# From monospecific to bispecific: Comparative safety of T-cell engagers BsAbs versus monospecific agents using clinical outcomes and FAERS data

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## Introduction

Bispecific antibodies (BsAbs) are reshaping cancer therapy by simultaneously targeting a tumor antigen and $CD_3$ on T cells, redirecting cytotoxic activity toward malignant cells. [1] This dual targeting yields heightened potency and potential to overcome resistance, but it also introduces distinct pharmacology and safety liabilities that set BsAbs apart from monospecific antibodies [2], [3]. In oncology, $CD_3$/$CD_{20}$ BsAbs exemplify this class: rapid T-cell engagement can drive profound anti-tumor responses, but also risks such as cytokine release syndrome, neurotoxicity, and on-target/off-tumor effects—risk profiles shaped by molecular design and pharmacokinetics[4]. As of 2025, 4 BsAbs $CD_3$/$CD_{20}$ with T-cell engagement mechanisms are approved in the US and EU relapsed/refractory diffuse large B-cell lymphoma (DLBCL) and relapsed/refractory follicular lymphoma (R/R FL).

**Our objective** is to quantitatively compare the safety of $CD_{20}$/$CD_3$ BsAbs against monospecific anti-$CD_{20}$ and anti-$CD_3$ antibodies, using a standardized label-based safety scoring system, clinical outcomes, and FAERS data to map the safety landscape and identify differentiating risk signals.

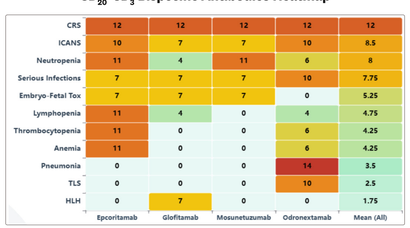
## Bispecific and monospecific mabs used in this analysis

| AGENT NAME | INDICATION & APPROVAL | MECHANISM OF ACTION | DOSING & ADMINISTRATION |
|---|---|---|---|
| Mosunetuzumab (Lunsumio) | FL 2022<br>Relapsed/Refractory Follicular Lymphoma | **Full-length IgG1-like BsAb**<br>Binds CD20 on B-cells & CD3 on T-cells; induces T-cell activation & redirected lysis. | Intravenous (IV)<br>Step-up dosing C1D1/D8/D15 |
| Glofitamab (Columvi) | DLBCL 2023<br>R/R Diffuse Large B-cell Lymphoma | **2:1 Format IgG-like BsAb**<br>Bivalent binding to CD20, monovalent to CD3; enhanced potency. | Intravenous (IV)<br>Obinutuzumab pretreatment req. |
| Epcoritamab (Epkinly) | DLBCL 2023<br>R/R Diffuse Large B-cell Lymphoma | **Subcutaneous IgG1 BsAb**<br>DuoBody technology; SC administration offers distinct PK profile. | Subcutaneous (SC)<br>Step-up dosing to mitigate CRS |
| Odronextamab (REGN1979) | DLBCL 2024*<br>Relapsed/Refractory DLBCL<br>*Regulatory status complex; multiple CRLs in US as of 2025-2026 | **Full-length IgG4-based BsAb**<br>Minimizes Fc effector function; relies purely on T-cell engagement. | Intravenous (IV)<br>Split dosing schedule |

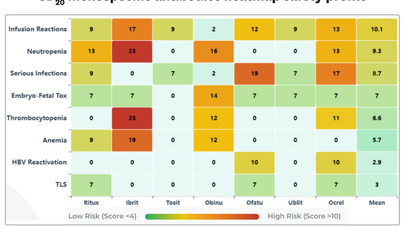
| Name | Mechanism of Action (MOA) | Indication | Company | Year |
|---|---|---|---|---|
| Rituximab | Apoptosis in CD20+ B-cell lines + CDC, ADCC, ADCP | Non-Hodgkin's Lymphoma (NHL) | Genentech | 1997 |
| Ibritumomab | Apoptosis in CD20+ B-cell lines using radiation (radio-immunoconjugate) | Non-Hodgkin's Lymphoma (NHL) | IDEC Pharma | 2002 |
| Tositumomab | Apoptosis in CD20+ B-cell lines using radiation (radio-immunoconjugate) | Non-Hodgkin's Lymphoma (NHL) | GSK | 2003 |
| Ofatumumab | Apoptosis in CD20+ B-cell lines + CDC, ADCC | Fludarabine-refractory Chronic Lymphocytic Leukemia (CLL) | GSK | 2009 |
| Obinutuzumab | Promotes direct cell death and enhanced ADCC | Chronic Lymphocytic Leukemia (CLL) | Genentech | 2013 |
| Ocrelizumab | Apoptosis in CD20+ B-cell lines + CDC, ADCC | Relapsing and Primary Progressive Multiple Sclerosis (MS) | Genentech | 2017 |
| Ublituximab | Apoptosis in CD20+ B-cell lines + CDC, ADCC, ADCP | Relapsing Forms of Multiple Sclerosis (MS) | TG Therapeutics | 2022 |

## Consensus ADR and scoring analysis

### $CD_{20}$*$CD_3$ Bispecific Antibodies Heatmap




### $CD_{20}$ monospecific antibodies heatmap safety profile




## Workflow from label to score

### 1. Data Extraction

SmPC/FDA Labels (Mosunetuzumab, Glofitamab, etc.)

### 2. Harmonization (MedDRA)

Mapping varied terms to Preferred Terms (PT)

### 3. Consensus Scoring

Application of weighted formula based on severity

**BBW** — High Weight

**>20%** — Freq Weight

### Data Sources & Harmonization

Primary data extracted from **Summary of Product Characteristics (SmPC)** and **FDA-approved drug labels**. Vocabulary standardized to **MedDRA Preferred Terms (PT)** to map varying terminologies (e.g., "hives" vs. "urticaria") into a unified dataset.

### Four Key Scoring Inputs

- **Black Box Warnings (BBW):** Life-threatening risks prioritized.
- **Warnings & Precautions:** Severe risks without BBW.
- **Grade 3-4 >10%:** Serious intervention required.
- **Incidence >20%:** Common burden (any grade).

### Analytical Outputs

Generation of **Consensus Scores** per ADR across drug classes. Results visualized via **Heatmaps** (intensity of risk) and **Radar Plots** (comparative safety footprint) to identify high-priority signals.

## Consensus ADRs Scoring System

$$S_i = \Sigma_j \left(w_B \cdot B_{ij} + w_G \cdot G_{ij} + w_W \cdot W_{ij} + w_F \cdot F_{ij}\right)$$

Calculated for each Adverse Drug Reaction (i) across n drugs

$B_{ij}$ Binary indicator: Drug j has **Black Box Warning** for ADR i

$G_{ij}$ Binary indicator: Drug j has **Grade 3-4** incidence >10%

$W_{ij}$ Binary indicator: Drug j has standard **Warning/Precaution**

$F_{ij}$ Binary indicator: Drug j has any-grade **Incidence >20%**

### WEIGHTING SYSTEM

**10** — **Black Box Warning ($w_B$)**
Highest priority; regulatory "red flag" for life-threatening risks

**7** — **Warnings & Precautions ($w_W$)**
Important clinical caution; requires monitoring

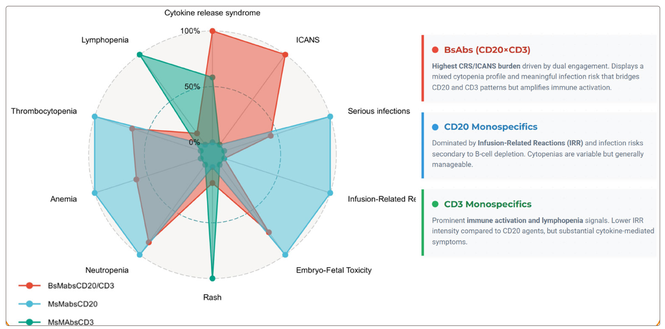
**4** — **Severe Toxicity ($w_G$)**
Grade 3-4 >10%; significant impact on patient safety & hospitalization

**2** — **High Incidence ($w_F$)**
Frequency >20%; "common burden" affecting quality of life

### Prioritization Thresholds

Scores are aggregated to identify high-signal ADRs. A consensus threshold is applied to filter low-relevance events and focus analysis on clinically meaningful safety patterns.

## Comparative analysis BsMbs vs MsMabs using clinical safety

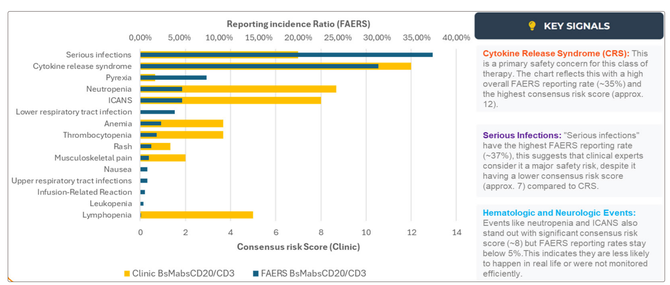



**BsAbs (CD20×CD3)**
**Highest CRS/ICANS burden** driven by dual engagement. Displays a mixed cytopenia profile and meaningful infection risk that bridges CD20 and CD3 patterns but amplifies immune activation.

**CD20 Monospecifics**
Dominated by **Infusion-Related Reactions (IRR)** and infection risks secondary to B-cell depletion. Cytopenias are variable but generally manageable.

**CD3 Monospecifics**
Prominent **immune activation and lymphopenia** signals. Lower IRR intensity compared to CD20 agents, but substantial cytokine-mediated symptoms.

## Comparative FAERS and clinical safety profile of $CD_{20}$/$CD_3$ antibodies




**KEY SIGNALS**

**Cytokine Release Syndrome (CRS):** This is a primary safety concern for this class of therapy. The chart reflects this with a high overall FAERS reporting rate (~35%) and the highest consensus risk score (approx. 12).

**Serious Infections:** "Serious infections" have the highest FAERS reporting rate (~37%), this suggests that clinical experts consider it a major safety risk, despite it having a lower consensus risk score (approx. 7) compared to CRS.

**Hematologic and Neurologic Events:** Events like neutropenia and ICANS also stand out with significant consensus risk score (~8) but FAERS reporting rates stay below 5%. This indicates they are less likely to happen in real life or were not monitored efficiently.

## Conclusion

- **Distinct safety footprint:** $CD_{20}$×$CD_3$ BsAbs generate a unique safety profile driven by immune activation (CRS/ICANS), distinct from the additive risks of monospecific CD20 and CD3 agents.
- **Universal vs. agent-specific risks:** While CRS is a universal class effect and ICANS is substantial across the board, hematologic toxicities and serious infection risks show significant heterogeneity among agents.

## References

[1] Acta Pharm Sin B. 2023 May 23;13(9):3583–3597.
[2] Front. Oncol., 10 February 2025 Sec. Cancer Molecular Targets and Therapeutics Volume 15 - 2025
[3] Front. Immunol., 29 May 2025 Sec. Cancer Immunity and Immunotherapy Volume 16 - 2025
[4] Mol Cancer. 2025 Aug 4;24:212.

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