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Release date: November 10, 2024; Expiration date: November 10, 2025

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Management of Immunotherapy-Related Toxicities
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Management of Immunotherapy-Related Toxicities

Disclosure of Relevant Financial Relationships

None of the planners for this educational activity have relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Individuals Who Provided Content Development and/or Authorship Assistance:

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John A. Thompson, MD, Panel Chair, has disclosed having equity interest/stock options in Alpine Immune Sciences; and serving as a scientific advisor for Mabquest.
Benjamin H. Kaffenberger, MD, MS, Panel Member, has disclosed receiving consulting fees from ADC Therapeutics, Biogen Idec, and Novartis Pharmaceuticals Corporation; and receiving grant/research support from Biogen Idec, InflaRx and Merck & Co., Inc.
Philippe Armand, MD, PhD, Panel Member, has disclosed receiving grant/research support from Adaptive Biotechnologies, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Genentech, Inc., IGM Biosciences, Kite Pharma, and Merck & Co., Inc.; receiving consulting fees from ATB Therapeutics, Bristol Myers Squibb, Enterome, Merck & Co., Inc., and Xencor; serving as a scientific advisor for ADC Therapeutics, Bristol Myers Squibb, Foresight Diagnostics, Genentech, Inc., Genmab, Merck & Co., Inc., Regeneron Pharmaceuticals, Inc., Roche Laboratories, Inc., and Xencor; and serving as an Officer, Director or any other fiduciary role for Tessa Therapeutics.
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Yinghong Wang, MD, PhD, Panel Member, has disclosed receiving consulting fees from AzurRx, Ilya Pharma, Sanarentaro, and Sorriso; and serving as a scientific advisor for MabQuest.

To view disclosures of external relationships for the NCCN Guidelines panel, go to NCCN.org/guidelines/guidelines-panels-and-disclosure/disclosure-panels

This activity is supported by educational grants from AstraZeneca; Bristol Myers Squibb; Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC; and Seagen. This activity is supported by a medical education grant from Exelixis, Inc. This activity is supported by an independent educational grant from Merck & Co., Inc., Rahway, NJ, USA.

Management of Immunotherapy-Related Toxicities, Version 2.2024

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Guidelines for the Management of Immunotherapy-Related Toxicities are intended to provide oncology practitioners with guidance on how to manage the wide-ranging and potentially fatal toxicities that may occur with cancer immunotherapy. The guidelines address immune-related adverse events related to immune checkpoint inhibitors, CAR T-cell therapies, and lymphocyte engagers (which include T-cell–engaging bispecific antibodies). These NCCN Guidelines Insights highlight recent guideline updates pertaining to the management of emerging toxicities related to cancer immunotherapy.

J Natl Compr Canc Netw 2024;22(9):582–592
doi:10.6004/jnccn.2024.0057

Overview

The aim of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Management of Immunotherapy-Related Toxicities is to provide oncology practitioners with recommendations on how to manage immune-related adverse events (irAEs) related to cancer immunotherapy. The NCCN Management of Immunotherapy-Related Toxicities Panel is 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. Recommendations for the management of irAEs related to immune checkpoint inhibitors (ICIs), chimeric antigen receptor (CAR) T-cell therapy, and the emerging class of lymphocyte engagers (including T-cell–engaging bispecific antibodies) are included in the current version of the guidelines.

The patient population eligible to receive cancer immunotherapy is expanding. Initially approved for the treatment of primarily advanced or metastatic disease, data indicate that ICIs may also provide clinical benefit in earlier settings for multiple cancer types.[1–9] Furthermore, other types of cancer immunotherapies, including 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.[10–14]

Clinicians should be aware that toxicities related to cancer immunotherapy are autoimmune in nature and can impact essentially any organ system.[15] The toxicity profiles of cancer immunotherapy and management strategies for irAEs are distinct from those of traditional chemotherapy.[15,16] Early recognition and prompt intervention are key goals for the management of

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*Provided content development and/or authorship assistance.

The full and most current version of these NCCN Guidelines is available at NCCN.org.

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 time frame can be challenging. Therefore, the NCCN Guidelines provide initial steps for oncology clinicians to assess and manage a patient's irAEs 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 NCCN Guidelines Insights summarize recent guideline updates regarding the management of emerging toxicities related to cancer immunotherapy, including ICI-related dermatologic toxicities, anti–B-cell maturation antigen (BCMA) CAR T-cell therapy–related toxicities, and lymphocyte engager–related toxicities. The NCCN panel will continue to update guideline recommendations for the management of immunotherapy-related toxicities annually based on consensus and clinical evidence.

Management of ICI-Related Toxicities

Dermatologic Toxicities

Dermatologic toxicities are the most common irAEs that occur with ICIs.[17–19] Most are low-grade; however, some can be severe, with a debilitating effect on quality of life. Earlier versions of the guidelines included recommendations for the following dermatologic irAEs: maculopapular rash, pruritus, blistering disorders, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN).

In 2022, panel members from different NCCN Member Institutions noted that patients treated with ICIs were experiencing dermatologic toxicities that were not acknowledged in the guidelines. The NCCN panel agreed to develop recommendations for the management of the following emerging ICI-related toxicities: lichen planus/lichenoid diseases, psoriasis/psoriasiform diseases, and oral toxicities.

Lichen Planus and Lichenoid Diseases

ICI-related lichen planus and lichenoid disease are characterized by violaceous (dark red/purple) papules and plaques without scale over the trunk and extremities, and significant pruritus.[18,20] Erosions and striae (white lines intersecting) in the oral and vulvar mucosa may also occur.[18,21] The mean time to onset is approximately 6 to 12 weeks after initiation of ICI treatment.[18] Up to 6% of patients who received ICI treatment have been reported to experience lichen planus or lichenoid disease.[22]

A single-center retrospective cohort study characterized the management of ICI-related lichenoid eruptions in 119 patients with various types of cancers.[21] Patients included 108 with lichenoid dermatitis, 15 with lichenoid mucositis, and 2 with lichenoid dermatoses. Topical steroids were the most frequently used treatments for the management of lichenoid dermatitis (81%). Other treatments included oral antihistamines, oral steroids, acitretin, intralesional triamcinolone, narrow-band UVB, and other unspecified nonsteroidal treatment. Treatments used for lichenoid mucositis included topical steroids, unspecified nonsteroidal treatments, oral steroids, and acitretin.

Another single-center retrospective study assessed lichenoid mucocutaneous eruptions in 20 patients with advanced cancer who received PD-1 or PD-L1 inhibitors.[20] Eruptions on the trunk, extremities, and/or mouth were reported. Topical steroids were used most frequently, although some patients were also treated with oral steroids or phototherapy.

Other documented treatments used for lichen planus and lichenoid reactions (either ICI-related or idiopathic) included steroids (topical, intralesional, or oral), tacrolimus, narrow-band UVB phototherapy, cyclosporine, doxycycline, acitretin, apremilast, and other nonsteroidal immunomodulators such as hydroxychloroquine, azathioprine, methotrexate, and mycophenolate mofetil.[23–25]

NCCN Recommendations

High-potency topical steroids (eg, clobetasol 0.05% or fluocinonide 0.05% [cream or ointment]) or tacrolimus (0.1% ointment) are recommended for all grades of lichen planus and lichenoid diseases (Figure 1). In general, gel can be considered for mucosal disease, solution for scalp disease, and cream/lotion/ointment for all other affected areas. Oral antihistamines, prednisone, and narrow-band UVB phototherapy (if available) are recommended for

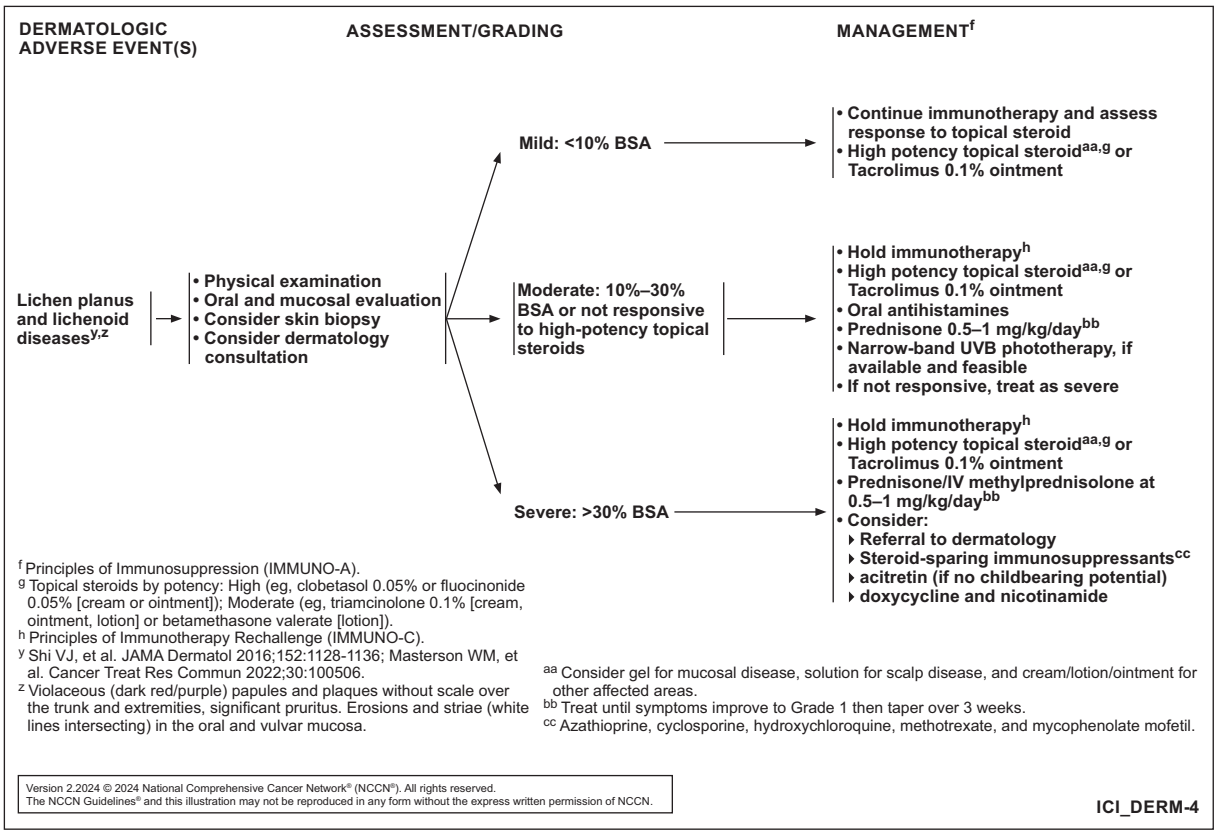


Figure 1. ICI_DERM-4. NCCN Clinical Practice Guidelines in Oncology for Management of Immunotherapy-Related Toxicities, Version 2.2024.

moderate lichen planus and lichenoid diseases. If severe, prednisone or intravenous methylprednisolone is recommended; other agents that can be considered include acitretin (if no childbearing potential), doxycycline in combination with nicotinamide, and other steroid-sparing immunosuppressants, such as azathioprine, cyclosporine, hydroxychloroquine, methotrexate, and mycophenolate mofetil. A referral to dermatology, if available, should also be considered for those with severe symptoms (Figure 1).

ICI treatment can be continued in patients experiencing mild lichen planus/lichenoid disease, whereas treatment should be held if the presentation is moderate or severe. Rechallenge with ICI can be considered when symptoms are controlled and if the extent of body surface area is <30%, especially if the patient is receiving a targeted biologic.

Psoriasis and Psoriasiform Diseases

ICI-related psoriasis and psoriasiform disease are characterized by thick, red, scaly plaques that are typically accentuated on extensor surfaces, scalp, umbilicus, and postauricular surfaces.[18,22,26] The time of onset is typically within 3 weeks of ICI treatment.[18] ICI-related psoriasis includes both de novo psoriasis and the exacerbation of existing psoriasis.[22,26]

A retrospective study characterized the treatments used for 115 patients with ICI-related psoriasis.[26] More than half of the patients presented with grade 1 psoriasis. Many patients were treated with only topical measures (59.1%), whereas 40.9% received both topical and systemic agents. Systemic therapies used included acitretin, systemic steroids, apremilast, methotrexate, and biologics specifically approved for psoriasis (eg, tumor necrosis factor [TNF]–alpha inhibitors, IL-23 inhibitors). Two patients received topical steroids in combination with narrow-band UVB phototherapy.

A separate systematic review of 60 published studies evaluated treatments used for the management of ICI-related psoriasis in 242 patients.[27] Topical steroids were the most common treatment used (83%). Other treatments included acitretin, systemic steroids, phototherapy, methotrexate, and biologics approved for psoriasis.

Systemic nonbiologics recommended by the American Academy of Dermatology (AAD)/National Psoriasis Foundation (NPF) guidelines for idiopathic psoriasis include acitretin, apremilast, cyclosporine, methotrexate, and others.[28] AAD/NPF also recommend a number of approved biologics for the treatment of idiopathic psoriasis.[29] Of note, systemic steroids have historically not been used for the treatment of psoriasis due to risk of a pustular rebound flare and are not currently recommended by the AAD/NPF guidelines for the management of psoriasis.[26,28,30]

NCCN Recommendations

High-potency topical steroids (eg, clobetasol 0.05% or fluocinonide 0.05% [cream or ointment]) and topical vitamin D analogs are recommended for all grades of ICI-related psoriasis and psoriasiform diseases (Figure 2). Narrow-band UVB phototherapy is recommended for moderate psoriasis, if available. Apremilast or acitretin (if no childbearing potential) can be considered if the irAE is deemed moderate or severe. Cyclosporine and methotrexate are recommended as additional treatment options for severe ICI-related psoriasis. The NCCN panel also recommends referral to a dermatologist for consideration of biologics approved

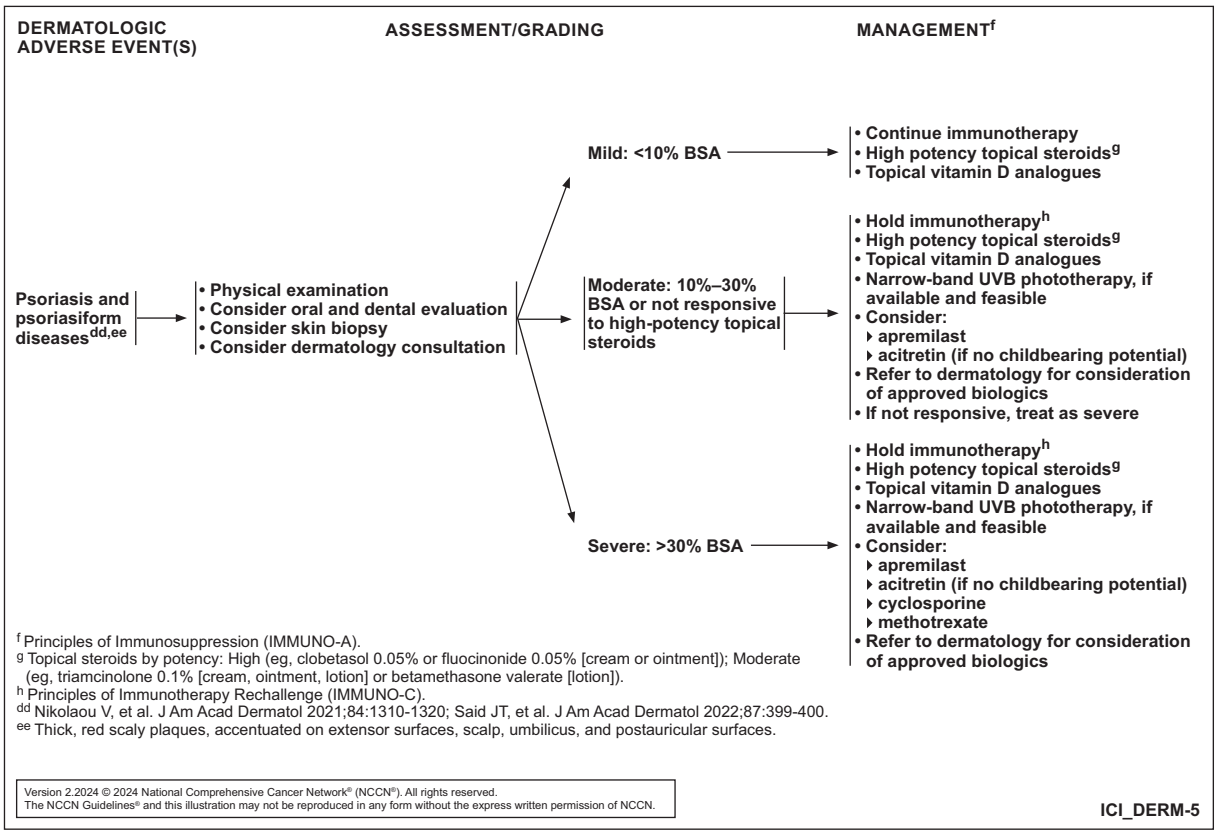


Figure 2. ICI_DERM-5. NCCN Clinical Practice Guidelines in Oncology for Management of Immunotherapy-Related Toxicities, Version 2.2024.

for the treatment of moderate or severe psoriasis.[29] Systemic steroids are not recommended for patients with ICI-related psoriasis/psoriasiform diseases (Figure 2).

Although ICI treatment can be continued in patients experiencing mild psoriasis/psoriasiform disease, the NCCN panel recommends holding ICI treatment if the patient's condition is moderate or severe. Rechallenge with ICI can be considered if symptoms are controlled and extent of body surface area is <30%, especially if the patient is receiving a psoriasis-targeted biologic.

Oral Toxicities

Specific ICI-related oral toxicities such as oral mucosa inflammation, dry mouth (sicca syndrome), and oral dysesthesia have historically not been well characterized within the context of clinical trials. However, these toxicities can have a detrimental effect on hydration, nutritional intake, and quality of life and therefore clinicians should be aware of how to identify and manage these irAEs.

Although recommendations for the management of ICI-related oral toxicities are located within the "Dermatologic Toxicity" section of the guidelines, the recommendations below were developed by a multidisciplinary group of panel members with expertise in medical oncology, dermatology, gastroenterology, rheumatology, and oncology pharmacy, and others who have had experience treating patients with ICI-related oral toxicities.

Oral Mucosa Inflammation

Oral mucosa inflammation is characterized by irritated gums and/or oropharynx, including red/white lesions, erosions, and/or ulcers, striae, or diffuse mucositis. The prevalence of ICI-related oral mucosal disorders is estimated to be approximately 3%.[31]

Data on the treatment of ICI-related oral mucosa inflammation are limited. A retrospective single-center study evaluated 152 patients with various types of cancer who experienced ICI-related oral mucositis.[32] Grade 1 or 2 mucositis was reported in 91% of patients. Oral ulcers or aphthae were reported in 97% of patients. No medical treatment was given to 11% of patients and more than half of patients were treated with only supportive medication, which consisted of viscous lidocaine, sucralfate, proton pump inhibitors (PPIs), and H2 blockers (also known as histamine H2 antagonists). The remainder of the patients received topical and/or systemic immunosuppressants (23.7%), which included oral prednisone and intravenous methylprednisolone. None of the patients in the study received nonsteroidal systemic immunosuppressants.

A systematic review of published reports (primarily case studies) similarly identified topical measures and oral/intravenous steroids as the primary management strategies used to treat 42 patients with ICI-related oral mucositis.[33]

NCCN Recommendations

Good oral hygiene (such as twice-daily toothbrushing, chlorhexidine or fluoride oral rinse if tooth brushing is too painful) and dietary modifications (eg, avoidance of crunchy, spicy, or acidic foods; avoidance of hot food/drinks) are recommended by the NCCN panel for all patients with oral mucosa inflammation (Figures 3 and 4). Referral to dermatology is recommended if available. A referral to dentistry should be considered for those

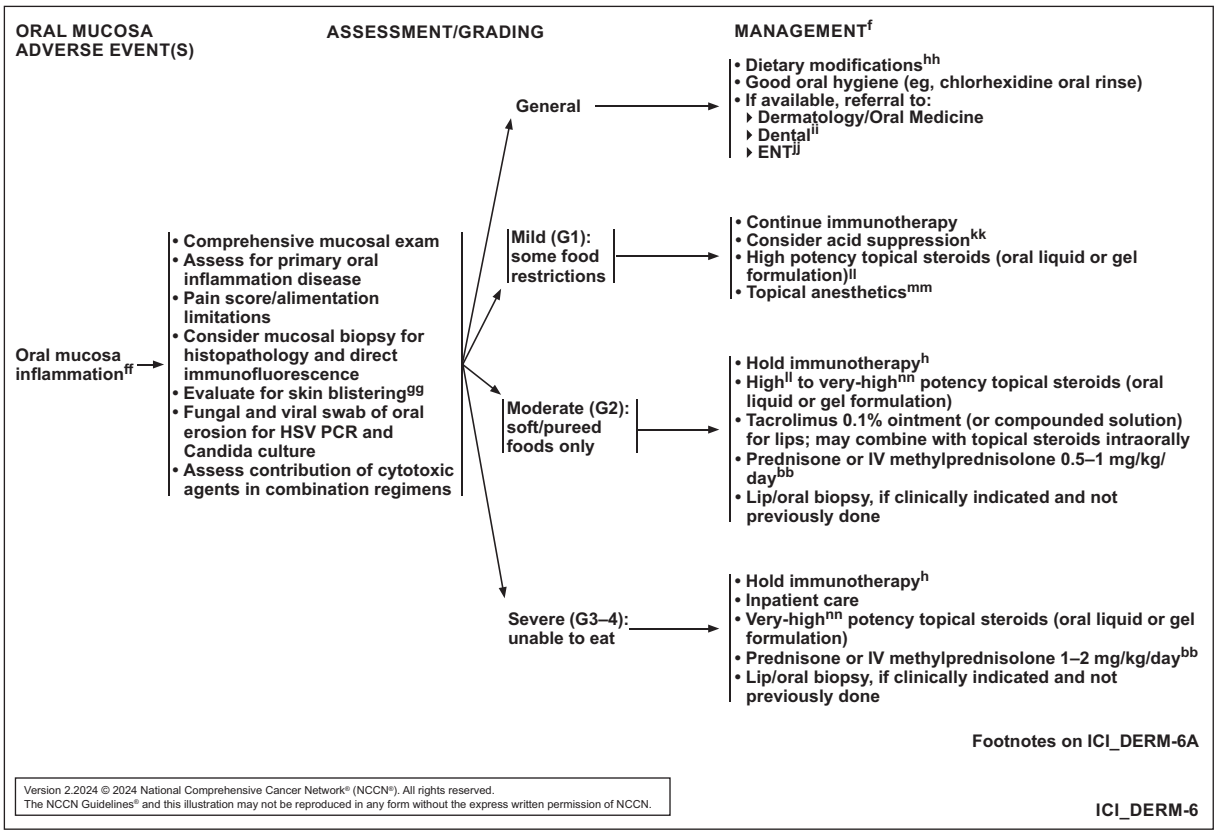


Figure 3. ICI_DERM-6. NCCN Clinical Practice Guidelines in Oncology for Management of Immunotherapy-Related Toxicities, Version 2.2024.

with mild symptoms and strongly considered for those with moderate or severe inflammation to ensure adequate hygiene and to protect against the risk of dental caries. If available, referral to an ear, nose, and throat (ENT) specialist is recommended to assist in the management of persistent mucositis or if there is oropharynx/larynx involvement (Figures 3 and 4).

In general, ICIs should be held for patients with moderate or severe symptoms; a lip or oral biopsy is also recommended if not previously done. Rechallenge with ICI can be considered after symptoms improve to grade 1 or better. Topical steroids in the form of oral liquid or gel formulation are recommended as the first line of therapy for oral mucosa inflammation. Topical calcineurin inhibitor tacrolimus ointment can be considered for moderate symptoms, whereas prednisone or intravenous methylprednisolone is an option for those with moderate or severe symptoms, including those who are unable to eat. Inpatient care is also recommended for patients with severe symptoms (Figure 3).

For the management of oral lichen planus, clinicians should follow the management recommendations for lichen planus and lichenoid disease described earlier.

Dry Mouth (Sicca Syndrome)

Dry mouth (also referred to as sicca syndrome) has been reported with ICI use.[34–36] Patients with sicca syndrome present with an abrupt onset of dry mouth that can cause difficulty with speaking, eating, swallowing, and/or staying asleep. Some patients, but

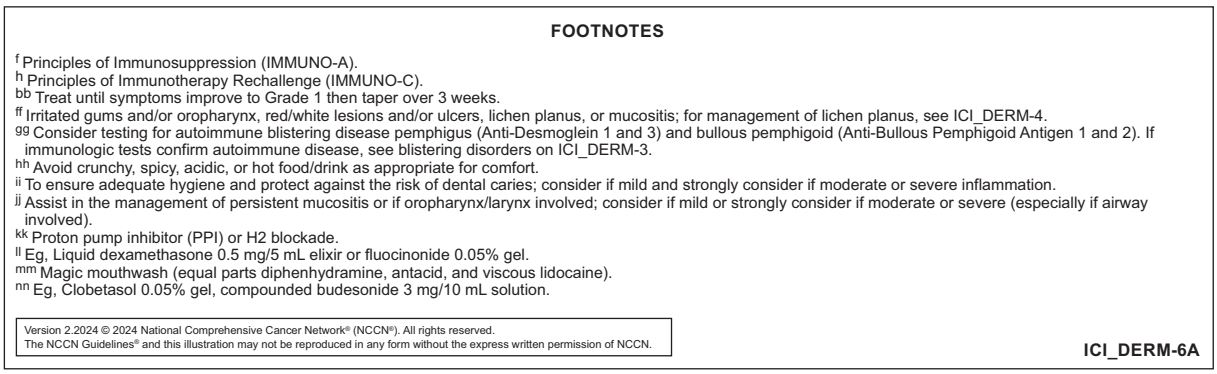


Figure 4. ICI_DERM-6A. NCCN Clinical Practice Guidelines in Oncology for Management of Immunotherapy-Related Toxicities, Version 2.2024.

not all, may experience dry eye.[36] Dry mouth (sicca syndrome) is estimated to occur in 2% to 11% of patients who receive ICI treatment.[31,34]

Data from a single-center study that included 20 patients who experienced ICI-related sicca syndrome showed that onset of the condition typically occurred within 3 months of treatment with ICIs.[35] Supportive care measures (including hydration and use of systemic sialagogues), steroids (eg, prednisone), and holding ICI therapy were the primary management strategies reported in the study.

Another study described management strategies based on ImmunoCancer International Registry (ICIR) data derived from 26 patients with various cancer types who developed sicca syndrome following ICI therapy.[36] Topical measures were initially used for most patients, whereas systemic steroids were administered to those for whom topical measures were ineffective. Use of other immunosuppressants in the second-line setting was also reported for select patients.

NCCN Recommendations

Dietary modifications and topical measures (such as saliva substitutes and mouth rinses) are recommended by the NCCN panel for all patients with dry mouth (sicca syndrome) (Figures 5 and 6). Prednisone and systemic sialagogues (ie, cevimeline or pilocarpine, to increase flow of saliva) are options for those with moderate or severe symptoms (Figure 5). Dry mouth from sicca syndrome may be partially improved with steroids but usually will require chronic care for salivary dysfunction. Clinicians should be aware that severe sicca syndrome, if left untreated, can result in dental caries and eventually the loss of teeth. Referral to rheumatology and dentistry is also recommended; inpatient care can be considered for those with severe dry mouth. Holding immunotherapy is recommended for those with moderate or severe dry mouth; rechallenge can be considered after symptoms become grade 1. When considering rechallenge, clinicians should have a discussion with patients regarding the risks of potential worsening symptoms compared with the benefits.

Oral Dysesthesia

Oral dysesthesia is generally described as oral pain with a "burning" sensation in the absence of, or disproportionate to, skin changes, oral sensitivity, dysgeusia, phantogeusia, or other altered sensation with normal clinical findings. In the literature, multiple terms have been used to describe this condition, including burning mouth syndrome and stomatodynia.[37] This irAE is often not an isolated event and may occur with other types of ICI-related oral toxicities, such as mucosal inflammation. The prevalence of ICI-related oral/oropharyngeal pain is estimated to be 4%.[31]

Data on the management of ICI-related oral dysesthesia are limited. However, several studies have investigated treatment options for non-ICI–related oral dysesthesia. Data from a single-center study found that some, but not all, patients with burning mouth syndrome treated with steroids experienced an improvement in symptoms.[38] Use of gabapentin has been evaluated within the context of a randomized, double-blind, placebo-controlled trial in patients with symptoms of burning in the mouth.[39] Of the 20 patients who received gabapentin alone, 10 experienced a reduction in burning sensation. Other topical

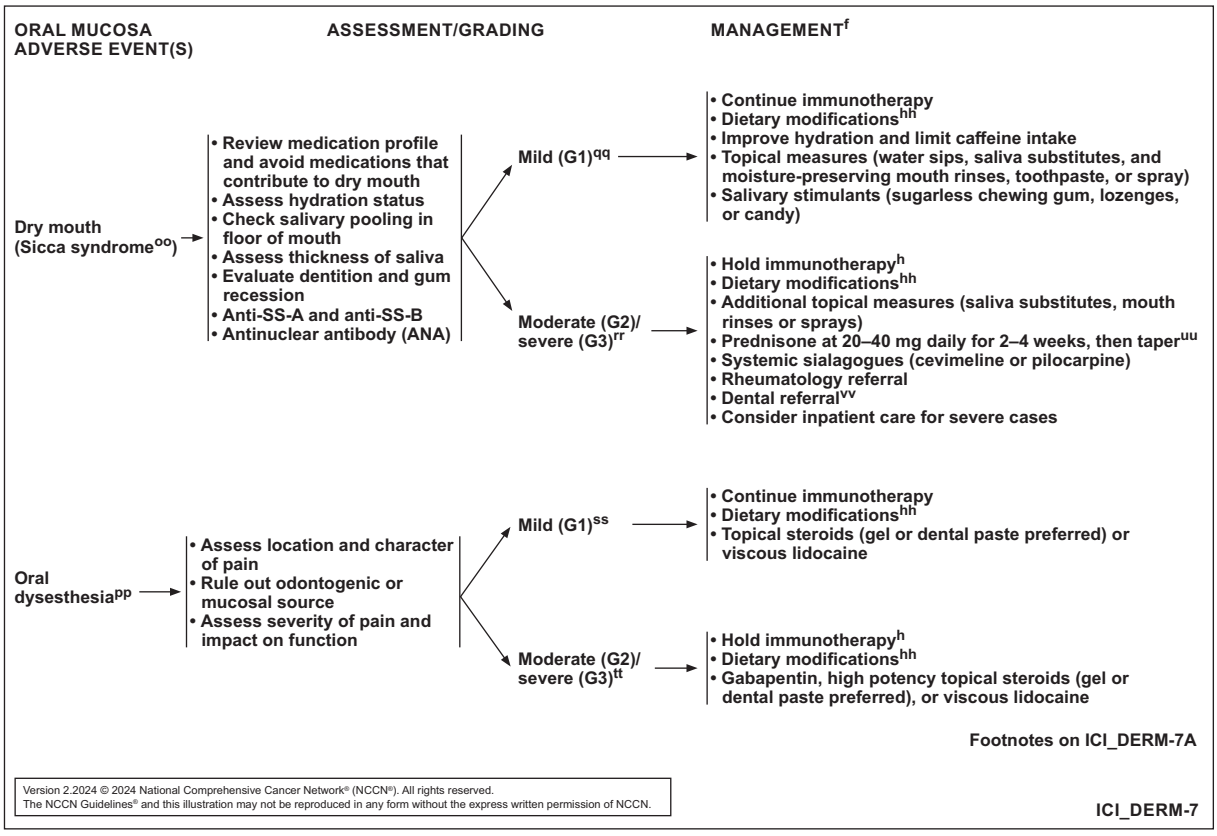
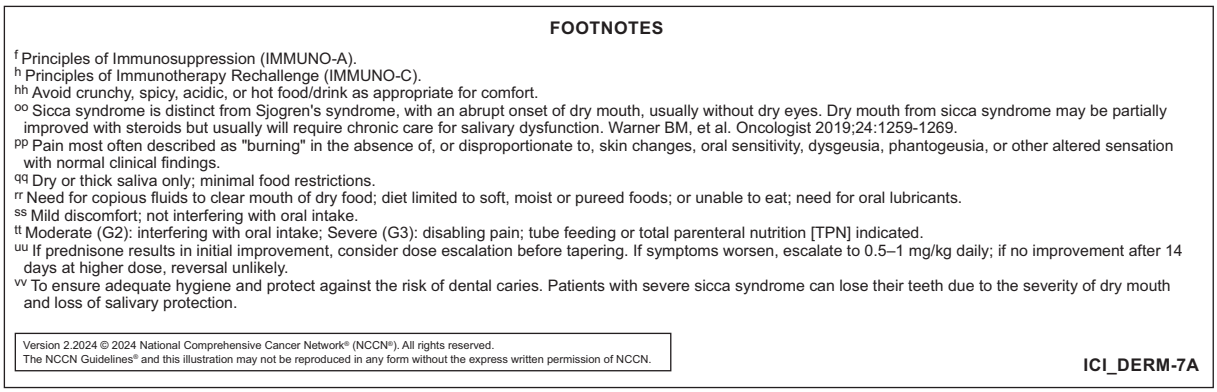


Figure 5. ICI_DERM-7. NCCN Clinical Practice Guidelines in Oncology for Management of Immunotherapy-Related Toxicities, Version 2.2024.


FOOTNOTES

[f] Principles of Immunosuppression (IMMUNO-A).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[hh] Avoid crunchy, spicy, acidic, or hot food/drink as appropriate for comfort.
[oo] Sicca syndrome is distinct from Sjogren's syndrome, with an abrupt onset of dry mouth, usually without dry eyes. Dry mouth from sicca syndrome may be partially improved with steroids but usually will require chronic care for salivary dysfunction. Warner BM, et al. Oncologist 2019;24:1259-1269.
[pp] Pain most often described as "burning" in the absence of, or disproportionate to, skin changes, oral sensitivity, dysgeusia, phantogeusia, or other altered sensation with normal clinical findings.
[qq] Dry or thick saliva only; minimal food restrictions.
[rr] Need for copious fluids to clear mouth of dry food; diet limited to soft, moist or pureed foods; or unable to eat; need for oral lubricants.
[ss] Mild discomfort; not interfering with oral intake.
[tt] Moderate (G2): interfering with oral intake; Severe (G3): disabling pain; tube feeding or total parenteral nutrition [TPN] indicated.
[uu] If prednisone results in initial improvement, consider dose escalation before tapering. If symptoms worsen, escalate to 0.5–1 mg/kg daily; if no improvement after 14 days at higher dose, reversal unlikely.
[vv] To ensure adequate hygiene and protect against the risk of dental caries. Patients with severe sicca syndrome can lose their teeth due to the severity of dry mouth and loss of salivary protection.

ICI_DERM-7A

Figure 6. ICI_DERM-7A. NCCN Clinical Practice Guidelines in Oncology for Management of Immunotherapy-Related Toxicities, Version 2.2024.

agents, psychotropic medications, and psychological therapy have also been used to treat oral dysesthesia[37,38]; however, high-quality data are needed, especially within the context of ICI treatment.

NCCN Recommendations

Dietary modifications are recommended by the NCCN panel for all patients with oral dysesthesia. Topical steroids or viscous lidocaine are generally considered first-line treatment options for oral dysesthesia (Figures 5 and 6). Gabapentin is an option for those with moderate or severe symptoms. ICI therapy should be held if symptoms interfere with oral intake (moderate/grade 2) or if patients are experiencing disabling pain and tube feeding or total parenteral nutrition is indicated (severe/grade 3). Rechallenge can be considered if symptoms become mild; however, the panel recommends initiating a discussion with patients about the risks of potential worsening symptoms compared with benefits.

Other ICI-Related Toxicities

Guideline recommendations for the management of other ICI-related toxicities have also been updated. Of note, recommendations for the management of endocrine, gastrointestinal, hepatobiliary, musculoskeletal, and ocular irAEs have been significantly revised in recent years. Please refer to the full version of these guidelines at NCCN.org to access the most up-to-date recommendations for the management of ICI-related toxicities.

Management of CAR T-Cell Therapy–Related Toxicities

CAR T cells are genetically reprogrammed T cells that express CARs, which are synthetic receptors designed to target surface antigens (such as those found on tumor cells).[40,41] Multiple CAR T-cell therapies are now approved for the treatment of relapsed/refractory hematologic malignancies.[13] Cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) are common acute toxicities related to available anti-CD19 and anti-BCMA CAR T-cell therapies and have been well characterized.[42] Other known toxicities include immune effector cell–associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS; previously referred to as hemophagocytic lymphohistiocytosis/macrophage activation syndrome [HLH/MAS]), prolonged cytopenias (also referred to as immune effector cell–associated hematotoxicity), infections, and hypogammaglobulinemia.[43–45] CAR T-cell therapy–related toxicities are generally reversible and are often managed by immunosuppressive medications. Refer to the full version of these guidelines at NCCN.org as well as the prescribing information for each agent for full recommendations pertaining to the management of CAR T-cell therapy–related toxicities.

Toxicities Specific to Anti-BCMA CAR T-Cell Therapy

Emerging data indicate that patients treated with anti-BCMA CAR T-cell therapy may experience unique neurotoxicities that do not fit under the current definition of ICANS.

Movement and Neurocognitive Treatment–Emergent Adverse Events

Movement and neurocognitive treatment–emergent adverse events (MNTs) have been reported with anti-BCMA CAR T-cell therapy agents.[46–49] 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.[48] The time to onset of MNTs is typically longer than that of ICANS.[48,50]

Approximately 3% of patients who received ciltacabtagene autoleucel from the CARTITUDE-1 and CARTITUDE-4 studies exhibited symptoms of parkinsonism consistent with MNTs.[50] Events that were grade ≥3 were reported in 2% of patients. Similar AEs were also reported following idecabtagene vicleucel treatment.[49,51] Potential risk factors identified include high baseline tumor burden, prior ICANS, CRS that was grade ≥2, and high CAR T-cell expansion/persistence.[48] 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; 1 patient experienced a dramatic improvement with cyclophosphamide treatment.[48,49,52]

The NCCN panel notes that the optimal management of MNTs is still under investigation (Figure 7). MNTs characterized so far have been levodopa unresponsive, which suggests that the pathophysiology of MNTs is distinct from Parkinson's disease.[47–49] For mild MNTs, steroids such as dexamethasone 10 mg 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 these therapies is based on very limited data; therefore, the decision to use these agents should be balanced against potential safety concerns such as infection risk.

TOXICITIES SPECIFIC TO ANTI-BCMA CAR T-CELL THERAPY

	Ciltacabtagene Autoleucel and Idecabtagene Vicleucel[a]
Other neurotoxicity events[f]	• Emerging data suggests 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) • **Movement and neurocognitive treatment-emergent adverse events (MNTs)** ▸ Manifestation is similar to Parkinson's disease with bradykinesia, asymmetric action and rest tremor, postural instability, hypophonia, personality change, and impaired memory.[d] ▸ Risk factors include high baseline tumor burden, grade ≥2 CRS, prior ICANS, high CAR T cell expansion/persistence.[e] There appears to be male predominance among the reported cases. ▸ Optimal management has not been determined. The characterized cases of MNTs are levodopa unresponsive. ◊ For mild symptoms, consider steroids such as 10 mg dexamethasone daily. ◊ For persistent, severe, or refractory symptoms, and if high circulating CAR T cell levels are detected,[e] consider chemotherapy such as cyclophosphamide to ablate the CAR T cells. ◊ Use of these therapies is currently based on very limited experience and should be balanced against potential safety concerns, such as infection risk. • **Peripheral neuropathy** ▸ Types of neuropathies reported include lower motor neuron facial paralysis, other cranial nerve palsy, peripheral sensory neuropathy, and peripheral motor neuropathy. ▸ For mild symptoms, consider treatment with steroids. ▸ Consider IVIG for acute inflammatory demyelinating polyneuropathy (AIDP)-type picture.

[a] See Prescribing Information for each agent and institutional protocols.
[d] 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, neurocognitive impairment.
[e] Absolute lymphocyte count (ALC), when very elevated, may be a surrogate for high CAR T cell expansion in this setting.
[f] Cohen AD, et al. Blood Cancer J 2022;12:32; Graham CE, et al. Blood 2023;142:1248-1252; Idecabtagene vicleucel package insert; Ciltacabtagene autoleucel package insert.

CART-4

Figure 7. CART-4. NCCN Clinical Practice Guidelines in Oncology for Management of Immunotherapy-Related Toxicities, Version 2.2024.

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.[48,50] Approximately 7% of patients who received ciltacabtagene autoleucel experienced peripheral neuropathy from the CARTITUDE-1 and CARTITUDE-4 studies.[50] 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, whereas that for cranial nerve palsies was 21 days.[50] Steroids were the primary treatment used for the limited number of patients with peripheral neuropathy.[48]

The NCCN panel notes that treatment with steroids can be considered for patients with mild peripheral neuropathy (Figure 7). For those with acute inflammatory demyelinating polyneuropathy (AIDP)–type picture, intravenous immunoglobulin (IVIG) can be considered in line with current treatment guidelines for AIDP.[53] Management strategies will likely change as more data on CAR T-cell–related peripheral neuropathy become available.

Management of Lymphocyte Engager Therapy–Related Toxicities

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.[12,54] 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,[11] but other variations of these molecules are also undergoing clinical investigation (ie, natural killer [NK] cell engagers, trispecific lymphocyte engagers).[12]

The NCCN panel received a comment during the institutional review process requesting the development of a new section focused on the management of toxicities related to this new class of therapies. The consensus was to create a new section titled "Management of Lymphocyte Engager Therapy–Related Toxicities" (see the full version of these guidelines on NCCN.org).

Similar to CAR T-cell therapy, CRS, ICANS, and infections are prominent possible toxicities associated with available T-cell–engaging bispecific antibodies.[55] Although there is high variability between products, available data suggest that the incidence of CRS appears somewhat lower and the incidence of neurologic toxicity appears much lower with T-cell–engaging bispecific antibodies than with CAR T-cell therapy.[55] 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.[42,55] 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, given that general strategies applicable to all available agents have not been established (Figure 8). 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,

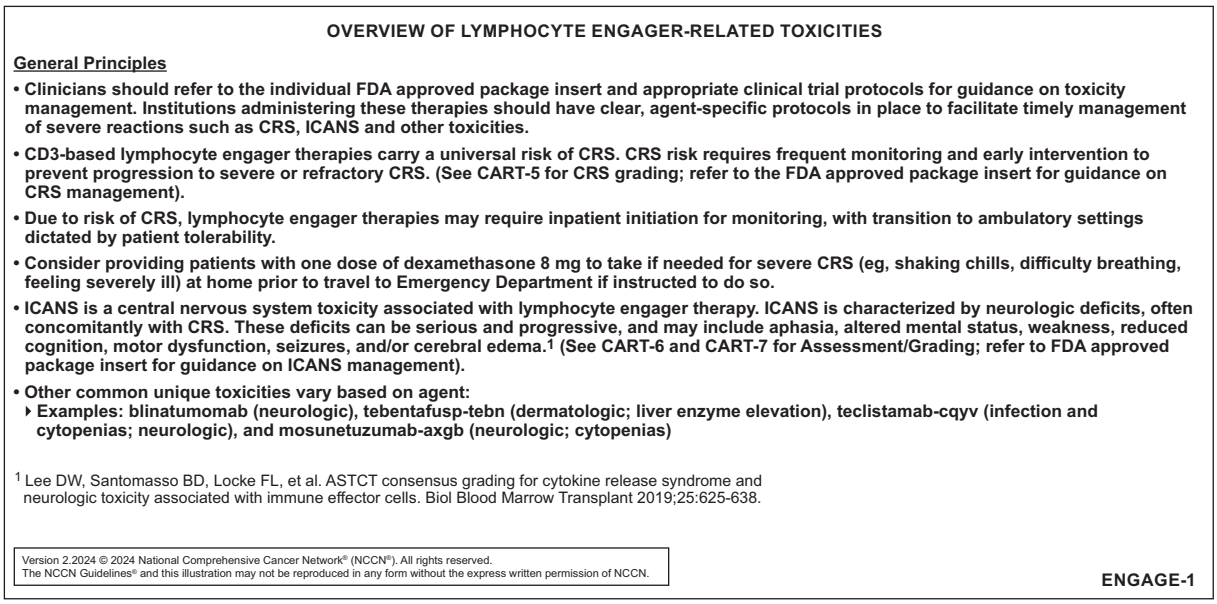


Figure 8. ENGAGE-1. NCCN Clinical Practice Guidelines in Oncology for Management of Immunotherapy-Related Toxicities, Version 2.2024.

dose modification according to the prescribing information can be considered for patients undergoing treatment with certain (but not all) T-cell–engaging bispecific antibodies,[55] because 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 × CD20 bispecific antibodies were recently developed by an international group of oncology practitioners based on their experience managing these toxicities in patients with lymphoma.[55] 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.

See Figure 8 for complete recommendations pertaining to the management of lymphocyte engager–related toxicities.

Summary

As the patient population eligible for cancer immunotherapy expands, the number of those who will experience toxicities related to these agents will continue to increase. The NCCN Guidelines for Management of Immunotherapy-Related Toxicities provide guidance on management of the wide spectrum of irAEs that may occur, including emerging toxicities reported with newly available immunotherapies. These guidelines will continue to be updated at least annually based on consensus, clinical experience, and emerging data. Please refer to the full version of these NCCN Guidelines at NCCN.org for the most up-to-date recommendations.

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