Safety Profiles of Bispecific Antibodies in Non-Hodgkin Lymphoma: A Meta-Analysis of Phase I-III Trials

ABCL-699

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INTRODUCTION

Bispecific antibodies (BsAbs) have emerged as a promising immunotherapy option for the treatment of relapsed/refractory non-Hodgkin lymphoma (NHL). Several BsAbs have been evaluated clinically and recent clinical trials have led to the approval of three bispecific antibodies in NHL including mosunetuzumab, epcoritamab and glofitamab. Despite these advances, the safety profile of BsAbs remains a critical concern, especially as therapies move into earlier lines of treatment and are used in combination with other agents This study systematically reviewed and analyzed the safety profile of BsAbs to provide a comprehensive understanding of the risks associated with these therapies.

OBJECTIVE

We aimed to systematically evaluate the safety profile of bispecific antibodies in the treatment of NHL by analyzing prevalence and severity of key adverse events, including infections, hematological toxicities, CRS and ICANS across multiple clinical trials.

METHODS

We performed a systematic review and meta-analysis following PRISMA guidelines. Comprehensive literature search was performed focusing on phase I—III clinical trials evaluating BsAbs in NHL. Studies were included if they reported on safety outcomes. Severities were defined based on the National Cancer Institute Common Terminology Criteria for Adverse Events. Data were extracted independently by two authors and analyzed using a generalized linear mixed model to estimate prevalence of AEs.

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RESULTS

Our review included 39 clinical trials, representing a total of 2,405 patients with NHL treated with BsAbs. Median age was 66 years (range: 55-84) having received a median of two prior lines of therapy (range 0-5). Median follow-up duration was 9.4 months.

Neutropenia: Overall prevalence of all grade was 38% (95% CI: 31-46), with grade ≥3 occurring in 26% of patients. Neutropenia was more common in patients receiving BsAbs in combination with chemotherapy or other immunomodulatory agents.

Infections: All grade infections were reported in 38% of patients (95% CI: 31-45), while grade ≥3 were observed in 12%. Higher incidence of all-grade infections was seen in combination therapy versus monotherapy (46%, vs. 30%). No significant differences were seen with grade ≥3 between these groups.

Cytokine Release Syndrome: CRS was the most common immune-related adverse event, seen in 48% (95% CI: 42-54). However, severe (grade ≥3) CRS was rare, affecting only 2%.

Immune Effector Cell-Associated Neurotoxicity Syndrome: ICANS was less common than CRS, with all-grade neurotoxicity reported in only 5% of patients (95% CI: 3-8). Grade ≥3 was rare, seen in only 1%.

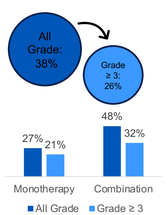
Subgroup Analyses: Study also stratified by lymphoma subtype and BsAbs product. Patients with diffuse large B-cell lymphoma (DLBCL) experienced highest rates of severe neutropenia (35%), while no significant difference in infection rates. Mosunetuzumab was associated with the lowest rate of infections. No significant differences in rates were seen in patients previously treated with CAR-T cells versus not.

ANTIBODIES

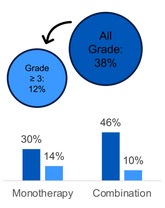


Blinatumomab - 5 studies
Epcoritamab - 9 studies
Glofitamab - 6 studies
Mosunetuzumab - 15 studies
AFM11 - 1 study
TNM-486 - 1 study
Odronextamab - 2 studies

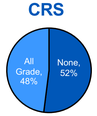
NEUTROPENIA



INFECTIONS



CRS



ICANS

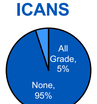
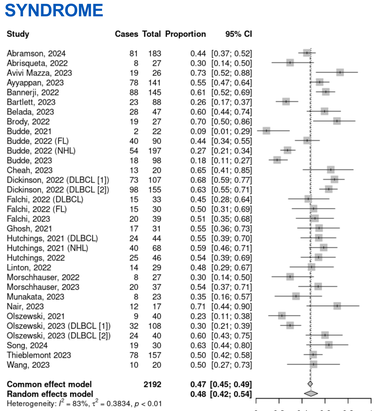


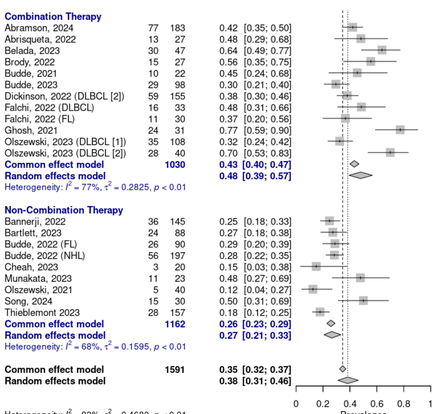
FIGURE 1. ALL GRADE CYTOKINE RELEASE SYNDROME



Study	Cases	Total	Proportion	95% CI
Abramson, 2024	81	183	0.44	[0.37; 0.52]
Abrisqueta, 2022	8	27	0.30	[0.14; 0.50]
Avivi Mazza, 2023	19	26	0.73	[0.52; 0.88]
Ayyappan, 2023	78	141	0.55	[0.47; 0.64]
Banerji, 2022	88	145	0.61	[0.52; 0.69]
Bartlett, 2023	23	88	0.26	[0.17; 0.37]
Belada, 2023	28	47	0.60	[0.44; 0.74]
Brody, 2022	19	27	0.70	[0.50; 0.86]
Budde, 2021	2	22	0.09	[0.01; 0.29]
Budde, 2022 (FL)	40	90	0.44	[0.34; 0.55]
Budde, 2022 (NHL)	54	197	0.27	[0.21; 0.34]
Budde, 2023	18	98	0.18	[0.11; 0.27]
Cheah, 2023	13	20	0.65	[0.41; 0.85]
Dickinson, 2022 (DLBCL [1])	73	107	0.68	[0.59; 0.77]
Dickinson, 2022 (DLBCL [2])	98	155	0.63	[0.55; 0.71]
Falchi, 2022 (DLBCL)	15	33	0.45	[0.28; 0.64]
Falchi, 2022 (FL)	15	30	0.50	[0.31; 0.69]
Falchi, 2023	20	39	0.51	[0.35; 0.68]
Ghosh, 2021	17	31	0.55	[0.36; 0.73]
Hutchings, 2021 (DLBCL)	24	44	0.55	[0.39; 0.70]
Hutchings, 2021 (NHL)	40	68	0.59	[0.46; 0.71]
Hutchings, 2022	25	46	0.54	[0.39; 0.69]
Linton, 2022	14	29	0.48	[0.29; 0.67]
Morschhauser, 2022	8	27	0.30	[0.14; 0.50]
Morschhauser, 2023	20	37	0.54	[0.37; 0.71]
Munakata, 2023	8	23	0.35	[0.16; 0.57]
Nair, 2023	12	17	0.71	[0.44; 0.90]
Olszewski, 2021	9	40	0.23	[0.11; 0.38]
Olszewski, 2023 (DLBCL [1])	32	108	0.30	[0.21; 0.39]
Olszewski, 2023 (DLBCL [2])	24	40	0.60	[0.43; 0.75]
Song, 2024	19	30	0.63	[0.44; 0.80]
Thieblemont 2023	78	157	0.50	[0.42; 0.58]
Wang, 2023	10	20	0.50	[0.27; 0.73]
Common effect model	**2192**		**0.47**	**[0.45; 0.49]**
Random effects model			**0.48**	**[0.42; 0.54]**

Heterogeneity: I^2 = 83%, τ^2 = 0.3834, p < 0.01

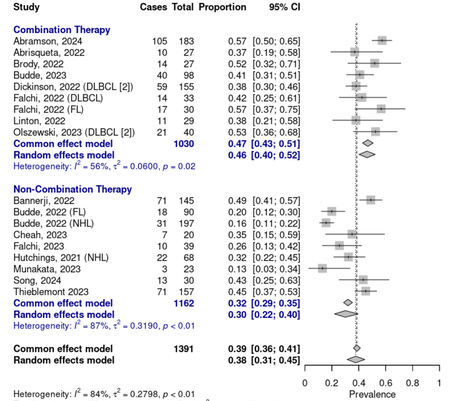
FIGURE 2. ALL GRADE NEUTROPENIA



Study	Cases	Total	Proportion	95% CI
Combination Therapy				
Abramson, 2024	77	183	0.42	[0.35; 0.50]
Abrisqueta, 2022	13	27	0.48	[0.29; 0.68]
Belada, 2023	30	47	0.64	[0.49; 0.77]
Brody, 2022	15	27	0.56	[0.35; 0.75]
Budde, 2021	10	22	0.45	[0.24; 0.68]
Budde, 2023	29	98	0.30	[0.21; 0.40]
Dickinson, 2022 (DLBCL [2])	59	155	0.38	[0.30; 0.46]
Falchi, 2022 (DLBCL)	16	33	0.48	[0.31; 0.66]
Falchi, 2022 (FL)	11	30	0.37	[0.20; 0.56]
Ghosh, 2021	24	31	0.77	[0.59; 0.90]
Olszewski, 2023 (DLBCL [1])	35	108	0.32	[0.24; 0.42]
Olszewski, 2023 (DLBCL [2])	28	40	0.70	[0.53; 0.83]
Common effect model		**1030**	**0.43**	**[0.40; 0.47]**
Random effects model			**0.48**	**[0.39; 0.57]**
Heterogeneity: I^2 = 77%, τ^2 = 0.2825, p < 0.01				
Non-Combination Therapy				
Bannerji, 2022	36	145	0.25	[0.18; 0.33]
Bartlett, 2023	24	88	0.27	[0.18; 0.38]
Budde, 2022 (FL)	26	90	0.29	[0.20; 0.39]
Budde, 2022 (NHL)	56	197	0.28	[0.22; 0.35]
Cheah, 2023	3	20	0.15	[0.03; 0.38]
Munakata, 2023	11	23	0.48	[0.27; 0.69]
Olszewski, 2021	5	40	0.12	[0.04; 0.27]
Song, 2024	15	30	0.50	[0.31; 0.69]
Thieblemont 2023	28	157	0.18	[0.12; 0.25]
Common effect model		**1162**	**0.26**	**[0.23; 0.29]**
Random effects model			**0.27**	**[0.21; 0.33]**
Heterogeneity: I^2 = 68%, τ^2 = 0.1595, p < 0.01				
Common effect model		**1591**	**0.35**	**[0.32; 0.37]**
Random effects model			**0.38**	**[0.31; 0.46]**

Heterogeneity: I^2 = 83%, τ^2 = 0.4680, p < 0.01
Test for subgroup differences (common effect): χ^2_1 = 52.89, df = 1 (p < 0.01)
Test for subgroup differences (random effects): χ^2_1 = 14.78, df = 1 (p < 0.01)

FIGURE 3. ALL-GRADE INFECTIONS



Study	Cases	Total	Proportion	95% CI
Combination Therapy				
Abramson, 2024	105	183	0.57	[0.50; 0.65]
Abrisqueta, 2022	10	27	0.37	[0.19; 0.58]
Brody, 2022	14	27	0.52	[0.32; 0.71]
Budde, 2023	40	98	0.41	[0.31; 0.51]
Dickinson, 2022 (DLBCL [2])	59	155	0.38	[0.30; 0.46]
Falchi, 2022 (DLBCL)	14	33	0.42	[0.25; 0.61]
Falchi, 2022 (FL)	17	30	0.57	[0.37; 0.75]
Linton, 2022	11	29	0.38	[0.21; 0.58]
Olszewski, 2023 (DLBCL [2])	21	40	0.53	[0.36; 0.68]
Common effect model		**1030**	**0.47**	**[0.43; 0.51]**
Random effects model			**0.46**	**[0.40; 0.52]**
Heterogeneity: I^2 = 56%, τ^2 = 0.0600, p = 0.02				
Non-Combination Therapy				
Bannerji, 2022	71	145	0.49	[0.41; 0.57]
Budde, 2022 (FL)	18	90	0.20	[0.12; 0.30]
Budde, 2022 (NHL)	31	197	0.16	[0.11; 0.22]
Cheah, 2023	7	20	0.35	[0.15; 0.59]
Falchi, 2023	10	39	0.26	[0.13; 0.42]
Hutchings, 2021 (NHL)	22	68	0.32	[0.22; 0.45]
Munakata, 2023	3	23	0.13	[0.03; 0.34]
Song, 2024	13	30	0.43	[0.25; 0.63]
Thieblemont 2023	71	157	0.45	[0.37; 0.53]
Common effect model		**1162**	**0.32**	**[0.29; 0.35]**
Random effects model			**0.30**	**[0.22; 0.40]**
Heterogeneity: I^2 = 87%, τ^2 = 0.3190, p < 0.01				
Common effect model		**1391**	**0.39**	**[0.36; 0.41]**
Random effects model			**0.38**	**[0.31; 0.45]**

Heterogeneity: I^2 = 84%, τ^2 = 0.2798, p < 0.01
Test for subgroup differences (common effect): χ^2_1 = 31.46, df = 1 (p < 0.01)
Test for subgroup differences (random effects): χ^2_1 = 7.72, df = 1 (p < 0.01)

DISCUSSION

Our analysis provides one of the first systemic evaluations of BsAbs safety profiles in early trials and publications of NHL.

These findings highlight the manageable safety profile of BsAbs in the treatment of NHL, particularly when compared to alternatives in the relapsed/refractory setting.

- Neutropenia rates were prevalent and consistent with myelosuppressive nature of immunotherapy. They appeared less severe compared to CAR-T which may be due to absence of lymphodepleting therapy.
- Infections were common, reflecting the immunocompromised state of patients. Specific pathogens were not always detailed, but viral, including SARS-CoV2 were prominent. Infections were more common with combination therapy, but this did not translate into a significant increase in severe (grade ≥3) infections.
- CRS occurred in almost half of patients but was rarely severe. Step-up dosing and corticosteroid use have been likely effective in reducing severity. ICANS prevalence was low, but lack of standardized criteria limits assessment.

Safety profiles were mostly consistent across different lymphoma subtypes. Overall, BsAbs show good tolerability and low treatment-associated mortality. The field should prioritize standardized safety reporting to optimize outcomes.

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REFERENCES