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

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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.

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



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Treatment	Trial (phase)	Key Efficacy Findings	Canadian Context and Clinical Role
2L Therapy			
Lenalidomide and Rituximab (R²)	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-R²	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-R²	EPCORE FL-1 (II)	ORR 95%, CR 83% Estimated 16-month PFS 85.5 vs 40.2% (Epcor-R2 vs R2)	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 for 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;

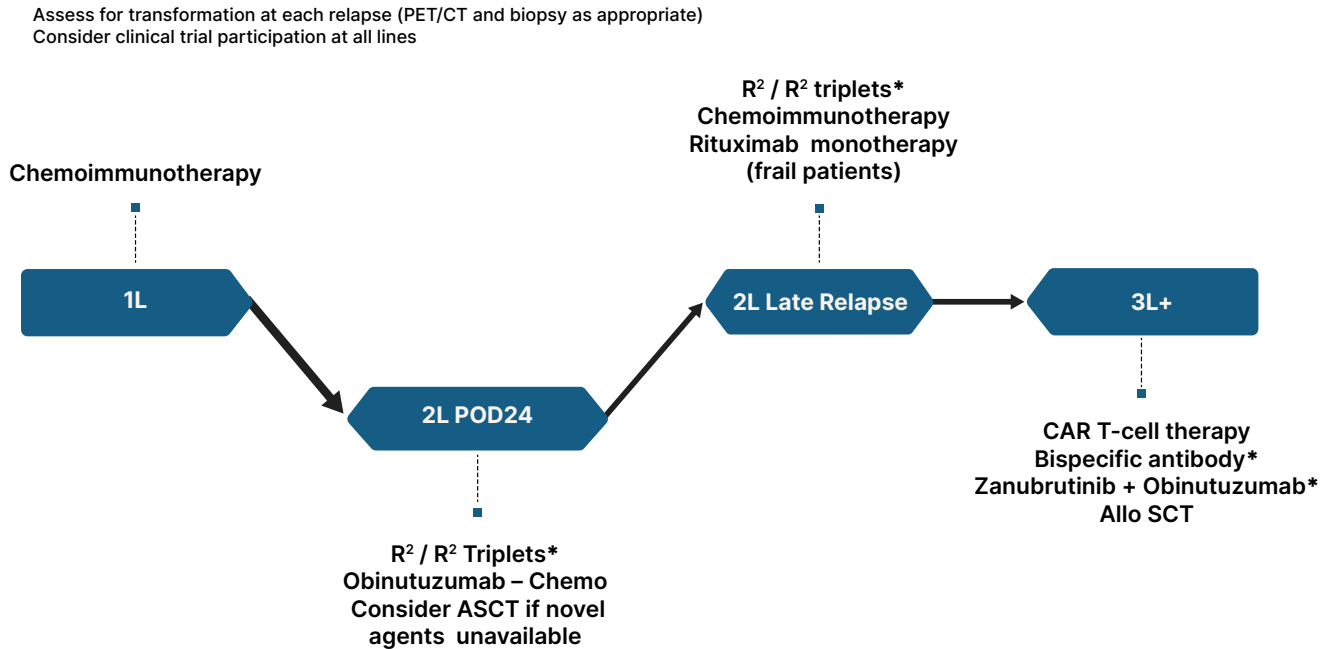


Figure 1. Flow diagram of proposed Canadian treatment pathway. A Potential Canadian Approach to the treatment of RR FL; *courtesy of Mary-Margaret Keating, MD, FRCPC.*

*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 bendamustine 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 R²-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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