# Paradigm Shift in the Treatment of Diffuse Large B-Cell Lymphoma: The Era of Bispecific Antibodies

**Won Seog Kim**
*Samsung Medical Center, Sungkyunkwan University School of Medicine, Korea*

Background: The therapeutic landscape of diffuse large B-cell lymphoma (DLBCL) remained relatively unchanged for nearly three decades following rituximab's integration until the recent emergence of T-cell engaging therapies. While CAR-T therapy has shown remarkable efficacy, its clinical implementation faces challenges including manufacturing complexity, limited accessibility, and toxicity management. Bispecific antibodies have emerged as promising alternatives with three agents—glofitamab, epcoritamab, and odronextamab—receiving regulatory approval.

Third-Line Treatment Efficacy: Phase II trials have demonstrated robust antitumor activity in heavily pretreated DLBCL patients. Epcoritamab achieved 63.1% overall response rate (ORR) and 38.9% complete response (CR) rate in 157 patients with median three prior therapies. Odronextamab showed 53% ORR and 53% CR rate in DLBCL patients without prior CAR-T therapy. Glofitamab monotherapy achieved 39% CR rate after at least two prior treatment lines.

Safety Profile: Bispecific antibodies demonstrated manageable safety profiles compared to CAR-T therapy. Cytokine release syndrome (CRS) occurred predominantly as grade 1-2 events (47.1% for epcoritamab), with grade 3 CRS in only 2.5%. Immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 6.4% of patients, with minimal treatment discontinuations.
Second-Line Breakthrough: The phase III STARGLO trial established glofitamab plus gemcitabine-oxaliplatin (Glofit-GemOx) superiority over R-GemOx in 274 transplant-ineligible R/R DLBCL patients. Glofit-GemOx demonstrated significantly superior outcomes: ORR 68.3% vs. 40.7%, CR rate 58.5% vs. 25.3%, and 2-year overall survival 54.4% vs. 33.6%, with 40-41% reduction in death risk. The combination showed manageable toxicity with CRS in 44.8% (grade 3-4: 2.3%) and ICANS in 2.3% (grade3-4:0.6%).
Future Directions: Multiple trials are investigating bispecific antibodies in first-line DLBCL treatment, potentially representing the next paradigm shift. Additional second-line trials with epcoritamab and odronextamab combinations are ongoing.
Challenges: Critical questions remain regarding optimal sequencing of T-cell engaging therapies, identification of effective combination partners, and patient selection biomarkers.

Conclusion: Bispecific antibodies are fundamentally transforming DLBCL treatment across all therapy lines. Their established third-line efficacy, emerging second-line superiority, and promising first-line investigations, combined with favorable safety profiles, convenient administration, and off-the-shelf availability, position them as accessible alternatives to CAR-T therapy. As clinical evidence matures, a complete restructuring of the DLBCL treatment algorithm is anticipated.