

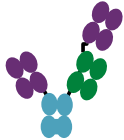
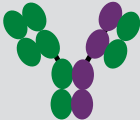
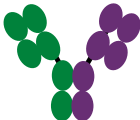
Bispecific Antibodies in Indolent B-Cell Lymphomas: A Summary Resource



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Mechanism of Action and Molecular Targets

Bispecific antibodies, used in B-cell lymphomas, target the CD3 and CD20 antigens expressed on the surface of B lymphocytes.¹⁻⁵

Agent	Targets	Design	Ig Fragment Formats
Mosunetuzumab	CD20 x CD3		- Humanized mouse IgG1-based Ab - Bivalent CD20 and monovalent CD3ε binding - Modified Fc devoid of FcγR and complement binding
Glofitamab	CD20 ₂ x CD3		- Immunized mouse IgG1-based Ab - Bivalent CD20 and monovalent CD3ε binding - Modified Fc devoid of FcγR and complement binding
Odronextamab	CD20 x CD3		- Fully human IgG4-based heterodimeric Ab - Monovalent CD19 and monovalent CD3ε binding - Fc-dependent effector function–minimized Ab with Fc of the anti-CD3ε heavy chain modified to reduce Protein A binding - Common κ light chain from anti-CD3ε mAb
Epcoritamab	CD20 x CD3		- Humanized mouse IgG1-based Ab - Monovalent CD20 and monovalent CD3ε binding - IgG1 Fc minimize Fc-dependent effector functions and to control Fab-arm exchange of mAb half-molecules, resulting in high bispecific product yield

Ab, antibody; IgG1, immunoglobulin G1; mAb, monoclonal antibody.

Bispecific Antibodies Under Investigation in B-Cell Lymphoma

The following bispecific antibodies are currently under investigation for indolent B-cell lymphomas, but none has been approved by the FDA for use as of April 5, 2022.

Mosunetuzumab	Comments
FDA approvals and recommendations in B-cell lymphomas	FDA granted breakthrough therapy designation to mosunetuzumab in July 2020 for the treatment of adults with R/R FL who have received ≥2 prior therapies
Indolent B-cell NHL	- Phase I/IIb study of mosunetuzumab in R/R NHL (n = 216)¹ – ORR in indolent NHL: 66.2%, with 48.5% in CR
FL	- Phase II study with mosunetuzumab as third line or greater in R/R FL after ≥1 anti-CD20 and alkylating agent (n = 90)² – ORR: 78.9%, with 58.7% in CR
Glofitamab	Comments
FDA approvals and recommendations in B-cell lymphomas	Glofitamab is not currently approved by the FDA but is under investigation as a treatment for B-cell NHL
B-cell NHL	- Phase I/II study of glofitamab with obinutuzumab pretreatment in B-cell NHL (n = 258)³ – ORR in indolent NHL: 81.3% overall, with 69.3% in CR
FL	- Phase I study of glofitamab as monotherapy or with obinutuzumab in R/R B-cell NHL (n = 44 with FL)⁴ – ORR in FL: 70.5%, with 47.7% in CR

Odronextamab	Comments
FDA approvals and recommendations in B-cell lymphomas	• Odronextamab is not currently approved by the FDA but is under investigation as a treatment for B-cell NHL
B-cell NHL	• Phase I study of odronextamab in R/R B-cell NHL (n = 127) ⁵ – ORR in FL (n = 28 treated with ≥5 mg): 92.9%, with 75% in CR

Epcoritamab	Comments
FDA approvals and recommendations in B-cell lymphomas	• Epcoritamab is not currently approved by the FDA but is under investigation as a treatment for B-cell NHL
B-cell NHL	• Phase I/II clinical evaluation in patients with CD20+ B-cell NHL (n = 68) ⁶ – ORR in FL: 90%, with 50% CR
FL	• EPCORE NHL-2 phase I/II trial with epcoritamab + R ² for R/R CD20+ FL (n = 16) ⁷ – ORR: 100% in 5 evaluable patients

CR, complete response; FL, follicular lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; ORR, overall response rate; R/R, relapsed/refractory; R², lenalidomide/rituximab.

Bispecific antibodies also are in clinical trials with various combinations for B-cell lymphomas.

Management of Adverse Events

- The safety profile of bispecific antibodies in B-cell lymphomas is not fully established. However, cytokine-release syndrome (CRS) and/or neurologic events have been reported in each of the bispecific antibodies, and injection-site reactions are common.
 - CRS: potentially life-threatening toxicity caused by immune activation of T-cells, resulting in elevated inflammatory cytokines and activation of other immune cells; key symptoms include fever, hypotension, and hypoxia.
 - Many ongoing clinical trials of these agents are employing step-up dosing to mitigate CRS events.
- Mosunetuzumab: In a phase I/Ib study in **R/R FL**, CRS occurred in 23% of patients, and was classified as serious in 6%.^{1,8} Median onset was 2 days, and most occurred in cycle 1. Other common adverse events (AEs) included neutropenia and hypophosphatemia.
- Glofitamab: In a phase I study in **R/R NHL**, CRS occurred in 50.3% of patients, with 46.7% grade <3. Neurologic AEs also were reported in 43.3% of patients at the recommended phase II dose, with immune effector cell–associated neurotoxicity syndrome–like events in 2 patients.⁴
- Odronextamab: In a phase I study in R/R NHL, grade ≥3 CRS occurred in 7% of patients. Most events resolved within 2 days, and none led to discontinuation. Treatment-related neurologic AEs occurred in 2.3%.⁵
- Epcoritamab: In a phase I/II study in R/R NHL, CRS occurred in 59% of patients; all cases were grade 1/2, and almost all occurred in cycle 1. Median time to resolution was 1-2 days. Neurologic AEs were reported in 6% of patients, and injection-site reactions occurred in 47% of patients. No febrile neutropenia occurred, and there were no treatment-related deaths.⁶

Selected Clinical Trials in Indolent B-Cell Lymphoma

Bispecific Antibody	Ongoing Clinical Trials
Mosunetuzumab	- Phase I study investigating mosunetuzumab + lenalidomide, glofitamab + lenalidomide, and glofitamab + lenalidomide + obinutuzumab in R/R FL (NCT04246086) - Phase III study investigating mosunetuzumab with lenalidomide + rituximab in R/R FL (NCT04712097) - Phase II study investigating mosunetuzumab with lenalidomide in untreated FL and MZL (NCT04792502) - Phase II study investigating mosunetuzumab with or without polatuzumab vedotin + obinutuzumab for untreated FL and MZL (NCT05169658)
Glofitamab	Phase I study investigating mosunetuzumab + lenalidomide, glofitamab + lenalidomide, and glofitamab + lenalidomide + obinutuzumab in R/R FL (NCT04246086)
Odronextamab	Phase II study to assess activity and safety of odronextamab in R/R B-cell NHL including FL and MZL (NCT03888105)
Epcoritamab	- Phase I/II study investigating epcoritamab combinations in B-cell NHL including untreated and R/R FL (NCT04663347) - Phase I/II study investigating epcoritamab in R/R B-cell NHL including FL and MZL (NCT04542824) - Phase I/II GEN3013 study investigating epcoritamab in R/R B-cell NHL including FL and MZL (NCT03625037) - Phase I/II study investigating GEN3009 with or without epcoritamab in R/R B-cell NHL including FL and MZL (NCT04358458)

References

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