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The intent of this handout is to provide background information regarding neurologic events and grading system management guidelines. This handout is not intended to provide treatment guidance for patients.

Neurologic Events Associated With Immunotherapy

Immuno-oncology therapies are associated with neurologic adverse events affecting the central and peripheral nervous system, including encephalitis, neuropathies, demyelinating diseases (eg, Guillain-Barré syndrome), and neurodegenerative disorders (eg, parkinsonism).[1-3] Therapies such as checkpoint inhibitors, CAR-T, and bispecific antibodies may lead to serious and life-threatening or fatal neurologic events.[2,4]

Immune effector cell–associated neurotoxicity syndrome (ICANS)

ICANS is a pathologic process involving the CNS following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells.[4]

Symptoms of neurologic events[4,5,*]

*Not encompassing of all symptoms; additional manifestations should be considered.

Consistent with ICANS

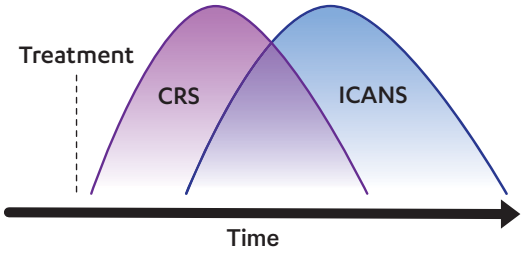
- Aphasia
- Altered consciousness level
- Agitation
- Delirium
- Seizures
- Encephalopathy
- Cognitive skill impairment/ difficulty concentrating
- Motor weakness

Excluded from ICANS definition

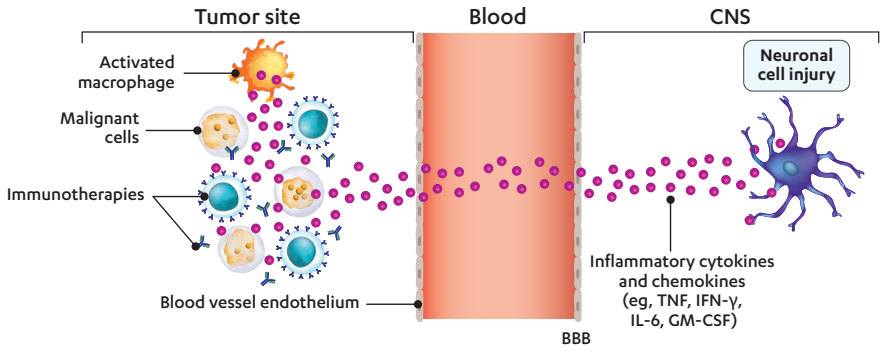
- Headache
- Tremor
- Myoclonus
- Asterixis
- Hallucinations
- Peripheral neuropathy
- Parkinsonism

Timing and pathophysiology of ICANS[4,6-13]

ICANS typically occurs after or concurrent with CRS



In ICANS, proinflammatory cytokines may leak into the vasculature, disrupting the BBB and causing neuronal cell injury



Ataxia

Ataxia is a condition of the nervous system marked by lack of muscle coordination, balance, and motor control.[14] Ataxia has been reported in patients receiving immunotherapy, including CAR-T therapy and bispecific antibodies.[15-18]

Possible mechanisms driving ataxia[19-22]

- Cytokine-mediated neurotoxicity
- Immune activation causing inflammation in the cerebellum
- Cytokine-mediated endothelial activation disrupting the BBB

BBB, blood-brain barrier; CAR-T, chimeric antigen receptor-T cell; CNS, central nervous system; CRS, cytokine release syndrome; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICANS, immune effector cell–associated neurotoxicity syndrome; IFN-γ, interferon gamma; IL-6, interleukin 6; TNF, tumor necrosis factor.

1. Guidon AC, Burton LB, Chwalisz BK, et al. *J Immunother Cancer*. 2021;9:e002890. 2. Burton LB, Eskian M, Guidon AC, Reynolds KL. *Neurooncol Adv*. 2021;3:v108-v120. **3.** Van Oekelen O, Aleman A, Upadhyaya B, et al. *Nat Med*. 2021;27:2099-2103. **4.** Lee DW, Santomasso BD, Locke FL, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638. **5.** Cohen AD, Parekh S, Santomasso BD, et al. *Blood Cancer J*. 2022;12:32. **6.** Morris EC, Neelapu SS, Giavridis T, Sadelain M. *Nat Rev Immunol*. 2022;22:85-96. **7.** Pan D, Richter J. *Curr Hematol Malig Rep*. 2024;19:237-245. **8.** Schuster SJ, Bartlett NL, Assouline S, et al. *Blood*. 2019;134:6. **9.** Budde LE, Sehn LH, Matasar M, et al. *Lancet Oncol*. 2022;23:1055-1065. **10.** Stein AS, Schiller G, Benjamin R, et al. *Ann Hematol*. 2019;98:159-167. **11.** Moreau P, Garfall AL, van de Donk NWCJ, et al. *N Engl J Med*. 2022;387:495-505. **12.** Lesokhin AM, Tomasson MH, Arnulf B, et al. *Nat Med*. 2023;29:2259-2267. **13.** Bumma N, Richter J, Jagannath S, et al. *J Clin Oncol*. 2024;42:2702-2712. **14.** NIH National Institute of Neurological Disorders and Stroke. Ataxia. Accessed December 15, 2025. https://www.ninds.nih.gov/health-information/disorders/ataxia. **15.** Janakiram M, Liu L, Goldsmith S, et al. *Blood Cancer J*. 2025;15:135. **16.** Chari A, Touzeau C, Schinke C, et al. *Lancet Haematol*. 2025;12:e269-e281. **17.** CARVYKTI™ (ciltacabtagene autoleucel). Prescribing information. Janssen Biotech, Inc; 2025. **18.** Bal S, Htut M, Berdeja JG, et al. *Blood*. 2024;144(suppl 1):2069. **19.** Gust J, Ponce R, Liles WC, et al. *Front Immunol*. 2020;11:577027. **20.** Parvez MSA, Ohtsuki G. *Brain Sci*. 2022;12:367. **21.** Afrough A, Abraham PR, Turer L, et al. *Acta Haematol*. 2025;148:300-314. **22.** Mitoma H, Adhikari K, Aeschlimann D, et al. *Cerebellum*. 2016;15:213-232.

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Neurologic Events Associated With Immunotherapy

Potential clinical factors associated with neurologic events[1-10]

Patient-/therapy-related
Age | High disease burden
Preexisting neurologic comorbidities and autoimmune diseases
CRS onset and severity | Therapy dose and/or combinations

Biomarkers
LDH | CRP | Fibrinogen | Ferritin

ASTCT ICANS consensus grading for adults[11]

CTCAE v5.0 grading is used to evaluate all neurologic events. The ASTCT recommends using the ICANS grading criteria (shown below) and CTCAE v5.0 to grade events that are not part of or consistent with the ICANS definition criteria.

	ICE score*	Depressed level of consciousness†	Seizure	Motor findings	Raised ICP/ cerebral edema
Grade 1	7-9	Awakens spontaneously	None	None	None
Grade 2	3-6	Awakens to voice	None	None	None
Grade 3	0-2	Awakens only to tactile stimulus	Any clinical seizure (focal or generalized) that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	None	Focal/local edema on neuroimaging‡
Grade 4	0 (patient is unarousable and unable to perform ICE)	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or stupor or coma	Life-threatening prolonged seizure (>5 min) or repetitive clinical or electrical seizures without return to baseline in between	Deep focal motor weakness, such as hemiparesis or paraparesis§	Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, or Cushing's triad

*A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable. †Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication). ‡Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0. §Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
Figure modified from Lee DW, Santomasso BD, Locke FL, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

Consider monitoring symptoms[11]

- Impairment in motor function (eg, handwriting changes)
- Changes in sensation (eg, numbness)
- Headache
- Speech disorders
- Convulsions
- Disturbances in consciousness
- Confusion
- Disorientation

Consider diagnostic testing[1]

- Serologic testing
- Brain MRI
- Lumbar puncture
- EEG
- EMG

Consider management strategies[1,6,9,11-14]

Multiple versions for ICANS management have been implemented in clinical trials with interventions as per the investigator's discretion. Given the onset of ICANS in relation to CRS, guidelines have included management based on CRS manifestation in addition to toxicity grade. **Consider partnering with a neurologic specialist to discuss supportive therapy and ICU requirements.**

Shown are select pharmacological management strategies for ICANS from established guidelines.[13,14] For more comprehensive guidance on supportive care related to CRS and neurologic event management, refer to your institutional guidelines, established guidelines (eg, ASCO,[13] CARTOX,[14] mSMART,[15] SITC,[7] and National Comprehensive Cancer Network® [NCCN®][16]), and the prescribing information.

CONCURRENT CRS

Consider administration of the following:

- Nonsedating antiepileptics
- Corticosteroids
- Anticytokine therapy (eg, anti–IL-6R)

NO CONCURRENT CRS

Consider administration of the following:

- Nonsedating antiepileptics
- Corticosteroids

ASCO, American Society of Clinical Oncology; ASTCT, American Society for Transplantation and Cellular Therapy; CARTOX, CAR T-Cell Therapy–Associated TOXicity; CRP, C-reactive protein; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; EEG, electroencephalogram; EMG, electromyography; ICANS, immune effector cell–associated neurotoxicity syndrome; ICE, immune effector cell–associated encephalopathy; ICP, intracranial pressure; ICU, intensive care unit; IL, interleukin; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; mSMART, Mayo Stratification of Myeloma and Risk-Adapted Therapy; SITC, Society for Immunotherapy of Cancer.

1. Burton LB, Eskian M, Guidon AC, Reynolds KL. *Neurooncol Adv*. 2021;3:v108-v120. **2.** Morris EC, Neelapu SS, Giavridis T, Sadelain M. *Nat Rev Immunol*. 2022;22:85-96. **3.** Stein AS, Schiller G, Benjamin R, et al. *Ann Hematol*. 2019;98:159-167. **4.** Ludwig H, Terpos E, van de Donk N, et al. *Lancet Oncol*. 2023;24:e255-e269. **5.** Gill V, Pelcovits A, Ollila T, et al. *Blood*. 2025;146:960-961. **6.** Salvaris R, Ong J, Gregory GP. *J Pers Med*. 2021;11:355. **7.** Maus MV, Alexander S, Bishop MR, et al. *J Immunother Cancer*. 2020;8:e001511. **8.** Wang Z, Han W. *Biomark Res*. 2018;6:4. **9.** Rivera AM, May S, Lei M, et al. *Crit Care Nurs Q*. 2020;43:191-204. **10.** Grant SJ, Grimshaw AA, Silberstein J, et al. *Transplant Cell Ther*. 2022;28:294-302. **11.** Lee DW, Santomasso BD, Locke FL, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638. **12.** Puzanov I, Diab A, Abdallah K, et al. *J Immunother Cancer*. 2017;5:95. **13.** Santomasso BD, Nastoupil LJ, Adkins S, et al. *J Clin Oncol*. 2021;39:3978-3992. Erratum in: *J Clin Oncol*. 2022;40:919. **14.** The University of Texas MD Anderson Cancer Center. IEC therapy toxicity assessment and management (also known as CARTOX) - adult. Published September 15, 2020. Accessed September 9, 2022. https://www.mdanderson.org/documents/for-physicians/algorithms/clinical-management/clin-management-cytokine-release-web-algorithm.pdf. **15.** Mayo Clinic. mSMART. Accessed March 10, 2023. https://www.msmart.org/mm-treatment-guidelines. **16.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Management of CAR T-Cell and Lymphocyte Engager-Related Toxicities V.2.2026. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed [December 15, 2025]. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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