National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Management of CAR T-Cell and Lymphocyte Engager-Related Toxicities

Version 1.2026 — October 23, 2025

NCCN Guidelines for Patients®

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

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NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

Updates in Version 1.2026 of the NCCN Guidelines for Management of CAR T-Cell and Lymphocyte Engager-Related Toxicities:

Global Changes
- New Guideline created using content sourced from the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities.
- References updated throughout the Guidelines.

CART-1
- Principles Of Patient Monitoring For CAR T-Cell–Related Toxicities
  - Before and During CAR T-Cell Infusion
    - ◊ 5th bullet modified: Start seizure prophylaxis on the day of infusion *when* ~~for chimeric antigen receptor (CAR) T-cell therapies~~ *there is high risk of ICANS based on patient factors or product type* ~~known to cause CAR T-cell–related neurotoxicity~~ (eg, *oral* levetiracetam 500–750 mg ~~orally~~ every 12 hours for 30 days).
    - ◊ 6th bullet modified: Baseline neurologic evaluation, including ICE scores (for adults) or Cornell Assessment of Pediatric Delirium (CAPD) scores (for children <12 years *or non-verbal adults*) prior to chimeric antigen receptor (CAR) T-cell therapy. Consider baseline brain MRI.
  - Post-CAR T-Cell Infusion
    - ◊ 2nd bullet modified: Hospitalization is warranted for patients at the first sign of ~~CRS or~~ neurotoxicity (including ~~fever, hypotension, or~~ change in mental status). *Patients with CRS who experience a response to tocilizumab and/or dexamethasone can be monitored closely in outpatient settings.*
    - ◊ 7th bullet modified: Monitor for CRS, neurotoxicity, and other toxicities for the duration recommended by the CAR product *prescribing information* ~~package insert~~ (at least 4 weeks and up to 3–6 months post-infusion [depending on the product used] for most patients). Patients should refrain from driving or hazardous activities for at least *2* ~~8~~ weeks following infusion.

CART-2
- Overview Of CAR T-Cell Therapy-Related Toxicities
  - Table header modified: Axicabtagene Ciloleucel, Brexucabtagene Autoleucel, Ciltacabtagene Autoleucel, Idecabtagene Vicleucel, Lisocabtagene Maraleucel, *Obecabtagene Autoleucel,* and Tisagenlecleucel (Also CART-3)

CART-3
- Overview Of CAR T-Cell Therapy-Related Toxicities
  - Immune Effector Cell-Associated Hematotoxicity (ICAHT)/Prolonged Cytopenias
    - ◊ 1st bullet, 1st sub bullet added: Consider evaluation for cytopenias.
  - Infection and Hypogammaglobulinemia
    - ◊ 2nd bullet, 1st sub bullet modified: After anti-CD19 CAR T-cell therapy, consider Ig replacement therapy for select patients with hypogammaglobulinemia (those with serum IgG levels <400–600 mg/dL AND serious or recurrent infections [particularly sinopulmonary]). Administer Ig replacement therapy as up to 400–500 mg/kg IVIG monthly or 100–200 mg/kg subcutaneous Ig (SCIG) weekly. Continue Ig replacement therapy until serum IgG levels normalize and infections resolve. In multiple myeloma (MM), Ig replacement therapy *(IVIG)* should be considered for patients with an IgG <400 mg/dL prior to the administration of B-cell maturation antigen (BCMA)-directed CAR T-cell therapy. Ig replacement therapy during CAR T-cell therapy in patients with MM is not guided by presence of infections.

Continued

Updates in Version 1.2026 of the NCCN Guidelines for Management of CAR T-Cell and Lymphocyte Engager-Related Toxicities:

CART-4
- Toxicities Specific To Anti-BCMA CAR T-Cell Therapy
  - 1st column modified: *Non-ICANS neurotoxicity* ~~Other neurotoxicity events~~
  - 2nd column
    - 3rd bullet modified: *IEC-Parkinsonism* ~~Movement and neurocognitive treatment-emergent AEs (MNTs)~~
      - 1st sub bullet modified: Manifestation is similar to Parkinson's disease *and may include* ~~with~~ bradykinesia, *rigidity, gait change,* asymmetric ~~action and rest~~ tremor, postural instability, hypophonia, personality change, and impaired memory.
      - 2nd sub bullet modified: Risk factors include high baseline tumor burden, grade ≥2 CRS, prior ICANS, high CAR T-cell expansion/persistence. ~~There appears to be male predominance among the reported cases.~~
      - 3rd sub bullet modified: Optimal management has not been determined. The characterized cases of *IEC-Parkinsonism* ~~MNTs~~ are levodopa unresponsive.
        - 1st sub sub bullet modified: For mild symptoms, consider steroids such as 10 mg dexamethasone *2-4 times a day for 3-5 days* ~~daily~~.
        - 2nd sub sub bullet modified: For persistent, severe, or refractory symptoms, and if high circulating CAR T-cell levels are detected, consider chemotherapy such as *high dose (2 g/m^2)* cyclophosphamide to ablate the CAR T cells.
        - 3rd sub sub bullet added: Other alternative strategies may include intrathecal chemotherapy or ruxolitinib.
    - 4th bullet modified: *IEC-cranial nerve palsy and IEC-polyradiculoneuritis* ~~Peripheral neuropathy~~
      - 2nd sub bullet modified: For mild symptoms *(such as unilateral facial nerve palsy), a short course of steroids, such as prednisone 1 mg/kg for 7-10 days recommended* ~~consider treatment with steroids~~.
      - 3rd sub bullet modified: Consider IVIG for acute inflammatory demyelinating polyneuropathy (AIDP)-type picture *or bilateral facial palsy*.
- Footnote f modified: Cohen AD, et al. Blood Cancer J 2022;12:32; Graham CE, et al. Blood 2023;142:1248-1252; Idecabtagene vicleucel *prescribing information* ~~package insert~~; Ciltacabtagene autoleucel *prescribing information* ~~package insert~~; *Graham CE, et al. Lancet Oncol 2025;26:e203-e213; Wirk B, Lim J. J Hematol 2025;14:146-151; Kelly K, et al. Blood Adv 2025;9:3613-3616.*
- Footnote g modified: Other signs and symptoms may include: micrographia, flat affect, reduced facial expression, bradyphrenia, hypomimia, impaired balance, bradykinesia, cogwheel rigidity, ~~gait disturbance, rigidity,~~ abnormal posture, decreased stride length, and neurocognitive impairment.
- Footnote i added: Blumenberg V, et al. Blood 2025;145:2788-2793; Graham CE, et al. Blood 2023;142:1248-1252; and Graham CE, et al. Lancet Oncol 2025:26.e203-e213.
- Footnote j added: Kelly K, et al. Blood Adv 2025;9:3613-3616.
- Footnote k added: Wirk B, Lim J. J Hematol 2025;14:146-151.

CART-5
- Toxicities Specific To Anti-BCMA CAR T-Cell Therapy
  - New section added: Immune Effector Cell (IEC)-Associated Enterocolitis
- Footnote l added: Fortuna GG, et al. Blood Cancer J 2024;14:180.

CART-6
- CRS Related To CAR T-Cell Therapy
  - Page content restructured into an algorithm format.

CART-7
- CRS Related To CAR T-Cell Therapy
  - Page content restructured into an algorithm format.

Continued

Updates in Version 1.2026 of the NCCN Guidelines for Management of CAR T-Cell and Lymphocyte Engager-Related Toxicities:

CART-7A

- Footnote o modified: Organ toxicities should receive a thorough workup and appropriate management. *Organ toxicities associated with CRS may be graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 but they do not influence CRS grading.*
- Footnote p added: Fever is defined as temperature >38°C not attributable to any other cause. In patients who have CRS then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is not required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension or hypoxia.
- Footnote v modified: *An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.* Under conditions of limited tocilizumab availability, consider one of the following conservation strategies: Limit tocilizumab use to a maximum of 2 doses during a CRS episode; Consider using steroids more aggressively during a CRS episode *when there is concurrent ICANS and*; If necessary, consider replacing second dose of tocilizumab with siltuximab or anakinra, although there is very limited evidence to support this approach. (Also CART-9A)
- Footnote z modified: Anakinra may be considered as the first choice for severe CRS refractory to anti–IL-6 therapy and high-dose corticosteroids. Other agents such as siltuximab, ruxolitinib, cyclophosphamide, IVIG, ATG, *dasatinib*, intrathecal chemotherapy, or extracorporeal cytokine adsorption with continuous renal replacement therapy (CRRT) may also be considered, although experience with these agents is limited. Use of these therapies should be balanced against potential safety concerns, such as infection risk.
- The following footnotes were removed:
  - See prescribing information for each agent.
  - For axicabtagene ciloleucel or brexucabtagene autoleucel, can consider tocilizumab if CRS symptoms persist for >24 hours.
  - For lisocabtagene maraleucel, consider tocilizumab for grade 1 CRS that develops <72 hours after infusion and consider adding dexamethasone 10 mg x 1. For CRS developing ≥72 hours after infusion, treat symptomatically.
  - Per the prescribing information for axicabtagene ciloleucel, consider the use of prophylactic steroids in patients after weighing the potential benefits and risks. Steroid prophylaxis for axicabtagene ciloleucel is dexamethasone 10 mg orally once daily for 3 days with the first dose starting pre-CAR T-cell infusion.
  - For axicabtagene ciloleucel, consider IV dexamethasone 10 mg every 24 hours after initial tocilizumab dosing, regardless of clinical response to tocilizumab. For lisocabtagene maraleucel, consider IV dexamethasone 10 mg every 12–24 hours if early-onset CRS. For idecabtagene vicleucel, consider IV dexamethasone 10 mg every 12–24 hours.

CART-9

- CAR T-Cell–Related Neurotoxicity Treatment
  - 7th bullet added: Follow and correct electrolyte abnormalities
  - 9th bullet added: See CART-4 for information about Non-ICANS neurotoxicity associated with anti-BCMA CAR T-cell therapy.
  - Bullet removed: An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines
  - Grade 1, 2nd column, 2nd bullet added: Consider 1 dose of IV dexamethasone 10 mg and reassess.

CART-9A

- Footnote removed: For lisocabtagene maraleucel or idecabtagene vicleucel, if ICANS develops <72 hours after infusion, consider IV dexamethasone 10 mg every 12–24 hours x 2 doses and reassess.

ENGAGE

- This section has been extensively revised.

PRINCIPLES OF PATIENT MONITORING FOR CAR T-CELL–RELATED TOXICITIES

Before and During CAR T-Cell Infusion	Post-CAR T-Cell Infusion
• Baseline cardiac assessment, such as echocardiogram. Consult with cardiology if previous cardiac history or concern from assessment. • Perform central venous access, preferably with double or triple lumen catheter, for IV fluid and possible vasopressors use. • Perform cardiac monitoring at least at the onset of grade 2 CRS until resolution to ≤ grade 1, clinically significant arrhythmia, and additionally as clinically indicated. • Tumor lysis prophylaxis and monitoring are recommended for patients with large tumor burden and aggressive histologies, as per standard institutional guidelines. • Start seizure prophylaxis on the day of infusion when there is high risk of ICANS based on patient factors or product type (eg, oral levetiracetam 500–750 mg every 12 hours for 30 days). • Baseline neurologic evaluation, including ICE scores (for adults) or Cornell Assessment of Pediatric Delirium (CAPD) scores (for children <12 years or non-verbal adults) prior to chimeric antigen receptor (CAR) T-cell therapy. Consider baseline brain MRI. • Baseline C-reactive protein (CRP) and serum ferritin (prior to lymphodepleting chemotherapy)[a] • Relevant serologic screening includes HIV, HBV, and HCV. Consider CMV and additional screening based on epidemiologic risk.	• Hospitalization or extremely close outpatient monitoring at centers with CAR T-cell experience. Close monitoring in the hospital is preferable with current products used for adults; however, extremely close outpatient monitoring may be possible at centers with outpatient transplant experience. • Hospitalization is warranted for patients at the first sign of neurotoxicity (including change in mental status). Patients with CRS who experience a response to tocilizumab and/or dexamethasone can be monitored closely in outpatient settings. • Monitor CBC, CMP (including magnesium and phosphorus), and coagulation profile daily. • CRP and serum ferritin should be rechecked at least 3 times per week for 2 weeks post-infusion. Consider daily checks during CRS. CRP can normalize prior to the onset of neurotoxicity. • Vital signs to allow clinical assessment for CRS should be done at least every 8 hours, or when the patient's status changes, during the peak window of CRS risk (typically the first 1–2 weeks post-infusion). • Neurotoxicity assessment should be done at least twice daily until hospital discharge, and urgently thereafter if there is a change in the patient's status or routinely every 2–4 weeks, extending to 2 months. Consider a physical assessment and/or tests to check handwriting and general function/gait (eg, Timed Up and Go [TUG] test). If neurologic concern develops, more frequent assessments are recommended. • Monitor for CRS, neurotoxicity, and other toxicities for the duration recommended by the CAR product prescribing information (at least 4 weeks and up to 3–6 months post-infusion [depending on the product used] for most patients). Patients should refrain from driving or hazardous activities for at least 2 weeks following infusion.

Overview of CAR T-Cell Therapy-Related Toxicities (CART-2)

[a] Assessing baseline values would allow for calculation of the CAR-HEMATOTOX score to predict the risk for immune effector cell-associated hematotoxicity (ICAHT) and infection. Rejeski K, et al. Blood 2021;138:2499-2513; Rejeski K, et al. J Hematol Oncol 2023;16:88.

Note: All recommendations are category 2A unless otherwise indicated.

OVERVIEW OF CAR T-CELL THERAPY-RELATED TOXICITIES

	Axicabtagene Ciloleucel, Brexucabtagene Autoleucel, Ciltacabtagene Autoleucel, Idecabtagene Vicleucel, Lisocabtagene Maraleucel, Obecabtagene Autoleucel, and Tisagenlecleucel[b]
Cytokine Release Syndrome (CRS) (CART-6)	• Typical time to onset: 2–3 days; however, CRS may occur as early as hours after infusion and as late as 10–15 days post-infusion; be aware of the typical onset for the specific product used. • Typical duration: 7–8 days; could be longer for specific products. • Manifestation may include fever, hypotension, tachycardia, hypoxia, and chills. CRS may be associated with cardiac, hepatic, and/or renal dysfunction. Consider cardiology follow-up for these symptoms. • Serious events may include hypotension, hypoxia, atrial fibrillation and ventricular tachycardia, cardiac arrest, cardiac failure, renal insufficiency, and capillary leak syndrome.[c]
Neurologic Toxicity/ Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) (CART-8)	• Typical time to onset: 4–10 days • Transient neurologic symptoms can be heterogeneous and include encephalopathy, delirium, aphasia, lethargy, headache, tremor, myoclonus, dizziness, motor dysfunction, ataxia, sleep disorder (eg, insomnia), anxiety, agitation, and signs of psychosis. • Serious events including seizures, depressed level of consciousness, as well as fatal and serious cases of cerebral edema have occurred.
Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome (IEC-HS)	• Definition of IEC-HS: The development of a pathologic and biochemical hyperinflammatory syndrome independent from CRS and ICANS that: 1) manifests with features of macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH); 2) is attributable to IEC therapy; and 3) is associated with progression or new onset of cytopenias, hyperferritinemia, coagulopathy with hypofibrinogenemia, and/or transaminitis. • Criteria for considering IEC-HS (previously called HLH/MAS): ▸ Elevated ferritin (>2 x ULN or baseline [at time of infusion]) and/or rapidly rising (per clinical assessment) ▸ For other criteria to identify IEC-HS and treatment options, refer to: Hines MR, et al. Transplant Cell Ther 2023;29:438.e1-438.e16.

[b] See prescribing information for each agent and institutional protocols.
[c] Alvi RM, et al. J Am Coll Cardiol 2019;74:3099-3108; Ghosh AK, et al. JACC CardioOncol 2020;2:97-109.

Continued

Note: All recommendations are category 2A unless otherwise indicated.

OVERVIEW OF CAR T-CELL THERAPY-RELATED TOXICITIES

	Axicabtagene Ciloleucel, Brexucabtagene Autoleucel, Ciltacabtagene Autoleucel, Idecabtagene Vicleucel, Lisocabtagene Maraleucel, Obecabtagene Autoleucel, and Tisagenlecleucel[b]
Immune Effector Cell-Associated Hematotoxicity (ICAHT)/ Prolonged Cytopenias	• Patients may exhibit cytopenias for weeks to months following lymphodepleting chemotherapy and CAR T-cell therapy infusion.[d,e] ▸ Consider evaluation for cytopenias. ▸ First-line management of cytopenias should be standard transfusion and growth factor support as needed. ▸ Optimal management of severe cytopenias refractory to standard management is still unclear; stem cell boosts can be considered if available, although data on this treatment are limited.
Infection and Hypogammaglobulinemia	• Recommend *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis (at minimum 6 months) and varicella zoster virus (VZV) prophylaxis, following CAR T-cell treatment. • Long-term B-cell aplasia and hypogammaglobulinemia can occur in patients with a complete remission after CAR T-cell therapy infusion. ▸ After anti-CD19 CAR T-cell therapy, consider immunoglobulin (Ig) replacement therapy for select patients with hypogammaglobulinemia (those with serum IgG levels <400–600 mg/dL AND serious or recurrent infections [particularly sinopulmonary]). Administer Ig replacement therapy as up to 400–500 mg/kg intravenous immunoglobulin (IVIG) monthly or 100–200 mg/kg subcutaneous Ig (SCIG) weekly. Continue Ig replacement therapy until serum IgG levels normalize and infections resolve. In multiple myeloma (MM), Ig replacement therapy (IVIG) should be considered for patients with an IgG <400 mg/dL prior to the administration of B-cell maturation antigen (BCMA)-directed CAR T-cell therapy. Ig replacement therapy during CAR T-cell therapy in patients with MM is not guided by presence of infections.

[b] See prescribing information for each agent and institutional protocols.
[d] Consider granulocyte colony-stimulating factor (G-CSF) for as long as necessary; however, granulocyte-macrophage colony-stimulating factor (GM-CSF) is not recommended in the setting of CAR T-cell therapy.
[e] Rejeski K, et al. Blood 2023;142:865-877.

Note: All recommendations are category 2A unless otherwise indicated.

TOXICITIES SPECIFIC TO ANTI-BCMA CAR T-CELL THERAPY

	Ciltacabtagene Autoleucel and Idecabtagene Vicleucel[b]
Non-ICANS Neurotoxicity[f]	• Emerging data suggest that other neurotoxicity events, with symptoms that do not fit the current definition for ICANS, may occur with anti-BCMA CAR T-cell therapy. • Typical time to onset is 11–108 days (later than ICANS) • IEC-Parkinsonism ▸ Manifestation is similar to Parkinson's disease and may include bradykinesia, rigidity, gait change, asymmetric tremor, postural instability, hypophonia, personality change, and impaired memory.[g] ▸ Risk factors include high baseline tumor burden, grade ≥2 CRS, prior ICANS, and high CAR T-cell expansion/persistence.[h] ▸ Optimal management has not been determined. The characterized cases of IEC-Parkinsonism are levodopa unresponsive. ◊ For mild symptoms, consider steroids such as 10 mg dexamethasone 2–4 times a day for 3–5 days. ◊ For persistent, severe, or refractory symptoms, and if high circulating CAR T-cell levels are detected,[h] consider chemotherapy such as high dose (2 g/m^2) cyclophosphamide[i] to ablate the CAR T cells. ◊ Other alternative strategies may include intrathecal chemotherapy[j] or ruxolitinib.[k] ◊ Use of these therapies is currently based on very limited experience and should be balanced against potential safety concerns, such as infection risk. • IEC-cranial nerve palsy and IEC-polyradiculoneuritis ▸ Types of neuropathies reported include lower motor neuron facial paralysis, other cranial nerve palsy, peripheral sensory neuropathy, and peripheral motor neuropathy. ▸ For mild symptoms (such as unilateral facial nerve palsy), a short course of steroids, such as prednisone 1 mg/kg for 7–10 days, is recommended. ▸ Consider IVIG for acute inflammatory demyelinating polyneuropathy (AIDP)-type picture or bilateral facial palsy.

Continued

[b] See prescribing information for each agent and institutional protocols.
[f] Cohen AD, et al. Blood Cancer J 2022;12:32; Graham CE, et al. Blood 2023;142:1248-1252; Idecabtagene vicleucel prescribing information; Ciltacabtagene autoleucel prescribing information; Graham CE, et al. Lancet Oncol 2025;26:e203-e213; Wirk B, Lim J. J Hematol 2025;14:146-151; Kelly K, et al. Blood Adv 2025;9:3613-3616.
[g] Other signs and symptoms may include: micrographia, flat affect, reduced facial expression, bradyphrenia, hypomimia, impaired balance, bradykinesia, cogwheel rigidity, abnormal posture, decreased stride length, and neurocognitive impairment.
[h] Absolute lymphocyte count (ALC), when very elevated, may be a surrogate for high CAR T-cell expansion in this setting.
[i] Blumenberg V, et al. Blood 2025;145:2788-2793; Graham CE, et al. Blood 2023;142:1248-1252; and Graham CE, et al. Lancet Oncol 2025:26.e203-e213.
[j] Kelly K, et al. Blood Adv 2025;9:3613-3616.
[k] Wirk B, Lim J. J Hematol 2025;14:146-151.

Note: All recommendations are category 2A unless otherwise indicated.

TOXICITIES SPECIFIC TO ANTI-BCMA CAR T-CELL THERAPY

	Ciltacabtagene Autoleucel and Idecabtagene Vicleucel[b]
Immune Effector Cell (IEC)-Associated Enterocolitis[l]	• Emerging data suggest IEC-associated enterocolitis is a distinct but rare complication of CAR T-cell therapy that can be associated with significant morbidity and mortality (due to bowel perforation and/or sepsis). • Typically presents with relatively acute-onset non-bloody diarrhea approximately 1–3 months after CAR T-cell infusion. • Infectious workup should be obtained and negative (eg, viral, *C. difficile*, enteric pathogens). • Colonoscopy with histopathologic examination uniformly demonstrate inflammation, including intraepithelial lymphocytosis and villous blunting. Where available, CAR-specific immunofluorescence stains may confirm CAR T-cell presence within the lamina propria. • Prompt initiation of systemic steroids is indicated if IEC-associated enterocolitis is suspected and infection has been ruled out. • In cases of steroid-refractory diarrhea or for recurrent diarrhea with steroid taper, infliximab or vedolizumab may be used as adjunctive or steroid-sparing agents.

[b] See prescribing information for each agent and institutional protocols.
[l] Fortuna GG, et al. Blood Cancer J 2024;14:180.

Note: All recommendations are category 2A unless otherwise indicated.

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Management of CAR T-Cell-Related Toxicities

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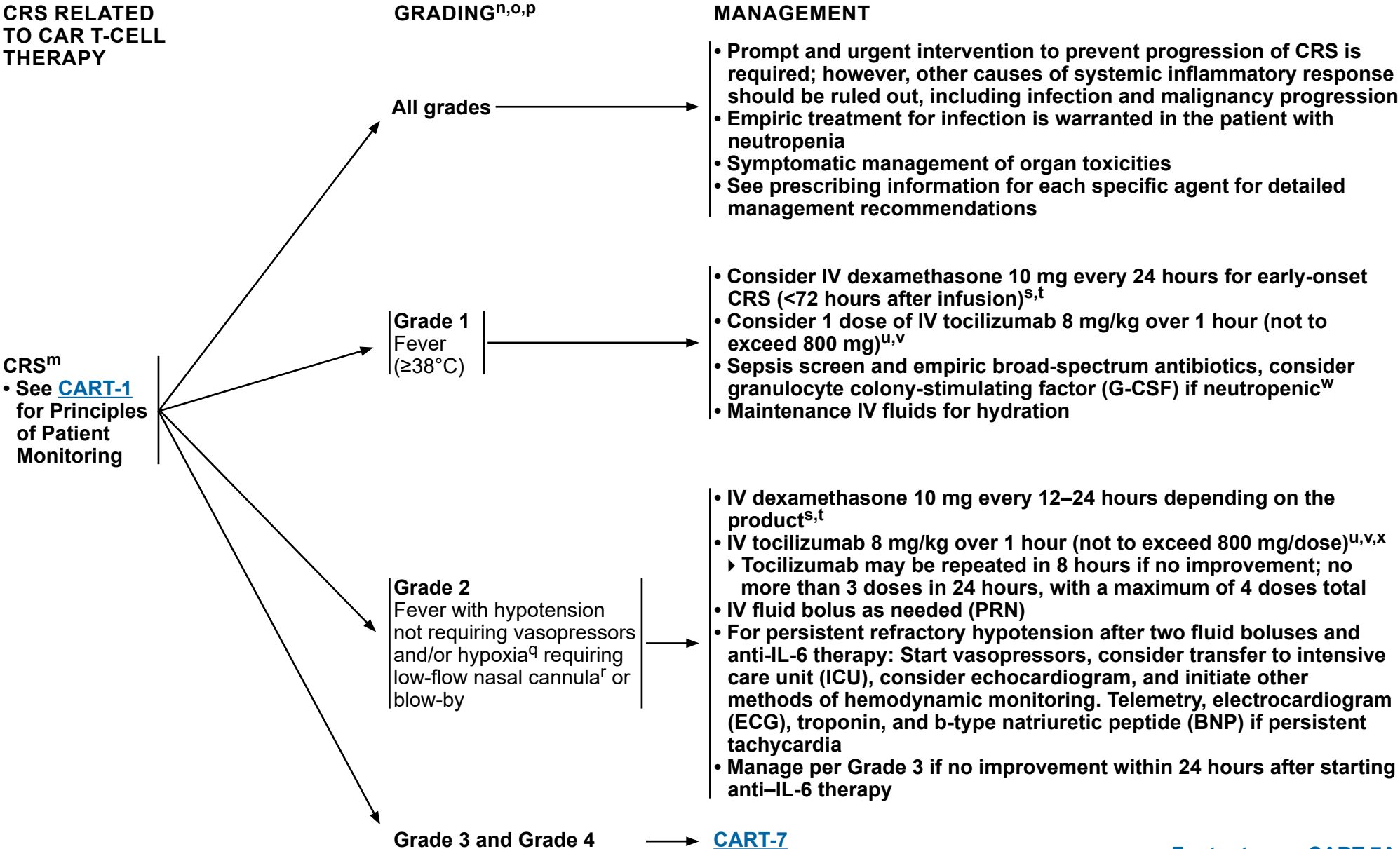

Footnotes on CART-7A

Note: All recommendations are category 2A unless otherwise indicated.

CRS RELATED TO CAR T-CELL THERAPY	GRADING[n,o,p]	MANAGEMENT
CRS Grade 3 Fever with hypotension requiring a vasopressor with or without vasopressin and/or hypoxia requiring high-flow cannula,[r] face mask, non-rebreather mask, or Venturi mask	→	• **ICU care, obtain echocardiogram, and perform hemodynamic monitoring** • **Supplemental oxygen** • **IV fluid bolus and vasopressors PRN** • **IV dexamethasone 10 mg every 6–12 hours depending on the product.[s,t] If refractory, manage as Grade 4** • **IV tocilizumab 8 mg/kg over 1 hour (not to exceed 800 mg/dose)[u,v,x] Repeat in 8 hours if no improvement; no more than 3 doses in 24 hours, with a maximum of 4 doses total if maximum dose not reached within 24-hour period**
CRS Grade 4 Fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (eg, continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, mechanical ventilation)	→	• **ICU care and hemodynamic monitoring** • **Mechanical ventilation PRN** • **IV fluid bolus and vasopressors PRN** • **IV dexamethasone 10 mg every 6 hours.[s,t] If refractory, consider 3 doses of IV methylprednisolone 1–2 g/day depending on the product. If refractory, consider dosing every 12 hours[y]** • **IV tocilizumab 8 mg/kg over 1 hour (not to exceed 800 mg/dose).[u,v,x] Repeat in 8 hours if no improvement; no more than 3 doses in 24 hours, with a maximum of 4 doses total if maximum dose not reached within 24-hour period** • **Other lines of therapy may be considered[z]**

Footnotes on CART-7A

Note: All recommendations are category 2A unless otherwise indicated.

FOOTNOTES

[m] If IEC-HS is suspected, refer to treatment options in Hines MR, et al. Transplant Cell Ther 2023;29:438.e1-438.e16.
[n] With permission from Elsevier: Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant 2019;25:625-638. DOI: https://doi.org/10.1016/j.bbmt.2018.12.758. This article is published under the terms of the Creative Commons Attribution-NonCommercial-No Derivatives License (CC BY NC ND).
[o] Organ toxicities should receive a thorough workup and appropriate management. Organ toxicities associated with CRS may be graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 but they do not influence CRS grading.
[p] Fever is defined as temperature >38°C not attributable to any other cause. In patients who have CRS then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is not required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension or hypoxia.
[q] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with a temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
[r] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/min.
[s] Antifungal prophylaxis and close monitoring for breakthrough infections per institutional guidelines should be strongly considered in patients receiving steroids for the treatment of CRS and/or neurotoxicity.
[t] Alternative steroids at an equivalent dose may be considered.
[u] Due to an increased risk of GI perforation with IL-6 inhibitors (tocilizumab), assess for history of clinically active diverticular disease prior to initiating therapy and use with caution in those patients.
[v] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines. Under conditions of limited tocilizumab availability, consider one of the following conservation strategies: limit tocilizumab use to a maximum of 2 doses during a CRS episode; consider using steroids more aggressively during a CRS episode when there is concurrent ICANS; and, if necessary, consider replacing second dose of tocilizumab with siltuximab or anakinra, although there is very limited evidence to support this approach.
[w] GM-CSF is not recommended in the setting of CAR T-cell therapy.
[x] After each dose, assess need for subsequent dosing.
[y] For example, IV methylprednisolone 1000 mg/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days.
[z] Anakinra may be considered as the first choice for severe CRS refractory to anti–IL-6 therapy and high-dose corticosteroids. Other agents such as siltuximab, ruxolitinib, cyclophosphamide, IVIG, antithymocyte globulin (ATG), dasatinib, intrathecal chemotherapy, or extracorporeal cytokine adsorption with continuous renal replacement therapy (CRRT) may also be considered, although experience with these agents is limited. Use of these therapies should be balanced against potential safety concerns, such as infection risk.

Note: All recommendations are category 2A unless otherwise indicated.

CAR T-CELL–RELATED NEUROTOXICITY GRADING

Immune Effector Cell-Associated Encephalopathy (ICE) Assessment Tool[n]

- **Orientation: orientation to year, month, city, hospital: 4 points**
- **Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points**
- **Following commands: ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point**
- **Writing: ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point**
- **Attention: ability to count backwards from 100 by 10: 1 point**

ICE Scoring

- **7–9, grade 1**
- **3–6, grade 2**
- **0–2, grade 3**
- **0 due to patient unarousable and unable to perform ICE assessment, grade 4**

ASTCT Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Consensus Grading for Adults[n]

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

Neurotoxicity Domain[aa]	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[bb]	7–9	3–6	0–2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[cc]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[dd]	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

[n] With permission from Elsevier: Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25:625-638. DOI: https://doi.org/10.1016/j.bbmt.2018.12.758. This article is published under the terms of the Creative Commons Attribution-NonCommercial-No Derivatives License (CC BY NC ND).

[aa] Other signs and symptoms such as headache, tremor, myoclonus, asterixis, and hallucinations may occur and could be attributable to IEC engaging therapies. Although they are not included in this grading scale, careful attention and directed therapy may be warranted.

[bb] 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.

[cc] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

[dd] 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.

Note: All recommendations are category 2A unless otherwise indicated.

Treatment (CART-9)

CAR T-CELL–RELATED NEUROTOXICITY TREATMENT

Assessment and Supportive Care Recommendations (all grades)

- **Neurologic assessment and grading at least twice a day to include cognitive assessment and motor weakness**
- **MRI of the brain with and without contrast (or brain CT if MRI is not feasible) for ≥ grade 2 neurotoxicity**
- **Neurology consultation at first sign of neurotoxicity**
- **Conduct electroencephalogram (EEG) for seizure activity for ≥ grade 2 neurotoxicity**
- **Aspiration precautions; IV hydration**
- **Consider prophylactic anakinra for patients at high risk of developing high-grade ICANS[ee]**
- **Follow and correct electrolyte abnormalities**
- **Use caution when prescribing medications that can cause central nervous system (CNS) depression (aside from those needed for seizure prophylaxis/treatment)**
- **See CART-4 for information about Non-ICANS neurotoxicity associated with anti-BCMA CAR T-cell therapy**

Treatment by Grade	No Concurrent CRS[gg]	Additional Therapy if Concurrent CRS[u]
Grade 1	• Supportive care • Consider 1 dose of IV dexamethasone 10 mg and reassess.	IV tocilizumab 8 mg/kg over 1 hour (not to exceed 800 mg/dose)[u,v,kk]
Grade 2	• Supportive care • 1 dose of IV dexamethasone 10 mg and reassess. Can repeat every 6–12 hours, if no improvement.	Anti-IL-6 therapy as per grade 1[kk] Consider transferring patient to ICU if neurotoxicity associated with grade ≥2 CRS
Grade 3[ff]	• ICU care is recommended. • IV dexamethasone 10 mg every 6 hours or IV methylprednisolone, 1 mg/kg every 12 hours.[s,hh] If not responsive to steroids or worsening symptoms, consider adding anakinra 100 mg every 6 hours.[ii] • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity.	Anti-IL-6 therapy as per grade 1[kk]
Grade 4[ff]	• ICU care, consider mechanical ventilation for airway protection • High-dose steroids.[s,jj] If not responsive to steroids, consider adding anakinra 100 mg every 6 hours.[ii] • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity. • Treat convulsive status epilepticus per institutional guidelines.	Anti-IL-6 therapy as per grade 1[kk]

Footnotes on CART-9A

Note: All recommendations are category 2A unless otherwise indicated.

FOOTNOTES

[s] Antifungal prophylaxis and close monitoring for breakthrough infections per institutional guidelines should be strongly considered in patients receiving steroids for the treatment of CRS and/or neurotoxicity.

[u] Due to an increased risk of GI perforation with IL-6 inhibitors (tocilizumab), assess for history of clinically active diverticular disease prior to initiating therapy and use with caution in those patients.

[v] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines. Under conditions of limited tocilizumab availability, consider one of the following conservation strategies: Limit tocilizumab use to a maximum of 2 doses during a CRS episode; Consider using steroids more aggressively during a CRS episode when there is concurrent ICANS; If necessary, consider replacing second dose of tocilizumab with siltuximab or anakinra, although there is very limited evidence to support this approach.

[ee] Park, JH, et al. Nat Med 2023;29:1710-1717; Nath K, et al. Blood 2023;142(Suppl):357.

[ff] Patients should undergo assessment for papilledema or other signs of elevated intracranial pressure (ICP). If ICP is excluded, a diagnostic lumbar puncture may be considered for patients with grade 3–4 neurotoxicity.

[gg] If dexamethasone is used for prophylaxis of CRS, there may be an increased risk of grade 4 and prolonged neurologic toxicities.

[hh] For axicabtagene ciloleucel or brexucabtagene autoleucel, IV methylprednisolone 1 g daily for 3–5 days may be preferable.

[ii] Gazeau N, et al. Transplant Cell Ther 2023;29:430-437.

[jj] For example, IV methylprednisolone 1000 mg/day (may consider twice a day) for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days.

[kk] Repeat tocilizumab every 8 hours PRN if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.

Note: All recommendations are category 2A unless otherwise indicated.

OVERVIEW OF LYMPHOCYTE ENGAGER-RELATED TOXICITIES

General Principles

- **The risks associated with each agent vary significantly; therefore, clinicians should refer to the individual FDA-approved prescribing information and appropriate clinical trial protocols for guidance on toxicity management after initiation of lymphocyte engagers (eg, T-cell–engaging bispecific antibodies). Institutions administering these therapies should have clear, agent-specific protocols in place to facilitate timely management of severe reactions such as CRS, ICANS, and other toxicities.**
- **Disease-specific NCCN Guidelines with recommendations for prophylaxis and management of lymphocyte-engager–related toxicities offer additional guidance and are referenced in this section where available.**

CRS

- **CD3-based lymphocyte engager therapies carry a universal risk of CRS.**
- **Patients at elevated risk for high-grade CRS or poor tolerance of CRS include those with high tumor burden, rapid tumor progression, high inflammatory markers (eg, ferritin, CRP), higher age, comorbidities, or rapid onset of CRS <4 hours from start of infusion.**
- **Signs and symptoms may include fever, hypotension, tachycardia, hypoxia, and chills. CRS may be associated with cardiac, hepatic, and/or renal dysfunction. Serious events may include hypotension, hypoxia, atrial fibrillation and ventricular tachycardia, cardiac arrest, cardiac failure, renal insufficiency, and capillary leak syndrome.**
- **CRS may occur as early as hours after infusion and as late as 10–15 days post-infusion; be aware of the typical onset for the specific product used. Typical time to onset: 1–3 days; typical duration: 7–8 days; however, may be longer for specific products.**
- **CRS risk requires frequent monitoring and early intervention to prevent progression to severe or refractory CRS.**
- **Due to risk of CRS, lymphocyte engager therapies may require inpatient initiation for monitoring, with transition to ambulatory settings dictated by patient tolerability.**
- **Consider providing patients with one dose of oral dexamethasone 8–12 mg to take if needed for severe CRS (eg, fever, chills, rigors, difficulty breathing, feeling severely ill) at home prior to travel to Emergency Department if instructed to do so.**
- **Prophylactic tocilizumab may be considered to reduce the risk of CRS (ie, in patients with MM prior to first dose of talquetamab-tgvs or teclistamab-cqyv). An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.**
- **See ENGAGE-3 for CRS grading.[a] For guidance on CRS management, refer to ENGAGE-3 and the FDA-approved prescribing information.**

Continued

[a] Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625-638.

Note: All recommendations are category 2A unless otherwise indicated.

OVERVIEW OF LYMPHOCYTE ENGAGER-RELATED TOXICITIES

ICANS

- **ICANS is a CNS toxicity associated with lymphocyte engager therapy.**
- **ICANS is characterized by neurologic deficits, often concomitantly with CRS. Transient neurologic symptoms can be heterogeneous and include encephalopathy, delirium, aphasia, lethargy, headache, tremor, myoclonus, dizziness, motor weakness, ataxia, sleep disorder (eg, insomnia), anxiety, agitation, and signs of psychosis. Serious events including seizures, depressed level of consciousness, as well as fatal and serious cases of cerebral edema have occurred. Typical onset occurs during step-up dosing.**
- **Early intervention to prevent progression to severe ICANS is important.**
- **See CART-8 for ICANS Assessment/Grading. For guidance on ICANS management, refer to ENGAGE-5 and the FDA-approved prescribing information.**

Other Toxicities

- **Other common toxicities vary based on agent; see ENGAGE-6 for additional information.**

Note: All recommendations are category 2A unless otherwise indicated.

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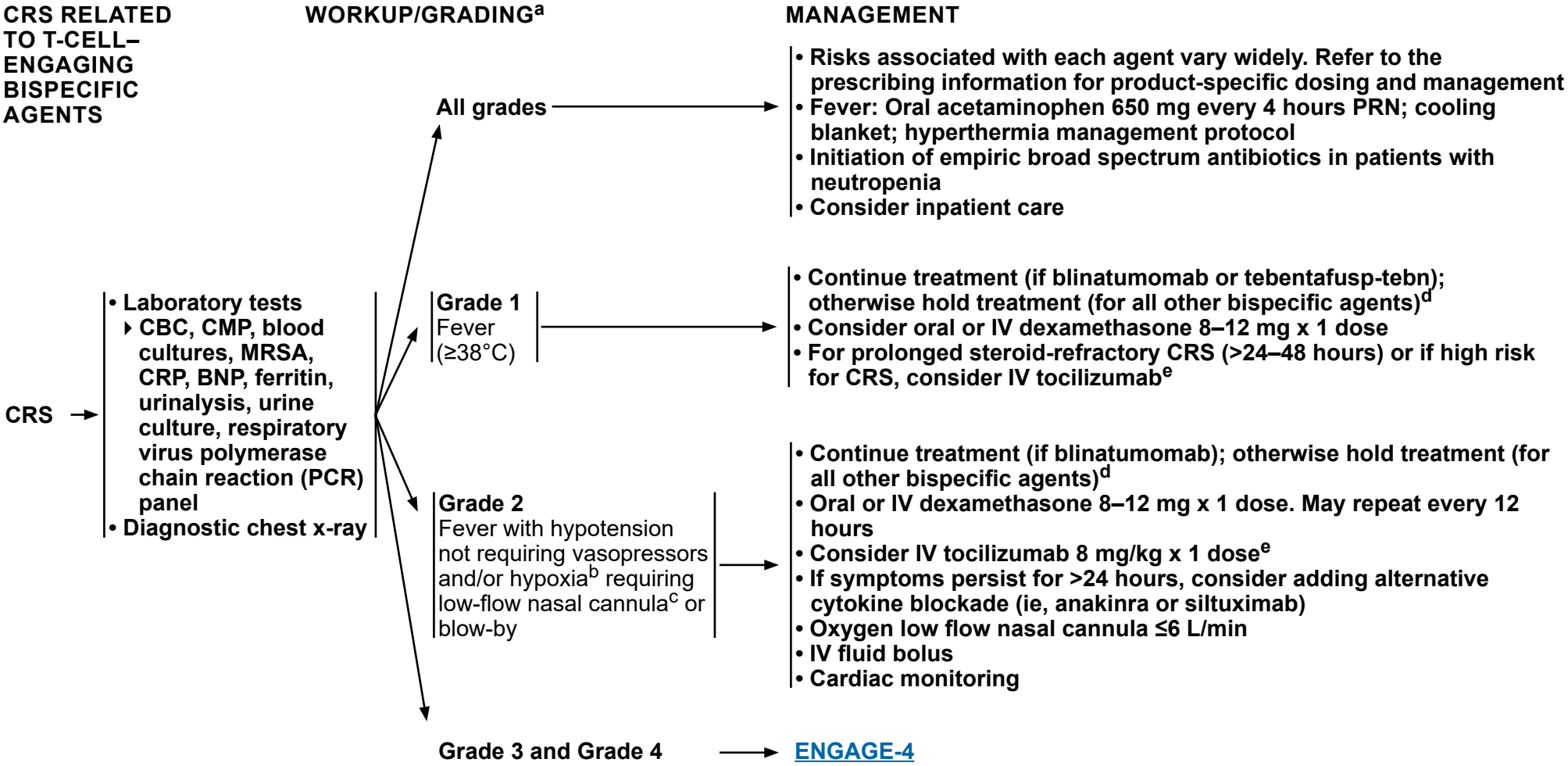

[a] Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625-638.

[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with a temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

[c] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/min.

[d] Considerations for Rechallenge of T-Cell–Engaging Bispecific Antibody Therapy After CRS (ENGAGE-7).

[e] Administer over 1 hour within 2 hours of onset. Maximum dose 800 mg; 3 doses in 24 hours; maximum of 4 doses. If no clinical improvement in oxygenation, hypotension, fever, or other symptoms, dosing may be repeated every 8 hours. Median time to response after first dose: hours to days (range is generally 1–12 days). An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

Note: All recommendations are category 2A unless otherwise indicated.

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CRS RELATED TO T-CELL–ENGAGING BISPECIFIC AGENTS	GRADING[a]	MANAGEMENT
CRS Grade 3[f] Fever with hypotension requiring a vasopressor with or without vasopressin and/or hypoxia requiring high-flow cannula,[c] face mask, non-rebreather mask, or Venturi mask	→	• **Hold treatment (for all bispecific agents)[d]** • **ICU care** • **IV fluid bolus PRN, vasopressors PRN** • **IV dexamethasone 10 mg x 1 dose. May repeat every 6 hours** • **IV tocilizumab 8 mg/kg x 1 dose[e]** • **If symptoms persist despite combination therapy with tocilizumab and steroids, consider adding alternative cytokine blockades (ie, anakinra or siltuximab)**
CRS Grade 4[f] Fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation, mechanical ventilation)	→	• **Permanently discontinue treatment (for all bispecific agents)[d]** • **ICU care** • **IV methylprednisolone 1000 mg every 24 hours x 3 days** • **IV tocilizumab 8 mg/kg x 1 dose[e]** • **If symptoms persist despite combination therapy with tocilizumab and steroids, consider adding alternative cytokine blockades (ie, anakinra or siltuximab)** • **Multiple vasopressors, excluding vasopressin** • **Positive pressure: CPAP, BiPAP, intubation** • **Echocardiogram**

[a] Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625-638.
[c] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/min.
[d] Considerations for Rechallenge of T-Cell–Engaging Bispecific Antibody Therapy After CRS (ENGAGE-7).
[e] Administer over 1 hour within 2 hours of onset. Maximum dose 800 mg; 3 doses in 24 hours; maximum of 4 doses. If no clinical improvement in oxygenation, hypotension, fever or other symptoms, dosing may be repeated every 8 hours. Median time to response after first dose: hours to days (range is generally 1–12 days). An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[f] Occurrence of Grade 3 or 4 CRS with T-cell–engaging bispecific agents is rare. Consider alternative etiologies (eg, infection).

Note: All recommendations are category 2A unless otherwise indicated.

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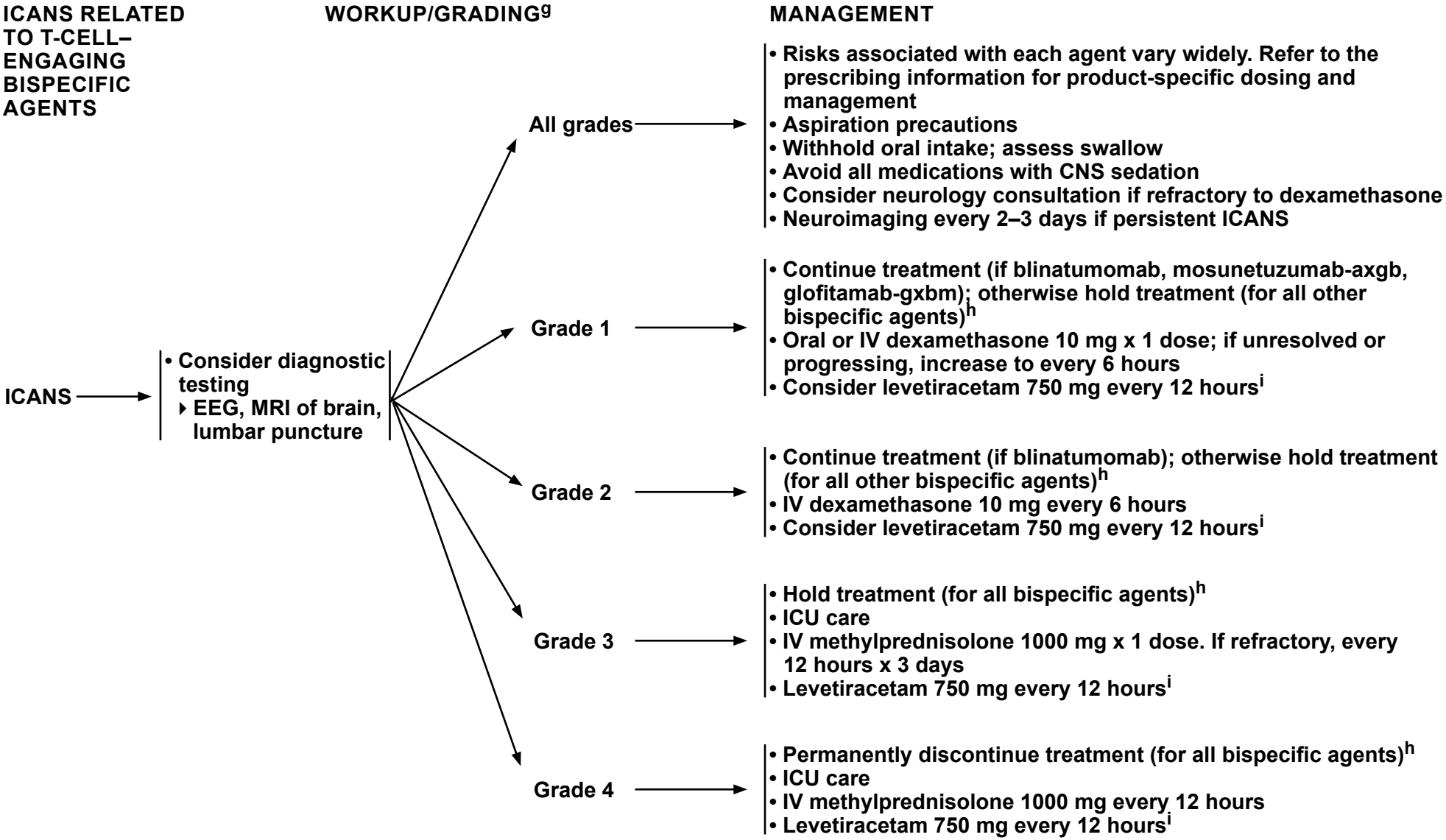

[g] Refer to CART-6 for ICANS grading.
[h] Considerations for Rechallenge of T-Cell–Engaging Bispecific Antibody Therapy After ICANS (ENGAGE-8).
[i] Depending on seizure risk associated with agent used.

Note: All recommendations are category 2A unless otherwise indicated.

OTHER TOXICITIES RELATED TO T-CELL–ENGAGING BISPECIFIC ANTIBODY THERAPY

The risks associated with each agent vary significantly; therefore, clinicians should refer to the individual FDA-approved prescribing information and appropriate clinical trial protocols for guidance on toxicity management after initiation of lymphocyte engagers (eg, T-cell–engaging bispecific antibodies).

- See disease-specific NCCN Guidelines for additional guidance on the management of common toxicities unique to each agent.
- Low-grade toxicities are typically managed by dose interruption until resolution of the toxicity, followed by re-challenge at the same or lower dose.

Cancer Type	Approved Agent	Infection Considerations[k]	Common Unique Toxicities
Multiple Myeloma (MM)	• Elranatamab-bcmm • Talquetamab-tgvs • Teclistamab-cqyv • Linvoseltamab-gcpt	• NCCN Guidelines for Multiple Myeloma	• Hypogammaglobulinemia • Specific to talquetamab-tgvs: dysgeusia, skin and nail changes • Specific to linvoseltamab-gcpt: musculoskeletal pain, fatigue, nausea, headache, and dyspnea
B-Cell Acute Lymphoblastic Leukemia (B-ALL)	• Blinatumomab	• NCCN Guidelines for Acute Lymphoblastic Leukemia	• See blinatumomab prescribing information (includes hypogammaglobulinemia, tumor lysis syndrome, liver enzyme elevations, and others)
B-Cell Lymphomas[j]	• Epcoritamab-bysp • Glofitamab-gxbm • Mosunetuzumab-axgb	• Neutropenia,[l] PJP prophylaxis,[m] VZV prophylaxis,[n] hypogammaglobulinemia[o]	• Hypogammaglobulinemia
Small Cell Lung Cancer	• Tarlatamab-dlle	• Neutropenia[l]	• Dysgeusia
Uveal Melanoma	• Tebentafusp-tebn	• N/A	• Rash, elevated LFTs

[j] Crombie JL, et al. Blood. 2024;143:1565-1575.
[k] NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[l] For patients with absolute neutrophil count (ANC) <0.5 x 10^9/L or clinically indicated, provide fluoroquinolone and fluconazole prophylaxis. For patients with ANC <1 x 10^9/L or clinically indicated, provide support with G-CSF.
[m] PJP prophylaxis is recommended until the end of therapy or until CD4 >0.2 x 10^9/L, whichever is longer.
[n] VZV prophylaxis is recommended until the end of therapy or until CD4 >0.2 x 10^9/L, whichever is longer.
[o] Ig levels should be monitored regularly and Ig replacement should be considered for individuals with recurrent, persistent, or severe infection and IgG <400 mg/dL.

Note: All recommendations are category 2A unless otherwise indicated.

CONSIDERATIONS FOR RE-CHALLENGE OF T-CELL–ENGAGING BISPECIFIC ANTIBODY THERAPY AFTER CRS

The risks associated with each agent vary significantly; therefore, clinicians should refer to the individual FDA-approved prescribing information and appropriate clinical trial protocols for guidance on toxicity management after initiation of lymphocyte engagers (eg, T-cell–engaging bispecific antibodies).

Agent	Current Dose	Next Dose
Glofitamab-gxbm IV Mosunetuzumab-axgb IV	• Grade 1 & 2: Interrupt therapy; if symptoms resolve, resume at 50% of rate • Grade 3: Hold	• Grade 1 & 2: CRS resolved at least 72 hours before next dose • Grade 3: Hospitalize for 24 hours for next dose
Elranatamab-bcmm Linvoseltamab-gcpt IV Talquetamab-tgvs SQ Teclistamab-cqyv SQ	• Hold dosing if not already completed administration	• Grade 1 & 2: CRS resolved for 24 hours • Grade 3: Hospitalize for 48 hours for next dose
Epcoritamab-bysp SQ	• Hold dosing if not already completed administration	• Grade 1 & 2: CRS resolved for 24 hours • Grade 3: Hospitalize for 24 hours for next dose
Blinatumomab continuous IV infusion	• Grade 1 & 2: Continue therapy • Grade 3: Interrupt; resume at 9 mcg/day; can be escalated to 28 mcg/day after 7 days	• N/A
Tarlatamab-dlle IV	• Hold; if symptoms resolve, resume at next scheduled dose	• Grade 1: CRS resolved for 24 hours • Grade 2 & 3: CRS resolved; hospitalize for at minimum 22 hours for next dose
Tebentafusp-tebn IV	• Grade 1: Continue therapy • Grade 2: Hold if not already administered • Grade 3 (first occurrence): Hold • Grade 3 (recurrent or >48 hours): Discontinue	• Grade 2 (recurrent or persistent): Premedicate with oral dexamethasone 4 mg 30 minutes prior to the next dose • Grade 3 (first occurrence): Premedicate with oral dexamethasone 4 mg 30 minutes before next dose, resuming at same dose; Resume escalation once dose tolerated • Grade 3 (recurrent or >48 hours): Permanently discontinue
All Grade 4: Permanently discontinue bispecific therapy.		

Note: All recommendations are category 2A unless otherwise indicated.

CONSIDERATIONS FOR RE-CHALLENGE OF T-CELL–ENGAGING BISPECIFIC ANTIBODY THERAPY AFTER ICANS

The risks associated with each agent vary significantly; therefore, clinicians should refer to the individual FDA-approved prescribing information and appropriate clinical trial protocols for guidance on toxicity management after initiation of lymphocyte engagers (eg, T-cell–engaging bispecific antibodies).

Agent	Current Dose	Next Dose
Mosunetuzumab-axgb IV	• Grade 1: Continue therapy • Grade 2 & 3: Hold therapy	• Grade 2 & 3: Resume if symptoms resolve to grade 1 or baseline for at least 72 hours • Grade 3 recurrent: Permanently discontinue
Glofitamab-gxbm IV	• Grade 1: Continue therapy • Grade 2: Hold therapy until symptoms improve to Grade 1 or baseline • Grade 3: Hold therapy	• Grade 3: Resume if symptoms resolve to grade 1 or baseline for at least 7 days
Elranatamab-bcmm SQ **Linvoseltamab-gcpt IV** **Talquetamab-tgvs SQ** **Teclistamab-cqyv SQ**	• Hold therapy	• Grade 2 & 3: Resume if symptoms resolved to grade 1 or baseline • Grade 3 recurrent: Permanently discontinue
Epcoritamab-bysp SQ	• Hold therapy	• Grade 3 recurrent: Permanently discontinue
Blinatumomab continuous IV infusion	• Grade 1 & 2: Continue therapy • Grade 3: Hold therapy until grade 1 for at least 3 days; resume at 9 mcg/day; can be escalated to 28 mcg/day after 7 days	• Grade 3: If toxicity occurred at 9 mcg/day or if no improvement to grade 1 within 7 days, permanently discontinue
Tarlatamab-dlle IV	• Hold therapy; if symptoms resolve, resume at next scheduled dose	• Grade 3: if no improvement to grade 1 within 7 days or if recurrent grade 3, permanently discontinue
Tebentafusp-tebn IV	• Hold therapy	• Hold until grade 1 or baseline • Resume at same dose; do not escalate if grade 3 during initial dose; resume escalation once dosing tolerated
All Grade 4: Permanently discontinue bispecific therapy.		

Note: All recommendations are category 2A unless otherwise indicated.

ABBREVIATIONS

AIDP	acute inflammatory demyelinating polyneuropathy
ALC	absolute lymphocyte count
ANC	absolute neutrophil count
ASTCT	American Society for Transplantation and Cellular Therapy
ATG	antithymocyte globulin
B-ALL	B-cell acute lymphoblastic leukemia
BCMA	B-cell maturation antigen
BiPAP	bilevel positive airway pressure
BNP	b-type natriuretic peptide
CAPD	Cornell Assessment of Pediatric Delirium
CAR	chimeric antigen receptor
CBC	complete blood count
CMP	comprehensive metabolic panel
CMV	cytomegalovirus
CNS	central nervous system
CPAP	continuous positive airway pressure
CRRT	continuous renal replacement therapy
CRS	cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
EEG	electroencephalogram
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
ICAHT	immune effector cell-associated hematotoxicity
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector cell-associated encephalopathy
ICP	intracranial pressure
ICU	intensive care unit
IEC	immune effector cell
IEC-HS	immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome
Ig	immunoglobulin
IgG	immunoglobulin G
IL	interleukin
IVIG	intravenous immunoglobulin
LFT	liver function test
MAS	macrophage activation syndrome
MM	multiple myeloma
MRSA	methicillin-resistant Staphylococcus aureus
PCR	polymerase chain reaction
PJP	*Pneumocystis jirovecii* pneumonia
PRN	as needed
SCIG	subcutaneous immunoglobulin
TUG	Timed Up and Go
ULN	upper limit of normal
VZV	varicella zoster virus

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

Discussion

This discussion corresponds to the NCCN Guidelines for Management of CAR T-Cell and Lymphocyte Engager-Related Toxicities, which includes content derived from the NCCN Guidelines for Management of Immunotherapy-Related Toxicities. MS-16 to MS-18 were updated on October 25, 2024. The remaining sections were updated on February 28, 2022.

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Overview

The aim of the NCCN Guidelines for Management of CAR T-Cell and Lymphocyte Engager-Related Toxicities is to provide oncology practitioners with recommendations on how to manage immune-related adverse events (irAEs) related to chimeric antigen receptor (CAR) T-cell therapy and the emerging class of lymphocyte engagers (including T-cell–engaging bispecific antibodies). These Guidelines are updated by the NCCN Management of Immunotherapy-Related Toxicities Panel, a multidisciplinary group of representatives from NCCN Member Institutions consisting of medical oncologists and hematologic oncologists with expertise in a wide array of disease sites, as well as experts from the fields of cardiology, dermatology, endocrinology, gastroenterology, hepatology, neurooncology, nephrology, ophthalmology, pulmonology, rheumatology, oncology nursing, and oncology pharmacy. This panel also updates the NCCN Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities, which provide recommendations for the management of irAEs related to immune checkpoint inhibitors (ICIs).

The patient population eligible to receive cancer immunotherapy is expanding. Novel cellular therapies (such as CAR T cells) and lymphocyte engagers (eg, T-cell–engaging bispecific antibodies) continue to be approved by the FDA, with additional agents under clinical investigation.[1-5]

Clinicians should be aware that toxicities related to cancer immunotherapy are autoimmune in nature and can impact essentially any organ system.[6] The toxicity profiles of cancer immunotherapy and management strategies for irAEs are distinct from those of traditional chemotherapy.[6,7] Early recognition and prompt intervention are key goals for the management of toxicities related to cancer immunotherapy. In general, a multidisciplinary approach is recommended, and consultation with an appropriate specialist for evaluation and treatment is encouraged to ensure optimal patient outcomes. Unfortunately, obtaining a specialist consultation within an urgent timeframe can be challenging. Therefore, the guidelines provide initial steps for oncology clinicians to assess and manage a patient's irAE while minimizing disruption to cancer treatment, particularly in situations when access to a specialist is limited. The guidelines also provide guidance on when inpatient care is needed.

These guidelines will be updated at least annually by the collaborative efforts of the panel members based on their clinical experience and available scientific evidence.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

Prior to the update of the NCCN Guidelines for Management of CAR T-Cell and Lymphocyte Engager-Related Toxicities, an electronic search of the PubMed database was performed to obtain key literature in the management of CAR T-cell and lymphocyte engager-related toxicities published since the previous Guidelines update, using the search terms: chimeric antigen receptor, CAR T, or bispecific T-cell engager, in combination with the terms toxicity, adverse, or safety. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[8]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guideline, Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies. The data from key

PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the Panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[9] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

CAR T-Cell Therapy

Chimeric antigen receptor (CAR) T-cells represent a newer class of immunotherapy agents that is increasingly being incorporated into the treatment regimens of certain refractory or relapsed hematological malignancies, specifically subtypes of B-cell non-Hodgkin lymphoma (NHL), adult and pediatric B-cell acute lymphoblastic leukemia (ALL), and multiple myeloma (MM). CAR T-cells are genetically reprogrammed T-cells that express CARs, synthetic receptors that can be designed to target tumor surface antigens.[10,11] This treatment is a type of adoptive cell therapy and can be referred to as a "living drug."[12] The intent of CAR T-cell therapy is to induce a potent anti-tumor immune response by merging the specificity of an antibody with the cytotoxic and memory functionality of T-cells.[11,13,14] Currently approved CAR T-cell anti-cancer therapies are generated from autologous T lymphocytes that are genetically modified to recognize and kill tumor cells that express specific antigens.[15-19] While CAR T-cell therapy has uniquely powerful activity in several B-cell malignancies, it is also accompanied by specific toxicities requiring specialized expertise in management. This text provides an overview of CAR T-cell therapies and NCCN recommendations for the management of CAR T-cell-related toxicities in patients with cancer based on available evidence and clinical experience. For a discussion of the efficacy data for CAR T-cell therapies, see the NCCN Guidelines for Treatment of Cancer by Site at www.NCCN.org.

Design and Structure of CARs

CARs are engineered proteins that include an antigen recognition domain, a hinge region, a transmembrane domain, and at least 1 intracellular domain (Figure 1).[12,20,21] The antigen recognition domain is an extracellular targeting domain derived from a single chain fragment variable (scFv) that mimics an antibody's antigen binding region and recognizes specific antigens expressed on the surface of tumor cells in a human leukocyte antigen (HLA) independent manner. For currently approved CAR T-cells, the scFv recognizes either cluster of differentiation 19 (CD19), for B-ALL and B-NHL, or B-cell maturation antigen (BCMA), for MM.[15-19] Some agents under investigation have antigen recognition domains with a different structure or target novel antigens. For example, the antigen recognition domain of ciltacabtagene

autoleucel is comprised of 2 llama-derived single variable domain on a heavy chain (VHH) domains that can bind 2 distinct BCMA epitopes.[22]

CAR T-cell therapies typically have an immunoglobulin (Ig)-like hinge domain that separates the antigen recognition domain from the transmembrane domain.[23] Approved agents have an IgG4, CD28, or CD8α hinge domain.[15-19] Optimization of this domain may increase access to the antigen and improve the efficiency of CAR expression and activity.[23]

It is critical for CAR constructs to have a transmembrane domain, which enables the CARs to be embedded within the T-cell membrane, and may contribute to CAR T-cell signaling.[23] Most available CAR T-cell therapies use a CD8α or CD28 transmembrane domain.[15-19]

Early studies also found that CAR constructs require a domain to activate T-cells, also known as a T-cell activation domain.[12] All approved agents utilize a CD3ζ signaling domain for this function.[15-19]

While the T-cell activation domain was the only intracellular domain included in “first-generation” CAR T-cell constructs, currently available “second-generation” CAR constructs now also include either a CD28 or 4-1BB intracellular co-stimulatory construct.[12,15-19,24] The binding of a co-stimulatory receptor such as CD28 or 4-1BB to its cognate ligand on an antigen-presenting cell (APC) provides an additional signal for normal T-cell activation; therefore, inclusion of a CD28 or 4-1BB co-stimulatory domain within CAR constructs enhances the activation, proliferation, and anti-tumor activity of CAR T-cells (Figure 1).[24,25] Different co-stimulatory domains appear to be associated with changes in expansion kinetics, persistence, and possibly toxicity.[24] Unfortunately, efforts to evaluate the superiority of each type of co-stimulatory domain based on efficacy and safety data have been inconclusive due to various factors, such as differences in other CAR domains, clinical trial design, and toxicity grading systems.[24] Newer-generation CAR constructs with more or different co-stimulatory domains, as well as with a variety of antigen targets, including solid tumor antigens, are currently under active development.[5]

Targets of Currently Approved CAR T-Cells

CD19

CD19 is a transmembrane glycoprotein that is a member of the immunoglobulin (Ig) superfamily and is an important regulator of B-cell signaling and B-cell activation.[26-29] Due to its expression at all stages of B-cell differentiation, except for hematopoietic stem cells, CD19 is considered a reliable B-cell biomarker.[29-31] Importantly, CD19 is retained on cells that have undergone neoplastic transformation.[29,31] Increased expression of CD19 has been found on most B-cell tumors, including B-cell ALL, chronic lymphocytic leukemia (CLL), and B-cell lymphomas.[30-36] Currently approved CD19 CAR T-cell therapies include tisagenlecleucel, axicabtagene ciloleucel, brexucabtagene autoleucel, and lisocabtagene maraleucel.[15,16,18,19]

BCMA

BCMA is a transmembrane protein that is a member of the tumor necrosis factor receptor (TNFR) superfamily.[37-39] Expressed on the surface of mature B cells, but not naïve B cells or other hematopoietic cells, BCMA is thought to promote the survival of plasma cells in the bone marrow.[37,38,40,41] BCMA was identified as a promising biomarker and drug target for MM based on several findings. Serum BCMA levels were observed to be higher in patients with MM compared to those without MM.[42,43] Multiple studies found that BCMA is expressed in malignant cells from patients with MM.[43-47] Furthermore, overexpression of BCMA promoted cell proliferation in both in vitro and in vivo models.[48] Currently the only BCMA-targeting CAR T-cell therapy approved in the US is idecabtagene vicleucel, which was approved in 2021 for the

treatment of MM.[17] Ciltacabtagene autoleucel is another BCMA-targeted CAR T-cell therapy that is being considered by the FDA approval for the treatment of relapsed or refractory MM.[49]

Overall CAR T-Cell Treatment Schema

CAR T-cell therapy is a multistep process that can take several weeks to complete.[50] The first step is leukapheresis, the procedure of collecting white blood cells (including T cells) from a patient's blood.[13,51,52] The cells are subsequently sent to a laboratory, where T cells are isolated, activated, and transduced with a CAR transgene (typically delivered via a lentiviral or retroviral vector). Transduced T cells are then expanded, harvested, and prepped for infusion.[13,51-53] Finally, patients are infused with the CAR T-cells. Prior to infusion, patients undergo lymphodepletion chemotherapy (LDC). The goal of LDC is to prevent immunologic rejection of the infused CAR T-cells in order to maximize their expansion and persistence. LDC typically consists of fludarabine and cyclophosphamide.[15-19,54,55] Bendamustine is an alternative option prior to tisagenlecleucel infusion in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) who had a prior Grade 4 hemorrhagic cystitis with cyclophosphamide or developed a resistance to a previous cyclophosphamide containing regimen.[19] Depending on the product, patients may be treated on an inpatient or outpatient basis. However, outpatient therapy requires a robust infrastructure for rapid evaluation and intervention for toxicity.

CAR T-Cell Therapy-related Toxicities and Management Strategies

Despite the promising benefits of CAR T-cell therapies in the treatment of certain cancers, clinicians need to be aware of the serious and potentially fatal toxicities that may occur with the use of this newer class of agents. Overall, the most common and unique toxicities associated with CAR T-cell therapies are cytokine release syndrome (CRS) and neurotoxicity, and are entirely distinct from the immune-related adverse events (irAEs) that occur with the use of immune-checkpoint inhibitors (ICIs). In addition, some toxicities (eg, hypogammaglobulinemia) are a direct result of on-target/off-tumor activity of the CAR T-cells, while others (eg, infections) may occur as an indirect consequence of the immunosuppressed state of the patient. Fortunately, CAR T-cell therapy-related toxicities are almost always reversible and can be managed by the judicious use of immunosuppressive medications.

Principles of Patient Monitoring

The NCCN panel has provided recommendations on monitoring patients who receive CAR T-cell therapies based on available evidence and clinical experience, as detailed below and on CART-1. For effective toxicity management, clinicians need to closely monitor patients before, during, and after CAR T-cell infusions to ensure the early recognition of and intervention for specific adverse reactions related to treatment. Patients with underlying organ dysfunction may experience additional complications when treated with CAR T-cell therapies; proactive management and multidisciplinary involvement is especially crucial for these patients.

Before and During CAR T-Cell Infusion

Due to the potential cardiac manifestations of CAR T-cell-related toxicities, especially for those with underlying risk,[56-59] a baseline cardiac assessment (such as an echocardiogram) is recommended. Consultation with cardiology may be warranted for patients with cardiovascular comorbidities at baseline. Central venous access, preferably with double or triple lumen catheter, for intravenous (IV) fluid and possible vasopressor use is recommended. Cardiac monitoring should be performed at the onset of clinically significant arrhythmia and additionally as clinically indicated. For patients with large tumor burden and aggressive histologies, standard tumor lysis prophylaxis and monitoring

are recommended. Seizure prophylaxis (eg, levetiracetam 500-750 mg orally every 12 hours for 30 days) are often used on the day of infusion, especially for CAR T-cell therapies that are known to cause more severe CAR T-cell-related neurotoxicity (eg, axicabtagene and brexucabtagene). Because of the potential for severe neurotoxicity, all patients should receive baseline neurological evaluation, including ICE scores (for adults) or CAPD scores (for children less than 12 years) prior to CAR T-cell therapy. Some centers require baseline brain magnetic resonance imaging (MRI). Assessment of C-reactive protein (CRP) and serum ferritin levels is recommended at baseline.

Post-CAR T-Cell Infusion

Hospitalization or extremely close outpatient monitoring at centers with CAR T-cell experience is recommended. Close monitoring in the hospital is preferred with current products for adults; however, extremely close outpatient monitoring may be possible at centers with outpatient transplant experience. Hospitalization is warranted for patients at the first sign of CRS or neurotoxicity, including fever, hypotension, or change in mental status. Complete blood count (CBC), complete metabolic panel (CMP), (including magnesium and phosphorus) and coagulation profiles should be monitored daily. CRP and serum ferritin should be rechecked at least 3 times per week for 2 weeks post-infusion. Daily levels can be considered if CRS occurs. Vital signs to allow clinical assessment for CRS should be done at least every 8 hours, or when the patient's status changes, during the peak window of CRS risk, which is typically the first 1-2 weeks post-infusion. The time to onset of fever, and therefore CRS, may be earlier in patients treated with CD28 costimulatory domain-containing products (axicabtagene ciloleucel and brexucabtagene autoleucel) compared with 4-1BB costimulatory domain-containing products (tisagenlecleucel, lisocabtagene maraleucel, and idecabtagene vicleucel). Note that CRS may normalize prior to the onset of neurotoxicity. Neurotoxicity assessment (as described below) should be done at least twice daily or when the patient's status changes. This is typically during the first 1-2 weeks post-infusion, but has been seen with later onset up to a month, and very rarely later. If neurologic concern develops, more frequent assessments are recommended. Patients should be monitored for CRS, neurotoxicity, and other toxicities for the duration recommended by the CAR product package insert (at least 4 weeks post-infusion for most patients). Patients should refrain from driving or hazardous activities for at least 8 weeks following infusion.

Management Strategies for CAR T-Cell Therapy-Related Toxicities

An overview of CAR T-cell therapy-related toxicities is shown on CART-2. The presentation and the management of specific toxicities related to CAR T-cell therapies are discussed in the following sections. **It is critical to recognize that the exact timing, frequency, severity, and optimal management of CAR T-cell-related toxicities vary between products, and are likely to vary further as newer products gain approval. The NCCN Guidelines attempt to provide guidance that is generally applicable, but clinicians must imperatively consult their institutional guidelines and the prescribing information for individual agents for specific management strategies.**

Cytokine Release Syndrome (CRS)

CRS has been reported with all FDA approved CAR T-cell therapies and is one of the most common adverse events that occur with both CD19- and BCMA-directed CAR T-cells. Due to the different grading scales used to assess CRS severity in clinical trials, differences in CAR T-cell design and generation, and clinical trial design (including study population, dose regimen, and treatment protocols), a wide range of CRS rates have been reported with different CAR T- cell therapies.[60-67] Therefore, toxicity rates from trials of different agents may not always be directly comparable.

Presentation and onset

CRS is defined by the American Society for Transplantation and Cellular Therapy (ASTCT) as a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells (eg, lymphocytes, myeloid cells).[68] Specific CRS manifestations may include fever, hypotension, tachycardia, hypoxia, and chills, and may be associated with cardiac, hepatic, and/or renal dysfunction. Serious events that may occur with CRS include hypotension, hypoxia, atrial fibrillation and ventricular tachycardia, cardiac arrest, cardiac failure, renal insufficiency, and capillary leak syndrome. The cardiovascular complications that attend CRS can be severe and even fatal for patients with underlying risk who receive CAR T-cell therapy,[56,57] again highlighting the importance of careful patient selection and close monitoring. The typical time to onset for CRS is 2-3 days, with a duration of 7-8 days, although CRS may occur within hours following CAR T-cell infusion and as late as 10-15 days post-infusion.[60,62-67]

Pathophysiology

The overactivation of immune effector cells lead to the release of inflammatory cytokines, which ultimately results in endothelial injury and capillary leak that can present clinically as hemodynamic instability and organ dysfunction.[69,70] Multiple cytokines have been implicated in CRS, including IL-6, IL-1, IFN-γ, and TNF-α.[69-75] IL-6 is considered a central mediator of CRS and is thought to provide an activating signal to CAR T-cells.[69] In normal conditions, IL-6 binds to membrane-bound IL-6 receptor (IL-6R) on certain immune effector cells and has anti-inflammatory properties; this is referred to as the classic signaling pathway. However, when IL-6 levels are increased (such as during CRS), IL-6 may bind to the soluble form of IL-6R (sIL-6R) and induce a pro-inflammatory response via activation of a trans signaling pathway.

Risk factors

Several risk factors for severe CRS have been identified, although these vary across studies and likely across indications.[69,70,76-79] These generally (but not always) include increased CAR T-cell expansion and higher tumor burden (including high disease burden in bone marrow).[69,70,78,79]

Grading

The NCCN Guidelines follow the ASTCT Consensus Grading scale for CRS, which used a consensus approach to harmonize the various CRS definitions and grading systems that were previously used in pivotal clinical trials.[68] The grades are defined by presence of fever (≥38°C), the severity of hemodynamic compromise, and that of hypoxia. Fever defines the onset of CRS, with a temperature of ≥38°C not attributable to any other cause being the only symptom required for the classification as grade 1 CRS. Other types of organ dysfunction were not included in the ASTCT grading criteria. Laboratory parameters (eg, CRP or specific cytokines) were also not included in the definition or the grading scale for CRS, as it was deemed that there was insufficient evidence to support their use in this context.[68] However, these parameters may become more important in the future with additional studies. Please refer to CART-3 of the algorithm for the adapted definitions of each CRS grade.

Overall Management Strategy for CRS

Management of CRS in patients who received CAR T-cell therapy consists of both direct targeting and non-specific immunosuppressive strategies to counter the overactive immune cells and increased cytokine levels. Generally, patients are administered a combination of tocilizumab and corticosteroids, in addition to receiving supportive care.

Anti-IL-6 Therapy

Tocilizumab is a humanized, IgG1κ anti-IL6R antibody that was approved by the FDA in 2017 for the treatment of severe or life-threatening CAR T-cell-induced CRS in adults and pediatric patients

aged 2 years and older.[80,81] Tocilizumab binds to both soluble and membrane-bound interleukin-6 receptor (IL-6R), and is hypothesized to block the downstream signal transduction pathways implicated in CRS.[82] Tocilizumab is currently the only anti-IL-6 therapy approved by the FDA for the treatment of CRS.

This approval was based on a retrospective study of patients with hematological malignancies who developed severe or life-threatening CRS and received tocilizumab after treatment with tisagenlecleucel (n=45) or axicabtagene ciloleucel (n=15) in prospective trials.[80,81] CRS was resolved within 14 days of the first tocilizumab dose in 69% and 53% of patients in the tisagenlecleucel and axicabtagene ciloleucel cohorts, respectively. No adverse reactions were reported in this study, although infections, cytopenias, elevated liver enzymes, and lipid dysregulation have been reported with tocilizumab use in clinical trials for other conditions.[80,81]

While approved for severe or life-threatening cases, many centers and the prescribing information for individual agents advise using tocilizumab at lower grades of CRS.[15-18,83] For example, the prescribing information for axicabtagene ciloleucel states that tocilizumab can be considered for Grade 1 CRS if CRS symptoms persist for more than 24 hours.[15] This is supported by data from an exploratory safety management cohort of the ZUMA-1 trial, which demonstrated that patients who received earlier intervention with tocilizumab and/or corticosteroids for CRS (as early as Grade 1) had numerically lower rates of ≥grade 3 CRS (2%) compared with patients who received intervention at later CRS grades (12%).[84]

A proposed alternative to tocilizumab is siltuximab, an anti-IL6 antibody that is approved for the treatment of Castleman's disease.[85] By targeting the same pathway as tocilizumab, siltuximab would theoretically also be a viable treatment option for CRS. An additional potential advantage of siltuximab over tocilizumab is that the latter targets the receptor for IL-6 without sufficient central nervous system (CNS) penetration. This causes a transient rise in serum IL-6 levels, which some have postulated may worsen neurotoxicity by increasing cerebrospinal fluid IL-6 levels.[73,86] This potential increase in the neurotoxicity is an important concern in general with the use of tocilizumab for CRS, and may support the more frequent use of corticosteroids in conjunction with tocilizumab in more recent management guidelines. For persistent refractory CRS after 1-2 doses of tocilizumab, the guideline recommends considering the addition of corticosteroids. Despite the theoretical advantage of the IL-6-targeting siltuximab, there is limited data in the formal clinical trial setting supporting the use of this agent for CRS.[86,87] Anakinra, an IL-1Ra antagonist currently approved for the treatment of several inflammatory conditions,[88] is considered another potential alternative to tocilizumab for the treatment of CRS following CAR T-cell therapy. The rationale for targeting IL-1 is primarily based on evidence from two preclinical studies, which demonstrated that IL-1 blockade protected against CRS in mouse models without impacting the anti-tumor activity of the CAR T-cells.[73,74] While there are some reports in patients that suggest anakinra may be effective for managing CAR T-cell therapy-associated CRS,[89,90] there is also limited data supporting use of anakinra in this setting. Data from ongoing clinical trials will shed light on whether siltuximab and anakinra are viable alternatives to tocilizumab for the treatment of CRS.

Corticosteroids

Corticosteroids play an important role in CRS management in addition to anti-IL-6 therapy. Although the use of corticosteroids may alleviate the symptoms of CRS, there is theoretical concern that the use of higher doses of steroids could suppress CAR T-cell expansion and persistence, and therefore reduce the antitumor benefit of CAR T-cells.[91] However, this concern has not been supported in most studies, and corticosteroids are a cornerstone of CRS management. Furthermore, in the context of axicabtagene, the use of corticosteroids, either with milder CRS (or even

prophylactically) appear to be associated with preserved efficacy, lower risk of severe CRS, and lower cumulative use of steroids.[84,92,93] The most commonly used corticosteroids are dexamethasone and methylprednisolone. For patients with neurological symptoms, dexamethasone may be preferred due to better penetration of the blood-brain-barrier.[94] If steroids are used for the management of CRS, a rapid taper should be used once symptoms begin to improve.

<u>Options for steroid-refractory CRS</u>

If CRS does not improve after tocilizumab and steroids, workup for infections need to be considered and managed as appropriate. In addition to siltuximab and anakinra, other agents can be considered for patients who are refractory to both tocilizumab and corticosteroids, including the Janus Associated Kinase (JAK) 1/2 inhibitor ruxolitinib, cyclophosphamide, extracorporeal cytokine adsorption with continuous renal replacement therapy (CRRT), intravenous IgG (IVIG), and anti-thymocyte globulin (ATG); however, data supporting the use of these agents are mostly anecdotal or from small case series.[15,95-100] This will likely change in the future as results from ongoing clinical trials mature.

NCCN Recommendations for CRS

Urgent intervention is required to prevent the progression of CRS; however, other potential causes of inflammatory response, including infections and malignancy progression, should be ruled out. Empiric treatment for infections is warranted in patients who are febrile and neutropenic. Organ toxicities associated with CRS may be graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, but clinicians should be aware that these do not influence CRS grading under the ASTCT system. Organ toxicities should receive a thorough workup and appropriate management. Fever is defined as a temperature that is above 38°C that is not attributable to any other cause. For patients with CRS who receive antipyretics or anticytokine therapy, such as tocilizumab or steroids, fever is not required to grade subsequent CRS severity. For these cases, hypotension or hypoxia will determine CRS grading. See below (as well as CART-3 and CART-3A) for detailed treatment recommendations for CRS by grade.

In general, after each dose of anti-IL-6 therapy or corticosteroids, the need for subsequent dosing should be assessed. As per the prescribing information for axicabtagene ciloleucel, consider the use of prophylactic corticosteroids in patients after weighing the potential benefits and risks. Steroid prophylaxis for axicabtagene ciloleucel is dexamethasone 10 mg orally once daily for three days, with the first dose starting pre-CAR T-cell infusion; however, use of dexamethasone in this setting may increase the risk of Grade 4 and prolonged neurologic toxicities. Additionally, antifungal prophylaxis should be strongly considered in patients receiving steroids for the treatment of CRS and/or neurotoxicity.

Grade 1 (fever ≥38°C): For prolonged CRS (longer than 3 days) in patients or those with significant symptoms, comorbidities, and/or are elderly, 1 dose of tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) can be considered. For patients treated with axicabtagene ciloleucel or brexucabtagene autoleucel, tocilizumab can be considered if CRS symptoms persist for >24 hours. For patients treated with lisocabtagene maraleucel, consider tocilizumab for grade 1 CRS that develops <72 hours after infusion, and consider adding 1 dose of dexamethasone 10 mg; for CRS that develops ≥72 hours after infusion, treat symptomatically. For patients who received idecabtagene or lisocabtagene, consider administering dexamethasone 10 mg IV every 24 hours for early-onset CRS (<72 hours after infusion). Additional supportive care for Grade 1 CRS includes sepsis screen and empiric broad spectrum antibiotics (especially in neutropenic patients), judicious

use of IV fluids, electrolyte repletion, and management of specific organ toxicities.

Grade 2 (fever with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula or blow-by): Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose) is recommended, and can be repeated in 8 hours if no improvement is observed. No more than 3 doses should be administered in 24 hours, with a maximum of 4 doses total. Dexamethasone 10 mg IV every 12-24 hours (or equivalent) can be considered (depending on the product) for persistent refractory hypotension after 1-2 doses of an anti-IL-6 therapy. Note that some centers and manufacturer recommendations suggest the use of corticosteroids routinely for grade 2 CRS. Cardiac monitoring should be performed at least at the onset of grade 2 CRS until resolution to Grade 1 or less. Additional supportive care for Grade 2 CRS includes IV fluid bolus as needed, management as per Grade 3 if no improvement is observed within 24 hours of initiating anti-IL6 therapy, and symptomatic management of organ toxicities. For those with persistent refractory hypotension after two fluid boluses and anti-IL-6 therapy, clinicians should start vasopressors, transfer the patient to an intensive care unit (ICU), consider an echocardiogram, and initiate more thorough methods of hemodynamic monitoring. Telemetry and electrocardiogram (EKG), along with assessment of troponin and brain natriuretic peptide (BNP) should be done if tachycardia persists.

Grade 3 (fever with hypotension requiring a vasopressor with or without vasopressin or hypoxia requiring high-flow cannula, face mask, nonrebreather mask, or Venturi mask): Anti-IL-6 therapy as per Grade 2 is recommended, if the maximum dose is not reached within a 24-hour period. Dexamethasone 10 mg IV (or equivalent) should be administered every 6 hours. Patient can be managed as Grade 4 if refractory to this treatment. Additional supportive care for Grade 3 CRS includes the transfer of the patient to the ICU, an echocardiogram, hemodynamic monitoring, supplemental oxygen, IV fluid bolus and vasopressors as needed, and symptomatic management of organ toxicities.

Grade 4 (fever with hypotension requiring multiple vasopressors, excluding vasopressin, and/or hypoxia requiring positive pressure [eg, continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), intubation, mechanical ventilation]): Anti-IL-6 therapy as per Grade 2 is recommended, if the maximum dose is not reached within a 24-hour period. Dexamethasone 10 mg IV (or equivalent) should be administered every 6 hours. If refractory, 3 doses of methylprednisolone 1000 mg/day IV can be considered; dosing every 12 hours can also be considered. For example, methylprednisolone IV 1000 mg/day can be administered for 3 days, followed by a rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days. Other agents such as anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG, ATG, or extracorporeal cytokine adsorption with CRRT might also be considered.

Tocilizumab availability may be limited due to the FDA Emergency Use Authorization for hospitalized patients with severe COVID-19.[101] Under these conditions, the NCCN panel recommends that the use of tocilizumab be limited to a maximum of 2 doses during a CRS episode. Clinicians should also consider using steroids more aggressively (eg, with the first or second dose of tocilizumab). If necessary, replacement of the second dose of tocilizumab with siltuximab or anakinra can be considered, although again there is limited evidence to support this approach and neither of these agents have received FDA approval for the treatment of CRS.

Neurotoxicity

Neurotoxicity is another adverse event that commonly occurs with CAR T-cell therapies. As with CRS rates, neurotoxicity incidence rates

following CAR T-cell therapy reported in clinical trials vary widely, and is due to many factors, including differences in grading scales, CAR design and development, and clinical trial design. The rates of CAR T-cell-related neurotoxicity can vary across products, and clinicians should familiarize themselves with their frequency for the product(s) they are using.

Presentation and onset

The neurotoxicity that occurs with CAR T-cell therapies has been termed Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS) by the ASTCT, and is defined as a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells.[68]

Occasionally, neurological adverse events may occur in the context of CRS, especially headaches. Neurological symptoms due to CRS typically happen earlier than ICANS and lack the more generalized encephalopathy and frequent language disturbances of the latter. It is very important to remember that ICANS, unlike CRS, is generally unresponsive to tocilizumab, which is unable to cross the BBB when administered intravenously.[72,102,103] Data from a preclinical study showed that prophylactic treatment with tocilizumab did not prevent CAR T-cell induced neurotoxicity in a mouse model.[73] Similarly, data from a small study in 43 patients who received CD19-directed CAR T-cell therapy suggested that early intervention therapy with tocilizumab did not have an impact on overall neurotoxicity rates or in preventing severe neurotoxicity events.[104] Other studies have also found that tocilizumab did not alleviate neurologic toxicities in patients treated with CD19-directed CAR T-cell therapies.[55,102]

Transient neurological symptoms reported to occur with CAR T-cell therapies can be heterogeneous and include encephalopathy, delirium, aphasia, lethargy, headache, tremor, myoclonus, dizziness, motor dysfunction, ataxia, sleep disorder (eg, insomnia), anxiety, agitation, and signs of psychosis. Serious events, such as seizures, depressed level of consciousness, and fatal and serious cases of cerebral edema, have also occurred. Despite similarities with other encephalopathies, the neurotoxicity associated with CAR T-cell therapy has distinct common features, including language disturbances, encephalopathy, and motor dysfunction, which are captured in the ASTCT consensus grading criteria for ICANS.[68,72,102,105] Headache alone is not considered a useful diagnostic symptom for ICANS, as it is very common and frequently co-occurs with fever. The ASTCT consensus guidelines include intracranial pressure and edema as domains for ICANS grading, but cerebral edema is very rare and it is unclear if it arises from a distinct pathophysiology.[68]

The typical time to onset of neurotoxicity is 4-10 days after receiving CAR T-cell therapy, with a duration of 14-17 days.[60,62-65,72,102,106] The duration may be slightly shorter with BCMA-directed CAR T-cell therapies.[67,107]

Pathophysiology

Although the pathophysiology is not yet fully understood, CAR T-cell-related neurotoxicity is thought to occur as a result of endothelium cell activation and leak in the central nervous system, leading to elevated inflammatory cytokines in the cerebrospinal fluid (CSF).[69,72,94,102,108,109] Several cytokines are implicated in the pathophysiology of CAR T-cell related neurotoxicity, including IL-6, IFNγ, and TNFα.

Risk factors

CRS is considered a strong risk factor for ICANS, with the severity of CRS correlating with that of ICANS.[66,72,102,105,109] Other possible ICANS risk factors may include higher disease burden, high baseline inflammatory state, pre-existing neurologic comorbidities, and higher

CAR T-cell dose.[72,94,102] High-grade ICANS is more common with CD19-directed CAR than BCMA-directed CAR.[60-67,107] As with CRS, reported risk factors and incidence vary across studies.[72,102,106,110]

Grading

The NCCN panel recommends following the ASTCT ICANS Consensus grading scale, which consists of an Immune Effector Cell-Associated Encephalopathy (ICE) score as a standardized assessment for encephalopathy, as well as the following four neurologic domains: level of consciousness, seizure, motor findings, and elevated ICP/cerebral edema (see CART-4).[68] The pediatric version incorporated the Cornell Assessment of Pediatric Delirium (CAPD) score in place of ICE assessment in children younger than 12 years or those with developmental delay.[68] The overall ICANS grade is the most severe symptom in any of the five domains.

By including only the most common and specific neurotoxicity symptoms that would trigger specific interventions, the ASTCT ICANS consensus grading scale improves the ease of grading compared to the method used by earlier trials, which was to grade by CTCAE multiple individual and often overlapping terms (such as encephalopathy and delirium). For seizures, the ASTCT ICANS grading scale considers any single clinical or subclinical electrographic seizure of any type to be a Grade 3 event, with prolonged or repetitive clinical or subclinical seizures without a return to baseline in between to be Grade 4.

The ICE component of the ASTCT ICANS grading scale is derived from a 10-point screening tool that enables the objective grading of overlapping encephalopathy terms.[68] ICE is a modified version of the CARTOX-10 screening tool, and evaluates the following abilities: 1) orientation, 2) naming, 3) command following, 4) writing, and 5) attention (see CART-4). In addition to contributing to the grade of ICANS, the ICE assessment can be used daily or every shift as a screen for the onset of ICANS during the at-risk period.

Please refer to CART-4 for additional details on use of the ICE screening tool and the ASTCT ICANS grading scale.

Management of ICANS/Neurotoxicities Related to CAR T-cell Therapy

Corticosteroids form the cornerstone of ICANS management, in addition to careful monitoring and supportive care. Tocilizumab is not recommended by the NCCN panel to treat neurotoxicity in patients treated with CAR T-cell therapies, unless there is concurrent CRS. It may be preferable to use corticosteroids alone in the patient with grade 1 CRS (fever alone) and higher grade ICANS due to the possibility that tocilizumab may exacerbate ICANS.

NCCN Recommendations

The panel recommends that clinicians use the ASTCT ICANS Consensus Grading Scale for Adults to grade any CAR T-cell-related neurotoxicity (see CART-4). The ICANS grade is determined by the most severe event (ie, ICE score, level of consciousness, seizure, motor findings, raised intracranial pressure (ICP)/cerebral edema) that is not attributable to any other cause (eg, sedating medication). The ICE score should be derived from the ICE Assessment Tool. This tool can be used to track a patient's status over time; however, clinical judgement is still necessary when using the ICE assessment. Other signs and symptoms such as headache, tremor, myoclonus, asterixis, and hallucinations may occur and could be attributable to immune effector-cell engaging therapies. Although they are not included in this grading scale, careful attention and directed therapy may be warranted.

Neurology consultation is recommended at the first sign of neurotoxicity. Upon a neurotoxicity diagnosis, neurologic assessment and grading should be performed at least twice a day to include cognitive assessment

and motor weakness. MRI of the brain with and without contrast (or brain CT, if MRI is not feasible) is recommended for those with neurotoxicity that is Grade 2 or higher. An electroencephalogram (EEG) for seizure activity should also be conducted for those patients. Clinicians should be cautious when prescribing medications that can cause CNS depression (excluding those needed for seizure prophylaxis or treatment). If dexamethasone is used for prophylaxis of CRS, there may be an increased risk of Grade 4 and prolonged neurologic toxicities.[15,93]

Treatment for neurotoxicity is based on ICANS grade (see CART-5). Supportive care alone is recommended for Grade 1 neurotoxicity. If ICANS develops within 72 hours after infusion of either lisocabtagene maraleucel or idecabtagene vicleucel, consider administering dexamethasone 10 mg IV every 12-24 hours for 2 doses and reassess.

For Grade 2 neurotoxicity, patients should receive supportive care and a dose of dexamethasone 10 mg IV, followed by reassessment. Dexamethasone may be repeated every 6-12 hours, if there is no improvement.

Dexamethasone 10 mg IV every 6 hours or methylprednisolone (1 mg/kg IV every 12 hours) is recommended for Grade 3 neurotoxicity; for patients who received axicabtagene ciloleucel or brexucabtagene autoleucel, methylprednisolone 1 g daily for 3-5 days may be preferable. High-dose corticosteroids are the recommended treatment option for Grade 4 neurotoxicity. For example, methylprednisolone IV 1000 mg/day (may consider twice a day) for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days. Convulsive status epilepticus should be treated as per institutional guidelines.

Patients with ≥Grade 3 neurotoxicity should receive ICU care. Clinicians should consider repeating neuroimaging (CT or MRI) every 2-3 days if the patient has persistent neurotoxicity that is grade 3 or higher. Patients should also undergo assessment for papilledema or other signs of elevated intracranial pressure. If elevated intracranial pressure is excluded, a diagnostic lumbar puncture may be considered for patients with grade 3-4 neurotoxicity. Antifungal prophylaxis should be strongly considered in patients receiving steroids for the treatment of CRS or neurotoxicity. If steroids are given for the management of ICANS, a fast taper should be used once there is improvement.

Tocilizumab can be used for the treatment of CRS in patients with neurotoxicity and CRS occurring concurrently. It may be preferable to use corticosteroids alone in the patient with grade 1 CRS (fever alone) and concurrent higher grade neurotoxicity due to the possibility that tocilizumab may exacerbate neurotoxicity. Consider transferring the patient to the ICU if the neurotoxicity is associated with CRS that is Grade 2 or higher.

Hemophagocytic lymphohistiocytosis/macrophage-activation syndrome (HLH/MAS)

HLH/MAS can be described as severe immunological syndromes caused by uncontrolled immune activation. This is thought to be the result of hyperactivation of macrophages and lymphocytes, increased production of proinflammatory cytokines, infiltration of lymphocytes and histiocytes in tissues and organs, and immune-mediated multiorgan failure.[83,111-113] Unlike HLH/MAS that occurs due to underlying genetic mutations (referred to as primary HLH/MAS), CAR T-cell therapy-induced HLH/MAS is considered a secondary HLH/MAS, as it is caused by an immune trigger.[112,114] One recent study estimated that HLH/MAS occurs in 3.5% of patients treated with CAR T cell therapy.[115] However, the true incidence of HLH/MAS has been debated, in part due to the close overlap in CRS and HLH/MAS symptoms.[83,114,116]

A clear diagnosis of HLH/MAS following CAR T-cell therapy can be difficult, as the clinical features and laboratory abnormalities can have substantial overlap with CRS (eg, high fevers, increased ferritin levels).[68,71,83,117,118] Most patients with moderate to severe CRS have laboratory abnormalities that meet the classic criteria for HLH, such as elevated CRP, hyperferritinemia, cytopenias, hypofibrinogenemia, coagulopathy, and elevated levels of several serum cytokines, including IL-6, INFγ, sIL-2Ra, and GM-CSF.[71,112] Clinical features associated with CAR T-cell induced HLH include fever, multiorgan dysfunction, and CNS issues (eg, headaches, vision disturbances, and issues related to walking), but patients may not have hepatosplenomegaly or evidence of hemophagocytosis.[68,83,111]

Because HLH/MAS symptoms resolve with the clinical management and resolution of CRS in most cases (and therefore there is no need to directly treat HLH/MAS), an expert panel convened by the ASTCT decided to exclude HLH/MAS from the definition of CRS.[68] Furthermore, a separate grading scale for HLH/MAS was not established, due to the degree of similarity with CRS and the lack of available CTCAE terms. Clinical management of HLH/MAS mirrors the strategies used for managing CRS, which consists of anti-IL-6 therapy and aggressive use of corticosteroids; the overall goal of this strategy is to suppress the overactive immune cells responsible for the symptoms.[83] A high mortality rate has been linked with refractory HLH/MAS,[119,120] and therefore prompt treatment is required. Some cases of late-onset HLH/MAS-like pathology may occur, which may be tocilizumab refractory. For these cases, corticosteroids and anakinra should be considered. There have been anecdotal reports of the resolution of HLH with anakinra administration.[115,121,122] As a last resort, etoposide may be an option for HLH/MAS that shows no improvement with these measures; this is primarily based on clinical experience with non-CAR T-cell associated HLH. [83,112,113,119,123] In general, this approach is not recommended due to etoposide's toxicity to T lymphocytes and lack of data in the CAR T-cell setting. Intrathecal cytarabine is another potential option for patients with HLH-associated neurotoxicity,[83] however, data supporting use of this agent in this setting is lacking.

NCCN Recommendations

The NCCN panel recommends the following criteria for when there is clinical concern for HLH/MAS: 1) Rapidly rising and high ferritin (>5000 ng/mL) with cytopenias in the context of fever, especially if accompanied by any of the following: Grade ≥3 increase in serum bilirubin, aspartate aminotransferase (AST), alanine transaminase (ALT); Grade ≥3 oliguria or increase in serum creatinine; or grade ≥3 pulmonary edema; 2) presence of hemaphagocytosis in bone marrow or organs based on histopathologic assessment of cell morphology and/or CD68 immunohistochemistry (IHC).

For HLH/MAS, treat as per CRS with tocilizumab and steroids, although the suspicion of HLH/MAS should prompt consideration of higher doses of steroids at a given CRS grade. If no improvement is observed within 48 hours, consider addition of anakinra to corticosteroids. Etoposide or intrathecal cytarabine can be considered as a last resort for HLH with CNS involvement.

Hypogammaglobulinemia

Hypogammaglobulinemia is another potential risk associated with CAR T-cell therapy and has been reported in up to 53% of patients who received CAR T-cell therapy in registrational clinical trials.[15-19]

Characterized by low antibody levels in the blood and an increased risk of infection,[124] hypogammaglobulinemia is a consequence of extremely low B-cell or plasma cell counts, referred to as B-cell or plasma cell aplasia, respectively. These types of aplasia are an expected result of the on-target/off-tumor activity associated with the successful use of

CAR T cell therapy, due to the presence of the targeted antigens on non-malignant B cells or plasma cells.[10,114]

Long-term hypogammaglobulinemia can occur, and even in patients with a complete remission after CAR T-cell therapy infusion. Hypogammaglobulinemia may be treated with the infusion of IVIG, a fractionated blood product derived from the plasma of thousands of individuals and contains antibodies against a wide range of pathogens.[125,126] However, at present there is no compelling data for the use of IVIG post CAR T-cell infusion in patients who do not experience frequent or severe infections with hypogammaglobulinemia, and institutional practices vary.

NCCN recommendations

After anti-CD19 CAR T-cell therapy, consider monthly 400-500 mg/kg IVIG replacement for select patients with hypogammaglobulinemia (those with serum IgG levels <400-600 mg/dL AND serious or recurrent infections [particularly bacterial]). IVIG should be continued until serum IgG levels normalize and infections are resolved. The optimal IgG threshold to use may depend on patient characteristics and infection frequency or severity.

Hematological Toxicities

Patients who receive CAR T-cell therapy are also at risk of hematological toxicities, including prolonged cytopenia, such as neutropenia, thrombocytopenia, anemia, and/or leukopenia.

Acute cytopenia is common in patients treated with CAR T-cell therapy; however, Grade 3 or higher prolonged cytopenia that remained unresolved weeks or months after infusion are reported frequently in patients treated with CAR T-cell therapies.[15-19] Clinicians should be aware that cytopenia may occur in the weeks to months following lymphodepleting chemotherapy and CAR T-cell therapy infusion.

Factors that may contribute to prolonged cytopenias include CRS and ICANS severity, disease burden, the number of prior therapies, baseline blood cell counts, peak CRP and ferritin levels, and CAR construct.[70,127,128] Although lymphodepletion may be a contributing factor, the pathophysiology of prolonged cytopenia following CAR T-cell infusion remains unclear.[129]

Cytopenias are generally managed with transfusion or growth factor support, if the possibility of myelodysplastic syndrome has been ruled out.[111,130,131] Growth factors may be considered for persistent cytopenias. The guidelines do not provide specific recommendations on the management of CAR T-cell therapy-associated cytopenia in the current version of the guidelines.

Infections

Infections following CAR T-cell therapy are common, and have been reported in up to 70% of patients who received a CAR T-cell therapy in registrational clinical trials for approved agents.[15-19] Bacterial, viral, and fungal infections have all been reported with use of CAR T-cell therapy.[132,133] Most infections occur soon after infusion and may occur for a number of reasons, including lymphodeleting or antecedent chemotherapy, CAR T-cell mediated B-cell or plasma cell depletion, prolonged cytopenias, corticosteroid treatment, or as a consequence of the malignancy itself.[111,134] The severity of CRS may also be associated with an increased risk of acute infections.[132-134] Other potential risk factors for severe infections within the first 30 days include ICANS, tocilizumab and corticosteroid use.[129] Patients remain at increased risk of complications for weeks to months after infusion.[66,132,135,136] Infections are generally managed using agents that target the source of infection. Additionally, prophylaxis against vesicular stomatitis virus (VSV)/herpes simplex virus (HSV) reactivation and *Pneumocystis jirovecii* pneumonia (PJP) infections is generally used for patients undergoing CAR T-cell

therapy and for several months following. The decision to administer antibacterial or antifungal prophylaxis should be risk-adjusted based on patient characteristics, such as prior lines of suppressive therapy, infection history, etc.[137] IVIG replacement therapy may be used for select patients. The guidelines recommend IVIG replacement for certain patients treated with anti-CD19 CAR T-cell therapy who experience serious or recurrent infections (particularly bacterial) concurrently with hypogammaglobulinemia. For additional guidance on infections and vaccinations, please refer to the NCCN Guidelines on the Prevention and Treatment of Cancer-Related Infections.

Movement and Neurocognitive Treatment-Emergent Adverse Events (MNTs)

Movement and neurocognitive treatment-emergent adverse events (MNTs) have been reported with anti-BCMA CAR T-cell therapy agents.[107,138-140] The manifestation of MNTs is similar to Parkinson's disease, with bradykinesia, asymmetric action and rest tremor, postural instability, hypophonia, personality change, and impaired memory.[139] The time to onset of MNTs is typically longer than that of ICANS.[139,141]

Approximately 3% of patients who received ciltacabtagene autoleucel from the CARTITUDE-1 and CARTITUDE-4 studies exhibited symptoms of parkinsonism consistent with MNTs.[141] Events that were grade 3 or higher were reported in 2% of patients. Similar AEs were also reported following idecabtagene vicleucel treatment.[17,140] Potential risk factors identified include high baseline tumor burden, prior ICANS, CRS that was grade 2 or higher, and high CAR T-cell expansion/persistence.[139] Data on how to manage MNTs are limited. However, improvement in symptoms was reported in a small number of patients with MNTs who received steroids such as dexamethasone initially; one patient experienced a dramatic improvement with cyclophosphamide treatment.[139,140,142]

The NCCN Panel notes that the optimal management of MNTs is still under investigation. MNTs characterized so far have been levodopa unresponsive, which suggests that the pathophysiology of MNTs is distinct from Parkinson's disease.[138-140] For mild MNTs, steroids such as 10 mg dexamethasone daily can be considered. For persistent, severe, or refractory MNTs, and if high circulating CAR T-cell levels are detected, chemotherapy such as cyclophosphamide can be considered. Clinicians should be aware that use of the therapies noted above is based on very limited data; therefore, the decision to use these agents should be balanced against potential safety concerns such as infection risk.

Data from ongoing trials will provide more insight into the optimal management strategies for anti-BCMA CAR T-cell therapy-related MNTs.

Peripheral Neuropathy

Peripheral neuropathy is another emerging neurotoxicity that has been reported with anti-BCMA CAR T-cell therapy and includes lower motor neuron facial paralysis, other cranial nerve palsy, peripheral sensory neuropathy, and peripheral motor neuropathy.[139,141] Approximately 7% of patients who received ciltacabtagene autoleucel experienced peripheral neuropathy from the CARTITUDE-1 and CARTITUDE-4 studies.[141] Cranial nerve palsies were also reported in 7% of patients in the same trials. The median time of onset for peripheral neuropathy was 57 days, while that for cranial nerve palsies was 21 days.[141] Steroids were the primary treatment used for the limited number of patients with peripheral neuropathy.[139]

The NCCN Panel notes that treatment with steroids can be considered for patients with mild peripheral neuropathy. For those with acute inflammatory demyelinating polyneuropathy (AIDP)-type picture, IV immunoglobulin (IVIG) can be considered in line with current treatment guidelines for AIDP.[143] Management strategies will likely change as more data on CAR T-cell–related peripheral neuropathy become available.

Summary: CAR T-cell Therapy

CAR T-cell therapies are a novel and revolutionary class of cancer therapies that have demonstrated efficacy against several types of cancers. However, data from clinical trials have shown that all approved CAR T-cell therapies are associated with unique adverse reactions, including CRS and neurologic toxicities. Patient monitoring before, during and after CAR T-cell therapy is critical for early recognition of potential toxicities and timely intervention. CAR T-cell related toxicities can generally be reversed through the use of appropriate management strategies, such as immunosuppressive agents. Due to the changing therapeutic landscape, recommendations for management of CAR T-cell toxicities will continue to evolve as data emerge from clinical trials evaluating novel treatment options.

Lymphocyte Engager Therapy

Lymphocyte engagers are engineered molecules (primarily antibody-based) that most often target both specific cell-surface molecules on immune cells and antigens on tumor cells; this bridging event enables the recruitment of immune cells to the site of tumor cells and their activation.[3,144] The number of available lymphocyte engager therapies for the treatment of patients with cancer has increased in recent years. Current agents in clinical use are all T-cell–engaging bispecific antibodies,[2] but other variations of these molecules are also undergoing clinical investigation (ie, natural killer [NK]-cell engagers, tri-specific lymphocyte engagers).[3]

Management of Lymphocyte Engager Therapy-Related Toxicities

Similar to CAR T-cell therapy, CRS, ICANS, and infections are prominent possible toxicities associated with available T-cell–engaging bispecific antibodies.[145] Although there is high variability between products, available data suggest that the incidence of CRS appears somewhat lower, and that of neurologic toxicity appears much lower, with T-cell–engaging bispecific antibodies than with CAR T-cell therapy.[145] Other reported toxicities associated with T-cell–engaging bispecific antibodies include tumor flare reaction, cytopenias, and tumor lysis syndrome.

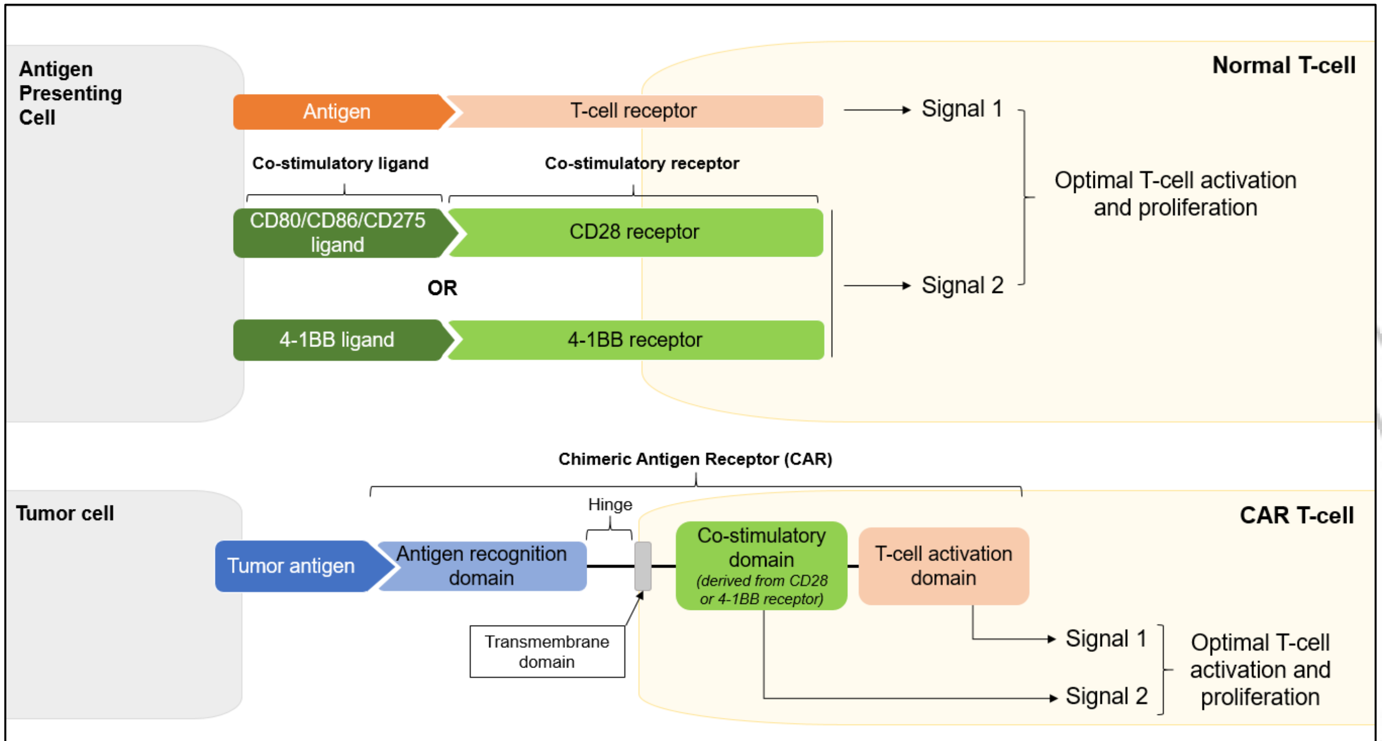
The American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading system should be used for lymphocyte engager-related CRS and ICANS.[68,145] However, the NCCN Panel recommends that clinicians consult the prescribing information and clinical trial protocols for each specific lymphocyte engager for guidance on CRS and ICANS management as general strategies applicable to all available agents have not been established. Institutions administering these therapies should have clear, agent-specific protocols in place to facilitate timely management of severe reactions. Patients who receive certain lymphocyte engagers may require inpatient initiation for monitoring, with transition to ambulatory settings dictated by patient tolerability due to risk of CRS.

Although CRS and ICANS occur with both CAR T-cell therapy and lymphocyte engagers, clinicians should keep in mind that there may be differences in management strategies. For example, dose modification according to the prescribing information can be considered for patients undergoing treatment with certain (but not all) T-cell–engaging bispecific antibodies,[145] as lymphocyte engagers are "off-the-shelf" therapies that are administered via multiple cycles over a period of time.

As clinicians learn more about the nature and scope of toxicities related to this new class of agents, optimal management strategies will continue to evolve. As an example, consensus recommendations on the management of toxicities related to CD3 x CD20 bispecific antibodies were recently developed by an international group of oncology practitioners based on their experience managing these toxicities in patients with lymphoma.[145] Guideline recommendations for the

management of lymphocyte engager-related toxicities will be expanded upon by the NCCN Panel in future iterations to reflect emerging clinical data and consensus opinion.

Figure 1: Optimal T-cell (and CAR T-cell) activity requires two signals



(Top) For the full activation and proliferation of T-cells, two signals are required. Signal 1 results from the interaction between the peptide antigen expressed on the antigen presenting cell (APC) and the T-cell receptor. Signal 2 results from the interaction between a co-stimulatory receptor (such as CD28 or 4-1BB) expressed on T-cells and its corresponding ligand expressed on APCs.

(Bottom) Chimeric antigen receptors are modular structures comprised of an antigen recognition domain, a hinge domain, a transmembrane domain, and at least 1 intracellular domain. Intracellular domains of currently available CAR T-cells include a co-stimulatory domain (derived from CD28 or 4-1BB) and a T-cell activation domain. Incorporation of both types of intracellular domains in a single construct is thought to enable CARs to transduce both Signal 1 and Signal 2 upon binding to the tumor antigen, thereby enhancing the activation and proliferation of CAR T-cells.

Please note that the schematic is not drawn to scale. Refer to the text for references.

References

1. CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers. 2022. Available at: https://www.cancer.gov/about-cancer/treatment/research/car-t-cells. Accessed August 12, 2024.
2. Bispecific Antibodies: An Area of Research and Clinical Applications. 2024. Available at: https://www.fda.gov/drugs/spotlight-cder-science/bispecific-antibodies-area-research-and-clinical-applications. Accessed August 9, 2024.
3. Fenis A, Demaria O, Gauthier L, et al. New immune cell engagers for cancer immunotherapy. Nat Rev Immunol 2024;24:471–486. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38273127.
4. Approved Cellular and Gene Therapy Products. 2024. Available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products. Accessed August 12, 2024.
5. Clinicaltrials.gov. 2024. Available at: https://www.clinicaltrials.gov/. Accessed August 12, 2024.
6. Ramos-Casals M, Brahmer JR, Callahan MK, et al. Immune-related adverse events of checkpoint inhibitors. Nature Reviews Disease Primers 2020;6:38. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32382051.
7. Johnson DB, Nebhan CA, Moslehi JJ, Balko JM. Immune-checkpoint inhibitors: long-term implications of toxicity. Nat Rev Clin Oncol 2022;19:254–267. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35082367.
8. PubMed. Available at: https://pubmed.ncbi.nlm.nih.gov/about/. Accessed October 23, 2024.
9. Freedman-Cass DA, Fischer T, Alpert AB, et al. The Value and Process of Inclusion: Using Sensitive, Respectful, and Inclusive Language and Images in NCCN Content. J Natl Compr Canc Netw 2023;21:434–441. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37156485.
10. June CH, Sadelain M. Chimeric Antigen Receptor Therapy. N Engl J Med 2018;379:64–73. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29972754.
11. Gross G, Waks T, Eshhar Z. Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity. Proc Natl Acad Sci U S A 1989;86:10024–10028. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2513569.
12. Sadelain M, Brentjens R, Riviere I. The basic principles of chimeric antigen receptor design. Cancer Discov 2013;3:388–398. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23550147.
13. Feins S, Kong W, Williams EF, et al. An introduction to chimeric antigen receptor (CAR) T-cell immunotherapy for human cancer. Am J Hematol 2019;94:S3–S9. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30680780.
14. Maus MV, Levine BL. Chimeric Antigen Receptor T-Cell Therapy for the Community Oncologist. Oncologist 2016;21:608–617. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27009942.
15. Prescribing Information: Axicabtagene ciloleucel suspension for intravenous infusion. 2024. Available at: https://www.fda.gov/media/108377/download?attachment. Accessed May 16, 2024.
16. Prescribing Information: Brexucabtagene autoleucel suspension for intravenous infusion. 2024. Available at: https://www.fda.gov/media/140409/download?attachment. Accessed May 16, 2024.
17. Prescribing Information: Idecabtagene vicleucel suspension for intravenous infusion. 2024. Available at: https://www.fda.gov/media/147055/download?attachment. Accessed August 9, 2024.
18. Prescribing Information: Lisocabtagene maraleucel suspension for intravenous infusion. 2024. Available at: https://www.fda.gov/media/145711/download?attachment. Accessed May 16, 2024.
19. Prescribing Information: Tisagenlecleucel suspension for intravenous infusion. 2024. Available at: https://www.fda.gov/media/107296/download?attachment. Accessed May 16, 2024.
20. Zhang C, Liu J, Zhong JF, Zhang X. Engineering CAR-T cells. Biomark Res 2017;5:22. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28652918.
21. Jayaraman J, Mellody MP, Hou AJ, et al. CAR-T design: Elements and their synergistic function. EBioMedicine 2020;58:102931. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32739874.

22. Zhao WH, Liu J, Wang BY, et al. A phase 1, open-label study of LCAR-B38M, a chimeric antigen receptor T cell therapy directed against B cell maturation antigen, in patients with relapsed or refractory multiple myeloma. J Hematol Oncol 2018;11:141. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30572922.
23. Guedan S, Calderon H, Posey AD, Jr., Maus MV. Engineering and Design of Chimeric Antigen Receptors. Mol Ther Methods Clin Dev 2019;12:145–156. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30666307.
24. Cappell KM, Kochenderfer JN. A comparison of chimeric antigen receptors containing CD28 versus 4-1BB costimulatory domains. Nat Rev Clin Oncol 2021;18:715–727. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34230645.
25. Chen L, Flies DB. Molecular mechanisms of T cell co-stimulation and co-inhibition. Nat Rev Immunol 2013;13:227–242. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23470321.
26. Stamenkovic I, Seed B. CD19, the earliest differentiation antigen of the B cell lineage, bears three extracellular immunoglobulin-like domains and an Epstein-Barr virus-related cytoplasmic tail. J Exp Med 1988;168:1205–1210. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2459292.
27. Tedder TF, Isaacs CM. Isolation of cDNAs encoding the CD19 antigen of human and mouse B lymphocytes. A new member of the immunoglobulin superfamily. J Immunol 1989;143:712–717. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2472450.
28. Wang K, Wei G, Liu D. CD19: a biomarker for B cell development, lymphoma diagnosis and therapy. Exp Hematol Oncol 2012;1:36. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23210908.
29. Tedder TF. CD19: a promising B cell target for rheumatoid arthritis. Nat Rev Rheumatol 2009;5:572–577. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19798033.
30. Nadler LM, Anderson KC, Marti G, et al. B4, a human B lymphocyte-associated antigen expressed on normal, mitogen-activated, and malignant B lymphocytes. J Immunol 1983;131:244–250. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6408173.
31. Scheuermann RH, Racila E. CD19 antigen in leukemia and lymphoma diagnosis and immunotherapy. Leuk Lymphoma 1995;18:385–397. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8528044.
32. Robbins BA, Ellison DJ, Spinosa JC, et al. Diagnostic application of two-color flow cytometry in 161 cases of hairy cell leukemia. Blood 1993;82:1277–1287. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7688993.
33. Uckun FM, Jaszcz W, Ambrus JL, et al. Detailed studies on expression and function of CD19 surface determinant by using B43 monoclonal antibody and the clinical potential of anti-CD19 immunotoxins. Blood 1988;71:13–29. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3257143.
34. Thalhammer-Scherrer R, Mitterbauer G, Simonitsch I, et al. The immunophenotype of 325 adult acute leukemias: relationship to morphologic and molecular classification and proposal for a minimal screening program highly predictive for lineage discrimination. Am J Clin Pathol 2002;117:380–389. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11888077.
35. Schwonzen M, Pohl C, Steinmetz T, et al. Immunophenotyping of low-grade B-cell lymphoma in blood and bone marrow: poor correlation between immunophenotype and cytological/histological classification. Br J Haematol 1993;83:232–239. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8457472.
36. Anderson KC, Bates MP, Slaughenhoupt BL, et al. Expression of human B cell-associated antigens on leukemias and lymphomas: a model of human B cell differentiation. Blood 1984;63:1424–1433. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6609729.
37. Laabi Y, Gras MP, Carbonnel F, et al. A new gene, BCM, on chromosome 16 is fused to the interleukin 2 gene by a t(4;16)(q26;p13) translocation in a malignant T cell lymphoma. EMBO J 1992;11:3897–3904. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1396583.
38. Laabi Y, Gras MP, Brouet JC, et al. The BCMA gene, preferentially expressed during B lymphoid maturation, is bidirectionally transcribed. Nucleic Acids Res 1994;22:1147–1154. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8165126.
39. Madry C, Laabi Y, Callebaut I, et al. The characterization of murine BCMA gene defines it as a new member of the tumor necrosis factor receptor superfamily. Int Immunol 1998;10:1693–1702. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9846698.

40. Thompson JS, Schneider P, Kalled SL, et al. BAFF binds to the tumor necrosis factor receptor-like molecule B cell maturation antigen and is important for maintaining the peripheral B cell population. J Exp Med 2000;192:129–135. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10880534.

41. O'Connor BP, Raman VS, Erickson LD, et al. BCMA is essential for the survival of long-lived bone marrow plasma cells. J Exp Med 2004;199:91–98. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14707116.

42. Sanchez E, Li M, Kitto A, et al. Serum B-cell maturation antigen is elevated in multiple myeloma and correlates with disease status and survival. Br J Haematol 2012;158:727–738. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22804669.

43. Lee L, Bounds D, Paterson J, et al. Evaluation of B cell maturation antigen as a target for antibody drug conjugate mediated cytotoxicity in multiple myeloma. Br J Haematol 2016;174:911–922. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27313079.

44. Seckinger A, Delgado JA, Moser S, et al. Target Expression, Generation, Preclinical Activity, and Pharmacokinetics of the BCMA-T Cell Bispecific Antibody EM801 for Multiple Myeloma Treatment. Cancer Cell 2017;31:396–410. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28262554.

45. Novak AJ, Darce JR, Arendt BK, et al. Expression of BCMA, TACI, and BAFF-R in multiple myeloma: a mechanism for growth and survival. Blood 2004;103:689–694. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14512299.

46. Friedman KM, Garrett TE, Evans JW, et al. Effective Targeting of Multiple B-Cell Maturation Antigen-Expressing Hematological Malignances by Anti-B-Cell Maturation Antigen Chimeric Antigen Receptor T Cells. Hum Gene Ther 2018;29:585–601. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29641319.

47. Salem DA, Maric I, Yuan CM, et al. Quantification of B-cell maturation antigen, a target for novel chimeric antigen receptor T-cell therapy in Myeloma. Leuk Res 2018;71:106–111. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30053652.

48. Tai YT, Anderson KC. Targeting B-cell maturation antigen in multiple myeloma. Immunotherapy 2015;7:1187–1199. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26370838.

49. Legend Biotech Announces Extension of PDUFA Date for Cilta-Cel. 2021. Available at: https://investors.legendbiotech.com/news-releases/news-release-details/legend-biotech-announces-extension-pdufa-date-cilta-cel. Accessed January 19, 2022.

50. CAR T-cell Therapy and Its Side Effects. 2021. Available at: https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/car-t-cell1.html. Accessed January 4, 2022.

51. Levine BL, Miskin J, Wonnacott K, Keir C. Global Manufacturing of CAR T Cell Therapy. Mol Ther Methods Clin Dev 2017;4:92–101. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28344995.

52. Boyiadzis MM, Dhodapkar MV, Brentjens RJ, et al. Chimeric antigen receptor (CAR) T therapies for the treatment of hematologic malignancies: clinical perspective and significance. J Immunother Cancer 2018;6:137. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30514386.

53. Wang X, Riviere I. Clinical manufacturing of CAR T cells: foundation of a promising therapy. Mol Ther Oncolytics 2016;3:16015. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27347557.

54. Kochenderfer JN, Dudley ME, Kassim SH, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. J Clin Oncol 2015;33:540–549. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25154820.

55. Turtle CJ, Hanafi LA, Berger C, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest 2016;126:2123–2138. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27111235.

56. Alvi RM, Frigault MJ, Fradley MG, et al. Cardiovascular Events Among Adults Treated With Chimeric Antigen Receptor T-Cells (CAR-T). J Am Coll Cardiol 2019;74:3099–3108. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31856966.

57. Ghosh AK, Chen DH, Guha A, et al. CAR T Cell Therapy-Related Cardiovascular Outcomes and Management: Systemic Disease or Direct Cardiotoxicity? JACC CardioOncol 2020;2:97–109. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34396213.

58. Fitzgerald JC, Weiss SL, Maude SL, et al. Cytokine Release Syndrome After Chimeric Antigen Receptor T Cell Therapy for Acute

Lymphoblastic Leukemia. Crit Care Med 2017;45:e124–e131. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27632680.
59. Burstein DS, Maude S, Grupp S, et al. Cardiac Profile of Chimeric Antigen Receptor T Cell Therapy in Children: A Single-Institution Experience. Biol Blood Marrow Transplant 2018;24:1590–1595. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29772353.
60. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med 2017;377:2531–2544. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29226797.
61. Jacobson C, Chavez JC, Sehgal AR, et al. Primary Analysis of Zuma-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients with Relapsed/Refractory (R/R) Indolent Non-Hodgkin Lymphoma (iNHL). Blood 2020;136:40–41. Available at: https://doi.org/10.1182/blood-2020-136834.
62. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med 2020;382:1331–1342. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32242358.
63. Shah BD, Ghobadi A, Oluwole OO, et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. Lancet 2021;398:491–502. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34097852.
64. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet 2020;396:839–852. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32888407.
65. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med 2019;380:45–56. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30501490.
66. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med 2018;378:439–448. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29385370.
67. Munshi NC, Anderson LD, Jr., Shah N, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. N Engl J Med 2021;384:705–716. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33626253.
68. Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant 2019;25:625–638. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30592986.
69. Varadarajan I, Kindwall-Keller TL, Lee DW. Management of Cytokine Release Syndrome. In: Lee DW, Shah NN, eds. Chimeric Antigen Receptor T-Cell Therapies for Cancer: Elsevier; 2020:45–64.
70. Hay KA, Hanafi LA, Li D, et al. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor-modified T-cell therapy. Blood 2017;130:2295–2306. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28924019.
71. Teachey DT, Lacey SF, Shaw PA, et al. Identification of Predictive Biomarkers for Cytokine Release Syndrome after Chimeric Antigen Receptor T-cell Therapy for Acute Lymphoblastic Leukemia. Cancer Discov 2016;6:664–679. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27076371.
72. Gust J, Hay KA, Hanafi LA, et al. Endothelial Activation and Blood-Brain Barrier Disruption in Neurotoxicity after Adoptive Immunotherapy with CD19 CAR-T Cells. Cancer Discov 2017;7:1404–1419. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29025771.
73. Norelli M, Camisa B, Barbiera G, et al. Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells. Nat Med 2018;24:739–748. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29808007.
74. Giavridis T, van der Stegen SJC, Eyquem J, et al. CAR T cell-induced cytokine release syndrome is mediated by macrophages and abated by IL-1 blockade. Nat Med 2018;24:731–738. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29808005.
75. Taraseviciute A, Tkachev V, Ponce R, et al. Chimeric Antigen Receptor T Cell-Mediated Neurotoxicity in Nonhuman Primates. Cancer Discov 2018;8:750–763. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29563103.

76. Jacobson CA, Hunter BD, Redd R, et al. Axicabtagene Ciloleucel in the Non-Trial Setting: Outcomes and Correlates of Response, Resistance, and Toxicity. J Clin Oncol 2020;38:3095–3106. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32667831.
77. Nastoupil LJ, Jain MD, Feng L, et al. Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium. J Clin Oncol 2020;38:3119–3128. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32401634.
78. Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet 2015;385:517–528. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25319501.
79. Turtle CJ, Hay KA, Hanafi LA, et al. Durable Molecular Remissions in Chronic Lymphocytic Leukemia Treated With CD19-Specific Chimeric Antigen Receptor-Modified T Cells After Failure of Ibrutinib. J Clin Oncol 2017;35:3010–3020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28715249.
80. Prescribing Information: Tocilizumab injection, for intravenous or subcutaneous use. Genentech, Inc; 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125472s044lbl.pdf. Accessed January 2022.
81. Le RQ, Li L, Yuan W, et al. FDA Approval Summary: Tocilizumab for Treatment of Chimeric Antigen Receptor T Cell-Induced Severe or Life-Threatening Cytokine Release Syndrome. Oncologist 2018;23:943–947. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29622697.
82. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124:188–195. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24876563.
83. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. Nat Rev Clin Oncol 2018;15:47–62. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28925994.
84. Topp MS, van Meerten T, Houot R, et al. Earlier corticosteroid use for adverse event management in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. Br J Haematol 2021;195:388–398. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34590303.
85. Prescribing Information: Siltuximab for injection, for intravenous use. EUSA Pharma (UK), Ltd.; 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125496s000lbl.pdf. Accessed January 2022.
86. Chen F, Teachey DT, Pequignot E, et al. Measuring IL-6 and sIL-6R in serum from patients treated with tocilizumab and/or siltuximab following CAR T cell therapy. J Immunol Methods 2016;434:1–8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27049586.
87. Frey NV, Levine BL, Lacey SF, et al. Refractory Cytokine Release Syndrome in Recipients of Chimeric Antigen Receptor (CAR) T Cells. Blood 2014;124:2296–2296. Available at: https://doi.org/10.1182/blood.V124.21.2296.2296.
88. Prescribing Information: Anakinra injection, for subcutaneous use. Swedish Orphan Biovitrum AB; 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/103950s5189lbl.pdf. Accessed January 2020.
89. Jatiani SS, Aleman A, Madduri D, et al. Myeloma CAR-T CRS Management With IL-1R Antagonist Anakinra. Clin Lymphoma Myeloma Leuk 2020;20:632–636 e631. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32553791.
90. Strati P, Ahmed S, Kebriaei P, et al. Clinical efficacy of anakinra to mitigate CAR T-cell therapy-associated toxicity in large B-cell lymphoma. Blood Adv 2020;4:3123–3127. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32645136.
91. Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med 2014;6:224ra225. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24553386.
92. Oluwole O FE, Munoz J et al. Prophylactic Corticosteroid Use with Axicabtagene Ciloleucel (Axi-Cel) in Patients (Pts) with Relapsed/Refractory Large B-Cell Lymphoma (R/R LBCL): One-Year Follow-up of ZUMA-1 Cohort 6 (C6) [abstract]. Presented at the American Society of Hematology Annual Meeting 2021. Abstract 2832.
93. Oluwole OO, Bouabdallah K, Munoz J, et al. Prophylactic corticosteroid use in patients receiving axicabtagene ciloleucel for large

B-cell lymphoma. Br J Haematol 2021;194:690–700. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34296427.
94. Maus MV, Alexander S, Bishop MR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune effector cell-related adverse events. J Immunother Cancer 2020;8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33335028.
95. Pan J, Deng B, Ling Z, et al. Ruxolitinib mitigates steroid-refractory CRS during CAR T therapy. J Cell Mol Med 2021;25:1089–1099. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33314568.
96. Kenderian SS, Ruella M, Shestova O, et al. Ruxolitinib Prevents Cytokine Release Syndrome after Car T-Cell Therapy Without Impairing the Anti-Tumor Effect in a Xenograft Model. Biology of Blood and Marrow Transplantation 2017;23:S19–S20. Available at: https://doi.org/10.1016/j.bbmt.2016.12.003.
97. Wei S, Gu R, Xu Y, et al. Adjuvant ruxolitinib therapy relieves steroid-refractory cytokine-release syndrome without impairing chimeric antigen receptor-modified T-cell function. Immunotherapy 2020;12:1047–1052. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32777959.
98. Constantinescu C, Pasca S, Tat T, et al. Continuous renal replacement therapy in cytokine release syndrome following immunotherapy or cellular therapies? J Immunother Cancer 2020;8:e000742. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32474415.
99. Liu Y, Chen X, Wang D, et al. Hemofiltration Successfully Eliminates Severe Cytokine Release Syndrome Following CD19 CAR-T-Cell Therapy. J Immunother 2018;41:406–410. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30198955.
100. Xiao X, He X, Li Q, et al. Plasma Exchange Can Be an Alternative Therapeutic Modality for Severe Cytokine Release Syndrome after Chimeric Antigen Receptor-T Cell Infusion: A Case Report. Clin Cancer Res 2019;25:29–34. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30322878.
101. Roche. Roche statement on global supply constraints of Actemra/RoActemra: Roche; 2021. Available at: https://www.roche.com/dam/jcr:a42a1844-a83e-470d-bebb-9badc8344d89/en/20210816_Roche_statement_global_Actemra_supply.pdf.
102. Santomasso BD, Park JH, Salloum D, et al. Clinical and Biological Correlates of Neurotoxicity Associated with CAR T-cell Therapy in Patients with B-cell Acute Lymphoblastic Leukemia. Cancer Discov 2018;8:958–971. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29880584.
103. Nellan A, McCully CML, Cruz Garcia R, et al. Improved CNS exposure to tocilizumab after cerebrospinal fluid compared to intravenous administration in rhesus macaques. Blood 2018;132:662–666. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29954750.
104. Gardner RA, Ceppi F, Rivers J, et al. Preemptive mitigation of CD19 CAR T-cell cytokine release syndrome without attenuation of antileukemic efficacy. Blood 2019;134:2149–2158. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31697826.
105. Gust J, Ceppi F, Turtle CJ. Neurotoxicities After CAR T-Cell Immunotherapy. In: Lee DW, Shah NN, eds. Chimeric Antigen Receptor T-Cell Therapies for Cancer: Elsevier; 2020:83–105.
106. Karschnia P, Jordan JT, Forst DA, et al. Clinical presentation, management, and biomarkers of neurotoxicity after adoptive immunotherapy with CAR T cells. Blood 2019;133:2212–2221. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30808634.
107. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet 2021;398:314–324. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34175021.
108. Titov A, Petukhov A, Staliarova A, et al. The biological basis and clinical symptoms of CAR-T therapy-associated toxicites. Cell Death Dis 2018;9:897. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30181581.
109. Rice J, Nagle S, Randall J, Hinson HE. Chimeric Antigen Receptor T Cell-Related Neurotoxicity: Mechanisms, Clinical Presentation, and Approach to Treatment. Curr Treat Options Neurol 2019;21:40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31327064.
110. Rubin DB, Al Jarrah A, Li K, et al. Clinical Predictors of Neurotoxicity After Chimeric Antigen Receptor T-Cell Therapy. JAMA Neurol 2020;77:1536–1542. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32777012.

111. Santomasso BD, Nastoupil LJ, Adkins S, et al. Management of Immune-Related Adverse Events in Patients Treated With Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline. J Clin Oncol 2021;39:3978–3992. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34724386.
112. Henter JI, Horne A, Arico M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124–131. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16937360.
113. Ramos-Casals M, Brito-Zeron P, Lopez-Guillermo A, et al. Adult haemophagocytic syndrome. Lancet 2014;383:1503–1516. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24290661.
114. Ceppi F, Summers C, Gardner RA. Hematologic and Non-CRS Toxicities. In: Lee DW, Shah NN, eds. Chimeric Antigen Receptor T-Cell Therapies for Cancer: Elsevier; 2020:107–112.
115. Sandler RD, Tattersall RS, Schoemans H, et al. Diagnosis and Management of Secondary HLH/MAS Following HSCT and CAR-T Cell Therapy in Adults; A Review of the Literature and a Survey of Practice Within EBMT Centres on Behalf of the Autoimmune Diseases Working Party (ADWP) and Transplant Complications Working Party (TCWP). Front Immunol 2020;11:524. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32296434.
116. Teachey DT, Bishop MR, Maloney DG, Grupp SA. Toxicity management after chimeric antigen receptor T cell therapy: one size does not fit 'ALL'. Nat Rev Clin Oncol 2018;15:218. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29434335.
117. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med 2014;371:1507–1517. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25317870.
118. Porter DL, Hwang WT, Frey NV, et al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. Sci Transl Med 2015;7:303ra139. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26333935.
119. Jordan MB, Allen CE, Weitzman S, et al. How I treat hemophagocytic lymphohistiocytosis. Blood 2011;118:4041–4052. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21828139.
120. Tamamyan GN, Kantarjian HM, Ning J, et al. Malignancy-associated hemophagocytic lymphohistiocytosis in adults: Relation to hemophagocytosis, characteristics, and outcomes. Cancer 2016;122:2857–2866. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27244347.
121. Shah NN, Highfill SL, Shalabi H, et al. CD4/CD8 T-Cell Selection Affects Chimeric Antigen Receptor (CAR) T-Cell Potency and Toxicity: Updated Results From a Phase I Anti-CD22 CAR T-Cell Trial. J Clin Oncol 2020;38:1938–1950. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32286905.
122. Major A, Collins J, Craney C, et al. Management of hemophagocytic lymphohistiocytosis (HLH) associated with chimeric antigen receptor T-cell (CAR-T) therapy using anti-cytokine therapy: an illustrative case and review of the literature. Leuk Lymphoma 2021;62:1765–1769. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33559517.
123. Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood 2015;125:2908–2914. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25758828.
124. NCI Dictionary of Cancer Terms. Available at: https://www.cancer.gov/publications/dictionaries/cancer-terms. Accessed January 19, 2022.
125. Doan A, Pulsipher MA. Hypogammaglobulinemia due to CAR T-cell therapy. Pediatr Blood Cancer 2018;65. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29230962.
126. Garcia-Lloret M, McGhee S, Chatila TA. Immunoglobulin replacement therapy in children. Immunol Allergy Clin North Am 2008;28:833–849, ix. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18940577.
127. Jain T, Knezevic A, Pennisi M, et al. Hematopoietic recovery in patients receiving chimeric antigen receptor T-cell therapy for hematologic malignancies. Blood Adv 2020;4:3776–3787. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32780846.
128. Fried S, Avigdor A, Bielorai B, et al. Early and late hematologic toxicity following CD19 CAR-T cells. Bone Marrow Transplant 2019;54:1643–1650. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30809033.
129. Logue JM, Zucchetti E, Bachmeier CA, et al. Immune reconstitution and associated infections following axicabtagene ciloleucel in relapsed or

refractory large B-cell lymphoma. Haematologica 2021;106:978–986. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32327504.
130. Nahas GR, Komanduri KV, Pereira D, et al. Incidence and risk factors associated with a syndrome of persistent cytopenias after CAR-T cell therapy (PCTT). Leuk Lymphoma 2020;61:940–943. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31793821.
131. Schaefer A, Saygin C, Maakaron J, et al. Cytopenias after Chimeric Antigen Receptor T-Cells (CAR-T) Infusion; Patterns and Outcomes. Biology of Blood and Marrow Transplantation 2019;25:S171. Available at: https://www.sciencedirect.com/science/article/pii/S1083879118311339.
132. Hill JA, Li D, Hay KA, et al. Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. Blood 2018;131:121–130. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29038338.
133. Park JH, Romero FA, Taur Y, et al. Cytokine Release Syndrome Grade as a Predictive Marker for Infections in Patients With Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia Treated With Chimeric Antigen Receptor T Cells. Clin Infect Dis 2018;67:533–540. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29481659.
134. Gill S, Brudno JN. CAR T-Cell Therapy in Hematologic Malignancies: Clinical Role, Toxicity, and Unanswered Questions. Am Soc Clin Oncol Educ Book 2021;41:1–20. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33989023.
135. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol 2019;20:31–42. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30518502.
136. Cappell KM, Sherry RM, Yang JC, et al. Long-Term Follow-Up of Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy. J Clin Oncol 2020;38:3805–3815. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33021872.
137. Hill JA, Seo SK. How I prevent infections in patients receiving CD19-targeted chimeric antigen receptor T cells for B-cell malignancies. Blood 2020;136:925–935. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32582924.
138. Martin T, Usmani SZ, Berdeja JG, et al. Ciltacabtagene Autoleucel, an Anti–B-cell Maturation Antigen Chimeric Antigen Receptor T-Cell Therapy, for Relapsed/Refractory Multiple Myeloma: CARTITUDE-1 2-Year Follow-Up. Journal of Clinical Oncology 2023;41:1265–1274. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35658469.
139. Cohen AD, Parekh S, Santomasso BD, et al. Incidence and management of CAR-T neurotoxicity in patients with multiple myeloma treated with ciltacabtagene autoleucel in CARTITUDE studies. Blood Cancer J 2022;12:32. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35210399.
140. Karschnia P, Miller KC, Yee AJ, et al. Neurologic toxicities following adoptive immunotherapy with BCMA-directed CAR T cells. Blood 2023;142:1243–1248. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37471607.
141. Prescribing Information: Ciltacabtagene autoleucel suspension for intravenous infusion. 2024. Available at: https://www.fda.gov/media/156560/download?attachment. Accessed August 9, 2024.
142. Graham CE, Lee WH, Wiggin HR, et al. Chemotherapy-induced reversal of ciltacabtagene autoleucel-associated movement and neurocognitive toxicity. Blood 2023;142:1248–1252. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37467494.
143. van Doorn PA, Van den Bergh PYK, Hadden RDM, et al. European Academy of Neurology/Peripheral Nerve Society Guideline on diagnosis and treatment of Guillain-Barre syndrome. Eur J Neurol 2023;30:3646–3674. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37814552.
144. Rolin C, Zimmer J, Seguin-Devaux C. Bridging the gap with multispecific immune cell engagers in cancer and infectious diseases. Cell Mol Immunol 2024;21:643–661. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38789528.
145. Crombie JL, Graff T, Falchi L, et al. Consensus recommendations on the management of toxicity associated with CD3xCD20 bispecific antibody therapy. Blood 2024;143:1565–1575. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38252906.