ASCO special articles

Management of Immune-Related Adverse Events in Patients Treated With Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline

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abstract

PURPOSE To increase awareness, outline strategies, and offer guidance on the recommended management of immune-related adverse events (irAEs) in patients treated with chimeric antigen receptor (CAR) T-cell therapy.

METHODS A multidisciplinary panel of medical oncology, neurology, hematology, emergency medicine, nursing, trialists, and advocacy experts was convened to develop the guideline. Guideline development involved a systematic literature review and an informal consensus process. The systematic review focused on evidence published from 2017 to 2021.

RESULTS The systematic review identified 35 eligible publications. Because of the paucity of high-quality evidence, recommendations are based on expert consensus.

RECOMMENDATIONS The multidisciplinary team issued recommendations to aid in the recognition, workup, evaluation, and management of the most common CAR T-cell–related toxicities, including cytokine release syndrome, immune effector cell–associated neurotoxicity syndrome, B-cell aplasia, cytopenias, and infections. Management of short-term toxicities associated with CAR T cells begins with supportive care for most patients, but may require pharmacologic interventions for those without adequate response. Management of patients with prolonged or severe CAR T-cell–associated cytokine release syndrome includes treatment with tocilizumab with or without a corticosteroid. On the basis of the potential for rapid decline, patients with moderate to severe immune effector cell–associated neurotoxicity syndrome should be managed with corticosteroids and supportive care.

Additional information is available at www.asco.org/supportive-care-guidelines.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Immunotherapy has revolutionized the treatment of many different types of cancers. Chimeric antigen receptor T-cell (CAR T) therapy is an expanding immunotherapeutic approach and is currently used for several hematologic neoplasms. CAR T therapy modifies T cells to redirect them to eradicate malignant cells and offers durable and sustained remissions in many patients. The most notable advantage of CAR T-cell therapy is the short treatment time needed, administered with a single infusion and close monitoring.[1] CAR T-cell therapy is regarded as a living drug, as cells are expected to persist in the long term with efficacy that may last for decades.[1,2] However, they can also be associated with severe toxicities, such as cytokine release syndrome (CRS) or immune effector cell–associated neurotoxicity syndrome (ICANS). Although these toxicities are most often manageable and reversible with proper supportive care, they can be fatal and they require close vigilance and prompt treatment. Timely recognition of these toxicities and early intervention reduce morbidity and mortality. The incidence of CRS has been reported to range from 57% to 93%, and ICANS from 20% to 70%, on the basis of the agent used.[3,4]

The guideline offers expert guidance on the diagnosis, evaluation, and management of CRS, ICANS, and other potential but less common toxicities related to CAR T-cell therapy, including hemophagocytic lymphohistiocytosis (HLH), B-cell aplasia, cytopenias, disseminated intravascular coagulation (DIC), and infections. With the increasing use of CAR T-cell therapy in cancer treatment regimens, it is imperative that clinicians are knowledgeable about the symptoms

THE BOTTOM LINE

Management of Immune-related Adverse Events in Patients Treated with CAR T-Cell Therapy: ASCO Guideline

Guideline Question

How should clinicians manage immune-related adverse events in adult patients with cancer treated with chimeric antigen receptor (CAR) T-cell therapy?

Target Population

Adult patients with cancer receiving treatment with CAR T-cell therapy alone.

Target Audience

Health care practitioners, including oncologists, other medical subspecialists, emergency medicine, internal and family medicine practitioners, nurses, and pharmacists, who provide care to patients with cancer, as well as patients receiving CAR T-cell therapy, and their caregivers.

Methods

An Expert Panel was convened to update the clinical practice guideline recommendations on the basis of a systematic review of the medical literature.

Key Recommendations

The following are general recommendations that should be followed. For specific CAR T–related toxicities management, see Tables 1-7.

It is recommended that clinicians manage toxicities as follows:

- Management of short-term toxicities associated with CAR T cells begins with supportive care for most patients, but may require pharmacologic interventions for those without adequate response.
- Management of patients with prolonged or severe CAR T-cell–associated cytokine release syndrome includes treatment with tocilizumab with or without a corticosteroid.
- On the basis of the potential for rapid decline, patients with moderate to severe immune effector cell–associated neurotoxicity syndrome should be managed with corticosteroids and best supportive care. Steroids should be rapidly tapered once symptoms improve to grade 1.

All recommendations in this guideline are consensus based with benefits outweighing harms.

Additional Resources

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

associated with these agents, how best to monitor them, and their recommended management.

GUIDELINE QUESTIONS

This clinical practice guideline focuses on one overarching clinical question: How should clinicians manage immune-mediated adverse events in adult patients with cancer treated with chimeric antigen receptor (CAR) T-cell therapy?

METHODS

Guideline Development Process

A multidisciplinary panel of medical oncology, neurology, hematology, emergency medicine, dermatology, gastroenterology, rheumatology, pulmonology, endocrinology, nursing, trialists, and patient advocacy experts was convened to develop the clinical practice guideline (Appendix Table A1, online only). The Expert Panel met via teleconference and webinar and corresponded through e-mail. On the basis of the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review and submitted to the *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical

Practice Guideline Committee before publication. All funding for the administration of this project was provided by ASCO.

ASCO guidelines are based on systematic reviews of the literature. A protocol for each systematic review defines parameters for a targeted literature search. Additional parameters include relevant study designs, literature sources, types of reports, and prespecified inclusion and exclusion criteria for literature identified.

A literature search of the PubMed database was performed on May 15, 2020, to obtain key literature on CAR T-cell–related toxicity published since 2017, using CAR T-cell–specific terms combined with safety, adverse events (AEs), and toxicity-specific terms. The search was updated on March 2, 2021. Articles were selected for inclusion in the systematic review of the evidence based on the following criteria:

- *Population*: Adult patients with cancer receiving treatment with CAR T therapy
- *Intervention*: Steroids, immunosuppressive therapy, dose modification of therapy, organ-specific management, hospitalization, consultation to subspecialties, and best supportive care
- *Comparator*: No intervention or best supportive care
- *Outcomes*: Hospitalization, AE-related morbidity or mortality, organ dysfunction on the basis of organ system affected, required treatment because of immune-mediated AEs, recovery from AEs, and health-related quality of life.

The search results were narrowed by selecting studies in humans published in English. Articles were excluded if they (1) involve investigational agents that have not yet received US Food and Drug Administration approval and (2) were clinical trial protocols.

The guideline recommendations are crafted, in part, using the *Guidelines Into Decision Support* (GLIDES) methodology.[5] In addition, a guideline implementability review was conducted. On the basis of the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice.

The ASCO Expert Panel and guidelines staff will work with cochairs to keep abreast of any substantive updates to the guideline. On the basis of formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at https://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

A total of 35 studies met the eligibility criteria of the systematic review and were pertinent to the development of the recommendations (Data Supplement, online only). Much of the evidence consisted of retrospective observational data in the form of case series and case reports. Such study designs represent low-quality evidence with an inherent risk of reporting bias, as only events of interest are described. Nonetheless, when describing a new entity in terms of its clinical manifestations, such reports provide important information to describe the range of phenotypes possible.[6] Other factors potentially contributing to the risk of bias in the included studies are the small sample sizes and retrospective nature of the evidence. Because of the limitations and low quality of the available evidence, the guideline panel developed expert opinion–based recommendations through an informal consensus process. Employment of formal consensus methodology was deemed unnecessary, favoring open discussion that allowed for the articulation of views and opinions instead.

RECOMMENDATIONS

All recommendations in this guideline are expert consensus based; benefits outweigh harms; strength of recommendation: moderate.

Clinical Question

How should clinicians manage immune-mediated adverse events in adult patients with cancer treated with chimeric antigen receptor (CAR) T-cell therapy?

1. General Recommendations

- In patients with active infection, CAR T-cell infusion should be delayed until the infection has been successfully treated or controlled.[7]
- Inactivated influenza and COVID-19 vaccination of patients and family members is recommended, as per local guidelines and ASCO guidance (https://www.asco.org/sites/new-www.asco.org/files/content-files/covid-19/2021-MSK-COVID19-VACCINE-GUIDELINES.pdf). Although the immunogenicity and efficacy of COVID-19 vaccines are uncertain in patients receiving immunomodulatory agents, the potential for benefit from vaccination likely outweighs these uncertainties for most patients.
- Strongly consider evaluation and/or transfer to a specialty center that has experience with CAR T toxicity management. If treated in an outpatient setting, it is advisable that patients remain within 2 hours of the treating center for 4-8 weeks post-therapy and should return to their treating center upon experiencing any toxicities.

2. Toxicity-Specific Recommendations

2.1. Identification, evaluation, and management of cytokine release syndrome. CRS is a disorder caused by the release of cytokines from bystander immune and nonimmune cells.[8] The onset of CRS is variable and dependent on the CAR T-cell product and patient population, with peaks at 2-7 days after infusion and delays of up to 3 weeks reported.[9]

Presenting symptoms related to CAR T-cell–induced CRS may include fever, tachycardia, hypoxia, nausea, headache, rash, shortness of breath, mild or serious hypotension requiring vasopressors, respiratory failure, coagulopathy, and/or multiorgan system failure.

Refer to Table 1 for a complete set of recommendations, definition of grades, and additional considerations.

Discussion. CRS is defined by CTCAE as a "disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines."[8] Multiple grading systems have been developed over the past few years to grade CRS. Because of variability in grading and management of CRS, consensus criteria were developed by the American Society of Transplantation and Cellular Therapy (ASTCT) in 2019.[10] The definition of CRS used to develop the ASTCT consensus criteria is "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. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction." CRS is primarily managed with interleukin-6 (IL-6) antagonists (tocilizumab) in lower-grade CRS and with corticosteroids in refractory, prolonged, or higher-grade CRS. Although there is limited experience with additional therapies, alternate IL-6 antagonist therapies including siltuximab and clazakizumab may be used for CRS refractory to tocilizumab. However, no direct comparative studies of the efficacy of available IL-6 antagonists have been conducted. Anakinra, an IL-1 receptor antagonist, has been shown to mitigate CRS in some CAR T-cell therapy recipients with high-grade CRS.[11]

2.2. Identification, Evaluation, and Management of CAR T–Related Neurotoxicity or Immune Effector Cell–Associated Neurotoxicity Syndrome

Neurotoxicity or ICANS is defined as a disorder characterized by a pathologic process involving the CNS following any immune effector therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema.[10]

The median time to onset is 4 days after infusion.[9]

Refer to Table 2 for a complete set of recommendations, definition of grades, and additional considerations.

TABLE 1. Cytokine Release Syndrome Recommendations

Grading (on the basis of ASTCT consensus grading)[10]	Management
Workup or evaluation and supportive care recommendations (all grades): CBC, CMP, magnesium, phosphorus, CRP, LDH, uric acid, fibrinogen, PT/PTT, and ferritin Assess for infection with blood and urine cultures, and a chest radiograph if fever is present If patient is neutropenic, follow institutional neutropenic fever guidelines Patients who experience grade 2 or higher CRS (eg, hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. Perform cardiac monitoring in patients who experience at least G2 CRS, clinically significant arrhythmia, and additionally as clinically indicated Consider screening for CMV and EBV Consider chest or abdominal CT imaging, brain MRI, and/or lumbar puncture.	
G1: Fever[a]: temperature ≥ 38°C not attributable to any other cause Hypotension: none Hypoxia: none	Offer supportive care with antipyretics, IV hydration, and symptomatic management of organ toxicities and constitutional symptoms May consider empiric broad-spectrum antibiotics if neutropenic. May consider G-CSF in accordance with product guidelines. Note: GM-CSF is not recommended In patients with persistent (> 3 days) or refractory fever, consider managing as per G2
G2: Fever[a]: temperature ≥ 38°C not attributable to any other cause *plus* Hypotension: not requiring vasopressors *And/or* Hypoxia: requiring low-flow nasal cannula (ie, oxygen delivered at ≤ 6 L/min) or blowby	Continue supportive care as per G1 and include IV fluid bolus and/or supplemental oxygen as needed Administer tocilizumab[42-44] 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). Repeat every 8 hours if no improvement in signs and symptoms of CRS; limit to a maximum of three doses in a 24-hour period, with a maximum of four doses total In patients with hypotension that persists after two fluid boluses and after one to two doses of tocilizumab, may consider dexamethasone 10 mg IV (or equivalent) every 12 hours for one to two doses and then reassess Manage per G3 if no improvement within 24 hours of starting tocilizumab
G3: Fever[a]: temperature ≥ 38°C not attributable to any other cause *plus* Hypotension: requiring a vasopressor with or without vasopressin *And/or* Hypoxia: requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Continue supportive care as per G2 and include vasopressors as needed Admit patient to ICU If echocardiogram was not already performed, obtain ECHO to assess cardiac function and conduct hemodynamic monitoring Tocilizumab as per G2 if maximum dose is not reached within 24-hour period plus dexamethasone 10 mg IV every 6 hours (or equivalent) and rapidly taper once symptoms improve If refractory, manage as per G4
G4: Fever[a]: temperature ≥ 38°C not attributable to any other cause *plus* Hypotension: requiring multiple vasopressors (excluding vasopressin) *And/or* Hypoxia: requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)	Continue supportive care as per G3 plus mechanical ventilation as needed Administer tocilizumab as per G2 if maximum is not reached within 24-hour period Initiate high-dose methylprednisolone at a dose of 500 mg IV every 12 hours for 3 days, followed by 250 mg IV every 12 hours for 2 days, 125 mg IV every 12 hours for 2 days, and 60 mg IV every 12 hours until CRS improvement to G1 If not improving, consider methylprednisolone 1,000 mg IV 2 times a day or alternate therapy[b]
Additional considerations: Organ toxicities associated with CRS may be graded according to CTCAE v5.0, but they do not influence CRS grading CRS may be associated with cardiac, hepatic, and/or renal dysfunction Earlier steroid use appears to reduce the rate of CAR T-cell treatment–related CRS and neurologic events and is recommended for some products (axicabtagene ciloleucel or brexucabtagene autoleucel)[45-47] Strongly consider antifungal prophylaxis in patients receiving steroids for the treatment of CRS and/or ICANS	

Abbreviations: ASTCT, American Society of Transplantation and Cellular Therapy; CAR T, chimeric antigen receptor T; BiPAP, bilevel positive airway pressure; CMP, comprehensive metabolic panel; CMV, cytomegalovirus; CPAP, continuous positive airway pressure; CRP, C-reactive protein; CRS, cytokine release syndrome; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; EBV, Epstein-Barr virus; G, grade; G-CSF, granulocyte-colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICANS, immune effector cell–associated neurotoxicity syndrome; ICU, intensive care unit; IV, intravenous; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PT, prothrombin time; PTT, partial thromboplastin time

[a]Fever is not required to grade subsequent CRS severity in patients who receive antipyretics or anticytokine therapy (steroids or tocilizumab). Instead, CRS grading is driven by hypotension and/or hypoxia.[10]

[b]Noting limited experience with other agents, alternate options may include anakinra, siltuximab, ruxolitinib, cyclophosphamide, and antithymocyte globulin.[11,46,48]

Discussion. ICANS is the second major side effect that develops in a substantial proportion of patients treated with CD19-targeted CAR T cells and a small percentage of patients treated with B-cell maturation agent (BCMA)-targeted CAR T cells. Clinical manifestations of ICANS include encephalopathy with confusion and behavioral changes, expressive aphasia or other language disturbance, dysgraphia, dysarthria, fine motor impairment and other weakness, tremor, myoclonus, and headache. In more severe cases, patients may become obtunded or develop seizures and require intubation for airway protection. In very rare cases, malignant cerebral edema may develop, which may be fatal. ICANS may occur concurrently with CRS, shortly after CRS abates, and with delayed onset occurring up to one month after infusion. ICANS is typically self-limited with symptoms most often lasting between 5 and 17 days. The time of onset, duration, and severity of ICANS may vary depending on the CAR product and the disease state of the patient. As for CRS, the ASTCT Consensus grading system is recommended for the grading of ICANS. The ICANS grading system incorporates the 10-point Immune Effector Cell–Associated Encephalopathy (ICE) score, a standardized assessment for encephalopathy, and evaluation of other neurologic domains including level of consciousness, severe motor weakness, seizures, and signs of elevated intracranial pressure or cerebral edema.[10] Patients are graded according to the most severe symptom in any of the five domains. For children younger than 12 years or those with developmental delay, the Cornell Assessment of Pediatric Delirium score[12] is used in place of the ICE assessment. The ICE assessment can be used as a daily screen for the onset of ICANS during the at-risk period.

The mainstay of treatment of ICANS is supportive care and corticosteroids. Tocilizumab does not resolve ICANS and may worsen it. Because of the possibility that tocilizumab may worsen neurotoxicity, the management of ICANS may take precedence over the management of low-grade CRS when the two occur simultaneously. Although cases of low-grade neurotoxicity may resolve without intervention, for grade 2 or higher ICANS, corticosteroids are generally used. Patients who do not show improvement within 24 hours should have repeat neuroimaging followed by CSF evaluation including opening pressure measurement, if possible. Several other therapeutic approaches are under investigation in clinical trials including anakinra, lenzilumab, and defibrotide.[13]

2.3. Identification, Evaluation, and Management of HLH

HLH is defined as a disorder in which histiocytes and lymphocytes build up in organs including the skin, spleen, and liver and destroy other blood cells. Proposed diagnostic criteria for CAR T-cell–related HLH include elevated ferritin of $>$ 10,000 ng/mL, along with at least two organ toxicities, including the presence of hemophagocytosis in bone marrow or organs, or at least grade 3 transaminitis, renal insufficiency, or pulmonary edema.[14] Presenting symptoms related to CAR T–induced HLH may include fever; enlarged spleen; enlarged liver; swollen lymph nodes; skin rash; jaundice; lung problems such as coughing and trouble breathing; digestive problems such as stomach ache, vomiting, and diarrhea; and nervous system problems such as headaches, trouble walking, vision disturbances, and weakness.

Refer to Table 3 for a complete set of recommendations, definition of grades, and additional considerations.

Discussion. HLH has been observed in recipients of CAR T-cell therapy; however, it is relatively rare with an incidence of approximately 3.5%.[15] Diagnosis can be challenging in the setting of CAR T-cell therapy because of somewhat similar presentation to CRS. Clinical distinction of CRS versus HLH may be made via presenting signs and symptoms. Diagnostic criteria for HLH associated with CAR T-cell therapy have been proposed,[14] and although grading systems also exist, none are validated or commonly used. As such, management is not necessarily specified by grade. Corticosteroids and IL-6 antagonist therapy have been used to treat HLH in CAR T-cell therapy recipients with grade 3 or greater organ toxicity. Etoposide may be used; however, data in CAR T-cell therapy recipients are lacking.[16] Anakinra has been used for refractory HLH in CAR T-cell therapy recipients; however, clinical efficacy is unclear.[11]

2.4. Identification, Evaluation, and Management of Cytopenias

Cytopenias, including anemias, thrombocytopenia, leukopenia, and neutropenia, are defined as a disorder causing a reduction in the number of mature blood cells. Presenting symptoms related to CAR T–induced cytopenias may include fatigue, weakness, shortness of breath, poor concentration, dizziness or feeling lightheaded, cold hands and feet, frequent infections, fever, bleeding, and bruising easily.

Refer to Table 4 for a complete set of recommendations, definition of grades, and additional considerations.

Discussion. Cytopenias may occur after CAR T-cell therapy. Acute cytopenia within 3 months of infusion of CAR T-cell therapy is more common. However, prolonged cytopenias may be seen in a small number of CAR T-cell recipients. The mechanism of prolonged cytopenias remains unclear and may be multifactorial. Growth factor support and corticosteroids may be used in cases not related to myelodysplastic syndrome.[17,18]

2.5. Identification, Evaluation, and Management of B-Cell Aplasia

B-cell aplasia is defined as a disorder caused by the depletion or absence of B cells. Presenting symptoms related to CAR T–induced B-cell aplasia may include frequent infections, and signs include low B-cell counts and low immunoglobulin levels.

Refer to Table 5 for a complete set of recommendations, definition of grades, and additional considerations.

TABLE 2. ICANS Recommendations

Grading (on the basis of ASTCT consensus grading)[10,a]	Management
Workup or evaluation and supportive care recommendations (all grades): Routine neurologic evaluation including the ICE score for cognitive assessment and assessment of motor weakness conducted at least two times a day Continually reassess for improvement or deterioration and escalate or de-escalate treatment and monitoring accordingly Serial monitoring of laboratory tests including CRP, ferritin, CBC, CMP, fibrinogen, and PT/PTT Consider seizure prophylaxis for CAR T-cell products known to be associated with ICANS or in patients at higher risk of seizure, such as those with seizure history, CNS disease, concerning EEG findings, or neoplastic brain lesions[4,49,50] Initiate neurology consultation in patients with signs of neurotoxicity Aspiration precautions and elevated head of bed Neuroimaging of the brain (MRI with and without contrast or CT if MRI is not available or feasible) for ≥ G2 neurotoxicity. For persistent grade ≥ 3 neurotoxicity, consider repeat neuroimaging (MRI or CT) every 2-3 days Lumbar puncture for ≥ G3 neurotoxicity and may consider for G2 EEG evaluation for unexplained altered mental status to assess seizure activity or for ≥ G2 neurotoxicity Monitor and correct severe hyponatremia	
G1: ICE score[b]: 7-9 with no depressed level of consciousness	No concurrent CRS Offer supportive care with IV hydration and aspiration precautions With concurrent CRS Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). Repeat every 8 hours as needed. Limit to a maximum of three doses in a 24-hour period; maximum total of four doses. Caution with repeated tocilizumab doses in patients with ICANS. Consider adding corticosteroids to tocilizumab past the first dose
G2: ICE score[b]: 3-6 *And/or* Mild somnolence awaking to voice	No concurrent CRS Offer supportive care as per G1 For high-risk products or patients, consider dexamethasone 10 mg IV × two doses (or equivalent) and reassess. Repeat every 6-12 hours if no improvement.[c] Rapidly taper steroids as clinically appropriate once symptoms improve to G1[d] With concurrent CRS Consider ICU transfer if ICANS associated with ≥ G2 CRS Administer tocilizumab as per G1 If refractory to tocilizumab past the first dose, initiate dexamethasone (10 mg IV every 6-12 hours[c]) or methylprednisolone equivalent (1 mg/kg IV every 12 hours). Continue corticosteroids until improvement to grade 1, and then rapidly taper as clinically appropriate[d]
G3: ICE score[b]: 0-2 *And/or* Depressed level of consciousness awakening only to tactile stimulus *And/or* Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention *And/or* Focal or local edema on neuroimaging	All G3 patients: Transfer patient to ICU No concurrent CRS Administer dexamethasone (10 mg IV every 6-12 hours[c]) or methylprednisolone equivalent (1 mg/kg IV every 12 hours). With concurrent CRS Administer tocilizumab as per grade 1 If refractory to tocilizumab past the first dose, initiate dexamethasone (10 mg IV every 6-12 hours[c]) or methylprednisolone equivalent (1 mg/kg IV every 12 hours). Continue corticosteroids until improvement to grade 1, and then rapidly taper as clinically appropriate[d]
G4: ICE score[b]: 0 (patient is unarousable and unable to perform ICE) *And/or* Stupor or coma *And/or* Life-threatening prolonged seizure (> 5 minutes) or repetitive clinical or electrical seizures without return to baseline in between *And/or* Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing or papilledema, cranial nerve VI palsy, or Cushing's triad	All G4 patients: Admit patient to ICU if not already receiving ICU care. Consider mechanical ventilation for airway protection No concurrent CRS Administer high-dose methylprednisolone IV 1,000 mg one to two times per day for 3 days If not improving, consider 1,000 mg of methylprednisolone two to three times per day or alternate therapy[e] Continue corticosteroids until improvement to grade 1, and then taper as clinically appropriate[d] Status epilepticus to be treated as per institutional guidelines With concurrent CRS Administer tocilizumab as per grade 1 in addition to methylprednisolone 1,000 mg IV one to two times per day for 3 days If not improving, consider 1,000 mg of methylprednisolone IV two to three times a day or alternate therapy[e] Continue corticosteroids until improvement to grade 1, and then taper as clinically appropriate[d]

NOTE[10]. (1) Other signs and symptoms such as headache, tremor, myoclonus, asterixis, parkinsonism, and hallucinations may occur and could be attributed to immune effector cell–engaging therapies. Although they are not included in the grading scale, careful attention and directed therapy may be warranted. (2) 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. (3) Decreased level of consciousness should be attributable to no other cause (eg, no sedating medication). (4) In cases of ICANS with concurrent CRS, tocilizumab use is directed at the concurrent CRS as tocilizumab has not been shown to mitigate neurologic toxicity. (5) Because of the possibility that tocilizumab may worsen ICANS, the management of ICANS may take precedence over the management of low-grade CRS when the two occur simultaneously. For example, a patient with grade 2 ICANS and fever alone (grade 1 CRS) should be given steroids.

Abbreviations: ASTCT, American Society of Transplantation and Cellular Therapy; CAPD, Cornell Assessment of Pediatric Delirium; CAR T, chimeric antigen receptor T; CMP, comprehensive metabolic panel; CRP, C-reactive protein; CRS, cytokine release syndrome; CT, computed tomography; ICANS, Immune effector cell–associated neurotoxicity syndrome; ICE, immune effector cell–associated encephalopathy; ICU, intensive care unit; IV, intravenous; MRI, magnetic resonance imaging; PT, prothrombin time; PTT, partial thromboplastin time.

[a]For children age $<$ 12 years, the CAPD is recommended to aid in the overall grading of ICANS.[12,51,52] A CAPD score of $\geq$ 9 is suggestive of delirium and should be considered grade 3 ICANS. The CAPD score may also be used in patients age $>$ 12 years with baseline developmental delay as it has been validated up to age 21 years.

[b]ICE Assessment Tool[10]: (1) Orientation: orientation to year, month, city, and hospital: 4 points. (2) Naming: ability to name three objects (eg, point to clock, pen, and button): 3 points. (3) Following commands: ability to follow simple commands (eg, show me 2 fingers or close your eyes and stick out your tongue): 1 point. (4) Writing: ability to write a standard sentence (eg, Our national bird is the bald eagle): 1 point. (5) Attention: ability to count backward from 100 by 10: 1 point.

[c]For some products that may be associated with more neurotoxicity (axicabtagene ciloleucel or brexucabtagene autoleucel), earlier administration of steroids starting at G1 ICANS and use of high-dose steroids at G3 may be an option.[45-47]

[d]ICANS flares have been reported with rapid steroid taper.[53] Close monitoring for ICANS relapse is encouraged during steroid taper.[53]

[e]Noting limited experience with other agents and alternate options for persistent or worsening ICANS may include anakinra, siltuximab, ruxolitinib, cyclophosphamide, antithymocyte globulin, or intrathecal hydrocortisone (50 mg) plus methotrexate (12 mg).[46,54]

Discussion. B-cell aplasia is due to on-target off-tumor effect of CD19-directed CAR T-cell therapy. B-cell aplasia can be prolonged post-CAR T-cell therapy, and there is variability in rates of prolonged B-cell aplasia. The main complications of B-cell aplasia are infections, which can be managed with infusion of intravenous immunoglobulins.[19-21]

2.6. Identification, Evaluation, and Management of DIC

DIC is defined as a disorder characterized by systemic pathologic activation of blood clotting mechanisms, which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors. Presenting symptoms related to CAR T–induced DIC may include bleeding, bruising, low blood pressure, shortness of breath, and confusion.

Refer to Table 6 for a complete set of recommendations, definition of grades, and additional considerations.

Discussion. Coagulopathies have been observed after CAR T-cell therapy and usually occur acutely, within the first few weeks after CAR T-cell infusion. DIC can occur with or without concurrent CRS. Recommended treatment is primarily supportive care and factor replacement on the basis of fibrinogen levels, partial thromboplastin time, and bleeding occurrences. Corticosteroids and IL-6 antagonist therapy can be used in the case of concurrent CRS or in the setting of severe bleeding complications. Evidence of other effective interventions is limited.[22,23]

2.7. Identification, Evaluation, and Management of Infections

Infections are defined as the presence of clinical findings plus corroborating laboratory, radiographic, histopathologic, and/or microbiologic evidence. Infections are classified as bacterial, viral, and fungal. Presenting symptoms related to CAR T–induced infections may include fever, nausea, worsening fatigue, headache, myalgias, and malaise.

Refer to Table 7 for a complete set of recommendations, definition of grades, and additional considerations.

Discussion. Infections are common after CAR T-cell therapy. Most infectious complications in CAR T-cell recipients occur early after CAR T-cell infusion. However, infectious complications can occur several weeks to months after CAR T-cell infusion. Late infections have been correlated with prolonged B-cell aplasia and corticosteroids use to treat CRS and/or ICANS.[24] Treatment is directed at the infectious source. Prophylactic antimicrobials are recommended for CAR T-cell recipients with prolonged cytopenias.

SURVIVORSHIP

ASCO promotes the use of survivorship care plans (SCPs) to enhance communication between the oncology team and patient and to improve communication and coordination of care between the oncology team and primary care provider (https://www.asco.org/practice-policy/cancer-care-initiatives/prevention-survivorship/survivorship/survivorship-5). Although SCPs are traditionally based on tumor type and treatments, they also contain individualized information about the given treatment(s), the need for future follow-up, tests for cancer and treatment-related toxicities, the potential chronic, long-term adverse effects from treatments, and health promotion after completion of treatment. SCPs for post-CAR T-cell therapy should include regularly scheduled follow-up visits. These patients are to be followed for up to 15 years as part of an ongoing registry to monitor long-term safety, as mandated by the US Food and Drug Administration,[25,26] and may be integrated into an existing SCP.

TABLE 3. HLH Recommendations

Workup or evaluation[55]:	
CBC with differential and coagulation studies (PT, aPTT, fibrinogen, and D-dimer)	
Liver function tests (ALT, AST, GGT, total bilirubin, albumin, and lactate dehydrogenase)	
Serum triglycerides (fasting) and serum ferritin	
Soluble IL-2 receptor alpha (sCD25 or sIL-2R) and/or CXCL9	
The following testing should be performed in all patients, on the basis of the signs and symptoms of specific organ involvement and/or the degree of suspicion for the presence of HLH[55]:	
Cultures of blood, bone marrow, urine, and CSF, and viral titers and quantitative PCR testing for EBV, CMV, adenovirus, and other suspected viruses. Follow levels of any identified virus during treatment with the appropriate antiviral therapy	
Bone marrow aspirate and biopsy	
Electrocardiograph, chest radiography, and echocardiogram	
Lumbar puncture with CSF analysis	
Brain MRI scan, with and without contrast. Imaging of the CNS may show parameningeal infiltrations, subdural effusions, necrosis, and other abnormalities	
Grading	**Management**[14,56,57]
All grades	Offer supportive care
	Use corticosteroids if the patient is deteriorating or unstable
	Although data are insufficient to recommend a transfusion threshold, replacement of fibrinogen should be considered in patients with a fibrinogen level below 150 mg/dL
	Manage G ≥ 3 organ toxicity with IL-6 antagonist plus corticosteroids
	If insufficient response after 48 hours, consider adding anakinra[11,58,59]
	Etoposide could be considered in severe, refractory cases, although there is a lack of data in this setting and concern for effect on lymphocytes.[16,60] Intrathecal cytarabine, with or without hydrocortisone, may also be considered for patients with HLH-associated neurotoxicity

Abbreviations: aPTT, activated partial thromboplastin time; CAR T, chimeric antigen receptor T; CMP, comprehensive metabolic panel; CMV, cytomegalovirus; CRP, C-reactive protein; CSF, cerebrospinal fluid; EBV, Epstein-Barr virus; G, grade; G-CSF, granulocyte-colony stimulating factor; GGT, gamma-glutamyl transferase; HLH, hemophagocytic lymphohistiocytosis; IL, interleukin; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PT, prothrombin time.

Although the acute toxicities of CAR T-cell therapy, such as CRS and ICANS, are well-defined, less is known about the long-term and late effects facing cancer survivors who receive CAR T-cell therapy, although data are beginning to emerge as survival of these patients increases. Long-term and late effects of CAR T-cell therapy may include cytopenias and infection, as well as B-cell aplasia and hypogammaglobulinemia.[27-29] Other late effects may include secondary malignancies, potential neurologic toxicities, fatigue, diminished bone health, and infertility.[27,28] Patients also often struggle with concerns about disease recurrence and cancer progression. Despite limitations in current knowledge, it remains important for clinicians to discuss some of the common late effects seen in the context of survivorship care and oncology, acknowledging the data gaps and the need for more robust long-term data from patients who received CAR T-cell therapy. These patients should continue to be monitored as they may require growth factors, transfusions, immunoglobulin infusions, and antimicrobial prophylaxis.[27,28]

Special Consideration During the COVID-19 Pandemic

The COVID-19 pandemic has increased the complexity of cancer care and required oncology practices to make operational changes to protect the safety of patients and staff, adjust to resource shortages, and comply with national and state restrictions on elective procedures (https://www.asco.org/sites/new-www.asco.org/files/content-files/2020-ASCO-Guide-Cancer-COVID19.pdf). With a gradual ease in pandemic-related restrictions, oncology practices are balancing the risks of COVID-19 with restoring patient access to diagnostics, treatments, and other critical cancer care services. These issues and recommendations are covered separately in the ASCO Special Report: A Guide to Cancer Delivery During the COVID-19 Pandemic.

Although the management of patients with cancer who may be affected by COVID-19 is beyond the scope of this guideline, patients undergoing immunotherapeutic treatment are of special concern, with both diagnostic and therapeutic implications. It can be challenging for clinicians to reach the correct diagnosis in patients receiving immunotherapy who develop symptoms consistent with either immune-related adverse events (irAEs) or COVID-19. Uncertainty around the correct diagnosis may then delay the initiation of appropriate management strategies, such as glucocorticoids for irAEs.

Vaccination of patients with cancer and family members for COVID-19 is, in general, recommended (https://www.asco.org/sites/new-www.asco.org/files/content-files/covid-19/2021-MSK-COVID19-VACCINE-GUIDELINES.pdf). Although the immunogenicity and efficacy of COVID-19 vaccines are uncertain in patients receiving immunomodulatory agents, the potential for benefit from vaccination likely outweighs these uncertainties for most patients.

TABLE 4. Cytopenia Recommendations

Workup or evaluation: CBC with differential, peripheral blood smear, reticulocyte count. If abnormalities are detected and further investigation is necessary for a diagnosis, proceed with bone marrow evaluation	
Grading	**Management**
G1: anemia: LLN—10.0 g/dL; neutropenia: > 1,500 per mm^3; thrombocytopenia: > 75,000 per mm^3	Offer supportive care
G2: anemia: < 10.0-8.0 g/dL; neutropenia: > 1,000 per mm^3; thrombocytopenia: > 50,000 per mm^3	Offer supportive care and/or consider corticosteroids If improved to ≤ G1, taper steroids over 4-6 weeks
G3: anemia: < 8.0/dL; neutropenia: > 500 per mm^3; thrombocytopenia: > 25,000 per mm^3 G4: anemia: life-threatening; neutropenia: < 500 per mm^3; thrombocytopenia: < 25,000 per mm^3	Critical care support Use high-dose methylprednisolone Consider growth factor support for neutrophil recovery, per institutional guidelines

Abbreviations: G, grade; LLN, lower limit of normal.

PATIENT AND CLINICIAN COMMUNICATION

As immunotherapeutic treatment for cancer continues to evolve with single agents and in new combinations, it is imperative that patients and family caregivers receive timely and up-to-date education about CAR T-cell therapies, their mechanism of action, and the clinical profile of possible irAEs. Patient and caregiver education should occur before initiating therapy and continue throughout treatment and survivorship. It should be emphasized that CAR T-cell therapy works differently than traditional chemotherapy and that these treatments elicit unique therapeutic responses and corresponding irAEs.[30] This response can be unique to each patient, and irAEs may occur across the treatment trajectory, from the start of treatment, and into survivorship. Most notably, the ability to influence immune response even after discontinuation of the immunotherapeutic agent is a unique feature and important education point for patients and their caregivers. As such, patients should be encouraged to alert all health care providers that they are receiving or have received CAR T-cell therapy and to report any changes in health status to each provider. This is important as patients are often seen by multiple providers and each provider should be aware of the potential for irAEs.

Using a questionnaire or standard assessment may assist the provider and patient to recognize possible irAEs. In addition, health care professionals should ask patients about any new symptoms or changes in their health—no matter how small they may seem. Minor changes in how a patient is feeling may indicate early signs of an AE, and patients may not attribute the change to their cancer treatment.[31] Consistent assessment and documentation at each encounter will also enable the clinical team to note changes that may occur over time. Close monitoring throughout treatment is important as minimal changes in a patient's baseline status may indicate an early irAE.

Wallet cards detailing symptoms to watch for and how to notify their health care provider may be an effective tool in empowering patients and their caregivers to recognize and manage irAEs and may be useful to other health care providers (eg, emergency department staff) caring for

TABLE 5. B-Cell Aplasia Recommendations

Workup or evaluation: Full blood count	
Grading	**Management**[7,49,61,62]
All grades	Recommend influenza and COVID vaccination for patients and family members Antiviral and PJP prophylaxis per institutional standards, for 6-12 months following CAR T-cell infusion and/or until the CD4 cell count is > 200 cells/μL Antifungal agents should be considered for high-risk patients including any patient receiving corticosteroids for management of CRS or ICANS
G1: asymptomatic, no intervention needed	Offer supportive care
G2: symptomatic (ie, recurrent infections), nonurgent intervention indicated	Consider treatment with IVIG replacement therapy at IgG levels < 400
G3: urgent intervention indicated G4: life-threatening	Consider treatment with IVIG replacement therapy at IgG levels < 400

Abbreviations: CAR T, chimeric antigen receptor T; CD4, cluster of differentiation; CRS, cytokine release syndrome; G, grade; G-CSF, granulocyte-colony stimulating factor; ICANS, immune effector cell–associated neurotoxicity syndrome; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; PJP, *Pneumocystis jiroveci* pneumonia.

TABLE 6. DIC

Workup or evaluation: Full blood count to assess platelet number, fibrinogen, PT, PTT, and d-dimer. A test scoring system developed by the ISTH may be used to help determine if DIC is present.[63] The higher the score, the more likely it is that DIC is present	
Grading	**Management**
G1: —	Offer supportive care
G2: laboratory findings with no bleeding	Use IL-6 antagonist with or without corticosteroids If improved to ≤ G1, taper steroids over 4-6 weeks
G3: laboratory findings with bleeding G4: life-threatening; urgent intervention indicated	Critical care support Use IL-6 antagonist and methylprednisolone IV 1,000 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 Consider replacement of fibrinogen in patients with a fibrinogen level below 150 mg/dL

Abbreviations: DIC, disseminated intravascular coagulation; G, grade; IL, interleukin; ISTH, International Society on Thrombosis and Haemostasis; PT, prothrombin time; PTT, partial thromboplastin time.

patients with a history of immunotherapy.[32] This card should include signs and symptoms that warrant emergency department or doctor visits and any contraindication after CAR T-cell drug administration. Information for health care professionals should include the date of CAR T-cell drug administration, contact of the treating oncologist, and precaution with prescribing corticosteroids or cytotoxic medications.

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[33]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[34-37] Access to CAR T-cell therapy is dependent on a complex interplay of several factors and stakeholders, including referring physicians, manufacturers, payers, and treatment facilities.[38] Evidence of disparate access to CAR T-cell therapy comes from recent systematic reviews;[39,40] however, more studies are necessary to thoroughly understand how the factors intersect to create and maintain disparities in

TABLE 7. Infections

Workup or evaluation: History and physical examination Full blood count Bacterial cultures and evaluation for other infection (fungal and viral)	
Grading	**Management**[7,49,61,62]
All grades	Antiviral and PJP prophylaxis per institutional standards, for 6-12 months following CAR T-cell infusion and/or until the CD4 cell count is > 200 cells/μL Antifungal agents should be considered for high-risk patients G-CSF should be considered in patients after CRS with > 7 days of neutropenia
G1: mild infection only	Offer supportive care Empiric antimicrobials (antibiotics such as levofloxacin or ciprofloxacin, antifungals such as fluconazole or antivirals such as valacyclovir or acyclovir) should be considered upon onset of fever
G2: mild infection; oral intervention indicated (eg, antibiotic, antifungal, or antiviral)	Start course of oral antimicrobials
G3: severe infection; IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Start IV antimicrobials
G4: life-threatening consequences; urgent intervention indicated	Critical care support

Abbreviations: CAR T, chimeric antigen receptor T; CD4, cluster of differentiation; CRS, cytokine release syndrome; G, grade; G-CSF, granulocyte-colony stimulating factor; IV, intravenous; PJP, *Pneumocystis jiroveci* pneumonia

cancer treatment, which include treatment facility characteristics, geographic location and distance to treatment facility, insurance type, age, race, and income.[38,39] Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCCs)—is challenging. Patients with MCCs are a complex and heterogeneous population, making it difficult to account for all the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude patients with MCCs, such as pre-existing autoimmune diseases, to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCC, including pre-existing autoimmune diseases, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCC and highlights the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the management and follow-up plan.

In light of these considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

EXTERNAL REVIEW AND OPEN COMMENT

The draft set of recommendations was submitted to an external reviewer with content expertise to obtain direct feedback. A public open comment period was also held from February 8 to February 22, 2021. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation. A total of 16 respondents, who had not previously reviewed the recommendations, either agreed or agreed with slight modifications to the majority of recommendations. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated before Clinical Practice Guidelines Committee review and approval.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners and survivors of cancer and caregivers and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

In conclusion, guidance on the management of toxicities related to CAR T-cell therapy is in demand. This guideline and its recommendations are intended to assist the clinician with strategies and best practices to rapidly recognize, diagnose, and coordinate with other medical subspecialties and manage these sets of unique toxicities. The rapidly evolving data on the topic of CAR T-cell therapy and its toxicities warrant our dedication to provide these updated analyses and recommendations routinely.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline Update (in press)
- Integration of Palliative Care into Standard Oncology Practice[41] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[33] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

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EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/supportive-care-guidelines.

EQUAL CONTRIBUTION

B.J.S. and K.B. were Expert Panel cochairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Management of Immune-Related Adverse Events in Patients Treated With Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline

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APPENDIX

TABLE A1. Management of Immune-Related Adverse Events Guideline Expert Panel Membership

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Marianne J. Davies, DNP	Smilow Cancer Hospital and Yale School of Nursing, New Haven, CT	Oncology nursing
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Jarushka Naidoo, MD	Beaumont Hospital, Dublin, Ireland and Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD	Thoracic oncology
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Tanyanika Phillips, MD	City of Hope, Antelope Valley and Duarte, CA	Medical oncology and PGIN rep
Laura D. Porter, MD	Colon Cancer Alliance, Washington, DC	Patient advocate
Cristina A. Reichner, MD	Georgetown University, Washington, DC	Pulmonology
Bianca Santomasso, MD, PhD	Memorial Sloan Kettering Cancer Center, New York, NY	Neuro-oncology
Carole Seigel	MGH Cancer Center, Boston, MA	Patient advocate
Jung Min Song, RN	Cleveland Clinic, Cleveland, OH	Oncology nursing
Alexander Spira, MD, PhD	Virginia Cancer Specialists and US Oncology, Fairfax, VA	Medical oncology
Maria Suarez-Almazor, MD	MD Anderson Cancer Center, Houston, TX	Rheumatology
Umang Swami, MD	Huntsman Cancer Institute, University of Utah, Salt Lake City, UT	GU oncology
John A. Thompson, MD	Seattle Cancer Care Alliance, University of Washington/Fred Hutchinson, Seattle, WA	Melanoma
Praveen Vikas, MD	University of Iowa, Iowa City, IA	Breast medical oncology and PGIN rep
Yinghong Wang, MD	MD Anderson Cancer Center, Houston, TX	Gastroenterology
Jeffrey S. Weber, MD, PhD	NYU Langone Medical Center, New York, NY	Melanoma
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