Neurotoxicity Across Major FDA-Approved CAR T-Cell Therapies: Systematic Comparison of Pivotal Trial and Real-World Data

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BACKGROUND

Six major FDA-approved CAR T-cell therapies with mature pivotal and real-world ICANS data were analyzed:

CD19-directed: axicabtagene ciloleucel (axi-cel, CD28), tisagenlecleucel (tisa-cel, 4-1BB), brexucabtagene autoleucel (brexu-cel, CD28), lisocabtagene maraleucel (liso-cel, 4-1BB)

BCMA-directed: idecabtagene vicleucel (ide-cel, 4-1BB), ciltacabtagene autoleucel (cilta-cel, 4-1BB)

Immune effector cell-associated neurotoxicity syndrome (ICANS) is a major potentially life-threatening toxicity with distinct product-specific neurologic profiles and important trial-vs-real-world differences that inform product selection and monitoring.

METHODS

• Systematic comparative analysis of published ICANS data from pivotal CAR T-cell trials and available real-world cohorts through May 2026

• **Data sources:** CIBMTR registries, Cell Therapy Consortium analyses, international multicenter studies, Flatiron Health analyses, FAERS pharmacovigilance data, and a Frontiers in Neurology 2024 meta-analysis

• **ICANS grading:** American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria applied uniformly across data sources

ABBREVIATIONS

ASTCT: American Society for Transplantation and Cellular Therapy • BCMA: B-cell maturation antigen • CAR-T: chimeric antigen receptor T-cell • CIBMTR: Center for International Blood and Marrow Transplant Research • CRS: cytokine release syndrome • FAERS: FDA Adverse Event Reporting System • ICANS: immune effector cell-associated neurotoxicity syndrome • LBCL: large B-cell lymphoma • OR: odds ratio

RESULTS — CD19-DIRECTED PRODUCTS

CD28-costimulated products carried the highest ICANS burden.

Axi-cel: trial any-grade ICANS 64–78% (grade ≥3: 28–34%), attenuating in real-world data to 54% any-grade / 26.4% grade ≥3

Brexu-cel: 60–63% any-grade in trials (grade ≥3: 25–31%); real-world grade ≥3 reached 28–35%, exceeding trial rates in B-ALL populations

Liso-cel (4-1BB): 30% (LBCL) to 46% (CLL) in trials; real-world LBCL data 26.0–26.6% any-grade / 9.2–10.0% grade ≥3 — the most trial-consistent product

Tisa-cel (4-1BB): lowest CD19 ICANS rates — trial 13–40%; real-world 17–27% any-grade, grade ≥3 6.1–9.0%

RESULTS — BCMA-DIRECTED PRODUCTS

BCMA-directed therapies demonstrated lower overall ICANS.

Ide-cel: 18% trial / 19% real-world ICANS (grade ≥3: 2–7%), with uniquely early onset at median day 2

Cilta-cel: 21–23% trial ICANS with fatal events (grade 5: 2%) and a distinct ***delayed neurotoxicity phenotype*** — parkinsonism, cranial nerve palsies, Guillain-Barré syndrome, and polyneuropathies — amplified in FAERS pharmacovigilance data

Meta-analysis: higher high-grade ICANS risk confirmed for CD19 vs. BCMA products (OR, 4.6) and for CD28 vs. 4-1BB costimulatory constructs

ICANS BY PRODUCT: TRIAL vs. REAL-WORLD

Product (Target / Costim)	Trial Any-Gr	Trial ≥Gr3	RW Any-Gr	RW ≥Gr3	Notes
Axi-cel (CD19 / CD28)	64–78%	28–34%	54%	26.4%	—
Brexu-cel (CD19 / CD28)	60–63%	25–31%	—	28–35%	Exceeds trial in B-ALL
Liso-cel (CD19 / 4-1BB)	30–46%	—	26.0–26.6%	9.2–10.0%	Most trial-consistent
Tisa-cel (CD19 / 4-1BB)	13–40%	—	17–27%	6.1–9.0%	Lowest CD19 rates
Ide-cel (BCMA / 4-1BB)	18%	2–7%	19%	—	Early onset (median d2)
Cilta-cel (BCMA / 4-1BB)	21–23%	Gr5: 2%	—	—	Delayed phenotype*

** Cilta-cel delayed neurotoxicity (parkinsonism, cranial nerve palsies, Guillain-Barré syndrome, polyneuropathies) typically presents weeks after CRS/ICANS resolve and requires prolonged post-infusion monitoring.*

OR 4.6
High-grade ICANS, CD19 vs BCMA

Day 2
Earliest median ICANS onset (ide-cel)

2%
Grade 5 (fatal) ICANS, cilta-cel

CONCLUSION

ICANS risk stratifies predictably by target antigen and costimulatory domain:

• CD28/CD19 products (axi-cel, brexu-cel) carry the highest acute neurotoxicity burden

• 4-1BB/CD19 products (tisa-cel, liso-cel) show more moderate, trial-consistent rates

• BCMA-directed products have lower overall ICANS, but cilta-cel carries a unique ***delayed neurotoxicity phenotype*** requiring prolonged monitoring

These findings should inform product selection, monitoring duration, and institutional CAR T-cell toxicity protocols.

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Scope note: This poster summarizes six index FDA-approved CAR T-cell products with the most mature pivotal and real-world ICANS datasets. Newer FDA approvals were not pooled because mature comparative real-world neurotoxicity data were limited at the May 2026 cutoff.