THERAPEUTIC ADVANCES in
Chronic Disease

Letter to the Editor

Bispecific T cell engagers targeting CD20/CD3 in B-cell lymphoma: latest updates from 2023 EHA annual meeting

Ther Adv Chronic Dis

2023, Vol. 14: 1–4

DOI: 10.1177/20406223231215701

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Keywords: B-cell lymphoma, BiTE, diffuse large B cell lymphoma, follicular lymphoma, immunotherapy

Received: 6 October 2023; revised manuscript accepted: 3 November 2023.

To the editor

B-cell lymphoma is the most prevalent subtype of malignant lymphoma with significant heterogeneity. Although treatments such as chemotherapy with the R-CHOP regimen, Bruton tyrosine kinase inhibitors, immunomodulators, and other molecular targeted therapies have shown considerable clinical efficacy, some patients still experience primary resistance or multiple recurrences. Therefore, there is an urgent need to develop novel therapeutic approaches. One promising development is the emergence of bispecific T-cell engagers (BiTEs), which utilize sophisticated antibody designs to simultaneously engage both B and T cells, thereby enhancing T-cell-mediated cytotoxicity. This novel strategy can potentially overcome the clinical challenges in B-cell lymphoma. Herein, we summarize the latest updates on BiTEs targeting CD20/CD3 in B-cell lymphoma from the 2023 EHA annual meeting.

CD20 × CD3 BiTEs in diffuse large B cell lymphoma

Glofitamab is a distinct CD20 × CD3 BiTE with a novel tumor T cell-binding configuration. Hutchings *et al.*[1] provided an update on a phase II study of 154 patients with relapsed or refractory diffuse large B cell lymphoma (R/R DLBCL), including 33% who had previously received CAR-T cells, receiving at least one dose of glofitamab monotherapy. Overall response rate (ORR) and complete response (CR) rates were 59% and 38%, respectively. Patients who achieved CR at the end of treatment showed a 1-year progression-free survival (PFS) rate of 80% and a 1-year overall survival (OS) rate of 94%. The incidence of cytokine release syndrome (CRS) rate was 64%, with only 3% grade 3 and 1% grade 4.

The phase II ELM-2 study[2] presented a 49% ORR and 31% CR rate in 140 patients with R/R DLBCL receiving odonextamab, with a median CR duration of 17.9 months. The most common adverse events (AEs) were CRS (55%), anemia (42%), and pyrexia (39%).

CD20 × CD3 BiTEs have also been reported as a first-line treatment option for high-risk DLBCL. In the EPCORE NHL-2 study,[3] all 46 patients with DLBCL with high International Prognostic Index (IPI) scores of 3–5 received an epcoritamab 48 mg + R-CHOP regimen. Of these patients, 76% achieved complete metabolic response (CMR). After a median follow-up of 11.5 months, the median PFS, OS, and duration of response were not reached. The most common AEs were neutropenia (64%), anemia (62%), CRS (60%), fatigue (40%), pyrexia (40%), injection-site reactions (38%), and nausea (38%).

CD20 × CD3 BiTEs in follicular lymphoma

Mosunetuzumab, a fully humanized, full-length anti-CD20/CD3 BiTE, has recently been approved in Europe for relapsed or refractory follicular lymphoma (R/R FL) treatment in adults who have received at least two prior systemic therapies. In a pivotal phase II study,[4] 49 of 90 (54%) enrolled patients achieved CR at the end of treatment, with a 24-month PFS of 77%.

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The ELM-2 study[5] demonstrated the efficacy of odronextamab in 131 patients with R/R FL grades 1–3a. The ORR and CR rates were 82% and 75%, respectively, with a median PFS of 20.2 months, and median OS was not reached. The most common AEs were CRS (56%), neutropenia (40%), and pyrexia (31%).

In the phase I/II EPCORE NHL-2 trial,[6] 109 patients received epcoritamab 48 mg + R^2, including 56% of patients with Follicular Lymphoma International Prognostic Index (FLIPI) 3-5 and 61% with stage IV disease. Among the 101 evaluable patients, the ORR was 97%, the CMR was 86%, with an estimated 6-month PFS of 93%. Notably, CMR was also promising in high-risk subgroups: 82% of patients with disease progression within 24 months (POD24) and 79% of patients with refractory to both anti-CD20 therapy and an alkylating agent, and 87% of patients with primary refractory disease. The most common AEs were CRS (48%: 46% grades 1–2, 2% grade 3), neutropenia (48%), injection-site reactions (38%), and fatigue (33%), which were all resolved without discontinuation.

CD20 × CD3 BiTEs in marginal zone lymphoma

The ELM-2 study[7] aims to evaluate the efficacy and safety of odronextamab monotherapy in relapsed or refractory marginal zone lymphoma (R/R MZL). Additionally, the OLYMPIA-5 trial[8] also aims to evaluate the efficacy and safety of odronextamab plus lenalidomide compared to the R^2 regimen in R/R MZL.

Conclusion

Advancements in BiTE immunotherapy for B-cell lymphoma were showcased at the 2023 EHA annual meeting, as summarized in Table 1. BiTEs targeting CD20/CD3 show high ORR and CR rates in B-cell lymphomas. These positive outcomes were particularly notable in patients with

Table 1. Updated studies on the bispecific T cell engagers targeting CD20/CD3 in B cell lymphomas from 2023 EHA annual meeting.

Abstract	NCT no.	Agent	Phase	Tumor type	No. patients	Median age (years)	Outcome	Safety
P1129	NCT03075696	Glofitamab	II	R/R-LBCL	154	NA	ORR: 59% CR: 38% 1 y PFS: 80% 1 y OS: 94%	CRS: 64% (Gr 1 48%, Gr 2 12%, Gr 3 3%, Gr 4 1%)
P1115	NCT03888105	Odronextamab	II	R/R DLBCL	140	66	ORR: 49% CR: 31% Median duration of CR: 17.9 m	CRS: 55% Anemia: 42% Pyrexia: 39%
P1116	NA	Epcoritamab + R-CHOP	I/II	UT DLBCL	47	64	ORR: 100% CMR: 76%	Neutropenia: 64% Anemia: 62% CRS: 60% Fatigue: 40% Pyrexia: 40% Injection-site reactions: 38% Nausea: 38%
P1078	NCT02500407	Mosunetuzumab	II	R/R FL	90	63	Best CR: 60% EOT CR: 54% 2 y PFS: 77%	Gr ⩾ 2 CRS: 33%/14% (with/without bone marrow burden)

(Continued)

Table 1. (Continued)

Abstract	NCT no.	Agent	Phase	Tumor type	No. patients	Median age (years)	Outcome	Safety
P1083	NCT03888105	Odronextamab	II	R/R FL grade 1–3a	131	61	ORR: 82% CR: 75% Median PFS: 20.2 m Median OS: not reached	CRS: 56% Neutropenia: 40% Pyrexia: 31%
S222	NCT04663347	Epcoritamab + R2	I/II	R/R FL	109	65	ORR: 97% CMR: 86% 6m PFS: 93%	CRS: 48% (Gr 1–2 46%, Gr 3 2%) Neutropenia: 48% Injection-site reactions: 38% Fatigue: 33%
PB2266	NA	Odronextamab + lenalidomide *versus* R2	III	R/R MZL	70	NA	NA	NA
PB2279	NCT03888105	Odronextamab	NA	R/R MZL	78	NA	NA	NA

B-NHL, B-cell non-Hodgkin's lymphoma; CMR, complete metabolic response; CR, complete response; CRS, cytokine release syndrome; EOT, end of treatment; Gr, grade; m, month; NA, not available; ORR, overall response rate; OS, overall survival; PFS, progression free survival; R/R DLBCL, relapsed or refractory diffuse large B cell lymphoma; R/R FL, relapsed or refractory follicular lymphoma; R/R MZL, relapsed or refractory marginal zone lymphoma; R/R-LBCL, relapsed or refractory large B cell lymphoma; UT DLBCL, previous untreated diffuse large B cell lymphoma; y, year.

R/R who underwent multiple lines of treatment and CAR-T therapy. Importantly, BiTE treatments resulted in a low incidence of grade 3 or higher CRS and other AEs. These studies highlighted the potential of BiTE as a promising treatment option for B-cell lymphoma. Further research is warranted to assess the efficacy and safety of BiTE monotherapy or in combination with chemotherapy as first-line treatment for B-cell lymphoma.

Declarations

Ethics approval and consent to participate

This study fully complied with the publication guidelines provided by 2023 EHA annual meeting. Participants could not be identified by personal information, so approval from the ethics committee was not needed.

Consent for publication

Not applicable.

Author contributions

Shenhe Jin: Conceptualization; Writing – original draft.

Yi Liu: Conceptualization; Writing – original draft.

Ye Zhang: Formal analysis; Writing – review & editing.

Fengping Zhou: Formal analysis; Writing – original draft.

Liangshun You: Conceptualization; Writing – review & editing.

Jin Zhang: Conceptualization; Writing – review & editing.

Acknowledgements

None.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research

was supported by Zhejiang Provincial Natural Science Foundation of China under Grant No. LQ21H160036.

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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