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Evaluation of cytokine release syndrome in non-Hodgkin lymphoma therapy with bispecific antibodies: A meta-analysis of clinical trials

Renan Gomes NASCIMENTO[1,2], Danilo Oliveira CERQUEIRA[3], Daniel Rodrigues BASTOS[4], Carolina DAGLI-HERNANDEZ[1]
[1]Faculdade de Ciências Farmacêuticas da Universidade de São Paulo (FCF-USP), São Paulo, Brasil; [2]Associação Paulista para o Desenvolvimento da Medicina (SPDM), São Paulo, Brasil; [3]Aché Laboratórios Farmacêuticos S.A (ALF), Guarulhos, Brasil; [4]Facultad de Ciencias Médicas de la Universidad Privada del Este (FCM-UPE), Ciudad del Este, Paraguai.

Corresponding author: Nascimento RG, renangomesfarmaceutico@gmail.com

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Abstract

Objectives: To provide a comprehensive analysis regarding the safety profile of bispecific antibodies (BsAbs), focusing on the prevalence of cytokine release syndrome (CRS) in patients with non-Hodgkin lymphoma (NHL). **Methods:** We performed a meta-analysis of phase 1 to 3 clinical trials with different BsAbs approved for commercialization (mosunetuzumab, glofitamab, odronextamab, and epcoritamab), administered as monotherapy or in combination with other anticancer therapies, both in first-line and in cases of relapsed/refractory disease, as well as in different NHL subtypes. **Results:** This meta-analysis provides pooled data from 40 clinical trial cohorts totaling information from 3,653 patients and 1,577 events on the safety of BsAbs (anti-CD20/CD3) in the treatment of NHL. The median age of participants was 64.4 years. The pooled prevalence of CRS of all grades and grade ≥3 was 43% and 7%, respectively. Stratification by treatment regimen (monotherapy versus combination therapy) showed that CRS of all grades was estimated at 47% (95% CI: 41–54%) in monotherapy and 35% (95% CI: 27–45%) in combination therapy, based on the included studies. However, the pooled prevalence estimates of severe CRS (grade ≥3) were similar between groups, with 7% (95% CI: 5–9%) in monotherapy and 6% (95% CI: 3–11%) in combination therapy. **Conclusion:** This meta-analysis provides a comprehensive descriptive synthesis of CRS prevalence among patients with NHL treated with bispecific antibodies (BsAbs). CRS of any grade was frequently reported, whereas severe events (grade ≥3) remained uncommon, particularly in the context of relapsed/refractory disease, which represented 90.61% of the included cohort. Given the clinical and methodological heterogeneity across trials and the non-comparative nature of the pooled estimates, these findings should be interpreted as descriptive evidence rather than direct comparative evidence of safety. Future research should focus on optimizing dosing strategies, incorporating prophylactic measures, standardizing CRS reporting, and improving toxicity management to better balance tolerability and efficacy of BsAbs in patients with NHL.

Keywords: bispecific antibodies; non-Hodgkin lymphoma; cytokine release syndrome; meta-analysis; clinical trial.

Avaliação de síndrome de liberação de citocinas na terapia do linfoma não Hodgkin com anticorpos biespecíficos: Uma metanálise de ensaios clínicos

Resumo

Objetivos: Fornecer uma análise abrangente quanto ao perfil de segurança dos anticorpos biespecíficos (BsAbs), com foco na prevalência da síndrome de liberação de citocinas (SLC) em pacientes com linfoma não Hodgkin (LNH). **Métodos:** Realizamos uma metanálise de ensaios clínicos de fase 1 a 3 com diferentes BsAbs aprovados para comercialização (mosunetuzumabe, glofitamabe, odronextamabe e epcoritamabe), aplicados em monoterapia ou em combinação com outras terapias anticâncer, tanto em primeira linha quanto em casos de doença recidivada/refratária, bem como em diferentes subtipos de LNH. **Resultados:** Esta metanálise fornece dados agrupados de 40 coortes de ensaios clínicos que totalizam informações de 3.653 pacientes e 1.577 eventos sobre a segurança de BsAbs (anti-CD20/CD3) no tratamento do LNH. A mediana de idade dos participantes foi de 64,4 anos. A prevalência agrupada de SLC de todos os graus e de grau ≥3 foi de 43% e 7%, respectivamente. A estratificação por regime de tratamento (monoterapia versus terapia combinada) mostrou que a CRS de todos os graus foi estimada em 47% (IC 95%: 41–54%) na monoterapia e 35% (IC 95%: 27–45%) na terapia combinada, com base nos estudos incluídos. No entanto, as estimativas de prevalência agrupadas de CRS grave (grau ≥3) foram semelhantes entre os grupos, com 7% (IC 95%: 5–9%) na monoterapia e 6% (IC 95%: 3–11%) na terapia combinada. **Conclusão:** Esta metanálise fornece uma síntese descritiva abrangente da prevalência de SLC entre pacientes com LNH tratados com anticorpos biespecíficos (BsAbs). A SLC de qualquer grau foi relatada com frequência, enquanto eventos graves (grau ≥3) permaneceram incomuns, particularmente no contexto de doença recidivada/refratária, que

representou 90,61% da coorte incluída. Dada a heterogeneidade clínica e metodológica entre os ensaios e a natureza não comparativa das estimativas agrupadas, esses achados devem ser interpretados como evidências descritivas, e não como evidências comparativas diretas de segurança. Pesquisas futuras devem se concentrar na otimização das estratégias de dosagem, na incorporação de medidas profiláticas, na padronização da notificação de eventos adversos relacionados à quimioterapia (CRS) e na melhoria do manejo da toxicidade para melhor equilibrar a tolerabilidade e a eficácia dos anticorpos biespecíficos (BsAbs) em pacientes com linfoma não Hodgkin (LNH).

Palavras-chave: anticorpos biespecíficos; linfoma não Hodgkin; síndrome da liberação de citocina; metanálise; ensaio clínico.

Introduction

Hematologic malignancies comprise a heterogeneous group of cancers affecting the blood, bone marrow, and lymphatic system, and are generally classified into several major subtypes, including leukemias, multiple myeloma (MM), Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL)[1]. With respect to NHL, the global incidence of this malignancy is estimated at approximately 457,000 new cases annually, with an associated mortality of approximately 254,000 deaths per year[2]. NHL represents a heterogeneous group of lymphoid neoplasms arising from B lymphocytes, T lymphocytes, or natural killer (NK) cells[3]. Current classification systems integrate clinical presentation, histopathological evaluation, immunophenotypic profiling, and specific molecular and genetic alterations[4]. Notably, approximately 85% of cases diagnosed worldwide correspond to B-cell lymphomas, which encompass a broad biological spectrum ranging from indolent (slow-growing) to highly aggressive (rapidly proliferative) disease entities[3]. The principal subtypes include diffuse large B-cell lymphoma (DLBCL), the most common form; follicular lymphoma (FL); Burkitt lymphoma (BL); mantle cell lymphoma (MCL); and marginal zone lymphoma (MZL)[5].

Despite significant advances over the past decades with the incorporation of monoclonal antibodies, antibody–drug conjugates, and immunotherapeutic strategies, approximately 30–40% of patients with non-Hodgkin lymphomas (NHL) ultimately develop relapsed or refractory disease[6, 7]. The combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has been established as the standard therapeutic backbone for NHL since the 1970s[8]. The subsequent addition of the chimeric anti-CD20 monoclonal antibody rituximab to CHOP (R-CHOP) significantly improved clinical outcomes, increasing the 5-year overall survival rate to approximately 58% in patients with relapsed or treatment-resistant disease[9]. Nevertheless, a substantial proportion of patients experience treatment limitations related to immunosuppression and therapy-associated toxicity, as well as incomplete or absent responses to first-line regimens. These outcomes are frequently driven by intrinsic and extrinsic molecular mechanisms within lymphoma cells, metabolic reprogramming, tumor microenvironment–associated hypoxia, and other pathways underlying primary or acquired therapeutic resistance[10].

In this context, bispecific antibodies (BsAbs) have emerged as an attractive and potentially transformative therapeutic strategy for patients with non-Hodgkin lymphoma (NHL)[11]. These agents are designed to simultaneously bind CD20 expressed on malignant B cells and CD3 on the surface of the patient's T lymphocytes (and, indirectly, engage cytotoxic immune effector mechanisms), thereby promoting T-cell activation, proliferation, and immune synapse formation. This dual targeting results in enhanced tumor cell lysis through immune redirection, improved tissue penetration, and increased molecular specificity[12]. Several BsAbs have been investigated in phase 1–3 clinical trials and have recently been incorporated into clinical practice for the treatment of NHL. These include intravenous mosunetuzumab, intravenous glofitamab, intravenous odronextamab, and subcutaneous epcoritamab[13].

Although these agents represent valuable therapeutic options for patients with NHL, BsAbs are associated with clinically significant treatment-related adverse events (AEs)[14]. The most frequently reported AEs include hematologic events, particularly leukopenia, dermatologic manifestations, such as dermatitis and cutaneous rash, and immunologic complications, including opportunistic infections secondary to hypogammaglobulinemia[14, 15]. Immune system modulation induced by BsAbs may also lead to a severe and potentially life-threatening complication known as cytokine release syndrome (CRS). CRS results from the massive release of pro-inflammatory cytokines—including interleukin IL-1, IL-6, tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ)—triggered by hyperactivation of lymphoid and myeloid immune cell compartments[16]. Clinically, CRS is primarily characterized by acute systemic inflammatory manifestations, including fever, hypoxia, and hypotension, and may progress to varying degrees of organ dysfunction, ranging from mild impairment to potentially fatal multiorgan failure[16, 17].

Therefore, the primary objective of this study was to provide a comprehensive analysis of the safety profile of BsAbs, with a particular focus on adverse events related to CRS, in patients with NHL. To this end, we conducted a meta-analysis of phase 1–3 clinical trials evaluating different BsAbs—including mosunetuzumab, glofitamab, odronextamab, and epcoritamab—administered either as monotherapy or in combination with other anticancer regimens. These studies included patients treated in both the frontline and relapsed/refractory settings, encompassing multiple NHL subtypes, such as diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and mantle cell lymphoma (MCL).

Methods

Eligibility Criteria

This meta-analysis included data from phase 1–3 clinical trials enrolling adult patients with NHL (≥18 years of age, or adult cohorts as defined in the original trial protocols) who received CD20-directed BsAbs, administered either as monotherapy or in combination with other anticancer therapies, regardless of prior lines of treatment, lymphoma subtype, or disease behavior. Studies conducted exclusively in pediatric or adolescent populations were not eligible for inclusion. Phase 1 trials were retained in the primary analysis because the main objective of this meta-analysis was to characterize the safety profile of BsAbs, particularly CRS events.

Although phase 1 studies frequently involve dose-escalation or dose-expansion cohorts, they provide clinically relevant early safety information, including dose-limiting toxicities, CRS occurrence, and mitigation strategies. Nevertheless, because these studies may introduce variability related to dose selection and treatment schedules, a sensitivity analysis excluding phase 1 trials was performed. The severity of AEs was independently assessed within each trial and was generally graded according to the NCI-CTCAE (*National Cancer Institute Common Terminology Criteria for Adverse Events*)[18]. Exclusion criteria comprised retrospective studies, case reports, case series, narrative or systematic reviews, preclinical *in vitro* or *in vivo* investigations, and publications not available in English.

Data Sources and Search Strategy

The study protocol was discussed and agreed upon in advance by all authors and was registered in PROSPERO (CRD420261413478). According to the PICO (Population, Intervention, Comparison and Outcomes) framework, this meta-analysis included: (P) patients with relapsed/refractory non-Hodgkin lymphoma; (I) treatment with bispecific antibodies (mosunetuzumab, glofitamab, epcoritamab, odronextamab); (C) treatment in monotherapy or combination therapy; and (O) incidence and severity of cytokine release syndrome, particularly in grade ≥3 events.

A comprehensive literature search was performed across major electronic databases, including *PubMed*, *Web of Science*, *Scopus*, and *Embase*, using a combination of keywords and controlled vocabulary terms related to "bispecific antibodies" and "non-Hodgkin lymphoma." The search strategy aimed to identify all phase 1–3 clinical trials (randomized or non-randomized) published within the last five years (January 2021 to December 2025) that evaluated the safety of BsAbs approved for commercialization by international regulatory agencies, including the *Food and Drug Administration* (FDA) and/or the *European Medicines Agency* (EMA), in patients with NHL, regardless of histological subtype, molecular characteristics, or treatment setting. Studies assessing BsAbs administered as monotherapy or in combination with other anticancer therapies were considered eligible.

Data Extraction and Quality Assessment

Study screening was conducted independently by two authors (RGN and DOC), and final study selection was determined by consensus. Reference lists of the included articles were manually reviewed to ensure completeness and minimize the risk of omitting relevant studies. Data extraction was performed using a standardized form and was independently verified by two authors. The following variables were extracted from each eligible study or cohort: first author, year of publication, study phase, NHL subtype, disease setting, sample size, median age, bispecific antibody evaluated, route of administration, therapeutic regimen, CRS events of any grade, grade ≥3 CRS events, CRS grading criteria when reported, and DOI. When available, information regarding premedication, step-up dosing, CRS duration, and CRS-related treatment discontinuation was also collected. Disagreements during study selection or data extraction were resolved by consensus. Risk of bias was qualitatively assessed using domains adapted from the Cochrane framework; however, a formal study-level application of validated design-specific tools was not performed.

Statistical Analysis

The prevalence of CRS was stratified according to severity (grade 1–2 vs. grade ≥3) and estimated using generalized linear mixed-effects models (GLMM) applied to study-level proportions of patients reported in the included clinical trials. All statistical analyses were performed using R software (*R Foundation for Statistical Computing, Vienna, Austria; version 4.x*) with the meta package from the *Comprehensive R Archive Network* (CRAN). Pooled proportions of CRS events were calculated using inverse-variance weighting following logit transformation of study-level proportions to stabilize variance. In addition, subgroup analyses were conducted to explore potential sources of bias and clinical heterogeneity. Prevalence estimates were reported under both fixed-effect and random-effects models, with corresponding 95% confidence intervals (95% CI). Between-study heterogeneity was estimated using the restricted maximum likelihood (REML) method, and the Hartung–Knapp adjustment was applied for inference under the random-effects model. Heterogeneity was quantified using the I^2 and τ^2 statistics and formally tested using Cochran's Q test. For interpretative purposes, heterogeneity was classified according to I^2 values as low when I^2 was <30%, moderate when I^2 ranged from 30% to 60%, and high when I^2 was >60%. Cochran's Q test was used to assess the statistical significance of heterogeneity, whereas τ^2 was reported as an estimate of between-study variance. These thresholds were used as operational criteria to aid interpretation and were not applied as exclusion criteria. A two-sided p-value ≤0.05 was considered statistically significant.

Predefined subgroup analyses were conducted according to treatment strategy (monotherapy vs. combination therapy), specific bispecific antibody (e.g., glofitamab, odronextamab, mosunetuzumab, and epcoritamab), and disease subtype DLBCL, FL, and MCL. Direct comparisons between selected subtypes (DLBCL vs. FL) were performed within a unified subgroup meta-analytic framework, with tests for subgroup differences calculated under both fixed-effect and random-effects assumptions. All analyses were repeated considering only severe events (CRS grade ≥3). Forest plots were generated using the meta package, preserving original study-specific confidence intervals and displaying pooled estimates for each subgroup as well as for the overall analysis.

Results

In this meta-analysis conducted through December 2025, a total of 1,998 scientific articles were initially identified through systematic database searches. After removal of duplicate records, the remaining studies were screened according to predefined inclusion criteria (Supplementary Table 1). The flowchart of the strategies for identifying and selecting the studies included in our meta-analysis is described in detail in Supplementary Figure 1. Following the screening and eligibility assessment process, 40 clinical trials investigating the safety of BsAbs in NHL were included in the quantitative synthesis. The study selection process is summarized in a flow diagram constructed using the PRISMA Flow Diagram framework, which illustrates the sequential stages of identification, screening, eligibility assessment, and inclusion of studies. The risk of bias was assessed in five domains adapted from the Cochrane Risk of Bias tool and ROB2 for clinical trials.

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Table 1. Characteristics of the Clinical Studies.

Author and Year of Publication	Bispecific Antibody	Study Phase	Subtype	"n"	Median Age	Therapeutic Regimen	DOI (Digital Object Identifier)
Abramson, 2024	Glofitamab	Phase 3 clinical trial	DLBCL – R/R	172	68	Combined with Gemcitabine + Oxaliplatin (Genmox)	10.1016/S0140-6736(24)01774-4
Ayyappan, 2023	Odronextamab	Phase 2 clinical trial	DLBCL – R/R	141	66	Monotherapy	10.1182/blood-2023-179818
Bachy, 2024	Odronextamab	Phase 2 clinical trial	NHL-B R/R	49	58	Monotherapy	10.1182/blood-2024-200150
Bannerji, 2022	Odronextamab	Phase 1 clinical trial	NHL-B R/R	145	67	Monotherapy	10.1016/S2352-3026(22)00072-2
Bartleet, 2023	Mosunetuzumab	Phase 2 clinical trial	DLBCL – R/R	88	66	Monotherapy	10.1182/bloodadvances.2022009260
Budde, 2021	Mosunetuzumab	Phase 1 clinical trial	NHL-B R/R	197	61	Monotherapy	10.1200/JCO.21.00931
Budde, 2024	Mosunetuzumab	Phase 2 clinical trial	NHL-B R/R	229	64	Monotherapy	10.1200/JCO.23.02329
Budde, 2023	Mosunetuzumab	Phase 2 clinical trial	LBCL R/R e FL R/R	98	68	Combined with Polatuzumab Vedotin	10.1038/s41591-023-02726-5
Budde, 2023	Mosunetuzumab	Phase 3 clinical trial	LBCL R/R	135	62	Combined with Polatuzumab Vedotin	10.1200/JCO-25-01957
Byun, 2023	Glofitamab	Phase 2 clinical trial	DLBCL – R/R	6	65	Combined with Lenalidomide + Poseltinib (LenaPosel)	10.1097/01.HS9.0000971524.36320.c6
Dickinson, 2022	Glofitamab	Phase 2 clinical trial	DLBCL – R/R	107	66	Monotherapy	10.1200/JCO.2022.40.16_suppl.7500
Falchi, 2022	Epcoritamab	Phase 2 clinical trial	DLBCL	33	66	Combined with Rituximab + Cyclophosphamide + Doxorubicin + Vincristine + Prednisone (R-CHOP)	10.1200/JCO.2022.40.16_suppl.7523
Falchi, 2023	Epcoritamab	Phase 2 clinical trial	DLBCL	47	64	Combined with Rituximab + Cyclophosphamide + Doxorubicin + Vincristine + Prednisone (R-CHOP)	10.1200/JCO.2023.41.16_suppl.7519
Falchi, 2023	Glofitamab	Phase 2 clinical trial	DLBCL – R/R	154	66	Monotherapy	10.1200/JCO.2023.41.16_suppl.7550
Fedovora, 2023	Glofitamab	Phase 1 clinical trial	NHL-B R/R	24	47	Monotherapy	10.1097/01.HS9.0000971612.16613.ad
Goto, 2025	Mosunetuzumab	Phase 2 clinical trial	FL R/R	19	72	Monotherapy	10.1007/s10147-024-02662-5
Gurion, 2024	Epcoritamab	Phase 2 clinical trial	DLBCL – R/R	40	71	Combined with Lenalidomide	10.1182/blood-2024-199301
Hutchings, 2021	Glofitamab	Phase 2 clinical trial	DLBCL – R/R	42	65	Combined with Polatuzumab Vedotin	10.1182/blood-2021-148359
Hutchings, 2021	Epcoritamab	Phase 2 clinical trial	NHL-B R/R	68	64	Monotherapy	10.1016/S0140-6736(21)00889-8
Hutchings, 2021	Glofitamab	Phase 1 clinical trial	NHL-B R/R	171	64	Monotherapy	10.1200/JCO.20.03175
Hutchings, 2025	Glofitamab	Phase 2 clinical trial	LBCL R/R	129	67	Combined with Polatuzumab Vedotin	10.1200/JCO-25-00992
Hutchings, 2025	Glofitamab	Phase 2 clinical trial	NHL-B R/R	84	63	Combined with Englumafusp Alfa (RO7227166)	10.1002/hon.3163_91
Karimi, 2025	Epcoritamab	Phase 2 clinical trial	DLBCL – R/R	29	58	Combined with Rituximab + Dexamethasone + Cytarabine + Oxaliplatin or Carboplatin (R-DHAX/C)	10.1200/JCO.2024.42.16_suppl.7032
Kerr, 2024	Epcoritamab	Phase 2 clinical trial	DLBCL	37	64	Combined with Polatuzumab Vedotin + Rituximab + Cyclophosphamide + Doxorubicin + Prednisone (Pola-R-CHP)	10.1016/S2152-2650(24)01527-1
Kim, 2024	Odronextamab	Phase 2 clinical trial	FL R/R	128	61	Monotherapy	10.1016/j.annonc.2024.08.2239
Kim, 2025	Odronextamab	Phase 2 clinical trial	DLBCL – R/R	127	67	Monotherapy	10.1038/s43018-025-00921-6
Matasar (1), 2024	Mosunetuzumab	Phase 2 clinical trial	NHL-B R/R	218	64	Monotherapy	10.1016/j.clml.2023.12.005

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Author and Year of Publication	Bispecific Antibody	Study Phase	Subtype	"n"	Median Age	Therapeutic Regimen	DOI (Digital Object Identifier)
Matasar (2), 2024	Mosunetuzumab	Phase 2 clinical trial	FL R/R	90	60	Monotherapy	10.1016/j.clml.2023.12.005
Merryman, 2023	Epcoritamab	Phase 2 clinical trial	FL R/R	109	65	Combined with Rituximab + Lenalidomide (R2)	10.1200/JCO.2023.41.16_suppl.7506
Minson, 2025	Glofitamab	Phase 2 clinical trial	LBCL	80	58	Combined with Polatuzumab Vedotin + Rituximab + Cyclophosphamide + Doxorubicin + Prednisone (Pola-R-CHP)	10.1200/JCO-25-00481
Morschhauser, 2021	Mosunetuzumab	Phase 1 clinical trial	FL R/R	27	59	Combined with Lenalidomide	10.1182/blood-2021-145694
Munakata, 2023	Mosunetuzumab	Phase 1 clinical trial	NHL-B R/R	23	63	Monotherapy	10.1093/jjco/hyad082
Olszewski, 2022	Mosunetuzumab	Phase 2 clinical trial	DLBCL – R/R	54	83	Monotherapy	10.1182/blood-2022-157768
Olszewski (1), 2022	Mosunetuzumab	Phase 2 clinical trial	DLBCL – R/R	36	73	Combined with Polatuzumab Vedotin	10.1182/blood-2022-159594
Olszewski (2), 2022	Mosunetuzumab	Phase 2 clinical trial	DLBCL – R/R	24	60	Combined with Polatuzumab Vedotin	10.1182/blood-2022-159594
Phillips, 2024	Glofitamab	Phase 2 clinical trial	MCL – R/R	60	72	Monotherapy	10.1200/JCO.23.02470
Sehn, 2024	Mosunetuzumab	Phase 2 clinical trial	FL R/R	90	60	Monotherapy	10.1182/blood.2024025454
Sehn, 2023	Mosunetuzumab	Phase 2 clinical trial	FL	90	63	Monotherapy	10.1097/01.HS9.0000971208.36694.eb
Song, 2023	Glofitamab	Phase 1 clinical trial	DLBCL – R/R	30	57	Monotherapy	10.3324/haematol.2023.283802
Thieblemont, 2023	Epcoritamab	Phase 2 clinical trial	DLBCL – R/R	157	64	Monotherapy	10.1200/JCO.22.01725
Topp, 2022	Glofitamab	Phase 1 clinical trial	DLBCL	56	68	Combined with Rituximab + Cyclophosphamide + Doxorubicin + Vincristine + Prednisone (R-CHOP)	10.1182/blood-2023-174081
Zhou, 2025	Glofitamab	Phase 1 clinical trial	DLBCL – R/R	10	68	Combined with Tislelizumab	10.1038/s41408-025-01404-8

Legend: NHL-B: Non-Hodgkin B-cell lymphoma; DLBCL: Diffuse large B-cell lymphoma; FL: Follicular lymphoma; MCL: Mantle cell lymphoma; LBCL: Large B-cell lymphoma; R/R: Relapsed/Refractory.

All clinical trials demonstrated consistent quality, and the overall risk of bias was low in approximately 80% of the studies, which supports the reliability of the included registries and subsequent pooled outcomes, although cautious interpretation is necessary (Supplementary Table 2).

All included records evaluated CD20-directed antibodies that had been approved by the Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA). Overall, this meta-analysis encompassed a total of 3,653 patients, with the majority of included publications consisting of full-text articles and phase 2 trials (72.5%). The investigated NHL subtypes included DLBCL, FL, and MCL. Regarding the specific BsAbs evaluated, the distribution of studies was as follows: epcoritamab (8 studies), glofitamab (14 studies), mosunetuzumab (13 studies), and odronextamab (5 studies). A comprehensive overview of the studies included in this meta-analysis is presented in Table 1.

All selected clinical trial records included in this meta-analysis reported at least one episode of CRS in patients exposed to anti-CD20/CD3 BsAb therapy (40 clinical trials comprising 3,653 patients and 1,577 CRS events. The overall pooled prevalence of CRS of any grade (1–5) was 43% (95% CI: 0.37–0.48), with high heterogeneity among studies (I^2 = 85.4%; P(Q test) <0.0001) (Figure 1A).

In contrast, grade ≥3 CRS was relatively uncommon, with a pooled prevalence of 7% (95% CI: 0.05–0.09) and low, statistically non-significant heterogeneity (I^2 = 20.3%; P(Q test) = 0.1731) (Figure 1B). Data regarding treatment discontinuation due to CRS were inconsistently reported among the included trials and were therefore not incorporated into the quantitative analysis. To evaluate whether phase 1 dose-escalation studies influenced the pooled estimates, we repeated the primary analysis after excluding phase 1 trials. In this sensitivity analysis, the pooled prevalence of CRS of any grade was 42% (95% CI: 0.36–0.48), with persistently high heterogeneity (I^2 = 87.3%; P(Q test) <0.0001) (Supplementary Figure 3A). For grade ≥3 CRS, the pooled prevalence was 3% (95% CI: 0.02–0.04), with heterogeneity below 30% and a non-significant Q test (I^2 = 29.8%; P(Q test) = 0.1250) (Supplementary Figure 3B). Overall, the exclusion of phase 1 trials did not materially alter the main interpretation that CRS of any grade is frequent and heterogeneous across clinical trial cohorts, whereas severe CRS remains uncommon.

Furthermore, we conducted a stratified analysis to evaluate CRS incidence according to specific BsAbs, with additional stratification by treatment strategy (monotherapy vs. combination therapy). The multidrug therapeutic regimens (bispecific antibody plus standard-of-care combinations) employed across the included clinical trials are detailed in Table 1.

Stratification by treatment regimen indicated that CRS of any grade was estimated at 47% (95% CI: 0.41–0.54; I^2 = 87.7%; P(Q test) <0.0001) in monotherapy and 35% (95% CI: 0.27–0.45; I^2 = 79.0%; P(Q test) <0.0001) in combination regimens (Figures 2A and 2B, respectively). However, no statistically significant difference was observed in the prevalence of grade ≥3 CRS between monotherapy and combination therapy. The pooled prevalence of severe CRS was 7% (95% CI: 0.05–0.09; I^2 = 20.3%; P(Q test) 0.1731) for monotherapy and 6% (95% CI: 0.03–0.11; I^2 = 22.3%; P(Q test) 0.2450) for combination therapy (Figures 3A and 3B, respectively). These findings indicate differences in pooled CRS estimates between treatment strategies; however, these should be interpreted descriptively due to the absence of direct comparisons.

A stratified analysis according to NHL subtype was performed for relapsed/refractory (R/R) FL and R/R DLBCL. Studies that did not clearly specify NHL subtype classification or that did not meet the minimum number of patients required for reliable subgroup analysis were excluded from this comparison. Tests for subgroup differences between R/R FL and R/R DLBCL demonstrated no statistically significant difference in the pooled prevalence of CRS of any grade (χ^2=0.48; P=0.2503) or grade ≥3 CRS (χ^2=1.93; P=0.1646) (Supplementary Figures 2A and 2B, respectively).

These findings suggest similar pooled CRS estimates between the evaluated subtypes; however, no formal comparative inference can be made.

Finally, we performed stratified analyses of CRS incidence according to each BsAb evaluated in the included clinical trials. Odronextamab presented a pooled CRS prevalence of 56% (95% CI: 52–60%; I^2 = 0%; P(Q test) 0.7877), whereas the other agents showed estimates of 50% (epcoritamab), 49% (glofitamab), and 30% (mosunetuzumab) (Figures 4A–4D, respectively). However, when the analysis was restricted to severe CRS events (grade ≥3), glofitamab showed a pooled estimate of 8% (95% CI: 5–12%; I^2 = 27.8%; P(Q test) 0.1974), within the range observed across agents. The corresponding estimates for the remaining agents were 7% (95% CI: 4–11%) for mosunetuzumab, 6% (95% CI: 2–12%) for epcoritamab, and 5% (95% CI: 1–15%) for odronextamab (Figures 5A–5D, respectively). These findings suggest variability in CRS incidence across CD20/CD3-targeting BsAbs, particularly for events of any grade, whereas severe CRS rates remained relatively low across agents.

Figure 1. Meta-analysis of cytokine release syndrome (CRS) rates from all clinical trials in which patients received bispecif-ic antibody (BsAb) therapy. Panels A and B represent the prevalence of CRS of all grades and grade ≥3, respectively.

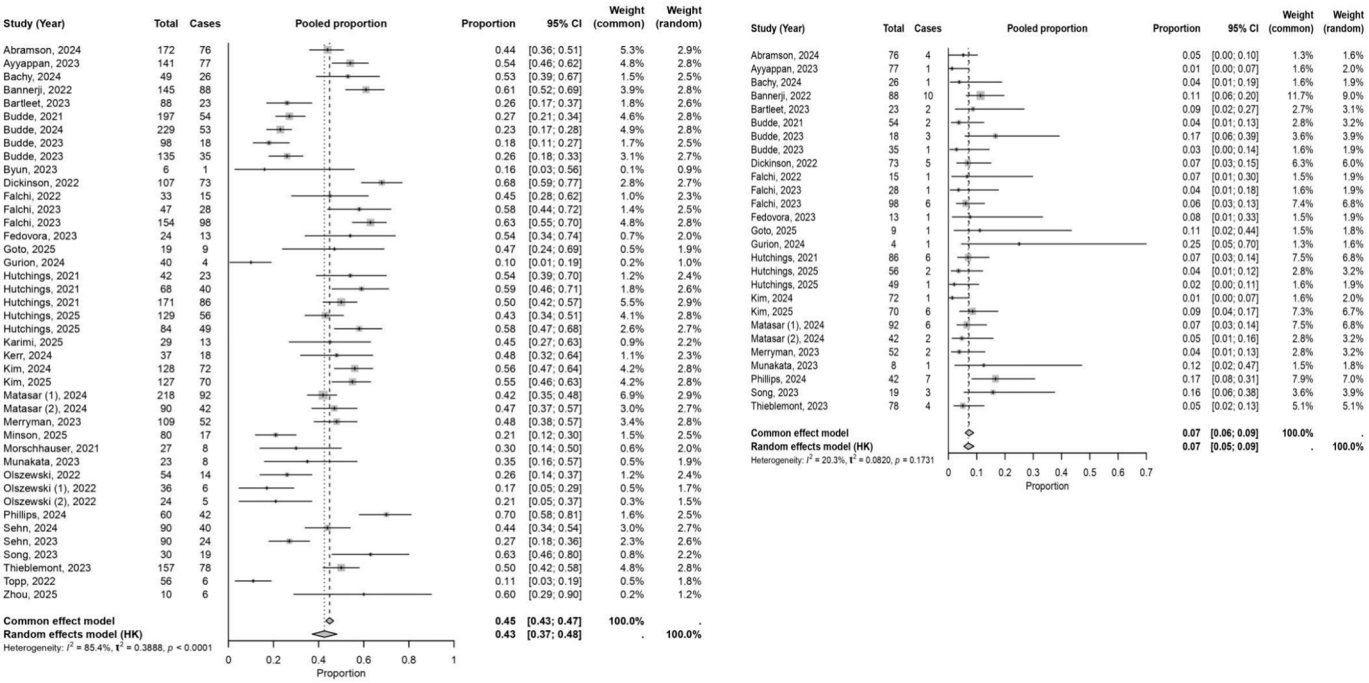

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Figure 2. Meta-analysis of cytokine release syndrome (CRS) rates stratified by patients who received bispecific antibodies (BsAb) in monotherapy versus patients who received BsAb in combination therapy. Panels A and B represent the prevalence of CRS of all grades in monotherapy and combination therapy, respectively.

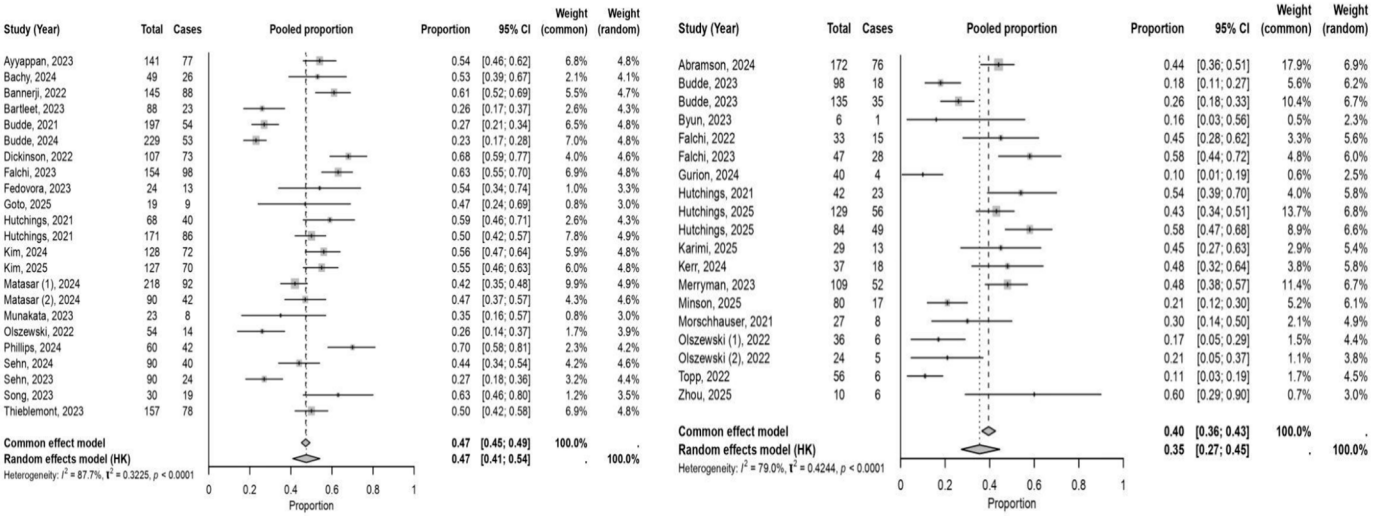

Figure 3. Meta-analysis of cytokine release syndrome (CRS) rates stratified by patients who received bispecific antibodies (BsAb) in monotherapy versus patients who received BsAb in combination therapy. Panels A and B represent the prevalence of grade ≥3 CRS in monotherapy and combination therapy, respectively.

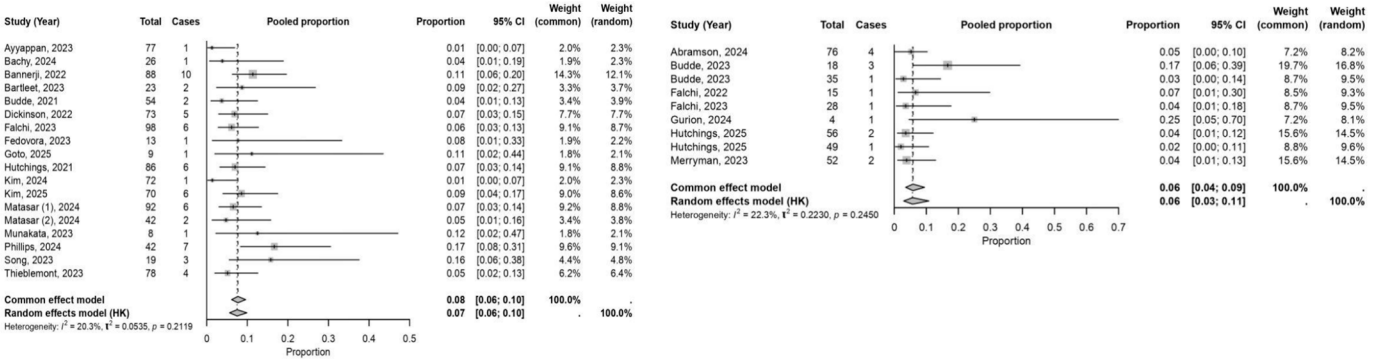

Figure 4. Meta-analysis of cytokine release syndrome (CRS) rates stratified for each bispecific antibody (BsAb) tested in clinical trials. Panels A, B, C, and D represent the prevalence of CRS of all grades for odronextamab, epcoritamab, glofitamab, and mosunetuzumab, respectively.

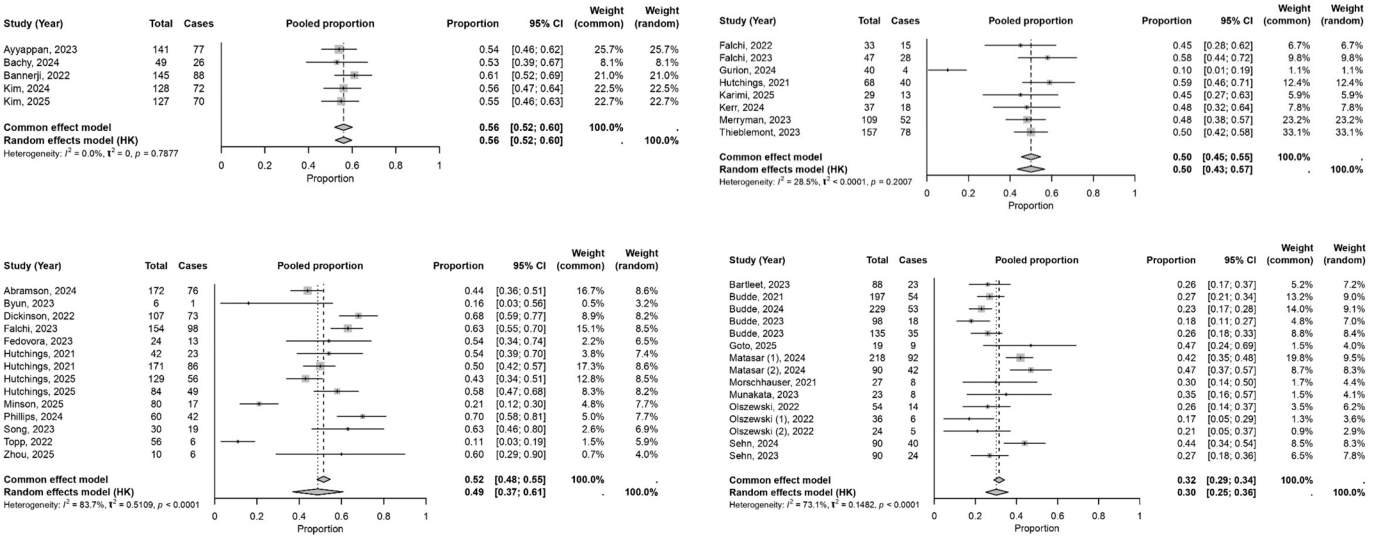

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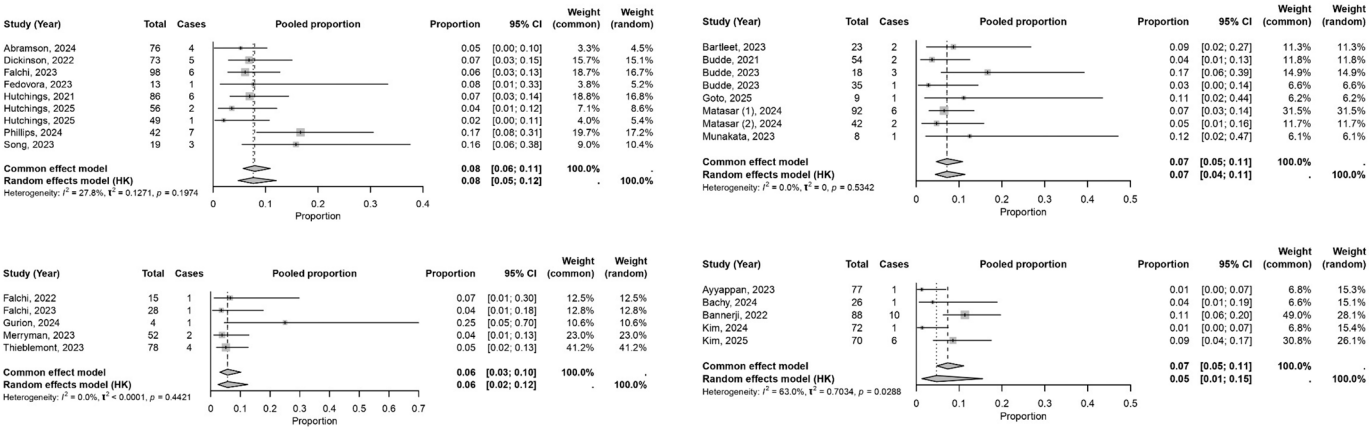
Figure 5. Meta-analysis of cytokine release syndrome (CRS) rates stratified for each bispecific antibody (BsAb) tested in clinical trials. Panels A, B, C, and D represent the prevalence of grade ≥3 CRS for glofitamab, mosunetuzumab, epcoritamab, and odronextamab, respectively.



Discussion

The R-CHOP regimen remains the standard first-line therapy for NHL; however, a substantial proportion of patients ultimately develop R/R disease[7]. In recent years, novel therapeutic modalities—including chimeric antigen receptor T-cell (CAR-T) therapies, antibody–drug conjugates, and BsAbs—have demonstrated promising clinical outcomes, leading to their progressive incorporation into routine clinical practice and representing a significant shift in the treatment paradigm of this major hematologic malignancy[6]. With respect to BsAbs, the therapeutic class investigated in the present study, these agents function by facilitating immune–tumor cell interactions, primarily through engagement of CD3 on T lymphocytes in conjunction with direct binding to the CD20 epitope expressed on malignant B cells. This dual-targeting mechanism promotes immune synapse formation, T-cell activation, and subsequent induction of cytotoxicity and apoptosis of tumor cells[11]. Despite their clinical efficacy, one of the principal concerns in routine practice remains CRS, a systemic inflammatory condition characterized by excessive cytokine release. Given its potential clinical severity, appropriate management and prevention of this AE constitute critical components of care, both to mitigate burden on public and private healthcare systems and to optimize patient outcomes[16].

This meta-analysis provides pooled data from 40 clinical trial cohorts comprising a total of 3,653 patients, offering a comprehensive evaluation of the safety profile of anti-CD20/CD3 BsAbs in the treatment of NHL. An important challenge encountered during the study selection process was that most clinical trials predominantly emphasized efficacy outcomes, and safety data were not consistently or comprehensively reported across all studies. Consequently, the primary objective of our work was to systematically characterize the safety profile—specifically with regard to CRS—of commercially approved BsAbs for the treatment of patients with NHL across different clinical subtypes. By restricting our analysis to phase 1–3 clinical trials published in high-impact, peer-reviewed journals, we aimed to ensure methodological rigor and data reliability. Focusing exclusively on prospective clinical trials allowed us to enhance the robustness of the analyzed outcomes, ensure greater internal validity, promote standardized adverse event grading (typically according to established criteria), evaluate controlled patient populations, and improve the reproducibility of our findings.

Additionally, several clinical trials included in this analysis directly supported the regulatory approval of CD20/CD3 BsAbs for incorporation into clinical practice. These pivotal studies include the GO29781 trial evaluating mosunetuzumab in R/R FL; the NP30179 trial assessing glofitamab R/R DLBCL; the EPCORE™ NHL-1 trial investigating epcoritamab in R/R DLBCL; and the pivotal ELM-2 trial evaluating odronextamab in R/R DLBCL, which received accelerated approval in August 2024 by the EMA [19-22].

CRS, although frequent, was predominantly of low grade. The pooled incidence of CRS of any grade was 44%, whereas severe cases (grade ≥3) occurred in 5% of patients, consistent with previous reports on CD20/CD3 BsAbs [23, 24]. Moreover, CRS was most commonly observed during the first exposure to BsAbs, and step-up dosing emerged as an important mitigation strategy for this clinically relevant adverse event. Finally, the safety profile of BsAbs with respect to CRS events remained consistent across clinical trials, including in the stratified analyses performed according to different NHL subtypes.

Regarding treatment regimens, the selected clinical trials adopted heterogeneous therapeutic strategies, and 45% of the studies included in our analysis administered CD20/CD3 BsAbs in combination with other agents or treatment protocols commonly used in hemato-oncology. Accordingly, we conducted a stratified analysis according to treatment strategy (monotherapy and combination therapy). The pooled estimates of CRS of any grade were 47% in monotherapy and 35% in combination therapy. However, no clinically meaningful differences were observed in the incidence of severe CRS (grade ≥3) between the two groups (7% vs. 6%, respectively). Several hypotheses may explain these findings. BsAbs administered as monotherapy may induce a more rapid and robust release of pro-inflammatory cytokines, potentially due to lower depletion of target immune effector cells (particularly T lymphocytes), resulting in immediate and unrestricted engagement with CD20-expressing malignant B cells[25, 26]. Additionally, the absence of concomitant agents with potential modulatory effects on cytokine release may contribute to higher overall CRS rates. Nevertheless, the lack of standardized safety reporting across trials, heterogeneity in patient characteristics, intrinsic differences among individual BsAbs, and variability in the use of premedication strategies (e.g., glucocorticoids) preclude direct comparative or causal inferences between treatment strategy.

Finally, we performed a stratified analysis of CRS cases according to each bispecific antibody evaluated in the clinical trials. Odronextamab was associated with the highest rates of CRS of any grade (56%, 95% CI: 52–60%) compared with the other agents within the same class. Notably, all clinical trials investigating odronextamab were conducted as monotherapy, which may partially explain the higher overall incidence of CRS observed with this agent. In lymphoma cell culture models with high CD20 expression, the administration of odronextamab combined with dexamethasone as premedication resulted in suppressed cytokine release while maintaining equivalent cytotoxic activity against neoplastic cells, demonstrating relevant translational value for clinical practice[27]. Additionally, stratified analysis of severe CRS (grade ≥3) did not reveal clinically meaningful differences among the bispecific antibodies, although glofitamab was associated with the highest pooled rate (8%, 95% CI: 5–12%). In a multicenter real-world data study including 155 patients with R/R DLBCL, glofitamab was associated with grade ≥3 CRS in 4% of patients[28]. It is important to contextualize these findings. The study by Shumilov et al. included exclusively patients with R/R DLBCL and evaluated glofitamab as monotherapy following mandatory pre-treatment with a single dose of obinutuzumab. In contrast, our meta-analysis incorporated 14 clinical trial cohorts totaling 1,125 patients, including six studies evaluating glofitamab monotherapy across different lymphoma subtypes. Therefore, direct comparisons between these datasets are limited by substantial heterogeneity in patient populations, disease subtypes, study design, and therapeutic strategies.

Despite the aforementioned strengths, our study has several limitations that should be acknowledged. First, substantial heterogeneity was observed across the included clinical trials, particularly regarding study design, patient characteristics, treatment regimens, and the implementation of premedication strategies to mitigate adverse events. Such variability may have influenced the pooled estimates and limits the precision of cross-trial comparisons. Second, adverse event reporting was not consistently standardized across studies, and safety outcomes were not always explicitly detailed. This inconsistency may have resulted in incomplete data capture and potential underestimation or overestimation of CRS incidence. Third, differences in lymphoma subtypes, disease biology, growth kinetics, and clinical behavior may have further contributed to heterogeneity in the observed safety outcomes. Fourth, although the risk of bias was assessed using the ROB2 tool, a formal trial-level risk-of-bias assessment using design-specific tools for each included clinical trial was not performed. Therefore, the methodological quality of individual trials was not used as an exclusion criterion. In addition, high heterogeneity for all-grade CRS and clinical variability across study phases, BsAb agents, treatment regimens, routes of administration, dose-escalation or step-up dosing strategies, premedication, and adverse event reporting standards should be considered when interpreting the pooled estimates. Finally, a considerable proportion of the included trials were early-phase studies (phase I), which are primarily designed to evaluate dose escalation and preliminary safety. The inclusion of phase 1 trials should also be interpreted with caution, as these studies often involve dose-escalation or dose-expansion designs and may not fully reflect the doses and treatment schedules adopted in later-phase trials or routine clinical practice. However, because CRS is a key safety endpoint in early clinical development of T-cell-engaging BsAbs, these trials were retained in the primary analysis. Importantly, a sensitivity analysis excluding phase 1 studies showed that the overall interpretation remained consistent, with CRS of any grade remaining frequent and heterogeneous, while severe CRS events remained uncommon.

Looking ahead, the role of anti-CD20/CD3 BsAbs in NHL warrants larger, well-designed phase III clinical trials, whether in monotherapy or combination regimens, in earlier lines of treatment and across more heterogeneous patient populations. Such efforts will be essential to better characterize the risk of CRS, refine administration strategies, and optimize prophylaxis and management approaches for patients receiving these agents. Currently, CRS management requires a multifaceted strategy due to the complex interplay of its underlying pathophysiological mechanisms[29]. Premedication with glucocorticoids, such as methylprednisolone or dexamethasone, remains one of the most commonly employed strategies to mitigate BsAb-induced CRS[30]. Emerging evidence suggests that these agents attenuate systemic inflammation by inhibiting the production of pro-inflammatory cytokines, as well as by rapidly reducing vascular permeability and tissue edema[16]. In cases of severe or potentially life-threatening CRS, Tocilizumab—a monoclonal antibody targeting the interleukin-6 (IL-6) signaling pathway—has demonstrated complete response rates of up to 69% within 14 days after the first dose, providing effective control of acute and potentially fatal inflammatory events[31].

Conclusion

Our meta-analysis, encompassing data from 40 clinical trials and a total of 3,653 patients with NHL, provides a comprehensive descriptive synthesis of CRS prevalence among patients treated with BsAbs. CRS of any grade was frequently reported across the included studies, whereas severe events (grade ≥3) remained uncommon. These findings are particularly relevant in the context of relapsed/refractory disease, which accounted for 90.61% of the included cohort. However, given the clinical and methodological heterogeneity across trials, the inclusion of early-phase studies, and the non-comparative nature of the pooled estimates, these results should be interpreted as descriptive evidence rather than direct comparative evidence of safety. Future research should focus on optimizing dosing strategies, incorporating prophylactic measures, standardizing CRS reporting, and refining toxicity management approaches to further improve therapeutic outcomes while maintaining an appropriate balance between tolerability and efficacy of BsAbs in patients with NHL.

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Contributors

Study conception and design: RGN and DOC. **Data processing:** RGN and DOC. **Literature search:** RGN and DOC. **Forest plot generation:** DRB. **Data analysis and interpretation:** RGN, DRB, and CDH. **Manuscript writing:** RGN, DOC, and CDH and **Critical content review:** CDH.

Declaration of conflicts of interest

The authors declare no conflicts of interest in relation to this article.

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