# Opportunistic Neurologic Infections With CD3-Engaging Bispecific Antibodies in Hematologic Malignancies: A FAERS Disproportionality Analysis

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**KEY FINDING:** CD3-engaging bispecific antibodies showed marked disproportionality for neurologic opportunistic infections, with the strongest signals among BCMA-directed agents and a reporting phenotype dominated by PML.

## INTRODUCTION

Bispecific antibodies (BsAbs) have emerged as an important therapeutic platform across hematologic malignancies, with CD3-engaging agents increasingly used in multiple myeloma and B-cell lymphomas.[1,2] By redirecting T cells against targets such as **B-cell maturation antigen (BCMA), G protein-coupled receptor class C group 5 member D (GPRC5D)**, CD19, and CD20, these therapies can produce profound immune dysfunction, including hypogammaglobulinemia and T-cell exhaustion, with infections now recognized as a major treatment-related complication.[1,2]

While neurologic toxicity has primarily been characterized in the context of immune effector cell-associated neurotoxicity syndrome (ICANS), the broader spectrum of neurologic complications, particularly opportunistic central nervous system (CNS) infections, remains poorly defined.[3] Rare infections such as progressive multifocal leukoencephalopathy (PML) can be devastating in immunocompromised patients, making early recognition and a better understanding of their association with CD3-engaging bispecific antibodies clinically important.[3]

## METHODS

1. **FAERS data window:** We analyzed FAERS quarterly ASCII files from **2022Q4 through 2026Q1**, defining this as the contemporary bispecific antibody era. This start point was chosen as teclistamab was approved in October 2022, marking the beginning of modern BCMA-directed CD3-engaging bispecific use in multiple myeloma.

2. **Report Deduplication and Cleaning:** FAERS reports were deduplicated by retaining the most recent report for each CASEID, prioritizing the latest FDA_DT and then the highest PRIMARYID. Data cleaning, deduplication, drug matching, MedDRA term extraction, and disproportionality calculations were performed using Python 3.12.13.

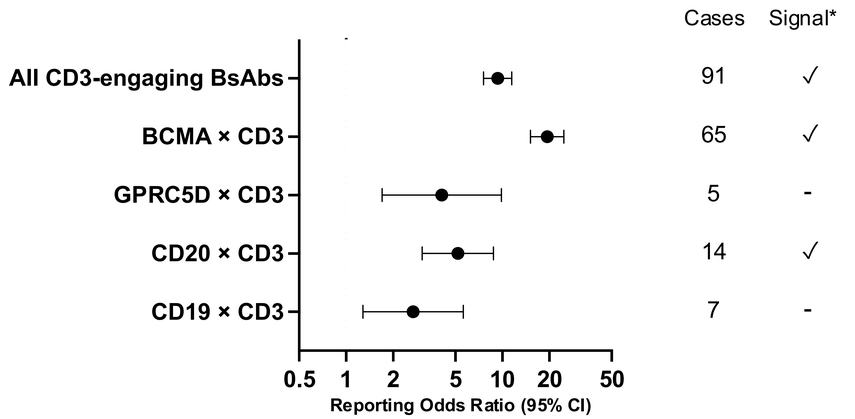
3. **Exposure Identification:** We focused on CD3-engaging bispecific antibodies used in hematologic malignancies because these agents redirect T cells and may create distinct immune-mediated infectious risks. Bispecific exposure was identified from the FAERS DRUG table using generic and brand names, and the primary analysis was restricted to primary suspect reports (ROLE_COD = PS)

4. **Outcome Definition:**
Neurologic opportunistic infections were defined using **31 CNS-tagged MedDRA preferred terms** extracted from the MedDRA Important Medical Event list.

5. **Disproportionality Analysis:** Reporting odds ratios (RORs) with 95% confidence intervals and shrinkage information components (ICs) were calculated using the full deduplicated FAERS database as the comparator. A signal was predefined as **≥3 cases, ROR025 >1, and IC025 >0**.

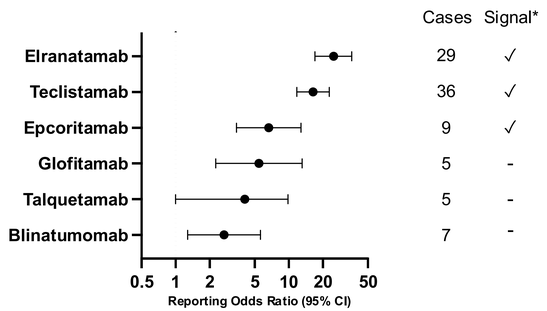
6. **Sensitivity Analyses and Visualization:** Sensitivity analyses excluded reports with major confounders for immunosupression to assess whether signals persisted after removing major structured confounders.
Figures were generated in GraphPad Prism 11.

## Figure 1. Class-Level Disproportionality of Opportunistic Neurologic Infections




*Signal defined as≥3 cases, ROR025 >1, and IC025 >0.

## Figure 2. Drug-Level Disproportionality of Opportunistic Neurologic Infections

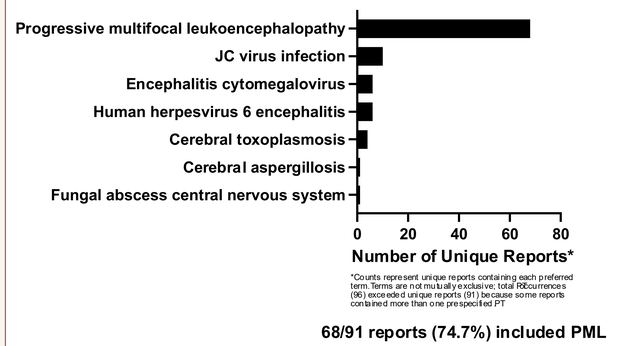



*Signal defined as 3 cases, ROR025 >1, and IC025 >0.

## KEY RESULTS

- **4,967,690** deduplicated FAERS reports
- **91 neurologic OI reports** among **12,565** primary-suspect BsAb reports. Overall: **ROR 9.34 (95% CI 7.58–11.50)**.
- Strongest class signal: **BCMA × CD3, n=65; ROR 19.36 (95% CI 15.12–24.78)**.
- Strongest drug-level signals: **elranatamab and teclistamab**.
- PML dominated the phenotype: **68/91 reports (74.7%).**

## Figure 3. Spectrum of Reported Opportunistic Neurologic Infections




*Counts represent unique reports containing each preferred term. Terms are not mutually exclusive; total RBcurrences (96) exceeded unique reports (91) because some reports contained more than one prespecified PT

**68/91 reports (74.7%) included PML**

## ROBUSTNESS CHECK

- To assess the stability of the observed signals, we performed prespecified sensitivity analyses excluding reports with major alternative risk factors for neurologic opportunistic infections, including HIV/AIDS, transplant/GVHD/HSCT, and CAR-T therapy. We also repeated the analysis after excluding blinatumomab, which predates the contemporary myeloma and lymphoma bispecific antibody era.
- Sensitivity analyses excluding the major confounders removed 90,933 FAERS reports but only 4/91 bispecific neurologic OI cases; the overall signal persisted (87 cases, ROR 11.34, IC025 2.36).
- Signals for BCMA-directed bispecifics, particularly teclistamab and elranatamab, persisted across these analyses, supporting the robustness of the primary findings.

## CONCLUSIONS AND CLINICAL INTERPRETATION

CD3-engaging BsAbs showed disproportionate reporting of neurologic opportunistic infections in FAERS, with the strongest and most consistent signals observed for BCMA-directed agents; PML/JC-virus–related events dominated the phenotype.

New neurologic symptoms during BsAbs should prompt consideration of opportunistic CNS infection, particularly in patients receiving prolonged BCMA-directed treatment.

## LIMITATIONS

- FAERS is a spontaneous reporting system and is subject to **underreporting, stimulated reporting, and reporting bias**.
- Lack of reliable exposure denominators prevents estimation of **incidence or absolute risk**.
- Residual confounding from underlying malignancy and prior or concomitant immunosuppressive therapies cannot be excluded.
- Disproportionality signals are **hypothesis-generating and do not establish causality**.

**References:**

1 Reynolds G, Cliff ERS, Mohyuddin GR, et al. Infections following bispecific antibodies in myeloma: a systematic review and meta-analysis. *Blood Adv*. 2023;7(19):5898-5903. doi:10.1182/bloodadvances.2023010539
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3 Gadoth A, Paran Y, Mina Y, et al. Bispecific antibodies are associated with progressive multifocal leukoencephalopathy. *Neurol Neuroimmunol Neuroinflamm*. 2026;13(5):e200633. doi:10.1212/NXI.0000000000200633.

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