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IMPORTANT UPDATES TO THE BREYANZI PRODUCT MONOGRAPH

BREYANZI® is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma (HGBCL), and DLBCL arising from follicular lymphoma who have refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy, and who are candidates for autologous hematopoietic stem cell transplant (HSCT).[1]

Please be advised that the Product Monograph for BREYANZI has been updated. The changes pertain to a reduction in the recommended duration of certain post-infusion patient monitoring activities.

The updated recommendations are as follows:

Patient proximity to treatment centre

Patients should be instructed to remain in proximity to the qualified treatment centre for at least **2 weeks** following infusion.

- The recommendation has been updated from '**at least 4 weeks**' to '**at least 2 weeks**' following infusion.

Monitoring for CRS

Patients should be monitored for signs and symptoms of CRS for at least **2 weeks** after infusion.

- The recommendation has been updated from '**at least 4 weeks**' to '**at least 2 weeks**' following infusion.

Monitoring neurologic toxicities

Patients should be monitored for signs and symptoms of neurologic toxicities for at least **2 weeks** after infusion.

- The recommendation has been updated from '**at least 4 weeks**' to '**at least 2 weeks**' following infusion.

Driving and hazardous activities restriction

Patients should refrain from driving or operating heavy or potentially dangerous machines for at least **4 weeks** after BREYANZI administration, or longer at the healthcare professional's discretion.

- The recommendation has been updated from '**at least 8 weeks**' to '**at least 4 weeks**' after BREYANZI administration.

Clinical use:
BREYANZI is not indicated for pediatric populations (<18 years of age).

Contraindications:
- In patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.

Most serious warnings and precautions:
- **Cytokine release syndrome (CRS):** including fatal or life-threatening reactions, can occur following treatment with BREYANZI. Delay the infusion of BREYANZI if the patient has unresolved serious events (including pulmonary events, cardiac events, or hypotension), including those after preceding chemotherapies, active uncontrolled infection or inflammatory disorder, or active graft-versus-host disease (GVHD). Monitor for CRS after treatment with BREYANZI. Treat severe or life-threatening CRS with tocilizumab with or without corticosteroids.
- **Neurologic toxicities:** including immune effector cell-associated neurotoxicity syndrome (ICANS), which may be fatal or life-threatening, occurred concurrently with CRS, after CRS resolution or in the absence of CRS following treatment with BREYANZI. Monitor for neurologic events after treatment with BREYANZI. Provide supportive care and/or corticosteroids as needed.
- **BREYANZI administration:** under the supervision of healthcare professionals experienced in hematological malignancies at a qualified treatment centre.

Other relevant warnings and precautions:
- BREYANZI is intended solely for autologous use.
- BREYANZI is for intravenous use only.
- Do not use a leukodepleting filter.
- Patients treated with BREYANZI should not donate blood, organs, tissues and cells for transplantation.
- There is no experience of use of BREYANZI in patients with primary central nervous system (CNS) lymphoma.
- Risk of secondary malignancies.
- Patients should refrain from driving or operating heavy or potentially dangerous machines for at least 4 weeks, or longer at the healthcare professional's discretion.
- Risk of tumour lysis syndrome (TLS).
- Risk of hypogammaglobulinemia.
- The safety of the use of live vaccines with BREYANZI has not been established.
- Risk of hypersensitivity.
- Risk of prolonged cytopenias.
- Risk of viral reactivation, febrile neutropenia, serious, life-threatening or fatal infections.
- Life-threatening and opportunistic infections have been reported in immunosuppressed patients.
- Pregnancy status of women of child-bearing age should be verified using a pregnancy test prior to starting BREYANZI treatment.
- Sexually active men and women who receive BREYANZI should use appropriate contraceptives.
- The safety and efficacy of BREYANZI in pregnant women has not been established. BREYANZI is not recommended for women who are pregnant and pregnancy after BREYANZI should be discussed with treating physician.
- Fetal/neonatal adverse reactions.
- It is unknown whether BREYANZI cells are excreted in human milk. Women who are breast-feeding should be advised of the potential risk to the breast-fed child.

For more information:
Please consult the BREYANZI Product Monograph for important information relating to adverse reactions, drug interactions, and dosing. The Product Monograph is also available by calling BMS Medical Information at **1-866-463-6267** or by email at medical.canada@bms.com.

Access the complete Product Monograph and learn more about BREYANZI

Reference: 1. BREYANZI Product Monograph. Bristol-Myers Squibb Canada.

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Relapsed Follicular Lymphoma in 2026: Evolving Treatment Strategies in the Canadian Context

Mary-Margaret Keating, MD, FRCPC

Introduction

Follicular lymphoma (FL) is the most common indolent lymphoma, characterized by a relapsing-remitting course over many years and repeated need for systemic therapy.[1] Although outcomes for many patients are excellent, with median overall survival (OS) now exceeding 20 years, a subset of patients experiences early relapse, treatment resistance, or histologic transformation associated with inferior outcomes.[2] Management of relapsed disease has relied on sequential chemoimmunotherapy, with treatment selection guided by duration of remission and patient fitness. This paradigm is now evolving with the availability of novel therapies such as chimeric antigen receptor (CAR) T-cell therapy.[3] In addition, maturation of data on lenalidomide-based triplet combinations and the emergence of bispecific antibodies are expected to further reshape treatment algorithms, pending Canadian funding decisions. This review outlines an updated approach to relapsed FL, focusing on treatment sequencing, evolving therapeutic strategies, and Canadian access considerations.

First-Line Therapy and Duration of Remission

First-line therapy for symptomatic FL in Canada remains largely unchanged, with bendamustine and rituximab (BR) commonly used, often followed by maintenance rituximab.[4] This approach results in a median remission measured in years, although outcomes remain heterogeneous and influenced by disease biology and treatment strategy.[5] Early progression within 24 months of first-line therapy (POD24) has historically defined a high-risk subgroup with an inferior survival and increased rate of transformation.[6,7]

Second-Line Therapy

The approach to second-line therapy for FL is evolving, with a shift away from repeated

traditional chemoimmunotherapy toward immune-based and targeted strategies. Treatment selection continues to be influenced by prior therapy, duration of response (DOR) and patient fitness, and access to novel therapies. However, distinctions between early and late relapse may become less clinically relevant as treatment options expand. Repeat biopsy at relapse should be performed prior to initiating subsequent therapy, particularly in patients with POD24 who have a higher rate of histologic transformation.[8,9]

Lenalidomide Plus Rituximab (R²) Foundation

The AUGMENT trial established lenalidomide plus rituximab (R²) an effective chemotherapy-free option for relapsed FL. This phase III study enrolled patients with FL and marginal zone lymphoma (MZL) who received at least one prior line of therapy and demonstrated a significant improvement in progression-free survival (PFS) with R² compared with rituximab monotherapy (39.4 vs. 14.1 months).[10] It is important to note that this trial excluded patients with rituximab-refractory disease and the use of rituximab monotherapy as the comparator likely selected for a relatively favorable risk population. This may partly explain the longer PFS seen with R² in AUGMENT compared with the R² control arms in the more recent phase III triplet trials. Although not uniformly reimbursed across Canada, R² is often accessible through compassionate programs and remains widely used in clinical practice. The PFS benefit was maintained in higher-risk populations, including patients with early relapse (POD24), supporting R² as a chemotherapy-sparing regimen and a foundation for the development of emerging triplet therapies.

Emerging Triplet Strategies

Given the established efficacy of R² in relapsed FL, recent studies have explored whether adding a third, time-limited targeted agent can deepen responses and prolong remissions, particularly in higher-risk disease. Among these strategies, the phase III EPCORE FL-1 trial evaluated the addition of the CD20/CD3 bispecific antibody, epcoritamab, to R², and demonstrated markedly improved response rates and PFS compared with R² alone, including overall response rates (ORR) of 95% vs. 79% and estimated 16-month PFS of 85.5% vs. 40.2%, respectively.[11] Safety data showed higher rates of grade ≥3 adverse events in the triplet arm (90% vs. 68%), although cytokine release syndrome (CRS) was predominantly low grade.[11]

An alternative approach was evaluated in the Phase III inMIND trial, in which the CD19 monoclonal antibody tafasitamab was added to R². The combination demonstrated a statistically significant improvement in PFS compared to R² alone (median 22.4 vs. 13.9 months; hazard ratio [HR]: 0.43), with an acceptable safety profile.[12] Although the magnitude of benefit appears more modest than that observed with epcoritamab-based therapy, cross-trial comparisons should be interpreted cautiously. This regimen may offer a more accessible and better-tolerated outpatient option, particularly for patients less suited to more intensive bispecific antibody-based therapies.

At present, none of these triplet combinations is publicly funded in Canada, although regulatory approval status and provincial access continue to evolve. It remains to be determined whether they will become available and how they may be positioned relative to one another based on patient fitness, access, and treatment goals.

Third-Line and Subsequent Therapy

Beyond triplet strategies, other immune-based approaches, including CAR T-cell therapy and bispecific antibody monotherapy, are important subsequent options.

CAR T-Cell Therapy

For heavily pretreated patients with FL requiring third-line and subsequent therapy, CAR T-cell therapy has emerged as a highly active treatment option capable of inducing deep and durable remissions. Axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) are approved in Canada based on the ZUMA-5 and ELARA studies, respectively.[13,14] Long-term follow-up from ZUMA-5 (median follow-up 64.4 months) demonstrated an ORR of 90%, a complete response (CR) rate of 75%, and a median PFS of 62 months with axi-cel.[15] Similarly, updated ELARA data, at a median follow-up of 29 months, demonstrated durable responses with tisa-cel, including an ORR of 86%, CR rate of 68%, with median PFS, OS, and DOR not reached.[16]

Both products are associated with risks, including CRS and immune effector cell-associated neurotoxicity syndrome (ICANS), although events are generally manageable at experienced centres. Access and treatment selection for CAR T-cell

therapy may be influenced by both patient and system-level factors, including fitness, patient preference, caregiver support, geographic access, referral logistics, manufacturing timelines, and provincial availability. A comprehensive review of cellular therapy in FL is beyond the scope of this article and has recently been reviewed in detail in Canadian Hematology Today.[35]

Bispecific Antibody Therapy

For patients with FL requiring third-line and subsequent therapy, CD20/CD3 bispecific antibodies have emerged as highly active off-the-shelf options alongside of CAR T-cell therapy. Long-term follow-up of the single-arm, phase II study examining fixed-duration, intravenous (IV) mosunetuzumab in patients with relapsed FL after at least two prior lines of therapy demonstrated an ORR of 78%, a CR rate of 60%, and a median PFS of 24 months.[17] Among responders, remissions were durable, with a median DOR not reached at a median follow-up of 37.4 months. More recently, a subcutaneous (SC) formulation of mosunetuzumab has been evaluated, which demonstrated similar efficacy and safety as the original intravenous formulation.[18]

Mosunetuzumab monotherapy is approved by Health Canada for relapsed or refractory FL after at least two prior lines of systemic therapy; although public reimbursement is not yet universal across Canada, compassionate access may be available.[36]

Single-agent epcoritamab has also demonstrated efficacy in relapsed FL. In the phase I/II EPCORE NHL-1 study, epcoritamab achieved an ORR of 83% and CR rate of 63% in 128 patients with FL who had received at least 2 prior lines of therapy.[19] Responses were durable, with 72% of patients remaining in CR at 18 months of follow-up. Unlike fixed-duration mosunetuzumab, epcoritamab was administered continuously until progression, with the injection frequency decreasing over time.

Odronextamab has similarly demonstrated meaningful activity as monotherapy in relapsed FL. In the long-term follow-up of the phase II ELM-2

Treatment	Trial (*phase*)	Key Efficacy Findings	Canadian Context and Clinical Role
2L Therapy			
Lenalidomide and Rituximab (R^2)	AUGMENT (III)	ORR 80%, CR 51% Median PFS 39.4 vs 14.1 months (R2 vs rituximab alone)	Health Canada approved, funding variable across provinces, often compassionate access Established chemo-free backbone
Tafasitamab-R^2	inMIND (III)	ORR 83.5%, CR 45% Median PFS 22.4 vs 13.9 months (tafa-R2 vs R2)	Health Canada approved, pending funding Improved outcomes over R^2
Epcor-R^2	EPCORE FL-1 (II)	ORR 95%, CR 83% Estimated 16-month PFS 85.5 vs 40.2% (Epcore-R2 vsR2)	Health Canada approved, pending funding High ORR with deep responses over R^2
3L+ Therapy			
Mosunetuzumab	GO29781 (II)	ORR 77.8%, CR 60% Median PFS 24 months	Health Canada approved, pending funding Durable remissions with fixed-duration, off-the-shelf therapy
Axi-cel (CAR T cell)	ZUMA-5 (II)	ORR 92%, CR 79% 5-year PFS approximately 50%	Health Canada approved and funded Most durable remission strategy for fit patients
Zanibrutinib + Obinutuzumab	ROSEWOOD (II)	ORR 68%, CR 39% Median PFS 28 vs 10.4 months (ZO vs obinutuzumab alone)	Health Canada approved, pending funding Compassionate access available fo zanubrutinib Well tolerated option for later lines

Table 1. Selected Contemporary Regimens in RR FL with Relevance to Canadian Practice; *courtesy of Mary-Margaret Keating, MD, FRCPC.*

Abbreviations: 2L: second-line; **3L+:** third-line and later; **CAR:** chimeric antigen receptor; **CR:** complete response; **ORR:** objective response rate; **PFS:** progression-free survival.

study, odronextamab achieved an ORR of 81% and a CR rate of 74%, with a median PFS of 23 months in heavily pretreated patients.[20] Treatment was administered intravenously and continued until progression.

Collectively, these studies support bispecific antibodies as highly active treatment options in multiple relapsed FL, with differences in route of administration, treatment duration, access and emerging long-term data that are likely to influence treatment selection.

Other Targeted Therapies

Among other treatment approaches, the phase II ROSEWOOD trial randomized patients with FL who had received ≥2 prior lines of therapy to the targeted combination of zanubrutinib plus obinutuzumab (ZO) versus obinutuzumab alone. The combination improved ORR (69% vs. 46%) and PFS (median 28 vs. 10.4 months; HR 0.50) compared with obinutuzumab alone.[21] While not directly comparable to bispecific antibodies or CAR T-cell therapy, this regimen offers a convenient, outpatient option that may be relevant based on patient characteristics, treatment preferences, and access. In Canada, this combination is not publicly funded, although access may be possible through compassionate programs.

Additional targeted therapies include the PI3K inhibitors, such as idelalisib, duvelisib, and copanlisib, which demonstrated meaningful activity in relapsed FL.[22] These agents received regulatory approval internationally, including conditional approval of idelalisib in Canada;

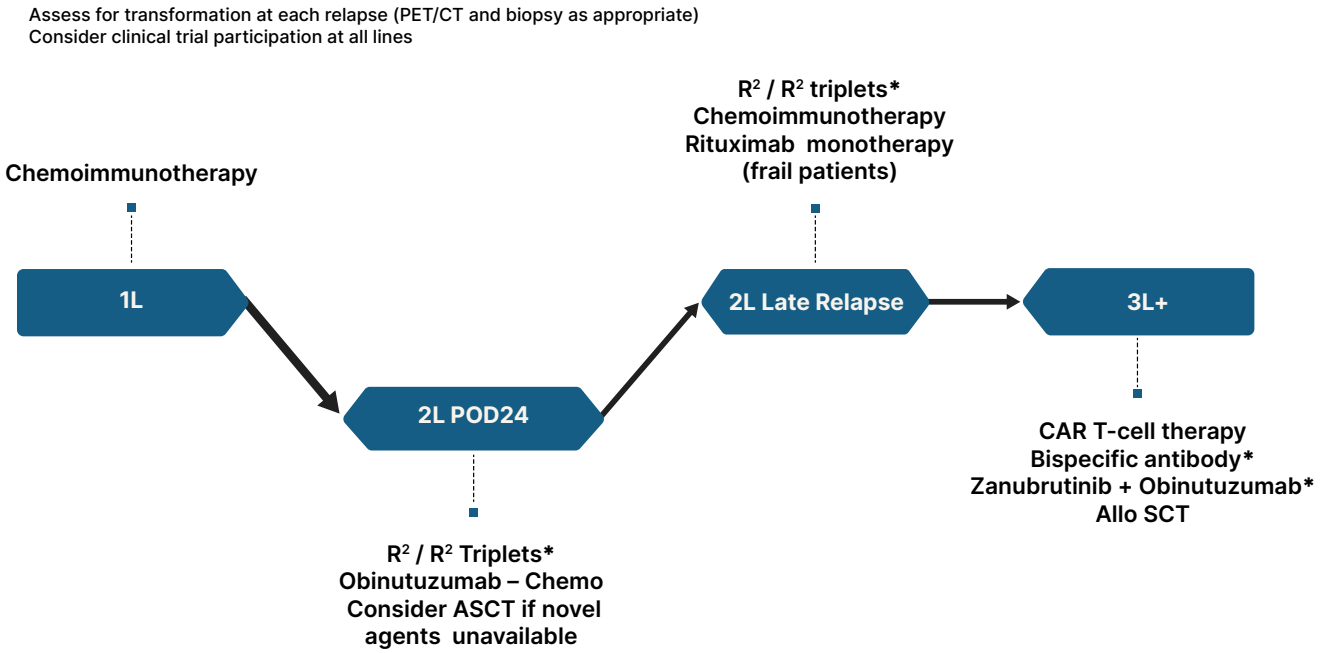

Figure 1. Flow diagram of proposed Canadian treatment pathway. A Potential Canadian Approach to the treatment of RR FL; *courtesy of Mary-Margaret Keating, MD, FRCPC*.

*Health Canada approved, pending funding

Abbreviations: 1L: first line of therapy; **2L:** second line of therapy; **3L:** third line of therapy; **R²:** lenalidomide + rituximab; **R² triplets:** tafasitamab-R² and epcoritamab-R²

however, concerns regarding immune-mediated toxicity, infectious complications, and overall safety ultimately led to withdrawal of several of these agents from the market.[22]

The EZH2 inhibitor tazemetostat also provided a well-tolerated oral treatment option for relapsed FL but was voluntarily withdrawn from global markets in early 2026 due to emerging safety concerns about secondary hematologic neoplasms identified in clinical trials.[23] These developments highlight the ongoing shift toward immune-based and cellular therapies in the management of relapsed FL.

Evolving Role of Chemoimmunotherapy and Stem Cell Transplantation

Repeat chemoimmunotherapy was previously common in relapsed FL, particularly when first-line treatment consisted of R-CHOP or R-CVP, and options beyond traditional chemoimmunotherapy were limited. In that context, bendamustine-based salvage produced remissions ranging from months to a few years, depending on prior therapy, relapse timing, and POD24 status.[24-29] However, these data are difficult to extrapolate to current practice, where BR is commonly used first-line and retreatment with bendamustine is limited by cumulative toxicity, T-cell suppression, infection risk, and, in younger patients, concerns about stem cell reserve.[30] As increasingly effective immune-based options become available, repeat chemoimmunotherapy is now generally reserved for selected patients with prolonged first remission when novel therapies are unavailable or unsuitable.

For patients with rituximab-refractory disease and POD24, the GADOLIN study evaluated bendamustine-obinutuzumab (BO) versus single-agent bendamustine, followed by maintenance obinutuzumab. The median PFS was 25.3 months in the BO group vs. 14 months with bedamustine monotherapy, leading to funding for this option for POD24 patients in Canada.[31] Although GADOLIN specifically evaluated BO, in

most Canadian provinces, obinutuzumab may also be combined with alternative chemotherapy backbones for patients with rituximab-refractory disease; however, the role of these approaches will likely decrease as access to other novel therapies improves.

Autologous and Allogeneic Transplantation

With increasing immunotherapy options and access to CAR T-cell therapy across Canada, the role of allogeneic and autologous stem cell transplant (auto-SCT) is becoming increasingly selective. Auto-SCT has historically been considered for younger, fit patients with chemotherapy-sensitive relapsed FL, particularly in the setting of early relapse or POD24, although retrospective studies have demonstrated variable long-term benefit even in high-risk populations.[32,33]

Allogeneic stem cell transplantation (allo-SCT) remains a potentially curative option in FL; however, the high median age at diagnosis, prolonged disease course, and significant treatment-related morbidity and mortality limit its use in most patients. Allogeneic transplantation is generally reserved for highly selected younger patients with multiply relapsed disease following or when unsuitable of other available therapies, including CAR T-cell therapy and bispecific antibodies.[34]

Summary

The management of relapsed FL is shifting rapidly toward immune-based, targeted and cellular therapies. Since our previous review in 2024, the treatment landscape in Canada has evolved substantially, including the approval and funding of CAR-T cell therapy for eligible patients in third-line and later settings and the emergence of CD20/CD3 bispecific antibodies as highly active treatment options. Novel R^2-based triplet combinations may further reshape treatment selection and sequencing. As access to these therapies expands, the role of repeat chemoimmunotherapy and stem cell transplantation will likely become increasingly selective. A proposed approach to treatment selection in relapsed FL by line of therapy is summarized in **Figure 1**.

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Financial Disclosures

M-M.K.: None declared.

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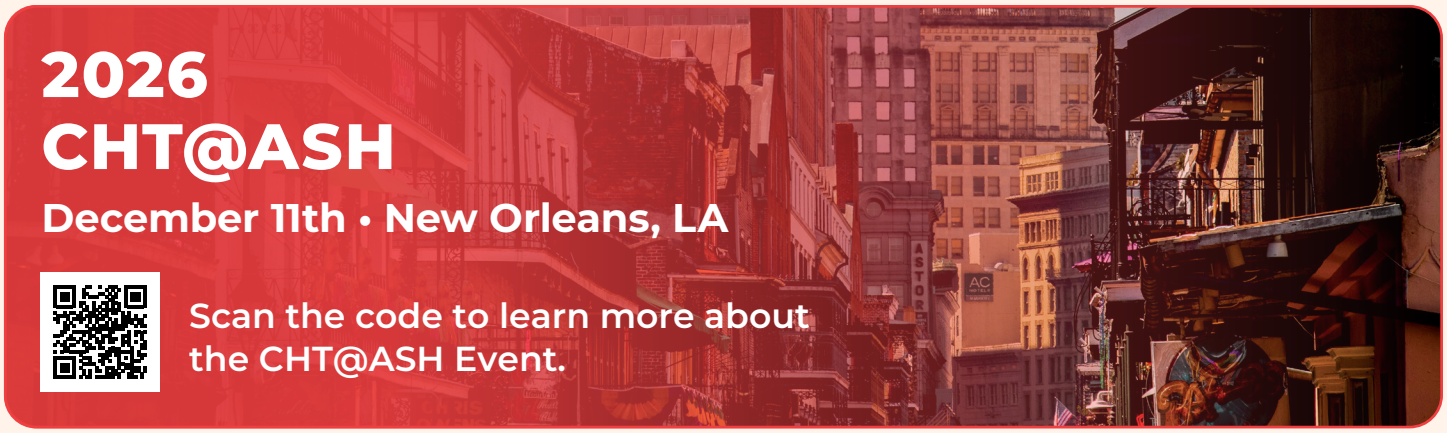

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Sequencing Therapies in Peripheral T-Cell Lymphoma

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Introduction

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of clinically aggressive mature T-cell neoplasms that represent approximately 10% of all non-Hodgkin lymphoma cases.[1] According to the most recent World Health Organization (WHO) classification and the International Consensus Classification (ICC),[2,3] there are over 30 distinct T and natural killer (NK) cell lymphomas. Although genetic and environmental factors are implicated in certain subtypes (e.g., *HTLV-1* in adult T-cell leukemia/lymphoma [ATLL]), most PTCLs are associated with genomic alterations acquired during normal T-cell development and differentiation.[1] The most common nodal PTCL subtypes, which will be the focus of this review, are PTCL-not otherwise specified (NOS), nodal T-follicular helper (TFH) lymphoma, including angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large cell lymphoma (ALCL).

TFH lymphomas are defined by the expression of at least two markers characteristic of normal TFH cells (CD10, BCL6, CXCL13, PD1, and ICOS).[2] This group comprises 3 distinct entities (angioimmunoblastic-type, follicular-type, and NOS) that have unique histologic patterns but share a common genetic landscape characterized by mutations in genes that regulate DNA and histone methylation, including *TET2, DNMT3A*, and *IDH2*.[4] Based on their pathogenesis involving epigenome dysregulation, these lymphomas appear particularly sensitive to epigenetic therapies, such as histone deacetylase (HDAC) inhibitors and azacitidine.[5,6]

PTCL-NOS encompasses a heterogeneous group of diseases and remains a diagnosis of exclusion. Among cases not classified as TFH lymphomas, two molecularly defined subgroups have been identified: PTCL-GATA3 and PTCL-TBX21, which resemble T helper 1 (Th1) and T helper 2 (Th2) cells, respectively.[4] These subgroups are associated with distinct clinical outcomes, with PTCL-GATA3 conferring a particularly poor prognosis. Importantly, these signatures may have treatment implications, as PTCL-GATA3 is associated with activation of the PI3K pathway, whereas PTCL-TBX21 appears more closely linked to STAT3 pathway activation. Ongoing research in this area will hopefully facilitate the development of more biologically targeted therapies and ultimately improve outcomes for these distinct PTCL subsets.

ALCLs are composed of large, pleomorphic CD30-positive T cells and are classified into four distinct entities: ALK-positive ALCL, ALK-negative ALCL, breast-implant-associated ALCL, and primary cutaneous ALCL. ALK-positive ALCL generally carries a more favourable prognosis than ALK-negative ALCL, in part due to the younger age at presentation.[7] Given the uniform expression of CD30 in ALCL, brentuximab vedotin (BV) has become a cornerstone of front-line therapy following the landmark ECHELON-2 trial, discussed below, which demonstrated both progression-free survival (PFS) and overall survival (OS) benefits with the incorporation of BV into an anthracycline-based regimen (BV-CHP).[8]

Historically, PTCL has been associated with inferior outcomes compared with aggressive B-cell lymphomas, with multiple national and international registry studies reporting 5-year PFS rates of approximately 20%–30% and 5-year OS rates of 30%–40%.[9] However, recent advances in identifying molecular biomarkers and understanding disease biology are increasingly enabling more individualized treatment approaches. This review will discuss an evidence-based approach to sequencing therapies for PTCL in both the front-line and relapsed/refractory settings.

Approach to Front-Line Therapy

As with the management of any malignancy, several factors must be considered when selecting a treatment approach for PTCL. Specifically, these include the histological subtype, immunohistochemistry (particularly CD30 expression), patient fitness, and transplant eligibility. This section outlines the approach to fit patients, which typically involves combination chemotherapy with or without immunotherapy (BV). For patients deemed unfit for intensive systemic chemotherapy, palliative-intent approaches may include single agents (e.g., oral etoposide or cyclophosphamide) with or without corticosteroids.

Chemotherapy

CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) has been compared with multiple alternative regimens in the front-line treatment of PTCL.[10-12] Despite retrospective studies demonstrating cure rates of <50%,[13,14] CHOP has remained the backbone of therapy for most PTCL subtypes, often with the addition of etoposide (CHOEP).[15,16] CHOEP is preferred in younger patients, largely based on an analysis of 7 prospective studies that demonstrated improved 3-year event-free survival (EFS) (75% vs. 51%) among younger (<60 years), good-risk patients (normal lactate dehydrogenase) treated with CHOEP compared with CHOP alone.[16] Notably, the benefit was most pronounced in ALK-positive ALCL, although a trend toward improved outcomes was also observed in other nodal PTCL subtypes.[16]

The landmark ECHELON-2 trial significantly changed the front-line treatment landscape for PTCL.[8] ECHELON-2 was an international phase III study investigating the use of BV, a CD30-directed antibody-drug conjugate linked to monomethyl auristatin E, a microtubule inhibitor. The study enrolled 452 patients with CD30-positive PTCL (>10% by immunohistochemistry), who were randomized to receive either BV-CHP or CHOP. With extended follow-up, patients treated with BV-CHP demonstrated estimated 5-year PFS and OS rates of 51% and 71%, respectively, compared with 43% and 61% with CHOP.[17] Importantly, approximately 70% of enrolled patients had ALCL. Although the study was underpowered to evaluate the efficacy in non-ALCL subtypes, no statistically significant improvement in PFS or OS was observed among patients with AITL or PTCL-NOS.[8,17] Based on these data, BV, in combination with CHP, has been approved by Health Canada for the front-line treatment of ALCL, as well as CD30-positive PTCL-NOS and AITL.

Several additional studies have evaluated the incorporation of novel targeted therapies into front-line treatment, including romidepsin,[18] azacitidine,[19] and belinostat.[20] Collectively, these studies demonstrated mixed efficacy results along with increased toxicity compared with CHOP alone. Therefore, these approaches have not yet been incorporated into standard front-line management.

Consolidation

Given the historically poor outcomes for PTCL and the high risk of relapse (5-year risk of 23% based on long-term follow-up),[9,21] numerous studies have evaluated the role of consolidation with autologous stem cell transplant (ASCT) or allogeneic stem cell transplant (allo-SCT).[22-27]

Although consolidative ASCT is considered standard practice at some institutions,[4] particularly for high-risk patients or those achieving complete remission (CR), this approach has largely been investigated through retrospective and single-arm phase II studies, with conflicting results. The largest prospective study was conducted by the Nordic group, in which 160 patients with newly diagnosed PTCL were treated with CHOP or CHOEP, followed by ASCT for those who achieved a partial or complete response.[22] At a median follow-up of 5 years, the estimated 5-year PFS and OS were 44% and 51%, respectively. Outcomes appeared most favourable in patients with ALK-negative ALCL (5-year PFS 61%), compared with AITL (49%) and PTCL-NOS (38%).[22] Similarly, several more recent retrospective studies have demonstrated improvements in EFS, PFS, and OS with consolidative ASCT among patients who responded to front-line therapy, particularly those who achieved CR.[15,23,24,26] In a nationwide Dutch registry study evaluating the role of etoposide and ASCT, the authors performed a sensitivity analysis restricted to patients who achieved CR and demonstrated a significantly improved 5-year OS in patients undergoing consolidation compared with those who did not (82% vs. 47%; $p<0.01$).[15]

In contrast, a propensity score-matched analysis by the LYSA group of patients with nodal PTCL demonstrated no significant benefit in either PFS or OS with consolidation ASCT.[28] Similarly, a subgroup analysis of patients achieving CR following BV-CHP enrolled on the ECHELON-2

study demonstrated improved PFS with ASCT consolidation (65% vs. 46%); however, this benefit was not observed among patients treated with CHOP.[29] To date, no randomized controlled trial has definitively established the benefit of ASCT consolidation, and this remains a subject of ongoing controversy and investigation.

Allo-SCT consolidation is often considered in eligible patients with PTCL. A randomized phase III trial compared ASCT and allo-SCT as consolidation strategies following front-line therapy in younger patients with PTCL.[27] Patients received four cycles of CHOEP followed by one cycle of DHAP (dexamethasone, high-dose cytarabine, and cisplatin) prior to proceeding to either ASCT or allo-SCT. Although a robust graft-versus-lymphoma effect was observed, with a 0% relapse rate at 3 years in the allo-SCT group, this was offset by substantially higher non-relapse mortality (23% vs. 0%).[27] The study was ultimately terminated early due to futility. Long-term follow-up of the AATT study similarly demonstrated a strong graft-versus-lymphoma effect, with a 7-year relapse rate of 8%, although this was again counterbalanced by high rates of non-relapse mortality (23%).[25]

Taken together, these studies suggest consolidative ASCT may be considered in patients with chemosensitive disease given the potential for improved long-term outcomes, particularly among higher-risk patients. Some guidelines recommend restricting this approach to patients achieving CR following front-line chemotherapy. However, this strategy is not uniformly adopted across Canadian institutions due to the absence of definitive randomized data. Two ongoing clinical trials are investigating the role of ASCT in patients with PTCL who achieve CR following front-line therapy (NCT05444712 and NCT06724237),[30,31] including the US-based ECOG study, in which Canadian centres are participating.[30]

Approach to Relapsed/Refractory PTCL

As previously discussed, more than 50% of patients with nodal PTCL, with the exception of ALK-positive ALCL, will ultimately experience disease relapse.[9] The median OS in the relapsed/refractory setting is less than 6 months, highlighting the need for novel therapies and the importance of considering clinical trial enrollment at each line of therapy.[32] Allo-SCT remains the only potentially curative treatment option in this setting.[33] As such, the choice of second-line therapy should take into account whether the patient is fit for an allo-SCT. Additional considerations include prior BV exposure, PTCL subtype (which may predict differential response to therapy), chemosensitivity, timing of relapse, and patient fitness.

In fit, transplant-eligible patients, most available evidence supports the use of allo-SCT over ASCT, except for ALCL and potentially late relapses post-front-line therapy. Patients with relapsed ALCL appear to have particularly favourable outcomes from ASCT, with reported 3-year PFS and OS rates of 53% and 65%, respectively, compared with 29% and 42% in PTCL-NOS.[34-37] Importantly, allo-SCT may provide durable disease control even in patients who relapse following ASCT or those with refractory disease, highlighting its curative potential. Collectively, these studies suggest that ASCT should be considered in relapsed ALCL when not previously utilized in the front-line setting, whereas allo-SCT should generally be favoured in patients with AITL and PTCL-NOS given the potential for long-term disease control and cure.[33-38]

Multi-agent chemotherapy, most commonly gemcitabine, cisplatin, and dexamethasone (GDP), is a frequently used salvage regimen in relapsed PTCL, particularly as a bridge to stem cell transplant. This approach is supported by a subset analysis of the LY.12 study, which demonstrated an overall response rate (ORR) of 38% in patients with PTCL intended to proceed to ASCT.[39] Among patients who ultimately underwent ASCT, the 2-year EFS and OS were 21% and 42%, respectively.[39] Given the limited treatment options in this setting, GDP-based salvage therapy remains a common approach in many Canadian institutions, including in patients ultimately planned for allo-SCT.

In patients who are not candidates for allo-SCT, several novel agents, as highlighted in **Table 1**, adapted from Moskowitz et al.,[4] may be considered. However, these therapies are generally unlikely to produce durable long-term remissions or a cure. Thus, treatments that can be continued without significant cumulative toxicity are generally preferred in this setting.[4] Single-agent approaches are generally favoured to minimize toxicity while preserving quality of life.

Pralatrexate is a folate analog metabolic inhibitor that competitively inhibits dihydrofolate reductase. In the phase II single-arm PROPEL study, pralatrexate demonstrated modest efficacy in relapsed/refractory PTCL with an ORR of 29%

Drug	Target	n	ORR, CR	Comments	Public access in Canada
GDP (gemcitabine, dexamethasone, cisplatin)[39]	Multi-agent chemotherapy	Salvage/bridge to transplant	ORR 38%	Commonly used as a bridging regimen prior to consolidative ASCT or allo-SCT in relapsed setting	Yes
Pralatrexate[40]	Folate	109	ORR 29%, CR 11%	Lower response rates observed in AITL	Yes
Brentuximab vedotin[41]	CD30	34	ORR 41% (54% in AITL), CR 24%	Most active in ALCL; re-treatment may be considered in select patients, particularly if relapse >6 months	Yes (ALCL)
Romidepsin[42]	HDAC inhibitor	130	ORR 25%, CR 15%	Durable responses reported in AITL (median PFS 29 months); withdrawn from Canadian market	No
Azacitidine[43]	Hypomethylating agent	86	ORR 33% (3 months)	Activity appears greater in TFH lymphomas, may be better used in combination with other agents.	No
Valemetostat[44]	EZH1/2 inhibitor	133	ORR 43%, CR 14%	Novel therapeutic strategy, most active in TFH lymphomas.	No
Belinostat[45]	HDAC inhibitor	129	ORR 26%, CR 11%	Most active in AITL	No

Table 1. Subtype-specific activity of drugs in relapsed/refractory nodal PTCLs[4]; *courtesy of Danyal Ladha, MD and Anca Prica, MD.*

Abbreviations: AITL: angioimmunoblastic T-cell lymphoma; **ALCL:** anaplastic large cell lymphoma; **allo-SCT:** allogeneic stem cell transplant; **ASCT:** autologous stem cell transplant; **CR:** complete response; **HDAC:** histone deacetylase; **ORR:** overall response rate; **PFS:** progression-free survival; **TFH:** T follicular helper.

and a CR rate of 11%.[40] The median PFS was 3.5 months, and responses were notably lower in patients with AITL (ORR: 8%).[40] Despite these limitations, pralatrexate remains a common standard-of-care option in Canada based on current funding algorithms.

HDAC inhibitors, including romidepsin, belinostat, and chidamide, have demonstrated varying degrees of efficacy in relapsed PTCL. Romidepsin was initially approved by the FDA based on a phase II study demonstrating durable responses in a subset of patients, particularly those with AITL (ORR 33%, with 19% of patients maintaining a response for >12 months).[42] However, a subsequent phase III study evaluating CHOP with or without romidepsin in the front-line setting failed to meet its primary endpoint, leading to the withdrawal of romidepsin from the Canadian market.[18] Belinostat has similarly demonstrated activity in phase II studies, with particularly favourable responses observed in AITL (ORR: 45.5% vs. 23.3% with PTCL-NOS).[45] A phase III trial incorporating belinostat in the front-line setting is ongoing.[46]

BV also remains active in the relapsed setting. A phase II study demonstrated efficacy with single-agent BV regardless of prior front-line BV exposure.[41] The greatest benefit was observed in patients with ALCL, with long-term follow-up demonstrating a 5-year PFS of 39% and a CR rate

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of 14% in the absence of a transplant, suggesting that durable remission and potential cure may be achievable in a minority of patients.[47] Based on these data, BV is a preferred second-line option for patients with ALCL relapsing more than 6 months following front-line therapy, particularly as a bridge to transplant alongside ALK inhibitors, such as alectinib or crizotinib, in ALK-positive disease.[4,38,47]

Azacitidine, another epigenetic therapy, has also demonstrated activity in TFH lymphomas. Although an initial retrospective series reported an ORR of 75% and CR of 50%, a subsequent phase III trial comparing azacitidine with investigator's choice therapy demonstrated more modest single-agent activity, with a 3-month ORR of 33% and median PFS of 5.6 months.[6,43] As such, azacitidine may ultimately be most effective in combination-based approaches rather than as monotherapy.

Valemetostat is an oral dual inhibitor of the histone methyltransferases EZH1 and EZH2, thereby increasing the expression of pro-apoptotic and tumour suppressor genes by altering histone methylation.[4] This is considered a promising therapeutic approach, given that epigenetic dysregulation is a hallmark of T-cell lymphomas. In a phase II single-arm study evaluating valemetostat in relapsed or refractory PTCL, the ORR and CR rates, as assessed by PET imaging, were 52.1% and 26.9%, respectively.[44] Responses were observed across all PTCL subtypes, with a trend towards greater efficacy in TFH lymphomas (ORR: 54%), compared with PTCL-NOS (31.7%) and ALCL (33%).[44]

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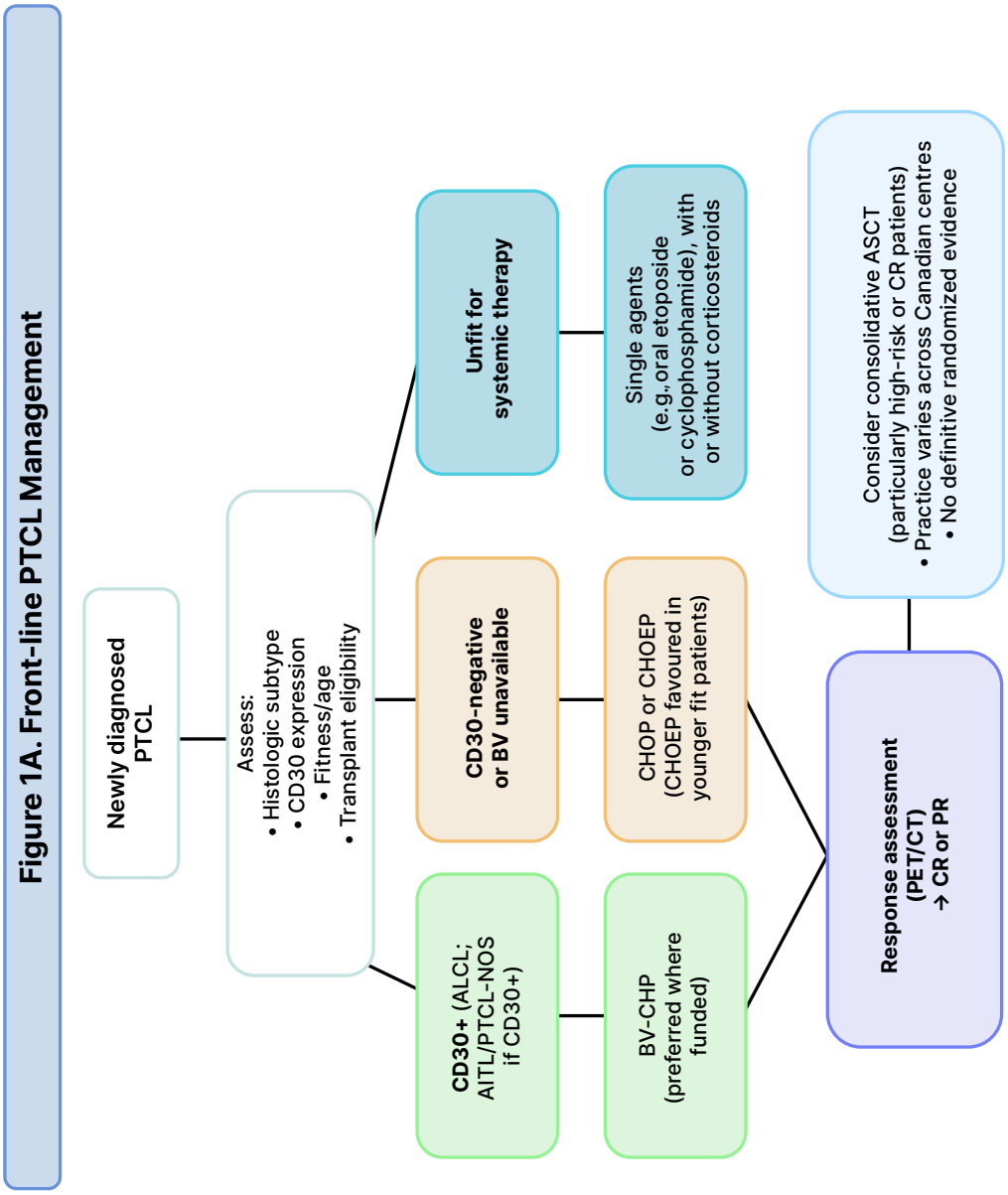
Figure 1A. Front-line PTCL Management
Newly diagnosed PTCL
Assess:
• Histologic subtype
• CD30 expression
• Fitness/age
• Transplant eligibility
Unfit for systemic therapy
Single agents (e.g., oral etoposide or cyclophosphamide), with or without corticosteroids
CD30-negative or BV unavailable
CHOP or CHOEP (CHOEP favoured in younger fit patients)
CD30+ (ALCL; AITL/PTCL-NOS if CD30+)
BV-CHP (preferred where funded)
Response assessment (PET/CT) → CR or PR
Consider consolidative ASCT (particularly high-risk or CR patients)
• Practice varies across Canadian centres
• No definitive randomized evidence

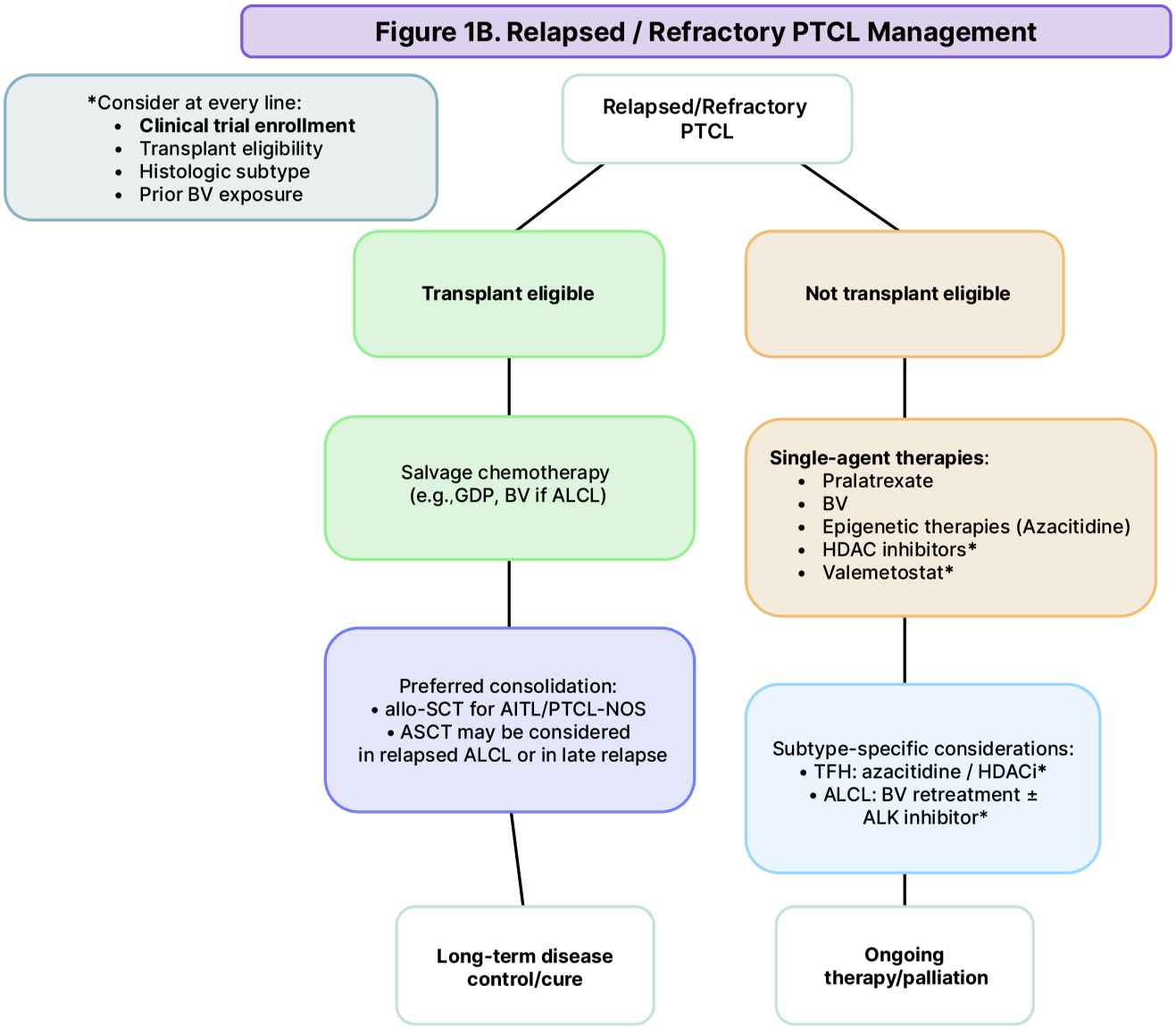

Figure 1. Approach to treatment of PTCL in the Canadian landscape in 2026; *courtesy of Danyal Ladha, MD and Anca Prica, MD.*
*Not funded in Canadian public healthcare system
Abbreviations: AITL: angioimmunoblastic T-cell lymphoma; **ALCL:** anaplastic large cell lymphoma; **allo-SCT:** allogeneic stem cell transplant; **ASCT:** autologous stem cell transplant; **BV:** brentuximab vedotin; **CHOP:** cyclophosphamide, doxorubicin, vincristine, and prednisone **CHOEP:** cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide; **CHP:** cyclophosphamide, doxorubicin, and prednisone; **HDAC:** histone deacetylase; **GDP:** gemcitabine/dexamethasone/cisplatin; **NOS:** not otherwise specified; **PET/CT:** positron emission tomography/computed tomography; **PTCL:** peripheral T-cell lymphoma; **TFH:** Follicular helper T cell.

Putting It All Together: The Canadian Landscape

As outlined in **Figure 1a**, front-line treatment approaches for PTCL in Canada primarily include CHOP, CHOEP, or BV-CHP. Treatment selection depends on several factors, including immunohistochemistry (BV is publicly funded only for patients whose tumour cells are CD30-positive, with some jurisdictions requiring at least 10% expression), patient age, and comorbidities. Consolidation with ASCT is controversial in the Canadian landscape, given the lack of randomized data to support this practice; some centres routinely consolidate patients in CR, while others do not, depending on how the data are interpreted. The aforementioned ongoing randomized controlled trials will hopefully provide more clarity to guide decision-making.

In the relapsed/refractory setting (**Figure 1b**), enrollment in clinical trials should be considered whenever feasible to facilitate access to novel therapies that are not publicly funded. Outside of a clinical trial setting, patients who are candidates for allo-SCT should be referred early to a transplant program and treated with an appropriate bridging strategy to achieve disease control. Pralatrexate remains a commonly utilized standard-of-care option in Canada; however, as previously discussed, its modest single-agent activity makes durable disease control unlikely in most patients.[40] In patients with ALCL, BV retreatment may be considered, particularly in those relapsing more than 6 months after front-line therapy,[38] followed by ASCT if not previously utilized in the front-line setting. For TFH lymphomas, preference should be given to epigenetic therapies, such as azacitidine, or HDAC inhibitors, where available, although HDAC inhibitors are currently not accessible in Canada.

Future Directions

A number of other strategies are currently being investigated, including the use of immune checkpoint inhibitors,[48] bispecific antibodies (AFM13),[49] and chimeric antigen receptor T-cell therapy (CAR T).[50] However, CAR T therapy in PTCL is associated with unique biologic and manufacturing challenges, including T-cell aplasia, fratricide, and contamination of CAR T products with malignant T cells.[50] Ongoing studies are evaluating strategies to overcome these limitations and improve the feasibility of cellular therapies in PTCL.

In conclusion, the treatment landscape for PTCL continues to evolve rapidly, and substantial advances over the past decade. Recent developments in the understanding of disease biology and molecular subtypes have enabled a more individualized approach to therapy selection and sequencing. Despite these advances, outcomes in relapsed/refractory disease remain poor, highlighting the importance of clinical trial enrollment whenever possible.

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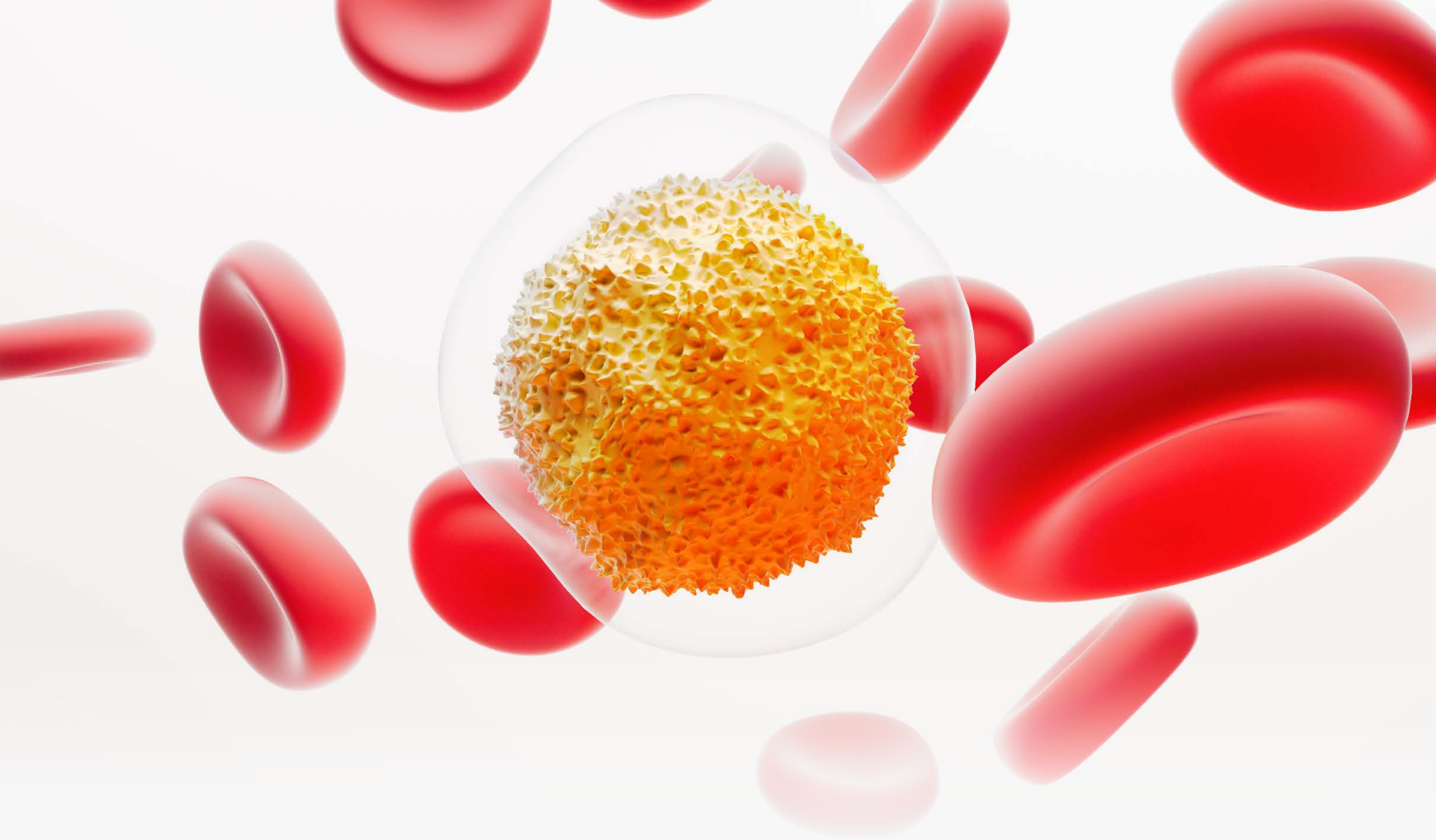

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Front-Line Management of Mantle Cell Lymphoma in Canada: A Practical, Risk-Adapted Approach

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Introduction

Mantle cell lymphoma (MCL) is a mature B-cell non-Hodgkin lymphoma (NHL) that accounts for approximately 5–7% of all lymphomas.[1] Its clinical presentation is heterogeneous, ranging from an indolent leukemic non-nodal subtype that may be managed with observation to highly aggressive disease characterized by *TP53* alterations, blastoid or pleomorphic morphology, and high Ki-67 expression. Although relatively uncommon, an estimated 500–600 new cases are diagnosed annually in Canada,[2] underscoring the importance of optimizing evidence-based management strategies. In this review, we discuss front-line treatment approaches for MCL within the Canadian practice landscape.

Indolent MCL

Approximately 10–15% of patients with MCL have indolent disease biology based on clinical and/or pathological features. An illustrative example is the leukemic non-nodal subtype, which is often SOX11-negative and presents with predominant bone marrow, peripheral blood, and splenic involvement. Nodal MCL can also exhibit an indolent behaviour, particularly when associated with low tumour burden, low Ki-67, and classic histology. Several studies have shown that these patients can be safely observed without compromising long-term outcomes.[3-5]

Limited-Stage MCL

True limited-stage MCL (non-bulky stage I–II) is uncommon, accounting for only about 5% of cases. Comprehensive staging with positron emission tomography/computed tomography (PET/CT), bone marrow biopsy, and gastrointestinal endoscopies is required to confirm limited-stage MCL, as bone marrow involvement is common and gastrointestinal involvement occurs in nearly 90% of patients.[6-8] Once limited-stage disease is confirmed, localized radiotherapy (4–24 Gy) may be considered, as retrospective series have reported high response rates and durable remissions.[9–11] Initial observation is also a reasonable approach for patients with asymptomatic disease, as clinical outcomes appear broadly similar to those of patients treated upfront.[3,12]

Advanced Stage MCL

Younger and Fit Patients

For the last two decades, the treatment of younger and fit patients has relied on intensive chemoimmunotherapy induction, followed by autologous stem cell transplant (ASCT) consolidation and maintenance rituximab (M-R). Although there is no strict age cut-off, this approach is generally reserved for patients younger than 65–70 years without significant medical comorbidities. Various induction regimens have been studied, including R-maxi-CHOP alternating with R + high-dose cytarabine,[13] 3 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) followed by 3 cycles of R-DHAP (rituximab, dexamethasone, cisplatin, and cytarabine),[14] 6 cycles of alternating R-CHOP/R-DHAP,[15] and R-DHAP x4.[16] These induction regimens yield overall response rates (ORRs) above 90% with complete response (CR) rates above 50%, with no regimen appearing clearly superior. Importantly, R-CHOP/R-DHAP was associated with an overall survival (OS) advantage compared to R-CHOP in the long-term follow-up of the MCL Younger Trial.[17]

Bendamustine and rituximab (BR) with ASCT and M-R is also a feasible front-line strategy

for younger, transplant-eligible patients.[18,19] A retrospective study conducted at BC Cancer compared 97 patients treated with BR to 232 patients treated with R-CHOP/R-DHAP in the MCL Younger trial.[20] The ORR was 90% (54% CR) with BR and 94% (54% CR) with R-CHOP/R-DHAP, with similar proportions of patients proceeding to ASCT (77% and 78%, respectively). There were no significant differences in progression-free survival (PFS) on unadjusted (hazard ratio [HR]: 0.87, 95% confidence interval [CI]: 0.53–1.41, p=0.56) or adjusted analyses (HR: 0.79, 95% CI: 0.45–1.37, p=0.40), suggesting that BR followed by ASCT and M-R may achieve outcomes comparable to R-CHOP/R-DHAP with ASCT, with the caveat that M-R was rarely incorporated in the latter regimen.

The benefit of ASCT consolidation after intensive induction in MCL is supported primarily by phase II studies, which reported 4–5-year PFS and OS rates of 56–73% and 64–81%, respectively.[14,21] However, the relative contribution of intensive induction versus ASCT to these outcomes remains unclear. The only randomized trial evaluating ASCT (post-CHOP-like induction) demonstrated a significant improvement in PFS (39 vs. 17 months), although no OS benefit was observed.[22] Similarly, in the MCL Younger trial, ASCT was associated with higher rates of minimal residual disease (MRD)-negativity,[15] a known predictor of survival.[23] Beyond transplantation itself, post-ASCT maintenance strategies may further improve disease control. In the LYMA trial, maintenance rituximab administered every 2 months for 3 years significantly improved survival, with 4-year PFS/OS of 83%/89% versus 64%/80% with observation.[16]

The role of consolidative ASCT has recently been challenged in two practice-changing clinical trials. The TRIANGLE study assessed whether ASCT could be omitted when introducing ibrutinib, a covalent Bruton's tyrosine kinase inhibitor (cBTKi), in the induction and maintenance phases of therapy. Patients were randomized to either R-CHOP/R-DHAP followed by ASCT (arm A), ibrutinib-R-CHOP/R-DHAP followed by ASCT and ibrutinib maintenance (arm A+I), or ibrutinib-R-CHOP/R-DHAP followed by ibrutinib maintenance alone (arm I). In the primary analysis, this study showed that arm A was not superior to arm I (3-year failure-free survival (FFS) of 72% vs. 86%; p=0.9979).[24] In the 4-year follow-up analysis, TRIANGLE confirmed the superiority of arm I over arm A for both FFS and OS, and showed that adding ASCT to the ibrutinib-containing regimen (arm A+I) did not prolong FFS. Moreover, ASCT plus ibrutinib (arm A+I) was associated with significantly higher rates of grade 3–5 hematologic toxicities and infections during maintenance and follow-up compared with ibrutinib alone (arm I).[25]

In the ECOG-ACRIN EA4151 trial, patients with MCL in complete remission after any induction regimen underwent PET/CT, bone marrow biopsy, and peripheral blood MRD-testing by clonoSEQ. Patients in CR with undetectable MRD (10^{-6}) were randomized to ASCT and 3 years of M-R (arm A) or 3 years of M-R alone (arm B). Patients with MRD-positive CR (arm C) or MRD-indeterminate CR (arm D) both received an ASCT and 3 years of M-R. When comparing arms A and B, the estimated OS HR was 1.11 (95% CI: 0.71-1.74; p=0.66) and the estimated PFS HR was 1.05 (95% CI: 0.71–1.56; p=0.79), confirming the lack of benefit of ASCT in patients in CR with undetectable MRD.[26]

Canadian perspective: For younger and fit patients, a TRIANGLE-based strategy incorporating R-CHOP plus ibrutinib alternating with R-DHAP, followed by two years of ibrutinib and three years of M-R without ASCT, would be preferred when there is access to a BTKi. In settings where BTKi are unavailable, cytarabine-containing induction or BR remain reasonable alternatives, with the decision to pursue consolidative ASCT guided by MRD status if possible. Rituximab maintenance should be offered to all patients.

Older or Unfit Patients

In patients who are not suitable for ASCT, rituximab-based chemoimmunotherapy followed by M-R has remained the standard of care until very recently. Several rituximab-containing regimens have been evaluated, including R-CHOP, BR, R-BAC (rituximab, bendamustine, and cytarabine), and VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone). In the European MCL Elderly study, R-CHOP was associated with an improved median OS compared with FCR (fludarabine, cyclophosphamide, and rituximab; 6.4 vs. 3.9 years). Among responders, maintenance rituximab further prolonged OS compared with interferon maintenance (9.8 vs. 7.1 years).[27,28]

R-CHOP was later compared to BR in two randomized studies in indolent NHL. The BRIGHT

trial (including patients with MCL) showed a PFS benefit favouring BR (5-year PFS HR: 0.61, 95% CI 0.45–0.85; p=0.0025),[29] confirmed in the phase III StiL trial (median PFS 69.5 vs. 31.2 months; HR: 0.58, 95% CI: 0.44–0.74; p<0.0001).[30] Given that both studies were conducted without M-R, the phase II StiL MAINTAIN trial randomized patients to M-R versus observation after BR, showing no PFS benefit.[31] However, real-world studies later demonstrated improved outcomes with M-R, as highlighted in a retrospective analysis of 4,216 patients with MCL, showing longer time to next treatment (HR: 1.96, 95% CI: 1.61–2.38; p<0.001) and improved OS (HR: 1.51, 95% CI: 1.19–1.92; p<0.001).[32] These findings were later supported by another large retrospective study of 911 patients across 27 US and Canadian academic centres, with M-R associated with longer median event-free survival (EFS: 49.9 months vs. 29.7 months; p<0.001) and OS (109.5 vs. 74.2 months; p<0.001).[33]

Two recent phase III trials have evaluated the incorporation of a covalent BTKi into BR and maintenance rituximab in the first-line treatment of ASCT-ineligible patients. The SHINE trial evaluated ibrutinib in combination with BR,[34] whereas the ECHO trial evaluated acalabrutinib in combination with BR.[35] Both studies showed that the addition of a cBTKi to BR and rituximab maintenance improves PFS but not OS. In the SHINE trial, there was a trend toward inferior OS in the ibrutinib arm, largely driven by an increased number of toxicity-related mortality. This was not observed in the ECHO trial, where a trend toward improved OS was seen in the experimental arm despite a 69% crossover rate. Interestingly, all patients appeared to benefit from the addition of a cBTKi regardless of their risk profile (blastoid/pleomorphic, TP53-mutant, Ki-67 >30%, high-risk MCL International Prognostic Index [MIPI]).

A key question is whether BR plus acalabrutinib upfront is superior to a sequential strategy of BR followed by acalabrutinib at relapse, particularly given that 69% of patients in the ECHO control arm received acalabrutinib at progression. However, real-world data suggest that not all patients survive to receive second-line therapy. In an Australian observational study, approximately 7% of patients with MCL died before second-line treatment,[36] while in a population-based study from Ontario, 39.3% of patients died following front-line therapy,[37] supporting the rationale for incorporating a cBTKi into initial treatment. Conversely, a multicentre study led by Mayo Clinic evaluated event-free survival 2 (EFS2) in 203 patients with MCL treated with front-line BR followed by a second-line cBTKi.[38] Using this sequential approach, the median EFS2 was 64.8 months (95% CI: 56.7–82.8), which is comparable to the median PFS of 66.4 months observed in the BR–acalabrutinib arm of ECHO. Therefore, given the higher risk of infectious and cardiovascular toxicities associated with adding a cBTKi, its use should be carefully weighed in older or frail patients but strongly considered in patients with higher-risk disease.

Finally, the phase III ENRICH trial compared a chemotherapy-free regimen (ibrutinib-rituximab) to standard chemoimmunotherapy (investigator's choice of BR or R-CHOP) in patients aged >60 years with untreated MCL.[39] After a median follow-up of 47.9 months, ibrutinib-rituximab was associated with superior PFS relative to immunochemotherapy (adjusted HR: 0.69, 95% CI: 0.52–0.90; p=0.0034). This benefit was only observed in comparison to the R-CHOP subgroup (HR: 0.37, 95% CI: 0.22–0.62) and not the BR subgroup (HR: 0.91, 95% CI: 0.66–1.25). Given the lower incidence of grade 3–4 neutropenia and the faster improvement in quality of life, the authors suggested that IR should be considered a new standard-of-care option for older adults with untreated MCL. Of note, this regimen should not be used for patients with blastoid disease, in whom a trend in favour of immunochemotherapy was observed (median PFS: 6.9 months vs. 21.1 months).

Canadian perspective: For older or unfit patients, BR plus acalabrutinib induction followed by two years of rituximab maintenance and continuous acalabrutinib until progression or unacceptable toxicity would be our preferred approach, particularly for those with higher-risk features (TP53 mutation, blastoid or pleomorphic morphology, Ki-67 >30%, or high-risk MIPI). In patients with low biological risk or significant concerns for cardiovascular or infectious toxicities, BR followed by rituximab maintenance or a chemotherapy-free approach with cBTKi–rituximab (2nd generation cBTKi preferred), followed by rituximab maintenance and continued cBTKi until progression or unacceptable toxicity, remain reasonable alternatives.

Frail Patients

Frail patients are more likely to experience treatment-related toxicity and poor outcomes.

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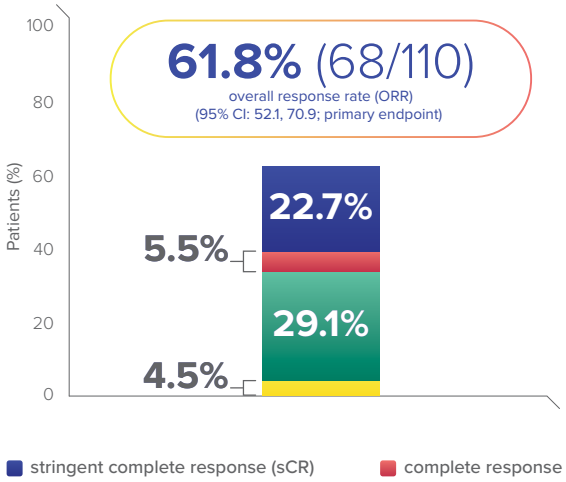
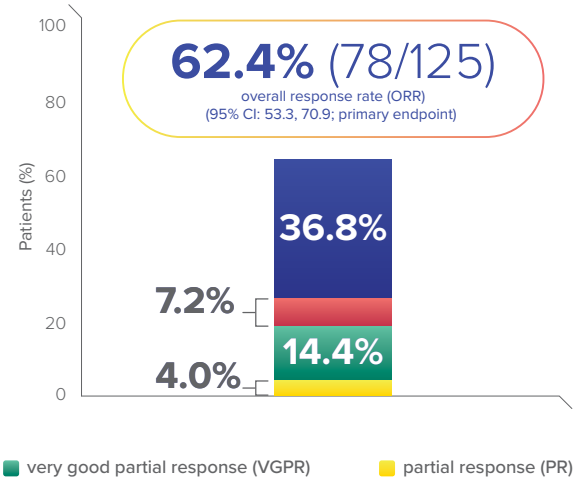


At 29.5 months (follow-up analysis; n=125):[1]



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Follow-up analysis: median duration of response (n=78): 21.6 months (95% CI: 14.9 months, NE) for responders

55.1% of the 78 responders in the MajesTEC-1 trial switched from weekly to biweekly dosing during the study[1]

For those who remain eligible for chemotherapy, options include R-chlorambucil, R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone), and attenuated R-CHOP or BR. A retrospective study conducted in the UK and Ireland reported outcomes of these regimens in 95 patients who were unfit for full-dose BR or R-CHOP.[40] The median PFS was 15 months, and patients treated with attenuated R-CHOP/BR had a superior PFS than those treated with R-chlorambucil/R-CVP (HR: 0.49; p=0.02) at the expense of more toxicity-related hospitalizations.

Chemotherapy-free approaches, such as ibrutinib-rituximab (ENRICH trial), acalabrutinib-rituximab (ALTAMIRA trial), and cBTKi monotherapy, are reasonable options for this patient population. In the multicenter phase II ALTAMIRA trial, investigators evaluated the safety and efficacy of acalabrutinib plus rituximab in elderly patients, achieving an ORR of 95% (61% CR), with a 1-year PFS and OS of 86.5% and 92.9%, respectively. These outcomes were significantly improved compared with matched real-world controls treated with standard therapies, supporting this combination as a front-line option.[41]

TP53-Mutated MCL

TP53-mutated disease is often associated with rapid progression, suboptimal response to standard chemoimmunotherapy, and poor survival outcomes.[42] Clinical trials or triple-therapy regimens incorporating an anti-CD20 monoclonal antibody, a cBTKi, and a BCL2 inhibitor should therefore be considered when available. The phase II BOVen trial evaluated zanubrutinib, obinutuzumab, and venetoclax in patients with untreated MCL harbouring *TP53* mutations, using an MRD-driven approach.[43] Despite its small sample size (n=25), outcomes were highly favourable, with an ORR of 96%, CR rate of 88%, and high MRD-negativity rates (95% at 10^{-5} sensitivity; 84% at 10^{-6}). With a median follow-up of 28.2 months, the 2-year PFS and OS were 72% and 76%, respectively.

References: 1. TECVAYLI® (teclistamab injection) Product Monograph. Janssen Inc. June 26, 2025. **2.** Data on file, Johnson & Johnson. October 13, 2023. **3.** Data on file, Johnson & Johnson. October 31, 2025.

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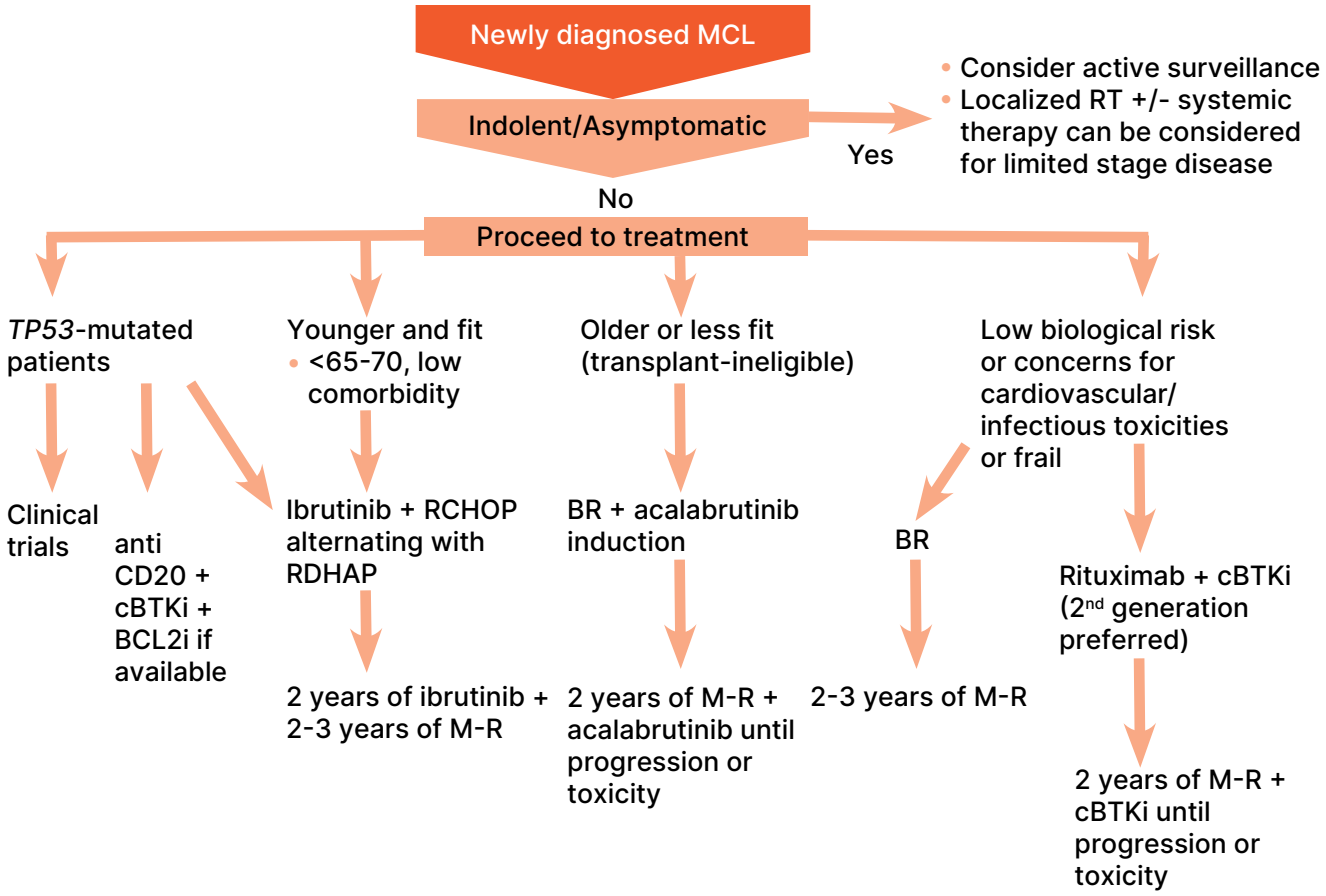

Figure 1. Proposed treatment algorithm for MCL in Canada in 2026; *courtesy of Justin Desroches, MD, FRCPC and Diego Villa, MD, MPH, FRCPC.*

Consistent with these findings, similar efficacy has been observed with an alternative triplet combination. In the phase II TRAVERSE trial evaluating acalabrutinib, venetoclax, and rituximab (AVR) in treatment-naïve MCL, the subgroup of patients with *TP53* mutations demonstrated high response rates, including an ORR of 88.2%, a CR rate of 64.7%, and MRD-negativity in 94.1% during induction.[44] Finally, in the treatment-naïve subgroup of the SYMPATICO trial, patients with *TP53* mutations also demonstrated meaningful responses to the ibrutinib–venetoclax doublet, with an ORR of 90%, a CR rate of 55%, a median PFS of 22.0 months, and a 3-year OS of 68%.[45]

Canadian perspective: Clinical trials or triple-therapy regimens should be offered to TP53-mutated patients. If these are not available, a TRIANGLE approach (younger/fit patients) or ECHO approach (older/unfit patients) would be recommended.

Future Directions and Conclusion

The front-line management of MCL is undergoing a rapid transition from chemotherapy-intensive approaches toward targeted treatment strategies. Among these, cBTKi are most likely to remain a central component of therapy. Data from TRIANGLE, ECHO, and ENRICH support the incorporation of these agents into front-line regimens across multiple patient populations, including transplant-eligible and transplant-ineligible patients. However, their optimal use may evolve away from prolonged maintenance therapy toward time-limited combinations aimed at achieving deep and durable remissions.

BCL2 inhibitors are also emerging as key partners in combinations with cBTKi. Early-phase studies evaluating combinations of anti-CD20 monoclonal antibodies, cBTKi, and venetoclax have demonstrated high rates of CR and MRD-negativity, particularly in

high-risk populations such as those with *TP53* mutations. These regimens raise the possibility of fixed-duration, MRD-guided treatment strategies, which may reduce long-term toxicity while preserving efficacy. Ongoing studies will determine whether such approaches can be generalized beyond high-risk subsets and ultimately challenge current continuous cBTKi maintenance therapy models.

Additionally, the role of chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies in the front-line setting is under investigation. Earlier integration of T-cell-directed therapies, as explored in the CARMAN,[46] WINDOW-3,[47] and GLOVe trials,[48] may enhance efficacy by capitalizing on improved T-cell fitness and lower disease burden. While their efficacy in relapsed/refractory MCL is well established, their use in front-line therapy is currently limited by logistical complexity, cost, and the emergence of highly effective targeted combinations. Nevertheless, front-line T-cell-directed therapies may have a future role in selected high-risk populations or as an early consolidation strategy in patients with detectable MRD following induction therapy.

Taken together, the front-line management of MCL continues to evolve with the integration of cBTKi, MRD-guided strategies, and emerging novel agents. In Canada particularly, treatment decisions must balance clinical efficacy, toxicity, and access to publicly funded therapies.

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BCL2 =B-cell lymphoma 2.

* Comparative clinical significance is unknown.

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Post CAR T-Cell Therapy Care: Monitoring and Toxicity Management

Justine Lai, PhD
Peng Wang, MD, PhD, FRCPC
Michael P. Chu, MD, FRCPC

Chimeric antigen receptor (CAR) T-cell therapy is an immunotherapy that has transformed the treatment of several hematologic malignancies. Unlike conventional cancer therapies, CAR T cells can cause unique immune-mediated toxicities, some of which can be severe and potentially life-threatening. As the use of CAR T-cell therapy expands, early recognition and standardized management of toxicities are increasingly important. With appropriate monitoring and management, these toxicities can be reduced. This review provides an overview of the management of patients after CAR T-cell therapy, as summarized in ***Figure 1****.*

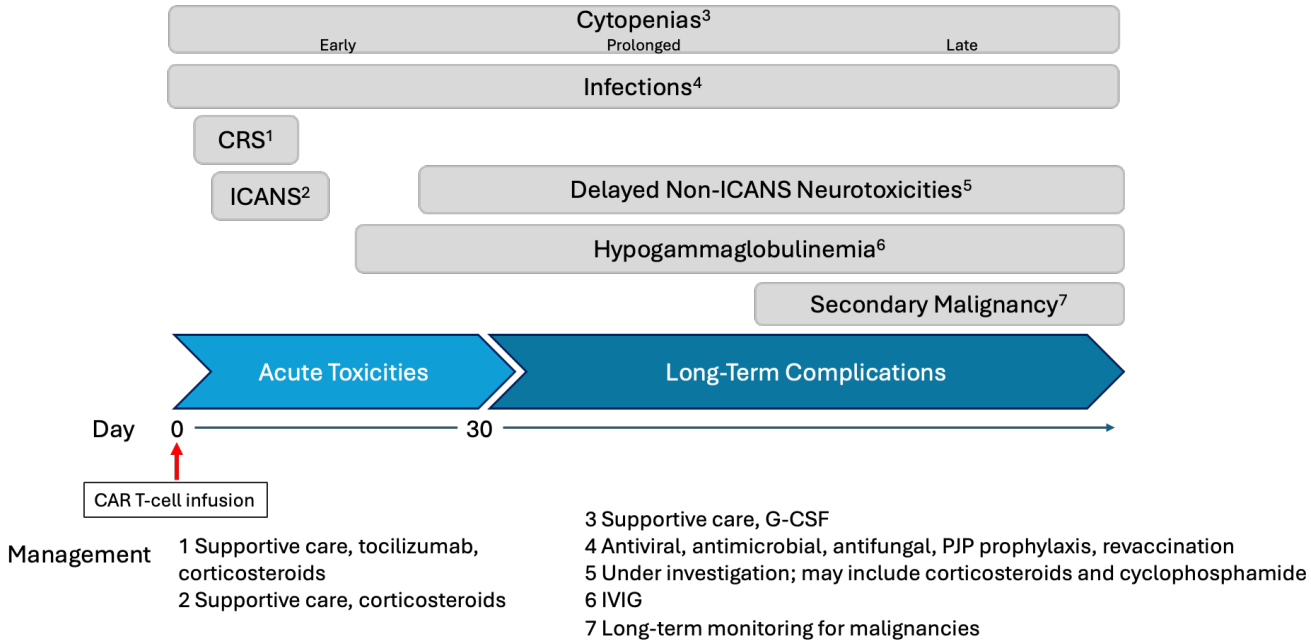

Figure 1. Timeline of toxicities, complications and management of patients following CAR T-cell infusion. Superscript numbers link toxicities to corresponding management strategies; *courtesy of Justine Lai, PhD, Peng Wang, MD, PhD, FRCPC, and Michael P. Chu, MD, FRCPC.*

Abbreviations: CAR: chimeric antigen receptor; **CRS:** cytokine release syndrome; **G-CSF:** granulocyte colony-stimulating factor; **ICANS:** immune effector cell-associated neurotoxicity syndrome; **IVIG:** intravenous immunoglobulin; **PJP:** Pneumocystis jirovecii pneumonia.

1. Overview of CAR T-Cell Treatment

Currently approved CAR T-cell therapy uses autologous T cells, which are genetically engineered to express receptors that bind to antigens on cancer cells, although allogeneic and in vivo CAR T approaches are currently being investigated in clinical trials. By combining the CAR with T-cell cytotoxicity, these cells can specifically target and kill tumour cells independent of traditional antigen presentation. CAR T cells can persist in the body for years, allowing for prolonged tumour cell killing.[1]

The standard process of manufacturing CAR T-cells is a complex, multi-step procedure.[2] It begins with leukapheresis, followed by isolation of CD3+ T cells, typically using magnetic beads. T cells are activated using anti-CD3 and anti-CD28 antibodies in combination with cytokine cocktails, then transduced with the CAR gene, commonly via viral vectors. These transduced cells are expanded *ex vivo* and subsequently reinfused into the patient. Prior to infusion, patients typically receive lymphodepleting chemotherapy to enhance CAR T-cell survival and durability of the response.[3]

The CAR structure influences activation kinetics, cytokine release magnitude, and the rate of T-cell expansion, thereby affecting both efficacy and toxicity.[4] CARs contain an extracellular domain responsible for target antigen recognition and an intracellular domain that activates the T cell. The extracellular domain most commonly consists of a single-chain variable fragment (scFv), hinge or spacer region, and transmembrane domain. The scFv provides antigen specificity and affinity, with higher affinity generally producing stronger, more sustained CAR activation and increased cytokine release. However, this may have the inverse effect in some cases, such as in solid tumours, due to T-cell exhaustion or activation-induced cell death.[5] The intracellular domain contains CD3ζ, the primary signalling component, and one or more co-stimulatory domains, most commonly CD28 or 4-1BB. CD28 is associated with rapid T-cell expansion and higher peak cytokine levels, leading to earlier and more severe toxicities. In contrast,

Grade	Fever	Hypotension	Hypoxia
Grade 1	≥38°C	None	None
Grade 2	≥38°C	Not requiring vasopressors; responds to fluid	Requiring minimal oxygen supplementation
Grade 3	≥38°C	Requiring one vasopressor	Requiring high-flow oxygen delivery
Grade 4	≥38°C	Requiring multiple vasopressors	Requiring positive-pressure ventilation

Table 1. CRS grading based on ASTCT consensus criteria; *courtesy of Justine Lai, PhD, Peng Wang, MD, PhD, FRCPC, and Michael P. Chu, MD, FRCPC.*

To meet the criteria for grade 2–4 CRS, fever, hypotension and/or hypoxia are required.

Abbreviations: ASTCT: American Society for Transplantation and Cellular Therapy; **CRS:** cytokine release syndrome.

4-1BB promotes slower CAR T expansion, greater persistence, lower cytokine levels, and reduced toxicities.

Five generations of CAR have been developed. Currently, the clinically approved CAR T-cell therapies are generally second-generation CARs, including an scFv, hinge and transmembrane domain, CD3ζ signalling domain, and one costimulatory domain.

There are currently five CAR T-cell therapies that are authorized by Health Canada for the treatment of hematologic malignancies. There are four anti-CD19 CAR T-cell products used primarily for relapsed/refractory B-cell lymphomas and leukemias: axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel, and brexucabtagene autoleucel.[6-9] Ciltacabtagene autoleucel targets B-cell maturation antigen (BCMA) for the treatment of relapsed/refractory multiple myeloma.[10]

2. Immediate Post-Infusion Monitoring

Immediate post-infusion monitoring requires hospitalization or close outpatient monitoring, with patients remaining near a healthcare facility for at least 10–14 days to monitor for toxicities.[11] During this period, history and physical examination, complete blood counts, complete metabolic profile (glucose, electrolytes, liver enzymes, bilirubin, and creatinine), and markers of inflammation (C-reactive protein [CRP] and ferritin) should be assessed daily. Vital signs should be monitored every four hours for those treated in the inpatient and daily for those treated in the outpatient setting. Coagulation profiles should be monitored at least twice a week. Patients should be daily assessed for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

3. Cytokine Release Syndrome

CRS is the most common toxicity observed following CAR T-cell infusion. It results from the hypersecretion of cytokines, including interleukin (IL)-6, IL-1, tumour necrosis factor (TNF)-α, and interferon (IFN)-γ, triggered by activation of CAR T-cells, and subsequently, innate immune cells, such as monocytes, dendritic cells, and macrophages. The clinical manifestations of CRS are broad, ranging from mild symptoms, including fever, fatigue, and rash, to severe symptoms, including tachycardia, hypoxia, hypotension, coagulopathy, and multiorgan dysfunction.[12] The onset of CRS is typically within 2–7 days following CAR T-cell infusion, although it may present as late as three weeks post-infusion.

Grading of CRS is standardized by the American Society for Transplantation and Cellular Therapy (ASTCT).[13] The ASTCT grading criteria are based on the presence of fever, which is required for all CRS grades, and the presence and severity of hypotension and hypoxia. CRS is graded on a scale from 1 to 4, as summarized in **Table 1**.

The incidence of CRS post-CAR T-cell therapy has ranged from 42–93% in clinical trials.[14] Several factors have been found to predict CRS incidence and severity, including high tumour burden, intensive lymphodepleting regimens, and pre-existing comorbidities.[12,15] Additionally, a low platelet count prior to lymphodepletion, and elevated lactate dehydrogenase (LDH), creatinine, CRP, and ferritin levels have been associated with

Grade	ICE Score	Level of Consciousness	Seizures	Elevated Intracranial Pressure/Cerebral Edema	Motor Weakness
Grade 1	7–9	Awakens spontaneously	None	None	None
Grade 2	3–6	Awakens to voice	None	None	None
Grade 3	0–2	Awakens to tactile stimulus	Any seizure that rapidly resolves	Focal/local edema on imaging	None
Grade 4	0	Unarousable or only responsive to vigorous or repeated stimulation	Repetitive or life-threatening prolonged seizure	Diffuse cerebral edema on imaging or clinical signs of elevated intracranial pressure	Deep focal weakness or paralysis

Table 2. ASTCT consensus grading of ICANS: *courtesy of Justine Lai, PhD, Peng Wang, MD, PhD, FRCPC, and Michael P. Chu, MD, FRCPC.*

The ICE score is a 10-point scale assessing orientation, naming, following commands, writing, and attention.

Abbreviations: ASTCT: American Society for Transplantation and Cellular Therapy; **ICANS: i**mmune effector cell-associated neurotoxicity syndrome; **ICE:** immune effector cell-associated encephalopathy.

an increased risk of CRS.[16,17] Treatment-related factors also contribute, with higher CAR T-cell doses having increased toxicity. Structural features of the CAR construct may also play a role, with CARs containing CD28 (e.g., axicabtagene ciloleucel) generally having higher rates of CRS than those with 4-1BB (e.g., tisagenlecleucel).[18]

Treatment of CRS depends on its grade. Based on ASTCT guidelines, treatment for grade 1 CRS is supportive care. For CRS grade ≥2, first-line therapy is tocilizumab, a Health Canada–authorized IL-6 receptor antagonist, which should be initiated promptly upon observation of CRS symptoms to reduce the likelihood of progression to a higher grade. Institutional practices vary, with some centres using tocilizumab as an early-intervention strategy for grade 1 CRS. Corticosteroids, including dexamethasone or methylprednisolone, are added for persistent or worsening symptoms of severe CRS (i.e., grades 3 or 4). In refractory CRS, alternative anti-cytokine therapies may be used, including siltuximab, an IL-6 antagonist, or anakinra, an IL-1 receptor antagonist.[19] Other targets to treat CRS currently under investigation include IFN-γ (emapalumab) and granulocyte-macrophage colony-stimulating factor (GM-CSF; lenzilumab).[12]

To mitigate the risk of CRS, several strategies are being used. Prophylactic tocilizumab and anakinra have both been shown in trials to decrease the incidence and severity of CRS.[20-22] Other strategies include prophylactic corticosteroids and fractionated dosing of CAR T cells over several days.[23]

4. Immune effector cell-associated neurotoxicity syndrome

ICANS is the second most common toxicity of CAR-T cell treatment after CRS, with an overall incidence of approximately 30% reported from clinical trials.[24] ICANS typically presents with a spectrum of neurological symptoms, including headache, confusion, aphasia, dysgraphia, dysarthria, tremor, seizures, and rarely, cerebral edema.[25] The median time to onset of ICANS is between 4 and 10 days post-infusion.[26] It is typically self-limited, with symptoms resolving after 5–17 days.[27] ICANS and CRS can co-occur, with ICANS generally presenting after the onset of CRS.[26]

The severity of ICANS in adults is graded from 1 to 4 according to the ASTCT consensus (**Table 2**).[26,28] Screening for ICANS using the immune effector cell-associated encephalopathy (ICE) score, a 10-point bedside assessment of cognitive function, should be performed daily during the high-risk period (day 0–14 post-infusion).[27] If a patient develops symptoms of ICANS, the grade should be assessed at least every 8 hours. Patients younger than 12 years of age or those with developmental delay should be assessed using the Cornell Assessment of Pediatric Delirium Score.

Monitoring for ICANS is important to allow early recognition and treatment, preventing morbidity and mortality, though it often presents later than CRS and can have a bimodal presentation. If ICANS is present, the

mainstay of treatment is supportive care and corticosteroids.[13] Management of grade 1 ICANS is mainly supportive, although dexamethasone may be considered. Grade 2–3 ICANS is managed with supportive care and dexamethasone, while grade 4 ICANS is treated with methylprednisolone. Anakinra can be administered to patients with grade 2–4 ICANS who are refractory to corticosteroids (i.e., no improvement after six hours of corticosteroids). Tocilizumab can be added for concurrent CRS for all grades of ICANS; however, it is not effective for isolated ICANS as it does not cross the blood-brain barrier and may increase circulating IL-6 levels, potentially worsening neurotoxicity if used alone.

Multiple clinical and biological factors have been correlated with the presence and severity of ICANS. The occurrence of CRS is one of the strongest predictors of ICANS, with ~90% of patients with ICANS previously experiencing CRS, and the risk increases with high-grade CRS.[29] A high pre-treatment tumour burden is also associated with an elevated risk of ICANS, likely due to greater tumour cell killing and stronger immune response.[25] Similar to CRS, a high dose of CAR T-cells and the use of a CD28 rather than a 4-1BB costimulatory domain have been linked to an increased risk of developing ICANS.[24,25] Elevated levels of inflammatory biomarkers, including CRP, serum ferritin, IL-6, IL-10, and IL-15, have also been correlated with ICANS.[29]

5. Non-ICANS Neurotoxicities

Neurotoxicities beyond ICANS have been reported following CAR T-cell infusion and are currently less well characterized. Among these, movement and neurocognitive toxicity (MNT) is a neurological complication associated with some anti-BCMA CAR T-cell therapies. In contrast to ICANS, MNT has a delayed onset, presenting weeks to months after infusion.[30] This toxicity is relatively uncommon, occurring in 2-10% of patients in clinical trials and real-world studies.[31] Risk factors for MNT include high tumour burden, older age, development of ICANS, and elevated peak absolute lymphocyte count (≥3 × 10^9/L) after infusion, indicating increased CAR-T cell expansion. The clinical features of MNT resemble those of Parkinson's disease and include bradykinesia, rigidity, tremor, postural instability, hypophonia, personality change, and cognitive impairment. Management of MNT remains under investigation; however, reported strategies include the use of corticosteroids and cyclophosphamide.

Other non-ICANS neurological complications after CAR T-cell therapy include cranial nerve palsies, most commonly involving the facial nerve, peripheral neuropathies, and myelopathies.[30] These complications are not well characterized, and further investigation is needed to better inform management strategies.

6. Long-Term Monitoring

Patients may experience persistent immune dysregulation following CAR T-cell infusion, necessitating long-term surveillance. Cytopenias are common immediately after infusion and typically resolve within the first 30 days. However, in some patients, cytopenias can be prolonged, lasting up to 90 days after infusion, or late, persisting more than 90 days after infusion.[32] Alternative etiologies for cytopenias include infection, lymphoma with bone marrow involvement, or therapy-related myelodysplastic syndrome or acute myeloid leukemia. Patients with cytopenias, including anemia, thrombocytopenia, and neutropenia, can present with fatigue, shortness of breath, easy bruising and bleeding, and frequent infections. The workup for cytopenias includes a CBC with differential, a peripheral blood smear, and a reticulocyte count.[27] First-line management includes supportive care and, for more severe cases, granulocyte colony-stimulating factor (G-CSF) to support neutrophil recovery.

B-cell aplasia is an on-target, off-tumour effect associated with anti-CD19 CAR T-cell therapy, and killing of B cells can persist for years.[1] Prolonged aplasia may lead to hypogammaglobulinemia, increasing the risk of infections. Patients often require intravenous immunoglobulin (IVIG) therapy, even when serum IgG levels do not fall below the traditional threshold of 0.4 mg/L, to prevent serious or recurrent infections.[33]

The immunosuppressed state following CAR T-cell therapy increases susceptibility to infections, which can occur for several months after infusion. To reduce this risk, antiviral prophylaxis is recommended for 6–12 months post-infusion.[32] Antibacterial prophylaxis can be initiated if neutropenia is detected and continued until it resolves. *Pneumocystis jiroveci pneumonia* (PJP) prophylaxis can be started 30 days after infusion and continued for at least six months,

or until CD4+ T cell counts exceed a threshold of 200 cells/mm^3.[34] Antifungal prophylaxis is not universally agreed upon but is considered important in patients with prolonged neutropenia or in those who require high-dose corticosteroids for more than 72 hours.[35]

Vaccination after CAR T-cell therapy is recommended to mitigate immune dysfunction. Influenza and coronavirus disease 2019 (COVID-19) vaccines can be given three months post-infusion, and other routine inactivated vaccines, such as the Tdap vaccine, and vaccines for Hepatitis B and pneumococcal disease can be initiated at six months.[34] Live-attenuated vaccines are generally contraindicated for at least 12 months after therapy.

7. Secondary Malignancy Monitoring

An important safety consideration for patients treated with CAR T-cell therapy is the development of secondary malignancies. The increased risk is multifactorial and may reflect factors independent of CAR T-cell therapy, including prior therapy exposure and underlying disease biology. There is a theoretical risk of secondary malignancies due to insertional mutagenesis associated with the viral vectors used in CAR T-cell production; however, documented cases are exceedingly rare.[36] Studies have shown that secondary malignancies have occurred in 4–16% of patients within five years after CAR T-cell infusion.[1] Given these findings, long-term monitoring is essential to detect and manage secondary malignancies.

8. Cell Therapies Beyond Second-Generation CAR T-Cell Therapies

Beyond traditional CAR T-cell therapy, other cell therapies and advancements to CAR T-cells, including T-cell-receptor (TCR)-engineered T cells, tumour-infiltrating lymphocytes (TILs), and next-generation CARs, are being investigated. These therapies have different efficacy, indications, and toxicity profiles compared with conventional CAR T-cell therapy, with some approaches potentially offering improved safety profiles. Unlike traditional CAR T-cells, TCR-engineered T cells recognize intracellular tumour antigens presented on major histocompatibility complex (MHC) molecules, expanding their potential to target solid tumours.[37] TCR-engineered T cells are associated with capillary leak syndrome, but with lower rates of CRS and ICANS. TIL therapy involves expansion and reinfusion of tumour-derived T cells without genetic modification, retaining native TCRs that may bind to unknown tumour antigens. This therapy is used in solid tumours, particularly melanoma. Compared with CAR T-cells, TILs have a more favourable safety profile, as they do not typically cause severe CRS or ICANS. However, capillary leak syndrome occurs in approximately a third of patients.[38] Additionally, fourth-generation (armoured) CAR T-cells are designed to overcome the immunosuppressive tumour microenvironment through expression of additional components, including cytokines and anti-programmed cell death protein 1 (PD)-1 antibodies.[39] These CARs have a toxicity profile similar to earlier generations of CARs, including CRS and ICANS, but with improved efficacy.[39,40]

Summary

CAR T-cell therapy has been highly effective in treating hematologic malignancies that have historically been challenging to manage; however, it is associated with unique and potentially life-threatening toxicities that require specialized care. Advancements in toxicity grading, clinical protocols, and early intervention strategies have reduced the severity of adverse events. As CAR T-cell therapy moves into earlier lines of treatment, the development of reliable predictive biomarkers and algorithm-driven strategies for toxicity prevention will be critical, particularly to support the safe expansion of outpatient CAR T-cell delivery.

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† Clinical significance has not been established.

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

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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.

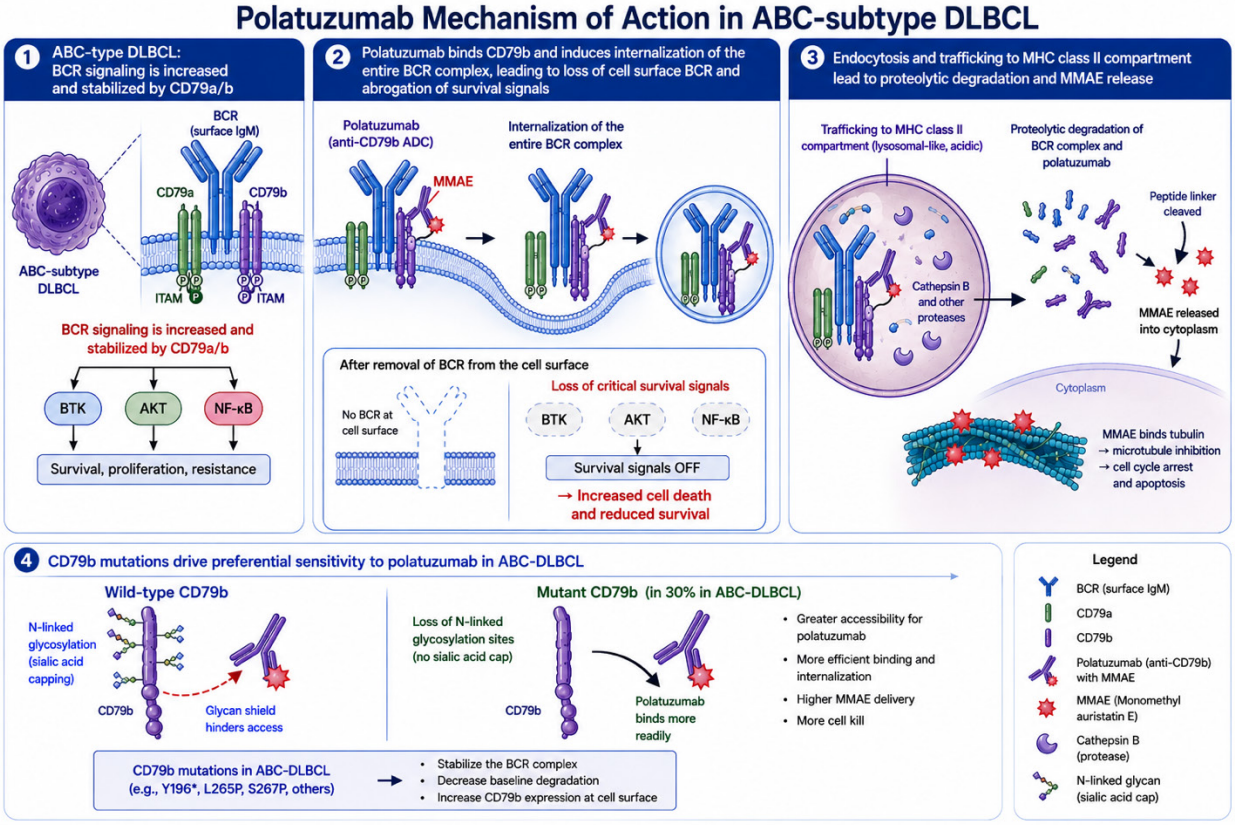

Figure 1. Proposed mechanisms underlying the preferential activity of polatuzumab vedotin in activated B-cell (ABC) diffuse large B-cell lymphoma (DLBCL); *courtesy of Jia Li Liu, MD and Nathalie A. Johnson, MD, PhD, FRCPC.*

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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