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# Cellular Therapy and Follicular Lymphoma: Where Do We Stand in 2025?

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## Introduction

Patients with low-risk follicular lymphoma (FL) have a median overall survival (OS) exceeding 20 years.[1] Whereas those with adverse features, such as a high Follicular Lymphoma International Prognostic Index (FLIPI) score or progression of disease within 24 months of front-line treatment (POD24) have inferior outcomes.[1] Standardized treatment in the second line and beyond is not firmly established and largely depends on patient fitness and medication access. The duration of response decreases with each line of therapy.[2] In this review, we evaluate the evidence for T-cell-redirecting therapies in FL.

## Chimeric Antigen Receptor T cell (CAR T) Therapy in FL

CAR T-cell therapy involves the modification of donor T-cells to induce the expression of chimeric antigen receptors (CARs), which are highly specified receptors that target specific antigens. CAR T-cell therapy can cause direct cellular toxicity to antigen-positive cells, while it also may recruit other components of the immune system, resulting in highly targeted anti-tumour effects. The persistence of CAR T-cells with a memory-like phenotype can result in long-term disease control years after the administration of this living drug. CAR T-cell therapy is highly effective in relapsed or refractory (r/r) FL, which has resulted in the regulatory approval of this therapy in the third-line setting. The following three autologous, second-generation CD19-targeting CAR T-cell therapies have the most mature evidence.

Axicabtagene ciloleucel (Yescarta) utilizes a CD28 co-stimulatory domain, which drives rapid T-cell expansion but results in shorter persistence. The ZUMA-5 Phase 2 trial evaluated patients with FL (n=124) or marginal zone lymphoma (n=24), and high-risk patients were well represented (**Table 1**).[3] With a median follow-up of 17.5 months, the overall response rates (ORR) and complete response (CR) rates in patients with FL were high at 94% and 79%.[3] No differences in ORR were detected in patients with POD24, prior autologous stem cell transplant (ASCT), or several lines of prior therapy.[3] Toxicity was manageable, with 18% of patients experiencing grade ≥3 immune effector cell–associated neurotoxicity syndrome (ICANS) and 6% experiencing grade ≥3 cytokine release syndrome (CRS) with one fatal event.[3] Long-term follow-up of the FL cohort showed an excellent median progression-free survival (PFS) of 40.2 months.[4]

Additional analyses revealed that patients with the lowest quartile of metabolic tumour volume (MTV) had nearly double the 36-month PFS compared to those with the highest MTV (60% vs. 33%).[4] Patients never exposed to bendamustine had the highest 36-month PFS (70%), and those exposed within 6 months had the lowest PFS (25%); however, it is likely that disease behaviour, such as early relapse, also plays into these results.[4] Interestingly, this study also showed that four patients died of drug-related adverse events (AE). It is important to note that 13 secondary primary malignancies (SPMs) were observed, including four that were fatal. None of these deaths were considered treatment-related, though SPMs are a known risk of CAR T-cell therapy and the second leading cause of non-relapse mortality.[4,5]

Tisagenlecleucel (Kymriah) utilizes a 4-1BB co-stimulatory domain, which drives more gradual T-cell expansion and prolonged persistence. The Phase 2 ELARA trial evaluated 97 patients with r/r FL after ≥2 prior therapies, which included many patients with high-risk features (**Table 1**).[6] High-risk features were prevalent; 63% of patients

| Trial | ZUMA-5 (3)<br>Phase II study | ELARA (6)<br>Phase II study | TRANSCEND FL (9)<br>Phase II study |
|---|---|---|---|
| **Product/trade name** | Axicabtagene ciloleucel/*Yescarta* | Tisagenlecleucel/*Kymriah* | Lisocabtagene maraleucel/*Breyanzi* |
| **Number of patients** | 124 (FL cohort) | 97 | 130 |
| **Median follow-up** | 17.5 months | 16.6 months | 18.9 months |
| **Population** | ≥2 prior lines of therapy, including anti-CD20 mAb and alkylating agent | ≥2 prior lines of therapy | ≥2 prior lines of therapy (+3L) or 1 prior line (2L) with POD24 and therapy initiation <6 months from diagnosis OR high tumour burden by mGELF |
| High-risk features | | | |
| *High tumour bulk by GELF* | 52% | Not reported | 56% |
| *POD24* | 55% | 62.9% | 45% |
| *FLIPI ≥3* | 44% | 59.8% | 53% |
| *Stage 3–4* | 85% | 85.6% | 87% |
| *Prior ASCT* | 24% | 36.1% | 25% |
| **ORR** | 94% | 86% | 97% |
| **CR rate** | 79% | 69% | 94% |
| **12-month PFS** | 79.1% | 67% | 83% |
| **12-month OS** | 94.2 % | 95% | 93% |
| **CRS (grade ≥3)** | 78% (6%) | 49% (0%) | 58% (1%) |
| **Neurologic events (grade ≥3)** | 56% (15%) | 23% (1%) | 15% (2%) |

**Table 1.** Landmark CAR-T cell therapy trials in follicular lymphoma; *courtesy of Hadel El-Haddad, MD and Hannah Cherniawsky, MD, MSc.*

**Abbreviations: ASCT:** autologous stem cell transplant; **CR:** complete response; **CRS:** cytokine release syndrome; **FL:** follicular lymphoma; **FLIPI:** Follicular Lymphoma International Prognostic Index; **mAb:** monoclonal antibody; **(m) GELF:** (modified) Groupe d'Etude des Lymphomes Folliculaires; **ORR:** objective response rate; **OS:** overall survival; **POD24:** progression of disease within 24 months of front-line treatment; **PFS:** progression-free survival

had POD24, 60% had FLIPI scores ≥3, and 36% had undergone prior ASCT.[6] With a median follow-up of 16.6 months, the ORR was 86%, and the CR rate was 69%.[6] Responses were similar in high-risk subgroups, including those with POD24, high tumour burden, and double-refractory disease.[6] Median PFS has not been met, even with longer follow-up data.[7] The estimated 12-month PFS and OS were 67% and 95%, respectively.[7] Grade ≥3 CRS and ICANS occurred in ≤1% of patients, and most cytopenias resolved by month 24.[6]

Exploratory analyses revealed improved outcomes in patients who, at baseline, had lower MTV, higher levels of naïve CD8+ T cells, and lower T-cell exhaustion marker expression.[7] A comparative analysis of Zuma-5 and ELARA suggested similar efficacy but lower adverse effects with tisagenlecleucel than with axicabtagene autoleucel.[8] Large-scale, comparative registry data are keenly awaited. Despite a lack of head-to-head comparison, prospective trials and similar retrospective series evaluating large B-cell lymphoma (LBCL) in the third line have significantly impacted prescribing.

Lisocabtagene maraleucel (Breyanzi) utilizes a 4-1BB co-stimulatory domain and a 1:1 CD4:CD8 ratio. The Phase 2 TRANSCEND FL trial enrolled patients to be treated in the third (3L+) or second (2L) line. Patients with high-risk features, namely POD24, systemic treatment within 6 months of diagnosis, and/or high tumour burden defined by the modified Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria, were included in this study.[9]

In the 3L+ cohort (n=101), the ORR was 97%, and the CR rate was 94%.[9] The high-risk 2L cohort (n=23) also had excellent results with an ORR and CR rate of 96%.[9] At a median follow-up of 18.9 months, the median PFS was not reached, though the 12-month point estimate was 83% overall.[9] Toxicity was manageable, with grade ≥3 CRS observed in 1% and grade ≥3 neurologic events in 2% of patients.[9] One treatment-emergent death occurred due to macrophage activation syndrome.[9] Another death due to progressive multifocal leukoencephalopathy was observed after the 90-day treatment-emergent period.[9]

## Bispecific Antibodies (BAbs) in FL

BAbs represent a novel immunotherapy in which an immunoglobulin (Ig) or Ig-like structure redirects cellular components of the host immune system to their target antigen. Most BAbs in the lymphoma space engage CD3 on host T cells and CD20 on lymphoma cells to promote cytotoxicity and phagocytosis of lymphomatous cells.

Mosunetuzumab is a first-in-class IgG-like CD20xCD3 BAb with the most mature evidence in FL. An ongoing Phase 1/2 study examined fixed-duration mosunetuzumab in 90 patients with r/r FL treated with ≥2 prior lines of therapy.[10] Patients with CR received 8 cycles of mosunetuzumab, whereas those with partial remission (PR) received up to 17 cycles if ongoing benefit was derived.[10] The most recent data showed that at 3 years of follow-up, a high ORR (77.8%) and CR rate (60.0%) was achieved.[11] The median PFS was 24 months, though the duration of response (DOR) has not yet been reached in patients attaining a CR, suggesting ongoing responses in patients with CR long after drug administration has stopped.[11]

Patients with POD24 also had excellent ORR (74%) and CR rates (69%).[10] Their 36-month PFS rate was nearly identical to their non-POD24 counterparts (42% vs. 44%), and the median time to the next treatment was not reached in either group.[11,12] Patients treated in the fourth line and beyond had lower ORR (73% vs. 86%), CR (55% vs. 69%), and 36-month PFS rates (36% vs. 54%).[12] Interestingly, patients aged ≥65 years had higher ORR, CR, and 36-month PFS rates than those aged <65 years in this study.[12] No treatment-related deaths were reported.[10] CRS was observed in 44% of patients, with only 2.2% being grade ≥3, and most events occurred during cycles 1–2.[10] Neurologic events were uncommon and mainly included low-grade headaches (11%), though ICANS was not explicitly reported.[10]

Early economic analyses have suggested improved cost-effectiveness with mosunetuzumab over commercial CAR T therapies.[13,14] However, these data are based on relatively newly available therapies in the US system. Mosunetuzumab is undergoing further investigations as a combination therapy in earlier lines of therapy in the CELESTIMO and MorningLyte trials.

Epcoritamab, another C20xCD3 BAb, has been evaluated in the third-line setting for FL in a Phase 2 dose expansion cohort of the

EPCORE NHL-1 trial. Key differences between this therapy and mosunetuzumab include indefinite, subcutaneous administration with a slightly different dosing frequency. Results of the pivotal cohort (n=128) show high ORR (82%) and CR rates (63%) with a rapid median time to response of 1.4 months.[15] At a median follow-up of 17.4 months, patients with CR had not reached median PFS; however, those attaining a PR had a median PFS of <6 months.[15] Measurable residual disease (MRD) data was collected in 91 (71%) patients, of whom 61 (67%) were MRD-negative. PFS was significantly higher in patients who were MRD-negative, even across high-risk subgroups.[15] This, in turn, leads to the question about potential therapy de-escalation in MRD-negative individuals.

In the pivotal cohort, CRS was observed in 66% of patients with 2 cases of grade 3 CRS (2%).[15] ICANS (as opposed to general neurotoxicity) was reported in 6% of patients with a 2% overall risk of grade ≥3 ICANS.[15] In the optimization cohort (n=86), which utilized prophylactic steroids during cycle 1 (n=86), no grade ≥3 CRS or ICANS was observed, though 49% of patients still had grade 1–2 CRS.[15]

Glofitamab is another CD3xCD20 IgG1 BAb with an additional CD20-binding moiety, creating a 2:1 lymphoma-to-T-cell binding ratio. Glofitamab has been extensively studied in aggressive lymphoma as mono or combination therapy with monoclonal antibodies, antibody-drug conjugates, or even CAR T-cell therapy. However, data in the FL space is less mature.

A small trial evaluated step-up dosing (SUD) of glofitamab with or without obinutuzumab.[16] In the combination treatment cohort (n=19), the ORR was impressive at 100%, with a CR rate of 74%.[16] In the monotherapy cohort (n=53), the ORR was 81%, with a CR rate between 67–72% across the tested dosing schemas.[16] CRS was the most common AE, occurring in 66% of patients receiving monotherapy and in 79% of those receiving combination therapy, with only one instance of grade 3 CRS across all patients.[16] Roughly one-third of patients across both cohorts had grade 1–2 AEs, and there were no ICANS-like events.[16] Investigation of glofitamab is ongoing in various lines of therapy, combinations, and histologies, including after CAR T-cell therapy failure.[17]

## CAR T vs. BAbs

Both CAR T and BAbs can result in deep and durable responses in patients with r/r FL, which has capsized the paradigm of diminishing returns with later lines of lymphoma therapy. However, both therapies have advantages and shortcomings.

While CAR T requires a single administration, autologous products come with a built-in delay due to manufacturing and the additional effort of collecting, transporting, and cryopreserving cellular material. BAbs are an “off the shelf” product that can be started quickly without risk of manufacturing failure. However, they require multiple and, in some cases, indefinite administration. CAR T is associated with higher rates of CRS and ICANS than BAbs. However, given that CAR T-cell therapy is often restricted to accredited centres, there is often greater expertise in managing severe or refractory cases. Conversely, step-up dosing used with BAbs makes their safety profile favourable; however, ongoing administration is required, which can be taxing to the patient and hospital resources.

Neither CAR T-cell therapy nor BAbs appear to be curative in FL. Both rely heavily on T-cell fitness and antigen persistence on target cells. Thus T-cell exhaustion and antigen loss can lead to relapse with either modality. Additionally, both have the on-target-off-tumour effects of B-cell aplasia, which can increase the risk of infection. However, this is more pronounced post-CAR T-cell therapy.

## Future Directions

Therapy sequencing is a critical question for r/r FL, as many patients will encounter both BAbs and CAR T on their therapeutic journey. Literature in the LBCL space has demonstrated comparable results with CAR T-cell therapy between those who did not previously receive CD20 BAbs and those who did.[18] Many patients in pivotal CAR T trials are BAbs-exposed and vice versa. The Bicar study examining the use of glofitamab in r/r non-Hodgkin Lymphoma (NHL) seeks to address this in a prospective manner.[17] In patients with LBCL long-term curability of CAR T-cell therapy has made if a preferred choice to BAbs.[19] However, the relevance of this is uncertain, as more and more patients are treated in the second line. The same evidence is not yet available for r/r FL but is keenly awaited.

Optimal supportive care, such as infection prophylaxis, remains a major question in the cellular therapy field. Looking further ahead, bicistronic CAR T-cells (containing two CARs targeting different antigens), novel targets, and NK cell redirecting therapy are all in various states of investigation. Only time will tell what our armamentariums of cellular therapies will look like in the future.

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