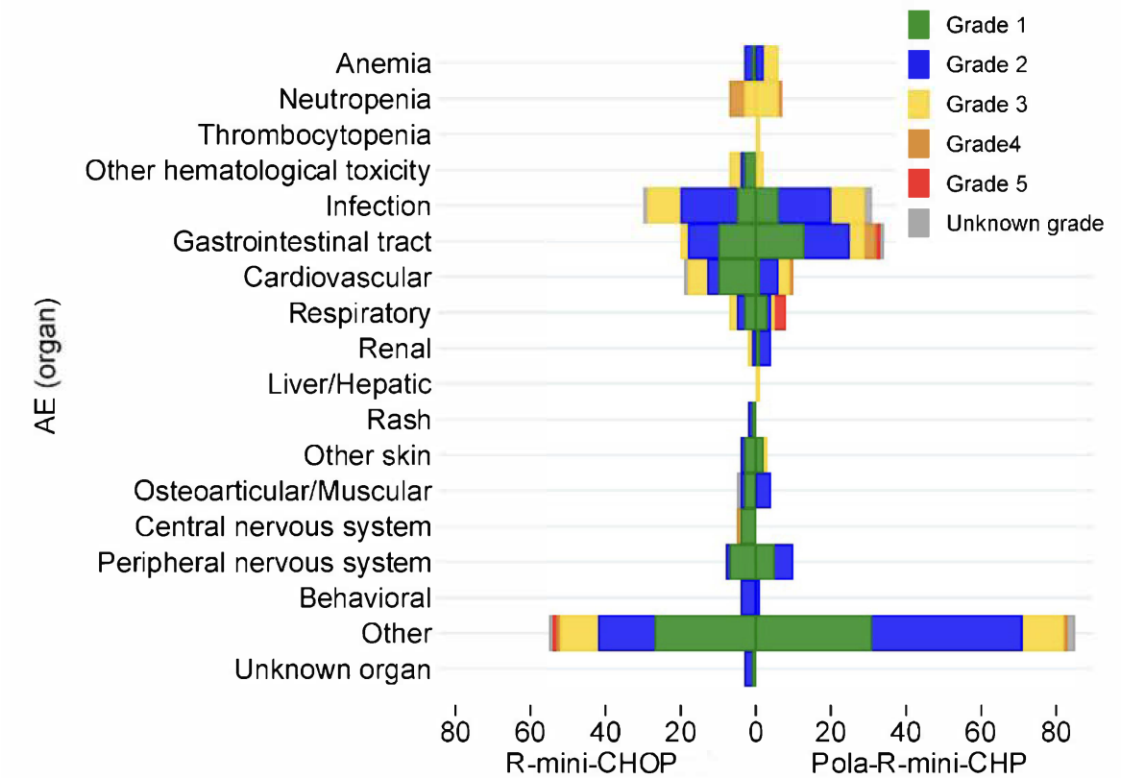
# Polar Bear Study Design




Jerkeman M, et al. Presented at: European Hematology Association (EHA) 2023 Congress; June 8-11, 2023; Frankfurt, Germany. Abstract S227. ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated September 19, 2024. https://clinicaltrials.gov/study/NCT04332822.

# More GI Toxicity with Pola-R-Mini-CHP (N=127)



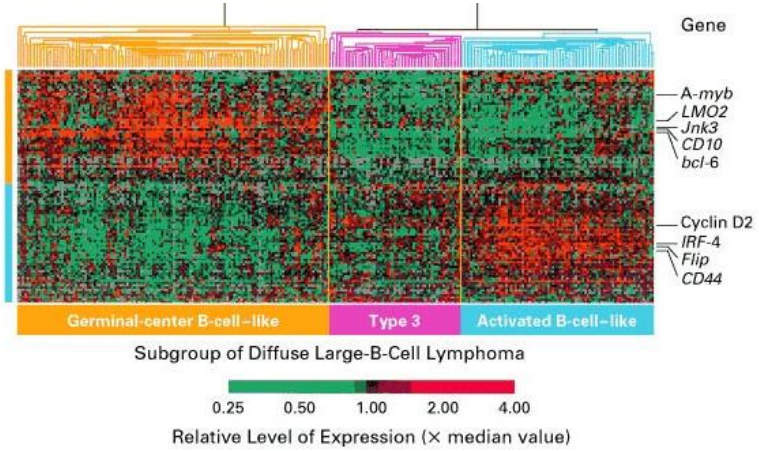

**Jerkeman M, et al. Presented at: European Hematology Association (EHA) 2023 Congress; June 8-11, 2023; Frankfurt, Germany. Abstract S227.**

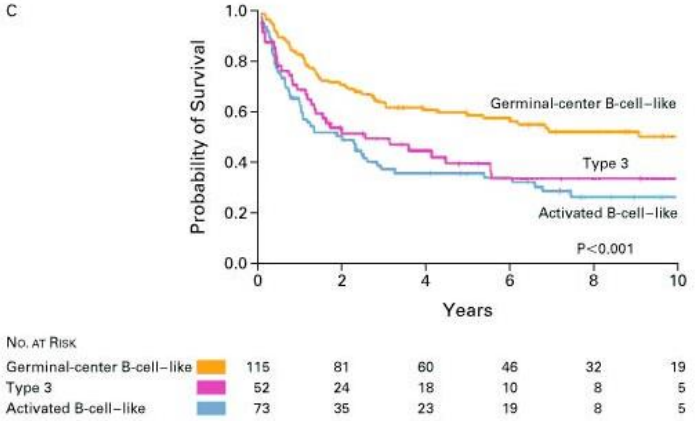
# Other Novel Combinations in Older Patients

- EPCORE® DLBCL-3: Fixed duration epcoritamab monotherapy (NCT05660967)
- R-Pola-Glo (NCT05798156)
- Tafasitamab, lenalinomide, and rituximab (NCT04974216)
- Zanubrutinib, lenalidomide, rituximab versus R-mini-CHOP (NCT04460248)

# Tailored Treatment Based on Genetic Subtypes

# Gene Expression Profiling: Germinal Center B-Like (GCB) and Activated B-Like (ABC)




More pts in ABC group >60 (*P*=0.05) and ECOG >1 (*P*=0.03)

5-year survival
GCB-like 60%
ABC-like 35%

**Despite inferior outcomes with ABC (non-GCB), both subtypes historically treated similarly**


Alizadeh AA, et al. *Nature*. 2000;403(6769):503-511. Rosenwald A, et al. *New Engl J Med*. 2002;346(25):1937-1947. Lenz G, et al. *Proc Natl Acad Sci U S A*. 2008;105(36):13520-13525.

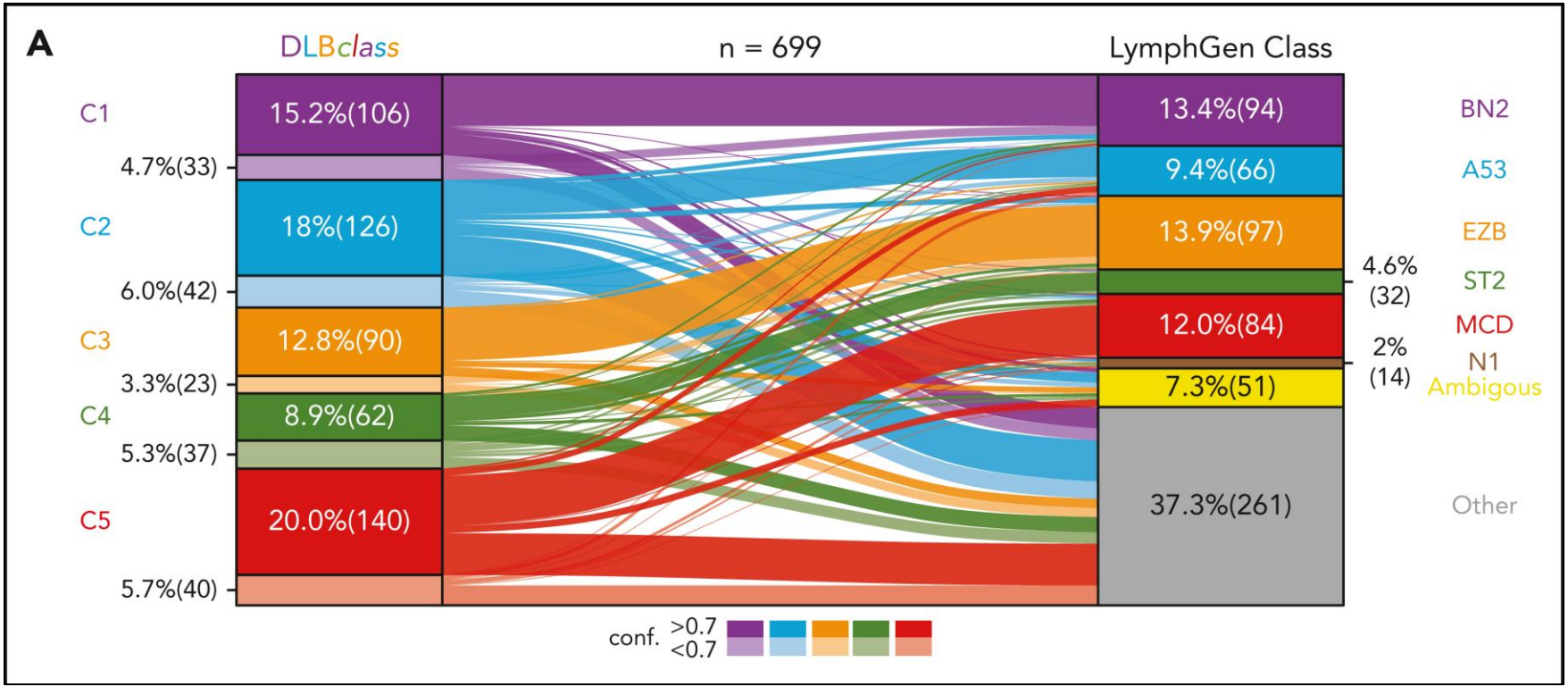
# Genetic Subtypes Further Categorize DLBCL

| DLBclass | LymphGen | Key Mutations | COO | Clinical Associations | 5YOS ('18) |
|---|---|---|---|---|---|
| C1 | BN2 | NOTCH2, BCL6, NF-κB | ABC | MZL | 65% |
| C2 | A53 | TP53 inactivation<br>CDKN2A copy loss | ABC/<br>GCB | Distinct survival differences between ABC and GCB | ABC: 33%<br>GCB: 100% |
| C3 | EZB<br>EZB-MYC+ | BCL2, EZH2, CREBBP, KMT2D | GCB | Common progenitor with FL | EZB: 68% |
| C4 | ST2 | SGK1, TET2, JAK2 | GCB | NLPHL<br>THR/LBCL | 84% |
| C5 | MCD | MYD88, CD79B | ABC | Extranodal sites | 26% |
| | N1 | NOTCH1, ID3 | ABC | Richter's transformation (CLL) | 36% |

**MZL = marginal zone lymphoma; NLPHL = Nodular lymphocyte-predominant Hodgkin lymphoma; THR = T-cell/histiocyte-rich; CLL = chronic lymphocytic leukemia.**

**Schmitz R, et al. *N Engl J Med*. 2018;378(15):1396-1407. Chapuy B, et al. *Nat Med*. 2018;24(5):679-690. Wright GW, et al. *Cancer Cell*. 2020;37(4):551-568. Chapuy B, et al. *Blood*. 2025;145(18):2041-2055.**

# DLB*class* and LymphGen Categorize into Subtypes




Schmitz R, et al. *N Engl J Med*. 2018;378(15):1396-1407. Chapuy B, et al. *Nat Med*. 2018;24(5):679-690. Wright GW, et al. *Cancer Cell*. 2020;37(4):551-568. Chapuy B, et al. *Blood*. 2025;145(18):2041-2055.

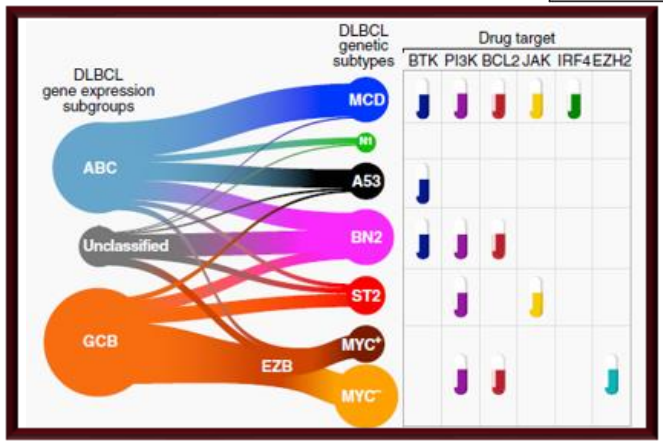
# LymphoMATCH Schema

Central Pathology Review

**DLBCL**
IPI 2-5

1 cycle chemotherapy allowed (ie, Pola-R-CHP or R-CHOP)

DLBclass
Stand-alone Notebook & GUI App
GitHub
Jupyter
Portal




**C5** (MCD)
- Pola R-CHP
- Pola R-CHP+ BTK Inhibitor

**C4** (ST2)
- Pola R-CHP
- Pola R-CHP + JAK2 Inhibitor

**C2** (A53)
- Pola R-CHP
- Pola R-CHP+ Subtype Agnostic Agent

**C1** (BN2)
- Pola R-CHP
- Pola R-CHP + Pathway Inhibitor

**C3** (EZB)
- Pola R-CHP
- Pola R-CHP + EZH2 inhibitor

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Wright GW, et al. *Cancer Cell*. 2020;37(4):551-568.

# ctDNA to Guide Treatment Decisions

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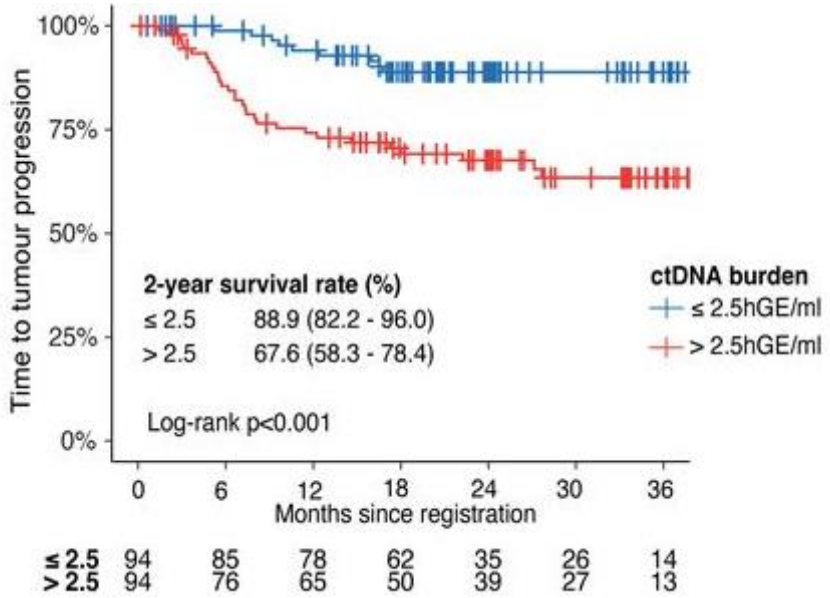
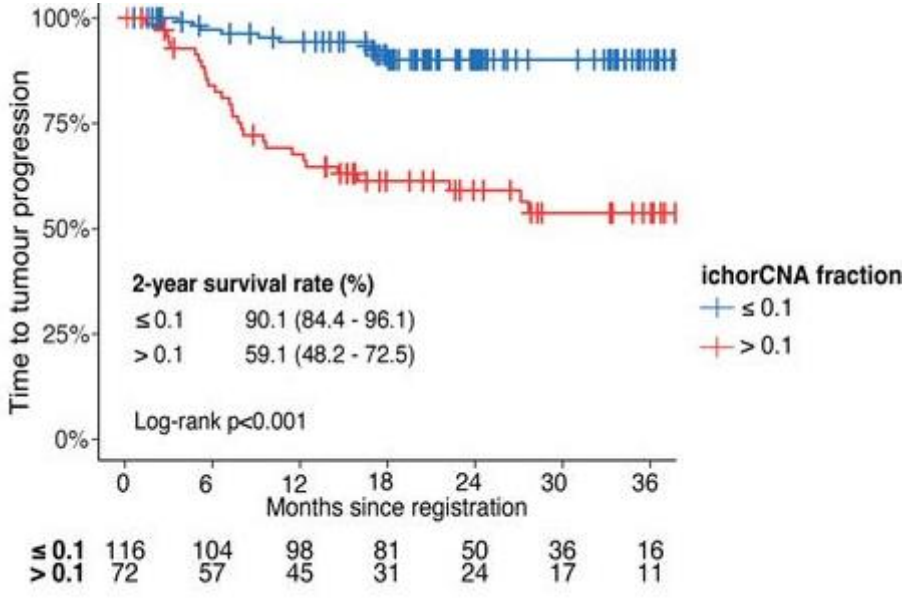
# Baseline ctDNA Value Identifies High-Risk Pts w/ DLBCL




**Prospective DIRECT study (N=188)**

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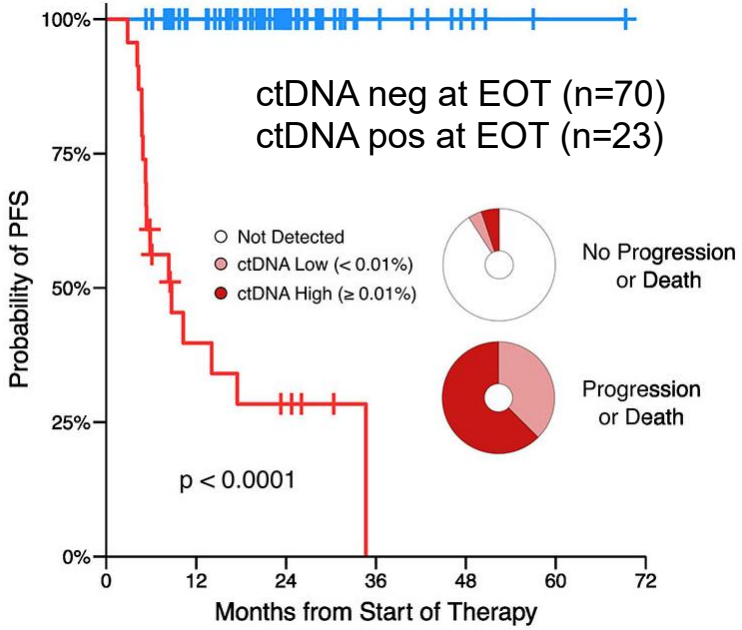
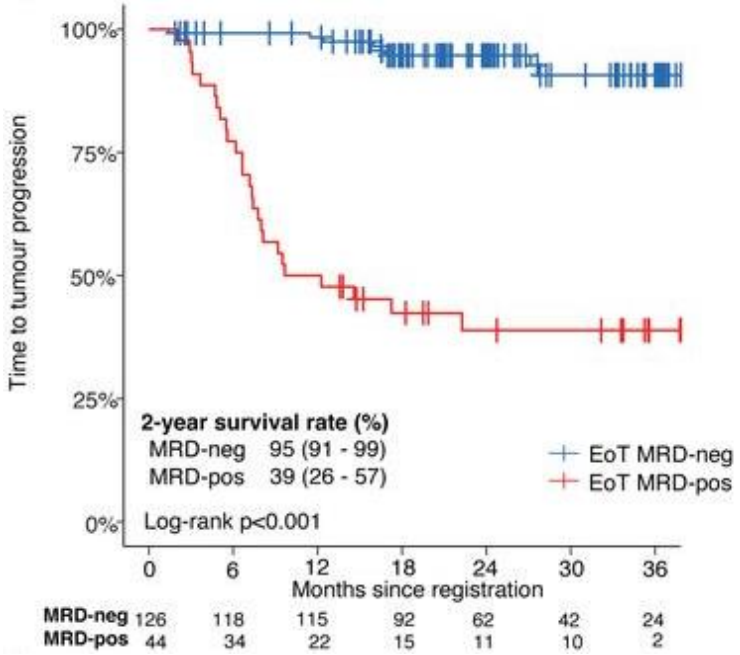
Krupka JA, et al. *Hematol Oncol*. 2025;43(S3):35-36.

# ctDNA+ at End of Treatment (EOT) Is Associated with Lower PFS



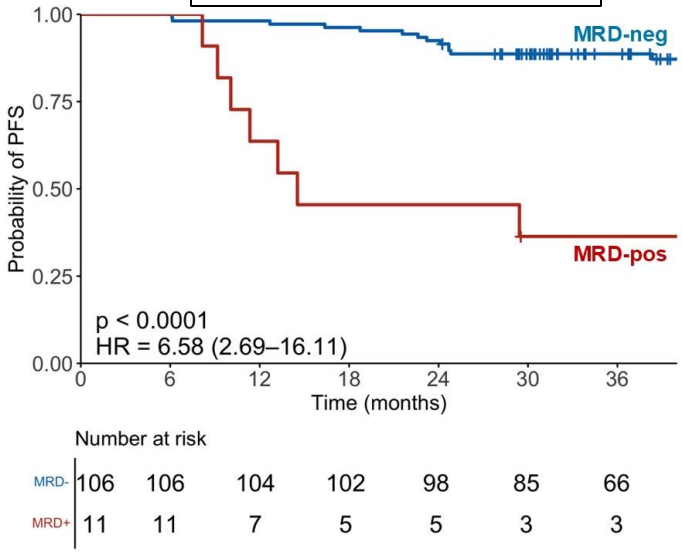





Roschewski M, et al. *Blood*. 2022;140(Suppl 1):785-786. Krupka JA, et al. *Hematol Oncol*. 2025;43(S3):35-36.
ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated June 18, 2025. https://clinicaltrials.gov/study/NCT04002947.
ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated December 18, 2024. https://clinicaltrials.gov/study/NCT00398177.
ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated September 19, 2024.
https://clinicaltrials.gov/study/NCT02529852. ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated April 11, 2025.
https://clinicaltrials.gov/study/NCT04231877. ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated October 16, 2024.
https://clinicaltrials.gov/study/NCT04134936.

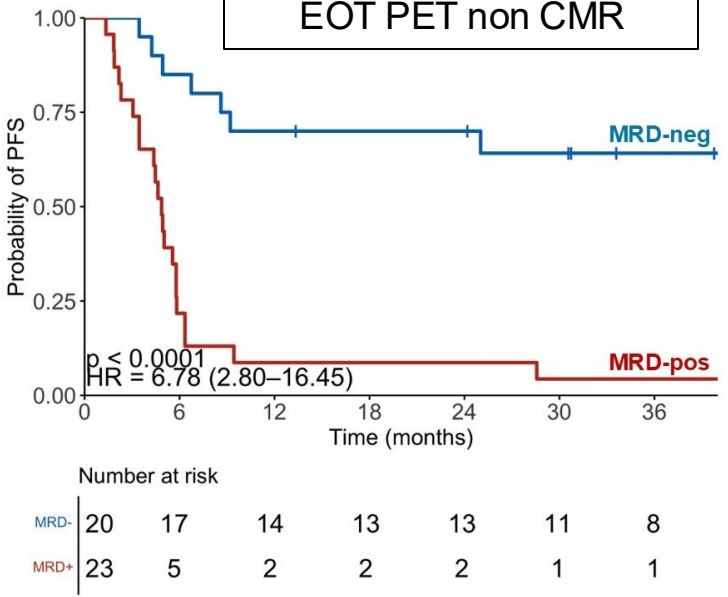
# EOT MRD Status Appears to Predict Outcomes Better than PET/CT

EOT PET CMR




ctDNA MRD neg: 3-yr PFS 89%
ctDNA MRD pos: 3-yr PFS 36%

EOT PET non CMR

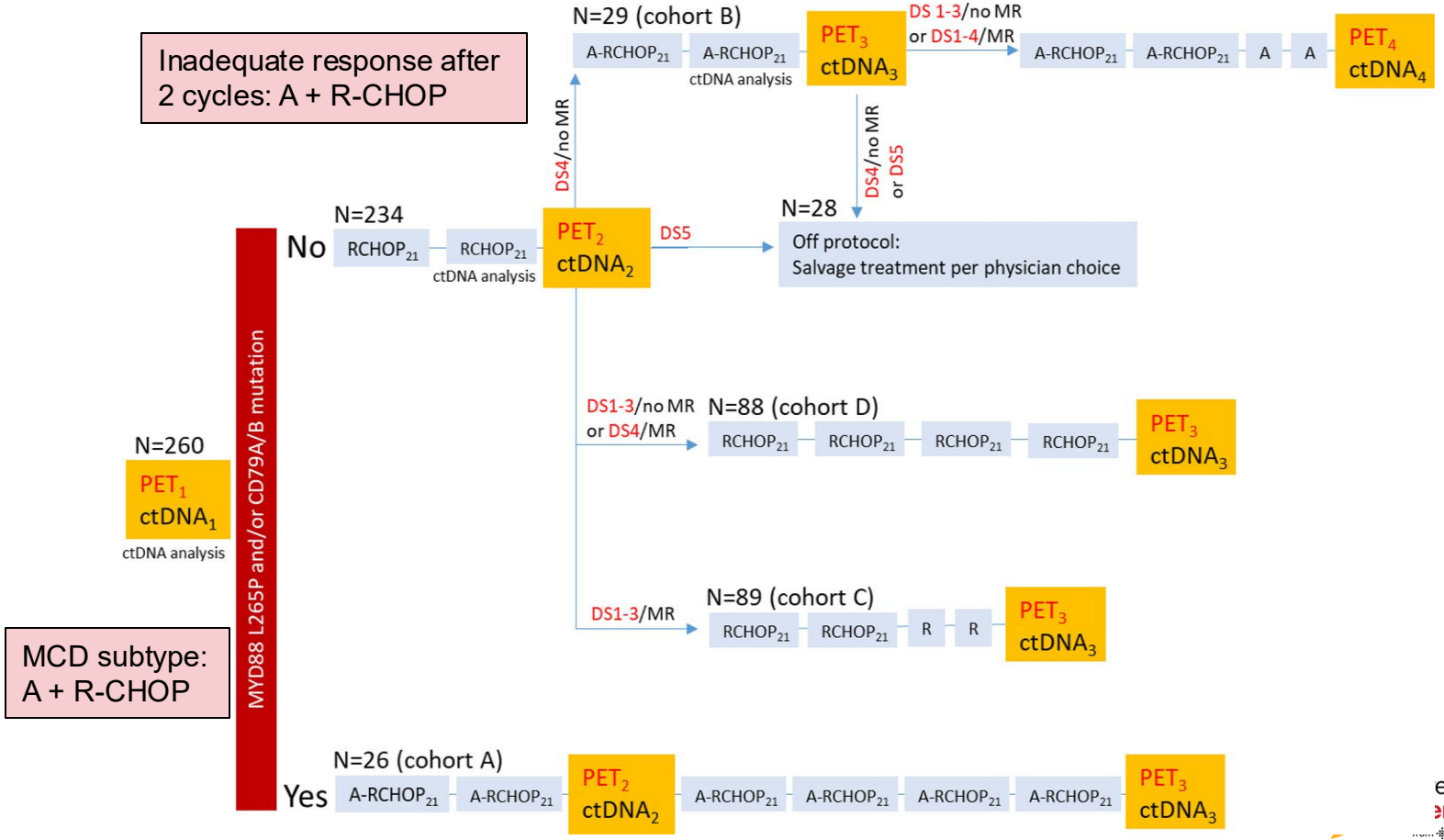



ctDNA MRD neg: 3-yr PFS 64%
ctDNA MRD pos: 3-yr PFS 4%

**Prospective HOVON study (N=160)**

Wang S, et al. *J Clin Oncol*. 2025;43(16 Suppl):7000.

# SAKK 38/19: Mutation Analysis and ctDNA/PET to Guide Therapy

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A = acalabrutinib. ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated March 28, 2025. https://clinicaltrils.gov/study/NCT0464067.

# Case Presentation

44-year-old female with left knee pain, found to have soft tissue/bone mass

- Biopsy of soft tissue/bone: diffuse large B cell lymphoma, GCB subtype
- FISH: MYC rearrangement, no BCL2 rearrangement
- PET/CT: Lymphadenopathy above/below diaphragm, LLE soft tissue/bone lesion
- Labs: normal CBC, CMP, LDH elevated at 316

**Enrolled on SKYGLO, randomized to experimental arm**

# Key Learning Points

- Pola-R-CHP is current standard of care for most pts with high risk IPI in US
- CAR T-cells and BsAb are being studied with immunochemotherapy in front line
- Multiple novel combinations are under investigation particularly in older pts
- Genetic subtypes may be used in future to tailor treatment decisionmaking
- ctDNA is likely to be used at diagnosis, during/after treatment, and in surveillance