ASCO special articles

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update

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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 immune checkpoint inhibitor (ICPi) therapy.

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

RESULTS A total of 175 studies met the eligibility criteria of the systematic review and were pertinent to the development of the recommendations. Because of the paucity of high-quality evidence, recommendations are based on expert consensus.

RECOMMENDATIONS Recommendations for specific organ system–based toxicity diagnosis and management are presented. While management varies according to the organ system affected, in general, ICPi therapy should be continued with close monitoring for grade 1 toxicities, except for some neurologic, hematologic, and cardiac toxicities. ICPi therapy may be suspended for most grade 2 toxicities, with consideration of resuming when symptoms revert ≤ grade 1. Corticosteroids may be administered. Grade 3 toxicities generally warrant suspension of ICPis and the initiation of high-dose corticosteroids. Corticosteroids should be tapered over the course of at least 4-6 weeks. Some refractory cases may require other immunosuppressive therapy. In general, permanent discontinuation of ICPis is recommended with grade 4 toxicities, except for endocrinopathies that have been controlled by hormone replacement. Additional information is available at www.asco.org/supportive-care-guidelines.

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ASSOCIATED CONTENT

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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. Immune checkpoint inhibitors (ICPis) targeting cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4), programmed cell death-1 (PD-1), and PD ligand 1 (PD-L1) work by preventing the receptors and ligands from binding to each other, thereby disrupting signaling so that T cells can recognize and attack cancer cells.[1] They are currently the standard of care in the treatment of several cancers, including a variety of solid-organ and hematologic malignancies. The use of ICPis is rising exponentially, with approximately 40% of patients with cancer in the United States in 2019 eligible for treatment with ICPis.[2] Clinical trials of immunotherapy also continue to expand with the development of novel ICPi agents and combination treatment. Ongoing evaluations for new therapeutic indications and across tumor types make this a rapidly changing field.

Despite the clinical benefits of the immune checkpoint blockade therapy, its use is associated with a spectrum of side effects, related to the mechanism of action, which is quite different from other systemic therapies such as cytotoxic chemotherapy (CTX). The side effects may involve any organ or system of the body; however, GI, dermatologic, hepatic, endocrine, and pulmonary toxicities predominate, and there should be a high level of suspicion that any changes are treatment-related. The incidence and onset of immune-related adverse effects (irAEs) vary based

THE BOTTOM LINE

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update

Guideline Question

How should clinicians manage immune-related adverse events (irAEs) in adult patients with cancer treated with immune checkpoint blockade antibodies therapy?

Target Population

Adult patients with cancer receiving treatment with immune checkpoint blockade inhibitors 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 ICPis, and their caregivers.

Methods

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

Key Recommendations

The following are general recommendations that should be followed irrespective of affected organs. For organ-specific and systemic toxicities' management, see Tables 1-11. Note that definitions of grades are found in each table and, for the most part, follow the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.[4]
It is recommended that clinicians manage toxicities as follows:

- Patient and family caregivers should receive timely and up-to-date education about immunotherapies, their mechanism of action, and the clinical profile of possible irAEs before initiating therapy and throughout treatment and survivorship.
- There should be a high level of suspicion that new symptoms are treatment-related.
- In general, ICPi therapy should be continued with close monitoring for grade 1 toxicities, except for some neurologic, hematologic, and cardiac toxicities.
- Consider holding ICPis for most grade 2 toxicities and resume when symptoms and/or laboratory values revert ≤ grade 1. Corticosteroids (initial dose of 0.5-1 mg/kg/d of prednisone or equivalent) may be administered.
- Hold ICPis for grade 3 toxicities and initiate high-dose corticosteroids (prednisone 1-2 mg/kg/d or equivalent). Corticosteroids should be tapered over the course of at least 4-6 weeks. If symptoms do not improve with 48-72 hours of high-dose steroid, infliximab may be offered for some toxicities.
- When symptoms and/or laboratory values revert ≤ grade 1, rechallenging with ICPis may be offered; however, caution is advised, especially in those patients with early-onset irAEs. Dose adjustments are not recommended. Rechallenge with PD-1/PD-L1 monotherapy may be offered in patients with toxicity from combined therapy with a CTLA-4 antagonist once recovered to ≤ grade 1.
- In general, grade 4 toxicities warrant permanent discontinuation of ICPis, except for endocrinopathies that have been controlled by hormone replacement.

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.

on the class and dose of ICPi administered, the type of cancer, and factors related to the patients. In general, patients receiving anti–PD-1 or PD-L1 antibodies have a lower incidence of any-grade irAEs than those treated with anti–CTLA-4 agents, with combinations increasing the incidence, severity, and onset of irAEs.[3] Variable onsets have been described for the different toxicities, from early occurrence within days to delayed onset up to 26 weeks, with a median onset of approximately 40 days.[3]

ICPi therapy can, in general, continue in the presence of mild irAEs, with close monitoring. However, moderate to severe irAEs may be associated with life-threatening declines in organ function and quality of life (QoL), and fatal outcomes have been reported; hence, these toxicities require early detection and proper management.

Combination therapy that includes ICPis plus CTX, targeted therapy, radiation therapy, intratumoral therapies, other immunomodulators, or adoptive cell therapy are being investigated and may offer additional long-term survival benefits. Although management of toxicities related to combination therapy is beyond the scope of this guideline, clinicians should be aware of the potential for novel toxicities with combination therapies and attempt to distinguish the causative agent(s) for appropriate management.

With the increasing use of immunotherapy in cancer treatment regimens, it is imperative that clinicians be knowledgeable about the symptoms 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 (AEs) in adult patients with cancer treated with immune checkpoint blockade antibodies? In addition, the guideline addresses how AEs related to steroid use can be prevented and managed.

METHODS

Guideline Development Process

A multidisciplinary panel of medical oncology, dermatology, gastroenterology, rheumatology, pulmonology, endocrinology, neurology, hematology, emergency medicine, 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. Based upon 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 (JCO)* 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 ICPi-related toxicity published since the literature search of the original guideline (August 30, 2017), using checkpoint inhibitor–specific terms combined with safety, 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 immune checkpoint blockade inhibitors alone (not in combination with CTX)
- Intervention: Steroids, immunosuppressive therapy, dose modification or discontinuation of therapy, organ-specific management, including hormone replacement, disease-modifying antirheumatic drugs, plasmapheresis, hospitalization, consultation to subspecialties, and best supportive care
- Comparator: No intervention or best supportive care
- Outcomes: Hospitalization, discontinuations of immunotherapy because of AE, AE-related morbidity or mortality, organ dysfunction based on organ system affected, required treatment because of immune-mediated AEs, retreatment with immunotherapy, recovery from AEs, and health-related QoL.

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; (2) were clinical trial protocols; and (3) focused solely on pediatric patients.

The guideline recommendations are crafted, in part, using the *Guidelines Into Decision Support* methodology.[5] In addition, a guideline implementability review was conducted. Based on 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 co-chairs to keep abreast of any substantive updates to the guideline. Based on 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 175 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 AEs in adult patients with cancer treated with immune checkpoint blockade antibodies?

1.0. Recommendations for identification, evaluation, and management of cutaneous toxicities. Immune-related cutaneous AEs are characterized as inflammatory dermatoses, bullous dermatoses, and severe cutaneous adverse reactions (SCARs), according to the CTCAE.[7] The median time to onset of skin toxicities is 4 weeks, but can range broadly from 2 to 150 weeks.[8-10] Rash or inflammatory dermatitis irAEs encompass erythema multiforme, lichenoid, eczematous, psoriasiform, morbilliform, and palmoplantar erythrodysesthesia, or hand-foot syndrome. Presenting symptoms related to immune therapy–induced rash or inflammatory dermatitis can vary but often include itch with or without rash, new or worsening skin lesions, including macules, papules, or plaques, and loss of skin pigmentation. For bullous dermatoses, presenting symptoms may also include new or worsening skin lesions, including bullae, persistent urticaria, or erosions on the skin or mucosal surfaces. SCAR includes Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis (although note that acute generalized exanthematous pustulosis is not always severe), and drug reaction with eosinophilia and systemic symptoms or drug-induced hypersensitivity syndrome. Presenting symptoms related to immune therapy–induced

SCAR may include fever, widespread rash, skin pain, skin sloughing, facial or upper-extremity edema, pustules, blisters, or erosions.

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

Discussion. Among the irAEs observed during treatment with ICPis, cutaneous toxicities, including rash, pruritis (with and without eruption), and vitiligo, are the most common, reported in up to 71.5% of individuals across ICPi therapy.[8,11-17] The proinflammatory microenvironment created by ICPi immune-mediated activity and the unrestrained activity of T cells contribute to the occurrence of irAEs, including cutaneous manifestations.[7,18-20] Although they may occur in the context of anti–PD-1[21-23] and anti–PD-L1 therapy,[24] cutaneous irAEs are more frequently observed with CTLA-4 inhibitors alone or in combination with anti–PD-1 agents.[8,25,26] Although cutaneous irAEs may occur in individuals with diverse tumor types,[27] they are most often reported in individuals with melanoma[7,28-32] and non–small-cell lung cancer (NSCLC).[33-36] Cutaneous toxicities are often the earliest observed irAEs,[26] typically noted within 3 weeks after the initiation of ipilimumab and within 6 weeks following the start of anti–PD-1 therapy; however, their onset can be delayed, even after completion of therapy. Severe cutaneous toxicities of grade 3 or higher, per CTCAE criteria, are observed in 3% or fewer individuals receiving monotherapy.[8] Despite the potential for lower-grade presentation, immune-related skin toxicities may cause increased symptom burden and affect health-related QoL among individuals treated with ICPis.[8,37,38]

Inflammatory presentations account for the overwhelming majority of cases and can include spongiotic (mimicking eczema), granulomatous,[39-42] psoriasiform,[43,44] lupus-like lichenoid,[45-48] and panniculitis.[49] The clinical presentations vary with focal to diffuse distributions, including flexural, inverse, and erythrodermic variants. Pruritus can be severe and is the most common associated symptom.[7] Vitiligo presents as well-demarcated depigmented macules and patches, reported primarily in patients with melanoma.[50-52] The variability in clinical presentation is mirrored in the variable timing of onset, ranging from inflammatory dermatoses, which usually present within the first one to two cycles of treatment, to vitiligo,[50-52] which can manifest months after treatment initiation. Immune-related alopecia (alopecia areata) has also been observed.[53,54] Therefore, assessment and monitoring for signs and symptoms of cutaneous irAE require a consistent and longitudinal approach on the part of both the provider and the patient to promote timely identification and management.

Once identified, cutaneous toxicities should be managed according to guidelines using an interprofessional approach through early engagement of a dermatologist to guide evidence-based specialty care.[17,55,56] This is particularly important as grading may necessitate stopping treatment to support early intervention with the goal of safe and timely return to treatment. Findings from large clinical development programs suggest that cutaneous irAEs may be a surrogate for clinical benefit, and it would be important to correctly identify these skin changes so that the ICPi therapy is not discontinued in these cases with good prognoses. However, certain manifestations, including bullous dermatoses,[57-60] and SCAR[61] such as Stevens-Johnson syndrome[62] and drug reaction with eosinophilia and systemic symptom, although rarer, will require temporary or permanent discontinuation of therapy.[63] Grade 4 toxicities will likely require hospitalization for management of infection risk, symptoms, wound care, and potential for supplemental nutrition. Although many cutaneous irAEs can be treated without permanent discontinuation of therapy,[12] irAEs can contribute to treatment noncompliance, discontinuation, or dose modification. Therefore, early identification and symptomatic or systemic management are pivotal to enhance compliance, treatment continuation, and ultimately therapeutic efficacy.

2.0. Recommendations for identification, evaluation, and management of GI toxicities. GI toxicities reported with ICPi use include colitis, hepatitis, gastritis, and enterocolitis. The median time to onset of GI toxicities is 6 weeks, with a wide range of 1-107.5 weeks.[9,10] Presenting symptoms related to ICPi-induced colitis may include abdominal pain, nausea, diarrhea, blood and mucous in the stool, and fever. Presenting symptoms related to ICPi-induced hepatitis may include jaundice, nausea or vomiting, anorexia, pain on the right side of the abdomen, dark urine (tea-colored), bleeding, or bruising more easily than normal.

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

Discussion. GI toxicities are some of the most common complications reported with ICPi use. Although the frequency of colitis reported in the literature ranges from 8% to 27%, the incidence of diarrhea is as high as 54% in patients treated with anti–CTLA-4 antibodies,[64,65] especially in patients who receive anti–CTLA-4 and anti–PD-1 combination therapy.[66] GI toxicity is less common with anti–PD-1 monotherapy, with the incidence of diarrhea reported to be ≤ 19%.[64] Frequency of intestinal perforation has been described at approximately 1% of patients with colitis.[64,67,68]

The most common clinical presentations of immune-related GI toxicities vary from very frequent and/or loose stools to colitis symptoms (eg, mucus in the stools, abdominal pain, fever, and rectal bleeding).[18] The onset of these GI symptoms is most often in the range of 5-10 weeks after initiation of ICPi but can occur or recur months after discontinuation of immunotherapy.[26,66] Furthermore, with an increase in PD-1/PD-L1 antibodies given with cytotoxic CTX, a pattern of early-onset diarrhea (within 1-2 weeks from initiating CTX or immunotherapy combination) may

TABLE 1. Cutaneous Toxicities

1.1. Rash or Inflammatory Dermatitis

Workup and evaluation	
Pertinent history and physical examination including examination of the oral mucosa, assessment for blister formation, and assessment of BSA involved. Review full list of patient medications to rule out other drug-induced cause for photosensitivity. Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, including prior or other recent cancer therapies, or a skin condition linked to another systemic disease or unrelated primary skin disorder. Recent or new complete blood count and comprehensive metabolic panel (if needed for skin differential diagnosis). Consider referral to dermatologist if autoimmune skin disease is suspected. Consider skin biopsy. Consider clinical monitoring with use of serial clinical photography.	
Grading (grading according to CTCAE criteria is a challenge for skin. Instead, severity may be based on BSA, tolerability, morbidity, and duration).	**Management**
G1: Rash covering < 10% BSA, which may or may not be associated with symptoms of pruritus or tenderness.	Continue ICPi. Treat with topical emollients and/or mild-moderate potency topical corticosteroids. Counsel patients to avoid skin irritants.
G2: Rash covering 10%-30% BSA with or without symptoms (eg, pruritus, burning, and tightness); limiting instrumental ADL; rash covering > 30% BSA with or without mild symptoms.	Consider holding ICPi and monitor weekly for improvement. If skin toxicity is not improved after 4 weeks, then regrade toxicity as grade 3. In addition, treat with topical emollients, oral antihistamines, and medium-to-high potency topical corticosteroids. Consider initiating prednisone (or equivalent) at dosing 0.5-1 mg/kg, tapering over 4 weeks. In patients with pruritis without rash, consider topical anti-itch remedies (eg, refrigerated menthol and pramoxine).
G3: Rash covering > 30% BSA with moderate or severe symptoms; limiting self-care ADL.	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming. Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids. May also consider phototherapy to treat severe pruritus. Initiate oral prednisone or equivalent (1 mg/kg/d) tapering over at least 4 weeks. Once downgraded to ≤ G1 and prednisone (or equivalent) below 10 mg/d, clinicians may consider resuming ICPi therapy with close monitoring and follow-up with dermatology in certain cases such as psoriasis. In patients with pruritis without rash, may treat with gabapentin, pregabalin, aprepitant, or dupilumab.
G4: Severe consequences requiring hospitalization or urgent intervention indicated or life-threatening consequences.	Immediate hold ICPi May admit patient immediately with direct oncology involvement and with an urgent consult by dermatology. Systemic steroids: IV methylprednisolone (or equivalent) dosed at 1-2 mg/kg with slow tapering when the toxicity resolves. Monitor closely for progression to SCAR. Consider alternative antineoplastic therapy over resuming ICPis if the skin irAE does not resolve to ≤ G1. If ICPis are the patient's only option, consider restarting once these side effects have resolved to a G1 level with close dermatology follow-up.

1.2. Bullous Dermatoses

Workup and evaluation
Physical examination Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease. Dermatology consultation for consideration of skin biopsy and direct immunofluorescence. Further serologic workup, such as ELISA testing or indirect immunofluorescence, may be pursued. Primer on monitoring for complicated cutaneous adverse drug reactions Review of systems: skin pain (like a sunburn), fevers, malaise, myalgias, arthralgias, abdominal pain, ocular discomfort or photophobia, sores or discomfort in the nares, sores or discomfort in the oropharynx, odynophagia, hoarseness, dysuria, sores or discomfort in the vaginal area for women or involving the meatus of the penis for men, sores in the perianal area, or pain with bowel movements. Physical examination includes vital signs and a full skin examination specifically evaluating all skin surfaces and mucous membranes (eyes, nares, oropharynx, genitals, and perianal area). Assess for lymphadenopathy, and facial or distal-extremity swelling (may be signs of DIHS/DRESS; see 1.3 Section). Assess for pustules or blisters or erosions in addition to areas of dusky erythema, which may feel painful to palpation.

(continued on following page)

TABLE 1. Cutaneous Toxicities (continued)

1.2. Bullous Dermatoses

Grading	Management
G1: Asymptomatic or blisters covering < 10% BSA and no associated erythema	If blisters are < 10% BSA, are asymptomatic and noninflammatory (such as the case with friction blisters or pressure blisters), cessation of ICPi is not necessary and only observation or local wound care is warranted. When symptomatic bullae or erosions, which are deroofed vesicles or bullae, are noted on the skin or mucosal surfaces, the cutaneous irAE is considered at least grade 2. See grade 2 management recommendations.
G2: Blistering that affects QoL and requires intervention based on diagnosis not meeting criteria for > grade 2. Blisters covering 10%-30% BSA.	Hold ICPi therapy and consult with dermatology for steroid-sparing options, workup, and to determine appropriateness of resuming. Attention given to general local wound care, which includes plain petrolatum ointment and bandages or plain petrolatum ointment gauze and bandage over any open erosions, which are left on the skin after the blister has popped or if the roof of the blister easily sloughs off. Initiate class 1 high-potency topical steroid, eg, clobetasol, betamethasone, or equivalent, and reassess every 3 days for progression or improvement. Low threshold to initiate treatment with prednisone (or equivalent) at 0.5-1 mg/kg/d dosing and taper over at least 4 weeks. Monitor patients closely for progression to greater BSA involvement and/or mucous membrane involvement. Consider following patients closely using serial photography.
G3: Skin sloughing covering > 30% BSA with associated pain and limiting self-care ADL.	Hold ICPi therapy and consider admitting patient. Administer IV methylprednisolone (or equivalent) 1-2 mg/kg and when appropriate convert to oral steroids, tapering over at least 4 weeks. If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic steroids and transition to steroid-sparing options (eg, IVIG and rituximab), as an alternative approach to treating the irAE. Consult with dermatology to determine appropriateness of resuming ICPi once symptoms improve.
G4: Blisters covering > 30% BSA with associated fluid or electrolyte abnormalities.	Permanently discontinue ICPi. Admit patient immediately and place under supervision of a dermatologist. Administer IV methylprednisolone (or equivalent) 1-2 mg/kg and when appropriate convert to oral steroids, with tapering over at least 4 weeks. If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic steroids and treat with steroid-sparing options, as an alternative approach to treating the irAE (eg, IVIG and rituximab).

1.3. SCAR

Workup and evaluation
- Total body skin examination with attention to examining ALL mucous membranes, as well as complete review of systems.
- Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, or a skin condition linked to another systemic disease.
- A biologic checkup including a CBC with DIFF, liver, and kidney function tests; consider UA in the context of DRESS to assess for associated nephritis in addition to the blood work. If the patient is febrile, blood cultures should be considered as well. Skin biopsies to assess for full-thickness epidermal necrosis, as is seen in SJS or TEN, as well as other possible etiologies like paraneoplastic pemphigus or other autoimmune blistering dermatoses or other drug reactions, such as AGEP.
- Follow patients closely using serial clinical photography.
- If mucous membrane involvement or blistering is noted on the skin, consider early admission to a burn center for further monitoring and management.
- Follow primer on monitoring for complicated cutaneous adverse drug reactions from section 1.2.

Grading	Management
All grades	In cases of suspected SJS or any mucous membrane involvement (not including isolated stomatitis), discontinue ICPi treatment and consult dermatology. Monitor closely for improvement regardless of grade.
G1 and G2: NA	For the SCAR adverse reactions, there are no grade 1 or 2 categories. If limited BSA is involved with bullae or erosions, there should remain high concern that this reaction will progress to grade 3 or 4.

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TABLE 1. Cutaneous Toxicities (continued)

1.3. SCAR

G3: Skin sloughing covering < 10% BSA with mucosal involvement–associated signs (eg, erythema, purpura, epidermal detachment, and mucous membrane detachment).	Hold ICPi therapy and consult with dermatology. Admit to burn unit and/or consult wound services with attention to supportive care including fluid and electrolyte balance, minimizing insensible water losses, and preventing infection. Treat skin with topical emollients and other petrolatum emollients, oral antihistamines, and high-strength topical corticosteroids. Dimethicone may also be offered as an alternative to petrolatum. Administer IV methylprednisolone (or equivalent) 0.5-1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks. Given the immune mechanism of action of these medicines, use of immune suppression (Table A2) is warranted and should be offered. The usual prohibition of corticosteroids for SJS is not relevant here, as the underlying mechanism is a T-cell immune-directed toxicity. Adequate suppression is necessary with corticosteroids or other agents and may be prolonged in cases of DRESS or drug hypersensitivity syndrome. For mucous membrane involvement of SJS or TEN, appropriate consulting services should be offered to guide management in preventing sequelae from scarring (eg, ophthalmology, otolaryngology, urology, or gynecology as appropriate).
G4: Skin erythema and blistering or sloughing covering ≥ 10% BSA with associated signs (eg, erythema, purpura, epidermal detachment, and mucous membrane detachment) and/or systemic symptoms and concerning associated blood work abnormalities (eg, liver function test elevations in the setting ;of DRESS or DIHS).	Permanently discontinue ICPi. Admit patient immediately to a burn unit or ICU with consulted dermatology and wound care services. Consider further consultations based on management of mucosal surfaces (eg, ophthalmology, urology, gynecology, or otolaryngology). Initiate IV methylprednisolone (or equivalent) 1-2 mg/kg, tapering when toxicity resolves to normal. IVIG or cyclosporine may also be considered in severe or steroid-unresponsive cases. Consider pain or palliative consultation and/or admission in patients presenting with DRESS manifestations.

Abbreviations: ADL, activity of daily living; AGEP, acute generalized exanthematous pustulosis; BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events; DIFF, differential test; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptom; ELISA, enzyme-linked immunosorbent assay; ICPi, immune checkpoint inhibitor; ICU, intensive care unit; irAE, immune-related adverse event; IV, intravenous; IVIG, intravenous immune globulin; NA, not available; QoL, quality of life; SCAR, severe cutaneous adverse reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; UA, urinalysis.

occur, and ascertaining the causative agent is important in guiding early management. Although clinical factors associated with ICPi-induced colitis have not been well established, nonsteroidal anti-inflammatory drug (NSAID) use is reported to be associated with an increase in ICPi-induced enterocolitis,[69] and care should be taken with NSAID use in this setting. There is a lot of similarity between ICPi-induced colitis and inflammatory bowel disease (eg, clinical presentations[70,71] and radiologic findings).[72] Computed tomography findings including mesenteric vessel engorgement; bowel wall thickening; and fluid-filled colonic distention.[72] The distribution of colitis has been reported to involve the descending colon more often than other parts of the colon.[64,72] The pathology from patients with ICPi colitis has demonstrated greater inflammatory changes than observed with classic inflammatory bowel disease.[72,73] The histologic picture is often characterized by marked mixed inflammatory cell infiltrates in the lamina propria, consisting of neutrophils, lymphocytes, plasma cells, and eosinophils, and also features of chronic inflammatory damage (crypt architecture distortion and Paneth cell metaplasia).[64,69,74,75] Inflammatory changes also tend to be more diffuse (75%).[64]

Once diarrhea symptoms are grade 2 or higher, or accompanied by apparent colitis symptoms, corticosteroid at 1-2 mg/kg is still the first-line treatment option. Endoscopic evaluation can add extra value to provide an objective measure of the colitis severity. Additionally, special consideration for endoscopy is encouraged when immunotherapy is given in combination with other systemic oncologic agents such as CTX and tyrosine kinase inhibitors, which are also known to cause diarrhea. Fecal calprotectin may be considered as an alternate, or adjunct, to endoscopic evaluation. The elevation of fecal calprotectin has been shown in inflammatory bowel disease to be a proxy for mucosal damage, and its normalization is associated with mucosal healing.[76,77] It should be noted that for malignancies involving the GI tract, fecal calprotectin has been observed to be elevated because of the presence of cancer-related luminal inflammation.[78,79]

For mild diarrhea (grade 1), conservative therapy alone is advised as the short-term use of any immunosuppressant (including topical forms like budesonide) should be practiced with caution, given the lack of supporting evidence for their efficacy. For patients with moderate or severe colitis who are refractory to initial corticosteroids and subsequent infliximab or vedolizumab, other alternative

TABLE 2. GI Toxicities

2.1. Colitis

Workup and evaluation

G2

Workup of blood (CBC, CMP, and TSH) and stool (culture, *C. diff*, parasite, CMV, or other viral etiology, O&P if appropriate) should be performed for the initial presentation, and also considered for immunosuppressant refractory cases.

Consider testing for fecal lactoferrin (for patient stratification to determine who needs more urgent endoscopy) and calprotectin (to follow-up on disease activity).

Screening labs (HIV, hepatitis A and B, and TB testing), repeated annually in patients who require biologic treatment, eg, infliximab or vedolizumab for $>$ 1 year until treatment is completed.

Consider reviewing concomitant medications that could alter the gut microbiome and their indications for prolonged use (eg, proton pump inhibitors, antibiotics, and probiotics).

Imaging, eg, CT scan of abdomen and pelvis for colitis-related symptoms (abdominal pain and bleeding) to rule out colitis-related complications, including typhlitis and bowel perforation or abscess.

GI endoscopy or colonoscopy with biopsy for patients who have positive stool inflammatory markers or colitis-related symptoms should be considered as there is evidence showing the presence of ulceration in the colon can predict steroid refractory course,[74] which may require early infliximab.

Repeat colonoscopy may be considered for cases grade $\geq$ 2 for disease activity monitoring to document complete remission, especially if there is a plan to resume ICPi. Mucosal healing on repeat endoscopy and/or fecal calprotectin level $\leq$ 116 μg/g can be considered the treatment target to guide decisions on when to stop biologic treatment and when to resume ICPi therapy.[74,75,80]

G3-4

Complete all recommendations as above and consider inpatient care.

Grading (based on CTCAE for diarrhea, as most often used clinically)	Management
All patients	Counsel all patients to be aware of and inform their health care provider immediately if they experience: abdominal pain, nausea, cramping, blood or mucus in stool, or changes in bowel habits. fever, abdominal distention, or constipation. For grade $\geq$ 2, consider permanently discontinuing CTLA-4 agents and may restart PD-1 or PD-L1 agents if patients recover to $\leq$ G1; concurrent immunosuppressant maintenance therapy should be considered only if clinically indicated in individual cases.
G1: Increase of $<$ 4 stools per day over baseline; mild increase in ostomy output compared with baseline	Continue ICPi. Alternatively, ICPi may be held temporarily and resumed if toxicity does not exceed grade 1 or resolves. May also include supportive care with medications such as loperamide if infection has been ruled out in patients with diarrhea only and not colitis-related symptoms as a temporary measure. Monitor for dehydration and recommend dietary changes. Patient should be closely monitored by phone or electronic medical system for symptoms changes by clinical providers every 3 days or more frequently if needed until stabilized. May obtain gastroenterology consult for prolonged G1 cases and consider endoscopy with biopsies.
G2: Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared with baseline	Hold ICPi at least until recovery to G1—see last bullets. May also include supportive care with medications such as loperamide if infection has been ruled out in patients with diarrhea only and not colitis-related symptoms as a temporary measure. Consider consult with gastroenterology for $\geq$ G2. Administer corticosteroids, unless diarrhea is transient, starting with initial dose of 1 mg/kg/day prednisone or equivalent until symptoms improve to G1, and then start taper over 4-6 weeks. Consider adding narrower-spectrum or more potent agents, including anti-TNF (infliximab) or anti-integrin (vedolizumab) antibody to patients whose colitis is corticosteroid-refractory (ie, no decrease by one grade in 72 hours) or dependent or with high-risk endoscopic features[a] on initial endoscopy examination. When symptoms improve to $\leq$ G1, taper corticosteroids over 4-6 weeks; may consider shorter tapers in patients also treated with biologics. Endoscopic evaluation with EGD or colonoscopy is highly recommended for cases grade $\geq$ 2 to stratify patients for early treatment of biologics based on the endoscopic findings. Resuming ICPi after symptoms improve to $\leq$ G1 may be considered when steroid taper is completed, risk and benefits reviewed if maintained on biologics, and/or if endoscopic and histologic remissions are achieved. Fecal calprotectin $\leq$ 116 μg/g may be considered as a surrogate for endoscopic and histologic remission.[80] Resuming PD-1/PD-L1 agent is associated with lower risk of flare-up; however, CTLA-4 inhibitor can still be considered in selected cases, such as in patients who have not yet responded or whose response is deemed inadequate.

(continued on following page)

TABLE 2. GI Toxicities (continued)

2.1. Colitis	
G3: Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared with baseline; and limiting self-care ADL	Follow G2 recommendations as listed, with the following additions for G3: Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent) until symptoms improve to G1, and then start taper over 4-6 weeks. Consider IV methylprednisolone, especially if concern for concurrent upper GI inflammation. Consider early introduction of infliximab or vedolizumab in addition to steroids in patients with high-risk endoscopic features[a] on initial endoscopy examination or inadequate response to steroids (persistent symptoms after 3 days). Consider hospitalization for patients with dehydration or electrolyte imbalance. Consider repeat colonoscopy in patients who are immunosuppression-refractory. Should consider permanently discontinuing CTLA-4 agents.
G4: Life-threatening consequences; urgent intervention indicated	Follow G2-G3 recommendations as listed, with the following additions for G4: Permanently discontinue treatment. Should provide inpatient care. Administer 1-2 mg/kg/d methylprednisolone or equivalent until symptoms improve to G1, and then start taper over 4-6 weeks. Consider early biologics (infliximab or vedolizumab) if inadequate response to steroids after 3 days. Consider lower GI endoscopy if symptoms are refractory, despite treatment or there is concern of new infections.
Additional considerations May consider fecal microbiota transplant,[81,82] JAK inhibitor tofacitinib,[83] or IL-12–blocking antibody ustekinumab[84] in patients who are refractory to the previous immunosuppressants. Patients with both irAE-related hepatitis and irAE-related colitis are less common, and management may include permanently discontinuing ICPi and offering other immunosuppressant agents (eg, prednisone and mycophenolate) that work systemically for both conditions. Infliximab is contraindicated for hepatic irAE. Currently, enteritis and/or gastritis alone as the cause of GI toxicity is uncommon and endoscopy with biopsy is recommended as the evaluation tool. It may be managed similarly to colitis including steroid and/or biologics etc	
2.2. Hepatitis	
Workup and evaluation: Monitor patient for abnormal liver blood tests: AST, ALT, and bilirubin before each infusion and/or consider weekly if grade 1 LFT elevations. No treatment is recommended for grade 1 LFT abnormality. Review medications and supplements that may cause hepatotoxicity and rule out abnormal liver enzymes from development or progression of liver metastases. Liver biopsy should be considered if the patient is steroid-refractory or if concern for other differential diagnoses that would alter medical management. For grade ≥ 2 Workup for other causes of elevated liver enzymes (eg, viral hepatitis, alcohol history, iron studies, thromboembolic event, or potential liver metastasis from primary malignancy) by doing blood work and imaging (ultrasound and cross-sectional imaging). If suspicion for primary autoimmune hepatitis is high, can consider ANA/ASMA/ANCA. If patients with elevated ALKP alone, GGT should be tested. For isolated elevation of transaminases, consider checking CK for other etiologies.	
Grading	**Management**
G1: Asymptomatic (AST or ALT > ULN to 3.0× ULN and/or total bilirubin > ULN to 1.5× ULN)	Continue ICPi with close monitoring; consider alternate etiologies. Consider monitoring labs 1-2 times weekly. Manage with supportive care for symptom control.
G2: Asymptomatic (AST or ALT > 3.0 to ≤ 5× ULN and/or total bilirubin > 1.5 to ≤ 3× ULN)	Hold ICPi temporarily. Patients should be advised to stop unnecessary medications and any known hepatotoxic drugs. Temporarily hold other potentially hepatotoxic oncologic agents. For grade 2 hepatic toxicity, may administer steroid (0.5-1 mg/kg/d prednisone) or equivalent if no improvement is seen after 3-5 days. Increase frequency of monitoring to every 3 days. If inadequate improvement after 3 days, consider adding mycophenolate mofetil. May initiate steroid taper when symptoms improve to ≤ G1 and may resume ICPi treatment when steroid ≤ 10 mg/d. Taper over at least 1 month. Consider hepatology consult for G2 and above. May resume if recover to ≤ G1 on prednisone ≤ 10 mg/d.

(continued on following page)

TABLE 2. GI Toxicities (continued)

2.2. Hepatitis

G3: AST or ALT 5-20× ULN and/or total bilirubin 3-10× ULN, OR symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; and reactivation of chronic hepatitis	Follow G2 recommendations as listed, with the following additions for G3: Consider permanently discontinuing ICPi if asymptomatic; permanently discontinue if symptomatic. Immediately start steroid 1-2 mg/kg methylprednisolone or equivalents. If steroid refractory, consider liver biopsy to rule out NASH, tumor, cholestatic variants, other drug-related hepatic inflammation, infection, or other autoimmune entity and consider adding azathioprine[b] or mycophenolate[c] if infectious cause is ruled out. Labs daily or every other day; consider inpatient monitoring for patients with AST/ALT > 8 × ULN and/or elevated total bilirubin 3× > ULN. If no improvement is achieved with steroid or for patients on ICPi therapy combined with a novel agent, with standard CTX, or with targeted therapy, refer to hepatologist for further pathologic evaluation of hepatitis. Steroid taper can be attempted around 4-6 weeks when ≤ G1, re-escalate if needed, optimal duration unclear. Consider transfer to tertiary care facility if necessary.
G4: AST or ALT > 20× ULN and/or total bilirubin > 10× ULN OR decompensated liver function (eg, ascites, coagulopathy, encephalopathy, and coma)	Follow G3 recommendations as listed, with the following additions for G4: Administer 2 mg/kg/d methylprednisolone equivalents.
Additional considerations Infliximab is contraindicated for immune-related hepatitis.	

Abbreviations: ADL, activities of daily living; ALKP, alkaline phosphatase; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ASMA, anti–smooth muscle antibodies; CK, creatine kinase; CMP, comprehensive metabolic panel; CMV, cytomegalovirus; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; CTLA, cytotoxic T-lymphocyte–associated antigen; CTX, chemotherapy; EGD, esophagogastroduodenoscopy; GGT, gamma-glutamyl transferase; ICPi, immune checkpoint inhibitor; IL, interleukin; irAE, immune-related adverse event; IV, intravenous; JAK, Janus kinase; LFT, liver function tests; NASH, nonalcoholic steatohepatitis; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; TB, tuberculosis; TNF, tumor necrosis factor; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

[a]High-risk endoscopic features include large deep ulceration, multiple ulcers, and extensive colitis beyond left colon.[74,75]

[b]Anecdotal experience suggests azathioprine may be beneficial in steroid-refractory immune-related hepatitis. If using azathioprine, should test for thiopurine methyltransferase deficiency.

[c]A case study reports use of mycophenolate mofetil in steroid-refractory immune-related hepatitis with some success.[85]

medical options (tofacitinib and ustekinumab) have been reported with very small sample sizes.[83,84] Fecal microbiota transplantation has also been demonstrated to achieve 75% efficacy in treating 15 refractory colitis cases.[81,82] Preliminary data suggest that GI toxicities are associated with improved survival and treatment outcomes in comparison to other immunotherapy treated patients.[86,87]

Compared with lower-GI toxicities, upper-GI toxicity is much less common and characterized by dysphagia, nausea or vomiting, and epigastric pain.[88,89] Patchy chronic duodenitis or chronic gastritis with rare granulomas may be identified on biopsies.[69,90] It can coexist with lower-GI toxicity or as an isolated condition. The treatment strategy is similar to colitis: corticosteroid followed by infliximab or vedolizumab for refractory cases based on case studies.[69,90,91]

Hepatotoxicity has been reported to occur in 2%-10% of patients treated with ipilimumab, nivolumab, and pembrolizumab monotherapy.[92-95] Combination treatment with ipilimumab and nivolumab has resulted in a reported 25%-30% all-grade hepatitis and approximately 15% incidence of grade 3 toxicity. Onset develops predominately within the first 6-12 weeks after treatment initiation.[96] Liver biopsy should be considered for the indication of exclusion for other etiologies for persistent or refractory hepatitis if blood work or imaging evaluations are not conclusive. For corticosteroid refractory cases, mycophenolate mofetil has been reported in a case study with some success.[97] The tumor necrosis factor α blocker infliximab is not recommended, given the concern of liver toxicity.[98] Other alternative immunosuppressive agents still need further data proof for efficacy and safety. The patient with pre-existing hepatitis who experiences ICPi-induced colitis is rare but represents a management challenge. Available options are more limited and should include permanent cessation of anti–CTLA-4 and possibly other ICPi treatment.

Symptomatic pancreatitis has also been reported in the literature, but it is rare.[70,99] Routine monitoring of amylase or lipase in asymptomatic patients is not recommended, and a standard workup for pancreatitis and its potential causes should be initiated if a patient develops suggestive symptoms or suspicious findings on a scan performed for other reasons such as tumor assessment. The role of corticosteroids in treating ICPi-mediated pancreatitis or pancreatic enzyme elevation is not clearly defined but could be considered in symptomatic disease when etiologies separate from ICPi-induced irAE are ruled out.[99-101]

Evidence of mucosal healing on follow-up endoscopy, or a fecal calprotectin level ≤ 116 μg/g, can be considered as

potential parameters to guide the timing of ICPi resumption to minimize the risk of colitis recurrence.[75,80] Toxicities such as hepatitis and pancreatitis also have some risk of recurrence.[102] These most often occur early and are generally low grade and manageable with standard treatments. Nonetheless, care should be taken to ensure that proper monitoring and management strategies are implemented.[102]

3.0. Recommendations for identification, evaluation, and management of lung toxicities. Pneumonitis is defined as focal or diffuse inflammation of the lung parenchyma, typically identified on computed tomography imaging. There are no symptomatic, pathologic, or radiographic features that are pathognomonic for pneumonitis, although presenting symptoms related to immune therapy–induced pneumonitis may include new or worsening cough, shortness of breath, increased oxygen requirement, chest pain, and/or fever. The median time to onset of pneumonitis is 34 weeks but can range from 1.5 to 127 weeks.[9,103]

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

Discussion. ICPi-related pneumonitis is an uncommon but potentially serious toxicity. The reported incidence of pneumonitis in studies investigating anti–PD-1/PD-L1 is variable and ranges from 0% to 10%,[103] with an overall incidence of 2.7% reported in a recent meta-analysis of 20 studies with PD-1 inhibition.[104] The toxicity is less common with anti–CTLA-4 treatment, with pneumonitis reported in < 1% of trial participants receiving ipilimumab.[105-109] A higher incidence is seen in patients who received combination ICPis than those who received ICPi monotherapy (10% *v* 3%, respectively, $P < .001$)[103] and patients treated with combinations may be less likely to experience resolution of the irAE compared with patients treated with monotherapy.[105,110] Newer data suggest that approximately 2% of patients with NSCLC or melanoma with immune-related toxicity experienced chronic pneumonitis, which persists despite ICPi discontinuation and may not resolve after > 3 months of corticosteroids.[111]

The risk of IPCi-related pneumonitis and pneumonitis-related deaths based on tumor type remains equivocal. The odds of all-grade pneumonitis were higher in NSCLC than in patients with melanoma (odds ratio [OR], 1.43; 95% CI, 1.08 to 1.89; $P = .005$) according to the Nishino et al[104] meta-analysis. Similarly, patients with renal cell carcinoma (RCC) were also significantly more likely to experience all-grade pneumonitis than patients with melanoma (OR, 1.59; 95% CI, 1.32 to 1.92; $P < .001$).[104] By contrast, other studies have reported similar rates of grade 3-4 pneumonitis across tumor types, but with more treatment-related deaths because of pneumonitis seen in patients with NSCLC.[105,112-114] In a multicenter, large, retrospective analysis, pneumonitis was reported in both former or current smokers (56%) and never smokers (44%).[103] Recent evidence also demonstrated no significant difference in the rates of irAEs, including pneumonitis, in patients who received thoracic radiotherapy and checkpoint inhibitors.[115]

Ground-glass opacities or patchy nodular infiltrates, predominantly in the lower lobes, are common findings on chest imaging.[116] Radiologic abnormalities vary but are often reported to be focal and very different from the diffuse pneumonitis associated with targeted agents.[116] Naidoo et al[103] reported on five distinct radiologic subtypes identified: chronic obstructive pneumonia–like, ground-glass opacities, hypersensitivity type, interstitial type, and pneumonitis not otherwise specified.

When the clinical picture is consistent with pneumonitis, the role of transbronchial biopsy is currently debated but generally not required. However, biopsy may have a role in assisting to rule out other etiologies like lymphangitic spread of tumor or infection or distinguishing chronic ICPi pneumonitis, which appears to have an organizing pneumonia–like appearance.[111] Ultimately, the decision to proceed with biopsy should be taken after careful risk-benefit analysis, with the optimal technique, number, size, and location of biopsies depending upon the suspected diagnosis, the anatomic distribution of the disease process, and the availability of interventional pulmonologists.

The treatment of patients with symptomatic ICPi pneumonitis with corticosteroids is recommended as an initial treatment, based on several studies that report clinical improvement in > 80% of cases.[103] However, ICPi pneumonitis may not clinically improve after > 48 hours of corticosteroid therapy, at which time it is deemed steroid-refractory. There is no standard immunosuppressive therapy for this clinical situation; however, options include infliximab, mycophenolate mofetil, intravenous immune globulin (IVIG), or cyclophosphamide, based on two large retrospective experiences.[117,118] There is an ongoing prospective cooperative group study that aims to address this clinically relevant question (NCT04438382).

In addition to typical findings of pneumonitis, sarcoid-like granulomatous reactions—including subpleural micronodular opacities and hilar lymphadenopathy, as well as pleural effusions—have been associated with both CTLA-4 and PD-1/PD-L1–targeted therapies.[105,107,119-122] Clinical manifestations are diverse and often patient-specific and can include cough, wheezing, fatigue, chest pain, or no symptoms at all. With varying clinical presentation, it is prudent for clinicians to be aware of the possibility of such immune-related pulmonary reactions, as they may mimic disease progression on imaging and examination. Biopsy may assist in confirming the diagnosis.

4.0. Recommendations for identification, evaluation, and management of endocrine toxicities. Immune-related endocrine AEs are characterized by the gland or organ affected and include primary hypothyroidism, thyrotoxicosis, primary adrenal insufficiency, hypophysitis, and diabetes.

TABLE 3. Lung Toxicities

3.1. Pneumonitis

Workup and evaluation Should include the following: Pulse oximetry and CT chest[123] preferably with contrast if concerned for other etiologies such as pulmonary embolus. For G2 or higher, may include the following infectious workup: nasal swab, sputum culture, and sensitivity, blood culture and sensitivity, urine culture, and sensitivity. COVID-19 evaluation—per institutional guidelines where relevant.	
Grading	**Management**
G1: Asymptomatic; confined to one lobe of the lung or < 25% of lung parenchyma; clinical or diagnostic observations only	Hold ICPi or proceed with close monitoring. Monitor patients weekly with history and physical examination, pulse oximetry; may also offer chest imaging (CXR, CT) if uncertain diagnosis and/or to follow progress. Repeat chest imaging in 3-4 weeks or sooner if patient becomes symptomatic. In patients who have had baseline testing, may offer a repeat spirometry or DLCO in 3-4 weeks. May resume ICPi with radiographic evidence of improvement or resolution if held. If no improvement, should treat as G2.
G2: Symptomatic; Involves more than one lobe of the lung or 25%-50% of lung parenchyma; medical intervention indicated; limiting instrumental ADL	Hold ICPi until clinical improvement to ≤ G1. Prednisone 1-2 mg/kg/d and taper over 4-6 weeks. Consider bronchoscopy with BAL ± transbronchial biopsy. Consider empiric antibiotics if infection remains in the differential diagnosis after workup. Monitor at least once per week with history and physical examination, pulse oximetry, consider radiologic imaging; if no clinical improvement after 48-72 hours of prednisone, treat as grade 3. Pulmonary and infectious disease consults if necessary.
G3: Severe symptoms; Hospitalization required: Involves all lung lobes or > 50% of lung parenchyma; limiting self-care ADL; oxygen indicated. G4: Life-threatening respiratory compromise; urgent intervention indicated (intubation)	Permanently discontinue ICPi. Empiric antibiotics may be considered. Methylprednisolone IV 1-2 mg/kg/d. If no improvement after 48 hours, may add immunosuppressive agent. Options include infliximab or mycophenolate mofetil IV or IVIG or cyclophosphamide (See Table A2 for dosing). Taper corticosteroids over 4-6 weeks[a] Pulmonary and infectious disease consults if necessary. May consider bronchoscopy with BAL ± transbronchial biopsy if patient can tolerate.

Abbreviations: ADL, activity of daily living; BAL, bronchoalveolar lavage; CT, computed tomography; CXR, chest x-ray; DLCO, diffusing capacity of lung for carbon monoxide; ICPi, immune checkpoint inhibitor; IV, intravenous; IVIG, intravenous immune globulin.

[a]Subset of patients may develop chronic pneumonitis and may require longer taper. Chronic pneumonitis is a described phenomenon where the incidence is not known, but < 2%.[111]

The median time to onset of endocrine toxicities is 14.5 weeks with a range of 1.5-130 weeks.[9] Presenting symptoms related to immune therapy-induced endocrinopathies vary and may include headache and visual changes, especially visual field changes in pituitary swelling. Presenting symptoms of hypothyroidism can include cold intolerance, dry skin, constipation, weight gain, and/or fatigue. Palpitations, heat intolerance, insomnia, frequent bowel movements, or weight loss may be present with thyrotoxicosis and nausea, vomiting, abdominal pain, weight loss, lightheadedness or orthostasis or syncope, and profound fatigue may be symptoms of adrenal insufficiency. Diabetes or diabetic ketoacidosis (DKA) may present with polyuria or polydipsia, nausea or vomiting, abdominal pain, and/or visual blurring.

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

Discussion. Endocrine AEs with immune checkpoint therapy present a unique clinical challenge for the nonendocrinologist who faces the need to identify endocrine dysfunction in a patient with often nonspecific symptoms or complex abnormal laboratory findings. In a systematic review and meta-analysis that included 7,551 patients in 38 randomized trials, the overall incidence of clinically significant endocrinopathies was approximately 10% of patients treated with checkpoint inhibitors.[124] Diverse therapies and ICPi combinations have varied rates of targeting individual organs; for example, hypophysitis is most commonly seen when ipilimumab is used,[125-128] and primary ovarian failure has not yet been reported.[124] However, there are sporadic autoimmune diseases (ADs) known for all endocrine organs and we anticipate the possibility of any endocrine organ may be a target of an irAE as the use of ICPis becomes more widespread.

Clinical measures of both the primary hormone and the corresponding pituitary hormone are needed to localize disease for the classically regulated axes and morning serum hormone values are required. For example, low morning cortisol suggests adrenal insufficiency but does not indicate whether the problem is pituitary or adrenal. Hypophysitis, pituitary mass, or iatrogenic causes are suggested if a simultaneously measured adrenocorticotropic hormone (ACTH) is low; in primary adrenal insufficiency (eg, Addison's or adrenal hemorrhage), the morning ACTH will be elevated. The same applies in evaluating the thyroid axis, where clinicians typically screen with the pituitary hormone rather than the primary hormone. Low thyroid-stimulating hormone (TSH) may be consistent with either hyperthyroidism or central hypothyroidism; so, a free thyroxine (FT4) level is needed to confirm a diagnosis. Drawing both TSH and FT4 is especially important when patients are symptomatic and hypothyroidism is suspected because, in hypophysitis, TSH can remain within the reference range in the laboratory assays but lack function as a result of altered glycosylation because of the pituitary disease, so that only an FT4 will pick up on the presence of hypothyroidism.

Distinguishing primary from secondary hormonal problems is necessary to ensure the appropriate treatment. For example, a critical step for preventing harm with hormone replacement is using hydrocortisone first when multiple pituitary hormones are missing. If thyroid hormone is replaced first when cortisol is low, the increase in cortisol metabolism can trigger an adrenal crisis. Thus, recognizing that a patient has central hypothyroidism can prompt evaluation for secondary adrenal insufficiency, the second most common hormonal loss with hypophysitis.[124] Similarly, fludrocortisone is needed in addition to hydrocortisone in most cases of primary adrenal insufficiency, which involves the loss of mineralocorticoid as well as glucocorticoid production by the adrenal gland, leading to more-profound blood pressure and electrolyte abnormalities,[129] but is generally not necessary in those with secondary or central adrenal insufficiency. Monitoring is also affected by localization, as pituitary hormones are not reliable indicators of status with central disease. TSH, in particular, is not helpful in monitoring therapy with levothyroxine in patients with central hypothyroidism, and FT4 should be used instead.[130]

Diagnosis of endocrine dysfunction is complicated by the physiologic changes in hormone levels that accompany acute illness and by the administration of medications that affect pituitary function, including many therapies that patients with cancer are on, such as narcotics and megestrol acetate. Most relevant for the patients administered ICPis is the effect of corticosteroids, given for many irAEs in diverse organ targets. High-dose corticosteroids suppress ACTH and may cause persistent central adrenal insufficiency when stopped as the system can take weeks to months to recover, depending on the length of exposure. Serum cortisol levels should not be routinely measured while patients are on corticosteroid therapy because of variable assay effects from synthetic corticosteroids, low endogenous levels from the exposure, and the fact that the patient is on supraphysiologic doses and therefore treated for any underlying adrenal insufficiency that might be present eventually. If a diagnosis is needed, for example, after acute treatment of presumed adrenal crisis is initiated, ACTH stimulation testing may be performed. Endogenous levels can also be directly measured 24 hours after the last dose of physiologic hydrocortisone replacement to assess for functional recovery. High-dose corticosteroids and the physiologic response to acute nonthyroidal illness can lead to a low T3 syndrome, with either central suppression of TSH or a mild elevation, which has not been shown to benefit from therapy.[65,66] Especially in difficult cases, endocrinology consult is recommended.

TABLE 4. Endocrine Toxicities

4.1. Thyroid

4.1.1. Primary hypothyroidism	
Workup and evaluation TSH, with the option of also including FT4, can be checked every 4-6 weeks as part of routine clinical monitoring for asymptomatic patients on ICPi therapy. TSH and FT4 should be used for case detection in symptomatic patients. Low TSH with a low FT4 is consistent with central hypothyroidism. Evaluate as per hypophysitis (see 4.3). Commonly develops after thyrotoxicosis phase of thyroiditis (4.1.2).	
Grading	**Management**
G1: TSH > 4.5 and < 10 mIU/L and asymptomatic	Should continue ICPi with monitoring of TSH (option for FT4) every 4-6 weeks as part of routine care.
G2: Moderate symptoms, able to perform ADL. TSH persistently > 10 mIU/L	May continue or hold ICPi until symptoms resolve to baseline. Consider endocrine consultation for unusual clinical presentations, concern for central hypothyroidism, or difficulty titrating hormone therapy. Prescribe thyroid hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels that persist over 10 mIU/L (measured 4 weeks apart).[131,132] Monitor TSH every 6-8 weeks while titrating hormone replacement to goal of TSH within the reference range. FT4 can be used to help interpret ongoing abnormal TSH levels on therapy, as TSH may take longer to normalize. Once adequately treated, repeat testing every 6-12 months or as indicated for a change in symptoms.
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until symptoms resolve to baseline with appropriate supplementation Endocrine consultation to assist with rapid hormone replacement. Hospital admission for developing myxedema (bradycardia, hypothermia, and altered mental status). Inpatient endocrinology consultation can assist with IV levothyroxine dosing, steroids, and supportive care. If there is uncertainty about whether primary or central hypothyroidism is present, hydrocortisone should be given before thyroid hormone is initiated. Myxedema coma is a life-threatening emergency requiring admission and a high level of care. Thyroid supplementation and reassessment as in G2.
Additional considerations For patients without risk factors (ie, < 70 years old, not frail, and without cardiac disease or multiple comorbidities), full replacement can be estimated using ideal body weight for a dose of approximately 1.6 mcg/kg/d. For those older than age 70 years and/or frail patients with multiple comorbidities (including cardiac disease), consider titrating up from a lower starting dose of 25-50 μg. Elevated TSH can be seen in the recovery phase of thyroiditis. In asymptomatic patients with FT4 that remains in the reference range, it is an option to monitor before treating to determine whether there is recovery to normal within 3-4 weeks. Progression or development of symptoms should be treated as per G2. Development of a low TSH on therapy suggests overtreatment or recovery of thyroid function and dose should be reduced or discontinued with close follow-up.	
4.1.2. Thyrotoxicosis	
Workup and evaluation TSH can be checked every 4-6 weeks as part of routine clinical monitoring for asymptomatic patients on ICPi therapy. TSH and FT4 should be used for case detection in symptomatic patients. T3 can be helpful in highly symptomatic patients with minimal FT4 elevations. Low TSH with a low FT4 is consistent with central hypothyroidism. Evaluate as per hypophysitis (see 4.3). Consider TSH receptor antibody testing if there are clinical features and suspicion of Graves' disease (eg, ophthalmopathy and T3 toxicosis).	
Grading	**Management**
G1: Asymptomatic or mild symptoms	Can continue ICPi. Beta-blocker (eg, atenolol or propranolol) for symptomatic relief. Close monitoring of thyroid function every 2-3 weeks after diagnosis to catch the transition to hypothyroidism, the most common outcome for transient subacute thyroiditis. Treat transition to elevated TSH and low FT4 as for primary hypothyroidism (see 4.1.1). For persistent thyrotoxicosis (> 6 weeks) consider endocrine consultation for additional workup.
G2: Moderate symptoms, able to perform ADL	Consider holding ICPi until symptoms return to baseline. Consider endocrine consultation. Beta-blocker (eg, atenolol or propranolol) for symptomatic relief. Hydration and supportive care. For persistent thyrotoxicosis (> 6 weeks) refer to endocrinology for additional workup and possible medical thyroid suppression.
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until symptoms resolve to baseline with appropriate therapy. Endocrine consultation for all patients. Beta-blocker (eg, atenolol or propranolol). Hydration and supportive care. Consider hospitalizing patients in severe cases as inpatient endocrine consultation can guide the use of additional medical therapies including steroids, SSKI, or thionamide (methimazole or propylthiouracil) and possible surgery.

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TABLE 4. Endocrine Toxicities (continued)

4.1. Thyroid

Additional considerations

- Thyroiditis is self-limited and the initial hyperthyroidism generally resolves in weeks with supportive care, most often to primary hypothyroidism or occasionally to normal. Persistent or symptomatic hypothyroidism developing after hyperthyroidism should be treated as above (4.1).
- GD has not been reported with ICPi specifically, but sporadic cases could occur. GD is generally persistent and is treated with antithyroid medical therapy, radioactive iodine, or surgery. Endocrine consultation is recommended if suspected.
- Physical examination findings of ophthalmopathy or thyroid bruit are diagnostic of Graves' disease and should prompt early endocrine referral.

4.2. Adrenal—Primary AI

Workup and evaluation

- Evaluate AM levels of ACTH (if > 2× ULN) and cortisol level (if < 3 μg/dL).
- Basic metabolic panel (Na, K, CO2, and glucose).
- Renin and aldosterone.
- Consider standard dose ACTH stimulation test for indeterminate results (AM cortisol > 3 μg/dL and < 15 μg/dL).
- Evaluate for precipitating cause of crisis such as infection.
- Adrenal CT for metastasis or hemorrhage (most common causes of primary AI).

Grading	Management
All grades	Referral to endocrinology. Education on steroid stress dosing, emergency injections, and a medical alert bracelet or necklace, accessory, or system.
G1: Asymptomatic or mild symptoms	Consider holding ICPi until patient is stabilized on replacement hormone. Endocrine consultation. Initiate replacement therapy with hydrocortisone (15-20 mg in divided doses—see additional considerations). Titrate hydrocortisone to maximum of 30 mg daily total dose for residual symptoms of AI. Reduce maintenance dosing for symptoms of iatrogenic Cushing's syndrome (eg, bruising, thin skin, edema, weight gain, hypertension, and hyperglycemia). Most primary AI will also require fludrocortisone (starting dose 0.05-0.1 mg/d). Adjust based on volume status, sodium level, and renin response (target upper half of the reference range).
G2: Moderate symptoms, able to perform ADL	Consider holding ICPi until patient is stabilized on replacement hormone. Endocrine consultation. See in clinic to assess need for hydration, supportive care, and hospitalization. Initiate outpatient corticosteroid treatment at 2-3 times maintenance (eg, hydrocortisone 30-50 mg total dose or prednisone 20 mg daily) to manage acute symptoms. Initiate fludrocortisone (0.05-0.1 mg/d). Decrease stress dose corticosteroids down to maintenance doses after 2 days. Maintenance therapy as in G1.
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until patient is stabilized on replacement hormone. Endocrine consultation. Inpatient management may be needed to provide: Normal saline (at least 2L). IV Stress dose steroids: Hydrocortisone 50-100 mg Q 6-8 hours initial dosing. Taper stress dose corticosteroids down to oral maintenance doses over 5-7 days. Maintenance therapy as in G1.

Additional considerations

- Primary and secondary adrenal insufficiency can be distinguished by the relationship between ACTH and cortisol. If the ACTH is low with low cortisol, then management is as per hypophysitis in section 4.3 for secondary (central) adrenal insufficiency.
- Using hydrocortisone allows for recreation of the diurnal rhythm of cortisol. Typically, 2/3 of the dose is given in the morning and 1/3 in the early afternoon. Long-acting steroids such as prednisone, rather than short-acting hydrocortisone, carry risk of over replacement but can be used in special circumstances, for example, if a patient is not able to adhere to a short-acting steroid regimen. Hydrocortisone 20 mg is equivalent to prednisone 5 mg.
- DHEA replacement is controversial but deficiency can be tested and replacement considered in women with low libido and/or energy who are judged to be otherwise well replaced.
- All patients need education on stress dosing for sick days, use of emergency injectables, when to seek medical attention for impending adrenal crisis, and a medical alert bracelet or necklace for adrenal insufficiency to trigger stress dose corticosteroids by emergency medical personnel. Therefore, early endocrinology consultation is appropriate.
- Endocrine consultation should be part of planning before surgery or high-stress treatments such as cytotoxic CTX at any time during a patient's care.

4.3. Pituitary—Hypophysitis

Workup and evaluation:

- Evaluate ACTH (AM), cortisol (AM), TSH, free T4, and electrolytes.
- Consider standard-dose ACTH stimulation testing for indeterminate results (AM cortisol > 3 μg/dL and < 15 μg/dL).
- Consider evaluating LH and testosterone in males, FSH, and estrogen in premenopausal females with fatigue, loss of libido and mood changes, or oligomenorrhea.
- Consider MRI brain w/wo contrast with pituitary or sellar cuts in all patients with new hormonal deficiencies and particularly those with multiple endocrine abnormalities ± new severe headaches or complaints of vision changes.
- Perform MRI brain w/wo contrast with pituitary or sellar cuts for all patients presenting with diabetes insipidus (DI is most commonly from metastatic disease).

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TABLE 4. Endocrine Toxicities (continued)

4.3. Pituitary—Hypophysitis

Grading	Management
All grades	Referral to endocrinology Education on steroid stress dosing, emergency injections, and a medical alert bracelet or necklace, accessory, or system.
G1: Asymptomatic or mild symptoms	Consider holding ICPi until patient is stabilized on replacement hormones. Endocrine consultation. Corticosteroid replacement for adrenal insufficiency with preference for hydrocortisone (15-20 mg in divided doses—see additional considerations section 4.2). Initiate other hormone replacement only after any needed adrenal replacement to avoid precipitating adrenal crisis. Thyroid hormone replacement if needed using dosing as above for primary hypothyroidism, with a goal FT4 in the upper half of the reference range (TSH is not accurate in central hypothyroidism). Testosterone or estrogen therapy if needed in those without contraindications (eg, prostate cancer, breast cancer, or history of DVT). Recommend education on stress dosing, emergency injectable, and a medical alert or necklace accessory or system.
G2: Moderate symptoms, able to perform ADL	Consider holding ICPi until patient is stabilized on replacement hormones. Endocrine consultation. Clinic evaluation to assess need for steroids and volume repletion. Consider oral pulse dose therapy in patients with MRI findings of swelling or threatened optic chiasm compression (prednisone 1 mg/kg/d (or equivalent). Taper over 1-2 weeks and transition to physiologic maintenance therapy once down to 5 mg prednisone equivalent. Hormonal supplementation as in G1.
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until patient is stabilized on replacement hormones. Endocrine consultation. Hospitalize or make an ED referral for: Normal saline (at least 2L) or monitored free water replacement if DI. IV Stress dose steroids: Hydrocortisone 50-100 mg Q6-8 hours initial dosing. Oral pulse dose therapy with Prednisone 1-2 mg/kg daily (or equivalent) tapered over at least 1-2 weeks to physiologic maintenance in patients with significant swelling on MRI, optic chiasm compression, severe headache, or visual changes. Taper stress dose corticosteroids down to oral maintenance doses over 5-7 days. Maintenance therapy as in G1.
Additional considerations: Please be aware of the need to start corticosteroids first when planning hormone replacement therapy for multiple deficiencies as other hormones accelerate the clearance of cortisol and can precipitate adrenal crisis. ACTH stimulation can give a false-negative result early in hypophysitis as adrenal reserve declines slowly after pituitary stimulation is lost. In the presence of clinical uncertainty, opt for replacement and test for ongoing need at 3 months. If prednisone or equivalent is started for mild or moderate symptoms, consider lower doses (average daily dose over two months of < 7.5 mg) because of report of reduced survival on higher doses[133] All patients need education on stress dosing for sick days, use of emergency steroid injectables, when to seek medical attention for impending adrenal crisis, and a medical alert bracelet for adrenal insufficiency to trigger stress dose corticosteroids by EMS. Steroid use for other irAEs can cause isolated central adrenal insufficiency with a low ACTH. In a patient with adrenal insufficiency, a recent history of treatment with corticosteroids, and no other central hormone deficiencies, the HPA axis should be tested for recovery after 3 months of maintenance therapy with hydrocortisone. Laboratory confirmation of AI should not be attempted in patients given high-dose corticosteroids for other irAEs until treatment is ready to be discontinued. AM cortisol in a patient on corticosteroids is not diagnostic as the measurement of therapeutic steroids in the assay for cortisol varies. Hydrocortisone needs to be held for 24 hours and other steroids for longer before endogenous function is assessed. Consider consulting endocrinology for recovery and weaning protocols using hydrocortisone in patients with symptoms of AI after weaning off corticosteroids.	

4.4. Diabetes

Workup and evaluation Monitor patients for symptoms of new or worsening DM (polyuria, polydipsia, and fatigue). Monitor glucose at baseline and with each treatment cycle while on therapy and at follow-up visits for at least 6 months. Laboratory evaluation in suspected CIADM should include: Urine and/or serum ketones. Anion gap on a metabolic panel. Anti-GAD or anti-islet cell antibodies. C-peptide levels.

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TABLE 4. Endocrine Toxicities (continued)

4.4. Diabetes

Grading	Management
G1: Asymptomatic or mild symptoms; T2DM with fasting glucose value > ULN to 160 mg/dL (>ULN to 8.9 mmol/L). No evidence of CIADM such as ketoacidosis or laboratory evidence of pancreatic autoimmunity.	Can continue ICPi with close clinical follow-up and laboratory evaluation. Refer to PCP for additional management or: May initiate oral therapy for those with new-onset T2DM. Intensify medical therapy for those with worsening T2DM.
G2: Moderate symptoms, able to perform ADL; T2DM with fasting glucose value > 160 to 250 mg/dL (> 8.9 to 13.9 mmol/L). No ketoacidosis or metabolic derangements but other evidence of CIADM at any glucose level.	May hold ICPi until glucose control is obtained. Urgent endocrine consultation for any patient with new-onset CIADM. Initiate insulin for CIADM (or as default therapy if there is any question about the diagnosis). Referral to ED or hospital admission if unable to initiate therapy, urgent outpatient specialist evaluation is not available, developing ketoacidosis, or other concern for CIADM.
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL; G3: > 250 to 500 mg/dL (> 13.9 to 27.8 mmol/L); G4: > 500 mg/dL (> 27.8 mmol/L). Ketoacidosis or other metabolic abnormality.	Hold ICPi until glucose control is obtained with reduction of toxicity to ≤ G1. Admit for inpatient management of DKA, volume and electrolyte resuscitation, and insulin initiation. Endocrine consultation for all patients. Insulin therapy appropriate for all patients.

Additional considerations

- Insulin therapy should be used in any case with significant hyperglycemia pending additional diagnostic workup if mechanism of DM is not known.
- Long-acting insulin therapy alone is not sufficient for CIADM because of the absence of pancreatic function after beta-cell destruction.
  - Starting total daily requirement can be estimated at 0.3-0.4 units/kg/d.
  - Half of daily requirements are typically given in divided doses as prandial coverage, while half should be administered as a once-daily long-acting homolog. This requires self-monitoring 4 or more times daily or the use of a continuous glucose monitor.
  - Sliding scale insulin can be used in conjunction with multiple daily injection regimens to accommodate the variability in glucose levels.
  - Decreased requirements after the initial acute admission for DKA are commonly seen in the so-called honeymoon period.
  - Education is critical to learn skills like responding to hypoglycemia, anticipating exercise, monitoring for DKA, or carbohydrate counting, and to transition to technologies such as insulin pumps. Early endocrinology consultation is a high priority for all patients.
- T2DM patients will need to increase the frequency of self-monitoring as therapy intensifies and agents that can cause hypoglycemia are added to their regimen.
- Steroids can exacerbate postprandial hyperglycemia, and endocrinology consult should be considered for initiating or managing insulin in patients with T2DM being started on high-dose steroids. If insulin is used, the doses generally needs to be adjusted again as steroids are tapered down.

Abbreviations: ACTH, adrenocorticotropic hormone; ADL, activities of daily living; AI, adrenal insufficiency; AM, morning; CIADM, checkpoint inhibitor-associated diabetes mellitus; CT, computed tomography; CTX, chemotherapy; DHEA, dehydroepiandrosterone; DI, diabetes insipidus; DKA, diabetic ketoacidosis; DM, diabetes mellitus; DVT, deep vein thrombosis; ED, emergency department; EMS, emergency medical services; FSH, follicle-stimulating hormone; FT4, free thyroxine; GAD, glutamic acid decarboxylase; GD, Graves' disease; HPA, hypothalamic pituitary adrenal; ICPi, immune checkpoint inhibitor; IV, intravenous; LH, luteinizing hormone; MRI, magnetic resonance imaging; PCP, primary care practioner; SSKI, potassium iodide; T2DM, type 2 diabetes mellitus; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

The response of the oncologist to the development of endocrine dysfunction may be different from other irAEs because organ failure can be managed with hormone replacement in the majority of cases and immunosuppressive agents have not shown significant benefit. For example, there is no good evidence at this time that high-dose corticosteroids improve the rate of pituitary hormone recovery.[126,128] It is also not essential that patients stop ICPi therapy, as hormone replacement is generally able to restore functional status quickly. Therefore, a clinical judgment is needed to balance benefits, such as the possibility of improved headache, with risks, such as corticosteroid adverse effects, on glycemic control and delay of therapy.

Rare cases of checkpoint inhibitor–associated diabetes mellitus (CIADM), which has a presumed autoimmune pathophysiology and presents like sporadic type 1 diabetes, present an analogous challenge to the clinician, who needs to rapidly distinguish these cases from the much more common cases of worsening glycemic control attributable to insulin resistance and type 2 diabetes mellitus. The acute risks of DKA from autoimmune beta-cell destruction require vigilance on the part of treating oncologists, despite the very low occurrence rate. New-onset hyperglycemia in a patient without risk factors for type 2 diabetes mellitus (eg, pre-existing disease and corticosteroid exposure) should raise the level of concern for CIADM. Acute onset of polyuria, polydipsia, weight loss, and lethargy are characteristic presenting features of diabetes that should be evaluated without delay. Urine ketones, acid base status, and electrolytes can be evaluated as screening for DKA and the need for inpatient evaluation. Antibodies, insulin, and C-peptide levels should also be sent to support diagnosis, although the initiation of therapy should not be delayed pending results. Insulin should be used to treat hyperglycemia in anyone where the diagnosis is in question. Endocrinology consultation is appropriate where the diagnosis of autoimmune diabetes is suspected even without evidence of DKA on presentation because of the complex treatment regimen and education required for anyone with this diagnosis. In situations where an outpatient endocrinology consultation is not readily available to the treating oncologist, hospitalization is appropriate for these patients. At this time, no immunosuppressive strategies are approved to treat type 1 diabetes and by extension are not considered to be indicated in CIADM.

5.0. Recommendations for identification, evaluation, and management of musculoskeletal toxicities. Immune-related musculoskeletal AEs are characterized as inflammatory arthritis (IA), myositis, and polymyalgia-like syndrome. The median time to onset is 38 weeks but can vary greatly from 1 to 127 weeks.[9] Presenting symptoms related to immune therapy–induced IA may include joint pain accompanied by joint swelling and/or inflammatory symptoms such as stiffness after inactivity or in the morning, lasting more than 30 minutes to 1 hour. It is important to note that improvement of symptoms with NSAIDs or corticosteroids, but not with opioids or other pain medications, may also be suggestive of IA. Presenting symptoms of immune therapy–induced myositis may include muscle pain and weakness. Patients with myositis can also develop myasthenia gravis–like syndrome and/or myocarditis (see cardiovascular and neurologic sections for further details), which can be life-threatening if respiratory muscles or myocardium are involved. Symptoms of polymyalgia-like syndrome related to ICPi therapy include pain and stiffness in proximal upper and lower extremities.

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

Discussion. Musculoskeletal symptoms such as arthralgia and myalgia are common in patients receiving ICPi therapy, as reported in up to 40% of those treated in clinical trials.[134,135] More severe inflammatory AEs are not as frequent but can have an important effect on patients' QoL because of their effect on function and daily activities.[136] The most common musculoskeletal and rheumatic irAEs are arthritis, polymyalgia-like syndromes, and myositis. These events can occur with either CTLA-4 or PD-1/PD-L1 antagonists but seem to be more frequent with the latter class of drugs and when these agents are used in combination.[134]

The clinical presentation of patients with immune-related arthritis secondary to ICPi can vary and affect large and/or small joints.[135] Some patients present with oligoarthritis of large joints, such as knees, ankles, or wrists. These patients can also have other features commonly seen with reactive arthritis, such as conjunctivitis or urethritis, and occasionally complain of back pain or cervical pain suggestive of sacroiliitis. Other patients present with symmetrical polyarthritis resembling rheumatoid arthritis and can have autoantibodies such as rheumatoid factor and/or anti-citrullinated protein antibody present in their sera. Many patients also develop sicca symptoms, with dry eyes and dry mouth[137]; autoantibodies, such as anti-SSA, and anti-SSB, have occasionally been found, but most patients tend to be seronegative. Arthritis can occur at any time during treatment with some patients first experiencing symptoms many months after initiation of ICPi therapy.[138] Most common differential diagnoses include other causes of joint pain, including degenerative joint disease or osteoarthritis and soft tissue rheumatic disorders, such as rotator cuff tendinitis, crystal arthropathies (gout and pseudogout), and septic arthritis. Patients with pre-existing crystal arthritis, soft tissue rheumatic syndromes, and osteoarthritis can also flare during ICPi therapy.[139,140] Inflammatory markers are usually very elevated in patients with ICPi-induced arthritis and are useful to differentiate these events from other rheumatic syndromes. NSAIDs alone are usually not sufficient to control symptoms, and corticosteroids and synthetic or biologic disease-modifying antirheumatic drugs might be required.[143-145] Intra-articular corticosteroid injections are an option if only one or two joints are affected.

Patients receiving ICPis can develop severe myalgia in their proximal upper and lower extremities, with severe fatigue resembling polymyalgia rheumatica.[146] These patients can also have arthralgia, and although typically they do not have definite synovitis, they can occasionally present with accompanying IA.[147] Ultrasound or magnetic resonance imaging (MRI) might also show a mild effusion in the shoulder joints. Patients experiencing a polymyalgia-like syndrome have pain but not true weakness. Differential diagnoses include inflammatory myositis, fibromyalgia, statin-induced myopathy, and other types of arthritis or soft tissue rheumatic syndromes. Rheumatoid factor and anti-citrullinated protein antibody are negative, and inflammatory markers are highly elevated. Creatine kinase (CK) levels should generally be within normal limits, differentiating this condition from myositis. Imaging with MRI and electromyography (EMG) should not show any evidence of myopathy or muscle inflammation.

Myositis is a rare complication of ICPis but can be severe and fatal. It is more common with anti–PD-1/PD-L1 than with anti–CTLA-4 agents.[135,148] It can present as reactivation of pre-existing paraneoplastic polymyositis or dermatomyositis or as a de novo myositis. The main symptom of inflammatory myositis is weakness, primarily in the proximal extremities, with difficulties in standing up, lifting arms, and moving around. In severe cases, patients can complain of myalgia as well. Patients with de novo myositis do not develop the typical rash seen with paraneoplastic dermatomyositis. Myositis can have a fulminant necrotizing course with rhabdomyolysis and can involve the myocardium, in which case it requires urgent treatment to avoid fatal complications.[149,150] Patients who present with concomitant myocarditis and/or myasthenia gravis have an ominous prognosis with high mortality rates.[151]

Laboratory tests may include autoantibody panels for myositis, although there is no evidence that any specific autoantibodies have a role in ICPi-associated myositis. Patients with concomitant myasthenia gravis may have positive anti-acetylcholine receptor and anti-striated muscle antibodies. Other diagnostic tests that may be useful include EMG, which can show muscle fibrillations indicative of myopathy, and/or MRI, which shows increased

TABLE 5. Musculoskeletal Toxicities

5.1. IA

Workup and evaluation

G1

Complete rheumatologic history and examination of all peripheral joints for tenderness, swelling, and range of motion. Examination of the spine.

Consider plain X-ray or imaging to exclude metastases and evaluate joint damage (erosions) if appropriate.

Consider autoimmune blood panel including ANA, RF, anti-CCP, and inflammatory markers (ESR and CRP) if symptoms persist. If symptoms are suggestive of reactive arthritis or affect the spine, consider HLA B27 testing.

G2:

Complete history and examination as above; laboratory tests as above.

Consider ultrasound ± MRI imaging of affected joints if clinically indicated (eg, persistent arthritis unresponsive to treatment, and suspicion for differential diagnoses such as metastatic lesions or septic arthritis). Consider arthrocentesis if septic arthritis or crystal-induced arthritis is suspected.

Consider early referral to a rheumatologist, if there is joint swelling (synovitis) or if symptoms persist > 4 weeks.

G3-4:

As for grade 2.

Seek rheumatologist advice and review.

Test for viral hepatitis B, C, and latent or active TB test before DMARD treatment. Repeated screening labs annually in patients who require biologic treatment for > 1 year until treatment is completed.

Monitoring

Patients with IA should be monitored with serial rheumatologic examinations, including inflammatory markers, every 4-6 weeks after treatment is instituted.

Grading	Management
All grades	Clinicians should follow reports of new joint pain to determine if IA is present. Question whether symptoms new since receiving ICPi.
G1: Mild pain with inflammation, erythema, or joint swelling	Continue ICPi. Initiate analgesia with acetaminophen and/or NSAIDs.
G2: Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	Consider holding ICPi. Escalate analgesia and consider higher doses of NSAIDS as needed. If inadequately controlled, initiate prednisone 10-20 mg/d or equivalent. If improvement, slow taper according to response during the next 4-6 weeks. If no improvement after initial 4 weeks treat as G3. If unable to lower corticosteroid dose to below 10 mg/d after 6-8 weeks, consider DMARD. Consider intra-articular steroid injections for large joints. Referral to rheumatology.
G3-4: Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; and limiting self-care ADL	Hold ICPi temporarily and may resume in consultation with rheumatology, if recover to ≤ G1. Initiate oral prednisone 0.5-1 mg/kg. If failure of improvement after 2 weeks or worsening in meantime, consider synthetic or biologic DMARD. Synthetic: methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine alone or in combination. Biologic: Consider anticytokine therapy such as TNFα or IL-6 antagonists. Note: As a caution, IL6 inhibition can cause intestinal perforation.[141] Although this is extremely rare, it should not be used in patients with concomitant immune-related colitis. Referral to rheumatology.

Additional considerations

Early recognition is critical to avoid erosive joint damage.

Corticosteroids can be used as part of initial therapy in IA, but because of likely prolonged treatment requirements, physicians should consider starting steroid-sparing agents earlier than one would with other irAEs.

Oligoarthritis can be treated early on with intra-articular steroids, consider early referral.

5.2. Myositis

Workup and evaluation

Complete rheumatologic and neurologic history regarding differential diagnosis and rheumatologic and neurologic examination including muscle strength, and examination of the skin for findings suggestive of dermatomyositis. Muscle weakness is more typical of myositis than pain. Consider pre-existing conditions that can cause similar symptoms.

Blood testing to evaluate muscle inflammation, CK, and aldolase. Transaminases (AST and ALT) and LDH can also be elevated.

Troponin to evaluate myocardial involvement. Other cardiac testing such as ECG and echocardiogram or cardiac MRI (see CV section for further details).

Autoantibody testing to evaluate possible concomitant myasthenia gravis (anti-AChR and antistriational antibodies)

Inflammatory markers (ESR and CRP).

Consider EMG, imaging (MRI), and/or biopsy on an individual basis when diagnosis is uncertain and overlap with neurologic syndromes such as myasthenia gravis is suspected.

Consider paraneoplastic autoantibody testing for myositis (eg, anti-TIF1γ, anti-NXP2, and other myositis autoantibodies as indicated), especially if patient had muscle-related manifestations before receiving ICPi

Urinalysis for rhabdomyolysis.

Monitoring

CK, ESR, CRP, and aldolase if CK has not been elevated.

G1: Complete examination and laboratory workup as above.

G2: Complete history and examination as above; autoimmune myositis blood panel; EMG, MRI imaging of affected joints. Early referral to a rheumatologist or neurologist.

G3-4: As for grade 2. Urgent referral to a rheumatologist or neurologist.

(continued on following page)

TABLE 5. Musculoskeletal Toxicities (continued)

5.2. Myositis

Grading	Management of Myositis Alone[a]
G1: Mild weakness with or without pain	Continue ICPi. If CK and/or aldolase are elevated and patient has muscle weakness may offer oral corticosteroids, starting prednisone at 0.5 mg/kg/day. Offer analgesia with acetaminophen or NSAIDs for myalgia if there are no contraindications. Consider holding statins.
G2: Moderate weakness with or without pain limiting age-appropriate instrumental ADL	Hold ICPi temporarily and may resume upon symptom control, if CK is normal and prednisone dose $<$ 10 mg; if worsens, treat as per G3. NSAIDs as needed. Referral to rheumatologist or neurologist. If CK is elevated ($\times$3 ULN or more), initiate prednisone or equivalent at 0.5-1 mg/kg/d. May require permanent discontinuation of ICPi in cases with G2 symptoms if patient had other objective findings of severe muscle involvement such as very elevated enzymes, or extensive involvement as determined by EMG, MRI or histology. ICPi should not be restarted until CK is normal and clinical manifestations of myositis are resolved.
G3-4: Severe weakness with or without pain; limiting self-care ADL	Hold ICPi. Consider hospitalization for patients with severe weakness severely limiting mobility, respiratory, dysphagia, or rhabdomyolysis. Urgent referral to rheumatologist and/or neurologist. Initiate prednisone 1 mg/kg/d or equivalent. For patients with severe compromise, start 1-2 mg/kg of methylprednisolone IV or higher dose bolus. Consider plasmapheresis in patients with acute or severe disease as guided by rheumatology or neurology. Consider IVIG therapy, noting onset of action is slower. Note: Plasmapheresis immediately after IVIG will remove immunoglobulin. Consider other immunosuppressant therapy including biologics (eg, rituximab), TNFα, or IL-6 antagonists if symptoms worsen or if no improvement after 2 weeks. Other synthetic immunosuppressants such as methotrexate, azathioprine, or mycophenolate mofetil could be considered for maintenance,[b] or if symptoms and CK levels do not resolve entirely after 4 weeks. Rituximab is used in primary myositis.[142] Consider permanent discontinuation of ICPi.

Additional considerations

Caution is advised with rechallenging.

With elevated transaminases, consider differential with immune-mediated hepatitis.

5.3. Polymyalgia-Like Syndrome

Workup and evaluation

G1: Complete rheumatologic history regarding differential diagnosis and examination of all joints and skin. Rarely patients may also develop concomitant GCA. Check for symptoms of temporal arteritis, such as headache, visual disturbances, or jaw claudication. Urgent referral to ophthalmologist if present and consider temporal artery biopsy as permanent visual loss can occur within days of symptom onset.

ANA, RF, and anti-CCP.

CK to evaluate differential diagnosis of myositis.

Inflammatory markers (ESR and CRP).

Monitoring: ESR and CRP

$\geq$ G2: Complete history and examination as above; autoimmune tests as required for differential diagnosis.

Early referral to a rheumatologist.

Grading	Management
G1: Mild stiffness and pain	Continue ICPi. Initiate analgesia with acetaminophen and/or NSAIDs if there are no contraindications.
G2: Moderate stiffness and pain; limiting age-appropriate instrumental ADL	Consider holding ICPi and resuming upon symptom control, prednisone $<$ 10 mg; if worsens, treat as per G3. Initiate prednisone 20 mg/d or equivalent. If symptoms improve, start to taper dose after 3-4 weeks. If no improvement or need for higher dosages after 4 weeks, escalate to G3. Consider referral to rheumatology.
G3-4: Severe stiffness and pain; limiting self- care ADL	Hold ICPi and may resume, in consultation with rheumatology, if recover to $\leq$ G2. However, note that cases of toxicity returning upon rechallenge have been reported. Referral to rheumatology. Should initiate prednisone 40 mg/d or equivalent. If no improvement or need for higher dosages for prolonged time, may offer a steroid sparing agent such as synthetic drugs (eg, methotrexate) or biologic agents (eg, IL-6 antagonists). Note: As caution, IL-6 inhibition can cause intestinal perforation. Although this is extremely rare, it should not be used in patients with immune-related colitis. Consider admission of patients with severe symptoms.

Additional considerations

IL-6 antagonists may be the preferred steroid-sparing agents for management of polymyalgia-like syndrome as they are already approved for use in patients with GCA.

Abbreviations: AChR, acetylcholine receptor; ADL, activity of daily living; ANA, antinuclear antibody; CCP, citrullinated protein antibody; CK, creatine kinase; CRP, C-reactive protein; CV, cardiovascular; DMARD, disease-modifying antirheumatic drug; EMG, electromyography; ESR, erythrocyte sedimentation rate GCA, giant cell arteritis; IA, inflammatory arthritis; ICPi, immune checkpoint inhibitor; IL, interleukin; irAE, immune-related adverse event; IV, intravenous; IVIG, intravenous immune globulin; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; RF, rheumatoid factor; TB, tuberculosis; TNF, tumor necrosis factor; ULN, upper limit of normal.

[a]Patients with myasthenia gravis–like syndrome or myocarditis and concomitant myositis should be hospitalized; see neurologic or cardiovascular sections, respectively, for further information.

[b]Strongly urge maintenance with synthetic immunosuppressants be undertaken in collaboration with rheumatology or neurology.

intensity and edema in affected muscles. Finally, biopsy can be performed to confirm the diagnosis. Differential diagnoses include generalized fatigue, polymyalgia rheumatica, fibromyalgia, AEs from concomitant therapies (eg, statins and corticosteroids), and muscle dystrophies. These other disorders (other than some muscle dystrophies or drug-induced myopathy) have normal CK.

Many rheumatic disorders have been documented as case reports of patients receiving ICPis, such as vasculitis and lupus-like syndromes.[152] Management and treatment principles are similar to those reported for other ICPi-induced rheumatic syndromes.

6.0. Recommendations for identification, evaluation, and management of renal toxicities. Immune-related renal toxicities include nephritis or acute kidney injury (AKI). The median time to onset of renal toxicities is 14 weeks but can range from 6.5 to 21 weeks.[9] Presenting symptoms related to immune therapy–induced renal toxicities may include urinary frequency, dark cloudy urine; fluid retention (edema) of face, abdomen and extremities; sudden weight gain; abdominal or pelvic pain; nausea or vomiting; high blood pressure; and/or change in mental status, such as drowsiness.

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

Discussion. AKI is an uncommon complication of checkpoint inhibitor immunotherapy. Initial studies estimated the incidence of any-grade AKI to be 1%-2% in patients treated with a single-agent ICPi and 4.5% in those treated with anti–CTLA-4 and anti–PD-1 combination therapy. The incidence of grade 3 or 4 AKI was < 1% with single agents and 1.6% with combination ICPis.[153,154] Emerging data now suggest a higher incidence rate of AKI (9.9%-29% range) with ICPi. The majority of this extra toxicity is grade 1 based on AKI network criteria[154] and typically involves electrolyte disturbances rather than declines in renal function.

In a retrospective series of 13 patients who underwent kidney biopsy at seven centers, renal toxicity was diagnosed a median of 91 days after initiation of checkpoint inhibitor immunotherapy (range 21-245 days).[155] The median peak serum creatinine was 4.5 mg/dL. Pathology from the kidney biopsies revealed acute tubulointerstitial nephritis in 12 cases and thrombotic microangiography in one patient. Two of 13 patients required transient hemodialysis, and two patients remained on hemodialysis at the time of publication.[155] ICPi was discontinued in all 13 patients. Eleven patients were treated with corticosteroids, and nine patients improved. One patient with thrombotic microangiopathy did not improve, despite glucocorticoids, and another patient transiently improved but then worsened. Two additional patients did not receive immunosuppression and did not recover renal function.

Checkpoint inhibitor therapy appears to be safe in patients with baseline renal impairment from a nonimmune basis (eg, prior nephrectomy, old age, and hypertension); however, patients with a renal allograft are at high risk of rejecting the transplanted kidney and requiring dialysis. Limited data suggest that the risk of renal allograft rejection with anti–CTLA-4 antibodies may be less than the near-universal rejection seen with PD1 pathway blockers.[156-159] Although some patients may be treated with PD-1 pathway blockers with preservation of their allografts by having adjustments in their immunosuppressive agents,[161] this approach should only be considered with multidisciplinary input from renal transplant nephrology team.

Patients should have serum creatinine checked before every dose of checkpoint inhibitor therapy. For those with new elevations in creatinine, one should consider holding therapy while other potential causes are evaluated (eg, recent intravenous [IV] radiographic contrast administration, dehydration, other nephrotoxic medicines including concomitant CTX, and urinary tract infection). Patients without other obvious causes or who do not respond to alternative treatment measures should be presumed to have immune-related renal toxicity and treated empirically. Renal biopsy is typically not necessary or recommended unless the AKI is refractory to steroids and other immunosuppressant agents.

7.0. Recommendations for identification, evaluation, and management of nervous system toxicities. Neurologic irAEs encompass a broad spectrum of neurologic syndromes including myasthenia gravis or myasthenic syndrome, myasthenia gravis with myositis overlap, aseptic meningitis, encephalitis, Guillain-Barré–like syndrome, and a variety of other peripheral neuropathy phenotypes, and demyelinating disorders.[162] The median time to onset of nervous system toxicities, in general, is 4 weeks and can range from 1 to 68 weeks.[10,163]

Presenting symptoms of myasthenia gravis may include fatigable or fluctuating muscle weakness, ptosis, double vision, dysphagia, dysarthria, facial muscle weakness, and/or head drop or neck weakness. Guillain-Barre syndrome can present with ascending, progressive muscle weakness, shortness of breath, facial weakness, numbness and tingling in the feet or hands, burning, stabbing, or shooting pain in affected areas, loss of balance, and coordination. As nerves that control involuntary bodily functions are damaged in ICPi-induced autonomic neuropathy, blood pressure, temperature control, digestion, bladder function, and sexual function may be affected and can present as GI difficulties such as new severe constipation or nausea, urinary problems, sexual difficulties, sweating abnormalities, sluggish pupil reaction, and orthostatic hypertension.

Aseptic meningitis may present with headache, photophobia, neck stiffness, nausea or vomiting, and occasionally fever. Mental status should be normal, in contrast to encephalitis. Encephalitis symptoms may include

TABLE 6. Renal Toxicities

Nephritis and renal dysfunction—diagnosis and monitoring
- Clinical presentation[160] and diagnosis
- Definite ICPi-related nephritis or AKI
  - Kidney biopsy-confirmed diagnosis compatible with ICPi nephritis or AKI, and after clinical review of risk factors.[a]
- Probable ICPi-related nephritis or acute renal failure:
  - BOTH of the following:
    - Sustained increase in serum creatinine ≥ 50% on at least two consecutive values or need for RRT, after clinical review of risk factors[a]
    - Absence of an alternative plausible etiology
  - AND at least one of the following:
    - Sterile pyuria (≥ 5 WBCs/hpf)
    - Concomitant or recent extrarenal irAE-eosinophilia (≥ 500 cells per μL)
- Possible ICPi-related nephritis or acute renal failure:
  - BOTH of the following:
    - Increase in serum creatinine ≥ 50%
    - Need for RRT nephritis or AKI is not readily attributable to alternative causes

Monitoring
- Monitor patients for elevated serum creatinine before every dose.
- Routine urinalysis is not necessary, other than to rule out UTIs etc
- For any suspected immune-mediated adverse reactions, exclude other causes (see below).
- For suspected renal irAE obtain urinalysis, consider referral to nephrology
- For patients receiving combination therapy with ICPis and other agents, assess the potential contribution of the non-iCPI treatment to the renal failure
- Assess for concomitant medications, prescribed and OTC, herbals, vitamins, nephrotoxic agents, or contrast media
- If no potential alternative cause of AKI is identified, then one can assume it is ICPi-related and should forego biopsy
- Swift treatment of autoimmune component is important.

6.1. Nephritis or AKI

Grading	Management
G1: Creatinine level increase of > 0.3 mg/dL; creatinine 1.5-2.0× above baseline	Consider temporarily holding ICPi and/or other potential contributing agents in combination regimens, pending consideration of potential alternative etiologies (recent IV contrast, medications, fluid status, and UTI) and baseline renal function. A change that is still < 1.5 ULN *could* be meaningful.
G2: Creatinine 2-3× above baseline	Hold ICPi temporarily. Consult nephrology. Evaluate for other causes (recent IV contrast, medications, and fluid status) If other etiologies are ruled out, administer 0.5-1 mg/kg/day prednisone equivalents. If worsening or no improvement after 1 week, increase to 1-2 mg/kg/day prednisone equivalents and permanently discontinue ICPi. If improved to ≤ G1, taper steroids over at least 4 weeks. If no recurrence of CRI discuss resumption of ICPi with patient after taking into account the risks and benefits. Resumption of ICPi can be considered once steroids have been successfully tapered to ≤ 10 mg/d or discontinued.
G3: Creatinine > 3 × baseline or > 4.0 mg/dL; hospitalization indicated G4: Life-threatening consequences; dialysis indicated; creatinine 6× above baseline	Permanently discontinue ICPi if ICPi is directly implicated in renal toxicity. Consult nephrology. Evaluate for other causes (recent IV contrast, medications, fluid status, and UTI). Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent).

Additional considerations:
- Monitor creatinine weekly.
- Reflex kidney biopsy should be discouraged until steroid treatment has been attempted.

6.2. Nephritis or AKI—Follow-Up

Grading	Management
G1: Creatinine level increase of > 0.3 mg/dL; creatinine 1.5-2.0× above baseline	If improved to baseline Resume routine creatinine monitoring.
G2: Creatinine 2-3× above baseline	If improved to grade 1 Taper corticosteroids over at least 4 weeks before resuming treatment with routine creatinine monitoring. If elevations persist > 7 days or worsen and no other cause found, treat as grade 3.

(continued on following page)

TABLE 6. Renal Toxicities (continued)

6.2. Nephritis or AKI—Follow-Up

Grading	Management
G3: Creatinine > 3 × baseline or > 4.0 mg/dL; hospitalization indicated	If improved to grade 1 Taper corticosteroids over at least 4 weeks. If elevations persist > 3 to 5 days or worsen, consider additional immunosuppression (eg, infliximab, azathioprine, cyclophosphamide [monthly], cyclosporine, and mycophenolate).
G4: Life-threatening consequences; dialysis indicated; creatinine 6× above baseline	If improved to grade 1: Taper corticosteroids over at least 4 weeks. If elevations persist > 2 to 3 days or worsen, consider additional immunosuppression (eg, infliximab, azathioprine, cyclophosphamide [monthly], cyclosporine, and mycophenolate).

NOTE. Data adapted from Gupta et al.[160]

Abbreviations: AKI, acute kidney injury; CRI, chronic renal insufficiency; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; OTC, over the counter; RRT, renal replacement therapy; ULN, upper limit of normal; UTI, urinary tract infection.

[a]Risk factors include prior or concomitant nephrotoxic agent(s) use and prior or concomitant extrarenal irAEs.

confusion, altered mental status, altered behavior, headaches, seizures, weakness, and gait instability. Other potentially immune-related demyelinating diseases include multiple sclerosis, transverse myelitis, acute-disseminated encephalomyelitis, optic neuritis, and neuromyelitis optica.

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

Discussion. ICPi-related neurologic toxicities were originally reported with 1% incidence; however, more recent analyses suggest they are more common.[162,164-166] An analysis of 59 trials totaling 9,208 patients reported the overall incidence of neurologic irAEs to be 3.8% in patients receiving anti–CTLA-4 antibodies, 6.1% in patients receiving anti–PD-1 antibodies, and 12.0% in patients receiving the combination of both.[162] However, the incidence of grade 3 and 4 irAEs was < 1% across all ICPis. A single-institution retrospective study found the real-world incidence of severe (grade 3 or higher) neurologic irAEs among 1,834 patients treated with ICPis to be 1.5%.[166] The peripheral nervous system is affected twice as commonly as the central nervous system.[167,168] Neurologic irAEs, along with myocarditis, have higher fatality rates than other irAEs.[169]

The initial evaluation should rule out central nervous system progression of cancer, seizure activity, infection, and metabolic derangement as causes of neurologic symptoms. Paraneoplastic neurologic syndromes and autoimmune encephalopathies should also be considered.[172] In patients presenting with headache (which, in isolation, could suggest aseptic meningitis), it is important to evaluate for new confusion, altered behavior, aphasia, seizure-like activity, or short-term memory loss, any of which might suggest encephalitis. The distinction is important because suspected encephalitis triggers a distinct workup and management from aseptic meningitis including autoimmune encephalitis and paraneoplastic antibody evaluation and consideration of pulse-dose steroids.[172,173]

For most neurologic irAEs, diagnostic workup should include MRI brain and/or spine imaging with and without contrast and CSF analysis including cytology to rule out leptomeningeal metastasis. CSF analysis is helpful in cases of clinical suspicion of encephalitis, aseptic meningitis, and sensorimotor neuropathy or Guillain-Barre syndrome, revealing lymphocytic pleocytosis and elevated protein in many cases. Abnormal leptomeningeal enhancement on neuroimaging may occur in aseptic meningitis, encephalitis, and sensory-motor neuropathy, underscoring the importance of checking CSF cytology, which should be negative. Nerve conduction studies and EMG may assist in the diagnosis of cases of sensory symptoms or weakness. Autonomic neuropathy may occur along with other neuropathy symptoms and should be screened for. Electroencephalogram helps rule out seizure activity in cases of encephalopathy.

8.0. Recommendations for identification, evaluation, and management of hematologic toxicities. Immune-related hematologic toxicities encompass a spectrum of conditions including hemolytic anemia, acquired thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome, aplastic anemia, lymphopenia, immune thrombocytopenia (ITP), and acquired hemophilia A. The median time to onset of hematologic toxicities in general is 5.7 weeks but can range from 1 to 84 weeks.[174,175] Patients with immune therapy–induced hemolytic anemia may present with weakness, paleness, jaundice, dark-colored urine, fever, and heart murmur. Immune-related TTP can present as fever, mild renal failure, and neurologic manifestations such as seizures, hemiplegia, and visual disturbances. Presenting symptoms related to immune therapy–induced hemolytic uremic syndrome may include bloody diarrhea, decreased urination or blood in the urine, abdominal pain, vomiting and occasionally fever, pallor, small, unexplained bruises or

TABLE 7. Nervous System Toxicities

7.1 Myasthenia Gravis

Workup and evaluation
- AChR and antistriated muscle antibodies in blood. If AChR antibodies are negative, consider MuSK and LPR4 antibodies in blood—while presence of antibodies is confirmatory, the absence of antibodies does not rule out the syndrome.
- Pulmonary function assessment with NIF and VC.
- CPK, aldolase, ESR, and CRP for possible concurrent myositis
- Consider MRI brain and/or spine depending on symptoms to rule out CNS involvement by disease or alternate diagnosis
- Troponin, ECG, and consider TTE and/or cardiac MRI to evaluate concomitant myocarditis (see CV section for further details)
- Electrodiagnostic studies, under neurologic consultation, including neuromuscular junction testing with repetitive stimulation and/or jitter studies, NCS to exclude neuropathy, and needle EMG to evaluate for concomitant myositis
- Inflammatory markers (ESR and CRP).
- Consider paraneoplastic workup
- Review and stop medications with known risk of worsening myasthenia: beta-blockers, IV magnesium, fluoroquinolones, aminoglycosides, and macrolide antibiotics.

Grading	Management
All grades	All grades warrant workup and intervention given potential for progressive MG to lead to respiratory compromise. Inpatient admission may be appropriate at all grades.
No G1	NA
G2: Some symptoms interfering with ADLs. MGFA severity class I (ocular symptoms and findings only) and MGFA severity class II (mild generalized weakness).	Hold ICPi and may resume in G2 patients (MGFA 1 and 2) only if symptoms resolve and steroid taper completed.[170] Neurology consultation. Strongly consider inpatient care as patients can deteriorate quickly. Pyridostigmine starting at 30 mg PO three times a day and gradually increase to maximum of 120 mg PO four times a day as tolerated and based on symptoms and wean based on improvement. These procedures should be done in close collaboration with the neurologist. Administer corticosteroids (prednisone 0.5 mg/kg[a] orally daily). Wean based on symptom improvement.
G3-4: Limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms or MGFA severity class III-V (moderate to severe generalized weakness to myasthenic crisis)	Follow G2 recommendations as listed, with the following additions for G3-4: Permanently discontinue ICPi. Admit patient, may need ICU-level monitoring. Continue steroids, taper should begin 3-4 weeks after initiation then wean based on symptom improvement. Initiate IVIG 2 G/kg IV over 5 days (0.4 G/kg/d) or plasmapheresis × 5 days. Consider adding rituximab if refractory to IVIG or plasmapheresis. Frequent pulmonary function assessment. Daily neurologic review.

7.2. Guillain-Barré syndrome

Workup and evaluation
- Neurologic consultation
- MRI spine w/wo contrast (rule out compressive lesion and evaluate for nerve root enhancement/thickening)
- Lumbar puncture: CSF analysis for cell count and differential, cytology for malignant cells, protein, glucose, and viral/bacterial cultures. Note that CSF typically has elevated protein and often elevated WBC as well, although this is not typically seen in classical Guillain-Barre.
- Consider paraneoplastic workup eg ANNA-1 antibody testing
- Serum antiganglioside antibody tests for GBS and its subtypes (eg, anti-GQ1b for Miller Fisher variant associated with ataxia and ophthalmoplegia).
- Flow cytometry in patients with hematologic malignancies
- Electrodiagnostic studies (NCS and EMG) to evaluate polyneuropathy
- Pulmonary function testing (NIF or VC)
- Frequent neuro checks

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TABLE 7. Nervous System Toxicities (continued)

7.2. Guillain-Barré syndrome

Grading	Management
All grades warrant workup and intervention given potential for progressive GBS to lead to respiratory compromise. Note, there is no G1 toxicity.	
No G1	NA
G2: Moderate: some interference with ADLs, symptoms concerning to patient. G3-4: Severe: limiting self-care and aids warranted, weakness limiting walking, ANY dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms.	Discontinue ICPi. Neurology consultation Admission to inpatient unit with capability of rapid transfer to ICU-level monitoring. Start IVIG (0.4 G/kg/d for 5 days for a total dose of 2 G/kg) or plasmapheresis. Note: plasmapheresis immediately after IVIG will remove immunoglobulin. Corticosteroids are usually not recommended for idiopathic GBS; however, in ICPi-related forms, a trial is reasonable (methylprednisolone 2-4 mg/kg/d), followed by slow steroid taper. Pulse steroid dosing (methylprednisolone 1 g daily for 5 days) may also be considered for G3-4 along with IVIG or plasmapheresis. After pulse steroids, taper steroids over 4-6 weeks. Frequent neuro checks and pulmonary function monitoring. Monitor for concurrent autonomic dysfunction. Nonopioid management of neuropathic pain, for example, pregabalin, gabapentin, or duloxetine. Treatment of constipation/ileus.

Additional considerations
Extreme caution with rechallenging for severe cases after complete resolution of symptoms and tapered off immunosuppression

7.3. Peripheral Neuropathy

Workup and evaluation
G1
Consider neurology consultation to guide neuropathy phenotype determination and workup
Serum testing for reversible neuropathy causes: HbA1c, vitamin B12, TSH, vitamin B6, folate, serum protein electrophoresis, and immunofixation, CPK
Consider additional testing guided by neuropathy phenotype: ANA, ESR, CRP, ANCA, anti–smooth muscle, SSA/SSB, RNP, anti-dsDNA, ganglioside ab, anti-MAG, anti-Hu (ANNA-1 ab), thiamine, Lyme, hepatitis B or C, and HIV
Consider MRI spine w/wo contrast
G2: In addition to the above
MRI spine advised, MRI brain if cranial nerve involvement, and MRI plexus if concern for plexus involvement
Consider lumbar puncture: CSF analysis for cell count and differential, cytology for malignant cells, protein, glucose, and viral or bacterial cultures. Consider EMG or NCS
G3-4: go to GBS algorithm

Grading	Management
G1: Mild: no interference with function and symptoms not concerning to patient. Note: any cranial nerve problem should be managed as moderate	Low threshold to hold ICPi and monitor symptoms for a week. If to continue, monitor very closely for any symptom progression.
G2: Moderate: some interference with ADLs, symptoms concerning to patient (ie, pain but no weakness or gait limitation).	Hold ICPi and resume once return to ≤ G1. Initial observation OR initiate prednisone 0.5-1 mg/kg/d (if progressing from mild). Gabapentin, pregabalin, or duloxetine for pain.
G3-4: Severe: limiting self-care and aids warranted, weakness limiting walking or respiratory problems (ie, leg weakness, foot drop, and rapidly ascending sensory changes). Severe may be GBS and should be managed as such.	Permanently discontinue ICPi. Admit patient. Neurology consultation. Initiate IV methylprednisolone 2-4 mg/kg/d and proceed as per GBS management.

7.4. Autonomic neuropathy

Workup and evaluation
An evaluation by neurologist or relevant specialist depending on organ system, with testing that may include:
Screen for other causes of autonomic dysfunction: diabetic screen, adrenal insufficiency, HIV, paraproteinemia, amyloidosis, and botulism; consider chronic diseases such as Parkinson's and other autoimmune screen.
Orthostatic vital signs.
Consider electrodiagnostic studies (NCS and EMG) to evaluate for concurrent polyneuropathy.
Consider paraneoplastic autoimmune dysautonomia antibody testing (eg, antiganglionic AChR, ANNA-1, and N-type voltage-gated calcium channel antibodies).

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TABLE 7. Nervous System Toxicities (continued)

7.4. Autonomic neuropathy

Grading	Management
G1: Mild: no interference with function and symptoms not concerning to patient.	Low threshold to hold ICPi and monitor symptoms for a week. If to continue, monitor very closely for any symptom progression.
G2: Moderate: some interference with ADLs, symptoms concerning to patient.	Hold ICPi and resume once return to ≤ G1 and off prednisone if used. Initial observation OR initiate prednisone 0.5-1 mg/kg/d (if progressing from mild). Neurology consultation.
G3-4: Severe: limiting self-care and aids warranted.	Permanently discontinue ICPi. Admit patient. Initiate methylprednisolone 1 g daily × 3 days followed by oral steroid taper. Neurology consultation.

7.5. Aseptic Meningitis

Workup and evaluation
- MRI brain w/wo contrast with pituitary or sellar cuts protocol.
- AM cortisol, ACTH to rule out adrenal insufficiency.
- Strongly consider lumbar puncture with CSF analysis for opening pressure, cell count and differential, cytology for malignant cells that could indicate leptomeningeal metastases, protein, glucose, gram stain, viral or bacterial cultures, PCR for HSV, and other viral PCRs depending on suspicion.
- May see elevated WBC in CSF with normal glucose, normal culture, and gram stain. May see reactive lymphocytes, neutrophils, or histiocytes on cytology.

Grading	Management
G1: Mild: no interference with function and symptoms not concerning to patient. Note: any cranial nerve problem should be managed as moderate.	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits.[171] Consider neurology consult Consider empiric antiviral (IV acyclovir) and antibacterial therapy until CSF results. Once bacterial and viral infection negative, may closely monitor off corticosteroids or consider oral prednisone 0.5-1 mg/kg/day or IV methylprednisolone 1 mg/kg/day if moderate or severe symptoms. Steroids can be tapered after 2-4 weeks, monitoring for symptom recurrence. Consider hospitalization for G3-4.
G2: Moderate: some interference with ADLs, symptoms concerning to patient (ie, pain but no weakness or gait limitation).	
G3-4: Severe: limiting self-care and aids warranted	

7.6. Encephalitis

Workup and evaluation
- Neurologic consultation.
- MRI brain w/wo contrast may reveal T2/FLAIR changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis or may be normal.
- Lumbar puncture with CSF analysis for opening pressure, cell count and differential, cytology for malignant cells that could indicate leptomeningeal metastases, protein, glucose, gram stain, viral or bacterial cultures, PCR for HSV and other viral PCRs depending on suspicion, oligoclonal bands, autoimmune encephalopathy, and paraneoplastic panels.
- May see elevated WBC with lymphocytic predominance and/or elevated protein.
- EEG to evaluate for subclinical seizures.
- Serum studies: Chem panel, CBC, ESR, CRP, ANCA (if suspect vasculitic process), thyroid panel including TPO and thyroglobulin, am cortisol and ACTH, GQ1b antibodies (Bickerstaff encephalitis and rhomboencephalitis), celiac antibody panel, and paraneoplastic and autoimmune encephalitis panels.
- Rule out concurrent anemia/thrombocytopenia, which can present with severe headaches and confusion.

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TABLE 7. Nervous System Toxicities (continued)

7.6. Encephalitis

Grading	Management
G1: Mild: No interference with function and symptoms not concerning to patient. Note: any cranial nerve problem should be managed as moderate.	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits. As above for aseptic meningitis suggest concurrent IV acyclovir until PCR results obtained and negative. Trial of methylprednisolone 1-2 mg/kg/d. Neurology consultation If severe or progressing symptoms or oligoclonal bands present, consider pulse corticosteroids (methylprednisolone 1 g IV daily for 3-5 days) plus IVIG 2 g/kg over 5 days (0.4 g/kg/d) or plasmapheresis. Taper steroids following acute management over at least 4-6 weeks. If positive for autoimmune encephalopathy or paraneoplastic antibody or limited or no improvement, consider rituximab in consultation. Admit patient for G3-4
G2: Moderate: some interference with ADLs, symptoms concerning to patient (ie, pain but no weakness or gait limitation).	
G3-4: Severe: Limiting self-care and aids warranted	

7.7. Demyelinating Diseases, Including Multiple Sclerosis, Transverse Myelitis, ADEM, ON, and NMO

Workup and evaluation
- Neurologic consultation.
- Ophthalmic or neuro-ophthalmic evaluation if ocular involvement
- MRI with contrast of brain, orbit, cervical, and thoracic spinal cord (tailor to examination finding).
- Lumbar puncture with CSF analysis including autoimmune encephalitis panel and oligoclonal bands, CNS demyelinating disease antibodies (aquaporin 4 and myelin oligodendrocyte glycoprotein), and viral PCRs especially JCV PCR to exclude progressive multifocal leukoencephalopathy.
- Serum studies: B12, HIV, RPR, ANA, Ro/La, TSH, aquaporin-4 IgG, paraneoplastic panel or anti-HU and anti–CRMP5-CV2, thyroid panel including TPO and thyroglobulin, am cortisol and ACTH, and paraneoplastic and autoimmune encephalitis panels.
- Evaluation for urinary retention and constipation.
- EEG to evaluate for subclinical seizures.
- Although less common, biopsy may provide definitive evidence of CNS demyelination.

Grading	Management
G1: Asymptomatic or mild symptoms; clinical or diagnostic observations only	Intervention not indicated. Continue immunotherapy unless symptoms worsen or do not improve.
G2: Moderate symptoms; minimal, limiting age-appropriate instrumental ADL	Stop ICPi. Neurology consultation. Start prednisone 1 mg/kg daily and taper over 1 month. Rule out infection.
G3: Severe or medically significant symptoms but not immediately life-threatening; limiting self-care ADL	Permanently discontinue ICPi. Neurology consultation. Nonopioid management of neuropathic pain, for example, pregabalin, gabapentin, or duloxetine. Admit patient for methylprednisolone pulse dosing 1 g/d and consider IVIG[b] or plasmapheresis if no improvement or symptoms worsen after 3 days.[c]
G4: Life-threatening consequences	Permanently discontinue ICPi. Neurology consultation. ICU level inpatient care. Start methylprednisolone pulse dosing 1 g/d and consider IVIG or plasmapheresis if no improvement or symptoms worsen after 3 days.[c]

Abbreviations: AChR, acetylcholine receptor; ACTH, adrenocorticotropic hormone; ADEM, acute-disseminated encephalomyelitis; ADL, activity of daily living; AM, morning; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; ANNA-1, antineuronal nuclear antibody type 1; CPK, creatine phosphokinase; CRP, C-reactive protein; CV, cardiovascular; dsDNA, double stranded DNA; EMG, electromyography; ESR, erythrocyte sedimentation rate; FLAIR, fluid-attenuated inversion recovery; GBS, Guillain-Barré syndrome; HSV, herpes simplex virus; ICPi, immune checkpoint inhibitor; ICU, intensive care unit; IV, intravenous; IVIG, intravenous immune globulin; JCV, John Cunningham virus; LPR4, lipoprotein-related 4; MAG, myelin-associated glycoprotein; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MRI, magnetic resonance imaging; MuSK, muscle-specific kinase; NA, not applicable; NCS, nerve conduction study; NIF, negative inspiratory force; NMO, neuromyelitis optica; ON, optic neuritis; PCR, polymerase chain reaction; PO, by mouth; RNP, ribonucleoprotein; RPR, rapid plasma reagin; SSA, Sjögren's syndrome A; SSB, Sjögren's syndrome B; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone; TTE, transthoracic echocardiogram; VC, vital capacity.

[a]The divergence from 1 mg/kg in the setting of MG is because of the potential short-term exacerbation of MG with high-dose steroid.

[b]IVIG 2 g/kg, administered in divided doses per package insert.

[c]Plasmapheresis immediately after IVIG will remove immunoglobulin.

bleeding from the nose and mouth, fatigue and irritability, confusion or seizures, high blood pressure, and/or swelling of the face, hands, feet, or the entire body. Immune therapy–induced aplastic anemia may include fatigue, shortness of breath, rapid or irregular heart rate, pallor, unexplained or easy bruising, bleeding, skin rash, dizziness, headache, and fever. Lymphopenia induced by ICPi therapy may present as fever, cough, runny nose, enlarged lymph nodes, painful joints, skin rash, and/or night sweats. Immune therapy–induced ITP may present as easy or excessive bruising, petechiae, usually on the lower legs, bleeding from the gums or nose, and blood in urine or stool. Acquired hemophilia A can present with subcutaneous bleeding and/or muscle, GI, genitourinary, and retroperitoneal bleeding.

Refer to Table 8 for a complete set of recommendations, definition of grades, and additional considerations for hematologic toxicities.

Discussion. Hematologic toxicities associated with ICPi are poorly described partially because of the infrequent occurrence but also possibly because of lack of recognition. This is further complicated by the increasing combinations of ICPis with myelosuppressive CTX. With increased use of ICPis and improved recognition of hematologic toxicities, cases of hematologic toxicities are expected to rise, establishing a need for clinical management guidelines. An interrogation of the WHO's pharmacovigilance database identified hemolytic anemia followed by ITP as the most common hematologic toxicities with a median time to onset of 40 days.[176]

A meta-analysis reported the pooled incidence for all grade and grade 3-5 anemia of 9.8% and 5%,[177] respectively. If multiple cell lines are affected,[178] evaluation for pure red cell aplasia,[179] autoantibodies,[180] aplastic anemia, and myelodysplasia must be considered. The majority of patients respond after holding the ICPi and are managed successfully with corticosteroids, IVIG, and growth factor support. Hemolytic anemia has been described as having a development of autoantibodies[180] and can commonly be treated by withholding ICPi, corticosteroids, and IVIG.

Thrombocytopenia is also relatively uncommon. The pooled incidence of thrombocytopenia is 2.8% for all grade and 1.8% for grade 3-5.[177] Evaluation for causes of thrombocytopenia must be undertaken, including evaluation of TTP, disseminated intravascular coagulation, myelodysplastic syndrome, as well as immune-mediated thrombocytopenia related to ICPi. Corticosteroids have been shown to be effective with transfusion support as required.

Factor-related acquired bleeding disorders have been described with factor VIII.[181,182] Involvement of hematologic expertise should be considered, including evaluation for antibody titer formation and choice of factor replacement. At low titer levels, simple factor replacement and corticosteroids may be effective; however, at high Bethesda unit levels > 5, bypassing agents such as factor VIII inhibitor bypass activity or factor VII may be required.

9.0. Recommendations for identification, evaluation, and management of cardiovascular toxicities. Cardiovascular toxicities from ICPis can include myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure, vasculitis, and venous thromboembolism. The median time to onset of cardiovascular toxicities is 6 weeks but can range from 2 to 54 weeks.[9] Presenting symptoms could include progressive fatigue, myalgia or weakness, palpitations, chest pain, presyncope or syncope, shortness of breath, and peripheral edema. Severe cases can present with cardiogenic shock or sudden death. Symptoms can often be masked by or coincident with other irAEs (eg, myositis, pneumonitis, and hypothyroidism) or pulmonary symptoms related to malignancy or comorbid conditions. The presenting symptoms related to immune therapy–induced vasculitis and VTE while variable may include pain, extremity swelling, increased skin vein visibility or purpuric rash, erythema, and cyanosis accompanied by unexplained fever, dyspnea, pleuritic pain, cough, wheezing, or hemoptysis.

Refer to Table 9 for a complete set of recommendations, definition of grades, and additional considerations for cardiovascular toxicities.

Discussion. Cardiovascular complications of ICPi therapy are rare but often result in devastating clinical consequences. Mortality is high, with death frequently because of refractory arrhythmia or cardiogenic shock.[149,191,192] These toxicities have been reported with all currently approved ICPi agents.[193] However, because of their rarity and involvement of major organs leading to rapidly fatal consequences, data are sparse and generally have included case reports or small case series.[194] Cardiovascular irAEs occur in < 0.1% of patients receiving these therapies based on a review of pharmaceutical safety databases.[149] The risk may be increased when combination therapy is used. In these safety data, combination therapy of CTLA-4 and PD-1/PD-L1 inhibitors had greater rates of cardiovascular complications than anti–PD-1 alone (0.28% *v* 0.06%).[149]

A wide range of cardiovascular complications have been reported. Pathology review shows occurrences of myocarditis, myocardial fibrosis, cardiomyopathy, heart failure, and conduction abnormalities, including heart block and cardiac arrest.[193] Pericarditis and pericardial effusions have been described as well.[195,196] There has also been a case report of irAE-associated acute coronary syndrome.[197] Based on results of myocardial biopsies, these complications are thought to be caused by lymphocytic infiltration of the myocardium and myocardial conduction system.[149] Pathology has also shown lymphocytic infiltration in the tumor specimens.

Immune-mediated myocarditis may result in heart failure and/or arrhythmia. The myocarditis may be fulminant, progressive, and life-threatening.[149,198] Acute heart failure may occur secondary to decreased cardiac function and

TABLE 8. Hematologic Toxicities

8.1. Hemolytic Anemia

Workup and evaluation
- History and physical examination (with special consideration of history of new drugs, insect, spider, or snake bites)
- Blood chemistry, CBC with evidence of anemia, macrocytosis, evidence of hemolysis on peripheral smear. LDH, haptoglobin, bilirubin, reticulocyte count, and free hemoglobin
- DIC panel, which could include PT or INR or PTT, and infectious causes
- Autoimmune serology
- PNH screening
- Direct and indirect bilirubin, direct agglutinin test, and if no obvious cause, bone marrow analysis, and cytogenetic analysis to evaluate MDS
- Evaluation for viral or bacterial (mycoplasma etc) causes of hemolysis studies
- Protein electrophoresis and cryoglobulin analysis
- Workup for BM failure syndrome if refractory including B12, folate, copper, parvovirus, iron, and thyroid, infection
- Glucose-6-phosphate dehydrogenase level
- Evaluation of common drug causes (ribavirin, rifampin, dapsone, interferon, cephalosporins, penicillins, NSAIDs, quinine or quinidine, fludarabine, ciprofloxacin, lorazepam, and diclofenac)
- Assessment of methemaglobinemia

Grading	Management
G1: Hgb < LLN to 10.0 g/dL; < LLN to 6.2 mmol/L; < LLN to 100 g/L	Continue ICPi with close clinical follow-up and laboratory evaluation.
G2: Hgb < 10.0 to 8.0 g/dL; < 6.2 to 4.9 mmol/L; < 100 to 80 g/L	Hold ICPi and strongly consider permanent discontinuation. Administer 0.5-1 mg/kg/d prednisone equivalents.
G3: Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated	Permanently discontinue ICPi. Should use clinical judgment and consider admitting the patient. Hematology consult. Prednisone 1-2 mg/kg/d (oral or IV equivalent depending on symptoms or speed of development). Consider RBC transfusion per existing guidelines. Do not transfuse more than the minimum number of RBC units necessary to relieve symptoms of anemia or to return a patient to a safe hemoglobin range (7-8 g/dL in stable, noncardiac inpatients). Should offer patients supplementation with folic acid 1 mg daily.
G4: Life-threatening consequences; urgent intervention indicated	Permanently discontinue ICPi. Admit patient. Hematology consult. IV prednisone corticosteroids 1-2 mg/kg/d. If no improvement on or if worsening on corticosteroids or severe symptoms on presentation, initiate other immunosuppressive drugs, such as rituximab, IVIG, cyclosporine, infliximab, MMF, or ATG. RBC transfusion per existing guidelines. Discuss with blood bank team before transfusions that a patient with possible ICPi SAE is in the hospital.

Additional considerations
- Monitor hemoglobin levels weekly until the steroid tapering process is complete. Thereafter, less frequent testing is needed.[183]

8.2 Acquired TTP

Workup and evaluation
- History with specific questions related to drug exposure (eg, CTX, sirolimus, tacrolimus, oxymorphone, antibiotics, and quinine)
- Hematology consult
- Physical examination, peripheral smear to check for schistocytes
- ADAMTS13 activity level and inhibitor titer
- LDH, haptoglobin, reticulocyte count, bilirubin, and urinalysis to rule out other causes
- Prothrombin time, activated partial thromboplastin time, and fibrinogen
- Blood group and antibody screen, and direct antiglobulin test
- Consider CT or MRI brain, echocardiogram, electrocardiogram
- Cytomegalovirus serology
- Note: this disorder is usually associated with severe drop in platelets and hemolysis or anemia precipitously (microangiopathy)

Grading	Management
All grades	The first step in the management of TTP is a high index of suspicion for the diagnosis and timely recognition. Hematology consult should immediately be called, as delay in identification is associated with increased mortality or morbidity. Initially, the patient should be stabilized, and any critical organ dysfunction stabilized.

(continued on following page)

TABLE 8. Hematologic Toxicities (continued)

8.2 Acquired TTP	
G1: Evidence of RBC destruction (schistocytosis) without anemia, renal insufficiency, or thrombocytopenia clinically G2: Evidence of RBC destruction (schistocytosis) without clinical consequence with G2 anemia and thrombocytopenia	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits, noting that there are currently no data to recommend restarting ICPi therapy. Administer 0.5-1 mg/kg/d prednisone.
G3: Laboratory findings with clinical consequences (G3 thrombocytopenia, anemia, and renal insufficiency > 2) G4: Life-threatening consequences, (eg, CNS hemorrhage or thrombosis or embolism or renal failure)	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits, noting that there are currently no data to recommend restarting ICPi therapy. In conjunction with hematology, initiate therapeutic PEX according to existing guidelines with further PEX dependent on clinical progress.[184-187] Administer methylprednisolone 1 g IV daily for 3 days, with the first dose typically administered immediately after the first PEX. For patient who has an initial platelet count response, discontinue PEX. May offer rituximab Consider caplacizumab if ADAMTS13 activity level is < 10 IU/dL or < 10% of normal, with an inhibitor or elevated anti-ADAMTS13 IgG.[184] If no exacerbation within 3-5 days after stopping PEX, taper steroids over 2-3 weeks, complete course of rituximab (if receiving), and discontinue caplacizumab (if receiving).[185]

8.3 HUS	
Workup and evaluation History and physical examination (special consideration for new history of high-risk drugs, hypertension, or cardiac causes) CBC with indices Blood smear morphology. Note that the presence of schistocytes on smear is critical for diagnosis Serum creatinine ADAMTS13 (to rule out TTP) Homocysteine or MMA Complement testing C3, C4, and CH50 (complement inhibitory antibodies for suspected familial) Evaluate reticulocyte count and MCV Evaluation of infectious cause including screening for viral EBV, CMV, and HHV6 Evaluation for nutritional causes of macrocytosis (B12 and folate) Pancreatic enzymes Evaluation for diarrheal causes, shiga toxin, and *Escherichia coli* 0157 Direct antibody test (Coombs test), haptoglobin, LDH, and other etiologies of anemia Evaluation for common drugs causing hemolysis (tacrolimus, cyclosporine, and sirolimus) Evaluation for neurologic changes (alteration in consciousness, concurrent confusion, seizures, pyramidal syndrome, and extrapyramidal syndrome with hypertonia)[188]	
Grading	**Management**
G1-2: Evidence of RBC destruction (schistocytosis) without clinical consequences of anemia, and thrombocytopenia grade II	Continue ICPi with close clinical follow-up and laboratory evaluation. Supportive care.
G3: Laboratory findings with clinical consequences (eg, renal insufficiency and petechiae) G4: Life-threatening consequences, (e.g., CNS thrombosis or embolism or renal failure)	Permanently discontinue ICPi. Hematology consult Begin therapy with eculizumab (anti-C5 antibody)[a] 900 mg weekly × 4 doses, 1,200 mg week 5, then 1,200 mg every 2 weeks. Red blood transfusion according to existing guidelines.

8.4 Aplastic Anemia	
Workup and evaluation History and physical examination (close attention to medications, exposure to radiation, toxins, and recent viral infections) CBC, smear, and reticulocyte count Viral studies including CMV, HHV6, EBV, and parvovirus Nutritional assessments including B12, folate, iron, copper, ceruloplasmin, and vitamin D Serum LDH and renal function Evaluation for infectious causes. Identify marrow hypo/aplasia BM biopsy and BM aspirate analysis Peripheral blood analysis including neutrophil count, proportion of GPI-negative cells by flow for PNH Flow cytometry to evaluate loss of GPI-anchored proteins Type and screen patient for transfusions and notify blood bank that all transfusions need to be irradiated and filtered	

(continued on following page)

TABLE 8. Hematologic Toxicities (continued)

8.4 Aplastic Anemia

Grading	Management
G1: mild: > 0.5 PMNs × 10^9/L hypocellular marrow, with marrow cellularity < 25%, Peripheral platelet count > 20,000, reticulocyte count > 20,000	Hold ICPi, provide growth factor support, and close clinical follow-up and laboratory evaluation. Supportive transfusions as per local guidelines.
G2: moderate: Hypocellular marrow < 25% and two of the following ANC < 500, peripheral platelet < 20,000 and reticulocyte < 20,000	Hold ICPi and provide growth factor support and close clinical laboratory evaluations daily. Hematology consult Administer horse ATG plus cyclosporine. Supportive transfusions as per local guidelines. All blood products should be irradiated and filtered. HLA typing and evaluation for bone marrow transplantation if patient is a candidate.
G3-4: severe: ANC < 200, platelet count < 20,000, reticulocyte count of < 20,000, plus hypocellular marrow < 25%.	As per G2 Hold ICPi and monitor weekly for improvement. If not resolved, discontinue treatment until AE has reverted to G1. If no response, repeat immunosuppression with rabbit ATG plus cyclosporine, and cyclophosphamide. For refractory patients, consider eltrombopag plus supportive care.

8.5. Lymphopenia

Workup and evaluation
- History (special attention to nutritional status and for lymphocyte depleting therapy such as fludarabine, ATG, steroids, cytotoxic CTX, and radiation exposure, as well as history of AD and family history of AD)
- Physical examination with special attention to spleen size
- CBC with differential, peripheral smear, and reticulocyte count
- CXR for evaluation of presence of thymoma
- Bacterial cultures and evaluation for infection (fungal, bacterial, and viral—specifically CMV or HIV)

Grading	Management
All grades	No specific action is required for lymphopenia G1-G3 and ICPi therapy should be continued. For G4 (< 250 PB lymphocyte count), continue ICPi therapy and initiate *Mycobacterium avium* complex prophylaxis and *Pneumocystis jirovecii* prophylaxis, CMV screening. HIV or hepatitis screening if not already done. May consider EBV testing if evidence of lymphadenopathy or hepatitis, fevers, and hemolysis occur c/w lymphoproliferative disease occurs.

8.6. ITP

Workup and evaluation
- History and physical examination (special attention for history of viral illness and lymphocyte depleting therapy such as fludarabine, ATG, steroids, and cytotoxic therapy)
- FH of autoimmunity or personal history of AD
- CBC, peripheral blood smear, and reticulocyte count
- Bone marrow evaluation only if abnormalities in the above testing results and further investigation is necessary for a diagnosis
- Patients with newly diagnosed ITP should undergo testing for HIV, HCV, HBV, and *H. pylori*
- Direct antigen test should be checked to rule out concurrent Evans' syndrome
- Nutritional evaluation
- BM evaluation if other cell lines affected and concern for aplastic anemia

Grading	Management
G1: Platelet count 75 to < 100/μL	Continue ICPi with close clinical follow-up and laboratory evaluation.
G2: Platelet count 50 to < 75/μL	Hold ICPi but monitor for improvement. If not resolved, interrupt treatment until AE has reverted to G1. Administer prednisone 1 mg/kg per day (dosage range, 0.5-2 mg/kg per day) orally for 4 weeks followed by taper over 4-6 weeks to the lowest effective dose. IVIG may be used in conjunction with corticosteroids if a more rapid increase in platelet count is required.

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TABLE 8. Hematologic Toxicities (continued)

8.6. ITP

G3: Platelet count 25 to < 50/μL	As per G2. Hematology consult. Consider as alternative to prednisone or dexamethasone 40 mg daily for 4 days. If IVIG is used, the dose should initially be 1 g/kg as a one-time dose. If previous treatment with corticosteroids and/or IVIG has been unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more potent immunosuppression. (*From American Society of Hematology guideline on ITP[189]—consult for further details)*
G4: Platelet count < 25/μL	

8.7. Acquired Hemophilia A

Workup and evaluation
- Hematology consult
- Full blood count to assess platelet number, fibrinogen, PT, PTT, and INR. The typical finding in patients with acquired hemophilia A is a prolonged aPTT with a normal PT.
- MRI, CT, and ultrasonography may be indicated to localize, quantify, and serially monitor the location and response of bleeding.
- Medication review to assess for alternative causes
- Determination of Bethesda unit level of inhibitor

Grading	Management
G1: Mild: 5%-40% of normal factor activity in blood; 0.05-0.4 IU/mL of whole blood	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits. Administer 0.5-1 mg/kg/d prednisone. Transfusion support as required. Treatment of bleeding disorders with hematology consult.
G2: Moderate: 1%-5% of normal factor activity in blood; 0.01-0.05 IU/mL of whole blood	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits. Administration of factor replacement (choice based on BU of titer). Administer 1 mg/kg/d prednisone ± rituximab (dose 375 mg/m^2 weekly × 4 weeks) and/or cyclophosphamide (dose 1-2 mg/kg/d). Choice of rituximab versus cyclophosphamide is patient specific and should be done with assistance of hematology consult. Prednisone, rituximab, and cyclophosphamide should be given for at least 5 weeks. Factors should be provided to increase level during bleeding episodes, with choice of factor based on presence or absence of inhibitor. Transfusion support as required for bleeding.
G3-4: Severe: < 1% of normal factor activity in blood; < 0.01 IU/mL of whole blood	Permanently discontinue ICPi. Admit patient. Administration of factor replacement; choice based on BU level of inhibitor. Bypassing agents may be used (Factor VII FEIBA). Caution should be taken in elderly patients and those with CAD. Prednisone corticosteroids 1-2 mg/kg/d (oral or IV depending on symptoms) ± rituximab (dose 375 mg/m^2 weekly × 4 weeks) and/or cyclophosphamide (dose 1-2 mg/kg/d). Transfusion support as required for bleeding. If worsening or no improvement add cyclosporine or immunosuppression or immunoadsorption.

Additional considerations
- Acquired hemophilia A requires special clinical and laboratory expertise. Consult and/or transfer to a specialist center is often appropriate. If consultation with or transfer to a hemophilia center is not immediately possible, then investigation and treatment should be initiated while a liaison is being established.[190]

Abbreviations: AD, autoimmune disease; AE, adverse event; ANC, antineutrophil cytoplasmic antibodies; ATG, antithymocyte globulin; BM, bone marrow; BU, Bethesda units; CAD, coronary artery disease; CMV, cytomegalovirus; CT, computed tomography; CTX, chemotherapy; CXR, chest x-ray; DIC, disseminated intravascular coagulation; EBV, Epstein-Barr virus; FH, family history; GPI, glycosylphosphatidylinositol; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV6, human herpesvirus 6; HUS, hemolytic uremic syndrome; ICPi, immune checkpoint inhibitor; INR, international normalized ratio; ITP, immune thrombocytopenia; IV, intravenous; IVIG, intravenous immune globulin; LDH, lactate dehydrogenase; LLN, lower limit of normal; MDS, myelodysplastic syndromes; MMA, methylmalonic acid; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; PEX, plasma exchange; PMN, polymorphonuclear cell; PNH, paroxysmal nocturnal hemoglobinuria; PT, prothrombin time; PTT, partial thromboplastin time; SAE, serious adverse event; TTP, thrombotic thrombocytopenic purpura.

[a]Patients should be immunized with a meningococcal vaccine at least 2 weeks before administering the first dose of eculizumab, unless the risks of delaying eculizumab therapy outweigh the risks of developing a meningococcal infection.

diminished ejection fraction.[149,192] Conduction abnormalities can include complete heart block.[149,192] A variety of dysrhythmias may occur including manageable supraventricular tachycardias or life-threatening ventricular tachycardias.[149,150,191,192,194,199-201]

There is no clear evidence regarding the efficacy or value of routine baseline or serial ECGs or troponin measurements in patients receiving checkpoint inhibitor therapy. Some centers obtain baseline testing, and others continue this through the initial period of therapy. Some centers stratify management

based on the magnitude of troponin changes.[194] Reported cases have invariably had elevations of troponin, CK, and CK-MB.[194] Brain natriuretic peptide will also be elevated in cases with decreased ejection fraction. Diagnostic evaluation should consider the possibility of other etiologies of the patient's symptoms and could include, for example, cardiac stress testing, heart catheterization, or cardiac MRI. ICPi myositis and myasthenia gravis often present concomitantly with myocarditis, and workup for these toxicities should be strongly considered. Because of the possibility of arrhythmia and progression to life-threatening arrhythmias or heart block, early cardiology involvement and continuous telemetry monitoring should be instituted.

At symptom presentation, an echocardiogram may reveal decreased left or right ventricular ejection fraction (with global or regional abnormalities). Cardiac MRI can demonstrate evidence of myocarditis but is less sensitive than endomyocardial biopsy.[194,198] Endomyocardial biopsy should be considered for patients who are unstable or failed to respond to initial therapy or in whom the diagnosis is in doubt. However, when the clinical suspicion is high, treatment should be offered empirically before confirmatory pathologic testing is obtained.

Although some cases are fulminant and progress to death, cardiac irAEs and their life-threatening manifestation (cardiac contractility and conduction abnormalities) can improve.[200] The data so far are insufficient to predict the likelihood of improvement. The aggressiveness of management must also take into account the status of the patient's malignancy and the overall prognosis.

Small retrospective series have found an elevated incidence of VTE, reported to range from 8%-30%, following treatment with immunotherapy.[202-207] Thus, management is directed at treating the VTE and preventing complications such as pulmonary embolism, avoiding immunosuppressive therapy, and, when the patient is stable, continuing ICPi in the absence of other irAEs. Vasculitis resulting from ICPis has been reported as large vessel vasculitis and both PNS and CNS vasculitides, with resolution upon holding therapy and/or corticosteroids.[208]

10.0. Recommendations for identification, evaluation, and management of ocular toxicities. Immune-related ocular toxicities include uveitis, iritis, and episcleritis. The median onset is 5 weeks but can range from 1 to 72 weeks.[209] Presenting symptoms related to immune therapy–induced ocular toxicities may include blurred vision, change in color vision, photophobia, distortion, scotomas, visual field changes, double vision, tenderness, pain with eye movement, eyelid swelling, proptosis, redness, and/or dryness.

Refer to Table 10 for a complete set of recommendations, definition of grades, and additional considerations for ocular toxicities.

Discussion. Ocular toxicities are considered uncommon and less complex in their management compared with other immune-related toxicities. A variety of ocular events have been reported with CTLA-4, PD-1/PD-L1–inhibiting agents, including uveitis, iritis, episcleritis, and blepharitis. The principal mechanism of ocular toxicity is inflammatory and often the ICPi can be safely continued as most presenting grades are mild and manageable with topical corticosteroids.

The overall incidence of uveitis with ICPis[217-221] is approximately 1%, although the incidence may be higher in patients receiving combination ICPis.[222] Symptoms of uveitis may not indicate the severity of the syndrome and therefore consultation with ophthalmology and slitlamp examination is essential. Rarely, panuveitis may lead to exudative retinal detachment and progress to blindness. Typical management includes topical corticosteroids often with the addition of cycloplegic agents and, in rare cases, systemic steroids.[223]

Episcleritis is a rare but clinically important event, occurring in $<$ 1% of treated patients.[218] Ophthalmology referral is recommended for all cases of episcleritis even if asymptomatic and holding immune checkpoint therapy until such evaluation is completed. Artificial tears, topical corticosteroids, and cycloplegic agents are typically used and highly effective in managing this toxicity, but in rare cases, systemic steroids may be required. Any visual compromise (vision $<$ 20/40) should prompt urgent ophthalmology referral to assess the need for more specific interventions. In case of recurrent events or a grade 4 presentation (vision 20/200 or worse), permanent discontinuation on ICPi is advised. Infliximab may be considered for severe and treatment-refractory cases, although this is based on case reports only.

11.0. Recommendations for identification, evaluation, and management of systemic toxicities. Infusion-related reactions (IRRs) are characterized by adverse reactions to the infusion of pharmacologic or biologic substances, commonly described as infusion reaction. Presenting symptoms related to immune-related infusion reactions typically manifest as low-grade fever, chills, headache, or nausea. High-grade reactions can include additional symptoms of tachycardia, blood pressure lability, hypoxemia, chest pain, cough, shortness of breath, wheezing, flushing, sweating, urticaria or pruritis, angioedema, and presyncope or syncope.[224-229]

Refer to Table 11 for a complete set of recommendations, definition of grades, and additional considerations for systemic toxicities.

Discussion. Infusion reactions associated with ICPis are uncommon, and mild IRRs require no intervention as symptoms are typically transient. For moderate IRRs, interruption of the infusion and slowing of the rate of infusion upon rechallenge can be effective. Administration of supportive therapies may be required, that is, IV fluids, diphenhydramine, acetaminophen, NSAIDs, or

TABLE 9. Cardiovascular Toxicities

9.1. Myocarditis, Pericarditis, Arrhythmias, Impaired Ventricular Function With Heart Failure, and Vasculitis

Workup and evaluation
- ECG
- Troponin, and CPK to rule out concurrent myositis, especially in patients treated with combination immune therapies. Alternative reasons for elevation should be ruled out.
- If elevated, troponin should be serially monitored. With elevated troponin, be aware of the potential for triple M irAEs—myositis, myasthenia, and myocarditis—and refer to subspecialties.
- BNP
- Echocardiogram
- Chest X-ray

Additional testing to be guided by cardiology and may include:
- Stress test
- Cardiac catheterization
- Cardiac MRI

Grading	Management
G1: Abnormal cardiac biomarker testing without symptoms and with no ECG abnormalities	All grades warrant workup and intervention, given the potential for cardiac compromise. Hold ICPi for G1 elevated troponin[a] and recheck troponin 6 hours later. May consider resuming once normalized or if believed not to be related to ICPi. Hold ICPi and discontinue for ≥ G2. For patients with grade ≥ 2, early (ie, within 24 hours) initiation of high-dose corticosteroids (1-2 mg/kg/d of prednisone, oral or IV depending on symptoms) should be considered as it is likely to be beneficial without adverse effects. Admit patient for cardiology consultation. Management of cardiac symptoms according to ACC/AHA guidelines and with guidance from cardiology. Immediate transfer to a coronary care unit should be considered for patients with elevated troponin or conduction abnormalities. For new conduction delay, consider a pacemaker. In patients without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or antithymocyte globulin.[210] Consider abatacept (costimulatory molecule blockade) or alemtuzumab (CD52 blockade) as additional immunosuppression in life-threatening cases.[211,212]
G2: Abnormal cardiac biomarker testing with mild symptoms or new ECG abnormalities without conduction delay	
G3: Abnormal cardiac biomarker testing with either moderate symptoms or new conduction delay	
G4: Moderate to severe decompensation, IV medication or intervention required, life-threatening conditions	

Qualifying statement: Treatment recommendations are based on anecdotal evidence and the life-threatening nature of cardiovascular complications. Holding checkpoint inhibitor therapy is recommended for all grades of complications. The appropriateness of rechallenging remains unknown. Note that infliximab has been associated with heart failure and is contraindicated at high doses (ie, > 5 mg/kg) in patients with moderate-severe heart failure.[213,214]

9.2 Venous Thromboembolism

Workup and evaluation
- Evaluation of signs and symptoms of PE or DVT may include:
  - Clinical prediction rule to stratify patients with suspected VTE
  - Venous ultrasound for suspected DVT
  - CTPA for suspected PE
  - Can also consider D-dimer for low-risk patients based on risk stratification by clinical prediction rule for DVT/PE when CT or Doppler not available or appropriate
  - V/Q scan is also an option when CTPA is not appropriate
  - Consider other testing, including ECG, chest radiography, BNP and troponin levels, and ABG

Grading	Management
G1: Venous thrombosis (eg, superficial thrombosis)	Continue ICPi. Warm compress. Clinical surveillance.

(continued on following page)

TABLE 9. Cardiovascular Toxicities (continued)

9.2 Venous Thromboembolism	
G2: Venous thrombosis (eg, uncomplicated deep vein thrombosis), medical intervention indicated	Continue ICPi. Management according to CHEST, ACC, and/or AHA guidelines and consider consult from cardiology or other relevant specialties. LMWH, VKA, dabigatran, rivaroxaban, apixaban, or edoxaban for initial anticoagulation treatment. For long-term anticoagulation, LMWH, edoxaban, rivaroxaban, or apixaban for at least 6 months are preferred over VKAs because of improved efficacy.[215,216] IV heparin is an acceptable alternative for initial use and oral anticoagulants are acceptable for the long term.
G3: Venous thrombosis (eg, uncomplicated PE), urgent medical intervention indicated	Hold ICPi and may reintroduce after risk and benefit are considered. Follow G2 anticoagulation recommendations.
G4: Life-threatening consequences; hemodynamic or neurologic instability; organ damage; loss of extremity(ies)	Hold ICPi and may reintroduce after risk and benefit are considered. Admit patient and management according to CHEST, ACC, and/or AHA guidelines and with guidance from cardiology. Respiratory and hemodynamic support. Follow G2 anticoagulation recommendations with further clinical management as indicated based on symptoms.
Additional considerations VTE prophylaxis in high-risk outpatients with cancer (Khorana score of 2 or higher before starting a new systemic regimen) may be offered thromboprophylaxis with apixaban, rivaroxaban, or LMWH, provided there are no significant risk factors for bleeding and no drug interactions, as per ASCO VTE guideline.[215] Although it may be impossible to determine the etiology of thromboembolic disease in patients with advanced cancer and the role, if any, that ICPi treatment plays, it is reasonable to remove the potential inciting agents, given the severity and life-threatening potential of grade 4 complications. Clinicians are to use clinical judgment and take into account the risks and benefits when deciding whether to discontinue ICPi treatment. Anticoagulant therapy duration should continue while on immunotherapy and consideration be given to continuing for an additional 6 months following completion of immunotherapy.[215]	

Abbreviations: ABG, arterial blood gas; ACC, American College of Cardiology; AHA, American Heart Association; BNP, brain natriuretic peptide; CHEST, American College of Chest Physicians; CPK, creatine phosphokinase; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; CTPA, computed tomography pulmonary angiography; DVT, deep vein thrombosis; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; LMWH, low-molecular-weight heparin; MRI, magnetic resonance imaging; PE, pulmonary embolism; US, ultrasound; VKA, vitamin K agonist; VTE, venous thromboembolism.

[a]According to CTCAE v5.0, G1 elevated troponin is defined as levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer.

other analgesics. For high-grade reactions, cessation of therapy, administration of IV corticosteroid, and urgent intervention per institutional guidelines is advised. Depending on the severity of IRR, premedication with diphenhydramine and acetaminophen may prevent subsequent IRRs.

There is variability of IRRs across the ICPis with the highest incidence reported with the anti–PDL-1 agent avelumab, with any-grade IRRs occurring in 25% and > grade 3 events occurring in < 1% of patients, the majority within the first four treatments. For this reason, premedication with acetaminophen and diphenhydramine for the first four infusions is included in prescribing instructions for avelumab as it has been shown to decrease the rate of severe IRRs.[232,233] The incidence of IRRs among other PD-1/L-1 inhibitors is < 10% with the lowest incidence of IRRs for ipilimumab monotherapy at < 1%.[224-229]

12.0. Recommendations for prevention and management of adverse effects related to steroid use. Refer to Table 12 for a complete set of recommendations for prevention and management of AEs related to steroid use.

Discussion. Steroids remain the most studied and valuable agents in the management of immunotherapy-related AEs. Higher steroid doses may be necessary and steroid usage is often prolonged, placing patients at significant risk for acute and long-term steroid-related toxicities. Evaluation of the patient's pre-existing conditions and careful monitoring of steroid-related complications is crucial. Prophylactic agents to prevent certain opportunistic infections along with preemptive measures to mitigate various toxicities are necessary for patients needing longer-term steroid use. The lowest possible dose of steroids should be used for the shortest possible duration to minimize the harmful impact of steroids. Certain patients with pre-existing conditions like diabetes mellitus or an immune-compromised status and the elderly will need special attention. Steroid tapers should be gradual and individualized based on the irAE's response to treatment and the patient's ability to tolerate steroids. A multidisciplinary approach may be used in management of certain steroid-related complications and institutional guidelines should be considered in decision making.

SURVIVORSHIP

According to the ASCO and the Institute of Medicine, survivorship in cancer is defined as the period between a new cancer diagnosis, followed by the duration of life during

TABLE 10. Ocular Toxicities

Evaluation, under the guidance of ophthalmology:
- Check vision in each eye separately
- Color vision
- Red reflex
- Pupil size, shape, and reactivity
- Fundoscopic examination
- Inspection of anterior part of eye with penlight
- Slitlamp examination
- Eye pressure
- Need to rule out myasthenia gravis

Prior conditions
- Exclude patients with history of active uveitis
- History of recurrent uveitis requiring systemic immunosuppression or continuous local therapy

Additional considerations:
- Clinicians should be aware that ocular irAEs commonly accompany other organ irAEs, and there should be a high level of clinical suspicion, as symptoms may not always be associated with severity. Patients with all grades of ocular symptoms should be referred to ophthalmology.

10.1. Uveitis or Iritis

Workup and evaluation: As per 10.0
- Ophthalmology consult should be universal for the symptoms described in 10.0.

Grading	Management
G1: Anterior uveitis with trace cells	Continue ICPi. Prompt referral to ophthalmology (usually within 1 week) Artificial tears.
G2: Anterior uveitis with 1+ or 2+ cells	Hold ICPi temporarily until after ophthalmology consult. Urgent ophthalmology referral. Topical corticosteroids (eg, 1% prednisolone acetate suspension), cycloplegic agents (eg, atropine), and systemic corticosteroids.[223] May resume ICPi treatment once off systemic steroids if patient has only ocular irAE, once corticosteroids are reduced to ≤ 10 mg prednisone equivalent. Continued topical or ocular steroids are permitted when resuming therapy to manage and minimize local toxicity. Retreat after return to ≤ G1.
G3: Anterior uveitis with 3+ or greater cells; intermediate posterior or pan-uveitis	Permanently discontinue ICPi. Urgent ophthalmology referral. Systemic corticosteroids and intravitreal or periocular/ or topical corticosteroids. Methotrexate may be used in patients who respond poorly to systemic corticosteroids or those with severe sight-threatening inflammation.[223]
G4: Best-corrected visual acuity of 20/200 or worse in the affected eye	Permanently discontinue ICPi. Emergent ophthalmology referral. Systemic corticosteroids—prednisone 1-2 mg/kg/d or methylprednisolone 0.8-1.6 mg/kg/d and intravitreal or periocular or topical corticosteroids per ophthalmologist opinion.

Additional considerations: Consider use of infliximab, other TNFα blockers, or IVIG in cases that are severe and refractory to standard treatment.[230,231]

10.2. Episcleritis

Workup and evaluation: As per 10.0

Grading	Management
G1: Asymptomatic	Continue ICPi. Prompt ophthalmology referral (usually within 1 week). Artificial tears.
G2: vision 20/40 or better	Hold ICPi therapy temporarily until after ophthalmology consult. Urgent ophthalmology referral. Topical corticosteroids (eg, 1% prednisolone acetate suspension), cycloplegic agents (eg, atropine), and systemic corticosteroids.[223]

(continued on following page)

TABLE 10. Ocular Toxicities (continued)

10.2. Episcleritis	
G3: Symptomatic and vision worse than 2/40	Permanently discontinue ICPi. Urgent ophthalmology referral. Systemic corticosteroids and topical corticosteroids with cycloplegic agents.
G4: 20/200 or worse	Permanently discontinue ICPi. Emergent ophthalmology referral. Systemic corticosteroids and topical corticosteroids with cycloplegic agents.
Additional considerations: Consider use of infliximab or other TNFα blockers in cases that are severe and refractory to standard treatment.[230,231]	

Abbreviations: ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IVIG, intravenous immune globulin; TNF, tumor necrosis factor.

and after cancer therapy. This stage in a patient's cancer journey can be subdivided into three phases—acute, extended, and permanent. Acute survivorship begins at the point of diagnosis and continues until the end of initial treatment. Extended survivorship begins once initial treatment is complete and continues for several months afterward, with a focus on the effects of cancer and its treatments. Permanent survivorship commences years after cancer treatment has ended, with long-term effects, risk reduction, and health promotion being the focus. Specific timelines that define these periods, particularly for subsets of patients by cancer type and treatment, have yet to be elucidated. Throughout a patient's cancer journey, the goal remains to provide comprehensive care to meet the unique needs of cancer survivors.

The concept of survivorship from immunotherapy is not new, as prior immunomodulating treatments for cancer such as high-dose interleukin-2 (IL-2) and tumor-infiltrating lymphocytes have been known to result in durable benefit spanning years in a small subset of patients with metastatic melanoma or RCC. However, with the expansion of the use of ICPi therapies across multiple tumor indications resulting in durable survival outcomes, the concept of survivorship care for patients receiving immunotherapy has once again risen to the fore. A new population in the era of cancer immunotherapy survivorship

TABLE 11. Systemic Toxicities

11.1. IRRs	
Workup and evaluation Physical examination including vital signs Pulse oximetry ECG if chest pain or sustained tachycardia	
Grading	**Management**
G1: Mild transient reaction; infusion interruption not indicated; intervention not indicated	Continue ICPi. May consider premedication with acetaminophen and an antihistamine for subsequent infusions.
G2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment; prophylactic medication indicated for ≤ 24 hours	Consider holding ICPi temporarily and/or reducing the rate of infusion to 50% (or per institutional guidelines). Offer symptomatic treatment with antihistamines, NSAIDs, opioids, and IV fluids as clinically appropriate. Offer prophylactic acetaminophen and an antihistamine per institution guidelines for subsequent infusions.
G3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae	Hold ICPi temporarily and consider resuming, at an infusion rate of 50% (or per institutional guidelines), once return to ≤ G1. Offer symptomatic treatment with antihistamines, NSAIDs, opioids, and IV fluids as clinically appropriate. Consider antihistamines and corticosteroid medications IV. Hospitalization for other clinical sequelae.
G4: Life-threatening consequences; urgent intervention indicated	Permanently discontinue ICPi. ICU level inpatient care.
Additional considerations Clinicians may consider switching to an alternate agent in the therapeutic class upon rechallenge or consider rechallenging with the offending immunotherapy agent through a desensitization procedure under the supervision of an allergist.	

Abbreviations: ICPi, immune checkpoint inhibitor; ICU, intensive care unit; IRR, infusion-related reaction; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug.

TABLE 12. Prevention and Management of Adverse Effects Related to Steroid Use

12.1. Pretreatment considerations
Baseline workup to include viral hepatitis B and C serology and consideration for latent or active TB test. In patients with pre-existing HIV, testing HIV viral load and CD4 count would be appropriate.
Patients with pre-existing comorbid conditions, such as DM, hypertension, HF, cataract, glaucoma, infection, or osteoporosis, should have their condition optimally managed before commencing steroids.
Ideal steroid dosing and duration is individualized and can vary by patient, oncologic agents, and type of irAE. Refer to each individual irAE section for more detail.
The lowest dose of steroids should be used for the shortest duration of time needed to achieve treatment goals and control deleterious effects of irAE, as the risk of toxicity with steroids is generally dose- and duration-dependent.
12.2. Prevention of opportunistic infection
Use of prophylaxis for an opportunistic infection with PJP may be considered once a patient has received a prednisone equivalent of ≥ 20 mg/d for 4 or more weeks or > 30 mg for 3 weeks or more. Physicians may proceed according to institutional guidelines.
The role of prophylactic fluconazole with prolonged steroid use (> 12 weeks) remains unclear and physicians should proceed according to institutional guidelines.[234]
Use of prophylaxis against herpes zoster reactivation may be offered to patients who have had zoster before and will be receiving corticosteroids.[235]
12.3. Monitoring for acute or short-term and long-term adverse effects
Patients should be routinely asked about adverse effects related to glucocorticoids. During treatment with glucocorticoids and depending upon individual risk factors such as dose and duration of glucocorticoid usage, other medications being used, and comorbidities, particular attention should be given to the following acute or short-term and long-term adverse effects:
Acute or short-term AEs
Increased vulnerability to infection
Insomnia
Anxiety
Diabetes or glucose intolerance
Hypertension
Cutaneous changes
Long-term AEs
Bone loss (osteopenia and osteoporosis) and fractures
Cataracts or glaucoma
Steroid myopathy
Relative adrenal insufficiency
Psychiatric disturbance
Gastric or duodenal ulcers
GI prophylaxis with PPI or H2 antagonist is recommended.
To limit steroid-induced bone loss, patient should receive adequate calcium (dietary or supplementation), vitamin D, and weight-bearing exercise should be encouraged when feasible. Bone-modifying agents may be offered to patients on steroids for > 3 months and are recommended for all patients with pre-existing osteoporosis. Patients with or at risk for osteoporosis who have long-term survival potential should undergo bone mineral density testing.[236]
12.4. Tapering of steroids
The length of steroid-taper should occur according to the type and severity of irAE, the initial steroid dose, and individual patient responses rather than other prespecified criteria.
Steroid taper should occur slowly, generally over 4-6 weeks.
Regular clinical evaluation should occur during steroid tapering as there is a risk of irAE rebound or recurrence.
In general, oral steroid tapering is recommended to occur over 4-6 weeks, with a reduction in prednisone or prednisolone of 10 mg every 3-7 days (as irAE allows) until the dose is 10 mg/d, and then reduced by 5 mg every 3-7 days for patients who respond quickly to steroids. For those who have received steroids for several weeks, tapering may be more prolonged.
In general, for patients who require IV steroids, tapering is recommended to occur over 4 weeks or longer. The initial IV conversion from methylprednisolone if ≥ 1 mg/kg/d would be to oral prednisone 1 mg/kg/day at minimum and then taper as above.
Longer steroid tapers (> 4-6 weeks) may be required for complete resolution or to avoid recurrence or rebound of irAE events.
Patients should be monitored for the symptoms of adrenal insufficiency after prolonged exogenous steroids
Stress doses may be needed in the event of illness, injury, and surgery
Option when ready to drop below 5 mg of prednisone or 0.5 mg of dexamethasone after a longer course with concern for iatrogenic adrenal insufficiency is to transition to hydrocortisone at physiologic dosing (10 mg in the morning and 5 mg in the afternoon). This allows for faster recovery of the HPA axis because it restores diurnal patterns.
If indicated to control disease, a simultaneous slow, low-dose taper of the long-acting steroid can be given (for example, decreasing by 1 mg prednisone per week).
HPA axis function can be tested 24 hours from last oral hydrocortisone (skip PM dose and hold AM dose for labs)—measured AM cortisol and ACTH will reflect endogenous function. Ambiguous results can be clarified with an ACTH stimulation test similarly prepared for.

Abbreviations: ACTH, adrenocorticotropic hormone; AE, adverse event; AM, morning; DM, diabetes mellitus; HF, heart failure; HPA, hypothalamic pituitary adrenal; irAE, immune-related adverse event; IV, intravenous; PJP, pneumocystis jirovecii pneumonia; PM, post meridiem; PPI, proton pump inhibitor; TB, tuberculosis.

has emerged and questions around what defines survivorship for those with stage IV disease are being explored, with some suggesting using the label 'thriver' instead. Identification of the specific needs and provision of comprehensive care for patients who may be classified as survivors after completion of ICPis is a clinically unmet need. This section is intended to offer initial guidance on survivorship care plans (SCPs) to health care providers for patients with any tumor type during and after immunotherapy.

ASCO promotes the use of 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). While 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.

Although there is no universally accepted definition of chronic irAEs, the multidisciplinary ASCO Guideline Panel defines chronic irAEs as symptoms developing during immunotherapeutic treatment and last from 6 months to 1 year after completion of treatment. The exceptions to this time frame are immune-related endocrinopathies, such as hypothyroidism, adrenal insufficiency, DM type I, and hypogonadism, which are often not reversible but managed with lifetime hormone replacement. Analyses of NSCLC survivors who were treated with anti–PD-(L)1 immunotherapy show that 36% survived $>$ 1 year after initiation of immunotherapy and that greater than half developed irAEs (https://cdn.webinar.net/resources/a35a1d54-91de-42e4-b583-36299776c945.pdf). Moreover, 27% of these patients required ongoing management of irAEs at 1 year with long-term immunosuppression (https://cdn.webinar.net/resources/a35a1d54-91de-42e4-b583-36299776c945.pdf). This suggests that the spectrum of immunotherapy toxicity in survivors may be unique and that an SCP should include info on immunotherapy toxicity and immunosuppression.

Late irAEs have been defined as acute symptoms with an onset that occurs later than 6 months after discontinuation of ICPi therapy,[237] although consensus around this definition is still developing and may be different for different immunotherapy toxicities. Late irAEs can include myocarditis with onset of G2 at 8 months after discontinuation, arthralgia with a median onset of 7.5 months after discontinuation, and rash G2-3 occurring $>$ 11 months after ICPi treatment discontinuation.[238] Compared with CTX, it is difficult to predict late irAEs or prevent irAEs consequences.

The postimmunotherapy survivor may also experience adverse effects seen in those treated with other anticancer agents or modalities. These can include psychosocial effects, such as fatigue that interferes with physical and social functioning as well as anxiety and depression, cognitive difficulties, sexual dysfunction, and trouble sleeping.[239-241] Fear of cancer recurrence, body image, and financial toxicity are also frequent psychosocial struggles of cancer survivors. The specific incidence and patterns seen in the postimmunotherapy survivor are not yet well established.

Fertility can also be affected in cancer survivors.[242] It is advised that patients of reproductive age use effective birth control during and for at least 5 months after immunotherapy.[243] Most clinical trials also require patients of reproductive age to use at least two anticonception methods while receiving anti–PD-1 agents for up to 6 months after the last dose. However, data supporting this recommendation are lacking.[244] Immunotherapeutic treatment can also affect conception in several ways, including immunotherapy-related endocrine dysfunction and direct effects on reproductive organs. The discussion about the risk of immunotherapy-related gonadotoxicity and the need for oncofertility counseling should be initiated with patients of childbearing age at the time of diagnosis.

irAEs themselves can also lead to long-term symptoms that require management.[245] For example, inflammatory arthropathy or peripheral neuropathy can result in long-term pain and discomfort. Adrenal insufficiency can lead to osteoporosis, weight gain, poor wound healing, possible changes in fertility, and adrenal crisis. Diabetes can result in long-term nephropathy, retinopathy, and neuropathy. A key aspect of survivorship care in patients treated with ICPis will be to establish a partnership with allied medical subspecialists who have clinical expertise in the management of these conditions that can occur as a result of ICPis.

Sequelae from treatments used to manage the irAE, such as steroids, other immune suppressive agents, and hormone replacement, can also occur. Chronic and late side effects from long-term use of steroids are well established and can include adrenal insufficiency, osteoporosis, compression fractures, myopathy, DM, gastritis, recurrent candidiasis, and thinning of the skin.

Evidence to guide survivorship for patients who receive immunotherapeutic agents in combination with CTX, targeted therapy, antiangiogenic therapy, and intratumoral injections is lacking, and management of these patients can be complex. Patients on immunotherapy or vascular endothelial growth factor receptor TKI combinations, for example, have longer progression-free survival (PFS) and are thus exposed to the vascular toxic effects of vascular endothelial growth factor receptor inhibitors for a longer time, perhaps leading to coronary artery disease and cerebral vascular disease as well as wasting associated with chronic diarrhea. Furthermore, management of patients previously exposed to cytotoxic therapy before immunotherapy is even more challenging because of the uncertainty of patients' response to each therapy.

SCPs for postimmunotherapy should include regularly scheduled follow-up visits. It also remains important for patients to follow-up with subspecialties to diminish complications from irAEs and treatments.

Overall QoL is typically excellent on immunotherapy,[245,246] but a clear understanding of chronic, late, and rare irAEs is not fully appreciated. Treatment-free survival is an emerging outcome measure with ICPis treatment that captures the time free of systemic anticancer therapy in all patients who initiate therapy and incorporates the possibility of persistent and/or late adverse effects of initial therapy to describe more completely the experience of every patient.[247] Investigators have theorized that there may be value in stopping treatment with ICPis earlier in responders, thereby extending their treatment-free survival without compromising their survival.[247,248] Such an approach may limit late complications and possibly financial toxicity, although this aspect of survivorship care specific to ICPis has not been fully explored. Ultimately, it is critical to educate and monitor patients after immunotherapeutic treatment to maintain their QoL. After completion of immunotherapy, patients need careful follow-up for chronic and late irAEs. The timing and content of medical information exchanged between care providers is vital to improve provider role clarity and knowledge, to ensure supportive and other care needs of the patient are met, and to care for psychosocial concerns and comorbid medical conditions for individuals living with, through, and beyond cancer.[249]

DISCUSSION OF CURRENT CONTROVERSIES, GAPS IN RESEARCH, AND FUTURE DIRECTIONS

Predicting irAEs

Current guidelines for the management of irAEs focus on the early identification of toxicities and timely initiation of treatment while providing direction for escalation of immunosuppressive therapies in the setting of severe and/or steroid refractory toxicities. Although studies are ongoing to identify patients at an increased risk for irAEs, comprehensive predictive models may be difficult to achieve.

Demographics

Clinical factors predictive of irAEs are not well defined aside from the known increased risk for patients with an underlying AD. A retrospective analysis of 455 patients with melanoma treated with ICPi at a single institution evaluated associations between patient demographics (age, sex, performance status, and comorbid conditions) and toxicity features (severity, hospitalization, and outcome of patients diagnosed with myocarditis, colitis, hepatitis, and pneumonitis) of both combination and monotherapy ICPi. Younger patients were at increased risk of severe irAEs, whereas increased death rate and length of hospitalization were more common in older patients. The toxicity profile of younger patients included higher rates of colitis and hepatitis, whereas pneumonitis and myocarditis were more common in older patients.[250]

Autoimmune Disease

Patients with pre-existing ADs are often not offered therapy with ICPis out of concern for exacerbation of symptoms and typically have been excluded from clinical trials involving these agents. However, data suggest that they may be safely treated.[251-253] A 2016 systematic review of case reports of patients with pre-existing ADs treated with ICPis found that only 41% of patients experienced an exacerbation of their pre-existing AD, despite 46% having active disease upon ICPi initiation.[288] Among 112 patients with pre-existing ADs in a 2019 retrospective cohort study, 70 patients (71%) experienced AD and/or other irAE(s), with pre-existing AD flare occurring in 53 patients (47%) and/or other irAE(s) in 47 patients (42%). There was a need for immunosuppressive therapy in 48 patients (43%) and permanent discontinuation of ICPi in 24 patients (21%). For patients requiring immunosuppressive therapy before initiating ICPi, the mPFS was shorter (3.8 months *v* 12 months; $P = .006$).[254]

A proposal for a selective immunosuppressive strategy for patients with ADs includes two steps for controlling ADs when using ICPi: (1) Rotation phase: discontinuation of all nonselective immunosuppressants and replacement with the most appropriate selective immunosuppression and assess for the stability of AD 2-4 weeks before the start of concomitant ICPi treatment, if timing allows based on the pace of cancer growth and urgency of treatment; 2. Maintenance phase: simultaneous selective immunosuppression and ICPis during the entire immunotherapy period.[255]

Biomarkers

Limiting the utility of existing biomarker data for irAE prediction in therapeutic decision making are variables in tumoral heterogeneity, tumor and immune microenvironment chronologic change, and precision of biomarker sampling. Several studies have identified potentially useful biomarkers, ranging from immune cell profiles and spatial relationships with tumor cells to cytokine varieties and concentrations, to B-cell populations and autoantibodies. However, these biomarkers have not been validated or incorporated into a clinically useful approach to weighing risk versus benefit of immunotherapy or identifying or managing any particular irAE.

A retrospective analysis of 18,000 anti–PD (aPD)1/L1–treated patients with 26 different cancer types experiencing irAEs investigated predictive models to identify biomarkers for irAEs using real-world pharmacovigilance and molecular omics data. Among markers known to correlate with irAEs and with treatment response, TCR diversity and CD8+ T-cell abundance demonstrated the greatest correlation with irAEs at 56% of the reporting odds ratio (ROR). Analysis of gene profiles predictive of irAEs demonstrated a positive correlation with the lymphocyte cytosolic protein 1, which is involved in T-cell activation and the adenosine diphosphate–dependent glucokinase, which is involved in

mediating metabolic shift during T-cell activation. There was no apparent correlation between treatment response and the combination of lymphocyte cytosolic protein 1 with adenosine diphosphate–dependent glucokinase.[256]

Several studies have shown the importance of cytokine levels and irAEs. Through modulation of cytokines in AD, discoveries of similar modulatory effects in irAEs offer hope for therapeutic benefit without impairing ICPi antitumor effects.

Specificity of cytokine responses to anti–CTLA-4 are seen with serum IL-17 concentrations in patients who develop severe grade 3 GI irAEs.[257,258] Lower baseline levels of IL-6 among patients with melanoma treated with anti–CTLA-4[259] and on-treatment increase in proinflammatory cytokines such as IL-6, soluble cluster of differentiation 163, and CXCL5 have been shown to correlate with greater risk of immune-mediated toxicity.[260,261] Upregulation of 11 cytokines both at baseline and early during treatment correlated with severe irAEs in patients with melanoma treated with combination ICPis and are integrated into the novel cytokine toxicity score.[262]

Pretreatment circulating autoantibodies measured in patients with melanoma receiving ICPi were analyzed in a cohort of 333 patients at 5 European centers. Elevated anti-MAGEB4 pretreatment levels were associated with longer overall survival (OS) ($P = .002$, hazard ratio [HR] = 0.77) and the development of irAEs ($P = .002$, HR = 1.27) in ipilimumab ± nivolumab–treated patients. Higher pretreatment anti-FGFR1 antibodies were associated with shorter survival ($P = .008$, HR = 1.27) and a lower frequency of irAEs ($P = .04$, HR = 0.69) in these patients.[263]

Combination Regimens With ICPi

Radiation. Thoracic radiation used in treatment protocols for lung cancer can cause radiation-induced lung injury (RILI). A recent review on the topic summarizes the risk factors for RILI such as age, sex, and comorbidities, whereas current smoking lowers RILI risk.[264] Several clinical trials are investigating radiation with various combinations of ICPi, targeted therapy, or CTX in patients with lung cancer. The pivotal PACIFIC trial proved that consolidation ICPi versus placebo following conformal external beam radiation therapy in unresectable stage III lung cancer improved survival for the ICPi cohort (from median OS not reached to 28.7 months; HR 0.68; 99.73% CI, 0.47 to 0.997; $P = .0025$) with tolerable increased risk of pneumonitis. The reported discontinuation rates of the trial regimen for pneumonitis were 4.8% in the ICPi group and 2.6% in the placebo group, and for radiation pneumonitis were 1.3% and 1.3%, respectively.[265] Studies evaluating ICPi with radiation of varying dosimetric parameters among many cancer types and disease stages are ongoing.

Chemotherapy. Combinations of CTX and ICPi have established efficacy in lung cancer; however, robust data of various chemotherapies in combination with ICPis and relative patterns of irAEs are not known. A single-institution retrospective review of 112 patients who received frontline ICPi alone and 37 who received CTX plus CPI for stage IV NSCLC demonstrated increased numbers of patients experiencing at least one irAE in the CTX plus CPI cohort (59% *v* 34%) and shorter time to irAE onset (6.0 m *v* 36.7 m, HR 1.8, $P = .0304$).[266]

Targeted therapy. Many therapies targeting metabolic and cell signaling pathways are now being studied in combination with ICPis in a variety of cancer types.

Combinations of ICPi with targeted therapy in stage IV melanoma have demonstrated mixed safety signals, with the combination of the aPD-L1, atezolizumab, with targeted therapies, vemurafenib, and cobimetinib, having gained regulatory approval in this setting with only slightly higher grade 3-4 TRAEs (79% in triplet group *v* 73% without ICPi). The combination of the aPD-1, pembrolizumab, with targeted therapies, dabrafentib, and trametinib, resulted in grade 3-5 toxicity of 58% in the triplet therapy group versus 25% with targeted therapy alone.[267,268]

Severe irAEs have been demonstrated with frontline use of ICPi monotherapy in patients with NSCLC with epidermal growth factor receptor oncogenic driver mutations. An observational study of 41 patients treated with aPD(L)1 followed by osimertinib reported 15% of patients experienced a severe irAE (grade 3-4 colitis, hepatitis, and pneumonitis). Among cases where there was < 3 months between the last dose of ICPi and the first dose of osimertinib, there was a higher incidence of irAEs of any grade.[269] If ICPi is initiated as first-line therapy in this patient population, as in cases where the driver mutation was not identified before treatment initiation, experts advise waiting 3 months before starting osimertinib from the last dose of ICPi. It is worth noting that none of the patients treated with erlotinib or afatinib following ICPi experienced severe irAEs.

A 2019 European retrospective registry study showed 462 of 551 evaluable patients with molecular alterations in *KRAS*, epidermal growth factor receptor, *BRAF, MET*, human epidermal growth factor receptor 2, anaplastic lymphoma kinase, *RET, ROS1*, and multiple drivers treated with ICPis (first line [5%], second line [41%], third line [26%], fourth line [13%], or in later lines [14%] of treatment), 50 (10.8%) had grade 3-5 irAEs with a pneumonitis rate shown to be in the expected range (13 cases, 2.8%).[270]

Ameliorating Risk

Prevention of irAEs is being studied in protocols combining other immunomodulators with ICPis; however, the safety and efficacy of such combinations have not demonstrated success to date.[271,272] Additional strategies in mitigating toxicities while maintaining efficacy, such as alternative dosing schema or increasing the interval between treatment infusions, appear promising; however, dose reductions of ICPi therapy during treatment should be avoided.

Rather, therapeutic adjustments by way of temporary interruption or permanent discontinuation of treatment are recommended.

Disease Control in Setting of Toxicity

The association of irAEs with improved efficacy remains controversial as there are variable outcomes among analyses.

A 2019 systematic review and meta-analysis sought to identify correlates between irAEs and patient outcomes across 48 clinical trials and 8,000 patients with eight different cancer histologies treated with either combination or monotherapy ICPi. A positive correlation with nivolumab was seen between ORR and the incidence rate of skin ($r = 0.79$, $P < .001$), GI ($r = 0.56$, $P = .006$), and endocrine irAEs ($r = 0.44$, $P = .05$), but not hepatic, pulmonary, and renal irAEs. A positive correlation with ORR to ipilimumab and nivolumab was seen with the incidence rate of skin ($r = 0.54$, $P = .04$) and GI irAEs ($r = 0.60$, $P = .02$), but not endocrine, hepatic, pulmonary, and renal irAEs.[273]

A 2021 systematic review and meta-analysis sought to assess the relationship between treatment efficacy and irAEs from 51 studies including patients with melanoma, lung, renal, urothelial, head and neck, and GI cancers. In this study, patients with irAEs had improved treatment efficacy irrespective of disease site, type of ICPi, or irAE; however, among patients with grade 3 or 4 irAEs, there was increased ORR but worse OS.[27]

In a multicenter cohort study of 623 patients with NSCLC treated with aPD-1 or aPD-L1 monotherapy, patients treated with aPD-L1 developed multisystem irAEs, most commonly pneumonitis thyroiditis (n = 7, 14%), hepatitis thyroiditis (n = 5, 10%), dermatitis pneumonitis (n = 5, 10%), and dermatitis thyroiditis (n = 4, 8%). Multisystem irAEs were associated with improved survival from ICPis in NSCLC, adjusting for treatment duration, in a multivariable model. Patients with one irAE and multisystem irAEs demonstrated incrementally improved OS (adjusted HRs [aHRs], 0.86; 95% CI, 0.66 to 1.12; $P = .26$; and aHR, 0.57; 95% CI, 0.38 to 0.85; $P = .005$, respectively) and PFS (aHR, 0.68; 95% CI, 0.55 to 0.85; $P = .001$; and aHR, 0.39; 95% CI, 0.28 to 0.55; $P < .001$, respectively) versus patients with no irAEs.[274]

Rechallenging

The decision to resume ICPi therapy after resolution of toxicity is challenging, with many factors to consider, such as previous tumor response, duration of treatment, type and severity of the toxicity, time to toxicity resolution, availability of alternate therapies, and patient performance status. In addition, the optimal duration of ICPi therapy is not defined. Early trials of ICPi used one year of therapy; later trials used 2 years of therapy or continued ICPi treatment until disease progression or patient intolerance. A patient's tumor response status is an important factor in deciding whether to resume ICPi. If a patient has achieved an objective response to initial ICPi, there is a reasonable likelihood that the response will be durable and that resumption of therapy (with attendant risk of recurrence of toxicity) may not be advisable. Conversely, for patients who have not yet responded or whose response is deemed inadequate, consideration of resumption of ICPi therapy after resolution of toxicity is reasonable. For some patients with a rapid resolution of certain moderate to severe irAEs after corticosteroid use, resumption of ICPi may be less precarious.

A large pharmacovigilance cohort study of individual case safety reports from the World Health Organization database VigiBase sought primarily to determine the rate of recurrence of an initial irAE upon ICPi rechallenge. A total of 24,079 irAEs cases were reviewed with 130 recurrences (28.8%; 95% CI, 24.8 to 33.1) of the initial irAE observed. Among irAEs, colitis (ROR, 1.77; 95% CI, 1.14 to 2.75; $P = .01$), hepatitis (ROR, 3.38; 95% CI, 1.31 to 8.74; $P = .01$), and pneumonitis (ROR, 2.26; 95% CI, 1.18 to 4.32; $P = .01$) were associated with a higher recurrence rate.[275]

From additional studies, rechallenge with ICPis after cessation for colitis and pneumonitis has been described. Recurrence of colitis was seen in up to one third of patients, with anti–CTLA-4 posing higher risk than anti–PD-1 alone, and there was a greater likelihood for recurrence among those with a more severe index event.[102,276] The more severe the index colitis event, the higher likelihood of a recurrence on ICPi resumption.[276] Among patients with pneumonitis rechallenged with anti–PD-L1, half of the patients experienced recurrence or new irAE with increased likelihood of irAE in patients with an early-onset index event.[277] The majority of such patients were managed successfully, but two deaths have been reported.[277]

Analysis of rechallenge with ICPis associated with specific malignancies has been reported. In a multicenter retrospective study of 80 patients with metastatic RCC for whom ICPi treatment was interrupted, 36 (45%) were restarted and 44 (55%) permanently discontinued treatment. Among those who resumed therapy, the median time before reinitiation was 0.9 months with subsequent irAEs occurring in 50% of patients (12 new and six recurrent) with 7 (19%) grade 3 events. Upon retreatment, there were responses among previous nonresponders (6 of 26 patients, 23%).[278] Among 180 patients with melanoma receiving ICPi, upon rechallenge, 38.9% experienced at least one grade ≥ 2 irAE, with 70% experiencing the same irAE, 25.7% experiencing a distinct irAE, and 4.3% with the same and a distinct irAE. GI irAEs were more likely to recur; however, there was no correlation between the severity of initial and subsequent irAEs.[279]

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 gradual easing 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 irAEs or COVID-19. COVID-19 can mimic commonly seen clinical presentations of irAEs, such as shortness of breath and cough in pneumonitis, elevated troponin or heart failure in myocarditis, and elevated liver function tests in hepatitis.[280] Furthermore, the radiographical appearance of COVID-19 and ICPi pneumonitis may be similar and include diffuse ground-glass opacities.[280-282] 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. Furthermore, clinicians should not pause ICPi therapy for vaccination but should consider avoiding scheduling ICPi therapy when vaccine side effects are expected (https://www.asco.org/sites/new-www.asco.org/files/content-files/covid-19/2021-MSK-COVID19-VACCINE-GUIDELINES.pdf).

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

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 immunotherapies, 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 immunotherapy works differently than traditional CTX and that these treatments elicit unique therapeutic responses and corresponding irAEs.[283] 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 an immunotherapeutic agent 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.

In most cases, irAEs can be managed with treatment interruption and/or supportive care and for some patients will involve a multidisciplinary team (eg, endocrinologist, pulmonologist, and gastroenterologist) to address specific symptoms.[284] Patients and caregivers need to know that AEs can often be

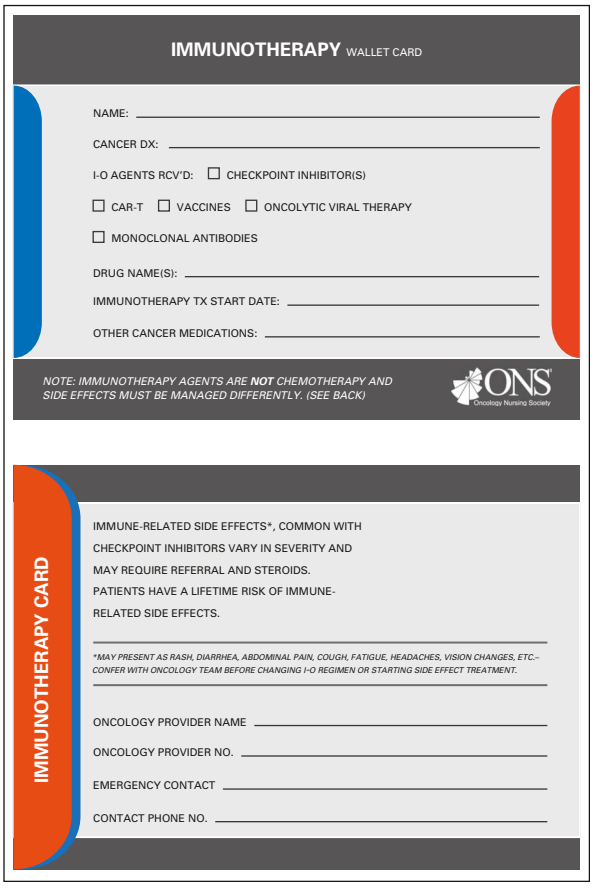

FIG 1. Immunotherapy wallet card. Reprinted courtesy of the Oncology Nursing Society. All rights reserved.

TABLE 13. Ongoing Studies

Title and ClinicalTrials.gov Identifier (NCT No.)	Status	Conditions	Interventions	Country
Treatment Efficacy of Corticosteroids, Mycophenolate Mofetil and Tacrolimus in Patients With Immune Related Hepatitis—NCT04810156	Not yet recruiting	Hepatitis, drug-induced	Drug: mycophenolate mofetil Drug: tacrolimus Drug: solu-medrol Drug: ursodeoxycholic acid	Denmark
Tofacitinib for the Treatment of Refractory Immune-related Colitis From Checkpoint Inhibitor Therapy—TRICK Study—NCT04768504	Not yet recruiting	Immune-mediated colitis	Drug: tofacitinib 10 mg	Canada
CD24Fc for the Treatment of Immune Related Adverse Events in Patients With Advanced Solid Tumors, TIRAEC Study—NCT04552704	Recruiting	Advanced malignant solid neoplasm	Biologic: CD24 extracellulardomain—IgG1 Fc domain recombinant fusion protein CD24Fc Drug: placebo administration	United States
Infliximab or Vedolizumab in Treating Immune Checkpoint Inhibitor-Related Colitis in Patients With Genitourinary Cancer or Melanoma—NCT04407247	Recruiting	Colitis Lung non–small-cell carcinoma Malignant GU system neoplasm Malignant solid neoplasm Melanoma	Biologic: infliximab Biologic: vedolizumab	United States
Study of Rituximab or Tocilizumab for Patients With Steroid-Dependent Immune-Related Adverse Events (irAEs)—NCT04375228	Not yet recruiting	irAEs Advanced solid tumor	Drug: rituximab Drug: tocilizumab	United States
Fecal Microbiota Transplantation in Treating Immune-Checkpoint Inhibitor Induced-Diarrhea or Colitis in Genitourinary Cancer Patients—NCT04038619	Recruiting	Colitis Diarrhea Malignant GU system neoplasm	Procedure: fecal microbiota transplantation Drug: loperamide	United States
Impact of Therapeutic Patient Education on the Toxicity of Immune Checkpoint Inhibitors in Oncology—NCT03948724	Recruiting	Melanoma NSCLC, renal, and head and neck cancer	Behavioral: therapeutic education program Behavioral: usual information	France
Checkpoint Inhibitor Induced Colitis and Arthritis—Immunomodulation With IL-6 Blockade and Exploration of Disease Mechanisms—NCT03601611	Completed	Solid tumor Colitis Arthritis	Drug: tocilizumab (RoACTEMRA)	Denmark
A Phase II Study of the Interleukin-6 Receptor Inhibitor Tocilizumab in Combination With Ipilimumab and Nivolumab in Patients With Unresectable Stage III or Stage IV Melanoma—NCT03999749	Recruiting	Melanoma	Drug: ipilimumab Drug: nivolumab Drug: tocilizumab	United States

Abbreviations: ICPi, immune checkpoint inhibitor; IL, interleukin; irAE, immune-related adverse event; NSCLC, non–small-cell lung cancer.

managed effectively, especially when they are identified early. In addition, education addressing the safe handling of medications, infection control, and safe sexual practices is important in supporting optimal management of irAEs.[283]

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.[285] 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 patients with a history of immunotherapy.[284] The Oncology Nursing Society has an immunotherapy wallet card available for patients and providers (Fig 1). Copies of the card or additional information can be obtained by e-mail at clinical@ons.org.

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[286]

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 through 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 the 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 CPGC 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*.

FUTURE RESEARCH

Clinical Trials in Development

The National Cancer Institute of Clinical Trials Database (https://www.clinicaltrials.gov/) was searched on March 26, 2021, for potential trials meeting the selection criteria for this systematic review. There were nine ongoing trials identified (Table 13) that would be eligible for inclusion in the update of this recommendation report in the future.

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.

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 Chimeric Antigen Receptor (CAR) T-Cell Therapy (in press)
- Integration of Palliative Care into Standard Oncology Practice[287] (https://ascopubs.org/doi/full/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[286] (https://ascopubs.org/doi/full/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 Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update

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APPENDIX

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

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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, 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
Christina Lacchetti, MHSc	American Society of Clinical Oncology, Alexandria, VA	ASCO Practice Guideline Staff, Health Research Methodologist

TABLE A2. Immunosuppressive Agents

Immunosuppressive Agents	Dosing	Indications	Contraindications and Cautions
Systemic corticosteroids	Oral/IV prednisone 0.5-2 mg/kg/d IV methylprednisolone 1-2 mg/kg/d Dexamethasone 10-20 mg IV	In general, from grade ≥ 2 irAE in any toxicity	Corticosteroids are contraindicated in patients with known hypersensitivity to prednisone or any excipients in the formulation. Warnings that there is a risk of alterations in endocrine function, increased risk of infections, alterations in CV and renal function, risk of GI complications, behavioral and mood disturbances, decreased bone density, ophthalmic effects, neuromuscular effects, and caution in pregnancy use as fetal harm can occur. Warnings that systemic absorption of topical corticosteroids has produced reversible HPA axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients. Systemic absorption is typically rare, and is related to potency, body surface area treated, and duration of therapy. Conditions that augment systematic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202020s000lbl.pdf
Topical steroids	Low strength Hydrocortisone 1%, 2.5% (class 7) Desonide 0.05% (class 6) Medium strength Betamethasone valerate 0.1% (class 4) Triamcinolone acetonide 0.1% (class 4) High strength Fluocinonide 0.05% (class 2) Highest strength Betamethasone dipropionate 0.05% (class 1) Halobetasol 0.05% (class 1)	Skin irAEs	
Biologic immunosuppressive agents			
Abatacept (CTLA-4 agonist)	500 mg IV once every 14 days × 5 doses	Life-threatening and steroid-refractory myocarditis	No contraindications. Warnings that concomitant use with a TNF antagonist can increase the risk of infections and serious infections. Hypersensitivity, anaphylaxis, and anaphylactoid reactions have been reported. Patients with a history of recurrent infections or underlying conditions predisposing to infections may experience more infections. Discontinue if a serious infection develops. Screen for latent TB infection before initiating therapy. Patients testing positive should be treated before initiating abatacept. Live vaccines should not be given concurrently or within 3 months of discontinuation. Based on its mechanism of action, abatacept may blunt the effectiveness of some immunizations. Patients with COPD may develop more frequent respiratory AEs. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125118s0086lbl.pdf
Alemtuzumab (anti-CD52)	30 mg IV single dose	Life-threatening and steroid-refractory myocarditis	Alemtuzumab is contraindicated in patients infected with HIV. Warning that alemtuzumab can causes serious, sometimes fatal, autoimmune conditions such as ITP and antiglomerular basement membrane disease. Monitor complete blood counts with differential serum creatinine levels, and urinalysis with urine counts at periodic intervals for 48 months after the last dose. Alemtuzumab may also cause serious and life-threatening infusion reactions and must be administered in a setting with appropriate equipment and personnel to manage anaphylaxis or serious infusion reactions. Monitor patients for 2 hours after each infusion. Make patients aware that serious infusion reactions can also occur after the 2-hour monitoring period. Alemtuzumab may also cause an increased risk of malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103948s5158lbl.pdf

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TABLE A2. Immunosuppressive Agents (continued)

Immunosuppressive Agents	Dosing	Indications	Contraindications and Cautions
Anakinra (anti-IL1)	100 mg SC once a day	Hematologic irAEs	Anakinra is contraindicated in patients known hypersensitivity to *E. coli*–derived proteins, anakinra, or to any component of the product. Warning that use in combination with TNF-blocking agents is not recommended. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported. The impact of treatment with anakinra on active and/or chronic infections and the development of malignancies is not known. Live vaccines should not be given concurrently with anakinra. Neutrophil counts should be assessed before initiating anakinra treatment and while receiving anakinra, monthly for 3 months, and thereafter quarterly for a period up to 1 year. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103950s5136lbl.pdf
ATG (immune depletion)	500 mg on day 1, titrating the dose by 250 mg increments to daily CD2/3 levels (aiming for levels of 50-100/μL) for a total of 5 days	Hematologic irAEs, severe cases of myocarditis	Contraindicated in patients with hypersensitivity to rabbit or horse proteins or to any product excipients or active acute or chronic infections, which would contraindicate any additional immunosuppression. Medical surveillance is required during thymoglobulin infusions. Serious immune-mediated reactions have been reported with the use of thymoglobulin and consist of anaphylaxis or severe CRS. https://products.sanofi.ca/en/Thymoglobulin.pdf
Caplacizumab (anti-vWF antibody)	First day: 11 mg IV bolus at least 15 minutes before plasma exchange, followed by 11 mg SC after completion of plasma exchange on day 1 Subsequent days during daily plasma exchange: 11 mg SC once a day following plasma exchange After plasma exchange period: 11 mg SC once a day for 30 days following last daily plasma exchange After initial treatment course: If sign(s) of persistent underlying disease, treatment may be extended for a maximum of 28 days	Acquired TTP	Contraindicated in patients with a previous severe hypersensitivity reaction to caplacizumabyhdp or to any of the excipients. Hypersensitivity reactions have included urticaria. Caplacizumab increases the risk of bleeding. In clinical studies, severe bleeding adverse reactions of epistaxis, gingival bleeding, upper GI hemorrhage, and metrorrhagia were each reported in 1% of subjects. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761112s000lbl.pdf
Dupilumab (anti–IL-4)	Initial dose of 600 mg (two 300 mg injections in different injection sites), followed by 300 mg given once every other week	Severe pruritic dermatitis	Dupilumab is contraindicated in patients with known hypersensitivity to dupilumab or any of its excipients. Warning that hypersensitivity reactions (including anaphylaxis), conjunctivitis, and eosinophilic conditions, have occurred in patients treated with dupilumab. Warning to not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of therapy with dupilumab. Also, treat patients with pre-existing helminth infections before initiating therapy with dupilumab. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761055s014lbl.pdf
Eculizumab (anti-C5a)	900 mg once a week × 4 doses, 1,200 mg week 5, then 1,200 mg once every 2 weeks	HUS	Eculizumab is contraindicated in patients with unresolved serious *Neisseria meningitidis* infection and patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying eculizumab treatment outweigh the risks of developing a meningococcal infection. Warning that life-threatening and fatal meningococcal infections have occurred in patients treated with eculizumab. Discontinue eculizumab in patients who are being treated for serious meningococcal infections and use caution when administering to patients with any other systemic infection. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125166s172lbl.pdf

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TABLE A2. Immunosuppressive Agents (continued)

Immunosuppressive Agents	Dosing	Indications	Contraindications and Cautions
Infliximab (anti–TNF-α)	5 mg/kg IV, second dose may be repeated 14 days later	Severe or steroid-refractory colitis, pneumonitis, myocarditis, arthritis, nephritis, uveitis, and hematologic irAEs	Infliximab at doses > 5 mg/kg is contraindicated in moderate to severe heart failure. It is also contraindicated in patients with previous severe hypersensitivity reaction to infliximab or known hypersensitivity to inactive components of infliximab or to any murine proteins. Warning with infliximab includes increased risk of serious infections leading to hospitalization or death. Discontinue infliximab if a patient develops a serious infection. Perform test for latent TB; if positive, start treatment for TB before starting infliximab. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. Cases of fatal HSTCL have been reported in patients treated with TNF blockers including infliximab. All infliximab cases were reported in patients with Crohn's disease or ulcerative colitis, the majority of whom were adolescent or young adult males. All had received AZA or 6-mercaptopurine concomitantly with infliximab at or before diagnosis. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/103772s5359lbl.pdf
Rituximab (anti-CD20)	375 mg/m^2 once a week × 4 doses	Dermatologic and hematologic irAEs, myositis, encephalitis, IVIG or plasmapheresis-refractory myasthenia gravis	No contraindications. Warnings for rituximab include fatal infusion reactions within 24 hours of rituximab infusion have been reported. Approximately 80% of fatal reactions occurred with the first infusion. Monitor patients and discontinue RITUXAN infusion for severe reactions. Tumor lysis syndrome, severe mucocutaneous reactions, some with fatal outcomes, and PML resulting in death have also been reported. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103705s5367s5388lbl.pdf
Tocilizumab (anti–IL-6)	8 mg/kg administered IV once per month or 162 mg administered SC once per week	irAEs refractory to TNF-α inhibitors	Tocilizumab is contraindicated in patients with known hypersensitivity to tocilizumab. Warning that use of tocilizumab can result in serious infections leading to hospitalization or death including TB, bacterial, invasive fungal, viral, and other opportunistic infections has occurred in patients receiving tocilizumab. If a serious infection develops, interrupt tocilizumab until the infection is controlled. Perform test for latent TB; if positive, start treatment for TB before starting tocilizumab. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125276s114lbl.pdf
Vedolizumab (α4/b7 integrin antagonist)	300 mg IV on weeks 0, 2, 6, and then once every 8 weeks thereafter	Colitis refractory to infliximab or infliximab contraindicated	Vedolizumab is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to vedolizumab or any of its excipients. Warnings for vedolizumab include hypersensitivity reactions (including anaphylaxis); infections—treatment with vedolizumab is not recommended in patients with active, severe infections until the infections are controlled. Although no cases of PML have been observed in clinical trials, JCV infection resulting in PML and death has occurred in patients treated with another integrin receptor antagonist. A risk of PML cannot be ruled out. Monitor patients for any new or worsening neurologic signs or symptoms. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125476s000lbl.pdf
Ustekinumab (anti–IL-12/IL-23)	Induction: ≤ 55 kg: 260 mg IV as single dose; > 55 kg to 85 kg: 390 mg IV as single dose; > 85 kg: 520 mg IV as single dose Maintenance: 90 mg SC once every 8 weeks; begin maintenance dosing 8 weeks after the IV induction dose	Colitis refractory to all immunosuppression treatments	Ustekinumab is contraindicated in patients who have a significant hypersensitivity to ustekinumab or any of its excipients. Warnings for ustekinumab include risk of infection, malignancies, and hypersensitivity reactions. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761044lbl.pdf

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TABLE A2. Immunosuppressive Agents (continued)

Immunosuppressive Agents	Dosing	Indications	Contraindications and Cautions
Nonbiologic immunosuppressive agents			
AZA (nonselective immunosuppressant)	50 mg/d with subsequent incremental increase by 25-50 mg once every 1-2 weeks up to 2 mg/kg/d	Steroid-refractory immune-related hepatitis, myositis, and nephritis	AZA is contraindicated in patients who have shown hypersensitivity to the drug. Patients with rheumatoid arthritis previously treated with alkylating agents (CYC, chlorambucil, melphalan, or others) may have a prohibitive risk of malignancy if treated with AZA. Warning that patients receiving immunosuppressants, including AZA, are at increased risk of developing lymphoma and other malignancies, particularly of the skin. Physicians should inform patients of the risk of malignancy with AZA. As usual, for patients with increased risk for skin cancer, exposure to sunlight and ultraviolet light should be limited. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/016324s034s035lbl.pdf
CYC (nonselective immunosuppressant)	1 to 2 mg/kg/d	Steroid-refractory pneumonitis, nephritis, and hematologic irAEs	Contraindications include hypersensitivity to CYC and urinary outflow obstruction. Warnings include urinary tract and renal toxicity. Cardiotoxicity, which may be fatal, has been reported. Monitor patients, especially those with risk factors for cardiotoxicity or pre-existing cardiac disease. Pulmonary toxicity leading to respiratory failure may also occur. Monitor patients for signs and symptoms of pulmonary toxicity. Secondary malignancies, veno-occlusive liver disease, and embryofetal toxicity can occur. Advise female patients of reproductive potential to avoid pregnancy. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/012141s090,012142s112lbl.pdf
Cyclosporine (CNIs)	1-2 mg/kg/d	Hematologic irAEs, SCAR, and nephritis	Contraindicated in patients with a hypersensitivity to cyclosporine and/or polyoxyethylated castor oil. Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe cyclosporine. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. Cyclosporine should be administered with adrenal corticosteroids but not with other immunosuppressive agents. Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Cyclosporine, when used in high doses, can cause hepatotoxicity and nephrotoxicity. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050573s039,050574s047,050625s053lbl.pdf
Eltrombopag (nonselective immunosuppressant)	Starting dose of 50 mg once daily	Refractory aplastic anemia	No contraindications. Warnings that eltrombopag may cause hepatotoxicity, increase the risk for development or progression of reticulin fiber deposition within the bone marrow, and may increase the risk for hematologic malignancies. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/022291lbl.pdf
Etoposide (topoisomerase II inhibitor)	150 mg/m^2 IV, twice weekly for weeks 1-2, and then once weekly	Severe or refractory HLH	Contraindicated in patients with a hypersensitivity to etoposide products. Warnings that etoposide may cause myelosuppression, secondary leukemias with long-term use, hypersensitivity reactions, and embryofetal toxicity. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020457s016lbl.pdf

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TABLE A2. Immunosuppressive Agents (continued)

Immunosuppressive Agents	Dosing	Indications	Contraindications and Cautions
Hydroxychloroquine (nonselective immunosuppressant)	200-400 mg daily, administered as a single dose or in two divided doses, but no more than 5 mg/kg/d calculated based upon actual body weight	Mild or moderate IA	Use of hydroxychloroquine is contraindicated in patients with known hypersensitivity to 4-aminoquinoline compounds. Use with caution in patients with GI, neurologic, or blood disorders. Prolonged used requires ophthalmologic monitoring for retinal toxicity. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf
IVIG (nonselective immunosuppressant)	2 g/kg over 2-5 days in divided doses of 400-500 mg/kg	Hematologic irAEs, SCAR, pneumonitis, myositis, MG, GBS, encephalitis, demyelinating disease, and uveitis	IVIG is contraindicated in those with a history of anaphylactic or severe systemic reaction to human immune globulin, hyperprolinemia, or IgA-deficient patients with antibodies to IgA and a history of hypersensitivity. Warning for IVIG use that thrombosis and renal dysfunction in predisposed patients can occur. For patients at risk of thrombosis, renal dysfunction, or failure, administer IVIG at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity. https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Package-Insert—Privigen.pdf
Leflunomide (nonselective immunosuppressant)	Loading dose of one 100 mg tablet per day for 3 days	Moderate or refractory IA	Contraindicated in pregnant women, or women of childbearing potential who are not using reliable contraception, patients with pre-existing acute or chronic liver disease, or those with serum ALT $> 2\times$ ULN before initiating treatment, patients with known hypersensitivity to leflunomide or any of the other components of leflunomide, and patients being treated with teriflunomide. Severe liver injury, including fatal liver failure, has been reported in some patients treated with leflunomide. Leflunomide is not recommended for patients with severe immunodeficiency, bone marrow dysplasia, or severe, uncontrolled infections. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020905s020lbl.pdf
MTX (nonselective immunosuppressant)	Starting dose of 15 mg PO once weekly, with daily folic acid supplementation	Moderate or refractory musculoskeletal and ocular irAEs	Contraindicated in pregnancy, alcoholism or liver disease, immunodeficiency syndromes, pre-existing blood dyscrasias, and hypersensitivity to MTX. Warnings for MTX include potential for organ system toxicity, may cause impairment of fertility, oligospermia, and menstrual dysfunction, elimination is reduced in patients with impaired renal function, ascites, or pleural effusions, may cause dizziness and fatigue, and may impair ability to drive or operate machinery. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210737s000lbl.pdf
MMF (nonselective immunosuppressant)	0.5-1 g PO once every 12 hours	Steroid-refractory hepatitis, nephritis, pneumonitis, myocarditis, myositis, and hematologic irAEs	MMF is contraindicated in patients with hypersensitivity to MMF, MPA, or any component of the drug product and in patients allergic to Polysorbate 80. Warning that use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Females of reproductive potential must be counseled regarding pregnancy prevention and planning. There is an increased risk of the development of lymphoma and other malignancies, particularly of the skin. There is also an increased susceptibility to infections, including opportunistic infections and severe infections with fatal outcomes. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/050722s035,050723s035,050758s033,050759s041lbl.pdf

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TABLE A2. Immunosuppressive Agents (continued)

Immunosuppressive Agents	Dosing	Indications	Contraindications and Cautions
Plasmapheresis (nonselective immunosuppressant)	Several courses as needed	Myastenia gravis, GBS, demyelinating disease, encephalitis, and myositis.	Contraindications include hemodynamic instability or septicemia, known allergy to fresh frozen plasma or replacement colloid or albumin, and known allergy to heparin. Warning that complications may occur, including hypocalcemia or hypomagnesemia, hypothermia, transfusion reactions, fluid and electrolyte imbalance, bleeding diatheses, hypotension, flushing, and GI symptoms like nausea and vomiting. https://www.ncbi.nlm.nih.gov/books/NBK560566/
Sulfasalazine (nonselective immunosuppressant)	Initial: 500 mg once daily or 1 g/d in 2 divided doses; increase weekly to maintenance dose: 2 g/d in 2 divided doses; maximum: 3 g/d (if response to 2 g/d is inadequate after 12 weeks of treatment)	Mild or moderate IA	Sulfasalazine tablets are contraindicated in patients with intestinal or urinary obstruction, patients with porphyria, and patients hypersensitive to sulfasalazine, its metabolites, sulfonamides, or salicylates. Only after critical appraisal should sulfasalazine tablets be given to patients with hepatic or renal damage or blood dyscrasias. Deaths associated with the administration of sulfasalazine have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia, other blood dyscrasias, renal and liver damage, irreversible neuromuscular and central nervous system changes, and fibrosing alveolitis. Sulfasalazine tablets should be given with caution to patients with severe allergy or bronchial asthma. Adequate fluid intake must be maintained to prevent crystalluria and stone formation. Patients with glucose-6 phosphate dehydrogenase deficiency should be observed closely for signs of hemolytic anemia. If toxic or hypersensitivity reactions occur, the drug should be discontinued immediately. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/007073s124lbl.pdf
Tofacitinib (Janus kinase inhibitor)	10 mg PO twice a day for 30 days	Colitis refractory to all immunosuppression treatments	No contraindications. Warning that serious infections leading to hospitalization or death, including TB and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving tofacitinib. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203214s024,208246s010lbl.pdf

Abbreviations: AE, adverse event; ATG, antithymocyte globulin; AZA, azathioprine; CNI, calcineurin inhibitor; COPD, chronic obstructive pulmonary disease; CRS, cytokine release syndrome; CTLA, cytotoxic T-lymphocyte–associated antigen; CV, cardiovascular; CYC, cyclophosphamide; GBS, Guillain-Barré syndrome; HLH, hemophagocytic lymphohistiocytosis; HPA, hypothalamic-pituitary-adrenal; HSTCL, hepatosplenic T-cell lymphoma; HUS, hemolytic uremic syndrome; IA, inflammatory arthritis; IL, interleukin; ITP, immune thrombocytopenia; IV, intravenous; IVIG, intravenous immune globulin; irAE, immune-related adverse event; JCV, John Cunningham virus; MMF, mycophenolate mofetil; MPA, mycophenolic acid; MTX, methotrexate; PML, progressive multifocal leukoencephalopathy; PO, by mouth; SC, subcutaneously; SCAR, severe cutaneous adverse reaction; TB, tuberculosis; TNF, tumor necrosis factor; TTP, thrombotic thrombocytopenic purpura; ULN, upper limit of normal; vWF, von Willebrand factor.

TABLE A3. Commonly Conducted Testing at Baseline Before Immune Checkpoint Inhibitor Therapy[a]

Baseline Testing
Clinical
Physical examination including PS, weight, BMI, heart rate and BP, and SPO2
Comprehensive history including autoimmune, organ-specific disease, endocrinopathy, neuropathy, and infectious disease
Comprehensive systems review should be performed with specific attention to bowel habits, respiratory symptoms, skin rash, arthralgias, and neurologic symptoms.
Laboratory
Complete CBC plus DIFF
Complete metabolic panel that may include serum electrolytes (Na, K, Ca, and CO2), liver function (AST, ALT, ALKP, and GGT), creatinine, CK, total bilirubin, and glucose
TSH, free T4
Imaging or other testing
Chest X-ray
CT
ECG

Abbreviations: ALKP, alkaline phosphatase; BMI, body mass index; BP, blood pressure; CK, creatine kinase; CT, computed tomography; DIFF, differential test; GGT, gamma-glutamyl transferase; PS, performance status; TSH, thyroid-stimulating hormone.

[a]Other testing may also be necessary, based on patient's history and pre-existing comorbidities and/or risk factors.

TABLE A4. Commonly Conducted Testing During irAE Management With Steroids[a]

Testing During irAE Management with Steroids
Clinical
Physical examination including blood pressure, weight, heart rate, and SPO2
Assess for presence of infection including oral Candida
Screen for classic symptoms of hyperglycemia or diabetes: polyuria, polydipsia, and weight loss
Eye examination, including assessment of increased intraocular pressure with therapy > 6 weeks
Laboratory
Complete CBC plus DIFF
Complete metabolic panel that may include serum electrolytes (Na, K, Ca, and CO2), liver function (AST, ALT, ALKP, and GGT), creatinine, CK, total bilirubin, and glucose
Imaging
Bone mineral density (during prolonged therapy)

Abbreviations: ALKP, alkaline phosphatase; CK, creatine kinase; DIFF, differential test; GGT, gamma-glutamyl transferase; irAE, immune-related adverse event.

[a]Other testing may also be necessary, based on patient's history and pre-existing comorbidities and/or risk factors.