Practical Hematologist

# New and Emerging Therapies for Relapsed/Refractory Follicular Lymphoma

**Loretta J. Nastoupil, MD**
Associate Professor
Department of Lymphoma/Myeloma
University of Texas MD Anderson Cancer Center
Houston, Texas

**Catherine S. Diefenbach, MD**
Associate Professor, Department of Medicine at
NYU Grossman School of Medicine
Director, Hematology Translational Research and
Director, Clinical Lymphoma Program
Perlmutter Cancer Center
New York, New York

## What is the current role of CAR T-cell therapy in relapsed/refractory (R/R) follicular lymphoma (FL)?

***Dr. Nastoupil:*** Chimeric antigen receptor (CAR) T-cell therapy is playing an increasingly important role in the third-line FL setting, where current outcomes are generally quite poor and the median progression-free survival (PFS) is 12 months or less. There are now two autologous CD19-directed CAR T-cell therapies that are approved for FL: axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel). Axi-cel was approved for FL based on findings from the ZUMA-5 clinical trial, which was a single-arm, phase 2 study that included FL patients with at least two prior lines of therapy.[1,2] With axi-cel treatment, these patients experienced a durable PFS of around 40 months and a favorable overall survival (OS) rate.[1,2] These benefits extended to high-risk patients who had progression within 24 months from initiation of first anti-CD20–containing chemoimmunotherapy (POD24).[2] When compared to the SCHOLAR-5 patient population, which represents standard of care across a number of different countries, axi-cel demonstrated favorable PFS and OS, in addition to a good overall response (OR) rate.[3,4] Axi-cel was also recently shown to demonstrate good efficacy among R/R FL patients in the real-world setting.[5]

Tisa-cel was approved for R/R FL based on the ELARA single-arm phase 2 clinical trial, which demonstrated favorable PFS and OS in a heavily pretreated patient population and in those with high-risk POD24.[6] Long-term follow-up confirmed the efficacy of this therapy, although those with high metabolic tumor volume did not have as favorable a complete response (CR) rate as the other subgroups, suggesting CAR T-cell therapy is probably better utilized in patients who are not heavily

pretreated with bulky disease.[7] Still, as with axi-cell, compared with standard of care (as represented in the ReCORD-FL trial), this agent is associated with promising outcomes.[8,9]

However, toxicity remains an issue with CAR T-cell therapies. In the ZUMA-5 study, the majority of patients (78%) experienced cytokine release syndrome (CRS) and 15% of participants had Grade 3 or higher neurotoxicity, which typically requires hospitalization.[10] Still, this effect was reversible with corticosteroids, and treatment-related mortality in the first 30 days was low. Tisa-cel is also associated with CRS (48%) and neurological events (10% any grade).[8]

***"One potential advantage of tisa-cel is its design as a 401-BB construct, which lends itself to more blunted T-cell expansion and better persistence, translating to a potentially safer toxicity profile."***

There are also late toxicities of CAR T-cell therapies; namely, prolonged cytopenias and opportunistic and viral infections. Monitoring of all CAR T-cell recipients beyond the first 30 days is essential, and some may require intravenous immunoglobulin (IVIG) replacement for significantly low immunoglobulin G levels and recurrent infections. It is recommended that these patients receive *Pneumocystis jirovecii* pneumonia (PJP) and Herpes simplex virus (HSV) prophylaxis for at least a year or until CD4 counts are recovered. At this point, it is also important to continue with recommended vaccinations including annual influenza, COVID-19 where appropriate, and potentially even repeating post-transplant vaccines.

## What are some of the most promising emerging treatments for R/R FL?

***Dr. Diefenbach:*** Antibody-drug conjugates (ADCs) are emerging as promising therapies for FL. For example, polatuzumab is an ADC that targets the CD79b antigen on the surface of B cells to deliver a microtubule-disrupting toxin - in this case monomethyl auristatin E (MMAE) - directly to the tumor cells. Interestingly, the therapeutic effect is not derived directly from the antigen-antibody binding, but by the byproduct of this binding, which is the opsonization of the chemotherapy moiety.

Polatuzumab was evaluated in heavily pretreated R/R FL patients in a single-arm phase 1b/2 study at either 1.4 or 1.8 mg/kg in combination with lenalidomide and obinutuzumab.[11] The primary endpoint was independent review committee (IRC)-assessed CR at the end of induction measured by positron emission tomography-computed tomography (PET-CT) scans, and the secondary endpoints included OR, PFS, OS, and biomarker analysis. At a median duration of follow-up of 43.5 months, the PFS had not been reached and the OS was excellent. At more than three years, greater than half of patients remain in remission.

In terms of safety, the primary Grade 3 and 4 adverse events (AEs) were either hematologic or infection-related. Once prophylaxis with granulocyte-colony stimulating factor (GCSF) was

instituted, the number of infections went down substantially. Despite the fact that 14 patients had Grade 3 thrombocytopenia, only two patients required platelet transfusions and only eight patients had Grade 3 anemia. In terms of secondary malignancies, there was one case of myelodysplastic syndrome, two cases of squamous cell carcinoma and one instance of likely relapse of lung cancer.

***"In all, polatuzumab represents an exciting development in FL: an outpatient-delivered therapy that is effective in heavily pretreated patients with minimal toxicity."***

Bispecific T-cell engagers (BiTEs) are also performing well in R/R FL. Mosunetuzumab-axgb is a first-in-class BiTE that binds to CD20 on B-cells and CD3 on T-cells. This agent was granted accelerated approval in December 2022 for R/R FL after two or more lines of systemic therapy. In a single-arm study, this agent produced an overall response rate (ORR) of 78% and a CR rate of 60%, with the majority of participants maintaining their response after 18 months.[12] The median 24-month PFS was 48%, and the median OS was 87%. There was consistent benefit in patients with double refractory disease who were POD24 positive.[13] Patients were also evaluated by mutation status via whole exome sequencing to assess whether known prognostic variants were more or less sensitive to mosunetuzumab.

***"Clinically meaningful responses to mosunetuzumab were confirmed among patients with common mutations such as T53, BCL-3, or CREBBP that are associated with a poor prognosis."***

Mosunetuzumab is a fixed-duration treatment that can be administered in the outpatient setting in a step-up manner to partially mitigate the CRS toxicity that can occur.[12] While 44% of the participants experienced any-grade CRS, only 1% had CRS Grade 3 or higher. Eleven percent of patients required corticosteroids, but only 8% of patients required tocilizumab and all events resolved. In short, mosunetuzumab demonstrates high activity in R/R FL with a very manageable safety profile.

Odronextamab is an alternate CD20/CD3 BiTE that was investigated in R/R B-cell non-Hodgkin lymphoma in the phase 1 ELM trial.[14] This BiTE demonstrated a very high ORR of 91%, a CR rate of 72%, and a median PFS of 17.1 months. Phase 2 of the ELM trial, which included an FL cohort, revealed an ORR of 81% and a CR of 75%.[15] In addition, the median duration of response and PFS was 20 months. These benefits were observed across high-risk subgroups. The safety profile was similar to mosunetuzumab, with low rates of Grade 3 or higher neutropenia, neurological events and CRS. Also like mosunetuzumab, this agent is 'off the shelf,' which is a significant advantage over CAR T-cell therapy.

Finally, epcoritamab is a subcutaneous CD20/CD3 BiTE that, when combined with lenalidomide and rituximab, was shown in the EPCORE NHL-2 Arm 2A to achieve an ORR of 100% and a complete

metabolic response (CMR) rate of 96% with manageable safety.[16] These patients were older and heavily pre-treated, with a high percentage of POD24-positivity. Neutropenia and COVID-19 infection were significant toxicities, as was CRS, although this was primarily limited to Grade 1 or 2 which fully resolved in all patients. This agent is also showing promise in previously untreated FL (EPCORE NHL-2 Arm 6).

In summary, CAR T-cell therapies and BiTEs offer new avenues for targeting FL pathogenesis with excellent efficacy in patients with numerous relapses and high-risk disease characteristics. While the safety of these agents must be carefully considered, current studies indicate that the AEs of CAR T-cell therapies and BiTEs can be clinically managed in most cases, offering hope for significantly improved outcomes in this challenging patient population.

To view the associated accredited activity please click here.

## References


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