About the Authors

Jia Li Liu, MD

Dr. Jia Li (Lily) Liu is a Hematology resident at McGill University. She completed her medical degree and Internal Medicine training at McGill University and is currently completing her Hematology training. Her research interests are in malignant hematology, with a focus on clinical outcomes and the evolving role of emerging therapies, including cellular therapy.

Affiliations
McGill University, Montreal, QC

Nathalie A. Johnson, MD, PhD, FRCPC

Dr. Nathalie Johnson is the Director of the division of Hematology at McGill University and holds the Louis Lowenstein Chair in Hematology and Oncology. She is a hematologist at the Jewish General Hospital in Montreal who performs translational and clinical research since 2010. Her research focuses on studying mechanisms of therapeutic resistance to conventional and novel therapies and identifying early relapsed lymphoma using plasma circulating tumor DNA. She is the primary investigator of several clinical trials that test novel treatments for patients with newly diagnosed or relapsed lymphoma. She is also the program director for Clinical Investigator Program at McGill University.

Affiliations:
Division Director and Louis Lowenstein Chair of Hematology at McGill University, Montreal, QC

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Front-line DLBCL Therapies in Canada in 2026: Biology Matters

Jia Li Liu, MD
Nathalie A. Johnson, MD, PhD, FRCPC

Introduction

Diffuse large B-cell lymphoma (DLBCL) is an aggressive lymphoma responsible for 30–40% of adult non-Hodgkin lymphoma cases. It can develop on its own or from indolent lymphoma.[1-2] R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) has been the front-line standard therapy choice since 2002, but about 20% of patients do not achieve a complete response, and 20–30% experience relapse.[3-4] While the International Prognostic Index (IPI) helps predict outcomes, certain biological features can signal a higher risk of treatment failure.[5] Historically, adding targeted therapies to R-CHOP has not improved outcomes. Recently, two phase III trials, POLARIX (targeting CD79b) and FRONTMIND (targeting CD19), showed improved progression-free survival (PFS) over R-CHOP. This review summarizes current front-line DLBCL therapy, emphasizing how biology can guide treatment choices.

Biologic Classifications

DLBCL classification has evolved with our growing understanding of tumour biology. This review focuses on high-risk biological features that influence clinical trial design and patient management.

Cell of Origin (COO)

A major advance in DLBCL has been the understanding of the cell of origin (COO), which predicts response to targeted therapy. DLBCL is classified into germinal centre B-cell (GCB) and activated B-cell (ABC) subtypes.[6] The ABC subtype, representing a later differentiation stage, is associated with worse outcomes and reduced chemotherapy sensitivity, likely due to persistent NF-κB pathway activation.[7] When genetic profiling is unavailable, the Hans algorithm (using immunohistochemistry [IHC] for assessment of expression of CD10, BCL6, and IRF4/MUM1) can approximate COO with about 80% concordance to gene expression profiling.[8] The Lymph2Cx assay (on the NanoString platform) offers gene expression profiling but is not widely accessible.[9]

MYC and *BCL2*

MYC and *BCL2* are key oncogenes in DLBCL, with *MYC* driving cell growth and *BCL2* blocking cell death.[10-12] "Double-hit" DLBCL has rearrangements in *MYC* and *BCL2* (detected by fluorescence in situ hybridization [FISH]) and is linked to poor prognosis due to its aggressive biology.[13] "Double-expressor" DLBCL shows high *MYC* and *BCL2* protein levels by IHC but no rearrangements, conferring an intermediate prognosis. Some DLBCL cases have a "dark zone" gene signature similar to double-hit biology but lack these rearrangements;[14,15] this can only be detected by NanoString technology in specialized centres.

Genomic Classifiers

Whole-exome sequencing has uncovered several genetic subtypes of DLBCL (such as C1-C5, LymphGen, and DLBclass),[2,5,16,17] defined by specific gene mutations (e.g., *MYD88, CD79B, BCL2, BCL6, NOTCH1/2, EZH2*). These classifications are not yet routinely used in clinical practice. CD5-positive DLBCL, seen in 5–10% of cases, is more aggressive and typically is associated with an ABC phenotype and *MYD88/CD79B*-mutated (MCD) genotype.[18]

Taken together, in the clinical setting, high-risk biology is still commonly assessed using the Hans classifier and FISH, with very few centres having access to COO determination by Lymph2Cx and dark zone signature by NanoString.

Front-line Chemoimmunotherapy

The landmark LNH-98.5 study by Coiffier *et al*. established R-CHOP as the front-line standard treatment for DLBCL in 2002.[3,4] Since then, newer studies have focused on reducing treatment for patients with low-risk, limited-stage disease and intensifying therapy for patients with high-risk, advanced-stage disease. Key clinical trials are summarized in **Table 1**.

Limited Stage Disease

Two important trials have studied the use of interim positron emission tomography (PET) scans to reduce therapy for limited-stage DLBCL. The phase III FLYER trial enrolled 594 patients under 60 years of age with early-stage, non-bulky disease and normal lactate dehydrogenase (LDH) levels. This trial established that four cycles of R-CHOP plus two doses of rituximab was just as effective as six cycles of R-CHOP.[19]

The LNH2009-1B trial, which enrolled 650 newly diagnosed low-risk patients (age-adjusted IPI =0) but aged 18–80 years, also used PET response after two cycles to guide therapy. Among patients with a PET-negative complete response, those who received four total cycles of R-CHOP did just as well as those who received six but experienced less toxicity. Older patients particularly benefited from the shorter regimen.[20]

These studies show that interim PET can safely guide a reduction in the number of R-CHOP cycles for selected patients with limited-stage, low-risk DLBCL without compromising disease control.

Advanced Stage

In advanced-stage DLBCL, research has focused on patients with poor outcomes, especially those with the ABC subtype, *BCL2*-positive disease, or double-hit DLBCL, to explore regimens that yield better outcomes than R-CHOP.

Regimens Tested in ABC-Type DLBCL, with Prospective COO Testing

R-CHOP + Ibrutinib

Bruton tyrosine kinase (BTK) is a key protein in B-cell signalling, especially in ABC-type DLBCL. Ibrutinib, a BTK inhibitor, was tested in the phase III PHOENIX trial, which compared R-CHOP plus ibrutinib to R-CHOP alone. The addition of ibrutinib did not improve response rates or survival overall. However, patients under 60 years of age had better outcomes with ibrutinib, while older patients had more side effects and did worse.[21]

R-CHOP + Lenalidomide

Lenalidomide is an immunomodulatory drug with activity in ABC-type DLBCL. The phase III ROBUST trial compared lenalidomide plus R-CHOP to R-CHOP alone in newly diagnosed ABC-DLBCL. Adding lenalidomide did not improve overall PFS, but some benefit was observed in exploratory analyses for higher-risk patients.[22]

R-CHOP + Bortezomib

Bortezomib, a proteasome inhibitor, targets the NF-κB pathway in ABC-type DLBCL. The phase II PYRAMID trial tested bortezomib plus R-CHOP (VR-CHOP) versus R-CHOP in non-GCB DLBCL. VR-CHOP did not improve survival but led to more toxicity, including thrombocytopenia and neurotoxicity.[23] The larger randomized phase III REMoDL-B study also evaluated the efficacy and safety of bortezomib +R-CHOP in over 800 patients whose tumours were classified by gene expression profiling as being ABC, GCB or molecular high-grade, which shares features with the “dark zone” signature characteristic of double hit biology. In this trial, patients received one cycle of RCHOP during the COO testing performed in “real time”, and patients were assigned to RCHOP or RCHOP + bortezomib for cycles 2–6, stratified by IPI and COO. While the primary analysis showed no benefit of adding bortezomib, at a 64-month follow-up, there was a 15% PFS and 13% OS advantage for patients with ABC DLBCL receiving bortezomib-RCHOP. Molecular high-grade was also associated with a superior PFS with the addition of bortezomib, but only 10% of patients were assigned to this group (**Table 1**).[24,25] Bortezomib-RCHOP was associated with a higher rate of neuropathy.

With the exception of REMoDL-B, these trials required prospective COO classification before randomization introduced screening delays and required patients to be clinically stable enough to await results, potentially introducing selection bias by excluding sicker patients unable to tolerate delayed therapy.

Trial	Inclusion Criteria	Median Follow-Up	Treatment Arms	Response	PFS/OS
Limited Stage					
FLYER[19] Phase III n=594	Untreated DLBCL Age 18–60 yrs Stage I–II Normal LDH No bulky disease	66 mos	R-CHOP x 4 + rituximab x 2 vs. R-CHOP x 6	**CR:** 91% for R-CHOP x 4 + R x 2 vs. 92% for R-CHOP	**3yr PFS:** 96% for R-CHOP x 4 + R x 2 vs. 93% for R-CHOP
LNH2009-1B[20] Phase III n=650	Untreated DLBCL Age 18–80 yrs	5.1 yrs	PET-adapted R-CHOP x 4 vs x 6	**ORR:** 99.4% in PET-adapted vs. 99.1% in standard arm	**3yr PFS:** 92.0% in PET-adapted vs. 89.2% in standard arm
Advanced Stage					
LNH-98.5[4] Phase III n=399	Untreated DLBCL Stage II–IV Age 60–80 yrs ECOG PS 0–2	2 yrs, 10 yrs	R-CHOP x 8 vs. CHOP x 8	**CR:** 76% for R-CHOP vs. 63% for CHOP (p=0.005)	**2yr OS:** 70% for R-CHOP vs. 57% for CHOP **10yr PFS:** 36.5% for R-CHOP vs. 20% for CHOP **10yr OS:** 43.5% for R-CHOP vs. 27.6% for CHOP
NCT01092182[29] Phase II n=53	Untreated *MYC*-rearranged aggressive BCL Age >18 yrs Any stage/ECOG PS	55.6 mos	DA-EPOCH-R x 6	**CR:** 73.6% **PR:** 13.2%	**2yr EFS:** 71% (95% CI : 56.5-81.4%) **2yr OS:** 76.7% (95% CI : 62.6-86.1%)
LNH03-7B[38] Phase II n=150	Untreated DLBCL Age >80 yrs ECOG PS 0–2	20 mos, 12.2 yrs	R-mini-CHOP x 6	**ORR:** 74% **CR:** 40%	**2yr OS:** 59% **2yr PFS:** 47% **10yr PFS:** 13.7% **10yr OS:** 15.8%
Front-line Targeted Therapies					
PHOENIX[21] Phase III n=838	Untreated non-GCB DLBCL Stage II–IV IPI >1 Age >18 yrs ECOG PS 0–2	34.8mo	Ibrutinib + R-CHOP x 6-8 vs. R-CHOP x 6-8	**CR:** 67.3% for Ibrutinib + R-CHOP vs. 68.0% for R-CHOP **ORR:** 89.3% for Ibrutinib + R-CHOP vs. 93.1% for R-CHOP	**PFS:** HR: 0.92 (95% CI: 0.71-1.18) Ibr + R-CHOP **OS:** HR: 0.99 (95% CI : 0.71-1.38) for ibrutinib + R-CHOP
ROBUST[22] Phase III n=570	Untreated CD20+ ABC-DLBCL Stage II–IV IPI >2 Age 18–80 yrs	27.1 mos	Lenalidomide + R-CHOP x 6 vs. R-CHOP x 6	**CR:** 69% for lenalidomide + R-CHOP vs. 65% for R-CHOP **ORR:** 91% in both arms	**PFS:** HR: 0.85 (95% CI: 0.63–1.14) for lenalidomide + R-CHOP

Trial	Inclusion Criteria	Median Follow-Up	Treatment Arms	Response	PFS/OS
PYRAMID[23] Phase II n=206	Untreated non-GCB DLBCL >1 measurable lesion Age >18 yrs ECOG PS 0–2	34 mos	Bortezomib + R-CHOP (VR-CHOP) x 6 vs. R-CHOP x 6	**CR:** 56% for VR-CHOP vs. 49% for R-CHOP **ORR:** 96% for VR-CHOP vs. 98% for R-CHOP	**2yr PFS:** 82.0% for VR-CHOP vs. 77.6% for R-CHOP (p=0.70) **2yr OS:** 93.0% for VR-CHOP vs. 88.4% for R-CHOP
REMoDL-B[25] Phase III n=801	Untreated DLBCL with sufficient diagnostic materials to classify into cell of origin subtypes Age ≥18 yrs Bulky stage I, II–IV ECOG PS 0–2	64 mos	R-CHOP x1 then Bortezomib (B) + R-CHOP vs R-CHOP for cycles 2–6	Not reported	**64mo PFS for ABC:** 69.4% for RB-CHOP vs. 54.4% for R-CHOP (HR, 0.65; 95% CI, 0.43-0.98) **64mo OS for ABC:** 80.4% for RB-CHOP vs. 67.4% for R-CHOP (HR, 0.58; 95% CI, 0.35-0.95) **64mo PFS for MHG:** 54.9% for RB-CHOP vs. 29.3% for R-CHOP (HR, 0.46; 95% CI, 0.26–0.84) **64mo OS for MHG:** 60.0% for RB-CHOP vs. 47.5% for R-CHOP (HR, 0.62; 95% CI, 0.32 to 1.20) No differences in PFS/OS for GCB
CAVALLI[27] Phase II n=211	Untreated *BCL2*+ DLBCL >1 measurable lesion IPI 2–5 Age >18 yrs ECOG PS 0–2	32.2 mos	Venetoclax + R-CHOP x 6 vs. R-CHOP controls from the GOYA study	**CR:** 69% for venetoclax + R-CHOP vs. 63% for R-CHOP **ORR:** 83% for venetoclax + R-CHOP vs. 80% for R-CHOP	**2yr PFS:** 80% for venetoclax + R-CHOP vs. 67% for R-CHOP **2yr OS:** 86% for venetoclax + R-CHOP vs. 81% for R-CHOP
POLARIX[32,33] Phase III n=879	Untreated CD20+ DLBCL IPI 2–5 Age 18–80 yrs ECOG PS 0–2	2 yr, 5 yr	Pola-R-CHP x 6 vs. R-CHOP x 6	**CR:** 78.0% for Pola-R-CHP vs. 74.0% for R-CHOP (p=0.16)	**2yr PFS:** 76.7% for Pola-R-CHP vs. 70.2% for R-CHOP (p=0.02) **2yr OS:** 88.7% for Pola-R-CHP vs. 88.6% for R-CHOP (p=0.75) **5yr PFS:** 64.9% for Pola-R-CHP vs. 59.1% for R-CHOP **5yr OS:** 82.3% for Pola-R-CHP vs. 79.5% for R-CHOP

Trial	Inclusion Criteria	Median Follow-Up	Treatment Arms	Response	PFS/OS
FRONT MIND[37] Phase III n=899	Untreated DLBCL IPI 3-5, aaIPI 2–3 Age 18–80 yrs ECOG PS 0-2	35.2 mos	Tafa-len-R-CHOP x 6 vs. R-CHOP x 6	**ORR:** 80.4% for Tafa-len-R-CHOP vs. 76.1% for R-CHOP (OR: 1.29, 95% CI: 0.94–1.78)	**2yr EFS:** 71.1% for Tafa-len-R-CHOP vs. 62.9% for R-CHOP (p=0.026) **Interim 2yr OS:** HR: 0.85 (95% CI: 0.63-1.14)
Frontline Cellular Therapy					
ZUMA-12[43] Phase II n=40	LBCL Positive PET2 Age >18 yrs ECOG PS 0–1	15.9 mos, 3 yrs	Axicabtagene ciloleucel (Axi-cel)	**CR:** 78% **ORR:** 89%	**15mo PFS:** not reached **3yr PFS:** 75.1% **3yr OS:** 81.1%
EPCORE NHL-2, Arm 1[46] Phase Ib/II n=47	Untreated CD20+ DLBCL IPI >3	11.5 mos	Epco + R-CHOP x 6 then Epco x 1 year	**CR:** 76% **ORR:** 100%	**PFS, OS:** not reached
COALITION[51] Phase II n=80	High-risk LBCL Age <65 ECOG PS 0–1	20.7 mos	Glofi + Pola-R-CHP vs. Glofi + R-CHOP then Glofi x 2	**CR:** 98% **ORR:** 100%	**2yr est. PFS:** 86% **2yr est. OS:** 92%

Table 1. Standard front-line treatment trials; *courtesy of Jia Li Liu, MD and Nathalie A. Johnson, MD, PhD, FRCPC.*

Abbreviations: aaIPI: age-adjusted International Prognostic index; **ABC:** activated B-cell; **CI:** confidence interval; **CIR:** complete response; **DLBCL:** diffuse large B-cell lymphoma; **ECOG PS:** Eastern Cooperative Oncology Group Performance Score; **EFS:** event-free survival; **Epco:** epcoritamab; **est:** estimated; **GCB:** germinal centre B-cell; **Glofi:** glofitamab; **IPI:** International Prognostic Index; **HR:** hazard ratio; **LBCL:** large B-cell lymphoma; **LDH:** lactate dehydrogenase; **MHG:** molecular high-grade; **mos:** months; **ORR:** objective response rate; **OS:** overall survival; **PET:** positron emission tomography; **PFS:** progression-free survival; **Pola-R-CHP:** polatuzumab, rituximab, cyclophosphamide, doxorubicin, prednisone; **PR:** partial response; **R-CHOP:** rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; **Tafa-len-R-CHOP:** tafasitamab, lenalidomide, R-CHOP; **yrs:** years.

BCL2 Inhibition in DLBCL

The *BCL2* protein is present in about half of DLBCL cases, mainly due to B cell receptor (BCR) signalling in the ABC-type and t(14;18) in the GCB-type.[26] The CAVALLI trial tested venetoclax (a *BCL2* inhibitor) with R-CHOP in patients with IPI 2–5. While overall complete response rates were similar to historical controls, patients with *BCL2*-positive tumours by IHC had longer PFS (hazard ratio [HR]: 0.55). However, 86% of patients experienced severe hematological side effects. Too few double-hit cases were included to draw firm conclusions for that group.[27]

Regimens Tested in Double-Hit DLBCL

Double-hit lymphomas represent approximately 5% of DLBCL, and there are no randomized controlled trials specifically addressing the needs of these high-risk patients. The preferred regimen is DA-R-EPOCH (dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin), based on studies showing better survival than with R-CHOP but with higher rates of side effects like infections and neuropathy.[28,29] Other regimens (rituximab combined with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine [R-HyperCVAD] and cyclophosphamide, vincristine, doxorubicin and high-dose methotrexate, alternating with ifosfamide, etoposide and high-dose cytarabine [CODOX-M/IVAC-R]) are more toxic.[28] One retrospective study found higher response and event-free survival rates with CODOX-M/IVAC-R than DA-R-EPOCH, but the overall survival (OS) was similar for the two regimens.[30] Central nervous system involvement is common and worsens prognosis in this group.[28]

Based on encouraging results in the CAVALLI trial, venetoclax was combined with DA-R-EPOCH in high-risk double-expressor and double-hit DLBCL in the Alliance A051701 trial. However, adding venetoclax did not improve PFS and led to higher toxicity and more deaths.[31]

Regimens Enrolling Patients with High-Risk IPI, Without Prospective COO Testing

POLARIX

The POLARIX study is the most important recent trial in DLBCL, and the only one to change front-line therapy in Canada since R-CHOP. In this randomized phase III trial, patients with newly diagnosed DLBCL (IPI 2–5) received either polatuzumab, rituximab, cyclophosphamide, doxorubicin, and prednisone (pola-R-CHP) or standard R-CHOP. Polatuzumab vedotin, which targets CD79b, replaces vincristine and delivers chemotherapy directly into lymphoma cells. POLARIX met its primary endpoint, with a 2-year PFS of 76.7% for pola-R-CHP versus 70.2% for R-CHOP (p=0.02). OS and complete response rates were similar. The safety profile was comparable between the regimens, though febrile neutropenia was more frequent with pola-R-CHP. Five-year follow-up confirmed a sustained PFS benefit, making this the first regimen to show meaningful improvement over R-CHOP in more than 20 years.[32,33]

Importantly, POLARIX demonstrates that DLBCL biology, specifically COO, matters in front-line therapy. In exploratory analyses, patients with the ABC subtype had a much greater benefit from pola-R-CHP. The 5-year PFS was 72.5% for pola-R-CHP versus 45.8% for R-CHOP, and 5-year OS was also higher (84.6% vs. 69.9%). Mechanistically, this is likely because polatuzumab targets CD79b, a critical component of the BCR complex. CD79b mutations, present in 30% of ABC-DLBCL, stabilize the BCR-CD79b complex and increase CD79b availability for drug binding. By targeting and degrading CD79b, polatuzumab both delivers a potent cytotoxin and disrupts essential survival pathways unique to ABC-DLBCL, resulting in greater clinical efficacy in this subgroup (**Figure 1**).[34-36] As a result, the overall PFS benefit in the POLARIX population is driven by the strong effect in ABC-DLBCL, with no benefit observed in GCB-DLBCL. Notably, COO was assessed centrally, but was not required for trial enrollment or treatment decision, making this regimen accessible in real-world practice.[32,33] Funding for pola-RCHP is contingent on ABC or non-GCB type in most Canadian provinces, except in Quebec, where it is approved for all DLBCL patients with an IPI of 2–5.

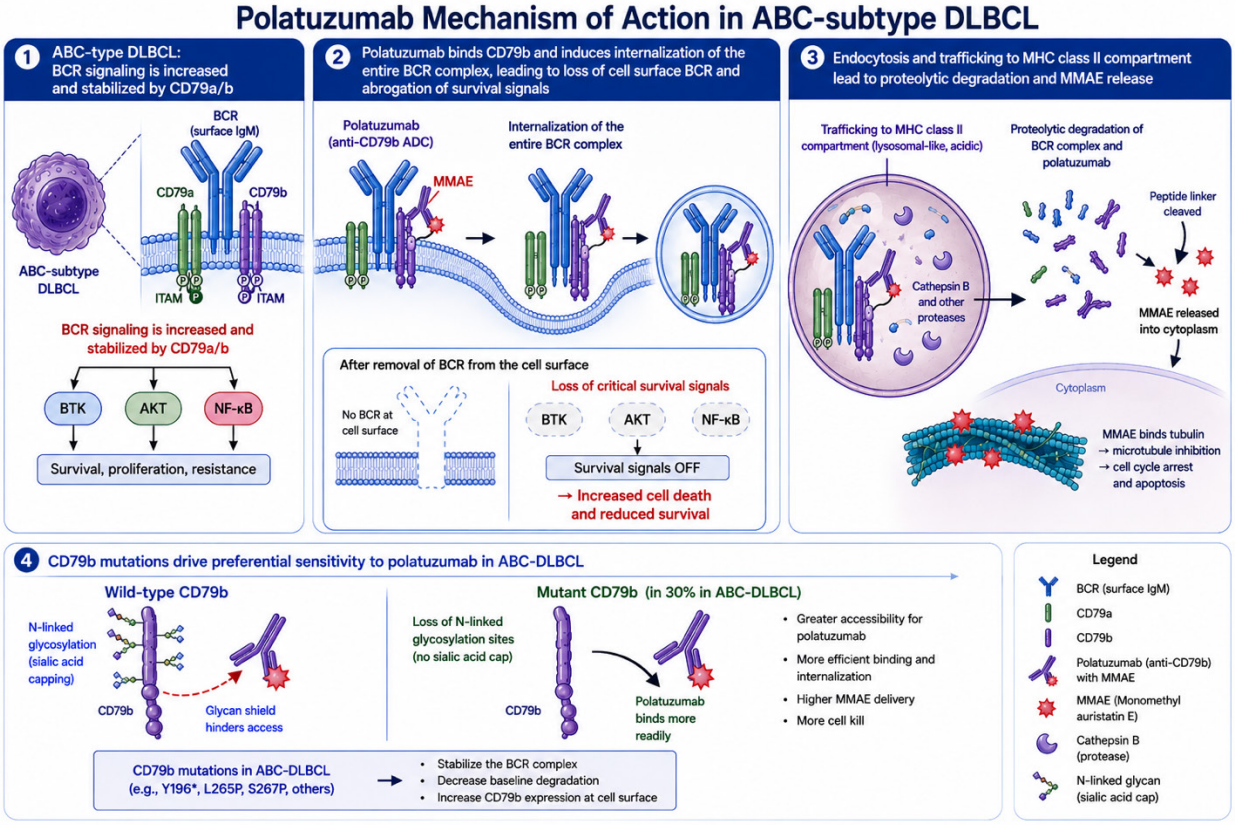

Figure 1. Proposed mechanisms underlying the preferential activity of polatuzumab vedotin in activated B-cell (ABC) diffuse large B-cell lymphoma (DLBCL); *courtesy of Jia Li Liu, MD and Nathalie A. Johnson, MD, PhD, FRCPC.*

In ABC-DLBCL, chronic B-cell receptor (BCR) signaling is maintained by the CD79a/CD79b complex. Polatuzumab vedotin binds CD79b, triggering internalization of the entire BCR complex and its trafficking to lysosomal MHC class II compartments, where proteolytic degradation cleaves the linker and releases the cytotoxic payload monomethyl auristatin E (MMAE) into the cytoplasm. Simultaneous removal of the BCR from the cell surface attenuates downstream survival signaling through Bruton's tyrosine kinase (BTK), AKT, and NF-κB. CD79b mutations, which are enriched in ABC-DLBCL, stabilize the BCR by reducing constitutive receptor degradation, resulting in increased surface CD79b expression and greater intracellular MMAE delivery following polatuzumab binding. In addition, loss of N-linked glycosylation, including terminal sialic acid residues, may reduce steric hindrance and enhance CD79b accessibility to polatuzumab, potentially increasing antitumour activity.[34-36]

FRONTMIND

The newly published FRONTMIND trial is the second study, after POLARIX, to show improved PFS over R-CHOP in the front-line setting. FRONTMIND was a randomized, double-blind, placebo-controlled phase III trial that enrolled 899 patients with high-intermediate or high-risk DLBCL or high-grade B-cell lymphoma, without requiring COO testing for eligibility. This differs from the ROBUST trial, which required confirmation of the ABC subtype by gene expression profiling prior to receiving therapy. In FRONTMIND, patients in the experimental arm received tafasitamab (an anti-CD19 monoclonal antibody, 12 mg/kg intravenous [IV] on days 1, 8, and 15) and lenalidomide (25 mg/day orally, days 1–10) alongside standard R-CHOP. In contrast, ROBUST used a lower lenalidomide dose (15 mg, days 1–14) and did not include tafasitamab. At a median follow-up of 35.2 months, tafa-len-R-CHOP improved 2-year PFS (71.1% vs. 62.9%; HR: 0.75; p=0.0194) compared to R-CHOP, but the OS

was similar. Grade >3 adverse events and fatal events were more frequent in the experimental arm, though total deaths were lower. Premature discontinuation rates were comparable. The improved outcomes in FRONTMIND may relate to its broader eligibility, higher lenalidomide dosing, and the addition of tafasitamab. However, this regimen has not been directly compared with pola-R-CHP, and it is too early to determine whether targeting CD19 in front-line therapy affects subsequent responses to CD19-directed therapies in second-line therapy.[37]

Advanced Age and Frail Patients

Most clinical trials of new regimens enroll only patients healthy enough to tolerate full-dose R-CHOP, excluding many older adults (>80 years) and those with frailty or significant comorbidities. Treating these vulnerable patients is especially challenging, as they often cannot tolerate standard R-CHOP due to increased risk of severe toxicity. For advanced-age and frail patients with DLBCL treated with curative intent, R-mini-CHOP (rituximab and reduced dose CHOP) is commonly used. In a phase II trial of patients older than 80 years, R-mini-CHOP achieved a 74% response rate, with 2-year OS and PFS rates of 59% and 47%, respectively.[38] While not directly compared with R-CHOP, R-mini-CHOP outcomes are likely inferior to standard therapy, but better than palliative care. New regimens with novel agents are under investigation for these patients, but interpreting their results is difficult because there is no standardized way to define who is "ineligible" for R-CHOP.

Future Directions

With the success of immunotherapy and chemotherapy combinations in DLBCL, the next wave of research is focused on integrating cell therapies and bispecific T-cell engagers (BiTEs) into front-line treatment. These novel approaches show activity in both GCB and ABC subtypes, potentially benefiting a broad range of patients.[39] CD19-directed chimeric antigen receptor-T cell (CAR T) therapy has already delivered strong results in relapsed/refractory DLBCL and received approval in the second-line setting.[40,41] Notably, the ongoing phase III ZUMA-23 trial is testing CAR T (axi-cel) in the front-line setting.[42] Uniquely, ZUMA-23 randomizes patients after they receive a single cycle of R-CHOP, instead of requiring full eligibility screening beforehand. This design is a major innovation as it allows enrolment of the sickest and highest-risk patients (such as those with IPI 4–5), providing rapid access to therapy before disease progression can occur during the conventional screening/waiting period. Early studies, like ZUMA-12, have shown promising response rates and long-term outcomes.[43] CAR-T toxicities, including cytokine release syndrome (CRS) and neurotoxicity (immune effector cell-associated neurotoxicity syndrome [ICANS]), are generally manageable and predictable.[44]

BiTEs, such as epcoritamab, glofitamab, and mosunetuzumab, are "off-the-shelf" immunotherapies that bring a patient's own T cells into direct contact with malignant B cells. These agents have shown significant activity in heavily pretreated DLBCL and are being tested as single agents and in combination with chemotherapy for transplant-ineligible and front-line patients. Large, randomized studies, such as EPCORE DLBCL-2 (epcoritamab with R-CHOP) and SKYGLO (glofitamab with Pola-R-CHP), are ongoing. BiTE toxicities (such as CRS and ICANS) are typically less frequent and less severe than with CAR T, but cytopenias and infections remain concerns.[45-48]

Finally, circulating tumour DNA (ctDNA)-guided approaches are emerging as a promising way to personalize front-line therapy. Highly sensitive ctDNA technologies (e.g., clonoSEQ, CAPP-Seq, PhasED-Seq) could guide early treatment escalation, de-escalation, or relapse detection, but remain investigational for now.[49,50]

Conclusion

Advances in our understanding of DLBCL biology have led to access to novel front-line therapies beyond R-CHOP, most notably with the introduction of Pola-R-CHP following the POLARIX trial. The POLARIX study clearly shows that tumour biology matters. Patients with ABC-type DLBCL, in particular, benefit from this targeted approach. However, there remains a significant unmet need for patients with primary refractory disease, as approximately 20% of patients do not achieve a complete response with R-CHOP or Pola-R-CHP.

Looking ahead, interpreting new front-line trial results is increasingly complex due to evolving trial designs, differences in control arms, and questions about how targeting specific antigens

in the front-line may impact the effectiveness of subsequent therapies. Continued research and careful analysis are essential to further improve outcomes for all patients with DLBCL.

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Correspondence

Nathalie A. Johnson, MD, PhD, FRCPC
Email: nathalie.johnson@mcgill.ca

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