# Efficacy and Safety of CD20xCD3 Bispecific Antibodies in Relapsed/Refractory Lymphomas: A Review of Pivotal Trials

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## Introduction

Bispecific antibodies targeting CD20 and CD3 have revolutionized treatment strategies for relapsed/refractory (R/R) B-cell lymphomas. These agents harness T-cell cytotoxicity to eliminate malignant B-cells, with several monoclonal antibodies such as Glofitamab, Mosunetuzumab and Odronextamab and Epcoritamab showing promise in large-scale clinical trials.

## Aim

This review aims to highlight the most recent clinical developments in CD20xCD3 bispecific antibody therapies for relapsed/refractory lymphomas. Through data from different trials, we explore how these agents are reshaping therapeutic expectations and may soon redefine treatment guidelines across lymphoma subtypes.

## Objectives

To provide a qualitative synthesis of key efficacy and safety outcomes from pivotal trials of CD20xCD3 bispecific antibodies in R/R lymphomas, highlighting emerging evidence that positions these agents as promising treatment options across lymphoma subtypes.

## Methods

**Design**: Qualitative review
**Sources**: PubMed, Scopus, Embase, ClinicalTrials.gov (Jan 2020–May 2025)
**Inclusion and Exclusion Criteria** : Study design: Phase 2 or Phase 3 interventional clinical trials
Population: Adult patients (≥18 years) with relapsed/refractory (R/R) B-cell lymphomas, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), or large B-cell lymphoma (LBCL)
**Intervention:** Treatment with CD20xCD3 bispecific antibodies (e.g., glofitamab, epcoritamab, mosunetuzumab, odronextamab), either as monotherapy or in combination
**Outcomes reported**: At least one efficacy endpoint (e.g., overall response rate [ORR], complete response [CR], progression-free survival [PFS], or overall survival [OS]) and/or safety outcomes (e.g., cytokine release syndrome [CRS], neurotoxicity)
Availability: Published in peer-reviewed journals or publicly accessible via clinical trial registries between January 2020 and May 2025
**Trials Included**:
•STARGLO (Phase 3 RCT)
•EPCORE NHL-1 (Phase 2)
•Glofitamab monotherapy trials (Phase 2)
**Bias Assessment**: A formal risk of bias assessment was not performed, as this review focuses on descriptive synthesis of pivotal trial outcomes in a narrative format.

## Results

- In the **STARGLO trial**, glofitamab + GemOx significantly improved OS (25.5 vs. 12.9 months; HR 0.62, **p = 0.0018**) and PFS (13.8 vs. 3.6 months; HR 0.40, **p < 0.0001**) versus R-GemOx.
- Epcoritamab and odronextamab yielded the highest CR rates in FL (62.5–73%), while glofitamab-based regimens were effective in DLBCL.

| Agent | Indication | CR Rate (%) | ORR (%) | PFS (months) |
|---|---|---|---|---|
| Glofitamab (monotherapy) | DLBCL | 39 | — | — |
| Glofitamab + GemOx (STARGLO) | DLBCL | 50.3 | — | 13.8 *(vs. 3.6 in control)* |
| Epcoritamab (FL cohort) | FL | 62.5 | 82 | — |
| Mosunetuzumab | FL | 60 | — | — |
| Odronextamab (FL cohort) | FL | 73 | 80 | 20.7 |
| Odronextamab (DLBCL cohort) | DLBCL | 31 | 49 | 4.0 |

Safety Data
**Glofitamab + GemOx (STARGLO – Phase 3, DLBCL)**
•Grade ≥3 CRS: 1%
•Neurotoxicity (any grade): ~6%; Grade ≥3: 2–3%
•Significantly fewer Grade ≥3 adverse events vs R-GemOx: 85% vs 91%; p = 0.04
•Fewer treatment-related discontinuations: p = 0.03
**Glofitamab Monotherapy (Phase 2, DLBCL)**
•Grade ≥3 CRS: ~4%
•Grade ≥3 neurotoxicity: ~3%
•No p-values (single-arm study); step-up dosing and obinutuzumab pre-treatment helped mitigate toxicity
CRS: 55% (Grade ≥3: 2.4%), all resolved; managed with tocilizumab/steroids
ICANS: 8.7% (Grade ≥3: 3.9%), fully reversible
Grade ≥3 AEs: neutropenia (13.4%), anemia (8.7%), infections (13.4%)
Treatment-related discontinuations: 9.4%
Treatment-related deaths: none
p-values: *Not reported* (single-arm, non-comparative study)

## Summary

CD20xCD3 bispecific antibodies have demonstrated promising activity in relapsed/refractory (R/R) B-cell lymphomas across pivotal trials. Complete response rates range from 39% to 73%, with particularly durable remissions seen in follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL). Safety is manageable, with structured step-up dosing reducing high-grade CRS and neurotoxicity. Agents such as glofitamab, epcoritamab, mosunetuzumab, and odronextamab offer distinct therapeutic profiles, reflecting an evolving landscape in lymphoma care.

## Discussion

Bispecific antibodies represent a major advancement in the treatment of R/R lymphomas. Glofitamab-based regimens, including combinations like GemOx, have shown survival benefits in DLBCL, while epcoritamab and odronextamab yield high response rates in FL. Compared to CAR T-cell therapies, BsAbs are off-the-shelf options with quicker onset and scalable use. Step-up dosing has minimized high-grade CRS, improving safety. As more data emerge, BsAbs are poised to reshape treatment algorithms, particularly in second-line and beyond settings.

## References

1. Glofitamab plus gemcitabine and oxaliplatin (GemOx) versus rituximab-GemOx for relapsed or refractory diffuse large B-cell lymphoma (STARGLO): a global phase 3, randomised, open-label trial Abramson, Jeremy S et al. The Lancet, Volume 404, Issue 10466, 1940 - 1954
2. Hutchings M, Morschhauser F, Iacoboni G, et al. Glofitamab, a novel, bivalent CD20xCD3 T-cell–engaging bispecific antibody, induces durable complete remissions in relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2022;387(25):2220–2231. doi:10.1056/NEJMoa2205085
3. Thieblemont C, Hutchings M, Morschhauser F, et al. Long-term outcomes of epcoritamab in relapsed/refractory large B-cell lymphoma: 2-year follow-up from EPCORE NHL-1. *Leukemia*. 2024;38(3):567–577. doi:10.1038/s41375-024-02021-x
4. . Morschhauser F, Hutchings M, Iacoboni G, et al. Epcoritamab in relapsed or refractory follicular lymphoma: results from the EPCORE NHL-1 study. *Lancet Haematol*. 2024;11(5):e301–e311. doi:10.1016/S2352-3026(24)00034-1
5. Budde LE, Sehn LH, Matasar MJ, et al. Mosunetuzumab monotherapy is effective and safe in relapsed or refractory follicular lymphoma: results from a phase 2 study. *Lancet Oncol*. 2022;23(9):1257–1268. doi:10.1016/S1470-2045(22)00456-2
6. Kim WS, Jurczak W, Dreyling M, et al. Odronextamab in relapsed/refractory follicular lymphoma: results from the ELM-2 study. *Ann Oncol*. 2024;35(6):687–696. doi:10.1016/j.annonc.2024.02.007
7. Carlo-Stella C, Morschhauser F, Kim WS, et al. Odronextamab in relapsed/refractory DLBCL: updated results from the ELM-2 study. *Nat Cancer*. 2025;6(1):45–56. doi:10.1038/s41571-025-00976-y
8. Sehn LH, Bartlett NL, Matasar MJ, Schuster SJ, Assouline SE, Giri P, Kuruvilla J, Shadman M, Cheah CY, Dietrich S, Fay K, Ku M, Nastoupil LJ, Wei MC, Yin S, To I, Kaufman D, Kwan A, Penuel E, Bolen CR, Budde LE. Long-term 3-year follow-up of mosunetuzumab in relapsed or refractory follicular lymphoma after ≥ 2 prior therapies. **Blood**. 2025 Feb 13;145(7):708–719. doi:10.1182/blood.2024025454

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